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Synthesis of Medium-Sized Cyclic Amines by Selective Ring Cleavage of Sulfonylated Bicyclic Amines

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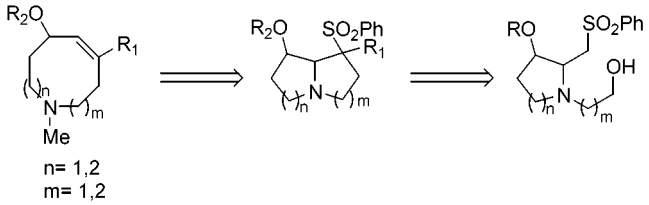
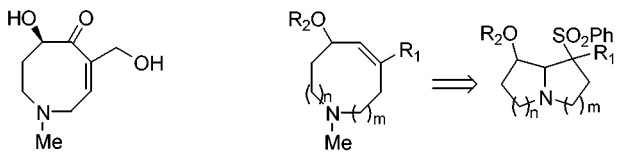
ABSTRACT



An efficient method of synthesis of functionalized medium-sized cyclic amines (eight- to ten-membered rings) by selective ring opening of sulfonylated bicyclic pyrrolizidine, indolizidine, and quinolizidine compounds is described. The key step is the selective cleavage of the central C–N bond of the bicyclic amine by means of a Julia-like desulfonylation process.

As a result of their interesting biological properties, the synthesis of functionalized medium-sized cyclic amines has received considerable attention in recent years.[1] For example, among the most common necic bases present in natural pyrrolizidine alkaloids, otonecine[2] has a unique structure of eight-membered cyclic amine, arising biosynthetically from the ring opening of a bicyclic pyrrolizidine precursor.[3] We describe herein that oxygenated eight-membered cyclic amines related to otonecine, as well as the homologous nine- and ten-membered rings, can be readily prepared by an unprecedented biomimetic ring cleavage process from pyrrolizidine, indolizidine, or quinolizidine bicyclic compounds. This procedure is based on the selective cleavage of the central C−N bond directed by an olefin-forming desulfonylation reaction[4] (Scheme 1).

Scheme 1



A few years ago, we reported that 3-oxygenated 2-sulfonylmethyl pyrrolidines and piperidines can be efficiently prepared by cyclization of aminosubstituted γ-oxygenated

(1) Most of the recent precedents on synthesis of medium-sized cyclic amines are based on ring closing methathesis procedures; see for instance: (a) Meyers, A. I.; Downing, S. V.; Weiser, M. J. *J. Org. Chem.* **2001**, *66*, 1413. (b) Heinrich, M. R.; Steglich, W. *Tetrahedron Lett.* **2001**, *42*, 3287. (c) Fujiwara, T.; Kato, Y.; Takeda, T. *Heterocycles* **2000**, *52*, 147. (d) Paquette, L. A.; Leit, S. M. *J. Am. Chem. Soc.* **1999**, *121*, 8126. (e) Visser, M. S.; Heron, N. M.; Didiuk, M. T.; Sagal, J. F.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1996**, *118*, 4291. (f) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108. For other recent synthetic approaches, see for instance: (g) Donohoe, T. J.; Raoof, A.; Linney, I. D.; Helliwell, M. *Org. Lett.* **2001**, *3*, 861 (ring opening of bicyclic compounds). (h) Bergmann, D. J.; Campi, E. M.; Jackson, W. R.; Patti, A. F.; Saylik, D. *Tetrahedron Lett.* **1999**, *40*, 5597 (cyclization of aminoalkenes). (i) Morís-Varas, F.; Quian, X.-H.; Wong, C.-H. *J. Am. Chem. Soc.* **1996**, *118*, 7647 (cyclization of aminoaldehydes). (j) Kitano, T.; Shirai, N.; Motoi, M.; Sato, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2851 (ring enlargement of six-membered rings).

(2) For the synthesis of (±)-otonecine, see: (a) Vedejs, E.; Galante, R. J.; Goekjian, P. G. *J. Am. Chem. Soc.* **1998**, *120*, 3113. (b) Niwa, H.; Sakata, T.; Yamada, K. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 2345. (c) Niwa, H.; Uosaki, Y.; Yamada, K. *Tetrahedron Lett.* **1983**, *24*, 5731.

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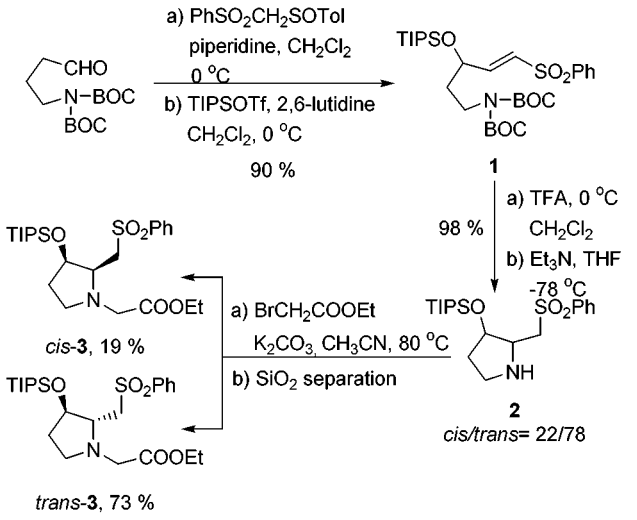
α,β-unsaturated sulfones, which are readily available by condensation of aminoprotected aldehydes with sulfonyl sulfinyl methanes.[5] Thus, the cyclization of the α,β-unsaturated sulfone **1** by initial N-BOC deprotection (CF_3CO_2H, CH_2Cl_2) and addition of Et_3N quantitatively afforded the pyrrolidine **2** as an inseparable 22/78 mixture of *cis*/*trans* isomers.[5a] Alkylation of **2** with ethyl bromoacetate (K_2CO_3, CH_3CN) and chromatographic separation gave *cis*-**3** and *trans*-**3** in 19% and 73% yields, respectively (Scheme 2).

Scheme 2



The pyrrolidines *cis*-**3** and *trans*-**3** were converted into the sulfonyl pyrrolizidines **5** (79% overall yield) and **6** (68% overall yield), respectively, by the following straightforward three-step sequence: reduction of the ester moiety ($LiAlH_4$, THF, 0 °C), mesylation (MsCl, Et_3N, CH_2Cl_2, 0 °C), and intramolecular alkylation of the α-sulfonyl carbanion (LHMDS, THF, 0 °C). The stereochemical assignment of pyrrolizidines **5** and **6** was unambiguously established by NOESY experiments (Figure 1).

With sulfones **5** and **6** in hand, we reasoned that by improving the leaving group ability of the β-amino moiety by conversion into its ammonium salt, a Julia-like desulfonylation reaction with C−C double bond formation and simultaneous cleavage of the C−N bond could be feasible.

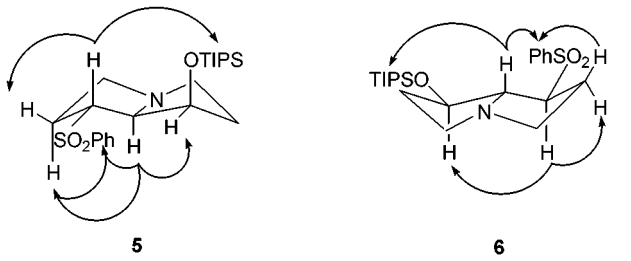
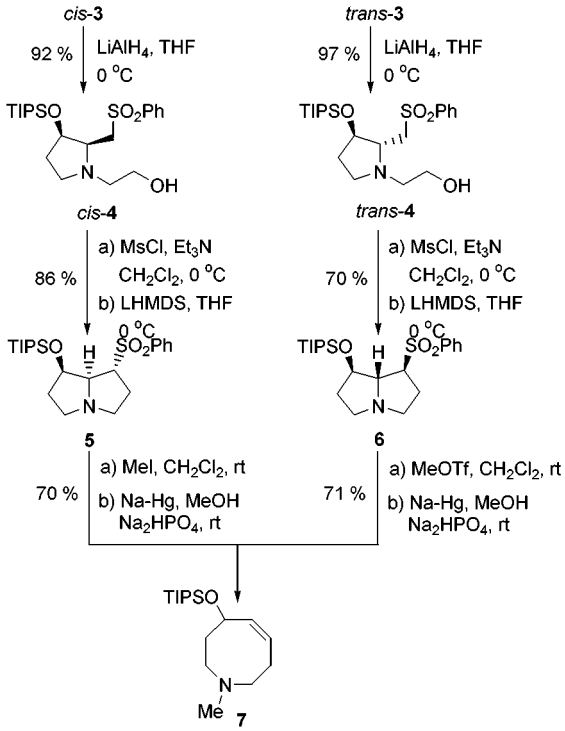


Figure 1. Significant NOESY correlations for the stereochemical assignment of pyrrolizidines **5** and **6**.

Gratifyingly, *N*-methylation of either **5** or **6** with excess of methyl iodide or methyl triflate[6] and further treatment of the crude resulting ammonium salt with Na−Hg under typical desulfonylation conditions[7] (Na_2HPO_4, MeOH, rt) afforded in both cases the eight-membered unsaturated cyclic amine **7** in good yields (70% and 71% yields, respectively) and as the only isolated product (Scheme 3).

Scheme 3



Interestingly, this ring cleavage process also took place from C-substituted sulfonyl pyrrolizidines. Thus, the treatment of the α-sulfonyl carbanion of **6** with dry formaldehyde

(3) For reviews on the synthesis, natural occurrence, and biological activities of pyrrolizidine alkaloids, see: (a) Mattocks, A. R. *Chemistry and Toxicology of Pyrrolizidine Alkaloids*; Academic Press: London, 1986. (b) *Natural Occurring Pyrrolizidine Alkaloids*; Rizk, A.-F. M., Ed.; CRC: Boston, 1991. (c) Casiraghi, G.; Zanardi, F.; Rassu, G.; Pinna, L. *Org. Prep. Proced. Int.* **1996**, *28*, 641. (d) Robins, D. J. *Nat. Prod. Rep.* **2000**, *17*, 213. (e) Liddell, J. R. *Nat. Prod. Rep.* **2000**, *17*, 455.

(4) For reviews on desulfonylation reactions and Julia reactions, see: (a) Nájera, C.; Yus, M. *Tetrahedron* **1999**, *55*, 10547. (b) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, 1993. (c) Kocienski, P. J., *Phosphorus Sulphur* **1985**, *24*, 97. For a recent reference, see: (d) Markó, I. E.; Murphy, F.; Kumps, L.; Ates, A.; Touillaux, R.; Craig, D.; Carballares, S.; Dolan, S. *Tetrahedron* **2001**, *57*, 2609.

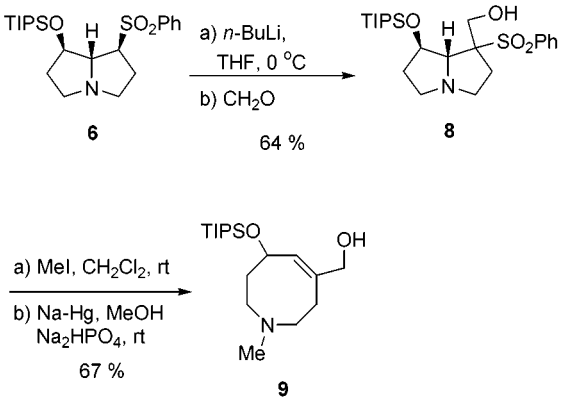
(5) (a) Carretero, J. C.; Gómez Arrayás, R. *J. Org. Chem.* **1998**, *63*, 2993. (b) Carretero, J. C.; Gómez Arrayás, R.; Storch de Gracia, I. *Tetrahedron Lett.* **1997**, *38*, 8537. (c) Carretero, J. C.; Gómez Arrayás, R.; Storch de Gracia, I. *Tetrahedron Lett.* **1996**, *37*, 3379. For the preparation of the starting amino-protected butyraldehyde, see Supporting Information.

(6) In all cases similar results were obtained by using methyl iodide or methyl triflate as alkylating agents. A large excess of these reagents (5 or 2 equiv, respectively) was required in order to ensure the complete methylation of the starting amine.

(7) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, 3477.

afforded the hydroxymethyl derivative **8** as a 5:1 mixture of epimers at C-1 (64% yield). N-Methylation of **8** with methyl iodide followed by reaction with Na−Hg (Na_2HPO_4, MeOH) led to the hydroxymethyl eight-membered cyclic amine **9** (67% yield), having the same carbon skeleton as otonecine. It is to be noted that although in this case there are two possible leaving groups at β-position with regard to the sulfone moiety, the hydroxyl group and the ammonium salt, the reaction occurred exclusively by elimination of the nitrogen moiety (Scheme 4).

Scheme 4



To explore the structural scope of this two-step selective cleavage process of bicyclic amines, next we studied the case of indolizidine and quinolizidine skeletons, which could yield nine-membered and ten-membered cyclic amines, respectively.

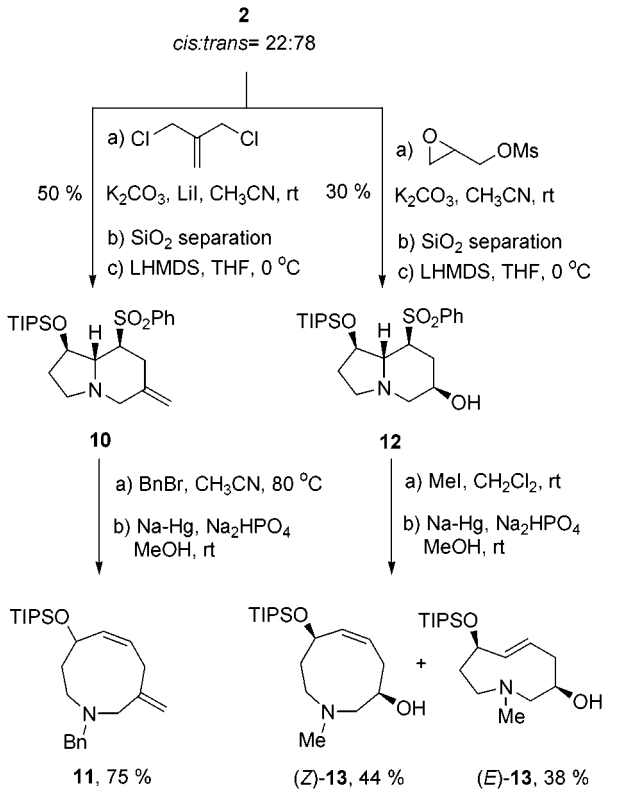
The 8-sulfonyl indolizidine compounds **10** and **12** were readily prepared from **2** (*cis:trans* = 22:78) by stepwise dialkylation reactions with 3-chloro-2-chloromethylpropene and glycidyl mesylate, respectively, as previously reported by us.[5a] *N*-Benzylation of **10** with benzyl bromide (CH_3CN, 80 °C) and desulfonylation (Na−Hg, Na_2HPO_4, MeOH, 0 °C) gave the nine-membered ring **11** in 75% yield (Scheme 5). It is worth noting that the formation of conjugated dienes by isomerization of the exocyclic double bond was not detected.

On the other hand, *N*-methylation of **12** (MeI, CH_2Cl_2, rt) and reaction with Na−Hg afforded in this case a mixture of both alkene diastereomers (*Z*)-**13** ($J_{5,6}$ = 10.9 Hz) and (*E*)-**13** ($J_{5,6}$ = 16.2 Hz), which were separated by flash chromatography (44% and 38% yields, respectively).

As extension of this procedure to a quinolizidine derivative, compound **16**[8] was readily prepared from the known piperidine **14**[5c] by reduction of the ester moiety ($LiAlH_4$), mesylation (MsCl, Et_3N), and intramolecular alkylation (LHMDS). Methylation of **16** with methyl triflate and reaction with Na−Hg afforded the 10-membered cyclic

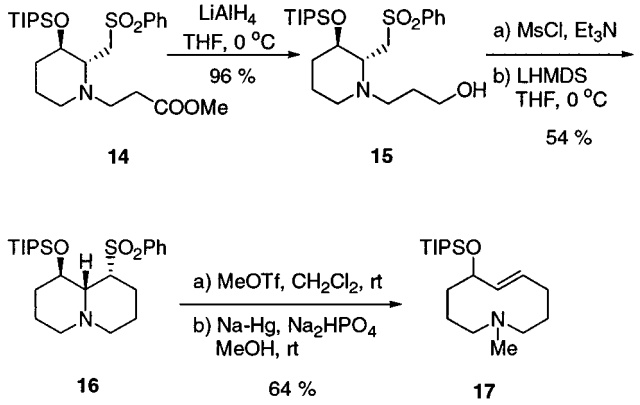
(8) The relative configuration of compound **16** was established by ^1H NMR ($J_{1,9a}$ = 8.9 Hz and $J_{9,9a}$ = 2.4 Hz in $CDCl_3$).

Scheme 5



amine **17** (64% yield). Unlike the case of pyrrolizidine and indolizidine skeletons, the ring expansion of the ammonium salt of the quinolizidine **16** produced exclusively the alkene of *trans* configuration ($J_{6,7}$ = 15.8 Hz) (Scheme 6).

Scheme 6



In summary, functionalized N-alkylated medium-sized cyclic amines (eight- to ten-membered rings) can be prepared by a Julia-like desulfonylation process from readily available sulfonylated pyrrolizidine, indolizidine, and quinolizidine bicyclic compounds. By using enantiomerically pure precur-

sors,[9] the application of this procedure to the enantioselective synthesis of otonecine is underway.

Acknowledgment. Financial support of this work by the *Ministerio de Ciencia y Tecnología* (BQU2000-0226) and the *Comunidad de Madrid* (project 07B/28/1999) is gratefully acknowledged. F.I. thanks the *Comunidad de Madrid* for a postdoctoral fellowship.

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

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(9) Carretero, J. C.; Domínguez, E. *J. Org. Chem.* **1992**, *57*, 3867.