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Total Synthesis of (+)-Aspidospermidine: A New Strategy for the Enantiospecific Synthesis of Aspidosperma Alkaloids

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Over the last three decades, aspidosperma alkaloids[1] have caught the attention of synthetic chemists due to the unique structural features of many of their members, and because of their important biological properties. Aspidospermidine (**1**), the parent structure, has been the primary target for most of the efforts toward aspidosperma alkaloids syntheses and has served as the ideal test case for newly developed synthetic strategies.[2,3] Among those strategies, Stork's Fischer-indole approach, Harley−Mason's indoloquinolizidine rearrangement approach, Büchi and Wenkert's Diels−Alder approach, and Overman's aza-Cope rearrangement approach have been at the forefront and have considerably enriched the chemistry of aspidosperma alkaloids. Most strategies were originally designed for their racemic syntheses; as such, many of these approaches cannot be readily developed into a feasible asymmetric total synthesis. Only a few asymmetric syntheses reported were derived from their racemic versions,[4] some involving the lengthy construction of intermediates. More than a decade ago, our group developed a powerful ketene lactonization reaction which can transfer the chirality of sulfur to as many as three contiguous carbon centers through a novel [3,3]-sigmatropic rearrangement of chiral vinyl sulfoxide with ketenes.[5] The reaction was later applied by our group and others to the total syntheses of natural products and had been demonstrated as a powerful tool for the construction of quaternary carbon atoms.[6] In this communication, through the total synthesis of (+)-aspidospermidine employing the ketene lactonization reaction, we reveal a unique approach to the enantiospecific synthesis of aspidosperma alkaloids.

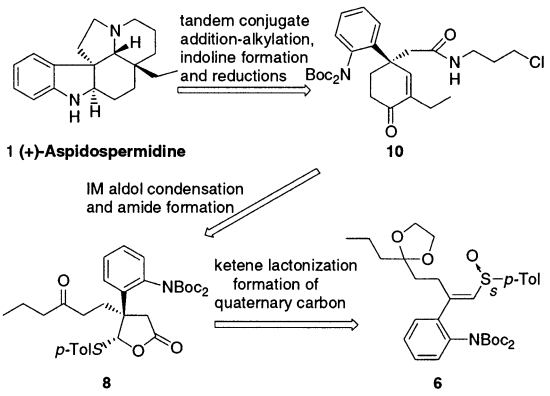
Scheme 1 elucidates the key synthetic events. First, the critical ketene lactonization reaction of chiral vinyl sulfoxide **6** enantiospecifically sets the quaternary carbon in lactone **8**. Compound **8** was transformed into an enone-amide structure **10** by lactone-opening, intramolecular aldol condensation, and then by amide formation reaction. From **10**, a structure with all of the necessary carbons, (+)-aspidospermidine **1** was obtained by a tandem conjugate addition-alkylation reaction followed by further elaboration.

The synthesis started with the protection of alkynyl ketone **2**[7] to provide alkynyl ketal **3** (93%). Treatment of **3** with *n*-BuLi and then $MgBr_2$ formed an alkynyl Grignard reagent, which was added to Evans' chiral *N*-sulfinyloxazolidinone **A**[8] to give chiral alkynyl sulfoxide **4** (83%)[9] (Scheme 2). HPLC analysis[10] of compound **4** showed the presence of only one enantiomer.

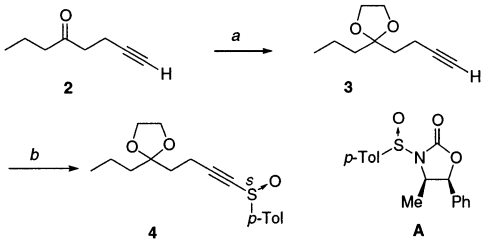
Compound **4** was then added to the cuprate reagent formed from transmetalation of the ortholithiated Boc-protected aniline (formed from compound **5** and 2 equivalents of *t*-BuLi) with $CuBr{\cdot}Me_2S$;[11] after introduction of a second Boc group, the stereodefined chiral vinylic sulfoxide **6** was obtained. With compound **6** in hand, we proceeded to perform the ketene lactonization reaction. Dichloroketene was generated in situ by the reaction of excess trichloroacetyl chloride with freshly prepared zinc−copper couple.[12] For the best results, compound **6** was added first to the zinc−copper couple/THF solution; then trichloroacetyl chloride was slowly added at −45 °C to afford the dichlorolactone **7** as a single diastereomer (78%). The quaternary carbon was formed in this step. After dechlorination with Et_3B/*n*-Bu_3SnH in refluxing benzene (94%) and deprotection of the ketal in acetone with a catalytic amount of *p*-TsOH, lactone **8** was generated (96%) (Scheme 3). To our delight, we were able to obtain crystals of compound **8**, and an X-ray crystallographical analysis was carried out.[13] The relative stereochemistry shown was consistent with the proposed [3,3]-sigmatropic rearrangement mechanism for the ketene lactonization reaction.

Opening of lactone **8** with pyrrolidine afforded aldehyde **9** (86%). Subsequent intramolecular aldol condensation under conditions of pyrrolidine and 33% aqueous acetic acid in 2-propanol gave a carboxylic acid. This acid was directly converted to amide **10** using the mixed anhydride protocol (64% over two steps). Interestingly, amide **10** can be formed from lactone **8** in a one-pot reaction by simply mixing **8** with 3-chloropropylamine hydrochloride and triethylamine in THF. However, the reaction usually took 5−8 days, and the yield varied significantly from 10 to 40%. Through a chiral

Scheme 1



Scheme 2 [a]



[a] (a) $HOCH_2CH_2OH$, benzene, cat. *p*-TsOH, reflux, 90%; (b) THF, *n*-BuLi, −78 °C, then $MgBr_2$, 0 °C, then **A** (4*R*, 5*S*)-4-methyl-5-phenyl-3-[(*R*)-*p*-tolysulfinyl]-2-isoxazolidinone, −78 °C, 83%.

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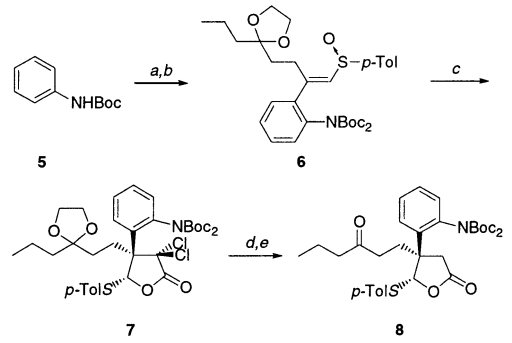
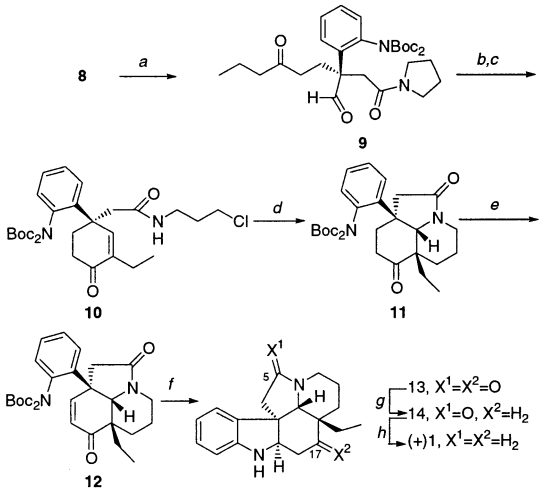
Scheme 3 [a]



[a] (a) Two equivalents of *t*-BuLi, 1 equivalent of $CuBr \cdot Me_2S$, then **4**, THF, −78 °C, 82%; (b) MeLi, Boc_2O, THF, −78 °C, 81%; (c) Zn(Cu), Cl_3CCOCl, THF, −45 °C, 78%; (d) *n*-Bu_3SnH, cat. Et_3B, benzene, reflux, 92%; (e) acetone, cat. *p*-TsOH, room temperature, 96%.

Scheme 4 [a]



[a] (a) Pyrrolidine, benzene, room temperature, 86%; (b) pyrrolidine, 2-propanol, 33% aqueous AcOH; (c) *i*-BuOCOCl, Et_3N, 3-chloropropylamine hydrochloride, THF, 0 °C, 64% (two steps); (d) NaH, DMF, 0 °C, 86%; (e) KHMDS, TMSCl, THF, −78 °C, then $Pd(OAc)_2/O_2$, DMSO, 60 °C, 80%; (f) 3 M HCl/2-propanol, reflux, 0.5 h, 90%; (g) $H_2NNH_2 \cdot H_2O$/$Na/HOCH_2CH_2OH$, 160 °C, 1 h, then 210 °C, 3 h, 75%; (h) $LiAlH_4$, THF reflux, 3 h, 90%.

HPLC analysis, amide **10** was determined to be a single enantiomer by comparison with the result of its racemic form, indicating that the above ketene lactonization reaction was a highly enantiospecific process.[14] Treatment of amide **10** with NaH initiated a tandem conjugate addition/intramolecular alkylation reaction sequence and furnished the tricyclic core structure **11** (86%). Compound **11** was oxidized to enone **12** (80%) through a modified Saegusa reaction.[15] A sequential deprotection-conjugate addition process under acidic condition completed the indoline ring giving 5,17-dioxo-aspidospermidine **13** (90%). Ketone **13** was then reduced by a Wolff−Kishner reduction[16] yielding 5-oxo-aspidospermidine **14** (75%). Finally, (+)-aspidospermidine **1** was obtained by the reduction of **14** with $LiAlH_4$ (90%) (Scheme 4). The spectroscopic data and optical rotation of **1** were fully consistent with reported values.[17]

In summary, we have developed a new, efficient strategy for the enantiospecific synthesis of aspidosperma alkaloids exemplified by the synthesis of (+)-aspidospermidine **1**. By employing this new strategy, other members of the family of aspidosperma alkaloids could be synthesized by starting with appropriately substituted anilines and alkynyl sulfoxides and by derivatization of advanced intermediates (e.g., from compound **14**[16]). In addition, with both enantiomers of Evans' chiral *N*-sulfinyloxazolidinone easily accessible, either enantiomer of aspidosperma alkaloids can be constructed. We are currently applying this new strategy in the total syntheses of aspidophytine[4f] and related structures; the results will be reported in due course.

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Supporting Information Available: Experimental procedures and spectroscopic data (IR, ^1H NMR, ^{13}C NMR, HRMS) (PDF). Crystal data for compound **8** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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