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Synthesis of biologically active natural products by [3+2] cycloaddition of non-stabilized azomethine ylides (AMY): Concepts and realizations

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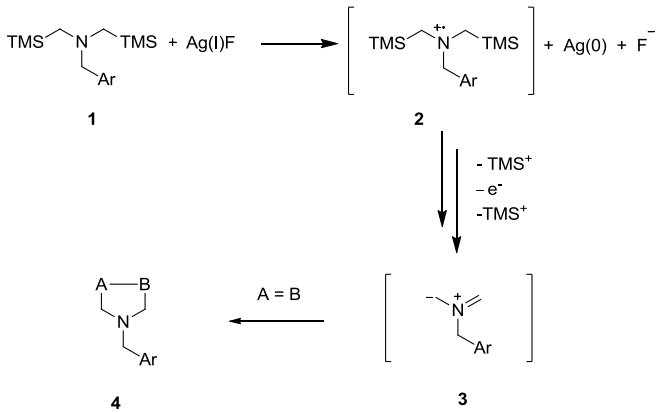
ABSTRACT

Non-stabilised azomethine ylides (AMY) which are represented as a zwitterionic form of a C-N-C unit having four electrons in three parallel atomic π orbitals perpendicular to the plane of the dipole, undergoes 1,3-dipolar cycloaddition to produce isolated as well as fused pyrrolidine ring system stereoselectively. Various new structural entities related to *x*-azatricyclo[*m.n*.0.0*a,b*]alkanes are constructed by the intramolecular 1,3-dipolar cycloaddition of nonstabilized cyclic azomethine ylides. The ylide is generated by the sequential double desilylation of *N*-alkyl α, α'-bis(trimethylsilyl)cyclic amines using Ag(I)F as a one-electron oxidant. Various alkaloids such as (±)-pancracine, (±)-brunsvigine, (±)-maritidine, (±)-crinine, (-)-vincodifformine and (+)-aspidospermidine have been synthesized employing AMY cycloaddition strategy.

1. Introduction

Isolated as well as fused pyrrolidine rings are common scaffolds found in vast number of biologically active alkaloids,[1] therefore, their construction in an efficient manner has attracted attention of a large number of synthetic organic chemists. Although, there are many approaches known to construct substituted pyrrolidine rings in regio- and stereo-selective manner,[2,3] [3+2]-cycloaddition reaction of azomethine ylides (AMY) with a suitable olefins is the most reliable and attractive approach.[4] Azomethine ylides[5] are represented by a zwitterionic structure with a C-N-C unit having four electrons in three parallel atomic π orbitals perpendicular to the plane of the dipole which reacts with another π system (olefins) involving a total of six π electrons [π4s + π2s] and is considered to proceed through a thermally allowed[6] concerted process, though, non-concerted possibility is also suggested.[7] A detailed account on the mechanistic discussion of AMY and its cycloaddition could be found in literature.[8] Our group has developed[9] an innovative concept to generate non-stabilized AMY **3** via one electron oxidation of N, N'-dialkylsilylamines **1** either by photoredox catalysis[9a] or by using Ag(I)F as one electron oxidant.[9b] Mechanistically, this reaction was rationalized considering sequential desilylation[10] from the amine radical cation **2**, thus, generated after one electron oxidation of corresponding amine. The resultant AMY reacts inter-or intra-molecularly with an activated olefin to generate fused or isolated pyrrolidine **4** scaffolds, respectively[9a,b,11] as shown in **Scheme 1**.



Scheme 1: Pyrrolidine ring generation through 1,3 dipolar cycloaddition.

This strategy was utilized to construct indolizidine and pyrrolizidine skeletons by [3+2]-cycloaddition[9b] of corresponding AMY **6**, generated by the sequential desilylation of **5**, with ethyl acrylate **7**. The cycloaddition provided two regeoisomeric pyrrolizidines **8** and **9** in 17:3 ratios. Since the isolation of pure diastereomers was difficult, the mixture was reduced by LAH to

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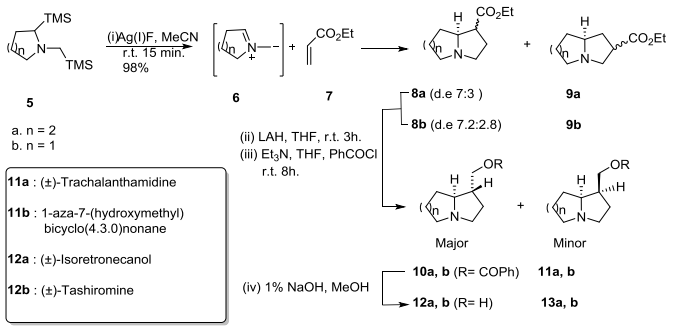
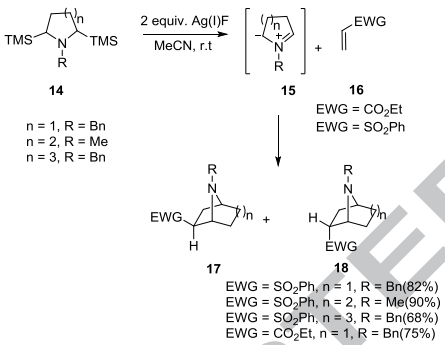
produce corresponding alcohols which upon derivatization with benzoyl chloride were separated to obtain pure diastereomers [**10** (major) and **11** (Minor)]. The stereochemical assignments were suggested on the basis of spectral comparison[12] after their conversion to alkaloids (±)-trachelanthamidine (**11a**) and (±)-isoretronecenol (**12a**). A similar sequence from **8b** provided a short synthesis of indolizidine natural products, 1-aza-7-(hydroxyl)-bicyclo[4:3:0] nonane[13a] (**11b**) and (±)-tashiromine (**12b**)[13b] as shown in **Scheme 2**.



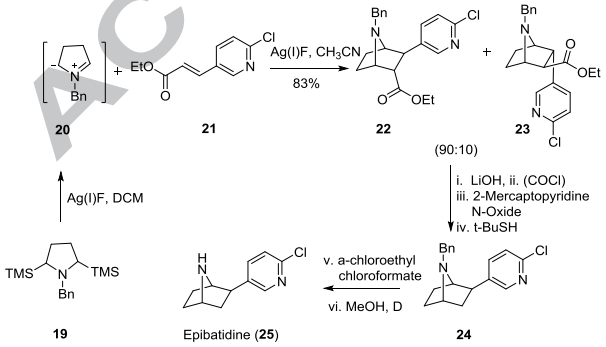
Scheme 2: Natural product synthesis through AMY

Furthermore, generation of cyclic AMYs[11] of the type **15** from **14** and their trapping with suitable dipolarophiles **16** was utilized to construct x-azabicylo[m.2.1]alkanes (**17** and **18**) ring system with good *exo*/*endo* selectivity[14] as shown in **Scheme 3**.



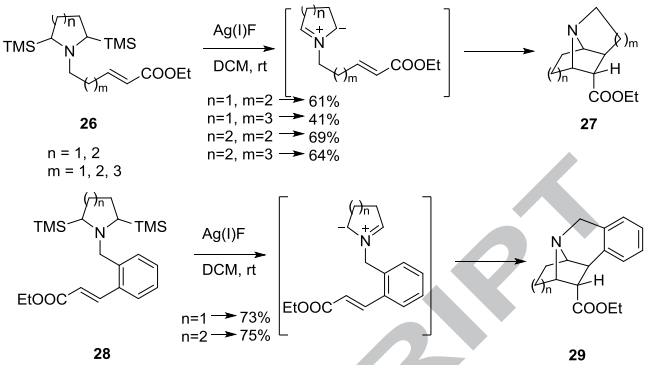
Scheme 3: Synthesis of x-azabicylo[m.2.1]alkanes

This strategy was extended for the synthesis of epibatidine[11c] (**25**), an entirely new class of analgesic alkaloid which possesses 7-azabicyclo [2.2.1] heptane skeleton to which a 5-(2-chloropyridinyl) substituent is attached in *exo*-orientation. (**Scheme-4**)



Scheme 4: Synthesis of Epibatidine.

Optically pure (-)-**24** was also synthesized[11c] by carrying out cycloaddition of **15** using chiral dipolarophile which produced corresponding cycloadducts in 9:1 diastereomeric mixture. As a part of further exploration of this reaction, substrates **26** and **28** on AMY generation and cycloaddition gave corresponding bicyclic products (**27** and **29)** in excellent yields and selectivity.[11e] **(Scheme 5)**



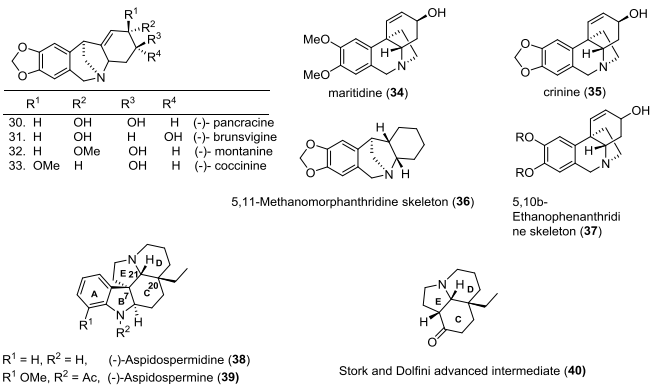
Scheme 5: Fused pyrrolidine ring generation through intramolecular 1,3-dipolar cycloaddition

Driven by these successes, synthesis of some important biologically active natural products were taken up to establish the efficacy this strategy

2. APPLICATION IN NATURAL PRODUCT SYNTHESIS

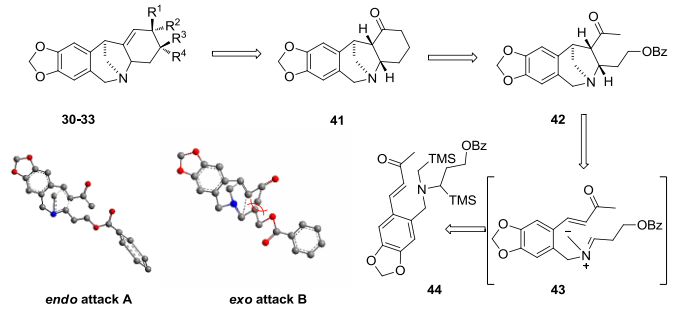
Amaryllidaceae class[15] of alkaloids are known to display wide range of biological activities[16,17] such as antitumor, antiviral, acetylcholinesterase (AChE) inhibitory, immunostimulatory, antimalarial, anxiolytic, antidepressive, anticonvulsive and weak hypotensive activity. Since majority of these alkaloids possesses fused pyrrolidine ring system, synthesis of some these natural products were selected to establish the efficacy this strategy.[18,19]

Figure 1: Pyrrolidine ring containing Amaryllidaceae and Aspidosperma alkaloids.



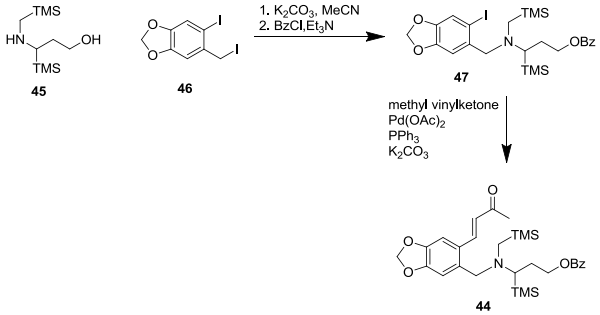
Therefore, we synthesized some of these natural products utilizing 1,3-dipolar cycloaddition of corresponding non-stabilized AMY generated through the concept delineated above.

At first, construction of alkaloids having pentacyclic 5,11-methanomorphanthridine scaffold, encompassing alkaloids of amaryllidaceae subclass such as [(±)-pancracine (**30**), (±)-brunsvigine (**31**) (±)-montanine (**32**), and (±)-coccinine (**33**),] which are associated with a variety of biological activities (Figure 1)[20] were initiated. We accomplished the synthesis of some of these alkaloids by [3+2]-cycloaddition of AMY **43**. While designing the synthetic route for **30**-**31**, it was envisioned that intramolecular *endo* attack (A) of AMY **43** on the "*re*" face of the α,β-unsaturated carbonyl moiety would be energetically more



Scheme 6: Retrosynthetic planning for alkaloids.

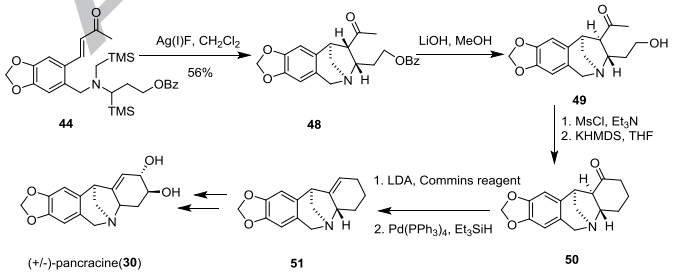
favored than *exo*-attack (B) due to steric repulsion. Such a cycloaddition was also expected to fulfill all the stereochemical requirements of **42** in a single step without using a starting material with fixed stereocenters. (**Scheme 6**)



Scheme 7: Synthesis of AMY precursor.

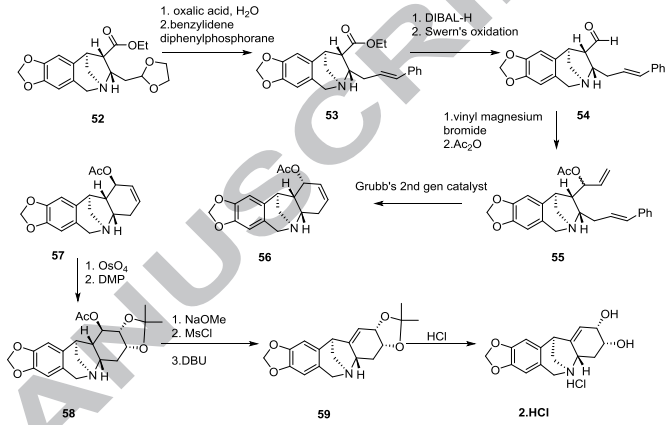
The cycloaddition precursor **44** was prepared (60 % yield) by the Heck coupling[21] of **47** with the methyl vinyl ketone (MVK, 8 equiv.). Synthesis of **47** was achieved in 81 % yield by the N-alkylation of **45** with benzyl iodide (**46)** in refluxing CH_3CN in the presence of activated K_2CO_3 followed by simple benzoylation of the primary hydroxyl group. The bis-silylated secondary amine **45** was synthesized easily from 3-propan-1-ol following literature protocol.[22] **(Scheme 7)**

Cycloaddtion of **44** in acetonitrile in the presence of Ag(I)F as one electron oxidant produced **48** smoothly in 56% yield which on debenzoylation with LiOH/MeOH gave **49**. Interestingly, the important C12 stereocenter epimerized during this reaction. Conversion of free –OH moiety to mesylate followed by intramolecular cyclization under kinetic control[23] using KHMDS furnished **50**. The resultant **50** was converted to enol triflate by enolisation using LDA followed by Commin's reagent[24] which on treatment with palladium (0) gave **51** in excellent yield. (±)-Pancracene (**30**) was synthesized from this intermediate by following known procedure.[25] (**Scheme 8**)



Scheme 8: Formal synthesis of (±)-pancracine.

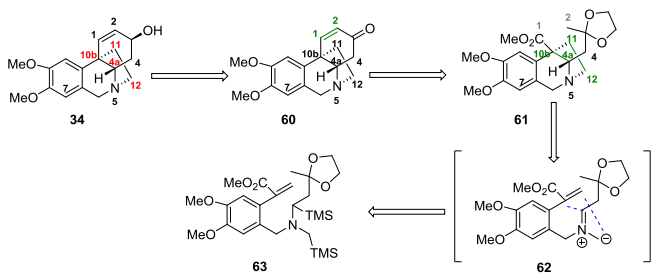
Relatively different synthetic sequence was adopted for the synthesis of (±)-brunsvigine (**31**) from **52,** formed by the cycloaddition of corresponding AMY precursor.[26] Acetal moiety deprotection of **52** by oxalic acid/THF-H_2O followed by one-carbon Wittig olefination[27] produced **53** which on **r**eduction with DIBAL-H and re-oxidation under Swern oxidation condition[28] gave **54**. Reaction of **54** with vinyl magnesium bromide followed by acetate protection of free –OH group produced **55** as a mixture of two diastereomers. Ring closing metathesis (RCM)[29] using Grubb's second-generation[30] catalyst with **55**.HCl salt in DCM produced corresponding cyclized products **56**:**57** in 1:2.5 ratio. The major diastereomer **57** was subjected to dihydroxylation followed by isopropylidine protection to generate **58**. After –O-acetate deprotection followed by mesylation, it was refluxed with DBU for 2 days in toluene to give **59**. Finally, the synthesis of **31** was completed after acetonide deprotection by passing HCl (gas) in its methanolic solution. (**Scheme 9**)



Scheme 9: Stereoselective synthesis of racemic brunsvigine.

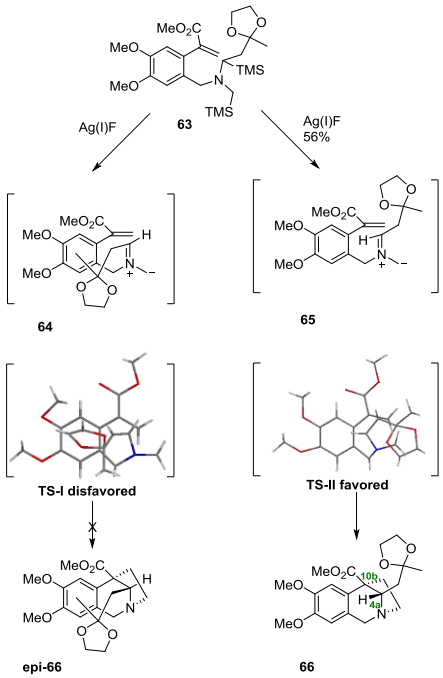
Maritidine (**34**), another important member of *Amaryllidaceae* alkaloids, isolated from *Pancratium maritimum*, *Pancratium tortuosum*, and *Zephyranthes* genera, is one of the first alkaloid to possess a 5,10b-ethanophenanthridine nucleus containing dimethoxy rather than methylenedioxy substituents at C-8 and C-9 positions of the crinine skeleton[31] (Figure 1). These alkaloids display structural complexities due to the presence of adjacent quaternary and tertiary carbon stereocenters with a fused pyrrolidine ring. Proper stereospecific installation of substituents has been the key challenge to the synthesis of these types of alkaloids.

While envisaging a novel route[32] towards the synthesis of **34** via oxomaritidine (**60)**, we constructed C1–C2 double bond by the cyclo-aldolization/ condensation of corresponding methylester **61**. After serious evaluation of **61**, it was convincing enough to evaluate an intramolecular [3 + 2]-cycloaddition of a non- stabilized AMY **62** with tethered geminally disubstituted dipolarophile for the formation of both C4a–C10b and C11–C12 bonds in one step which would also generate required stereocenters of **61** in a single step. The corresponding AMY was generated in situ from the corresponding α,α'-bis(trimethylsilyl-methyl) alkyl amine **63** using Ag(I)F as one electron oxidant. **(Scheme 10)**



Scheme 10: Retrosynthetic analysis of Maritidine.

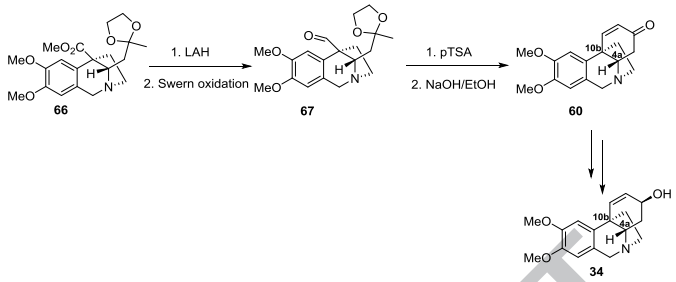
The requisite precursor **63** was synthesized by the simple transformation of commercially available veratryl alcohol and methyl vinyl ketone.[33]



Scheme 11: Rationale for regio- and stereoselectivity.

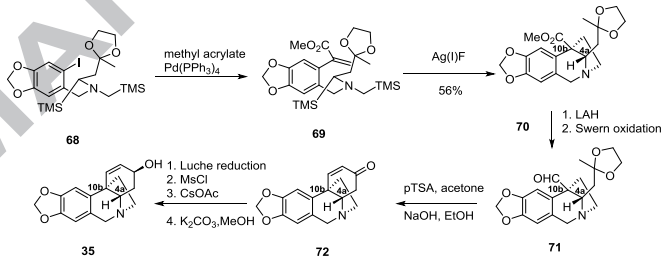
Regio- as well as stereoselectivity issues, the two important aspects of this cycloaddition protocol, were critically scrutinized at the planning stage. The origin of the 5,10b-ethanophenanthridine regiochemistry during cycloaddition was envisioned on the basis of the change in the lowest unoccupied 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 **63** 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 C4a position. For illustration, it was envisioned that the alkyl ketal moiety in AMY **64** 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) (**Scheme 11**) resulting in the epimeric *epi*-4a-**66**. On the other hand, TS-II, in which the alkyl ketal side chain of AMY **65** and the aromatic ring are distantly away from each other, would generate the desired C4a stereochemistry **66**. Thus, it was anticipated that substrate-controlled stereo- electronic effect would favor during cycloaddition of **63** and 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.

The above hypothesis was corroborated by isolating **66** (56%) as a single diastereomer by the cycloaddition of AMY, generated from **63** by the treatment with Ag(I)F in dichloromethane at ambient temperature and inert atmosphere. Cycloadduct **66** was easily transformed to oxomaritidine (**60)** by following a series of simple transformations such as LAH reduction, Swern oxidation[34] to generate **67** followed by careful deketalization using p-TSA and intramolecular aldol reaction. Oxomaritidine (**60)** was transformed to maritidine (**34**) by following the literature procedure.[35] (**Scheme 12**)



Scheme 12: Synthesis of oxo-Maritidine and Maritidine

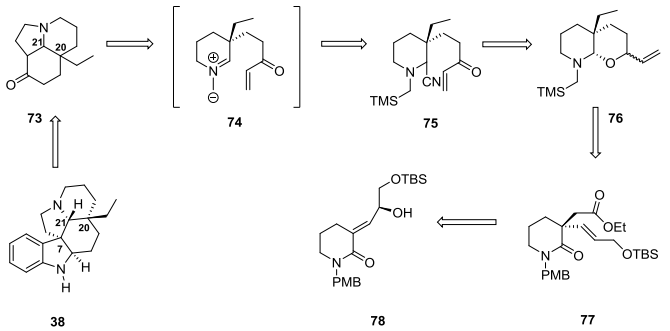
After accomplishing the total synthesis of **34**, our focus was shifted towards synthesizing the (±)-crinine (**35**) because of its structural complexities and pronounced biological activities[36]. Subsequent study has also shown this molecule to be highly selective in inducing apoptosis against tumor cells at low concentration.[37] Furthermore, this alkaloid is also shown to possess immune-stimulant, antitumor and antiviral activities.[36] The only structural difference between **35** and **34** is the presence of methylene dioxy group at aromatic ring instead of dimethoxy. Therefore, entire synthetic sequence was carried out identically[35] except starting with appropriately substituted starting material **68.** (**Scheme 13**)



Scheme 13: Synthesis of crinine alkaloid.

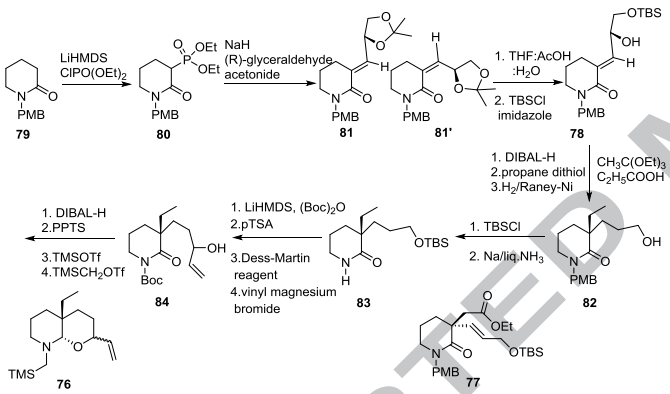
Structurally intricate and bio-enriched *Aspidosperma* alkaloids[38] such as **38** and **39** constitute a unique class having pentacyclic[6.5.6.6.5] ABCDE ring frameworks with contiguous *cis*-stereocenters at C-7, C-21 and C-20 (all carbon quaternary) as a common skeletal feature (Figure 1). Some members of this class of alkaloid [vincristine, vinblastine] are well known drugs for cancer chemotherapy[39] whereas other members like vincadifformine (cytotoxic),[40] tabersonine (pronounced inhibitory effect against SK-BR-3 human cancer cell lines, better than cisplatin),[41] and jerantinine-E (stronger in vitro cytotoxicity against human KB cells, IC50 < 1 μg/mL)[42] are known to be pharmacologically important alkaloids.

The basic pentacyclic framework of **38**, common to most of these pharmacologically active alkaloids, has been an attractive synthetic target for the showcasing of any new synthetic methodologies. Therefore, development of an efficient strategy for the construction of **38** still invites great interest. One of the most exploited approaches for the construction of this pentacyclic alkaloid in racemic[43] as well as in enantioselective[44] form has been the indolization of the 6a-ethyloctahydro-1H-pyrrolo-[3,2,1-ij]quinolin-9(2H)-one (tricyclic core **73**).[45] Therefore, from a synthetic point of view, how to expeditiously establish such a privileged core **73** with the crucial C-20 all-carbon quaternary stereocenter is an important issue in developing asymmetric synthesis of **38** and structurally related bisindole alkaloids.



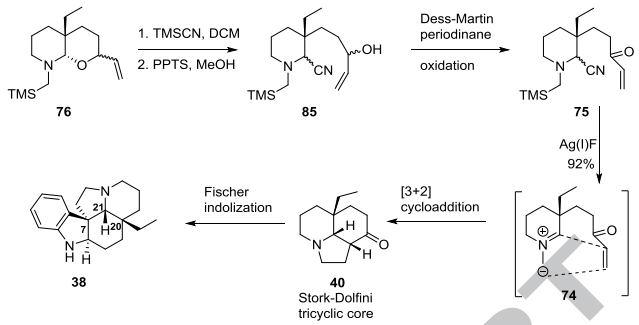
Scheme 14: Retrosynthetic analysis of Aspidospermidine.

Since structural framework **73** embodies a fused pyrrolidine framework (E-ring) and all-carbon quaternary stereocenter at C-3 position of D-ring (a piperidine ring), a strategy was designed to construct C-ring with the required ketone functionality encompassing these two rings. Since, a strategy of creating all carbon quaternary stereocenter (both enantiomers) at C-3 position of cyclic amides using Johnson-Claisen rearrangement was available[46] and an obvious choice of intramolecular [3 + 2] cycloaddition of AMY **74** was proposed for the construction of fused pyrrolidine moiety, the reasonable retrosynthetic strategy looked simple (**Scheme 14**) for the synthesis of aspidospermidine.



Scheme 15: Synthesis of AMY precursor for Aspidospermidine.

Reaction of **79** with LiHMDS in THF at −78 °C, followed by the addition of diethyl chlorophosphate furnished corresponding phosphonate **80** which on Wittig−Horner olefination with (*R*)-(+)-glyceraldehyde acetonide gave a separable mixture of **81** and **81'** in 3:2 ratios. Compound **81** was subjected to acetonide deprotection followed by silylation of free hydroxyl group to obtain **78**. Johnson−Claisen rearrangement of **78** with triethyl orthoacetate in the presence of a catalytic amount of propionic acid produced **77** streospecifically which was reduced to the corresponding aldehyde using DIBAL-H at low temperature. Furthermore, dithioacetalization of the aldehyde moiety followed by reductive desulfurization (Raney nickel) afforded **82** in 69% yield. Protection of the free hydroxyl moiety as −OTBS ether followed by PMB deprotection[47] (Na/liq. NH_3) produced **83** which was transformed to **76** as shown in **Scheme 15**. N-Boc protection [LiHMDS and $(Boc)_2O$] followed by deprotection of the −OTBS group using a catalytic amount of *p*-TSA in MeOH at −10 °C followed by Dess−Martin periodinane oxidation and vinylmagnesium addition furnished **84** which on reduction by DIBAL-H gave corresponding hemiaminal. This hemiaminal on treatment with PPTS followed by careful N-Boc-deprotection using TMSOTf and triethylamine and N-alkylation with $TMSCH_2OTf$ in the presence of K_2CO_3 resulted in the formation of N-(trimethylsilylmethyl)aminal **76.** (**Scheme 15**)



Scheme 16: Synthesis of aspidospermidine.

However, this compound failed to generate azomethine ylide, therefore, it was manipulated to **85** via TMSCN addition followed by PPTS treatment. Oxidation of **85** by Dess-Martin reagent produced **75**. It was visualized that **75** on treatment with a Lewis acid will lead to the generation of iminium ion by the opening of the aminal ring which subsequently would undergo desilylation to give azomethine ylide **74**. Intramolecuclar [3 + 2] cycloaddition of this ylide with a tethered dipolarophile produced (−)-**40** in stereospecific manner presumably involving nonstabilized azomethine ylide **74** as the intermediate.[2,48] This important intermediate was converted to aspidospermidine (**38**) via Fischer indolization.[49] (**Scheme 16**)

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Highlights

- Developed non-stabilized AMY *via* one electron oxidation of N,N'-dialkylsilylamines
- Synthesized indolizidine and pyrrolizidine frameworks by [3+2]-cycloaddition of AMY
- Synthesis of epibatidine alkaloid having 7-azabicyclo [2.2.1] heptane skeleton
- Synthesis of (±)-pancracine, (±)-brunsvigine, maritidine, crinine
- Synthesis of (-)-vincodifformine and (+)-aspidospermidine

Graphical abstract

Synthesis of biologically active natural products by [3+2] cycloaddition of non-stabilized azomethine ylides (AMY): Concepts and realizations

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