ORGANIC LETTERS

2005
Vol. 7, No. 14
2949−2952

# Ring Expansion of Azetidinium Ylides: Rapid Access to the Pyrrolizidine Alkaloids Turneforcidine and Platynecine

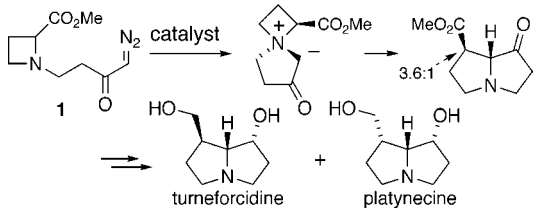
**John A. Vanecko and F. G. West*,†**

*Department of Chemistry, University of Utah, 315 South 1400 East, Room 2020, Salt Lake City, Utah 84112-0850*

*frederick.west@ualberta.ca*

**Received April 25, 2005**

## ABSTRACT




**Azetidinecarboxylate esters react readily with metallocarbenes in an inter- or intramolecular fashion to generate azetidinium ylides. Efficient [1,2]-shift by the ester-substituted carbon furnishes ring-expanded pyrrolidine products. In the case of substrate 1, this provides access to the pyrrolizidine alkaloids turneforcidine and platynecine via a high-yield, five-step sequence starting with readily available methyl 1-benzylazetidine-2-carboxylate.**

The Stevens [1,2]-shift[1] of cyclic ammonium ylides permits the efficient construction of functionalized pyrrolidines, piperidines, or other azacycles.[2] In this process, an exocyclic ammonium substituent that can support a transient radical center[3,4] migrates to the neighboring ylide carbon. One of the most convenient strategies for generating such ylides involves the transition metal-catalyzed decomposition of diazocarbonyl compounds with pendant amino groups.[5] When the amine (**1**) is part of a preexisting ring system, this approach furnishes transient spirocyclic ylides **2** whose [1,2]-shift leads to fused bicyclic products **3** with bridgehead nitrogen atoms (Scheme 1).[6] The spiro-to-fused strategy is especially appealing as a route to the necine base class of

† Current address: Department of Chemistry, University of Alberta, W5-67 Chemistry Centre, Edmonton, AB, T6G 2G2, Canada.

(1) (a) Sato, Y.; Shirai, N. *Yakugaku Zasshi* **1994**, *114*, 880−887. (b) Markó, I. E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, pp 913−974. Lepley, A. R.; Guimanini, A. G. In *Mechanisms of Molecular Migrations*; Thyagarajan, B. S., Ed.; Interscience: New York, 1971; Vol. 3, pp 297−440.

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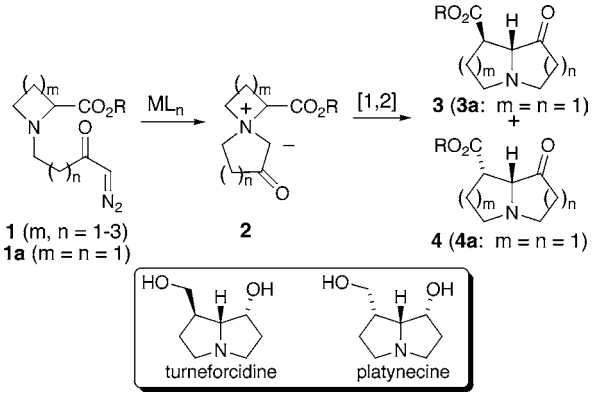
(4) For a recent report that suggests an alternative ion-pair-mediated mechanism, see: Hanessian, S.; Mauduit, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3810−3813.

(5) Review: Clark, J. S.; West, F. G. In *Nitrogen, Oxygen and Sulfur Ylides in Synthesis: A Practical Approach*; Clark, J. S., Ed.; Oxford University Press: Oxford, 2002; pp 115−134.

(6) (a) Saba, A. *Tetrahedron Lett.* **2003**, *44*, 2895−2989. (b) Vanecko, J. A.; West, F. G. *Org. Lett.* **2002**, *4*, 2813−2816. (c) Padwa, A.; Beall, L. S.; Eidell, C. K.; Worsencroft, K. J. *J. Org. Chem.* **2001**, *66*, 2414−2421. (d) Chelucci, G.; Saba, A.; Valenti, R.; Bacchi, A. *Tetrahedron: Asymmetry* **2000**, *11*, 3449−3453. (e) Naidu, B. N.; West, F. G. *Tetrahedron* **1997**, *53*, 16565−16574. (f) Wright, D. L.; Weekly, R. M.; Groff, R.; McMills, M. C. *Tetrahedron Lett.* **1996**, *37*, 2165−2168.

10.1021/ol050915o CCC: $30.25 
**Published on Web 06/09/2005**

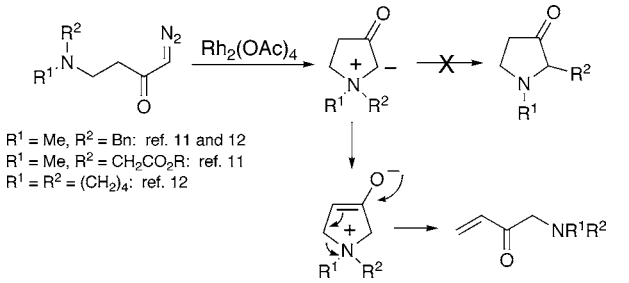
**Scheme 1**




pyrrolizidine alkaloids,[7] as exemplified by turneforcidine[8] and platynecine.[9] Successful application of this approach would convert an azetidinecarboxylate **1a** with a pendant diazoketone into pyrrolizidines **3a/4a**,[10] in which the ester and ketone are properly positioned for reduction to the C-7 and C-9 secondary and primary alcohols found in many of the naturally occurring pyrrolizidines. Here we describe the successful execution of this strategy, including the synthesis of (±)-turneforcidine and (±)-platynecine from methyl 1-benzylazetidine-2-carboxylate, in five steps.

A potential limitation in the application of the spiro-ylide methodology to pyrrolizidines was the availability of alternative ylide decomposition pathways. In the case of five-membered ylides containing an endocyclic carbonyl, we[11] and Padwa[12] had observed products derived from an apparent proton-transfer/fragmentative ring-opening process, isolated to the exclusion of any of the desired [1,2]-shift products (Scheme 2). In sharp contrast, Clark has obtained high yields of five-membered ylide-derived products when the available rearrangement pathway involves a concerted [2,3]-shift.[13,14] On the basis of these results, we inferred that the stepwise [1,2]-shift, which is generally observed to occur less readily

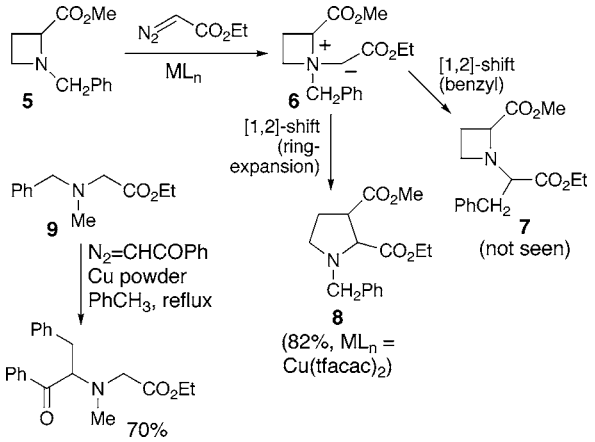
**Scheme 2**




than the [2,3]-shift,[15] is sufficiently slow to permit the intervention of the undesired pathway. The strained azetidinium ylide **2a** presented an interesting question: Could release of ring-strain lower the barrier to homolytic cleavage and allow the [1,2]-shift pathway to compete with the fragmentation process? With this in mind, we chose to examine the behavior of methyl 1-benzylazetidine-2-carboxylate **5**[16] in the presence of ethyl diazoacetate and various transition metal catalysts.

We anticipated that ylide **6** would be generated under these conditions (Scheme 3), and its behavior might offer insight

**Scheme 3**




into the reactivity of azetidinium ylides toward ring expansion. Ylide **6** possesses two groups on nitrogen that might reasonably be expected to participate in [1,2]-shift processes. Migration of the benzyl substituent would lead to azetidine **7**, while migration of the ester-substituted carbon would furnish pyrrolidine **8**. In prior studies, we have found that

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(10) For previous preparation of **3a** and/or **4a**, see refs 8c, 8e, and 8f.

(11) Naidu, B. N. Ph.D. Dissertation, University of Utah, Salt Lake City, UT, 1994.

(12) Padwa, A.; Hasegawa, T.; Liu, B.; Zhang, Z. *J. Org. Chem.* **2000**, *65*, 7124−7133.

(13) Clark, J. S.; Hodgson, P. B.; Goldsmith, M. D.; Blake, A. J.; Cooke, P. A.; Street, L. J. *J. Chem. Soc., Perkin Trans. 1* **2001**, 3325−3337.

(14) For related observations involving oxonium ylide [1,2]- and [2,3]-shifts, see: (a) Marmsäter, F. P.; Vanecko, J. A.; West, F. G. *Tetrahedron* **2002**, *58*, 2027−2040. (b) Marmsäter, F. P.; Vanecko. J. A.; West, F. G. *Org. Lett.* **2004**, *6*, 1657−1660.

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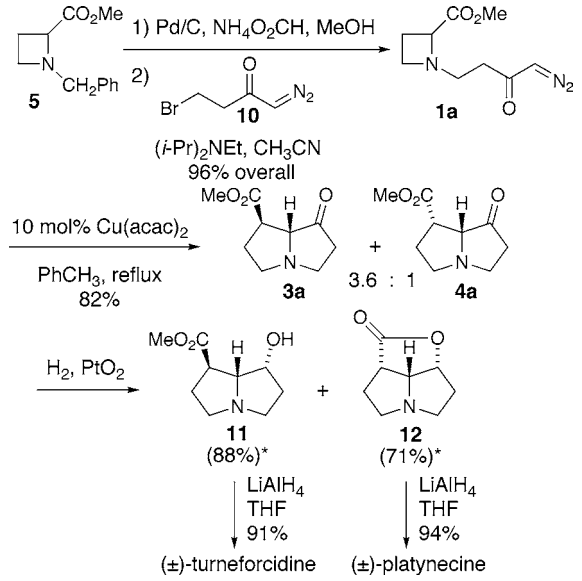
(16) Rodebaugh, R. M.; Cromwell, N. H. *J. Heterocycl. Chem.* **1968**, 309.

either $CH_2Ar$ or $CH_2CO_2R$ groups undergo efficient migration.[2f,17] However, in a previous case (**9**) in which both possibilities were available, we observed exclusive migration of the benzyl group.[17,18] This selectivity was rationalized in terms of the greater stability of the putative benzylic radical intermediate. In contrast to this result, when racemic **5** was treated with ethyl diazoacetate and 10 mol % $Cu(tfacac)_2$ in refluxing toluene, the exclusive product was pyrrolidine diester **8** (82%; 1:1 mixture of diastereomers).[19] Rhodium(II) acetate and other soluble copper catalysts ($Cu(acac)_2$ and $Cu(tfacac)_2$) gave qualitatively comparable results, although with somewhat lower yields. Under no circumstances was the benzyl [1,2]-shift product **7** isolated. 3-Carboxyproline derivatives such as **8** are of interest as rigid aspartic acid analogues.[20] This constitutes an exceedingly short and convenient route to such compounds. Moreover, these results suggested that the corresponding spirocyclic azetidinium ylide might undergo efficient rearrangement to the pyrrolizidine system in competition with the undesired fragmentation.

Given the positive results with **5**, we then set out to examine the intramolecular version of this ring expansion. Reductive debenzylation of **5** under transfer hydrogenation conditions (Pd/C, ammonium formate)[21] followed by immediate coupling of the volatile intermediate with 4-bromo-1-diazobutan-2-one **10**[22] furnished substrate **1a** in high yield (Scheme 4). Treatment of **1a** with $Cu(acac)_2$ or $Rh_2(OAc)_4$

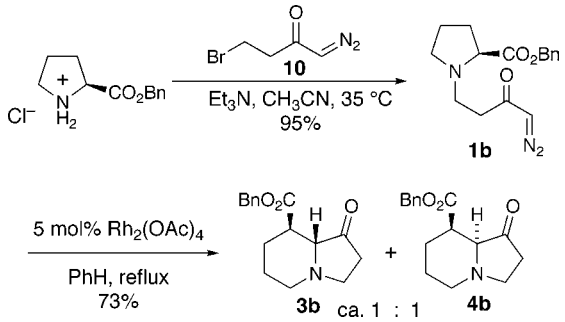
**Scheme 4**




provided an inseparable mixture of diastereomers **3a** and **4a** in 81−82% yield (3.6:1 dr). Other soluble copper(II) catalysts gave comparable or slightly lower yields, and the diastereomer ratio did not vary to any great extent with catalyst or reaction conditions.[23] This mixture was then carried on through the known sequence[8f,h] to prepare (±)-turneforcidine and (±)-platynecine. Ketone reduction ($H_2$, $PtO_2$) gave hydroxyester **11** (88% based on the starting ratio) and lactone **12** (71% based on the starting ratio), which were easily separable. Each was then treated with $LiAlH_4$ to give the natural products in high overall yield.

The optimized conditions were also investigated for homologous diazoketone **1b**, prepared from commercially available proline benzyl ester hydrochloride and **10** (Scheme 5).[24] Under these conditions, only trace amounts of the

**Scheme 5**




desired indolizidines **3b** and **4b** were obtained, along with a side product that resisted characterization. However, lower reaction temperatures (reflux in benzene or $CH_2Cl_2$) did furnish 50−62% of **3b**/**4b** as an inseparable mixture. After a survey of a variety of catalysts, solvents, and reaction temperatures, $Rh_2(OAc)_4$ in refluxing benzene was found to provide the best result. The aforementioned side product was the main component isolated from all experiments carried out in refluxing toluene. Indolizidines **3b** and **4b** were significantly more sensitive than their pyrrolizidine counterparts **3a**/**4a**, undergoing substantial decomposition after as little as 30 min at rt. As a result, no attempt at further elaboration was made.

We have shown that ammonium ylides derived from azetidine-2-carboxylates undergo efficient ring-expansion via the Stevens [1,2]-shift. The intermolecular process offers a short route to 3-carboxyproline derivatives, while the intramolecular variant has been used in a five-step synthesis of

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(18) Complete preference for benzylic migration in ring expansion of morpholinium ylides has also been noted. See refs 6a and 6d.

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(21) Ram, S.; Spicer, L. D. *Tetrahedron Lett.* **1987**, *28*, 515−516.

(22) Rosenquist, N. R.; Chapman, O. L. *J. Org. Chem.* **1976**, *41*, 3326−3327.

(23) However, epimerization of the initial product mixture could be effected via slow elution through a silica gel column using a less polar eluant to furnish **3a** + **4a** in a 94:6 ratio. For n related example, see ref 13.

(24) Saba and co-workers have recently reported a similar approach to indolizidines using doubly stabilized metallocarbene intermediates: Muroni, D.; Saba, A.; Culeddu, N. *Tetrahedron: Asymmetry* **2004**, *15*, 2609−2614.

turneforcidine and platynecine from readily available methyl 1-benzylazetidine-2-carboxylate. Preliminary studies indicate that these conditions may also be applicable to indolizidine-containing targets. Further studies to enhance the diastereoselectivity of the intermolecular reaction and to explore the question of chirality transfer via the transient quaternary ammonium center in the case of enantiomerically pure azetidine starting materials will be reported in due course.

**Acknowledgment.** This work was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

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

OL050915O