A Short Stereocontrolled Synthesis of Hydroxyethylene Dipeptide Isosteres

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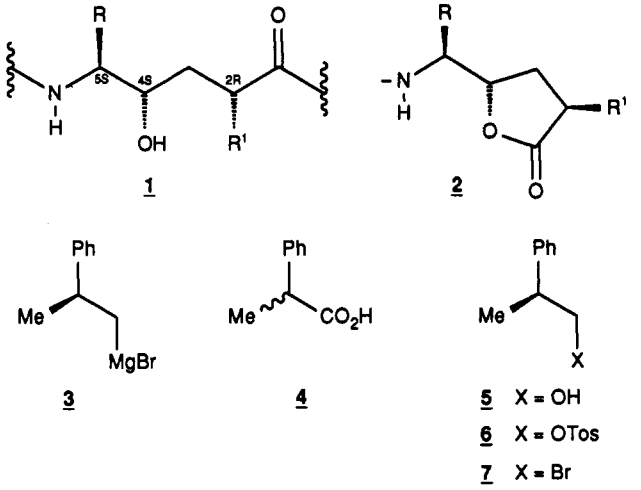
A stereocontrolled synthesis of protected hydroxyethylene dipeptide isosteres **14** and **16** is described. It provides the 2*R*,4*S*,5*S* epimers required for the preparation of aspartic proteinase inhibitors. The choice of a benzene ring as a precursor to the carboxylic acid function has enabled us to use the readily accessible chiral Grignard reagent **3** which reacts with the protected α-amino aldehyde **8** stereoselectively. Kilogram quantities of **16** have been produced by this route in a satisfactory overall yield. The combination of N- and O-protecting groups employed facilitates the incorporation of **14** or **16** into peptide-based enzyme inhibitors.

Introduction

During the past decade or so we have carried out a systematic development of novel dipeptide isosteres which contain a nonhydrolyzable mimic of the tetrahedral transition state formed during the hydrolysis of an amide bond.[1,2] We have demonstrated that such stable isosteres can give rise to potent inhibitors of aspartic proteinases when incorporated into substrates in place of the scissile P_1–P_1' dipeptide.[2-4]

Following the introduction by us in 1980[5] of the hydroxyethylene isosteres **1** and their successful utilization in producing potent inhibitors of human renin,[4,6] a number of other laboratories have also used them in the development of inhibitors for aspartic proteinases such as renin[7] and the HIV-1 proteinase.[8] Many new syntheses of hydroxyethylene dipeptide isosteres have been described.[9] Several of them provide **1** in its lactonized form (**2**) which can be ring-opened with amines (e.g. see ref 9a) or transformed into the *N*-Boc, *O*-TBDMS protected form of **1**[10] prior to incorporation into inhibitors. The Boc, TBDMS combination is not ideal, since when the acid is used to acylate an amino acid derivative, subsequent removal of the Boc group under acidic conditions also cleaves the TBDMS resulting in re-lactonization and cleavage of the amino acid fragment.[10] A few syntheses of **1** are applicable only to a limited choice of R,R^1 side chains or fail to provide adequate steric control.[9] In any event a synthon incorporating the correct stereochemistry at C2 would be advantageous. Toward this end we describe a convenient synthesis of the 2*R*,4*S*,5*S*-hydroxyethylene isostere **1** (R = CH_2Ch, R^1 = Me) using such a synthon. The synthesis also lends itself to large-scale application. A preliminary report of this work was presented at a meeting in 1990.[11]



Results and Discussion

In order to obviate the lactonization problem[10] and to control the stereochemistry at C2, we decided to use the chiral Grignard reagent **3** as one of the two synthons. Rich and his co-workers have reported[33] the use of a similar Grignard reagent having a benzyloxymethyl group rather than phenyl. Reaction of **3** with aldehyde **8** (Scheme I) provides the carbon skeleton of the isostere with the phenyl substituent acting as a precursor to the carboxyl function in **1**.

Resolution of the starting material 2-phenylpropionic acid (**4**) has been described[12] and the absolute configuration of (+)-2-phenylpropanol obtained by reduction of the levorotatory acid (−)-**4** has been shown[13] to be *R*. Ac-

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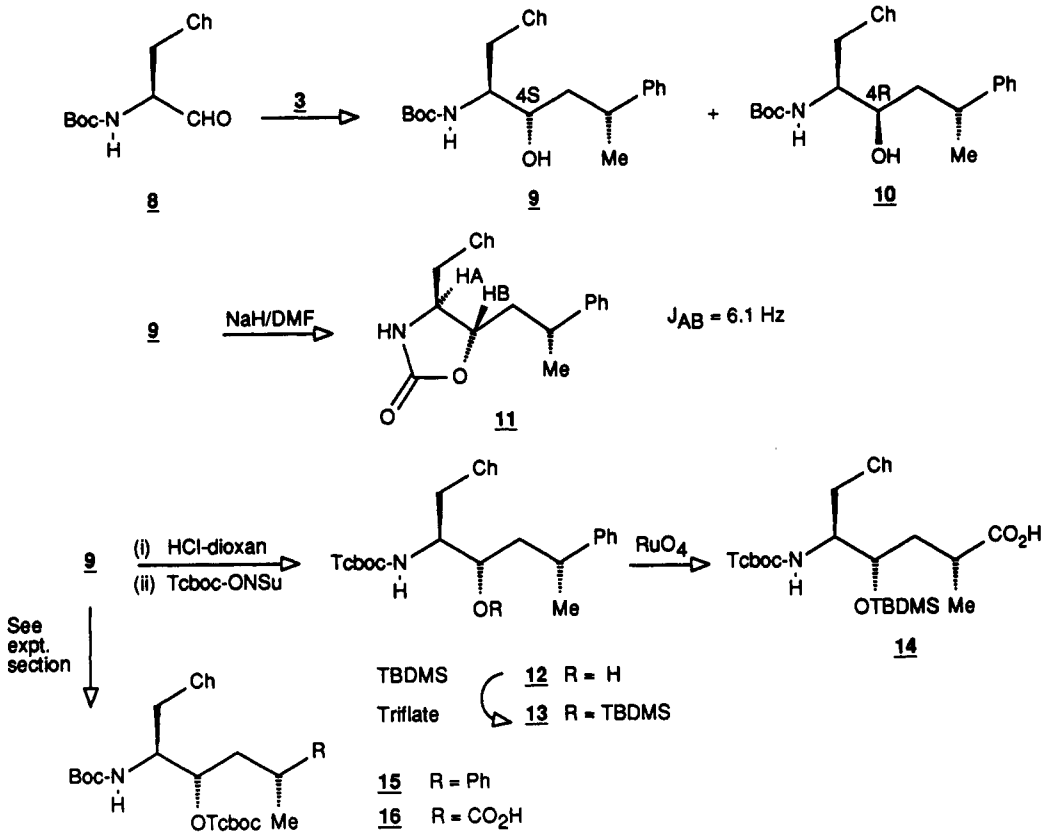
Scheme I



cordingly, the (+)-acid, obtained by resolution of **4** with (*R*)-(+)-α-methylbenzylamine, was reduced with Red-Al to the *S*-(−)-alcohol **5** which was transformed via the tosylate **6** into bromide **7** and finally into the Grignard reagent **3**. The latter reacted smoothly with the aldehyde **8**[32] at room temperature to give a 6:1 mixture of the two diastereomers **9** and **10** which were readily separated by flash chromatography on silica.

The less polar diastereomer **9** was shown to have the required *S*-configuration at C4 by conversion into the oxazolidinone **11** and determination of the coupling constant between H_A and H_B (Scheme I). It has been shown by Futagawa and his co-workers[14] that a trans relationship of H_A and H_B in oxazolidinones gives rise to a coupling constant of 4.5–6 Hz, whereas the cis isomer exhibits a coupling constant of 9–10 Hz. We found J_{AB} = 6.1 Hz for **11**. The predominant formation of the *S*-epimer **9** can be expected if one envisages a chelation-controlled addition of the Grignard reagent to the aldehyde.[15]

In view of the tendency of *N*-Boc-protected 3-hydroxy-4-amino acid derivatives to lactonize during the removal of the Boc group,[10] we replaced the Boc with 2′,2′,2′-trichloro-1′,1′-dimethylethoxycarbonyl (Tcboc).[16] The latter is stable to both acid and base but can be removed readily by zinc in acetic acid. Following removal of the Boc group in **9**, Tcboc was introduced by treatment with *N*-(2′,2′,2′-trichloro-1′-1′-dimethylethyl)succinimidoyl carbonate (prepared by the method of Paquet[17]) rather than via the commercially available chloroformate, in order to obviate any reaction at the hydroxy group. The resulting N-protected alcohol **12** was further protected at the hydroxy function with TBDMS. Attempts to introduce the latter failed both under standard conditions[18] (TBDMS-Cl, imidazole, DMF) and using DBU as the base.[19] However, the fully protected amino alcohol **13** was obtained in 80% yield on treatment of **12** with TBDMS-triflate and 2,6-lutidine[20] at −10 °C. At room temperature TBDMS-triflate reacted also at the urethane function.[21]

We now came to the key step of our synthesis: conversion of the 2-phenyl substituent into carboxy[22] without the loss of chiral integrity at C2. In our hands, the RuO_4-based protocol of Sharpless[23] gave intractable mixtures. No reaction was observed when we applied the method used by Chakraborti and Ghatak[24] for the oxidation of bicyclic compounds containing bridgehead phenyl groups [*cis*-(2,2′-bipyridyl)$_2$RuCl$_2$·2H$_2$O[25] and sodium periodate]. Finally we found the procedure described by Yoshifuji and his co-workers[26] for the oxidation of urethane-protected diamino acids to amides suitable: the treatment of **13** in ethyl acetate with 10% aqueous $NaIO_4$ containing RuO_2·xH_2O for 3 h at room temperature gave 87% yield of the protected acid **14** which was found to be a stable

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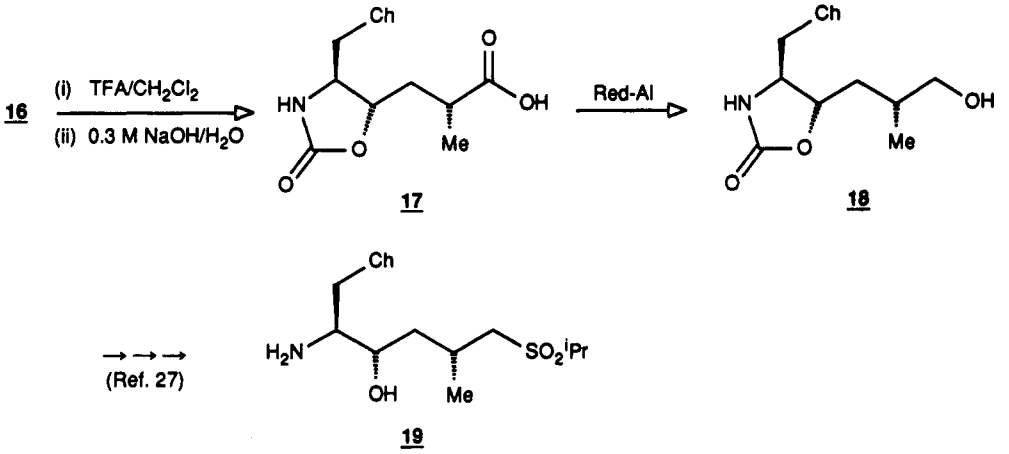
Scheme II



crystalline solid. We have found no evidence of epimerization at C2 in **14** by ^{1}H NMR or TLC and no diastereomers were observed when **14** was incorporated into peptidic renin inhibitors.[6]

Removal of the Tcboc group (Zn powder in 90% acetic acid–H_2O) was complete in a few hours and the TBDMS protection remained unaffected. Renin inhibitors containing this isostere could be treated with tetrabutylammonium fluoride in THF to remove the TBDMS protecting group cleanly.

The Tcboc, TBDMS combination served us well for making a variety of renin inhibitors[6] from **14**. However, when we needed kilogram amounts of one specific inhibitor, the *N*-Boc, *O*-Tcboc compound **16** was chosen to expedite the synthesis on a large scale. Thus **9** and **10** could be O-protected using Tcboc-Cl and the phenyl compound **15** crystallized (95% EtOH) to remove the unwanted 4*R* diastereomer. Degradation of the benzene ring by the procedure described above gave **16** (see Experimental Section for the synthesis of **15** and **16** on a kilogram scale). During the incorporation of **16** into enzyme inhibitors, it was important to remove the Boc group first followed by the Tcboc to prevent lactonization.

Treatment of Boc-deprotected **16** with 0.3 M NaOH/H_2O gave the oxazolidinone **17** in almost quantitative yield, in contrast to the direct oxidation of **11** using the RuO_4 protocol, which furnished **17** in low yield. Subsequent reduction of **17** with Red-Al gave the alcohol **18**—an intermediate which could be converted to another type of hydroxyethylene isostere (**19**)[27] (see Scheme II).

The versatility of this route is further enhanced by the fact that it appears to be applicable to the synthesis of hydroxyethylene isosteres **1** bearing a variety of side-chain groups R and R^1. Using similar methodology we have prepared the hydroxyethylene isosteres of Cha-Val and Leu-Val. The paper by Aaron et al.[12] describing resolution of acid **4** gives details for several other substituted phenylacetic acids, which using our protocol would lead to isosteres **1** having, e.g., R^1 = Et, Pr, ^{i}Pr, ^{t}Bu, and CF_3.

Finally, it should be noted that the RuO_4 oxidation conditions are compatible with other urethane protecting groups, e.g., *p*-nitrobenzyloxycarbonyl and halogenated benzyloxycarbonyl,[28] thus extending the scope of the synthesis. The Fmoc protecting group[29] can be introduced by removing the Tcboc group from **14** followed by reaction with Fmoc-ONSu. This provides a compound which can be incorporated by solid-phase methodology.[30]

Conclusions

In summary we report a versatile new synthesis of hydroxyethylene dipeptide isosteres amenable to large-scale production. The route provides the required 2*R*,4*S*,5*S* isomer diastereoselectively and will tolerate a range of useful protecting groups.

Experimental Section

Melting points were determined on a Büchi 510 apparatus and are uncorrected. Proton nuclear magnetic resonance spectra were recorded on a JEOL 270 MHz instrument unless indicated otherwise. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Mass spectra were determined by M-Scan Ltd, Sunninghill, Ascot, U.K. TLC was performed on 0.25-mm thickness silica gel 60 F254 plates (Merck) and compounds were visualized by UV light and/or by spraying with fluorescamine (1% in acetone) or with exposure to Cl_2 followed by spraying with 1% starch–1% KI in water. For flash chromatography, E. Merck silica gel 230–400 mesh was used. THF was distilled from sodium hydride and used immediately. Petrol refers to petroleum ether fractions, bp 60–80 °C. Elemental analyses were performed by Mikrokemi AB, Uppsala, Sweden.

(*S*)-(+)-2-Phenylpropionic Acid (4). (±)-2-Phenylpropionic acid (500 g, 3.33 mol) in 95% ethanol (1.34 L) was treated with (*R*)-(+)-α-methylbenzylamine (199 g, 1.645 mol). The solution was chilled as rapidly as possible to 4 °C. After 2 days, the salt was filtered off, 232 g. Recrystallization from toluene–ethanol (4:1, 1.25 L) gave the pure salt of **4**, 148 g. Partitioning between ether and 1 M HCl gave the free (+)-acid, 160 g (32%), as a colorless liquid: $[\alpha]^{21}_D$ +76.5° (*c* 1, EtOH) (95% ee) (lit.[12] $[\alpha]^{20}_D$ = +81.1° (*c* 1, EtOH)).

(*S*)-(−)-2-Phenyl-1-propanol (5). Acid (+)-**4** (84.6 g, 563 mmoles) in dry toluene (250 ml) was added with rapid stirring to a solution of 70% Red-Al (483 mL, ~1.690 mol) in toluene diluted with dry toluene (400 mL) at such a rate as to maintain the temperature at 70–80 °C. After addition, the reaction was kept at 90 °C for 2 h and then at room temperature overnight. The reaction mixture was cooled in an ice bath and 3 M HCl/H_2O was added slowly with rapid stirring (pH 1). The acidic aqueous layer was extracted twice with ether and the combined organic

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layers were washed with water, 0.5 M $NaHCO_3$, and brine, dried over Na_2SO_4, filtered, and evaporated to give 73.2 g (95%) of a light yellow liquid which was used without purification in the next step.

(*S*)-(−)-2-Phenyl-1-(tosyloxy)propane (6). Alcohol 5 (46 g, 338 mmol) was dissolved in 800 mL of dry pyridine and cooled (ice bath), and solid tosyl chloride (128.8 g, 670 mmol) was added at such a rate as to maintain the reaction temperature below 4° C. Stirring was continued for 0.5 h and the reaction mixture was left (without stirring) in a refrigerator overnight. It was carefully poured into ice-cold 3 M HCl/H_2O with rapid stirring. Ether was added and the organic phase was separated. The aqueous phase was extracted twice with ether and the combined ether phases were washed repeatedly with ice-cold 3 M HCl until the water phase remained acidic and no smell of pyridine could be detected when a few drops of the ether phase was evaporated on a watch glass. The organic phase was then washed with H_2O, 0.5 M $NaHCO_3$, and brine, dried over Na_2SO_4, and filtered and the ether was evaporated, leaving 95.7 g (97.6%) of a white solid which was used in the next step without further purification.

(*S*)-(−)-1-Bromo-2-phenylpropane (7). To a solution of crude 6 (72 g, 0.338 mol) in dry acetone (300 mL) was added with rapid stirring anhydrous LiBr (58.7 g, 0.676 mol). The mixture was refluxed in the dark for 18 h. The acetone was evaporated and the residue partitioned between ether and H_2O. The aqueous phase was extracted with ether (3x) and the ether layers were washed with brine and dried (Na_2SO_4). Evaporation gave an oil which was distilled, giving 7 as a colorless liquid, 52 g (78% over two steps): bp 100–103 °C at 12 mmHg (lit.[13a] bp 105–106 °C at 11 mmHg); $[\alpha]^{20}_D$ = −18.1° (*c* 1, EtOH) (lit.[31] $[\alpha]^{19}_D$ = −19° (*c* 0.83, benzene)).

(2*R*,4*S*,5*S*)-5-[(*tert*-Butyloxycarbonyl)amino]-6-cyclohexyl-4-hydroxy-2-phenylhexane (9). A suspension of magnesium (1.46 g, 60 mmol) in freshly distilled THF (10 mL) was warmed to 40–50 °C under N_2 and treated with 1,2-dibromoethane (600 mg) followed by dropwise addition of 7 (8 g, 40.16 mmol) in THF (5 mL). The temperature was kept at 40–50 °C with gentle cooling. After addition of the bromide was complete the mixture was stirred for 30 min. A solution of Boc-L-cyclohexylalaninal (*8*)[32] (3.3 g, 12.8 mmol) in THF (10 mL) was added at room temperature over 15 min. After a further 30 min of stirring, the greenish mixture was poured into 0.3 M $KHSO_4$ and the product extracted with ether (3x). The ether extracts were washed with brine, dried, and concentrated to an oil, 6.6 g. Purification by flash chromatography (25% EtOAc–petrol) gave 9 as a colorless oil, 3.2 g (66%): TLC R_f 0.3 in the above system; ^{1}H NMR ($CDCl_3$) δ 0.8 (m, 2 H), 1.05–1.21 (m + d, *J* = 6.9 Hz at 1.19, 9 H), 1.36 (s, 9 H), 1.49–1.80 (m, 7 H), 1.94 (br, 1 H), 2.90 (m, 1 H), 3.16 (m, 1 H), 3.50 (m, 1 H), 4.50 (d, *J* = 9.2 Hz, 1 H), 7.15 (m, 5 H); HRMS (FAB) found $[M + H]^+$ 376.2843 (calcd M = 375.2775).

(2*R*,4*S*,5*S*)-6-Cyclohexyl-4-hydroxy-2-phenyl-5-[(2,2,2-trichloro-1′,1′-dimethylethoxycarbonyl)amino]hexane (12). Compound 9 (3.2 g, 8.52 mmol) was treated with 4 M HCl–dioxane (50 mL) for 1 h at room temperature. The solution was evaporated and the residue in CH_2Cl_2 (20 mL) neutralized with Et_3N to pH 9 on wet indicator paper. Tcboc-ONSu (3.0 g, 9.37 mmol) was added. TLC showed complete reaction after 1.5 h (R_f 0.35 in 25% EtOAc–petrol). The solution was evaporated and the product partitioned between ether and H_2O. The ethereal layer was washed with 0.3 M $KHSO_4$, H_2O, and brine. On evaporation the crude product was chromatographed on silica (25% EtOAc–petrol), giving 12 as an oil, 2.8 g (70%): ^{1}H NMR ($CDCl_3$) δ 0.86 (m, 2 H), 1.10–1.40 (m + d, *J* = 6.9 Hz at 1.27, 9 H), 1.53–1.85 (m, 8 H), 1.90 (s, 6 H), 2.96 (m, 1 H), 3.28 (m, 1 H), 3.56 (m, 1 H), 4.69 (d, 0.2 H), and 4.89 (d, *J* = 9.5 Hz, 0.8 H) [rotamers], 7.3 (m, 5 H); HRMS (FAB) found $[M + H]^+$ = 478.1685 (calcd M = 477.1597).

(2*R*,4*S*,5*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-cyclohexyl-2-phenyl-5-[(2′,2′,2′-trichloro-1′,1′-dimethylethoxycarbonyl)amino]hexane (13). 12 (2.4 g, 5 mmol) was dissolved in dry CH_2Cl_2 (50 mL) and treated with 2,6-lutidine (1.34 g, 12.5 mmol) and cooled to −10 °C, and *tert*-butyldimethylsilyl triflate (1.72 g, 6.5 mmol) was added. After 30 min, water and ethyl acetate were added. The EtOAc layer was washed with 0.3 M $KHSO_4$, H_2O, and brine, dried over Na_2SO_4, filtered, and evaporated. The oil was chromatographed (flash) on silica, eluting with 5% EtOAc in petrol, giving 13, 2.37 g (80%) as an oil: ^{1}H NMR ($CDCl_3$) δ 0.02 (s, 6 H), 0.85 (m, 2 H + s, 9 H), 1.09–1.28 (m, 10 H), 1.54–1.76 (m, 6 H), 1.78 (s, 3 H), 1.86 (s, 3 H), 2.82 (m, 1 H), 3.63 (m, 2 H), 4.66 (d, 0.2 H), and 4.76 (d, *J* = 9.5 Hz, 0.8 H) [rotamers], 7.2 (m, 5 H); HRMS (FAB) found $[M + H]^+$ = 592.2542 (calcd M = 591.2472).

(2*R*,4*S*,5*S*)-4-[(*tert*-Butyldimethylsilyl)oxy]-6-cyclohexyl-2-methyl-5-[(2′,2′,2′-trichloro-1′,1′-dimethylethoxycarbonyl)amino]hexanoic Acid (14). Compound 13 (700 mg, 1.01 mmol) in EtOAc (40 ml) was treated with 10% $NaIO_4$ in H_2O (120 ml) and stirred vigorously. RuO_4 (120 mg) was added and the yellow mixture stirred for 3 h at room temperature. The layers were allowed to settle and the EtOAc was withdrawn with a Pasteur pipette. More EtOAc was added, the mixture was briefly stirred, and the EtOAc was once again withdrawn. This was repeated once more. The combined EtOAc extracts were evaporated and the residue was chromatographed on silica (flash) eluting with 20% EtOAc–petrol containing 0.5% acetic acid, giving 14, 580 mg (87%). Dissolution in petrol and chilling gave a white solid, mp 145–146 °C dec: ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 3 H), 0.09 (s, 3 H), 0.89 (m + s, 11 H), 1.1–1.5 (m, 10 H), 1.63–1.83 (m, 5 H), 1.86–1.94 (m + 4 × s, pair of rotamers, 7 H), 2.63 (m, 1 H), 3.73 (m, 2 H), 4.80 (d, *J* = 9.5 Hz, 0.8 H) + 4.90 (d, 0.2 H) [rotamers]; HRMS (FAB) found $[M + H]^+$ = 560.2117 (calcd M = 559.2044).

(2*R*,4*S*,5*S*)-5-[(*tert*-Butyloxycarbonyl)amino]-6-cyclohexyl-2-phenyl-4-[(2′,2′,2′-trichloro-1′,1′-dimethylethoxycarbonyl)oxy]hexane (15). A 60-L reaction vessel flushed with nitrogen was charged with crude 9 containing approximately 10% of 10 (3.276 kg, 8.73 mol) dissolved in 40 L of dry CH_2Cl_2. Pyridine (1.180 kg, 14.84 mol) was added and the mixture was cooled to 0 °C. Tcboc-Cl (2.159 kg, 8.73 mol) dissolved in 20 L of dry CH_2Cl_2 was then added during 2 h with continued cooling. The reaction mixture was then allowed to reach room temperature and stirring continued overnight. After 16 h more, Tcboc-Cl (432 g, 0.2 equiv) and pyridine (236 g, 0.34 equiv) dissolved in 2 L of CH_2Cl_2 were added with cooling. The reaction mixture was subsequently stirred for 24 h at room temperature. CH_2Cl_2 was evaporated in vacuo and the residue distributed between 20 L of toluene and 20 L of H_2O. The aqueous phase was subsequently extracted twice with 10 L of toluene. The combined organic phases were washed with 2 × 20 L of 0.3 M $KHSO_4$ and 10 L of H_2O. The organic phase was evaporated in vacuo to give a yellow crystalline residue (4.840 kg). Crystallization from 95% EtOH gave white flakes (3.630 kg, 72% yield), mp 127–129 °C dec: 4*S*/*R* 98:2 determined by HPLC (Lichrospher RP Select B, 35% MeCN-H_2O containing 0.1% TFA, flow 1 mL/min; UV detection 220 nm); ^{1}H NMR ($CDCl_3$) δ 0.6–2.0 (m, 15 H), 1.26 (d, 3 H), 1.44 (s, 9 H), 1.89 (s, 3 H), 1.94 (s, 3 H), 2.75–2.90 (m, 1 H), 3.75–3.90 (m, 1 H), 4.45–4.55 (m, 2 H), 7.1–7.5 (m, 5 H) (Varian 200 MHz); FABMS $(M + H)^+$ = 580. Anal. Calcd for $C_{28}H_{42}Cl_3NO_5$: C, 58.08; H, 7.31; N, 2.42. Found: C, 58.3; H, 7.7; N, 2.4.

(2*R*,4*S*,5*S*)-5-[(*tert*-Butyloxycarbonyl)amino]-6-cyclohexyl-4-[(2′,2′,2′-trichloro-1′,1′-dimethylethoxycarbonyl)-oxy]hexanoic Acid (16). To a two-phase system consisting of 15 (1.5 kg, 2.3 mol) in EtOAc (40 L) and $NaIO_4$ (15.7 kg, 73.4 mol) in H_2O (145 L) was added $RuO_2 \cdot xH_2O$ (70 g, 0.53 mol). Stirring was maintained at such a rate as to keep the organic layer slightly yellow (RuO_4). The reaction was monitored by TLC (EtOAc, heptane, HOAc 10:10:1) and the starting material was usually consumed after 55–60 h (sometimes the reaction may require addition of an extra amount of $NaIO_4$ to go to completion). After separation of the EtOAc phase, the water phase was extracted twice with EtOAc (15 L). The combined organic phases were evaporated in vacuo and the black semisolid residue was taken up in heptane (70 L) and applied to a silica gel column, and the product was eluted with a stepwise gradient (Heptane/EtOAc, 1:0, 4:1, 3:2). Fractions containing the product were pooled and

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evaporated in vacuo to give 868 g (69%) of a white solid, mp 168–170 °C dec: ^{1}H NMR ($CDCl_3$) δ 0.65–2.1 (m, 15 H), 1.24 (d, 3 H), 1.44 (s, 9 H), 1.92 (s, 6 H), 2.50–2.68 (m, 1 H), 3.80–3.95 (m, 1 H), 4.57 (d, 1 H), 4.70–4.95 (m, 1 H) (Varian 200 MHz); FABMS $(M + H)^+$ = 547. Anal. Calcd for $C_{23}H_{38}Cl_3NO_7$: C, 50.51; H, 7.00; N, 2.56. Found: C, 50.2; H, 7.2; N, 2.5.

Oxazolidinone 11. To a solution of **9** (0.65 g, 1.73 mmol) in dry DMF (6 mL) was added 55% NaH in paraffin oil (125 mg, 5.2 mmol). After 3 h of stirring at room temperature the mixture was poured into satd NH_4Cl (7 mL). H_2O (7 mL) was added and the product extracted into CH_2Cl_2 (3 × 10 mL). After drying (Na_2SO_4), the material (0.58 g) was purified on silica (heptane–EtOAc, 4:1), giving pure **11**, 0.48 g (92%): mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (m, 1 H), 1.14 (m, 7 H), 1.3 (d, 3 H), 1.65 (m, 5 H), 1.77 (t, 1 H), 2.01 (m, 1 H), 3.03 (m, 1 H), 3.43 (m, 1 H_A), 3.80 (m, 1 H_B), 5.97 (s, 1 H), 7.28 (m, 5 H); $J_{HA,B}$ = 6.1 Hz [Bruker 500 MHz].

Abbreviations. Tcboc, 2′,2′,2′-trichloro-1′,1′-dimethylethoxycarbonyl; Ch, cyclohexyl; Red-Al, sodium bis(2-methoxyethoxy)-aluminum hydride.

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Supplementary Material Available: Proton NMR spectra of compounds **9**, **11**, **12**, **13**, and **14** (5 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 the ACS; see any current masthead page for ordering information.