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Planned and unplanned halogenations in route to selected oroidin alkaloids

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Abstract—Highly diastereoselective, substrate-controlled, halogenation/ring contraction sequences delivered the naturally occurring chlorinated and unnatural brominated and iodinated axinellamine core structure. An unexpected azide displacement of the chlorinated cyclopentane, which proceeded with retention of stereochemistry, suggested a modification of the Scheuer/Kinnel proposal that may account for the related natural product massadine. Two unsuccessful routes to access the stereochemistry proposed for palau'amine were S_N2 displacement of the bromo- and iodocyclopentane with excess chloride anion and an intramolecular directed chlorination pathway. Finally, an unexpected chlorination during our phakellstatin synthesis proceeded with retention of stereochemistry during tosylation possibly resulting from neighboring group participation.

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1. Introduction

More than 3800 halogenated organic compounds, primarily bearing chlorine or bromine, have been isolated from natural sources including bacteria, fungi, plants, marine organisms, insects, and higher organisms including humans.[1] The structural diversity and large but still increasing number of halogenated organics found in nature is truly astounding. As a primary reservoir for chlorine on earth, oceans have an average chlorine concentration of 19.4 g L^{-1} and contain ~26 Zg (zettagram=10^{21} g) Cl in total.[2] More than 1000 halogen-containing natural products have been isolated from marine organisms and not unexpectedly, this accounts for a large portion of the naturally occurring halogenated natural products.[1] Among these, oroidin family of marine alkaloids was isolated from various species of marine sponges.[3] Our interest in this class of alkaloids has led to stereoselective approaches[4] to various members including the phakellins (e.g., **2**) and phakellstatins,[5] and palau'amines (**3**)[6] and the axinellamines (**4**) (Fig. 1).[7] This family of marine alkaloids has garnered much interest from a number of synthetic groups.[8] One of the most challenging aspects of these compounds is the highly substituted cyclopentane core structure, which includes a chlorine bearing stereocenter. This paper describes both planned and unplanned halogenations in our synthetic studies toward several members of the oroidin-derived marine alkaloids.

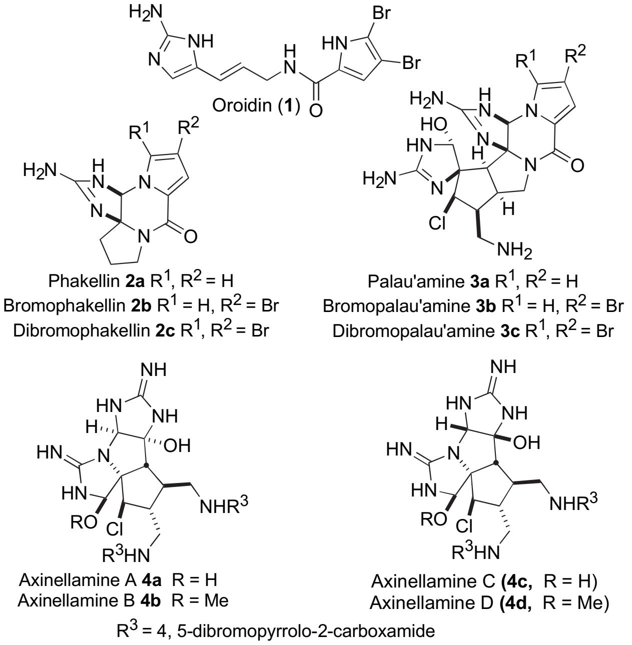

Figure 1. Oroidin-derived marine alkaloids.

1.1. Unified strategy toward axinellamine and palau'amine

Considering the structural similarities of the axinellamines and palau'amines, the two alkaloids were envisioned to arise from a common core structure, which differ in the relative stereochemistry of the chlorine and aminomethylene bearing stereocenters. Imidazolone annulation onto the common

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Keywords: Oroidin alkaloids; Stereoselective chlorination; Bromination; Iodination.

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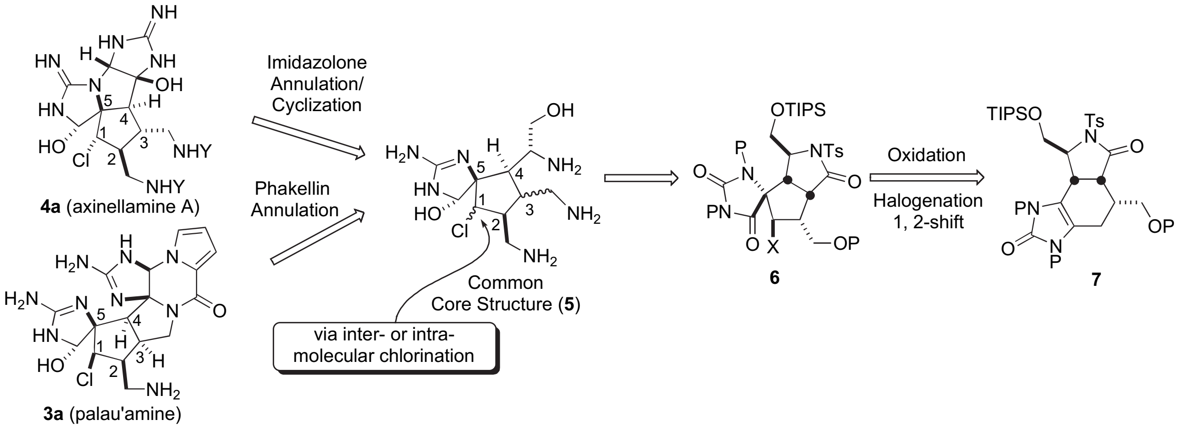


Scheme 1. Abbreviated retrosynthesis of axinellamine and palau'amine showing key oxidation/halogenation/ring contraction (1,2-shift) sequence.

core structure followed by cyclization would introduce the pyrrolidine ring required for axinellamine.

Alternatively, phakellin annulation[4c] onto the common core structure would allow access to palau'amine (Scheme 1). The core structure **5** could be derived from intermediate **7**, which was in turn synthesized by an enantioselective Diels–Alder reaction,[4d,e] followed by inter- or intramolecular chlorination.

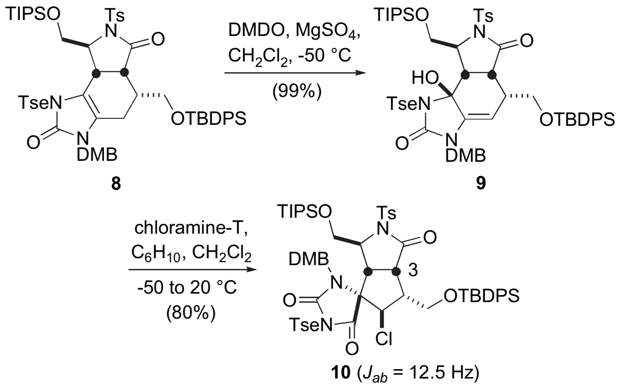
2. Results and discussion

2.1. Intermolecular chlorination/bromination/ iodination

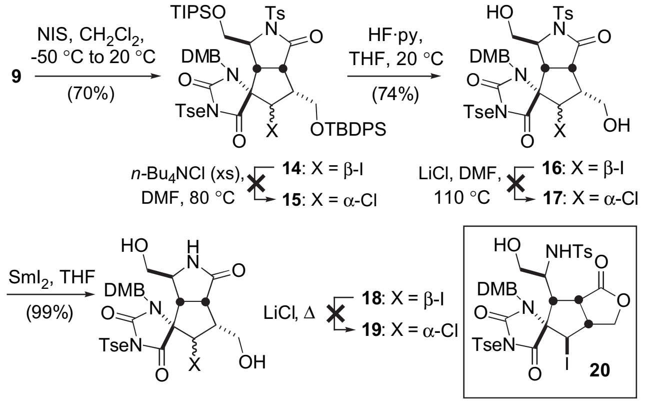
As reported previously, Diels–Alder adduct **8** was oxidized by dimethyldioxirane to give allylic alcohol **9**, which then underwent intermolecular stereoselective chlorination and a concomitant 1,2-shift/ring contraction to yield functionalized chlorocyclopentane **10** (Scheme 2).[4] This cyclopentane contains five stereocenters, identical to the proposed structure of axinellamine with the exception of C3.[9] The high stereoselectivity of oxidation and chlorination is due to the distinct cup-shaped topology of tricycle **8** and allylic alcohol **9**, respectively.

In order to install the stereochemistry at the chlorine bearing center as proposed for palau'amine, which is opposite to that of axinellamine, we considered S_N2 displacement of an appropriate leaving group. Bromination of allylic alcohol **11** with *N*-bromosuccinimide also led to the ring contraction process and delivered bromocyclopentane **12** (Scheme 3). However, attempts to displace the bromide with excess chloride anion under a variety of conditions led to no reaction.

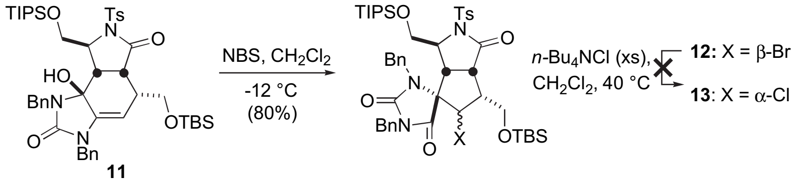
Allylic alcohol **9** could also be iodinated and following ring contraction provided iodocyclopentane **14** (Scheme 4). Iodide **14** was prepared with the expectation that this compound may undergo a more facile reverse Finkelstein



Scheme 2. Oxidation/chlorination/1,2-shift cascade of Diels–Alder adduct **8** leading to spirocycle **10**.



Scheme 4. Iodination/rearrangement sequence leading to iodocyclopentanes **14** and attempted S_N2 displacements.



Scheme 3. Bromination/rearrangement leading to bromocyclopentane **12** and attempted S_N2 displacement.

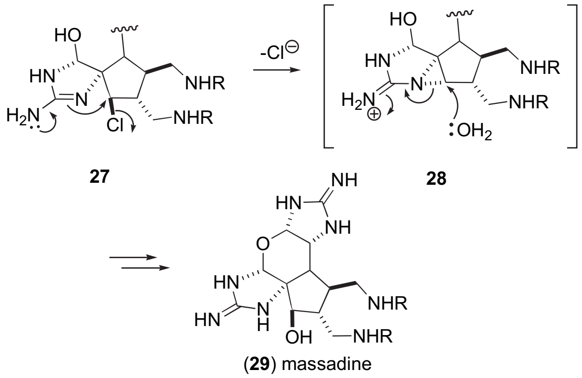
process under forcing conditions, however, no displacement was observed under several conditions to provide the desired α-chloro compound **15**. Silyl deprotection was attempted to remove any steric impedance, however, this did not facilitate the displacement. Instead, the only observed product in this case was lactam opening by the pendent alcohol to deliver lactone **20**. To prevent lactam cleavage, the *N*-tosyl group was removed;[10] however, further attempts at chlorination were also unsuccessful. The unreactivity of these spirocyclic systems toward S_N2 displacement is likely a result of the necessity of the nucleophile to enter the concave face and the adjacent spiro quaternary center. However, sterically less demanding nucleophiles were readily introduced (vide infra).

2.2. Halogen displacement with azide anion

Substitution of chloride was ultimately achieved unexpectedly during conversion of the pendant tosylate of spirocycle **21** to an azide during studies toward axinellamine. The chlorine atom was also displaced concomitantly and surprisingly with retention of stereochemistry as determined by coupling constant analysis to yield bisazide **23** (Scheme 5). As expected, displacement of iodide in spirocycle **22** was more facile and led to higher yields of the corresponding azide **24**.

Retention of stereochemistry may be rationalized by invoking neighboring group participation proceeding through an aziridinium ion **26** (Scheme 6). Following the facile tosylate displacement, intramolecular substitution by the proximal benzylated nitrogen atom, which appears well situated to displace the chloride of spirohydantoin **25**, leads to net retention of stereochemistry of the cyclopentyl azide **23**.

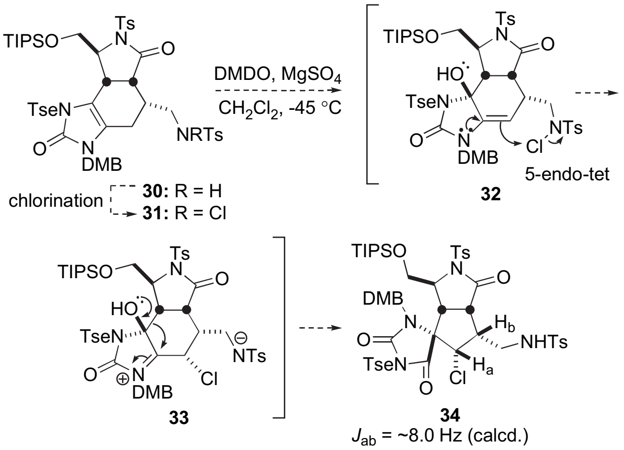
Considering the relative facility of this process with a spirohydantoin leads us to speculate that this may be a more facile process with the electron rich cyclic guanidine found in these natural products (e.g., **27**). Thus, a possible biosynthetic pathway leading to the recently isolated oroidin-derived alkaloid, massadine[11] may involve a related retentive displacement of a chloride proceeding through the aziridine **28** ultimately leading to massadine **29** (Scheme 7). A related process was recently proposed for the natural product, fasicularin.[12]



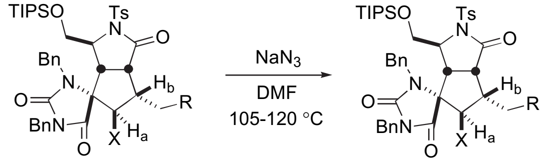
Scheme 7. Hypothesis for massadine biosynthesis involving retentive chloride displacement by water.

2.3. Intramolecular chlorination

In another approach toward introduction of the cyclopentane stereochemistry proposed for palau'amine, an intramolecular directed chlorination strategy was studied (Scheme 8). We envisioned that a pendant electrophilic chlorine source, such as a chloro-*p*-toluenesulfonamide, might deliver

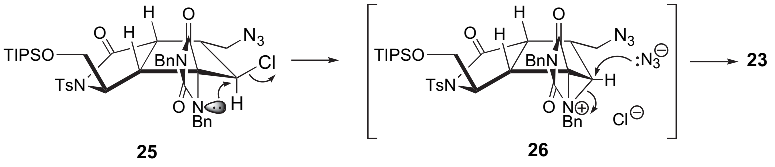


Scheme 8. Proposed oxidation/intramolecular chlorination/1,2-shift cascade.



21: X = Cl, R = OTs (J_{ab} = 12.5 Hz)
22: X = I, R = OTBDPS (J_{ab} = 13.5 Hz)
23: X = N_3, R = N_3 (41%, J_{ab} = 11.1 Hz)
24: X = N_3, R = OTBDPS (75%, J_{ab} = 11.0 Hz)

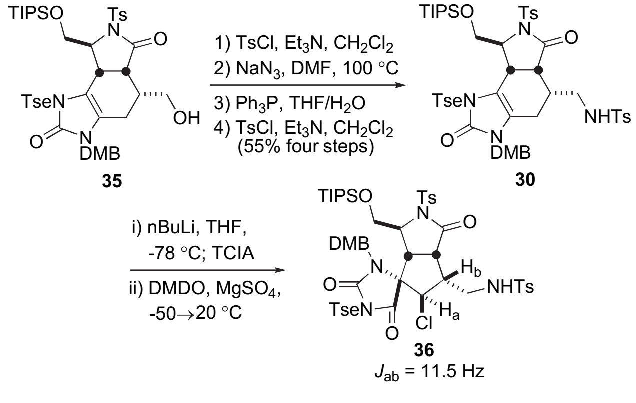
Scheme 5. Retentive displacement of cyclopentyl halides with azide anion.



Scheme 6. Proposed mechanism for retentive chloride displacement by azide ion.

chlorine in an intramolecular fashion to the concave face of tricycle **32** to deliver cyclopentane **34** following ring contraction. This strategy is reminiscent of an intramolecular directed chlorination reported by Breslow and Guo.[13] While the proposed trajectory would be an exception to Baldwin's rule (5-*endo*-tet),[14] there are numerous exceptions including attack at heteroatoms.[15]

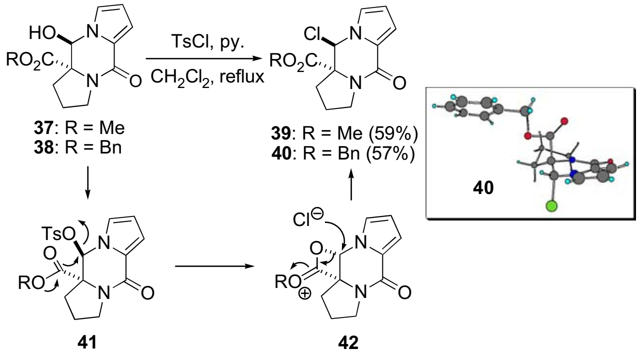
Preparation of the substrate for the proposed intramolecular chlorination began with Diels–Alder adduct **35**,[4] which was converted to sulfonamide **30** through an efficient four-step sequence (Scheme 9). In a model study with a simple *N*-sulfonamide (not shown), the intermediate chlorosulfonamide produced by deprotonation and chlorination could be isolated and purified. While the chlorinated adduct derived from *N*-sulfonamide **30** could not be purified, a one-pot, two-step protocol involving deprotonation and chlorination with trichloroisocyanuric acid (TCIA) [16] produced the presumed chlorinated adduct as evidenced by thin layer chromatographic analysis. The crude *N*-chlorosulfonamide was directly subjected to oxidation with DMDO; however, this process only delivered the β-chlorocyclopentane **36**. The stereochemistry was determined by coupling constant analysis and comparison to that obtained by deliberate intermolecular chlorination (see adduct **10**, Scheme 2). Chlorocyclopentane **36** presumably arises from more facile intermolecular chlorination. A modeling study suggested one possible explanation for this result. The cup-shaped conformation of the intermediate allylic alcohol **32** (see Scheme 8) and boat conformation of the cyclohexene, places the *N*-chlorosulfonamide in a pseudoequatorial position far removed from the nucleophilic carbon of the intermediate enamine (cf. **32**).



Scheme 9. Formation of sulfonamide **30** and attempted one-pot, two-step intramolecular chlorination.

2.4. An unexpected chlorination toward phakellstatin

In studies directed toward the related marine alkaloid phakellstatin, another retentive chlorination process was observed. The chlorides **39** and **40** were formed when carbinolamine **37** and **38**, respectively, were exposed to tosyl chloride under refluxing conditions (Scheme 10). Related chlorinations are known for benzylic and allylic alcohols.[17] The stereochemical outcome pointing toward a net retentive substitution process was confirmed by X-ray analysis of chloride **40** (inset, Scheme 10). Two possible rationalizations for this stereochemical outcome can be proposed including an S_N1 process followed by the attack of chloride from the most accessible face opposite to the ester substituent. Alternatively, neighboring group participation of the pendant ester could also leads to net retention proceeding through a transient β-lactone intermediate **42**.



Scheme 10. An unexpected retentive chlorination during tosylation of carbinolamines **37/38** (inset: X-ray crystal structure of chloride **40**).

3. Conclusion

The previously reported chlorination/ring contraction sequence leading to the highly functionalized chlorocyclopentane core structure of axinellamine and related oroidin alkaloids has been extended to provide brominated and iodinated cyclopentanes. In efforts to achieve the stereochemistry proposed for palau'amine attempted invertive displacement of these halogens by excess chloride was unsuccessful. An unexpected displacement of chloride by azide ion proceeding with retention of stereochemistry prompted us to propose a related process in the biogenesis of massadine. An attempted intramolecular directed chlorination was studied but led exclusively to an intermolecular chlorination process. An additional retentive displacement was observed in studies toward phakellstatin leading to a halogenated product during tosylation. The diversity of halogenated natural products, especially marine derived metabolites, will continue to drive studies of stereoselective halogenation reactions such as those described herein.

4. Experimental

4.1. General

All nonaqueous reactions were carried out under a nitrogen atmosphere in oven-dried glassware. Tetrahydrofuran, dichloromethane, and dimethylformamide (all from EM Science) were dried and purified by MBRAUN solvent purification system (water content ~10 ppm). Solutions of dimethyldioxirane (DMDO) in acetone were prepared according to literature procedures.[18] All other commercially available reagents were used as received unless specified otherwise.

Infrared spectra were recorded with a Nicolet Impact 410 FTIR spectrometer. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Unity-500/Inova-500 spectrometer. Mass spectra were obtained on a MDS Sciex (Concord, Ontario, Canada) API Qstar Pulsar (for ESI), or a ThermoFinnigan (San Jose, California) LCQ Deca Mass Spectrometer (for APCI) at the Mass Spectrometry Application and Collaboration Facility (Texas A&M University). Flash column chromatography was performed using 60 Å silica gel (EM Science, 230–400 mesh) as a stationary phase.

4.1.1. Bromospirohydantoin 12. To a cooled (−12 °C) solution of allylic alcohol **11** (9.9 mg, 0.011 mmol) in 50 μL CH_2Cl_2 was added *N*-bromosuccinimide (4.5 mg, 0.025 mmol) in 150 μL CH_2Cl_2. After 1.5 h the reaction mixture was diluted with water and CH_2Cl_2 and then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (SiO_2, 20% EtOAc/hexane) gave bromospirocycle **12** as a light yellow foam (8.6 mg, 80%): R_f=0.58 (20% EtOAc/hexane); $[\alpha]_D^{25}$ −29.8 (*c* 1.28, CH_2Cl_2); IR (thin film) 1752, 1716 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.07 (d, *J*=8.5 Hz, 2H), 7.48 (d, *J*=8.5 Hz, 2H), 7.45 (d, *J*=6.0 Hz, 2H), 7.41 (d, *J*=7.5 Hz, 2H), 7.34–7.28 (m, 6H), 5.31 (d, *J*=16.0 Hz, 1H), 4.70 (d, *J*=15.0 Hz, 1H), 4.65 (d, *J*=15.0 Hz, 1H), 4.63 (br s, 1H), 4.33 (d, *J*=16.0 Hz, 1H), 4.12 (d, *J*=12.5 Hz, 1H), 4.07 (dd, *J*=3.5, 10.5 Hz, 1H), 4.03 (d, *J*=9.0 Hz, 1H), 3.89 (dd, *J*=2.0, 10.5 Hz, 1H), 3.84 (dd, *J*=3.0, 9.5 Hz, 1H), 3.46 (t, *J*=8.5 Hz, 1H), 3.30 (d, *J*=9.0 Hz, 1H), 3.15–3.08 (m, 1H), 2.45 (s, 3H), 0.95–0.92 (m, 21H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ 174.2, 171.9, 157.7, 146.7, 138.5, 137.2, 136.9, 130.8, 129.49, 129.47, 129.43, 129.3, 128.9, 128.7, 128.5, 76.8, 65.7, 61.3, 59.8, 50.7, 49.0, 47.9, 47.5, 46.3, 43.4, 26.4, 21.6, 18.4, 18.3, 12.7; HRMS (ESI) calcd for $C_{47}H_{66}BrN_3O_7SSi_2$ [M+H]: 952.3422; found: 952.3370.

4.1.2. Iodospirohydantoin 14. To a slurry of allylic alcohol **9** (55.0 mg, 0.048 mmol) and $MgSO_4$ (∼100 mg) in CH_2Cl_2 at −50 °C was added *N*-iodosuccinimide (13.0 mg, 0.058 mmol). The reaction was allowed to warm to ambient temperature slowly and stirring was continued for 16 h. The reaction mixture was then filtered and the filtrate was concentrated in vacuo. Column purification (SiO_2 gel, 20→30% EtOAc/hexane) afforded the iodocyclopentane **14** as a colorless foam (32.0 mg, 52%): R_f=0.39 (40% EtOAc/hexane); IR (thin film) 2935, 2858, 1716, 1455 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 8.26 (d, *J*=8.0 Hz, 2H), 7.97 (m, 2H), 7.87 (d, *J*=8.0 Hz, 2H), 7.83 (m, 2H), 7.48 (d, *J*=2.0 Hz, 1H), 7.35 (dd, *J*=2.0, 8.0 Hz, 1H), 7.20–7.29 (m, 6H), 6.84 (d, *J*=8.0 Hz, 2H), 6.77 (d, *J*=8.0 Hz, 2H), 6.38 (d, *J*=8.0 Hz, 1H), 5.85 (d, *J*=16.0 Hz, 1H), 4.89 (s, 1H), 4.63 (d, *J*=16.0 Hz, 1H), 4.60 (t, *J*=10.0 Hz, 1H), 4.39 (d, *J*=13.5 Hz, 1H), 4.25 (dd, *J*=2.0, 11.0 Hz, 1H), 4.19 (dd, *J*=4.0, 10.0 Hz, 1H), 4.14 (d, *J*=11.0 Hz, 1H), 3.89 (m, 1H), 3.81 (d, *J*=8.5 Hz, 1H), 3.63 (s, 3H), 3.56–3.61 (m, 2H), 3.43 (m, 1H), 3.31 (s, 3H), 3.24 (m, 1H), 2.94 (m, 1H), 1.88 (s, 3H), 1.85 (s, 3H), 1.21 (s, 9H), 0.91–0.99 (m, 21H); ^{13}C NMR (125 MHz, benzene-d_6) δ 174.48, 171.74, 156.60, 150.30, 150.01, 144.84, 144.68, 136.42, 136.18, 136.01, 135.70, 133.78, 133.62, 130.39, 129.81, 129.76, 129.55, 129.10, 129.06, 128.20, 128.01, 127.95, 127.82, 122.14, 113.79, 112.18, 77.86, 65.42, 61.42, 61.24, 55.68, 55.32, 50.56, 50.36, 48.59, 48.44, 45.84, 33.25, 30.08, 26.99, 25.96, 21.06, 21.02, 19.40, 18.11, 18.05, 12.11; HRMS (MALDI) calcd for $C_{61}H_{78}IN_3O_{11}S_2Si_2$ [M+Na]: 1298.3559; found: 1298.3560.

4.1.3. Iodocyclopentane 16. To a solution of iodocyclopentane **14** (11.0 mg, 0.0086 mmol) in THF (0.20 mL) was added HF·pyridine (70%, 50 μL, excess) at 20 °C. After 21 h, the reaction was quenched with satd $NaHCO_3$ (1 mL) and H_2O (3 mL) and then extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine and further dried over Na_2SO_4. After removal of solvent, the crude product was purified by flash column chromatography (SiO_2, 60→80% EtOAc/hexane) to give alcohol **16** as a colorless film (5.6 mg, 74%): R_f=0.22 (60% EtOAc/hexane); IR (thin film) 3493, 1711 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 8.06 (d, *J*=8.0 Hz, 2H), 7.84 (d, *J*=8.0 Hz, 2H), 7.41 (dd, *J*=2.0, 8.0 Hz, 1H), 7.35 (d, *J*=2.0 Hz, 1H), 6.83 (d, *J*=8.0 Hz, 2H), 6.69 (d, *J*=8.0 Hz, 2H), 6.57 (d, *J*=8.0 Hz, 1H), 5.62 (d, *J*=16.0 Hz, 1H), 4.77 (s, 1H), 4.72 (d, *J*=13.0 Hz, 1H), 4.47 (d, *J*=16.0 Hz, 1H), 4.02 (m, 1H), 3.91 (m, 2H), 3.73 (s, 3H), 3.66–3.72 (m, 2H), 3.48–3.52 (m, 1H), 3.43 (d, *J*=9.0 Hz, 1H), 3.35 (s, 3H), 3.18–3.23 (m, 1H), 3.10 (dd, *J*=9.0, 6.0 Hz, 1H), 3.06 (t, *J*=9.0 Hz, 1H), 2.96 (m, 1H), 1.86 (s, 3H), 1.77 (s, 3H), 1.36 (s, 1H), 1.06 (s, 1H); ^{13}C NMR (125 MHz, benzene-d_6) δ 175.30, 174.26, 169.91, 156.60, 150.37, 150.09, 145.27, 144.82, 135.90, 135.27, 130.20, 129.90, 129.51, 129.28, 128.80, 128.20, 127.56, 122.29, 113.73, 112.38, 77.66, 63.70, 61.60, 59.93, 59.08, 55.71, 55.37, 50.78, 49.39, 49.35, 47.45, 45.93, 33.12, 31.82, 30.09, 26.33, 22.91, 21.06, 21.05, 20.41, 14.21, 14.08; HRMS (ESI) calcd for $C_{36}H_{40}IN_3O_{11}S_2$ [M+Li]: 888.1309; found: 888.1329.

4.1.4. Lactam 18. To a solution of iodocyclopentane **16** (3.7 mg, 0.0042 mmol) in THF (0.10 mL) was added SmI_2 (0.1 M solution in THF, 130 μL, 0.013 mmol) at 0 °C. After 30 min, a further portion of SmI_2 (0.10 mL) was added. The blue reaction mixture was stirred at ambient temperature for 10 min. The reaction was then quenched with satd $NaHCO_3$ (2 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed sequentially with water and brine, and then dried over Na_2SO_4. Removal of solvent afforded lactam **18** as a colorless film and of sufficient purity for subsequent reactions (3.0 mg, 99%): R_f=0.14 (EtOAc); IR (thin film) 3345, 1711 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 7.82 (d, *J*=8.0 Hz, 2H), 7.27 (d, *J*=2.0 Hz, 1H), 7.12 (dd, *J*=2.0, 8.0 Hz, 1H), 6.81 (d, *J*=8.0 Hz, 2H), 6.61 (d, *J*=8.0 Hz, 1H), 5.31 (s, 1H), 4.97 (d, *J*=16.0 Hz, 1H), 4.66 (d, *J*=12.5 Hz, 1H), 4.42 (br s, 1H), 4.16 (d, *J*=12.5 Hz, 1H), 4.06 (d, *J*=16.0 Hz, 1H), 3.95 (m, 1H), 3.74 (s, 3H), 3.60–3.65 (m, 1H), 3.51–3.56 (m, 1H), 3.38 (s, 3H), 3.33 (t, *J*=4.5 Hz, 1H), 3.18 (d, *J*=8.5 Hz, 1H), 3.10–3.15 (m, 3H), 2.98 (m, 1H), 2.90 (m, 1H), 2.68 (t, *J*=8.5 Hz, 1H), 1.85 (s, 3H), 1.32 (br s, 1H); ^{13}C NMR (125 MHz, benzene-d_6) δ 178.02, 174.52, 156.83, 150.45, 150.06, 144.83, 135.93, 130.05, 129.88, 128.73, 128.39, 127.37, 121.51, 113.31, 112.27, 77.35, 65.16, 59.93, 59.18, 55.46, 50.79, 48.46, 48.16, 47.40, 45.31, 33.04, 30.08, 26.91, 21.04, 14.21, 14.15, 14.08; HRMS (MALDI) calcd for $C_{29}H_{34}IN_3O_9S$ [M+H]: 728.1139; found: 728.1118.

4.1.5. Bisazide 23. To a solution of spirohydantoin **21** (68.5 mg, 0.072 mmol) in 500 μL DMF was added NaN_3

(77.3 mg, 1.189 mmol) and the reaction mixture was heated to 120 °C. After 16 h the reaction mixture was concentrated in vacuo and purified by flash chromatography (SiO_2, 0→60 EtOAc/hexane) to give bisazide **23** as a light yellow foam (24.3 mg, 41%): R_f=0.67 (30% EtOAc/hexane); $[\alpha]_D^{25}$ −22.3 (*c* 1.14, CH_2Cl_2); IR (thin film) 2116, 1716 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.08 (d, *J*=8.4 Hz, 2H), 7.51 (d, *J*=8.4 Hz, 2H), 7.44 (d, *J*=6.6 Hz, 2H), 7.43–7.29 (m, 8H), 5.35 (d, *J*=16.5 Hz, 1H), 4.71 (d, *J*=15.0 Hz, 1H), 4.65 (d, *J*=15.0 Hz, 1H), 4.65 (app t, *J*=1.8 Hz, 1H), 4.39 (d, *J*=16.5 Hz, 1H), 4.09–3.90 (m, 3H), 3.97 (d, *J*=11.1 Hz, 1H), 3.59 (dd, *J*=6.0, 12.9 Hz, 1H), 3.48 (t, *J*=8.4 Hz, 1H), 3.21 (d, *J*=8.7 Hz, 1H), 3.08–2.97 (m, 1H), 2.45 (s, 3H), 0.96–0.92 (m, 21H); ^{13}C NMR (125 MHz, acetone-d_6) δ 173.8, 172.5, 157.7, 146.8, 138.4, 137.2, 136.5, 130.7, 129.7, 129.4, 129.3, 128.8, 128.6, 128.43, 128.41, 128.3, 126.7, 75.2, 66.5, 65.4, 61.5, 49.5, 47.1, 46.6, 46.2, 44.0, 43.1, 21.5, 18.2, 18.1, 12.6; HRMS (ESI) calcd for $C_{41}H_{51}N_9O_6SSi$ [M+H]: 826.3531; found: 826.3458.

4.1.6. Azidocyclopentane 24. To a mixture of iodocyclopentane **22** (10 mg, 0.0078 mmol) and NaN_3 (34 mg, 0.52 mmol) in a dry vial was added anhydrous DMF (0.40 mL). The reaction vessel was purged with nitrogen and sealed and then heated to 105 °C. After 12 h, the reaction was cooled to ambient temperature, H_2O was added, and then the mixture was extracted with EtOAc. The organics were washed with brine and then dried over Na_2SO_4. Concentration in vacuo and column purification (SiO_2, 25% EtOAc/hexane) afforded the azidocyclopentane **24** as a colorless film (7.0 mg, 75%): R_f=0.38 (6:4 hexane/EtOAc); IR (thin film) 2926, 2113, 1716, 1113 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 8.21 (d, *J*=8.0 Hz, 2H), 7.91 (m, 2H), 7.87 (d, *J*=8.0 Hz, 2H), 7.76 (m, 2H), 7.54 (d, *J*=2.0 Hz, 1H), 7.42 (dd, *J*=2.0, 8.0 Hz, 1H), 7.19–7.27 (m, 6H), 6.84 (d, *J*=8.0 Hz, 2H), 6.77 (d, *J*=8.0 Hz, 2H), 6.50 (d, *J*=8.0 Hz, 1H), 5.94 (d, *J*=16.0 Hz, 1H), 4.87 (s, 1H), 4.74 (d, *J*=16.0 Hz, 1H), 4.60 (dd, *J*=6.0, 11.0 Hz, 1H), 4.32 (d, *J*=11.0 Hz, 1H), 4.17–4.22 (m, 2H), 4.07 (d, *J*=9.5 Hz, 1H), 3.67 (s, 3H), 3.55–3.62 (m, 4H), 3.36 (m, 1H), 3.35 (s, 3H), 3.20 (m, 1H), 2.91 (m, 1H), 1.87 (s, 3H), 1.84 (s, 3H), 1.19 (s, 9H), 0.88–0.94 (m, 21H); ^{13}C NMR (125 MHz, benzene-d_6) δ 173.66, 172.29, 156.93, 150.72, 150.20, 144.88, 144.67, 136.31, 136.19, 135.84, 135.78, 133.64, 133.52, 130.19, 129.80, 129.53, 129.09, 129.01, 128.21, 128.02, 127.82, 127.63, 120.86, 112.72, 112.60, 75.24, 66.59, 65.29, 62.29, 61.31, 55.76, 55.44, 50.48, 47.78, 47.37, 47.20, 45.80, 33.35, 30.08, 26.95, 21.07, 21.01, 19.30, 18.06, 18.00, 12.04; HRMS (ESI) calcd for $C_{61}H_{78}N_6O_{11}S_2Si_2$ [M+Li]: 1197.4869; found: 1197.4800.

4.1.7. Sulfonamide 30. To a mixture of alcohol **35** (35 mg, 0.039 mmol) and TsCl (11 mg, 0.059 mmol) was added anhydrous CH_2Cl_2 (0.40 mL), followed by triethylamine (~80 μL, excess). The reaction mixture was stirred vigorously for 36 h at 23 °C and then extracted with CH_2Cl_2 (3×10 mL). The organic layer was washed with satd $NaHCO_3$ and brine, and then dried over Na_2SO_4. Purification by column chromatography (SiO_2, 50→80% EtOAc/hexane) afforded the tosylate as a colorless foam (35 mg, 85%), which was carried directly to the next step: R_f=0.61 (EtOAc); IR (thin film) 2940, 2863, 1742, 1690 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 7.75 (d, *J*=8.0 Hz, 4H), 7.60 (d, *J*=8.0 Hz, 2H), 6.97 (d, *J*=2.0 Hz, 1H), 6.81 (dd, *J*=8.0, 2.0 Hz, 1H), 6.72 (d, *J*=8.0 Hz, 2H), 6.68 (d, *J*=8.0 Hz, 2H), 6.65 (d, *J*=8.0 Hz, 2H), 6.60 (d, *J*=8.0 Hz, 1H), 4.58 (d, *J*=15.5 Hz, 1H), 4.47 (dd, *J*=8.0, 10.0 Hz, 1H), 4.38 (dd, *J*=7.0, 10.0 Hz, 1H), 4.32 (m, 2H), 4.04–4.17 (m, 4H), 3.88 (m, 1H), 3.74 (d, *J*=6.5 Hz, 1H), 3.60 (s, 3H), 3.37 (s, 3H), 3.22 (dd, *J*=3.0, 7.0 Hz, 1H), 2.86 (dt, *J*=4.0, 14.0 Hz, 1H), 2.06 (dd, *J*=4.0, 15.0 Hz, 1H), 1.92 (s, 3H), 1.89 (m, 1H), 1.86 (s, 3H), 1.85 (s, 3H), 1.76 (m, 1H), 1.17–1.20 (m, 21H); ^{13}C NMR (125 MHz, benzene-d_6) δ 172.83, 153.76, 150.50, 149.74, 144.78, 144.38, 144.20, 137.76, 135.92, 133.94, 130.19, 129.86, 129.71, 129.43, 128.21, 128.03, 127.82, 127.54, 119.89, 119.05, 114.32, 112.32, 111.88, 70.85, 66.60, 65.39, 64.59, 63.95, 59.93, 55.75, 55.49, 52.77, 44.34, 41.77, 36.32, 34.82, 34.31, 30.86, 30.09, 21.16, 21.05, 21.01, 19.73, 18.20, 18.19, 12.15; HRMS (ESI) calcd for $C_{52}H_{67}N_3O_{12}S_3Si$ [M+Li]: 1056.3816; found: 1056.3789.

The crude tosylate (43.0 mg, 0.041 mmol) and NaN_3 (26 mg, 0.41 mmol) were dissolved in anhydrous DMF (1.0 mL) and the flask was purged with nitrogen and sealed. The reaction mixture was heated to 100 °C. After stirring for 16 h, water was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organics were washed with brine and dried over Na_2SO_4. The azide was obtained in sufficient purity (38 mg, 100%) for the next step. To a mixture of the azide (38 mg, 0.041 mmol) and triphenylphosphine (54 mg, 0.20 mmol) in a dry flask was added THF (0.8 mL), followed by water (25 μL). The mixture was stirred vigorously at room temperature. After 12 h, the reaction mixture was concentrated in vacuo and azeotroped with benzene. The crude mixture was subjected to flash column purification (SiO_2, 2→5% $MeOH/CH_2Cl_2$) to yield an amine (27.3 mg, 75%).

To a mixture of the amine (27 mg, 0.030 mmol) and *p*-toluenesulfonyl chloride (21 mg, 0.11 mmol) were added CH_2Cl_2 (0.60 mL) and triethylamine (0.10 mL). The reaction mixture was stirred at 23 °C for 20 h and then partitioned between CH_2Cl_2/H_2O. The organic layer was washed with satd $NaHCO_3$, brine, and then dried over Na_2SO_4. Purification by flash column chromatography (50→75% EtOAc/hexane) afforded sulfonamide **30** as a colorless foam (26 mg, 83%): R_f=0.48 (80% EtOAc/hexane); IR (thin film) 2945, 2868, 2361, 1690 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 7.79 (d, *J*=8.0 Hz, 2H), 7.77 (d, *J*=8.0 Hz, 2H), 7.64 (d, *J*=8.0 Hz, 2H), 7.03 (d, *J*=2.0 Hz, 1H), 6.87 (dd, *J*=2.0, 8.0 Hz, 1H), 6.82 (d, *J*=8.0 Hz, 2H), 6.75 (d, *J*=8.0 Hz, 2H), 6.73 (d, *J*=8.0 Hz, 2H), 6.64 (d, *J*=8.0 Hz, 1H), 4.94 (t, *J*=6.5 Hz, 1H), 4.69 (d, *J*=15.5 Hz, 1H), 4.35–4.39 (m, 2H), 4.10–4.24 (m, 4H), 3.91 (m, 1H), 3.84 (d, *J*=7.0 Hz, 1H), 3.65 (s, 3H), 3.39 (s, 3H), 3.28 (dd, *J*=3.0, 7.0 Hz, 1H), 3.18–3.24 (m, 2H), 2.86 (dt, *J*=4.0, 14.0 Hz, 1H), 2.11 (dd, *J*=4.0, 15.0 Hz, 1H), 1.97 (s, 3H), 1.95 (s, 3H), 1.91 (m, 1H), 1.88 (s, 3H), 1.72 (m, 1H), 1.19–1.21 (m, 21H); ^{13}C NMR (125 MHz, benzene-d_6) δ 173.64, 153.81, 150.44, 149.67, 144.94, 144.25, 142.79, 138.17, 137.79, 135.83, 130.30, 129.75, 129.67, 129.53, 127.59, 127.33, 119.94, 114.48, 112.31, 111.93, 65.29, 64.63, 55.83, 55.50, 52.74, 45.15, 44.35, 42.83, 36.32, 35.14, 34.78, 30.08, 21.20, 21.03, 20.50, 18.23, 18.22, 18.10, 12.17, 12.08; HRMS (ESI) calcd for $C_{52}H_{68}N_4O_{11}S_3Si$ [M+Li]: 1055.3976; found: 1055.3530.

4.1.8. 2-Chloro-3-carbomethoxy-pyrrole 39. A solution of 10.9 mg (0.04 mmol) of carbinolamine **38** and 16.6 mg (0.08 mmol) of *p*-toluenesulfonyl chloride (TsCl) in 1 mL CH_2Cl_2 was treated with 7 μL (0.08 mmol) pyridine. After 5 h at reflux, the solvent was removed in vacuo and the residue was purified by flash chromatography (SiO_2, 25% EtOAc/CH_2Cl_2) to afford 2-chloro-3-carbomethoxy-pyrrole **39** as a faint pink solid (6.9 mg, 59%): R_f=0.6 (50% CH_2Cl_2/EtOAc); IR (thin film) 2956, 1747, 1646, 1418 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.18 (dd, *J*=1.5, 2.6 Hz, 1H), 7.05 (s, 1H), 6.79 (ddd, *J*=0.8, 1.6, 3.7 Hz, 1H), 6.28 (dd, *J*=2.6, 3.7 Hz, 1H), 3.7–3.75 (m, 2H), 3.67 (s, 3H), 2.62 (ddd, *J*=8.0, 9.5, 13.5 Hz, 1H), 2.41 (ddd, *J*=4.1, 7.5, 11.5 Hz, 1H), 2.10–2.18 (m, 1H), 1.96–2.0 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 172.10, 156.60, 125.79, 124.49, 115.23, 112.81, 74.00, 72.68, 53.93, 45.48, 35.59, 22.53; HRMS (ESI) calcd for $C_{12}H_{13}ClN_2O_3$ [M+H]: 269.0693; found: 269.0626.

4.1.9. 2-Chloro-3-carbobenzyloxy-pyrrole 40. Chloride **40** was prepared in an identical manner to that described for chloride **39**: R_f=0.72 (50% CH_2Cl_2/EtOAc); IR (thin film) 2950, 1747, 1650, 1419 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.30–7.32 (m, 3H), 7.18–7.21 (m, 2H), 7.14 (dd, *J*=1.7, 2.7 Hz, 1H), 7.06 (s, 1H), 6.79 (ddd, *J*=0.5, 1.5, 3.6 Hz, 1H), 6.27 (dd, *J*=3.0, 3.6 Hz, 1H), 5.15 (app d, *J*=0.5 Hz, 2H), 3.72 (dd, *J*=6.5, 8.0 Hz, 2H), 2.63 (ddd, *J*=8.0, 9.5, 13.5 Hz, 1H), 2.41 (ddd, *J*=4.2, 7.5, 13.0 Hz, 1H), 2.09–2.16 (m, 1H), 1.91–1.97 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 171.5, 156.7, 136.3, 129.3, 129.1, 128.5, 125.8, 124.5, 115.3, 112.8, 74.1, 72.6, 68.6, 45.5, 35.5, 22.5; HRMS (ESI) calcd for $C_{18}H_{17}ClN_2O_3$ [M+H]: 345.1006; found: 345.1034.

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