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A Suzuki Cross-Coupling and Intramolecular Aza-Michael Addition Reaction Sequence Towards the Synthesis of 1,10b-*epi*-7-Deoxypancratistatins and Their Cytotoxicity Studies

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The development of an efficient approach to the construction of a phenanthridone is described. The convergent strategy commences with the preparation of Suzuki cross-coupling reaction precursors, arylboronic acid **12** and α-iodo enone **19**, from piperonylamine (**9**) and (–)-D-quinic acid (**10**), respectively. The coupling of **12** and **19** followed by a key intramolecular aza-Michael addition produced phenanthridone **21** featuring a *cis*-fused B–C ring junction. The syntheses of compounds **25** and **26**, both of which are C-1 and C-10b epimers of the naturally occurring potent antitumor agent 7-deoxypancratistatin (**2**), from **21** are elaborated in detail in this paper. The cytotoxicities of **25** and **26** were evaluated against three different cancer cell lines. Compound **26** served as a moderate growth inhibitor of THP-1 monocytic cells (GI_{50} = 14.5 μg/mL).

Introduction

The highly oxygenated phenanthridones, namely pancratistatin (**1**)[1] and 7-deoxypancratistain (**2**)[2] along with their congeners[3] narciclasine (**3**) and lycoricidine (**4**) (Figure 1), isolated from plants of the *Amaryllidaceae* species, are known for their broad spectrum of pharmacological profiles such as cytotoxicity, insect antifeedent activity and antiviral properties.[4–6] The low natural abundance[7] coupled with structural complexity of these compounds have triggered considerable research activities in the synthetic arena.

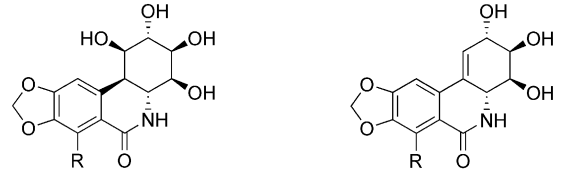

Figure 1. A few representatives of oxygenated phenanthridones.

The problems in using these molecules as therapeutic agents (low abundance) have been addressed by various research groups in two different dimensions over two decades. One of the dimensions has been the quest for short, high-yielding syntheses of the naturally occurring pancratistatins. This task promoted the screening and development of a great number of existing and new methodologies[8–11] for their capabilities. The other dimension is looking for potential and more bio-available derivatives of pancratistatin. This particular search has resulted in the syntheses of various truncated and unnatural derivatives,[12–14] through which the scientific community has been enlightened with a substantial amount of structure-activity information. The milestones crossed in this area have been extensively reviewed at many different occasions.[15]

The synthetic study of these natural products has been enriched with the successful demonstration of several retrosynthetic disconnections to date. However, the interesting molecular framework still continues to fuel innovative ideas for its efficient construction. A literature survey of synthetic reports revealed that a practical approach emphasized the cyclization of the B ring with preconstructed A and C rings in a convergent fashion. The different modes of cyclization reported for the formation of the B ring include (i) C-6–N

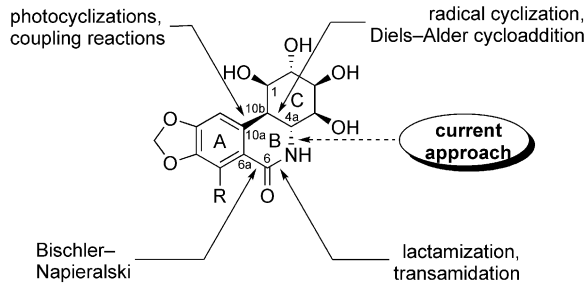

Figure 2. Various cyclization strategies for B-ring closure.

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bond formation by lactamization[8b] and transamidation[8d,10b] reactions, (ii) C-6–C-6a bond formation with Banwell's modified Bischler–Napieralski[9a,9c,10d] reaction, (iii) C-10a–C-10b bond formation through either photocyclizations like PET-,[10f] aryl-enamide-[10a] or Lewis-acid-mediated coupling reactions of an arene with an allyl triflate[9b] or epoxide[10e] and (iv) C-4a–C-10b bond formation by radical cyclization of an oxime ether[8d] and Diels–Alder cycloadditions[11d] (Figure 2).

Background Concept

On careful scrutiny of these catalogued strategies of B-ring closure, we noticed that cyclization through C-4a–N bond formation has not been explored, even though it may offer an attractive, practical and general strategy for the synthesis of *Amaryllidaceae* constituents. In this context, we envisioned a retrosynthetic approach as shown in Figure 3.

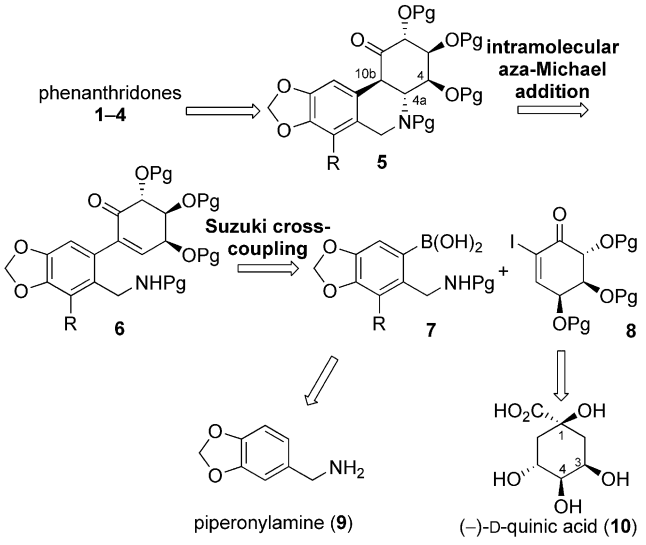


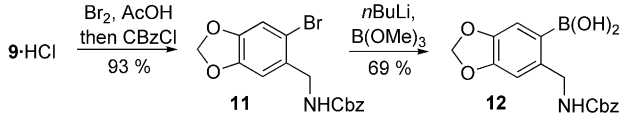
Figure 3. Retrosynthetic plan for phenanthridones **1**–**4**.

While designing the above strategy, we envisioned that access to phenanthridones **1**–**4** could be realized easily from the β-amino carbonyl compound **5**, which in turn could be obtained through an intramolecular aza-Michael[16] reaction of the potential precursor **6**. The stereochemical origin at C-4a of compound **5** was believed to be controlled by the adjacent stereocenter at C-4, which might direct the approach of the amine nucleophile to the opposite face of C-4a of the enone. The crucial *trans*-B–C ring junction (C-4a and C-10b) was expected to arise through the resultant, thermodynamically stable, *trans*-perhydroquinoline-like system. The key precursor **6** could be obtained by a Suzuki cross-coupling reaction[17] between subunits **7** and **8**, which were proposed to be obtained easily from commercially available piperonylamine (**9**) and (–)-D-quinic acid (**10**). The selection of (–)-D-quinic acid was made considering (i) its *syn*-3,4-dihydroxy stereochemistry, akin to the stereocenters present in the C ring of the alkaloid, (ii) the ability of the C-3 and C-4 stereocenters to direct the installation of the required functionalities at C-2 and C-4 stereoselectively and (iii) its natural abundance. We describe herein the detailed results of our studies towards the synthesis of the phenanthridone class of alkaloids.

Results and Discussion

Synthesis of Arylboronic Acid 12

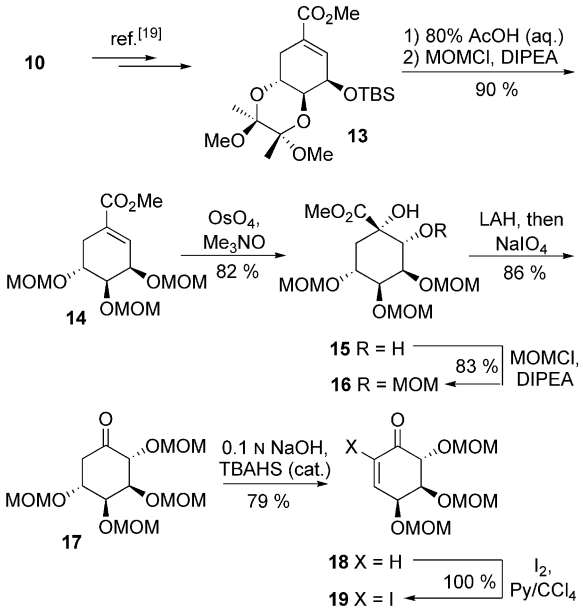
The aromatic bromination of the hydrochloride salt of the piperonylamine (**9**·HCl) by applying a procedure analogous to that of Tietze et al.[18] gave the corresponding 6-bromo derivative, which, upon basification followed by benzyl carbamate protection of the resultant free amine, produced **11** in 93% yield. Lithium exchange of the bromide with *n*BuLi/THF at –78 °C followed by quenching with excess trimethyl borate gave one of the Suzuki cross-coupling precursors (**12**) in 69% yield (Scheme 1).



Scheme 1. Synthesis of **12**.

Stereocontrolled Synthesis of α-Iodo Enone 18

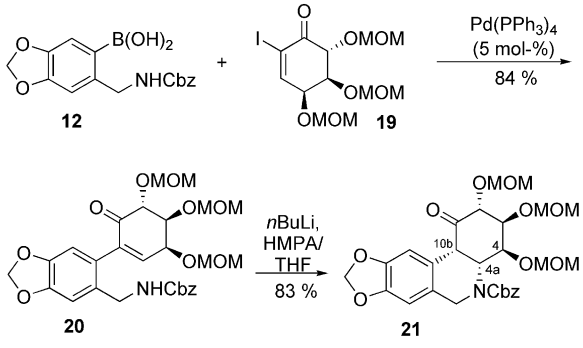
The synthesis of the most significant precursor **19** (Scheme 2) in our synthetic design commenced with the introduction of an oxygen functionality at the C-2 position to form an appropriately hydroxy-protected quinic acid derivative. Towards this end, the regioselective elimination of the 1-hydroxy group with Whitehead's[19] protocol gave **13** in 70% overall yield (over three steps). To avoid unforeseen complications during the advanced stage of the synthesis, we removed the butane diacetal and silyl protections of **13** and reprotected the free hydroxy groups as their corresponding methoxymethyl ethers (**14**). Subsequently, the catalytic osmylation of the double bond of **14** and the selective monoprotection of the resultant diol gave **16** in 68% yield (over two steps). The reduction of the ester moiety of **16** by $LiAlH_4$/THF at 50 °C produced the corresponding diol, which, upon sodium periodate cleavage, gave **17** in 86% yield. Next, we attempted to eliminate the 5-(methoxymethoxy) group with Cs_2CO_3, *t*BuOK and 1,3-diazabicyclo[5.4.0]undecane (DBU) to obtain the corresponding enone **18**. However, these reactions produced a complex mixture. Luckily, the reaction of **17** with 0.1 M aqueous NaOH in the presence of catalytic amounts of tetrabutylammonium hydrogen sulfate (TBAHS) in DCM cleanly produced **18** in 79% yield. Compound **18** was converted into the target precursor **19** quantitatively by applying Johnson's iodination protocol.[20]



Scheme 2. Synthesis of **19**.

Suzuki Cross-Coupling/Intramolecular Aza-Michael Addition

The easy accessibility of both of the coupling partners **12** and **19** guided us to carry out a Suzuki cross-coupling to obtain the aza-Michael precursor **20**. In this context, refluxing (20 min) of an equimolar mixture of **12** and **19** with 5 mol-% of $Pd(PPh_3)_4$ in benzene/ethanol (2:1) produced **20** in 84% yield (Scheme 3). The characteristic doublet at δ = 6.81 (J = 3.7 Hz) ppm in the ^{1}H NMR spectrum and the signal of an olefinic CH group at δ = 145.1 ppm in the ^{13}C NMR spectrum of **20** confirmed its structure.



Scheme 3. Suzuki cross-coupling/intramolecular aza-Michael addition sequence.

The crucial intramolecular aza-Michael addition to **20** was carried out with *n*BuLi in hexamethylphosphoramide (HMPA)/THF (10:1) at –78 °C to provide cyclized product **21** as a single diastereomer in 83% yield. The role of HMPA was very crucial in this key reaction, as without HMPA, the reaction failed to bring about the required reorganization. Compound **21** was fully characterized by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry (Scheme 3).

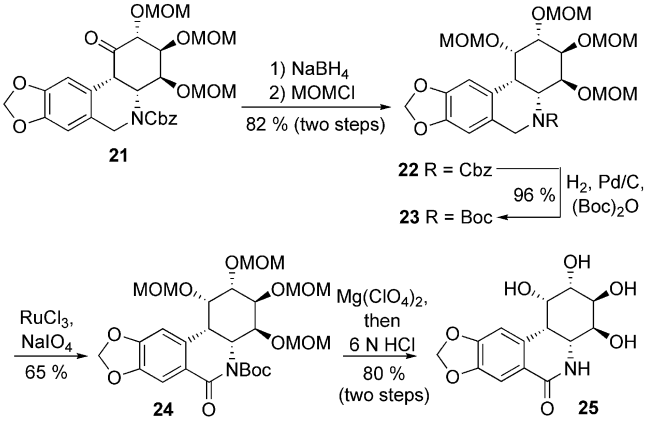
The relative stereochemistry of the newly formed C-4a and C-10b centers (B–C ring junction) was deduced by carefully examining the coupling constants between the attached protons (4a-H and 10b-H) in the ^{1}H NMR spectrum of **21**. For example, 10b-H appeared as a doublet (J = 6.8 Hz) at δ = 4.02 ppm, coupling only with 4a-H [signal at δ = 3.97 (dd, J = 6.8, 9.3 Hz) ppm]. Generally, for the *trans*-B–C ring junction, the coupling constant observed for 10b-H is more than 10 Hz.[10a,10f] However, the lower value (6.8 Hz) observed indicated a *cis* relationship between 4a-H and 10b-H. The additional coupling constant (J = 9.3 Hz) of 4a-H was accounted for by the coupling of 4a-H with 4-H. The higher J value observed between 4-H and 4a-H clearly confirmed a *trans*-diaxial coupling, establishing the *trans* relationship for 4a-H and 4-H. These particular coupling constants (J = 6.8, 9.3 Hz) indicated that the amine nucleophile approached C-4a on the opposite face from the 4-alkoxy group, producing the C-4a–N bond with the required configuration at C-4a. The unexpected emergence of the *cis*-fused B–C ring junction during cyclization was quite disappointing to us. The most probable explanation for this observation is that the protonation of the lithium enolate intermediate, formed during the aza-Michael reaction, was governed by the C-4a–N bond stereochemistry.

We also attempted to invert the stereochemistry at C-10b of **21** through epimerization with several bases but unsuccessfully. It was surprising to note that our effort to epimerize C-10b with DBU in boiling benzene led to a retro-Michael reaction and the aromatization of the C-ring by β-elimination of the methoxymethoxy group at C-3. The results from the above studies support the thermodynamic stability of the *cis*-fused ring junction in these phenanthridones.[10a,13d,21]

1,10b-*epi*-7-Deoxypancratistatin and the Corresponding Amine Hydrochloride

Although the approach based on an intramolecular aza-Michael addition produced the *cis*-fused phenanthridone, we proceeded with our planned synthetic sequence and achieved the *cis* analogues of 7-deoxypancratistatin (Scheme 4). The sodium borohydride reduction of **21** in MeOH at 0 °C afforded the corresponding 1-hydroxylated molecule. This reaction sequence completed the installation of all the hydroxy functionalities at the periphery of the C-ring. However, the stereochemistry of this newly created center could not be established, as the coupling constants were not well defined, probably due to the bent conformation of the *cis*-fused ring. In order to complete the total synthesis of **25** and with the hope that 6-benzylic oxidation might result in a crystalline solid for X-ray analysis to confirm all the newly generated stereocenters, we proceeded with benzylic oxidation. However, this step required a prior protection of the 1-hydroxy group, and thus, it was protected as the methoxymethyl ether (**22**, 82% combined yield). Stirring of **22** with $RuCl_3/NaIO_4$ (in situ generation of RuO_4)[22] in $CCl_4/CH_3CN/H_2O$ (1:1:2) at room tempera-

ture produced a very complex reaction mixture, possibly due to the interference of the more activated benzyl group of the Cbz protecting group. Therefore, we replaced the benzyl carbamate with the corresponding *tert*-butyl carbamate and subjected it to oxidation as described above. We were pleased that it underwent smooth oxidation resulting in **24** in 62% yield (over two steps). Since the global deprotection of **24** gave a mixture of partially deprotected products in variable yields, we adopted a two-step deprotection strategy to complete the synthesis. Initially, the removal of the *tert*-butoxycarbonyl group of imide **24** selectively by $Mg(ClO_4)_2/CH_3CN$[23] followed by refluxing of the resultant amide in HCl/MeOH afforded 1,10b-*epi*-7-deoxypancratistatin (**25**) {m.p. 298–304 °C. $[a]_D^{27}$ = +88.3 (c = 0.35 in DMSO)} in 80% overall yield. The X-ray analysis of the crystalline solid confirmed the structure of **25** as shown in Figure 4.



Scheme 4. Synthesis of 1,10b-*epi*-7-deoxypancratistatin (**25**).

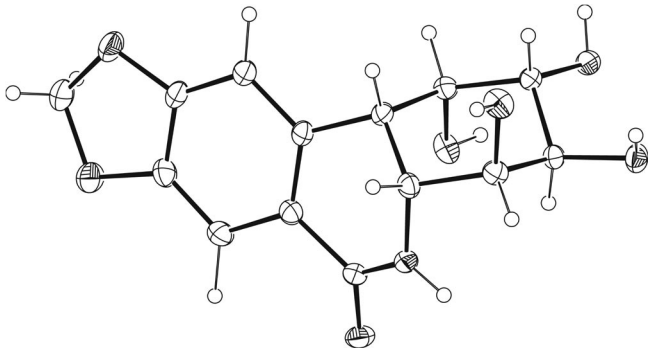
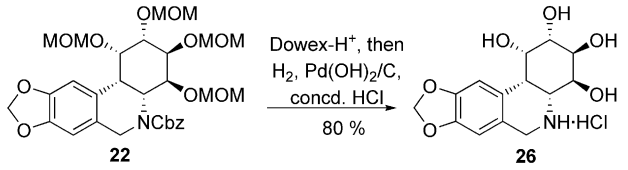


Figure 4. ORTEP diagram of 1,10b-*epi*-7-deoxypancratistatin (**25**).

For the purpose of evaluating its biological profile, compound **26** {m.p. 214–218 °C (with decomposition), $[a]_D^{27}$ = +40.8 (c = 0.5 in H_2O)} was also synthesized (Scheme 5) by refluxing **22** with an equal amount of DOWEX H^+ resin in MeOH, followed by hydrogenating the resulting tetrol in acidic MeOH (80% yield).



Scheme 5. Synthesis of amine hydrochloride **26**.

Evaluation of the Cytotoxicity of 25 and 26

Although the cytotoxicities of the 10b-epimer of 7-deoxypancratistatin have been studied[10g,10h] against human cancer cell lines, the 1,10b-epimers (**25** and **26**) were new, and no biological activity data were available. Therefore, we screened them against murine P388 lymphocytic leukemia and two other human cancerous cell lines, MCF-7 (breast adenocarcinoma) and THP-1 (promonocytic leukemia). Compound **25** exhibited 100-fold less activity (GI_{50} = 44.5 μg/mL) than natural **2** (GI_{50} = 0.44 μg/mL) against murine P388. The analogue **26** also showed a similar activity (GI_{50} = 50.0 μg/mL) in the murine P388 cell line. However, the GI_{50} of THP-1 monocytic cells with **26** was 14.5 μg/mL in comparison to that of **25** (GI_{50} > 100 μg/mL). In the breast cancer MCF-7 cell line, the analogues **25** and **26** displayed a similar range of activity of 74.6 and 85.3 μg/mL, respectively.

Conclusions

A new synthetic strategy has been developed for the synthesis of the phenanthridone class of alkaloids by employing a Suzuki cross-coupling/aza-Michael reaction sequence. This approach also highlighted the use of cheaply available (–)-D-quinic acid as a starting material for the most difficult C-ring construction in the synthesis of this class of alkaloids. Although the intramolecular aza-Michael reaction for the B-ring closure of the present synthesis produced an incorrect *cis*-fused phenanthridone, the potential of this stereoselective reaction could be more appropriately exploited in the total synthesis of other members of this family like γ-lycorane, fortucine and siculinine, which feature *cis*-B–C ring junctions.[15a,24] Compound **25** was less cytotoxicity against the studied cancer cell lines, but **26** showed some activity against THP-1 monocytic cells, raising the hope that subtle variations in its structure may enhance the possibility of developing this molecule as a therapeutic agent.

Experimental Section

General: Unless mentioned, all reactions were performed under argon. All commercially available reagents were used without further purification. Thin-layer chromatography was performed with aluminum plates precoated with silica gel 60. Compounds were visualized by heating after dipping in a solution of $Ce(SO_4)_2$ (2.5 g) and $(NH_4)_6Mo_7O_{24}$ (6.25 g) in 10% aqueous H_2SO_4 (250 mL). Column

chromatography was performed with silica gel (100–200 and 230–400 mesh). Melting points were recorded with a Büchi B-540 melting point apparatus and reported uncorrected. Optical rotations were measured with a Jasco P-1030 polarimeter. IR spectra were recorded with a Shimadzu Infrared Fourier Transform spectrometer. NMR spectra were recorded with Bruker ACF 200, MSL 300, AV400 and DRX 500 MHz spectrometers. Mass spectrometry was carried out with a PE SCIEX API QSTAR pulser (LC-MS). Microanalyses were conducted with a Carlo–Erba CHNS-O EA 1108 elemental analyzer. CCDC-691503 (for **25**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Benzyl (6-bromo-1,3-benzodioxol-5-yl)methylcarbamate (11): To a suspension of piperonylamine salt (**9**·HCl, 5 g, 26.65 mmol) in glacial acetic acid (25 mL) was added bromine (2.73 mL, 53.30 mmol). The solid dissolved to form a clear red solution, which was stirred at room temperature for an additional 3 h. Saturated aqueous Na_2SO_3 was added until decolorization was achieved. The reaction mixture was cooled in an ice bath and made strongly basic by adding 20% aqueous NaOH. To this mixture, DCM (100 mL) and benzyl chloroformate (4.2 mL, 29.31 mmol) were added, and the temperature was maintained at 0 °C. The biphasic solution was warmed to room temperature and stirred for a further 6 h. The aqueous layer was extracted with DCM (2 × 50 mL). The combined organic extracts were washed with water (2 × 75 mL) and brine (1 × 75 mL) and dried with Na_2SO_4. The solution was filtered and concentrated under reduced pressure. The crude solid was recrystallized from EtOAc/hexanes (1:9) to afford **11** (9 g, 93%) as white crystals, m.p. 96–97 °C. R_f = 0.30 (hexanes/EtOAc, 9:1). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.34 (s, 5 H), 6.98 (s, 1 H), 6.90 (s, 1 H), 5.95 (s, 2 H), 5.27 (br. s, 1 H), 5.10 (s, 2 H), 4.33 (d, J = 6.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 156.2, 147.7, 147.4, 136.3, 130.7, 128.4, 128.0, 113.8, 112.6, 109.8, 101.7, 66.8, 45.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3446, 3018, 1718, 1506, 1215 cm^{-1}. MS (ESI): *m*/*z* (%) = 388 (27) [M + 2 + Na]$^+$, 386 (27) [M + Na]$^+$, 343 (9), 301 (18), 264 (100). $C_{16}H_{14}BrNO_4$ (363.01): calcd. C 52.77, H 3.87, N 3.85; found C 52.69, H 3.82, N 3.71.

6-[(Benzyloxycarbonylamino)methyl]-1,3-benzodioxol-5-ylboronic Acid (12): To a solution of carbamate **11** (5 g, 13.74 mmol) in dry THF (70 mL) was added *n*BuLi (2 M hexane, 17.5 mL, 34.92 mmol) at –78 °C over a period of 10 min. The resultant dark yellow solution was stirred at the same temperature for 20 min, and trimethyl borate (18.0 mL, 158.73 mmol) was added rapidly in one portion. The solution became colorless, and the reaction mixture was stirred at –78 °C for a further 30 min. The reaction mixture was warmed to room temperature over 2 h before it was quenched with a large excess of saturated aqueous NH_4Cl (50 mL). The heterogeneous mixture was stirred for 1 h and extracted with EtOAc (3 × 60 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was purified by column chromatography (silica gel, elution with 45% EtOAc/hexanes) to provide **12** (3.12 g, 69%) as a white amorphous solid, m.p. 152–153 °C. R_f = 0.30 (hexanes/EtOAc, 3:2). ^{1}H NMR (200 MHz, [D$_6$]DMSO, 25 °C): δ = 8.15 (s, 2 H), 7.67 (br. s, 1 H), 7.34 (s, 5 H), 7.00 (s, 1 H), 6.80 (s, 1 H), 5.96 (s, 2 H), 5.02 (s, 2 H), 4.28 (d, J = 6.1 Hz, 2 H) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO, 25 °C): δ = 157.1, 148.8, 145.9, 139.0, 137.4, 128.8, 128.2, 113.4, 108.4, 101.1, 66.0, 44.1 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2926, 1693, 1462, 1250 cm^{-1}. MS (ESI): *m*/*z* (%) = 380 (50) [M + 2 MeOH – 2 H_2O + Na]$^+$, 326 (22), 188 (15), 156 (100). $C_{16}H_{16}BNO_6$ (329.11): calcd. C 58.39, H 4.90, N 4.26; found C 58.45, H 4.72, N 4.09.

Methyl (3*R*,4*S*,5*R*)-3,4,5-Tris(methoxymethoxy)cyclohex-1-enecarboxylate (14): A solution of **13** (12 g, 28.85 mmol) in 80% aqueous acetic acid was immersed in an oil bath at 80 °C and stirred overnight. The resultant yellow solution was distilled at 50 °C under high vacuum to remove the volatile materials. The brown pasty residue was triturated with hexanes to facilitate the precipitation, and the solvent was decanted after settling. The process of trituration was repeated (approximately four times) to afford the triol as a chalky powder (4.95 g, 95%) after drying under vacuum. The triol obtained was subjected to the next step without further purification. To a stirred solution of the above intermediate (4.95 g, 26.33 mmol) in dry DCM (80 mL) was successively added DIPEA (16.51 mL, 94.79 mmol) and MOMCl (10 mL, 131.65 mmol) dropwise at 0 °C. The yellow solution was warmed to room temperature and stirred for 14 h before water (100 mL) was added. The aqueous layer was extracted with DCM (2 × 70 mL), and the organic layers were combined, dried (Na_2SO_4), filtered and concentrated to produce a yellow oil. The oil was then purified by column chromatography (silica gel, elution with 20% EtOAc/hexanes) to yield **14** (7.60 g, 95%) as a colorless oil. R_f = 0.50 (hexanes/EtOAc, 4:1). $[a]_D^{27}$ = –82.8 (c = 1.12 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 6.85 (br. s, 1 H), 4.77 (d, J = 2.9 Hz, 2 H), 4.74 (s, 2 H), 4.69 (s, 2 H), 4.50 (m, 1 H), 4.11 (m, 1 H), 3.95 (dd, J = 6.4, 3.8 Hz, 1 H), 3.73 (s, 3 H), 3.40 (s, 3 H), 3.38 (s, 3 H), 3.36 (s, 3 H), 2.65–2.81 (tdd, J = 18.6, 4.7, 2.3 Hz, 1 H), 2.33–2.48 (tdd, J = 18.6, 4.1, 1.5 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 166.6, 136.3, 129.2, 96.8, 96.0, 95.6, 74.2, 72.5, 70.8, 55.6, 55.5, 55.4, 51.7, 28.5 ppm. IR (neat): $\tilde{\nu}$ = 2953, 1717, 1439, 1036 cm^{-1}. MS (ESI): *m*/*z* (%) = 323 (100), 320 (7), 318 (43), 271 (17). $C_{14}H_{24}O_8$ (320.15): calcd. C 52.49, H 7.55; found C 52.42, H 7.41.

Methyl (1*S*,2*R*,3*R*,4*S*,5*R*)-1,2-Dihydroxy-3,4,5-tris(methoxymethoxy)-cyclohexanecarboxylate (15): Trimethylamine *N*-oxide dihydrate (3.57 g, 32.12 mmol) was added to a solution of **14** (7.34 g, 22.94 mmol) in a mixture of *t*BuOH (62 mL), pyridine (3.5 mL) and water (3.5 mL). The solution was stirred until all solids were dissolved, and a crystal of OsO_4 was added at room temperature. The resulting stirred yellow solution was immersed in an oil bath at 80 °C and heated for 15 h. The reaction mixture was cooled, solid Na_2SO_3 (1 g) was added, and the mixture was stirred for 30 min. The solvent was removed by rotary evaporation, the residue was redissolved in EtOAc (150 mL) and partitioned with a minimum amount of water (50 mL). The aqueous layer was extracted with EtOAc (2 × 75 mL). The organic layers were combined, dried (Na_2SO_4) and purified by column chromatography (silica gel, elution with 60% EtOAc/hexanes) to give **15** (6.66 g, 82%) as white crystals, m.p. 83–84 °C. R_f = 0.30 (hexanes/EtOAc, 2:3). $[a]_D^{27}$ = –8.7 (c = 1.62 in $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.83–4.62 (m, 6 H), 4.20 (d, J = 10.0 Hz, 1 H), 4.08 (m, 1 H), 4.01 (dd, J = 6.2, 3.4 Hz, 1 H), 3.92 (dd, J = 10, 2.8 Hz, 1 H), 3.79 (s, 3 H), 3.41 (s, 3 H), 3.39 (s, 3 H), 3.38 (s, 3 H), 3.12 (br. s, 1 H), 2.38–2.26 (dd, J = 15.0, 3.5 Hz, 1 H), 2.09–1.96 (ddd, J = 15.0, 2.3, 1.5 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 173.8, 96.9, 95.9, 76.3, 74.4, 71.4, 55.6, 55.5, 52.7, 32.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3471, 2893, 1730, 1255, 1151 cm^{-1}. MS (ESI): *m*/*z* (%) = 377 (17) [M + Na]$^+$, 372 (13) [M + NH_4]$^+$, 355 (3) [M + H]$^+$, 279 (44), 246 (24), 218 (100), 190 (35), 156 (24). $C_{14}H_{26}O_{10}$ (354.15): calcd. C 47.45, H 7.40; found C 47.32, H 7.33.

Methyl (1*S*,2*R*,3*S*,4*S*,5*R*)-1-Hydroxy-2,3,4,5-tetrakis(methoxymethoxy)cyclohexanecarboxylate (16): A solution of MOMCl (3.49 mL,45.90 mmol) in dry DCM (35 mL) was added to the predissolved solution of **15** (6.5 g, 18.36 mmol) in dry DCM (60 mL) and DIPEA (6.40 mL, 36.72 mmol) by utilizing a syringe pump at room temperature over a period of 2 h. The mixture was stirred for

a further 6 h before water (80 mL) was added to it. The aqueous layer was extracted with DCM (2 × 75 mL). The combined organic extracts were dried (Na_2SO_4) and filtered. Removal of the solvent by rotary evaporation gave a dark brown paste, which was purified by column chromatography (silica gel, elution with 45% EtAOc/hexanes) to give **16** (6.07 g, 83%) as a pale yellow paste. R_f = 0.30 (hexanes/EtOAc, 1:1). $[\alpha]_D^{27}$ = –51.0 (*c* = 1.13 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.89–4.56 (m, 8 H), 4.19 (s, 1 H), 4.17 (d, *J* = 2.2 Hz, 1 H), 4.10 (m, 1 H), 3.98 (dd, *J* = 6.7, 3.5 Hz, 1 H), 3.78 (s, 3 H), 3.67 (br. s, 1 H), 3.39 (s, 3 H), 3.38 (s, 6 H), 3.28 (s, 3 H), 2.43–2.30 (dd, *J* = 14.9, 3.7 Hz, 1 H), 2.03–1.90 (ddd, *J* = 14.9, 2.7. 1.3 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 173.9, 98.3, 96.9, 96.5, 96.2, 78.6, 77.8, 76.8, 74.5, 74.4, 56.2, 55.7, 55.6, 55.5, 52.7, 33.1 ppm. IR (neat): $\tilde{\nu}$ = 3460, 2895, 1745, 1443, 1244, 1150 cm^{-1}. MS (ESI): *m*/*z* (%) = 421 (30) $[M + Na]^+$, 416 (13) $[M + NH_4]^+$, 259 (100), 229 (19), 199 (28). $C_{16}H_{30}O_{11}$ (398.18): calcd. C 48.24, H 7.59; found C 48.22, H 7.80.

(2*R*,3*S*,4*S*,5*R*)-2,3,4,5-Tetrakis(methoxymethoxy)cyclohexanone (17): To a suspension of LAH (0.86 g, 22.61 mmol) in dry THF (25 mL) at 0 °C was cannulated dropwise a solution of **16** (4.5 g, 11.30 mmol), dissolved in dry THF (40 mL), over a period of 30 min. The reaction mixture was warmed to room temperature and then stirred at 50 °C in an oil bath for 18 h. The suspension was cooled to room temperature and poured *cautiously* (by washing the flask with EtOAc) into Na_2SO_4 (approximately 50 g). The mixture was mixed thoroughly and put aside for 2 h. The milky white suspension was filtered through a Büchner funnel, and the inorganic material was washed with EtOAc (150 mL). The filtrate was dried (Na_2SO_4) and concentrated under reduced pressure to obtain the crude diol (4.0 g), which was carried forward to the next step without further purification. The crude diol (4.0 g) was dissolved in phosphate buffer (pH = 7, 35 mL) and cooled to 0 °C. Solid $NaIO_4$ (3.65 g, 17.04 mmol) was added in portions over a period of 10 min, while the temperature was maintained at 0–5 °C. The reaction mixture was stirred at the same temperature for additional 20 min and extracted with EtOAc (3 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated by rotary evaporation. The residue was subjected to column chromatography (silica gel, elution with 30% EtOAc/hexanes) to produce **17** (3.29 g, 86% over two steps) as a colorless paste. R_f = 0.30 (hexanes/EtOAc, 3:1). $[\alpha]_D^{27}$ = –10.2 (*c* = 1.02 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 4.90–4.59 (m, 8 H), 4.52 (d, *J* = 10.1 Hz, 1 H), 4.20–4.04 (m, 3 H), 3.41 (s, 3 H), 3.40 (s, 3 H), 3.39 (s, 3 H), 3.32 (s, 3 H), 2.91–2.80 (dd, *J* = 14.3, 3.5 Hz, 1 H), 2.64–2.52 (ddd, *J* = 14.3, 3.3, 1.1 Hz, 1 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 204.4, 97.2, 96.8, 96.5, 96.2, 80.1, 77.0, 76.2, 74.4, 55.7, 55.6, 55.4, 41.4 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2895, 2359, 1732, 1030 cm^{-1}. MS (ESI): *m*/*z* (%) = 377 (14) $[M + K]^+$, 361 (100) $[M + Na]^+$, 123 (10). $C_{14}H_{26}O_9$ (338.16): calcd. C 49.70, H 7.75; found C 49.54, H 7.67.

(4*S*,5*S*,6*R*)-4,5,6-Tris(methoxymethoxy)cyclohex-2-enone (18): To a solution of **17** (3.00 g, 8.88 mmol) in distilled DCM (260 mL) was added aqueous NaOH (0.1 N, 65 mL) at 0 °C. To the vigorously stirred biphasic solution was added a catalytic amount of tetrabutylammonium hydrogen sulfate (0.15 g, 0.44 mmol), and the mixture was stirred at the same temperature until the starting material was completely consumed (GC monitoring). The reaction mixture was separated in a separatory funnel, and the aqueous layer was extracted with DCM (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and filtered, and the solvent was distilled off under reduced pressure. The crude material was purified by column chromatography (silica gel, elution with 30% EtOAc/ hexanes) to produce **18** (1.94 g, 79%) as a colorless oil. R_f = 0.30 (hexanes/EtOAc, 3:1). $[\alpha]_D^{27}$ = +113.1 (*c* = 1.62 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 6.90 (dd, *J* = 10.2, 4.5 Hz, 1 H), 6.05 (d, *J* = 10.2 Hz, 1 H), 4.86–4.71 (m, 6 H), 4.53 (dd, *J* = 4.2, 4.0 Hz, 1 H), 4.46 (d, *J* = 8.7 Hz, 1 H), 4.10 (dd, *J* = 8.6, 3.4 Hz, 1 H), 3.42 (s, 3 H), 3.38 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 196.1, 145.7, 129.2, 96.9, 96.7, 76.9, 71.5, 55.9, 55.7, 55.6 ppm. IR (neat): $\tilde{\nu}$ = 2951, 1703, 1441, 1113 cm^{-1}. MS (ESI): *m*/*z* (%) = 299 (100) $[M + Na]^+$. $C_{12}H_{20}O_7$ (276.12): calcd. C 52.17, H 7.30; found C 52.06, H 7.27.

(4*S*,5*S*,6*R*)-2-Iodo-4,5,6-tris(methoxymethoxy)cyclohex-2-enone (19): Iodine (4.05 g, 15.94 mmol), dissolved in CCl_4/pyridine (1:1, 20 mL), was added dropwise under argon to a solution of **18** (1.76 g, 6.38 mmol) in CCl_4/pyridine (1:1, 20 mL) at 0 °C. The mixture was stirred for 1 h, during which time the mixture was warmed to room temperature. The mixture was diluted with EtOAc (100 mL) and washed successively with HCl (1 N, 5 × 20 mL), saturated aqueous $NaHCO_3$ (1 × 30 mL), aqueous $Na_2S_2O_3$ (20%, 40 mL) and dried (Na_2SO_4). After filtration and concentration of the organic layers under reduced pressure, the residue was subjected to column chromatography (silica gel, elution with 25% EtOAc/hexanes) to afford **19** (2.56 g, quantitative) as a pale yellow oil. R_f = 0.30 (hexanes/EtOAc, 4:1). $[\alpha]_D^{27}$ = +85.9 (*c* = 1.32 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.67 (d, *J* = 4.6 Hz, 1 H), 4.85–4.71 (m, 6 H), 4.56 (d, *J* = 8.0 Hz, 1 H), 4.51 (d, *J* = 4.4 Hz, 1 H), 4.15 (dd, *J* = 8.0, 3.3 Hz, 1 H), 3.41 (s, 3 H), 3.39 (s, 3 H), 3.36 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 190.0, 154.4, 103.8, 96.9, 96.7, 96.5, 76.7, 75.7, 73.4, 56.0, 55.7, 55.6 ppm. IR (neat): $\tilde{\nu}$ = 2895, 1693, 1443, 1034 cm^{-1}. MS (ESI): *m*/*z* (%) = 441 (7) $[M + K]^+$, 425 (100) $[M + Na]^+$, 403 (≤1) $[M + H]^+$, 327 (5). $C_{12}H_{19}IO_7$ (402.02): calcd. C 35.84, H 4.76; found C 35.90, H 4.86.

Benzyl {6-[(3*S*,4*S*,5*R*)-3,4,5-Tris(methoxymethoxy)-6-oxocyclohex-1-enyl]-1,3-benzodioxol-5-yl}methylcarbamate (20): To a solution of **19** (1 g, 2.49 mmol) in distilled benzene (20 mL) was added a solution of **12** (0.82 g, 2.49 mmol) in ethanol (14 mL), aqueous Na_2CO_3 (2 M, 8 mL) and a catalytic amount of $Pd(PPh_3)_4$ (0.14 g, 0.12 mmol). The vigorously stirring yellow solution was heated in an oil bath at 65 °C under argon for 20 min, producing a dark brown mixture. The mixture was cooled and diluted with water (20 mL) and extracted with EtOAc (3 × 75 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, elution with 30% EtOAc/hexanes) to yield **20** (1.17 g, 84%) as a dark orange paste. R_f = 0.30 (hexanes/EtOAc, 2:1). $[\alpha]_D^{27}$ = +69.5 (*c* = 1.16 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.32 (s, 5 H), 6.90 (s, 1 H), 6.81 (d, *J* = 3.7 Hz, 1 H), 6.51 (s, 1 H), 5.93 (s, 2 H), 5.39 (br. s, 1 H), 5.07 (s, 2 H), 4.86 (d, *J* = 7.0 Hz, 1 H), 4.81–4.70 (m, 6 H), 4.50 (d, *J* = 7.6 Hz, 1 H), 4.27 (dd, *J* = 7.5, 2.9 Hz, 1 H), 4.02 (br. s, 2 H), 3.41 (s, 3 H), 3.40 (s, 3 H), 3.37 (s, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 194.8, 156.2, 147.9, 146.8, 145.1, 139.3, 136.6, 131.1, 128.2, 127.8, 127.5, 109.6, 109.3, 101.2, 96.9, 96.8, 96.4, 77.2, 76.9, 71.4, 66.5, 55.9, 55.6, 55.5, 42.7 ppm. IR (neat): $\tilde{\nu}$ = 2895, 1730, 1713, 1693, 1504, 1485, 1371, 1240, 1042 cm^{-1}. MS (ESI): *m*/*z* (%) = 583 (29) $[M + H + Na]^+$, 582 (100) $[M + Na]^+$, 577 (12) $[M + NH_4]^+$, 560 (13). $C_{28}H_{33}NO_{11}$ (559.21): calcd. C 60.10, H 5.94, N 2.50; found C 60.24, H 5.76, N 2.43.

Benzyl (2*R*,3*S*,4*S*,4a*R*,11b*S*)-2,3,4-Tris(methoxymethoxy)-1-oxo-2,3,4,4a,6,11b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-5(1*H*)-carboxylate (21): To a stirred solution of **20** (0.7 g, 1.25 mmol) in dry THF (12 mL) was added HMPA (1.20 mL) at room temperature. The solution temperature was decreased to –78 °C, and *n*BuLi

(1.62 M in hexane, 1 mL, 1.62 mmol) was added over a period of 10 min. The resultant clear solution was stirred at the same temperature for 30 min. A solution of *p*-toluenesulfonic acid (TSA, 0.36 g, 1.88 mmol) in THF (3 mL) was added dropwise, and the mixture was stirred for a further 10 min. Saturated aqueous $NaHCO_3$ (10 mL) was added after warming the reaction mixture to room temperature, and the mixture was extracted with EtOAc (3 × 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was subjected to column chromatography (silica gel, elution with 25% EtOAc/hexanes) to give **21** (0.57 g, 83%) as a pale yellow paste. R_f = 0.40 (hexanes/EtOAc, 2:1). $[\alpha]_D^{27}$ = +56.9 (*c* = 0.64 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.34 (m, 5 H), 6.65 (s, 1 H), 6.61 (s, 1 H), 5.93 (dd, *J* = 4.6, 1.5 Hz, 2 H), 5.24–5.03 (m, 3 H), 5.98–4.80 (m, 2 H), 4.80–4.61 (m, 6 H), 4.59 (d, *J* = 3.3 Hz, 1 H), 4.48 (dd, *J* = 6.7, 5.3 Hz, 1 H), 4.02 (d, *J* = 6.8 Hz, 1 H), 3.97 (dd, *J* = 9.3, 6.8 Hz, 1 H), 3.65 (d, *J* = 15.8 Hz, 1 H), 3.40 (d, *J* = 15.8 Hz, 1 H), 3.35–3.32 (m, 7 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 205.3, 155.9, 147.0, 136.1, 128.5, 128.4, 128.2, 128.1, 128.0, 124.9, 108.5, 107.0, 101.1, 96.6, 96.5, 79.4, 75.5, 73.7, 67.7, 55.9, 55.8, 55.6, 54.8, 50.0, 44.4 ppm. IR (neat): $\tilde{\nu}$ = 2954, 1730, 1713, 1693, 1487, 1217, 1039 cm^{-1}. MS (ESI): *m*/*z* (%) = 598 (23) $[M + K]^+$, 582 (39) $[M + Na]^+$, 560 (2) $[M + H]^+$, 361 (86), 331 (100). $C_{28}H_{33}NO_{11}$ (559.21): calcd. C 60.10, H 5.94, N 2.50; found C 60.02, H 5.87, N 2.64.

Benzyl (1*S*,2*S*,3*S*,4*S*,4a*R*,11b*S*)-1,2,3,4-Tetrakis(methoxymethoxy)-2,3,4,4a,6,10b-hexahydro[1,3]dioxolo[4,5-*j*]phenanthridine-5(1*H*)-carboxylate (22): Sodium borohydride (0.1 g, 2.68 mmol) was added to a solution of **21** (0.5 g, 0.89 mmol) in dry MeOH (10 mL). The resulting mixture was stirred for 12 h and then quenched by the addition of excess saturated aqueous NaCl. The brownish suspension was stirred overnight and extracted with EtOAc (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4), and the solvent was distilled off. The residue (0.44 g) was concentrated to dryness and used for the next step without purification. To a solution of the above crude alcohol (0.44 g, 0.78 mmol) in dry DCM (8 mL) were successively added DIPEA (0.68 mL, 3.92 mmol) and MOMCl (0.6 mL, 7.84 mmol) dropwise at 0 °C. The yellow solution was warmed to room temperature and stirred for 12 h before water (10 mL) was added. The aqueous layer was extracted with DCM (2 × 7 mL), and the organic layers were combined, dried (Na_2SO_4), filtered and concentrated to produce an orange paste, which was purified by column chromatography (silica gel, elution with 30% EtOAc/hexanes) to yield **22** (0.44 g, 82% over two steps) as a colorless paste. R_f = 0.30 (hexanes/EtOAc, 7:3). $[\alpha]_D^{27}$ = –17.1 (*c* = 1.24 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.72 (br. s, 1 H), 6.50 (br. s, 1 H), 5.87 (dd, *J* = 5.2, 1.4 Hz, 2 H), 5.35–5.02 (m, 2 H), 4.90–4.60 (m, 8 H), 4.53–4.20 (m, 4 H), 4.09 (apparent s, 1 H), 4.00–3.81 (m, 2 H), 3.58 (br. s, 1 H), 3.39 (s, 2 × 3 H), 3.29 (s, 3 H), 3.22 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 156.0, 145.6, 137.0, 136.6, 128.4, 128.2, 128.0, 127.5, 124.7, 109.7, 105.2, 100.5, 97.6, 97.1, 96.4, 95.4, 75.62, 74.5, 71.3, 71.2, 67.2, 66.8, 55.9, 55.7, 55.6, 55.4, 50.5, 42.9, 39.2 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2891, 1693, 1487, 1217, 1035 cm^{-1}. MS (ESI): *m*/*z* (%) = 628 (100) $[M + Na]^+$. $C_{30}H_{39}NO_{12}$ (605.25): calcd. C 59.50, H 6.49, N 2.31; found C 59.39, H 6.25, N 2.22.

***tert*-Butyl (1*S*,2*S*,3*S*,4*S*,4a*R*,11b*S*)-1,2,3,4-Tetrakis(methoxymethoxy)-2,3,4,4a,6,11b-hexahydro-[1,3]dioxolo[4,5-*j*]phenanthridine-5(1*H*)-carboxylate (23):** A mixture of **22** (0.4 g, 0.66 mmol) and $(Boc)_2O$ (0.2 mL, 0.86 mmol) in distilled MeOH (12 mL) was hydrogenated at atmospheric pressure in the presence of 10% Pd on charcoal (40 mg) for 7 h. The reaction mixture was passed through a short pad of Celite, and the solvent was removed by rotary evaporation. The residue was purified by column chromatography (silica gel, elution with 25% EtOAc/hexanes) to afford **23** (0.36 g, 96%) as a colorless gum. R_f = 0.30 (hexanes/EtOAc, 3:1). $[\alpha]_D^{27}$ = –18.5 (*c* = 0.80 in $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.71 (br. s, 1 H), 6.49 (s, 1 H), 5.86 (dd, *J* = 5.2, 1.4 Hz, 2 H), 4.90–4.60 (m, 8 H), 4.52 (br. s, 1 H), 4.42–4.28 (m, 2 H), 4.28–4.00 (m, 2 H), 3.95–3.75 (m, 2 H), 3.55 (br. s, 1 H), 3.40 (s, 2 × 3 H), 3.36 (s, 3 H), 3.21 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ = 145.5, 127.5, 125.0, 109.7, 105.2, 100.4, 96.3, 95.2, 79.7, 77.2, 76.8, 75.6, 74.2, 71.1, 55.6, 55.4, 50.4, 42.9, 39.0, 28.3 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2891, 1695, 1485, 1365, 1151, 1037 cm^{-1}. MS (ESI): *m*/*z* (%) = 594 (100) $[M + Na]^+$. $C_{27}H_{41}NO_{12}$ (571.26): calcd. C 56.73, H 7.23, N 2.45; found C 56.56, H 7.16, N 2.56.

***tert*-Butyl (1*S*,2*S*,3*S*,4*S*,4a*R*,11b*S*)-1,2,3,4-Tetrakis(methoxymethoxy)-6-oxo-2,3,4,4a,6,11b-hexahydro[1,3]dioxolo[4,5-*j*]phenanthridine-5(1*H*)-carboxylate (24):** To a vigorously stirred solution of **23** (0.24 g, 0.42 mmol) in distilled CH_3CN/CCl_4 (1:1, 20 mL) was added aqueous $NaIO_4$ (0.27 g in 15 mL of H_2O) and $RuCl_3$ (24 mg). After being stirred for 3 h, the reaction mixture was diluted with DCM (30 mL), and the aqueous phase was extracted with DCM (3 × 15 mL) and EtOAc (3 × 15 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was diluted with diethyl ether (20 mL), filtered through a pad of Celite and concentrated. The residue was purified by column chromatography (silica gel, elution with 40% EtOAc/hexanes) to give **24** (0.16 g, 65%) as a colorless paste. R_f = 0.30 (hexanes/EtOAc, 1:1). $[\alpha]_D^{27}$ = +27.2 (*c* = 1.25 in $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.74 (s, 1 H), 7.57 (s, 1 H), 5.98 (d, *J* = 12.1 Hz, 2 H), 5.01 (dd, *J* = 11.1, 4.8 Hz, 1 H), 4.81 (s, 2 H), 4.78 (d, *J* = 7.1 Hz, 1 H), 4.72 (d, *J* = 7.1 Hz, 1 H), 4.68 (d, *J* = 6.8 Hz, 1 H), 4.58 (d, *J* = 7.1 Hz, 1 H), 4.46 (dd, *J* = 7.6, 7.1 Hz, 2 H), 4.38 (dd, *J* = 5.1, 3 Hz, 1 H), 4.10 (apparent s, 1 H), 3.94 (s, 1 H), 3.92 (apparent s, 1 H), 3.89 (t, *J* = 5.1 Hz, 1 H), 3.42 (s, 3 H), 3.40 (s, 3 H), 3.30 (s, 3 H), 3.24 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 162.2, 152.4, 150.8, 146.5, 135.3, 123.2, 109.4, 108.3, 101.4, 97.5, 96.6, 95.7, 82.8, 77.2, 77.1, 75.3, 74.9, 72.0, 55.9, 55.8, 55.7, 53.1, 39.4, 28.0 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 2895, 1764, 1693, 1483, 1242, 1151, 1038 cm^{-1}. MS (ESI): *m*/*z* (%) = 609 (100) $[M + H + Na]^+$, 586 (7) $[M + H]^+$, 508 (19), 486 (15). $C_{27}H_{39}NO_{13}$ (585.24): calcd. C 55.38, H 6.71, N 2.39; found C 55.23, H 6.91, N 2.18.

1,10b-*epi*-7-Deoxypancratistatin (25): To a solution of **24** (0.1 g, 0.17 mmol) in dry CH_3CN (1 mL) was added a catalytic amount of solid $Mg(ClO_4)_2$ (8 mg, 0.036 mmol) at room temperature. The stirred mixture was heated in an oil bath at 50 °C for 1.5 h. The mixture was cooled to room temperature and partitioned between EtOAc (10 mL) and water (5 mL) in a separating funnel. The aqueous layer was extracted with EtOAc (2 × 5 mL). The organic extracts were combined, dried (Na_2SO_4), filtered and subjected to rotary evaporation to afford the pure amide (75 mg, 90%) as white solid, which was forwarded to the next step. To a solution of the above intermediate (75 mg, 0.15 mmol) in MeOH (4 mL) was added HCl (6 N, 2 mL), and the reaction mixture was refluxed for 18 h. The solvent was evaporated to dryness to afford a brown solid, which was triturated with distilled MeOH (2 mL), and allowed to settle. The solvent was decanted. The trituration was repeated once again, and removal of the solvent afforded 1,10b-*epi*-7-deoxypancratistatin (**25**, 42 mg, 89%) as an off-white solid, m.p. 298–305 °C. R_f = 0.20 ($CHCl_3$/MeOH, 4:1). $[\alpha]_D^{27}$ = +88.3 (*c* = 0.35 in DMSO). ^1H NMR (400 MHz, $[D_6]$DMSO, 25 °C): δ = 7.22 (s, 1 H), 6.89 (s, 1 H), 5.99 (d, *J* = 5.3 Hz, 2 H), 3.95 (s, 1 H), 3.80–3.62 (m, 4 H), 2.99 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO, 25 °C): δ = 164.6, 149.9, 146.3, 135.7, 125.8, 107.4, 106.2, 101.4, 73.8, 70.6, 69.7, 67.0, 55.3, 38.4 ppm. MS (ESI): *m*/*z* (%) = 332 (16) $[M + Na]^+$, 310 (20) [M +

H]$^+$, 301 (21), 295 (100), 253 (98). $C_{14}H_{15}NO_7$ (309.08): calcd. C 54.37, H 4.89, N 4.53; found C 54.31, H 4.76, N 4.58.

Amine Hydrochloride 26: To a solution of **22** (70 mg, 0.116 mmol) in MeOH (2 mL) was added pre-activated Dowex 50WX2-400 resin (90 mg). The heterogeneous mixture was refluxed with stirring for 14 h. The mixture was cooled, filtered through a short pad of Celite, and the filtrate was concentrated by rotary evaporation to afford a brown residue, which was purified by column chromatography (silica gel, elution with 5% MeOH/$CHCl_3$) to produce the corresponding tetrol (40 mg, 80%) as an amorphous white solid. To a solution of the above tetrol (40 mg, 0.093 mmol) in distilled MeOH (2 mL) was added concentrated HCl (2 drops), and the mixture was hydrogenated in the presence of 20% $Pd(OH)_2$ on carbon (8 mg) under atmospheric pressure for 12 h. After passing the mixture through a pad of Celite, the solvent was evaporated to dryness to afford **26** (31 mg, ca. 100%) as a pale yellow solid, m.p. 214–216 °C with decomposition. $[\alpha]_D^{27}$ = +40.8 (c = 0.5 in H_2O). ^{1}H NMR (500 MHz, D_2O, 25 °C): δ = 6.73 (s, 1 H), 6.60 (s, 1 H), 5.85 (d, J = 3.0 Hz, 1 H), 4.28 (d, J = 7.5 Hz, 1 H), 4.25 (dd, J = 3.1, 2.8 Hz, 1 H), 4.09 (m, 2 H), 3.93 (dd, J = 10.3, 3.4 Hz, 1 H), 3.88 (dd, J = 10.3, 2.5 Hz, 1 H), 3.62 (m, 1 H), 3.20 (m, 1 H) ppm. ^{13}C NMR (125 MHz, D_2O, 25 °C): δ = 147.1, 146.7, 125.0, 121.5, 107.8, 105.6, 101.2, 74.7, 69.6, 68.7, 66.6, 57.4, 45.5, 35.1 ppm. MS (ESI): m/z (%) = 296 (100) [M – Cl]$^+$. $C_{14}H_{18}ClNO_6$ (331.08): calcd. C 50.69, H 5.47, N 4.22; found C 50.44, H 5.59, N 4.18.

Supporting Information (see footnote on the first page of this article): Copies of ^{1}H and ^{13}C NMR spectra of all new compounds, cytotoxicity data of **25** and **26**.

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