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A Concise and Convergent Route to 5,8-Disubstituted Indolizidine and 1,4-Disubstituted Quinolizidine Ring Cores by Diastereoselective Aza-Diels–Alder Reaction

José Barluenga,* Carlos Mateos, Fernando Aznar, and Carlos Valdés

Instituto Universitario de Química Organometálica "Enrique Moles", Unidad asociada al C.S.I.C., Universidad de Oviedo, 33071 Oviedo, Spain

barluenga@sauron.quimica.uniovi.es

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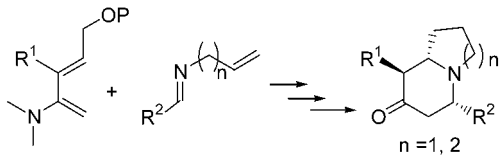
ABSTRACT



A short and convergent synthesis of 5,8-disubstituted indolizidine and 1,4-quinolizidine scaffolds is described. The key steps of the synthetic pathway are the aza-Diels–Alder reaction of a 2-aminodiene with an *N*-allyl or *N*-homoallylaldimine and a ring-closing metathesis. The bicyclic alkaloid analogues are obtained with total diastereoselectivity and through a common pathway.

The bicyclic structural motifs of indolizidine and quinolizidine are found in a great number of naturally occurring alkaloids, isolated from a variety of terrestrial and marine sources such as bacteria, fungi, higher plants, invertebrates, and vertebrates. Many of the members of these families of alkaloids display a wide range of physiological activity. The 5,8-disubstituted indolizidines **I** and 1,4-disubstituted quinolizidines **II** are among the most common structural patterns (Figure 1).[1]

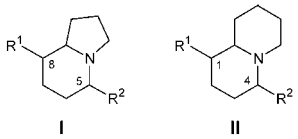


Figure 1. Indolizidine and quinolizidine scaffolds.

Accordingly, novel strategies for the stereoselective synthesis of these "izidine"-type alkaloids continue to gain great attention.

However, although there are in the literature a number of syntheses of particular members of these types of alkaloids, mainly of indolizidines, most of them require a large number of steps and are restricted to a very particular structure.[2]

On the other hand, in the recent years our group has been exploring several synthetic applications of 2-amino-1,3-butadienes in the aza-Diels−Alder reaction.[3,4] In a previous paper, we described the synthesis of the natural indolizidine

(1) (a) Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, Chapter 1. (b) Michael, J. P. *Alkaloids Chem. Biol.* **2001**, *55*, 91. (c) Michael, J. P. *Nat. Prod. Rep.* **2001**, *5*, 520 and references therein.

(2) Some relevant references regarding enantioselective synthesis of indolizidine and quinolizidine alkaloids: (a) Back, T. G.; Nakajima, K. *J. Org. Chem.* **2000**, *65*, 4543−4552. (b) Pearson, W. H.; Bergmeier, S. C.; Willians, J. P. *J. Org. Chem.* **1992**, *57*, 3977. (c) Kawakami, T.; Ohtake, H.; Arakawa, H.; Okachi, T.; Imada, Y.; Murahashi, S. *Org. Lett.* **1999**, *1*, 107−110. (d) Comins, D. L.; LaMunyon, D. H.; Chen, X. *J. Org. Chem.* **1999**, *64*, 3736−3740. (e) Kündig, E. P.; Ratni, H. *Org. Lett.* **1999**, *1*, 1997−1999.

(3) (a) Barluenga, J.; Aznar F.; Valdés, C.; Cabal, M. P.; *J. Org. Chem.* **1993**, *58*, 3391−3396. (b) Barluenga, J.; Aznar, F.; Valdés, C.; Martín, A.; García-Granda, S.; Martín, E. *J. Am. Chem. Soc.* **1993**, *115*, 4403−4404. (c) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C.; Fernández, M.; Cabal, M. P.; Trujillo, J. *Chem. Eur. J.* **1996**, *2*, 805−811. (d) Barluenga, J.; Aznar, F.; Valdés, C.; Ribas, C. *J. Org. Chem.* **1998**, *63*, 3918−3924.

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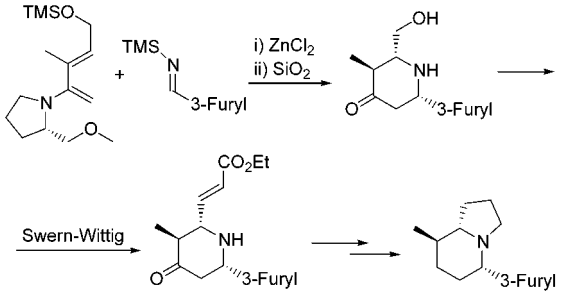
(−)-Nupharamine by subsequent transformations of an enantiopure piperidone, obtained by cycloaddition with an imine (Scheme 1).[5]

Scheme 1. Asymmetric Synthesis of (−)-Nupharamine Obtained from a Chiral 2-Aminodiene and a Trimethylsilylimine



These results encouraged us to initiate a research project oriented toward the development of a new methodology for the synthesis of structurally diverse indolizidines and quinolizidines that will allow for the rapid assembly of both bicyclic scaffolds through a common pathway and that may be adapted in a future project to solid-supported parallel synthesis.[6]

We envisioned a very convergent route to these classes of bicyclic alkaloids, in which the last annelation process should be a ring-closing-metathesis reaction (Figure 2).[7] The

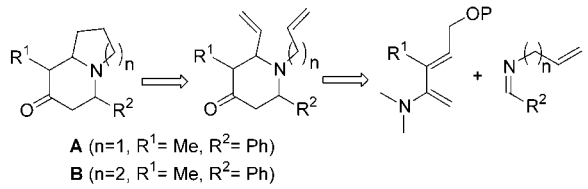


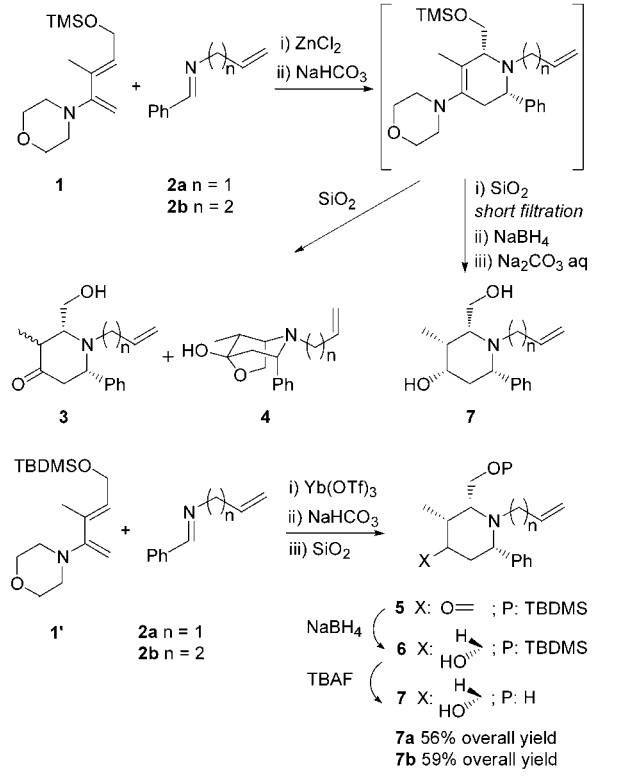
Figure 2. Retrosynthetic analysis of bicyclic alkaloids.

heterocyclic diene required for the cyclization could be obtained directly by the cycloaddition reaction of a functionalized 2-aminodiene with an *N*-alkenyl-substituted imine, in which the length of the alkyl chain will determine the size of the new ring. In this manner, the relatively complex bicyclic structures would be assembled in a stereoselective fashion in a very reduced number of steps. We report herein our model studies, which have led to a convenient route for the diastereoselective synthesis of substituted indolizidines and quinolizidines.

Indolizidinone **A** and quinolizidinone **B** were chosen as model synthetic targets. The ketone functionality was carried along the process, since the presence of an additional functional group may allow for further modifications that will increase the structural diversity. To keep the number of steps to a minimum, the ketone functionality was not protected, and therefore a strategy compatible with its presence was required.

The synthesis of the functionalized *N*-allyl- and *N*-homoallylpiperidones was not straightforward. Although the cycloaddition reaction between the aminodiene **1** and the N-substituted imines **2** occurred mildly in a diasteroselective fashion in the presence of $ZnCl_2$, the simultaneous hydrolysis of the enamine and the silyl ether by filtration through a silica gel column gave rise to a mixture of two compounds. Deprotection of the alcohol followed by enamine hydrolysis gave the same result. The observation of two different compounds was attributed to the presence of an equilibrium between the desired hydroxyketone **3** and the hemiketal **4** (Scheme 2).[8]

Scheme 2. Cycloaddition Reactions of 2-Aminodienes with *N*-Alkenylimines



(4) For reviews, see: (a) Boger, D. L.; Weinreb, S. M. *Hetero Diels−Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987, Chapter 2. (b) Waldmann, H. *Synthesis* **1994**, *535*. (c) Weinreb, S. M. *Acc. Chem. Res.* **1985**, *18*, 16. (d) Waldmann, H. *Synlett* **1995**, 133. (e) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, 190. (f) Weinreb, S. M.; *Top. Curr. Chem.* **1997**, *190*, 131. (g) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (h) Yao, S.; Saaby, S.; Hazell, R. G.; Jørgensen, K. A. *Chem. Eur. J.* **2000**, *6*, 2435−2448.

(5) Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1999**, *64*, 3736−3740.

(6) Recent reviews concerning solid-phase organic synthesis: (a) Dörwald, F. Z. *Organic Chemistry in Solid Phase*; Wiley−VCH: Weinheim, Germany, 2000. (b) Seneci, P. *Solid-Phase Synthesis and Combinatorial Technologies*; Wiley: New York, 2000. (c) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549−1581. (d) Sammelson, R. E.; Kurth, M. J. *Chem. Rev.* **2001**, *101*, 137−202. (e) Guillier, F.; Orain, D.; Bradley, M. *Chem. Rev.* **2000**, *100*, 2091−2157. (f) Wendeborn, S.; de Mesmaeker, A.; Wolfgang, K.; Brill, D.; Berteina, S. *Acc. Chem. Res.* **2000**, *32*, 215−224.

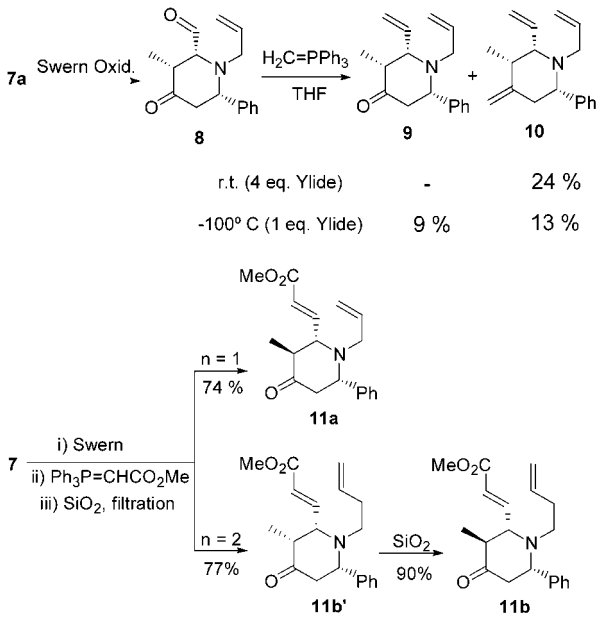
(7) For a recent example of the synthesis of bicyclic alkaloids making use of the RCM reaction, see: Liras, S.; Allen, M. P.; Blake, J. F. *Org. Lett.* **2001**, *3*, 3483−3486.

It seemed that hydroxy and ketone functionalities could not coexist in this particular structure. In a first approximation, the problem was overcome by hydrolysis of the enamine by filtration through a very short SiO_2 pad, in an attempt to minimize the cleavage of the TMS ether, followed by in situ reduction of the ketone with $NaBH_4$ and final deprotection of the silyl ether by basic hydrolysis. This strategy led to dihydroxypiperidine **7**, although with very poor yields.[9]

Therefore, we moved to the more robust TBDMS ether as protecting group for the hydroxy functionality in the starting 2-aminodiene. The best results in the cycloaddition reaction were achieved with diene **1′** by the use of $Yb(OTf)_3$ (20 mol %) as a Lewis acid. Then, hydrolysis of the enamine moiety by SiO_2 filtration, stereoselective reduction of the ketone with $NaBH_4$, and deprotection of the TBDMS ether by treatment with tetrabutylammonium fluoride led to dihydroxypiperidines **7**, which were isolated in fair overall yields based on the starting imine, as single diastereoisomers.[10]

The next step was the conversion of diols **7** into the dienes required for the ring-closing metathesis. Our first efforts were conducted toward the simple construction of terminal olefins, which are known to react smoothly with Grubbs catalyst.[11] Therefore, diol **7a** was oxidized under the Swern conditions yielding the dicarbonyl compound **8**, which was subsequently exposed to the simplest phosphorus ylide at a low temperature. However, the extremely mild conditions applied (1 equiv of ylide, −100 °C) were not sufficient to distinguish between the two carbonyl groups, and a mixture of mono- and dimethylenated compounds **9** and **10** were formed. After some experimentation, we found that the formation of **10** (less interesting because of the loss of the ketone functionality) could not be avoided but induced with total selectivity, although with low yields (Scheme 3).

Scheme 3. Synthesis of Dienes by a Swern−Wittig Sequence

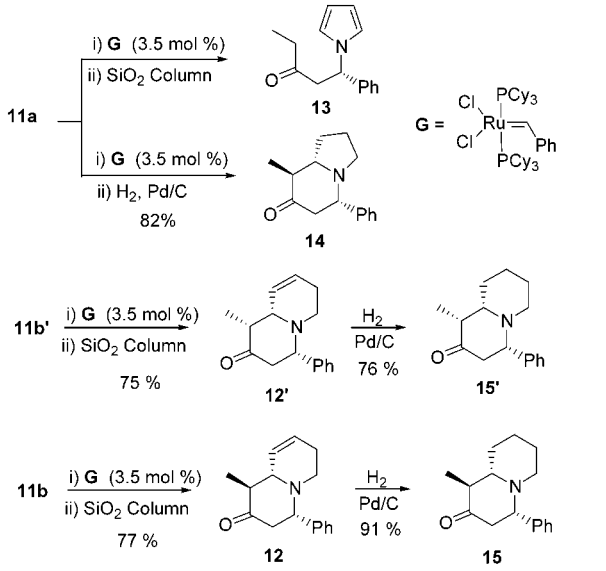


To accomplish the olefination with superior chemoselectivity and more efficiently, we examined the use of a less reactive, stabilized phosphorus ylide like methylenemethoxycarbonyltriphenylphosphorane. Thus, when dihydroxypiperidine **7** was subjected to Swern oxidation followed by Wittig reaction in a one-pot procedure, the α,β-unsaturated ester **11** was obtained with total chemoselectivity and fair yields, leaving the ketone functionality untouched (Scheme 3).

It should be noted that esters **11** underwent complete epimerization of the stereogenic center bearing the methyl group after silica gel chromatography, as we observed after comparison of the proton NMR spectra of the crude and isolated compounds. Interestingly, in the case of the cycloadduct **11b**, derived from *N*-homoallylimine, it was possible to obtain also the nonepimerized piperidone (kinetic isomer) **11b′** via rapid filtration. The subsequent reaction sequence was carried out with both isomers independently.

The ring-closing metathesis was successfully performed with **11a** using Grubbs catalyst **G**.[12] However, the unsaturated bicyclic derivative could not be purified as it underwent aromatization to pyrrol **13**. Therefore, the crude reaction mixture was hydrogenated in situ to afford indolizidinone **14**. On the other hand, **11b** and **11b′** underwent RCM under the same reaction conditions to generate the unsaturated bicyclic products **12′** and **12**, respectively, which were properly isolated independently. Final catalytic hydrogenation furnished both epimeric quinolizidinones **15′** and **15**, respectively (Scheme 4).

Scheme 4. Cyclization to Yield the Bicyclic Scaffolds by Ring-Closing Metathesis Reaction



In conclusion, we have presented a diastereoselective synthetic route to functionalized and substituted indolizidine

(8) This process had not been observed for the analogous N−H-substituted piperidones but was known for carbocycles with the same arrangement of ketone and hydroxy functionalities. Barluenga, J.; Aznar, F.; Ribas, C.; Valdés, C. *J. Org. Chem.* **1998**, *63*, 10052.

and quinolizidine structures. The construction of the bicyclic scaffolds is carried out in a convergent manner, in a reduced number of steps, and with a common pathway for both structures. Moreover, the simplicity of the synthetic route should make possible an application in parallel solid-supported synthesis by the proper introduction of diverse dienes and imines. On the other hand, the asymmetric version may be carried out starting with an adequate chiral 2-aminodiene as previously described. We are currently working toward these aims, and our progress will be reported in due course.

Acknowledgment. This research was supported by the Comisión Ministerial de Ciencia y Tecnología (CICYT) and European Commission (Fondos FEDER 1FD97-0632).

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

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(9) The low yield of the reaction sequence is motivated by several reasons, mainly, the partial deprotection of the silyl ether and the difficulty of purification of the final compound from the reaction crude.

(10) The relative stereochemistry of the stereogenic centers of compounds **7a** and **7b**, depicted in Scheme 2, was deduced by the analysis of ^{1}H NMR spectra and NOESY experiments.

(11) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.

(12) It is worth noting that very few examples have been reported to date of the participation of α,β-unsaturated esters in ring-closing metathesis. Overkleeft, H. S.; Pandit, U. K. *Tetrahedron Lett.* **1996**, *37*, 547−550. Moreover, very scarce examples have described the participation of tertiary amines in ring-closing metathesis promoted by Grubbs catalysts: Fu, G. C.; Nguyen S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856−9857. Martin, S. F.; Humphrey, J. M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866−867.