and rotary evaporated to obtain the title product, which was directly employed in the next step: ^{1}H NMR (Me_2SO-d_6) δ 3.86 (s, 3, OMe), 7.71 (s, 1, imidazole CH), 8.46 (s, 1, imidate CH).

3. 1-Aminoadenine (13). The above 4(5)-cyano-5(4)-[(methoxymethylene)amino]imidazole was dissolved in dry acetonitrole (60 mL). To the resulting solution was added hydrazine hydrate (0.34 mL, 6.9 mmol) dropwise with a syringe needle. After the addition, the mixture was stirred under N_2 at room temperature for 30 min. The precipitated solid was filtered in vacuo and recrystallized from a mixture of CH_3CN–MeOH into colorless crystals of **13** (0.87 g, 5.83 mmol, 79%), mp 210 °C: ^{1}H NMR (Me_2SO-d_6) δ 6.33 (br s, 2, NH_2, exchangeable with D_2O), 7.89 (s, 1, CH), 8.13 (s, 1, CH).

Anal. Calcd for $C_5H_6N_6 \cdot {}^1/_8H_2O$: H_2O: C, 39.40; H, 4.10; N, 55.17. Found: C, 39.36; H, 4.09; N, 55.05.

The HCl salt of the above compound, prepared by passing dry HCl gas in methanolic solution of the compound for 30 min, had spectral data identical with those reported for **13**·HCl.[2a]

4. 1,2,4-Triazolo[5,1-*i*]purine (12). A mixture of compound **13** (300 mg, 2 mmol), trimethyl orthoformate (15 mL, 0.14 mol), and trifluoroacetic acid (0.05 mL, 0.65 mmol) was heated at reflux under N_2 for 2 h. The reaction mixture was evaporated to dryness on a rotary evaporator, and the residue was triturated with CH_3CN to obtain a solid, which was recrystallized from a mixture of CH_3CH–MeOH–H_2O into colorless crystals of **12** (278 mg, 1.74 mmol, 87%), mp >250 °C. The ^{1}H NMR,[2a] UV,[12] and mass spectral data[2a] of this compound were identical with the reported values.

4-Cyano-5-[(methoxymethylene)amino]-1-methylpyrazole (18). A mixture of 5-amino-4-cyano-1-methylpyrazole,[16] (2 g, 16.4 mmol) trimethyl orthoformate (50 mL, 0.46 mol), and trifluoroacetic acid (0.1 mL, 1.3 mmol) was heated at reflux under N_2 for 1 h. The reaction mixture was cooled and rotary evaporated to dryness. The residual oil was directly employed in the next step. Further purification of the oil, if desired, can be effected by distillation in a Kugelrohr apparatus [oven temperature 94–106 °C (0.25 mmHg)] to obtain **18** as a colorless oil, which solidifies upon cooling in a refrigerator overnight (2.3 g, 14.0 mmol, 86%): ^{1}H NMR (Me_2SO-d_6) δ 3.68 (s, 3, N-Me), 3.95 (s, 3, OMe), 7.87 (s, 1, imidazole CH), 8.49 (s, 1, imidate CH); IR (KBr) 2230 cm^{-1}.

***N*-Amino-*N*-methyl-*N'*-(1-methyl-4-cyanopyrazol-5-yl)formamidine (19).** To an ice-cooled solution of methylhydrazine (0.53 mL, 10 mmol) in dry acetonitrile (10 mL) was added dropwise a solution of the imidate **18** (1.15 g, 7.0 mmol) in 10 mL of dry acetonitrile over a period of 10–15 min. After the addition was complete, the ice–water bath was removed, and the reaction mixture was stirred at room temperature overnight. The mixture was evaporated to dryness on a rotary evaporator, and the solid residue was recrystallized from ether or benzene into colorless needles (1.11 g, 6.23 mmol, 89%), mp 103–105 °C: ^{1}H NMR (Me_2SO-d_6) δ 3.21 (s, 3, side chain CH_3), 3.59 (s, 3, ring CH_3), 5.28 (s, 2, NH_2, exchangeable with D_2O), 7.67 (s, 1, pyrazole CH), 8.33 (s, 1, side chain CH); mass spectrum (70 eV), *m/e* 178 (M^+), 163 ($M^+ - CH_3$); IR (KBr) 2200 cm^{-1} (C≡N).

Anal. Calcd for $C_7H_{10}N_6$: C, 47.18; H, 5.66; N, 47.16. Found: C, 47.20; H, 5.68; N, 47.12.

3-(5-Amino-1-methylpyrazol-4-yl)-1-methyl-1,2,4-triazole (20) and 5-Amino-4-cyano-1-methylpyrazole. A mixture of **19** (500 mg, 2.8 mmol), dry toluene (10 mL), dry MeOH (10 mL), and trifluoroacetic acid (0.05 mL, 0.65 mmol) was heated at reflux under N_2 for 3 days. The reaction mixture was cooled and worked up by employing the procedure described above for the rearrangement of **8b** to **9** and **10** except that the eluting solvent system for flash chromatography was $CHCl_3$–MeOH (50:1). The first product to elute from the column was **5-amino-4-cyano-1-methylpyrazole** (165 mg, 1.35 mmol, 48%), mp 222 °C (lit.[16] mp 222–223 °C): ^{1}H NMR (Me_2SO-d_6)δ 3.52 (s, 3, Me), 6.48 (br s, 2, NH_2, exchangeable with D_2O), 7.49 (s, 1, CH). The physical data and chemical yield for compound **20**, which followed, are as follows: colorless needles from benzene; 214 mg, 1.2 mmol, 43%; mp 177–179 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.58 (s, 3, pyrazole CH_3), 3.84 (s, 3, triazole CH_3), 5.75 (br s, 2, NH_2, exchangeable with D_2O), 7.47 (s, 1, pyrazole CH), 8.36 (s, 1, triazole CH); mass spectrum (70 eV), *m/e* 178 (M^+), 163 ($M^+ - CH_3$); UV λ_{max} (EtOH) 239 nm (ϵ 12 260), (pH 0.1) 262 (11 000), 231 (9600), (pH 13) 237 (12 000).

Anal. Calcd for $C_7H_{10}N_6$: C, 47.18; H, 5.66; N, 47.16. Found: C, 47.09; H, 5.71; N, 47.07.

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Registry No. **3** (R = Me, X = Z = N, Y = CH), 23142-09-8; **5**, 111267-84-6; **6**, 111267-85-7; **7**, 6268-73-1; **8b**, 111267-86-8; **9**, 60598-48-3; **10**, 111267-87-9; **11a**, 111267-88-0; **11b**, 111267-89-1; **12**, 4022-94-0; **13**, 72621-40-0; **13**·HCl, 111267-90-4; **18**, 111267-91-5; **19**, 111267-92-6; **20**, 111267-93-7; $(CN)_2CHNH_2 \cdot TsOH$, 5098-14-6; $(CN)_2CHNH_2$, 5181-05-5; $MeOCH{=}NCH(CN)_2$, 111267-83-5; $PhCH_2NH_2$, 100-46-9; 9-benzyl-6-chloropurine, 1928-76-3; 9-benzyladenine, 4261-14-7; 5(4)-amino-4(5)-cyanoimidazole, 5098-11-3; 5-amino-4-cyano-1-methylpyrazole, 5334-41-8.

A Convenient Palladium-Catalyzed Coupling Approach to 2,5-Disubstituted Pyridines

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2,5-Dibromopyridine has been found to undergo a regioselective palladium-catalyzed coupling reaction with terminal acetylenes and arylzinc halides to give the corresponding 2-alkynyl-5-bromo- and 2-aryl-5-bromopyridines, respectively, in 70%–90% isolated yields. To complement this chemistry, the triflate derived from 2-methyl-5-pyridinol was found to participate in a palladium-catalyzed reaction with terminal acetylenes leading to the corresponding 5-alkynyl-2-methylpyridines. These intermediates can be further manipulated to afford a broad range of 2,5-disubstituted pyridines.

In recent years, there has been considerable interest in the regioselective preparation of disubstituted pyridines, but no convenient, practical approach to 2,5-dialkyl- and 2-aryl-5-alkylpyridines has yet been described. Existing routes to such compounds involve attack of an electrophile on a 1-lithio-2-substituted-1,2-dihydropyridine formed from addition of an alkyllithium to pyridine followed by oxidation of the resulting dihydropyridine,[1-4] by reaction

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Table I. Reaction of 2,5-Dibromopyridine with Terminal Acetylenes

acetylene	R	product	% yield[a]	mp, bp, °C (mm)
2a	$(CH_3)_3Si$	**3a**	74	59–61
2b	$CH_3(CH_2)_3$	**3b**	91	90–100 (0.01)
2c	$HOCH_2$	**3c**	74	127–129
2d	$CH_3O_2C(CH_2)_3$	**3d**	74	105–110 (0.05)
2e	C_6H_5	**3e**	70	98.5–100

[a] Yield data represent isolated yields.

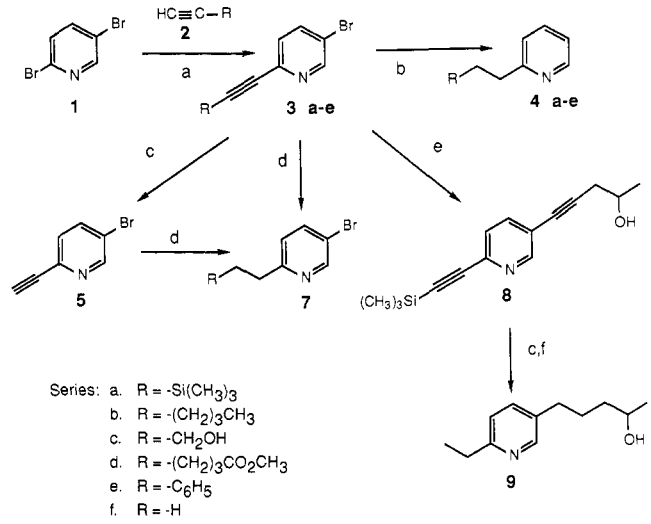
of 5-lithio-2-methylpyridine formed from the relatively inaccessible 5-bromo-2-methylpyridine with a ketone,[5] or by nucleophilic attack of a Grignard reagent on a 1-(phenoxycarbonyl)-3-bromo- or trialkylstannylpyridinium salt followed by oxidation and hydrolysis.[6,7] An interesting multistep synthesis of substituted pyridines from α,β-unsaturated aldehydes has also been described.[8] Parham has shown that 2,5-dibromopyridine can be lithiated selectively to give 2-bromo-5-lithiopyridine, which should provide a source of 2-bromo-5-alkylpyridines.[9] The limitations of these procedures in terms of yield and convenience prompted us to seek a new method that would satisfy our need for multigram quantities of various 2,5-dialkylpyridines.

Previous work has shown that 2- and 3-bromopyridines undergo palladium(0)-catalyzed coupling with terminal acetylenes in the presence of cuprous iodide and an alkylamine solvent.[10,11] We have now found that commercially available 2,5-dibromopyridine (1) reacts regioselectively with terminal acetylenes **2** under similar reaction conditions to give the 5-bromo-2-alkynylpyridines **3** in 70%–90% isolated yields. Several examples of this reaction are shown in Table I.

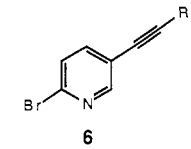
Under standard reaction conditions, 1 equiv each of **1** and **2** is dissolved in 3 mL/mmol of freshly distilled triethylamine, the vessel is flushed with argon, and 2 mol % each of cuprous iodide and bis(triphenylphosphine)palladium dichloride is added successively. The resulting reaction is mildly exothermic, and larger scale runs require cooling to maintain the mixture at room temperature. The reactions were complete in 1–2 h, and the crude products were generally isolated by crystallization or preparative liquid chromatography. The reaction is dependent on the palladium catalyst. When equimolar amounts of the reagents **1** and **2a** were mixed together with cuprous iodide in triethylamine, no reaction was evident by thin-layer chromatography analysis after 24 h. When 2 mol % of bis(triphenylphosphine)palladium dichloride was added to this mixture, a reaction ensued immediately and was complete in 2 h, leading to a 72% yield of **3a**.

In order to ascertain the regiochemistry of the coupling products **3a–e**, they were hydrogenated over palladium on carbon to give the known 2-alkylpyridines **4a–e**. Proton NMR indicated that each possessed a single pyridine α-proton, clearly showing that they were 2- and not the corresponding 3-substituted pyridines, which would have resulted from initial displacement of the bromine atom in the 5-position of **1**. Since proton NMR of the isolated products **3** would not reveal the presence of trace contamination by the corresponding regioisomers **6**, the regiochemical purity of **3c** and **3d** was confirmed by GC/MS analysis, which indicated there were no detectable isomeric impurities present. No doubt small amounts of **6** as well as bisalkynylated materials are formed during the coupling reaction, but these materials are removed along with other minor impurities during the purification process.

Scheme I[a]



[a] (a) CuI, $[(C_6H_5)_3P]_2PdCl_2$, NEt_3, room temperature; (b) Pd(C), H_2, Et_3N, EtOH; (c) NaOH, MeOH; (d) H_2, PtO_2, EtOH; (e) CuI, $[(C_6H_5)_3P]_2PdCl_2$, NEt_3, CH_2Cl_2, 5-pentyn-2-ol; (f) H_2, Pd(C), EtOH.



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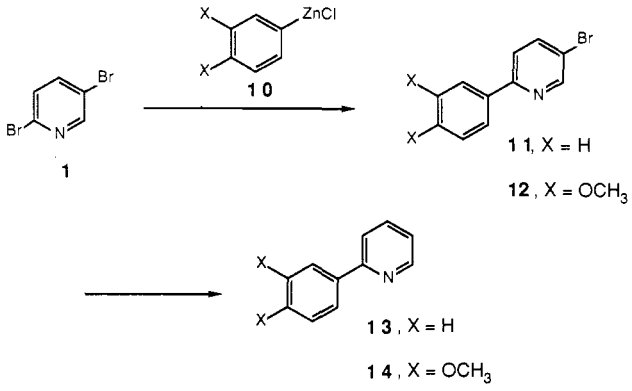
The bromoalkynylpyridines **3** are useful precursors for other 2,5-disubstituted pyridines as shown in Scheme I. Treatment of the (trimethylsilyl)acetylene **3a** with sodium hydroxide afforded the desilylated product **5**. The triple bonds of **3** and **5** can be selectively reduced when conditions are controlled to minimize reductive debromination. For example, when **3c** and **5** were hydrogenated over platinum oxide in ethanol and the reaction stopped when 2 equiv of hydrogen was consumed, the 5-bromo-2-substituted-pyridines **7c** and **7f** were obtained in 82% and 77% yields, respectively.

Like 3-bromopyridine itself, the bromine atom of **3** is capable of undergoing palladium-catalyzed coupling reactions. To illustrate this, the (trimethylsilyl)alkynyl derivative **3a** was allowed to react with 4-pentyn-2-ol in the presence of cuprous iodide and bis(triphenylphosphine)palladium dichloride under essentially the same conditions as the first coupling. This reaction led to the bis(alkynyl)pyridine **8** in 86% yield. The conversion of **8** to the 2-ethyl-5-pyridinepentanol **9** was achieved by hydrolysis of the trimethylsilyl moiety and catalytic hydrogenation and proceeded in high yield as shown in Scheme I.

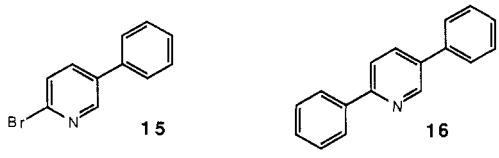
A similar regioselectivity is seen in the palladium-catalyzed coupling of **1** with arylzinc halides. When **1** was allowed to react with phenyl- or (3,4-dimethoxyphenyl)zinc

(1) Doyle, P.; Yates, R. R. J. *Tetrahedron Lett.* **1970**, 3371.
(2) Giam, C. S.; Knaus, E. E.; Lockart, R. A.; Keener, I. G. *Can. J. Chem.* **1975**, *53*, 2305.
(3) Knaus, E. E.; Ondrus, T. A.; Giam, C. S. *J. Heterocycl. Chem.* **1976**, *13*, 789.
(4) Giam, C. S.; Ueno, K. *J. Am. Chem. Soc.* **1977**, *99*, 3166.
(5) Casrissimi, M.; de Maglio, P.; Gentili, P.; Manzardo, S.; Ravenna, F. *Farmaco, Ed. Sci.* **1980**, *34*, 1039.
(6) Comins, D. L.; Mantlo, N. B. *J. Heterocycl. Chem.* **1983**, *20*, 1239.
(7) Comins, D. L.; Mantlo, N. B. *Tetrahedron Lett.* **1987**, *28*, 759.
(8) Konno, K.; Hashimoto, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1986**, *27*, 3865.
(9) Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 257.
(10) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
(11) Tilley, J. W.; Levitan, P.; Lind, J.; Welton, A. F.; Crowley, H. J.; Tobias, L. D.; O'Donnell, M. *J. Med. Chem.* **1987**, *30*, 185.

Scheme II



chloride under the conditions described by Negishi[12] for biphenyl production from aryl bromides, the 5-bromo-2-arylpyridines **11** and **12** were formed in 74% and 72% yields, respectively (Scheme II). The regiochemistry of this process was verified as above by reductive debromination of the products to the 2-phenylpyridines **13** and **14**

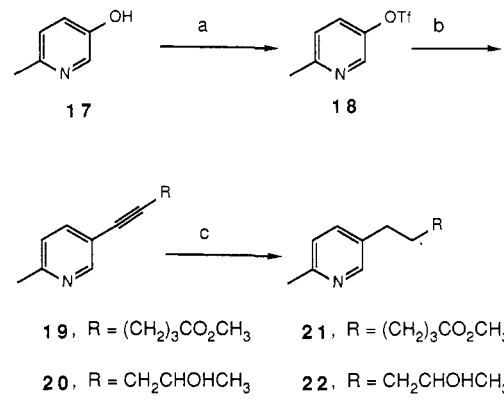


whose NMR spectra were unequivocally consistent with the assigned structures. From the reaction of phenylzinc chloride, we also isolated a 1% yield of the regioisomer **15** and a 5% yield of 2,5-diphenylpyridine (**16**), providing a measure of the selectivity of this process.

The methodology described above should allow for the synthesis of a variety of 2-alkyl- and 2-aryl-5-substituted-pyridines by further manipulation of the bromine atom in the 5-position of compounds like **3**, **7**, or **11** but does not permit the preparation of 2-methyl-5-substituted-pyridines. In order to address this issue, we have taken advantage of a recent report of the coupling of aryl triflates with terminal alkynes.[13] The commercially available 2-methyl-5-pyridinol (**17**) was readily converted to the corresponding triflate ester **18** by reaction with *N*-phenyltriflimide.[14] The utility of **18** is illustrated by its reactions with methyl 5-hexynoate and 4-pentyn-2-ol (Scheme III). When carried out in the presence of bis(triphenylphosphine)palladium dichloride in a mixture of dimethylformamide and triethylamine at 100 °C, the reaction was complete within 3 h and led to the corresponding coupling products **19** and **20**. Catalytic hydrogenation of the triple bonds of the crude products afforded the 2-methyl-5-substituted-pyridines **21** and **22** in 69% and 81% overall yields, respectively.

In summary, we have applied the palladium-catalyzed coupling of terminal acetylenes and arylzinc halides to 2,5-dibromopyridine, which contains two reactive bromine atoms, and have found that reaction takes place selectively at the 2-position, leading to 5-bromo-2-substituted-pyridines, which should prove to be versatile intermediates for the synthesis of 2,5-disubstituted pyridines. Since these procedures cannot be adapted to the preparation of 2-methyl-5-substituted-pyridines, we have investigated the reactivity of the triflate derivative **18** and found that it

Scheme III[a]



[a] (a) Phenyltriflimide, triethylamine, CH_2Cl_2; (b) terminal acetylene, $[(C_6H_5)_3P]_2PdCl_2$, triethylamine, DMF; (c) H_2, Pd (C).

readily couples with terminal acetylenes, thus complementing the above work.

Experimental Section

Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected. Proton magnetic resonance spectra were recorded on a Varian XL-100, XL-200, or XL-400 spectrometer, and shifts are reported in ppm downfield from tetramethylsilane used as an internal reference. Infrared spectra were obtained on a Beckman IR-9 or IR-12 spectrometer for all new compounds and are in accord with the assigned structures. Mass spectra were taken on a CEC 21-110 mass spectrometer at 70 eV. Preparative high-pressure liquid chromatography (HPLC) was performed on silica gel Prep-Pak 500 cartridges with a Waters Associates Prep LC 500A instrument. Silica gel chromatography employed Kieselgel 60, 230–400 mesh, as supplied by E. Merck, Darmstadt, under a nitrogen pressure of 2–5 psi. Bulb-to-bulb distillation employed a Büchi Kugelrohr apparatus; distillation was carried out at the reported air bath temperatures until distillation ceased. Dry dichloromethane was distilled from P_2O_5, DMF was dried over Linde 3A sieves, and triethylamine was distilled from calcium hydride. Concentration refers to removal of solvent under aspirator pressure using a Büchi rotary evaporator.

5-Bromo-2-[2-(trimethylsilyl)ethynyl]pyridine (3a). A solution of 15.0 g (0.0633 mol) of 2,5-dibromopyridine (**1**), 9.0 mL (0.0637 mol) of (trimethylsilyl)acetylene (**2a**), and 0.27 g (0.0014 mol) of cuprous iodide in 200 mL of triethylamine was purged by the passage of argon through the solution, and 1.0 g (0.0014 mol) of bis(triphenylphosphinyl)palladium dichloride was added all at once. The reaction mixture was cooled in an ice bath for 1 h and allowed to stir at room temperature for 1 h. The mixture was diluted with 400 mL of ether, washed with water (4 × 75 mL) with saturated brine (75 mL), dried over potassium carbonate, filtered, and concentrated to a dark oil. This material was passed through a silica gel plug, eluting with 1:1 ether–hexane, and purified by HPLC, eluting with 49:1 hexane-ethyl acetate, and crystallized from hexane to give 11.86 g (74%) of **3a**: mp 56–59 °C; MS, *m/z* (relative intensity) 255 (20), 253 (20), 240 (100), 238 (100); NMR ($CDCl_3$) δ 0.23 (s, 9 H), 7.33 (d, 1 H, J = 8 Hz), 7.76 (d of d, 1 H, J = 8 Hz, J = 1.5 Hz), 8.51 (d, 1 H, J = 1.5 Hz). Anal. Calcd for $C_{10}H_{12}BrNSi$: C, 47.25; H, 4.76; N, 5.51; Br, 31.43. Found: C, 47.49; H, 4.79; N, 5.52; Br, 31.62.

5-Bromo-2-(1-hexynyl)pyridine (3b): MS, *m/z* (relative intensity) 239 (60), 238 (63), 237 (65), 236 (57), 210 (100), 208 (100); NMR ($CDCl_3$) δ 0.94 (t, 3 H, J = 7 Hz), 1.47 (m, 2 H), 1.59 (m, 2 H), 2.43 (t, 2 H, J = 7 Hz), 7.24 (d, 1 H, J = 8 Hz), 7.72 (d of d, 1 H, J = 8 Hz, J = 1.5 Hz), 8.58 (d, 1 H, J = 1.5 Hz). Anal. Calcd for $C_{11}H_{12}BrN$: C, 55.48; H, 5.08; N, 5.88; Br, 33.56. Found: C, 55.73; H, 5.10; N, 5.97; Br, 33.65.

3-(5-Bromo-2-pyridinyl)-3-propyn-1-ol (3c): MS, *m/z* (relative intensity) 213 (25), 211 (26), 184 (96), 182 (100); NMR ($CDCl_3$) δ 4.32 (d, 2 H, J = 3 Hz), 5.45 (t, 1 H, J = 3 Hz), 7.45 (d, 1 H, J = 8 Hz), 8.05 (d of d, 1 H, J = 8 Hz, J = 1 Hz), 8.68 (d, 1 H, J = 1 Hz). Anal. Calcd for C_8H_6BrNO: C, 45.31; H, 2.85;

(12) Negishi, E.-i.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821.
(13) Chen, Q.-Y.; Yang, Z.-Y. *Tetrahedron Lett.* **1986**, *27*, 1171.
(14) Hendrickson, J. B.; Bergeron, R. *Tetrahedron Lett.* **1973**, 4607.

N, 6.61; Br, 37.68. Found: C, 45.19; H, 2.88; N, 6.60; Br, 37.78.

Methyl 6-(5-bromo-2-pyridinyl)-5-hexynoate (3d): MS, *m/z* (relative intensity) 283 (7), 281 (8), 252 (7), 250 (7), 212 (100), 210 (100); NMR (Me_2SO) δ 1.81 (quintet, 2 H, J = 7 Hz), 2.47 (t, 2 H, J = 7 Hz), 2.50 (t, 2 H, J = 7 Hz), 3.60 (s, 3 H), 7.44 (d, 1 H, J = 8 Hz), 8.03 (d of d, 1 H, J = 8 Hz, J = 1.5 Hz), 8.65 (d, 1 H, J = 1.5 Hz). Anal. Calcd for $C_{12}H_{12}BrNO_2$: C, 51.09; H, 4.29; N, 4.96; Br, 28.32. Found: C, 51.32; H, 4.50; N, 4.97; Br, 28.49.

5-Bromo-2-(phenylethynyl)pyridine (3e): MS, *m/z* (relative intensity) 259 (100), 257 (100), 178 (15); NMR ($CDCl_3$) δ 7.35 (m, 4 H), 7.49 (m, 2 H), 7.82 (d of d, 1 H, J = 8 Hz, J = 1.5 Hz), 8.68 (d, 1 H, J = 1.5 Hz). Anal. Calcd for $C_{13}H_8BrN$: C, 60.49; H, 3.12; N, 5.43; Br, 30.96. Found: C, 60.55; H, 3.01; N, 5.46; Br, 30.81.

2-[2-(Trimethylsilyl)ethyl]pyridine (4a). A solution of 109 mg (0.43 mmol) of **3a** in 10 mL of ethanol and 0.15 mL of triethylamine was hydrogenated over 12 mg of 10% palladium on carbon. The reaction mixture was filtered, and the residue obtained after concentration of the filtrate was taken up in 100 mL of ether. The organic solution was washed with 2 × 25 mL of water and 25 mL of saturated sodium chloride solution, dried ($MgSO_4$), and concentrated. Bulb-to-bulb distillation of the residue at an air bath temperature of 120 °C (0.1 mm) afforded 58 mg (75%) of **4a**: NMR ($CDCl_3$) δ 0.02 (s, 9 H), 0.96 (m, 2 H), 2.79 (m, 2 H), 7.10 (d of d, 1 H, J = 8 Hz, J = 5 Hz), 7.19 (d, 1 H, J = 8 Hz), 7.60 (t of d, 1 H, J = 8 Hz, J = 1.5 Hz), 8.54 (d of d, 1 H, J = 5 Hz, J = 1.5 Hz).

2-Hexylpyridine (4b) was obtained as above. Reduction of 100 mg (0.42 mmol) of **3b** afforded 62 mg (90%) of **4b** after bulb-to-bulb distillation at an air bath temperature of 100 °C (0.1 mm): NMR ($CDCl_3$) δ 0.88 (t, 3 H, J = 7 Hz), 1.32 (m, 6 H), 1.72 (m, 2 H), 2.79 (t, 2 H, J = 7 Hz), 7.10 (d of d, 1 H, J = 8 Hz, J = 5 Hz), 7.19 (d, 1 H, J = 8 Hz), 7.60 (t of d, 1 H, J = 8 Hz, J = 1.5 Hz), 8.56 (d of d, 1 H, J = 5 Hz, J = 1.5 Hz).

2-Pyridinepropanol (4c) was obtained as above. Reduction of 220 mg (1.04 mmol) of **3c** afforded 100 mg (70%) of **4c** after bulb-to-bulb distillation at an air bath temperature of 100 °C (0.1 mm): NMR (Me_2SO) δ 1.82 (m, 2 H), 2.76 (t, 2 H, J = 7 Hz), 3.44 (m, 2 H), 4.51 (t, 1 H, J = 5 Hz), 7.19 (d of d of d, 1 H, J = 8 Hz, J = 5 Hz, J = 1 Hz), 7.25 (d of d, 1 H, J = 8 Hz, J = 1 Hz), 7.69 (t of d, 1 H, J = 8 Hz, J = 2 Hz), 8.47 (d of d, 1 H, J = 5 Hz, J = 2 Hz).

Methyl 2-pyridinehexanoate (4d) was obtained as above. Reduction of 250 mg (0.89 mmol) of **3d** afforded 160 mg (87%) of **4d** after bulb-to-bulb distillation at an air bath temperature of 100 °C (0.05 mm): NMR (Me_2SO) δ 1.28 (m, 2 H), 1.54 (m, 2 H), 1.64 (m, 2 H), 2.28 (t, 2 H, J = 7 Hz), 2.68 (t, 2 H, J = 7 Hz), 3.66 (s, 3 H), 7.16 (d of d of d, 1 H, J = 8 Hz, J = 5 Hz, J = 1 Hz), 7.22 (d of d, 1 H, J = 8 Hz, J = 1 Hz), 7.65 (t of d, 1 H, J = 8 Hz, J = 2 Hz), 8.44 (d of d, 1 H, J = 5 Hz, J = 2 Hz).

2-(2-Phenylethyl)pyridine (4e) was obtained as above. Reduction of 120 mg (0.46 mmol) of **3e** afforded 79 mg (93%) of **4e**: NMR ($CHCl_3$) δ 3.10 (m, 4 H), 7.10–7.38 (m, 7 H), 7.62 (t of d, 1 H, J = 8 Hz, J = 1.5 Hz), 8.63 (d of d, 1 H, J = 5 Hz, J = 1.5 Hz).

5-Bromo-2-ethynylpyridine (5). A solution of 12.75 g (0.050 mol) of **3a** in 150 mL of methanol and 50 mL of 1 N sodium hydroxide was stirred for 2 h at room temperature, and 3.0 mL (0.05 mol) of acetic acid was added. The mixture was concentrated to $^1/_3$ volume, and the residue was extracted with 300 mL of ether. The organic layer was washed with 2 × 50 mL of water and 50 mL of saturated sodium chloride and dried (K_2CO_3). Evaporation to dryness afforded 8.60 g (94%) of **5**, mp 82–85 °C. A portion was purified for analysis by flash chromatography on silica gel, eluting with ethyl acetate, and sublimation, mp 84–86 °C: MS, *m/z* (relative intensity) 183 (97), 181 (100), 102 (48); NMR ($CDCl_3$) δ 3.22 (s, 1 H), 7.36 (d, 1 H, J = 8 Hz), 7.79 (d of d, 1 H, J = 8 Hz, J = 1.5 Hz), 8.65 (d, 1 H, J = 1.5 Hz). Anal. Calcd for C_7H_4BrN: C, 46.19; H, 2.22; N, 7.70; Br, 43.90. Found: C, 45.91; H, 2.14; N, 7.68; Br, 44.16.

5-Bromo-2-pyridinepropanol (7c). A solution of 1.06 g (5.00 mmol) of **3c** in 25 mL of ethanol and 0.5 mL of triethylamine was hydrogenated over 46 mg (0.20 mmol) of PtO_2 for 1 h. Hydrogen uptake amounted to 266 mL (theoretical 233 mL). The reaction mixture was filtered and concentrated. The residue was taken up in ethyl acetate, washed with water, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography over 100 g of silica gel, eluting with ethyl acetate. The early fractions contained 17 mg of recovered starting material. Later fractions containing **7c** were concentrated and purified by evaporative distillation to afford 827 mg (82%), bp 130 °C (0.05 mm, air bath temperature): MS, *m/z* (relative intensity) 186 (18), 184 (18), 173 (100), 171 (100); NMR ($CDCl_3$) δ 1.94 (m, 2 H), 2.87 (t, 2 H, J = 7 Hz), 3.01 (br, 1 H),3.70 (t, 2 H, J = 7 Hz), 7.10 (d, 1 H, J = 8 Hz), 7.65 (d of d, 1 H, J = 8 Hz, J = 1.5 Hz), 8.57 (d, 1 H, J = 1.5 Hz). Anal. Calcd for $C_8H_{10}BrNO$: C, 44.47; H, 4.66; N, 6.48; Br, 36.98. Found: C, 44.63; H, 4.80; N, 6.69; Br, 37.27.

5-Bromo-2-ethylpyridine (7f). A solution of 1.00 g (5.5 mmol) of **5** as obtained above in 25 mL of ethanol was hydrogenated over 42 mg of platinum oxide at atmospheric pressure. After 4 h, hydrogen uptake amounted to 283 mL (theoretical 255 mL), and the mixture was filtered and concentrated. The residue was purified by flash chromatography over 100 g of silica gel, eluting with 5% ethyl acetate–hexane followed by bulb-to-bulb distillation to afford 0.77 g (77%) of **7f**, bp 135–145 °C (150 mm, air bath temperature): MS, *m/z* (relative intensity) 187 (53), 186 (100), 185 (54), 184 (100), 159 (18), 157 (18); NMR ($CDCl_3$) δ 1.28 (t, 3 H, J = 7 Hz), 2.79 (q, 2 H, J = 7 Hz), 7.09 (d, 1 H, J = 8 Hz), 7.76 (d of d, 1 H, J = 8 Hz, J = 2 Hz), 8.61 (d, 1 H, J = 2 Hz).

(±)-5-[6-[2-(Trimethylsilyl)ethynyl]-3-pyridinyl]-4-pentyn-2-ol (8). A solution of 9.78 g (0.0385 mol) of **3a** and 0.19 g (0.001 mol) of cuprous iodide in 150 mL of triethylamine and 50 mL of dichloromethane was deoxygenated with argon, and 3.4 g (0.040 mol) of pentyn-2-ol and 0.70 g (0.001 mol) of bis(triphenylphosphine)palladium dichloride were added. The reaction mixture became dark and was allowed to stir overnight and was concentrated. The residue was dissolved in ether, washed with water and brine, dried over potassium carbonate, and concentrated. The crude product was filtered through a plug of silica gel, eluting with 50% ethyl acetate–hexane, and was purified by preparative HPLC, eluting with 33% ethyl acetate–hexane, to give 8.51 g (86%) of **8**, mp 79–80 °C: MS, *m/z* (relative intensity) 257 (18), 242 (28), 213 (100), 198 (80); NMR ($CDCl_3$) δ 0.24 (s, 9 H), 1.31 (d, 3 H, J = 7 Hz), 1.87 (d, 1 H, J = 5 Hz), 2.60 (m, 2 H), 4.05 (m, 1 H), 7.37 (d, 1 H, J = 8 Hz), 7.63 (d of d, 1 H, J = 8 Hz, J = 1.5 Hz), 8.58 (d, 1 H, J = 1.5 Hz). Anal. Calcd for $C_{15}H_{19}NOSi$: C, 69.99; H, 7.44; N, 5.44. Found: C, 70.05; H, 7.57; N, 5.31.

(±)-6-Ethyl-α-methyl-3-pyridinebutanol (9). A solution of 8.51 g (0.033 mmol) of **8** in 60 mL of methanol and 15 mL of 2.5 N sodium hydroxide was stirred for 1 h and diluted to 300 mL with ethyl acetate. The organic layer was washed with water and brine and dried over potassium carbonate. The residue obtained after filtration and concentration was dissolved in 150 mL of ethanol and hydrogenated over 700 mg of 10% palladium on carbon. Upon cessation of hydrogen uptake, the reaction mixture was filtered and concentrated, and the residue was freed of solvent by bulb-to-bulb distillation to afford 5.61 g (88%) of **9**, bp 110–115 °C (0.1 mm): MS, *m/z* (relative intensity) 192 (63), 178 (10), 174 (11), 133 (100); NMR ($CDCl_3$) δ 1.19 (d, 3 H, J = 7 Hz), 1.28 (t, 3 H, J = 7 Hz), 1.48 (m, 2 H), 1.62 (m, 2 H), 1.74 (m, 1 H), 2.60 (t, 2 H, J = 7 Hz), 2.78 (q, 2 H, J = 7 Hz), 3.92 (m, 1 H), 7.05 (d, 1 H, J = 8 Hz), 7.39 (d of d, 1 H, J = 8 Hz, J = 1.5 Hz), 8.31 (d, 1 H, J = 1.5 Hz). Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.25. Found: C, 74.74; H, 10.28; N, 7.40.

5-Bromo-2-phenylpyridine (11). Bromobenzene (5.0 mL, 7.47 g, 0.0476 mol) was added dropwise to a solution of 31.3 mL (0.050 mol) of 1.6 M *n*-butyllithium in hexane in 50 mL of THF while the mixture was cooled in a dry ice–acetone bath. Upon completion of the addition, the reaction mixture was allowed to stir at −70 °C for 40 min. In a separate flask, 6.48 g (0.0476 mol) of freshly fused zinc chloride was dissolved in 70 mL of THF, and the solution was transferred via a double tipped syringe needle under argon pressure to the phenyllithium solution. The resulting mixture was allowed to warm to room temperature over 30 min. In a separate flask, 0.6 g (0.85 mmol) of bis(triphenylphosphine)palladium dichloride was suspended in 50 mL of THF, and 1.7 mL (1.7 mmol) of a 1 M solution of diisobutylaluminum hydride in toluene was added. After 15 min, 11.0 g (0.0466 mol) of 2,5-dibromopyridine followed immediately by the phenylzinc chloride solution were added, and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was con-

centrated, and the residue was dissolved in ethyl acetate, washed with water and saturated sodium chloride solution, and dried (K_2CO_3). The residue obtained from filtration and evaporation was passed through a plug of silica gel and purified by HPLC, eluting with 2% ethyl acetate–hexane. The first eluting product (R_f 0.5) amounted to 8.63 g of **11**, mp 71–74 °C. Recrystallization from hexane afforded 8.07 g (74%), mp 74–76 °C (lit.[6] mp, 74–75 °C).

The second compound to elute (R_f 0.4) amounted to 0.78 g of a mobile oil, which consisted of a mixture of **11** and two less polar substances. Rechromatography on 100 g of silica gel, eluting with 2% ethyl acetate–hexane, afforded 319 mg of a partly crystalline mixture, which was crystallized from hexane to give 106 mg (1%) of 2-bromo-5-phenylpyridine (**15**), mp 78–79 °C: MS, *m/z* (relative intensity) 237 (68), 235 (69), 154 (100), 127 (72); NMR ($CDCl_3$) δ 7.39–7.51 (m, 6 H), 7.60 (d of d, 1 H, *J* = 8 Hz, *J* = 2.5 Hz), 8.55 (d, 1 H, *J* = 2.5 Hz). Anal. Calcd for $C_{11}H_8BrN$: C, 56.44; H, 3.44; N, 5.98; Br, 34.13. Found: C, 56.25; H, 3.52; N, 5.92; Br, 34.07.

The methanol washes contained a sparingly soluble substance, which was rechromatographed over 100 g of silica gel, eluting with dichloromethane, to give 0.58 g of a white solid, mp 170–172 °C. Recrystallization from ethyl acetate–hexane afforded 0.50 g (5%) of 2,5-diphenylpyridine (**16**), mp 172–174 °C (lit.[15] mp 171.5–172.5 °C): MS, *m/z* (relative intensity) 231 (100).

5-Bromo-2-(3,4-dimethoxyphenyl)pyridine (12) was prepared as described above for **11**. With 2.30 g (10.0 mmol) of 3,4-dimethoxybromobenzene and 2.36 g (10.0 mmol) of 2,5-dibromopyridine as starting materials, there was obtained 2.34 g (72%) of **12**, mp 65–67 °C (ether–hexane): MS, *m/z* (relative intensity) 295 (95), 293 (100), 280 (20), 278 (20); NMR ($CDCl_3$) δ 3.95 (s, 3 H), 4.00 (s, 3 H), 6.93 (d, 1 H, *J* = 8 Hz), 7.47 (d of d, 1 H, *J* = 8 Hz, *J* = 1 Hz), 7.57 (d, 1 H, *J* = 8 Hz), 7.61 (d, 1 H, *J* = 1 Hz), 7.81 (d of d, 1 H, *J* = 8 Hz, *J* = 1.5 Hz), 8.68 (d, 1 H, *J* = 1.5 Hz). Anal. Calcd for $C_{13}H_{12}BrNO_2$: C, 53.08; H, 4.11; N, 4.78; Br, 27.16. Found: C, 53.21 H, 3.98; N, 4.89; Br, 26.98.

2-Phenylpyridine (13) was obtained as above for **4a**. Reduction of 200 mg (0.85 mmol) of **11** afforded 126 mg (95%) of **13** after bulb-to-bulb distillation at an air bath temperature of 100 °C (0.1 mm): NMR ($CHCl_3$) δ 7.26 (m, 1 H), 7.51 (m, 3 H), 7.78 (m, 2 H), 8.06 (m, 2 H), 8.75 (d of d, 1 H, *J* = 8 Hz, *J* = 1 Hz).

2-(3,4-Dimethoxyphenyl)pyridine (14) was obtained as above for **4a**. Reduction of 294 mg (1.00 mmol) of **12** afforded 187 mg (87%) of **14**, mp 70–72 °C. Recrystallization from hexane–ethyl acetate afforded 135 mg, mp 73–75 °C: MS, *m/z* (relative intensity) 215 (100), 214 (38), 200 (25); NMR ($CDCl_3$) δ 3.97 (s, 3 H), 4.03 (s, 3 H), 6.97 (d, 1 H, *J* = 8.5 Hz), 7.19 (d of d, 1 H, *J* = 5 Hz, *J* = 2 Hz), 7.52 (d of d, 1 H, *J* = 8.5 Hz, *J* = 2 Hz), 7.67 (d, 1 H, *J* = 2 Hz), 7.69 (d of d, 1 H, *J* = 8 Hz, *J* = 2 Hz), 7.72 (t of d, 1 H, *J* = 8 Hz, *J* = 2 Hz), 8.66 (d of d, 1 H, *J* = 5 Hz, *J* = 2 Hz). Anal. Calcd for $C_{13}H_{13}NO_2$: C, 72.54; H, 6.09; N, 6.51. Found: C, 72.20; H, 6.06; N, 6.47.

6-Methyl-3-pyridinyl Trifluoromethanesulfonate (18). A suspension of 7.48 g (0.0685 mol) of 5-hydroxy-2-methylpyridine (**17**) and 24.4 g (0.0682 mol) of ditriflic phenylimide in 175 mL of dichloromethane was cooled in an ice bath as 10 mL (0.072 mol) of dry triethylamine was added over 10 min. The mixture was held at 0 °C for 1 h and was allowed to warm to room temperature over 18 h. The mixture was washed with 2 × 50 mL of 1 N sodium hydroxide and 50 mL of half-saturated potassium carbonate and dried over potassium carbonate. Filtration and evaporation afforded a yellow oil, which was purified by bulb-to-bulb distillation to give 14.48 g (87%) of **18**, bp 65–70 °C (0.1 mm): MS, *m/z* (relative intensity) 241 (19), 225 (4), 108 (32), 28 (100); NMR ($CDCl_3$) δ 2.60 (s, 3 H), 7.25 (d, 1 H, *J* = 8 Hz), 7.52 (d of d, 1 H, *J* = 8 Hz, *J* = 2 Hz), 8.46 (d, 1 H, *J* = 2 Hz). Anal. Calcd for $C_7H_6F_3NO_2S$: C, 34.86; H, 2.51; N, 5.81; F, 23.63; S, 13.29. Found: C, 35.06; H, 2.51; N, 6.06; F, 23.67; S, 13.41.

Methyl 6-(6-Methyl-3-pyridinyl)-5-hexynoate (19). Argon was passed through a solution of 2.52 g (10.4 mmol) of **18** and 1.40 g (11.1 mmol) of methyl 5-hexynoate in 25 mL of DMF and 9 mL of triethylamine for 15 min, and 0.14 g (0.20 mmol) of bis(triphenylphosphine)palladium dichloride was added. The bath temperature was raised to 95 °C for 3 h, and the mixture was cooled. The reaction mixture was diluted with water and extracted with ethyl acetate. The combined extracts were washed with water and saturated sodium chloride solution and dried (K_2CO_3). The residue obtained after filtration and concentration was chromatographed over 100 g of silica gel, eluting with 35% ethyl acetate–hexane. The product-containing fractions were combined, concentrated, and freed of solvent by bulb-to-bulb distillation to give 1.56 g (69%) of **19**, bp 120 °C (0.05 mm, air bath temperature): MS, *m/z* (relative intensity) 217 (73), 158 (53), 144 (100), NMR ($CDCl_3$) δ 1.95 (quintet, 2 H, *J* = 7 Hz), 2.52 (d, 2 H, *J* = 7 Hz), 2.53 (d, 2 H, *J* = 7 Hz), 2.55 (s, 3 H), 3.70 (s, 3 H), 7.07 (d, 1 H, *J* = 8 Hz), 7.54 (d of d, 1 H, *J* = 8 Hz, *J* = 1.5 Hz), 8.53 (d, 1 H, *J* = 1.5 Hz). Anal. Calcd for $C_{13}H_{15}NO_2$: C, 71.87; H, 6.96; N, 6.45. Found: C, 71.77; H, 7.03; N, 6.30.

Methyl 6-Methyl-3-pyridinehexanoate (21). A solution of 1.39 g (6.34 mmol) of **19** in 25 mL of ethanol was hydrogenated over 0.10 g of 10% palladium on carbon at atmospheric pressure overnight. After completion of hydrogen uptake, the mixture was filtered, concentrated, and purified by bulb-to-bulb distillation to give 1.403 (quantitative) of **21**, bp 130 °C (0.05 mm, air bath temperature): MS, *m/z* (relative intensity) 221 (6), 190 (11), 120 (100); NMR ($CDCl_3$) δ 1.36 (m, 2 H), 1.65 (m, 4 H), 2.31 (t, 2 H, *J* = 7 Hz), 2.52 (s, 3 H), 2.57 (t, 2 H, *J* = 7 Hz), 3.67 (s, 3 H), 7.04 (d, 1 H, *J* = 8 Hz), 7.34 (d of d, 1 H, *J* = 8 Hz, *J* = 1.5 Hz), 8.66 (d, 1 H, *J* = 1.5 Hz). Anal. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65; N, 6.33. Found: C, 70.32; H, 8.72; N, 6.14.

(±)-α,6-Dimethyl-3-pyridinebutanol (22) was obtained as above for **21**. From 1.00 g (4.15 mmol) of **18**, there was obtained 606 mg (81%) of **22**, bp 105–110 °C (0.1 mm, air bath temperature): MS, *m/z* (relative intensity) 179 (3), 178 (4), 119 (100); NMR ($CDCl_3$) δ 1.19 (d, 3 H, *J* = 7 Hz), 1.65 (m, 4 H), 2.48–2.64 (m, 4 H), 2.44 (s, 3 H), 2.59 (t, 2 H, *J* = 7 Hz), 3.84 (m, 1 H), 7.06 (d, 1 H, *J* = 8 Hz), 7.39 (d of d, 1 H, *J* = 8 Hz, *J* = 1.5 Hz), 8.31 (d, 1 H, *J* = 1.5 Hz). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56; N, 7.81. Found: C, 73.69; H, 9.81; N, 8.16.

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Registry No. **1**, 624-28-2; **2a**, 1066-54-2; **2b**, 693-02-7; **2c**, 107-19-7; **2d**, 77758-51-1; **2e**, 536-74-3; **3a**, 111770-80-0; **3b**, 111770-81-1; **3c**, 111770-82-2; **3d**, 111770-83-3; **3e**, 111770-84-4; **4a**, 17890-16-3; **4b**, 1129-69-7; **4c**, 2859-68-9; **4d**, 111770-85-5; **4e**, 2116-62-3; **5**, 111770-86-6; **7c**, 111770-87-7; **7f**, 38749-90-5; **8**, 111770-88-8; **9**, 111770-89-9; **11**, 27012-25-5; **12**, 111770-90-2; **13**, 1008-89-5; **14**, 79445-44-6; **15**, 107351-82-6; **16**, 15827-72-2; **17**, 1121-78-4; **18**, 111770-91-3; **19**, 111770-92-4; **20**, 111770-94-6; **21**, 111770-93-5; **22**, 111770-95-7; $MeCH(OH)CH_2C{\equiv}CH$, 87302-64-5; C_6H_5Br, 108-86-1; 3,4-$(MeO)_2C_6H_3Br$, 2859-78-1.

(15) Chalk, A. J. *Tetrahedron* **1974**, *30*, 1387.