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Total Synthesis of (−)-Leuconicine A and B

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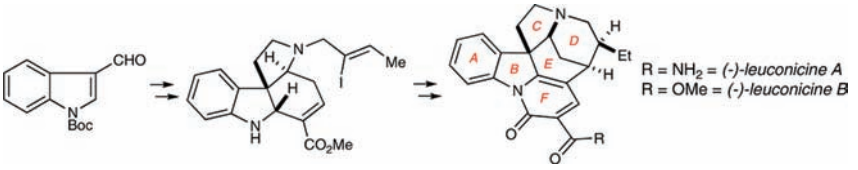
ABSTRACT



Concise asymmetric total syntheses of *Strychnos* alkaloids (−)-leuconicine A (14 steps, 9% overall yield) and B (13 steps, 10% overall yield) have been accomplished. Key steps include (1) our sequential one-pot spiro-cyclization/intramolecular aza-Baylis-Hillman method to prepare the ABCE framework; (2) a novel domino acylation/Knoevenagel cyclization to prepare the F-ring; and (3) a Heck cyclization to access the D-ring.

In 2009, Kam and co-workers isolated novel hexacyclic *Strychnos* alkaloids (−)-leuconicine A (**1**) and B (**2**) from extracts of the Malaysian plant *Leuconotis* (Apocynaceae) *maingayi* (Figure 1).[1] The leuconicines are structurally related to known *Strychnos* alkaloids (−)-akuammicine (**3**)[2] and (−)-strychnine (**4**)[3] yet distinguish themselves by the presence of a 3-acyl-2-pyridone F-ring and an ethyl, as opposed to ethylidene, substituent on the D-ring.

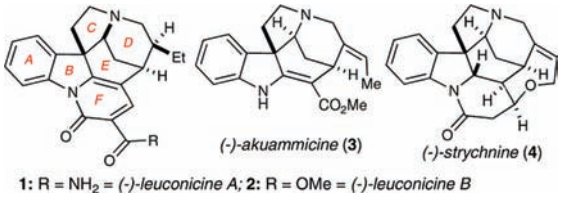


Figure 1. Structures of (−)-leuconicine A (**1**), (−)-leuconicine B (**2**), (−)-akuammicine (**3**), and (−)-strychnine (**4**).

We recently completed concise total syntheses of akuammicine (**3**) and strychnine (**4**) in racemic form.[4] Therein we employed our one-pot sequential biscyclization protocol involving (1) spirocyclization of a functionalized indole 3-carbinamide followed by (2) an intramolecular aza-Baylis−Hillman reaction to quickly access the ABCE tetracyclic framework of the *Strychnos* alkaloids.[5] In order to render our current synthesis asymmetric, we employed a method recently reported by Yus[6] wherein *N*-*tert*-butanesulfinimines[7] are prepared and allylated *in situ* to afford homoallylic amines in high yields and diastereoselectivities (Scheme 1). To this end, commercial *N*-tosyl indole-3-carboxaldehyde (**4**) was treated with (*R*)-*N*-*tert*-butanesulfinamide (**5**), $Ti(OEt)_4$, allylbromide, and indium metal to furnish homoallylic amine **6** in 87% yield (dr = 10:1).

Removal of the chiral auxiliary and the *N*-tosyl group was accomplished by sequential treatment with 4 M HCl in dioxane followed by magnesium in MeOH to afford **7** in 75% yield (one pot). Alkylation with known (*Z*)-2-iodobutenyl bromide[8] and acylation with bromoacetyl chloride furnished amide **8** in 83% yield over two steps.

Chemoselective cross-metathesis between **8** and methyl acrylate was accomplished with 10 mol % of the Hoveyda−Grubbs second-generation catalyst,[9] affording biscyclization substrate **9** in 80% yield. Thus, the key step was realized by the addition of AgOTf and 2,6-di-*tert*-Bu-4-Me-pyridine (DTBMP) in PhMe at rt for 2.5 h, which afforded spiroindolenine **10**; subsequent addition of 2.5 equiv of DBU to the

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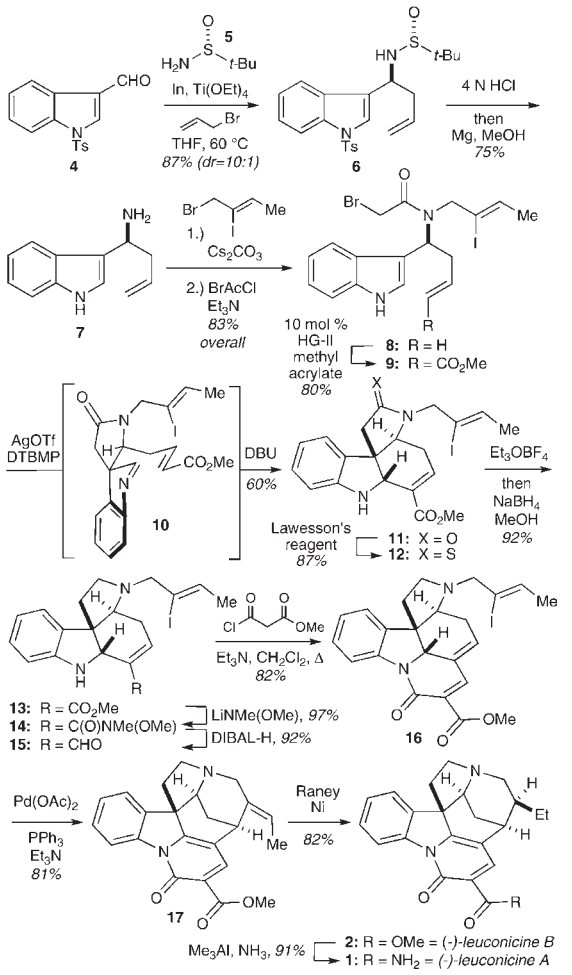
Scheme 1. Synthesis of (−)-Leuconicine A (**1**) and B (**2**)



reaction mixture and stirring for 12 h delivered tetracycle **11** in 60% yield. The same tactic had been employed in our synthesis of akuammicine (**3**).[4]

To adjust the oxidation state of the C-ring, the Raucher protocol[10] was recruited. Thus, thionation with Lawesson's reagent afforded **12** in 87% yield. Alkylation with Et_3OBF_4 and subsequent thioimidate reduction with $NaBH_4$ furnished **13** in 92% yield.[4] Functional group interconversion between methyl ester **13** and aldehyde **15** was best realized by stepwise Weinreb amidation[11] [i.e., LiN(OMe)Me] to access **14** and then DIBAL-H reduction, providing enal **15** in 89% yield over two steps.

(10) Raucher, S.; Klein, P. *Tetrahedron Lett*. **1984**, *21*, 4061.
(11) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett*. **1981**, *22*, 3815.

It was envisioned that the F-ring could be prepared by adding a malonyl linchpin between the indoline nitrogen and aldehyde moieties of **15**. This approach entails (1) acylation of the indoline with a methyl malonyl electrophile and (2) an intramolecular Knoevenagel condensation. Optimal one-pot execution of this plan included heating a solution of **15**, methyl malonyl chloride, and Et_3N in CH_2Cl_2 for 3 h wherein pentacycle **16** was isolated in 82% yield.

Endgame commenced with Rawal's elegant solution to preparing the D-ring of *Strychnos* alkaloids. Specifically, the intramolecular Heck reaction was effected by treatment of **16** with catalytic $Pd(OAc)_2$, PPh_3 in Et_3N to furnish dehydroleuconicine B (**17**) in 81% yield.[12] Chemoselective reduction of the ethylidene moiety with Raney Ni afforded (−)-leuconicine B (**2**) in 82% yield.[13] Weinreb aminolysis of **2** with dimethylaluminum amide[14] secured (−)-leuconicine A (**1**) in 91% yield. Spectral data for **1** and **2** (e.g., ^1H and ^{13}C NMR, IR, optical rotation) were in agreement with those reported by Professor Kam.[1,15]

In summary, we have completed concise total syntheses of *Strychnos* alkaloids (−)-leuconicine A (**1**, 14 steps, 9% overall yield) and B (**2**, 13 steps, 10% overall yield) from commercial starting materials. Key steps include (1) our one-pot, sequential spirocyclization/intramolecular aza-Baylis−Hillman method to assemble the ABCE framework; (2) a novel domino acylation/Knoevenagel cyclization to prepare the F-ring; and (3) an intramolecular Heck cyclization to access the D-ring.

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Supporting Information Available. Experimental procedures, characterization of compounds **1**, **2**, **10**, **12**−**14**, **18**−**19**, **21**, **23**−**24** (including ^1H and ^{13}C NMR spectra). This material is available free of charge via the Internet at http://pubs.acs.org.

(12) Rawal, V. H.; Michoud, C. *Tetrahedron Lett*. **1991**, *14*, 1695.
(13) Hydrogenation (1 atm) of the ethylidene with Pd or Pt catalysts was not effective.
(14) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett*. **1977**, *18*, 4171.
(15) Prof. Kam has reported a new value for the optical rotation of natural **2** {$[\alpha]^{25}_D$ −720 ($CHCl_3$, *c* 1.55)}, which replaces the originally reported value {$[\alpha]^{25}_D$ +527 ($CHCl_3$, *c* 0.24)} in ref 1 (personal communication).