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Synthesis of Diazepinones via Intramolecular Transamidation

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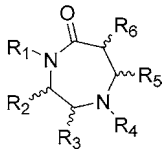
ABSTRACT



The synthesis of a collection of bicyclic fused azepinones via an intramolecular β-lactam ring-opening strategy is reported. Depending on the chirality of the various inputs, complete stereocontrol of product formation is achieved.

The concept of developing synthetic pathways leading to the efficient (3−5 step) synthesis of collections of small molecules having rich skeletal and stereochemical diversity has recently gained importance.[1] Complexity-generating reactions such as cycloadditions[2] are ideally suited for this purpose, since they generate molecular frameworks that can be potentially converted into alternate scaffolds via inter- and intramolecular reactions, and several examples of this approach in natural product-like synthesis have been reported.[3] In addition to the design of synthetic strategies affording compounds with broad representations in chemistry space, ideally, the library members should also possess suitable synthetic handles for facile post-screening manipulations.

The Staudinger reaction[4] has proven to be a versatile method for the synthesis of β-lactams, and this methodology has been used in the solid-phase synthesis of a combinatorial library by Gallop et al.[5] We envisioned that the use of a bifunctional amine component in the imine formation followed by the [2 + 2] cycloaddition would afford diastereomeric mixtures of β-lactams **3**. Unmasking the latent amine functionality followed by intramolecular ring opening would result in the formation of seven-membered lactams such as **4**.

There has been considerable interest in the synthesis of 7−10-membered lactams as constituents of natural products[6] and cell-signaling pathway inhibitors;[7] however, these ring structures are difficult to access using conventional ring-closure methods.[8] Typically, approaches toward the synthesis of these rings have included attempted cyclizations of dipeptides[9] or intramolecular cyclization[10] of an appropriately functionalized precursor moiety. Recently, an elegant intramolecular Staudinger ligation strategy has been reported that provides access to 7−9-membered lactams.[11] In this manu-

(1) Schreiber, S. L. *Science* **2000**, *287*, 1964.
(2) (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (c) Inanaga, K.; Takasu, K.; Ihara, M. *J. Am. Chem. Soc.* **2004**, *126*(5), 1352. (d) Padwa, A., Pearson, W. H., Eds. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Wiley: New York, 2002; p 59.
(3) (a) Belanger, G.; Deslongchamps, P. *J. Org. Chem.* **2000**, *65*, 7070. (b) Lee, D.; Sello, J. K.; Schreiber, S. L. *Org. Lett.* **2000**, *2*, 709. (c) Brooking, P.; Crawshaw, M.; Hird, N. W.; Jones, C.; MacLachlan, W. S.; Readshaw, S. A.; Wilding, S. *Synthesis* **1999**, 1986.
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(5) Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253.
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(7) Breitenlechner, C. B.; Wegge, T.; Berillon, L.; Graul, K.; Marzenell, K.; Friebe, W.; Thomas, U.; Schumacher, R.; Huber, R.; Engh, R. A.; Masjost, B. *J. Med. Chem.* **2004**, *47* (6), 1375.
(8) (a) Nubbemeyer, U. *Top. Curr. Chem.* **2001**, *216*, 125. (b) Evans, P. A.; Holmes, A. B. *Tetrahedron* **1991**, *47*, 9131.
(9) Bosch, I.; Romea, P.; Urpí, F.; Vilarrasa, J. *Tetrahedron Lett.* **1993**, *34*, 4671.
(10) (a) Bieräugel, H.; Jansen, P. T.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Org. Lett.* **2002**, *4*, 2673. (b) Bieräugel, H.; Schoemaker, H. E.; Hiemstra, H.; van Maarseveen, J. H. *Org. Biomol. Chem.* **2003**, *1*, 1830.
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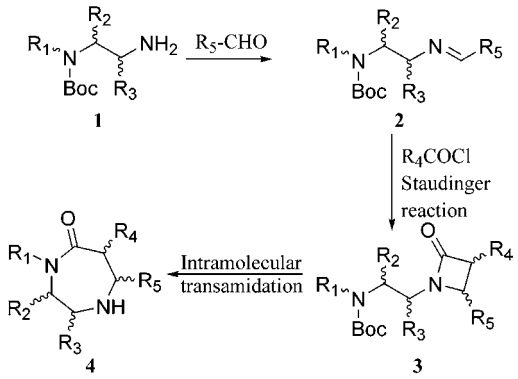
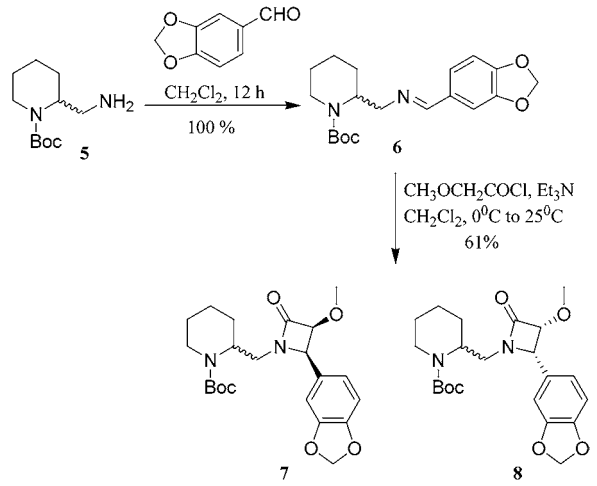
Scheme 1. Synthesis of Macrolactams via Intramolecular Ring Expansion



script, we report a concise synthetic strategy outlined in Scheme 1 for the synthesis of seven-membered lactams, wherein substitution patterns of up to six positions can be varied, four of these in a stereospecific manner.

As a model reaction, the imine formed via the treatment of 2-aminomethylpiperidine-1-*tert*-butyl carboxylic acid ester and 3,4-methylenedioxybenzaldehyde was reacted with methoxyacetyl chloride, first at 0 °C and then at room temperature, to afford **7** and **8** as a mixture of diastereomers (diastereomeric ratio = 48:52, Scheme 2). The cis configuration of

Scheme 2



the subtituents on the β-lactam was confirmed by X-ray analysis (Figure 1) and is consistent with prior reports of the propensity for these [2 + 2] cycloadditions to afford only the cis adducts.[12]

Starting with an enantiomerically enriched amine such as (*R*)-2-aminomethyl pyrrolidine **9** afforded β-lactams **11** and

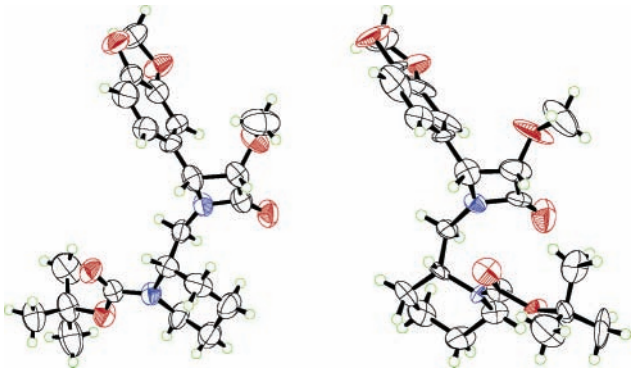
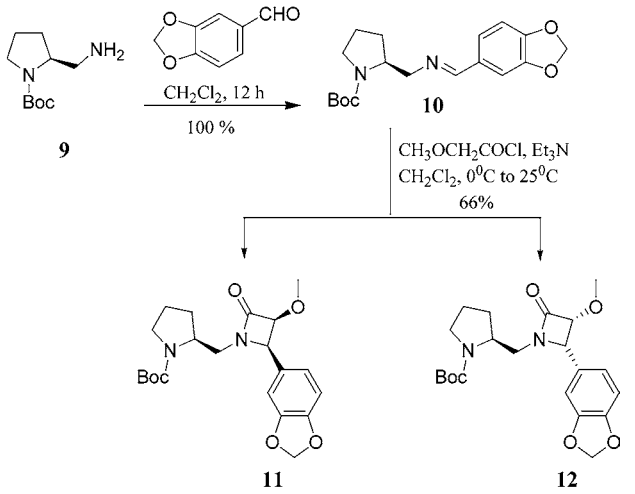


Figure 1. Cycloadducts from the [2 + 2] cycloaddition of **6** and CH_3OCH_2COCl to afford **7** and **8**.

12 exclusively as a 47:53 diastereomeric mixture, whereas the corresponding (*S*)-2-aminomethyl pyrrolidine afforded the epimers of **11** and **12** (Scheme 3).

Scheme 3



Further stereocontrol of the intermediate β-lactam product composition can be achieved via use of the ketene generated from the Evans−Sjogren oxazolidinone[13] to afford the β-lactam as a single diastereomer (data not shown).

Deprotection of the *tert*-butoxycarbonyl amino moiety of **8** using 4 N HCl/dioxane followed by heating the resulting amine **13** in *N*,*N*-dimethylformamide at 200 °C for 40 min (twice for 20 min each) in a sealed tube using single-mode microwave irradiation[14] afforded facile conversion to the desired [1,4]diazepin-5-one in 70% yield (Scheme 4),

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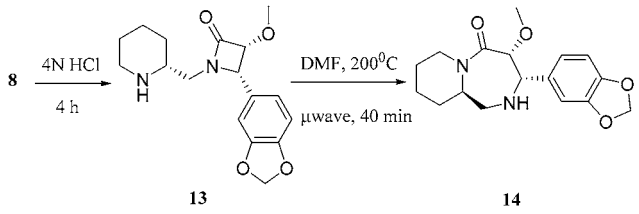
Scheme 4



Alternately, heating **8** in acetonitrile in a sealed tube at 190 °C using single-mode microwave irradiation for 45 min resulted in the formation of **14** in 50% yield over two steps. It is important to note that no epimerization was observed in any of the compounds synthesized in this study at these elevated temperatures.

Several interesting trends were observed in the intramolecular transamidation. When the amine input in the β-lactam-forming reaction was 2-aminomethyl piperidine, the deprotected β-lactams had to heated in the microwave at elevated temperatures to effect transamidation. However, when the amine input was either a (±)3-aminopiperidine or 2-aminomethyl thiazolidine, the intramolecuar transamidation occurred at room temperature during the course of removal of the *tert*-butoxycarbonyl protecting group. Furthermore, in both these cases, the intermediate β-lactam was susceptible to ring opening with either water or methanol to afford the corresponding propionic acid or its methyl ester, respectively.

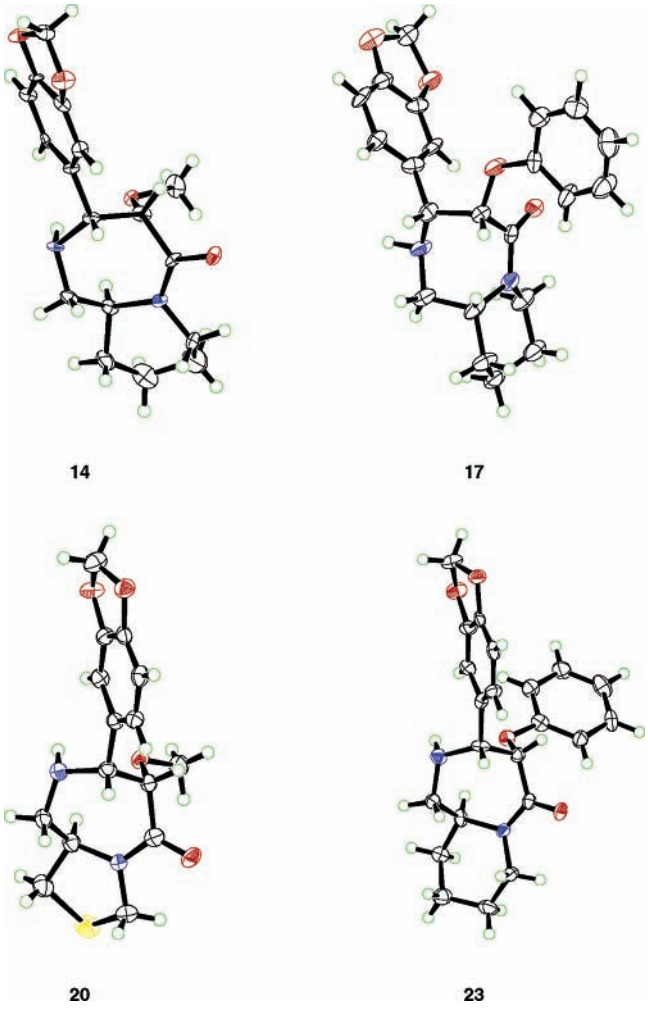


Figure 2. Crystal structures of **14**, **17**, **20**, and **23** (epimer of **17**).

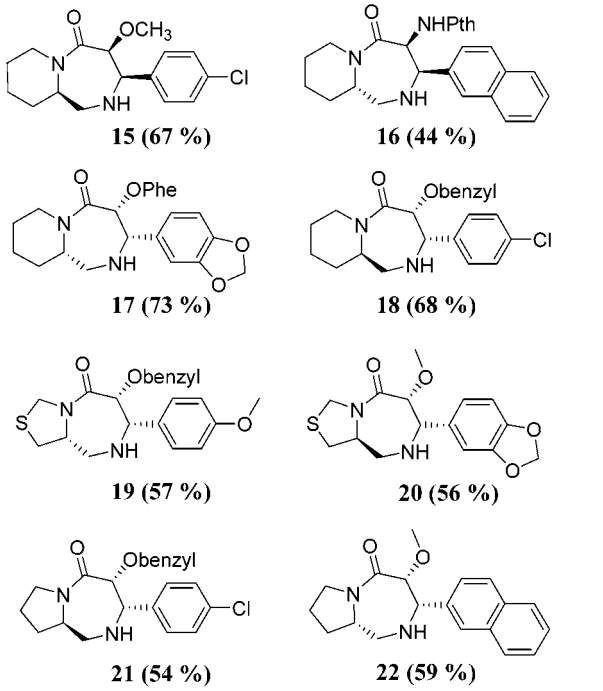


Figure 3. Representative [1,4]diazepin-5-ones synthesized by the intramolecular transamidation of β-lactams with tethered amines.

This methodology has been used to synthesize a library of 120 [1,4]diazepin-5-ones, some of which are shown in Figure 3. Initial experiments indicate that this methodolgy can be used for the synthesis of [1,5]diazacan-2-one, 1,5-diaza-bicyclo[4.3.1]decan-2-one, and 1,5-diaza-bicyclo[4.1.1]-octan-2-one ring systems (data not shown) via the use of the appropriate amine input in the Staudinger reaction. These represent interesting examples of template diversity (as opposed to functional group diversity) that can be accomplished using similar chemical manipulations in the design of novel ligands.

The *O*-benzyl and *N*-phthalamido moieties can be deprotected[15] to afford, along with the N1-nitrogen, convenient

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(18) During the course of this work, two reports describing the use of β-lactams as useful precursors for the synthesis of macrolactams have appeared. (a) Banfi, L.; Guanti, G.; Rasparini, M. *Eur. J. Org. Chem.* **2003**, *7*, 1319. (b) Klapars, A.; Parris, S.; Anderson, K. W.; Buchwald, S. L. *J. Am. Chem. Soc.* **2004**, *126* (11), 3529.

synthetic handles for further structural manipulation of these low-molecular-weight templates.[16]

Finally, it is anticipated that this methodology can be extended to access bicyclic oxazepinones,[17] and future communications will report on these studies.[18]

Acknowledgment. Dr. Tom Pagano and Rodger Hendry from the Abbott Structural Chemistry group performed the high-resolution NMR and X-ray crystallography experiments, respectively.

Supporting Information Available: Experimental details and characterization data of representative diazapenones **15**−**22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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