# Studies toward the Large-Scale Synthesis of the HIV Proteinase Inhibitor Ro 31-8959

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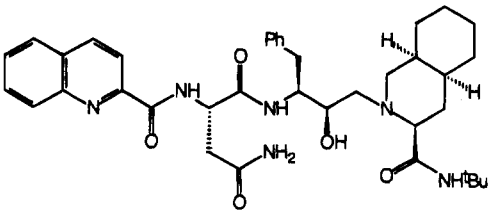
Ro 31-8959 (**1**), a potent and selective inhibitor of HIV proteinase, is currently in phase III clinical trials. Six approaches for the large-scale synthesis of this compound have been studied. All routes employ an initial disconnection to an electrophilic L-phenylalanine homologue equivalent **13** and the decahydroisoquinoline derivative **5**. They differ in adopting either an epoxide, a cyclic sulfate, or an aldehyde as the electrophilic entity and develop chirality from L-phenylalanine, dimethyl D-tartrate, or a Sharpless epoxidation. The preferred route starts from *N*-phthaloyl-L-phenylalaninyl chloride and uses tris((trimethylsilyl)oxy)ethene to effect homologation to hydroxy ketone **30**, which is elaborated in a five-step two-pot procedure to *N*-phthaloyl epoxide **33** and hence **1**. Kilogram quantities of Ro 31-8959 have been prepared using this route.

## Introduction

Since the identification of the human immunodeficiency virus (HIV) as the causative entity of the acquired immune deficiency syndrome (AIDS), extensive efforts have been made to elucidate the replicative processes of the virus and to identify suitable targets for antiviral therapy. One particularly attractive target is the HIV-encoded proteinase which has been shown to be essential for core protein maturation and viral infectivity.[1] This molecular target has been the subject of several recent reviews.[2]

We have previously reported preliminary structure–activity relationships of a series of inhibitors of HIV proteinase which contain the hydroxyethylamine transition-state mimetic. This moiety was designed to mimic the dipeptides Phe-Pro and Tyr-Pro that occur as cleavage sequences in both the natural viral polyprotein and in synthetic substrates. Since amide bonds *N*-terminal to proline are rarely cleaved by mammalian endopeptidases, we reasoned that these inhibitors should exhibit high selectivity for the viral enzyme. These expectations were realized in Ro 31-8959 (**1**), a highly potent and selective inhibitor of HIV proteinase, which was selected for development and is currently undergoing phase III clinical trials. It is important to note that the *R* configuration of the hydroxyethylamine moiety in **1** is crucial for maximum activity,[3,4] although in some quite closely related inhibitors the *S* configuration is preferred.[5] The publication of a number of approaches to hydroxyethylamine dipeptide isosteres prompts us to report here our work directed to developing a large-scale synthesis of Ro 31-8959.




**1**

## Initial Synthesis

During the synthesis of compounds for structure–activity studies, we had used the phenylalanine-derived epoxide **6a** as the key building block for the hydroxyethylamine dipeptide isostere. This was prepared from a phenylalanine-derived mixed anhydride by treatment with diazomethane and acidolysis to afford chloromethyl ketone **2**.[6] Reduction with sodium borohydride gave an approximately 3:1 mixture of the diastereomeric alcohols **3** and **4**, which were separated by crystallization.[7] Treatment of the chlorohydrins **3** and **4** with potassium hydroxide then gave the corresponding epoxides **6a** and **7**. Assignment of the stereochemistry of the alcohols **3** and **4** was based on the $^1$H NMR spectra of the 2-oxazolidinones **11a** and **12a** obtained on treatment of the epoxides **6a** and **7** with sodium thiophenoxide. Signals due to H-5 for **11a** and **12a** appeared at $\delta$ 4.76 and 4.37, respectively, compared with values of $\delta$ 4.7–4.8 and 4.2–4.3 reported for the analogous *cis*- and *trans*-substituted

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(1) (a) Kohl, N. E.; Emini, E. A.; Schleif, W. A.; Davis, L. J.; Heimbach, J. C.; Dixon, R. A. F.; Scolnick, E. M.; Sigal, I. S. *Proc. Nat. Acad. Sci. U.S.A.* **1988**, *85*, 4686. (b) Gottlinger, H. G.; Sodroski, J. G.; Haseltine, W. A. *Proc. Nat. Acad. Sci. U.S.A.* **1989**, *86*, 5781. (c) Peng, C.; Ho, B. K.; Chang, T. W.; Chang, N. T. *J. Virol.* **1989**, *63*, 2550.

(2) (a) Martin, J. A. *Antiviral Res.* **1992**, *17*, 265. (b) Huff, J. R. *J. Med. Chem.* **1991**, *34*, 2305. (c) Wlodawer, A.; Erikson, J. W. *Annu. Rev. Biochem.* **1993**, *62*, 543. (d) Meek, T. D. *J. Enzyme Inhib.* **1993**, *6*, 65. (e) Debouk, C. *AIDS Research and Human Retroviruses* **1992**, *8*, 153. (f) Robins, T.; Plattner, J. *J. of Acquired Immune Deficiency Syndromes* **1993**, *6*, 162. (g) Clare, M. *Perspect. Drug Discovery Des.* **1993**, *1*, 49. (h) Norbeck, D. W.; Kempf, D. J. *Ann. Rep. Med. Chem.* **1991**, *26*, 141. (i) Tomasselli, A. G.; Howe, W. J.; Sawyer, T. K.; Wlodawer, A.; Heinrikson, R. L. *Chim. Oggi* **1991**, *9*, 6.

(3) (a) Roberts, N. A.; Martin, J. A.; Kinchington, D.; Broadhurst, A. V.; Craig, J. C.; Duncan, I. B.; Galpin, S. A.; Handa, B. K.; Kay, J.; Krohn, A.; Lambert, R. W.; Merrett, J. H.; Mills, J. S.; Parkes, K. E. B.; Redshaw, S.; Ritchie, A. J.; Taylor, D. L.; Thomas, G. J.; Machin, P. J. *Science* **1990**, *248*, 358. (b) Handa, B. K.; Machin, P. J.; Martin, J. A.; Redshaw, S.; Thomas, G. J. British Patent 8908035.2, 1989.

(4) Krohn, A.; Redshaw, S.; Ritchie, J. C.; Graves, B. J.; Hatada, M. H. *J. Med. Chem.* **1991**, *34*, 3340.

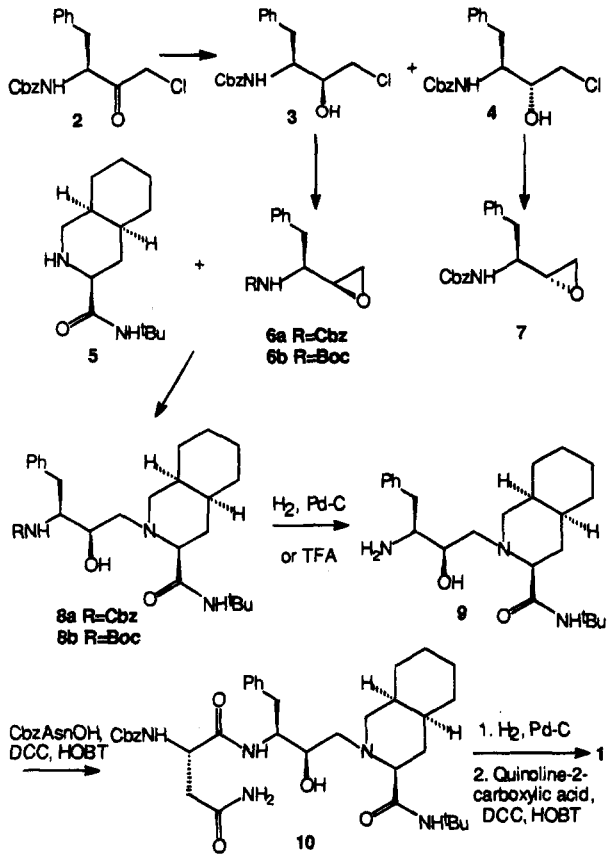
(5) Rich, D. H.; Sun, C.-Q.; Prasad, J. V. N. V.; Pathiasseril, A.; Toth, M. V.; Marshall, G. R.; Clare, M.; Mueller, R. A.; Houseman, K. *J. Med. Chem.* **1991**, *34*, 1222.

(6) Shaw, E. *Methods in Enzymology*; Hirs, C. H. W., Ed.; Academic Press: New York and London; 1967, Vol. 11, p 677.

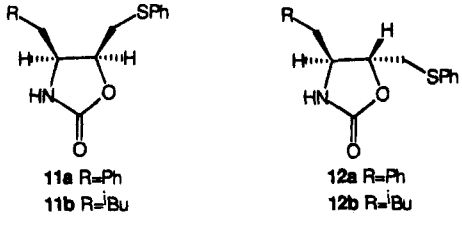
(7) For the preparation of the analogous leucine derived chlorohydrin, see: Dufour, M.-N.; Jouin, P.; Poncet, J.; Pantaloni, A.; Castro, B. *J. Chem. Soc., Perkin Trans. I* **1986**, 1895.

0022-3263/94/1959-3656$04.50/0 

**Scheme 1**




oxazolidinones **11b** and **12b** derived from *N*-Boc-L-leucine.[8] Similarly, coupling constants $J_{4,5}$ for **11a** and **12a** were 7.1 and 4.4 Hz, compared with values of 7–8 and 4–5 Hz for **11b** and **12b**. In addition, a strong NOE was observed between the 4- and 5-protons for **11a** while no such effect was seen for **12a**. The major epoxide **6a** was opened with the decahydroisoquinoline **5** to give **8a** in good yield. Deprotection gave **9**, which was coupled with *N*-Cbz-L-asparagine and further elaborated to Ro 31-8959 (**1**) as shown in Scheme 1.

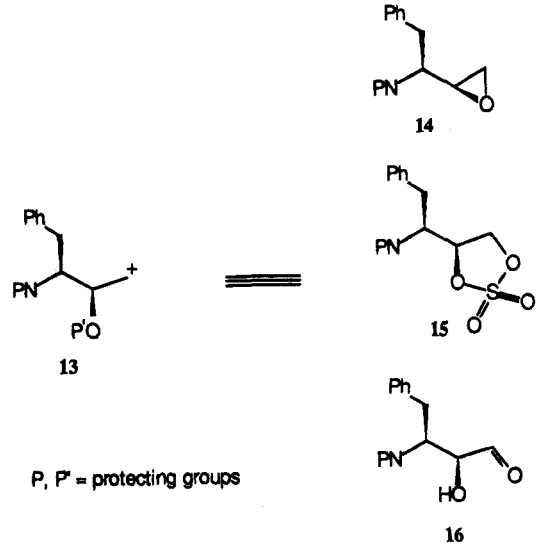



While this route was satisfactory for the preparation of small quantities of a range of analogues required for the elucidation of structure–activity relationships, the identification of Ro 31-8959 (**1**) as a candidate for clinical trials necessitated the synthesis of kilogram quantities. Therefore, an alternative synthesis which avoided the use of diazomethane, or other reagents impractical for scale up, was required.

## Alternative Syntheses

**Strategy.** We regarded our original retrosynthetic disconnection of **1**, to a chiral electrophilic phenylalanine

**Scheme 2**




homologue and the decahydroisoquinoline **5**, as the most attractive option, since this allowed us to continue using **5**, an intermediate for which we already had a convenient synthesis.[9] Therefore our objective became the development of a synthetic equivalent of electrophile **13**, such as a protected α-amino epoxide **14**, a cyclic sulfate **15**, or a β-hydroxy aldehyde **16** (Scheme 2).

Five approaches were examined. Three started from phenylalanine and required a one-carbon homologation with a diastereoselective reaction to form the alcohol chiral center. Of the remaining two routes, one employed a Sharpless epoxidation of 4-phenyl-2-buten-1-ol to generate both chiral centers, while the other used dimethyl D-tartrate which already contains both chiral centers in the starting material.

A considerable amount of information is available on the diastereoselectivity of the reactions of phenylalanine and other amino acid analogues.[10] Key to this discussion is the fact that amino acid aldehyde and ketone analogues containing a singly protected nitrogen react predominantly in a chelation-controlled fashion, whereas analogues containing doubly protected nitrogen give the Felkin–Ahn product. Wittig olefination of the singly *N*-protected L-α-amino aldehyde **17** (X = BocNH) followed by epoxidation is unsuitable for our purposes since the *u* diastereomer **19** is the predominant product.[11] The reaction of sulfonium ylides with the *N*-Boc protected α-amino aldehyde **17** (X = BocNH) is no more attractive since an approximately 1:1 mixture of the *u* **19** and *l* **20** isomers is formed.[12] Reaction of the doubly protected α-amino aldehyde **17** (X = $Bn_2N$) with a sulfonium, or an arsonium, ylide has been shown to proceed with nonchelation control to give largely the *l* diastereomer **20**.[13] However, we felt that the toxicity of the organoarsenic reagent, which gives the best selectivity, and the relatively harsh conditions often needed to cleave *N*-benzyl protecting groups would render this route unsuitable for our requirements (Scheme 3).

(8) Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487.

(9) Martin, J. A.; Redshaw, S. British Patent 8927913.7, 1989.

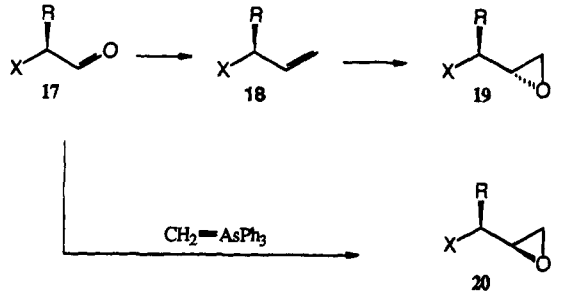
(10) Coppola, G. M.; Schuster, H. F. *Asymmetric Synthesis: Construction of Chiral Molecules using Amino Acids*; John Wiley and Sons: New York, 1987.

(11) Dellaria, J. F.; Maki, R. G.; Bopp, B. A.; Cohen, J.; Kleinert, H. D.; Luly, J. R.; Merits, I.; Plattner, J. J.; Stein, H. H. *J. Med. Chem.* **1987**, *30*, 2137.

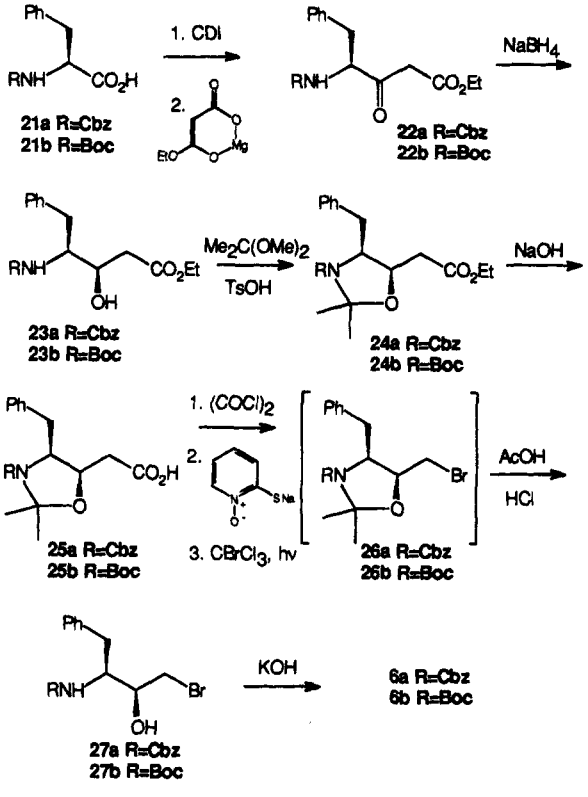
(12) Evans, B. E.; Rittle, K. E.; Homnick, C. F.; Springer, J. P.; Hirshfield, J.; Veber, D. F. *J. Org. Chem.* **1985**, *50*, 4615.

(13) Reetz, M. T.; Binder, J. *Tetrahedron Lett.* **1989**, *30*, 5425.

**Scheme 3**




**Scheme 4**

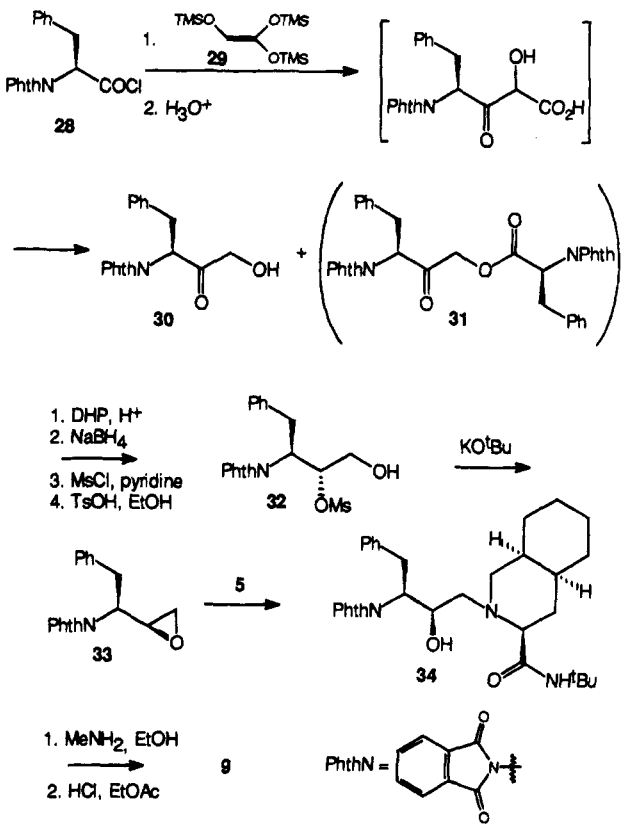



**Hydroxy Ester Route.** The preparation of 4-amino-3-keto esters and their reduction to statine derivatives in a chelation-controlled manner has been described by Maibaum and Rich.[14] This readily provides a potential synthetic intermediate with both the desired chiral centers (Scheme 4). Thus, the 3-hydroxy ester **23b** was obtained by carbonyldiimidazole activation of *N*-Boc-L-phenylalanine (**21b**) and reaction with the magnesium enolate of the half ethyl ester of malonic acid, followed by reduction with sodium borohydride. This afforded a 3:1 mixture of diastereomers in which the desired 3*R*,4*S* isomer **23b** predominated and was conveniently purified by crystallization from methylcyclohexane/ethyl acetate. The *N*-Cbz-protected hydroxy ester **23a** was prepared analogously from **21a**.

Reaction of 3-hydroxy esters **23a** or **b** with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid gave the protected derivatives **24a** or **b** in good yield and hydrolysis of the ester function then yielded the carboxylic acids **25a** or **b**. Conversion of the acids to their acid chlorides was accomplished without loss of protecting groups using oxalyl chloride in toluene in the presence of a trace of dimethylformamide. The acid chlorides were converted to the alkyl bromides **26a** or **b** by using the

(14) Maibaum, J.; Rich, D. H. *J. Org. Chem.* **1988**, *53*, 869.

**Scheme 5**

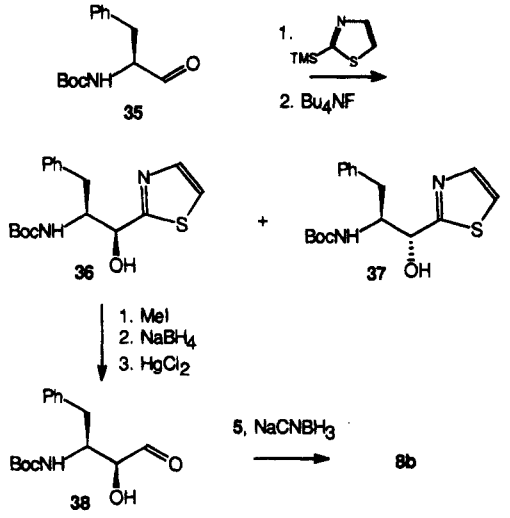



radical-mediated decarboxylative bromination procedure of Barton.[15] Since the bromides **26a** or **b** could not conveniently be separated from the 2-((trichloromethyl)thio)-pyridine byproduct, they were deprotected by acid treatment to give the bromohydrins **27a** or **b** from which unchanged 2-((trichloromethyl)thio)pyridine could easily be removed by trituration with petroleum ether. Treatment of these bromohydrins with potassium hydroxide solution yielded the desired epoxides **6a** or **b**, which were coupled with decahydroisoquinoline derivative **5** in refluxing 2-propanol. Deprotection gave the key intermediate **9**, which was elaborated to Ro 31-8959 in the usual way.

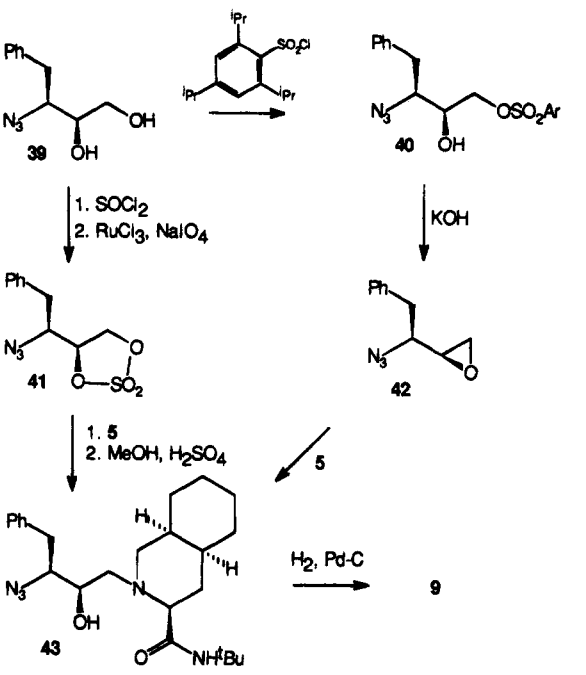
**Tris((trimethylsilyl)oxy)ethene Route.** The tris-((trimethylsilyl)oxy)ethene chemistry developed by Wissner for the preparation of α-hydroxymethyl ketones from acid chlorides offered a potentially attractive method of preparing a homophenylalanine synthon of the sort required (Scheme 5).[16] Because we expected that the benzyloxycarbonyl group would be labile under the rather forcing conditions required for the reaction, phthaloyl protection was chosen. In practice, we found thermal conditions for the condensation were superior to Lewis acid catalysis, and rather more than two equivalents of the ketene acetal **29** were required for optimal yields. Although the second equivalent is presumably acting as a scavenger for hydrogen chloride, attempts to replace it by triethylamine or lutidine resulted in the formation of essentially racemic product, presumably *via* the ketene,[17] whereas the addition of propylene oxide or styrene oxide gave lower yields of chiral material, with significant amounts (20–25%) of the ester **31** also being formed.

(15) Barton, D. H. R.; Crich, D.; Motherwell, W. B. *Tetrahedron Lett.* **1983**, *24*, 4979.
(16) Wissner, A. *J. Org. Chem.* **1979**, *44*, 4617.
(17) Rathke, M. W.; Sullivan, D. F. *Tetrahedron Lett.* **1973**, 1297.

**Scheme 6**




**Scheme 7**




As expected for an *N*-diprotected substrate, reduction of the hydroxymethyl ketone **30** using sodium borohydride gave the nonchelation-controlled *S,R*-diol as the major diastereomer. However, inversion was achieved *via* mesylate **32**. Thus, protection of the primary alcohol as the tetrahydropyranyl ether, reduction of the ketone, mesylation, and removal of the ether protecting group gave **32**. The sequence of reactions from **30** to **32** was carried out with no purification, and the required *S,R*-mesylate **32** crystallized out of the final reaction mixture in homochiral form. The mesylate was then cyclized to the protected epoxide **33** using potassium *tert*-butoxide in DMF. Reaction with the decahydroisoquinoline **5** was carried out in DMF at 120 °C, conditions that are appreciably more vigorous than were required for the singly *N*-protected epoxides **6a** or **b**. Finally, dephthaloylation to the key intermediate **9** was achieved by sequential treatment with ethanolic methylamine and hydrogen chloride in ethyl acetate, conditions that not only avoided a toxic reagent but gave slightly higher yields than the more usual hydrazine method.

**2-(Trimethylsilyl)thiazole Route.** Dondoni has reported the use of 2-(trimethylsilyl)thiazole as a synthetic equivalent of a formyl anion for the homologation of aldehydes.[18] *N*-Boc-L-phenylalaninal (**35**) would thus give the α-hydroxy aldehyde **38** ideally suited to reductive coupling with decahydroisoquinoline **5** to give the required dipeptide isostere (Scheme 6).[19] Treatment of **35** with 2-(trimethylsilyl)thiazole in THF at room temperature followed by desilylation gave a mixture of alcohols **36** and **37** in the ratio 2:3.[20] The separation of these diastereomers, which has not previously been described, was accomplished following acetylation of the mixture of alcohols with acetic anhydride in pyridine in the presence of 4-(dimethylamino)pyridine. Chromatographic separation of the acetates was then possible, and hydrolysis with ethanolic sodium hydroxide regenerated the diastereomerically pure alcohols. Conversion of **36** to the aldehyde **38** was achieved by quaternization of the thiazole nitrogen followed by borohydride reduction and mercury(II) chloride mediated hydrolysis. Reductive amination was then achieved by treating aldehyde **38** with decahydroisoquinoline **5** in the presence of sodium cyanoborohydride. Finally, removal of the protecting group with trifluoroacetic acid gave amino alcohol **9**, identical to that obtained in earlier syntheses.

**Azido Diol Routes.** The known azido diol **39**[21] was identified as an attractive synthon which contains all the required carbon atoms and stereocenters present in the epoxide. It can be synthesized with high stereoselectivity either from 2-butyne-1,4-diol using a Sharpless epoxidation to introduce the chirality or from dimethyl D-tartrate, which provides both the required chiral centers.[22] Although the azido diol could have been elaborated to the *N*-Cbz or *N*-Boc epoxides **6a** or **b**, we felt that it should be possible to use the azide as the protected form of the amine and avoid additional protection and deprotection steps (Scheme 7). Two possible azido derivatives were considered, cyclic sulfate **41** and epoxide **42**. Treatment of **39** with triisopropylbenzenesulfonyl chloride gave good selectivity for the primary alcohol and allowed isolation of the product (**40**) by crystallization. Ring closure to epoxide **42** was achieved by treatment with potassium hydroxide in ethanol.[23] Coupling with the decahydroisoquinoline derivative **5** in refluxing ethanol followed by

(18) (a) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1988**, *53*, 1748. *(b)* Dondoni, A.; Fantin, G.; Fogagnolo. M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 693. (c) Dondoni, A.; Fantin, G.; Fogagnolo, M.; Medici, A.; Pedrini, P. *J. Org. Chem.* **1989**, *54*, 702.

(19) After we had completed this work, aldehyde **38** was reported to be formed in a mixture of diastereomers from **36** and **37** and was used in a solid-phase synthetic approach to phenylalaninylproline hydroxyethylamine dipeptide isosteres. Tourwé, D.; Piron, J.; Defreyn, P.; Van Binst, G. *Tetrahedron Lett.* **1993**, *34*, 5499.

(20) Stereochemical assignments of **36** and **37** were made by comparison with published data, which were based on NMR spectral data of the diastereomeric oxazolidinones derived from them: Dondoni, A.; Fantin, G.; Fogagnolo, M.; Pedrini, P. *J. Org. Chem.* **1990**, *55*, 1439.

(21) Caron, M.; Carlier, P. R.; Sharpless, K. B. *J. Org. Chem.* **1988**, *53*, 5185.

(22) After completion of this work an alternative synthesis of the azide **39** from diethyl D-tartrate was published: Ghosh, A. K.; McKee, S. P.; Lee, H. Y.; Thompson, W. J. *J. Chem. Soc., Chem. Commun.* **1992**, 273.

(23) Since completion of this work, two related approaches to the azido epoxide **42** have been reported. (a) Ghosh, A. K.; Thompson, W. J.; Holloway, M. K.; McKee, S. P.; Duong, T. T.; Lee, H. Y.; Munson, P. M.; Smith, A. M.; Wai, J. M.; Darke, P. L.; Zugay, J. A.; Emini, E. A.; Schleif, W. A.; Huff, J. R.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 2300. (b) Bennett, F.; Girijavallabhan, V. M.; Patel, N. *J. Chem. Soc., Chem. Commun.* **1993**, 737.

hydrogenation then gave the required Ro 31-8959 precursor **9**.

Alternatively, sulfate **41** could be prepared in high (>95%) yield by treatment of the diol **39** with thionyl chloride followed by a ruthenium tetraoxide catalyzed oxidation of the cyclic sulfite intermediate.[24] The product was sufficiently pure to couple with the decahydroisoquinoline **5**. Interestingly, the sulfate **41** displayed appreciably higher reactivity than either epoxides **6a,b** or epoxide **33** and coupled with the decahydroisoquinoline derivative **5** at room temperature. The resulting sulfate monoester was hydrolyzed by treatment with refluxing methanolic sulfuric acid and hydrogenated to form the required Ro 31-8959 precursor **9**.

## Conclusions

The original synthesis of Ro 31-8959 involved the use of diazomethane and was unsuitable for large-scale production. Of the five alternative procedures investigated, three would have required further development before any significant scale-up could be undertaken. The fact that the desired *S*-alcohol **36** was the minor product of reaction of the aldehyde **35** with 2-(trimethylsilyl)-thiazole precluded this route for large-scale synthesis. In the azido diol route from 2-butyne-1,4-diol, both the overall yield of the cyclic sulfate and the atom efficiency were very high,[25] but we were concerned both about the irritant nature of the propargyl halide and about the possible instability of the alkyl azide intermediates. The use of propargyl halides is avoided in the alternative preparation of the azido diol **39** from dimethyl D-tartrate but the concern about the possible instability of the azide intermediates remained and these approaches were therefore also eliminated. Both of the remaining procedures are reasonably short. The overall yields in the hydroxy ester route (30% and 25% respectively for **6a** and **6b**) are higher than the tris((trimethylsilyl)oxy)ethene route (13%). However, concerns about the acid-labile protecting groups during the formation of the acid chloride from **25** led us to adopt the tris((trimethylsilyl)oxy)ethene process for kilogram-scale preparations.

## Experimental Section

**General.** Melting points were determined in open capillary tubes and are uncorrected. Unless otherwise indicated, solvents and reagents were used as received, and magnesium sulfate was used for drying. Flash chromatography was performed on silica gel (Sorbsil C60 40/60A) and evaporation was carried out under reduced pressure on a rotary evaporator. $^1$H NMR spectra were recorded at 300 or 400 MHz, $^{13}$C NMR at 75.5 MHz. The chemical shifts are reported in ppm relative to TMS as standard, and coupling constants are in hertz. Mass spectra were recorded on a magnetic sector spectrometer using electron ionization (EI) at 70 eV, chemical ionization (CI) using ammonia, or fast atom bombardment (FAB) using a thioglycerol matrix.

**2-[3(*S*)-(Benzyloxyformamido)-2(*R*)-hydroxy-4-phenylbutyl]-*N*-*tert*-butyldecahydro-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (8a).** A solution of **6a** (1.0 g, 3.37 mmol) and **5** (0.80 g, 3.36 mmol) in dry 2-propanol (10 mL) was stirred under nitrogen and heated at 80 °C for 6 h. After cooling, the solvent was evaporated and the residue purified by flash chromatography using ethyl acetate/hexane (1:1) for the elution to give **8a** (1.55 g, 86%) as a white foam. $^1$H NMR ($CD_3OD$) $\delta$ 1.03–2.20 (m, 14H),.1.31 (s, 9H), 2.60 (dd, 1H), 2.67 (dd, 1H), 2.78 (dd, 1H), 3.00 (dd, 1H), 3.07 (dd, 1H), 3.83 (m, 1H), 3.95 (dt, 1H), 4.90 (AB, 2H), 7.02–7.31 (m, 10H). Anal. Calcd for $C_{32}H_{45}N_3O_4$: C, 71.74; H, 8.47; N, 7.84. Found: C, 71.86; H, 8.55; N, 7.65. MS (FAB) *m/z* 536 $[M + H]^+$.

**2-(3(*S*)-Amino-2(*R*)-hydroxy-4-phenylbutyl)-*N*-*tert*-butyldecahydro-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (9).** A solution of **8a** (1.0 g, 1.87 mmol) in ethanol (50 mL) was hydrogenated at atmospheric temperature and pressure in the presence of 10% palladium on carbon catalyst for 24 h. The catalyst was removed by filtration and the filtrate evaporated to leave **9** (0.75 g, 100%) as a gum which slowly crystallized. A sample recrystallized from acetonitrile gave analytically pure material, mp 173–175 °C. $[\alpha]^{20}_D$ −104.9° (*c* = 0.5% in MeOH). $^1$H NMR ($CD_3OD$) $\delta$ 1.18–1.92 (m, 11H), 1.31 (s, 9H), 2.02 (ddd, 1H), 2.15 (dd, 1H), 2.20 (dd, 1H), 2.44 (dd, 1H), 2.59 (dd, 1H), 2.68 (dd, 1H), 2.96–3.03 (m, 2H), 3.07 (dd, 1H), 3.65 (m, 1H), 7.16–7.31 (m, 5H). Anal. Calcd for $C_{24}H_{39}N_3O_2$: C, 71.78; H, 9.79; N, 10.46. Found: C, 71.46; H, 9.88; N, 10.36. MS (FAB) *m/z* 402 $[M + H]^+$.

**2-[3(*S*)-[[*N*-(Benzyloxycarbonyl)-L-asparaginyl]amino]-2(*R*)-hydroxy-4-phenylbutyl]-*N*-*tert*-butyldecahydro-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (10).** A solution of **9** (562 mg, 1.4 mmol) in tetrahydrofuran (20 mL) was cooled in an ice/salt bath and treated with Cbz-L-asparagine (372 mg, 1.4 mmol), 1-hydroxybenzotriazole hydrate (189 mg, 1.4 mmol), dicyclohexylcarbodiimide (317 mg, 1.54 mmol), and N-ethylmorpholine (161 mg, 1.4 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 64 h, diluted with ethyl acetate, and filtered. The filtrate was washed with 10% aqueous sodium carbonate solution and brine. The solvent was then evaporated and the residue chromatographed on silica gel using dichloromethane/methanol (9:1) for the elution. Fractions containing material of $R_f$ = 0.37 were combined and evaporated. The resulting material was precipitated from methanol/diethyl ether to give **10** (438 mg, 48%). Anal. Calcd for $C_{36}H_{51}N_5O_6$: C, 66.54; H, 7.91; N, 10.78. Found: C, 66.54; H, 7.93; N, 10.81. MS (FAB) m/z 650 $[M + H]^+$.

***N*-*tert*-Butyldecahydro-2-[2(*R*)-hydroxy-4-phenyl-3(*S*)-[[*N*-(2-quinolylcarbonyl)-L-asparaginyl]amino]butyl]-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (1).** A solution of **10** (4.76 g, 7.3 mmol) in ethanol (73 mL) was hydrogenated over 10% palladium-on-charcoal at atmospheric pressure and temperature for 16 h. The catalyst was then removed by filtration and the filtrate evaporated. The residue was redissolved in toluene and the solution evaporated to give a pale yellow foam. This was dissolved in tetrahydrofuran (36.5 mL), and the solution was cooled in an ice bath and stirred during the addition of quinaldic acid (1.26 g, 7.3 mol), 1-hydroxybenzotriazole hydrate (985 mg, 7.3 mol), dicyclohexylcarbodiimide (1.5 g, 7.3 mmol), and *N*-ethylmorpholine (840 mg, 7.3 mmol). The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The mixture was filtered and the filtrate washed with water, 10% aqueous sodium carbonate solution, and brine. The solvent was evaporated and the residue chromatographed on silica gel using dichloromethane/methanol (92.5:7.5) for the elution. Fractions containing material of $R_f$ = 0.23 were combined and evaporated. The resulting material was triturated with diethyl ether to give **1** (3.09 g, 63%) as a white foam. $[\alpha]^{20}_D$ −55.9° (*c* = 0.5% in MeOH). Anal. Calcd for $C_{38}H_{50}N_6O_5$: C, 68.04; H, 7.51; N, 12.53. Found ($H_2O$ free): C, 68.04; H, 7.31; N, 12.35. MS(FAB) *m/z* 671 $[M + H]^+$.

**Ethyl 4(*S*)-(Benzyloxyformamido)-3-oxo-5-phenylpentanoate (22a).** *N*-Cbz-L-phenylalanine (100 g, 0.33 mol) was reacted according to the procedure of Maibaum and Rich[14] to give **22a** (131 g) as a white solid suitable for subsequent use. Recrystallization of a sample from ethanol gave material with mp 69–70 °C. $[\alpha]^{20}_D$ −60.4° (*c* = 1.0% in MeOH). $^1$H NMR ($CDCl_3$) $\delta$ 1.25 (t, *J* = 7 Hz, 3H), 3.01 and 3.18 (dq, *J* = 6, 13 Hz, 2H), 3.46 (q, *J* = 15 Hz, 2H), 4.16 (q, *J* = 7 Hz, 2H), 4.69 (q, *J* = 7 Hz, 1H), 5.08 (s, 2H), 5.31 (d, *J* = 7 Hz, 1H), 7.1–7.4 (m, 10H). Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.34; H, 6.26; N, 3.69. MS (FAB) *m/z* 370 $[M + H]^+$.

**Ethyl 4(*S*)-(*tert*-Butoxyformamido)-3(*R*)-hydroxy-5-phenylpentanoate (23b).** A solution of crude **22b**[14] (63.3 g, 0.19 mol) in ethanol (500 mL) was cooled to −15 °C in an ice/

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(25) Trost, B. M. *Science* **1991**, *254*(5032), 1471.

salt bath and stirred while sodium borohydride (5.0 g, 0.13 mol) was added portionwise over 15 min. The mixture was stirred at −10 °C to −15 °C for 1 h, a white crystalline precipitate separating during this time. Glacial acetic acid (20 mL) was added dropwise and the mixture evaporated. The residue was dissolved in dichloromethane (500 mL) and the solution washed with ice cold 1 M hydrochloric acid (500 mL), water (250 mL), and saturated sodium hydrogen carbonate solution (250 mL). After drying ($Na_2SO_4$), the solution was filtered and the filtrate evaporated to give the crude product as a white solid which was a mixture of 3*R*,4*S* and 3*S*,4*S* diastereomers (3.2:1 ratio respectively as determined by HPLC on a Hypersil 3μ-0DS column using a mobile phase of 40% $CH_3CN$/0.05 M triethylammonium phosphate at 1.0 mL/min with UV detection at 220 nm. Retention times were 8.8 and 10.6 min, respectively). Two recrystallizations from methylcyclohexane/ethyl acetate (50:1) gave **23b** (31 g, 53% from Boc-Phe-OH) with a diastereomeric purity of 98% by HPLC, mp 139−140 °C, $[\alpha]^{20}_D$ −14.7° (*c* = 1.0% in MeOH). $^1$H NMR ($CDCl_3$) δ 1.29 (t, *J* = 7 Hz, 3H), 1.34 (s, 9H), 2.41−2.64 (m, 2H), 2.82 and 3.0 (dm, 2H), 3.59 (bs, 1H), 3.86 (bs, 1H), 3.99 (bs, 1H), 4.19 (q, *J* = 7 Hz, 2H), 4.55 (bd, 1H), 7.15−7.23 (m, 5H). Anal. Calcd for $C_{18}H_{27}NO_5$: C, 64.07; H, 8.07; N, 4.15. Found: C, 64.24; H, 8.28; N, 4.43. MS (FAB) *m*/*z* 338 [M + H]$^+$. The enantiomeric purity of the isolated *N*-Boc-protected β-hydroxy ester **23b** was assessed by HPLC using an α-glycoprotein stationary phase and eluting with 5% 2-propanol/0.01 M $KH_2PO_4$ at 1.0 mL/min with UV detection at 215 nm. Retention times were 5.2 min for the 3*S*,4*S* isomer and 8.5 min for the 3*R*,4*S* isomer. The system gave base-line separation of the enantiomers in a sample of hydroxy ester prepared from *N*-Boc-D,L-phenylalanine, establishing that no detectable racemization had occurred during activation of the amino acid carboxyl function.

**Ethyl 4(*S*)-(Benzyloxyformamido)-3(*R*)-hydroxy-5-phenylpentanoate (23a).** Crude **22a** (96 g, 0.24 mol) was reduced according to the above procedure to give 88 g of crude product as a 3:1 mixture of 3*R*,4*S* and 3*S*,4*S* diastereomers. Two recrystallizations from methylcyclohexane/ethyl acetate (9:1) gave **23a** (47 g, 51% from Cbz-Phe-OH) with a diastereomeric purity of 99%, mp 142−144 °C. $[\alpha]^{20}_D$ −31.7° (*c* = 0.99% in MeOH). $^1$H NMR ($CDCl_3$) δ 1.26 (t, *J* = 7 Hz, 3H), 2.42−2.62 (m, 2H), 2.84−2.99 (dm, 2H), 3.48 (d, *J* = 3 Hz, 1H), 3.82−4.09 (bm, 2H), 4.17 (q, *J* = 7 Hz, 2H), 4.87 (d, 9 Hz, 1H), 5.02 (s, 2H), 7.1−7.39 (m, 10H). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.79; N, 3.77. Found: C, 67.95; H, 6.80; N, 3.81. MS (FAB) *m*/*z* 372 [M + H]$^+$.

**Ethyl 4(*S*)-Benzyl-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-5(*R*)-oxazolidineacetate (24b).** A mixture of **23b** (31.0 g, 0.092 mol), *p*-toluenesulfonic acid monohydrate (1.0 g, 5 mmol), and 2,2-dimethoxypropane (550 mL) was stirred at room temperature for 24 h and then heated at 50 °C for 7 h. The reaction mixture was diluted with ethyl acetate (1 L), washed with saturated sodium hydrogen carbonate (2 × 500 mL) and brine (250 mL), then dried, filtered, and evaporated to give **24b** (34.3 g, 99%). Recrystallization from hexane gave analytically pure material (27.7 g, 80%), mp 102.5−104.5 °C. $[\alpha]^{20}_D$ −51.4° (*c* = 1.0% in MeOH). $^1$H NMR ($CDCl_3$) δ 1.19 (t, *J* = 7 Hz, 3H), 1.40 and 1.46 (ds, 9H), 1.5−1.7 (dds, 6H), 2.40−2.70 (dm, 2H), 2.72−3.04 (m, 2H), 3.80−4.01 (m, 2H), 4.29−4.54 (dm, 2H), 7.10−7.34 (m, 5H). Anal. Calcd for $C_{21}H_{31}NO_5$: C, 66.82; H, 8.28; N, 3.71. Found: C, 66.80; H, 8.42; N, 3.72. MS (CI) *m*/*z* 378 [M + H]$^+$.

**Ethyl 4(*S*)-Benzyl-3-(benzyloxycarbonyl)-2,2-dimethyl-5(*R*)-oxazolidineacetate (24a).** A mixture of **23a** (44.8 g, 0.12 mol), *p*-toluenesulfonic acid monohydrate (1.0 g, 5.3 mmol), and 2,2-dimethoxypropane (550 mL) was stirred and heated at 60 °C for 2 h. A further 0.5 g (2.7 mmol) of *p*-toluenesulfonic acid was added and heating at 60 °C continued for 3 h. The mixture was then worked up as described in the preceding example to give, after a single recrystallization from *n*-hexane, **24a** (44.1 g, 89%), mp 64−66 °C. A second recrystallization from *n*-hexane provided an analytically pure sample with mp 64−67 °C. $[\alpha]^{20}_D$ −58.6° (*c* = 1.0% in MeOH). $^1$H NMR ($CDCl_3$) δ 1.14 (t, *J* = 7 Hz, 3H), 1.60 (s, 3H), 1.70 (s, 3H), 2.39−2.80 (dm, 2H), 2.80−3.09 (m, 2H), 3.80−4.0 (m, 2H), 4.37−4.55 (m, 2H), 4.63−5.19 (m, 2H), 7.03 7.38 (m, 10H). Anal. Calcd for $C_{24}H_{29}NO_5$: C, 70.05; H, 7.10; N, 3.40. Found: C, 69.93; H, 6.95; N, 3.36. MS (FAB) *m*/*z* 412 [M + H]$^+$.

**4(*S*)-Benzyl-3-(*tert*-butoxycarbonyl)-2,2-dimethyl-5(*R*)-oxazolidineacetic Acid (25b).** To a solution of **24b** (26.5 g, 70.3 mmol) in ethanol (75 mL) was added 1 M aqueous sodium hydroxide (75 mL). The resulting suspension was stirred at room temperature for 18 h to give a clear solution. This was concentrated to remove ethanol and then diluted with water (100 mL). The solution was washed with diethyl ether (2 × 50 mL), then acidified to pH 5 by addition of 10% aqueous citric acid, and extracted with dichloromethane (3 × 50 mL). The combined organic extracts were washed with water (50 mL), then dried ($Na_2SO_4$), filtered, and evaporated to give **25b** (24.5 g, 100%) as a syrup which crystallized on standing. Recrystallization from methylcyclohexane gave material with mp 124−126 °C. $[\alpha]^{20}_D$ −47.3° (*c* = 1.0% in MeOH). $^1$H NMR ($CDCl_3$) δ 1.39 and 1.44 (ds, 9H), 1.5−1.7 (dds, 6H), 2.44 and 2.72 (dm, 2H), 2.72−3.08 (m, 2H), 4.22−4.50 (m, 2H), 7.09−7.32 (m, 5H). Anal. Calcd for $C_{19}H_{27}NO_5$: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.61; H, 7.82; N, 4.08. MS (FAB) *m*/*z* 350 [M + H]$^+$.

**4(*S*)-Benzyl-3-(benzyloxycarbonyl)-2,2-dimethyl-5(*R*)-oxazolidineacetic Acid (25a). 24a** (43 g, 105 mmol) was hydrolyzed by the above procedure to give 37.0 g (92%) of **25a** as a syrup. $^1$H NMR ($CDCl_3$) δ 1.60 and 1.71 (ds, 6H), 2.50 and 2.72 (dm, 2H), 2.85 (m, 2H), 4.35 (m, 1H) and 4.48 (m, 1H), 4.61−5.21 (m, 2H), 7.0−7.5 (m, 10H).

**1-Bromo-3(*S*)-(*tert*-butoxyformamido)-4-phenyl-2(*S*)-butanol (27b).** To a stirred solution of **25b** (24.5 g, 70 mmol) in toluene (370 mL), cooled to −15 °C in an ice/salt bath, was added oxalyl chloride (34.5 mL) followed by dimethylformamide (0.5 mL). The mixture was stirred at <0 °C for 1 h and then evaporated at <20 °C. The residue was redissolved in toluene (300 mL) and the solution filtered and evaporated again to give the acid chloride (25.5 g) as a yellow syrup. This was dissolved in bromotrichloromethane (150 mL) and the solution added dropwise to a stirred suspension of 2-mercaptopyridine *N*-oxide, sodium salt (12.7 g, 85 mmol) and 4-(dimethylamino)pyridine (0.36 g, 3 mmol) in bromotrichloromethane (250 mL) which was heated at 80 °C under argon and irradiated using a 150-W tungsten filament lamp. The mixture was heated at 80 °C and irradiated for 1 h and then evaporated and the residue partitioned between hexane (500 mL) and water (2 × 200 mL). The hexane solution was dried ($Na_2SO_4$) and evaporated to a yellow oil (36.6 g) which was a mixture of protected bromohydrin and 2-((trichloromethyl)thio)pyridine. A solution of this mixture in glacial acetic acid (176 mL) was treated with water (44 mL) followed by concentrated hydrochloric acid (5.8 mL) and then stirred at room temperature for 3 h. The mixture was diluted with water (500 mL) and the solid product filtered off and washed on the filter with water (100 mL) and petroleum ether (bp 40−60 °C; 2 × 100 mL) to give **27b** (14.2 g, 59%) as a cream-colored solid, mp 147 °C dec. Recrystallization from 2-propanol (120 mL) gave analytically pure product (9.7 g), mp 156 °C dec. $[\alpha]^{20}_D$ −35° (*c* = 1.0% in MeOH). $^1$H NMR ($CDCl_3$) δ 1.39 (s, 9H), 2.84−3.05 (m, 2H), 2.7−3.25 (bs, 1H), 3.40−3.60 (m, 2H), 3.89 (bm, 2H), 4.60 (bd, 1H), 7.19−7.38 (m, 5H). Anal. Calcd for $C_{15}H_{22}BrNO_3$: C, 52.34; H, 6.44; N, 4.07. Found: C, 52.56; H, 6.44; N, 4.22. MS (FAB) *m*/*z* 344, 346 [M + H]$^+$.

**3(*S*)-(Benzyloxyformamido)-1-bromo-4-phenyl-2(*S*)-butanol (27a).** By a procedure analogous to that described above, **25a** (3.4 g, 8.9 mmol) was converted to a mixture of **26a** and 2-((trichloromethyl)thio)pyridine. A solution of this mixture in ethanol (10 mL) was treated with concentrated hydrochloric acid (10 mL) to give a suspension which was stirred at room temperature for 24 h. The mixture was concentrated to remove ethanol, then diluted with water (50 mL), and extracted with dichloromethane (75 mL, 2 × 25 mL). The combined extracts were washed with saturated sodium hydrogen carbonate solution, then dried, filtered, and evaporated. The residue was triturated with petroleum ether (bp 40−60 °C, 50 mL) and filtered to give **27a** (2.7 g, 80%), mp 139−141 °C. Recrystallization from 2-propanol gave material (2.1 g, 75%) with mp 145−146 °C. A second recrystallization gave analytically pure product, mp 146−147 °C. $[\alpha]^{20}_D$ −17.8° (*c* = 1.0% in MeOH). $^1$H NMR ($CDCl_3$) δ 2.8−3.08 (m, 2H), 2.75−3.05 (bs, 1H), 3.39−3.60 (m, 2H), 3.85 (bm, 1H), 3.99 (m, 1H), 4.82 (bd, 1H), 5.04

(s, 2H), 7.13–7.40 (m, 10H). Anal. Calcd for $C_{18}H_{20}BrNO_3$: C, 57.16; H, 5.33; N, 3.70. Found: C, 57.44; H, 5.02; N, 3.81. MS (FAB) $m/z$ 378, 380 $[M + H]^+$.

**1(*S*)-[1(*S*)-(*tert*-Butoxyformamido)-2-phenylethyl]oxirane (6b).** A suspension of **27b** (9.3 g, 27 mmol) in methanol (270 mL) was stirred and cooled in ice while a solution of potassium hydroxide (1.7 g, 30 mmol) in methanol (50 mL) was added during 5 min. The mixture was stirred at room temperature for 3 h and then concentrated to remove methanol, and the residue was partitioned between dichloromethane (300 mL) and water (2 × 100 mL). The dichloromethane solution was dried ($Na_2SO_4$), filtered, and evaporated to give **6b** (7.1 g, 100%) as a white solid, mp 122–125 °C. Recrystallization from *n*-hexane gave analytically pure material with mp 122–124.5 °C. $[\alpha]^{20}_D$ −8.1° ($c$ = 1.0% in MeOH). $^1$H NMR ($CDCl_3$) $\delta$ 1.39 (s, 9H), 2.77–3.02 (m, 5H), 3.70 (bs, 1H), 4.44 (bs, 1H), 7.2–7.4 (m, 5H). Anal. Calcd for $C_{15}H_{21}NO_3$: C, 68.42; H, 8.04; N, 5.32. Found: C, 68.24; H, 8.05; N, 5.08. MS (FAB) $m/z$ 264 $[M + H]^+$.

**1(*S*)-[1(*S*)-(Benzyloxyformamido)-2-phenylethyl]oxirane (6a).** By the procedure described above from **27a** (1.5 g, 3.97 mmol) was obtained, after recrystallization of the crude product from 2-propanol, **6a** (1.1 g, 92%), mp 99–101 °C. $[\alpha]^{20}_D$ −25.9° ($c$ = 1.02% in MeOH). $^1$H NMR ($CDCl_3$) $\delta$ 2.69–3.05 (m, 5H), 3.75 (m, 1H), 4.70 (br, 1H), 5.03 (s, 2H), 7.14–7.39 (m, 10H). Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.47; H, 6.46; N, 4.96.

**2-[3(*S*)-(*tert*-Butoxyformamido)-2(*R*)-hydroxy-4-phenylbutyl]-*N*-*tert*-butyldecahydro-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (8b).** A solution of **6b** (5.26 g, 20 mmol) and **5** (4.76 g, 20 mmol) in 2-propanol was stirred at 70 °C for 9 h and then at ambient temperature for 16 h. The solvent was then evaporated and the residue chromatographed on silica gel using diethyl ether/*n*-hexane/methanol (47.5:47.5:5) for the elution to give 8b (8.36 mg, 84%) as a white foam. $[\alpha]^{20}_D$ −72.4° ($c$ = 0.5% in MeOH). Anal. Calcd for $C_{29}H_{47}N_3O_4$: C, 69.43; H, 9.44; N, 8.37. Found: C, 69.33; H, 89.50; N, 8.20. MS (FAB) $m/z$ 502 $[M + H]^+$.

**2-(3(*S*)-Amino-2(*R*)-hydroxy-4-phenylbutyl)-*N*-*tert*-butyldecahydro-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (9) from 8b.** A solution of **8b** (8.04 g, 16 mmol) in trifluoroacetic acid (24 mL) was stirred at ambient temperature for 1 h and the solvent was then evaporated. The residue was re-evaporated with toluene and then dissolved in dichloromethane. This solution was washed with 10% aqueous sodium carbonate solution and brine and then evaporated. The residue was triturated with diethyl ether to give **9** (5.55 g, 86%) as a cream-colored solid, identical to that obtained previously.

**1-Hydroxy-4-phenyl-3(*S*)-phthalimido-2-butanone (30).** A mixture of *N*-phthaloyl-(*S*)-phenylalaninyl chloride **(28)**[26] (31.35 g, 0.1 mol) and 1,1,2-tris((trimethylsilyl)oxy)ethene **(29)**[16] (62.8 g, 0.215 mol) was heated at 95–100 °C for 4 h. The resulting liquid was cooled to room temperature and treated with a solution of 0.6 M aqueous hydrochloric acid (40 mL) in dioxane (100 mL). The two-phase mixture was heated to 80–85 °C for 30 min and then cooled to room temperature. Sodium chloride (15 g) was added, and the product was extracted with diethyl ether (100 mL and then 50 mL). The combined organic solutions were washed with saturated aqueous sodium hydrogen carbonate solution, dried ($Na_2SO_4$), and evaporated. The residue was crystallized from ethyl acetate (50 mL)/*n*-hexane (90 mL) to give **30** (19.5 g, 63%) as a buff-colored solid, mp 108–112 °C. $[\alpha]^{20}_D$ −187.9° ($c$ = 0.876%, EtOH). $^1$H NMR ($CDCl_3$) $\delta$ 2.98 (s, br, 1H), 3.44 (dd, $J$ = 11.16, 14.2 Hz, 1H), 3.56 (dd, $J$ = 5.26, 14.2 Hz, 1H), 4.37 (d, $J$ = 19 Hz, 1H), 4.39 (d, $J$ = 19 Hz, 1H), 5.13 (dd, $J$ = 5.26, 11.16 Hz, 1H), 7.19–7.10 (m, 5H), 7.71 (dd, $J$ = 3.06, 5.40 Hz, 2H), 7.78 (dd, $J$ = 3.06, 5.40 Hz, 2H). Anal. Calcd for $C_{18}H_{15}NO_4$: C, 69.89; H, 4.89; N, 4.53. Found: C, 69.68; H, 4.85; N, 4.42. MS (FAB) $m/z$ 310 $([M + H]^+$, 60), 250 (100).

**2(*R*)-(Methanesulfonyloxy)-4-phenyl-3(*S*)-phthalimido-1-butanol (32).** To a stirred solution of **30** (34.09 g, 0.11 mol) in dichloromethane (80 mL) were added dihydropyran (10.16 g, 0.12 mol) and *p*-toluenesulfonic acid monohydrate (150 mg). The solution was stirred at 20 °C for 16 h, washed with saturated aqueous sodium carbonate and brine, and then evaporated. The residue was dissolved in tetrahydrofuran (220 mL) and the solution cooled in an ice/salt bath. A solution of sodium borohydride (10.8 g, 0.29 mol) in water (20 mL) was added dropwise to the stirred solution at such a rate as to maintain the internal temperature <0 °C. The mixture was stirred for a further 15 min at 0 °C and then diluted with water. The pH of the solution was adjusted to 7 by the addition of 2 M aqueous sulfuric acid and most of the tetrahydrofuran removed by evaporation. The resulting solution was extracted with dichloromethane. The organic solution was washed with brine and evaporated. The crude product was dissolved in pyridine (110 mL) and methanesulfonyl chloride (15.11 g, 0.13 mol) added dropwise to the stirred solution. The reaction mixture was stirred for 16 h at 20 °C and then evaporated. The residue was partitioned between ethyl acetate and 2 M aqueous sulfuric acid, and the organic solution was washed with brine and evaporated. The product was dissolved in ethanol (154 mL) and treated with *p*-toluenesulfonic acid monohydrate (1.1 g). After being stirred at 20 °C for 1 h, the mixture was allowed to stand at 4 °C overnight. The precipitated solid was filtered off and washed with ethanol and diethyl ether. Recrystallization from ethanol gave **30** (12.62 g, 29%) as a white solid, mp 180–182 °C. $[\alpha]^{20}_D$ −100.5° ($c$ = 0.4% in MeOH). $^1$H NMR ($(CD_3)_2SO$) $\delta$ 3.12 (dd, $J$ = 4.58, 13.53 Hz, 1H), 3.35 (s, 3H), 3.32 (dd, $J$ = 12.40, 13.53 Hz, 1H), 3.87 (ddd, $J$ = 4.24, 6.04, 13.10 Hz, 1H), 3.96 (ddd, $J$ = 2.47, 5.07, 13.10 Hz, 1H), 4.79 (ddd, $J$ = 4.58, 9.46, 12.40 Hz, 1H), 5.19 (ddd, $J$ = 2.47, 4.24, 9.46 Hz, 1H), 5.43 (dd, $J$ = 5.07, 6.04 Hz, 1H), 7.06–7.14 (m, 5H), 7.76 (s, 4H). Anal. Calcd for $C_{19}H_{19}NO_6S$: C, 58.60; H, 4.92; N, 3.60. Found: C, 58.67; H, 4.92; N, 3.54. MS (FAB) $m/z$ 390 ($[M + H]^+$, 100), 294 (36), 250 (53), 200 (68).

**2(*S*)-[2-Phenyl-1(*S*)-phthalimidoethyl]oxirane (33).** To a solution of **32** (150 g, 0.386 mol) in dimethylformamide (350 mL) was added a solution of potassium *tert*-butoxide (47.5 g, 0.424 mol) in dimethylformamide (250 mL) at <30 °C. After being stirred at 20 °C for a further 1 h, the solution was poured onto a mixture of toluene (1 L), concentrated hydrochloric acid (50 mL), and ice (500 g). The layers were separated and the aqueous layer further extracted with toluene (2 × 500 mL). The combined organic solutions were washed with water (2 × 500 mL), saturated aqueous sodium hydrogen carbonate (500 mL), water (2 × 500 mL), and brine (2 × 500 mL), then dried, and evaporated. The residue was triturated with methanol (250 mL) and filtered, and the filter cake was washed with a further 200 mL of methanol to give **33** (78.4 g, 69%) as a cream-colored solid, mp 180–182 °C. $[\alpha]^{20}_D$ −155.2° ($c$ = 0.5% in $CH_2Cl_2$). $^1$H NMR ($(CD_3)_2SO$) $\delta$ 2.59 (dd, $J$ = 2.67, 4.7 Hz, 1H), 2.78 (dd, $J$ = 3.95, 4.7 Hz, 1H), 3.20 (dd, $J$ = 5.12, 13.78 Hz, 1H), 3.44 (dd, $J$ = 11.18, 13.78, 1H), 3.52 (ddd, $J$ = 2.67, 3.95, 6.51 Hz, 1H), 4.13 (ddd, $J$ = 5.12, 6.51, 11.18 Hz, 1H), 7.20–7.08 (m, 5H), 7.82 (s, 4H). Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.48; H, 5.10; N, 4.49. MS (FAB) $m/z$ 294 ($[M + H]^+$, 100), 250 (37), 186 (33).

***N*-*tert*-Butyldecahydro-2-(2(*R*)-hydroxy-4-phenyl-3(*S*)-phthalimidobutyl)-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (34).** A solution of **5** (14.52 g, 61 mmol) and **33** (17.87 g, 61 mmol) in dimethylformamide (120 mL) was heated at 120 °C for 8.5 h and the solvent then evaporated. The residue was partitioned between ethyl acetate and water and the organic solution washed with brine. The solvent was evaporated and the residue chromatographed on silica gel using diethyl ether/*n*-hexane/methanol (9.5:9.5:1) for the elution to give **34** (25.9 g, 80%) as an off-white foam [$R_f$ = 0.22, diethyl ether/*n*-hexane/methanol]. A sample crystallized from the same solvent gave analytically pure material. Anal. Calcd for $C_{32}H_{41}N_3O_4$: C, 72.29; H, 7.77; N, 7.90. Found: C, 72.21; H, 7.77; N, 7.85. MS (FAB) $m/z$ 532 $[M + H]^+$.

**2-(3(*S*)-Amino-2(*R*)-hydroxy-4-phenylbutyl)-*N*-*tert*-butyldecahydro-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (9) from 34.** A partial solution of **34** (26.55 g, 50 mmol) in ethanol (100 mL) was treated with 33% ethanolic methylamine (25 mL), and the mixture was stirred at ambient temperature for 1 h. The solvent was then evaporated and the

(26) Sheehan, J. C.; Chapman, D. W.; Roth, R. W. *J. Am. Chem. Soc.* **1952**, *74*, 3822.

resulting gum taken up in ethanol (250 mL) and treated with 4 M hydrogen chloride in ethyl acetate (250 mL). The mixture was stirred at ambient temperature overnight and then evaporated. The residue was dissolved in water and the solution washed with ethyl acetate. The aqueous solution was basified (solid sodium carbonate) and extracted with dichloromethane. The dichloromethane extracts were washed with brine and evaporated. The resulting brownish solid was triturated with diethyl ether to give **9** (17.48 g, 87%) as a white solid which was identical in all respects to previous samples.

**2-[2(*S*)-(*tert*-Butoxyformamido)-1(*S*)-hydroxy-3-phenylpropyl]thiazole (36).** Reaction of *N*-(*tert*-butoxycarbonyl)-(*S*)-phenylalaninal (**35**) (10 mmol) with 2-(trimethylsilyl)-thiazole (2.4 g, 15 mmol) in tetrahydrofuran (50 mL) gave, after deprotection with *N*-tetrabutylammonium fluoride (15 mmol), a mixture of **36** and **37** (2.6 g) in 38:62 ratio by NMR.[20] A solution of the alcohols in dry pyridine (23 mL) was treated with 4-(dimethylamino)pyridine (0.95 g, 7.7 mmol) followed by acetic anhydride (0.80 mL, 9.1 mmol) to give a clear yellow solution which was stood for 16 h at room temperature. The pyridine was evaporated and the residue re-evaporated with toluene (3 × 10 mL) and then partitioned between ethyl acetate (50 mL) and sodium hydrogen carbonate solution (50 mL). The organic extract was washed with brine, and the aqueous phase was back extracted with ethyl acetate (2 × 50 mL). The combined ethyl acetate extracts were dried ($Na_2SO_4$) and evaporated to give a mixture of acetates (2.7 g, 92%) as a gummy solid. This mixture was separated by flash chromatography using ethyl acetate/hexane (1:1) for the elution to give pure (*S*)-acetate (0.50 g, 19%), mp 129–130 °C. $^1H$ NMR ($CDCl_3$) $\delta$ 1.37 (s, 9H), 2.11 (s, 3H), 2.86 (d, 2H), 4.58 (m, 1H), 5.43 (d, 1H), 6.04 (d, 1H), 7.2 (m, 5H), 7.38 (d, 1H), 7.84 (d, 1H). MS (FAB) $m/z$ 377 $[M + H]^+$. Measured mass 377.1539; calculated mass 377.1535; elemental composition $C_{19}H_{25}N_2O_4S$ $[M + H]^+$.

A solution of the above acetate (0.47 g, 1.25 mmol) in ethanol (1.25 mL) was treated with 1 M sodium hydroxide solution (2.5 mL) followed by more ethanol (5 mL) to give a clear solution. This was left to stand at room temperature for 15 min. The solvent was evaporated and the residual solid partitioned between ethyl acetate (30 mL) and brine (15 mL). The organic phase was washed with water (15 mL) and the aqueous phases were extracted with ethyl acetate (15 mL and then 10 mL). The combined ethyl acetate extracts were dried ($Na_2SO_4$) and evaporated to give **36** (0.43 g, 13%), mp 112–120 °C. $^1H$ NMR ($CDCl_3$) $\delta$ 1.37 (s, 9H), 2.93 (m, 2H), 4.27 (m, 1H), 4.83 (d, 1H), 5.12 (s, 1H), 5.23 (br, s, 1H), 7.25 (m, 5H), 7.36 (d, 1H), 7.81 (d, 1H). MS (FAB) $m/z$ 335 $[M + H]^+$. Measured mass 335.1442, calculated mass 335.1429; elemental composition $C_{17}H_{23}N_2O_3S$ $[M + H]^+$.

**3(*S*)-(*tert*-Butoxyformamido)-2(*S*)-hydroxy-4-phenyl-1-butanal (38).** A solution of **36** (0.42 g, 1.25 mmol) in acetonitrile (12.5 mL) was treated with methyl iodide (1 mL, 15 mmol) and then boiled under reflux for 17 h. After cooling, a second portion of methyl iodide (1 mL) was added and the solution was heated for a further 3 h to complete the reaction. The solvent was evaporated and the residual gum was triturated with diethyl ether (12 mL) to give a solid which was triturated with a further two portions of ether (15 mL) and filtered to give the *N*-thiazolium iodide (0.57 g, 96%), mp 95–115 °C. $^1H$ NMR ($(CD_3)_2SO$) $\delta$ 1.2 (s, 9H), 2.74 (m, 1H), 3.05 (m, 1H), 3.92 (m, 1H), 4.19 (s, 3H), 5.16 (t, 1H – reduced to doublet by $D_2O$ shake), 7.21 (m, 6H), 7.4 (d, 1H – removed by $D_2O$ shake), 8.24 (d, 1H), 8.36 (d, 1H). MS (FAB) $m/z$ 349 [cation]$^+$. Measured mass 349.1590, calculated mass 349.1586; elemental composition $C_{18}H_{25}N_2O_3S$ [cation]$^+$.

A solution of the above *N*-thiazolium iodide (0.24 g, 0.50 mmol) in dry methanol (10 mL) was stirred at −10 °C and treated with sodium borohydride (38 mg, 1.0 mmol). After 1 h, acetone (10 drops) was added and the solvent was evaporated. The residue was partitioned between dichloromethane (25 mL) and brine (25 mL) and the organic layer was washed with water (25 mL). The aqueous phases were extracted with dichloromethane (25 mL) and the combined organic extracts dried ($Na_2SO_4$) and evaporated to give the crude thiazolidine as a mixture of diastereomers (0.19 g). $^1H$ NMR($(CD_3)_2SO$) $\delta$ 1.21 (d, 9H), 2.18 (d, 3H), 2.77–3.4 (m, 5H), 3.85 (m, 1H), 4.19 (dd, 1H), 4.95 (dd, 1H – removed by $D_2O$ wash), 6.50 (dd, 1H), 7.16 (m, 5H). MS (FAB) $m/z$ 353 $[M + H]^+$. Measured mass 353.1894, calculated mass 353.1899; elemental composition $C_{18}H_{29}N_2O_3S$ $[M + H]^+$.

A solution of the above thiazolidine in dry acetonitrile (3 mL) was stirred and treated with a solution of mercury(II) chloride (160 mg, 0.6 mmol) in acetonitrile/water (4:1, 9 mL). Stirring was continued for 15 min. Solvents were evaporated and the residue was partitioned between dichloromethane (50 mL) and brine (50 mL). The organic layer was washed with water (50 mL) and the aqueous layers extracted with dichloromethane (50 mL). The combined organic extracts were dried ($Na_2SO_4$) and evaporated to give **38** (0.145 g) as a sticky solid which was used immediately without further purification. $^1H$ NMR ($CDCl_3$) $\delta$ 1.4 (s, 9H), 2.87 (m, 2H), 3.91 (d, 1H), 4.2 (br, 2H), 4.87 (d, 1H), 7.25 (m, 5H), 9.48 (s, 1H). MS (FAB) $m/z$ 280 $[M + H]^+$. Measured mass 280.1560, calculated mass 280.1549; elemental composition $C_{15}H_{22}NO_4$ $[M + H]^+$.

**2-[3(*S*)-(*tert*-Butoxyformamido)-2(*R*)-hydroxy-4-phenylbutyl]-*N*-*tert*-butyldecahydro-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (8b).** To a stirred solution of **5** (0.71 g, 3.0 mmol) in dry methanol (2 mL) was added 1 M methanolic hydrogen chloride (0.1 mL), followed by a solution of **38** (0.14 g, 0.5 mmol) in dry methanol (2 mL), sodium cyanoborohydride (44 mg, 0.70 mmol) in a single portion, and 3-Å molecular sieves (150 mg). The mixture was stirred for 16 h at ambient temperature. Further portions of sodium cyanoborohydride (22 mg, 0.35 mmol) and 3-Å sieves (50 mg) were added and the mixture was stirred for a further 24 h and then left to stand for 72 h without stirring. The mixture was filtered and the filtrate evaporated. The residual oil was partitioned between dichloromethane (50 mL) and brine (50 mL). The organic extract was washed with 5% aqueous citric acid (50 mL) followed by 10% aqueous sodium bicarbonate (50 mL). The aqueous layers were extracted with dichloromethane (2 × 50 mL) and the combined organic extracts dried ($Na_2SO_4$). Evaporation gave the crude product (0.25 g) as a gum which was purified by flash chromatography using methanol/dichloromethane (1:9) for the elution to give **8b** (0.145 g, 56% from **36**) which was identical to that obtained previously. Amine **5** was recovered from the citric acid extract by treatment with $Na_2CO_3$ and extraction with $CH_2Cl_2$.

**4(*S*)-(1(*S*)-Azido-2-phenylethyl)-1,3,2-dioxathiolane 2,2-Dioxide (41).** Thionyl chloride (175 $\mu$L, 2.4 mmol) was added to a solution of **39** (414 mg, 2 mmol) in carbon tetrachloride (5 mL) and the mixture refluxed with calcium chloride drying tube protection for 30 min. The resulting solution was cooled in an ice bath, acetonitrile (5 mL), ruthenium(III) chloride trihydrate (5 mg), sodium metaperiodate (642 mg, 3 mmol), and water (7.5 mL) added successively, and the mixture was stirred vigorously at room temperature for 1 h. Diethyl ether (20 mL) and water (20 mL) were added, the layers were separated, and the aqueous phase was extracted with diethyl ether (2 × 10 mL). The organic layers were combined and washed with water (10 mL), saturated aqueous sodium hydrogen carbonate solution (10 mL), and brine (10 mL). After drying, the solution was filtered through Hyflo and evaporated to give **41** (518 mg, 96%). $^1H$ NMR ($CDCl_3$) $\delta$ 2.86 (ABX, $J$ = 14, 8 Hz, 2H), 3.06 (ABX, $J$ = 14, 5 Hz, 1H), 4.11 (m, 1H), 4.60–4.77 (m, 3H), 7.23–7.40 (m, 5H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 36.87, 60.40, 69.67, 80.48, 127.77, 129.09, 129.36, 134.57. IR (film) $\nu_{max}$ 2125 (s), 1395(s), 1215(s). MS (FAB) $m/z$ 270 $[M + H]^+$.

**2-(3(*S*)-Azido-2(*R*)-hydroxy-4-phenylbutyl)-*N*-*tert*-butyldecahydro-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (43) from 41.** A solution of freshly prepared **41** (0.64 g, 2.38 mmol) in dry tetrahydrofuran (5 mL) was added to a stirred solution of **5** (0.56 g, 2.36 mmol) in dry tetrahydrofuran (15 mL) and the clear solution was stirred at room temperature under argon overnight. Thin layer chromatography on a silica gel plate developed in ethanol/ethyl acetate (1:9) and sprayed with ninhydrin showed the presence of unreacted **5**. Additional **6** (0.15 g, 0.56 mmol) in dry tetrahydrofuran (2 mL) was added, a further similar addition made after 6 h, and the reaction solution stirred at room temperature under argon for a further 18 h. The reaction was evaporated to leave a white solid residue. This solid was suspended in a 10% solution of concentrated

sulfuric acid in 70% aqueous methanol (25 mL) and the mixture was stirred and boiled under reflux for 3 h. Methanol (20 mL) was added, and the mixture was stirred and boiled under reflux until a clear solution formed and then for an additional 1 h. The methanol was removed by evaporation under reduced pressure and the residue was treated with water (25 mL). The mixture was cooled in ice and made alkaline by the addition of 10 M sodium hydroxide solution (11 mL). The mixture was extracted with ethyl acetate (2 × 30 mL), and the organic extracts were combined and washed with brine (2 × 30 mL). The solution was dried and evaporated to leave a mainly solid residue. Crystallization from ethyl acetate/hexane (1:3) gave pure **43** (0.67 g, 67%) as white needles, mp 153–5 °C. Anal. Calcd for $C_{24}H_{37}N_5O_2$: C, 67.42; H, 8.72; N, 16.38. Found: C, 67.38; H, 8.65; N, 16.30. $[\alpha]^{20}_D$ ($c$ = 1% in $CHCl_3$) −75.7°. $^1H$ NMR $\delta$ ($CDCl_3$) 1.32 (s, 9H) 1.2–2.05 (m, 12H), 2.42 (m, 2H), 2.65–3.13 (m, 5H), 3.65 (m, 3H), 5.9 (bs, 1H), 7.28 (m, 5H). $^{13}C$ NMR $\delta$ ($CDCl_3$) 20.95, 26.03, 26.21, 28.87, 30.74, 31.18, 33.43, 36.21, 36.81, 51.30, 58.51, 60.90, 67.07, 70.44, 71.10, 126.92, 128.79, 129.55, 137.81, 173.51. MS (CI) $m/z$ 428 $[M + H]^+$. DSC mp 153 °C. Decomposition commences at 170 °C and is complete by 280 °C.

**2-(3(*S*)-Amino-2(*R*)-hydroxy-4-phenylbutyl)-*N*-*tert*-butyldecahydro-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (9) from 43.** A solution of **43** (0.2 g, 0.47 mmol) in ethanol (5 mL) was hydrogenated at 50 psi and room temperature for 24 h over 10% palladium on charcoal (50 mg). The catalyst was removed by filtration through G/FA filter paper and washed with ethanol (2 × 3 mL). The filtrates were combined and evaporated to leave an off-white solid residue. The crude product was dissolved in chloroform (3 mL), the solution was filtered through an Acrodisc filter, to remove a trace amount of catalyst, and the filter was washed with chloroform (2 × 2 mL). The filtrates were combined and evaporated to give **9** (0.19 g, 100%) as a white foam. Proton NMR and MS data were identical to those obtained for the authentic amino compound.

**3(*S*)-Azido-1-((2,4,6-triisopropylbenzenesulfonyl)oxy)-4-phenyl-2(*R*)-butanol (40).** A solution of **39** (1.03 g, 5 mmol) and triethylamine (1.05 mL, 7.5 mmol) in dry dichloromethane (20 mL) was stirred under argon and cooled in ice–salt. 2,4,6-Triisopropylbenzenesulfonyl chloride (2.27 g, 7.5 mmol) was added, and the solution stirred and allowed to warm to room temperature overnight. Stirring at room temperature was continued for a further 24 h. Water (4 mL) was added and the mixture was stirred for 1 h to hydrolyze any excess acid chloride. The reaction mixture was shaken with water (20 mL), and the organic phase was separated and washed successively with water (20 mL), 1 M sulfuric acid (20 mL), water (20 mL), and finally saturated sodium hydrogen carbonate solution (20 mL). The solution was dried and evaporated to leave a pale brown oil (2.27 g) which readily crystallized. Recrystallization from methylcyclohexane (23 mL) with storage in the freezer for 48 h gave **40** (0.8 g, 35%) as white crystals, mp 75–77 °C. $^1H$ NMR ($CDCl_3$) $\delta$ 1.3 (d, 18H), 2.85 (d, 1H), 3.15 (d, 1H) 3.0 (m, 2H) 3.78 (m, 1H), 3.90 (m, 1H), 4.2 (m, 4H), 7.30 (m, 7H). MS (FAB) $m/z$ 474 $[M + H]^+$.

**2(*S*)-(1(*S*)-Azido-2-phenylethyl)oxirane (42).** A solution of potassium hydroxide (0.21 g, 3.7 mmol) in ethanol (10 mL) was added to a stirred solution of **40** (1.33 g, 2.8 mmol) in ethanol (40 mL) and stirring at room temperature was continued for a further 1.5 h. The clear solution was evaporated and the residue was partitioned between dichloromethane (30 mL) and water (30 mL). The lower phase was removed, and the aqueous layer was treated with saturated brine (5 mL) and further extracted with dichloromethane (2 × 20 mL). The organic solutions were combined, washed with brine (30 mL), dried, and evaporated to leave **42** (0.52 g, 97%) as a colorless mobile oil. $^1H$ NMR ($CDCl_3$) $\delta$ 2.75–2.95 (m, 5H), 3.50 (m, 1H), 7.20 (m, 5H). $^{13}C$ NMR ($CDCl_3$) $\delta$ 38.08, 45.03, 52.91, 63.46, 126.87, 128.58, 129.24, 136.48.

**2-(3(*S*)-Azido-2(*R*)-hydroxy-4-phenylbutyl)-*N*-*tert*-butyldecahydro-(4a*S*,8a*S*)-isoquinoline-3(*S*)-carboxamide (43) from 42.** A solution of **42** (80% ee) (0.378 g, 2 mmol) in ethanol (2 mL) was added to a stirred solution of **5** (0.476 g, 2 mmol) in ethanol (8 mL) and the solution boiled under reflux for 5 h. The solution deposited white crystals on standing at room temperature overnight. The mixture was evaporated to leave a pale yellow solid. Two recrystallizations from ethyl acetate/hexane (1:1) gave **43** (0.165 g, 19%) as white needles. These were found to be 90% pure by HPLC but also showed the presence of 7% of the diastereomer derived from the enantiomeric epoxide. Proton NMR and MS data were in all major respects identical to that obtained from the authentic coupled product.

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**Supplementary Material Available:** Experimental details for the preparation of **6a** and **7** by the diazomethane route, for **11a** and **12a**, and a full description of the preparation of **39** from either 2-butyne-1,4-diol, or from dimethyl D-tartrate acid (12 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from ACS; see any current masthead page for ordering information.