30 g (85% yield) of (*R,S*)-1; ^{1}H NMR ($CDCl_3$) δ 3.68 (3 H, s), 3.15–2.98 (2 H, m), 2.73–2.62 (1 H, m), 2.31 (3 H, s), 1.22 (3 H, d). Anal. Calcd for $C_7H_{12}O_3S$: C, 47.71; H, 6.86; S, 18.19. Found: C, 47.50; H, 7.00; S, 18.22.

Ethyl (*R,S*)-2-Mercaptopropionate (4). 2-Mercaptopropionic acid (20 g, 189 mmol) and *p*-toluenesulfonic acid (200 mg, 1 mmol) were dissolved in ethanol (200 mL). The solution was refluxed for 16 h, and the solvent was evaporated. The residue was dissolved in ether, washed with 5% aqueous sodium hydroxide, dried (Na_2SO_4), and evaporated to dryness, affording 25 g (98% yield) of (*R,S*)-4; ^{1}H NMR ($CDCl_3$) δ 4.17 (2 H, q), 3.50 (1 H, m), 2.13 (1 H, d), 1.52 (3 H, d), 1.28 (3 H, t). Anal. Calcd for $C_5H_{10}O_2S$: C, 44.75; H, 7.51; S, 23.89. Found: C, 44.61; H, 7.55; S, 23.95.

Ethyl (*R,S*)-2-(Acetylthio)propionate (2). Acetyl chloride (16 g, 205 mmol), dissolved in anhydrous diethyl ether, was added dropwise to a solution of (*R,S*)-4 (26 g, 194 mmol) and triethylamine (30 g, 208 mmol) in anhydrous diethyl ether (300 mL). The mixture was stirred overnight at room temperature. The precipitate was filtered off, and the solution was washed with 5% hydrochloric acid and dried (Na_2SO_4). The solvent was evaporated, and the residue was purified by chromatography on silica gel, using hexane/ether (95:5) as eluant, affording 25.9 g (76% yield) of (*R,S*)-2; ^{1}H NMR ($CDCl_3$) δ 4.10 (1 H, q), 4.06 (2 H, q), 2.28 (3 H, s), 1.46 (3 H, d), 1.22 (3 H, t). Anal. Calcd for $C_7H_{12}O_3S$: C, 47.71; H, 6.86; S, 18.19. Found: C, 47.63; H, 6.77; S, 18.24.

Enzymatic Hydrolysis of Methyl (*R,S*)-3-(Acetylthio)-2-methylpropionate (1). To a magnetically stirred suspension of (*R,S*)-1 (2 g, 11 mmol) in 0.05 N phosphate buffer, pH 7 (25 mL), at 25 °C was added porcine pancreatic lipase (150 mg), and the pH was maintained at 7 with 0.05 aqueous sodium hydroxide. The hydrolysis was allowed to proceed to 60% of conversion (5 h). The reaction mixture was extracted with ether. The organic layer was washed with 5% aqueous sodium hydroxide, dried (Na_2SO_4), and then evaporated to dryness. Chromatography on silica gel using hexane/ether (95:5) as eluant afforded 570 mg (28% yield) of (*S*)-(−)-1: $[\alpha]^{25}_D$ = −13.1° (*c* = 1, $CHCl_3$), ee = 20%.

Enzymatic Thiotransesterification of Methyl (*R,S*)-3-(Acetylthio)-2-methylpropionate (1). To a solution of (*R,S*)-1 (2 g, 11 mmol) and 1-propanol (3 g, 50 mmol) in hexane (17 mL) was added porcine pancreatic lipase (2 g), and the suspension was stirred at 25 °C. After 72 h (51% conversion), the enzyme was filtered off, and the solution was diluted with water and extracted with ether. The organic layer was dried (Na_2SO_4) and evaporated to dryness. Chromatography on silica gel with hexane/ether (95:5) as eluant afforded 840 mg (42% yield) of (*S*)-(−)-1 [$[\alpha]^{25}_D$ = −62.7° (*c* = 1, $CHCl_3$), ee = 95%] and 590 mg (39% yield) of (*R*)-(+)-methyl 3-mercapto-2-methylpropionate (3) [$[\alpha]^{25}_D$ = +26.2° (*c* = 1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.69 (3 H, s), 2.83–2.55 (3 H, m), 1.48 (1 H, t), 1.23 (3 H, d)]. Anal. Calcd. for $C_5H_{10}O_2S$: C, 44.75; H, 7.51; S, 23.89. Found: C, 44.90; H, 7.48; S, 23.79.

Acetylation of (*R*)-(+)-Methyl 3-Mercapto-2-methylpropionate (3). (*R*)-3, $[\alpha]^{25}_D$ = +26.2° (*c* = 1, $CHCl_3$) (500 mg, 3.7 mmol), was dissolved in acetic anhydride (2 mL). The solution was stirred for 8 h at 60 °C. The mixture was diluted with ether and washed with aqueous sodium carbonate. The organic layer was dried (Na_2SO_4) and evaporated to dryness. Chromatography on silica gel with hexane/ether (95:5) as eluant afforded 550 mg (83% yield) of (*R*)-(+)-1; $[\alpha]^{25}_D$ +58.2° (*c* = 1, $CHCl_3$), ee = 88%.

Enzymatic Hydrolysis of Ethyl (*R,S*)-2-(Acetylthio)-propionate (2). To a magnetically stirred suspension of (*R,S*)-2 (2 g, 11 mmol) in 0.05 N phosphate buffer, pH 7 (25 mL) at 25 °C, was added lipase P (150 mg), and the pH was maintained at 7 with 0.05 N aqueous sodium hydroxide. The hydrolysis was allowed to proceed to 65% of conversion (4 h). The reaction mixture was extracted with ether, dried (Na_2SO_4), and evaporated to dryness. Chromatography on silica gel, using hexane/ether (98:2) as eluant, afforded 600 mg (30% yield) of (*S*)-(−)-2; $[\alpha]^{25}_{578}$ = −15.3° (*c* = 1, $CHCl_3$), ee = 11%.

Enzymatic Thiotransesterification of Ethyl (*R,S*)-2-(Acetylthio)propionate (2). To a solution of (*R,S*)-2 (2 g, 11 mmol) and 1-propanol (3 g, 50 mmol) in hexane (17 mL) was added lipase P (2 g), and the suspension was stirred at 25 °C. After 32 h (55% conversion), the enzyme was filtered off, and the solution was diluted with water and extracted with ether. The organic layer was dried (Na_2SO_4) and evaporated to dryness. Chromatography on silica gel with hexane/ether (98:2) as eluant afforded 800 mg (40% yield) of (*S*)-(−)-2 [$[\alpha]^{25}_{578}$ = −110° (*c* = 1, $CHCl_3$), ee = 80%] and 426 mg (28% yield) of (*R*)-(+)-4 [$[\alpha]^{25}_D$ = +27.1° (*c* = 1, $CHCl_3$), ee = 45%].

Registry No. (*R,S*)-1, 97101-46-7; (*S*)-(−)-1, 86961-08-2; (*R*)-(+)-1, 86961-07-1; (*R,S*)-2, 128899-61-6; (*S*)-(−)-2, 128822-70-8; (*R*)-(+)-3, 86961-09-3; (*R*)-(+)-4, 103616-07-5; (*R,S*)-4, 66707-26-4; methyl methacrylate, 80-62-6; thioacetic acid, 507-09-5; 2-mercaptopropionic acid, 79-42-5; lipase P, 9001-62-1.

An Asymmetric Synthesis of Aporphine and Related Alkaloids via Chiral Formamidines. (+)-Glaucine, (+)-Homoglaucine, and (−)-8,9-Didemethoxythalisopavine

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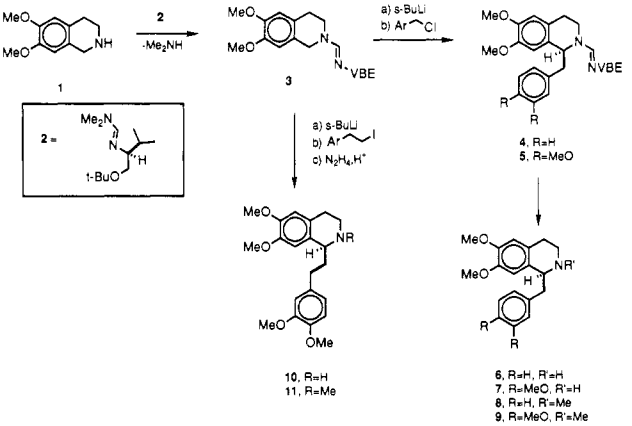
The use of chiral formamidines as a tool for reaching a number of chiral nonracemic alkaloids has been demonstrated in earlier reports from this laboratory.[1] The fact that they are prepared in either racemic fashion or as pure enantiomers makes the formamidine methodology a rather viable route to these systems and other elaborated amines.[2]

We now report further developments in this area by describing our synthesis of the natural aporphine (+)-glaucine (**12**), the homoaporphine (+)-homoglaucine (**13**), and the isopavine (−)-didemethoxythalisopavine (**15**), all reached in high enantiomeric excess starting from the readily available dimethoxytetrahydroisoquinoline **1**.[3] The



synthetic route followed was similar to that reported earlier[1] and required the attachment of the chiral auxiliary via the dimethylamino-substituted formamidine **2**. Thus, heating **1** and **2** in toluene gave the requisite formamidine **3** in 90–92% yield. The key asymmetric step in the entire sequence was implemented by metalation of **3** with *sec*-butyllithium at −78 °C followed by cooling the resulting lithio anion to −100 °C and adding the appropriate aryl-alkyl halide. In this fashion we obtained two adducts **4** and **5** prepared from addition of benzyl chloride and 3,5-

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0022-3263/90/1955-5659$02.50/0

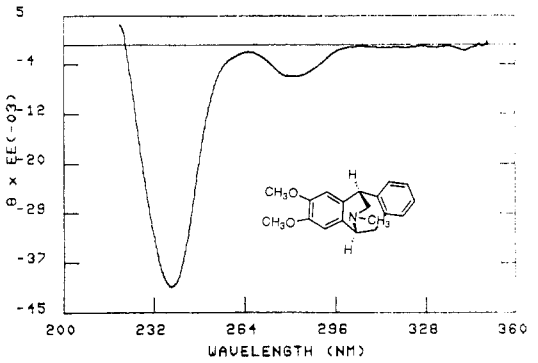


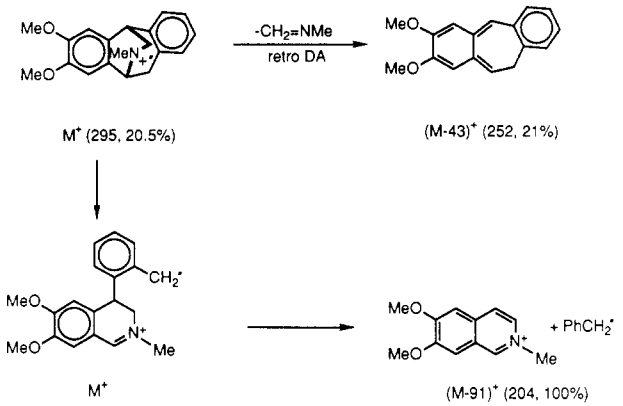
Figure 1. CD spectrum of **15** in methanol.

dimethoxybenzyl chloride, respectively. Using a more recent modification and improvement in the experimental procedure, we found that the adducts need not be removed from the reaction vessel. The THF solution was quenched with methanol and after in vacuo removal of the volatiles, the hydrazine–acetic acid–ethanol solution was added to remove the formamidine auxiliary.

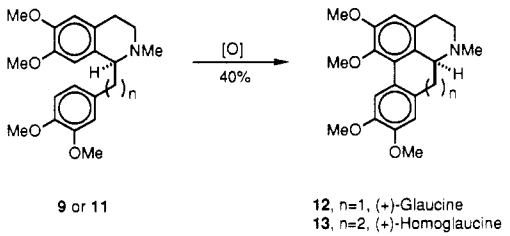
Since all the target compounds in this study contained an *N*-methyl group, the NH compounds **6** and **7** were treated with a 37% formalin solution and sodium borohydride, furnishing the required intermediates **8** and **9** after chromatography, in 70 and 66% overall yields (from **3**), respectively. The final step to the aporphines was next implemented and several techniques using nonphenolic oxidative couplings were considered. Since a recent report using ruthenium tetrakis(trifluoroacetate)[4] claimed to be superior to the earlier methods using vanadium oxyfluoride[5] or thallium trifluoroacetate,[6] this was promptly attempted on the tetramethoxy isoquinoline **9**. However, repeating the oxidative coupling as described in the literature gave little or none of the expected product. After consultation with the authors,[4] who informed us that it was necessary to utilize *hydrated* ruthenium salts and that the source of the reagent was also crucial to the success of the coupling, we were able to affect the oxidative coupling to (+)-glaucine (**12**) in 40% yield. Alternatively, we were also able to reach this alkaloid by using the VOF_3–TFAA–FSO_3H[5] or the TTFA[6] reagent, each producing the product in 40% yield. The specific rotation of glaucine obtained from this route was +100° and compared to the literature value of +115° indicated an optical purity of 87%. However, earlier studies from this laboratory,[1] which described the synthesis of **7**, led to (−)-norcoralydine in 98.5% ee. Since it is hard to imagine any loss of optical activity in going from **7** to (−)-norcoralydine, this supported our contention that the specific rotation obtained for glaucine **12** was not necessarily an accurate representation of its enantiomeric purity; a contention that has been repeatedly stated on earlier occasions by the senior author. Whether the rotational discrepancies were the result of polarimeter performance, slight impurities, or operator error, it serves to indicate that one should always be on guard when estimating enantiomeric purity by optical rotation.

The route to (+)-homoglaucine (**13**) required that we first prepare (+)-homolaudanosine (**11**) reported earlier.[1] Using the above-mentioned experimental improvements, now gave us an overall yield of 60%, compared to an earlier yield of 46%. When this material was subjected to the

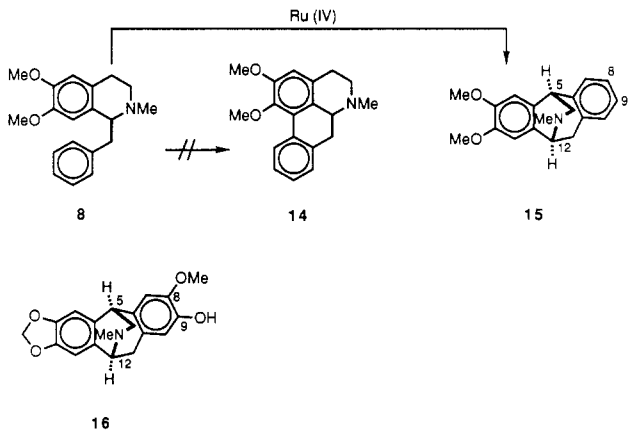
Scheme I



oxidative coupling using TTFA we obtained a 40–45% yield of the homoaporphinoid system (+)-**13**.



Treatment of the isoquinoline **8** with the ruthenium oxidizing agent, in an attempt to prepare optically active nuciferine **14**, gave a single product, which did not show any characteristics of (+)-nuciferine (^1H NMR,[7] ^{13}C NMR,[8] CD spectrum,[9] and mass spectrum). It was found after



complete spectral examination that the product from the oxidation of **8** was, in fact, an isopavine (**15**), which was obtained in 66% yield. Confirmation of the structure of the isopavine was gathered first by comparison with the CD spectrum of (−)-amurensine (**16**),[10] which was very similar. Both compounds exhibited split negative CD curves centered at 283–285 and 238–240 nm (Figure 1). (Other isopavines are also known[11] to possess the same absolute configuration as amurensine and **15**, namely, 5*S*,12*S*.) Another valuable set of data that confirmed the structure of **15** was the mass spectrum. The fragmentation pattern exhibited the typical behavior of the isopavine

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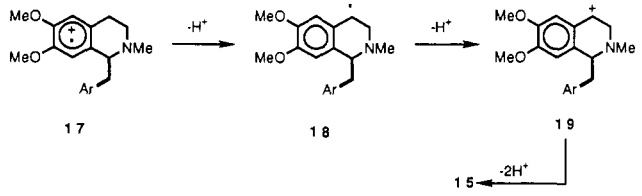
nucleus,[12] which differentiates it from the pavines and other isoquinoline alkaloids. The key fragment was the presence of only one isoquinolinium ion and a retro-Diels–Alder process, which resulted in the loss of $CH_2{=}NCH_3$ unit (Scheme I). The foregoing, in our opinion, provided sufficient evidence for the unusual process that had occurred during the oxidation of the isoquinoline 8. The formation of the isopavine may be regarded as a cyclization originating from the intermediate radical cation 17,[13] which first undergoes loss of a proton to give the benzylic radical 18. Further oxidation to 19 is followed by attack on the pendent phenyl moiety. The absence of methoxyl groups in the 1-benzyl group of the isoquinoline is probably the reason why the radical ion 17 is slow to couple to the expected biaryl, nuciferine.



Experimental Section

General Procedure for Alkylation of 3. Formamidine Cleavage and Reductive Methylation to 8, 9, and 11. To a solution of 1.1 g of 3[1] (3.0 mmol) in 50 mL of THF was added 1.05 equiv of *sec*-BuLi (1.3 M, cyclohexane, Aldrich) at −78 °C. The solution was allowed to stir for 1 h and then transferred to a −100 °C cooling bath for 0.5 h, and 1.05 equiv of the appropriate alkyl halide in 5 mL of THF was added dropwise during 1 h. The mixture was allowed to stir for 5 h at −100 °C and quenched with methanol. The cooling bath was removed and when the solution reached room temperature the solvents were removed in vacuo. The residue was immediately dissolved in 11 mL of ethanol and 5 mL of water, and 0.75 mL of hydrazine (24 mmol) and 0.54 mL of acetic acid (9 mmol) were added. After stirring the solution under argon at 50 °C overnight, it was partitioned between saturated $NaHCO_3$ and dichloromethane. The aqueous phase was extracted again with dichloromethane, and the combined organic layers were washed with brine and dried over K_2CO_3. The solvent was removed in vacuo and the remaining oil was heated to 100 °C/0.1 mmHg to remove (*S*)-valinol *tert*-butyl ether. The crude alkylated tetrahydroisoquinoline was dissolved in 75 mL of methanol and 5 mL of 37% formalin solution was added. The solution was allowed to stir at ambient temperature for 0.5 h. Sodium borohydride (2.5 g) was carefully added and after 1 h, the solvent was removed in vacuo and the residue was partitioned between 5% aqueous NaOH and dichloromethane. The aqueous layer was extracted again with dichloromethane and the combined organic layers were washed with brine and dried over K_2CO_3. Concentration in vacuo gave crude **8**, **9**, and **11**, which were purified by flash chromatography on silica gel (Aldrich 951) or by recrystallization.

(+)-1-Benzyl-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (8). Alkylation of **3** (1.05 g, 2.90 mmol) with benzyl chloride according to the general procedure gave crude **8**, which was purified on 30 g of silica gel (25% EtOAc, 5% Et_3N in hexane) to give 600 mg (69.6%) of pure **8**: hydrochloride salt mp 202–204 °C dec (EtOH/ether); $[\alpha]^{25}_D$ +124.2° (*c* 0.62, EtOH) (free base); IR (neat) 2931, 2833, 2791, 1610, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.52 (s, 3 H), 2.73–2.81 (m, 4 H), 3.15–3.22 (m, 2 H), 3.47 (s, 3 H), 3.69 (dd, 1 H, J_1 = 8 Hz, J_2 = 4.5 Hz), 3.81 (s, 3 H), 5.91 (s, 1 H), 7.07 (s, 1 H), 7.09 (d, 1 H, J = 1.4 Hz), 7.16–7.26 (m, 3 H).

(+)-Laudanosine (9). Alkylation of **3** (1.1 g, 3 mmol) with 3,4-dimethoxybenzyl chloride, treatment with hydrazine, and methylation gave the crystalline product, which was recrystallized from ethyl acetate to give 702 mg (65.5%) of pure **9**; mp 88–90 °C (lit.[14] mp 89 °C): hydrochloride salt mp 148–150 °C (EtOH/ether); $[\alpha]^{25}_D$ +96.6° (*c* 0.41, EtOH); lit[15] −107 ± 3° (*c* 0.7, EtOH, free base from resolution of racemate); IR ($CDCl_3$) 2954, 2932, 2852, 1515 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.51 (s, 3 H), 2.53–2.79 (m, 4 H), 3.08–3.14 (m, 2 H), 3.55 (s, 3 H), 3.66 (dd, 1 H, J_1 = 7.5 Hz, J_2 = 5.1 Hz), 3.76 (s, 3 H), 3.81 (s, 3 H), 3.82 (s, 3 H), 6.04 (s, 1 H), 6.53 (s, 1 H), 6.57–6.63 (m, 2 H), 6.73 (d, 1 H, J = 8 Hz).

(+)-Homolaudanosine (11). 3,4-Dimethoxyphenethyl iodide was used to alkylate **3** (1.16 g, 3.2 mmol). The crude product was purified on 30 g of silica gel (10% Et_3N in EtOAc) to give 716 mg (60%) of pure **11**: $[\alpha]^{25}_D$ +11.1° (*c* 1.17, $CHCl_3$), lit.[16] +11° (*c* 0.21, $CHCl_3$); IR (neat) 3000, 2932, 2841, 2773, 1608, 1590, 1514 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.97–2.05 (m, 2 H), 2.45–2.54 (m, 1 H), 2.45 (s, 3 H), 2.61–2.76 (m, 4 H), 3.11–3.16 (m, 1 H), 3.39 (t, 1 H, J = 5.4 Hz), 3.80 (s, 3 H), 3.83 (s, 9 H), 6.52 (s, 1 H), 6.55 (s, 1 H), 6.68–6.78 (m, 3 H).

(+)-Glaucine (12). Laudanosine **9** was coupled with VOF_3 according to the literature[17] to give glaucine in 40% yield: $[\alpha]^{25}_D$ +100° (*c* 3.2, $CHCl_3$), lit.[17] +115° ($CHCl_3$); IR ($CHCl_3$) 3022, 1522 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz[4]) δ 2.49–2.70 (m, 3 H), 2.52 (s, 3 H), 2.95–3.45 (m, 4 H), 3.62 (s, 3 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 3.90 (s, 3 H), 6.56 (s, 1 H), 6.75 (s, 1 H), 8.06 (s, 1 H).

(+)-Homoglaucine (13). (+)-Homolaudanosine (**11**) was coupled with VOF_3 as described[5] or with $Tl(O_2CCF_3)_3$ as reported for the synthesis (±)-*o*-methylkreysigine[6] in 40% yield: $[\alpha]^{25}_D$ +24.6° (*c* 2.84, EtOH); IR ($CHCl_3$) 3022, 1522 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 2.15–2.81 (m, 5 H), 2.35 (s, 3 H), 3.06–3.46 (m, 4 H), 3.44 (s, 3 H), 3.90 (s, 3 H), 3.94 (s, 3 H), 6.65 (s, 1 H), 6.77 (s, 1 H), 7.08 (s, 1 H).

(−)-8,9-Didemethoxythalisopavine (15). To a stirred suspension of ruthenium(IV) oxide hydrate (400 mg, 3 mmol, Alfa) in 30 mL of dichloromethane were added TFA (3.8 mL) and TFAA (1.9 mL). After cooling the mixture to 0 °C, a solution of (+)-**8** (229 mg, 0.77 mmol) in 10 mL of dichloromethane was added and immediately after that 0.55 mL of boron trifluoride etherate. The cooling bath was removed and the mixture was stirred at room temperature for 62 h. The reaction mixture was cooled to 0 °C and quenched with 30% ammonium hydroxide until pH 10 was reached. The solids were removed by filtration over Celite and washed several times with dichloromethane. The combined organic layers washed with brine, dried over K_2CO_3, and evaporated. The residue was chromatographed over 12 g of silica gel (45% EtOAC, 5% Et_3N in hexane) to give 150 mg of pure (−)-**15**: $[\alpha]^{25}_D$ −135° (*c* 2.6, EtOH), hydrochloride salt mp 187–189 °C dec (EtOH/ether); IR (neat) 3024, 1576, 1509 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.48 (s, 3 H), 2.88 (dd, 1 H, J_1 = 10.5 Hz, J_2 = 4.6 Hz), 2.98 (dd, 1 H, J_1 = 17.5 Hz, J_2 = 3.1 Hz), 3.53 (dd, 1 H, J_1 = 10.6 Hz, J_2 = 1.5 Hz), 3.57 (dd, 1 H, J_1 = 17.5 Hz, J_2 = 3.9 Hz), 3.73 (m, 1 H), 3.84–3.88 (m, 1 H, covered by OCH_3 region), 3.84 (s, 3 H), 6.74 (s, 1 H), 6.76 (s, 1 H), 7.00–7.13 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75.47 MHz) 38.26, 45.10, 46.29, 55.90, 56.04, 59.61, 62.18, 108.93, 109.93, 125.62, 126.55, 127.43, 130.32, 131.17, 133.61, 135.10, 142.48, 147.48, 147.80; UV λ_{max} (MeOH) 284 nm; CD −238.4 nm, −283.2 nm (MeOH); MS CI (NH_3) $(M + 1)^+$ −296 (100); EI *m/z* 295 (20.5), 294 (29), 252 (21), 204 (100), 179 (24), 136 (24), 135 (84); partial assignment of ^{13}C spectra was done based on DEPT and C-H correlation experiments. Anal. Calcd for $C_{19}H_{21}NO_2$: C, 77.28; H, 7.11; N, 4.74. Found: C, 76.95; H, 7.03; N, 4.54.

Acknowledgment. We are grateful to the National Science Foundation, The National Institutes of Health,

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and Bristol-Myers-Squibb for financial support of this work.

Registry No. 3, 128778-92-7; 8, 128778-93-8; 8·HCl, 128778-95-0; 9, 2688-77-9; 9·HCl, 6392-34-3; 11, 85611-40-1; 12, 475-81-0; 13, 128778-94-9; 15, 128709-13-7; $PhCH_2Cl$, 100-44-7; 3,4-$(MeO)_2C_6H_3CH_2Cl$, 7306-46-9; 3,4-$(MeO)_2C_6H_3(CH_2)_2I$, 64728-23-0.

Synthesis of 1,4-Dinitroanthracene-9,10-dione. Stepwise Substitution of the Nitro Groups by Diamines Leading to 1-[(Aminoalkyl)amino]-4-nitroanthracene-9,10-diones and Unsymmetrical 1,4-Bis[(aminoalkyl)amino]anthracene-9,10-diones

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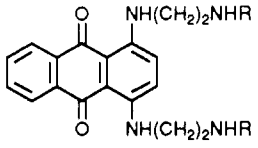
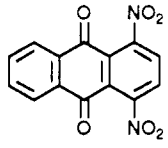
In connection with the synthesis of analogues related to **1** for antitumor evaluations,[1,2] we report preparative pathways to 1,4-dinitroanthracene-9,10-dione (**2**) and a study of the displacements of the nitro groups of **2** by various diamines.



1

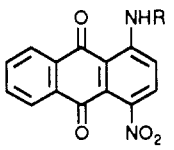


2

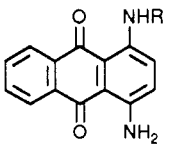
The regiospecific substitution of a nitro group by a nucleophile from an activated benzenoid substrate is a useful preparative route.[3-10] One preparative drawback to this procedure is the competitive reduction of the nitro group to an amino functionality which has been found in a few cases.[5,9] Anion-radical intermediates have been proposed as precursors in the substitution of some nitro benzenoid substrates.[10-12]

Substitutions of the nitro group of 1-nitroanthracene-9,10-diones have been utilized in the preparation of azido,[13,14] amino,[15-21] and alkoxyanthracene-9,10-diones.[22-24] In the substitution of 1-chloro- and 1-nitroanthracene-9,10-dione, the nitro group is displaced by amines such as piperidine about 50 times faster than the chloro group.[16,18] As in the nitro benzenoid substrates, evidence has been presented for an anion-radical intermediate in the substitution (or reduction) of 1-nitroanthracene-9,10-dione.[22]

The synthesis of **2** has been previously reported by a Japanese group[25] using a two-step oxidation [$(NH_4)_2S_2O_8$ followed by CrO_3] of 1-amino-4-nitroanthracene-9,10-dione (**3a**) in a 14% yield.



3a: R = H
b: R = $(CH_2)_2N(CH_3)_2$
c: R = $(CH_2)_2NH(CH_2)_2OH$
d: R = $(CH_2)_2NH_2$



4a: R = H
b: R = $(CH_2)_2N(CH_3)_2$
c: R = $(CH_2)_2NH(CH_2)_2OH$
d: R = $(CH_2)_2NH_2$

However, all attempts by our group to repeat this procedure have been unsuccessful. On the other hand, treatment of **3a** with trifluoroacetic acid and hydrogen peroxide (90%)[26] readily leads to **2** in a good yield. Although **3a** can be prepared from 1-aminoanthracene-9,10-dione via a four-step sequence,[27] we have also found that treatment of the commercially available 1,4-diaminoanthracene-9,10-dione (**4a**) with trifluoroperacetic acid (prepared by mixing trifluoroacetic anhydride with 90% hydrogen peroxide) leads to high yields of **2** (84%).

With **2** being readily available, we then investigated the displacements of the nitro groups with several diamino substrates. Some representative substitutions of **2** are tabulated in Table I.

The data presented in Table I indicates that good yields of the monosubstitution products related to **3** (entries 1, 3, and 4) can be obtained from the reactions performed for short periods in neat diamine or dioxane as the solvent. A small amount of the reduction of the nitro group to an amino group was found in the reaction of **2** with 1,2-diaminoethane (entry 4). Reduction and bis-substitution occurred in the reaction performed for longer periods (entry 2).

The preparation of unsymmetrically substituted 1,4-bis[(aminoalkyl)amino]anthracene-9,10-diones by sequential displacements of the nitro substituents by diamines was then examined.

Treatment of **2** with *N*,*N*-dimethylethylenediamine (8

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