Studies on the Preparation of 3,4-Disubstituted 2-Methoxypyridines

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The synthesis of 2-methoxy-4-methylpyridine-3-carbonitrile (**3**) and its conversion, by way of alkylation of the C(4) methyl group, into the pyridyl acetic acid ester **6** is described.

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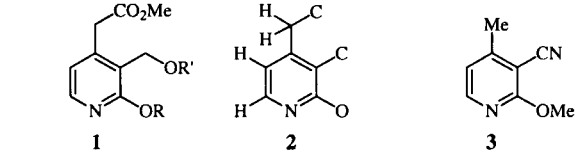
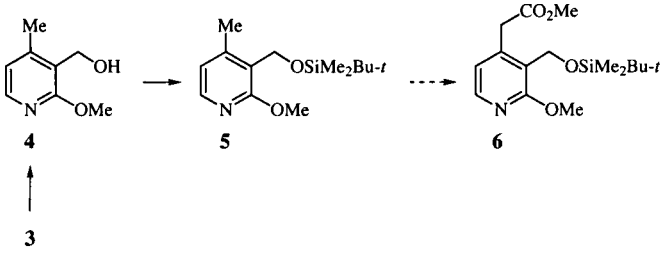
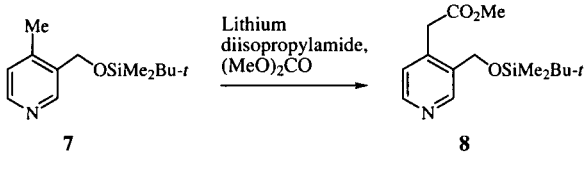
In connection with other work, we needed to prepare compounds of type **1** (R = alkyl, R' = protecting group). The monocyclic substructure (see **2**) appears to be unknown [1] and, in our hands, the preparation of an example of the ester **1** was initially troublesome. We eventually decided to explore a route by way of 2-methoxy-4-methylpyridine-3-carbonitrile (**3**) [2], which we intended to deprotonate on the C(4) methyl, and convert into **6** (= **1**, R = Me, R' = $SiMe_2Bu$-*t*), along the lines shown in Scheme 1. The proposed route is based on the report [3] that **7** is convertible into **8** in high yield (Eq. 1), under the conditions shown.



1 **2** **3**

Scheme 1



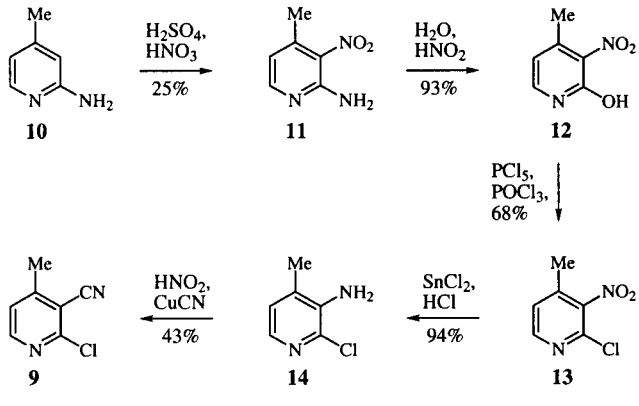


Eq 1

We decided to prepare **3** from the known nitrile **9** (see Scheme 2) [4]. We expected, of course [5], that the halogen of **9** could be displaced by alkoxides, leading, after further elaboration, to the desired compounds of type **1**.

Nitrile **9** was made by the combination of literature procedures summarized in Scheme 2 [4b,6], starting from commercially available and inexpensive **10** [7]. Nitration [8] gave the 3-nitropyridine **11**, easily separated (25% yield) by steam distillation from the 5-nitro isomer that is also formed. Diazotization (93%) served to replace the amino group by hydroxyl (**11** → **12**) [9] and this, in turn, was replaced (68%) by chlorine (**12** → **13**) [9b]. Reduction (**13** → **14**, 94%), using stannous chloride/hydrochloric acid [10], and Sandmeyer reaction (nitrous acid, copper(I) cyanide, potassium cyanide, 30°) then gave **9** [4b] in 43% yield. This route was easily done on a sufficiently large scale to afford 5-6 g batches of **9**.

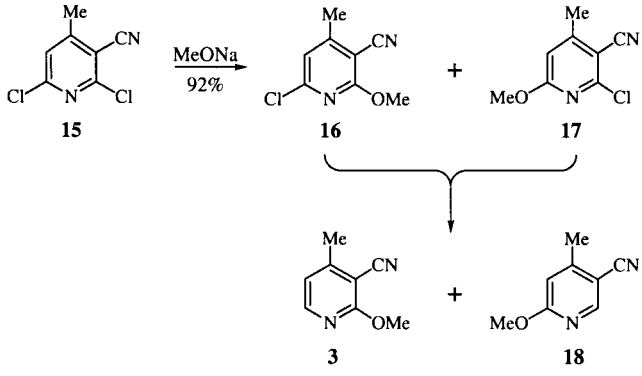
Scheme 2



Following a general procedure [5] for halide displacement, **9** was treated with sodium methoxide, leading to **3** in 96% yield. At a later stage we developed an alternative route (Scheme 3) to the same nitrile. In this approach, the readily accessible dichloro nitrile **15** [11], was treated with sodium methoxide (1 equivalent), to afford (92%) a 9:11 (^{1}H nmr) mixture of **16** and **17**, respectively. Hydrogenolysis then gave the easily separable chlorine-free compound **18** and (in 36% yield) **3**.

Nitrile **3** was easily reduced in 63% yield (Scheme 1, **3** → **4**, diisobutylaluminum hydride, sodium borohydride), and the product was silylated (*t*-butyldimethylsilyl chloride) to afford **5** in 97% yield. Surprisingly, our attempts to acylate

Scheme 3



this compound (*cf.* Eq. 1) were uniformly unsuccessful, although we were easily able to repeat the conversion of **7** into **8**, exactly as reported [3] in the original literature. A control experiment, in which equimolar amounts of **5** and **7** were treated with lithium diisopropylamide and dimethyl carbonate, gave a complex mixture containing **8** and **5**, but no **6**, as judged by ^{1}H nmr analysis.

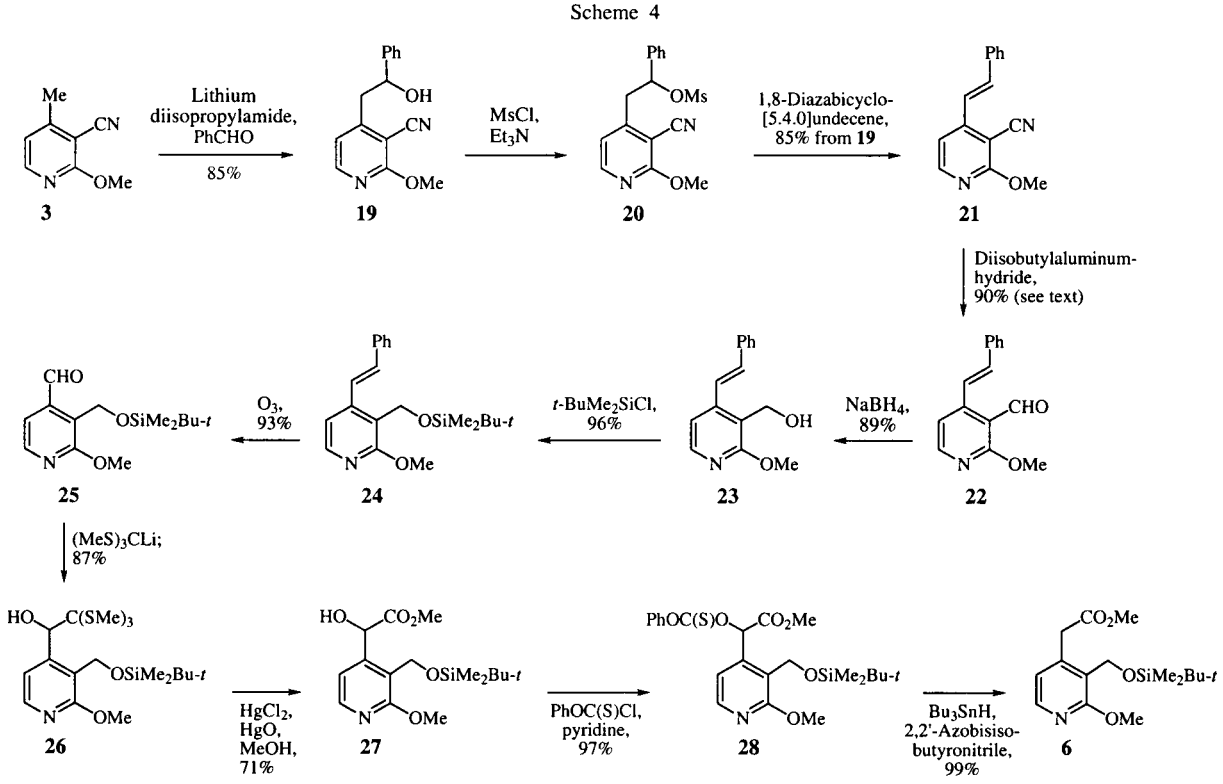
In contrast, nitrile **3** was easily alkylated, by treatment with lithium diisopropylamide and benzaldehyde [12], to afford **19** in 85% yield (Scheme 4). Compound **19** was the basis of the following less direct route to the desired target. Mesylation (**19** → **20**, methanesulfonyl chloride, triethylamine), followed by treatment with diazabicyclo[5.4.0]-undec-7-ene, produced the *E*-olefin **21** (85% from **19**). Reduction to the aldehyde (**21** → **22**, diisobutylaluminum hydride) was not straightforward, in the sense that, on a small scale (*ca* 300 mg of **21**) the yield was 90%, but on an appreciably larger scale (*ca* 5 g of **21**) reduction could not be driven to completion, even by use of a three-fold excess of the hydride, and recycling of recovered starting material was necessary in order to obtain a comparable yield. Further reduction with sodium borohydride then afforded the expected alcohol **23**, and this was easily silylated (*t*-butyldimethylsilyl chloride, imidazole, 96%), giving the desired product **24**.

Ozonolytic cleavage of **24** produced aldehyde **25** (93%), in which the original C(4) carbon substituent of **3** is now electrophilic. Therefore, compounds **3** and **25** represent a complementary pair, with the C(4) carbon substituent of **3** able to behave as a nucleophile (after deprotonation) and, in **25**, as an electrophile.

Treatment of **25** with [tris(methylthio)]methyllithium [13] (**25** → **26**), and methanolysis [13] in the presence of mercuric chloride and mercuric oxide afforded ester **27**, from which the hydroxyl was removed by radical deoxygenation to give a suitably protected example of the compound type we required (**27** → **28**, 97%; **28** → **6**, 99%).

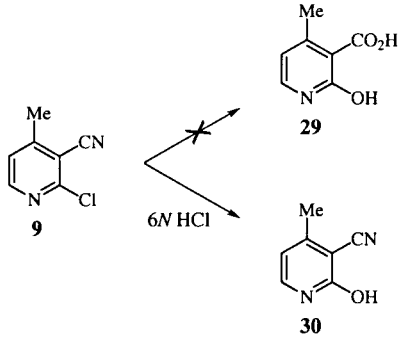
During the course of this work we tried to hydrolyze **9** to hydroxy acid **29** under the conditions (6*N* hydrochloric acid, reflux) described [4b] in the literature. The product has the reported mp (247°) but is, in fact, the hydroxynitrile **30** [14]. Likewise, attempts to hydrolyze **3** and **21**

Scheme 4



under the same conditions (6*N* hydrochloric acid, reflux, 12 hours) served only to replace the methoxy group by hydroxyl; in both cases the hindered nitrile group remained intact.

Scheme 5



EXPERIMENTAL

Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of argon that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst [15] and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 hours before use (120°) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water-aspirator vacuum at, or below, room temperature, using a rotary evaporator.

Commercial thin layer chromatography (tlc) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid [16] or *p*-anisaldehyde [17], followed by charring with a heat gun, or by examination under uv light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by syringe or cannula. Dry tetrahydrofuran was distilled from sodium and benzophenone ketyl. *N,N*-Dimethylformamide and pyridine were stirred overnight with crushed calcium hydride, and then distilled (under water pump vacuum in the case of *N,N*-dimethylformamide), with protection from moisture.

The ir (FT) measurements were made as casts from dichloromethane, using potassium bromide plates. The nmr spectra were measured in deuterochloroform. The ^{13}C nmr were measured at 75.5 MHz.

The symbols s', d', t', and q' used for ^{13}C nmr signals indicate zero, one, two, or three attached hydrogens, respectively.

2-Methoxy-4-methylpyridine-3-carbonitrile (**3**).

The following procedure is different from that reported [2] in the literature. A solution of sodium methoxide was prepared by addition of sodium (35 mg, 1.52 mmoles) to stirred methanol (5 ml) at room temperature (argon atmosphere). After all the sodium had reacted, a solution of **9** [4] (160 mg, 1.05 mmoles) in methanol (5 ml) was injected and, after 30 minutes, the mixture was refluxed for 1 hour. The resulting mixture was cooled to room temperature and most of the methanol was evaporated. The residue was partitioned between water and ether, and the organic layer was dried (potassium carbonate). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:4 ethyl acetate-hexane, gave **3** (150 mg, 96%), mp 95° (lit [4] 87-88°); ir: (FT) 1385, 1591, 2226 cm^{-1}; ^1H nmr (200 MHz): δ 2.50 (s, 3 H), 4.04 (s, 3 H), 6.85 (d, J = 5.2 Hz, 1 H), 8.18 (d, J = 5.2 Hz, 1 H); ^{13}C nmr: δ 19.9 (q'), 54.2 (q'), 97.0 (s'), 114.3 (s'), 118.1 (d'), 149.8 (d'), 154.5 (s'), 164.5 (s'); exact mass: Calcd. for $C_8H_8N_2O$: 148.0636. Found: 148.0631.

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 65.00; H, 5.26; N, 19.06.

2-Chloro-6-methoxy-4-methylpyridine-3-carbonitrile (**17**) and 6-Chloro-2-methoxy-4-methylpyridine-3-carbonitrile (**16**).

Sodium (4.5 g, 195.6 mmoles) was added in small portions to a stirred solution of **15** [11] (36.6 g, 196 mmoles) in methanol (800 ml), a water bath being used to keep the temperature below 40°. After the last portion of sodium had reacted the mixture was stirred for a further 30 minutes, and then most of the methanol was evaporated. Chloroform (300 ml) and water (200 ml) were added to the resulting slurry, and the aqueous layer was extracted twice with chloroform (2 x 100 ml). The combined organic extracts were dried (sodium sulfate) and evaporated to give a cream-colored solid (32.8 g, 92%) that was a 9:11 mixture (^1H nmr) of **16** and **17**; ^1H nmr (200 MHz): δ 2.50 (two overlapping s, 3 H), 3.97 (s, 1.67 H), 4.05 (s, 1.37 H), 6.60 (s, 0.48 H), 6.90 (0.38 H). The material was filtered through a short column of flash chromatography silica gel, using 1:4 ethyl acetate-hexane, and used directly in the next step. The filtration is essential in order to remove a contaminant that poisons the catalyst in the next step.

6-Methoxy-4-methylpyridine-3-carbonitrile (**18**) and 2-Methoxy-4-methylpyridine-3-carbonitrile (**3**).

A suspension of the mixture of **16** and **17** (10.0607 g, 55.09 mmoles), sodium acetate (4.4982 g, 54.84 mmoles) and 10% palladium/charcoal (0.9879g) in methanol (200 ml) was shaken with hydrogen at 50 psi for 3 hours (Parr shaker). The mixture was filtered, and most of the methanol was evaporated. Chloroform (100 ml) and water (100 ml) were added to the residue, and the aqueous layer was extracted with chloroform (2 x 50 ml). The combined organic extracts were dried (sodium sulfate) and evaporated. Flash chromatography of the resulting solid over silica gel (10 x 35 cm), using 1:4 ethyl acetate-hexane, gave **3** (2.8312 g, 35%) as a white solid, identical to material obtained from **9**, and gave **18** (3.3463 g, 41%) also as a white solid, mp 95-98°. Compound **18** had ir: (FT) 1374, 2222 cm^{-1}; ^1H nmr (400 MHz): δ 2.44 (d, J = 0.8 Hz, 3 H), 3.94 (s, 3 H), 6.65-6.68 (m, 1 H), 8.39 (s, 1 H); ^{13}C nmr (100 MHz): δ 20.1 (q'), 54.4 (q'), 104.3 (s'), 111.9 (d'), 116.9 (s'), 152.3 (d'), 152.7 (s'), 166.6 (s'); exact mass: Calcd. for $C_8H_8N_2O$: 148.0636. Found: 148.0637.

Anal. Calcd. for $C_8H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.99; H, 5.39; N, 18.89.

3-Hydroxymethyl-2-methoxy-4-methylpyridine (**4**).

Diisobutylaluminum hydride (1 *M* in dichloromethane, 9.98 ml, 9.98 mmoles) was injected over *ca* 10 minutes into a stirred and cooled (ice-water bath) solution of **3** (0.9238 g, 6.24 mmoles) in ether (20 ml) (argon atmosphere). Stirring was continued for 1 hour

and then 4 *M* hydrochloric acid (5 ml) was added. The cold bath was removed and stirring was continued for 45 minutes. The aqueous phase was removed, and the organic phase was washed with water (5 ml) and brine (5 ml), dried (magnesium sulfate), and evaporated at atmospheric pressure (the product is volatile, and evaporation should not be done under reduced pressure). The residue was dissolved in methanol (20 ml), and the solution was cooled (ice-water bath). Sodium borohydride (0.4725 g, 12.49 mmoles) was added, the cold bath was removed, and the mixture was stirred for 2 hours and then most of the methanol was evaporated under reduced pressure. The residue was partitioned between ethyl acetate (50 ml) and water (25 ml), and the organic phase was washed with brine (25 ml), dried (magnesium sulfate), and evaporated. Flash chromatography of the resulting oil over silica gel (2.5 x 20 cm), using 4:1 ethyl acetate-hexanes, gave **4** (0.6010 g, 63%) as pure (^{1}H nmr) white crystals, mp 41-42°; ir: (FT) 3600-3100 cm^{-1}; ^{1}H nmr (deuterodichloromethane, 200 MHz): δ 2.33 (s, 3 H), 3.36 (t, J = 5.0 Hz, 1 H), 3.88 (s, 3 H), 4.62 (d, J = 5.0 Hz, 2 H), 6.69 (d, J = 5.2 Hz, 1 H), 7.87 (d, J = 5.2 Hz, 1 H); ^{13}C nmr (deuterodichloromethane, 50.3 MHz): δ 18.4 (q'), 53.6 (q'), 56.3 (t'), 119.8 (d'), 121.6 (s'), 145.6 (d'), 148.6 (s'), 162.6 (s'); exact mass: Calcd. for $C_8H_{11}NO_2$: 153.0790. Found: 153.0791.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.47; H, 7.14; N, 9.18.

3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-methoxy-4-methylpyridine (**5**).

t-Butyldimethylsilyl chloride (2.1563 g, 14.31 mmoles) and imidazole (0.9733 g, 14.30 mmoles) were added to a stirred solution of **4** (0.8807 g, 7.15 mmoles) in dry dichloromethane (30 ml) (argon atmosphere). Stirring was continued for 45 minutes, by which time all of the starting material had reacted (tlc control; silica gel, 50:50 ethyl acetate-hexanes). The solution was washed with water (15 ml) and brine (15 ml), dried (magnesium sulfate), and evaporated. Flash chromatography of the resulting oil over silica gel (2.5 x 20 cm), using 1:1 ethyl acetate-hexanes, gave **5** (1.6468 g, 97%) as a pure (^{1}H nmr), colorless oil; ir: (FT) 1256 cm^{-1}; ^{1}H nmr (deuterodichloromethane, 200 MHz): δ 0.07 (s, 6 H), 0.90 (s, 9 H), 2.37 (s, 3 H), 3.91 (s, 3 H), 4.57 (s, 2 H), 6.72 (d, J = 5.1 Hz, 1 H), 7.93 (d, J = 5.1 Hz, 1 H); ^{13}C nmr (deuterodichloromethane, 50.3 MHz): δ -5.3 (q'), 18.6 (q'), 18.6 (s'), 26.0 (q'), 53.5 (q'), 56.7 (t'), 119.8 (d'), 121.5 (s'), 145.8 (d'), 149.8 (s'), 162.3 (s'); exact mass: Calcd. for $C_{13}H_{22}NO_2Si$: (M - CH_3) 252.1420. Found: 252.1418.

Anal. Calcd. for $C_{14}H_{25}NO_2Si$: C, 62.87; H, 9.42; N, 5.24. Found: C, 63.09; H, 9.49; N, 5.22.

4-(2-Hydroxy-2-phenylethyl)-2-methoxypyridine-3-carbonitrile (**19**).

Lithium diisopropylamide was prepared by dropwise addition of butyllithium (1.6 *M* solution in hexanes, 23 ml, 36.9 mmoles) to a stirred and cooled (0°) solution of diisopropylamine (5.2 ml, 36.9 mmoles) in tetrahydrofuran (100 ml). The solution was stirred for 15 min at 0°, cooled to -78° and then, after 10 minutes, a solution of **3** (2.75 g, 18.5 mmoles) in tetrahydrofuran (20 ml) was injected over *ca* 20 min to produce a pale yellow solution. After 30 minutes at -78°, a solution of benzaldehyde (3.91 g, 36.9 mmoles) in tetrahydrofuran (10 ml) was injected, and stirring at -78° was continued for 15 minutes. The cold bath was removed, and stirring was continued for 2 hours. Saturated aqueous ammonium chloride (30 ml) was added, and the mixture was extracted with ethyl acetate (3 x 50 ml). The combined organic extracts were dried (sodium sulfate) and evaporated. Flash chromatography of the residue over silica gel (3.5 x 25 cm), using 2:3 ethyl acetate-hexane, gave **19** (4.0 g, 85%) as a colorless oil; ^{1}H nmr (200 MHz): δ 2.34 (br s, 1 H), 3.17 (d, J = 7.2 Hz, 2 H), 4.04 (s, 3 H), 5.02 (t, J = 7.2 Hz, 1 H), 6.85 (d, J = 4.8 Hz, 1 H), 7.28-7.40 (m, 5 H), 8.19 (d, J = 4.8 Hz, 1 H).

2-Methoxy-4-(2-phenylethenyl)pyridine-3-carbonitrile (**21**).

Freshly distilled methanesulfonyl chloride (2.8 ml, 36.16 mmoles) was added dropwise to a stirred and cooled (0°) solution of **19** (6.11 g, 24.00 mmoles) and triethylamine (6.6 ml, 47.35 mmoles) in dry tetrahydrofuran (200 ml). The cold bath was removed, and the mixture was stirred for a further 30 minutes, by which time a precipitated had formed. 1,8-Diazabicyclo-[5.4.0]undec-7-ene (7.2 ml, 48.22 mmoles) was injected, and stirring at room temperature was continued for 30 minutes. The mixture was partitioned between ether and water, the organic layer was separated, dried (sodium sulfate) and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 3:17 ethyl acetate-hexane, gave **21** (4.82 g, 85%) as a single (*E*) isomer; ir: (FT) 1388, 1551, 1583, 2223 cm^{-1}; ^{1}H nmr (400 MHz): δ 4.08 (s, 3 H), 7.25-7.62 [m, including d (1 H, J = 5.5 Hz) at δ 7.24, 8 H in all], 8.25 (d, J = 5.5 Hz, 1 H); ^{13}C nmr: δ 54.6 (q'), 94.9 (s'), 112.1 (d'), 114.5 (s'), 122.1 (d'), 127.7 (d'), 129.0 (d'), 129.6 (d'), 135.2 (s'), 137.5 (d'), 149.9 (d'), 151.1 (s'), 165.3 (s'); exact mass: Calcd. for $C_{15}H_{12}N_2O$: 236.0950. Found: 236.0946.

2-Methoxy-4-(2-phenylethenyl)pyridine-3-carbaldehyde (**22**).

Diisobutylaluminum hydride (1 *M* in dichloromethane, 2.0 ml, 2.0 mmoles) was injected over *ca* 5 min into a stirred and cooled (-78°) solution of **21** (324 mg, 1.37 mmoles) in dichloromethane (10 ml). Stirring at -78° was continued for 1.5 hours and then methanol (0.5 ml), Celite (1 g), sodium sulfate (2 g), and a few drops of water were added. The cold bath was removed and the stirred mixture was allowed to warm to room temperature and filtered. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 15 cm), using 3:17 ethyl acetate-hexane, gave **22** (300 mg, 90%), ir: (FT) 1678 cm^{-1}; ^{1}H nmr (300 MHz): δ 4.05 (s, 3 H), 7.22-7.43 [m, including d (1 H, J = 6.0 Hz) at δ 7.22, and d (1 H, J = 16.0 Hz) at δ 7.80, 5 H in all], 7.56-7.62 (m, 2 H), 8.19 (d, J = 16.0 Hz, 1 H), 8.25 (d, J = 6.0 Hz, 1 H) , 10.56 (s, 1 H); ^{13}C nmr: δ 55.8 (q'), 116.3 (d'), 117.0 (s'), 126.4 (d'), 129.3 (d'), 130.7 (d'), 130.9 (d'), 137.9 (d'), 138.4 (s'), 150.5 (s'), 152.9 (d'), 193.4 (d'); exact mass: Calcd. for $C_{15}H_{13}NO_2$: 239.0946. Found: 239.0947.

When this reaction is done on a 5 g-scale only half of the material is reduced, even using an excess of diisobutylaluminum hydride (3 equivalents) and/or a longer time (overnight). The total yield remains around 88%, after correction for recovered starting material.

2-Methoxy-4-(2-phenylethenyl)pyridin-3-ylmethanol (**23**).

Sodium borohydride (1.00 g, 26.0 mmoles) was added in small portions to a stirred and cooled (0°) solution of **22** (1.97 g, 8.25 mmoles) in methanol (150 ml). The mixture was stirred for a further 1 hour and then most of the methanol was evaporated. Water (100 ml) and ethyl acetate (100 ml) were added, and the aqueous layer was extracted with ethyl acetate (2 x 30 ml). The combined organic extracts were dried (sodium sulfate) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:3 ethyl acetate-hexane, gave **23** (1.77 g, 89%); ir: (FT) 1495, 1633, 3355 cm^{-1}; ^{1}H nmr (300 MHz): δ 2.25 (t, J = 6.8 Hz,

1 H), 4.02 (s, 3 H), 4.84 (d, J = 6.8 Hz, 2 H), 7.05-7.57 [m, including d (1 H, J = 6.0 Hz) at δ 7.08, 8 H in all], 8.05 (d, J = 6.0 Hz, 1 H); ^{13}C nmr: δ 53.9 (q'), 56.5 (t'), 114.3 (d'), 119.8 (s'), 123.3 (d'), 127.1 (d'), 128.8 (d'), 128.9 (d'), 135.0 (d'), 136.5 (s'), 145.7 (d'), 146.3 (s'), 162.9 (s'); exact mass: Calcd. for $C_{15}H_{15}N_2O$: 241.1103. Found: 241.1103.

3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-methoxy-4-(2-phenylethenyl)pyridine (**24**).

t-Butyldimethylsilyl chloride (2.03 g, 13.5 mmoles) in *N,N*-dimethylformamide (5 ml) was added to a stirred and cooled (0°) solution of **23** (3.26 g, 13.5 mmoles) and imidazole (1.84 g, 27.0 mmoles) in *N,N*-dimethylformamide (5 ml) at 0°. The ice bath was removed and the mixture was stirred at room temperature overnight. The mixture was diluted with ether (40 ml), washed with water (2 x 10 ml) and brine (10 ml), and dried (sodium sulfate). Evaporation of the solvent gave pure (^{1}H nmr) **24** (4.6 g, 96%); ir: (FT) 837, 1074, 1593 cm^{-1}; ^{1}H nmr (deuterodichloromethane, 300 MHz): δ 0.12 (s, 6 H), 0.92 (s, 9 H), 3.97 (s, 3 H), 4.90 (s, 2 H), 7.18 (d, J = 6.0 Hz, 1 H), 7.20-7.44 (m, 4 H), 7.52-7.60 (m, 3 H), 8.08 (d, J = 6.0 Hz, 1 H); ^{13}C nmr (deuterodichloromethane): δ -5.1 (q'), 18.6 (s'), 26.1 (q'), 53.8 (q'), 56.6 (t'), 114.0 (d'), 120.2 (s'), 124.8 (d'), 127.4 (d'), 128.8 (d'), 129.2 (d'), 134.0 (d'), 137.3 (s'), 146.1 (d'), 147.3 (s'), 163.2 (s'); exact mass: Calcd. for $C_{20}H_{26}O_2Si$: (M - CH_3) 340.1733. Found: 340.1726.

3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-methoxypyridine-4-carbaldehyde (**25**).

An ozone-oxygen stream was bubbled through a stirred and cooled (-78°) solution of **24** (52.3 mg, 0.147 mmole) in dry dichloromethane (3 ml) until a blue color appeared (about 10 minutes). Oxygen was passed through the solution for 5 minutes to remove the excess of ozone, and triphenylphosphine (50 mg, 0.19 mmole) was added. The cold bath was removed, and the stirred mixture was allowed to warm to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using 1:9 ethyl acetate-hexane, gave **25** (38.4 mg, 93%); ir: (FT) 837, 1072, 1594, 1705 cm^{-1}; ^{1}H nmr (deuterodichloromethane, 360 MHz): δ 0.10 (s, 6 H), 0.88 (s, 9 H), 3.99 (s, 3 H), 5.05 (s, 2 H), 7.11 (d, J = 2.0 Hz, 1 H), 8.21 (d, J = 2.0 Hz, 1 H), 10.58 (s, 1 H); ^{13}C nmr (deuterodichloromethane): δ -4.8 (q'), 18.8 (s'), 26.4 (q'), 54.7 (q'), 56.8 (t'), 114.3 (d'), 125.2 (s'), 143.9 (s'), 147.2 (s'), 162.5 (s'), 192.7 (s'); exact mass: Calcd. for $C_{14}H_{23}NO_3Si$: 281.1447. Found: 281.1442.

1-[3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-methoxypyrid-4-yl]-2,2,2-[tris(methylthio)]ethanol (**26**).

Butyllithium (1.6 *M* in hexanes, 7.7 ml, 12.3 mmoles) was added to a solution of tris(methylthio)methane (1.89 g, 12.3 mmoles) in tetrahydrofuran (80 ml) at -78°. The mixture was stirred for 30 minutes, and a solution of **25** (2.88 g, 10.25 mmoles) in tetrahydrofuran (45 ml plus 5 ml as a rinse) was added. The mixture was stirred for 15 minutes, the cold bath was removed and, after the mixture had warmed to room temperature, saturated aqueous ammonium chloride (20 ml), water (30 ml) and ethyl acetate (80 ml) were added. The aqueous layer was extracted with ethyl acetate (2 x 30 ml). The combined organic extracts were washed with brine, and dried (sodium sulfate). Evaporation of the solvent and flash chromatography of the residue over silica gel (3.5 x 15 cm), using 2:3 ethyl acetate-hexane, gave **26** (3.88 g, 87%); ir: (FT) 816, 1050, 1571, 1595, 3456 cm^{-1}; ^{1}H nmr (deuterodichloromethane, 400 MHz): δ 0.04 (s, 3 H), 0.12 (s, 3 H), 0.80 (s, 9 H), 2.10 (s, 9 H), 3.54 (s, 1 H), 3.92 (s, 3 H), 5.00 (AB q, J = 12.0, $\Delta\nu_{AB}$ = 8.3 Hz, 2 H), 5.56 (s, 1 H), 7.47 (d, J = 6.0 Hz, 1 H), 8.08 (d, J = 6.0 Hz, 1 H); ^{13}C nmr (deuterodichloromethane): δ -5.3 (q'), -4.9 (q'), 14.3 (q'), 18.5 (s'), 26.1 (q'), 53.8 (q'), 57.0 (t'), 72.9 (d'), 75.8 (s'), 118.1 (d'), 122.4 (s'), 145.4 (d'), 148.9 (s'), 162.0 (s'). A satisfactory mass spectrum could not be obtained.

Methyl 2-[3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-methoxypyrid-4-yl]-2-hydroxyethanoate (**27**).

A mixture of **26** (3.15 g, 7.24 mmoles), mercuric chloride (7.86 g, 28.96 mmoles) and mercuric oxide (2.62 g, 12.1 mmoles) in 12:1 methanol-water (170 ml) was stirred at room temperature for 4 hours. The mixture was filtered and the solid residue was washed with dichloromethane (2 x 30 ml). The combined filtrates were diluted with water (150 ml) and extracted with dichloromethane (2 x 150 ml). The combined organic extracts were washed with brine and dried (magnesium sulfate). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 15 cm), using 1:2 ethyl acetate-hexane, gave **27** (1.75 g, 71%); ir: (FT) (chloroform cast) 836, 1060, 1576, 1597, 1746, 3441 cm^{-1}; ^{1}H nmr (300 MHz): δ 0.10 (s, 6 H), 0.89 (s, 9 H), 3.76 (s, 3 H), 3.94 (s, 3 H), 4.31 (d, J = 7.0 Hz, 1 H), 4.90 (AB q, J = 13.0, $\Delta\nu_{AB}$ = 9.0 Hz, 2 H), 5.57 (d, J = 7.0 Hz, 1 H), 6.85 (d, J = 5.0 Hz, 1 H), 8.10 (d, J = 5.0 Hz, 1 H); ^{13}C nmr: δ -5.4 (q'), -5.3 (q'), 18.3 (s'), 25.9 (q'), 52.9 (q'), 53.7 (q'), 56.3 (t'), 70.6 (d'), 116.2 (d'), 120.8 (s'), 146.6 (d'), 149.0 (s'), 161.9 (s'), 173.1 (s'); exact mass: Calcd. for $C_{12}H_{18}NO_5Si$: (M - *t*-Bu) 284.0954. Found: 284.0958.

Methyl 2-[3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-methoxypyrid-4-yl]-2-[(phenoxy)thiocarbonyloxy]ethanoate (**28**).

Phenyl thiochloroformate (0.55 ml, 3.92 mmoles) was added to a stirred solution of **27** (1.22 g, 3.565 mmoles) and pyridine (1.45 ml, 17.8 mmoles) in dichloromethane (50 ml) at room temperature. The mixture was stirred for 2 hours, and the solvent was then evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:4 ethyl acetate-hexane, gave **28** (1.57 g, 97%); ir: (FT) (chloroform cast) 836, 1066, 1201, 1761 cm^{-1}; ^{1}H nmr (deuterodichloromethane, 200 MHz): δ 0.07 (s, 3 H), 0.11 (s, 3 H), 0.90 (s, 9 H), 3.75 (s, 3 H), 3.98 (s, 3 H), 4.95 (s, 2 H), 7.00-7.18 [m, including d (1 H, J = 6.0 Hz) at δ 7.04, 3 H in all], 7.28-7.50 (m, 3 H), 8.18 (d, J = 6.0 Hz, 1 H); ^{13}C nmr (deuterodichloromethane): δ -5.3 (q'), 18.6 (s'), 26.0 (q'), 53.2 (q'), 54.1 (q'), 56.6 (t'), 78.0 (d'), 116.0 (d'), 122.1 (d'), 122.2 (s'), 127.2 (d'), 130.0 (d'), 143.4 (s'), 146.9 (d'), 153.9 (s'), 162.2 (s'), 168.1 (s'), 194.5 (s'); exact mass: Calcd. for $C_{23}H_{31}NO_6SSi$: 477.1641. Found: 477.1640.

Methyl 2-[3-[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl]-2-methoxypyrid-4-yl]ethanoate (**6**).

Tributylstannane (1.31 ml, 4.88 mmoles) and 2,2'-azobis[2-methylpropionitrile] (50 mg) were added to a solution of **28** (1.55 g, 3.25 mmoles) in toluene (50 ml). The mixture was refluxed for 2 hours, and then the solvent was evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:4 ethyl acetate-hexanes, gave **6** (1.05 g, 99 %); ir: (FT) 837, 1063, 1081, 1576, 1598, 1744 cm^{-1}; ^{1}H nmr (200 MHz): δ 0.06 (s, 6 H), 0.90 (s, 9 H), 3.70 (s, 3 H), 3.84 (s, 2 H), 3.95 (s, 3 H), 4.79 (s, 2 H), 6.80 (d, J = 6.0 Hz, 1 H), 8.04 (d, J = 6.0 Hz, 1 H); ^{13}C nmr: δ -5.4 (q'), 18.3 (s'), 25.9 (q'), 37.4 (t'), 52.1 (q'), 53.5 (q'), 56.5 (t'), 119.3 (d'), 121.7 (s'), 145.0 (d'), 145.7 (d'), 161.9 (s'), 171.0 (s'); exact mass: Calcd. for $C_{15}H_{24}NO_4Si$: (M - CH_3) 310.1475. Found: 310.1460.

Anal. Calcd. for $C_{16}H_{27}NO_4Si$: C, 59.04; H, 8.36; N, 4.30. Found: C, 58.95; H, 8.38; N, 4.24.

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[12] Direct acylation of **3** (*cf.* Eq. 1) was not explored, since such a route would require reduction of the nitrile to a hydroxymethyl group *without* ring closure to form a lactone. We felt that this might be problematic and, in the event, treatment of **6** with hydrogen fluoride resulted in spontaneous lactonization. The lactone had: ir: (FT) 1074, 1607, 1732 cm^{-1}; ^1H nmr (360 MHz): δ 3.66 (s, 2 H), 3.96 (s, 3 H), 5.37 (s, 2 H), 6.74 (d, J = 4.0 Hz, 1 H), 8.08 (d, J = 4.0 Hz, 1 H); ^{13}C nmr: δ 34.5 (t'), 53.7 (q'), 65.4 (t'), 113.7 (s'), 115.5 (d'), 141.9 (s'), 147.0 (d'), 159.3 (s'), 168.8 (s'); exact mass: Calcd. for $C_9H_9NO_3$: 179.0582. Found: 179.0583.

Anal. Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.06; H, 4.94; N, 7.74.

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[14] Compound **30** had ir: (FT) 1732, 1739, 2228, 3428 cm^{-1}; ^1H nmr (200 MHz): δ 2.50 (s, 3 H), 2.4-2.9 (br, 1 H), 5.45 (d, J = 6.8 Hz, 1 H), 6.74 (d, J = 6.8 Hz, 1 H); exact mass: Calcd. for C_7H_6NO: 134.0480. Found: 134.0478.

Anal. Calcd. for C_7H_6NO: C, 62.68; H, 4.51; N, 20.88. Found: C, 62.32; H, 4.31; N, 20.55.

[15] Supplied by Chemical Dynamics Corp., South Plainfield, N. J.

[16] Phosphomolybdic acid (15 g) and ceric ammonium nitrate (2.5g) dissolved in a mixture of water (485 ml) and concentrated sulfuric acid (15 ml).

[17] *p*-Anisaldehyde (15 drops) was added to concentrated sulfuric acid (6 ml) and ethanol (94 ml).