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Graphical Abstract

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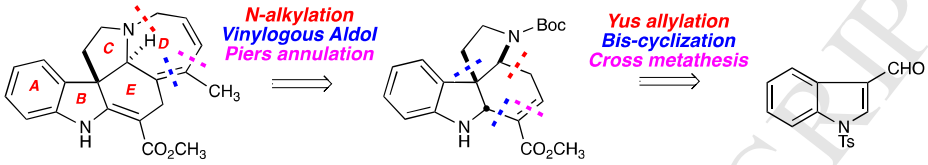

(–)-melotenine A (**1**) ABCE tetracycle **4**

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Asymmetric total synthesis of (–)-melotenine A

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ABSTRACT

We have developed a sequential one-pot Mitsunobu/intramolecular aza-Baylis–Hillman reaction to construct the ABCE tetracyclic core of the *Strychnos* alkaloids and applied this method to the total synthesis of (–)-melotenine A (**1**), a novel rearranged *Aspidosperma* alkaloid with potent cytotoxic activity. Additional key steps in the synthesis included (1) a Piers annulation of a vinyl iodide and a methyl ketone to prepare the D ring and (2) a site-selective intermolecular vinylogous aldol reaction to functionalize the E ring.

1. Introduction

(–)-Melotenine A (**1**) was isolated from the cane extracts of *Melodinus tenuicaudatus* by Luo and co-workers in 2010.[1] Its structure represents a rearranged monoterpene indole alkaloid possessing an *Aspidosperma*-like skeleton (Figure 1).[1] (–)-Melotenine A (**1**) features an intriguing pentacyclic framework with an unprecedented dihydroazepine D ring fused to a tetracyclic pyrrolo[2,3-*d*]carbazole nucleus (ABCE framework), which is a hallmark of *Strychnos* and *Aspidosperma* members. Furthermore, (–)-**1** exhibited more potent cytotoxic activity against several human cancer cell lines than that of cisplatin.[1]

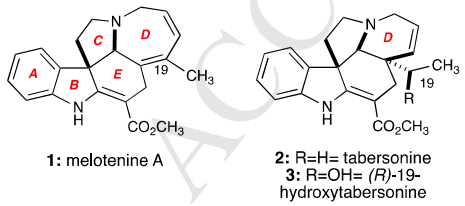
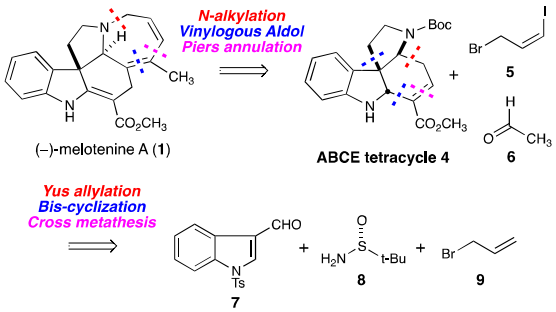


Figure 1 (–)-Melotenine A (**1**) and tabersonine (**2**), and *(R)*-19-hydroxytabersonine (**3**).

Our group has been engaged in the development and application of novel synthetic methodologies for efficient construction of complex indole alkaloids over the past few years.[2] Our success with the efficient total syntheses of *Strychnos* and *Aspidosperma* alkaloids prompted us to take on the challenge of synthesizing the arranged monoterpene indole alkaloid, (–)-melotenine A (**1**).[3] Herein, we would like to provide a full account of process that ultimately led the first successful total synthesis of (–)-melotenine A (**1**).

2. Retrosynthesis

Despite the elegant nature of Luo's biogenetic hypothesis,[1] we devised an alternative strategy to realize the first asymmetric synthesis of (–)-melotenine A (**1**). The retrosynthetic analysis of **1** is shown in Scheme 1.



Scheme 1 Retrosynthesis of (–)-melotenine A (**1**)

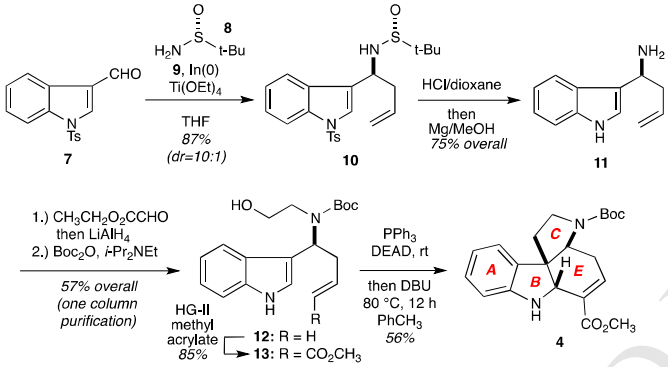
We envisioned the dihydroazepine D ring could be prepared through an annulation reaction first reported by Piers and co-workers wherein a vinyl lithium species is generated from a vinyl iodide in the presence of a methyl ketone (see the purple disconnection above).[4] Significantly, we reasoned the rate of halogen-metal exchange would be faster than either deprotonation of or addition to the methyl ketone, which would allow the intramolecular addition of the vinyl lithium species to the pendant ketone. The requisite substrate, in turn, would be derived from a vinylogous aldol reaction[5] of the ABCE tetracycle **4** and acetaldehyde **6**. Tetracycle **4** would be prepared by designing an asymmetric variant of the streamlined one-pot, bis-

cyclization method for the synthesis of functionalized pyrrolo[2,3-*d*]carbazoles.[2d] To this end, we recruited arguably the most efficient method for the preparation of asymmetric amines, namely chiral sulfinimines (*N*-sulfinyl imines) pioneered by Davis[6] and later expanded by Ellman.[7] Thus, **4** would be prepared by asymmetric allylation, using an efficient one-pot procedure, reported by Yus and co-workers,[8] of the *N*-sulfinylimine derived from the commercial aldehyde **7** and (*R*)-*N*-*tert*-butanesulfinamide **8**.

3. Forward Synthesis

*3.1. Synthesis of (–)-N^b-Boc ABCE tetracycle **4***

The forward synthesis started with the synthesis of (–)-*N*^{b}-Boc ABCE tetracycle **4**, which is shown in Scheme 2. Our synthesis of (–)-**4** 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** and subsequent Barbier formation of an allyl indium species resulted in stereoselective addition to the preformed *N*-sulfinylimine to afford homoallylic sulfonamide **10** in 87% yield (dr = 10:1).[8]



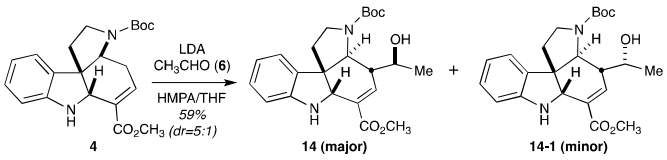
Scheme 2 Synthesis of (–)-*N*^{b}-Boc ABCE tetracycle **4**

Removal of the chiral auxiliary and indole *p*-toluenesulfonamide groups was accomplished by treatment of **10** with 4M HCl in 1,4-dioxane followed by Mg^0 in MeOH to give **11** in 75% yield in a single pot. Hydroxyethylation of gramine **11** was realized by stepwise condensation with ethyl glyoxyaldehyde and reduction of the intermediary imine 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)[9] furnished enoate (–)-**13** in 85% yield. Subjection of (–)-**13** to the sequential one-pot Mitsunobu/intramolecular aza-Baylis–Hillman reaction smoothly delivered (–)-**4** as a single stereoisomer in 56% overall yield.

3.2. Vinylogous aldol reaction

The installation of the D ring in (–)-**35** required site-selective functionalization of tetracycle (–)-**11** 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 due to sterics; moreover, its formation should be further suppressed by the directing effect of the Boc protection group.[10]

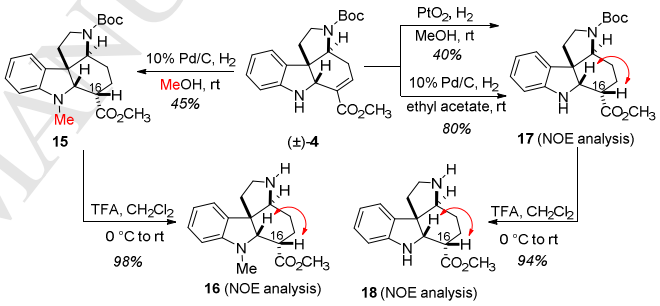
In the event (Scheme 3), treatment of (–)-**4** with 4 equivalents of LDA in THF and HMPA followed by addition of acetaldehyde furnished alcohols **14** and **14-1** as a mixture of diastereomers in 59% yield (dr = 5:1).



Scheme 3 Vinylogous aldol reaction of (–)-**4**

*3.3. Catalytic hydrogenation of the vinylogous aldol product **14***

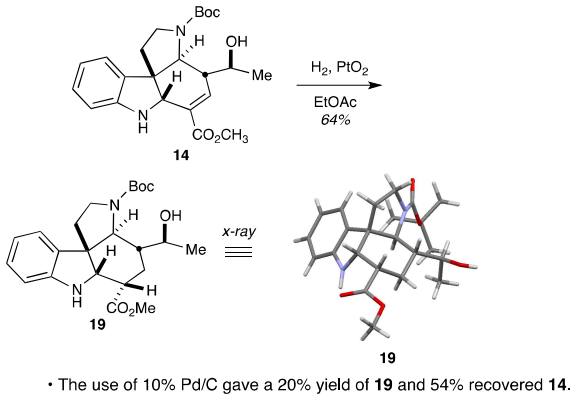
Before the catalytic hydrogenation was carried out on the vinylogous aldol product **14**, (±)-**4** was chosen for the model study (Scheme 4). The N_a-methylated product **15** was deprotected with TFA to yield **16** in 98% yield. A survey of the literature revealed that those conditions have been successfully applied in the transformation of *N*-benzyl to *N*-methyl for the total synthesis of sarpagine and ajmaline-related alkaloids.[11]



Scheme 4 Catalytic hydrogenation of (±)-**4**

Switching the catalyst from 10% Pd/C to PtO_2 resulted in the highly stereoselective formation of desired product **17**, which was isolated in 40% yield and deprotected with TFA to yield **18**. Furthermore, a more efficient catalytic hydrogenation was realized by using 10% Pd/C as the catalyst and ethyl acetate as the solvent. NOE analysis of **16**, **17** and **18** confirmed the stereochemistry of C16 in all of these compounds, which is ascribed to the preferential attack from the convex face of the C16-C17 enoate. At this stage, it was unclear what the effects of the pendant hydroxyl group or the *N*-Boc group in the real system would be during the course of the hydrogenation.[10]

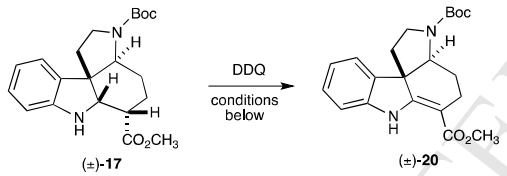
With the catalytic hydrogenation conditions in hand, we set out to test those conditions on the vinylogous aldol product **14**. As shown in Scheme 5, with 10% Pd/C as catalyst and ethyl acetate as solvent, the desired product was obtained as a single diastereoisomer in only 20% yield while 53% of the starting material was recovered. However, a 64% yield of **19** was achieved with PtO_2 as the catalyst and the stereochemistry of **19** was unambiguously confirmed by the single-crystal X-ray analysis (CCDC # = 1430541).



Scheme 5 Catalytic hydrogenation of the vinylogous aldol product **14**

3.4. Indoline oxidation

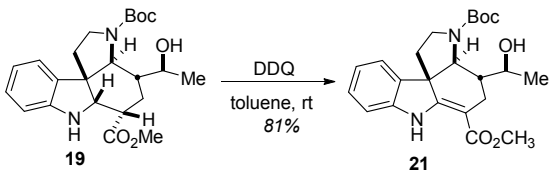
Considering the difficulty associated with the oxidation of indolines,[2e] we found it prudent to conduct a model study first. To this end, catalytic hydrogenation product **17** was chosen as the model substrate. Gratifyingly, subjection of **17** to DDQ[12] afforded the desired oxidation product **20** in 72% yield after refluxing in 1,4-dioxane for one hour. In addition, various solvents was screened to further improve the efficiency of this reaction. Toluene was found to facilitate the reaction at room temperature and an acceptable 66% yield of **20** was obtained (Scheme 6).



Solvent	Temperature	Yield
dioxane	reflux	72%
benzene	rt	71%
toluene	rt	66%

Scheme 6 Indoline oxidation of (±)-**17** with DDQ

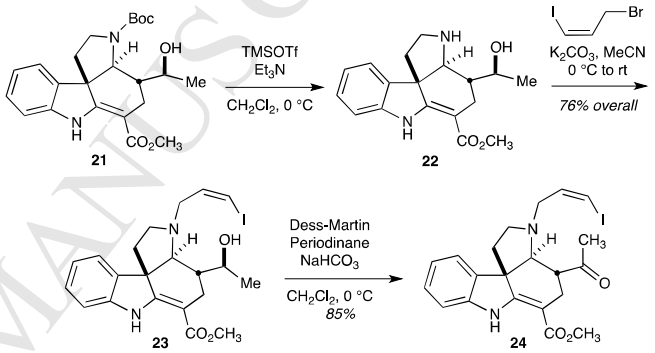
The optimized conditions were then applied to the oxidation of alcohol **19**. In the event, the desired vinylogous carbamate **21** was obtained in 81% yield (Scheme 7). Thus, the successful sequential catalytic hydrogenation and indoline oxidation made possible the isomerization of the olefin in **14** to the requisite anilinoacrylate position in vinylogous carbamate **20**.



Scheme 7 Indoline oxidation of **19** with DDQ

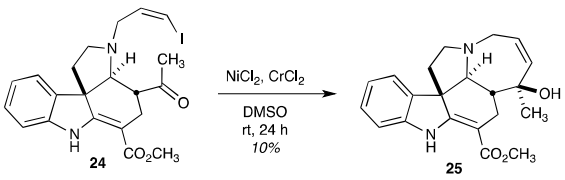
3.5. Cyclization of D ring

Preparation of the D ring cyclization substrate **24** required three steps (Scheme 8). First, treatment of **21** with TMSOTf and Et_3N selectively removed the *N*-Boc group.[13] Intermediate **22** was directly used for the following step without purification. Second, chemoselective alkylation of the C ring nitrogen atom with (Z)-3-bromo-1-iodopropene[14] in the presence of the C19 alcohol installed the remaining three carbon atoms, and the alkylated product **23** was obtained in 76% overall yield. Third, the C19 alcohol was oxidized with the Dess–Martin periodinane (DMP).[15] Interestingly, if the C19 alcohol oxidation was performed before the N4 alkylation, the latter turned out to be very sluggish and messy. It is also worth noting that the venerable Swern oxidation[16] was first tried for the oxidation of C19 alcohol. Unfortunately, incomplete conversion was observed and an unsatisfactory yield (i.e., < 30%) of the desired product was isolated. Corey–Kim conditions were also unsuccessful for the oxidation of this substrate.[17] It is important to note that regarding the DMP oxidation, the replacement of $NaHCO_3$ with pyridine led to a slight decrease in the yield (75%).



Scheme 8 Synthesis of the D ring cyclization substrate **24**

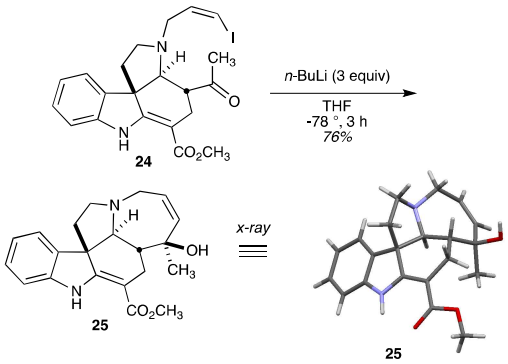
The Nozaki–Hiyama–Kishi (NHK) reaction is a powerful synthetic method for chemoselective formation of carbon-carbon bonds between aldehyde or ketone electrophiles and alkenyl, alkynyl, aryl, allyl or vinylchromium nucleophiles under very mild conditions. Accordingly, it has found widespread application in the total syntheses of complex natural products.[18] Taking into consideration of the plethora of reactive functionalities found in **24** (e.g., the acidity of the hydrogen on N1, the acidity of the hydrogens α to the ketone, and the liability of the vinyl iodide to strong bases through an E2 pathway), the NHK reaction was first recruited for the formation of the D ring. In addition, Kuehne had successfully employed this tactic in his elegant synthesis of mossambine.[19] The results are shown in Scheme **9**. Unfortunately, the presumed vinylchromium intermediate proved not sufficiently reactive toward the pendant ketone moiety in **24**, and the desired pentacycle **25** was isolated in only 10% yield, along with other decomposed products, which were not characterized.



Scheme 9 Nozaki–Hiyama–Kishi reaction of **24**

Since the vinyl chromium intermediate was not strong enough, it was logical to enlist a more nucleophilic vinylmetal species. Inspection of the literature revealed that Piers and co-workers reported an annulation reaction wherein a vinyllithium species derived from a vinyl iodide precursor was generated with *n*-butyl lithium in the presence of methyl ketones to form bicyclic tertiary alcohols.[4,14] That this reaction proceeds with such selectivity is striking.[20]

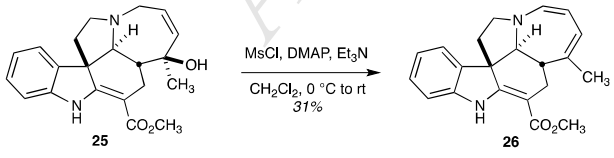
Thus, treatment of **24** with 3 equivalents of *n*BuLi at -78 °C for three hours smoothly afforded tetrahydroazepinol **25** in 76% yield. Recrystallization of **25** gave material suitable for single-crystal X-ray analysis (CCDC # = 1430540), which unambiguously confirmed the structure of the ABCDE framework (Scheme 10). The stereoselectivity of this annulation proceeds in full accordance with the Felkin–Anh model for asymmetric induction.[21]



Scheme 10 Piers annulation of **24**

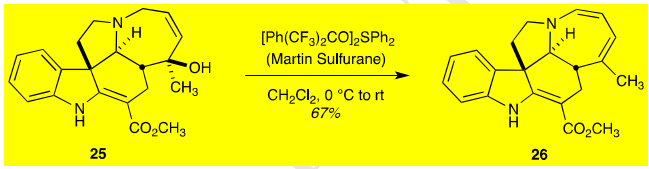
3.6. Endgame

After successfully installing the D ring of melotenine A (**1**) via the Piers annulation, what remained for the completion of this project was the regioselective dehydration of the tertiary, allylic C19 carbinol. Ultimately, this seemingly simple task of dehydration proved to be very challenging. For the dehydration of **25**, the *syn* orientation of the C19 hydroxyl and C20 hydrogen precluded an E2 elimination scenario. However, we reasoned that the tertiary, allylic carbocation should readily form; this would be followed by elimination with a suitable base.[22] When **25** was treated with MsCl in the presence of Et_3N and catalytic amounts of DMAP, dienamine **26** was the sole product obtained (Scheme 11). It appears the gramine nitrogen activates the allylic system possibly forming an aziridinium intermediate prior to elimination form the dienamide.



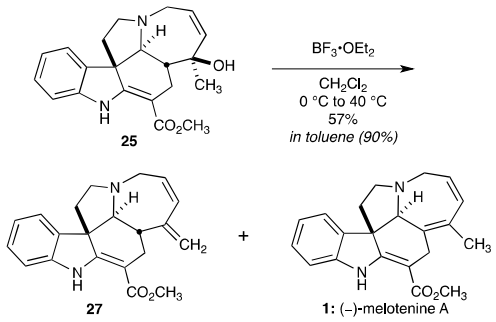
Scheme 11 Dehydration of **25** with MsCl to form dienamine **26**

Alternatively, the Burgess dehydration reaction has been long known to undergo *syn*-selective elimination for both secondary and tertiary alcohols.[23] However, subjection of **25** to the Burgess reagent showed no sign of the desired product. Next, attention was turned to the E1 elimination via the generation of a carbocation at C19 for the aforementioned reason. Martin sulfurane-promoted dehydration has been long known as a quick and efficient way for elimination of secondary and tertiary alcohols to alkenes.[24] The elimination of tertiary alcohols by Martin sulfurane in particular is believed to be via an E1 pathway.[25] Nonetheless, only dienamine **26** was formed on treatment of **25** with Martin sulfurane (Scheme 12).



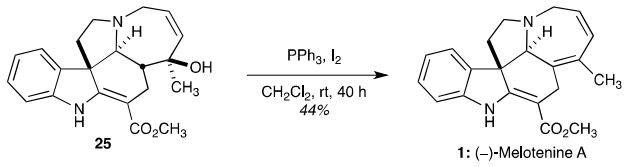
Scheme 12 Dehydration of **25** with Martin sulfurane

Recourse to Brønsted acids such as TsOH also proved fruitless.[26] We also attempted Posner's BF_3•OEt_2-mediated tertiary carbinol dehydration.[27] Most importantly, this method is highly regioselective and routinely affords the more substituted and stable alkene, which was precisely what we were seeking. However, this highly promising dehydration also failed to give us the desired product. To our surprise, the terminal alkene **27** was obtained in 57% yield. Replacement of CH_2Cl_2 with toluene further increased the yield of terminal alkene to 90% yield (Scheme 13). This product, which proved to be stubbornly stable, was not pursued further.



Scheme 13 Dehydration of **25** with BF_3•OEt_2 to access dienamine **27**

Fortuitously, Alvarez–Manzaneda[28] and co-workers reported a variant of the Appel reaction for carbinol dehydration in 2004. This protocol was conducted under mild conditions using PPh_3 and I_2. When we applied these conditions on our substrate (i.e., carbinol **25**), melotenine A was isolated in 44% yield (Scheme 14). 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 (–)-melotenine isolated by Luo and co-workers.[1]



Scheme 14 Dehydration of **25** with the modified Appel dehydration

4. Conclusion

In summary, the asymmetric total synthesis of rearranged *Aspidoperma* alkaloid (–)-melotenine A was achieved in 14 steps and 1% overall yield from commercial starting materials. 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.

5. Experimental section

General Information. All reactions containing moisture or air sensitive reagents were performed in oven-dried glassware under nitrogen or argon. Tetrahydrofuran, diethyl ether and dichloromethane were passed through two columns of neutral alumina prior to use. *i*-Pr_2NEt, and Et_3N were all distilled from CaH_2 prior to use. All other reagents were purchased from commercial sources and used without further purification. All solvents for work-up procedures were used as received. Flash column chromatography was performed according to the procedure of Still using ICN Silitech 32-63 D 60Å silica gel with the indicated solvents.[29] For all RCM reactions, CH_2Cl_2 was deaerated by bubbling Argon (1 min/mL). Thin layer chromatography was performed on Analtech $60F_{254}$ silica gel plates. Detection was performed using UV light, $KMnO_4$ stain, PMA stain and subsequent heating. ^1H and ^{13}C NMR spectra were recorded on a 500 MHz instrument in $CDCl_3$ at 298K. Chemical shifts are indicated in parts per million (ppm) and internally referenced to residual solvent signals. Splitting patterns are abbreviated as follows: s (singlet), d (doublet), bs (broad singlet), bd (broad doublet), t (triplet), q (quartet) and m (multiplet).

(±)-3-(tert-Butyl) 6-methyl (3aS,6S,6aS,11bR)-7-methyl-1,2,3a,4,5,6,6a,7-octahydro-3H-pyrrolo[2,3-d]carbazole-3,6-dicarboxylate ***15***: A solution of **4** (200 mg, 0.54 mmol) in MeOH (10 mL) containing 10% Pd/C (287 mg, 0.27 mmol) was stirred under H_2 at rt for 22 h. The catalyst was removed by filtration through Celite, and the filter cake was washed with EtOAc. The combined filtrates were concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with 20% EtOAc in hexanes to afford 94 mg (45%) of **15** as a white foam.

(±)-Methyl (3aS,6S,6aS,11bR)-7-methyl-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]carbazole-6-carboxylate ***16***: A solution of **15** (83 mg, 0.215 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C and followed by slow addition of TFA (0.256 mL, 3.34 mmol). The resulting mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with careful addition of saturated aq. $NaHCO_3$ (5 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (4 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with CH_2Cl_2/MeOH/29% aq. NH_4OH (100:1:0.05) → CH_2Cl_2/MeOH/29% aq. NH_4OH (100:5:0.05) to afford 62 mg (98%) of **16** as a pale gum. IR (neat) 2946, 2862, 1731, 1605, 1485, 1196, 1163, 1022, 741 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.12 (td, *J* = 7.6, 1.2 Hz, 1H), 6.97 (dd, *J* = 7.3, 0.8 Hz, 1H), 6.70 (td, *J* = 7.4, 0.8 Hz, 1H), 6.44 (d, *J* = 7.7 Hz, 1H), 3.78 (d, *J* = 7 Hz, 1H), 3.72(s, 3H), 3.37 (dd, *J* = 11.5, 5.9 Hz, 1H), 3.20 – 3.16 (m, 2H), 2.75 (s, 3H), 2.51 (ddd, *J* = 9.0, 7.0, 4.0 Hz, 1H), 2.32 – 2.25 (m, 1H), 1.90 – 1.77 (m, 2H), 1.73 – 1.60 (m, 2H), 1.60 – 1.52 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 150.7, 135.0, 127.9, 121.0, 117.9, 107.0, 70.2, 59.6, 53.1, 51.9, 44.2, 42.4, 38.6, 32.8, 25.4, 21.6; HRMS (ESI) calc'd for $C_{17}H_{22}N_2O_2$ + Na = 309.1579, found 309.1577.

(±)-3-(tert-Butyl) 6-methyl (3aS,6S,6aS,11bS)-1,2,3a,4,5,6,6a,7-octahydro-3H-pyrrolo[2,3-d]carbazole-3,6-dicarboxylate ***17***: A solution of **4** (670 mg, 1.81 mmol) in EtOAc (30 mL) containing 10% Pd/C (193 mg, 0.18 mmol) was stirred under H_2 at rt for 24 h. The catalyst was removed by filtration through Celite, and the filter cake was washed with EtOAc. The combined filtrates were concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with 20% EtOAc in hexanes to afford 536 mg (80%) of **17** as a white foam. IR (neat) 2974, 1732, 1684, 1392, 1170, 1117, 1093, 871, 744 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 – 6.99 (m, 2H), 6.72 (dd, *J* = 13.1, 5.7 Hz, 1H), 6.63 (d, *J* = 7.7 Hz, 1H), 4.39 (s, 1H), 4.08 (s, 1H), 3.75 – 3.66 (m, 4H), 3.61 (d, *J* = 9.5 Hz, 1H), 3.41 (ddd, *J* = 11.2, 9.6, 6.7 Hz, 1H), 2.29 (td, *J* = 10.2, 4.4 Hz, 1H), 2.18 (ddd, *J* = 12.4, 6.6, 3.1 Hz, 1H), 1.80 – 1.73 (m, 1H), 1.69 – 1.60 (m, 1H), 1.58– 1.52 (m, 2H), 1.52 – 1.42 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 154.8, 149.0, 131.3, 128.3, 122.0, 118.9, 109.8, 79.4, 64.4, 58.4, 54.4, 51.6, 45.8, 45.4, 28.5, 24.7, 20.2; HRMS (ESI) calc'd for $C_{21}H_{28}N_2O_4$ + H = 373.2127, found 373.2127.

(±)-Methyl (3aS,6S,6aS,11bR)-2,3,3a,4,5,6,6a,7-octahydro-1H-pyrrolo[2,3-d]carbazole-6-carboxylate ***18***: A solution of **17** (201 mg, 0.54 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C and followed by slow addition of TFA (0.62 mL, 8.1 mmol). The resulting mixture was allowed to warm to rt and stirred overnight. The reaction was quenched with careful addition of saturated aq. $NaHCO_3$ (20 mL) at 0 °C. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (4 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with CH_2Cl_2/MeOH/29% aq. NH_4OH (100:1:0.05) → CH_2Cl_2/MeOH/29% aq. NH_4OH (100:5:0.05) to afford 138 mg (94%) of **18** as a pale gum. IR (neat) 3364, 2931, 2866, 1720, 1606, 1481, 1463, 1259, 1196, 1170, 1093, 1053, 910, 740 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.07 – 7.01 (m, 2H), 6.74 (dd, *J* = 11.4, 3.9 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 4.46 (m, 1H), 3.76 (s, 1H), 3.71 (s, 3H), 3.55 (d, *J* = 9.9 Hz, 1H), 3.18 – 3.15 (m, 2H), 2.81 (s, 1H), 2.41 – 2.33 (m, 1H), 2.20 (dt, *J* = 15.5, 9.0 Hz, 1H), 1.91 – 1.83 (m, 1H), 1.77 – 1.63 (m, 3H), 1.61 – 1.52 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.2, 149.4, 131.7, 127.9, 121.7, 118.9, 110.0, 64.5, 57.6, 53.8, 51.9, 46.0, 44.3, 40.0, 26.0, 19.6; HRMS (ESI) calc'd for $C_{16}H_{20}N_2O_2$ + H = 273.1603, found 273.1614.

(±)-3-(tert-Butyl) 6-methyl (3aS,11bR)-1,2,3a,4,5,7-hexahydro-3H-pyrrolo[2,3-d]carbazole-3,6-dicarboxylate ***20***: To a solution

of **17** (50 mg, 0.134 mmol) in toluene (5 mL) was added a solution of DDQ (33.6 mg, 0.148 mmol) in toluene (5 mL). The reaction mixture was stirred in the dark (i.e., wrapped in Al foil) at rt for 6 h. The reaction mixture was filtered through a short pad of Celite, and the filter cake was washed with toluene. The combined filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography eluting with 20% EtOAc in hexanes to afford 33 mg (66%) of **20** as a pale foam. IR (neat) 3366, 2972, 1677, 1609, 1466, 1386, 11277, 1200, 1171, 1113, 1090,1042, 876, 777, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.96 (s, 1H), 7.17 (td, *J* = 7.7, 1.1 Hz, 1H), 7.11 (d, *J* = 7.4 Hz, 1H), 6.89 (td, *J* = 7.5, 0.8 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 4.20 (m, 1H), 3.77 (s, 3H), 3.65– 3.55 (m, 2H), 2.69 (ddd, *J* = 15.7, 4.6, 3.5 Hz, 1H), 2.31 – 2.16 (m, 2H), 2.12 – 2.05 (m, 1H), 1.85 (ddd, *J* = 12.7, 6.7, 1.3 Hz, 1H), 1.57 – 1.53 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 162.3, 154.6, 143.3, 135.8, 128.2, 121.7, 120.9, 109.2, 94.6, 79.7, 60.1, 55.0, 50.7, 44.4, 38.2, 29.5, 28.5, 19.4; HRMS (ESI) calc'd for $C_{21}H_{24}N_2O_4$ + H = 371.1971, found 371.1972.

(±)-Methyl (4aS,4a1S,11bR)-4-methyl-4a,4a1,5,7,12,13-hexahydroazepino[3,2,1-hi]indolo[3,2-d]indole-6-carboxylate ***26***: To a stirred solution of tertiary alcohol (±)-**25** (12 mg, 0.034 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added Martin sulfurane (46 mg, 0.068 mmol) in CH_2Cl_2 (1 mL). The resulting solution was stirred at 0 °C for 2 h. The reaction was quenched by addition of saturated aq. $NaHCO_3$ (3 mL) at 0 °C. The organic layer was separated and the aqueous was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with 10% EtOAc in hexanes + 1% triethylamine to afford 8 mg (67%) of (±)-**26** as an off-white solid. IR (neat) 3369, 2917, 2865, 1678, 1610, 1478, 1466, 1436, 1273, 1238, 1208, 1169, 1086, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.22 (s, 1H), 7.30 (d, *J* = 7.4 Hz, 1H), 7.15 (t, *J* = 7.7 Hz, 1H), 6.86 (t, *J* = 7.4 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 6.36 (d, *J* = 8.7 Hz, 1H), 5.76 (d, *J* = 6.7 Hz, 1H), 5.00 – 4.94 (m, 1H), 3.91 – 3.85 (m, 1H), 3.31 (td, *J* = 9.8, 1.5 Hz, 1H), 3.18 (dd, *J* = 16.9, 3.4 Hz, 1H), 2.72 (dd, *J* = 16.9, 10.1 Hz, 1H), 2.50 (d, *J* = 4.4 Hz, 1H), 2.34 – 2.26 (m, 1H), δ 1.94 – 1.88 (m, 1H), 1.81 (s, 3H), 1.80 – 1.77 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 160.9, 143.3, 138.8, 135.3, 134.6, 128.2, 123.3, 121.1, 120.8, 108.9, 100.3, 92.1, 71.3, 56.4, 51.1, 50.6, 43.6, 33.3, 22.7, 20.7; HRMS (ESI) calc'd for $C_{21}H_{22}N_2O_2$ + H = 335.1760, found 335.1749.

(±)-Methyl (4aS,4a1S,11bR)-4-methylene-1,4,4a,4a1,5,7,12,13-octahydroazepino[3,2,1-hi]indolo[3,2-d]indole-6-carboxylate ***27***: To a stirred solution of tertiary alcohol (±)-**25** (7 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added BF_3• OEt_2 (12 µL, 0.1 mmol). The resulting solution was heated to 40 °C and stirred at that temperature for 16 h. The reaction was quenched by addition of saturated aq. $NaHCO_3$ (3 mL) at rt. The organic layer was separated and the aqueous was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic layers were washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column column chromatography eluting with 10% EtOAc in hexanes to afford 4 mg (57%) of (±)-**27** as an off-white solid. IR (neat) 3350, 2917, 2849, 2360, 2340, 1683, 1609, 1465, 1436, 1241, 1201, 1082 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.03 (s, 1H), 7.34 (d, *J* = 7.3 Hz, 1H), 7.12 (td, *J* = 7.7, 1.2 Hz, 1H), 6.84 (dd, *J* = 10.9, 4.1 Hz, 1H), 6.78 (d, *J* = 7.7 Hz, 1H), 6.21 (d, *J* = 12.1 Hz, 1H), 5.69 – 5.62 (m, 1H), 5.15 (s, 1H), 5.08 (s, 1H), 3.79 – 3.72 (m, 4H), 3.58 (d, *J* = 16.5 Hz, 1H), 3.28 – 3.23 (m, 1H), 3.16 (d, *J* = 8.4 Hz, 1H), 3.06– 2.98 (m, 2H), 2.79 (dd, *J* = 16.5, 7.6 Hz, 1H), 2.66 (dd, *J* = 16.5, 7.6 Hz, 1H), 2.46 (dt, *J* = 12.2, 9.1 Hz, 1H), 1.84 – 1.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 162.9, 149.3, 143.9, 137.1, 134.1, 127.8, 127.5, 123.2, 120.3, 114.9, 108.7, 93.0, 66.3, 55.8, 51.4, 51.0, 50.3, 38.8, 37.8, 26.5; HRMS (ESI) calc'd for $C_{21}H_{22}N_2O_2$ + H = 335.1760, found 335.1759.

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Supplementary Material

Supplementary data (^1H and ^{13}C data NMR spectra for **16**, **17**, **18**, **20**, **26**, and **27)** can be found in the online version, at http://dx.doi.org/j.tet.2016.xx.xxx.

References and notes

1. Feng, T.; Li, Y.; Liu, Y.-P.; Cai, X.-H.; Wang, Y.-Y.; Luo, X.-D. *Org. Lett.* **2010**, *12*, 968.
2. (a) Sirasani, G.; Paul, T.; Dougherty, W.; Kassel, S.; Andrade, R. B. *J. Org. Chem.* **2010**, *75*, 3529; (b) Sirasani, G.; Andrade, R. B. In *Strategies and Tactics in Organic Synthesis*; Michael, H., Ed.; Academic Press: 2013; Vol. 9, p 1; (c) Sirasani, G.; Andrade, R. B. *Org. Lett.* **2011**, *13*, 4736; (d) Sirasani, G.; Andrade, R. B. *Org. Lett.* **2009**, *11*, 2085; (e) Teijaro, C. N.; Zhao, S.; Kokkonda, P.; Andrade, R. B. *Synthesis* **2015**, *47*, 1547; (f) Kokkonda, P.; Brown, K. R.; Seguin, T. J.; Wheeler, S. E.; Vaddypally, S.; Zdilla, M. J.; Andrade, R. B. *Angew. Chem. Int. Ed.* **2015**, *54*, 12632; (g) Zhao, S.; Andrade, R. B. *J. Am. Chem. Soc.* **2013**, *135*, 13334.
3. Zhao, S.; Sirasani, G.; Vaddypally, S.; Zdilla, M. J.; Andrade, R. B. *Angew. Chem. Int. Ed.* **2013**, *52*, 8309.
4. (a) Piers, E.; Marais, P. C. *Tetrahedron Lett.* **1988**, *29*, 4053; (b) Piers, E.; Cook, K. L. *Chem. Commun.* **1996**, 1879.
5. (a) Casiraghi, G.; Zanardi, F.; Appendino, G.; Rassu, G. *Chem. Rev.* **2000**, *100*, 1929; (b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076.
6. (a) Davis, F. A. *J. Org. Chem.* **2006**, *71*, 8993; (b) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003; (c) Zhou, P.; Chen, B.-c.; Davis, F. A. In *Advances in Sulfur Chemistry* 2000; Vol. 2, p 249; (d) Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403; (e) A. Davis, F.; Chen, B.-C. *Chem. Soc. Rev.* **1998**, *27*, 13; (f) Davis, F. A.; Portonovo, P. S.; Reddy, R. E.; Chiu, Y.-h. *J. Org. Chem.* **1996**, *61*, 440; (g) Davis, F. A.; Reddy, R. E.; Szewczyk, J. M. *J. Org. Chem.* **1995**, *60*, 7037.
7. (a) Robak, M. T.; Herbage, M. A.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 3600; (b) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984.
8. González-Gómez, J. C.; Medjahdi, M.; Foubelo, F.; Yus, M. *J. Org. Chem.* **2010**, *75*, 6308.
9. Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.
10. (a) Beak, P.; Meyers, A. I. *Acc. Chem. Res.* **1986**, *19*, 356; (b) Campos, K. R. *Chem. Soc. Rev.* **2007**, *36*, 1069.
11. (a) Fu, X.; Cook, J. M. *J. Org. Chem.* **1993**, *58*, 661; (b) Yu, P.; Wang, T.; Li, J.; Cook, J. M. *J. Org. Chem.* **2000**, *65*, 3173.

12. Wenkert, E.; Orito, K.; Simmons, D. P.; Ardisson, J.; Kunesch, N.; Poisson, J. *J. Org. Chem.* **1983**, *48*, 5006.
13. (a) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870; (b) Kuehne, M. E.; Xu, F. *J. Org. Chem.* **1998**, *63*, 9434.
14. Piers, E. *Synthesis* **1998**, *1998*, 590.
15. (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155; (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277; (c) Ireland, R. E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
16. Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651.
17. (a) Corey, E. J.; Kim, C. U. *J. Am. Chem. Soc.* **1972**, *94*, 7586; (b) Tidwell, T. T. *Synthesis* **1990**, *1990*, 857.
18. (a) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 12349; (b) Fürstner, A.; Shi, N. *J. Am. Chem. Soc.* **1996**, *118*, 2533; (c) Cintas, P. *Synthesis* **1992**, *1992*, 248; (d) Avalos, M.; Babiano, R.; Cintas, P.; L. Jimenez, J.; C. Palacios, J. *Chem. Soc. Rev.* **1999**, *28*, 169; (e) Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.
19. Kuehne, M. E.; Wang, T.; Seraphin, D. *J. Org. Chem.* **1996**, *61*, 7873.
20. Cooke, M. P.; Houpis, I. N. *Tetrahedron Lett.* **1985**, *26*, 4987.
21. Nguyen Trong, A.; Eisenstein, O.; Lefour, J. M.; Tran Huu Dau, M. E. *J. Am. Chem. Soc.* **1973**, *95*, 6146.
22. Yadav, J. S.; Mysorekar, S. V. *Synth. Commun.* **1989**, *19*, 1057.
23. (a) Atkins, G. M.; Burgess, E. M. *J. Am. Chem. Soc.* **1968**, *90*, 4744; (b) Burgess, E. M.; Penton, H. R.; Taylor, E. A. *J. Org. Chem.* **1973**, *38*, 26.
24. Martin, J. C.; Arhart, R. J. *J. Am. Chem. Soc.* **1971**, *93*, 4327.
25. Li, J. J. In *Name Reactions for Functional Group Transformations*; John Wiley & Sons, Inc.: 2010, p 159.
26. D'Onofrio, F.; Scettri, A. *Synthesis* **1985**, *1985*, 1159.
27. Posner, G. H.; Shulman-Roskes, E. M.; Oh, C. H.; Carry, J.-C.; Green, J. V.; Clark, A. B.; Dai, H.; Anjeh, T. E. N. *Tetrahedron Lett.* **1991**, *32*, 6489.
28. Alvarez-Manzaneda, E. J.; Chahboun, R.; Cabrera Torres, E.; Alvarez, E.; Alvarez-Manzaneda, R.; Haidour, A.; Ramos, J. *Tetrahedron Lett.* **2004**, *45*, 4453.
29. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.