JOC*Note*

# Practical Synthesis and Elaboration of Methyl 7-Chloroindole-4-carboxylate

Phil B. Alper* and KhanhLinh T. Nguyen

*The Genomics Institute of the Novartis Foundation, 10675 John Jay Hopkins, San Diego, California 92121-1125*

*palper@gnf.org*

*Received September 10, 2002*

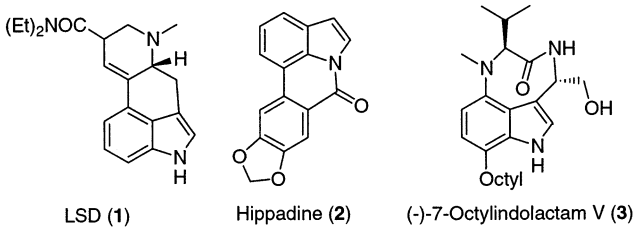
**Abstract:** A synthesis of a previously unknown indole derivative is presented. The route reported herein allows for the preparation of multihundred gram quantities of material without any chromatographic purification. Conditions are presented for the Pd-catalyzed elaboration of one of the "diversity generating elements" of this important pharmacophore.

The prominence of the indole nucleus in medicinally important natural products and synthetic pharmaceuticals can hardly be overstated.[1] As a result, the chemistry of the substituted indole has received an enormous amount of attention.[2] The revolution of combinatorial chemistry of small molecules[3] assured that the synthesis of indole-containing lead compounds would be accelerated in a manner similar to all other scaffolds.[4]

It was the tremendous variety of biological activities associated with indoles that made them a scaffold of choice for a multiple assay high throughput screening effort such as the one at our institute. We wanted to design an indole core that would allow for synthesis of a diverse set of molecules, which could elicit the greatest possible variety of biological responses possible from a single starting point.

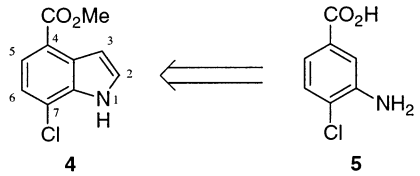
When thinking about the design of such a scaffold, it was desirable to leave the pyrrole ring unsubstituted since this ring has a rich chemistry associated with it. To introduce appropriate handles for diversification chemistry, we needed to choose which positions of the benzene ring were to be modified.

Figure 1 shows three natural products that have nonrelated biological activities. Lysergic acid diethyl amide (**1**) is a hallucinogen and CNS activator[5] in addition to a plethora of physiological effects.[6] Hippadine (**2**) causes reversible inhibition of fertility in male rats without antimitotic activity.[7] (−)-7-Octylindolactam V (**3**) is a protein kinase C modulator.[8] The structural properties that these molecules share is their substitution in




LSD (**1**) Hippadine (**2**) (-)-7-Octylindolactam V (**3**)

**FIGURE 1.** Representative indole-containing substances.




**4** **5**

**FIGURE 2.** Designed indole scaffold and proposed starting material.

positions 4 and 7 of the indole nucleus. It was therefore decided to equip our scaffold with chemically orthogonal substituents at positions 4 and 7.

Figure 2 shows the structure of the scaffold **4** chosen for further study along with the proposed starting material **5**. With the inherent alkylative, electrophilic, and nucleophilic properties of positions 1, 2, and 3 and the diverse chemistries available to the substituents at

(1) (a) Gribble, G. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 2, p 207. (b) Ban, Y.; Murakami, Y.; Iwasawa, Y.; Tsuchia, M.; Takano, N. *Med. Res. Rev.* **1998**, *8* (2), 231. (c) Saxton, J. E. *The Chemistry of Heterocyclic Compounds*; Wiley: New York, 1983; Vol. 25, Part IV.

(2) For some leading reviews, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (b) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: New York, 1996; Vol. 2, p 119. (c) Hughes, D. L. *Org. Prep. Proc. Int.* **1993**, 607.

(3) For some introductory reviews, see: (a) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*(10), 1385. (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (c) Balkenhohl, F.; von dem Bussche-Hunnefeld, C.; Lansky, A.; Zechel, C. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2288.

(4) (a) Hutchins, S. M.; Chapman, K. T. *Tetrahedron Lett.* **1996**, *37*(28), 4869. (b) Yun, W.; Mohan, R. *Tetrahedron Lett.* **1996**, *37*(40), 7189. (c) Hughes, I. *Tetrahedron Lett.* **1996**, *37*(42), 7595. (d) Cheng, Y.; Chapman, K. T. *Tetrahedron Lett.* **1997**, *38*(9), 1497. (e) Fagnola, M. C.; Visentin, I. C. G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*(13), 2307. (f) Zhang, H.-C.; Marianoff, B. E. *J. Org. Chem.* **1997**, *62*, 1804. (g) Arumugam, V.; Routledge, A.; Abell, C.; Balasubramanian, S. *Tetrahedron Lett.* **1997**, *38*(36), 6473. (h) Collini, M. D.; Ellingboe, J. W. *Tetrahedron Lett.* **1997**, *38*(46), 7963. (i) Fokas, D.; Ryan, W. J.; Casebier, D. S.; Coffen, D. L. *Tetrahedron Lett.* **1998**, *39*, 2235. (j) Zhang, H.-C.; Brumfield, K. K.; Jaroskova, L.; Maryanoff, B. E. *Tetrahedron Lett.* **1998**, *39*, 4449. (k) Smith, A. L.; Stevenson, G. I.; Swain, C. J.; Castro, J. L. *Tetrahedron Lett.* **1998**, *39*, 8317. (l) Wang, Y.; Huang, T.-N. *Tetrahedron Lett.* **1998**, *39*, 9605. (m) Stephensen, H.; Zaragoza, F. *Tetrahedron Lett.* **1999**, *40*, 5799. (n) Wang, H.; Ganesan, A. *Org. Lett.* **1999**, *1*(10), 1647. (o) Zhang, H.-C.; Ye, H.; Moretto, A. F.; Brumfield, K. K.; Maryanoff, B. E. *Org. Lett.* **2000**, *2*(1), 89. (p) Kraxner, J.; Arlt, M. Gmeiner, P. *Synlett* **2000**,(1), 125. (q) Tois, J.; Franzen, R.; Aitio, O.; Huikko, K.; Taskinen, J. *Tetrahedron Lett.* **2000**, *41*, 2443. (r) Ketcha, D. M.; Wilson, L. J.; Portlock, D. E. *Tetrahedron Lett.* **2000**, *41*, 6253. (s) Smith, A.; Stevenson, G. I.; Lewis, S.; Patel, S.; Castro, J. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2693. (t) Stevenson, G. I.; Smith, A. L.; Lewis, S.; Michie, S. G.; Neduvelil, J. G.; Patel, Sm.; Marwood, R.; Patel, Sh.; Castro, J. L. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2697. (u) Nettekoven, M. *Tetrahedron Lett.* **2000**, *41*, 8251. (v) Meseguer, B.; Alonso-Diaz, D.; Griebenow, N.; Herget, T.; Waldmann, H. *Chem. Eur. J.* **2001**, *6*(21), 3943. (w) Cooper, L. C.; Chicchi, G. G.; Dinell, K.; Elliott, J. M.; Hollingsworth, G. J.; Kurtz, M. M.; Locker, K. L.; Morrison, D.; Shaw, D. E.; Tsao, K.-L.; Watt, A. P.; Williams, A. R.; Swain, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1233.

(5) (a) Jenner, P.; Luscombe, G.; Marsden, C. D. *Br. J. Pharmocol.* **1983**, *80*, Suppl. 667P. (b) Kaiser, C.; Jain, T. *Med. Res. Rev.* **1985**, *5*, 145.

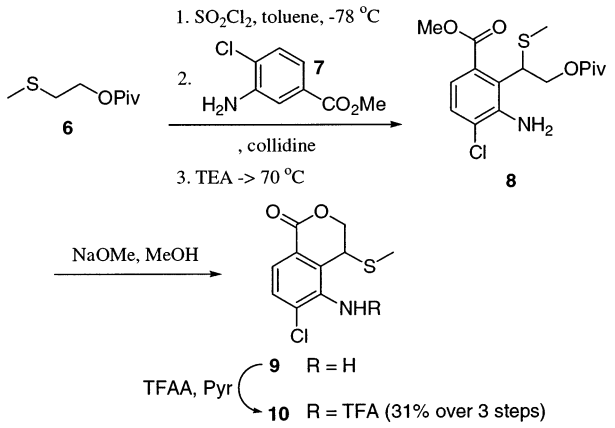
(6) (a) Bowers, M. B., Jr.; Salamonsson, L. A. *Biochem. Pharmocol.* **1982**, *31*, 4093. (b) Mornex, R.; Hugues, B. *J. Pharmocol.* **1983**, *14* (Suppl. 3), 81.

(7) Chattopadhyay, S.; Chattopadhyay, U.; Mathur, P. P.; Saini, K. S.; Ghosal, S. *Planta Med.* **1983**, *49*, 252.

(8) Kazanietz, M. G.; Areces, L. B.; Bahador, A.; Mischak, H.; Goodnight, J.; Mushinski, J. F.; Blumberg, P. M. *Mol. Pharmacol.* **1993**, *44*, 298.

10.1021/jo026434p CCC: $25.00 
Published on Web 02/08/2003

**SCHEME 1. Synthesis of the First Crystalline Intermediate**



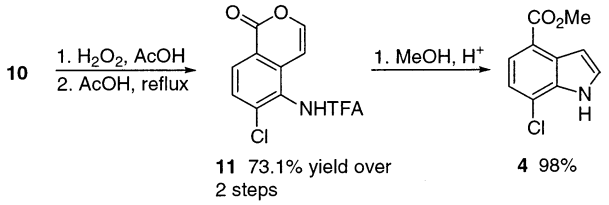

positions 4 and 7, this was thought to be a good starting point for development of libraries of lead generating compounds.

The synthesis of 4,7-disubstituted indoles with a carboxylate equivalent in the 4 position and a leaving group or precursor in the 7 position has been explored by several synthetic methods. However, most of these routes suffered from either the probability of regiochemical problems leading to isolation difficulties,[9] the need for chromatography,[10] or the need for multistep manipulations from the reported compound to get to the desired material.[11]

In this paper, we report the development of a large scale, practical synthesis of **4** from **5** along with a method for functionalizing the chloride via Pd catalysis. The chemistry that we chose to install the pyrrole ring was the Sommelet−Hauser rearrangement of aryl sulfilimines.[12] Since this chemistry had been applied to the synthesis of indoles derivatives,[13] and specifically 2-chloro-substituted indoles,[13e] we felt that this would be a fruitful pathway.

The synthesis (Scheme 1) started by coupling 2-methylthioethyl 1,1-dimethyl acetate **6** (available in 97% yield from 2-methylthioethanol) with methyl 3-amino-4-chlorobenzoate (**7**) (available on large scale in 80% yield from **5**) to form a sulfilimine (Scheme 1). The classical conditions of activation using chlorine gas were quite inconvenient, and the use of NCS either to activate the sulfide alone or to do the reaction in the presence of both **6** and **7** led to unsatisfactory results. Activation of **6** using $SO_2Cl_2$ turned out to generate a very electrophilic species that readily coupled with **7** at low temperature in the presence of collidine. The resulting sulfilimine was directly treated with excess triethylamine and heated to 70 °C to generate, after aqueous workup, the rearrangement product **8** as an oil, which was carried on without purification.

**SCHEME 2. Final Steps to the Desired Compound**




The next transformation required to make the indole by the reported route[13d,e] was to make the *p*-toluenesulfonamide from **8**, which would hopefully be crystalline. In our hands, all attempts to effect this transformation met with failure. An alternate pathway had to be taken, and the first order of business was to find a crystalline intermediate that could easily be purified.

Treatment of **8** with NaOMe in MeOH effected the cleavage of the pivalate ester and subsequent spontaneous cyclization to the lactone (**9**), also an oil. Lactone **9** was treated with TFAA and pyridine, and the resulting trifluoroacetamide **10** was crystalline and insoluble in methylene chloride. These properties enabled isolation of pure **10** in a single crystallization in 31% yield after three steps.

To get **10** to **4**, the sulfide had to be eliminated to the double bond. This was accomplished by oxidizing to the diastereomeric mixture of sulfoxides with a stoichiometric amount of hydrogen peroxide and without isolation eliminating methyl sulfinic acid by refluxing in AcOH to generate the isocoumarin **11** as a solid (Scheme 2). Finally, treatment of **11** with sulfuric acid in refluxing methanol afforded **4** as a pure substance in nearly quantitative yield after aqueous workup. In this way, more than 250 g of **4** was prepared in the laboratory without the need for a single chromatographic purification.

We next focused our attention on functionalizing **4** to generate useful derivatives. Palladium-catalyzed carbon−carbon bond forming chemistry has become a mainstay of the organic chemist because of its reliability and tolerance of sensitive functional groups.[14] The longstanding condition of needing aromatic bromides or iodides in order to effect C−C bond forming reactions has recently been overcome,[15] and it is now possible to use chlorides.

(9) (a) Bowman, R. E.; Goodburn, T. G.; Reynolds, A. A. *J. Chem. Soc., Perkin Trans. 1* **1972**, 1121. (b) Ponticello, G. S.; Baldwin, J. J.; Lumma, P. K.; McClure, D. E. *J. Org. Chem.* **1980**, *45*, 6. (c) Nagasaka, T.; Yuge, T.; Ohki, S. *Heterocycles* **1977**, 371.

(10) (a) Dobson, D.; Todd, A.; Gilmore, J. *Synth. Commun.* **1991**, 611. (b) Santangelo, F.; Casagrande, C.; Norcini, G.; Gerli, F. *Synth. Commun.* **1993**, 2717. (c) Ohno, M.; Shimizu, S.; Eguchi, S. *Heterocycles* **1991**, 1199. (d) Dobbs, A. *J. Org. Chem.* **2001**, *66*, 638.

(11) Cannon, J. G.; Lukszo, J.; Max, G. A. *J. Heterocycl. Chem.* **1983**, 149.

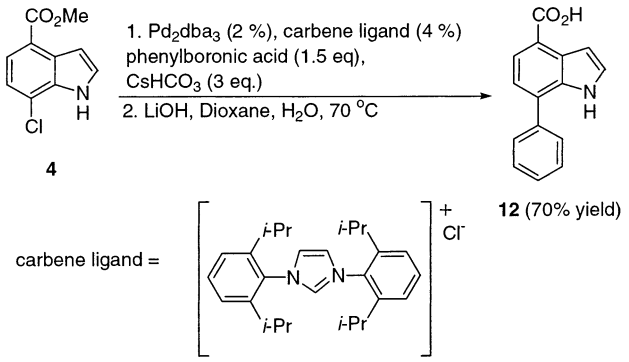
(12) For reviews, see: (a) Claus, P. K.; Rieder, W.; Hofbauer, P. *Tetrahedron* **1975**, *31*, 505. (b) Gilchrist, T. L.; Moody, C. J. *Chem. Rev.* **1977**, *77* (3), 409. (c) Oae, S. *Sulfilimines and Related Derivatives*; American Chemical Society: Washington, DC, 1983; p 7.

(13) For the original references for the Gassman indole synthesis, see: (a) Gassman, P. A.; van Bergen, T. J.; Gilbert, D. P.; Cue, B. W., Jr. *J. Am. Chem. Soc.* **1974**, *96*(17), 5495. (b) Gassman, P. A.; van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*(17), 5508. (c) Gassman, P. A.; Gruetzmacher, G.; van Bergen, T. J. *J. Am. Chem. Soc.* **1974**, *96*(17), 5512. For another approach, see: (d) Murai, Y.; Masuda, G.; Inoue, S.; Sato, K. *Heterocycles* **1991**, *32*(7), 1377. (e) Murai, Y.; Kobayashi, S.; Inoue, S.; Sato, K. *Heteocycles* **1992**, *34*(5), 1017.

(14) For a general review, see: (a) *Metal Catalyzed Cross Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Wienheim, Germany, 1998. For an outstanding monograph on the applications of Pd chemsitry to heterocyclic synthesis, see: Li, J. J.; Gribble, G. W. *Palladium in Heterocyclic Chemistry: A Guide for the Synthetic Chemist*; Baldwin, J. E. et. al., Eds.; Pergamon: New York, 2000.

(15) (a) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722. (b) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1998**, *37*, 3387. (c) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413. (d) Zhang, C.; Huang, J.; Trudell, M. L.; Nolan, S. P. *J. Org. Chem.* **1999**, *64*, 3804. (e) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550. (f) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.

**SCHEME 3. Pd-Catalyzed Arylation of 4**




We wanted to make use of this chemistry to make an $sp^2-sp^2$ C−C bond at position 7 of **4**.

After screening several different reaction conditions, the biaryl indole acid **12** was generated from **4** (Scheme 3), showing that the scaffold can effectively be substituted and made into interesting derivatives. Because it is known that the indole NH can function in a Pd-mediated arylation,[16] we used $CsHCO_3$ as a base instead of $Cs_2CO_3$ to avoid indole NH deprotonation.

In summary, a nine-step synthesis has been developed that delivers a previously unknown indole scaffold in an overall yield of 17.8% from commercially available starting material. The synthesis is robust and scalable to deliver hundreds of grams of material. It was also shown that the halide on **4** can be readily substituted using Pd chemistry.

The production of chemical libraries starting from this scaffold and the screening of these libraries for biological activity are currently ongoing. The results of these studies will be reported in due course.

**Acknowledgment.** This work was supported by the Novartis Charitable Foundation.

**Supporting Information Available:** Characterization data and experimental procedures for the preparation of **4**−**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO026434P

(16) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*(10), 1403.