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Expedient Synthesis of Pyrrolo[1,2-*a*]indoles: Preparation of the Core of Yuremamine

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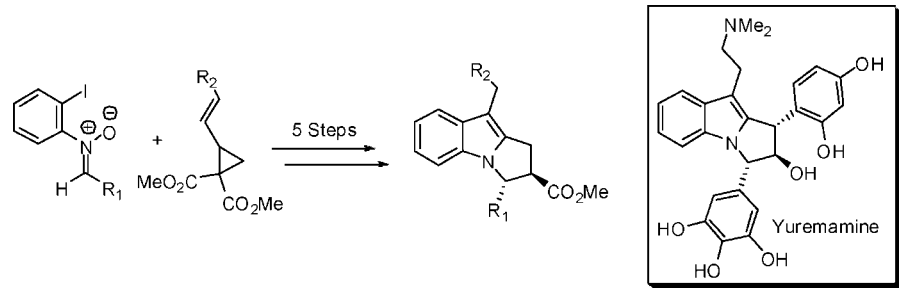
ABSTRACT



Pyrrolo[1,2-*a*]indoles are conveniently prepared from tetrahydro-1,2-oxazines, which in turn are generated through the reaction of nitrones with 1,1-cyclopropanediesters. The synthetic route proves to be highly diastereoselective and provides access to the core of the recently discovered pyrrolo[1,2-*a*]indole natural product yuremamine.

The pyrrolo[1,2-*a*]indole tricyclic ring structure is a common motif[1] found in a number of naturally occurring products (Figure 1). To date, much of the research which has been conducted within this family of alkaloids has been directed toward mitomycin C **1a** and its analogues due to its antitumor and chemotherapeutic properties.[2] Another member of this family, yuremamine **2**, is a new phytoindole recently isolated from the stem bark of *Mimosa hostilis*.[3] Yuremamine piqued our interest due in part to its biological profile associated with traditional use in a medico-religious tea (known to cause hallucinogenic and psychoactive effects) and its fascinating molecular architecture.

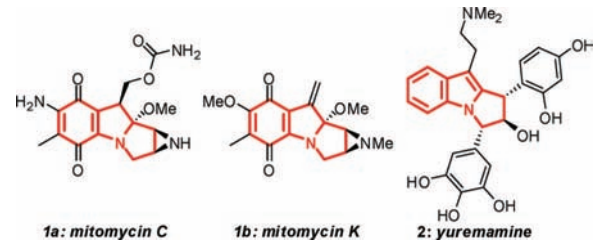


Figure 1. Mitomycin C and yuremamine, highlighting the common pyrrolo[1,2-*a*]indole core.

(1) Synthesis of pyrrolo[1,2-*a*]indoles: (a) Manian, R. D. R. S.; Jayashankaran, J.; Ragunathan, R. *Synlett* **2007**, 874. (b) Borah, H. N.; Deb, M. L.; Boruah, R. C.; Bhuyan, P. J. *Tetrahedron Lett.* **2005**, 3391. (c) Yavari, I.; Adib, M.; Sayahi, M. H. J. *Chem. Soc., Perkin Trans. 1* **2002**, 1517. (d) Padwa, A.; Fryxell, G. E.; Gasdaska, J. R.; Venkatramanan, M. K.; Wong, G. S. *J. Org. Chem.* **1989**, *54*, 644. (e) Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 199.

(2) For excellent leading references on mitomycin synthetic studies as well as total syntheses, see: (a) Namiki, H.; Chamberland, S.; Gubler, D. A.; Williams, R. M. *Org. Lett.* **2007**, *9*, 5341. (b) Williams, A. L.; Srinivasan, J. M.; Johnston, J. M. *Org. Lett.* **2006**, *8*, 6047. (c) Coleman, R. S.; Felpin, F.-X.; Chen, W. *J. Org. Chem.* **2004**, *69*, 7309. (d) Danishefsky, S. J.; Schkeryantz, J. M. *Synlett* **1995**, 475. (e) Fukuyama, T.; Yank, L. *J. Am. Chem. Soc.* **1989**, *111*, 8303. (f) Fukuyama, T.; Nakatsubo, F.; Cocuzza, A. J.; Kishi, Y. *Tetrahedron Lett.* **1977**, 4295.

(3) Vepsäläinen, J. J.; Auriola, S.; Tukiainen, M.; Ropponen, N.; Callaway, J. *Planta Med.* **2005**, *71*, 1049.

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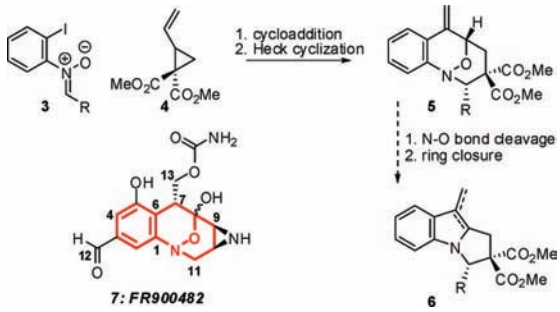
In 2003, we disclosed the two-step preparation of skeletal congeners of FR900482 employing the nitrone/1,1-cyclopropanediester cycloaddition.[4] The individual components were functionalized with Heck donor and acceptor moeities preinstalled to allow for the union of C6 and C7 (FR900482 numbering) of the core framework, post cycloaddition (see Scheme 1).

Scheme 1. Conversion of the FR900482 Skeletal Congeners to Pyrrolo[1,2-*a*]indoles

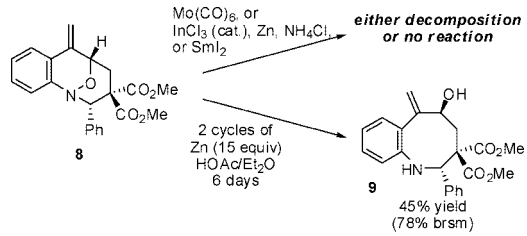


Though tetrahydro-1,2-oxazines are not a common motif in nature, their transformation into the more ubiquitous pyrrolidine heterocycles was also explored.[5] This useful strategy was later exploited in the successful total synthesis of nakadomarin A.[6]

With the recent isolation of yuremamine we gained a renewed interest in the functionalization of the FR900482 skeletal congeners as it was plausible that through N−O bond cleavage and subsequent displacement of the alcohol by the aniline nitrogen a synthesis of pyrrolo[1,2-*a*]indoles would be achieved (Scheme 1).

Our studies commenced with the N−O bond cleavage of the FR900482 skeletal congener **8** (Scheme 2). In our

Scheme 2. Representative Attempts at N−O Bond Cleavage

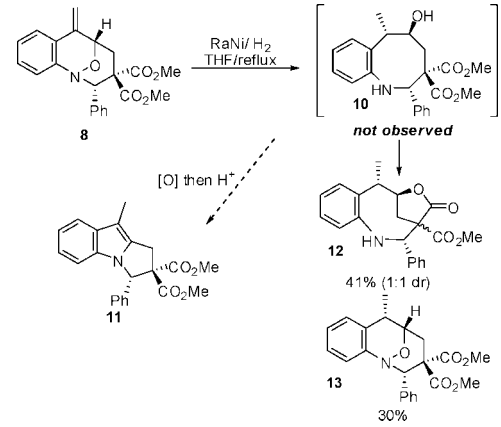


previous work,[5] we were unable to perform the N−O bond reduction in the presence of the diester moiety due to the propensity of the product amino alchohol to undergo a retro-Mannich-type fragmentation. What had *not* been investigated, however, was whether this same fragmentation would proceed when the tetrahydro-1,2-oxazine was further annealed to the phenyl ring as in the FR900482 skeletal congeners. We postulated (through entropic considerations) that this second attachment might attenuate the retro-Mannich and impart significant ring strain to the system which could be relieved through cleavage of the N−O bond, thus allowing mild conditions for reduction. To this end, **8** was prepared as previously disclosed[4] and submitted to various conditions known to reduce N−O bonds.[7]

Of the methods employed, only the acidic zinc reduction[8] was capable of providing the desired amino alcohol **9** but ultimately proved inefficient synthetically, requiring large excesses of zinc and failure to proceed to completion even over extended reaction times.

We next envisioned a hydrogenolysis of the N−O bond, which, with concomitant reduction of the olefin, would yield amino alcohol **10**. Oxidation and an ensuing condensative ring closure would furnish the desired pyrrolo[1,2-*a*]indole **11** (Scheme 3). Ambient hydrogenation conditions resulted

Scheme 3. Investigation of a Hydrogenolysis Route



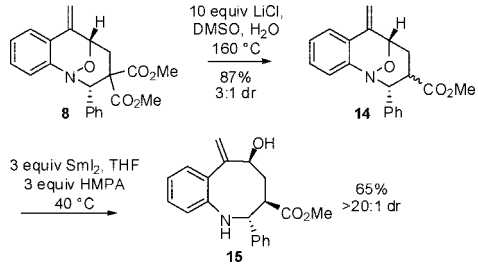
in complete reduction of the exomethylene moiety, but no amino alcohol was observed. At higher temperatures, some N−O bond cleavage was achieved, but the transient amino alcohol lactonized with one of the ester moieties providing **12** as a mixture of diastereomers along with **13**, where the styrenyl double bond had undergone hydrogenation.

At this juncture, it became clear that the diester moiety would require further derivatization to avoid the problems incurred during N−O bond cleavage. To this end, a Krapcho decarboxylation was most practical in terms of simplicity, accessibility, and step economy. After moderate investigation, the optimal conditions were found to be heating at 160 °C in damp DMSO with 10 equiv of lithium chloride, supplying

(4) (a) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023. (b) Young, I. S.; Kerr, M. A. *Org. Lett.* **2004**, *6*, 139.
(5) Young, I. S.; Williams, J. L.; Kerr, M. A. *Org. Lett.* **2005**, *7*, 953.
(6) Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465.
(7) For representative examples, see: $Mo(CO)_6$: (a) Tranmer, G. K.; Tam, W. *Org. Lett.* **2002**, *4*, 4101. $InCl_3$: (b) Cicchi, S.; Bonanni, M.; Cardona, F.; Revuelta, J.; Goti, A. *Org. Lett.* **2003**, *5*, 1773. SmI_2: (c) Natale, N. R. *Tetrahedron Lett.* **1982**, *23*, 5009.
(8) Gallos, J. K.; Stathakis, C. I.; Kotoulas, S. S.; Koumbis, A. E. *J. Org. Chem.* **2005**, *70*, 6884.

the monoester product **14** as a mixture of diastereomers (Scheme 4).

Scheme 4. Successful N−O Bond Reduction

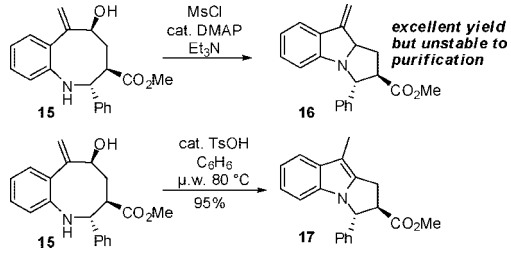


With monoester **14** in hand, we revisited the samarium diiodide mediated N−O bond cleavage employed in our previous pyrrolidine synthesis.[5] At refluxing conditions, we were pleased to find moderate amounts (35%) of the desired amino alcohol product **15** as a single diastereomer. The origin of the low isolated yield was suspected to lie in a tendency for retro-Mannich fragmentation. Attempts to cleave the N−O bond at decreased temperatures failed to produce satisfactory results.

It has been shown that supplementing samarium diiodide with electron-donating ligands such as HMPA can greatly increase the reductive potential of the reactant.[9] With this in mind, we turned to this ligand in the samarium mediated N−O bond cleavage, hoping to induce cleavage at lower temperatures and increase yields. This was realized by employing 3 equiv each of SmI_2 and HMPA at 40 °C until all of the starting material was consumed as indicated by TLC. In the event, amino alcohol **15** was produced in 65% yield as a single diastereomer.

With amino alcohol **15** in hand, the final transannular ring closure was examined. Two modes of accomplishing this transformation were envisaged, both of which were successful (Scheme 5). First, mesylation of the alcohol

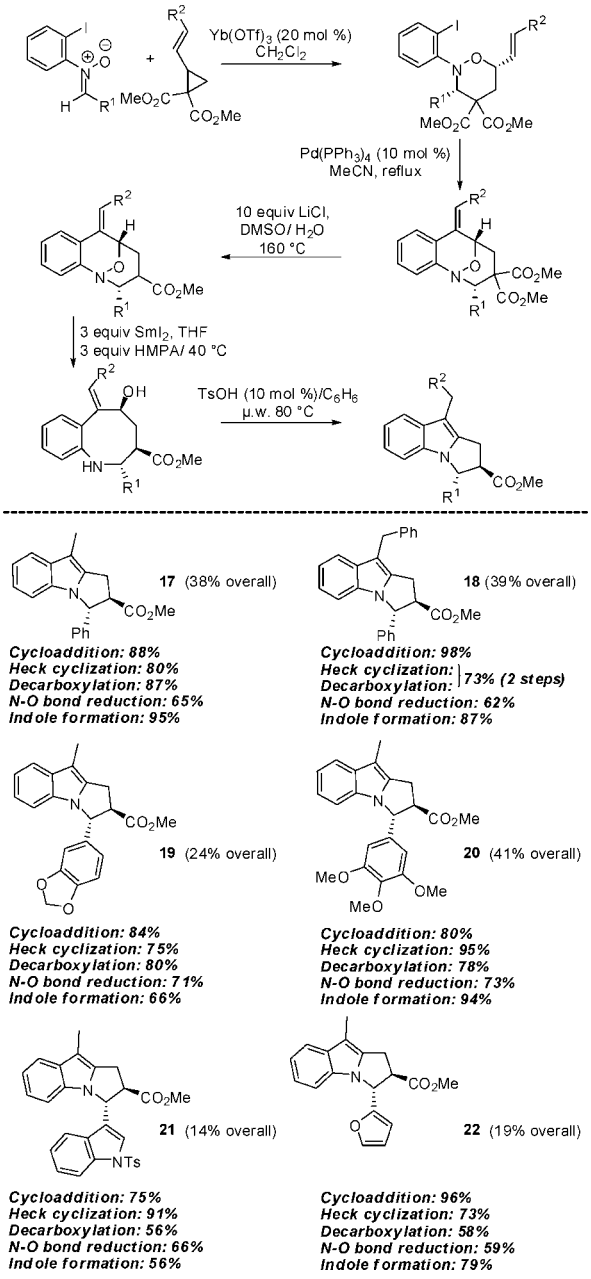
Scheme 5. Transannular Ring Closure



followed by in situ displacement by the aniline nitrogen provided the transiently stable pyrrolo[1,2-*a*]indole **16**

(9) (a) Hasegawa, E.; Curran, D. P. *Tetrahedron Lett.* **1993**, *34*, 1717. (b) Prasad, E.; Flowers, R. A. *J. Am. Chem. Soc.* **2002**, *124*, 6895.

Scheme 6. Extension of the Methodology



bearing an exomethylene moiety, a functional group present in mitomycin K. Compound **16** was not stable to chromatography and was only visible by crude ^{1}H NMR after mild aqueous workup.

The second and more useful strategy for the transannular ring closure was a microwave mediated acid catalyzed allylic displacement. Exceedingly facile and high yielding, this became the route of choice to furnish the desired pyrrolo[1,2-*a*]indole **17** and related entities.

With the details of each synthetic operation established, several diverse examples were carried through the five-step sequence (cycloaddition, Heck cyclization, Krapcho decar-

boxylation, SmI_2-mediated N−O bond reduction, and acid-catalyzed indole formation) illustrated in Scheme 6.[10]

Several points from Scheme 6 are worthy of note. Compound **20** is notable because the aryl aldehyde used for the formation of the nitrone results in the positioning of a trimethoxyphenyl group where required for the synthesis of yuremamine. The issue of relative stereochemistry was resolved using NMR experiments. The decarboxylation product en route to pyrroloindole **17** (formed as a 3:1 mixture of diastereomers) showed no useful NOE correlations; however, the corresponding primary alcohol (the product of LAH reduction), also a 3:1 epimeric mixture was more cooperative. Detailed NOE examination of this compound indicated a trans relationship between the hydroxymethyl group and the phenyl substituent. Corroborating this evidence is the fact that the coupling constants between the methine protons adjacent to the ester and the phenyl moieties are 6.4 Hz and suggestive of a trans disposition.

In the case of pyrroloindole **18**, the Heck cyclization required the use of microwave irradiation. This furnished a mixture of products which were inseparable and were decarboxylated as a mixture to give a single monoester with the indicated olefinic geometry. This issue is of course ultimately inconsequential since this geometry is lost upon the formation of the benzopyrrole.

In summary, we have developed an efficient synthesis of pyrrolo[1,2-*a*]indoles which bear useful functionality on the saturated ring. This functionality is ideally positioned for the eventual total synthesis of a series of natural products including yuremamine. Efforts to prepare this target are underway in our laboratory.

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

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(10) Full experimental details and characerization data for all compounds in Scheme 6 are included in the Supporting Information.