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Intramolecular Hetero Diels–Alder (Povarov) Approach to the Synthesis of the Alkaloids Luotonin A and Camptothecin†

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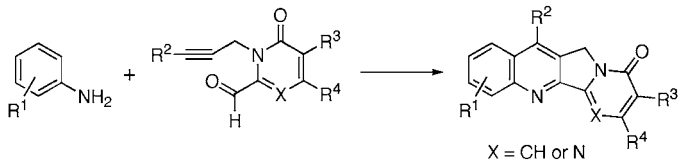
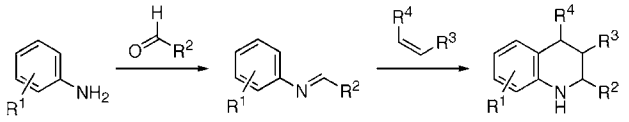
ABSTRACT



Pyrrolo[3,4-*b*]quinolines can be formed through the coupling of anilines with *N*-propargylic substituted heterocyclic aldehydes in the presence of mild Lewis acid catalysts (Ln(OTf)$_3$). The coupling proceeds through sequential imine formation and a formal intramolecular aza-Diels–Alder (Povarov) reaction. This approach was applied in a total synthesis of luotonin A and a formal synthesis of camptothecin.

Aza Diels−Alder reactions constitute one of the most convenient routes to the synthesis of N-heterocycles.[1] One variant, originally developed in the laboratories of Povarov,[2] are the reactions between electron-deficient Schiff bases and electron-rich alkenes (Scheme 1). The tetrahydroquinoline[3] obtained through the Povarov reaction can be viewed as being formed through either a concerted hetero Diels−Alder reaction or via a stepwise Mannich reaction followed by an intramolecular electrophilic aromatic substitution. The Povarov reaction can be protic or Lewis acid catalyzed and has attracted considerable recent attention because it allows the construction of tetrahydroquinolines in a multicomponent fashion.[4]

Scheme 1. Formation of Tetrahydroquinolines from the Povarov Reaction



Despite the large number of natural products that have tetrahydroquinoline, dihydroquinoline, or quinoline rings embedded in their structures, there have been only a few other examples of the use of the Povarov reaction in total synthesis.[5−7] Our group recently reported the application of the Povarov reaction in the first total synthesis of the alkaloid martinelline, which has a hexahydropyrrolo[3,2-*c*]quinoline

† This paper is dedicated to Prof. Ed. Piers for his contributions to the field of organic synthesis.

(1) For a review on the hetero Diels−Alder reaction see: Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* **2001**, *57*, 6099−6138.

(2) Povarov, L. S. *Russ. Chem. Rev.* **1967**, *36*, 656−670 and references therein.

(3) For a review of tetrahydroquinoline synthesis, see: Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031−15070.

(4) For recent reviews on multicomponent reactions, see: (a) Orru, R. V. A.; de Greef, M. *Synthesis* **2003**, 1471−1499. (b) Zhu, J. *Eur. J. Org. Chem.* **2003**, 1133−1144. (c) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168−3210. (d) Bienaymé, H.; Hulme, C.; Oddon, G.; Schmitt, P. *Chem. Eur. J.* **2000**, *6*, 3321−3329.

(5) Powell, D. A.; Batey, R. A. *Org. Lett.* **2002**, *4*, 2913−2916.

(6) Xia, C. F.; Heng, L. S.; Ma, D. W. *Tetrahedron Lett.* **2002**, *43*, 9405−9409.

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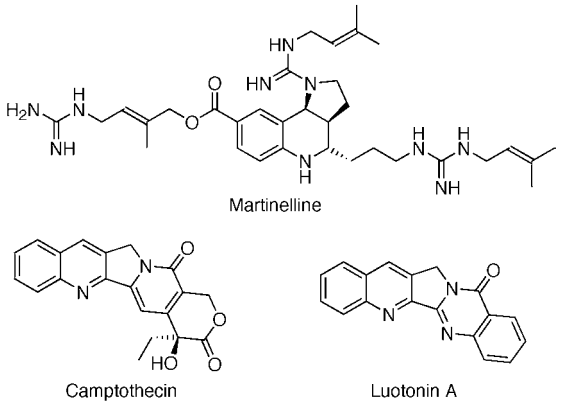


Figure 1. Pyrroloquinoline alkaloids.

core (Figure 1).[5] We were interested in further showcasing this useful reaction in other alkaloid syntheses and more specifically in developing intramolecular variants. We now report a concise intramolecular Povarov strategy for the formation of pyrrolo[3,4-*b*]quinolines that has been applied in a formal synthesis of camptothecin, as well as a total synthesis of luotonin A (Figure 1).

Pyrrolo[3,4-*b*]quinoline-based alkaloids have attracted significant interest due to their intriguing structures and biological activity. The most well-known example is camptothecin, a novel alkaloid isolated from the stem wood of the chinese tree, *Camptotheca acuminata*, which has potent antitumor activity. Since its isolation in 1966 and its structure elucidation by Wall and co-workers,[8] the compound has been the subject of numerous syntheses,[9−14] in part, because of its relationship to the antineoplastic chemotherapeutic drugs irinotecan and topotecan, which are camptothecin analogues. Luotonin A is a structurally related cytotoxic alkaloid first isolated in 1997 from the aerial parts of *Peganum nigellastrum Bunge*.[15] This plant has a history of use in Chinese traditional medicine for the treatment of various conditions, including rheumatism and inflammation. Luotonin A is active in vitro against the murine leukemia P-388 cell line at a concentration of 1.8 μg/mL[13] and has been the subject of several syntheses.[7,16] Particularly noteworthy is an intermolecular Povarov route to the synthesis of luotonin A, reported by Stevenson and co-workers.[7]

We envisaged an intramolecular Povarov reaction[17,18] could form the key ring-forming reaction in a general approach to the syntheses of these alkaloids and their analogues (Figure 2). This disconnection would employ an intramolecular aza-Diels−Alder reaction of an imine derived from the aniline **2**, heterocyclic aldehyde **3**, and propargylic halide **4**. The resultant dihydroquinoline ring could then be oxidized to the quinoline ring present in both camptothecin and luotonin A. This modular approach should also provide a convenient method for analogue synthesis.

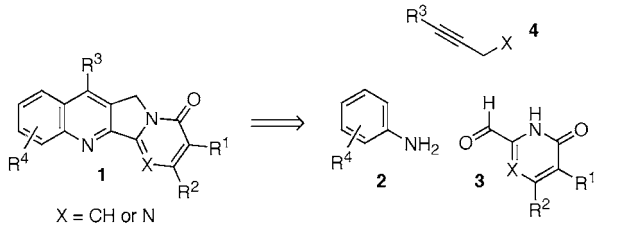


Figure 2. Proposed retrosynthesis of the pyrrolo[3,4-*b*]quinoline core **1** of Camptothecin and Luotonin A.

Our initial goal was the synthesis of camptothecin, which would require a pyridone precursor. Pyridone **5** was constructed in a one-pot protocol using commercially available pyruvic acid dimethylacetal, dimethylacetamide dimethylacetal, and cyanoacetamide.[19,20] Despite various attempts to optimize the reaction, the yield for this transformation

(8) Wall, M. E.; Wani, M. C.; Cook, C. E.; Palmer. K. H.; MacPhail, A. T.; Sim, G. A. *J. Am. Chem. Soc*. **1966**, *88*, 3888−3890.

(9) For a recent review on Camptothecins, see: Du, W. *Tetrahedron* **2003**, *59*, 8649−8687.

(10) For approaches involving construction of the C ring via sp^2-sp^2 C−C bond formation followed by N-alkylation, see: (a) Comins, D. L.; Baevsky, M. F.; Hong, H. *J. Am. Chem. Soc*. **1992**, *114*, 10971−10972. (b) Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255−4257. (c) Bennasar, M.-L.; Zulaica, E.; Juan, C.; Alonso, Y.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 7465−7474.

(11) For approaches involving construction of the B and C rings using a 4 + 1 radical annulation reaction, see: (a) Curran, D. P.; Liu, H. *J. Am. Chem. Soc.* **1992**, *114*, 5863−5864. (b) Curran, D. P.; Liu, H.; Josien, H.; Ko, S.-B. *Tetrahedron* **1996**, *52*, 11385-11404. (c) Curran, D. P.; Du, W. *Org. Lett.* **2002**, *4*, 3215−3218. (d) Bowman, W. R.; Bridge, C. F.; Brookes, P.; Cloonan, M. O.; Leach, D. C. *J. Chem. Soc., Perkin Trans. 1* **2002**, 58−68.

(12) For Friedlander condensation approaches to form the B ring, see: (a) Hutchinson, C. R. *Tetrahedron* **1981**, *37*, 1047−1065. (b) Ejima, A.; Terasawa, H.; Sugimori, M.; Tagawa, H. *Tetrahedron Lett.* **1989**, *30*, 2639−2640. (c) Jew, S.-S.; Ok, K.-D.; Kim, H.-J.; Kim, M. G.; Kim, J. M.; Cho, Y.-S. *Tetrahedron: Asymmetry* **1995**, *6*, 1245−1248. (d) Shen, W.; Coburn, C. A.; Bornmann, W. G.; Danishefsky, S. J. *J. Org. Chem.* **1997**, *62*, 6588−6597.

(13) For inter- or intramolecular Michael addition approaches to D ring construction, see: (a) Ciufolini, M. A.; Roschangar, F. *Tetrahedron* **1997**, *53*, 11049-11060. (b) Chavan, S. P.; Venkatraman, M. S. *Tetrahedron Lett.* **1998**, *39*, 6745−6748.

(14) For Diels−Alder reaction approaches to B, C, and D ring formation, see: (a) Fortunak, J. M. D.; Mastrocola, A. R.; Mellinger, M.; Sisti, N. J.; Wood, J. L.; Zhuang, Z.-P. *Tetrahedron Lett.* **1996**, *37*, 5679−5682. (b) Fortunak, J. M. D.; Kitteringham, J.; Mastrocola, A. R.; Mellinger, M.; Sisti, N. J.; Wood, J. L.; Zhuang, Z.-P. *Tetrahedron Lett.* **1996**, *37*, 5683−5686. (c) Blagg, B. S. J.; Boger, D. L. *Tetrahedron* **2002**, *58*, 6343−6349. (d) Toyata, M.; Komori, C.; Ihara, M. *J. Org. Chem.* **2000**, *65*, 7110−7113. (e) Rigby, J. H.; Danca, D. M. *Tetrahedron Lett.* **1997**, *38*, 4969−4972.

(15) Ma, Z.-Z.; Hano, Y.; Nomura, T.; Chen, Y.-J. *Heterocycles* **1997**, *46*, 541−546.

(16) For recent syntheses, see: (a) Azizian, J.; Mohammadi, A. A.; Ardakani, F.; Karimi, A. R.; Mohammadizadeh, M. R. *Heterocycles* **2004**, *63*, 791−795. (b) Cagir, A.; Jones, S. H.; Eisenhauer, B. M.; Gao, R.; Hecht, S. M. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2051−2054. (c) Mhaske, S. B.; Argade, N. P. *J. Org. Chem.* **2004**, *69*, 4563−4566 and references therein.

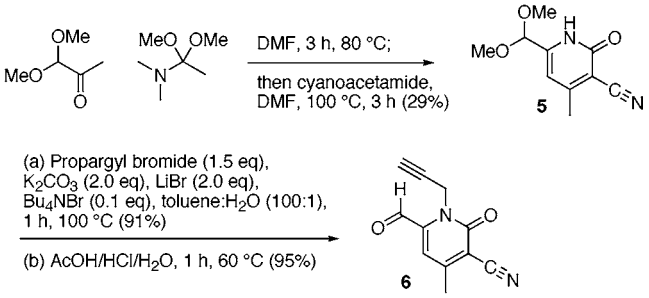
(17) There have been few reports of intramolecular Povarov reactions; see: (a) Laschat, S.; Lauterwein, J. *J. Org. Chem.* **1993**, *58*, 2856−2861. (b) Wölfling, J.; Frank, E.; Schneider, G.; Tietze, L. F. *Eur. J. Org. Chem.* **1999**, 3013−3020. (c) Magomedov, N. A. *Org. Lett.* **2003**, *5*, 2509−2512.

(18) An intramolecular Diels−Alder reaction has been used to form the B ring of topotecan, via activation of an *N*-aryl imidate with trimethyloxonium fluoroborate; see: refs 14a and 14b.

(19) Stockley, M.; Clegg, W.; Fontana, G.; Golding, B. T.; Martin, N.; Rigoreau, L. J. M.; Smith, G. C. M.; Griffin, R. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2837−2841.

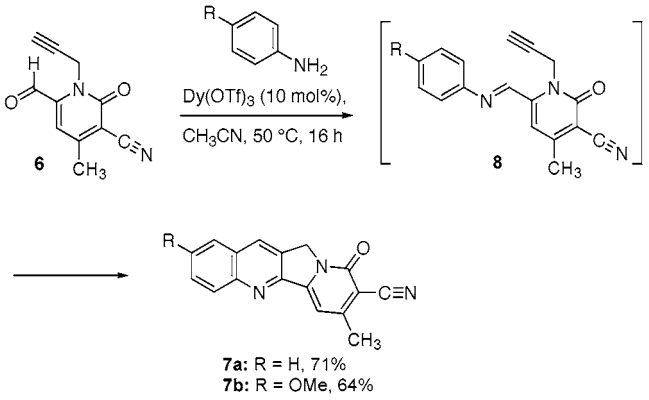
remained low. Alkylation using propargyl bromide, following a modified Ricoh procedure[21] used previously by Curran and co-workers,[22] provided the N-alkylated pyridone in 91% yield. Cleavage of the acetal was achieved using HCl/AcOH/H_2O, to give the desired pyridone aldehyde **6** in three steps with an overall yield of 25% (Scheme 2).

Scheme 2. Synthesis of Pyridone **6**



Optimized conditions for the key Povarov reaction between aldehyde **6** and aniline involved heating it at 50 °C for 16 h in the presence of 10 mol % Dy(OTf)$_3$ to afford the desired quinoline **7a** in 71% yield after recrystallization from hot methanol (Scheme 3). The corresponding dihydroquinoline

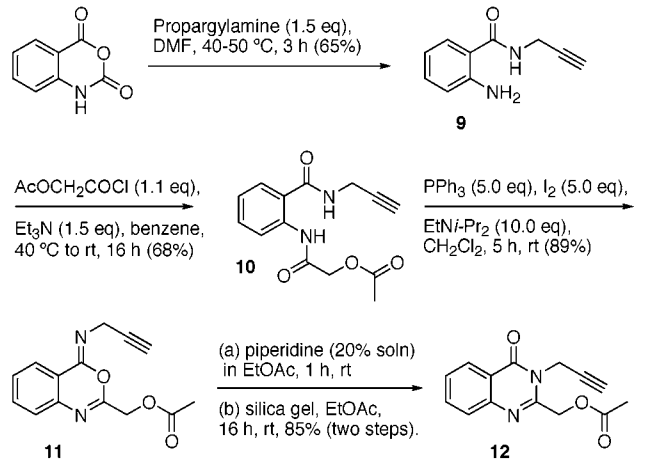
Scheme 3. Intramolecular Povarov Reaction to Form Camptothecin and Topotecan Precursor **7**



intermediate was not observed in the presence of Dy(OTf)$_3$, with oxidation to **7a** presumably occurring in situ. When the reaction was performed at room temperature for the same length of time, imine **8a** was obtained in 84% yield. Treatment of **8a** at 50 °C for 16 h in the absence of Dy(OTf)$_3$ led to a mixture of **7a** and the corresponding 1,2-dihydroquinoline. The formation of **7a** constitutes a formal synthesis of camptothecin.[23] Reaction of **6** with *p*-anisidine using Dy(OTf)$_3$ under the same conditions gave **7b** in 64% yield, a compound that could be used as a topotecan precursor.

The synthesis of luotonin A using an analogous approach requires the use of an quinazolinone aldehyde precursor. Ring-opening of commercially available isatoic anhydride with propargylamine gave 2-amino benzamide **9** in 65% yield.[24] N-Acylation of **9** with acetoxyacetyl chloride proceeded to give **10** in 68% yield. Both of these reactions can be carried out on a multigram scale. Various methods were investigated in order to obtain the quinazolinone ring system. Treatment of **10** with sodium carbonate[25] resulted in side reactions, whereas no reaction occurred in the presence of TMSCl.[26] We turned our attention to work done independently by Snider[27] and Ganesan[28] on the synthesis of fumiquinazolines. They employed chemistry developed by Mazurkiewicz on the synthesis and rearrangement of 4-imino-4*H*-3,1-benzoxazines.[29] Reaction of **10** with triphenylphosphine and iodine in the presence of Hünig's base afforded **11** in 89% yield. A two-step, one-pot rearrangement of **11** using piperidine followed by silica gel gave quinazolinone **12** in 85% yield (Scheme 4).

Scheme 4. Synthesis of Quinazolinone **12** from Isatoic Anhydride



The final steps in the synthesis of luotonin A involve removal of the acetate group from **12** using 1 M sodium hydroxide in THF/H_2O and subsequent oxidation using Dess−Martin periodinane to give the aldehyde precursor **13** in good yield over the two steps. Intramolecular Povarov reaction between **13** and aniline occurred in the presence of 10 mol % Dy(OTf)$_3$ in acetonitrile for 24 h to give luotonin A (Scheme 5). Again, oxidation of the initially formed 1,2-

(20) For leading references on the synthesis of pyridones, see: Carles, L.; Narkunan, K.; Penlou, S.; Rousset, L.; Bouchu, D.; Cuifolini, M. A. *J. Org. Chem.* **2002**, *67*, 4304−4308.
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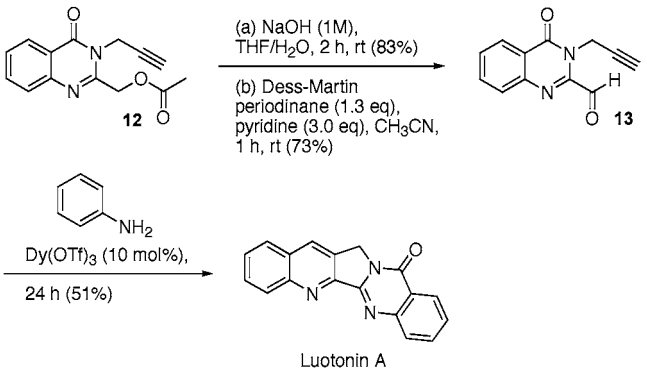
(22) Liu, H.; Ko, S.-B.; Josien, H.; Curran, D. P. *Tetrahedron Lett.* **1995**, *36*, 8917−8920.
(23) Eckert, H. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 208−210.
(24) Usifoh, C. O.; Scriba, G. K. E. *Arch. Pharm. Pharm. Med. Chem.* **2000**, *333*, 261−266.
(25) Bergman, J.; Brynolf, A. *Tetrahedron* **1990**, *46*, 1295−1310.
(26) O'Mahony, D. J. R.; Krchnák, V. *Tetrahedron Lett.* **2002**, *43*, 939−942.
(27) He, F.; Snider, B. B. *J. Org. Chem.* **1999**, *64*, 1397−1399.
(28) Wang, H.; Ganesan, A. *J. Org. Chem.* **1998**, *63*, 2432−2433.
(29) Mazurkiewicz, R. *Monatsh. Chem.* **1989**, *120*, 973−980.

Scheme 5. Intramolecular Povarov Route to the Synthesis of Luotonin A



dihydroquinoline presumably occurred in situ, with isolation of luotonin A in 51% yield after purification by column chromatography. Interestingly, this reaction had to be conducted at room temperature, since significant decomposition occurred at 50 °C.

In conclusion, an intramolecular Povarov reaction approach has been demonstrated in syntheses of the pyrroloquinoline[3,4-*b*] core of both camptothecin and a total synthesis of luotonin A. These syntheses underline the power of inverse-electron demand hetero Diels−Alder reactions for alkaloid synthesis, particularly when conducted in an intramolecular fashion. Further applications of this concise and convergent approach will be reported in due course.

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

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