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Article

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Diversity-Oriented Approach Towards the Syntheses of *Amaryllidaceae* Alkaloids *via* a Common Chiral Synthon

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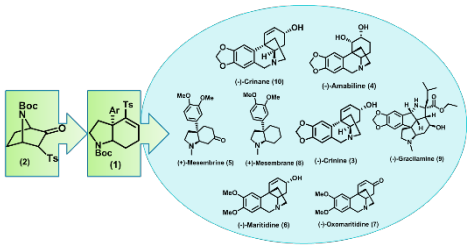
KEYWORDS: Amaryllidaceae alkaloids, natural product synthesis, all carbon quaternary stereocenter, conjugate addition.

ABSTRACT: Functionalized hydroindole (**1**), a common chiral synthon, for versatile transformations to synthesize broad range of *Amaryllidaceae* alkaloids (AA) including (-)-crinine, (-)-crinane, (-)-amabiline, (+)-mesembrine, (-)-maritidine, (-)-oxomaritidine and (+)-mesembrane is reported. Scaffold **1** is found as a prime structural motif in a wide variety of the AA's and is a novel synthon towards designing a divergent route for the synthesis of these natural products. This is established in a few steps, starting from a chiral aza-bicycloheptene sulfone scaffold (**2**) via conjugate addition and concomitant stereoselective ring opening with allylmagnesium bromide, a key step that generates a crucial quaternary stereocenter, fixing the stereochemistry of the rest of the molecule at an early stage. One carbon truncation followed by intramolecular reductive amination led to the desired core **1** in multi-gram scale.



Introduction

The potential of alkaloids, in general, could be understood by the fact that over one-third (35.9%) of the alkaloids which have been examined biologically are pharmaceutically significant.[1] Many plants rich in alkaloids, are highly valued as these are the sources of bioactive constituents that exist in trace amounts and are hard to obtain for its commercial application.[2] *Amaryllidaceae* alkaloids (AA) are a class of structurally diverse and biologically active natural products with distinctly important pharmacological activities exhibited by its constituent members[3] such as anticancer, acetylcholinesterase (AChE) inhibitory activity, anti-malarial, antimicrobials, antidepressants.[4] Hydrobromide salt of galantamine, an *Amaryllidaceae* alkaloid marketed as *Reminyl* is a potent drug for the treatment of mild to moderately severe dementia of the Alzheimer type, which produces beneficial effects even after the drug treatment has been withdrawn.[5] In the past few decades, *Amaryllidaceae* alkaloids have attracted remarkable attention from the synthetic community, and extensive efforts have been made towards the total and formal syntheses of these classes of fascinating molecules.[6-8] Although a large number of synthetic approaches have been reported, a unified and divergent stereospecific approach with viability on a gram scale synthesis still represents an attractive goal. Therefore, while planning a conceptually new synthetic route, we envisioned a common chiral synthon that could be transformed into array of desired natural products of the *Amaryllidaceae* family. The evolution of scalable synthetic route to chiral hydroindole core, embedded in the structure of numerous *Amaryllidaceae* alkaloids, would render an opportunity to access these natural products in adequate amount enabling to explore their pharmacological properties.

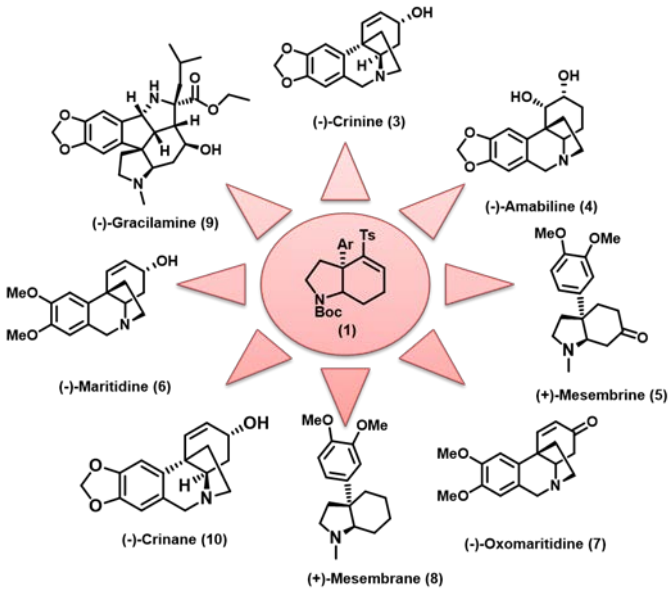


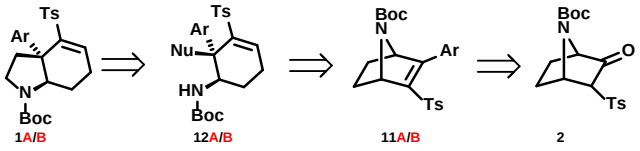
Figure 1 *Amaryllidaceae* alkaloids with the hydroindole core.

In previous literature reports, dearomatization using inter- / intra-molecular phenolic oxidative coupling of derived phenols followed by aza-Michael addition reactions, have been the vastly exploited approach to build these natural products.[9]

The quaternary stereocenter with an aromatic substituent present on the ring junction is the characteristic feature common to all the targeted AA with the hydroindole core.[7b,10] Reports on the enantioselective building of the quaternary center usually involves either enantioselective intramolecular desymmetrization[9b,11], asymmetric alkylations, enantioselective Michael addition or metal catalyzed asymmetric cross coupling reactions.[11–13] Some linear lengthy approaches towards the total syntheses for mentioned AA's (Fig. 1) are also present; they are target-oriented[14–15] with little emphasis on the preparation of diverse molecular skeletons from a common intermediate.[10f,13e,16] Herein, we report an efficient unified strategy towards the scalable, asymmetric synthesis of numerous AA with the hydroindole core and 5,10*b* ethanophenanthridine skeleton.

Results and discussion

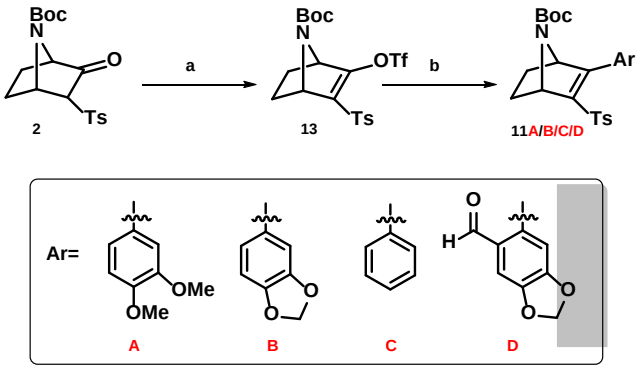
Based upon our previous experiences of building natural products utilizing the chiral ketone scaffold **2**[17]**,** we sought to exploit it to design a retrosynthetic route to common divergent intermediate **1** which is outlined in Scheme 1. We planned to build the requisite hydroindole moiety from selective ring opening of aryl substituted sterically congested 7-azabicyclo heptenesulfone followed by an intramolecular amination reaction. The strained bicyclic framework plays an interesting role in controlling the stereoselectivity by allowing the nucleophile to attack only from the *exo*- face while blocking the *endo*-face.[17] This reaction serves as a boon for the synthetic design as it fixes the stereochemistry of the crucial quaternary center in the early stages of the synthesis. Furthermore, the stereochemistry of the quaternary center serves as the handle for the rest of the stereocenters present in the molecular framework. Potentially general Suzuki conditions were screened and developed that facilitated the installation of different aromatic fragment merely by changing the boronic acids so that natural products with variable aromatic fragments at the hydroindole ring junction could be targeted at the same time.



Scheme 1 Retrosynthetic plan for the chiral common synthon.

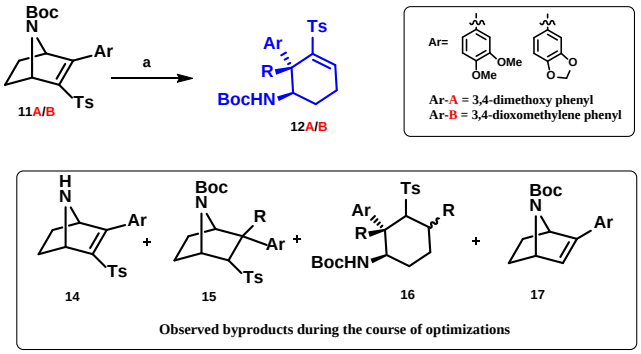
Synthesis of Common Chiral Synthon (1)

Our studies commenced from the preparation of both enantiomers of the chiral scaffold **2**, which is available in 6 steps starting from TMS acetylene in 100 g scale *via* the strategy of desymmetrization developed in our laboratory.[18] The Suzuki coupling[19] of the enol triflate of the 7-aza-bicyclic heptenesulfone **2** was a strenuous task to be accomplished. The challenges were due to i) the instability of the enol triflate ii) the tosyl group present in the substrate acts as a poison to the palladium catalyst resulting in its low catalysis efficiency[20]. Upon screening several bases and reaction conditions, to our surprise the reaction proceeded magnificently with silver carbonate as a base and acetonitrile as a solvent. The enol triflate **13** was prepared and used immediately for further carrying out the coupling reaction. Having optimized conditions in hand, the reaction was carried out with several boronic acids (3,4- dimethoxy phenyl boronic acid, 3,4-Methylenedioxy phenyl boronic acid, 3-Formylphenyl boronic acid and phenyl boronic acid) using 5 mol% $Pd(OAc)_2$, 10 mol% $(o\text{-}Tol)_3P$, 2 equiv. Ag_2CO_3, CH_3CN, at 80 °C affording aryl-substituted-7-aza-bicyclic heptenesulfone in excellent yield (Scheme 2).



Scheme 2 Installation of desired aromatic fragment. a) NaH, Tf_2O, Et_2O, 0 °C b) $ArB(OH)_2$, $Pd(OAc)_2$, $P(o\text{-}tol)_3$, Ag_2CO_3, CH_3CN, 80 °C, 66% (2 steps)

The crucial conjugate addition and simultaneous ring opening by a nucleophile at trisubstituted electrophilic center on a structurally rigid bicyclic framework was yet another major goal to be achieved (Scheme 3).[21] Our primary aim was to construct fused pyrolidine ring system with an aromatic substituent on the ring junction. Therefore, we chose vinylmagnesium bromide at first as a nucleophile for the conjugate addition.



Scheme 3 Preparation of 12A/B a) AllylMgBr, NHC-3 (1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride), $Cu(OTf)_2$, Et_2O, -7 °C, 95%. R = Allyl.

Several reaction conditions in the initial phases of optimization (Table 1), by varying catalyst, solvents at several different temperatures, unfortunately gave decomposition products (**14-17**) or recovery of the starting material.

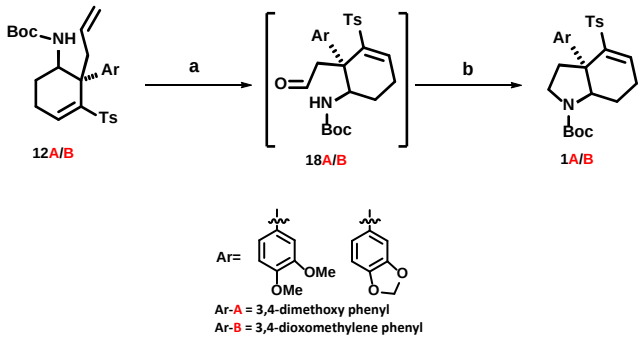
Later in a trial attempt with methylmagnesium bromide and copper triflate, we observed ring opening with a series of by-products forming simultaneously exacerbating the difficulties. Nevertheless, this was a major clue that encouraged us to optimize the reaction condition and we changed nucleophile to allyl magnesium bromide and did thorough screening of several catalyst-solvent systems.

After optimized conditions in hand using allylmagnesium bromide (1.5 equiv.) in the presence of copper triflate (0.3%), NHC-3 (1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride), 0.5%) in diethyl ether at -7 °C afforded **12 A** and **12 B** in 95% yield. The reaction was optimized up to the scale of 15.0 grams that enabled us to make these alkaloids on gram scale.

S/no.	Substrate	Nucleophile source	Catalytic system, solvent	T (°C)	Time (min)	Isolated Yield (%)
1.	11C	Vinyl MgBr	THF	-10 °C–rt	120	Trace
2.	11C	Vinyl MgBr	$CuBr_2$.DMS, Et_2O	-10 °C–rt	120	No
3.	11C	Divinyl Zinc	THF	-10 °C–rt	120	Trace
4.	11C	Divinyl Zinc	$CuBr_2$.DMS, Et_2O	-10 °C–rt	30	No
5.	11C	TBSOEtMgBr	$CuBr_2$.DMS, Et_2O	-10 °C–rt	120	Trace
6.	11C	TBSOEtBr, nBuLi	CuI, THF	-10 °C–rt	120	No
7.	11A	MeMgBr	THF	-10 °C–rt	120	No
8.	11A	MeMgBr	CuI, THF	-10 °C–rt	120	No
9.	11A	MeMgBr	CuCl, Et_2O	-10 °C–rt	120	Trace
10.	11A	MeMgBr	$CuBr_2$.DMS, Et_2O	-10 °C–rt	120	35
11.	11A	MeMgBr	$CuBr_2$.DMS, Et_2O	-7 °C –rt	30	60
12.	11B	Allyl MgBr	$Cu(OTf)_2$, NHC-1, Et_2O	-7 °C	30	40
13.	11B	Allyl MgBr	$Cu(OTf)_2$, NHC-1, Et_2O	-7 °C	10	75
14.	11B	Allyl MgBr	$Cu(OTf)_2$, NHC-2, Et_2O	-7 °C	10	72
15.	11B	Allyl MgBr	$Cu(OTf)_2$, NHC-3, Et_2O	-7 °C	10	80
16.	**11B**	**Allyl MgBr**	**$Cu(OTf)_2$, NHC-3, Et_2O/CH_2Cl_2**	**-7 °C**	**10**	**95**
17.	**11A**	**Allyl MgBr**	**$Cu(OTf)_2$, NHC-3, Et_2O/CH_2Cl_2**	**-7 °C**	**10**	**95**

Table 1 Optimization table for the ring opening reaction.

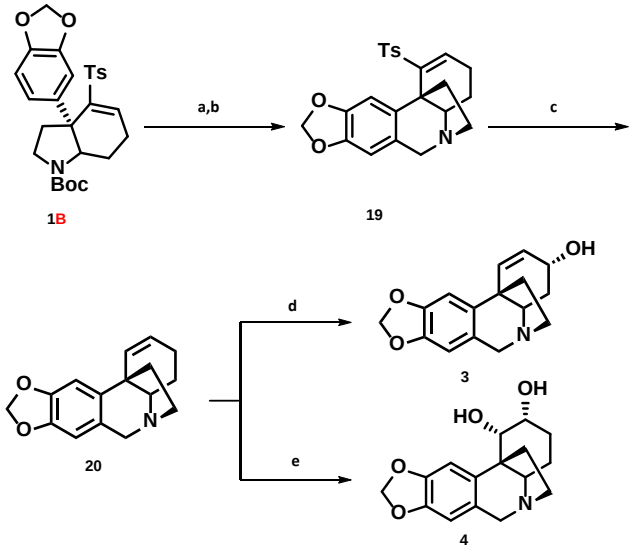
The *exo*-attack of the nucleophile to α, β-unsaturated double bond of the rigid 7-azabicyclic system guaranteed stereoselectivity and the formation of the undesired isomer was not at all observed during the course of reaction. Time played an important role in controlling this reaction. For example, if the reaction was allowed to stir for more than 10 minutes, it led to the formation of many undesired products including the di allylated one (**16**). Further transformations of **12 A/B** to **1 A/B** involved oxidative cleavage of one carbon of the olefinic moiety, using OsO_4/ $NaIO_4$ followed by the reductive amination under acidic conditions using sodium cyanoborohydride, which gave desired hydroindole core in 71% yields as shown in Scheme 4. These chiral common synthons were successfully exploited towards the synthesis of various AA, testifying the robustness of our designed synthetic plan on a multigram scale.



Scheme 4 Preparation of a common chiral synthon 1A/B a) OsO_4, $NaIO_4$, Acetone:Water (1:1) then $NaCNBH_3$, THF:AcOH (9:1), 25 °C, 71%.

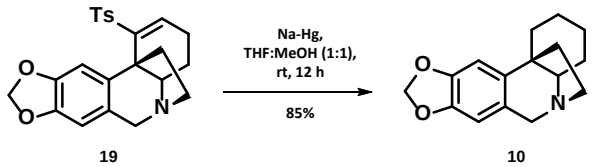
Total Synthesis of (-)-Crinine, (-)-Crinane and (-)-Amabiline from 1B

The bicyclic core **1B** synthesized from **(-)-2** represents a versatile precursor for many of the *Amaryllidaceae* alkaloids including, the structurally complex dinitrogenous pentacyclic cage like alkaloid (-)-gracilamine which was synthesized in 6 steps from this advanced intermediate.[17] Alkaloids (-)-crinine (**3**) and (-)-amabiline (**4**) were synthesized from **1B** *via N*-Boc deprotection followed by Pictet-Spengler type cyclization using formic acid and paraformaldehyde, obtaining **19** in high yield (95%).[22] The detosylation of **19** with sodium amalgam led to the formation of **20**, which on allylic oxidation with SeO_2[23] gave **(-)-3** in 80% yield. The dihydroxylation of the same using OsO_4 and NMO gave **(-)-4** (76%). These exceedingly simple conditions effectively helped us to accomplish the task of synthesizing these two natural products in respectable yields (Scheme 5).



Scheme 5 Total synthesis of (-)-crinine (**3**) and (-)-amabiline (**4**) (a) TFA, CH_2Cl_2, 0 °C, 6 h; (b) $(HCHO)_n$, TFA, reflux, 95% (2 steps); (c) Na-Hg, $B(OH)_3$, THF:MeOH (1:1), rt, 2 h 84%; (d) SeO_2, $NaHCO_3$, Dioxane, 102 °C, 16 h, 80%; (e) OsO_4, NMO, Acetone: H_2O (9:1), 6 h, 76%. TFA = Trifluoroacetic acid, NMO = N-Methyl morpholine N-Oxide.

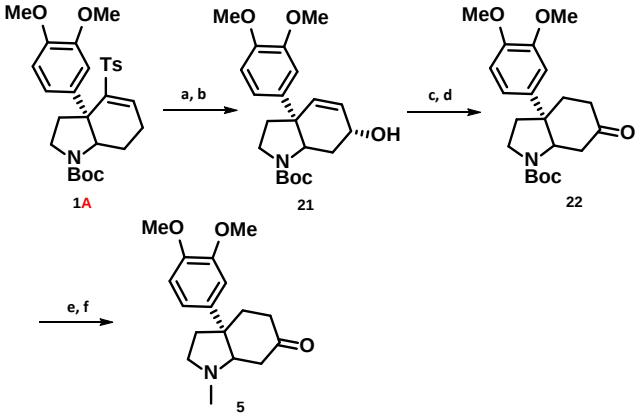
With **19** in hand, the synthesis of (-)-crinane (**10**) became extremely effortless (Scheme 6) where the advance intermediate **19** was subjected to detosylation with excess sodium amalgam, which removed the tosyl group and simultaneously led to reduction of the double bond quantitatively and yielded **(-)-10** (85%).



Scheme 6 Total synthesis of (-)-crinane (**10**) a) Na-Hg, THF:MeOH (1:1), rt, 12 h 85%.

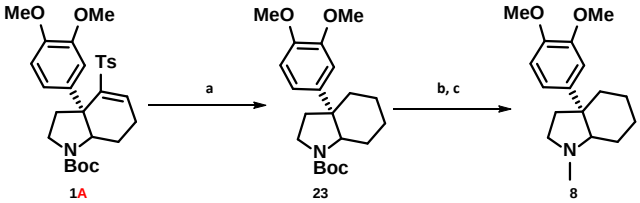
Synthesis of (+)-Mesembrine and (+)-Mesembrane

In an initial demonstration of the utility of **1A** prepared from the chiral ketone scaffold **2**, we attempted the total synthesis of (+)-mesembrine and (+)-mesembrane. Thus, we started the synthesis from detosylation of "synthon" **1A** followed by allylic oxidation with selenium dioxide, which gave intermediate **21** (80% over two steps). We attempted to reduce the olefinic double bond in **21** by subjecting it to Pd-C hydrogenation, which unfortunately removed the hydroxyl group. Therefore, an alternative strategy using Raney-Nickel for hydrogenation, resulted in clean hydrogenation product, which on DMP oxidation furnished **22** (85% over two steps).[24] The only task remained to accomplish the synthesis was the introduction of the *N*-methyl group in the molecular framework. The *N*-Boc deprotection and *N*-methylation using a formalin solution and sodium cyanoborohydride in acetonitrile, maintaining the high dilution, gave (+)-mesembrine in 80% yield over two steps as outlined in Scheme 7.



Scheme 7 Total synthesis of (+)-Mesembrine (**5**). (a) Na-Hg, $B(OH)_3$, THF:MeOH (1:1), rt, 2 h; (b) SeO_2, $NaHCO_3$, Dioxane, 102 °C, 16 h, 80% (2 steps); (c) Raney Ni, H_2, EtOH 65 °C 2 h. (d) DMP CH_2Cl_2, 0 °C, 1 h, 85% (2 steps); (e) TFA, CH_2Cl_2, 0 °C, 8 h; (f) HCHO (35%) w/w aq. sol. $NaCNBH_3$, 25 °C, 10 min., 80% (2 steps). TFA = Trifluoroacetic acid DMP = Dess-Martin periodinane.

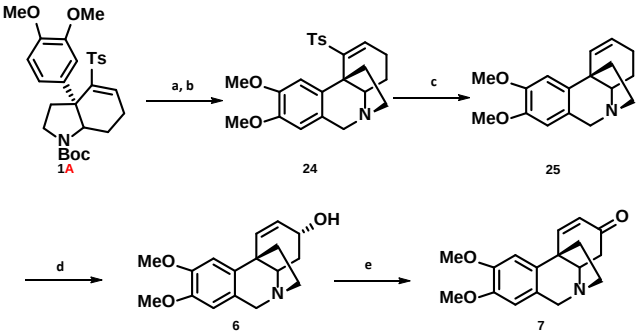
To complete the synthesis of (+)-mesembrane (**8**), **1A** was subjected to desulfonylation using excess of sodium amalgam without boric acid which simultaneously reduced the double bond *via* Boveault Blanc type reduction[25] to furnish **23** in 85% yield. Similar protocol for *N*-methylation were followed as in the case of mesembrine to yield **8** in excellent yields (Scheme 8).



Scheme 8 Total synthesis of (+)-Mesembrane (**8**) (a) Na-Hg, THF:MeOH (1:1), rt, 12 h 85%; (b) TFA, CH_2Cl_2, 0 °C, 8 h; (c) HCHO (35%) w/w aq. sol. $NaCNBH_3$, 25 °C, 10 min., 85% (2 steps). TFA = Trifluoroacetic acid.

Synthesis of (-)-Maritidine and (-)-Oxomaritidine from 1A

To begin with the synthesis of (-)-maritidine (**6**), advance intermediate **1A** was subjected to *N*-Boc deprotection using TFA followed by Pictet Spengler type cyclization resulting in the formation of required 5,10*b* ethanophenanthridine skeleton **24** in excellent yields (86%). Detosylation using sodium amalgam yielded **25,** which on allylic oxidation with selenium dioxide accomplished the synthesis of (-)-maritidine (Scheme 9). The allylic alcohol in **(-)-6** was oxidised using DMP to obtain (-)-oxomaritidine (7) in respectable yield (98%).



Scheme 9 Total synthesis of (-)-maritidine (**6**) and (-)-oxomaritidine (**7**) (a) TFA, CH_2Cl_2, 0 °C, 6 h; (b) (HCHO)n, TFA, reflux, 86% (2 steps); (c) Na-Hg, $B(OH)_3$, THF:MeOH (1:1), rt, 2 h 84%; (d) SeO_2, $NaHCO_3$, Dioxane, 102 °C, 16 h, 80%; (e) DMP CH_2Cl_2, 0 °C, 1 h, 98%. TFA = Trifluoroacetic acid, DMP = Dess-Martin periodinane.

Conclusions

We have accomplished the enantioselective total syntheses of seven biologically active natural products on a gram scale through a unified strategy. Analytical data for the synthesized natural product matched perfectly with the previous reported data of the natural products. Our studies unambiguously encourage and set a platform for the synthesis of a broad range of congeners of this class which could allow in-depth studies towards their pharmaceutical applications.

EXPERIMENTAL SECTION

General Procedure. All moisture-sensitive reactions were performed under an atmosphere of argon and glassware was dried in an oven at 125 °C prior to use. Dry tetrahydrofuran (THF) and diethyl ether (Et_2O) were obtained by passing commercially available pre-dried, oxygen free formulations through activated alumina columns and dried by distillation over sodium/benzophenone. Toluene and benzene were distilled over calcium hydride and stored over 4Å molecular sieves. Pyridine and triethylamine (Et_3N) were distilled over potassium hydroxide. Solvents used for chromatography were distilled at respective boiling points using known procedures. Reactions were monitored by thin layer chromatography (TLC, 0.25 mm, 60F254) and visualized by using UV light, ethanolic solution of phosphomolybdic acid (PMA), iodine, ninhydrin and $KMnO_4$ solution. Column chromatography was performed on silica gel 60-120/100-200/ 230-400 mesh. Typical syringe and cannula techniques were used to transfer air and moisture sensitive reagents. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrometer. 1H NMR spectra were recorded on BRUKER 400 UltraShield, BRUKER AC-600

and BRUKER 800 ULTRASHIELD PLUS instruments using deuterated chloroform as standard. Chemical shifts are reported in ppm. Proton coupling constants (*J*) are reported as absolute values in Hz and multiplicity (bs, broadened; s, singlet; d, doublet; t, triplet; dd, doublet of doublet; dt, doublet of triplet; td, triplet of doublet; qd, quartet of doublet; dq, doublet of quartet; dt, doublet of triplet; p, pentet; m, multiplet). ^{13}C NMR spectra were recorded on BRUKER 400 UltraShield, BRUKER 600 UltraShield and BRUKER 800 ULTRASHIELD PLUS instruments operating at 101 MHz, 150 MHz and 201 MHz respectively. ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ = 77.16). Due to presence of *N*-Boc protecting group some of the spectra are showing rotameric nmr signals. Electro spray ionization (ESI) mass spectrometry (MS) experiments were performed on Agilent Technologies 6530Accurate-Mass Q-TOF LC/MS. Optical rotations were measured on a Digipol 781 M6U Automatic Polarimeter. HPLC were performed on Agilent Technologies 1260 Infinity.

Preparation of tert-butyl (1R,4S)-2-(benzo[d][1,3]dioxol-5-yl)-3-tosyl-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate (11B) To a suspension of sodium hydride (0.164 g, 4.1 mmol) in diethylether (20 mL), taken in a two neck jacketed flask equipped with argon inlet and circulatory chiller at -10 ºC, was added a solution of **2** (1.0 g, 2.74 mmol) in 10 mL diethylether and stirred for 1.5 hour. Temperature was raised to -3 ºC and triflic anhydride (0.69 mL, 4.1 mmol) was added. The solution was stirred for 1 hour, quenched with water (10 mL), extracted with ethyl acetate (3X10 mL), dried over sodium sulfate, concentrated under vacuum to obtain crude enol triflate as a semi solid residue.

The solution of enol triflate in acetonitrile (15 mL) was added 3,4-methylenedioxyphenyl boronic acid (0.448 g, 2.7 mmol), $Pd(OAc)_2$ (0.03 g, 0.135 mmol), tri-o-tolyl phosphine (0.082 g, 0.27 mmol) and silver carbonate (0.798 g, 2.9 mmol) and the reaction mixture was stirred at 80 ºC for 3 h. The progress of reaction was monitored by TLC. After completion, it was concentrated under vacuum and purified by chromatography on silica gel (15% EtOAc/Hexane) to obtain **11B** (0.85 g, 66%) as a semisolid. TLC R_f =0.6 (EtOAc:Hexane = 1:3, ninhydrin). IR (film): *vmax* = 2922, 1706, 1486, 1153, cm^{-1}. ^{1}H NMR (400 MHz, CDCl3) δ 7.72 (d, *J* = 8.4 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.08 (m, 2H), 6.82 (d, *J* = 8.8, Hz, 1H), 5.99 (s, 2H), 4. 92 (m, 2H), 2.39 (s, 3H), 2.08 (m, 2H), 1.67 (m, 1H), 1.40 (m, 1H), 1.28 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 149.2, 147.5, 144.4, 138.1, 129.8, 127.7, 124.4, 123.9, 110.0, 108.2, 101.6, 80.9, 67.6, 64.3, 28.0, 21.6. HRMS (*m/z*): [M + Na]$^+$ calcd for $C_{25}H_{27}NNaO_6S^+$ 492.1451, found 492.1455. [α]D^{22} = +147.2° (*c* = 2.5, MeOH). **Note: 11A**, **11C** and **11D** were also prepared by using exactly the same procedure by using 3,4-dimethoxy phenyl boronic acid, phenyl boronic acid and 3-formylphenylboronic acid, respectively (data's attached).

Tert-butyl (1R,4S)-2-(3,4-dimethoxyphenyl)-3-tosyl-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate (11A): TLC R_f=0.5 (EtOAc:Hexane = 3:7, ninhydrin). IR (film): *vmax* = 2942, 1650, 1506, 1151 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 2.0 Hz, 1H), 7.25 (dd, *J* = 6.7, 4.0 Hz, 3H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.98 (bs, 1H), 4.93 (bs, 1H), 3.91 (s, 6H), 2.38 (s, 3H), 2.09 – 2.07 (m, 2H), 1.71 – 1.67 (m, 1H), 1.27 (m, 1H), 1.22 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.1, 150.7, 149.1, 148.4, 148.3, 144.4, 138.2, 134.3, 129.7, 127.5, 123.0, 122.6, 119.1, 113.3, 111.5, 110.5, 110.4, 80.8, 64.4, 56.2, 56.1, 56.0, 28.0, 21.6. HRMS (*m/z*): [M + Na]$^+$ calcd for $C_{26}H_{31}NNaSO_6{}^+$ 508.1764, found 508.1753.

Tert-butyl (1R,4S)-2-phenyl-3-tosyl-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate (11C): TLC R_f =0.5 (EtOAc:Hexane = 3:7, ninhydrin). IR (film): *vmax* = 2977, 1709, 1491, 1257, cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.4 Hz, 2H), 7.53 – 7.51 (m, 2H), 7.39 – 7.37 (m, 3H), 7.26 – 7.23 (m, 2H), 4.96 – 4.92 (m, 2H), 2.38 (s, 3H), 2.12 – 2.04 (m, 2H), 1.70 (m, 1H), 1.55 (s, 1H), 1.46 – 1.42 (m, 1H), 1.29 – 1.24 (m, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.2, 144.5, 138.1, 130.5, 129.9, 129.8, 129.4, 128.2, 127.8, 80.9, 77.1, 67.7, 64.2, 28.1, 21.7. HRMS (*m/z*): [M + Na]$^+$ calcd for $C_{24}H_{27}NNaO_4S^+$ 448.1553, found 448.1495.

Tert-butyl (1R,4S)-2-(6-formylbenzo[d][1,3]dioxol-5-yl)-3-tosyl-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate (11D), TLC R_f =0.5 (EtOAc:Hexane = 1:1, ninhydrin). IR (film): *vmax* = 2977, 1709, 1491, 1257, cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.59 (d, *J* = 8.4 Hz, 2H), 7.38 (s, 1H), 7.26 – 7.24 (m, 2H), 6.66 (s, 1H), 6.08 (d, *J* = 1.6 Hz, 2H), 4.98 (s, 1H), 4.74 (s, 1H), 2.38 (s, 3H), 2.19 – 2.05 (m, 2H), 1.75 – 1.69 (m, 1H), 1.52 – 1.46 (m, 1H), 1.27 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 188.4, 152.2, 149.3, 145.1, 137.2, 130.0, 129.4, 128.0, 111.3, 106.9, 102.6, 81.5, 68.9, 63.4, 53.5, 27.9, 21.7. HRMS (*m/z*): [M + Na]$^+$ calcd for $C_{26}H_{27}NNaO_7S^+$ 520.1400, found 520.1455.

Preparation of tert-butyl ((1*R*,2*S*)-2-allyl-2-(benzo[d][1,3]dioxol-5-yl)-3-tosylcyclohex-3-en-1-yl)carbamate (12B) Copper triflate (0.035 g, 0.095 mmol) and 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride (0.435 g, 0.127 mmol) were taken in a dried two neck jacketed flask equipped with argon balloon and magnetic stir bar. It was evacuated under high vacuum for 15 minutes and flushed with argon, diluted with 10 mL diethyl ether. The suspension was cooled to -7 ºC and allylmagnesium bromide (0.8 M, 7.99 mL) was added. After 10 minutes, solution of **11B** (1.5 g, 3.19 mmol) in 3 mL dichloromethane was added and stirred for additional 10 minutes. The reaction mixture was quenched with aqueous solution of ammonium chloride (10 mL), extracted with ethyl acetate (3 X10 mL), dried over sodium sulfate, concentrated under vacuum and purified by chromatography on silica gel (30% EtOAc/Hexane) to obtain **12B** (1.54 g, 95%) in solid form (mp 160.4–162.00 °C). TLC R_f =0.4 (EtOAc:Hexane = 1:3, ninhydrin). IR (film): *vmax* = 2920, 1698, 1488, 1040 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (bs, 1H), 7.28 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.64 (d, *J* = 7.2 Hz, 1H), 6.46 (bs, 2H), 5.98 – 5.96 (m, 1H), 5.76 (d, *J* = 22.4 Hz, 2H), 5.19 (d, *J* = 17.2 Hz, 1H), 5.10 (d, *J* = 10.4 Hz, 1H), 4.57 (d, *J* = 9.6 Hz, 1H), 4.11 – 4.07 (m, 1H), 3.24 – 3.05 (m, 2H), 2.50 (bs, 2H), 2.35 (s, 3H), 1.95 (m, 1H), 1.71 (bs, 1H), 1.21 (d, *J* = 53.2 Hz, 9H). **^{13}C** NMR (101 MHz, $CDCl_3$) δ 155.0, 147.3, 146.5, 146.2, 143.6, 143.5, 139.3, 136.4, 135.0, 129.5, 127.6, 122.1, 118.2, 109.5, 107.4, 101.2, 79.7, 57.2, 49.5, 38.5, 28.5, 25.3, 21.9. HRMS (*m/z*): [M + Na]$^+$ calcd for $C_{28}H_{33}NNaO_6S^+$ 534.1921, found 534.1924. [α]D^{22} = -5.6° (*c* = 5, MeOH). **Note: 12A** was also prepared by using exactly the same procedure starting with **11A**.

Tert-butyl ((1S,2R)-1-allyl-3',4'-dimethoxy-6-tosyl-1,2,3,4-tetrahydro-[1,1'-biphenyl]-2-yl)carbamate (12A) TLC R_f =0.5 (EtOAc:Hexane = 2:3, ninhydrin). IR (film): *vmax* = 2934, 1706, 1518, 1257 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ

7.38 (s, 1H), 7.18 (d, *J* = 7.6 Hz, 2H), 7.05 (d, *J* = 8.0 Hz, 2H), 6.79 (m, 1H), 6.56 (d, *J* = 8.4 Hz, 1H), 6.48 (s, 1H), 6.02 (m, 1H), 5.18 (d, *J* = 17.2 Hz, 1H), 5.10 (d, *J* = 10.0 Hz, 1H), 4.63 (d, *J* = 10.0 Hz, 1H), 4.26 (m, 1H), 3.82 (s, 3H), 3.57 (s, 3H), 3.30 (m, 1H), 3.08 (m, 1H), 2.54 (d, *J* = 2.8 Hz, 2H), 2.35 (s, 3H), 2.06 – 1.89 (m, 1H), 1.76 (m, 1H), 1.23 (s, 9H).^{13}C NMR (101 MHz, $CDCl_3$) δ 154.9, 147.9, 147.0, 146.4, 143.2, 142.8, 138.8, 133.8, 132.1, 129.1, 127.2, 121.4, 118.3, 111.7, 109.9, 55.8, 55.2, 49.1, 38.8, 29.7, 28.2, 24.9, 24.7, 21.5. HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{29}H_{37}NNaSO_6^+$ 550.2234, found 550.2235.

Preparation of tert-butyl (3aS,7aR)-3a-(benzo[d][1,3]dioxol-5-yl)-4-tosyl-2,3,3a,6,7,7a-hexahydro-1H-indole-1-carboxylate (1B) To a solution of **12B** (1.25 g, 2.44 mmol) in dioxane-water (9:3, 12 mL) was added 2,6-lutidine (0.567 mL, 4.8 mmol), OsO_4 (2.5% in t-butanol, 0.495 g, 0.048 mmol), and $NaIO_4$ (2.1 gm, 9.75 mmol). The reaction mixture was stirred at 25 °C and progress was monitored by TLC. After the reaction was completed, water (10 mL) and CH_2Cl_2 (30 mL) were added to it. The organic layer was separated, and the water layer was extracted by CH_2Cl_2 (3X15 mL). The combined organic layer was washed with brine (15 mL) and dried over sodium sulfate. The solvent was removed under vacuum to obtain a crude residue which was dissolved in 20 mL AcOH:THF (1:9) and sodium cyanoborohydride (0.283 g, 4.5 mmol) was added. The reaction mixture was stirred at room temperature for 12 hours, neutralized with saturated sodium bicarbonate solution (7 mL), washed with brine solution (10 mL) and extracted with ethyl acetate (3X10 mL). Solvent was evaporated under vacuum and crude residue was purified by chromatography on silica gel (25% EtOAc/Hexane) to obtain **1B** (0.865 g, 71%) as white amorphous solid (mp 239.8–241.2 °C). TLC R_f =0.5 (EtOAc:Hexane = 2:3, ninhydrin). IR (film): *vmax* = 2920, 1681, 1643, 1400 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (s, 1H), 7.17 – 7.12 (m, 2H), 6.98 (d, *J* = 6.9 Hz, 2H), 6.62 (d, *J* = 6.0 Hz, 1H), 6.45 (t, *J* = 8.0 Hz, 1H), 6.25 (d, *J* = 24.0 Hz, 1H), 5.82 – 5.73 (m, 2H), 3.93 (d, *J* = 7.6 Hz, 1H), 3.79 (d, *J* = 7.6 Hz, 1H), 3.47 – 3.35 (m, 2H), 3.16 – 3.05 (m, 1H), 2.53 – 2.42 (m, 3H), 2.31 (s, 3H), 2.20 (d, *J* = 9.6 Hz, 1H), 2.03 (d, *J* = 9.2 Hz, 1H), 1.64 (m, 1H), 1.33 (d, *J* = 10.4 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 147.7, 147.3, 146.9, 143.0, 142.3, 139.1, 133.9, 129.2, 127.4, 121.3, 121.1, 109.1, 108.7, 107.9, 107.8, 101.3, 79.8, 67.3, 52.1, 51.2, 45.0, 44.7, 33.5, 32.8, 28.7, 24.9, 24.6, 24.4, 21.8. HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{27}H_{31}NNaO_6S^+$ 520.1764, found 520.1771. $[\alpha]D^{22}$ = -188.9° (*c* = 1.25, MeOH). **Note: 1A** was also prepared by using exactly the same procedure starting with **12A** (data attached).

Tert-butyl(3aS,7aR)-3a-(3,4-dimethoxyphenyl)-4-tosyl-2,3,3a, 6,7,7a-hexahydro-1H-indole-1-carboxylate (1A): TLC R_f =0.5 (EtOAc:Hexane = 1:1, ninhydrin). IR (film): *vmax* = 2921, 1597, 1516, 1386, 1143 cm^{-1}. ^{1}H NMR (400 MHz, CDCl3) δ 7.38 (m, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.95 (t, *J* = 8.0 Hz, 2H), 6.70 (d, *J* = 8.4 Hz, 1H), 6.50 (d, *J* = 8.4 Hz, 1H), 6.28 (d, *J* = 27.6 Hz, 1H), 3.99 (dd, *J* = 10.6, 4.0 Hz, 1H), 3.80 (s, 3H), 3.63 – 3.38 (m, 5H), 3.23 – 3.12 (m, 1H), 2.55 – 2.44 (m, 3H), 2.30 (s, 3H), 2.22 – 2.01 (m, 1H), 1.74 – 1.65 (m, 1H), 1.33 (d, *J* = 13.7 Hz, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.1, 148.1, 147.4, 147.1, 142.9, 141.9, 138.9, 131.9, 128.8, 127.1, 120.1, 111.0, 110.3, 79.5, 77.1, 66.8, 60.5, 55.8, 55.2, 51.7, 50.7, 44.8, 44.5, 33.1, 32.4, 28.5, 24.3, 21.4. HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{28}H_{35}NNaO_6S^+$ 536.2077, found 536.2068.

Preparation of (5*S*,11b*S*)-1-tosyl-4,4a-dihydro-3H,6H-5,11b-ethano[1,3]dioxolo[4,5-j]phenanthridine (19): A solution of **1B** (3 g, 6.03 mmol) in 100 mL dichloromethane was taken in a round bottom flask equipped with magnetic stir bar under argon atmosphere. The reaction mixture was cooled to 0 °C and trifluoroacetic acid (0.461 mL, 6.03 mmol) was added slowly. The solution was stirred for 6 hours. After the completion, the reaction mixture was quenched with saturated solution of $NaHCO_3$ (50 mL) and allowed to stir for another 1 hour until the bubbling ceased. The organic layer was extracted with dichloromethane (3X50 mL), dried over sodium sulfate and concentrated under vacuum to obtain *N*-Boc deprotected material as a white solid residue.

The crude *N*-Boc deprotected material was dissolved in trifluoroacetic acid (50 mL) under argon atmosphere and paraformaldehyde (0.27 g, 9.0 mmol) was added. The reaction mixture was heated at 85 °C on an oil bath for 12 hours. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was neutralized by adding saturated solution of $NaHCO_3$ very slowly until the bubbling ceased. The organic layer was extracted with dichloromethane (3X50 mL), concentrated under vacuum and purified by chromatography on silica gel (5% MeOH/CH_2Cl_2) to obtain **19** (2.33 g, 95%) as a solid (mp 155.5-156.2 °C).

TLC R_f = 0.5 (MeOH:CH_2Cl_2 = 1:9, ninhydrin). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.0 Hz, 2H), 7.59 (s, 1H), 7.34 (d, *J* = 8.0 Hz, 2H), 6.69 (d, *J* = 6.8 Hz, 1H), 6.51 (s, 1H), 5.93 (d, *J* = 6.4 Hz, 2H), 4.86 (d, *J* = 16 Hz, 1H), 4.25 (d, *J* = 16.4 Hz, 1H) 3.97 (m, 1H), 3.78 (d, *J* = 12.4 Hz, 1H), 3.42 (m, 1H), 3.16 – 3.09 (m, 1H), 2.51 – 2.47 (m, 1H), 2.44 (s, 3H), 2.33 – 2.19 (m, 3H), 1.40 – 1.31 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.4, 147.1, 145.0, 143.8, 139.5, 135.4, 130.3, 127.6, 118.8, 107.9, 106.6, 101.7, 70.6, 59.0, 51.9, 50.1, 39.9, 29.7, 24.3, 21.6, 21.1 ppm. IR (film): *vmax* = 2924, 1596, 1383, 1240, 1077 cm^{-1}. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{23}H_{24}NO_4S^+$ 410.1421, found 410.1411. $[\alpha]D^{22}$ = -217.75° (*c* = 0.4, EtOH).

Preparation of (5*S*,11b*S*)-4,4a-dihydro-3H,6H-5,11b-ethano[1,3]dioxolo[4,5-j]phenanthridine (20): To a stirring solution of boric acid (1.50 g, 24.4 mmol) in anhydrous methanol (50 mL) was added a solution of **19** (2.0 g, 4.88 mmol) in 50 mL THF. The reaction mixture was stirred at room temperature and sodium amalgam (3.50 g, 7%) was added four times portion wise in 10 min interval while stirring at ambient temperature. The reaction mixture was allowed to stir for additional 2 hours. The progress of the reaction was monitored by TLC and after the completion of the reaction, water (30 mL) was added dropwise, extracted with dichloromethane (3X50 mL). The combined organic layer was washed with brine (5 mL) and dried over sodium sulfate. Solvent was evaporated to give colorless sticky liquid which was purified by chromatography on silica gel (5% MeOH/CH_2Cl_2) to obtain **20** (1.04 g, 84%) as a sticky material. TLC R_f =0.4 (MeOH:CH_2Cl_2 = 1:9, ninhydrin). IR (film): *vmax* = 3021, 2916, 1383, 1115 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (s, 1H), 6.48 (s, 1H), 6.32 (d, *J* = 10.0 Hz, 1H), 5.88 (dd, *J* = 6.2 Hz, 1.2 Hz, 2H), 5.80 –

5.77 (m, 1H), 4.45 (d, *J* = 16.8 Hz, 1H), 3.82 (d, *J* = 16.8 Hz, 1H), 3.52 – 3.45 (m, 1H), 3.18 (dd, *J* = 12.8 Hz, 3.6 Hz, 1H), 2.95 – 2.88 (m, 1H), 2.25 – 2.14 (m, 3H), 2.09 – 2.02 (m, 1H), 1.90 (m, 1H), 1.68 – 1.57 (m, 1H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 146.2, 139.1, 127.9, 127.5, 125.1, 107.3, 103.5, 101.2, 67.6, 62.1, 52.8, 45.0, 44.7, 30.1, 25.0, 24.2 ppm. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{16}H_{18}NO_2^+$ 256.1332, found 256.1326. $[\alpha]D^{24}$ = -65.3° (*c* = 0.5 in EtOH).

Preparation of (-)-Crinine (3): To a solution of **20** (1.0 g, 3.91 mmol) in dioxane (50 mL) was added 0.3 g sodium bicarbonate and SeO_2 (0.65 g, 5.86 mmol) and resulting suspension was immersed in an oil bath set at 102 °C and stirred for 16 h under argon atmosphere. The progress of reaction was monitored by TLC. After completion, the reaction was cooled to room temperature and filtered through a celite pad. The filtrate was concentrated and the residue was purified by chromatography on silica gel (20% MeOH/CH_2Cl_2) affording **3** (0.847 g, 80%) as a pale yellow solid (mp 207.5 – 208.2 °C). TLC R_f =0.3 (MeOH:CH_2Cl_2 = 1:4, ninhydrin). IR (film): *vmax* = 3350, 2926, 1397, 1160 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.84 (s, 1H), 6.59 (d, *J* = 10.0 Hz, 1H), 6.49 (s, 1H), 6.05 – 5.95 (m, 1H), 5.90 (dd, *J* = 6, 1.2 Hz, 2H), 4.41 (d, *J* = 16.8 Hz, 1H), 4.37 – 4.33 (m, 1H), 3.79 (d, *J* = 16.8 Hz, 1H), 3.38 (m, 2H), 2.92 – 2.89 (m, 1H), 2.21 – 2.14 (m, 1H), 2.02 – 1.98 (m, 1H), 1.98 – 1.91 (m, 1H), 1.83 – 1.68 (m, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 146.4, 137.3, 131.1, 128.0, 124.2, 107.2, 103.2, 101.1, 63.5, 63.1, 61.2, 52.9, 44.7, 43.3, 31.8. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{16}H_{18}NO_3^+$ 272.1281, found 272.1279. $[\alpha]D^{24}$ = -27.7° (*c* = 0.25, $CHCl_3$).

Preparation of (-)-Amabiline (4): To a solution of **20** (1.0 g, 3.91 mmol) in acetone-water (9:1, 100 mL) was added N-methyl morpholine N-oxide (0.567 mL, 4.8 mmol), OsO_4 (2.5% in t-butanol, 0.495 g, 0.048 mmol). The reaction mixture was stirred at 25 °C and progress was monitored by TLC. After the reaction was completed, $Na_2S_2O_3$ (20 mL) was added to it and was allowed to stir for another 1 hour. The whole reaction mixture was evaporated under high vacuum to remove the solvent. The organic layer was extracted by CH_2Cl_2 (3X50 mL). The combined organic layer was dried over sodium sulfate. The solvent was removed under vacuum to obtain a crude residue which was purified by chromatography on basic alumina (5% MeOH/CH_2Cl_2) to obtain (-)-amabiline **(4)** (0.86 g, 76 %) as white solid (mp 239.8–241.2 °C). TLC R_f =0.3 (MeOH:CH_2Cl_2 = 1:3, ninhydrin). IR (film): *vmax* = 3368, 2919, 1599, 1481 cm^{-1}. ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.80 (s, 1H), 6.48 (s, 1H), 5.90 (m, 2H), 4.59 (d, *J* = 2.5 Hz, 1H), 4.32 (d, *J* = 16.8 Hz, 1H), 4.11 – 4.06 (m, 1H), 3.70 (d, *J* = 16.2 Hz, 1H), 3.31 – 3.23 (m, 2H), 2.79 – 2.75 (m, 1H), 2.07 – 1.96 (m, 2H), 1.87 – 1.79 (m, 3H), 1.36 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 146.9, 146.3, 136.9, 107.0, 103.8, 101.0, 69.6, 68.9, 63.3, 61.6, 50.8, 49.9, 37.6, 26.8, 25.4. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{16}H_{20}NO_4^+$ 290.1387, found 290.1385. $[\alpha]D^{24}$ = -34.7° (*c* = 0.5, EtOH).

Preparation of (-)-Crinane (10): To a stirring solution of **19** (2.0 g, 4.88 mmol) in THF:MeOH (1:1, 50 mL), sodium amalgam (3.50 g, 7%) was added four times portion wise in 10 min interval while stirring at the ambient temperature. The reaction mixture was allowed to stir for additional 12 hours. The progress of the reaction was monitored by TLC and after the completion of the reaction, water (30 mL) was added dropwise, extracted with dichloromethane (3X50 mL). The combined organic layer was washed with brine (5 mL) and dried over sodium sulfate. Solvent was evaporated to give colorless sticky liquid which was purified by chromatography on silica gel (5% MeOH/CH_2Cl_2) to obtain (-)-Crinane (**10**) (1.06 g, 85%) as a solid foam. TLC R_f =0.4 (MeOH:CH_2Cl_2 = 1:9, ninhydrin). IR (film): *vmax* = 2361, 2343, 1736, 1486, 1378, 1259 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (s, 1H), 6.45 (s, 1H), 5.88 (s, 2H), 4.44 (d, *J* = 16.8 Hz, 1H), 3.84 (d, *J* = 16.8 Hz, 1H), 3.48 – 3.44 (m, 1H), 2.96 – 2.87 (m, 2H), 2.34 – 2.26 (m, 2H), 1.90 (d, *J* = 10.0 Hz, 1H), 1.78 – 1.76 (m, 3H), 1.62 (m, 1H), 1.54 – 1.44 (m, 1H), 1.32 (m, 1H), 1.31 – 1.16 (m, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 146.8, 146.1, 141.4, 124.3, 106.5, 103.5, 101.0, 67.7, 61.4, 51.9, 43.2, 37.3, 29.9, 28.9, 27.0, 24.2, 21.7. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{16}H_{20}NO_2^+$ 258.1489, found 258.1426. $[\alpha]D^{24}$ = -9.3° (*c* = 0.75 in $CHCl_3$).

Preparation of tert-butyl (3a*R*)-3a-(3,4-dimethoxyphenyl)-6-hydroxy-2,3,3a,6,7,7a-hexahydro-1H-indole-1-carboxylate (21): To a stirring solution of boric acid (0.60 g, 9.7 mmol) in anhydrous methanol (15 mL) was added a solution of **1A** (1.0 g, 1.94 mmol) in 15 mL THF. The reaction mixture was stirred at room temperature and sodium amalgam (0.8 g, 7%) was added four times portion wise in 10 min interval while stirring at ambient temperature. The reaction mixture was allowed to stir for additional 2 hours. The progress of reaction was monitored by TLC and after the completion of the reaction, water (6 mL) was added drop wise, extracted with ethyl acetate (3X50 mL). The combined organic layer was washed with brine (5 mL) and dried over sodium sulfate. Solvent was evaporated to give colorless sticky liquid.

To a crude solution (1.0 g, 2.78 mmol) in dioxane (10 mL) was added 0.03 g sodium bicarbonate and SeO_2 (0.462 g, 4.17 mmol) and resulting suspension was immersed in an oil bath set at 102 °C and stirred for 16 hours under argon atmosphere. The progress of reaction was monitored by TLC. After completion, the reaction was cooled to room temperature and filtered through a celite pad. The filtrate was concentrated and the residue was purified by chromatography on silica gel (30% EtOAc/Hexane) affording **21** (0.835 g, 80 %) as a yellow semisolid. TLC R_f =0.5 (EtOAc:Hexane = 1:1, ninhydrin). IR (film): vmax = 2973, 2836, 1688, 1453, 1127 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.97 – 6.91 (m, 2H), 6.83 (m, 1H), 6.02 (d, *J* = 10.0 Hz, 1H), 5.60 (d, *J* = 9.6 Hz, 1H), 4.30 (bs, 1H), 3.89 (s, 3H), 3.86 (s, 3H), 3.80 – 3.63 (m, 1H), 3.21 – 3.18 (m, 1H), 2.54 – 2.51 (m, 1H), 2.40 – 2.35 (m, 1H), 1.84 – 1.77 (m, 3H), 1.63 – 1.54 (m, 1H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.7, 148.9, 148.0, 135.5, 133.0, 132.6, 119.4, 110.9, 110.3, 79.9, 63.6, 62.4, 62.1, 56.0, 50.9, 46.0, 45.8, 36.1, 31.9, 31.0, 28.6. HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{21}H_{29}NNaO_5^+$ 398.1938, found 398.1943. $[\alpha]D^{22}$ = +138.9° (*c* = 1.25, MeOH).

Preparation of *tert*-butyl (3a*R*)-3a-(3,4-dimethoxyphenyl)-6-oxooctahydro-1H-indole-1-carboxylate (22) : To a solution of **21** (1.5 g, 4.0 mmol) in ethanol (30 mL) was added Raney Nickel (catalytic amount) and resulting suspension was immersed in an oil bath set at 75 °C and stirred for 2 hours under hydrogen atmosphere. The progress of the reaction was monitored by TLC. After completion, the reaction was cooled to room temperature and filtered through a celite pad. The filtrate was concentrated under high vacuum.

The residue was dissolved in dry CH_2Cl_2 (20 mL) and was cooled to 0 °C, added DMP (1.69 g, 4.0 mmol), the reaction was allowed to stir for 1 h. The progress of the reaction was monitored by TLC, neutralized with saturated sodium bicarbonate solution (20 mL), washed with brine solution (10 mL) and extracted with ethyl acetate (3X20 mL). Solvent was evaporated under vacuum and crude residue was purified by chromatography on silica gel (20% EtOAc/Hexane) to obtain **22** (1.27 g, 85 %) as a white sticky liquid. TLC R_f =0.5 (EtOAc:Hexane = 3:7, ninhydrin). IR (film): *vmax* = 2923, 1688, 1461, 1396, 1255 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ δ 6.82 (m, 3H), 4.89– 4.46 (m, 1H), 3.87 (s, 3H), 3.86 (s, 3H), 3.44– 3.38 (m, 3H), 2.92 (dd, *J* = 15.6, 6.0 Hz, 1H), 2.69 (m, 1H), 2.43 – 2.04 (m, 6H), 1.46 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.6, 149.1, 147.9, 137.7, 118.0, 111.2, 109.5, 80.1, 60.3, 56.1, 56.0, 44.5 36.7, 33.3, 28.6. HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{21}H_{29}NNaO_5^+$ 398.1938, found 398.1937. $[\alpha]D^{24}$ = +98.6° (*c* = 0.5, MeOH).

Preparation of (+)-Mesembrine (5): To a solution of **22** (1.0 g, 2.66 mmol) in CH_2Cl_2 (15 mL), trifluoroacetic acid (0.20 mL, 2.66 mmol) was added at 0 °C and stirred for 8 hours. The reaction mixture was quenched with saturated sodium bicarbonate solution (10 mL) and extracted with dichloromethane (3X15 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude residue was dissolved in chloroform and passed through a small pad of basic alumina and concentrated under reduced pressure.

It was then dissolved in acetonitrile (10 mL) followed by addition of formaldehyde (.025 mL of a 35% w/w aqueous solution) and $NaCNBH_3$ (0.167 g, 2.66 mmol). The resulting mixture was stirred at room temperature for 10 minutes and was quenched with saturated sodium bicarbonate solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (3X10 mL) and dried over sodium sulfate, purified by column chromatography on basic alumina (2-4% MeOH/DCM) to afford pure (+)-mesembrine (0.614 g, 80 %) as a colourless oil. TLC R_f =0.5 (MeOH:CH_2Cl_2 = 3:7, ninhydrin). IR (film): νmax = 2923, 2853, 1688, 1517, 1396 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$ δ 6.95 (dd, *J* = 8.4, 1.8 Hz, 1H), 6.91 (d, *J* = 1.8 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.15 – 3.11 (m, 1H), 2.96 (t, *J* = 3.6 Hz, 1H), 2.60 – 2.56 (m, 2H), 2.46 – 2.41 (m, 1H), 2.37 – 2.29 (m, 4H), 2.28 – 2.16 (m, 3H), 2.17 – 2.03 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.6, 149.1, 147.6, 140.4, 118.0, 111.1, 110.1, 77.1, 70.5, 56.0, 55.0, 47.6, 40.7, 40.2, 39.0, 36.4, 35.4. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{24}NO_3^+$ 290.1751, found 290.1740. $[\alpha]D^{24}$ = +63.8° (*c* = 0.25, MeOH).

Preparation of tert-butyl (3a*R*)-3a-(3,4-dimethoxyphenyl)octahydro-1H-indole-1-carboxylate (23): To a stirring solution of **1A** (1.0 g, 1.94 mmol) in (1:1) THF:MeOH (20 mL), sodium amalgam (0.8 g, 7%) was added four times portion wise in 10 min interval while stirring at the ambient temperature. The reaction mixture was allowed to stir for additional 12 hours. The progress of reaction was monitored by TLC and after the completion of the reaction, water (6 mL) was added drop wise, extracted with ethyl acetate (3X50 mL). The combined organic layer was washed with brine (5 mL) and dried over sodium sulfate. Solvent was evaporated to give colorless sticky liquid which was purified by chromatography on silica gel (10% EtOAc/Hexane) to obtain **23** (0.6 g, 85%) as a semi solidsolid. TLC R_f =0.6 (EtOAc:Hexane = 1:9, ninhydrin). IR (film): *vmax* = 2923, 2853, 1396 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.85– 6.78 (m, 3H), 4.22–4.02 (m, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.34 – 3.29 (m, 1H), 3.06 – 2.95 (m, 1H), 2.33 (m, 1H), 2.07 (m, 2H), 1.88 (bs, 1H), 1.75 – 1.51 (m, 4H), 1.52 – 1.34 (m, 10H), 1.25 (t, *J* = 11.2 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 154.4, 148.7, 147.1, 140.6, 117.9, 111.0, 109.3, 79.0, 59.7, 58.8, 55.9, 47.7, 47.1, 43.6, 43.1, 35.6, 33.8, 32.3, 29.2, 28.7, 28.6, 23.5. HRMS (*m/z*): $[M + Na]^+$ calcd for $C_{21}H_{31}NO_4Na^+$ 384.2145, found 384.2126. $[\alpha]D^{20}$ = +262.3° (*c* = 0.25, MeOH).

Preparation of (+)-Mesembrane (8): To a solution of **23** (1.0 g, 2.76 mmol) in CH_2Cl_2 (15 mL), trifluoroacetic acid (0.20 mL, 2.76 mmol) was added at 0 °C and stirred for 8 hours. The reaction mixture was quenched with saturated sodium bicarbonate solution (10 mL) and extracted with dichloromethane (3X15 mL). The organic layer was dried over sodium sulfate and concentrated under vacuum. The crude residue was dissolved in chloroform and passed through a small pad of basic alumina and concentrated under reduced pressure.

It was then dissolved in acetonitrile (10 mL) and formaldehyde (0.025 mL of a 35% w/w aqueous solution) and $NaCNBH_3$ (0.173 g, 2.76 mmol) was added. The resulting mixture was stirred at room temperature for 10 minutes and was quenched with saturated sodium bicarbonate solution (10 mL). The reaction mixture was extracted with CH_2Cl_2 (3X10 mL) and dried over sodium sulfate, purified by column chromatography on basic alumina (2-4% MeOH/DCM) to afford pure (+)-mesembrane (**8**) (0.646 g, 85 %) as a pale yellow oil. TLC R_f =0.3 (MeOH:CH_2Cl_2 = 1:4, ninhydrin). IR (film): *vmax* = 2923, 2853, 1396 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$ δ 6.93 – 6.89 (m, 2H), 6.81 (d, *J* = 8.4 Hz, 1H), 3.89 (s, 3H), 3.87 (s, 3H), 3.25 (m, 1H), 2.58 (m, 1H), 2.33 (s, 3H), 2.32– 2.31 (m, 1H) 1.95 – 1.79 (m, 5H), 1.55 (m, 3H), 1.37 (m, 1H), 1.16 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.7, 146.9, 140.4, 119.0, 110.8, 110.7, 68.8, 56.0, 55.9, 54.5, 47.6, 41.1, 40.7, 36.1, 23.8, 23.0, 20.5. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{26}NO_2^+$ 276.1958, found 276.1946. $[\alpha]D^{20}$ = +15.9° (*c* = 0.25, MeOH).

Preparation of (5*S*,10b*S*)-8,9-dimethoxy-1-tosyl-4,4a-dihydro-3H,6H-5,10b-ethanophenanthridine (24). A solution of **1A** (2 g, 3.90 mmol) in 100 mL dichloromethane was taken in a round bottom flask equipped with magnetic stir bar under argon atmosphere. The reaction mixture was cooled to 0 °C and trifluoroacetic acid (0.30 mL, 3.90 mmol) was added slowly. The solution was stirred for 6 hours. After the completion, the reaction mixture was quenched with saturated solution of $NaHCO_3$ (50 mL) which was allowed to stir for another 1 hour until the bubbling ceased. The organic layer was extracted with dichloro methane (3X50 mL), dried over sodium sulfate and concentrated under vacuum to obtain *N*-Boc deprotected material as a white solid residue.

The *N*-Boc deprotected material was dissolved in trifluoroacetic acid (50 mL) under argon atmosphere and paraformaldehyde (0.175 g, 5.85 mmol) was added. The reaction mixture was heated at 85 °C on an oil bath for 12 hours. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was neutralized by adding saturated solution

of $NaHCO_3$ very slowly until the bubbling ceased. The organic layer was extracted with dichloromethane (3X50 mL), it was concentrated under vacuum and purified by chromatography on silica gel (5% MeOH/CH_2Cl_2) to obtain **24** (1.427 g, 86 %) as a solid (mp 211.3- 211.8 °C). TLC R_f = 0.5 (MeOH:CH_2Cl_2 = 1:9, ninhydrin). IR (film): *vmax* = 2919, 1596, 1384, 1311, 1263 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, *J* = 8.4 Hz, 2H), 7.62 (s, 1H), 7.32 (d, *J* = 8.0 Hz, 2H), 6.60 (t, *J* = 4.4 Hz, 1H), 6.49 (s, 1H), 4.45 (d, *J* = 17.2 Hz, 1H), 3.93 (s, 3H), 3.88 (d, *J* = 17.6 Hz, 1H), 3.81 (s, 3H), 3.33 – 3.28 (m, 2H), 3.09 – 2.99 (m, 1H), 2.89 – 2.82 (m, 1H), 2.44 (s, 3H), 2.25 – 2.18 (m, 3H), 1.73 – 1.69 (m, 1H), 1.31 – 1.24 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 150.1, 147.4, 146.5, 144.1, 143.0, 140.7, 137.8, 129.9, 127.7, 124.5, 110.2, 109.3, 71.6, 62.3, 56.2, 56.0, 54.0, 50.1, 43.7, 25.7, 24.2, 21.6. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{24}H_{28}NO_4S^+$ 426.1734, found 426.1720. $[\alpha]D^{22}$ = -17.75° (*c* = 0.4, EtOH).

Preparation of (5*S*,10b*S*)-8,9-dimethoxy-4,4a-dihydro-3H,6H-5,10*b*-ethanophenanthridine (25): To a stirring solution of boric acid (1.44 g, 23.45 mmol) in anhydrous methanol (50 mL) was added a solution of **24** (2.0 g, 4.69 mmol) in 50 mL THF. The reaction mixture was stirred at room temperature and sodium amalgam (3.25 g, 7%) was added four times portion wise in 10 min interval while stirring at the ambient temperature. The reaction mixture was allowed to stir for additional 2 hours. The progress of reaction was monitored by TLC and after the completion of the reaction; water (30 mL) was added drop wise, extracted with dichloromethane (3X50 mL). The combined organic layer was washed with brine (5 mL) and dried over sodium sulfate. Solvent was evaporated which gave colorless sticky liquid and purified by chromatography on silica gel (5% MeOH/CH_2Cl_2) to obtain **25** (1.069 g, 84%) as a semisolid. TLC R_f =0.4 (MeOH:CH_2Cl_2 = 1:9, ninhydrin). IR (film): *vmax* = 2934, 2850, 1607, 1462, 1263 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$)δ 6.84 (s, 1H), 6.52 (s, 1H), 6.45 (dd, *J* = 10.0, 1.6 Hz, 1H), 5.81 – 5.77 (m, 1H), 4.44 (d, *J* = 16.8 Hz, 1H), 3.88 (s, 3H), 3.81 (s, 3H), 3.37 (d, *J* = 16.8 Hz, 1H), 3.41 – 3.35 (m, 1H), 3.14 – 3.10 (dd, *J* = 13.0, 4.0 Hz, 1H), 2.91 – 2.84 (m, 1H), 2.21 – 2.16 (m, 3H), 2.06 – 1.99 (m, 1H), 1.79 – 1.76 (m, 1H), 1.66 – 1.55 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.1, 147.0, 138.1, 128.0, 126.7, 124.9, 109.6, 105.7, 67.1, 61.9, 55.8, 55.7, 52.5, 45.1, 43.7, 24.8, 24.3. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{22}NO_2^+$ 272.1645, found 272.1632. $[\alpha]D^{24}$ = -65.3° (*c* = 0.5 in EtOH).

Preparation of (-)-Maritidine (6): To a solution of **25** (1.0 g, 3.68 mmol) in dioxane (50 mL) was added 0.3 g sodium bicarbonate and SeO_2 (0.612 g, 5.52 mmol) and resulting suspension was immersed in an oil bath set at 102 °C and stirred for 16 h under argon atmosphere. The progress of reaction was monitored by TLC. After completion, the reaction was cooled to room temperature and filtered through a celite pad. The filtrate was concentrated and the residue was purified by chromatography on silica gel (20% MeOH/CH_2Cl_2) affording **6** (0.844 g, 80%) as a white solid (mp 230.6 –231.1 °C). TLC R_f =0.6 (MeOH:CH_2Cl_2 = 1:9, Ninhydrin). IR (film): *vmax* = 2922, 1589, 1384, 1238, cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 6.85 (s, 1H), 6.67 (d, *J* = 10.0 Hz, 1H), 6.52 (s, 1H), 5.99 – 5.95 (m, 1H), 4.43 (d, *J* = 16.8 Hz, 1H), 4.39 – 4.31 (m, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.78 (d, *J* = 16.8 Hz, 1H), 3.48 – 3.33 (m, 2H), 2.94 – 2.87 (m, 1H), 2.19 (m, 1H), 2.03 – 1.95 (m, 1H), 1.94 – 1.91 (m, 1H), 1.77 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 147.6, 147.4, 137.2, 132.4, 127.6, 125.3, 110.0, 105.9, 67.2, 64.3, 63.1, 62.2, 56.2, 56.0, 53.7, 44.3, 44.1, 32.9. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{22}NO_3^+$ 288.1594, found 288.1586. $[\alpha]D^{24}$ = -27.7° (*c* = 0.25, $CHCl_3$).

Preparation of (-)-Oxomaritidine (7): To a solution of **6** (1.0 g, 3.48 mmol) in dry CH_2Cl_2 (20 mL) cooled to 0 °C, was added DMP (1.47 g, 3.48 mmol) and the reaction was allowed to stir for 1 hour. The progress of the reaction was monitored by TLC, neutralized with sat. sodium bicarbonate solution (5 mL), washed with brine solution (5 mL) and extracted with ethyl acetate (3X20 mL). Solvent was evaporated under vacuum and crude residue was purified by chromatography on silica gel (10% MeOH/CH_2Cl_2) to obtain **7** (0.971 g, 98%) as a white solid (mp 145.5 – 146.7 °C). TLC R_f =0.6 (MeOH:CH_2Cl_2 = 1:9, ninhydrin). IR (film): *vmax* = 2928, 1675, 1607, 1513, 1461, 1314 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, *J* = 10.4 Hz, 1H), 6.91 (s, 1H), 6.58 (s, 1H), 6.10 (d, *J* = 10.0 Hz, 1H), 4.42 (d, *J* = 17.6 Hz, 1H), 3.91 (s, 3H), 3.84 (s, 3H), 3.81 (d, *J* = 16.8 Hz, 1H), 3.68 (dd, *J* = 13.2, 5.6 Hz, 1H), 3.61 – 3.52 (m, 1H), 3.08 – 2.97 (m, 1H), 2.71 (dd, *J* = 16.8, 5.6 Hz, 1H), 2.49 (dd, *J* = 16.8, 13.0 Hz, 1H), 2.40 (m, 1H), 2.22 – 2.15 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 198.2, 149.6, 148.2, 147.8, 135.0, 129.0, 125.4, 110.3, 105.7, 69.2, 61.7, 56.4, 56.1, 54.3, 45.0, 44.5, 40.3. HRMS (*m/z*): $[M + H]^+$ calcd for $C_{17}H_{20}NO_3^+$ 286.1438, found 286.1425. $[\alpha]D^{24}$ = -47.7° (*c* = 0.25, MeOH).

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publication website.

^1H and ^{13}C spectra of all new compounds.

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