ether, and washed successively with 0.25 N HCl (2 × 75 mL), saturated aqueous $NaHCO_3$ (2 × 75 mL), and brine (1 × 50 mL). The organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure with a rotary evaporator to afford 18.5 g of a clear oil. The material was purified by column chromatography (150 g of silica gel, eluted first with hexanes and then with EtOAc) to afford 12.25 g (95%) of a clear oil. IR ($CHCl_3$): 3020, 2990, 2950, 2880, 1740, 1660, 1450, 1265, 1095, 845 cm^{-1}. ^1H NMR: δ 0.06 (s, 3), 0.08 (s, 3), 0.85 (s, 9), 2.60 (m, 4), 3.17 (s, 3), 3.67 (s, 3), 3.70 (s, 3), 4.63 (m, 1). ^{13}C NMR: δ -5.28, -4.95, 17.70, 25.50, 31.73, 39.46, 42.41, 51.22, 61.07, 66.20, 171.27, 194.57. Anal. Calcd for $C_{14}H_{29}NO_5Si$: C, 52.63; H, 9.15; N, 4.38. Found: C, 52.47; H, 9.12; N, 4.29.

Methyl (*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-(dimethoxyphosphinyl)-5-oxohexanoate (15). Under an argon atmosphere into an oven-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar and rubber septum was placed 11.05 mL of 1.7 M *n*-BuLi in hexanes. The system was cooled to -78 °C and 2.20 mL (2.52 g, 20.3 mmol) of dimethyl methylphosphonate was added dropwise by syringe. During the addition, a mixture of 2 mL of THF and 2 mL of ether was added to the system to aid in stirring. The reaction mixture was stirred for 15 min after the completion of the addition and cooled to -110 °C (ether/liquid N_2). To the system was added streamwise a solution of 5.00 g (15.65 mmol) of amide **14** in 2 mL of a 1:1 mixture of ether and THF. The syringe that delivered the amide was rinsed with 0.5 mL of THF. The mixture was stirred at -110 °C for 15 min, then allowed to warm to -80 °C over 15 min, and stirred for an additional 15 min. An ice-cold mixture of 20 mL of 1 M H_3PO_4 and 60 mL of ether was added to the flask. The cooling bath was removed and the mixture allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc. The organic fractions were combined, dried over $MgSO_4$, and concentration under reduced pressure with a rotary evaporator to obtain 6.25 g of a clear oil. The material was purified by column chromatography (150 g of silica gel, 2:1 hexanes/EtOAc as eluant) to obtain 1.25 g of recovered amide **14** and 3.69 g (62%, 82% based on recovered starting material) of phosphonate **15** as a clear oil. The IR and ^1H NMR spectral data are in agreement with those previously reported for this compound.[1b] ^{13}C NMR: δ -5.12, -4.94, 17.75, 25.55, 42.00, 42.67 (d, J = 128.2), 50.93, 51.43, 52.86 (d, J = 1.6), 52.98 (d, J = 1.6), 65.26, 171.16, 199.78 (d, J = 6.4).

Registry No. 1, 91424-40-7; (±)-8, 57605-95-5; (*R*)-8, 42177-25-3; (*S*)-8, 15914-84-8; 9, 113794-42-6; (*R,R*)-10, 113794-43-7; (*S,S*)-10, 113794-49-3; 11, 113794-44-8; 12, 113794-45-9; 13, 113794-46-0; 14, 113794-47-1; 15, 96555-58-7; MeNHOMe, 6638-79-5; $H_3CCH_2CH_2CO_2CH_2CCl_3$, 57392-44-6; $EtOCOCH_2CH(OH)CH_2CO_2Et$, 32328-03-3; $MeP(O)(OEt)_2$, 756-79-6; *t*-BuSi(Me$_2$)Cl, 18162-48-6; 1-naphthaldehyde, 66-77-3; bis(dimethyl-*tert*-butylsilyl) ether, 91424-39-4; dimethyl 3-[(*tert*-butyldimethylsilyl)oxy]pentanedioate, 113794-48-2; 3-[(*tert*-butyldimethylsilyl)oxy]-5-(methoxycarbonyl)pentanoic acid, 109744-49-2.

Total Synthesis of Oxynitidine via Lithiated Toluamide-Imine Cycloaddition[1]

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Received December 7, 1987

We have demonstrated that *trans*-3-aryl-4-substituted-3,4-dihydro-1(2*H*)-isoquinolones are readily available from a one-pot procedure involving cycloaddition of lithiated *N,N*-diethyl-*o*-toluamides with benzaldimines followed by electrophilic trapping of the 4-lithio-3-aryl-3,4-dihydro-1-(2*H*)-isoquinolone that is generated under the basic reaction conditions.[3] We felt that this methodology would afford direct access to intermediates (e.g., **9**) for the synthesis of benzo[*c*]phenanthridine alkaloids.[4] We now report a total synthesis of the benzo[*c*]phenanthridine alkaloid oxynitidine (**13**)[5] that utilizes this annelation-trapping strategy to assemble all of the carbon atoms in a single step.

Preliminary Studies

In a model study, *N,N*-diethyl-*o*-toluamide (**1**) was deprotonated with LDA in THF at -70 °C and treated sequentially with 1 equiv of piperonal *N*-methylimine (**3**) and 1.5 equiv of bromoacetaldehyde dimethyl acetal to afford the *trans*-3,4-disubstituted 3,4-dihydroisoquinolone **4** in 54% yield (Scheme I). Numerous attempts were made to cyclize **4** to a tetracyclic compound under a variety of acidic conditions and with a number of Lewis acids.[6] However, these attempts were uniformly unsuccessful (<5% yield of cyclized products). On the basis of ^1H NMR spectroscopic evidence, the 3-aryl group and the 4-(2,2-dimethoxyethyl) side chain of **4** are pseudoaxially oriented[7] ($J_{3,4}$ = 0.0 Hz), which may account for the observed lack of intramolecular cyclization. The lack of propensity for cyclizations to occur in a related system was observed by Shamma and Tomlinson,[8] who were able to cyclodehydrate an acid of type **7** (specifically the 7,8-methylenedioxy analogue of **7**) only under specialized conditions (methanesulfonic acid, phosphorus pentoxide).[9] Accordingly, acetal **4** was hydrolyzed to the aldehyde **6**, which was oxidized with permanganate under phase-transfer conditions[10] to acid **7** (96% from **4**). Treatment of acid **7** with methanesulfonic acid-phosphorus pentoxide then gave the desired ketone **10** in 71% yield. Conversion to the benzo[*c*]phenanthridine **12** was then accomplished by utilizing Cushman and Cheng's protocol of sodium borohydride reduction followed by dehydration-dehydrogenation by heating in acetic acid with palladium on carbon.[11] Compound **12** was thus obtained in 47% yield along with a small amount (15%) of the hydrogenolysis product **14**.

Synthesis of Oxynitidine

For the preparation of oxynitidine (**13**), the readily available amide **2**[12] was condensed with **3** and treated with

(1) Contribution No. 761 from the Institute of Organic Chemistry.
(2) Syntex Postdoctoral Fellow, 1987-1988.

(3) (a) Clark, R. D. *Heterocycles* **1985**, *23*, 825. (b) Clark, R. D.; Jahangir *J. Org. Chem.* **1987**, *52*, 5378.
(4) Reviews on the benzophenanthridine alkaloids: (a) Krane, B. D.; Fagbule, M. O.; Shamma, M. *J. Nat. Prod.* **1984**, *47*, 1. (b) Simanek, V. In *The Alkaloids*; Brossi, A., Ed.; Academic: Orlando, FL, 1985; Vol. 26, pp 185-234.
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(6) These included the following: HCl/HOAc; H_2SO_4/HOAc; H_2SO_4 neat; 6 N HCl, dioxane; CH_3SO_3H, P_2O_5; $SnCl_4$; CF_3SO_3H in CH_2Cl_2.
(7) Cushman, M.; Choong, T. C.; Valka, S. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067.
(8) Shamma, M.; Tomlinson, H. H. *J. Org. Chem.* **1978**, *43*, 2852.
(9) Although the related acid **9** was cyclized to **11** under standard conditions (poly(phosphoric acid), 52% yield, ref 11), the yield of **10** was found to be considerably better under Shamma's conditions (vide infra).
(10) Herriott, A. W.; Picker, D. *Tetrahedron Lett.* **1974**, 1511.
(11) Cushman, M.; Cheng, L. *J. Org. Chem.* **1978**, *43*, 286.

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bromoacetaldehyde dimethyl acetal as before. However, a difficultly separable mixture of alkylated and unalkylated 3,4-dihydro-1(2*H*)-isoquinolone was obtained. We felt that the low reactivity of bromoacetaldehyde dimethyl acetal might be a contributing factor to the low yield of product and hence sought a more reactive electrophile.[13] Ethylene oxide proved to be the alkylating agent of choice and led to the formation of alcohol **5** in 68% yield. Oxidation of **5** was most satisfactorily carried out in two steps using Swern oxidation[14] to aldehyde **8** followed by permanganate oxidation,[10] which afforded the known acid **9** in 63% yield.[15] This acid was previously cyclized by Cushman and Cheng with poly(phosphoric acid) to ketone **11**, which was subsequently converted to nitidine chloride (**16**).[11] We cyclized **9** using methanesulfonic acid–phosphorus pentoxide[8] and obtained **11** in 80% yield. Acid **9** had spectral properties (^{1}H NMR, MS) in agreement with those reported[11] although our melting point was considerably higher than the reported value (Experimental Section). The derived ketone **11** had spectral properties and melting point in agreement with those reported and was identical (TLC) with an authentic sample.[11] Sodium borohydride reduction of **11** followed by heating in acetic acid with palladium on carbon afforded oxynitidine **13** in 49% yield accompanied by 15% of the hydrogenolysis product **15**.

Conclusion

Thus we have synthesized the benzo[*c*]phenanthridine alkaloid oxynitidine in six steps (17% overall yield) from amide **2** and imine **3**. Since both the intermediate ketone **11**[11] and oxynitidine[5f] have been converted to nitidine chloride **16**, our work also constitutes a formal total synthesis of this alkaloid. Our cycloaddition–electrophilic trapping approach offers a more direct route to key intermediates for benzo[*c*]phenanthridine synthesis (e.g., **9** and **11**) than the previous homophthalic ester[8]– and homophthalic anhydride[11]–imine condensation routes.

Experimental Section

Proton magnetic resonance spectra were measured on Varian HA-100 and Bruker WM 300 instruments and are reported in ppm downfield from an internal standard of tetramethylsilane. Mass spectra were obtained in either an Atlaswerke CH-4 or CH-7 instrument. Medium-pressure (flash) chromatography was performed with 230–400 Merck Kieselgel. Melting points are uncorrected. Elemental analyses were obtained from the Syntex analytical department.

6-Methylveratraldehyde. A solution of 6-bromoveratraldehyde ethylene acetal[16] (20.23 g, 70 mmol) in 200 mL of dry THF was cooled to −78 °C under nitrogen, and 52.4 mL of 1.6 *n*-butyllithium in hexane (84 mmol) was added dropwise with constant stirring. After 30 min at −78 °C, 20 mL of methyl iodide was added to the solution, and the resulting mixture was stirred for a further 1 h at this temperature. The mixture was then warmed slowly to room temperature and quenched with saturated ammonium chloride solution. The mixture was thoroughly extracted with ether, and the combined ether extracts were dried (Na_2SO_4). Removal of the solvent in vacuo gave 6-methylveratraldehyde ethylene acetal (16 g, 100%) as an oil that solidified on standing: NMR ($CDCl_3$) δ 7.25 (s, 1 H), 6.80 (s, 1 H), 6.00 (s, 1 H), 4.20 (m, 4 H), 4.00 (s, 6 H), 2.50 (s, 3 H). This compound was used in the next step without further purification.

A solution of the above acetal (15.5 g) in 100 mL of THF and 50 mL of 10% HCl solution was stirred at room temperature overnight. The reaction mixture was concentrated in vacuo and thoroughly extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo to give 11.36 g (91%) of 6-methylveratraldehyde as an oil that solidified on standing: mp 73–74 °C (lit.[17] mp 76 °C); NMR ($CDCl_3$) δ 10.32 (s, 1 H), 7.45 (s, 1 H), 6.82 (s, 1 H), 4.06 (s, 3 H), 4.03 (s, 3 H), 2.76 (s, 3 H). Anal. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.44; H, 6.63.

2-Methyl-4,5-dimethoxybenzoic Acid. To a stirred solution of 15 g of silver nitrate in 60 mL of water was added a solution of 3 g of sodium hydroxide in 60 mL of water, and the resulting mixture was stirred for 15 min. Silver oxide, thus formed, was filtered and washed several times with water until washings were free of nitrate ions. The wet silver oxide was transferred to a flask containing a solution of 12.0 g of sodium hydroxide in 100 mL of water, and the resulting mixture was stirred for 15 min at 50–60 °C before it was added to a solution of 11.0 g of 6-methylveratraldehyde in 100 mL of ethanol. Stirring was continued at this temperature until no more aldehyde was left (1–2 h). The reaction mixture was concentrated to half of its original volume and washed twice with ether. The aqueous layer was acidified with concentrated HCl and extracted thoroughly with CH_2Cl_2. The CH_2Cl_2 extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to give 11.56 g (91%) of 2-methyl-4,5-dimethoxybenzoic acid: mp 139–141 °C (EtOH–H_2O); NMR ($CDCl_3$) δ 7.64 (s, 1 H), 6.73 (s, 1 H), 3.95 (s, 6 H), 2.63 (s, 3 H).

2-Methyl-4,5-dimethoxy-*N*,*N*-diethylbenzamide (2). To a suspension of 2-methyl-4,5-dimethoxybenzoic acid (3.0 g) in 50 mL of CH_2Cl_2 containing 2 mL of pyridine was slowly added 20 mL of oxalyl chloride with stirring. After an additional 2 h of stirring, the excess of oxalyl chloride was removed in vacuo and the last traces of oxalyl chloride were removed by codistillation with benzene. The acid chloride thus obtained was redissolved in 150 mL of CH_2Cl_2 and carefully treated with 8 mL of diethylamine at 0 °C. The reaction mixture was diluted with water (20 mL), the organic layer was separated, and the aqueous layer was extracted twice with CH_2Cl_2. The organic extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to give 2-methyl-4,5-dimethoxy-*N*,*N*-diethylbenzamide as an oil: 3.47 g (90%); NMR ($CDCl_3$) 6.68 (s, 2 H), 3.97 (s, 3 H), 3.94 (s, 3 H), 3.75–2.90 (m, 4 H), 2.23 (s, 3 H), 1.50–0.85 (m, 6 H).

(±)-*trans*-3-(1,3-Benzodioxol-5-yl)-3,4-dihydro-4-(2,2-dimethoxyethyl)-2-methyl-1(2*H*)-isoquinolone (4). A solution of *N*,*N*-diethyl-*o*-toluamide (1) (1.79 g, 11 mmol) in 10 mL of THF was added dropwise to a solution of LDA (from 1.68 mL (12 mmol) of diisopropylamine and 7.5 mL (12 mmol) of 1.6 M *n*-BuLi in hexane) in 20 mL of THF at −70 °C. The reaction mixture was allowed to stir with gradual warming to −45 °C over 2 h and then cooled back to −70 °C. Bromoacetaldehyde dimethyl acetal (2.83 mL, 24 mmol) was added, and the resulting mixture was stirred at −70 °C for 1 h and then allowed to warm gradually to room temperature over a 3-h period. After quenching with saturated ammonium chloride solution, the resulting mixture was concentrated in vacuo, diluted with water, and thoroughly extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (40% EtOAc–hexane), affording 1.99 g (54%) of **4**: mp 133–134 °C (EtOAc); NMR ($CDCl_3$) δ 8.15 (m, 1 H), 7.40–7.30 (m, 2 H), 6.99 (m, 1 H), 6.63 (d, J = 8.5 Hz, 1 H), 6.50–6.42 (m, 2 H), 5.85 (m, 2 H), 4.62 (s, 1 H), 4.35 (dd, J = 6.7, 4.3 Hz, 1 H), 3.40 (s, 3 H), 3.31 (s, 3 H), 3.17–3.10 (m, 1 H), 3.14 (s, 3 H), 2.19–2.14 (m, 1 H), 1.95–1.92 (m, 1 H); MS *m/e* (relative intensity) 369 (6, M^+), 338 (6), 306 (6), 279 (100), 278 (34), 90 (5), 75 (18). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.27; H, 6.28; N, 3.76.

(±)-*trans*-3-(1,3-Benzodioxol-5-yl)-3,4-dihydro-4-(2-hydroxyethyl)-6,7-dimethoxy-2-methyl-1(2*H*)-isoquinolone (5). This reaction was carried out in the same manner as that described above except a solution of ethylene oxide (5 equiv) 1.3

(12) Amide **2** was prepared from 6-methylveratraldehyde; see Experimental Section.

(13) The lower yield in the dimethoxy case relative to **4** may relate to side reactions involving lithiation of the oxygenated 3,4-dihydro-1-(2*H*)-isoquinolone ring. The use of the very reactive electrophile *tert*-butyl bromoacetate did not lead to alkylated product.

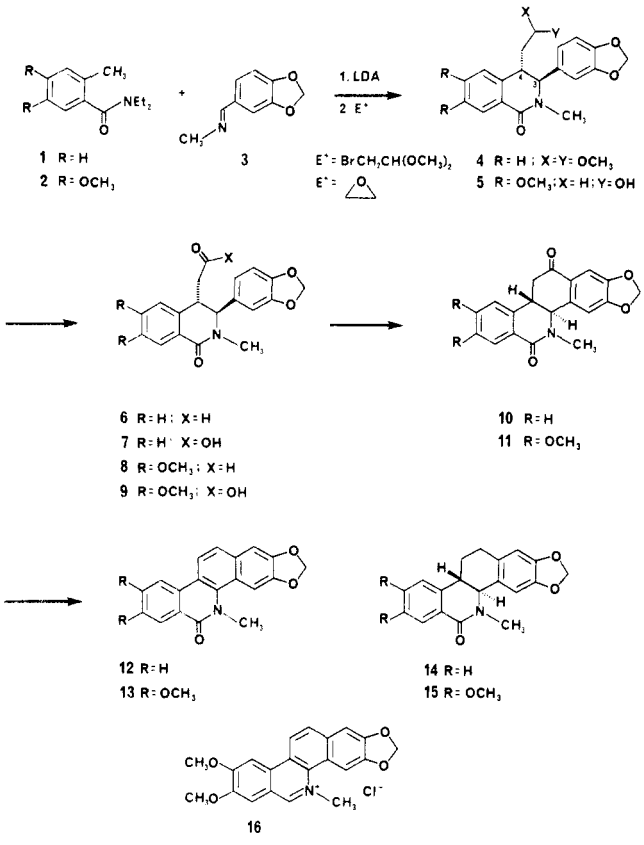
(14) Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.

(15) Direct oxidation of **5** to **9** could not be effected in reasonable yield, e.g., with phase transfer permanganate or Jones' oxidations.

(16) Charlton, J. L.; Alauddin, M. M. *J. Org. Chem.* **1986**, *51*, 3490.

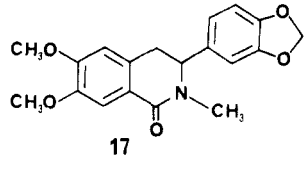
(17) Alexandre, St. P. *Helv. Chim. Acta* **1939**, *22*, 550.

Scheme I



M in diethyl ether was used as electrophile. The crude residue, after the usual workup, was chromatographed on silica gel (5% MeOH–CH_2Cl_2) to give **5** (68%): foam; NMR ($CDCl_3$) δ 7.65 (s, 1 H), 6.66 (d, J = 8.2 Hz, 1 H), 6.52–6.49 (m, 3 H), 5.88 (AB q, J = 1.4 Hz, 2 H), 4.52 (s, 1 H), 3.94 (s, 3 H), 3.92–3.77 (m, 2 H), 3.84 (s, 3 H), 3.70–3.62 (m, 1 H), 3.12 (s, 3 H), 2.14–2.02 (m, 1 H), 1.93 (m, 1 H), 1.90 (br s, 1 H, exchanges with D_2O); MS m/e (relative intensity) 385 (18), 340 (5), 222 (17), 191 (100), 164 (18). Exact mass calcd for $C_{21}H_{23}NO_6$: 385.1525. Found: 385.1523.

Also from the above reaction was isolated unalkylated product **17** in 10% yield: mp 207–210 °C; NMR ($CDCl_3$) δ 7.65 (s, 1 H), 6.69 (d, J = 8.5 Hz, 1 H), 6.55 (m, 2 H), 6.48 (s, 1 H), 5.91 (AB q, J = 1.3 Hz, 2 H), 4.64 (dd, J = 6.8, 2.9 Hz, 1 H), 3.94 (s, 3 H), 3.87 (s, 3 H), 3.58 (dd, J = 15.7, 6.8 Hz, 1 H), 3.06 (s, 3 H), 2.89 (dd, J = 15.7, 2.9 Hz, 1 H); MS m/e (relative intensity) 341 (21, M^+), 312 (8), 220 (31), 178 (100), 162 (28), 150 (85), 135 (29), 121 (9). Exact mass calcd for $C_{19}H_{19}NO_5$: 341.126. Found: 341.125.



(±)-*trans*-3-(1,3-Benzodioxol-5-yl)-4-(carboxymethyl)-3,4-dihydro-2-methyl-1(2*H*)-isoquinolone (7). A solution of 2 g (5.42 mmol) of the acetal **4** in 100 mL of acetone and 50 mL of 5% HCl solution was stirred for 1 h at 50–60 °C. The reaction mixture was concentrated in vacuo and thoroughly extracted with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried (Na_2SO_4), and evaporated to give 1.75 g (100%) of the aldehyde **6** as a gum: NMR ($CDCl_3$) δ 9.92 (s, 1 H), 8.20 (m, 1 H), 7.47 (m, 2 H), 7.10 (m, 1 H), 6.70 (s, 3 H), 5.93 (s, 2 H), 4.55 (s, 1 H), 3.70 (m, 2 H), 3.20 (s, 3 H), 3.00 (m, 1 H). The aldehyde **6** was used in the following reaction without further purification.

To a vigorously stirring solution of 600 mg (3.8 mmol) of potassium permanganate in 20 mL of water were added tetrabutylammonium bromide (200 mg) and 880 mg (2.72 mmol) of the aldehyde **6** in 20 mL of benzene. The mixture was stirred at room temperature until TLC showed complete consumption of the aldehyde (ca. 1 h), and it was then diluted with 50 mL of CH_2Cl_2 and treated with 10% sodium bisulfite solution to remove the excess permanganate. The resulting mixture was acidified with HCl, the organic layer was separated, and the aqueous layer was thoroughly extracted with CH_2Cl_2. The combined organic extracts were evaporated in vacuo, and the residue was dissolved in 10% sodium carbonate solution and washed twice with ether. The aqueous layer was made acidic with HCl and thoroughly extracted with CH_2Cl_2. The CH_2Cl_2 extracts were combined, washed with brine, dried (Na_2SO_4), and evaporated to yield a foam, which was crystallized from methanol to give 890 mg (96%) of the acid **7**: mp 190–192 °C; NMR ($CDCl_3$) δ 8.14 (m, 1 H), 7.37 (m, 2 H), 7.08 (m, 1 H), 6.64 (d, J = 7.9 Hz, 1 H), 6.55–6.51 (m, 2 H), 5.88 (AB q, J = 1.2 Hz, 2 H), 4.69 (s, 1 H), 3.54 (dd, J = 9.8, 4.4 Hz, 1 H), 3.15 (s, 3 H), 2.95 (dd, J = 16.8, 9.8 Hz, 1 H), 2.67 (dd, J = 16.8, 4.4 Hz, 1 H); MS m/e (relative intensity) 339 (58, M^+), 324 (3), 279 (100), 218 (6), 172 (8), 164 (49), 148 (77). Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.26; H, 5.01; N, 4.13. Found: C, 66.85; H, 4.96; N, 4.10.

(±)-*trans*-3-(1,3-Benzodioxol-5-yl)-4-(carboxymethyl)-3,4-dihydro-6,7-dimethoxy-2-methyl-1(2*H*)-isoquinolone (9). A solution of oxalyl chloride (0.9 mL, 10 mmol) in 20 mL of dry CH_2Cl_2 was cooled under nitrogen to −60 °C. To this a solution of 1.8 mL of dimethyl sulfoxide (25 mmol) in 10 mL of CH_2Cl_2 was added, and the resulting mixture was stirred for 10 min at −60 °C. A solution of the alcohol **5** (3 g, 7.8 mmol) in 10 mL of CH_2Cl_2 was added to the above solution, the resulting mixture was stirred for a further 15 min, and then 7 mL (50 mmol) of dry triethylamine was added. The cooling bath was removed, the reaction mixture was allowed to warm to room temperature, 30 mL of water was added, and stirring was continued for a further 10 min. The organic layer was separated and the aqueous layer was extracted several times with CH_2Cl_2. The combined CH_2Cl_2 extracts were washed with brine, dried (Na_2SO_4), and evaporated to give a residue that was chromatographed on silica gel (33% hexane–EtOAc) to give 2.1 g (70%) of the aldehyde **8** as a foam: NMR ($CDCl_3$) δ 9.86 (s, 1 H), 7.64 (s, 1 H), 6.68 (d, J = 8.4 Hz, 1 H), 6.59–6.56 (m, 2 H), 6.46 (s, 1 H), 5.90 (AB q, J = 1.3 Hz, 2 H), 4.47 (s, 1 H), 3.94 (s, 3 H), 3.83 (s, 3 H), 3.56 (dd, J = 8.1, 4.3 Hz, 1 H), 3.13 (dd, J = 18.7, 8.1 Hz, 1 H), 3.08 (s, 3 H), 2.80 (dd, J = 18.7, 4.3 Hz, 1 H); MS m/e (relative intensity) 383 (16, M^+), 355 (9), 339 (17), 324 (4), 191 (100). The aldehyde **8** was used in the next step without further purification.

The aldehyde **8** was oxidized to the corresponding acid **9** in 90% yield with potassium permanganate under phase-transfer conditions as described for the oxidation of **6**: mp 228–229 °C (MeOH) (lit.[11] mp 206–207 °C); NMR ($CDCl_3$) δ 9.30 (s, 1 H, exchanges with D_2O), 7.66 (s, 1 H), 6.69 (d, J = 8.3 Hz, 1 H), 6.58–6.54 (m, 3 H), 5.90 (AB q, J = 1.4 Hz, 2 H), 4.66 (s, 1 H), 3.96 (s, 3 H), 3.84 (s, 3 H), 3.47 (dd, J = 9.7, 4.3 Hz, 1 H), 3.15 (s, 3 H), 2.96 (dd, J = 16.8, 9.7 Hz, 1 H), 2.69 (dd, J = 16.8, 4.3 Hz, 1 H); MS m/e (relative intensity) 399 (51, M^+), 339 (39), 236 (10), 208 (100), 191 (34), 164 (45). Anal. Calcd for $C_{21}H_{21}NO_7$: C, 63.15; H, 5.30; N, 3.51. Found: C, 62.96; H, 5.21; N, 3.46.

(±)-*trans*-4b,5,11b,12-Tetrahydro-12-methyl-[1,3]benzodioxolo[5,6-*c*]phenanthridine-6,13-dione (10). A solution of 2.5 g of phosphorus pentoxide in 17 mL of methanesulfonic acid was warmed to 50 °C and to this was added 250 mg (0.74 mmol) of the acid **7**. The reaction mixture was stirred for 2 h at 50 °C, poured cautiously onto crushed ice, and extracted with $CHCl_3$. The $CHCl_3$ extracts were combined, washed successively with 10% sodium hydroxide solution, water, and brine, and dried (Na_2SO_4). The solvent was removed in vacuo and the residue was crystallized from $CHCl_3$–MeOH to give the ketone **10** (167 mg, 71%); mp 249–252 °C; NMR ($CDCl_3$) δ 8.16 (dd, J = 7.6, 1.4 Hz, 1 H), 7.54 (dt, J = 7.6, 1.4 Hz, 1 H), 7.47 (s, 1 H), 7.44 (t, J = 7.5 Hz, 1 H), 7.24 (d, J = 7.6, 1 H), 6.91 (s, 1 H), 6.10 (AB q, J = 1.2 Hz, 2 H), 4. 94 (d, J = 11.5, 1 H), 3.60 (m, 1 H), 3.33 (dd, J = 15.8, 4.3 Hz, 1 H), 3.16 (s, 3 H), 2.63 (dd, J = 15.8, 14.4 Hz, 1 H); MS m/e (relative intensity) 321 (89, M^+), 320 (32), 306 (6), 292 (74), 279 (100), 264 (22), 190 (51), 147 (78). Anal. Calcd for $C_{19}H_{15}NO_4$: C, 71.02; H, 4.71; N, 4.36. Found: C, 70.99; H, 4.68; N, 4.28.

(±)-*trans*-4b,5,11b,12-Tetrahydro-2,3-dimethoxy-12-methyl-[1,3]benzodioxolo[5,6-*c*]phenanthridine-6,13-dione (11): 80% yield; mp 272–274 °C (lit.[11] mp 272–274 °C); NMR ($CDCl_3$) δ 7.67 (s, 1 H), 7.46 (s, 1 H), 6.94 (s, 1 H), 6.69 (s, 1 H),

6.10 (AB q, J = 1.2 Hz, 2 H), 4.90 (d, J = 11.7 Hz, 1 H), 3.96 (s, 3 H), 3.95 (s, 3 H), 3.55 (m, 1 H), 3.31 (dd, J = 15.9, 4.3 Hz, 1 H), 3.17 (s, 3 H), 2.64 (dd, J = 15.9, 13.9 Hz, 1 H); MS m/e (relative intensity) 381 (54, M^+), 353 (7), 352 (11), 350 (7), 232 (12), 191 (18), 165 (100), 147 (16). This compound was identical (TLC) with an authentic sample.[11]

12-Methyl-[1,3]benzodioxolo[5,6-*c*]phenanthridin-13(12*H*)-one (12). The ketone **10** (400 mg, 1.25 mmol) was dissolved in 100 mL of 2-propanol by warming on a steam bath, and the solution was treated with 200 mg of $NaBH_4$ at room temperature. After 3 h, the solvent was removed in vacuo and the residue was cautiously acidified with concentrated HCl and extracted with $CHCl_3$. The combined $CHCl_3$ extracts were washed successively with 2% sodium hydroxide solution, water, and brine, dried (Na_2SO_4), and evaporated. The crude mixture of alcohols thus obtained was dissolved in 100 mL of acetic acid and stirred at reflux with 200 mg of 10% Pd–C overnight. After cooling to room temperature, the reaction mixture was filtered through Celite, and the residue was washed with $CHCl_3$. The combined filtrate and washings were concentrated in vacuo, and the residue was treated with 2% sodium hydroxide solution and extracted thoroughly with $CHCl_3$. The combined $CHCl_3$ extracts were washed with brine, dried (Na_2SO_4), and evaporated, and the residue was chromatographed on silica gel ($CHCl_3$) to give 179 mg (47%) of **12**: mp 235–237 °C; NMR ($CDCl_3$) δ 8.54 (d, J = 7.9 Hz, 1 H), 8.25 (d, J = 7.9 Hz, 1 H), 8.10 (d, J = 8.8 Hz, 1 H), 7.76 (t, J = 8.3 Hz, 1 H), 7.62 (s, 1 H), 7.60–7.55 (m, 2 H), 7.17 (s, 1 H), 6.10 (s, 2 H), 3.97 (s, 3 H); MS m/e (relative intensity) 303 (100, M^+), 302 (82), 274 (24), 245 (18), 216 (17). Exact mass calcd for $C_{19}H_{13}NO_3$: 303.0895. Found: 303.0892. Anal. Calcd for $C_{19}H_{13}NO_3$: C, 75.24; H, 4.32; N, 4.62. Found: C, 75.29; H, 4.36; N, 4.57.

Also isolated was 58 mg (15%) of the tetrahydro compound **14**: mp 192–193 °C; NMR ($CDCl_3$) δ 8.10 (dd, J = 7.7, 1.4 Hz, 1 H), 7.48 (dt, J = 7.5, 1.5 Hz, 1 H), 7.39 (t, J = 7.5, 1.3 Hz, 1 H), 7.30 (d, J = 7.5 Hz, 1 H), 6.72 (s, 1 H), 6.66 (s, 1 H), 5.96 (AB q, J = 1.4 Hz, 2 H), 4.72 (d, J = 11.5 Hz, 1 H), 3.13 (dt, J 12.2, 3.1 Hz, 1 H), 3.11 (s, 3 H), 3.01–2.77 (m, 2 H), 2.55–2.47 (m, 1 H), 1.66 (dq, J = 11.9, 4.7 Hz, 1 H); MS m/e (relative intensity) 307 (76, M^+), 279 (100), 278 (59), 189 (19), 172 (21). Exact mass calcd for $C_{19}H_{17}NO_3$: 307.1208. Found: 307.1207. Anal. Calcd for $C_{19}H_{17}NO_3$: C, 74.25; H, 5.58; N, 4.56. Found: C, 74.35; H, 5.53; N, 4.51.

Oxynitidine (2,3-Dimethoxy-12-methyl-[1,3]benzodioxolo[5,6-*c*]phenanthridin-13(12*H*)-one) (13). The ketone **11** (200 mg) was reduced and dehydrogenated as described for **10** to give a mixture that was chromatographed on silica gel (3% MeOH–CH_2Cl_2) to give 74 mg (49%) of oxynitidine **13**: mp 280–283 °C (lit.[5f] mp 284–285 °C); NMR ($CDCl_3$) δ 8.00 (d, J = 8.7 Hz, 1 H), 7.94 (s, 1 H), 7.65 (s, 1 H), 7.60 (s, 1 H), 7.57 (d, J = 8.7 Hz, 1 H), 7.19 (s, 1 H), 6.11 (s, 2 H), 4.11 (s, 3 H), 4.06 (s, 3 H), 3.99 (s, 3 H); MS m/e (relative intensity) 363 (100, M^+).

Also isolated was 30 mg (15%) of the tetrahydro compound **15**: mp 225–227 °C; NMR ($CDCl_3$) δ 7.64 (s, 1 H), 6.77 (s, 1 H), 6.74 (s, 1 H), 6.66 (s, 1 H), 5.96 (AB q, J = 1.9 Hz, 2 H), 4.70 (d, J = 11.4 Hz, 1 H), 3.96 (s, 3 H), 3.95 (s, 3 H), 3.11 (s, 3 H), 3.10–2.78 (m, 3 H), 3.50 (m, 1 H), 2.70 (m, 1 H); MS m/e (relative intensity) 367 (100, M^+), 252 (6), 339 (93), 338 (36), 324 (15), 232 (31), 165 (92). Exact mass calcd for $C_{21}H_{21}NO_5$: 367.1420. Found: 367.1422.

Acknowledgment. We thank Dr. J. M. Muchowski for his constant encouragement and advice during the course of this work. We also thank Professor M. Cushman for providing a sample of compound **11**. The manuscript was prepared by Lani Russell.

Registry No. **1**, 2728-04-3; **2**, 113975-92-1; **2** (acid), 20736-28-1; **2** (acid chloride), 91940-89-5; **3**, 113975-93-2; **4**, 113975-94-3; **5**, 113975-95-4; **6**, 113975-96-5; **7**, 113975-97-6; **8**, 113975-98-7; **9**, 64036-04-0; **10**, 113975-99-8; **11**, 64036-03-9; **12**, 113976-00-4; **13**, 548-31-2; **14**, 113976-01-5; **15**, 56221-65-9; **17**, 87922-31-4; $BrCH_2CH(OMe)_2$, 7252-83-7; 6-bromoveratraldehyde ethylene acetal, 103477-58-3; 6-methylveratraldehyde ethylene acetal, 113976-02-6; 6-methylveratraldehyde, 7721-62-2; ethylene oxide, 75-21-8.

Highly Reactive Copper- and Nickel-Mediated Coupling of Aroyl Chlorides

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Received November 10, 1987

Reductive coupling of benzoyl chlorides using sodium amalgam,[1-4] lithium amalgam,[5] tetracarbonylnickel,[6] pentacarbonyliron,[7] hexaalkylditin,[8] 1,2:5,6-dibenzocyclooctatetraene dianion,[9] and mercury cathode[10,11] to give a mixture of *cis*- and *trans*-α,α'-stilbenediol dibenzoates has been previously reported. The mechanism proposed involves reduction of the acid chloride to generate the acyl radical.[7,12] Recently, we have found similar results using highly reactive zerovalent copper and nickel.

We previously reported the direct oxidative addition of highly reactive zerovalent copper to organic halides.[13-17] The exceptionally high reactivity of this copper suggests that it may also be a very good electron donor to carry out the reductive coupling of acid chlorides. In this paper, we report the results of this study.

Table I summarizes some reactions of aroyl chlorides with highly reactive zerovalent copper.[18] The yields are superior to those reported earlier using sodium amalgam (0–10%),[1-4] tetracarbonylnickel (0–30%),[6] pentacarbonyliron (52–56%),[7] hexaalkylditin (20–64%),[8] and 1,2:5,6-dibenzocyclooctatetraene dianion (51%).[9] The reaction conditions are extremely mild (−78 °C) and the stereoselectivity (predominantly *cis* isomer)[12] is considerably higher than reported previously.[1-11] It is also noteworthy that the effects of solvent on the reductive

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(18) Spectral data are as follows. *cis-p,p'*-Dichlorostilbene-α,α'-diol bis(*p*-chlorobenzoate): mp 167–168 °C; IR (KBr) 1740, 1590, 1485, 1400, 1265, 1240, 1170, 1080, 1045, 1005, 845, 820, 745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.25 (d, 4 H), 7.32 (d, 4 H), 7.36 (d, 4 H), 7.94 (d, 4 H). *cis*-α,α'-Stilbenediol bis(*p*-chlorobenzoate): mp 159–161 °C; IR (KBr) 1740, 1590, 1485, 1440, 1400, 1250, 1235, 1125, 1105, 1080, 1005, 840, 760, 745, 690, 670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26 (m, 6 H), 7.35 (d, 4 H), 7.39 (d, 4 H), 7.97 (d, 4 H); ^{13}C NMR ($CDCl_3$) δ 127.57, 128.44, 128.96, 129.09 (2 C), 131.43, 133.03, 139.06, 140.27, 163.30; MS (EI) m/e (relative intensity) 488 (M^+, 1.1), 139 (100.0). Calcd for $C_{28}H_{18}O_4Cl_2$ (M^+) m/e 488.0582; found m/e 488.0592. *trans*-α,α'-Stilbenediol bis(*p*-chlorobenzoate): mp 231–232 °C; MS (EI) m/e (relative intensity) 488 (M^+, 0.6), 139 (100.0). *p,p'*-Dichlorobenzil: mp 194–196 °C (lit.[30] mp 195–197 °C); IR (KBr) 1660, 1585, 1570, 1485, 1400, 1315, 1205, 1170, 1090, 1075, 1005, 875, 830, 760, 725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.50 (d, 4 H), 7.92 (d, 4 H).

0022-3263/88/1953-2381$01.50/0