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Direct Methoxypyridine Functionalization Approach to Magellanine-Type *Lycopodium* Alkaloids

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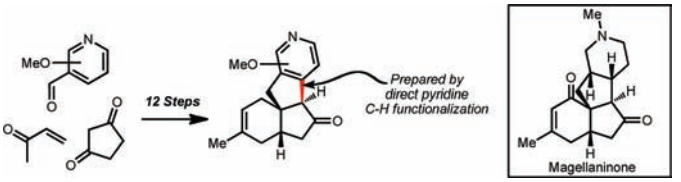
ABSTRACT



A concise enantioselective approach to the tetracyclic core of the magellanine-type *Lycopodium* alkaloids is reported. Key to this approach is the use of the Hajos–Parrish reaction to set a challenging quaternary stereocenter, thereby guiding the stereoselectivity for the remainder of the synthesis, as well as the use of a palladium-mediated direct pyridine functionalization reaction to forge the tetracyclic core.

The *Lycopodium* alkaloid magellanine (**1**, Figure 1) has served as a forum to highlight creative synthetic strategies and methods for almost two decades. Overman was first to report a highly elegant total synthesis of **1** in 1993, featuring a Prins-pinacol rearrangement.[1] Since this initial report, there have been many other reports of inventive syntheses, as well as approaches, toward magellanine.[2,3] Magellanine and the related *Lycopodium* alkaloids[4] magellaninone (**2**) and paniculatine (**3**) are characterized by a tetracyclic core that possesses up to six contiguous stereocenters, one of which is quaternary. This framework presents a formidable synthetic challenge, which is further heightened by the highly basic tertiary amine group. Not surprisingly, the majority of syntheses of these molecules have focused on introducing the amine group (and therefore the piperidine ring) in the late stages of the synthesis, thus realizing a 'bottom-up' strategy. In this report, we present an alternative 'top-down' approach (see Figure 1) to the magellanine-type alkaloids, which is enabled by the use of methoxypyridine intermediates.

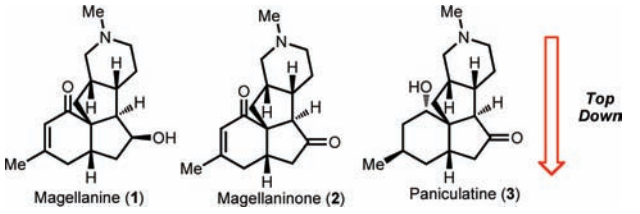


Figure 1. Magellanine-type *Lycopodium* alkaloids.

Our laboratory has previously shown the utility of methoxypyridines as surrogates for piperidines and pyridones in complex molecule synthesis.[5] This approach

(1) Hirst, G. C.; Johnson, T.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 2992–2993.

(2) For other previous syntheses of magellanine-type alkaloids, see: (a) Paquette, L.; Williams, J. P., St.; Laurent, D.; Friedrich, D.; Pinard, E.; Roden, B. *J. Am. Chem. Soc.* **1994**, *116*, 4689–4696. (b) Mukai, C.; Kozaka, T.; Miyakoshi, N. *J. Org. Chem.* **2007**, *72*, 10146–10154. (c) Liao, C. *Pure Appl. Chem.* **2005**, *77*, 1221–1234. (d) Takahashi, T.; Ishizaki, M.; Niimi, Y.; Hoshino, O.; Hara, H. *Tetrahedron* **2005**, *61*, 4053–4065.

(3) For a particulary pertinent previous approach, see: (a) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1–8. (b) Sandham, D.; Meyers, A. I. *J. Chem. Soc., Chem. Commun.* **1995**, 2511–2512.

(4) For a recent review on *Lycopodium* alkaloids, see: Gang, D. R.; Ma, X. *Nat. Prod. Rep.* **2004**, *21*, 752–772.

(5) For selected examples, see: (a) Sarpong, R.; Larson, K. K. *J. Am. Chem. Soc.* **2009**, *131*, 13244–13245. (b) Bisai, V.; Sarpong, R. *Org. Lett.* **2010**, *12*, 2551–2553. (c) Bisai, A.; West, S. P.; Sarpong, R. *J. Am. Chem. Soc.* **2008**, *130*, 7222–7223.

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offers several advantages, notably the fact that 2-methoxypyridines possess a less basic nitrogen atom than the corresponding unsubstituted pyridine. This is supported by a pK_a of 3.06 for 2-methoxypyridinium ion versus a pK_a of 5.23 for pyridinium (see Figure 2).[6] The mitigated basicity of 2-methoxypyridines can be attributed to inductive electron-withdrawing effects of the alkoxy group.[7] Additionally, steric shielding of the nitrogen lone pair by the alkoxy group is pronounced in the favored conformer, **B** (see Figure 2), which avoids pseudo $A_{1,3}$ interactions and also minimizes dipoles between the nitrogen and oxygen lone pairs.[8]

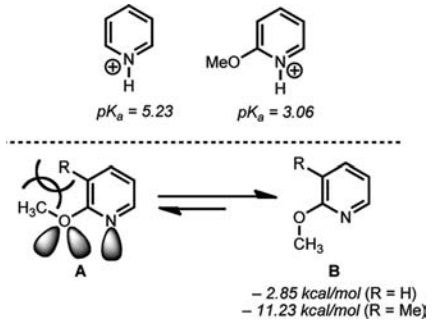
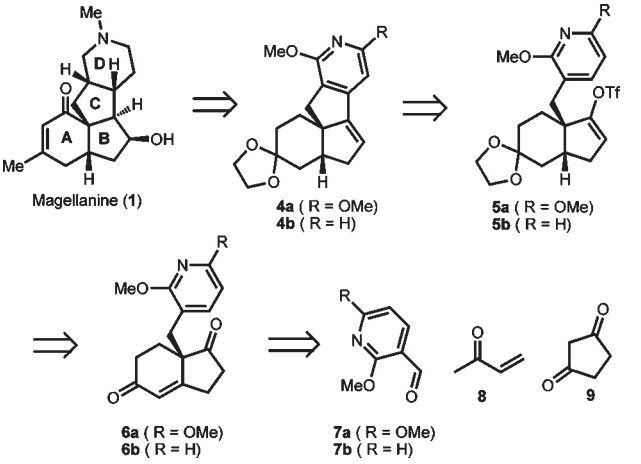


Figure 2. Basicity considerations of the pyridine nitrogen.[9]

With the appreciation for the mitigated basicity of methoxypyridines in mind, we envisioned a retrosynthetic analysis for magellanine (and congeners) that would bring the natural product(s) back to tetracycle **4** (Scheme 1). Two variants of this late-stage intermediate were planned: a dimethoxypyridine containing tetracycle (**4a**) as well as a monomethoxypyridine variant (**4b**). In the forward sense, appropriate functionalization and oxidation level adjustments of rings A and B in **4a/b** would set the stage for access to the magellanine-type alkaloids. By analogy to the related precedent of Meyers,[3] the methoxypyridine ring could be transformed to the necessary piperidine moiety, bearing the correct stereochemistry at the C/D ring fusion, through a N-methylation/global reduction protocol. Tetracycles **4a/b** could arise from vinyl triflate **5a/b** by a direct functionalization of the pyridine C4 position using a palladium-mediated C−C bond formation that has its origins in the instructive studies of Fagnou[10] and Echavarren.[11] This transformation is particulary powerful since it requires no prefunctionalization of the pyridine starting material. Vinyl triflate **5a/b** may, in turn, arise from Hajos−Parrish ketone derivative **6a/b**, which could be prepared enantioselectively from pyridine aldehyde **7a/b**, methyl vinyl ketone (**8**), and 1,3-cyclopentanedione (**9**) following the protocol of Brittain and co-workers.[12]

Scheme 1. Retrosynthetic Analysis of Magellanine and Congeners



Our synthetic studies to arrive at tetracycle **4a**, described herein, are illustrative of the approach to **4b** as well, which is presented in its entirety in the Supporting Information. The synthesis of **4a** commenced with a Knoevenagel condensation of commercially available aldehyde **7a** and 1,3-cyclopentanedione (**9**) to afford adduct **10** in 83% yield (Scheme 2). Hydrogenation of the double bond proceeded without event to afford C2-functionalized dione/vinylogous acid **11**. Acid **11** was subjected to proline-catalyzed Hajos−Parrish reaction conditions in the presence of methyl vinyl ketone (**8**) to provide the aldol product, which was smoothly dehydrated in the presence of HCl and MeOH to give enone **6a** in 83% yield and 87% ee (absolute configuration was not determined; enantiomer assigned by analogy to related annulations employing L-proline). This reaction sets the stereochemistry of the all carbon quaternary center present in the natural product, which we envision using to guide the stereoselectivity for the rest of the synthesis. Of note, an analogous Robinson annulation employing derivatives of **11** which lack the methoxy groups proceeded to give the corresponding bicyclic enones (**12** and **13**, Figure 3) in drastically lower yield. Furthermore, these reactions could not be scaled above 100 mg without significant accompanying decomposition. The derivative with the methoxy group para to the alkyl substituent (**14**) was also formed in a very low yield. This

(6) Manallack, D. T.; Gancia, E.; Pitt, W. R.; Wong, M. G.; Lloyd, E. J.; Tehan, B. G. *Quant. Struct.-Act. Relat.* **2002**, *21*, 473–485.

(7) For discussion on inductive effects in substituted pyridines, see: Joule, J. A.; Mills, K. *Heterocyclic Chemistry*, 5th ed.; Blackwell Science Ltd.: Cambridge, 2010; pp 125−175 (particularly relevant, pp 125−126).

(8) See ref 6 and Blonski, W. J. P.; Hruska, T. A.; Wildman, T. A. *Org. Magn. Reson.* **1984**, *22*, 505–509.

(9) Molecular modeling computations were performed at the B3LYP/6-31G* level of theory using an IEF-PCM simulation of THF as solvent.

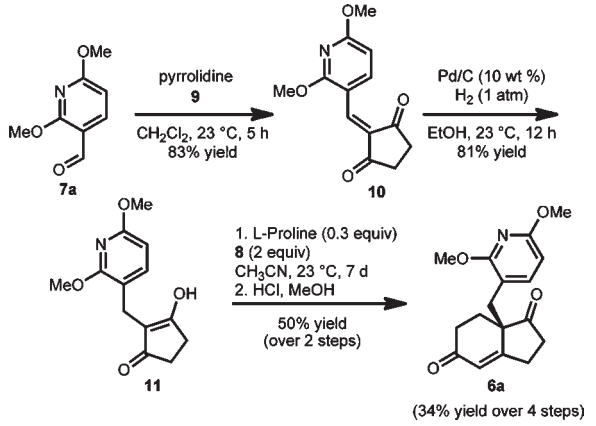
(10) (a) Fagnou, K.; Campeau, L.; Parisien, M.; Leblanc, M. *J. Am. Chem. Soc.* **2004**, *126*, 9186–9187. (b) Fagnou, K.; Campeau, L.; Stuart, D. R.; Leclerc, J.; Bertrand-Laperle, M.; Villemure, E.; Sun, H.; Lasserre, S.; Guimond, N.; Lecavallier, M. *J. Am. Chem. Soc.* **2009**, *131*, 3291–3306.

(11) (a) Echavarren, A. M.; Maseras, F.; Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C. *J. Am. Chem. Soc.* **2007**, *129*, 6880–6886. (b) Echavarren, A. M.; Garcia-Cuadrado, D.; Braga, A. A. C.; Maseras, F. *J. Am. Chem. Soc.* **2006**, *128*, 1066–1067.

(12) Brittain, D. E.; Kennedy, J. W. J.; Vietrich, S.; Weinmann, H. *J. Org. Chem.* **2008**, *73*, 5151–5154.

outcome likely results from significant basicity of the pyridine nitrogen in **12**–**14**, which curtails the yield of the Hajos–Parrish reaction. It appears that a methoxy group ortho to the alkyl substituent in the pyridine moeity (as in **6b**) has a higher population of conformer **B** (see Figure 2) to avoid increased $A_{1,3}$ strain, which more effectively blocks the nitrogen lone pair. This in turn leads to a higher yield of the bicyclic enone products, and the reactions can be performed on multigram scale. Additional blocking groups (as in **11**) further enhance the yield of the Hajos–Parrish reaction.

Scheme 2. Synthesis of Hajos–Parrish Ketone Derivative **6a**



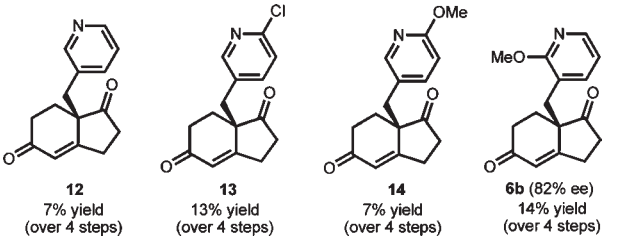


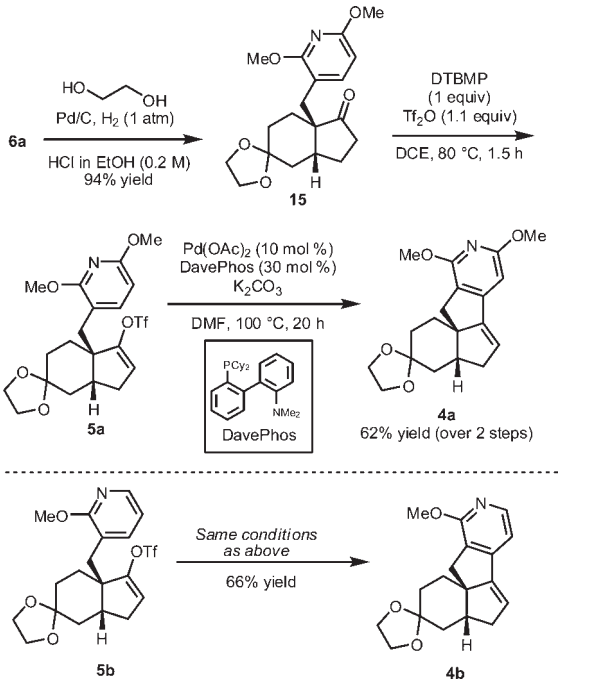
Figure 3. Other Hajos–Parrish ketone derivatives.

Thus, carefully designed methoxypyridines can be used to tune the basicity of the pyridine nitrogen, which facilitates reactions that would normally be very low yielding.

As shown in Scheme 3, bicyclic enone **6a** was readily advanced to vinyl triflate **5a** in two steps. This synthetic sequence entailed a tandem ketalization/hydrogenation of enone **6a** to afford ketal **15** in 94% yield as a single diastereomer.[13] Interestingly, when the two steps to reach **15** were performed separately, the diastereoselectivity was poor and the yield was significantly lower. With ketal **15** in hand, we were able to effect a soft enolization of the carbonyl group to give vinyl triflate **5a**.

In the key step to furnish the tetracyclic core (**4a/b**) of the magellanine-type alkaloids, vinyl triflates **5a/b** were

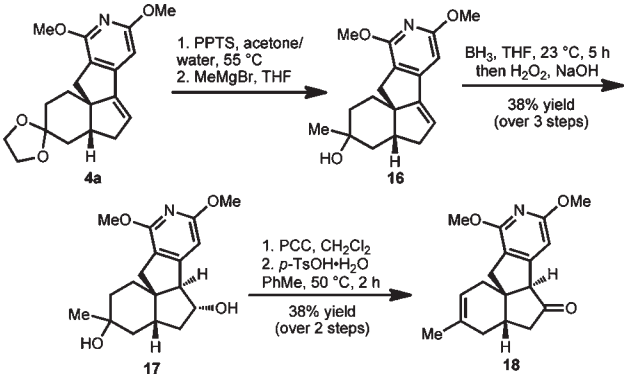
Scheme 3. Synthesis of the Tetracycles



subjected to the conditions identified by Echavarren to be optimal for direct palladium-catalyzed arylation of pyridines.[11] Gratifyingly, tetracycle **4a** was obtained in 62% yield over the two steps. This sequence has been conducted on a >3 g scale without a drop in yield. Additionally, vinyl triflate **5b**, bearing a monomethoxy pyridine, afforded a 66% yield of **4b** under the same conditions.

With access to tetracycles **4a** and **4b**, we have begun to explore the functionalization of these late-stage intermediates to afford advanced precursors to the magellanine-type alkaloids. Hydrolysis of the ketal group of **4a** followed by addition of methyl magnesium bromide into the resulting carbonyl moiety yields tertiary alcohol **16** as a single diastereomer (Scheme 4).[14] Hydroboration of the B-ring alkene group of **16** was accomplished under standard conditions to provide

Scheme 4. Functionalization of the A/B Rings of **4a**

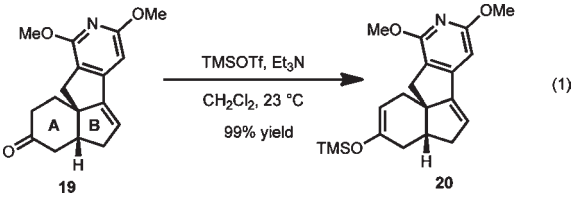


(13) Parsons, P. J.; Hudson, P. *Synlett* **1992**, *11*, 867–868.

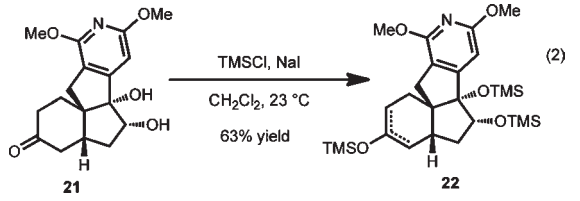
(14) The newly formed stereocenter was not rigorously determined.

diol **17** following oxidative workup. Further oxidation of the secondary hydroxy group using pyridinium chlorochromate gave a keto alcohol that could be dehydrated to afford a single regioisomer of advanced tetracycle **18**.

Our efforts thus far toward the magellanine-type alkaloids have yielded several insights. Most importantly, we have found that the regioselectivity of the double bond placement in the A-ring of the tetracycle is highly dependent on the number of sp^2-hybridized carbon atoms in the B-ring (see eqs 1 and 2). Thus, while **19** yields exclusively one regioisomer of silyl enol ether **20**, diol **21** leads to a regioisomeric mixture of silyl enol ether products (**22**). These observations were, indeed, applied to the synthesis of **18**.



(1)



(2)

In conclusion, we have developed an efficient synthetic sequence to the tetracyclic core of the magellanine-type *Lycopodium* alkaloids. Our strategy features a variant of the enantioselective Hajos–Parrish reaction, which sets a challenging quaternary center early in the synthesis. This single stereocenter has been shown to guide the stereoselective manipulation of the core. Additionally, a powerful palladium-catalyzed C–C bond forming reaction was utilized to assemble the strained tetracyclic core of the magellanine-type *Lycopodium* alkaloids without the nescessity of prefunctionalization. Efforts are underway to apply these lessons to the total synthesis of the magellanine-type *Lycopodium* alkaloids.

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Supporting Information Available. Experimental details and characterization for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.