Enantioselective Synthesis of Spiro[indolizidine-1,3'-oxindoles]

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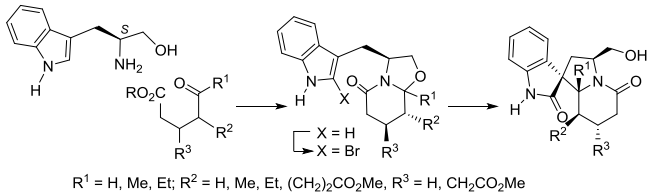
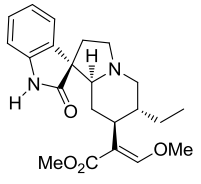
Supporting Information Placeholder



ABSTRACT: A three-step procedure for the enantioselective synthesis of spiro[indolizidine-1,3´-oxindoles], consisting of a stereoselective cyclocondensation reaction between (*S*)-tryptophanol and a prochiral or racemic δ-oxoester, bromination of the resulting oxazolopiperidone lactam, and a final stereoselective spirocyclization, is reported.

The tetracyclic spiro[indolizidine-1,3'-oxindole] ring system is a ubiquitous structural motif present in over one hundred indole alkaloids,[1] some of them isolated from plant species used in traditional Oriental medicine[2] (Figure 1). Many of these oxindole alkaloids, as well as those containing the more simple tricyclic spiro[pyrrolidine-3,3'-oxindole] moiety, show interesting biological activities[3] and have inspired the development of new potential therapeutic agents.[4] For the above reasons, and also because of their complex molecular architecture, spirooxindoles have received considerable synthetic attention.[5]


Rhynchophylline

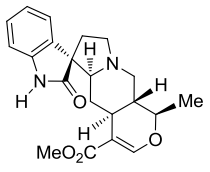

Mitraphylline

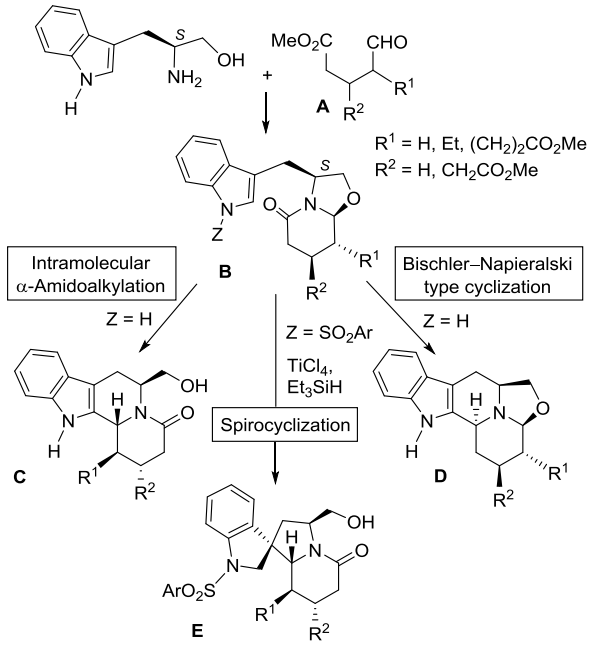
Figure 1. Representative bioactive oxindole alkaloids.

A well-established procedure for the asymmetric construction of the spiro[indolizidine-1,3'-oxindole] framework is the biomimetic oxidative rearrangement of indolo[2,3-*a*]quinolizidine derivatives.[6] Another approach involves the use of intramolecular Mannich reactions of iminium ions derived from 2-hydroxytryptamines. Although the latter reactions have been extensively used to generate tricyclic spiro[pyrrolidine-3,3'-oxindoles],[7] with the exception of the pioneering work by van Tamelen almost fifty years ago,[8] they have not been applied to directly assemble the tetracyclic spiro[indolizidine-1,3'-oxindole] skeleton.[9] The enantioselective organocatalytic version of this methodology, via cyclic *N*-acyl iminium ions derived from 2-halotryptamines, has recently been explored.[10] However, in spite of all the synthetic efforts in the field, the development of direct and efficient stereoselective methodologies to access enantiopure spiro[indolizidine-1,3'-oxindoles], with their characteristic all-carbon spiro stereocenter vicinal to another stereogenic center, still remains a challenging synthetic goal.

In previous work, we have reported[11] stereoconvergent cyclocondensation reactions between tryptophanol and δ-oxo esters **A**, either prochiral or as mixtures of stereoisomers, leading to enantiopure oxazolopiperidone lactams **B**, which can undergo three complementary regio- and stereocontrolled types of cyclization to form either indolo[2,3-*a*]quinolizidines **C** or **D**[11,12] or spiro[indoline-3,1'-indolizidines][13] **E** (Scheme 1).

The spirocyclization reaction occurs with complete regio- and stereocontrol by treatment of the lactam with TFA or a Lewis acid ($TiCl_4$, $BF_3{\cdot}Et_2O$) in the presence of Et_3SiH. The success of the reaction depends on the presence of a deactivating arylsulfonyl group on the indole nitrogen. The *N*-acyl iminium ion resulting from the oxazolidine ring-opening attacks the indole 3-position to generate a spiroindoleninium intermediate, which

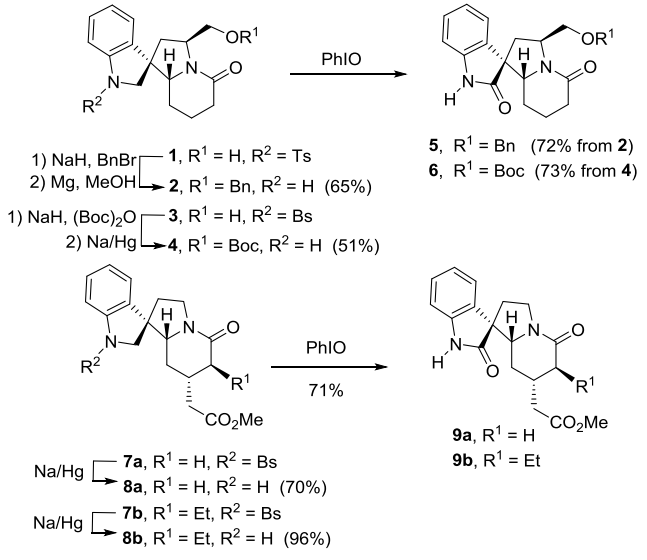
Scheme 1. Complementary Types of Cyclization from Tryptophanol-Derived Lactams



after trapping by Et_3SiH affords a single spiroindoline in excellent yield. The reaction involves the generation of two contiguous stereogenic centers, one of them quaternary.

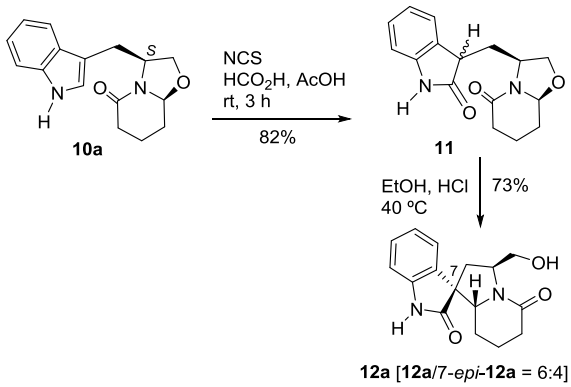
With a procedure in hand for the direct assembly of enantiopure spiro[indoline-3,1'-indolizidines], access to the corresponding spirooxindoles would simply require the oxidation of the indoline moiety. This was satisfactorily accomplished using iodosobenzene as the oxidant.[14] Under these conditions, the oxidation of *N*-unsubstituted *O*-protected spiroindolines **2** and **4** provided the respective oxindoles **5** and **6** in yields higher than 70% (Scheme 2). The procedure was also successfully applied to spiroindolines **8a** and **8b**, which lack the hydroxymethyl chain, to give the corresponding tetracyclic spirooxindoles **9a** and **9b**, the latter being an advanced intermediate in the synthesis of *ent*-rhynchophylline and *ent*-isorynchophylline.[15]

Scheme 2. Oxidation of Spiro[indoline-3,1'-indolizidines] to Spirooxindoles



Although the above oxidations satisfactorily led to spiro[indolizidine-1,3'oxindoles], we decided to explore alternative procedures that would allow direct access to these tetracyclic derivatives by spirocyclization of tryptophanol-derived oxazolopiperidone lactams. Despite the failure of previous efforts to build this tetracyclic spiro system by intramolecular Mannich reaction between a 2-oxo-2,3,4,5-tetrahydropyridinium cation and an oxindole,[10a,b] we decided to investigate the spirocyclization of lactam **11**. The oxindole moiety of this masked *N*-acyl iminium cation was generated in excellent yield by NCS oxidation of the indole ring of tryptophanol-derived lactam **10a**. After some unsuccessful attempts (TFA, CH_2Cl_2, rt; aq HCl, reflux), gratifyingly, the desired spirocyclization occurred by treatment of **11** (mixture of epimers) with HCl/EtOH at 40 ºC to afford in 73% yield a mixture (6:4 ratio) of spirooxindole **12a** and its C-7 epimer (Scheme 3).

Scheme 3. Generation of a Spirooxindole by Intramolecular Attack of an N-Acyl Iminium Ion to an Oxindole

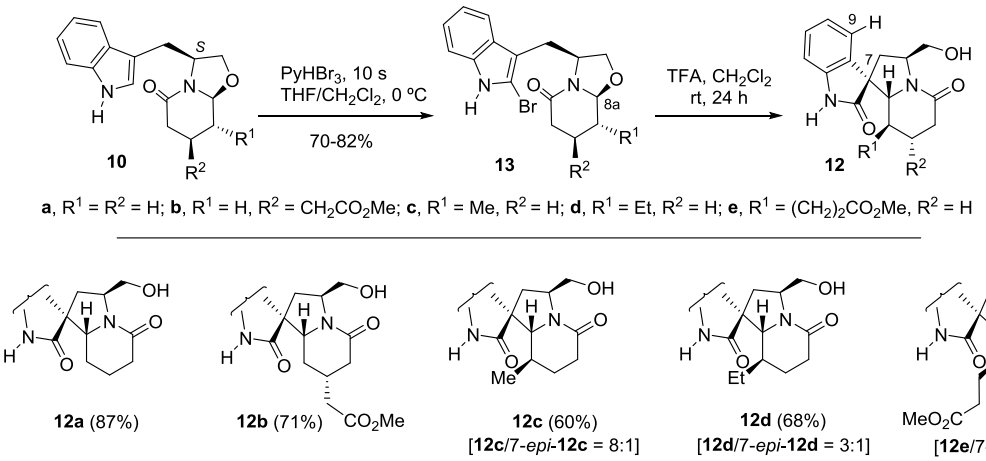


This promising result prompted us to search for more stereoselective spirocyclizations leading to spiro[indolizidine-3,1'-oxindoles]. We focused our attention on the spirocyclization of 2-bromoindoles **13**,[16] which were easily accessible by Py·HBr_3-promoted bromination[17] of tryptophanol-derived lactams **10** (Scheme 4). To our delight, treatment of **13a** with TFA at rt for 24 h provided spirooxindole **12a** in 87% yield as a single stereoisomer. The same result was obtained from the 8a-epimer of **13a**, thus making evident that spirocyclization occurs via the *N*-acyl iminium cation resulting from the opening of the oxazolidine ring. Similarly, bromolactam **13b**, which incorporates a substituent at the piperidone 4-position, was stereoselectively converted to a single oxindole **12b** in 71% yield.

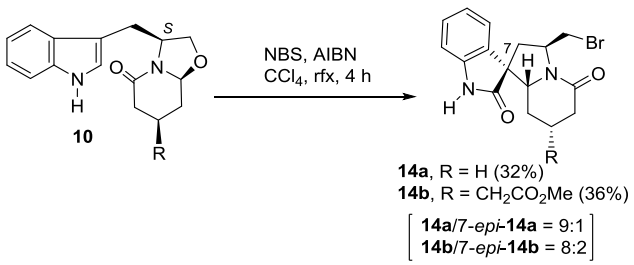
The procedure was also applied to bromolactams **13c-e**, substituted at the piperidone 5-position, although in these cases the corresponding spirooxindoles **12c-e**[18] were obtained together with minor amounts of the respective epimers at the spiro carbon.[19] The relative stereochemistry of the spiro carbon in these epimers can be assigned by ^1H NMR from the shielding (0.23-0.35 ppm) of the aromatic H-9 proton caused by the nearby piperidone carbonyl group in the major 7*R* epimers **12c-e** (also **14a,b**; see below).

Interestingly, the use of NBS/AIBN[20] in the bromination of lactams **10a** and **10b** resulted in the direct generation of spirooxindoles **14** (with minor amounts of the corresponding C-7 epimers),[18] in which the hydroxy group of the hydroxymethyl substituent had undergone substitution by bromine (Scheme

Scheme 4. Access to Spiro[indolizidine-1,3'-oxindoles] from 2-Bromoindoles



Scheme 5. Direct Generation of Spirooxindoles

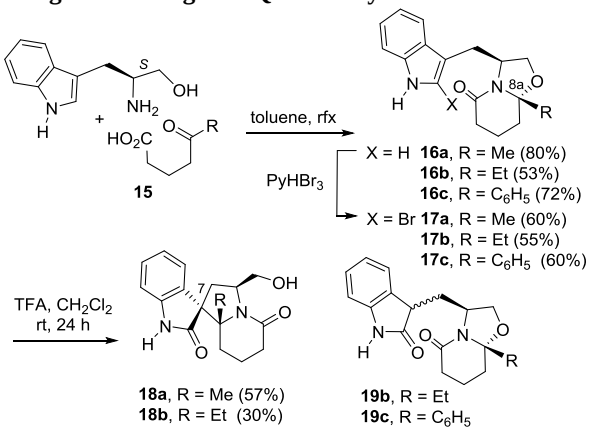


5). Due to the low yields, these conditions were not further explored.

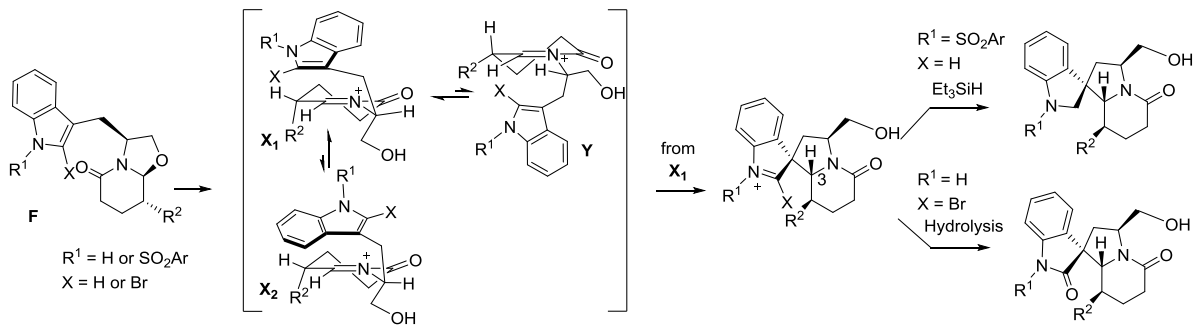
To expand the scope of the methodology, we applied it to tryptophanol-derived lactams bearing a substituent at the 8a position. The required lactams **17** were prepared by cyclocondensation of (*S*)-tryptophanol with ketoacids **15**, followed by bromination with $PyHBr_3$ (Scheme 6). A subsequent treatment of **17a** or **17b** with TFA stereoselectively provided the respective tetracyclic spirooxindoles **18a** or **18b**, in a process that involves the generation of two contiguous quaternary stereogenic centers.[18] In contrast, a similar treatment from the phenyl-substituted lactam **17c** did not bring about the spirocyclization, and only caused the conversion of the 2-bromoindole moiety to an oxindole, leading to **19c**.[21]

A rationale for the origin of the stereoselectivity in the above spirocyclizations to either spiroindolines or spirooxindoles is provided in Scheme 7, which highlights the decisive role played by the hydroxymethyl group as an element of stereocontrol. The initially formed *N*-acyl iminium cation approaches the indole 3-position under stereoelectronic control[22] as depicted in conformation $\mathbf{X_1}$, via a transition state that avoids the interaction between the carbonyl and hydroxymethyl groups (see **Y**). The electrophilic attack occurs from the *Si* face of the iminium cation, thus originating the *R* configuration at C-3. On the other hand, in conformation $\mathbf{X_1}$ the indole ring is oriented in a way that it allows an antiperiplanar arrangement of the π-bonds system involved in the spirocyclization, (in contrast with conformation $\mathbf{X_2}$), thus determining the *R* configuration at the spiro carbon. Theoretical calculations (M062X/6-31G(d) combined with solvation effects using the MST method)[23] confirmed that spirocyclization of **F** (R_1 = $C_6H_5SO_2$; X = R_2 = H) involving conformation $\mathbf{X_1}$ is kinetically favored over cyclizations involving $\mathbf{X_2}$- or **Y**-type conformations (see Supporting Information).

Scheme 6. Access to Spiro[indolizidine-1,3'-oxindoles] Bearing Two Contiguous Quaternary Stereocenters



Scheme 7. Stereochemical Outcome of the Spirocyclization



In conclusion, we have reported a straightforward procedure for the enantioselective synthesis of spiro[indolizidine-3,1'-oxindoles] from (*S*)-tryptophanol and prochiral or racemic δ-oxoesters. In only three synthetic steps, a stereoselective cyclocondensation reaction, bromination of the resulting oxazolopiperidone lactam, and a final stereoselective spirocyclization, the procedure provides practical access to enantiopure tetracyclic spirooxindoles containing up to three contiguous stereogenic centers, or even two adjacent quaternary stereocenters.

ASSOCIATED CONTENT

Supporting Information

Complete experimental procedures, copies of ^{1}H and ^{13}C NMR spectra of all new compounds, crystallographic data for **12c**, **14a**, and **18a**, and computational details. This material is available free of charge via internet at http://pubs.acs.org.

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REFERENCES

(1) (a) Saxton J. E. in *The Alkaloids: Chemistry and Physiology*, Manske, R. H. F., Ed.: Academic Press: New York, 1968, Vol. 10, p 521. (b) Bindra, J. S. in *The Alkaloids*, Manske, R. H. F., Ed.: Academic Press: New York, 1973, Vol. 14, p 83.

(2) For reviews, see: (a) Heitzman, M. E.; Neto, C. C.; Winiarz, E.; Vaisberg, A. J.; Hammond, G. B. *Phytochemistry* **2005**, *66*, 5. (b) Tang, W.; Eisenbrand, G. in *Handbook of Chinese Medicinal Plants*, Wiley, 2011, vol. 2, p 1213. (c) Zhou, J.-Y.; Zhou, S.-W. *Fitoterapia* **2012**, *83*, 617. (d) Ndagijimana, A.; Wang, X.; Pan, G.; Zhang, F.; Feng, H.; Olaleye, O. *Fitoterapia* **2013**, *86*, 35. (e) Zhang, Q.; Zhao, J. J.; Xu, J.; Feng, F.; Qu, W. *J. Ethnopharmacol.* **2015**, *173*, 48.

(3) For reviews, see: (a) Shi, J.-S.; Yu, J.-X.; Chen, X.-P.; Xu, R.-X. *Acta Pharmacol. Sin.* **2003**, *24*, 97. (b) Zhou, J.; Zhou, S. *J. Ethnopharmacol*. **2010**, *132*, 15. (c) Yu, B.; Yu, D-Q.; Liu, H.-M. *Eur. J. Med. Chem.* **2015**, *97*, 673. (d) Ye, N.; Chen, H.; Wold, E. A.; Shi, P.-Y.; Zhou, J. *ACS Infect. Dis.* **2016**, *2*, 382.

(4) For a review, see: Galliford, C. V; Scheidt, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 8748.

(5) For reviews, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, 2209. (b) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, 3003. (c) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal*. **2010**, *325*, 1381. (d) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165. (e) Santos, M. M. M. *Tetrahedron* **2014**, *70*, 9735. (f) Tsukano, C.; Takemoto, Y. *Heterocycles* **2014**, *89*, 2271. (g) Fonseca, G. O.; Cook, J. M. *Organic Chemistry Insights* **2016**, *6*, 1. (h) Pavlovska, T. L.; Redkin, R. G.; Lipson, V. V.; Atamanuk, D. V. *Mol. Diversity* **2016**, *20*, 299.

(6) (a) Finch, N.; Taylor, W. I. *J. Am. Chem. Soc.* **1962**, *84*, 1318. (b) Martin, S. F.; Benage, B.; Geraci, L. S.; Hunter, J. E.; Mortimore, M. *J. Am. Chem. Soc.* **1991**, *113*, 6161. (c) Deiters, A.; Pettersson, M.; Martin S. F. *J. Org. Chem.* **2006**, *71*, 6547. (d) Nagata, K.; Ishikawa, H.; Tanaka, A.; Miyazaki, M.; Kanemitsu, T.; Itoh, T. *Heterocycles* **2010**, *81*, 1791.

(7) (a) Castedo, L.; Harley-Mason, J.; Kaplan, M. *Chem Commun*. **1969**, 1444. (b) Ban, Y.; Seto, M.; Oishi, T. *Chem. Pharm. Bull.* **1975**, *23*, 2605. (c) Brown, R. T.; Chapple, C. L.; Platt, R. *Tetrahedron Lett.* **1976**, *17*, 1401. (d) Ponglux, D.; Wongseripipatana, S.; Aimi, N.; Nishimura, M.; Ishikawa, M.; Sada, H.; Haginiwa, J.; Sakai, S.-I. *Chem. Pharm. Bull.* **1990**, *38*, 573. (e) von Nussbaum, F.; Danishefsky S. J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2175. (f) Wanner, M. J.; Ingemann, S.; van Maarseveen, J. H.; Hiemstra, H. *Eur. J. Org. Chem.* **2013**, 1100.

(8) van Tamelen, E. E.; Yardley, J. P.; Miyano, M.; Hinshaw, Jr. W. B. *J. Am. Chem. Soc.* **1969**, *91*, 7333.

(9) For an alternative approach involving a cross-dehydrogenative coupling from 3-(2-bromoethyl)indolin-2-one and a pyridine derivative, see: Xu, J.; Shao, L.-D.; Li, D.; Deng, X.; Liu, Y.-C.; Zhao, Q.-S.; Xia, C. *J. Am. Chem. Soc.* **2014**, *136*, 17962.

(10) (a) Wu, X.; Lui, Q.; Fang, H.; Chen, J.; Cao, W.; Zhao, G. *Chem. Eur. J.* **2012**, *18*, 12196. (b) Antonchick, A. P.; López-Tosco, S.; Parga, J.; Sievers, S.; Schürmann, M.; Preut, H.; Höing, S.; Schöler, H. R.; Sterneckert, J.; Rauh, D.; Waldmann, H. *Chem. Biol.* **2013**, *20*, 500. (c) Förster, T.; López-Tosco, S.; Ziegler, S.; Antonchick, A. P.; Waldmann, H. *ChemBioChem* **2017**, *18*, 1. See also: (d) Zhang, H.; Ma, X.; Kand, H.; Hong, L.; Wang, R. *Chem. Asian J.* **2013**, *8*, 542.

(11) (a) 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. See also: (b) Allin, S. M.; Thomas, C. I.; Doyle, K.; Elsegood, M. R. J. *J. Org. Chem.* **2005**, *70*, 357.

(12) (a) Amat, M.; Gómez-Esqué, A.; Escolano, C.; Santos, M. M. M.; Molins, E.; Bosch, J. *J. Org. Chem.* **2009**, *74*, 1205. (b) Pérez, M.; Arioli, F.; Rigacci, G.; Santos, M. M. M.; Gómez-Esqué, A.; Escolano, C.; Florindo, P.; Ramos, C.; Bosch, J. Amat, M. *Eur. J. Org. Chem.* **2011**, 3858. (c) Amat, M.; Llor, N.; Subrizi, F.; Pérez, M.; Molins, E.; Bosch, J. *Eur. J. Org. Chem.* **2013**, 1246.

(13) Amat, M.; Santos, M. M. M.; Gómez, A. M.; Jokic, D.; Molins, E.; Bosch, J. *Org. Lett.* **2007**, *9*, 2907.

(14) Moriarty, R. M.; Vaid, R. K.; Duncan, M. P.; Ochiai, M.; Inenaga, M.; Nagao, Y. *Tetrahedron Lett.* **1988**, *29*, 6913.

(15) Amat, M.; Ramos, C.; Pérez, M.; Molins, E.; Florindo, P.; Santos, M. M. M.; Bosch, J. *Chem. Commun*. **2013**, *49*, 1954.

(16) For early work on Mannich-type spirocyclizations of 2-halotryptophan or 2-halotryptamine imines leading to spirooxindoles, see: Miyake, F. Y.; Yakushijin, K.; Horne, D. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5357.

(17) Grieco, P. A.; Hon, Y. S.; Perez-Medrano, A. *J. Am. Chem. Soc.* **1988**, *110*, 1630.

(18) The absolute configuration of spirooxindoles **12c**, **14a**, and **18a** was unambiguously established by X-ray crystallographic analysis. CCDC 1556168, CCDC 1556166, and CCDC 1556167 contains the supplementary crystallographic data for these compound. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(19) Spirooxindoes **12c-e** did not undego isomerization to the corresponding C-7 epimers under a variety of acidic conditions (HCl-MeOH, 40 ºC, 24-72h; TFA, 40-72 ºC, 24-72h).

(20) For the use of these conditions in the bromination at the indole C-2 of 3-methylindole, see: Liu, R.; Zhang, P.; Gan. T.; Cook, J. M. *J. Org. Chem*. **1997**, *62*, 7447.

(21) No spirocyclization was observed when **19c** was subjected to an additional treatment with HCl-EtOH (rt, 24h) under the conditions satisfactorily used for **11**.

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

(23) (a) Zhao, Y.; Truhlar, D. G. *Theor. Chem. Acc*. **2008**, *120*, 215. (b) Soteras, I.; Curutchet, C.; Bidon-Chanal, A.; Orozco, M.; Luque, F. J. *J. Mol. Struct. (THEOCHEM)* **2005**, *727*, 29.