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Synthesis of spiroindolenine derivatives by a tandem radical-oxidation process

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ABSTRACT

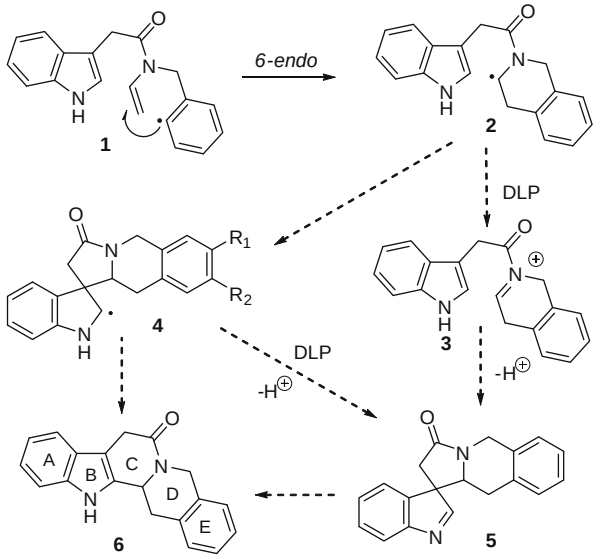
In the present work, a novel stereoselective radical cyclization/oxidation/spirocyclization cascade process using a mixture of *n*-Bu_3SnH/ dilauroyl peroxide is described. The proposed mechanism for this later process combines a 6-*endo* cyclization of an aryl radical onto an enamide double bond, and a consecutive oxidative-ionic spirocyclization at C-3 of an indole nucleus. All processes led to the construction of new spiroindolenine derivatives in a one-step synthesis starting from relatively simple starting materials. The organic peroxide appears to act as the initiator and the oxidant.

Indole alkaloids have been the object of numerous studies due to their structural diversity and significant biological and pharmacological activities.[1] The pentacyclic system common to several natural product families, such as yohimbane[2–5] and its isomers, which possesses an aromatic E-ring **6** (Scheme 1), has been the subject of several synthetic approaches by different methodologies.[6] During the course of our ongoing studies on the radical-oxidative addition to heteroaromatic systems, we recently embarked on an investigation of the radical cascade process depicted in Scheme 1. Ishibashi has previously used a *6-endo* cyclization for the synthesis of a variety of fused heterocyclic systems,[7] and we envisioned that a similar process might afford radical **2** from the initial radical **1**. Earlier, we showed that a radical alpha to a nitrogen atom could be oxidized under tin hydride-mediated conditions.[8] Thus, the use of a mixture of *n*-Bu_3Sn/dilauroyl peroxide (DLP) suggested the possible combination of this *6-endo* radical cyclization with a Pictet–Spengler type ring closure of the acyliminium ion **3**, which would be derived from oxidation of the intermediate radical **2**.[9] Based on the pioneering work of van Tamelen et al.[6a,b,10] on related acyliminium ion cyclizations (e.g., **3**), kinetic cyclization could take place at C-3 of the indole system, affording the indolenine **5**, which could undergo a Wagner–Meerwein rearrangement to the pentacyclic, thermodynamic product **6**.[11,12]

The direct cyclization of radical **2** to radical **4** is also possible, but the mismatched polarity resulting from the nucleophilic nature of both the radical and the aromatic system is likely to disfavor this reaction pathway. Regardless of whether this latter process occurred, the outcome of the overall reaction would be the same, with the DLP serving to oxidize the radical **4** to the indolenine **5** in a pathway similar to that reported previously.[8] Our initial results of such a process are described herein.

The enamides **11a–b** necessary for the tandem reaction process were prepared in four steps (Scheme 2) from the corresponding *o*-bromoaldehydes **8a–c**. The amines **9a–c** were synthesized by reductive amination of 2-thiophenylethylamine **7**[13] and aldehydes **8a–c**. Acylation of amines **9a–c** with 3-indolacetic acid provided the amides **10a–c**, which were sequentially oxidized to the sulfoxides and then subjected to thermolysis in refluxing xylene to give the enamides **11a–b** (Scheme 2).

Optimization of the conditions for the radical reaction was examined using enamide **11a**. Using a syringe pump, a solution of *n*-Bu_3SnH and DLP in benzene or toluene was slowly added to a refluxing solution of **11a**. In the first experiment using 1.3 equiv



Scheme 1. Radical-oxidative process.

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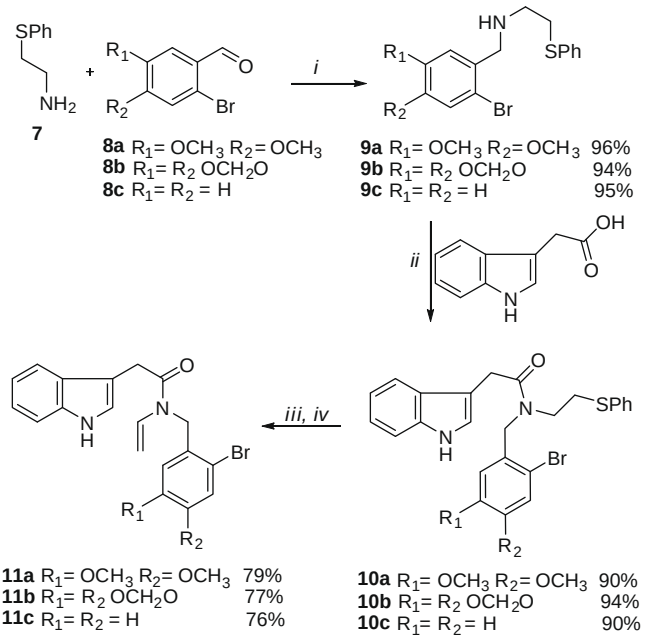
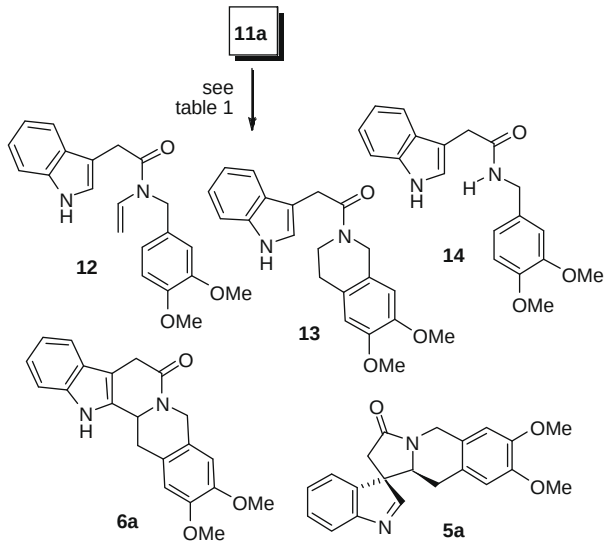


Scheme 2. Reagents and conditions: (i) MeOH, 8 h, rt, then $NaBH_4$, 1 equiv, 12 h. rt; (ii) DCC, CH_2Cl_2, rt 3 h; (iii) MCPBA, 1.5 equiv CH_2Cl_2, rt, 3 h; (iv) $NaHCO_3$, 1 equiv, 120 h, xylene, reflux.



Scheme 3. Tandem radical-oxidation process.

of *n*-Bu_3SnH and 1.5 equiv of DLP in benzene at reflux temperature, **12**, the compound of premature reduction, was obtained as the major product (Table 1, entry 1, Scheme 3), accompanied by a minor amount (5%) of **13**, another product of premature reduction (Scheme 3), as well as starting material (~20%). Interestingly, the desired pentacyclic product **6a** was not observed in the reaction mixture, but the indolenine **5a** was isolated as a single diastereoisomer (18%). In an attempt to minimize premature reduction of the intermediate radicals, and thus improve the yield of **5a**, the reaction was carried out using $[(CH_3)_3Si]_3SiH$ as the propagating agent, but the reaction profile did not change (entry 2). Prolonging the addition time of the *n*-Bu_3SnH/DLP solution and the utilization of 2 equiv of DLP both served to favor the production of **5a** (entries 3 and 4). Finally, compound **5a** was produced most efficiently when toluene was used as the solvent (entries 4 and 6).[14] Further increases in both reaction time and DLP neither reduced the formation of **12** and **13**, nor increased the production of **5a**. Dibenzoyl peroxide and dicumyl peroxide were also examined. Although the desired product was isolated, these peroxides proved to be less efficient than DLP in the production of **5a** (entries 7 and 8).

A significant amount of the product **14**, which comes from the hydrolysis of the enamide moiety in the starting material, was formed in all the experiments. This product was formed presumably as a consequence of the lauric acid produced from the peroxide during the oxidation process. Attempts to avoid this side product by the addition of Na_2CO_3 to the reaction mixture, did not improve the yields. We also searched for the dimers and/or trimers of the indolenine **5a** by HPLC/MS analysis of the crude reaction mixture, but they were not present. To gain insights into the reaction mechanism, the process was carried out using a catalytic amount of ACN (1,1′-azobis(cyclohexanecarbonitrile) as the initiator (entry 9). Interestingly, the major product formed in this experiment was the tetrahydroisoquinoline **13**, and no trace of the product which would be formed by reduction of the radical **4** was observed. The lack of this latter product suggests that the cyclization of the radical **2** to the spiro-radical **4** is slower than formation of iminium ion **5** in the presence of excess of DLP or reduction to **13** in the presence of Bu_3SnH, when a catalytic amount of ACN is used. These results are not conclusive, however, and more experiments must be performed to firmly establish the actual mechanistic pathway.

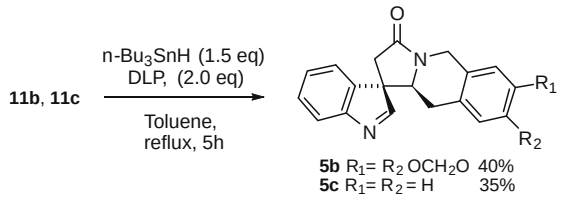
Under the optimized conditions (entry 4),[14] acyl enamides **11b** and **11c** also afforded the corresponding indolenines **5b** and **5c** as the major products (Scheme 4).

The structure of **5a** was confirmed by its NMR spectral features. The ^1H NMR spectrum of compound **5a** showed a signal at δ 8.26 ppm (singlet 1H), and two groups of signals at δ 4.05–4.02 ppm and δ 2.9–2.49, typical for an A_2X system for protons at 10′ and 10a′. The ^{13}C NMR spectrum exhibits the signals at δ

Table 1
Optimization of product yield

Entry	Conditions[a]	*t* (h)	Yield (%)			
			5a	**12**	**13**	**14**
1	*n*-Bu_3SnH (1.3 equiv) DLP, (1.5 equiv), benzene, reflux	3	18	25	5	5
2	$[(CH_3)_3Si]_3SiH$ (1.5 equiv) DLP, (1.5 equiv), benzene, reflux	3	20	20	nd	15
3	*n*-Bu_3SnH (1.5 equiv) DLP, (2.0 equiv), benzene, reflux	5	25	nd	11	16
4	*n*-Bu_3SnH (1.5 equiv) DLP, (2.0 equiv), toluene reflux	5	40	15	10	12
5	$[(CH_3)_3Si]_3SiH$ (1.5 equiv) DLP, (2.0 equiv), benzene, reflux	5	32	nd	12	15
6	$[(CH_3)_3Si]_3SiH$ (1.5 equiv) DLP, (2.0 equiv), toluene, reflux	5	37	10	10	14
7	*n*-Bu_3SnH (1.5 equiv) DBP, (2.0 equiv), toluene, 95 °C	5	20	nd	nd	nd
8	*n*-Bu_3SnH (1.5 equiv) DCP, (2.0 equiv), chlorobenzene	5	24	nd	nd	nd
9	*n*-Bu_3SnH (1.5 equiv) ACCN (0.5 equiv), toluene	5	Traces	23	28	

[a] *Concentration*: 0.1 mmol/mL for both the starting material and the added solution of *n*-Bu_3SnH/DLP.



Scheme 4. Spirocyclization of **11b** and **11c**.

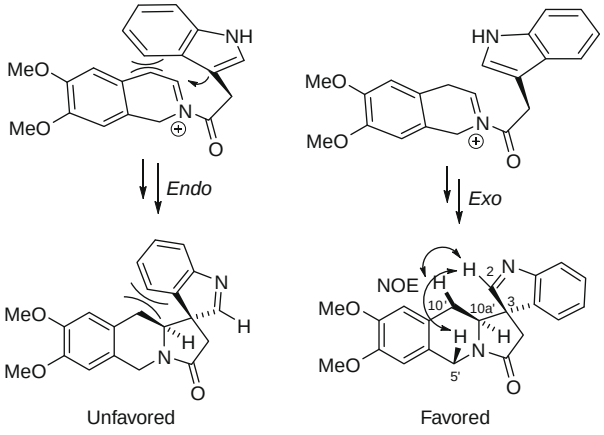


Figure 1. Stereoselectivity in the spirocyclization process.

172.9 ppm (C-2) and δ 59.9 ppm (C-3), assigned to a C-imine and C-spiro quaternary carbon, respectively, values confirmed by a distortionless enhancement by polarization transfer (DEPT) experiment. The heteronuclear single quantum correlation (HSQC) experiment showed the correlation C-H 172.9–8.26 ppm and established the occurrence of the C–H imine. The stereochemistry of **5a** was supported by a NOESY experiment which confirmed the correlation between protons C-2 and one of the C-10′protons and the C-5′ proton (Fig. 1). The high diastereoselectivity of the process can be rationalized on the basis of the endo/exo models in the cyclization process as depicted in Figure 1. It is likely that there is a strong steric repulsion between the hydroisoquinoline ring and the aromatic ring of the indole nucleus in the *endo* model. In contrast, these stereoelectronic interactions are alleviated in the *exo* model, facilitating the formation of **5a**. In a previous study of related systems, the mixture of the two possible diastereoisomers was observed. Apparently, the presence of the fused benzene ring in the piperidine moiety (isoquinoline moiety) is responsible for the repulsive interactions in the present system.

Finally, several reaction conditions, such as *p*-toluenesulfonic acid or BF_3–Et_2O in refluxing toluene, or trifluoromethanesulfonic acid in hot dioxane (100 °C)[11] all failed to transform the spirocyclic system **5a** into the corresponding pentacyclic system **6a**. Initially, no reaction was observed and only decomposition of the starting material occurred after longer reactions times (5 h).

In summary, in the present work, we report a novel, stereoselective, tandem *6-endo* radical cyclization–oxidation-ionic spirocyclization process, using a *n*-Bu_3SnH/DLP mixture, which has given access to new spiroindolenines. The organic peroxide acts as both the initiator and the oxidant.

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14. *General procedure. 7′,8′-dimethoxy-10′,10a′-dihydro-2′H-spiro[indole-3,1′-pyrrolo[1,2-b]isoquinolin]-3′(5′H)-one* (**5a**): To a deaerated solution of enamide **11a** (0.15 g, 0.35 mmol) and Na_2CO_3 (0.03 g, 0.35 mmol) in 5 mL of toluene at 95 °C, a solution of *n*-Bu_3SnH (0.15 g, 0.52 mmol) (0.1 mmol/mL) and 0.27 g (0.72 mmol) of dilauroyl peroxide in toluene (5 mL), was added dropwise (syringe pump) over 5 h. The reaction mixture was then cooled and the solvent was removed under reduced pressure. The crude residue was stirred with an 8% solution of KF in water (10 mL) over night. Then, saturated solution of $NaHCO_3$ was added (250 mL) and the resulting mixture was extracted with CH_2Cl_2 (3×25 mL). The organic layer was dried over Na_2SO_4. The solvent was then removed under reduced pressure and the residue was purified by flash chromatography on silica gel (Hexanes–EtOAc) to give **5a** (0.049 g, 40% yield) as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 8.26 (s, 1H), 7.70 (d, J = 7.50 Hz, 1H), 7.45–7.42 (m, 2H), 7.33 (dd, J = 7.5, 15 Hz, 1H), 6.64 (s, 1H), 6.49 s, 1H), 4.96 (d, J = 17.0 Hz, 1H), 4.41 (d, J = 17.0 Hz, 1H), 4.03 (dd, J = 4.0, 11.5 Hz, 1 H), 3.86 (s, 3H), 3.77 (s, 3H), 2.91–2.75 (m, 3H), 2.51 (dd, J = 4.0, 15.0, Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 172.9, 171.6, 154.6, 148.4, 148.0, 139.6, 129.1, 127.3, 124.1, 122.9, 121.6, 121.3, 111.6, 109.2, 60.3, 59.9, 56.0, 55.9, 42.9, 36.4, 31.3. IR (film): 3342, 3010, 2925, 2854, 1684, 1516, 1462, 1264, 1107, 753. MS (EI) m/z = 348 (100%). HRMS calcd for $C_{21}H_{20}O_3N_2$: 349.1552. Found 349.1542.
9a,10-Dihydro-5H-spiro[[1,3]dioxolo[4,5-g]pyrrolo[1,2-b]isoquinoline-9,3′-indol]-7(8H)-one (**5b**) (40% yield) as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 8.24

(s, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.45–7.42 (m, 2H), 7.33 (dd, *J* = 7.5, 15.0 Hz, 1H), 6.62 (s, 1H), 6.46 (s, 1H), 5.92 (s, 1H), 4.91 (d, *J* = 17 Hz, 1H), 4.39 (d, *J* = 17 Hz, 1H), 4.01 (dd, *J* = 4.0, 11.5 Hz, 1H), 2.87–2.75 (m, 3H), 2.47 (dd, *J* = 4.0, 15 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 172.7, 171.5, 154.7, 147.1, 146.7, 139.1, 129.1, 127.3, 125.2, 124.1, 121.7, 121.3, 108.7, 106.4, 101.5, 60.1, 59.1, 43.2, 36.4, 31.7. IR (film): 3323, 3054, 2923, 2849, 1688, 1484, 1239, 1037. MS (EI) *m*/*z* = 332 (20%). HRMS calcd for $C_{20}H_{16}O_3N_2$: 333.1239. Found 333.1241.

10′,10a′-Dihydro-2′H-spiro[indole-3,1′-pyrrolo[1,2-b]isoquinolin]-3′(5′H)-one (**5c**) (30% yield) as yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm: 8.26 (s, 1H), 7.70 (d, J = 7.5 Hz, 1H), 7.47–7.42 (m, 2H), 7.33 (dd, *J* = 7.5, 15 Hz, 1H), 7.23–7.15 (m, 3H), 7.04–7.01 (m, 1H), 5.02 (d, *J* = 17 Hz, 1H), 4.51 (d, *J* = 17 Hz, 1H), 4.06 (dd, *J* = 4.0, 11.5 Hz, 1H), 2.96–2.77 (m, 3H), 2.59 (dd, *J* = 4.0, 15 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ ppm: 172.7, 171.6, 154.6, 139.3, 132.1, 131.0, 129.1, 129.0, 127.3, 127.2, 127.0, 126.7, 121.6, 121.3, 60.1, 59.9, 43.2, 36.4, 31.7. IR (film): 3340, 3026, 2927, 2855, 1687, 1478, 1243, 1039. MS (EI) *m*/*z* = 288 (70%). HRMS calculated for $C_{19}H_{16}ON_2$: 289.1341. Found 289.1343.