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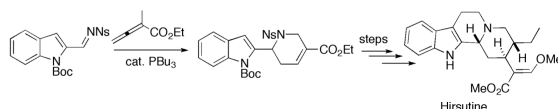
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Total Synthesis of (±)-Hirsutine: Application of Phosphine-Catalyzed Imine–Allene [4 + 2] Annulation

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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 H₃N₂) with an EC₅₀ value of 0.40–0.57 $\mu\text{g/mL}$; thus, hirsutine is 10–20 times more 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 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.

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

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.

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

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**.^{8c} At this point, the classic method for methylation, using HCl and MeOH, failed.^{8c} 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.^{8f,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 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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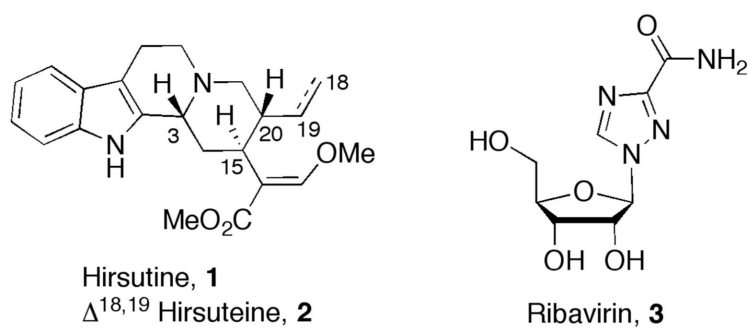
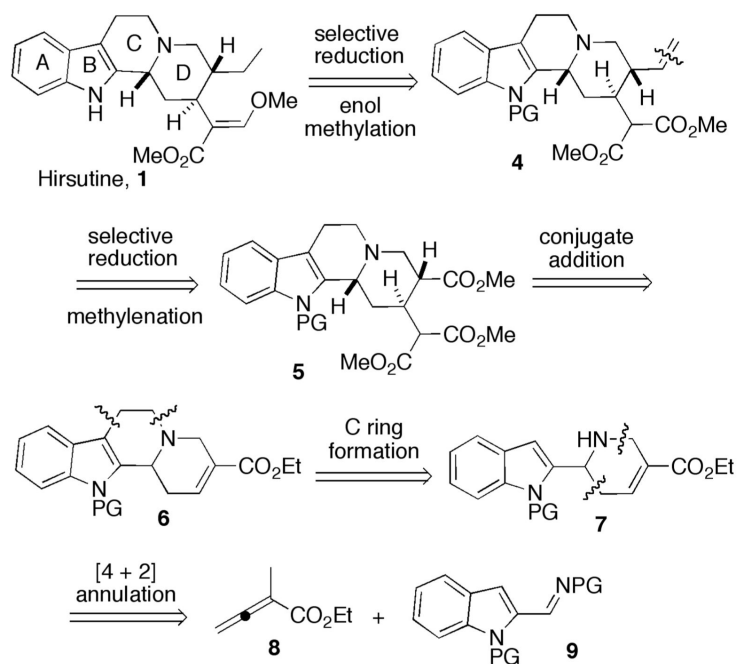
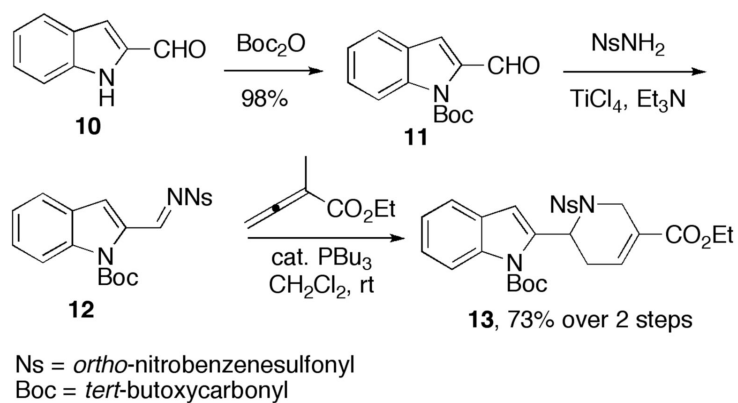


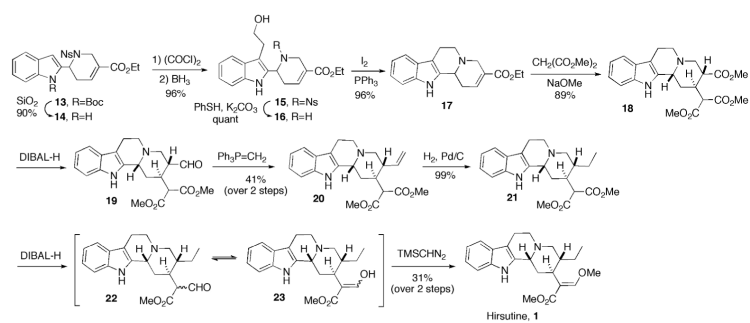
Figure 1.
Structures of hirsutine, hirsuteine, and ribavirin.



Scheme 1.
Retrosynthetic analysis of hirsutine



Scheme 2.
[4 + 2] Annulation in the synthesis of intermediate



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