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# An Application of the Phosphine-Catalyzed [4 + 2] Annulation in Indole Alkaloid Synthesis: Formal Syntheses of (±)-Alstonerine and (±)-Macroline

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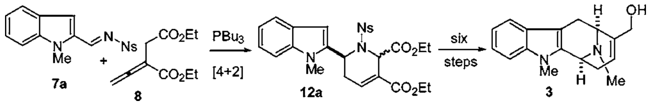
## ABSTRACT



**An application of the phosphine-catalyzed [4 + 2] annulation in the formal synthesis of alstonerine and macroline is reported. A phosphine-catalyzed [4 + 2] reaction between imine 7a and allene 8 formed the D ring of the target indole alkaloids. A subsequent intramolecular Friedel–Crafts acylation provided the C ring of the bridged tetracycle. Deprotection, followed by methylation of the bridged nitrogen, deoxygenation of the C6 ketone, and reduction of the C16 carbethoxy group provided the previously known intermediate 3.**

Macroline indole alkaloids are isolated from various species of *Alstonia* and show multiple biological activities, including hypotensive, antiamoebic, and antimalarial properties.[1] Alstonerine, along with 12 other alkaloids isolated from the root bark of *Alstonia macrophylla*, was recently reported to exhibit cytotoxic activity against two human lung cancer cell lines.[2] The first total synthesis of *Alstonia* macroline alkaloids, (+)-macroline (**1**) and (−)-alstonerine (**2**), was accomplished by Cook and collaborators, in which they built the bridged tetracyclic intermediate **4** via Pictet−Spengler cyclization and Dieckman condensation, starting from D-(+)-tryptophan (Figure 1).[3] The C16 ketone functionality in **4** was converted into the allylic alcohol moiety in **3** over five chemical steps.

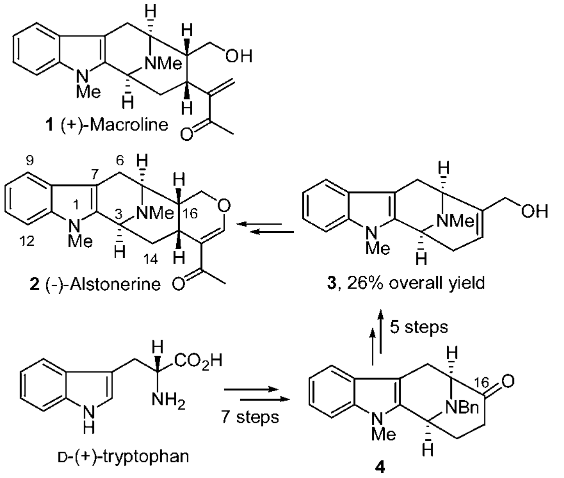


**Figure 1.** Cook's synthesis of (−)-alstonerine and (+)-macroline.[3]

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(1) (a) Burkhill, I. H. *A Dictionary of Economic Products of the Malay Peninsular, Crown Agents for the Colonies*; London, 1935. (b) Henry, T. A. *The Plant Alkaloids*, 4th ed.; J andA Churchill Ltd.: London, 1949. (c) Wright, C. W.; Allen, D.; Cai, Y.; Phillipson, J. D.; Said, I. M.; Kirby, G. C.; Warhurst, D. C. *Phytother. Res.* **1992**, *6*, 121. (d) Bi, Y.; Hamaker, L. K.; Cook, J. M. The Synthesis of Macroline Related Alkaloinds. In *Studies in Natural Products Chemistry, Vol. 13, Bioactive Natural Products, Part A*; Basha, F. Z., Rahman, A., Eds.; Elsevier Science: Amsterdam, 1993; Vol. 13, p 383. (e) Hamaker, L. K.; Cook, J. M. The Synthesis of Macroline Related Sarpagine Alkaloids. In *Alkaloids: Chemical and Biological Perspectives*; Elsevier: New York, 1995; Vol. 9, p 23. (f) Keawpradub, N.; Kirby, G. C.; Steele, J. C. P.; Houghton, P. J. *Planta Med.* **1999**, *65*, 690.

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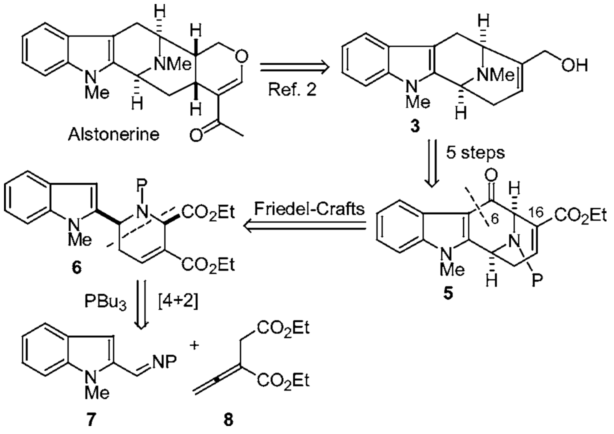
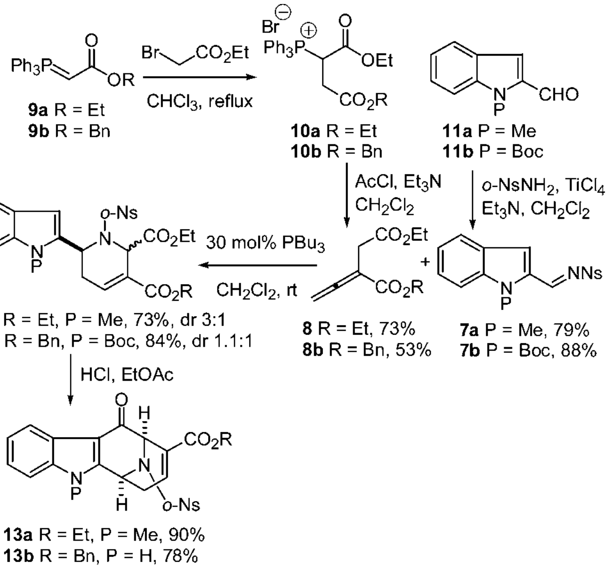
As part of our ongoing research program in the area of nucleophilic catalysis using phosphines,[4,5] we disclosed a [4 + 2] annulation between 2-alkyl-2,3-butadienoates and imines.[6] We envisioned, as an entry into the various macroline indole alkaloids, to employ our [4 + 2] annulation between allenes and imines. Specifically, use of allenoate **8**, combined with imine **7**, derived from indole-2-carboxaldehyde, can afford tricycle **6** (Scheme 1). Acid-mediated intramolecular Friedel−Crafts acylation of **6** can provide quick access to tetracycle **5**, which can be a common intermediate for further elaboration to macroline indole alkaloids. Especially, deprotection of the $N_b$-sulfonyl group, followed by methylation, reductive deoxygenation of the C6 ketone, and reduction of the $\alpha,\beta$-unsaturated ester to the allylic alcohol were envisaged to furnish intermediate **3**, which was a precursor to alstonerine and macroline.[2] Herein, we report a nine-step synthesis of this key intermediate **3** in 31% overall yield.

**Scheme 1.** Retrosynthetic Plan for the Construction of **3**



**Scheme 2.** Synthesis of Tetracycle **13a/b** via Phosphine-Catalyzed [4 + 2] Annulation/Intramolecular Friedel−Crafts Acylation



Our synthesis commenced with the preparation of previously unreported allenoate **8** (Scheme 2). Commercially available [(alkoxycarbonyl)methylene]triphenylphosphorane **9a**/**b** was reacted with ethyl bromoacetate to provide phosphonium bromide **10a**/**b**. Treatment of **10a**/**b** with acetyl chloride (1 equiv) in the presence of triethylamine (Et$_3$N, 2 equiv) furnished the desired diester allenes **8** and **8b** in 73 and 53% yield, respectively, over two steps. *o*-Nitrobenzenesulfonamide was condensed with indole-2-carboxaldehydes **11a** and **11b** under the influence of titanium(IV) chloride (TiCl$_4$) and Et$_3$N to provide imines **7a** and **7b** in 79 and 88% yield, respectively. Thus formed, solid imine **7a**/**b** was reacted with allenoate **8**/**8b** in the presence of 30 mol % of tributylphosphine in methylene chloride at room temperature. The [4 + 2] annulation products **12a** and **12b** were obtained in 73 and 84% yield as a 3:1 and 1:1 mixture of diastereoisomers, respectively. The poorer diastereoselectivity for imine **7b**, derived from $N_a$-Boc-protected indole-2-carboxaldehyde, is in accord with our observation that imines derived from benzaldehydes with bulky (bigger than fluoride) *ortho*-substituents displayed poorer *cis*-diastereoselectivity.[5] The acid-catalyzed epimerization of the C5 carboxylic ester had previously been observed,[7] so we proceeded to treat the mixture of inseparable diastereoisomers **12a** with hydrochloric acid (HCl) in ethyl acetate at room temperature. This resulted in the facile intramolecular Friedel−Crafts acylation to give bridged bicycle **13a** in 90% yield.[8] For **12b**, deprotection of the *tert*-butoxycarbonyl group on the indole nitrogen ($N_a$-Boc) and the concomitant intramolecular Friedel−

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(6) Zhu, X.-F.; Lan, J.; Kwon, O. *J. Am. Chem. Soc.* **2003**, *125*, 4716.

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Crafts cyclization under the influence of HCl provided **13b** in 78% yield. The connectivity of the carbon framework in **13a**/**b** was unequivocally established by a single-crystal X-ray analysis of the bridged tetracycle **13b** (Figure 2).[9]

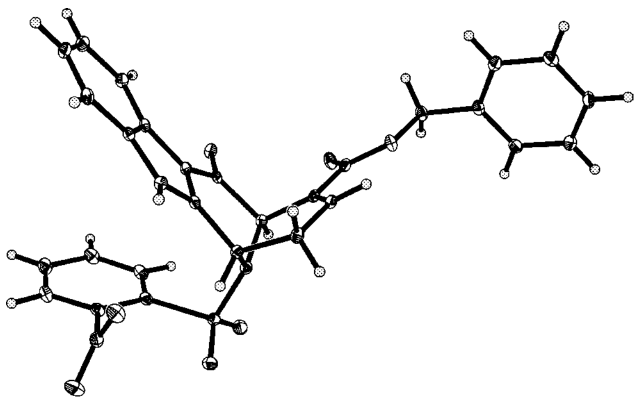
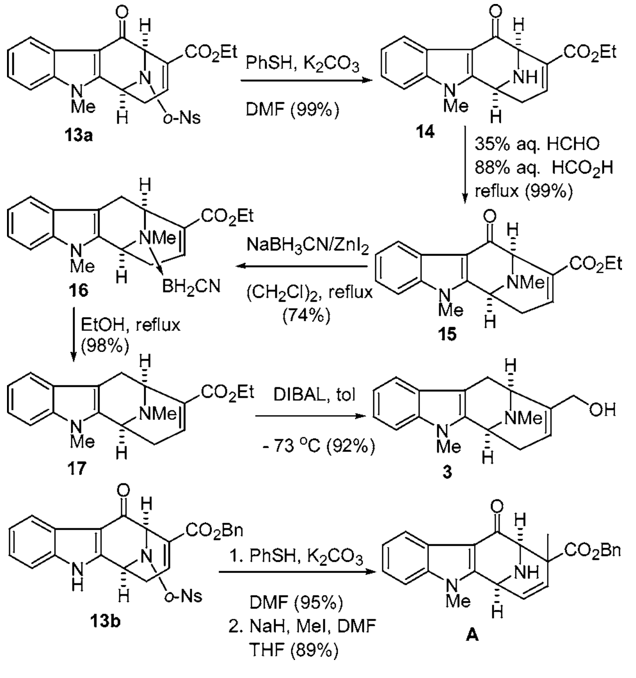


**Figure 2.** ORTEP plot of compound **13b**.

**Scheme 3.** Completion of the Synthesis of **3**



The desired $N_b$-methyl allylic alcohol **3** was prepared as outlined in Scheme 3. Fukuyama's denosylation proceeded uneventfully and gave secondary amine **14** in a quantitative yield.[10] $N_b$-Methylation was accomplished in 99% yield via the Eschweiler−Clarke method, employing 35% aqueous formaldehyde and 87% aqueous formic acid under reflux.[11] It is worth mentioning that any attempt to introduce the $N_b$-methyl group under basic conditions ($K_2CO_3$ or NaH) was hampered by a competitive $\gamma$-deprotonation of the $\alpha,\beta$-unsaturated ester moiety, followed by a deconjugative $\alpha$-methylation at C16 to form **A**.[12] Reductive deoxygenation of the C6 ketone group turned out to be challenging. The Clemmensen reduction and the Wolff−Kishner reduction (as well as other procedures using $Bu_4NBH_4$, $NaCNBH_3$, $NaBH_4$, $BH_3$, $LiAlH_4$, and trialkylsilane, with or without Lewis acids or protic acids) only resulted in the C6 alcohol or no reaction.[13] The desired aryl alkane was obtained in 74% yield as a complex with cyanoborane (see **16**)[14] using $ZnI_2$−$NaCNBH_3$.[15] The amine−borane **16**[16] was converted to the free amine **17** in 98% yield by heating to reflux in ethanol for 10 h.[17] Compound **17** was subsequently reduced by DIBAL to the known intermediate **3** in 92% yield. The spectral data of **3** ($^{1}$H NMR, $^{13}$C NMR, MS) are in agreement with the data reported by Cook.[3a]

To conclude, the phosphine-catalyzed [4 + 2] annulation is successfully applied for the first time in the synthesis of macroline-type indole alkaloids. Use of diester allene **8** proved to be useful for the construction of the bridged tetracyclic framework of the *Alstonia* class of indole alkaloids when the [4 + 2] annulation was combined with succeeding intramolecular Friedel−Crafts acylation. The $\alpha,\beta$-unsaturated ester moiety in the D ring, also formed in the [4 + 2] annulation, provides a ready handle for the elaboration of the D ring. As an example, a previously known intermediate **3** for the synthesis of alstonerine and macroline was synthesized in 31% overall yield over nine steps from commercially available starting materials. Our future efforts will focus on the asymmetric synthesis of biologically relevant indole alkaloids using the [4 + 2] annulation.

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

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(9) The connectivity and relative stereochemistry of this compound were confirmed by X-ray crystallographic analysis. Crystallographic data for **13b** has been deposited with the Cambridge Crystallographic Data Centre as a supplementary number CCDC 274276. CCDC 274276 contains the supplementary crystallographic data for this paper. These data can be obtained online free of charge (or from the Cambridge Crystallographic Data Center, 12, Union Road, Cambridge CB2 1EZ, UK.; fax: (+44) 1223−336−033; or deposit@ccdc.cam.ac.uk).

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(12) The relative stereochemistry at C16 has not been determined. See Supporting Information for detailed discussion on the synthesis **A**.

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