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Synthesis of 2-Dienylindole, SB 242784, by a Three-Component Palladium-Catalyzed Coupling Reaction

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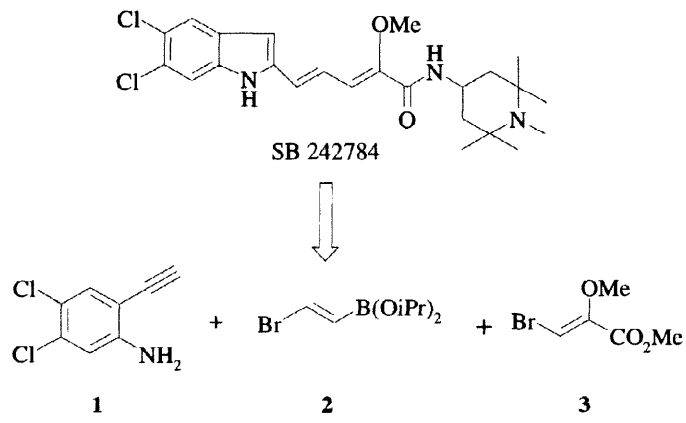
Abstract: The synthesis of SB 242784 using a novel one-pot Castro-Stephens-Suzuki reaction as the key reaction is described. © 1998 Elsevier Science Ltd. All rights reserved.

SB 242784, a compound in development for the treatment of osteoporosis, has been synthesized utilizing a palladium-catalyzed three-component coupling reaction. The critical reaction in the synthesis uses diisopropyl-*E*-bromovinylboronate, **2**, in an unprecedented tandem Castro-Stephens-Suzuki reaction with compounds **1** and **3** to provide an advanced ynediene intermediate in the synthesis of SB 242784. Key aspects of the route described herein are its highly convergent nature, complete stereocontrol, and previously unreported manner in which **2** is used.



The initial synthesis of SB 242784 was centered on successive Wittig-type reactions to form the diene moiety[1], which gave mixtures of double bond isomers requiring chromatographic separation. An organometallic approach which would conserve double bond geometry and also result in a more convergent synthesis was desired. Suzuki and others[2,3] have used bromovinylboronates in palladium-catalyzed coupling reactions with organozinc reagents followed by a Suzuki coupling to access *trans*-disubstituted olefins in a stereoselective fashion. The chemoselectivity in these reactions is achieved because base is required to activate the boronate ester, thereby preventing polymerization of the starting material. It was felt that **2** could provide a unique entry to the diene portion of SB 242784.

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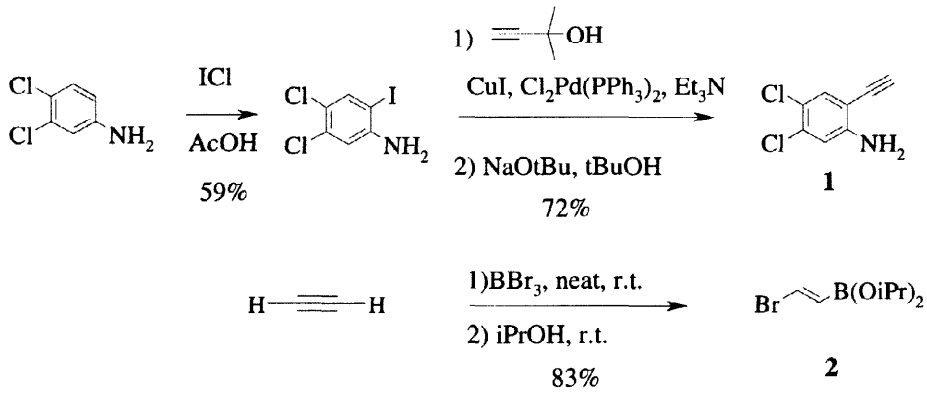
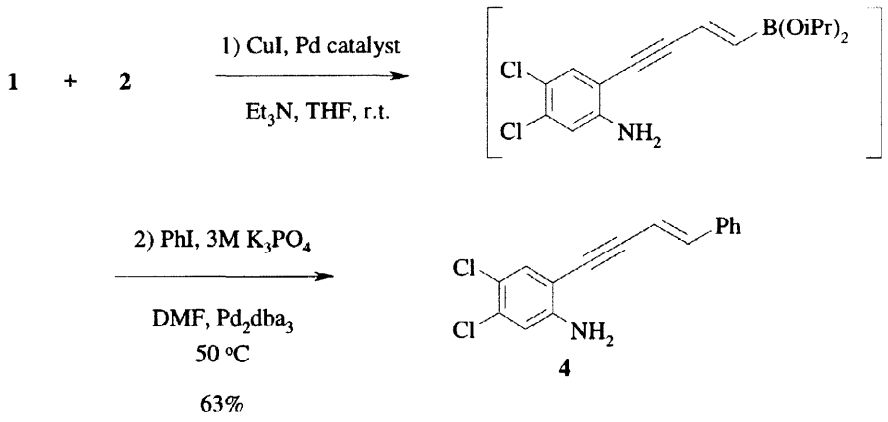
Initial attempts using either a 2-zincindole or a zinc acetylide, however, proved to be unfruitful. Attention was turned to a tandem Castro-Stephens-Suzuki coupling to provide an alkynyl aniline which would then be cyclized to an indole.[4] If successful the Castro-Stephens approach would greatly simplify, and potentially expand, the synthetic utility of the reaction by obviating the use of a zinc acetylide, formed from the corresponding lithium acetylide. Although the Castro-Stephens reaction, like a Suzuki reaction, requires a base to undergo cross-coupling, it was believed that the amine base necessary for this transformation would not induce reaction at the boronate ester.

Scheme 1



The preparations of **1** and **2** are outlined in Scheme 1. The alkynyl aniline **1** was produced in three steps from 3,4-dichloroaniline by iodination followed by Castro-Stephens coupling and subsequent alkyne deprotection.[5] The boronate ester **2** was produced according to literature methods starting from acetylene and BBr_3.[6] Unsaturated ester **3** was prepared in two steps from bromopyruvic acid by formation of the dimethylketal methyl ester[7a] followed by elimination of methanol.[7b]

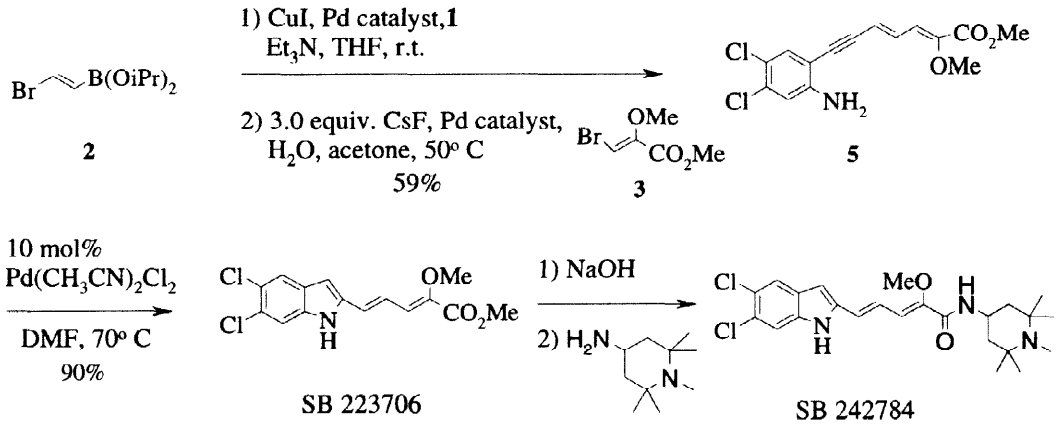


(1)

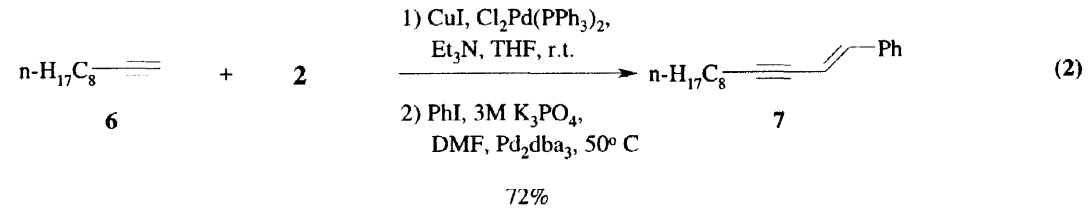
^1H NMR studies on the reaction of **1** with **2** under Castro-Stephens conditions(1.0 equiv. **1**, 1.0 equiv.**2**, 2.0 equiv. NEt_3, 2.5 mol% $PdCl_2(PPh_3)_2$ and 5 mol% CuI in THF) indicated that the reaction occurred exclusively at the carbon bearing the bromide. A model study of the Suzuki reaction found that the one-pot

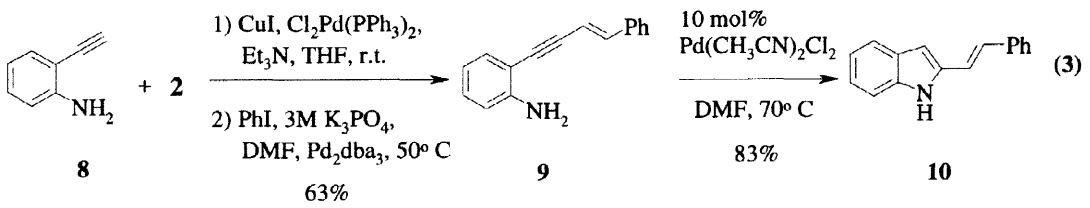
tandem sequence gave a 63% yield of **4** (eq 1) by addition of iodobenzene, DMF, and 3M aq. K_3PO_4. Attempts to apply these conditions to the synthesis of SB 242784, however, provided <15% of the desired ynediene **5**. A screen of various other Suzuki reaction conditions eventually showed that a modification of conditions reported by Wright *et al*[8,9] resulted in a 59% yield of **5** after chromatography (Scheme 2). No other double bond stereoisomers were observed in the crude reaction mixtures. Treatment of **5** with $Pd(CH_3CN)_2Cl_2$[4] effected cyclization to give indole SB 223706 in 90% yield, which could then be carried on to SB 242784.

Scheme 2



This tandem Castro-Stephens-Suzuki reaction has been extended to the preparation of various ynediene systems and other 2-vinylindoles as exemplified in eq.2 and eq. 3. Full results will be published in due course. The exceptionally mild reaction conditions suggest that this reaction could provide quick entry into a wide variety of polyene systems with defined stereochemistry.





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7. a) Chari, R.V.; Kozarich, J.W. *J. Org. Chem.* **1982**, *47*, 2355. b) Preparation of **3**: Methyl-2,2-dimethoxy-3-bromo-propanoate(28 g, 123.4 mmol) was placed in a 100 mL round bottom flask which was fitted with a stir bar, Dean-Stark trap, reflux condenser, and nitrogen inlet. The neat oil was treated with PTSA(0.22 g, 1.16 mmol) and was heated under N_2 in an oil bath set a 210° C. Methanol evolution began immediately. The reaction was continued until methanol generation ceased (~ 1 h). The dark oil was cooled to 25° C and was dissolved in 150 mL hexane. The stirred solution was stirred for 0.25h with silica gel (Merck, 230-400 mesh, grade 9385, 5g) and filtered. The solvent was removed by vacuum distillation to yield a thin yellow oil(20.7 g, 86 %). ^{1}H NMR (300MHz, $CDCl_3$, TMS/ppm) δ 6.92 (s, 1 H), 3.80 (apparent s, 6 H).

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9. Procedure for the preparation of **5**: Compound **2**(80 μL, 0.34 mmol) was dissolved in 1 mL of THF in a 5 mL round bottom equipped with a magnetic spinbar and condenser. 2-ethynylaniline, **1**(80 mg, 0.34mmol, 1.0 equiv.), was added to the flask followed by CuI(2 mg, 5 mol%), $Pd(PPh_3)_2Cl_2$(5 mg, 2.5 mol%) and Et_3N(94 μL, 0.68 mmol, 2.0 equiv.). After stirring for one hour at ambient temperature, the reaction was complete as indicated by disappearence of **1** by TLC(SiO_2, 30% EtOAc in hexanes, UV visualization). A 1:1 mixture of acetone:H_2O(2 mL) was added to the reaction followed by compound **3**(60 mg, 0.3 mmol, 0.9 equiv.), CsF(150 mg, 0.10mmol, 3.0 equiv.), and Pd_2dba_3(3 mg, 1 mol%). The mixture was heated to 50° C and was complete in 2h as observed by TLC. The mixture was diluted with EtOAc(15mL) and washed with H_2O(2 x 10 mL). The organic layer was rotary evaporated and **5** isolated by radial chromatography(SiO_2, 2 mm thickness, 20% EtOAc in hexanes) as a yellow solid. Yield = 58 mg(59%). ^{1}H NMR (300MHz, $CDCl_3$, TMS/ppm) δ 7.34 (s, 1H), 7.02 (dd, 1H, J = 11.5, 15.6 Hz), 6.79 (s, 1H), 6.73 (d, 1H, J = 11.5 Hz), 6.06 (d, 1H, J = 15.6 Hz), 3.81 (s, 3H), 3.77 (s, 3H).