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Graphical Abstract

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Total Synthesis of (–)-Vindoline

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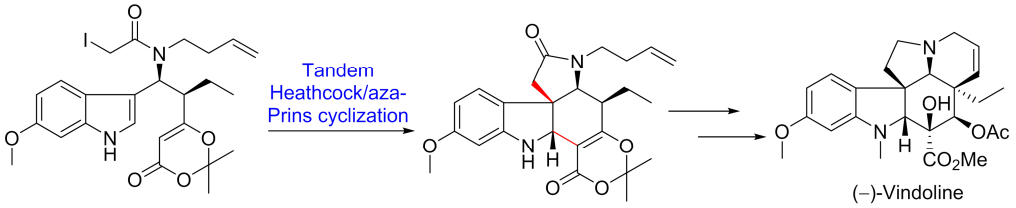

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ABSTRACT

In this full paper, a stereocontrolled strategy for the total synthesis of (–)-vindoline is described. This synthetic route features: 1) rapid construction of the stereochemical center at C19 through a highly diastereoselective vinylogous Mannich addition; 2) tandem Heathcock/aza-Prins cyclization to install rings C and E in vindoline; 3) oxidative transformation of β-ketoester to enone; 4) stereoselective inversion of C4 stereochemistry with triphenylphosphine and carbon tetrabromide followed by Brønsted acid.

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1. Introduction

Vinblastine (**1**, Fig. 1), isolated from *Catharanthus roseus*, is one of the most famous *Vinca* alkaloids because of its significant anti-cancer activities.[1] More than 50 years ago, vinblastine was found to be a potent inhibitor of tubulin polymerization and was clinical used for treatment of various carcinomas.[2] Even today, vinblastine and its analogue vincristine (**2**) remain efficacious antitumor drugs.[3] Vindoline, a major alkaloid isolated from *Catharanthus roseus*,[4] constitutes the most complex fragment of vinblastine and serves as a precursor for biosynthesis[5] and total synthesis[6] of vinblastine-type alkaloids. Structurally, vindoline features a pentacyclic framework and a fully substituted cyclohexane ring with six contiguous stereocenters (three of which are congested quaternary carbon centers).

The formidable challenge presented by vindoline made it a prevailing synthetic target. To date, a number of elegant strategies have been developed towards the syntheses of vindoline and its related alkaloids.[7] Among them, tandem processes leading to the construction of the highly substituted cyclohexane core present in vindoline and related alkaloids are especially attractive.[6d,7k-m,7o-t,8] Some representative examples towards the synthesis of vindoline-related natural alkaloids are indicated in Fig. 2. Inspired by these well-designed cascade processes, we recently developed a Heathcock/aza-Prins sequence to provide access to the core structures of vindoline-related natural alkaloids.[9, 10]

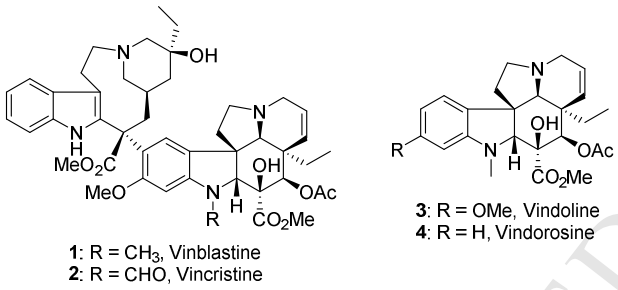


Fig. 1. Natural alkaloids containing vindoline structure unit.

In our previous work, we have established a scalable synthetic route towards the synthesis of (**–**)-vindorosine (**4**). We were also able to access the key scaffold for (–)-vindoline based on a highly diastereoselective vinylogous Mannich addition and an intramolecular Heathcock/aza-Prins cyclization.[10] In this full paper, we report the enantioselective total synthesis of (–)-vindoline, which constitutes part of our current efforts towards the final synthesis of anti-cancer drug vinblastine.

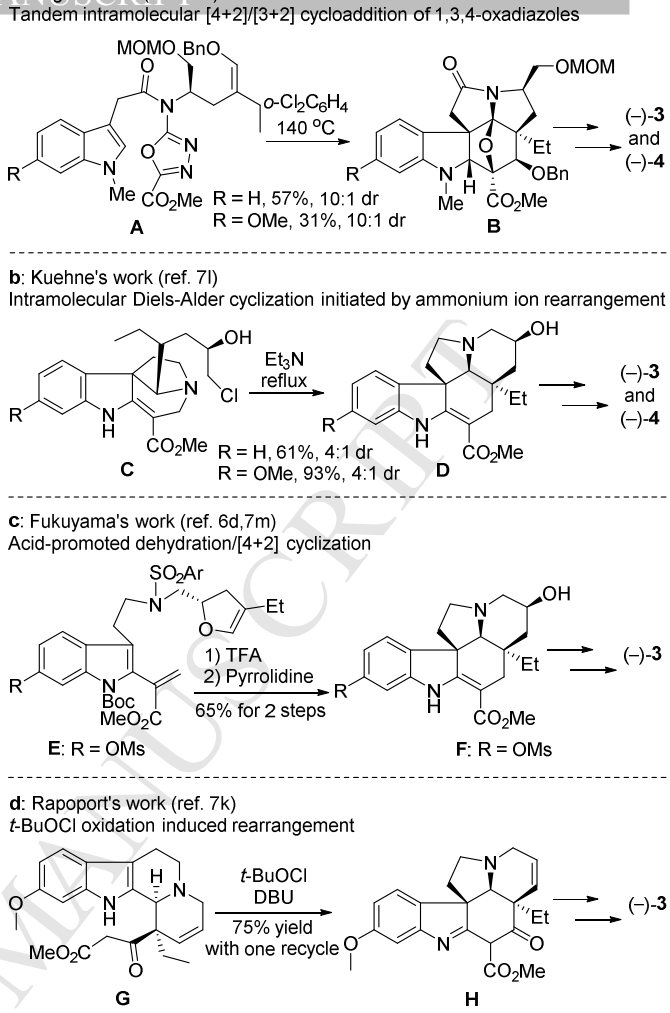
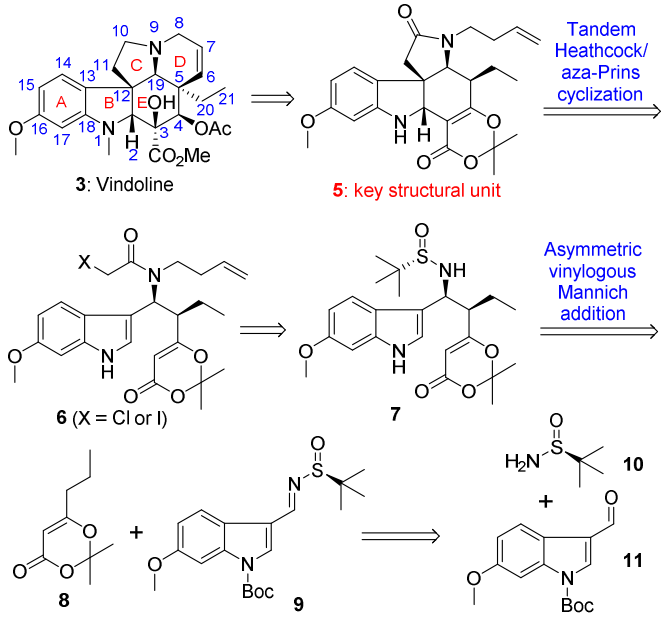


Fig. 2. Representative cascade procedures for vindoline-related natural alkaloids. MOM = methoxymethyl, Bn = benzyl, Boc = *tert*-butoxycarbonyl, Ar = 2,4-dinitrobenzensulfonyl, TFA = trifluoroacetic acid, DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, Ms = mesyl.

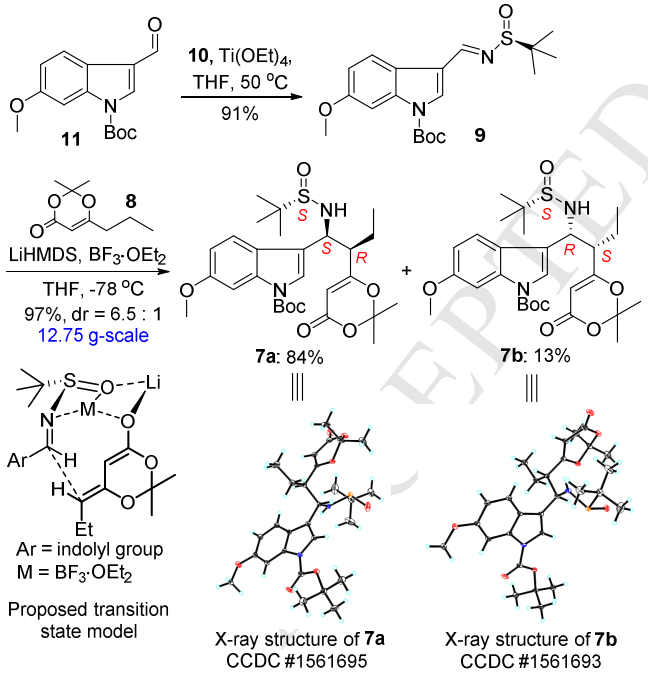
2. Results and discussion



Scheme 1. Retrosynthetic analysis of (–)-Vindoline.

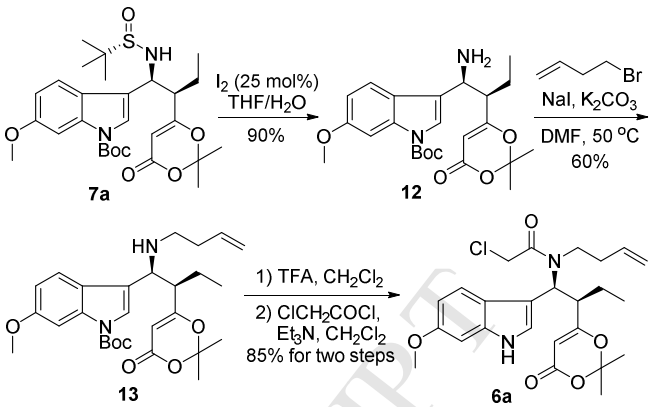
The retrosynthetic analysis of (–)-Vindoline is illustrated in Scheme 1. We planned to obtain (–)-Vindoline from key intermediate **5**, which could in turn be elaborated by an intramolecular Heathcock/aza-Prins cyclization from amide compound **6**. Amide **6** could be obtained by procedures involving deprotection, *N*-alkylation and amidation from **7**, sequentially. Compound **7** could be prepared by a diastereoselective vinylogous Mannich reaction between ethyldioxinone **8** and *N*-*tert*-butanesulfinyl imine **9**, which could be obtained by condensation of commercially available indolyl aldehyde **11** and enantiomerically pure *tert*-butanesulfinamide.

We began our total synthesis with the condensation of commercially available indolyl aldehyde **11** and *tert*-butanesulfinamide. According to our predicting model for the diastereoselective vinylogous Mannich addition (Scheme 2), (S_S)-*tert*-butanesulfinamide was used to ensure correct stereochemistry at C19 (Scheme 2). This reaction proceeded well in the presence of $Ti(OEt)_4$ to afford the desired *N*-*tert*-butanesulfinylimine **9** in 91% yield.[11] Next, we carried out the diastereoselective vinylogous Mannich addition between *N*-*tert*-butanesulfinyl imine **9** and the dioxinone-derived lithium dienolate generated *in situ* from compound **8**.[12] The desired product **7a** (84% isolated yield) was readily obtained on a multigram scale in the presence of BF_3•Et_2O in tetrahydrofuran (THF) together with its diastereomer **7b** (13% isolated yield). The absolute configurations of **7a** and its diasteromer **7b** were established by X-ray crystallography and the absolute configurations of these two diasteromers were shown in Scheme 2.[13] The X-ray crystallographic experimental results are in fully accordance with our predicting model.



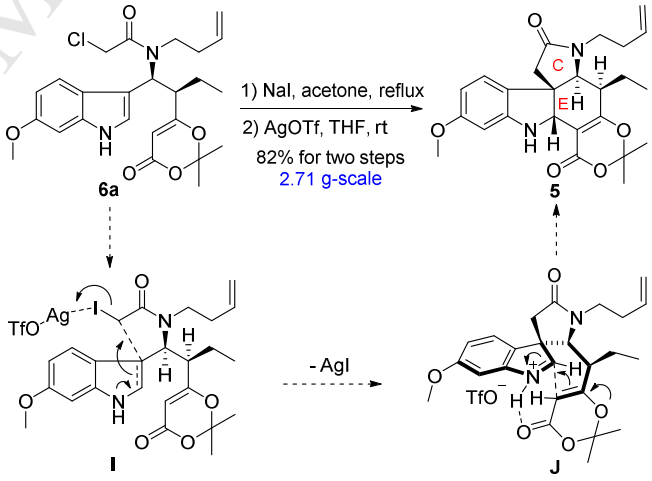
Scheme 2. The diastereoselective vinylogous Mannich reaction. THF = tetrahydrofuran, HMDS = hexamethyldisilazide, dr = diastereomeric ratio.

With sulfinamide **7a** in hand, we next conducted selective deprotection of the *tert*-butanesulfinyl group using iodine (25 mol%) in THF and H_2O.[14] Primary amine **12** was obtained in 90% isolated yield (Scheme 3). Treatment of amide **12** with 3-butenyl bromide in the presence of K_2CO_3 and NaI afforded the secondary amine **13**, which was subsequently converted into the desired amide **6a** by means of deprotection with trifluoroacetic acid and amidation with chloroacetyl chloride.



Scheme 3. Synthesis of the amide **6a**.

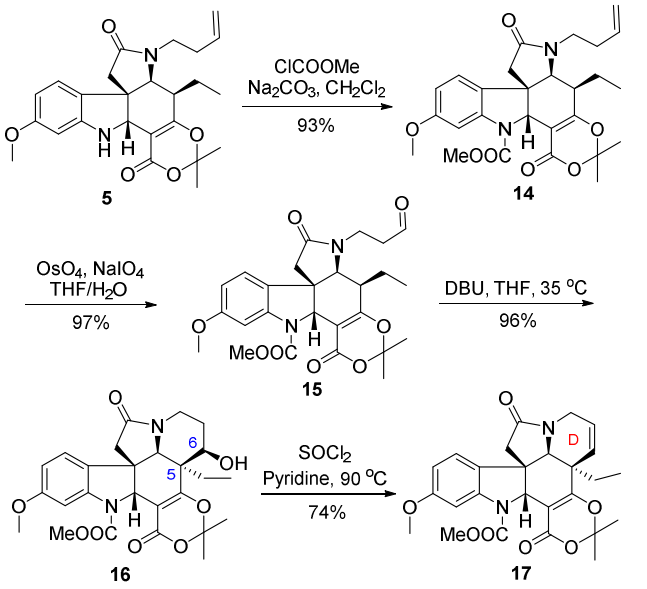
Next, the key Heathcock/aza-Prins cyclization was investigated. Treatment of indolyl chloroacetamide **6a** with silver trifluoromethansulfonate in THF did not provide desired product **5** due to the low reactivity of chloroacetamide. Therefore, displacement of chloroacetamide **6a** (2.71 g) with NaI in acetone followed by addition of silver trifluoromethansulfonate in THF at room temperature afforded the desired product (**5**) in 82% isolated yield over two steps (Scheme 4). The possible pathway is indicated in Scheme 4, silver-mediated intramolecular S_N2 substitution of indolyl haloacetamide resulted the rigid lactam spiroindolenine (transition-state I, Heathcock process) which relocated the newly generated iminium salt spatially close to the dioxinone moiety to effect the formation of ring E (transition-state J, aza-Prins procedure).



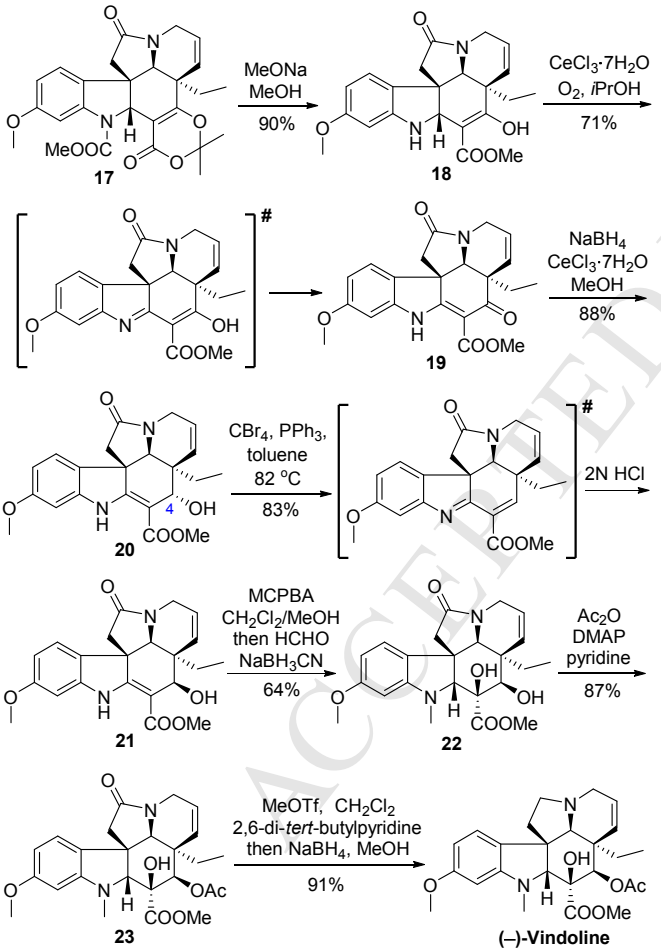
Scheme 4. The key Heathcock/aza-Prins cyclization. Tf = trifluoromethanesulfonyl.

Having accomplished the key cascade cyclization, we next began to investigate the construction of the D-ring of (–)-Vindoline. Treatment of lactam **5** with methyl chloroformate in the presence of Na_2CO_3 afforded carbamate **14** (93%), which was subsequently converted to the corresponding aldehyde **15** (97%) through an oxidative cleavage of the terminal double bond (Scheme 5). Intramolecular aldol condensation of aldehyde **15** in the presence of different bases, such as Cs_2CO_3, K_2CO_3, and NaH, failed to give the desired product (**16**). To our delight, the alcohol product **16** was finally obtained in 96% isolated yield as a single stereoisomer when 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was used as base in this aldol reaction.[15] Dehydration of compound **16** by heating with thionyl chloride in pyridine successfully provided olefin **17** in 74% yield. It is noteworthy

that dehydration of **16** did not proceeded under a number of other conditions such as dehydration with Burgess reagent, Martin's sulfuane and $(CF_3CO)_2O/Et_3N$.



Scheme 5. The construction of the ring D.



Scheme 6. Total Synthesis of (–)-vindoline. *m*-CPBA = *meta*-chloroperbenzoic acid, DMAP = *N*,*N*-4-dimethylaminopyridine.

The final stage of the total synthesis of (–)-vindoline is described in Scheme 6. Treatment of carbamate **17** with NaOMe in methanol in a sealed-tube at 92 °C provided the desired product **18** as a mixture of enol and ketone tautomers (enol/ketone = 1:1) in 90% isolated yields. Our initial plan was to introduce the hydroxy group at the C3 position by oxidation of β-ketoester **18** with $CeCl_3·7H_2O$ under an oxygen atmosphere.[16] Unfortunately, we failed to get the desired product. Interestingly, the reaction proceeded and resulted in an unprecedented oxidation to afford enone **19** in 71% isolated yield. Radical oxidation of amine to imine followed by relocate the conjugate system might account for this result (Scheme 6, **18**→**19**). Luche reduction of enone **19** provided enol **20** as a single diasteromer. The stereochemistry at C4 was unforturnately *S*-configuration by NOE experiments. Because the stereochemistry at C4 in (–)-vindoline is *R*-configuration, therefore, we had to reverse the stereochemistry at C4. Unexpectedly, treatment of **20** with carbon tetrabromide in the presence of triphenylphosphine in toluene followed by saturated $NaHCO_3$ (our previous procedure for the synthesis of vindorosine)[10] did not afford the desired enol **21**. Changing the base to Na_2CO_3 or K_2CO_3 also failed to effect the reaction. To our delight, treatment of **20** with carbon tetrabromide and triphenylphosphine in toluene followed by 2N HCl provided enol **21** in 83% isolated yield. The plausible intermediate for this transformation is shown in Scheme 6.[17] We believed a conjugated imine might be formed when treatment of **20** with carbon tetrabromide in the presence of triphenylphosphine and Michael addition of water mediated by acid provided the desired enol. This is an interesting case that more electron rich conjugated system deters the base-mediated Michael addition. Conversion of enol **21** to diol **22** was achieved by following Fukuyama's one-pot process[7m], which involved oxidation of **21** with *meta*-chloroperbenzoic acid in the presence of saturated sodium bicarbonate (10% MeOH in dichloromethane) and subsequent reductive amination with formaldehyde and sodium cyanoborohydride. Selective acetylation of **22** with acetic anhydride followed by reductive removal of the lactam carbonyl with sodium borohydride in the presence of MeOTf (Boger's procedure[7s]) furnished (–)-vindoline.

3. Conclusion

In conclusion, a concise and stereocontrolled strategy for the total synthesis of (–)-vindoline is disclosed based on the multigram-scale vinylogous Mannich addition and the gram-scale Heathcock/aza-Prins cyclization. Other important findings in our synthesis include the oxidation of β-ketoester to enone and stereoselective inversion of C4 stereochemistry with triphenylphosphine and carbon tetrabromide followed by hydrochloric acid. As a continuation of our studies on asymmetric total synthesis of vinblastine, the total synthesis of velbanamine fragment of vinblastine is being actively pursued in our laboratory.

4. Experimental section

4.1 General information

Melting points were measured on a Hanon MP 430 auto melting-point system. The infrared (IR) spectra were obtained on a Nicolet iS10 FTIR spectrometer with 4 cm^{-1} resolution and 32 scans between wavenumber of 4000 cm^{-1} and 400 cm^{-1}. Samples were prepared as KBr disks with 1 mg of samples in 100 mg of KBr. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were obtained on a Bruker Avance 400 or 600 spectrometers at 400 or 600 MHz. Carbon-13 nuclear magnetic resonance (^{13}C-NMR) was obtained on Bruker Avance 400 or 600 spectrometers at 100 or 125 MHz. Chemical shifts are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS) for all recorded NMR spectra. High Resolution Mass spectra were taken on AB QSTAR Pulsar mass spectrometer or Aglient LC/MSD TOF mass spectrometer. Optical rotations were recorded on a JASCO P-2000 polarimeter. All novel compounds were

characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS. The known compounds were characterized by ^{1}H NMR and ^{13}C NMR. Silica gel (200–300 mesh) for column chromatography and silica GF_{254} for TLC were produced by Merch Chemicals Co. Ltd. (Shanghai). THF used in the reactions were dried by distillation over metallic sodium and benzophenone. Starting materials and reagents used in reactions were obtained commercially from Acros, Aldrich and Adamas-beta®, and were used without purification, unless otherwise indicated. All moisture-sensitive reactions were conducted in dried glassware under a positive pressure of dry nitrogen or argon. Reagents and starting materials were accordingly transferred via syringe or cannula. Unless otherwise stated, all other reactions were also performed under a dry nitrgen atmosphere. Reaction temperatures refer to the external oil bath temperature.

4.2 Experimental procedures and data for synthetic intermediates

*4.2.1 Sulfinimine **9***. A mixture of aldehyde **11** (10.30 g, 37.40 mmol), (*S*)-*tert*-butanesulfonamine (5.44 g, 44.90 mmol) and $Ti(OEt)_4$ (28.3 mL, 44.90 mmol) in THF (200 mL) was stirred at 50 °C for 12 h. The reaction was quenched with water (25 mL) and the resulting suspension was filtered through a short pad of Silica gel (200–300 mesh). The solid cake was washed with ethyl acetate, and the separated organic layer was washed with brine. The organic layer was dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with petroleum ether/EtOAc (5:1) to afford sulfinimine **9b** (12.90 g, 91%) as a white solid, m.p.: 144-146 °C. R_f = 0.27 (petroleum ether: ethyl acetate = 9:1). $[\alpha]_D^{20}$ = 11.7 (*c* 0.49, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3452, 3136, 2979, 1737, 1598, 1577, 1493, 1372, 1321, 1290, 1278, 1237, 1178, 1096, 1073, 849, 765. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.67 (1H, s), 8.14 (1H, d, *J* = 8.8 Hz), 7.94 (1H, s), 7.75 (1H, brs), 6.97 (1H, dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz), 3.88 (3H, s), 1.69 (9H, s), 1.27 (9H, s). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 158.8, 156.1, 149.1, 137.5, 132.0, 122.9, 120.6, 118.0, 113.5, 99.4, 85.1, 57.4, 55.7, 28.2, 22.6. **HRMS** (EI+) *m/z* found: 401.1505, Calcd for $C_{19}H_{26}N_2O_4S$+Na: 401.1505.

*4.2.2 Ethyldioxinone **8***. Meldrum acid (8.64 g, 60.00 mmol) was stirred in dichloromethane (70 mL) and pyridine (10.8 mL, 132.00 mmol) at −10 °C for 10 min. To this mixture, a solution of butyryl chloride (7.20 mL, 66.00 mmol) was added dropwise at −10 ºC. The resulting mixture was then stirred at room temperature for 4 h. The reaction mixture was treated with HCl (6%, 60 mL) and washed with water (2 × 60 mL). The aqueous phases were back-extracted with dichloromethane (50 mL). The combined organic phases were dried over anhydrous sodium sulfate. After removal of the solvent, the residue was dissolved in freshly distilled toluene (75 mL) under argon. The mixture was heated to reflux. To the refluxing mixture was added acetone (2.20 mL, 30.0 mmol) in one portion. The mixture was refluxed for 5 h. After removal of the solvent, the residue was purified by flash column chromatography eluting with petroleum ether/EtOAc (10:1) to afford ethyldioxinone **8** (9.10 g, 89%) as a pale yellow oil. R_f = 0.35 (petroleum ether: ethyl acetate = 10:1). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 5.21 (1H, s), 2.18 (2H, t, *J* = 7.4 Hz), 1.66 (6H, s), 1.59-1.54 (2H, m), 0.95 (3H, t, *J* = 7.4 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.0, 161.6, 106.4, 93.3, 35.6, 25.1, 19.3, 13.6. The spectra were identical to those reported in the literature.[12]

*4.2.3 Sulfinamide **7a** and diastereomer **7b***. To a solution of sulfinimine **9** (12.75 g, 33.70 mmol) in THF (150 mL) was added BF_3•Et_2O (4.1 mL, 33.70 mmol) at –78 °C. In the mean time, to a stirred solution of ethyldioxinone **8** (11.47 g, 67.40 mmol) in THF (200 mL) was added lithium bis(trimethylsilyl)amide (1.0 M in THF, 74.2 mL, 74.2 mmol) at –78 °C. The resulting mixtures were stirred at –78 °C for 1 h. Then, the solution of dioxinone-derived lithium dienolate was transferred to the solution of sulfinimine at –78 °C. Stirring was continued at –78 °C for 3 h. The reaction was then quenched with saturated *aq*. NH_4Cl (150 mL) at –78 °C. The cooling bath was removed and the mixture was warmed to rt, followed by extraction with EtOAc (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with petroleum ether/EtOAc (5:1 to 3:1) to afford sulfinamide **7a** (15.51 g, 84%) and its diasteromer **7b** (2.40 g, 13%).

7a: White solid, m.p.: 150-152 °C. R_f = 0.33 (petroleum ether: ethyl acetate = 1:1). $[\alpha]_D^{20}$ = -11.4 (*c* 0.71, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3436, 2977, 1728, 1639, 1490, 1371, 1277, 1230, 1160, 1094, 1062, 1009, 900, 771. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.74 (1H, brs), 7.46 (1H, s), 7.44 (1H, d, *J* = 7.6 Hz), 6.89 (1H, d, *J* = 7.6 Hz), 5.32 (1H, s), 4.66 (1H, t, *J* = 8.0 Hz), 3.86 (3H, s), 3.60 (1H, d, *J* = 6.4 Hz), 2.73 (1H, dt, J_1 = 9.6 Hz, J_2 = 4.0 Hz), 1.74 (3H, s), 1.69 (3H, s), 1.65 (9H, s), 1.48-1.41 (2H, m), 1.15 (9H, s), 0.83 (3H, t, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.8, 160.8, 158.3, 149.6, 137.1, 122.7, 121.6, 119.9, 119.5, 112.5, 106.8, 100.0, 96.7, 84.1, 56.5, 55.7, 54.4, 52.8, 28.3, 26.7, 24.3, 22.8, 22.7, 11.9. **HRMS** (EI^+) *m/z* found: 571.2450, Calcd for $C_{28}H_{40}N_2O_7S$+Na: 571.2448.

7b: White solid, m.p.: 136-137 °C. R_f = 0.31 (petroleum ether: ethyl acetate = 2:1). $[\alpha]_D^{20}$ = 102.0 (*c* 0.37, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3441, 2966, 1739, 1630, 1459, 1383, 1273, 1219, 1157, 1092, 1054, 793, 767. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.78 (1H, brs), 7.50 (1H, s), 7.44 (1H, d, *J* = 7.6 Hz), 6.85 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.0 Hz), 5.44 (1H, s), 4.59 (1H, dd, J_1 = 9.6 Hz, J_2 = 1.2 Hz), 3.87 (3H, s), 3.64 (1H, s), 2.72 (1H, dt, J_1 = 10.4 Hz, J_2 = 3.6 Hz), 1.80 (3H, s), 1.74 (3H, s), 1.66 (9H, s), 1.56-1.44 (1H, m), 1.36-1.24 (1H, m), 1.12 (9H, s), 0.80 (3H, t, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.0, 160.3, 158.2, 149.5, 137.5, 125.0, 121.5, 120.9, 117.3, 112.3, 107.2, 99.6, 97.0, 84.1, 55.7, 55.5, 53.1, 51.6, 28.3, 25.6, 25.3, 22.7, 22.6, 11.7. **HRMS** (EI^+) *m/z* found: 571.2447, Calcd for $C_{28}H_{40}N_2O_7S$+Na: 571.2448.

*4.2.4 Amine **12***. To a solution of sulfinyl amine **7a** (13.77 g, 26.40 mmol) in THF/H_2O (5:1, 360 mL) was added iodine (1.68 g, 6.60 mmol, 0.25 equiv) in portions (5 × 336 mg, every 2 hours) at 50 °C under air. The progress of the reaction was monitored by TLC until the sulfinyl amine had been completely consumed. Et_3N (9 mL) was then added to the reaction mixture at room temperature, and the resulting mixture was then extracted with EtOAc (3 × 150 mL). The combined organic phase were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with petroleum ether/EtOAc/Et_3N (2:1:0.01 to 1:1:0.01) to afford amine **12** (10.40 g, 90%) as a yellow solid. M.p.: 51-53 °C. R_f = 0.47 (petroleum ether: ethyl acetate: Et_3N = 1:1:0.01). $[\alpha]_D^{20}$ = -42.0 (*c* 0.40, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3439, 2970, 2936, 1732, 1629, 1571, 1489, 1444, 1383, 1274, 1228, 1157, 1089, 1035, 1009, 902, 850, 808, 768. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (1H, brs), 7.51 (1H, d, *J* = 8.8 Hz), 7.41 (1H, s), 6.88 (1H, dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz), 5.37 (1H, s), 4.22 (1H, d, *J* = 9.2 Hz), 3.87 (3H, s), 2.52 (1H, dt, J_1 = 9.6 Hz, J_2 = 3.6 Hz), 1.75 (3H, s), 1.71 (3H, s), 1.66 (9H, s), 1.58 (2H, brs), 1.53-1.45 (1H, m), 1.43-1.32 (1H, m), 0.81 (3H, t, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.1, 160.9, 158.1, 149.8, 137.0, 123.2, 122.6, 121.9, 120.2, 112.2, 106.6, 99.7, 96.0,

83.9, 55.7, 54.0, 50.6, 28.3, 25.5, 25.3, 23.0, 12.0. **HRMS** (EI^+) *m/z* found: 467.2154, Calcd for $C_{24}H_{32}N_2O_6$+Na: 467.2153.

*4.2.5 Secondary amine **13***. To a solution of amine **12** (10.30 g, 23.40 mmol) and 3-butenyl bromide (15.00 mL, 112.32 mmol) in DMF (400 mL) was added NaI (34.00 g, 234.00 mmol) and K_2CO_3 (3.8 g, 28.08 mmol). The reaction mixture was stirred at 50 °C under Ar for 12 h. Water (600 mL) was then added at room temperature, and the resulting mixture was then extracted with EtOAc (3 × 200 mL). The combined organic phase were washed with water (400 mL), brine (300 mL), and dried over Na_2SO_4. filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with petroleum ether/EtOAc (4:1) to afford secondary amine **13** (7.01 g, 60%) as a yellow oil. R_f = 0.52 (petroleum ether: ethyl acetate = 4:1). $[\alpha]_D^{20}$ = -44.6 (*c* 0.40, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3439, 2974, 2936, 2836, 1731, 1630, 1570, 1489, 1443, 1384, 1273, 1229, 1158, 1088, 1009, 906, 809, 768. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.75 (1H, brs), 7.56 (1H, d, *J* = 8.8 Hz), 7.36 (1H, brs), 6.87 (1H, d, *J* = 8.8 Hz), 5.70-5.60 (1H, m), 5.37 (1H, s), 5.00 (1H, d, *J* = 15.2 Hz), 4.97 (1H, d, *J* = 9.2 Hz), 3.88 (3H, s), 3.84 (1H, d, *J* = 10.0 Hz), 2.55-2.49 (2H, m), 2.44-2.38 (1H, m), 2.11 (2H, q, *J* = 6.4 Hz), 1.75 (3H, s), 1.73 (3H, s), 1.68 (9H, s), 1.45-1.36 (1H, m), 1.32-1.26 (2H, m, CH and NH), 0.76 (3H, t, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.4, 161.1, 158.0, 149.8, 137.1, 136.5, 122.9, 120.7, 120.4, 116.5, 112.0, 106.6, 99.7, 95.9, 83.8, 57.5, 55.7, 52.6, 46.7, 34.3, 28.3, 25.7, 25.0, 22.8, 11.9. **HRMS** (EI^+) *m/z* found: 521.2622, Calcd for $C_{28}H_{38}N_2O_6$+Na: 521.2622.

*4.2.6 Amide **6a***. To a solution of secondary amine **13** (6.32 g, 12.76 mmol) in CH_2Cl_2 (170 mL) was added trifluoroacetic acid (36 mL). The reaction mixture was stirred at room temperature for 20 h and quenched with saturated *aq.* $NaHCO_3$. The aqueous solution was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with brine (250 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The resulting residue was dissolved in CH_2Cl_2 (150 mL), and Et_3N (3.2 mL, 19.14 mmol) and chloroacetyl chloride (1.2 mL, 15.31 mmol) was added at 0 °C. The reaction mixture was stirred at room temperature for 2 h and quenched with saturated *aq.* $NaHCO_3$. The aqueous solution was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with petroleum ether/EtOAc (1:1) to afford amide **6a** (5.17 g, 85%) as a rotamer (94:6). White solid, m.p.: 197-198 °C. R_f = 0.39 (petroleum ether: ethyl acetate = 1:1). $[\alpha]_D^{20}$ = -40.6 (*c* 0.20, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3424, 2966, 1734, 1625, 1445, 1272, 1163, 1112, 1030, 1012, 916, 841, 767. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.49/8.28 (0.06H/0.94H, s), 7.57/7.48 (0.94H/0.06H, d, *J* = 8.8 Hz), 7.28 (1H, s), 6.88 (1H, d, *J* = 2.0 Hz), 6.81 (1H, dd, J_1 = 8.8 Hz, J_2 = 2.0 Hz), 5.66 (1H, brs), 5.49-5.40 (1H, m), 5.39 (1H, s), 4.90 (1H, d, *J* = 10.0 Hz), 4.71 (1H, dd, J_1 = 17.2 Hz, J_2 = 1.2 Hz), 3.98 (2H, s), 3.84 (3H, s), 3.39-3.31 (1H, m), 3.24 (2H, brs), 1.86 (1H, brs), 1.77 (3H, s), 1.70 (3H, s), 1.56-1.53 (3H, m), 0.86 (1H, t, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.7, 166.7, 161.1, 157.1, 136.7, 133.9, 121.7, 119.9, 117.7, 113.7, 110.5, 106.9, 95.7, 94.8, 55.8, 49.2, 42.0, 34.3, 26.5, 24.1, 23.2, 12.1. **HRMS** (EI^+) *m/z* found: 497.1818, Calcd for $C_{25}H_{31}ClN_2O_5$+Na: 497.1814.

*4.2.7 Lactam **5***. To a solution of amide **6a** (2.71 g, 5.69 mmol) in acetone (150 mL) was added NaI (8.54 g, 56.90 mmol, 10 equiv). The mixture was heated at reflux for 4 h. Water (150 mL) was then added to the reaction mixture at room temperature. The resulting mixture was then extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with brine (150 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting crude product (iodoamide) was used in the next reaction without purification. The crude iodoamide was dissolved in freshly distilled THF (150 mL) under Ar at 0 °C. Silver trifluoromethanesulfonate (3.24 g, 11.38 mmol, 2 equiv) was added in one portion and the resulting mixture was then removed from the ice bath and warmed to room temperature. Once the starting material had been consumed (TLC, typically within 1 h), the mixture was filtered through a short pad of Celite, which was rinsed three times with EtOAc (3 × 150 mL). The solution was transferred to a separatory funnel and washed with a mixed solution of saturated *aq.* $NaHCO_3$ and saturated *aq.* $Na_2S_2O_3$ (1:1, 150 mL) and then with brine (200 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography eluting with petroleum ether/EtOAc (1:1) to afford lactam **5** (2.06 g, 82%) as a yellow solid. M.p.: 122-124 °C. R_f = 0.36 (petroleum ether: ethyl acetate = 1:1). $[\alpha]_D^{20}$ = -16.1 (*c* 0.51, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 1711, 1693, 1635, 1616, 1498, 1405, 1379, 1310, 1267, 1216, 1158, 1110, 843. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.93 (1H, d, *J* = 8.4 Hz), 6.20 (1H, dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz), 6.16 (1H, d, *J* = 2.4 Hz), 5.89-5.78 (1H, m), 5.26 (1H, s), 5.18 (1H, dd, J_1 = 17.2 Hz, J_2 = 1.2 Hz), 5.13 (1H, dd, J_1 = 10.0 Hz, J_2 = 1.2 Hz), 4.57 (1H, s), 4.02-3.95 (2H, m), 3.73 (3H, s), 2.87-2.80 (1H, m), 2.65 (2H, s), 2.59-2.54 (1H, m), 2.43-2.37 (2H, m), 1.70 (3H, s), 1.61 (3H, s), 1.59-1.53 (1H, m), 1.45-1.33 (1H, m), 1.02 (3H, t, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.4, 167.9, 161.2, 161.1, 149.8, 134.9, 127.1, 122.4, 117.6, 106.7, 104.2, 101.9, 95.5, 65.7, 62.4, 55.4, 47.9, 47.3, 42.3, 40.6, 31.9, 26.6, 23.9, 21.3, 12.7. **HRMS** (EI^+) *m/z* found: 439.2228, Calcd for $C_{25}H_{30}N_2O_5$+H: 439.2233.

*4.2.8 Carbamate **14***. To a solution of lactam **5** (2.01 g, 4.58 mmol) in CH_2Cl_2 (150 mL) was added ClCOOMe (7.4 mL, 91.67 mmol) and Na_2CO_3 (9.72 g, 91.67 mmol). The resulting mixture was stirred at room temperature for 12 h. Water (50 mL) was then added to the reaction mixture. The mixture was then extracted with CH_2Cl_2 (3 × 80 mL). The combined organic phases were washed with water (100 mL) and brine (100 mL) respectively, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with petroleum ether/EtOAc (1:1) to afford carbamate **14** (2.45 g, 93%) as a white solid. M.p.: 91-93 °C. R_f = 0.38 (petroleum ether: ethyl acetate = 1:1). $[\alpha]_D^{20}$ = -29.9 (*c* 0.31, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3439, 2955, 1735, 1701, 1641, 1616, 1502, 1443, 1418, 1273, 1251, 1201, 1098, 914, 763. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.49 (1H, s), 7.03 (1H, d, *J* = 8.4 Hz), 6.61 (1H, d, *J* = 8.0 Hz), 5.83-5.73 (1H, m), 5.16-5.0910 (3H, m), 3.88 (1H, s), 3.87 (3H, s), 3.85 (3H, s), 3.74-3.67 (1H, m), 3.08-3.02 (1H, m), 2.84 (1H, d, *J* = 17.6 Hz), 2.63 (1H, d, *J* = 17.6 Hz), 2.51-2.48 (1H, m), 2.39-2.37 (1H, m), 2.32-2.25 (1H, m), 1.94-1.81 (1H, m), 1.73 (3H, s), 1.67 (3H, s), 1.59-1.52 (1H, m), 0.96 (3H, t, *J* = 7.2 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.1, 167.6, 161.0, 159.1, 153.8, 143.5, 134.9, 123.3, 117.4, 110.2, 106.8, 101.7, 101.3, 68.9, 64.9, 55.7, 53.0, 49.4, 45.4, 42.1, 41.1, 32.2, 26.5, 23.9, 19.6, 13.6. **HRMS** (EI^+) *m/z* found: 519.2102, Calcd for $C_{27}H_{32}N_2O_7$+Na: 519.2102.

*4.2.9 Aldehyde **15***. To a solution of the alkene **14** (3.46 g, 6.97 mmol) in THF/H_2O (1:1, 300 ml) was added an aqueous solution of OsO_4 (2 wt% in H_2O, 2.5 ml, 0.19 mmol) and 4-methylmorpholine-*N*-oxide (3.30 g, 20.91 mmol). The reaction mixture was stirred at rt for 12 h. $NaIO_4$ (3.80 g, 17.43 mmol) was added in one portion and the resulting mixture was stirred at rt for an additional 2 h. The saturated *aq.* $Na_2S_2O_3$ (650 mL) was then added and the mixture was then extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine

(100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to afford aldehyde **15** (3.37 g, 97%) as a white solid. M.p.: 107-109 °C. R_f = 0.46 (ethyl acetate). $[\alpha]_D^{20}$ = -33.2 (*c* 0.31, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3439, 2957, 1727, 1640, 1617, 1501, 1443, 1375, 1251, 1201, 1166, 1101. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.80 (1H, s), 7.48 (1H, s), 7.02 (1H, d, *J* = 8.0 Hz), 6.62 (1H, d, *J* = 8.4 Hz), 5.17 (1H, s), 3.91 (1H, s), 3.81 (3H, s), 3.80 (3H, s), 3.73-3.66 (1H, m), 3.48-3.41 (1H, m), 3.00-2.92 (1H, m), 2.82 (1H, d, *J* = 17.6 Hz), 2.69-2.63 (1H, m), 2.63 (1H, d, *J* = 17.6 Hz), 2.53 (1H, d, *J* = 10.0 Hz), 1.86-1.78 (1H, m), 1.74 (3H, s), 1.68 (3H, s), 1.58-1.50 (1H, m), 0.96 (3H, t, *J* = 7.2 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.1, 173.5, 167.4, 161.0, 159.0, 153.8, 143.5, 123.3, 110.2, 106.9, 101.9, 101.4, 69.4, 64.9, 55.7, 53.1, 49.5, 45.3, 42.4, 42.0, 36.1, 26.7, 23.8, 19.7, 13.6. **HRMS** (EI^+) *m/z* found: 521.1894, Calcd for $C_{26}H_{30}N_2O_8$+Na: 521.1894.

*4.2.10 Alcohol **16**.* To a solution of aldehyde **15** (3.37 g, 6.76 mmol) in THF (150 ml) was added DBU (1.30 mL, 8.11 mmol). The reaction mixture was stirred at 35 °C for 6 h. The saturated *aq*. NH_4Cl (60 mL) was then added to the reaction mixture at rt. The resulting mixture was then extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with brine (100 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to afford alcohol **16** (3.25 g, 96%) as a white solid. M.p.: 228-229 °C. R_f = 0.29 (ethyl acetate). $[\alpha]_D^{20}$ = -135.1 (*c* 0.82, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 1702, 1629, 1504, 1445, 1416, 1373, 1277, 1255, 1202, 1100, 1044, 915, 782, 734. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48 (1H, s), 7.14 (1H, d, *J* = 8.0 Hz), 6.62 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 5.31 (1H, s), 4.17 (1H, dd, J_1 = 13.2 Hz, J_2 = 4.0 Hz), 3.82 (3H, s), 3.79 (3H, s), 3.65 (1H, td, J_1 = 11.2 Hz, J_2 = 3.6 Hz), 3.65 (1H, s), 3.04 (1H, d, *J* = 18.0 Hz), 2.74-2.72 (1H, m), 2.70 (1H, d, *J* = 18.0 Hz), 2.25 (1H, d, *J* = 12.4 Hz), 1.99 (1H, d, *J* = 12.4 Hz), 1.94-1.87 (1H, m), 1.78 (3H, s), 1.74 (3H, s), 1.61 (1H, s), 1.44-1.35 (1H, m), 0.52 (3H, t, *J* = 7.2 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 171.4, 169.5, 161.3, 160.0, 153.6, 143.0, 124.9, 123.6, 110.4, 106.6, 104.8, 101.6, 72.3, 68.8, 64.5, 55.8, 53.0, 48.0, 47.3, 47.3, 38.6, 29.8, 28.0, 24.4, 22.5, 7.3. **HRMS** (EI^+) *m/z* found: 521.1897, Calcd for $C_{26}H_{30}N_2O_8$+Na: 521.1894.

*4.2.11 Olefin **17**.* A stirred solution of thionyl chloride (140 μL, 1.68 mmol) in anhydrous pyridine (18 mL) was added alcohol **16** (700.0 mg, 1.40 mmol) in one portion and the resulting mixture was heated at 90 °C for an additional 40 min. The reaction mixture was quenched with saturated *aq*. $NaHCO_3$ (30 mL) at rt. The mixture was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (80 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to afford olefin **17** (520.0 mg, 74%) as a white solid. M.p.: 225-227 °C. R_f = 0.41 (ethyl acetate). $[\alpha]_D^{20}$ = -127.6 (*c* 0.23, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 1725, 1693, 1631, 1495, 1416, 1376, 1287, 1254, 1202, 1108, 1038, 882, 810, 760, 723. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.48 (1H, s), 7.12 (1H, d, *J* = 8.4 Hz), 6.66 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 5.91 (1H, dt, J_1 = 10.4 Hz, J_2 = 2.8 Hz), 5.60 (1H, dt, J_1 = 10.0 Hz, J_2 = 2.0 Hz), 5.31 (1H, s), 4.20 (1H, dt, J_1 = 19.6 Hz, J_2 = 2.8 Hz), 3.82 (3H, s), 3.79 (3H, s), 3.65 (1H, s), 3.59 (1H, d, *J* = 19.2 Hz), 3.08 (1H, d, *J* = 18.4 Hz), 2.71 (1H, d, *J* = 18.4 Hz), 1.70 (3H, s), 1.69 (3H, s), 1.58-1.48 (1H, m), 1.48-1.39 (1H, m), 0.56 (3H, t, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 172.2, 170.3, 161.0, 160.9, 153.7, 142.7, 127.1, 126.4, 124.8, 123.5, 110.4, 106.2, 101.6, 100.6, 67.4, 64.6, 55.7, 53.0, 47.5, 46.8, 44.4, 40.8, 29.0, 27.6, 22.8, 7.7. **HRMS** (EI^+) *m/z* found: 503.1794, Calcd for $C_{26}H_{28}N_2O_7$+Na: 503.1789.

*4.2.12 Tautomers **18**.* Sodium (766.0 mg, 33.30 mmol) was added to methanol (20 mL) in a tube at 0 °C. After addition, the tube was removed from the ice bath and warmed to room temperature. After stirring at room temperature for 30 min, olefin **17** (160.0 mg, 0.33 mmol) was added to the tube as a solid in one portion and the resulting mixture was stirred for an additional 30 min. The tube was then sealed with a terflon screw top and the mixture was heated at 95 °C for an additional 30 h. The saturated *aq*. NH_4Cl (10 mL) was then added to the reaction mixture at rt. The resulting mixture was then extracted with EtOAc (3 × 15 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to afford the product as a mixture of ketone and enol tautomers **18** (119.0 mg, 1:1, 90%) as a white solid. M.p.: 200-201 °C. R_f = 0.39 (ethyl acetate). $[\alpha]_D^{20}$ = -141.0 (*c* 0.44, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 2955, 1733, 1694, 1618, 1440, 1414, 1363, 1294, 1199, 1164, 853, 807. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.62 (0.5H, s), 7.05 (0.5H, d, *J* = 8.0 Hz), 7.01 (0.5H, d, *J* = 8.4 Hz), 6.35-6.30 (1H, m), 6.19 (0.5H, d, *J* = 2.4 Hz), 6.14 (0.5H, d, *J* = 2.4 Hz), 5.96-5.85 (1.5H, m), 5.47 (0.5H, dt, J_1 = 10.0 Hz, J_2 = 2.4 Hz), 5.02 (0.5H, d, *J* = 3.2 Hz), 4.66 (0.5H, s), 4.31-4.11 (2.5H, m), 3.84 (1.5H, s), 3.81(1.5H, s), 3.76 (1.5H, s), 3.71 (1.5H, s), 3.68-3.57 (1H, m), 3.17 (0.5H, d, *J* = 18.0 Hz), 2.86 (0.5H, d, *J* = 17.2 Hz), 2.68 (0.5H, d, *J* = 17.2 Hz), 2.61 (0.5H, d, *J* = 17.6 Hz), 1.83-1.70 (1H, m), 1.50-1.39 (0.5H, m), 1.37-1.30 (0.5H, m), 0.74 (1.5H, t, *J* = 7.2 Hz), 0.52 (1.5H, t, *J* = 7.2 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 204.3, 177.3, 173.1, 172.4, 170.3, 161.6, 161.2, 151.2, 150.5, 128.9, 128.8, 124.5, 124.1, 123.5, 123.4, 123.3, 122.4, 105.0, 104.5, 97.4, 96.4, 95.8, 68.6, 64.4, 63.8, 62.6, 55.5, 55.5, 55.0, 52.7, 52.6, 52.3, 50.0, 48.0, 47.6, 45.8, 44.8, 40.9, 40.1, 29.8, 26.9, 8.1, 7.8. **HRMS** (EI^+) *m/z* found: 397.1756, Calcd for $C_{22}H_{24}N_2O_5$+H: 397.1758.

*4.2.13 Enone **19**.* To a solution of tautomers **18** (247.0 mg, 0.62 mmol) in *i*PrOH (50 mL) and CH_2Cl_2 (5 mL) was added $CeCl_3$•$7H_2O$ (70.0 mg, 0.19 mmol) and the mixture was heated at 35 °C under oxygen (1 atm) for 48 h. The saturated *aq*. $NaHCO_3$ (15 mL) was then added to the reaction mixture at rt, and the resulting mixture was extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to afford enone **19** (174.0 mg, 71%) as a yellow solid. M.p.: 212-214 °C. R_f = 0.22 (ethyl acetate). $[\alpha]_D^{20}$ = 24.5 (*c* 0.30, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3439, 2966, 1692, 1630, 1584,1501, 1453, 1382, 1279, 1265 1118, 810, 729. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.12 (1H, s), 7.23 (1H, d, *J* = 8.4 Hz), 6.66-6.62 (2H, m), 6.06 (1H, d, *J* = 10.4 Hz), 5.95 (1H, ddd, J_1 = 10.4 Hz, J_2 = 4.0, J_3 = 1.2 Hz), 4.54 (1H, ddd, J_1 = 18.0 Hz, J_2 = 4.0 Hz, J_3 = 1.2 Hz), 3.94 (1H, s), 3.84 (3H, s), 3.82 (3H, s), 3.59 (1H, d, *J* = 18.0 Hz), 2.74 (1H, d, *J* = 17.6 Hz), 2.64 (1H, d, *J* = 17.2 Hz), 1.45-1.35 (1H, m), 1.32-1.23 (1H, m), 0.76 (3H, t, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 193.8, 175.5, 169.2, 167.1, 161.2, 142.6, 128.0, 127.2, 124.0, 122.2, 108.9, 98.9, 96.6, 59.4, 55.9, 52.0, 51.0, 50.4, 48.4, 39.9, 34.6, 7.7. **HRMS** (EI^+) *m/z* found: 417.1414, Calcd for $C_{22}H_{22}N_2O_5$+Na: 417.1421.

*4.2.14 Enol **20**.* To a solution of enone **19** (209.0 mg, 0.53 mmol) in MeOH (30 mL) was added $CeCl_3$•$7H_2O$ (218.0 mg, 0.59 mmol) and the mixture was stirred at rt for 30 min. Sodium borohydride (31.0 mg, 0.80 mmol) was then added to the mixture. After stirring at room temperature for an additional 20 min, the saturated *aq*. NH_4Cl (10 mL) was added and the resulting mixture

was then extracted with EtOAc (3 ×20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to afford enol **20** (185.0 mg, 88%) as a white solid. M.p.: 198-200 °C. R_f = 0.36 (petroleum ether : ethyl acetate = 1:2). $[\alpha]_D^{20}$ = -19.4 (*c* 0.55, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3377, 2954, 1685, 1655, 1617, 1459, 1431, 1383, 1279, 1221, 1116, 850, 727. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.56 (1H, s), 7.10 (1H, d, *J* = 8.8 Hz), 6.49 (1H, s), 6.48 (1H, d, *J* = 8.4 Hz), 5.93-5.85 (2H, m), 5.67 (1H, s), 4.56 (1H, s), 4.56 (1H, dd, J_1 = 17.6 Hz, J_2 = 3.2 Hz), 3.90 (1H, s), 3.88 (3H, s), 3.79 (3H, s), 3.58 (1H, d, *J* = 18.0 Hz), 2.72 (1H, d, *J* = 18.0 Hz), 2.55 (1H, d, *J* = 17.6 Hz), 1.70-1.56 (1H, m), 0.99-0.92 (1H, m), 0.66 (3H, t, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.0, 168.2, 164.4, 160.8, 143.6, 131.4, 128.6, 123.5, 121.8, 106.9, 97.3, 93.3, 71.1, 60.6, 55.7, 51.6, 48.1, 47.7, 44.6, 39.8, 22.0, 8.00. **HRMS** (EI^+) *m/z* found: 397.1755, Calcd for $C_{22}H_{24}N_2O_5$+H: 397.1763.

*4.2.15 Enol **21***. To a solution of enol **20** (168.0 mg, 0.42 mmol) in dry toluene (25 mL) was added triphenylphosphine (223.0 mg, 0.85 mmol) and carbon tetrabromide (282.0 mg, 0.85 mmol). The mixture was stirred at rt under argon for 20 min. The mixture was then heated at 82 °C under argon for 4 h. After cooling to rt, toluene was removed under reduced pressure and HCl (2 N, 10 mL) were added, and the resulting mixture was then stirred at rt for 3 h. The reaction was quenched by saturated *aq*. $NaHCO_3$ and was then extracted with EtOAc (3 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with CH_2Cl_2/THF (2:1) to afford alcohol enol **21** (140.0 mg, 83%) as a white solid. M.p.: 118-119 °C. R_f = 0.38 (CH_2Cl_2 : THF = 2:1). $[\alpha]_D^{20}$ = -87.9 (*c* 0.64, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3417, 2919, 1677, 1617, 1500, 1457, 1236, 1191, 1115, 725. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 9.29 (1H, brs), 7.11 (1H, d, *J* = 8.8 Hz), 6.49 (1H, s), 6.48 (1H, dd, J_1 = 7.2 Hz, J_2 = 2.4 Hz), 6.13 (1H, ddd, J_1 = 10.4 Hz, J_2 = 4.0 Hz, J_3 = 1.6 Hz), 5.70 (1H, dt, J_1 = 10.0 Hz, J_2 = 2.0 Hz), 4.70 (1H, s), 4.67 (1H, ddd, J_1 = 18.0 Hz, J_2 = 4.0 Hz, J_3 = 1.6 Hz), 3.80 (1H, s), 3.79 (3H, s), 3.77 (3H, s), 3.60 (1H, d, *J* = 18.0 Hz), 3.16 (1H, d, *J* = 16.8 Hz), 2.52 (1H, d, *J* = 16.8 Hz), 1.88 (1H, d, *J* = 1.6 Hz), 1.07-0.92 (2H, m), 0.69 (3H, t, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 170.8, 168.3, 167.8, 160.7, 143.7, 129.6, 128.9, 127.6, 121.9, 106.9, 97.4, 93.9, 70.8, 62.6, 55.7, 51.4, 50.0, 48.2, 43.0, 39.5, 29.9, 7.6. **HRMS** (EI^+) *m/z* found: 397.1758, Calcd for $C_{22}H_{24}N_2O_5$+H: 397.1758.

*4.2.16 Diol **22***. To a solution of enol **21** (132 mg, 0.33 mmol) in methanol/dichloromethane (1:9, 15 mL) and a saturated aqueous solution of sodium bicarbonate (5.0 mL) at 0 °C was added *m*-chloroperoxybenzoic acid (85 % w%, 82 mg, 0.40 mmol). After stirring for 10 min at 0 ºC, 37% aqueous formaldehyde (0.57 mL) and sodium cyanoborohydride (83 mg 1.32 mmol) were added and pH of the solution was adjusted to 3.0 with 10% hydrochloric acid in methanol. After stirring for 10 min, an additional sodium cyanoborohydride (83 mg 1.32 mmol) was added and stirring was continued at room temperature for 30 min. Sodium carbonate was added to adjust pH of th solution to 9~10. After stirring for 30 min at room temperature, the reaction mixture was then extracted with CH_2Cl_2 (3 × 25 mL). The combined organic phases were washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to afford diol **22** (91.0 mg, 64%) as a white solid. M.p.: 92-93 °C. R_f = 0.28 (ethyl acetate : MeOH = 100:1). $[\alpha]_D^{20}$ = -31.2 (*c* 0.22, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3432, 2926, 1735, 1685, 1654, 1618, 1504, 1438, 1233, 1092. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.97 (1H, d, *J* = 8.4 Hz), 6.62 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 6.09 (1H, d, *J* = 2.4 Hz), 5.95 (1H, dt, J_1 = 10.8 Hz, J_2 = 2.8 Hz), 5.65 (1H, dt, J_1 = 10.8 Hz, J_2 = 2.8 Hz), 4.14 (1H, dt, J_1 = 19.2 Hz, J_2 = 2.8 Hz), 4.01 (1H, d, *J* = 8.0 Hz), 3.94 (1H, s), 3.86 (3H, s), 3.78 (3H, s), 3.61 (1H, d, *J* = 18.8 Hz), 3.48 (1H, s), 3.84 (1H, d, *J* = 5.6 Hz), 2.76 (1H, d, *J* = 16.8 Hz), 2.73 (3H, s), 2.55 (1H, d, *J* = 16.8 Hz), 2.41 (1H, dd, J_1 = 8.0 Hz, J_2 = 2.4 Hz), 1.65-1.56 (1H, m), 1.19-1.10 (1H, m), 0.73 (3H, t, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 174.8, 171.6, 161.6, 153.8, 128.1, 123.6, 123.3, 122.9, 104.7, 96.6, 81.2, 79.7, 73.1, 61.3, 55.6, 53.3, 51.8, 50.5, 40.9, 39.5, 39.0, 33.6, 7.6. **HRMS** (EI^+) *m/z* found: 429.2020, Calcd for $C_{23}H_{28}N_2O_6$+H: 429.2020.

*4.2.17 Ester **23***. To a solution of **22** (50.0 mg, 0.12 mmol) and DMAP (3.0 mg, 0.024 mmol) in pyridine (0.50 mL), acetic anhydride (0.25 mL) was added under Ar. The reaction mixture was stirred at room temperature for 2 h, then diluted with EtOAc followed by the addition of saturated aqueous NH_4Cl at 0 °C. The mixture was extracted with EtOAc, and the combined organic phases were washed sequentially with water, saturated aqueous $NaHCO_3$, saturated aqueous NaCl, and dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc (100 : 3 : 3) to afford ester **23** (49.0 mg, 87%) as a white solid. M.p.: 89-90 °C. R_f = 0.29 (ethyl acetate : MeOH = 100:1). $[\alpha]_D^{20}$ = -17.6 (*c* 0.53, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3432, 2962, 1741, 1686, 1660, 1618, 1503, 1438, 1372, 1233, 1168, 1038, 979, 735. **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.98 (1H, d, *J* = 8.4 Hz), 6.62 (1H, dd, J_1 = 8.4 Hz, J_2 = 2.4 Hz), 6.11 (1H, d, *J* = 2.0 Hz), 5.91 (1H, dt, J_1 = 10.4 Hz, J_2 = 3.2 Hz), 5.40 (1H, s), 5.28 (1H, dt, J_1 = 10.4 Hz, J_2 = 2.0 Hz), 4.17 (1H, dt, J_1 = 19.2 Hz, J_2 = 2.8 Hz), 3.96 (1H, s), 3.79 (3H, s), 3.62 (1H, d, *J* = 18.8 Hz), 3.50 (1H, s), 2.85 (1H, d, *J* = 17.2 Hz), 2.68 (3H, s), 2.67 (1H, d, *J* = 16.8 Hz), 2.03 (3H, s), 1.67-1.58 (1H, m), 1.31-1.23 (1H, m), 0.59 (3H, t, *J* = 7.6 Hz). **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.7, 171.8, 170.0, 161.7, 153.6, 128.4, 123.6, 123.0, 122.8, 104.9, 96.5, 81.8, 78.5, 75.2, 60.8, 55.6, 53.3, 51.5, 50.3, 41.4, 39.5, 38.4, 32.1, 21.0, 7.6. **HRMS** (EI^+) *m/z* found: 471.2127, Calcd for $C_{25}H_{30}N_2O_7$+H: 471.2126.

4.2.18 (–)-Vindoline. Methyl trifluoromethanesulfonate (28 μL, 0.21 mmol) was added in portions to a solution of **23** (33 mg, 0.07 mmol) and 2,6-di-*tert*-butylpyridine (48 μL, 0.21 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature for 2 h, and concentrated under a positive flow of N_2. The residue was dissolved in dry MeOH (3 mL), and treated with $NaBH_4$ (8.4 mg, 0.21 mmol). The reaction mixture was stirred at room temperature for 15 min, diluted with EtOAc, and quenched with saturated aqueous NH_4Cl followed by the addition of 28–30% aqueous NH_4OH. The aqueous layer was extracted with EtOAc (3 ×15 mL), and the combined organic layer was washed with saturated aqueous NaCl, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by flash chromatography eluting with EtOAc to afford (–)-vindoline (30.2 mg, 91%) as a white solid. M.p.: 153-155 °C. R_f = 0.34 (ethyl acetate). $[\alpha]_D^{20}$ = -16.0 (*c* 0.47, $CHCl_3$). Lit[7q]: $[\alpha]_D^{20}$ = -17 (*c* 0.4, $CHCl_3$). **FTIR** (KBr, thin film) cm^{-1}: 3439, 2962, 1741, 1617, 1502, 1436, 1371, 1243, 1168, 1121, 1033. **^{1}H NMR** (600 MHz, C_6D_6): δ 8.54 (1H, brs), 6.65 (1H, d, *J* = 8.2 Hz), 6.37 (1H, dd, J_1 = 8.2 Hz, J_2 = 1.3 Hz), 6.05 (1H, d, *J* = 1.4 Hz), 5.95 (1H, s), 5.48 (1H, dd, J_1 = 10.1 Hz, J_2 = 4.4 Hz), 5.26 (1H, d, *J* = 10.1 Hz,), 3.84 (1H, s), 3.41 (3H, s), 3.39 (3H, s), 2.92 (1H, dd, J_1 = 16.1 Hz, J_2 = 4.7 Hz), 2.88 (1H, td, J_1 = 9.2 Hz, J_2 = 1.8 Hz), 2.43 (3H, s), 2.36 (1H, s), 2.28–2.21 (2H, m), 2.14–2.08 (1H, m), 2.03 (1H, ddd, J_1 = 13.7 Hz, J_2 = 9.5 Hz, J_3 = 2.3 Hz), 1.94–1.89 (1H, m), 1.90 (3H, s), 1.58-1.52 (1H, m), 0.47 (3H, t, *J* = 7.4 Hz). **^{13}C NMR** (150 MHz, C_6D_6): 172.5, 170.5, 161.8, 154.6, 1314, 126.8,

124.1, 123.1, 105.3, 96.3, 83.7, 79.5, 76.7, 68.8, 55.0, 53.3, 52.7, 51.6, 51.5, 44.1, 43.9, 37.6, 31.6, 20.9, 8.3. **HRMS** (EI^+) *m/z* found: 457.2333, Calcd for $C_{25}H_{32}N_2O_6$+H: 457.2333. The NMR spectra of our synthesis sample were in fully agreement with those reported in the literature.[6i,7q]

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Appendix A. Supplementary data

Supplementary data associated with this article can be found at https://doi.org/10.1016/j.tet.2018XX.XXX.

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