

Total Synthesis of ($\pm$)-Hirsutine: Application of Phosphine-Catalyzed Imine–Allene [4 + 2] Annulation

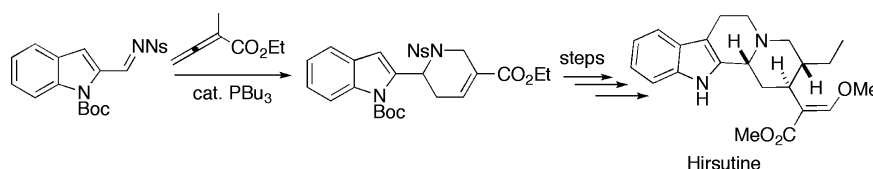
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ABSTRACT



The total synthesis of the indole alkaloid hirsutine has been achieved, with a key step being the application of our phosphine-catalyzed [4 + 2] annulation of an imine with ethyl α -methylallenoate. From commercially available indole-2-carboxaldehyde, the target was synthesized in 14 steps and 6.7% overall yield.

The hooks of *Uncaria rhynchophylla*, *U. sinensis*, and *U. macrophylla* are used in traditional Chinese herbal medicine as spasmolytic, analgesic, and sedative treatments for many symptoms associated with hypertension and cerebrovascular disorders.¹ Many compounds have been isolated from these plants, including indole alkaloids, oxyindole alkaloids, and phenylpropanoids.² Hirsutine (**1**) and hirsuteine (**2**), two of the major indole alkaloids isolated from the *Uncaria* species, have been demonstrated to exert central depressive and vasodilatory effects,^{3,4} as well as protective effects (through inhibition of Ca^{2+} influx) against neuronal death in cultured rat cerebellar granule cells.⁵ In addition, hirsutine displays antihypertensive, negative chronotropic, and antiarrhythmic activity.⁶ Recently, hirsutine has attracted the attention of the medical

community for its ability to inhibit the growth of influenza A virus (subtype H_3N_2) with an EC_{50} value of 0.40–0.57 $\mu\text{g/mL}$; thus, hirsutine is 10–20 times more

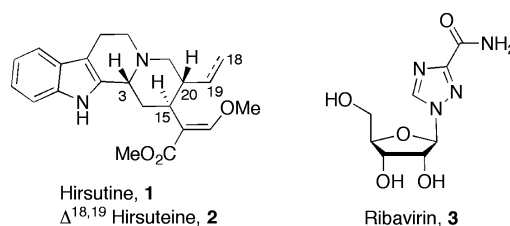


Figure 1. Structures of hirsutine, hirsuteine, and ribavirin.

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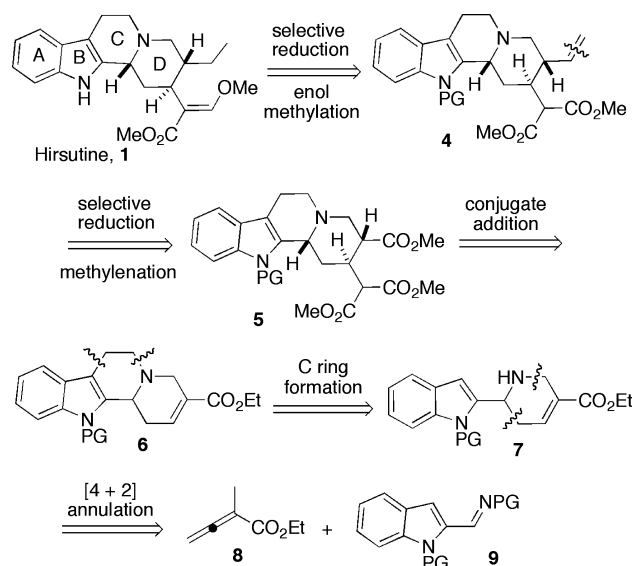
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potent than the clinically used drug ribavirin (**3**, Figure 1).⁷ Many research groups have taken the initiative to study and synthesize hirsutine and its various derivatives in the hope that these compounds will find significant medicinal use.⁸

Of all the various approaches toward functionalized 1,2,5,6-tetrahydropyridines, our phosphine-catalyzed [4 + 2] annulation of α -methylallenoates with imines has emerged as one of the premiere methodologies.⁹ Although many natural products contain a tetrahydropyridine motif, the phosphine-catalyzed [4 + 2] annulation has not been applied previously to the synthesis of fused tetracyclic indole alkaloids.^{9b,10} Herein, we disclose our total synthesis

Scheme 1. Retrosynthetic Analysis of Hirsutine



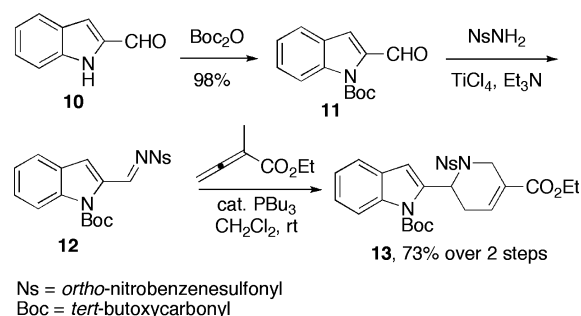
of hirsutine using our [4 + 2] annulation methodology as a key step. The strategy developed in this study should also be applicable as a new route for the synthesis of other corynantheine indole alkaloids.

Scheme 1 outlines our retrosynthetic analysis of hirsutine. We envisioned the β -methoxy acrylate motif to arise from methylation of the enol form of the corresponding aldehyde, which would result from partial reduction of the malonate functionality in intermediate **4**. We suspected that the vinyl group, which could be hydrogenated to the ethyl group in hirsutine, of **4** could be introduced through selective reduction of the isolated ester group in **5** in the presence of the malonate moiety, followed by Wittig

olefination. We expected the malonate group to be installed through a diastereoselective conjugate addition of the malonate anion onto the functionalized enoate tetracycle **6**,¹¹ which would be derived through intramolecular N-alkylation of the free amine of the tricycle **7**. In the key step, we anticipated the indole tricycle **7** to result directly from our phosphine-catalyzed [4 + 2] annulation between ethyl α -methylallenoate (**8**) and a suitably protected 2-indolylimine (**9**).

Our synthesis of hirsutine (Scheme 2) commenced with Boc protection of the commercially available indole 2-carboxaldehyde (**10**).^{12,13} We then reacted the *N*-Boc-protected aldehyde **11** with *o*-nitrobenzenesulfonamide (NsNH₂) in the presence of Et₃N and catalytic TiCl₄ to give the *N*-(*o*-nosyl)imine **12**.¹⁴ Because this imine is hydrolytically labile, we performed the transformations from the aldehyde **11** to the annulation product **13** in one pot. The phosphine-catalyzed annulation of the crude imine **12** with ethyl α -methylallenoate (**8**) proceeded smoothly under modified conditions to give compound **13**. Accordingly, we obtained compound **13** in 73% yield from the aldehyde **11** over two steps.

Scheme 2. [4 + 2] Annulation in the Synthesis of Intermediate **13**



Ns = *ortho*-nitrobenzenesulfonyl
Boc = *tert*-butoxycarbonyl

We removed the Boc group from compound **13** cleanly, using SiO₂ in refluxing toluene, in 90% yield (Scheme 3).¹⁵ Acylation at the C3 position of the indole moiety in **14** with oxalyl chloride, followed by reduction of the resulting keto acid chloride with borane, furnished the requisite tryptophol **15**. To the best of our knowledge, this transformation is the first example of the reduction of a chlorooxalyl group with borane, instead of its trapping as an alkyl oxalate ester derivative.¹⁶

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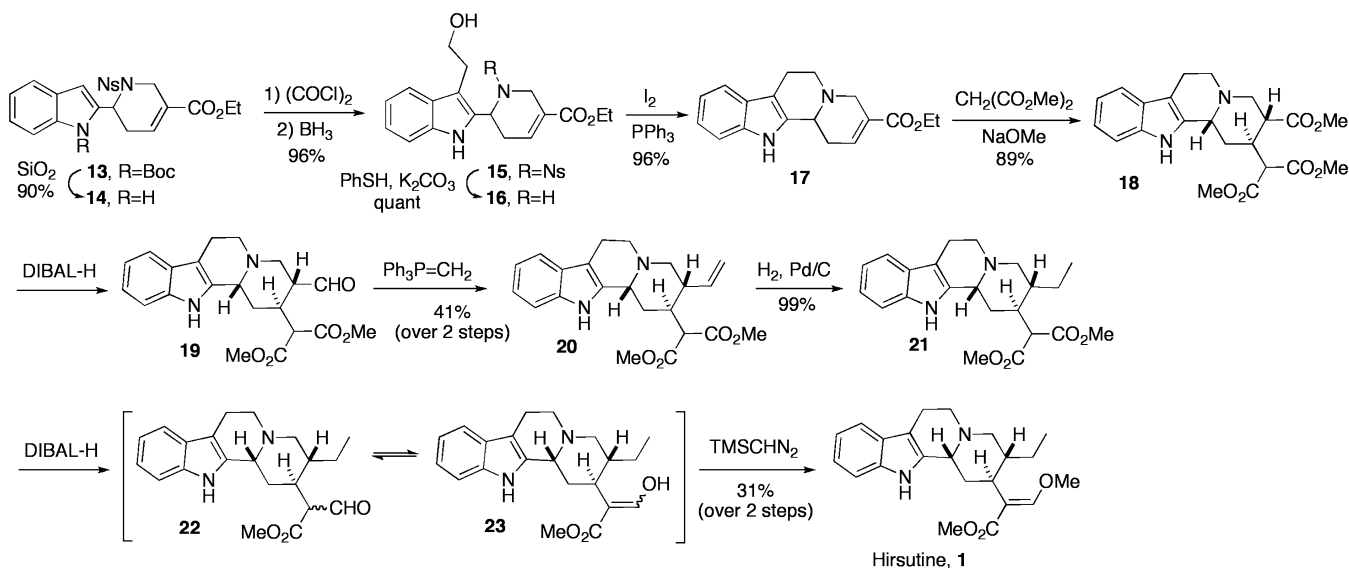
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Scheme 3. Synthesis of Hirsutine, **1**



The nosyl group of **15** was readily removed in the presence of PhSH and K₂CO₃ in MeCN at 50 °C.¹⁷ Formation of the C-ring through intramolecular N-alkylation proceeded smoothly under the influence of I₂ and PPh₃ to give the tetracycle **17**.¹⁸ To install the desired relative stereochemistry at the C3 and C15 positions of hirsutine, we opted for the Michael addition onto the enoate **17**, which would favor axial addition. To our delight, Michael addition with dimethyl malonate anion provided the triester **18** in 89% yield as a single diastereoisomer. Compound **18** exhibited the same relative stereochemistry as that found in hirsutine, as confirmed through X-ray diffraction analysis.¹⁹

Another key transformation was the selective reduction of the triester **18**. The literature appears to be lacking in any precedents for the reduction of an isolated ester in the presence of a malonate ester moiety. After screening many reducing reagents and conditions, we obtained compound **19** in 20% isolated yield after the reaction of **18** with DIBAL-H at –78 °C. We confirmed the structure of **19** through X-ray diffraction analysis.¹⁹ Unfortunately, standard olefination conditions, including those of classic Wittig,²⁰ Tebbe,²¹ Takai,²² and Wilkinson²³ reactions, failed to provide the

methylenation product. We found, however, that the Wittig reaction proceeded smoothly in the presence of DMSO to give the olefin **20**.²⁴ Because the aldehyde **19** was labile toward SiO₂, we decided to use the crude product from the selective reduction of **18** directly for the Wittig olefination, obtaining the alkene **20** in 41% yield over two steps from the triester **18**.

After reducing the vinyl group through hydrogenation,^{25,26} we reduced the malonate group of **21** selectively to give the monoaldehyde **22**.^{8d} At this point, the classic method for methylation, using HCl and MeOH, failed.^{8d} Nevertheless, TMSCHN₂ proved effective in methylating the aldehyde oxygen atom to furnish hirsutine (**1**) in 31% yield over two steps from **21**.²⁷ The spectral data of our synthetic sample matched those reported in the literature.^{8g,28}

Our synthesis exhibits several salient features: (i) phosphine-catalyzed [4 + 2] annulation of ethyl α-methylallenoate with an imine; (ii) reduction of a chlorooxalyl group with borane to install the tryptophol motif, followed by N-alkylation to form ring C; (iii) diastereoselective Michael addition of the malonate anion to establish the correct relative configuration at C15 and C20 of hirsutine; and (iv) selective

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(19) CCDC 874946 for compound **18** and CCDC 874752 for compound **19** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre at www.ccdc.cam.ac.uk/data_request/cif.

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reduction of an isolated ester in the presence of a malonate moiety. This synthesis also provided, in eight steps and 59% yield, the key tetracyclic intermediate **17**, which should be useful in the preparation of other corynantheine indole alkaloids. Further investigations into the syntheses of other corynantheine indole alkaloids and the enantioselective synthesis of hirsutine are underway.

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allenoates (synthesized in the National Key Technologies R&D Program of China, 2012BAK25B03, CAU) as the substrates. This material is based upon work supported by the NSF under equipment grant no. CHE-1048804.

Supporting Information Available. Representative experimental procedures and spectral data for all new compounds. Crystallographic data for compounds **18** and **19**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.