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Explorations on the Total Synthesis of the Unusual Marine Alkaloid Chartelline A

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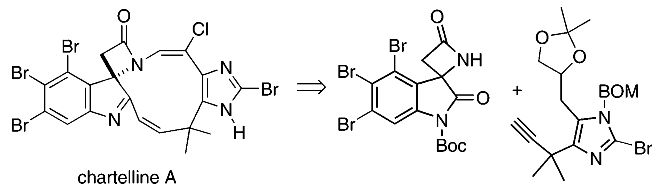

In work directed toward a total synthesis of chartelline A (**1a**), a strategy was investigated to construct the 10-membered ring of this marine alkaloid via an intramolecular aldehyde/β-lactam cyclocondensation to form the macrocyclic enamide functionality. Therefore, spiro-β-lactam and imidazole fragments were first prepared. Tribromooxindole β-lactam **24** was synthesized from commercially available 5-nitroisatin (**18**) in seven steps and 30% overall yield via a Staudinger ketene−imine [2 + 2]-cycloaddition strategy. The requisite 2-bromoimidazole subunit **40** bearing a terminal alkyne and a masked aldehyde was efficiently prepared from the readily available imidazole ester **25** in 10 steps. With both advanced intermediates available, the addition of the lithium acetylide generated from 2-bromoimidazole subunit **40** to the γ-lactam carbonyl group of *N*-Boc-tribromooxindole **24** was investigated, affording the desired *N*-Boc-aminal **41**. Hydrolysis of the acetonide moiety of **41**, followed by oxidative cleavage of the resulting diol, gave the aldehyde **42**. Unfortunately, treatment of aldehyde **42** with *p*-toluenesulfonic acid did not give the desired 10-membered macrocyclic (*Z*)-enamide **46**, but rather the highly unsaturated seven-membered ring compound **44**.

Introduction and Background

In the 1980s, Christophersen and co-workers reported the isolation of a small group of unique, highly halogenated indole−imidazole alkaloids, chartellines A (**1a**), B (**1b**), and C (**1c**), from the marine bryozoan *Chartella papyracea* (Ellis and Solander) collected in the North Sea.[1−3] The structure and stereochemistry of chartelline A was unambiguously established by X-ray crystallography. Furthermore, the absolute configuration of the stereogenic center at C(20) was also determined by X-ray to be *S*. Chartellines B and C have also been assigned the *S* configuration on the basis of comparisons of their CD spectra with that of chartelline A. Due to the 2-bromoimidazole ring, the chartellines can exist in two tautomeric forms derived from prototropic exchange between *N*-5 and *N*-7. The *N*-5-*H* isomer predominates in solution based upon NMR spectral analysis, while the *N*-7-*H* isomer (as shown in the structures) was observed in the solid state by X-ray analysis. According to the crystal structure, the central 10-membered ring of chartelline A adopts a rigid, tublike conformation, which indicates that there is very little conjugation present between the ring systems (see structure **A**). Thus, the indolenine system is almost perpendicular to the spiro-β-lactam ring and is close to parallel to the imidazole ring.

Chartelline A lacks any significant antimicrobial activity against a representative series of microorganisms, including Gram-negative and Gram-positive bacteria, as well as molds.[1b] Chartelline A was also found to be inactive in the National Cancer Institute leukemia screen (3PS31) at a dose level of 5.60

(1) (a) Chevolot, L.; Chevolot, A.-M.; Gajhede, M.; Larsen, C.; Anthoni, U.; Christophersen, C. *J. Am. Chem. Soc*. **1985**, *107*, 4542. (b) Anthoni, U.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. *J. Org. Chem*. **1987**, *52*, 4709. (c) Nielsen, P. H.; Anthoni, U.; Christophersen, C. *Acta Chem. Scand.* **1988**, *B42*, 489.

(2) The chartellamides are biogenetically related β-lactams isolated from the same organism: Anthoni, U.; Bock, K.; Chevolot, L.; Larsen, C.; Nielsen, P. H.; Christophersen, C. *J. Org. Chem*. **1987**, *52*, 5638. For synthetic studies, see: Pinder, J. L.; Weinreb, S. M. *Tetrahedron Lett.* **2003**, *44*, 4141.

(3) Several additional related alkaloids that are not β-lactams have also been isolated: (a) Rahbaek, L.; Anthoni, U.; Christophersen, C.; Nielsen, P. H.; Petersen, B. O. *J. Org. Chem*. **1996**, *61*, 887. (b) Rahbaek, L.; Christophersen, C. *J. Nat. Prod*. **1997**, *60*, 175. For synthetic work in this area, see: Korakas, P.; Chaffee, S.; Shotwell, J. B.; Duque, P.; Wood, J. L. *Proc. Nat. Acad. Sci. U.S.A.* **2004**, *101*, 12054.

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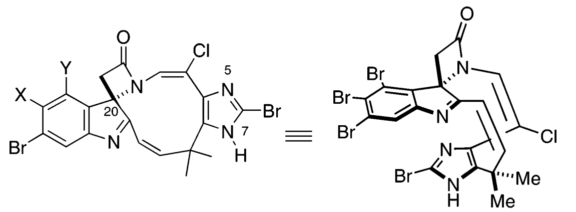


1a chartelline A, X = Y = Br
1b chartelline B, X = H, Y = Br
1c chartelline C, X = Y = H

A

mg/kg and exhibited an ED_{50} of 29 and 31 μg/mL in the in vitro KB and PS tests, respectively.[1b] Despite this lack of biological activity, however, the structural novelty and complexity of the chartellines make them worthy targets for total synthesis.

We have previously described some preliminary feasibility studies on synthesis of the spiro-β-lactam unit of the chartellines via a strategy involving a Staudinger [2 + 2]-cycloaddition.[4] Moreover, the Isobe group has reported two other methods to build model spiro-β-lactams related to these alkaloids.[5] More recently, Baran et al. have disclosed an elegant strategy for construction of the pentacyclic ring system of the chartellines.[6] In this paper are outlined some of our ongoing studies on these natural products which we hope will ultimately lead to a total synthesis of chartelline A.[7]

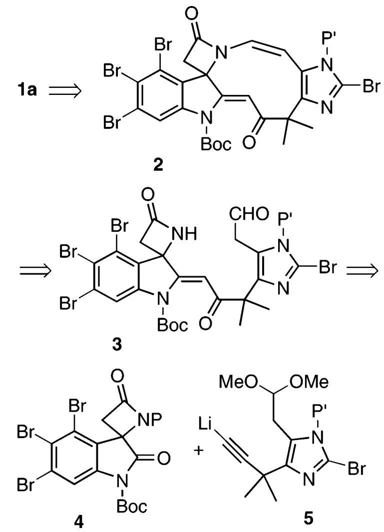
Retrosynthetic Plan

Our first-generation synthetic strategy for chartelline A is outlined in Scheme 1. The plan was to prepare the 10-membered enamide **2** via cyclodehydration of aldehyde β-lactam **3**. Enamide **2** would be β-chlorinated[8] and the system further manipulated to produce chartelline A (**1a**). Intermediate **3** would ultimately arise from coupling of a metal acetylide like **5** with an activated *N*-acyllactam **4** using methodology which we have previously tested.[4]

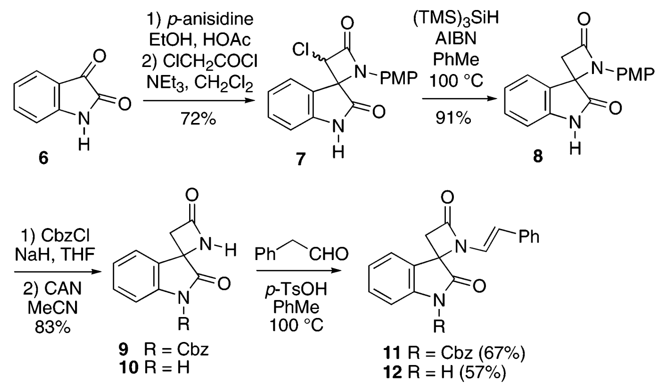
Results and Discussion

Preliminary Model Studies. Prior to executing the strategy in Scheme 1, a simple nonhalogenated model system was initially explored to test some of the important steps. Thus, isatin (**6**) was first converted to the corresponding imine with *p*-anisidine (Scheme 2). This imine was found to undergo smooth Staudinger [2 + 2]-cycloaddition with chloroketene to afford a high yield of a 5:1 mixture of stereoisomeric α-chloro-β-lactams **7**.[9,10] Free radical dechlorination of the mixture **7** with

SCHEME 1



SCHEME 2

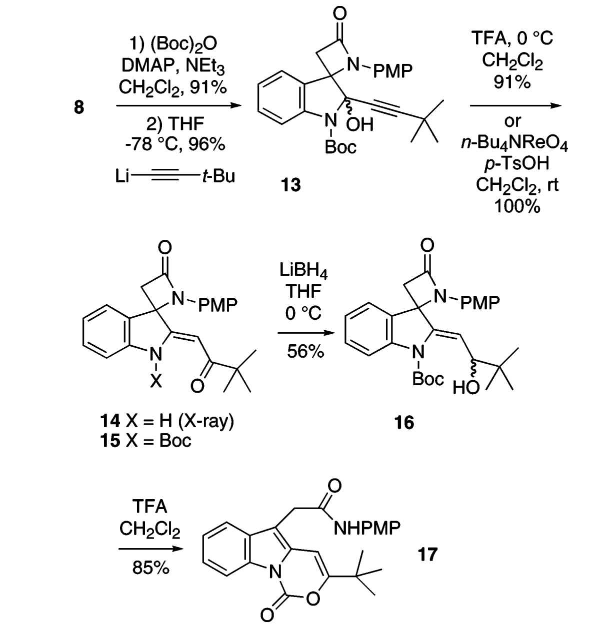


AIBN and $(TMS)_3SiH$ provided the β-lactam **8** in 91% yield.[11] Subsequent Cbz protection of the γ-lactam moiety of **8** and removal of the PMP protecting group with ceric ammonium nitrate at 0 °C gave the required *NH* β-lactam **9** in high overall yield. We were pleased to find that reaction of β-lactam **9** with phenylacetaldehyde in the presence of *p*-toluenesulfonic acid as catalyst produced the desired model enamide **11** in good yield. Although the configuration of the enamide here is *E*, we believe that in the actual natural product system the (*Z*)-configuration of the 10-membered enamide will result from the cyclocondensation of **3**, since the (*E*)-isomer is considerably more strained. It was also found that bis-*NH*-lactam **10** undergoes selective condensation at the β-lactam moiety with phenylacetaldehyde under the same conditions to produce enamide **12** in moderate yield.

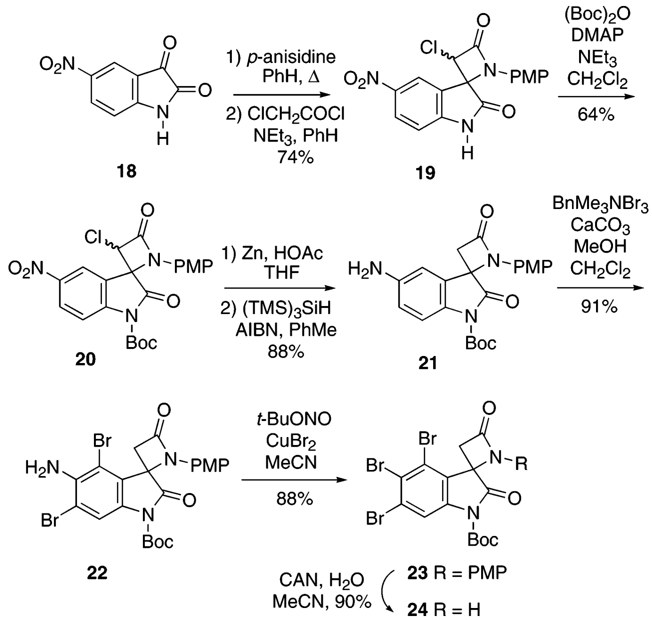
In some additional trial experiments, lactam **8** was converted to the corresponding *N*-Boc γ-lactam, to which lithio *tert*-butylacetylide could be added chemoselectively, producing **13** as a mixture of stereoisomers (Scheme 3).[12] This adduct mixture then underwent a Meyer−Schuster rearrangement[13] promoted by trifluoroacetic acid to generate vinylogous amide **14** in which

(4) Lin, X.; Weinreb, S. M. *Tetrahedron Lett.* **2001**, *42*, 2631.
(5) (a) Nishikawa, T.; Kajii, S.; Isobe, M. *Chem. Lett.* **2004**, *33*, 440. (b) Nishikawa, T.; Kajii, S.; Isobe, M. *Synlett* **2004**, 2025.
(6) Baran, P. S.; Shenvi, R. A.; Mitsos, C. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3714.
(7) Taken from: (a) Lin, X. Ph.D. Thesis, The Pennsylvania State University, University Park, PA, 2002. (b) Sun, C. Ph.D. Thesis, The Pennsylvania State University, University Park, PA, 2005.
(8) See, for example: (a) Shrestha-Dawadi, P. B.; Lugtenburg, J. *Eur. J. Org. Chem*. **2003**, 4654. (b) Diller, D.; Bergmann, F. *Chem. Ber*. **1977**, *110*, 2956.
(9) For reviews of the Staudinger reaction, see: Palomo, C.; Aizpurua, J. M.; Ganboa, I.; Oiarbide, M. *Eur. J. Org. Chem*. **1999**, 3223 and references therein.
(10) For Staudinger cycloadditions of isatin imines, see: (a) Singh, G. S.; Mehrotra, K. N. *Ind. J. Chem*. **1985**, *24B*, 129. (b) Joshi, K. C.; Jain, R.; Sharma, V. *J. Ind. Chem. Soc.* **1986**, 430. (c) Skiles, J. W.; McNeil, D. *Tetrahedron Lett.* **1990**, *31*, 7277. (d) Joshi, K. C.; Dandia, A.; Bhagat, S. *J. Fluorine Chem.* **1990**, *48*, 169.
(11) Bandini, E.; Favi, G.; Martelli, G.; Panunzio, M.; Piersanti, G. *Org. Lett*. **2000**, *2*, 1077.
(12) Padwa, A.; Dean, D. C.; Fairfax, D. J.; Xu, S. L. *J. Org. Chem*. **1983**, *58*, 4646.
(13) (a) Omar, E. A.; Tu, C.; Wigal, C. T.; Braun, L. L. *J. Heterocycl. Chem*. **1992**, *29*, 947. (b) Mamouni, A.; Daich, A.; Decroix, B. *Synth. Commun*. **1998**, *28*, 1839.

SCHEME 3



SCHEME 4



the Boc protecting group had been lost. The (*Z*)-*s*-*cis*-geometry of this compound was established by X-ray crystallography.[14] An interesting alternative here is to effect the Meyer−Schuster rearrangement of **13** under milder conditions using tetrabutylammonium perrhenate and *p*-toluenesulfonic acid via the procedure of Narasaka et al.,[15] which led to vinylogous amide **15** still bearing the Boc group.

To generate the α,*β*-unsaturated imine functionality of the chartellines, the intention was to reduce the carbonyl group of the vinylogous amide functionality of a compound such as **14** or **15**, followed by elimination. Several reducing agents (e.g., $NaBH_4/CeCl_3$, $Zn(BH_4)_2$, DIBALH, etc.) were tried to convert **15** to the corresponding alcohol, and it was eventually found that lithium borohydride was effective for this transformation, giving **16** in moderate yield. Exposure of *N*-Boc alcohol **16** to trifluoroacetic acid, however, afforded the interesting but undesired product **17** in good yield. In future work, it will be necessary to further investigate the transformation of an intermediate like **16** to the requisite unsaturated imine.

Synthesis of the Tribrominated *β*-Lactam Moiety. Our original plan was to prepare the required tribromo *β*-lactam segment **4** using the Staudinger cycloaddition approach outlined in Scheme 2 starting from 4,5,6-tribromoisatin. Although this isatin could be conveniently prepared,[7a,16] it proved difficult to use due to solubility issues, and more importantly, various imines derived from this compound did not undergo a Staudinger cycloaddition. Therefore, an alternative sequence was developed commencing from commercially available 5-nitroisatin (**18**). Condensation of 5-nitroisatin with *p*-anisidine gave the *N*-PMP imine as a bright red solid. However, upon treatment of this imine under the same Staudinger experimental conditions used for the simple isatin-derived model system (cf. Scheme 2), no desired *β*-lactam product **19** was observed (Scheme 4). After extensive experimentation, however, it was found that slow addition of a solution of chloroacetyl chloride (10 equiv) in benzene to a mixture of the *N*-PMP imine derived from **18** and TEA in benzene at reflux afforded α-chloro-*β*-lactam **19** as a mixture of stereoisomers in good yield. Since problems again arose here with the solubility of subsequent intermediates bearing a *γ*-lactam NH, a Boc group was installed on **19** at this point to produce **20**. The nitro group of **20** was reduced to the amine with zinc in acetic acid, which also partially removed the chlorine in the *β*-lactam. The crude mixture was therefore subjected to free-radical dehalogenation[11] to generate aniline **21** in high overall yield. This compound could be halogenated with benzyltrimethylammonium tribromide to afford dibromoaniline **22**. The Doyle modification[17] of the Sandmeyer reaction was then used to transform aniline **22** in one pot to the tribromo compound **23**. Finally, the PMP protecting group could be removed with ceric ammonium nitrate, yielding the requisite free *β*-lactam **24**.

Preparation of the Imidazole Fragment. The synthesis of the imidazole unit began with known imidazole ester **25**, which is readily prepared from histidine.[18] It was found that *N*-protection of the imidazole **25** as a SEM or BOM derivative afforded regioisomeric mixtures which were quite inconvenient to use for subsequent steps. However, the imidazole could be protected regioselectively as the *N*-trityl compound **26** (Scheme 5). α,α-Dimethylation of ester **26** could best be effected with methyl iodide using potassium *tert*-butoxide as the base to afford compound **27** in good yield. The ester functionality of **27** was then reduced with lithium aluminum hydride, and the resulting alcohol **28** was converted to the acetate **29**. The next step in the sequence was to elaborate the imidazole ring further via bromination at C(5), but unfortunately, the trityl group proved to be incompatible with this transformation. It was therefore necessary at this point to switch protecting groups, and this could be done simply by treating trityl compound **29** with benzyloxymethyl chloride, leading to BOM-protected imidazole **30**.

(14) We are grateful to Dr. Louis J. Todaro (Single-Crystal X-ray Facility, Department of Chemistry, Hunter College, CUNY) for the X-ray analysis of compound **14**.

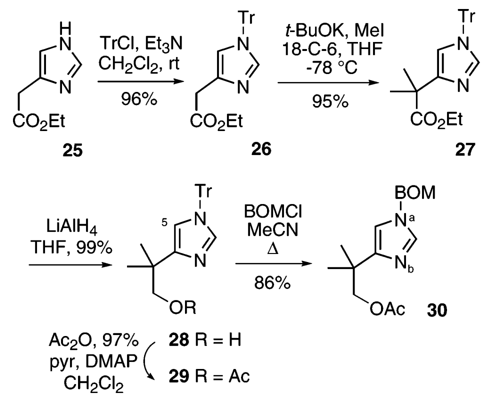
(15) (a) Narasaka, K.; Kusama, H.; Hayashi, Y. *Chem. Lett.* **1991**, 1413. (b) Narasaka, K.; Kusama, H.; Hayashi, Y. *Tetrahedron* **1992**, *48*, 2059.

(16) Synthesized by a variation of the preparation of 4,6-dibromoisatin: Jnaneshwar, G. K.; Deshpande, V. H. *J. Chem. Res., Synop.* **1999**, 632.

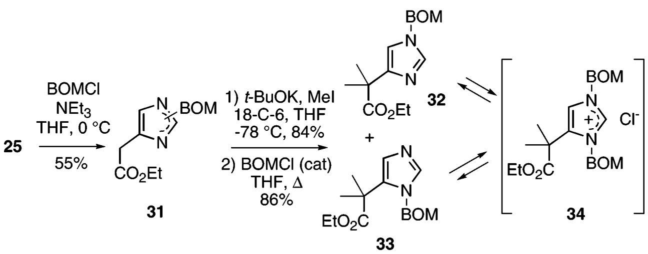
(17) Doyle, M. P.; Van Lente, M. A.; Mowat, R.; Fobare, W. F. *J. Org. Chem.* **1980**, *45*, 2570.

(18) Bauer, H.; Tabor, H. *Biochem. Prepr.* **1957**, *5*, 97.

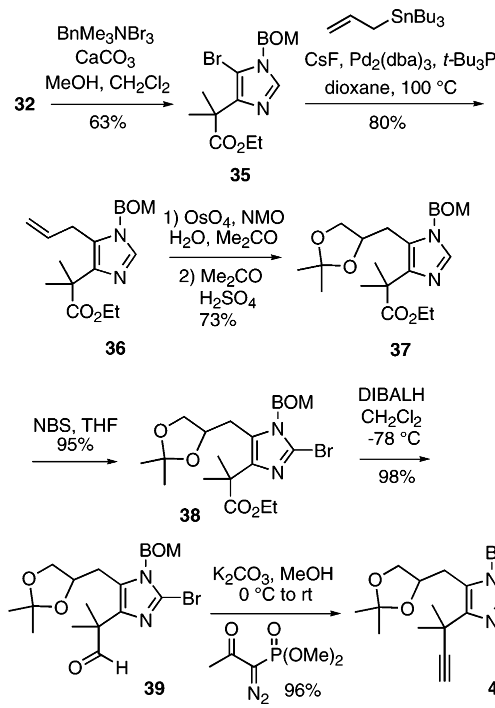
SCHEME 5



SCHEME 6



SCHEME 7



We were surprised to find, however, that in this product the BOM group was on N_a rather than N_b as anticipated on the basis of literature analogy.[19] This result, and a consideration of the mechanism of the formation of **30** (vide infra), led us to investigate a shorter, more efficient route to the desired imidazole fragment.

We therefore returned to imidazole ester **25** which was first converted to a ∼2:1 mixture of regioisomeric BOM-protected compounds **31** (Scheme 6). Without separation, this mixture of esters was dimethylated as was done for **26** to generate a mixture of regioisomeric alkylation products **32** and **33**. Once again without separation, this regioisomeric mixture was heated with a catalytic amount of BOMCl in THF which caused complete equilibration to the more stable BOM-isomer **32** in high yield.[20] It seems likely that this equilibration proceeds via the bis-BOM intermediate **34** and is thermodynamically driven. A similar equilibration is probably occurring in the transformation of trityl compound **29** to BOM-protected imidazole **30**.[19]

To continue the synthesis, imidazole ester **32** was brominated at C(5) to afford **35**, which underwent a Stille coupling with allyltributylstannane to afford allylated imidazole **36** (Scheme 7). The terminal double bond in intermediate **36** could be cleaved to the corresponding aldehyde, but under no conditions could an acetal of this compound be formed (cf. **5**). A convenient alternative was to first dihydroxylate olefin **36**[21] followed by conversion of the diol to the well-behaved acetonide **37**. It was then possible to brominate imidazole **37** at C(2) with NBS to produce **38** in high yield, and DIBALH reduction then produced aldehyde **39**. Using the Ohira modification of the Seyferth−Gilbert reaction, aldehyde **39** could be converted directly into terminal alkyne **40** in excellent yield.[22−24]

Coupling of the β-Lactam and Imidazole Segments. With the requisite β-lactam and alkyne components in hand, we began to investigate coupling procedures. In some preliminary studies, it was discovered that β-lactams protected on nitrogen with either TBS or *tert*-butyl groups did not react at the γ-lactam functionality with the lithium acetylide derived from **40**. Moreover, a PMP group on the spiro-β-lactam could not be removed after the coupling event. It was eventually found that the best solution was simply to react unprotected β-lactam **24** with 2 equiv of the lithium acetylide generated from alkyne **40** to produce adduct **41** in good yield, along with the excess alkyne which could be easily recovered by chromatography and recycled (Scheme 8). The acetonide **41** was next hydrolyzed to the corresponding diol in high yield and cleaved with lead tetraacetate to generate aldehyde **42**. Exposure of this aldehyde to *p*-toluenesulfonic acid in toluene at room temperature produced an unstable, bright yellow compound that did not appear from spectral data to be the desired macrocyclic enamide **46**, but which was tentatively assigned structure **44**. We believe that compound **44** probably arises via aldol-type cyclization of vinylogous amide aldehyde intermediate **43** to produce the seven-membered ring in the product. This material was converted to the more stable bis-Boc compound **45**, but due to the

(19) (a) Brown, T.; Jones, J. H.; Richards, J. D. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1553. (b) Brown, T.; Jones, J. H. *J. Chem. Soc., Chem. Commun.* **1981**, 648. (c) Colombo, R.; Colombo, F.; Jones, J. H. *J. Chem. Soc., Chem. Commun.* **1984**, 292. (d) Fletcher, A. C. S.; Jones, J. H.; Ramage, W. I.; Stachulski, A. V. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2261. (e) Hodges, J. C. *Synthesis* **1987**, 20. (f) Chivikas, C. J.; Hodges, J. C. *J. Org. Chem.* **1987**, *52*, 3591. (g) He, Y.; Chen, Y.; Du, H.; Schmid, L. A.; Lovely, C. J. *Tetrahedron Lett.* **2004**, *45*, 5529. (h) Bhagavatula, L.; Premchandran, R. H.; Plata, D. J.; King, S. A.; Morton, H. E. *Heterocycles* **2000**, *53*, 729.

(20) We thank Pooja Aggarwal for conducting the transformations shown in Scheme 6.

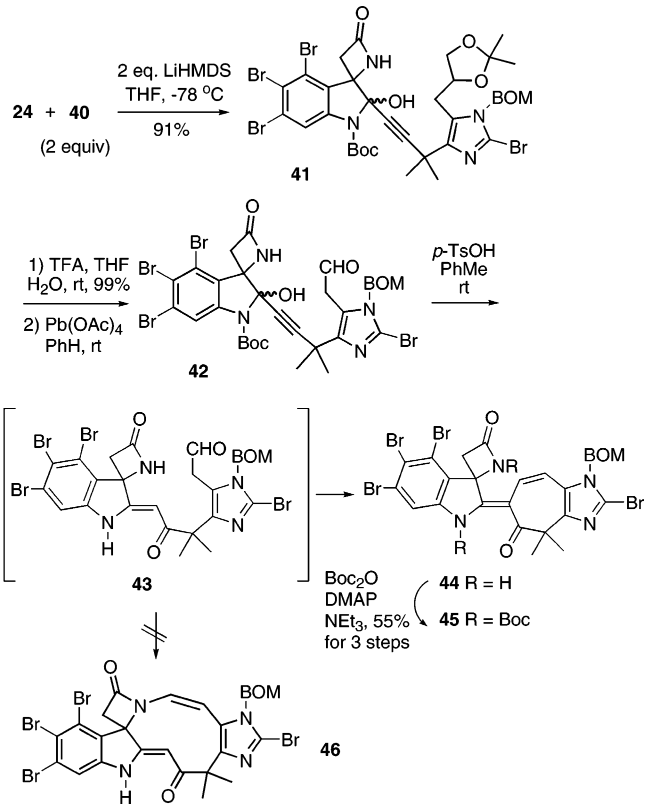
(21) (a) Van Rheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, *17*, 1973. (b) Van Rheenen, V.; Cha, D. Y.; Hartley, W. M. *Org. Synth.* **1988**, *50*, 342.

(22) (a) Seyferth, D.; Marmor, R. S.; Hilbert, P. *J. Org. Chem.* **1971**, *36*, 1379. (b) Gilbert, J. C.; Weerasooriya, U. *J. Org. Chem.* **1979**, *44*, 4997.

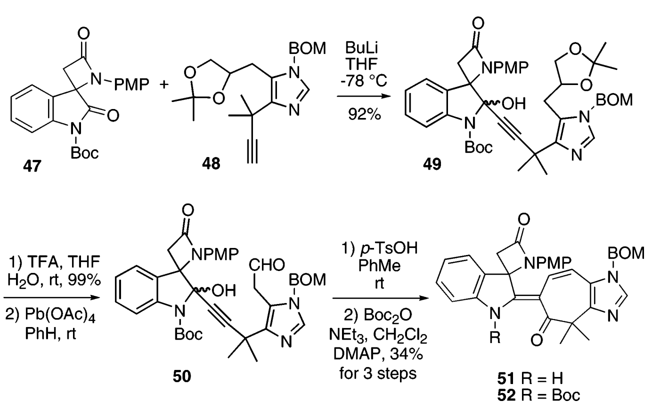
(23) For an example of the use of the Seyferth−Gilbert reagent with an aldehyde having an adjacent quaternary center, see: Trost, B. M.; Fleitz, F. J.; Watkins, W. J. *J. Am. Chem. Soc.* **1996**, *118*, 5146.

(24) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.

SCHEME 8



SCHEME 9



existence of Boc rotamers it was difficult to unambiguously confirm its structure by NMR.

We therefore decided to investigate a related system where cyclization to a 10-membered enamide like **46** was not possible and which we thought might be more amenable to detailed NMR analysis. Thus, terminal alkyne **48** was deprotonated with *n*-butyllithium, and the resulting acetylide was combined with *N*-Boc lactam **47**, producing adduct **49** (Scheme 9). As was done in Scheme 8, acetonide **49** was hydrolyzed to the diol and then cleaved to afford aldehyde **50**. Subsequent cyclization of this compound with *p*-TsOH in toluene led to the bright yellow pentacycle **51**, which was immediately converted to the stable mono-Boc compound **52**. A series of 2D NMR experiments on **52** (HMQC, HMBC, NOESY, see the Supporting Information) were then carried out to conclusively prove the structure of this compound. We believe the failure of amido aldehyde **43** to undergo cyclization to the desired enamide product **46** is probably due to the strain in this macrocyclic system due to the (*Z*)-vinylogous amide geometry. Thus, nucleophilic attack on the aldehyde functionality by the vinylogous amide to form **44** is the preferred mode of reaction.

Conclusion

In this paper, we have described the preparation of two key building blocks which are potentially useful for a total synthesis of the marine metabolite chartelline A (**1a**). Tribromo spiro-β-lactam **24** can be synthesized in eight steps from commercially available 5-nitroisatin (**18**) in about 30% overall yield. The imidazole fragment **40** can be prepared from readily available imidazole ester **25** in 10 steps. Although it is possible to couple these units by chemoselective addition of the lithium acetylide derived from alkyne **40** to the *N*-Boc γ-lactam functionality of **24**, our first-generation strategy for formation of the 10-membered ring of the natural product by a β-lactam/aldehyde cyclocondensation failed. We are currently attempting to modify the strategy to utilize intermediates described here to effect a total synthesis of chartelline A (**1a**).

Experimental Section

Preparation of α-Chloro-β-lactam 19. A solution of 5-nitroisatin (**18**, 2.52 g, 12.7 mmol) and *p*-anisidine (1.58 g, 12.7 mmol) in benzene (25 mL) was heated at reflux overnight with a Dean–Stark trap. The reaction mixture was cooled to rt, and the solvent was evaporated to give the imine as a red solid that was used directly in the next step without purification.

To a refluxing solution of the above imine (104 mg, 0.35 mmol) and triethylamine (0.49 mL, 3.5 mmol) in 10 mL of dry benzene was added chloroacetyl chloride (0.279 mL, 3.5 mmol) dropwise over 3 h. The solution was refluxed overnight and cooled to rt, and saturated $NaHCO_3$ solution was added. The mixture was extracted with EtOAc, and the combined organic layers were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (30–50% EtOAc/hexanes gradient) to yield α-chloro-β-lactam **19** (1:1 mixture of diastereoisomers, 97 mg, 74%) as an orange solid: IR (KBr) 3247, 1774, 1629, 1512 cm^{-1}; ^{1}H NMR (360 MHz, THF-d_8) δ 10.74 (s, 0.5H), 10.69 (s, 0.5H), 8.44–8.27 (m, 2H), 7.16 (t, J = 7.8 Hz, 1H), 7.04 (d, J = 7.4 Hz, 2H), 6.74 (d, J = 7.4 Hz, 2H), 5.58 (s, 0.5 H), 5.40 (s, 0.5H), 3.64 (s, 3H); ^{13}C NMR (75 MHz, THF-d_8) δ 174.4, 172.3, 159.9, 159.8, 158.2, 158.1, 149.8, 149.1, 144.5, 144.1, 130.1, 128.7, 128.6, 125.1, 123.7, 122.8, 121.5, 119.5, 119.4, 115.3, 115.2, 111.7, 111.6, 67.3, 66.6, 64.8, 64.4, 55.6; HRMS (APCI+) calcd for $C_{17}H_{13}N_3O_5Cl$ (MH$^+$) 374.0538, found 374.0555.

Synthesis of *N*-Boc Lactam 20. To a solution of the β-lactam **19** (129 mg, 0.35 mmol), DMAP (42 mg, 0.35 mmol), and triethylamine (48 μL, 0.35 mmol) in 8 mL of dry methylene chloride was added Boc anhydride (113 mg, 0.52 mmol) at rt. The solution was stirred for 10 min at rt and then evaporated. The residue was purified by flash column chromatography (10–20% EtOAc/hexanes) to yield the *N*-Boc lactam **20** (105 mg, 64%) as a white solid: IR (KBr) 2982, 1786, 1744, 1513 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.37–8.20 (m, 3H), 6.99–6.94 (m, 2H), 6.74–6.71 (m, 2H), 5.28 (s, 0.35H), 5.25 (s, 0.65H), 3.68 (s, 3H), 1.64 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 167.2, 158.7, 158.5, 157.5, 157.4, 147.8, 147.6, 145.3, 144.9, 144.8, 144.5, 128.0, 127.9, 127.7, 127.6, 123.2, 122.1, 120.9, 119.3, 119.2, 119.1, 116.4, 116.2, 114.7, 114.6, 86.9, 86.6, 66.7, 65.7, 65.0, 64.6, 55.2, 27.7; HRMS (APCI+) calcd for $C_{22}H_{21}ClN_3O_7$ (MH$^+$) 474.1062, found 474.1093.

Synthesis of Aniline 21. To a solution of nitro α-chloro-β-lactam **20** (1.040 g, 2.20 mmol) in 50 mL of THF was added Zn dust (4.32 g, 66.1 mmol) in one portion and AcOH (2.52 mL, 44.1 mmol) dropwise. The mixture was stirred at rt overnight and filtered, and the filter cake was washed thoroughly with EtOAc. The combined filtrate was concentrated, and saturated $NaHCO_3$ solution was added. The mixture was extracted with EtOAc. The organic extract was dried over $MgSO_4$ and concentrated to afford a mixture of aniline **21** and undechlorination aniline (1:2) as a yellow solid, which was used directly for the next reaction.

The above mixture was dissolved in 25 mL of toluene, and $(TMS)_3SiH$ (1.02 mL, 3.30 mmol) and a catalytic amount of AIBN were added. The mixture was heated at 100 °C overnight. The solution was evaporated in vacuo and the residue was purified by flash column chromatography (2−5% MeOH/CH_2Cl_2 gradient) to give the aniline β-lactam **21** (795 mg, 88%) as a yellow solid: IR (KBr) 3476, 3381, 2986, 1782, 1766, 1514 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$ + CD_3OD) δ 7.74−7.71 (m, 1H), 6.78−6.95 (m, 2H), 6.74−6.69 (m, 4H), 3.68 (s, 3H), 3.52 (d, J = 14.7 Hz, 1H), 3.20 (d, J = 14.7 Hz, 1H), 2.26 (s, 2H), 1.60 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$ + CD_3OD) δ 172.5, 162.6, 156.5, 148.8, 144.4, 131.2, 129.8, 124.7, 118.4, 117.0, 116.9, 114.5, 109.6, 85.0, 60.5, 55.3, 50.7, 27.9; HRMS (APCI+) calcd for $C_{22}H_{24}N_3O_5$ (MH^+) 410.1710, found 410.1697.

Preparation of Dibromoaniline 22. To a solution of aniline **21** (1.47 g, 3.58 mmol) in a mixture of CH_2Cl_2−MeOH (60 mL:24 mL) were added benzyltrimethylammonium tribromide (2.93 g, 7.52 mmol) and calcium carbonate powder (896 mg, 8.96 mmol) at rt, and the mixture was stirred for 30 min. The solid calcium carbonate was filtered off, the filtrate was concentrated, and water was added to the residue. The mixture was extracted with CH_2Cl_2. The organic layer was then dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (CH_2Cl_2) to yield dibromo aniline **22** as a white solid (1.85 g, 91%): IR (KBr) 3466, 3368, 2980, 1774, 1735, 1512 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.19 (s, 1H), 6.99−6.96 (m, 2H), 6.79−6.74 (m, 2H), 4.60 (br s, 2H), 3.71 (s, 3H), 3.60 (d, J = 14.6 Hz, 1H), 3.40 (d, J = 14.6 Hz, 1H), 1.62 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 171.6, 162.2, 157.1, 148.7, 140.5, 132.6, 130.6, 122.0, 119.8, 118.3, 114.9, 110.2, 105.8, 85.9, 62.0, 55.7, 48.2, 28.1; HRMS (APCI+) calcd for $C_{22}H_{22}BrN_3O_5$ (MH^+) 565.9921, found 565.9886.

Synthesis of Tribromide 23. To a solution of dibromo aniline **22** (1.25 g, 2.20 mmol) in 55 mL of MeCN was added $CuBr_2$ (2.46 g, 11.0 mmol), followed by *t*-BuONO (437 μL, 3.31 mmol), and the solution was then heated at 50 °C for 1 h. The reaction mixture was diluted with saturated $NaHCO_3$ solution, extracted with EtOAc, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (20−50% EtOAc/hexanes) to yield tribromide **23** as a white solid (1.22 g, 88%) along with the γ-lactam product (109 mg, 9%), which had lost the Boc group: IR (KBr) 2980, 1781, 1736, 1512 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.44 (s, 1H), 6.97−6.94 (m, 2H), 6.76−6.73 (m, 2H), 3.68 (s, 3H), 3.64 (d, J = 14.7 Hz, 1H), 3.44 (d, J = 14.7 Hz, 1H), 1.64 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 170.9, 161.8, 157.1, 148.3, 141.4, 130.3, 128.3, 124.9, 123.2, 122.9, 120.3, 118.3, 114.9, 86.6, 61.8, 55.6, 48.2, 28.0; HRMS (ESI+) calcd for $C_{22}H_{20}Br_3N_2O_5$ (MH^+) 628.8917, found 628.8862.

Synthesis of β-Lactam 24. To a solution of β-lactam **23** (322 mg, 0.510 mmol) in 7 mL of MeCN was added dropwise CAN (839 mg, 1.53 mmol) in 5 mL of water at 0 °C. The solution was stirred for 1.5 h at 0 °C, and saturated Na_2SO_3 was added. The mixture was extracted with EtOAc, and the organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (15−25% EtOAc/hexanes gradient) to yield β-lactam **24** (241 mg, 90%) as a white solid: IR (KBr) 3222, 2980, 1785, 1744, 1584 cm^{-1}; ^{1}H NMR (360 MHz, THF-d_8) δ 8.37 (s, 1H), 7.46 (br s, 1H), 3.50 (d, J = 14.4 Hz, 1H), 3.20 (dd, J = 1.8, 14.4 Hz, 1H), 1.60 (s, 9H); ^{13}C NMR (75 MHz, THF-d_8) δ 173.1, 165.2, 149.7, 142.5, 127.6, 127.2, 124.4, 123.3, 119.9, 85.5, 58.2, 28.1; HRMS (APCI+) calcd for $C_{15}H_{14}Br_3N_2O_4$ (MH^+) 522.8498, found 522.8499.

(1-Trityl-1*H*-imidazol-4-yl)acetic Acid Ethyl Ester (26). To a solution of imidazole ester **25** (0.95 g, 6.17 mmol) in CH_2Cl_2 (100 mL) at rt were added trityl chloride (2.05 g, 7.40 mmol) and NEt_3 (1.02 mL, 7.40 mmol). The reaction mixture was stirred overnight at rt and then evaporated. The residue was purified by flash column chromatography (40% EtOAc/hexanes) to yield the protected imidazole **26** (2.30 g, 96%) as a white solid: mp 152−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 1.3 Hz, 1H), 7.29−7.26 (m, 9H), 7.14−7.11 (m, 6H), 6.77 (d, J = 1.3 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 3.58 (s, 2H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.8, 142.1, 138.0, 133.8, 129.4, 127.8, 127.7, 119.4, 74.9, 60.3, 34.4, 13.8; HRMS calcd for $C_{26}H_{24}N_2O_2$ (MH^+) 397.1915, found 397.1936.

2-Methyl-2-(1-trityl-1*H*-imidazol-4-yl)propionic Acid Ethyl Ester (27). To a solution of imidazole **26** (6.10 g, 15.4 mmol) in dry THF (360 mL) were added *t*-BuOK (6.91 g, 61.6 mmol) and 18-crown-6 (0.814 g, 3.08 mmol) at −78 °C. The resulting solution was stirred for 0.5 h at −78 °C, and MeI (3.83 mL, 61.6 mmol) was then added. The mixture was stirred at −78 °C for 2 h, and water was added. The mixture was extracted with ether, and the organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (30−50% EtOAc/hexanes gradient) to yield imidazole ester **27** (6.22 g, 95%) as a white solid: mp 116−117 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35−7.31 (m, 10H), 7.14−7.10 (m, 6H), 6.64 (d, J = 1.4 Hz, 1H), 4.09 (q, J = 7.1 Hz, 2H), 1.52 (s, 6H), 1.16 (t, J = 7.1 Hz, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 176.3, 145.3, 142.5, 138.0, 129.8, 128.0, 127.9, 117.5, 75.2, 60.6, 43.1, 25.4, 14.1; HRMS calcd for $C_{28}H_{28}N_2O_2$ (MH^+) 425.2228, found 425.2223.

2-Methyl-2-(1-trityl-1*H*-imidazol-4-yl)propan-1-ol (28). To a solution of imidazole ester **27** (0.80 g, 1.9 mmol) in dry THF (80 mL) was added $LiAlH_4$ (1.0 M in Et_2O, 2.3 mL, 2.3 mmol) at rt. The solution was stirred for 3 h and quenched with 1.0 mL of 15% KOH solution. The resulting solution was stirred overnight, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (80% EtOAc/hexanes) to yield alcohol **28** (0.7 g, 99%) as a white solid: mp 143−144 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34−7.30 (m, 10H), 7.14−7.10 (m, 6H), 6.55 (d, J = 1.4 Hz, 1H), 3.57 (s, 2H), 1.21 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 142.4, 138.1, 129.7, 128.1, 128.0, 116.3, 75.2, 73.0, 36.1, 24.9; HRMS calcd for $C_{26}H_{26}N_2O$ (MH^+) 383.2122 (MH^+), found 383.2121.

Acetic Acid 2-Methyl-2-(1-trityl-1*H*-imidazol-4-yl)propyl Ester (29). To a solution of the above alcohol **28** (0.680 g, 1.78 mmol) in dry CH_2Cl_2 (45 mL) were added pyridine (0.288 mL, 3.56 mmol), acetyl chloride (0.165 mL, 2.31 mmol), and a catalytic amount of DMAP at rt. The solution was stirred overnight, and brine was added. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (40% EtOAc/hexanes) to yield acetate **29** (0.730 g, 97%) as a pale yellow oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.35−7.30 (m, 10H), 7.14−7.11 (m, 6H), 6.55 (s, 1H), 4.10 (s, 2H), 1.96 (s, 3H), 1.26 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.9, 146.7, 142.5, 138.2, 129.7, 127.9, 117.0, 75.1, 72.1, 35.4, 24.6, 20.8; HRMS calcd for $C_{28}H_{28}N_2O_2$ (MH^+) 425.2224, found 425.2209.

Acetic Acid 2-(1-Benzyloxymethyl-1*H*-imidazol-4-yl)-2-methylpropyl Acid Ester (30). To a solution of trityl-protected imidazole **29** (1.24 g, 2.92 mmol) in MeCN (136 mL) was added BOMCl (3.24 mL, 23.4 mmol). The reaction mixture was heated and stirred in an oil bath at 90 °C for 48 h. Saturated $NaHCO_3$ was then added, and the resulting solution was stirred for 10 min. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by flash column chromatography (50−100% EtOAc/hexanes gradient) to yield the BOM-protected imidazole **30** (763 mg, 86%) as a colorless oil: IR (film) 3034, 2971, 1733, 1500 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 1.3 Hz, 1H), 7.36−7.27 (m, 5H), 6.82 (d, J = 1.3 Hz, 1H), 5.27 (s, 2H), 4.44 (s, 2H), 4.15 (s, 2H), 2.02 (s, 3H), 1.32 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 170.9, 149.0, 136.7, 136.2, 128.5, 128.1, 127.8, 114.0, 75.0, 72.0, 70.0, 35.4, 24.5, 20.8; HRMS calcd for $C_{17}H_{22}N_2O_3$ (MH^+) 303.1703, found 303.1700.

(1-Benzyloxymethyl-1*H*-imidazol-4-yl)acetic Acid Ethyl Ester and (3-Benzyloxymethyl-3*H*-imidazol-4-yl)acetic Acid Ethyl Ester (31). To a solution of imidazole ester **25** (3.0 g, 19.5 mmol) in 24 mL of THF were added triethylamine (9.2 mL, 66.2 mmol) and 94% BOMCl (4.9 mL, 33.1 mmol) at 0 °C. The resulting solution was then warmed to rt and stirred for 1.5 h. The mixture was concentrated in vacuo, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with water, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (0−20% MeOH/EtOAc gradient) to yield a mixture of BOM-protected imidazole regioisomers **31** as a clear yellow-brown oil (2.94 g, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) (∼2:1 mixture of regioisomers) δ 7.5 (s, 1H, major and minor), 7.43−7.19 (m, 5H, major and minor), 7.02 (s, 1H, minor), 6.98 (s, 1H, major), 5.33 (s, 2H, major), 5.25−5.24 (m, 2H, minor), 4.41 (s, 2H, minor), 4.37 (s, 2H, major), 4.20−4.06 (m, 2H, major and minor), 3.69 (s, 2H, major), 3.64 (s, 2H, minor), 1.29−1.13 (m, 3H, major and minor).

2-(1-Benzyloxymethyl-1*H*-imidazol-4-yl)-2-methylpropionic Acid Ethyl Ester (32) and 2-[3-(Benzyloxy)methyl-3*H*-imidazol-4-yl]-2-methylpropionic Acid Ethyl Ester (33). To a solution of BOM-protected imidazole regioisomers **31** (2.65 g, 9.66 mmol) in 80 mL of THF at −78 °C were added *t*-BuOK (6.50 g, 57.97 mmol) and 18-crown-6 (0.84 g, 2.42 mmol). After the solution was stirred for 30 min at −78 °C, MeI (3.0 mL, 48.30 mmol) was added, and the resulting solution was stirred for 1 h at −78 °C. The reaction mixture was diluted with water and warmed to rt, and the aqueous layer was extracted with ether. The extract was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash column chromatography on silica gel (0−20% MeOH/EtOAc gradient) to afford a mixture BOM-protected imidazole regioisomers **32** and **33** as a clear light yellow oil (2.44 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) (mixture of regioisomers) δ 7.52 (s, 1H, major), 7.51−7.26 (m, 5H, major), 6.92 (s, 1H, major), 5.27 (s, 2H, major), 4.49 (s, 2H, major), 4.14 (q, J = 7.1 Hz, 2H, major), 1.58 (s, 6H, major), 1.22 (t, J = 7.1 Hz, 3H, major); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 136.4, 128.9, 128.6, 128.5, 128.2, 128.1, 124.3, 114.7, 75.5, 70.7, 32.7, 27.7, 25.7, 14.3; HRMS calcd for $C_{17}H_{22}N_2O_3$ (MH^+) 302.3724, found 303.1717.

2-(1-Benzyloxymethyl-1*H*-imidazol-4-yl)-2-methylpropionic Acid Ethyl Ester (32). To a solution of BOM imidazole regioisomers **32** and **33** (2.19 g, 7.27 mmol) in 24 mL of THF was added a catalytic amount of 94% BOMCl (54 μL, 0.36 mmol) at rt. The resulting solution was then warmed and stirred in an oil bath at 70 °C for 3 h. The mixture was concentrated in vacuo, and the residue was purified by flash column chromatography on silica gel (EtOAc) to yield BOM imidazole **32** as a clear light yellow oil (1.89 g, 86%): IR (film) 2980, 2935, 1727, 1500, 1455, 1455 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.51−7.26 (m, 5H), 6.92 (s, 1H), 5.27 (s, 2H), 4.49 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 1.58 (s, 6H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 136.4, 128.9, 128.6, 128.5, 128.2, 128.1, 124.3, 114.7, 75.5, 70.7, 32.7, 27.7, 25.7, 14.3; HRMS calcd for $C_{17}H_{22}N_2O_3$ (MH^+) 302.3724, found 303.1717.

2-(1-Benzyloxymethyl-5-bromo-1*H*-imidazol-4-yl)-2-methylpropionic Acid Ethyl Ester (35). To a solution of imidazole **32** (379 mg, 1.25 mmol) in 42 mL of CH_2Cl_2/MeOH (5:2) were added benzyltrimethylammonium tribromide (672 mg, 1.72 mmol) and $CaCO_3$ powder (215 mg, 2.15 mmol) at rt. The mixture was stirred until the orange color faded (∼4 h). The solid calcium carbonate was filtered off, the filtrate was concentrated, and water was then added to the residue. The mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (50−100% EtOAc/hexanes gradient) to yield 5-bromoimidazole **35** as a colorless oil (303 mg, 63%): IR (film) 2978, 2919, 1725 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.31−7.24 (m, 5H), 5.26 (s, 2H), 4.46 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 1.59 (s, 6H), 1.19 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.4, 143.0, 136.5, 136.0, 128.3, 127.9, 127.5, 98.8, 73.8, 70.0, 60.6, 43.1, 25.0, 13.9; HRMS (APCI+) calcd for $C_{17}H_{22}N_2O_3Br$ (MH^+) 381.0814, found 318.0794.

2-(5-Allyl-1-benzyloxymethyl-1*H*-imidazol-4-yl)-2-methylpropionic Acid Ethyl Ester (36). Under an atmosphere of argon, a solution of 5-bromoimidazole **35** (303 mg, 0.795 mmol) in 5 mL of dioxane and a solution of *t*-Bu_3P (121 μL, 0.040 mmol, 10% in hexane) were added sequentially to a Schlenk tube charged with $Pd_2(dba)_3$ (15 mg, 0.016 mmol) and CsF (266 mg, 1.75 mmol). Allyltributylstannane (271 μL, 0.875 mmol) was then added by syringe, the Schlenk tube was sealed and placed in a 100 °C oil bath, and the mixture was stirred overnight. The reaction mixture was then cooled to rt, diluted with EtOAc, and filtered through a pad of silica gel. The silica gel was washed thoroughly with EtOAc, and the combined washings were concentrated in vacuo. The residue was purified by flash column chromatography (50−80% EtOAc/hexanes gradient) to yield allyl imidazole **36** as a colorless oil (217 mg, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.35−7.23 (m, 5H), 5.87−5.74 (m, 1H), 5.18 (s, 2H), 5.02 (dd, J = 10.2, 1.2 Hz, 1H), 4.86 (d, J = 17.2 Hz, 1H), 4.38 (s, 2H), 4.09 (q, J = 7.1 Hz, 2H), 3.42−3.40 (m, 2H), 1.58 (s, 6H), 1.17 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 142.3, 136.2, 135.6, 134.6, 128.4, 127.9, 127.7, 123.3, 115.9, 73.3, 69.4, 60.4, 43.2, 27.2, 26.0, 13.8.

2-[1-Benzyloxymethyl-5-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-1*H*-imidazol-4-yl]-2-methylpropionic Acid Ethyl Ester (37). To a mixture of *N*-methylmorpholine *N*-oxide (371 mg, 3.17 mmol) and allyl imidazole **36** (217 mg, 0.634 mmol) in water (7 mL) and acetone (3.5 mL) was added osmium tetraoxide (193 μL, 0.032 mmol, 4% in water) at rt. The mixture was stirred overnight. The solution was then concentrated, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by flash column chromatography (0−10% MeOH/EtOAc gradient) to yield the diol (235 mg, 99%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.21 (m, 6H), 5.53 (d, J = 11.0 Hz, 1H), 5.18 (d, J = 11.0 Hz, 1H), 4.38 (s, 2H), 4.09 (q, J = 6.9 Hz, 2H), 3.95 (br s, 2H), 3.83−3.80 (m, 1H), 3.58 (dd, J = 3.0, 11.1 Hz, 1H), 3.42 (dd, J = 6.4, 10.8 Hz, 1H), 2.78 (d, J = 6.4 Hz, 2H), 1.56 (s, 6H), 1.17 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 141.9, 136.1, 128.4, 128.0, 127.7, 123.9, 73.8, 71.6, 69.7, 65.9, 60.8, 43.6, 27.1, 26.2, 26.0, 13.8.

To a stirred solution of the above diol (224 mg, 0.596 mmol) in 21 mL of dry acetone was added concentrated H_2SO_4 (87 μL). The reaction mixture was stirred for 2 d, and saturated $NaHCO_3$ was slowly added. Acetone was evaporated, and the residue was extracted with CH_2Cl_2. The organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by preparative TLC (50−100% EtOAc/hexanes gradient) to yield acetonide **37** (184 mg, 74%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (s, 1H), 7.35−7.24 (m, 5H), 5.67 (d, J = 11.0 Hz, 1H), 5.20 (d, J = 11.0 Hz, 1H), 4.38 (s, 2H), 4.40 (ABq, J = 18.0, 11.8 Hz, 2H), 4.19−4.02 (m, 4H), 3.55 (t, J = 7.8 Hz, 1H), 2.92−2.89 (m, 2H), 1.61 (s, 3H), 1.60 (s, 3H), 1.40 (s, 3H), 1.28 (s, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.6, 142.2, 136.3, 136.2, 128.4, 128.0, 127.7, 123.3, 109.2, 75.8, 74.0, 69.5, 69.0, 60.6, 43.5, 27.3, 26.6, 26.4, 26.0, 25.4, 14.0; HRMS (APCI+) calcd for $C_{23}H_{33}N_2O_5$ (MH^+) 417.2390, found 417.2364.

2-[1-Benzyloxymethyl-2-bromo-5-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-1*H*-imidazol-4-yl]-2-methylpropionic Acid Ethyl Ester (38). To a solution of imidazole **37** (108 mg, 0.260 mmol) in dry THF (10 mL) was added NBS (69 mg, 0.40 mmol) at 0 °C. The mixture was stirred at 0 °C overnight, and 10% $Na_2S_2O_3$ solution was added. The mixture was extracted with EtOAc, and the organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (20−30% EtOAc/hexanes gradient) to yield 2-bromoimidazole **38** (122 mg, 95%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35−7.27 (m, 5H), 5.73 (d, J = 11.2 Hz, 1H), 5.33 (d, J = 11.2 Hz, 1H), 4.38 (ABq, $J = 15.5$, 11.8 Hz, 2H), 4.18−4.03 (m, 4H), 3.54 (t, $J = 7.6$ Hz, 1H), 2.89 (d, $J = 6.0$ Hz, 2H), 1.58 (s, 3H), 1.57 (s, 3H), 1.39 (s, 3H), 1.28 (s, 3H), 1.21 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3, 142.9, 136.7, 128.4, 128.0, 127.6, 126.9, 118.3, 109.4, 75.7, 74.3, 70.2, 69.0, 60.8, 43.6, 28.0, 26.6, 26.5, 26.1, 25.4, 14.0; HRMS (APCI+) calcd for $C_{23}H_{32}N_2O_5Br$ (MH^+) 495.1495, found 495.1494.

2-[1-Benzyloxymethyl-2-bromo-5-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-1*H*-imidazol-4-yl]-2-methylpropionaldehyde (39). To a solution of ester **38** (157 mg, 0.318 mmol) in CH_2Cl_2 (15 mL) was added DIBALH (3.18 mL, 1.0 M in CH_2Cl_2) dropwise at −78 °C. The mixture was stirred at −78 °C overnight, and an additional 1.59 mL of DIBALH was added. After 7 h at −78 °C, EtOAc and saturated NH_4Cl were added, and the mixture was stirred at rt overnight. The reaction mixture was filtered and concentrated. The residue was purified by flash column chromatography (20−30% EtOAc/hexanes gradient) to yield the aldehyde **39** (140 mg, 98%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.39−7.28 (m, 5H), 5.73 (d, $J = 11.2$ Hz, 1H), 5.36 (d, $J = 11.2$ Hz, 1H), 4.56 (ABq, $J = 15.0$, 12.0 Hz, 2H), 4.16−4.05 (m, 2H), 3.55−3.50 (m, 1H), 2.92−2.79 (m, 2H), 1.46 (s, 3H), 1.458 (s, 3H), 1.41 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.7, 139.6, 136.6, 128.7, 128.5, 128.0, 127.6, 119.4, 109.6, 75.9, 74.4, 70.6, 69.1, 47.9, 28.0, 26.5, 25.4, 22.2, 21.9; HRMS (APCI+) calcd for $C_{21}H_{28}N_2O_4Br$ (MH^+) 451.1213, found 451.1236.

1-Benzyloxymethyl-2-bromo-5-(2,2-dimethyl[1,3]dioxolan-4-ylmethyl)-4-(1,1-dimethylprop-2-ynyl)-1*H*-imidazole (40). To a solution of Ohira's diazoketophosphonate[24] (142 mg, 0.741 mmol) in 8 mL of MeOH at 0 °C were added K_2CO_3 (136 mg, 0.99 mmol) and imidazole aldehyde **39** (223 mg, 0.494 mmol) in 8 mL of MeOH. The mixture was stirred for 30 min at 0 °C and at rt for 4 h. The reaction was quenched with saturated NH_4Cl solution and diluted with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (10−25% EtOAc/hexanes gradient) to yield acetylene **40** (212 mg, 96%) as a colorless oil: ^{1}H NMR (360 MHz, $CDCl_3$) δ 7.37−7.27 (m, 5H), 5.68 (d, $J = 11.2$ Hz, 1H), 5.38 (d, $J = 11.2$ Hz, 1H), 4.54 (ABq, $J = 13.3$, 12.1 Hz, 2H), 4.41−4.34 (m, 1H), 4.06 (dd, $J = 8.1$, 6.1 Hz, 1H), 3.62 (t, $J = 7.9$ Hz, 1H), 3.55 (dd, $J = 15.5$, 3.3 Hz, 1H), 3.08 (dd, $J = 15.5$, 8.4 Hz, 1H), 2.30 (s, 1H), 1.62 (s, 3H), 1.61 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 142.9, 136.8, 128.5, 128.0, 127.6, 126.6, 118.3, 109.3, 90.6, 76.5, 74.3, 70.4, 70.1, 68.9, 31.8, 31.4, 31.2, 27.7, 26.6, 25.5; HRMS (APCI+) calcd for $C_{22}H_{28}N_2O_3Br$ (MH^+) 447.1283, found 447.1262.

Preparation of Alkyne 41. To a solution of imidazole alkyne **40** (245 mg, 0.548 mmol) in 4 mL of dry THF was added LiHMDS (575 μL, 1.0 M in THF, 0.575 mmol) at −78 °C. The solution was stirred at −78 °C for 30 min and at rt for 5 min and recooled to −78 °C. A solution of *N*-Boc lactam **24** (144 mg, 0.274 mmol) in 1 mL of dry THF was added at −78 °C. The mixture was stirred for 2 h at −78 °C, and water was added. The mixture was extracted with Et_2O, and the organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (20−50% EtOAc/hexanes gradient) to provide alkyne **41** (mixture of diastereoisomers, 242 mg, 91%) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.10−8.08 (m, 1H), 7.37−7.27 (m, 5H), 6.31 (br s, 0.25H), 6.28 (br s, 0.25H), 5.85 (br s, 0.25H), 5.70 (br s, 0.25H), 5.57−5.43 (m, 1H), 5.34−5.27 (m, 1H), 4.58−4.52 (m, 2H), 4.45−4.20 (m, 1H), 4.03−3.96 (m, 1H), 3.92−3.76 (m, 2H), 3.64−3.57 (m, 0.5H), 3.39−3.25 (m, 1.5H), 3.10−3.02 (m, 1H), 1.65−1.51 (m, 15H), 1.41−1.38 (m, 3H), 1.30−1.26 (m, 3H); HRMS (APCI+) calcd for $C_{37}H_{41}Br_4N_4O_7$ (MH^+) 968.9703, found 968.9690.

Preparation of Aldehyde 42. To a stirred solution of acetonide **41** (242 mg, 0.249 mmol) in 10 mL of THF/H_2O (4:1) was added dropwise 2.64 mL of TFA at rt. The mixture was stirred at rt overnight. The reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O. The organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography (30−100% EtOAc/hexanes gradient) to provide the diol (19 mg, 99%) as a white solid: ^{1}H NMR (300 MHz, THF-d_8) δ 8.25−8.23 (m, 1H), 7.31−7.01 (m, 6H), 5.72−5.65 (m, 1H), 5.42−5.34 (m, 1H), 4.53 (m, 3H), 3.98−3.10 (m, 8H), 1.65−1.62 (m, 3H), 1.58−1.56 (m, 12H); HRMS (APCI+) calcd for $C_{34}H_{37}Br_4N_4O_7$ (MH^+) 928.9390, found 928.9334.

To a solution of the above diol(12 mg, 0.013 mmol) in dry benzene (1 mL) was added $Pb(OAc)_4$ (6 mg, 0.014 mmol) under argon at rt. The mixture was stirred for 10 min, diluted with EtOAc, and washed with saturated $NaHCO_3$. The organic phase was dried over $MgSO_4$ and concentrated to afford the aldehyde **42**, which was used directly for the next reaction: ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.62 (s, 0.5H), 9.56 (s, 0.5H), 8.10 (br s, 1H), 7.40−7.31 (m, 5H), 7.01 (s, 0.5H), 6.22 (s, 0.5H), 5.30 (d, $J = 12.1$ Hz, 2H), 4.52 (d, $J = 10.6$ Hz, 2H), 4.09−3.94 (m, 2.5H), 3.77 (d, $J = 15.0$ Hz, 0.5H), 3.41 (d, $J = 15.0$ Hz, 0.5H), 3.12 (d, $J = 15.0$ Hz, 0.5H), 1.66−1.46 (m, 15H); HRMS (APCI+) calcd for $C_{34}H_{37}Br_4N_4O_7$ (MH^+) 928.9390, found 928.9334.

Synthesis of Seven-Membered-Ring Compound 44. To a solution of aldehyde **42** (0.013 mmol) in dry toluene (10 mL) were added flame-dried 4 Å molecular sieves and *p*-TsOH (29 mg, 0.15 mmol) at rt. The mixture was stirred at rt overnight. Saturated $NaHCO_3$ was added, and the mixture was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated to yield the unstable seven-membered vinylogous amide **44** (6 mg) as a yellow solid, which was used directly for the next reaction without further purification: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 12.66 (br s, 1H), 7.31−7.26 (m, 5H), 7.12 (d, $J = 11.6$ Hz, 1H), 6.58 (d, $J = 11.6$ Hz, 1H), 6.15 (br s, 1H), 5.40 (s, 2H), 4.56 (s, 2H), 3.70−3.68 (m, 2H), 1.55 (m, 3H), 1.28 (m, 3H); HRMS (APCI+) calcd for $C_{28}H_{23}Br_4N_4O_3$ (MH^+) 778.8498, found 778.8566.

Synthesis of the Bis-*N*-Boc Lactam 45. To a solution of the vinylogous amide **44** (6 mg, 0.008 mmol), DMAP (1.5 mg, 0.012 mmol), and triethylamine (1.6 μL, 0.012 mmol) in 1 mL of dry CH_2Cl_2 was added Boc anhydride (3.3 mg, 0.015 mmol) at rt. The solution was stirred at rt overnight and then evaporated. The residue was purified by preparative TLC (hexanes/EtOAc/CH_2Cl_2 = 4:2:1) to yield the *N*-Boc lactam **45** (7 mg, 55% for three steps) as a yellow solid: ^{1}H NMR (300 MHz, CD_2Cl_2) δ 8.19 (s, 1H), 7.37−7.27 (m, 5H), 6.58 (d, $J = 11.6$ Hz, 1H), 6.02 (br d, $J = 11.6$ Hz, 1H), 5.39 (ABq, $J = 20.0$, 11.4 Hz, 2H), 4.57 (s, 2H), 4.03 (br s, 1H), 3.40 (br s, 1H), 1.59 (s, 3H), 1.45 (s, 9H), 1.23 (s, 3H), 1.10 (br s, 9H); ^{1}H NMR (300 MHz, toluene-d_8, 70 °C) δ 7.20 (s, 1H), 7.13−6.97 (m, 5H), 6.29 (d, $J = 11.6$ Hz, 1H), 5.90 (d, $J = 11.6$ Hz, 1H), 4.82 (ABq, $J = 13.8$, 11.3 Hz, 2H), 4.18 (s, 2H), 3.92 (d, $J = 15.1$ Hz, 1H), 2.96 (d, $J = 15.1$ Hz, 1H), 1.97 (s, 3H), 1.42 (s, 3H), 1.30 (s, 9H), 1.25 (br s, 9H); ^{13}C NMR (75 MHz, toluene-d_8, 70 °C) δ 199.3, 162.0, 150.0, 149.5, 144.8, 143.6, 137.2, 130.4, 130.4, 130.2, 128.8, 128.7, 128.3, 127.9, 126.7, 122.4, 121.5, 121.24, 121.19, 114.4, 84.9, 83.5, 74.1, 71.0, 65.8, 54.0, 49.4, 28.2, 28.0, 21.7, 21.4; LRMS (APCI+) calcd for $C_{38}H_{39}Br_4N_4O_7$ (MH^+) 978.95, found 978.9.

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Supporting Information Available: Experimental procedures for the compounds in Schemes 2, 3, and 9 and copies of proton and carbon NMR spectra of new compounds. Also included are X-ray data for compound **14**. This material is available free of charge via the Internet at http://pubs.acs.org.

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