Natural Products

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Total Synthesis of (−)-Melotenine A**

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Monoterpene indole alkaloids belonging to the *Aspidosperma* class of natural products, which include over 250 unique members, continue to fascinate organic chemists because of their complex molecular architectures and diverse biological activities.[1] In 2010, Luo and co-workers isolated (−)-melotenine A [(−)-**1**], an intriguing pentacyclic alkaloid with an unprecedented dihydroazepine D ring fused to a tetracyclic pyrrolo[2,3-d]carbazole nucleus (ABCE framework) characteristic of *Strychnos* and *Aspidosperma* members from the plant *Melodinus tenuicaudatus* (Figure 1).[2] Furthermore, **1** exhibited potent cytotoxic activity against several cancer cell lines. The authors hypothesized that **1** was derived biogenetically from tabersonine (**2**)[3] by a stepwise process consisting of 1) oxidation at C19 to afford (*R*)-19-hydroxytabersonine (**3**), 2) ionization of **3** to form a secondary carbocation, 3) Wagner–Meerwein rearrangement to form the seven-membered ring and, finally 4) loss of H19 to form the tetrasubstituted alkene.

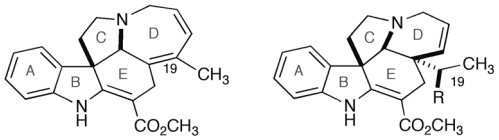
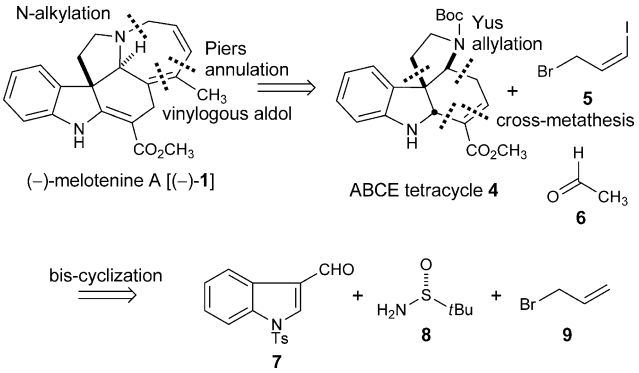


Figure 1. Structures of (−)-melotenine A [(−)-**1**], tabersonine (**2**), and proposed biogenetic precursor (*R*)-19-hydroxytabersonine (**3**).

Despite the tempting nature of Luo's biogenetic hypothesis, we devised an alternate, abiotic strategy to realize the first asymmetric synthesis of (−)-**1**. The retrosynthetic analysis is shown in Scheme 1. We envisioned the dihydroazepine D ring would be derived from an annulation, reported by Piers et al.,[4] of a vinyl lithium species and a methyl ketone. The latter, in turn, would be derived from a vinylogous aldol reaction of the ABCE tetracycle **4** and acetaldehyde (**6**). The tetracycle **4** would be prepared by an improved variation of our one-pot, bis-cyclization method for the synthesis of functionalized pyrrolo[2,3-*d*]carbazoles.[5] Thus, **4** would be prepared by a an allylation, as reported by Yus and co-workers,[6] of the *N*-sulfinylimine derived from the commercial aldehyde **7** and *N*-sulfinylamine **8**.[7]



Scheme 1. Retrosynthesis of (−)-melotenine A [(−)-**1**]. Boc = *tert*-butoxycarbonyl, Ts = 4-toluenesulfonyl.

The synthesis of (−)-**1**, which is outlined in Scheme 2, began by condensing commercial *N*-tosyl indole-3-carboxaldehyde (**7**) and (*R*)-*N*-*tert*-butanesulfinamide (**8**) with Ti(OEt)$_4$ and In^0. Addition of allyl bromide (**9**) resulted in Barbier formation of an allyl indium species which stereoselectively added to the preformed *N*-sulfinylimine to afford homoallylic sulfinamide **10** in 87% yield (d.r. = 10:1).[6] Removal of the chiral auxiliary and sulfonamide groups was accomplished by treatment with 4 M HCl in 1,4-dioxane followed by Mg^0 in MeOH to give **11** in 75% yield (one pot). Hydroxyethylation of gramine **11** was realized by stepwise condensation with ethyl glyoxaldehyde and reduction with LiAlH$_4$. Protection of the secondary amine with Boc afforded **12** in 57% overall yield. Cross-metathesis of **12** with methyl acrylate in the presence of the second-generation Hoveyda–Grubbs catalyst (HG-II)[8] gave the enoate **13** in 85% yield.

With the bis-cyclization substrate **13** in hand, we were poised to evaluate our new route to **4**. While our previous method[5] successfully accessed the pyrrolo[2,3-*d*]carbazoles scaffold, the pyrrolidinone C ring required extra reductive steps to arrive at the desired pyrrolidine oxidation state, thus rendering target syntheses less step efficient.[9,10] We drew inspiration from Brak and Ellman who recently demonstrated 3-β-hydroxyethyl indoles were converted into spiro[cyclopropyl]indolenines under Mitsunobu conditions.[11] Accordingly, the treatment of **13** with DEAD and PPh$_3$ in toluene led to smooth spirocyclization to form the pyrrolidine C ring. Addition of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) and heating to 80 °C for 12 hours furnished **4** in 56% yield.[12]

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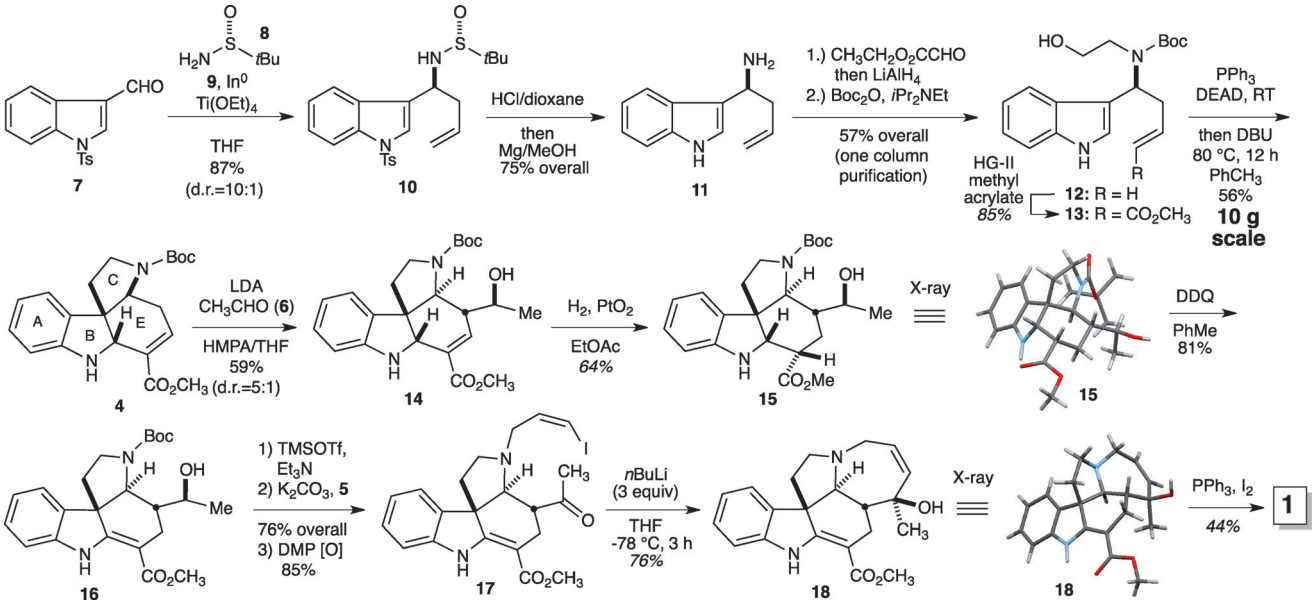

Scheme 2. Total synthesis of (−)-melotenine A [(−)-**1**]. DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, DEAD = diethylazodicarboxylate, HMPA = hexamethylphosphoramide, LDA = lithiumdiisopropylamide, Tf = trifluoromethanesulfonyl, THF = tetrahydrofuran, TMS = trimethylsilyl.

Significantly, this method resulted in the formation of a single stereoisomer and was easily scaled to ten grams.

The installation of the D ring in (−)-**1** required site-selective functionalization of **4** at the C20-position. We reasoned that a vinylogous aldol reaction would serve as a viable tactic. Furthermore, inspection of molecular models revealed the undesired α regioisomer would be disfavored for reasons of sterics. In the event, treatment of **4** with 4 equivalents of LDA in THF and HMPA followed by acetaldehyde (**6**) furnished **14** as the major diastereomer in 59% yield (d.r. = 5:1).[13] Isomerization of the olefin in **14** to the requisite β-anilinoacrylate position was accomplished by sequential platinum-catalyzed hydrogenation (64% yield) to afford **15** and DDQ-mediated oxidation to furnish **16** (81% yield). Single-crystal X-ray analysis of **15** confirmed the stereochemical course of the previous vinylogous aldol reaction.

Preparation of the Piers annulation substrate **17** required three steps. First, treatment of **16** with TMSOTf and Et_3N selectively removed the *N*-Boc group.[14] Second, chemoselective alkylation of the C ring nitrogen atom with (*Z*)-3-bromo-1-iodopropene (**5**)[15] in the presence of the C19 alcohol installed the remaining three carbon atoms. Third, the C19 alcohol was oxidized with the Dess–Martin periodinane (DMP). With **17** in hand, we were positioned to close the D ring using the Piers protocol. In the event, treatment of **17** with 3 equivalents of *n*BuLi at −78 °C for 3 hours smoothly afforded the tetrahydroazepinol **18** in 76% yield. Recrystallization of **18** gave material suitable for single-crystal X-ray analysis, which unambiguously confirmed the structure of the ABCDE framework.

The endgame in the asymmetric synthesis of (−)-melotenine A required regioselective dehydration of the tertiary, allylic C19 carbinol. To this end, we screened a variety of reaction conditions and ultimately found success in the Appel protocol (i.e., PPh_3, I_2), which furnished (−)-**1** in 44% yield.[18] Spectroscopic data for synthetic (−)-melotenine A (e.g., ^1H and ^{13}C NMR spectroscopy, and IR) were in complete agreement with those reported for natural (−)-**1** by Luo and co-workers.[2,16]

In summary, we have completed the first asymmetric total synthesis of the rearranged *Aspidoperma* alkaloid (−)-melotenine A ((−)-**1**; 14 steps, 1% overall yield) from commercial starting materials.[17] Key steps include 1) a Piers annulation to prepare the D ring, 2) an intermolecular vinylogous aldol reaction to functionalize the E ring, and 3) a novel sequence to prepare the ABCE tetracycle using Mitsunobu activation of an *N*-hydroxyethyl gramine intermediate and subsequent heating with DBU.

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