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Regioselective Sonogashira Couplings of 2,4-Dibromoquinolines. A Correction

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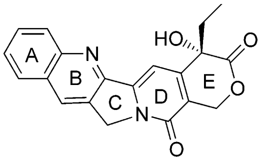
Received January 29, 2003

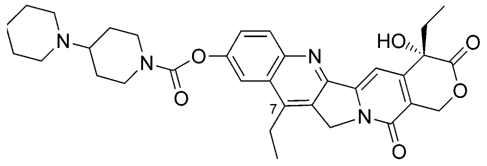
Abstract: Heteronuclear multiple bond correlation (HMBC) was used to determine the regiochemical outcome of palladium-catalyzed carbon−carbon bond formation between 2,4-dibromoquinolines and terminal acetylenes. The observed regioselectivity of these coupling reactions is opposite to that reported in the literature for analogous reactions.

For several years, we have dedicated part of our research program to the development of short syntheses of (*S*)-camptothecin (**1**) and derivatives. Through this effort, we recently accomplished a six-step asymmetric synthesis of (*S*)-camptothecin utilizing a convergent approach in which enantiopure DE rings were combined with an AB ring fragment prepared from commercially available quinoline derivative **3**.[1] It was envisioned that clinically useful camptothecin analogues, some with a C-7 substituent[2] such as irinotecan (**2**), could be made in a similar manner starting from a readily available 2,4-dibromoquinoline. Reisch and Gunaherath[3] reported that 2,4-dibromoquinoline (**4**) could be monosubstituted with various terminal alkynes (Scheme 1), and they proposed that the alkynyl substituent in the product was positioned at C-4 as determined by NOE of the corresponding 2-methoxy-4-alkynylquinolines **6**. However, when we attempted to prepare quinoline **12** using this strategy (Scheme 2), it was determined using 2D $^1H-^{13}C$ HMBC NMR that regioisomer **11** was produced, indicating that the Sonogashira coupling[4] of 2,4-dibromoquinolines results in a preferential carbon−carbon bond formation at C-2 rather than C-4.



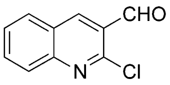
1

(*S*)-camptothecin



2

irinotecan



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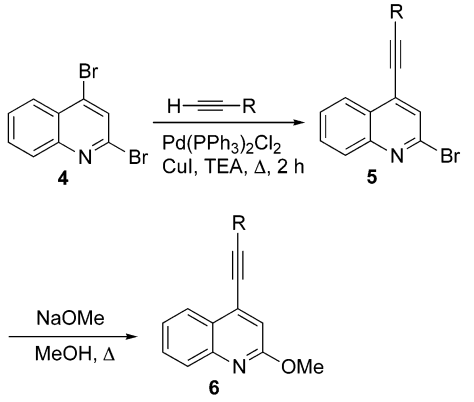
SCHEME 1. Reported Regioselective Couplings of 4



R = -Ph, -C(Me)(OH)Ph, -CH(OH)Me, $-CO_2Et$, -CH(OH)Me, $-C(NH_2)Me_2$, $-(CH_2)_7CH_3$

The 2,4-dibromoquinoline **4** was prepared from the corresponding diol **7** using a known procedure.[3] Formylation via halogen-directed metalation[5] followed by sodium borohydride reduction afforded alcohol **9**. The Sonogashira coupling of **9** with 1.2 equiv of trimethylsilylacetylene worked in good yield at room temperature to provide quinoline **10**, which was subsequently converted to quinoline **11** using diimide reduction.[6] The 2-(trimethylsilylethyl)quinoline **11** provided $^3J_{CH}$ couplings available for HMBC correlation, and the NMR

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[1] Comins, D. L.; Nolan, J. M. *Org. Lett.* **2001**, *3*, 4255.

[2] (a) Sawada, S.; Yokokura, T.; Miyasaka, T. In *The Camptothecins: From Discovery to the Patient*; Pantazis, P., Giovanella, B. C., Rothenberg, M. L., Eds.; Ann. N. Y. Acad. Sci.: New York, 1996; Vol. 803, p 13. (b) Cai, J. C.; Hutchinson, C. R. In *The Alkaloids: Chemistry and Pharmacology*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 21, p 101. (c) Fang, F. G.; Xie, S.; Lowery, M. W. *J. Org. Chem.* **1994**, *59*, 6142. (d) Fang, F. G.; Bankston, D. D.; Huie, E. M.; Johnson, M. R.; Kang, M.; LeHoullier, C. S.; Lewis, G. C.; Lovelace, T. C.; Lowery, M. W.; McDougald, D. L.; Meerholz, C. A.; Partridge, J. J.; Sharp, M. J.; Xie, S. *Tetrahedron* **1997**, *53*, 10953. (e) Dallavalle, S.; Ferrari, A.; Biasotti, B.; Merlini, L.; Penco, S.; Gallo, G.; Marzi, M.; Tinti, M. O.; Martinelli, R.; Pisano, C.; Carminati, P.; Carenini, N, Beretta, G.; Perego, P., De Cesare, M.; Pratesi, G.; Zunino, F. *J. Med. Chem.* **2001**, *44*, 3264. (f) Sawada, S.; Okajima, S.; Aiyama, R.; Nokata, K.; Furuta, T.; Yokokura, T.; Sugino, E.; Yamagushi, K.; Miyasaka, T. *Chem. Pharm. Bull.* **1991**, *39*, 1446.

[3] Reisch, J.; Gunaherath, G. M. K. B. *J. Heterocycl. Chem.* **1993**, *30*, 1057.

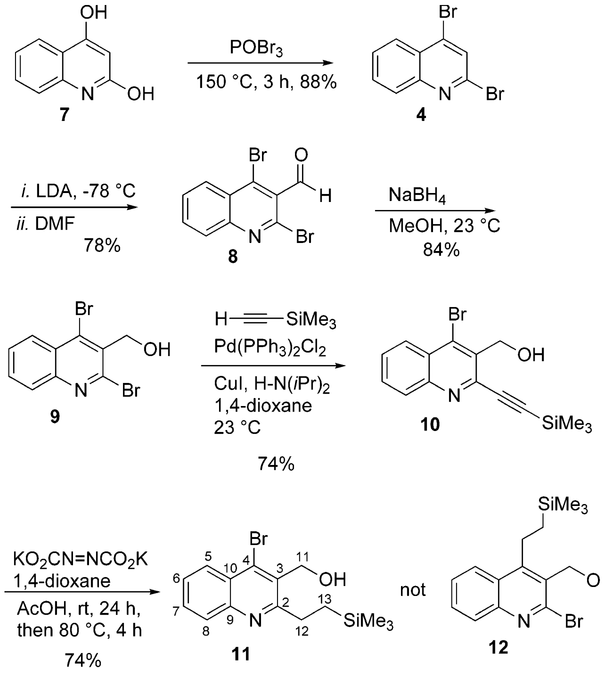
[4] (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) For a review, see: Sonogashira, K. In *Comprehensive Organic Synthesis;* Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 3, p 521.

[5] (a) Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120. (b) Marsais, F.; Godard, A.; Queguiner, G. *J. Heterocycl. Chem.* **1989**, *26*, 1589. (c) Rewcastle, G. W.; Katritzky, A. R. *Adv. Heterocycl. Chem.* **1993**, *56*, 155. (d) Mongin, F.; Queguiner, G. *Tetrahedron* **2001**, *57*, 4059.

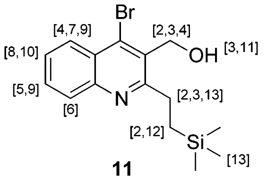
[6] To the best of our knowledge, this is the first reported diimide reduction of silylacetylenes. For a recent review on diimide reductions, see: Pasto, D. J.; Taylor, R. T. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons, Inc.; New York, 1991; Vol. 40, p 91.

10.1021/jo034122w CCC: $25.00

SCHEME 2



experiment revealed that the α-silyl protons at C-13 (1.04 ppm) correlate to the same carbon (C-2, 164.8 ppm) as the benzyl protons at C-11 (5.05 ppm). Furthermore, the C-11 benzyl protons also correlate with the same carbon (C-4, 137.5 ppm) as the aromatic proton at C-5 (8.16 ppm). These results in combination with ^{13}C NMR and HETCOR data provide an unequivocally assigned structure for quinoline **11**. The complete HMBC correlations ($^2J_{CH}$ and $^3J_{CH}$) for quinoline **11** are shown in Figure 1.

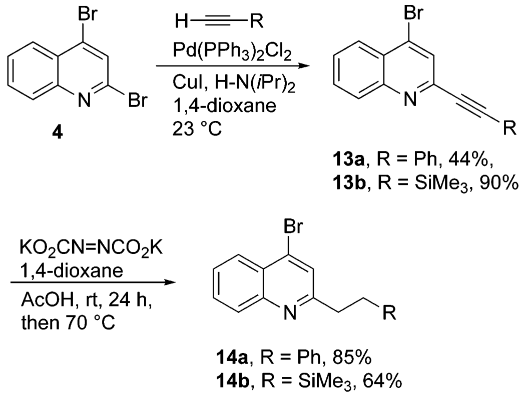


11

FIGURE 1. HMBC correlations ($^2J_{CH}$ and $^3J_{CH}$).

To determine if the regioselectivity was general for various 2,4-dibromoquinolines, additional studies were carried out. As reported, 2,4-dibromoquinoline (**4**) was coupled to phenylacetylene to give a monosubstituted product (**13a**, Scheme 3). The ^{1}H NMR spectra and melting point for **13a** were in agreement with the reported data by Reisch and Gunaherath for the assigned structure **5** (Scheme 1, R = Ph).[7] Diimide reduction of **13a** afforded **14a**, and the assigned regiochemistry was confirmed by HMBC. Additionally, **4** was coupled with trimethysilylacetylene to give **13b** and then subsequently reduced to afford **14b**. Again, using HMBC, the substitution was confirmed for C-2, further demonstrating the generality and regioselectivity of the Sonogashira reaction of 2,4-dibromoquinolines.

SCHEME 3



Although the coupling reaction of dibromoquinoline **9** provided the unwanted regioisomer **10**, in respect to the synthesis of camptothecin derivatives, the studies have clarified the general reactivity and regioselectivity of the Sonogashira coupling reaction with 2,4-dibromoquinolines.[8]

Experimental Section

2,4-Dibromoquinoline-3-carbaldehyde (8). To a solution of diisopropylamine (0.28 mL, 2.02 mmol) in THF (2 mL) was added *n*-BuLi (2.39 M in hexanes, 0.84 mL, 2.02 mmol) at 0 °C, and the mixture was allowed to stir for 30 min. The solution was cooled to −78 °C, a solution of 2,4-dibromoquinoline (526 mg, 1.83 mmol) in THF (4 mL) was added via a double-tipped needle, and the mixture was stirred for 1 h. DMF (0.18 mL, 1.35 mmol) was added neat, and the mixture was stirred for an additional 30 min before quenching with glacial AcOH/satd NH_4Cl mixture (1:1, 0.5 mL). The organic layer was extracted with Et_2O, washed with water and brine, dried ($MgSO_4$), and then concentrated in vacuo to afford a crude solid. Purification by radial PLC (silica gel, hexanes, then ethyl acetate/hexanes, 5:95) afforded the desired compound as a white solid (430 mg, 78%): mp 147−149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (t, 1H, J = 7.2 Hz), 7.88 (t, 1H, J = 8.4 Hz), 8.05 (d, 1H, J = 8.4 Hz), 8.35 (d, 1H, J = 8.4 Hz), 10.40 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 127.3, 128.0, 128.5, 129.3, 129.5, 133.8, 138.1, 139.6, 149.0, 190.5; FTIR (film) 1547, 1697, 2889 cm^{-1}; exact mass for $C_{10}H_5NOBr_2$ (M + 1H) requires m/z 313.8816, found m/z 313.8819.

(2,4-Dibromoquinolin-3-yl)methanol (9). To a solution of **8** (242 mg, 0.77 mmol) in MeOH (10 mL) was added $NaBH_4$ (38 mg, 1.00 mmol) slowly at ambient temperature. When the reaction was complete (TLC analysis), it was quenched with water (2 mL). The mixture was extracted with Et_2O (20 mL), and the combined extracts were washed with water and brine. After drying ($MgSO_4$) and concentrating in vacuo, the crude solid was purified by radial PLC (silica gel, ethyl acetate/hexanes, 20:80) to provide **9** as a yellow solid (205 mg, 84%): mp 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (s, 1H), 5.18 (s, 2H), 7.64 (t, 1H, J = 8.0 Hz), 7.73 (t, 1H, J = 6.8 Hz), 7.97 (d, 1H, J = 8.4 Hz), 8.15 (d, 1H, J = 8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 65.6, 127.5, 128.0, 128.8, 129.0, 131.6, 133.3, 137.7, 143.6, 148.0; FTIR (film) 1477, 1552, 2942, 3032, 3321, 3386 cm^{-1}; exact mass for $C_{10}H_7NOBr_2$ (M + 1H) requires m/z 315.8973, found m/z 315.8976.

(4-Bromo-2-(trimethylsilanylethynyl)quinolin-3-yl)methanol (10). To quinoline **9** (200 mg, 0.63 mmol), $Pd(PPh_3)_2Cl_2$ (44 mg, 0.06 mmol), and CuI (12 mg, 0.06 mmol) in a flame-dried round-bottomed flask were added dioxane (3 mL) and

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(7) When we repeated this reaction following the reported procedure as closely as possible ($Pd(PPh_3)_2Cl_2$, CuI, TEA), a 59% yield of **13a** was isolated along with 24% of starting material **4**. No C-4 substitution was observed.

(8) For regioselective Sonogashira couplings of dibromopyridines, see: (a) Tilley, J. W.; Zawoiski, S. *J. Org. Chem.* **1988**, *53*, 386. (b) Chambers, R. D.; Hall, C. W.; Hutchinson, J.; Millar, R. W. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1705.

diisopropylamine (0.11 mL, 0.76 mmol). The heterogeneous mixture was deoxygenated with argon for 20 min, trimethylsilylacetylene (0.11 mL, 0.76 mmol) was added dropwise, and the reaction was stirred at ambient temperature overnight (14 h). The reaction mixture was filtered though silica gel, and the filter cake was washed with Et_2O (10 mL). The resulting organic layer was separated, washed with water and brine, dried ($MgSO_4$), and concentrated in vacuo to give a crude solid. The desired compound **10** (156 mg, 74%) was isolated after purification via radial PLC (silica gel, ethyl acetate/hexanes, 5:95) as an orange solid (156 mg, 74%): mp 97−98 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 0.33 (s, 9H), 2.54 (t, 1H, $J = 6.9$ Hz), 5.22 (d, 2H, $J = 6.9$ Hz), 7.64 (t, 1H, $J = 6.9$ Hz), 7.75 (t, 1H, $J = 6.9$ Hz), 8.08 (d, 1H, $J = 8.4$ Hz), 8.20 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ −0.6, 63.7, 100.4, 101.9, 127.5, 127.6, 129.1, 129.9, 131.1, 134.7, 136.4, 143.1, 147.9; FTIR (film) 1547, 1566, 2897, 2958, 3382 cm^{-1}; exact mass for $C_{15}H_{16}NOBrSi$ (M + 1H) requires *m/z* 334.0263, found *m/z* 334.0268.

[4-Bromo-2-(2-trimethylsilanylethyl)quinolin-3-yl]methanol (11). To a solution of **10** (94 mg, 0.28 mmol) in dioxane (5 mL) was added potassium azodicarboxalate (818 mg, 4.22 mmol) followed by the slow addition of glacial AcOH (0.70 mL, 11.81 mmol, in 2 mL dioxane) over 24 h using a syringe pump at ambient temperature. After complete addition of AcOH, the solution was warmed to 80 °C for 4 h during which time the reaction color changed from yellow to white. The reaction mixture was extracted with Et_2O (10 mL), and the combined extracts were washed with water and brine. The solution was dried ($MgSO_4$) and concentrated in vacuo. Purification by radial PLC (silica gel, ethyl acetate/hexanes, 5:95) provided **11** as a white solid (84 mg, 88%). Recrystallization from hexanes gave an analytically pure sample: mp 105−106.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 0.08 (s, 9H), 1.04 (m, 2H), 2.27 (t, 1H, $J = 6.8$ Hz), 3.12 (m, 2H), 5.05 (d, 2H, $J = 6.4$ Hz), 7.56 (t, 1H, $J = 8.0$ Hz), 7.70 (t, 1H, $J = 8.0$ Hz), 8.01 (d, 1H, $J = 8.4$ Hz), 8.16 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.5, 17.5, 31.6, 62.4, 126.9, 127.3, 127.5, 129.2, 130.5, 131.5, 137.5, 148.1, 164.8; FTIR (film) 1614, 2894, 2951, 3356 cm^{-1}; exact mass for $C_{15}H_{20}NOBrSi$ (M + 1H) requires *m/z* 338.0584, found *m/z* 338.0584.

4-Bromo-2-(phenylethynyl)quinoline (13a). To 2,4-dibromoquinoline (109 mg, 0.380 mmol), $Pd(PPh_3)_2Cl_2$ (27 mg, 0.038 mmol), and CuI (7 mg, 0.038 mmol) in a flame-dried round-bottomed flask were added dioxane (3 mL) and diisopropylamine (0.064 mL, 0.456 mmol), and the heterogeneous mixture was deoxygenated with argon for 20 min. Phenylacetylene (0.042 mL, 0.380 mmol) was added dropwise, and the reaction was stirred at ambient temperature overnight (15 h). The reaction mixture was filtered though silica gel, and the filtrate was extracted with Et_2O. The combined organic extracts were washed with saturated NH_4Cl, brine, and water and then dried ($MgSO_4$) and concentrated in vacuo to give a crude mixture of product and starting material. The residue was purified by radial PLC (silica gel, hexanes, then ethyl acetate/hexanes, 5:95) to afford starting material (27 mg, 25%) and **13a** as a yellow solid (51 mg, 44%): mp 96−97 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.39 (m, 3H), 7.64 (m, 3H), 7.76 (t, 1H, $J = 7.6$ Hz), 7.91 (s, 1H), 8.11 (d, 1H, $J = 8.4$ Hz), 8.15 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 88.4, 91.1, 121.9, 126.8, 127.0, 128.2, 128.5, 128.7, 129.6, 130.0, 131.1, 132.5, 134.0, 143.5, 148.7.

4-Bromo-2-(trimethylsilanylethynyl)quinoline (13b). To 2,4-dibromoquinoline (1.037 g, 3.61 mmol), $Pd(PPh_3)_2Cl_2$ (254 mg, 0.36 mmol), and CuI (688 mg, 0.36 mmol) in a flame-dried round-bottomed flask were added dioxane (10 mL) and diisopropylamine (0.61 mL, 4.34 mmol), and the heterogeneous mixture was deoxygenated with argon for 20 min. Trimethylsilylacetylene (0.61 mL, 4.34 mmol) was added dropwise, and the reaction mixture was stirred at ambient temperature overnight (15 h). The reaction mixture was filtered though silica gel, and the filtrate was extracted with Et_2O. The combined organic extracts were washed with water and brine and then dried ($MgSO_4$) and concentrated in vacuo to give a crude mixture of product and starting material. The crude mixture was purified first by Kugerohr distillation (140 °C) to remove palladium residue and then by radial PLC (silica gel, hexanes) to afford **13b** as a colorless oil (507 mg, 46%): ^1H NMR (400 MHz, $CDCl_3$) δ 0.30 (s, 9H), 7.63 (t, 1H, $J = 7.2$ Hz), 7.75 (t, 1H, $J = 6.8$ Hz), 7.84 (s, 1H), 8.09 (d, 1H, $J = 8.4$ Hz), 8.14 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.3, 96.9, 103.0, 126.4, 126.8, 127.9, 128.3, 129.8, 130.8, 133.7, 142.8, 148.3; FTIR (film) 1572, 2355, 2964 cm^{-1}; exact mass for $C_{14}H_{14}NBrSi$ (M + 1H) requires *m/z* 304.0157, found *m/z* 304.0143.

4-Bromo-2-(phenylethyl)quinoline (14a). To a solution of **13a** (78 mg, 0.253 mmol) and potassium azodicarboxalate (737 mg, 3.80 mmol) in dioxane (5 mL) at 60 °C was added glacial AcOH (0.61 mL, 10.63 mmol, in 5 mL dioxane) over 24 h using a syringe pump. After complete addition of AcOH, the solution was allowed to stir for an additional 8 h at 60 °C. The reaction mixture was extracted with Et_2O, and the extracts were washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by radial PLC (silica gel, hexanes, then ethyl acetate/hexanes, 5:95) provided **14a** as a colorless oil (67 mg, 85%): ^1H NMR (400 MHz, $CDCl_3$) δ 3.16 (m, 2H), 3.26 (m, 2H), 7.20−7.33 (m, 5H), 7.55 (s, 1H), 7.74 (t, 1H, $J = 7.6$ Hz), 8.07 (d, 1H, $J = 8.4$ Hz), 8.14 (d, 1H, $J = 8.0$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 35.8, 40.7, 125.6, 126.3, 126.5, 126.8, 127.2, 128.7, 129.5, 130.5, 134.3, 141.3, 148.7, 161.8; FTIR (film) 1586, 2855, 2924, 3025, 3060 cm^{-1}; exact mass for $C_{17}H_{14}NBr$ requires *m/z* 311.0310, found *m/z* 311.0301.

4-Bromo-2-(2-trimethylsilanylethyl)quinoline (14b). To a solution of **13b** (105 mg, 0.35 mmol) and potassium azodicarboxalate (1.0 g, 5.18 mmol) in dioxane (10 mL) at ambient temperature was added glacial AcOH (0.83 mL, 14.49 mmol, in 5 mL dioxane) over 24 h using a syringe pump. After complete addition of AcOH, the solution was warmed to 80 °C for 4 h during which time the reaction color changed from yellow to white. The reaction mixture was extracted with Et_2O, and the extracts were washed with water and brine. The organic layer was dried ($MgSO_4$) and concentrated in vacuo. Purification by radial PLC (silica gel, hexanes, then ethyl acetate/hexanes, 5:95) provided the desired product as a colorless oil (67 mg, 63%): ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 9H), 1.03 (m, 2H), 2.92 (m, 2H), 7.54 (t, 1H, $J = 7.6$ Hz), 7.63 (s, 1H), 7.70 (t, 1H, $J = 6.8$ Hz), 8.01 (d, 1H, $J = 8.4$ Hz), 8.15 (d, 1H, $J = 8.4$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.5, 17.1, 33.5, 124.9, 126.4, 126.7, 127.0, 129.3, 130.4, 134.3, 148.6, 165.1; FTIR (film) 1586, 1614, 2895, 2951, 3062 cm^{-1}; exact mass for $C_{14}H_{18}NBrSi$ (M + 1H) requires *m/z* 308.0470, found *m/z* 308.0488.

Acknowledgment. NMR and mass spectra were obtained at NCSU instrumentation laboratories, which were established by grants from the North Carolina Biotechnology Center and the National Science Foundation (Grant Nos. CHE-9509532 and CHE-0078253).

Supporting Information Available: General experimental information, characterization data, and copies of ^1H and ^{13}C NMR spectra for **8**, **9**, **10**, **11**, **13b**, and **14a**,**b**, 2D $^1H-^{13}C$ HMBC spectra for **11** and **14a**,**b**, and a comparison table of NMR data for **13a**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034122W