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# Synthesis of Tetrahydroisoquinocarbazoles via C-2 Alkylation of Indoles with 2-Alkoxypropylanoate Esters

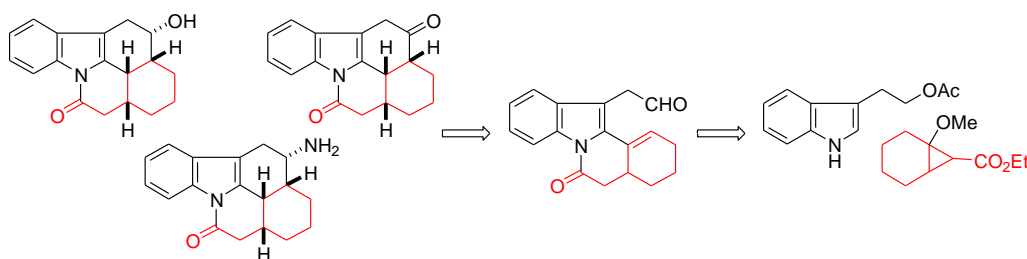
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## ABSTRACT



A concise method for the synthesis of several tetrahydroisoquinocarbazole derivatives is reported, where the core is prepared in 6 steps from tryptophol in 51% overall yield. The pentacyclic analogs are constructed via a dipolar C-2 alkylation of a 3-substituted indole with a 2-alkoxypropylanoate ester, and a SmBr<sub>2</sub>-HMPA mediated ketyl-alkene ring closure.

Considerable synthetic attention has been directed at the development of efficient methods towards the construction and derivatization of indole containing compounds, as this important subunit constitutes the core of a plethora of biologically active natural products.<sup>1</sup> Our research group has recently developed a methodology for

C-2 alkylation of 3-substituted indoles with 2-alkoxypropylanoate esters to give useful indole products,<sup>2</sup> complete with ester and alkene functional group handles for further synthetic manipulation.

Biologically active, fused indole compounds such as the vinca alkaloids have inspired synthetic and medicinal interest in a large class of related tetrahydroisoquinocarbazole analogs, most of which exhibit antiarrhythmic activity.<sup>3,4</sup> Among the most potent

(1) Asymmetric C-3 Friedel-Craft reactions: a) Wang, Y.-Q.; Song, J.; Hong, R.; Li, H.; Deng, L. *J. Am. Chem. Soc.* **2006**, *128*, 8156-8157. b) Palomo, C.; Oiarbide, M.; Kardak, B. G.; Garcia, J. M.; Linden, A. *J. Am. Chem. Soc.* **2005**, *127*, 4154-4155. c) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780-10781. Alkylations: a) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314-6315. b) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592-4593. Radical couplings: Baran, P. S.; Richter, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 7450-7451. Arylations: a) Deprez, N. R.; Kalyani, D.; Krause, A.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 4972-4973. b) Wang, X.; Lane, B. S.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 4996-4997. c) Bressy, C.; Alberico, D.; Lautens, M. *J. Am. Chem. Soc.* **2005**, *127*, 13148-13149. Michael-additions: Zhou, J.; Tang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 9030-9031. C-H activation: Davies, H. M. L.; Manning, J. R. *J. Am. Chem. Soc.* **2006**, *128*, 1060-1061. N-arylations: Antilla, J. C.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 11684-11688.

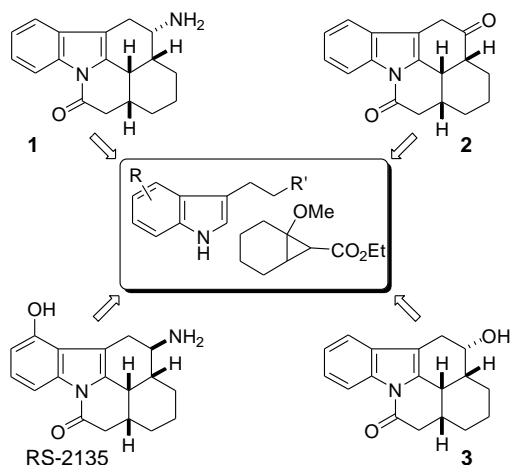
(2) Bajtos, B.; Yu, M.; Zhao, H.; Pagenkopf, B. L. *J. Am. Chem. Soc.* **2007**, *129*, 9631-9634.

(3) a) Simoji, Y.; Saito, F.; Tomita, K.; Morisawa, Y. *Heterocycles* **1991**, *32*, 2389-2397. b) Simoji, Y.; Tomita, K.; Hashimoto, T.; Saito, F.; Morisawa, Y.; Mizuno, H.; Yorikane, R.; Koike, H. *J. Med. Chem.* **1992**, *35*, 816-822. c) Fukazawa, T.; Simoji, Y.; Hashimoto, T.; *Tetrahedron: Asymmetry* **1996**, *7*, 1649-1658. d) Hashimoto, T.; Fukazawa, T.; Masuko, H.; Shimoji, Y.; Koike, H.; Mizuno, H. Eur. Patent, 1991, EP 415776 A2. e) Hiraoka, T.; Birdsall, N. J. M.; Gharagozloo, P.; Lazareno, S. UK Patent, 1996, GB 2 292 685 A.

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members of this class, RS-2135 has attracted the most attention because of its relatively low toxicity. In the only synthetic approach to these compounds reported thus far, Simoji and Hashimoto employed an elegant intramolecular Diels-Alder reaction to construct the core.<sup>3a-d</sup> Herein, we report the short syntheses of several related tetrahydroisoquinocarbazoles (**1**, **2**, and **3**, Scheme 1) by employing the C-2 alkylation of indoles with donor acceptor (DA) cyclopropanes and a SmBr<sub>2</sub>-HMPA mediated reductive cyclization as key synthetic steps.

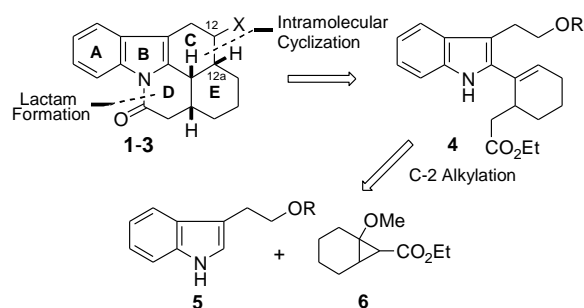
**Scheme 1.** Application of C-2 Alkylation of Indoles with DA Cyclopropanes



From our initial retrosynthetic analysis, we identified the disconnection between C-12 and C-12a as being strategically important as it simplifies the target core to indole **4**, which is readily available from our C-2 alkylation methodology (Scheme 2). It was anticipated that ring C could be constructed by several strategies, including hydrometallation of alkene **4**, followed by appropriate ring closure conditions. The same disconnection would also allow radical cyclizations to be explored, such as selenoester or samarium(II) iodide mediated ring closures. The lactam bond could be constructed via a base induced cyclization with the indole nitrogen and ester moiety in intermediate **4**,<sup>2</sup> which would be accessible from C-2 alkylation between 3-substituted indole **5** and DA cyclopropane **6**.

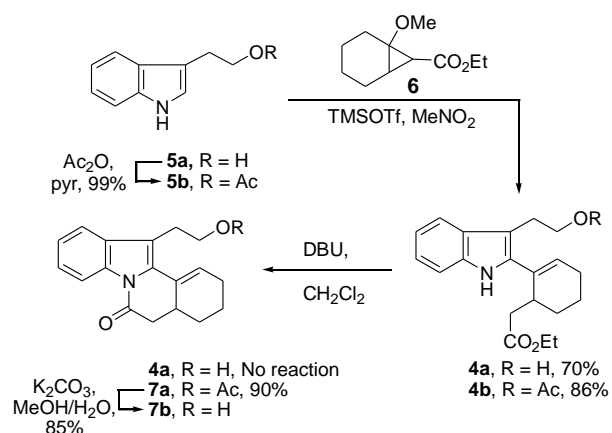
c) Yorikane, R.; Hiroshi, M.; Itoh, Y.; Miyake, S.; Koike, H. *J. Cardiovasc. Pharmacol.* **1994**, *24*, 28–36. d) Sakuta H.; Okamoto K.; Watanabe Y. *Br. J. Pharmacol.* **1993**, *109*, 866–872. e) Yorikane, R.; Sada, T.; Koike, H. *J. Cardiovasc. Pharmacol.* **1993**, *21*, 430–434. f) Yorikane, R.; Sada, T.; Koike, H. *J. Cardiovasc. Pharmacol.* **1992**, *20*, 955–960.

**Scheme 2.** Retrosynthetic Analysis



The synthesis commenced with the C-2 alkylation of commercially available tryptophol (**5a**) with cyclopropane **6** to give indole **4a** in a moderate 70% yield (Scheme 3).<sup>5</sup> However, closure of the D-ring with this intermediate under basic conditions proved elusive. Acting on speculation that the free alcohol was interfering in the lactamization process, acylated derivative **5b** was employed instead, and the C-2 alkylation product was obtained in 86% yield. The resulting indole **4b** was effectively converted to the lactam without difficulty upon treatment with DBU. Subsequent deprotection of the alcohol allowed access to indole **7b**, thus setting the stage to explore ring C construction.

**Scheme 3.** C-2 Alkylation and Lactam Formation



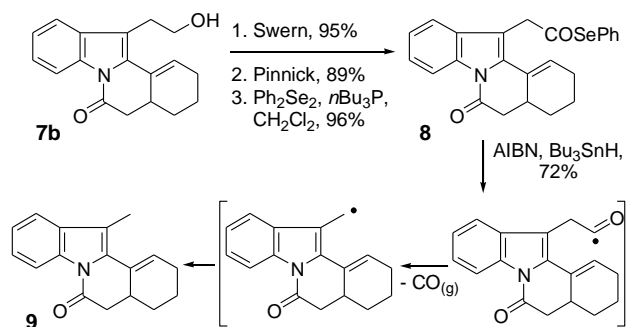
Early approaches for ring C assembly involved elaborating alkene **7b** via hydrometallation strategies, potentially supplying a collection of suitable handles (OH, halides) with which to facilitate cyclization. Unfortunately, all attempts at alkene functionalization with **7b** led to starting material recovery or substrate decomposition.

(5) Identical results were obtained from either diastereotopic cyclopropane or mixtures.

While initially opting for alkene elaboration prior to cyclization, a revised strategy involved exploring radical mediated ring closures. Selenoesters have long been recognized as precursors to acyl radicals that actively participate in inter- and intramolecular alkene addition reactions.<sup>6</sup> Despite the usual preference for free radicals to undergo 5-*exo-trig* over 6-*endo-trig* cyclizations, Boger and co-workers demonstrated that in some cases the latter is favored.<sup>6</sup>

Encouraged by these reports, selenoester **8** was prepared via a three step sequence commencing with Swern oxidation of alcohol **7b** (Scheme 4). The resulting aldehyde was immediately oxidized and treated with diphenyl diselenide and tributylphosphine, providing cyclization precursor **8** in 81% yield over three steps. An acyl radical was then generated from selenoester **8**, but regrettably, a stabilized radical is formed after rapid decarbonylation, ultimately giving 3-methyl indole **9** as the exclusive product.

**Scheme 4.** Selenoester Cyclization Approach



Operating through the aldehyde oxidation state appeared to be an attractive means to further explore a radical cyclization strategy while precluding the undesired decarbonylation. In this regard, both inter- and intramolecular carbonyl-alkene/alkyne reductive coupling reactions mediated by samarium(II) iodide are well documented.<sup>7</sup> Both aldehydes and ketones participate as coupling partners, but a large majority of these radical induced cyclizations with aldehydes employ electrophilic  $\alpha,\beta$ -unsaturated esters or allylic leaving groups including halides, sulfides, and sulfones.<sup>8</sup>

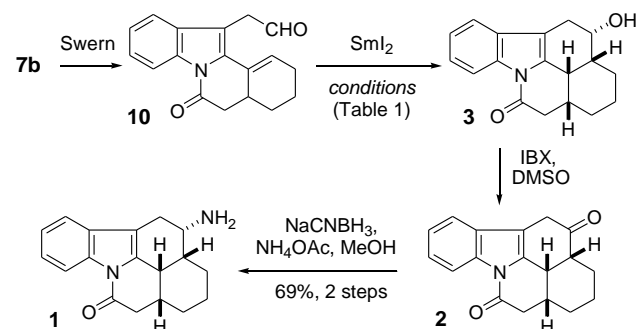
(6) Boger, D. L.; Mathvink, R. J. *J. Org. Chem.* **1992**, *57*, 1429–1443, and references therein.

(7) a) Kagan, H. B. *J. Alloys Compd.* **2006**, *408-412*, 421–426. b) Edmonds, D. J.; Johnston, D.; Procter, D. *J. Chem. Rev.* **2004**, *104*, 3371–3403. c) Dahlen, A.; Hilmersson, G. *Eur. J. Inorg. Chem.* **2004**, *17*, 3393–3403. d) Kagan, H. B. *Tetrahedron* **2003**, *59*, 10351–10372. e) Molander, G. A.; Harris, C. R. *Tetrahedron* **1998**, *54*, 3321–3354. f) Skrydstrup, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 345–347. g) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307–338. h) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29–68.

(8)  $\alpha,\beta$ -Unsaturated esters: a) Villar, H.; Guibe, F. A. *Tetrahedron Lett.* **2002**, *43*, 9517–9520. b) Johnston, D.; Francon, N.; Edmonds, D. J.; Procter, D. *J. Org. Lett.* **2001**, *3*, 2001–2004. c) Johnston, D.; McCusker, C. F.; Muir, K.; Procter, D. *J. Chem. Soc., Perkin Trans. 1*

The aldehyde cyclization precursor was efficiently prepared by Swern oxidation of alcohol **7b**, which was immediately treated with 2.2 equivalents of 0.1 M SmI<sub>2</sub> in THF (Scheme 5). Two major reaction products were obtained under these conditions, including the desired secondary alcohol **3** and **7b** from aldehyde reduction in a 1.2:1.0 ratio (Table 1, entry 1).

**Scheme 5.** Completion of Several Tetrahydroisoquinocarbazoles



**Table 1.** Optimization Data for SmI<sub>2</sub> Cyclization with Additives

entry	additives (equiv) <sup>a</sup>	ratio of 3:7b	yield (%) <sup>b</sup>
1	-	1.2:1.0	80
2	HMPA (8.8)	2.0:1.0	85
3	H <sub>2</sub> O (22)	>99:1	33
4	MeOH (22)	>99:1	42
5	LiBr (8.8)	1.4:1.0	91
6	LiBr (8.8), HMPA (110)	>99:1	78

<sup>a</sup> Relative to aldehyde **10**, with 2.2 equivalents of 0.1 M SmI<sub>2</sub> in each reaction. <sup>b</sup> Combined isolated yield of **3** and **7b**, for both steps starting from alcohol **7b**.

Efforts to optimize this cyclization involved exploring various additives such as Lewis bases (HMPA), proton sources (H<sub>2</sub>O, MeOH), and inorganic salts (LiBr), all of which have been documented to profoundly affect SmI<sub>2</sub> mediated reactions.<sup>7</sup> According to Flowers and co-workers, the oxidation potential of SmI<sub>2</sub> alone is -1.33 V (vs. Ag/AgNO<sub>3</sub> in THF), and was found to increase to a maximum of -2.05 V with four equivalents of added HMPA.<sup>9</sup> When these conditions were applied to the intramolecular coupling reaction, an increase in selectivity

**2000**, 681–695. d) Enholm, E. J.; Satici, H.; Trivellas, A. *J. Org. Chem.* **1989**, *54*, 5841–5843. e) Enholm, E. J.; Trivellas, A. *J. Am. Chem. Soc.* **1989**, *111*, 6463–6465. Allylic halides: a) Matsuda, F.; Sakai, T.; Okada, N.; Miyashita, M. *Tetrahedron Lett.* **1998**, *39*, 863–864. b) Souppe, J.; Namy, J. L.; Kagan, H. B. *Tetrahedron Lett.* **1982**, *23*, 3497–3500. Sulfides and sulfones: a) Kan, T.; Nara, S.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5111–5113. b) Kan, T.; Hosokawa, S.; Oikawa, M.; Ito, S.; Matsuda, F.; Shirahama, H. *J. Org. Chem.* **1994**, *59*, 5532–5534.

(9) Shabangi, M.; Flowers II, R. A. *Tetrahedron Lett.* **1997**, *38*, 1137–1140.

toward cyclization over aldehyde reduction was observed (Table 1, entry 2).

Protic additives such as water and methanol have also been shown to influence similar radical processes,<sup>7</sup> as they likely activate the reagent through metal coordination and protonate anionic intermediates.<sup>10</sup> Although these proton sources improved selectivity for the cyclization product **3** over aldehyde reduction, significantly lower yields were accompanied with considerable decomposition (Table 1, entries 3 and 4).

Inorganic salts such as LiBr have been shown to participate in displacement reactions with SmI<sub>2</sub>, producing soluble SmBr<sub>2</sub>.<sup>11</sup> Cyclizations with the soluble SmBr<sub>2</sub> reducing agent provided an unfavorable mixture of **3** and **7a**, although in excellent combined yield (Table 1, entry 5). Flowers also found that the addition of 50 equivalents of HMPA significantly improved the reducing ability of SmBr<sub>2</sub> (−2.07 V for SmBr<sub>2</sub> versus −2.63 V for SmBr<sub>2</sub>–HMPA).<sup>11</sup> Optimal results were achieved by a combination of several known additives, specifically LiBr and HMPA (Table 1, entry 6). The SmBr<sub>2</sub>–HMPA reductant prepared under Flowers' conditions displayed excellent selectivity for cyclization to **3** in 78% yield. The relative stereochemistry of **3** was established by extensive NMR analysis.<sup>12</sup>

To further illustrate the utility of this approach additional modifications were made to the functionalized core (Scheme 5). Oxidation of alcohol **3** with IBX proceeded smoothly to afford ketone **2**, which was advanced to amine **1** after reductive amination. Presumably, other functionalized cores can be accessed by elaboration of the starting indole or cyclopropane.

In summary, we have reported the most efficient and highest yielding route to several tetrahydroisoquinocarbazoles, where the core (**3**) was prepared in 6 steps from tryptophol in 51% overall yield. This work highlights for the first time the synthetic utility of the dipolar C-2 alkylation of 3-substituted indoles with 2-alkoxycyclopropanoate esters, and provides an attractive route to other biologically active members of this class, including RS-2135. The synthesis also features a selective SmBr<sub>2</sub>–HMPA promoted ring closure of an aldehyde onto a sterically congested trisubstituted alkene.

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**Supporting Information Available:** General experimental procedures and characterization of all new compounds, and copies of NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(11) Knettle, B. W.; Flowers II, R. A. *Org. Lett.* **2001**, *3*, 2321–2324.

(12) <sup>1</sup>H, <sup>13</sup>C, gCOSY, gHSQC, and NOESY for **1**, **2**, and **3** can be found in the Supporting Information.