# Synthesis of 3-Deaza-β-hydroxyhistidine Derivatives and Their Use for the Preparation of Substituted Pyrrolo[2,3-*c*]pyridine-5-carboxylates via the Pictet−Spengler Reaction

Jean-François Rousseau and Robert H. Dodd*

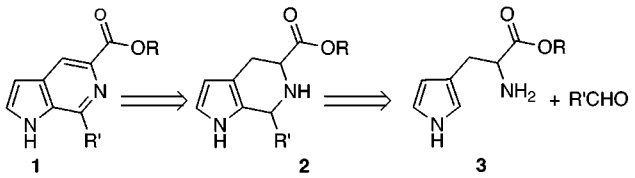
*Institut de Chimie des Substances Naturelles, Centre National de la Recherche Scientifique, Avenue de la Terrasse, 91198 Gif-sur-Yvette Cedex, France*

*Received October 31, 1997*

On account of their isosteric relationship to indole, pyrrolopyridine derivatives have received continual attention over the past years, and new methods for the preparation of their functionalized forms are always of interest.[1] In relation to several pharmacologically oriented research programs in our own laboratory, we have been interested in developing efficient syntheses of multiply substituted pyrrolo[2,3-*c*]pyridines (hereinafter referred to as 6-azaindoles), particularly those carrying a carboxylate group at the C-5 position (e.g., **1**, Scheme 1). While this class of compounds has generally been prepared by construction of the fused pyrrole ring from a suitably substituted pyridine ring,[2−4] we have recently described the use of a complementary strategy in which the pyridine ring is built up from a pyrrole precursor, that is, from a pyrrole-2-carboxaldehyde.[5] Alternatively, simple retrosynthetic analysis (Scheme 1) suggests that 6-azaindoles of type **1** should also be available via dehydrogenation of the corresponding tetrahydro derivatives **2**, themselves prepared by a Pictet−Spengler-type condensation of an aldehyde, R′CHO, with the 3-deazahistidine derivative **3**. A possible complicating factor in the latter reaction would be competive cyclization at the C-4 position of the pyrrole ring rather than at the C-2 position.

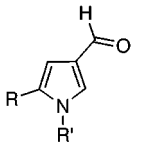
The Pictet−Spengler reaction generally refers to condensations of tryptamines or tryptophans with aldehydes or ketones to give the corresponding β-carboline derivatives and has for decades been the method of choice for the preparation of these compounds.[6] However, while this reaction has been successfully extended to histidine and related imidazoles,[7,8] it has not, to the best of our knowledge, been applied to pyrrole derivatives such as

**Scheme 1**




**3**. In this paper then, we describe the efficient synthesis of the starting pyrrole derivative **3** from pyrrole-3-carboxaldehyde by two different methods (either via a Wittig reaction or a condensation with a glycine anion equivalent) as well as the Pictet−Spengler reaction of this type of compound with aldehydes to provide the corresponding 6-azaindoles.

Our first objective was the synthesis of the amino acid precursor of general formula **3**. The 2-carboxylic acid derivative of **3** has been recently isolated from a mushroom and its synthesis described by Shirahama.[9] Their synthetic scheme relied on the condensation of the Horner−Emmons reagent **5**, developed by Schmidt,[10] with the 4-formylpyrrole-2-carboxylate derivative **4a.** It thus seemed reasonable to expect that this methodology could be successfully applied to a decarboxylated version of **4a**. Since 3-acetyl-1-(benzenesulfonyl)pyrrole[11] is readily available by Friedel−Crafts acylation of 1-(benzenesulfonyl)pyrrole and can in turn be efficiently transformed into the 3-carboxaldehyde derivative **4b**,[12] the latter was




**4a** : R = $CO_2Me$; R' = Boc
**4b** : R = H; R' = $SO_2Ph$

chosen as the starting material for our study. Thus, the anion of **5**, generated in THF using sodium hydride as base, reacted with **4b** to give an approximately 3:2 mixture of the *Z* and *E* isomers **6**, respectively[13] (Scheme 2). Reduction of the double bond of **6** (*Z*,*E* mixture) and removal of the Cbz blocking group could be achieved in one step by catalytic hydrogenation to give **8,** but yields were low. Better results were obtained when the stepwise procedure of Shirahama was used.[9] Thus, the exocyclic double bond of **6** was first reduced by the action of sodium borohydride and nickel chloride hexahydrate to give **7a** in 93% yield. Hydrogenolysis of **7a** using palladium on carbon as catalyst then allowed removal of the Cbz protecting group, to give **8**, in acceptable yield (73%).

With amine **8** at our disposal, it was now possible to investigate whether this compound could undergo a Pictet−Spengler type reaction. While treatment of **8** in

(1) For reviews, see: Willette, R. E. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1968; Vol. 9, p 27. Yakhontov, L. N.; Prokopov, A. A. *Russ. Chem. Rev.* **1980**, *49*, 428. Greenhill, J. V. In *Comprehensive Heterocyclic Chemistry*; Katritzky, J. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 4, Part 3, p 497.

(2) Dodd, R. H.; Ouannès, C.; Robert-Gero, M.; Potier, P. *J. Med. Chem.* **1989**, *32*, 1272.

(3) Dodd, R. H.; Doisy, X.; Potier, P.; Potier, M.-C.; Rossier, J. *Heterocycles* **1989**, *28*, 1101.

(4) Dellouve-Courillon, C.; Dorey, G.; Poissonnet, G.; Doisy, X.; Potier, P.; Dodd, R. H. *Tetrahedron* **1990**, *46*, 3245.

(5) Dekhane, M.; Potier, P.; Dodd, R. H. *Tetrahedron* **1993**, *49*, 8139.

(6) For a review of the Pictet−Spengler reaction, see: Cox, E.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797.

(7) Klutchko, S.; Hodges, J. C.; Blankley, C. J.; Colbry, N. L. *J. Heterocycl. Chem.* **1991**, *28*, 97 and references therein.

(8) Sanchez-Sanchez, M. M.; Tel-Alberdi, L. M.; Rioseras, M. J.; Rico-Ferreira, M. R.; Bermejo-Gonzalez, F. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 191.

(9) Yamano, K.; Shirahama, H. *Tetrahedron* **1992**, *48*, 1457.

(10) Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53.

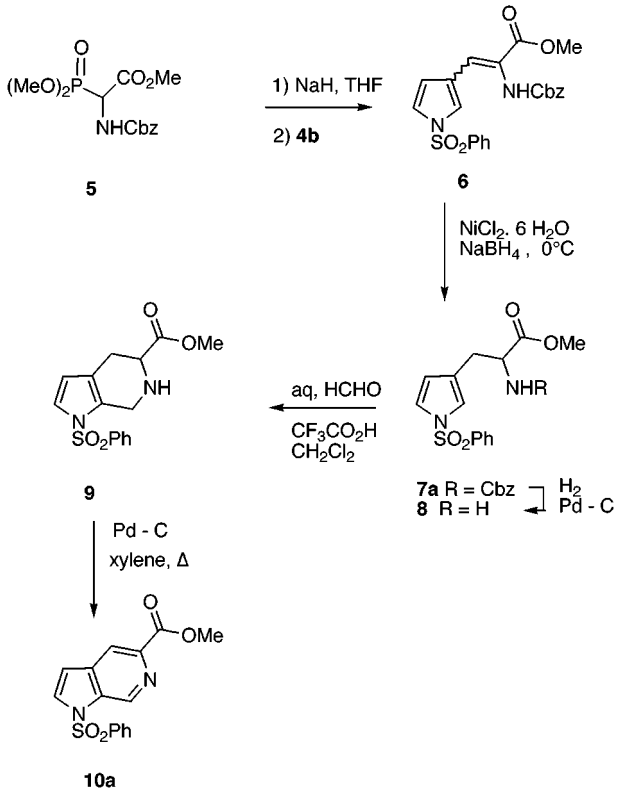
(11) Kakushima, M.; Hamel, P.; Frenette, R.; Rokach, J. *J. Org. Chem.* **1983**, *48*, 3214.

(12) Xiao, D.; Ketcha, D. M. *Org. Prep. Proc. Int.* **1995**, *27*, 503.

(13) Although the *Z* and *E* geometries of **6** were not rigorously established, it has been shown that, when sodium hydride is used as the base, reagent **5** reacts with aromatic aldehydes to give predominantly the *Z* isomer. See ref 10.

S0022-3263(97)02005-7 CCC: $15.00 
Published on Web 03/28/1998

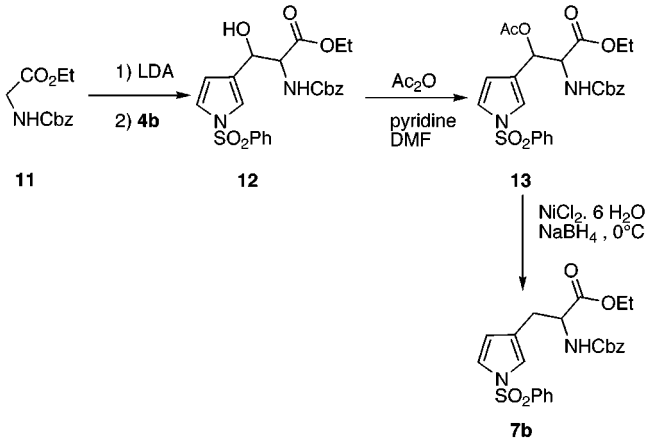
**Scheme 2**




dichloromethane with 1 equiv of an aqueous solution of formaldehyde resulted in no discernible reaction, addition of 2 equiv of trifluoroacetic acid led to exclusive formation of the tetrahydro-6-azaindole **9**, the product of Pictet−Spengler condensation. The presence, in the $^1$H NMR spectrum of **9**, of two doublets at 6.82 and 7.80 ppm ($J$ = 3.6 Hz) corresponding to the two vinylic protons of the pyrrole ring indicates that cyclization had indeed occurred at the C-2 position of **8** rather than at the C-4 position. Moreover, dehydrogenation of the tetrahydro derivative **9** under the same conditions known to dehydrogenate tetrahydro-$\beta$-carboline derivatives (reflux in xylene in the presence of palladium on carbon)[14,15] gave 6-azaindole **10a,** the NMR data ($^1$H, $^{13}$C) for which were practically identical to those of analogous 6-azaindoles we have prepared using other methodologies (see also below).[2−5]

Having now shown that application of the Pictet−Spengler reaction to a pyrrole derivative such as **8** is indeed a viable route to the 6-azaindole nucleus, we proceeded to find a more advantageous method for the preparation of the starting amine **8**, and this is for the following reasons. First, though the Horner−Emmons reagent **5** is commercially available, it is expensive and its preparation from glyoxylic acid is tedious.[10] Second, the overall yield of the condensation of **5** with pyrrolecarboxaldehyde **4** followed by reduction of the double bond (68%), though relatively satisfactory, begs for improvement. Finally, and more seriously, reagent **5** reacts only with aldehydes, not with ketones.[10] The latter, in place of the aldehyde in **4**, would have allowed introduction of substituents at C-4 of the 6-azaindoles, a highly desirable goal within the pharmacological context of our research program.

**Scheme 3**




In view of these limitations, another route was developed to the starting amines of type **8** which makes use of the anion derived from ethyl (*N*-Cbz)glycinate (**11**) (Scheme 3). Reaction of the latter with alkyl and aromatic aldehydes and ketones has been shown to allow efficient preparation of α-amino-$\beta$-hydroxy acids.[16,17] With pyrrole-3-carboxaldehyde **4b**, reaction with the anion of **11** (prepared in THF using LDA as base) gave an excellent yield (94%) of the $\beta$-hydroxy-3-deazahistidine derivative **12**. The latter was then easily converted into **7b,** that is, the ethyl ester analogue of the compound obtained using the Horner−Emmons reagent (Scheme 2), by acetylation of the secondary hydroxyl group to give **13** followed by treatment with sodium borohydride/nickel chloride. However, as depicted in the following scheme, it is not necessary to transform **12** into **7b** prior to effecting the Pictet−Spengler reaction since **12** serves this purpose very well. Thus, hydrogenolysis of the Cbz protecting group of **12** (an inseparable mixture of the anti and syn isomers) gave the free amines **14** and **15** in a 3:2 ratio which could be separated by chromatography or by fractional crystallization in ethanol (Scheme 4). The relative configurations of the vicinal hydroxy and amine substituents of **14** and **15** were determined by transformation of the latter into the oxazolidine-2-thiones **16** and **17**, respectively, using carbon disulfide and triethylamine. It has been shown that for both oxazolidine-2-thiones and oxazolidin-2-ones having substituents at C-4 and C-5, the cis-substituted derivatives consistently display, in their $^1$H NMR spectra, H-4/H-5 coupling constants of higher value ($J$ = 8−9.5 Hz) than the corresponding trans derivatives ($J$ = 5−8 Hz).[18] For compound **16**, this value corresponds to 9.5 Hz, indicating a cis geometry at C-4/C-5 and, by extrapolation, an anti configuration for the starting amino alcohol **14**. Similarly, an H-4/H-5 coupling constant of 6.3 Hz for **17** points to a trans arrangement of these protons and a syn geometry for the precursor **15**.

When **14** and **15** were separately treated with formaldehyde and trifluoroacetic acid in dichloromethane,

(14) Soerens, D.; Sandrin, J.; Ungemach, F.; Mokry, P.; Wu, G. S.; Yamanaka, E.; Hutchins, L.; DiPierro, M.; Cook, J. M. *J. Org. Chem.* **1979**, *44*, 535.

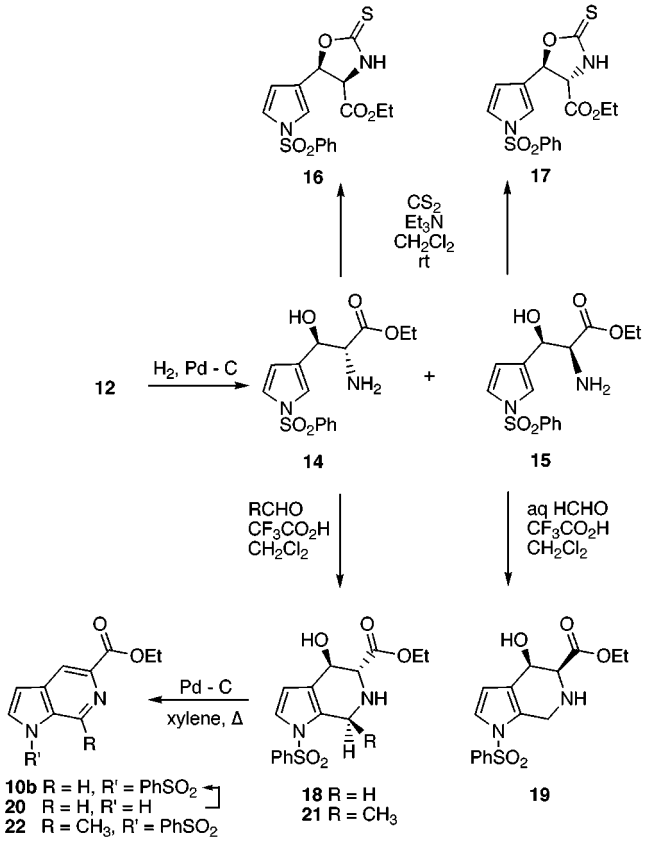
(15) Dorey, G.; Poissonnet, G.; Potier, M.-C.; Prado de Carvalho, L.; Venault, P.; Chapouthier, G.; Rossier, J.; Potier, P.; Dodd, R. H. *J. Med. Chem.* **1989**, *32*, 1799.

(16) Dikshit, D. K.; Singh, S. *Tetrahedron Lett.* **1988**, *29*, 3109.

(17) Shanzar, A.; Somekh, L.; Butina, D. *J. Org. Chem.* **1979**, *44*, 3967.

(18) Moreno-Manas, M.; Padros, I. *J. Heterocycl. Chem.* **1993**, *30*, 1235. Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308. Saeed, A.; Young, D. W. *Tetrahedron* **1992**, *48*, 2507.

**Scheme 4**

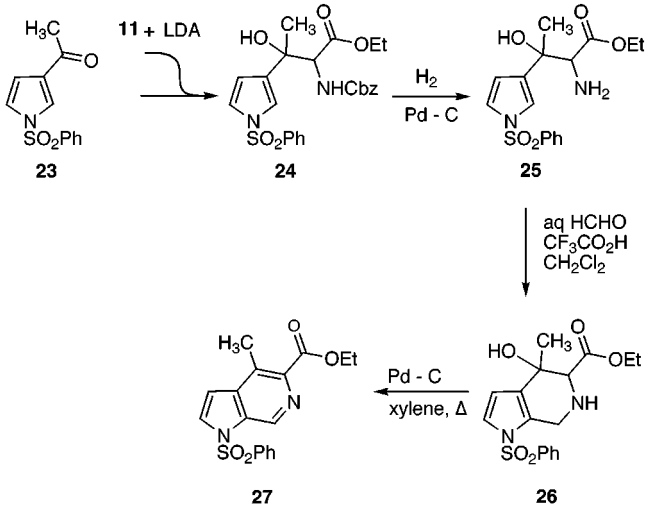



approximately 80% yields of the racemic 4-hydroxy-4,5,6,7-tetrahydro-6-azaindole-5-carboxylates **18** and **19**, respectively, were obtained. Compound **18** was subjected to the standard dehydrogenation conditions (palladium on carbon in refluxing xylene) to give 6-azaindole **10b** in almost quantitative yield. There was no observable trace of the 4-hydroxy derivative of **10b** which would have resulted from dehydrogenation (rather than dehydration) of the C-4/C-5 bond. Palladium on carbon has been observed to also promote dehydration in $\beta$-carboline derivatives having appropriately disposed hydroxy groups.[14] Both **10b** prepared via the glycine anion route and **10a** prepared by the Wittig−Horner route have essentially identical $^1$H and $^{13}$C NMR spectra. As an ultimate structural characterization of these compounds, compound **10b** was prepared by benzenesulfonylation of **20**, itself prepared by an independent method[5] and for which the structure was unambiguously determined by X-ray crystallography.[19]

The synthetic utility of the glycine anion/Pictet−Spengler condensation route to substituted 6-azaindoles is illustrated by the following two examples. When compound **14** (anti isomer) was condensed with acetaldehyde in the presence of trifluoroacetic acid, the Pictet−Spengler product **21** was obtained in 82% yield as a single diastereoisomer. An anti configuration of the C-7 methyl group of **21** with respect to the C-5 substituent was substantiated by the observation of an NOE enhancement of 3.7% between this methyl group and H-5. The formation of single diastereoisomers was also reported in analogous Pictet−Spengler reactions of $\beta$-methyltryptophan methyl esters with various aldehydes, including

(19) Chiaroni, A.; Riche, C.; Dekhane, M.; Dodd, R. H. *Acta Crystallogr.* **1994**, *C50*, 1343.

**Scheme 5**




acetaldehyde.[20] Treatment of **21** with palladium on carbon again gave the product of dehydration/dehydrogenation in the form of the 7-methyl-6-azaindole-5-carboxylate **22**.

Finally, as shown in Scheme 5, the glycine anion strategy can, unlike the Wittig−Horner procedure, allow preparation of a 4-substituted-6-azaindole (e.g., **27**). Thus, reaction of 3-acetyl-1-(benzenesulfonyl)pyrrole (**23**)[11] with the anion generated from **11** and LDA afforded the tertiary alcohol **24** in 78% yield as a 7:3 mixture of diastereomers. The Cbz group of the latter was removed by hydrogenolysis to give **25**, which in the presence of TFA condensed with formaldehyde in Pictet−Spengler fashion to yield **26**.[21] The 4-methyl-6-azaindole-5-carboxylate **27** was then cleanly formed when **26** was treated with palladium on carbon in refluxing xylene.

In conclusion, the presently described methodology allows efficient preparation of 4,5- and 5,7-substituted 6-azaindole derivatives and can obviously be extended to include further substitutions at the C-2 and/or C-3 positions, insofar as the starting pyrrolecarboxaldehydes are available.

## Experimental Section

**General.** Melting points are uncorrected. IR spectra of samples were obtained as KBr pellets. $^1$H and $^{13}$C NMR chemical shifts are given as $\delta$ values with reference to $Me_4Si$ as internal standard. TLC and preparative chromatography were performed on Merck silica gel 60 plates with fluorescent indicator. The plates were visualized with UV light (254 or 366 nm) and, for TLC, with a 3.5% solution of phosphomolybdic acid in ethanol. All column chromatography was conducted on Merck 60 silica gel (230−240 mesh) at medium pressure (200 mbar). All solvents were distilled and stored over 4-Å molecular sieves before use. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

**Methyl (*E*)- and (*Z*)-2-[*N*-(Benzyloxycarbonyl)amino]-3-[3-*N*-(benzenesulfonyl)pyrrolyl]propenoate (6).** To a stirred suspension of sodium hydride (384 mg of a 50% dispersion in oil; 8 mmol) in anhydrous THF (10 mL) was added dropwise at room temperature under argon a solution of *N*-(benzyloxycar-

(20) Behforouz, M.; West, S. J.; Chakrabarty, C.; Rusk, D. A.; Zarrinmayeh, H. *Heterocycles* **1992**, *34*, 483.

(21) Compound **26** was prepared from the major diastereomer of **25**, obtained in pure form by crystallization of the diastereomeric mixture (see Experimental Section). The relative configurations of the chiral centers of **26** and of the major and minor diastereomers of **24** and **25** have not been established.

bonyl)phosphonoglycine trimethyl ester[10] (**5**; 2.7 g, 8.4 mmol) in THF (5 mL). After gas evolution had ceased (about 15 min), a solution of compound **4b**[12] (2.0 g, 8.4 mmol) in THF (5 mL) was added and the reaction mixture was stirred for 2 h. The latter was then quenched by addition of saturated aqueous ammonium chloride, and the mixture was extracted with dichloromethane (3 × 100 mL). The organic extracts were combined, washed with saturated aqueous sodium chloride (150 mL), and dried over sodium sulfate. Removal of the solvents under reduced pressure left a residue which was purified by column chromatography on silica gel (heptane−ethyl acetate, 7:3). The first compound to be eluted was (*Z*)-**6** obtained in 45% yield as a yellow solid: mp 111 °C (methanol); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 3.77 (s, 3H), 5.15 (s, 2H), 6.53 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 6.90 (s, 1H, exchangeable with $D_2O$), 7.10 (dd, 1H, $J$ = 2.3 and 3.2 Hz), 7.30 (s, 5H), 7.31 (s, 1H), 7.46 (t, 2H, $J$ = 7.7 Hz), 7.55 (dd, 1H, $J$ = 1.5 and 2.3 Hz), 7.59 (t, 1H, $J$ = 7.7 Hz), 7.87 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 52.3, 67.3, 116.0, 120.3, 120.7, 122.9, 123.3, 127.0, 127.1, 128.3, 128.4, 128.7, 129.5, 134.1, 135.9, 138.9, 154.7, 165.8; IR (KBr) 1715, 1648 cm$^{-1}$; CIMS *m*/*z* 441 (MH)$^+$. Anal. Calcd for $C_{22}H_{20}N_2O_6S{\cdot}0.5CH_3OH$: C, 59.20; H, 4.86; N, 6.14; S, 7.02. Found: C, 59.17; H, 4.61; N, 5.81; S, 7.29.

Continued elution of the chromatography column provided (*E*)-**6** in 28% yield, also as a yellow powder: mp 101 °C (ethyl acetate−heptane); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 3.77 (s, 3H), 5.15 (s, 2H), 6.53 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.10 (dd, 1H, $J$ = 2.3 and 3.2 Hz), 7.36 (br s, 6H), 7.46 (t, 2H, $J$ = 7.7 Hz), 7.53 (dd, 1H, $J$ = 1.5 and 2.3 Hz), 7.59 (t, 1H, $J$ = 7.7 Hz), 7.87 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 52.4, 67.4, 114.0, 121.2, 121.7, 123.5, 127.0, 127.1, 128.1, 128.2, 128.5, 129.6, 134.4, 136.0, 138.3, 154.5, 165.6; IR (KBr) 1715 cm$^{-1}$; HRCIMS calcd for $C_{22}H_{21}N_2O_6S$ *m*/*z* 441.1120, found 441.1132. Anal. Calcd for $C_{22}H_{20}N_2O_6S{\cdot}1.0H_2O$: C, 57.63; H, 4.84; N, 6.11; S, 6.99. Found: C, 57.51; H, 5.13; N, 6.21; S, 7.11.

**Methyl (*R*,*S*)-2-[*N*-(Benzyloxycarbonyl)amino]-3-[3-*N*-(benzenesulfonyl)pyrrolyl]propanoate (7a).** A solution of compound **6** (227 mg, 0.52 mmol) in methanol (10 mL) was treated at 0 °C under argon with nickel chloride hexahydrate (125 mg, 0.52 mmol), and after the mixture had stirred for 5 min, sodium borohydride (200 mg, 5.16 mmol) was added in small portions. The solution was stirred for 1 h at 0 °C, saturated aqueous ammonium chloride (30 mL) was added, and the mixture was extracted with dichloromethane (4 × 50 mL). The organic extracts were combined, washed with saturated aqueous sodium chloride (100 mL), dried over sodium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (heptane−ethyl acetate, 65:35), providing compound **7a** (as a white solid in 93% yield): mp 87 °C (heptane); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 2.91 (d, 2H, $J$ = 5.0 Hz), 3.63 (s, 3H), 4.55 (dt, 1H, $J$ = 5.0 and 8.0 Hz), 5.08 (s, 2H), 5.38 (d, 1H, $J$ = 8.0 Hz, exchangeable with $D_2O$), 6.19 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 6.95 (dd, 1H, $J$ = 1.5 and 2.3 Hz), 7.07 (dd, 1H, $J$ = 2.3 and 3.2 Hz), 7.44 (t, 2H, $J$ = 7.7 Hz), 7.56 (t, 1H, $J$ = 7.7 Hz), 7.78 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 29.6, 52.3, 54.1, 67.0, 114.8, 119.1, 121.1, 123.1, 126.6, 128.1, 128.2, 128.5, 129.4, 133.9, 136.1, 138.8, 156.0, 172.1; IR (KBr) 3380, 1717 cm$^{-1}$; HRCIMS calcd for $C_{22}H_{23}N_2O_6S$ *m*/*z* 443.1277, found 443.1284. Anal. Calcd for $C_{22}H_{22}N_2O_6S{\cdot}1.4H_2O$: C, 56.50; H, 5.34; N, 5.99; S, 6.85. Found: C, 56.41; H, 5.09; N, 5.91; S, 7.03.

**Methyl(*R*,*S*)-2-Amino-3-[3-*N*-(benzenesulfonyl)pyrrolyl]-propanoate (8).** A solution of compound **7a** (211 mg, 0.48 mmol) in ethanol (10 mL) was hydrogenated for 3 h at atmospheric pressure in the presence of 5% palladium on carbon (40 mg). The reaction mixture was then filtered through Celite, the filter pad was washed copiously with ethanol, and the filtrate and washings were evaporated to dryness under reduced pressure, affording compound **8** as a yellow oil in 73% yield: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 2.02 (br s, 2H, exchangeable with $D_2O$), 2.81 (ddd, 2H, $J$ = 5.0, 6.9, and 14.3 Hz), 3.60 (br s, 4H), 6.17 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.01 (dd, 1H, $J$ = 1.5 and 2.3 Hz), 7.10 (dd, 1H, $J$ = 2.3 and 3.2 Hz), 7.54 (t, 2H, $J$ = 7.7 Hz), 7.60 (t, 1H, $J$ = 7.7 Hz), 7.80 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 31.9, 52.1, 54.7, 67.0, 114.8, 119.2, 121.4, 123.1, 126.7, 129.5, 133.9, 138.8, 172.1; IR (KBr) 3420, 1730 cm$^{-1}$. HRCIMS calcd for $C_{14}H_{17}N_2O_4S$ *m*/*z* 309.0909, found 309.0920.

**Ethyl (2*RS*,3*RS*)-2-[*N*-(Benzyloxycarbonyl)amino]-3-hydroxy-3-[3-*N*-(benzenesulfonyl)pyrrolyl]propanoate (12).** A freshly prepared solution of LDA in anhydrous THF (141 mL of a 0.13 M solution; 18.3 mmol) was treated dropwise at −78 °C under argon with a solution of *N*-(benzyloxycarbonyl)glycine ethyl ester (**11**; 1.88 g, 7.9 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h at −78 °C, and a solution of 1-(benzenesulfonyl)pyrrole-3-carboxaldehyde (**4b**; 2.23 g, 9.49 mmol) in THF (10 mL) was added dropwise. The reaction mixture was stirred for 70 min at −78 °C, and after addition of saturated aqueous ammonium chloride (30 mL), it was allowed to warm to room temperature. The mixture was extracted with dichloromethane (4 × 150 mL); the organic extracts were combined, washed with saturated aqueous sodium chloride (200 mL), and dried over sodium sulfate. Evaporation of the solvents under reduced pressure left an oily residue which was purified by column chromatography on silica gel (dichloromethane−ethanol, 98:2), affording compound **12**, a pale-yellow viscous syrup, as an inseparable mixture of diastereomers (3:2) in 94% overall yield: $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.11 (2t, 3H, $J$ = 7.1 Hz), 3.28 (d, 0.4H, $J$ = 5.2 Hz, exchangeable with $D_2O$), 3.76 (d, 0.6H, $J$ = 5.5 Hz, exchangeable with $D_2O$), 4.05 (q, 1.2H, $J$ = 7.1 Hz), 4.14 (q, 0.8H, $J$ = 7.1 Hz), 4.52 (dd, 0.4H, $J$ = 2.4 and 9.4 Hz), 4.67 (dd, 0.6H, $J$ = 3.3 and 8.0 Hz), 5.01 (dd, 0.6H, $J$ = 3.3 and 5.5 Hz), 5.08 (s, 2H), 5.12 (dd, 0.4H, $J$ = 2.4 and 5.2 Hz), 5.63 (d, 0.6H, $J$ = 8.0 Hz, exchangeable with $D_2O$), 5.76 (d, 0.4H, $J$ = 9.4 Hz, exchangeable with $D_2O$), 6.19 (dd, 0.6H, $J$ = 1.5 and 3.2 Hz), 6.27 (dd, 0.4H, $J$ = 1.5 and 3.2 Hz), 7.00 (dd, 1H, $J$ = 2.3 and 3.2 Hz), 7.13 (dd, 0.6H, $J$ = 1.5 and 2.3 Hz), 7.19 (dd, 0.4H, $J$ = 1.5 and 2.3 Hz), 7.36 (s, 5H), 7.46 (t, 2H, $J$ = 7.7 Hz), 7.59 (t, 1H, $J$ = 7.7 Hz), 7.87 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 13.9, 14.0, 59.2, 59.4, 61.8, 61.9, 67.2, 67.3, 68.6, 69.5, 112.1, 112.2, 118.2, 118.4, 121.4, 127.3, 127.9, 129.0, 129.1, 129.3, 129.9, 134.5, 136.0, 136.2, 138.8, 156.5, 156.8, 169.7, 170.6; IR (KBr) 3340, 1720 cm$^{-1}$; CIMS *m*/*z* 473 (MH)$^+$, 455 (MH − $H_2O$)$^+$. Anal. Calcd for $C_{23}H_{24}N_2O_7S$: C, 58.46; H, 5.12; N, 5.93; S, 6.78. Found: C, 58.22; H, 5.25; N, 5.98; S, 6.61.

**Ethyl (2*RS*,3*RS*)-2-[*N*-(Benzyloxycarbonyl)amino]-3-acetoxy-3-[3-*N*-(benzenesulfonyl)pyrrolyl]propanoate (13).** A solution of compound **12** (3.6 g, 7.6 mmol) in DMF (50 mL) was treated at room temperature with acetic anhydride (6 mL) and pyridine (6 mL). The reaction mixture was stirred for 15 h, water (50 mL) was added, and the mixture was extracted with ethyl acetate (4 × 75 mL). The organic extracts were combined and washed with 0.5 M hydrochloric acid solution (150 mL) and saturated aqueous sodium chloride (150 mL). The organic phase was dried over sodium sulfate, the solvents were removed under reduced pressure, and the solid residue was crystallized from methanol, affording compound **13** as an inseparable mixture of diastereomers (3:2) in 90% yield: mp 108 °C; $^1$H NMR (250 MHz, $CDCl_3$) *major isomer* $\delta$ 2.01 (s, 3H), 3.14 (t, 3H, $J$ = 7.1 Hz), 4.10 (q, 2H, $J$ = 7.1 Hz), 4.93 (dd, 1H, $J$ = 3.3 and 9.0 Hz), 5.10 (s, 2H), 5.34 (d, 1H, $J$ = 9.0 Hz, exchangeable with $D_2O$), 6.14 (d, 1H, $J$ = 3.3 Hz), 6.23 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.10 (dd, 1H, $J$ = 2.3 and 3.2 Hz), 7.13 (dd, 1H, $J$ = 1.5 and 2.3 Hz), 7.30 (s, 5H), 7.46 (t, 2H, $J$ = 7.7 Hz), 7.59 (t, 1H, $J$ = 7.7 Hz), 7.87 (d, 2H, $J$ = 7.7 Hz); *minor isomer* $\delta$ 2.02 (s, 3H), 3.14 (t, 3H, $J$ = 7.1 Hz), 4.10 (q, 2H, $J$ = 7.1 Hz), 4.70 (dd, 1H, $J$ = 3.3 and 9.8 Hz), 5.05 (s, 2H), 5.56 (d, 1H, $J$ = 9.8 Hz), 6.14 (d, 1H, $J$ = 3.3 Hz), 6.28 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.10 (dd, 1H, $J$ = 2.3 and 3.2 Hz), 7.13 (dd, 1H, $J$ = 1.5 and 2.3 Hz), 7.30 (s, 5H), 7.46 (t, 2H, $J$ = 7.7 Hz), 7.59 (t, 1H, $J$ = 7.7 Hz), 7.87 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) *major isomer* $\delta$ 13.9, 20.6, 56.8, 61.9, 67.2, 69.6, 112.4, 114.9, 118.9, 121.5, 124.3, 126.8, 128.3, 128.4, 128.7, 129.5, 134.1, 136.2, 138.6, 155.9, 168.6, 169.9; *minor isomer* $\delta$ 13.9, 20.6, 57.5, 61.9, 67.0, 69.3, 112.5, 115.0, 119.1, 121.4, 124.1, 126.7, 128.3, 128.4, 128.7, 129.2, 133.8, 136.2, 138.8, 155.6, 168.6, 169.5; IR (KBr) 3371, 1725, 1720, 1710 cm$^{-1}$; EIMS *m*/*z* 514 (M)$^+$. Anal. Calcd for $C_{25}H_{26}N_2O_8S$: C, 58.36; H, 5.09; N, 5.44; S, 6.23. Found: C, 58.25; H, 5.29; N, 5.62; S, 6.01.

**Ethyl (*R*,*S*)-2-[*N*-(Benzyloxycarbonyl)amino]-3-[3-*N*-(benzenesulfonyl)pyrrolyl]propanoate (7b).** Following the same procedure as for the preparation of **7a**, compound **13** (3.5 g, 7.7 mmol) in methanol (100 mL) was treated at 0 °C with nickel chloride hexahydrate (1.87 g, 7.7 mmol) and, after 5 min, with sodium borohydride (2.9 g, 77.1 mmol). After 1 h, the reaction mixture was worked up as before, and the crude product was

purified by chromatography on silica gel (heptane−ethyl acetate, 65:35). First eluted was compound **7b** obtained as a white solid in 57% yield: mp 99−100 °C (ethyl acetate); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.17 (t, 3H, $J$ = 7.1 Hz), 2.91 (d, 2H, $J$ = 5.6 Hz), 4.09 (q, 2H, $J$ = 7.1 Hz), 4.53 (dt, 1H, $J$ = 5.6 and 8.0 Hz), 5.09 (s, 2H), 5.39 (d, 1H, $J$ = 8.0 Hz, exchangeable with $D_2O$), 6.13 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 6.97 (dd, 1H, $J$ = 1.5 and 2.3 Hz), 7.08 (dd, 1H, $J$ = 2.3 and 3.2 Hz), 7.33 (s, 5H), 7.44 (t, 2H, $J$ = 7.7 Hz), 7.56 (t, 1H, $J$ = 7.7 Hz), 7.78 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.0, 29.6, 54.1, 61.4, 66.8, 114.8, 119.0, 121.1, 123.1, 126.5, 128.0, 128.1, 128.4, 129.3, 133.7, 136.1, 138.8, 155.6, 171.3; IR (KBr) 3380, 1730 cm$^{-1}$; CIMS $m/z$ 457 $(MH)^+$. Anal. Calcd for $C_{23}H_{24}N_2O_6S$: C, 60.51; H, 5.30; N, 6.14; S, 7.02. Found: C, 60.54; H, 5.49; N, 6.19; S, 6.91.

Continued elution of the chromatography column allowed recovery of unreacted starting material **13** in 34% yield.

**Ethyl (2*S*,3*S*)- and (2*R*,3*R*)-2-Amino-3-hydroxy-3-[3-*N*-(benzenesulfonyl)pyrrolyl]propanoate (14) and Ethyl (2*R*,3*S*)- and (2*S*,3*R*)-2-Amino-3-hydroxy-3-[3-*N*-(benzenesulfonyl)pyrrolyl]propanoate (15).** A solution of compound **12** (1.75 g, 3.71 mmol) in ethanol (50 mL) containing 5% palladium on carbon (400 mg) was stirred under an atmosphere of hydrogen for 2 h. The reaction mixture was then filtered through Celite, the filter pad was washed with ethanol, and the combined filtrate and washings were evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane−ethanol, 98:2), first providing compound **14** as a pale-yellow solid in 53% yield: mp 75 °C (ethanol); $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.09 (t, 3H, $J$ = 7.1 Hz), 2.50 (br s, 3H, exchangeable with $D_2O$), 3.50 (d, 1H, $J$ = 4.7 Hz), 4.03 (q, 2H, $J$ = 7.1 Hz), 4.72 (d, 1H, $J$ = 4.7 Hz), 6.25 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.10 (dd, 1H, $J$ = 2.3 and 3.2 Hz), 7.12 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.46 (t, 2H, $J$ = 7.7 Hz), 7.56 (t, 1H, $J$ = 7.7 Hz), 7.87 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 14.0, 59.7, 61.2, 69.0, 112.2, 118.2, 121.3, 126.8, 129.4, 129.6, 134.0, 139.0, 173.1; IR (KBr) 3370, 1734 cm$^{-1}$; CIMS $m/z$ 339 $(MH)^+$. Anal. Calcd for $C_{15}H_{18}N_2O_5S$: C, 53.24; H, 5.36; N, 8.28; S, 9.47. Found: C, 53.24; H, 5.12; N, 8.21; S, 9.61.

Continued elution of the chromatography column provided **15** as a white solid in 35% yield: mp 123−125 °C (ethanol); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.21 (t, 3H, $J$ = 7.1 Hz), 1.50 (br s, 3H, exchangeable with $D_2O$), 3.73 (d, 1H, $J$ = 5.1 Hz), 4.09 (q, 2H, $J$ = 7.1 Hz), 4.90 (d, 1H, $J$ = 5.1 Hz), 6.25 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.06 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.10 (dd, 1H, $J$ = 2.3 and 3.2 Hz), 7.46 (t, 2H, $J$ = 7.7 Hz), 7.56 (t, 1H, $J$ = 7.7 Hz), 7.87 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 14.2, 59.2, 61.4, 68.7, 112.2, 118.3, 121.4, 126.9, 128.5, 129.6, 134.0, 139.0, 173.1; IR (KBr) 3370, 1724 cm$^{-1}$; CIMS $m/z$ 339 $(MH)^+$. Anal. Calcd for $C_{15}H_{18}N_2O_5S{\cdot}0.2H_2O$: C, 52.68; H, 5.42; N, 8.19; S, 9.37. Found: C, 52.69; H, 5.38; N, 8.15; S, 9.36.

**Ethyl (4*R*,5*R*)- and (4*S*,5*S*)-5-[3-*N*-(Benzenesulfonyl)-pyrrolyl]-2-thioxooxazolidine-4-carboxylate (16).** To a solution of compound **14** (61.5 mg, 0.18 mmol) in anhydrous dichloromethane (10 mL), held at 0 °C under argon, was added carbon disulfide (13 $\mu$L, 0.22 mmol). The solution was allowed to come to room temperature, and triethylamine (30 $\mu$L, 0.22 mmol) was slowly added. The reaction mixture was stirred for 15 h at room temperature, aqueous hydrochloric acid (10 mL of a 0.1 M solution) was added, and the organic phase was separated. The aqueous phase was extracted with dichloromethane (4 × 25 mL); the organic extracts were combined and washed with saturated aqueous sodium hydrogen carbonate (10 mL) and then with saturated aqueous sodium chloride (10 mL). The organic phase was dried over sodium sulfate, the solvent was removed under reduced pressure, and the residue was purified by column chromatography on silica gel (dichloromethane−ethanol, 95:5) affording a tan solid in 34% yield: mp 80 °C (ethyl acetate); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.90 (t, 3H, $J$ = 7.1 Hz), 3.80 (q, 3H, $J$ = 7.1 Hz), 4.84 (d, 1H, $J$ = 9.5 Hz), 6.01 (d, 1H, $J$ = 9.5 Hz), 6.30 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.15 (dd, 1H, $J$ = 1.5 and 2.3 Hz), 7.30 (dd, 1H, $J$ = 3.2 and 2.3 Hz), 7.60 (t, 2H, $J$ = 7.7 Hz), 7.66 (t, 1H, $J$ = 7.7 Hz), 7.81 (s, 1H, exchangeable with $D_2O$), 7.92 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 13.7, 62.2, 62.3, 79.9, 111.9, 119.9, 121.6, 121.8, 127.1, 129.7, 134.4, 138.5, 167.0, 189.6; IR (KBr) 3142, 1745 cm$^{-1}$; CIMS $m/z$ 381 $(MH)^+$. Anal. Calcd for $C_{16}H_{16}N_2O_5S_2{\cdot}0.7CH_3CO_2C_2H_5$: C, 51.08; H, 4.92; N, 6.34; S, 14.50. Found: C, 51.47; H, 4.88; N, 6.71; S, 14.77.

**Ethyl (4*R*,5*S*)- and (4*S*,5*R*)-5-[3-*N*-(Benzenesulfonyl)-pyrrolyl]-2-thioxooxazolidine-4-carboxylate (17).** The procedure described above for the preparation of **16** allowed transformation of compound **15** into **17**, a colorless oil, in 35% yield: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.32 (t, 3H, $J$ = 7.1 Hz), 4.30 (q, 2H, $J$ = 7.1 Hz), 4.44 (d, 1H, $J$ = 6.3 Hz), 5.85 (d, 1H, $J$ = 6.3 Hz), 6.37 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.15 (dd, 1H, $J$ = 1.5 and 2.3 Hz), 7.30 (dd, 1H, $J$ = 3.2 and 2.3 Hz), 7.60−7.70 (m, 4H, partly exchangeable with $D_2O$), 7.92 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.2, 63.1, 63.6, 79.9, 111.2, 119.0, 122.5, 124.6, 127.1, 129.8, 134.5, 138.5, 167.0, 187.7; IR (KBr) 3137, 1744 cm$^{-1}$; HRCIMS calcd for $C_{16}H_{17}N_2O_5S_2$ $m/z$ 381.0579, found 381.0601.

**Ethyl (2*RS*,3*RS*)-2-[*N*-(Benzyloxycarbonyl)amino]-3-hydroxy-3-[3-*N*-(benzenesulfonyl)pyrrolyl]butanoate (24).** Using the same procedure as for the preparation of **12**, glycine derivative **11** (3.46 g, 14.6 mmol) in THF (10 mL) was added to a freshly prepared solution of LDA in THF (146 mL of a 0.2 M solution; 29.2 mmol) maintained at −78 °C. After 1 h, a solution of compound **23**[11] (4.0 g, 16.1 mmol) in THF (10 mL) was added, and the reaction mixture was stirred for 70 min at − 78 °C. The usual workup gave a crude product which was purified by chromatography on silica gel (dichloromethane), affording compound **24**, a white solid, as an inseparable mixture of diastereomers (A:B, 7:3) in 78% overall yield: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 0.90 (t, 3H, $J$ = 7.1 Hz), 1.46 (s, 3H), 3.30 (br s, 1H, exchangeable with $D_2O$), 3.82 (q, 1.4H, $J$ = 7.1 Hz), 3.87 (q, 0.6H, $J$ = 7.1 Hz), 4.48 (d, 1H, $J$ = 9.3 Hz), 5.10 (s, 1.4H), 5.12 (s, 0.6H), 5.67 (d, 0.6H, $J$ = 9.3 Hz, exchangeable with $D_2O$), 5.87 (d, 1.4H, $J$ = 9.3 Hz, exchangeable with $D_2O$), 6.23 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.10 (m, 2H), 7.36 (s, 5H), 7.46 (t, 2H, $J$ = 7.7 Hz), 7.59 (t, 1H, $J$ = 7.7 Hz), 7.85 (d, 0.6H, $J$ = 7.7 Hz), 7.88 (d, 1.4H, $J$ = 7.7 Hz); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 13.6 (A), 13.9 (B), 26.6, 61.3 (A), 61.7 (B), 67.1 (B), 67.3 (A), 72.8 (B), 73.0 (A), 110.5 (B), 110.7 (A), 117.0 (A), 117.5 (B), 121.1 (A), 121.3 (B), 126.7 (B), 126.9 (A), 128.0, 128.2, 128.5, 129.4, 133.9, 136.1, 138.9, 156.1 (B), 156.3 (A), 171.0 (B), 171.2 (A); IR (KBr) 3400, 1734 cm$^{-1}$; CIMS $m/z$ 469 $(MH - H_2O)^+$. Anal. Calcd for $C_{24}H_{26}N_2O_7S{\cdot}0.1H_2O$: C, 59.03; H, 5.41; N, 5.74; S, 6.57. Found: C, 58.81; H, 5.63; N, 5.67; S, 6.69.

**Ethyl (2*RS*,3*RS*)-2-Amino-3-hydroxy-3-[3-*N*-(benzenesulfonyl)pyrrolyl]butanoate (25).** Using the same procedure as for the preparation of **14** and **15**, compound **24** (5.5 g, 11.3 mmol; 7:3 diastereomeric mixture) in ethanol (120 mL) was hydrogenated for 4 h at atmospheric pressure in the presence of 10% palladium on carbon (240 mg). The usual workup left a crude product which was purified by chromatography on silica gel (dichloromethane−ethanol, 95:5), affording compound **25** as a white solid (7:3 diastereomeric mixture) in 92% overall yield. Crystallization of this material in ethanol provided the major diastereomer of **25** as a white solid: mp 126−127 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.09 (t, 3H, $J$ = 7.1 Hz), 1.55 (s, 3H), 2.40 (br s, 3H, exchangeable with $D_2O$), 3.46 (s, 1H), 3.97 (q, 2H, $J$ = 7.1 Hz), 6.14 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.04 (dd, 1H, $J$ = 1.5 and 2.3 Hz), 7.07 (dd, 1H, $J$ = 2.3 and 3.2 Hz), 7.45 (t, 2H, $J$ = 7.7 Hz), 7.58 (t, 1H, $J$ = 7.7 Hz), 7.82 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 14.0, 26.0, 61.2, 62.8, 71.7, 112.2, 117.3, 121.0, 126.8, 129.4, 133.6, 133.9, 139.0, 173.2; IR (KBr) 3360, 1730 cm$^{-1}$; CIMS $m/z$ 353 $(MH)^+$. Anal. Calcd for $C_{16}H_{20}N_2O_5S$: C, 54.53; H, 5.72; N, 7.95; S, 9.10. Found: C, 54.34; H, 5.64; N, 7.84; S, 9.05.

Evaporation of the mother liquor provided the minor diastereomer of **25** (contaminated with ∼15% of the previous diastereomer) as an oil which could not be crystallized: $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.09 (t, 3H, $J$ = 7.1 Hz), 1.55 (s, 3H), 2.40 (br s, 3H, exchangeable with $D_2O$), 3.51 (s, 1H), 4.07 (q, 2H, $J$ = 7.1 Hz), 6.24 (dd, 1H, $J$ = 1.5 and 3.2 Hz), 7.04 (dd, 1H, $J$ = 1.5 and 2.3 Hz), 7.07 (dd, 1H, $J$ = 3.2 and 2.3 Hz), 7.45 (t, 2H, $J$ = 7.7 Hz), 7.58 (t, 1H, $J$ = 7.7 Hz), 7.82 (d, 2H, $J$ = 7.7 Hz); IR (KBr) 3360, 1730 cm$^{-1}$; HRCIMS calcd for $C_{16}H_{21}N_2O_5S$ $m/z$ 353.1171, found 353.1176.

**Pictet−Spengler Reactions. General Procedure.** A solution of the amine (**8**, **14**, **15**, or **25**; 1 mmol) in dichloromethane (50 mL) was treated at room temperature with formaldehyde (37% aqueous solution, 1 mmol) or acetaldehyde

(1 mmol). Trifluoroacetic acid (2 mmol) was then slowly added over 15 min, and the reaction mixture was stirred for 1−2 h. Saturated aqueous sodium hydrogen carbonate (5 mL) was added, and the organic phase was separated. The aqueous phase was extracted with dichloromethane (2 × 50 mL); the organic extracts were combined, washed with saturated aqueous sodium chloride (25 mL), and dried over magnesium sulfate. Removal of the solvent under reduced pressure left a residue which was purified by column chromatography on silica gel using the developer indicated. The following compounds were prepared in this manner.

**Methyl (*R,S)*-1-(Benzenesulfonyl)-4,5,6,7-tetrahydropyrrolo[2,3-*c*]pyridine-5-carboxylate (9).** Compound **9**, prepared from **8** and formaldehyde as described above, was obtained as a white solid in 52% yield after chromatography (dichloromethane−ethanol, 98:2): mp 65 °C (dichloromethane); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 2.40 (br s, 1H, exchangeable with $D_2O$), 2.63 (dd, 1H, $J$ = 9.4 and 15.6 Hz), 2.81 (dd, 1H, $J$ = 4.8 and 15.6 Hz), 3.61 (dd, 1H, $J$ = 4.8 and 9.4 Hz), 3.73 (s, 3H), 4.01 (d, 1H, $J$ = 16.4 Hz), 4.24 (d, 1H, $J$ = 16.4 Hz), 6.13 (d, 1H, $J$ = 3.3 Hz), 7.15 (d, 1H, $J$ = 3.3 Hz), 7.50 (t, 2H, $J$ = 7.7 Hz), 7.61 (t, 1H, $J$ = 7.7 Hz), 7.78 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 26.4, 42.1, 52.6, 54.9, 112.6, 120.6, 121.6, 126.8, 129.2, 129.7, 134.1, 138.9, 172.3; IR (KBr) 3330, 1738 cm$^{-1}$; HRCIMS calcd for $C_{15}H_{17}N_2O_4S$ *m/z* 321.0909, found 321.0886. Anal. Calcd for $C_{15}H_{16}N_2O_4S{\cdot}0.8H_2O$: C, 53.82; H, 5.30; N, 8.37; S, 9.58. Found: C, 53.48; H, 4.76; N, 8.19; S, 9.57.

**Ethyl (4*S*,5*S)*- and (4*R*,5*R*)-1-(Benzenesulfonyl)-4-hydroxy-4,5,6,7-tetrahydropyrrolo[2,3-*c*]pyridine-5-carboxylate (18).** Compound **18**, prepared from **14** and formaldehyde as described above, was obtained as a white powder in 79% yield after chromatography (dichloromethane−ethanol, 95:5): mp 116 °C (ethanol); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.24 (t, 3H, $J$ = 7.1 Hz), 2.40 (br s, 2H, exchangeable with $D_2O$), 3.47 (d, 1H, $J$ = 6.2 Hz), 4.02 (d, 1H, $J$ = 16.4 Hz), 4.22 (q, 2H, $J$ = 7.1 Hz), 4.23 (d, 1H, $J$ = 16.4 Hz), 4.80 (d, 1H, $J$ = 6.2 Hz), 6.37 (d, 1H, $J$ = 3.3 Hz), 7.18 (d, 1H, $J$ = 3.3 Hz), 7.50 (t, 2H, $J$ = 7.7 Hz), 7.61 (t, 1H, $J$ = 7.7 Hz), 7.78 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.1, 41.8, 61.6, 62.1, 65.5, 111.2, 121.8, 124.1, 126.8, 128.4, 129.6, 134.1, 139.0, 171.6; IR (KBr) 3330, 1720 cm$^{-1}$; CIMS *m/z* 351 $(MH)^+$. Anal. Calcd for $C_{16}H_{18}N_2O_5S{\cdot}0.1H_2O$: C, 54.57; H, 5.21; N, 7.55; S, 9.10. Found: C, 54.57; H, 5.41; N, 7.77; S, 8.91.

**Ethyl (4*S*,5*R*)- and (4*R*,5*S*)-1-(Benzenesulfonyl)-4-hydroxy-4,5,6,7-tetrahydropyrrolo[2,3-*c*]pyridine-5-carboxylate (19).** Compound **19**, prepared from **15** and formaldehyde as described above, was obtained as a white solid in 78% yield after chromatography (dichloromethane−ethanol, 98:2): mp 86 °C (ethanol); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.24 (t, 3H, $J$ = 7.1 Hz), 2.40 (br s, 2H, exchangeable with $D_2O$), 3.44 (d, 1H, $J$ = 2.3 Hz), 3.83 (d, 1H, $J$ = 16.6 Hz), 4.19 (d, 1H, $J$ = 16.6 Hz), 4.20 (q, 2H, $J$ = 7.1 Hz), 4.70 (d, 1H, $J$ = 2.3 Hz), 6.27 (d, 1H, $J$ = 3.3 Hz), 7.14 (d, 1H, $J$ = 3.3 Hz), 7.50 (t, 2H, $J$ = 7.7 Hz), 7.61 (t, 1H, $J$ = 7.7 Hz), 7.78 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.1, 42.8, 61.3, 61.4, 63.4, 111.8, 121.4, 124.0, 126.7, 129.5, 129.6, 134.1, 138.6, 170.8; IR (KBr) 3329, 2983, 1742 cm$^{-1}$; CIMS *m/z* 351 $(MH)^+$. Anal. Calcd for $C_{16}H_{18}N_2O_5S{\cdot}1.2C_2H_5OH$: C, 54.28; H, 6.26; N, 6.91; S, 7.90. Found: C, 54.13; H, 6.15; N, 6.97; S, 8.19.

**Ethyl (4*R*,5*R*,7*S*-) and (4*S*,5*S*,7*R*)-1-(Benzenesulfonyl)-4-hydroxy-7-methyl-4,5,6,7-tetrahydropyrrolo[2,3-*c*]pyridine-5-carboxylate (21).** Compound **21**, prepared from **14** and acetaldehyde as described above, was obtained as a white solid in 82% yield after chromatography (dichloromethane−ethanol, 98:2): mp 80 °C (ethanol); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.29 (t, 3H, $J$ = 7.2 Hz), 1.54 (d, 3H, $J$ = 6.4 Hz), 3.67 (d, 1H, $J$ = 7.8 Hz), 4.22 (q, 2H, $J$ = 7.2 Hz), 4.44 (q, 1H, $J$ = 6.4 Hz), 4.74 (d, 1H, $J$ = 7.8 Hz), 6.38 (d, 1H, $J$ = 3.4 Hz), 7.16 (d, 1H, $J$ = 3.4 Hz), 7.48 (t, 2H, $J$ = 7.7 Hz), 7.59 (t, 1H, $J$ = 7.7 Hz), 7.72 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 13.5, 21.4, 46.5, 57.4, 60.9, 66.5, 111.7, 123.3, 124.6, 126.5, 129.5, 134.0, 134.6, 139.2, 172.4; IR (KBr) 3325, 1735 cm$^{-1}$; CIMS *m/z* 365 $(MH)^+$. Anal. Calcd for $C_{17}H_{20}N_2O_5S{\cdot}0.25H_2O$: C, 55.35; H, 5.60; N, 7.59; S, 8.69. Found: C, 55.25; H, 5.63; N, 7.39; S, 8.79.

**Ethyl (4*RS*,5*RS*)-1-(Benzenesulfonyl)-4-hydroxy-4-methyl-4,5,6,7-tetrahydropyrrolo[2,3-*c*]pyridine-5-carboxylate (26).** Compound **26**, prepared as described above from **25** (the major, crystalline diastereomer) and formaldehyde, was obtained as a tan solid in 70% yield after chromatography (dichloromethane−ethanol, 98:2): mp 90 °C (dichloromethane−ethanol); $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 1.09 (t, 3H, $J$ = 7.1 Hz), 1.55 (s, 3H), 3.97 (q, 2H, $J$ = 7.1 Hz), 4.02 (d, 1H, $J$ = 16.4 Hz), 4.76 (s, 1H), 4.86 (d, 1H, $J$ = 16.4 Hz), 6.20 (d, 1H, $J$ = 3.3 Hz), 7.08 (d, 1H, $J$ = 3.3 Hz), 7.50 (t, 2H, $J$ = 7.7 Hz), 7.61 (t, 1H, $J$ = 7.7 Hz), 7.78 (d, 2H, $J$ = 7.7 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 13.6, 41.3, 61.1, 61.6, 65.0, 108.8, 121.3, 123.6, 126.7, 126.9, 130.2, 133.5, 138.8, 166.5; IR (KBr) 3400, 1733 cm$^{-1}$; CIMS *m/z* 365 $(MH)^+$. Anal. Calcd for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 56.32; H, 5.53; N, 7.22; S, 8.67.

**General Procedure for the Aromatization of the Tetrahydroazaindole Derivatives 9, 18, 21, and 26.** A solution of the tetrahydroazaindole (0.1−1 mmol) in xylene (25 mL) containing 10% palladium on carbon (25−300 mg) was refluxed for 12 h. The reaction mixture was cooled and filtered through a pad of Celite, and the filter pad was washed copiously with ethanol. The filtrate and washings were combined and evaporated to dryness under reduced pressure, leaving the crude product which was purified as indicated below.

**Methyl 1-(Benzenesulfonyl)pyrrolo[2,3-*c*]pyridine-5-carboxylate (10a).** This was prepared from **9** (56 mg, 0.18 mmol) and palladium on carbon (20 mg) as described above. The crude product was purified by crystallization in dichloromethane, affording **10a** as a white powder in 74% yield: mp 150 °C; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 4.03 (s, 3H), 6.82 (d, 1H, $J$ = 3.6 Hz), 7.45 (t, 2H, $J$ = 7.7 Hz), 7.60 (t, 1H, $J$ = 7.7 Hz), 7.80 (d, 1H, $J$ = 3.6 Hz), 7.98 (d, 2H, $J$ = 7.7 Hz), 8.41 (s, 1H), 9.46 (s, 1H); $^{13}$C NMR (50 MHz, $CDCl_3$) $\delta$ 53.2, 108.7, 118.9, 127.1, 129.8, 130.7, 132.9, 134.8, 135.5, 136.8, 137.5, 141.5, 165.4; IR (KBr) 1732 cm$^{-1}$; EIMS *m/z* 316 $(M)^+$. Anal. Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.82; N, 8.86; S, 10.13. Found: C, 56.92; H, 4.09; N, 8.81; S, 10.15.

**Ethyl 1-(Benzenesulfonyl)pyrrolo[2,3-*c*]pyridine-5-carboxylate (10b).** This was prepared from **18** (39 mg, 0.11 mmol) and palladium on carbon (35 mg) as described above. The crude product was purified by crystallization in ethyl acetate−heptane, affording **10b** as pale-yellow needles in 95% yield: mp 152−153 °C; $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.44 (t, 3H, $J$ = 7.1 Hz), 4.46 (q, 2H, $J$ = 7.1 Hz), 6.80 (d, 1H, $J$ = 3.6 Hz), 7.45 (t, 2H, $J$ = 7.7 Hz), 7.56 (t, 1H, $J$ = 7.7 Hz), 7.78 (d, 1H, $J$ = 3.6 Hz), 7.98 (d, 2H, $J$ = 7.7 Hz), 8.40 (s, 1H), 9.40 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.4, 61.9, 108.7, 118.8, 127.0, 129.8, 130.7, 132.9, 134.8, 135.5, 136.8, 137.5, 141.5, 165.4; IR (KBr) 1714 cm$^{-1}$; EIMS *m/z* 330 $(M)^+$. Anal. Calcd for $C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48; S, 9.70. Found: C, 58.04; H, 4.36; N, 8.47; S, 9.77.

**Ethyl 1-(Benzenesulfonyl)-7-methylpyrrolo[2,3-*c*]pyridine-5-carboxylate (22).** This was prepared from **21** (40 mg, 0.11 mmol) and palladium on carbon (35 mg) as described above. The crude product was purified by crystallization in dichloromethane−hexane, affording compound **22** as a white solid in 96% yield: mp 152 °C; $^1$H NMR (200 MHz, $CDCl_3$) $\delta$ 1.43 (t, 3H, $J$ = 7.1 Hz), 2.88 (s, 3H), 4.46 (q, 2H, $J$ = 7.1 Hz), 6.84 (d, 1H, $J$ = 3.7 Hz), 7.46 (t, 2H, $J$ = 7.7 Hz), 7.59 (t, 1H, $J$ = 7.7 Hz), 7.67 (t, 2H, $J$ = 7.7 Hz), 8.06 (d, 1H, $J$ = 3.7 Hz), 8.24 (s, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 14.5, 25.3, 62.0, 108.0, 117.1, 126.6, 129.8, 133.1, 133.9, 134.5, 139.0, 139.2, 140.9, 145.6, 165.3; IR (KBr) 1735 cm$^{-1}$; CIMS *m/z* 345 $(MH)^+$. Anal. Calcd for $C_{17}H_{16}N_2O_4S$: C, 59.29; H, 4.68; N, 8.13; S, 9.31. Found: C, 59.51; H, 4.91; N, 8.31; S, 9.17.

**Ethyl 1-(Benzenesulfonyl)-4-methylpyrrolo[3,4-*c*]pyridine-5-carboxylate (27).** This was prepared from **26** (352 mg, 0.97 mmol) and palladium on carbon (310 mg) as described above. The crude product was purified by column chromatography on silica gel (dichloromethane) affording compound **27** as pale-yellow needles in 88% yield: mp 149 °C (hexane); $^1$H NMR (250 MHz, $CDCl_3$) $\delta$ 1.30 (t, 3H, $J$ = 7.2 Hz), 2.58 (s, 3H), 4.31 (q, 2H, $J$ = 7.2 Hz), 6.69 (d, 1H, $J$ = 3.6 Hz), 7.30 (t, 2H, $J$ = 7.7 Hz), 7.45 (t, 1H, $J$ = 7.7 Hz), 7.60 (d, 1H, $J$ = 3.6 Hz), 7.78 (d, 2H, $J$ = 7.7 Hz), 9.10 (s, 1H); $^{13}$C NMR (62.5 MHz, $CDCl_3$) $\delta$ 14.5, 15.8, 61.7, 107.5, 127.0, 129.4, 129.7, 131.8, 132.9, 134.7, 137.6, 137.9, 140.2, 166.5; IR (KBr) 1725 cm$^{-1}$; EIMS *m/z* 345 $(MH)^+$. Anal. Calcd for $C_{17}H_{16}N_2O_4S{\cdot}0.1H_2O$: C, 58.83; H, 4.73; N, 8.07; S, 9.24. Found: C, 58.99; H, 4.68; N, 8.10; S, 9.25.

**Preparation of 10b via Benzenesulfonylation of Ethyl Pyrrolo[2,3-*c*]pyridine-5-carboxylate (20).** A solution of compound **20** (100 mg, 0.53 mmol) (prepared by the method of ref 5) in anhydrous THF (50 mL) was treated at 0 °C under argon with sodium hydride (25 mg of a 50% dispersion in oil; 0.53 mmol). The mixture was stirred for 1 h, benzenesulfonyl chloride (81 $\mu$L, 0.63 mmol) was added, and stirring was continued for 2 h at 0 °C. At the end of the reaction period, saturated aqueous ammonium chloride (20 mL) was added, and the solution was extracted with ethyl acetate (3 × 50 mL). The organic extracts were combined, washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated to dryness under reduced pressure. The residue was crystallized in ethyl acetate−heptane, affording compound **10b** in 82% yield, identical in all respects to the same compound prepared from **18**.

**Acknowledgment.** We thank Dr. P. Dauban for a critical reading of this manuscript.

JO972005T