of HOAc. The solvents were removed in vacuo. The residue was taken up in H_2O (40 mL), washed with Et_2O and CH_2Cl_2, concentrated, and chromatographed on Dowex 1-X8 (100-200 mesh, formate form) with elution by H_2O to yield 64 mg (56%) of 1′,2′,2″-d_3-2′-deoxyguanosine (**22b**) as a white powder, mp >300 °C. ^1H NMR (d_6-DMSO): δ 7.89 (s, H8, 1H), 6.65 (br s, NH_2, 2), 4.33 (d, H3′, 1), 3.80 (m, H4′, 1), 3.55 (dd, H5″, 1), 3.47 (dd, H5′, 1); $J_{3',4'}$ = 2.4, $J_{4',5'}$ = 4.3, $J_{4',5''}$ = 4.4, $J_{5',5''}$ = 11.5 Hz. ^{13}C NMR (d_6-DMSO) δ 157.9, 154.5, 150.9, 135.1, 116.7, 87.6, 82.1 (weak multiplet), 70.7, 61.8. ^2H NMR (H_2O): δ 6.06 (br s, D1′), 2.57 (br s, D2′), 2.30 (br s, D2″). MS (FAB$^+$): m/z 271 (M + H), 152, 120. UV (H_2O): λ_{max} (ϵ) 252 (13000), 272 nm (sh).

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Registry No. 1, 5336-08-3; 2, 78138-89-3; **3a**, 34371-14-7; **3b**, 131132-17-7; **4a**, 83159-91-5; **4b**, 131132-08-6; α-**5a**, 131132-08-6; β-**5a**, 131132-25-7; α-**5b**, 131132-09-7; β-**5b**, 131232-93-4; **6a**, 131131-90-3; **6b**, 131132-10-0; α-**7a**, 131131-91-4; β-**7a**, 131132-26-8; α-**7b**, 131132-11-1; β-**7b**, 131132-28-0; α-**8a**, 131131-92-5; β-**8a**, 131132-27-9; α-**8b**, 131132-12-2; β-**8b**, 131132-29-1; **9a**, 131131-93-6; **9b**, 131132-13-3; **10a**, 131131-94-7; **10b**, 131132-14-4; **11a**, 131131-95-8; **11b**, 131132-15-5; **12a**, 131131-96-9; **12b**, 131132-16-6; **13**, 131131-97-0; **14a**, 131131-98-1; **14b**, 131132-18-8; **15**, 131131-99-2; **16**, 131132-00-8; **17**, 131132-01-9; **18a**, 131132-02-0; **18b**, 131132-19-9; **19a**, 131132-03-1; **19b**, 131132-20-2; **20**, 131132-04-2; **21**, 131132-05-3; **21** N^3 isomer, 131132-24-6; **21** N^7 isomer, 131132-23-5; **22a**, 131132-06-4; **22b**, 131132-22-4; **23**, 131132-07-5; thymine, 65-71-4; uracil, 66-22-8; 6-chloropurine, 87-42-3; 2-amino-6-chloropurine, 10310-21-1; 3,7-[bis(1′-deuterio-3′,5′-di-*O*-*p*-toluoyl-2′-deoxyribosyl)]-2-[*N*-[(di-*n*-butylamino)methylene]-amino]-3*H*,7*H*-purin-6-one, 131132-21-3; sodium 2-cyanoethoxide, 131513-78-5.

Supplementary Material Available: ^1H NMR spectra of compounds **5a**, **5b**, **13**, **15**, **16**, and **21** (6 pages). Ordering information is given on any current masthead page.

Synthesis of the Phthalide Isoquinoline Alkaloids (-)-Egenine, (-)-Corytensine, and (-)-Bicuculline by Asymmetric Carbonyl Addition of Chiral Dipole-Stabilized Organometallics

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The asymmetric addition of metalated [(methylenedioxy)isoquinolyl]oxazolines is 100% selective for the erythro (α-hydroxybenzyl)isoquinoline diastereomers, with 2:1 selectivity of the two possible erythro stereoisomers. Enrichment to 100% ee after removal of the auxiliary and conversion to (-)-bicuculline and (+)-bicuculline diol establish the absolute configuration of the major addition product. Inversion of the C-9 hydroxyl affords entry into the threo series as well. The asymmetric carbonyl addition was used to synthesize, for the first time, the phthalide-isoquinoline hemiacetals corytensine and egenine, confirming the previously assigned structures and absolute configurations, and establishing the identity of egenine with decumbensine and of corytensine with epi-α-decumbensine.

The phthalide-isoquinoline alkaloids are a class of tetracyclic (α-hydroxybenzyl)isoquinoline lactones that are usually oxygenated on carbons 6, 7, 4′, and 5′.[1] One of the more important members of this class is bicuculline, **1**, which is of interest as a $GABA_A$ antagonist.[2] Its presumed biosynthetic precursor is the hemiacetal egenine, **2**.[3] Bicuculline and egenine both possess the erythro relative configuration at positions 1 and 9; bicuculline has been isolated as either enantiomer and as the racemate[1] (although only the (+) enantiomer is active as a $GABA_A$ antagonist[2b]), while egenine was isolated as the (+) enantiomer.[3] The threo diastereomers of bicuculline and egenine are the lactone (-)-capnoidine, **3** (and its enantiomer (+)-adlumidine),[1] and the hemiacetal corytensine, **4**, isolated as the (+) enantiomer.[4] In 1988, two (α-hydroxybenzyl)isoquinoline alkaloids were isolated from *Corydalis decumbens* (Thunb.) Pers. (Papaveraceae), named decumbensine and epi-α-decumbensine, and assigned structures **5** and **6**, respectively.[5] In 1989, Rozwadowska synthesized compounds **5** and **6** and found that spectra of the synthetic material did not match the published spectra of decumbensine and epi-α-decumbensine.[6] In this paper, we present evidence that decumbensine and egenine are identical and that epi-α-decumbensine and corytensine are identical.[7]

For the past several years, the asymmetric alkylation of isoquinolines, α to nitrogen, has been a topic of current interest.[8] The seminal contribution to this field was Meyers' asymmetric alkylation of chiral formamidines.[8a]

(1) Blaskó, G.; Gula, D. J.; Shamma, M. *J. Nat. Prod.* **1982**, *45*, 105-122.
(2) (a) Simmonds, M. A. *Neuropharmacology* **1980**, *19*, 39. For a molecular modeling study of the bicuculline-GABA receptor, see: (b) Aprison, M. H.; Lipkowitz, K. B. *J. Neurosci. Res.* **1989**, *23*, 129-135.
(3) Gözler, B.; Gözler, T.; Shamma, M. *Tetrahedron* **1983**, *39*, 577-580.
(4) Wu, T. S.; Huang, S. C.; Lu, S. T.; Wu, Y. C.; McPhail, D. R.; McPhail, A. T.; Lee, K. H. *Heterocycles* **1988**, *27*, 1565-1568.
(5) Zhang, J.-S.; Xu, R.-S.; Quirion, J. C. *J. Nat. Prod.* **1988**, *51*, 1241-1242.
(6) Rozwadowska, M. D.; Mateká, D.; Brôzda, D. *Tetrahedron Lett.* **1989**, *30*, 6215-6218. See also ref 24.
(7) The possibility of this correlation was first suggested by Rozwadowska.[6]
(8) (a) Meyers, A. I.; Fuentes, L. M. *J. Am. Chem. Soc.* **1984**, *105*, 117-118. (b) Meyers, A. I.; Guiles, J. *Heterocycles* **1989**, *28*, 295-301. (c) Meyers, A. I.; Dickman, D. A.; Boes, M. *Tetrahedron* **1987**, *43*, 5095-5108 and references cited therein. (d) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175-181, 4726 and references cited therein. (e) Rein, K.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211-2217 and references cited therein. (f) Bartolotti, L. J.; Gawley, R. E. *J. Org. Chem.* **1989**, *54*, 2980-2982. (g) Gawley, R. E.; Rein, K. S.; Chemburkar, S. *J. Org. Chem.* **1989**, *54*, 3002-3004. (h) Rein, K. S.; Gawley, R. E. *Tetrahedron Lett.* **1990**, *31*, 3711-3714.

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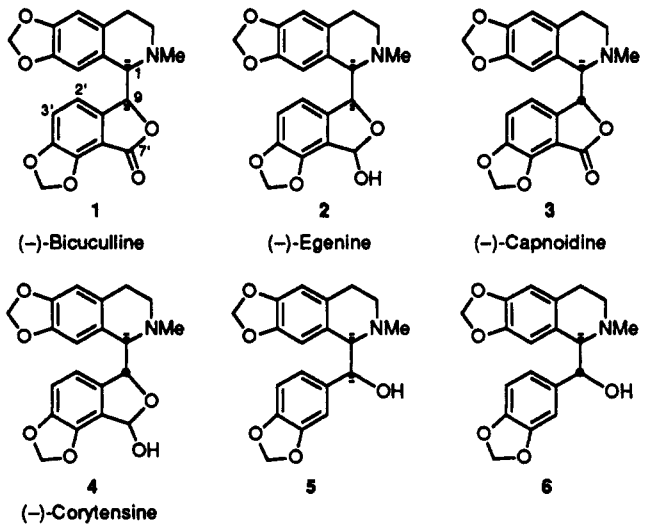
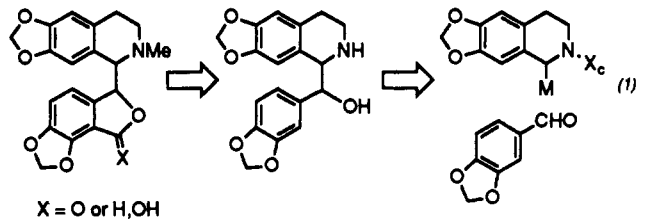


The Meyers group has used this elegant methodology for the synthesis of a number of isoquinoline alkaloids by asymmetric alkylation.[8b,c] For the past few years, we have been studying similar systems designed to address some of the problems inherent in the formamidine systems.[8d,e] In addition, our more recent efforts have focused on theoretical models accounting for the selectivity in dipole-stabilized organometallics,[8f] acyclic stereoselection in alkylation processes,[8g] and face selectivity in the addition of chiral isoquinolyloxazoline Grignards to aldehydes.[8h] The latter process creates two stereocenters (four possible stereoisomers) in one operation. With reference to the (α-hydroxybenzyl)isoquinoline alkaloids described above, the disconnection between the two stereocenters is an esthetically pleasing and potentially efficient one. The resulting retrosynthesis (eq 1) illustrates the approach.

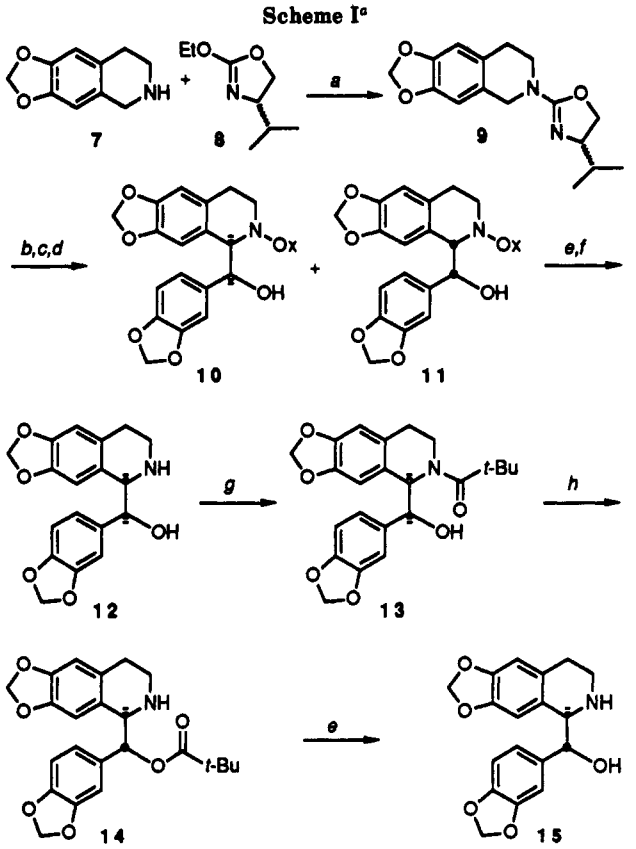


Following aldehyde addition, removal of the auxiliary and methylation, a directed metalation was planned for the incorporation of the lactone or hemiacetal carbonyl. Herein we report the first syntheses of the phthalideisoquinoline hemiacetals (-)-egenine and (-)-corytensine, as well as the lactone (-)-bicuculline using this asymmetric carbonyl addition strategy. Aside from the merit and pleasure inherent in a synthetic investigation, execution of the plan provides the key to the unraveling of the stereochemical outcome (relative and absolute configurations) of the asymmetric additions.[9]

Results and Discussion

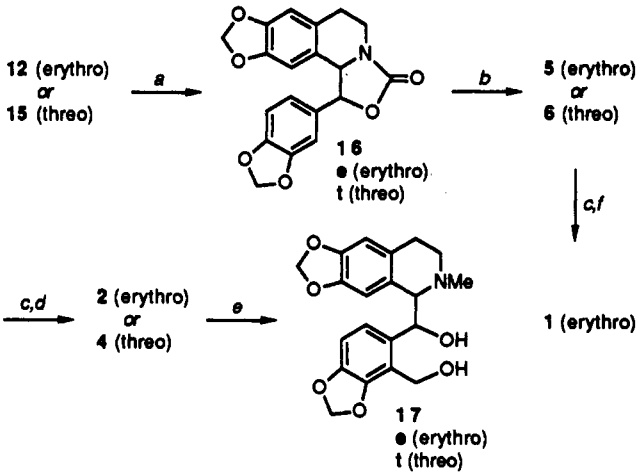
Synthesis of the (α-Hydroxybenzyl)tetrahydroisoquinolines. As shown in Scheme I, 6,7-(methylenedioxy)tetrahydroisoquinoline 7[10] was condensed with ethoxyoxazoline 8[8d] to afford the isoquinolyloxazoline 9 in

Scheme I[a]



[a] (a) *p*-TsOH; (b) *t*-BuLi, THF; (c) $MgBr_2 \cdot OEt_2$; (d) ArCHO; (e) $LiAlH_4$; (f) (+)-tartaric acid; (g) *t*-BuCOCl; (h) TFA, TFAA, Δ.

Scheme II[a]



[a] (a) $COCl_2$; (b) $LiAlH_4$; (c) *n*-BuLi; (d) DMF; (e) $NaBH_4$; (f) CO_2.

78% yield. Lithiation and transmetalation with magnesium bromide,[11] followed by addition of piperonal, afforded exclusively the erythro diasteromers **10** and **11** as an inseparable mixture. Reaction of the lithium derivative gives a mixture of both erythro and threo addition products, as shown by 400-MHz NMR. NMR was of no use, however, in analyzing the ratio of the two erythro diastereomers. The **10**/**11** ratio was determined by Pirkle analysis of the naphthamides, after removal of the oxa-

(9) For a preliminary report of a portion of this work, see ref 8h. For a review of the addition of nitrogen-stabilized anions to carbonyls, see: Gawley, R. E.; Rein, K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 1, Chapter 2.1.

(10) (a) Decker, H.; Becker, P. *Liebigs Ann. Chem.* **1913**, *395*, 342-362. (b) Haworth, R. D.; Perkin, W. H., Jr.; Rankin, J. *J. Chem. Soc.* **1924**, *125*, 1686-1701.

(11) (a) Seebach, D.; Syfrig, M. A. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 248-249. (b) Seebach, D.; Hansen, J.; Seiler, P.; Gromek, J. M. *J. Organomet. Chem.* **1985**, *285*, 1-13. (c) Seebach, D.; Huber, I. M. P. *Chimia* **1985**, *39*, 233-234. (d) Seebach, D.; Huber, I. M. P.; Syfrig, M. A. *Helv. Chim. Acta* **1987**, *70*, 1357-1377.

Table I. Selected Proton and Carbon Chemical Shifts for (-)-Egenine and (-)-Corytensine

	NCH_3	1	5	8	9	2′	3′	7′
egenine (^1H)	2.51	3.89[a]	6.58	6.80	5.40[a]	5.65[b]	6.53[b]	6.34
egenine (^{13}C)	43.97	64.91	108.65	107.58	86.94	114.60	108.31	97.88
corytensine (^1H)	1.96	3.68	6.60	6.71	5.29	6.84[c]	6.84[c]	6.25
corytensine (^{13}C)	46.70	68.53	108.13	106.84	89.79	113.78[d]	108.88[d]	97.60

[a] d, J = 3.6. [b] d, J = 7.6. [c] Second order AB quartet. [d] Assigned by analogy to egenine.

zoline (vide infra). It is noteworthy that none of the threo compound was formed, since in a related case, the magnesium derivative of a chiral 6,7-dimethoxyisoquinoline pivalamide apparently gives a 3:2 mixture of erythro and threo diastereomers.[12] Reduction of the 10/11 mixture afforded amino alcohol **12** in 90% yield.

At the time we began this work, we were not certain how the enantiomeric excess of compounds such as **12** might be determined. In previous work,[8] the enantiomeric excess of the alkylation products was determined by Pirkle analysis of the corresponding naphthamides.[13] However, the present compounds have two stereocenters and two possible sites of reactivity with the α-naphthoyl chloride derivatizing agent. In work reported elsewhere,[14] we have found that reaction of (α-hydroxybenzyl)isoquinolines with α-naphthoyl chloride (even when taken in excess) affords only *N*-naphthamide to the exclusion of O-acylation, and that the order of elution of enantiomers is unaffected by the second stereocenter. Thus, the ratio of enantiomers was determined to be 2:1, and **12** was enriched to 100% ee by a single recrystallization of the (+)-tartrate salt.

Acylation of the nitrogen and inversion by the method of Seebach[11] afforded pivaloate **14**. Reduction afforded the threo amino alcohol **15** in 60% overall yield from **12**. As shown in Scheme II, methylation of both **12** and **15** was achieved in two steps: cyclization with phosgene and reduction. A comparison with the published spectral data for decumbensine and epi-α-decumbensine indicated that neither natural product matched either **6** or **5**. It was at about this time that Rozwadowska reported the synthesis of **6** and **5** in racemic form and noted the mismatch.[6] The Polish workers went on to suggest that epi-α-decumbensine and corytensine might be one and the same. Unfortunately, samples of the natural products were not available.[15]

Elaboration by Directed Metalation and Stereochemical Correlation. As shown in Scheme II, directed metalation of the 6′-position of either **5** or **6** and formylation with dimethylformamide afforded **2** (egenine) or **4** (corytensine) in 31% yield (along with unreacted starting material). For the purpose of establishing the absolute configuration of our synthetic materials, we felt we could not rely solely on correlation with these two compounds for the following reasons. In the case of egenine several of the NMR assignments did not agree with ours (vide infra), and neither copies of the original spectra nor a comparison sample were available.[16] In the case of corytensine, the structure was midrawn when transcribing the X-ray structure, and the original paper[4] erroneously concluded that corytensine and egenine were both erythro compounds, differing only in the absolute configuration at the hemiacetal carbon (C-7′).[17]

Shamma, in his original paper, reduced (+)-egenine to (-)-bicucullinediol (**17e**).[3] Because the relative and absolute stereochemistry of the latter compound, as well as its threo diasteromer adlumidinediol (**17t**), are well established,[18] we chose to correlate relative and absolute configuration by reduction of synthetic **2** and **4** to **17e** and **17t**. Thus, reduction of **2** afforded **17e** in 75% yield, and the negative rotation established the abolute configuration as 1*R*,9*S*. The rotation also confirmed the optical purity of **17e**, and therefore of **2** and **5**. Similar reduction of **4** afforded **17t** in 74% yield, and its positive rotation confirmed its configuration as 1*R*,9*R*. These assignments were further corroborated by the conversion of **5** to (-)-bicuculline in 44% yield (100% ee) by sequential directed metalation, carbonation, and lactonization.

Decumbensine, Epi-α-decumbensine, Egenine, and Corytensine. With the structures of **17e** and **17t** firmly established, we were in a position to compare the spectral data for synthetic **2** and **4** with the reported data for egenine,[3] corytensine,[4] decumbensine, and epi-α-decumbensine.[5] Our assignments, which were made using a combination of COSY, HETCOR, off-resonance, and NOE techniques, are shown in Table I.

For egenine, there is good agreement with the published data, although several of the peaks were misassigned. Specifically, the signals at 6.58, 6.53, 6.34, and 5.65 were assigned to positions 3′, 2′, 5, and 7′, respectively.[3] Additionally, the 6.58 signal was reported to be a doublet, where we find a singlet.[3] Shamma rationalized the appearance of five doublets in his spectrum by suggesting that the hemiacetal proton at position 7′ was split by the alcoholic proton; however, we did not observe such vicinal coupling even after azeotropic drying. Our ^1H NMR data match that reported for decumbensine almost exactly.[5] The carbon spectrum of natural egenine was not reported, but our data nearly match that reported for decumbensine. The reason for the misassigned structure became apparent when the spectrum was recorded at 20 and 100 MHz: a single peak seen at 124 ppm at 20 MHz is resolved into two peaks at 123.99 and 124.11 at 100 MHz. Moreover, egenine does not give a molecular ion under EI conditions in the mass spectrometer.[3] Fragmentation might give a fragment that could be mistaken for a molecular ion having the formula corresponding to structure **5**,[19] although an impurity might also be to blame.[20] The peak in the proton NMR at 6.34 was mistaken to be an aromatic proton,[5] when in fact it resides on C-7′. Our rotation data match that of natural egenine, although opposite in sign, indicating that the material isolated from *F. vaillantii* is optically pure. The alkaloid isolated from *C. decumbens* shows a specific rotation corresponding to an optical purity of 60% ee.

For corytensine, our ^1H NMR data match the published data[4] almost exactly; the ^{13}C data also match, except that

(12) The *N*-pivalamide of a 6,7-dimethoxytetrahydroisoquinoline having a carboxylate in the 3-position affords a 3:2 mixture of diastereomers (Huber, I. M. P.; Seebach, D. *Helv. Chim. Acta* **1987**, *70*, 1944–1954), whereas the same compound lacking the carboxyl is erythro selective.[11c]

(13) (a) Pirkle, W. H.; Welch, C. J. *J. Org. Chem.* **1984**, *49*, 138–140. (b) Pirkle, W. H.; Welch, C. J.; Mahler, G. S.; Meyers, A. I.; Fuentes, L. M.; Boes, M. *J. Org. Chem.* **1984**, *49*, 2504–6.

(14) Rein, K. S.; Gawley, R. E. *J. Org. Chem.* **1991**, *56*, 839–841.

(15) Zhang, J.-S., private communication.

(16) Shamma, M., private communication.

(17) A corrigendum has appeared: *Heterocycles* **1990**, *31*, 575.

(18) Nonaka, G.; Nishioka, I. *Chem. Pharm. Bull.* **1975**, *23*, 294–298.

(19) Quirion, J. C., private communication.

(20) Using synthetic egenine, we could not produce a CI spectrum that lacked a molecular ion.

the peak at 113.78 is listed as a singlet in off-resonance,[4] whereas we find a doublet.[21] The ^{1}H NMR spectrum for epi-α-decumbensine corresponds to that of corytensine, except for a singlet that we and Wu et al.[4] observe at 6.71, whereas the epi-α-decumbensine data[5] indicate a singlet at 6.07.[22] No ^{13}C data were published for epi-α-decumbensine.

Summary. The asymmetric addition of metalated [(methylenedioxy)isoquinolyl]oxazolines is 100% selective for the erythro diasteromer, with the two possible stereoisomers obtained in a 2:1 ratio. Enrichment to 100% ee after removal of the auxiliary is accomplished quite simply, and conversion of the erythro (α-hydroxybenzyl)isoquinolines to (-)-bicuculline and (+)-bicucullinediol establish the relative and absolute configuration of the stereocenters of the major addition product. Seebach inversion of the C-9 hydroxyl provides a simple entry into the threo (α-hydroxybenzyl)isoquinoline series as well. The asymmetric carbonyl addition was used to synthesize, for the first time, the phthalideisoquinoline hemiacetals egenine and corytensine, confirming the previously assigned structures and absolute configurations, and establishing the identity of egenine with decumbensine and of corytensine with epi-α-decumbensine.[24]

Experimental Section

Tetrahydrofuran was distilled from sodium benzophenone ketyl immediately prior to use. All other solvents were distilled before use. NMR spectra were recorded in $CDCl_3$. Radial chromatography was performed using a Harrison Research Model 7924T chromatatron. Flash chromatography was performed with Merck 9385 silica gel. Melting points are uncorrected. All reactions were run under an inert atmosphere of nitrogen. HPLC analyses were performed on a Varian Vista 5000 LC, using a Groton Technologies PF1 diode array detector, and a Hewlett-Packard 3392A integrator. The stationary phase was a Bakerbond chiral DNBPG covalent Pirkle column. The naphthamides of **12** and **15** were eluted with 35% i-PrOH/65% hexane.

(*S*)-5,6,7,8-Tetrahydro-6-[4,5-dihydro-4-(1-methylethyl)-2-oxazolyl]-1,3-dioxolo[4,5-*g*]isoquinoline (9). A solution of the isoquinoline **7**[10] (5.0 g, 28.2 mmol), the ethoxyoxazoline **8**[8d] (4.85 g, 31.1 mmol), and a catalytic amount of *p*-toluenesulfonic acid in benzene (100 mL) was refluxed for 6 h. Upon cooling, the reaction mixture was washed with saturated Na_2CO_3, dried over $MgSO_4$, filtered, and evaporated in vacuo. The product was distilled from CaH_2 immediately before use to yield 6.35 g (78%) of the product: ^{1}H NMR (60 MHz) 0.83 (2 H, d, J = 6.6 Hz), 0.94 (2 H, d, J = 6.6 Hz), 1.66 (1 H, sept, J = 6.6 Hz), 2.74 (2 H, t, J = 6 Hz), 3.58 (2 H, t, J = 6.0 Hz), 3.87-4.30 (5 H, m), 4.45 (2 H, s), 5.88 (2 H, s), 6.55 (2 H, s); ^{13}C NMR (20 MHz) 160.4, 145.7, 126.9, 125.9, 108.0, 105.7, 100.3, 70.1, 69.7, 46.9, 42.5, 32.8, 28.1, 18.4, 17.2; IR (neat) 1640 (C=N); mp 47-49 °C. Anal. Calcd for $C_{16}H_{20}N_2O_3$: C, 66.65; H, 6.99. Found: C, 66.56; H, 7.00.

[*R*-(*R,*S**,*S**)]-α-1,3-Benzodioxol-5-yl-5,6,7,8-tetrahydro-6-[4,5-dihydro-4-(1-methylethyl)-2-oxazolyl]-1,3-dioxolo[4,5-*g*]isoquinoline-5-methanol (10 and 11).** To a solution of the isoquinoline (2.34 g, 8.10 mmol), in 80 mL of THF at -78 °C was added dropwise (via syringe) 5.6 mL of *n*-butyllithium (1.6 M solution in hexane). The reaction mixture was stirred at -78 °C for 10 min, whereupon 6.1 mL of magnesium bromide etherate (2.56 M solution in ether) was added via syringe. The reaction mixture was warmed to 0 °C for 20 min and then cooled to -78 °C. Piperonal (1.58 g, 10.6 mmol) was added as a THF solution (2 M), via syringe. This mixture was stirred for 15 h at -78 °C, allowed to warm to room temperature, and diluted with saturated ammonium chloride. The layers were separated, and the aqueous phase was extracted with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. the product was purified by flash chromatography (50:50 hexane/ethyl acetate to 100% ethyl acetate) to yield 1.94 g (88%) of a white solid: ^{1}H NMR (400 MHz) 0.87 (3 H, d, J = 8 Hz), 0.97 (3 H, d, J = 8 Hz), 1.54-1.57 (1 H, m), 1.62 (1 H, sext, J = 8 Hz), 2.21-2.28 (1 H, m), 2.93-3.00 (1 H, m), 3.11-3.17 (1 H, m), 3.91 (1 H, q, J = 8 Hz), 4.06 (1 H, t, J = 8 Hz), 4.44 (1 H, t, J = 8 Hz), 4.97 (1 H, s), 5.36 (1 H, s), 5.90 (2 H, q, J = 1.6 Hz), 5.95 (1 H, d, J = 1.4 Hz), 5.97 (1 H, d, J = 1.4 Hz), 6.25 (1 H, d, J = 8 Hz), 6.42 (1 H, s), 6.59 (1 H, s), 6.10 (1 H, d, J = 8 Hz), 6.86 (1 H, s); ^{13}C NMR (100 MHz) 18.26, 18.67, 28.03, 33.60, 42.12, 64.64, 69.15, 72.30, 82.01, 100.64, 100.95, 107.34, 107.66, 107.69, 107.80, 120.15, 126.77, 129.19, 135.19, 146.42, 146.54, 146.95, 164.05; IR ($CHCl_3$) 3600-3300 (broad, OH), 1665 (C=N). Anal. Calcd for $C_{24}H_{26}N_2O_6$: C, 65.75; H, 5.98. Found: C, 65.59; H, 6.00.

[*R*-(*R,*S**)]-α-1,3-Benzodioxol-5-yl-5,6,7,8-tetrahydro-1,3-dioxolo[4,5-*g*]isoquinoline-5-methanol (12).** A solution of the oxazoline-substituted isoquinolinemethanols **10** and **11** (1.94 g, 4.43 mmol) in THF (40 mL) was added dropwise to a suspension of LAH (840 mg) in THF (75 mL) at 0 °C. The reaction mixture was refluxed for 15 h. Upon cooling to 0 °C, the reaction mixture was diluted with an equal amount of ether, and the excess LAH was decomposed by the dropwise addition of water (3 mL). The solid was filtered, and the organic phase was washed with brine. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by radial chromatography, eluting with 10% MeOH/90% CH_2Cl_2 to give 1.29 g (90%) of a white solid. Pirkle analysis of the naphthamide[14] showed a 2:1 mixture of isomers: ^{1}H NMR (400 MHz) 2.44-2.61 (4 H, m), 2.73-2.87 (2 H, m), 4.11 (1 H, d, J = 4 Hz), 4.84 (1 H, d, J = 4 Hz), 5.87-5.92 (4 H, m), 6.51 (1 H, s), 6.66-6.75 (4 H, m); ^{13}C NMR (20 MHz) 29.9, 40.5, 60.7, 75.9, 100.7, 100.9, 107.1, 107.8, 108.8, 120.0, 128.0, 129.5, 135.5, 145.5, 146.2, 146.9, 147.6; IR 3300 (broad OH, NH); MS (EI) 328 (M + 1), 310 (M - 17, loss of OH), 176 (M - 151, isoquinoline, 100); mp 69.5-72.5 °C. The product was taken up in acetone (10 mL) and was added to a solution of L-tartaric acid (592 mg, 3.9 mmol) in 10 mL of methanol. The solution was allowed to stand at -4 °C overnight. The solid was filtered and recrystallized from water and acetone to yield 606 mg of the tartrate of **12**. Pirkle analysis of the naphthamide[14] indicated that **12** was enriched to 100% ee: mp (L-tartrate) 193-194.5 °C dec; $[\alpha]_D$ (L-tartrate) -30.6° (c 0.55, H_2O). Anal. Calcd (for tartrate) $C_{22}H_{23}NO_{11}$: C, 55.35; H, 4.85. Found: C, 55.07; H, 4.90.

[*R*-(*R,*S**)]-α-1,3-Benzodioxol-5-yl-5,6,7,8-tetrahydro-6-(2,2-dimethyl-1-oxopropyl)-1,3-dioxolo[4,5-g]isoquinoline-5-methanol (13).** To a suspension of the tartrate of **12** (1.33 g, 2.79 mmol) in CH_2Cl_2 (50 mL) was added an equal volume of saturated Na_2CO_3. The mixture was cooled to 0 °C, and a solution of pivaloyl chloride (368 mg, 3.07 mmol) in CH_2Cl_2 (5 mL) was added dropwise. The reaction mixture was allowed to warm slowly to room temperature over 12 h. The layers were separated, and the organic phase was washed with 10% HCl and brine and dried over $MgSO_4$. The solution was filtered and evaporated in vacuo. The product was purified by radial chromatography, eluting with 50:50 hexane/ethyl acetate to yield 1.00 g (87%) of a white solid: ^{1}H NMR (60 MHz) 1.27 (9 H, s), 2.06-2.76 (4 H, m), 5.15 (1 H, d, J = 3 Hz), 5.81 (1 H, d, J = 3 Hz), 5.89 (2 H, s), 5.93 (2 H, s), 6.50 (1 H, s), 6.53-6.67 (2 H, m), 6.79 (1 H, s); ^{13}C NMR (20 MHz) 179.6, 147.4, 146.8, 146.6, 146.2, 134.9, 127.5, 125.9, 119.4, 108.0, 107.8, 107.6, 106.9, 100.8, 100.7, 79.7, 60.2, 41.6, 38.9, 28.7, 28.1; DCIMS (CH_4) 412 (M + 1), 394 (100, M - OH), 261 (loss of $(OCH_2O)C_6H_3CHOH$), 151, 176.

[*R*-(*R,*R**)]-(1,3-Benzodioxol-5-yl)(5,6,7,8-tetrahydro-1,3-dioxolo[4,5-g]isoquinolin-5-yl)methyl 2,2-Dimethylpropanoic Acid Ester (14).** To the pivalamide **13** (1.26 g, 3.07 mmol) was added a solution of 10% trifloroacetic anhydride in trifluoroacetic acid (13 mL). The reaction mixture was refluxed for 4 h and then cooled to 0 °C. The pH was adjusted to 8 by the addition of saturated Na_2CO_3. The mixture was extracted

(21) This also must be an error, since a total of 9 singlets were reported.[4]

(22) We suspect that this discrepancy is due to an error such that the 6.07 should have been 6.70.

(23) Teitel, S.; Brossi, A. *J. Org. Chem.* **1972**, *37*, 1879-81.

(24) **Note Added in Proof.** Since acceptance of this manuscript, we have learned that Rozwadowska has synthesized egenine and corytensine by DIBAL reduction of bicuculline and adlumidine, and reached the same conclusion regarding the identity of decumbensine and epi-α-decumbensine: Rozwadowska, M. D.; Matecka, D. *Liebigs Ann. Chem.*, in press. We are grateful to Professor Rozwadowska for informing us of her work prior to publication.

with three 20-mL portions of CH_2Cl_2. The combined organic phases were dried over anhydrous Na_2CO_3, filtered, and evaporated in vacuo. The residue was purified by radial chromatography, eluting with 10% MeOH/90% CH_2Cl_2 to give 1.17 g (93%) of a yellow oil: ^1H NMR (60 MHz) 1.09 (9 H, s), 1.95–2.55 (4 H, m), 4.19 (1 H, d, J = 5.4 Hz), 5.83 (2 H, s), 5.93 (2 H, s), 6.02 (1 H, d, J = 5.4 Hz), 6.26 (1 H, s), 6.53 (1 H, s), 6.70–6.83 (3 H, m); ^{13}C NMR (100 MHz) 176.98, 147.73, 147.20, 146.17, 145.30, 132.16, 129.45, 126.90, 120.29, 108.62, 108.21, 107.19, 107.10, 101.08, 100.57, 77.19, 60.08, 40.15, 38.80, 29.77, 27.02; DCIMS (CH_4) 412 (M + 1), 310 (M - $OCOC(CH_3)_3$), 176 (100, M - $(OCH_2O)C_6H_3CHOCOC(CH_3)_3$).

[*R*-(*R,*R**)]-α-1,3-Benzodioxol-5-yl-5,6,7,8-tetrahydro-1,3-dioxolo[4,5-*g*]isoquinoline-5-methanol (15).** A solution of the pivaloate **14** (501 mg, 1.22 mmol) in THF (10 mL) was added dropwise to a suspension of LAH (139 mg) in THF at 0 °C. The reaction mixture was refluxed for 6 h. Upon cooling to 0 °C and diluting with an equal volume of ether, the excess LAH was decomposed by the dropwise addition of water (1.0 mL). The solid was filtered, and the organic phase was washed with brine. The organic phase was dried over $MgSO_4$ and filtered, and the solvent was removed in vacuo. The residue was purified by radial chromatography, eluting with 10% MeOH/90% CH_2Cl_2 to give 242 mg (60%) of the product as a white solid: ^1H NMR (400 MHz) 2.67–2.79 (2 H, m), 2.97–3.05 (1 H, m), 3.12–3.20 (1 H, m), 3.88 (1 H, d, J = 6 Hz), 4.62 (1 H, d, J = 6 Hz), 5.84 (1 H, s), 5.86 (1 H, s), 5.97 (2 H, s), 6.01 (1 H, s), 6.55 (1 H, s), 6.73 (1 H, d, J = 7 Hz), 6.77 (1 H, d, J = 7 Hz), 6.91 (1 H, s); ^{13}C NMR (100 MHz) 147.75, 147.01, 146.19, 145.31, 135.89, 128.86, 127.71, 120.69, 108.65, 107.93, 107.45, 107.22, 100.97, 100.60, 74.90, 61.57, 39.48, 29.72; DCIMS (CH_4) 328 (M + 1), 310 (M - OH), 176 (100, M - $(OCH_2O)C_6H_3CHOH$); IR 3300 (broad, OH, NH); mp 153.5–155 °C; $[\alpha]_D$ +90° (c 0.72, $CHCl_3$). Anal. Calcd for $C_{18}H_{17}NO_5 \cdot 0.25H_2O$: C, 65.15; H, 5.32. Found: C, 65.44; H, 5.30.

General Procedure for the Preparation of Oxazolidones 16e and 16t. To a solution of **15** or the tartrate of **12** in CH_2Cl_2 was added an equal volume of saturated Na_2CO_3. The reaction mixture was cooled to 0 °C and 3 equiv of a 1.94 M solution of phosgene in toluene was added dropwise. The reaction mixture was stirred overnight. The layers were separated, and the organic phase was washed with 10% HCl and brine. The organic phase was dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was recrystallized from $CHCl_3$.

(1*S*)-*cis*-1,5,6,10b-Tetrahydro-1-(1,3-benzodioxol-5-yl)-3*H*-oxazolo[4,3-*a*]-1,3-dioxolo[4,5-*g*]isoquinolin-3-one (16e) was obtained in 98% yield (254 mg) as a white solid from 351 mg of the tartrate of **12**: ^1H NMR (400 MHz) 2.55–2.59 (1 H, m), 2.83–2.89 (1 H, m), 3.05–3.12 (1 H, m), 4.14–4.18 (1 H, m), 5.26 (1 H, d, J = 8 Hz), 5.72 (1 H, d, J = 8 Hz), 5.82 (2 H, s), 5.87 (1 H, s), 5.88 (1 H, s), 6.06 (1 H, s), 6.47 (1 H, s), 6.49 (1 H, s), 6.59 (1 H, d, J = 8 Hz), 6.63 (1 H, d, J = 8 Hz); ^{13}C NMR (100 MHz) 28.6 (t), 39.0 (t), 59.2 (d), 80.6 (d), 100.9 (t), 101.1 (t), 106.9 (d), 107.1 (d), 107.8 (d), 108.9 (d), 121.3 (d), 123.5 (s), 127.8 (s), 129.0 (s), 146.1 (s), 146.5 (s), 147.7 (s), 147.9 (s), 157.2 (s); mp 217–219 °C; $[\alpha]_D$ -219.6° (c 0.25, $CHCl_3$). Anal. Calcd for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28. Found: C, 64.41; H, 4.31.

(1*S*)-*trans*-1,5,6,10b-Tetrahydro-1-(1,3-benzodioxol-5-yl)-3*H*-oxazolo[4,3-*a*]-1,3-dioxolo[4,5-*g*]isoquinolin-3-one (16t) was obtained in 86% yield (464 mg) as a white solid from 500 mg of **15**: ^1H NMR (400 MHz) 2.65 (1 H, d, J = 14 Hz), 2.95–3.02 (1 H, m), 3.09–3.20 (1 H, m), 4.11–4.17 (1 H, m), 4.80 (1 H, d, J = 7 Hz), 5.04 (1 H, d, J = 7 Hz), 5.93 (2 H, s), 6.03 (2 H, s), 6.33 (1 H, s), 6.63 (1 H, s), 6.87 (1 H, d, J = 7 Hz), 6.95 (1 H, d, J = 7 Hz), 6.99 (1 H, s); ^{13}C NMR (20 MHz) 156.9, 148.6, 147.2, 146.7, 131.3, 127.0, 126.4, 121.3, 109.3, 108.5, 107.6, 104.5, 101.5, 101.1, 83.8, 61.6, 38.5, 28.1; mp 128–131 °C; $[\alpha]_D$ -31.6° (c 0.7, $CHCl_3$). Anal. Calcd for $C_{19}H_{15}NO_6$: C, 64.59; H, 4.28. Found: C, 64.42; H, 4.27.

General Procedure for the Reduction of Oxazolidinones 16e and 16t. A solution of the oxazolidinone in THF was added dropwise to a cooled (0 °C) suspension of LAH (3 equiv) in THF. The reaction mixture was refluxed for 15–20 h. Upon cooling to 0 °C and diluting with an equal volume of ether, the excess LAH was decomposed by the dropwise addition of water. The resulting solid was filtered, and the solution was washed with brine. The organic phase was dried over $MgSO_4$ and filtered, and the solvent was evaporated in vacuo. The crude product was recrystallized from Et_2O.

[*R*-(*R,*S**)]-α-1,3-Benzodioxol-5-yl-5,6,7,8-tetrahydro-6-methyl-1,3-dioxolo[4,5-*g*]isoquinoline-5-methanol (5)** was obtained in 95% yield (337 mg) as a white solid from 368 mg of **16e**: ^1H NMR (400 MHz) 2.49–2.64 (3 H, m), 2.57 (3 H, s), 2.90 (1 H, t, J = 6 Hz), 3.70 (1 H, d, J = 4 Hz), 4.93 (1 H, d, J = 4 Hz), 5.85 (1 H, d, J = 1.4 Hz), 5.88 (1 H, d, J = 1.4 Hz), 5.92 (2 H, q, J = 1.2 Hz), 6.00 (1 H, s), 6.53 (1 H, s), 6.59 (1 H, d, J = 4 Hz), 6.61 (1 H, s), 6.70 (1 H, d, J = 4 Hz); ^{13}C NMR (20 MHz) 27.2, 44.0, 49.4, 70.0, 74.5, 100.6, 100.7, 107.1, 107.6, 108.1, 108.6, 119.6, 125.5, 129.9, 135.4, 145.1, 146.1, 146.5, 147.3; IR 3350 (OH, broad); MS (EI) 342 (M + 1), 324 (M - 17, loss of OH), 190 (M - 151, isoquinoline, 100); CIMS (isobutane) 342 (M + 1, 100), 324 (M - 17, loss of OH), 190 (isoquinoline), 151 (benzylic alcohol); $[\alpha]_D$ -15° (c = 1.08, $CHCl_3$). Spectral data were identical with literature reports.[6]

[*R*-(*R,*R**)]-α-1,3-Benzodioxol-5-yl-5,6,7,8-tetrahydro-6-methyl-1,3-dioxolo[4,5-*g*]isoquinoline-5-methanol (6)** was obtained in 86% yield (379 mg) as a white solid from 460 mg of **16t**: ^1H NMR (400 MHz) 2.51 (3 H, 3), 2.41–2.58 (1 H, m), 2.79–3.0 (2 H, m), 3.25–3.39 (1 H, m), 3.33 (1 H, d, J = 9 Hz), 4.29 (1 H, d, J = 9 Hz), 5.52 (1 H, s), 5.78 (1 H, d, J = 1 Hz), 5.82 (1 H, d, J = 1 Hz), 5.96 (2 H, d, J = 2 Hz), 6.54 (1 H, s), 6.61 (1 H, d, J = 8 Hz), 6.72 (1 H, d, J = 8 Hz), 6.87 (1 H, s); ^{13}C NMR (20 MHz) 147.7, 147.2, 146.3, 144.8, 135.4, 127.2, 125.3, 121.9, 109.5, 108.2, 107.8, 107.7, 100.9, 100.5, 75.6, 69.9, 44.4, 42.0, 23.0; IR 3400 (broad, OH, NH); DCIMS (CH_4) 342 (M + 1), 324 (M - 17, loss of OH), 190 (isoquinoline, 100); mp 115.5–117.5 °C; $[\alpha]_D$ +177° (c 0.35, $CHCl_3$). Spectral data were identical with literature reports.[6]

Metalation of 5 and 6. A solution of the isoquinoline **5** or **6**, 0.05 M in THF, was cooled to -45 °C. *n*-BuLi (3 equiv) was added via syringe. The solution was stirred at -45 °C for 2 h.

Quench with DMF. To the 6′-lithiated **5** or **6** was added DMF (3 equiv) via syringe. The reaction mixture was allowed to warm to room temperature and washed with brine. The aqueous phase was washed with ethyl acetate, and the combined phases were dried over $MgSO_4$, filtered, and evaporated in vacuo. The residue was purified by radial chromatography, eluting with 10% MeOH/CH_2Cl_2.

Egenine (2) was obtained in 31% yield (70 mg) from 209 mg of **5** along with 122 mg (58%) of unreacted **5**: ^1H NMR (400 MHz) 1.78–1.85 (1 H, m), 1.98–2.04 (1 H, m), 2.36–2.42 (1 H, m), 2.51 (3 H, s), 2.67–2.74 (1 H, m), 3.88 (1 H, d, J = 3.6 Hz), 5.40 (1 H, d, J = 3.6 Hz), 5.65 (1 H, d, J = 7.6 Hz), 5.96 (2 H, d, J = 1.2 Hz), 6.03 (2 H, d, J = 1.2 Hz), 6.34 (1 H, s), 6.53 (1 H, d, J = 7.6 Hz), 6.58 (1 H, s), 6.80 (1 H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) 22.30 (t), 43.97 (q), 45.91 (t), 64.91 (t), 86.94 (d), 97.88 (d), 100.89 (t), 101.68 (t), 107.57 (d), 108.31 (d), 108.65 (d), 114.60 (d), 123.99 (s), 124.11 (s), 128.60 (s), 133.09 (s), 141.45 (s), 146.42 (s), 146.58 (s), 148.17 (s); IR 3500–3200 (broad OH); DCIMS (CH_4) 370 (M + 1), 190, 179, 163; $[\alpha]_D$ -214° (c 0.55, $CHCl_3$), -94° (c 0.55, MeOH) (lit. +214°, and +99° for the [*S*-(*R**,*S**)] isomer).[3]

Corytensine (4) was obtained in 31% yield (101 mg) from 305 mg of **6** along with 150 mg (49%) of unreacted **6**: ^1H NMR (400 MHz) 1.96 (3 H, s), 2.37–2.49 (2 H, m), 2.91–2.94 (1 H, m), 3.09–3.13 (1 H, m), 3.68 (1 H, s), 5.23 (1 H, s), 5.89 (1 H, s), 5.94 (1 H, s), 6.04 (1 H, s), 6.08 (1 H, s), 6.25 (1 H, s), 6.60 (1 H, s), 6.71 (1 H, s), 6.84 (2 H, AB quartet, J = 8.5); ^{13}C NMR (100 MHz) 148.16 (s), 146.34 (s), 146.10 (s), 141.60 (s), 135.18 (s), 130.50 (s), 128.60 (s), 124.09 (s), 113.78 (d), 108.88 (d), 108.13 (d), 106.84 (d), 101.84 (t), 100.87 (t), 97.66 (d), 89.79 (s), 68.53 (d), 53.80 (t), 46.70 (q), 29.22 (t); DCIMS (CH_4) 370 (M + 1), 190 isoquinoline, 100); mp 208–210 °C; $[\alpha]_D$ -138° (c 0.5, $CHCl_3$) (lit. +168° for the [*S*-(*R**,*R**)]isomer).[4]

Bicuculline (1). To a solution of metalated **5** (97 mg, 0.28 mmol) was introduced a stream of CO_2. The reaction mixture was allowed to warm to room temperature whereupon an equal volume of water was added. The layers were separated, and the aqueous phase was washed with ethyl acetate. The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo to yield 30 mg (31%) of unreacted starting material. The aqueous phase was made acidic by the addition of concentrated HCl and stirred for 45 min. The solution was made basic by the addition of Na_2CO_3 and washed with three 15-mL portions of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, filtered, and

evaporated in vacuo. The residue was purified by radial chromatography, eluting with 10% $MeOH/CH_2Cl_2$ to yield 46 mg (44%) of product: $[\alpha]_D$ −125° (c 0.2, $CHCl_3$) (lit. −128).[23]

Reduction of Egenine and Corytensine. To a solution of the phthalide isoquinoline hemiacetal in ethanol was added 1 molar equiv of $NaBH_4$. The reaction mixture was stirred overnight at room temperature. After removal of the solvent in vacuo, saturated ammonium chloride was added, and the mixture was extracted with three portions of CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and evaporated in vacuo. The residue was purified by radial chromatography, eluting with 10% $MeOH/CH_2Cl_2$.

Bicucullinediol (17e) was obtained in 73% yield (8 mg) from 11 mg of **2**: $[\alpha]_D$ +16.3° (c, 0.4, $CHCl_3$) (lit. −17° for the [S-(R*,S*)] isomer).[18]

Adlumidinediol (17t) was obtained in 74% yield (14 mg) from 19 mg of **4**: $[\alpha]_D$ +25° (c 0.3, $CHCl_3$) (lit. −24° for the [S-(R*,R*)] isomer).[18]

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Supplementary Material Available: NMR spectra for compounds **2**, **4–6**, and **12–16** (18 pages). Ordering information is given on any current masthead page.

Synthesis and Electrochemical Properties of Benzo[*b*]naphtho[2,3-*e*][1,4]dioxin-6,11-quinones and Their *N,N'*-Dicyano Quinone Diimine Derivatives

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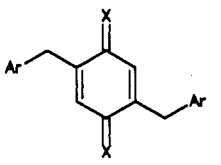
The reaction of 2,3-dichloro-1,4-naphthoquinone (1) and catechols **2** in pyridine affords a series of substituted benzo[*b*]naphtho[2,3-*e*][1,4]dioxin-6,11-quinones **3**. The latter compounds are transformed to the corresponding *N,N'*-dicyano quinone diimines **4**, by treating them with *N,N'*-bis(trimethylsilyl)carbodiimide. The electrochemical studies of compounds of the type **3** and **4** in DMF and CH_2Cl_2, respectively, by means of cyclic voltammetry are reported. The experimental reduction potentials provide information on electron–electron repulsion in the dianionic states of **3** and **4**, and hence on their potential use as acceptor components in charge-transfer complexes and organic conductors.

Introduction

The attainment of electrical conductivity in organic materials composed of electron-donor–acceptor (EDA) complexes depends upon fulfilling some well-defined criteria.[1] One of these is the requirement of a partial degree of the transfer of charge (ρ) from donor to acceptor. In principle, ρ may be "tuned" via suitable substitution to vary the electron affinity of the acceptor and/or ionization potential of the donor. The propensity of any donor–acceptor pair to form a variety of stoichiometric complexes considerably reduces the chemist's control over predetermination of ρ. To a large extent stoichiometric control may be achieved by preparing single molecular entities, in which both donor and acceptor units are *chemically linked* by electronically noninteracting or weakly interacting linkages.

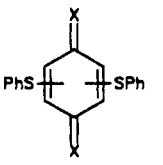
In accord with this strategy we have reported on compounds that contain two donors (D) linked to an acceptor (A) as in I or II,[1-3] or two acceptors linked to one donor, as in III.[4a] Attempts to synthesize planar CH_2-bridged D_2A molecules lead to new tetracyanopentacenquinodimethane acceptors (TCPQ).[4b]



I

X = O, N–CN, $C(CN)_2$

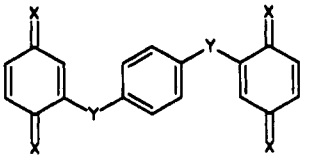
Ar = C_6H_5, p–$MeOC_6H_4$, β–Naphthyl



II

X = O, N–CN

(2,6–and 2,5–isomers)



III

(X = O, N–CN; Y = CH_2, S)

In spite of the rather surprising tendency for many of these compounds to form the segregated stacks necessary

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(2) (a) Becker, J. Y.; Bernstein, J.; Bittner, S.; Levi, N.; Shaik, S. S.; Zer-Zion, N. *J. Org. Chem.* **1988**, *53*, 1689. (b) Bittner, S.; Harlev, E. *Synthesis* **1989**, 868.

(3) Becker, J. Y.; Bernstein, J.; Bittner, S.; Harlev, E.; Sarma, J. A. R. P.; Shaik, S. S. *Nouv. J. Chem.* **1988**, *12*, 875; *Chem. Materials* **1988**, *1*, 412.

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