



A convergent approach to batzelladine alkaloids. Total syntheses of (+)-batzelladine E, (–)-dehydrobatzelladine C, and (+)-batzelladine K

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ABSTRACT

We recently reported a convergent strategy to access the polycyclic guanidinium alkaloid (+)-batzelladine B via an aldol addition–retro-aldol–aza-Michael addition cascade. Here we describe the application of this approach toward the total syntheses of (+)-batzelladine E, (–)-dehydrobatzelladine C, and (+)-batzelladine K. The identification of suitable methods to functionalize a common tropane core by electrophilic alkylation and nucleophilic 1,2-addition were essential to generalizing this approach. We provide evidence for the intermediacy of an acyllallene species in the cascade reaction.

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1. Introduction

The batzelladines are a family of marine alkaloids that possess a tricyclic guanidinium core (Fig. 1).^{1–5} Two linear hydrocarbon side chains of varying length extend from this system. The guanidinium residue is embedded in an *anti*- or *syn*-2,5-disubstituted pyrrolidine ring, as exemplified by (+)-batzelladine A (**1**) and (+)-batzelladine B (**3**), respectively.¹

The challenges presented by this ring system have attracted considerable attention from synthetic chemists over the preceding decades.^{6–26} We recently disclosed the first total synthesis of the *syn*-pyrrolidine alkaloid (+)-batzelladine B (**3**) by a convergent approach.²⁷ As shown in Scheme 1A, diastereoselective electrophilic alkylation of the enoxysilane **7** using Waser's reagent (TMS-EBX)²⁸ provided the alkylation product **8** (>80%). A key step then involved the conversion of the tropane intermediate **8** to the bicyclic guanidine **12** by an aldol addition–retro-aldol–aza-Michael addition cascade, using lithium benzyl octanoate (**9**) as nucleophile. Hydrogenolysis and decarboxylation then afforded the ketone **13** (48% from **8**).

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As outlined in Scheme 1B, this convergent approach could conceivably enable access to additional targets by modulating the

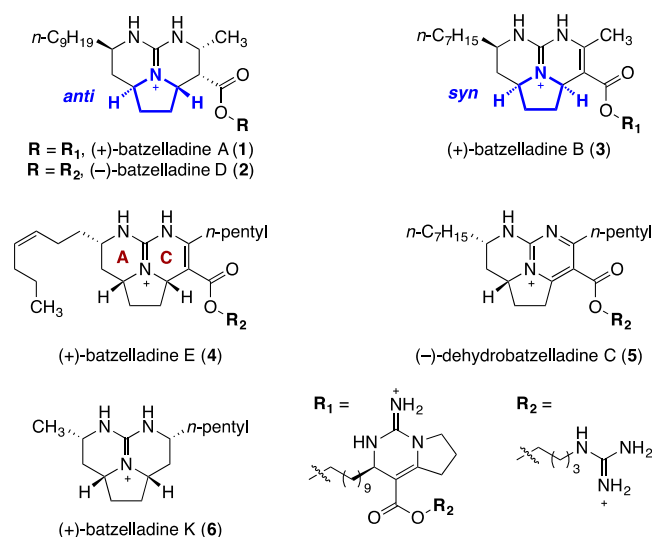
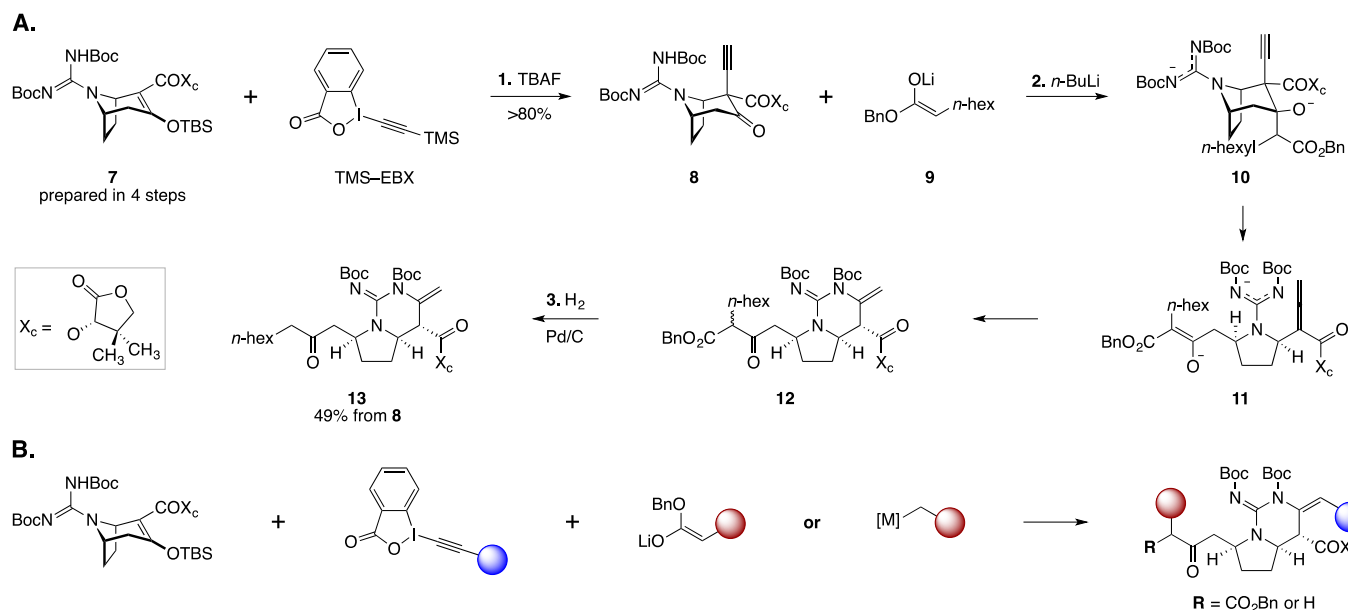


Fig. 1. Structures of (+)-batzelladine A (**1**), (–)-batzelladine D (**2**), (+)-batzelladine B (**3**), (+)-batzelladine E (**4**), (–)-dehydrobatzelladine C (**5**), and (+)-batzelladine K (**6**).



Scheme 1. A. Synthesis of the bicyclic guanidine **13**, a precursor to (+)-batzelladine **B** (**3**), via an aldol addition–retro-aldol–aza-Michael addition cascade. B. Outline of a general synthetic strategy toward *syn*-pyrrolidine guanidinium natural products.

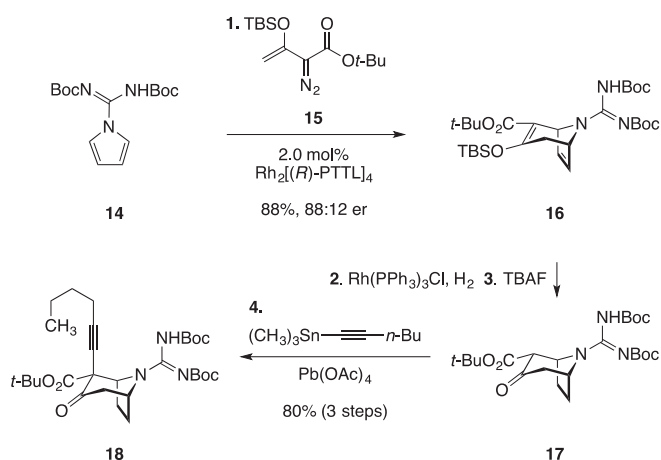
alkynylation and nucleophilic reagents. In particular we sought to investigate the suitability of unstabilized nucleophiles in the addition, as this would eliminate the extraneous decarboxylation required in the original synthesis (**12** → **13**, Scheme 1A). Here we describe the realization of this goal and the syntheses of (+)-batzelladine **E** (**4**),¹ (–)-dehydrobatzelladine **C** (**5**),³ and (+)-batzelladine **K** (**6**).⁴

2. Results and discussion

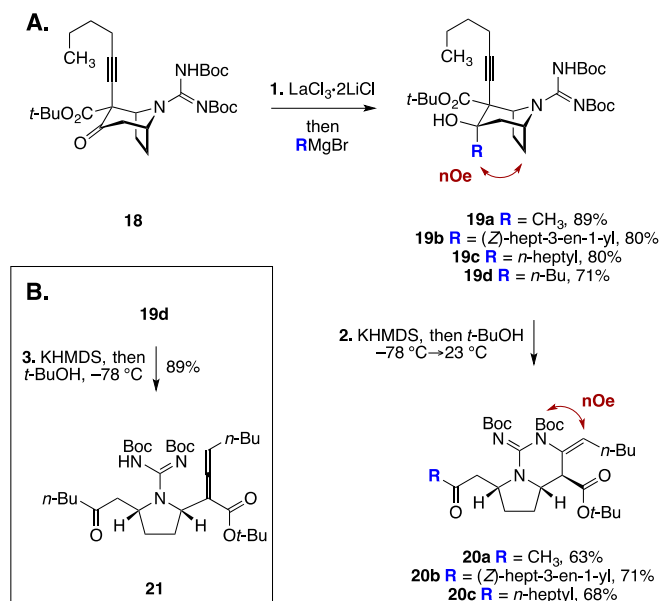
Our synthetic route began with the *N*-amidinylpyrrole **14**, which is accessible in two steps and 75% yield from 3-pyrroline (Scheme 2).²⁷ In our original work, we prepared the dehydrotropane intermediate **7** by a double stereo-differentiating, formal [4 + 3] cycloaddition using a chiral α -diazoester and a chiral dirhodium catalyst. In the present work, we employed a chiral catalyst and the achiral α -diazoester **15** instead, as this combination provided acceptable levels of stereoselectivity. Moreover, the use of a

bulky *tert*-butyl ester was necessary in the subsequent organometallic addition (vide infra). Because (+)-batzelladine **E** (**4**), (–)-dehydrobatzelladine **C** (**5**), and (+)-batzelladine **K** (**6**) are pseudoenantiomeric with respect to the positionally-equivalent sites within (+)-batzelladine **B** (**3**), the pseudoenantiomeric dehydrotropane **16** was prepared. In the event, heating **14** and **15** with dirhodium(II) tetrakis[*N*-phthaloyl-(*R*)-*tert*-leucinate] (Rh₂[(*R*)-pttl]₄) as catalyst provided the dehydrotropane **16** in 88% yield and 88:12 er.^{27,29} The β -ketoester **17** was obtained by selective hydrogenation of the less-hindered olefin with chlorotris(triphenylphosphine)rhodium(I) as catalyst, followed by cleavage of the enoxysilane (tetra-*n*-butylammonium fluoride, TBAF). Treatment of the unpurified product **17** with lead(IV) acetate in the presence of trimethylstannyl(butyl)acetylene then furnished the α -alkynyl- β -ketoester **18** as a single diastereomer (¹H NMR analysis; 80% from **16**).^{30,31} The relative stereochemistry of **18** was assigned by analogy to **8**. The use of trimethylstannyl(butyl)acetylene in the alkynylation allows for introduction of the requisite C-ring extension and a handle for construction of the C-ring in a single operation (see Fig. 1).

The addition of unstabilized nucleophiles to the tropane **18** proved to be challenging. In our original synthesis using ester enolates as nucleophiles, the initial product formed following the retro-aldol nucleosides an acidic β -ketoester function, which can neutralize the ester enolate leaving group (see **10** → **11**, Scheme 1). When unstabilized nucleophiles are employed, this acidic proton is not present, and products derived from elimination of the guanidine substituent were frequently observed. After extensive experimentation, we found that pre-complexation of the alkyne **18** with lanthanum(III) chloride bis(lithium chloride) complex³² (1 equiv) for 1 h at –40 °C, followed by treatment with an excess of an organomagnesium reagent at the same temperature resulted in clean and efficient conversion to the corresponding 1,2-addition products **19a–d** (71–89%, Scheme 3). In each instance, a single diastereomer was formed, and the relative stereochemistry was established by 2D NOESY analysis. This analysis revealed the nucleophile added to the *endo*-face of the ketone. While isolation of **19a–d** decreases the efficiency of the synthesis, this was mitigated



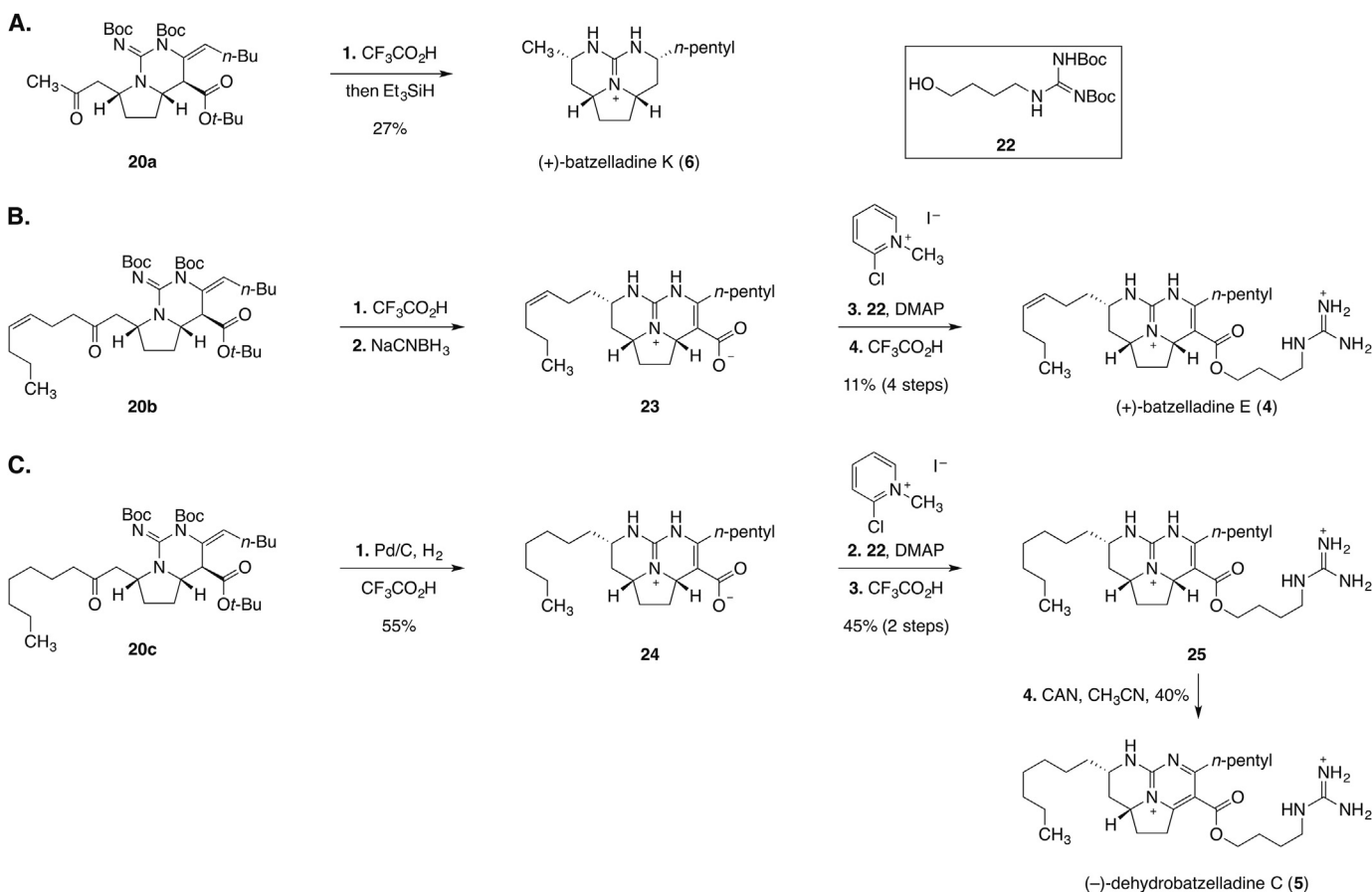
Scheme 2. Synthesis of the α -alkynyl- β -ketoester **18**.

Scheme 3. Synthesis of the bicyclic guanidines **20a–c**.

by the generality of the addition, which allows for a high degree of modularity. The use of unstabilized nucleophiles in the addition eliminates the extraneous decarboxylation step in our earlier route (**12** → **13**, Scheme 1A).

Having identified a robust and general method for incorporation of the A-ring carbon atoms, we next turned to effecting the remainder of the retro-aldol–aza-Michael cascade to access the desired bicyclic guanidines. Exposure of the addition products **19a–c** to two equivalents of potassium bis(trimethylsilyl)amide (KHMDS) in tetrahydrofuran at -78°C resulted in rapid opening of the tropane ring by a retro-aldol reaction. Low-temperature dilution of these reaction mixtures with *tert*-butanol permitted the isolation of allenes arising from γ -protonation of the resulting ester enolates (**19d** → **21**, Scheme 3B), in line with previous studies.³³ This finding supports the acylallene postulated as an intermediate in the aldol addition–retro-aldol–aza-Michael used to access (+)-batzelladine B (**3**). Simply aging (2.5 d) the diluted reaction mixtures at 23°C resulted in smooth conversion to the corresponding bicyclic guanidines **20a–c** in 63–71% yield. These products were obtained exclusively as *E* exocyclic alkene isomers (2D NOESY analysis).

With the bicyclic intermediates **20a–c** in hand, the syntheses of (+)-batzelladine E (**4**), (–)-dehydrobatzelladine C (**5**), and (+)-batzelladine K (**6**) were accomplished in 1–4 steps (Scheme 4). Treatment of the bicycle **20a** with trifluoroacetic acid at 0°C effected cleavage of the *tert*-butyl ester and two *tert*-butoxycarbonyl (Boc) protecting groups (Scheme 4A). In situ cyclo-dehydration, decarboxylation of the liberated acid, and reduction of the two resulting enamine residues with triethylsilane then provided (+)-batzelladine K (**6**, 27%). Alternatively, global deprotection of the bicycle **20b** with trifluoroacetic acid, followed by intramolecular reductive amination, generated the tricyclic acid **23** (Scheme 4B). The carboxylic acid **23** was unstable toward purification and was used directly. Stepwise coupling³⁴ with the alcohol

Scheme 4. Completion of the total syntheses of (+)-batzelladine K (**6**), (+)-batzelladine E (**4**), and (–)-dehydrobatzelladine C (**5**).

22 and cleavage of the newly introduced Boc protective groups with trifluoroacetic acid provided (+)-batzelladine E (**4**, 11% from **20b**). Finally, reductive amination of **20c** with palladium on carbon under dihydrogen in trifluoroacetic acid generated the tricyclic acid **24** (55%, Scheme 4C). The same protocol used to convert **23** to **4** was then employed to access **25** (45%). Oxidation of **25** with ceric ammonium nitrate provided (–)-dehydrobatzelladine C (**5**, 40%).¹⁵

3. Conclusion

In summary, we have generalized our route to (+)-batzelladine B (**3**) to access (+)-batzelladine E (**4**), (–)-dehydrobatzelladine C (**5**), and (+)-batzelladine K (**6**). A lead(IV) acetate-mediated alkylation of a β -ketoester and the addition of unstabilized nucleophiles to the tropane core enabled generalization of our synthetic strategy. The isolation of the stable acyllallene **21** supports the involvement of these intermediates in our rearrangement cascade. We envision that further development should allow adaption of this strategy to more elaborate guanidinium alkaloids.

4. Experimental section

4.1. General experimental procedures

All reactions were performed in single-neck, flame-dried, round-bottomed flasks fitted with rubber septa under a positive pressure of argon, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless steel cannula, or were handled in a nitrogen-filled drybox (working oxygen level <10 ppm). Organic solutions were concentrated by rotary evaporation at 28–32 °C. Flash-column chromatography was performed as described by Still et al.,³⁵ employing silica gel (60 Å, 40–63 μ m particle size) purchased from Silicycle (Quebec, Canada). Analytical thin-layered chromatography (TLC) was performed using glass plates pre-coated with silica gel (0.25 mm, 60 Å pore size) impregnated with a fluorescent indicator (254 nm). TLC plates were visualized by exposure to ultraviolet light (UV) and/or submersion in aqueous *para*-anisaldehyde (PAA), followed by brief heating on a hot plate (120 °C, 10–15 s).

4.2. Materials

Commercial solvents and reagents were used as received with the following exceptions. Dichloromethane was purified according to the method of Pangborn et al.³⁶ Tetrahydrofuran was distilled from sodium–benzophenone under an atmosphere of nitrogen immediately before use. The molarities of commercial organo-magnesium halide solutions were determined using the method described by Love et al.³⁷ Lanthanum(III) chloride and lithium chloride were dried under vacuum (~150 mTorr) for 16 h at 125 °C, with vigorous stirring, and stored in a nitrogen-filled drybox.³² Solid potassium bis(trimethylsilyl)amide was stored in a nitrogen-filled drybox. Trifluoroacetic acid was fractionally distilled and degassed by three freeze-pump-thaw cycles prior to each use. (Z)-1-Bromohept-3-ene,³⁸ the *N*-amidinylpyrrole **14**,²⁷ *tert*-butyl 3-((*tert*-butyldimethylsilyloxy)-2-diazobut-3-enoate (**15**),³⁹ trimethylstannyl(butyl)acetylene,³¹ and the guanyl alcohol **22**,⁴⁰ were prepared according to literature procedures.

4.3. Instrumentation

Proton nuclear magnetic resonance spectra (¹H NMR) were recorded at 500 or 600 MHz at 23 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to residual

protium in the NMR solvent (CHCl₃, δ 7.26; CHD₂OD, δ 3.31). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and/or multiple resonances, b = broad, app = apparent), coupling constant in Hertz, integration, and assignment. Proton-decoupled carbon nuclear magnetic resonance spectra (¹³C NMR) were recorded at 125 MHz at 24 °C, unless otherwise noted. Chemical shifts are expressed in parts per million (ppm, δ scale) downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent (CDCl₃, δ 77.0; CD₃OD, δ 49.0). Distortionless enhancement by polarization transfer spectra [DEPT (135)] were recorded at 125 MHz at 24 °C, unless otherwise noted. ¹³C NMR and DEPT (135) data are combined and represented as follows: chemical shift, carbon type [obtained from DEPT (135) experiments]. Attenuated total reflectance Fourier transform infrared (ATR-FTIR) spectra were obtained using a Thermo Electron Corporation Nicolet 6700 FTIR spectrometer referenced to a polystyrene standard. Data are represented as follows: frequency of absorption (cm^{–1}), intensity of absorption (s = strong, m = medium, w = weak, br = broad). Analytical ultra high-performance liquid chromatography/mass spectrometry (UPLC/MS) was performed on a Waters UPLC/MS instrument equipped with a reverse-phase C₁₈ column (1.7 μ m particle size, 2.1 \times 50 mm), dual atmospheric pressure chemical ionization (API)/electrospray (ESI) mass spectrometry detector, and photodiode array detector. Samples were eluted with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid \rightarrow 100% acetonitrile containing 0.1% formic acid over 0.75 min, followed by 100% acetonitrile containing 0.1% formic acid for 0.75 min, at a flow rate of 800 μ L/min. High-resolution mass spectrometry (HRMS) were obtained on a Waters UPLC/HRMS instrument equipped with a dual API/ESI high-resolution mass spectrometry detector and photodiode array detector. Unless otherwise noted, samples were eluted over a reverse-phase C₁₈ column (1.7 μ m particle size, 2.1 \times 50 mm) with a linear gradient of 5% acetonitrile–water containing 0.1% formic acid \rightarrow 95% acetonitrile–water containing 0.1% formic acid for 1 min, at a flow rate of 600 μ L/min. Preparative high performance liquid chromatography (HPLC) was performed on a Waters Sunfire™ preparative reverse-phase C₈ SymmetryPrep™ column (7.0 μ m particle size, 19 \times 300 mm). Samples were detected with a Waters Diode Array Detector (DAD) G1315B. Analytical chiral stationary phase supercritical fluid chromatography (SFC) was performed on a Waters Investigator SFC System instrument equipped with a RegisPack (TM) column (5.0 μ m particle size, 4.6 \times 250 mm) heated to 35 °C. Samples were detected with a UV/VIS detector.

Note: For positional assignments of synthetic intermediates, as well as the structure of **S1**, see the [Supplementary Material](#).

4.4. Preparation of lanthanum(III) chloride bis(lithium chloride) complex

Solutions of lanthanum(III) chloride bis(lithium chloride) complex were prepared by a modification of a published procedure.³² A mixture of dried lanthanum(III) chloride (880 mg, 3.60 mmol, 1 equiv) and dried lithium chloride (300 mg, 7.10 mmol, 1.97 equiv) was dissolved in tetrahydrofuran (5.0 mL) at 24 °C. The resulting solution was stirred for 4 h at 23 °C before use. These solutions were freshly prepared immediately before each Grignard addition (**18** \rightarrow **19a–d**).

4.5. Synthesis of the dehydrotropane **16**

Tetrakis[*N*-phthaloyl-(*R*)-*tert*-leucinato]dirhodium(II) ethyl acetate adduct (690 mg, 485 μ mol, 0.020 equiv) was added to a suspension of the *N*-amidinylpyrrole **14** (7.50 g, 24.3 mmol, 1 equiv) in

hexanes (1.3 L) in a three-neck round-bottomed flask at 23 °C. The reaction vessel was fitted with a reflux condenser, an addition funnel, and a rubber septum. The reaction vessel was then placed in a heating mantle prewarmed to 68 °C. The resulting turbid green mixture was stirred vigorously for 2 h at 68 °C. A solution of *tert*-butyl-3-((*tert*-butyldimethylsilyloxy)-2-diazobut-3-enoate (**15**; 10.1 g, 33.9 mmol, 1.40 equiv) in hexanes (170 mL) was added dropwise via addition funnel over 2 h at 68 °C. The reaction mixture became progressively more homogeneous over the course of the addition. Upon completion of the addition, the product mixture was cooled to 23 °C over 30 min. The cooled product mixture was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–pentane initially, grading to 35% ethyl acetate–pentane, one step) to provide the dehydrotropene **16** as a light yellow, crystalline solid (12.4 g, 88%). The enantiomeric ratio (er) was determined to be 88:12 by chiral stationary phase supercritical fluid chromatography. The absolute stereochemical configuration was assigned by analogy to the literature.^{27,29} $R_f = 0.25$ (15% ethyl acetate–pentane; UV, PAA). ^1H NMR (600 MHz, CDCl_3): δ 10.43 (bs, 1H, NH), 6.50 (dd, $J = 6.0, 2.6$ Hz, 1H, H_2), 5.95 (dd, $J = 6.0, 2.6$ Hz, 1H, H_3), 5.28 (bs, 1H, H_1), 5.03 (bs, 1H, H_4), 3.13 (app d, $J = 17.5$ Hz, 1H, H_5), 1.84 (app d, $J = 17.8$ Hz, 1H, H_5), 1.48 (s, 18H, $\text{H}_{7,8}$), 1.47 (s, 9H, H_6), 0.90 (s, 9H, H_9), 0.18 (s, 3H, H_{10}), 0.16 (s, 3H, H_{10}). ^{13}C NMR (125 MHz, CDCl_3): δ 163.3 (C), 157.5 (C), 153.5 (C), 151.4 (C), 150.0 (C), 137.4 (CH), 127.3 (CH), 116.0 (C), 82.0 (C), 79.8 (2 \times C), 59.07 (CH), 57.3 (CH), 33.0 (CH₂), 28.3 (3 \times CH₃), 28.2 (3 \times CH₃), 25.8 (6 \times CH₃), 18.5 (C), –3.87 (CH₃), –3.71 (CH₃). IR (ATR-FTIR), cm^{-1} : 2978 (w), 1749 (m), 1717 (m), 1612 (m). HRMS-Cl (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{50}\text{N}_3\text{O}_7\text{Si}$, 580.3413; found, 580.3385.

4.6. Synthesis of the tropene **51**

Chlorotris(triphenylphosphine)rhodium(I) (296 mg, 320 μmol , 0.015 equiv) was added to a solution of the dehydrotropene **16** (12.4 g, 21.4 mmol, 1 equiv) in 2-propanol (71 mL) at 23 °C. The resulting heterogeneous red suspension was then sealed in a stainless steel hydrogenation chamber. The chamber was flushed with dihydrogen (3 \times 10 atm) and then charged to 30 atm dihydrogen. The reaction mixture was stirred under dihydrogen for 18 h at 23 °C. The product mixture was then removed from the chamber, the solution was collected, and then concentrated. In preparative scale experiments, the residue obtained was used directly in the following step. An analytically-pure sample of the tropene **51** could be obtained by flash-column chromatography (eluting with 20% ethyl acetate–hexanes). $R_f = 0.25$ (20% ethyl acetate–pentane; UV, PAA). ^1H NMR (600 MHz, CDCl_3): δ 10.36 (bs, 1H, NH), 4.75 (bd, 2H, $\text{H}_{1,4}$), 3.16 (app d, $J = 17.7$ Hz, 1H, H_5), 2.25–2.15 (m, 2H, $\text{H}_{2,3}$), 2.03–1.95 (m, 1H, H_2), 1.93 (app d, $J = 17.5$ Hz, 1H, H_5), 1.67 (m, 1H, H_3), 1.48 (s, 18H, $\text{H}_{7,8}$), 1.45 (s, 9H, H_6), 0.92 (s, 9H, H_9), 0.19 (s, 3H, H_{10}), 0.16 (s, 3H, H_{10}). ^{13}C NMR (125 MHz, CDCl_3): δ 163.6 (C), 162.9 (C), 158.1 (C), 152.0 (C), 150.5 (C), 115.6 (C), 81.7 (C), 79.7 (2 \times C), 57.1 (CH), 52.6 (CH), 40.2 (CH₂), 34.5 (CH₂), 28.7 (CH₂), 28.3 (3 \times CH₃), 28.2 (3 \times CH₃), 28.1 (3 \times CH₃), 25.8 (3 \times CH₃), 18.6 (C), –3.7 (CH₃), –4.1 (CH₃). IR (ATR-FTIR), cm^{-1} : 2980 (w), 1746 (m), 1716 (m), 1607 (m). HRMS-Cl (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{52}\text{N}_3\text{O}_7\text{Si}$, 582.3569; found, 582.3524.

4.7. Synthesis of the β -ketoester **17**

A solution of tetrabutylammonium fluoride in tetrahydrofuran (1.0 M, 44.8 mL, 44.8 mmol, 2.10 equiv) was added dropwise via syringe pump over 15 min to a solution of the unpurified tropene **51** obtained in the preceding step (nominally 21.4 mmol, 1 equiv) in tetrahydrofuran (210 mL) at –78 °C. The resulting brown mixture

was stirred for 30 min at –78 °C. The cold product mixture was diluted with saturated aqueous ammonium chloride solution (300 mL). The diluted product mixture was warmed over 2 h to 23 °C, with stirring. The warmed product mixture was diluted with ethyl acetate (200 mL). The resulting biphasic mixture was transferred to a separatory funnel, and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 \times 200 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (2 \times 350 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. In preparative experiments, the residue obtained was used directly in the following step. An analytically pure sample of the β -ketoester **17** could be obtained by flash-column chromatography (eluting with 25% ethyl acetate–hexanes). The product was obtained as a single C9 diastereomer (^1H NMR analysis, stereochemistry not assigned), $R_f = 0.34$ (25% ethyl acetate–pentane; UV, PAA). ^1H NMR (500 MHz, CD_3OD): δ 4.65 (bs, 1H, H_1), 4.56 (bs, 1H, H_4), 3.19 (m, 1H, H_5), 2.35 (app t, $J = 14.1$ Hz, 1H, H_5), 2.30–2.21 (m, 1H, H_2), 2.17–2.07 (m, 2H, $\text{H}_{3,9}$), 1.92 (m, 1H, H_2), 1.76–1.68 (m, 1H, H_3), 1.58 (s, 9H, H_6), 1.48 (s, 9H, H_8), 1.43 (s, 9H, H_7). ^{13}C NMR (125 MHz, CD_3OD): δ 203.8 (C), 170.9 (C), 168.7 (C), 168.4 (C), 151.1 (C), 83.0 (C), 82.9 (C), 80.5 (C), 55.7 (CH), 53.9 (CH), 37.9 (CH), 35.4 (CH₂), 29.7 (CH₂), 28.6 (6 \times CH₃), 28.4 (CH₂), 28.1 (3 \times CH₃). IR (ATR-FTIR), cm^{-1} : 2933 (w), 1728 (m), 1724 (m), 1601 (m). HRMS-Cl (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{23}\text{H}_{38}\text{N}_3\text{O}_7$, 468.2704; found, 468.2673.

4.8. Synthesis of the alkyne **18**

Trimethylstannyl(butyl)acetylene (6.79 g, 27.6 mmol, 1.29 equiv) was added dropwise via syringe to a solution of the unpurified β -ketoester **17** obtained in the previous step (nominally 21.4 mmol, 1 equiv) in dichloromethane (110 mL) at 0 °C. Immediately upon completion of the addition, lead(IV) acetate (13.2 g, 29.8 mmol, 1.39 equiv) was added in one portion. The cooling bath was removed and the reaction mixture was warmed over 2 h to 23 °C. The product mixture was diluted sequentially with 1.0 M aqueous hydrogen chloride solution (150 mL), water (50 mL), and ethyl acetate (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (3 \times 100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–pentane) to afford the alkyne **18** as a clear yellow liquid (9.35 g, 80% from **16**). The alkyne **18** was obtained as a single stereoisomer. The configuration of the newly-formed stereocenter was assigned by analogy to related compounds.²⁷ $R_f = 0.21$ (10% ethyl acetate–pentane; UV, PAA). ^1H NMR (600 MHz, CDCl_3): δ 10.22 (bs, 1H, NH), 4.84 (bs, 1H, H_1), 4.59 (bs, 1H, H_4), 3.59 (app bs, 1H, H_{5a}), 2.33 (m, 1H, H_{5b}), 2.22 (dd, $J = 14.4, 2.2$, 1H, H_{2a}), 2.20–2.12 (m, 3H, $\text{H}_{3a}, \text{H}_9$), 2.06–1.95 (m, 1H, H_{2b}), 1.68–1.58 (m, 1H, H_{3b}), 1.57–1.42 (m, 27H, H_{6-8}), 1.45–1.38 (m, 2H, H_{10}), 1.38–1.30 (m, 2H, H_{11}), 0.86 (t, $J = 7.2$ Hz, 3H, H_{12}). ^{13}C NMR (125 MHz, CDCl_3): δ 199.6 (C), 165.7 (C), 152.8 (C), 82.9 (2 \times C), 82.0 (C), 79.7 (C), 74.2 (C), 63.8 (C), 63.1 (CH), 56.0 (CH), 44.7 (CH₂), 30.1 (CH₂), 28.1 (3 \times CH₃), 27.9 (6 \times CH₃), 27.6 (CH₂), 25.2 (CH₂), 21.8 (CH₂), 18.4 (CH₂), 13.5 (CH₃). Note: Two carbamate ^{13}C shifts were not detected due to line broadening. IR (ATR-FTIR), cm^{-1} : 3009 (w), 2933 (w), 1745 (m), 1725 (m). HRMS-Cl (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{29}\text{H}_{46}\text{N}_3\text{O}_7$, 548.3330; found, 548.3301.

4.9. Synthesis of the alcohol **19a**

A solution of lanthanum(III) chloride bis(lithium chloride) complex in tetrahydrofuran (0.72 M, 7.94 mL, 5.72 mmol, 1.01 equiv) was added dropwise via syringe to a solution of the alkyne **18** (3.10 g, 5.67 mmol, 1 equiv) in tetrahydrofuran (110 mL) at -40°C . The resulting turbid yellow mixture was stirred for 1 h at -40°C . A solution of methyl magnesium bromide in ether (3.0 M, 6.60 mL, 19.8 mmol, 3.49 equiv) was added dropwise via syringe. The resulting mixture was stirred for 3 h at -40°C . The cold dark yellow product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (60 mL), water (60 mL), and ethyl acetate (100 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4×100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (50 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 15% ethyl acetate–hexanes) to afford the alcohol **19a** as a viscous yellow oil (2.84 g, 89%). The alcohol **19a** was obtained as a single stereoisomer (^1H NMR analysis). The configuration of the newly-formed stereocenter was assigned by analogy to **19b** (vide infra). $R_f = 0.22$ (15% ethyl acetate–hexanes; UV, PAA). ^1H NMR (600 MHz, CDCl_3): δ 10.27 (bs, 1H, NH), 4.60 (m, 2H, $\text{H}_{1,4}$), 3.69 (app s, 1H, H_{5a}), 2.29–2.12 (m, 4H, $\text{H}_{2a,5b,9}$), 2.11–2.05 (m, 1H, H_{3a}), 1.91–1.81 (m, 1H, H_{2b}), 1.67 (app d, $J = 15.3$ Hz, 1H, H_{3b}), 1.49–1.46 (m, 30H, $\text{H}_{6-8,13}$), 1.43–1.38 (m, 4H, $\text{H}_{10,11}$), 0.90 (t, $J = 6.9$ Hz, 3H, H_{12}). ^{13}C NMR (125 MHz, CDCl_3): δ 170.1 (C), 163.1 (C), 151.6 (C), 150.5 (C), 87.3 (C), 82.8 (C), 81.1 (C), 79.0 (C), 77.9 (C), 74.0 (CH), 64.0 (C), 55.9 (CH), 54.5 (C), 40.9 (CH₂), 30.2 (CH₂), 30.0 (CH₂), 28.3 ($3 \times \text{CH}_3$), 28.1 ($3 \times \text{CH}_3$), 28.0 ($3 \times \text{CH}_3$), 27.1 (CH₂), 25.5 (CH₂), 21.7 (CH₃), 18.3 (CH₂), 13.6 (CH₃). IR (ATR-FTIR), cm^{-1} : 3300 (br), 2971 (m), 1725 (m), 1626 (m). HRMS-Cl (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{50}\text{N}_3\text{O}_7$, 564.3643; found, 564.3599.

4.10. Synthesis of the alcohol **19b**

4.10.1. Preparation of (*Z*)-hept-3-en-1-yl magnesium bromide

Neat (*Z*)-1-bromohept-3-ene (303 mg, 1.71 mmol, 0.19 equiv) was added to dry magnesium turnings (218 mg, 8.97 mmol, 1.00 equiv) at 23°C . The reaction vessel was placed in an oil bath that had been preheated to 50°C . The mixture was stirred for 3 min at 50°C . The reaction vessel was then removed from the oil bath. A solution of (*Z*)-1-bromohept-3-ene (1.21 g, 6.84 mmol, 0.76 equiv) in tetrahydrofuran (8.6 mL) was added via syringe. The reaction mixture was returned to the oil bath at 50°C . The reaction mixture was stirred for 45 min at 50°C . The product mixture was cooled over 30 min to 23°C . The cooled solution of (*Z*)-hept-3-en-1-yl magnesium bromide obtained in this way (nominally 1.04 M) was used immediately in the following step.

4.10.2. Synthesis of the alcohol **19b**

A solution of lanthanum(III) chloride bis(lithium chloride) complex in tetrahydrofuran (0.72 M, 2.56 mL, 1.84 mmol, 1.01 equiv) was added dropwise via syringe to a solution of the alkyne **18** (1.00 g, 1.83 mmol, 1 equiv) in tetrahydrofuran (31 mL) at -40°C . The resulting turbid yellow mixture was stirred for 1 h at -40°C . A solution of (*Z*)-hept-3-en-1-yl magnesium bromide in tetrahydrofuran (nominally 1.04 M, 6.40 mL, 6.66 mmol, 3.64 equiv) was then added dropwise via syringe at -40°C . The reaction mixture was stirred for 3 h at -40°C . The dark yellow product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (30 mL), water (30 mL), and ethyl acetate (50 mL). The

resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4×60 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes) to afford the alcohol **19b** as a viscous yellow oil (943 mg, 80%). The alcohol **19b** was obtained as a single stereoisomer (^1H NMR analysis). The relative stereochemical configuration was determined by 2D-NOESY analysis (NOE from H_{13} to H_3 observed). $R_f = 0.18$ (10% ethyl acetate–hexanes; UV, PAA). ^1H NMR (500 MHz, CDCl_3): δ 10.32 (bs, 1H, NH), 5.39–5.30 (m, 2H, $\text{H}_{15,16}$), 4.67–4.55 (m, 2H, $\text{H}_{1,4}$), 3.97 (app s, 1H, H_{5a}), 2.25–2.21 (m, 6H, $\text{H}_{2a,5b,9,17}$), 2.05–1.95 (m, 2H, H_{14}), 1.94–1.85 (m, 2H, $\text{H}_{2b,3a}$), 1.79 (app d, $J = 14.1$, 1H, H_{3b}), 1.50 (s, 9H, H_6), 1.47 (s, 18H, $\text{H}_{7,8}$), 1.45–1.31 (m, 8H, $\text{H}_{10,11,13,18}$), 0.90 (app t, 6H, $\text{H}_{12,19}$). ^{13}C NMR (125 MHz, CDCl_3): δ 170.7 (C), 163.1 (C), 151.6 (C), 150.5 (C), 129.9 (CH), 129.8 (CH), 87.8 (C), 82.9 (C), 81.1 (C), 79.1 (C), 77.2 (C), 75.6 (CH), 64.6 (C), 56.0 (CH), 54.4 (C), 41.5 (CH₂), 38.3 (CH₂), 30.2 (CH₂), 29.3 (CH₂), 28.3 ($3 \times \text{CH}_3$), 28.1 ($3 \times \text{CH}_3$), 27.1 ($3 \times \text{CH}_3$), 27.2 (CH₂), 25.3 (CH₂), 22.8 (CH₂), 21.7 (CH₂), 20.6 (CH₂), 18.4 (CH₂), 13.8 (CH₃), 13.6 (CH₃). IR (ATR-FTIR), cm^{-1} : 3349 (br), 3009 (w), 2973 (w), 1729 (m), 1603 (m). HRMS-Cl (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{36}\text{H}_{60}\text{N}_3\text{O}_7$, 646.4426; found, 646.4376.

4.11. Synthesis of the alcohol **19c**

A solution of lanthanum(III) chloride bis(lithium chloride) complex in tetrahydrofuran (0.72 M, 2.56 mL, 1.84 mmol, 1.00 equiv) was added dropwise via syringe to a solution of the alkyne **18** (1.00 g, 1.83 mmol, 1 equiv) in tetrahydrofuran (31 mL) at -40°C . The resulting turbid yellow mixture was stirred for 1 h at -40°C . A solution of *n*-heptylmagnesium bromide in ether (1.0 M, 6.40 mL, 6.40 mmol, 3.50 equiv) was added dropwise via syringe. The reaction mixture was stirred for 3 h at -40°C . The cold, dark yellow product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (30 mL), water (30 mL), and ethyl acetate (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4×60 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes) to afford the alcohol **19c** as a viscous yellow oil (948 mg, 80%). The alcohol **19c** was obtained as a single diastereomer (^1H NMR analysis). The configuration of the newly-formed stereocenter was assigned by analogy to **19b** (vide supra). $R_f = 0.18$ (10% ethyl acetate–hexanes; UV, PAA). ^1H NMR (600 MHz, CDCl_3): δ 10.32 (bs, 1H, NH), 4.60 (app br s, 2H, $\text{H}_{1,4}$), 3.84 (app s, 1H, H_{5a}), 2.25–2.15 (m, 2H, $\text{H}_{2a,5b}$), 2.15–2.07 (m, 2H, H_9), 1.92–1.83 (m, 2H, $\text{H}_{2b,3a}$), 1.77 (app d, $J = 14.2$, 1H, H_{3b}), 1.66–1.56 (m, 4H, $\text{H}_{10,13}$), 1.50 (s, 9H, H_7), 1.48 (s, 9H, H_8), 1.47 (s, 9H, H_6), 1.46–1.37 (m, 4H, $\text{H}_{14,15}$), 1.31–1.2 (m, 8H, $\text{H}_{11,16-18}$), 0.91 (t, $J = 6.9$ Hz, 3H, H_{12}), 0.87 (t, $J = 6.5$ Hz, 3H, H_{19}). ^{13}C NMR (125 MHz, CDCl_3): δ 170.7 (C), 163.1 (C), 151.6 (C), 150.5 (C), 87.7 (C), 82.9 (C), 81.1 (C), 79.1 (C), 77.5 (C), 75.7 (CH), 64.6 (C), 56.1 (CH), 54.5 (C), 41.6 (CH₂), 38.4 (CH₂), 31.8 (CH₂), 30.3 (CH₂), 30.1 (CH₂), 29.4 (CH₂), 28.3 ($3 \times \text{CH}_3$), 28.1 ($3 \times \text{CH}_3$), 27.8 ($3 \times \text{CH}_3$), 27.2 (CH₂), 25.3 (CH₂), 22.7 (CH₂), 22.5 (CH₂), 21.7 (CH₂), 18.4 (CH₂), 14.1 (CH₃), 13.6 (CH₃). IR (ATR-FTIR), cm^{-1} : 3374 (br, w), 2948 (w), 1725 (m), 1610 (m). HRMS-Cl (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{36}\text{H}_{62}\text{N}_3\text{O}_7$,

648.4582; found, 648.4536.

4.12. Synthesis of the alcohol **19d**

A solution of lanthanum(III) chloride bis(lithium chloride) complex in tetrahydrofuran (0.72 M, 11.2 mL, 8.06 mmol, 0.98 equiv) was added dropwise via syringe to a solution of the alkyne **18** (4.50 g, 8.22 mmol, 1 equiv) in tetrahydrofuran (110 mL) at -40°C . The resulting turbid yellow mixture was stirred for 1 h at -40°C . A solution of *n*-butylmagnesium bromide in tetrahydrofuran (2.0 M, 14.0 mL, 28.0 mmol, 3.41 equiv) was added dropwise via syringe at -40°C . The reaction mixture was stirred for 3 h at -40°C . The cold, dark yellow product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (100 mL), water (100 mL), and ethyl acetate (150 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4×100 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% ethyl acetate–hexanes) to afford the alcohol **19d** as a viscous yellow oil (3.52 g, 71%). The alcohol **19d** was obtained as a single diastereomer (^1H NMR analysis). The configuration of the newly-formed stereocenter was assigned by analogy to **19b** (vide supra). $R_f = 0.23$ (10% ethyl acetate–hexanes; UV, PAA). ^1H NMR (600 MHz, CDCl_3): δ 10.31 (bs, 1H, NH), 4.64–4.57 (m, 2H, $\text{H}_{1,4}$), 3.82 (s, 1H, H_{5a}), 2.24–2.15 (m, 3H, $\text{H}_{2a,9}$), 2.15–2.06 (m, 3H, $\text{H}_{2b,3a,5b}$), 1.90–1.83 (m, 2H, H_{10}), 1.77 (d, $J = 14.3$, 1H, H_{3b}), 1.49 (s, 9H, H_7), 1.46 (s, 18H, $\text{H}_{6,8}$), 1.44–1.36 (m, 4H, $\text{H}_{13,14}$), 1.31–1.23 (m, 4H, $\text{H}_{11,15}$), 0.93–0.85 (m, 6H, $\text{H}_{12,16}$). ^{13}C NMR (125 MHz, CDCl_3): δ 170.7 (C), 163.1 (C), 151.6 (C), 150.5 (C), 87.7 (C), 82.9 (C), 81.1 (C), 79.1 (C), 77.5 (C), 75.7 (CH), 64.6 (C), 56.2 (CH), 54.4 (C), 41.3 (CH_2), 38.4 (CH_2), 30.3 (CH_2), 28.3 ($3 \times \text{CH}_3$), 28.1 ($3 \times \text{CH}_3$), 27.8 ($3 \times \text{CH}_3$), 27.2 (CH_2), 25.3 (CH_2), 24.7 (CH_2), 23.2 (CH_2), 21.7 (CH_2), 18.4 (CH_2), 14.2 (CH_3), 13.6 (CH_3). IR (ATR-FTIR), cm^{-1} : 3352 (br, w), 2970 (w), 1727 (m), 1605 (m). HRMS-Cl (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{56}\text{N}_3\text{O}_7$, 606.4113; found, 606.4049.

4.13. Synthesis of the ketone **20a**

A solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 4.00 mL, 4.00 mmol, 2.15 equiv) was added dropwise via syringe to a solution of the alcohol **19a** (1.05 g, 1.86 mmol, 1 equiv) in tetrahydrofuran (38 mL) at -78°C . The resulting turbid yellow mixture was stirred for 2.5 h at -78°C . The cold mixture was then diluted with a mixture of *tert*-butanol and ether (1:1 v/v, 2.5 mL) at -78°C . The reaction mixture was warmed over 20 min to 23°C , and the warmed mixture was stirred for 2.5 d at 23°C . The light yellow product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (30 mL) and ethyl acetate (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4×50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (200 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes) to afford the ketone **20a** as a viscous yellow oil (661 mg, 63%). The ketone **20a** was obtained as a single alkene and C15 stereoisomer (^1H NMR analysis). The configuration of C15 was assigned by analogy to related

compounds.²⁷ The configuration of the alkene was obtained assigned by 2D-NOESY spectroscopy (NOE from H_{14} to H_7 observed). $R_f = 0.27$ (35% ethyl acetate–hexanes; UV, PAA). ^1H NMR (600 MHz, CDCl_3): δ 5.83 (t, $J = 7.8$ Hz, 1H, H_{14}), 4.46 (t, $J = 7.9$ Hz, 1H, H_4), 3.87 (td, $J = 9.5, 6.3$ Hz, 1H, H_1), 3.46 (d, $J = 9.3$ Hz, 1H, H_{15}), 2.99 (dd, $J = 16.7, 3.3$ Hz, 1H, H_{5a}), 2.40 (dd, $J = 16.6, 9.8$, 1H, H_{5b}), 2.17–2.12 (m, 4H, $\text{H}_{2a,3a,9}$), 2.10 (s, 3H, H_{13}), 1.84 (dd, $J = 12.8, 6.9$ Hz, 1H, H_{3b}), 1.74–1.65 (m, 1H, H_{2b}), 1.48 (s, 9H, H_6), 1.45 (s, 9H, H_8), 1.45 (s, 9H, H_7), 1.40–1.31 (m, 4H, $\text{H}_{10,11}$), 0.89 (t, $J = 6.9$ Hz, 3H, H_{12}). ^{13}C NMR (125 MHz, CDCl_3): δ 206.6 (C), 168.8 (C), 159.7 (C), 150.6 (C), 150.2 (C), 132.2 (CH), 127.8 (C), 81.9 (C), 81.8 (C), 78.9 (C), 59.0 (CH), 55.7 (CH), 53.2 (CH), 46.3 (CH_2), 30.8 (CH_2), 30.5 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 28.2 ($3 \times \text{CH}_3$), 28.0 ($3 \times \text{CH}_3$), 28.0 ($3 \times \text{CH}_3$), 27.7 (CH_2), 22.5 (CH_2), 13.9 (CH_3). IR (ATR-FTIR), cm^{-1} : 2979 (w), 2932 (w), 1736 (m), 1679 (m). HRMS-Cl (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{30}\text{H}_{50}\text{N}_3\text{O}_7$, 564.3643; found, 564.3609.

4.14. Synthesis of the ketone **20b**

A solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 3.18 mL, 3.18 mmol, 2.20 equiv) was added dropwise via syringe to a solution of the alcohol **19b** (930 mg, 1.44 mmol, 1 equiv) in tetrahydrofuran (29 mL) at -78°C . The resulting turbid yellow mixture was stirred for 2.5 h at -78°C . The solution was then diluted with a mixture of *tert*-butanol and ether (1:1 v/v, 2.5 mL) at -78°C . The diluted mixture was warmed over 20 min to 23°C , and the warmed solution was stirred for 2.5 d at 23°C . The light yellow product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (30 mL) and ethyl acetate (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4×60 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes) to afford the ketone **20b** as a viscous yellow oil (660 mg, 71%). The ketone **20b** was obtained as a single alkene and C21 stereoisomer (^1H NMR analysis). The configuration of C21 was assigned by analogy to related compounds.²⁷ The configuration of the alkene was obtained assigned by 2D-NOESY spectroscopy (NOE from H_{20} to H_7 observed). $R_f = 0.26$ (30% ethyl acetate–hexanes; UV, PAA). ^1H NMR (600 MHz, CDCl_3): δ 5.84 (t, $J = 7.8$ Hz, 1H, H_{20}), 5.39–5.35 (m, 1H, H_{15}), 5.35–5.26 (m, 1H, H_{16}), 4.47 (t, $J = 9.0$ Hz, 1H, H_4), 3.87 (td, $J = 9.4, 6.0$ Hz, 1H, H_1), 3.46 (d, $J = 9.4$ Hz, 1H, H_{21}), 3.01 (dd, $J = 16.5, 3.3$ Hz, 1H, H_{5a}), 2.45–2.37 (m, 2H, H_{13}), 2.36 (app d, 9.3 Hz, 1H, H_{5b}), 2.30–2.22 (m, 2H, H_{17}), 2.19–2.07 (m, 3H, $\text{H}_{2a,9}$), 2.05–1.96 (m, 2H, H_{14}), 1.85 (dd, $J = 12.7, 6.7$ Hz, 1H, H_{3a}), 1.76–1.58 (m, 2H, $\text{H}_{2b,3b}$), 1.49 (s, 9H, H_6), 1.45 (s, 9H, H_8), 1.44 (s, 9H, H_7), 1.41–1.32 (m, 6H, $\text{H}_{10,11,18}$), 0.93–0.83 (m, 6H, $\text{H}_{12,19}$). ^{13}C NMR (125 MHz, CDCl_3): δ 208.5 (C), 168.8 (C), 159.8 (C), 150.6 (C), 150.2 (C), 132.2 (CH), 131.0 (CH), 127.8 ($2 \times \text{CH}$), 81.9 (C), 81.8 (C), 78.9 (C), 58.8 (CH), 55.7 (CH), 53.3 (CH), 45.5 (CH_2), 43.1 (CH_2), 30.9 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 28.3 ($3 \times \text{CH}_3$), 28.0 ($6 \times \text{CH}_3$), 27.8 (CH_2), 22.7 (CH_2), 22.6 (CH_2), 21.5 (CH_2), 13.9 (CH_3), 13.7 (CH_3). IR (ATR-FTIR), cm^{-1} : 2957 (w), 1727 (m), 1720 (m), 1604 (m). HRMS-Cl (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{36}\text{H}_{60}\text{N}_3\text{O}_7$, 646.4426; found, 646.4383.

4.15. Synthesis of the ketone **20c**

A solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 3.24 mL, 3.24 mmol, 2.10 equiv) was added dropwise via syringe to a solution of the alcohol **19c** (1.00 g, 1.54 mmol, 1

equiv) in tetrahydrofuran (31 mL) at -78°C . The resulting turbid yellow mixture was stirred for 2.5 h at -78°C . The solution was then diluted with a mixture of *tert*-butanol and ether (1:1 v/v, 2.5 mL) at -78°C . The diluted mixture was warmed over 20 min to 23°C , and the warmed solution was stirred for 2.5 d at 23°C . The light yellow product mixture was diluted sequentially with saturated aqueous ammonium chloride solution (30 mL) and ethyl acetate (50 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4×60 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (30 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 30% ethyl acetate–hexanes) to afford the ketone **20c** as a viscous yellow oil (680 mg, 68%). The ketone **20c** was obtained as a single alkene and C21 stereoisomer (^1H NMR analysis). The configuration of C21 was assigned by analogy to related compounds.²⁷ The configuration of the alkene was obtained assigned by 2D-NOESY spectroscopy (NOE from H_{20} to H_7 observed). $R_f = 0.24$ (30% ethyl acetate–hexanes; UV, PAA). ^1H NMR (600 MHz, CDCl_3): δ 5.83 (t, $J = 7.8$ Hz, 1H, H_{20}), 4.46 (t, $J = 8.3$ Hz, 1H, H_4), 3.87 (td, $J = 9.5, 6.1$ Hz, 1H, H_1), 3.46 (d, $J = 9.4$ Hz, 1H, H_{21}), 2.99 (dd, $J = 16.4, 3.2$ Hz, 1H, H_{5a}), 2.42–2.30 (m, 3H, $\text{H}_{5b,13}$), 2.20–2.00 (m, 4H, $\text{H}_{2a,3a,9}$), 1.85 (dd, $J = 12.8, 6.9$ Hz, 1H, H_{3b}), 1.77–1.65 (m, 1H, H_{2b}), 1.55–1.46 (m, 11H, $\text{H}_{14}, \text{H}_6$), 1.45 (s, 9H, H_8), 1.43 (s, 9H, H_7), 1.44–1.30 (m, 4H, $\text{H}_{10,11}$), 1.30–1.15 (m, 8H, H_{15-18}), 0.92–0.83 (m, 6H, $\text{H}_{12,19}$). ^{13}C NMR (125 MHz, CDCl_3): δ 209.2 (C), 168.8 (C), 159.7 (C), 150.6 (C), 150.2 (C), 132.2 (CH), 127.8 (C), 81.9 (C), 81.8 (C), 78.8 (C), 59.0 (CH), 55.7 (CH), 53.4 (CH), 45.3 (CH₂), 43.4 (CH₂), 31.7 (CH₂), 30.9 (CH₂), 29.6 (CH₂), 29.4 (CH₂), 29.2 (CH₂), 29.0 (CH₂), 28.3 ($3 \times \text{CH}_3$), 28.0 ($6 \times \text{CH}_3$), 27.8 (CH₂), 23.7 (CH₂), 22.6 (CH₂), 22.6 (CH₂), 14.0 (CH₃), 13.9 (CH₃). IR (ATR-FTIR), cm^{-1} : 2959 (w), 2931 (w), 1719 (m), 1609 (m). HRMS-Cl (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{36}\text{H}_{62}\text{N}_3\text{O}_7$, 648.4582; found, 648.4551.

4.16. Synthesis of the allene **21**

A solution of potassium bis(trimethylsilyl)amide in tetrahydrofuran (1.0 M, 4.03 mL, 4.03 mmol, 2.11 equiv) was added dropwise via syringe to a solution of the alcohol **19d** (1.16 g, 1.91 mmol, 1 equiv) in tetrahydrofuran (38 mL) at -78°C . The resulting turbid yellow mixture was stirred for 2.5 h at -78°C . The solution was diluted with a mixture of *tert*-butanol and ether (1:1 v/v, 5.0 mL) at -78°C . The diluted product mixture was stirred for 10 min at -78°C . The mixture was then diluted sequentially with saturated aqueous ammonium chloride solution (30 mL) and ethyl acetate (30 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4×50 mL). The organic layers were combined and the combined organic layers were washed with saturated aqueous sodium chloride solution (100 mL). The washed organic layer was dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by flash-column chromatography (eluting with 20% ethyl acetate–hexanes) to afford the allene **21** as a colorless oil (1.03 g, 89%). $R_f = 0.19$ (20% ethyl acetate–hexanes; UV, PAA). ^1H NMR (600 MHz, CDCl_3): δ 5.69 (t, $J = 7.4$ Hz, 1H, H_{20}), 4.87 (bs, 1H, H_1), 4.52 (bs, 1H, H_4), 3.27 (dd, $J = 16.2, 3.7$ Hz, 1H, H_{5a}), 2.45–2.35 (m, 2H, H_{13}), 2.25–2.15 (m, 2H, $\text{H}_{2a,5b}$), 2.15–2.07 (m, 2H, H_9), 1.85 (dd, $J = 12.1, 5.8$ Hz, 1H, H_{3a}), 1.70–1.63 (m, 1H, H_{2b}), 1.63–1.56 (m, 1H, H_{3b}), 1.56–1.50 (m, 2H, H_{10}), 1.46 (s, 27H, H_{6-8}), 1.44–1.35 (m, 4H, $\text{H}_{14,15}$), 1.35–1.24 (m, 2H, H_{11}), 0.94–0.86 (m, 6H, $\text{H}_{12,16}$). ^{13}C NMR (125 MHz, CDCl_3): δ 209.6

(C), 208.3 (C), 165.9 (C), 161.1 (C), 145.9 (C), 130.6 (C), 104.6 (CH), 98.0 (C), 96.9 (C), 81.6 (C), 81.5 (C), 58.1 (CH), 56.3 (CH), 49.8 (CH₂), 47.3 (CH₂), 42.9 (CH₂), 39.8 (CH₂), 33.1 (CH₂), 31.1 (CH₂), 28.4 ($3 \times \text{CH}_3$), 28.1 ($6 \times \text{CH}_3$), 27.9 (CH₂), 26.0 (CH₂), 22.3 (CH₂), 22.0 (CH₂), 13.8 (CH₃), 13.8 (CH₃). IR (ATR-FTIR), cm^{-1} : 2950 (w), 1728 (m), 1701 (m), 1606 (s). HRMS-Cl (m/z): $[\text{M} + \text{H}]^+$ calcd for $\text{C}_{33}\text{H}_{56}\text{N}_3\text{O}_7$, 606.4113; found, 606.4061.

4.17. Synthesis of (+)-batzelladine **K** (**6**)

Chilled (-15°C), freshly-distilled, and degassed trifluoroacetic acid (8.3 mL) was added to a round-bottomed flask containing the neat ketone **20a** (235 mg, 417 μmol , 1 equiv) precooled to 0°C . The reaction mixture was stirred for 3 h at 0°C . Triethylsilane (134 μL , 839 μmol , 2.01 equiv) was then added. The resulting mixture was stirred for 1 h at 0°C . The cold product mixture was diluted with methanol (2.0 mL). The diluted product mixture was filtered through a pad of celite (0.8×4 cm). The filter cake was washed with methanol (3×3.0 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by preparative high-performance liquid chromatography (eluting with 0.1% formic acid–5% acetonitrile–water initially, grading to 0.1% formic acid–49% acetonitrile–water over 15 min, 10 injections) to furnish (+)-batzelladine **K** (**6**) as a colorless oil (33.0 mg, 27%). $R_f = 0.21$ (10% methanol–dichloromethane; UV, PAA). ^1H NMR (600 MHz, CDCl_3): δ 9.61 (bs, 1H, NH), 9.36 (bs, 1H, NH), 3.69–3.60 (m, 2H, $\text{H}_{4,7}$), 3.55–3.47 (m, 1H, H_2), 3.40–3.32 (m, 1H, H_9), 2.25–2.17 (m, 3H, $\text{H}_{3a,6a,8a}$), 2.18–2.11 (m, 1H, H_{5a}), 1.75–1.67 (m, 2H, $\text{H}_{5b,6b}$), 1.65–1.60 (m, 1H, H_{11a}), 1.53–1.45 (m, 1H, H_{11b}), 1.39–1.26 (m, 6H, H_{12-14}), 1.33 (d, $J = 5.8$ Hz, 3H, H_1), 1.27–1.17 (m, 2H, $\text{H}_{3b,8b}$), 0.89 (t, $J = 6.9$ Hz, 3H, H_{15}). ^{13}C NMR (125 MHz, CDCl_3): δ 150.0 (C), 56.0 (CH), 55.8 (CH), 50.2 (CH), 45.8 (CH), 36.2 (CH₂), 34.4 (CH₂), 33.9 (CH₂), 31.5 (CH₂), 30.4 (CH₂), 30.4 (CH₂), 24.9 (CH₂), 22.5 (CH₂), 20.3 (CH₃), 13.9 (CH₃). IR (ATR-FTIR), cm^{-1} : 3358 (br), 2974 (w), 1688 (w), 1629 (w). HRMS-Cl (m/z): $[\text{M}]^+$ calcd for $\text{C}_{15}\text{H}_{28}\text{N}_3$, 250.2278; found, 250.2284.

4.18. Synthesis of (+)-batzelladine **E** (**4**)

4.18.1. Synthesis of the carboxylic acid **23**

Chilled (-15°C), freshly-distilled, and degassed trifluoroacetic acid (5.7 mL) was added to a round-bottomed flask containing the neat ketone **20b** (185 mg, 286 μmol , 1 equiv) precooled to 0°C . The reaction mixture was stirred for 3 h at 0°C . The cold product mixture was diluted with methanol (2.0 mL). The diluted product mixture was filtered through a pad of celite (0.8×4.0 cm). The filter cake was washed with methanol (3×3.0 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was dissolved in methanol (4.8 mL) and the resulting solution was cooled to 0°C . Sodium cyanoborohydride (19.0 mg, 302 μmol , 1.06 equiv) was then added to the solution in one portion. The reaction mixture was stirred for 2 h at 0°C . The reaction mixture was allowed to warm over 1 h to 23°C and was stirred for 17 h at 23°C . The light yellow product mixture was cooled to 0°C and the cooled solution was diluted sequentially with 1 M aqueous hydrochloric acid solution (5.0 mL) and ethyl acetate (5.0 mL). The resulting biphasic mixture was transferred to a separatory funnel and the layers that formed were separated. The aqueous layer was extracted with ethyl acetate (4×5.0 mL). The organic layers were combined and the combined organic layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. Attempted isolation of **23** resulted in complex mixtures of unidentifiable decomposition products. Consequently, the residue obtained was used directly in the following step.

4.18.2. Synthesis of (+)-batzelladine E (**4**)

N-Methyl-2-chloropyridinium iodide (88.9 mg, 348 μ mol, 1.22 equiv) was added in one portion to a solution of the carboxylic acid **23** (nominally 286 μ mol, 1 equiv) in acetonitrile (960 μ L) at 23 °C. The reaction was stirred for 1 h at 23 °C. The alcohol **22** (95.7 mg, 289 μ mol, 1.01 equiv) and 4-dimethylaminopyridine (26.6 mg, 218 μ mol, 0.74 equiv) were then added in sequence. The reaction vessel was then placed in an oil bath that had been preheated to 40 °C. The reaction mixture was stirred for 2 h at 40 °C. The product mixture was then cooled over 30 min to 23 °C. The cooled product mixture was filtered through a pad of celite (0.8 \times 4.0 cm). The filter cake was washed with ethyl acetate (3 \times 5.0 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was then cooled (neat) to 0 °C. Chilled (–15 °C), freshly distilled, degassed trifluoroacetic acid (5.7 mL) was then added. The reaction mixture was stirred for 3 h at 0 °C. The cold product mixture was diluted with methanol (2.0 mL). The diluted product mixture was filtered through a pad of celite (0.8 \times 4.0 cm). The filter cake was rinsed with methanol (3 \times 3.0 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 10% methanol–dichloromethane). The fractions containing product were combined and the combined fractions were concentrated. The residue obtained was further purified by preparative thin-layer chromatography (eluting with 5% methanol–dichloromethane) to furnish (+)-batzelladine E (**4**) as a colorless solid (15.3 mg, 11% from **20b**). R_f = 0.21 (10% methanol–dichloromethane; UV, PAA). ^1H NMR (600 MHz, CD_3OD): δ 5.47–5.35 (m, 2H, $\text{H}_{23,24}$), 4.50 (dd, J = 6.8, 4.1, 1H, H_8), 4.21 (t, J = 6.1, 2H, H_5), 3.82–3.76 (m, 1H, H_{11}), 3.55–3.51 (m, 1H, H_{13}), 3.21 (t, J = 7.0, 2H, H_2), 2.79–2.73 (m, 1H, H_{16a}), 2.66–2.60 (m, 1H, H_{16b}), 2.56–2.49 (m, 1H, H_{9a}), 2.42 (ddd, J = 13.3, 5.3, 2.8 Hz, 1H, H_{12a}), 2.22 (q, J = 7.5 Hz, 2H, H_{22}), 2.18–2.12 (m, 1H, H_{10a}), 2.05 (q, J = 7.2 Hz, 2H, H_{25}), 1.80–1.69 (m, 5H, $\text{H}_{3,4,21a}$), 1.69–1.53 (m, 5H, $\text{H}_{9b,10b,17,21b}$), 1.43–1.33 (m, 5H, $\text{H}_{12b,18,26}$), 1.29 (app bs, 2H, H_{19}), 0.91 (m, 6H, $\text{H}_{20,27}$). ^{13}C NMR (125 MHz, CD_3OD): δ 166.3 (C), 158.7 (C), 148.6 (C), 147.6 (C), 132.3 (CH), 129.0 (CH), 102.7 (C), 65.0 (CH₂), 58.2 (CH), 57.2 (CH), 51.1 (CH), 42.0 (CH₂), 34.8 (CH₂), 34.0 (CH₂), 34.0 (CH₂), 32.6 (CH₂), 31.7 (CH₂), 30.3 (CH₂), 29.0 (CH₂), 27.5 (CH₂), 27.0 (CH₂), 26.7 (CH₂), 24.0 (CH₂), 23.8 (CH₂), 23.4 (CH₂), 14.3 (CH₃), 14.1 (CH₃). IR (ATR-FTIR), cm^{-1} : 3354 (br), 2958 (w), 2484 (br), 1670 (s). HRMS-Cl (m/z): [M] $^{2+}$ calcd for $\text{C}_{27}\text{H}_{48}\text{N}_6\text{O}_2$, 244.6931; found, 244.6941.

4.19. Synthesis of the carboxylic acid **24**

A round-bottomed flask was charged with the ketone **20c** (330 mg, 510 μ mol, 1 equiv) and palladium on carbon (10 wt%, 100 mg, 93.9 μ mol, 18 mol%). The reaction vessel was sealed with a rubber septum and the headspace was evacuated. The evacuated vessel was back-filled with argon (balloon, 1 atm). This process was repeated three times. The vessel was then cooled in an ice bath to 0 °C. Chilled (–15 °C), freshly-distilled, and degassed trifluoroacetic acid (10 mL) was added. The reaction mixture was stirred for 45 min at 0 °C. The headspace in the reaction vessel was evacuated and then backfilled with dihydrogen (balloon, 1 atm) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was warmed over 20 min to 23 °C. The warmed reaction mixture was stirred for 40 min at 23 °C. The product mixture was cooled to 0 °C. The headspace in the reaction vessel was purged with argon. The product mixture was diluted with methanol (1.0 mL). The diluted product mixture was filtered through a pad of celite (0.8 \times 4 cm). The filter cake was washed with methanol (3 \times 3.0 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by

flash-column chromatography (eluting with 10% methanol–dichloromethane) to provide the carboxylic acid **24** as a white solid (106 mg, 55%). R_f = 0.17 (10% methanol–dichloromethane; UV, PAA). ^1H NMR (600 MHz, CD_3OD): δ 4.54 (dd, J = 9.6, 6.3 Hz, 1H, H_1), 3.81–3.75 (m, 1H, H_4), 3.53–3.46 (m, 1H, H_{13}), 2.80–2.75 (m, 1H, H_{8a}), 2.61–2.55 (m, 1H, H_{8b}), 2.52–2.46 (m, 1H, H_{2a}), 2.40 (ddd, J = 13.2, 5.1, 2.7 Hz, 1H, H_{5a}), 2.19–2.10 (m, 1H, H_{3a}), 1.75–1.55 (m, 5H, $\text{H}_{2b,3b,9,14a}$), 1.55–1.50 (m, 1H, H_{14b}), 1.49–1.40 (m, 3H, $\text{H}_{5b,10}$), 1.40–1.25 (m, 12H, $\text{H}_{11,15-19}$), 0.97–0.88 (m, 6H, $\text{H}_{12,20}$). ^{13}C NMR (125 MHz, CD_3OD): δ 171.5 (C), 163.2 (C), 147.9 (C), 117.3 (C), 58.9 (CH), 57.2 (CH), 51.4 (CH), 35.2 (CH₂), 34.3 (CH₂), 33.3 (CH₂), 32.9 (CH₂), 32.7 (CH₂), 31.0 (CH₂), 30.5 (CH₂), 30.3 (CH₂), 28.8 (CH₂), 27.8 (CH₂), 26.3 (CH₂), 23.7 (CH₂), 23.5 (CH₂), 14.4 (CH₃), 14.4 (CH₂). IR (ATR-FTIR), cm^{-1} : 3335 (br), 2970 (w), 1729 (s), 1699 (m). HRMS-Cl (m/z): [M] $^+$ calcd for $\text{C}_{22}\text{H}_{38}\text{N}_3\text{O}_2$, 376.2959; found, 376.2979.

4.20. Synthesis of the bis(guanidine) **25**

N-Methyl-2-chloropyridinium iodide (90.5 mg, 354 μ mol, 1.20 equiv) was added to a solution of the carboxylic acid **24** (111 mg, 294 μ mol, 1 equiv) in acetonitrile (980 μ L) at 23 °C. The reaction mixture was stirred for 1 h at 23 °C. The alcohol **22** (97.8 mg, 295 μ mol, 1.00 equiv) and 4-dimethylaminopyridine (27.0 mg, 221 μ mol, 0.75 equiv) were then added in sequence. The reaction vessel was placed in an oil bath that had been preheated to 40 °C. The reaction mixture was stirred for 2 h at 40 °C. The mixture was then cooled to 23 °C. The cooled mixture was filtered through a pad of celite (0.8 \times 4 cm). The filter cake was washed with ethyl acetate (3 \times 5.0 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was transferred to a round-bottomed flask. The reaction vessel was sealed with a rubber septum and the headspace was evacuated. The evacuated vessel was back-filled with argon (balloon, 1 atm). This process was repeated three times. The vessel was then cooled in an ice bath to 0 °C. Chilled (–15 °C), freshly-distilled, and degassed trifluoroacetic acid (5.7 mL) was added to the mixture. The reaction mixture was stirred for 3 h at 0 °C. The cold product mixture was diluted with methanol (2.0 mL). The diluted product mixture was filtered through a pad of celite (0.8 \times 4 cm). The filter cake was washed with methanol (3 \times 3.0 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by flash-column chromatography (eluting with 5% methanol–dichloromethane) to afford the bis(guanidine) **25** as a colorless oil (64.8 mg, 45% yield over 2 steps). Small amounts of inseparable impurities are observable in the NMR spectra of **25**. R_f = 0.10 (5% methanol–dichloromethane; UV, PAA). ^1H NMR (600 MHz, CD_3OD): δ 4.54 (dd, J = 9.9, 6.1 Hz, 1H, H_8), 4.23–4.18 (m, 2H, H_5), 3.81–3.76 (m, 1H, H_{11}), 3.53–3.48 (m, 1H, H_{13}), 3.22 (t, J = 7.0, 2H, H_2), 2.78–2.71 (m, 1H, H_{16a}), 2.66–2.61 (m, 1H, H_{16b}), 2.55–2.47 (m, 1H, H_{9a}), 2.41 (ddd, J = 13.3, 5.4, 2.8 Hz, 1H, H_{12a}), 2.16 (dd, J = 12.8, 8.6 Hz, 1H, H_{10a}), 1.78–1.51 (m, 10H, $\text{H}_{9b,10b,12b,17,21a,3,4}$), 1.49–1.25 (m, 15H, $\text{H}_{18,19,21b,22-26}$), 0.95–0.85 (m, 6H, $\text{H}_{20,27}$). ^{13}C NMR (125 MHz, CD_3OD): δ 166.3 (C), 158.7 (C), 148.5 (C), 147.6 (C), 102.68 (C), 65.0 (CH), 58.2 (CH), 57.2 (CH), 51.5 (CH₂), 42.0 (CH₂), 34.9 (CH₂), 34.0 (2 \times CH₂), 32.9 (CH₂), 32.7 (CH₂), 31.7 (CH₂), 30.5 (CH₂), 30.3 (CH₂), 29.0 (CH₂), 27.5 (CH₂), 27.0 (CH₂), 26.7 (CH₂), 26.3 (CH₂), 23.7 (CH₂), 23.4 (CH₂), 14.4 (CH₃), 14.3 (CH₃). IR (ATR-FTIR), cm^{-1} : 3359 (br, w), 2972 (w), 1749 (m), 1716 (m). HRMS-Cl (m/z): [M] $^{2+}$ calcd for $\text{C}_{27}\text{H}_{50}\text{N}_6\text{O}_2$, 245.7009; found, 245.7001.

4.21. Synthesis of (–)-dehydrobatzelladine C (**5**)

Ceric ammonium nitrate (72.4 mg, 132 μ mol, 1.00 equiv) was added in one portion to a solution of the bis(guanidine) **25** (64.8 mg, 132 μ mol, 1 equiv) in acetonitrile (2.6 mL) at 23 °C. The

reaction mixture was stirred for 2 h at 23 °C. The product mixture was filtered through a pad of celite (0.8 × 4 cm). The filter cake was washed with methanol (3 × 3.0 mL). The filtrates were combined and the combined filtrates were concentrated. The residue obtained was purified by preparative high-performance liquid chromatography (eluting with 0.1% formic acid–5% acetonitrile–water initially, grading to 0.1% formic acid–49% acetonitrile–water over 15 min, 8 injections) to furnish (–)-dehydrobatzelladine C (**5**) as a colorless oil (26.0 mg, 40%). R_f = 0.18 (15% methanol–dichloromethane; UV, PAA) ^1H NMR (600 MHz, CD_3OD): δ 8.46 (bs, 2H, 2 × NH), 4.64–4.54 (m, 1H, H_{11}), 4.37 (t, J = 6.4 Hz, 2H, H_5), 3.85–3.76 (m, 1H, H_{13}), 3.57 (dd, J = 18.9, 8.5 Hz, 1H, H_{9a}), 3.49–3.35 (m, 1H, H_{9b}), 3.23 (t, J = 7.0 Hz, 2H, H_2), 3.08 (t, J = 7.7 Hz, 2H, H_{16}), 2.69–2.61 (m, 1H, H_{10a}), 2.57 (dt, J = 13.6, 3.7 Hz, 1H, H_{12a}), 2.09–1.95 (m, 1H, H_{10b}), 1.90–1.80 (m, 3H, $\text{H}_{4,21a}$), 1.79–1.63 (m, 5H, $\text{H}_{3,17,21b}$), 1.62–1.53 (m, 1H, H_{12b}), 1.51–1.43 (m, 2H, H_{22}), 1.42–1.25 (m, 12H, $\text{H}_{18,19,23-26}$), 0.94–0.86 (m, 6H, $\text{H}_{20,27}$). ^{13}C NMR (125 MHz, CD_3OD): δ 181.3 (C), 166.9 (C), 164.7 (C), 158.8 (C), 152.3 (C), 122.7 (C), 66.5 (CH), 63.1 (CH), 53.3 (CH), 42.0 (CH_2), 38.5 (CH_2), 35.1 (CH_2), 34.1 (CH_2), 32.9 (CH_2), 32.7 (CH_2), 31.0 (CH_2), 30.6 (CH_2), 30.3 (CH_2), 30.2 (CH_2), 30.1 (CH_2), 26.9 (CH_2), 26.7 (CH_2), 26.0 (CH_2), 23.7 (CH_2), 23.5 (CH_2), 14.4 (CH_3), 14.3 (CH_3). IR (ATR-FTIR), cm^{-1} : 3350 (br), 2930 (w), 2476 (br), 1672 (s). HRMS-Cl (m/z): $[\text{M}]^{2+}$ calcd for $\text{C}_{27}\text{H}_{48}\text{N}_6\text{O}_2$, 244.6931; found, 244.6941.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.tet.2018.04.050>.

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