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Construction of the 5,10b-Phenanthridine Skeleton Using [3+2]-Cycloaddition of a Non-Stabilized Azomethine Ylide: Total Synthesis of (±)-Maritidine and (±)-Crinine Alkaloids

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Vicinal quaternary and tertiary stereocenters of the 5,10bphenanthridine skeleton 1 are constructed simultaneously in one step by the [3+2]-cycloaddition of non-stabilized azomethine ylide 9, generated by sequential double desilylation of 10 utilizing silver(I) fluoride as a one-electron oxidant. The regio- as well as stereochemical origin of this cycloaddition reaction is explained through a favorable transition state 9''. The strategy is successfully applied for the total synthesis of the biologically active alkaloids (\pm)-maritidine (1a), (\pm)-crinine (1b), and their analogues (1d, 1e, and 1f).

Introduction

Alkaloids 1–4, isolated from plants of the *Amaryllida*ceae^[1–4] family have long been a source of structurally intriguing target molecules that continue to challenge the capabilities of contemporary organic synthesis. The family has produced over 500 structurally diverse alkaloids with a wide range of interesting physiological effects, including antitumor, antiviral, acetylcholinesterase inhibitory, immunostimulatory and antimalarial activities.^[5,6] Maritidine (**1a**) and its structural analogues, isolated from *Pancratium maritimum*, *Pancratium tortuosum*, and *Zephyranthes* genera,^[7–11] is the first alkaloid with the 5,10b-ethanophenanthridine nucleus containing dimethoxy rather than methylenedioxy substituents at the C-8 and C-9 positions of the crinine skeleton (Figure 1). These alkaloids possess fused tetracyclic skeletons displaying adjacent quaternary and tertiary carbon stereocenters with fused pyrrolidine ring systems for which stereochemical incorporation is the



Figure 1. Representative members of Amaryllidaceae alkaloids.

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critical element in their synthesis. Alkaloid **1a** is of particular interest due to its cytotoxic properties^[12–15] and limited supplies from natural sources.^[16–23]

A number of synthetic efforts have been employed to solve the challenging problem of incorporating these steri-

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cally congested stereocenters into the 5,10b-ethanophenanthridine structural framework. In this context, intramolecular oxidative para-para phenolic coupling[24-28] and Pictet-Spengler cyclization^[19-38] of 3-aryl hydroindole derivatives have emerged as the two main strategies. In the former approach, spiro-fused dienone precursor 7 is obtained by the para-para coupling of substituted norbelladine derivatives employing various oxidizing agents,^[24,25,27] photochemical cyclization,^[26] intramolecular Heck reaction,^[39] and cyclization of an intermediate iron carbonyl complex.^[27,28] Substituted 3a-arylhydroindoles 6, which are used for the Pictet-Spengler reaction, are synthesized through key reactions such as regioselective reduction of 1methyl-3,3-disubstituted pyrrolidine-2,5-dione,^[30] intramolecular ene cyclization^[31] of an appropriately constructed acylnitroso olefin, or condensation of 3-arylated Δ^1 -pyrrolinium salts with tert-butyl 3-oxopent-4-enoate.[32] A few other approaches reported for the synthesis of 1 have involved intramolecular cycloamination reactions from an appropriate spiro precursor for the carbon-nitrogen bond formation in the construction of the substituted angular phenanthridine skeleton (Figure 2).^[40]



Figure 2. Summary of the strategies reported for the synthesis of **1**.

From the above introductory remarks, it is apparent that these approaches employ sequential generation of vicinal quaternary and tertiary stereocenters along with the use of cyclic precursors for C-ring formation. Moreover, the Pictet–Spengler cyclization route has produced only the dihydromaritidine, whose oxidative transformation into maritidine has so far been unsuccessful. Therefore, we surmised that a strategy that could deliver all the stereocenters in one step would significantly advance the syntheses of these classes of alkaloids.



Our continuing interest in exploring the application of non-stabilized azomethine vlides, generated by the sequential double desilylation of α, α' -bis(trimethylsilylmethyl)alkylamines^[41–42] in the total synthesis of alkaloids^[43–45] with complex architecture, and the need to develop a concise and versatile strategy to synthesize these types of alkaloids, led us to envisage the synthesis of 1a through an intramolecular 1,3-dipolar cycloaddition of a non-stabilized azomethine ylide (AMY). This strategy emerged from our success in the construction of examples of the fused polycyclic 5,11methanomorphanthridine class of alkaloids through the use of non-stabilized azomethine cycloaddition reactions.^[45] We report herein full details^[46] of the intramolecular [3+2]-cycloaddition of a non-stabilized azomethine ylide as a route for the stereoselective synthesis of (\pm) -maritidine (1a) and (\pm) -crinine (1b).

Results and Discussion

Retrosynthetic Plan

While designing a route to 5,10b-ethanophenanthridine alkaloids such as maritidine and crinine via oxomaritidine **1e** and oxocrinine **1f**, respectively, we speculated on the formation of the C¹–C² double bond by cycloaldolization/condensation of the corresponding δ -keto aldehyde from **8**, which possesses vicinal quaternary and tertiary stereocenters at the ring fusion center (Figure 3). A detailed evaluation of the structural framework of **8** revealed the presence of a fused pyrrolidine ring (BD rings) with adjacent vicinal quaternary and tertiary stereocenters.



Figure 3. Retrosynthetic analysis for maritidine and crinine types of *Amaryllidaceae* alkaloids.

Therefore, we envisioned that an intramolecular [3+2]cycloaddition reaction of non-stabilized azomethine ylide **9** with a tethered geminally disubstituted dipolarophile would result in the construction of both C^{4a} - C^{10b} and C^{11} - C^{12} bonds in one step with the required stereochemistry of **8**.

The corresponding azomethine ylide intermediate could be easily generated in situ from the corresponding α, α' -bis(trimethylsilylmethyl)alkylamine **10** using silver(I) fluoride as a one-electron oxidant, using a protocol developed in our group.^[41–42]

Regio- as well as stereochemical issues, the two important aspects of this cycloaddition strategy, were evaluated at the planning stage of the synthesis itself. The origin of the 5,10b-ethanophenanthridine regiochemistry during cycloaddition, in contrast to that of the 5,11-methanophenanthridine skeleton,^[45] was considered to arise from the change in the LUMO energy of the dipolarophile due to its conjugation with the aromatic ring and the ester moiety present on the same carbon. The cycloaddition reaction of 10 was envisaged to generate the vicinal quaternary and tertiary carbon stereocenters in one step, with the orientation of substituents in the dipole directing the stereochemical outcome at the C-4a position. For example, it was hypothesized that the alkyl ketal moiety of the dipole in AMY 9' may experience severe stereoelectronic congestion with the tethered aromatic ring flanked between the dipole and the dipolarophile as shown in TS-I (Figure 4), resulting in the epimeric C-4a stereochemistry of cycloadduct 8. On the other hand TS-II, in which the alkyl ketal side chain of AMY 9'' and the aromatic ring are distant from each other, may generate the desired C-4a stereochemistry in 8. Thus, we anticipated that suitable substrate controlled stereoelectronic factors operating during cycloaddition of 9'' would reinforce the stereochemical outcome of the formation of the tricyclic skeleton and lead to a suitable stereochemical disposition of substituents required for assembling the Cring of the target alkaloid.



Figure 4. Proposed transition state model for the [3+2]-cycloaddition step.

The requisite key precursor **10** for the transformation was envisaged to be obtained from modified Stille coupling^[47] of the corresponding aryl iodide **11** and a suitable vinylstannane **12**.^[48] The aryl iodide **11** could, in turn, be synthesized by alkylation of the bis-silylated (alkylamino)-alkyl-substituted ketal **13** with the diiodo component **14**. These components may be obtained from commercially available aryl methyl alcohol and methyl vinyl ketone (MVK).



Scheme 1. Synthesis of the precursor for cycloaddition.

Synthesis of (\pm) -Maritidine (1a): With the above design in mind, we began by synthesizing the key precursor 10a (73% yield) by a modified Stille coupling between appropriately substituted aryl iodide 11a and vinyl stannane 12 by following Corey's protocol.^[47] The Stille precursor was obtained in 70% yield by N-alkylation of 13 with the corresponding di-iodo component 14a, in the presence of anhydrous K₂CO₃ in CH₃CN. Secondary amine 13 was synthesized from 15 as shown in Scheme 1. Compound 15 was readily obtained from 16 by following a sequence of reactions similar to those previously reported.^[45] Compound 16 was obtained in 70% yield by an aza-Michael reaction between BocNH₂ and methyl vinyl ketone, followed by NaBH₄-mediated reduction. Compound 15, on oxidation with 2-iodoxybenzoic acid (IBX) followed by ketalization, gave ketal 20 in 85% yield. N-Boc deprotection of 20, followed by N-alkylation with iodomethyltrimethylsilane, gave bis-silvlated compound 13 in 70% yield.

With key precursor **10a** in hand, we performed the crucial cycloaddition reaction by dropwise addition of its solution (2.87 mmol) dissolved in dichloromethane (15 mL) to a stirring mixture of flame-dried silver(I) fluoride in anhydrous dichloromethane. To our delight, the reaction gave the desired cycloadduct **8a** in 56% isolated yield along with some other minor unidentifiable impurities. The yield of **8a** was optimized up to 68% by manipulating the rate of the addition of **10a** to the stirring suspension of properly dried silver(I) fluoride. The cycloadduct was fully characterized by ¹H and ¹³C NMR experiments. The stereochemical assignment was established based on extensive COSY, NOESY and HETCOR NMR spectroscopic studies (Scheme 2).^[49]

After the successful synthesis and complete characterization of the fused tricyclic intermediate **8a** with the ABD ring, the next task towards completing the synthesis of the natural product was to construct ring C. In order to proceed further, cycloadduct **8a** was subjected to diisobutylaluminum hydride (DIBAL-H) mediated reduction. However, this reaction led to the reduction of ester functionality along with ketal deprotection, presumably through coordination of the alkoxy aluminum with the ketal oxygen atom



Scheme 2. Synthesis of tricyclic core of maritidine.

followed by deprotection of the ketal group to give the stable hemiketal **21** as shown in Scheme 3.

Thus, we were compelled to adopt a two-step protocol to obtain **23**. Lithium aluminum hydride (LAH) mediated reduction of the ester moiety of **8a**, followed by Swern oxidation, produced the aldehyde-ketal **23a** in 81% yield. In an attempt to perform one-pot ketal deprotection and aldol condensation, **23a** was initially stirred overnight with 80% acetic acid. However, these conditions produced only the ketal deprotected compound in poor yield along with traces of **1e**. Therefore, **23a** was subjected to *trans*-ketalization using *p*-toluenesulfonic acid (*p*-TsA) and acetone to obtain the corresponding δ -keto aldehyde, which was immediately treated with NaOH/EtOH to obtain **1e** in 65% yield. The spectroscopic data of **1e** was also found to be in excellent agreement with the reported data.^[39]

Although the synthesis of **1e** concludes the formal total synthesis of **1c** and **1a**, we proceeded further to complete the total synthesis of **1a** by subjecting **1e** to Luche reduction,^[50] which produced **1c**. Mesylation, followed by substitution using CsOAc and saponification of the resultant acetate, gave **1a** in 45% yield (Scheme 4). The spectroscopic data of **1a** were found to be in excellent agreement with those of the reported compound.^[39a]



Scheme 3. DIBAL-H reduction of 8a.



Scheme 4. Synthesis of maritidine.

Synthesis of (\pm)-Crinine (1b): After accomplishing the total synthesis of 1a, we turned our attention towards the total synthesis of (\pm)-crinine (1b). The crinine alkaloids elicit continued interest in the synthetic community due in part to their intriguing physiological activities,^[51,52] as exemplified by a recent study that unveiled the highly selective apoptosis induction properties against tumor cells at micromolar concentrations. Crinine alkaloids have also been shown to possess immuno-stimulant, antitumor, and antiviral activities.^[53]

The synthesis of **1b** was accomplished through the cycloaddition of **10b** by following identical synthetic steps to those described above for **1a** (Scheme 5).

The stereochemistry of the cycloadduct was confirmed by submitting **22b** to detailed COSY, NOESY, and HETCOR NMR spectroscopic studies. The spectroscopic data of **1b** was found to be in good agreement with those of the reported compound.^[39b]

Conclusions

We have successfully developed a conceptually new and versatile protocol for the construction of 5,10b-eth-anophenanthridine alkaloids. The significance of the approach has been demonstrated by synthesizing (\pm) -maritidine, (\pm) -crinine, and some of their analogues (1d, 1e, and 1f).

Experimental Section

General: All reactions requiring anhydrous conditions were performed under a positive pressure of argon using oven-dried glassware (110 °C), which were cooled under argon. Solvents for anhydrous reactions were dried according to Perrin and Armarego.^[54] Benzene, CH₂Cl₂, and triethylamine were both distilled from CaH₂ and stored over molecular sieves and KOH, respectively. THF and diethyl ether were distilled from sodium benzophenone ketyl. Solvents used for chromatography were distilled at their respective boiling points using known procedures. Petroleum ether (PE) used in the experiments was of 60–80 °C boiling range.

All commercial reagents were obtained from Sigma–Aldrich or Lancaster Chemical Co. (UK). *s*-Butyllithium was titrated using diphenylacetic acid as an indicator. Trimethylsilyl chloride (TMSCl) and methanesulfonyl chloride (MsCl) were distilled before use. Progress of the reactions was monitored by TLC, which was performed on plates pre-coated with silica gel 60 (Merck, 230– 400 mesh). Compounds were visualized by heating after dipping in alkaline solution of either KMnO₄ or (NH₄)₆Mo₇O₂₄ (6.25 g) in aqueous H₂SO₄ (250 mL). Column chromatography was performed



Scheme 5. Synthesis of crinine.



with silica gel 60–120/100–200/230–400 mesh. Standard syringe and cannula techniques were used to transfer air- and moisture-sensitive reagents.

IR spectra were recorded with a Perkin-Elmer infrared spectrometer model 599-B and model 1620 FTIR. ¹H NMR spectra were recorded with Bruker ACF 200, Bruker AV 400, or Bruker DRX 500 instruments using deuterated solvent. Chemical shifts are reported in ppm. Proton coupling constants (J) are reported as absolute values in Hz; multiplicity is reported as follows: broad (br.), singlet (s), doublet (d), triplet (t), doublet of triplet (dt), doublet of doublet of doublet (ddd), multiplet (m). ¹³C NMR spectra were recorded with Bruker ACF 200, AV 400, or Bruker DRX 500 instruments operating at 50 MHz, 100 MHz, and 125 MHz, respectively. ¹³C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ = 77.0 ppm). Mass spectra were recorded with a PE SCIEX API QSTAR pulsar (LC-MS) and high resolution mass spectra (HRMS) were recorded with an MSI (U.K.) Autoconcept instrument operating in the electron impact mode of ionization (70 eV) at the National Chemical Laboratory, Pune, India.

tert-Butyl 2,6-Dimethyl-1,3-oxazinane-3-carboxylate (18): To a stirring solution of the N-Boc derivative of the aminobutanol 16 (14 g, 73.99 mmol) in benzene (220 mL) and pyridinium *p*-toluenesulfonate (PPTS; 0.93 g, 3.7 mmol) in a 500 mL round-bottomed flask, acetaldehyde diethyl acetal (11.6 mL, 81.38 mmol) was added at r.t. slowly. The reaction mixture was subjected to azeotropic distillation for a period of 16-18 h using a long distillation head. The vapor temperature was maintained between 67-71 °C. After completion of the reaction, the brown reaction mixture was allowed to cool and washed with saturated NaHCO3 (100 mL), water $(2 \times 100 \text{ mL})$, brine $(2 \times 50 \text{ mL})$, dried with Na₂SO₄, and concentrated under reduced pressure. The residue was purified by vacuum distillation (b.p. 75-78 °C/1 Torr) to obtain 18 (13.86 g, 87%) as a colorless oil. $R_{\rm f}$ = 0.3 (PE/EtOAc, 85:15). IR (neat): $\tilde{v}_{\rm max}$ = 2977, 2934, 1698, 1410, 1366, 1337, 1161, 1092, 945, 861 cm $^{-1}$. ¹H NMR $(CDCl_3, 200 \text{ MHz}): \delta = 5.74 \text{ (br. q, } J = 6.35, 10.56 \text{ Hz}, 1 \text{ H}; \text{ CH}),$ 3.92 (m, 2 H; H of CH and H of CH₂), 3.06 (m, 1 H; CH₂), 1.45 (m, 2 H; CH₂), 1.40 [s, 9 H; (CH₃)₃], 1.38 (d, J = 6.32 Hz, 3 H; CH₃), 1.11 (d, J = 6.06 Hz, 3 H; CH₃) ppm. ¹³C NMR (CDCl₃, 100 MHz): $\delta = 153.4$, 79.8, 78.3, 64, 36.2, 32.7, 28.3, 21.7, 15.6 ppm. MS: $m/z = 238.27 [M + Na]^+$. $C_{11}H_{21}NO_3$ (215.29): calcd. C 61.37, H 9.83, N 6.51; found C 61.19, H 9.65, N 6.32.

tert-Butyl 2,6-Dimethyl-4-(trimethylsilyl)-1,3-oxazinane-3-carboxylate (19): A solution of 18 (10 g, 46.46 mmol) in anhydrous THF (92 mL) was charged into a 250 mL two-necked round-bottomed flask equipped with magnetic stirring bar and an argon gas balloon, and was cooled to -78 °C. TMEDA (9 mL, 92.91 mmol) followed by sBuLi (1.5 M in cyclohexane, 62 mL, 92.91 mmol) were introduced to the stirring mixture dropwise over a period of 30 min. The mixture was further stirred for 4 h at -78 °C. TMSCl (13.6 mL, 106.84 mmol) was added dropwise to the reaction mixture at -78 °C, which was then warmed to r.t. slowly and further stirred for 2 h. The reaction was quenched by addition of saturated aqueous NH₄Cl (40 mL). The mixture was extracted with ethyl acetate $(3 \times 120 \text{ mL})$ and the combined organic layer was washed with brine (2×75 mL), dried with Na₂SO₄ and concentrated under vacuum. The yellowish mixture was purified by column chromatography (ethyl acetate/PE, 3:97) to obtain 19 (11.35 g, 85%) as a colorless oil. $R_{\rm f} = 0.3$ (PE/EtOAc, 95:5). IR (neat): $\tilde{v}_{\rm max} = 2977, 2934$, 1698, 1416, 1365, 1318, 1289, 1248, 1168, 1096, 843 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ = 5.78 (q, J = 6.44 Hz, 1 H; CH), 3.97 (m, 1 H, CH), 2.69 (dd, J = 2.91 Hz, 1 H, 12.38; CH), 1.47 (d, J =6.57 Hz, 3 H; CH₃), 1.42 [s, 9 H; (CH₃)₃], 1.35 (d, J = 5.69 Hz, 1

H; CH₂), 1.21 (d, J = 6.32 Hz, 1 H; CH₂), 1.12 (d, J = 6.07 Hz, 3 H; CH₃), 0.05 [s, 9 H; (CH₃)₃] ppm. ¹³C NMR (CDCl₃, 50 MHz): $\delta = 154.6, 83.7, 79.4, 65.8, 40.3, 34.5, 28.2, 21.9, 16.1, 0.4$ ppm. MS: m/z = 310 [M + Na]⁺. C₁₄H₂₉NO₃Si (287.47): calcd. C 58.49, H 10.17, N 4.87; found C 58.30, H 10.01, N 4.65.

N-(2-Iodo-4,5-dimethoxybenzyl)-2-(2-methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)-N-[(trimethylsilyl)methyl]ethanamine (11a): To a stirring solution of 14a (7 g, 17.39 mmol) in anhydrous CH₃CN (51 mL), K₂CO₃ (12 g, 86.95 mmol) and bis-silylated (alkylamino)alkyl-substituted ketal 13 (5 g, 17.39 mmol) were added at r.t. The resulting suspension was heated to reflux for 8 h. On completion of the reaction, the mixture was cooled, filtered, and the solvent was evaporated under vacuum. The resultant pasty mass was taken in EtOAc and washed with H_2O (2×50 mL), brine (2×40 mL), dried with Na₂SO₄, and concentrated under vacuum to obtain a red-brown mass, which was purified by column chromatography (PE/ethyl acetate, 95:5) to obtain 11a as a pale-yellow oil (6.88 g, 70%). $R_{\rm f} = 0.4$ (PE/EtOAc, 90:10). IR (neat): $\tilde{v}_{\rm max} = 2953$, 2843, 1682, 1595, 1501, 1464, 1437, 1376, 1250, 1207, 1152, 1048, 838 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.24 (s, 1 H; CH), 7.18 (s, 1 H; CH), 3.86 [s, 6 H; (CH₃)₂], 3.87–3.74 [m, 4 H; (CH₂)₂], 3.62 (d, J = 15.31 Hz, 1 H; CH₂), 3.40 (d, J = 15.31 Hz, 1 H; CH₂), 2.36 (dd, J = 4.02, 7.28 Hz, 1 H; CH), 2.24 (d, J = 14.56 Hz, 1 H; CH₂), 2.15 (four-lines pattern, J = 4.27, 14.81, 4.01, 14.55 Hz, 1 H; CH₂), 1.92 (d, J = 14.55 Hz, 1 H; CH₂), 1.82 (four-lines pattern, J = 7.53, 14.81, 7.28, 14.56 Hz, 1 H; CH₂), 1.30 (s, 3 H; CH₃), 0.12 [s, 9 H; (CH₃)₃], 0.02 [s, 9 H; (CH₃)₃] ppm. ¹³C NMR (CDCl₃, 100 MHz): $\delta = 149.2, 148, 134.8, 121.1, 112.7, 109.9, 87, 64.3, 64.2,$ 63.7, 56, 55.8, 49.6, 44.4, 34, 24.3, -0.2, -0.9 ppm. MS: m/z = 566.55[M + H]⁺. C₂₂H₄₀INO₄Si₂ (565.63): calcd. C 46.72, H 7.13, N 2.48; found C 46.61, H 7.01, N 2.40.

Methyl 2-[4,5-Dimethoxy-2-({[2-(2-methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)ethyl][(trimethylsilyl)methyl]amino}methyl)phenyl]acrylate (10a): A 100 mL two-necked round-bottomed flask was charged with LiCl (0.9 g, 21.22 mmol) and flame-dried under high vacuum. Upon cooling, [Pd(PPh₃)₄] (0.061 g, 0.53 mmol) and CuCl (1.75 g, 17.68 mmol) were added, and the mixture was degassed (3-4 times) under high vacuum with an argon purge. Anhydrous DMSO (25 mL) was introduced with concomitant stirring, followed by the sequential addition of 11a (2 g, 3.53 mmol) and vinyl stannane compound 12 (1.59 g, 4.24 mmol), both diluted with DMSO (1 mL). The resulting mixture was rigorously degassed (4 times) by the freeze-thaw cycles (-78 to 25 °C, Ar). The reaction mixture was stirred at r.t. for 1 h followed by heating at 60 °C for 2 h. Following completion of the coupling as monitored by TLC, the reaction mixture was cooled, diluted with Et₂O (70 mL), and washed with a mixture of brine $(2 \times 40 \text{ mL})$ and 5% aqueous NH₄OH (100 mL). The aqueous layer was further extracted with ethyl acetate $(2 \times 100 \text{ mL})$, and the combined organic layers were washed with water $(2 \times 100 \text{ mL})$, brine $(2 \times 50 \text{ mL})$, dried with Na₂SO₄ and concentrated under reduced pressure. The reddishbrown residue was purified by column chromatography (PE/ethyl acetate, 90:10) to yield 10a (1.35 g, 73%) as a yellow viscous liquid. $R_{\rm f} = 0.3$ (PE/EtOAc, 80:20). IR (CHCl₃): $\tilde{v}_{\rm max} = 3018$, 2956, 2873, 2852, 1720, 1600, 1509, 1465, 1440, 1376, 1249, 1216, 1136, 1048, 838, 756 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 7.31 (s, 1 H; CH), 6.60 (s, 1 H; CH), 6.47 (br. d, J = 1.26 Hz, 1 H; CH), 5.64 (br. d, J = 1.25 Hz, 1 H; CH), 3.88 (s, 3 H; CH₃), 3.87–3.80 [m, 4 H; $(CH_2)_2$], 3.84 (s, 3 H; CH₃), 3.72 (s, 3 H; CH₃), 3.37 (q, J = 14.56, 16.81, Hz, 2 H; CH₂), 2.37 (dd, J = 4.27, 7.53 Hz, 1 H; CH), 2.11 $(d, J = 14.56 \text{ Hz}, 1 \text{ H}; \text{ CH}_2), 2.01 (dd, J = 4.26, 14.56 \text{ Hz}, 1 \text{ H};$ CH_2), 1.86 (d, J = 14.56 Hz, 1 H; CH_2), 1.71 (dd, J = 7.53, 14.56 Hz, 1 H; CH₂), 1.24 (s, 3 H; CH₃), 0.06 [s, 9 H; (CH₃)₃], 0.01

[s, 9 H; (CH₃)₃] ppm. ¹³C NMR (CDCl₃, 50 MHz): δ = 167.1, 148.7, 146.7, 140.8, 129, 128.6, 128.3, 112.5, 111.3, 109.9, 64.2, 64, 56.1, 55.8, 55.7, 52.1, 49.4, 44, 33.7, 24.1, -0.3, -0.9 ppm. MS: *m*/*z* = 524.3 [M + H]⁺. C₂₆H₄₅NO₆Si₂ (523.81): calcd. C 59.62, H 8.66, N 2.67; found C 59.48, H 8.50, N 2.50.

Synthesis of 8a from 10a: A solution of 10a (1.5 g, 2.87 mmol) in anhydrous CH₂Cl₂ (15 mL) was introduced dropwise over a period of 1 h into an argon-flushed 500 mL two-neck flask containing flame-dried AgF (1.82 g, 14.33 mmol) in anhydrous CH₂Cl₂ (200 mLCH₂Cl₂). The color of the reaction mixture gradually turned to dark-brown with concomitant deposition of silver on the inner surface of the flask in the form of a mirror. The progress of reaction was monitored periodically by TLC. After completion, the reaction mixture was filtered through a small plug of basic alumina (eluent MeOH) and the solvent was evaporated to obtain a crude brown residue, which was purified by silica gel chromatography (PE/acetone, 75:25) to obtain 8a (0.73 g, 68%) as yellow gummy liquid. $R_{\rm f} = 0.4$ (PE/Acetone, 60:40). IR (CHCl₃): $\tilde{v}_{\rm max} = 3018$, 2956, 1730, 1611, 1518, 1466, 1260, 1215, 1130, 854, 754 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 6.49 (s, 1 H; CH), 6.27 (s, 1 H; CH), 4.39 (d, J = 16.81 Hz, 1 H; CH₂), 3.94 [m, 4 H; (CH₂)₂], 3.80 (br. s, 4 H; CH₃, CH₂), 3.77 [s, 6 H; (CH₃)₂], 3.56 (br. d, J = Hz, 1 H 7.78; CH), 3.36 (m, 1 H; CH₂), 2.76 (m, 1 H; CH₂), 2.48 (m, 1 H; CH₂), 2.12 (m, 1 H; CH₂), 1.67 (dd, *J* = 9.54, 14.56 Hz, 1 H; CH₂), 1.56 (dd, J = 2.51, 14.56 Hz, 1 H; CH₂), 1.42 (s, 3 H; CH₃) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 174.3, 148.3, 147.4, 134.2, 123.5, 109.5, 109.1, 108.1, 66.3, 64.6, 64.2, 61.4, 57.3, 55.9, 55.8, 51.8, 50.8, 38.3, 37.9, 23.8 ppm. MS: $m/z = 378.27[M + H]^+$. C₂₀H₂₇NO₆ (377.43): calcd. C 63.64, H 7.21, N 3.71; found C 63.50, H 7.15, N 3.65.

Reduction of 8a to 22a: To a suspension of LAH (0.12 g, 3.18 mmol) and anhydrous THF (8 mL) in a 25 mL two-necked round-bottomed flask equipped with magnetic stirring bar and an argon balloon system at 0 °C, was added dropwise by using a cannula, a solution of 8a (0.6 g, 1.59 mmol) dissolved in anhydrous THF (1 mL) over a period of 2 min. The reaction mixture was warmed to r.t. and stirred for 24 h. After completion of reaction, the suspension was cooled to 0 °C and quenched by dropwise addition of 1 N NaOH. The mixture was then stirred at r.t. for 2 h. The whole mass was taken up into CH₂Cl₂ (25 mL) and washed with water. The aqueous layer was then partitioned with CH₂Cl₂ $(2 \times 10 \text{ mL})$, and the combined organic layer was shaken with brine and dried with Na₂SO₄. The solvent was removed in vacuo to obtain a gummy mass, which, on column chromatography (CH₂Cl₂/ MeOH, 85:15), afforded 22a as a yellow gummy liquid (0.528 g, 90%). $R_{\rm f} = 0.3$ (CH₂Cl₂/MeOH, 80:20). IR (CHCl₃): $\tilde{v}_{\rm max} = 3449$, 3018, 2959, 2937, 2854, 2343, 2359, 1610, 1516, 1466, 1260, 1215, 1045, 854, 754 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): δ = 6.92 (s, 1 H; CH), 6.54 (s, 1 H; CH), 4.64 (d, J = 16.23 Hz, 1 H; CH₂), 4.36 $(d, J = 13.20 \text{ Hz}, 1 \text{ H}; \text{ CH}_2), 4.11 (d, J = 16.50 \text{ Hz}, 1 \text{ H}; \text{ CH}_2),$ 4.04-3.99 [m, 4 H; (CH₂)₂], 3.90 (d, J = 13.20 Hz, 1 H; CH₂), 3.89(s, 3 H; CH₃), 3.82 (s, 3 H; CH₃), 3.67 (br. t, J = 4.95, 15.13, 10.18 Hz, 1 H; CH), 3.61 (t, J = 4.24 Hz, 1 H; CH₂), 3.06 (fivelines pattern, J = 7.98, 14. 85 Hz, 1 H; CH₂), 2.18 (m, 2 H; CH₂), 1.91 (m, 1 H; CH₂), 1.85 (m, 1 H; CH₂), 1.43 (s, 3 H; CH₃) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 148.4, 147.4, 133.8, 121.7, 109.5, 109.4, 107.4, 64.8, 64.5, 64.4, 60.7, 60.3, 56.1, 56, 51.6, 51.2, 37, 36.6, 24 ppm. MS: $m/z = 350.3[M + H]^+$. $C_{19}H_{27}NO_5$ (349.42): calcd. C 65.31, H 7.79, N 4.01; found C 65.20, H 7.60, N 3.90.

DIBAL-H Mediated Reduction of 8a to 21: The cycloadduct **8a** (0.050 g, 0.132 mmol) was taken in a 10 mL two-necked round-bot-tomed flask charged with argon. Anhydrous CH₂Cl₂ (0.4 mL) was

added to the reaction flask and the solution was cooled to -78 °C. To the solution of cycloadduct in anhydrous CH₂Cl₂ was added DIBAL-H (1.2 M in toluene, 0.278 mmol) at -78 °C and the mixture was stirred at the same temperature for 30 min. The reaction was quenched by addition of a few drops of a saturated aq. sodium potassium tartrate solution. Solid sodium sulfate was added to the reaction flask and the mixture was further stirred at r.t. for 1 h and then filtered through a sintered funnel. Concentration of the reaction mixture followed by column chromatography (EtOAc/hexane, 70%) afforded 21 as a gummy liquid in 70% yield. $R_{\rm f} = 0.2$ (hexane/EtOAc, 10:90). ¹H NMR (CDCl₃, 400 MHz): $\delta = 6.51$ (s, 1 H; CH), 6.42 (s, 1 H; CH), 4.40 (d, J = 16.82 Hz, 1 H; CH₂), 4.28 (d, J = 11.04 Hz, 1 H; CH₂), 4.21 (d, J = 11.04 Hz, 1 H; CH₂), 3.88 (d, J = 16.82 Hz, 1 H; CH₂), 3.83 (s, 3 H; CH₃), 3.81 (s, 3 H; CH₃), 3.38–3.33 (m, 2 H; H of CH and H of CH₂), 2.87–2.80 (m, 1 H; CH₂), 2.42–2.35 (m, 2 H; CH₂), 1.94–1.86 (m, 2 H; CH₂), 1.48 (s, 3 H; CH₃) ppm. MS: $m/z = 306.36 [M + H]^+$.

Oxidation of 22a to 23a: To a mixture of DMSO (0.15 mL, 2.15 mmol) in CH_2Cl_2 (3 mL), oxalyl chloride (0.19 mL, 2.15 mmol) was added dropwise at -78 °C, and the resulting mixture was stirred for 15 min. A solution of alcohol 20a (0.5 g, 1.43 mmol) in CH₂Cl₂ (1 mL) was added dropwise to the reaction flask at -78 °C. The mixture was stirred for 1 h, then triethylamine (1 mL, 7.15 mmol) was added dropwise and the resultant mixture was gradually warmed to r.t.. over 1 h by removing the cooling bath and stirred for a further 1 h. The reaction mixture was quenched with water (5 mL) and extracted with CH₂Cl₂ $(2 \times 25 \text{ mL})$. The combined organic layer was washed with brine, dried with Na₂SO₄, filtered and concentrated under vacuum. Purification of the residue by silica gel column chromatography (CH₂Cl₂/MeOH, 92:8) afforded aldehyde 23a (0.447 g, 90%) as a gummy liquid. $R_{\rm f} = 0.3$ (CH₂Cl₂/MeOH, 85:15). IR (CHCl₃): $\tilde{v}_{\rm max}$ = 3018, 2930, 2854, 1713, 1609, 1516, 1464, 1362, 1260, 1217, 1119, 1032, 856, 756 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 9.93 (s, 1 H; CH), 6.60 (s, 1 H; CH), 6.27 (s, 1 H; CH), 4.48 (d, J = 16.81 Hz, 1 H; CH₂), 3.90 [m, 4 H; (CH₂)₂], 3.83 (br. s, 4 H; CH₃ and CH), 3.80 (s, 3 H, CH₃), 3.60 (t, J = 4.95 Hz, 1 H; CH), 3.35 (dt, J =3.26, 10.42, 13.30 Hz, 1 H; CH₂), 2.81 (five-lines pattern, J = 8.03, 8.28, 5.27, 6.52, Hz, 1 H; CH₂), 2.53 (ddd, J = 6.53, 10.79, 17.07 Hz, 1 H; CH₂), 1.88 (m, 1 H; CH₂), 1.67 (dd, J = 6.53, 14.56 Hz, 1 H; CH₂), 1.61 (dd, J = 3.51, 14.55 Hz, 1 H; CH₂), 1.37 (s, 3 H; CH₃) ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 202.2, 148.6, 147.6, 132.2, 124, 109.7, 109.4, 108.2, 64.7, 64.5, 64.4, 61.5, 61.4, 56, 55.9, 51.3, 39.4, 34.76, 24 ppm. MS: $m/z = 348.4 [M + H]^+$. $C_{19}H_{25}NO_5$ (347.41): calcd. C 65.69, H 7.25, N 4.03; found C 65.50, H 7.10, N 3.91.

Oxomaritidine (1e) from 23a: To a solution of 23a (0.020 g, 0.06 mmol) in acetone (0.18 mL), pTSA (0.011 g, 0.06 mmol) was added at r.t., and the reaction mixture was stirred for 3 h. Progress of the reaction was monitored by TLC. On completion of the reaction, the solvent was evaporated under vacuum and the residue was dissolved in CH₂Cl₂ (25 mL) and washed with saturated NaHCO₃ $(2 \times 10 \text{ mL})$, brine $(2 \times 5 \text{ mL})$, dried with Na₂SO₄ and concentrated under vacuum to obtain a crude mass, which was used in the next step without any purification. To a stirred solution of the crude reaction mixture of δ-keto aldehyde (0.014 g, 0.05 mmol) in EtOH (2 mL) at r.t. was added solid NaOH (0.011 g, 0.28 mmol) and the resulting mixture was stirred for 20 h. The reaction mixture was concentrated and the residue was dissolved in CH₂Cl₂ (20 mL), washed with water (5 mL), brine $(2 \times 5 \text{ mL})$, dried with anhydrous Na₂SO₄, filtered and concentrated. Purification of the residue by flash column chromatography (CH₂Cl₂/MeOH, 95:5) afforded 1e as a white powder (0.011 g, 65% over two steps). $R_{\rm f} = 0.4$ (CH₂Cl₂/

MeOH, 90:10). IR (CHCl₃): $\hat{v}_{max} = 2961$, 2925, 1682, 1609, 1515, 1261, 1220, 1134, 1038 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): $\delta =$ 7.70 (d, J = 10.17 Hz, 1 H; CH), 6.90 (s, 1 H; CH), 6.55 (s, 1 H; CH), 6.12 (d, J = 10.18 Hz, 1 H; CH), 4.43 (d, J = 16.78 Hz, 1 H; CH₂), 3.90 (s, 3 H; CH₃), 3.86 (d, J = 16.90 Hz, 1 H; CH₂), 3.83 (s, 3 H; CH₃), 3.67 (dd, J = 5.77, 12.93 Hz, 1 H; CH), 3.58 (ddd, J = 3.85, 10.73, 13.76 Hz, 1 H; CH₂), 3.03 (ddd, J = 6.5, 9.0, 13.14 Hz, 1 H; CH₂), 2.71 (dd, J = 5.50, 16.78 Hz, 1 H; CH₂), 2.49 (dd, J = 13.21, 16.78 Hz, 1 H; CH₂), 2.40 (ddd, J = 3.85, 9.08, 12.65 Hz, 1 H; CH₂), 2.17 (ddd, J = 6.43, 10.58, 12.24 Hz, 1 H; CH₂) ppm. ¹³C NMR (CDCl₃, 100 MHz): $\delta = 197.4$, 148.8, 148.2, 147.9, 134.2, 129, 124.1, 110.1, 105.4, 68.7, 61.1, 56.2, 55.9, 53.8, 44.5, 44.3, 39.6 ppm. MS: m/z = 286.5 [M + H]⁺, 308.6 [M + Na]⁺, 324.6 [M + K]⁺.

Maritidine (1a) from Oxomaritidine (1e):^[39a] To a solution of 1e (0.066 g; 0.02 mmol) in anhydrous MeOH (0.7 mL) was added NaBH₄ (0.016 g, 0.05 mmol) and CeCl₃·7H₂O (0.172 g, 0.05 mmol) at r.t. After stirring for 45 min at the same temperature, the reaction mixture was filtered through Celite (elution with MeOH) and the solvents evaporated. The residue was extracted with CHCl₃ $(2 \times 5 \text{ mL})$ and the combined organic layers were washed with aqueous saturated NaHCO₃, dried with Na₂SO₄, evaporated and used directly for the further synthesis of maritidine. To a solution of the crude reaction mixture of epi-maritidine 1c (0.066 g, 0.02 mmol) in anhydrous CH₂Cl₂ (0.5 mL), was added MsCl $(12 \,\mu\text{L}, 0.11 \,\text{mmol})$ and Et₃N $(15 \,\mu\text{L}, 0.11 \,\text{mmol})$ at r.t. After stirring the reaction mixture for 1 h at r.t., the solvent was removed under reduced pressure and the residue was dissolved in DMF (0.5 mL) and transferred by using a syringe to a flask containing CsOAc (0.063 g, 0.33 mmol). The resulting greenish suspension was stirred at r.t. for 40 h then filtered (elution with EtOAc). The combined filtrates were dissolved in 1 N HCl and the aqueous solution was washed with Et_2O (2 × 5 mL). The aqueous phase was basified with saturated K₂CO₃ to pH 12 and then extracted with CH₂Cl₂ $(2 \times 10 \text{ mL})$. The combined organic layers were washed with water $(2 \times 5 \text{ mL})$, brine (5 mL), and dried using Na₂SO₄. Filtration, followed by solvent evaporation under reduced pressure gave the crude allylic acetate, which was immediately dissolved in anhydrous MeOH (0.5 mL) containing powdered K_2CO_3 (0.026 g)0.19 mmol). After stirring the reaction mixture for 2 h at r.t., the solvent was removed in vacuo. The residue was dissolved in CH2Cl2 (20 mL) and washed with saturated NaHCO₃ (5 mL). The combined organic layers were washed with water, brine, dried with anhydrous Na₂SO₄ and concentrated. Preparative thin layer chromatography of the reaction mixture (CH₂Cl₂/MeOH/Et₃N, 9:1:1) yielded 1a (0.03 g, 45% over 4 steps) as a white powder. $R_{\rm f}$ = 0.4 (CH₂Cl₂/MeOH/Et₃N, 90:10:10). IR (CHCl₃): \tilde{v}_{max} = 3406, 3019, 2956, 2925, 2853, 1610, 1514, 1464, 1311, 1262, 1133, 1092, 1039 cm⁻¹. ¹H NMR (CDCl₃, 400 MHz): δ = 6.85 (s, 1 H; CH), 6.65 (d, J = 9.9 Hz, 1 H; CH), 6.52 (s, 1 H; CH), 5.99 (dd, J = 9.8, 5 Hz, 1 H; CH), 4.46 (d, J = 16.3 Hz, 1 H; CH₂), 4.36 (m, 1 H; CH), 3.88 (s, 3 H; CH₃), 3.83 (d, J = 16.5 Hz, 1 H; CH₂), 3.82 (s, 3 H; CH₃), 3.5–3.40 (m, 2 H; H of CH and H of CH₂), 2.93 (m, 1 H; CH₂), 2.21 (m, 1 H; CH₂), 2.06 (m, 1 H; CH₂), 1.96 (m, 1 H; CH₂), 1.77 (m, 1 H) ppm. MS: $m/z = 288 [M + H]^+$.

N-{(6-Iodobenzo[d][1,3]dioxol-5-yl)methyl}-2-(2-methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)-N-[(trimethylsilyl)methyl]ethanamine (11b): To a stirring solution of 14b (7 g, 18.048 mmol) in anhydrous CH₃CN (54 mL), K₂CO₃ (12.47 g, 90.24 mmol) and the bissilylated (alkylamino)alkyl-substituted ketal 13 (5.189 g, 18.048 mmol) were added at r.t. The resultant suspension was heated to reflux for 8 h. On completion of the reaction, the mixture was cooled, filtered, and the solvent was evaporated under vacuum.



The resultant pasty mass was taken in EtOAc (150 mL) and washed with H₂O (2×50 mL), brine (2×40 mL), dried with Na₂SO₄, and concentrated under vacuum to obtain a red-brown mass, which was purified by column chromatography (PE/ethyl acetate, 97:3) to obtain 11b as a pale-yellow oil (6.44 g, 65%). $R_{\rm f} = 0.5$ (PE/EtOAc, 90:10). IR (CHCl₃): \tilde{v}_{max} = 3015, 2953, 1683, 1503, 1474, 1247, 1040, 935, 837, 757, 667 cm⁻¹. ¹H NMR (CDCl₃, 200 MHz): δ = 7.25 [s, 2 H; (CH)₂], 6.01 (ABq, J = 1.39, 5.06 Hz, 2 H; CH₂), 3.96-3.88 [m, 3 H; $(CH_2)_2$], 3.83 [dd, J = 3.66, 9.34 Hz, 1 H; $(CH_2)_2$], $3.59 (d, J = 15.66 Hz, 1 H; CH_2), 3.42 (d, J = 15.66 Hz, 1 H; CH_2),$ 2.41 (dd, J = 3.80, 7.20 Hz, 1 H; CH), 2.24 (d, J = 14.66 Hz, 1 H; CH_2), 2.23 (dd, J = 3.90, 14.78 Hz, 1 H; CH_2), 1.96 (d, J =14.65 Hz, 1 H; CH₂), 1.89 (dd, J = 7.20, 14.78 Hz, 1 H; CH₂), 1.36 (s, 3 H; CH₃), 0.16 [s, 9 H; (CH₃)₃], 0.09 [s, 9 H; (CH₃)₃] ppm. ¹³C NMR (CDCl₃, 50 MHz): *δ* = 148.3, 146.8, 135.9, 118, 110.1, 109.8, 101.3, 86.5, 64.3, 64.2, 64.1, 49.4, 44.3, 33.9, 24.3, -0.41, -0.95 ppm. MS: $m/z = 550.23 [M + H]^+$.

Methyl 2-[6-({[2-(2-Methyl-1,3-dioxolan-2-yl)-1-(trimethylsilyl)ethyl]-[(trimethylsilyl)methyl]amino}methyl)benzo[d][1,3]dioxol-5yl]acrylate (10b): A 100 mL two-necked round-bottomed flask was charged with LiCl (0.93 g, 21.85 mmol) and flame-dried under high vacuum. Upon cooling, [Pd(PPh₃)₄] (0.42 g, 0.36 mmol) and CuCl (1.80 g, 18.21 mmol) were added and the mixture was degassed (3-4 times) under high vacuum with an argon purge. Anhydrous DMSO (26 mL) was introduced with concomitant stirring, followed by sequential addition of **11b** (2 g, 3.64 mmol) and vinyl stannane compound 12 (1.639 g, 4.37 mmol), both diluted with DMSO (1 mL). The resulting mixture was rigorously degassed (4 times) by freeze-thaw cycles (-78 to 25 °C, Ar). The reaction mixture was stirred at r.t. for 1 h then heated at 60 °C for 2 h. Following completion of the coupling (reaction monitored by TLC), the reaction mixture was cooled, diluted with Et₂O (70 mL), and washed with a mixture of brine $(2 \times 40 \text{ mL})$ and 5% aqueous NH₄OH (100 mL). The aqueous layer was further extracted with ethyl acetate $(2 \times 100 \text{ mL})$, and the combined organic layers were washed with water $(2 \times 100 \text{ mL})$, brine $(2 \times 50 \text{ mL})$, dried with Na₂SO₄, and concentrated under reduced pressure. The reddishbrown residue was purified by column chromatography (PE/ethyl acetate, 90:10) to yield 10b (1.44 g, 73%) as a yellow viscous liquid. $R_{\rm f} = 0.3$ (PE/EtOAc, 80:20). IR (CHCl₃): $\tilde{v}_{\rm max} = 2951, 1723, 1679,$ 1622, 1503, 1480, 1375, 1247, 1105, 1041, 938, 837, 752, 667 $\rm cm^{-1}.$ ¹H NMR (CDCl₃, 400 MHz): δ = 7.25 (s, 1 H; CH), 6.59 (s, 1 H; CH), 6.47 (d, J = 1.50 Hz, 1 H; CH), 5.96 (ABq, J = 10.54 Hz, 2 H; CH₂), 5.64 (d, *J* = 1.75 Hz, 1 H; CH), 3.92–3.84 [m, 4 H; $(CH_2)_2$], 3.73 (s, 3 H; CH₃), 3.34 (d, J = 14.80 Hz, 1 H; CH₂), 3.30 $(d, J = 14.80 \text{ Hz}, 1 \text{ H}; \text{CH}_2), 2.37 (dd, J = 4.02, 7.53 \text{ Hz}, 1 \text{ H}; \text{CH}),$ 2.11 (d, J = 14.81 Hz, 1 H; CH₂), 2.03 (dd, J = 4.02, 14.56 Hz, 1 H; CH₂), 1.84 (d, J = 14.56 Hz, 1 H; CH₂), 1.72 (dd, J = 7.52, 14.56 Hz, 1 H; CH₂), 1.26 (s, 3 H; CH₃), 0.08 [s, 9 H; (CH₃)₃], 0.03 [s, 9 H; (CH₃)₃] ppm. ¹³C NMR (CDCl₃, 100 MHz): δ = 167, 147.6, 145.4, 140.9, 133, 129.2, 128.7, 110, 109.6, 108.6, 100.9, 64.2, 64, 56.2, 52.2, 49.1, 43.8, 33.7, 24.1, -0.3, -0.9 ppm. HRMS (EI): calcd. for C₂₅H₄₁NO₆Si₂: 507.2472; found 507.2466.

Synthesis of 8b from 10b: A solution of 10b (1.5 g, 2.957 mmol) in anhydrous CH_2Cl_2 (20 mL) was introduced dropwise over a period of 1 h into an argon-flushed 500 mL two-necked flask containing flame-dried AgF (1.876 g, 14.78 mmol) in anhydrous CH_2Cl_2 (200 mL). The color of the reaction mixture gradually turned to dark-brown with concomitant deposition of silver on the inner surface of the flask in the form of a mirror. The progress of the reaction was monitored periodically by TLC. After completion, the reaction mixture was filtered through a small plug of basic alumina

(eluent MeOH) and the solvent was evaporated to obtain a crude brown residue, which was purified by silica gel chromatography (PE/ethyl acetate, 45:55) to obtain **8b** (0.587 g, 56%) as yellow gummy liquid. $R_{\rm f} = 0.3$ (PE/EtOAc, 10:90). IR (CHCl₃): $\tilde{v}_{\rm max} =$ 2956, 1730, 1671, 1504, 1483, 1437, 1246, 1119, 1039, 935, 753, 722 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): δ = 6.46 (s, 1 H; CH), 6.29 (s, 1 H; CH), 5.87 (ABq, J = 6.12 Hz, 2 H; CH₂), 4.36 (d, J =16.87 Hz, 1 H; CH₂), 3.97-3.91 [m, 4 H; (CH₂)₂], 3.89-3.85 (m, 1 H; CH₂), 3.77 (s, 3 H; CH₃), 3.54 (br. d, J = 8.80 Hz, 1 H; CH), 3.35 (m, 1 H; CH₂), 2.76 (m, 1 H; CH₂), 2.48 (m, 1 H; CH₂), 2.11 (m, 1 H; CH₂), 1.66 (dd, J = 9.78, 14.43 Hz, 1 H; CH₂), 1.55 (dd, $J = 2.20, 14.42 \text{ Hz}, 1 \text{ H}; \text{ CH}_2), 1.42 \text{ (s, 3 H; CH}_3) \text{ ppm}.$ ¹³C NMR $(CDCl_3, 125 \text{ MHz}): \delta = 174.1, 146.7, 146.1, 135.2, 124.8, 109.5,$ 106.3, 105.1, 100.9, 66.2, 64.6, 64.3, 61.6, 57.8, 52.0, 50.8, 38.2, 38.0, 23.8 ppm. HRMS (EI): calcd. for C₁₉H₂₃NO₆: 361.1525; found 361.1552.

Reduction of 8b to 22b: To a suspension of LAH (0.126 g, 3.322 mmol) and anhydrous THF (9 mL) in a 25 mL two-necked round-bottomed flask equipped with magnetic stirring bar and an argon balloon system at 0 °C, was added dropwise by using a cannula, a solution of 8b (0.6 g, 1.661 mmol) dissolved in anhydrous THF (1 mL) over a period of 2 min. The reaction mixture was warmed to r.t. and stirred for 24 h. After completion of the reaction, the suspension was cooled to 0 °C and quenched by dropwise addition of 1 N NaOH, then stirred at r.t. for 2 h. The whole mass was dissolved in CH₂Cl₂ (25 mL) and washed with water. The aqueous layer was then partitioned with CH_2Cl_2 (2×25 mL), and the combined organic layer was shaken with brine and dried with Na₂SO₄. The solvent was removed in vacuo to obtain a gummy mass, which was purified by column chromatography (CH₂Cl₂/ MeOH, 85:15) to afford **22b** as a yellow gummy liquid (0.5 g, 90%). $R_{\rm f} = 0.3$ (CH₂Cl₂/MeOH, 80:20). IR (CHCl₃): $\tilde{v}_{\rm max} = 3455$ (br), 3016, 2957, 1622, 1505, 1480, 1378, 1238, 1143, 1041, 939, 857, 667 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): δ = 6.90 (s, 1 H; CH), 6.45 (s, 1 H; CH), 5.88 (ABq, J = 0.91, 15.56 Hz, 2 H; CH₂), 4.43 (d, J = 16.78 Hz, 1 H; CH₂), 4.30 (d, J = 13.13 Hz, 1 H; CH₂), 3.97 [s, 4 H; (CH₂)₂], 3.86 (d, J = 13.13 Hz, 1 H; CH₂), 3.81 (d, J = 16.78 Hz, 1 H; CH₂), 3.34 (t, J = 4.27 Hz, 1 H; CH), 3.28 (br. d, J = 3.97, 10.98, 16.48 Hz, 1 H; CH₂), 2.88 (br. d, J = 6.72, 8.55, 14.35 Hz, 1 H; CH₂), 2.07 (dd, J = 4.89, 14.96 Hz, 1 H; CH₂), 1.86 (dd, J = 3.97, 14.96 Hz, 1 H; CH₂), 1.79 (ddd, J = 3.97, 8.85, 12.51 Hz, 1 H; CH₂), 1.67 (ddd, J = 6.24, 10.65, 12.32 Hz, 1 H; CH₂), 1.39 (s, 3 H, CH₃) ppm. ¹³C NMR (CDCl₃, 125 MHz): δ = 146.5, 146.1, 136.5, 126.1, 109.9, 106.4, 104.1, 100.7, 64.4, 64.3, 63.5, 61.46, 61.44, 51.4, 50.7, 38.4, 37.9, 23.4 ppm. HRMS (EI): calcd. for C₁₈H₂₃NO₅: 333.1576; found 333.1556.

Swern Oxidation of 22b to 23b: To a mixture of DMSO (0.21 mL, 3 mmol) in CH₂Cl₂ (3 mL), oxalyl chloride (0.25 mL, 3 mmol) was added dropwise at -78 °C, and the resulting mixture was stirred for 15 min. A solution of alcohol 22b (0.5 g, 1.5 mmol) in CH₂Cl₂ (1.5 mL) was added dropwise to the reaction flask at -78 °C. The mixture was stirred for 1 h, triethylamine (1.04 mL, 7.5 mmol) was added dropwise, and the resultant mixture was gradually warmed to r.t. over 1 h by removing the cooling bath and the mixture was stirred for another 1 h. The reaction mixture was quenched with water (5 mL) and extracted with CH_2Cl_2 (2 × 25 mL), and the combined organic layer was washed with brine, dried with Na₂SO₄, filtered, and concentrated under vacuum. Purification of the residue by silica gel column chromatography (CH₂Cl₂/MeOH, 94:6) afforded the aldehyde **23b** (0.447 g, 90%) as a gummy liquid. $R_{\rm f}$ = 0.4 (CH₂Cl₂/MeOH, 90:10). IR (CHCl₃): ṽ_{max} = 2927, 1713, 1672, 1504, 1484, 1379, 1239, 1091, 1039, 936, 857, 755 cm⁻¹. 1 H NMR $(CDCl_3, 400 \text{ MHz}): \delta = 9.86 \text{ (s, 1 H; CH)}, 6.56 \text{ (s, 1 H; CH)}, 6.30$

(s, 1 H; CH), 5.91 (s, 2 H; CH₂), 4.46 (d, J = 17.06 Hz, 1 H; CH₂), 3.95–3.87 [m, 4 H; (CH₂)₂], 3.83 (d, J = 16.81 Hz, 1 H; CH₂), 3.59 (br. t, J = 5.27 Hz, 1 H; CH), 3.38 (ddd, J = 3.52, 10.80, 13.56 Hz, 1 H; CH₂), 2.83 (five-lines pattern, J = 8.04, 14.81 Hz, 1 H; CH₂), 2.54 (ddd, J = 6.52, 10.54, 12.29 Hz, 1 H; CH₂), 1.87 (seven-lines pattern, J = 3.27, 8.79, 12.30 Hz, 1 H; CH₂), 1.74 (dd, J = 6.53, 14.81 Hz, 1 H; CH₂), 1.62 (dd, J = 4.02, 14.81 Hz, 1 H; CH₂), 1.37 (s, 3 H; CH₃) ppm. ¹³C NMR (CDCl₃, 100 MHz): $\delta = 201.4$, 147.1, 146.4, 133, 125, 109.2, 107.1, 105.4, 101, 64.59, 64.56, 64.4, 61.7, 61.5, 51.3, 39.1, 34.7, 24 ppm. HRMS (EI): calcd. for C₁₈H₂₁NO₅: 331.1420; found 331.1403.

Synthesis of Oxo-crinine (1f) from 23b: To a solution of 19b (0.020 g, 0.06 mmol) in acetone (0.18 mL), pTSA (0.023 g, 0.12 mmol) was added at r.t., and the reaction mixture was stirred for 3 h. Progress of the reaction was monitored by TLC. On completion of reaction, the solvent was evaporated under vacuum and the residue was dissolved in CH2Cl2 (25 mL) and washed with saturated NaHCO₃ (2×10 mL), brine (2×5 mL), dried with Na₂SO₄, and concentrated under vacuum to obtain a crude mass, which was used in the next step without any purification. To a stirred solution of the crude reaction mixture of δ keto aldehyde (0.014 g, 0.05 mmol) in EtOH (2.1 mL) at r.t. was added solid NaOH (0.012 g, 0.292 mmol) and the resulting mixture was stirred for 20 h. The reaction mixture was concentrated and the residue was dissolved in CH₂Cl₂ (20 mL), washed with water (5 mL), brine $(2 \times 5 \text{ mL})$, dried with anhydrous Na₂SO₄, filtered, and concentrated. Purification of the residue by flash column chromatography (CH₂Cl₂/MeOH, 95:5) afforded 1f as a white powder (0.011 g, 65%) over two steps). $R_{\rm f} = 0.5$ (CH₂Cl₂/MeOH, 85:15). IR (CHCl₃): $\tilde{v}_{\rm max}$ = 3014, 2926, 1708, 1681, 1504, 1483, 1398, 1315, 1247, 1159, 1109, 1039, 1001, 935, 854, 754, 667 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): δ = 7.61 (d, J = 10.37 Hz, 1 H; CH), 6.90 (s, 1 H; CH), 6.51 (s, 1 H; CH), 6.09 (d, J = 10.4 Hz, 1 H; CH), 5.92 (ABq, 2 H; CH₂), 4.41 (d, J = 16.79 Hz, 1 H; CH₂), 3.81 (d, J = 16.79 Hz, 1 H; CH₂), 3.64 (dd, J = 5.8, 13.12 Hz, 1 H; CH), 3.54 (ddd, J = 3.97, 10.38,13.74 Hz, 1 H; CH₂), 3.00 (ddd, J = 6.10, 8.85, 14.65 Hz, 1 H; CH_2), 2.70 (dd, J = 5.80, 16.79 Hz, 1 H; CH_2), 2.47 (dd, J = 13.13, 16.79 Hz, 1 H; CH₂), 2.37 (ddd, J = 3.97, 8.8, 12.82 Hz, 1 H; CH₂), 2.17 (ddd, J = 6.10, 10.38, 12.20 Hz, 1 H; CH₂) ppm. ¹³C NMR $(CDCl_3, 125 \text{ MHz}): \delta = 198, 149.4, 146.5, 146.3, 135.9, 128.8,$ 126.2, 107.2, 102.5, 101, 68.8, 61.7, 54, 44.76, 44.7, 40 ppm. HRMS (EI): calcd. for C₁₆H₁₅NO₃: 269.1052; found 269.1073.

Synthesis of epi-Crinine (1d) from 1f: To a solution of 1f (0.010 g, 0.037 mmol) in anhydrous MeOH (1 mL) was added NaBH₄ (0.026 g, 0.074 mmol) and CeCl₃·7H₂O (0.028 g, 0.074 mmol) at r.t. After stirring for 45 min at same temperature, the reaction mixture was filtered through Celite (elution with MeOH) and the solvents evaporated. The residue was extracted with $CHCl_3$ (2 × 25 mL) and the combined organic layers were washed with aqueous saturated NaHCO₃, dried with Na₂SO₄ and the solvents evaporated in vacuo to obtain a gummy mass, which was purified by column chromatography (CH₂Cl₂/MeOH, 85:15) to afford 1d as a yellow gummy liquid (9 mg, 90%). $R_{\rm f} = 0.3$ (CH₂Cl₂/MeOH, 80:20). IR (CHCl₃): $\tilde{v}_{max} = 3142$ (br), 3018, 2926, 1506, 1483, 1365, 1317, 1232, 1091, 1039, 1001, 935, 862, 754, 667 cm $^{-1}$. $^1\mathrm{H}$ NMR (CDCl_3, 500 MHz): δ = 6.80 (s, 1 H; CH), 6.48 (s, 1 H; CH), 6.39 (dd, J = 2.13, 10.37 Hz, 1 H; CH), 5.89 (ABq, 2 H; CH₂), 5.79 (d, J =10.37 Hz, 1 H; CH), 4.45 (d, J = 16.48 Hz, 1 H; CH₂), 4.4 (m, 1 H; CH), 3.83 (d, J = 16.78 Hz, 1 H; CH₂), 3.50 (ddd, J = 4.23, 10.30, 13.62 Hz, 1 H: CH₂), 3.29 (dd, J = 3.66, 13.42 Hz, 1 H; CH_2), 2.95 (ddd, J = 6.10, 9.15, 15.45 Hz, 1 H; CH_2), 2.25–2.08 (m, 3 H; CH₂ and H of CH), 1.64 (four-lines pattern, J = 11.90 Hz, 1 H; CH₂) ppm. ¹³C NMR (CDCl₃, 125 MHz): δ = 146.3, 145.9,

138.2, 131.5, 128.5, 125.2, 106.9, 102.8, 100.8, 67.5, 66.7, 61.8, 53.1, 44.7, 44.4, 34.6 ppm. MS: *m*/*z* = 272.2 [M + H]⁺.

Synthesis of Crinine (1b) from epi-Crinine (1d): To a solution of epicrinine 1d (0.090 g, 0.033 mmol) in anhydrous CH₂Cl₂ (0.75 mL) was added MsCl ($20 \,\mu$ L, $0.172 \,mmol$) and Et₃N ($23 \,\mu$ L, 0.172 mmol) at r.t. After stirring the reaction mixture for 1 h at r.t., the solvent was removed under reduced pressure and the residue was dissolved in DMF (0.75 mL) and transferred by using a syringe to a flask containing CsOAc (0.100 g, 0.518 mmol). The resulting greenish suspension was stirred at r.t. for 40 h then filtered (elution with EtOAc). The combined filtrates were dissolved in 1 N HCl (5 mL) and the aqueous solution was washed with Et_2O (2 × 5 mL). The aqueous phase was basified with saturated aqueous K₂CO₃ to pH 12 and then extracted with CH_2Cl_2 (2×10 mL). The combined organic layers were washed with water $(2 \times 5 \text{ mL})$, brine (5 mL), and dried using Na₂SO₄. Filtration, followed by solvent evaporation under reduced pressure gave the crude allylic acetate, which was immediately dissolved in anhydrous MeOH (0.75 mL) containing powdered K₂CO₃ (0.041 g, 0.297 mmol). After stirring the reaction mixture for 2 h at r.t., the solvent was removed in vacuo. The residue was dissolved in CH2Cl2 (20 mL) and washed with saturated NaHCO₃ (5 mL). The combined organic layers were washed with water, brine, dried with anhydrous Na₂SO₄, and concentrated. Preparative thin layer chromatography of the reaction mixture (CH₂Cl₂/MeOH/Et₃N, 9:1:1) yielded **1b** (4.5 mg, 50% over 3 steps) as a white powder. $R_{\rm f} = 0.4$ (CH₂Cl₂/MeOH/Et₃N, 90:10:10). IR (CHCl₃): $\tilde{v}_{max} = 3325$ (br), 2926, 1504, 1484, 1317, 1234, 1039, 757 cm⁻¹. ¹H NMR (CDCl₃, 500 MHz): $\delta = 6.78$ (s, 1 H; CH), 6.55 (d, J = 10.07 Hz, 1 H; CH), 6.47 (s, 1 H; CH), 5.98 (dd, J = 4.88),10.07 Hz, 1 H; CH), 5.89 (ABq, 2 H; CH₂), 4.49 (d, J = 16.48 Hz, 1 H; CH₂), 4.36 (m, 1 H; CH), 3.83 (d, J = 16.48 Hz, 1 H; CH₂), 3.47-3.44 (m, 2 H; H of CH and H of CH₂), 2.91 (ddd, J = 6.41, 8.85, 13.43 Hz, 1 H; CH₂), 2.18 (ddd, J = 3.96, 8.85, 12.82 Hz, 1 H; CH₂), 1.97–1.94 (m, 2 H; H of CH₂ and H of CH₂), 1.75 (ddd, J = 3.97, 13.74 Hz, 1 H; CH₂) ppm. ¹³C NMR (CDCl₃, 75 MHz): $\delta = 146.3, 145.9, 138.2, 132.1, 131.4, 128.6, 127.6, 107, 102.9, 100.8,$ 63.7, 63, 61.8, 53.1, 44.48, 44.42, 32.1 ppm. MS: m/z = 272.2 [M + $H]^+.$

Supporting Information (see also the footnote on the first page of this article): Copies of the ¹H and ¹³C NMR spectra for compounds **11a**, **10a**, **8a**, **22a**, **21**, **23a**, **1e**, **1a**, **11b**, **10b**, **8b**, **22b**, **23b**, **1f**, **1d**, **1b** and a Table for comparison of NMR spectroscopic data for compounds **1a** and **1b** with the literature.

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