ORGANIC LETTERS

2011
Vol. 13, No. 20
5536–5539

Trifluoroacetic Acid-Promoted Synthesis of 3-Hydroxy, 3-Amino and Spirooxindoles from α-Keto-*N*-Anilides

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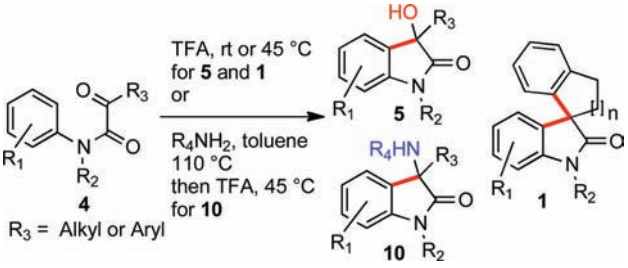
Received August 21, 2011

ABSTRACT



Ketoanilides containing alkyl side chains were readily cyclized to 3-hydroxy-2-oxindoles or spirooxindoles by a single or double intramolecular Friedel–Crafts reaction in the presence of trifluoroacetic acid (TFA) at room temperature or at 45 °C. α-Iminocarboxamides, generated in situ from ketoamides, cyclized similarly to 3-aminooxindoles under identical conditions.

3,3-Disubstituted oxindoles are structural subunits found in a wide range of natural and synthetic compounds that display interesting biological and pharmacological properties.[1] Consequently, a number of elegant synthetic strategies have been developed for the synthesis of this class of heterocycle.[2] Recently, diversely *ortho*-prefunctionalized α-ketoanilides (boronate,[3] halide[4]) have been converted to 3-hydroxyoxindoles through metal-catalyzed cyclization processes.

Cyclization of α-ketoamides by way of an intramolecular Friedel–Crafts reaction is an attractive way for the synthesis of 3-hydroxyoxindoles.[5] However, this approach was limited essentially to the synthesis of 3-aryl containing oxindoles. Indeed, competing enolization and/or

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(1) For recent reviews on oxindoles, see: (a) Marti, C.; Carreira, E. M. *Eur. J. Org. Chem.* **2003**, *12*, 2209–2219. (b) Trost, B.; Brennan, M. K. *Synthesis* **2009**, 3003–3025. (c) Zhou, F.; Liu, Y.-L.; Zhou, J. *Adv. Synth. Catal.* **2010**, *352*, 1381–1407. (d) Millemaggi, A.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2010**, 4527–4547. For a review on 3-hydroxyoxindoles, see: (e) Peddibhotla, S. *Curr. Bioact. Compd.* **2009**, *5*, 20–38.

(2) Selected recent examples: (a) Zheng, K.; Yin, C.; Liu, X.-H.; Lin, L.; Feng, X. *Angew. Chem., Int. Ed.* **2011**, *50*, 2573–2577. (b) Zhang, Z.; Zheng, W.; Antilla, J. C. *Angew. Chem., Int. Ed.* **2011**, *50*, 1135–1138. (c) Lui, Z.; Gu, P.; Shi, M.; McDowell, P.; Li, G. *Org. Lett.* **2011**, *13*, 2314–2317. (d) Badillo, J. J.; Arevalo, G. E.; Fettinger, J. C.; Franz, A. K. *Org. Lett.* **2011**, *13*, 418–421. (e) Hanhan, N. V.; Sahin, A. H.; Chang, T. W.; Fettinger, J. C.; Franz, A. K. *Angew. Chem., Int. Ed.* **2010**, *49*, 744–747. (f) Liu, Y.-L.; Wang, B.-L.; Cao, J.-J.; Chen, L.; Zhang, Y.-X.; Wang, C.; Zhou, J. *J. Am. Chem. Soc.* **2010**, *132*, 15176–15178. (g) Bui, T.; Candeias, N. R.; Barbas, C. F., III *J. Am. Chem. Soc.* **2010**, *132*, 5574–5575. (h) Deng, J.; Zhang; Ding, P.; Jiang, H.; Wang, W.; Li, J. *Adv. Synth. Catal.* **2010**, *352*, 833–838.

(3) Tomita, D.; Yamatsugu, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 6946–6948.

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(5) (a) Lopatin, W.; Sheppard, C.; Owen, T. C. *J. Org. Chem.* **1978**, *43*, 4678–4679. (b) Aoyama, H.; Omote, Y.; Hasegawa, T.; Shiraishi, H. *J. Chem. Soc., Perkin I* **1976**, 1556–1558. For Friedel–Crafts conditions using 2,2-dimethoxy arylacetanilides as precursor, see:(c) Ly, T.-M.; Laso, N. M.; Zard, S. Z. *Tetrahedron* **1998**, *54*, 4889–4898. (d) Sai, K. K. S.; Esteves, P. M.; da Penha, E. T.; Klumpp, D. A. *J. Org. Chem.* **2008**, *73*, 6506–6512.

(6) Under super acid reaction conditions, alkyl-substituted α-ketoamides produced α,β-unsaturated amides; see ref 5b.

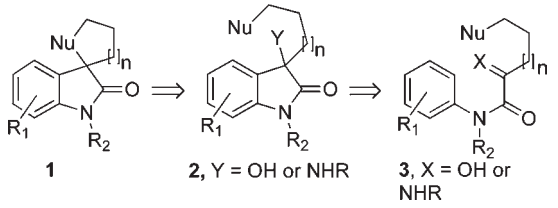
(7) Formation of 3-methylene oxindoles from 3-hydroxy oxindoles is well precedented, see for example: Munusamy, R.; Dhathathreyan, K.; Balsubramanian, K. K.; Vankatachalan, C. S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1154–1166.

10.1021/ol202263a
Published on Web 09/29/2011

dehydration of the resulting tertiary alcohol can completely suppress the formation of 3-alkyl containing oxindoles[6] or prevent the isolation of 3-hydroxy oxindoles[7] when using β-alkylated ketoamides.[8]

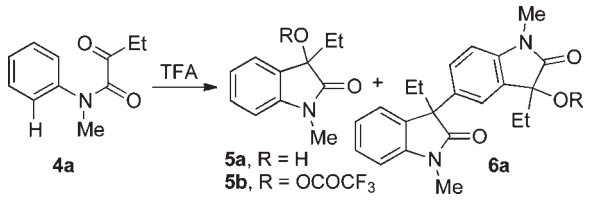
In connection with our general interest in oxindole synthesis[9] and the development of strategies starting from unfunctionalized anilides,[10] we decided to evaluate the possibility of building spirooxindoles **1** in a tandem fashion[11] by performing a double cyclization of α-ketoanilides with concurrent generation of all-carbon quaternary center (Nu = π-nucleophile) as depicted in Scheme 1.[12] We report herein that, under acidic conditions, intramolecular Friedel–Crafts reaction of **3** takes place readily to afford 3-alkyl(aryl)-3-hydroxy-2-oxindoles **2**. With an appropriately tethered nucleophile, a second cyclization occurred to directly provide the spirooxindoles **1**. In addition, we document that 3-amino-oxindoles can be prepared from the corresponding α-ketoamides under identical conditions.

Scheme 1. Double Cyclization Sequence for the Synthesis of Spiro-2-oxindole



We selected *N*-methyl-2-oxo-*N*-phenylbutanamide (**4a**) as a model substrate for the survey of reaction conditions (Scheme 2). While AcOH was inefficient for promoting the cyclization even at 45 °C, we found that the desired cyclization proceeded readily at room temperature in the presence of trifluoroacetic acid (TFA). In pure TFA, the reaction was complete within 6 h, whereas in a mixture of solvents (DCM/TFA or tol/TFA, v/v = 1/1), a longer reaction time (24 h) was needed to reach completion.[13] At higher concentration (*c* 0.9 M), a dimerization product **6a** was produced together with **5a**. However, the dimer was formed only in a trace amount at *c* = 0.4 M and was not detected at *c* = 0.09 M. We also noticed the formation of a variable amount of trifluoroacetate **5b** (R = CF_3CO, 5–10% and up to 40% yield for some other substrates). This product is readily hydrolyzed to **5a** (R = H) upon workup with aqueous NaOH solution before extraction. Overall, under our optimized conditions [TFA, *c* 0.09M, rt, 6 h, then aqueous NaOH (3N) at rt for 1 h], cyclization of **4a** afforded **5a** in 94% yield.

Scheme 2. Intramolecular Arylation of α-Ketoanilide **4a**



The scope of this process was next examined (Table 1). The reaction was found to be general leading to the expected 3-hydroxy-2-oxindoles in yields ranging from 50 to 94%. Notably and in sharp contrast to other related literature work, diverse alkyl side-chains, such as methyl, ethyl, isobutyl, and phenethyl, were tolerated. As expected, aryl-substituted α-ketoamide **4h** was an excellent substrate, furnishing the corresponding 3-phenyl-3-hydroxy-2-oxindole (**5h**) in 83% yield. A tertiary amide was mandatory for the cyclization, as no oxindole was formed in the case of 2-oxo-*N*-phenylbutanamide (not shown). *N*-Benzyl derivative **4i** afforded oxindole **5i** in 58% yield, indicating that the benzyl residue did not participate in the cyclization reaction. Cyclization of a tetrahydroquinoline derivative **4j** furnished tricyclic oxindole **5j** in 85% yield (entry 9). Substituted anilides bearing electron-donating groups at the *para*-position (OMe, Me) cyclized smoothly to generate the expected oxindoles **5d**, **5g** and **5h** (entries 3, 6 and 7). The presence of a weak electron-withdrawing group (chlorine) at the *para*-position of anilide was also tolerated furnishing compound **5e** in an excellent 89% yield. Gentle heating (45 °C) and longer reaction time were however required in this case in order to drive the reaction to completion.

Anilides containing a functionalized alkyl side chain such as a bromoalkyl or a secondary hydroxyl group were compatible with the reaction conditions (Scheme 3). Treatment of 3-bromo-*N*-methyl-2-oxo-*N*-phenylpropanamide

(8) For a recent enantioselective synthesis of 3-alkyl-3-hydroxy-2-oxindole from *ortho* functionalized α-ketoanilides, see: Yin, L.; Kanai, M.; Shibasaki, M. *Angew. Chem., Int. Ed.* **2011**, *50*, 7620–7623.

(9) (a) Jaegli, S.; Vors, J.-P.; Neuville, L.; Zhu, J. *Tetrahedron* **2010**, *66*, 8911–8921. (b) Jaegli, S.; Erb, W.; Retailleau, P.; Vors, J.-P.; Neuville, L.; Zhu, J. *Chem.—Eur. J.* **2010**, *16*, 5863–5867. (c) Erb, W.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2009**, *74*, 3109–3115. (d) Jaegli, S.; Vors, J.-P.; Neuville, L.; Zhu, J. *Synlett* **2009**, 2997–2999. (e) Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem.—Eur. J.* **2007**, *13*, 961–967. (f) Bonnaterre, F.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2006**, *8*, 4351–4354. 3-(Diarylmethylenyl)oxindoles: (g) Pinto, A.; Neuville, L.; Zhu, J. *Tetrahedron Lett.* **2009**, *50*, 3602–3605. (h) Pinto, A.; Neuville, L.; Zhu, J. *Angew. Chem., Int. Ed.* **2007**, *46*, 3291–3295. (i) Pinto, A.; Neuville, L.; Retailleau, P.; Zhu, J. *Org. Lett.* **2006**, *8*, 4927–4930.

(10) (a) Wei, H.-L.; Piou, T.; Dufour, J.; Neuville, L.; Zhu, J. *Org. Lett.* **2011**, *13*, 2244–2247. (b) Jaegli, S.; Dufour, J.; Wei, H.-L.; Piou, T.; Duan, X.-H.; Vors, J.-P.; Neuville, L.; Zhu, J. *Org. Lett.* **2010**, *12*, 4498–4501.

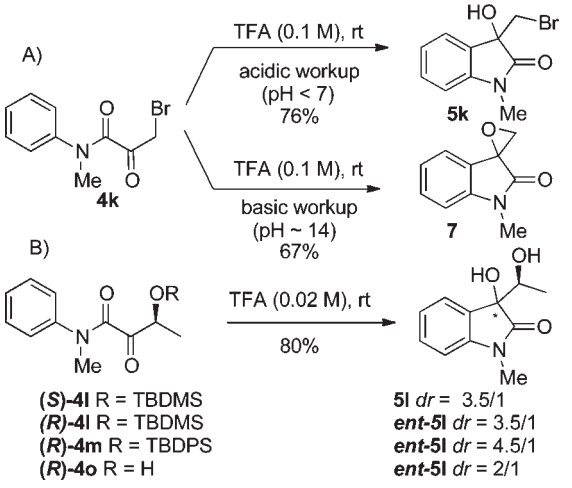
(11) For general reviews on the domino process, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115–136. For a monograph, see: (b) *Domino Reactions in Organic Synthesis*; Tietze, L. F., Brasche, G., Gericke, K., Eds.; Wiley-VCH: Weinheim, 2006.

(12) For a recent review on Friedel–Crafts reaction, see: Bandini, M.; Emer, E.; Tommasi, S.; Umani-Ronchi, A. *Eur. J. Org. Chem.* **2006**, 3527–3544.

(13) For the benficial effect of performing Friedel–Crafts processes in concentrated or pure TFA, see: (a) Youn, S. W.; Bihn, J. H. *Tetrahedron Lett.* **2009**, *50*, 4598–4601. (b) Wu, Y.-C.; Liu, L.; Liu, Y.-L.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2007**, *72*, 9383–9386. (c) Ma, S.; Zhang, J. *Tetrahedron* **2003**, *59*, 6273–6283.

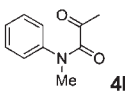
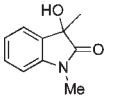
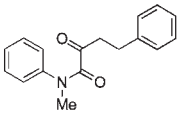
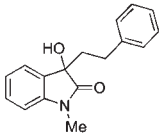
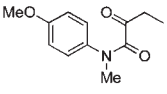
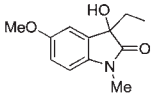
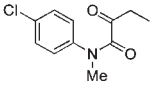
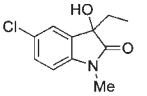
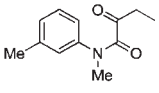
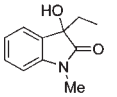
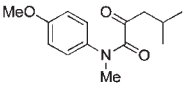
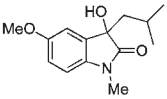
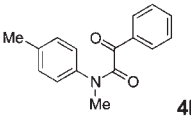
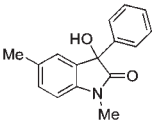
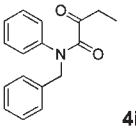
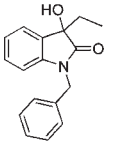
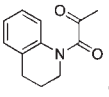
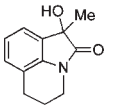
4k under standard conditions, without basic aqueous workup, afforded 3-(bromomethyl)-3-hydroxy-2-oxindole **5k** in 76% yield. On the other hand, upon basic aqueous workup, a second cyclization took place leading to spiro-epoxyoxindole **7** in 67% yield.[14] Therefore, by simply modifying the workup procedure, we were able to obtain two sets of heterocycles that can in principle be further functionalized in different ways.[15] Cyclization of TBS-protected *N*-methyl (*S*)-3-hydroxy-2-oxo-*N*-phenyl butanamide[16] (**4l**) occurred smoothly, furnishing the deprotected diol **5l** in 80% yield. A modest but significant diastereselectivity (*dr* = 3.5/1) was observed. Analysis of SFC traces (IB column) of **5l** and *ent*-**5l**, obtained by cyclization of (*S*)-**4l** and (*R*)-**4l**, respectively, allowed us to conclude that no epimerization occurred during the cyclization (see Supporting Information). We have also examined the role of the hydroxy protective group on the diastereoselectivity of this cyclization. When (*R*)-**4m** (R = TBDPS) was submitted to the cyclization, the deprotected diol *ent*-**5l** was again obtained but with increased diastereoselectivity (*dr* = 4.5/1). On the other hand, cyclization of unprotected alcohol (*R*)-**4o** afforded *ent*-**5l** as a 2/1 mixture of diasteromers. These results indicated that when (*R*)-**4l** (R = TBDMS) and (*R*)-**4m** (R = TBDPS) were submitted to our cyclization conditions, partial *O*-deprotection occurred before cyclization and that much better diastereoselectivity could be expected if a bulky but acid-stable *O*-protective group was installed in **4o**.[17]

Scheme 3. Cyclization of Functionalized α-Ketoamides



We next turned our attention to the synthesis of spirooxindoles through a double intramolecular Friedel–Crafts reaction of α-ketoamides bearing a tethered arene.[18] The reactivity of compound **8a** (R = H, *n* =

Table 1. Synthesis of 3-hydroxy-2-oxindoles: substrate scope

entry	substrate (**4**)	product (**5**)	yield (%)[b]
1	 **4b**		**5b**, 69%
2	 **4c**		**5c**, 67%
3	 **4d**		**5d**, 80%[d]
4[c]	 **4e**		**5e**, 89%
5	 **4f**		**5f**, R = 6-Me, **5f'**, R = 4-Me, (1/1.2) 50%
6	 **4g**		**5g**, 68%
7[c]	 **4h**		**5h**, 83%[d]
8	 **4i**		**5i**, 58%[d]
9	 **4j**		**5j**, 85%

[a] General conditions: **4** in TFA (C = 0.09 M), rt then NaOH (3.0 M) up to pH = 13. [b] Isolated yield. [c] At 45 °C. [d] Basic workup with 3.0 N NaOH was not required.

(14) (a) Schulz, V.; Davoust, M.; Lemarie, M.; Lohier, J.-F.; Sopkova de Oliveira Santos, J.; Metzner, P.; Briere, J.-F. *Org. Lett.* **2007**, *9*, 1745–1748 and references cited therein. (b) Inoue, M.; Furuyana, H.; Sakazaki, M.; Hirama, M. *Org. Lett.* **2001**, *3*, 2863–2865.

(15) Structural diversity derived from work-up procedure, see: Gámez-Montaño, R.; González-Zamora, E.; Potier, P.; Zhu, J. *Tetrahedron* **2002**, *58*, 6351–6358.

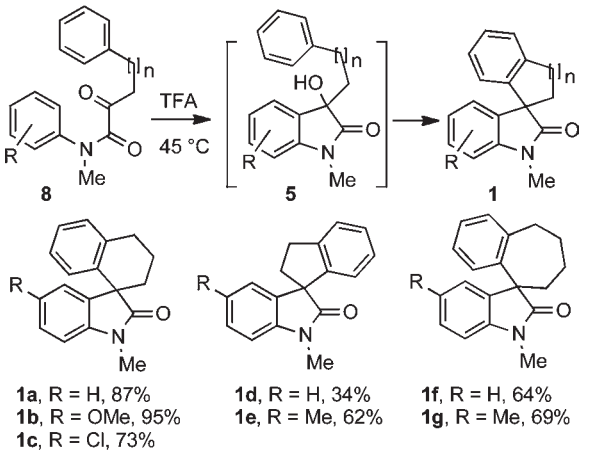
(16) Optically pure **4l** was prepared from D-threonine through amide bond formation and oxidative transamination.

(17) We thank reviewers for suggesting these control experiments.

(18) Two-step synthesis of 3,3′-alkyl-aryl oxindoles has been documented, see: England, D. B.; Merey, G.; Padwa, A. *Org. Lett.* **2007**, *9*, 3805–3807. *N*-methyl oxindoles were found to be unsuitable substrates under their conditions, see ref 23 of this work.

(19) The formation of 5-membered rings using Friedel–Crafts alkylation is known to be difficult: (a) Khalaf, A. A.; Roberts, R. M. *J. Org. Chem.* **1969**, *34*, 3571–3575. The following ring formation preference, 6 > 7 and 6 > 5, has been established: (b) Johnson, W. S. *Org. React.* **1944**, *2*, 114–177. (c) Fillion, E.; Fishlock, D.; Wilsily, A.; Goll, J. M. *J. Org. Chem.* **2005**, *70*, 1316–1327.

Scheme 4. Synthesis of Spirooxindoles **1** by Double Intramolecular Arylation of α-Ketoanilides

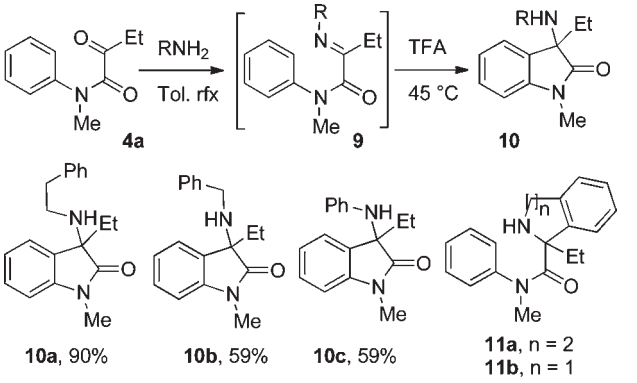


2, Scheme 4) was initially evaluated and we were delighted to isolate spirooxindole **1a** in 87% yield upon exposure of **8a** to TFA (0.04 M, 45 °C, 24 h). The 4-methoxy and 4-chloro-substituted anilides (**8b**, **8c**) underwent spirocyclization smoothly to afford tetracyclic compounds **1b** and **1c** in yields of 95 and 73%, respectively. The reaction was not limited to the formation of spiro tetrahydronaphthalenes, as 5- and 7-membered carbospirocycles **1d**−**1g** were also formed under similar conditions. The reduced yield of spiroindene **1d** can be accounted for by the competitive dimerization/polymerization of the hydroxyoxindole intermediate.[19] Such a competitive pathway was markedly reduced when 4-substituted anilides were used leading to **1e** in 62% yield. The yields of the seven-membered spirooxindoles **1f** and **1g** (64 and 69%, respectively) were quite remarkable as a related intramolecular S_EAr reaction of 3-bromoindolin-2-one produced the cyclic product in only 13% yield.[20]

The 3-aminooxindoles have recently been proven to be of interest in medicinal chemistry.[21] Having established conditions for the synthesis of 3-hydroxyoxindoles by the Friedel−-Crafts reaction, we reasoned that the 3-amino-2-oxindoles could be similarly synthesized from α-iminocarboxamides which could, in turn, be generated in situ from α-ketoamides.

The synthesis of compound **9a** (R = $PhCH_2CH_2$, Scheme 5) was easily achieved by heating phenethylamine with α-ketoamide **4a** in toluene at reflux for 18 h.[22] A substoichiometric amount of acid (0.5 equivalent of TFA) was required to effectively promote the formation of compounds **9b** (R = Bn) and **9c** (R = Ph) from the corresponding amine. Evaporation of the volatile, followed by stirring the crude iminocarboxamides in pure TFA at 45 °C for 4 h, provided the corresponding 3-aminooxindoles **10** in yields ranging from 59 to 90%. Neither 1,2,3,4-tetrahydroisoquinoline-1-carboxamide **11a** nor isoindoline-1-carboxamide **11b** via Pictet−Spengler reaction were produced in the reaction.[23] A 5-*exo*-trig cyclization mode leading to oxindoles might be kinetically more favorable than the alternative 5-*endo*-trig or 6-*endo*-trig processes encountered in the Pictet−Spengler reaction. The aniline derived product **10c** was found to be stable, and the possible Hofmann−Martius rearrangement was not observed under our reaction conditions.[24]

Scheme 5. Synthesis of 3-Amino-2-oxindoles



In summary, we have demonstrated the utility of the intramolecular Friedel−Crafts reaction for the synthesis of diversely functionalized 3,3′-disubstituted oxindoles and spirooxindoles from readily accessible α-keto-*N*-arylacetamides bearing alkyl side chain residues. In TFA, α-ketoanilides **4** cyclized readily at room temperature to afford the 3-hydroxy-3-alkyl(aryl)-2-oxindoles **5**, while α-iminocarboxamides **9**, prepared in situ from α-ketoamides, cyclized under similar conditions to 3-amino-3-alkyl-2-oxindoles **10** in good to excellent yield. From an appropriately functionalized substrate **8**, a double cyclization took place leading to spirooxindoles **1** with the creation of an all carbon chiral quaternary center.

Acknowledgment. Financial supports from ICSN, CNRS (France) and EPFL (Switzerland) are gratefully acknowledged. I.G. thanks ICSN and EPFL for a doctoral fellowship.

Supporting Information Available. Supporting Information for this article, including experimental procedures, product characterization and copies of the ^1H and ^{13}C NMR spectra of all reported oxindoles. This material is available free of charge via the Internet at http://pubs.acs.org.

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