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Efficient Strategy for the Construction of Both Enantiomers of the Octahydropyrroloquinolinone Ring System: Total Synthesis of (+)-Aspidospermidine

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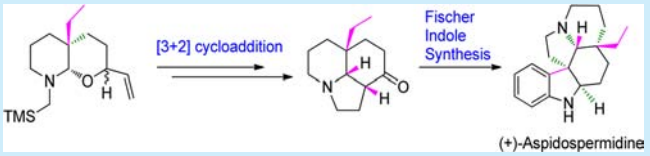
Supporting Information

ABSTRACT: An efficient and highly stereoselective intramolecular [3 + 2] cycloaddition of nonstabilized azomethine ylide generated from a designed bicyclic aminal precursor is reported for the synthesis of both (−)- and (+)-octahydropyrroloquinolinone. One of the enantiomers is further advanced to accomplish the total synthesis of (+)-aspidospermidine.



Structurally complex Aspidosperma alkaloids (**1**−**4**), which are present in many natural sources,[1] constitute one structurally unique class having pentacyclic {[6.5.6.6.5] ABCDE ring system} frameworks with contiguous *cis*-stereocenters at C-7, C-21, and C-20 (all carbon quaternary) as a common structural feature (Figure 1). Some members of this class of

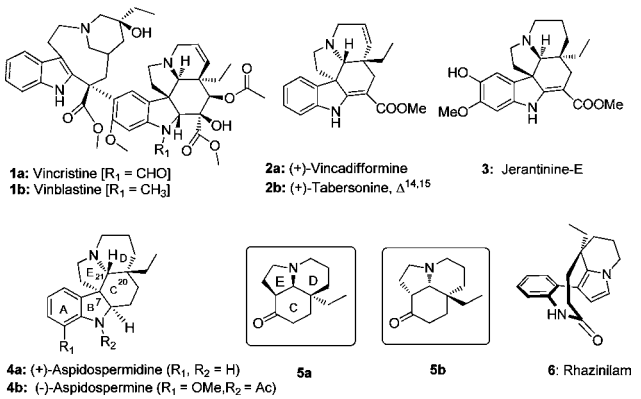


Figure 1. Some of the representative structures of the Aspidosperma class of alkaloids and tricyclic cores.

alkaloids, such as vincristine (**1a**) and vinblastine (**1b**), which has the most complex architecture of this family, have been widely used as drugs for cancer chemotherapy.[2] Other important members are vincadifformine (**2a**, cytotoxic),[3] tabersonine (**2b**, pronounced inhibitory effect against SK-BR-3 human cancer cell lines, better than cisplatin),[4] and jerantinine-E (**3**, stronger in vitro cytotoxicity against human KB cells, IC_{50} < 1 μg/mL),[5] which are known to be pharmacologically important alkaloids.

The basic pentacyclic framework of **4**, common to most of these pharmacologically active alkaloids, has been an attractive target for the showcasing of any new synthetic methodologies.[6−8] Therefore, development of an efficient strategy for the construction of **4** still invites great interest.[7aa−ac]

One of the most exploited approaches for the construction of this pentacyclic alkaloid in racemic[6,9] as well as in enantioselective[10] form has been the late-stage construction of an indole moiety onto the 6a-ethyloctahydro-1*H*-pyrrolo-[3,2,1-*ij*]quinolin-9(2*H*)-one (tricyclic core **5**) originally prepared by Stork and Dolfini.[6] Some other important strategies include indoloquinolizidine rearrangement[11] and E-ring[12] or D-ring[13] closing of differently constructed ABCD or ABCE ring system, respectively. A few other approaches worth mentioning are Diels−Alder cycloaddition[14] of appropriately functionalized indole derivative, intramolecular [4 + 2]/[3 + 2] cycloaddition cascade[8p] of a 1,3,4-oxadiazole, and a reductive transannular cascade strategy from rhazinilam[7aa] (**6**). Another recent report utilizes an integrated oxidation/reduction/cyclization sequence of an intermediate obtained by a palladium-catalyzed decarboxylative vinylation.[7ac]

Although significant development has taken place since Stork's indolization[6] of tricyclic core **5** approach for constructing the Aspidosperma class of alkaloids, this methodology still remains the hallmark in this field. Therefore, from a synthetic point of view, how to expeditiously establish such a privileged core **5** with the crucial C-20 all-carbon quaternary stereocenter would be an important issue in developing asymmetric synthesis of **4** and structurally related bisindole alkaloids. Furthermore, if the strategy provides both enantiomers[15] (most of these alkaloids are produced naturally in both enantiomers)[1] it would be an added advantage.

Since structural framework **5** 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

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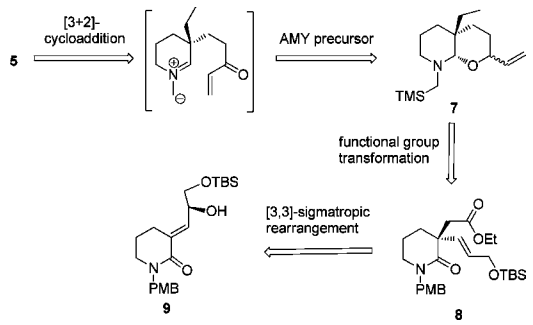
required to construct C-ring with the required ketone functionality encompassing these two rings. Since, we have reported a strategy of creating all carbon quaternary stereocenter (both enantiomers) at C-3 position of cyclic amides using Johnson-Claisen rearrangement[16] and fused pyrrolidine moiety by intramolecular [3 + 2] cycloaddition of nonstabilized azomethine ylide (AMY),[17] we envisaged a retrosynthetic approach of assembling **5** as shown in Scheme 1.

Scheme 1. Retrosynthetic Analysis of (−)-Tricyclic Core



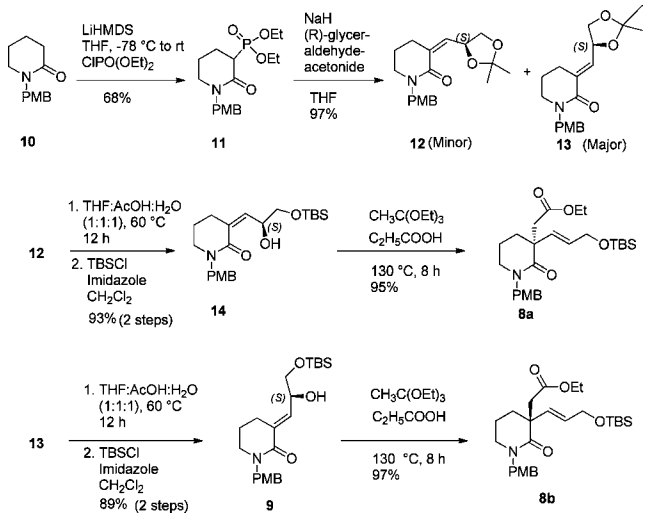
It may be pertinent to mention that most of the approaches[10] known so far for the construction of **5** in enantiomerically pure form have used variously prepared enantiomerically pure Stork's intermediate (4,4-dialkylated cyclohexanone) except, Aube's[10a] approach of an intramolecular Schmidt reaction of enantiomerically enriched (ee = 84−86%) chiral [4.3.0]bicyclic dione. The lack of an efficient strategy to synthesize this tricyclic cores (**5**) kindled our interest in developing a new strategy using our group chemistry.

In the beginning of the synthesis itself, it was envisioned that **7** may undergo intramolecular [3 + 2] cycloaddition on treatment with a Lewis acid to produce **5**. Compound **7** itself was visualized to be derived from **8** by simple functional group transformations. The synthesis of **8** in enantiomerically pure form was planned to be accessed by [3,3]-sigmatropic rearrangement of **9**. Herein, we disclose our successful effort of accomplishing the construction of both **5a** as well as **5b** and utilization of **5a** for the total synthesis of (+)-aspidospermidine (**4a**).

Our synthesis commenced with the preparation of both enantiomers of 3,3-dialkylpiperidinones (**8a**) and (**8b**) in enantiomerically pure form by the [3,3]-sigmatropic rearrangement as shown in Scheme 2. Reaction of **10** with LiHMDS in THF at −78 °C, followed by the addition of diethyl chlorophosphate, furnished the corresponding phosphonate **11** in 68% yield. Wittig−Horner olefination (NaH, 0 °C) of **11** with (*R*)-(+)-glyceraldehyde acetonide gave a mixture of **12** and **13** in 2:3 ratio in 97% yield, which was easily purified by flash column chromatography. Various attempts to improve the selectivity, however, did not succeed. Both diasteromers were separately subjected to acetonide deprotection (CH_3COOH/THF/H_2O = 1:1:1, 60 °C) followed by selective TBS protection at −15 °C to obtain **14** and **9** in 93% and 89% yields, respectively. It is important to mention here that these reactions have been successfully performed on a multigram scale (20 g scale).

Johnson−Claisen rearrangement[16] of **14** as well as **9** by refluxing (8 h) with triethyl orthoacetate in the presence of a catalytic amount of propionic acid gave **8a** and **8b** in 95% and

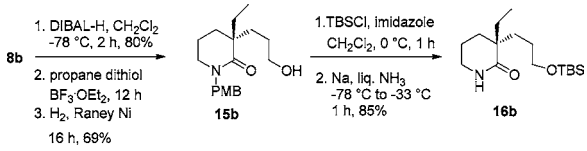
Scheme 2. Synthesis of 3,3-Dialkylpiperidinone



97% yields, respectively, with >99% ee (determined by chiral HPLC: Chiralcel OD-H column, IPA/*n*-hexane = 10:90).

In order to transform **8b** $[[\alpha]^{24}_{D}$ −15.38 (*c* 0.84, $CHCl_3$)] to **16b**, it was first reduced to the corresponding aldehyde (80% yield) using DIBAL-H at −78 °C (Scheme 3). Furthermore,

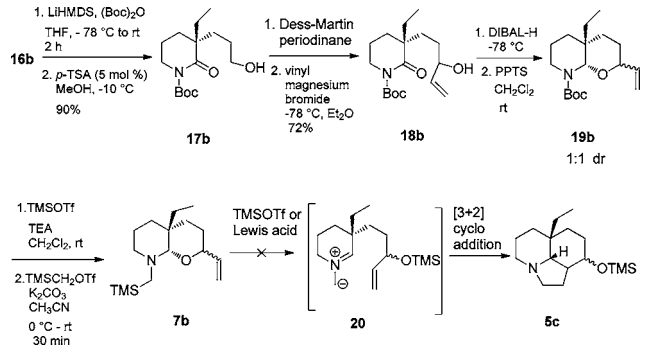
Scheme 3. Synthesis of 16b



dithioacetalization of the aldehyde moiety followed by reductive desulfurization (Raney nickel, H_2, EtOH, reflux) afforded **15b** in 69% yield. The protection of the free hydroxyl moiety as the −OTBS ether followed by PMB deprotection (Na/liq NH_3)[18] produced **16b** $[[\alpha]^{24}_{D}$ +19.67 (*c* 0.36, $CHCl_3$)] in 85% yield.

Having **16b** (multiple grams) in hand, we devised its transformation to **19b** as shown in Scheme 4. *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 provided **17b** in excellent yield (90%). Oxidation of **17b** with Dess−Martin periodinane (CH_2Cl_2, 0 °C, 30 min) followed by the addition of vinylmagnesium bromide afforded **18b** in 72% yield. Reduction of **18b** using DIBAL-H at −78 °C

Scheme 4. Synthesis of 7b



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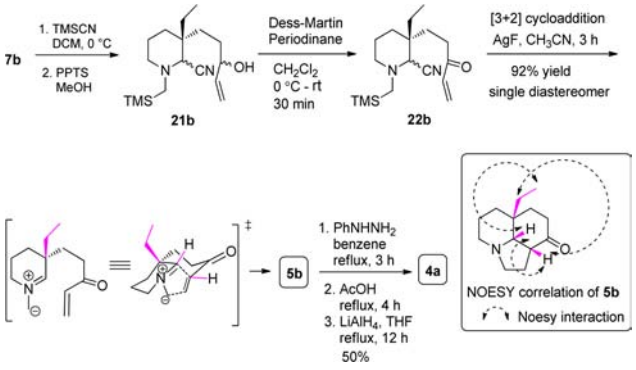
resulted in the corresponding hemiaminal, which on treatment with PPTS in dichloromethane furnished **19b** as a mixture of diastereomers (1:1). Careful *N*-Boc-deprotection of **19b** using TMSOTf and triethylamine followed by *N*-alkylation with $TMSCH_2OTf$ in the presence of K_2CO_3 resulted in the formation of *N*-(trimethylsilylmethyl)aminal **7b**.

It was visualized that **7b** on treatment with a Lewis acid will lead to the generation of iminium ion by the opening of the aminal ring, which would subsequently undergo desilylation to give azomethine ylide intermediate. Intramolecular [3 + 2] cycloaddition of this ylide with a tethered dipolarophile would give tricyclic core **5c**. As per the planned strategy, **7b** was reacted with different Lewis acids (TMSOTf, TMSOTf/CsF, $BF_3{\cdot}OEt_2$, and TFA), but to our surprise no any observable product was formed (starting material recovered in 90−95%).

To explore an alternative strategy of generating nonstabilized azomethine ylide, we visualized precursor **22b** (Scheme 5). For

Scheme 5. Synthesis of (−)-5b



synthesis of this precursor, **7b** was first treated with TMSCN at 0 °C in dichloromethane followed by the treatment of PPTS in methanol at rt, which gave **21b**. Oxidation of **21b** with Dess−Martin periodinane (CH_2Cl_2, 0 °C, 30 min) produced **22b**. It may be emphasized that transformation from **18b** to **22b** was carried out without any column chromatography (73% yield over seven steps).[19]

At this stage, **22b** (0.39 mmol) was stirred (3 h) with AgF (0.47 mmol) in acetonitrile at room temperature which, to our delight, produced (−)-**5b** as a single diastereomer (92% isolated yield) [$[\alpha]^{24}_D$ −23.81 (*c* 0.5, $CHCl_3$); lit.[10b] $[\alpha]^{29}_D$ −24.4 (*c* 0.88, $CHCl_3$)] presumably involving nonstabilized azomethine ylide as the intermediate.[20,21] All contiguous *cis*-stereochemistry of this molecule was established by detailed 2D NOESY spctroscopy.

Furthermore, we carried out Fischer indole cyclization[8c] of **5b** to obtain dehydroaspidospermidine which on reduction with $LiAlH_4$ gave (+)-**4a** in 50% yield [$[\alpha]^{24}_D$ +20.14 (*c* 0.5, EtOH); lit.[8a] $[\alpha]^{29}_D$ +20.6 (*c* 0.64, EtOH)]. All other spectral data of (+)-**4a** (NMR and mass) were found to be in agreement with the literature report.[8c]

After the successful synthesis of **5b**, the same strategy was carried out starting from **8a** [$[\alpha]^{24}_D$ +12.19 (*c* 0.31, $CHCl_3$)] to accomplish the synthesis of **5a** [$[\alpha]^{24}_D$ +21.62 (*c* 0.5, $CHCl_3$)].

In conclusion, we have successfully developed an enantioselective route for the synthesis of both (−)- and (+)-tricyclic core **5b** using an efficient and highly stereoselective intramolecular [3 + 2] cycloaddition of nonstabilized azomethine ylide from a designed precursor. The total synthesis of (+)-aspidospermidine was also accomplished by indolization of **5**. Further study is in progress for the synthesis of jerantinine E (**3**) using this strategy and will be revealed in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00374.

Complete experimental details and characterization data for all products (PDF)

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Notes

The authors declare no competing financial interest.

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