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## Intermolecular Diels–Alder Cycloaddition for the Construction of Bicyclo[2.2.2]diazaoctane Structures: Formal Synthesis of Brevianamide B and Premalbrancheamide

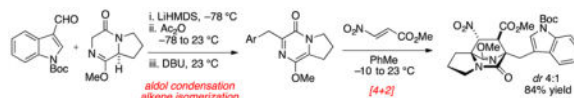
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### Abstract

A stereoselective intermolecular Diels–Alder cycloaddition of an intermediate pyrazinone with both achiral and chiral acrylate-derived dienophiles provides rapid access to the bicyclo[2.2.2]diazaoctane core shared among several prenylated indole alkaloids. The product derived from cycloaddition with 2-nitroacrylate required an additional five to six synthetic operations to intercept established precursors to premalbrancheamide and brevianamide B. The chemistry detailed in this manuscript constitutes a formal total synthesis (12 steps each) of these [2.2.2]diazabicyclic natural products from proline methyl ester.

### Graphical abstract



## INTRODUCTION

Isolated by Birch and Wright in 1969, the brevianamides were the first metabolites discovered that possess the bicyclo[2.2.2]-diazaoctane architecture.<sup>1</sup> The [2.2.2]diazabicyclic alkaloid family has since grown and now numbers nearly 100 distinct fungal-derived prenylated indole natural products.<sup>2</sup> Intriguing biological activity is found across the family, and the alkaloids exhibit antitumor, antihelminthic, insecticidal, and selective phosphodiesterase (PDE1) inhibition and neuroprotective properties.<sup>2,3</sup> As a result, the [2.2.2]diazabicyclic alkaloids are lead compounds in the treatment of several diseases and cancer.

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### Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02744. Spectroscopic data (<sup>1</sup>H NMR and <sup>13</sup>C NMR) for all new compounds as well as known compounds **2** and **28** (PDF)

### Notes

The authors declare no competing financial interest.

Within the [2.2.2]diazabicyclic alkaloid family, metabolites can possess either the *syn* or *anti* stereochemical configuration at C19 (brevianamide numbering).<sup>4</sup> Continued isolation efforts have revealed enantiomeric<sup>5</sup> and epimeric<sup>6</sup> metabolites from different fungal organisms (e.g., (+)-, (–)-stephacidin A, and 6-*epi*-stephacidin A, Figure 1), a discovery that only increases the allure of these alkaloids.

Because of potent and diverse bioactivities as well as appealing molecular structure, the entire alkaloid group has attracted the attention of the synthetic community. Efforts directed to the synthesis of various congeners have revealed several methods for the construction of the [2.2.2]diazabicyclic core: (1) S<sub>N</sub>2' cyclization, (2) biomimetic intramolecular Diels–Alder cycloaddition (IMDA), (3) *N*-acyliminium-initiated cyclization, (4) oxidative enolate coupling, (5) radical cyclization, and (6) Dieckmann condensation with an isocyanate component.<sup>7,8</sup>

The epimeric [2.2.2]diazabicycles **1** and **2** are the most simple structures that contain all rings apparent within these natural products. The *syn*-configured **1** can be converted to premalbrancheamide, the biogenic precursor to more highly halogenated compounds (e.g., malbrancheamide A and B).<sup>9</sup> The *anti*-configured **2** is not a natural product but has served as the penultimate intermediate in several syntheses of brevianamide B (**3**).<sup>10,8a</sup> The synthesis of compounds **1** or **2** have been a proving ground for methods to construct the [2.2.2]-diazabicyclic ring system, and the chemistry revealed in these studies is often applied to more elaborate targets within the natural product family.

The development of the biomimetic IMDA cycloaddition by Williams has resulted in the total synthesis of several [2.2.2]diazabicyclic alkaloids and led to important insights into the biogenesis of these alkaloids.<sup>11</sup> As an example of this chemistry, diketopiperazine **4** can be isomerized to the reactive pyrazinone intermediate **7**, which undergoes cycloaddition to give the diastereomers **5** and **6** (dr 2:1, Figure 2, entry 1). Because the pyrazinone Diels–Alder precursor **7** is achiral, the observed cycloadducts are racemic. Production of asymmetric [2.2.2]diazabicyclic alkaloids via the IMDA has been realized using a chiral aminal auxiliary precursor **8**<sup>8d</sup> (e.g., entry 3) as well as two other nonracemic substrates.<sup>11a,12</sup> Additionally, Johnston and co-workers recently extended the IMDA chemistry using a hydrogen bonding catalyst to modulate the diastereo- and enantioselectivity of the reaction (entry 2).<sup>13</sup> In this way, *syn*-fused **5** can be produced in up to 4:1 dr and up to 44% ee depending on the catalyst used. In many ways, this represents a normal evolution of reaction development, where an initial reaction is rendered diastereoselective first with auxiliaries and later made to be a catalytic enantioselective process.

## RESULTS AND DISCUSSION

This manuscript describes our efforts toward **1** and **2** that focus on an intermolecular Diels–Alder cycloaddition for the construction of the [2.2.2]diazabicyclic system.

The Diels–Alder reaction is naturally efficient (forming two bonds in concerted fashion), and the intermolecular variant is intrinsically convergent. We believed that a strategy based on intermolecular cycloaddition might offer improvements in efficiency over several known

routes and potentially permit selective formation of either diastereomer **1** or **2** based on modulation of the reaction conditions. Most importantly, the fundamentals of the pyrazinone intermolecular Diels–Alder cycloaddition are not fully understood, and we viewed a synthesis of **1** and **2** as an instructive target to advance this chemistry in more detail.

We previously established that pyrazinone Diels–Alder precursors can be prepared in a single step by a domino aldol condensation/alkene isomerization sequence.<sup>14</sup> Accordingly, our proposed synthesis toward **1** and **2** planned to engage the requisite pyrazinone **10** prepared in this manner with a suitable acrylate-derived dienophile to afford cycloadduct **3** (Scheme 1). Subsequent addition of an organometallic reagent (*e.g.*, MeMgBr) to the ester to afford an intermediate tertiary alcohol would then permit Friedel–Crafts cyclization to produce the quaternary carbon and complete the ring system. Because both **1** and **2** are known, we anticipated that verification of stereochemical outcome from the intermolecular cycloaddition could be quickly determined by comparing to published spectroscopic data or authentic standards.

Although this synthesis plan appeared concise, there were significant regiochemical and stereochemical ambiguities with regard to the intermolecular cycloaddition as well as fundamental questions regarding reactivity. We predicted that a modest preference for the *endo* cycloadduct might be enforced (leading to the *anti*-bicyclo fusion).

In order to evaluate the intermolecular cycloaddition, pyrazinone **14** was prepared in one reaction vessel starting from the proline-derived diketopiperazine (DKP) **12** (Scheme 2).<sup>15</sup> The reaction sequence is initiated by enolization (LiHMDS, 1.1 equiv) followed by aldol addition to the indole carboxaldehyde. The intermediate  $\beta$ -alkoxy adduct was acylated (Ac<sub>2</sub>O, 1.1 equiv) and treated with base (DBU, 1.4 equiv) in order to effect elimination to the exocyclic diene in **13** and subsequent isomerization to the DKP azadiene **14**. Based on experimental evidence, the exocyclic diene in **13** is short-lived and isomerizes rapidly to the endocyclic azadiene **14**, the apparent thermodynamic alkene isomer and only identified product from the reaction.

Although isolable, azadiene **14** proved somewhat difficult to manipulate. The pyrazinone decomposed on exposure to silica gel and was reactive with air, undergoing decomposition within hours at room temperature.<sup>16</sup> Nonetheless, we became experienced at handling **14** as the unpurified product mixture (obtained in 94% yield from the  $\beta$ -acetoxyaldol adduct, 90–95% pure by <sup>1</sup>H NMR) or as a homogeneous material obtained by recrystallization, albeit in diminished yield (42%). In practice, we also found it convenient to isolate and purify the intermediate  $\beta$ -acetoxy adduct and advance material through the elimination and isomerization to form **14** as needed.

We first attempted Diels–Alder cycloaddition of **14** with ethyl acrylate and observed three products in a 3:1:1 ratio.<sup>17</sup> The major product **15** was obtained in 48% isolated yield and corresponds to cycloaddition from the *endo* transition state. Due to the inconvenience of handling metastable pyrazinone **14**, we also attempted a “one pot” reaction in order to circumvent isolation of the reactive intermediate. Addition of ethyl acrylate to the reaction vessel following completion of the aldol condensation and alkene isomerization sequence

produced a low yield (15%) of desired cycloadduct **15**. The observed major product **16** (50% yield) was the result of Michael addition. Formation of the Michael adduct could be almost completely avoided with addition of a stoichiometric amount of acetic acid (in order to buffer the basicity of residual DBU) prior to addition of acrylate. In this way, the desired major cycloadduct **15** was obtained in a commensurate amount (40% isolated yield) and identical stereoselection (3:1:1) as compared to the two-step sequence. Overall, this intermolecular Diels–Alder reaction sequence required five to six steps from commercially available proline methyl ester to create the [2.2.2]diazabicyclic structure; however, the dominant product possessed the undesired regiochemistry and would not permit synthesis of **2** in a straightforward manner.

In the course of preparing suitable acrylate precursors, we observed that the acrylamide derivative of Oppolzer's sultam was more selective in engaging pyrazinone substrate **14** and could effectively introduce asymmetry to and improve diastereoselection in the cycloaddition.<sup>18</sup> The thermal cyclo-addition of **14** with acryloyl camphor sultam afforded cycloadduct **17** in 62% yield as an apparent single diastereomer (>19:1) as determined by <sup>1</sup>H NMR on the unpurified reaction product mixture (Scheme 2, blue highlight).<sup>19</sup> The acyl sultam in **17** could be converted with lithio benzyl alcohol into the corresponding ester **18**.<sup>20</sup>

In order to obtain the desired regiochemistry whereby the carboxyl moiety is positioned proximal to the indole nucleus, we attempted cycloaddition with methyl 2-nitroacrylate (**19**), a dienophile substrate that can be effective in reversing cycloaddition regioselectivity.<sup>21</sup> In the event, nitroacrylate **19** was more reactive than ethyl acrylate and cycloaddition with pyrazinone **14** was achieved near ambient temperatures. Two regioisomeric cycloadducts **20** and **21** (ratio 1:4) were produced in 84% combined yield (Scheme 3). Both cycloadducts arise from orientation of the nitro function in the *endo* transition state. The dominant cycloadduct **21** possessed the desired regiochemistry and we turned our attention to the three remaining tasks to assemble the complete ring system relevant to the [2.2.2]diazabicyclic alkaloid family: (1) removal of the nitro group, (2) methylation of the ester (MeMgBr), and (3) Friedel–Crafts cyclization.

Direct radical reduction of the secondary nitro group in **21** was attempted (Bu<sub>3</sub>SnH, AIBN, PhMe, 110 °C), although only the product resulting from elimination (**23**) was observed. Performing the reduction at lower temperatures (70–80 °C) afforded mostly elimination product **23** but also a limited quantity (ca. 10% yield) of **25**, thereby validating the stereochemistry of the cycloaddition. Due to the strong propensity for elimination, we found it operationally most convenient to expose the 1:4 mixture of cycloadducts **20** and **21** to DBU, which promoted elimination to the two isomeric unsaturated ester products. The major isomer **23** was easily separated by chromatography from the regioisomeric product **22**. Hydrogenation of the unsaturation in **23** gave a nearly equal mixture of *syn*- and *anti*-fused products **24** and **25**.

Both diastereomers **24** and **25** were advanced in a short number of operations to intercept known compounds. Product **24** was converted to *anti*-fused **2**, a well-established intermediate toward brevianamide B.<sup>22</sup> Toward this end, the ester in **24** was consumed with excess MeMgBr to afford the derived tertiary alcohol. Acidic hydrolysis<sup>23</sup> of the lactim

ether functionality to give the lactam **26** was required prior to Friedel–Crafts cyclization of the indole on the derived tertiary carbocation. Intermediate **27**, which features the tertiary alcohol and lactam structures, cleanly underwent indole BOC deprotection and cyclization to give the desired annulated product **2** in 83% yield. The spectral data for product **2** thus obtained was identical to all properties of an authentic sample provided by Williams.

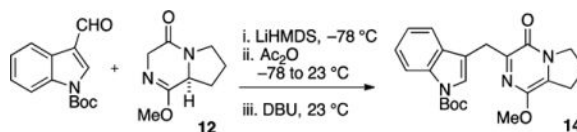
The analogous lactim hydrolysis on *syn*-fused intermediate **25** intercepted the known lactam **28**, an intermediate produced by Baran and co-workers in the course of their synthesis of **1** and more complex natural products.<sup>24</sup>

The synthesis of **2** and **28** constitute 12-step formal total syntheses of both brevianamide B (**3**) and premalbrancheamide, representative *anti*- and *syn*-fused [2.2.2]diazabicyclic alkaloid natural products. The synthetic strategy based on intermolecular pyrazinone cycloaddition is convergent and provides a direct entry to the [2.2.2]diazabicyclic feature (four to five steps from proline methyl ester). Further insight into the pyrazinone Diels–Alder was obtained in this study. In particular, we demonstrated that the use of a 2-nitroacrylate dienophile was required to obtain the desired regiochemistry. Extension of this intermolecular cycloaddition with chiral nitroacrylate derivatives<sup>25</sup> could enable construction of structures in either enantiomeric series. Additionally, we plan to continue to explore other possible stereoselective operations, such as directed or diastereoselective reduction, in the application of this synthetic strategy to more intricate and bioactive natural products in the [2.2.2]diazabicyclic prenylated indole alkaloid family.

## EXPERIMENTAL SECTION

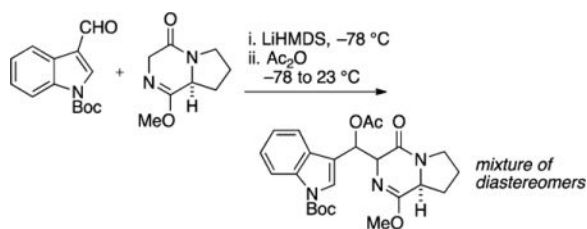
### General Information

All reactions were carried out under an atmosphere of nitrogen in flame-dried or oven-dried glassware with magnetic stirring unless otherwise indicated. Acetonitrile, THF, toluene, and Et<sub>2</sub>O were degassed with argon and purified by passage through a column of molecular sieves and a bed of activated alumina. Dichloromethane was distilled from CaH<sub>2</sub> prior of use. All reagents were used as received unless otherwise noted. Flash column chromatography was performed using silica gel (230–400 mesh). Analytical thin-layer chromatography was performed on 60 Å glass plates. Visualization was accomplished with UV light, anisaldehyde, ceric ammonium molybdate (CAM), potassium permanganate, or ninhydrin, followed by heating. <sup>1</sup>H NMR spectra were recorded on a 400 MHz spectrometer and are reported in ppm using solvent as an internal standard (CDCl<sub>3</sub> at 7.26 ppm) or tetramethylsilane (0.00 ppm). Proton-decoupled <sup>13</sup>C NMR spectra were recorded on a 400 MHz spectrometer and are reported in ppm using solvent as an internal standard (CDCl<sub>3</sub> at 77.0 ppm). All compounds were judged to be homogeneous (>95% purity) by <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy unless otherwise noted as mixtures. Mass spectra data analysis was obtained through positive electrospray ionization (ICR-MS w/NaCl).



***tert*-Butyl 3-((1-Methoxy-4-oxo-4,6,7,8-tetrahydropyrrolo-[1,2-*a*]pyrazin-3-yl)methyl)-1*H*-indole-1-carboxylate (**14**)**

To diketopiperazine (DKP) **12**<sup>8d</sup> (384 mg, 2.29 mmol) in PhMe (8 mL) and DMF (8 mL) at  $-78\text{ }^{\circ}\text{C}$  was added LiHMDS (2.50 mL, 1.0 M in THF, 1.1 equiv) dropwise over 5 min by syringe. After the mixture was stirred for 15 min at  $-78\text{ }^{\circ}\text{C}$ , *N*-Boc-indole carboxaldehyde (0.56 g, 1.0 equiv) in PhMe (8 mL) was added, and the reaction was stirred for an additional 15 min at  $-78\text{ }^{\circ}\text{C}$ . Ac<sub>2</sub>O (0.28 mL, 3.0 mmol, 1.3 equiv) was added, and the cooling bath was removed. The reaction mixture was stirred at rt for 3 h, at which time DBU (0.48 mL, 3.2 mmol, 1.4 equiv) was added and the reaction was stirred at rt for 18 h. The reaction was then diluted with 0.1 M HCl (50 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with satd aqueous NaHCO<sub>3</sub> and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The resulting product (0.91 g, quant mass recovery, ca. 95% pure by <sup>1</sup>H NMR) was recrystallized (hexanes/EtOAc) to afford analytically pure **14** (0.38 g, 42% yield) as a yellow amorphous solid. Pyrazinone **14** can be stored (in the dark) for several weeks under inert gas at  $-15\text{ }^{\circ}\text{C}$  without appreciable degradation: TLC (100% EtOAc) *R*<sub>f</sub> 0.40 (UV/CAM); IR (film) 2976, 2939, 1730, 1653, 1584, 1579, 1452, 1369, 1349, 1256, 1157, 1080, 1046, 1016, 855, 750 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.10 (s, 1H), 7.75 (d, *J* = 7.3 Hz, 1H), 7.61 (s, 1H), 7.29–7.19 (m, 2H), 4.19 (s, 2H), 4.14 (t, *J* = 7.0 Hz, 2H), 3.82 (s, 3H), 3.04 (t, *J* = 7.4 Hz, 2H), 2.21 (q, *J* = 7.4 Hz, 2H), 1.65 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 154.0, 149.8, 149.6, 142.5, 135.5, 130.8, 125.4, 124.2, 124.1, 122.2, 120.0, 116.7, 115.0, 83.3, 54.8, 49.5, 28.4, 28.2, 28.1, 21.6; exact mass calcd for C<sub>22</sub>H<sub>25</sub>N<sub>3</sub>O<sub>4</sub> [M + Na]<sup>+</sup> 418.1743, found 418.1735.

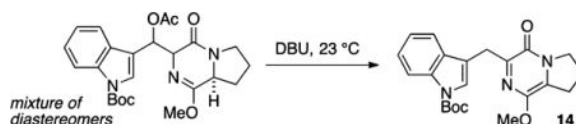


***tert*-Butyl 3-(Acetoxy((8*a**S*)-1-methoxy-4-oxo-3,4,6,7,8,8*a*-hexahydropyrrolo[1,2-*a*]pyrazin-3-yl)methyl)-1*H*-indole-1-carboxylate**

To DKP **12** (2.16 g, 12.9 mmol) in THF (71 mL) at  $-78\text{ }^{\circ}\text{C}$  was added LiHMDS (14.1 mL, 1 M in THF) dropwise and the mixture stirred for 30 min at  $-78\text{ }^{\circ}\text{C}$ . *N*-Boc-indole carboxaldehyde (3.31 g, 13.5 mmol) was added as a solution in THF (10 mL) dropwise over 5 min, and the reaction was stirred for an additional 30 min at  $-78\text{ }^{\circ}\text{C}$ . Ac<sub>2</sub>O (1.82 mL, 19.3 mmol) and pyridine (1.55 mL, 19.3 mmol) were each added dropwise over 5 min, and the cold bath was removed. The reaction was allowed to warm to rt and stir for 16 h and was then diluted with HCl (20 mL, 0.1 M) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with satd aqueous NaHCO<sub>3</sub> (50 mL), saturated NaCl (50 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated in vacuo to afford the β-acetoxy product as a mixture of four diastereomers. The resulting residue was purified by flash column chromatography on silica gel (gradient elution: 30% → 100% EtOAc in hexanes). The four diastereomers were collected together to afford a pale yellow amorphous solid (5.32 g, 91% yield): mp 58.0–59.1  $^{\circ}\text{C}$ ; TLC (80% EtOAc in hexanes) *R*<sub>f</sub> 0.25–0.35 (UV/CAM); IR (film)

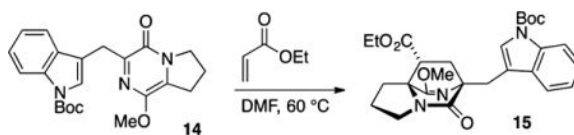


2980, 2945, 2886, 1732, 1676, 1657, 1451, 1368, 1338, 1310, 1252, 1219, 1152, 1080, 1017, 947, 853, 839, 764, 747, 700, 631, 600, 592  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 8.13–8.01 (m, 1H), 7.96–7.91 (m, 1H), 7.74–7.52 (m, 1H), 7.32–7.18 (m, 2H), 6.89–6.41 (m, 1H), 4.77–4.28 (m, 1H), 4.05–3.94 (m, 1H), 3.79–3.72 (m, 3H), 3.70–3.63 (m, 1H), 3.50–3.31 (m, 1H), 2.31–2.22 (m, 1H), 2.16–2.01 (m, 3H), 1.93–1.69 (m, 2H), 1.62–1.29 (m, 1H), 1.66–1.64 (m, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.2, 169.8, 169.4, 165.9, 165.5, 165.2, 165.1, 163.4, 163.1, 162.5, 162.4, 149.6, 149.7, 149.5, 135.3, 135.1, 129.8, 129.5, 128.9, 128.6, 125.6, 125.4, 125.0, 124.7, 124.6, 124.4, 124.3, 124.1, 122.7, 122.6, 122.5, 122.3, 121.8, 120.8, 120.4, 120.0, 118.6, 116.9, 116.8, 116.7, 115.2, 115.1, 114.8, 84.1, 83.6, 83.6, 71.1, 71.0, 70.4, 66.0, 65.8, 63.7, 63.4, 56.9, 56.8, 56.6, 56.3, 53.8, 53.7, 53.6, 44.6, 44.4, 44.3, 44.2, 29.6, 29.4, 29.1, 28.7, 28.3, 28.2, 28.1, 22.6, 22.4, 21.9, 21.7, 21.3, 21.2, 21.1; exact mass calcd for  $\text{C}_{24}\text{H}_{29}\text{N}_3\text{O}_6\text{Na}$   $[\text{M} + \text{Na}]^+$  478.1949, found 478.1946.



#### ***tert*-Butyl 3-((1-Methoxy-4-oxo-4,6,7,8-tetrahydropyrrolo-[1,2-*a*]pyrazin-3-yl)methyl)-1*H*-indole-1-carboxylate (**14**)**

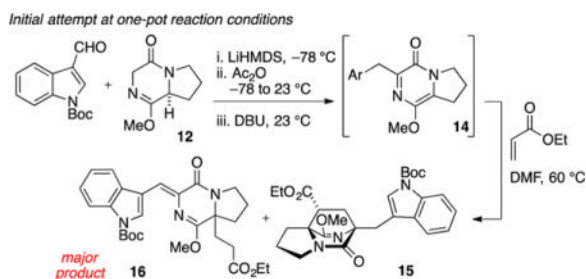
A flame-dried flask was charged with  $\beta$ -acetoxy aldol addition product (1.37 g, 3.00 mmol), wrapped in aluminum foil, flushed with  $\text{N}_2$  gas for 10 min, and dissolved in PhMe (15 mL) and DMF (3 mL). To the reaction flask was added DBU (0.89 mL, 6.00 mmol), and the reaction was stirred for 16 h, diluted with HCl (20 mL, 0.2 M), and extracted with EtOAc (3  $\times$  30 mL). The combined organic extracts were washed with satd aqueous  $\text{NaHCO}_3$  (50 mL) and saturated NaCl (50 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated in vacuo to afford pyrazinone **14** as a yellow amorphous solid (1.12 g, 94% yield). Vide infra for spectral information.



#### **Ethyl (6*R*\*,8*R*\*,8*aS*\*)-6-((1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)methyl)-9-methoxy-5-oxo-2,3,5,6,7,8-hexahydro-1*H*-6,8*a*-(azenometheno)indolizine-8-carboxylate (**15**)**

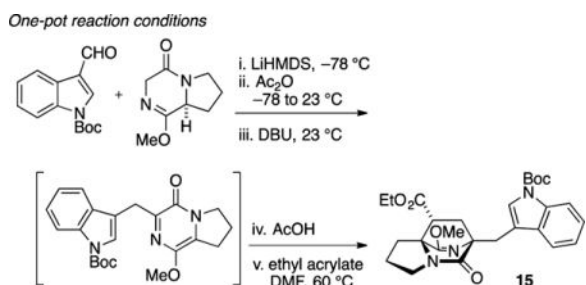
A flame-dried flask was charged with pyrazinone **14** (227 mg, 0.575 mmol) and fitted with a reflux condenser. The starting material was dissolved in DMF (3.8 mL, 0.15 M), and the reaction vessel was degassed (evacuated and backfilled with  $\text{N}_2 \times 5$ ). Ethyl acrylate (0.12 mL, 114 mg, 1.14 mmol) was added, and the reaction vessel was heated at 60  $^\circ\text{C}$  for 24 h, cooled to rt, and concentrated in vacuo to afford a brown oil. Analysis of the unpurified reaction mixture reveals a 3:1:1 mixture of diastereomers. Purification by flash column chromatography on silica gel (gradient elution: 30%  $\rightarrow$  100% EtOAc in hexanes) afforded product **15** (138 mg, 48% yield) as a colorless oil: TLC (60% EtOAc in hexane)  $R_f$  0.30 (CAM); IR (film) 2985, 2945, 2876, 1736, 1683, 1642, 1456, 1416, 1308, 1260, 1156, 1085, 1016, 852, 768, 745  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ) 8.10 (br s, 1H), 7.78 (d,  $J = 7.5$  Hz,

1H), 7.68 (s, 1H), 7.24 (m, 2H), 4.05 (m, 2H), 3.75 (s, 3H), 3.50–3.30 (m, 2H), 3.44 (d,  $J=14.8$  Hz, 1H), 3.34 (d,  $J=14.8$  Hz, 1H), 2.78 (dd,  $J=9.8, 5.5$  Hz, 1H), 2.61 (m, 1H), 2.05–1.85 (m, 4H), 1.80 (dd,  $J=13.2, 5.5$  Hz, 1H), 1.64 (s, 9H), 1.18 (t,  $J=7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.3, 163.0, 160.8, 149.5, 134.9, 132.1, 130.3, 129.0, 128.4, 128.2, 125.3, 124.7, 123.0, 118.9, 116.1, 155.5, 115.1, 104.8, 83.7, 65.6, 60.7, 54.3, 43.8, 35.0, 32.4, 29.0, 28.2, 28.1, 20.2, 14.0; exact mass calcd for  $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_6$  [ $\text{M} + \text{Na}$ ] $^+$  518.2261, found 518.2259.



***tert*-Butyl (*Z*)-3-((8a-(3-Ethoxy-3-oxopropyl)-1-methoxy-4-oxo-6,7,8,8a-tetrahydropyrrolo[1,2-*a*]pyrazin-3(4*H*)-ylidene)-methyl)-1*H*-indole-1-carboxylate (**16**)**

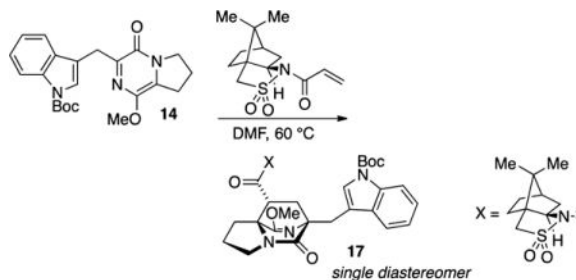
The reaction was executed according to the conditions previously described for the preparation of **14**. Prior to aqueous workup of **14** (0.38 mmol, assuming quantitative formation), ethyl acrylate (0.080 mL, 0.76 mmol, 2 equiv) was added, and the reaction was warmed to 60 °C and stirred for an additional 24 h. The reaction mixture was diluted with 0.2 M HCl (30 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with satd aqueous  $\text{NaHCO}_3$  and brine, dried ( $\text{Na}_2\text{SO}_4$ ), and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (gradient elution: 40 → 100% EtOAc in hexane) to afford **15** (28 mg, 15% yield) and **16** (94 mg, 50% yield) as a yellow oil. Data for compound **16**: TLC (60% EtOAc in hexane)  $R_f$  0.50 (UV, CAM); IR (film) 2980, 2880, 1732, 1680, 1646, 1456, 1411, 1300, 1270, 1154, 1018, 740  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ); 8.60 (s, 1H), 8.18 (d,  $J=7.4$  Hz, 1H), 7.84 (dd,  $J=7.4, 1.6$  Hz, 1H), 7.34 (m, 2H), 4.10–3.92 (m, 2H), 4.01 (s, 3H), 2.22–2.00 (m, 8H), 3.40 (m, 4H), 1.67 (s, 9H), 1.14 (t,  $J=7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.3, 162.9, 160.8, 149.5, 132.0, 130.2, 128.3, 124.6, 123.0, 118.8, 116.0, 115.4, 115.1, 83.6, 65.6, 60.7, 54.3, 43.8, 35.0, 32.3, 28.9, 28.2, 28.0, 20.0, 14.0; exact mass calcd for  $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_6$  [ $\text{M} + \text{Na}$ ] $^+$ , 518.2261, found 518.2257.



The reaction was executed according to the conditions previously described conditions used for the preparation of **14**. Prior to aqueous workup of **14** (0.1 mmol, assuming quantitative

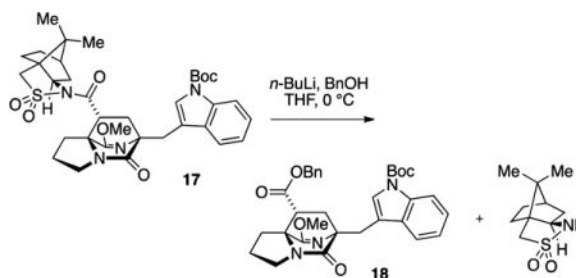


formation), AcOH (6  $\mu$ L, 0.1 mmol, 1 equiv) and ethyl acrylate (20  $\mu$ L, 0.2 mmol, 2 equiv) were added, and the reaction was warmed to 60 °C and stirred for an additional 24 h. The reaction mixture was diluted with 0.2 M HCl (10 mL) and extracted with EtOAc (3  $\times$  10 mL). The combined organic layers were washed with satd aqueous NaHCO<sub>3</sub> and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (gradient elution: 40  $\rightarrow$  100% EtOAc in hexane) to afford **15** (20 mg, 40% yield). Vide infra for spectral information.



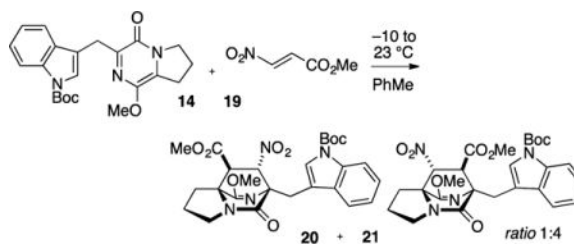
***tert*-Butyl 3-(((6*R*,8*R*,8*aS*)-8-((7*aR*)-8,8-Dimethyl-2,2-dioxidohexahydro-3*H*-3*a*,6-methanobenzo[*c*]isothiazole-1-carbonyl)-9 – methoxy – 5 – oxo – 2, 3, 7, 8 – tetrahydro – 1*H* – 6, 8*a* -(azenometheno)indolizin-6(5*H*)-yl)methyl)-1*H*-indole-1-carboxylate (**17**)**

To a flame-dried flask were added acryloyl (+)-camphorsultam (135 mg, 0.51 mmol) and pyrazinone **14** (188 mg, 0.48 mmol). The flask was fitted with a condenser and flushed with N<sub>2</sub>. The reactants were dissolved in DMF (3.2 mL, 0.15 M), and the vessel was evacuated and backfilled with N<sub>2</sub> ( $\times$ 5) before heating to 60 °C. After being heated for 24 h, the reaction mixture was cooled to rt and concentrated in vacuo to afford a brown oil. Analysis of the unpurified reaction mixture by <sup>1</sup>H NMR reveals a single cycloadduct as well as some unreacted sultam dienophile. Purification by flash column chromatography on silica gel (gradient elution: 30%  $\rightarrow$  70% EtOAc in hexanes) afforded cycloadduct **17** (260 mg, 62% yield) as a colorless oil: TLC (80% EtOAc in hexane) *R*<sub>f</sub> 0.3 (CAM); [ $\alpha$ ]<sup>25</sup><sub>D</sub> = +59 (*c* 1.0, CH<sub>2</sub>Cl<sub>2</sub>); IR (film) 3854, 3744, 3061, 2986, 2882, 2360, 2337, 1730 1683, 1648, 1635, 1452, 1363, 1351, 1308, 1298, 1268, 1258, 1218, 1164, 1135, 1083, 1015, 987, 768, 735, 667, 533 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 8.1 (s, 1H), 7.77 (d, *J* = 1.14 Hz, 1H), 7.66 (s, 1H), 7.23 (m, 2H), 3.77 (s, 3H), 3.75 (m, 1H), 3.52–3.42 (m, 4H), 3.38 (d, *J* = 13.7 Hz, 1H), 3.30 (d, *J* = 14.8 Hz, 1H), 2.47 (dd, *J* = 11.7, 6.6 Hz, 1H), 2.15–1.81 (m, 10H), 1.68 (dd, *J* = 13.3, 5.5 Hz, 1H), 1.66 (s, 9H), 1.30 (m, 2H), 1.15 (s, 3H), 0.96 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.2, 170.9, 169.5, 149.8, 135.1, 132.1, 125.5, 123.6, 121.9, 120.4, 116.5, 114.8, 83.1, 66.3, 66.2, 65.4, 54.5, 53.1, 49.0 48.2, 47.7, 44.6, 43.2, 38.5, 34.9, 32.9, 28.8, 28.2, 27.2, 26.3, 24.4, 20.9, 19.8; exact mass calcd for C<sub>35</sub>H<sub>44</sub>N<sub>4</sub>O<sub>7</sub>S [M + Na]<sup>+</sup> 687.2823, found 687.2813.



**Benzyl (6*R*,8*R*,8*aS*)-6-((1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)methyl)-9-methoxy-5-oxo-2,3,5,6,7,8-hexahydro-1*H*-6,8*a*-(azenometheno)indolizine-8-carboxylate (**18**)**

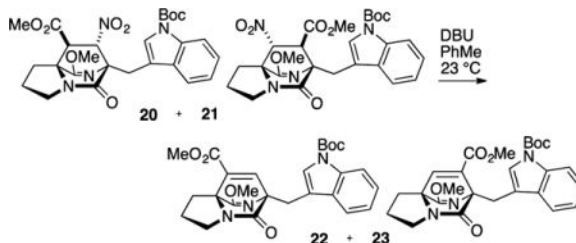
To a flame-dried reaction flask under N<sub>2</sub> were added BnOH (13  $\mu$ L, 0.12 mmol) and THF (0.6 mL), the vessel was cooled to  $-78$   $^{\circ}$ C, and a solution of *n*-BuLi (3.0 M in pentane, 33  $\mu$ L, 0.01 mmol) was added. In a separate flask, sultam adduct **17** (20 mg, 0.03 mmol) was dissolved in THF (0.25 mL), and the solution was transferred via cannula to the reaction flask (which contained the LiOBn solution). After the cannula wire was rinsed with an additional 0.15 mL of THF, the  $-78$   $^{\circ}$ C cooling bath was exchanged for an ice/water bath (0  $^{\circ}$ C). The reaction mixture was stirred at 0  $^{\circ}$ C for 8 h, diluted with satd aq NH<sub>4</sub>Cl (15 mL), and extracted with EtOAc (3  $\times$  10 mL). The combined organic extracts were washed with satd aq NaHCO<sub>3</sub> and brine, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The resulting oil was purified by flash column chromatography on silica gel (gradient elution: 30%  $\rightarrow$  70% EtOAc in hexanes) to afford the benzyl ester **18** as a light yellow oil (13 mg, 75% yield): TLC (60% EtOAc in hexane) *R*<sub>f</sub> 0.6 (CAM); [ $\alpha$ ]<sub>D</sub><sup>25</sup> = +25 (*c* 0.3, CH<sub>2</sub>Cl<sub>2</sub>); IR (film) 2985, 2942, 2882, 2358, 2330, 1730, 1686, 1639, 1452, 1370, 1308, 1257, 1160, 1085, 1015, 912, 857, 746, 668, 664 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) 8.11 (s, 1H), 7.77 (d, *J* = 8.0 Hz, 1H), 7.66 (s, 1H), 7.34–7.28 (m, 4H), 7.24–7.18 (m, 3H) 5.06 (d, *J* = 12.1 Hz, 1H), 4.98 (d, *J* = 12.1 Hz, 1H), 3.65 (s, 3H), 3.50 (m, 1H), 3.45 (d, *J* = 14.8 Hz, 1H), 3.35 (m, 1H), 3.34 (d, *J* = 14.8 Hz, 1H), 2.84 (dd, *J* = 10.2, 5.5 Hz, 1H), 2.57 (dd, *J* = 13.3, 5.1 Hz, 1H), 2.10–1.85 (m, 4H), 1.84 (dd, *J* = 13.3, 5.5, 1H), 1.66 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  172.4, 171.4, 169.6, 135.3, 132.3, 128.8, 125.8, 124.1, 122.3, 120.7, 116.7, 115.1, 83.4, 67.2, 66.6, 65.9, 54.6, 49.3, 43.6, 34.2, 30.6, 29.1, 28.5, 28.4, 24.9, 13.8; exact mass calcd for C<sub>32</sub>H<sub>35</sub>N<sub>3</sub>O<sub>6</sub> [M + Na]<sup>+</sup> 580.2418, found 580.2405.



**Methyl (6*S*<sup>\*</sup>,7*S*<sup>\*</sup>,8*S*<sup>\*</sup>,8*aS*<sup>\*</sup>)-6-((1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)methyl)-9-methoxy-7-nitro-5-oxo-2,3,5,6,7,8-hexa-hydro-1*H*-6,8*a*-(azenometheno)indolizine-8-carboxylate (**20**) and Methyl (6*S*<sup>\*</sup>,7*R*<sup>\*</sup>,8*R*<sup>\*</sup>,8*aS*<sup>\*</sup>)-6-((1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)methyl)-9-**

**methoxy-8-nitro-5-oxo-2,3,5,6,7,8-hexahydro-1*H*-6,8a-(azenometheno)indolizine-7-carboxylate (21)**

A dry flask was charged with pyrazinone **14** (531 mg, 1.34 mmol) and flushed with N<sub>2</sub> gas for 30 min and dissolved in toluene (7 mL). A separate flask was charged with nitroacrylate **19** (158 mg, 1.21 mmol) and flushed with N<sub>2</sub> gas for 30 min and dissolved in toluene (2 mL). The reaction flask containing pyrazinone **14** was cooled to -10 °C (ice/salt bath). The nitroacrylate solution was dropwise to the reaction vessel over 10 min. The reaction was allowed to stir and slowly warm to rt overnight (16 h). The solution was concentrated in vacuo to afford a brown oil, which contained the two regioisomeric cycloadducts **20** and **21** in a 1:4 ratio (as judged by <sup>1</sup>H NMR on the unpurified reaction mixture). The resulting residue was purified by flash column chromatography on silica gel (gradient elution: 10% → 80% EtOAc in hexanes). A small amount of pure **21** (40 mg) was obtained for analytical purposes and the bulk of the material was obtained as a yellow oil that was comprised of a 1:4 mixture of **20** and **21** (593 mg, 84% yield): TLC (80% EtOAc in hexanes) *R*<sub>f</sub> 0.30, 0.35 (CAM/UV). IR (film) 3052, 2980, 2950, 1733, 1704, 1641, 1608, 1559, 1477, 1452, 1410, 1370, 1309, 1219, 1197, 1158, 1086, 1016, 979, 937, 897, 857, 811, 768, 747, 703, 656 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ 8.13 (d, *J* = 5.9 Hz, 1H), 7.76 (d, *J* = 1.6, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.29 (dt, *J* = 8.2, 1.2 Hz, 1H) 7.21 (dt, *J* = 7.8, 0.8 Hz, 1H), 5.05 (d, *J* = 4.3 Hz, 1H), 3.77 (s, 3H) 3.76 (s, 3H), 3.62–3.52 (m, 3H), 3.34 (d, *J* = 4.3 Hz, 1H), 3.30 (d, *J* = 15.7 Hz, 1H), 2.72–2.66 (m, 1H), 2.25–2.00 (m, 3H), 1.68 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>): δ 169.6, 169.1, 168.7, 149.7, 135.1, 132.0, 125.5, 124.0, 121.9, 120.5, 115.3, 114.9, 88.9, 83.3, 68.6, 65.3, 55.4, 53.1, 51.0, 44.0, 28.2, 27.2, 26.8, 24.3; exact mass calcd for C<sub>26</sub>H<sub>30</sub>N<sub>4</sub>O<sub>8</sub>Na [M + Na]<sup>+</sup> 549.1953, found 549.1956.

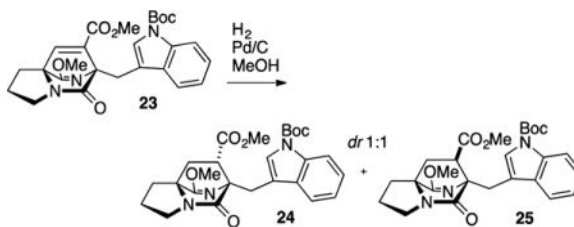


**Methyl (6*S*<sup>\*</sup>,8*aS*<sup>\*</sup>)-6-((1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)methyl)-9-methoxy-5-oxo-2,3,5,6-tetrahydro-1*H*-6,8a-(azenometheno)indolizine-8-carboxylate (22) and Methyl (6*S*<sup>\*</sup>,8*aS*<sup>\*</sup>)-6-((1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)methyl)-9-methoxy-5-oxo-2,3,5,6-tetrahydro-1*H*-6,8a-(azenometheno)indolizine-7-carboxylate (23)**

A flask was charged with cycloadducts **20** and **21** (ratio 1:4, 588 mg, 1.12 mmol), flushed with N<sub>2</sub> gas, and dissolved in PhMe (18 mL). To the reaction vessel was added DBU (277 μL, 1.86 mmol), and the reaction mixture was stirred for 16 h at rt, diluted with HCl (0.1 M, 10 mL), and extracted with EtOAc (3 × 15 mL). The combined organic portions were washed with saturated NaHCO<sub>3</sub> (20 mL) and saturated NaCl (20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated in vacuo to give the α,β-unsaturated methyl ester regioisomers **22** and **23** in a 1:4 ratio as judged by <sup>1</sup>H NMR on the unpurified reaction mixture. The residue was purified by flash column chromatography on silica gel (gradient elution: 20% → 80% EtOAc in hexanes) to afford the minor regioisomer **22** as a light yellow oil (62.1 mg, 12%

yield) and **23** as a pale yellow powder (376 mg, 70% yield). Spectroscopic data reported for **22**: TLC (40% EtOAc in hexanes)  $R_f$  0.45 (CAM/UV); IR (film) 2890, 2884, 1721, 1688, 1634, 1607, 1451, 1369, 1339, 1327, 1308, 1267, 1256, 1244, 1157, 1086, 1044, 1003, 984, 910, 856, 746, 732, 665  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.10 (d,  $J = 7.0$  Hz, 1H), 7.83 (d,  $J = 7.5$  Hz, 1H), 7.68 (s, 1H), 7.50 (s, 1H), 7.33–7.29 (m, 1H), 7.27–7.23 (m, 1H), 3.80 (s, 3H), 3.73 (d,  $J = 12.1$  Hz, 3H), 3.59 (dd,  $J = 15.3, 1.2$  Hz, 2H), 3.49–3.44 (m, 1H), 3.19–3.12 (m, 1H), 2.87–2.76 (m, 2H), 2.14–2.04 (m, 1H), 1.98–1.87 (m, 1H), 1.66 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  175.4, 169.6, 162.8, 152.8, 149.8, 138.2, 135.1, 131.7, 124.9, 124.1, 122.3, 120.0, 116.1, 115.0, 83.4, 74.0, 69.4, 56.3, 51.8, 43.0, 28.2, 26.7, 25.6, 25.4; exact mass calcd for  $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_6$   $[\text{M} + \text{Na}]^+$  502.1949, found 502.1944.

Spectroscopic data reported for  $\alpha,\beta$ -unsaturated methyl ester **23**: mp 94.0–95.0  $^\circ\text{C}$ ; TLC (40% EtOAc in hexanes)  $R_f$  0.28 (CAM/UV); IR (film) 2980, 2949, 2882, 1722, 1690, 1640, 1607, 1451, 1370, 1339, 1304, 1256, 1221, 1155, 1080, 1017, 995, 978, 930, 907, 856, 835, 764, 739, 619  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.06 (s, 1H), 7.81 (dd,  $J = 7.1, 1.3$  Hz, 1H), 7.62 (s, 1H), 7.28–7.20 (m, 2H), 7.13 (s, 1H), 4.07 (dd,  $J = 15.6, 0.8$  Hz, 1H), 3.79 (s, 3H), 3.64 (dd,  $J = 15.6, 0.8$  Hz, 1H), 3.40 (s, 3H), 3.40–3.35 (m, 1H), 3.25–3.19 (m, 1H), 2.74 (m, 1H), 2.25–2.18 (m, 1H), 2.10–2.00 (m, 2H), 1.63 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  174.4, 169.7, 164.6, 150.0, 147.5, 144.4, 135.1, 132.3, 124.5, 124.0, 122.1, 120.7, 117.6, 114.9, 83.1, 75.7, 67.6, 56.3, 52.1, 42.7, 28.4, 26.8, 25.5, 25.3; exact mass calcd for  $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_6$   $[\text{M} + \text{Na}]^+$  502.1949, found 502.1944.

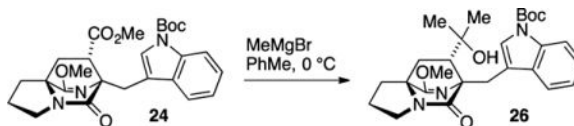


**Methyl (6*S*<sup>\*</sup>,7*S*<sup>\*</sup>,8*aS*<sup>\*</sup>)-6-((1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)methyl)-9-methoxy-5-oxo-2,3,5,6,7,8-hexahydro-1*H*-6,8a-(azenometheno)indolizine-7-carboxylate (**24**) and Methyl (6*S*<sup>\*</sup>,7*R*<sup>\*</sup>,8*aS*<sup>\*</sup>)-6-((1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)-methyl)-9-methoxy-5-oxo-2,3,5,6,7,8-hexahydro-1*H*-6,8a-(azenometheno)indolizine-7-carboxylate (**25**)**

Unsaturated ester **23** (182 mg, 0.378 mmol) was dissolved in MeOH (4 mL) at rt, and 10% Pd/C (25 mg) was added. One balloon of  $\text{H}_2$  gas was used to sparge the reaction mixture (10 min); a second balloon was maintained above the reaction mixture during the course of the reaction to provide an atmosphere of  $\text{H}_2$ . When TLC indicated consumption of starting material (1 h), the reaction mixture was filtered through Celite, and the filter pad was washed with MeOH. After removal of the solvent in vacuo, a white powder was obtained that contained an equal mixture of diastereomers as judged by  $^1\text{H}$  NMR on the unpurified reaction mixture. The mixture was purified by flash chromatography on silica gel (20% to 100% EtOAc in hexanes) to afford **24** (77 mg, 43% yield) and **25** (78 mg, 43% yield), both obtained as a colorless amorphous solids. Spectroscopic data for **24**: TLC (60% EtOAc in hexanes)  $R_f$  0.36 (CAM/UV); IR (film) 2980, 2948, 2883, 1732, 1730, 1695, 1687, 1641, 1476, 1457, 1452, 1416, 1371, 1360, 1308, 1257, 1213, 1185, 1161, 1084, 1016, 913, 857,

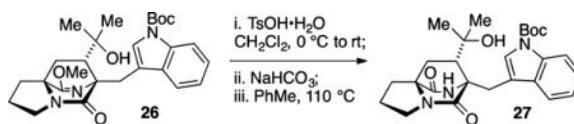
768, 745, 701, 672  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.07 (d,  $J$  = 5.8 Hz, 1H), 7.76 (s, 1H), 7.74 (d,  $J$  = 2.0 Hz, 1H), 7.24–7.19 (m, 2H), 3.78 (s, 3H), 3.54 (d,  $J$  = 14.8 Hz, 1H), 3.47 (s, 3H), 3.44–3.31 (m, 2H), 3.22 (d,  $J$  = 14.9 Hz, 1H), 3.06 (q,  $J$  = 4.7 Hz, 1H), 2.65–2.58 (m, 1H), 2.09–1.87 (m, 5H), 1.63 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.4, 171.0, 169.9, 149.9, 134.9, 132.3, 125.7, 123.6, 121.9, 120.3, 116.7, 114.8, 82.8, 69.3, 64.1, 54.7, 51.8, 45.8, 43.4, 37.3, 28.6, 28.2, 27.5, 24.4; exact mass calcd for  $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_6\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  504.2105, found 504.2102.

Spectroscopic data for **25**: TLC (60% EtOAc in hexanes)  $R_f$  0.43, (CAM/UV); IR (film) 2979, 2948, 2881, 1731, 1693, 1690, 1689, 1452, 1437, 1419, 1370, 1343, 1301, 1258, 1218, 1162, 1120, 1084, 1045, 1013, 990, 856, 767, 747, 666  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.09 (s, 1H), 7.79 (d,  $J$  = 7.8 Hz, 1H), 7.68 (s, 1H), 7.25 (t,  $J$  = 6.2 Hz, 1H), 7.19 (t,  $J$  = 7.8 Hz, 1H), 3.75 (s, 1H), 3.71 (s, 3H), 3.68 (s, 3H), 3.29 (d,  $J$  = 15.3 Hz, 1H), 2.76 (q,  $J$  = 5.1 Hz, 1H), 2.60–2.54 (m, 1H), 2.08–1.83 (m, 5H), 1.66 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.9, 172.4, 169.8, 149.9, 135.2, 132.3, 125.5, 123.8, 121.8, 121.1, 116.5, 114.8, 83.1, 68.9, 63.3, 54.7, 52.1, 45.2, 43.5, 36.3, 28.7, 28.2, 27.2, 24.6; exact mass calcd for  $\text{C}_{26}\text{H}_{31}\text{N}_3\text{O}_6\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  504.2105, found 504.2102.



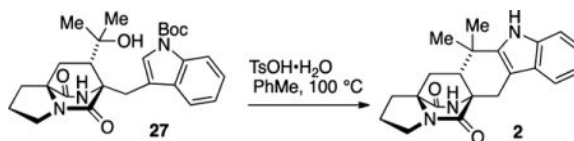
***tert*-Butyl 3-(((6*S*\*,7*S*\*,8*aS*\*)-7-(2-Hydroxypropan-2-yl)-9-methoxy-5-oxo-2,3,7,8-tetrahydro-1*H*-6,8*a*-(azenometheno)-indolizin-6(5*H*)-yl)methyl)-1*H*-indole-1-carboxylate (**26**)**

A flame-dried flask was charged with **24** (12.5 mg, 0.026 mmol) and flushed with  $\text{N}_2$  gas for 10 min, dissolved in toluene (0.52 mL), and cooled to 0 °C. To this solution was added MeMgBr (74  $\mu\text{L}$ , 0.104 mmol, 1.4 M in THF). The reaction was stirred for 1 h at 0 °C, diluted with  $\text{NH}_4\text{Cl}$  (10 mL), and extracted with EtOAc ( $3 \times 10$  mL). The combined organic layers were washed with saturated NaCl (40 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated in vacuo. The resulting product was purified by flash chromatography on silica gel (50%  $\rightarrow$  100% EtOAc in hexanes) to afford the derived lactim tertiary alcohol **26** as a white foam (7.4 mg, 59% yield): TLC (80% EtOAc in hexanes)  $R_f$  0.35 (CAM/UV); IR (film) 3406, 2976, 2945, 2880, 1726, 1661, 1451, 1424, 1368, 1354, 1256, 1207, 1155, 1103, 1080, 1011, 955, 924, 856, 820, 743  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.05 (br s, 1H), 7.84–7.82 (m, 1H), 7.69 (s, 1H), 7.24–7.18 (m, 2H), 3.75 (d,  $J$  = 14.8 Hz, 1H), 3.69 (s, 3H), 3.51 (d,  $J$  = 14.9 Hz, 1H), 3.47–3.41 (m, 1H), 3.28–3.22 (m, 1H), 2.50 (dt,  $J$  = 12.9, 7.4 Hz, 1H), 2.35 (dd,  $J$  = 9.8, 6.2 Hz, 1H), 2.04 (dd,  $J$  = 12.9, 9.8, 1H), 1.97–1.82 (m, 3H), 1.76 (br s, 1H), 1.63 (s, 9H), 1.41 (dd,  $J$  = 12.9, 6.2 Hz, 1H), 1.32 (s, 3H), 1.22 (s, 3H);  $^{13}\text{C}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  171.5, 169.8, 150.0, 134.8, 132.6, 125.5, 123.3, 121.7, 120.7, 118.8, 114.7, 82.7, 74.2, 71.7, 63.4, 54.1, 51.9, 43.2, 37.9, 31.2, 28.6, 28.2, 25.9, 24.2; exact mass calcd for  $\text{C}_{27}\text{H}_{35}\text{N}_3\text{O}_5\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  504.2469, found 504.2468.



***tert*-Butyl 3-(((6*S*,7*S*,8*aS*)-7-(2-Hydroxypropan-2-yl)-5,9-diox-otetrahydro-1*H*-6,8a-(epiminomethano)indolizin-6(5*H*)-yl)-methyl)-1*H*-indole-1-carboxylate (27)**

A reaction flask was charged with lactim tertiary alcohol **26** (15.8 mg, 0.033 mmol) and flushed with N<sub>2</sub> gas for 10 min, dissolved in CH<sub>2</sub>Cl<sub>2</sub> (3.5 mL), and cooled to 0 °C. To the reaction flask was added *p*-TsOH·H<sub>2</sub>O (7.3 mg, 0.038 mmol). The reaction was stirred and slowly warmed to ambient temperature over 6 h. The reaction mixture was diluted with satd aq NaHCO<sub>3</sub> (10 mL), and extracted with EtOAc (4 × 10 mL). The combined organic layers were washed with saturated NaCl (40 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated in vacuo. The resulting product (which contained some amino methyl ester) was dissolved in toluene (3 mL) and stirred at 110 °C for 18 h. The solution was concentrated in vacuo to obtain lactam tertiary alcohol **27** (15.5 mg, 95% yield) which was used without further purification: TLC (80% EtOAc in hexanes) *R*<sub>f</sub> 0.32 (CAM/UV); IR (film) 3393, 2928, 1688, 1682, 1674, 1451, 1367, 1339, 1310, 1258, 1221, 1153, 1085, 1022, 961, 934, 856, 802, 745, 694, 665, 592 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 8.12 (d, *J* = 7.4 Hz, 1H), 7.64 (s, 1H), 7.60 (d, *J* = 7.1 Hz, 1H), 7.33–7.16 (m, 2H), 5.70 (br s, 1H), 4.01 (d, *J* = 15.6 Hz, 1H), 3.64–3.52 (m, 2H), 3.40 (dt, *J* = 11.8, 6.6 Hz, 1H), 2.65 (dt, *J* = 12.9, 7.4 Hz, 1H), 2.36 (s, 1H), 2.31 (dd, *J* = 10.2, 6.6 Hz, 1H), 2.13 (dd, *J* = 13.3, 10.2 Hz, 1H), 1.97 (apparent quint, *J* = 7.0 Hz, 2H), 1.82–1.74 (m, 2H), 1.66 (s, 9H), 1.45 (s, 3H), 1.30 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 172.4, 169.3, 149.6, 135.1, 131.5, 126.8, 124.5, 122.9, 118.0, 115.5, 114.6, 83.7, 73.8, 66.8, 65.8, 50.7, 44.2, 36.2, 32.0, 28.2, 24.1, 23.7, 23.5; exact mass calcd for C<sub>26</sub>H<sub>33</sub>N<sub>3</sub>O<sub>5</sub>Na [M + Na]<sup>+</sup> 490.2312, found 490.2312.

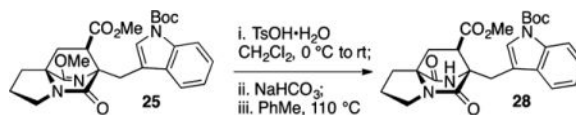


**12,12-Dimethyl-2,3,11,12,12a,13-hexahydro-1*H*,5*H*,6*H*-5a,13a-(epiminomethano)indolizino[7,6-*b*]carbazole-5,14-dione (2)**

A reaction flask was charged with lactam tertiary alcohol **27** (11.5 mg, 0.025 mmol), fitted with a reflux condenser, and flushed with N<sub>2</sub> gas for 10 min. PhMe (3.7 mL) and *p*-TsOH·H<sub>2</sub>O (4.7 mg, 0.025 mmol) were added, and the reaction vessel was heated to 100 °C for 6 h. After being cooled to rt, the reaction was diluted with satd aqueous NaHCO<sub>3</sub> (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with saturated NaCl (40 mL), dried (Na<sub>2</sub>SO<sub>4</sub>), filtered, and concentrated in vacuo to obtain **2** as a white powder (7.1 mg, 83% yield). The material thus obtained was >95% pure as judged by <sup>1</sup>H NMR and further purification was not performed: TLC (100% EtOAc) *R*<sub>f</sub> 0.45 (CAM/UV); IR (film) 3325, 3310, 3233, 3221, 3210, 2990, 2947, 2901, 1656, 1670, 1451, 1404, 1369, 1339, 1300, 1258, 1196, 1161, 1092, 1011, 922, 860, 802, 772, 748, 718, 698, 644, 594; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.89 (br s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.18 (td, *J* = 7.5, 1.3 Hz, 1H), 7.12 (td, *J* = 7.5, 1.2 Hz, 1H), 5.88 (br s, 1H), 3.93



(d,  $J = 18$  Hz, 1H), 3.54 (t,  $J = 6.9$  Hz, 2H), 2.91 (d,  $J = 18$  Hz, 1H), 2.81 (quint,  $J = 6.7$  Hz, 1H), 2.34 (dd,  $J = 9.8, 4.3$  Hz, 1H), 2.18–1.99 (m, 4H), 1.89–1.82 (m, 1H), 1.33 (s, 3H), 1.28 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.7, 169.0, 139.6, 136.4, 127.2, 122.1, 119.7, 118.3, 110.7, 103.6, 67.1, 61.6, 45.7, 44.2, 34.5, 32.6, 29.1, 29.0, 25.3, 24.5, 23.9. exact mass calcd for spray dimer  $\text{C}_{42}\text{H}_{46}\text{N}_6\text{O}_4\text{Na}$  [ $\text{M} + \text{M} + \text{Na}$ ] $^+$  721.3473, found 721.3476. The spectral data for **2** were identical with an authentic sample provided by Williams (Colorado State University).



### Methyl (6*S*,7*R*,8*aS*)-6-((1-(*tert*-Butoxycarbonyl)-1*H*-indol-3-yl)methyl)-5,9-dioxohexahydro-1*H*-6,8*a*-(epiminomethano)-indolizine-7-carboxylate (**28**)

A reaction flask was charged with lactim methyl ester **25** (48 mg, 0.099 mmol) and flushed with  $\text{N}_2$  gas for 10 min, dissolved in  $\text{CH}_2\text{Cl}_2$  (10 mL), and cooled to  $0\text{ }^\circ\text{C}$ . To the reaction flask was added  $p\text{TsOH}\cdot\text{H}_2\text{O}$  (24 mg, 0.13 mmol), and the reaction was stirred for 6 h while slowly warming to rt. The reaction mixture was diluted with satd aq  $\text{NaHCO}_3$  (10 mL) and extracted with EtOAc ( $4 \times 10$  mL). The combined organic layers were washed with saturated NaCl (40 mL), dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and concentrated in vacuo. The resulting product (which contained some amino methyl ester) was dissolved in toluene (10 mL) and stirred at  $110\text{ }^\circ\text{C}$  for 18 h. The solution was concentrated in vacuo to obtain the lactam **28** as a white powder (15.7 mg, 88% yield). The material thus obtained was  $>95\%$  pure as judged by  $^1\text{H}$  NMR, and further purification was not performed: TLC (70% EtOAc in hexanes)  $R_f$  0.30 (CAM/UV); IR (film) 3175, 3117, 3082, 3051, 2978, 2936, 2882, 1736, 1724, 1690, 1450, 1385, 1362, 1312, 1254, 1196, 1153, 1092, 1308, 1018, 964, 934, 922, 899, 849, 837, 768, 745, 691, 563;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  8.15 (d,  $J = 8.2$  Hz, 1H), 7.71 (s, 1H), 7.59 (d,  $J = 7.5$  Hz, 1H), 7.36 (td,  $J = 7.6, 1.2$  Hz, 1H), 7.29 (td,  $J = 7.6, 1.2$  Hz, 1H), 5.75 (br s, 1H), 3.82 (s, 3H), 3.66–3.53 (m, 3H), 3.30 (dd,  $J = 9.8, 4.7$  Hz, 1H), 3.19 (d,  $J = 15.6$  Hz, 1H), 2.73–2.66 (m, 1H), 2.28–2.15 (m, 2H), 2.10–1.98 (m, 2H), 1.85–1.79 (m, 1H), 1.69 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  172.3, 171.6, 166.4, 149.4, 135.4, 130.8, 126.2, 125.0, 123.3, 118.1, 115.7, 112.4, 84.1, 66.1, 63.4, 52.7, 48.2, 44.3, 34.8, 28.9, 28.2, 24.3, 24.0. exact mass calcd for  $\text{C}_{25}\text{H}_{29}\text{N}_3\text{O}_6\text{Na}$  [ $\text{M} + \text{Na}$ ] $^+$  490.1949, found 490.1948. Spectral data agrees with that reported by Baran.<sup>24</sup>

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

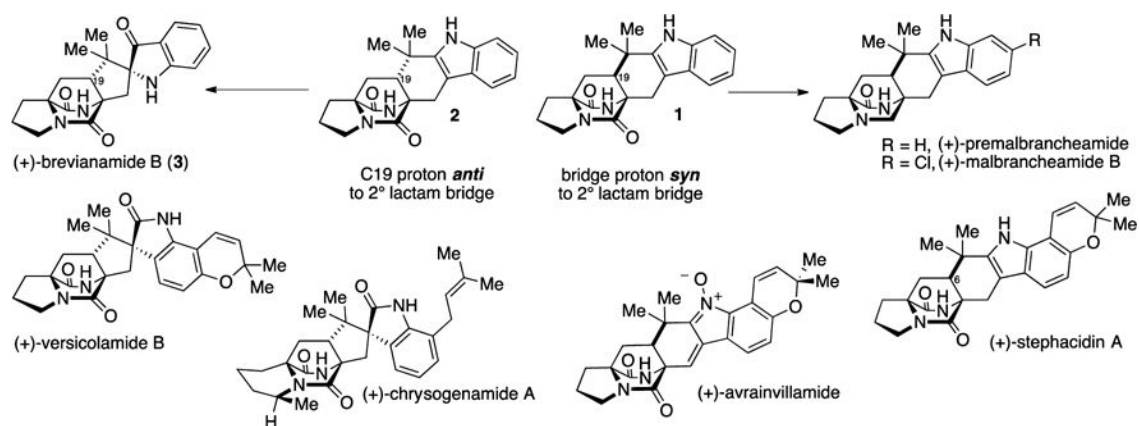
## Acknowledgments

We thank Professor Robert M. Williams (Colorado State University) for authentic samples of **1** and **2**. We acknowledge primary support from the National Institutes of Health (R15 GM107702 to J.R.S.). The donors of the ACS Petroleum Research Fund supported early aspects of this work. Support was also provided by the Camille and Henry Dreyfus Foundation (Henry Dreyfus Teacher–Scholar Award to J.R.S.). The NSF MRI provided funds for the acquisition and upgrade of a 400 MHz NMR Spectrometer (Award No. 1337295).

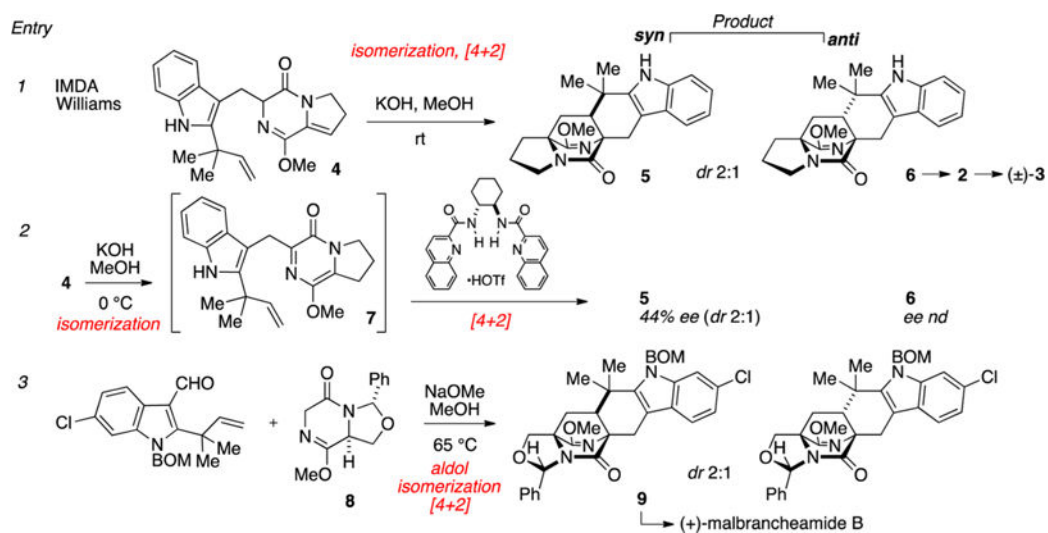
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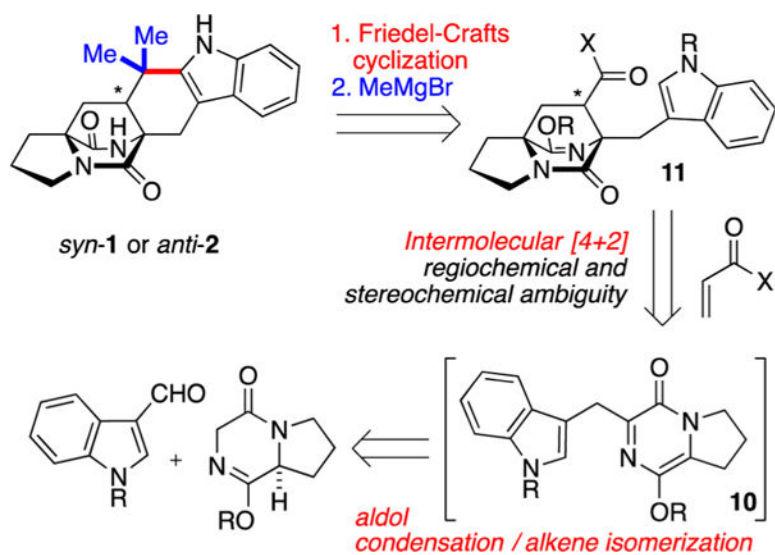
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**Figure 1.**  
[2.2.2]Diazabicyclic natural products with *syn* and *anti* fusion.

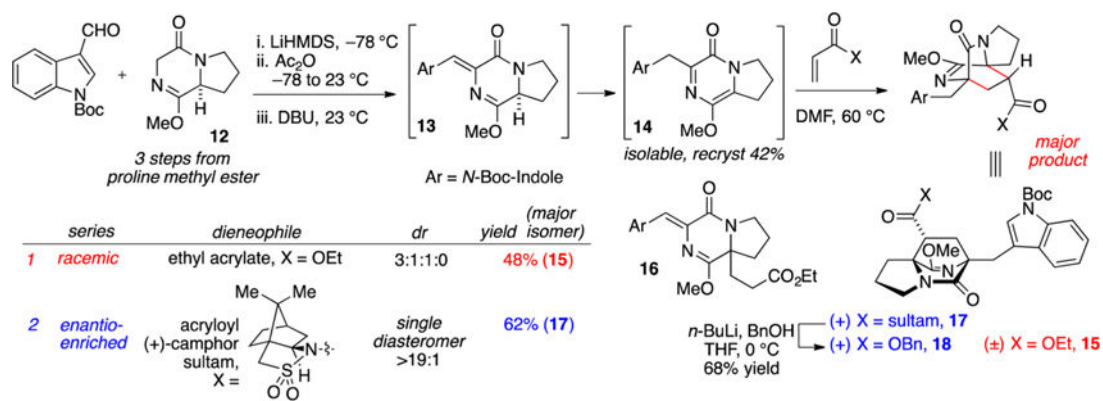


**Figure 2.** Intramolecular Diels–Alder approaches to the formation of [2.2.2]diazabicyclic structures.

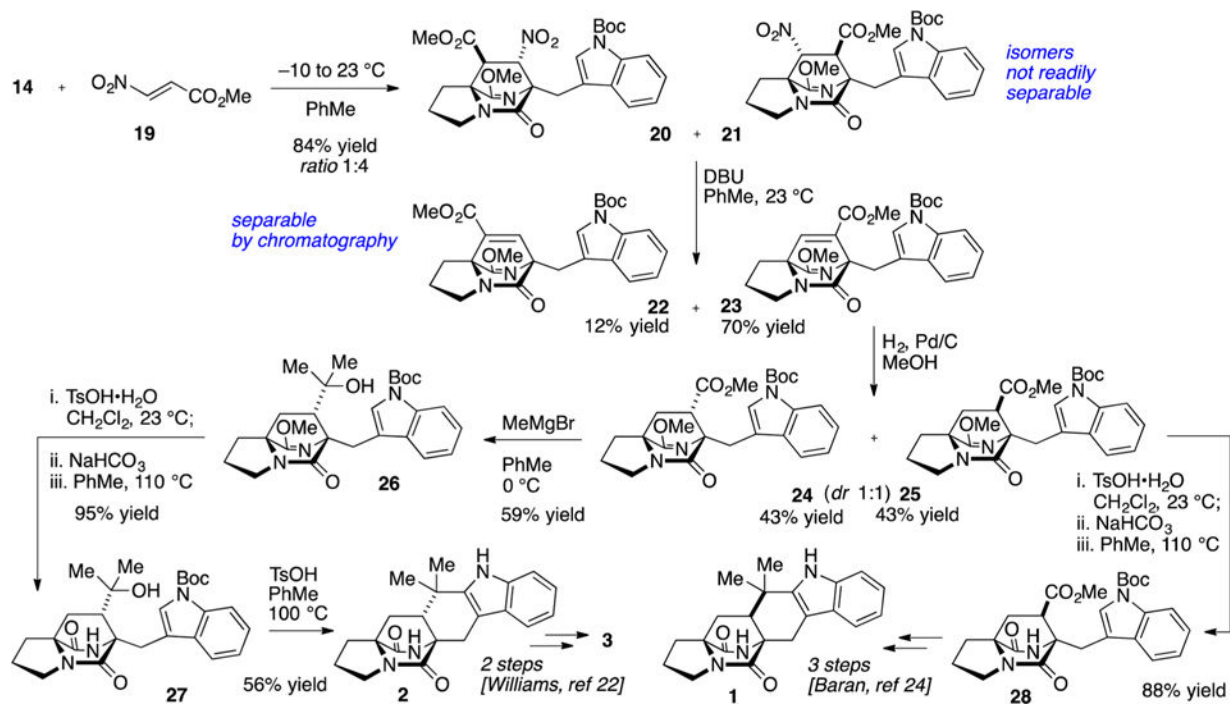


**Scheme 1.**  
Retrosynthesis Featuring an Intermolecular [4 + 2] Reaction



**Scheme 2.**

Intermolecular Diels–Alder Cycloaddition with Acrylate Dienophiles



**Scheme 3.**  
Cycloaddition with Nitroacrylate and Formal Synthesis of Brevianamide B and Premalbrancheamide