

Enantioselective Spirocyclizations from Tryptophanol-Derived Oxazolopiperidone Lactams

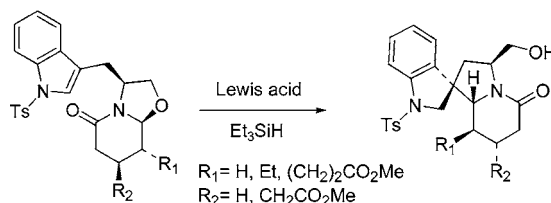
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ABSTRACT



A straightforward synthetic route to enantiopure spiro[indole-3,3'-indolizidine] is reported. The key step is a Lewis acid promoted cyclization of a *N*_α-tosyltryptophanol-derived oxazolopiperidone lactam in the presence of Et₃SiH.

Aminoalcohol-derived oxazolopiperidone lactams are exceptionally versatile building blocks for the synthesis of enantiopure polysubstituted piperidines bearing virtually any type of substitution pattern, including structurally diverse natural products and bioactive compounds.¹ These lactams are easily available by a cyclocondensation reaction of a prochiral or racemic δ -oxo(di)acid derivative with a chiral nonracemic aminoalcohol, generally phenylglycinol. This aminoalcohol constitutes a chiral latent form of ammonia, and a final debenzoylation is needed to remove the phenylethanol appendage.²

A substantial advancement on previous work was the use of (*S*)-tryptophanol as the aminoalcohol partner in cyclocondensation reactions. In these cases, tryptophanol not only constitutes the source of chirality but also can be used to assemble complex polycyclic targets, such as substituted indolo[2,3-*a*]quinolizidine derivatives, by intramolecular α -amidoalkylation upon the indole ring³ (Scheme 1).

We report here an alternative mode of cyclization of tryptophanol-derived oxazolopiperidone lactams, leading to enantiopure spiro derivatives in a highly stereoselective process that involves the generation of a quaternary stereocenter.

This spirocyclization was unexpectedly observed when we attempted the reductive opening of the oxazolidine ring of lactam **1**. Under the conditions (Et₃SiH, TiCl₄) satisfactorily

(2) For recent work, see: (a) Amat, M.; Bosch, J.; Hidalgo, J.; Cantó, M.; Pérez, M.; Llor, N.; Molins, E.; Miravittles, C.; Orozco, M.; Luque, J. *J. Org. Chem.* **2000**, *65*, 3074. (b) Amat, M.; Cantó, M.; Llor, N.; Escolano, C.; Molins, E.; Espinosa, E.; Bosch, J. *J. Org. Chem.* **2002**, *67*, 5343. (c) Amat, M.; Llor, N.; Hidalgo, J.; Escolano, C.; Bosch, J. *J. Org. Chem.* **2003**, *68*, 1919. (d) Amat, M.; Pérez, M.; Llor, N.; Escolano, C.; Luque, F. J.; Molins, E.; Bosch, J. *J. Org. Chem.* **2004**, *69*, 8681. (e) Amat, M.; Escolano, C.; Lozano, O.; Gómez-Esqué, A.; Grier, R.; Molins, E.; Bosch, J. *J. Org. Chem.* **2006**, *71*, 3804. (f) Amat, M.; Bassas, O.; Llor, N.; Cantó, M.; Pérez, M.; Molins, E.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 7872. (g) Amat, M.; Lozano, O.; Escolano, C.; Molins, E.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 4431. See also references cited therein.

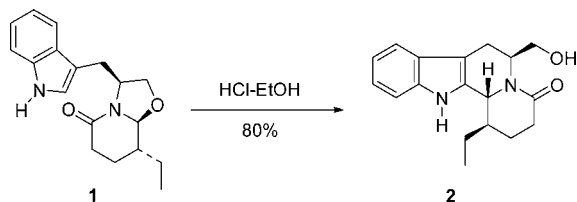
(3) (a) Bassas, O.; Llor, N.; Santos, M. M. M.; Grier, R.; Molins, E.; Amat, M.; Bosch, J. *Org. Lett.* **2005**, *7*, 2817. (b) Allin, S. M.; Thomas, C. I.; Allard, J. E.; Doyle, K.; Elsegood, M. R. J. *Eur. J. Org. Chem.* **2005**, 4179. (c) Allin, S. M.; Khera, J. S.; Witherington, J.; Elsegood, M. R. J. *Tetrahedron Lett.* **2006**, *47*, 5737. (d) Amat, M.; Santos, M. M. M.; Bassas, O.; Llor, N.; Escolano, C.; Gómez-Esqué, A.; Molins, E.; Allin, S. M.; McKee, V.; Bosch, J. *J. Org. Chem.* **2007**, *72*, 5193.

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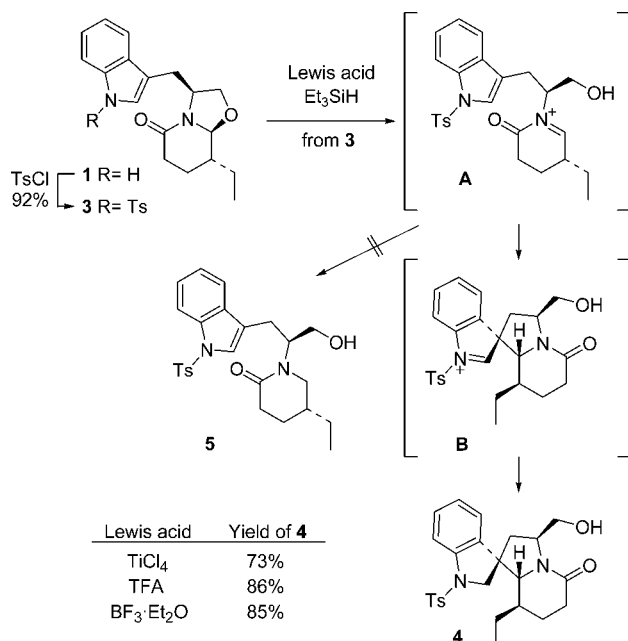
(1) For reviews, see: (a) Romo, D.; Meyers, A. I. *Tetrahedron* **1991**, *47*, 9503. (b) Meyers, A. I.; Brengel, G. P. *Chem. Commun.* **1997**, 1. (c) Groaning, M. D.; Meyers, A. I. *Tetrahedron* **2000**, *56*, 9843. (d) Escolano, C.; Amat, M.; Bosch, J. *Chem.—Eur. J.* **2006**, *12*, 8198.

Scheme 1. Enantioselective Entry to the Indolo[2,3-*a*]quinolizidine System



used for the selective cleavage of the C–O bond in related phenylglycinol-derived oxazolopiperidone lactams, tryptophanol-derived lactam **1** underwent cyclization to indoloquinolizidine **2**, thus making evident that the TiCl_4 -promoted amidoalkylation reaction on the indole 2-position occurs faster than the reduction of the initially formed intermediate *N*-acyliminium cation. To deactivate the indole ring toward the electrophilic attack, lactam **1**^{3d} was converted (92% yield) to the *N*-tosyl derivative **3** under the usual phase transfer conditions (TsCl , Bu_4NCl , NaOH , CH_2Cl_2). To our surprise, treatment of **3** with Et_3SiH – TiCl_4 in refluxing CH_2Cl_2 for 3 days led to a single spiro derivative **4** (73% yield) instead of to the expected piperidone **5**. The chemical yield of **4** was even higher when TFA (86%) or $\text{BF}_3 \cdot \text{Et}_2\text{O}$ (85%) was used as the Lewis acid in the reductive process. As illustrated in Scheme 2, these results can be accounted for by consider-

Scheme 2. Enantioselective Spirocyclization



ing an electrophilic attack of the initially formed *N*-acyliminium⁴ species **A** on the indole 3-position to generate

(4) For a recent review on cyclizations of *N*-acyliminium ions, see: Maryanoff, B. E.; Zhang, H.-C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431.

an intermediate spiroindoleninium cation **B**, which is trapped intermolecularly⁵ by the reductant.

The regioselectivity of the above cyclization is in accordance with previous observations for the electrophilic substitution in 3-substituted indoles,⁶ although some reports indicate that cyclization can occur by direct attack at the indole 2-position.⁷ Interestingly, whereas *N*-acyliminium cation **A** undergoes spirocyclization faster than reduction, in the presence of Et_3SiH the resultant *N*-tosyl spiroindoleninium cation **B** undergoes reduction to spiro tetracycle **4** instead of the usual rearrangement to an indolo[2,3-*a*]quinolizidine. This probably reflects that in the *N*-tosyl series the 3→2 migration is slower than in the above unsubstituted indole series.

The relative configuration of **4** was deduced from NOESY experiments (Figure 1) and can be rationalized on the basis

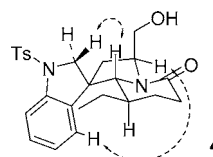


Figure 1. Key NOESY correlations of **4**.

of a stereoelectronically controlled axial approach⁸ of the indole ring to the electrophilic carbon center in the conformation **A**₁ depicted in Figure 2, via a transition state in which the $\text{A}^{1,3}$ strain between the $\text{CH}_2\text{OH}/\text{CO}$ and $\text{Et}/=\text{CH}$ groups is minimized. The alternative mode of cyclization from conformation **A**₂ would suffer from strong interaction between these groups.

The hydroxymethyl substituent plays a decisive role as a stereocontrol element in determining the relative stereochemistry of the stereocenters generated in the cyclization step.⁹ This was demonstrated since a similar spirocyclization with TiCl_4 in the presence of Et_3SiH from tosyl lactam **7**, which lacks the ethyl substituent at the piperidine β -position, led again to a single enantiopure spiro derivative **8** in

(5) (a) For the trapping of a spiroindoleninium cation, generated via a Pummerer reaction, by water, see: Padwa, A.; Kuethe, J. T. *J. Org. Chem.* **1998**, *63*, 4256. For examples of intramolecular trapping of a spiroindoleninium intermediate by a nucleophilic residue to furnish polycyclic indolines, see: (b) Büchi, G.; Matsumoto, K. E.; Nishimura, H. *J. Am. Chem. Soc.* **1971**, *93*, 3299. (c) Biswas, K. M.; Dhara, R. N.; Halder, S.; Mallik, H.; Sinha-Chaudhuri, A.; De, P.; Brahmachari, A. S. *Synth. Commun.* **1993**, *23*, 379. (d) van Maarseveen, J. H.; Scheeren, H. W.; Kruse, C. G. *Tetrahedron* **1993**, *49*, 2325. (e) Wilkins, D. J.; Jackson, A. H.; Shannon, P. V. R. *J. Chem. Soc., Perkin Trans. 1* **1994**, 299. (f) Nyerges, M.; Rudas, M.; Bitter, I.; Töke, L.; Szántay, C. J., Jr. *Tetrahedron* **1997**, *53*, 3269. (g) He, F.; Bo, Y.; Altom, J. D.; Corey, E. J. *J. Am. Chem. Soc.* **1999**, *121*, 6771. (h) Liu, J.-L.; Hino, T.; Tsuruoka, A.; Harada, N.; Nakagawa, M. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3487. (i) Turet, L.; Markó, I. E.; Tinant, B.; Declercq, J.-P.; Touillaux, R. *Tetrahedron Lett.* **2002**, *43*, 6591.

(6) For reviews, see: (a) Ungemach, F.; Cook, J. M. *Heterocycles* **1978**, *9*, 1089. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.

(7) (a) Casnati, G.; Dossena, A.; Pochini, A. *Tetrahedron Lett.* **1972**, 5277. (b) Kowalski, P.; Bojarski, A. J.; Mokrosz, J. L. *Tetrahedron* **1995**, *51*, 2737.

(8) Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Pergamon: Oxford, 1983.

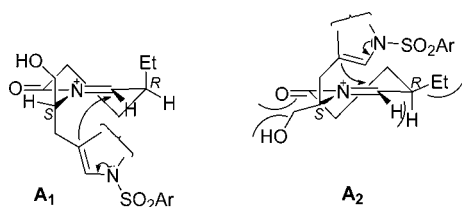


Figure 2. Stereochemical outcome of spirocyclization of **3**.

excellent yield (88%). Lactam **7** was easily prepared (93% yield) by tosylation of the known^{3b} tryptophanol-derived lactam **6**. The absolute configuration of **8** was confirmed by X-ray crystallographic analysis¹⁰ (Figure 3).

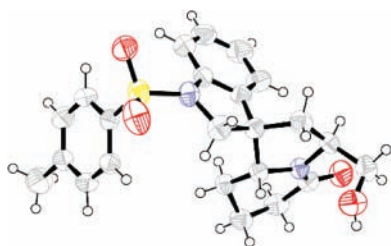


Figure 3. Molecular structure of spiro derivative **8**.

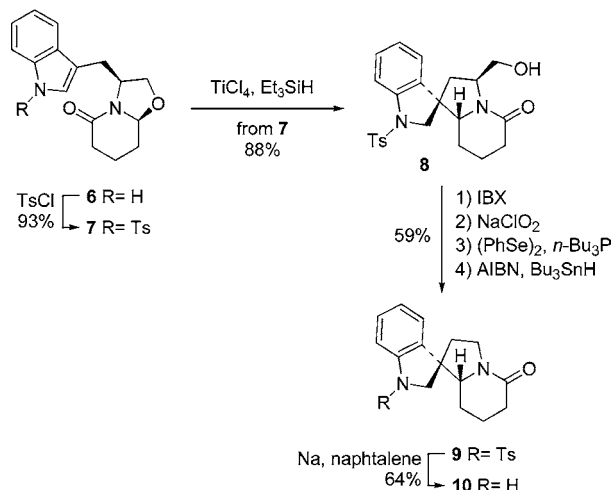
Illustrating the synthetic utility of the methodology, the removal of the hydroxymethyl appendage of **8** to give the enantiopure spiroindoline **9** was satisfactorily accomplished (59% overall yield), following the procedure recently developed by Allin,^{3b} by oxidation to a carboxylic acid **8'** followed by a radical reductive decarbonylation via a seleno derivative. The subsequent removal of the tosyl substituent gave **10** (Scheme 3).

Taking into account that the spiro[indole-3,3'-indolizidine] moiety is present in a large number of *Aspidosperma*,

(9) For related cyclizations where a substituent α to the amide nitrogen acts as an element of stereocontrol, see: (a) Maryanoff, B. E.; McComsey, D. F.; Duhl-Emswiler, B. A. *J. Org. Chem.* **1983**, *48*, 5062. (b) Maryanoff, B. E.; McComsey, D. F.; Almond, H. R., Jr.; Mutter, M. S.; Bemis, G. W.; Whittle, R. R.; Olofson, R. A. *J. Org. Chem.* **1986**, *51*, 1341. (c) Huizenga, R. H.; Pandit, U. K. *Tetrahedron* **1992**, *48*, 6521. (d) Allin, S. M.; Northfield, C. J.; Page, M. I.; Slawin, A. M. Z. *Tetrahedron Lett.* **1998**, *39*, 4905. (e) Heaney, H.; Taha, M. O. *Tetrahedron Lett.* **2000**, *41*, 1993. (f) Bahajaj, A. A.; Vernon, J. M.; Wilson, G. D. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1446. (g) Nielsen, T. E.; Meldal, M. *J. Org. Chem.* **2004**, *69*, 3765. See also ref 3.

(10) The experiment was done on a Enraf-Nonius CAD4 diffractometer using graphite monochromated Mo K α radiation. The structure was solved by direct methods (SHELXS-86) after applying Lorentz, polarization, and absorption (empirical PSI scan method) corrections. Full matrix least-squares refinement (SHELXL-93) using anisotropic thermal parameters for non-H atoms and riding thermal parameters for H atoms (positioned at calculated positions) converged to an *R* factor of 0.0377 (calculated for the reflections with $I > 2\sigma(I)$). Crystal data: C₂₃H₂₆N₂O₄S, orthorhombic, space group *P*2₁2₁2₁, *a* = 10.055(2) Å, *b* = 10.084(2) Å, *c* = 20.606(2) Å, *V* = 2089.3(6) Å³, μ (Mo K α) = 0.188 mm⁻¹, *D*_c = 1.356 mg/m³. Approximate dimensions: 0.32 × 0.28 × 0.10 mm³. Data collection was up to a resolution of $2\theta = 49.9^\circ$ producing 3970 reflections. Maximum and minimum heights at the final difference Fourier synthesis were 0.155 and -0.177 e⁻Å⁻³.

Scheme 3. Enantioselective Synthesis of Spiro[indole-3,3'-indolizidine] Derivative **10**



Strychnos, and oxindole¹¹ (Figure 4) alkaloids, many of them with strong bioactivity profiles, we decided to study if the above spiro cyclizations would represent a general synthetic entry to this tetracyclic ring system.

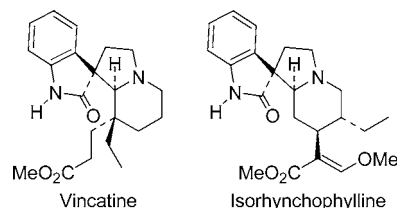
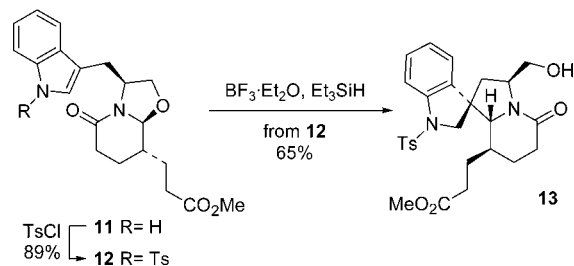


Figure 4. Representative oxindole alkaloids.

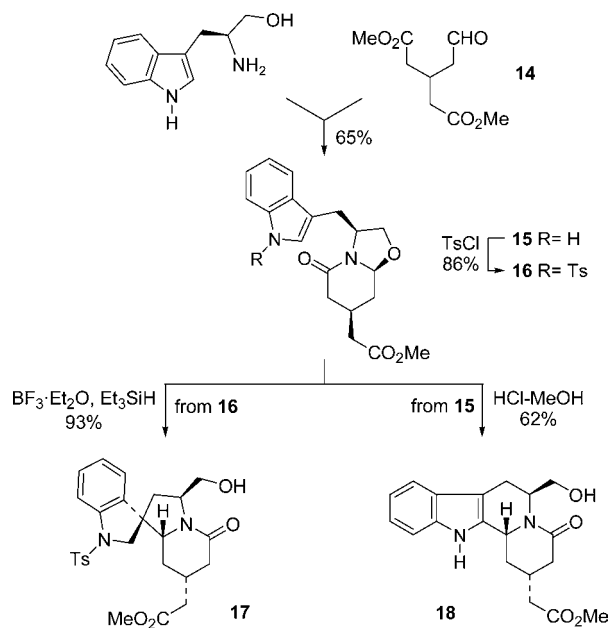
For this reason, we selected the known^{3d} lactam **11** (Scheme 4), which incorporates the propionate chain present

Scheme 4. Stereocontrolled Access to Spiro[indole-3,3'-indolizidine]-8'-propionate Derivatives



at the piperidine 3-position in the oxindole alkaloid vincatine, and lactam **15** (Scheme 5), which bears an acetate chain at the piperidine 4-position, as does isorhynchophylline. The required lactam **15** was prepared in 74% yield by cyclocon-

Scheme 5. Regio- and Stereocontrolled Cyclizations of Lactams **15** and **16**



condensation of tryptophanol with prochiral oxodiester **14**, in a process that involves the desymmetrization¹² of two enantiotopic acetate chains. Satisfactorily, tosylation of lactams **11** and **15** followed by treatment of the resulting *N*-tosylindoles **12** and **16** with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in the presence of Et_3SiH gave the respective spiroindolines **13** and **17** as single isomers in good yields. Finally, to fully illustrate the versatility of tryptophanol-derived oxazolopiperidone lactams, lactam **15** was cyclized (62% yield) to indoloquinolizidine **18** by treatment with HCl in methanol.

The unprecedented method of generating spiroindolines reported herein involves a formal addition to the indole 2,3-

double bond by sequential attack of an *N*-acyliminium species and a hydride ion. These stereoselective spirocyclizations significantly expand the potential of tryptophanol-derived oxazolopiperidone lactams as chiral building blocks for the enantioselective synthesis of complex piperidine-containing derivatives. The starting lactams are easily accessible by a cyclocondensation reaction of (*S*)-tryptophanol with an appropriate prochiral or racemic δ -oxo(di)ester, and by simply modulating the reactivity of the indole ring by tosylation, they undergo regio- and stereocontrolled cyclization reactions at either the 2- or 3-indole position, providing straightforward access to the indolo[2,3-*a*]quinolizidine¹³ and spiro[indole-3,3'-indolizidine] frameworks characteristic of several groups of indole alkaloids.

Acknowledgment. Financial support from the Ministry of Science and Technology (Spain)-FEDER (Project CTQ2006-02390/BQU) and the DURSI, Generalitat de Catalunya (Grant 2005SGR-0603), is gratefully acknowledged. Thanks are also due to the Fundação para a Ciência e Tecnologia (Lisbon, Portugal) and the Ministry of Education and Science (Spain) for a postdoctoral Grant to M.M.M.S. and D.J., respectively.

Supporting Information Available: ^1H NMR and ^{13}C NMR spectra for compounds **3**, **4**, **7**, **8**, **8'**, **10**, **12**, **13**, and **15–18**. Crystallographic data in CIF format for **8**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) (a) Southon, I. W.; Buckingham, J. In *Dictionary of Alkaloids*; Chapman and Hall: London, 1989; pp 922, 1129. (b) Brown, R. T. Indoles, The Monoterpenoid Indole Alkaloids. In *The Chemistry of Heterocyclic Compounds*; Saxton, J. E., Weissberger, A., Taylor, E. C., Eds.; Wiley: New York, NY, 1983; Vol. 25, Part 4, pp 85–97. (c) For a review on the construction of the spiro[pyrrolidine-3,3'-oxindole] moiety present in oxindole alkaloids, see: Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209.

(12) (a) For related desymmetrizations, see ref 2f. See also: (b) Tite, T.; Lallemand, M.-C.; Poupon, E.; Kunesch, N.; Tillequin, F.; Gravier-Pelletier, C.; Le Merrer, Y.; Husson, H.-P. *Bioorg. Med. Chem.* **2004**, *12*, 5091. For reviews, see: (c) Ward, R. S. *Chem. Soc. Rev.* **1990**, *19*, 1. (d) Danieli, B.; Lesma, G.; Passarella, D.; Riva, S. In *Advances in the Use of Synthons in Organic Chemistry*; Dondoni, A., Ed.; JAI Press: London, 1993; Vol. 1, pp 143–219. (e) Magnuson, S. R. *Tetrahedron* **1995**, *51*, 2167. (f) Schoffers, E.; Golebiowski, A.; Johnson, C. R. *Tetrahedron* **1996**, *52*, 3769. (g) Willis, M. C. *J. Chem. Soc., Perkin Trans. I* **1999**, 1765. (h) Danieli, B.; Lesma, G.; Passarella, D.; Silvani, A. *Curr. Org. Chem.* **2000**, *4*, 231. (i) García-Urdiales, E.; Alfonso, I.; Gotor, V. *Chem. Rev.* **2005**, *105*, 313.

(13) For the conversion of indolo[2,3-*a*]quinolizidines to oxindole derivatives, see: (a) Ito, M.; Clark, C. W.; Mortimore, M.; Goh, J. B.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 8003. (b) Deiters, A.; Pettersson, M.; Martin, S. F. *J. Org. Chem.* **2006**, *71*, 6547.