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Divergent Total Syntheses of (−)-Aspidospermine and (+)-Spegazzinine

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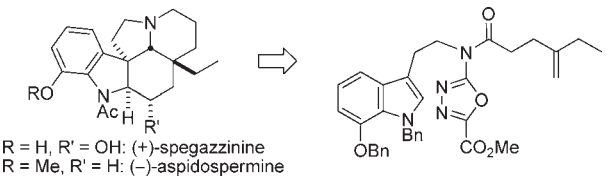
ABSTRACT



Divergent total syntheses of (+)-spegazzinine (1) and (−)-aspidospermine (2) and their extensions to the synthesis of C19-*epi*-aspidospermine and C3-*epi*-spegazzinine are detailed, confirming the relative stereochemistry and establishing the absolute configuration of (+)-spegazzinine. A powerful intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of a 1,3,4-oxadiazole provided the pentacyclic skeleton and all the requisite stereochemistry of the natural products in a single reaction that forms three rings, four C−C bonds, and five stereocenters.

The *Aspidosperma* alkaloids continue to generate considerable interest due to their structural diversity, stereochemical complexity, central biosynthetic role in plants, and interesting biological properties. One member, spegazzinine (**1**, Figure 1), was first isolated in 1956 from *Aspidosperma chakensis* Spegazzini by Djerassi.[1] It has since been shown to be a potent inhibitor of mitochondrial photophosphorylation in spinach and oxidative phosphorylation in rat liver mitochondria.[2] Aspidospermine (**2**), first isolated from the bark of *Aspidosperma quebrancho*[3] in the late 1800s and from many other plant sources since,[4] exhibits a wide range of biological activities, including diuretic, vasoconstriction, hypertensive,[5] and respiratory stimulant properties.[6,7] While spegazzinine has not yet been prepared by total synthesis, aspidospermine continues to be an attractive synthetic target[8] as a result of its prominent position among the *Aspidosperma* alkaloids. However, all reported syntheses of aspidospermine proceed through **3**, relying on a late-stage Fischer indole synthesis using *o*-methoxyphenylhydrazine originally disclosed by Stork and Dolfini nearly 50 years ago.[8a]

The stereochemistry of the C3 alcohol in **1** was assigned[9] based on an 8 Hz coupling constant of C2−H with its neighboring C3−H in the ^{1}H NMR of the closely related natural product spegazzinidine, which differs from **1** only by incorporation of an additional C16 hydroxyl group. The large coupling constant was interpreted to be indicative of a trans diaxial relationship between the two hydrogens, although this assignment and that of spegazzinidine have not been confirmed.

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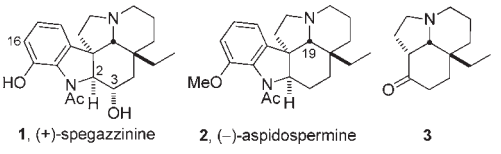


Figure 1. Natural products and intermediate ketone **3**.

In recent efforts targeting additional key members of the *Aspidosperma* alkaloids including minovine,[10] fendleridine,[11] vindorosine and vindoline,[12] and their extension to the total synthesis of vinblastine[13] and related natural products including vincristine,[14] and key analogues,[15] we developed a powerful intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of 1,3,4-oxadiazoles that provides the pentacyclic core and all the stereochemistry of the natural products in a single step (Figure 2).[16] Herein, we report the extension of these studies to the total synthesis of **1** and **2**. This strategy was viewed as especially suited for spegazzinine, whose C3 alcohol can be directly introduced upon reduction of a stable cyanohydrin formed after reductive oxido bridge cleavage of a nitrile derived from such a cycloaddition product. An added bonus of the approach is that late stage modification of a route needed to explore the spegazzinine C3 alcohol stereochemistry also permits a divergent[17] synthesis of aspidospermine, entailing removal of the C3 alcohol in an approach fundamentally different from all prior reports.

The key cycloaddition is initiated by an intramolecular Diels–Alder reaction of a 1,3,4-oxadiazole with a tethered dienophile.[18,19] Loss of N_2 from the initial cycloadduct generates a 1,3-dipole, which is stabilized by the complementary substitution at the dipole termini. The regioselectivity of the subsequent 1,3-dipolar cycloaddition is dictated by the tether, but is reinforced by the intrinsic polarity of the reacting

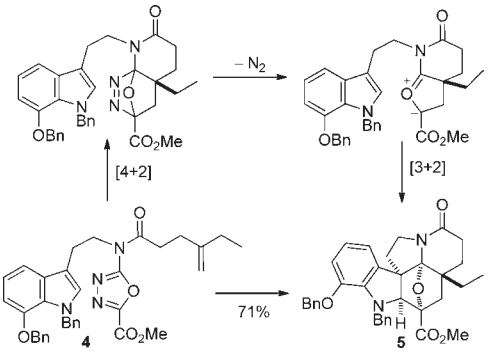
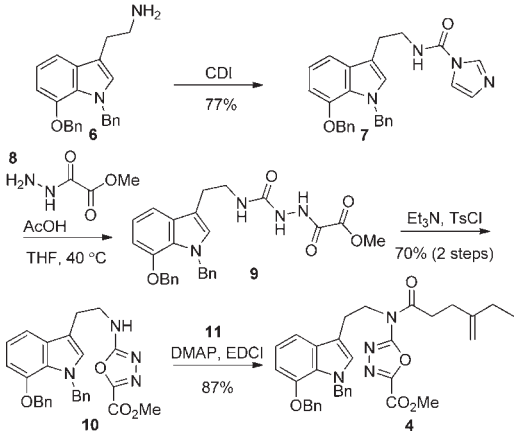


Figure 2. Cycloaddition cascade.

partners and provides an endo indole [3 + 2] cycloaddition, where the dipolarophile is sterically directed to the face opposite the newly formed six-membered ring.[16,20] Four C–C bonds, three rings, five stereocenters, and the complete natural product skeleton are assembled in a single transformation.

The precursor tryptamine **6** to the key cycloaddition substrate **4** was prepared from 7-benzyloxyindole and modeled on a route first disclosed by Corey (Supporting Information (SI) Scheme 1).[21] Tryptamine **6** was treated with 1,1-carbonyldiimidazole (CDI) to afford urea **7** (Scheme 1). Addition of methyl oxalyl hydrazide (**8**) to **7** (HOAc–THF, 40 °C, 16 h) furnished **9**, which was converted to the 1,3,4-oxadiazole **10** (70%, 2 steps) upon treatment with TsCl and Et_3N. Coupling of **10** and 4-ethyl-4-pentenoic acid (**11**) provided **4** (87%).

Scheme 1



The key intramolecular [4 + 2]/[3 + 2] cycloaddition was accomplished by warming a solution of **4** at 180 °C in *o*-dichlorobenzene (*o*-DCB) to provide **5** as a single diastereomer in yields as high as 71% (Scheme 2). The stereochemistry of **5** was confirmed upon X-ray analysis[22] of **15** and was in accordance with expectations. Treatment of **5** with NH_3–MeOH cleanly provided the primary amide, and its

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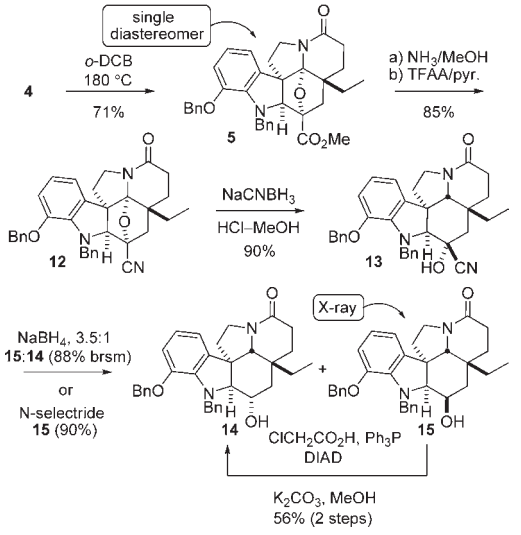
Scheme 2



dehydration upon treatment with trifluoroacetic anhydride (TFAA) and pyridine afforded nitrile **12** (85%).

Reductive oxido bridge opening of **12** was accomplished with $NaCNBH_3$ in HCl−MeOH to provide the stable cyanohydrin **13** as a single diastereomer, resulting from convex face hydride reduction of the intermediate *N*-acyliminium ion. A number of reducing reagents were screened for the further reduction of **13**, and the most direct for the synthesis of **1** proved to be $NaBH_4$, which provided a 3.5:1 mixture of **15:14** in 66% yield (88% brsm). Larger or alternative reducing reagents failed to improve upon the ratio, favoring alcohol **15**.[22] However, increased yields (90%) of **15** were achieved through the use of *N*-selectride but required inversion of the C3 alcohol stereochemistry to access **1**. Mitsunobu inversion of the C3 alcohol in **15** could be accomplished to provide the chloroacetate (3 equiv of chloroacetic acid,[23] 4 equiv of Ph_3P, 4 equiv of DIAD, toluene, 1 h, 56%), with competitive alcohol elimination accounting for the remainder of the reaction product. Hydrolysis of the chloroacetate with K_2CO_3 in aqueous MeOH provided **14**, bearing the requisite C3 alcohol stereochemistry for spegazzinine.

The amide carbonyl of **14** was reductively removed with $LiAlH_4$ (63%) to provide the tertiary amine, which was globally deprotected upon treatment with H_2−Pd/C to afford phenol **16** (Scheme 3). Due to the polarity of **16**, the crude material was carried forward into the *N*-acetylation reaction, which after treatment with K_2CO_3 in MeOH completed the first total synthesis of spegazzinine (**1**). Resolution of racemic **1** by chiral phase chromatography provided both natural (+)-**1** and *ent*-(−)-**1**, the former of

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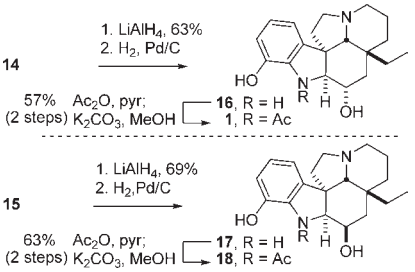
Scheme 3



which proved identical in all respects to an authentic sample of (+)-spegazzinine generously provided by GSK, establishing its identity and confirming the relative stereochemistry of the natural product.

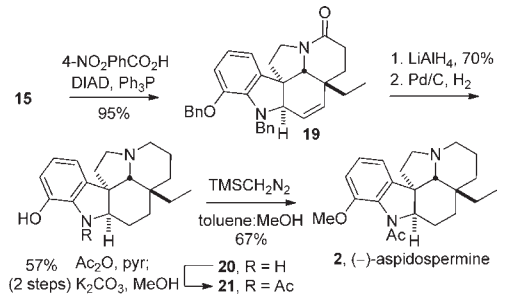
With ample amounts of **15** in hand, we also prepared C3-*epi*-spegazzinine (**18**) featuring the C3 alcohol diastereomer (Scheme 3). Reduction of **15** with $LiAlH_4$ provided the amine, which was globally deprotected with H_2−Pd/C and subsequently acetylated to provide C3-*epi*-spegazzinine (**18**). The ^1H NMR of **18** differed significantly from that of the natural product, further confirming the stereochemical assignment for synthetic **1**. Most notably, the C2−H coupling constant in **18** is 5.5 Hz, significantly smaller than the 7.8 Hz coupling constant observed for synthetic **1** and consistent with the cis relationship of the C2/C3 hydrogens.

In order to determine the absolute configuration of (+)-spegazzinine, racemic **5** was resolved by chiral phase chromatography to provide (+)-**5** and (−)-**5** (SI Scheme 2). Each enantiomer was carried forward independently to the thioamide of **13**, where crystallization and X-ray analysis of the natural enantiomer[24] determined their absolute configuration. Elaboration of this intermediate to **1** defined the absolute configuration of (+)-spegazzinine to be as shown in Figure 1.

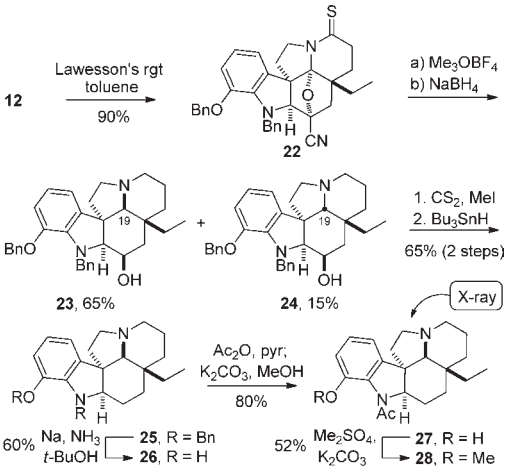
The attractive feature of the approach was its potential late stage modification to provide aspidospermine, simply requiring removal of the C3 alcohol. Capitalizing on the observation that olefin **19** formed competitively with Mitsunobu alcohol displacement, the divergent synthesis of **2** proved straightforward (Scheme 4). Mitsunobu activation of **15** was optimized (3 equiv of 4-nitrobenzoic acid, 4 equiv of Ph_3P, 4 equiv of DIAD, toluene) to afford exclusively the elimination product **19** (95% by LCMS). $LiAlH_4$ reduction of the amide carbonyl followed by reduction of the double bond and benzyl deprotection effected by H_2−Pd/C provided phenol **20**. *N*-Acetylation provided **21**, which upon treatment with $TMSCH_2N_2$ afforded racemic aspidospermine. Resolution of **2** by chiral phase chromatography provided both natural (−)- and *ent*-(+)-aspidospermine (**2**), completing its total synthesis. Remarkably, and to the best of our knowledge, this constitutes the first total synthesis of aspidospermine that does not rely on the Stork late-stage Fischer indole synthesis to provide the natural product.

(24) The X-ray structure of thioamide (−)-**33** has been deposited with the Cambridge Crystallographic Data Centre (CCDC868362).

Scheme 4



Scheme 5



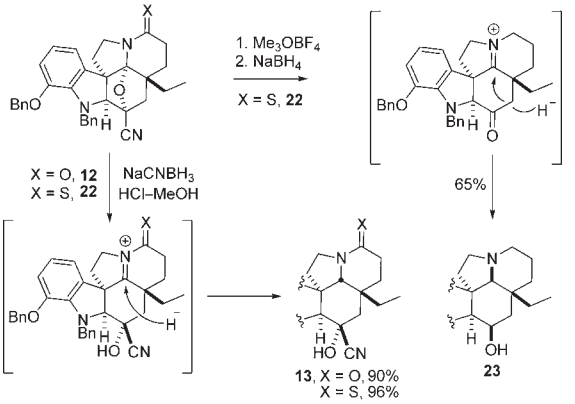


Figure 3. Proposed route for the formation of **23**.

In the course of our studies, we also observed an unprecedented stereochemical outcome for the reduction of an oxido bridge in the cascade cycloadducts. *S*-Methylation of thioamide **22**, prepared by treatment of **12** with Lawesson's reagent, with Meerwein's reagent followed by reduction of the *S*-methyl thioimidate with $NaBH_4$ provided alcohol **23** as the major product (Scheme 5). Not only was the C3 ketone released and reduced under these conditions, but hydride delivery to the intermediate iminium ion occurred from the bottom (concave) face, providing predominantly the thermodynamically less stable and unnatural stereochemistry at C19.[25] This is in contrast to the treatment of **12** with $NaCNBH_3$ under the acidic conditions described earlier, which affords exclusively **13** containing the natural C19 diastereomer present in the *Aspidosperma* alkaloids. Since the thioamide **22**, like **12**, also undergoes top (convex) face reduction with $NaCNBH_3$ (96%) under acidic conditions where the cyanohydrin is stable (Figure 3), its atypical behavior under basic conditions suggests that the cyanohydrin collapses to the ketone prior to iminium ion reduction, and hydride delivery now occurs predominantly from the increasingly more accessible bottom face to both the iminium ion and the ketone to produce **23**.

Alcohol **23** was converted to the methyl dithiocarbonate, which was deoxygenated under Barton–McCombie conditions to afford **25** (Scheme 5). The benzyl groups were removed by treatment with Na and *t*-BuOH in THF–NH_3,[11] cleanly affording phenol **26**. *N*-Acetylation, followed by phenol methylation, provided C19-*epi*-aspidospermine (**28**) whose unnatural C19 stereochemistry and unusual trans-fused 6,5-ring system were confirmed by X-ray analysis.[26]

Herein, the divergent total syntheses of (−)-aspidospermine (**2**) and (+)-spegazzinine (**1**) and their extension to the synthesis of C19-*epi*-aspidospermine and C3-*epi*-spegazzinine are reported, constituting the first total synthesis of (+)-spegazzinine and the first reported total synthesis of (−)-aspidospermine that does not rely on a late-stage Fischer indole synthesis. The pentacyclic skeleton and all the requisite stereochemistry of the natural products were assembled by a tandem intramolecular [4 + 2]/[3 + 2] cycloaddition cascade of a 1,3,4-oxadiazole that forms three rings, four C–C bonds, and five stereocenters including three contiguous quaternary centers in a single operation. Further exploration of the cascade cycloaddition reactions of 1,3,4-oxadiazoles and their applications are in progress and will be reported in due course.

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Supporting Information Available. Full experimental details are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(26) The X-ray structure of **28** has been deposited with the Cambridge Crystallographic Data Centre (CCDC850757).