Pure Appl. Chem., Vol. 84, No. 7, pp. 1597–1619, 2012.
http://dx.doi.org/10.1351/PAC-CON-11-10-12

Stereoselective construction of 5,11-methanomorphanthridine and 5,10b-phenanthridine structural frameworks: Total syntheses of (±)-pancracine, (±)-brunsvigine, (±)-maritidine, and (±)-crinine*

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Abstract: The core structure of the complex pentacyclic 5,11-methanomorphanthridine skeleton and the vicinal quaternary and tertiary stereocenters of the 5,10b-phenanthridine skeleton are constructed stereospecifically in one step employing intramolecular 1,3-dipolar cycloaddition of a nonstabilized azomethine ylide (AMY) generated by the sequential double desilylation of appropriate bis-trimethylsilylmethyl amines using Ag(I)F as a single-electron oxidant. The strategy is successfully applied for the total synthesis of biologically active alkaloids such as (±)-pancracine, (±)-brunsvigine, (±)-maritidine, and (±)-crinine.

Keywords: alkaloid synthesis; cycloadditions; organic synthesis; stereocontrolled synthesis.

INTRODUCTION

Alkaloids isolated from plants of the *Amaryllidaceae* [1–4] family are endowed with a variety of physiological activities [5,6] such as antitumor, antiviral, acetylcholinesterase (AChE) inhibitory, immunostimulatory, antimalarial, anxiolytic, antidepressive, anticonvulsive, and weak hypotensive activity and have long been a source of structurally intriguing target molecules that challenge the capabilities of contemporary organic synthesis. *Amaryllidaceae* alkaloids are classified into 18 subgroups on the basis of their structural frameworks of which montanine type (**1**), crinine type (**2**), lycorine type (**3**), and pancratistatine type (**4**) are a few important examples (Fig. 1).

While the crinine class of alkaloids possesses a phenanthridine skeleton with a fused tetracyclic skeleton displaying adjacent quaternary and tertiary carbon stereocenters, the montanine class is based on a unique linearly fused pentacyclic 5,11-methanomorphanthridine skeleton (Fig. 2). A major challenge in devising a synthetic strategy for these alkaloids is stereocontrolled incorporation of the fused pyrrolidine ring system in a polycyclic structural framework. Although a few elegant synthetic strategies are known, an efficient and conceptually new route has remained elusive. In this context, we became interested in the scope of exploiting our strategy for stereospecific assembly of substituted pyrrolidine ring systems by [3 + 2]-cycloaddition of a nonstabilized azomethine ylide (AMY), generated by sequential double desilylation of *N*,*N*′-bis(trimethylsilylmethyl)alkyl amines [7] for the construction of the core structure of these alkaloids.

Pure Appl. Chem.* **84, 1543–1667 (2012). A collection of invited papers based on presentations at the 23rd International Conference on Heterocyclic Chemistry (ICHC-23), Glasgow, UK, 31 July–4 August 2011.
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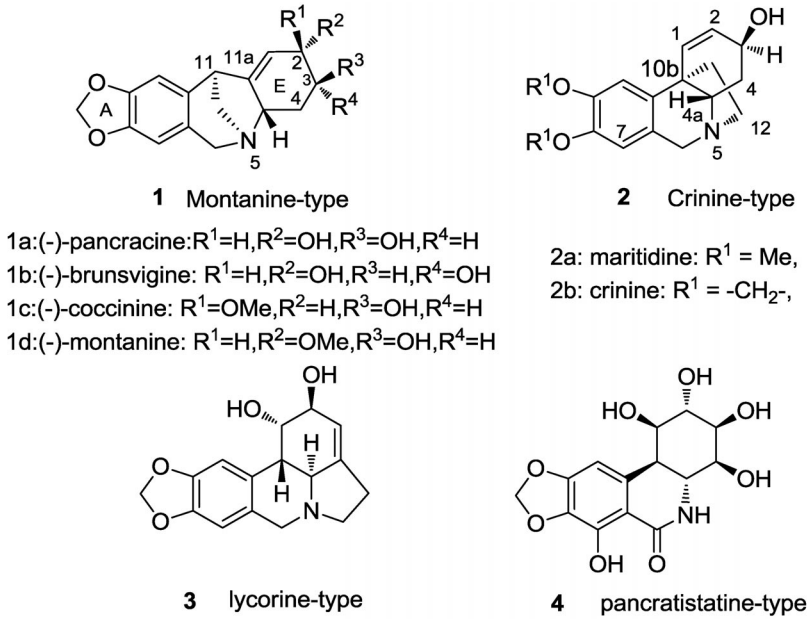


Fig. 1 Representative members of *Amaryllidaceae* alkaloids.

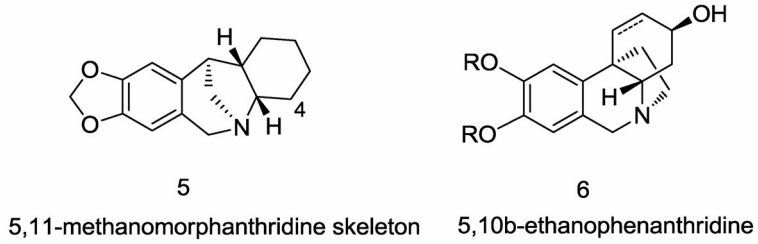


Fig. 2 Basic skeleton for crinine and montanine alkaloids.

Our concept and strategies for the syntheses of both of these classes of alkaloids are described here in detail [8–11].

STEREOSELECTIVE SYNTHESES OF 5,11-METHANOMORPHANTHRIDINE ALKALOIDS

The montanine alkaloids, possessing 5,11-methanomorphanthridine skeleton, display identical structural features except for the oxygen substitution in the E-ring (i.e., methoxy or hydroxyl) and the stereochemistries at C-2 and C-3.

Owing to structural complexities and important biological activities associated with these alkaloids, considerable synthetic efforts have been directed toward their syntheses. Literature survey has revealed that the construction of the core pentacyclic 5,11-methanomorphanthridine skeleton (**5**) has mainly been achieved through only three strategies as shown in Fig. 3. Hoshino and co-workers [12] accomplished the synthesis of **1** in a racemic form from a precursor of type **5**, obtained by the Pictet–Spengler reaction of the corresponding **7**. Jin and Weinreb [13] also used a similar cyclization protocol starting from a compound of type **8** for their synthesis of (–)-pancracine (**1a**) and (–)-coccinine (**1c**). In another approach, Hoshino and co-workers [14] used radical cyclization of a precursor of type

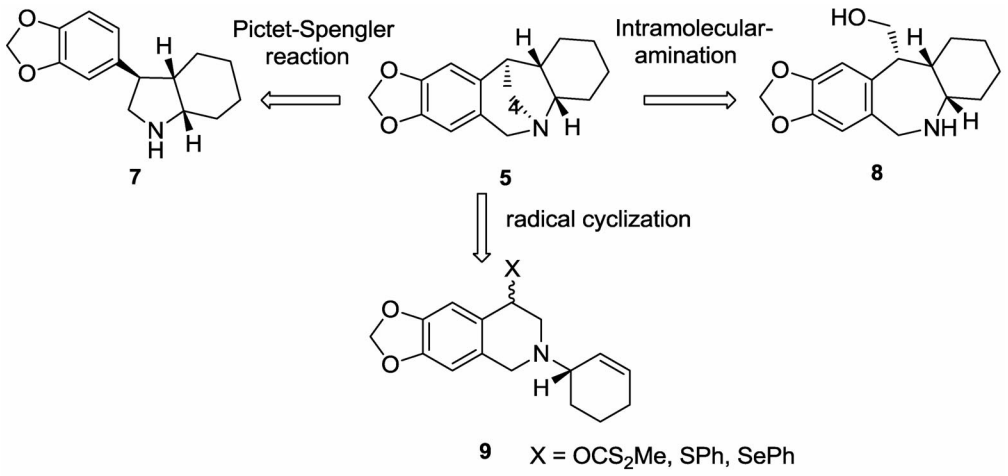


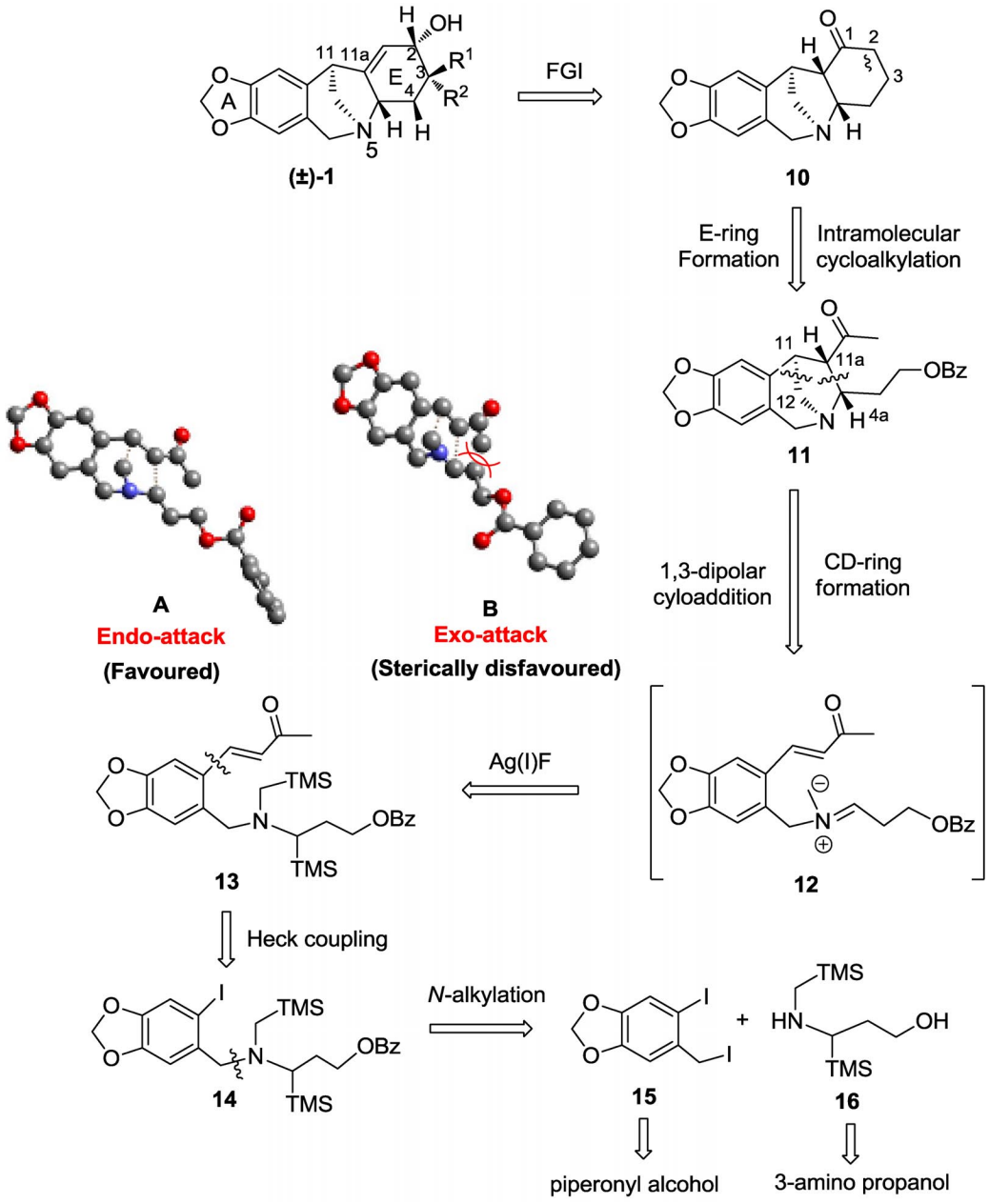
Fig. 3 Main strategies adopted toward the synthesis of 5,11-methanomorphanthridine alkaloid skeleton.

9 to construct skeleton **5**. Overman [15], Pearson [16], Ikeda [17], Sha [18], Banwell [19], Chang [20], Hashimoto [21], and Pansare [22] have all used precursors of type **7** in their respective elaborations of these alkaloids. However, in all these strategies, the syntheses were elaborated from a precursor having desired stereochemistry at C-4a and C-11a and relative disposition of the methylene bridge of **5** which involved its construction in a stepwise manner.

We viewed the synthesis of **5** from an entirely different angle (Scheme 3) employing [3 + 2] cycloaddition of a nonstabilized AMY (**12**) for the construction of the substituted CD-ring system, which on further elaboration by employing a suitable C–C bond-forming reaction would provide the E-ring.

RETROSYNTHESIS

While designing the synthetic route, it was envisioned that intramolecular *endo* attack (A) of AMY **12** on the "*re*" face of the α,β-unsaturated carbonyl moiety would be energetically more favored than *exo* attack (B) due to steric repulsion. Such a cycloaddition was also expected to fulfill all the stereochemical requirements of **5** in a single step without using a starting material with fixed stereocenters. Enthused by the above concept and design, we pursued our synthetic journey and the same is described below as it developed.

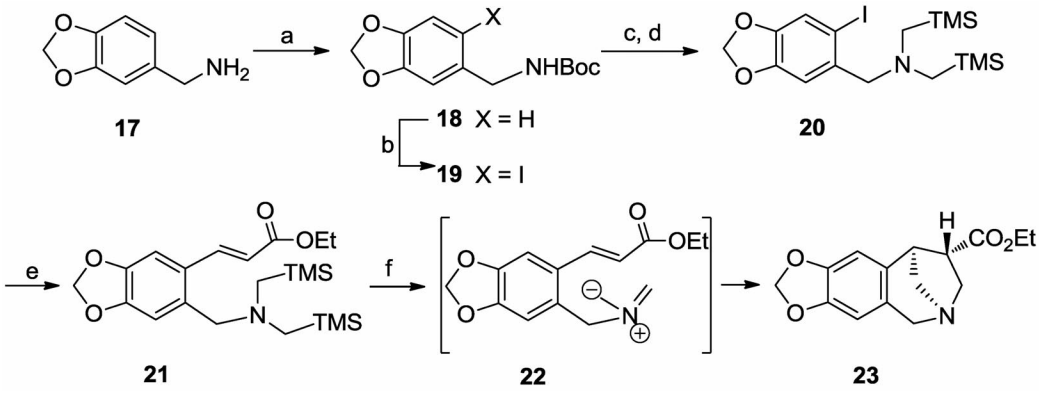


Scheme 1 Proposed synthesis of (±)-pancracine.

MODEL STUDIES

To check the feasibility of the proposed strategy, we studied the intramolecular [3 + 2]-cycloaddition of a nonstabilized AMY **22**, as shown in Scheme 4. Key precursor **21** was prepared in 72 % yield by the Heck coupling of **20** with the ethyl acrylate (8 equiv). Compound **20** was prepared in 78 % yield by deprotection of the N-Boc moiety of **19** using TFA followed by N-alkylation with (iodomethyl)trimethylsilane in the presence of excess of K_2CO_3 in dry CH_3CN. The crucial cycloaddition step involved dropwise addition of **21** to a stirred heterogeneous mixture of flame-dried Ag(I)F

(2.5 equiv) in dry CH_3CN at room temperature (rt). Chromatographic purification of the crude mass gave expected tetracyclic core **23** of the 5,11-methanomorphanthridine in 65 % yield. The relative stereochemistry of **23** was confirmed by 2D NMR studies.



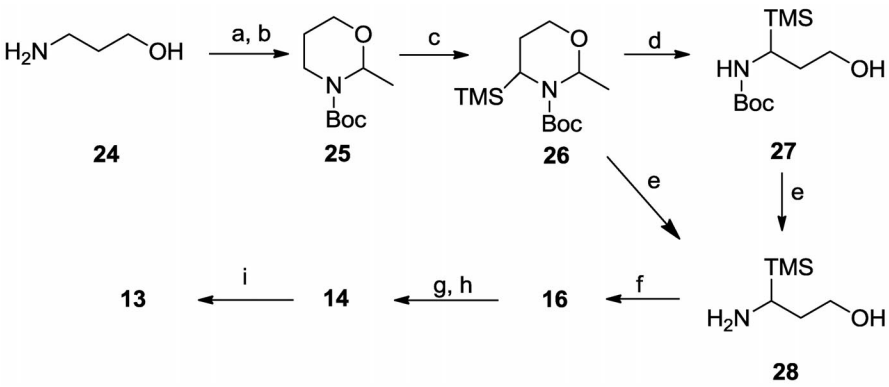
Scheme 2 Synthesis of model **23**. *Reagents and conditions*: (a) $(Boc)_2O$, NaOH, H_2O, 0 °C → rt, overnight, 90 %; (b) I_2, CF_3COOAg, $CHCl_3$, 1 h, 70 %; (c) TFA, DCM, 0 °C → rt, 4 h, quant.; (d) ICH_2TMS, K_2CO_3, CH_3CN, reflux, 10 h, 78 %; (e) ethyl acrylate, $Pd(OAc)_2$, PPh_3, K_2CO_3, CH_3CN, reflux, 10 h, 64 %; (f) Ag(I)F, CH_3CN, rt, 12 h, 65 %.

Enthused by the success of the concept, we proceeded with the proposed synthesis of the montanine type of alkaloids through this strategy.

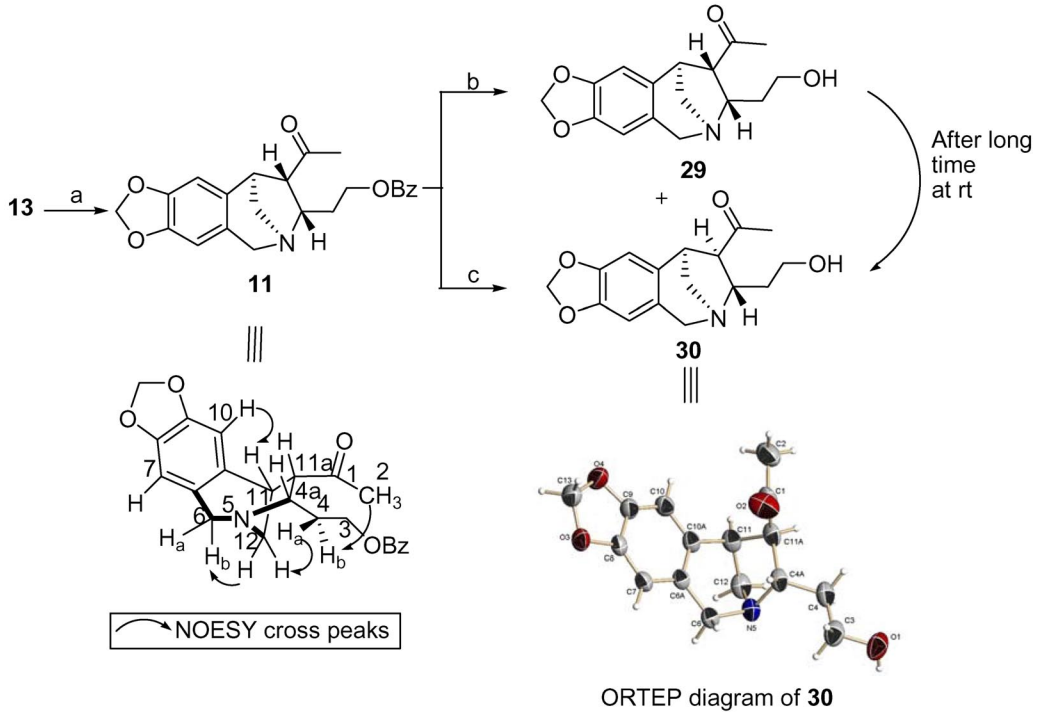
FORMAL TOTAL SYNTHESIS OF (±)-PANCRACINE

Initially, we focused our attention on synthesizing **10**, an advanced intermediate utilized by Overman et al. [15] in the total synthesis of the (±)-pancracine (**1a**), by the intramolecular cycloalkylation of **14**. The cycloaddition precursor **13** was prepared (60 % yield) by the Heck coupling of **14** with the methyl vinyl ketone (MVK, 8 equiv). Synthesis of **13** was achieved in 81 % yield by the N-alkylation of **16** with **15** in refluxing CH_3CN in the presence of activated K_2CO_3 followed by simple benzoylation of the primary hydroxyl group. The bis-silyated secondary amine **16** was synthesized (61 % overall yield) easily from 3-propan-1-ol (**24**) as shown in Scheme 3.

The intramolecular cycloaddition of AMY **12**, generated from **13** by following the standard cycloaddition protocol, gave **11** (56 % isolated yield) as a single diastereoisomer (Scheme 6). The stereochemical assignments of **11** were made by extensive correlation spectroscopy (COSY), nuclear Overhauser spectroscopy (NOESY), and heteronuclear correlation (HETCOR) NMR spectral studies [23]. With fused tetracyclic **11** in hand, the only task toward completing the formal synthesis of **1a** remained the construction of the E-ring through a cycloalkylation strategy. While debenzoylation of **11** by stirring with LiOH/MeOH at rt resulted in an unexpected epimerized alcohol **30** in 98 % yield (confirmed by X-ray crystallography) [24], reaction at 0 °C gave **29** (Scheme 4). Since C11a stereochemistry at this stage was irrelevant toward accomplishing the synthesis of final natural product, we continued further with **30** itself. Cycloalkylation attempt from corresponding mesylate derivative of **30** using lithium diisopropylamide/tetrahydrofuran (LDA/THF) [25] at –78 °C, surprisingly, produced rearranged **34** (65 % yield), possibly involving thermodynamic enolate **32** (Scheme 5) as an intermediate. This unexpected result led us to explore an alternative strategy of generating kinetic enolate from **30** using potassium bis(trimethylsilyl)amide (KHMDS)/THF [26] at –78 °C, which produced expected cyclized product **33** (11a-*epi*-**10**) in 58 % yield. In order to complete the formal total synthesis of **1a**,

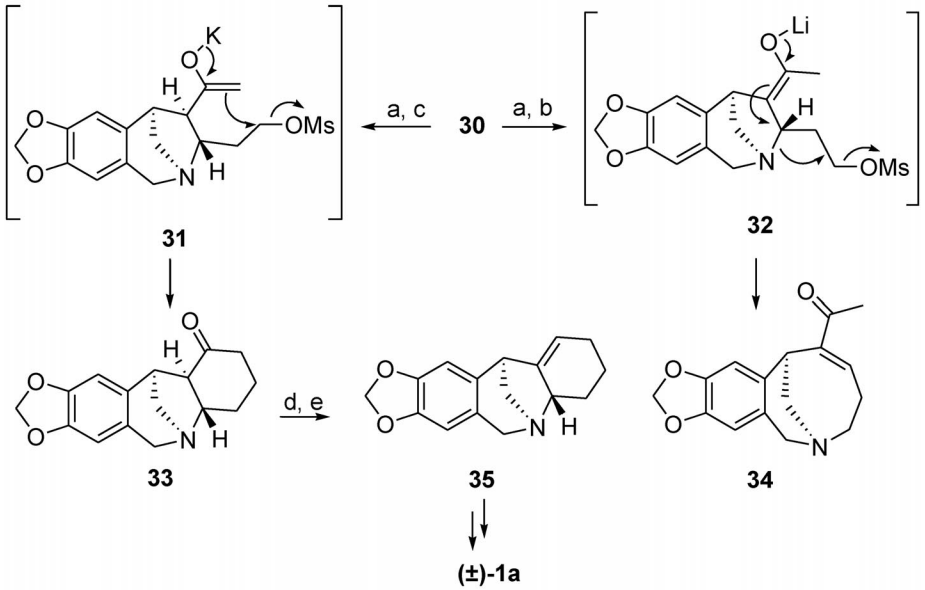


Scheme 3 Synthesis of cycloaddition precursor **13**. *Reagents and conditions*: (a) $(Boc)_2O$, Et_3N, CH_2Cl_2, 0 °C to rt, 36 h; (b) $CH_3CH(OEt)_2$, PPTS, benzene, reflux, 10 h, 90 % over two steps; (c) *s*-BuLi, TMEDA, THF, –78 °C, 4 h then TMSCl, 2 h, 92 %; (d) *p*-TSA, MeOH-H_2O, rt, 4 h, quant.; (e) 1N HCl, dioxane, 45 min, reflux, 92 %; (f) ICH_2TMS, K_2CO_3, CH_3CN, reflux, 10 h, 80 %; (g) **15**, K_2CO_3, CH_3CN, reflux, 10 h; (h) BzCl, Et_3N, CH_2Cl_2, 0 °C to rt, 6 h, 81 %; (i) $Pd(OAc)_2$, PPh_3, K_2CO_3, MVK, CH_3CN, reflux, 12 h, 60 %.



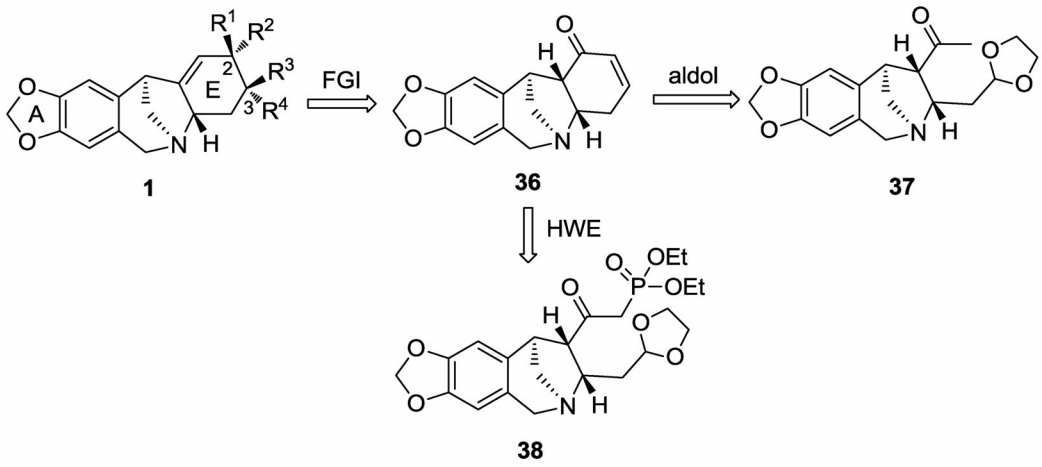
Scheme 4 Synthesis of **11**. *Reagents and conditions*: (a) Ag(I)F, CH_3CN, rt, 12 h, 56 %; (b) LiOH/MeOH, at 0 °C; (c) LiOH/MeOH, rt, 3 h, 98 %.

compound **33** was transformed to **35** (71 % yield) by reductive elimination of its corresponding enol triflate using $Pd(PPh_3)_4/Et_3SiH$ in THF [27]. The required enol triflate from **33** was generated by the reaction of the corresponding lithium enolate of **33** with the Comins reagent [28].

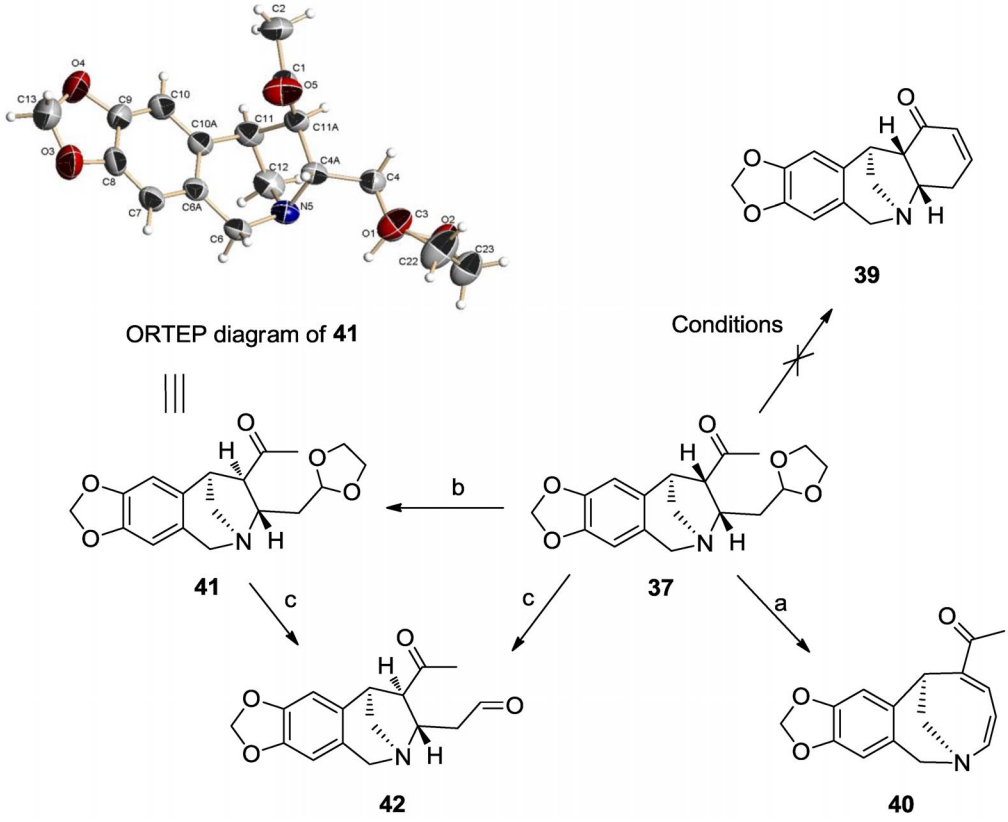


Scheme 5 Synthesis of (±)-**1a**. *Reagents and conditions*: (a) MsCl, Et_3N, DCM, 0 °C → rt, 15 min, quant.; (b) LDA, THF, –78 °C → rt, 5 h, 60 %; (c) KHMDS, THF, –78 °C → rt, 5 h, 58 %; (d) LDA, THF, Comins reagent, –78 °C → rt, 6 h; (e) $Pd(PPh_3)_4$, Et_3SiH, LiCl, THF, 60 °C, 24 h, 71 % over two steps.

After accomplishing the synthesis of **35** [8], an advanced intermediate used by Overman's group [15] in the synthesis of **1a**, we realized the limitation of this approach for the synthesis of other members of this class of alkaloids. Therefore, we turned our attention to designing a general route for the synthesis of other alkaloids of this class. Since there are variety of oxygen substituents at C-2 and C-3 in the E-ring, we envisioned **36** as an ideal precursor as its olefinic moiety could be useful for installing various oxygen functionalities stereoselectively. The synthesis of **36** was visualized either by an intramolecular aldol reaction of **37** or by Howards–Wadsworth–Emmons (HWE) olefination of **38** (Scheme 6). At first, we initiated the synthesis of **36** through an intramolecular Mukaiyama-type aldol reaction [29] of **37**, synthesized in 51 % yield by the usual cycloaddition reaction using appropriate substrate, by treating with trimethylsilyl trifluoromethanesulfonate (TMSOTf) (2 equiv) in the presence of 2,6-lutidine (3 equiv) in THF at –20 °C [30] which, unfortunately, gave an unexpected compound whose structure was tentatively assigned as **40**. This unanticipated failure also prompted us to evaluate the classical acid/base-catalyzed intramolecular aldol reaction [31] from the unmasked aldehyde obtained from **37**. Toward this end, deprotection of the dioxolane moiety of **37** was attempted initially under mild reaction conditions, viz.: (a) PPh_3, CBr_4, THF, 0 °C [32]; (b) dichlorodicyano-*p*-benzoquinone (DDQ), CH_3CN:H_2O (9:1), rt [33]; (c) TMSI, CH_3CN [34], however, none of the above-mentioned reaction conditions produced anticipated aldehyde. Surprised with these observations, we stirred **37** with 3N HCl in THF-H_2O (1:1) at rt, which also, unfortunately, produced an epimerized **41** and not the expected aldehyde. The structure of **41** was elucidated by detailed spectral analyses and confirmed by single-crystal X-ray crystallography [35]. Ultimately, deprotection of dioxolane moiety was achieved producing **42**, presumably involving **41**, in moderate yield (56 %) by refluxing **37** with 3N HCl for 10 h. Our entire attempt to transform **47** to corresponding aldol product under various acidic/basic conditions, however, again failed [31]. Therefore, we abandoned this route.

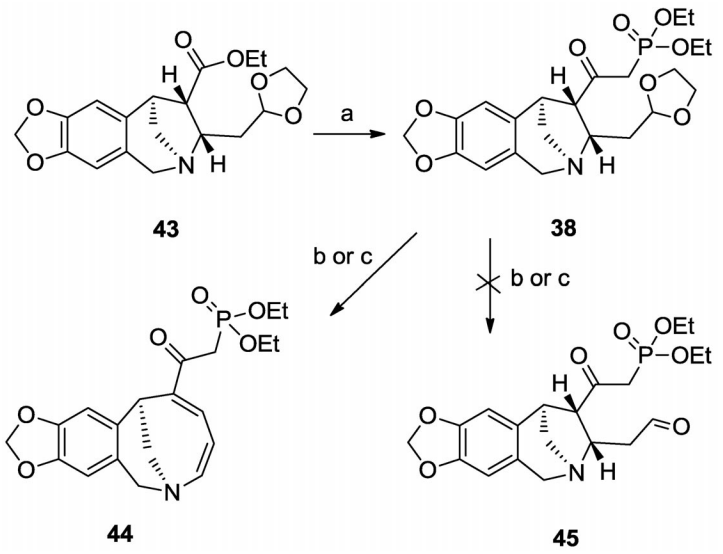


Scheme 6 General route for synthesis of **1**.



Scheme 7 Attempts for aldol reaction. *Reagents and conditions*: (a) TMSOTf, 2,6-lutidine, DCM, –20 °C → rt, 61 %; (b) 3N HCl, THF-H_2O, rt, 8 h, 90 %; (c) 3N HCl, THF-H_2O, reflux, 10 h, 56 %.

With these unanticipated hurdles, we envisioned to obtain **36** by intramolecular HWE reaction [36] of a corresponding aldehyde obtained from β-ketophosphonate **38**, synthesized (92 % yield) by the reaction of the lithium salt of the diethyl methylphosphosphonate on **43**. Similar to earlier observations, here also our attempt to deprotect dioxalone moiety of **38** to produce corresponding aldehyde under a variety of reaction conditions such as 3N HCl/THF-H_2O, oxalic acid/THF-H_2O failed, and it produced a rearrangement product identified as **44** (68 % yield) along with some other unidentified compounds (Scheme 8).

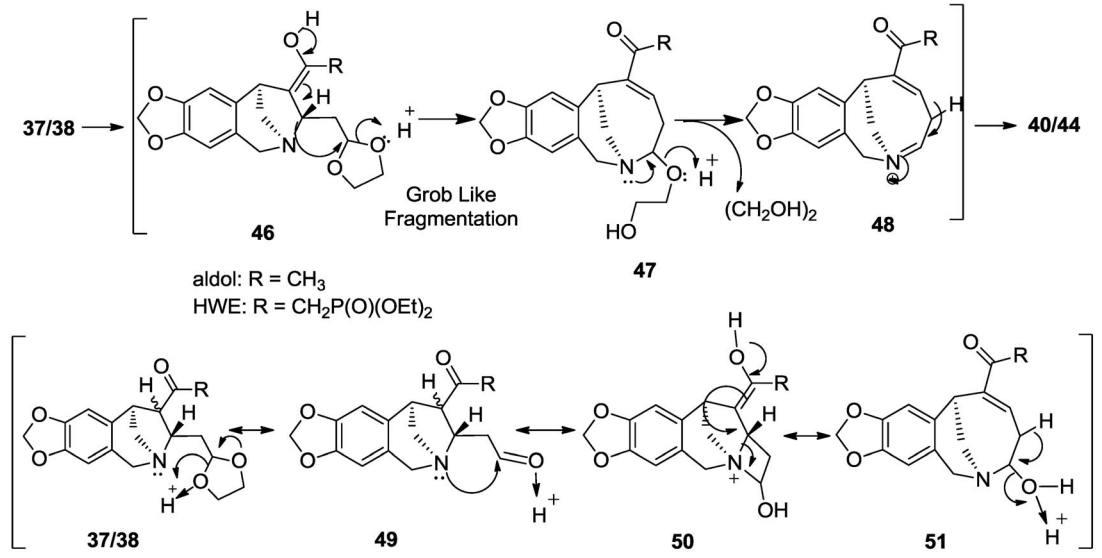


Scheme 8 Synthesis of β-ketophosphonate **38**. *Reagents and conditions*: (a) $CH_3PO(OEt)_2$, *n*-BuLi, at 0 °C then **43**, THF, 92 %; (b) 3N HCl, THF-H_2O (1:1), reflux, 10 h, 56 %; (c) oxalic acid, THF-H_2O (1:1), reflux, 10 h, 68 %.

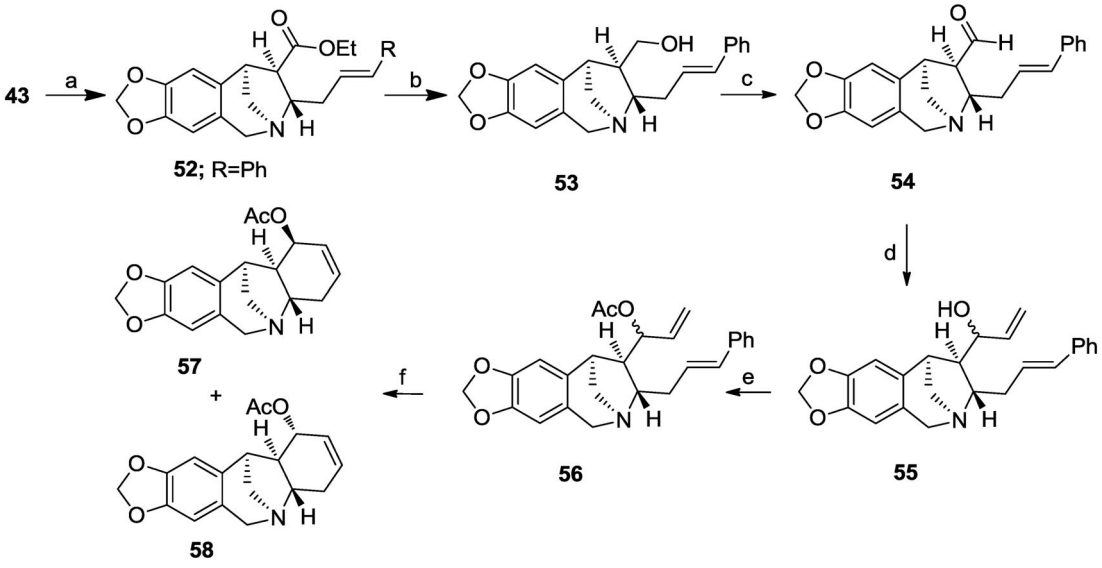
Mechanistically, this rearrangement was rationalized by invoking the thermodynamic enol-ether **46** followed by rearrangement either via Gröb-type fragmentation [37] or by involving azetidium salt intermediate **50** as shown in Scheme 9. Therefore, it may be concluded that during deprotection of the dioxolane moiety from both **37** as well as **38** either rearranges from five- to seven-membered ring to relieve strain or reaction stops at **41** with the epimerization at C11a center, which probably does not allow the cyclic enone **39** to be formed as it would lead to a conformationally strained system having three sp^2 carbons in the E-ring with "*anti*" stereochemistry at C11a and C4a.

With the above disappointing results and conclusion in mind, we proceeded to install C_2=C_3 double bond by ring-closing metathesis (RCM) of **56**, easily obtainable from **43** as shown in Scheme 10. Acetal moiety of **43** was deprotected by heating with oxalic acid/THF-H_2O (1:1), and corresponding aldehyde was subsequently subjected to one-carbon Wittig olefination using benzylidenetriphenylphosphorane (equivalent to one carbon Wittig) to obtain **52** in 60 % yield. Reduction of **52** first to alcohol **53** (96 % yield) using DIBAL-H (2.2 equiv) in dry dichloromethane (DCM) at –78 °C followed by standard Swern oxidation gave corresponding **54** quantitatively. Aldehyde **54** was straightway treated with vinylmagnesium bromide (1 M solution in THF) at 0 °C to produce **55** quantitatively as a mixture of two diastereomers. At this stage, exact diastereomeric ratios could not be ascertained; therefore, hydroxyl group of **55** was protected as acetate **56** by employing standard protocol [Ac_2O/TEA/DMAP (cat.)] and established the diastereomeric ratio as 2.5:1.

As per our planned strategy, the mixture of both of the diastereomers of **56** was forwarded to RCM utilizing original Grubb's reaction condition employing either first or second-generation [38] cat-



Scheme 9 Plausible mechanism for formation of rearrangement products.



Scheme 10 RCM route. *Reagents and conditions*: (a) (i) oxalic acid, THF-H_2O (1:1), reflux, 24 h; (ii) benzylidenediphenylphosphorane then aldehyde, 0 °C → rt, overnight, 60 %; (b) DIBAL-H, DCM, –78 °C → rt, 1 h, 96 %; (c) $(COCl)_2$, DMSO, DCM, –78 °C, 2 h then TEA, quant.; (d) vinylmagnesium bromide, THF, 0 °C → rt, 6 h, quant.; (e) Ac_2O, TEA, DMAP, DCM, 0 °C → rt, 4 h, 95 %; (f) **56.HCl**, Grubb's 2nd-generation catalyst (10 mol %), benzene, reflux, 12 h, 93 %.

alyst in DCM, which failed to give any product. However, this observation was not very surprising as it is known [39] that free/unprotected amine coordinates with the ruthenium catalyst and reduces the catalytic activity. Fortunately, it is also known that ammonium salts are tolerated very well by the [Ru] catalyst [40]. Therefore, metathesis of **56** was first examined in the presence of different acids such as *p*-TSA [41], $Ti(O^iPr)_4$ [42], and HCl [43] using Grubb's first-generation catalyst, but all the experi-

ments gave primarily starting material back even after 2–3 days. Finally, the reaction using Grubb's second-generation catalyst with **56.HCl** salt in DCM at 40 °C produced corresponding cyclized products **57:58** (2.5:1) in 93 % yield. Both these diastereomers (**57** and **58**) were isolated pure by flash column chromatography and were characterized by ^{1}H and ^{13}C NMR spectral analyses. The C_1-OAc stereochemistry for both the diastereomers was assigned on the basis of the extensive COSY and NOESY NMR studies. The NOESY spectrum of **58** revealed the presence of NOE cross-peak between H_1 and H_{4a}, suggesting "*syn*" relative stereochemistry between each other (Fig. 4) and the acetoxy group being in the "*endo*" position.

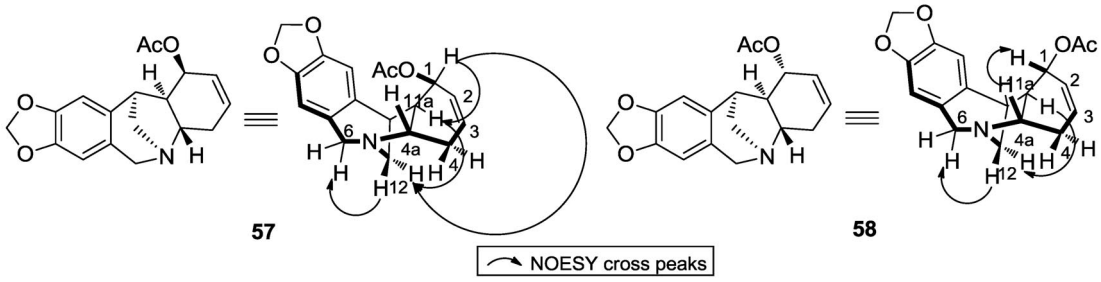


Fig. 4 Stereochemical assignment of **57** and **58**.

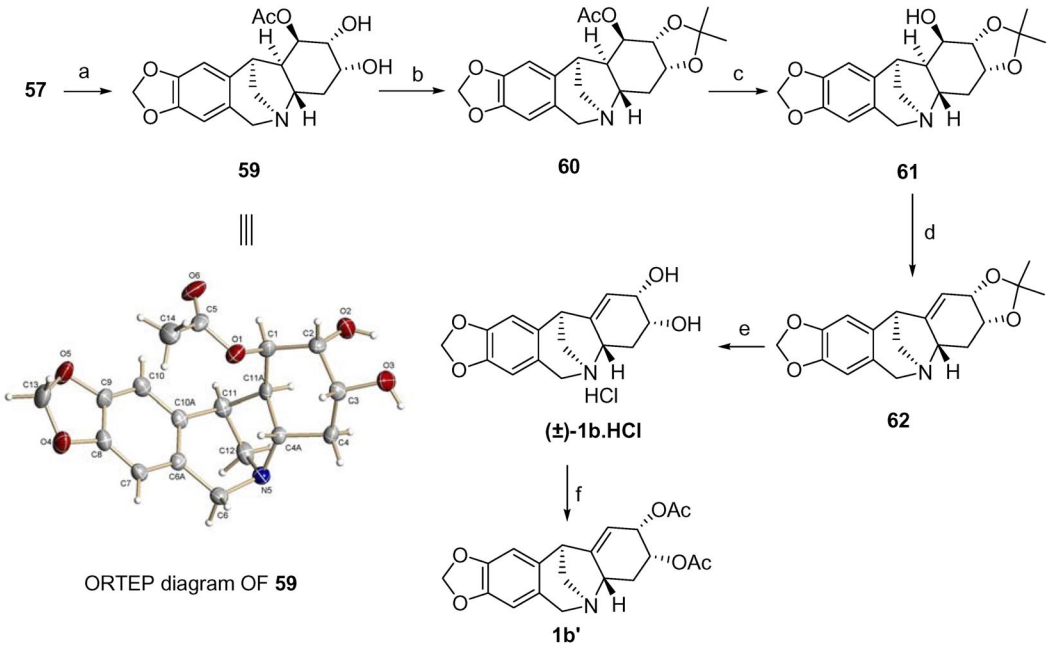
At this stage, we realized the potential of both these diastereomers (**57** and **58**) for the synthesis of the target natural products by functional group interconversions by exploiting the stereochemistry of allylic acetoxy functionality to direct the hydroxylation of olefinic double bond. In this context, we attempted first the total synthesis of (±)-brunsvigine (**1b**), an important member of this class.

SYNTHESIS OF (±)-BRUNSVIGINE (1b)

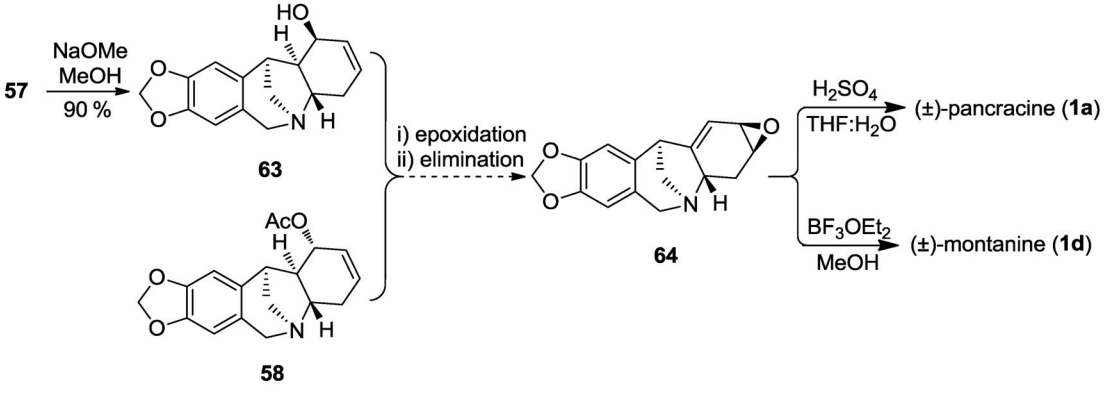
In order to achieve the total synthesis of (±)-brunsvigine (**1b**), the major diastereomer **57** was subjected to dihydroxylation using OsO_4/pyridine in ^{t}BuOH in the presence of trimethylamine *N*-oxide as a co-oxidant and obtained **59** quantitatively as a white crystalline solid.

Compound **59** was transformed to **60** in 95 % yield by isopropylidine protection (2,2-dimethoxypropane/*p*-TSA) of the vicinal dihydroxyl groups before installing the pivotal Δ-double bond [25a,29] required to complete the total synthesis of **1b**. Initially, dehydrogenative elimination of acetate moiety was attempted by using diazabicycloundecane (DBU) [39] at elevated temperature in benzene/toluene; however, it failed to yield the desired **62**. Therefore, acetate moiety was deprotected and mesylated, which on refluxing with DBU for 2 days in toluene gave **62** in 89 % yield. Finally, to complete the synthesis of **1b**, acetonide moiety was deprotected by passing HCl (gas) in its methanolic solution. For further purification and characterization, **1b.HCl** was directly transformed into corresponding diacetate derivative **1b'** (95 % yield) using acetic anhydride and triethylamine in presence of catalytic amount of *N*,*N*-dimethylaminopyridine (DMAP) (Scheme 11). The spectral data of compounds **62** as well as **1b'** (diacetate derivative) were found to be in excellent agreement with the values reported in the literature [18].

After successful synthesis of (±)-brunsvigine (**1b**), we visualized the scope of this strategy for the synthesis of other members of this class of alkaloids such as the (±)-pancracine (**1a**) and the (±)-montanine (**16**) from either one of the diastereomers (**57** or **58**) through the intermediate **64** as shown in Scheme 12. Toward transforming **57** to **64**, it was envisaged that **63**, obtained by acetate hydrolysis of either **57** or **58**, can deliver epoxide **64** depending on the sequence of epoxidation. Compound **64** on treatment with either H_2SO_4/THF-H_2O or $BF_3{\cdot}OEt_2$/MeOH can produce either (±)-pancracine (**1a**) or (±)-montanine (**1d**), respectively [12].



Scheme 11 Total synthesis of (±)-brunsvigine (**1b'**). *Reagents and conditions*: (a) OsO_4, trimethylamine *N*-oxide, pyridine, *t*-butanol-H_2O, 18 h, quant.; (b) DMP, *p*-TSA, acetone, rt, 6 h, 95 %; (c) NaOMe, MeOH, rt, 4 h, 91 %; (d) (i) MsCl, TEA, DMAP, DCM, 0 °C → rt, 5 h, quant.; (ii) DBU, toluene, 110 °C, 2d, 89 %; (e) HCl (gas), MeOH, 30 min., quant.; (f) Ac_2O, DMAP, pyridine, 20 h.



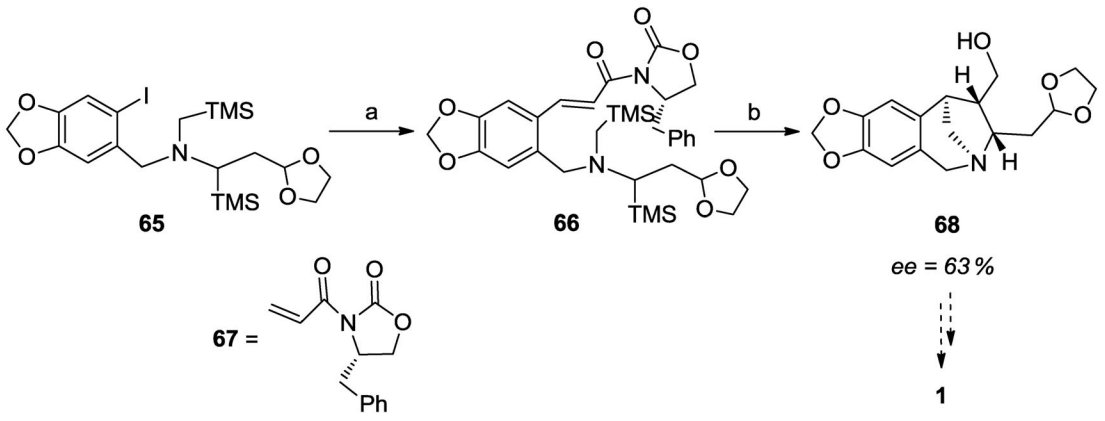
Scheme 12 Outline for the synthesis of (±)-pancracine (**1a**) and (±)-montanine (**1d**).

DEVELOPMENT OF A CHIRAL AUXILIARY-BASED ASYMMETRIC 1,3-DIPOAR CYCLOADDITION STRATEGY FOR THE SYNTHESIS OF THE ENANTIOMERICALLY ENRICHED 5,11-METHANOMORPHANTHRIDINE SKELETON

After successful synthesis of the 5,11-methanomorphanthridine alkaloids in racemic form, we turned our attention toward developing a general protocol for the synthesis of these alkaloids in enantiomerically enriched form. Most of the asymmetric approaches known for the synthesis of the montanine alkaloids are mainly based on chiral pool strategies except two recent reports where formal synthesis of the pancracine [21,22] is based on organocatalytic approaches. Since asymmetric 1,3-dipolar cyclo-

addition of AMYs with a variety of alkenes has emerged as one of the most powerful strategy for the construction of enantiopure pyrrolidine ring systems [44,45], developing an asymmetric [3 + 2]-cycloaddition approach for assembling the 5,11-methanomorphanthridine structural framework appeared worth exploring as it would be an entirely new concept in this area.

In this regard, we designed our strategy from the same intermediate **65** and equipped it with the Evans' oxazolidinone chiral auxiliary (Scheme 13) by the Heck coupling of known **67** [46] and obtained **66** in 65 % yield. The cycloaddition of **66** gave corresponding cycloadduct, which was subjected to lithium aluminum hydride (LAH) reduction without purification and characterization and obtained **68** (46 % yield, ee, 63 %, after single crystallization) [47]. Compound **68** can now easily be converted to RCM products **57** and **58** through **56** as discussed earlier in Scheme 10.



Scheme 13 Synthesis of **68**. *Reagents and conditions*: (a) $Pd(OAC)_2$, PPh_3, K_2CO_3, **67**, CH_3CN, reflux, 12 h, 65 %; (b) (i) Ag(I)F, CH_3CN, rt, 18 h; (ii) LAH, THF, 0 °C → rt, 86 %.

CONSTRUCTION OF 5,10B-ETHANOPHENANTHRIDINE STRUCTURAL FRAMEWORK

The maritidine (**2**a) and its structural analogues, isolated from *Pancratium maritimum*, *Pancratium tortuosum*, and *Zephyranthes* genera, are the first alkaloids with the 5,10b-ethanophenanthridine nucleus (**6**) containing dimethoxy rather than methylenedioxy substituents at C-8 and C-9 positions of the crinine skeleton. These alkaloids exhibit a wide range of interesting physiological effects, including antitumor, antiviral, acetylcholinesterase inhibitory, immunostimulatory, and antimalarial activities. The crinine (**2b**) is of particular interest owing to its cytotoxic properties and limited supplies from natural sources. Structurally, these alkaloids possess fused tetracyclic skeletons displaying adjacent quaternary and tertiary carbon stereocenters with the fused pyrrolidine ring systems for which stereochemical incorporation is the critical element in their synthesis.

A number of synthetic efforts have been employed to solve the challenging problem of incorporating these sterically congested stereocenters into the 5,10b-ethanophenanthridine structural framework. In this context, intramolecular oxidative *para–para* phenolic coupling [48–51] and Pictet–Spengler cyclization [48–67] of 3-aryl hydroindole derivatives have emerged as the two main strategies. In the former approach, spiro-fused dienone precursor **69** is obtained by the *para–para* coupling of the substituted norbelladine derivatives employing various oxidizing agents [48,49,51], photochemical cyclization [50], intramolecular Heck reaction [68], and cyclization of an iron carbonyl complex [51,52] intermediate. Substituted 3a-arylhydroindoles **70**, which are used for the Pictet–Spengler reaction, are synthesized through regioselective reduction of 1-methyl-3,3-disubstituted pyrrolidine-2,5-dione [59], intramolecular ene cyclization [60] of an appropriately constructed acylnitroso olefin, or condensation of 3-arylated Δ1-pyrrolinium salts with the *tert*-butyl 3-oxopent-4-enoate [61]. A few

other approaches reported for the synthesis of **2** 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 (Fig. 5) [69].

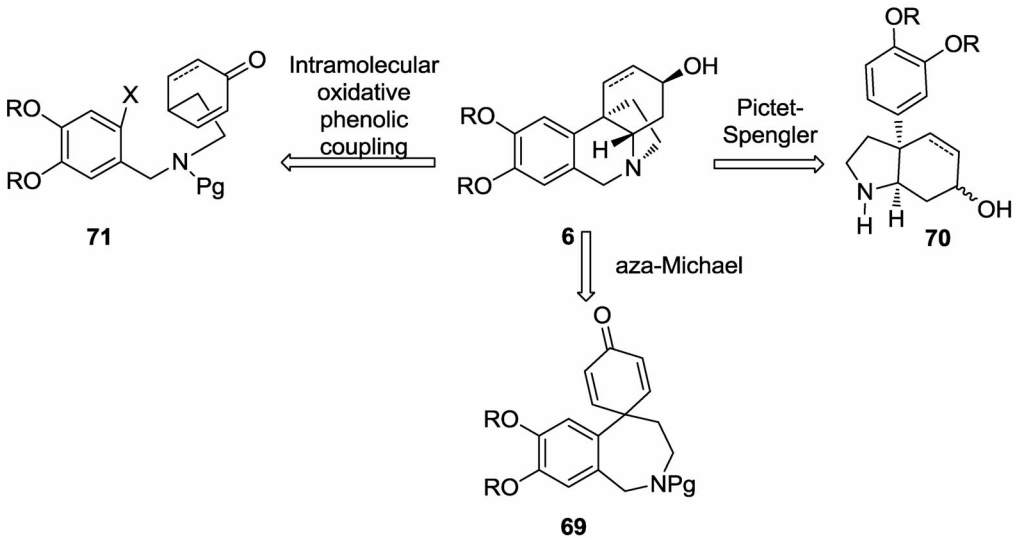
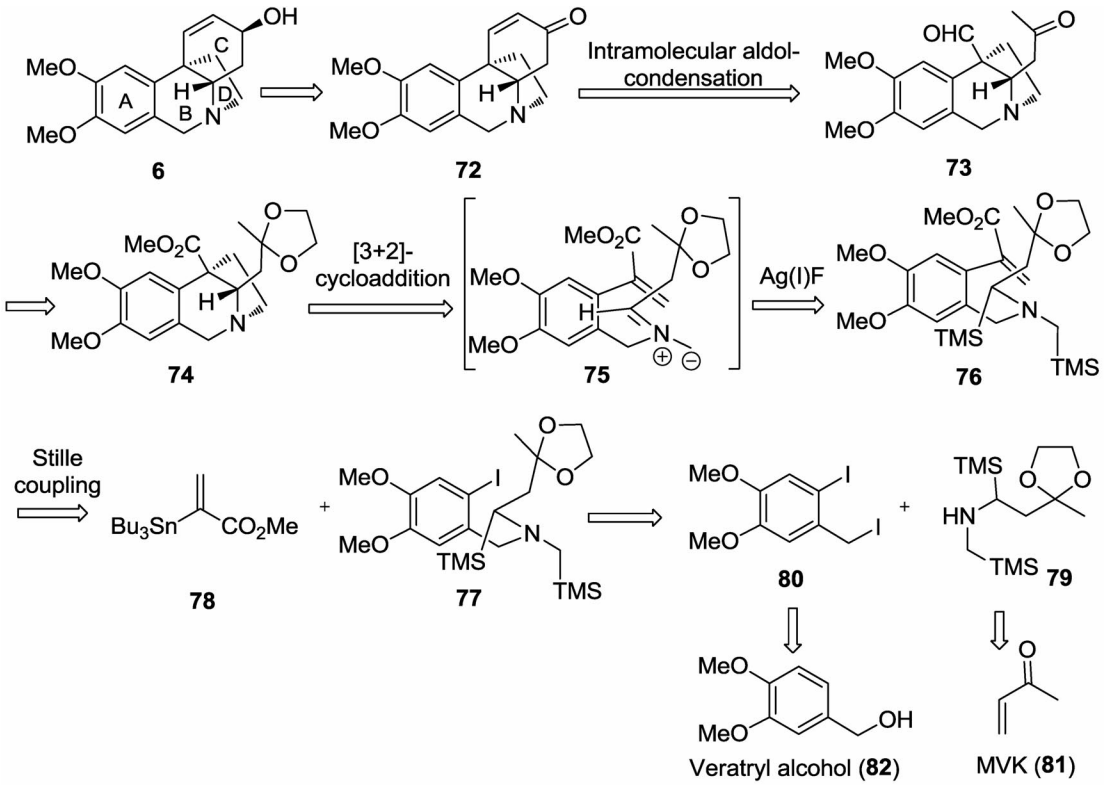


Fig. 5 Summary of the strategies reported for the synthesis of **2**.

RETROSYNTHESIS

While designing a versatile route to the 5,10b-ethanophenanthridine alkaloids such as maritidine via oxomaritidine **72**, we speculated the formation of C_1–C_2 double bond by the cyclo-aldolization/condensation of corresponding δ-keto aldehyde **73**, easily obtainable from **74**. A serious evaluation of **74** structure revealed the presence of fused pyrrolidine ring (BD rings) with adjacent vicinal quaternary and tertiary stereocenters. Thus, it was presumed that an intramolecular [3 + 2]-cycloaddition of a non-stabilized AMY **75** with tethered geminally disubstituted dipolarophile would result in the formation of both C_{4a}–C_{10b} and C_{11}–C_{12} bonds in one step, generating required stereocenters of **72** in a single step. The corresponding AMY could be generated in situ from the corresponding α,α'-bis(trimethylsilylmethyl) alkyl amine **76** as shown in Scheme 14.

The requisite precursor **76** required for the key transformation was proposed to be synthesized from modified Stille coupling [70] of corresponding aryl iodide **77** and a suitable vinyl stannane **78** [71]. The aryl iodide **77** can be synthesized by alkylation of bis-silylalkyl amine ketal **79** and diiodo component **80**. These components in turn may be obtained from commercially available veratryl alcohol (**82**) and MVK (**81**).



Scheme 14 Retrosynthetic analysis for maritidine.

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 was speculated on the basis of the change in the lowest unoccupied molecular orbital (LUMO) energy of the dipolarophile owing to its conjugation with the aromatic ring and ester moiety present on the same carbon. The cycloaddition reaction of **76** was visualized to generate the vicinal quaternary and tertiary carbon stereocenters in one step with the orientation of substituents in the dipole deciding the stereochemical outcome at C_{4a} position. For illustration, it was hypothesized that the alkyl ketal moiety in AMY (**75a**) may experience severe stereoelectronic congestion with the tethered aromatic ring flanked between the dipole and the dipolarophile as shown in transition state-I (**TS-I**) (Fig. 6) resulting in epimeric *epi-4a*-**74**. On the other hand, **TS-II**, in which the alkyl ketal side chain of AMY **75** and the aromatic ring are distantly away from each other, may generate the desired C_{4a} stereochemistry (**74**). Thus, we anticipated that substrate-controlled stereoelectronic favor during cycloaddition of **75** would reinforce the stereochemical outcome in the tricyclic skeleton with suitable stereochemical disposition of the substituents required for assembling of the C-ring of the target alkaloid.

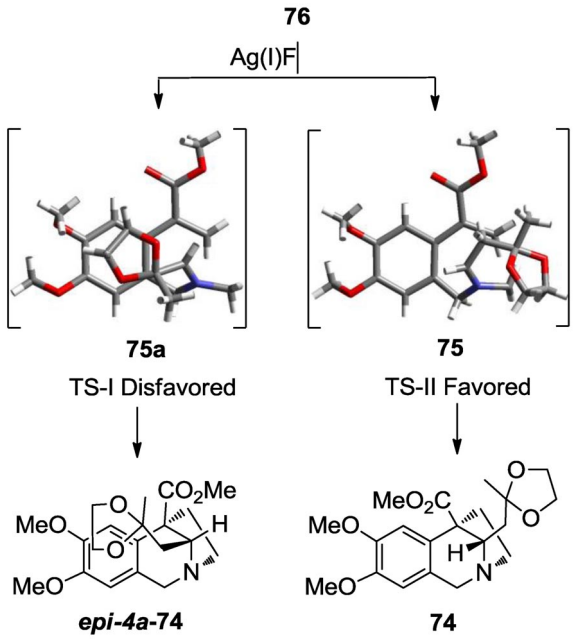
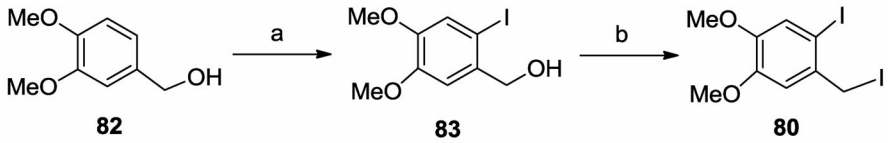


Fig. 6 Proposed TS model for [3 + 2]-cycloaddition step.

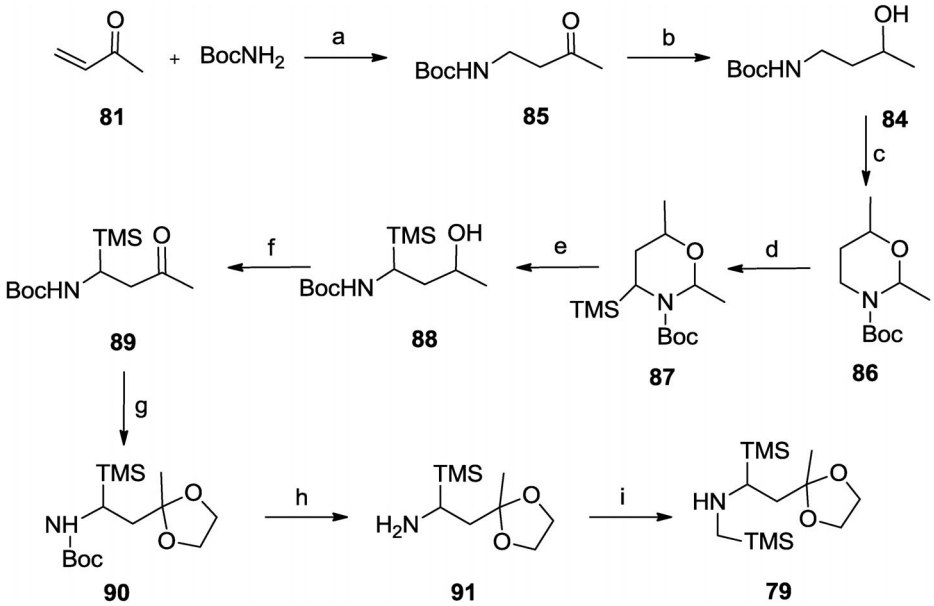
SYNTHESIS OF (±)-MARITIDINE

Our synthesis started with the assembling of the key precursor **76**, which involved coupling of **79** and **80** followed by Stille coupling with a suitably substituted vinyl stannane (**78**). Aromatic electrophilic iodination [72] of commercially available veratryl alcohol (**82**) with the iodine using silver trifluoroacetate as a Lewis acid afforded **83**, which was converted to **80** in quantitative yield by treating with NaI and TMSCl in CH_3CN at rt (Scheme 15).



Scheme 15 Synthesis of **80**. *Reagents and conditions*: (a) I_2, CF_3COOAg, DCM, rt, 65 %; (b) NaI, TMSCl, CH_3CN, rt, quant.

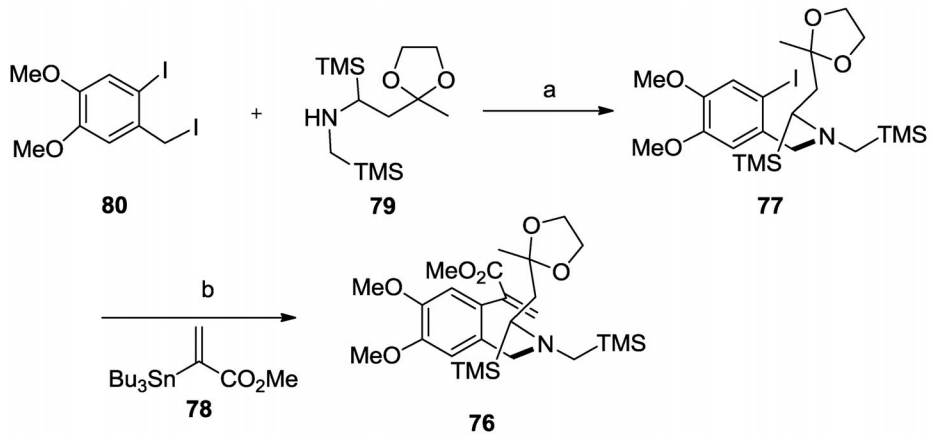
The other component **79** was obtained by following the sequence as shown in Scheme 16. The *N*-Boc-protected amino butanol **84** was synthesized (70 % yield) in two steps starting from the commercially available MVK (**81**) and $BocNH_2$. Refluxing a solution of **84** and acetaldehyde diethyl acetal in the presence of a catalytic amount of pyridinium *p*-toluenesulfonate (PPTS) in benzene, while azeotropic removal of ethanol, gave N-Boc protected cyclic amine **86** quantitatively. Treatment of **86** with *s*-BuLi/TMEDA at –78 °C in THF followed by the addition of TMSCl gave **87** in 85 % yield [73]. The amino acetal deprotection of **87** by stirring with *p*-TSA in MeOH gave corresponding amino alcohol **88** in quantitative yield, which upon oxidation using *o*-iodosoxybenzoic acid (IBX) in refluxing EtOAc produced **89** in 90 % yield. The ketalization of **89** by refluxing with the ethylene glycol and catalytic *p*-TSA in benzene, while azeotropic removal of the water, gave **90** in 80 % yield which on N-Boc



Scheme 16 Synthesis of **79**. *Reagents and conditions*: (a) BF_3:OEt_2, dry DCM, 4 h, 70 %; (b) $NaBH_4$, dry MeOH, 0 °C → rt, 4 h, quant.; (c) $CH_3CH(OCH_2CH_3)_2$, PPTS, dry C_6H_6, reflux, 87 %; (d) s-BuLi, TMEDA, dry THF, –78 °C then TMSCl, 85 %; (e) *p*-TSA , methanol:water 9:1, rt, quant.; (f) IBX, EtOAc, reflux, 90 %; (g) ethylene glycol, *p*-TSA, benzene, Dean-stark, 80 %; (h) (i) TFA, dry DCM; (ii) $TMSCH_2I$, K_2CO_3, CH_3CN, reflux, 70 %.

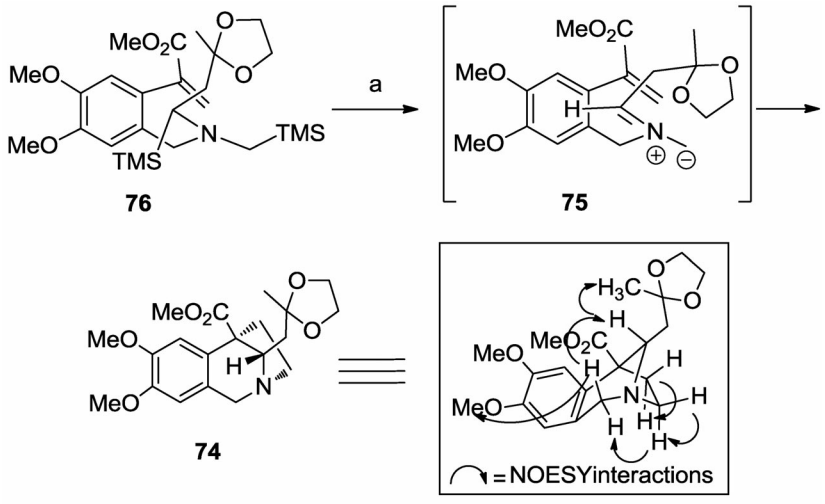
deprotection using trifluoroacetic acid (TFA) in dry DCM at rt, followed by the N-alkylation using iodomethyl trimethylsilane in presence of the excess of K_2CO_3 in refluxing acetonitrile afforded bis-silylated amine **79** in 70 % yield.

Having both the fragments **79** and **80** in hand, we coupled them together by refluxing in dry CH_3CN in the presence of anhydrous K_2CO_3 to obtain **77** in 70 % yield as shown in Scheme 17. Stille coupling of **77** with suitably substituted vinyl stannane **78** using Corey's protocol [74] {LiCl, CuCl, cat. $[Pd(PPh_3)_4]$ dry DMSO at rt} followed by heating at 60 °C for 2 h gave key **76** in 73 % yield. Usual



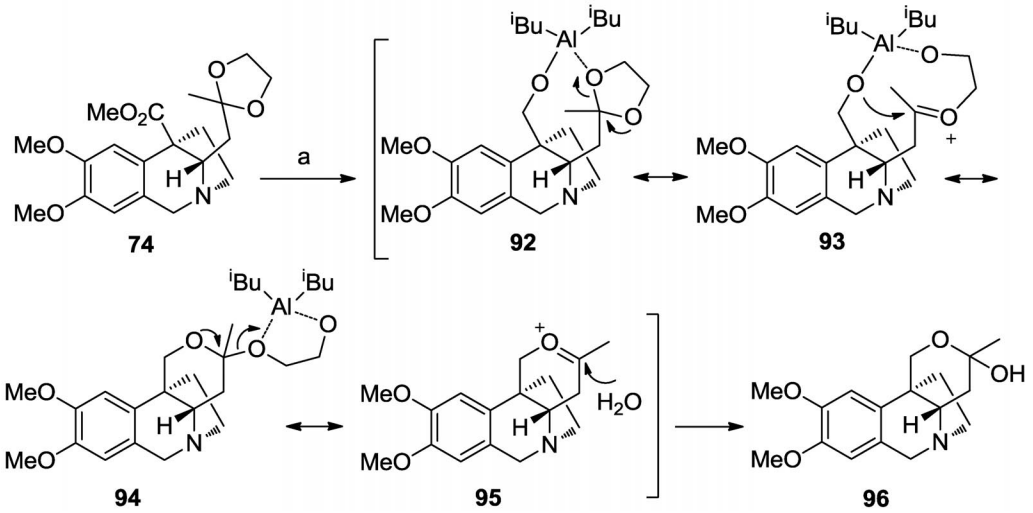
Scheme 17 Synthesis of **76**. *Reagents and conditions*: (a) K_2CO_3, CH_3CN, reflux, 70 %; (b) **78**, LiCl, CuCl, $Pd(PPh_3)_4$, DMSO, 73 %.

cycloaddition of the AMY generated from **76** produced **74** as a yellow gummy liquid in 56 % yield. The stereochemical assignment of **74** was assigned by extensive COSY, NOESY, and HETCOR NMR studies (Scheme 18).



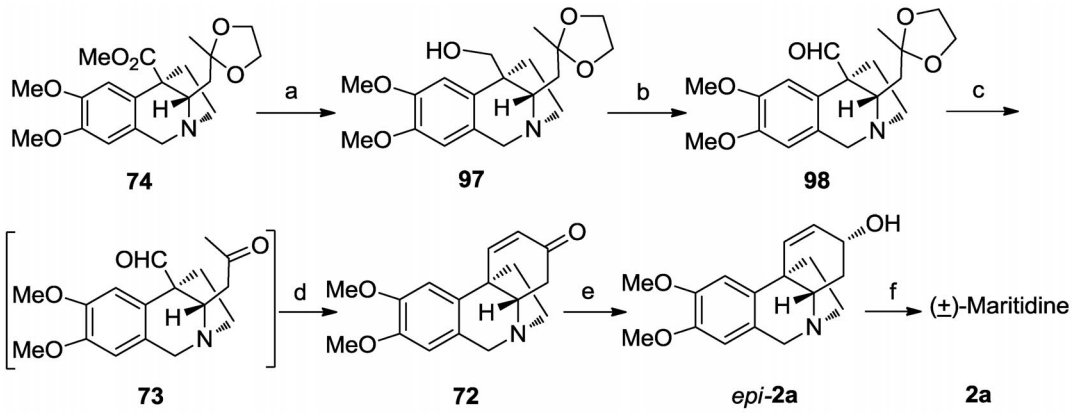
Scheme 18 Synthesis of tricyclic core of maritidine. *Reagents and conditions*: (a) Ag(I)F, DCM, rt, 56 %.

After successful synthesis and complete characterization of **74** with ABD ring, the next task toward the completion of the synthesis of the natural product remained the construction of ring C. In order to proceed further along the proposed synthesis, **74** was subjected to diisobutylaluminum (DIBAL) reduction. However, this reaction led to the reduction of ester functionality along with ketal deprotection presumably via coordination of alkoxy aluminum with ketal oxygen followed by the deprotection of ketal group to give stable hemiketal **96** (Scheme 19). Thus, we adopted a two-step protocol of reduction–oxidation involving LAH reduction of **74** followed by Swern oxidation, which gave **98** in 90 % yield. The deprotection of the ketal moiety of **98** using *p*-TSA in acetone followed by stir-



Scheme 19 DIBAL-H reduction of **74**. *Reagents and conditions*: (a) DIBAL-H, DCM, –78 °C.

ring with ethanolic NaOH afforded oxomaritidine **72** as a white powder in 65 % yield [69a] (Scheme 20). Reduction of **72** under Luche reduction [75] condition gave *epi*-maritidine (*epi*-**2a**), which upon mesylation followed by substitution using CsOAc and saponification gave maritidine **2a** in 45 % yield (Scheme 20). The spectral data of **2a** were found in good agreement with those of the reported one [68a].

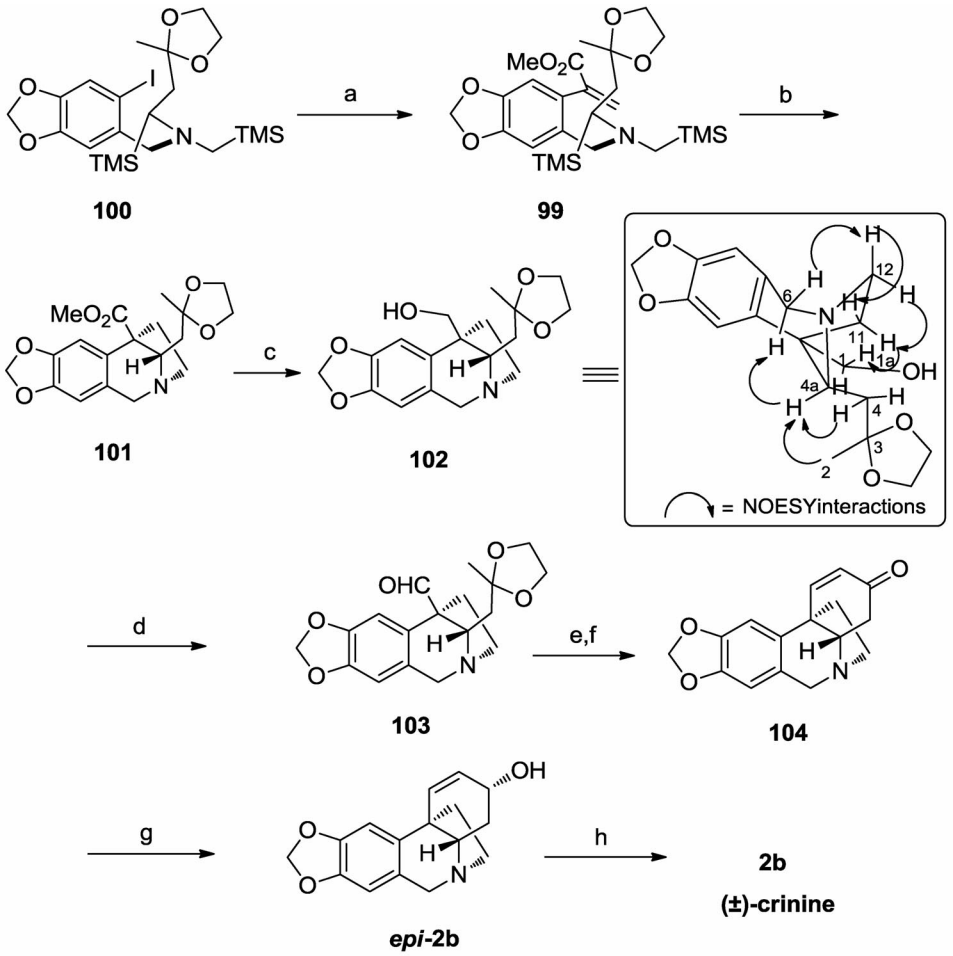


Scheme 20 Synthesis of maritidine. *Reagents and conditions*: (a) LAH, THF, rt, 90 %; (b) $(COCl)_2$, DMSO, DCM, –78 °C, 3 h then Et_3N, 90 %; (c) *p*-TSA, acetone; (d) NaOH, EtOH, rt, 65 %; (e) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, rt, 90 %; (f) (i) MsCl, Et_3N, DCM, (ii) CsOAc, DMF, (iii) K_2CO_3, MeOH, 50 %.

SYNTHESIS OF (±)-CRININE (2b)

After accomplishing the total synthesis of **2a**, we focused toward synthesizing the (±)-crinine (**2b**). The crinine type of alkaloids elicits continued interest in the synthetic community owing in part to their intriguing physiological activities [5,6], as exemplified by the recent study unveiling highly selective apoptosis induction properties against tumor cells at as low as micromolar concentration. The crinine alkaloids are also shown to possess immunostimulant, antitumor, and antiviral activities [76].

The synthesis of **2b** was accomplished via the cycloaddition of **99** by following identical synthetic steps as described above for **2a** (Scheme 20). The stereochemistry of **102** was established by detailed COSY, NOESY, and HETCOR studies. The spectral data of **2b** were found in good agreement with that of the reported one [68b].



Scheme 21 Synthesis of (±)-crinine (**2b**). *Reagents and conditions*: (a) **79**, LiCl, CuCl, cat. Pd(PPh3)4, DMSO, 73 %; (b) Ag(I)F, dry DCM, 56 %; (c) LAH, THF, rt, 90 %; (d) $(COCl)_2$, DMSO, DCM, –78 °C, 3 h then Et_3N, 90 %; (e) *p*-TSA, acetone; (f) NaOH, EtOH, rt, 65 %; (g) $NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, rt, 90 %; (h) (i) MsCl, Et_3N, DCM, (ii) CsOAc, DMF, (iii) K_2CO_3, MeOH, 50 %.

CONCLUSION

We have successfully developed a conceptually new and versatile protocol for the construction of the 5,11-methanomorphanthridine and 5,10b-phenanthridine structural frameworks using [3 + 2]-cycloaddition of a nonstabilized AMY as a key step. The strategy is successfully applied for the total syntheses of (±)-pancracine, (±)-brunsvigine, (±)-maritidine, and (±)-crinine alkaloids.

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23. The absence of NOESY cross-peaks for 4a-H–12-H and 11a-H–12-H clearly confirm the *endo* orientation of C-12 in **11** and *J*(C-11a,C-4a) = 8.74 Hz for the *cis* configuration of C-11a and C-4a.
24. X-ray analysis of **30** ($C_{16}H_{19}NO_4$): CCDC-271169 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via <www.ccdc.cam.ac.uk/data_request/cif>.
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47. HPLC conditions: Chiralcel column: OD-H (250_4.6 mm), ethanol/petroleum ether (10:90), flow rate 0.5 mL/min (280 psi), retention times of 27 and 30 min, ee (obsd.) ≈ 63 %.
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