A General, Catalytic, and Enantioselective Synthesis of (*S*)-γ-[(*S*)-1-Aminoalkyl]-γ-lactones†

Núria Aguilar, Albert Moyano,* Miquel A. Pericàs,* and Antoni Riera

Unitat de Recerca en Síntesi Asimètrica, Departament de Química Orgànica, Facultat de Química, Universitat de Barcelona, Martí i Franquès 1-11, 08028 Barcelona, Spain

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A catalytic asymmetric synthesis of *N*-phthaloyl (*S*)-γ-[(*S*)-1-aminoalkyl]-γ-lactones, widely used intermediates in the preparation of hydroxyethylene dipeptide isosteres, is described. The highly enantiopure epoxy alcohols arising from the Sharpless epoxidation of (*E*)-allyl alcohols are first converted to (*S*)-*N*-phthaloyl-[(*S*)-1-aminoalkyl]oxiranes by means of an efficient four-step sequence involving the regio- and stereoselective ring opening of the starting epoxide by azide, reduction, phthaloylation, and intramolecular Mitsunobu cyclization of the intermediate phthalimido diol. Treatment of the resulting oxirane with lithium (1*R*)-menthyloxyacetylide in the presence of boron trifluoride etherate, followed by in situ hydrolysis of the ynol ether, leads to a (4*R*,5*S*)-5-phthalimido-4-hydroxy ester. A Mitsunobu reaction with *p*-nitrobenzoic acid (which establishes the correct (*S*)-configuration at C-4) and subsequent selective saponification of the benzoate and cyclization of the inverted hydroxy ester afford the target N-protected (*S*)-γ-[(*S*)-1-aminoalkyl]-γ-lactones. Using this methodology, lactones **19** and **26** were obtained in seven steps from the readily available epoxy alcohols **5** and **20**, respectively, in high enantiomeric purity.

Introduction

2,5-Disubstituted (2*R*,4*S*,5*S*)-5-amino-4-hydroxypentanoic acids (**1**) provide the structural motif of the hydroxyethylene dipeptide isostere unit and are therefore present in some of the most efficient and selective inhibitors of the key aspartic proteases, renin[1] and the virally encoded HIV-1 protease (see Figure 1).[2]

Due to the pharmacological significance, of δ-amino-γ-hydroxy acids **1**, several synthetic strategies directed toward the stereocontrolled preparation of these compounds have been explored in the past few years.[3−6] An important number of these routes rely on the alkylation of N-protected (*S*)-γ-[(*S*)-1-aminoalkyl]-γ-lactones **2**, which takes place almost exclusively from the C_2-*re* face of the corresponding enolate (Scheme 1). The requisite γ-lactones are, in turn, usually obtained from N-protected α-amino aldehydes or other α-amino acid derivatives by means of more or less stereospecific reaction sequences which depend on the chirality of the starting amino acid to direct the formation of the stereogenic center of the lactone ring.[3] A catalytic asymmetric synthesis of lactones **2** from readily available achiral starting materials that could provide access to both enantiomers and that could accommodate a large variety of R^1 substituents would obviously be of interest but is conspicuously absent from the literature. We report in this paper the full

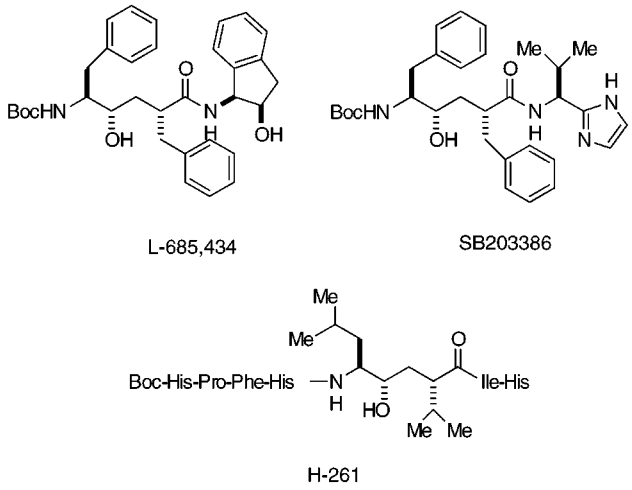
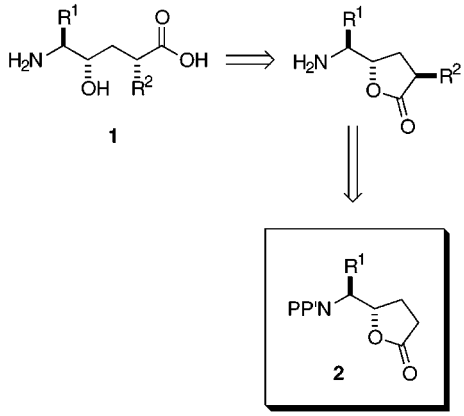


Figure 1. Representative examples of aspartic protease inhibitors.

Scheme 1



† We dedicate this paper to our colleague Francesc Trull, in memoriam.

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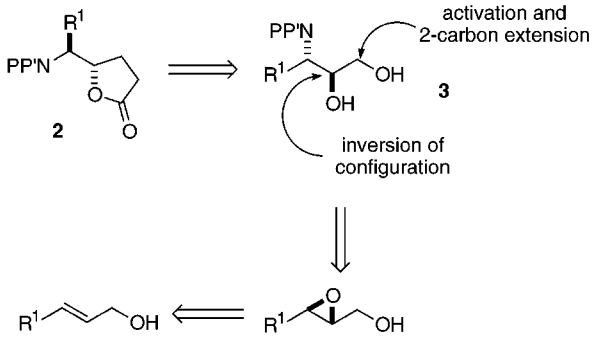
details of a novel synthetic procedure which fulfills these requirements and which allows the efficient and enantioselective preparation of lactones **2** from (*E*)-allyl alcohols through the use of the catalytic Sharpless epoxidation[7] as the only external source of chirality.

Results and Discussion

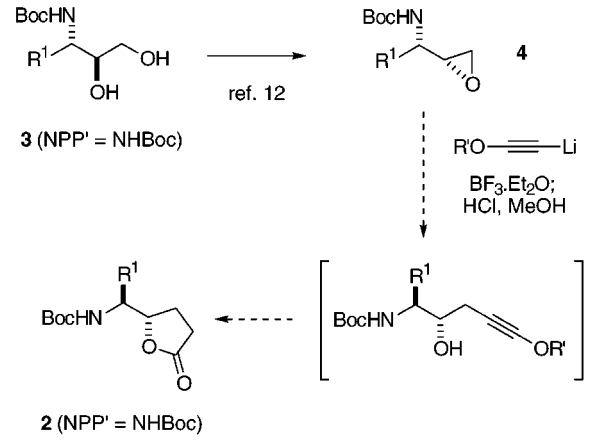
In an ongoing line of research of our laboratory, we have been exploring the synthetic utility of anti N-protected 3-amino-1,2-alkanediols of general structure **3**, which can be obtained in high enantiomeric purity by asymmetric epoxidation of (*E*)-allyl alcohols, followed by the regio- and stereoselective ring opening (by primary amines or by other nitrogen nucleophiles) of the resulting epoxy alcohols.[8] In particular, aminodiols **3** with NPP′ = NHBoc have been efficiently transformed into α-amino acids,[9] β-amino acids,[10a,d] β-amino-α-hydroxy acids,[10b−d] and γ-amino-β-hydroxy acids.[11] A simple retrosynthetic analysis of lactones **2** shows that these compounds can also be derived from aminodiols **3** by activation of the primary hydroxyl, substitution by an acetate enolate synthon, and inversion of configuration at C-2 (Scheme 2).

Scheme 2



Attempting to implement this synthetic strategy for the first time and taking into account that anti aminodiols **3** can be converted into the corresponding syn (1-aminoalkyl)epoxides **4**,[12] we explored the feasibility of effecting the regioselective opening of the oxirane ring in **4** with a 1-alkoxyacetylide, followed by in situ acid-promoted cyclization of the resulting β-hydroxyalkyne to the γ-lactone (Scheme 3). It is worth noting that epoxides **4** do not react directly with simple acetate enolates,[3a] so that the use of an 1-alkoxyacetylene as an acetic acid enolate synthetic equivalent appeared to be an attractive way to overcome this difficulty.

Scheme 3



To investigate the feasibility of this approach, we prepared (*R*)-2-[(*S*)-1-(*t*-butoxycarbonylamino)-2-phenylethyl]oxirane (**4**, $R^1 = CH_2Ph$), chosen as a model, by means of the methodology previously developed in our laboratory.[12] Nevertheless, the reaction of this epoxide with the lithium derivatives of several 1-alkoxyethynes (*n*-decyloxyethyne, *t*-butoxyethyne, and (1*R*)-menthyloxyethyne) under the conditions reported by Schreiber for a related transformation (2.5 molar equiv of the acetylide, 2.5 molar equiv of boron trifluoride etherate, THF, −78

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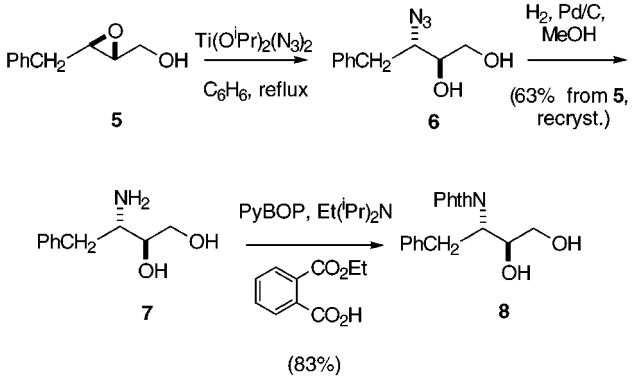
Scheme 4

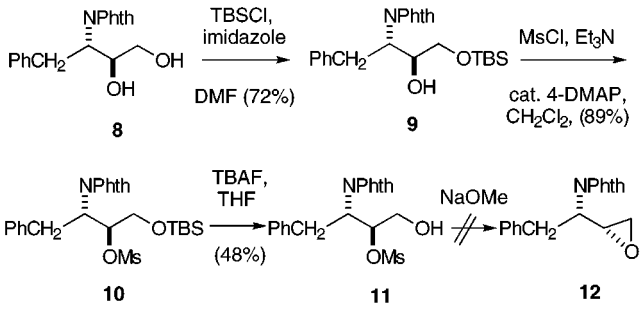


°C)[13] did not lead to the desired lactone, complex mixtures of products being obtained in all instances.[14] Given that the origin of these problems could be traced both to the instability of the *t*-butoxycarbonylamino function in the presence of boron trifluoride and to the acidic nature of the carbamate NH, a change in the nature of the nitrogen protecting group was next investigated. We reasoned that the phthaloyl function should be more suitable for our purposes due to its greater resistance to acidic media (relative to that of the benzyloxycarbonyl or *t*-butoxycarbonyl groups)[15].

We set out, therefore, to prepare the previously unknown (2*S*,3*S*)-4-phenyl-3-phthalimido-1,2-butanediol **8** in order to assay its conversion into the corresponding *syn*-epoxide. The preparation of the phthalimido diol **8**, which took place according to our expectations, is summarized in Scheme 4.

(2*R*,3*R*)-2,3-Epoxy-4-phenylbutan-1-ol **5** (obtained in 94% ee by catalytic Sharpless epoxidation of (*E*)-4-phenyl-2-buten-1-ol with D-(−)-DIPT)[16] was first treated with titanium (diazido)diisopropoxide in refluxing benzene,[17] affording the expected (2*S*,3*S*)-4-phenyl-3-azidobutan-1,2-diol (**6**) in essentially quantitative yield. Without further purification, **6** was submitted to catalytic hydrogenation to provide the corresponding amino diol **7** in 90% yield.

Scheme 5



To increase its optical purity, this compound was recrystallized from ethyl acetate. In this way, enantiomerically pure **7** could be readily secured from epoxy alcohol **5** in a 63% global yield. Finally, **7** was converted into the desired phthalimido diol **8** by means of the PyBOP mediated procedure recently developed in our laboratories.[18] According to the ^{19}F NMR spectrum of the Mosher diester,[19] the enantiomeric purity of the so-prepared **8** is higher than 98.5%.

With **8** in our hands, all that remained for the synthesis of the *syn*-epoxide **12** was the silylation of the primary hydroxyl, the mesylation of the secondary one, and the fluoride-induced desilylation−cyclization of the resulting silyloxy mesylate, as we had previously established for the preparation of the *N*-Boc analogue **4** (R^1 = CH_2Ph). Although the first two steps of the sequence took place uneventfully (Scheme 5), all our attempts to obtain **12** from the mesylate **10** were unsuccessful. In effect, while the treatment of **10** with anhydrous tetrabutylammonium fluoride (TBAF) in THF allowed the isolation of the unstable hydroxy mesylate **11** in moderate yields, the subsequent assays of base-induced cyclization of **11** (obtained either in situ or after isolation) under a variety of conditions (KO^{t}Bu, NaOMe, or *n*BuLi in THF, KO^{t}Bu/DMF) led either to the recovery of the starting material or to the production of complex mixtures of products in which the desired epoxide **12** could not be identified. Eventually, the activation of the hydroxyl group of **9** as a triflate (triflic anhydride, Et^{i}Pr$_2$N, CH_2Cl_2) and the subsequent reaction with TBAF/NaOMe produced the epoxide **12** in low yields together with substantial amounts of the starting phthalimido diol **8**.[20]

It is worth noting here that although **12** could also in principle be obtained from a *syn*-*N*-phthaloyl-3-amino-1,2-diol (ultimately arising from a *cis*-epoxy alcohol through nucleophilic ring opening), this approach is very likely to meet with serious practical difficulties. In effect, it is well-known that, in general, the Sharpless epoxidation of (*Z*)-allyl alcohols takes place with rates and enantioselectivities lower than that of the corresponding (*E*)-allyl alcohols;[7c] moreover, the nucleophilic ring opening of *cis*-epoxy alcohols proceeds with low yields and/or regioselectivities.[9d,10c]

In view of the difficulties encountered in the preparation of the *syn*-(1-phthalimidoalkyl)epoxides, we decided to invert the order of synthetic operations in Scheme 2

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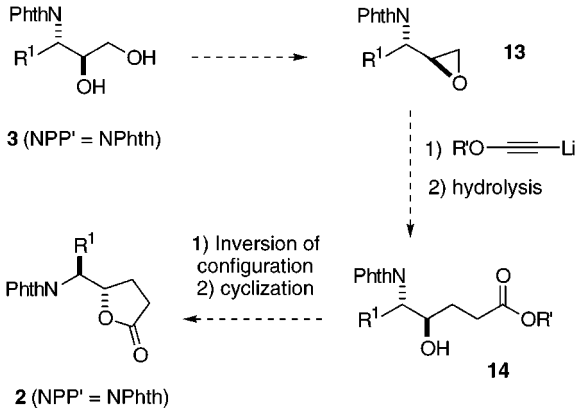
(20) Similar negative results were obtained in the attempted conversion of (2*S*,3*S*)-*N*-phthaloyl-3-aminobutan-1,2-diol[18] into the corresponding (*R*)-2-[(*S*)-1-phthalimidoethyl]oxirane.

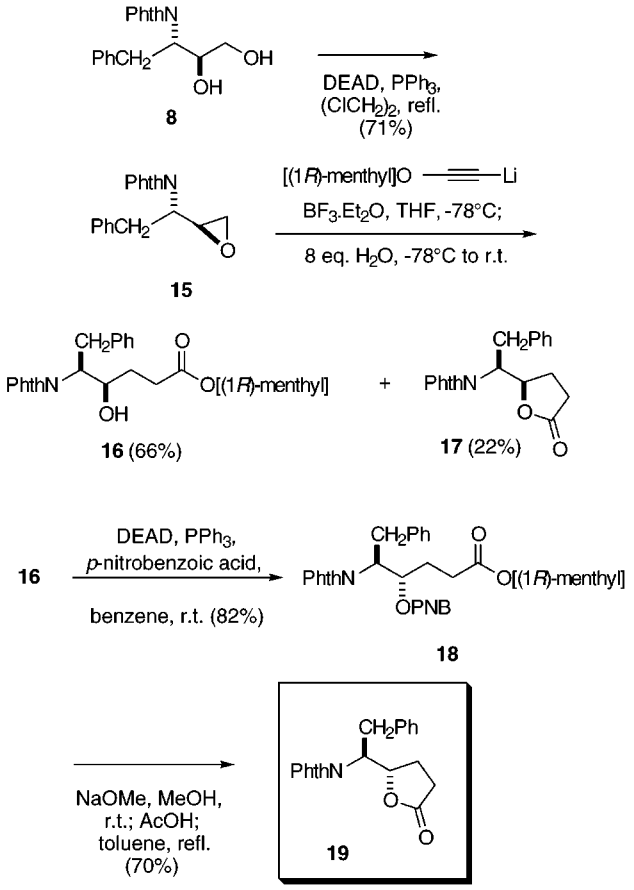
Scheme 6



and postpone the configuration inversion at C-2 to a more advanced stage after the two-carbon extension of the starting amino diol. According to this new strategy, the starting *anti*-3-phthalimido-1,2-alkanediol **3** would be first converted to an anti epoxide (**13**), which by opening with alkoxyacetylide (as a synthetic equivalent of an acetic ester enolate) and by careful hydrolysis should furnish an intermediate hydroxyester **14**. Due both to its ready availability[21] and to the possibility of controlled hydrolysis, (1*R*)-menthyloxyethyne was selected as the alkoxyacetylene of choice for this application. Inversion of configuration of the secondary alcohol of **14** followed by cyclization would then provide the phthaloyl-protected lactone **2** (Scheme 6).

The implementation of this approach in the case of the phthalimido diol **8** is outlined in Scheme 7. In the first place, the intramolecular Mitsunobu reaction[12,22] of **8** (1.07 equiv of DEAD, 1.07 equiv of Ph_3P in refluxing dichloroethane) cleanly accomplished the desired conversion into oxirane **15** with complete retention of configuration at C-2, as demonstrated by the fact that the global chemical purity of **15**, measured by DSC techniques,[23] was higher than 98.9%, in accordance with the enantiomeric purity of **8**. Exposure of a THF solution of **15** to lithium (1*R*)-menthyloxyacetylide[21] in the presence of boron trifluoride etherate at low temperature followed by carefully controlled hydrolysis of the ynol ether (8 equiv of water and slow warming to rt) gave, after chromatographic purification, the stereoisomerically pure (4*R*)-hydroxyester **16** in good yield (66%).[24] The requisite inversion of configuration at C-4 could then be easily performed by Mitsunobu methodology, with *p*-nitrobenzoic acid as the nucleophile,[10c,25] and the (4*S*)-diester **18** was obtained in high yield. The selective hydrolysis of the *p*-nitrobenzoate moiety in **18** was best accomplished with 2 equiv of NaOMe in MeOH at rt. The intermediate (4*S*)-hydroxy ester, which was not isolated, was directly submitted to acid-promoted cyclization to afford the

Scheme 7



N-phthaloyl lactone **19**, a new potential precursor of selective HIV-1 protease inhibitors such as L-685,434[2c] and SB203386.[26]

An additional assessment of the versatility of our approach was provided by the stereoselective synthesis of the *N*-phthaloyl-(*S*)-γ-[(*S*)-1-amino-3-methylbutyl]-γ-lactone **26**, a valuable potential intermediate in the synthesis of the aspartic protease inhibitor H-261[27] (Scheme 8). The key phthalimidodiol intermediate **21** was obtained in 46% overall yield from the known[28] epoxy alcohol **20** (89% ee) by means of the azide opening−hydrogenation−phthaloylation sequence that we have just described and converted to the oxirane **22** in 69% yield. As in the previous case, the boron trifluoride-mediated reaction of **22** with lithium (1*R*)-menthyloxyacetylide, followed by hydrolysis, gave access to the hydroxy ester **23** (61% yield), as well as to minor amounts of the (5*R*)-lactone **24**.[29] The inverted *p*-nitrobenzoate **25**, arising from **23** by Mitsunobu reaction, could be selectively saponified by exposure to NaOMe/MeOH, and the resulting hydroxy ester led to the target lactone **26** by being heated in a weakly acidic toluene solution. The ee of **26**, measured by HPLC, was not less than 97.6%,

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(22) (a) Mitsunobu, O. *Synthesis* **1981**, 1−28. (b) Robinson, P. L.; Barry, C. N.; Bass, S. W.; Jarvis, S. E.; Evans, S. A., Jr. *J. Org. Chem.* **1983**, *48*, 5396−5398.

(23) Jacques, J.; Collet, A.; Wilen, S. H. *Enantiomers, Racemates, and Resolutions*; John Wiley & Sons: New York, 1981; pp 151−159.

(24) Small amounts (ca. 20%) of the (*R*)-γ-[(*S*)-1-phthalimidoalkyl]-γ-lactone **17** could also be isolated, although not in totally pure form, from the reaction mixture. This compound showed both ^1H and ^{13}C NMR spectra clearly different from that of its diastereomer **19**.

(25) Martin, S. F.; Dodge, J. A. *Tetrahedron Lett.* **1991**, *32*, 3017−3020.

(26) Abdel-Meguid, S. S.; Metcalf, B. W.; Carr, T. J.; Demarsh, P.; Desjarlays, R. L.; Fisher, S.; Green, D. W.; Ivanoff, L.; Lambert, D. M.; Murthy, K. H. M.; Petteway, S. R.; Pitts, W. J.; Tomaszek, T. A.; Winborne, E.; Zhao, B.; Dreyer, G.; Meek, T. D. *Biochemistry* **1994**, *33*, 11671−11677.

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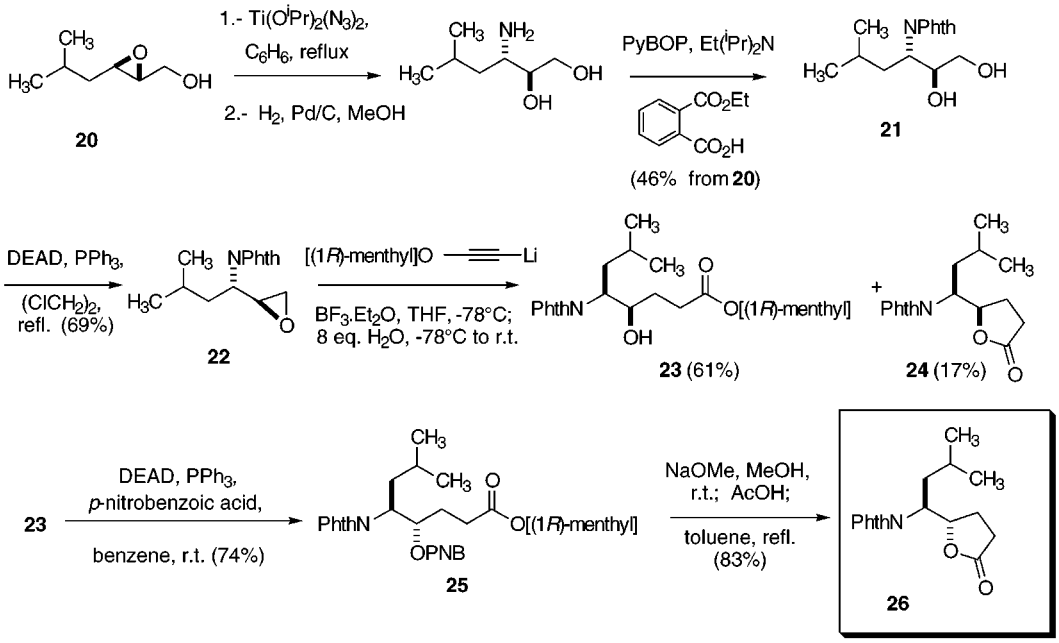
(28) (a) Wood, J. L.; Jones, D. R.; Hirschmann, R.; Smith, A. B., III. *Tetrahedron Lett.* **1990**, *31*, 6329−6330. (b) Bertelli, L.; Fiaschi, R.; Napolitano, E. *Gazz. Chim. Ital.* **1993**, *123*, 521−524.

(29) Minor amounts (17% yield estimated by NMR) of the (5*R*)-lactone **24** were also obtained after chromatographic purification.

Scheme 8



indicating that a significant enantiomeric enrichment had taken place along the reaction sequence, probably at the level of the ester **23**. Finally, it is worth mentioning that lactone **26** of very high enantiomeric purity (ee higher than 99.97%, according to HPLC) can be obtained if the intermediate *p*-nitrobenzoate **25** is submitted to a single recrystallization from hexane.

In summary, we report in this article a new approach for the highly enantioselective preparation of N-protected (*S*)-γ-[(*S*)-1-aminoalkyl]-γ-lactones **2**, which takes place in only seven steps from the chiral epoxy alcohols generated by the catalytic asymmetric epoxidation of (*E*)-allyl alcohols. Contrary to most of the previous routes to these important precursors of the δ-amino-γ-hydroxy acid unit of hydroxyethylene dipeptide isosteres, the present one does not rely on the availability of specific enantiopure α-amino acids or α-amino aldehydes as starting materials, and all steps take place with complete stereochemical control. Moreover, both enantiomers of lactones **2** are equally available through this approach, given that the precursor epoxy alcohols can be obtained in both enantiomeric forms.

Experimental Section

General. Melting points were determined in an open capillary tube and are uncorrected. Optical rotations were measured at rt (23 °C). Infrared spectra were recorded using NaCl film or KBr pellet techniques. ^{1}H NMR spectra were recorded at 200 or 300 MHz in $CDCl_3$, unless specified otherwise, with tetramethylsilane as internal standard. ^{13}C NMR spectra were recorded at 50.3 or 75.4 MHz in $CDCl_3$, unless specified otherwise, with $CHCl_3$ as internal standard. Signal multiplicities were established by DEPT experiments. Mass spectra were recorded at 70 eV ionizing voltage; ammonia was used for chemical ionization (CI) and glycerol for fast atom bombardment (FAB). High-resolution mass spectra (CI) were performed by the "Servicio de Espectrometría de Masas, Universidad de Córdoba". Elemental analyses were performed by the "Servei d'Anàlisis Elementals del CSIC de Barcelona". THF was distilled from sodium benzophenone ketyl, and benzene and toluene were dried over sodium. Dichloromethane, 1,2-dichloroethane, and DMF were distilled from CaH_2. Commercially available pure dry methanol (Aldrich) was used when indicated. All reactions were performed in flame- or oven-dried glassware under a N_2 atmosphere. Reaction progress was followed by TLC. Silica gel (70−230 mesh) was used for column chromatography; hexanes−ethyl acetate mixtures of increasing polarity were used as eluents, unless specified otherwise.

(*2S,3S*)-3-Amino-4-phenylbutane-1,2-diol, 7. To a preheated (70−80 °C) suspension of $Ti(O^iPr)_2(N_3)_2$[17b] (5.47 g, 21.9 mmol, 1.3 equiv) in dry benzene (80 mL) under argon was added a solution of (*2R,3R*)-2,3-epoxy-4-phenylbutan-1-ol (**5**)[16] (2.99 g, 18.2 mmol) of 94% ee (HPLC, CHIRALCEL OD column) in dry benzene (100 mL), and the mixture was heated at 70−80 °C for 10−15 min. Benzene was eliminated in vacuo, and the resulting crude was vigorously stirred with a mixture of diethyl ether (335 mL) and 5% aqueous H_2SO_4 (130 mL) until both layers were completely transparent. The mixture was transferred to a separation funnel, and the aqueous layer was then extracted twice with dichloromethane. The combined organic layers were dried over Na_2SO_4, and the solvent was eliminated in vacuo. The crude (2*S*,3*S*)-3-azido-4-phenylbutane-1,2-diol **6** thus obtained was dissolved in methanol (40 mL), and the solution was added on a suspension of 10% Pd/C (0.377 g) in methanol (40 mL) under hydrogen (1 atm). The suspension was stirred at rt for 24 h and then filtered over Celite. Methanol was evaporated in vacuo, and 2.96 g of (2*S*,3*S*)-3-amino-4-phenylbutane-1,2-diol **7** (90% yield) was obtained as a yellow solid. Recrystallization from ethyl acetate gave 2.07 g (63% yield) of enantiomerically enriched **7**: mp 105−107 °C; $[\alpha]_D = -34.2$ (c = 1.37, MeOH); IR (KBr) ν_{max} 3300, 3080, 2920, 2860, 1610, 1080, 1050 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD) δ 2.42−2.59 (m, 1H), 2.95−3.05 (m, 2H), 3.55−3.77 (m, 3H), 7.20−7.38 (m, 5H) ppm; ^{13}C NMR (50 MHz, CD_3OD) δ 40.0 (CH_2), 56.2 (CH), 64.8 (CH_2), 75.4 (CH), 127.4 (CH), 129.6 (CH), 130.4 (CH), 140.4 (Cq) ppm; MS (CI) *m/z* (relative intensity) 182 (MH^+, 100), 199 (MNH_4^+, 6). Anal. Calcd for $C_{10}H_{15}NO_2$: C, 66.27; H, 8.35; N, 7.72. Found: C, 66.27; H, 8.33; N, 7.80.

(*2S,3S*)-4-Phenyl-3-phthalimidobutane-1,2-diol, 8. To a suspension of PyBOP (2.84 g, 5.46 mmol, 1.1 equiv) in dry THF (10 mL) was added a solution of 2-ethoxycarbonylbenzoic acid[30] (1.08 g, 5.46 mmol, 1.1 equiv) in THF (10 mL) and Et^{i}Pr$_2$N (1.27 mL, 7.44 mmol, 1.5 equiv), and the resulting mixture was stirred for 30−40 min at rt. Afterwards, this

(30) 2-(Ethoxycarbonyl)benzoic acid was obtained in essentially quantitative yield by refluxing phthalic anhydride in absolute ethanol: *Beilstein*, H**9**, 797b.

solution was added to a suspension of **7** (0.898 g) in THF (10 mL) at 0 °C, and the mixture was stirred at rt for 3 h. The solvent was eliminated in vacuo, and the residue was heated at 85 °C overnight. The reaction mixture was then dissolved in 250 mL of dichloromethane and washed with saturated $NaHCO_3$ solution (2 × 100 mL) and with brine (100 mL). The organic layer was dried (Na_2SO_4) and evaporated to give a crude product which was purified by column chromatography to yield 1.28 g of (2*S*,3*S*)-4-phenyl-3-phthalimidobutane-1,2-diol (**8**) (83%) as a white solid: mp 91−93 °C; $[\alpha]_D = -177.7$ (*c* = 1.05, CH_2Cl_2) [ee > 98.5%]; IR (KBr) ν_{max} 3480, 3020, 2950, 1785, 1710 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 3.22−3.43 (m, 2H), 3.58−3.75 (m, 2H), 4.20−4.32 (m, 1H), 4.55−4.62 (m, 1H), 7.08−7.20 (m, 5H), 7.62−7.81 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.3 (CH_2), 56.5 (CH), 65.1 (CH_2), 72.8 (CH), 123.9 (CH), 127.3 (CH), 129.2 (CH), 129.9 (CH), 132.6 (Cq), 135.4 (CH), 139.5 (Cq), 169.6 (Cq) ppm; MS (CI) *m*/*z* (relative intensity) 312 (MH^+, 15), 329 (MNH_4^+, 100). Anal. Calcd for $C_{18}H_{17}NO_4 \cdot H_2O$: C, 65.64; H, 5.81; N, 4.25. Found: C, 65.59; H, 5.59; N, 4.26. According to ^{19}F NMR (282.2 MHz, $CDCl_3$, TFA as external reference), a single set of signals (−72.03, −72.61 ppm for the (*S*)-diester; −72.30, −72.57 ppm for the (*R*)-diester) was observed for each one of the corresponding Mosher diesters of **8**.

(2*S*,3*S*)-1-(*tert*-Butyldimethylsilyloxy)-3-(phthalimido)-4-phenylbutan-2-ol, 9. A solution of the diol **8** (0.500 g, 1.61 mmol), *tert*-butyldimethylsilyl chloride (0.275 g, 1.76 mmol, 1.1 equiv), and imidazole (0.240 g, 3.54 mmol, 2.2 equiv) in anhydrous DMF (2 mL) was stirred at rt for 24 h. The mixture was then poured over water (10 mL) and extracted with dichloromethane (3 × 10 mL). The combined organic layers were washed with saturated NH_4Cl solution (25 mL) and dried over Na_2SO_4. After the organic layers were concentrated in vacuo, purification of the residue by column chromatography gave 0.496 g (72%) of **9**: white solid; mp 63−65 °C; $[\alpha]_D = -125.0$ (*c* = 1.08, $CHCl_3$) IR (KBr) ν_{max} 3480, 3030, 2930, 2860, 1780, 1715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.02 (s, 3H), 0.03 (s, 3H), 0.92 (s, 9H), 3.33 (d, *J* = 8 Hz, 2H), 3.48 (broad d, 1H), 3.58−3.68 (m, 2H), 4.20−4.38 (m, 1H), 4.62−4.78 (m, 1H), 7.10 (s, 5H), 7.60−7.78 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.8 (CH_3), 18.0 (Cq), 25.6 (CH_3), 33.1(CH_2), 54.2 (CH), 63.7 (CH_2), 72.3 (CH), 123.2 (CH), 126.0 (CH), 128.2 (CH), 128.7 (CH), 130.9 (Cq), 133.8 (CH), 137.8 (Cq), 168.4 (Cq); MS (CI) *m*/*z* (relative intensity) 426 (MH^+, 43), 443 (MNH_4^+, 100). Anal. Calcd for $C_{24}H_{31}NO_4Si$: C, 67.73; H, 7.34; N, 3.29. Found: C, 67.52; H, 7.34; N, 3.32.

(1*S*,2*S*)-1-(*tert*-Butyldimethylsilyloxy)methyl-2-phthalimido-3-phenylpropyl Methanesulfonate, 10. To a solution of **9** (0.256 g, 0.60 mmol) in dry dichloromethane (0.5 mL) were added Et_3N (93 μL, 0.66 mmol, 1.1 equiv) and 4-DMAP (12 mg). The mixture was cooled at −15 °C, and methanesulfonyl chloride (50 μL, 0.66 mmol, 1.1 equiv) in dichloromethane (1 mL) was added. The mixture was stirred at rtovernight. Dichloromethane (20 mL) was then added to the reaction mixture, and it was washed with 5% aqueous HCl (2 × 20 mL), saturated $NaHCO_3$ (25 mL), and brine (25 mL). After the mixture was dried (Na_2SO_4) and the solvent was evaporated, 0.271 g of **10** (89%) were obtained: colorless oil; $[\alpha]_D = -94.0$ (*c* = 1.4, $CHCl_3$); IR (film) ν_{max} 3040, 2940, 2860, 1780, 1720, 1320, 1185 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ −0.02 (s, 3H), −0.05 (s, 3H), 0.81 (s, 9H), 3.14 (s, 3H), 3.22−3.58 (m, 2H), 3.77−3.98 (m, 2H), 4.78−4.92 (m, 1H), 5.25−5.36 (m, 1H), 7.12 (s, 5H), 7.63−7.75 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ −5.67 (CH_3), 18.2 (Cq), 25.7 (CH_3), 33.9 (CH_2), 38.7 (CH_3), 52.4 (CH), 63.2 (CH_2), 81.5 (CH), 123.2 (CH), 126.7 (CH), 128.4 (CH), 128.8 (CH), 131.0 (Cq), 134.0 (CH), 136.7 (Cq), 168.5 (Cq); MS (CI) *m*/*z* (relative intensity) 521 (MNH_4^+, 100). HRMS (CI) calcd for $C_{25}H_{34}NO_6SSi$ [MH^+] 504.1878, found 504.1855.

(*S*)-[(*S*)-2-Phenyl-1-phthalimidoethyl]oxirane, 15.[31] To a solution of (2*S*,3*S*)-4-phenyl-3-phthalimidobutane-1,2-diol (**8**) (0.600 g, 1.93 mmol) and Ph_3P (0.540 g, 2.06 mmol, 1.07 equiv) in dry 1,2-dichloroethane (8 mL) was added dropwise a solution of DEAD (0.372 g, 2.06 mmol, 1.07 equiv) in dry 1,2-dichloroethane (7 mL), and the mixture was refluxed for 38 h. The solvent was evaporated in vacuo to give a crude product which was purified by column chromatography to give 0.401 g of the oxirane **15** (71%): white solid; mp 131−132 °C (lit.[31] mp 180−182 °C; we have no explanation for this discrepancy); $[\alpha]_D = -156.1$ (*c* = 1.14, CH_2Cl_2) [lit.[31] $[\alpha]^{20}_D = -155.2$ (*c* = 0.5% in CH_2Cl_2)]; [ee > 98.9%, according to DSC]; IR (KBr) ν_{max} 3080, 2960, 2930, 1780, 1710 cm^{-1}; ^1H NMR (300 MHz, d_6-DMSO) δ 2.58 (dd, *J* = 4.8 Hz, *J*′ = 2.7 Hz, 1H), 2.77 (dd, *J* = 4.8 Hz, *J*′ = 3.9 Hz, 1H), 3.19 (dd, *J* = 13.8 Hz, *J*′ = 5.1 Hz, 1H), 3.44 (dd, *J* = 13.8 Hz, *J*′ = 11.1 Hz, 1H), 3.52 (ddd, *J* = 6.6 Hz, *J*′ = 4.1 Hz, *J*″ = 2.7 Hz, 1H), 4.12 (ddd, *J* = 11.1 Hz, *J*′ = 5.1 Hz, *J*″ = 6.1 Hz), 7.09−7.19 (m, 5H), 7.80 (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 35.6 (CH_2), 46.5 (CH_2), 51.8 (CH), 55.7 (CH), 123.3 (CH), 126.6 (CH), 128.4 (CH), 128.8 (CH), 131.4 (Cq), 134.0 (CH), 136.9 (Cq), 168.0 (Cq) ppm.

(1*R*)-Menthyl (4*R*,5*S*)-4-Hydroxy-6-phenyl-5-phthalimidohexanoate, 16. To a solution of the oxirane **15** (0.173 g, 0.59 mmol) in dry THF (2 mL) at −78 °C was added dropwise freshly distilled $BF_3 \cdot Et_2O$ (180 μL, 1.46 mmol, 2.5 equiv), and the mixture was stirred at the same temperature for 40 min. Meanwhile, to a solution of (*1R*)-menthyloxyethine[21] (0.317 g, 1.76 mmol, 3 equiv) in dry THF (1 mL) at −78 °C was added a 1.4 M solution of *n*BuLi in hexanes (1.06 mL, 1.46 mmol, 2.5 equiv), and the mixture was also stirred at −78 °C for 40 min. This solution was added over the first one, and the mixture was stirred at −78 °C for 1.5 h. Finally, H_2O (85 μL, 4.70 mmol, 8 equiv) was added, and the mixture was allowed to slowly reach rt. Subsequently, diethyl ether (10 mL) was added, and the reaction mixture was washed with saturated $NaHCO_3$ (2 × 10 mL) and with brine (10 mL). The organic layer was dried (Na_2SO_4), and the solvents were evaporated in vacuo to give a crude product which was purified by column chromatography to yield (*1R*)-menthyl-(*4R*,*5S*)-4-hydroxy-6-phenyl-5-phthalimidohexanoate (**16**) (0.192 g, 66% yield) as a colorless oil. A fraction containing 46 mg (22% estimated by NMR) of impure (*5R*)-5-[(*1S*)-2-phenyl-1-phthalimidoethyl]-dihydrofuran-2(*3H*)-one (**17**) was also isolated.

(1*R*)-Menthyl (4*R*,5*S*)-hydroxy-6-phenyl-5-phthalimidohexanoate (16): colorless oil; $[\alpha]_D = -125.1$ (*c* = 1.58, $CHCl_3$); IR (film) ν_{max} 3460, 3020, 2950, 2920, 2860, 1775, 1715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.71−0.91 (m, 12H), 1.10−2.00 (m, 8H), 2.39−2.61 (m, 2H), 3.21−3.42 (m, 2H), 3.79−3.81 (m, 1H), 4.17−4.22 (m, 1H), 4.47 (dt, *J* = 10.5 Hz, *J*′ = 5.8 Hz, 1H), 4.68 (td, *J* = 4.4 Hz, *J*′ = 11.0 Hz, 1H), 7.11 (s, 5H), 7.62−7.81 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.2 (CH_3), 20.7 (CH_3), 22.0 (CH_3), 23.3 (CH_2), 26.2(CH), 29.5(CH_2), 31.0 (CH_2), 31.3 (CH), 33.0 (CH_2), 34.2 (CH_2), 40.8 (CH_2), 46.9 (CH), 58.2 (CH), 72.3 (CH), 74.4 (CH), 123.3 (CH), 126.3 (CH), 128.3 (CH), 129.0 (CH), 131.3 (Cq), 134.1 (CH), 137.7 (Cq), 168.2 (Cq), 173.5 (Cq) ppm; MS (CI) *m*/*z* (relative intensity) 353 (M − $C_{10}H_{18}^+$, 15), 492 (MH^+, 28), 509 (MNH_4^+, 100). HRMS (CI) calcd for $C_{30}H_{38}NO_5$ [MH^+] 492.2750, found 492.2765.

(5*R*)-5-[(1*S*)-2-Phenyl-1-phthalimidoethyl]dihydrofuran-2(3*H*)-one (17): colorless oil; IR (film) ν_{max} 3020, 2930, 2860, 1775, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.85−1.98 (m, 1H), 2.01−2.15 (m, 1H), 2.55−2.61 (m, 2H), 3.39−3.45 (m, 2H), 4.50 (td, *J* = 9.6 Hz, *J*′ = 6 Hz, 1H), 5.19−5.30 (m, 1H), 7.12 (s, 5H), 7.69−7.73 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.5 (CH_2), 28.2 (CH_2), 35.4 (CH_2), 55.8 (CH), 79.0 (CH), 123.4 (CH), 126.7 (CH), 128.5 (CH), 128.8 (CH), 131.0 (Cq), 134.3 (CH), 136.7 (Cq), 168.0 (Cq), 176.5 (Cq) ppm.

(1*R*)-Menthyl (4*S*,5*S*)-4-(*p*-Nitrophenylcarbonyloxy)-6-phenyl-5-phthalimidohexanoate, 18. To a solution of **16** (0.186 g, 0.38 mmol) in dry benzene (9 mL) were added sequentially PPh_3 (0.487 g, 1.86 mmol, 4.9 equiv) and *p*-nitrobenzoic acid (0.273 g, 1.63 mmol, 4.4 equiv). The resulting suspension was cooled at 0 °C, and DEAD (0.29 mL, 1.85 mmol, 4.9 equiv) was added via syringe. The mixture was stirred at rt for 24 h. The solvent was evaporated in vacuo to

(31) Parkes, K. E. B.; Bushnell, D. J.; Crackett, P. H.; Dunsdon, S. J.; Freeman, A. C.; Gunn, M. P.; Hopkins, R. A.; Lambert, R. W.; Martin, J. A.; Merrett, J. H.; Redshaw, S.; Spurden, W. C.; Thomas, G. J. *J. Org. Chem.* **1994**, *59*, 3656−3664.

give a crude product which was purified by column chromatography to yield 0.198 g of hexanoate **18** (82%): colorless oil; IR (film) ν_{max} 2960, 2920, 2860, 1780, 1730, 1720 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.72−0.95 (m, 12H), 1.10−1.98 (m, 6H), 2.01−2.45 (m, 4H), 3.21 (dd, J = 5.1 Hz, J' = 13.9 Hz, 1H), 3.58 (dd, J = 11.8 Hz, J' = 13.9 Hz, 1H), 4.66 (td, J = 4.4 Hz, J' = 10.6 Hz, 1H), 4.83 (ddd, J = 5.5 Hz, J' = 7.0 Hz, J'' = 11.8 Hz, 1H), 5.80−5.90 (m, 1H), 7.15 (s, 5H), 7.58−7.75 (m, 4H), 8.05−8.25 (m 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.8 (CH_3), 21.3 (CH_3), 22.5 (CH_3), 23.8 (CH_2), 26.7 (CH), 27.7 (CH_2), 30.7 (CH_2), 31.8 (CH), 34.6 (CH_2 × 2), 41.3 (CH_2), 47.4 (CH), 56.0 (CH), 75.0 (CH), 75.1 (CH), 123.7 (CH), 124.0 (CH), 127.3 (CH), 129.1 (CH), 129.2 (CH), 131.5 (CH), 134.6 (CH), 135.3 (Cq), 137.1 (Cq), 152.3 (Cq), 165.2 (Cq), 168.3 (Cq), 172.3 (Cq) ppm; MS (FAB) 641 (MH^+), 663 (MNa^+).

(5*S*)-5-[(1*S*)-2-Phenyl-1-phthalimidoethyl]dihydrofuran-2(3*H*)-one, 19. To a suspension of hexanoate **18** (50 mg, 0.078 mmol) in dry methanol (1 mL) was added a solution of sodium methoxide (8.4 mg, 0.156 mmol, 2 equiv) in dry methanol (1 mL), and the mixture was stirred for 6 h at rt. Acetic acid was then added dropwise until the pH was slightly acidic, and the solvent was eliminated in vacuo. Finally, dry toluene (3 mL) was added, and the solution was refluxed overnight. Toluene was evaporated in vacuo to give a crude product which was purified by column chromatography to yield 19 mg of the lactone **19** (70%): white solid; mp 152−153 °C; $[\alpha]_D$ = −73.1 (c 0.78, $CHCl_3$); IR (KBr) ν_{max} 3030, 2945, 1785, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.01−2.19 (m, 1H), 2.41−2.71 (m, 3H), 3.07 (dd, J = 5.1 Hz, J' = 13.8 Hz, 1H), 3.40 (dd, J = 11.1 Hz, J' = 13.8 Hz, 1H), 4.58 (ddd, J = 4.9 Hz, J' = 9.7 Hz, J'' = 11.1 Hz, 1H), 5.18−5.30 (m, 1H), 7.17 (s, 5H), 7.62−7.78 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.5 (CH_2), 28.8 (CH_2), 33.5 (CH_2), 56.4 (CH), 76.6 (CH), 123.3 (CH), 126.9 (CH), 128.6 (CH), 128.8 (CH), 131.4 (Cq), 134.0 (CH), 136.1 (Cq), 168.0 (Cq), 175.8 (Cq) ppm; MS (CI) m/z (relative intensity) 353 (MNH_4^+, 100). Anal. Calcd for $C_{20}H_{17}NO_4$: C, 71.63; H, 5.11; N, 4.18. Found: C, 71.54; H, 5.23; N, 4.19.

(2*S*,3*S*)-5-Methyl-3-phthalimidohexane-1,2-diol, 21. (a) To a preheated (70−80 °C) suspension of $Ti(O^iPr)_2(N_3)_2$[17b] (3.92 g, 15.7 mmol, 1.3 equiv) in dry benzene (60 mL) under argon was added a solution of (2*R*,3*R*)-2,3-epoxy-5-methylhexane-1-ol[28] (**20**) (1.60 g, 12.3 mmol) of 89% ee in dry benzene (65 mL), and the resulting mixture was heated at 70−80 °C for 10−15 min. Benzene was eliminated in vacuo, and the residue was vigorously stirred with a mixture of diethyl ether (250 mL) and 5% aqueous H_2SO_4 (98 mL) until both layers were completely transparent. The mixture was transferred to a separation funnel, and the aqueous layer was extracted with dichloromethane (2 × 100 mL). The combined organic layers were dried over Na_2SO_4, and the solvents were eliminated in vacuo. The crude (2*S*,3*S*)-3-azido-5-methylhexan-1,2-diol thus obtained was dissolved in dry methanol (30 mL), and the solution was added to a suspension of 10% Pd/C (0.213 g) in methanol (30 mL) under hydrogen atmosphere (1 atm). The suspension was stirred at rt for 30 h and then filtered over Celite. Methanol was eliminated in vacuo to yield the expected (2*S*,3*S*)-3-amino-5-methylhexan-1,2-diol which was used in the next step without purification. (b) To a suspension of PyBOP (4.24 g, 8.15 mmol, 1.1 equiv) in dry THF (10 mL) were sequentially added a solution of 2-ethoxycarbonylbenzoic acid[30] (1.61 g, 8.15 mmol, 1.1 equiv) in THF (10 mL) and Et^iPr_2N (2.6 mL, 11.1 mmol, 1.5 equiv), and the resulting mixture was stirred for 30−40 min at rt. This solution was then added to a suspension of the unpurified amino diol obtained in (a) in THF (10 mL) at 0 °C, and the mixture was stirred at rt for 3 h. The solvent was eliminated in vacuo, and the mixture heated at 85 °C overnight. The reaction mixture was then solved in dichloromethane (20 mL) and washed with saturated $NaHCO_3$ solution (10 mL) and with brine (10 mL). The organic layer was dried (Na_2SO_4) and evaporated to give a crude product which was purified by column chromatography to afford 1.57 g of the diol **21** (46% overall yield): colorless oil; $[\alpha]_D$ = −12.7 (c = 1.26, $CHCl_3$); IR (film) ν_{max} 3460, 2980, 2900, 1780, 1710, 1150 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, J = 6.2 Hz, 3H), 0.92 (d, J = 6.2 Hz, 3H), 1.38−1.42 (m, 1H), 1.54−1.68 (m, 1H), 2.17−2.31 (m, 1H), 2.80 (broad s, 2H), 3.58−3.63 (m, 2H), 4.02−4.18 (m, 1H), 4.30−4.41 (m, 1H), 7.72−7.87 (m, 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 21.3 (CH_3), 23.6 (CH_3), 24.9 (CH), 36.2 (CH_2), 51.5 (CH), 63.9 (CH_2), 72.9 (CH), 123.5 (CH), 131.5 (Cq), 134.3 (CH), 169.0 (Cq) ppm; MS (CI) m/z (relative intensity) 278 (MH^+, 41), 295 (MNH_4^+, 100). HRMS (CI) calcd for $C_{15}H_{20}NO_4$ [MH^+] 278.1392, found 278.1379. Conditions for GC determination of the enantiomeric purity of **20**: α-DEX 120 (30 m) column, 80 °C; t_R(2*R*,3*R*) 53.0 min, t_R(2*S*,3*S*) 54.8 min.

(*S*)-[(*S*)-3-Methyl-1-phthalimidobutyl]oxirane, 22. The procedure described above for the synthesis of **15** was followed using these reactives and amounts: (2*S*,3*S*)-5-methyl-3-phthalimidohexane-1,2-diol (**21**) (0.527 g, 1.90 mmol), PPh_3 (0.563 g, 2.15 mmol, 1.1 equiv), DEAD (0.375 g, 2.15 mmol, 1.1 equiv), and 1,2-dichloroethane (16 mL). After purification, 0.343 g (69% yield) of the oxirane **22** was obtained: colorless oil; $[\alpha]_D$ = −1.38 (c = 1.98, $CHCl_3$); IR (film) ν_{max} 2970, 2880, 1780, 1720, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88−0.92 (m, 6H), 1.44−1.58 (m, 1H), 1.73 (ddd, J = 5.1 Hz, J' = 9 Hz, J'' = 13.9 Hz, 1H), 2.18 (dd, J = 3.9 Hz, J' = 4.8 Hz, 1H), 2.58 (dd, J = 2.4 Hz, J' =4.8 Hz, 1H), 2.94 (ddd, J = 4.8 Hz, J' = 10.7 Hz, J'' = 14.7 Hz, 1H), 3.50 (ddd, J = 2.4 Hz, J' = 3.9 Hz, J'' = 7.7 Hz, 1H), 3.95 (ddd, J = 4.8 Hz, J' = 7.7 Hz, J'' = 10.7 Hz, 1H), 7.72−7.87 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.6 (CH_3), 23.0 (CH_3), 24.9 (CH), 38.6 (CH_2), 46.1 (CH_2), 52.3 (CH), 52.6 (CH), 123.3 (CH), 131.7 (Cq), 134.1 (CH), 168.1 (Cq) ppm; MS (CI) m/z (relative intensity) 260 (MH^+, 42), 277 (MNH_4^+, 100). HRMS (CI) calcd for $C_{15}H_{18}NO_3$ [MH^+] 260.1287, found 260.1278.

(1*R*)-Menthyl (4*R*,5*S*)-4-Hydroxy-7-methyl-6-phthalimidooctanoate, 23. The procedure described above for the synthesis of **16** was followed using these reactives and amounts: (*S*)-[(*S*)-3-methyl-1-phthalimidobutyl]oxirane (**22**) (0.309 g, 1.19 mmol), freshly distilled $BF_3{\cdot}OEt_2$ (370 μL, 2.95 mmol, 2.5 equiv), (1*R*)-menthyloxyethine (0.640 g, 3.55 mmol, 3 equiv), 1.85 M solution of *n*BuLi in hexanes (1.16 mL), H_2O (170 μL, 9.52 mmol, 8 equiv), and THF (6 mL). After chromatographic purification, 0.333 g of **23** (61% yield) was obtained. A fraction containing 62 mg of impure (5*R*)-5-[(1*S*)-3-methyl-1-phthalimidobuthyl]dihydrofuran-2(3*H*)-one **24** was also isolated (17% yield estimated by NMR).

(1*R*)-Menthyl (4*R*,5*S*)-4-hydroxy-7-methyl-6-phthalimidooctanoate 23: colorless oil; $[\alpha]_D$ = −30.7 (c = 1.21, $CHCl_3$); IR (film) ν_{max} 3460, 2960, 2930, 2870, 1775, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.71−0.94 (m, 18H), 1.25−1.98 (m, 10H), 2.15−2.22 (m, 1H), 2.38−2.57 (m, 2H), 3.55 (s, 1H), 4.05−4.10 (m, 1H), 4.21−4.30 (m, 1H), 4.65 (td, J = 4.5 Hz, J' = 10.9 Hz, 1H), 7.72−7.87 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.3 (CH_3), 20.7 (CH_3), 21.4 (CH_3), 22.0 (CH_3), 23.4 (CH_2), 23.7 (CH_3), 25.0 (CH), 26.2 (CH), 29.5 (CH_2), 31.0 (CH_2), 31.4 (CH), 34.2 (CH_2), 35.5 (CH_2), 40.9 (CH_2), 47.0 (CH), 54.9 (CH), 72.9 (CH), 74.3 (CH), 123.4 (CH), 131.8 (Cq), 134.2 (CH), 168.4 (Cq), 173.7 (Cq) ppm. MS (CI) m/z (relative intensity) 319 ([M − $C_{10}H_{18}$]$^+$, 89), 458 (MH^+, 100), 475 (MNH_4^+, 29).

(5*R*)-5-[(1*S*)-3-Methyl-1-phthalimidobutyl]dihydrofuran-2(3*H*)-one, 24: colorless oil; IR (film) ν_{max} 2960, 2930, 2880, 1790, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, J = 6.6 Hz, 3H), 0.92 (d, J = 6.6 Hz, 3H), 1.37−150 (m, 1H), 1.69−1.78 (m, 1H), 1.82−1.95 (m, 1H), 2.10−2.33 (m, 2H), 2.51−2.57 (m, 2H), 4.34 (ddd, J = 3.3 Hz, J' = 9.6 Hz, J'' = 11.7 Hz, 1H), 5.04 (ddd, J = 6.7 Hz, J' = 8.1 Hz, J'' = 9.5 Hz, 1H), 7.76−7.88 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 (CH_3), 23.4 (CH_3), 24.9 (CH), 25.4 (CH_2), 28.1 (CH_2), 38.1 (CH_2), 53.2 (CH), 79.5 (CH), 123.5 (CH), 131.3 (Cq), 134.3 (CH), 168.2 (Cq), 176.2 (Cq) ppm.

(1*R*)-Menthyl (4*S*,5*S*)-7-Methyl-4-(*p*-nitrophenylcarbonyloxy)-5-phthalimidooctanoate, 25. The procedure described above for the synthesis of **18** was followed using these reactives and amounts: (1*R*)-menthyl (4*R*,5*S*)-4-hydroxy-7-methyl-6-phthalimidooctanoate (**23**) (0.28 g, 0.612 mmol), PPh_3 (0.79 g, 3.02 mmol, 4.9 equiv), *p*-nitrobenzoic acid (0.453 g, 2.70 mmol, 4.4 equiv), DEAD (0.47 mL, 3.00 mmol, 4.9 equiv), and dry benzene (12 mL). After purification, 0.281 g of **25** (74% yield) was obtained: white solid; mp 66.5−67.5 °C; $[\alpha]_D$

= −7.48 (*c* = 0.98, $CHCl_3$); IR (KBr) ν_{max} 2960, 2940, 2880, 1780, 1735, 1715 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.73−0.94 (m, 18H), 1.22−2.50 (m, 13H), 4.54−4.68 (m, 2H), 5.63−5.79 (m, 1H), 7.68−7.79 (m, 4H), 8.08−8.22 (m 4H) ppm; ^{13}C NMR (50 MHz, $CDCl_3$) δ 16.3 (CH_3), 20.7 (CH_3), 21.2 (CH3), 21.9 (CH_3), 23.3 (CH_2), 23.3 (CH_3) 25.0 (CH), 26.2 (CH), 27.1 (CH_2), 30.1 (CH_2), 31.3 (CH), 34.1 (CH_2), 36.4 (CH_2), 40.7 (CH_2), 46.9 (CH), 52.5 (CH), 74.5 (CH), 75.0 (CH), 123.2 (CH), 123.4 (CH), 130.9 (CH), 131.5 (Cq), 134.0 (CH), 134.8 (Cq), 150.5 (Cq), 164.1 (Cq), 168.3 (Cq), 171.8 (Cq) ppm; MS (CI) *m*/*z* (relative intensity) 624 (MNH_4^+, 8). Anal. Calcd for $C_{34}H_{42}N_2O_8$: C, 67.31; H, 6.98; N, 4.61. Found: C, 67.70; H, 7.28; N, 4.42.

(5*S*)-5-[(1*S*)-3-Methyl-1-phthalimidobutyl]dihydrofuran-2(3*H*)-one, 26. The same procedure described above for the synthesis of **19** was followed using these reactives and amounts: (1*R*)-menthyl (4*S*,5*S*)-7-methyl-4-(*p*-nitrophenylcarbonyloxy)-5-phthalimidooctanoate (**25**) (0.112 g, 0.185 mmol), sodium methoxide (20 mg, 0.37 mmol, 2 equiv), dry methanol (4.7 mL), and toluene (6 mL). After flash chromatography purification, 46 mg of **26** was obtained (83% yield): white solid; mp 130−131 °C; $[\alpha]_D$ = +38.1 (*c* = 1.40, $CHCl_3$); [ee 97.8%]; IR (KBr) ν_{max} 2960, 2915, 2870, 1780, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, *J* = 6.6 Hz, 3H), 0.95 (d, *J* = 6.6 Hz, 3H), 1.24 (ddd, *J* = 3.3 Hz, *J*′ = 10.5 Hz, *J*″ = 13.8 Hz, 1H), 1.44−1.54 (m, 1H), 1.90−2.00 (m, 1H), 2.27 (ddd, *J* = 3.4 Hz, *J*′ = 12.1 Hz, *J*″ = 13.7 Hz, 1H), 2.39−2.52 (m, 1H), 2.58−2.64 (m 2H), 4.34 (ddd, *J* = 3.3 Hz, *J*′ = 9.9 Hz, *J*″ = 12.0 Hz, 1H), 5.11 (ddd, *J* = 6.6 Hz, *J*′ = 8.7 Hz, *J*″ = 9.9 Hz, 1H), 7.71−7.85 (m, 4H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3 (CH_3), 23.5 (CH_3), 24.7 (CH), 26.4 (CH_2), 28.8 (CH_2), 35.7 (CH_2), 53.7 (CH), 78.8 (CH), 123.3 (CH), 131.7 (Cq), 134.0 (CH), 168.3 (Cq), 175.8 (Cq) ppm; MS (CI) *m*/*z* (relative intensity) 319 (MNH_4^+, 100), 336 ($MN_2H_7^+$, 1). Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.35; N, 4.65. Found: C, 67.74; H, 6.35; N, 4.63. Conditions for the determination of the enantiomeric purity of **26** by HPLC analysis: CHIRALCEL ODR (25 cm) column, 10% $NaClO_4$ 0.1 M/ 90% MeOH, 0.5 mL/min, 27 °C, λ = 254 nm; t_R(1*S*,5′*S*) 11.3 min, t_R(1*R*,5′*R*) 12.7 min.

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Supporting Information Available: ^{13}C NMR spectra of compounds **10**, **16**, **18**, **21**, **22**, and **23** (7 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.

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