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Synthesis of Indolocarbazoles via Sequential Palladium Catalyzed Cross-Coupling and Benzannulation Reactions

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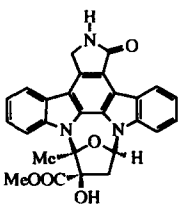
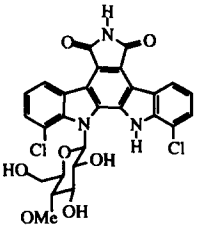
Abstract: Differentially substituted indolocarbazoles are readily prepared via a synthetic route employing two palladium catalyzed reactions. First, biindoles are prepared from a palladium catalyzed cross coupling reaction. Second, a new palladium catalyzed benzannulation reaction employing biindolyl iodides and alkynes provides indolocarbazoles. © 1997 Elsevier Science Ltd.

Indolocarbazole natural products belong to an interesting structural class and often possess potent biological activities including antitumor and protein kinase C inhibitory properties.[1] A few structures representative of naturally occurring indolocarbazoles are shown in Figure 1. Most feature an indolocarbazole core with a centrally fused lactam or imide ring and N-glycosylation. Their novel structures and significant biological activities have prompted many synthetic efforts directed toward the synthesis of the natural products and their structural analogues.[2] Even with the apparent simplicity of the indolocarbazole aglycone, numerous diverse approaches to this ring system have been devised; each with their particular attributes.[2] We report herein new indolocarbazole syntheses employing sequential palladium catalyzed reactions for efficient construction of differentially substituted products.[3]

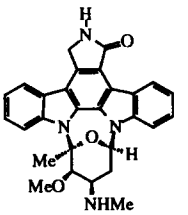
Figure 1



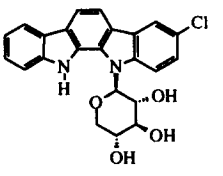
K252a



Rebeccamycin



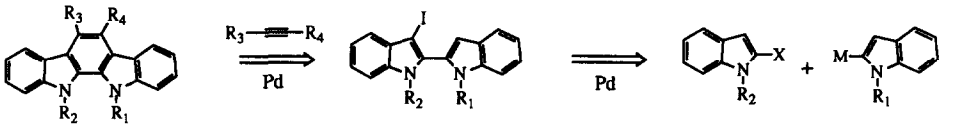
Staurosporine



Tjipanazole

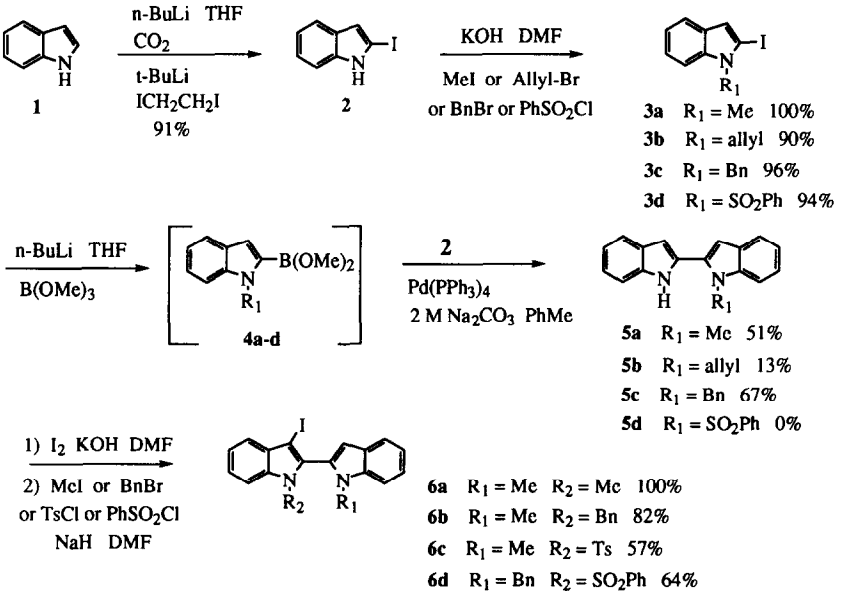
Palladium catalyzed arylations[4] have become increasingly common and cyclizations employing intramolecular alkyne insertion coupled with arylation were recently reported.[5] We envisioned a new palladium catalyzed benzannulation reaction using a 2-halobiaryl and an alkyne coreactant such that oxidative addition, alkyne insertion and arylation would create a new aromatic ring. Thus, our synthetic plan for the preparation of indolocarbazoles employs initial cross couplings of indoles to provide functionalized 2,2'-biindolyls and then new benzannulation reactions via alkyne insertion to complete the central benzene ring of indolocarbazoles (Scheme 1).

Scheme 1

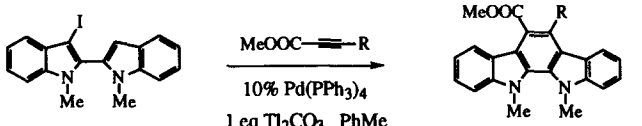


The initial goal was preparation of 2,2'-biindolyl iodides which would serve as substrates for the benzannulation reactions (Scheme 2). Indole was iodinated at the 2-position using the procedure of Bergman and Venemalm[6] and then N-protected. Suzuki cross coupling[7] of the *in situ* generated boronic esters **4** and 2-iodoindole, **2**, provided unsymmetrical 2,2'-biindolyls **5**.[8,9] The reaction is sensitive to the nature of the indole protecting group (**5a**, **5c** vs **5b**, **5d**) although the reasons are not clear other than the possibility of insertion in the case of the allyl group. Stille cross-coupling reactions[10] using indole tin reagents are successful, but result in lower yields. A Negishi cross-coupling[11] employing the zinc analogue of **4** failed due to deprotonation of **2** by the indolezinc intermediate. Iodination at the 3'-position using the procedure of Bocchi and Palla[12] followed by N'-protection yielded iodide substrates **6**.

Scheme 2



Using iodides **6**, we next explored their use in palladium catalyzed benzannulation reactions (eq 1-3). Reaction of **6a** with three equivalents of DMAD, 10 mol % $Pd(PPh_3)_4$, and one equivalent thallium carbonate in toluene yielded indolocarbazole **7** in 54% yield.[13] The product was readily identified by the doublet at 8.21 ppm in the ^1H NMR spectrum for the bay region proton. Methyl heptynoate gave a comparable yield of the unsymmetrical indolocarbazole **8**.

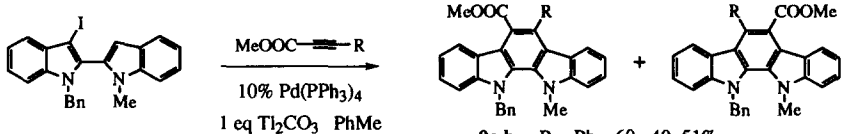


6a

7 R = COOMe 54%
8 R = Bu 56%

(1)

Unsymmetrical biindolyl iodide **6b** provided similar yields of benzannulated products, but somewhat surprisingly, the reactions were only low to modestly regioselective (eq 2). The products were not separable, and thus the structures of the major regioisomers could not be assigned, but the ratios of products were readily determined from the ^1H NMR spectra. The regiochemistry of benzannulation is set by the regiochemistry of initial alkyne insertion. While alkene insertions are generally quite selective,[14] alkyne insertions can be much less so and are generally dominated by steric considerations of the alkyne reactants.[15]

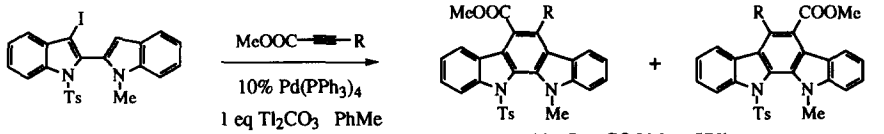


6b

9a,b R = Ph 60 : 40 51%
10a,b R = CH_2OTHP 80 : 20 56%

(2)

Switching to an electron withdrawing protecting group on the iodide substituted indole unit did not appreciably change the regioselectivity of reaction (eq 3). This supports the proposal that the regiochemistry of alkyne insertion, and hence the benzannulation reaction, is dictated by steric considerations and only minimally, if at all, on electronic factors of either the indole or the alkyne.



6c

11 R = COOMe 57%
12a,b R = Ph 67 : 33 88%
13a,b R = Bu 60 : 40 58%

(3)

In summary, we have demonstrated that substituted indolocarbazoles can be formed from a new palladium catalyzed benzannulation reaction using substrates readily prepared by palladium catalyzed cross coupling reactions. This strategy should provide convenient access to indolocarbazole natural products and their analogues, and aromatic compounds in general, though regiochemical issues must still be addressed.

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9. In a typical palladium catalyzed cross coupling reaction, butyllithium (2.72 mL, 4.35 mmol, 1.6 M in hexane) was added to **3c** (1.315 g, 3.95 mmol) in THF (10 mL) at -78°C. After stirring 20 min, trimethyl borate (534 mg, 5.14 mmol) was added dropwise and the reaction mixture was warmed to 0°C and stirred 1.5 h. The solvent was removed *in vacuo* and toluene (10 mL) was added to the yellow oil followed by Na_2CO_3 (3.95 mL, 2M in H_2O) and **2** (959 mg, 3.95 mmol, in 3 mL of toluene). $Pd(PPh_3)_4$ (0.4 mmol) in THF (3 mL) was added and the reaction was heated at reflux for 18 h. The mixture was extracted into ether (100 mL), washed with H_2O (2x 50 mL), dried ($MgSO_4$) and the solvent was removed *in vacuo*. Purification by flash chromatography (90:10 hexane:ethyl acetate) yielded 790 mg (62%) of **5c** as a yellow solid. IR (thin film) cm^{-1}: 3410, 3100, 1495, 1452, 1437, 1394, 1338, 1323, 908, 783, 748, 727, 694. ^1H NMR (360 MHz, $CDCl_3$) δ: 5.59 (s, 2H), 6.54 (s, 1H), 6.83 (s, 1H), 7.11-7.13 (m, 3H), 7.13-7.37 (m, 8H), 7.58 (d, 1H, J = 7.87 Hz), 7.72 (d, 1H, J = 7.35 Hz), 8.21 (s, 1H). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 47.80, 101.72, 102.32, 110.20, 110.79, 120.33, 120.50, 120.70, 120.74, 122.58, 122.75, 125.86 (2C), 127.42, 127.96, 128.73, 129.01 (2C), 129.20, 133.19, 136.29, 137.99, 138.34. MS: 322 (M^+, 100), 267 (21), 245 (16), 231 (60), 217 (17), 186 (16), 162 (42), 113 (24). Mass calcd for $C_{23}H_{18}N_2$: 322.1470; Found: 322.1464.
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13. In a typical palladium catalyzed benzannulation reaction, **6a** (78 mg, 0.202 mmol), methyl heptynoate (85 mg, 0.606 mmol), $Pd(PPh_3)_4$ (0.02 mmol), and Tl_2CO_3 (127 mg, 0.27 mmol) in toluene (6.5 mL) were heated at reflux for 20 h under N_2. Filtration through a pad of silica gel and purification by flash chromatography (75:25 hexane:ethyl acetate) yielded 45 mg (56%) of **8** as a white solid. IR (thin film) cm^{-1}: 2955, 2872, 1725, 1557, 1470, 1431, 1348, 1321, 1242, 1192, 1138, 743. ^1H NMR (360 MHz, $CDCl_3$) δ: 1.04 (t, 3H, J = 7.37 Hz), 1.58-1.68 (m, 2H), 1.84-1.93 (m, 2H), 3.31 (t, 2H, J = 8.10 Hz), 4.08 (s, 3H), 4.14 (s, 3H), 4.15 (s, 3H), 7.27-7.31 (m, 1H), 7.35-7.41 (m, 1H), 7.47-7.54 (m, 4H), 7.90 (d, 1H, J = 7.94 Hz), 8.17 (d, 1H, J = 8.11 Hz). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 13.95, 23.08, 31.02, 32.38, 36.25, 36.61, 52.19, 110.19, 110.40, 119.25, 119.65, 120.21, 120.40, 120.76, 120.94, 122.13, 123.15, 124.58, 125.05 (2C), 125.57, 128.47, 130.77, 144.13, 144.64, 171.09. MS: 398.2 (100, M^+), 355.1 (56), 297.1 (18), 281.1 (6). Mass calcd for $C_{26}H_{26}N_2O_2$: 398.1994; Found: 398.1995.
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