of a small energy leak from the higher anthracene state (^1B) directly into the σ^* orbital of the S^+–C bond. This is not a large effect. Even in I most of the excitation energy takes the usual route via ^1L_a, and for that reason the quantum yield of acid production by I is very much lower than, e.g., that of triphenylsulfonium salts where the critical σ^* orbital is populated exclusively from a relatively high-lying excited state of the phenyl group.

Experimental Section

Compounds I to III were prepared from the respective anthryl phenyl sulfides by treating these with silver hexafluoroantimonate and methyl iodide.

In the first phase of synthesis, 5.5. g (0.05 mol) of thiophenol and 50 mL of dimethylformamide were placed into a 250-mL three-necked, round-bottom flask equipped with a paddle stirrer, an addition funnel, and a condenser. The mixture was cooled to 0 °C in an ice–water bath, and then 1.2 g (0.05 mol) of sodium hydride was added in small portions. In the synthesis of I, 5.14 g of 9-bromoanthracene in 25 mL of dimethylformamide was introduced into the solution, and this was refluxed for 10 h. After being cooled, the contents were poured into ice–water and the precipitate of the product filtered off and recrystallized from hexane: yellow crystals, yield 64%, mp 90–91 °C.

In the preparation of II, bromoanthracene was replaced by 1-chloroanthracene, dimethylformamide by dimethylacetamide. The product was obtained in 52% yield; pale yellow crystals, mp 103–104 °C.

In the preparation of III 2-chloroanthracene and dimethylacetamide were used. The product yield was 68%: pale yellow crystals, mp 149–150 °C.

In the second phase of synthesis silver hexafluoroantimonate was added to a solution of the appropriate anthryl phenyl sulfide as well as 1 g of methyl iodide in 20 mL of methylene chloride. The mixture was stirred at room temperature for 3 h. The insoluble silver salt was then filtered off, and the volume of the solution was reduced to about 3 mL. The solution was added dropwise to diethyl ether where the product precipitated. The ether was decanted, and the raw product (a yellow gum) was recrystallized from acetonitrile–ether.

I: light yellow crystals, yield 30%, mp 140–141 °C; ^1H NMR δ 4.45 (3 H), 7.8–9.5 (14 H). Anal. Calcd: C, 46.95; H, 3.19; S, 5.97. Found: C, 46.93; H, 3.03; S, 6.14.

II: light yellow crystals, yield 29%, mp 170–171 °C; ^1H NMR δ 4.2 (3 H), 7.9–9.2 (14 H). Anal. Calcd: C, 46.95; H, 3.19; S, 5.97. Found: C, 46.91; H, 3.03; S, 5.86.

III: light yellow crystals, yield 19%, mp 201–203 °C; ^1H NMR δ 4.3 (3 H), 7.9–9.3 (14 H). Anal. Calcd: C, 46.95; H, 3.19: S, 5.97. Found: C, 46.98; H, 3.07; S, 6.13.

Solutions (5×10^{-4} M) in analytical-grade dichloromethane were exposed in a standard 1-cm spectroscopic cell to the radiation beam of a Bausch and Lomb monochromator. The light source was a 150-W xenon lamp (Osram) attached to a stabilized power supply. The spectral width of the radiation beam was ±3 nm; its intensity was determined for each wavelength setting by ferrioxalate actinometry.[12] In the range from 400 to 260 nm the radiation intensity varied from 2.51×10^{-10} to 0.169×10^{-10} einstein/cm^2 s. Exposure times were in the range from 10 to 120 min. The optical density of the solutions varied between 1.5 and 4. For exposures at 260 and 280 nm the solutions were diluted to keep their optical density below a value of 4.

Acid formation was determined by mixing the photolyte with a standard solution of an indicator dye[13] and monitoring the degree of bleaching of that dye. The indicator system was calibrated with monomethylsulfonic acid.

Registry No. I, 137719-80-3; II, 137719-82-5; III, 137719-84-7; 9-bromoanthracene, 1564-64-3; thiophenol, 108-98-5; 1-chloroanthrazene, 4985-70-0; 2-chloroanthracene, 17135-78-3.

(12) Kurien, K. C. *J. Chem. Soc. B* **1971**, 2081.
(13) McKean, D. R.; Schaedeli, U.; MacDonald, S. A. *J. Polym. Sci.; Polym. Chem. Ed.* **1989**, *27*, 3927.

Azatetralone Synthesis via Regioselective Grignard Coupling and Parham Cyclization

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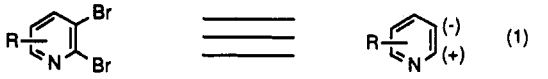
During the course of efforts directed toward the novel aldose reductase inhibitors **20** and **21**, the need for an asymmetric synthesis of azatetralone **16** was encountered. Methods have been reported for the synthesis of achiral azatetralone **15**, but were not amenable for the preparation of chiral azatetralone **16**.[1] To this end, a novel sequence of pyridine functionalization was developed from a 2,3-dibromopyridine derivative depicted by the synthon below. The pyridine annulation route to azatetralones **15** and **16**, via a 2,3-dibromopyridine derivative, allows access to other 2,3-disubstituted pyridines.



(1)

Electrophilic and nucleophilic elaboration of pyridines was known. Kumada has demonstrated alkylation and arylation of halopyridines, bromothiophenes, haloquinolines, halobenzenes, and haloisoquinolines by Grignard reagents, catalyzed by nickel/phosphine complexes (1,2-bis(diphenylphosphino)ethane(dppe)nickel(II) chloride and 1,3-bis(diphenylphosphino)propane(dppp)nickel(II) chloride).[2] These bromide displacements were facile in pyridine systems independent of the position of the halide as evidenced by the displacement of bromide in 2-, 3-, and 4-bromopyridine with dppe/$NiCl_2$ and 2-methylbutylmagnesium chloride in ether at reflux affording the alkylated products in 67%, 72%, and 53% yields, respectively.[3]

In previous transmetalation studies with pyridines by Parham and co-workers, halogen–metal exchange on 2,5-dibromopyridine afforded 2-bromo-5-lithiopyridine as determined by proton and deuterium quenching.[4] These workers had not anticipated metalation at the 5-position because the 2-position is more electronegative and initial coordination of butyllithium with the heteroatom would favor metalation at the 2-position. This halogen–metal exchange and other pyridine metalations led these workers to suggest that the reactions were the result of thermodynamic control.[5] Thus, functionalization of halopyridines by cross coupling with Grignard reagents, catalytic in nickel/phosphine complexes, and by transmetalation was precedented.

(1) (a) Lipinski, C. A. Eur. Pat. Appl. 85307712.1 (b) Hoffman, J. M.; Phillips, B. T.; Cochran, D. W. J. *Org. Chem.* **1984**, *49*, 193. (c) Mader, M., Bohlmann, F. *Tetrahedron Lett.* **1965**, 171. (d) *Acta Pharm. Suec.* **1980**, *17*, 288. (e) LeBel, N. A.; Caprathe, B. W. *J. Org. Chem.* **1985**, *50*, 3938. (f) Skattebol, L.; Berg-Nielsen, K. *Acta Chem. Scand.* **1978**, *B32*, 553. (g) Noguchi, M.; Yamamoto, T.; Kajigaeshi, S. *Heterocycles* **1990**, 563.

(2) (a) Kumada, M.; Sumitani, K.; Tamao, K. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (b) Kumada, M.; Sumitani, K.; Tamao, K., *Org. Synth.* **1980**, *58*, 127. (c) Kumada, M.; Tamao, K.; Kodama, S.; Nakajima, I. *Tetrahedron* **1982**, *38*, 3347.

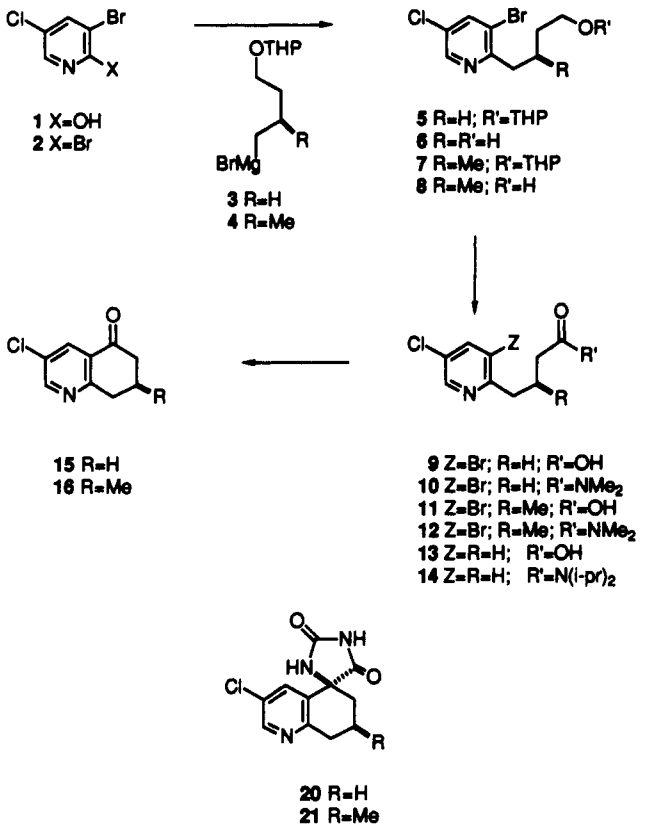
(3) Pino, P.; Piccolo, O.; Straub, B.; Consiglio, G.; Tran, D. C. *Helv. Chim. Acta* **1982**, *65*, 2102.

(4) Parham, W. E.; Boykin, D. W. *J. Org. Chem.* **1977**, *42*, 257.

(5) After completion of our research, French workers described transmetalations of polyhalopyridines and similarly attributed the isomerization of the initially formed mixture of lithiopyridines into the substituted 3-lithiopyridines as a result of thermodynamic control. Branger, G.; Mallet, M.; Marsais, F.; Queguiner, G. *J. Organomet. Chem.* **1990**, *382*, 319.

0022-3263/92/1957-0761$03.00/0

Scheme I

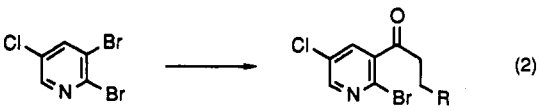


Results and Discussion

Regiospecific displacement of one halogen in 2,3-dibromo-5-chloropyridine (2) is described in the context of the synthesis of azatetralones 15 and 16 (Scheme I). The known pyridone 1[6] was converted into 2 (71%) by heating in dimethylformamide with phosphorus oxybromide.[7] Regiospecific displacement of the 2-bromo substituent in 2 with the known Grignard reagent 3[8] was achieved under the catalytic influence of dppp/$NiCl_2$ (0.1 equiv) at 0 °C affording 5 in 79% chromatographed yield.[9] Single and double displacements of aromatic halogens with the Grignard reagents and the aforementioned nickel(II)/phosphine ligands have been reported, but regiospecific displacement of one halogen in a polyhalogenated aromatic system has not been reported to our knowledge. While one might anticipate that the 2-position of pyridine 2 would be more electron deficient than the 3-position, and therefore possess enhanced reactivity with respect to catalyzed Grignard displacement, it was not expected that this reactivity would manifest complete regioselective displacement, especially in light of the precedent where displacement at any pyridine position was facile. The dppp catalyst was clearly superior in the coupling to dppe, as the latter yielded only 25% conversion to the product 5 after 24 h.[10]

Completion of the azatetralone 15 synthesis proceeded as follows. Hydrolysis of the tetrahyropyranyl protecting group in 5 with pyridinium tosylate in ethanol afforded a 97% yield of the alcohol 6 as a white solid.[11] Oxidation of 6 with Jones reagent gave the acid 9 (61%) as a colorless oil which solidified on standing. Intramolecular Parham cyclization was intended to conclude the azatetralone 15 synthesis.[12] Treatment of the acid 9 with *n*-butyllithium generated the azatetralone 15 in 12–19% yield. Unreacted 9 was the major product obtained from the cyclization, the 3-protonated pyridine 13 was also isolated. During the Parham cyclization, it was observed that after 1 equiv of *n*-butyllithium was added, a white precipitate formed. Isolation of the precipitate at this point gave recovered acid 9 which implied that the insolubility of the carboxylic acid lithium salt prevented metalation at the 3-position. Use of more dilute conditions and/or the use of more polar solvents such as dimethyl sulfoxide or 1,3-dimethyl-2-imidazolidinone did not improve the conversion.[13] To overcome the solubility problem, three amides were prepared (dimethyl, diisopropyl, and pyrrolidine) from the acid 9 employing 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride and the corresponding amine.[14] The best amide for cyclization was the dimethyl derivative 10 which provided a 50% yield of azatetralone 15. While all of the amides generated 15, the diisopropylamide afforded more of the reduced pyridine 14, whereas the pyrrolidine amide gave more recovered starting material under comparable reaction conditions. Application of this approach with the known chiral Grignard reagent 4[15] produced the azatetralone 16 in comparable yield.

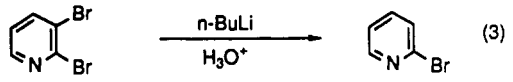
Having established a method to prepare azatetralones 15 and 16, we were interested in determining the transmetalation behavior of a 2,3-dibromopyridine. Transmetalation studies of 2 demonstrated that the 3-lithio material was formed exclusively with *n*-butyllithium. This result was determined by proton quenching studies and by comparison of other proton NMR data.[16] Condensation of this 3-lithio derivative of 2 with γ-butyrolactone and δ-valerolactone afforded 63% and 49% chromatographed yields, respectively, of the keto alcohols 17 and 18. The crude keto alcohol 17 was isolated more readily after oxidation with pyridinium chlorochromate to afford a 57% yield of the ketoaldehyde 19 after two steps.



2,3-Dibromopyridine[17] was investigated to further probe the unique transmetalation reaction of 2 and to determine if the 5-chloro substituent was responsible for this metalation behavior. Transmetalation of 2,3-dibromopyridine employing the conditions used with 2 and subsequent

(6) Quallich, G. J.; Murtiashaw, C. W. Eur. Pat. Appl. 91301571.5.
(7) The yield was based on recovered starting material 1.
(8) Grieco, P. A.; Larsen, S. D. *J. Org. Chem.* **1986**, *51*, 3553.
(9) The minimum amount of catalyst, purchased from Strem Chemicals Inc., necessary for the coupling was not determined.
(10) None of the desired product was formed with bis(triphenylphosphine)nickel(II) chloride as the catalyst.
(11) Grieco, P. A.; Yoshikoshi, A.; Miyashita, N. *J. Org. Chem.* **1977**, *42*, 3772.
(12) Parham and co-workers have assembled a variety of ring systems by low-temperature transmetalation of a halogen, often bromine, with *n*- or *tert*-butyllithium and subsequent intramolecular cyclization. Electrophiles examined included carboxylic acids, halogens, epoxides, and Schiff bases. (a) Parham, W. E.; Jones, L. D.; Sayed, Y. *J. Org. Chem.* **1975**, *40*, 2394. (b) Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300. (c) Snieckus, V.; Hahn, W. R.; Alo, B. I.; Shankaran, K.; Sibi, M. P. *Tetrahedron Lett.* **1987**, *28*, 2933.
(13) The sodium salt was also insoluble under the conditions mentioned.
(14) Sheehan, J. C.; Cruickshank, P. A.; Boshart, G. L. *J. Org. Chem.* **1961**, *26*, 2525.
(15) Suzuki, S.; Mori, F.; Takigawa, T.; Ibata, K.; Ninagawa, Y.; Nishida, T.; Mizuno, M.; Tanaka, Y. *Tetrahedron Lett.* **1983**, *24*, 5103.
(16) The ortho coupling constant of $J(3\text{-}4)$ = 8 Hz could only be obtained by protonation at the 3-position.
(17) Abramovitch, R. A.; Helmer, F.; Liveris, M. *J. Org. Chem.* **1969**, *34*, 1730.

protonation generated 2-bromopyridine as the sole reaction product in 54% yield.[18] 3-Bromopyridine, corresponding to metal–halogen exchange at the 2-position, could not be detected in the crude reaction product by HPLC. Thus, regiospecific carbon–carbon bond formation at the 2- or 3-position of pyridine **2** was demonstrated affording great flexibility in preparing differentially functionalized 2,3-disubstituted pyridine derivatives.[19]



(3)

In summary, a novel unoptimized method to prepare azatetralones **15** and **16** has been achieved by regioselective addition of a Grignard reagent to a polyhalogenated pyridine ring and subsequent Parham cyclization. This route to annulate pyridines also affords access to 2,3-disubstituted pyridines from the corresponding dibromo derivatives. The azatetralone synthesis and the unique metalation behavior of 2,3-dibromopyridines will add to the existing methods for pyridine functionalization.

Experimental Section

Melting points were determined with Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded in $CDCl_3$ at 250 MHz. Infrared spectra were recorded in $CHCl_3$ unless noted otherwise. Microanalyses were performed by the Pfizer Analytical Department.

2,3-Dibromo-5-chloropyridine (2). 3-Bromo-5-chloropyridone **1** (33.51 g, 161 mmol) was dissolved in dimethylformamide (251 mL) at ambient temperature. Phosphorus(V) tribromide oxide (52.12 g, 182 mmol) was added and the reaction heated to 80 °C for 72 h. After cooling, the reaction was poured onto ice. Vacuum filtration provided the product as a tan solid. The crude product was taken up in ether and the pH of the water adjusted to 13. The aqueous layer was extracted three times with ether, the combined organic extracts were treated with magnesium sulfate, and solvent was removed under vacuum. The product was dissolved in boiling hexane and decolorizing carbon was added to the crude product, and the contents were heated to reflux and then filtered through Celite. The clear colorless filtrate was stripped under vacuum to yield the product **2** as a white solid (18.1 g, 45%), mp 39.5–43 °C. Starting pyridone **1** was recovered from aqueous solution by adjusting the pH to 1 with concentrated hydrochloric acid. Filtration of the precipitate and drying under vacuum provided (13.84 g, 40%) of clean starting pyridone **1**: IR (neat) 3060, 1538, 1405, 1370, 1135, 1030, 905 cm^{-1}; ^1H NMR δ 8.28 (d, J = 2 Hz), 7.89 (d, J = 2 Hz); ^{13}C NMR δ 146.93, 141.45, 141.02, 131.34, 124.01. Anal. Calcd for $C_5H_2Br_2ClN$: C, 22.13; H, 0.74; N, 5.16. Found: C, 21.93; H, 0.53; N, 4.90.

3-Bromo-5-chloro-2-[4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-butyl]pyridine (5). To a solution of 2,3-dibromo-5-chloropyridine (2.0 g, 7.38 mmol) in tetrahydrofuran (7.4 mL) at ambient temperature was added 1,3-bis(diphenylphosphino)propanenickel(II) chloride (dppp, 0.4 g, 0.74 mmol). The solution was cooled to 0 °C, and the Grignard reagent **3** (11 mL) was added over 30 min. Five minutes after the addition of the Grignard reagent, the reaction was quenched with water (50 mL) and saturated aqueous ammonium chloride (50 mL). The quenched reaction was extracted with ether (2 × 50 mL), and the organic extracts were combined and dried with magnesium sulfate. Removal of the solvent under vacuum provided 3.48 g of crude product. Chromatography on 80 g of silica with 10% ethyl acetate/hexane gave the THP-protected alcohol **5** as a colorless oil (2.04 g, 79%): IR (neat) 3060, 2940, 2880, 1380, 1120, 1040 cm^{-1}; ^1H NMR δ 8.4 (d, J = 2.5 Hz, 1 H), 7.83 (d, J = 2.5 Hz, 1 H), 4.56 (t, J = 2.5 Hz, 1 H), 3.75 (m, 2 H), 3.40 (m, 2 H), 2.95 (t, J = 12 Hz, 2 H), 1.67 (m, 10 H); ^{13}C NMR δ 158.7, 146.6, 139.3, 129.3, 120.8, 98.8, 67.2, 62.2, 36.6, 30.8, 29.4, 25.5, 25.0, 19.6. Anal. Calcd for $C_{14}H_{19}BrClNO_2$: C, 48.22; H, 5.49; N, 4.02. Found: C, 48.52; H, 5.42; N, 4.02.

3-Bromo-5-chloro-2-(4-hydroxybutyl)pyridine (6). A solution of the THP-protected alcohol **5** (2.0 g, 5.74 mmol) in ethanol (53 mL) was treated with pyridinium *p*-toluenesulfonate (148 mg, 0.59 mmol) and heated to 55 °C for 5.5 h. The solvent was removed under vacuum, and the colorless oil remaining was chromatographed on silica (60 g) with 35% ethyl acetate/hexane to afford the product alcohol **6** as a white solid, mp 55–56 °C (1.466 g, 97%): IR (Nujol mull) 3160, 1380, 1040 cm^{-1}; ^1H NMR δ 8.35 (d, J = 2 Hz, 1 H), 7.80 (d, J = 2 Hz, 1 H), 3.65 (t, J = 10 Hz, 2 H), 2.97 (s, 1 H), 2.90 (t, J = 10 Hz, 2 H), 1.71 (m, 4 H); ^{13}C NMR δ 158.6, 146.4, 139.5, 129.5, 121.0, 62.2, 36.2, 32.1, 24.4. Anal. Calcd for $C_9H_{11}BrClNO$: C, 40.86; H, 4.19; N, 5.29. Found: C, 41.02; H, 4.15; N, 5.14.

3-Bromo-5-chloro-2-(3-carboxypropyl)pyridine (9). A solution of the alcohol **6** (8.8 g, 33.3 mmol) in acetone (98 mL) at 0 °C was treated dropwise with Jones reagent[20] (21 mL, 56.2 mmol) over 30 min. Upon completion of the addition the reaction was stirred for 30 min at 0 °C. Isopropyl alcohol (20 mL) was then added at 5 °C and then the reaction stirred for 15 min. The dark green solids were filtered off and washed with isopropyl alcohol (100 mL). The solvent was removed under vacuum yielding a paste. This residue was treated with ethyl acetate (100 mL) and water (100 mL). The phases were separated, and the organic phase was extracted with aqueous saturated sodium bicarbonate (3 × 75 mL). The basic aqueous extracts were acidified to pH 2 with 6 N HCl and extracted with ethyl acetate (2 × 100 mL). The organic extracts were dried with magnesium sulfate, and the solvent was removed under vacuum affording the carboxylic acid **9** as an oil which solidified to a white solid on standing, mp 87–89 °C (5.69 g, 61%): IR (Nujol mull) 3050, 1710, 1575, 1280 cm^{-1}; ^1H NMR δ 10.5 (bs, 1 H), 8.44 (d, J = 2.5 Hz, 1 H), 7.83 (d, J = 2.5 Hz, 1 H), 2.98 (t, J = 7 Hz, 2 H), 2.45 (t, J = 7 Hz, 2 H), 2.05 (dd, J = 7, 7 Hz, 2 H); ^{13}C NMR δ 178.5, 157.6, 146.4, 139.8, 129.9, 121.1, 35.6, 33.3, 23.1. Anal. Calcd for $C_9H_9BrClNO_2$: C, 38.81; H, 3.26; N, 5.03. Found: C, 38.77; H, 3.23; N, 5.00.

3-Bromo-5-chloro-2-[3-[(*N*,*N*-dimethylamino)carbonyl]-propyl]pyridine (10). Dimethylamine gas was bubbled through a solution of the carboxylic acid **9** (200 mg, 0.719 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (DECD, 106 mg, 0.836 mmol) in methylene chloride (20 mL) at ambient temperature for 30 min. Water (15 mL), aqueous HCl (4 N, 15 mL), and saturated aqueous sodium chloride (10 mL) were added to the reaction. The organic phase was separated and treated with magnesium sulfate, and the solvent was removed under vacuum to yield the dimethylamide product as an oil (137 mg, 62%): IR (neat) 3420, 2940, 1640, 1430, 1640, 1430, 1050 cm^{-1}; ^1H NMR δ 8.42 (d, J = 2.5 Hz, 1 H), 7.82 (d, J = 2.5 Hz, 1 H), 3.01 (s, 3 H), 3.00 (t, J = 8 Hz, 2 H), 2.94 (s, 3 H), 2.40 (t, J = 8 Hz, 2 H), 2.08 (dt, J = 7, 7 Hz, 2 H); ^{13}C NMR δ 172.5, 158.2, 146.5, 139.4, 129.5, 121.1, 36.2, 35.4, 32.6, 29.7, 23.5. Anal. Calcd for $C_{11}H_{14}BrClN_2O$: C, 43.23; H, 4.62; N, 9.17. Found: C, 43.02; H, 4.50; N, 9.19.

3-Chloro-7,8-dihydro-5(2*H*)-quinolinone (15). The dimethylamide **10** (50 mg, 0.164 mmol) in diisopropyl ether (2 mL) was cooled to −70 °C, and *tert*-butyllithium (150 μL, 0.255 mmol) was added in one portion. The reaction was stirred for 45 min and then quenched with 2 N HCl. Water (10 mL) and diisopropyl ether (10 mL) were added and the phases separated. The aqueous phase was again extracted with diisopropyl ether (2 × 10 mL). The combined organic extracts were treated with sodium sulfate, and the solvent was removed under vacuum affording 24 mg of an amber oil. The oil was chromatographed on silica with 30% ethyl acetate/hexane yielding the azatetralone **15** as white needles, mp 84–86 °C (15.5 mg, 50%): IR (nujol) 2960, 2930, 2860, 1690, 1572, 1540, 1469, 1385, 1290, 1050, 990 cm^{-1}; ^1H NMR δ 8.58 (d, J = 2.5 Hz, 1 H), 8.18 (d, J = 2.5 Hz, 1 H), 3.10 (t, J = 10 Hz, 2 H), 2.65 (t, J = 10 Hz, 2 H), 2.16 (m, 2 H); ^{13}C NMR δ 196.6,

(18) Transmetalation of 2-bromo-3-fluoro- and 2-bromo-3-chloropyridine gave the 2-bromo-3-halo-4-lithiopyridines. Mallet, M.; Queguiner, G. *Tetrahedron* **1986**, *42*, 2253.

(19) Numerous examples of 2-halopyridine derivatives undergoing reaction with enolates, stabilized carbanions, nitrogen, and oxygen nucleophiles exist in the literature. For a general discussion, see: Barton, D. H. R.; Ollis, W. D. *Comprehensive Organic Chemistry*; Pergamon Press: New York, 1979; Vol. 2; p 30.

(20) Fieser, L. F.; Fieser, M. *Reagents for Organic Synthesis*; Wiley: New York, 1967; Vol. 1, p 142.

161.4, 152.2, 134.1, 130.8, 128.7, 38.2, 32.0, 21.7. Anal. Calcd for C_9H_8ClNO: C, 59.52; H, 4.44; N, 7.71. Found: C, 59.60; H, 4.19; N, 7.65.

3-Bromo-5-chloro-2-[2(*S*)-methyl-4-[(tetrahydro-2*H*-pyran-2-yl)oxy]butyl]pyridine (7). This series was synthesized using the same conditions employed for the desmethyl series (4.97 g, 65%): IR 2931, 2865, 1453, 1440, 1430, 1373, 1355, 1354, 1185, 1117, 1071, 1020, 975 cm^{-1}; ^1H NMR δ 8.41 (d, J = 2.5 Hz, 1 H), 7.82 (d, J = 2.5 Hz, 1 H), 4.55 (bs 1 H), 3.80 (m, 2 H), 3.42 (m, 2 H), 2.90 (m, 2 H), 1.62 (m, 9 H), 0.95, (d, J = 7 Hz, 1.5 H), 0.89 (d, J = 7 Hz, 1.5 H); α_D = +1.32° (c = 1.06; EtOH). Anal. Calcd for $C_{15}H_{21}BrClNO_2$: C, 49.67; H, 5.84; N, 3.86. Found: C, 49.89; H, 5.85; N, 3.94.

3-Bromo-5-chloro-2-(4-hydroxy-2(*S*)-methylbutyl)pyridine (8) (3.09 g, 84%): IR 3606, 3396, 2949, 2926, 2874, 1566, 1428, 1374, 1191, 1033, 997 cm^{-1}; ^1H NMR δ 8.42 (d, J = 2 Hz, 1 H), 7.85 (d, J = 2 Hz, 1 H), 3.72 (m, 2 H), 2.89 (dq, J = 6, 7 Hz, 2 H), 2.23 (dq, J = 6, 7 Hz, 1 H) 2.09 (m, 1 H), 1.59 (m, 2 H), 0.97 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 157.8, 146.2, 139.7, 129.5, 121.6, 60.6, 43.2, 39.3, 29.7, 19.9; α_D = −2.29 (c = 1.04 acetone). Anal. Calcd for $C_{10}H_{13}BrClNO$: C, 43.12; H, 4.70; N, 5.03. Found: C, 43.31; H, 4.65; N, 5.02.

3-Bromo-5-chloro-2-[2(*S*)-methyl-3-carboxypropyl]-pyridine (11) (755 mg, 68%): mp 59–60 °C; IR 3496, 2958, 1711, 1565, 1513, 1429, 1374, 1271, 1193, 1119, 1033 cm^{-1}; ^1H NMR δ 8.45 (d, J = 2 Hz, 1 H), 7.88 (d, J = 2 Hz, 1 H), 2.96 (d, J = 7 Hz, 2 H), 2.55 (m, 1 H), 2.35 (m, 2 H), 1.05 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 178.0, 156.9, 146.3, 139.8, 129.9, 121.7, 42.6, 40.7, 30.0, 19.8. Anal. Calcd for $C_{10}H_{11}BrClNO_2$: C, 41.06; H, 3.79; N, 4.79. Found: C, 41.36; H, 3.68; N, 4.77.

3-Bromo-5-chloro-2-[2(*S*)-methyl-3-[(*N*,*N*'-dimethylamino)carbonyl]propyl]pyridine (12) (190 mg, 41%): IR 3419, 2958, 2870, 1632, 1565, 1495, 1440, 1427, 1400, 1373, 1350, 1195, 1117, 1055, 1032 cm^{-1}; ^1H NMR δ 8.38 (d, J = 2 Hz, 1 H), 7.80 (d, J = 2 Hz, 1 H), 2.95 (s, 3 H), 2.87 (m, 2 H), 2.86 (s, 3 H), 2.61 (dq, J = 7, 6 Hz, 1 H), 2.29 (dq, J = 6, 7 Hz, 2 H), 0.98 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 171.9, 157.5, 146.3, 139.4, 129.5, 121.5, 43.6, 39.9, 37.4, 35.4, 29.9, 20.2. Anal. Calcd for $C_{12}H_{16}BrClN_2O$: C, 45.09; H, 5.05; N, 8.76. Found: C, 44.86; H, 5.11; N, 8.96.

(7*S*)-3-Chloro-7,8-dihydro-7-methyl-5(2*H*)-quinolinone (16) (15.4 mg, 57%): mp 50–52 °C; IR 2953, 1693, 1578, 1555, 1445, 1382, 1348, 1271, 1203, 1159, 907 cm^{-1}; ^1H NMR δ 8.62 (d, J = 2.5 Hz, 1 H), 8.20 (d, J = 2.5 Hz, 1 H), 3.11 (m, 1 H), 2.77 (m, 2 H), 2.38 (m, 2 H), 1.15 (d, J = 6 Hz, 3 H); ^{13}C NMR δ 196.9, 160.8, 152.4, 134.1, 130.8, 128.2, 46.3, 40.2, 29.2, 21.2; HRMS (EI) m/z (M^+) 195.044 34 (calcd for $C_{10}H_{10}ClNO$ 195.0449); α_D = +27 (c = 0.8 $CDCl_3$). Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.62; H, 5.24; N, 7.43.

2-Bromo-3-(4-hydroxy-1-oxobutyl)-5-chloropyridine (17). 2,3-Dibromo-5-chloropyridine **2** (4.0 g, 14.7 mmol) in diisopropyl ether (27 mL) was added dropwise to a solution of *n*-butyllithium (9.7 mL, 14.7 mmol) in isopropyl ether (40 mL) at −78 °C over 30 min. A creamy yellow precipitate formed on addition of **2** which was stirred 10 min after the addition was complete. Butyrolactone (2.53 g, 29.4 mmol) was added neat to the suspension and stirred for 10 min. The reaction was quenched with water and aqueous saturated ammonium chloride (1:1, 20 mL), and the contents were allowed to warm to ambient temperature, and extracted with ether (100 mL). The organic phase was washed with water (3 × 50 mL) and brine (50 mL) and treated with magnesium sulfate, and solvents were removed under vacuum to afford the crude product as a thick yellow oil (3.79 g). The crude product could be employed directly for the pyridinium chlorochromate oxidation or purified by chromatography to yield an off-white solid (2.59 g, 63%), mp 62–63 °C: IR 3598, 3443, 2928, 2877, 1705, 1600, 1565, 1522, 1395, 1194, 1122 cm^{-1}; ^1H NMR δ 8.35 (d, J = 2.5 Hz, 1 H), 7.62 (d, J = 2.5 Hz, 1 H), 3.70 (dd, J = 5, 6 Hz, 2 H), 3.03 (t, J = 7 Hz, 2 H), 1.96 (dd, J = 7, 6 Hz, 2 H), 1.41 (t, J = 5 Hz, 1 H); ^{13}C NMR δ 201.4, 149.8, 139.2, 136.6, 135.0, 131.7, 61.7, 39.3, 26.6. Anal. Calcd for $C_9H_9BrClNO_2$: C, 38.81; H, 3.26; N, 5.03. Found: C, 38.91; H, 3.22; N, 4.95.

2-Bromo-3-(5-hydroxy-1-oxopentyl)-5-chloropyridine (18). 2,3-Dibromo-5-chloropyridine **2** (3.0 g, 11.1 mmol) in diisopropyl ether (20 mL) was added to a solution of *n*-butyllithium (7.4 mL, 11.1 mmol in hexane) in diisopropyl ether (20 mL) at −78 °C. Five minutes after the addition of **2**, δ-valerolactone was added neat to the resulting yellow suspension. The reaction was stirred 10 min at −78 °C, water (2 mL) was then added, and the contents were allowed to warm to ambient temperature. Methylene chloride and water were added, the phases were separated, the organic phase was washed with brine and treated with sodium sulfate, and the solvent was removed under vacuum to yield an oil (2.47 g) which crystallized, mp 84–88 °C. Recrystallization of the crude product from cyclohexane yielded **18** as a white solid, mp 90–92 °C (1.2 g, 49%).

2-Bromo-3-(1,4-dioxobutyl)-5-chloropyridine (19). A suspension of pyridinium chlorochromate (112 mg, 0.539 mmol) in methylene chloride (0.7 mL) was charged with keto alcohol **17** (100 mg, 0.359 mmol) in methylene chloride (1.0 mL). After the reaction stirred for 3 h at ambient temperature it was diluted with ether (0.7 mL) and the organic phase decanted from a black gum. The gum was extracted with ether (2 × 0.7 mL), the combined organic extracts were filtered through a pad of silica, and solvents were removed under vacuum to afford a light brown oil (80 mg). Chromatography on silica eluting with 10% ethyl acetate/hexane yielded the product as a white solid (44 mg, 57% overall from **2**), mp 32–37 °C: IR 2981, 2901, 1709, 1200, 1524, 1533, 1391, 1353, 1121 cm^{-1}; ^1H NMR δ 9.83 (s, 1 H), 8.41 (d, J = 2.2 Hz, 1 H), 7.78 (d, J = 2.2 Hz, 1 H), 3.16 (dd, J = 6, 7 Hz, 2 H), 3.0 (dd, J = 5, 7 Hz, 2 H); ^{13}C NMR δ 199.7, 199.3, 150.0, 138.9, 137.0, 134.8, 131.8, 38.1, 34.8. Anal. Calcd for $C_9H_7BrClNO_2$: C, 39.09; H, 2.55; N, 5.07. Found: C, 39.16; H, 2.30; N, 5.03.

Registry No. **1**, 137628-16-1; **2**, 137628-17-2; **3**, 137628-32-1; **4**, 137628-33-2; **5**, 137628-18-3; **7**, 137628-20-7; **8**, 137628-21-8; **9**, 137628-22-9; **10**, 137628-23-0; **11**, 137628-24-1; **12**, 137628-25-2; **13**, 137628-26-3; **14**, 137628-27-4; **15**, 127724-75-8; **16**, 137628-28-5; **17**, 137628-29-6; **18**, 137628-30-9; **19**, 137628-31-0; dimethylamine, 124-40-3; butyrolactone, 96-48-0; δ-valerolactone, 542-28-9.

Simple Performic Acid Oxidation of Acetylthio Group to Sulfonic Acid and Its Application in Syntheses of 2-Substituted Taurines[1]

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The acetylthio group is convertible into a sulfonic acid group by several oxidative reagents such as peracetic acid,[2] potassium persulfate,[3] etc. Since such oxidants often require severe reaction conditions and/or complicated workups, we sought other reagents to circumvent these problems. Performic acid, containing 30% hydrogen peroxide and 98% formic acid in a 1:10 ratio, was found to give the best results. We now describe the successful application of this oxidant to the syntheses of 2-substituted taurines **5**, which we have previously prepared[4] by the substitution method.[5] Among the 2-substituted taurines, D-cysteinolic acid (**5e**)[4] is a marine taurine derivative.[6]

Six (hydroxyethyl)carbamates **2** were prepared from protected α-amino acids **1** by the reported method[4,7] as

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