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Cyclic Imine Nitro-Mannich/Lactamization Cascades: A Direct Stereoselective Synthesis of Multicyclic Piperidinone Derivatives

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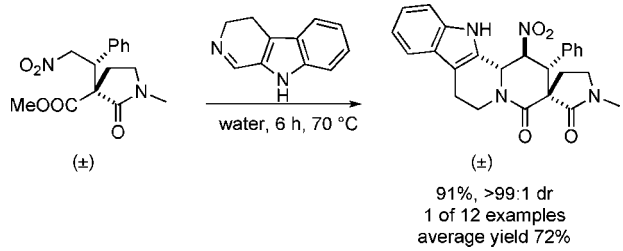
ABSTRACT



An efficient nitro-Mannich/lactamization cascade of γ-nitro esters with cyclic imines for the preparation of architecturally complex multicyclic piperidinone ring-containing structures has been developed. The reaction is broad in scope and stereoselective and may be coupled to an enantioselective nitroolefin Michael addition reaction as part of a highly enantio- and diastereoselective multicomponent process.

Multicyclic piperidine ring-containing structures[1] are common among complex alkaloid natural products of which pumiliotoxin 251D,[2] reserpine,[3] and nakadomarin A[4] are representative (Figure 1).

As part of ongoing research efforts targeting the stereoselective synthesis of nitrogen-containing heterocyclic compounds, we recently described a stereoselective formal synthesis of (3*S*,4*R*)-paroxetine[5] (Figure 1). The work constituted an effective extension of Mühlstädt's nitro-Mannich chemistry,[6] and an adduct from our bifunctional thiourea-catalyzed Michael addition reaction[7] was reacted with the imine of benzylamine and formaldehyde to afford a cyclized Mannich product. This reaction sequence provides a straightforward synthesis of monocyclic piperidinones, but

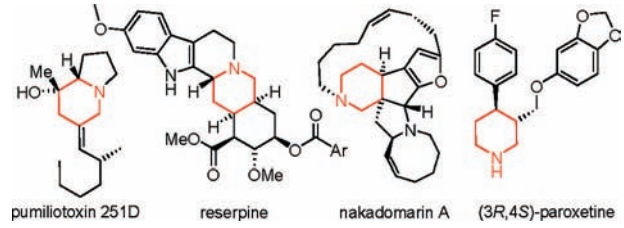


Figure 1. Piperidine ring-containing natural products and pharmaceutical molecules.

(1) For reviews of the synthesis of piperidine, see: (a) Bates, R. W.; Kanicha, S.-E. *Tetrahedron* **2002**, *58*, 5957. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem.* **2003**, 3693. (c) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun.* **1998**, 633. (d) O'Hogan, D. *Nat. Prod. Rep.* **2000**, *17*, 435. (e) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (f) Weintraub, P. M.; Sabol, J. S.; Kane, J. M.; Borcherding, D. R. *Tetrahedron* **2003**, *59*, 2953. (g) Husson, H.-P.; Royer, J. *Chem. Soc. Rev.* **1999**, *28*, 383. (h) Escolano, C.; Amat, M.; Bosch, J. *Chem.−Eur. J.* **2006**, *12*, 8198.

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(3) (a) Chen, F.-E.; Huang, J. *Chem. Rev.* **2005**, *105*, 4671. (b) Woodward, R. B.; Bader, F. E.; Bickel, H.; Frey, A. J.; Kierstead, R. W. *Tetrahedron* **1958**, *110*, 5925. (c) Schlitter, E. In *The Alkaloids: Chemistry and Physiology*; Manske, R. H. F., Ed.; Academic Press: New York, 1965; Vol. VIII, p 287. (d) Muiler, J. M.; Schlitter, E.; Bein, H. J. *Experientia* **1953**, *9*, 368.

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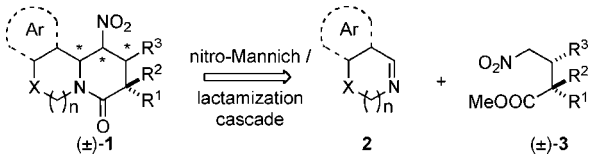
to our knowledge the stereoselective construction of complex polycyclic ring systems of generic structure **1** in Scheme 1

Scheme 1. Nitro-Mannich/Lactamization Cascade for the Construction of Multicyclic Piperidinone Derivatives



via reaction of cyclic imines **2**[8] with γ-nitro esters **3**[9] has yet to be reported.

As a range of procedures for the preparation of cyclic imines are known and as the nitro esters can be readily constructed via Michael addition reactions, a powerful reaction sequence to architecturally complex piperidine ring-containing *multicyclic* structures emerges that could be useful in both library synthesis and total synthesis alike. Attracted by the simplicity and potential synthetic utility of the method, we began our investigations and herein describe the findings.

Initially, feasibility studies were performed on a representative nitro ester **3a** (1 equiv) and cyclic imine **2a** (2 equiv, Figure 2). These were reacted in solvents ranging from apolar aprotic to polar protic and reactivity assessed by

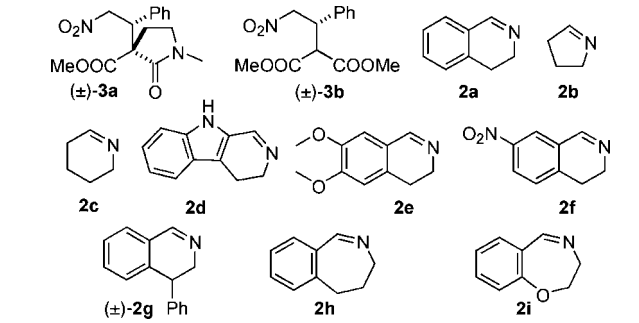
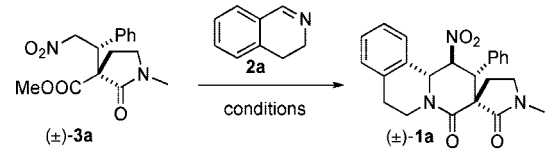


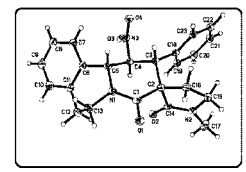
Figure 2. Nitro ester and cyclic imine starting materials.

measuring conversion after an arbitrary 24 h period. The results are presented in Table 1. At elevated temperatures in

Table 1. Feasibility and Optimization Studies in the Nitro-Mannich/Lactamization Cascade Using **3a** and **2a**



X-ray structure of **1a**



entry	solvent	temp	conversion	yield	dr
1	hexane	reflux	~0	–	–
2	toluene	70 °C	4%	–	–
3	THF	reflux	10%	–	–
4	MeCN	70 °C	10%	–	–
5	$CHCl_3$	reflux	4%	–	–
6	EtOH	70 °C	8%	–	–
7	MeOH	reflux	10%	–	–
8	H_2O	RT	4%	–	–
9	H_2O	70 °C	61%	42%	>99:1
10[a]	H_2O	70 °C	~100%	76%	>99:1
11	neat	70 °C	11%	–	–

[a] Results after 48 h.

aprotic solvents such as hexane, toluene, tetrahydrofuran, acetonitrile, and chloroform, little or no conversion to the desired product **1a** was observed (entries 1−5). The polar protic solvents ethanol and methanol at elevated temperatures were then investigated, and again only low conversions were obtained (8 and 10%, respectively, entries 6 and 7). Surprised by the significant difference between these results and those from our previous studies,[5b] we then turned to water as a reaction solvent. Pleasingly, at room temperature, a small amount of conversion was observed. At 70 °C for 24 h, a

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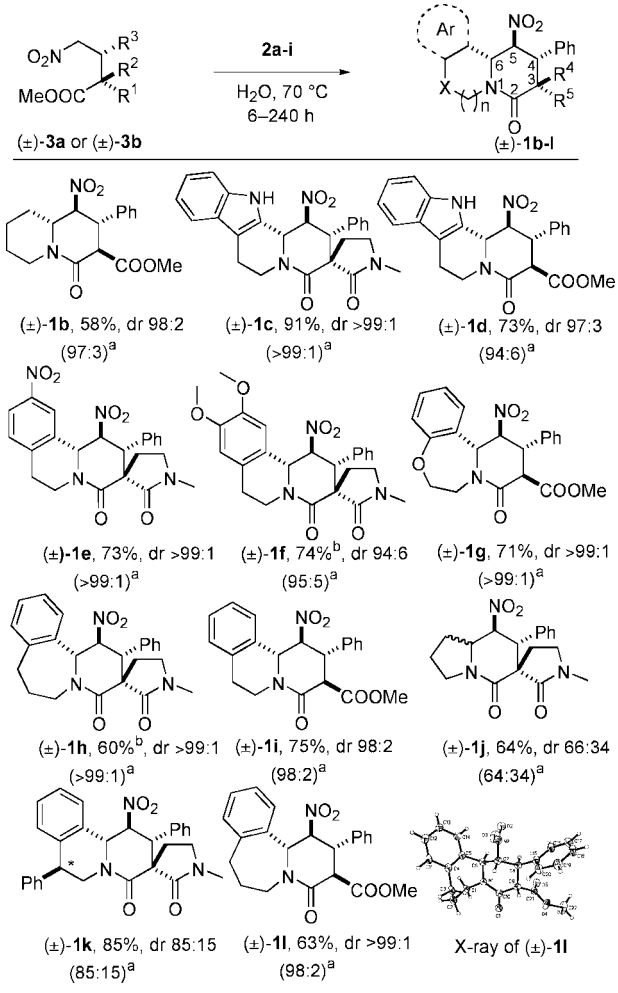
(9) For the synthesis of **3a** and **3b**, see Supporting Information.

respectable 61% conversion was noted, and after 48 h, upon full conversion, the desired product **1a** was isolated in 76% yield as a single diastereoisomer[10] (entries 8−10). The relative stereochemistry of **1a** was unambiguously determined by single crystal X-ray diffraction. The fact that water was acting as the superior reaction solvent[11] in this cascade was confirmed by heating a mixture of the imine **2a** and the nitroester **3a** in the absence of solvent at 70 °C for 24 h, and only 11% conversion was observed (entry 11).

With preferred conditions identified, the reaction scope was then investigated. A range of five-, six-, and seven-membered ring imines **2a**−**i** (Figure 2), prepared by literature or modified literature procedures,[8] were reacted with nitro esters **3a** and **3b** using water as the reaction solvent, and the results are presented in Scheme 2.

Scheme 2. Scope of the Cyclic Imine Nitro-Mannich/Lactamization Cascade



[a]dr in crude product. [b]1:1 H_2O:MeOH mixture used as a solvent.

Employing the optimal reaction conditions, products **1b**−**1l** were formed in moderate to good yields. With the exception of **1j**, good to excellent diastereocontrol was observed in all cases. The stereochemistry of **1l** was unambiguously determined by single crystal X-ray analysis. By comparison of the ^{1}H NMR spectra of **1b**−**1k** to those of **1a** and **1l**, their stereochemistries were assigned by analogy. Interestingly, when the chiral imine **2g** was employed in the nitro-Mannich/lactamization cascade with nitro ester **3a** under the standard conditions, a significant bias toward one of the possible eight diastereomeric products **1k** was observed (dr 85:15). The stereochemistry of the major product was determined by NOE experiments[12] and by ^{1}H NMR coupling constant analysis. Similar analysis of the minor diastereoisomer **1k′** revealed it to be epimeric at the benzylic stereogenic center (C*) of the tetrahydroisoquinoline ring.[12] As **2g** and **3a** were racemic, a moderate degree of molecular recognition between the pairs of reacting enantiomers was witnessed resulting in a predominant diastereomeric product with five defined stereogenic centers.

The high diastereocontrol in the majority of the reactions is notable and worthy of further comment. Assuming the mechanism involves a reversible and unselective nitro-Mannich reaction[6e] followed by an irreversible lactamization step, it is plausible that the overall reaction diastereomeric excess is determined by the differential rates of lactamization of the diastereomeric intermediates. This in turn will be determined by the relative positioning of the substituents around the newly forming piperidinone ring in the transition state; from the observed product structures, equatorial placement at C6 is preferred. Equatorial placement of the nitro group at C5 is also likely but not necessary.[13] This Curtin−Hammett principle argument is supported in part by the lowered diastereoselectivity in the formation of **1j**, presumably due to the higher nucleophilicity and greater conformation freedom of the pyrrolidine ring system.

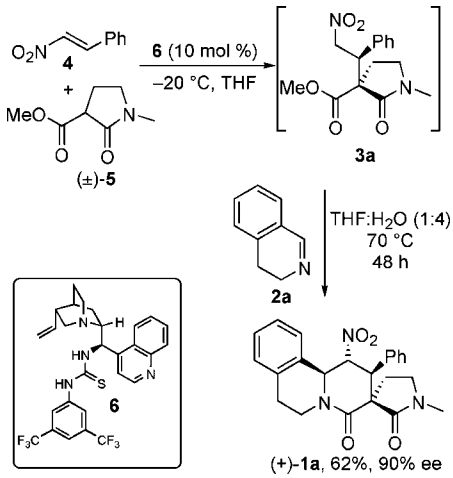
The argument is also supported in part by the stereocontrol observed in the formation of **1k** where equatorial placement of substituents around the central piperidone ring *and* the tetrahydroisoquinoline is most favored in the transition state leading to product.

With the nitro-Mannich/lactamization cascade optimized and scoped, we then investigated the feasibility of a one-pot enantio- and diastereoselective three-component coupling reaction. For enantiocontrol, we wanted to exploit bifunctional catalyst **6**[7] in the Michael addition step. For this to be possible, the solvent choice was important as protic solvents such as water are not compatible with the Michael addition step but beneficial for the cascade. Thus, THF was chosen owing to its suitability in the Michael addition reaction and its miscibility with water which could be added to the pot along with the cyclic imine. Thus β-nitrostyrene **4**[14] and **5**[15] were reacted at −20 °C until complete, then imine **2a** was

(10) Only one diastereomer was observed by ^{1}H NMR spectroscopy.
(11) Klijn, J. E.; Engrerts, B. F. N. *Nature* **2005**, *435*, 746.
(12) See Supporting Information for details.
(13) Postcyclization equilibration at C5 would give the same outcome.
(14) Liu, J.-T.; Yao, C.-F. *Tetrahedron Lett.* **2001**, *42*, 6147.
(15) For the synthesis of racemic nucleophile **5**, see Supporting Information.
(16) Absolute stereochemistry assigned by analogy with previous results of Michael addition to nitroolefin electrophiles catalyzed by **6**; see ref 7b.

added neat in one portion followed by additional water (4 volume equiv) and the mixture heated to 70 °C for 48 h. Pleasingly, the desired product was isolated in 62% yield as a single diastereoisomer with an ee of 90% (Scheme 3).[16]

Scheme 3. Enantio- and Diastereoselective, One-Pot, Three-Component Michael/Nitro-Mannich/Lactamization Sequence



As well as demonstrating its compatibility with bifunctional catalyst **6**, this one-pot reaction sequence confirmed the configurational stability of the Michael adducts during the nitro-Manich/lactamization cascade.

In summary, an efficient stereoselective nitro-Mannich/lactamization reaction cascade of γ-nitro esters and cyclic imines for the preparation of multicyclic piperidinone ring-containing structures has been developed. The reaction is broad in scope and stereoselective and may be coupled to the asymmetric nitroolefin Michael addition reaction as part of an enantio- and diastereoselective multicomponent process. Further developments to this work and its application in total synthesis are ongoing in our laboratory, and the results will be disclosed in due course.

Acknowledgment. We gratefully acknowledge the European Commission for a Marie Curie Fellowship [to P.J. (MEIF-CT-2006-039981)].

Supporting Information Available: Experimental procedures and spectroscopic data for products **1**−**3** and **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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