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Synthesis of Indolocarbazoles via Annulations of Chromium Carbene Complexes

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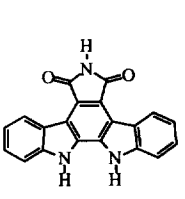
Abstract: The synthesis of indolocarbazoles containing hydrogen bonding functionality mimicking the pharmacophore contained within bioactive indolocarbazole natural products is reported. The indolocarbazoles are prepared via palladium catalyzed cross coupling of indoles followed by photochemical and thermal annulation reactions of chromium carbene complexes. © 1997 Elsevier Science Ltd.

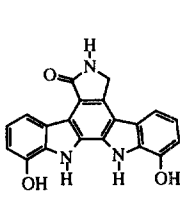
The indolocarbazole natural products have emerged as an important structural class based upon their high degree of biological activity which includes antitumor properties and, in particular, inhibition of protein kinase C.[1] Staurosporine was the first member of this class to be discovered[2] and since 1977 many related natural products have been reported.[3] This in turn has spawned many synthetic efforts directed toward the synthesis of these natural products and structural analogues.[4, 5]

Several representative structures of indolocarbazoles are shown in Scheme 1. The key structural feature of the pharmacophore within these compounds is the presence of hydrogen bonding moieties at the top and bottom of a rigid indolocarbazole scaffold.[6] We report herein two new syntheses of indolocarbazoles via chromium carbene complexes which provide access to structures with new patterns of hydrogen bonding functionality on the central benzene ring.

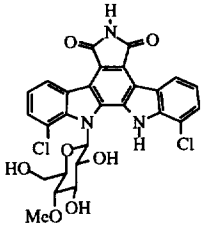
Scheme 1



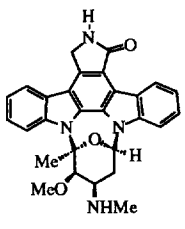
Arcyriaflavin A



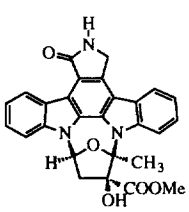
BE-13793C



Rebeccamycin



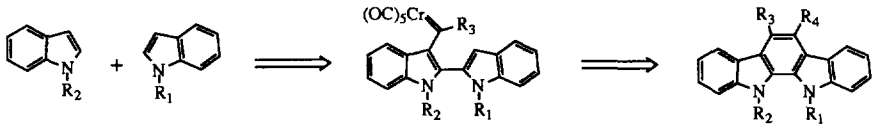
Staurosporine



K252a

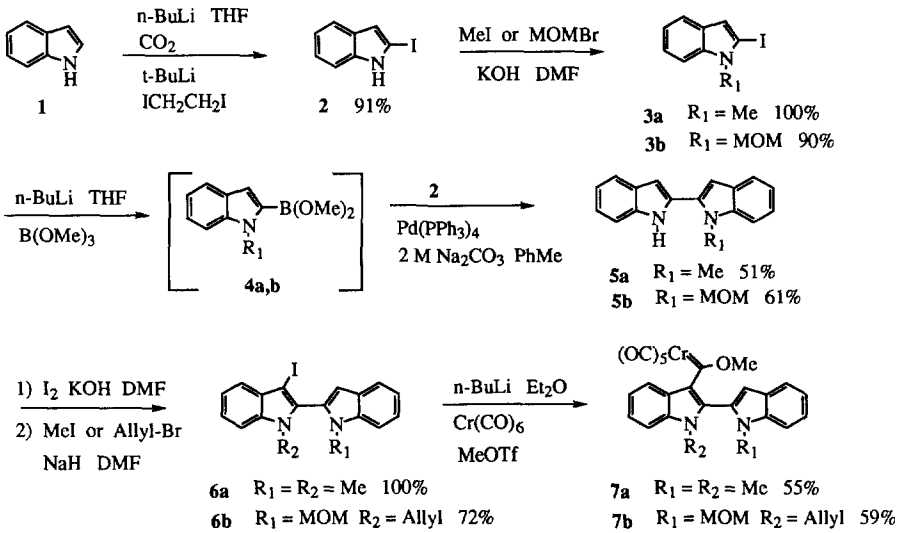
We envisioned a versatile synthetic strategy to form differentially substituted indolocarbazoles via initial palladium catalyzed cross coupling of two indoles to form 2,2'-biindolyls, conversion to Fischer chromium carbene complexes and, finally, benzannulation reactions[7,8] (Scheme 2).

Scheme 2



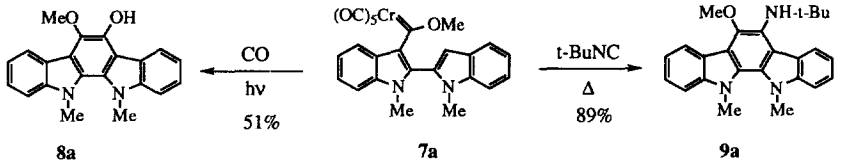
Preparation of the key chromium carbene complexes **7a** and **7b** is illustrated in Scheme 3. Indole was iodinated at the 2 position using the procedure of Bergman and Venemalm[9] and then N-protected. Suzuki cross coupling[10] of the *in situ* generated boronic esters **4** and 2-iodoindole, **2**, provided unsymmetrical 2,2'-biindolyls **5**. Iodination at the 3' position using the procedure of Bocchi and Palla[11] followed by N' protection yielded iodides **6**. Hindered rotation about the 2-2' bond was evident from the diastereotopic AB patterns in the ^1H NMR spectrum for the protons in the CH_2 groups of **6b**. Preparation of carbene complex **7a** was accomplished under the standard conditions of metal halogen exchange, addition to chromium hexacarbonyl and methylation with methyl triflate.[12] However, differentially protected biindolyls were problematic. We had earlier prepared allyl/benzyl and benzyl/phenylsulfonyl protected 2,2'-biindolyl iodides, but they failed to yield carbene complexes under the usual conditions. The difficulty may be due to steric hindrance by the two large protecting groups preventing anion addition to chromium hexacarbonyl. In contrast, employing the smaller allyl and methoxymethyl protecting groups in **6b** allowed for successful formation of carbene complex **7b**.

Scheme 3



With carbene complexes **7a** and **7b** in hand, we examined their use in benzannulation reactions to construct the central ring of the indolocarbazoles with concomitant formation of hydrogen bonding moieties (Schemes 4 and 5). Following our earlier reports on photochemical benzannulation reactions,[7] photolysis of **7a** generated product **8a** in 51% yield via the intermediacy of a photogenerated ketene.[13] The product was readily apparent from the two doublets at 8.22 and 8.37 ppm in the ^{1}H NMR spectrum for the bay region protons and the phenolic proton at 9.37 ppm. Complex **7a** also underwent an aminobenzannulation reaction.[8] Addition of tert-butyl isonitrile to the carbene complex formed an intermediate ketenimine which cleanly underwent thermal cyclization producing amine **9a** in 89% yield.[14] Again, the benzannulated product was obvious from the bay region protons at 8.35 and 8.77 ppm in the ^{1}H NMR spectrum.

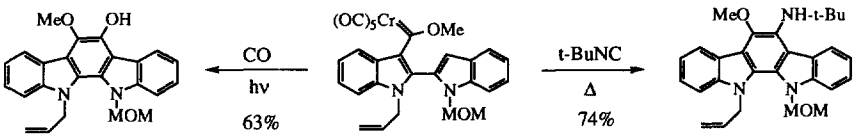
Scheme 4



8a **7a** **9a**

Finally, we turned our attention to carbene complex **7b** which contains removable protecting groups (Scheme 5). In analogy to complex **7a**, both photochemical and isonitrile-initiated thermal annulation reactions were successful, generating products **8b** and **9b** in 63% and 74% yields, respectively. Again, the products had characteristic low field resonances in the ^{1}H NMR spectra for the bay region protons and, in contrast with iodide **6b** and carbene **7b**, the protons in the CH_2 groups of the products did not display diastereotopic AB patterns in the ^{1}H NMR spectra.

Scheme 5



8b **7b** **9b**

In summary, we have shown that complex and sterically encumbered 2,2'-biindolyl chromium carbene complexes can be prepared and subsequently employed in annulation reactions. This strategy provides access to indolocarbazoles containing hydrogen bonding functionality mimicking important protein kinase C inhibiting indolocarbazole natural products.

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13. Preparation of **8a**: Carbene **7a** (38 mg, 0.077 mmol) was dissolved in toluene (3 mL) in a Pyrex pressure tube. The pressure tube was purged with N_2 and then evacuated and filled with 20 psi of CO (2x). Photolysis for 3 h employing a 450 W medium pressure mercury lamp held in a quartz cooling well gave complete reaction as evidenced by disappearence of the bright-red color of the carbene. The crude product was plated onto diatomacious earth and purified by flash chromatography (75:25 hexane:ethyl acetate) to yield 13 mg (51%) of **8a** as a white solid. R_f = 0.47 (75:25 hexane:ethyl acetate). IR (KBr) cm^{-1}: 3500-3100 (br), 3050, 3020, 2980, 2940, 1600, 1504, 1458, 1421, 1363, 1321, 1261, 1155, 1095, 989, 922, 790, 741, 640. ^1H NMR (360 MHz, DMSO) δ: 3.93 (s, 3H), 4.14 (s, 3H), 4.16 (s, 3H), 7.21-7.27 (m, 2H), 7.42-7.48 (m, 2H), 7.59-7.63 (m, 2H), 8.22 (d, 1H, *J* = 7.74 Hz), 8.37 (d, 1H, *J* = 7.68 Hz), 9.37 (s, 1H). ^{13}C NMR (90 MHz, DMSO) δ: 36.52, 36.81, 60.86, 110.32, 110.79, 113.84, 116.75, 119.76, 119.85, 121.97, 122.57, 122.68, 123.26, 124.02, 124.97, 125.36, 126.32, 135.20, 139.09, 143.01, 143.53. MS: 330.1 (85, M^+), 315.1 (100), 287.1 (6), 244.1 (5), 165.1 (7), 143.6 (6). Mass calcd for $C_{21}H_{18}N_2O_2$: 330.1368; Found: 330.1371.
14. Preparation of **9a**: t-Butyl isonitrile (0.021 mL, 0.186 mmol) was added to a solution of carbene **7a** (46 mg, 0.093 mmol) in toluene (3 mL) at 0°C. The carbene reacted completely within 1 h as evidenced by TLC and then the reaction mixture was refluxed 5h. The crude reaction mixture was plated onto diatomacious earth and purified by flash chromatography (90:10 hexane:ethyl acetate) yielding 32 mg (89%) of **9a** as a yellow solid. R_f = 0.67 (75:25 hexane:ethyl acetate). IR (thin film) cm^{-1}: 2960 (broad), 1453, 1318, 1153, 1091, 744. ^1H NMR (360 MHz, $CDCl_3$) δ: 1.32 (s, 9H), 4.01 (s, 3H), 4.13 (s, 3H), 4.16 (s, 3H), 7.26-7.36 (m, 3H), 7.46-7.54 (m, 4H), 8.35 (d, 1H, *J* = 7.80 Hz), 8.77 (d, 1H, *J* = 7.87 Hz). ^{13}C NMR (90 MHz, $CDCl_3$) δ: 29.94 (3C), 30.71, 36.27, 36.53, 60.52, 109.70, 109.80 (2C), 116.75, 119.16, 120.06, 122.34 (2C), 123.11 (2C), 123.33, 124.66, 124.93 (2C), 126.91, 143.87, 144.18, 145.47. MS: 385.2 (100, M^+), 370.2 (8), 328.1 (62), 314.1 (70), 300.1 (20), 384.1 (17), 270.1 (7). Mass calcd for $C_{25}H_{27}N_3O$: 385.2151; Found: 385.2150.

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