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Exploratory studies toward a total synthesis of the marine ascidian metabolite perophoramidine

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ABSTRACT

A strategy for a total synthesis of the marine alkaloid perophoramidine has been investigated. Key steps which have been tested include a tandem intramolecular Heck/carbonylation reaction and a stereoselective allylation of a pentacyclic δ-lactam to produce the C-4/20 vicinal quaternary centers having the requisite relative configuration of the metabolite.

1. Introduction and background

In 2002, Ireland and co-workers reported the isolation of an unusual heterocyclic compound, perophoramidine, from the marine ascidian *Perophora namei* collected in the Philippines.[1] Based upon spectral analysis, this metabolite was assigned structure **1**, which contains among other notable features six rings including two amidine units, two chlorines, and a bromine. In addition, perophoramidine has two adjacent quaternary carbons at C-4/20. Perophoramidine has cytotoxicity against the HCT116 colon carcinoma cell line and also induces apoptosis via PARP cleavage.

This alkaloid is related in structure to the communesin family of metabolites, exemplified by communesins A (**2**) and B (**3**), which were isolated by Numata et al. in 1993 from a *Penicillium* mold found growing on the marine alga *Enteromorpha intestinalis*.[2–4] An interesting feature of the communesins is that the contiguous quaternary centers at C-7/8 are opposite in relative configuration to the corresponding ones in perophoramidine (**1**). Communesins A and B were found to have in vitro cytotoxic activity against P-388 lymphoid leukemia cells (Fig. 1).[2]

The closely related perophoramidine and the communesin structures are presumed to arise via a common biogenetic pathway, independently proposed by Stoltz[5,6] and by Funk.[7] Funk and Fuchs have successfully implemented these ideas and completed the first total synthesis of racemic perophoramidine (**1**) via a biomimetically-patterned route.[7a] In addition, Rainier and co-workers have recently reported an approach to dehaloperophoramidine.[8,9] In this paper we describe our ongoing efforts toward a new total synthesis of perophoramidine.

2. Synthetic plan

We have recently published the development of a general strategy involving a tandem halogen-selective intramolecular Heck reaction/carbonylation sequence[10] to construct the C/E/F portion and one of the quaternary centers of the communesins and perophoramidine.[11] It is our plan to apply such methodology to specifically access perophoramidine (**1**). Thus, we originally proposed to effect a Heck cyclization/carbonylation beginning with dichloro iodo substrate **7** to produce γ-lactam ester **6** (Scheme 1).[11c] This compound would then be transformed into pentacyclic δ-lactam amidine **5**, and the lactam enolate would be allylated to produce key intermediate **4**. Based upon a close analogy in the work of the Rainier group,[8] we anticipated that this alkylation would occur stereoselectively from the least hindered face of the molecule to provide the desired perophoramidine relative stereochemistry at the two adjacent C-4/20 quaternary centers. It should then be possible to transform the allyl δ-lactam **4** to the natural product **1**. In this paper we report some of our exploratory studies on implementing the strategy outlined in Scheme 1.

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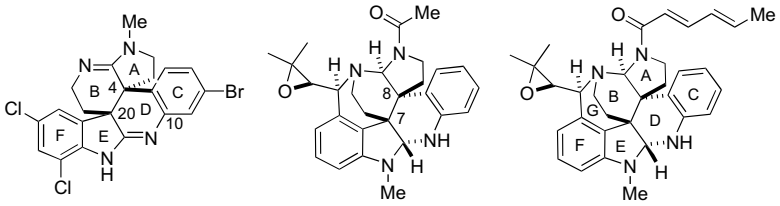
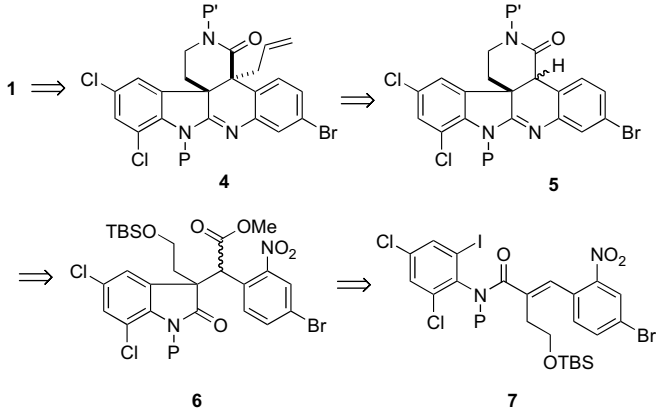


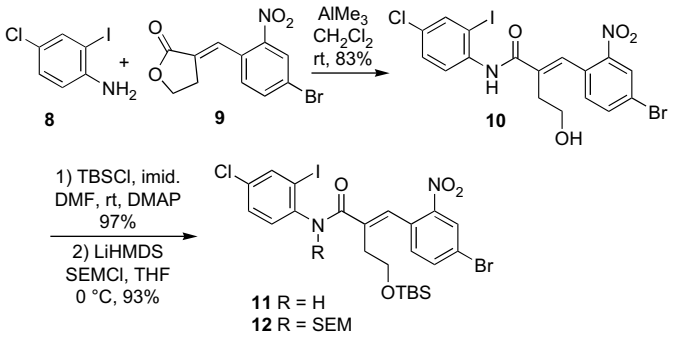
Figure 1. Structures of perophoramidine and the communesins.



Scheme 1. Retrosynthetic strategy.

3. Results and discussion

In our recent paper we reported that the tandem intramolecular Heck cyclization/carbonylation of unsaturated amide **7** (P=MOM) afforded the desired tricyclic ester **6** in moderate yield along with some reductive (non-carbonylated) Heck product.[11c] It was subsequently found, however, that this transformation is quite capricious, particularly upon scaleup. Therefore, we decided to first explore some Heck/carbonylation reactions of related systems with varied substitution in the F-ring as well as different protecting groups on the nitrogen of the α,β-unsaturated amide. The substrates for this study were prepared as is exemplified for the iodo chloro unsaturated amide **12** in Scheme 2. Thus, condensation of the aluminum amide reagent[12] derived from commercially available aniline **8** with unsaturated lactone **9**[11c] afforded amide **10** in high yield. The alcohol functionality of **10** was protected as silyl ether **11** and the amide nitrogen was N-alkylated with SEM-Cl to produce **12**.



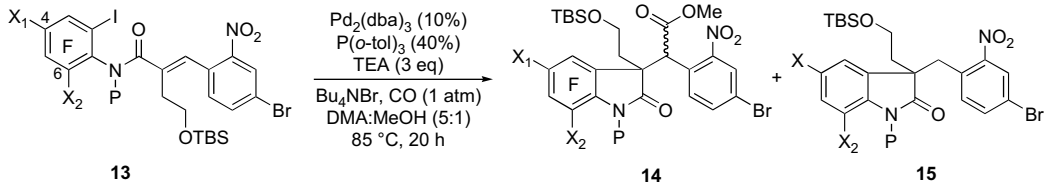
Scheme 2.

Using this same approach, the substrates **13** shown in Table 1 were prepared. The tandem intramolecular Heck cyclization/carbonylation was investigated with each of these systems using the standard set of experimental conditions shown. These exploratory reactions were generally conducted on approximately 50 mg scales. Since products **14**, **15** and the starting material **13** were not easily separable, the reaction mixtures were first partially purified by column chromatography, and the resulting products were analyzed by proton NMR. In the case of the 4,6-dichlorinated F-ring substrates in entries 1 and 2, a large variation was found with the two amide protecting groups. While the MOM-protected system **13** did give some of the desired diastereomeric ester products **14**, a significant amount of reductive Heck product **15** was usually formed (entry 1).[13] To our surprise, however, the analogous SEM-protected unsaturated amide was unreactive in the Heck process (entry 2). In the case of the non-chlorinated substrates in entries 3 and 4, the cyclizations tended to be very slow and significant amounts of starting material were recovered. This result may be due to a sluggish oxidative insertion of Pd^0 into the iodo compounds lacking the electron withdrawing chlorine substituents. The C-4 monochloro substrates in entries 5 and 6 both provided significant amounts of the desired Heck/carbonylation products **14** with lesser amounts of reductive Heck products **15** and starting materials. It is possible that the dichloro substrates have an unfavorable amide conformation for the cyclization relative to the monochloro systems due to steric interactions between the C-6 halogen and the amide nitrogen protecting group. The slightly larger SEM group (entry 2) may experience an enhanced steric effect relative to the MOM compound (entry 1). From a preparative point of view, the SEM-protected system in entry 6 proved to be the most useful (vide infra). It should be noted that Fuchs and Funk[7a] have reported the feasibility of effecting a late-stage F-ring chlorination in their total synthesis of perophoramidine (**1**).

Since some of the dichloro lactone **16** was available from our earlier work,[11c] we initially explored a few further transformations of this compound (Scheme 3). Thus, the lactone **16** was opened with benzylamine in refluxing toluene to afford hydroxyamide **17** as a mixture of diastereomers. The alcohol functionality of **17** was initially converted to the tosylate **18**, and then to the bromide **19**. In an attempt to intramolecularly N-alkylate the secondary amide functionality of **19** to produce the corresponding *N*-benzyllactam (cf. **5**), the compound was heated at 60 °C with cesium carbonate in DMF. To our surprise, the products of this reaction proved to be a 1:5 mixture of the epimeric pentacyclic lactams **20** and **21**. Removal of the MOM protecting group from the major isomer **21** provided γ-lactam **22**, whose structure was firmly established by X-ray crystallography.[14]

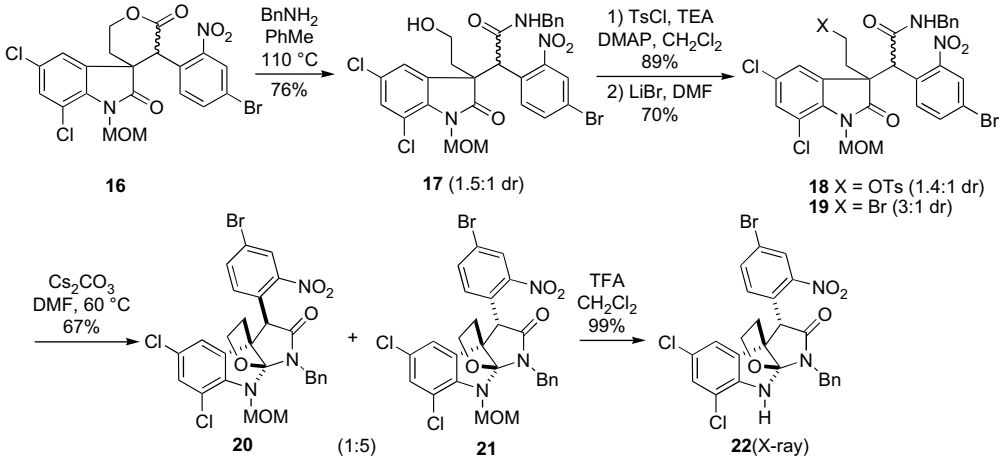
In order to further explore the elaboration of a Heck/carbonylation product toward perophoramidine, we opted to continue the route with the monochloro-*N*-SEM compound in entry 6 (Table 1) since we could prepare this intermediate in reasonable quantity. Therefore, iodo chloro substrate **12** (~6.6 g) was subjected to the standard intramolecular Heck/carbonylation conditions (Scheme 4). However, since the desired product was not separable from the starting material or the reductive Heck product, the TBS protecting group was first removed from the crude material to afford ester

Table 1
Tandem Heck reaction/carbonylation

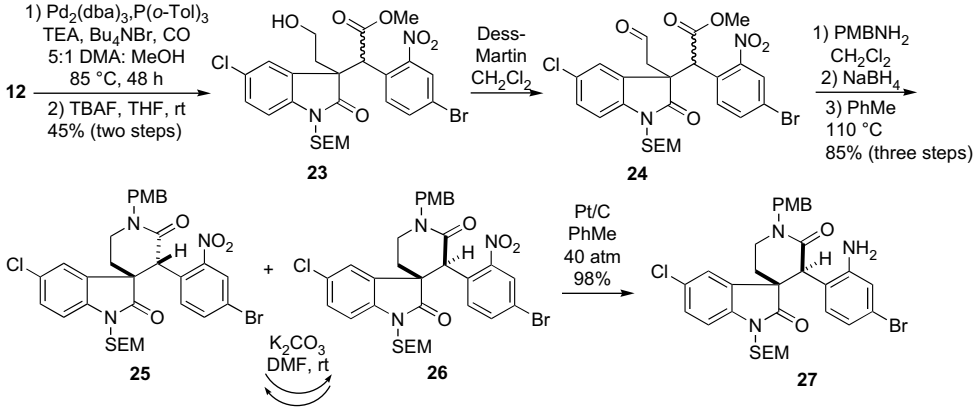


13 **14** **15**

Entry	X_1	X_2	P	**14** (%)	**15** (%)	**13** (%)
1	Cl	Cl	MOM	30	25	45
2	Cl	Cl	SEM	Trace	—	90
3	H	H	MOM	25	—	75
4	H	H	SEM	28	11	61
5	Cl	H	MOM	57	31	12
6	Cl	H	SEM	53	23	24



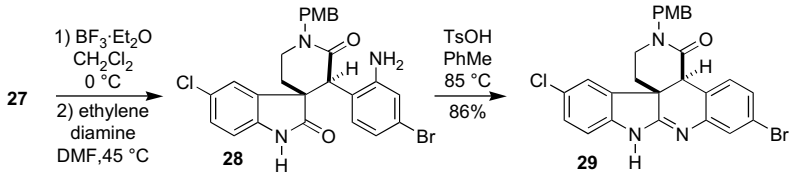
Scheme 3.



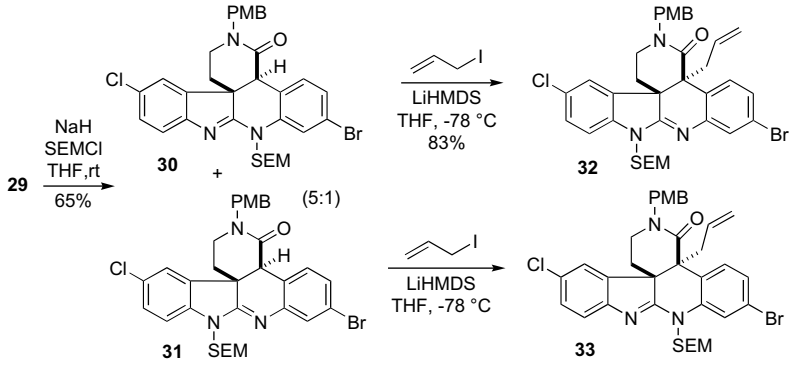
Scheme 4.

alcohol **23**, which could then be isolated by column chromatography as a 1:1 mixture of diastereomers in 45% total yield based on iodide **12**.

To continue the synthesis, alcohol **23** was oxidized with the Dess–Martin periodinane to aldehyde **24** (1:1 diastereomer mixture), which was subjected to a reductive amination sequence with *p*-methoxybenzylamine. The resulting aminoester was then thermally cyclized to afford a chromatographically separable mixture of PMB-protected δ-lactams **25** and **26** as a 1:1.66 mixture of diastereomers. Although the trans isomer **25** was not useful for formation of the lower amidine (vide infra), it was found that the cis and trans isomers can be easily equilibrated with potassium carbonate in DMF at rt. For example, a 2:1 mixture of **25**:**26** can be equilibrated to a 2:1 mixture favoring the desired cis isomer **26** (see Section 5). It should be noted that a similar epimerization was required in the Rainier work prior to formation of the lower amidine.[8] Catalytic hydrogenation of the nitro group of **26** over 5% platinum on carbon then afforded the aniline **27** in high yield.



Scheme 5.



Scheme 6.

Attempts were initially made to directly cyclize the SEM-protected *cis*-γ-lactam aniline **27** to the lower amidine, but we were unable to effect this transformation cleanly. Therefore, using a modification of literature procedures,[15] the SEM group of protected lactam **27** was removed via a two-step sequence to afford NH lactam **28** (Scheme 5). We were pleased to find that this compound cyclized smoothly to the desired pentacyclic lactam amidine **29** simply by heating with *p*-toluenesulfonic acid in toluene (86% overall yield from lactam **27**). However, it was observed that the corresponding *trans* lactam aniline prepared from intermediate **25** could not be cyclized to generate the lower amidine under similar conditions, perhaps for reasons of strain. In addition, we have been unable to effect an in situ epimerization/cyclization of the *trans* lactam aniline.

Our next goal was to introduce the C4 quaternary center with the requisite perophoramidine configuration into this pentacyclic system. To do so, however, it was first necessary to protect the amidine functionality. Thus, treatment of **29** with SEMCl in the presence of sodium hydride led to a separable 5:1 mixture of *N*-SEM amidines **30** and **31** (Scheme 6). The major lactam isomer **30** can be deprotonated with lithium hexamethyldisilazide followed by addition of allyl iodide, which led to a single alkylation product **32** in good yield. Allylation of the minor SEM-protected isomer **31** under the same reaction conditions afforded the desired product **33** in similar yield. The stereochemistry of the alkylation products was assigned as shown by analogy with the work of Rainier et al.,[8] and by comparison with spectra of a similar compound obtained in their work.

4. Conclusion

We have tested the feasibility of executing the strategy outlined in Scheme 1 for synthesis of perophoramidine (**1**). The optimum substrate for the key tandem Heck cyclization/carbonylation step proved to be the F-ring C-4 monochlorinated system **12**. Therefore it will be necessary to introduce the remaining C-6 chlorine at a late stage in the synthesis, as was done by Fuchs and Funk.[7] It is also possible to prepare and stereoselectively alkylate a pentacyclic amidine δ-lactam like **30** to form the contiguous quaternary C-4/20 centers of the alkaloid. Our intention is to utilize what we have learned from the work outlined here to complete a total synthesis of perophoramidine.

5. Experimental

5.1. General methods

All non-aqueous reactions were carried out under a positive atmosphere of argon in flame-dried glassware unless otherwise noted. Anhydrous THF, CH_2Cl_2, and toluene were obtained from a solvent dispensing system. All other solvents and reagents were used as obtained from commercial sources without further purification unless noted. ^1H and ^{13}C NMR spectra were recorded on Bruker DPX-300, CDPX-300, AMX-360 or DRX-400 MHz spectrometers. Infrared spectral data were recorded using a Perkin–Elmer 1600 FTIR. Flash column chromatography was performed using Sorbent Technologies silica gel 60 (230–400 mesh).

*5.1.1. (E)-2-(4-Bromo-2-nitrobenzylidene)-N-(4-chloro-2-iodophenyl)-4-hydroxybutanamide (**10**)*

A mixture of lactone **9**[11c] (15.20 g, 51.00 mmol), 4-chloro-2-iodoaniline (**8**, 13.08 g, 51.00 mmol), and dichloromethane (360 mL) was cooled to 0 °C, and 2.0 M trimethylaluminum in hexanes (40.8 mL, 81.6 mmol) was slowly added. The reaction mixture was stirred for 24 h and gradually warmed to rt. The mixture was then slowly poured into ice in small aliquots. The thick slurry was diluted with a 3:3:1 solution of brine, water, and 1 N HCl. The aqueous layers were thoroughly extracted with THF. The organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The resulting solid was triturated using 50 mL of dichloromethane. The title compound **10** was obtained as an insoluble, bright yellow solid (23.26 g, 83%). R_f=0.13 (2:1 hexanes/EtOAc); ^1H NMR (THF-d_8, 360 MHz) δ 8.33 (d, J=2.0 Hz, 1H), 8.10 (d, J=8.8 Hz, 1H), 7.87–7.94 (m, 2H), 7.71 (d, J=8.4 Hz, 1H), 7.69 (s, 1H), 7.38 (dd, J=8.8, 2.4 Hz, 1H), 3.64 (t, J=6.1 Hz, 2H), 2.60 (t, J=6.0 Hz, 2H).

*5.1.2. (E)-2-(4-Bromo-2-nitrobenzylidene)-4-(tert-butyldimethyl silyloxy)-N-(4-chloro-2-iodophenyl)butanamide (**11**)*

A mixture of alcohol **10** (5.00 g, 9.1 mmol), imidazole (926 mg, 13.6 mmol), *tert*-butyldimethylsilyl chloride (1.57 g, 10.4 mmol), and DMAP (110 mg, 0.91 mmol) in DMF (90 mL) was stirred at rt for 2 h. The mixture was then poured into aqueous NH_4Cl and was

extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude residual oil was purified via column chromatography, eluting with 9:1 hexanes/EtOAc. The silyl ether **11** was isolated as a viscous yellow oil (5.83 g, 97%). R_f=0.65 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (d, J=2.0 Hz, 1H), 8.28 (br s, 1H), 8.25 (d, J=8.9 Hz, 1H), 7.74–7.83 (m, 2H), 7.62 (s, 1H), 7.57 (d, J=8.3 Hz, 1H), 7.34 (dd, J=8.8, 2.4 Hz, 1H), 3.72 (t, J=5.9 Hz, 2H), 2.66 (t, J=5.8 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 166.7, 148.0, 138.2, 138.0, 137.1, 136.5, 133.1, 131.2, 130.2, 129.3, 128.0, 122.5, 90.4, 61.5, 31.3, 25.9, 18.3, −5.5; HRMS-ES $[M+H]^+$ calcd for $C_{23}H_{27}BrClIN_2O_4Si$: 664.9736, found: 664.9735.

5.1.3. (E)-2-(4-Bromo-2-nitrobenzylidene)-4-(tert-butyldimethylsilyloxy)-N-(4-chloro-2-iodophenyl)-N-((2-(trimethylsilyl)ethoxy)methyl)butanamide (**12**)

A solution of amide **11** (6.04 g, 9.07 mmol) in THF (91 mL) was cooled to −78 °C and 1.0 M lithium bis-(trimethylsilyl)amide in THF (9.5 mL, 9.5 mmol) was slowly added over 10 min. After stirring the mixture for an additional 20 min, 2-(trimethylsilyl)ethoxymethyl chloride (2.01 mL, 11.33 mmol) was added. The reaction mixture was then warmed to 0 °C. After stirring for 2 h, the mixture was poured into aqueous NH_4Cl and was extracted with EtOAc. The organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude residual oil was purified via column chromatography, eluting with 9:1 hexanes/EtOAc. The title compound **12** was isolated as a viscous yellow oil (6.67 g, 93%). R_f=0.44 (5:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz, broad due to amide rotamers) δ 8.02–8.34 (m, 1H), 7.88 (br s, 1H), 6.65–7.80 (m, 5H), 5.13–5.89 (m, 1H), 4.65 (br s, 1H), 3.28–4.01 (m, 4H), 2.10–2.76 (m, 2H), 0.75–0.94 (m, 2H), 0.86 (s, 9H), 0.03 (s, 6H), −0.07 (br s, 9H); HRMS-ES $[M+H]^+$ calcd for $C_{29}H_{42}BrClIN_2O_5Si_2$: 794.0527, found: 794.0528.

5.1.4. N-Benzyl-2-(4-bromo-2-nitrophenyl)-2-(5,7-dichloro-3-(2-hydroxyethyl)-1-(methoxymethyl)-2-oxoindolin-3-yl)-acetamide (**17**)

To lactone **16**[11c] (86.9 mg, 0.16 mmol) were added toluene (2.8 mL) and benzylamine (61 μL, 0.56 mmol), and the mixture was stirred at 110 °C for 6 h. The mixture was cooled, poured into water, and was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude residual oil was purified via column chromatography, eluting with 2.5:1 hexanes/EtOAc. The title compound **17** was isolated as an off-white foam as an inseparable 1.5:1 mixture of diastereomers (86.5 mg, 76%). R_f=0.33 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, J=1.9 Hz, 0.41H), 7.65–7.85 (m, 1.59H), 7.41 (dd, J=8.6, 2.0 Hz, 0.59H), 7.17–7.45 (m, 5H), 7.03–7.15 (m, 2H), 6.96 (t, J=5.8 Hz, 0.59H), 6.80 (d, J=2.0 Hz, 0.41H), 6.60 (t, J=5.8 Hz, 0.41H), 5.23 (d, J=10.7 Hz, 0.41H), 5.16 (d, J=10.7 Hz, 0.41H), 5.11 (d, J=10.7 Hz, 0.59H), 5.01 (d, J=10.7 Hz, 0.59H), 4.85 (s, 0.59H), 4.68 (s, 0.41H), 4.49 (dd, J=15.0, 6.1 Hz, 0.59H), 4.39 (dd, J=14.9, 6.2 Hz, 0.41H), 4.30 (dd, J=15.0, 5.6 Hz, 0.59H), 4.18 (dd, J=14.9, 5.3 Hz, 0.41H), 3.28–3.42 (m, 1H), 3.29 (s, 1.23H), 3.15–3.28 (m, 0.59H), 3.00 (s, 1.77H), 2.10–2.42 (m, 2H); LRMS (ES+) calcd for $C_{27}H_{24}BrCl_2N_3O_6$ $[M+Na]^+$: 636.0, found: 635.9.

5.1.5. 2-(3-(2-(Benzylamino)-1-(4-bromo-2-nitrophenyl)-2-oxoethyl)-5,7-dichloro-1-(methoxymethyl)-2-oxoindolin-3-yl)ethyl 4-methylbenzenesulfonate (**18**)

To alcohol **17** (187.2 mg, 0.294 mmol), *p*-toluenesulfonyl chloride (61.6 mg, 0.323 mmol), and DMAP (7.2 mg, 0.059 mmol) was added a solution of TEA (123 μL, 0.882 mmol) in dichloromethane (2.9 mL) and the reaction mixture was stirred for 2 h. The mixture was then poured into saturated $NaHCO_3$ and was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude residual oil was purified by column chromatography, eluting with 3:1 hexanes/EtOAc. The tosylate **18** was isolated as a white solid as an inseparable 1.4:1 mixture of diastereomers (206.1 mg, 89%). R_f=0.64 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00 (d, J=1.9 Hz, 0.41H), 7.87 (d, J=1.9 Hz, 0.59H), 7.66–7.84 (m, 1.59H), 7.39–7.58 (m, 3H), 6.98–7.38 (m, 8H), 6.84 (d, J=2.0 Hz, 0.41H), 6.46 (t, J=5.7 Hz, 0.59H), 6.18 (t, J=5.7 Hz, 0.41H), 5.22 (d, J=11.0 Hz, 0.41H), 5.15 (d, J=11.0 Hz, 0.41H), 5.12 (d, J=10.9 Hz, 0.59H), 5.00 (d, J=10.9 Hz, 0.59H), 4.71 (s, 0.59H), 4.51 (s, 0.41H), 4.38–4.49 (m, 1H), 4.09–4.30 (m, 1H), 3.43–3.77 (m, 2H), 3.32 (s, 1.23H), 2.99 (s, 1.77H), 2.79 (dt, J=14.2, 4.9 Hz, 0.41H), 2.41 (s, 3H), 2.18–2.38 (m, 1.59H).

5.1.6. N-Benzyl-2-(4-bromo-2-nitrophenyl)-2-(3-(2-bromoethyl)-5,7-dichloro-1-(methoxymethyl)-2-oxoindolin-3-yl)acetamide (**19**)

A mixture of tosylates **18** (31.1 mg, 39.3 μmol), lithium bromide (27.3 mg, 0.314 mmol), and DMF (0.69 mL) was heated at 70 °C for 3 h. The mixture was then cooled to rt, poured into water, and extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude oil was purified by column chromatography, eluting with 5:1 hexanes/EtOAc. The bromide **19** was isolated as a white solid as an inseparable 3:1 mixture of diastereomers (19.3 mg, 70%). R_f=0.52 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (s, 0.25H), 7.95 (d, J=2.0 Hz, 0.75H), 7.82 (d, J=2.1 Hz, 0.75H), 7.74 (dd, J=8.5, 2.1 Hz, 0.75H), 7.20–7.35 (m, 5H), 7.00–7.13 (m, 2H), 6.92 (d, J=2.0 Hz, 0.25H), 6.39 (t, J=5.8 Hz, 0.75H), 6.13 (t, J=5.8 Hz, 0.25H), 5.31 (d, J=10.7 Hz, 0.25H), 5.21 (d, J=10.7 Hz, 0.25H), 5.20 (d, J=10.7 Hz, 0.75H), 5.12 (d, J=10.7 Hz, 0.75H), 4.76 (s, 0.75H), 4.62 (s, 0.25H), 4.39–4.54 (m, 1H), 4.14–4.29 (m, 1H), 3.33 (s, 0.75H), 3.08 (s, 2.25H), 2.30–2.95 (m, 4H); LRMS (ES+) calcd for $C_{27}H_{23}Br_2Cl_2N_3O_5$ $[M+Na]^+$: 719.9, found: 719.9.

5.1.7. Conversion of bromides **19** to lactams **20** and **21**

A mixture of bromides **19** (19.3 mg, 27.5 μmol), cesium carbonate (44.8 mg, 0.138 mmol), and DMF (0.55 mL) was heated at 60 °C for 1 h. The mixture was then cooled to rt, poured into water, and extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude residual oil was purified via column chromatography, eluting with 5:1 hexanes/EtOAc to afford **20** and **21** as a 1:5 mixture of diastereomers (11.4 mg, 67%). ^{1}H NMR ($CDCl_3$, 300 MHz) (*major diastereomer*) δ 8.05 (d, J=2.0 Hz, 1H), 8.42 (dd, J=8.4, 2.0 Hz, 1H), 7.20–7.42 (m, 5H), 6.97 (d, J=2.1 Hz, 1H), 6.47 (d, J=8.4 Hz, 1H), 6.25 (d, J=2.0 Hz, 1H), 4.90 (d, J=9.8 Hz, 1H), 4.8 (d, J=15.6 Hz, 1H), 4.72 (d, J=15.6 Hz, 1H), 4.71 (d, J=9.8 Hz, 1H), 4.50 (s, 1H), 3.93–4.15 (m, 2H), 3.28 (s, 3H), 2.53–2.74 (m, 2H); LRMS (ES+) calcd for $C_{27}H_{22}BrCl_2N_3O_5$ $[M+Na]^+$: 640.0, found: 640.0.

5.1.8. Synthesis of lactam **22**

A mixture of MOM-protected cyclization products **20** and **21** (10.1 mg, 16.3 μmol), dichloromethane (0.33 mL), and TFA (4 μL, 50 μmol) was stirred for 2 h at rt. The mixture was then poured into aqueous $NaHCO_3$ and was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude residual oil was purified via chromatography, eluting with 4:1 hexanes/EtOAc to afford a white solid, which was a 5:1 mixture of diastereomers (9.3 mg, 99%). The isomers were separated by preparative TLC eluting with 2.5:1 hexanes/EtOAc, and the major isomer **22** was crystallized from CH_2Cl_2/hexanes for X-ray analysis. Major diastereomer **22**: R_f=0.43 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.04 (d, J=2.0 Hz, 1H), 7.30–7.55 (m, 6H), 6.89 (d, J=1.9 Hz, 1H), 6.56 (d, J=8.4 Hz, 1H), 6.44 (d, J=1.9 Hz, 1H), 4.97 (d, J=14.6 Hz, 1H), 4.59 (s, 1H), 4.49 (s, 1H), 4.47 (d, J=14.2 Hz, 1H), 3.87–4.02 (m, 2H), 2.61 (t, J=6.4, 1.8 Hz, 2H);

HRMS-ES $[M+H]^+$ calcd for $C_{25}H_{19}BrCl_2N_3O_4$: 573.9936, found: 573.9940.

*5.1.9. Methyl 2-(4-bromo-2-nitrophenyl)-2-(5-chloro-3-(2-hydroxyethyl)-2-oxo-1-((2-(trimethylsilyl)ethoxy)methyl)indolin-3-yl)acetate (**23**)*

A 500 mL Schlenk flask was charged with the Heck-carbonylation precursor **12** (6.67 g, 8.38 mmol), $(dba)_3$ dipalladium(0) (767.6 mg, 0.84 mmol), tri-*o*-tolylphosphine (1.02 g, 3.35 mmol), and *n*-tetrabutylammonium bromide (5.40 g, 16.78 mmol). *N*,*N*-Dimethylacetamide (204 mL) was added and the resulting mixture was stirred for 10 min. MeOH (41 mL) and then TEA (5.84 mL, 41.9 mmol) were added. After stirring the mixture for an additional 10 min, carbon monoxide was introduced. The sealed reaction flask was then heated at 85 °C for 48 h. After cooling to rt, the mixture was diluted with 1 L of EtOAc and was washed three times with water. The aqueous layers were back-extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude oil was partially purified via column chromatography, eluting with 9:1 hexanes/EtOAc. Because the desired ester could not be separated from the reductive Heck by-product or the starting material, the crude mixture was used directly in the next step.

To the above mixture were added THF (320 mL) and glacial acetic acid (4.80 mL, 83.4 mmol), followed by 1.0 M tetrabutylammonium fluoride in THF (25.2 mL, 25.2 mmol). The reaction mixture was stirred for 24 h at rt, poured into water, and the biphasic mixture was then carefully neutralized with aqueous $NaHCO_3$. The phases were separated and the aqueous layers were extracted with EtOAc. The combined organic extract was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude residual oil was purified via column chromatography, eluting with 3.5:1 hexanes/EtOAc. The hydroxyester **23** was isolated as a yellow solid (2.32 g, 45% over two steps, mp 50–56 °C), which was an inseparable 1:1 mixture of diastereomers. R_f=0.55 (1:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.07 (d, *J*=2.1 Hz, 0.5H), 7.92 (d, *J*=2.1 Hz, 0.5H), 7.68 (dd, *J*=8.5, 2.1 Hz, 0.5H), 7.56 (d, *J*=2.1 Hz, 0.5H), 7.46 (dd, *J*=8.5, 2.1 Hz, 0.5H), 7.42 (d, *J*=8.5 Hz, 0.5H), 7.25–7.33 (m, 1.5H), 7.02 (d, *J*=8.4 Hz, 0.5H), 6.89 (d, *J*=8.4 Hz, 0.5H), 6.85 (d, *J*=2.1 Hz, 0.5H), 5.18 (s, 0.5H), 5.11 (s, 0.5H), 5.09, 5.04 (ABq, *J*=11.1 Hz, 1H), 4.92, 4.86 (ABq, *J*=11.0 Hz, 1H), 3.62 (s, 1.5H), 3.61 (s, 1.5H), 3.50–3.60 (m, 1H), 3.28–3.46 (m, 2H), 3.06–3.28 (m, 1H), 2.15–2.34 (m, 2H), 1.14 (dd, *J*=7.0, 4.7 Hz, 0.5H), 0.96 (dd, *J*=6.8, 4.8 Hz, 0.5H), 0.75–0.93 (m, 2H), −0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 177.9, 177.8, 170.04, 169.98, 150.84, 150.76, 141.7, 141.5, 135.2, 134.9, 133.0, 132.9, 130.0, 129.6, 129.2, 129.0, 128.6, 128.1, 128.0, 127.5, 126.8, 126.6, 125.3, 124.8, 122.7, 122.3, 111.2, 110.8, 70.4, 70.0, 66.4, 66.2, 58.5, 53.3, 52.8, 52.61, 52.56, 49.8, 49.6, 38.6, 35.5, 17.9, 17.8, −1.4, −1.45; IR (thin film) ν (cm^{-1}) 3467, 1724, 1535; HRMS-ES $[M+H]^+$ calcd for $C_{25}H_{31}BrClN_2O_7Si$: 613.0772, found: 613.0758.

*5.1.10. Methyl 2-(4-bromo-2-nitrophenyl)-2-(5-chloro-2-oxo-3-(2-oxoethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)indolin-3-yl)-acetate (**24**)*

To a mixture of alcohol **23** (500 mg, 0.814 mmol) and Dess–Martin periodinane (520 mg, 1.22 mmol) was added dichloromethane (8 mL), and the reaction mixture was stirred for 1 h at rt. Saturated aqueous $Na_2S_2O_3$ (10 mL) was added and the biphasic mixture was vigorously stirred for 5 min. The mixture was separated and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude residual oil was purified via column chromatography, eluting with 4:1 hexanes/EtOAc. The aldehyde **24** was isolated as a yellow solid (493 mg, 99%, mp 57–62 °C) consisting of an inseparable 1:1 mixture of diastereomers. R_f=0.44 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.37 (s, 0.5H), 9.34 (s, 0.5H), 8.11 (d, *J*=2.1 Hz, 0.5H), 8.02 (dd, *J*=7.9, 1.0 Hz, 0.5H), 7.97 (dd, *J*=7.8, 1.7 Hz, 0.5H), 7.91 (d, *J*=2.1 Hz, 0.5H), 7.71 (dd, *J*=8.5, 2.1 Hz, 0.5H), 7.54 (d, *J*=8.5 Hz, 0.5H), 7.49 (d, *J*=2.1 Hz, 0.5H), 7.38–7.47 (m, 1H), 7.22–7.30 (m, 1H), 7.17 (dt, *J*=7.8, 1.7 Hz, 0.5H), 7.03–7.10 (m, 1.5H), 6.89 (d, *J*=8.4 Hz, 0.5H), 5.15, 5.05 (ABq, *J*=11.2 Hz, 1H), 5.07 (s, 0.5H), 5.00 (s, 0.5H), 4.95, 4.81 (ABq, *J*=11.1 Hz, 1H), 3.88 (d, *J*=17.9 Hz, 0.5H), 3.46–3.69 (m, 2H), 3.64 (s, 3H), 3.32–3.40 (m, 0.5H), 3.15 (d, *J*=7.3 Hz, 0.5H), 3.10 (d, *J*=7.0 Hz, 0.5H), 0.78–0.98 (m, 2H), −0.05 (s, 4.5H), −0.06 (s, 4.5H); ^{13}C NMR ($CDCl_3$, 75 MHz) 196.4, 196.2, 176.7, 176.3, 170.0, 169.7, 150.3, 141.9, 141.4, 135.6, 134.9, 132.6, 132.2, 130.2, 129.5, 129.2, 128.5, 128.4, 128.3, 127.6, 126.1, 125.0, 124.0, 122.9, 111.5, 111.0, 70.3, 70.0, 66.4, 66.2, 52.9, 52.8, 51.1, 50.1, 49.8, 48.9, 48.6, 45.9, 17.9, 17.8, −1.4, −1.5; IR (thin film) ν (cm^{-1}) 1728, 1536; HRMS-ES $[M+H]^+$ calcd for $C_{25}H_{29}BrClN_2O_7Si$: 611.0616, found: 611.0628.

*5.1.11. 3′-(4-Bromo-2-nitrophenyl)-5-chloro-1′-(4-methoxy benzyl)-1-((2-(trimethylsilyl)ethoxy)methyl)spiro[indoline-3,4′-piperidine]-2,2′-dione (**25** and **26**)*

A mixture of aldehyde **24** (493 mg, 0.806 mmol), dichloromethane (16 mL), and *p*-methoxybenzylamine (0.110 mL, 0.847 mmol) was stirred for 30 min at rt, and the solvent was removed in vacuo. The crude imine was dissolved in methanol (10 mL). The reaction mixture was cooled to 0 °C and sodium borohydride (91.5 mg, 2.42 mmol) was added. After 1 h, the reaction mixture was poured into aqueous NH_4Cl and the aqueous layer was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo.

A mixture of the above crude aminoester and toluene (25 mL) was heated at 110 °C for 5 h. The solvent was removed in vacuo and the crude residual oil was purified via column chromatography, eluting with 4:1 hexanes/EtOAc. The lactam was isolated as a light yellow solid (702 mg, 85% over three steps), consisting of a mixture of diastereomers in a 1.66:1 cis/trans ratio. The isomers were separated by careful chromatography of the mixture. *cis*-Diastereomer **26**: R_f=0.29 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86 (d, *J*=2.0 Hz, 1H), 7.59 (dd, *J*=8.5, 2.0 Hz, 1H), 7.36 (d, *J*=8.6 Hz, 2H), 7.31 (d, *J*=8.5 Hz, 1H), 7.22 (dd, *J*=8.4, 2.0 Hz, 1H), 6.91–7.00 (m, 3H), 6.85 (d, *J*=8.4 Hz, 1H), 5.01 (s, 1H), 4.96, 4.52 (ABq, *J*=14.2 Hz, 2H), 4.93, 4.85 (ABq, *J*=11.0 Hz, 2H), 3.82 (s, 3H), 3.51–3.69 (m, 1H), 3.39–3.48 (m, 1H), 3.24–3.38 (m, 2H), 2.03–2.17 (m, 2H), 0.70–1.00 (m, 2H), −0.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.9, 166.9, 159.3, 150.4, 139.4, 135.7, 133.5, 130.7, 130.04, 129.98, 129.3, 129.1, 128.3, 127.5, 123.6, 121.6, 114.2, 111.1, 69.6, 66.3, 55.3, 52.0, 50.5, 48.3, 42.5, 29.6, 17.6, −1.4; IR (thin film) ν (cm^{-1}) 1717, 1532, 1248; HRMS-ES $[M+H]^+$ calcd for $C_{32}H_{36}BrClN_3O_6Si$: 700.1245, found: 700.1219.

trans-Diastereomer **25**: R_f=0.27 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (d, *J*=2.1 Hz, 1H), 7.39 (d, *J*=8.6 Hz, 2H), 7.32 (dd, *J*=8.5, 2.1 Hz, 1H), 7.21 (dd, *J*=8.4, 2.1 Hz, 1H), 6.95 (d, *J*=8.7 Hz, 2H), 6.84 (d, *J*=8.4 Hz, 1H), 6.64 (d, *J*=2.0 Hz, 1H), 6.61 (d, *J*=8.5 Hz, 1H), 5.23 (s, 1H), 5.10, 4.30 (ABq, *J*=14.0 Hz, 2H), 4.93, 4.85 (ABq, *J*=11.1 Hz, 2H), 3.83 (s, 3H), 3.53–3.69 (m, 2H), 3.18–3.27 (m, 1H), 2.95–3.04 (m, 1H), 2.43–2.53 (m, 1H), 1.78–1.87 (m, 1H), 0.63–0.89 (m, 2H), −0.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 176.0, 166.8, 159.5, 151.3, 140.2, 134.6, 132.6, 130.3, 130.0, 129.3, 129.2, 128.7, 128.4, 128.1, 127.4, 124.6, 121.6, 114.4, 111.4, 69.6, 65.9, 55.3, 52.4, 50.5, 47.1, 43.0, 30.8, 17.6, −1.4; IR (thin film) ν (cm^{-1}) 1724, 1536, 1248; HRMS-ES $[M+H]^+$ calcd for $C_{32}H_{36}BrClN_3O_6Si$: 700.1245, found: 700.1226.

*5.1.12. Equilibration of 3′-(4-bromo-2-nitrophenyl)-5-chloro-1′-(4-methoxybenzyl)-1-((2-(trimethylsilyl)ethoxy)methyl)spiro [indoline-3,4′-piperidine]-2,2′-dione (**25** and **26**)*

A mixture of a 1:2 cis/trans mixture of lactam diastereomers (193 mg, 0.276 mmol), finely powdered potassium carbonate

(110 mg, 0.796 mmol), and DMF (10 mL) was stirred for 18 h at rt. The mixture was then diluted with EtOAc and was poured into aqueous NH_4Cl. The aqueous layers were extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude oil was purified via column chromatography, eluting with 4:1 hexanes/EtOAc. The title compound was isolated as a light yellow solid (174 mg, 90%), consisting of a separable mixture of lactam diastereomers in a 2:1 cis/trans ratio.

5.1.13. 3′-(2-Amino-4-bromophenyl)-5-chloro-1′-(4-methoxybenzyl)-1-((2-(trimethylsilyl)ethoxy)methyl)spiro[indoline-3,4′-piperidine]-2,2′-dione (**27**)

A mixture of *cis*-lactam **26** (30.2 mg, 43.0 μmol), 5% platinum on carbon (20.1 mg, 5.16 μmol), and toluene (3.3 mL) was placed in a high-pressure reaction vessel, and was flushed with H_2. The hydrogen pressure was increased to 40 atm and the reaction mixture was stirred for 5 h at rt. The pressure was released, the suspension was diluted with EtOAc, and was filtered through Celite. The solvent was removed in vacuo to give the title compound **27** as a single diastereomer, which was used in the next step without further purification (light yellow solid, 28.3 mg, 98%). R_f=0.27 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33 (d, J=8.6 Hz, 2H), 7.11–7.29 (br m, 2H), 6.89 (br m, 3H), 6.82 (d, J=8.3 Hz, 1H), 6.10–6.77 (br m, 2H), 4.93 (br s, 2H), 4.88 (d, J=14.4 Hz, 1H), 4.50 (d, J=14.4 Hz, 1H), 3.86–4.23 (br m, 2H), 3.79 (s, 3H), 2.80–3.83 (br m, 4H), 2.13–2.40 (br m, 1H), 1.80–2.02 (br m, 1H), 0.55–0.97 (br m, 2H), −0.09 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.3, 159.1, 139.7, 129.8, 128.8, 123.2, 121.9, 120.7, 119.9, 114.0, 111.0, 69.6, 66.1, 55.2, 52.0, 50.4, 47.4, 17.5, −1.4 (both the proton and carbon spectra show broadened peaks); IR (thin film) ν (cm^{-1}) 3425, 3353, 1712, 1247; HRMS-ES $[M+H]^+$ calcd for $C_{32}H_{38}BrClN_3O_4Si$: 670.1503, found: 670.1516.

5.1.14. Synthesis of amidine **29**

A solution of SEM-protected oxindole **27** (28.3 mg, 42.1 μmol) in dichloromethane (28 mL) was cooled to 0 °C, and boron trifluoride etherate (47.6 μL, 376 μmol) was added in three equal portions over the course of 4 h. The reaction was monitored by TLC until all starting material had been consumed. At this time, the reaction mixture was poured into aqueous $NaHCO_3$. The phases were separated and the aqueous layer was extracted with EtOAc. The combined organic extract was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo.

A mixture of the above crude *N*,*O*-hemiaminal, DMF (1.7 mL), and ethylenediamine (14.1 μL, 211 μmol) was heated at 45 °C for 1 h. The mixture was diluted with EtOAc and was poured into water. The aqueous layer was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. This crude mixture was predominantly the deprotected oxindole **28**, along with a small amount of amidine **29**. The mixture was used without further purification.

A mixture of the above crude oxindole, *p*-toluenesulfonic acid monohydrate (24.0 mg, 126 μmol), and toluene (10.5 mL) was heated at 85 °C for 5 min. After cooling, the solution was poured into aqueous $NaHCO_3$ and was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The desired amidine **29** was isolated as a light yellow solid (18.9 mg, 86% over three steps). For characterization purposes, this material was triturated with dichloromethane and hexanes. R_f=0.45 (1:4 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.51 (d, J=8.2 Hz, 1H), 7.35 (d, J=8.5 Hz, 2H), 7.17–7.29 (m, 4H), 7.03 (d, J=8.2 Hz, 1H), 6.92 (d, J=8.5 Hz, 2H), 6.64 (s, 1H), 5.05 (d, J=14.0 Hz, 1H), 4.35 (d, J=14.0 Hz, 1H), 3.83 (s, 1H), 3.80 (s, 3H), 3.37 (ddd, J=25.0, 12.4, 5.4 Hz, 1H), 3.23 (dd, J=12.9, 6.6 Hz, 1H), 2.36 (ddd, J=25.7, 12.6, 6.7 Hz, 1H), 1.34 (dd, J=13.6, 4.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 165.9, 159.6, 140.9, 130.2, 129.33, 129.27, 128.1, 127.6, 127.1, 123.7, 122.9, 122.3, 118.8, 114.9, 114.4, 55.3, 50.2, 45.0, 43.0, 24.5; HRMS-ES $[M+H]^+$ calcd for $C_{26}H_{22}BrClN_3O_2$: 522.0584, found: 522.0562.

5.1.15. Preparation of SEM-amidines **30** and **31**

To a mixture of amidine **29** (19.0 mg, 36.3 μmol) in THF (0.40 mL) was added a 60% dispersion of sodium hydride in mineral oil (19 mg, 0.475 mmol) and the reaction mixture was stirred for 10 min. 2-(Trimethylsilyl)ethoxymethyl chloride (9.6 μL, 55 μmol) was added and the reaction mixture was stirred for 30 min, poured into aqueous NH_4Cl, and was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude solid consisted of a 5:1 mixture of *N*-SEM regioisomers **30** and **31**, which were separated via preparative TLC, eluting with 2:1 hexanes/EtOAc (total yield: 15.5 mg, 65%). The desired *N*-SEM protected amidines were isolated as light yellow solids.

Major isomer **30**: R_f=0.45 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (d, J=1.9 Hz, 1H), 7.50 (dd, J=8.2, 1.0 Hz, 1H), 7.35 (d, J=8.7 Hz, 2H), 7.18–7.27 (m, 3H), 6.92 (d, J=8.7 Hz, 2H), 6.61 (s, 1H), 6.01 (d, J=10.9 Hz, 1H), 5.10 (d, J=11.0 Hz, 1H), 5.04 (d, J=14.0 Hz, 1H), 4.34 (d, J=14.0 Hz, 1H), 3.80 (s, 3H), 3.60–3.78 (m, 3H), 3.42 (ddd, J=24.9, 12.5, 5.9 Hz, 1H), 3.23 (dd, J=12.9, 6.5 Hz, 1H), 2.35 (ddd, J=25.4, 13.0, 6.9 Hz, 1H), 1.17–1.30 (m, 1H), 0.80–1.07 (m, 2H), −0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 171.3, 166.0, 159.6, 153.0, 139.6, 137.8, 130.2, 129.3, 129.2, 128.2, 128.0, 126.7, 122.74, 122.67, 119.2, 119.1, 118.8, 114.4, 75.2, 66.0, 55.3, 50.2, 49.5, 44.7, 43.3, 24.6, 17.8, −1.4; HRMS-ES $[M+H]^+$ calcd for $C_{32}H_{36}BrClN_3O_3Si$: 652.1398, found: 652.1384.

Minor isomer **31**: R_f=0.48 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (dd, J=8.3, 1.2 Hz, 1H), 7.30–7.39 (m, 3H), 7.19–7.23 (m, 2H), 6.95 (d, J=8.5 Hz, 1H), 6.92 (d, J=8.6 Hz, 2H), 6.64 (d, J=1.9 Hz, 1H), 5.40 (d, J=10.9 Hz, 1H), 5.16 (d, J=10.9 Hz, 1H), 5.03 (d, J=14.0 Hz, 1H), 4.35 (d, J=14.0 Hz, 1H), 3.61 (s, 1H), 3.60 (ddd, J=16.2, 8.4, 2.3 Hz, 2H), 3.28 (ddd, J=25.1, 12.3, 5.4 Hz, 1H), 3.16 (dd, J=12.7, 6.5 Hz, 1H), 2.31 (ddd, J=25.7, 12.4, 6.8 Hz, 1H), 1.27 (dd, J=13.6, 4.1 Hz, 1H), 0.72–1.03 (m, 2H), −0.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 166.7, 166.2, 159.5, 145.1, 142.6, 131.3, 130.1, 129.2, 128.25, 128.17, 127.7, 127.4, 124.0, 122.1, 120.1, 114.4, 110.6, 70.5, 66.3, 55.3, 50.2, 45.5, 43.7, 42.6, 24.1, 17.7, −1.4; HRMS-ES $[M+H]^+$ calcd for $C_{32}H_{36}BrClN_3O_3Si$: 652.1398, found: 652.1381.

5.1.16. Allylation of SEM-amidine **30**

A solution of *N*-SEM protected amidine **30** (15.3 mg, 23.4 μmol) in THF (1.50 mL) was cooled to −78 °C and 1.0 M lithium bis(-trimethylsilyl)amide in THF (117 μL, 0.117 mmol) was slowly added. The reaction mixture was stirred for 15 min and allyl iodide (21.4 μL, 0.234 mmol) was added. After stirring for 2 h, the reaction mixture was quenched with aqueous NH_4Cl and then warmed to rt. The mixture was poured into water and was extracted with EtOAc. The organic extract was washed with brine, dried over $MgSO_4$, and the solvent was removed in vacuo. The crude solid was purified via preparative TLC, eluting with 2:1 hexanes/EtOAc. The desired allylated amidine **32** was isolated as a colorless oil (13.5 mg, 83%) as a single diastereomer. R_f=0.52 (2:1 hexanes/EtOAc); ^{1}H NMR ($CDCl_3$, 360 MHz) δ 7.52 (d, J=1.9 Hz, 1H), 7.50 (d, J=8.4 Hz, 1H), 7.31 (d, J=8.7 Hz, 2H), 7.15–7.24 (m, 3H), 6.90 (d, J=8.7 Hz, 2H), 6.63 (d, J=1.2 Hz, 1H), 5.93 (d, J=10.9 Hz, 1H), 5.18–5.32 (m, 1H), 5.04 (d, J=10.9 Hz, 1H), 4.95 (d, J=13.9 Hz, 1H), 4.57 (d, J=10.0 Hz, 1H), 4.39 (d, J=14.0 Hz, 1H), 4.34 (dd, J=17.1, 1.4 Hz, 1H), 3.80 (s, 3H), 3.64–3.76 (m, 2H), 3.45 (ddd, J=25.2, 12.5, 5.7 Hz, 1H), 3.21 (dd, J=12.9, 5.9 Hz, 1H), 2.76 (dd, J=14.2, 6.9 Hz, 1H), 2.48 (ddd, J=26.1, 13.2, 6.7 Hz, 1H), 2.14 (dd, J=14.2, 8.1 Hz, 1H), 1.19 (dd, J=13.6, 4.9 Hz, 1H), 0.89–1.07 (m, 2H), −0.04 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 172.6, 168.7, 159.5, 153.6, 139.5, 136.4, 132.7, 130.0, 129.3, 129.2, 128.4, 127.9,

126.8, 123.3, 123.1, 122.6, 119.4, 118.8, 118.7, 114.4, 75.1, 66.1, 55.3, 54.1, 50.8, 49.6, 43.3, 40.6, 27.3, 17.8, −1.4; HRMS-ES $[M+H]^+$ calcd for $C_{35}H_{40}BrClN_3O_3Si$: 692.1711, found: 692.1715.

The alkylation product **33** from the minor SEM-protected amidine **31** was prepared via a similar procedure. R_f=0.54 (2:1 hexanes/EtOAc); ^1H NMR ($CDCl_3$, 360 MHz) δ 7.49 (d, J=6.3 Hz, 1H), 7.28–7.34 (m, 3H), 7.16–7.23 (m, 2H), 6.91 (d, J=8.4 Hz, 1H), 6.90 (d, J=8.6 Hz, 2H), 6.66 (d, J=2.0 Hz, 1H), 5.39 (d, J=11.0 Hz, 1H), 5.30–5.41 (m, 1H), 4.99 (d, J=11.2 Hz, 1H), 4.95 (d, J=10.1 Hz, 1H), 4.37 (d, J=14.0 Hz, 1H), 4.20 (d, J=16.8 Hz, 1H), 3.80 (s, 3H), 3.64 (t, J=8.1 Hz, 2H), 3.34 (ddd, J=25.2, 12.6, 5.2 Hz, 1H), 3.15 (dd, J=12.9, 5.6 Hz, 1H), 2.86 (dd, J=14.2, 5.2 Hz, 1H), 2.43 (ddd, J=26.1, 13.2, 6.5 Hz, 1H), 2.24 (dd, J=14.2, 9.7 Hz, 1H), 1.29 (dd, J=13.7, 4.5 Hz, 1H), 0.86–1.04 (m, 2H), −0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 168.9, 167.9, 159.4, 143.3, 134.0, 129.9, 129.6, 129.0, 128.5, 128.3, 128.2, 127.8, 124.7, 124.3, 122.2, 117.6, 114.4, 110.5, 70.9, 66.4, 55.3, 50.8, 50.2, 48.2, 42.6, 41.0, 26.9, 17.8, −1.4; HRMS-ES $[M+H]^+$ calcd for $C_{35}H_{40}BrClN_3O_3Si$: 692.1711, found: 692.1695.

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