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Access to the Surugatoxin Alkaloids: Chemo-, Regio-, and Stereoselective Oxindole Annulation

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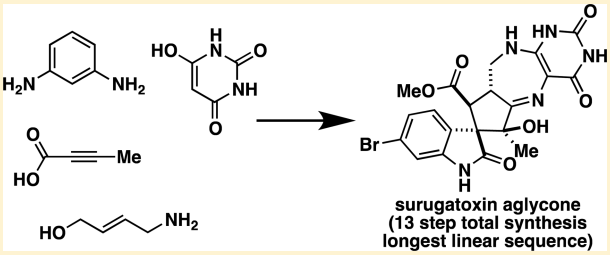
Supporting Information

ABSTRACT: We report the synthesis of an aglycone of the surugatoxin family. The synthesis of this surugatoxin core was accomplished in 13 steps using a new oxindole annulation and late-stage enamine oxidation.



INTRODUCTION

The surugatoxins—prosurugatoxin (**1**), neosurugatoxin (**2**), and surugatoxin (**3**) (Figure 1A)—are a family of spirooxindole alkaloids that have demonstrated nanomolar activity for neuronal nicotinic acetylcholine receptors.[1] These pentacyclic marine natural products are composed of (5,7) or (6,6) C,D rings conjoining spirooxindole dioxopyrimidines. The (5,7) C,D ring congeners, **1** and **2**, were originally obtained in quantities of 39.0 and 5.0 mg, respectively, by extracting 1.0 kg of midgut gland tissue from the Japanese ivory shell (*Babylonia japonica*) from Suruga Bay (Japan).[2] A Gram-positive coryneform bacterium[3] was identified as the source of these surugatoxins; however, the toxins have not been detected since 1981, and all existing supplies have been depleted.

Inoue and co-workers have prepared **1** (27 steps, 0.2% yield, 3.2 mg, racemic),[4] **2** (27 steps, 0.5% yield, 1.4 mg, enantiopure),[5] and **3** (25 steps, 0.4% yield, 24.0 mg, enantiopure).[6] Additionally, a previous study confirmed similar bioactivity in an ethyl ester analogue to prosurugatoxin.[7] With advanced intermediate **4** as a guide (available in 13−17 steps),[8] their syntheses of **1** and **2** use a late-stage retroaldol−aldol sequence to generate the desired spirocycle and vicinal stereocenter (C7, C9) in low yield after separation from the other three diastereomers.[4,5] Although not amenable to analogue production and inadequate for the production of useful quantities for biological testing, the Inoue approach converts the (5,7) C,D ring system to the (6,6) system and has established the former as a progenitor for all family members. The contiguous stereoarray in the C ring with an oxidation-sensitive dioxopyrimidine poses a significant synthetic challenge. We describe a concise, direct synthesis of the surugatoxin aglycone **5** to re-establish supplies of this fascinating alkaloid family.

RESULTS

Retrosynthetically the surugatoxin aglycone **5** arises from spirooxindole **6** via a stereoselective enamine oxidation to establish the critical C9 quaternary center (Figure 1B). Spirooxindole **6** is the crucial retron and can be assembled from bicyclic cyclopentenone **7** via a chemo-, regio-, and stereoselective intermolecular oxindole annulation. The annulation provides a single diastereomer at C7 and streamlines the preparation of the C ring.

The establishment of the spirooxindole quaternary center at C7 was crucial to the synthesis. We surmised that conjugate addition[9] in **9** would provide high stereoselectivity, with the hydroxymethyl directing the addition (Figure 2). To test this hypothesis, we synthesized the tethered iodoaniline (**11**; Figure 2A) via Weinreb's conditions.[10] Attempted lithium−halogen exchange with *t*-BuLi,[11] Knochel's reagents,[12] and cuprates proved unpromising. Heck cyclizations[13] with unprotected or silylated substrates were attempted under the conditions of Overman[14] and Shibasaki,[15] but protodehalogenation proved dominant. Amide-directed metalation of the arene also failed (Figure 2B).[16]

Turning away from metal and cationic cyclizations, we devised a reaction to add *m*-phenylenediamine directly to the strained bicycle. We hypothesized that the phenylenediamine would rupture the lactone and forge the critical C−C bond with the installed *p*-amino group (Figure 2C). The cyclopentenone (**13**) was produced in four steps[17] and exposed to *m*-phenylenediamine under several conditions. The screening of solvents provided various results, including slow rate and/or N-conjugate addition to the enone. A solvent-free melt of *m*-phenylenediamine and **13** not only accelerated the condensation and reduced the requisite equivalents of *m*-phenylenediamine but also favored **14** with high stereoinduction and minimal traces of the epimeric methyl at C9 (>15:1 diastereomeric ratio.). Extensive ^{1}H NMR and X-ray structural[18] analyses confirmed the desired core stereochemistry at

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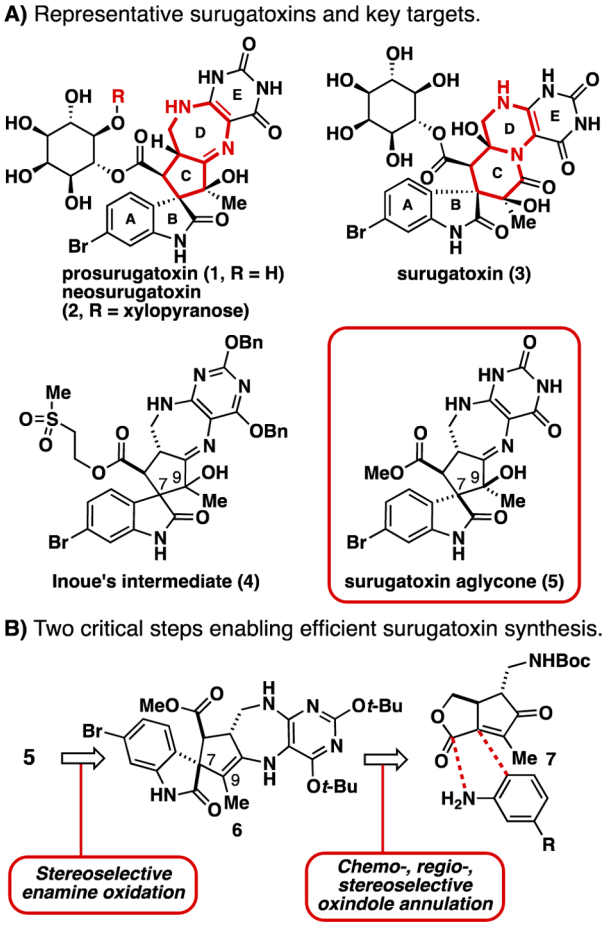

Figure 1. Surugatoxins and a new approach to oxindole synthesis.

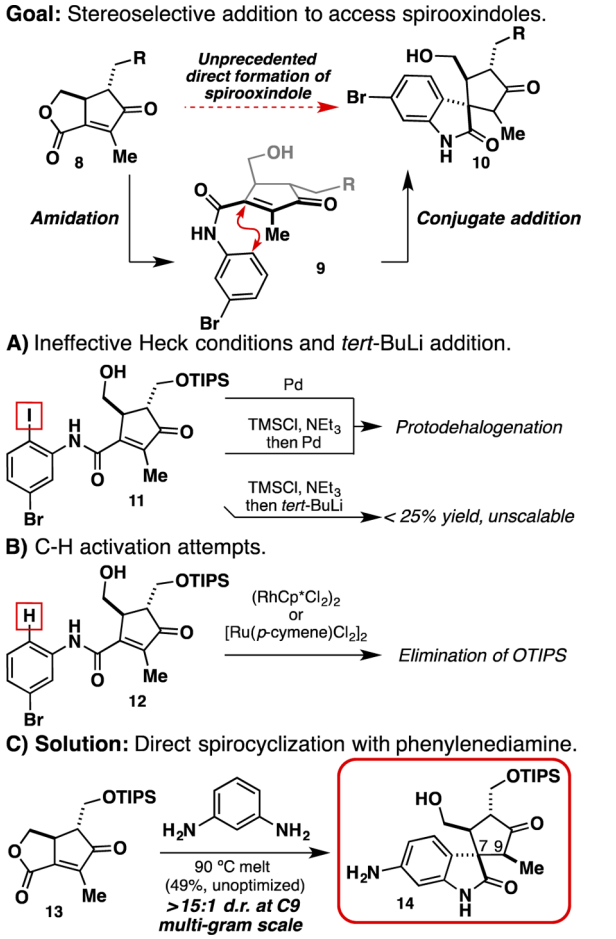

Figure 2. Discovery of a spirocyclization for efficient synthesis of the surugatoxins.

C7 and C9. The reaction was repeated multiple times on a gram scale without difficulty.

With all the requisite functionality of the toxin core in model compound **14**, we began the assault on **5**. Boc-amine-protected alkyne ester **15** was converted to racemic intermediate **7** in 57% overall yield (Scheme 1).[19] The *m*-phenylenediamine melt was repeated with **7** to yield a product epimeric at C9 (**16** and **17**) in a 1:3.8 selectivity and 81% overall yield. The quaternary center at C7 was a single stereoisomer.[20] The minor C9 methyl isomer (**16**) was prone to degradation and, to simplify the reaction analysis, was not carried forward. As in the preparation of **14**, the multigram scale was consistent in yield and stereoselectivity. Protected amine **17** was converted to a bromide (**18**) in acceptable yield via diazonium formation with stoichiometric tosic acid, *tert*-butyl nitrite, and tetrabutylammonium bromide/cupric bromide.[21] Alcohol **18** was converted to ester **19** in 49% yield in two steps, with minor epimerization of the intermediate aldehyde. The addition of the E ring was achieved with 3.5 equivalents of 6-chloro-2,4-bis-*tert*-butoxy-5-nitropyrimidine **20**—produced from 5-nitrobarbituric acid in two steps[22]—via condensation of deprotected amine **19** to deliver **21** in 77% yield. The D ring was forged via reduction of the nitropyrimidine with Raney Ni,[23] followed by condensation promoted by camphorsulfonic acid.[24] The enamine **6** had noted oxygen sensitivity, and all attempts to isolate the intermediate led to degradation. Instead, it was pushed directly to the hydroxy imine with buffered *m*-chloroperoxybenzoic acid. The reduction can be conducted on a reasonable scale (5−100 mg), whereas the condensation−oxidation sequence is best conducted with smaller quantities (10−15 mg).

The oxidation provided the hydroxy imine as a single diastereomer at C9 in 63% yield overall. Full spectroscopic analysis showed a strong nuclear Overhauser effect (NOE) between the arene ortho C−H and ester α-H, but weak methyl interactions led us to conclude that epimer **22** was generated (Scheme 1, vide infra).[25] Deprotection of **22** with dilute trifluoroacetic acid in dichloromethane delivered *epi*-surugatoxin aglycone **23** in 97% yield.

The enamine **6** stereospecifically attacked *m*-CPBA from the undesired bottom face of the structure and required an inversion at C9. Epimerization of **22** was uneventful and generated **24** in acceptable yield (38%). A strong NOE between the arene C−H, ester α-H, and the methyl group confirmed the targeted stereochemistry. Gentle deprotection with dilute trifluoroacetic acid provided the desired surugatoxin aglycone **5** in 95% yield. We noted that deprotection time was crucial to the isolation of **5**. Extended exposure of **24** to the deprotection condition resulted in a mixture of surugatoxin aglycone (**5**) and *epi*-surugatoxin aglycone (**22**). Strangely, the generation of aglycone **5** was not detected during the deprotection of **22**. Once isolated, **5** converted slowly to *epi*-surugatoxin (**23**) over several hours, presumably via a C9 dehydration/rehydration sequence.[26] These data suggest that *epi*-surugatoxin is likely the thermodynamically preferred stereoisomer within this alkaloid family.

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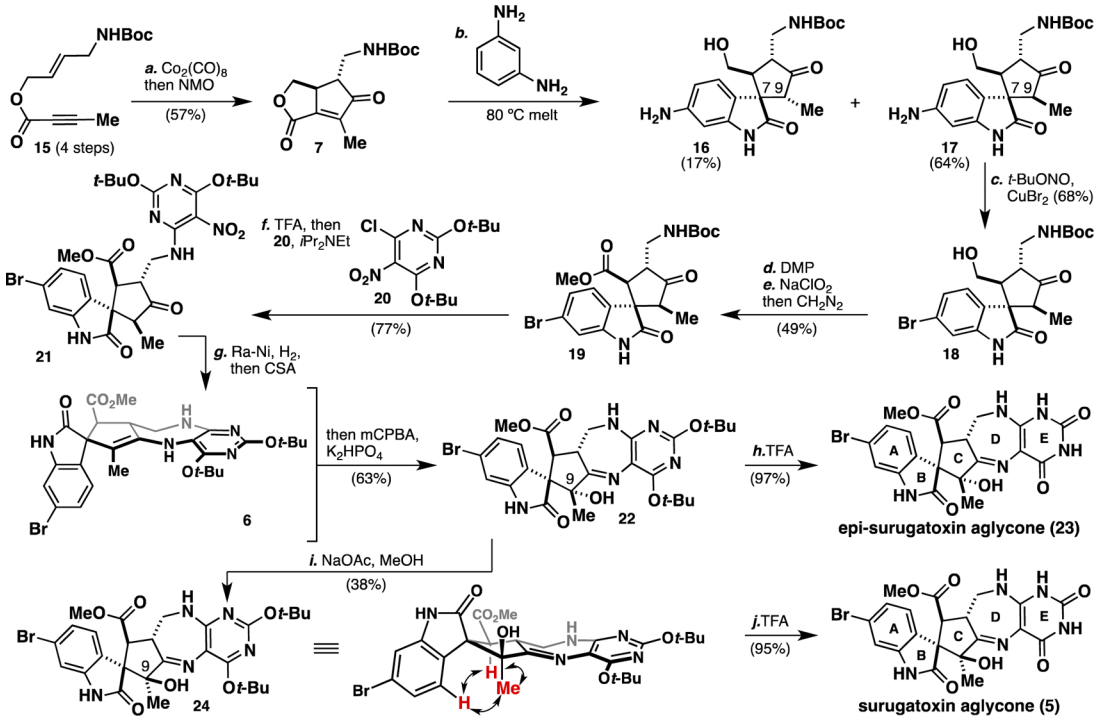
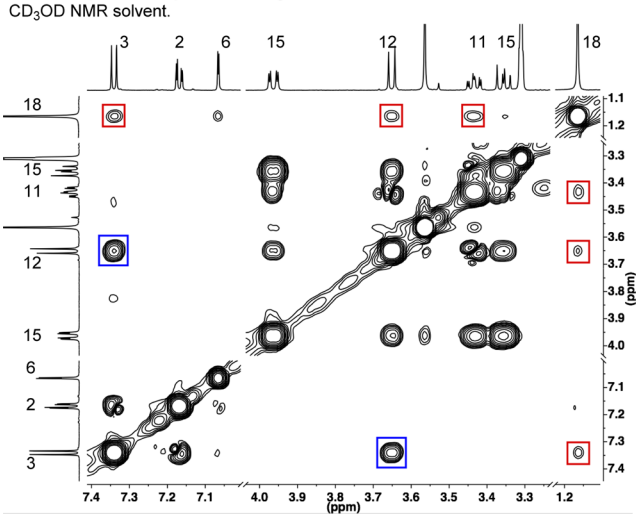
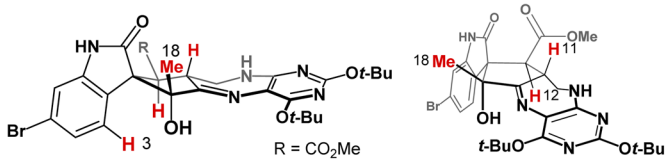
Scheme 1. Synthesis of Aglycone 5[a]



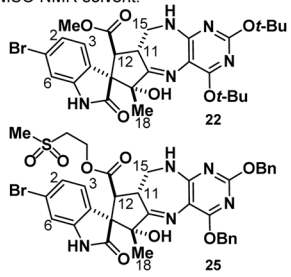
[a]Reagents and conditions: (a) $Co_2(CO)_8$ (1.2 equiv), DCM, 0 to 23 °C, 14.5 h, then NMO (8 equiv) 0 °C, 3 h, 57%; (b) *m*-phenylenediamine (1.15 equiv), 80 °C, 4 h, 81% (3.81:1 dr); (c) *t*-BuONO (1.1 equiv), *p*-TsOH (1.1 equiv), $CuBr_2$ (0.1 equiv), TBAB (4 equiv), MeCN, 23 °C, 0.25 h, 68%; (d) DMP (1.3 equiv), DCM, 0 °C, 0.5 h; (e) $NaClO_2$ (1.5 equiv), NaH_2PO_4 (1.5 equiv), 2-methyl-2-butene (4 equiv), THF, *t*-BuOH, H_2O, 23 °C, 0.5 h, then Et_2O, CH_2N_2, 0 °C, 49% (two steps); (f) TFA, DCM, 0 °C, 0.3 h, then 20 (3.5 equiv), *i*-Pr_2NEt (5 equiv), THF, 0 °C,1 h, then *i*-Pr_2NEt (1.7 equiv) 2 h, 77%; (g) Ra−Ni, H_2, THF, 23 °C, then CSA (0.9 equiv), MeCN, −35 °C, 0.16 h, then K_2HPO_4 (10 equiv), *m*-CPBA (1.1 equiv), 23 °C, 0.5 h, 63%; (h) TFA, DCM, 0 °C, 0.5 h, 97%; (i) NaOAc, MeOH, 65 °C, 1 h, 38%; (j) TFA, DCM, 0 °C, 0.1 h, 95%. CSA = camphor-10-sulfonic acid, DMP = Dess−Martin periodinane, *m*-CPBA = 3-chloroperoxybenzoic acid, NMO = 4-methylmorpholine *N*-oxide, TBAB = tetrabutylammonium bromide, TFA = trifluoroacetic acid.

A - NOE Spectra of epimeric-surugatoxin 22. Weak nOe correlations between C18 (Me) and equidistant C3, C11, and C12 (red box). Strong nOe from C3 to C12 (blue box). CD_3OD NMR solvent.





B - Comparison ^{1}H-NMR. Epimeric-surugatoxin aglycone **22** versus Inoue's stereoisomer **25**. DMSO NMR solvent.



Position	Observed Signal 22 ppm (*J* Hz)	Reported Signal 25 ppm (*J* Hz)
2	7.12 (d, 7.9, 1.9)	7.13 (dd, 8.1, 1.8)
3	7.28 (d, 8.0)	7.25-7.50 (m)
6	6.96 (d, 1.8)	6.98 (d, 1.8)
11	3.23 (br t, 10.2)	3.27 (m)
12	3.63 (d, 9.6)	3.71 (d, 9.2)
15	3.79 (ddd, 11.6, 7.3, 2.3)	3.90 (dd, 9.2, 7.1)
15	3.17 (td, 8.9, 2.4)	3.27 (m)
18	0.99 (s)	1.02 (s)

Figure 3. NOE analysis of synthetically prepared *epi*-surugatoxin **22** and a comparison to Inoue's stereoisomer.

DISCUSSION

The confirmation of the C ring stereochemistry was crucial for future endeavors with this class of alkaloids. An NOE analysis was performed and provided valuable insight into the C ring stereochemical assignments of isomers **22** and **24**. The initially formed stereoisomer **22** failed to exhibit the expected strong NOE between C18 and the C3 and C12 hydrogens but possessed weaker correlations to the C3, C11, and C12 sites (Figure 3a). Moreover, Inoue[27] previously separated and spectroscopically characterized each of the C7 and C9 stereoisomers without obtaining the NOE data (see the Supporting Information). The chemical shifts and coupling constants in the ^{1}H NMR spectra of **22** correlated reasonably well with one of Inoue's stereoisomers (**25**, Figure 3b). The

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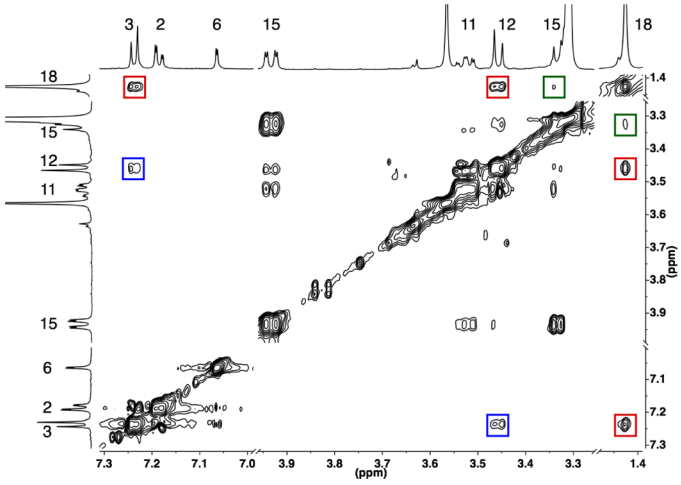
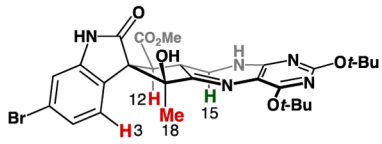
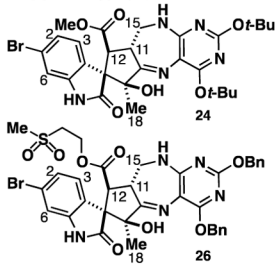
A - NOE Spectra of surugatoxin aglycone 24. Strong nOe correlations between C18 (Me) and C3, C12 (red box) with weak correlation to C15 (green box). Strong nOe from C3 to C12 (blue box). CD_3OD NMR solvent.





B - Comparison ^{1}H-NMR. Surugatoxin aglycone **24** versus Inoue's stereoisomer **26.** DMSO NMR solvent.



Position	Observed Signal 24 ppm (*J* Hz)	Reported Signal 26 ppm (*J* Hz)
2	7.15 (dd, 8.0, 1.9)	7.15 (dd, 8.1, 1.8)
3	7.26 (d, 7.9)	7.25 (d, 8.1)
6	6.94 (d, 1.9)	6.94 (d, 1.8)
11	3.28 (td, 9.5, 2.8)	3.39 (m)
12	3.61 (d, 9.8)	3.61 (d, 9.9)
15	3.74 (ddd, 12.1, 7.2, 2.8)	3.81 (ddd, 12.5, 6.6, 2.6)
15	3.18 (dd, 11.2, 10.0)	3.17 (ddd, 12.5, 8.8, 1.5)
18	1.27 (s)	1.28 (s)

Figure 4. NOE confirmation of surugatoxin aglycone **24** C-ring stereochemistry.

C18 methyl signal was diagnostic of the stereochemistry with the observed signal (0.99 ppm) matching the reported signal (1.02 ppm). The weak NOE correlations could also be explained by the C18 methyl residing in a pseudoequatorial position resulting in an equidistant, through-space correlation to the three protons of C3, C11, and C12. Concerns about epimerization at C7, C11, or C12 were allayed by the strong C3 to C12 NOE signal and the preservation of chemical shift for C2, C3, and C6. The coupling constants between the C11 and C12 protons were relatively similar to intermediate **24**, thus supporting the retention of configuration.

The NOE analysis was then performed on the unstable surugatoxin aglycone **24** and displayed the desired correlation between C18 to C3 and C12 (Figure 4a). A weak NOE was also observed to a C15 pseudoaxial proton. The proton NMR spectra were then compared to Inoue's stereoisomer **26** (Figure 4b). The arene signals (C2, C3, C6) of surugatoxin aglycone **24** aligned well, with minor differences in chemical shift and coupling constants in the C,D ring signals (C11, C12, C15). The methyl signal (C18) was also consistent with intermediate **26**. Overall, the comparative NOE and NMR data analysis between the synthetically prepared *epi-* and surugatoxin aglycones in the present work and earlier intermediates prepared by Inoue provided suitable evidence for the structural assignments.

In summary, the core of the surugatoxin natural product family has been prepared in nine linear steps from ester **15** and 13 linear steps from ethanolamine. Key transformations include a chemo-, regio-, stereoselective oxindole annulation, the addition of a fully functionalized pyrimidine E ring, and the oxidation of an in situ generated enamine.

EXPERIMENTAL SECTION

(±)-(3a*S*,4*R*)-6-Methyl-4-(((triisopropylsilyl)oxy)methyl)-3a,4-dihydro-1*H*-cyclopenta[*c*]furan-1,5(3*H*)-dione (13). Compound **13** was prepared from (*E*)-4-((triisopropylsilyl)oxy)but-2-en-1-yl but-2-ynoate.[17,28]

To a solution of but-2-ynoic acid (4.990 g, 59.30 mmol, 1.05 equiv) in DCM (200 mL) were added (*E*)-4-((triisopropylsilyl)oxy)but-2-en-1-ol (13.80 g, 56.48 mmol, 1.0 equiv) and DMAP (690.0 mg, 5.648 mmol, 0.1 equiv). The flask was charged with DCC (11.77 g, 57.04 mmol, 1.01 equiv). After consumption of alcohol was observed by TLC (1.5 h), the precipitated salts were filtered and rinsed with DCM. The filtrate was condensed and purified by silica gel column chromatography (10:1 hexanes/EtOAc, v/v) to yield the product as a clear, colorless liquid (16.9 g, 54.43 mmol, 96%): R_f = 0.61 (4:1, hexanes/EtOAc, v/v); ^{1}H NMR (500 MHz, $CDCl_3$)* δ 5.90−5.85 (m, 2H), 4.66 (d, *J* = 4.6 Hz, 2H), 4.27 (d, *J* = 3.0 Hz, 2H), 1.98 (s, 3H), 1.06 (d, *J* = 6.3 Hz, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 135.4, 122.3, 85.8, 72.5, 65.9, 63.0, 18.1, 12.1, 4.0; IR (film, cm^{-1}) 2943, 2891, 2865, 2242, 1709; HRMS (DART) *m*/*z* calcd for $C_{17}H_{29}O_3Si^-$ (M − H)$^-$ actual 309.1891, found 309.1895. * Denotes a rotameric population of 9:1; signals listed of major rotamer.

To a solution of (*E*)-4-((triisopropylsilyl)oxy)but-2-en-1-yl but-2-ynoate (4.00 g, 12.88 mmol, 1.0 equiv) in DCM (130 mL) was added $Co_2(CO)_8$ (5.285 g, 15.45 mmol, 1.2 equiv) at 0 °C followed by warming to 23 °C for 14.5 h. After the solution was cooled to 0 °C, *N*-methylmorpholine oxide (3.019 g, 25.76 mmol, 2.0 equiv) was added after 15 min. Three additional portions (total 8.0 equiv) were added over 15 min intervals. After being warmed to 23 °C, the suspension was stirred for 3 h. The solids were then removed by filtration, with the filter cake rinsed with DCM and EtOAc. The filtrate was washed with 1 M HCl and brine and dried with Na_2SO_4. The reaction was concentrated, and the residue was purified by flash column chromatography (10:1, hexanes/EtOAc, v/v) to yield compound **13** as a light orange solid (2.123 g, 6.2717 mmol, 49%). Although spectroscopically identical, the material can be converted to an off-white solid with decolorizing charcoal in warm EtOAc: mp 43−46 °C; R_f = 0.30 (4:1, hexanes/EtOAc, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65 (t, *J* = 8.6 Hz, 1H), 4.00 (t, *J* = 9.2 Hz, 1H), 3.95 (dd, *J* = 10.1, 5.7 Hz, 1H), 3.90 (dd, *J* = 10.1, 3.7 Hz, 1H), 3.60 (ddt, *J* = 9.5, 8.4, 3.2 Hz, 2H), 2.50 (dt, *J* = 5.5, 3.6 Hz, 1H), 1.85 (d, *J* = 3.2 Hz, 3H), 1.02−0.80 (m, 21H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 207.4, 165.5, 154.3, 143.1, 72.9, 60.6, 56.8, 44.0, 17.7, 17.7, 11.6, 8.6; IR(film, cm^{-1}) 2942, 2889, 2865, 1774, 1720, 1681; HRMS (DART) *m*/*z* calcd for $C_{18}H_{29}O_4Si^-$ (M − H)$^-$ actual 337.1841, found 337.1844.

(±)-(1*S*,2*S*,3*R*,5*S*)-6′-Amino-2-(hydroxymethyl)-5-methyl-3-(((triisopropylsilyl)oxy)methyl)spiro[cyclopentane-1,3′-indoline]-2′,4-dione (14). Cyclopentenone **13** (1.6054 g, 4.74 mmol, 1.0 equiv) and *m*-phenylenediamine (563.9 mg, 5.217 mmol, 1.1 equiv) were combined in a capped flask flushed under argon. The vessel was heated to 90 °C and stirred for 2 h. The crude mixture was purified by flash column chromatography (1:1 hexanes/EtOAc, v/v) to yield compound **14** as a slightly yellow solid (1.0438 g, 2.337 mmol, 49%). X-ray quality crystals were obtained by dissolving **14** in hot chloroform, adding hexanes, and allowing to cool slowly: mp 203−206 °C; R_f = 0.11 (1:1, DCM/EtOAc, v/v); ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 10.23 (s, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 6.23 (dd, *J* = 7.9, 2.0 Hz, 1H), 6.15 (d, *J* = 2.0 Hz, 1H), 5.34 (s, 2H), 4.53 (s, 1H), 4.11 (dd, *J* = 9.2, 2.8 Hz, 1H), 3.90 (dd, *J* = 9.3, 2.6 Hz, 1H), 3.37 (t, *J* = 9.8 Hz, 1H), 3.23 (d, *J* = 10.2 Hz, 1H), 2.78 (q, *J* = 5.3 Hz, 1H), 2.37 (q, *J*

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= 6.8 Hz, 1H), 1.03 (d, J = 5.6 Hz, 21H), 0.65 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 215.6, 179.1, 148.7, 143.7, 121.9, 116.8, 107.4, 96.3, 62.4, 61.1, 55.6, 53.7, 52.9, 46.1, 17.8, 17.8, 11.4, 7.5; IR (film, cm^{-1}) 3467, 3378, 3281, 3223, 2941, 2865, 1748, 1700, 1631, 1511, 1461, 1348, 1309, 1257, 1164, 1148, 1126, 1088, 1014, 991, 966, 882, 833, 771, 719, 689, 643; HRMS (DART) m/z calcd for $C_{24}H_{37}N_2O_4Si^-$ $(M - H)^-$ actual 445.2528, found 445.2532.

(*E*)-4-((*tert*-Butoxycarbonyl)amino)but-2-en-1-yl But-2-ynoate (15). A solution of but-2-ynoic acid (801.0 mg, 9.52 mmol, 1.0 equiv), *tert*-butyl (*E*)-(4-hydroxybut-2-en-1-yl)carbamate[28] (1.78 g, 9.52 mmol, 1.0 equiv), and DMAP (116.3 mg, 0.952 mmol, 0.1 equiv) in DCM (7.0 mL) was charged with DIC (1.5 mL, 9.62 mmol, 1.01 equiv). Additional but-2-ynoic acid (80.1 mg, 0.952 mmol, 0.1 equiv) was added after 50 min, and full consumption of alcohol was then observed. After an additional 10 min, the precipitated salts were filtered and rinsed with DCM and EtOAc. The filtrate was concentrated and purified by flash column chromatography (4:1, hexanes/EtOAc, v/v) to yield compound **15** as a white solid (2.18 g, 8.606 mmol, 90%): mp 38−40 °C; R_f = 0.48 (2:1, hexanes/EtOAc, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.67 (m, 2H), 4.81 (s, 1H), 4.53 (dd, J = 5.9, 1.2 Hz, 2H), 3.65 (d, J = 5.5 Hz, 2H), 1.90 (s, 3H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6, 153.1, 132.6, 124.1, 85.8, 79.2, 72.1, 65.3, 41.6, 28.3, 3.66; IR (film, cm^{-1}) 3347, 2977, 2241, 1704, 1511; HRMS (DART) m/z calcd for $C_{13}H_{20}NO_4^+$ $(M + H)^+$ actual 254.1392, found 254.1391.

(±)-*tert*-Butyl (((3a*S*,4*R*)-6-Methyl-1,5-dioxo-3,3a,4,5-tetrahydro-1*H*-cyclopenta[*c*]furan-4-yl)methyl)carbamate (7). To a solution of tetrolic ester **15** (2.50 g, 9.87 mmol, 1.0 equiv) in DCM (98 mL) was added $Co_2(CO)_8$ (4.049 g, 11.84 mmol, 1.2 equiv) at 0 °C followed by warming to 23 °C for 11.5 h. After the solution was cooled to 0 °C, *N*-methylmorpholine oxide (2.31 g, 19.74 mmol, 2.0 equiv) was added after 15 min. Three additional portions (total 8.0 equiv) were added over 10 min intervals. After being warmed to 23 °C, the suspension was stirred for 2.5 h. The solids were then removed by filtration, with the filter cake rinsed with DCM and EtOAc. The filtrate was washed with 1 M HCl and brine and dried with Na_2SO_4. The reaction was concentrated, and the residue was purified by flash column chromatography (3:1, hexanes/EtOAc, v/v) to yield compound **7** as a light orange solid (1.589 g, 5.63 mmol, 57%). Although spectroscopically identical, the material can be converted to an off-white solid with decolorizing charcoal in warm EtOAc: mp 154−157 °C; R_f = 0.27 (hexanes/EtOAc, 2:1, v/v); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.96 (s, 1H), 4.81 (t, J = 8.6 Hz, 1H), 4.08 (t, J = 9.1 Hz, 1H), 3.55 (dt, J = 11.9, 5.5 Hz, 2H), 3.51−3.39 (m, 2H), 2.59 (q, J = 5.0 Hz, 1H), 2.03 (d, J = 3.2 Hz, 3H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN) δ 208.6, 165.6, 156.3, 154.5, 143.4, 80.1, 73.2, 56.3, 45.0, 38.8, 28.4, 9.1; IR (film, cm^{-1}) 3360, 2979, 2254, 1772, 1721, 1684, 1525; HRMS (DART) m/z calcd for $C_{14}H_{18}NO_5^-$ $(M - H)^-$ actual 280.1191, found 280.1180.

(±)-*tert*-Butyl (((1*S*,2*R*,4*R*,5*S*)-6′-Amino-5-(hydroxymethyl)-2-methyl-2′,3-dioxospiro[cyclopentane-1,3′-indolin]-4-yl)methyl)carbamate and (±)-*tert*-Butyl (((1*S*,2*S*,4*R*,5*S*)-6′-Amino-5-(hydroxymethyl)-2-methyl-2′,3-dioxospiro[cyclopentane-1,3′-indolin]-4-yl)methyl)carbamate (16 and 17). Cyclopentenone 7 (400.0 mg, 1.422 mmol, 1.0 equiv) and *m*-phenylenediamine (179.2 mg, 1.564 mmol, 1.15 equiv) were combined and partially dissolved with 0.4 mL of chloroform in a capped flask flushed under argon. The vessel was heated to 70 °C with periodic venting of chloroform. The heat was increased to 80 °C and stirred for 4 h. The crude mixture was purified by flash column chromatography (97:3, DCM/MeOH, v/v) to yield compound **17** as a yellow solid (354.8 mg, 0.911 mmol, 64%) and the minor diastereomer **16** as a light yellow film (95.8 mg, 0.246 mmol, 17%).

Major Diastereomer (±)-*tert*-Butyl (((1*S*,2*S*,4*R*,5*S*)-6′-Amino-5-(hydroxymethyl)-2-methyl-2′,3-dioxospiro[cyclopentane-1,3′-indolin]-4-yl)methyl)carbamate (17): mp 104−109 °C; R_f = 0.26 (9:1, DCM/MeOH, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.04 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.39−6.30 (m, 1H), 6.23 (d, J = 2.3 Hz, 1H), 5.36 (s, 1H), 3.94 (s, 3H), 3.55 (d, J = 7.7 Hz, 4H), 3.01 (d, J = 11.4 Hz, 1H), 2.48 (q, J = 7.0 Hz, 2H), 1.43 (d, J = 3.9 Hz, 9H), 0.84 (d, J = 6.9 Hz, 3H); ^{1}H NMR (500 MHz, CD_3CN) δ 8.73 (s, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.33 (dd, J = 8.0, 2.0 Hz, 1H), 6.24 (d, J = 2.0 Hz, 1H), 6.00 (s, 1H), 5.44 (s, 1H), 4.33 (s, 3H), 3.47 (dt, J = 12.4, 7.1 Hz, 4H), 3.40 (dd, J = 10.5, 4.4 Hz, 1H), 3.32 (dt, J = 13.8, 5.6 Hz, 1H), 2.74 (dt, J = 11.3, 5.7 Hz, 1H), 2.63 (q, J = 6.8 Hz, 1H), 2.47 (ddd, J = 11.9, 8.2, 4.4 Hz, 1H), 1.40 (s, 9H), 0.72 (d, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 217.2, 180.2, 157.5, 149.4, 144.1, 123.8, 118.7, 109.3, 97.7, 79.7, 62.3, 57.2, 53.8, 51.9, 50.6, 41.9, 28.6, 8.2; IR (film, cm^{-1}) 3347, 2977, 2934, 1737, 1694, 1634, 1511; HRMS (DART) m/z calcd for $C_{20}H_{26}N_3O_5^-$ $(M - H)^-$ actual 388.1878, found 388.1863.

Minor diastereomer (±)-*tert*-butyl (((1*S*,2*R*,4*R*,5*S*)-6′-amino-5-(hydroxymethyl)-2-methyl-2′,3-dioxospiro[cyclopentane-1,3′-indolin]-4-yl)methyl)carbamate (16): mp 45−48 °C; R_f = 0.47 (9:1, DCM/MeOH, v/v); ^{1}H NMR (300 MHz, CD_3CN) δ 8.75 (s, 1H), 7.17 (t, J = 2.2 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 6.91 (dd, J = 8.3, 1.8 Hz, 1H), 6.51 (ddd, J = 8.0, 2.3, 1.0 Hz, 1H), 5.60 (s, 1H), 4.11−3.79 (m, 3H), 3.68 (dd, J = 5.0, 1.8 Hz, 2H), 3.36 (dt, J = 13.7, 5.8 Hz, 1H), 3.20 (ddd, J = 13.8, 7.8, 6.2 Hz, 1H), 3.10 (s, 1H), 2.48 (ddd, J = 8.1, 5.8, 2.5 Hz, 1H), 1.82 (d, J = 2.0 Hz, 3H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, CD_3CN) δ 209.3, 165.5, 162.3, 157.0, 147.6, 141.1, 139.8, 130.5, 112.6, 111.1, 107.8, 79.5, 63.1, 49.8, 48.1, 41.6, 28.5, 9.6, 1.8; IR (film, cm^{-1}) 3350, 3000, 2978, 2928, 2875, 1694, 1611, 1538; HRMS (DART) m/z calcd for $C_{20}H_{26}N_3O_5^-$ $(M - H)^-$ actual 388.1878, found 388.1877.

(±)-*tert*-Butyl (((1*S*,2*S*,4*R*,5*S*)-6′-Bromo-5-(hydroxymethyl)-2-methyl-2′,3-dioxospiro[cyclopentane-1,3′-indolin]-4-yl)methyl)carbamate (18). A solution of aniline oxindole **17** (115.3 mg, 0.296 mmol, 1.0 equiv), *p*-TsOH (56.0 mg, 0.326 mmol, 1.1 equiv), $CuBr_2$ (6.6 mg, 0.0296 mmol, 0.1 equiv), and TBAB (381.7 mg, 1.184 mmol, 4.0 equiv) were combined in freshly distilled MeCN (5.2 mL). Lastly, *t*-BuONO was added (39.0 μL, 0.326 mmol, 1.1 equiv) dropwise at 23 °C. The reaction was deemed complete by TLC after 15 min, diluted with DCM, and poured into water. The mixture was extracted with DCM and washed with brine, and the combined organics were dried with Na_2SO_4. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (98:2, DCM/MeOH, v/v) to yield compound **18** as an off-white foam (91.5 mg, 0.201 mmol, 68%): R_f = 0.42 (9:1 DCM/MeOH, v/v); ^{1}H NMR (500 MHz, CD_3CN) δ 8.62 (br s, 1H), 7.24 (dd, J = 8.0, 1.8 Hz, 1H), 7.18 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 1.8 Hz, 1H), 5.76 (br s, 1H), 3.52 (dd, J = 10.9, 7.4 Hz, 1H), 3.45−3.37 (m, 2H), 3.33 (dt, J = 14.0, 5.7 Hz, 1H), 2.72 (q, J = 6.9 Hz, 1H), 2.68 (dt, J = 15.8, 5.6 Hz 1H), 2.58 (ddd, J = 11.1, 7.3, 5.6 Hz, 1H), 1.42 (s, 9H), 0.73 (dd, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN) δ 216.0, 178.8, 157.4, 144.8, 131.0, 126.0, 125.0, 121.9, 113.5, 79.6, 62.2, 57.5, 53.8, 51.3, 50.2, 41.6, 28.5, 8.1; IR (film, cm^{-1}) 3304, 2977, 2933, 1739, 1701, 1614, 1513; HRMS (DART) m/z calcd for $C_{20}H_{26}BrN_2O_5^+$ $(M + H)^+$ actual 453.1020, found 453.1022.

(±)-Methyl (1*R*,2*S*,3*R*,5*S*)-6′-Bromo-3-(((*tert*-butoxycarbonyl)amino)methyl)-5-methyl-2′,4-dioxospiro[cyclopentane-1,3′-indoline]-2-carboxylate (19). To a solution of alcohol **18** (228.9 mg, 0.5049 mmol, 1.0 equiv) in DCM (10.0 mL) was added Dess−Martin periodinane (278.4 mg, 0.6564 mmol, 1.3 equiv) at 0 °C. After 30 min, the reaction was deemed complete by TLC. The suspension was partially condensed and subjected to a silica gel plug (2:1, hexanes/EtOAc, v/v) to yield the aldehyde as a yellow solid. The aldehyde was immediately dissolved in a mixture of THF/*t*-BuOH/H_2O (4.5:4.5:1.5 mL) and 2-methyl-2-butene (206.0 μL, 1.942 mmol, 4.0 equiv), and sodium chlorite (65.9 mg, 0.7285 mmol, 1.5 equiv) and sodium phosphate monobasic (100.5 mg, 0.7285 mmol, 1.5 equiv) were added at 23 °C. After 30 min, the reaction was deemed complete by TLC, and the solution was adjusted to pH = 1 with 1 M HCl. Ethyl acetate was added, and the combined organics were dried with Na_2SO_4. The product was condensed and carried to the next step without additional purification. The acid was dissolved in ether (10.0 mL), and diazomethane in ether was added at 0 °C until an excess of diazomethane remained as indicated by yellow color and confirmed by TLC. The solution was allowed to warm to 23 °C, and argon was bubbled through until the bright yellow color faded to pale yellow. The solvent was carefully removed by rotary evaporation, and the

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residue was purified by flash column chromatography (2.5:1, hexanes/EtOAc v/v) to yield compound **19** as a white foam (119.8 mg, 0.2489 mmol, 49% over three steps): R_f = 0.43 (1:1, hexanes/EtOAc, v/v); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.24 (dd, J = 7.8, 1.7 Hz, 1H), 7.07 (d, J = 1.7 Hz, 1H), 7.01 (d, J = 7.8 Hz, 1H), 4.98 (s, 1H), 3.66−3.64 (m, 2H), 3.61 (s, 3H), 3.55 (br d, J = 11.2 Hz, 1H), 3.35 (dt, J = 11.2, 4.9 Hz, 1H), 2.51 (q, J = 6.9 Hz, 1H), 1.46 (s, 9H), 0.90 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 214.5, 180.3, 172.2, 158.7, 145.6, 130.8, 126.4, 124.9, 122.9, 114.1, 80.3, 57.9, 54.6, 52.6, 51.5, 50.9, 41.5, 28.7, 8.0; IR (film, cm^{-1}) 3246, 2977, 2510, 2188, 1742, 1710, 1614; HRMS (DART) m/z calcd for $C_{21}H_{26}BrN_2O_6^+$ $(M + H)^+$ actual 481.0969, found 481.0968.

2,4-Di-*tert*-butoxy-6-chloro-5-nitropyrimidine (20). A solution of 2,4,6-trichloro-5-nitropyrimidine[28] (760.0 mg, 3.327 mmol, 1.0 equiv) was dissolved in DMF (20 mL) and cooled to −50 °C using a dry ice acetonitrile bath. Sodium *tert*-butoxide (639.1 mg, 6.655 mmol, 2.0 equiv) was added in portions, and the reaction was allowed to warm to room temperature over 45 min. The reaction was judged complete by TLC, diluted with ethyl ether, and poured into water. Several water washes and a brine wash was performed. The crude mixture was dried over $MgSO_4$ and then concentrated. The mixture was purified by flash column chromatography (4:1 hexanes/DCM v/v to 3.5:1.5 hexanes/DCM v/v). The pyrimidine (**20**) was isolated as a yellow solid (393.0 mg, 1.294 mmol, 39%): mp 68−70 °C; R_f = 0.39 (1:1, hexanes:DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.55 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 161.0, 151.8, 129.2, 86.8, 83.8, 28.1, 28.0; IR (film, cm^{-1}) 2982, 2935, 1578, 1533, 1405; HRMS (DART) m/z calcd for $C_{12}H_{19}ClN_3O_4^+$ $(M + H)^+$ actual 304.1059, found 304.1055.

(±)-Methyl (1*R*,2*S*,3*R*,5*S*)-6′-Bromo-3-(((2,6-di-*tert*-butoxy-5-nitropyrimidin-4-yl)amino)methyl)-5-methyl-2′,4-dioxospiro[cyclopentane-1,3′-indoline]-2-carboxylate (21). To a solution of amine ester **19** (51.2 mg, 0.10637 mmol, 1.0 equiv) in DCM (2.1 mL) at 0 °C was added TFA (735.0 μL). After 20 min, the deprotection was deemed complete by TLC. The solution was diluted with toluene and concentrated. The intermediate was immediately dissolved in THF (2.1 mL) and cooled to 0 °C. Pyrimidine **20** (113.0 mg, 0.3722 mmol, 3.5 equiv) and Hünig's base (87.0 μL, 0.5318 mmol, 5.0 equiv) were added. After 60 min, additional Hünig's base (30.0 μL, 0.1833 mmol, 1.7 equiv) was added. The reaction was deemed complete by TLC after 120 min. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (3:1, hexanes/EtOAc v/v) to yield compound **21** as a yellow solid (52.8 mg, 0.08153 mmol, 77%) and compound **20** as a yellow solid (76.8 mg, 0.2528 mmol, 87% recovery): mp 225−228 °C; R_f = 0.63 (1:1 hexanes/EtOAc, v/v); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (t, J = 5.6 Hz, 1H), 8.26 (s, 1H), 7.23 (dd, J = 7.9, 1.6 Hz, 1H), 7.08 (d, J = 1.7 Hz, 1H), 7.03 (d, J = 8.0 Hz, 1H), 4.09 (dt, J = 13.9, 5.6 Hz, 1H), 4.04 (dt, J = 13.9, 5.8 Hz, 1H), 3.63−3.59 (m, 1H), 3.59 (s, 3H), 3.37 (d, J = 11.4 Hz, 1H), 2.61 (q, J = 6.9 Hz, 1H), 1.65 (s, 9H), 1.62 (s, 9H), 0.92 (d, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.0, 178.4, 170.3, 165.9, 162.5, 159.0, 143.1, 128.4, 126.0, 123.4, 122.5, 113.8, 113.7, 85.4, 82.2, 56.1, 54.0, 52.8, 51.5, 48.9, 42.0, 28.8, 28.6, 8.1; IR (film, cm^{-1}) 3344, 2979, 1743, 1583, 1565; HRMS (DART) m/z calcd for $C_{28}H_{35}BrN_5O_8^+$ $(M + H)^+$ actual 648.16635, found 648.16639.

(±)-Methyl (6*R*,7*R*,8*S*,8a*R*)-6′-Bromo-2,4-di-*tert*-butoxy-6-hydroxy-6-methyl-2′-oxo-8,8a,9,10-tetrahydro-6*H*-spiro[cyclopenta[*e*]pyrimido[4,5-*b*][1,4]diazepine-7,3′-indoline]-8-carboxylate (22). To a solution of compound **21** (20.8 mg, 0.0321 mmol, 1.0 equiv) in THF (2.1 mL) was added a slurry of Raney Ni 2800 under argon atmosphere. The atmosphere was then flushed with hydrogen and stirred at 23 °C until the reaction was deemed complete. The suspension was diluted with EtOAc, and the particulates were removed by filtration through a plug of Celite. The resulting solution was concentrated by rotary evaporation and used without further purification due to instability on silica gel. The residue was dissolved in tetrahydrofuran, equally partitioned between four reaction vials and concentrated prior to glovebox admittance. The four identical samples were carried forward simultaneously. In a glovebox under nitrogen atmosphere, the residue (5.1 mg, 0.0080 mmol, 1.0 equiv) was dissolved in MeCN (300 μL) and chilled to −35 °C. After removal from the glovebox freezer, CSA (1.7 mg, 0.0074 mmol, 0.9 equiv) in MeCN (200 μL) was added, and the combined solution was allowed to warm to 23 °C over 10 min. To the solution was added a slurry of K_2HPO_4 (14.0 mg, 0.0803 mmol, 10.0 equiv) in MeCN (100 μL) followed by *m*-CPBA (2.0 mg, 0.0090 mmol, 1.1 equiv) in MeCN (100 μL). The four parallel reaction vials were removed from the glovebox and allowed to stir at 0 °C for 30 min, after which they were judged complete by TLC and LC/MS. Ethyl acetate was added, and the solutions were poured into water. The combined organics were washed with 1 M $NaHCO_3$ three times and then brine and dried with Na_2SO_4. The solvent was removed by rotary evaporation, and the residue was purified by flash column chromatography (97:3 $CHCl_3$/MeOH v/v) to yield compound **22** as a yellow film (12.4 mg, 0.0201 mmol, 63%): R_f = 0.66 (90:10 DCM/MeOH, v/v); ^{1}H NMR (600 MHz, CD_3OD) δ 7.34 (d, J = 8.0 Hz, 1H), 7.17 (dd, J = 8.0, 1.7 Hz, 1H), 7.06 (d, J = 1.7 Hz, 1H), 3.96 (dd, J = 11.7, 2.6 Hz, 1H), 3.65 (d, J = 10.0 Hz, 1H), 3.56 (s, 3H), 3.43 (ddd, J = 10.0, 8.9, 2.6 Hz, 1H), 3.35 (dd, J = 11.8, 8.8 Hz, 1H), 1.60 (s, 9H), 1.58 (s, 9H), 1.16 (s, 3H); ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ 10.56 (s, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.12 (dd, J = 7.9, 1.9 Hz, 1H), 6.96 (d, J = 1.8 Hz, 1H), 5.69 (s, 1H), 3.79 (ddd, J = 11.6, 7.3, 2.3 Hz, 1H), 3.63 (d, J = 9.6 Hz, 1H), 3.48 (s, 3H), 3.23 (br t, J = 10.2 Hz, 1H), 3.17 (td, J = 8.9, 2.4 Hz, 1H), 1.53 (s, 9H), 1.52 (s, 9H), 0.99 (s, 3H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 178.4, 171.6, 169.0, 166.9, 159.7, 156.5, 144.7, 128.0, 127.7, 123.5, 120.6, 111.5, 105.7, 80.9, 79.8, 78.6, 62.5, 51.9, 49.0, 47.9, 47.6, 28.4, 28.3, 17.9; IR (film, cm^{-1}) 3239, 2976, 2928, 1709, 1612, 1568; HRMS (DART) m/z calcd for $C_{28}H_{35}BrN_5O_6^+$ $(M + H)^+$ actual 616.1771, found 616.1774.

***epi*-Surugatoxin Aglcyone ((±)-Methyl (6*R*,7*R*,8*S*,8a*R*)-6′-Bromo-6-hydroxy-6-methyl-2,2′,4-trioxo-1,3,4,6,8,8a,9,10-octahydro-2*H*-spiro[cyclopenta[*e*]pyrimido[4,5-*b*][1,4]diazepine-7,3′-indoline]-8-carboxylate) (23).** To a suspension of compound **22** (6.3 mg, 0.01023 mmol, 1.0 equiv) in DCM (1 mL) was added TFA (50 μL) at 0 °C. After 30 min, the reaction was deemed complete by LC/MS. The solution was diluted with toluene and concentrated to yield compound **23** as a yellow solid (TFA salt, 6.1 mg, 0.00986 mmol, 97%): mp dec >120 °C; R_f = 0.72 (RP_{18} TLC plate, 1:1 MeCN/H_2O, v/v); ^{1}H NMR (600 MHz, CD_3OD) δ 7.33 (d, J = 8.0 Hz, 1H), 7.16 (dd, J = 8.0, 1.8 Hz, 1H), 7.06 (d, J = 1.8 Hz, 1H), 4.01 (dd, J = 12.1, 2.7 Hz, 1H), 3.63 (d, J = 10.2 Hz, 1H), 3.56 (s, 3H), 3.48 (ddd, J = 10.3, 8.6, 2.6 Hz, 1H), 3.31 (solvent occluded, 1H), 1.18 (s, 3H); ^{1}H NMR (600 MHz, $DCON(CD_3)_2$) δ 7.41 (d, J = 8.0 Hz, 1H), 7.18 (dd, J = 8.0, 1.9 Hz, 1H), 7.11 (d, J = 1.9 Hz, 1H), 4.10 (m, 1H), 3.74 (d, J = 10.1 Hz, 1H), 3.55 (s, 3H), 3.41 (ddd, J = 10.4, 8.5, 2.6 Hz, 1H), 3.26 (dd, J = 11.7, 8.4 Hz, 1H), 1.10 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ 178.2, 171.4, 169.8, 165.9, 162.3, 148.9, 144.6, 128.0, 127.5, 123.4, 120.6, 111.4, 100.3, 80.8, 62.4, 51.9, 48.8, 47.6, 47.1, 18.2; IR (film, cm^{-1}) 3122, 2925, 2256, 1706, 1589; HRMS (DART) m/z calcd for $C_{20}H_{19}BrN_5O_6^+$ $(M + H)^+$ actual 504.0513, found 504.0518.

The deuterated solvent occluded the H-signal on C15. A diluted sample including THF successfully moved the C15 signal allowing a full collection of data: ^{1}H NMR (600 MHz, CD_3OD + THF) δ 7.32 (d, J = 8.1 Hz, 1H), 7.15 (dd, J = 8.0, 1.8 Hz, 1H), 7.05 (d, J = 1.8 Hz, 1H), 3.98 (dd, J = 12.1, 2.7 Hz, 1H), 3.62 (d, J = 10.3 Hz, 1H), 3.56 (s, 3H), 3.47 (ddd, J = 10.4, 8.5, 2.8 Hz, 1H), 3.27 (dd, J = 12.3, 8.4 Hz, 1H), 1.18 (s, 3H).

(±)-Methyl (6*S*,7*R*,8*S*,8a*R*)-6′-Bromo-2,4-di-*tert*-butoxy-6-hydroxy-6-methyl-2′-oxo-8,8a,9,10-tetrahydro-6*H*-spiro[cyclopenta[*e*]pyrimido[4,5-*b*][1,4]diazepine-7,3′-indoline]-8-carboxylate (24). To a solution of compound **22** (26.2 mg, 0.04250 mmol, 1.0 equiv) in MeOH (1.50 mL) was added NaOAc (54.4 mg) and the solution heated to 65 °C under argon in a sealed tube. After 60 min, the crude reaction mixture was purified by a preparatory TLC plate. The desired epimer was segregated with the undesired epimers combined and resubjected to the epimerization condition. Overall, four epimerization/preparatory purifications were performed to provide recovered **22** (3.4 mg) and **24** as a yellow solid (8.6 mg, 0.01394 mmol, 38% yield based on recovered **22**): mp dec >190 °C; R_f = 0.61 (90:10 DCM/MeOH, v/v); ^{1}H NMR (600 MHz, CD_3OD) δ

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7.24 (d, J = 8.0 Hz, 1H), 7.18 (dd, J = 8.0, 1.8 Hz, 1H), 7.06 (d, J = 1.8 Hz, 1H), 3.93 (dd, J = 12.1, 2.8 Hz, 1H), 3.56 (s, 3H), 3.53 (ddd, J = 10.0, 9.0, 2.8 Hz, 1H), 3.46 (d, J = 10.0 Hz, 1H), 3.32 (dd, J = 12.0, 8.9 Hz, 1H), 1.63 (s, 9H), 1.60 (s, 9H), 1.43 (s, 3H); ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ 10.35 (s, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.15 (dd, J = 8.0, 1.9 Hz, 1H), 6.94 (d, J = 1.9 Hz, 1H), 4.43 (s, 1H), 3.74 (ddd, J = 12.1, 7.2, 2.8 Hz, 1H), 3.61 (d, J = 9.8 Hz, 1H), 3.49 (s, 3H), 3.28 (td, J = 9.5, 2.8 Hz, 1H), 3.18 (dd, J = 11.2, 10.0 Hz, 1H), 1.53 (s, 9H), 1.52 (s, 9H), 1.27 (s, 3H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$) δ 178.4, 171.8, 171.1, 166.7, 159.5, 156.4, 145.6, 127.8, 126.8, 123.0, 120.7, 111.7, 106.1, 80.7, 80.3, 78.6, 62.1, 52.0, 47.8, 46.4, 46.0, 28.5, 28.3, 24.1; IR (film, cm^{-1}) 3255, 3112, 2976, 2926, 2854, 1737, 1713, 1614, 1567; HRMS (DART) m/z calcd for $C_{28}H_{35}BrN_5O_6^+$ $(M + H)^+$ actual 616.1771, found 616.1793.

Surugatoxin Aglycone ((±)-Methyl (6*S*,7*R*,8*S*,8a*R*)-6′-Bromo-6-hydroxy-6-methyl-2,2′,4-trioxo-1,3,4,6,8,8a,9,10-octahydro-2*H*-spiro[cyclopenta[*e*]pyrimido[4,5-*b*][1,4]diazepine-7,3′-indoline]-8-carboxylate) (5). To a suspension of compound **24** (3.9 mg, 0.0063 mmol, 1.0 equiv) in DCM (750 μL) was added TFA (6.0 μL) at 0 °C. After 6 min, the reaction was diluted with toluene and concentrated. The crude mixture was analyzed by ^{1}H NMR and deemed incomplete. The reaction was set up again, and after 2 min the solution was diluted with toluene and concentrated to yield compound **5** as a yellow film (TFA salt, 3.7 mg, 0.0060 mmol, 95%): R_f = 0.72 (RP_{18} TLC plate, 1:1 MeCN/H_2O, v/v); ^{1}H NMR (600 MHz, CD_3OD) δ 7.20 (d, J = 8.0 Hz, 1H), 7.17 (dd, J = 8.0, 1.8 Hz, 1H), 7.06 (d, J = 1.8 Hz, 1H), 3.97 (br d, J = 12.1 Hz, 1H), 3.60−3.56 (m, 1H), 3.56 (s, 3H), 3.47 (d, J = 10.1 Hz, 1H), 3.23 (dd, J = 12.1, 8.5 Hz, 1H), 1.37 (s, 3H); ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ 10.59 (br s, 1H), 10.35 (br s, 1H), 10.0 (br s, 1H), 7.23 (d, J = 8.0 Hz, 1H), 7.13 (dd, J = 8.0, 1.8 Hz, 1H), 6.91 (d, J = 1.8 Hz, 1H), 3.81 (dd, J = 12.0, 6.2 Hz, 1H), 3.57 (s, 1H), 3.50−3.48 (overlapped, 1H), 3.49 (s, 3H), 3.09 (d, J = 12.0, 1H), 1.23 (s, 3H); ^{13}C NMR (200 MHz, $(CD_3)_2SO$) δ 178.3, 171.0, 168.3, 168.2, 162.7, 149.1, 145.6, 127.9, 126.7, 122.8, 120.6, 111.6, 100.7, 80.8, 62.0, 51.9, 48.8, 46.7, 46.2, 24.4; IR (film, cm^{-1}) 3273, 2922, 2852, 1714, 1609; HRMS (DART-ESI) m/z calcd for $C_{20}H_{18}BrN_5O_6Na^+$ $(M + Na)^+$ actual 526.0333, found 526.0336. Note: surugatoxin aglycone **5** showed notable degradation over several hours. The HSQC, HMBC, and ^{13}C spectra contained *epi*-surugatoxin aglycone (**23**) as the confirmed impurity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02053.

NMR spectra for all new compounds (PDF)

Crystallographic data for compound **14** (CIF)

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Notes

The authors declare no competing financial interest.

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(26) See the Supporting Information for details.

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