The Synthesis of Symmetrical (2-indolyl)ethynes and Reduced Congeners *via* Palladium-catalyzed Couplings of 2-Bromoindole Precursors

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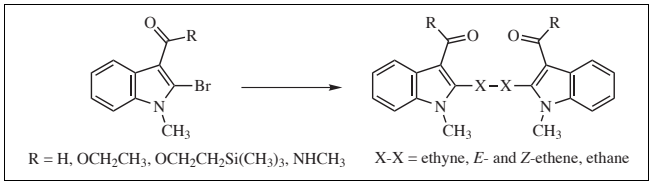

Starting from a series of 2-bromo-1-methylindole precursors (**1b-e**) activated in the 3-position with aldehyde, ester, or amide functionality, two approaches have been developed toward the synthesis of 2,2'-bis(indolyl)ethynes and reduced congeners *via* palladium(0)- or palladium(II)-catalyzed couplings. The first approach utilized Sonogashira coupling of (trimethylsilyl)acetylene to introduce the two-carbon linker followed by desilylation and further coupling with starting 2-bromoindole. A second shorter and more efficient route engaged the starting 2-bromoindole in a double Stille coupling with bis(tributylstannyl)acetylene or (*E*)-1,2-bis(tributylstannyl)ethylene to provide desired homodimers in one step. Subsequent transformations of dimeric intermediates led to target acids **7a-c** and derived amides **8a-c** and **9**. When tested against a panel of tyrosine kinases, each target compound was found to be inactive.

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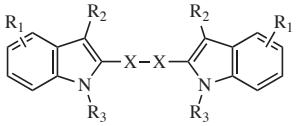
Introduction.

Previous reports from our laboratories have detailed the synthesis and structure-activity relationships of a large series of indoline-2-thione dimers [1] and second generation congeners, the indoline-2-selenone dimers [2]. Both classes constitute a novel class of small molecule inhibitors of a broad range of tyrosine kinases including the epidermal growth factor receptor tyrosine kinase (EGFr TK). Reversal experiments with various thiols suggest that these agents interact with the EGFr TK *via* a sulfhydryl exchange mechanism. In an attempt to better understand this putative mechanism of action, and to explore the possibility that replacement of the connecting sulfur and selenium bridges with all-carbon functionality might result in inhibitors interacting with the receptor *via* a "styryl pharmacophore" structural motif [3], we decided to synthesize a small series of 2,2'-functionalized bis-1-methyl-1*H*-indole-3-carboxylic acid derivatives. For this series, the connecting linker is drawn from two-carbon ethyne, *Z*- or *E*-1,2-ethene, or ethane fragments (Figure 1). We expected that these replacements would also provide compounds of greater chemical and metabolic stability [4]. In this paper, we present two approaches in which easily obtained 3-substituted-2-bromo-1-methylindole precursors are coupled in stepwise fashion under Sonogashira conditions with (trimethylsilyl)acetylene, or are engaged in a double Stille coupling with bis-(tributylstannyl)acetylene or (*E*)-1,2-bis-(tributylstannyl)ethylene to provide access to a series of bis(2-indolyl)ethynes and reduced congeners.

Figure 1



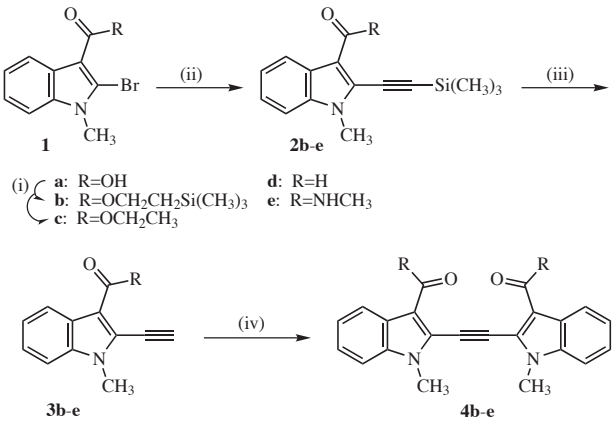
Results and Discussion.

There are a number of reports in the literature for the construction of homo- [5,6] or hetero- [7-9] 2-and 3-ß-(arylvinyl)indoles. In these cases, the target compounds are constructed *via* Wittig chemistry on appropriately substituted indolyl 2- or 3-carboxaldehyde and phosphonium salt precursors. More recently, Larock *et al.* [10] have reported on the palladium/copper-catalyzed Sonogashira coupling of various *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-bromoindole-3-carboxaldehydes with various terminal acetylenes. These adducts were subsequently converted to a series of β- and γ-carboline target compounds. Rather than apply precedented Wittig chemistry to construct our target compounds, we decided to apply Larock chemistry to our readily available 2-bromoindole substrates.

Palladium-catalyzed Couplings with (Trimethylsilyl)-acetylene.

Our first approach to the synthesis of 2,2'-bis(indolyl)ethyne derivatives is outlined in Scheme 1. For our purposes, we choose to evaluate a range of 3-carbonyl derivatives of 2-bromo-1-methylindole (**1c**-**e**) that we had synthesized for a previous study [2], and which would allow for additional functional modification at the 3-position. We also decided to include an additional ester (**1b**) in this study as it would provide for much greater organic solubility in subsequent chemical transformations (see below). Accordingly, palladium(0)- or palladium(II)-catalyzed reaction on substrates **1b**-**e** with (trimethylsilyl)acetylene, utilizing coupling conditions previously described [10,11], provided **2b**-**e** in

Scheme 1[a]



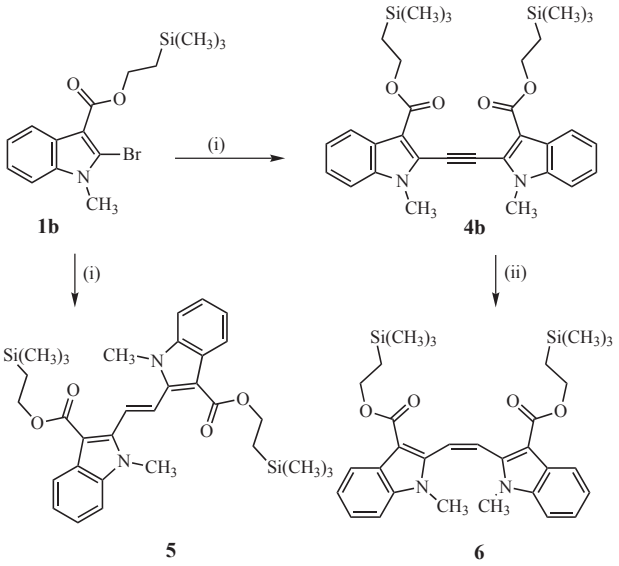
[a](i) $SOCl_2$, $ClCH_2CH_2Cl$, 75 °C, then ROH/NEt_3 or *i*-Pr_2NEt. (ii) for **1b**,**c**, TMS-acetylene, copper(I) iodide, $Pd(PPh_3)_4$, DBU, toluene, 85 °C; for **1d**,**e**, TMS-acetylene, copper(I) iodide, $Pd(PPh_3)_2Cl_2$, NEt_3, THF or *p*-dioxane. (iii) K_2CO_3 or NEt_3/CH_3OH. (iv) for **3c**, copper(I) iodide, $Pd(PPh_3)_4$, DBU, toluene, 80 °C, **1c**; for **3d**,**e**, copper(I) iodide, $Pd(PPh_3)_2Cl_2$, NEt_3, THF or *p*-dioxane, **1d**,**e**.

40-67% yield. A side product (isolated in 9% yield) in the synthesis of **2b** was dimer **4b**, which resulted from *in situ* base cleavage of the acetylenic trimethylsilyl function followed by coupling with 2-bromo substrate **1b**. This side product was observed by TLC in similar couplings on **1c-e**. We attempted to exploit this finding by adjusting conditions such that the 2,2'-bis(indolyl)ethynes **4b-e** could be generated directly from **1b-e** in a one-pot procedure. However, reaction of **1b** with bis(trimethylsilyl)acetylene under the conditions of D'Auria [12] provided only a trace of **4b**. With this result, we decided to complete the synthesis of target homodimers *via* a stepwise process. Accordingly, trimethylsilyl cleavage of isolated **2b-e** with methoxide (generated from triethylamine or potassium carbonate in methanol [13]) proceeded cleanly to give the somewhat unstable **3b-e** in 71-95% yield. Using the palladium(0) conditions discussed above, **3c-e** were then coupled with **1c-e** to provide homodimers **4c-e**, respectively, in high yield. However, the gross insolubility of **4c-e**, even in hot dipolar aprotic solvents, precluded crystallizing these to analytical purity, or toward utilizing these in subsequent chemical transformations. At this stage, we decided to approach the synthesis of our target homodimers *via* a shorter, potentially more efficient double Stille coupling approach utilizing the much more highly organic soluble 2-(trimethylsilyl)ethyl ester **1b**.

Double Stille Coupling of Bis(tributylstannyl)acetylene and (*E*)-1,2-Bis(tributylstannyl)ethylene.

Double Stille coupling of **1b** was investigated with commercially available bis(tributylstannyl)acetylene and (*E*)-1,2-bis(butylstannyl)ethylene (Scheme 2). Such an approach had been previously exemplified in the work of Staley [14] and Cummins [15]. Thus, reaction of 0.5 equivalent of bis(tributylstannyl)acetylene with ester **1b** utilizing palladium(0) catalysis afforded the 2,2'bis(indolyl)ethyne **4b** in 82% yield. Similarly, reaction

Scheme 2[a]



[a](i) 0.5 equiv. $(Bu_3SnC)_2$ or $[(E)\text{-}Bu_3SnCH]_2$; $Pd(PPh_3)_4$, BHT, toluene, reflux. (ii) 10% Pd/C, NEt_3-formic acid, THF.

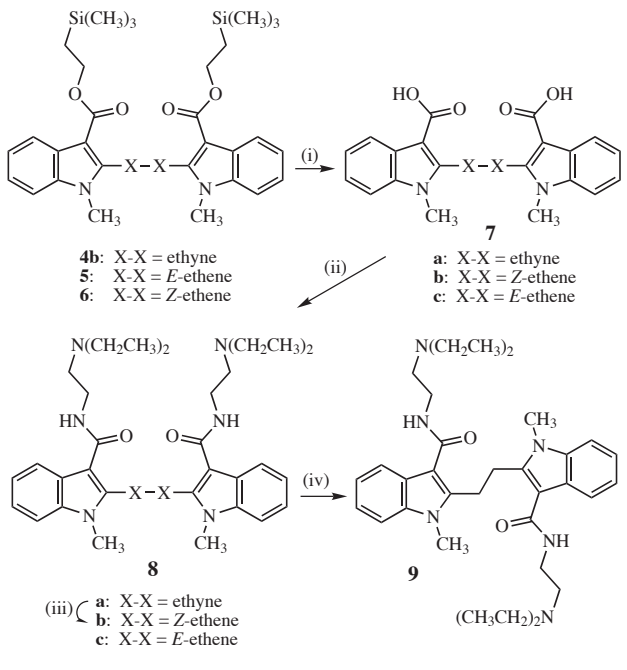
of (*E*)-1,2-bis(tri-*n*-butylstannyl)ethylene with **1b** provided the (*E*)-2,2'-(bisindolyl)-1,2-ethene **5** in 77% yield. Because of the absence of a good preparation of pure (*Z*)-1,2-bis(tributylstannyl)ethylene [16] to utilize in a double Stille coupling, we synthesized the (*Z*)-2,2'-

(bisindolyl)-1,2-ethene **6** by controlled reduction of **4b**. Initially, reaction of **4b** under standard methods of catalytic hydrogenation of an alkyne to a *cis*-olefin proceeded sluggishly to give **6** in poor yield. However, triethylammonium formate mediated transfer hydrogenation conditions [17] provided **6** in excellent yield without any over reduction to the fully saturated ethane analogue **9**, even after prolonged heating. Care was taken to carry out the synthesis of olefins **5** and **6**, along with subsequent transformations of these alkenes, under low light conditions as exposure of a solution of either compound to normal laboratory lighting resulted in a photoisomerization to a *cis-trans* mixture. For example, storage of an acidic solution of the *trans* isomer **5** in deuterium oxide under fluorescent lighting at 25° C for four days resulted in a *ca*. 1:1 mixture of *E*- and *Z*-olefins, **5** and **6**, respectively. Such photoisomerization of stilbazoles is well precedented [18].

Schotten-Bauman Aylations.

Conversion of the two-carbon linked 2,2'-bisindolyl 2-(trimethylsilyl)ethyl esters **4b**, **5**, and **6** to target compounds **8 a-c** and **9** is delineated in Scheme 3. Briefly, fluoride-mediated cleavage of the 2-(trimethylsilyl)ethyl ester functionality [19] in **4b**, **5**, and **6** proceeded uneventfully to provide acids **7a-c** in 86-98% yield. The coupling of acids **7a,c** with *N*,*N*-diethylethylenediamine under Schotten-Bauman conditions gave the respective target amides **8a,c** in 55-58% yield. Reaction of the *Z*-alkene **7b** under the same conditions did not afford **8b**, but provided an unidentified product showing incorporation of only one *N*,*N*-diethylethylenediamine side chain moiety. The desired product was obtained in 74% yield from **8a** *via* the same transfer hydrogenation conditions discussed above. The final target compound **9** incorporating the bridging ethane functionality was synthesized in 84% yield from high pressure catalytic hydrogenation of *E*-alkene **8c**. Compounds **8 a-c** and **9** are highly water soluble when isolated as dihydrochloride salts.

Scheme 3[a]



[a](i) *n*-Bu_4NF, THF. (ii) for **8a**,**c**, $SOCl_2$, $ClCH_2CH_2Cl$, 75 °C, and then $NH_2CH_2CH_2NEt_2$. (iii) 10% Pd/C, NEt_3-formic acid, THF. (iv) for **8c**, 20% Pd/C, H_2 (570 psi), CH_3OH.

Biological Evaluation.

Compounds **7 a-c**, **8a-c**, and **9** when tested against selected members of a panel of tyrosine kinases [20] displayed no inhibitory activity ($IC_{50} > 10\ \mu M$).

Conclusions.

We have developed two approaches toward the synthesis of 2,2'-bis(indolyl)ethynes and corresponding ethene and ethane congeners utilizing palladium-catalyzed coupling chemistry. The first route in which readily synthesized 3-substituted-2-bromo-1-methylindole precursors are coupled under Sonogashira conditions in stepwise fashion with (trimethylsilyl)acetylene is less efficient in overall yield and ease of synthesis. However, it offers an advantage of potentially being useful for the synthesis of 2,2'-indolyl heterodimers, an area not explored in this study but exemplified by Larock [10]. The second route in which the same indole precursors are engaged in a double Stille coupling with bis-(tributylstannyl)acetylene or (*E*)-1,2-bis(tributylstannyl)-ethylene is quite short and efficient, and provides ready access to a series of symmetrical 2,2'-bis(indolyl)ethynes and reduced congeners.

EXPERIMENTAL

Melting points were taken on a Thomas-Hoover Unimelt capillary melting point apparatus and are uncorrected. Proton magnetic resonance (^1H NMR) spectra were measured on a Varian Unity 400 spectrometer. Chemical shifts are reported as δ values in ppm (parts per million) downfield from internal tetramethylsilane. The following abbreviations are used to describe peak patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet. Mass spectra were performed either in the EI or CI (utilizing 1% ammonia in methane) mode on a VG Masslab Trio-2A

mass spectrometer. Combustion analyses were determined on a CEC 440 Elemental Analyzer (CHN analysis) or by Robertson Microlit Laboratories, Inc., Madison, NJ. Column chromatography was carried out in the flash mode utilizing Merck 230-400 mesh silica gel. Analytical TLC was carried out on Merck (Kiesegel 60F-254) silica gel plates with detection by UV light. All reaction solvents were reagent grade or distilled-in-glass, and were stored over activated 3A (for lower alcohols) or 4A molecular sieves. Following normal workup procedures, organic extracts were dried over anhydrous magnesium sulfate prior to concentration. All reactions were run under a positive pressure of nitrogen. The synthesis and subsequent reactions of *E*- and *Z*-alkenes of this study (compounds **5**, **6**, **7 b,c**, and **8 b,c**) were carried out under conditions of low laboratory light due to their liability toward photoisomerization.

2-Bromo-1-methyl-1*H*-indole-3-carboxylic acid, 2-(trimethylsilyl)ethyl ester (**1b**).

A mixture of 9.15 g (36 mmol) of 2-bromo-1-methyl-1*H*-indole-3-carboxylic acid (**1a**) [2], 7.9 mL (108 mmol) of thionyl chloride, 1 drop of *N*,*N*-dimethylformamide, and 43 mL of 1,2-dichloroethane was stirred at 75 ºC for 2 h. The solution was cooled and concentrated to a solid that was co-evaporated twice with 100 mL portions of 1,2-dichloroethane. The solids were dissolved in 45 mL of tetrahydrofuran, and the solution was added dropwise to a cooled solution of 13 mL (90 mmol) of 2-(trimethylsilyl)ethanol and 18.8 mL (108 mmol) of *N*,*N*-diisopropylethylamine in 25 mL of tetrahydrofuran. The mixture was heated at reflux for 13 h, cooled, and concentrated to an oil that was distributed between dichloromethane and water. The organic phase was washed with brine, dried, and concentrated to an oil that was purified by column chromatography eluting sequentially with 100:0, 97.5:2.5, and 95:5 hexanes:ethyl acetate. The combined product fractions were concentrated to an oil that was crystallized from 2,2,4-trimethylpentane to leave 9.0 g (71 %) of **1b**, mp 55-56 ºC, in two crops; R_f 0.20 (95:5 hexanes:ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 9H), 1.20-1.26 (m, 2H), 3.84 (s, 3H), 4.45-4.49 (m, 2H), 7.23-7.35 (m, 3H), 8.15-8.18 (m, 1H); MS (CI^+): *m/z* (relative %) 355 (24), 353 (20), 328 (34), 326 (29), 312 (41), 310 (36), 238 (78), 236 (100).

Anal. Calcd. for $C_{15}H_{20}BrNO_2Si \cdot 0.05\ C_8H_{18}$: C, 51.38; H, 5.85; N, 3.89. Found: C, 51.69; H, 5.78; N, 3.91.

2-Bromo-1-methyl-1*H*-indole-3-carboxylic acid, ethyl ester (**1c**).

Similar reaction as described above utilizing 10 g of acid **1a**, 8.6 mL of thionyl chloride, 60 mL of ethanol, and 21 mL of triethylamine at 25 ºC overnight followed by chromatography gave 8.14 g (73 %) of **1c**, mp 104-106 ºC; R_f 0.43 (dichloromethane); ^{1}H NMR ($CDCl_3$): δ 1.47 (t, *J* = 7 Hz, 3H), 3.85 (s, 3H), 4.44 (q, *J* = 7 Hz, 2H), 7.24-7.36 (m, 3H), 8.15-8.17 (m, 1H); MS (CI^+): *m/z* (relative %) 284 (100), 283 (96), 282 (99), 281 (96), 238 (69), 236 (56).

Anal. Calcd. for $C_{12}H_{12}BrNO_2$: C, 51.09; H, 4.29; N, 4.96. Found: C, 51.34; H, 4.29; N, 4.96.

1-Methyl-2-[(trimethylsilyl)ethynyl]-1*H*-indole-3-carboxylic acid, 2-(trimethylsilanyl)ethyl ester (**2b**).

A solution of 4.5 g (12.7 mmol) of 2-(trimethylsilyl)ethyl ester **1b**, 3.56 mL of (trimethylsilyl)acetylene, 6.1 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene, and 50 mL of toluene was treated with 737 mg of copper(I) iodide and then with 737 mg of tetrakis(triphenylphosphine)palladium(0). The mixture was heated at 80 ºC for 45 min, cooled, and concentrated to a residue that was diluted with ethyl acetate and filtered. The filtrate was washed twice with 2.5 % aqueous hydrochloric acid, dried, and filtered over a pad of silica gel. After washing the pad with ethyl acetate, the filtrate was concentrated *in vacuo* to leave 5.52 g of a solid that was dissolved in a minimum volume of 95:5 hexanes:ethyl acetate (plus a little dichloromethane to effect solution), and then the mixture was purified by column chromatography. The column was eluted with 97.5:2.5 hexanes:ethyl acetate to give some initial mixed fractions followed by fractions of higher R_f material, corresponding to product **2b**. The column was further eluted with a 95:5 mixture to strip off bisaryl bi-product **4b**. Pure fractions of higher R_f material were crystallized from 4:1 2,2,4-trimethylpentane:ethyl acetate to leave 2.03 g (43 %) of **2b**, mp 96-97 ºC; R_f 0.31 (95:5 hexanes:ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 9H), 0.34 (s, 9H), 1.20-1.24 (m, 2H), 3.84 (s, 3H), 4.43-4.47 (m, 2H), 7.24-7.35 (m, 3H), 8.20-8.23 (m, 1H); MS (CI^+): *m/z* (relative %) 372 (32), 371 (47), 329 (15), 328 (51), 255 (19), 254 (100).

Anal. Calcd. for $C_{20}H_{29}NO_2Si_2 \cdot 0.4\ H_2O$: C, 63.41; H, 7.93; N, 3.70. Found: C, 63.44; H, 7.80; N, 3.61.

Fractions containing pure lower R_f material were crystallized from ethyl acetate to give 338 mg (9 %) of **4b**, mp 172-173 ºC. Yields for both products reflect additional processing of mixed fractions and the mother liquor.

1-Methyl-2-[(trimethylsilyl)ethynyl]-1*H*-indole-3-carboxylic acid, ethyl ester (**2c**).

Similar reaction on 1.55 g (5.5 mmol) of ester **1c**, 1.54 mL (11 mmol) of (trimethylsilyl)acetylene, 2.64 mL of 1,8-diazabicyclo[5.4.0]undec-7-ene, 320 mg of copper(I) iodide, 320 mg of tetrakis(triphenylphosphine)palladium(0), and 24 mL of toluene at 85 ºC for 45 min followed by workup and column chromatography eluting with 9:1 hexanes:ethyl acetate gave 675 mg (41 %) of **2c**, mp 72-73 ºC, following crystallization from 2,2,4-trimethylpentane; R_f 0.55 (dichloromethane); No attempt was made to isolate the bis-aryl side product; ^{1}H NMR ($CDCl_3$): δ 0.34 (s, 9H), 1.45 (t, *J* = 7 Hz, 3H), 3.85 (s, 3H), 4.42 (q, *J* = 7 Hz, 2H), 7.23-7.34 (m, 3H), 8.19-8.22 (m, 1H); MS (CI^+): *m/z* (relative %) 300 (55), 299 (100), 284 (19), 256 (11), 254 (23), 182 (44).

Anal. Calcd. for $C_{17}H_{21}NO_2Si$: C, 68.19; H, 7.07; N, 4.68. Found: C, 67.90; H, 7.05; N, 4.40.

1-Methyl-2-[(trimethylsilyl)ethynyl]-1*H*-indole-3-carbaldehyde (**2d**).

To an ice-cooled mixture of 8.81 g (36 mmol) of aldehyde **1d** [2], 18.5 mL of triethylamine, 1.30 g (1.85 mmol) of dichlorobis(triphenylphosphine)palladium(II), 352 mg (1.85 mmol) of copper(I) iodide, and 56 mL of tetrahydrofuran was added 8.82 mL (62 mmol) of (trimethylsilyl)acetylene. Cooling was removed and the dark mixture was stirred at 25 ºC for 6 h. The mixture was concentrated to an oil that was diluted with

dichloromethane, and then filtered over a pad of silica gel. The filtrate was washed with water, dried, then concentrated to a solid that was dissolved in hot 2,2,4-trimethylpentane. The mixture was purified by column chromatography eluting with 4:1 hexanes:ethyl acetate. The product fractions were combined, and concentrated to a solid that was crystallized from 2,2,4-trimethylpentane. The solids were collected and dried to leave 5.45 g (57%) of **2d**, mp 124-125 ºC, in two crops; R_f 0.26 (95:5 hexanes:ethyl acetate). Further processing of the mother liquor afforded 0.93 g (10%) of additional product, mp 122-123 ºC, in two crops; ^{1}H NMR ($CDCl_3$): δ 0.34 (s, 9H), 3.85 (s, 3H), 7.29-7.40 (m, 3H), 8.29-8.32 (m, 1H), 10.18 (s, 1H); MS (CI^+): *m/z* (relative %) 257 (71), 256 (100), 255 (87), 240 (47), 181 (26).

Anal. Calcd. for $C_{15}H_{17}NOSi \cdot 0.2\ H_2O$: C, 69.56; H, 6.77; N, 5.41. Found: C, 69.68; H, 6.64; N, 5.18.

1-Methyl-2-[(trimethylsilyl)ethynyl]-1*H*-indole-3-carboxylic acid methylamide (**2e**).

Similar reaction on 1.07 g (4 mmol) of carboxamide **1e** [2], 1.13 mL (8 mmol) of (trimethylsilyl)acetylene, 38 mg of copper(I) iodide, 2.0 mL of triethylamine, 141 mg of dichlorobis(triphenylphosphine)palladium(II), and 6 ml of *p*-dioxane at 80 ºC for 5 h, followed by workup and column chromatography eluting with 9:1 dichloromethane:ethyl acetate, afforded 456 mg (40 %) of **2e**, mp 108-110 ºC, after crystallization from 2,2,4-trimethylpentane; R_f 0.21 (4:1 hexanes:ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 0.36 (s, 9H), 3.01 (d, *J* = 5 Hz, 3H; collapses to s with D_2O wash), 3.82 (s, 3H), 7.12 (br s, exchanges with D_2O), 7.23-7.35 (m, 3H), 8.48 (d, *J* = 8 Hz, 1H); MS (EI^+): *m/z* (relative %) 285 (33), 284 (95), 255 (33), 254 (100).

Anal. Calcd. for $C_{16}H_{20}N_2OSi \cdot 0.04\ C_8H_{18}$: C, 67.83; H, 7.23; N, 9.69. Found: C, 67.45; H, 7.00; N, 9.29.

The compound slowly decomposes on standing at room temperature.

2-Ethynyl-1-methyl-1*H*-indole-3-carboxylic acid, 2-(trimethylsilyl)ethyl ester (**3b**).

A mixture of 4.94 g (13.3 mmol) of 2-(trimethylsilyl)ethyl ester **2b**, 0.93 mL (6.7 mmol) of triethylamine, 55 mL of methanol, and 15 mL of tetrahydrofuran was stirred at 25 °C for 8 h. The solution was concentrated to a solid residue that was dissolved in dichloromethane and filtered through a pad of silica gel. The filtrate was concentrated and the solids were crystallized from 1:1 hexanes:ethyl acetate to give 3.79 g (95%) of pure **3b** in several crops, mp 94-96 °C; R_f 0.5 (95:5 hexanes:ethyl acetate); ^{1}H NMR ($CDCl_3$): δ 0.09 (s, 9H), 0.34 (s, 9H), 1.23 (t, *J* = 8.7 Hz, 2H), 3.82 (s, 1H), 3.87 (s, 3H), 4.48 (t, *J* = 8.7 Hz, 2H), 7.26-7.37 (m, 3H), 8.19 (d, *J* = 8 Hz, 1H); MS (CI^+): *m/z* (relative %) 299 (41), 256 (49), 212 (33), 199 (28), 182 (100).

Anal. Calcd. for $C_{17}H_{21}NO_2Si$: C, 68.19; H, 7.07; N, 4.68. Found: C, 67.82; H, 7.01; N, 4.58.

2-Ethynyl-1-methyl-1*H*-indole-3-carboxylic acid, ethyl ester (**3c**).

Similar reaction of 375 mg (1.25 mmol) of ethyl ester **2c**, 38 mg of potassium carbonate, and 7.5 mL absolute ethanol for 1 h gave 256 mg (90 %) of **3c**, mp 140.5-142.5 °C, in two crops; R_f 0.38 (dichloromethane); ^{1}H NMR ($CDCl_3$): δ 1.45 (t, *J* = 7 Hz, 3H), 3.82 (s, 1H), 3.88 (s, 3H), 4.44 (q, *J* = 7 Hz, 2H), 7.26-7.37 (m, 3H), 8.16-8.19 (m, 1H); MS (CI^+): *m/z* (relative %) 228 (97), 227 (100), 200 (57), 182 (49).

Anal. Calcd. for $C_{14}H_{13}NO_2 \cdot 0.5\ H_2O$: C,71.17; H,5.97; N, 5.93. Found: C, 71.40; H, 5.60; N, 5.76.

2-Ethynyl-1-methyl-1*H*-indole-3-carbaldehyde (**3d**).

Similar reaction of 6.54 g (25.3 mmol) of aldehyde **2d**, 250 mg of potassium carbonate, and 100 mL of methanol for 1 h gave 3.69 g (80 %) of **3d**, mp 119-121 °C, in two crops; ^{1}H NMR ($CDCl_3$): δ 3.82 (s, 1H), 3.86 (s, 3H), 7.31-7.41 (m, 3H), 8.31 (d, *J* = 8 Hz, 1H), 10.18 (s, 1H); MS (CI^+): *m/z* (relative %) 184 (100), 183 (55), 156 (13), 154 (18).

Anal. Calcd. for $C_{12}H_9NO$: C, 78.67; H, 4.95; N, 7.65. Found: C, 78.30; H, 4.96; N, 7.32.

2-Ethynyl-1-methyl-1*H*-indole-3-carboxylic acid methylamide (**3e**).

Reaction was carried out on **2e** as described for **2d** to give **3e**, mp 149-151 °C, in 71 % yield; ^{1}H NMR ($CDCl_3$): δ 3.04 (d, *J* = 5 Hz, 3H; collapses to s with D_2O wash), 3.84 (s, 3H), 3.96 (s, 1H), 6.86 (br s, exchanges with D_2O), 7.24-7.37 (m, 3H), 8.42-8.44 (m, 1H); MS (EI^+): *m/z* (relative %) 213 (60), 212 (95), 183 (38), 182 (100).

Anal. Calcd. for $C_{13}H_{12}N_2OCl \cdot 0.2\ H_2O$: C, 72.34; H, 5.79; N, 12.98. Found: C, 72.68; H, 5.69; N, 12.81.

Bis[2-(trimethylsilyl)ethyl] 2,2'-(1,2-ethynediyl)bis[1-methyl-1*H*-indole-3-carboxylate] (**4b**).

A solution of 1.772 g (5 mmol) of 2-(trimethylsilyl)ethyl ester **1b**, 1.41 mL (2.6 mmol) of 97 % bis(tributylstannyl)acetylene, and 15 mL of toluene was stored at 25 °C for 15 min, and then treated with 24 mg of 2,6-di-*tert*-butyl-4-methylphenol and 430 mg of tetrakis(triphenylphosphine)palladium(0). The mixture was heated at reflux for 9.5 h, cooled, and diluted to solution with dichloromethane. The solution was filtered over a pad of silica gel, and the pad was thoroughly washed. The filtrate was evaporated to near dryness, and the solids were boiled in *ca*. 60 mL of ethyl acetate. The hot suspension was filtered, and then the filtrate was stored at 25 °C. The solids were collected, washed sparingly with ethyl acetate, and dried to leave 1.17 g (82 %) of **4b**, mp 172 - 173 °C, in two crops; ^{1}H NMR ($CDCl_3$): δ 0.10 (s, 18H), 1.22-1.28 (m, 4H), 4.16 (s, 6H), 4.48-4.52 (m, 4H), 7.26-7.40 (m, 6H), 8.18-8.20 (m, 2H); MS (CI^+): *m/z* (relative %) 573 (55), 501 (33), 455 (28), 428 (33), 427 (100).

Anal. Calcd. for $C_{32}H_{40}N_2O_4Si_2 \cdot 0.3\ H_2O$: C, 66.47; H, 7.08; N, 4.84. Found: C, 66.54; H, 6.97; N, 4.70.

Bis[2-(trimethylsilyl)ethyl] (*E*)-2,2'-(1,2-ethenediyl)bis[1-methyl-1*H*-indole-3-carboxylate] (**5**).

As described for the synthesis of **4b**, a mixture of 3.54 g (10 mmol) of 2-(trimethylsilyl)ethyl ester **1b**, 4.04 g (5.4 mmol) of (*E*)-1,2-bis(tributylstannyl)ethylene, 860 mg of tetrakis(triphenylphosphine)palladium(0), 60 mg of 2,6-di-*tert*-butyl-4-methylphenol, and 20 mL of toluene was heated at reflux for 18 h. Workup afforded 2.22 g (77 %) of **5**, mp 231-233 °C; ^{1}H NMR ($CDCl_3$): δ 0.10 (s, 18H), 1.23-1.27 (m, 4H), 4.13 (s, 6H), 4.44-4.48 (m, 4H), 7.26-7.36 (m, 4H), 7.42 (d, *J* = 8 Hz, 2H), 7.90 (s, 2H), 8.19-8.21 (m, 2H); MS (CI^+): *m/z* (relative %) 575 (13), 574 (16), 457 (15), 357 (18), 339 (26), 284 (31), 85 (100).

Anal. Calcd. for $C_{32}H_{42}N_2O_4Si_2$: C, 66.86; H, 7.36; N, 4.87. Found: C, 66.57; H, 7.14; N, 4.84.

Bis[2-(trimethylsilyl)ethyl] (*Z*)-2,2'-(1,2-ethenediyl)bis[1-methyl-1*H*-indole-3-carboxylate] (**6**).

To a 50 °C solution of 345 mg (0.6 mmol) of alkyne **4b**, 1.2 mL of triethylamine, and 6 mL of tetrahydrofuran was added slowly 0.24 mL of 97 % formic acid. The solution was treated with 30 mg of 10 % palladium on charcoal (activated), and with the same amount of catalyst every 15 min to a total of 150 mg. After the fifth addition, the mixture was heated an additional 30 min. The mixture was filtered through a pad of silica gel which was washed well with ethyl acetate. The filtrate was washed twice with water, dried, and concentrated to a foam. Crystallization from hexanes at -20 °C afforded 318 mg (92 %) of **6**, mp 116-118 °C, in three crops; ^{1}H NMR ($CDCl_3$): δ 0.11 (s, 18H), 1.23-1.27 (m, 4H), 3.09 (s, 6H), 4.47-4.51 (m, 4H), 7.09 (d, *J* = 8 Hz, 2H), 7.19-7.27 (m, 4H), 7.46 (s, 2H), 8.17 (d, *J* = 7 Hz, 2H); MS (CI^+): *m/z* (relative %) 575 (100), 459 (26), 385 (86), 357 (47), 283 (65).

Anal. Calcd. for $C_{32}H_{42}N_2O_4Si_2$: C, 66.86; H, 7.36; N, 4.87. Found: C, 67.25; H, 7.35; N, 4.81.

2,2'-(1,2-Ethynediyl)bis[1-methyl-1*H*-indole-3-carboxylic acid], bis(tetrabutylammonium) salt (**7a**).

To an ice-cold suspension of 344 mg (0.6 mmol) of alkyne **4b** in 5 mL of tetrahydrofuran was added 1.8 mL of tetrabutylammonium fluoride (1 *M* in tetrahydrofuran). The mixture was stirred at 25 °C for 2.5 h, and then stored at 5 °C. The solids were collected, washed with ethyl acetate, and dried to leave 251 mg (49 %) of **7a**, mp 196-200 °C. The filtrate was concentrated to an oil that was triturated in hot ethyl acetate, and then processed as above to leave 194 mg (37%) of a less pure second crop; ^{1}H NMR (DMSO-d_6): δ 0.93 (t, *J* = 7 Hz, 24H), 1.30 (q, *J* = 7 Hz, 16H), 1.52-1.59 (m, 16H), 3.13-3.17 (m, 16H), 4.00 (s, 6H), 7.01-7.05 (m, 2H), 7.13-7.17 (m, 2H), 7.34 (d, *J* = 8 Hz, 2H), 8.30 (d, *J* = 7 Hz, 2H).

Anal. Calcd. for $C_{22}H_{14}N_2O_4 \cdot 2\ C_{16}H_{36}N \cdot 0.5\ H_2O$: C, 75.04; H, 10.15; N, 6.48. Found: C, 75.13; H, 9.88; N, 6.51.

In another run on the same scale, the reaction mixture was concentrated and the solids were diluted with 5 mL of glacial acetic acid. The mixture was stirred at 25 °C for 5 h, and then diluted with 10 mL of *N*,*N*-dimethylformamide. The solids were collected and dried to leave 196 mg (79 %) of product, mp 218-224 °C (dec) that was *ca*. 90 % free acid by ^{1}H NMR analysis; ^{1}H NMR (DMSO-d_6): δ 4.08 (s, 6H), 7.28 (t, *J* = 8 Hz, 2H), 7.38 (t, *J* = 7 Hz, 2H), 7.62 (d, *J* = 8 Hz, 2H), 8.11 (d, *J* = 8 Hz, 2H).

(*Z*)-2,2'-(1,2-Ethenediyl)bis[1-methyl-1*H*-indole-3-carboxylic acid] (**7b**).

Reaction was carried out on 559 mg (0.97 mmol) of **5** as described above for the synthesis of **7a**. The mixture was concentrated to an oil that was ice cooled, and then diluted with 5 mL of glacial acetic acid. After storage at 5 °C, the solids were collected, washed sparingly with acetic acid, and dried at 100 °C /3mm/16 h to leave 334 mg (91 %) of **7b**, mp 260-265 °C (dec), in two crops; ^{1}H NMR (CD_3OD/NaOD): δ 3.03 (s, 6H), 7.05-7.10 (m, 6H), 7.53 (s, 2H), 8.23-8.25 (m, 2H).

Anal. Calcd. for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.21; H, 5.13; N, 7.26.

(*E*)-2,2'-(1,2-Ethenediyl)bis[1-methyl-1*H*-indole-3-carboxylic acid] (**7c**).

Reaction with fluoride was carried out on 1 mmol of **6** as described above for the synthesis of **7a**. Utilizing the workup procedure described above for the synthesis of **7b** provided **7c**, mp >280 °C (dec), in 98 % yield; ^{1}H NMR (CD_3OD /NaOD): δ 4.06 (s, 6H), 7.10-7.14 (m, 2H), 7.20-7.24 (m, 2H), 7.40 (d, *J* = 8 Hz, 2H), 8.07 (s, 2H), 8.19 (d, *J* = 8 Hz, 2H).

Anal. Calcd. for $C_{22}H_{18}N_2O_4 \cdot 0.2\ C_2H_4O_2 \cdot 0.3\ H_2O$: C, 68.67; H, 4.99; N, 7.15. Found: C, 68.54; H, 5.06; N, 6.95.

2,2'-(1,2-Ethynediyl)bis[*N*-[2-(diethylamino)ethyl]-1-methyl-1*H*-indole-3-carboxamide] (**8a**).

A 25 °C suspension of 194 mg (0.53 mmol) of compound **7a** in 4 mL of 1,2-dichloroethane was treated with dropwise addition of thionyl chloride. A drop of *N*,*N*-dimethylformamide was added and the solution was heated at 75 °C for 3 h. The viscous suspension was concentrated, the solids were co-evaporated twice with dichloromethane, and then evacuated at 1 mm/50 °C/30 min. The solids were suspended in 4 mL dichloromethane, and then treated dropwise at 0 °C with 0.74 mL (5.3 mmol) of *N*,*N*-diethylethylenediamine. Cooling was removed and the mixture was stirred at 25 °C for 14 h. The solution was diluted with dichloromethane, and then washed with 5% aqueous sodium bicarbonate. The organic phase was dried, and concentrated to a solid that was purified by column chromatography eluting sequentially with 100:0:0, 95:5:1, and 90:10:1 ethyl acetate:methanol: triethylamine. Product fractions were combined and concentrated to a solid that was crystallized from 2-propanol to afford 111 mg (37 %) of **8a**, mp 167-168 °C. Additional processing of the filtrate gave 55 mg (18 %) of a second crop, mp 165-167 °C; ^{1}H NMR (CD_3OD/NaOD): δ 1.05 (t, *J* = 7 Hz, 12H), 2.63 (q, *J* = 7 Hz, 8H), 2.78 (t, *J* = 7 Hz, 4H), 3.65 (t, *J* = 7 Hz, 4H), 4.02 (s, 6H), 7.25-7.29 (m, 2H), 7.36-7.41 (m, 2H), 7.51 (d, *J* = 8 Hz, 2H), 8.11 (d, *J* = 8 Hz, 2H).

Anal. Calcd. for $C_{34}H_{44}N_6O_2$: C, 71.80; H, 7.80; N, 14.78. Found: C, 71.45; H, 7.65; N, 14.65.

(*Z*)-2,2'-(1,2-Ethenediyl)bis[*N*-[2-(diethylamino)ethyl]-1-methyl-1*H*-indole-3-carboxamide] (**8b**).

Reaction of alkyne **8a** under transfer hydrogenation conditions was carried out as described for the synthesis of **6** except that only two charges of catalyst were required. After 30 min, the mixture was filtered through Celite® and the pad was washed well with ethyl acetate. The filtrate was diluted with 5 % aqueous hydrochloric acid and the phases were separated. The aqueous layer was adjusted to pH 10 with dilute aqueous sodium hydroxide, and then extracted three times with ethyl acetate. The combined organic phases were dried and concentrated to an oil that was stored at 25 °C for several days. The precipitated solids were triturated in *i*-propyl ether, and collected to leave 137 mg (74 %) of **8b**, mp 112-116 °C; ^{1}H NMR ($CDCl_3$/D_2O): δ 1.02 (t, *J* = 7 Hz, 12H), 2.49-2.55 (m, 12H), 3.28 (s, 6H), 3.35 (t, *J* = 7 Hz, 4H), 7.15-7.23 (m, 6H), 7.24 (s. 2H), 7.84-7.86 (m, 2H).

Anal. Calcd. for $C_{34}H_{46}N_6O_2$: C, 71.55; H, 8.12; N, 14.72. Found: C, 71.24; H, 8.07; N, 14.50.

(*E*)-2,2'-(1,2-Ethenediyl)bis[*N*-[2-(diethylamino)ethyl]-1-methyl-1*H*-indole-3-carboxamide] dihydrochloride (**8c**).

Reaction of (*E*)-alkene **7c** was carried out as described above for the synthesis of **8a** to give **8c**, mp 194-196 °C, in 58 % yield following crystallization from ethanol. Treating a methanolic solution of **8c** with excess 8.5 *M* hydrogen chloride in 2-propanol gave the dihydrochloride salt, mp 281-285 °C; ^{1}H NMR (D_2O): δ 1.28 (t, *J* = 7 Hz, 12H), 3.24 (q, *J* = 7 Hz, 8H), 3.34 (t, *J* = 6 Hz, 4H), 3.71 (t, *J* = 6 Hz, 4H), 3.83 (s, 6H), 7.24 (s. 2H), 7.35-7.39 (m, 2H), 7.45-7.49 (m, 2H), 7.60 (d, *J* = 8 Hz, 2H), 7.85 (d, *J* = 8 Hz, 2H).

Anal. Calcd. for $C_{34}H_{46}N_6O_2 \cdot 2$ HCl: C, 63.44; H, 7.52; N, 13.06; Cl^-, 11.02. Found: C, 63.45; H, 7.61; N, 13.04; Cl^-, 10.99.

2,2'-(1,2-Ethanediyl)bis[*N*-[2-(diethylamino)ethyl]-1-methyl-1*H*-indole-3-carboxamide] (**9**).

A solution of 368 mg (0.64 mmol) of (*E*)-alkene **8c**, 200 mg of 20% palladium on charcoal, and 10 mL of methanol was hydrogenated at 25 °C and 573 psi for 17.5 h. The mixture was filtered over Celite®, the pad was washed well with methanol, and the filtrate was concentrated. The solids were triturated in 2-propanol and collected to leave 310 mg (84 %) of **9**, mp 173-175 °C; ^{1}H NMR ($CDCl_3/D_2O$): δ 1.06 (t, *J* = 7 Hz, 12H), 2.60 (q, *J* = 7 Hz, 8H), 2.67 (t, *J* = 6 Hz, 4H), 3.49 (t, *J* = 6 Hz, 4H), 3.59 (s, 4H), 3.87 (s, 6H), 7.18-7.26 (m, 4H), 7.35 (d, *J* = 8 Hz, 2H), 7.82 (d, *J* = 8 Hz, 2H); MS (Cl^+): *m/z* (relative %) 602 (1), 574 (23), 474 (8), 375(7), 99 (36), 86 (100).

Anal. Calcd. for $C_{34}H_{48}N_6O_2$: C, 71.30; H, 8.45; N, 14.67. Found: C, 71.30; H, 8.10; N, 14.51.

REFERENCES

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[1] B. D. Palmer, G. W. Rewcastle, A. M. Thompson, M. Boyd, H. D. H. Showalter, A. D. Sercel, D. W. Fry, A. J. Kraker and W. A. Denny, *J. Med. Chem.*, **38**, 58 (1995).

[2] H. D. H. Showalter, A. D. Sercel, B. M. Leja, C. D. Wolfangel, L. A. Ambroso, W. L. Elliott, D. W. Fry, A. J. Kraker, C. T. Howard, G. H. Lu, C. W. Moore, J. M. Nelson, B. J. Roberts, P. W. Vincent, W. A. Denny and A. M. Thompson. *J. Med. Chem.*, **40**, 413 (1997).

[3] T. R. Burke, Jr., *Drugs of the Future*, **17**, 119 (1992).

[4] J. F. Callahan, K. A. Newlander and W. F. Huffman, *Tetrahedron Lett.*, **32**, 7203 (1991).

[5] O. Dann, H. P. Wolff, R. Schlee and J. Ruff, *Liebigs Ann. Chem.*, 2164 (1986).

[6] L. Capuano, S. Drescher, V. Hammerer and M. Hanisch, *Chem. Ber.*, **121**, 2259 (1988).

[7] O. Dann, H. Char, P. Fleischmann and H. Fricke, *Liebigs Ann. Chem.*, 438 (1986).

[8] A. Andreani, M. Rambaldi, A. Locatelli, F. Andreani, G. Poglayen and M. Degli Esposti, *Eur. J. Med. Chem.*, **27**, 729 (1992).

[9] S. Elango and P. C. Srinivasan, *Tetrahedron Lett.*, **34**, 1347 (1993).

[10a] H. Zhang and R. C. Larock, *J. Org. Chem.*, **67**, 7048 (2002); [b] H. Zhang and R. C. Larock, *Tetrahedron Lett.*, **43**, 1359 (2002).

[11] R. S. Paley, J. A. Lafontaine and M. P. Ventura, *Tetrahedron Lett.*, **34**, 3663 (1993).

[12] M. D'Auria, *Syn. Commun.*, **22**, 2393 (1992).

[13] M. J. Marsella, K. Yoon, S. Estassi, F. S. Tham, D. B. Borchardt, B. H. Bui, and P. R. Schreiner, *J. Org. Chem.*, **70**, 1881 (2005).

[14a] D. A. Siesel and S. W. Staley, *J. Org. Chem.*, **58**, 7870 (1993); [b] D. A. Siesel and S. W. Staley, *Tetrahedron Lett.*, **34**, 3679 (1993).

[15] C. H. Cummins, *Tetrahedron Lett.*, **35**, 857 (1994).

[16] A. Barbero, P. Cuadrado, I. Fleming, A. M. Gonzalez, F. J. Pulido, and R. Rubio, *J. Chem. Soc., Perkin Trans. 1*, 1657 (1993).

[17] J. R. Weir, B. A. Patel and R. F. Heck, *J. Org. Chem.*, **45**, 4926 (1980).

[18] S. O. Sablin, M. J. Krueger, T. P. Singer, S. O. Bachurin, A. B. Khare, S. M. N. Efange and S. E. Tkachenko, *J. Med. Chem.*, **37**, 151 (1994) and references cited therein.

[19] P. Sieber, *Helv. Chim. Acta*, **60**, 2711 (1977).

[20] D. W. Fry, A. J. Kraker, R. C. Connors, W. L. Elliott, J. M. Nelson, H. D. H. Showalter, and W. R. Leopold, *Anti-Cancer Drug Design*, **9**, 331 (1994).