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

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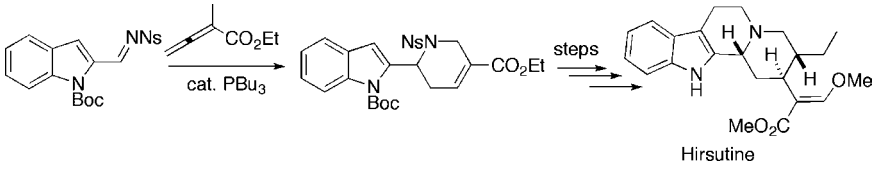
ABSTRACT



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 H_3N_2) with an EC_{50} value of 0.40−0.57 μg/mL; thus, hirsutine is 10−20 times more

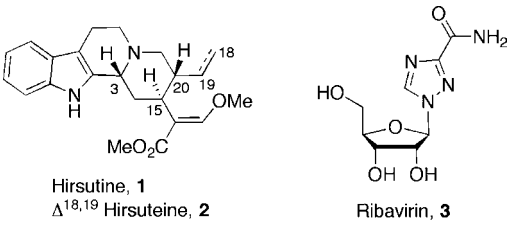


Figure 1. Structures of hirsutine, hirsuteine, and ribavirin.

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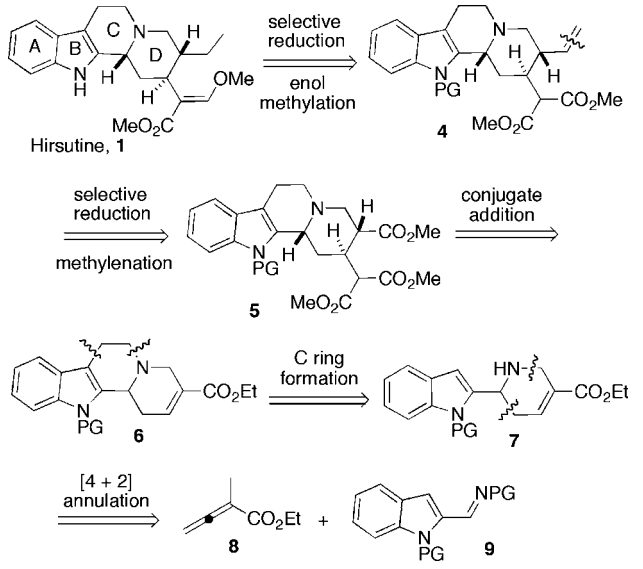
potent than the clinically used drug ribavirin (**3**, Figure 1).[7] Many research groups have taken the initiative to study and synthesize hirsutine and its various derivatives in the hope that these compounds will find significant medicinal use.[8]

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

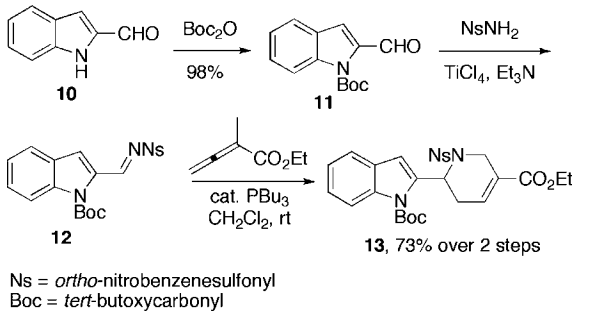


of hirsutine using our [4 + 2] annulation methodology as a key step. The strategy developed in this study should also be applicable as a new route for the synthesis of other corynantheine indole alkaloids.

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 ($NsNH_2$) in the presence of Et_3N and catalytic $TiCl_4$ 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**



We removed the Boc group from compound **13** cleanly, using SiO_2 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]

(9) (a) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716–4717. (b) Wurz, R. P.; Fu, G. C. *J. Am. Chem. Soc.* **2005**, *127*, 12234–12235. (c) Lu, K.; Kwon, O. *Org. Synth.* **2009**, *86*, 212–224. (d) Xiao, H.; Chai, Z.; Wang, H.-F.; Wang, X.-W.; Cao, D.-D.; Liu, W.; Lu, Y.-P.; Yang, Y.-Q.; Zhao, G. *Chem.—Eur. J.* **2011**, *17*, 10562–10565. (e) Fan, Y. C.; Kwon, O. Phosphine Catalysis. In *Science of Synthesis*; List, B., Ed.; Asymmetric Organocatalysis, Vol. 1, Lewis Base and Acid Catalysts; Georg Thieme: Stuttgart, 2012; pp 723–782.

(10) For the application of Kwon's [4 + 2] annulation to the synthesis of bridged tetracyclic indole alkaloids, see: Tran, Y. S.; Kwon, O. *Org. Lett.* **2005**, *7*, 4289–4291.

(11) Rosenmund, P.; Casutt, M.; Wittich, M. *Liebigs Ann. Chem.* **1990**, 233–238.

(12) Although the starting material **10** is commercially available, it can be synthesized from indole-2-carboxylic acid through sequential reduction ($LiAlH_4$) and oxidation (activated MnO_2); see: Jeught, S. V.; Vos, N. D.; Masschelein, K.; Ghiviriga, I.; Stevens, C. V. *Eur. J. Org. Chem.* **2010**, 5444–5453.

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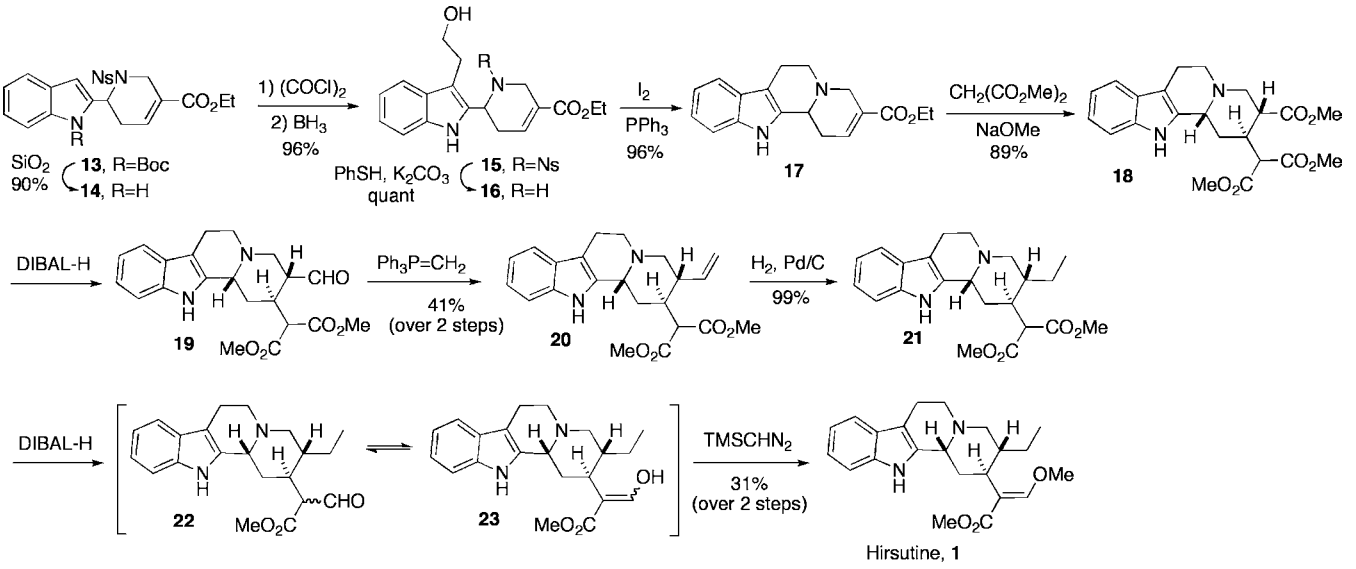
(17) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373–6374.

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



The nosyl group of **15** was readily removed in the presence of PhSH and K_2CO_3 in MeCN at 50 °C.[17] Formation of the C-ring through intramolecular N-alkylation proceeded smoothly under the influence of I_2 and PPh_3 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 Wilkinson[23] 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 SiO_2, 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, $TMSCHN_2$ 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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(27) Aoyama, T.; Terasawa, S.; Sudo, K.; Shioiri, T. *Chem. Pharm. Bull.* **1984**, *32*, 3759–3760.

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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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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.