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THE COBALT WAY TO VITAMIN B_6

REGIOSELECTIVE CONSTRUCTION OF THE TETRASUBSTITUTED PYRIDINE NUCLEUS BY COBALT-CATALYZED ALKYNE–NITRILE COOLIGOMERIZATIONS

CAROL A. PARNELL and K. PETER C. VOLLHARDT*
Department of Chemistry, University of California, and the Materials and Molecular Research Division, Lawrence Berkeley Laboratory, Berkeley, CA 94720, U.S.A.

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Abstract—Cocyclization of bis(trimethylsilyl)- and bis(trimethylstannyl)di-2-propynyl ether with acetonitrile provides a synthetic entry into 1,3-dihydro-6-methyl-4,7-bis(trimethylsilyl)- and bis(trimethylstannyl)-furo[3,4-*c*]pyridines. Regioselective electrophilic substitution of the respective silyl or stannyl groups allows for a regiocontrolled construction of tetrasubstituted pyridines. This method has been applied to a total synthesis of vitamin B_6.

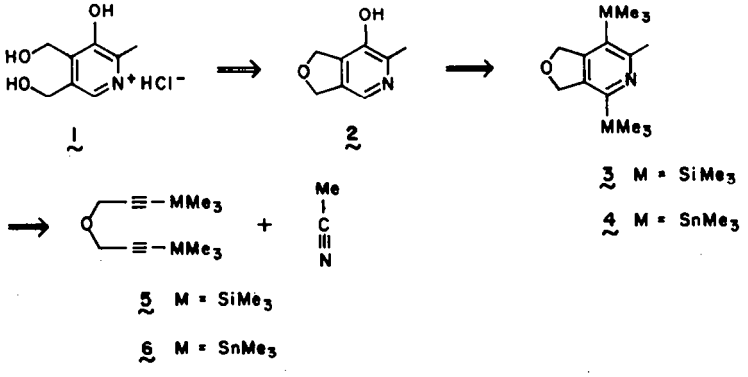
Regioselective construction of substituted pyridines is of primary medicinal synthetic importance.[1] We have shown[2] that control over the substitution pattern of the pyridine nucleus can be exerted by employing a cobalt catalyst[3] in [2+2+2] cycloadditions of α,ω-diynes with nitriles and α,ω-cyanoalkynes with alkynes. This report details a regioselective entry into the tetrasubstituted pyridine nucleus by the η^5-cyclopentadienyl dicarbonyl cobalt [$CpCo(CO)_2$] catalyzed cocyclization of bis(trimethylsilylated) and stannylated diyne ethers with acetonitrile, and the subsequent elaboration of the Group 4-based substituents. The methodology has been applied to the total synthesis of vitamin B_6 (**1**).

Of the many syntheses[4] of **1** perhaps the most efficient ones employ [4+2] cycloaddition strategies.[4,5] In contrast, our approach, shown in Scheme 1, retrosynthetically cleaves the 6-membered ring at three locations to furnish three functional units, potentially allowing for increased versatility and efficiency.

RESULTS AND DISCUSSION

Initially, it was thought that the silylated diyne **5** would provide a suitable starting material for our approach. It was anticipated to be readily available by silylating di-2-propynyl ether, and the bulky trimethylsilyl substituents were expected to slow down the rate of formation of unwanted side products such as cyclobutadiene complexes[6] or diyne trimers.[3] Moreover, it was hoped that the bissilylpyridine **3**, formed by cocyclization of **5** with acetonitrile, would selectively protodesilylate at the 2-position[7] to leave the 3-silyl position open to further chemical manipulation. Webster has determined that the relative rates of hydrolysis of 2-$Me_3MC_5H_4N$ are (M=) Ge: 10^{-4}, Si: 1, Sn: 22.[8] This order of reactivity is in agreement with that expected for nucleophilic substitution at the metal.[9]

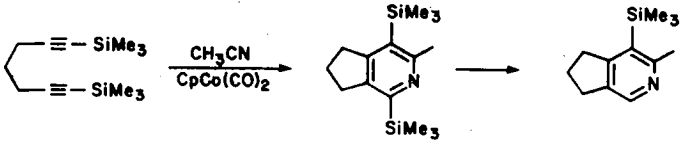
Examination of the literature indicated that there could have been a potential problem associated with the cyclization of **5**. Although cobaltacyclopentadienes have been isolated from silylated 1,6-heptadiynes,[10] we were concerned with the failure of 1,8-bis(trimethylsilyl)-1,7-octadiyne to cyclize with alkynes to give pyridines.[11] Instead this material furnished the corresponding cyclobutadiene complex.[6b] Although the rate of cyclobutadiene formation from **5** was anticipated to be slower than that of the corresponding octadiyne due to the higher degree of strain involved in generating a bicyclo[3.2.0] system, it was not clear which reaction pathway would predominate. Because



Scheme 1. Synthetic strategy *en route* to vitamin B_6.

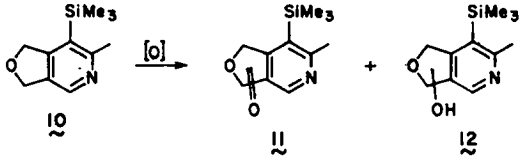
of this uncertainty, a model study was conducted with the readily available 1,7-bis(trimethylsilyl)-1,6-heptadiyne **7**.[12] Gratifyingly, the reaction of **7** with acetonitrile in the presence of $CpCo(CO)_2$ gave bissilylpyridine **8** which protodesilylated on chromatography (neutral Al_2O_3, activity III) to afford **9** in good overall yield (76%).

In light of this successful result, diyne **5** was prepared via the silylation of bis-2-propynyl ether and then cocyclized with acetonitrile in the presence of $CpCo(CO)_2$ to give bis(trimethylsilyl)furo[3,4-*c*]pyridine **3** (Scheme 1). Purification (chromatography on neutral Al_2O_3) afforded 7-trimethylsilylfuro[3,4-*c*]pyridine **10** (68% from **5**).



7 **8** **9**

With **10** in hand, we turned our attention to the problem of aromatic hydroxylation. There are potentially several methods available for this transformation. A direct one-step $Pb(OAc)_4$–CF_3CO_2H oxidative aryl–silicon cleavage sequence[13] was hoped to be applicable to this system, since several reactions using $Pb(OAc)_4$ had been carried out in the presence of pyridine.[14] Disappointingly, when **10** was treated with $Pb(OAc)_4$ (1 equiv) and trifluoroacetic acid (4 equiv) only recovered starting material was obtained. It was possible that the lead was consumed by complexation to nitrogen, therefore the reaction was conducted with 2 equiv of $Pb(OAc)_4$. Oxidation occurred, unfortunately not at the 3-position, to give



10 **11** **12**

the lactone **11**. The position of the carbonyl group is uncertain; comparison of the ^{1}H-NMR shift of the pyridine 2-hydrogen (δ 9.01) for **11** with the corresponding chemical shifts reported for 3-carbomethoxypyridine (δ 9.2 in $CDCl_3$)[15] and 4-carbomethoxypyridine (δ 9.0 in CCl_4) did not permit an unambiguous assignment. No enhancement was observed in attempts to determine the structure by NOE experiments. Furthermore, the literature reports on the tendency for oxidation to occur preferentially at the 3- or 4-position of methylpyridines are conflicting. It is well established that in the pyridine nucleus, methyl groups in positions 2, 4, or 6 are readily oxidized and those in the 3- and 5-positions remain unattacked.[16] However, in vitamin B_6 an interesting anomaly has been reported. Oxidation of pyridoxine with permanganate afforded the 4-lactone, whereas oxidation of pyridoxine 3-methyl ether gave the lactone of 4-hydroxymethyl-5-methoxy-6-methylnicotinic acid.[17] One could argue that the large trimethylsilyl substituent at the 3-position of **10** would force the bulky lead oxidant to seek out position 5. Interestingly, oxidation took place readily also in the presence of just oxygen to give the same lactone (in addition to hydroxy derivative **12**), making this argument less convincing. Presently, no firm structural assignment can be made for this lactone.

We next turned our attention to the potential of converting **10** to the corresponding 3-halopyridine which might then be subjected to various hydroxylation procedures[19,20] including direct nucleophilic substitution.[22,23] Although pyridine undergoes nucleophilic substitution more readily than benzene as a consequence of its π-deficiency,[1] the order of reactivity at the ring (4 > 2 ≫ 3) was in our disfavor.[21] Another point of concern was the difficulty with which electrophilic substitution might proceed at the normally unreactive pyridine nucleus. We were encouraged by our earlier finding that 3-bromination proceeded smoothly in the case of 2,3-bis(trimethylsilyl)-5,6,7,8-tetrahydroisoquinoline.[2b]

The 3-trimethylsilylcyclopenta[1,2-*c*]pyridine **9** was used as a model system for the halogenation since it was more stable to air oxidation and could be prepared in larger quantities and stored over longer periods of time. Bromination of **9** in chloroform afforded the corresponding 3-bromoderivative **13** in good yield (73%). However, attempts to effect nucleophilic displacement[22,23] were unsuccessful.

At this point we were concerned not only with the failure of these methods, but also with the possibility that furo[3,4-*c*]pyridine **10** would give the oxidation product **11** upon attempted halogenation. Indeed, treatment of **10** with ICl or Br_2 gave **11**.

Another method was therefore sought which would allow substitution before oxidation. In contrast to the order of relative reactivities for silicon, germanium and tin compounds in nucleophilic substitution (*vide supra*), the corresponding order in electrophilic cleavage reactions are Si < Ge ≪ Sn.[24] Thus, a 3-trimethylstannylpyridine [potentially prepared by cocyclization of a bis(trimethylstannyl)diyne with acetonitrile] might permit hydroxylation before oxidation.

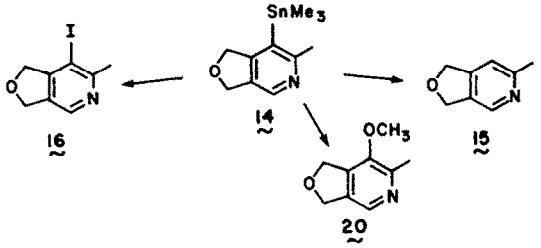
Two procedures were available for the direct conversion of aryl-tin compounds to phenols. The success of the first method, mercury(II) catalyzed tin–lead exchange,[25] was anticipated to be dependent on the enhanced reactivity of aryl–tin bonds (vs silicon) to electrophilic substitution, thus avoiding oxidation α to the ether oxygen. The second process, metal–metal exchange with an alkyllithium, is well precedented.[26] It was thought that treatment of the resulting aryllithium with either molecular oxygen or nitrobenzene[20] would result in the desired 3-hydroxypyridine. As an alternative to these strategies, it was hoped that it would be possible to cleave the highly reactive aryl–tin bond with iodine and thus provide an entry to the 3-

oxygenated compound via nucleophilic iodide displacement. With several options available for the hydroxylation, we began to explore the unknown potential of stannyl alkynes in cobalt-catalyzed cyclizations.

Treatment of dilithiobis-2-propynyl ether with trimethylstannyl chloride followed by rapid work-up with cold, saturated, aqueous NH_4Cl, and high vacuum distillation afforded **6** (52%) (Scheme 1). Only a few bis(trimethylstannyl)diynes are known, apparently a reflection of the high susceptibility of the alkynyl–tin bond to cleavage on exposure to light, oxygen, heat, and moisture.[26,27] Indeed, decomposition of **6** was observed before, during, and after distillation. The instability of **6** necessitated rapid purification techniques and immediate use in subsequent cyclization reactions.

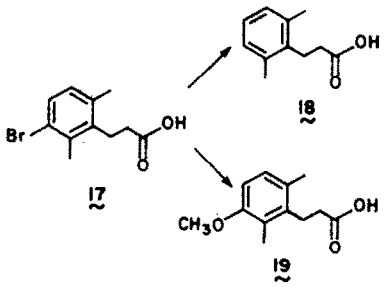
Cyclization of **6** with acetonitrile in *m*-xylene gave the bis(trimethylstannyl)furo[3,4-*c*]pyridine **4** which was rapidly monodestannylated upon chromatographic purification to afford **14** in moderate yield (45% from **6**). The relatively low yield may be due to diyne decomposition; the cyclization reaction mixture, normally of a deep red color, turned black within 15 min and much precipitate was observed during work-up. Furthermore, it was necessary to use relatively long (2–3 days) reaction times to observe complete disappearance of starting material. The 3-trimethylstannylpyridine **14** was also found to be unstable and was used immediately in further transformations.

Attempts at direct hydroxylation of **14** by exposure to: (1) BuLi, followed by molecular oxygen, (2) BuLi, and subsequently nitrobenzene,[20] (3) $Pb(OAc)_4$ and trifluoroacetic acid,[13] or (4) BuLi then $B(OCH_3)_3$, AcOH and H_2O_2[19] gave complex product mixtures which contained primarily destannylated pyridine **15** (by ^{1}H-NMR) and recovered starting material. Since this direct approach was not feasible, an iododemetallation displacement sequence was attempted.



Following the procedure developed by Yamamoto,[28] **14** was reacted with iodine in $CHCl_3$ to give 1,3-dihydro-6-methyl-7-iodofuro[3,4-*c*]pyridine (**16**) in excellent yield (99%). Disappointingly, treatment of the iodide with either (1) BuLi, followed by O_2 or (2) BuLi then $B(OCH_3)_3$, AcOH, and H_2O_2 gave starting material and **15** as the major products.

Attempts to displace the iodide with NaOMe in HMPA (a method developed by Testaferri[23] for the nucleophilic hydroxylation of unactivated aryl halides), or NaOMe in DMF, catalyzed by 0.3 equiv of $CuCl_2$[29] were equally unsuccessful. It was thought possible that the failure of the copper mediated reaction was due to the merely catalytic amounts of the metal employed.[30,31] Cuprous oxide promotes the reduction of aryl halides in the presence of methoxide relative to displacement. For example, when bromoacid **17** (1 equiv) was heated with cuprous iodide (0.3 equiv) in collidine, only the reduction product **18** was isolated.[31] Increasing the amount of cuprous iodide to 1.3 equiv afforded a maximized yield of 82% of the desired substitution product **19**. Presumably, traces of moisture in the reaction mixture transform cupric chloride to cuprous oxide, the latter catalyzing reduction.[31]



Gratifyingly, when **16** (1 equiv) was reacted with CuI (1.3 equiv) and NaOMe (6 equiv) in collidine with careful exclusion of moisture, the 3-methoxypyridine derivative **20** was formed in 37% non-optimized yield.

In addition to characterization by standard spectroscopic techniques, the structure of **20** was verified chemically by comparison to independently synthesized **20**,[32] prepared by dehydration of vitamin B_6 with sulfuric acid to give 3-hydroxyfuro[3,4-*c*]pyridine **2** and methylation with methyl iodide.

Methoxy ether **20** was then converted to vitamin B_6 in 2 steps using the literature procedures:[32,33] (1) HBr, Δ; (2) AgCl, H_2O, Δ. Although our route to the vitamin is presently inferior to others, it does provide a valuable and potentially general synthetic entry into the pyridoxine nucleus and other substituted pyridines carrying a variety of functional groups. It also demonstrates the utility of stannyl alkynes in cobalt catalyzed cyclizations and their subsequent regioselective elaboration.

CONCLUSION

The synthetic potential of the Co-catalyzed cooligomerization of an α,ω-bis(trimethylstannyl)-diyne was demonstrated by the novel synthesis of vitamin B_6. The extremely labile tin substituent was used to provide access to derivatives not available through replacement of the less reactive silicon. Although there are difficulties in handling the unstable tin compounds, further research efforts which concentrate on circumventing this problem (e.g. using radical scavengers in the cyclization medium or other more stable trialkyl- or triarylstannyl groups) should enhance the utility of these reagents.

Note added in proof. A conceptually identical strategy to vitamin B_6 has been employed by the Hoffmann-La Roche group (Basle) and appeared after submission of this work.[35]

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Varian EM-390 (90 MHz) or on home-built 200 and 250 MHz high field Fourier Transform instruments. The latter were equipped with Nicolet 1180 data collection systems, Cryomagnetics Inc. magnets and electronics assembled by Mr Rudi Nunlist, staff scientist. Spectra are reported in δ referenced to the solvent's ($CDCl_3$) residual proton peak using δ 7.24. ^{13}C-NMR spectra were measured at 25.14 MHz with a Nicolet TT-23 spectrometer or

at 63.07 MHz with the UCB-250 spectrometer. Chemical shifts are expressed in δ, referenced to the central peak of the $CDCl_3$ triplet (77.0 ppm downfield from TMS). IR spectra were observed on Perkin–Elmer 337 or Perkin–Elmer 681 spectrometers, and are reported in cm^{-1}. Mass spectra and elemental analyses were performed by the Mass Spectral Service and Microanalytical Laboratory of the University of California, Berkeley, California. On occasion, because of the presence of silicon or reactive tin, completely satisfactory elemental analyses could not be obtained. M.ps and b.ps are uncorrected. M.ps were determined on a Thomas–Hoover Unimelt apparatus. Column chromatography was carried out using Alfa aluminum oxide, activated CAMAG, 95+%, 60 mesh to which 6% water had been added (activity III), or EM reagents silica gel 60, 70–230 mesh ASTM. Preparative TLC was performed on plates prepared from EM reagents silica gel PF-254 with $CaSO_4 \cdot \frac{1}{2}H_2O$ using a spinning plate, continuous elution system (Chromatotron, Harrison Research) under N_2. Anhydrous ether was used as received. Solvents were dried by distillation from an appropriate drying agent under N_2. All reactions were conducted under N_2 unless otherwise stated.

3,3-Bis(trimethylsilyl)-di-2-propynyl ether (**5**). Di-2-propynyl ether[34] (15.166 g, 0.167 mol) was dissolved in 200 ml abs ether and cooled to −78° (dry ice/acetone bath). BuLi (225.87 ml, 0.339 mol, 1.5 M in hexane) was added via syringe and the soln was warmed to room temp over a period of 1.5 hr, then cooled to −78°. Trimethylsilyl chloride (36.80 g, 0.339 mol) was added over a period of 20 min via a pressure-equalizing dropping funnel and the mixture was warmed to room temp and stirred for 12 hr. The solution was cooled in an ice–water bath, diluted with water, extracted with ether and dried ($MgSO_4$). Concentration, followed by distillation gave **5** (37.24 g, 0.156 mol, 94%): colorless liquid, b.p. 69–69.5°, 0.65 T; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 4.20 (s, 4H), 0.15 (s, 18H); IR (neat) 2950, 2900, 2850, 2160, 1340, 1250, 1085, 995, 840, 760; *m/e* (rel intensity) 238 (M^+, 0.3), 237 (0.7), 223 (6), 207 (8), 200 (13), 199 (65), 193 (50), 165 (26), 147 (18), 97 (24), 73 (100); ^{13}C-NMR ($CDCl_3$) δ 100.6, 91.4, 56.9, −0.4; HRMS calc ($C_{12}H_{22}OSi_2$): 238.1209. Found: 238.1204. (Found: C, 59.64; H, 9.28. Calc ($C_{12}H_{22}OSi_2$): C, 60.44; H, 9.29%.)

1,3 - Dihydro - 6 - methyl - 4,7 - bis[trimethylsilyl]furo[3,4 - c]pyridine (**3**) *and* *1,3 - dihydro - 6 - methyl - 7 - trimethylsilylfuro[3,4-c]pyridine* (**10**). A soln of **5** (3.0 g, 12.61 mmol) and $CpCo(CO)_2$ (0.057 g, 0.317 mmol) in 15 ml deoxygenated *m*-xylene was added via syringe pump over a period of 6 hr to a soln of 60 ml deoxygenated *m*-xylene, CH_3CN (5.16 g, 126.05 mmol) and $CpCo(CO)_2$ (25 μl) at reflux while irradiating with a 250 W GE-ENH slide projector lamp. After 18 hr, an additional 150 μl of $CpCo(CO)_2$ was added and heating was continued for 18 hr. An aliquot of the mixture was concentrated and the ^{1}H-NMR spectrum of **3** was obtained: ^{1}H-NMR (250 MHz, $CDCl_3$) δ 5.08 (s, 2H), 5.03 (s, 2H), 2.68 (s, 3H), 0.33 (s, 9H), 0.29 (s, 9H). The soln was cooled to room temp, stirred with Al_2O_3 (neutral, activity III, 5 g) and 25 ml MeOH for 3 hr, then concentrated by rotary evaporation. The brown oily residue was dissolved in CH_2Cl_2 and the desired product was extracted into 3 N HCl. The aqueous layer was washed with CH_2Cl_2, neutralized by the slow addition of sat aq $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), concentrated by rotary evaporation and chromatographed (SiO_2, CH_2Cl_2) to afford **10** (1.78 g, 8.62 mmol, 68%): clear colorless oil; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.33 (s, 1H), 5.03 (s, 2H), 5.025 (s, 2H), 2.63 (s, 3H), 0.32 (s, 9H); IR (neat) 2950, 2880, 2820, 1575, 1540, 1410, 1250, 1050, 835; *m/e* (rel intensity) 207 (M^+, 20), 206 (86), 192 (17), 178 (8), 162 (3), 149 (69), 135 (52), 120 (79), 107 (60), 92 (57), 84 (57), 77 (78), 73 (24), 49 (100); ^{13}C-NMR ($CDCl_3$) δ 161.2, 154.9, 141.7, 131.2, 125.4, 74.1, 70.8, 26.2, 0.8; microdistillation for analysis: oil bath temp 90°, 0.125 T. (Found: C, 63.49; H, 8.25; N, 6.77. Calc ($C_{11}H_{17}NOSi$): C, 63.77; H, 8.21; N, 6.76%.)

2 - Methyl - 3,6 - bis(trimethylsilyl)cyclopenta[1,2 - c]pyridine (**8**) *and* *2 - methyl - 3 - trimethylsilylcyclopenta[1,2-c]pyridine* (**9**). A soln of 7[12] (2.0 g, 8.47 mmol) and $CpCo(CO)_2$ (25 μl) in 13 ml deoxygenated *m*-xylene was added via syringe pump over a period of 6 hr to a mixture of CH_3CN (3.47 g, 84.75 mmol) and $CpCo(CO)_2$ (25 μl) in 50 ml boiling, deoxygenated *m*-xylene while irradiating with a 250 W GE-ENH slide projector lamp. After heating for 10 hr, the soln was cooled to room temp and the volatiles were removed by vacuum transfer to give the crude **8** (1.97 g, 7.11 mol, 84%): brown oil; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 2.79 (t, J = 7.5, 4H), 2.54 (s, 3H), 1.88 (q, J = 7.5, 2H), 0.26 (s, 9H), 0.22 (s, 9H). Filtration of **8** through Al_2O_3 (basic, activity III, CH_2Cl_2) gave **9** (1.32 g, 6.44 mmol, 76%): colorless oil; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.24 (s, 1H), 2.89 (t, J = 7.4, 2H), 2.77 (t, J = 7.4, 2H), 2.57 (s, 3H), 1.96 (q, J = 7.4, 2H), 0.32 (s, 9H); IR (neat) 2990, 1580, 1545, 1410, 1360, 1260, 820; *m/e* (rel intensity) 205 (M^+, 21), 191 (16), 190 (100), 132 (9), 73 (7), 59 (8), 43 (5); microdistillation for analysis: oil bath temp 50°, 0.05 T; HRMS calc ($C_{12}H_{19}NSi$): 205.1367. Found: 205.1277. (Found: C, 68.87; H, 9.09; N, 6.30. Calc ($C_{12}H_{19}NSi$): C, 70.24; H, 9.27; N, 6.83%.)

1 (or 3) - Hydro - 3 (or 1) - oxo - 6 - methyl - 7 - trimethylsilylfuro[3,4-c]pyridine (**11**). A soln of $Pb(OAc)_4$ (0.0814 g, 0.183 mmol) in 2 ml dry trifluoroacetic acid was cooled to 0°. Silylpyridine **10** (0.038 g, 0.183 mmol) in 1 ml trifluoroacetic acid was added. The mixture, which immediately turned light green, was warmed to room temp. After 3 hr, an aqueous quench of an aliquot showed only starting material by TLC and ^{1}H-NMR. An additional equivalent of $Pb(OAc)_4$ (0.0814 g, 0.183 mmol) was added and the soln was heated to reflux for 3 hr. The mixture was diluted with CH_2Cl_2, extracted with sat aq $NaHCO_3$, dried ($MgSO_4$) and concentrated. Chromatography (SiO_2, CH_2Cl_2 : acetone, 10 : 1) gave lactone **11** (0.0244 g, 0.110 mmol, 60%): colorless oil; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 9.01 (s, 1H), 5.30 (s, 2H), 2.78 (s, 3H), 0.42 (s, 9H); IR ($CHCl_3$) 2950, 2880, 2715, 1760, 1585, 1570, 1400, 1360, 1340, 1280, 1240, 1215, 1050, 1020, 920, 860, 630; *m/e* (rel intensity) 221 (M^+, 36), 207 (16), 206 (100), 178 (22), 136 (15), 125 (6), 107 (10), 75 (17), 73 (20); HRMS calc ($C_{11}H_{15}NO_2Si$): 221.0944. Found: 221.0864.

This compound was observed by ^{1}H-NMR and TLC in the reaction of **10** with *m*-CPBA and in the decomposition of a sample of **10** which had been stored under N_2 in the presence of light.

1 (or 3) - Hydro - 3 (or 1) - hydroxy - 6 - methyl - 7 - trimethylsilylfuro[3,4-c]pyridine (**12**). This compound was isolated (SiO_2, CH_2Cl_2 : acetone, 4 : 1) from a sample of **10** which had been stored in the presence of trace amounts of oxygen for 3 days: ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.34 (s, 1H), 6.53 (s, 1H), 5.15 (d, J = 13, 1H), 4.96 (d, J = 13, 1H), 2.66 (s, 3H), 0.42 (s, 9H), hydroxyl proton not observed; IR ($CHCl_3$) 3500–2300 (OH), 1590, 1560, 1410, 1380, 1310, 1240, 1150, 1050, 1000, 850, 730; *m/e* (rel intensity) 223 (M^+, 10), 222 (6), 209 (16), 208 (100), 206 (13), 191 (14), 190 (79), 164 (8), 162 (11), 148 (3), 134 (70), 133 (7), 121 (3), 91 (8), 77 (13), 75 (52), 73 (15); HRMS calc ($C_{11}H_{17}NO_2Si$): 223.1020. Found: 223.1030.

2-Methyl-3-bromocyclopenta[1,2-c]pyridine (**13**). Bromine (0.722 g, 4.52 mmol) was added via syringe to a soln of **9** (0.842 g, 4.11 mmol) in 10 ml $CHCl_3$. The red soln was stirred for 24 hr then diluted with CH_2Cl_2, washed with sat aq $Na_2S_2O_8$, dried ($MgSO_4$) and concentrated by rotary evaporation. The brown oil was filtered (SiO_2, CH_2Cl_2) to give **13** (0.635 g, 2.995 mmol, 73%): clear colorless oil; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.17 (s, 1H), 2.97 (t, J = 7.5, 2H), 2.88 (t, J = 7.5, 2H), 2.58 (s, 3H), 2.07 (q, J = 7.5, 2H); IR (neat) 2960, 2825, 1590, 1450, 1430, 1380, 1140, 940; *m/e* (rel intensity) 212 (M^+, 65), 211 (79), 210 (60), 133 (1), 132 (26), 131 (27), 130 (27), 117 (28), 103 (15), 89 (11), 73 (12), 65 (39), 40 (100); Kugelrohr microdistillation for analysis: air temp 130°, 0.30 T. (Found: C, 50.96; H, 4.55; Br, 37.50; N, 6.38. Calc ($C_9H_{10}BrN$): C, 50.94; H, 4.72; Br, 37.74; N, 6.60%.)

3,3-Bis(trimethylstannyl)di-2-propynyl ether (**6**). BuLi (50.638 ml, 0.076 mol, 1.5 M in hexane) was added via syringe to a soln of di-2-propynyl ether[34] (3.40 g, 0.36 mol) in 175 ml anhydrous ether at −78°. The cooling bath was removed and the mixture was stirred for 1.5 hr then cooled to −78°.

Trimethylstannyl chloride (15.50 g, 0.077 mol) in 75 ml ether was carefully added via a pressure-equalizing dropping funnel. The solution was warmed to room temp, stirred for 12 hr, diluted with ether and rapidly extracted with cold sat aq NH_4Cl. The organic extracts were dried ($MgSO_4$), concentrated and distilled into an ice cooled receiver to give the highly unstable diyne **6** (7.898 g, 0.019 mol, 52%): clear colorless oil which rapidly turns brown and hydrolyzes in the presence of traces of moisture, b.p. 110–115°, 0.05 T; ^{1}H-NMR (200 MHz, $CDCl_3$) δ 4.17 (s, 4H), 0.22 (s, 18H); IR (neat) 2990, 2910, 2820, 2150, 1440, 1340, 1190, 1080, 770 (C–Sn); *m/e* (rel intensity) molecular ion not observed, 413 (0.3), 411 (4), 409 (6), 407 (15), 405 (19), 403 (16), 401 (8), 399 (3), 331 (13), 329 (17), 327 (15), 197 (12), 195 (12), 169 (22), 167 (18), 165 (100), 163 (75), 161 (45), 137 (5), 135 (21), 133 (15); ^{13}C-NMR ($CDCl_3$) δ 104, 91, 58, −0.4; microdistillation for analysis: oil bath temp 160°, 0.025 T. (Found: C, 35.13; H, 5.55. Calc ($C_{12}H_{22}OSn_2$): C, 34.36; H, 5.24%.)

1,3-*Dihydro*-6-*methyl*-4,7-*bis(trimethylstannyl)furo*[3,4-c]*pyridine* (**4**) *and* 1,3-*dihydro*-6-*methyl*-7-*trimethylstannylfuro*[3,4-c]*pyridine* (**14**). A soln of freshly distilled **6** (3.41 g, 8.13 mmol) and $CpCo(CO)_2$ (50 μl) in 11 ml anhydrous, deoxygenated *m*-xylene was added via syringe pump over a period of 4 hr to anhydrous CH_3CN (3.33 g, 81.31 mmol) and $CpCo(CO)_2$ in 50 ml boiling, anhydrous, deoxygenated *m*-xylene while irradiating with a 250 W GE-ENH slide projector lamp. The mixture, which turned black within 20 min, was monitored using ^{1}H-NMR by following the disappearance of the diyne absorption for the methylene protons at δ 4.17. After 24 hr, $CpCo(CO)_2$ (100 μl) and anhydrous CH_3CN (3.33 g, 81.31 mmol) were added. The reaction was complete after a total of 48 hr. The solution was cooled to room temp and the volatiles were removed by vacuum transfer to give crude **4**: dark oil; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 5.06 (s, 2H), 4.99 (s, 2H), 2.64 (s, 3H), 0.35 (s, 9H), 0.33 (s, 9H); *m/e* (rel intensity) molecular ion not observed, 450 (7), 448 (20), 447 (11), 446 (25), 443 (24), 442 (10), 331 (5), 329 (7), 284 (13), 282 (13), 169 (19), 167 (25), 165 (100), 163 (74), 162 (23), 151 (10), 150 (16), 149 (15), 148 (17), 137 (16), 135 (53), 134 (25), 133 (42), 131 (21), 121 (9), 120 (19), 119 (12), 118 (13), 117 (7), 106 (60), 105 (25), 91 (95), 81 (10), 79 (11), 69 (25), 55 (19). Chromatography (Al_2O_3, neutral, activity III, CH_2Cl_2) of **4** afforded the desired compound **14** (1.088 g, 3.655 mmol, 44%): pale yellow oil; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.31 (s, 1H), 5.06 (s, 2H), 4.98 (s, 2H), 2.60 (s, 3H), 0.35 (s, 9H); IR (neat) 2980, 2900, 2850, 1760, 1590, 1540, 1420, 1365, 1050, 900, 770; *m/e* (rel intensity) 299 (21), 298 (M^+, 8), 297 (17), 288 (15), 285 (11), 284 (100), 282 (78), 280 (48), 269 (11), 267 (11), 254 (31), 252 (27), 250 (17), 165 (100), 149 (18), 135 (24), 134 (24), 120 (15), 106 (12), 77 (16); microdistillation for analysis: oil bath temp 140°, 0.05 T; HRMS calc ($C_{11}H_{17}NOSn$): 297.0327. Found: 297.0367. (Found: C, 46.03; H, 5.74; N, 4.91. Calc ($C_{11}H_{17}NOSn$): C, 44.34; H, 5.71; N, 4.70%.)

1,3-*Dihydro*-6-*methyl*-7-*iodofuro*[3,4-c]*pyridine* (**16**). Iodine (0.1143 g, 0.450 mmol) was added to a solution of **14** (0.134 g, 0.450 mmol) in 15 ml $CHCl_3$. The reaction flask was wrapped in aluminum foil to exclude light. The soln was stirred at room temp for 18 hr, diluted with $CHCl_3$, then washed with sat aq $Na_2S_2O_8$ and sat aq KF (to remove the trimethylstannyl iodide).[28] The dark brown soln was dried (Na_2SO_4), concentrated and chromatographed on SiO_2 (CH_2Cl_2) to afford **16** (90.1 mg, 0.444 mmol, 99%): colorless, viscous oil; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.25 (s, 1H), 5.24 (br s, 2H), 4.93 (t, J = 2, 2H), 2.70 (s, 3H); IR ($CHCl_3$) 2960, 2860, 1595, 1390, 1265, 1140, 1050, 900, 810; *m/e* (rel intensity) 261 (M^+, 100), 260 (30), 234 (3), 233 (39), 232 (23), 205 (12), 149 (13), 133 (10), 107 (10), 106 (67), 105 (24), 104 (22), 77 (40), 71 (19), 57 (28); HRMS calc (C_8H_8INO): 260.9623. Found: 260.9653.

1,3-*Dihydro*-6-*methyl*-7-*methoxyfuro*[3,4-c]*pyridine* (**20**). Sodium (0.058 g, 2.528 mmol) was added in one portion to 1 ml MeOH. When dissolution was complete, freshly distilled 2,4,6-collidine (3 ml) was added, followed by vacuum-dried cuprous iodide (0.104 g, 0.548 mmol) in 3 ml collidine, and iodide **16** (0.110 g, 0.421 mmol). The mixture was heated to reflux for 16 hr, then cooled to room temp, diluted with CH_2Cl_2, extracted with sat aq NH_4OH and dried (Na_2SO_4). The collidine was removed by vacuum transfer and the brown residue was chromatographed (SiO_2, CH_2Cl_2: acetone, 5:1) to give **20** (0.025 g, 0.152 mmol, 36%): colorless oil; ^{1}H-NMR (250 MHz, $CDCl_3$) δ 8.05 (s, 1H), 5.23 (t, J = 2, 2H), 5.06 (br s, 2H), 3.82 (s, 3H), 2.47 (s, 3H); IR (neat) 2980, 2955, 2920, 2840, 1610, 1570, 1450, 1390, 1340, 1270, 1240, 1050, 915, 800; *m/e* (rel intensity) 165 (M^+, 100), 164 (31), 149 (2), 137 (12), 136 (34), 134 (25), 122 (37), 121 (12), 107 (21), 106 (30), 94 (15), 79 (13), 77 (11), 65 (13), 51 (43).

Vitamin B_6 *hydrochloride* (**1**). Compound **20** (10.0 mg, 0.0606 mmol) was dissolved in 2 ml 48% HBr and heated for 2 hr. The mixture was concentrated by rotary evaporation to give crude 2-methyl-3-hydroxy-4,5-bis(bromomethyl)pyridine hydrobromide (17.7 mg, 0.0471 mmol, 78%). This compound was converted to vitamin B_6 hydrochloride[32,33] by boiling in 2 ml H_2O for 20 min, and then removing bromide ion with freshly prepared AgCl. The solution was filtered, the filtrate evaporated to dryness, then dissolved in 0.02 ml H_2O in 1 ml EtOH. The addition of 0.5 ml acetone precipitated vitamin B_6 hydrochloride (6.5 mg, 0.032 mmol, 68%): colorless, powdery crystals, m.p. 209–210° (dec), no depression on admixture of an authentic sample of the vitamin.

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