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

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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-Butyloxy carbonyl
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
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
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<tr>
<td>HPLC</td>
<td>High performance liquid chromatography</td>
</tr>
<tr>
<td>hv</td>
<td>light</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>IP₃</td>
<td>D-&lt;i&gt;myo&lt;/i&gt;-inositol-1,4,5-triphosphate</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared (spectrum)</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>Lithium tri-sec-butylborohydride</td>
</tr>
<tr>
<td>m</td>
<td>Multiplet or medium</td>
</tr>
<tr>
<td>m</td>
<td>Mass</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>&lt;i&gt;m&lt;/i&gt;-Chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
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<tr>
<td>min</td>
<td>minutes</td>
</tr>
<tr>
<td>mol</td>
<td>Mole</td>
</tr>
<tr>
<td>mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>Ms</td>
<td>Mesyl (methanesulfonyl)</td>
</tr>
<tr>
<td>NBS</td>
<td>&lt;i&gt;N&lt;/i&gt;-Bromosuccinimide</td>
</tr>
<tr>
<td>NMO</td>
<td>&lt;i&gt;N&lt;/i&gt;-Methylmorpholine &lt;i&gt;N&lt;/i&gt;-oxide</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance</td>
</tr>
<tr>
<td>[O]</td>
<td>Oxidation</td>
</tr>
<tr>
<td>&lt;i&gt;p&lt;/i&gt;-BrBz</td>
<td>&lt;i&gt;p&lt;/i&gt;-Bromobenzoyl</td>
</tr>
<tr>
<td>PDC</td>
<td>Pyridinium dichromate</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PhH</td>
<td>Benzene</td>
</tr>
<tr>
<td>PIP₂</td>
<td>L-&lt;i&gt;α&lt;/i&gt;-Phosphatidyl-&lt;i&gt;myo&lt;/i&gt;-inositol-4,5-biphosphate</td>
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<tr>
<td>PKC</td>
<td>Protein kinase C</td>
</tr>
<tr>
<td>PMB</td>
<td>&lt;i&gt;p&lt;/i&gt;-Methoxybenzyl</td>
</tr>
<tr>
<td>PPA</td>
<td>Polyphosphoric acid</td>
</tr>
<tr>
<td>ppm</td>
<td>Parts per million</td>
</tr>
<tr>
<td>PPSE</td>
<td>Polyphosphoric acid trimethylsilyl ester</td>
</tr>
<tr>
<td>Py</td>
<td>Pyridine</td>
</tr>
<tr>
<td>s</td>
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</tr>
<tr>
<td>t</td>
<td>Triplet</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
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<tr>
<td>TBS</td>
<td>&lt;i&gt;tert&lt;/i&gt;-Butyldimethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>Trifluoromethanesulfonyle</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
</tbody>
</table>
THP  
Tetrahydropyranyl

TLC  
Thin layer chromatography

TMS  
Trimethylsilyl

Ts  
p-Toluenesulfonyl (tosyl)

TsOH  
p-Toluenesulfonic acid

w  
Weak

z  
Charge

Δ  
Heat at reflux
1.1 Background and Introduction.

1.1.1 Isolation and Biological Activity.

In 1977 Ōmura 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*
In 1985 Sezaki reported the isolation and structure of the first example of a furanosylated indolocarbazole, SF-2370 (2). 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.

*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). 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, Alzheimer’s disease, and other neurodegenerative disorders.

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. TAN-1030a, along with many interesting minor metabolites, has been independently isolated by Fredenhagen, from the staurosporine producing strain *Streptomyces longisporoflavus*.11
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. 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).

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.

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. 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

Cell surface receptor → Agonist (hormone) → Phospholipase C → DAG → Protein Kinase C → Protein → Physiological Response

L-α-Phosphatidyl-D-myo-inositol-4,5-biphosphate (PIP2) → D-myo-inositol-1,4,5-triphosphate (IP3) → Endoplasmic Reticulum → Ca(II) → Protein → Protein → ATp → ADP

Phospholipase C → diacyl glycerol (DAG)
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.\textsuperscript{15,16} These investigations focused on staurosporine (1) and rebeccamycin (9), respectively. Through feeding experiments using L-[5-\textsuperscript{3H}]tryptophan, L-[\textsuperscript{\beta}-\textsuperscript{14C}]tryptophan, and DL-[\textsuperscript{\alpha-\textsuperscript{13C}}]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 \textit{Streptomyces staurosporeus} from D-glucose (15), presumably via the shikimic acid pathway.\textsuperscript{17} Furthermore, through a feeding experiment with (\textsuperscript{15}NH\textsubscript{4})\textsubscript{2}SO\textsubscript{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 preceded (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. 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-2H7]-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’-CD3 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 longosphoroflavus*\(^{19}\). 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., $6 \rightarrow 33 \rightarrow 2$). The interesting ring contraction of oxime 6 to amine 33 has been demonstrated in the laboratory (conditions in parenthesis).\textsuperscript{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. 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, Mann, and later Moldenhauser developed a double Fischer indolization of 37 or 35 to provide upon oxidation indolocarbazole 38 directly.

**Scheme 1.3.2**

1. PhNH$_3$$^+$Br$^-$, $\Delta$
2. Pd/C, CO$_2$

1.3.1.2 Winterfeld's Approach to Staurosporinone.

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., \( 41 \rightarrow 42 \), Scheme 1.3.3).

**Scheme 1.3.3**

\[
\begin{array}{c}
\text{1. } \text{Ac}_2\text{O, DMAP} \\
\text{2. } \text{TiCl}_3 \\
\text{3. } \text{NaHCO}_3 \\
(29\% \text{ yield})
\end{array}
\]

\[
\text{hv}
\]

\[
\begin{array}{c}
\text{(65\% \text{ yield})}
\end{array}
\]

1.3.1.3 Magnus' Approach.\(^{28}\)

Shortly 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 efficient 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., \( 48 \rightarrow 49 \) or \( 48 \rightarrow 50 \), Scheme 1.3.4) to potentially allow for the regioselective introduction of a carbohydrate moiety.
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.
1.3.1.5 The Kaneko/Clardy Approach.\textsuperscript{30}

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

\textit{Scheme 1.3.6}
1.3.1.6 Bergman’s First Approach.\textsuperscript{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. $n$-BuLi (2 equiv)
2. t-BuLi
3. I$_2$ (0.5 equiv)
4. H$^+$
5. CH$_2$N$_2$
   (38% yield)

1. BnNH$_2$
2. DDQ
3. TsOH
   (60% yield)

1.3.1.7 The Bergman and Gribble Methods.\textsuperscript{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**

Bergman
1. toluene, $\Delta$
2. PhNHNH$_2$
   MeOH, AcOH
   (82% yield, R=H)

Gribble
1. toluene, $\Delta$
2. m-CPBA
3. PhNHNH$_2$
   (81% yield, R=Me)

1. PPSE
2. Pd/C, $\Delta$
   (68% yield, R=H/52% yield, R=Me)

59
56b R = H
56c R = Me

60a R = H
60b R = Me

21a R = H
21c R = Me
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

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$_3$SiH 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. NaBH₄
2. Et₃SiH, TFA
(95% yield)

1. $\text{Pd/C}$
2. NaOH, MeOH
3. $\text{Ac}_2\text{O}, 100 \degree\text{C}$
4. NH₃, H₂O
(52% yield)

1. NaBH₄
2. Et₃SiH, TFA
(95% yield)

1. $\text{PPh}_3$
2. H₃O⁺
(43% yield)

1. NaBH₄
2. Et₃SiH, TFA
3. $\text{PPh}_3$
(48% yield)

1.3.1.9 The Moody Approach.$^{34}$

The Moody synthesis centered on the utilization of pyranoidolone 70 to control an intramolecular Diels-Alder reaction with subsequent aromatization to carbazole 71 by loss of CO₂ 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.
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

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. Wallace and Bergman 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.

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 glycosylation 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.\textsuperscript{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.
1.3.1.14 The Prudhomme Degradation.\textsuperscript{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).

\textit{Scheme 1.3.16}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {9} ++(1,2.5) node {1. Zn(Hg) HCl, EtOH} ++(1.5,-3) node {	extcolor{red}{(47\% yield)}};
\node at (3,0) {81} ++(1,2.5) node {2. HClO\textsubscript{4}} ++(1.5,-3) node {	extcolor{red}{(30\% yield)}};
\node at (6,0) {4a} ++(1,2.5) node {Pd/C HCO\textsubscript{2}H} ++(1.5,-3) node {	extcolor{red}{(63\% yield)}};
\end{tikzpicture}
\end{center}

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\textsubscript{4} followed by treatment with

\textit{Scheme 1.3.17}

\begin{center}
\begin{tikzpicture}
\node at (0,0) {20a} ++(1,2.5) node {Pd(OAc)\textsubscript{2} AcOH} ++(1.5,-3) node {	extcolor{red}{110 °C (75\% yield)}};
\node at (3,0) {21a} ++(1,2.5) node {1. LiAlH\textsubscript{4}} ++(1.5,-3) node {	extcolor{red}{(63\% yield)}};
\node at (6,0) {4a} ++(1,2.5) node {2. Pd/C, H\textsubscript{2}};
\end{tikzpicture}
\end{center}
palladium to complete the synthesis of 4a (Scheme 1.3.17). Lown reported the sequence shown in Scheme 1.3.18, 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).

Scheme 1.3.18

![Scheme 1.3.18 diagram]

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

Scheme 1.3.20

![Scheme 1.3.20 diagram]
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**

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).

**1.3.2.2 Danishefsky’s Staurosporine Glycal Precursor.**

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).
1.3.2.3 The Bayer Synthesis of the K252a Carbohydrate.\textsuperscript{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 \textsuperscript{95} followed by reductive ozonolysis and acid mediated cyclization produced the racemic dimethoxy furanose [(±)-\textsuperscript{97}].

\textit{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 \(98\) occurred in the presence of \(\text{Ag}_2\text{O}\) 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\textsuperscript{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 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.\textsuperscript{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 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., $\text{38} + \text{113} \rightarrow \text{114}$, Scheme 1.3.30). 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., $\text{115} \rightarrow \text{116}$).

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. Specifically, epoxidation of glycal (-)-$\text{76}$ and reaction with maleimide $\text{117}$ formed one of the indole $N$-glycosidic linkages. Cyclization of maleimide $\text{118}$ and exo glycal formation set the stage for the critical second glycosidation. Treatment of olefin $\text{119}$ with iodine and $t$-BuOK followed by radical dehalogenation provided the pyranosylated indolocarbazole $\text{120}$ in 64% yield. Protecting group removal and methylation were achieved as shown in Scheme 1.3.31 (i.e., $\text{120} \rightarrow \text{121}$). Finally, reduction of imide $\text{121}$ provided a 1:1 mixture of $\text{1}$ and $\text{122}$. 
1.3.3.2.3 The Bayer Synthesis of (±)-K252a.\textsuperscript{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).
1.4 Notes and References.


(7) For a comprehensive review, see reference 3d.


CHAPTER TWO


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
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)\textsuperscript{3} was viewed as the most efficient approach (i.e., $2 \Rightarrow 4+97$, 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.\textsuperscript{4}

\textit{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 cyclofuranosylation (e.g., \(4 + 97 \rightarrow 2\)) and palladium mediated C-N bond formation in the carbazole synthesis (e.g., \(125 \rightarrow 4\)). Diels-Alder cycloaddition of indolepyrrolidone 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-SnBu₃) was initially explored as the substrate; however, under certain conditions ring closure occurred in the absence of tin. Thus, carbazole could be produced in up to 80% yield (e.g., \(130 \rightarrow 131\), Scheme 2.2.1) using Pd(PPh₃)₄ (1.1 equiv), Na₂CO₃ 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).
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 to a halopyrrolidone 128 (X = Br, I).\(^9\) 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 132\(a\)\(^12\) 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).\(^13\)

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., 132\(a\)+73\(→\)4a, Scheme 2.2.3).\(^14\)
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). Initial attempts to 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 1H-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
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%\text{±}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\textsubscript{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\textsuperscript{'}-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\textsuperscript{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 MsN₃ 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.
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).
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, 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 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 2.3.1
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). 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 \((\pm)-147\) and \((\pm)-148\); 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 \((\pm)-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. To support this structural assignment, the coupling of furanose (±)-97 with carbazole (131) was investigated. Under identical conditions (CSA, C₂H₄Cl₂, 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).

Scheme 2.3.4

![Scheme 2.3.4](image)

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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{25,26} Thus, exposure of (±)-147 to TFA and thioanisole (cation scavenger)\textsuperscript{27,28} in CH$_2$Cl$_2$ 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.\textsuperscript{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, a compound that appeared well suited for subsequent Lewis acid promoted [1,2]-allylic migration. 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). 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$_2$O 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$_2$O 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 materials.
bis Mosher ester (157) to samples prepared from $S$-$(\cdot)$- and $R$-$(\cdot)$-citramalic acid (158) established that $S$-$(\cdot)$-1-buten-3-ol (153, 98% ee) had furnished ketoester $R$-$(\cdot)$-155 (95% ee, see Figure 2.4.1).

*Figure 2.4.1*
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\(^{10}\) 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**

\[
\begin{align*}
\text{S\-\(-\)\-152b} & \xrightarrow{1. \text{Ethyl Vinyl Ether, } H^+} \text{HO} \xrightarrow{2. \text{NaBH}_4} \text{OMe} \\
& \xrightarrow{3. \text{CS}_2, \text{MeI}} \xrightarrow{4. \text{Bu}_3\text{SnH}, ^2} \xrightarrow{5. \text{H}^+, \text{MeOH}} \text{R\-\(-\)\-159} \\
& \quad \text{(44\% yield)} \\
\text{R\-\(-\)\-160} & \xrightarrow{1. \text{DIBAL, CH}_2\text{Cl}_2} \xrightarrow{2. \text{DMAP, } 25 \degree \text{C}} \text{Ph} \\
& \quad \text{HO} \xrightarrow{\text{O}_3, \text{NaOH}} \text{MeOH} \\
& \quad \text{(79\% yield)} \\
& \quad \text{Ph} \xrightarrow{\text{O}_3, \text{Ph}} \text{OMe} \\
& \quad \text{161}
\end{align*}
\]

**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 BF₃•Et₂O 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) as an initial substrate. Thus, exposure of R-(-)-167 to diazoester 150 and catalytic Rh₂(OAc)₄ (PhH, 80 °C, 20 min), followed by introduction of BF₃•Et₂O 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.\textsuperscript{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).

\textit{Scheme 2.5.2}

\begin{center}
\includegraphics[width=\textwidth]{scheme2.5.2.png}
\end{center}
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 ($\text{Et}_2\text{O}$) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride ($\text{CH}_2\text{Cl}_2$), benzene, and triethylamine ($\text{Et}_3\text{N}$) were distilled from calcium hydride. Methyl sulfoxide (DMSO), 1,2-dichloroethane, and $\text{BF}_3\cdot\text{OEt}_2$ 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 Haake-Buchler variable temperature melting point apparatus (model: MFB 595 8020) and are uncorrected. Infrared spectra were recorded on a Midac M-1200 FTIR. $^1\text{H}$ and $^{13}\text{C}$ NMR spectra were recorded on Bruker AM-500 or Bruker WM-250 spectrometers. Chemical shifts are reported relative to internal Me$_4$Si ($^1\text{H}$ and $^{13}\text{C}$, $\delta$ 0.00 ppm) or chloroform ($^1\text{H}$, $\delta$ 7.27 ppm, $^{13}\text{C}$, $\delta$ 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 \( R-(+)-\text{MTPA} \) (DCC, \( \text{CH}_2\text{Cl}_2 \)) followed by purification and 500 MHz \(^1\text{H}\) NMR analysis in benzene-\( \text{d}_6 \). Where possible an identical analysis was performed employing a racemic mixture of alcohols.

2.6.2 Preparative Procedures:

Preparation of Carbazole (131).
**Carbazole (131).** A mixture of iodide 130 (0.10 g, 0.34 mmol, 1.0 equiv), Pd(PPh₃)₄ (0.43 g, 0.37 mmol, 1.1 equiv) and Na₂CO₃ (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:Et₃N eluent) provided carbazole 131 (44 mg, 80% yield) as a white solid.

**Preparation of Indolepyrrolidone 134.**

**Indolepyrrolidone 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 Rh₂(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 H₂O (150 mL), brine solution (150 mL), dried over MgSO₄ 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-d₆) 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); ¹³C NMR (62.5 MHz, DMSO-d₆) 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 C₁₂H₁₁N₂O₂ (M+H) 215.0821].

Preparation of tetramic acids 139b-e.
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$_2$Cl$_2$ (95 mL) at 0 °C was added a solution of ethyl hydrogen malonate (6.26 g, 47.4 mmol, 1.0 equiv) in CH$_2$Cl$_2$ (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$_2$Cl$_2$ (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$_2$O (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$_2$O (100 mL). The layers were separated and the benzene layer further extracted with H$_2$O (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 N2 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/CH2Cl2); 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-d₆, 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); ¹³C NMR (125 MHz, DMSO-d₆, 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 C₁₁H₁₇NO₄ (M⁺) 227.1158]; Anal. Calcd for C₁₁H₁₇NO₄:  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/CH₂Cl₂); 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-d₆) 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); ¹³C NMR (125 MHz, DMSO-d₆) 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 C₁₆H₁₉NO₆ (M⁺) 321.1212]; Anal. Calcd for C₁₆H₁₉NO₆:  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/CH₂Cl₂); 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-d₆) 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); ¹³C NMR (125 MHz, DMSO-d₆) 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 C₁₅H₁₇NO₅ (M⁺) 291.1107]; Anal. Calcd for C₁₅H₁₇NO₅: 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/CH₂Cl₂); 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-d₆) 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); ¹³C NMR (125 MHz, DMSO-d₆) 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 C₁₄H₁₅NO₄ (M⁺) 261.1101]; Anal. Calcd for C₁₄H₁₅NO₄: 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.
**Diazot lactams 132b-e.** A solution of ester 139 (33.5 mmol, 1.0 equiv) and H$_2$O (1mL) was heated to reflux in CH$_3$CN (1.5 L) for 2 h. The volume of CH$_3$CN 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$_3$CN (168 mL) via addition funnel followed by Et$_3$N (9.34 mL, 67.0 mmol, 2.0 equiv) in CH$_3$CN (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$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 3.88 (s, 2H), 1.47 (s, 9H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 185.7, 161.7, 66.7, 55.7,
53.3, 28.0; high resolution mass spectrum (CI) m/z 182.0929 [calcd for C₈H₁₂N₃O₂ (M+H) 182.0930]; Anal. Calcd for C₈H₁₁N₃O₂: 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 (CCl₄) 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₃H₁₄N₃O₄ (M+H) 276.0984]; Anal. Calcd for C₁₃H₁₃N₃O₄: 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 (CCl₄) 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₂H₁₂N₃O₃ (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 (CCl₄) 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\(_3\)) \(\delta\) 7.37-7.25 (comp m, 5H), 4.60 (s, 2H), 3.70 (s, 2H); ¹³C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 185.5, 161.7, 135.1, 128.9, 128.1, 128.1, 65.8, 53.8, 46.5; high resolution mass spectrum (Cl) \(m/z\) 219.0779 [calcd for C\(_{11}\)H\(_{10}\)N\(_3\)O\(_2\) (M+H) 216.0773]; Anal. Calcd for C\(_{11}\)H\(_9\)N\(_3\)O\(_2\): 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 \textit{in vacuo}, the residue was dissolved in EtOAc (15 mL), washed with 1N NaOH (15 mL) solution, and dried over MgSO₄. 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-d₆) 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); ¹³C NMR (125 MHz, DMSO-d₆) δ 172.4, 139.2, 139.1, 132.9, 127.8, 125.4, 125.2, 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 C₂₀H₁₃N₃O (M⁺) 311.1059].

\textit{nat}-K252a (4a):² mp >300 °C; ¹H NMR (400 MHz, DMSO-d₆) 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); ¹³C NMR (100 MHz, DMSO-d₆) δ 172.6, 139.3, 139.2, 133.0, 128.0, 125.4, 125.2, 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 m), 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-d₆) 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), 7.70 (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); ¹³C NMR (62.5 MHz, DMSO-d₆) 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 C₂₄H₂₂N₃O₁ (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-d₆) δ 11.50 (br s, 1H), 11.35 (br s, 1H), 7.70 (d, J = 7.8 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); ¹³C NMR (62.5 MHz, DMSO-d₆) 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 C₂₉H₂₄N₃O₃ (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-d₆) 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); ¹³C NMR (62.5 MHz, DMSO-d₆) 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 C₂₈H₂₂N₃O₂ (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.
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), Rh2(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 N2 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-d₆) 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); ¹³C NMR (125 MHz, acetone-d₆) 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,
Preparation of Acetoacetate 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\(^\text{17}\) (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\(_2\)O 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\(_2\)O (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\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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.**

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 dissolved 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$_2$Cl$_2$: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$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$OH+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$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$OH+H) 231.0869].

Preparation of Esters (±)-97a,b.
Esters (±)-97a,b. A solution of acetates 144a,b (1.31 g, 5.00 mmol) in MeOH (50 mL) was treated with K$_2$CO$_3$ (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$_2$O and filtered through silica gel (Et$_2$O 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$_2$Cl$_2$: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$^{-1}$; $^1$H 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$_8$H$_{13}$O$_5$ (M-CH$_3$OH+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, CDCl₃) δ 5.07 (dd, J = 0.9, 5.7 Hz, 1H), 3.79 (s, 3H), 3.42 (s, 1H), 3.36 (s, 3H), 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₈H₁₃O₅ (M-CH₃OH+H) 189.0763].

Preparation of Indolocarbazoles (±)-147 and (±)-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 CH₂Cl₂ (50 mL), and washed with 10% NaHCO₃ solution (50 mL). The organic layer was dried with Na₂SO₄.
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% CH₂Cl₂/hexanes:MeOH, 3 elutions) or by HPLC (190:10:1 CH₂Cl₂: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-d₆) 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 (s, J = 7.3, 14.0 Hz, 1H), 2.13 (s, 3H), 2.00 (dd, J = 4.7, 14.0 Hz, 1H); ¹³C NMR (125 MHz, DMSO-d₆) 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 C₃₆H₃₂N₃O₇ (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-d₆) 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 = 7.5 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$_3$O$_7$ (M+H) 618.2240].

**Preparation of Ketone (±)-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$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$) $\delta$ 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.**
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 CH₂Cl₂ (25 mL), and washed with 10% NaHCO₃ solution (20 mL). The organic layer was dried with Na₂SO₄ 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:CH₂Cl₂:hexanes, 3 elutions) or HPLC (190:10:1 CH₂Cl₂: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, CDCl₃) 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); 13C NMR (125 MHz, CDCl3) δ 204.4, 202.9, 171.5, 170.2, 170.0, 149.4, 148.5, 139.9, 139.6, 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 C37H35N3O8 (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; 1H NMR (500 MHz, CDCl3) 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); 13C NMR (125 MHz, CDCl3) δ 205.0, 203.0, 171.7, 170.4, 170.1, 149.3, 148.5, 139.7, 139.5, 139.4, 139.4,
Preparation of (±)-K252a (2).

(±)-K252a (2). To a stirred solution of indolocarbazole (±)-147 (17.0 mg, 0.028 mmol, 1 equiv) in CH₂Cl₂ (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 NaHCO₃ solution to neutralize the reaction mixture. The organic layer was separated, evaporated, and purified via preparative TLC (1:20:20 MeOH:CH₂Cl₂: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$_3$O$_5$ (M+H) 468.1559].

**Preparation of Ketone (+)-155.**

![Chemical Structure](image)

**Ketone (+)-155.** A stirred solution of methyl 2-diazo-3-oxobutanoate (150) (2.13 g, 15.0 mmol, 1.0 equiv), alcohol (S)-(+)153 (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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 198.5, 162.7, 130.9, 123.5, 78.3, 52.5, 42.2, 24.1, 17.8; high resolution mass spectrum (Cl) m/z 187.0966 [calcd for C₉H₁₅O₄ (M+H) 187.0970].

Preparation of Ketone (-)-152b.

**Ketone (-)-152b.** A solution of ketone (+)-155 (3.35 g, 18.0 mmol, 1.0 equiv) in benzene (180 mL) was treated with BF₃•OEt₂ (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: [α]²⁰ₒ = -32.13° (c 1.08, CHCl₃); 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, CDCl₃) 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}\text{C} \text{ NMR (125 MHz, CDCl}_3 \text{) \delta 204.2, 170.8, 130.5, 122.9, 83.8, 53.1, 38.5, 24.7, 17.9; high resolution mass spectrum (Cl) m/z 187.0969 [calcd for C}_9\text{H}_{15}\text{O}_4 \text{(M+H) 187.0970].}

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

![Image of (-)-152b](image)

**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)-(+)\text{-153}^{36} (0.286 mL, 3.3 mmol, 1.1 equiv) \text{Rh}_2\text{(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\text{3}•\text{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\text{2}O eluent) to provide ketone (-)-152b (418 mg, 75% yield) as a colorless oil.

**Preparation of Triol 156.**
Triol 156. To a cooled (0 °C) solution of ketone (+)-155 (1.56 g, 8.38 mmol, 1.0 equiv) in CH₂Cl₂ (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 MgSO₄. 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 H₅IO₆ (1.20 g, 5.26 mmol) in H₂O (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 NaBH₄ (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 MgSO₄. Evaporation of the filtrate produced a colorless oil which was filtered through silica gel (5% MeOH/CH₂Cl₂ 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 CH₂Cl₂ (15 mL) and MeOH (3 mL) was treated with O₃ until the solution turned a
pale blue (5-6 minutes). The mixture was purged with argon before an excess of NaBH₄ (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/CH₂Cl₂ eluent) provided triol (R)-156 (245 mg, 25% yield over 3 steps).

**Preparation of Ester (−)-159.**

![Structure of Ester (−)-159](image)

**Ester (−)-159.** To a solution of alcohol (−)-152b (382 mg, 2.05 mmol, 1.0 equiv) in ethylvinyether (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 ethylvinyether (1.4 mL) was added twice to replace evaporated solvent. The reaction mixture was cooled to 25 °C and quenched by adding Et₃N (45 µL). The mixture was partitioned between Et₂O (4 mL) and H₂O (0.4 mL). The organic layer was separated and washed with H₂O (0.5 mL), saturated NaCl solution (0.5 mL), dried over MgSO₄, 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 NaBH₄ (58 mg, 6.1 mmol). The reaction mixture was stirred for 2 hours at 0 °C, quenched by addition of H₂O (136 µL) and then partitioned between H₂O (3 mL) and Et₂O (30 mL). The organic layer was dried over
MgSO₄ 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(SiMe₃)₂ (9.4 mL, 0.4 M in toluene, 3.8 mmol). The mixture was stirred for 5 minutes and treated with CS₂ (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 NH₄Cl solution (15 mL), and diluted with CH₂Cl₂ (120 mL). The organic layer was washed with H₂O (30 mL), saturated NaCl solution (30 mL), dried over MgSO₄, and concentrated in vacuo to afford an oil (659 mg) that was used without further purification.

A solution of n-Bu₃SnH (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 CH₂Cl₂ (133 mL) and H₂O (67 mL). The aqueous layer was further extracted with CH₂Cl₂ (3 x 67 mL). The combined organic layers were dried over MgSO₄ 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): [α]₂⁰D -8.53° (c 1.06, CHCl₃); 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 176.6, 129.6, 124.7, 78.0, 52.4, 42.4, 31.6, 18.0, 7.8; high resolution mass spectrum (Cl) m/z 173.1177 [calcd for C₉H₁₇O₃ (M+H) 173.1178].

Preparation of Diester (-)-160.

![Diester (-)-160](image)

**Diester (-)-160.** A cooled solution (-78 °C) of olefin (-)-159 (153 mg) in CH₂Cl₂ (4.3 mL) and 2.5 N NaOH (1.2 mL) in MeOH, was treated with O₃ until the solution turned pale blue. Diethylether (14 mL) and H₂O (14 mL) were added and the reaction mixture was allowed to warm to 25 °C followed by extraction with Et₂O (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, [α]²⁰D -13.88°(c 1.03, CHCl₃).

Preparation of Esters (+)-97a,b and Ketone (-)-166.
Esters (+)-97\textsubscript{a,b} and Ketone (-)-166. A solution of olefin (-)-152\textsubscript{b} (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\textsubscript{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 \textit{in vacuo} and the crude product dissolved 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 \textit{in vacuo}. Flash chromatography (20% EtOAc/hexanes eluent) afforded a mixture of diastereomeric furanoses (+)-97\textsubscript{a,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\textsubscript{2}Cl\textsubscript{2}:EtOAc eluent) a mixture of alcohols (+)-97\textsubscript{b} and (-)-166 was eluted first followed by furanose (+)-97\textsubscript{a} 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 (+)-97\textsubscript{b}, followed by ketone (-)-166, both as colorless oils.

\textit{(+)-97\textsubscript{a}:} mp 63-64°; \([\alpha]^{20}_D + 9.66°\) (c 1.03, CHCl\textsubscript{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
(+)-97b: mp 81-82°; [α]$_{20}^D$ + 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$^{-1}$;
$^1$H 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 (Cl) m/z 189.0771 [calcd for C$_8$H$_{13}$O$_5$ (M-CH$_3$OH+H) 189.0763].

(-)-166:  [α]$_{20}^D$ - 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$^{-1}$; $^1$H 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$_8$H$_{13}$O$_5$ (M-CH$_3$OH+H) 189.0776].

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

![Indolocarbazoles (-)-147 and (-)-148](image)

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$_2$Cl$_2$ (50 mL), and washed with 10% NaHCO$_3$ solution (50 mL). The organic layer was dried with Na$_2$SO$_4$ 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$_2$Cl$_2$/hexanes:MeOH, 3 elutions) or by HPLC (190:10:1 CH$_2$Cl$_2$: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$_6$) $\delta$ 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$_6$) $\delta$ 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$_3$O$_7$ (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$_6$) $\delta$ 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\(_6\) \( \delta \) 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 \( \text{C}_{36}\text{H}_{32}\text{N}_{3}\text{O}_{7} \) \( \text{(M+H)} \) 618.2240].

**Preparation of (-)-K252a (2).**

![Chemical structure of (-)-K252a](image)

(-)-K252a (2). To a stirred solution of indolocarbazole (-)-147 (17.0 mg, 0.028 mmol, 1 equiv) in \( \text{CH}_2\text{Cl}_2 \) (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 \( \text{NaHCO}_3 \) solution to neutralize the reaction mixture. The organic layer was separated, evaporated, and purified via preparative TLC (1:20:20 MeOH:CH\(_2\)Cl\(_2\):hexanes, 3 elutions) to afford (-)-K252a [2, 10.3 mg, 82% yield] as a pale yellow solid: mp 263-265° (dec.); \([\alpha]^{20}\) \( \text{D} \) -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\(^{-1}\);
\textsuperscript{1}H NMR (500 MHz, DMSO-d\textsubscript{6}) \( \delta \) 9.20 (d, \( J = 7.9 \text{ Hz}, 1 \text{H} \)), 8.63 (s, 1H), 8.05 (d, \( J = 7.7 \text{ Hz}, 1 \text{H} \)), 7.93 (d, \( J = 8.5 \text{ Hz}, 1 \text{H} \)), 7.89 (d, \( J = 8.3 \text{ Hz}, 1 \text{H} \)), 7.47 (comp m, 2H), 7.35 (app.t, \( J = 7.4 \text{ Hz}, 1 \text{H} \)), 7.28 (app.t, \( J = 7.4 \text{ Hz}, 1 \text{H} \)), 7.14 (dd, \( J = 5.0, 7.2 \text{ Hz}, 1 \text{H} \)), 6.34 (s, 1H), 5.02 (d, \( J = 17.6 \text{ Hz}, 1 \text{H} \)), 4.97 (d, \( J = 17.6 \text{ Hz}, 1 \text{H} \)), 3.92 (s, 3H), 3.38 (dd, \( J = 7.5, 14.0 \text{ Hz}, 1 \text{H} \)), 2.14 (s, 3H), 2.01 (dd, \( J = 4.9, 14.0 \text{ Hz}, 1 \text{H} \)); \textsuperscript{13}C NMR (125 MHz, DMSO-d\textsubscript{6}) \( \delta \) 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) \textit{m/z} 468.1561 [calcd for C\textsubscript{27}H\textsubscript{22}N\textsubscript{3}O\textsubscript{5} (M+H) 468.1559].

**Preparation of Ketone (+)-168.**

\[ \text{Ketone (+)-168.} \]

A stirred solution of methyl 2-diazo-3-oxobutanoate [(150) 10 g, 70.4 mmol, 1.0 equiv], (\( R \))-(\(-\))-nonen-3-ol\textsuperscript{33} [(167) 10.8 g, 75.9 mmol, 1.1 equiv], and Rh\textsubscript{2}(OAc)\textsubscript{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\textsubscript{3}•OEt\textsubscript{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: \([\alpha]_{D}^{20} +19.41^\circ \) (c 1.03, CHCl\textsubscript{3}); IR (thin film/NaCl) 3788.3 (m),
Preparing 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 O₃ 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 dissolved 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:CH2Cl2: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); [α]20D -9.00° (c 1.16, CHCl3); 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 172.1, 109.9, 105.4, 84.5, 56.4, 52.8, 49.0, 40.5, 14.5; high resolution mass spectrum (Cl) m/z 189.0773 [calcd for C₈H₁₃O₅ (M-CH₃OH+H) 189.0763].

(-)-97b: mp 81-82 °C (EtOAc); [α]20D -122.55° (c 1.10, CHCl₃); 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), 754.6 (m), 673.3 (m) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 172.1, 109.9, 105.4, 84.5, 56.4, 52.8, 49.0, 40.5, 14.5; high resolution mass spectrum (Cl) m/z 189.0773 [calcd for C₈H₁₃O₅ (M-CH₃OH+H) 189.0763].
750.9 (m), 685.7 (m) cm−1; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 170.4, 110.5, 103.8, 83.1, 55.5, 52.5, 49.2, 40.5, 15.7; high resolution mass spectrum (Cl) m/z 189.0778 [calcd for C₈H₁₃O₅ (M-CH₃OH+H) 189.0763].

(+)-166: [α]²⁰D +19.55° (c 1.12, CHCl₃); 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₈H₁₃O₅ (M-CH₃OH+H) 189.0763].

Preparation of Indolocarbazoles (+)-147 and (+)-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 CH₂Cl₂ (50 mL), and washed with 10% NaHCO₃ solution (50 mL). The organic layer was dried with Na₂SO₄ 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% CH₂Cl₂/hexanes:MeOH, 3 elutions) or by HPLC (190:10:1 CH₂Cl₂:EtOAc:MeOH eluent).

(+)-147: mp >250 °C (dec., MeOH/CH₂Cl₂); [α]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-d₆) 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); 13C 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$_3$O$_7$ (M+H) 618.2240].

(+) -148: mp 260-270 °C (dec., MeOH/CH$_2$Cl$_2$); [α]$^2$$_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$^{-1}$; 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 (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); 13C 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$_3$O$_7$ (M+H) 618.2240].
Preparation of (+)-K252a (2).

(+)-K252a (2). To a stirred solution of indolocarbazole (+)-147 (17.0 mg, 0.028 mmol, 1 equiv) in CH₂Cl₂ (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 NaHCO₃ solution to neutralize the reaction mixture. The organic layer was separated, evaporated, and purified via preparative TLC (1:20:20 MeOH:CH₂Cl₂:hexanes, 3 elutions) to afford (+)-K252a [2, 10.8 mg, 84% yield] as a pale yellow solid:  mp 264-267 °C (dec., acetone); [α]²⁰D +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-d₆) 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); ¹³C NMR (125 MHz, DMSO-d₆) 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_{3}O_{5} (M+H) 468.1559].

\((-\text{nat-K252a})\):\(^{2}\) mp 262-273 °C (dec.); \([\alpha]^{20}_{D} +52^\circ\) (c 0.1, MeOH); \(^{1}\text{H}\) NMR (400 MHz, DMSO-d\(_{6}\)) \(\delta\) 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); \(^{13}\text{C}\) NMR (100 MHz, DMSO-d\(_{6}\)) \(\delta\) 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.


(3) For examples of single step cyclofuransylation of indolocarbazoles, see:  

(4) Based on a report by Raphael that a benzyl protecting could not be removed from the lactam nitrogen, it seemed wise to proceed in this most general manner.  

(5) a) For the palladium catalyzed cross coupling of aryl halides with tin amides, see: Kosugi, M.; Kameyama, M.; Migita, T. *Chem Lett.* **1983**, *927*. 

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A similar Pd(0) mediated ring closure has been developed for the preparation of the β-carboline skeleton, see: Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782.


Recently, Buchwald has developed improved procedures for this type of aryl amination, see; Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215.


Pirrung has reported the 1,3 dipolar cycloaddition of a diazo ketone with *N*-acetylylindole, see; Pirrung, M. C.; Zhang, J.; Lackey, K.; Sternbach, D. D.; Brown, F. *J. Org. Chem.* **1995**, *60*, 2112.

In terms of substrates, this approach is similar to attempted Diels-Alder reactions between maleimides 56 and biindole 73 (see Scheme 1.3.13). These efforts have met with limited success, see: a) Kaneko, T.; Wong,

(15) Protected glycine esters \textbf{138b-e} were prepared according to known literature procedures, see:  

(16) For the synthesis of (+)-staurosporine, see Chapter 3.


(18) In the actual course of events, these studies paralleled our efforts to optimize the preparation of aglycons \textbf{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 \(^1\text{H}-\text{NMR}\) between \(\alpha\) and \(\beta\) 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 1H-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.

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


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

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


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.
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.


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 ¹H NMR) of derived allylic alcohol establish an optical purity of 98% ee.

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

These studies were performed simultaneously in the racemic series.

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.
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.

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.


The material obtained proved identical to a sample purchased from Aldrich chemical company.

APPENDIX ONE: SYNTHETIC SUMMARY
FOR K252c (4a) AND (+)-K252a (2)
**Figure A.1.1** The Synthesis of K252c (4a) and Aglycon 4c.

1. $\text{HO}_2\text{CCH}_2\text{CO}_2\text{Et}$, DCC, DMAP  
2. NaOEt, EtOH  
70-80% yield

1. $\text{CH}_3\text{CN}$, $\text{H}_2\text{O}$  
2. MsN$_3$, Et$_3$N  
80-90% yield

1. KO$_t$-Bu  
300 °C  
2. NH$_4$Cl  
80% yield

$\text{R} = \text{H}$  
$\text{R} = 3,4\text{-DMB}$

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

1. $\text{Rh}_2(\text{OAc})_4$, PhH  
2. BF$_3$•Et$_2$O  
(77% yield)  
3. TFA, CH$_2$Cl$_2$  
thioanisole, 6 h  
(83% yield)

1. $\text{O}_3$, DMS  
2. MeOH, $p$-TSA  
(80% yield)

1. $\text{4c}$, CSA, 48 h  
$\text{C}_2\text{H}_4\text{Cl}_2$  
(80% yield)  
2. separate 2:1 mixture of regioisomers  
3. TFA, CH$_2$Cl$_2$ thioanisole, 6 h  
(83% yield)

$\text{R} = \text{H}$ (K252c, 25% yield)  
$\text{R} = 3,4\text{-DMB}$ (62% yield)
APPENDIX TWO: SPECTRA RELEVANT TO CHAPTER TWO
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.
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.
Figure A.2.7

DMB
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.
Figure A.2.10

[Chemical structure image]

N O

HO CO

PMB

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

Figure A.2.12 13C NMR (125 MHz, DMSO-d6) of compound 139d.
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.
Figure A.2.16
Figure A.2.17  Infrared Spectrum (CCl₄) of compound 132b.

Figure A.2.18  ¹³C NMR (125 MHz, CDCl₃) of compound 132b.
Figure A.2.20  Infrared Spectrum (CCl₄) of compound 132c.

Figure A.2.21  ¹³C NMR (125 MHz, CDCl₃) of compound 132c.
Figure A.2.22
Figure A.2.23  Infrared Spectrum (CCl₄) of compound 132d.

Figure A.2.24  ¹³C NMR (125 MHz, CDCl₃) of compound 132d.
Figure A.2.25
Figure A.2.26  Infrared Spectrum (CCl₄) of compound 132e.

Figure A.2.27  ¹³C NMR (125 MHz, CDCl₃) of compound 132e.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.
*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.
Figure A.2.82
Figure A.2.83  Infrared Spectrum (thin film/NaCl) of compound (-)\textbf{152b}.

Figure A.2.84  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound (-)\textbf{152b}.
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

H₃C

MeO

MeO

OMe

OH

(+)

δ
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.
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.
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.
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.
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.2.104  Infrared Spectrum (thin film/NaCl) of compound (-)-2.

Figure A.2.105  $^{13}$C NMR (125 MHz, DMSO-$d_6$) of compound (-)-2.
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.
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.
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.
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.
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.
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.2.125  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 CRYSTALLOGRAPHY REPORT FOR FURANOSE (±)-144a

A. Crystal Data

Empirical Formula .................................................................................. C\textsubscript{11}H\textsubscript{18}O\textsubscript{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:

\begin{align*}
    a & \text{..........................................................} 7.752 (5)\text{Å} \\
    b & \text{..........................................................} 21.447 (4)\text{Å} \\
    c & \text{..........................................................} 8.243 (3)\text{Å} \\
    \beta & \text{..........................................................} 104.88 (4)° \\
    V & \text{..........................................................} 1325 (1)\text{Å}^3
\end{align*}

Space Group .......................................................................................... P2\textsubscript{1}/a (#14)

Z value .................................................................................................. 4
Dcalc .................................................................................................................. 1.315 g/cm³
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 ........................................................................................ Σ w (Fo² - Fc²)²
Least-squares Weights ...................................................................................... 4Fo²/s²(Fo²)
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-/Å³
Minimum Peak in Final Diff. Map ..............................................................-0.16 e-/Å³

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

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X-RAY CRYSTALLOGRAPHY REPORT FOR FURANOSE (±)-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:

\[
\begin{align*}
\text{a} & : 8.625 (3)\text{Å} \\
\text{b} & : 22.44 (1)\text{Å} \\
\text{c} & : 8.157 (2)\text{Å} \\
\beta & : 118.87 (2)° \\
V & : 1382 (2)\text{Å}^3
\end{align*}
\]

Space Group ..................................................................................P2\(_1\)/a (#14)

Z value.................................................................................................4

(X-ray Numbering)
Dcalc ................................................................................................. 1.260 g/cm³
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 ........................................................................ Σ w (Fo² - Fc²)²
Least-squares Weights ........................................................................ 4Fo²/σ²(Fo²)
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-/Å³
Minimum Peak in Final Diff. Map ....................................................... -0.28 e-/Å³

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

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EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula: \( \text{C}_9\text{O}_6\text{H}_{16} \)

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 (2\( \theta \) range): 25 (17.3 - 33.8°)

Omega Scan Peak Width at Half-height: 0.22

Lattice Parameters:

\[ a = 7.619 (8)\text{Å} \]
\[ b = 9.66 (1)\text{Å} \]
\[ c = 7.595 (8)\text{Å} \]
\[ \alpha = 91.3 (1)^\circ \]
\[ \beta = 98.6 (1)^\circ \]
\[ \gamma = 99.24 (9)^\circ \]
\[ V = 545 (2)\text{Å}^3 \]

Space Group: \( P_{-1} (#2) \)
Z value.................................................................2
Dcalc ......................................................................................1.342 g/cm³
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 .................................................. \( \sum w (\Delta F)^2 \)
Least-squares Weights .................................................. \( 4F₀^2/σ^2(F₀^2) \)
p-factor ........................................................................... 0.02
Anomalous Dispersion .................................................... All non-hydrogen atoms

No. Observations (I>3.00σ(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-/Å³

Minimum Peak in Final Diff. Map .......................................................... -0.18 e-/Å³

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

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CHAPTER THREE


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\textsubscript{50} = 1.9±0.2 nM) similar to FK-506 (IC\textsubscript{50} = 0.39±0.12 nM), cyclosporine (IC\textsubscript{50} = 2.5±0.8 nM) and staurosporine (IC\textsubscript{50} = 1.3±0.2 nM).\textsuperscript{4}

\textit{Figure 3.1.1}

\textbf{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\textsuperscript{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

\textit{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 dehydrati on) 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 Tiffaneeu-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). As shown in Scheme 3.1.3, the planned ring expansion could occur 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).

Scheme 3.2.1

3.2.1.2 Glycosidation Studies.

Importantly, bis-cycloglycosidative coupling of aglycon 38 to furanose (±)-97 (CSA, C2H4Cl2, 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 oxidation8 produced aldehyde (±)-176 and the corresponding MTM-ether (±)-177. The former was converted to ester (±)-178 via chlorite oxidation and methylation (CH2N2).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 LiBH₄ reduction and Moffatt oxidation (63% yield, two steps). Upon exposure to BF₃•OEt₂ in Et₂O, 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 ¹H-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 NaBH₄ followed by treatment with Ac₂O 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-<i>p</i>-bromo benzoxylation.
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).\textsuperscript{11}

\textit{Scheme 3.2.7}

\textbf{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)\textsubscript{3} and montmorillonite clay K-10. Removal of the clay by filtration followed by solvent exchange with Et\textsubscript{2}O and exposure of the crude product\textsuperscript{12} to BF\textsubscript{3}•OEt\textsubscript{2} led to the slow formation of new compound.\textsuperscript{13} After 24 h at ambient temperature, the product was isolated and
found to be spectroscopically accordant with the elusive $\alpha$-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 benzylation 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. 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
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 NaBD₄ 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).
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 BF₃•OEt₂ (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 prepared via the previously developed 11 step sequence. To set the stage for ring expansion, ester (+)-147 was subjected to the LiBH₄ 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 BF₃•OEt₂ 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.
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→(+)-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 [Bu₂Sn(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
OsO₄/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 Bu₄NBr in THF) occurred cleanly to afford bis-ether (-)-212 and set the stage for a stereoselective reduction (H₂/PtO₂) 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

![Scheme depicting synthesis of (+)-staurosporine (1)]
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. Thus treatment of ketone (+)-171 with O-benzyl hydroxylamine hydrochloride followed by Mel, KOH, and Bu₄NBr 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 (Et₂O) and tetrahydrofuran (THF) were distilled from sodium/benzophenone ketyl. Methylene chloride (CH₂Cl₂), benzene, and triethylamine (Et₃N) were distilled from calcium hydride. Methyl sulfoxide (DMSO), 1,2-dichloroethane, and BF₃•OEt₂ 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.
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$_4$Si ($^1$H and $^{13}$C, $\delta$ 0.00 ppm) or chloroform ($^1$H, $\delta$ 7.27 ppm, $^{13}$C, $\delta$ 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.
**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\(_2\)Cl\(_2\) (100 mL), and washed with 10% NaHCO\(_3\) solution. The organic layer was dried over Na\(_2\)SO\(_4\) 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\(^{-1}\); \(^1\)H NMR (500 MHz, acetone-d\(_6\) \(\delta\) 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\(_6\) \(\delta\) 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\(_2\)O\(_4\) (M\(^+\)) 412.1423].
Ester (±)-174, Method B. To a solution of ketone (±)-181 (100 mg, 0.26 mmol) in 1:1 MeOH/CH₂Cl₂ (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.

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 N₂ (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 H₂O (3 x 10 mL), and the combined aqueous layers were back extracted with CH₂Cl₂ (3 x 15 mL). All organic layers were combined, dried over Na₂SO₄, 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), 1099.4 (m), 745.1 (s) cm⁻¹; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₆H₂₂N₂O₃S (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, CDCl₃) δ 8.95 (s, 1H), 8.16 (app.t, J = 8.2 Hz, 1H), 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₄H₁₈N₂O₃ (M⁺) 382.1317].
Preparation of Ester (±)-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 NaH₂PO₄ that had been acidified to pH 2 with 1 N HCl (2.0 mL) and a solution of NaClO₂ (200 mg, 2.21 mmol, 8.4 equiv). The mixture was stirred for 10 min and then treated with CH₂N₂ in Et₂O until a yellow color persisted. The reaction mixture was diluted with H₂O (5 mL), extracted with Et₂O (3 x 10 mL), and the combined organic extracts dried over Na₂SO₄. 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), 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-d₆) 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), 7.59 (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); ¹³C NMR (125 MHz, CDCl₃) 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
Preparation of Diol (±)-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 LiBH₄ (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 CH₂Cl₂ (3 x 50 mL). The combined organic phases were dried over Na₂SO₄. 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-d₆) 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-
$\text{d}_6$) $\delta$ 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 (El) $m/z$ 384.1472 [calcd for C$_{24}$H$_{20}$N$_2$O$_3$ (M$^+$)  
384.1474].

**Preparation of Aldehyde ($\pm$)-180.**

![Chemical structure of Aldehyde ($\pm$)-180](image)

**Aldehyde ($\pm$)-180.** To a stirred solution of diol ($\pm$)-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$_2$O (3 x 20 mL), and the combined aqueous layers were back 
evacuated with CH$_2$Cl$_2$ (3 x 30 mL). All organic layers were combined, dried over 
Na$_2$SO$_4$, 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₄H₁₈N₂O₃ (M⁺) 382.1317].

Preparation of Hydroxy ketone (±)-181.
Hydroxy ketone (±)-181. A suspension of aldehyde (±)-180 (75 mg, 0.196 mmol, 1.0 equiv) in Et$_2$O (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$_2$Cl$_2$ (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$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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 (El) m/z 382.1315 [calcd for C$_{24}$H$_{18}$N$_2$O$_3$ (M$^+$) 382.1317].

Preparation of Diol (±)-184.
**Diol (±)-184.** To a stirred room temperature solution of ketone (±)-181 (100 mg, 0.26 mmol, 1.0 equiv) in 1:1 MeOH: CH2Cl2 (10 mL) was added NaBH4 (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 CH2Cl2 (3 x 10 mL). The combined organic layers were dried with Na2SO4 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-d₆) 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); ¹³C NMR (125 MHz, DMSO-d₆) 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,
Preparation of Bis-Acetate (±)-182.

Bis-Acetate (±)-182. A solution of diol (±)-184 (25 mg, 0.07 mmol, 1.0 equiv) in CH2Cl2 (0.7 mL) was treated with Et3N (0.03 mL, 0.22 mmol, 3.0 equiv) followed by Ac2O (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 H2O (1.0 mL) and extracted with CH2Cl2 (3 x 2 mL). Organic layers were combined, dried over Na2SO4, 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, CDCl3) 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); ¹³C NMR (125 MHz, CDCl3) 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_{2}O_{5} (M^{+}) 468.1685].

Preparation of Bis \( p \)-bromobenzoate (±)-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), \text{Et}_3\text{N} (23 \mu\text{L}, 0.164 mmol, 2.1 equiv), and 4-dimethylaminopyridine (2 mg, 0.016 mmol, 0.1 equiv) were heated to reflux in \text{CH}_2\text{Cl}_2 (1.0 \text{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\(^{-1}\); \text{1H NMR (500 MHz, CDCl}_3\) \(\delta\) 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$_3$) $\delta$ 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$_2$O$_5$Br$_2$ (M$^+$) 748.0208].

**Preparation of Methoxy ketone (±)-186.**

![Methoxy ketone (±)-186](image)

**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$$\cdot$OEt$_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$_3$N (6.1 mL) and CH$_2$Cl$_2$ (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)
\text{cm}^{-1}; ^1\text{H NMR} (500 MHz, DMSO-d_6) \delta 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\text{C NMR} (125 MHz, DMSO-d_6) \delta 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_{2}O_{3} (M^+) 396.1474].

**Preparation of Alcohol (±)-192.**

![Chemical structure of (±)-192](image)

**Alcohol (±)-192. Method A.** To a stirred solution of ketone (±)-186 (12
mg, 0.03 mmol, 1.0 equiv) in 1:1 MeOH: \text{CH}_2\text{Cl}_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 \textit{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$_2$Cl$_2$ (3 x 1 mL). The combined organic layers were dried with Na$_2$SO$_4$ 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$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$O$_3$ (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 $\mu$L, 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$_2$O (2.0 mL). Extraction of the solution with CH$_2$Cl$_2$ (3 x 10 mL), drying over Na$_2$SO$_4$, 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.**
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 H2O (5 mL) and extracted with CH2Cl2 (3 x 10 mL). The combined organic layers were dried over Na2SO4, 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, CDCl₃) δ 8.16 (d, J = 7.9 Hz, 1H), 8.09 (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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₆H₂₄N₂O₃ (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 H₂O (5 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄, 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.

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-d₆) 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); \(^{13}\text{C}\) NMR (125 MHz, DMSO-\text{d}6) \(\delta\) 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\(_{3}\)O\(_{3}\) (M\(^{+}\)) 411.1583].

**Preparation of Amine (±)-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$_2$SO$_4$ 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$_2$Cl$_2$ 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$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_3$O$_2$ (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 Na₂SO₄. Purification of the residue by flash chromatography (10% MeOH/CH₂Cl₂ 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₆H₂₅N₃O₂ (M⁺) 411.1947].

Preparation of Ketones (±)-199 and (±)-200.
Ketones \((\pm)-199\) and \((\pm)-200\). To a suspension of aldehyde \((\pm)-176\) (56 mg, 0.147 mmol, 1.0 equiv) in Et\(_2\)O (15.0 mL) was added BF\(_3\)•OEt\(_2\) (20 \(\mu\)L, 0.161 mmol, 1.1 equiv). The mixture was stirred vigorously for 7 h and then treated with CH\(_2\)Cl\(_2\) (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 \((\pm)-200\) (12 mg, 21% yield), was isolated as a yellow foam: IR (thin film/NaCl) 3461.9 (br m), 2924.5 (m), 1731.8 (s), 1447.5 (m), 1389.4 (m), 1307.5 (s), 1227.4 (s), 1133.2 (s), 747.2 (s) cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 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\(_3\)) \(\delta\) 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\(_2\)O\(_3\) (M\(^{+}\)) 382.1317].

The second compound to elute, ketone \((\pm)-199\) (36 mg, 64% yield), was isolated as a white solid: mp >230 °C (dec.); IR (thin film/NaCl) 3458.1 (br m),
Preparation of Diastereomeric Alcohols (±)-201.

Diastereomeric Alcohols (±)-201. To a mixture of ketone 199 (20 mg, 0.05 mmol, 1.0 equiv), Mel (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-Bu4NBr (3 mg, 0.01 mmol, 0.2 equiv). The mixture was stirred under N2 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$_2$Cl$_2$ (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$_2$Cl$_2$ (3 x 2mL). The combined organic layers were dried with Na$_2$SO$_4$ and purified by preparative TLC (1% MeOH/CH$_2$Cl$_2$ 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$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 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$_3$) $\delta$ 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$_2$O$_3$ (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$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.16 (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); \(^{13}\text{C} \) NMR (125 MHz, CDCl\(_3\)) \( \delta \) 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\(_2\)O\(_3\) (M\(^+\)) 398.1630].

**Preparation of Epoxide (±)-202.**

![Diagram of Epoxide (±)-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\(_4\)NBr (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\( \ominus \)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\(^{-1}\); \(^1\text{H} \) NMR (500 MHz, DMSO-d\(_6\)) \( \delta \) 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,
Preparation of Ketone (±)-203.

**Ketone (±)-203.** A solution of epoxide (±)-202 (50 mg, 0.14 mmol, 1.0 equiv) in CDCl₃ (13.7 mL) was treated with BF₃•OEt₂ (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; ¹H NMR (500 MHz, CDCl₃) 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$_3$) $\delta$ 203.4, 138.6, 138.6, 127.1, 125.6, 125.3, 125.3, 124.5, 121.8, 121.6, 120.7, 120.5, 120.3, 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$_2$O (M$^+$) 366.1368].

Preparation of Diol (+)-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$_2$Cl$_2$ (3 x 20 mL) and the combined organic phases were dried over Na$_2$SO$_4$ and chromatographed (1:1 hexanes:EtOAc eluent) to afford diol (+)-204 (127 mg, 89% yield) as a white solid: mp >225 °C (dec.); $\left[\alpha\right]$$^20$$_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\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-\(d_6\)) \(\delta\) 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-\(d_6\)) \(\delta\) 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\(_3\)O\(_6\) (M+H) 590.2291].

Preparation of Aldehyde (+)-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 N₂ (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 H₂O (3 x 5.0 mL) and the combined aqueous layers were back extracted with CH₂Cl₂ (3 x 10.0 mL). All organic layers were combined, dried over Na₂SO₄, 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 hexanes:EtOAc eluent) to furnish aldehyde (+)-170 (280 mg, 71% yield, 63% yield 2 steps) as a yellow powder: mp >205 °C (dec.); [α]²⁰D +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-d₆) 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, 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$_3$O$_6$ (M+H) 588.2135].

**Preparation of Ketone (+)-171.**

![Diagram of (+)-171](image)

**Ketone (+)-171.** To a suspension of aldehyde (+)-170 (100 mg, 0.170 mmol, 1.0 equiv) in Et$_2$O (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.); [α]**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-d₆, 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-d₆) 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 C₃₅H₃₀N₃O₆ (M+H) 588.2135].

**Preparation of Methoxy Ketone 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 transferred to a stirred solution of aldehyde (+)-170 (90 mg, 0.15 mmol, 1.0 equiv) in CHCl₃ (0.6 mL). After 0.5 h the reaction mixture was filtered and the filtrate evaporated in vacuo. The residue was dissolved in Et₂O (15 mL) under an inert atmosphere, treated with BF₃•OEt₂ (0.39 mL, 3.15 mmol, 21.0 equiv), and stirred for 7 days at 25 °C. The reaction was diluted with CH₂Cl₂ (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: ¹H NMR (500 MHz, DMSO-d₆, 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); ¹³C NMR (125 MHz, DMSO-d₆, 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,
Preparation of Ester (+)-147.

Ester (+)-147. To a solution of ketone (+)-171 (10 mg, 0.017 mmol, 1.0 equiv) in 1:1 MeOH/CH₂Cl₂ (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.

Ether (±)-206. A solution of diol (±)-184 (38 mg, 0.10 mmol, 1.0 equiv) and Bu₂Sn(OMe)₂ (25 µL, 0.11 mmol, 1.1 equiv) in benzene (5.0 mL) was heated to reflux with azeotropic removal of H₂O (Dean-Stark apparatus) for 1 h. The solvent was removed in vacuo, followed by addition of CH₃CN (5.0 mL), MeI (6.8 µL, 0.11 mmol, 1.1 equiv), and Ag₂O (25 mg, 0.11, 1.1 equiv). The resulting mixture was heated at reflux over 4 h, diluted with H₂O (3 mL), and extracted with CH₂Cl₂ (3 x 2 mL). The combined organic extracts were dried over Na₂SO₄ 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-d₆) δ 8.18 (d, J = 7.0 Hz, 1H), 8.11 (d, J = 7.7 Hz, 1H), 7.97 (d, J = 8.1 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); ¹³C NMR (125 MHz, acetone-d₆) 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 (El) \( m/z \) 398.1630 [calcd for \( C_{25}H_{22}N_2O_3 \) (M+) 398.1630].

**Preparation of Diol (+)-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\(_2\)Cl\(_2\):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\(_2\)Cl\(_2\) (3 x 20 mL). The combined organic phases were dried with Na\(_2\)SO\(_4\) and chromatographed (1:1 hexanes:EtOAc eluent) to afford alcohol (+)-207 (81 mg, 95% yield) as a white solid: mp 174-176 °C (dec.); \([\alpha]^{20}_D +37^\circ\) (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\(^{-1}\); \(^1\)H NMR (500 MHz, acetone-d\(_6\)) \( \delta \) 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); 13C NMR (125 MHz, acetone-d6) 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 C35H32N3O6 (M+H) 590.2291].

Preparation of Alcohol (+)-208.

![Chemical structure of (+)-208](image)

**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 H2O. Extraction of the solution with CH2Cl2 (3 x 10 mL), drying over Na2SO4 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.); [α]20D +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, CDCl3) 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); ¹³C NMR (125 MHz, CDCl3, 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 C36H34N3O6 (M+H) 604.2448].
Preparation of (+)-RK286c (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), H₂O (1.0 mL) was added and the derived mixture extracted with CH₂Cl₂ (3 x 5mL). The combined organic layers were washed with saturated aqueous NaHCO₃ (5 mL), dried over Na₂SO₄, and evaporated to a residue which was purified by preparative TLC (5% MeOH/CH₂Cl₂) to provide (+)-RK-286c (7, 6 mg, 75% yield) as a pale white powder: mp >255 °C (dec.); [α]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 (s), 1117.3 (m), 743.8 (s) cm⁻¹; ¹H NMR (500 MHz, DMSO-d₆) δ 9.27 (d, J = 7.9 Hz, 1H), 8.47 (br s, 1H), 7.99 (app.t, J = 7.4 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); ¹³C NMR (125 MHz, DMSO-d₆) 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_{3}O_{4} (M+H) 454.1767].

(+)-nat-RK286c (7): \(^2\) mp >265 °C (dec.); [α]^{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 = 16.8 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.

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; $[\alpha]_{20}^{20}$ +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) $\delta$ 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$_6$) $\delta$ 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$_3$O$_5$ (M+H) 586.2342].

Diol (+)-210. To a stirred solution of 4-methylmorpholine-N-oxide (6 mg, 0.05 mmol, 1.2 equiv) and OsO₄ (0.6 mL of a 2.5% solution in t-BuOH, 0.05 mmol, 1.2 equiv) in 4:1 acetone:H₂O (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, NaHSO₃ (100 mg) in H₂O (1.0 mL) was added and the resulting black solution was stirred for 20 min, filtered, and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over Na₂SO₄, 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; [α]₂₀° +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-d₆) 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$_6$) $\delta$ 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$_3$O$_7$ (M+H) 620.2397].

**Preparation of (+)-MLR-52 (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$_2$O (1.0 mL) and then extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic layers were washed with saturated aqueous NaHCO$_3$ (5 mL), dried over Na$_2$SO$_4$, and evaporated to a residue. Purification by preparative TLC (5% MeOH/CH$_2$Cl$_2$) 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-d₆) 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), 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); ¹³C NMR (125 MHz, DMSO-d₆) 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 C₂₇H₂₄N₃O₅ (M+H) 470.1716].

(+)-nat-MLR-52 (8):⁴ mp 263-268 °C; [α]₂⁰ D +68° (c 0.093, MeOH); ¹H NMR (not reported MHz, DMSO-d₆) 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); ¹³C NMR (not reported MHz, DMSO-d₆) 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.

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 solvent 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.); \([\alpha]_{D}^{20} -18^\circ \) (c 0.1, CH₂Cl₂); 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-d₆) 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); ¹³C NMR (125 MHz, DMSO-
d_6) \delta 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) \textit{m/z} 603.2238 [calcd for C_{35}H_{31}N_{4}O_{6} (M+H) 603.2244].

Preparation of Methyl Ether (-)-212.

Methyl Ether (-)-212. To a mixture of oxime (-)-211 (90 mg, 0.15 mmol, 1.0 equiv), Mel (88 \mu L, 1.42 mmol, 9.5 equiv), and powdered KOH (88 mg, 1.58 mmol, 10.5 equiv) in THF (15 mL) was added \textit{n}-Bu_4NBr (10 mg, 0.03 mmol, 0.2 equiv). The mixture was stirred under N_2 for 30 min, solvent was removed \textit{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 \textit{>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\textsuperscript{-1}; ^1H NMR (500 MHz, DMSO-d_6, 345 K) \delta 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); 13C NMR (125 MHz, DMSO-d6) 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 C37H35N4O6 (M+H) 631.2557].

Preparation of Amine (+)-213a.

Amine (+)-213a. A mixture of methyl ether (-)-212 (85 mg, 0.13 mmol, 1.0
equiv) and PtO2 (28 mg) in a 60% aqueous acetic acid (15.0 mL) was place in a
flask capped with a H2 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$_2$Cl$_2$ (40 mL) and washed with 1.0 N NaOH (8.0 mL). The aqueous layer was back-extracted with CH$_2$Cl$_2$ (2 x 15 mL) and the combined organic layers were dried over Na$_2$SO$_4$, 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$_2$Cl$_2$ eluent) of the above residue to afford amine (+)-213a as a yellow powder: mp >275 °C (dec.); [$\alpha$]$^D_{20}$ +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$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$, 310 K) $\delta$ 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) $\delta$ 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, 119.6, 116.0, 115.4, 114.6, 111.6, 111.6, 107.4, 91.3, 84.2, 80.2, 57.5, 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$_4$O$_5$ (M+H) 603.2610].

Preparation of Methyl Amine (+)-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 N₂ 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 BH₃•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 vacuo (5 x 5.0 mL). The remaining residue was treated with CH₂Cl₂ (7.0 mL) and 1.0 N NaOH (5.0 mL). The biphasic mixture was separated, and the aqueous layer was extracted with CH₂Cl₂ (3 x 7.0 mL). The combined organic layers were dried over Na₂SO₄, evaporated, and purified by flash chromatography (5% MeOH/CH₂Cl₂ eluent) to furnish methyl amine (+)-213b [80 mg, 91% yield, 2 steps from (-)-212] as a
yellow solid: mp 225-230 °C (dec.); \([\alpha]^{20}_D +22^\circ\) (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) \(\delta\) 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\(_3\)) \(\delta\) 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\(_4\)O\(_5\) (M+H) 617.2764].

Preparation of (+)-Staurosporine (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 H₂O (1.0 mL), adjusted to pH 10 with 5.0 N NaOH, and extracted with CH₂Cl₂ (3 x 5mL). The combined organic layers were dried over Na₂SO₄, and evaporated to a pale yellow residue which was purified by preparative TLC (5% MeOH/CH₂Cl₂ eluent) to provide (+)-staurosporine (1, 6 mg, 70% yield) as a yellow powder: mp 273-280 °C (dec.); [α]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, CDCl₃) 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), 7.94 (app.t, J = 7.7 Hz, 1H), 7.90 (app.t, J = 7.5 Hz, 1H), 7.37 (app.t, J = 7.3 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); ¹³C NMR (125 MHz, CDCl₃) 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;

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high resolution mass spectrum (FAB) m/z 467.2085 [calcd for C$_{28}$H$_{27}$N$_{4}$O$_{3}$ (M+H) 467.2083].

(+)-nat-Staurosporine (1): mp 270 °C (dec.); [α]$^{25}_D$ +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.
**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, solvent was removed *in vacuo*, and the residue purified by flash chromatography (2:1 hexanes:EtOAc eluent) to provide oxime ether (-)-214 (75 mg, 85% yield) as a yellow foam: \([\alpha]_{20}^{D} -20^\circ \text{ (c 0.1, CH}_2\text{Cl}_2)\); 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\(^{-1}\); \(^1\)H NMR (500 MHz, DMSO-d\(_6\)) \(\delta\) 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\(_6\)) \(\delta\) 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,
Preparation of Ether (-)-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-Bu4NBr (6 mg, 0.02 mmol, 0.2 equiv). The mixture was stirred under N2 for 30 min, solvent was removed in vacuo, and the residue was subjected to flash chromatography (2:1 ∅ hexanes:EtOAc eluent) to provide methoxy oxime ether (-)-215 (53 mg, 68% yield) as a yellow powder: mp >230 °C (dec.); [α]20D = -36° (c 0.1, CH2Cl2); 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, CDCl₃) 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\(_3\)) \( \delta \) 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.**

![Chemical Structure of (-)-216](image)

**Amide (-)-216.** To a stirred solution of ether (-)-215 (50 mg, 0.071 mmol, 1.0 equiv) in anisole (385 \( \mu \)L, 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\(_2\)O (1.0 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 5 mL). The combined organic layers were washed with saturated aqueous NaHCO\(_3\) (5 mL), dried over Na\(_2\)SO\(_4\), and evaporated to a residue, which was
purified by preparative TLC (5% MeOH/CH₂Cl₂) to provide amide (-)-216 (10 mg, 25% yield) as a white foam: \([\alpha]_{20}^{D} -8^\circ\) (c 0.1, CHCl₃); 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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₃₄H₂₈N₄O₄ (M⁺) 556.2111].
Preparation of (-)-TAN-1030a (6).

(-)-TAN-1030a (6). A solution of amide (-)-216 (9 mg, 0.02 mmol, 1.0 equiv) in CDCl₃ (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 \textit{in vacuo} leaving a deep red residue which was dissolved in CH₂Cl₂ (3 mL) and washed with an aqueous 10% Na₂S₂O₇ solution (3 x 2 mL). The pale yellow organic layer was dried over Na₂SO₄ and purified by preparative TLC (5% MeOH/CH₂Cl₂ eluent) to provide TAN-1030a (6, 2 mg, 24% yield) as a white foam: [\(\alpha\)]₂⁰D -4° \(\text{(c 0.1, CHCl₃)}\); 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; \(^1\)H NMR (500 MHz, DMSO-d₆) \(\delta\) 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\(_6\)) \(\delta\) 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), 7.04 (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\(_6\)) \(\delta\) 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


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


(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.
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.


For the synthesis of K252a, see Chapter 2.

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

With this substrate, decomposition of the starting material to intractable materials competes with product formation.

Recently Fredenhagen has reported the effect of H₂SO₄ on TAN-1030a, see: Fredenhagen, A.; Peter, H. H. *Tetrahedron* **1996**, *52*, 1235.

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).

(+) -171

\[ \text{HONH}_2\cdot\text{HCl} \rightarrow \text{NaOAc} \] (95% yield)

\[ \text{(-)-211} \rightarrow \text{MeI, KOH} \rightarrow \text{(-)-212} \] (90% yield)

\[ \text{H}_2, \text{PtO}_2 \rightarrow (96\% \text{ yield}) \]

\[ \text{BH}_3\cdot\text{SMe}_2 \rightarrow \text{TFA, Anisole} \rightarrow (67\% \text{ yield, two steps}) \]

\[ \text{(-)-213a} \rightarrow \text{(+)-Staurosporine (1)} \]

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

(+) -171

\[ \text{BnONH}_2\cdot\text{HCl} \rightarrow \text{NaOAc} \] (85% yield)

\[ \text{(-)-214} \rightarrow \text{MeI, KOH} \rightarrow \text{(-)-215} \] (68% yield)

\[ \text{TFA, anisole} \rightarrow (25\% \text{ yield}) \]

\[ \text{TMSI, CDCl}_3 \rightarrow (24\% \text{ yield}) \]

\[ \text{TAN-1030a (6)} \]
APPENDIX FIVE: SPECTRA RELEVANT TO CHAPTER THREE
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.
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.
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.
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

[Chemical structure image]
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.5.17  Infrared Spectrum (thin film/NaCl) of compound (±)-180.

Figure A.5.18  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound (±)-180.
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.
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.
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.
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.
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.
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.
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.
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.5.44  Infrared Spectrum (thin film/NaCl) of compound (±)-193.

Figure A.5.45  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound (±)-193.
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.
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.
Figure A.5.52

(±)-201 diastereomer 1
*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.
Figure A.5.55

(±)-201 diastereomer II
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.
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.
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.
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.
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.
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.
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.
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.
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.
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.5.86  Infrared Spectrum (thin film/NaCl) of compound (+)-7.

Figure A.5.87  $^{13}$C NMR (125 MHz, DMSO-$d_6$) of compound (+)-7.
Figure A.5.89  Infrared Spectrum (thin film/NaCl) of compound (+)-209.

Figure A.5.90  $^{13}$C NMR (125 MHz, acetone-\text{d}_6) of compound (+)-209.
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.5.95  Infrared Spectrum (thin film/NaCl) of compound (+)-8.

Figure A.5.96  $^{13}$C NMR (125 MHz, DMSO-$d_6$) of compound (+)-8.
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.
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.
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.5.107  Infrared Spectrum (thin film/NaCl) of compound (+)-213b.

Figure A.5.108  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound (+)-213b.
Figure A.5.110  Infrared Spectrum (thin film/NaCl) of compound (+)-1.

Figure A.5.111  $^{13}$C NMR (125 MHz, CDCl$_3$) of compound (+)-1.
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.
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.
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.
APPENDIX SIX: X-RAY CRYSTALLOGRAPHY REPORTS
RELEVANT TO CHAPTER TWO
X-RAY CRYSTALLOGRAPHY REPORT FOR INDOLOCARBAZOLE (±)-185

EXPERIMENTAL DETAILS

A. Crystal Data
Empirical Formula ......................................................... C_{38.5}H_{26}N_{2}O_{6.5}Br_{2}
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
\[ \beta = 91.45 \pm 0.02 (\text{deg}) \]
\[ V = 6998.3 (3) \text{Å}^3 \]

Space Group \( \text{C2/c} \) \(#15\)

Z value \( = 8 \)

\( D_{\text{calc}} = 1.481 \text{g/cm}^3 \)

\( F_{000} = 3144 \)

\( \mu(\text{MoK}\alpha) = 23.41 \text{cm}^{-1} \)

B. Intensity Measurements

Diffractometer \( \text{Enraf-Nonius CAD-4} \)

Radiation \( \text{MoK}\alpha (\lambda = 0.71069 \text{Å}) \)

Temperature \( 23 \text{°C} \)

Attenuator \( \text{Zr foil (factor} = 20.4) \)

Take-off Angle \( 2.8\text{°} \)

Detector Aperture \( 2.0-2.5 \text{mm hor}/2.0 \text{mm vert.} \)

Crystal to Detector Distance \( 21 \text{cm} \)

Scan Type \( \omega-2\theta \)

Scan Rate \( 1.0 - 16.5 \text{°/min (in omega)} \)

Scan Width \( (0.95 + 0.83 \tan \theta)\text{°} \)

\( 2\theta_{\text{max}} = 52.6\text{°} \)

No. of Reflections Measured

Total: \( 7660 \)

Unique: \( 7369 \) \( (\text{R}_{\text{int}} = 0.041) \)

Corrections \( \text{Lorentz-polarization Absorption} \)

\( \text{(trans. factors: 0.72 - 1.51)} \)

Decay \(-27.00\% \text{ decline}\)
C. Structure Solution and Refinement

Structure Solution .......................................................................................... Direct Methods
Refinement ........................................................................................................ Full-matrix least-squares
Function Minimized .............................................................................................. \[ \sum w (F_o - F_c)^2 \]
Least-squares Weights ......................................................................................... \( 4F_o^2/\sigma^2(F_o^2) \)
p-factor .................................................................................................................. 0.03
Anomalous Dispersion ......................................................................................... All non-hydrogen atoms
No. Observations (I>3.00\(\sigma(I)\)) .................................................................. 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-/Å³
Minimum Peak in Final Diff. Map ....................................................................... -1.23 e-/Å³

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

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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.

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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.