Hydroxylated Pyrrolidines. Enantiospecific Synthesis of *all-cis* 2,3,4,5-Substituted Pyrrolidine Derivatives from Serine

Sharad K. Verma, M. Nieves Atanes, J. Hector Busto, Dung L. Thai, and Henry Rapoport*

Department of Chemistry, University of California, Berkeley, Berkeley, California 94720

rapoport@cchem.berkeley.edu

Received October 17, 2001

We report the enantiospecific synthesis of the sterically congested *all-cis* 2,3,4,5-substituted pyrrolidines **4**, **5**, and **6**, from either D- or L-serine. Hemiaminal intermediate **13** is converted to the fully substituted pyrrolidine **15** by way of a tandem Wittig−Michael reaction. The *endo* stereochemistry of the *C*-3 methyl group of compound **15** is set by stereoselective reduction of the double bond in **11**, driven by a preference for hydrogenation from the rear side of the molecule. The *all-cis* configuration of these fully substituted pyrrolidines has been established by X-ray analysis of compound **6**. Removal of the benzenesulfonyl group from the highly substituted and functionalized intermediate **15** is successfully accomplished by sodium naphthalenide reduction.

Hydroxylated pyrrolidines, which have been considered as aza mimics of monosaccharides, have evoked considerable interest in recent years owing to both their enormous therapeutic potential and applications as catalysts in asymmetric synthesis. The pyrrolidine structural unit is among the most commonly occurring structural cores in a large number of biologically active alkaloids,[1] including glycosidase inhibitors,[2] excitatory amino acid inhibitors,[3] and ACE inhibitors.[4] In addition to their underexplored medicinal importance, their applications as catalysts in asymmetric synthesis have included their use in the stereoselective reduction of ketones[5] and asymmetric Diels−Alder reactions.[6] Thus, efforts to better understand their chemistry and biochemistry remain active areas of investigation.

Previous work from this laboratory has described the enantiocontrolled synthesis of trisubstituted pyrrolidine **3** from hemiaminal **1**, derived from L-serine, where all of the substituents have a *cis* relationship.[7] The key transformation involved is a tandem Wittig−Michael reaction which leads to the pyrrolidine ring system (Figure 1). On the basis of these results, we sought to further extend this methodology and investigate the extent to which the tandem Wittig−Michael reaction could be utilized to prepare pyrrolidines with more steric congestion around the ring. Although there is a significant amount of information available on the synthesis of pyrrolidines,[8] considerably less of this includes the synthesis of 2,3,4,5-tetrasubstituted pyrrolidines.[9] We now report the synthesis of the hydroxylated *all-cis* tetrasubstituted pyrrolidines **4**, **5**, and **6**, along with related compounds from D- and L-serine.[10] These fully substituted *all-cis* pyrrolidines represent a unique stereochemical arrangement among the relatively small number of compounds of this type whose syntheses have been reported (Figure 2). [9]

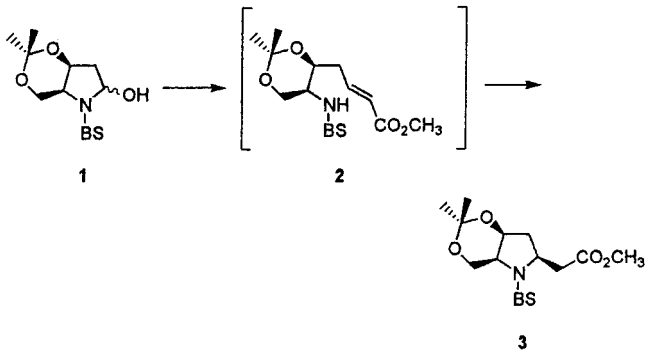


Figure 1. Enantiocontrolled synthesis of *all-cis* trisubstituted pyrrolidine from L-serine; ref 7.

Results and Discussion

Preparation of Tetrasubstituted Pyrrolidines from Serine. Hemiaminal **8** was obtained from ozonolysis of

(1) Pearson, W. H. *Studies in Natural Product Chemistry. Vol 1*; Atta-Ur-Rahman, Ed; Elsevier: Amsterdam, 1988; pp 323−358.

(2) (a) Lombardo, M.; Fabbroni, S.; Trombini, C. *J. Org. Chem.* **2001**, *66*, 1264−1268. (b) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W.; Long, D. D.; Frederiksen, S. M.; Marquess, D. G.; Lane, A. L.; Watkin, D. J.; Winkler, D. A. *Tetrahedron: Asymmetry* **2000**, *11*, 1645−1680 and references therein. (c) Fleet, G. W. *Tetrahedron Lett.* **1998**, *39*, 6091−6094. (d) Fleet, G. W. *Top. Med. Chem.* **1988**, *65*, 149−162. (e) Schwartz, R. T.; Datema, R.; *Trends Biochem. Sci.* **1984**, *9*, 32−34. (f) Wehner, V.; Jager, V. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1169−1171, and references therein.

(3) Bridges, R. J.; Lovering, F. E.; Humphrey, J. M.; Stanley, M. S.; Blakely, T. N.; Cristopharo, M. F.; Chamberlin, A. R. *Bioorg. Med. Chem. Lett.* **1993**, *3*, 115−121, and references therein.

(4) (a) Petrillo, E. W.; Ondetti, M. A. *Med. Res. Rev.* **1982**, *2*, 1−41. (b) Cheung, H. S.; Cushman, D. W. *Biochim. Biophys. Acta*. **1973**, *293*, 451−463.

(5) Corey, E. J.; Bakshi, R. K.; Shibata, S. J. *J. Am. Chem. Soc.* **1987**, *109*, 5551−5553.

(6) Kobayashi, S.; Murakami, M.; Harada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, 1341−1344.

(7) Hart, B. P.; Rapoport, H. *J. Org. Chem.* **1999**, *64*, 2050−2056.

(8) (a) Reggelin, M.; Heinrich, T. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2883−2886. (b) Pichon, M.; Figadere, B. *Tetrahedron: Asymmetry* **1996**, *7*, 927−964, and references therein.

(9) (a) Masaki, Y.; Oda, H,; Kazuta, K.; Usui, A.; Itoh, A.; Zu, F. *Tetrahedron Lett.* **1992**, *33*, 5089−5092. (b) Yoda, H.; Yamazaki, H.; Kawauchi, M.; Takabe, K. *Tetrahedron: Asymmetry* **1995**, *6*, 2669−2772. (c) Campanini, L.; Dureault, A.; Depezay, J.-C. *Tetrahedron Lett.* **1995**,*33*, 8015−8018. (d) Thompson, D. K.; Hubert, C. N.; Wightman, R. H. *Tetrahedron* **1993**, *49*, 3827−3840. (e) Palmer, A. M.; Jäger, V. *Eur. J. Org. Chem.* **2001**, 2547−2558.

(10) The enantiomers of **7** through **15** were also synthesized from D-serine.

10.1021/jo011008+ CCC: $22.00
Published on Web 01/31/2002

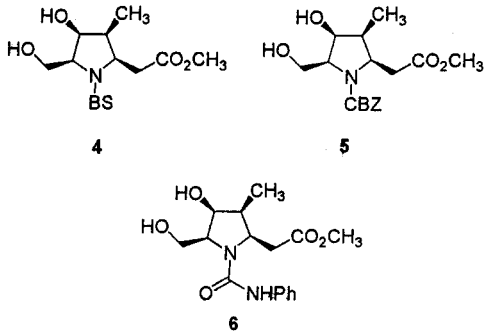


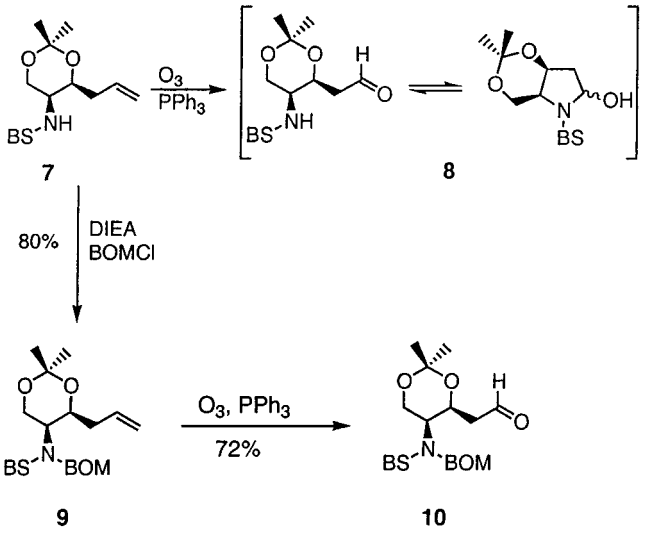
Figure 2. *all*-cis 2,3,4,5-substituted pyrrolidines.

amino olefin **7**, which was prepared from L- serine under nonracemizing conditions.[10,11] The carbon atom adjacent to the aldehyde carbon in **8** correlates to the position where the introduction of further functionality was planned. The fact that ozonolysis product **8** exists primarily as the hemiaminal, however, so decreased the reactivity of the α-hydrogens that an alternative was needed.[12] This was accomplished by replacing the remaining proton on the nitrogen atom of amino olefin **7** with a suitable protecting group.

Considerations for such a suitable protecting group included that it be stable under the conditions involved for ozonolysis, and deprotection should allow for its selective removal in the presence of the benzenesulfonyl group, while not affecting any other parts of the molecule. After considerable exploration of a number of protecting groups, particularly carbamates, a benzyl-oxymethyl (BOM) protecting group was found to be optimal for these purposes. Treatment of sulfonamide **7** with benzyl chloromethyl ether (BOMCl) and diisopropylethylamine for 24 h gave fully protected compound **9** (80%), which underwent ozonolysis at −78 °C smoothly, forming amino aldehyde **10**, now unable to cyclize to a hemiaminal (Scheme 1).

For substitution at the α-position, we considered the use of an iminium ion, the Mannich intermediate, since a variety are available,[13] and such substitution should allow for further manipulation. Thus, the stereospecific installation of an α-methyl group that would be syn to the isopropylidene ketal was envisaged to occur over two steps from aldehyde **10**. It was projected that α-methylene compound **11**, a potentially versatile intermediate for further synthesis, would undergo hydrogenation preferentially from the less sterically hindered rear side of the molecule, to avoid, for example, forming a product having a destabilizing 1,3 interaction. The synthesis of olefin **11** was accomplished under very mild conditions. Amino aldehyde **10** was treated with the Mannich intermediate *N*,*N*-dimethylmethyleneammonium chloride and triethylamine for 24 h, followed by crystalization to give α,*β*-unsaturated aldehyde **11** (74%). Reduction of **11** with hydrogen (60 psi) and Pd/C in ethyl acetate gave the reduced product as a single diastereomer in quantitative yield, initially assigned the stereochemistry of **12**. X-ray

Scheme 1. Conversion to the N,N-Protected Aldehyde



analysis of an intermediate produced later confirmed the stereochemical assignment of the newly formed methyl group. Removal of the BOM protecting group in **12** was accomplished next by hydrogenolysis with H_2 (1 atm) and $Pd(OH)_2/C$, followed by exposure to triethylamine to afford hemiaminal **13** (87%, Scheme 2).

The dramatic specificities in the hydrogenation reactions to reduce the carbon−carbon double bond, hydrogenolytically remove the BOM protecting group, and not reduce the aldehyde carbonyl in **11** are carried out separately over two steps with different palladium catalysts in different solvents, as opposed to a single procedure to accomplish both tasks. Such attempts did not give **13**, but instead gave mixtures of 3-formyl-substituted pyrrolidines. This would suggest that BOM deprotection occurs more rapidly than olefin reduction and the intermediate generated undergoes a Michael addition to give the products observed. This sequence could be avoided by using Pd/C in ethyl acetate in the first hydrogenation to reduce the olefin, as the BOM group is retained under such conditions.

The formation of tetrasubstituted pyrrolidine **15** was accomplished by treatment of hemiaminal intermediate **13** with the ylide of trimethyl phosphonoacetate at low temperature, followed by warming to room temperature overnight. The resulting tetrasubstituted pyrrolidine **15** was obtained as a single diastereomer in good yield (75%, Scheme 2). The kintetics and stereochemistry of this transformation as it pertains to the synthesis of trisubstituted pyrrolidines has been discussed in previous work.[7] The enantiomer of **15** was prepared similarly, starting from D-serine.[10]

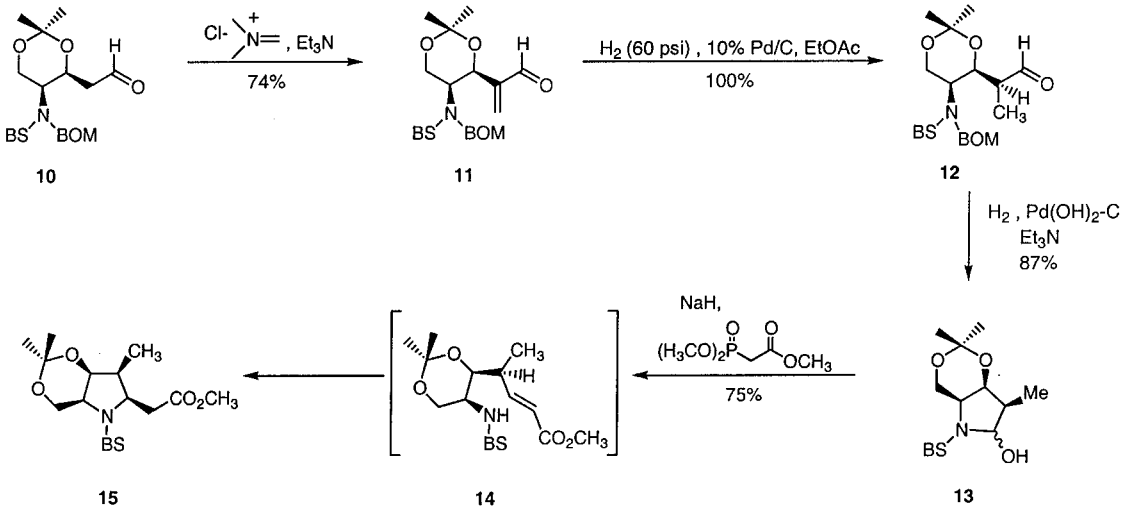
To confirm the absolute stereochemistry of the pyrrolidine product **15**, a suitable crystalline compound was sought for X-ray analysis. It was projected that by enhancing π-stacking and/or hydrogen bonding interactions, such a derivative might be obtained. Indeed, such a derivative was found in pyrrolidine **6**. Exchange of the benzenesulfonyl protecting group in **15**, accomplished by electrolytic reduction of **15**, followed by treatment with phenyl isocyanate and triethylamine, afforded the phenyl carbamoyl derivative **16** (46%, two steps).[14] Removal of the ketal in **16** with concentrated HCl cleanly furnished diol **6** in quantitative yield as a crystalline solid (Scheme

(11) Folmer, J. J.; Acero, C.; Thai, D. L.; Rapoport, H. *J. Org. Chem.* **1998**, *63*, 8170−8182.

(12) Alternative substitutions at the alpha position of aldehyde **8** were very sluggish. Classical methods (e.g., enolate formation followed by trapping) were found to be quite poor. Reactions typically gave low yields of diastereomeric mixtures, along with decomposition products.

(13) Dean, R. T.; Padgett, H. C.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 7448−7449.

Scheme 2. Stereospecific Introduction of an α-Methyl Group and Closure to the Pyrrolidine



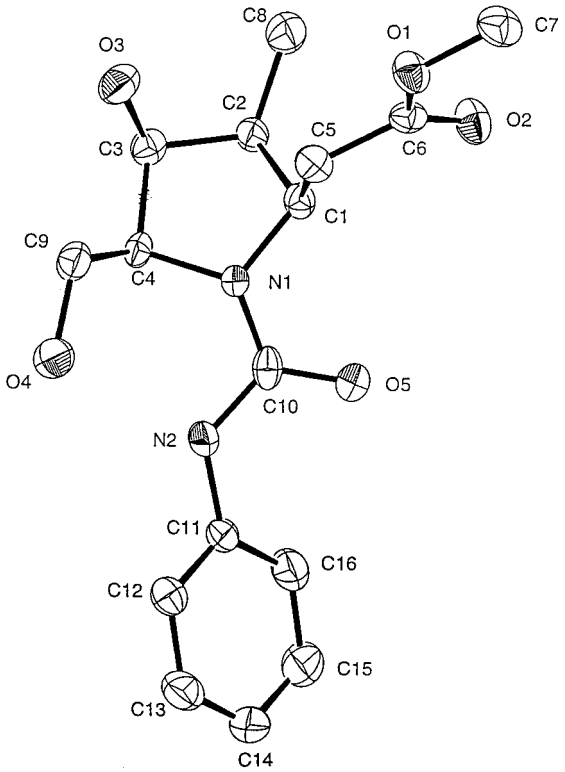


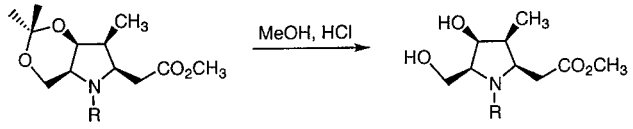
Figure 3. Structure of (2*S*,3*S*,4*S*, 5*S*)-4-hydroxy-5-hydroxymethyl-2-methoxycarbonylmethyl-3-methyl-1-phenylcarbamoylpyrrolidine (**6**) as determined by X-ray crystallography (arbitrary numbering system).

3). X-ray analysis of a crystal of **6** established the *all-cis* configuration of this tetrasubstituted pyrrolidine, providing the basis for stereochemical assignments made in this and related congeners (Figure 3).

In pursuing the synthesis of crystalline derivatives, it was observed that removal of the benzenesulfonyl group could also be accomplished quite well by reduction with sodium and naphthalene. The synthesis of **17** entailed sodium naphthalenide reduction[15] of **15** and capture of its intermediary anion in situ with benzyl chloroformate

(14) Roemmele, R. C.; Rapoport, H. *J. Org. Chem.* **1988**, *53*, 2367−2371.

Scheme 3. N-Derivatives of Tetrasubstituted Pyrrolidine Diol



15, R = BS
16, R = CONHPh
17, R = CBZ

4, R = BS
5, R = CBZ
6, R = CONHPh

(CBZCl). Acid-promoted deprotection of the ketal in crude **17** gave the diol compound **5** in 53% overall yield for the three steps.[16] Treatment of **15** under similar ketal deprotection conditions furnished **4** (80%).

Conclusion

The synthesis of tetrasubstituted pyrrolidines having an *all-cis* configuration has been rarely reported. In the work described, a method for the synthesis of such compounds has been demonstrated, and it will be of interest to further explore this methodology as it pertains to the stereochemical synthesis of highly substituted pyrrolidines.

Experimental Section

Methods and Materials. Melting points are uncorrected. All reactions were conducted under an atmosphere of nitrogen, and solvents were distilled before use unless otherwise noted. THF was distilled from sodium/benzophenone. CH_2Cl_2 was distilled from CaH_2. CH_3CN was distilled from P_2O_5 and then from CaH_2. EtOAc, hexanes, 2-propanol, methanol, anhydrous DME, and chloroform were used as purchased. Tetraethylammonium bromide (TEAB) was recrystallized four times from absolute EtOH and dried in the kugelrohl at 65 °C under vacuum overnight. 4-Phenylphenol was recrystallized from absolute EtOH and then sublimed at 100 °C/25 Torr. ^1H and ^{13}C NMR were taken in $CDCl_3$ at room temperature unless otherwise stated. Chemical shifts are reported in ppm (δ) with

(15) (a) Sodium naphthalenide was generated as described: Bergmeir, S. C.; Seth, P. P. *Tetrahedron Lett.* **1999**, *40*, 6181−6184. (b) Ji, S.; Gortler, L. B.; Waring, A.; Battisti, A.; Bank, S.; Closson, W. D.; Wriede, P. *J. Am. Chem. Soc.* **1967**, *89*, 5311−5312.

(16) These conditions have been utilized even more successfully in this lab for the removal of benzensulfonyl groups from highly functionalized trisubstituted pyrrolidines, providing yields of 70−80%.

reference to tetramethylsilane (TMS) as an internal standard. Column chromatography was performed using EM Science silica gel (230−400 mesh). Ozonolysis was done using a Welsbach Model 816 ozone generator set at 90V, 2 L/min. Elemental analyses were determined by the Microanalytical Laboratories, and X-ray crystallography was carried out by the CHEXRAY Facility, University of California, Berkeley.

(4*S*,5*S*)-5-(*N*-Benzyloxymethyl-*N*-phenylsulfonyl)amino-4-allyl-2,2-dimethyl-1,3-dioxane (9). Sulfonamide **7** (9.25 g, 0.03 mol) was dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. To this solution were added *N*,*N*-diisopropylethylamine (36.0 mL, 0.21 mol) and then benzyl-oxymethyl chloride (18.0 mL, 0.13 mol) dropwise via syringe under a stream of nitrogen. The pale yellow mixture was removed from the cold bath and stirred under nitrogen for 24 h, and the dark red mixture was then evaporated to afford a gelatinous residue. Chromatography (1/4, EtOAc/ hexanes) gave **9** (10.2 g, 80%) as a colorless oil: $[\alpha]_D^{22}$ +28.1° (*c* 5.0, $CHCl_3$); ^{1}H NMR δ 1.32 (s, 3H), 1.38 (s, 3H), 2.25−2.33 (m, 2H), 3.52−3.58 (bs, 1H), 3.64 (dd, *J* = 12.7, 2.1, 1H), 3.86 (dd, *J* = 12.7, 4.2, 1H), 4.03−4.07 (m, 1H), 4.49−4.62 (m, 2H), 4.97−5.04 (m, 1H), 5.05 (dd, *J* = 17.2, 1.8, 1H), 5.19 (d, *J* = 9.6, 1H), 5.35 (d, *J* = 9.6, 1H), 5.78 (dddd, *J* = 17.0, 10.3, 6.7, 3.2, 1H), 7.25−7.41 (m, 6H), 7.47−7.53 (m, 2H), 7.91−7.94 (m, 2H); ^{13}C NMR δ 19.0, 28.8, 36.0, 52.0, 62.7, 70.2, 71.5, 77.2, 99.1, 116.8, 127.5, 127.8, 128.0, 128.3, 128.5, 132.6, 134.6, 138.0, 141.0. Anal. Calcd for $C_{23}H_{29}NO_5S$: C, 64.0; H, 6.7; N, 3.3. Found: C, 64.0; H, 6.8; N, 3.1.

(4*S*,5*S*)-5-(*N*-Benzyloxymethyl-*N*-phenylsulfonyl)amino-4-(2′-oxoethyl)-2,2-dimethyl-1,3-dioxane (10). Amino olefin **9** (11.1 g, 25.8 mmol) was dissolved in CH_2Cl_2 (200 mL) and cooled to −78 °C. Oxygen was bubbled through the solution for 20 min at −78 °C, followed by ozone (2L/min, 90 V), until a blue color persisted (ca. 30 min). Excess ozone was removed by bubbling a stream of oxygen through the reaction mixture until it became colorless. The mixture was removed from the cold bath and triphenylphosphine (9.5 g, 36.4 mmol) was added with stirring for 2 h as the mixture came to rt. The solvent was then evaporated and the residue chromatographed (1/3, EtOAc/hexanes) to give aldehyde **10** (8.0 g, 72%) as a foam: $[\alpha]_D^{22}$ +43.1° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 1.31 (s, 3H), 1.44 (s, 3H), 2.72 (dd, *J* = 7.2, 1.2, 1H), 2.84 (dd, *J* = 5.4, 0.6, 1H), 3.46 (br s, 1H), 3.68 (dd, *J* = 12.9, 1.8, 1H), 3.94 (dd, *J* = 12.9, 3.9, 1H), 4.57-4.59 (m, 2H), 4.68−4.72 (m, 1H), 5.19 (d, *J* = 9.6, 1H), 5.38 (d, *J* = 9.6, 1H), 7.24-7.54 (m, 8H), 7.89−7.92 (m, 2H), 9.66 (s, 1H); ^{13}C NMR δ 18.6, 29.0, 45.7, 51.1, 62.7, 66.4, 70.1, 77.0, 99.3, 127.4, 127.5, 127.9, 128.3, 128.8, 132.7, 137.7, 140.2, 199.5. Anal. Calcd for $C_{22}H_{27}NO_6S$: C, 61.0; H, 6.3; N, 3.2. Found: C, 60.9; H, 6.3; N, 3.2.

(4*S*,5*S*)-5-(*N*-Benzyloxymethyl-*N*-phenylsulfonyl)amino-4-(1′-methylene-2′-oxoethyl)-2,2-dimethyl-1,3-dioxane (11). Aldehyde **10** (5.8 g, 13.4 mmol) was dissolved in CH_2Cl_2 (100 mL), and added sequentially were *N*,*N*-dimethylmethyleneammonium chloride (3.10 g, 33.2 mmol) and triethylamine (3.65 mL, 26.2 mmol) dropwise via syringe. After stirring for 24 h at rt under an N_2 blanket, saturated $NaHCO_3$ (50 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic layer was dried over $MgSO_4$, filtered, and evaporated, leaving an off-white solid residue which was recrystallized from hexanes/EtOAc to give α,β-unsaturated aldehyde **11** (4.5 g, 74%): mp 147−149 °C; $[\alpha]_D^{22}$ +67.6° (*c* 0.6, $CHCl_3$); ^{1}H NMR δ 1.42 (s, 3H), 1.47 (3H), 3.61 (br s, 1H), 3.74 (d, *J* = 12.6, 1H), 4.04 (dd, *J* = 12.6, 3.7, 1H), 4.54−4.56 (m, 2H), 5.12 (d, *J* = 3.7, 1H), 5.21 (d, *J* = 9.7, 1H), 5.31 (d, *J* = 9.6, 1H), 6.22 (s, 1H), 6.41 (s, 1H), 7.22-7.40 (m, 7H), 7.45-7.51 (m, 1H), 7.86−7.90 (m, 2H), 9.45 (s, 1H); ^{13}C NMR δ 18.4, 29.3, 50.5, 62.4, 68.7, 70.0, 76.9, 99.5, 127.2, 127.4, 128.0, 128.2, 128.6, 132.5, 134.3, 137.9, 140.3, 146.4, 192.5. Anal. Calcd for $C_{23}H_{27}NO_6S$: C, 62.0; H, 6.1; N, 3.1. Found: C, 62.0; H, 6.3; N, 3.0.

(4*S*,5*S*)-5-(*N*-Benzyloxymethyl-*N*-phenylsulfonyl)amino-4-[(1′*S*)-1′-methyl-2′-oxoethyl]-2,2-dimethyl-1,3-dioxane (12). α,β-Unsaturated aldehyde **11** (3.4 g, 7.6 mmol) was dissolved in EtOAc (50 mL) and 10% Pd−C (630 mg) added. The reaction mixture was shaken with hydrogen in a Parr apparatus at 60 psi for 2 h and then filtered through Celite. The filter pad was washed copiously with EtOAc and evaporated to provide α-methylaldehyde **12** as a colorless oil in quantitative yield: $[\alpha]_D^{22}$ +110.4° (*c* 0.5, $CHCl_3$); ^{1}H NMR δ 1.04 (d, *J* = 6.9, 3H), 1.28 (s, 3H), 1.39 (s, 3H), 2.90−2.97 (m, 1H), 3.58 (dd, *J* = 12.9, 2.1, 1H), 3.70 (br s, 1H), 3.87 (dd, *J* = 12.9, 3.9, 1H), 4.17 (dd, *J* = 9.6, 3.3, 1H), 4.51 (dd, *J* = 11.7, 6.3, 2H), 5.21 (d, *J* = 9.9, 1H), 5.37 (d, *J* = 9.9, 1H), 7.21−7.54 (m, 8H), 7.89 (dd, *J* = 8.4, 3.0, 2H), 9.66 (d, *J* = 3.0, 1H); ^{13}C NMR δ 9.7, 18.5, 28.5, 46.4, 49.8, 62.9, 70.0, 73.2, 77.2, 99.2, 127.4, 127.8, 128.1, 128.5, 128.7, 132.7, 137.5, 140.4, 203.2.

(3*S*,4*S*,5*S*)-2,4-Dihydroxy-5-hydroxymethyl-3-methyl-1-(phenylsulfonyl)pyrrolidine Isopropylidene Ketal (13). Aldehyde **12** (3.0 g, 6.7 mmol) was dissolved in MeOH (100 mL), and H_2O (1 mL) and 20% $Pd(OH)_2$−C (3.0 g) were added. The reaction mixture was hydrogenated (1 atm) with vigorous stirring for 2 h and filtered through Celite, and the filter pad was washed copiously with MeOH. To the combined filtrate was added triethylamine (1.8 mL, 12.9 mmol), and the mixture was stirred for 90 min and evaporated to an oily residue. Chromatography (1/2, EtOAc/hexanes) gave **13** (1.9 g, 87%) as a foam: $[\alpha]_D^{22}$ +38.2° (*c* 1.5, $CHCl_3$); ^{1}H NMR δ 1.01 (d, *J* = 7.1, 3H), 1.30 (s, 3H), 1.33 (s, 3H), 1.70−1.80 (m, 1H), 3.46-3.53 (m, 1H), 4.02−4.08 (m, 1H), 4.17−4.20 (m, 3H), 5.21−5.30 (m, 1H), 7.41−7.55 (m, 3H), 7.84−7.91 (m, 2H); ^{13}C NMR δ 7.9, 19.5, 28.1, 42.2, 57.4, 61.1, 73.0, 87.6, 98.6, 126.8, 129.3, 132.8, 139.7. Anal. Calcd for $C_{15}H_{21}NO_5S$: C, 55.0; H, 6.5; N, 4.3. Found: C, 54.8; H, 6.6; N, 4.0.

(2*S*,3*S*,4*S*,5*S*)-4-Hydroxy-5-hydroxymethyl-2-methoxycarbonylmethyl-3-methyl-1-(phenylsulfonyl)pyrrolidine Isopropylidene Ketal (15). To a suspension of 95% NaH (600 mg, 25 mmol) in THF (180 mL) at − 30 °C was added trimethyl phosphonoacetate (4.1 mL, 25 mmol) dropwise via syringe, and the reaction mixture was stirred for 1 h. To the cloudy white mixture was added a THF solution (15 mL) of aminal **13** (3.5 g, 10.7 mmol) dropwise via syringe, and the mixture was stirred at −30 °C for 4 h and then allowed to come to room temperature overnight. To the clear homogeneous solution was added 50 mL of phosphate buffer, pH 7. After being stirred for 30 min, the aqueous phase was extracted with EtOAc (4 × 50 mL), and the combined organic layer was dried, ($MgSO_4$), filtered, and evaporated to an oil. Chromatography (1/2, EtOAc/hexanes) gave **15** (3.1 g, 75%) as a thick, colorless oil: $[\alpha]_D^{22}$ −4.6° (*c* 1.0, $CHCl_3$); ^{1}H NMR δ 0.86 (d, *J* = 7.1, 3H), 1.31 (s, 3H), 1.39 (s, 3H), 1.60−1.65 (m, 1H), 2.79 (dd, *J* = 16.4, 5.2, 1H), 2.92 (dd, *J* = 8.4, 1H), 3.57 (q, *J* = 5.2, 1H), 3.68 (s, 3H), 3.91−4.00 (m, 2H), 4.09 (dd, *J* = 12.4, 6.4, 1H), 4.20−4.24 (dd, *J* = 13.2, 8.0, 1H), 7.50−7.64 (m, 3H), 7.81−7.87 (m, 2H); ^{13}C NMR δ 8.2, 21.1, 26.0, 38.3, 40.1, 51.5, 59.0, 60.8, 62.8, 72.7, 98.9, 127.3, 129.1, 132.9, 137.0, 172.1. Anal. Calcd for $C_{18}H_{25}NO_6S$: C, 56.4; H, 6.6; N, 3.7. Found: C, 56.4; H, 6.7; N, 3.5.

(2*S*,3*S*,4*S*,5*S*)-4-Hydroxy-5-hydroxymethyl-2-methoxycarbonylmethyl-3-methyl-1-phenylcarbamoylpyrrolidine Isopropylidene Ketal (16). An electrolysis cell was filled with an CH_3CN solution of Et_4NBr (0.1 M), and argon was bubbled through the solution for 1 h. The current was set at 1.73 eV, and pre-electrolysis of Hg resulted in a stable background reading of 0.1 mA after 15 min. 4-Phenylphenol (754 mg, 4.44 mmol) was added to the cathode solution, and argon was bubbled through the solution for 15 min. Pre-electrolysis of the solution resulted in a background reading of 1.6 mA in 2 h. A CH_3CN solution of pyrrolidine **15** (680 mg, 1.77 mmol) was added, with an intial current reading of 25 mA. After 12 h of electrolysis, the current was 1.1 mA. The cathode solution was decanted from the Hg which was washed with CH_2Cl_2 (3 × 30 mL). The combined filtrates were evaporated, the residue was dissolved in CH_2Cl_2 (100 mL) and washed with freshly prepared 0.1 M KOH (3 × 100 mL) and brine (50 mL), and the combined organic layer was dried ($MgSO_4$), filtered, and evaporated. Chromatography (9/1, CH_2Cl_2/MeOH) gave 300 mg (69%) of the secondary amine as a colorless oil. To a −10 °C solution of this oil in CH_2Cl_2 (10 mL) were added Et_3N (0.072 mL, 0.66 mmol) and phenyl isocyanate (0.080 mL, 0.66 mmol). After stirring the mixture for 2 h, H_2O (15 mL) was added. The aqueous layer was extracted with CH_2-

Cl_2 (3 × 75 mL), and the combined organic layer was dried ($MgSO_4$), filtered, and evaporated to an oil. Chromatography (3/7, EtOAc/hexanes) gave carbamoyl derivative **16** (150 mg, 68%) as a colorless oil: $[\alpha]_D^{22}$ + 38.7° (*c* 1.4, $CHCl_3$);^{1}H NMR δ 1.06 (d, J = 7.2, 3H), 1.39 (s, 3H), 1.41 (s, 3H), 2.33−2.43 (m, 1H), 2.79 (dd, J = 18.3, 2.4, 1H), 3.05 (dd, J = 18.3, 9.3, 1H), 3.75 (s, 3H), 3.81−3.92 (m, 1H), 4.08−4.22 (m, 3H), 4.26−4.36 (m, 1H), 6.93−7.02 (m, 1H), 7.21−7.31 (m, 2H), 7.45−7.54 (m, 2H), 8.82 (br s, 1H); ^{13}C NMR δ 9.2, 20.5, 27.4, 36.9, 41.6, 52.4, 56.6, 57.9, 62.0, 71.1, 98.1, 119.1, 122.3, 128.6, 139.8, 155.8, 176.5. Anal. Calcd for $C_{19}H_{26}N_2O_5$: C, 63.0; H, 7.2; N,7.7. Found: C, 62.7; H, 7.0; N, 7.4.

(2*S*,3*S*,4*S*,5*S*)-4-Hydroxy-5-hydroxymethyl-2-methoxycarbonylmethyl-3-methyl-1-phenylcarbamoylpyrrolidine (6). To a solution of pyrrolidine acetonide **16** (150 mg, 0.41 mmol) in MeOH (5 mL) was added concentrated HCl (0.05 mL) at rt. The reaction mixture was stirred for 2 h and then evaporated. Chromatography (4/1, EtOAc/hexanes) gave crystalline diol **6** (133 mg, 100%): mp 152−154 °C; $[\alpha]_D^{22}$ −2.6° (*c* 1.1, $CHCl_3$);^{1}H NMR δ 1.07 (d, J = 6.9, 3H), 2.15−2.22 (m, 1H), 2.69 (dd, J = 2.1, 18.0, 1H), 2.92 (dd, J = 18.0, 9.9, 1H), 3.38 (bs, 1H), 3.76 (s, 3H), 3.80−3.94 (m, 2H), 4.19−4.33 (m, 3H), 4.5 (bs, 1H), 6.94−7.03 (m, 1H), 7.20−7.30 (m, 2H), 7.41−7.48 (m, 2H), 8.95 (br s, 1H). ^{13}C NMR δ 9.4, 36.5, 41.6, 52.4, 58.6, 63.1, 64.6, 73.8, 119.6, 122.7, 128.7, 139.4, 157.2, 176.0. Anal. Calcd for $C_{16}H_{22}N_2O_5$: C, 59.6; H, 6.9; N, 8.7. Found: C, 60.0; H, 7.1; N, 8.7.

(2*S*,3*S*,4*S*,5*S*)-4-Hydroxy-5-hydroxymethyl-2-methoxycarbonylmethyl-3-methyl-1-(phenylsulfonyl)pyrrolidine (4). To a solution of pyrrolidine acetonide **15** (960 mg, 2.5 mmol) in MeOH (25 mL) was added concentrated HCl (0.6 mL) at room temperature. The reaction mixture was stirred for 3 h and evaporated, and the residue was chromatographed (4/1, EtOAc/hexanes) to give diol **4** (690 mg, 80%) as a colorless oil: $[\alpha]_D^{22}$ −11.2° (*c* 0.7, $CHCl_3$);^{1}H NMR δ 0.85 (d, J = 6.9, 3H), 1.36−1.40 (m, 1H), 2.72−2.78 (m, 2H), 3.50−3.53 (m, 1H), 3.66 (s, 3H), 3.97 (bs, 1H), 4.04−4.19 (m, 4H), 7.48−7.62 (m, 3H), 7.79−7.82 (m, 2H); ^{13}C NMR δ 8.8, 38.0, 40.8, 51.9, 61.2, 62.6, 65.0, 75.8, 127.4, 129.2, 133.1, 136.2, 172.6. Anal. Calcd for $C_{15}H_{21}NO_6S$: C, 52.5; H, 6.2; N,4.1. Found: C, 52.4; H, 6.2; N, 4.4.

(2*S*,3*S*,4*S*,5*S*)-4-Hydroxy-5-hydroxymethyl-2-methoxycarbonyl-3-methyl-1-(benzyloxycarbonyl)pyrrolidine (5). To a −78 °C THF solution (15 mL) of sulfonamide **15** (310 mg, 0.81 mmol) was added 4 mL of a DME solution of sodium naphthalenide, dropwise via syringe, until the end point was reached (indicated by persistence of a dark olive green color). To the contents were added 10 mL of 1 M AcOH (in H_2O)/THF (1/1) at −78 °C, and stirring was continued at rt over 45 min. To the homogeneous solution were added K_2CO_3 (350 mg, 2.49 mmol) and benzyl chloroformate (0.400 mL, 2.83 mmol), the mixture was stirred at rt for 2 h, and 1 M NaH_2PO_4 (10 mL) was added. The aqueous layer was extracted with EtOAc (4 × 15 mL), and the combined organic layer was dried ($MgSO_4$), filtered, and evaporated. The resulting crude oily solid was dissolved in MeOH (20 mL), concentrated HCl (0.3 mL) was added dropwise, and the mixture was stirred at rt for 45 min. Evaporation of the mixture and chromatography of the residue, eluting initially with 1/1 hexane/EtOAc andthen 1/2 hexane/EtOAc, gave **5** (145 mg, 53%) as a white solid: mp 79−81 °C. $[\alpha]_D^{22}$ +49.7° (*c* 0.3, $CHCl_3$);^{1}H NMR 0.76 (d, J = 7.2, 3H), 0.80−0.90 (bs, 1H), 1.50−1.54 (m, 1H), 2.58−2.60 (m, 2H), 3.25 (s, 3H), 3.60−3.67 (m, 1H), 3.72−3.77 (m, 1H), 3.82−3.92 (m, 1H), 4.01−4.06 (m, 1H), 4.32−4.38 (m, 1H), 4.92 (d, J = 12.4, 1H), 5.05 (d, J = 12.4, 1H), 6.99−7.01 (m, 1H), 7.05−7.09 (m, 3H), 7.19 (d, J = 7.6, 2H); ^{13}C NMR δ 8.9, 36.5, 41.1, 51.7, 58.3, 61.9, 64.1 67.4, 75.8, 127.8, 128.3, 128.6, 136.2, 156.0, 173.0. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.5; H, 6.9; N,4.2. Found: C, 60.7; H, 7.0; N, 4.1.

Acknowledgment. We gratefully thank the following agencies for fellowship support: S.K.V. for a National Research Service Award, NIH, DHHS; M.N.A. for a Fulbright/Ministerio de Educacion y Cienca, Spain, award; J.H.B. for an award from the Universidad de la Rioja, Logroño, Spain.

JO011008+