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Further Investigation of the Intermolecular Diels-Alder Cycloaddition for the Synthesis of Bicyclo[2.2.2]diazaoctane Alkaloids

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Abstract

The convergent synthesis of bicyclo[2.2.2]diazaoctane structures using an intermolecular Diels–Alder cyclo-addition between a pyrazinone and commercially available fumarate or maleate precursors is reported. High reactivity and stereoselection is observed with both dienophile substrates. Structure validation was achieved by conversion of cycloadducts into known [2.2.2]diazabicyclic compounds or into crystalline derivatives suitable for X-ray analysis. The cycloadduct derived from reaction of pyrazinone and maleic anhydride underwent selective anhydride ring opening and intersected an established precursor in the synthesis of brevianamide B.

Graphical Abstract

Brevianamide B and stephacidin A are two of the most iconic natural products in the bicyclo[2.2.2]diazaoctane family (Figure 1). Brevianamide B was among the first isolated metabolites to reveal the [2.2.2]diazabicyclic architecture.¹ It possesses the *anti*-stereochemistry at C19 and a spirocyclic indoline ring system.² In contrast, stephacidin A displays the *syn*-configuration at the [2.2.2]bicyclo ring juncture, a linearly fused ring system, and contains higher oxidation state chromenindole.³ Stephacidin A is a potent cytotoxic agent and has been one of the most targeted members of this natural product family for total synthesis.⁴ These stereochemical and structural differences between these two examples are representative of the family in general.²

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Notes

The authors declare no competing financial interest.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b02403.

Spectroscopic data (¹H NMR and ¹³C NMR) for all new compounds as well as known compounds 14 and 20 (PDF)

X-ray crystallographic data for compound 11 (CIF)

Studies into the isolation,⁵ biosynthesis,⁶ and synthesis⁷ of prenylated indole alkaloids that possess the bicyclo[2.2.2]-diazaoctane architecture remain an active area of research.

New methods for the synthesis of bicyclo[2.2.2]diazaoctane natural products continue to be revealed,⁸ including the recent development an organocatalyzed Michael addition strategy, the first catalytic enantioselective approach to these molecules.⁹ The biomimetic synthesis strategy pioneered by Williams remains a leading tool for construction of molecules in this natural product family and has provided the foundation to understand the intramolecular hetero-Diels–Alder cycloaddition of pyrazinone intermediates.^{7,10}

Investigation of the intermolecular Diels–Alder reaction of pyrazinone intermediates offer a convergent complementary method for the synthesis of bicyclo[2.2.2]diazaoctane architectures that is competitive with both intramolecular cyclo-addition strategies as well as other methods to assemble the key scaffold. Our preliminary efforts in this area revealed several insights and trends regarding the reactivity, regioselectivity, and stereoselectivity of the intermolecular cycloaddition of pyrazinone intermediates.¹¹ Three insights are summarized: (1) Intermolecular cycloaddition favors normal electron demand conditions and proceeds readily with dienophiles bearing electron-withdrawing groups. As an example, cyclo-addition of pyrazinone 1 with acrylate precursors is complete in 8 h at 60 °C in DMF (Scheme 1; eq 1). Using the more electron deficient nitroacrylate precursor 3, cycloaddition proceeded at a comparable rate at much lower temperatures (<0 °C) in a less polar solvent (eq 2). (2) The major products resulting from cycloaddition favor orientation of the most electron-withdrawing function in the *endo* orientation (See 2, 5; eq 1, eq 2). (3) The major cycloadduct regioisomer results from positioning the most withdrawing group distal to the indole nucleus (2, 5; eq 1, eq 2).

Armed with this knowledge set, we sought to confirm and extend our understanding of the intermolecular cycloaddition of pyrazinone intermediates and further focus our attention on operationally simple reactions that employ readily available and inexpensive starting materials. To this end, we decided to explore the cycloaddition of pyrazinone 1 (prepared in 4 steps and 80% yield from proline methyl ester¹²) with maleate and fumarate dienophile partners 6 and 7 (Scheme 1; eq 3, 4). By using dieneophiles 6 and 7 as substrates, we hoped to replicate the high reactivity of nitroacrylate as a dienophile (see eq 2) and achieve greater selectivity in the reaction. Because nitroacrylate 3 requires three steps¹³ to prepare often requiring use of either stoichiometric mercury salts¹⁴ or toxic N₂O₄ gas¹⁵ and is sensitive and prone to polymerization, we anticipated that the overall efficiency and practicality of an intermolecular Diels–Alder synthetic route to [2.2.2]diazabicyclic cycloadducts could be improved by using the ubiquitous maleate and fumarate starting materials.

The [4+2] cycloaddition of pyrazinone 1 with dimethyl fumarate (6) proceeded readily in toluene at room temperature and afforded a single diastereomer of cycloadduct 8b (dr >20:1) (Scheme 1; eq 3). The structure of cycloadduct 8b was confirmed by X-ray analysis¹⁶ on the derived lactam 11, which was prepared by hydrolysis of the lactim ether to the intermediate ammonium salt 10 (Scheme 2). On basification and warming, intermediate 10 re-established the [2.2.2]bicyclic architecture found in 11 in preference to 5-exo attack of the pendant amine at the alternative carboxyl and formation of a [3.2.1]bicyclic scaffold. We believe that

the observed high selectivity for 8b in the cycloaddition is rationalized by orientation of the carboxyl group located distal to the indole nucleus in the *endo* transition state, which minimizes developing nonbonding interactions with the pyrrolidine ring. Additionally, the necessary *exo* orientation of the carboxyl oriented adjacent to the indole nucleus in 8b appears to avoid an eclipsing *syn* pentane interaction with the aryl residue in a fashion similar to the observed solid state X-ray structure depicted on the lactam derivative 11 (Scheme 2).

Cycloaddition of the pyrazinone 1 with maleic anhydride proceeded readily at room temperature and provided an 8:1 *endo/exo* ratio of cycloadducts 9a and 9b in 58% and 7% isolated yields (Scheme 1). Lowering the reaction temperature below 0 °C did not noticeably improve the selectivity; however, increasing the temperature to 50 °C resulted in diminished selectivity and cycloadducts 9a and 9b were obtained as a 6:1 ratio.

We turned our attention to converting both the C6-*syn* fused (stephacidin numbering) adduct 8b and the C6-*anti* configured product 9a to the decarboxylated known structures 13 and 20, intermediates that have been intercepted in the course of previous syntheses of the [2.2.2]diazabicyclic structure C18-*oxo*-premalbrancheamide (14) and the natural product brevianamide B (Scheme 2). We were unable to determine conditions that permitted selective carboxyl functionalization on fumarate adduct 8b; formation of intermediate 12 (and subsequent elaboration to 13) could not be achieved in our hands. However, with maleic anhydride cycloadduct 9a we observed a general preference for regioselective nucleophilic anhydride ring opening (Scheme 2).

Excess methanol and DMAP showed a propensity for attack of the alcohol at the carbonyl distal to the indole nucleus in 9a (Scheme 2). The carboxylic acid functional group in the derived ring-opened product (not shown) was incompatible with the acid sensitive lactim ether functionality. Therefore, direct in situ esterification of the intermediate carboxylate with BnBr was performed, rendering the bis-ester product stable and permitting isolation of predominantly ester 15 in preference to the isomeric product 16 (ratio 9:1). The regioselectivity in the anhydride opening can be rationalized from a conformer where the indole shields the proximal carbonyl of the anhydride in 9a. Modified reaction conditions using lithio benzyl alcohol for anhydride opening, followed by esterification with TMS-diazomethane, gave the opposite selectivity. In this way, a 1:7 ratio of 15 to 16 could be obtained. With the differentiated ester functions in 16, selective excision of the benzyl ester to give monoester compound 19 was achieved in four synthetic operations. This sequence was accomplished by removal of the acid-sensitive lactim ether and installation of the derived lactam in 17. The benzyl ester in 17 was then converted to the intermediate carboxylic acid (H₂, Pd/C) in preparation for conversion to an active ester capable of undergoing radical decarboxylation. We found that esterification with N-hydroxyphthalimide (NHPI) to give product 18 was an easy reaction to execute, provided good yield (80%), and the product was stable to both the ensuing purification on silica gel as well as long-term storage.¹⁷ After months in storage at 4 °C, the NHPI ester 18 showed no discernible hydrolysis or other decomposition. Most importantly, phthalimido ester 18 possessed the desired reactivity to permit radical hydrodecarboxylation. In our hands, decarboxylation to 19 could not be achieved with visible light photoinitiated¹⁸ conditions,

however, 18 was cleanly decarboxylated using thermally initiated conditions (AIBN in MeCN at 80 °C) with *t*-butyl thiol and Hantzsch ester.¹⁹ The resulting hydrodecarboxylation product 19 was converted into the anti-fused structure 20, a known compound and frequently employed intermediate in the synthesis of brevianamide B.²⁰ We found that consumption of the ester in 19 with MeMgBr in toluene to the derived tertiary alcohol (not isolated), followed by acidification and warming the reaction mixture led directly to Friedel–Crafts cyclization of the indole nucleus and direct formation of known compound 20 in 61% yield. Material prepared in this manner was verified by comparison to physical and spectral properties of previously synthesized material.^{11,21} Using established reactions, product 20 has previously been converted into brevianamide B in two steps (via oxidation and pinacol rearrangement).^{4e,22} As such, the synthesis of 20 represents a formal total synthesis of the natural product.

In summary, we have reported a synthetically useful variant for stereoselective intermolecular Diels–Alder cycloaddition for the synthesis of [2.2.2]diazabicyclic structures using abundant dienophile components derived from fumaric and maleic acids. These cycloaddition reactions serve as additional examples that support the fundamental understanding of the intermolecular cycloaddition of pyrazinone intermediates. Subsequent transformations on the derived maleic anhydride cycloadduct established a synthetic path to a known compound previously prepared in the synthesis of the natural product brevianamide B. The chemistry described in this note provides a robust and operationally simple method for the synthesis of [2.2.2]diazabicyclic alkaloids and related derivatives.

EXPERIMENTAL SECTION

General Experimental Considerations.

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 Et₂O were degassed with argon and purified by passage through a column of molecular sieves and/or a bed of activated alumina. Dichloromethane was distilled from CaH₂ 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. ¹H NMR spectra were recorded on a 400 MHz spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 7.26 ppm) or tetramethylsilane (0.00 ppm). Proton-decoupled ¹³C NMR spectra were recorded on a 400 MHz spectrometer and are reported in ppm using solvent as an internal standard (CDCl₃ at 77.0 ppm). Mass spectra data analysis was obtained through positive electrospray ionization (ICR-MS w/NaCl). All compounds were judged to be homogeneous (>95% purity) by ¹H and ¹³C NMR spectroscopy unless otherwise noted as mixtures. The asterisk in the names for all new compounds indicates that the compound is present as a racemic mixture. Single crystal X-ray analysis was performed using graphite-monochromated Cu Kα radiation with a three-circle diffractometer. Initial space group determination was based on a matrix consisting of 120 frames. Structures were solved using intrinsic phasing. Least-squares

refinement for all structures was carried out on F². The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in riding positions and refined isotropically.

Dimethyl (6R*,7R*,8R*,8aR*)-6-((1-(*tert*-Butoxycarbonyl)-1H-indol-3-yl)methyl)-9-methoxy-5-oxo-2,3,5,6,7,8-hexahydro-1H-6,8a-(azenometheno)indolizine-7,8-dicarboxylate (8b**).**

A dry flask was charged with pyrazinone **1** (200 mg, 0.51 mmol) and dimethyl fumarate (146 mg, 1.01 mmol). The reaction flask was then flushed with N₂ gas (10 min) and PhMe (5 mL) was added and the vessel was repeatedly evacuated (40 Torr) and backfilled with N₂ gas. The reaction flask was covered in foil to exclude ambient light. After stirring at rt for 16 h, the reaction solution was concentrated in vacuo. The resulting residue contained a single cycloadduct **8b** (dr >20:1 as judged by ¹H NMR of the unpurified reaction mixture).

Purification of the residue by flash column chromatography on silica gel (gradient elution: 20% → 100% EtOAc in hexanes) afforded cycloadduct **8b** as a light yellow oil (240 mg, 88% yield): TLC (60% EtOAc in hexanes), R_f 0.28 (UV, CAM); IR (film) 1729, 1685, 1638, 1450, 1256, 1155, 1082, 1015 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 8.3 Hz, 1H), 7.77 (dd, *J* = 7 Hz, 0.9 Hz, 1H), 7.74 (s, 1H), 7.27 (td, *J* = 7.5 Hz, 1.2 Hz, 1H), 7.19 (td, *J* = 7.8 Hz, 1.2 Hz, 1H), 3.72 (s, 3H), 3.71 (s, 3H), 3.64 (s, 3H), 3.56 (m, 1H), 3.51 (m, 1H), 3.49 (d, *J* = 15.2 Hz, 1H), 3.26 (d, *J* = 15.2 Hz, 1H), 3.16 (d, *J* = 5.5 Hz, 1H), 3.03 (d, *J* = 5.5 Hz, 1H), 2.62 (m, 1H), 2.05 (m, 2H), 1.95 (m, 1H), 1.66 (s, 9H); ¹³C NMR (400 MHz, CDCl₃) δ 171.5, 170.8, 170.6, 169.5, 149.9, 132.2, 125.6, 123.8, 121.8, 120.8, 116.0, 114.8, 83.1, 68.5, 64.8, 54.9, 52.9, 52.5, 50.0, 43.5, 28.2, 28.1, 28.1, 27.1, 24.5; HRMS (ESI-ICR) *m/z*: [M+Na]⁺ Calcd for C₂₈H₃₃N₃O₈Na 562.2160; found 562.2162.

Dimethyl (6S*,7R*,8R*,8aS*)-6-((1-(*tert*-Butoxycarbonyl)-1H-indol-3-yl)methyl)-5,9-dioxohexahydro-1H-6,8a-(epiminomethano)indolizine-7,8-dicarboxylate (11**).**

A dry flask was charged with cycloadduct **8b** (275 mg, 0.51 mmol) and flushed with N₂ gas for 10 min, dissolved in CH₂Cl₂ (5 mL), and cooled to 0 °C. To the reaction flask was added

*p*TsOH·H₂O (115 mg, 0.61 mmol) in one lot. After stirring for 2 h at 0 °C, the reaction mixture was diluted with saturated aq NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (4 × 10 mL). The combined organic layers were washed with saturated aq NaCl (50 mL), dried with (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting residue was dissolved in toluene (5 mL) and stirred at 80 °C for 18 h. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (gradient elution: 40% → 100% EtOAc in hexanes) to afford lactam **11** as a pale yellow solid (250 mg, 94% yield): mp 96.8–97.9 °C; TLC (60% EtOAc in hexanes) R_f 0.28 (UV, CAM); IR (film) 3218, 1723, 1695, 1450, 1387, 1255, 1205, 1158, 1095 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.73 (s, 1H), 7.60 (d, *J* = 8.2 Hz, 1H), 7.36 (td, *J* = 8.2 Hz, 1.2 Hz, 1H), 7.28 (td, *J* = 7.4 Hz, 1.2 Hz, 1H), 5.85 (s, 1H), 3.83 (s, 3H), 3.71 (s, 3H), 3.69 (d, *J* = 5.3 Hz, 1H), 3.61 (d, *J* = 15.6 Hz, 1H), 3.61 (m, 1H), 3.58 (m, 1H), 3.44 (d, *J* = 4.7 Hz, 1H), 3.20 (d, *J* = 15.7 Hz, 1H), 2.75 (m, 1H), 2.09 (m, 2H), 1.98 (m, 1H), 1.69 (s, 9H); ¹³C NMR (400 MHz, CDCl₃) δ 170.4, 169.8, 169.5, 166.3, 149.4, 135.3, 130.7, 126.3, 125.0, 123.2, 118.2, 115.6, 112.0, 84.0, 68.0, 62.9, 53.0, 52.9, 52.4, 51.7, 44.3, 28.5, 28.1, 24.3, 24.1; HRMS (ESI-ICR) *m/z*: [M+Na]⁺ Calcd for C₂₇H₃₁N₃O₈Na 548.2003; found 548.2006. A single crystal of **11** was obtained by slow evaporation from Et₂O and its structure was determined by X-ray crystallographic analysis (see Supporting Information).

***tert*-Butyl 3-(((3aS*,4R*,9aR*,9bR*)-10-methoxy-1,3,5-trioxo-1,3,3a,8,9,9b-hexahydro-7H-4,9a-(azenometheno)furo-[3,4-g]indolizin-4(5H)-yl)methyl)-1H-indole-1-carboxylate (9a) and *tert*-Butyl 3-(((3aR*,4R*,9aR*,9bS*)-10-methoxy-1,3,5-trioxo-1,3,3a,8,9,9b-hexahydro-7H-4,9a-(azenometheno)furo-[3,4-g]indolizin-4(5H)-yl)methyl)-1H-indole-1-carboxylate (9b).**

A dry flask was charged with pyrazinone **1** (200 mg, 0.51 mmol) and maleic anhydride (98 mg, 1.01 mmol) and flushed with N₂ gas for 10 min. Toluene (10 mL) was added and the vessel was repeatedly evacuated (40 Torr) and backfilled with N₂ gas. The reaction flask was covered in foil to exclude ambient light. After stirring for 16 h, the reaction solution was concentrated *in vacuo* to give a pale yellow solid containing the two diastereomeric cycloadducts **9a** and **9b** in an 8:1 ratio (as judged by ¹H NMR of the unpurified reaction mixture). The mixture was purified by flash column chromatography on silica gel (gradient elution: 20% → 100% EtOAc in hexanes) to afford **9a** (144 mg, 58% yield) and **9b** (18 mg, 7% yield) as pale yellow solids. Data for **9a**: mp. 126.4–128.2 °C; TLC (60% EtOAc in hexanes) R_f 0.23 (UV, CAM); IR (film) 1781, 1688, 1631, 1450, 1368, 1252, 1216, 1155, 1076, cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.06 (d, *J* = 7 Hz, 1H), 7.83 (dd, *J* = 7 Hz, 1.6 Hz, 1H), 7.74 (s, 1H), 7.26 (td, *J* = 7.1 Hz, 1.6 Hz, 1H), 7.23 (td, *J* = 7.4 Hz, 1.6 Hz, 1H), 3.88 (dd, *J* = 14.5 Hz, 0.8 Hz, 1H), 3.70 (s, 3H), 3.62 (d, *J* = 14.5 Hz, 1H), 3.60 (d, *J* = 8.6 Hz, 1H), 3.45 (m, 1H), 3.38 (d, *J* = 8.2 Hz, 1H), 3.35 (m, 1H), 2.68 (dt, *J* = 14.1 Hz, 7.4 Hz, 1H), 2.48 (dt, *J* = 14.1 Hz, 7.1 Hz, 1H), 2.03 (m, 2H), 1.67 (s, 9H); ¹³C NMR (400 MHz, CDCl₃) δ 169.5, 168.3, 167.6, 167.2, 149.9, 134.8, 132.0, 126.2, 123.8, 122.0, 120.7, 116.0,

114.8, 83.2, 69.2, 65.4, 55.4, 51.2, 47.6, 43.9, 28.2, 27.2, 25.7, 23.9; HRMS (ESI-ICR) m/z : $[M+Na]^+$ Calcd for $C_{26}H_{27}N_3O_7Na$ 516.1741; found 516.1740.

Data for 9b: mp 114.3–115.5 °C; TLC (60% EtOAc in hexanes) R_f 0.33 (UV, CAM); IR (film) 1780, 1683, 1451, 1368, 1254, 1217, 1154, 1076, cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 7.8 Hz, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.79 (s, 1H), 7.29 (td, J = 7.8 Hz, 1.2 Hz, 1H), 7.21 (td, J = 7.5 Hz, 0.9 Hz, 1H), 3.76 (d, J = 14.8 Hz, 1H), 3.76 (s, 3H), 3.59 (m, 1H), 3.57 (d, J = 15.3 Hz, 1H), 3.45 (d, J = 9.4 Hz, 1H), 3.29 (m, 1H), 3.12 (d, J = 9.4 Hz, 1H), 2.69 (m, 2H), 2.11 (m, 1H), 1.89 (m, 1H), 1.65 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 171.8, 169.2, 167.8, 167.0, 149.7, 136.4, 131.7, 131.7, 126.1, 124.1, 122.0, 121.2, 115.3, 114.8, 83.5, 68.3, 65.8, 55.6, 48.0, 47.6, 44.4, 28.1, 26.0, 25.1, 24.6; HRMS (ESI-ICR) m/z : $[M+Na]^+$ Calcd for $C_{26}H_{27}N_3O_7Na$ 516.1741; found 516.1738.

7-Benzyl 8-methyl (6R*,7R*,8S*,8aR*)-6-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-9-methoxy-5-oxo-2,3,5,6,7,8-hexahydro-1H-6,8a-(azenometheno)indolizine-7,8-dicarboxylate (15) and 8-Benzyl 7-methyl (6R*,7R*,8S*,8aR*)-6-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-9-methoxy-5-oxo-2,3,5,6,7,8-hexahydro-1H-6,8a-(azenometheno)indolizine-7,8-dicarboxylate (16).

To a flame-dried reaction flask under N_2 was added $BnOH$ (232 μL , 2.23 mmol) and THF (2 mL). The reaction vessel was then cooled to $-78^\circ C$, and a solution of $n-BuLi$ (2.2 M in hexanes, 932 μL , 2.03 mmol) was added and stirred for 15 min at $-78^\circ C$. The $LiOBn$ solution was transferred via syringe to a second flask containing cycloadduct 9a (1.00 g, 2.03 mmol) in THF (17 mL). The reaction was stirred at $-78^\circ C$ for 30 min, diluted with 20 mL of saturated NH_4Cl , and extracted with CH_2Cl_2 (4×25 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The resulting solid was immediately dissolved in $PhMe$ (20 mL) and cooled to $0^\circ C$ and a solution of TMS-diazomethane (2 M in hexanes, 1.22 mL, 2.44 mmol) and MeOH (2 mL) were introduced. The reaction was stirred at $0^\circ C$ for 30 min and an additional portion of TMS-diazomethane (2 M in hexanes, 0.61 mL, 1.22 mmol) was added. The reaction stirred at $0^\circ C$ for an additional 30 min (1 h total) and concentrated *in vacuo* to afford a mix of compounds 15 and 16 in a 1:7 ratio (as judged by the unpurified 1H NMR). The reaction mixture was purified by flash column chromatography on silica gel (gradient elution: 20% $\rightarrow$ 100% EtOAc in hexanes) to afford pure 16 (599 mg, 48% yield) and 15 (126 mg, 10% yield) both as amorphous solids.

Data for 15: TLC (80% EtOAc in hexanes) R_f 0.59 (UV, CAM); IR (film) 1780, 1730, 1679, 1451, 1250, 1155 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 6.9 Hz, 1H), 7.74 (s, 1H), 7.69 (d, J = 7.9 Hz, 1H), 7.25 (m, 7H), 5.01 (d, J = 12.1 Hz, 1H), 4.72 (d, J = 12.5 Hz, 1H), 3.76 (s, 3H), 3.56 (d, J = 14.8 Hz, 1H), 3.54 (d, J = 11.1 Hz, 1H), 3.45 (m, 1H), 3.38 (s, 3H), 3.29 (m, 1H), 3.25 (d, J = 14.8 Hz, 1H), 3.17 (d, J = 11.1 Hz, 1H), 2.83 (m, 1H), 1.92 (m, 3H), 1.63 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.2, 170.0, 169.7, 169.1, 149.9,

135.1, 132.2, 128.5, 128.4, 126.0, 123.6, 121.9, 120.6, 116.2, 114.7, 83.0, 68.5, 66.9, 64.9, 54.9, 53.6, 51.8, 49.9, 43.5, 28.8, 28.2, 27.4, 24.5. HRMS (ESI-ICR) m/z : $[M+Na]^+$ Calcd for $C_{34}H_{37}N_3O_8Na$ 638.2473; found 638.2475.

Data for **16**: TLC (60% EtOAc in hexanes) R_f 0.49 (UV, CAM); IR (film) 1779, 1726, 1680, 1451, 1256, 1155 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 7.4 Hz, 1H), 7.76 (s, 1H), 7.74 (d, 1H), 7.34 (m, 5H), 7.21 (m, 2H), 5.06 (d, J = 12.1 Hz, 1H), 4.99 (d, J = 12.1 Hz, 1H), 3.75 (s, 3H), 3.53 (d, J = 14.4 Hz, 1H), 3.49 (d, J = 11.0 Hz, 1H), 3.45 (m, 1H), 3.29 (d, 1H), 3.28 (m, 1H), 3.27 (s, 3H), 3.21 (d, J = 11 Hz, 1H), 2.82 (m, 1H), 1.92 (m, 3H), 1.63 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 170.0, 169.4, 169.2, 132.1, 132.0, 131.9, 128.6, 128.4, 126.0, 123.6, 121.9, 120.4, 116.2, 114.7, 68.5, 67.1, 64.9, 54.8, 53.9, 51.6, 49.6, 43.5, 28.9, 28.2, 27.4, 24; HRMS (ESI-ICR) m/z : $[M+H]^+$ Calcd for $C_{34}H_{38}N_3O_8$ 616.2653; found 616.2646.

8-Benzyl 7-methyl (6S*,7R*,8S*,8aS*)-6-((1-(tert-Butoxycarbonyl)-1H-indol-3-yl)methyl)-5,9-dioxohexahydro-1H-6,8a-(epiminomethano)indolizine-7,8-dicarboxylate (17).

A dry reaction flask was charged with lactim ether 16 (261 mg, 0.424 mmol) and flushed with N_2 gas for 10 min, dissolved in CH_2Cl_2 (2.1 mL), and cooled to 0 °C. To the reaction flask was added pTsOH· H_2O (85 mg, 0.446 mmol), and the reaction was stirred for 7 h at 0 °C. The reaction mixture was diluted with saturated aq $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (4 × 10 mL). The combined organic layers were washed with saturated aq $NaCl$ (40 mL), dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The resulting product was dissolved in toluene (2.1 mL) and stirred at 80 °C for 18 h. The solution was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel (gradient elution: 40% → 100% EtOAc in hexanes) to afford lactam 17 (195 mg, 77% yield) as a light yellow amorphous solid: TLC (60% EtOAc in hexanes) R_f 0.47 (UV, CAM); IR (film) 1695, 1458, 1257, 1153, 1079 cm^{-1} ; 1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.9 Hz, 1H), 7.68 (s, 1H), 7.66 (d, J = 3.6 Hz, 1H), 7.31 (m, 8H), 5.98 (s, 1H), 5.12 (d, J = 12.1 Hz, 1H), 5.08 (d, J = 12.1 Hz, 1H), 3.67 (d, J = 14.5 Hz, 1H), 3.56 (m, 1H), 3.44 (m, 1H), 3.40 (s, 3H), 3.35 (d, J = 8.2 Hz, 1H), 3.33 (d, J = 14.5 Hz, 1H), 2.79 (m, 1H), 1.97 (m, 1H), 1.85 (m, 1H), 1.67 (s, 9H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 169.1, 169.0, 168.4, 167.2, 149.5, 135.1, 134.8, 131.0, 128.7, 128.6, 126.9, 124.6, 122.9, 118.7, 115.3, 112.8, 83.7, 68.0, 67.5, 63.2, 52.4, 51.9, 48.6, 44.4, 28.4, 28.2, 24.3, 23.4; HRMS (ESI-ICR) m/z : $[M+Na]^+$ Calcd for $C_{33}H_{35}N_3O_8Na$ 624.2316; found 624.2317.

(6S*,7R*,8S*,8aS*)-6-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-7(methoxycarbonyl)-5,9-dioxohexahydro-1H-6,8a-(epiminomethano)indolizine-8-carboxylic acid.

Lactam **17** (364 mg, 0.607 mmol) was dissolved in EtOAc (6 mL) at rt, and 10% Pd/C (65 mg) was added. One balloon of H₂ gas was used to sparge the reaction mixture (10 min), and another balloon of H₂ gas was left above the reaction to maintain an atmosphere of H₂. The reaction mixture was stirred at rt for 1 h, flushed with N₂, filtered through Celite, and the filter pad was washed with additional portions of EtOAc (3 × 10 mL). The filtrate was concentrated *in vacuo* to afford the derived carboxylic acid (285 mg, 92% yield) as a white solid that was used without further purification: TLC (5% MeOH in CHCl₃ with 1% AcOH) R_f 0.22 (UV, CAM); IR (film) 3366, 1736, 1680, 1453, 1257, 1158, 1081, cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 7.4 Hz, 1H), 7.67 (s, 1H), 7.29 (m, 2H), 6.57 (s, 1H), 6.57 (br s, 1H), 3.68 (d, *J* = 14.8 Hz, 1H), 3.65 (s, 3H), 3.51 (m, 2H), 3.45 (d, *J* = 14.5 Hz, 1H), 3.40 (d, *J* = 11.3 Hz, 1H), 3.36 (d, *J* = 11.4 Hz, 1H), 2.77 (m, 1H), 2.00 (m, 3H), 1.67 (s, 9H); ¹³C NMR (400 MHz, CDCl₃) δ 169.6, 167.3, 149.6, 135.1, 131.1, 126.9, 124.5, 122.8, 119.0, 115.3, 113.0, 83.8, 68.2, 63.4, 52.6, 52.3, 48.4, 44.5, 28.3, 28.2, 24.3, 23.6; HRMS (ESI-ICR) *m/z*: [M+H]⁺ Calcd for C₂₆H₃₀N₃O₈ 512.2027; found 512.2030.

8-(1,3-Dioxoisindolin-2-yl) 7-methyl (6S*,7R*,8S*,8aS*)-6-((1-(tert-butoxycarbonyl)-1H-indol-3-yl)methyl)-5,9-dioxohexahydro-1H-6,8a-(epiminomethano)indolizine-7,8-dicarboxylate (18**).**

A dry flask was charged with carboxylic acid (100 mg, 0.196 mmol), flushed with N₂ gas for 10 min, dissolved in CH₂Cl₂ (4 mL), and the vessel was cooled to 0 °C. EDC (56 mg, 0.294 mmol), DMAP (5 mg, 0.039 mmol), and N-hydroxylphthalimide (NHPI) (48 mg, 0.29 mmol) were successively added to the flask and the reaction was stirred and allowed to warm to rt over 6 h. The reaction mixture was diluted with 0.1 M HCl (20 mL) and extracted

with CH₂Cl₂ (3 × 15 mL). The combined organic layers were washed with saturated aq NaHCO₃ (25 mL), saturated aq NaCl (25 mL), dried (Na₂SO₄), filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel (gradient elution: 10% → 80% EtOAc in hexanes) to afford **18** (104 mg, 80% yield) as a colorless solid: mp 162.4–164.3 °C; TLC (60% EtOAc in hexanes) R_f 0.64 (UV, CAM); IR (film) 1814, 1784, 1743, 1700, 1452, 1257, 1155, 1080 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.14 (d, *J*=7.8 Hz, 1H), 7.90 (m, 2H), 7.83 (m, 2H), 7.69 (s, 1H), 7.59 (dd, *J*=6.7 Hz, 1.2 Hz, 1H), 7.33 (td, *J*=7.4 Hz, 1.5 Hz, 1H), 7.29 (td, *J*=7 Hz, 1.2 Hz, 1H), 5.96 (s, 1H), 3.88 (s, 3H), 3.78 (d, *J*=14.8 Hz, 1H), 3.60 (m, 1H), 3.56 (d, *J*=5.9 Hz, 1H), 3.48 (m, 1H), 3.47 (d, *J*=5.8 Hz, 1H), 3.29 (d, *J*=14.8 Hz, 1H), 2.90 (ddd, *J*=13.3 Hz, 7.9 Hz, 4.7 Hz, 1H), 2.42 (td, *J*=14.1 Hz, 8.2 Hz, 1H), 2.15 (m, 1H), 1.96 (m, 1H), 1.67 (s, 9H); ¹³C NMR (400 MHz, CDCl₃) δ 170.0, 169.3, 167.4, 166.3, 149.5, 135.2, 135.1, 134.2, 130.9, 128.7, 127.1, 124.7, 124.2, 123.4, 123.1, 118.3, 115.5, 112.3, 83.9, 68.5, 63.6, 52.9, 50.7, 47.8, 45.1, 28.2, 26.6, 24.1, 23.2; HRMS (ESI-ICR) *m/z*: [M+H]⁺ Calcd for C₃₄H₃₃N₄O₁₀ 657.2191; found 657.2183.

Methyl (6S*,7R*,8aS*)-6-((1-(tert-Butoxycarbonyl)-1H-indol-3-yl)methyl)-5,9-dioxohexahydro-1H-6,8a-(epiminomethano)-indolizine-7-carboxylate (19**).**

A flame-dried flask was charged with phthalimidoyl ester **18** (36 mg, 0.054 mmol), flushed with N₂ gas for 10 min, and dissolved in CH₃CN (1 mL). To the reaction vessel was added Hantzsch ester (Diethyl 1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylate, 15 mg, 0.059 mmol), AIBN (1 mg, 0.0054 mmol), and *t*-BuSH (30 μL, 0.268 mmol), and the reaction vessel was fitted with a reflux condenser and heated to 80 °C with stirring for 1 h. After cooling to rt, the reaction mixture was diluted with saturated aq NaHCO₃ (10 mL) and extracted with CH₂Cl₂ (3 × 10 mL). The combined organic layers were washed with saturated aq NaCl (20 mL), dried over anhydrous Na₂SO₄, filtered, and concentrated *in vacuo*. The resulting residue was purified by flash column chromatography on silica gel (gradient elution: 20% → 100% EtOAc in hexanes) to afford **19** (15 mg, 60% yield) as a colorless oil. The structure of **19** was validated by comparison to known material: TLC (80% EtOAc in hexanes) R_f 0.46 (UV, CAM); IR (film) 1786, 1745, 1733, 1452, 1256, 1159, 1084 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.13 (d, *J*=7.9 Hz, 1H), 7.64 (s, 1H), 7.57 (dd, *J*=7.1 Hz, 1.2 Hz, 1H), 7.32 (td, *J*=7.1 Hz, 1.2 Hz, 1H), 7.27 (td, *J*=7.4 Hz, 1.2 Hz, 1H), 5.83 (s, 1H), 3.76 (s, 3H), 3.70 (d, *J*=14.9 Hz, 1H), 3.51 (d, *J*=15.2 Hz, 1H), 3.51 (m, 1H), 3.15 (d, *J*=14.9 Hz, 1H), 3.05 (dd, *J*=10.4 Hz, 4.9 Hz, 1H), 2.73 (dt, *J*=13.3 Hz, 6.7 Hz, 1H), 2.28 (dd, *J*=13.5 Hz, 10.3 Hz, 1H), 2.18 (dd, *J*=13.7 Hz, 5.1 Hz, 1H), 2.00 (m, *J*=7.0 Hz, 2H), 1.80 (dt, *J*=13.3 Hz, 7.0 Hz, 1H), 1.67 (s, 9H); ¹³C NMR (400 MHz, CDCl₃) δ 171.9,

171.6, 167.2, 131.0, 126.8, 124.7, 123.0, 118.3, 115.5, 112.9, 83.8, 66.7, 63.9, 53.4, 52.3, 46.0, 44.3, 36.1, 28.9, 28.2, 24.3, 23.5; HRMS (ESI-ICR) m/z : $[M+H]^+$ Calcd for $C_{25}H_{30}N_3O_6$ 468.2129; found 468.2127.

12,12-Dimethyl-2,3,11,12,12a,13-hexahydro-1H,5H,6H-5a,13a-(epiminomethano)indolizino[7,6-b]carbazole-5,14-dione (20).

A flame-dried flask was charged with ester **19** (11 mg, 0.024 mmol), with a reflux condenser, and flushed with N_2 gas for 10 min. Following dissolution of the starting material in toluene (1.0 mL) and cooling to 0 °C, a solution of MeMgBr (54 μ L, 0.075 mmol, 1.4 M in THF) was introduced. The reaction was stirred for 1 h at 0 °C and pTsOH·H₂O (19 mg, 0.096 mmol) was added and the reaction vessel was heated to 110 °C. After heating for 3 h, the reaction was cooled to RT, diluted with saturated aqueous NaHCO₃ (10 mL), and extracted with EtOAc (3 $\times$ 10 mL). The combined organic layers were washed with saturated NaCl (40 mL), dried (Na₂SO₄), filtered, and concentrated in vacuo. The resulting residue was purified by flash chromatography on silica gel (50% to 100% EtOAc in hexanes) to afford **20** (5 mg, 61% yield) as a white powder. The spectral data for **20** was identical with material previously prepared in our laboratory¹¹ and a sample provided by R. M. Williams (Colorado State University) as well as data reported by Simpkins.¹⁹

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Representative bicyclo[2.2.2]diazaoctane metabolites with *anti* or *syn* configuration.

Scheme 1.

Intermolecular Cycloaddition of Pyrazinone Precursors with Electron-Deficient Dienophiles

Scheme 2.

Structure Validation of Cycloadducts and Formal Synthesis of Brevianamide B