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Total Synthesis of (+)-*epi*-Condyfoline

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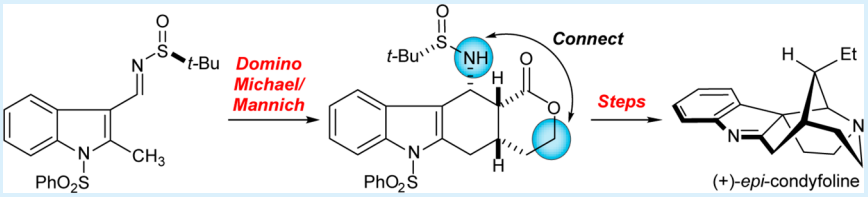
Supporting Information



ABSTRACT: Herein, we report the first asymmetric total synthesis of aspidospermatan indole alkaloid (+)-*epi*-condyfoline (**1**) in 15 steps from commercially available 2-methylindole-3-carboxaldehyde. Key steps include (1) our domino Michael/Mannich annulation method of *N*-sulfinyl metallodienamines to set three contiguous stereocenters, (2) LiHMDS-mediated cyclization of an ω-tosyloxy *N*-sulfinamide to prepare the signature indole-fused 2-azabicyclo[3.3.1]nonane framework, and (3) DMTSF-promoted spirocyclization of a dithioacetal intermediate to access the final pyrrolidine ring. Functional group manipulations delivered the targeted alkaloid (+)-*epi*-condyfoline (**1**) in 13 steps and 1.25% overall yield from *N*-sulfinylimine (+)-**8**.

The monoterpene indole alkaloids of the aspidospermatan type, which are closely related to the more populous and well-known *Strychnos* class (>500), represent a biogenetic minority with a mere 37 members as of 2019.[1] Nevertheless, the aspidospermatan alkaloids continue to attract attention from the synthetic community owing to their signature architectural complexity.[2] The structure of condylocarpine (**4**), first isolated in 1961,[3] was confirmed in 1962 via semisynthesis from its biosynthetic precursor, stemmadenine (Figure 1).[4] The absolute stereochemistry of (+)-**4** and (+)-tubotaiwine (**3**) was established by correlation with the *Strychnos* alkaloid akuammicine by Schumann and Schmid in 1963. In the course of those studies, (+)-*epi*-condyfoline (**1**) was isolated presumably by isomerization of the C20 ethyl group from an intermediary iminium species.[5] To date, the isolation of (+)-*epi*-condyfoline (**1**) from natural sources has not been reported.

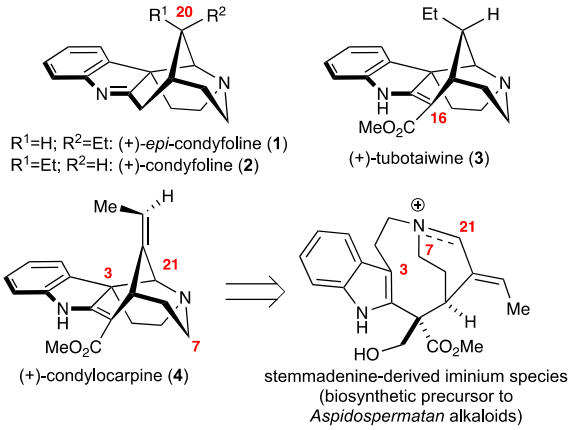
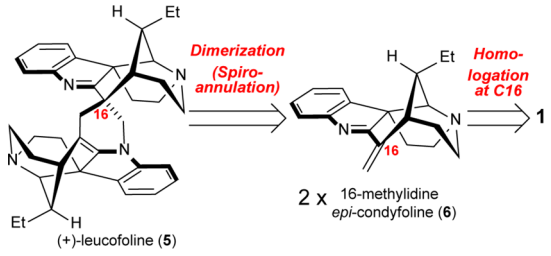


Figure 1. Structures of aspidospermatan alkaloids **1**–**4** and stemmadenine-derived C7–C21 iminium precursor.

In 1968, Harley-Mason reported the first total synthesis of an aspidospermatan alkaloid, (±)-condyfoline (**2**), by the biomimetic oxidative cyclization of a stemmadenine derivative.[6] Harley-Mason later employed a Bischler–Napieralski reaction of a carbomethoxy-functionalized stemmadenine derivative to access (±)-tubotaiwine (**3**).[7] In 1991, Bosch demonstrated the power of thionium ion-mediated cyclizations for the synthesis of the pyrrolidine ring of tubotaiwaine (**3**).[8] Most recently, Overman reported elegant and concise total asymmetric syntheses of (+)-tubotaiwaine (**3**) and (+)-condylocarpine (**4**) featuring an intramolecular oxidative enolate coupling to prepare the tetracyclic 2-azabicyclo[3.3.1]nonane framework.[9]

In 2010, Kam and co-workers isolated the first example of an aspidospermatan–aspidospermatan alkaloid, (+)-leucofoline (**5**), from *Leuconotis griffithii* (Scheme 1).[10] Retrosynthetically,

Scheme 1. Retrosynthesis of (+)-Leucofoline (5) Featuring a Biomimetic Dimerization of 6 Derived from (+)-(1)



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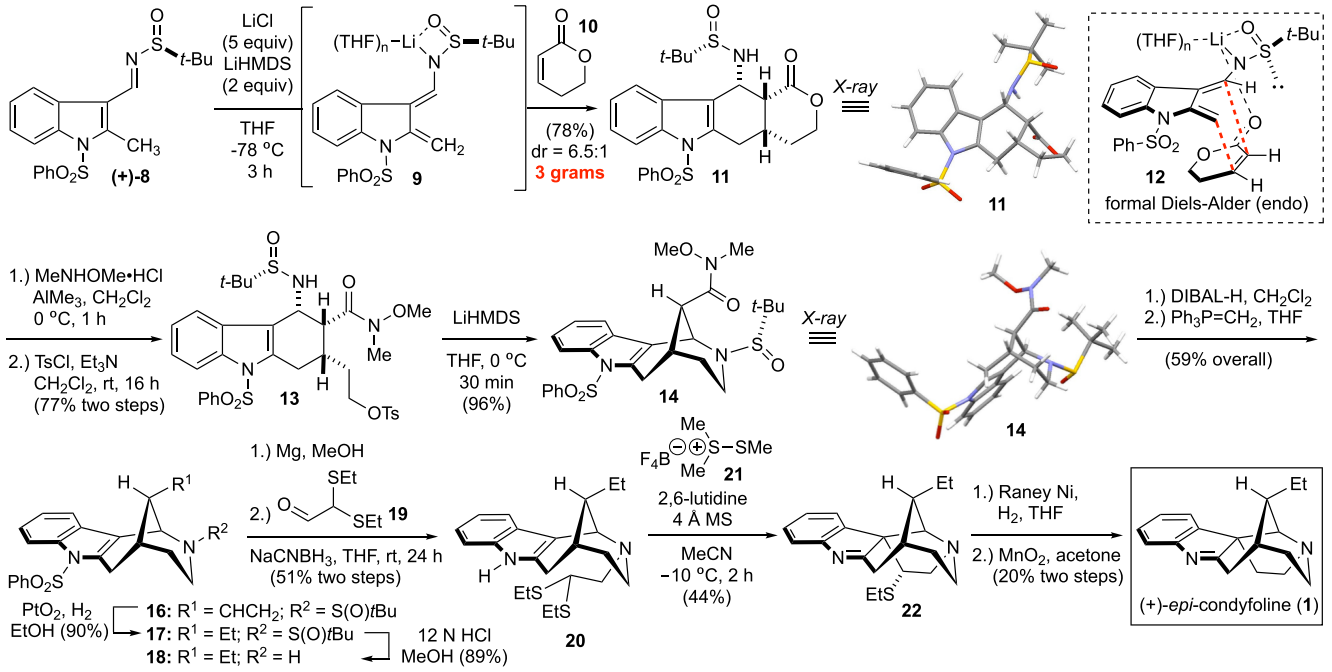
Scheme 2. Total Synthesis of (+)-*epi*-Condyfoline (1) Featuring a Domino Michael/Mannich Annulation Reaction



we reasoned **5** could be assembled in a biomimetic manner via dimerization of 16-methylidine *epi*-condyfoline (**6**). In 2015, we and others successfully employed a related diastereoselective spiroannulation of monomer (−)-dihydrovalparicine to synthesize *Strychnos*−*Strychnos* alkaloids (−)-leucoridines A and (−)-C.[11,12] Accordingly, we targeted (+)-*epi*-condyfoline (**1**) as a subgoal en route to **5**.

In 2013, we discovered a novel domino Michael/Mannich annulation reaction and employed it in the concise total syntheses of *Aspidosperma* alkaloids (−)-aspidospermidine, (−)-tabersonine, and (−)-vincadifformine.[13,14] Furthermore, we recognized that appropriate substitution on the *β*-carbon of the Michael acceptor could allow access to the hallmark aspidospermatan 2-azabicyclo[3.3.1]nonane framework following appropriate functional group interconversion (see graphical abstract). Tactically, we were inspired by Ellman and coworkers, who demonstrated sulfinamide anions smoothly cyclize with primary tosylates in their synthesis of (−)-aurantioclavine.[15]

The synthesis of (+)-*epi*-condyfoline (**1**) is shown in Scheme 2 and commenced by condensation of commercially available 2-methylindole-3-carboxaldehyde with (*S*)-*tert*-butanesulfinamide. Subsequent protection of the indole nitrogen with NaH and benzenesulfonyl chloride in the presence of DMAP afforded *N*-sulfinylimine **8** in 68% over two steps (see the Supporting Information for details).[13] The domino Michael/Mannich annulation of *N*-sulfinylimine **8** with lactone **10** in the presence of LiCl furnished the desired tetracyclic lactone **11** in 78% yield (dr = 6.5:1) on a 3 g scale. The *relative* and *absolute* stereochemistry of **11** was confirmed by single-crystal X-ray analysis, which can be rationalized by drawing an analogy to an *endo*-Diels−Alder transition state **12**, despite the fact that, mechanistically, the annulation proceeds by sequential intermolecular Michael and intramolecular Mannich reactions.

Ring opening of lactone **11** was accomplished by $AlMe_3$-mediated Weinreb amidation with *N*,*O*-dimethylhydroxylamine·HCl. Tosylation of the resulting primary alcohol afforded tosylate **13** in 77% over two steps. With **13** in hand, we screened several conditions to effect the key cyclization step. Gratifyingly, treatment of **13** with LiHMDS in THF at 0 °C furnished tetracycle **14** in 96% yield. The structure of **14** was confirmed by single-crystal X-ray analysis (Scheme 2). At this stage, we turned our attention toward converting the Weinreb amide moiety in **14** to the requisite ethyl functionality in **1**. To this end, **14** was reduced to the aldehyde in 78% yield with DIBAL-H. Subsequent Wittig methylenation afforded olefin **16** in 76% yield. Hydrogenation of **16** with Adams' catalyst in EtOH proceeded without incident to deliver **17** in 93% yield. Removal of the *N*-sulfinyl auxiliary with 12 N HCl in MeOH furnished tetracyclic amine **18** in 89% yield. Deprotection of the benzenesulfonyl group was accomplished with Mg in MeOH (see the Supporting Information for details).

Installation of the final pyrrolidine ring in (+)-*epi*-condyfoline (**1**) proved immensely challenging. All attempts at deploying previously successful tactics from either *Aspidosperma* or *Strychnos* campaigns failed.[13,14,16,17] The strategic application of thionium ions prepared by Pummerer rearrangement for indole spirocyclization at C3 was first demonstrated by Magnus in his elegant syntheses of *Aspidosperma* alkaloids.[18,19] Ultimately, recourse to Bosch's thionium ion-mediated cyclization of dithioacetals was made.[20] Notably, Overman also employed this powerful tactic to prepare the pyrrolidine ring in his syntheses of **3** and **4**.[9] Accordingly, reductive alkylation of **18** with bis(ethylthio)acetaldehyde (**19**) in the presence of $NaCNBH_3$ in THF delivered dithioacetal **20** in 51% over two steps.[21] Dimethyl(thiomethyl)sulfonium tetrafluoroborate (DMTSF, **21**) is an effective and chemoselective activator of dithioacetals to generate reactive thionium ions.[22] In our hands, the desired cyclization of **20** → **22** with DMTSF in CH_2Cl_2 (i.e., conditions employed by Bosch and Overman) led to significant product decomposition.[9,20] Inspection of the literature revealed that Ogasawara

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successfully activated dithioacetals in a similar context using a combination of $AgNO_3$, 3 Å MS, SiO_2, and NCS in CH_3CN buffered with 2,6-lutidine.[23] We reasoned the use of 2,6-lutidine could prevent decomposition of the sensitive indolenine product from adventitious acid. In the event, DMTSF-mediated spirocyclization of **20** → **22** using 2 equiv of 2,6-lutidine and 4 Å MS in deaerated CH_3CN at −10 °C for 2 h smoothly afforded pentacyclic thioether **22** in 44% yield. The stereochemical assignment of **22** was made using ^1H and 2D NMR experiments (see the Supporting Information for details) and is consistent with those reported by Bosch and Overman.[9,20]

Having assembled the complete aspidospermatan framework in **22**, the final task in the total synthesis of (+)-*epi*-condyfoline (**1**) was to carry out chemoselective desulfurization in the presence of the indolenine. Realization of this goal proved difficult. Therefore, **22** was subjected to hydrogenation with Raney Ni, wherein both the thioether and imine were reduced. Notably, the use of EtOH as solvent resulted in undesired reductive alkylation of the indole nitrogen. Heating a mixture of **22** and Raney Ni in THF at 60 °C under 1 atm of H_2 for 5 h proved successful. Oxidation of the resulting indoline with *t*-BuOCl or $Pb(OAc)_4$ was not successful. Ultimately, treatment with MnO_2 afforded (+)-*epi*-condyfoline (**1**) in 20% yield over two steps. The structure of (+)-**1** was rigorously established using a combination of ^1H, ^{13}C, and 2D NMR experiments, IR, HRMS (see the Supporting Information for details), in addition to comparison of optical rotation with values reported by Schumann and Schmid.[5,24]

In conclusion, we have completed the first asymmetric total synthesis of (+)-*epi*-condyfoline (**1**) in 13 steps and 1.25% overall yield from *N*-sulfinylimine (+)-**8**. Highlights of the synthesis included the application of the domino Michael/Mannich annulation reaction of *N*-sulfinyl metallodienamines, which proceeded in high yield and good diastereoselectivity. Thionium chemistry developed by Bosch and employed by Overman was leveraged to access the pentacyclic framework of **1**. The synthesis presented herein provides a viable route toward the dimeric alkaloid (+)-leucofoline (**5**), which requires one-carbon homologation and acid-mediated, diastereoselective spiroannulation in analogy to the synthesis of (−)-leucoridines A and (−)-C.[11,12]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b03762.

Experimental procedures and characterization data (PDF)

Accession Codes

CCDC 1961748−1961749 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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