1.56 (d, 3, J = 7 Hz, Me), 3.07, 3.45 (s, 3 each, acetal methoxyls), 3.62 (s, 3, ester OMe), 4.65 (br s, 1, H-3), 4.72 (d, 1, J = 8 Hz, O_2CH), 5.63 (q, 1, J = 7 Hz, H-19), 7.0-7.4 (m, 4, Ar Hs).

Geissoschizol (2). The **8c** → **8d** conversion was repeated with 22 mg (0.068 mmol) of ester **15c** and 5 mg (0.13 mmol) of lithium aluminum hydride, yielding 19 mg (94%) of colorless, crystalline alcohol **2**: mp 99-103 °C (CH_2Cl_2-C_6H_{14}) (lit.[13] mp 190-194 °C dec); UV, IR, and ^1H NMR spectrally identical with literature data;[15a,39] ^{13}C NMR δ 12.8 (C-18), 18.1 (C-6), 31.5 (C-15), 32.5 (C-14), 35.6 (C-16), 51.0 (C-5), 53.4 (C-3), 53.9 (C-21), 61.4 (C-17), 107.1 (C-7), 110.9 (C-12), 117.9 (C-9), 119.3 (C-10), 120.9 (C-19), 121.3 (C-11), 127.3 (C-8), 133.9 (C-2), 135.9 (C-20 or C-13), 136.2 (C-13 or C-20).

Geissoschizine (3). A solution of 14 mg (0.035 mmol) of ester **15d** and 3 mL of a 4 N hydrochloric acid solution in 4 mL of THF was stirred at room temperature for 18 h. Enough saturated sodium bicarbonate solution was added to neutralize the solution, and the mixture was extracted with methylene chloride. The extract was washed with 5% sodium hydroxide solution and brine, dried, and evaporated, leading to the recovery of 5 mg (36%) of starting ester **15d**. The aqueous, alkaline solution was neutralized with citric acid and extracted with methylene chloride. The extract was washed with brine, dried, and evaporated. Crystallization of the residue from chloroform yielded 5 mg (63%, based on consumed **15d**) of colorless, crystalline ester **3**: mp 185-188 °C ($CHCl_3$) (lit.[13] mp 187-189 °C); spectrally identical with literature data.[40,41]

Acknowledgment. The authors are indebted to P. D. R. Moeller for NMR technical assistance and to the U.S. Public Health Service for financial support.

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Synthetic Studies on the Lithiated Toluamide-Imine Cycloaddition Route to (±)-Corydalic Acid Methyl Ester[1]

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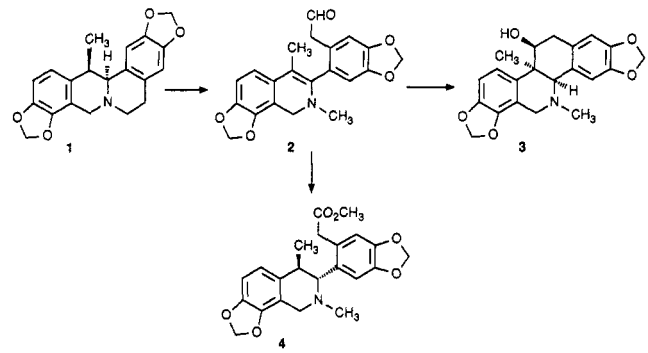
A total synthesis of (±)-corydalic acid methyl ester (**4**) was accomplished. Initial attempts to prepare the key intermediate **5** by condensation of lithiated toluamide **6** with benzaldimine **8** followed by trapping with iodomethane failed. This was apparently due to lack of deprotonation of the initial adduct **17** under the reaction conditions. However, condensation of the 6-ethyl *N,N*-diethylamide **14** with **8** stereospecifically afforded **5** after ring closure of the initially formed adduct **23**. The vinyl group of **5** was converted to the phenylacetic acid side chain, and subsequent reduction of the lactam furnished the racemic natural product **4**.

Corydalic acid methyl ester (**4**) is a tetrahydroisoquinoline alkaloid isolated along with protoberberine and benzo[*c*]phenanthridine alkaloids from *Corydalis incisa* Pers.[3] This alkaloid is presumably derived from aldehyde **2**, a hypothetical biosynthetic intermediate in the conversion of the tetrahydroprotoberberine alkaloids (e.g. tetrahydrocorysamine, **1**) to the benzo[*c*]phenanthridines (e.g. corynoline, **3**).[4] The development of a route to *trans*-3,4-disubstituted 3,4-dihydro-1(2*H*)-isoquinolones by cycloaddition of lithiated *o*-toluamides and benzaldimines followed by electrophilic trapping[5] prompted us to undertake a synthesis of (±)-corydalic acid methyl ester, utilizing this methodology.[6,7] Reported herein are the results of these investigations, which resulted in a stereospecific total synthesis of racemic **4**.

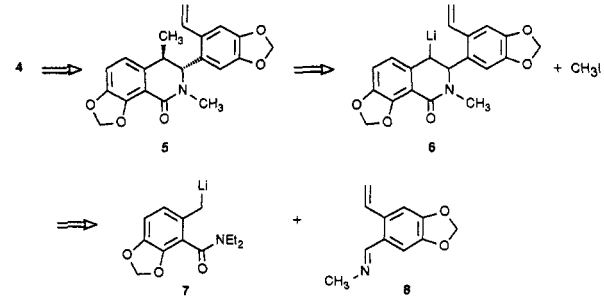
Results and Discussion

Our initial synthetic strategy (Scheme II) involved the preparation of key intermediate **5** by methylation of lithio derivative **6**, which would be available from condensation of lithiated toluamide **7** with benzaldimine **8** followed by

Scheme I



Scheme II



(1) Contribution No. 775 from the Institute of Organic Chemistry.
(2) Syntex Postdoctoral Fellow, 1987-1988.
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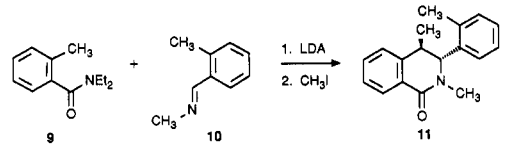
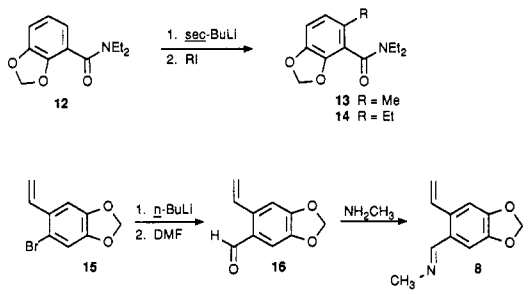
(5) (a) Clark, R. D.; Jahangir *J. Org. Chem.* **1987**, *52*, 5378. (b) Clark, R. D.; Jahangir *J. Org. Chem.* **1988**, *53*, 2378.
(6) Some of this work has been presented in preliminary form: Clark, R. D.; Jahangir *Heterocycles* **1988**, *27*, 871.
(7) A total synthesis of (±)-4 has been reported: ref 4a. A biomimetic synthesis from the protoberberine alkaloid corysamine has also been carried out: Hanaoka, M.; Yoshida, S.; Mukai, C. *J. Chem. Soc., Chem. Commun.* **1984**, 1703.

0022-3263/89/1954-1174$01.50/0

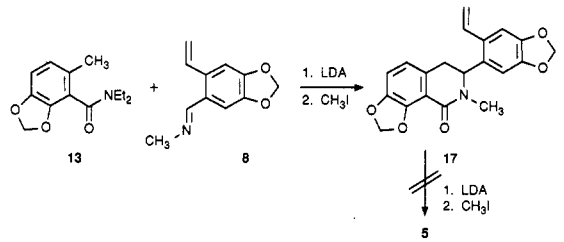
Scheme III



Scheme IV



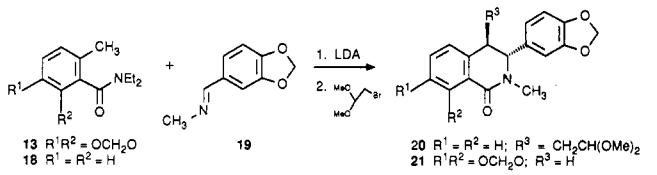
Scheme V



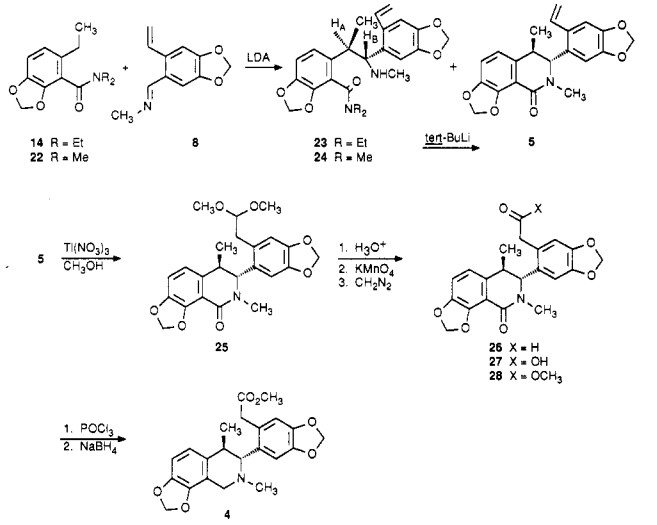
in situ deprotonation. On the basis of the results of previous studies, methylation of **6** was expected to stereospecifically produce the desired trans stereoisomer **5**.[5] An initial model study (Scheme III) established that this would be the case and that ortho substitution in the benzaldimine was tolerated. Addition of a mixture of **9** and **10** to a −70 °C THF solution of lithium diisopropylamide (LDA) followed by warming to −45 °C and addition of iodomethane provided the trans stereoisomer **11** in 45% yield.

The requisite *N,N*-diethyltoluamide **13** and benzaldimine **8** for the key condensation step (Scheme II) were prepared as described in Scheme IV. Ortho lithiation[8] of the *N,N*-diethylamide of 2,3-(methylenedioxy)benzoic acid **12** followed by alkylation with iodomethane afforded **13**[8b] in 75% yield. The known bromostyrene **15**,[9] prepared from 6-bromopiperonal and methylene triphenylphosphorane, was converted to aldehyde **16** and thence to imine **8** in standard fashion. However, addition of a mixture of **8** and **13** to a −70 °C THF solution of LDA followed by iodomethane quench as before gave the unalkylated cycloadduct **17** in 61% yield instead of the desired methylated derivative **5** (Scheme V). The condensation step was allowed to proceed at temperatures ranging from −70 °C to −40 °C before addition of iodomethane, but conditions for effecting the methylation were not found. Attempts to deprotonate **17** with LDA in THF at from −70 °C to −40 °C followed by addition of iodomethane were also unsuccessful. It appeared that **17** was not deprotonated under these conditions since deuterium oxide quench

Scheme VI



Scheme VII



failed to give deuterium incorporation (^{1}H NMR analysis).[10]

On the basis of circumstantial evidence, we believe that the failure of **17** to undergo deprotonation under the conditions of the cycloaddition reaction is a result of the 7,8-methylenedioxy substitution in the 3,4-dihydro-1-(2*H*)-isoquinolone. In previous studies on the preparation of intermediates for the synthesis of benzo[*c*]-phenanthridines, we had noted a similar phenomenon (Scheme VI).[5b] Thus, condensation of the lithio derivative of toluamide **18** with imine **19** followed by trapping with bromoacetaldehyde dimethylacetal afforded the 4-alkylated product **20** in 54% yield. On the other hand, the corresponding methylenedioxy derivative **13** afforded the 4-unsubstituted 3,4-dihydro-1(2*H*)-isoquinolone **21** under the same reaction conditions. A rationale for this effect of 7,8-methylenedioxy substitution on preventing deprotonation at the 4-position of the 3-substituted 3,4-dihydro-1(2*H*)-isoquinolones **17** and **21** is not readily apparent. It appears not to be simply a result of alkoxy substitution meta and para to the C-4 benzylic position since we have previously obtained C-4 alkylated products from 6,7-dimethoxy 3,4-dihydro-1(2*H*)-isoquinolones.[5b] Nor does aromatic ring deprotonation appear to be involved since deuterium incorporation was not observed. A possible explanation is that the acidity of the C-4 benzylic protons is reduced by the methylenedioxy group thereby preventing deprotonation.[11]

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(10) Temperatures higher than −40 °C were not investigated since previous work indicated that lithio species such as **6** underwent various side reactions (e.g. stilbene formation) above this temperature (ref 5a). In the case of **17**, we also observed what appeared to be products resulting from cleavage of the 7,8-methylenedioxy group. Also on the basis of our previous results we regard the possibility that the anion, if formed, quenches by alkylation or deuteration on oxygen as unlikely. Stronger bases were not investigated, and in light of later results (vide infra) this two-step sequence would probably not be competitive in any case.

The inability to introduce the C-4 methyl group by alkylation of **6** necessitated a change in strategy involving introduction of the methyl group prior to the condensation step, i.e. using the 6-ethylamide **14** instead of toluamide **13**. The preparation of **14** from **12** (55% yield) was analogous to that of **13**, thereby maintaining the same number of steps in the overall sequence. Previous results from condensation of *N,N*-diethyl-2-(3-butenyl)benzamide with a benzaldimine indicated that while the *trans*-3,4-dihydro-1(2*H*)-isoquinolone would ultimately be obtained, an additional ring closure step might be anticipated.[5a] This, in fact, proved to be the case. Condensation of **8** and **14** in the presence of LDA initially at −70 °C with subsequent warming to room temperature afforded the adduct **23** in 50% yield along with 28% of the desired trans cycloadduct **5** (Scheme VII). The two products were readily separable by fractional crystallization and/or chromatography. As determined by ^{1}H NMR analysis, **23** and **5** were obtained as single diastereomers. The stereochemistry of **23** was assigned on the basis of the J_{AB} of 10.5 Hz, which is consistent with the staggered conformation expected for the erythro diastereomer (**23**). The formation of this diastereomer could be the result of a transition state in which the lithio derivative of **14** and the imine **8** adopt a staggered conformation to minimize steric interactions.[12] It is also possible that **23** represents a thermodynamic product resulting from equilibration. The trans stereochemistry of **5** was assigned from the J_{AB} of 1.3 Hz for H-3 and H-4, which is characteristic of *trans*-3,4-disubstituted dihydroisoquinolones.[4,5,13] Subsequent treatment of **23** with 2 equiv of *tert*-butyllithium in THF at −30 °C smoothly effected ring closure to **5** in 84% yield. Thus the overall yield of **5** obtained by this two-step sequence was 70%.[14]

Attempts to obtain **5** as the sole product directly from the condensation of **8** and **14** were unsuccessful.[15] Reasoning that the steric bulk of the *N,N*-diethylamide group was hindering the ring closure of **23** to **5**,[16] we investigated the corresponding dimethylamide **22**.[17] However, this modification offered no improvement as under the same reaction conditions as used previously for condensation of **8** and **14**, the condensation with **22** afforded essentially the same amount of **5** (30%) and slightly less of the adduct **24** (35%). An attempt to circumvent the isolation of adduct **24** by condensing **8** and **22** at −70 °C followed by warming to −50 °C and addition of 2 equiv of *tert*-butyllithium and stirring for 1 h at −30 °C did improve the yield of **5** but only to 43% (with 8% of **24** also isolated). Therefore, we were not able to improve upon the original two-step sequence in which adduct **23** was isolated and then cyclized to give a 70% overall yield of **5**.

The inability to obtain complete ring closure to **5** during these condensations remains puzzling. Close monitoring of the reaction mixtures by TLC, or quenching and isolation, revealed that while **5** was formed to a certain degree even at −70 °C, adduct **23** (or **24**) remained the major product even upon warming to room temperature. The observation that **23** was converted to **5** in high yield upon treatment with *tert*-butyllithium implies that in the original condensation reaction mixture, the additional amine components present (diethyl- and diisopropylamine) may induce an unfavorable equilibrium in which the methylamino group of **23** is not deprotonated sufficiently to close to **5**.[18]

Conversion of **5** to corydalic acid methyl ester was completed as shown in Scheme VII. Treatment of **5** with thallium trinitrate in methanol[19] afforded acetal **25**, which was hydrolyzed to the somewhat unstable aldehyde **26**. Oxidation with the aqueous permanganate–benzene–tetrabutylammonium bromide system[20] followed by diazomethane esterification afforded the known methyl ester **28**[4a] in an overall yield of 60% from **5**. Conversion of **28** to (±)-corydalic acid methyl ester (**4**) was effected in 66% yield as described by Cushman and Wong[4a] by treatment with phosphorus oxychloride followed by sodium borohydride reduction of the iminium chloride intermediate.[21] Racemic **4** thus obtained had spectral properties and melting point in accord with those reported[4a] and was identical by TLC with an authentic sample kindly provided by Professor Cushman.

Conclusion

The studies reported herein revealed several limitations of the lithiated toluamide–benzaldimine cycloaddition methodology. Nonetheless, the first stereospecific total synthesis of (±)-corydalic acid methyl ester was achieved, which proceeded in 28% overall yield from the point of convergence of the readily available intermediates **8** and **14**. With the previously reported syntheses of certain tetrahydroprotoberberines[5a] and benzo[*c*]-phenanthridines,[5b] this methodology has now been utilized for the preparation of examples of all three classes of alkaloids represented represented in Scheme I.

Experimental Section

Proton magnetic resonance spectra were recorded at 100, 300, or 500 MHz. Medium-pressure (flash) chromatography was performed with 230–400 mesh Merck kieselgel. Melting points are uncorrected.

(±)-*trans*-*N*-Methyl-3-(2-methylphenyl)-4-methyl-3,4-dihydro-1(2*H*)-isoquinolone (11). A solution of *N,N*-diethyl-*o*-toluamide **9** (950 mg, 5 mmol) and imine **10** (800 mg, 6 mmol) in 6 mL of dry THF was added dropwise to a −70 °C solution of LDA (from 0.84 mL (6 mmol) of diisopropylamine and 3.75 mL (6 mmol) of 1.6 M *n*-BuLi in hexane) in 10 mL of THF. The reaction mixture was allowed to stir with gradual warming to −45

(11) We thank a referee for offering the following as a possible explanation. An *o*-dimethoxybenzene could chelate lithium between the oxygens, and this would decrease the electron-donating ability of the oxygens and make C-4 deprotonation more facile. A similar chelate would not be possible for a methylenedioxy group because of the bridging methylene. In this case, the C-4 benzylic protons would experience the full electron-donating effect of the oxygens and a resulting decrease in acidity. This may also imply that chelation of lithium between the methylenedioxy C-8 oxygen and the amide carbonyl does not enhance the acidity of the C-4 benzylic protons.

(12) Similar to the transition state described by Felkin: Cherest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199.

(13) Cushman, M.; Choong, T.-C.; Valko, S. T.; Koleck, M. P. *J. Org. Chem.* **1980**, *45*, 5067.

(14) There was no evidence for formation of the cis isomer of **5** either from the initial condensation or from closure of **23**. This appears to have been fortuitous since our inability to deprotonate **17** with LDA implies that the cis isomer of **5**, if formed, might not equilibrate to the trans isomer (**5**).

(15) These attempts included adding stronger bases (*t*-BuLi) to the reaction mixture and prolonged reaction times.

(16) In certain other cyclocondensations we have observed more facile ring closure with *N,N*-dimethylamides. Jahangir, unpublished results.

(17) Because *N,N*-dimethylamides cannot be ortho metalated and alkylated in the same manner as *N,N*-diethylamides (ref 8), the preparation of **22** varied from that of **14**. Thus the cyclohexyl imine of piperonal was lithiated and condensed with dimethylcarbamoyl chloride. The resulting aldehydo amide was methylenated (methylenetriphenylphosphorane) and then hydrogenated to give **22**.

(18) In theory, the addition of *t*-BuLi to the **8**, **22** condensation mixture should have solved this problem. However, while the yield of desired product was increased (to 43%), decomposition processes apparently kept the yield from being higher.

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(20) Herriott, A. W.; Picker, D. *Tetrahedron Lett.* **1974**, 1511.

(21) Kuehne, M. E.; Shannon, P. J. *J. Org. Chem.* **1977**, *42*, 2082.

°C over 2 h and then cooled back to −70 °C. Iodomethane (1.24 mL, 20 mmol) was added, and the mixture was stirred below −60 °C for 1 h and then allowed to warm to room temperature. The reaction mixture was then quenched with saturated ammonium chloride solution, and thoroughly extracted with EtOAc. The combined EtOAc extracts were washed with brine, dried (Na_2SO_4), and evaporated in vacuo. The residue was chromatographed on silica gel (10–50% EtOAc–hexane) to give 590 mg (44.5%) of compound **11** of mp 130–131 °C (EtOAc–hexane): IR ($CHCl_3$) 1640 cm^{-1}; NMR ($CDCl_3$) δ 8.18 (m, 1 H), 7.33 (m, 2 H), 7.20–7.07 (m, 2 H), 6.95 (m, 2 H), 6.70 (m, 1 H), 4.67 (d, J = 1 Hz, 1 H), 3.08 (s, 3 H), 3.01 (dq, J = 7.2, 1 Hz, 1 H), 2.42 (s, 3 H), 1.49 (d, J = 7.1 Hz, 3 H); MS m/e (relative intensity) 265 (39, M^+), 250 (6), 174 (30), 132 (100), 104 (29). Anal. Calcd for $C_{18}H_{19}NO$: C, 81.51; H, 7.17; N, 5.28. Found: C, 81.15; H, 7.07; N, 5.24.

***N,N*-Diethyl-6-ethyl-2,3-(methylenedioxy)benzamide (14).** A solution of 2 mL of TMEDA in 100 mL of dry THF was cooled to −78 °C under dry nitrogen, and 36.9 mL of 1.3 M *sec*-butyllithium (48 mmol) in cyclohexane was added dropwise with constant stirring. After 15 min a solution of 4.84 g (40 mmol) of amide **12** in 40 mL of THF was added dropwise. After 1 h at −78 °C, 20 mL of iodoethane in 40 mL of THF 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 ethyl acetate, and the combined extracts were washed with brine and dried (Na_2SO_4). Removal of the solvent in vacuo and chromatography on silica gel (40% EtOAc–hexane) gave 5.5 g (55%) of **14** as a colorless oil: IR (film) 1630 cm^{-1}; NMR ($CDCl_3$) δ 6.75 (d, J = 8 Hz, 1 H), 6.70 (d, J = 8 Hz, 1 H), 5.96 (d, J = 1.4 Hz, 1 H), 5.91 (d, J = 1.4 Hz, 1 H), 3.75 (m, 1 H), 3.43 (m, 1 H) 3.21 (m, 2 H), 2.53 (q, 7.5 Hz, 2 H), 1.25 (t, J = 7.15 Hz, 3 H), 1.19 (t, J = 7.5 Hz, 3 H), 1.09 (t, J = 7.15 Hz, 3 H); MS m/e (relative intensity) 249 (2, M^+), 234 (4), 220 (4), 206 (15), 177 (12), 149 (100). Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.41; H, 7.78; N, 5.59.

1-Bromo-2-ethenyl-4,5-(methylenedioxy)benzene (15). Sodium hydride (7 g, 0.175 mol, 60% oil dispersion) and 600 mL of freshly distilled THF were added to a dry three-necked flask equipped with condenser, magnetic stirrer, and dry nitrogen flow. To this suspension was added methyltriphenylphosphonium bromide (49 g, 0.13 mol), and the resulting mixture was stirred for 15 min. 6-Bromopiperonal (20 g, 0.087 mol) was added slowly while stirring, and the reaction mixture was gently heated under reflux for 2 h. The reaction mixture was cooled, and excess sodium hydride was decomposed by careful addition of MeOH. The reaction mixture was diluted with 200 mL of water, the organic layer was separated, and the aqueous layer was thoroughly extracted with ether. The combined organic extracts were washed with brine and dried (Na_2SO_4), a small amount of the radical inhibitor *tert*-butyl-3,4-catechol was added, and the solvent was removed in vacuo. The residue obtained was filtered through a short silica gel (60–200 mesh) column, first eluting with hexanes to remove mineral oil and then with 20% THF–hexane to give the styrene **15**[9] (19.1 g, 96%) as a colorless oil, which was stored in the cold under argon until further use.

2-Ethenyl-4,5-(methylenedioxy)benzaldehyde (16). To a solution of bromostyrene **15** (10 g, 44 mmol) in 500 mL of dry THF at −70 °C was added dropwise 21.2 mL (53 mmol) of 2.5 M *n*-butyllithium in hexane, and the resulting mixture was stirred for 30 min under dry nitrogen at −70 °C. To this a solution of 6.8 mL (88.1 mmol) of dimethylformamide in 20 mL of THF was added dropwise, and the resulting mixture was stirred for 1 h at −70 °C and then allowed to warm gradually to room temperature over 1 h. After the reaction was quenched with saturated ammonium chloride solution, the resulting mixture was diluted with 200 mL of water. The organic layer was separated, and the aqueous layer was thoroughly extracted with ether. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated. The crude product obtained as an oil was passed through a neutral alumina column, first eluting with hexane and then with EtOAc–hexane (1:1) to give 7.56 g (97%) of **16** as an oil, which solidified on standing: IR (KBr) 1684 cm^{-1}; NMR ($CDCl_3$) δ 10.20 (s, 1 H), 7.40 (dd, J = 17.3, 10.9 Hz, 1 H), 7.28 (s, 1 H), 6.96 (s, 1 H), 6.04 (s, 2 H), 5.60 (dd, J = 17.3, 1.0 Hz, 1 H), 5.46 (dd, J = 10.9, 1 Hz, 1 H); MS m/e (relative intensity), 176 (66, M^+), 175 (21), 148 (54), 147 (100). Anal. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58. Found: C, 67.93; H, 4.55.

[2-Ethenyl-4,5-(methylenedioxy)benzylidene]methylamine (8). To a solution of 13.5 g (76.7 mmol) of aldehyde **16** in 150 mL of CH_2Cl_2 was added 15 g of 40% aqueous methylamine and 50 g of activated 3A molecular sieves, and the resulting mixture was stirred under argon for 24 h. It was then filtered, and the residue was washed several times with CH_2Cl_2. The combined CH_2Cl_2 filtrates were removed in vacuo to give 12.88 g (89%) of **8** as a colorless oil, which solidified on standing: IR ($CHCl_3$) 1640, 1613, 1503, 1478 cm^{-1}; NMR ($CDCl_3$) δ 8.54 (q, J = 1.6 Hz, 1 H), 7.37 (s, 1 H), 7.14 (dd, J = 17.3, 10.9 Hz, 1 H), 6.91 (s, 1 H), 5.96 (s, 2 H), 5.52 (dd, J = 17.3, 1.1 Hz, 1 H), 5.33 (dd, J = 10.9, 1.1 Hz, 1 H), 3.49 (d, J = 1.6, Hz, 3 H); MS m/e (relative intensity) 189 (17, M^+), 188 (100).

(±)-*N*-Methyl-3-[2-ethenyl-4,5-(methylenedioxy)-phenyl]-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (17). This reaction was carried out with amide **13** (1.175 g, 5 mmol) in the same manner as that described above for **11**. The proton NMR of the crude product indicated only a small amount (ca. 5%) of methylated product **5**. Chromatographic purification (SiO_2, EtOAc) and recrystallization from EtOAc gave 1.07 g (61%) of **17**: mp 204–205 °C; IR ($CHCl_3$, film) 1635 cm^{-1}; NMR ($CDCl_3$) δ 6.96 (s, 1 H), 6.91 (dd, J = 17.1, 10.9 Hz, 1 H), 6.75 (d, J = 7.8 Hz, 1 H), 6.42 (s, 1 H), 6.40 (d, J = 7.8 Hz, 1 H), 6.19 (d, J = 1.3 Hz, 1 H), 6.12 (d, J = 1.3 Hz, 1 H), 5.91 (d, J = 1.3 Hz, 1 H), 5.86 (d, J = 1.3 Hz, 1 H), 5.57 (dd, J = 17.1, 1.1 Hz, 1 H), 5.33 (dd, J = 10.9, 1.1 Hz, 1 H), 4.98 (dd, J = 6.7, 3.0 Hz, 1 H), 3.45 (dd, J = 15.5, 6.7 Hz, 1 H), 3.03 (s, 3 H), 2.88 (dd, J = 15.5, 3.0 Hz, 1 H); MS m/e (relative intensity) 351 (100, M^+), 336 (13), 322 (39), 188 (41), 162 (91), 134 (88). Anal. Calcd for $C_{20}H_{17}NO_5$: C, 68.37; H, 4.88; N, 3.99. Found: C, 68.13; H, 5.07; N, 3.77.

(±)-*trans*-*N*-Methyl-3-[2-ethenyl-4,5-(methylenedioxy)-phenyl]-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1-(2*H*)-isoquinolone (5) and (±)-*erythro*-*N*-Methyl-1-[2-ethenyl-4,5-(methylenedioxy)phenyl]-2-[2-[(*N*,*N*-diethylamino)carbonyl]-3,4-(methylenedioxy)phenyl]propylamine (23). A solution of LDA was prepared at −70 °C by addition of 3.75 mL (6 mmol) of 1.6 M *n*-butyllithium in hexane to 0.84 mL (6 mmol) of diisopropylamine in 10 mL of dry THF under dry nitrogen. A solution of amide **14** (1.25 g, 5 mmol) in 3 mL of THF was added slowly at such a rate to maintain the internal temperature below −65 °C, and the resulting mixture was stirred for 10 min. A solution of imine **8** (1.04 g, 5.5 mmol) in 3 mL of THF was added dropwise, and the resulting mixture was stirred at −70 °C for 2 h. The mixture was then warmed gradually to room temperature and quenched with saturated ammonium chloride solution. The mixture was thoroughly extracted with ethyl acetate; the combined ethyl acetate extracts were washed with brine and dried (Na_2SO_4). On concentration of the ethyl acetate, a solid separated, which was collected by filtration and identified as adduct **23** (1.0 g). The mother liquor was subjected to flash chromatography (silica gel, EtOAc) to give 510 mg (28%) of cyclized product **5**: mp 199–202 °C (EtOAc); IR (KBr) 1649 cm^{-1}; NMR ($CDCl_3$) δ 6.97 (s, 1 H), 6.82 (dd, J = 17, 10.8 Hz, 1 H), 6.75 (d, J = 7.8 Hz, 1 H), 6.40 (d, J = 7.8 Hz, 1 H), 6.34 (s, 1 H), 6.15 (d, J = 1.3 Hz, 1 H), 6.12 (d, J = 1.3 Hz, 1 H), 5.90 (d, J = 1.3 Hz, 1 H), 5.84 (d, J = 1.4 Hz, 1 H), 5.60 (dd, J = 17, 1.1 Hz, 1 H), 5.34 (dd, J = 10.8, 1.1 Hz, 1 H), 4.66 (d, J = 1.3 Hz, 1 H), 3.06 (s, 3 H), 2.96 (dq, J = 7, 1.3 Hz, 1 H), 1.40 (d, J = 7 Hz, 3 H); MS m/e (relative intensity) 365 (100, M^+), 350 (6), 336 (7), 206 (21), 188 (11), 176 (91), 148 (66), 147 (27). Anal. Calcd for $C_{21}H_{19}NO_5$: C, 69.03; H, 5.24; N, 3.83. Found: C, 68.88; H, 5.24; N, 3.74.

An additional 100 mg of **23** was obtained from the above chromatography upon further elution. The total yield of **23** was 1.1 g (50%): mp 210–214 °C (EtOAc); IR (KBr) 1650 cm^{-1}; NMR ($CDCl_3$) δ 7.16 (d, J = 8 Hz, 1 H), 7.06 (d, J = 8 Hz, 1 H), 7.00 (m, 3 H), 6.07 (d, J = 1.4 Hz, 1 H), 6.03 (s, 2 H), 6.01 (d, J = 1.4 Hz, 1 H), 5.36 (dd, J = 10.8, 0.8 Hz, 1 H), 4.59 (d, J = 10.5 Hz, 1 H), 3.84 (m, 1 H), 3.45 (m, 2 H), 3.25 (m, 1 H), 3.13 (dq, J = 10.5, 6.9 Hz, 1 H), 2.27 (s, 3 H), 1.34 (t, J = 7 Hz, 3 H), 1.14 (d, J = 6.9 Hz, 3 H), 1.10 (t, J = 7 Hz, 3 H); MS m/e (relative intensity) 438 (5, M^+), 248 (5), 220 (5), 190 (100), 175 (14), 161

(26); exact mass calcd for $C_{25}H_{30}N_2O_5$ 438.2155, found 438.2156.

Cyclization of Adduct 23 to 5. A suspension of 1 g (2.28 mmol) of adduct **23** in 90 mL of dry THF was treated with 2.3 mL (4.6 mmol) of *tert*-butyllithium in pentane at -70 °C under dry nitrogen. The reaction mixture was slowly warmed to -30 °C and then stirred at this temperature for 1 h. The mixture was then quenched with saturated ammonium chloride solution and thoroughly extracted with ethyl acetate. The combined organic extracts were washed with brine, dried (Na_2SO_4), and evaporated, and the residue was chromatographed on silica gel (EtOAc), affording 700 mg (84%) of product homogeneous on TLC. It proved to be identical with **5** (TLC, ^1H NMR).

(±)-*trans*-*N*-Methyl-3-[2-[(methoxycarbonyl)methyl]-4,5-(methylenedioxy)phenyl]-4-methyl-7,8-(methylenedioxy)-3,4-dihydro-1(2*H*)-isoquinolone (28). A solution of 250 mg (0.68 mmol) of **5** in 15 mL of MeOH was treated dropwise with a solution of 465 mg (1.05 mmol) thallium trinitrate trihydrate in 5 mL of MeOH at room temperature. The resulting mixture was stirred for 15 min and then was diluted with 50 mL of CH_2Cl_2 and filtered. The filtrate was concentrated in vacuo to one-third of its volume and diluted with 50 mL of CH_2Cl_2 and then washed with 10% NaOH solution. The organic layer was separated, washed with brine, and dried (Na_2SO_4), and solvent was removed in vacuo to give acetal **25** as a foam, which was used in the next step without purification.

A solution of the acetal **25** obtained above in 25 mL of acetone and 10 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 aldehyde **26** as a foam in quantitative yield: NMR ($CDCl_3$) δ 9.77 (m, 1 H), 6.75 (d, J = 7.0 Hz, 1 H), 6.65 (s, 1 H), 6.40 (d, J = 7 Hz, 1 H), 6.35 (s, 1 H), 6.10 (s, 2 H), 6.0 (m, 2 H), 4.43 (s, 1 H), 3.70 (br s, 2 H), 3.0 (s, 3 H), 2.95-2.75 (m, 1 H), 1.35 (d, J = 7.0 Hz, 3 H); MS m/e (relative intensity) 381 (20, M^+), 366 (5), 353 (17), 218 (16) 176 (200), 148 (76), 147 (32). The aldehyde **26** was used at once in the following reaction without further purification.

To a vigorously stirred solution of 133 mg (0.84 mmol) of potassium permanganate in 15 mL of water were added tetrabutylammonium bromide (50 mg) and a solution of the above aldehyde **26** in 10 mL of benzene. The mixture was stirred at room temperature until TLC showed complete consumption of the aldehyde (ca 2 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 10% HCl solution, the organic layer was separated, and the aqueous layer was throughly extracted with CH_2Cl_2. The combined organic extracts were evaporated in vacuo, and the residue was dissolved in 10% sodium hydroxide solution and washed twice with ether. The aqueous layer was made acidic with concentrated 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 220 mg (81%) of acid **27** as a foam.

Esterification of acid **27** (200 mg) with diazomethane and purification on silica gel (EtOAc) gave 170 mg (82%) of the methyl ester **28**: mp 193-194 °C (EtOAc-hexane) (lit.[4a] mp 190-192 °C); IR ($CHCl_3$) 1730, 1640 cm^{-1}; NMR ($CDCl_3$) δ 6.78 (d, J = 7.8 Hz, 1 H), 6.71 (s, 1 H), 6.42 (d, J = 7.8 Hz, 1 H), 6.35 (s, 1 H), 6.16 (d, J = 1.1 Hz, 1 H), 6.13 (d, J = 1.1 Hz, 1 H), 5.88 (d, J = 1.3 Hz, 1 H), 5.84 (d, J = 1.3 Hz, 1 H), 4.64 (d, J = 1.1 Hz, 1 H), 3.74 (s, 3 H), 3.60 (d, J = 3.9 Hz, 2 H), 3.02 (s, 3 H), 2.90 (q, J = 7.1 Hz, 1 H), 1.42 (d, J = 7.1 Hz, 3 H); MS m/e (relative intensity) 411 (25, M^+), 396 (13), 380 (5), 379 (5), 218 (24), 176 (100), 148 (76), 147 (32). Anal. Calcd for $C_{22}H_{21}NO_7$: C, 64.23; H, 5.11; N, 3.41. Found: C, 63.90; H, 5.03; N, 3.36.

(±)-Corydalic Acid Methyl Ester (4). The amide **28** (50 mg) was converted to corydalic acid methyl ester (**4**) (32 mg, 66%) with $POCl_3$, and then $NaBH_4$, according to the two-step procedure described by Cushman and Wong:[4a] mp 145-147 °C (lit.[4a] mp 144-147 °C). The synthetic compound proved to be identical with the authentic sample in several solvent systems on silica gel TLC and had NMR and mass spectral data in agreement with those reported.[3,4a]

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Registry No. (±)-**4**, 88610-31-5; (±)-**5**, 118514-50-4; **8**, 118514-51-5; **9**, 2728-04-3; **10**, 18100-53-3; (±)-**11**, 118514-52-6; **12**, 70946-19-9; **13**, 70946-07-5; **14**, 118514-53-7; **15**, 79809-06-6; **16**, 3811-52-7; (±)-**17**, 118514-54-8; (±)-**23**, 118514-55-9; (±)-**25**, 118537-28-3; (±)-**26**, 118514-56-0; (±)-**27**, 118514-57-1; (±)-**28**, 88610-30-4; 6-bromopiperonal, 15930-53-7.

A Versatile and Stereocontrolled Synthesis of Hydroxyethylene Dipeptide Isosteres

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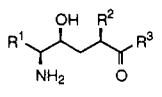
An asymmetric synthesis of the hydroxyethylene dipeptide isostere unit **1** is described. The synthesis provides excellent stereocontrol over all three chiral centers and is amenable to variation of substituents R_1 and R_2. Key intermediate (*S*)-**11** has been obtained by two different asymmetric routes and also by chemical resolution. Bromolactonization of the carboxamide **20** afforded with high 1,3-induction the trans disubstituted γ-lactone **22**, which after conversion to the azido compound **29** was ring opened and reduced to the target compound **6**.

In the course of our work on dipeptide mimics we became interested in the stereoselective synthesis of 2,5-disubstituted 5-amino-4-hydroxypentanoic acid derivatives **1**. Such "hydroxyethylene dipeptide isosters" are of considerable interest as transition state analogues,[1] e.g. in renin inhibitors where they replace the scissile dipeptide unit (Leu-Val) of angiotensinogen, the natural substrate of renin. Syntheses of hydroxyethylene dipeptide mimics were first reported by Szelke[2] and Rich[3] in 1983 and more



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