

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

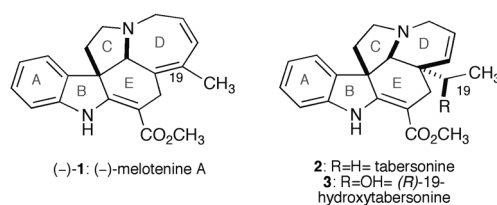
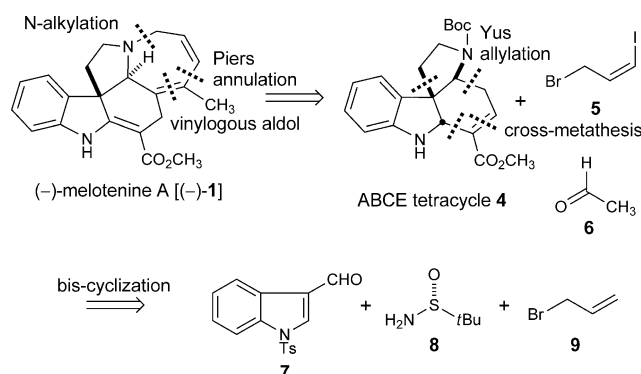


Figure 1. Structures of (–)-melotenine A [(–)-**1**], tabersonine (**2**), and proposed biogenetic precursor (*R*)-19-hydroxytabersonine (**3**).

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.

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



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

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 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]

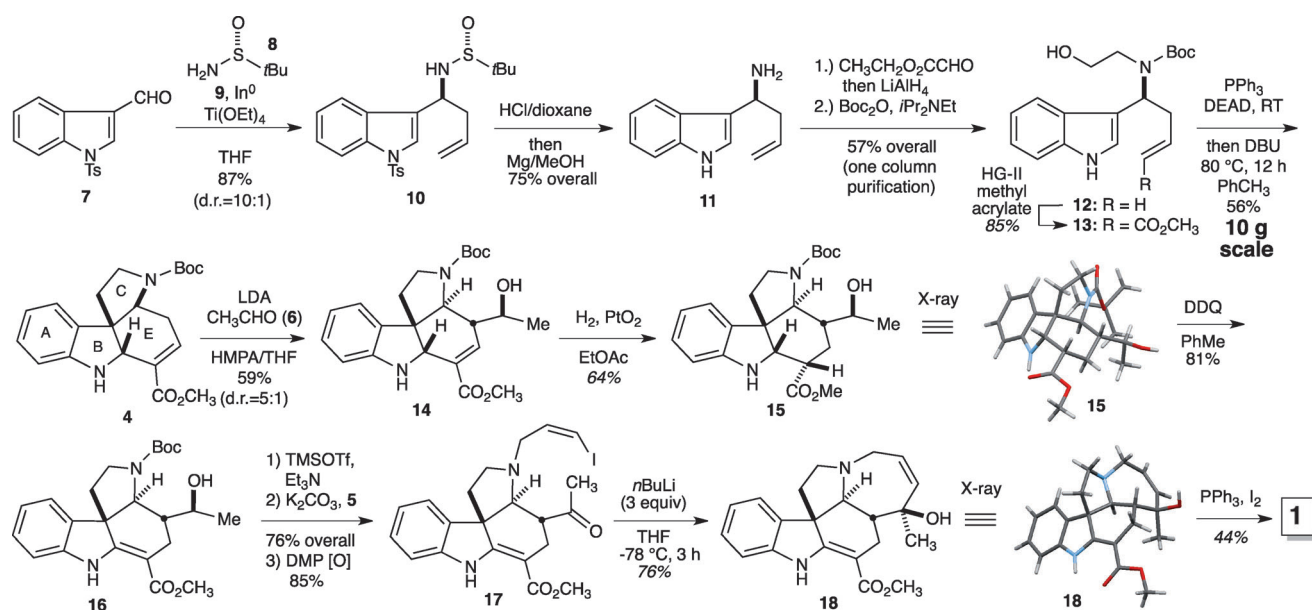
The synthesis of (–)-**1**, which is outlined in Scheme 2, began by condensing commercial *N*-tosyl indole-3-carboxaldehyde (**7**) and (*R*)-*N*-*tert*-butanesulfinamide (**8**) with Ti(OEt)₄ and In⁰. Addition of allyl bromide (**9**) resulted in Barbier formation of an allyl indium species which stereoselectively 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 4M HCl in 1,4-dioxane followed by Mg⁰ 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 LiAlH₄. 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 PPh₃ 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 Et₃N selectively removed the *N*-Boc group.^[14] Second, chemo-selective 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., PPh₃, I₂), which furnished (–)-1 in 44% yield.^[18]

Spectroscopic data for synthetic (–)-melotenine A (e.g., ¹H and ¹³C 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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