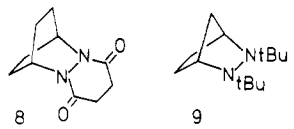
-0.09 (C≡N), and 0.13 (C≡N). A slightly bent form is calculated to be slightly stabler than the planar one. The experimental ESR spectrum suggests a much larger difference in nitrogen spin densities, since the a(N) values are in a 7:3 ratio. The ESR spectrum of $(8)^{+\cdot}$ has a(2N) = 9.6 G,[13] so the larger a(N) value for **1(CN)** should presumably be assigned to the *tert*-butylated nitrogen. The sum of the nitrogen splittings in $\mathbf{1(CN)}^{+\cdot}$ is 92% as large as the sum of them in the di-*tert*-butyl model $(9)^{+\cdot}$,[3] sug-



8 9

gesting that the cyano substituent only perturbs the hydrazine radical cation group rather weakly, i.e., that A and C do predominate.

Conclusion

Electron removal from an α-cyanohydrazine is substantially more difficult than from a β- or γ-cyanohydrazine, but slightly less so than a $\Delta E^{\circ\prime}$ vs. σ_I plot would predict. The principal reason for the different behavior of cyano substitution on electron loss from a hydrazine and an ionization to give a carbocation is suggested to be conjugative stabilization of the neutral form of an α-cyanohydrazine. Most of the spin density in α-cyanohydrazine radical cation $\mathbf{1(CN)}^{+\cdot}$ appears to be in the hydrazine nitrogen p orbitals, and the nitrogen splitting constants were in a 7:3 ratio.

Experimental Section

2-Cyano-3-*tert*-butyl-1,2,3-diazabicyclo[2.2.1]heptane (1-(CN)) was prepared by the method of Snyder and co-workers.[4] A large excess of KCN in water was added to 0.25 g (1.04 mmol) of $1^+Br_4^-$ in CH_2Cl_2.[3] After 2 h of stirring the aqueous layer was separated and washed twice with CH_2Cl_2, and the combined organic layers were dried with sodium sulfate and evaporated to give **1(CN)** as a white solid: mp 60–61 °C; 0.13 g (70%): ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9 H), 1.36 (d, J = 10.1, 1 H), 1.45–1.60 (m, 1 H), 1.6–1.7 (m, 2 H), 1.82–1.92 (m, 1 H), 2.0–2.14 (m, 1 H), 3.63 (br, 1 H), 3.92 (br, 1 H); ^{13}C NMR ($CDCl_3$) δ 27.33, 27.92, 30.61, 35.84, 58.08, 59.50, 62.68 (cyano nitrogen not observed); empirical formula $C_{10}H_{17}N_3$ established by high-resolution mass spectroscopy; IR (CCl_4) 2960, 2190, 1360, 1220, 1070 cm^{-1}.

1,1-(1,5-Cyclooctyl)-2-*tert*-butyl-2-cyanohydrazine (2(CN)) was prepared from the corresponding diazenium salt[2] by the same method as **1(CN)** in 50% yield: mp 80–81 °C; ^{1}H NMR ($CDCl_3$) v 1.25 (s, 9 H), 1.38 (dd, J = 13.9, 6.6 Hz, 2 H (2e, 4e)), 1.48–1.82 (complex, 4 H (3e, 6e, 7e, 8e)), 1.87–2.18 (complex, 4 H (3a, 6a, 7a, 8a)), 2.64 (m, 2 H), (2a, 4a)), 3.17 (br t, 2 H, 1, 5)); ^{13}C NMR ($CDCl_3$, see text); empirical formula $C_{13}H_{23}N_3$ established by high-resolution mass spectroscopy; IR (CCl_4) 2980, 2930, 2180, 1460, 1370 cm^{-1}.

(Cyanomethyl)trimethylhydrazine (3(CN)) was prepared by treating trimethylhydrazine with formaldehyde and cyanide under the conditions of Hamilton, Harris, and Winter[6] and obtained as an oil in 39% yield; ^{1}H NMR (acetone-d_6) δ 2.30 (s, 6 H), 2.35 (s, 3 H), 3.0 (s, 2 H); empirical formula $C_5H_{11}N_3$ established by high-resolution mass spectroscopy; IR (CCl_4) 2960, 2930, 2820, 2220, 1460, 1120, 1040 cm^{-1}. The cyclic voltammetric and ESR experiments were performed as previously described.[3]

Acknowledgment. We thank the National Science Foundation for generous financial support of this work under Grants CHE 77-24627 and 80-26111. We thank Timothy Clark of the University of Erlangen—Nürnberg for helpful discussions and a copy of the MNDO program.

Registry No. **1(Me)**, 42842-99-9; **1(CN)**, 87207-04-3; $\mathbf{1(CN)}^{+\cdot}$, 87207-05-4; $\mathbf{1(CN)}$-$d_2^{+\cdot}$, 87207-06-5; **2(Me)**, 87226-19-5; **2(CN)**, 87207-07-6; **3(Me)**, 50599-41-2; **3(CN)**, 87207-08-7; **4(Me)**, 60678-65-1; **4(CN)**, 74773-78-7.

α-Amino Acids as Chiral Educts for Asymmetric Products. Chirally Specific Syntheses of Tylophorine and Cryptopleurine

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Chirally specific total syntheses of major representatives of the phenanthroindolizidine and phenanthroquinolizidine alkaloids have been completed from (*S*)-α-amino acids as educts. This was achieved in each case by utilizing a key intramolecular Friedel–Crafts acylation to produce both the tylophorine and cryptopleurine ring systems optically intact. The amido ketones resulting from these cyclizations were further elaborated to the desired natural product alkaloids in good overall yields. Both alkaloids, derived from (*S*)-α-amino acids, are dextrorotatory and exhibit positive CD curves. Assignments of absolute stereochemistry are made, and several discrepancies with prior assignments are discussed.

The phenanthroindolizidine and phenanthroquinolizidine alkaloids have been subjects of numerous biological and chemical studies. Several of these natural products are powerful vesicants,[1-3] often highly toxic,[4] and can modulate the growth of various normal and abnormal mammalian tissues.[5-7] Numerous comprehensive reviews[8-11] are available which summarize efforts to determine chemical structure and stereochemistry and to synthesize these interesting classes of heterocyclic compounds.

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Our interest stems from the observation that none of these natural products has been synthesized in a chirally specific fashion. Racemic or partially racemic mixtures of these alkaloids have been prepared and were instrumental in final structural assignments.[2,12-21] The biosynthetic pathways also have been elucidated[22-24] and have served as synthetic models.[25]

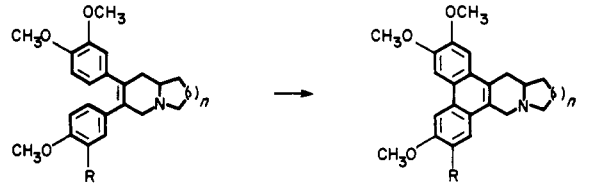
In the most commonly reported synthetic sequence, the desired heterocycle is coupled with a phenanthrene residue through a 9-halomethyl moiety. Completion of the alkaloid skeleton then proceeds under Friedel–Crafts conditions. Many phenanthroindolizidines, using proline esters,[26-30] and phenanthroquinolizidines, using pipecolate esters,[31-33] have been prepared by this approach. One syntheses of cryptopleurine[34] focused on the alkylation of pyridine-2-carboxaldehyde followed by intramolecular Friedel–Crafts condensation. In each case, racemic products resulted due to the drastic conditions employed for ring closure into the phenanthrene.

The intermolecular Diels–Alder reaction between phenanthroquinodimethane and 2,4,4-trimethylpyrroline gave a poor yield of the desired phenanthroindolizidine[35] and could not be extended to more complicated examples. However, the intramolecular Diels–Alder approach to tylophorine has had some success. An acyl imine prepared by thermolysis of the intermediate acetylated hydroxymethyl compound ultimately afforded racemic tylophorine in 5% overall yield in eight steps from methyl 2,3,6,7-tetramethoxyphenanthrene-9-carboxylate.[36]

Metalation of a phenanthrenecarboxamide[37] followed by reaction with pyridine-2-carboxaldehyde has also been applied. The phthalide intermediate was converted to racemic cryptopleurine (49% yield). Similarly, racemic tylophorine was obtained in 38% yield. Thus the organometallic approach is useful only for the preparation of racemic phenanthroindolizidine and -quinolizidine alkaloids.

The other common sequence to these alkaloids is exemplified by phenanthrene formation after coupling the aromatic residues with the appropriate heterocycle. Thus phenanthrene formation by photolytic cyclization of a pyrrolidine–stilbene gave the desired ring system. A major drawback of this route lies in the preparation of optically pure (*S*)-5-oxoprolinol. Overall, antofine was prepared with 50% enantiomeric excess.[38] Similarly, photolytic cyclization of a stilbene yielded the cryptopleurine skeleton.[39] Both methods also afforded the unwanted 3,4,6-trimethoxy isomers and required tedious separation. The same quinolizidinone precursor could be efficiently cyclized by anodic oxidation.[40]

Oxidative ring closure of the substituted stilbene with thallium(III) trifluoroacetate leads directly to racemic tylophorine (**1**) and cryptopleurine (**2**) with only minor



1: R = OCH_3, *n* = 1
2: R = H, *n* = 2

amounts of the regioisomers.[41] Vanadium(V) trifluoride oxide also was effective in the preparation of racemic tylophorine,[42] although these synthetic processes are not readily adaptable to the preparation of optically pure natural products.

Synthetic Plan. After our reexamination of Friedel–Crafts acylations as applied to methoxylated aromatics and amino acids,[43,44] we approached the synthesis of optically pure tylophorine and cryptopleurine by planning to link the phenanthrene with the appropriate optically pure amino acid. The key reaction would involve ring closure via a Lewis acid catalyzed acylation with preservation of optical integrity as in **3** → **4**. Our observations of simple intermolecular acylations[44] indicated than an amido acid might be the preferred substrate as in **5** → **6**. These ketones could then be converted by various reduction sequences to optically pure natural products. Our principal objectives thus included an efficient synthesis of functionalized phenanthrenes, an amine alkylation scheme

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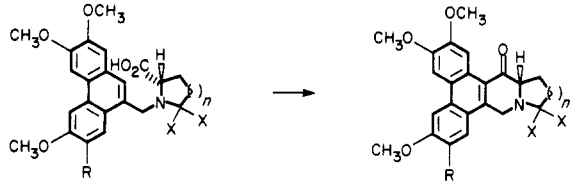
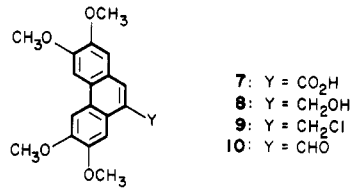


a: R = OCH_3, n = 1
b: R = H, n = 2
X,X = H_2
X,X = O

3 **4**
5 **6**

beginning with readily available optically pure α-amino acids, and acylation and reduction procedures which would retain optical integrity.

Phenanthrene Formation. (A) Pschorr Synthesis. The preparation of 2,3,6,7-tetramethoxyphenanthrene-9-carboxylic acid (**7**) and 2,3,6-trimethoxyphenanthrene-9-carboxylic acid (**11**) proceeded in a straightforward fash-



7: Y = CO_2H
8: Y = CH_2OH
9: Y = CH_2Cl
10: Y = CHO

ion.[2,45] Then diborane reduction of **7** afforded the corresponding alcohol **8** which was readily converted to the desired unstable 9-(chloromethyl)phenanthrene **9**.[14] Alternatively, **8** was oxidized with MnO_2[46] to the more stable aldehyde **10**. In either case, however, the desired alkylating agents were available in relatively poor overall yield.

A similar reaction sequence was employed for the preparation of phenanthrene **11**.[28] Pschorr cyclization could afford only one phenanthrene isomer in this case; however, substantial quantities of the iodostilbene[28] were isolated. It was photolytically cyclized,[47] affording high overall yields of the desired product. Conversion of **11** to the corresponding carbinol **12** followed by treatment with phosphorous tribromide afforded the desired bromide **13**[31] as a stable crystalline alkylating agent.

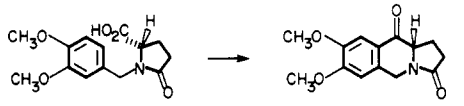
(B) Oxidative Cyclization. The ability of various transition-metal salts and oxides to oxidatively cyclize oxygenated stilbenes to phenanthrenes is well documented.[41] Procedures involving the use of VOF_3[42,48,49] seemed particularly appropriate for the oxidation of cyanostilbene **14**, prepared by condensation of veratraldehyde and (3,4-dimethoxyphenyl)acetonitrile. The resulting stilbene **14** possessed the *Z* configuration[50] and was oxidized to the desired phenanthrene **15** in high yield and with complete regiospecificity. The conversion of nitrile **15** to aldehyde **10** was then achieved by diisobutylaluminum hydride reduction. Thus in three steps and 89% overall yield a useful stable phenanthrene suitable for later alkylations was prepared.

Attempts to prepare 2,3,6-trimethoxy-9-cyanophenanthrene by this route were unsuccessful. Treatment of the stilbene with VOF_3/TFA resulted in extensive oxidate decomposition. As a result, we focused on the Pschorr route for the preparation of this cryptopleurine-related ring system.

***N*-Phenanthrenylmethyl Amino Acids. Preparation and Cyclization.** Proline benzyl ester was best alkylated with 9-(chloromethyl)phenanthrene **9** in DMF/benzene/K_2CO_3 at 80–85 °C. Yields were poor due to the apparent instability of the alkylating agent. Along with the carbinol **8**, the optically active amino ester was isolated and hydrolyzed to the corresponding amino acid **3a**. As an alternative to the halomethyl approach, reductive alkylation of proline ester with aldehyde **10** was examined. Schiff base formation was sluggish, and in a reducing medium with H_2/Pd/C, $NaBH_4$, or $NaCNBH_3$, phenanthrene carbinol **8** was the principal product isolated.

The AlX_3-catalyzed cyclization of **3a** was a disappointment. Acid chloride,[44] on treatment with $AlBr_3$, $AlCl_3$, or other Lewis acids, failed to yield amino ketone. A variety of polyphosphate esters were also ineffective in promoting this cyclization. Due to this failure of Friedel–Crafts cyclization of **3a** under racemization free conditions, we considered it also unlikely as a route to cryptopleurine via **3b**, and further efforts in this area were abandoned.

***N*-Phenanthrylmethyl Amido Acids.** The next synthetic plan was designed to exploit the reactivity of amido acids by using Friedel–Crafts acylation conditions. Our previous work indicated that amido acid chlorides exhibit greater reactivity toward aromatic ethers when compared with their amino acid counterparts.[44] As a model, *N*-(3,4-dimethoxybenzyl)pyroglutamic acid (**16**) was prepared



16 **17**

via reductive alkylation and converted to its acid chloride. $AlCl_3$-promoted cyclization afforded optically active ketone **17** in high overall yield, while cyclization of the amino acid chloride analogue of **16** failed. On the basis of this successful alternative, syntheses of the corresponding tylophorine and cryptopleurine skeleta were pursued.

Alkylation and Cyclization of Diisopropyl (*S*)-(+)-Glutamate. Due to the instability of 2,3,6,7-tetramethoxy-9-chloromethylphenanthrene (**9**), we needed to prepare a more suitable alkylating agent. Although the desired N-alkylated amino ester **18a** was prepared in limited quantities by this route, reductive alkylation with an aromatic aldehyde was a more attractive possibility. The convenient preparation of the 9-cyanophenanthrene **15** and ready availability of optically pure glutamic acid diesters made this approach feasible.

The diisopropyl ester of glutamic acid was used to prevent premature pyroglutamate formation, and azeotropic condensation of the amino ester and phenanthrenealdehyde **10** occurred readily in the presence of a catalytic amount of glacial acetic acid. The initial Schiff base was rapidly converted to the corresponding aminal, and this served to avoid any racemization of the intermediate Schiff base. The crude aminal was then reduced with $NaCNBH_3$, yielding the desired *N*-(phenanthrylmethyl)-glutamate **18a**.

Cyclization in warm MeOH/HOAc afforded amido ester **19** which in turn was hydrolyzed to amido acid **5a** in good overall yield. It is interesting to note that during pyroglutamate formation in MeOH/HOAc, the methyl ester of **19** was not formed, but the γ-methyl ester of **18a** was observed. Apparently the terminal isopropyl ester must undergo transesterification prior to cyclization since under

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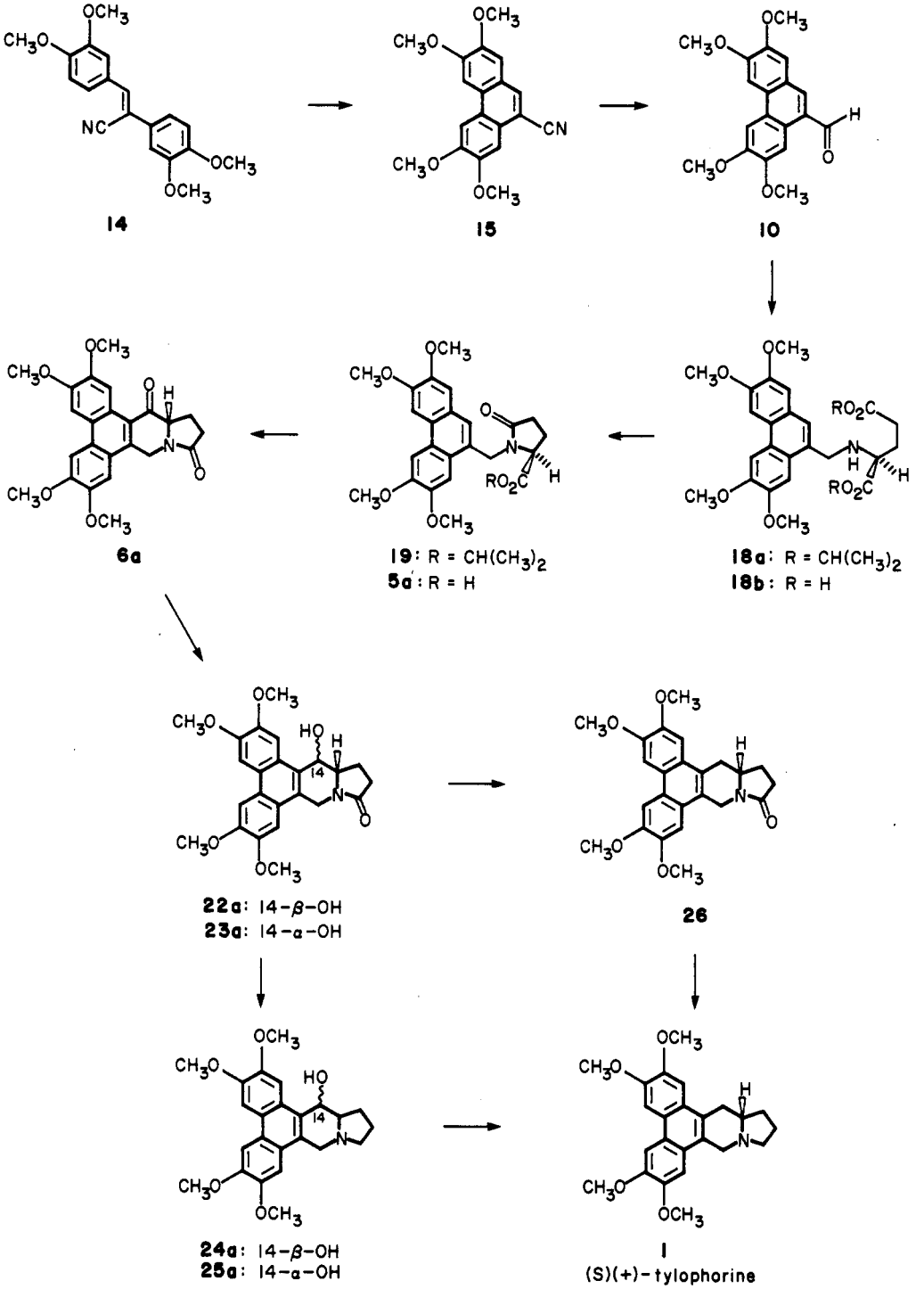
Scheme I. Synthesis of (*S*)-(+)-Tylophorine from (*S*)-Glutamic Acid



any other conditions **18a** cannot be cyclized directly (Scheme I). By methods previously described[44] it was confirmed that these transformations were achieved without detectable racemization (<1%).

Alkylation and Cyclization of Diisopropyl (*S*)-(+)-α-Aminoadipate. Although a similar scheme seemed directly applicable for the preparation of **5b**, several major differences immediately appeared. First was the need to prepare optically pure α-aminoadipic acid[51] and to avoid the aminal intermediate which would require larger amounts of a more valuable amino diester. Second, 2,3,6-trimethoxy-9-cyanophenanthrene could not be prepared by oxidation with VOF_3. A Pschorr synthesis was required for the 9-carboxylic acid **11** which was reduced to the corresponding carbinol **12**. Direct alkylation of the amino group via bromide **13** seemed more appropriate than reductive alkylation in this case.

Optically pure diisopropyl α-aminoadipate[51] was coupled with 2,3,6-trimethoxy-9-(bromomethyl)phenanthrene (**13**)[31] in DMF/benzene, affording the alkylated diester **20a** in high yield. Ester **20a** could not be cyclized to **21** via elimination of alcohol as was the case in the transformation **18a** → **19**. Fusion was unsuccessful, and treatment with warm pyridine gave partially racemized **5b**, as with **5a**. However, cyclization of diacid **20b** was readily achieved in boiling water in contrast to our failure to convert **18b** to **5a** by this technique.

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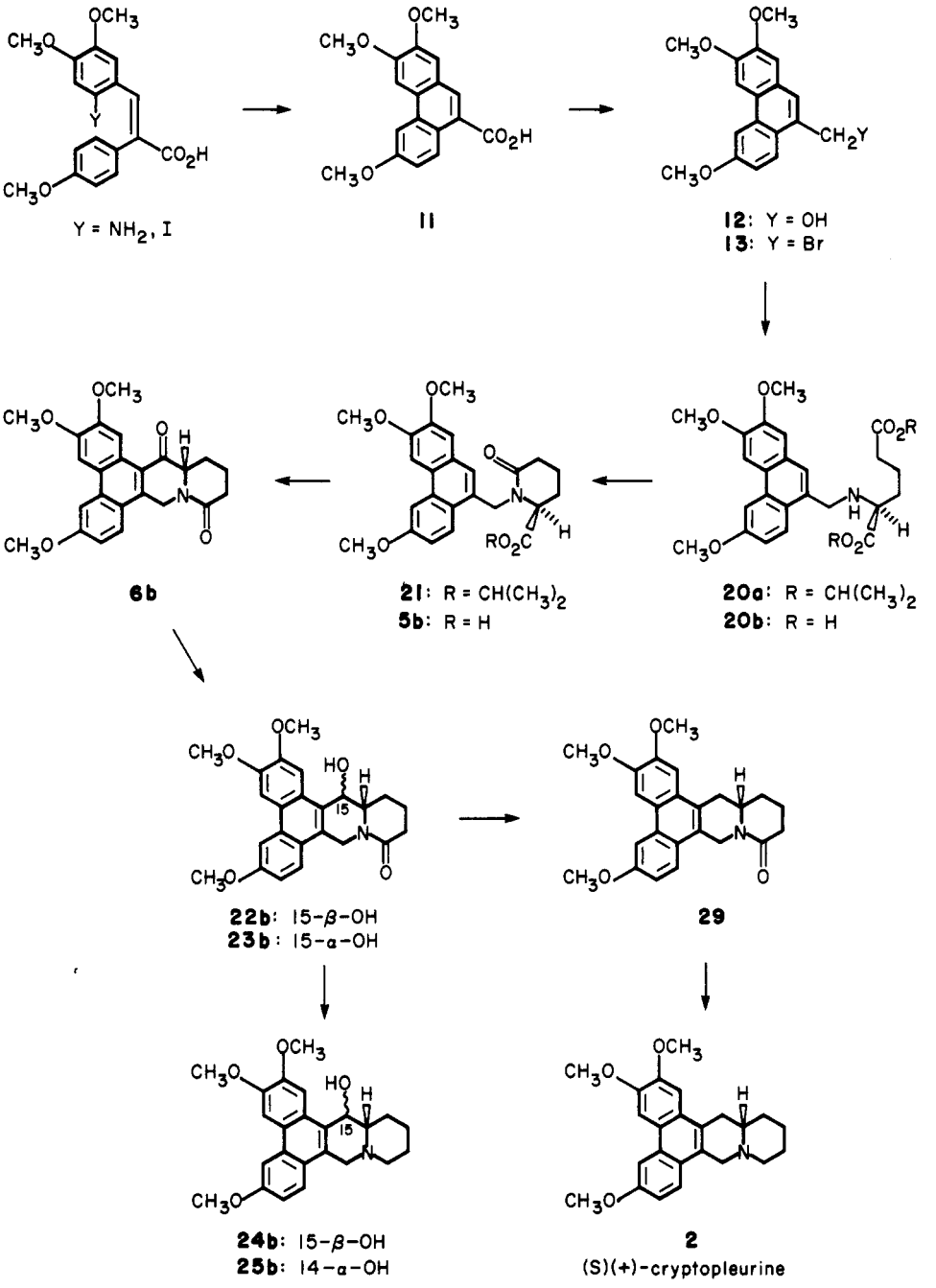
Scheme II. Synthesis of (*S*)-(+)-Cryptopleurine from (*S*)-α-Aminoadipic Acid



Cyclization of *N*-Phenanthrylmethyl Amido Acids 5a,b. Amido acids **5a,b** were conveniently converted to acid chlorides by the action of oxalyl chloride and DMF. As in the conversion of **16** to **17**, the acid chloride of **5a** was treated with $AlCl_3$ (200 mol %), yielding phenanthrene amido ketones with partial cleavage of the aromatic ethers. After exhaustive remethylation, optically active tetramethoxy ketone **6a** was formed. This ketone was obtained in nearly quantitative yield by the action of $SnCl_4$ in refluxing CH_2Cl_2 without any demethylation. Assessment of optical purity was postponed until final comparison with the natural product, tylophorine. Similarly, the acid chloride of **5b** was converted to optically active **6b** in nearly quantitative yield.

These ketones exhibited markedly diagnostic ultraviolet absorptions. Prior to acylation, the phenanthrene moiety displays an intense absorption in the 240–280-nm range ($\epsilon \sim 70\,000$). After cyclization, phenanthrene absorption is significantly attenuated ($\epsilon \sim 35\,000$). Here, the principal chromophore appears to be either an α- or β-acylated naphthalene with additional aromatic conjugation contributing little to the overall stabilization of the π–π^* excited state. Upon reduction of the ketone carbonyl, the phenanthrene chromophore is restored to its original absorption intensity.

The NMR absorption of these ketones is also characteristically indicative. Upon cyclization (Scheme II), the C-1 H of each phenanthrene undergoes a major downfield shift of approximately 1.5 ppm due to the deshielding effect of the newly created carbonyl. This effect is reversed after reduction of these ketones to amido alcohols, thus providing a convenient structural probe.

Reduction of Amido Ketones 6a,b. Catalytic Hydrogenation to Amido Alcohols 22 and 23. The hydrogenation of these aromatic ketones with Pd/C (10%) as catalyst under a large variety of conditions afforded

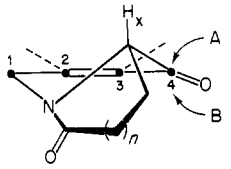


Figure 1. Model of [6,5] amido ketone **6a** illustrating steric interactions for attack at the ketone carbonyl.

mixtures of the corresponding diastereomeric alcohols. On the other hand, reduction of **6a** with Pearlman's catalyst afforded the 14-β alcohol **22a** as a major product with a trace of the 14-α alcohol **23a**. Similarly, **6b** gave rise to a 9/1 mixture of **22b/23b**. One recrystallization afforded a pure sample of each β-amido alcohol.

The stereochemical assignments are based on both chemical behavior and analysis of the NMR absorption. The β-amido alcohols are considerably more stable to dehydration than their α counterparts. The NMR coupling constants (6–8 Hz) for the trans diaxial methine hydrogen interactions of the acetates of **22a** and **22b** are consistent with this assignment and those of similar compounds.[52]

Hydride Reduction to Amido Alcohols 22 and 23. Chemical reduction of **6a** and **6b** was examined by using a variety of hydride reagents. In each case, the simple borohydride and aluminum hydride reagents afforded diastereomeric mixtures although the β alcohols were largely favored. Use of bulkier hydride reagents such as K- or L-Selectride (Aldrich) in THF afforded α alcohols **23a** and **23b** as the exclusive products of reduction of **6a** and **6b**, respectively. Marked differences between the two ring systems were seen in the rate of reduction of the ketones. [6,5] ketone **6a** was reduced to amido alcohol **23a** in 1 min whereas [6,6] ketone **6b** generally required from 1 to 2 h.

Stereochemical assignments are again based on both chemical and spectroscopic considerations. Samples of pure α alcohols **23a,b** were more easily dehydrated than β alcohols **22a** or **22b**. Also, the α alcohols were more easily converted to chlorides than their diastereomers. The NMR absorbtions of the acetates of **23a,b** exhibited a small coupling constant for the cis methine hydrogen interactions, consistent with the literature.[52]

Diastereomeric Selectivity in the Reduction of [6,5] Ketone 6a and [6,6] Ketone 6b. Examination of molecular models reveals a striking aspect of the three-dimensional configuration of these ketones. Both the [6,5] **6a** and the [6,6] **6b** ring-fused phenanthrenes exhibit a distinct molecular cavity illustrated by Figure 1. Carbons 1–4 of the cyclohexene-like backbone are coplanar as dictated by the phenanthrene moiety. This results in the formation of two distinctly different ketone spatial environments of which face A would be the more exposed. Bulky hydride reagents more easily approach this face, resulting in the formation of α alcohols. The exclusivity exhibited by the [6,5] ring-fused ketone **6a** becomes less pronounced in the [6,6] case where the β-face cavity has been expanded slightly by insertion of an additional sp^3 carbon.

The selectivity observed on catalytic reduction of **6a,b** is harder to explain and may involve complexation with an activated catalytic surface. The in situ reduction of $Pd(OH)_2/C$ may provide a situation where double ligation of a catalytic site would be more easily achieved from the B face of these ketones. Assuming such a catalyst-ketone adsorption, a predominance of the β alcohol would be anticipated.

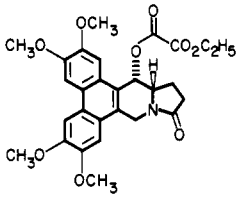
Reduction of Amido Alcohols 22 and 23 to Amino Alcohols 24 and 25. Reduction of the amide carbonyls of **22a** and **23a** was straightforward. Treatment with $LiAlH_4$ in refluxing THF afforded the optically active amino alcohols **24a** and **25a** in good yield. Acetylation of these alcohols allowed reconfirmation of the original stereochemical assignments by NMR analysis of their respective coupling constants for the methine hydrogens.

Having demonstrated the preparation of both tylophorine-related amino alcohols, we first prepared the cryptopleurine-related isomer **25b** by $LiAlH_4$ reduction. The crude amino alcohol **25b** was extremely unstable and underwent facile dehydration and apparent aromatization.[31] Similar difficulties were experienced in the conversion of **22b** to **24b**, consistent with the indications[53] that alcohol elimination would be a major problem.

Deoxygenation of Amido Alcohols 22a and 23a to Phenanthro Amide 26. The sluggish conversion of β alcohol **22a** to the corresponding benzyl chloride led to the use of **23a** for this first step in oxygen removal. The α-amido alcohol was treated with $SOCl_2$, affording only the β-chloride which was catalytically reduced to the desired optically active amide **26**. The alternative treatment of **23a** with oxalyl chloride/DMF followed by catalytic reduction did not yield the expected product. Instead, mixed diester **27** was formed, and its was inert to further reduction.

Deoxygenation of Amido Alcohols 22b and 23b to Phenanthro Amide 29. The methods employed in the [6,5] **23a** system were ineffective for the [6,6] cryptopleurine series due to instability of the intermediate benzyl chloride derived from **23b**. Prepared by the action of $SOCl_2$, the chloride was rapidly converted to the diastereomeric chloride which underwent elimination. The presence of pyridine acclerated decomposition, and excess HCl accelerated isomerization. Catalytic reduction of these mixtures yielded crude amide **29** which could not be readily purified.

As an alternative, we investigated a reduction scheme involving first preparation of the iodide using trimethylsilyl iodide prepared in situ.[54] This led to the formation of both iodides **28**, however, this mixture of diastereomers was



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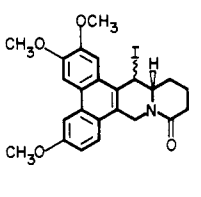

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cleanly and rapidly reduced with $NaCNBH_3$, thus affording the desired optically active amide **29**. Due to the slight racemization of ketone **6b** during the Selectride reaction, amide **29** was best prepared from the mixture of alcohols **24b** and **25b** obtained with $NaBH_4$ and subjected to the iodide procedure above. Deoxygenation in this fashion afforded optically pure amide.

Preparation of (*S*)-(+)-Tylophorine (1) and (*S*)-(+)-Cryptopleurine (2). The conversion of amides **26** and **29** to the desired alkaloids was accomplished by straightforward reduction with $LiAlH_4$ in refluxing THF. In the case of tylophorine (1), identical material resulted on treatment of amino alcohol **25a** with oxalyl chloride/

(52) Poettinger, T.; Wiegrebe, W. *Arch. Pharm.* **1981**, *314*, 240.

(53) Foldeak, S.; Hegyes, P. *Tetrahedron* **1980**, *36*, 641.

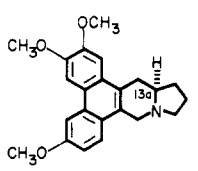
(54) Morita, T.; Okamoto, Y.; Sakurai, H. *Synthesis* **1981**, 32.

Table I. Assignments of Absolute Stereochemistry to Some Phenanthroindolizidine and Phenanthroquinolizidine Alkaloids

compd	source	[α]	abs config	CD
tylophorine	natural[58]	−	*S*	−
cryptopleurine	natural[58]	−	*R*	+
antofine (**30**)	natural[56]	−	*R*	+
tylocrebrine (**31**)	natural[58]	−	*S*	−
(*S*)-(+)-tylophorine (**1**)	synthesis, from (*S*)-glutamic acid	+	*S*	+
(*S*)-(+)-cryptopleurine (**2**)	synthesis, from (*S*)-α-aminoadipic acid	+	*S*	+

DMF followed by immediate catalytic hydrogenolysis. The parallel conversion to cryptopleurine (**2**) could not be effected due to the instability of [6,6] amino alcohol **25b**. The properties of the phenanthrene alkaloids thus synthesized were identical with those of the natural products[55] except for the optical data. Naturally occurring tylophorine has been reported to have the *S* configuration and a specific rotation of −12°. Our synthetic sample has the *S* configuration, based on its synthesis from (*S*)-glutamic acid, but its rotation is +12°. Naturally occurring cryptopleurine has been assigned the *R* configuration and exhibits a specific rotation of −105°. Our synthetic sample has the *S* configuration again, and exhibits a rotation of +105°. Thus the rotation of our synthetic material is consistent for the optical antipode of cryptopleurine, having been derived from (*S*)-α-aminoadipic acid. However, the specific rotation together with our stereochemical assignment for synthetic tylophorine conflict with earlier reports for naturally occurring tylophorine.

Assignment of Absolute Stereochemistry to Tylophorine and Cryptopleurine. The assignment of absolute configuration for these phenanthrene alkaloids seems to focus upon two sources. Investigation of the stereochemistry of antofine (**30**) via exhaustive ozonolysis



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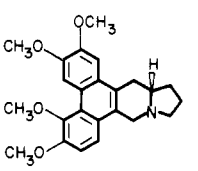

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led to the conclusion[56] that this alkaloid contains the elements of D-proline, thus possessing the *R* configuration at C-13a. This determination was made by treatment of the amino acid degradation residue with the D-amino acid oxidase in competitition with L-proline. The principal drawback of this evidence lies in the fact that the oxidation procedure afforded a very poor yield of a mixture of four amino acids: glycine, β-alanine, γ-aminobutyric acid, and proline.

The same degradation technique was utilized to assign the absolute configuration of tylophorine.[57] In this case, a 5.1-g sample of tylophorine was exhaustively oxidized, affording 20 mg of a mixture of four amino acids, one of which was pyrrolidine-2-acetic acid. Examination by GC of a dipeptide formed with *N*-(trifluoroacetyl)-(*S*)-proline led to the conclusion that this residue had the *S* configuration. Therefore, it was claimed that tylophorine possesses the *S* configuration at C-13a. Unfortunately, the certainty of this observation suffers from the same limitation as does that of the antofine degradation.

For examination of the absolute configuration of cryptopleurine and tylocrebrine (**31**), their ORD and CD data were compared with that obtained for tylophorine.[58] The sample of tylophorine exhibited a negative Cotton effect, as did **31**. However, cryptopleurine exhibited a postive response. It was therefore concluded that tylocrebrine possessed the *S* configuration, whereas the *R* configuration was assigned to cryptopleurine.

Our conclusions relating to the absolute configuration of **1** and **2** are based totally upon synthesis. In each case, we begin with an (*S*)-amino acid, and the asymmetric integrity is preserved throughout the resction sequences employed. Although opportunities for racemization exist, inversion of configuration is not tenable. We are therefore forced to concluded that (*S*)-tylophorine is the dextrorotatory isomer. We have no rational explanation for the discrepancy with the natural product literature. Our data concerning the stereochemistry of cryptopleurine is also in disagreement with the literature. We find (*S*)-cryptopleurine to be dextrorotatory and exhibit a positive CD curve. Table I summarizes our results and those reported by others.

Summary

Our routes to (*S*)-(+)-tylophorine (**1**) and (*S*)-(+)-cryptopleurine (**2**) from (*S*)-glutamic acid and (*S*)-α-aminoadipic acid, respectively, are summarized in Schemes I and II. Intramolecular Friedel–Crafts acylation was the key reaction in each case, affording optically pure amido ketones. It is important to note that both *S* ketones are dextrorotatory and exhibit positive CD absorptions. Variation in the number and substitution pattern of the methoxyl groups does not play a major role in altering the dispersion of circularly polarized light. The same observations also may be made for heterocyclic ring size in these two systems. Ketone reduction in each system did not result in any major rotational perturbation. This is again illustrated by the fact that both amides are also dextrorotatory and exhibit positive CD's as well. Therefore, one would anticipate that the fully reduced alkaloids would exhibit similar rotational properties, and such is the case.

Experimental Section

General Methods. Melting points were determined by using a Mel-Temp apparatus and are uncorrected. GC analyses were performed with a Hewlett-Packard 402 gas chromatography by using a 6-ft column of 10% SE-30 on Chromosorb W. Infrared spectra were determined as Nujol mulls by using a Perkin-Elmer 137 spectrophotometer. NMR spectra were obtained on $CDCl_3$ solutions, unless otherwise specified, with internal Me_4Si and were taken with Varian T-60, Varian EM-390, and Berkeley UCB-250 instruments. UV spectra were obtained in $CHCl_3$ unless otherwise specified by using a Varian Cary 219 spectrophotometer. Optical rotations were measured with a Perkin-Elmer 241 polarimeter in a 10-cm cell. HPLC analyses were made with an Altex Model 110A dual pump system accompanied by a Hitachi Model 100-30 detector. Normal-phase separations were made by using a Lichosorb Si-60 5-μm column (3.2 × 250 mm); reverse-phase separations were made with a Lichrosorb C-18 10-μm column (3.2

(55) We are indebted to Dr. T. R. Govindachari for a sample of tylophorine from *Tylophora indica*.
(56) Wiegrebe, W.; Faber, L.; Breyhan, T. *Arch. Pharm.* **1971**, *304*, 188.
(57) Govindachari, T. R.; Rajagopalan, T. G.; Viswanathan, N. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1161.
(58) Gellert, E.; Rudzats, R.; Craig, J. C.; Roy, S. K.; Woodard, R. W. *Aust. J. Chem.* **1978**, *31*, 2095.

× 250 mm). Unless otherwise specified, reactions were conducted in a nitrogen atmosphere with magnetic stirring at room temperature, and organic product solutions were dried over $MgSO_4$, filtered, and evaporated with a Berkeley rotory evaporator at reduced pressure.

2,3,6,7-Tetramethoxyphenanthrene-9-carboxylic Acid (7). (*E*)-2-(3,4-Dimethoxyphenyl)-3-(2-nitro-4,5-dimethoxyphenyl)-cinamic acid was prepared in 80% yield as a bright yellow solid, mp 186 °C (lit.[2] mp 185° C). Reduction to the corresponding amino acid was conveniently carried out: 87% yield; mp 194 °C (lit.[28] mp 193–194 °C). Pschorr cyclization afforded **7** as a tan solid: 30% yield; mp 285 °C (lit.[2] mp 285 °C).

2,3,6,7-Tetramethoxy-9-(hydroxymethyl)phenanthrene (8). To a stirred suspension of acid **7** (17.1 g, 50 mmol) in THF (500 mL) was added BH_3-THF (1 M, 150 mL, 300 mol %) in three portions over 1 h. Upon completion of addition, the reaction mixture was warmed (35–40 °C) for another hour, quenched (HOAc), and evaporated, and the residue was partitioned between 350-mL portions of CH_2Cl_2 and 1 N NaOH. The organic layer was dried, filtered, and evaporated, affording alcohol **8**: 94% yield; mp 184–186 °C (lit.[2] mp 185 °C).

2,3,6,7-Tetramethoxy-9-(chloromethyl)phenanthrene (9) was prepared from alcohol **8** as described.[14] It was used immediately in the alkylation reactions.

2,3,6,7-Tetramethoxy-9-formylphenanthene (10). To a stirred chloroform solution of alcohol **8** (3.28 g, 10 mmol) was added 5 g of γ-MnO_2[46] in four portions over 1 h, and then the suspension was warmed (40–45 °C) for an additional hour, filtered, and evaporated, affording 3.19 g (98% yield) of aldehyde **10** as a bright yellow solid: mp 219–220 °C (from hexane/CH_2Cl_2); IR 1670 cm^{-1}; NMR δ 4.05 (6 H, s), 4.10 (3 H, s), 4.13 (3 H, s), 7.18 (1 H, s), 7.55 (3 H, m), 7.83 (1 H, s), 8.75 (1 H, s); UV λ_{max} 262 nm (ε 40160), 271 (50000), 286 (28870), 301 (27260), 345 (11770). Anal. Calcd for $C_{19}H_{18}O_5$: C, 69.9; H, 5.6. Found: C, 69.7; H, 5.7.

2,3,6-Trimethoxyphenanthrene-9-carboxylic Acid (11). (*E*)-2-(4-Methoxyphenyl)-3-(2-nitro-4,5-dimethoxyphenyl)-cinnamic acid was prepared in 90% yield by the described method.[28] Trace amounts of the trans isomer were easily removed by fractional recrystallization from EtOH; mp 186 °C (lit.[18] mp 185 °C). Reduction to the corresponding amino acid was achieved in 93% yield as described,[2] and trituration with hot acetone afforded the amino acid, mp 206 °C (lit.[28] mp 206 °C). Pschorr cyclization gave acid **11** and iodostilbene. The two products were initially separated by fractional crystallization to give **11** in 65% yield. Iodostilbene was isolated in 20% yield from the mother liquor and, as a 3% solution in dioxane, converted to **11** photolytically by using a Hanovia UV lamp and a Pyrex filter. In this fashion, the desired phenanthrene acid **11** was obtained: 85% combined yield; mp 220 °C (lit.[28] mp 219 °C).

2,3,6-Trimethoxy-9-(hydroxymethyl)phenanthrene (12). The reduction of 9-carboxyphenanthrene **11** was carried out in 95% yield as described above for the conversion of **7** to **8**; mp 187 °C (lit.[31] mp 186 °C).

2,3,6-Trimethoxy-9-(bromomethyl)phenanthrene (13). This bromide was prepared as described.[31] The bromide was immediately used for alkylation reactions without further purification.

2,3,6,7-Tetramethoxy-9-cyanophenanthrene (15). To a solution of veratraldehyde (16.6 g, 0.1 mol) and (3,4-dimethoxyphenyl)acetonitrile (17.7 g, 100 mol %) in EtOH (absolute, 500 mL) was added in one portion freshly prepared 1 M NaOEt (absolute EtOH, 110 mL). The reaction mixture was heated to 85 °C for 1 h, cooled, and filtered, and the product was washed with small portions of cold EtOH, affording cyanostilbene **14** as a bright yellow solid: 98% yield; mp 154–155 °C; IR 2200, 1620 cm^{-1}; NMR δ 4.05 (3 H, s), 4.09 (3 H, s), 4.14 (3 H, s), 4.15 (3 H, s), 7.19 (1 H, s), 7.52 (1 H, s), 7.72 (1 H, s), 7.75 (1 H, s), 8.01 (1 H, s); UV λ_{max} 241 nm (ε 17850), 290 (sh), 348 (21340), 483 (980). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.6; H, 5.3; N, 4.3. Found: C, 70.3; H, 5.4; N, 4.3.

To a chilled solution of 32.6 g (0.1 mol) of **14** in 2 L of CH_2Cl_2 was added 300 mL of TFA followed by 36.2 g (0.3 mol) of VOF_3. After being stirred for 2 days at 5 °C, the reaction mixture was quenched with cold aqueous citric acid, and the organic phase was washed with 1 M aqueous citric acid (3 × 500 mL), 3 M NH_4OH (4 × 500 mL), H_2O (2 × 500 mL), and brine. The organic layer was dried, filtered through a short silica gel column, and evaporated to give phenanthrenenitrile **15**: 95% yield; mp 267–269 °C; IR 2210–1620 cm^{-1}; NMR δ 4.03 (3 H, s), 4.05 (3 H, s), 4.13 (6 H, s), 7.15 (1 H, s), 7.47 (1 H, s), 7.69 (2 H, m), 7.93 (1 H, s); UV λ_{max} 250 nm (sh), 266 (ε 104360), 279 (47310), 290 (63460), 303 (sh), 319 (22310), 332 (28590), 354 (9360), 373 (10640). Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.6; H, 5.3; N, 4.3. Found: C, 70.3; H, 5.4; N, 4.3.

(*S*)-*N*-[(2,3,6,7-Tetramethoxy-9-phenanthryl)methyl]-proline (3a) was prepared via alkylation of benzyl prolinate as described[28] with crude chloride **9** (150 mol %) in benzene/DMF in the presence of K_2CO_3 (200 mol %), affording the benzyl ester of **3a**: 67% yield; mp 157–158 °C (lit.[28] mp 157.5–158 °C); $[\alpha]^{23}_D$ −31.5° (*c* 1, $CHCl_3$) (lit.[28] [α] −30°).

The alkylated benzyl ester (2.57 g, 5.0 mmol) was hydrolyzed in MeOH/1 N KOH at room temperature for 12 h. The solution was evaporated, and the residue was dissolved in water, washed with Et_2O, acidified with 6 N HCl, and evaporated. Trituration with hot *tert*-butyl alcohol afforded N-alkylated proline **3a**, as the hydrochloride: 2.14 g (93% yield); mp 215–217 °C dec (lit.[28] mp 214–216 °C); $[\alpha]^{23}_D$ −18.5° (*c* 1.75, 90% EtOH) (lit.[28] [α] −15°).

Preparation of (*S*)-(+)-7,8-Dimethoxy-1,2,3,10a-tetrahydro-3-oxopyrrolo[1,2-*h*]isoquinolin-10(5*H*)-one (17). (*S*)-(+)-*N*-[(3,4-Dimethoxyphenyl)methyl]glutamic acid was prepared by reductive alkylation of glutamic acid (14.7 g, 0.1 mol) in 2 M NaOH (100 mL) with veratraldehyde (22.1 g, 133 mol %) dissolved in dioxane (20 mL). This two-phase reaction mixture was degassed, charged with 5 g of Pd/C (10%), and hydrogenated for 24 h. Filtration and washing with CH_2Cl_2 (3 × 150 mL) followed by acidification to pH 3.0 and cooling to 4 °C overnight gave a precipatate which was filtered and washed successively with cold water and acetone. The alkylated amino acid thus was obtained: 96% yield; mp 136–137 °C; IR 1735 cm^{-1}; NMR (Me_2SO-d_6, TFA-*d*) δ 1.73–2.57 (4 H, m), 3.63 (6 H, s), 3.73 (1 H, t), 3.98 (2 H, br) 6.90 (2 H, s), 6.95 (1 H, s); $[\alpha]^{23}_D$ +10.0° (*c* 1, 6 N HCl). Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.6; H, 6.4; N, 4.7. Found: C, 56.4; N, 6.4; N, 4.7.

Fusion (160 °C) of the above amino acid gave **(*S*)-(+)-*N*-(3,4-dimethoxybenzyl)pyroglutamic acid (16)**: mp 154–155 °C (from EtOAc/MeOH/hexane; IR 1715, 1630 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6) δ 1.90–194.4 (4 H, m), 3.83 (6 H, s), 3.90 (1 H, t), 4.42 (2 H, AB q, J_{AB} = 14 Hz, $\Delta\nu_{AB}$ = 62.5 Hz, δ_A 4.94, δ_B 3.90), 6.73 (3 H, s), 10.75 (1 H, br); $[\alpha]^{23}_D$ +52.5° (*c* 2, MeOH). Anal. Calcd for $C_{14}H_{17}NO_5$: C, 60.2; H, 6.1; N, 5.0. Found: C, 60.4; H, 6.1; N, 4.9.

To a stirred solution of **16** (0.26 g, 1.0 mmol) in CH_2Cl_2 (12 mL) was added oxalyl chloride (100 μL, 113 mol %) and DMF (5 μL). After 2 h, the solution was brought to reflux, $SnCl_4$ (0.24 mL, 200 mol %) was added, and the solution was poured into ice–water after 3 h. Extractive isolation with aqueous $NaHCO_3$ gave **17**: 223 mg (91% yield), mp 182 °C dec (from EtOAc/hexane); IR 1700, 1675 cm^{-1}; NMR ($CDCl_3$/MeSO-d_6) δ 2.18–2.88 (4 H, s), 3.93 (3 H, s), 3.97 (3 H, s), 4.28 (1 H, t, *J* = 5 Hz), 4.72 (2 H, AB q, J_{AB} = 17 Hz, $\Delta\nu$ = 51.3 Hz, δ_A 5.14, δ_B 4.29), 6.74 (1 H, s), 7.50 (1 H, s); UV (MeOH) λ_{max} 234 nm (ε 20800), 278 (12270), 3.5 (8450); $[\alpha]^{23}_D$ +21.0° (*c* 1, MeOH). Anal. Calcd for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.8; N, 5.4. Found: C, 64.3; H, 5.8; N, 5.3.

Diisopropyl Glutamate. To a suspension of (*S*)-(+)-glutamic acid (50.0 g, 0.34 mol) in 2-propanol/toluene (1350 mL, 1/1) was added 22.0 mL (120 mol %) of concentrated H_2SO_4. The solution was rapidly refluxed for 24 h under a Soxhlet apparatus containing 3-Å molecular sieves, evaporated to about 200 mL, diluted with cold saturated $NaHCO_3$ (600 mL), adjusted to pH 9.5, and extracted with CH_2Cl_2 (4 × 300 mL). Drying and evaporating the combined organic phases left the diester as a light yellow oil: 78.4 g (99% yield); IR (neat) 3385, 1730 cm^{-1}; NMR δ 1.45 (12 H, d, *J* = 6 Hz), 1.52 (2 H, s), 1.60–2.60 (4 H, m), 3.35 (1 H, dd, J_{AX} = 8 Hz, J_{BX} = 6 Hz), 4.96 (2 H, heptet, *J* = 6Hz); $[\alpha]^{23}_D$ +16.8° (*c* 2, MeOH).

Diisopropyl (*S*)-(−)-*N*-[(2,3,6,7-Tetramethoxy-9-phenanthryl)methyl]glutamate (18a). To a refluxing CH_2Cl_2 solution (200 mL) of aldehyde **10** (3.26 g, 10 mmol) were added 2.31 g (100 mol %) of diisopropyl glutamate and 5 drops of glacial acetic acid. After 2 h of reflux under a Soxhlet apparatus containing 3-Å sieves, an additional 100 mol % of glutamate was

added in two portions, 30 min apart, together with 5 more drops of HOAc. Refluxing was continued for an additional 3 h and then the solution was evaporated, affording the aminal as a crude orange oil: IR (neat) 3300, 1710 cm^{-1}; NMR δ 1.25 (6 H, d, J = 6 Hz), 1.3 d, J = 6 Hz), 2.1–2.7 (10 H, m), 3.97 (3 H, s), 4.06 (9 H, s), 4.15 (2 H, m), 4.98 (4 H, J = 6 Hz), 6.9–7.8 (6 H, m).

To the crude aminal dissolved in isopropyl alcohol (100 mL) was added 1 mL of HOAc followed by excess $NaCNBH_3$ (1.26 g, 200 mol %). A pH of 5–7 was maintained by periodic additions of HOAc, and the reaction was maintained at room temperature. Upon completion of reduction (TLC), the solution was evaporated, and a small sample of the residue was purified by extractive isolation to give amino diester **18a**: mp 79–80 °C; IR 1730 cm^{-1}; NMR δ 1.18 (6 H, d, J = 6 Hz), 1.30 (6 H, d, J = 6 Hz), 1.6–2.7 (5 H, m), 3.37 (1 H, t, J = 7 Hz), 3.94 (3 H, s), 4.18 (9 H, s), 4.2 (2 H, m), 4.98 (2 H, m, J = 6 Hz), 7.38 (1 H, s), 7.62 (3 H, m); $[\alpha]^{23}_D$ −13.5° (c 2, CH_2Cl_2).

A solution of the crude amino diester **18a** in MeOH (50 mL) and acetic acid (25 mL) was stirred at 45 °C for 3 h at which point the solution was evaporated. A portion of the residue was purified in the usual extractive manner to give alkylated pyroglutamate ester **19**: mp 159–160 °C; IR 3350, 1735, 1675 cm^{-1}; NMR δ 1.17 (6 H, d, J = 6 Hz), 1.7–2.75 (4 H, m), 3.69 (1 H, t, J = 7 Hz), 3.99 (6 H, s), 4.16 (6 H, s), 4.84 (2 H, AB q, J_{AB} = 18 Hz, $\Delta\nu$ = 70.2 Hz, δ_A 5.46, δ_B 4.29), 4.92 (1 H, m, J = 6Hz), 4.00 (1 H, s), 7.24 (1 H, s), 7.42 (1 H, s), 7.65 (2 H, m); $[\alpha]^{23}_D$ +69.3° (c 2, CH_2Cl_2). Anal. Calcd for $C_{27}H_{31}NO_7$: C, 67.3; H, 6.5; N, 2.9. Found: C, 67.0; H, 6.5; N, 2.8.

(*S*)-(+)-*N*-[(2,3,6,7-Tetramethoxy-9-phenanthryl)methyl]pyroglutamic Acid (5a). To the crude alkylated pyroglutamate ester **19** in dioxane (40 mL) was added 2 N KOH (20 mL) and MeOH (30 mL). After 1 h, the solution was cooled (4 °C), acidified to pH 4 with H_3PO_4, chilled overnight, and filtered. Recrystallization of the precipitate from MeOH gave alkylated pyroglutamic acid **5a**: 88% overall yield (from aldehyde **10**); mp 300–302 °C dec; IR 1735, 1640 cm^{-1}; NMR (pyridine-d_5) δ 1.8–2.8 (4 H, m), 3.30 (3 H, s), 3.98 (6 H, s), 4.04 (3 H, s), 5.14 (2 H, AB q, J_{AB} = 15 Hz, $\Delta\nu_{AB}$ = 66 Hz, δ_A 5.67, δ_B 4.61), 7.13 (1 H, s), 7.54 (1 H, s), 7.83 (1 H, s), 7.87 (1 H, s), 7.30 (1 H, s), 11.63 (1 H, s); UV λ_{max} 261 nm (ϵ 64 035), 284 (sh), 290 (32 324), 304 (18 990), 324 (2100), 341 (2500), 357 (1940); $[\alpha]^{23}_D$ +54.3° (c 2, 1 N NaOH). Anal. Calcd for $C_{24}H_{25}NO_7$: C, 65.6; H, 5.7; N, 3.2. Found: C, 65.7; H, 5.8; N, 3.2.

(*S*)-(+)-*N*-[(2,3,6-Trimethoxy-9-phenanthryl)methyl]-6-carboxy-2-piperidinone (5b). (*S*)-α-Aminoadipic acid[51] was converted to diisopropyl (*S*)-α-aminoadipate in 93% yield by using the process described for the synthesis of the corresponding glutamate diester. The diester was isolated as a light yellow oil suitable for reaction without further purification: IR (neat) 3360, 1720 cm^{-1}; NMR δ 1.23 (6 H, d, J = 6 Hz), 1.25 (6 H, d, J = 6 Hz), 1.4-2.5 (8 H, m), 3.33 (1 H, t, br), 4.90 (1 H, heptet, J = 6 Hz), 4.92 (1 H, heptet, J = 6 Hz).

To a solution (100 mL; DMF/benzene, 1/1) of 2,3,6-trimethoxy-9-(bromomethyl)phenanthrene[31] (**13**; 3.61 g, 10 mmol) was added powdered anhydrous K_2CO_3 (300 mol %), followed by 2.6 g (108 mol %) of the crude diisopropyl (*S*)-α-aminoadipate. The suspension was heated quickly to 80 °C with stirring for 3 h, cooled in an ice bath, and diluted with H_2O and benzene, and the phases were separated. The aqueous phase was extracted with benzene (3 × 50 mL), and the combined organic phases were dried, filtered, and evaporated, leaving crude alkylated diester **20a** in 94% yield. This crude product was then dissolved in aqueous methanol (30 mL, 30% H_2O) and heated with 6 N KOH (4 mL, 128 mol %) for 4 h, the solution was evaporated, and the residue was diluted with water (100 mL) and extracted with Et_2O (3 × 50 mL). the aqueous phase was then adjusted to pH 7 with H_3PO_4, heated to boiling for 45 min, cooled to room temperature, and adjusted to pH 3 (H_3PO_4). The resulting precipitate of amido acid **5b** was obtained: 86% yield (from phenanthrene acid **11**); mp 248–250 °C; IR 1720 cm^{-1}; NMR ($CDCl_3$/Me_2SO-d_6) δ 1.55–2.55 (6 H, m), 4.00 (3 H, s), 4.02 (3 H, s), 4.08 (3 H, s), 3.8–4.0 (1 H, m), 5.10 (2 H, AB q, J_{AB} = 15 Hz, $\Delta\nu$ = 183 Hz, δ_A 6.12, δ_B 4.08), 7.16 (2 H, m), 7.84 (1 H, s), 7.86 (1 H, m), 8.01 (1 H, d, J = 9 Hz); UV λ_{max} 257 nm (ϵ 35 397), 280 (21 992); $[\alpha]^{23}_D$ +133° (c 1, 1 N NaOH). Anal. Calcd for $C_{24}H_{25}NO_6$: C, 68.1; H, 5.9; N, 3.3. Found: C, 67.7; H, 5.9; N, 3.2.

Table II

catalyst	distribution, % 22a (β)	23 (α)
PtO_2	67	33
Pd/C, 10%	80	20
$Pd(OH)_2$/C	90	10
$Pd(OH)_2$/C (40 °C)	96	4

(*S*)-2,3,6,7-Tetramethoxyphenanthro[9,10-*b*]-11,14-indolizidinedione (6a). To a solution of (phenanthrylmethyl)pyroglutamic acid **5a** (2.2 g, 5 mmol) in CH_2Cl_2 (150 mL) was added oxalyl chloride (0.5 mL, 112 mol %) and DMF (100 μL). The reaction mixture was stirred for 1.5 h and brought to reflux, $SnCl_4$ (2.5 mL, 207 mol %) was added, reflux was continued for an additional 4 h, the solution was cooled to room temperature, and cold 3 N HCl (50 mL) was added. The organic phase was separated, washed consecutively with 1 N HCl (2 × 50 mL), saturated $NaHCO_3$ (2 × 50 mL) and brine, dried, filtered, and evaporated to afford amido ketone **6a**: 1.98 g (94%); bright yellow crystalline solid; mp 228–230 °C then 260 °C dec; IR 1685, 1670 cm^{-1}; NMR δ 2.5 (4 H, m), 4.00 (3 H, s), 4.05 (6 H, s), 4.08 (3 H, s), 4.0 (1 H, br), 4.89 (2 H, AB q, J = 19 Hz, $\Delta\nu$ = 58 Hz, δ_A 5.37, δ_B 4.40), 6.98 (1 H, s), 7.50 (2 H, s), 8.88 (1 H, s); UV λ_{max} 262 nm (ϵ 34 400), 275 (33 400), 2.1 (29 390), 298 (sh), 353 (11 280), 407 (sh); $[\alpha]^{23}_D$ +159° (c 1, CH_2Cl_2); $[\theta]_{259}$ +14 210° (c 10^{-3}, EtOH); mass spectrum, m/z (relative intensity) 421 (M^+, 39). Anal. Calcd for $C_{24}H_{23}NO_6$: C, 68.4; H, 5.5; N, 3.3. Found: C, 68.4; H, 5.8; N, 3.3.

(*S*)-2,3,6-Trimethoxyphenanthro[9,10-*b*]-11,15-quinolizidinedione (6b). Cyclization of **5b** was performed identically with the cyclization of **5a**. Amido ketone **6b** was isolated: 93% yield; bright yellow solid; mp 236 °C dec; IR 1675, 1640 cm^{-1}; NMR δ 1.8–2.15 (2 H, m), 2.2–2.65 (4 H, m), 4.05 (3 H, s), 4.16 (6 H, s), 4.24 (1 H, t, J = 3.5 Hz), 5.40 (2 H, AB q, J_{AB} = 16 Hz, $\Delta\nu$ = 517.5 Hz, δ_A 6.43, δ_B 4.36), 7.26 (1 H, s), 7.77 (2 H, s), 8.08 (1 H, d, J = 9 Hz), 8.96 (1 H, s); UV λ_{max} 251 nm (ϵ 20 500), 272 (22 280), 279 (sh), 288 (20 870), 302 (sh), 344 (3830); mass spectrum, m/z (relative intensity) 435 (M^+, 23); $[\alpha]^{23}_D$ +175° (c 1, CH_2Cl_2); $[\theta]_{282}$ +14 030° (c 1.3 × 10^{-3}, EtOH). Anal. Calcd for $C_{24}H_{23}NO_5$: C, 71.1; H, 5.7; N, 3.5. Found: C, 70.8; H, 5.7; N, 3.4.

(13a*S*,14*R*)-14-Hydroxy-2,3,6,7-tetramethoxyphenanthro[9,10-*b*]-11-indolizidinone (22a) and (13a*S*,14*S*)-14-Hydroxy-2,3,6,7-tetramethoxyphenanthro[9,10-*b*]-11-indolizidinone (23a). (A) By Catalytic Hydrogenation. Several catalysts, solvents, and conditions were employed for the reduction of **6a**, yielding the 14-β- and 14-α-amido alcohols **22a** and **23a**, respectively. The reductions were performed in dioxane and/or THF at room temperature with 5 wt % catalyst and H_2 at 30 psi. The product distributions, as determined by HPLC using ultraviolet detection (280 nm), are summarized in Table II.

Reduction using $Pd(OH)_2$/C catalyst in dioxane at 40 °C afforded the most selective (24/1) reduction to the β isomer. One recrystallization from acetone afforded pure amido alcohol **22a**: 95% yield; mp 170–173 °C then 213 °C dec; IR 3400, 1675 cm^{-1}; NMR δ 2.10–2.8 (4 H, m), 3.72 (3 H, s), 3.82–4.17 (11 H, m), 4.84 (2 H, AB q, J_{AB} = 17.5 Hz, $\Delta\nu$ = 220 Hz, δ_A 5.28, δ_B 4.40), 5.11 (1 H, br d, J = 7.5 Hz), 7.08 (1 H, s), 7.74 (1 H, s), 4.76 (1 H, s), 7.89 (1 H, s); UV λ_{max} 262 nm (ϵ 51 610), 285 (sh), 290 (28 950), 304 (16 290), 316 (sh), 325 (sh), 342 (2660), 358 (2140); exact mass calcd for $C_{24}H_{25}NO_6$ μ/z 423.1681, found 423.1664.

The acetate of **22a** was prepared by acylation in CH_2Cl_2 with acetyl chloride (105 mol %) and Et_3N (105 mol %): mp 228 °C dec; NMR δ 6.61 (1 H, d, J = 6.8 Hz, C-14 H); Anal. Calcd for $C_{26}H_{27}NO_7$: C, 67.1; H, 5.8; N, 3.0. Found: C, 66.8; H, 5.8; N, 3.0.

(B) By Hydride Reduction. The hydride reduction of **6a** to the mixture of isomeric amido alcohols **22a** and **23a** was examined in THF with various hydrides. The isomer distribution is summarized in Table III.

The L-Selectride reduction gave **23a**: 95% yield (after recrystallization from acetone); mp 262 °C dec; NMR δ 2.2–2.8 (4 H, m), 3.81 (3 H, 5), 3.91 (1 H, d, J = 8.2 Hz), 4.09 (3 H, s), 4.10 (3 H, s), 4.12 (3 H, s), 3.95–4.20 (2 H, m), 4.78 (2 H, AB q, J_{AB} = 17.5 Hz, $\Delta\nu$ = 202.5, δ_A 5.18, δ_B 4.37), 6.86 (1 H, s), 7.62 (1 H,

Table III

hydride	distribution, % 22a	23a
$LiAlH_4$	55	45
$Li(OBu\text{-}t)_3AlH$	50	50
KBH_4	40	60
$LiBH_4$	37	63
$NaBH_4$	35	65
$NaCNBH_3$	57	43
K-Selectride[a]	6	94
L-Selectride[a]	3	97

[a] Obtained from Aldrich.

Table IV

hydride	distribution, % 22b	23b
$LiAlH_4$	55	45
$LiBH_4$	40	60
$NaBH_4$	38	62
L-Selectride	10	90

s), 7.74 (1 H, s), 7.79 (1 H, s); UV λ_{max} 245 nm (sh), 253 (sh), 261 (ε 58 640), 284 (24 580), 390 (28 310), 304 (15 000), 315 (sh), 326 (sh), 341 (2370), 358 (2210); $[\alpha]^{23}_D$ +67.0° (c 1, $CHCl_3$), $[\theta]_{315}$ +2684° (c 4 × 10^{-2}, EtOH).

As described for **22a**, **23a** was converted to its acetate: 94% yield; mp 202 °C dec; NMR δ 6.83 (1 H, d, J = 2.1 Hz, C-14 H). Anal. Calcd for $C_{26}H_{27}NO_7$: C, 67.1; H, 5.8; N, 3.0. Found: C, 66.6; H, 5.7; N, 3.0.

(14a*S*,15*R*)-15-Hydroxy-2,3,6-trimethoxyphenanthro[9,10-*b*]-11-quinolizidinone (22b) and (14a*S*,15*S*)-15-Hydroxy-2,3,6-trimethoxyphenanthro[9,10-*b*]-11-quinolizidinone (23b). (A) By Catalytic Hydrogenation. The catalytic reduction of **6b** to a mixture of the 15-β and 15-α isomeric amido alcohols **22b** and **23b** was investigated as described above for **6a**. In no instance was the β alcohol **22b** the preferred product. In most cases a 1/1 mixture was observed, and with $Pd(OH)_2/C$ catalyst, a 60/40 ratio was achieved.

(B) By Hydride Reduction. The hydride reduction of **6b** to mixtures of **22b** and **23b** was investigated in a similar fashion, and the results are summarized in Table IV.

The L-Selectride reduction in THF afforded the desired C-15 α-amido alcohol **23b** in an isomeric ratio of 9/1 from which it was isolated in 87% yield after one recrystallization from EtOAc: mp 216 °C dec; IR 3330, 1650 cm^{-1}; NMR δ 1.6–2.6 (6 H, m), 2.90 (1 H, d, J = 8 Hz), 3.64 (1 H, t, J = 7 Hz), 3.97 (3 H, s), 4.08 (6 H, s), 4.92 (1 H, d, J = 8 Hz), 4.97 (2 H, AB q, J_{AB} = 20 Hz, Δν = 362.5 Hz, δ_A 5.69, δ_B 4.24), 7.06 (1 H, d, J = 10 Hz), 7.53 (1 H, s), 7.68 (3 H, m); UV λ_{max} 259 nm (ε 42 400), 278 (sh), 283 (24 070), 309 (sh), 336 (1020); $[\alpha]^{23}_D$ +76.3° (c 1, MeOH). Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.7; H, 6.2; N, 3.4. Found: C, 70.6; H, 6.3; N, 3.3.

As described above, **23b** was acylated, and the acetate was isolated: 89% yield; mp 259 °C dec; IR 1715, 1640 cm^{-1}; NMR δ 6.66 (1 H, d, J = 1.5 Hz, C-15 H).

(14*R*)- and (14*S*)-14-Hydroxy-2,3,6,7-tetramethoxyphenanthro[9,10-*b*]indolizidine (24a and 25a) and (15*R*)- and (15*S*)-15-Hydroxy-2,3,6-trimethoxyphenanthro[9,10-*b*]-quinolizidine (24b and 25b). Conversion of amido alcohols **22a,b** and **23a,b** to amino alcohols **24a,b**, and **25a,b**, respectively, was carried out. In all cases, the starting amido alcohols were treated with $LiAlH_4$ (200 mol %) in refluxing THF. Reactions were complete after 1 h, and the usual isolation afforded the amino alcohols as yellow precipitates after purification by preparative thin-layer chromatography. These amino alcohols were found to be extremely air sensitive.

24a from 22a: 61% yield; mp 245 °C dec; IR 3380 cm^{-1}; NMR δ 6.66 (1 H, d, J = 7 Hz, C-14 H of acetate). Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.4; H, 6.6; N, 3.4. Found: C, 70.3; H, 6.6; N, 3.4.

25a from 23a: 73% yield; mp 270 °C dec; IR 3250 cm^{-1}; NMR δ 6.74 (1 H, d, J = 2 Hz, C-14 H of acetate); exact mass calcd for $C_{24}H_{27}NO_5$ m/z 409.1889, found 409.1874; $[\alpha]^{23}_D$ +44.5° (c 1, $CHCl_3$); $[\theta]_{319}$ +5300° (c 3 × 10^{-2}, EtOH). Anal. Calcd for $C_{24}H_{27}NO_5$: C, 70.4; H, 6.6; N, 3.4. Found: C, 69.9; H, 6.5; N, 3.3.

24b from 22b: 29% yield; too unstable to characterize.

25b from 23b: 36% yield; too unstable to characterize.

(*S*)-2,3,6,7-Tetramethoxyphenanthro[9,10-*b*]-11-indolizidinone (26). To a solution of C-14 α alcohol **23a** (422 mg, 1.0 mmol) in CH_2Cl_2 (50 mL) was added $SOCl_2$ (0.1 mL, 105 mol %). After 1 h, the solution was evaporated, and the residue was dissolved in absolute EtOH (35 mL) and hydrogenated by using 10% Pd/C for 4 h. The reaction mixture was filtered and evaporated, and the residue was partitioned between $CHCl_3$ and aqueous $NaHCO_3$ (60 mL of each). The aqueous phase was washed with $CHCl_3$ (3 × 25 mL), and the combined organic phases were dried, filtered, and evaporated to give amide **26**: 93% yield; mp 238–240 °C then 274 °C dec; IR 1670 cm^{-1}; UV λ_{max} 259 nm (ε 73 400), 285 (sh), 290 (42 000)8 305 (23 440), 324 (2160), 340 (2320), 356 (1940), 367 (360); NMR δ 2.3–3.1 (4 H, m), 3.22 (1 H, m), 3.98 (3 H, s), 4,02 (3 H, s), 4.09 (6 H, s), 4.73 (2 H, AB q, J = 17 Hz, Δν = 52.8 Hz, δ_A 5.17, δ_B 4.29), 6.90 (1 H, s), 7.10 (1 H, s), 7.71 (2 H, s); $[\alpha]^{23}_D$ +27.6° (c 0.5, $CHCl_3$). Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.7; H, 6.2; N, 3.4. Found: C, 70.4; H, 6.0; N, 3.4.

(*S*)-2,3,6-Trimethoxyphenanthro[9,10-*b*]-11-quinolizidinone (29). Conversion of amido alcohol **23b** to the phenanthrene amide **29**. To a solution of C-15 α alcohol **23b** (203 mg, 0.5 mmol) in CH_3CN (20 mL) was added ground anhydrous NaI (188 mg, 250 mol %) followed by chlorotrimethylsilane (135 mg, 200 mol %) added dropwise over 10 min. The mixture was warmed to 35 °C for 20 min, cooled to room temperature, and treated with $NaCNBH_3$ (200 mol %) in three portions over 10 min. After 30 min the mixture was evaporated, and the residue partitioned between CH_2Cl_2 and aqueous $NaHCO_3$ (40 mL of each). The aqueous layer was washed with CH_2Cl_2 (3 × 50 mL), and the combined organic phases dried, filtered, and evaporated to give amide **29**: 89% yield; mp 231–233 °C; IR 1675 cm^{-1} NMR δ 1.8–2.4 (6 H, m), 2.95–3.2 (2 H, m), 3.91 (1 H, m), 4.02 (3 H, s), 4.07 (3 H, s), 4.14 (3 H, s), 5.14 (2 H, AB q, J_{AB} = 2 Hz, Δν = 375 Hz, δ_A 5.89, δ_B 4.39), 7.22 (2 H, m), 7.88 (3 H, m); UV λ_{max} 262 nm (ε 31 260), 283 (sh), 288 (19 840), 313 (sh), 344 (1290); mass spectrum, m/z (relative intensity) 391 (M^+, 84); $[\alpha]^{23}_D$ +28.5° (c 1, CH_2Cl_2); $[\theta]_{297}$ +12 500° (c 1.2 × 10^{-3}, EtOH). Anal. Calcd for $C_{29}H_{25}NO_4$: C, 73.6; H, 6.4; N, 3.6. Found: C, 73.8; H, 6.5; N, 3.6.

Tylophorine (1) and Cryptopleurine (2). The following general procedure was used for the reduction of each phenanthrene amide. To hot THF (50 mL) containing 0.30 mmol of amide was added $LiAlH_4$ (100 mol %) in one portion. After 1 h of being refluxed, the solution was cooled to room temperature and quenched with $Na_2SO_4 \cdot 10H_2O$, and after conventional isolation, phenanthroindolizidine **1** and phenanthroquinolizidine **2** were isolated in 96% and 88% yields, respectively, as light yellow solids.

The **(*S*)-(+)-tylophorine (1)** synthesized from (*S*)-glutamic acid was identical with a sample isolated from natural sources[55] as determined by HPLC coinjection (1.5% MeOH in $CHCl_3$). The synthetic and natural material were also identical in all physical properties with the exception of optical rotation data: mp 282–284 °C dec; IR 1620, 1530, 1520 cm^{-1}; NMR δ 1.60–2.38 (4 H, m), 2.39–2.63 (2 H, m), 2.93 (1 H, t, J = 17.5 Hz), 3.39 (1 H, d, J = 16 Hz), 3.49 (1 H, t, J = 6 Hz), 4.06 (6 H, s), 4.13 (6 H, s), 4.17 (2 H, AB q, J = 15 Hz, Δν = 245 Hz, δ_A 4.66, δ_B 3.68), 7.16 (1 H, s), 7.33 (1 H, s), 7.83 (1 H, s); UV λ_{max} 251 nm (sh), 25. (ε 73 180), 282 (sh), 291 (42 340), 305 (24 490), 324 (sh), 340 (2710), 357 (1870); mass spectrum, m/z (relative intensity) 393 (M^+, 21), 324 (95); $[\alpha]^{23}_D$ +15° (c 0.7, $CHCl_3$); $[\theta]_{262}$ +7020° (c 2.2 × 10^{-3}, EtOH).

HPLC analysis of the sample isolated from natural sources indicated the presence of several impurities similar in polarity to tylophorine itself. Mass spectral analysis indicated that at least one of these more polar fractions contained a benzylic alcohol functional group. Coninjection of this fraction on HPLC with freshly prepared **25a** supported our conclusion that the natural sample of tylophorine contained such an impurity.

The **(*S*)-(+)-cryptopleurine (2)** synthesized from (*S*)-α-aminoadipic acid had properties identical with those reported for natural cryptopleurine:[19] mp 196–197 °C; IR 1615, 1535, 1505 cm^{-1}; NMR δ 1.36–2.13 (8 H, m), 2.78–2.96 (1 H, m), 3.02–3.17

(1 H, m), 3.20–3.24 (1 H, d, J = 15 Hz), 4.01 (3 H, s), 4.05 (2 H, AB q, J_{AB} = 20 Hz, $\Delta\nu$ = 210 Hz, δ_A 4.47, δ_B 3.63), 4.07 (3 H, s), 4.11 (3 H, s), 7.20 (1 H, d, J = 10 Hz), 7.26 (1 H, s), 7.80 (1 H, d, J = 10 Hz), 7.91 (2 H, s); UV λ_{max} 259 nm (ϵ 47 170), 287 (28 740), 302 (sh), 312 (sh), 344 (1260); mass spectrum. m/z (relative intensity) 377 (M^+, 24), 294 (100); $[\alpha]^{23}_D$ +106° (c 1.0, $CHCl_3$); $[\theta]_{285}$ +16 000° (c 2.8 × 10^{-3}, EtOH).

Registry No. (*S*)-(+)-**1**, 482-20-2; (*S*)-(+)-**2**, 87302-53-2; **3a**·HCl, 30061-20-2; **3a** (benzyl ester), 30061-09-7; **5a**, 87227-00-7; **5b**, 87227-01-8; **6a**, 87227-03-0; **6b**, 87227-04-1; **7**, 35676-02-9; **8**, 30062-15-8; **9**, 30062-19-2; **10**, 71779-56-1; **11**, 30062-39-6; **12**, 30062-14-7; **13**, 33329-56-5; (*Z*)-**14**, 37629-72-4; **15**, 87226-94-6; **16**, 87226-96-8; **17**, 87226-95-7; **18a**, 87226-97-9; **18a** (aminal), 87226-98-0; **19**, 87226-99-1; **20a**, 87227-10-9; **20b**, 87227-11-0; **22a**, 87227-05-2; **22a** (acetate), 87227-06-3; **22b**, 87227-07-4; **23a**, 87302-54-3; **23a** (acetate), 87302-55-4; **23b**, 87302-56-5; **24a**, 87302-57-6; **24b**, 87302-59-8; **25a**, 87302-58-7; **25b**, 87302-60-1; **26**, 87302-61-2; **28** (β-iodo), 87227-12-1; **28** (α-iodo), 87302-63-4; **29**, 87302-62-3; (*E*)-2-(3,4-dimethoxyphenyl)-3-(2-nitro-4,5-dimethoxyphenyl)cinnamic acid, 87227-08-5; (*E*)-2-(3,4-dimethoxyphenyl)-3-(2-amino-4,5-dimethoxyphenyl)cinnamic acid, 87227-09-6; (*E*)-2-(4-methoxyphenyl)-3-(2-nitro-4,5-dimethoxyphenyl)cinnamic acid, 68742-13-2; (*E*)-2-(4-methoxyphenyl)-3-(2-amino-4,5-dimethoxyphenyl)cinnamic acid, 68742-17-6; veratraldehyde, 120-14-9; (3,4-dimethoxyphenyl)acetonitrile, 93-17-4; (*S*)-(+)-*N*-[(3,4-dimethoxyphenyl)methyl]glutamic acid, 87249-38-5; (*S*)-(+)-glutamic acid, 56-86-0; benzyl prolinate, 41324-66-7; diisopropyl glutamate, 25975-47-7; (*S*)-α-aminoadipic acid, 1118-90-7; diisopropyl (*S*)-α-aminoadipate, 87227-02-9.

Dialkyl (3-Aryl-1,2,4-oxadiazol-5-yl)phosphonates: Synthesis and Thermal Behavior—Evidence for Monomeric Alkyl Metaphosphate

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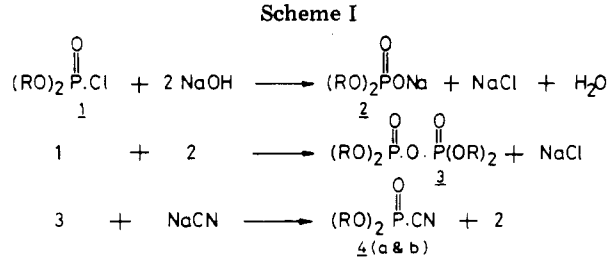
Dialkyl (3-aryl-1,2,4-oxadiazol-5-yl)phosphonates **6a–h** have been obtained by 1,3-dipolar cycloaddition of arenenitrile oxides **5a–f** to dialkyl phosphorocyanidates (**4a** and **4b**) in yields ranging between 30% and 58%. A standardized method for obtaining cyanidates **4a** and **4b** has been established. The diethyl thiophosphorocyanidate (**4c**) is less reactive than **4a** and **4b**, only the 3-(4′-nitrophenyl) derivative **6i** being obtainable. While the IR and NMR spectra of **6a–i** were unexceptional, their UV spectra showed evidence of conjugative interaction in high degrees between the phosphonate and heterocyclic moieties as well as a varying conjugative interaction between the heterocyclic and aryl moieties. The oxadiazoles **6a–h** are thermally labile and yield trialkyl phosphates **7** as the only identifiable products. A mechanism based on the intermediacy of monomeric alkyl metaphosphate **11** in the formation of trialkyl phosphate was postulated, and supportive evidence in the form of trapping the metaphosphate with acetophenone has been obtained.

Even though a number of reports have described the cycloaddition of 1,3-dipolar species to phosphorus(V) activated multiple bonds, such as those in olefinic,[1] acetylenic,[2] or allenic[3] groups, the potential of the method has scarcely been exploited—an enormous range of variation in structural or substitution patterns is possible even if only a perfunctory list of the potentially accessible phosphonates (e.g., heteroaryl phosphonates) is drawn up.

The present paper describes the synthesis, spectral properties, and thermal behavior of several hitherto unknown dialkyl (3-aryl-1,2,4-oxadiazol-5-yl)phosphonates **6a–h** prepared by 1,3-dipolar cycloaddition of arenenitrile oxides **5** to dialkyl phosphorocyanidates **4a,b**. The synthesis of one thiophosphonate (**6i**) by a similar reaction is also described. In the methods employed for the isolation of oxadiazolylphosphonates, the concomitant and somewhat unexpected formation of trialkyl phosphates was noticed. The complicity of thermal decomposition was suspected, and the thermal behavior of the phosphonates **6** was investigated in some detail. Chemical evidence which confirms the role of thermally generated monomeric alkyl metaphosphate in the formation of trialkyl phosphates has been obtained.

Scheme I



Results and Discussion

Dialkyl Phosphorocyanidates 4a,b. The phosphorus–carbon bond forming reaction in the synthesis of oxadiazolylphosphonates **6** described here depends on the availability of dialkyl phosphorocyanidates **4**. The first reported synthesis of **4b** employed a reaction between

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