(CH), 73.13 (C), 81.37 (C), 171.42 (C), 176.49 (C).

(2*S*,4*R*)-4-Phenyl-*N*-(9-(9-phenylfluorenyl))proline *tert*-Butyl Ester (10d). To a solution of **15** (84 mg, 0.17 mmol) in 5 mL of dry THF were added BH_3·THF (1 M, 5 mL) and $NaBH_4$ (5 mg, 0.15 mmol), and the reaction mixture was stirred at room temperature for 2 days. The reaction was quenched by pouring the mixture into 0.5 M H_3PO_4 (10 mL), and the product was extracted into ether (3 × 20 mL). Drying and evaporating gave a crude product mixture, which was purified by MPLC (2% EtOAc in hexane) to give pure **10d** (17 mg, 21 %) and recovered **15** (65 mg, 77%).

10d: R_f 0.52; ^{1}H NMR δ 1.31 (s, 9 H), 1.93 (m, 1 H), 2.78 (dd, 1 H, J = 8.3, 10.6 Hz), 3.36 (dd, J = 5.3, 6.0 Hz), 3.52 (dd, 1 H, J = 8.2, 9.0 Hz), 3.58 (m, 1 H); ^{13}C NMR δ 27.94 (CH_3), 38.49 (CH_2), 42.51 (CH), 56.82 (CH_2), 61.39 (CH), 79.81 (C), 175.22 (C); HRMS calcd for $C_{34}H_{34}NO_2$ (MH^+) 488.2589, found 488.2576.

(2*S*)-*N*-(9-(9-Phenylfluorenyl))glutamic Acid α-*tert*-Butyl Ester (17). The unsymmetrical diester **3** (2.29 g, 5 mmol) was dissolved in 40 mL of THF. Lithium hydroxide monohydrate (250 mg, 6 mmol) in 4 mL of distilled H_2O was added, and the reaction mixture was refluxed for 4 h. The solvent was evaporated, and the residue was partitioned between 100 mL of half saturated Na_2CO_3 and ether (50 mL). The aqueous layer was acidified to pH 6.5 with 1 M H_3PO_4 and extracted with EtOAc (2 × 100 mL), and the organic extracts were combined, dried, filtered, and evaporated to give **17** as a white foam (2.35 g, 106%); after 48 h in high vacuum (0.3 mmHg, 40 °C) 2.22 g (100%): R_f 0.49; mp 60–62 °C (EtOAc–isooctane); ^{1}H NMR δ 1.21 (s, 9 H), 1.6–1.85 (m, 2 H), 2.2–2.5 (m, 2 H), 2.58 (dd, 1 H, J = 4.7, 7.5 Hz), 7.2–7.8 (m, 13 H); ^{13}C NMR δ 27.76 (CH_3), 29.19 (CH_2), 31.57 (CH_2), 55.54 (CH), 72.97 (C), 81.63 (C), 173.83 (C), 177.39 (C). Anal. Calcd for $C_{28}H_{29}NO_4$: C, 75.8; H, 6.6; N, 3.2. Found: C, 76.0; H, 6.9; N, 3.0.

Acknowledgment. Partial financial support from the Academy of Finland (to A.M.P.K.) is gratefully acknowledged. We also thank M. J. Krische, President's Undergraduate Fellow, for skillful technical assistance.

Registry No. **1**, 1499-55-4; **2**, 119595-72-1; **3**, 119595-73-2; **4a**, 119595-74-3; **4b**, 119619-09-9; **4c**, 119595-75-4; **4e**, 119595-76-5; **5a**, 119595-77-6; **5b**, 119595-78-7; **5c**, 119595-79-8; **5e**, 119595-80-1; **6a**, 119595-81-2; **6b**, 119595-82-3; **6c**, 119595-83-4; **6e**, 119595-84-5; **7a**, 119677-62-2; **7b**, 119595-85-6; **7c**, 119677-63-3; **8**, 119595-86-7; **9a**, 119595-87-8; **9b**, 119595-88-9; **9c**, 119595-89-0; **9e**, 119595-90-3; **10a**, 119677-64-4; **10b**, 119595-91-4; **10c**, 119595-92-5; **10d**, 119595-93-6; **11a**, 119595-94-7; **12a**, 23009-50-9; **12b**, 31101-27-6; **12c**, 119595-95-8; **13a**, 6734-41-4; **13b**, 6734-44-7; 13c, 119595-96-9; **14**, 119595-97-0; **15**, 119595-98-1; **16**, 119595-99-2; **17**, 119596-00-8; MeI, 74-88-4; F_3CSO_3Pr, 29702-90-7; $BrCH_2CN$, 590-17-0; 9-bromo-9-phenylfluorene, 55135-66-5; η^6-benzene chromium tricarbonyl, 12082-08-5.

Chirospecific Synthesis of β-Hydroxy α-Amino Acids

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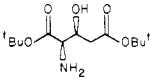
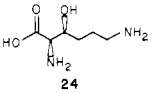
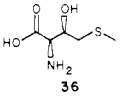
A variety of β-hydroxy α-amino acids have been synthesized with complete enantiomeric purity from L-serine. These include β-hydroxyglutamic acid, β-hydroxypipecolic acid, β-hydroxylysine, β-hydroxyproline, and β-hydroxymethionine. The syntheses proceed by the ready addition of vinyl- and allylmagnesium bromide and (methylthio)methyllithium to the carboxyl group of *N*-(phenylsulfonyl)serine to give high yields of the corresponding ketones. These particular organometallic reagents were chosen because by further manipulation they allow the introduction of a wide scope of functionalities. By judicious choice of reducing agent, either diastereomeric amino alcohol can be obtained with high preference on reduction of the amino ketone. The original serine primary hydroxyl group can then be selectively oxidized to give the amino acid in high overall yield and >99% ee.

Introduction

The chirospecific synthesis of β-hydroxy α-amino acids has long been of interest, sparked in part by the possible use of such compounds as potent enzyme inhibitors.[1a-c] Further interest stems from their use as attractive starting materials for chirospecific natural product synthesis. Their utility lies in their two set stereocenters and multifunctionalities, all of which are differentiable. Recently several syntheses of such compounds have appeared in the literature.[2-6] However, usually the synthesis of only one hydroxy amino acid is reported, and the possibility for generalization of the procedure is limited. We now report the

Table I. Summary of Yields in Synthetic Sequences

compounds	overal yield,[a] % syn diastereomer (anti)
 14	30 (24)
 19	33 (26)
 24	20 (16)
 29	37 (31)
 36	30 (24)

[a] From serine.

(1) (a) Walsh, C. *Tetrahedron* **1982**, *38*, 871. (b) Ayi, A. I.; Guedj, R. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2045. (c) Khomutov, R. M.; Kovaleva, G. K.; Severin, E. S. *Izv. Akad. Nauk SSR. Seriya Khim.* **1966**, *11*, 1925.

(2) (a) Evans, D. A.; Sjogren, E. B.; Weber, A. E.; Conn, R. E. *Tetrahedron Lett.* **1987**, *28*, 39. (b) Evans, D. A.; Weber, A. E. *J. Am. Chem. Soc.* **1987**, *109*, 7151. (c) Seebach, D.; Juaristi, E.; Miller, D. D.; Schickli, C.; Weber, T. *Helv. Chim. Acta* **1987**, *70*, 237.

(3) Belokon, Y. N.; Bulychev, A. G.; Vitt, S. V.; Struchkov, Y. T.; Batsanov, A. S.; Timofeeva, T. V.; Tsyryapkin, V. A.; Ryzhov, M. G.; Lysova, L. A.; Bakhmutov, V. I.; Belikov, V. M. *J. Am. Chem. Soc.* **1985**, *107*, 4252.

(4) (a) Hanessian, S.; Sahoo, S. P. *Can. J. Chem.* **1984**, *62*, 1400. (b) Vidal-Cros, A.; Gaudry, M.; Marquet, A. *J. Org. Chem.* **1985**, *50*, 3163. (c) Saito, S.; Bunya, N.; Inaba, M.; Moriwake, T.; Torii, S. *Tetrahedron Lett.* **1985**, *26*, 5309. (d) Hirama, M.; Hioki, H.; Ito, S. *Tetrahedron Lett.* **1988**, *29*, 3125.

(5) Cooper, J.; Gallagher, P. T.; Knight, D. W. *J. Chem. Soc., Chem. Commun.* **1988**, 509.

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development of a general and simple methodology that can be used to synthesize a variety of β-hydroxy α-amino acids containing other functions as well. This is achieved from inexpensive, readily available starting materials in high optical purity (>99%) and high overall yield (16–37%) as summarized in Table I.

Of the large volume of literature on the synthesis of β-substituted α-amino acids, the approaches that lead to products of high enantiomeric purity either involve the use of a chiral auxiliary, which is subsequently cleaved,[2,3,5] or a chiral educt, which is retained in the target compound.[4,6,7] For the former type, aldol condensations have been used extensively, including chiral enol haloacetates and isothiocyanoacetates[2a,b] and chiral enolates of imidazolinones and isoxazolidinones of a variety of amino acids.[2c] A chiral Ni(II) complex of glycine has been used to prepare threonine and several other hydroxy amino acids in 80–98% ee.[3] Yeast can also be used as a "chiral auxiliary", and such an enzymatic reduction yielded *cis*-3-hydroxyproline in 80% ee.[5]

The second approach has involved the use of either a sugar or an amino acid as the chiral educt. The use of a sugar generally requires the removal of unwanted stereocenters, resulting in a longer synthetic sequence.[4a–c] L-Serine has been used via an oxazolidine aldehyde and a pyranone to synthesize threo-β-hydroxyglutamic acid in 10% overall yield.[6]

Finally, in previous work from this laboratory, it was shown that the synthesis of D-threonine and D-allothreonine is quite facile, beginning with L-serine and proceeding through an organometallic reaction on the N-protected amino acid.[7] Building on that example we set β-hydroxyglutamic acid as our initial target. The overall yield and general ease with which we were able to make this compound prompted us to extend our scheme into a general method for the synthesis of β-hydroxy α-amino acids. The hydroxyl group is available for further transformations, and the process permits the introduction of many additional functionalities at other positions in the molecule. We have chosen five representatively diverse targets to test the scope and utility of our strategy. These are β-hydroxyglutamic acid, containing a diacid moiety; β-hydroxymethionine, containing a thioether linkage; β-hydroxylysine, a diamino compound; and β-hydroxyproline and β-hydroxypipecolic acid, five- and six-membered cyclic amino acids. Both the erythro and threo forms in the D-amino acid series of all these compounds have been synthesized in high yields and with >99% optical purity.

General Synthetic Strategy. By beginning our syntheses with L-serine, we have present the α-amino stereocenter and an hydroxyl group that will later be oxidized to the acid functionality in our final product. Scheme I outlines our general plan. Protecting the nitrogen of serine as the sulfonamide **2** is the most efficacious. Proceeding with unprotected hydroxyl and forming the trianion of **2** with *n*-BuLi, we can add virtually any primary organometallic reagent (we chose vinyl, allyl, and (methylthio)methyl) to the carboxyl group and obtain ketone **3** free from tertiary alcohol. Reduction of the ketone can yield either diastereomer of **4** with at least a 5/1 preference, depending on the reducing agent (see Table II). The diastereomers then can be easily separated on silica gel, either directly at the alcohol stage or after conversion of the diol to the isopropylidene derivative. Manipulation of the vinyl or allyl moiety of **4** can lead to a variety of functionalities, including an acid, an amine or alcohol, or to the introduction of a leaving group adaptable for intramolecular displacement to form a cyclic derivative. Specific oxidation of the primary hydroxyl of the newly functionalized amino diol **4** will yield the acid **5** that gives, upon removal of the N-protecting group, the amino acid **6**. These β-hydroxy α-amino acids also are potential substrates for diastereomeric interconversion at the β-carbon by the methodology used in the threonine–allothreonine example.

Scheme I. General Procedure for β-Hydroxy α-Amino Acid Synthesis

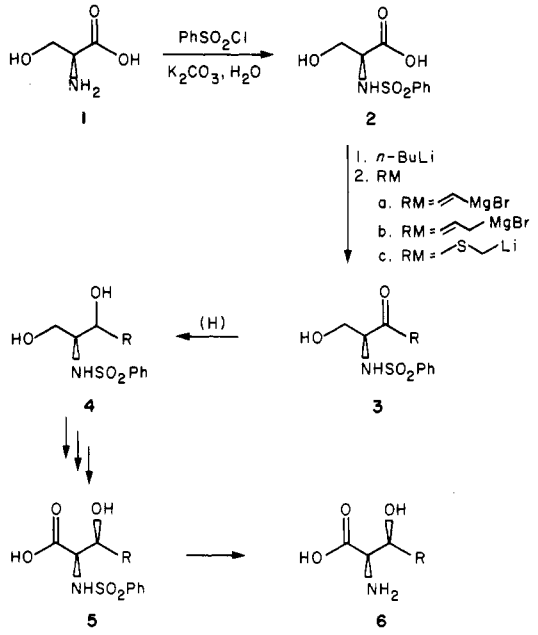
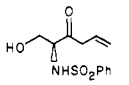
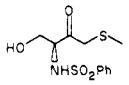
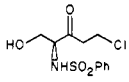


Table II. Reduction of Amino Ketones

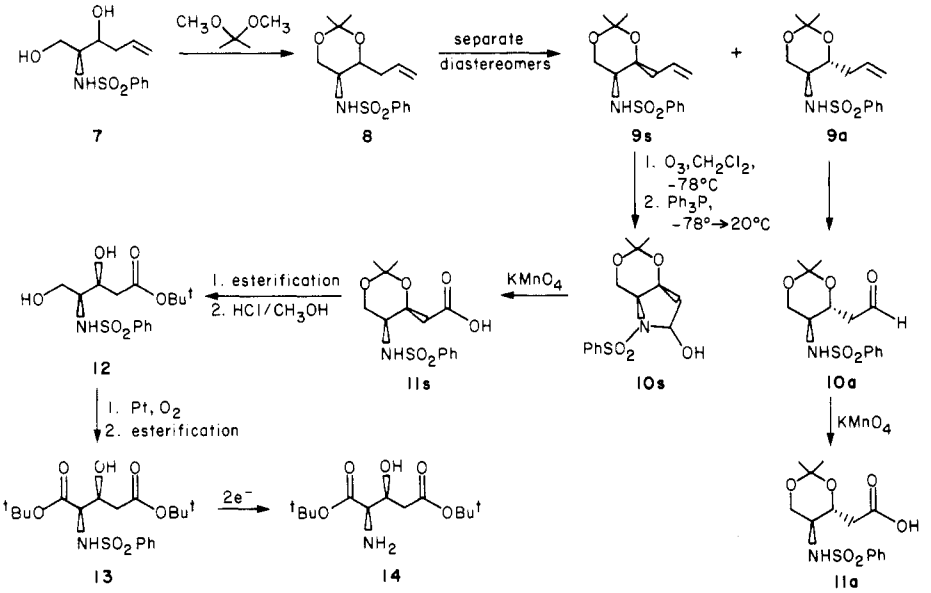
ketone	reducing agent	ratio, syn/anti
 **3b**	L-Selectride	9/1
	$LiBH_4$	1/6
 **3c**	L-Selectride	9/1
	$LiBH_4$	1/6
 **25**	K-Selectride	>9/1
	$LiBH_4$	1/5

β-Hydroxyglutamic Acid. Initial studies toward the synthesis of β-hydroxyglutamic acid began with CBZ-serine. Addition of allylmagnesium bromide led to the β,γ-unsaturated ketone accompanied by the α,β-unsaturated ketone and a substantial amount of recovered CBZ-serine. The isomerization appeared to be occurring during the quench of the reaction, but varying the quenching procedure did not result in a significant change in the product ratio. By changing the amino protecting group to phenylsulfonyl we were able to obtain the β,γ-unsaturated ketone **3b** in high yield and without any α,β-unsaturated isomer. Several attempts to ketalize allyl ketone **3b** resulted in first isomerization of the double bond, then internal Michael addition of the primary alcohol, and lastly ketalization.

Having failed to ketalize the carbonyl, we decided to reduce it to the alcohol. Previous work in our group had shown that both diastereomers could be obtained fairly

(6) Garner, P. *Tetrahedron Lett.* **1984**, *25*, 5855.
(7) Maurer, P. J.; Takahata, H.; Rapoport, H. *J. Am. Chem. Soc.* **1984**, *106*, 1095.

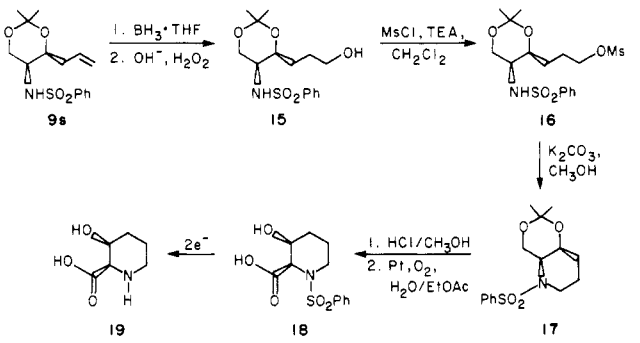
Scheme II. Synthesis of β-Hydroxyglutamic Acid



selectively from such a reduction depending on the nature of the reducing agent.[7] A large variety of hydrides were tried including some, $Zn(BH_4)_2$ and $PhMe_2SiH$ in particular, that caused isomerization of the double bond. L-Selectride in THF gave a 9/1, syn/anti, amino alcohol ratio and $LiBH_4$ in i-PrOH gave a 1/6, syn/anti, ratio of **7** in nearly quantitative yield with no isomerization of the double bond. Since reduction did not give a pure diastereomer, it was necessary to find a means of separating these amino diols. Preparative reverse-phase HPLC was successful, but in a practical sense could not be used to separate large quantities of material. At first, we derivatized the alcohols with hydrophobic groups with the intent of reducing the polarity of the compound and moving to a normal-phase solvent system. The secondary alcohol proved unreactive to esterification, probably the result of strong intramolecular hydrogen bonding. To overcome this we sought to prepare a cyclic derivative between the two alcohols. Both the carbonate and thionocarbonate could be formed but in low yields. However, a series of 1,3-dioxane derivatives, namely the cyclohexylidene, isopropylidene, and methylene derivatives, all could be prepared in very high yields. The cyclohexylidene and isopropylidene derivatives proved the most useful as both were separable on normal-phase HPLC. The isopropylidene also was separable on a medium-pressure liquid chromatography system using 0.8% 2-propanol/CH_2Cl_2 as the eluting solvent to give **9s** and **9a**. This process is shown in Scheme II; for clarity in this and the following schemes only the syn diastereomer will be shown unless the products are different for the two diastereomers.

Ozonolysis of **9s** in CH_2Cl_2 at −78 °C with Ph_3P in the isolation yielded the hemiaminal **10s** while the ozonolysis of **9a** gave the aldehyde **10a**. Both could be oxidized with $KMnO_4$ in acetone/water to yield the open chain acids, **11s** and **11a**, respectively. The isopropylidene then was removed without hydrolysis of the *tert*-butyl ester with catalytic HCl in MeOH.[8] A Pt/oxygen oxidation selectively oxidized the primary alcohol of **12** to give a highly polar hydroxy diacid. To aid in its purification, the di-*tert*-butyl ester **13** was formed and electrolyzed to yield amine **14** in 30% overall yield from serine.[9]

Scheme III. Synthesis of β-Hydroxypipecolic Acid



β-Hydroxypipecolic Acid and β-Hydroxylysine. Scheme III shows that the double bond of **9s** may be hydroborated and oxidized to form an alcohol, **15**, which can be mesylated in methylene chloride to give **16**. Displacing the mesylate internally with the sulfonamide anion generated by addition of potassium carbonate in methanol yielded bicycle **17**. Hydrolysis of the isopropylidene ketal with aqueous HCl in methanol, followed by platinum/oxygen oxidation, gave hydroxy acid **18**. Lastly, deprotection of the nitrogen yielded β-hydroxypipecolic acid **19** in 33% overall yield for the diastereomer shown.

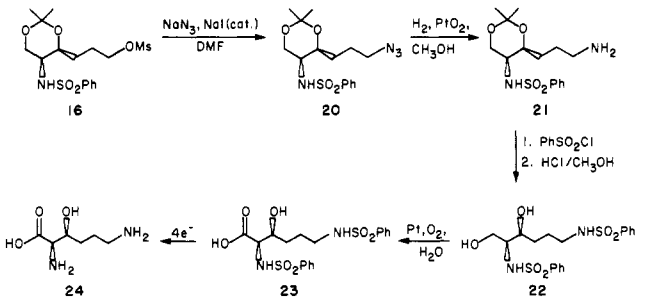
Introducing the second amino group to prepare the lysine derivative was not trivial. Initial attempts to introduce the amine by a hydroboration/amination procedure on **9s** resulted in only a 35% yield of the desired product.[10a] The mechanism of this reaction is believed to be analogous to that of a sodium borohydride reduction. There is a rearrangement of the initially formed trialkylborane when a nitrogen is introduced as hydroxylamine-*O*-sulfonic acid. Subsequent alkyl rearrangements are slower for the dialkyl- and monoalkylborane; this was probably the reason for our low yield since only one alkyl group was rearranging. This problem can be avoided in reductions by using bulky dialkylboranes[10b] as the boronating agents. These bulky alkyl groups will be slow to rearrange, and

(8) Compound **12** is an hydroxy analogue of statine, a β-hydroxy γ-amino acid, and thus shows the utility of this methodology for the synthesis of members of this class of compounds.

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

(10) (a) Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565. (b) Verbit, L.; Heffron, P. J. *J. Org. Chem.* **1967**, *32*, 3199.

Scheme IV. Synthesis of β-Hydroxylysine



thus only the desired, less hindered, alkyl groups will rearrange to form amine. Disiamylborane was used, but a rearrangement could not be effected with hydroxylamine-*O*-sulfonic acid. Chloramine also would not affect the desired rearrangement; therefore, the hydroboration/amination procedure was abandoned.

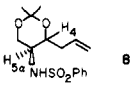
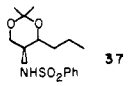
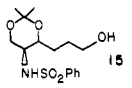
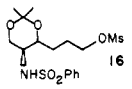
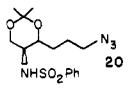
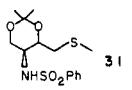
A Mitsunobu type transformation of alcohol **15** to azide **20** was attempted with diethyl azodicarboxylate, Ph_3P, and HN_3, but a multitude of products was obtained. Mesylate **16**, as outlined in Scheme IV, then became our key intermediate. Direct displacement of **16** with freshly activated NaN_3 was unsuccessful, but use of a catalytic amount of NaI along with the large excess of NaN_3 allowed the reaction to proceed smoothly. It is interesting to note that the formation of iodide from mesylate **16** was quite easy with NaI in acetone, but subsequent reaction of this iodide with NaN_3 was poor.

Reduction of the azide with PtO_2/H_2 at 1 atm yielded amine **21**, which was immediately protected as its phenyl sulfonamide. The isopropylidene ketal was hydrolyzed to give diol **22**, which was oxidized with platinum and oxygen yielding hydroxy diamino acid **23**. Finally, electrolytic removal of the sulfonyl group gives β-hydroxylysine **24** in 20% overall yield for the syn diastereomer.

β-Hydroxyproline. First HCl was added across the double bond of ketone **3a** as shown in Scheme V to form chloro ketone **25**. K-Selectride reduction yielded the syn diastereomer of diol **26** almost exclusively while a $LiBH_4$ reduction yielded the anti diastereomer with a 5/1 preference. Once again ring closure readily occurred by simply forming the sulfonamide anion with K_2CO_3 in MeOH and intramolecularly displacing the chloride to form pyrrolidine **27**. At this stage diastereomers may be separated, no prior derivatization being necessary. Oxidation of diol **27** yielded an acid that was best isolated as ester **28**. The phenylsulfonyl protecting group was then removed by electrolysis, but the use of cation exchange chromatography to recover the free amine also hydrolyzed the *tert*-butyl ester, and we thus obtained the free amino acid **29** in 37% overall yield for the syn diastereomer from serine.

Polyhydroxylated pyrrolidines and polyhydroxylated piperidines[11a-c] have been shown to be potent glycosidase inhibitors.[12a,d] Our β-hydroxylproline and β-hydroxypipecolic acid syntheses seem well-suited for expansion into the synthesis of a large variety of such iminopentitols and iminohexitols. For example, diol **27** as a free amine was recently isolated from *Castanospermum australe*, and the analogous six-membered ring diol is the dihydro product resulting from hydrogenation of a newly discovered hydroxybaikian.[13,14] By simply manipulating the double bond in both of our synthetic series, one or two more hydroxyl groups could be introduced, presumably with asymmetric control from the two stereocenters already present.

Table III. Summary of Isopropylidene Coupling Constants

compound	syn, $J_{5a,4a}$, Hz	anti, $J_{5a,4b}$, Hz
 8	1.8	9.3
 37	1.6	9.0
 15	1.8	–
 16	–	9.5
 20	1.8	–
 31	1.6	9.4

β-Hydroxymethionine. (Methylthio)methyl ketone **3c** can be reduced specifically to yield diol **30** in the same ratio of syn/anti isomers and with the same reducing agents as in the case of allyl ketone **3b**. As shown in Scheme VI, the diols were best derivatized to isopropylidene ketals **31** with 2,2-dimethoxypropane in order to separate the diastereomers. We next tried a platinum/oxygen oxidation of the diastereomerically pure diols **30** obtained by acidic hydrolysis of the isopropylidene ketal. During this procedure the thioether of **30** was rapidly oxidized to the sulfone, and it became apparent that thioether protection was required. A benzylsulfonium salt was prepared by reacting isopropylidene **31** with benzyl triflate[15] with concomitant cleavage of the isopropylidene ketal, most likely by traces of trifluoromethanesulfonic acid present in the reaction mixture. Sulfonium salt **32** was convenient to handle and could be chromatographed and selectively oxidized to the acid **33**. Complete oxidation could not be achieved without some oxidation of the secondary alcohol. The addition of 2-propanol to the oxidation reaction slowed this overoxidation, which is not uncommon. To avoid this, the oxidation is frequently stopped before completion and the starting material is recovered and recycled. In the present instance, about a 1/1 mixture of **32** and **33** was obtained, and this mixture was hydrogenolyzed with $Pd/C/H_2$ to give a mixture of acid **34** and diol **30**. Acid **34** is highly water soluble, and diol **30** is thus simply removed by an extractive process. Crude acid **34** is obtained by evaporating the water. Analytical data were obtained on *tert*-butyl ester **35**. Electrolysis removes the phenylsulfonyl protecting group from **34** to give, after ion-exchange chromatography, β-hydroxymethionine in 30% overall yield from serine for the syn diastereomer.

(11) (a) Fellows, L. E.; Bell, E. A.; Lynn, D. G.; Pilkiewicz, F.; Miura, I.; Nakanishi, K. *J. Chem. Soc., Chem. Commun.* **1979**, 977. (b) Jones, D. W. C.; Nash, R. J.; Bell, E. A.; Williams, J. M. *Tetrahedron Lett.* **1985**, *26*, 3125. (c) Ohfune, Y.; Kurokawa, N. *Tetrahedron Lett.* **1985**, *26*, 5307.

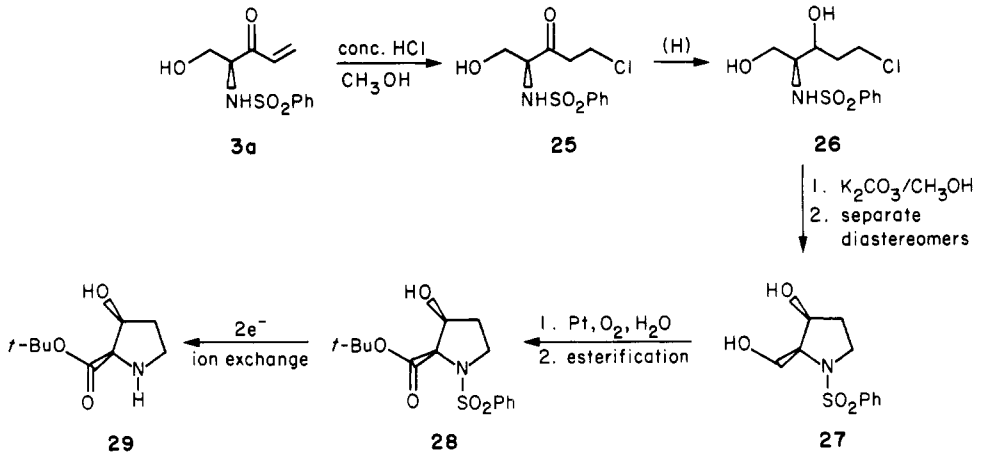
(12) (a) Evans, S. V.; Hayman, A. R.; Fellows, L. E.; Shing, T. K. M.; Derome, A. E.; Fleet, G. W. J. *Tetrahedron Lett.* **1985**, *26*, 1465. (b) Fleet, G. W. J.; Nicholas, S. J.; Smith, P. W.; Evans, S. V.; Fellows, L. E.; Nash, R. J. *Tetrahedron Lett.* **1985**, *26*, 3127. (c) Fleet, G. W. J. *Tetrahedron Lett.* **1985**, *26*, 5073. (d) Rule, C. J.; Wurzburg, B. A.; Ganem, B. *Tetrahedron Lett.* **1985**, *26*, 5379.

(13) Nash, R. J.; Bell, E. A.; Fleet, G. W. J.; Jones, R. H.; Williams, J. M. *J. Chem. Soc., Chem. Commun.* **1985**, 738.

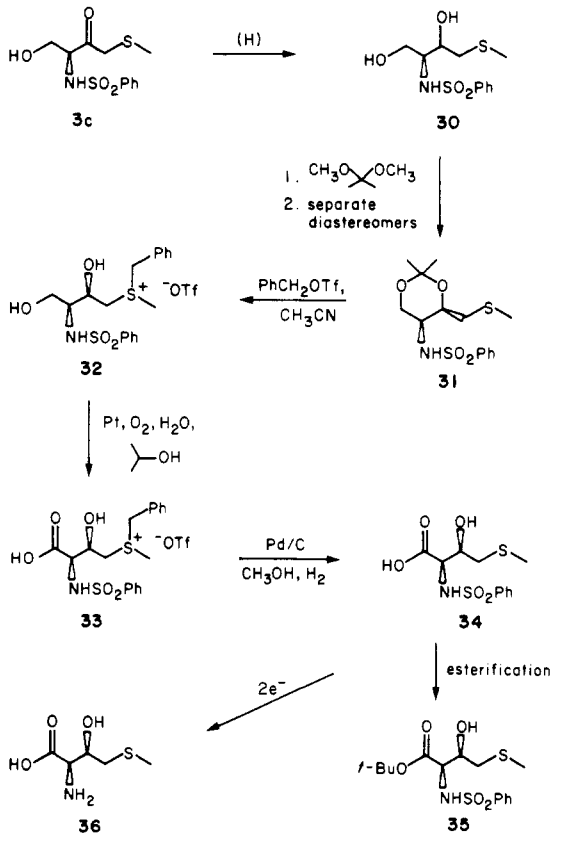
(14) Kusano, G.; Ogawa, H.; Takahashi, A.; Nozoe, S.; Yokoyama, K. *Chem. Pharm. Bull.* **1987**, *35*, 3482.

(15) Lemieux, R. U.; Kondo, T. *Carbohydr. Res.* **1974**, *35*, C4.

Scheme V. Synthesis of β-Hydroxyproline



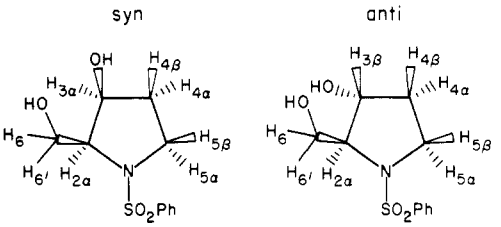
Scheme VI. Synthesis of β-Hydroxymethionine



Absolute Stereochemistry and Enantiomeric Purity. 1,3-Dioxane **9s** is important not only as a key synthetic intermediate to three diverse β-hydroxy α-amino acids but also as the compound that we used to determine diastereomer identity and enantiomeric purity.

The 1,3-dioxane ring present in **9s** prefers a chair conformation, and we were thus able to use the Karplus correlation that the coupling constant between protons on neighboring carbon atoms is dependent on the dihedral angle between them. A large coupling constant denotes a trans and anti stereochemistry, and a small coupling constant denotes a cis or syn stereochemistry.[8] For the isopropylidene ketal **9s** the coupling constant J_{ab} as shown in Table III is 1.8 Hz, indicating a cis stereochemistry. For **9a**, J_{ab} is 9.3 Hz, indicating a trans stereochemistry. This same analysis was applied to thioether **31**, also an isopropylidene ketal, and once again the coupling constants in Table III are consistent with the assignments made.[16]

Table IV. NOE Interactions of Syn and Anti Proline Diols



proton	NOE observed[a]	proton	NOE observed
$H_{2\alpha}$, $H_{5\beta}$ (overlap)	$H_{3\alpha}$ (m), $H_{4\beta}$ (m), $H_{5\alpha}$ (s), $H_{6,6'}$ (m)	$H_{2\alpha}$	$H_{6'}$ (s), $H_{4\alpha}$ (m), $H_{4\beta}$ (w)
$H_{3\alpha}$	$H_{2\alpha}$ (s), $H_{4\beta}$ (w), $H_{4\alpha}$ (m), $H_{5\alpha}$ (m)	$H_{3\beta,6'}$	$H_{2\alpha}$ (m), H_6 (vs), $H_{5\beta}$ (vw), $H_{4\alpha}$ (w)
$H_{4\beta}$	$H_{3\alpha}$ (W), $H_{4\alpha}$ (vs), $H_{5\beta}$ (w)	$H_{4\beta}$	$H_{3\beta}$ (m), $H_{5\beta}$ (m), $H_{4\alpha}$ (vs)
$H_{4\alpha}$	$H_{3\alpha}$ (m), $H_{4\beta}$ (vs), $H_{5\beta}$ (w), $H_{5\alpha}$ (m)	$H_{4\alpha}$	$H_{2\alpha}$ (m), $H_{5\alpha}$ (m), $H_{5\beta}$ (w), $H_{4\beta}$ (vs)
$H_{5\alpha}$	$H_{3\alpha}$ (m), $H_{2\alpha}$ (vs), $H_{4\beta}$ (w), $H_{4\alpha}$ (w)	$H_{5\beta}$	$H_{3\beta,6'}$ (vs), $H_{4\beta}$ (m)
$H_{6,6'}$	$H_{2\alpha,5\beta}$ (vs), $H_{5\alpha}$ (w)	$H_{5\alpha}$	$H_{2\alpha}$ (w), $H_{5\beta}$ (vs), $H_{4\alpha}$ (w), $H_{4\beta}$ (vw)
		H_6	$H_{2\alpha}$ (s), $H_{3\beta,6'}$ (vs)

[a] Key: w, weak: m, moderate; s, strong; vs, very strong.

We did not form isopropylidenes in our hydroxyproline synthesis, and the coupling constants of both the syn and anti diastereomers of **27** were similar, thus we could not assign stereochemistry with confidence using Karplus correlation. Each diastereomer should, however, exhibit different NOE interactions. These interactions are summarized in Table IV. On the basis of these data we assign syn stereochemistry to the product arising from the Selectride reduction and anti stereochemistry to that arising from the $LiBH_4$ reduction. In all cases a lithium borohydride reduction in 2-propanol leads to the anti stereochemistry predominating and the Selectride reduction in THF leads to a preference for the syn stereochemistry.

The optical purity of **9s** was shown first by proving diastereomeric purity with HPLC and then by proving enantiomeric purity by derivatization as the mandelate. Compound **9s** was first hydrogenated to saturate the side chain. The *N*-phenylsulfonyl protecting group was then removed with Na in ammonia/THF, 1/1, and the free amine was derivatized by using both D,L- and L-mandelic acid. It was then shown that the D,L-mixture could be separated on HPLC and that it was possible to detect 0.5%

(16) Batterham, T. J. *NMR Spectra of Simple Heterocycles*; John Wiley and Sons: New York, 1973, p 404.

of the D-derivative present in the L-derivative. 1,3-Dioxane **9s** has >99% enantiomeric excess, and thus the reduction conditions used on the amino ketones are nonracemizing.

We have established that our reduction conditions do not racemize our initial α-amino chiral center, but what about the platinum/oxygen oxidation of a primary alcohol to an acid, included in all our syntheses? Previous work has shown that this is a nonracemizing reaction,[17] but further evidence was desirable. If there is any appreciable time spent at the aldehyde stage it is conceivable that the α-center could be epimerizing. To test this the N-protected pipecolic acids were first converted to the methyl esters using diazomethane. If any epimerization at the α-center of the anti derivative had occurred we would have formed the enantiomer of the syn compound. We therefore did not have to further derivatize our methyl esters but simply subject them to HPLC analysis. After finding a system to separate a mixture of esters, a doping experiment showed that there was only 0.5% of the syn isomer present in the anti; therefore, we had a 99% diastereomeric excess, and no epimerization had occurred at the α-center. The same was true for the syn diastereomer. It is worth noting that this 0.5% could have arisen from incomplete initial separation of **9s** and **9a**.

Conclusion

We have presented a general, versatile method that can be applied to the synthesis of a wide variety of β-hydroxy α-amino acids. The method is applicable to a large variety of compounds of this class with multifunctionality through simple extension. Also, through our hydroxyglutamic acid synthesis in which they are intermediates, we have demonstrated the potential of this method to produce a large variety of β-hydroxy γ-amino acids. Accompanying this synthetic versatility is the fact that these procedures result in complete enantiomeric integrity.

Experimental Section

General. Tetrahydrofuran (THF) was distilled immediately prior to use from sodium/benzophenone, *N,N*-dimethylformamide (DMF) and acetonitrile (CH_3CN) were distilled from CaH_2, methylene chloride (CH_2Cl_2) was distilled from P_2O_5, and all water was deionized and filtered through a 0.25-mm filter cartridge. Solvents used for high-performance and medium-pressure liquid chromatography were spectral grade and filtered and degassed prior to use. Unless otherwise noted all nonaqueous reactions were carried out under an inert (N_2) atmosphere with magnetic stirring. Temperatures refer to bath temperatures. Organic solutions were dried over Na_2SO_4 and then evaporated with a Berkeley rotary evaporator (water aspirator) followed by static evaporation with an oil pump. Melting points (pyrex capillary) are uncorrected. Proton magnetic resonance spectra (^1H NMR) were measured downfield relative to internal tetramethylsilane at 250 MHz in $CDCl_3$ unless otherwise noted. All NOE determinations were done with a Bruker 500-MHz spectrometer. Medium-pressure liquid chromatography (MPLC) was done with silica gel 60 packed Michel–Miller columns, either 30 × 2 cm or 30 × 4 cm, with a Perkin-Elmer Series I LC pump. Analytical high-performance liquid chromatography (HPLC) was carried out with either an Altex Ultrapak or IBM ODS 10-μL column on an Altex 100A system. Elemental analyses and mass spectra were obtained from the Analytical Laboratory, College of Chemistry, University of California, Berkeley, CA.

***N*-(Phenylsulfonyl)-L-serine (2)** was prepared as described[7] except that the filtrate was washed with ether before acidifying to pH 1 with concentrated H_3PO_4, resulting in an 85% yield.

(*S*)-4-[(Phenylsulfonyl)amino]-5-hydroxy-3-pentenone (3a).[17,18] To 10 g (40.8 mmol) of *N*-(phenylsulfonyl)-L-serine in 500 mL of THF at −78 °C was added dropwise over 15 min 68 mL (0.1 mol) of *n*-BuLi in hexanes, and the solution was stirred for 15 min. The heterogeneous mixture was warmed to −40 °C, and 100 mL (152 mmol) of vinylmagnesium bromide in THF was added, followed by warming to room temperature. After stirring for 18 h, the reaction mixture was poured into 1 M H_3PO_4 (0 °C, 300 mL) and extracted with EtOAc (3 × 200 mL). The organic extracts were combined, washed with saturated $NaHCO_3$ (1 × 500 mL) and saturated NaCl (1 × 500 mL), dried, and evaporated to yield 8 g (31.8 mmol, 78%) of vinyl ketone **3a** after recrystallization from EtOAc/hexanes: mp 110–111 °C (lit.[18] mp 110–111 °C); ^1H NMR δ 3.2 (m, 2 H), 3.9 (b s, 1 H), 4.0 (m, 1 H), 5.1 (m, 2 H), 5.7 (m, 1 H), 5.9 (d, 1 H, J = 6.45 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H).

(*S*)-5-[(Phenylsulfonyl)amino]-6-hydroxy-4-hexenone (3b).[18] *N*-(Phenylsulfonyl)-L-serine (2.45 g, 10 mmol) was dissolved in 100 mL of hot THF, and the solution was flushed with N_2 and cooled to −78 °C. *n*-Butyllithium (15 mL, 1.58 M, 24 mmol) was added dropwise over 15 min, and the resulting suspension was warmed to 0 °C, whereupon 35 mL (0.8 M, 28 mmol) of allylmagnesium bromide[19] was added dropwise over 15 min. After warming to room temperature, the reaction mixture was stirred for 18 h and then quenched by pouring onto 1 M H_3PO_4 at 0 °C. The layers were separated, and the aqueous phase was extracted with diethyl ether (2 × 100 mL). The organic phases were combined, washed with saturated $NaHCO_3$ (1 × 200 mL) and saturated NaCl (1 × 200 mL), dried, and evaporated. The residual white solid was recrystallized from EtOAc/hexanes to yield 2.04 g (7.8 mmol, 78%) of allyl ketone **3b**: mp 109–110 °C (lit.[18] mp 108–109 °C); ^1H NMR δ 2.0–2.1 (b s, 1 H), 3.2-3.3 (m, 2 H), 3.9 (m, 3 H), 5.1 (q, 2 H), 6.7 (m, 1 H), 6.9 (b s, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ 72.9° (*c* 2, $CHCl_3$).

(Methylthio)methyllithium. To 16 mL (1.56 M, 25 mmol) of *n*-BuLi in hexanes was added dropwise, at 10 °C, 3.75 mL (2.90 g, 25 mmol) of TMEDA. After the mixture was stirred for 10 min, 1.77 mL (1.5 g, 25 mmol) of dimethyl sulfide was added, and the solution was stirred at room temperature overnight. A white precipitate had formed, and the reaction mixture was used as this suspension.[20]

(*S*)-3-[(Phenylsulfonyl)amino]-4-hydroxy-1-(methylthio)-2-butanone (3c). To 1.0 g (4.1 mmol) of *N*-(phenylsulfonyl)-L-serine (**2**) in 50 mL of THF was added dropwise at −78 °C 7.89 mL (12.2 mmol) of *n*-BuLi in hexanes. The solution was stirred for 0.5 h, and then the (methylthio)methyllithium prepared above was added via cannula. After being warmed to room temperature the suspension was stirred for 18 h, poured onto 50 mL of 1 M H_3PO_4 (0 °C), and extracted with CH_2Cl_2 (3 × 50 mL). The organic layers were combined, washed with saturated $NaHCO_3$ (1 × 50 mL) and saturated NaCl (1 × 50 mL), dried, and evaporated to give (methylthio)butanone **3c** as a white solid that could be recrystallized from EtOAc/hexanes: yield 0.95 g (3.3 mmol, 80%); mp 102–105 °C; ^1H NMR δ 1.8 (s, 3 H), 2.1 (b s, 1 H, OH), 3.1 (d, 1 H, J = 13.9 Hz), 3.4 (d, 1 H, J = 13.9 Hz), 3.8 (dd, 1 H, J = 4.0, 11.4 Hz), 3.9 (dd, 1 H, J = 8.1, 11.4 Hz), 4.3 (q, 1 H, J = 3.83, 7.28 Hz), 5.8 (d, 1 H, J = 6.8 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H); IR (KBr pellet) 3520, 3310, 2980, 1710, 1350, 1180, 760, 740, 690 cm^{-1}; $[\alpha]^{20}_D$ 69.8° (*c* 0.58, $CHCl_3$). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 45.7; H, 5.2; N, 4.8. Found: C, 45.9; H, 5.3; N, 4.9.

General Procedure for the Reduction of Amino Ketones. The amino ketone (3.7 mmol) was dissolved in 50 mL of solvent and taken to the reaction temperature, and then 300 mol % of reducing agent was added (301 mg of $LiBH_4$ or 11.1 mL of 1 M Selectride). Borohydride reductions were carried out in i-PrOH at −23 °C, and Selectride reductions were carried out at −78 °C in THF. All reactions were stirred for 2 h before being quenched with 20 mL of 1/1 acetic acid/water. After warming to room temperature, the reaction mixture was evaporated to dryness, and the residue was dissolved in saturated $NaHCO_3$ (in Selectride reductions the aqueous layer was first extracted with hexanes) and extracted with 4/1 $CHCl_3$/i-PrOH (3 × 50 mL). The organic

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(19) Hwa, J. C.; Sims, H. *Organic Syntheses*; Baumgarten, H. E., Ed.; Wiley: New York, 1973; Collect. Vol. V, p 608.

(20) Peterson, D. J. *J. Org. Chem.* **1967**, *32*, 1717.

layers were combined, dried, and evaporated to give the alcohol in 95% yield in all cases.

(4*S*,5*S*)-5-[(Phenylsulfonyl)amino]-4,6-dihydroxyhexene [(*S*,*S*)-7]: clear oil; analytical HPLC, Altex 10μ ODS, 3 mL/min, 15% CH_3CN/H_2O, t_R 12 min; ^1H NMR δ 2.0 (m, 2 H), 3.3 (b s, 1 H), 3.4 (b s, 3 H), 3.6 (m, 1 H, J = 4.04 Hz), 3.9 (b t, 1 H, J = 5.94 Hz), 4.9 (m, 2 H), 5.6 (m, 1 H), 6.0 (d, 1 H, J = 7.25 Hz), 7.5 (m, 3 H), 7.9 (m, 2 H). Anal. Calcd for $C_{12}H_{17}NO_4S$: C, 53.1; H, 6.3; N, 5.1. Found: C, 53.5; H, 6.3; N, 4.8.

(4*R*,5*S*)-5-[(Phenylsulfonyl)amino]-4,6-dihydroxyhexene [(*R*,*S*)-7]: clear oil; T_R 14 min; ^1H NMR δ 2.2 (m, 2 H), 2.4 (b s, 2 H), 3.2 (m, 1 H), 3.6 (m, 1 H), 3.7 (m, 1 H), 3.9 (m, 1 H), 5.0 (b m, 2 H), 5.4 (b d, 1 H), 5.6 (m, 1 H), 7.6 (m, 3 H), 7.9 (dd, 2 H, J = 1.34, 2.98 Hz); $[\alpha]^{20}_D$ −14.7° (*c* 2.5, $CHCl_3$).

(2*R*,3*S*)-3-[(Phenylsulfonyl)amino]-2,4-dihydroxy-1-(methylthio)butane [(*R*,*S*)-30]: yellow solid; mp 134–135 °C; ^1H NMR (acetone-d_6) δ 2.1 (s, 3 H), 2.4 (m, 2 H, J = 4.63, 6.94, 13.61 Hz), 3.5 (b m, 3 H), 3.9 (b t, 1 H, J = 4.60 Hz), 4.0 (dq, 1 H, J = 1.32, 4.71, 6.30 Hz), 4.1 (d, 1 H, J = 4.56 Hz), 6.2 (b d, 1 H, J = 6.46 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ −9.4° (*c* 1.6, acetone). Anal. Calcd for $C_{11}H_{17}NO_4S_2$: C, 45.3; H, 5.9; N, 4.8. Found: C, 45.7; H, 6.0; N, 4.6.

(2*S*,3*S*)-3-[(Phenylsulfonyl)amino]-2,4-dihydroxy-1-(methylthio)butane [(*S*,*S*)-30]: yellow oil; ^1H NMR δ 2.0 (s, 3 H), 2.5 (dd, 1 H, J = 8.67, 13.86 Hz), 2.7 (dd, 1 H, J = 4.65, 13.86 Hz), 3.1 (b s, 1 H), 3.3 (b m, 1 H), 3.4 (b d, 1 H), 3.6 (b d, 1 H), 3.7 (m, 1 H), 3.9 (dd, 1 H, J = 2.24, 11.44 Hz), 6.1 (d, 1 H, J = 8.76 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ 10.7° (*c* 0.2, acetone).

General Procedure for Isopropylidene Formation. To 3.7 mmol of diol in 50 mL of THF was added 5.5 mL (4.62 g, 44.4 mmol) of 2,2-dimethoxypropane and 50 mg of toluenesulfonic acid, and the solution was stirred for 3 h at room temperature. It was then poured onto 50 mL of saturated $NaHCO_3$, stirred for 10 min, and extracted with 4/1 $CHCl_3$/i-PrOH (3 × 40 mL). The organic layers were combined, washed with 1 M H_3PO_4 (1 × 10 mL), dried, and evaporated to yield 3.2 mmol (87%) of 1,3-dioxane.

(4*S*,5*S*)-5-[(Phenylsulfonyl)amino]-4-allyl-2,2-dimethyl-1,3-dioxane (9s): white solid; chromatographed (MPLC, silica, 0.8% i-PrOH/CH_2Cl_2), first compound to elute; recrystallized from EtOAc/hexanes, mp 143–144 °C; ^1H NMR δ 1.4 (2 s, 6 H), 1.6 (m, 1 H), 2.1 (m, 1 H), 3.1 (dddd, 1 H, J = 1.8, 1.8, 1.8, 10.2 Hz), 3.4 (dd, 1 H, J = 1.8, 12.2 Hz), 3.9 (dd, 1 H, J = 1.8, 12.1 Hz), 3.9 (ddd, 1 H, J = 1.8, 5.1, 8.3 Hz), 5.0 (m, 2 H), 5.3 (d, 1 H, J = 10.2 Hz), 5.7 (m, 1 H), 7.5 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ 13.6° (*c* 2.12, $CHCl_3$). Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.8; H, 6.8; N, 4.5. Found: C, 57.5; H, 6.8; N, 4.5.

(4*R*,5*S*)-5-[(Phenylsulfonyl)amino]-4-allyl-2,2-dimethyl-1,3-dioxane (9a): white solid that forms from a clear viscous oil on standing; second compound to elute from chromatography (above); mp 77–78 °C; ^1H NMR δ 1.3 (ds, 6 H), 2.0 (m, 1 H), 2.3 (m, 1 H), 3.2 (dddd, 1 H, J = 5.4, 8.9, 9.3, 9.6 Hz), 3.45 (dd, 1 H, J = 4.7, 8.9 Hz), 3.55 (ddd, 1 H, J = 3.0, 8.3, 9.6 Hz) 3.65 (dd, 1 H, J = 5.3, 11.7 Hz), 5.0 (m, 2 H), 5.7 (m, 1 H), 5.9 (d, 1 H, J = 9.3 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ 27.9° (*c* 1.63, $CHCl_3$).

(4*R*,5*S*)-5-[(Phenylsulfonyl)amino]-2,2-dimethyl-4-[(methylthio)methyl]-1,3-dioxane (31a): white solid, elutes first from chromatography system above; mp 80–82 °C; ^1H NMR δ 1.4 (ds, 6 H), 2.0 (s, 3 H), 2.5 (m, 2 H), 3.4 (ddd, 1 H, J = 1.6, 1.7, 10.2 Hz), 3.4 (dd, 1 H, J = 1.9, 12.1 Hz), 3.9 (ddd, 2 H, J = 1.7, 1.7, 4.7 Hz), 5.3 (d, 1 H, J = 9.8 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ 25° (*c* 0.54, $CHCl_3$). Anal. Calcd for $C_{14}H_{21}NO_4S_2$: C, 50.7; H, 6.4; N, 4.2. Found: C, 51.1; H, 6.4; N, 4.1.

(4*S*,5*S*)-5-[(Phenylsulfonyl)amino]-2,2-dimethyl-4-[(methylthio)methyl]-1,3-dioxane (31s): clear oil that elutes second in this series; ^1H NMR δ 1.3 (ds, 6 H), 2.0 (s, 3 H), 2.4 (dd, 1 H, J = 6.87, 14 Hz), 2.65 (dd, 1 H, J = 3.0, 14.0 Hz), 3.3 (b m, 1 H), 3.5 (dd, 1 H, J = 8.9, 11.5 H), 3.65 (dd, 1 H, J = 5.4, 11.5 Hz), 3.7 (dddd, 1 H, J = 3.0, 6.8, 9.4 Hz), 5.7 (b s, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ 14.6° (*c* 1.1, $CHCl_3$).

Ozonolysis of Allyl-1,3-dioxanes 9s and 9a. Into 700 mg (2.26 mmol) of **9s** or **9a** in 50 mL of CH_2Cl_2 at −78 °C was bubbled ozone until a blue color persisted. Excess ozone was removed by bubbling a stream of oxygen through the reaction mixture until it became colorless. Triphenylphosphine (651 mg, 2.49 mmol) was added, the solution was warmed to room temperature, and then the solvent was evaporated. The residue was used in the next step without further purification; however, it can be chromatographed with 5% i-PrOH/$CHCl_3$ to yield either aminal **10s** or aldehyde **10a** as clear oils in 80–85% yield.

Hemiaminal 10s: clear oil; ^1H NMR δ 1.3 (s, 3 H), 1.4 (s, 3 H), 1.7 (ddd, 1 H, J = 4.17, 5.53, 14.03 Hz), 2.0 (d, 1 H, J = 14.01 Hz), 3.5 (q, 1 H, J = 3.72, 7.48 Hz), 3.8 (d, 1 H, J = 11.43 Hz), 4.1 (d, 1 H, J = 3.51 Hz), 4.4 (t, 1 H, J = 3.75 Hz), 5.5 (dd, 1 H, J = 5.53, 11.41 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H).

(4*R*,5*S*)-5-[(Phenylsulfonyl)amino]-4-(2-oxoethyl)-2,2-dimethyl-1,3-dioxane (10a): clear oil; ^1H NMR δ 1.3 (s, 3 H), 1.4 (s, 3 H), 2.6 (m, 2 H), 3.2 (m, 1 H), 3.5 (dd, 1 H, J = 9.34, 11.65 Hz), 3.6 (dd, 1 H, J = 5.61, 11.66 Hz), 4.1 (m, 1 H), 5.1 (d, 1 H, J = 9.26 Hz), 7.6 (m, 3 H), 7.9 (d, 2 H), 9.6 (s, 1 H).

(4*R*,5*S*)-5-[(Phenylsulfonyl)amino]-4-(2-carboxyethyl)-2,2-dimethyl-1,3-dioxane (11a). To 320 mg (1.02 mmol) aldehyde **10a** in 30 mL of acetone at room temperature was added a solution of 405 mg (2.55 mmol) of $KMnO_4$ in 8 mL of water, and the solution was stirred for 2 h. Aqueous formaldehyde was added dropwise until the purple color due to excess $KMnO_4$ had disappeared. The resulting MnO_2 was removed by filtration, the filtrate was evaporated to 10 mL, and an additional 20 mL of water was added before acidifying to pH 4 at 0 °C with 1 M H_3PO_4. The aqueous phase was extracted with 4/1 $CHCl_3$/i-PrOH (3 × 40 mL) and drying and evaporating the combined organic phase gave acid **11a** as a clear oil: ^1H NMR (acetone-d_6) δ 1.2 (s, 3 H), 1.4 (s, 3 H), 2.1 (dd, 1 H, J = 9.32, 16.30 Hz), 2.6 (dd, 1 H, J = 2.50, 16.12 Hz), 3.1 (b m, 1 H), 3.4 (dd, 1 H, J = 5.59, 11.52 Hz), 3.6 (dd, 1 H, J = 10.33, 11.50 Hz), 4.2 (dt, 1 H, J = 2.44, 9.62 Hz), 7.1 (b s, 1 H), 7.5 (m, 3 H), 7.9 (d, 2 H).

(4*S*,5*S*)-5-[(Phenylsulfonyl)amino]-4-(2-carboxyethyl)-2,2-dimethyl-1,3-dioxane (11s) was prepared by oxidation with $KMnO_4$ as described for acid **11a**. It is a clear oil; ^1H NMR δ 1.3 (s, 3 H), 1.4 (s, 3 H), 2.5 (d, 2 H, J = 6.09 Hz), 3.2 (d, 2 H, J = 9.98 Hz), 3.9 (m, 1 H), 4.3 (t, 1 H, J = 6.21 Hz), 5.6 (d, 1 H, J = 9.90 Hz), 6.1 (b s, 1 H), 7.6 (m, 3 H), 7.9 (d, 2 H).

(4*S*,5*S*)-5-[(Phenylsulfonyl)amino]-4-[2-(*tert*-butoxycarbonyl)ethyl]-2,2-dimethyl-1,3-dioxane (11s-*tert*-Butyl ester). To a 3.06 mmol of crude acid **11s** in 40 mL of 4/1 *tert*-butyl alcohol/CH_2Cl_2, was added 2.45 g (12.2 mmol) of *N*,*N*′-diisopropyl-*O*-*tert*-butylisourea, the solution was heated at 40 °C for 18 h, cooled to room temperature, and filtered, and the filtrate was evaporated to dryness. The solid white residue was partitioned between water and CH_2Cl_2, the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic phases were dried and evaporated. Chromatography (flash, silica, 1/1 EtOAc/hexanes) of the residue gave **11s-*tert*-butyl ester** as a colorless oil in 65% yield from 1,3-dioxane **9s**: ^1H NMR δ 1.2 (s, 3 H), 1.3 (s, 3 H), 1.3 (s, 9 H), 2.4 (m, 2 H), 3.2 (m, 2 H), 3.8 (dd, 1 H, J = 1.33, 11.97 Hz)8 4.2 (dt, 1 H, J = 1.29, 6.61 Hz), 5.5 (d, 1 H, J = 10.21 Hz), 7.5 (m, 3 H), 7.9 (d, 2 H, J = 6.81 Hz).

(4*R*,5*S*)-5-[(Phenylsulfonyl)amino]-4-[2-(*tert*-butoxycarbonyl)ethyl]-2,2-dimethyl-1,3-dioxane (11a-*tert*-butyl ester) was prepared from crude acid **11a** as described for the 4*S*,5*S* diastereomer: yellow solid; mp 98–99 °C; ^1H NMR (250 MHz, $CDCl_3$) δ 1.2 (s, 3 H), 1.3 (s, 3 H), 1.3 (s, 9 H), 2.1 (dd, 1 H, J = 7.80, 16.11 Hz), 2.5 (dd, 1 H, J = 3.98, 16.10 Hz), 3.1 (b m, 1 H), 3.4 (m, 2 H), 4.0 (m, 1 H), 5.7 (b s, 1 H), 7.5 (m, 3 H), 7.9 (d, 2 H, J = 1.2 Hz); $[\alpha]^{20}_D$ −8.6° (*c* 0.5, $CHCl_3$). Anal. Calcd for $C_{18}H_{27}NO_6S$: C, 56.1; H, 7.1; N, 3.6. Found: C, 56.0; H, 7.0; N, 3.6.

***tert*-Butyl (3*S*,4*S*)-4-[(Phenylsulfonyl)amino]-3,5-dihydroxypentanoate (12).** To 200 mg (0.52 mmol) of the *tert*-butyl ester of 1,3-dioxane **11s** in 20 mL of methanol was added five drops of saturated HCl in methanol, and the solution was stirred at room temperature for 3 h. Water (50 mL) was added, and the reaction mixture was extracted with $CHCl_3$ (3 × 50 mL), which was dried and evaporated. The residue was chromatographed (flash, silica, 1/1 EtOAc/hexanes) to give a quantitative yield of dihydroxy ester **12** as a white solid: mp 106–107 °C; ^1H NMR δ 1.5 (s, 9 H), 2.3 (dd, 1 H, J = 3.98, 16.88 Hz), 2.4 (dd, 1 H, J = 9.0, 16.96 Hz), 3.2 (b m, 2 H), 3.4 (m, 1 H), 3.6 (m, 1 H), 4.0 (d, 1 H, J = 3.2 Hz), 4.2 (m, 1 H), 5.9 (d, 1 H, J = 8.91 Hz), 7.5 (m, 3 H)8 7.9 (d, 2 H); $[\alpha]^{20}_D$ −30.3° (*c* 0.4, $CHCl_3$).

***tert*-Butyl (3*R*,4*S*)-4-[(phenylsulfonyl)amino]-3,5-dihydroxypentanoate** was prepared form the *tert*-butyl ester of 1,3-dioxane **11a** as described for the 3*S*,4*S* diastereomer: mp 97–98

°C; ^{1}H NMR δ 1.4 (s, 9 H), 2.4 (dd, 1 H, J = 9.4, 16.44 Hz) 2.6 (dd, 1 H, J = 2.50, 16.12 Hz), 3.2 (b m, 2 H), 3.3 (m, 1 H), 3.8 (b d, 1 H, J = 10.18 Hz)8 4.0 (b s, 2 H), 6.1 (d, 1 H, J = 8.84 Hz), 7.5 (m, 3 H), 7.9 (d, 2 H); $[\alpha]^{20}_D$ −18.2° (c 0.16, $CHCl_3$). Anal. Calcd for $C_{15}H_{23}NO_6S \cdot {}^1/_2H_2O$: C, 50.8; H, 6.8; N, 3.9. Found: C, 50.5; H, 6.5; N, 3.9.

General Procedure for Pt/O_2 Oxidation of Diols to Hydroxy Acids. To 0.30 mmol of diol in 10 mL of water at 60 °C (if necessary for homogeneity, EtOAc was used as a cosolvent and the reaction was conducted in water/EtOAc, 4/1) was added 3 mL of i-PrOH and 50 wt % of freshly prepared PtO_2[21] that had been prereduced with H_2 in 5 mL of water. Oxygen was bubbled through the suspension at 60 °C until either all of the starting material had been consumed or a higher R_f spot began to appear on TLC, usually 18 h. This spot was an indication that overoxidation of the secondary alcohol to ketone was taking place followed by decarboxylation of the resulting β-keto acid to yield a less polar ketone. The reaction mixture was cooled to room temperature, and the catalyst was removed by filtration (Whatman no. 50 hardened filter paper). For hydroxyproline, hydroxyglutamic acid, and hydroxymethionine this filtrate was simply evaporated to dryness and the crude residue was taken on to subsequent reactions. For hydroxypipecolic acid and hydroxylysine the filtrate was made alkaline (pH 9, K_2CO_3) and extracted with 4/1 $CHCl_3$/i-PrOH (3 × 30 mL) to remove any unreacted starting material and higher R_f product. The aqueous phase was then acidified to pH 1 (concentrated H_3PO_4) and extracted again with 4/1 $CHCl_3$/i-PrOH (3 × 30 mL). This second series of organic extracts was dried and evaporated to yield N-protected hydroxy amino acid in from 80 to 87% yield.

Esterification of Crude Products from Pt/O_2 Oxidation. The crude hydroxy acid, obtained by evaporation of the solvent in the previous oxidation, was suspended in 20 mL of 4/1 *tert*-butyl alcohol/CH_2Cl_2, 480 mg (2.4 mmol) of *N,N'*-diisopropyl-*O-tert*-butylisourea was added, and the solution was refluxed for 48 h. Water was added to the reaction mixture, the mixture was cooled to room temperature, and then it was stirred for an additional hour. After filtration and concentration of the filtrate to 10 mL, the aqueous solution was extracted with 4/1 $CHCl_3$/i-PrOH (3 × 20 mL), which was dried and evaporated. The residue was chromatographed (preparative TLC, 500 μm, 1/1 EtOAc/hexanes) to yield the product. Only one of the two diastereomers in each of the three series was so treated.

Removal of the *N*-Phenylsulfonyl Protecting Group. In all cases, the *N*-phenylsulfonyl hydroxy amino acids or esters were deprotected to the free amines by the recently described electrochemical reduction.[9]

Di-*tert*-butyl (2*R*,3*S*)-*N*-(Phenylsulfonyl)-3-hydroxyglutamate (13). The diol **12** was oxidized to **(2*R*,3*S*)-*N*-(phenylsulfonyl)-3-hydroxyglutamic acid γ-*tert*-butyl ester** [^{1}H NMR (acetone-d_6) δ 1.5 (s, 9 H), 2.5 (dd, 1 H, J = 8.92, 14.28 Hz), 2.7 (dd, 1 H, J = 5.35, 14.30 Hz), 4.1 (m, 1 H), 4.3 (m, 1 H), 6.8 (b d, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H); for the diastereomeric **(2*R*,3*R*)-*N*-(phenylsulfonyl)-3-hydroxyglutamic acid γ-*tert*-butyl ester**: ^{1}H NMR (acetone-d_6) δ 1.4 (s, 9 H), 2.5 (ddd, 2 H, J = 5.93, 7.51, 16.52 Hz), 4.1 (b d, 1 H, J = 6.36 Hz), 4.5 (dt, 1 H, J = 2.33, 7.55 Hz), 6.4 (b d, 1 H, J = 8.40 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H)] by the general Pt/O_2 oxidation procedure, followed by direct esterification of the acid. The di-*tert*-butyl ester **13** was obtained in 85% yield from diol **12**: ^{1}H NMR δ 1.2 (s, 9 H), 1.5 (s, 9 H), 2.5 (m, 2 H), 3.2 (d, 1 H, J = 5.91 Hz), 3.8 (dd, 1 H, J = 6.46, 9.36 Hz), 4.1 (m, 1 H), 5.4 (d, 1 H, J = 9.19 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ −10.0° (c 0.6, $CHCl_3$). Anal. Calcd for $C_{19}H_{29}NO_7S$: C, 54.9; H, 7.0; N, 3.4. Found: C, 54.9; H, 7.1; N, 3.5.

Di-*tert*-butyl (2*R*,3*S*)-3-hydroxyglutamate (14) was obtained in 85% yield by the general electrolytic procedure for removal of the phenylsulfonyl group. Instead of isolation by ion exchange, the product was extracted into $CHCl_3$ and then chromatographed with 1/9 i-PrOH/$CHCl_3$: ^{1}H NMR (acetone-d_6) δ 1.2 (s, 9 H), 1.5 (s, 9 H), 2.5 (dd, 1 H, J = 3.23, 16.74 Hz), 3.4 (m, 1 H), 3.6 (m, 1 H), 4.2 (quin, 1 H, J = 3.60 Hz); MS m/e calcd for $C_{13}H_{25}NO_5$ 275.3422, found 275.3419.

(4*S*,5*S*)-5-[(Phenylsulfonyl)amino]-2,2-dimethyl-4-(3-hydroxypropyl)-1,3-dioxane (15). To 100 mg (0.32 mmol) of **9s** in 20 mL of THF at room temperature was added 0.18 mL (0.16 mmol) of borane–THF complex, and the mixture was stirred for 1 h. Water (0.5 mL) was added, and the solution was warmed to 45 °C, and then 0.5 mL of 3 M NaOH was added followed by 0.5 mL of 30% H_2O_2. The resulting emulsion was stirred for 0.5 h and then cooled to room temperature, the layers were separated, and the aqueous phase was extracted with diethyl ether (2 × 10 mL) before the organics were combined, dried, and evaporated to yield 100 mg (0.31 mmol, 91%) of alcohol **15** as a colorless viscous oil: ^{1}H NMR δ 1.3 (m, 8 H), 1.5 (m, 2 H), 2.2 (b s, 1 H), 3.15 (dd, 1 H, J = 1.73, 9.98 Hz), 3.3 (dd, 1 H, J = 1.66, 12.27 Hz), 3.5 (m, 2 H), 3.8 (m, 2 H), 5.5 (d, 1 H, J = 10 Hz), 7.5 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ 14.2° (c 1.73, $CHCl_3$). Anal. Calcd for $C_{15}H_{23}NO_5S$: C, 54.7; H, 7.0; N, 4.2. Found: C, 54.6; H, 7.1; N, 4.2.

(4*R*,5*S*)-5-[(Phenylsulfonyl)amino]-2,2-dimethyl-4-(3-hydroxypropyl)-1,3-dioxane was prepared in the same way as diastereomer **(4*S*,5*S*)-15**. It was a colorless oil: ^{1}H NMR δ 1.4 (ds, 6 H), 1.4 (b m, 3 H), 1.6 (q, 2 H), 1.8 (m, 1 H), 3.1 (b m, 1 H), 3.6 (b m, 4 H), 5.7 (b s, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ 16.3° (c 4.0, $CHCl_3$).

(4*S*,5*S*)-5-[(Phenylsulfonyl)amino]-2,2-dimethyl-4-[3-(methylsulfonoxy)propyl]-1,3-dioxane (16). To 100 mg (0.31 mmol) of alcohol **15** in 20 mL of CH_2Cl_2 at 0 °C was added 0.11 mL (81 mg, 0.8 mmol) of triethylamine and 49 μL (73 mg, 0.64 mmol) of methanesulfonyl chloride. The mixture was stirred for 0.5 h, poured onto 30 mL of saturated $NaHCO_3$, and stirred for another 15 min, after which the layers were separated and the aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic phases was dried and evaporated to give mesylate **16** as a clear colorless oil in 92% yield (113 mg, 0.28 mmol): ^{1}H NMR δ 1.4 (m, 6 H), 1.7 (b m, 4 H), 3.0 (s, 3 H), 3.1 (m, 1 H), 3.3 (dd, 1 H, J = 1.77, 12.18 Hz), 3.9 (m, 2 H, J = 1.59, 12.06 Hz), 4.2 (m, 2 H), 5.5 (d, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H).

(4*R*,5*S*)-5-[(Phenylsulfonyl)amino]-2,2-dimethyl-4-[3-(methylsulfonoxy)propyl]-1,3-dioxane was prepared in the same way as diastereomer **(4*S*,5*S*)-16** as a colorless oil: ^{1}H NMR δ 1.3 (ds, 6 H), 1.4 (m, 1 H), 1.7 (m, 3 H), 3.0 (s, 3 H), 3.1 (m, 1 H), 3.5 (b m, 3 H), 4.1 (m, 2 H), 5.6 (d, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H).

(2*S*,3*S*)-3-Hydroxy-2-(hydroxymethyl)-1-(phenylsulfonyl)piperidine Acetonide (17). To 50 mg (0.12 mmol) of mesylate **16** in 10 mL of methanol was added 51 mg (0.37 mmol) of calcined K_2CO_3, and the mixture was stirred at room temperature for 4 h. The methanol was evaporated, and the residue was dissolved in saturated $NaHCO_3$ before being extracted with EtOAc (3 × 30 mL). The combined organic phase was dried and evaporated to yield piperidine **17** quantitatively as a clear oil: ^{1}H NMR δ 1.2 (b m, 2 H), 1.4 (ds, 6 H), 1.6 (m, 2 H), 1.7 (m, 2 H), 3.6 (b m, 2 H), 3.9 (m, 1 H), 4.1 (m, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ 78.8° (c 2.2, $CHCl_3$). Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.9; H, 6.8; N, 4.5. Found: C, 57.6; H, 6.8; N, 4.4.

(2*S*,3*R*)-3-Hydroxy-2-(hydroxymethyl)-1-(phenylsulfonyl)piperidine acetonide was obtained in the same manner as diastereomer **(2*S*,3*S*)-17** as a clear oil: ^{1}H NMR δ 1.3 (b m, 1 H), 1.4 (ds, 6 H), 1.8 (b m, 3 H), 2.4 (m, 2 H), 3.8 (m, 1 H), 4.0 (dq, 1 H, J = 4.23, 9.16, 11.20 Hz), 4.3 (dd, 1 H, J = 10.33, 12.18 Hz), 4.4 (dd, 1 H, J = 4.77, 12.26 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ 91.8° (c 1.0, $CHCl_3$).

General Procedure for the Hydrolysis of Acetonides to 1,3-Diols. To 0.32 mmol of the acetonide in 5 mL of MeOH was added 5 mL of 1 M aqueous HCl, and the solution was stirred at room temperature for 1 h. The solution was then evaporated, and the residue was suspended in saturated $NaHCO_3$. Extracting with 3/1 $CHCl_3$/i-PrOH (3 × 15 mL) and drying and evaporating the combined organic phase gave the 1,3-diols quantitatively.

(2*R*,3*S*)-*N*-(Phenylsulfonyl)-3-hydroxypipecolic Acid (18). When 1,3-dioxane **17** was treated with methanolic HCl under the standard conditions it was cleaved to the intermediate 1,3-diol.

(2*S*,3*S*)-3-Hydroxy-2-(hydroxymethyl)-1-(phenylsulfonyl)piperidine [^{1}H NMR (acetone-d_6) δ 1.4 (m, 1 H), 1.6 (m, 3 H), 3.0 (dt, 1 H, J = 2.71, 14.08 Hz), 3.2 (b s, 1 H), 3.6 (b

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m, 3 H), 4.0 (dd, 1 H, J = 5.46, 11.36 Hz), 4.2 (dd, 1 H, J = 5.64, 12.63 Hz), 4.6 (b s, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H)]. Oxidation under the standard Pt/O_2 conditions gave pipecolic acid **18**: ^1H NMR δ 1.5 (m, 1 H), 1.6 (m, 1 H), 1.9 (m, 2 H), 3.2 (dt, 1 H, J = 12.55 Hz), 3.6 (dd, 1 H, J = 1.63, 12.69 Hz)8, 4.4 (d, 1 H, J = 2.13 Hz), 4.8 (s, 1 H), 5.9 (s, 2 H), 7.5 (m, 3 H) 7.9 (m, 2 H).

The diastereomeric **(2*R*,3*R*)-*N*-(phenylsulfonyl)-3-hydroxypipecolic acid [(2*R*,3*R*)-18]** was obtained in the same way via the intermediate 1,3-diol, **(2*S*,3*R*)-3-hydroxy-2-(hydroxymethyl)-1-(phenylsulfonyl)piperidine** [^1H NMR δ 1.3 (m, 1 H), 1.7 (m, 3 H), 2.6 (b s, 1 H), 2.8 (b s, 1 H), 3.1 (dt, 1 H, J = 2.97, 12.02 Hz), 3.7 (m, 3 H), 4.0 (d, 1 H, J = 2.16 Hz), 4.1 (dt, 1 H, J = 1.44, 6.95 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H)]. For **(2*R*,3*R*)-18**: ^1H NMR (acetone-d_6) δ 1.4 (m, 1 H), 1.6 (dt, 1 H, J = 3.72, 13.19 Hz), 1.7 (m, 1 H), 1.9 (dt, 1 H, J = 3.66, 12.98 Hz), 3.3 (dt, 1 H, J = 2.98, 12.68 Hz), 3.6 (m, 1 H), 4.3 (dd, 1 H, J = 2.87, 5.71 Hz), 4.7 (d, 1 H, J = 2.50 Hz), 6.2 (s, 2 H), 7.6 (m, 3 H), 7.9 (m, 2 H). Anal. Calcd for $C_{12}H_{15}NO_5S\cdot{}^3/_4H_2O$: C, 48.2; H, 5.6; N, 4.7. Found: C, 48.3; H, 5.3; N, 4.6.

(2*R*,3*R*)-3-Hydroxypipecolic acid (19) was obtained by electrolytic cleavage of the phenylsulfonyl group from **(2*R*,3*R*)-18** in 88% yield: ^1H NMR (D_2O) δ 1.7 (m, 2 H), 2.0 (m, 2 H), 3.1 (m, 1 H), 3.3 (m, 1 H), 3.6 (d, 1 H, J = 6.93 Hz), 4.1 (m, 1 H); ^{13}C NMR (500 MHz, D_2O) δ 21.36, 30.79, 45.06, 64.76, 68.61, 173.13; MS (EI) m/e calcd for $C_5H_{10}NO$ ($C_6H_{11}NO_3 - CO_2$) 100.1397, found 100.1757.

(4*S*,5*S*)-5-[(Phenylsulfonyl)amino]-2,2-dimethyl-4-(3-azidopropyl)-1,3-dioxane (20). To 50 mg (0.15 mmol) of mesylate **16** in 10 mL of DMF at 80 °C was added 59 mg (0.9 mmol) of freshly activated NaN_3[22] and 0.9 mg (0.015 mmol) of NaI. The mixture was stirred for 18 h and cooled to room temperature, and the DMF was evaporated with a Kugelrohr apparatus. The residue was dissolved in water and extracted into 4/1 $CHCl_3$/i-PrOH (3 × 30 mL), the extracts were combined, dried, and evaporated, and the residue was chromatographed (preparative TLC, 500 μm, 5% i-PrOH in $CHCl_3$) to yield 43 mg (0.12 mmol, 78%) of azide **20** as a yellow oil: ^1H NMR δ 1.2 (b m, 2 H), 1.3 (2 s, 6 H), 1.6 (b m, 2 H), 3.2 (b m 3 H), 3.4 (dd, 1 H, J = 1.9, 12.1 Hz), 3.9 (b m, 2 H), 5.4 (b d, 1 H, J = 10.01 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H).

(4*R*,5*S*)-5-[(Phenylsulfonyl)amino]-2,2-dimethyl-4-(3-azidopropyl)-1,3-dioxane was prepared in the same manner as described for diastereomer **(4*S*,5*S*)-20** as a yellow oil: ^1H NMR δ 1.3 (m, 1 H), 1.4 (ds, 6 H), 1.6 (m, 3 H), 3.1 (b m, 3 H), 3.5 (dd, 2 H, J = 9.20, 11.62 Hz), 3.6 (dd, 1 H, J = 5.48, 11.63 Hz), 5.4 (d, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H).

(4*S*,5*S*)-5-[(Phenylsulfonyl)amino]-2,2-dimethyl-4-(3-aminopropyl)-1,3-dioxane (21). To 250 mg (0.76 mmol) of azide **20** in 40 mL of MeOH was added 75 mg (0.33 mmol) of PtO_2 (freshly prepared), and the mixture was stirred with H_2 (1 atm) for 3 h. The catalyst was removed by filtration through Celite, and the filtrate evaporated to give amide **21** quantitatively as a clear oil: ^1H NMR δ 1.2 (s, 3 H), 1.3 (s, 3 H), 1.1–1.3 (m, 4 H), 2.4 (b s, 1 H), 2.6 (t, 2 H, J = 8.6 Hz), 3.2 (d, 1 H, J = 2.9 Hz), 3.4 (dd, 1 H, J = 3.6, 17.8 Hz), 3.9 (m, 2 H), 7.5 (m, 3 H), 7.9 (m, 2 H); MS m/e calcd for $C_{15}H_{24}NO_4S$ 328.4240, found 328.4443.

(4*R*,5*S*)-5-[(Phenylsulfonyl)amino]-2,2-dimethyl-4-(3-aminopropyl)-1,3-dioxane was prepared as described for diastereomeric amine **(4*S*,5*S*)-21** and obtained as a clear oil: ^1H NMR δ 1.2 (m, 1 H), 1.3 (s, 3 H), 1.4 (s, 3 H), 1.6 (m, 2 H), 1.7 (m, 1 H), 2.7 (t, 2 H, J = 6.17 Hz), 3.2 (dd, 1 H, J = 7.49, 16.89 Hz), 3.5 (b d, 2 H, J = 7.59 Hz), 3.7 (b t, 1 H, J = 8.22 Hz), 5.0 (b s, 3 H), 7.5 (m, 3 H), 7.9 (m, 2 H).

(2*S*,3*S*)-3-Hydroxy-2,6-bis[(phenylsulfonyl)amino]hexanol (22). To 100 mg (0.29 mmol) of amine **21** in 30 mL of 1/1 THF/water was added 100 mg (0.73 mmol) of K_2CO_3 and 74 μL (0.58 mmol) of phenylsulfonyl chloride. The mixture was stirred overnight at room temperature and then concentrated to 10 mL and adjusted to pH 6 (1 M H_3PO_4) before extracting with CH_2Cl_2 (3 × 20 mL). The combined organic phase was dried and evaporated to yield 122 mg (0.26 mmol, 90%) of the isopropylidene bis(sulfonamide) as a clear oil: ^1H NMR δ 1.4 (ds, 6 H), 1.5 (m, 3 H), 1.8 (m, 1 H, J = 3.22 Hz), 2.9 (dd, 2 H, J = 1.99, 5.97 Hz), 3.1 (dd, 1 H, J = 1.42, 10.05 Hz), 3.3 (dd, 1 H, J = 1.60, 12.18 Hz), 3.8 (m, 2 H), 5.1 (t, 1 H, J = 6.0 Hz), 5.5 (d, 1 H, J = 10.03 Hz), 7.5 (m, 6 H), 7.9 (d, 4 H). In general this intermediate **(4*S*,5*S*)-5-[(phenylsulfonyl)amino]-2,2-dimethyl-4-[3-[(phenylsulfonyl)amino]propyl]-1,3-dioxane** was not isolated, but the isopropylidene group was hydrolyzed in the same reaction simply by adding 1 N HCl until pH 1 and by stirring an additional 3 h to give **(2*S*,3*S*)-22** as a clear oil: ^1H NMR δ 1.2 (m, 1 H), 1.5 (m, 3 H), 2.8 (septet, 2 H, J = 6.86 Hz), 3.2 (m, 1 H), 3.4 (m, 1 H), 3.6 (b s, 2 H), 3.7 (m, 1 H), 3.8 (m, 1 H), 5.6 (t, 1 H, J = 6.0 Hz), 6.0 (d, 1 H, J = 8.71 Hz), 7.5 (m, 6 H), 7.9 (m, 4 H).

Diastereomeric **(2*S*,3*R*)-22** was obtained in an analogous manner: ^1H NMR δ 1.2 (m, 1 H), 1.6 (b m, 3 H), 2.0 (b s, 2 H), 3.0 (m, 1 H), 3.1 (m, 1 H), 3.4–3.6 (m, 4 H), 5.6 (t, 1 H, J = 5.97 Hz), 6.2 (d, 1 H, J = 8.35 Hz)8 7.6 (m, 6 H), 7.9 (m, 4 H); MS m/e calcd for $C_{18}H_{24}N_2O_6S_2$ 428.5214, found 428.5211.

(2*R*,3*S*)-3-Hydroxy-2,6-bis[(phenylsulfonyl)amino]hexanoic acid (23). Oxidation of diol **22** by the general procedure using Pt/O_2 gave the hydroxy acid **23**: ^1H NMR δ 1.2–1.6 (b m, 4 H)8 2.8 (b m, 2 H), 3.2 (b s, 1 H), 3.6 (b s, 1 H), 3.8 (b m, 1 H), 5.4 (t, 1 H), 6.1 (d, 1 H), 7.5 (m, 6 H), 7.9 (m, 4 H); $[\alpha]^{20}_D$ −28.6° (c 0.24, MeOH). Anal. Calcd for $C_{18}H_{22}NO_7S_2\cdot H_2O$: C, 46.9; H, 5.2; N, 6.1. Found: C, 46.7; H, 4.9; N, 5.9.

(2*R*,3*R*)-3-Hydroxy-2,6-bis[(phenylsulfonyl)amino]hexanoic acid was prepared in the manner described for its diastereomer **(2*R*,3*S*)-23**: ^1H NMR (acetone-d_6) δ 1.4–1.8 (b m, 4 H), 2.9 (dd, 2 H, J = 6.35, 12.61 Hz), 3.9 (m, 1 H, J = 3.59 Hz), 6.5 (b t, 1 H, J = 5.32 Hz), 6.7 (b d, 1 H, J = 8.15 Hz), 7.6 (m, 6 H), 7.9 (m, 4 H). Anal. Calcd for $C_{18}H_{22}NO_7S_2$: C, 48.9; H, 5.0; N, 6.3. Found: C, 48.7; H, 5.0; N, 6.0.

(2*R*,3*S*)-3-Hydroxylysine (24) was obtained in 76% yield from the bis(*N*-phenylsulfonyl) derivative **23** by the general electrolytic cleavage process: ^1H NMR (D_2O) δ 1.6 (m, 2 H), 1.8 (m, 2 H), 3.0 (b t, 2 H), 3.3 (b s, 1 H), 3.8 (m, 1 H).

In a similar manner, the diastereomeric **(2*R*,3*R*)-24** was obtained: ^1H NMR (D_2O) δ 1.5 (m, 2 H), 1.8 (m, 2 H), 3.0 (m, 2 H), 3.6 (b s, 1 H), 4.0 (m, 1 H); ^{13}C NMR (D_2O) δ 30.04, 34.38, 45.40, 52.27, 76.10; MS m/e calcd for $C_6H_{14}N_2O_3$, MH^+, 163.194, found 163.180.

(2*S*)-2-[(Phenylsulfonyl)amino]-5-chloro-1-hydroxy-3-pentanone (25). To 50 mg (0.2 mmol) of **3a** at 0 °C was added 4 mL of a saturated solution of HCl in MeOH. The solution was stirred for 0.5 h and then evaporated to dryness, and the residue was dissolved in saturated $NaHCO_3$ and extracted with 4/1 $CHCl_3$/i-PrOH (4 × 20 mL). The extracts were combined, dried, and evaporated to yield chloro ketone **25** as a white solid: 45 mg, 0.16 mmol, 80%; ^1H NMR ($CDCl_3/D_2O$) δ 3.0 (m, 2 H), 3.6 (t, 1 H, J = 6.12 Hz), 3.8 (m, 1 H), 4.0 (m, 2 H), 7.6 (m, 3 H), 7.9 (m, 2 H). Anal. Calcd for $C_{11}H_{14}NO_4SCl$: C, 45.3; H, 4.8; N, 4.8. Found: C, 45.3; H, 5.1; N, 4.8.

(2*S*,3*S*)-3-Hydroxy-2-(hydroxymethyl)-1-(phenylsulfonyl)pyrrolidine (27). Chloro ketone **25** was reduced to chloro diol **26** by the standard reduction procedure. To 100 mg (0.34 mmol) of the resulting mixture of diastereomers of **(3*R*,-*S*,2*S*)-2-[(phenylsulfonyl)amino]-5-chloro-1,3-dihydroxypentanes (26)** in 20 mL of MeOH was added 145 mg (1.06 mmol) of K_2CO_3. The mixture was stirred at room temperature for 2 h, the solvent was evaporated, and the residue was dissolved in saturated $NaHCO_3$ (20 mL) and extracted with 4/1 $CHCl_3$/i-PrOH (3 × 20 mL). The combined organic phase was dried and evaporated to give the mixture of diastereomeric pyrrolidines in 92% yield (81 mg, 0.31 mmol), which was separated chromatographically at this stage (MPLC, silica, 0.8% i-PrOH in $CHCl_3$).

(2*S*,3*S*)-27: ^1H NMR (acetone-d_6) δ 1.5 (m, 1 H), 1.8 (m, 1 H), 3.3 (m, 1 H), 3.5 (b m, 2 H), 3.9 (d, 2 H, J = 5.71 Hz), 4.2 (dd, 1 H, J = 5.64, 11.40 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H). Anal. Calcd for $C_{11}H_{15}NO_4S$: C, 51.4; H, 5.9; N, 5.4. Found: C, 51.7; H, 6.0; N, 5.3.

(2*S*,3*R*)-27: ^1H NMR (acetone-d_6) δ 1.7 (td, 1 H, J = 4.22, 6.99, 12.39 Hz), 2.1 (m, 1 H), 2.9 (s, 1 H), 3.2 (dq, 1 H, J = 6.44, 8.82, 11.02 Hz), 3.4 (dd, 1 H, J = 1.9, 8.12 Hz), 3.5 (m, 1 H), 3.7 (d, 1 H, J = 2.52 Hz), 3.8 (m, 1 H), 4.0 (dt, 1 H, J = 1.14, 5.81

(22) To activate sodium azide, a slurry was prepared with a mortar and pestle of NaN_3 and hydrazine hydrate. This slurry was transferred to a 500-mL Erlenmeyer flask, and hot water was added sparingly until all solids dissolved. The solution was allowed to cool to room temperature and the NaN_3 was precipitated with acetone. Solid was collected by vacuum filtration and thoroughly dried in vacuo before use.

Hz), 4.3 (b s, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H).

Oxidation of diols **27** by the general Pt/O_2 procedure yielded the corresponding prolines.

(2*R*,3*R*)-*N*-(Phenylsulfonyl)-3-hydroxyproline: ^1H NMR (D_2O) δ 1.7 (dd, 1 H, J = 3.30, 10.43 Hz), 1.9 (m, 1 H), 3.3 (m, 1 H), 3.5 (m, 1 H), 4.1 (b s, 1 H), 4.4 (dd, 1 H, J = 1.88, 3.90 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H).

(2*R*,3*S*)-*N*-(Phenylsulfonyl)-3-hydroxyproline: ^1H NMR (D_2O) δ 1.7 (m, 1 H), 1.8 (m, 1 H), 3.4 (m, 1 H), 3.6 (m, 1 H), 4.3 (d, 1 H, J = 6.48 Hz), 4.5 (q, 1 H, J = 5.23, 11.52 Hz), 7.5 (m, 3 H), 7.9 (m, 2 H).

Esterification of the 2*R*,3*R* diastereomer by the standard procedure gave **(2*R*,3*R*)-*N*-(phenylsulfonyl)-3-hydroxyproline *tert*-butyl ester (28)** in 78% yield from diol **27**: ^1H NMR δ 1.4 (s, 9 H), 1.9 (m, 1 H, J = 6.54 Hz), 2.2 (m, 1 H), 3.5 (dd, 1 H, J = 3.01, 9.52 Hz), 3.6 (dt, 1 H, J = 2.52, 6.33 Hz), 4.1 (b s, 1 H), 4.4 (b m, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H); $[\alpha]^{20}_D$ 25.4° (*c* 3.9, CH_3CN). Anal. Calcd for $C_{15}H_{21}NO_5S$: C, 55.0; H, 6.5; N, 4.3. Found: C, 54.8; H, 6.5; N, 4.4.

Electrolytic removal of the phenylsulfonyl group followed by ion-exchange chromatography gave **(2*R*,3*R*)-3-hydroxyproline** in 85% yield: ^1H NMR (D_2O) δ 2.0 (m, 1 H), 2.1 (m, 1 H), 3.5 (b m, 3 H), 4.1 (d, 1 H, J = 3.67 Hz); MS *m/e* calcd for $C_5H_9NO_3$ 131.0584, found 131.0723.

Benzyl[(2*R*,3*R*)-2,4-dihydroxy-3-[(phenylsulfonyl)amino]-1-butyl]methylsulfonium Triflate (32). To 145 μL (1.02 mmol) of trifluoromethanesulfonic anhydride in CH_2Cl_2 (15 mL) at −45 °C was added a solution of 188 μL (1.02 mmol) of benzyl alcohol and 174 μL (1.02 mmol) of Hunig's base in 5 mL of CH_2Cl_2, and the solution was stirred for 15 min.[15] Thioether **31** (280 mg, 0.85 mmol) in 5 mL of CH_2Cl_2 was added, and after the mixture was stirred for 0.5 h, water (40 mL) was added and the mixture was warmed to room temperature where it was stirred an additional 15 min. The layers were separated, and the aqueous phase was extracted twice more with CH_2Cl_2 (40 mL). The combined organic phase was dried and evaporated, and the residue was chromatographed (flash, silica, 10% i-PrOH in $CHCl_3$) to yield sulfonium salt **32** (384 mg, 0.72 mmol, 85%) as a 2/1 mixture of diastereomers at the sulfur: ^1H NMR (acetone-d_6) δ 2.9 (s, 2 H), 3.0 (s, 1 H), 3.2-3.6 (b m, 4 H), 4.0 (m, 1 H), 4.8 (m, 3 H), 7.2 (b d, 1 H), 7.6 (m, 8 H), 7.9 (m, 2 H); MS (EI) *m/e* calcd for $C_{12}H_{15}NO_6S_3F_3$ ($C_{19}H_{24}NO_7S_3F_3$ − C_7H_7 − H_2O) 422.0014, found 422.0422.

The corresponding sulfonium salt **(2*S*,3*S*)-32** was obtained in 82% yield: ^1H NMR (acetone-d_6) δ 2.6 (s, 2 H), 2.7 (s, 1 H), 3.2 (m, 2 H), 3.5 (b m, 2 H), 3.7 (m, 1 H), 4.4 (m, 1 H), 4.6 (dd, 1 H, J = 5.44, 14.68 Hz), 6.9 (d, 1 H), 7.3 (m, 5 H), 7.6 (m, 3 H), 7.9 (m, 2 H).

(2*R*,3*R*)-3-Hydroxy-*N*-(phenylsulfonyl)methionine (34). To 300 mg of crude **33**, obtained directly from a Pt/O_2 oxidation of **32**, in 300 mL of MeOH was added 100 mg of 10% Pd/C, and the mixture was stirred under a balloon of hydrogen at room temperature for 0.5 h. The catalyst was removed by filtration, the filtrate was evaporated to dryness, and the residue was dissolved in water (30 mL) and extracted with 4/1 $CHCl_3$/i-PrOH (3 × 30 mL). The combined organic phase was dried and evaporated to give recovered **(*S*,*R*)-30** that can be recycled (110 mg, 0.38 mmol, 44% recovered). The remaining aqueous phase was evaporated to yield crude **34** as a yellow oil (70 mg, 0.27 mmol) in 49% yield, based on recovered **30**: ^1H NMR (acetone-d_6) δ 1.9 (m, 1 H), 2.0 (s, 3 H), 2.2 (m, 1 H), 3.6 (m, 2 H), 7.6 (m, 3 H), 7.9 (m, 2 H).

(2*R*,3*S*)-3-Hydroxy-*N*-(phenylsulfonyl)methionine was prepared similarly and obtained as a yellow oil along with recovered diol **(*R*,*R*)-30**: 57% yield from **31**; ^1H NMR (acetone-d_6) δ 2.0 (s, 3 H), 2.2 (m, 1 H), 2.5 (m, 1 H), 3.5 (m, 1 H), 3.9 (m, 1 H), 6.5 (b s, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H).

(2*R*,3*R*)-*N*-(Phenylsulfonyl)-3-hydroxymethionine *tert*-Butyl Ester (35). Application of the standard esterification procedure to acid **34** gave *tert*-butyl ester **35**: ^1H NMR δ 1.1 (s, 9 H), 2.0 (s, 3 H), 2.6 (dd, 1 H, J = 7.70, 13.80 Hz), 2.7 (dd, 1 H, J = 5.74, 13.82 Hz), 3.2 (m, 1 H), 3.5 (m, 1 H), 5.4 (d, 1 H, J = 9.02 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H). Anal. Calcd for $C_{15}H_{23}NO_5S_2$: C, 49.8; H, 6.4; N, 3.9. Found: C, 49.8; H, 6.8; N, 4.1.

Electrolytic cleavage of the phenylsulfonyl group from acid **34** gave **(2*R*,3*R*)-3-hydroxymethionine (36)** in 73% yield: ^1H NMR (D_2O) δ 2.2 (s, 3 H), 2.4 (m, 2 H), 4.0 (m, 1 H), 4.1 (b s, 1 H).

(4*S*,5*S*)-5-[(Phenylsulfonyl)amino]-2,2-dimethyl-4-propyl-1,3-dioxane. To 400 mg (1.28 mmol) of olefin **9s** in 50 mL of THF was added 80 mg of 10% Pt/C, and the mixture was shaken with hydrogen (50 psi, 40 °C) overnight. The catalyst was removed by filtration, and the filtrate was evaporated to dryness to yield the saturated product quantitatively: ^1H NMR δ 0.9 (m, 5 H), 1.3 (m, 8 H), 3.1 (dd, 1 H, J = 1.72, 10.0 Hz), 3.4 (dd, 1 H, J = 1.59, 12.0 Hz), 3.8 (m, 2 H), 5.5 (d, 1 H, J = 10.0 Hz), 7.6 (m, 3 H), 7.9 (m, 2 H); IR (thin film) 3310, 2950, 1350, 1180 cm^{-1}.

(4*S*,5*S*)-5-Amino-2,2-dimethyl-4-propyl-1,3-dioxane. To the crude (4*S*,5*S*)-5-[(phenylsulfonyl)amino]-2,2-dimethyl-4-propyl-1,3-dioxane, obtained in the above reaction, in 10 mL of refluxing ammonia was added sodium until a blue color persisted for a period of 10 min, and then ammonium chloride was added to dissipate the color. After the ammonia was allowed to evaporate, the residue was dissolved in water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was dried and evaporated to give the free amine in 90% yield (200 mg, 1.15 mmol): ^1H NMR δ 0.9 (m, 5 H), 1.4 (ds, 6 H), 1.5 (m, 2 H), 3.7 (dd, 1 H, J = 1.8, 13.5 Hz), 3.9 (m, 2 H), 4.1 (dd, 1 H, J = 2.1, 13.5 Hz).

Mandelic Acid Amide of (4*S*,5*S*)-5-Amino-2,2-dimethyl-4-propyl-1,3-dioxane. To 100 mg (0.7 mmol) of D,L- or L-mandelic acid in 5 mL of THF at −15 °C was added 77 μL (71 mg, 0.7 mmol) of 4-methylmorpholine and 91 μL (96 mg, 0.7 mmol) of isobutyl chloroformate. After stirring for 10 min, a solution of 110 mg (0.64 mmol) of (4*S*,5*S*)-5-amino-2,2-dimethyl-4-propyl-1,3-dioxane in 5 mL of THF was added, and stirring was continued for an additional 0.5 h. The reaction was quenched with 10% citric acid (10 mL) and extracted with 3/1 $CHCl_3$/i-PrOH (3 × 20 mL). These extracts were combined, washed with saturated $NaHCO_3$ (1 × 50 mL), dried, and evaporated, giving the coupled product in 85% yield (170 mg, 0.6 mmol).

(2*R*,3*S*)-3-Hydroxy-2-(methoxycarbonyl)-1-(phenylsulfonyl)piperidine. To 3 mg (10 μmol) of hydroxy acid **18** in 1 mL of diethyl ether at 0 °C was added 1 mL of 0.2 M diazomethane in .1 mL of ether. The solution was stirred for 5 min at 0 °C and then warmed to room temperature, and the excess diazomethane was allowed to evaporate. After the diethyl ether was evaporated, the residue was subjected to HPLC: ^1H NMR δ 1.6 (m, 3 H), 1.9 (m, 1 H), 2.8 (m, 1 H), 3.1 (m, 1 H), 3.5 (s, 3 H), 3.8 (m, 2 H), 7.6 (m, 3 H), 7.9 (m, 2 H).

(2*R*,3*R*)-3-Hydroxy-2-(methoxycarbonyl)-1-(phenylsulfonyl)piperidine: ^1H NMR δ 1.5 (m, 2 H), 1.9 (m, 2 H), 3.2 (dt, 1 H), 3.6 (s, 3 H), 3.8 (m, 2 H), 4.2 (m, 1 H), 7.6 (m, 3 H), 7.9 (m, 2 H).

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