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Concise, Enantioselective Total Synthesis of (−)-Alstonerine

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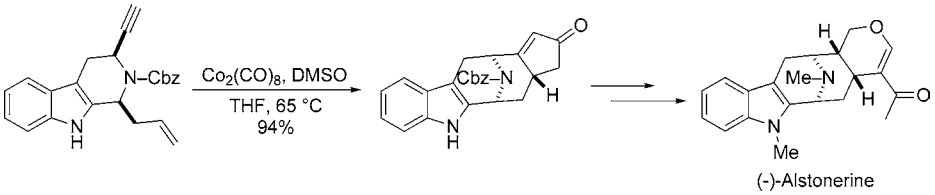
ABSTRACT



A novel enantioselective total synthesis of (−)-alstonerine has been completed that requires only 15 steps from L-tryptophan. The synthesis features the first application of a Pauson−Khand reaction to synthesize an azabridged bicyclic skeleton.

The macroline/sarpagine class of indole alkaloids is a rich source of biologically active natural products, some of which exhibit hypotensive, antiamoebic, and antimalarial activities.[1] For example, alstonerine (**1**) has recently been reported to exhibit cytotoxic activity against two human lung cancer cell lines.[2] The alkaloids of this family contain an azabicyclo-[3.3.1] substructure that is annelated to an indole ring. It is thus fitting that a number of strategies have been devised to access this structural motif including sequential Pictet−Spengler and Dieckmann condensations,[3] ring-closing metathesis,[4] phosphine-catalyzed [4+2] annulation/Friedel−Crafts cyclization,[5] or aza-Diels−Alder/intramolecular Heck reaction.[6] As a representative member of the macroline/sarpagine family, two total syntheses and one formal synthesis of **1** have been reported.[5,7]

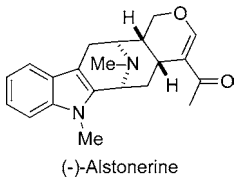


Figure 1. Structure of (−)-alstonerine (**1**).

In the context of a longstanding interest in alkaloid synthesis, we have been intrigued by designing and developing novel and general strategies for the facile preparation of representative members of different alkaloid families.[8] We have recently explored a number of transition metal-catalyzed reactions for the construction of ring systems common to a number of alkaloids. In the context of some investigations toward developing some new cascade reactions,[9] we became interested in examining the potential of the Pauson−Khand reaction (PKR) for alkaloid synthesis. The intramolecular

(1) (a) Lounasmaa, M.; Hanhinen, P.; Westersund, M. *The Sarpagine Group of Indole Alkaloids*; Academic Press: San Diego, CA, 1999; Vol. 52. (b) Hamaker, L. K.; Cook, J. M. The Synthesis of Macroline Related Sarpagine Alkaloids. In *Alkaloids*: *Chemical and Biological Perspectives*; Elsevier Science: New York, 1995; Vol. 9. (c) Keawpradub, N.; Kirby, G. C.; Steele, J. C. P.; Houghton, P. J. *Planta Med*. **1999**, *65*, 690.

(2) Keawpradub, N.; Eno-Amooquaye, E.; Burke, P. J.; Houghton, P. J. *Planta Med*. **1999**, *65*, 311.

(3) Bi, Y.; Hamaker, L. K.; Cook, J. M. The Synthesis of Macroline Related Indole Alkaloids. In *Studies in Natural Products Chemistry*; Pergamon, London, 1994; Vol. 9.

(4) Neipp, C. E.; Martin, S. F. *J. Org. Chem.* **2003**, *68*, 8867.

(5) Tran, Y. S.; Kwon, O. *Org. Lett*. **2005**, *7*, 4289.

(6) Kuthe, J. T.; Wong, A.; Davies, I. W.; Reider, P. J. *Tetrahedron Lett*. **2002**, *43*, 3871.

(7) (a) Bi, Y.; Zhang, L.-H.; Hamaker, L. K.; Cook, J. M. *J. Am. Chem. Soc*. **1994**, *116*, 9027. (b) Liao, X.; Zhou, H.; Wearing, X. Z.; Ma, J.; Cook, J. M. *Org. Lett*. **2005**, *7*, 3501.

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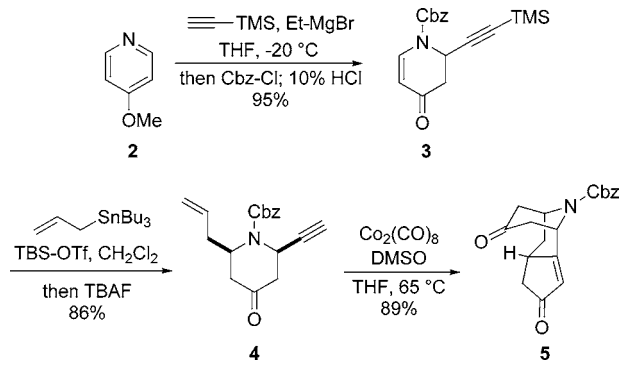
version of the PKR has been applied to the syntheses of a few natural products,[10] but its use has overwhelmingly been limited to forming fused bicyclo[3.3.0]octenones and bicyclo[4.3.0]nonenones.[11,12]

Our ongoing efforts to develop concise routes for the elaboration of azabridged bicyclic structures led us to query whether the scope of the PKR might be extended to include cyclizations of cis-2,6-disubstituted piperidine enynes. Considering the absolute lack of precedent for such a PKR, the simple model substrate **4** was first prepared to explore the feasibility of such a construction (Scheme 1). Thus, by

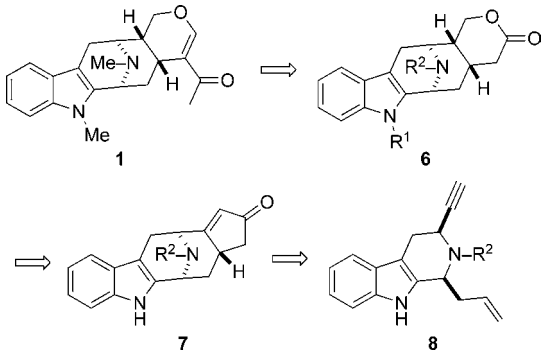
Scheme 1. Model System



analogy with previous work in our laboratories,[4,13] reaction of 4-methoxypyridine (**2**) with the anion derived from trimethylsilylacetylene in the presence of Cbz-Cl gave the unsaturated piperidinone **3**. Lewis acid mediated conjugate addition of allyltribuyltin followed by treatment of the intermediate silyl acetylene with TBAF provided the enyne substrate **4** in >19:1 diastereoselectivity. To our delight, the ensuing PKR proceeded cleanly to give **5** as a single diastereomer. To our knowledge, this represents the first example of a PKR to provide an azabridged bicyclic product.

Having thus established the underlying viability of using PKRs to form azabicyclo[3.3.1]bicyclononanes fused with cyclopentenones, a retrosynthetic approach to (−)-alstonerine (**1**) was formulated as shown in Scheme 2. We envisioned

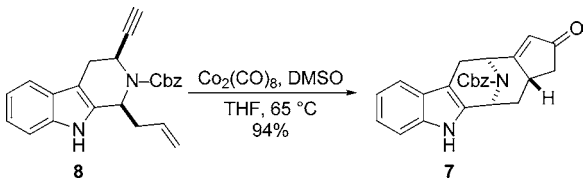
Scheme 2. Retrosynthesis



that **1** could be accessed from the lactone **6**, which would in turn be accessed via regioselective oxidation of the cyclopentenone **7** that would arise from the pivotal PKR of the known enyne **8**.[4]

In the event, the PKR of enyne **8** with stoichiometric amounts of $Co_2(CO)_8$ gave cyclopentenone **7** in excellent yield as a single diastereomer (Scheme 3). It was essential

Scheme 3. The Pauson−Khand Reaction



to utilize high-quality $Co_2(CO)_8$ and DMSO as the promoter to obtain optimal yields. Numerous catalytic variants only provided recovered starting material.[14]

The next stage of the synthesis involved elaboration of the cyclopentenone ring to a lactone, and we anticipated that protection of the indole would be required to prevent inadvertent oxidation of the indole ring. Thus, the Boc-carbamate **9** was prepared from **7** in virtually quantitative yield (Scheme 4). We then hoped to generate an enolate or silyl enol ether regioselectively by reduction of the cyclopentenone moiety. However, numerous attempts employing dissolving metal,[15] copper hydride reagents,[16] and Stryker's reagent[17] and attempted trapping of the enolate thus produced with various oxidants or silylating agents were unsuccessful.

(8) For selected recent examples, see: (a) Fellows, I. M.; Kaelin, D. E., Jr.; Martin, S. F. *J. Am. Chem. Soc.* **2000**, *122*, 10781. (b) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003. (c) Humphrey, J. M.; Liao, Y.; Ali, A.; Rein, T.; Wong, Y.-L.; Chen, H.-J.; Courtney, A. K.; Martin, S. F. *J. Am. Chem. Soc.* **2002**, *124*, 8584. (d) Martin, S. F. *Acc. Chem. Res.* **2002**, *35*, 895. (e) Washburn, D. G.; Heidebrecht, R. W., Jr.; Martin, S. F. *Org. Lett.* **2003**, *5*, 3523. (f) Deiters, A.; Chen, K.; Eary, T.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 4541. (g) Brenneman, J. B.; Machauer, R.; Martin, S. F. *Tetrahedron* **2004**, *60*, 7301. (h) Amorde, S.; Judd, A.; Martin, S. F. *Org. Lett.* **2005**, *7*, 2031. (i) Andrade, R. B.; Martin, S. F. *Org. Lett.* **2005**, *7*, 5733. (j) Simila, S. T. U.; Reichelt, A.; Martin, S. F. *Tetrahedron Lett.* **2006**, *47*, 2933. (k) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547.

(9) Ashfeld, B. L.; Miller, K. A.; Smith, A. J.; Tran, K.; Martin, S. F. *Org. Lett.* **2005**, *7*, 1661.

(10) (a) Cassayre, J.; Zard, S. Z. *J. Am. Chem. Soc.* **1999**, *121*, 6072. (b) Jiang, B.; Xu, M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2543. (c) Ishizaki, M.; Niimi, Y.; Hoshino, O.; Hara, H.; Takahashi, T. *Tetrahedron* **2005**, *61*, 4053.

(11) (a) Brummond, K. M.; Kent, J. L. *Tetrahedron* **2000**, *56*, 3263. (b) Boñaga, L. V. R.; Krafft, M. E. *Tetrahedron* **2004**, *60*, 9795.

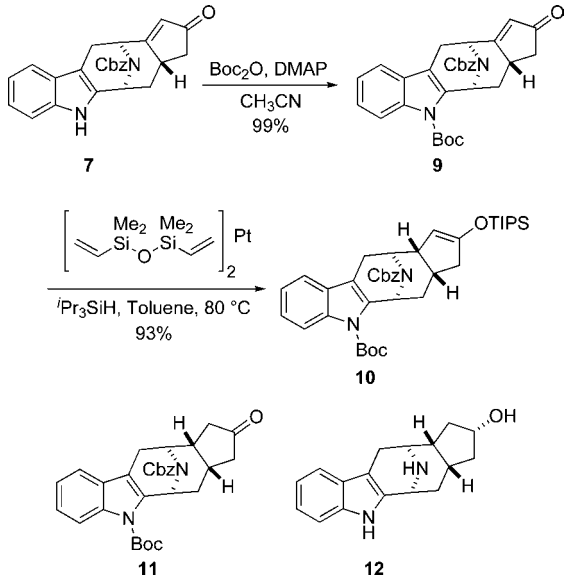
(12) For examples of PKR to synthesize carbon bridged bicycles: (a) Kerr, W. J.; McLaughlin, M.; Morrison, A. J.; Pauson, P. L. *Org. Lett.* **2001**, *3*, 2945. (b) Lovely, C. L.; Seshadri, H.; Wayland, B. R.; Cordes, A. W. *Org. Lett.* **2001**, *3*, 2607. (c) Winkler, J. D.; Lee, E. C. Y.; Nevels, L. I. *Org. Lett.* **2005**, *7*, 1489.

(13) (a) Brown, J. D.; Foley, M. A.; Comins, D. L. *J. Am. Chem. Soc.* **1988**, *110*, 7445. (b) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719.

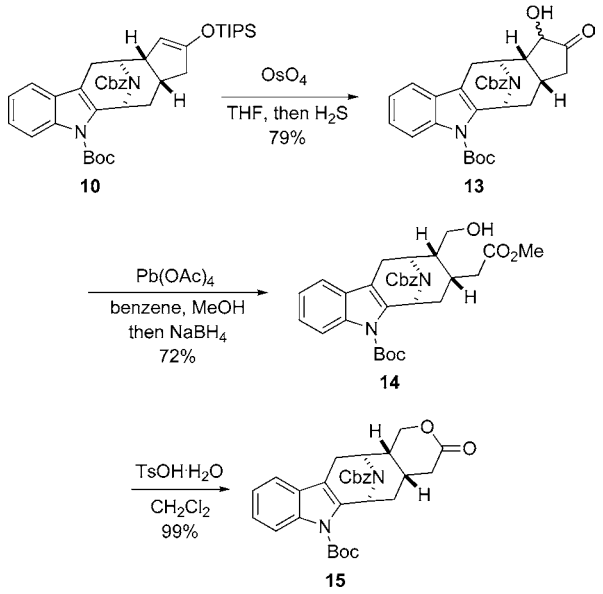
(14) (a) Pagenkopf, B. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1996**, *118*, 2285. (b) Tang, Y.; Deng, L.; Zhang, Y.; Dong, G.; Chen, J.; Yang, Z. *Org. Lett.* **2005**, *7*, 593. (c) Jeong, N.; Sung, B. K.; Choi, Y. K. *J. Am. Chem. Soc.* **2000**, *122*, 6771. (d) Koga, Y.; Kobayashi, T.; Narasaka, K. *Chem. Lett.* **1998**, 249.

(15) Caine, D. *Org. React.* **1976**, *23*, 1.

Scheme 4. Hydrosilylation



Scheme 5. Oxidation



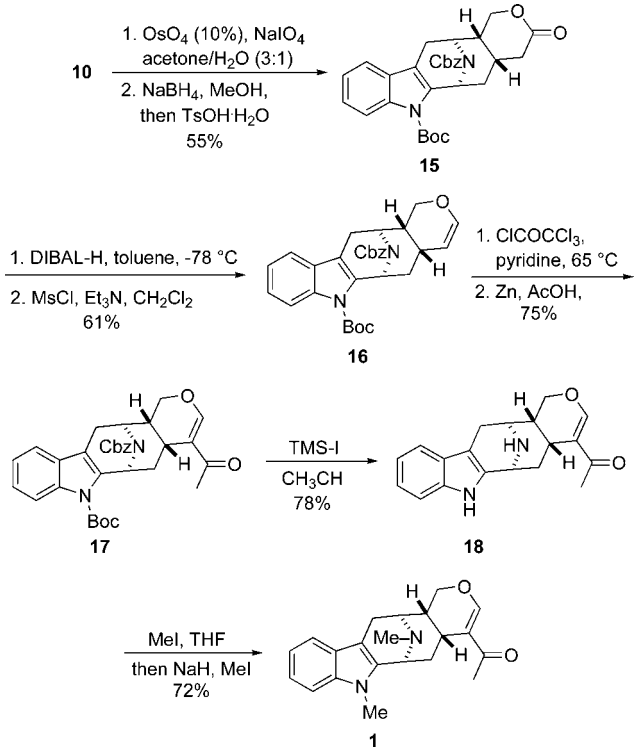
Eventually we discovered that reduction of the enone with catalytic platinum divinyltetramethyl disiloxane complex (Karstedt's catalyst) in the presence of triisopropylsilane gave the TIPS-silyl enol ether **10** in excellent yield.[18] Less bulky silanes such as TES-H and TBS-H provided a significant amount of the saturated ketone **11** (∼20−30%), presumably via silane dimerization that formed molecular hydrogen that simply reduced the alkene in the presence of the platinum catalyst.[19]

To verify the stereochemistry of the PKR and the subsequent hydrosilylation steps, the silyl enol ether **10** was converted into the crystalline amino alcohol **12** in four steps [(a) TBAF, THF; (b) $NaBH_4$, THF; (c) silica gel, 100 °C; (d) H_2, Pd/C, EtOAc] and approximately 50% overall yield. X-ray analysis of **12** confirmed that the relative stereochemistry of **12** matched that of **1**, so completion of the synthesis could be envisioned.

Our first strategy for oxidizing the cyclopentanone enol ether and preparing the requisite lactone ring commenced with oxidation of **10** with OsO_4 to provide a mixture of epimeric α-hydroxy ketones **13** in good yield (Scheme 5). Subsequent oxidative cleavage of the mixture of hydroxy ketones with $Pb(OAc)_4$ afforded an aldehyde/methyl ester, which was reduced in situ to give hydroxy ester **14**. Lactonization of **14** under acidic conditions then provided the lactone **15**.

Despite the success of this approach to the key lactone **15**, use of toxic osmium and lead reagents in stoichiometric amounts prompted us to explore more efficacious routes to **15**. While the oxidative cleavage of silyl enol ethers is well-known, application of Johnson−Lemieux conditions to effect such transformations is surprisingly rare.[20] Gratifyingly, we found that the silyl enol ether **10** was oxidatively cleaved using a catalytic amount (10 mol %) of OsO_4 and $NaIO_4$ to give an intermediate aldehyde/carboxylic acid. The crude reaction mixture was then simply treated with $NaBH_4$ to reduce the aldehyde selectively to afford a hydroxyester that

Scheme 6. Completion of the Synthesis of **1**



(16) (a) Tsuda, T.; Satomi, H.; Hayashi, T.; Saegusa, T. *J. Org. Chem.* **1987**, *52*, 439. (b) Jurkauskas, V.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 2892. (c) Lipshutz, B. H.; Frieman, B. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 6345.

(17) Mahoney, W. S.; Brestensky, D. M.; Stryker, J. M. *J. Am. Chem. Soc.* **1988**, *110*, 291.

(18) Johnson, C. R.; Raheja, R. K. *J. Org. Chem.* **1994**, *59*, 2287.

(19) Denmark, S. E.; Forbes, D. C. *Tetrahedron Lett.* **1992**, *33*, 5037.

cyclized after quenching the reaction with acid to deliver the lactone **15** (Scheme 6). Treatment of **15** with DIBAL-H afforded a lactol that was then converted into the dihydropyran **16** by dehydration. Numerous attempts to directly introduce the necessary acetyl group onto the dihydropyran utilizing various Lewis acids ($AlCl_3$, BF_3) and acylating agents (acetyl chloride, acetic anhydride) afforded complex product mixtures with Friedel−Crafts acylation at C(5) of the indole ring as a major side product.[21] We thus developed a two-step strategy for effecting this conversion that was inspired by work we had performed a number of years ago. Namely, heating **16** with excess trichloroacetyl chloride in pyridine afforded an intermediate trichloroacetyl derivative,[22] which was reduced with zinc and acetic acid to provide the desired acetyl compound **17**. This reaction sequence should prove widely useful for the facile synthesis of C-2 acylated glycals, a motif widely found in biologically active natural products.[23] Removal of both carbamate protecting groups from **17** with TMS-I cleanly yielded **18**. The bis-secondary amine **18** was then treated with MeI in THF to methylate first the bridging secondary amine, and then NaH and additional MeI were added to alkylate the more recalcitrant indole nitrogen atom to furnish **1**. The spectral data for synthetic **1** (^{1}H and ^{13}C NMR) were consistent with those previously reported,[7b] and the optical rotation ($[\alpha]^{25}_D$ −187 (*c* 0.30, EtOH)) was comparable to that reported in the literature ($[\alpha]^{25}_D$ −190 (*c* 0.32, EtOH)).[7a]

In summary, a concise, enantioselective total synthesis of (−)-alstonerine (**1**) has been completed that requires only 15 chemical operations from L-tryptophan and proceeds in 4.4% overall yield. Moreover, the synthesis features the first example of a PKR to form an azabridged bicyclic structure. Other synthetic highlights include a demanding 1,4-enone hydrosilylation followed by an oxidative cleavage and a new, mild two-step protocol to acetylate cyclic enol ethers. Other applications of the PKR to synthesize azabridged bicyclic structures are in progress and will be reported in due course.

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Supporting Information Available: Copies of ^{1}H and ^{13}C NMR spectra for all new compounds and a CIF file for **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Liras, J. L.; Lynch, V. M.; Anslyn, E. V. *J. Am. Chem. Soc.* **1997**, *119*, 8191.

(21) Priebe, W.; Grynkiewicz, G.; Neamati, N. *Tetrahedron Lett*. **1992**, *33*, 7681.

(22) Martin, S. F.; Benage, B.; Williamson, S. A.; Brown, S. P. *Tetrahedron* **1986**, *42*, 2903.

(23) (a) Guella, G.; Dini, F.; Tomei, A.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1* **1994**, 161. (b) Hooper, G. J.; Davies-Coleman, M. T. *Tetrahedron* **1995**, *51*, 9973. (c) Kam, T.-S.; Jayashankar, R.; Sim, K.-M.; Yoganathan, K. *Tetrahedron Lett.* **1997**, *38*, 477.