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Novel Small Renin Inhibitors Containing 4,5- or 3,5-Dihydroxy-2-substituted-6-phenylhexanamide Replacements at the P_2–P_3 Sites

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Abstract—Renin inhibitors containing a 4,5- or a 3,5-dihydroxy-2-substituted-6-phenylhexanamide fragment at the P_2–P_3 sites have been prepared and evaluated. The four possible diastereomeric diols of the two series of inhibitors were synthesized to determine the optimal configuration of the carbinol centers for these replacements. The most potent inhibitors of each series, **1a** and **2c** have a molecular weight of only 503 and IC_{50} values of 23 and 20 nM in a human plasma renin assay at pH 6.0. Their very low aqueous solubility limited their further evaluation. The efficacy of these P_2–P_3 replacements is a result of their ability to maintain the important hydrogen-bonds with the enzyme. Due to conformational differences with the dipeptide, adjustment at the P_2 side chain was required. These 4,5- and 3,5-dihydroxyhexanamide segments could be seen as novel N-terminal dipeptide replacements.

Introduction

The renin–angiotensin system plays a central role in the regulation of blood pressure and the maintenance of sodium and volume homeostasis (Fig. 1).[1] Despite the success of angiotensin converting enzyme (ACE) inhibitors in the treatment of hypertension and congestive heart failure, there have been reports of side-effects. The most common side-effect, a dry and persistent cough, is attributed to the potentiation of bradykinin, one of the ACE substrates which include angiotensin I.[2,3] This side-effect as well as the success of ACE inhibitors have been incentives to look at other modes of intervention in the same enzymatic cascade such as renin inhibition[4,5] and angiotensin II antagonism.[6] Renin, an aspartyl protease, constitutes a very attractive target because this highly specific enzyme has only one natural substrate, angiotensinogen, and is involved in the first and rate-limiting step in the cascade. The potential of renin as a target was recognized two decades ago. The search for potent and orally active renin inhibitors has generated an enormous medicinal chemistry effort but with limited success so far.[4,5] The poor oral efficacy encountered with most highly potent (IC_{50} values $\leq$ 1 nM) peptide/peptidomimetic renin inhibitors has been attributed to poor absorption, first-pass metabolism and/or proteolytic degradation. A popular strategy to tackle these problems has been to design less peptidic inhibitors.[7–15] Recently, several groups have also reported small renin inhibitors (MW$\ll$600) with good in vitro potencies.[16–20] We have evaluated two series of small and non-peptidic inhibitors possessing a dipeptide replacement for the P_2–P_3 segment in conjunction with a known diol transition state analogue:[21] 4,5- and 3,5-dihydroxyhexanamide derivatives **1** and **2** (Fig. 2). The proposed inhibitors **1** and **2** span only from the P_3 to P_1' positions. It was clearly established in the case of peptidic renin inhibitors that the P_3 carbonyl interacts strongly with the enzyme while the P_2–P_3 amide NH was defined as a noncritical hydrogen-bond.[22] In order to be useful, these P_2–P_3

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replacements must achieve the critical hydrogen-bonds with the enzyme and also orient the P_3 side chain while missing a P_4 residue. The syntheses, stereochemical requirements, and properties of inhibitors **1** and **2** are discussed.

Chemistry

The two *syn*-diols (**1a** and **1b**) in the 4,5-dihydroxyhexanamide series bearing a cyclopropylmethyl at position 2 were first made to test the viability of this type of P_2–P_3 replacements (Scheme 1). Asymmetric alkylation[23] of **3** with allylic bromide **4** followed by the cleavage of the chiral auxiliary with LiOOH[24] provided γ,δ-unsaturated acid **6**. The 2-substituted hexenoic acid possesses the *R* configuration corresponding to that of the natural amino acid. Coupling of the acid **6** with 2(*S*)-amino-1-cyclohexyl-6-methyl-3(*R*),4(*S*)-heptanediol (**7**)[25] afforded unsaturated amide **8**. Catalytic osmylation of **8** led to a 7/3 mixture of *syn*-isomers **1a** and **1b**, which were separated by reverse-phase HPLC. Isomer **1a** was also prepared starting with *S*-phenyllactic acid to establish the absolute configuration of the two carbinol centers on the P_2–P_3 replacement. (*S*)-Phenyllactic acid was transformed to aldehyde **9** by first benzylation of the hydroxyl followed by successive reduction of the acid with LAH and oxidation of the resulting primary

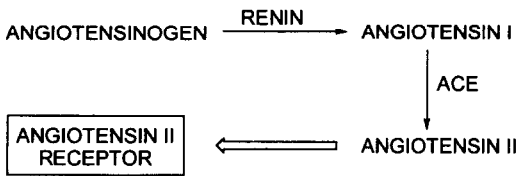


Figure 1. Renin–angiotensin system.

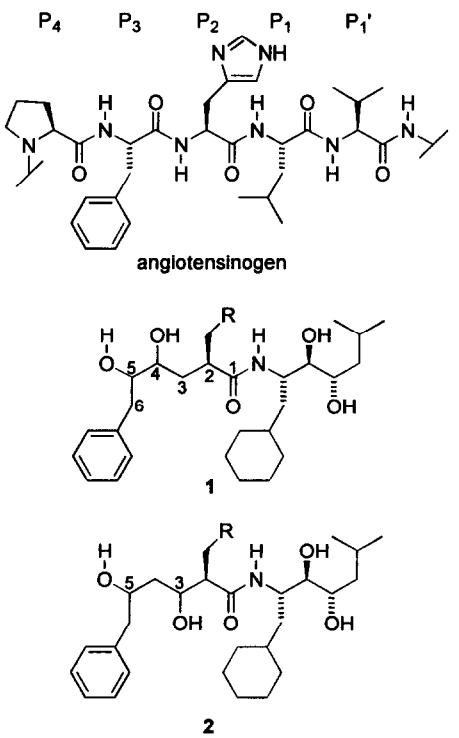
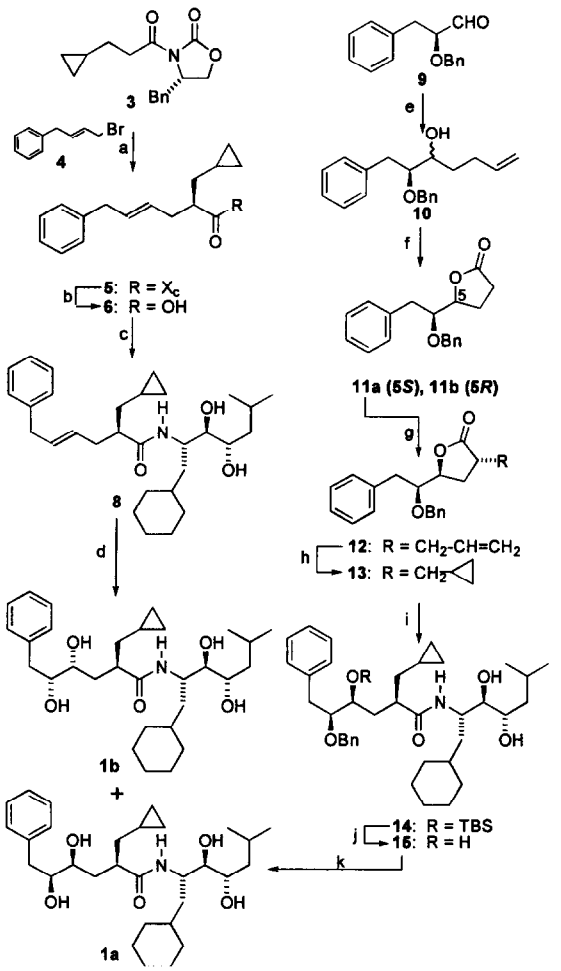


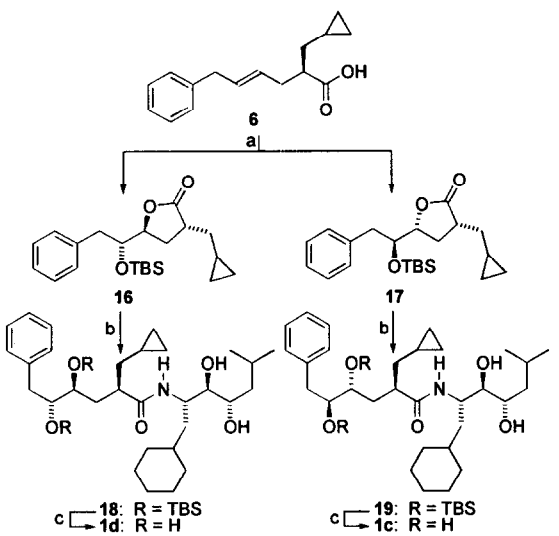
Figure 2. 4,5- and 3,5-Dihydroxy-6-phenylhexanamide derivatives.



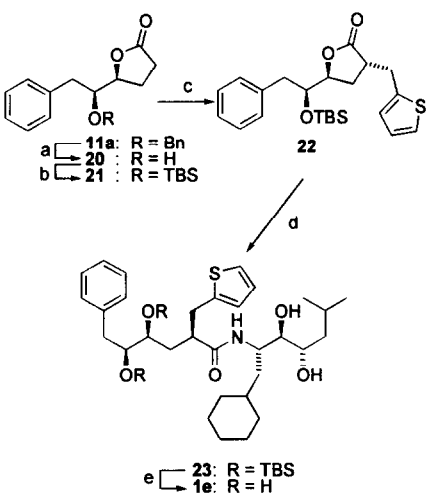
Scheme 1. *Reagents and conditions*: (a) LDA, THF, −78 °C then DMPU, **4**, −78 °C to 0 °C, 56%; (b) LiOOH, THF–H_2O, 0 °C to 25 °C, 92%; (c) *i*-Pr_2NEt, BOP·PF_6, **7**, MeCN, 40%; (d) OsO_4, NMMO, THF, 60%; (e) CH_2=$CHCH_2CH_2MgBr$, Et_2O, −78 °C, 76%; (f) (i) O_3, MeOH, then DMS, −78 °C to 25 °C; (ii) Jones' reagent, 0 °C, 73%; (g) LDA, CH_2=$CHCH_2Br$, THF, −78 °C, 76%; (h) CH_2N_2, $Pd(OAc)_2$, Et_2O, 0 °C, 88%; (i) (i) 2 N NaOH, MeOH, 25 °C; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 4 °C; (iii) *i*-Pr_2NEt, HOBT, BOP·PF_6, **7**, CH_2Cl_2, 64%; (j) Bu_4NF, THF, 25 °C to Δ, 87%; (k) H_2, $Pd(OH)_2$/C, EtOH, 91%.

alcohol using Swern protocol. The chelation-controlled addition of 3-butenylmagnesium bromide to the aldehyde **9** gave an inseparable mixture (ca. 8/1) of epimers of alcohol **10**. Cleavage of the terminal double bond of **10** with O_3/Me_2S followed by the oxidation of the resulting lactol gave lactones **11a** and **11b** (ratio ca. 8/1), which were easily separated by flash chromatography. Alkylation[26] of **11a** with allyl bromide gave predominantly the *trans* disubstituted lactone **12**. This lactone was treated with CH_2N_2 in presence of $Pd(OAc)_2$ to give the cyclopropylmethyl derivative **13**. Saponification of the lactone **13** followed by silylation of the resulting hydroxyacid salt, hydrolysis of the silyl ester and finally coupling of the acid with amine **7** gave amide **14**. Cleavage of the silyl ether and hydrogenolysis of the benzyl ether led to a compound identical to the major component of the osmylation of **8**, inhibitor **1a**. The corresponding *anti* diols (**1c** and **1d**) were prepared starting with unsaturated acid **6** (Scheme 2). Treatment of **6** with MCPBA followed by silylation of the resulting hydroxylactones afforded a 1/1 mixture of lactones **16** and **17**, which were easily separated by flash chromatography. The absolute configuration of the two newly formed stereogenic centers in lactones **16** and **17** was determined easily by chemical correlation using minor lactone **11b** obtained earlier. The minor *cis* and major *trans* 3,5-disubstituted lactones obtained by allylation of the enolate of **11b** were respectively transformed into **17** and the enantiomer of **16** after cyclopropanation and protective group manipulation (Bn to TBS). From lactones **16** and **17**, inhibitors **1d** and **1c** were obtained respectively using the series of steps described for **14** followed by the cleavage of the two silyl protective groups.

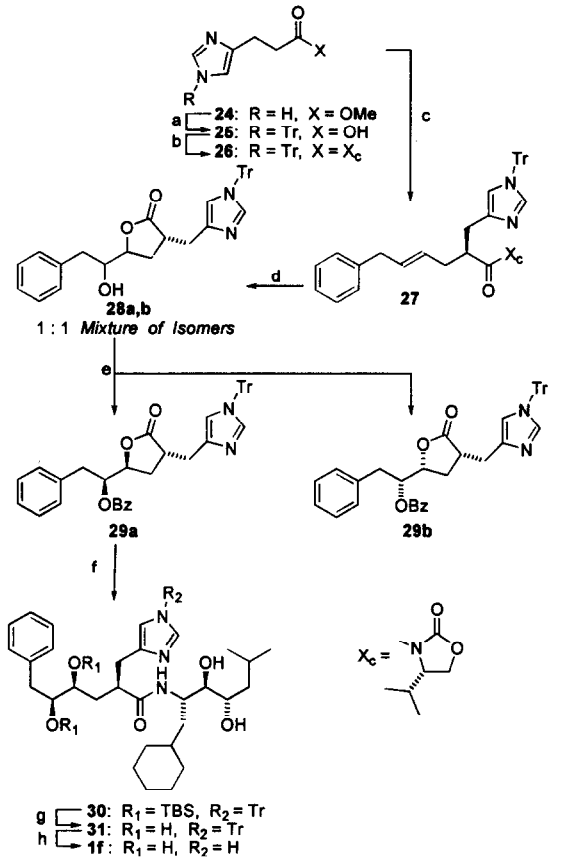
The corresponding P_2 2-thienylmethyl and 4-imidazolylmethyl analogues of **1a** were prepared using similar approaches. For the thienylmethyl analogue, the P_2 side chain was introduced by alkylation of lactone **21** with 2-(chloromethyl)thiophene[27] (Scheme 3). The resulting lactone **22** was then transformed to inhibitor **1e** as it was described above. In the case of the imidazolyl derivative (Scheme 4), the Evans' alkylation of **26**, readily available from **24**,[28] afforded **27**. Catalytic osmylation of **27** followed by the cleavage of the chiral auxiliary and lactonization gave a 1/1 mixture of hydroxylactones **28a,b**, which were separated as their benzoate derivatives **29a** and **29b**. The stereochemical correlation of the *trans* and *cis*-3,5-disubstituted lactones, **29a** and **29b**, respectively, was first based on ^1H NMR ($J_{4,5}$, $\Delta\delta_{4gem}$).[29–31] The *trans* isomer **29a** is characterized by $J_{4,5}$ of 4.1 and 8.9 Hz and $\Delta\delta_{4gem}$ of 0.14 ppm compared to $J_{4,5}$ of 6.4 and 9.9 Hz and $\Delta\delta_{4gem}$ of 0.43 ppm for the *cis* isomer **29b**. These results were confirmed by NOE and ROESY experiments that clearly established the proximity in space for H_3 and H_5 for the *cis* isomer **29b**. Inhibitor **1f** was obtained from **29a** using the sequence described previously with the additional hydrogenolysis of the trityl protective group.



Scheme 2. *Reagents and conditions:* (a) (i) MCPBA, CH_2Cl_2, 0 °C to 25 °C, 80%; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to 25 °C; (iii) separation of diastereoisomers, 88%; (b) (i) LiOH, THF–H_2O, 25 °C; (ii) TBSOTf, 2,6-lutidine, DMF, 25 °C; (iii) K_2CO_3, MeOH–THF–H_2O, 25 °C; (iv) BOP·PF_6, *i*-Pr_2NEt, **7**, 71% from **16**, 67% from **17**; (c) 5% HF in MeCN, 25 °C, 38% from **18**, 56% from **19**.



Scheme 3. *Reagents and conditions*: (a) H_2, $Pd(OH)_2/C$, EtOH, 84%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 25 °C, 87%; (c) LDA, HMPA, 2-($ClCH_2$)thiophene, THF, −78 °C to −50 °C, 44%; (d) (i) 1 N NaOH, THF–MeOH, 0 °C; (ii) TBSOTf, 2,6-lutidine, DMF, 0 °C to 25 °C; (iii) K_2CO_3, MeOH–THF, H_2O, 25 °C; (iv) BOP·PF_6, *i*-Pr_2NEt, **7**, CH_2Cl_2, 52%; (e) 5% HF in MeCN, 25 °C, 62%.



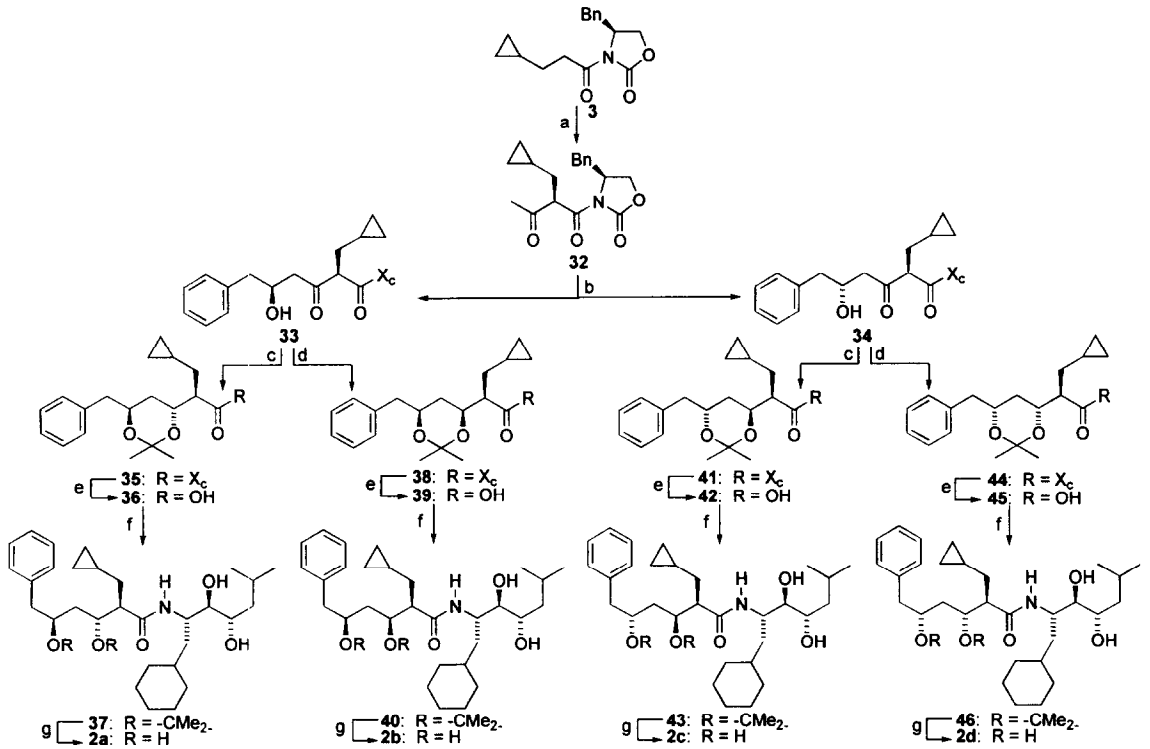
Scheme 4. *Reagents and conditions*: (a) (i) Et_3N, TrCl, CH_2Cl_2, 25 °C; (ii) LiOH, THF–H_2O, 25 °C, 96%; (b) Et_3N, PivCl, THF, −78 °C to 0 °C then X_c-Li, −78 °C, 84%; (c) NaHMDS, **4**, THF, −78 °C, 48%; (d) (i) OsO_4, NMMO, THF–H_2O, 25 °C; (ii) LiOOH, THF–H_2O, 0 °C; (iii) TFA, THF, 0 °C, 60%; (e) (i) BzCl, Et_3N, DMAP, CH_2Cl_2, 0 °C, 91%; (ii) separation of isomers; (f) (i) LiOH, THF–H_2O, 25 °C; (ii) TBSOTf, 2,6-lutidine, DMF, 0 °C; (iii) 1 N NaOH, THF, 0 °C; (iv) BOP·PF_6, *i*-Pr_2NEt, **7**, CH_2Cl_2, 60%; (g) 10% HF in MeCN, 79%; (h) H_2, $Pd(OH)_2/C$, 88%.

The four isomers in the 3,5-dihydroxyhexanamide series bearing a cyclopropyl substituent at position 2 were prepared from β-ketoimide **32**, which was obtained by acylation[32] of **3** (Scheme 5). The aldol reaction[33] of the titanium enolate of **32** with phenylacetaldehyde gave a mixture of **33** and **34** in a 2/1 ratio. The poor selectivity reflects the absence of substituent on the enolate. Selective reduction of these two diastereomeric β-hydroxyketones afforded the four possible diol diastereomers. Reduction of β-hydroxyketone **33** by $NaBH(OAc)_3$[34] gave preferentially the expected *anti* diol, which was isolated as the acetonide **35**. The configuration of stereocenters at positions 2, 3, and 5 of **35** and the three other diastereomers was confirmed by the ^{13}C NMR of the acetonides[35] and the ^1H NMR ($J_{3,4}$) of the corresponding δ-lactones. Upon removal of the chiral auxiliary of **35** using LiOOH, the resulting acid was coupled with amine **7** to give **37** with low yield. Inhibitor **2a** was obtained by simple hydrolysis of acetonide **37** in the presence of acidic resin. Starting with β-hydroxyketone **33** but using DIBAL[36] as reducing agent, the *syn* diol was selectively obtained and purified as its acetonide derivative **38**. Using the same sequence of steps described above for the *anti* isomer, **38** was transformed into inhibitor **2b**. Similarly, isomeric β-hydroxyketone **34** was converted into inhibitors **2c** and **2d**.

Results and discussion

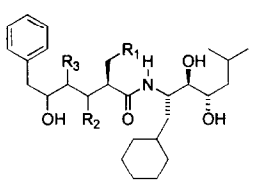
A small lipophilic side chain such as the cyclopropylmethyl group was selected for the P_2 position since it was found to be a good replacement for the histidine side chain in many of our peptidic renin inhibitors. To our surprise, the four 4,5-dihydroxyhexanamide diastereomers, **1a–d**, showed a good level of potency, having IC_{50} values of 23–59 nM (Table 1). The most potent inhibitor is *syn* 4,5-diol **1a** with an IC_{50} of 23 nM. The configuration of the carbinol centers appears not to be very crucial for potency, since a twofold loss of potency is observed when the configuration at C-4 is inverted (cf. **1a** and **1c**, **1b** and **1d**) compared to a maximum of threefold loss with the inversion of C-5 (cf. **1a** and **1d**, **1b** and **1c**). The X-ray analysis of crystal structures of renin complexed with **1a** and **1d**[37] showed, in each case, that the 4*S* hydroxyl interacts with Ser-219 in a fashion similar to that of the amide carbonyl normally found in this position. The C-5 hydroxyl of **1a** and **1d**, although of opposite configuration, are also hydrogen-bonded to the side chain hydroxyl group of Ser-219. Although the conformation of the P_3 benzyl is different in these two compounds, the aromatic rings occupy more or less the same position in the S_3 pocket. Clearly, for the four diastereomers, the C-4 and C-5 hydroxyls are able to maintain the critical hydrogen-bonds with the enzyme. In the case of related renin inhibitors having a hydroxyethylene isostere at the P_2–P_3 sites,[9] it was also observed that the configuration at C-4 had little impact on potency.

Although the level of potency was very interesting for such small inhibitors, compounds **1a–d** could not be evaluated in an animal model because of their very low solubility in water (≪1 μg/mL at pH 7.4). The P_2 side chain appeared to be the only site available for modifications that may improve the water solubility of this series of compounds. The most potent inhibitor **1a** was selected as the starting point for this exercise. The imidazolylmethyl derivative **1f** was made first, since it possesses the histidine side chain present at P_2 in the renin substrate. Inhibitor **1f** was, as expected, significantly



Scheme 5. *Reagents and conditions*: (a) LDA, MeCOCl, THF, −78 °C, 51%; (b) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, −15 °C to −78 °C then PhCHO, **33**/**34**, 2/1 mixture, 82%; (c) (i) $NaBH(OAc)_3$, MeCN–AcOH, 25 °C; (ii) $Me_2C(OMe)_2$, *p*-TsOH, DMF, 25 °C, 69% from **33**, 41% from **34**; (d) (i) DIBAL, −78 °C, CH_2Cl_2, −78 °C; (ii) $Me_2C(OMe)_2$–DMF, *p*-TsOH, 25 °C, 23% from **33**, 35% from **34**; (e) LiOOH, THF–H_2O, 0 °C to 25 °C; (f) *i*-Pr_2NEt, BOP-PF_6, **7**, MeCN, 27% from **35**, 68% from **38**, 70% from **41**, 22% from **44**; (g) Amberlite® H^+, MeOH, H_2O, 66% from **37**, 100% from **40**, 95% from **43**, 84% from **46**.

Table 1. In vitro potencies of 2-substituted dihydroxyphenylhexanamide derivatives



Compound	Configuration	R_3	R_2	R_1	IC_{50} (nM)[a]
1a	*syn* (4*S*,5*S*)	OH	H	cyclopropyl	23
1b	*syn* (4*R*,5*R*)	OH	H	cyclopropyl	41
1c	*anti* (4*R*,5*S*)	OH	H	cyclopropyl	49
1d	*anti* (4*S*,5*R*)	OH	H	cyclopropyl	59
1e	*syn* (4*S*,5*S*)	OH	H	2-thienyl	320
1f	*syn* (4*S*,5*S*)	OH	H	1*H*-imidazol-4-yl	1010
2a	*anti* (3*R*,5*S*)	H	OH	cyclopropyl	590
2b	*syn* (3*S*,5*S*)	H	OH	cyclopropyl	96
2c	*anti* (3*S*,5*R*)	H	OH	cyclopropyl	20
2d	*syn* (3*R*,5*R*)	H	OH	cyclopropyl	260

[a]Determined using a human plasma renin assay at pH 6.0.

more soluble in water (9 μg/mL at pH 7.4) than the cyclopropylmethyl derivative. To our surprise, with an IC_{50} of 1010 nM, **1f** was found to be 40-fold less potent than **1a**. Similarly, the thienylmethyl analogue **1e** had an IC_{50} of 320 nM, a 14-fold loss in this case. It appears that 5-membered heterocycles are not well tolerated at P_2 for this series of inhibitors. The same observation was reported for renin inhibitors possessing a P_2–P_3 hydroxyethylene isostere when P_2 alkyl and 1-triazolylmethyl side chains were compared.[9] The authors noted that "this may in part be a further manifestation of the conformational differences between the hydroxyethylene isostere and the native dipeptide". Moreover, it is also interesting to note a 50-fold difference in potency between the hydroxyethylene isostere **1f** and a P_2–P_3 peptidic inhibitor reported earlier by Abbott (IC_{50} = 20 nM, ex. 25, EP-229667).[38] The crystal structure overlap[37] of the **1a**–renin complex[37] and that of a P_2–P_3 peptidic inhibitor such as CGP 38'560[39] and renin clearly highlights these conformational differences. As noted earlier, the backbone atoms of the P_3 residue are positioned differently in **1a** and CGP 38'560 with the result that the phenyl group of **1a** is inserted deeper into the S_3 pocket. In addition, the orientation of the P_2 side chain, the point of interest here, is also different in **1a** and CGP 38'560 (Fig. 3). In **1a**, the point of attachment of the cyclopropyl group to the methylene is an sp^3 carbon. Therefore, the cyclopropyl ring can reach the S_2 pocket and adopt a position close to the one occupied by the imidazolyl ring in CGP 38'560 and this, despite a different orientation given by the methylene linker. In the case of imidazolyl analogue **1f**, the fact that the point of attachment is an sp^2 carbon should orient the 5-membered ring away from the S_2 pocket, a position clearly different from the imidazolyl group in CGP 38'560. Therefore, the introduction of a 5-membered heterocycle at position 2 in inhibitor **1** greatly perturbs the interaction between the inhibitor and the enzyme.

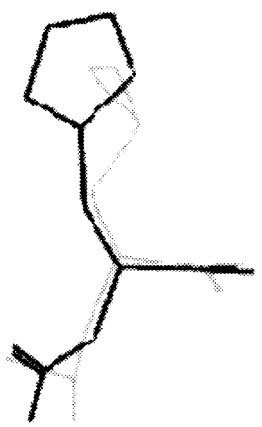
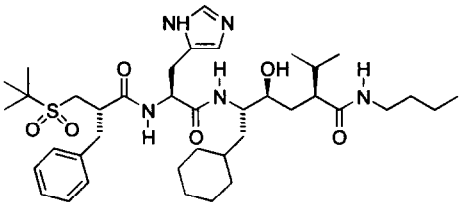
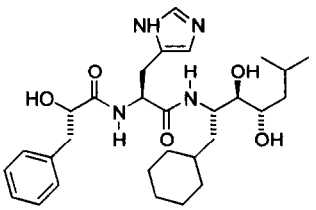


Figure 3. P_2 segment view of the overlap[37] of the crystal structures of inhibitor **1a** (gray lines) and CGP 38'560[39] (black lines) in complex with renin.



CGP 38'560



example 25
EP-229667[38]

For the 3,5-dihydroxyhexanamide series, the four diastereomers were made in order to identify the optimal configuration of the carbinols for potency. In contrast to the potencies of the 4,5-dihydroxyhexanamide series, the range of IC_{50} values exhibited by the 3,5-dihydroxyhexanamides was broader (20 to 590 nM). Inhibitor **2c**, the *anti*-3*S*,5*R* diastereomer, constitutes the most potent of the four at 20 nM. Its *syn*-3*S*,5*S* epimer, inhibitor **2b**, is slightly less potent with an IC_{50} of 96 nM. The two other diastereomers, **2a** (*anti*-3*R*,5*S*) and **2d** (*syn*-3*R*,5*R*) demonstrated poor potencies at 590 and 260 nM, respectively. A 3*S* configuration appears to be important for good potency. Interestingly, the inhibitors having the *R* configuration at C-5 produced the most potent inhibitors. This contrasts with the configurational requirements observed for the 4,5-dihydroxyhexanamide series, in which the *S* configuration conferred a twofold increase in potency. In the crystal structure of the renin–**2b** complex,[37] the C-3 hydroxyl can form a hydrogen-bond with the Ser-219, as can the C-4 hydroxyl in **1a**. It seems that this critical hydrogen-bond is possible without major perturbations to other sites, only for the 3*S* configuration in **2b**. The P_2 side chain of **2b** overlaps also very well with those of inhibitors **1a** and **1d**. Unfortunately, inhibitors **2** also suffer from poor aqueous solubility, precluding their evaluation in vivo.

Conclusion

This exercise led to the identification of two small and potent renin inhibitors, **1a** and **2c**. They have IC_{50} values of ca. 20 nM and a molecular weight of 503. Unfortunately, the potency and the water solubility of

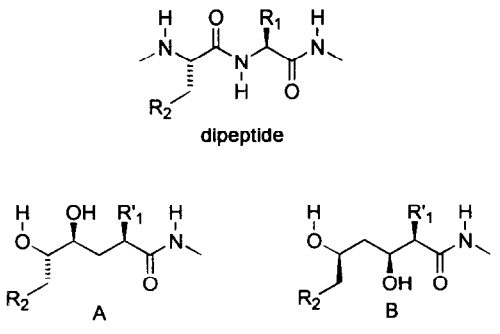


Figure 4. 4,5- and 3,5-Dihydroxyhexanamide as N-terminal dipeptide replacements.

these two inhibitors could not be further improved. Nevertheless, the substituted 4,5- and 3,5-dihydroxyhexanamide fragments **A** and **B** which possess the optimal configuration for potency shown in **1a** and **2c** could be seen as novel N-terminal dipeptide replacements (Fig. 4). The efficacy of these P_2–P_3 dihydroxyhexanamide dipeptide replacements is the result of their ability to maintain the important hydrogen-bonds with the enzyme. Adjustments at the P_2 side chain were nevertheless necessary to compensate for the conformational differences with the dipeptide.

Experimental

General methods

Melting points were determined on an electrothermal melting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX400 (^{1}H, ^{13}C) and AC200 (^{13}C) spectrometers. IR spectra were recorded on a Perkin–Elmer 781 spectrophotometer. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. Analytical thin-layer chromatography (TLC) was carried out on precoated (0.25 mm) Merck silica gel F-254 plates. THF, ether and toluene were distilled from sodium/benzophenone immediately prior to use. CH_2Cl_2, HMPA, *i*-Pr_2NEt, *i*-Pr_2NH were distilled from CaH_2. MeOH was distilled from Mg.

3-(3-Cyclopropyl-1-oxopropyl)-4(*S*)-(phenylmethyl)-2-oxazolidinone (3). To a cold (0 °C), stirred ethereal solution of CH_2N_2 (100 mL, 0.6 M) containing 3-(1-oxo-4-pentenyl)-4(*S*)-phenylmethyl-2-oxazolidinone[40] (5.56 g, 21.4 mmol), was added $Pd(OAc)_2$ (240 mg, 1.07 mmol) in small portions. The reaction mixture was stirred at 0 °C for 30 min. Subsequently, the catalyst was removed by filtration through Celite® and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography (Hex/EtOAc, 6/1) to give **3** (5.57 g, 95%) as a white solid: mp 44–45 °C; $[\alpha]_D^{26}$ +102.7° (*c* 1.09, MeOH); IR (KBr) ν_{max} 1780, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36–7.21 (m, 5H), 4.71–4.65 (m, 1H), 4.23–4.16 (m, 2H), 3.31 (dd, *J* = 3.5, 13.4 Hz, 1H), 3.13–2.98 (m, 2H), 2.77 (dd, *J* = 9.5, 13.4 Hz, 1H), 1.63–1.56 (m, 2H), 0.85–0.75 (m, 1H), 0.52–0.40 (m, 2H), 0.15–0.08 (m, 2H); MS (CI) *m/z* 274 (MH^+); Anal. calcd for $C_{16}H_{19}NO_3$: C, 70.29; H, 7.01; N, 5.12. Found: C, 70.46; H, 7.05; N, 5.10.

(*E*)-1-Bromo-4-phenyl-2-butene (4). To an ice-cold solution of 1-phenyl-3-buten-2-ol prepared by addition of vinylmagnesium bromide to phenylacetaldehyde[41] at −10 °C (6.3 g, 42.5 mmol) and 1,5-hexadiene (4.0 mL, 34.0 mmol) in 1,2-dichloroethane (50 mL), was added $SOBr_2$ (4.9 mL, 63.8 mmol). After the mixture was stirred at 0 °C for 1.5 h, H_2O (25 mL) was added and the mixture was extracted with Et_2O. The organic layer was washed successively with water, saturated aq $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (Hex) followed by bulb-to-bulb distillation (94 °C, 0.07 mm) to give a colorless oil (5.6 g, 75%) that consisted of 15% of the isomeric 2-bromo-1-phenyl-3-butene and 85% of **4**: IR (neat) ν_{max} 1655 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33–7.17 (m, 5H), 5.94 (dt, *J* = 6.7, 15.1 Hz, 1H), 5.77 (dtt, *J* = 1.3, 7.6, 15.1 Hz, 1H), 3.97 (d, *J* = 7.6 Hz, 2H), 3.41 (d, *J* = 6.7 Hz, 2H); MS (EI) *m/z* 210/212 (M^+).

3-[(*E*)-2(*R*)-(Cyclopropylmethyl)-1-oxo-6-phenyl-4-hexenyl]-4(*S*)-(phenylmethyl)-2-oxazolidinone (5). A 1.6 M hexane solution of *n*-BuLi (10.8 mL, 17.3 mmol) was added dropwise to a cold (0 °C), stirred solution of *i*-Pr_2NH (2.53 mL, 18.1 mmol) in THF (50 mL), and the resultant mixture was stirred at 0 °C for 15 min. After the reaction mixture was cooled to −78 °C, a solution of **3** (4.50 g, 16.5 mmol) in THF (10 mL) was added. This mixture was stirred for 1 h at −78 °C, and successive additions of DMPU (3.98 mL, 33.0 mmol) and a solution of **4** (5.21 g, 24.7 mmol) in THF (10 mL) were made. After the reaction mixture was stirred at −78 °C for 15 min, it was allowed to warm slowly to 0 °C (1.5 h) and stirred at that temperature for 1 h. A saturated aq NH_4Cl solution was added and the mixture was extracted with Et_2O (300 mL). The organic layer was washed successively with 1 N HCl (50 mL), saturated aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex/EtOAc, 9/1) gave **5** (3.75 g, 56%), of which the diastereomeric ratio (49/1) was determined by HPLC on Chiracel-OD column (UV detection 215 nm) using 10% EtOH in Hexanes: $[\alpha]_D^{25}$ +89.5° (*c* 1.23 MeOH); IR (neat) ν_{max} 1780, 1695 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35–7.12 (m, 5H), 5.68 (dt, *J* = 6.6, 15.3 Hz, 1H), 5.55 (dt, *J* = 6.9, 15.3 Hz, 1H), 4.67–4.62 (m, 1H), 4.16–4.05 (m, 3H), 3.33 (d, *J* = 6.6 Hz, 1H), 3.19 (dd, *J* = 3.2, 13.4 Hz, 1H), 2.50 (dt, *J* = 6.7, 14.0 Hz, 1H), 2.44 (dd, *J* = 10.2,

13.4 Hz, 1H), 2.35 (dt, J=6.3, 14.0 Hz, 1H), 1.56–1.52 (m, 2H), 0.75–0.69 (m, 1H), 0.45–0.36 (m, 2H), 0.10–0.03 (m, 2H); MS (FAB) m/z 404 (MH^+); Anal. calcd for $C_{26}H_{29}NO_3$: C, 77.37; H, 7.24; N, 3.47. Found: C, 77.40, H, 7.29; N, 3.53.

(*E*)-2(*R*)-(Cyclopropylmethyl)-6-phenyl-4-hexenoic acid (6). To a cold (0 °C), stirred solution of **5** (3.30 g, 8.18 mmol) in THF/H_2O (4/1; 40 mL) was added successively a 30% solution of H_2O_2 (2.32 mL, 20.5 mmol) and $LiOH \cdot H_2O$ (412 mg, 9.82 mmol). When the additions were completed, the ice bath was removed and the mixture was stirred at room temperature for 1 h. Additional aliquots of H_2O_2 (2.32 mL) and $LiOH \cdot H_2O$ (412 mg) were added after 1 and 2 h, and the mixture was then stirred for 15 h. H_2O (25 mL) was added and the mixture was concentrated. To the cold (0 °C) aqueous layer was added solid Na_2SO_3 until no peroxide was detected. The aqueous solution was washed with CH_2Cl_2 (3×100 mL), acidified with solid citric acid and extracted with EtOAc (2×100 mL). The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (Hex/EtOAc, 4/1) gave **6** (1.85 g, 92%) as a light-yellow oil, which was then subjected to Kugelrohr distillation (250 °C, 0.7 mm) to afford a colorless oil: $[\alpha]_D^{25}$ +5.6° (c 2.02, MeOH); IR (neat) ν_{max} 3600–2400, 1710 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.16 (m, 5H), 5.67 (dt, J=6.7, 15.1 Hz, 1H), 5.50 (dt, J=7.0, 15.1 Hz, 1H), 3.34 (d, J=6.7 Hz, 1H), 2.62–2.55 (m, 1H), 2.41 (dt, J=7.2, 14.0 Hz, 1H), 2.30 (dt, J=6.7, 14.0 Hz, 1H), 1.59 (dt, J=7.6, 14.0 Hz, 1H), 1.44 (dt, J=6.4, 14.0 Hz, 1H), 0.76–0.69 (m, 1H), 0.50–0.42 (m, 2H), 0.12–0.01 (m, 2H); MS (FAB) m/z 245 (MH^+).

(*E*)-*N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-6-phenyl-4-hexenamide (8). To a solution of acid **6** (160 mg, 0.66 mmol) in MeCN (10 mL) was added successively **7**[25] (160 mg, 0.66 mmol), i-Pr_2NEt (0.34 mL, 1.98 mmol) and BOP·PF_6 (320 mg, 0.73 mmol). The reaction mixture was stirred for 1 h at room temperature, and was then diluted with EtOAc. The organic phase was washed with 0.5 N HCl and brine, and then dried ($MgSO_4$) and concentrated. After purification by flash chromatography (Hex/EtOAc, 5/1), the desired olefin **8** (123 mg, 40% from **5**) was obtained: $[\alpha]_D^{25}$ −41.8° (c 0.75, MeOH); IR ($CHCl_3$) ν_{max} 3430, 2920, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.29 (t, J=7.3 Hz, 2H), 7.21–7.15 (m, 3H), 5.65 (dt, J=6.9, 14.9 Hz, 1H), 5.55 (d, J=9.2 Hz, 1H), 5.50–5.42 (m, 1H), 4.54–4.38 (br s, 1H), 4.38 (td, J=4.9, 9.4 Hz, 1H), 3.34 (d, J=6.7 Hz, 2H), 3.29–3.20 (m, 2H), 2.38–2.33 (m, 1H), 2.30–2.18 (m, 2H), 1.95–1.51 (m, 10H), 1.43–1.09 (m, 8H), 0.97–0.80 (m, 2H), 0.93 (d, J=6.7 Hz, 3H), 0.83 (d, J=6.7 Hz, 3H), 0.72–0.65 (m, 1H), 0.48–0.42 (m, 2H), 0.13–0.05 (m, 1H), 0.03–0.01 (m, 1H); MS (FAB) m/z 470 (MH^+); Anal. calcd for $C_{30}H_{47}NO_3$: C, 76.71; H, 10.09; N, 2.98. Found: C, 76.49; H, 10.22; N, 2.97.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-4(*R*),5(*R*)-dihydroxy-6-phenylhexanamide (1b) and 4(*S*),5(*S*) isomer (1a).** A solution of alkene **8** (79 mg, 0.17 mmol), NMMO (40 mg, 0.34 mmol) and a catalytic amount of OsO_4 (0.1 mL of a 2.5 w/v% solution in t-butanol) in THF (50 mL) was stirred at 25 °C for 4 h. After the addition of a 10% aq Na_2SO_3 solution, the mixture was diluted with EtOAc. The organic layer was washed with 0.1 M H_3PO_4 and brine, and dried ($MgSO_4$). Filtration and concentration of the organic phase gave a residue that was purified by flash chromatography (2% MeOH in $CHCl_3$) to give a 30/70 mixture (51 mg, 60%) of **1b** and **1a**. Subsequently, this mixture was resolved by reverse-phase HPLC (Whatman Magnum column, 0.94×50 cm; MeCN/water solvent system containing 0.06% TFA; spectrophotometric detection at 220 nm) to give pure fractions of **1b** (first to elute) and **1a**. Compound **1b** was obtained as an amorphous white solid: $[\alpha]_D^{25}$ −12.8° (c 0.58, MeOH); IR (KBr) ν_{max} 3280–3400 (broad), 1615 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.67 (d, J=9.0 Hz, 1H), 7.27–7.22 (m, 4H), 7.18–7.14 (m 1H), 4.76 (d, J=3.0 Hz, 1H), 4.71 (d, J=6.3 Hz, 1H), 4.29 (d, J=6.0 Hz, 1H), 4.21 (d, J=7.2 Hz, 1H), 4.14 (td, J=4.2, 9.4 Hz, 1H), 3.62–3.56 (m, 1H), 3.35–3.22 (m, 1H), 3.11 (br t, J=8.7 Hz, 1H), 2.93 (br t, J=7.6 Hz, 1H), 2.71 (dd, J=3.0, 13.8 Hz, 1H), 2.59 (dd, J=9.6, 13.8 Hz, 1H), 2.55–2.50 (m, 1H), 1.82–1.53 (m, 10H), 1.45 (br t, J=11.8 Hz, 1H), 1.39–1.26 (m, 1H), 1.24–1.06 (m, 5H), 1.00 (ddd, J=4.7, 8.4, 13.4 Hz, 1H), 0.95–0.78 (m, 2H), 0.86 (d, J=6.6 Hz, 3H), 0.73 (d, J=6.6 Hz, 3H), 0.67–0.59 (m, 1H), 0.36–0.29 (m, 2H), 0.05–0.04 (m, 2H); HRMS calcd for $C_{30}H_{50}NO_5$ (MH^+): 504.3689. Found: 504.3709; Anal. calcd for $C_{30}H_{49}NO_5$: C, 71.53; H, 9.81; N, 2.78. Found: C, 71.04; H, 9.88; N, 2.90. **1a** was identical to compound obtained from **15** (see below).

(2*S*,3*S*)- and (2*S*,3*R*)-2-Benzyloxy-1-phenyl-6-hepten-3-ol (10). To a stirred solution of (*S*)-hydroxy-3-phenylpropionic acid **9** (15.0 g, 90.4 mmol) in THF (450 mL) was added NaH (60% dispersion in oil, 9.00 g, 226 mmol). Upon completion of gas evolution, benzyl bromide (10.8 mL, 181 mmol) was added and the reaction mixture was stirred for 7 days. The mixture was diluted with water and Et_2O, and the phases were separated. After the aqueous solution was acidified by the addition of dilute HCl, it was extracted twice with EtOAc. The combined EtOAc extracts were washed with brine, dried ($MgSO_4$) and concentrated. Subsequently, the crude residue was dissolved in THF (300 mL) and to the resultant solution was added

$LiAlH_4$ (8.54 g, 225 mmol). After the reaction mixture was stirred for 60 h, successive additions of Celite® (25.6 g), H_2O (26 mL), 2 N aq NaOH (12.8 mL) and H_2O (230 mL) were made. The resultant mixture was well-agitated and filtered, and the aqueous filtrate phase was washed with EtOAc. Concentration of the combined organic layers gave a residue which was coevaporated with benzene. Purification of this material by flash chromatography (Hex/EtOAc, 3/1) afforded (*S*)-2-benzyloxy-3-phenylpropanol (16.3 g, 75%); ^{1}H NMR ($CDCl_3$) δ 7.37–7.20 (m, 10H), 4.56 (d, J = 11.6 Hz, 1H), 4.50 (d, J = 11.6 Hz, 1H), 3.74–3.69 (m, 1H), 3.67 (dd, J = 3.5, 11.5 Hz, 1H), 3.51 (dd, J = 5.9, 11.5 Hz, 1H), 2.95 (dd, J = 6.0, 13.8 Hz, 1H), 2.81 (dd, J = 6.8, 13.8 Hz, 1H), 1.81 (br s, 1H); MS (EI) m/z 242 (M^+).

Dimethyl sulfoxide (3.23 mL, 45.5 mmol) was added dropwise to a stirred, cold (−78 °C) solution of oxalyl chloride (2.52 mL, 28.9 mmol) in dry CH_2Cl_2 (155 mL). After the resultant solution was stirred for 10 min, a solution of (*S*)-2-benzyloxy-3-phenylpropanol (5.00 g, 20.7 mmol) in CH_2Cl_2 (52 mL) was added dropwise over 20 min. The reaction mixture was stirred at −78 °C for 30 min before the rapid addition of Et_3N (14.41 mL, 103.3 mmol). The resultant suspension was diluted with water and extracted with EtOAc. The combined organic extracts were washed successively with saturated aq NH_4Cl, water and brine, dried ($MgSO_4$) and concentrated to give aldehyde **9** which was immediately dissolved in Et_2O (20 mL).

This solution was then added dropwise over 15 min to a cold (−78 °C), stirred solution of 3-butenylmagnesium bromide (0.64 M in Et_2O, 71.0 mL, 45.5 mmol) in Et_2O (155 mL). After 1 h, the mixture was diluted with Et_2O (100 mL) and the resultant mixture was washed successively with saturated aq NH_4Cl and brine. The organic phase was dried ($MgSO_4$) and concentrated. Purification of the residue by flash chromatography (Hex/EtOAc, 10/1) gave a 8/1 mixture of 3*S* and 3*R* epimers (4.82 g, 76%) **10**: IR (neat) ν_{max} 3620–3220, 1640, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.36–7.20 (m, 10H), 5.84–5.74 (m, 1H), 5.08–4.92 (m, 2H), 4.46 (d, J = 11.1 Hz, 1H), 4.43 (d, J = 11.1 Hz, 1H), 3.53–3.48 (m, 2H), 3.0–2.88 (m, 2H), 2.21–2.06 (m, 3H), 1.65–1.56 (m, 2H); MS (EI) m/z 296 (M^+); Anal. calcd for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.03; H, 8.22.

5(*S*) and 5(*R*)-[1(*S*)-Benzyloxy-2-phenylethyl]dihydrofuran-2(3*H*)-one (11a and 11b). A stream of O_3 was bubbled through a cold (−78 °C), stirred solution of the 8/1 mixture (533 mg, 1.80 mmol) of **10** in MeOH (20 mL) until the reaction mixture became persistently blue. After the system was flushed with a slow stream of nitrogen to remove excess O_3, Me_2S (1.5 mL) was added. The resultant solution was warmed gradually to room temperature, at which stirring was continued for an additional 4 h. After the mixture was concentrated, the residue was dissolved in acetone (2 mL), and the resultant solution was cooled to 0 °C prior to being titrated with Jones' reagent (1 equiv). The mixture was stirred at room temperature for 15 min and then concentrated under reduced pressure. The residue was dissolved in EtOAc and the resulting solution was washed successively with saturated aq solution of $NaHCO_3$, H_2O, and brine, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex/EtOAc, 10/1 then 3/1) gave the monosubstituted lactone **11a** (390 mg, 73%) as a white amorphous solid: R_f 0.27 (Hex/EtOAc, 3/1); $[\alpha]_D^{25}$ +54.5° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1770 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39–7.23 (m, 10H), 4.61 (d, J = 11.8 Hz, 1H), 4.51 (d, J = 11.8 Hz, 1H) 4.46 (ddd, J = 3.2, 5.3, 8.1 Hz, 1H), 3.61 (td, J = 3.2, 6.7, 7.6 Hz, 1H), 3.03 (dd, J = 6.7, 13.7 Hz, 1H), 2.95 (dd, J = 7.6, 13.7 Hz, 1H), 2.68–2.59 (m, 1H), 1.47–2.38 (m, 1H), 2.25–2.11 (m, 1H), 2.05–1.97 (m, 1H); MS (EI) m/z 296 (M^+); Anal. calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 76.77; H, 6.89. The pure minor 5*R* diastereomer was also obtained from repurification of mixed fractions of a few runs. **11b**: R_f 0.32 (Hex/EtOAc, 2/1) $[\alpha]_D^{26}$ −43.5° (*c* 1.64, MeOH); IR (neat) ν_{max} 1775 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34–7.20 (m, 10H), 4.50 (d, J = 11.1 Hz, 1H), 4.49–4.44 (m, 1H), 4.42 (d, J = 11.1 Hz, 1H), 3.95 (td, J = 3.5, 6.5 Hz, 1H), 2.90 (dd, J = ~6.5, 13.9 Hz, 1H), 2.80 (dd, J = 6.5, 13.9 Hz, 1H), 2.60 (ddd, J = 6.7, 10.2, 17.8 Hz, 1H), 2.46 (ddd, J = 6.8, 10.2, 17.8 Hz, 1H), 2.35–2.27 (m, 1H), 2.23–2.14 (m, 1H); HRMS (EI) calcd for $C_{16}H_{20}O_3$ (M^+): 296.1412. Found: 296.1419.

5(*S*)-[1(*S*)-Benzyloxy-2-phenylethyl]-3(*R*)-(2-propenyl)dihydrofuran-2(3*H*)-one (12). To a cold (−78 °C), stirred solution of *i*-Pr_2NH (340 mL, 2.44 mmol) in THF (10 mL) was added a 1.5 M solution of BuLi in hexanes (1.42 mL, 2.13 mmol). After the resultant solution was stirred for 20 min at −78 °C, a solution of γ-lactone **11a** (450 mg, 1.52 mmol) in THF (1 mL) was added at a rate to maintain the internal temperature below −65 °C (5 min). The reaction mixture was stirred for an additional 20 min at −78 °C prior to the dropwise addition of allyl bromide (200 μL, 2.28 mmol). Subsequently, the mixture was stirred for 2 h and then quenched by the addition of saturated aq NH_4Cl (2 mL). The resultant mixture was diluted with EtOAc (20 mL) and the aqueous phase extracted with EtOAc. The combined organic layers were washed successively with water and brine, dried ($MgSO_4$), filtered and concentrated. Subjection of the residue to flash chromatography (Hex/EtOAc, 10/1) gave the desired γ-lactone **12** (386 mg, 76%) as a white amorphous solid and small amounts of the 3*S* isomer (63 mg) and substrate **11a** (23 mg). **12**: R_f 0.68 (Hex/EtOAc, 3/1); $[\alpha]_D^{25}$ +56.4° (*c* 1.22, $CHCl_3$);

IR ($CHCl_3$) ν_{max} 1770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.22 (m, 1H), 5.78–5.67 (m, 1H), 5.09–5.05 (m, 1H), 4.63 (d, J = 11.4 Hz, 1H), 4.47 (d, J = 11.4 Hz, 1H), 4.37 (td, J = 3.2, 8.6 Hz, 1H), 3.57 (ddd, J = 2.5, 6.0, 8.6 Hz, 1H), 2.58–2.51 (m, 1H), 2.24–2.16 (m, 1H), 2.08 (ddd, J = 3.2, 9.5, 13.0 Hz, 1H), 1.96–1.89 (m, 1H); MS (CI) m/z 337 (MH^+); Anal. calcd for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.89; H 7.27.

5(*S*)-[1(*S*)-Benzyloxy-2-phenylethyl]-3(*R*)-(cyclopropylmethyl)dihydrofuran-2(3*H*)-one (13). To a cold (0 °C), stirred 0.68 M solution of CH_2N_2 in Et_2O (25 mL) containing lactone **12** (147 mg, 0.44 mmol) was added $Pd(OAc)_2$ (3.0 mg, 0.01 mmol). After 10 min, the reaction mixture was quenched by the addition of acetic acid and then concentrated under reduced pressure. The residue was subjected to flash chromatography (Hex/EtOAc, 10/1) to give the desired product **13** (136 mg, 88%) as white needles: $[\alpha]_D^{25}$ +38.1° (c 1.05, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1765 cm ^{1}; ^1H NMR ($CDCl_3$) δ 7.37–7.23 (m, 10H), 4.63 (d, J = 11.5 Hz, 1H), 4.47 (d, J = 11.8 Hz, 1H), 4.41 (dt, J = 3.2, 8.6 Hz, 1H), 3.59 (ddd, J = 2.9, 6.4, 8.3 Hz, 1H), 3.05 (dd, J = 6.0, 13.4 Hz, 1H), 2.97 (dd, J = 8.3, 13.4 Hz, 1H), 2.97 (dd, J = 8.3, 13.4 Hz, 1H), 2.93–2.85 (m, 1H), 2.17 (ddd, J = 3.5, 9.5, 13.0 Hz, 1H), 2.05–1.96 (m, 1H), 1.65–1.58 (m, 1H), 1.45–1.38 (m, 1H), 0.76–0.64 (m, 1H), 0.53–0.40 (m, 2H), 0.15–0.00 (m, 2H); MS (CI) m/z 351 (MH^+); Anal. calcd for $C_{23}H_{26}O_3$: C, 78.82; H, 7.48. Found: C, 78.34; H, 7.50.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-5(*S*)-benzyloxy-4(*S*)-[(*tert*-butyldimethylsilyl)oxy]-2(*R*)-(cyclopropylmethyl)-6-phenylhexamide (14).** An aq 2 N NaOH solution (178 mL) was added to a vigorously stirred solution of lactone **13** (41.5 mg, 0.12 mmol) in methanol (3.5 mL) and H_2O (190 mL). After the reaction mixture was stirred for 2 h, the solvent was removed under reduced pressure and the residue was taken in CH_2Cl_2 (2 mL). To this cold (4 °C), stirred solution was added sequentially TBSOTf (407 μL, 1.77 mmol) and 2,6-lutidine (275 μL, 2.36 mmol), and the resultant mixture was stirred for 18 h at 4 °C. Subsequently, the mixture was diluted with EtOAc (10 mL) and the organic phase was separated. The combined organic extracts were washed successively with water, saturated aq $NaHCO_3$, a 10% (w/v) aq solution of citric acid, and brine. After being dried ($MgSO_4$), the organic layer was concentrated to give a residue that was immediately dissolved in CH_2Cl_2 (2 mL). To this solution was added successively i-Pr_2NEt (41 μL, 0.23 mmol), HOBt (32 mg, 0.24 mmol) and BOP·PF_6 (63 mg, 0.14 mmol). The resultant mixture was stirred at 25 °C for 5 min prior to the addition of **7** (43 mg, 0.18 mmol). After the pH of the reaction mixture was adjusted to 8.0–8.5 with i-Pr_2NEt, the reaction mixture was stirred for 3 h. The reaction mixture was then extracted with EtOAc and the combined organic extracts were washed successively with 0.5 N aq HCl, saturated aq $NaHCO_3$, H_2O and brine, dried ($MgSO_4$), filtered and concentrated. Purification of the residue by flash chromatography (Hex/EtOAc, 10/1) gave amide **14** (53.3 mg, 64%) as a white foam: $[\alpha]_D^{25}$ −53.7° (c 1.00, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3600–3100, 1650 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.09 (m, 10H), 5.66 (d, J = 9.2 Hz, 1H), 4.67 (d, J = 3.2 Hz, 1H), 4.42 (d, J = 11.5 Hz, 1H), 4.43–4.35 (m, 1H), 4.27 (d, J = 11.5 Hz, 1H), 3.95–3.86 (m, 1H), 3.62–3.54 (m, 1H), 3.34–3.19 (m, 2H), 3.07–2.99 (m, 1H), 2.74–2.64 (m, 1H), 2.60–2.50 (m, 1H), 2.35–2.17 (m, 2H), 2.02–1.88 (m, 1H), 1.85–0.69 (m, 25H), 0.97 (s, 9H), 0.87 (d, J = 6.7 Hz, 3H), 0.54–0.44 (m, 1H), 0.13 (s, 3H), 0.07 (s, 3H); MS (FAB) m/z 708 (MH^+); Anal. calcd for $C_{43}H_{69}NO_5Si$: C, 72.94; H, 9.82; N, 1.98. Found: C, 72.87; H, 10.06; N, 1.81.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-5(*S*)-benzyloxy-4(*S*)-hydroxy-6-phenylhexanamide (15).** To a solution of **14** (49.5 mg, 0.07 mmol) in THF (1 mL) was added a 1 M solution of TBAF in THF (77 μL, 0.08 mmol). The mixture was briefly heated at reflux (10 min) and then allowed to stand at room temperature for 18 h. After the addition of EtOAc (5 mL), the organic phase was washed successively with H_2O and brine, dried ($MgSO_4$), filtered and concentrated. Purification of the residue by flash chromatography (Hex/EtOAc, 7/3) gave the desired γ-hydroxyamide **15** (36.5 mg, 87%) as a white solid: $[\alpha]_D^{25}$ −54.0° (c 0.50, MeOH); IR (KBr) ν_{max} 3550–3100, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.59 (d, J = 8.7 Hz, 1H), 7.29–7.09 (m, 10H), 4.77 (d, J = 6.3 Hz, 1H), 4.68 (d, J = 3.6 Hz, 1H), 4.59 (d, J = 5.4 Hz, 1H), 4.42 (d, J = 11.4 Hz, 1H), 4.22–4.10 (m, 2H), 3.62–3.54 (m, 1H), 3.53–3.45 (m, 1H), 3.16–3.06 (m, 1H), 2.98–2.84 (m, 2H), 2.70–2.59 (m, 2H), 1.9–0.5 (m, 21H), 0.85 (d, J = 6.9 Hz, 3H), 0.73 (d, J = 6.3 Hz, 3H), 0.40–0.25 (m, 2H), 0.10–0.05 (m, 2H); MS (FAB) m/z 594 (MH^+); Anal. calcd for $C_{37}H_{55}NO_5$: C, 74.83; H, 9.34; N, 2.36. Found: C, 74.78; H, 9.55; N, 2.30.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-4(*S*),5(*S*)-dihydroxy-6-phenylhexanamide (1a).** A solution of benzyl ether **15** (1.63 g, 2.75 mmol) in EtOH/MeOH 1/1 (20 mL) containing 20% $Pd(OH)_2/C$ (327 mg) was stirred under an atmosphere of H_2 for 18 h. The reaction mixture was then filtered through a pad of Celite® and the pad washed with EtOH. The combined filtrate and washings were evaporated to dryness and the residue was triturated with Et_2O to afford the title compound **9** (1.27 g, 91%) as a white solid: $[\alpha]_D^{25}$ −29.5° (c 0.50, MeOH); IR (KBr) ν_{max} 3700–3120, 1600 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.54 (d, J = 9.0 Hz, 1H), 7.3–7.1 (m, 5H), 4.76 (d, J = 6.3 Hz, 1H), 4.69–4.61 (m, 1H), 4.37 (d, J = 5.4 Hz,

1H), 4.30 (d, J=6.3 Hz, 1H), 4.20–4.10 (m, 1H), 3.47–3.36 (m, 1H), 3.17–3.04 (m, 1H), 2.98–2.88 (m, 1H), 2.76–2.50 (m, 4H), 1.85–0.55 (m, 21H), 0.85 (d, J=6.6 Hz, 3H), 0.72 (d, J=6.6 Hz, 3H), 0.40–0.35 (m, 2H), 0.01–0.05 (m, 2H); MS (FAB) m/z 504 (MH^+); Anal. calcd for $C_{30}H_{49}NO_5$: C, 71.53; H, 9.81; N, 2.78. Found: C, 71.45; H, 10.04; N, 2.70.

5(*S*)-[1-(*R*)-[(*tert*-Butyldimethylsilyl)oxy]-2-phenylethyl]-3(*R*)-(cyclopropylmethyl)dihydrofuran-2(3*H*)-one (16) and 5(*R*)-[1-(*S*)-[(*tert*-butyldimethylsilyl)oxy]-2-phenylethyl]-3(*R*)-(cyclopropylmethyl)dihydrofuran-2(3*H*)-one (17). To an ice-cold solution of **6** (1.28 g, 5.24 mmol) in CH_2Cl_2 (20 mL) was added MCPBA (1.17 g, 6.81 mmol). The reaction mixture was stirred at 0 °C for 15 min then at 25 °C for 15 h. The mixture was taken up in EtOAc (300 mL), washed with 5% $Na_2S_2O_3$, 1 N HCl (50 mL), saturated $NaHCO_3$ (50 mL) and brine, dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (Hex/EtOAc, 2/1) provided a 1/1 mixture of hydroxylactones (1.10 g, 80%) as a colorless oil: IR (neat) ν_{max} 3420, 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.23 (m, 10H), 4.43 (dt, J=4.2, 8.3 Hz, 1H), 4.32 (ddd, J=4.5, 5.8, 10.1 Hz, 1H), 4.14 (dt, J=4.8, 8.3 Hz, 1H), 4.07 (dt, J=4.4, 8.6 Hz, 1H), 2.93–2.69 (m, 6H), 2.59 (ddd, J=4.4, 9.6, 13.1 Hz, 1H), 2.47 (ddd, J=6.0, 8.9, 12.4 Hz, 1H), 2.16–2.05 (m,2H), 1.88 (br s, 1H), 1.77–1.65 (m, 2H), 1.58 (br s, 1H), 1.53–1.46 (m, 2H), 0.80–0.77 (m, 2H), 0.52–0.47 (m, 4H), 0.18–0.08 (m, 4H); MS (FAB) m/z 261 (MH^+). To an ice-cold solution of hydroxylactones (0.96 g, 3.69 mmol) and 2,6-lutidine (1.29 mL, 11.13 mmol) in CH_2Cl_2 (15 mL) was added TBSOTf (1.69 mL, 7.38 mmol). The reaction mixture was stirred at 0 °C for 15 min, then at room temperature for 15 min. The solution was acidified by the addition of 10% HCl and extracted with EtOAc. The combined organic extracts were washed with saturated $NaHCO_3$ and brine, then dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (Hex/EtOAc, 9/1 then 6/1) gave **16** (R_f 0.77; Hex/EtOAc, 2/1) as a colorless oil (605 mg, 44%) and **17** (R_f 0.66; Hex/EtOAc, 2/1) as a colorless oil (608 mg, 44%). **16**: $[\alpha]_D^{25}$ +12.0° (c 1.41 MeOH); IR (film) ν_{max} 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33–7.16 (m, 5H), 4.34 (ddd, J=2.5, 4.4, 8.2 Hz, 1H), 4.21 (ddd, J=2.5, 6.0, 8.0 Hz, 1H), 2.86 (dd, J=6.0, 13.7 Hz, 1H), 2.82–2.76 (m, 1H), 2.72 (dd, J=8.0, 13.7 Hz, 1H), 2.60 (ddd, J=4.4, 10.0, 12.6 Hz, 1H), 1.95 (td, J=8.2, 12.6 Hz, 1H), 1.64 (ddd, J=4.9, 7.7, 14.0 Hz, 1H), 1.46 (ddd, J=6.6, 8.5, 14.0 Hz, 1H), 0.89 (s, 9H), 0.91–0.73 (m, 1H), 0.53–0.44 (m, 2H), 0.16–0.06 (m, 2H), 0.06 (s, 3H), −0.08 (s, 3H); MS (FAB) m/z 375 (MH^+); Anal. calcd for $C_{22}H_{34}O_3Si$: C, 70.54; H, 9.15. Found: C, 70.55; H, 9.38. **17**: $[\alpha]_D^{25}$ −23.6° (c 1.01 MeOH); IR (film) ν_{max} 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32–7.19 (m, 5H), 4.29–4.24 (m, 2H), 2.80 (dd, J=6.7, 13.7 Hz, 1H), 2.72 (dd, J=6.5, 13.7 Hz, 1H), 2.71–2.62 (m, 1H), 2.30 (ddd, J=5.6, 9.0, 12.3 Hz, 1H), 2.20–2.12 (m, 1H), 1.69 (ddd, J=4.4, 7.9, 14.1 Hz, 1H), 1.46 (ddd, J=6.4, 9.1, 14.1 Hz, 1H), 0.85 (s, 9H), 0.84–0.74 (m, 1H), 0.54–0.46 (m, 2H), 0.18–0.10 (m, 1H), 0.10–0.04 (m, 1H), 0.04 (s, 3H), −0.15 (s, 3H); MS (FAB) m/z 375 (MH^+); Anal. calcd for $C_{22}H_{34}O_3Si$: C, 70.54, H, 9.15. Found: C, 70.75, H, 9.34.

4(*S*),5(*R*)-Bis[(*tert*-butyldimethylsilyl)oxy]-*N*-[1(*S*)-(cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-6-phenylhexanamide (18). A solution of **16** (458.5 mg, 1.22 mmol) and $LiOH{\cdot}H_2O$ (205.6 mg, 4.90 mmol) in THF (6.6 mL) and H_2O (1.65 mL) was stirred at room temperature overnight. The mixture was concentrated and the residue was azeotropically distilled with benzene (3×10 mL) using a rotary evaporator to remove traces of water. To an ice-cold solution of the white residue and 2,6-lutidine (2.85 mL, 24.50 mmol) in CH_2Cl_2 (4.8 mL) and DMF (1.6 mL) was added TBSOTf (4.22 mL, 18.37 mmol). The mixture was stirred at room temperature overnight. The mixture was diluted with EtOAc (50 mL) and washed with cold 10% citric acid (2×15 mL), saturated $NaHCO_3$ (20 mL) and brine, then dried ($MgSO_4$) and concentrated. The silyl ester was treated with K_2CO_3 (254 mg, 1.83 mmol) in a mixture of MeOH/THF/H_2O (3/1/1) (10/3.3/3.3 mL) at room temperature overnight. EtOAc (250 mL) and brine (10 mL) were then added and the mixture acidified with cold 10% citric acid. The phases were separated and the organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (Hex/EtOAc, 4/1) gave the corresponding acid (550 mg, 88%) as a colorless oil. To a solution of this acid (444 mg, 0.87 mmol) and BOP·PF_6 (426.4 mg, 0.96 mmol) in DMF (4.4 mL), was added **7** (235 mg, 0.96 mmol) and *i*-Pr_2NEt (0.53 mL, 3.06 mmol). The reaction mixture was stirred at room temperature for 1 h. The mixture was diluted with EtOAc (150 mL), washed with 1 N HCl (2×25 mL), saturated $NaHCO_3$ (2×25 mL) and brine, dried ($MgSO_4$), filtered and concentrated. Purification of the residue by the flash chromatography (Hex/EtOAc, 6/1) gave **18** (518 mg, 81%) as a white foam: mp 61–62 °C; $[\alpha]_D^{26}$ −20.5° (c 1.01 MeOH); IR (KBr) ν_{max} 3390, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.26–7.17 (m, 5H), 5.38 (d, J=8.9 Hz, 1H), 4.41–4.35 (m, 1H), 3.81 (t, J=6.7 Hz, 1H), 3.56 (d, J=8.9 Hz, 1H), 3.31–3.22 (m, 2H), 2.77 (dd, J=6.0, 13.6 Hz, 1H), 2.69 (dd, J=7.3, 13.6 Hz, 1H), 2.42 (m, 1H), 2.00–1.94 (m, 2H), 1.79–1.19 (m, 17H), 0.95 (d, J=6.7 Hz, 3H), 0.91 (s, 9H), 0.85 (d, J=6.7 Hz, 3H), 0.83 (s, 9H), 0.95–0.83 (m, 2H), 0.79–0.69 (m, 1H), 0.48–0.46 (m, 2H), 0.10–0.02 (m, 2H), 0.06 (s, 3H), 0.00 (s, 6H), −0.03 (s, 3H); MS (FAB) m/z 732 (MH^+); Anal. calcd for $C_{42}H_{77}NO_5Si_2$: C, 68.87; H, 10.60; N, 1.91. Found: C, 68.69; H, 10.85; N, 1.92.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-4(*S*),5(*R*)-dihydroxy-6-phenylhexanamide (1d).** A 5% solution of aqueous HF 40% in MeCN (3 mL) was added to **18** (164 mg, 0.22 mmol) and the resulting solution was stirred at room temperature for 1 h. EtOAc (50 mL) was added and the solution washed with saturated $NaHCO_3$ (15 mL) and brine, dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex/EtOAc/EtOH, 15/10/1) followed by trituration of the solid with hot ether gave **1d** (43 mg, 38%) as a white solid: mp 202–203 °C; $[\alpha]_D^{25}$ −16.3° (*c* 0.52, MeOH); IR (KBr) ν_{max} 3340, 1615 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.56 (d, *J* = 9.0 Hz, 1H), 7.26–7.12 (m, 5H), 4.77–4.70 (m, 1H), 4.44–4.42 (m, 1H), 4.16 (br s, 1H), 3.37 (br s, 1H), 3.26–3.20 (m, 1H), 3.12–3.07 (m, 1H), 2.95–2.84 (m, 2H), 2.68–2.60 (m, 1H), 2.43 (dd, *J* = 9.6, 13.8 Hz, 1H), 1.86 (t, *J* = 12.1 Hz, 1H), 1.81–1.51 (m, 8H), 1.45 (t, *J* = 11.7 Hz, 1H), 1.36–0.93 (m, 8H), 0.93–0.72 (m, 2H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.72 (d, *J* = 6.6 Hz, 3H) 0.67–0.63 (m, 1H), 0.36–0.34 (m, 2H), 0.06–0.00 (m, 2H); MS (FAB) *m/z* 504 (MH^+); Anal. calcd for $C_{30}H_{49}NO_5$: C, 71.51; H, 9.81; N, 2.78. Found: C, 71.18; H, 9.94; N, 2.76.

4(*R*),5(*S*)-Bis[(*tert*-butyldimethylsilyl)oxy]-*N*-[1(*S*)-(cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-6-phenylhexanamide (19). Using conditions similar to those described for the preparation of **18**, **17** (501 mg, 1.33 mmol) was transformed to the corresponding acid in quantitative yield. From this acid (397 mg, 0.78 mmol), **19** (385 mg, 67%) was obtained as a white solid: mp 134–135 °C; $[\alpha]_D^{25}$ −13.9° (*c* 1.01 MeOH); IR (KBr) ν_{max} 3390, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.18–7.11 (m, 5H), 5.42 (d, *J* = 8.9 Hz, 1H), 4.37 (td, *J* = 4.3, 9.5 Hz, 1H), 3.78 (t, *J* = 6.8 Hz, 1H), 3.62 (dd, *J* = 1.9, 8.9 Hz, 1H), 3.30 (td, *J* = 3.2, 8.6 Hz, 1H), 3.24 (d, *J* = 8.3 Hz, 1H), 2.74 (dd, *J* = 8.0, 13.7 Hz, 1H), 2.65 (dd, *J* = 5.4, 13.7 Hz, 1H), 2.36 (tt, *J* = 3.4, 10.0 Hz, 1H), 1.97–1.03 (m, 20H), 0.95 (d, *J* = 7 Hz, 3H), 0.94 (s, 9H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.83 (s, 9H), 1.01–0.82 (m, 2H), 0.71–0.64 (m, 1H), 0.51–0.39 (m, 2H), 0.17–0.11 (m, 1H), 0.12 (s, 3H), 0.03–0.00 (m, 1H), −0.03 (s, 3H), −0.08 (s, 3H), −0.33 (s, 3H); MS (FAB) *m/z* 732 (MH^+); Anal. calcd for $C_{42}H_{77}NO_5Si_2$: C, 68.82; H, 10.60; N, 1.91. Found: C, 68.66; H, 10.79; N, 1.95.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-4(*R*),5(*S*)-dihydroxy-6-phenylhexamide (1c).** Compound **1c** (63 mg, 56%) was obtained from **19** (164 mg, 0.22 mmol) as a white solid using a method identical to that employed for **1c**: mp 134–135 °C; $[\alpha]_D^{25}$ −30.5° (*c* 0.51 MeOH); IR (KBr) ν_{max} 3360 (br), 1615 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.56 (d, *J* = 8.4 Hz, 1H), 7.26–7.16 (m, 5H), 4.74–4.71 (m, 1H), 4.43–4.39 (m, 1H), 4.14 (br s, 1H), 3.41 (br s, 1H), 3.30 (m, 1H), 3.11 (br s, 1H), 2.94–2.86 (m, 2H), 2.59 (br s, 1H), 2.45 (br s, 1H), 1.83–1.41 (m, 12H), 1.41–1.00 (m, 8H), 0.95–0.70 (m, 2H), 0.87 (d, *J* = 6.3 Hz, 3H), 0.74 (d, *J* = 6.3 Hz, 3H), 0.69–0.58 (m, 1H), 0.35–0.33 (m, 2H), 0.05–0.01 (m, 2H); MS (FAB) *m/z* 504 (MH^+); Anal. calcd for $C_{30}H_{49}NO_5$: C, 71.51; H, 9.81; N, 2.78. Found: C, 71.15; H, 9.97; N, 2.74.

5(*S*)-[1(*S*)-Hydroxy-2-phenylethyl]dihydrofuran-2(3*H*)-one (20). A solution of benzyl ether **11a** (2.08 g, 7.03 mmol) in EtOH (30 mL) containing $Pd(OH)_2/C$ (820 mg) was stirred under an atmosphere of H_2 for 48 h. The reaction mixture was then filtered through a pad of Celite® and the pad washed with EtOH. The combined filtrate and washings were evaporated and the residue so obtained was purified by flash chromatography (Hex/EtOAc, 4/1 then 1/1) to afford alcohol **20** (1.22 g, 84%) as a colorless oil: $[\alpha]_D^{25}$ +50.8° (*c* 1.00, $CHCl_3$); IR (neat) ν_{max} 3700–3120, 1850–1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40–7.20 (m, 5H), 4.43 (dt, *J* = 3.2, 7.3 Hz, 1H), 3.87–3.75 (m, 1H), 3.00–2.85 (m, 2H), 2.80–2.56 (m, 2H), 2.55–2.40 (m, 1H), 2.30–2.14 (m, 2H); MS (EI) *m/z* 206 (M^+); Anal. calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.78; H, 7.09.

5(*S*)-[1(*S*)-[(*tert*-Butyldimethylsilyl)oxy]-2-phenylethyl]dihydrofuran-2(3*H*)-one (21). To a cooled (0 °C) solution of hydroxylactone **20** (1.12 g, 5.43 mmol) in CH_2Cl_2 (25 mL) was added TBSOTf (1.40 mL, 5.98 mmol) and 2,6-lutidine (950 μL, 8.15 mmol). The mixture was stirred at room temperature for 45 min and was then diluted with CH_2Cl_2. The organic phase was washed sequentially with a saturated aqueous solution of $NaHCO_3$ (2×) and brine (2×), dried ($MgSO_4$), filtered and evaporated to dryness. The residue was purified by flash chromatography (Hex/EtOAc, 7/3) to give the silylated derivative **21** (1.50 g, 87%) as a colorless oil: $[\alpha]_D^{25}$ +60.8° (*c* 1.00, $CHCl_3$); IR (film) ν_{max} 1780 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.20 (m, 5H), 4.41–4.34 (m, 1H), 3.92–3.85 (m, 1H), 3.30 (dd, *J* = 8.3, 13.4 Hz, 1H), 2.79 (dd, *J* = 6.4, 13.4 Hz, 1H), 2.61 (ddd, *J* = 6.4, 10.2, 17.6 Hz, 1H), 2.45 (ddd, *J* = 6.4, 10.2, 17.6 Hz, 1H), 2.25–2.00 (m, 2H), 0.90 (s, 9H), 0.09 (s, 3H), −0.01 (s, 3H); MS (EI) *m/z* 263 $(M-t\text{-}Bu)^+$; Anal. calcd for $C_{18}H_{28}O_3Si$: C, 67.46; H, 8.81. Found: C, 67.79; H, 9.14.

5(*S*)-[2-Phenyl-1(*S*)-[(*tert*-butyldimethylsilyl)oxy]ethyl]-3(*S*)-(2-thienylmethyl)dihydrofuran-2(3*H*)-one (22). A solution of lactone **21** (888 mg, 2.77 mmol) in THF (4 ml) was added (5 min) to a cold solution of LDA in THF (16 mL) [prepared from *i*-Pr_2NH (322 mg, 3.19 mmol) and a 1.6 M solution of *n*-BuLi in hexanes (2.0 mL, 3.19 mmol)]. The reaction mixture was stirred at −78 °C for 30 min. HMPA (496 mg, 2.77 mmol) was

added dropwise to the mixture followed 10 min later by a solution of 2-(chloromethyl)thiophene[27] (735 mg, 5.54 mmol) in THF (2 mL). The reaction mixture was stirred at −78 °C for 1 h, allowed to warm (45 min) to −50 °C and stirred at that temperature for 1.2 h. MeOH (300 μL) and saturated NH_4Cl (10 mL) were successively added to the mixture. The reaction mixture was diluted with EtOAc (150 mL), washed with H_2O (2×50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Purification and separation by flash chromatography (Hex/EtOAc, 10/1 then 5/1) gave **22** (512 mg, 44%) as a colorless oil (R_f 0.43; Hex/EtOAc, 5/1) along with a small amount of the minor diastereomer (43 mg, 4%; R_f 0.36, Hex/EtOAc, 5/1) and some starting material (204 mg, 23%). **22**: $[\alpha]_D^{25}$ +17.2° (*c* 0.95, MeOH); IR (KBr) ν_{max} 1775 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.19 (m, 5H), 7.14 (dd, *J* = 1.0, 5.2 Hz, 1H), 6.91 (dd, *J* = 3.5, 5.2 Hz, 1H), 6.81 (dd, *J* = 1.0, 3.5 Hz, 1H), 4.22 (dt, *J* = 2.6, 8.9 Hz, 5-H), 3.81 (ddd, *J* = 2.6, 5.5, 9.1 Hz, 1′-H), 3.38 (dd, *J* = 4.1, 14.9 Hz, 1H), 3.10 (qd, *J* = 4.1, 9.5 Hz, 1H), 2.99 (dd, *J* = 9.1, 13.2 Hz, 1H), 2.94 (dd, *J* = 9.5, 14.9 Hz, 1H), 2.78 (dd, *J* = 5.5, 13.2 Hz, 1H), 2.16 (ddd, *J* = 2.6, 9.5, 13.0 Hz, 4-H), 2.00 (dt, *J* = 8.9, 9.5, 13.0 Hz, 4-H), 0.89 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); MS (FAB) *m/z* 417 (MH^+); Anal. calcd for $C_{23}H_{32}O_3SiS$: C, 66.30; H, 7.74. Found: C, 66.21; H, 7.83.

4(*S*),5(*S*)-Bis[(*tert*-butyldimethylsilyl)oxy]-*N*-[1(*S*)-(cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-6-phenyl-2(*S*)-(2-thienylmethyl)hexanamide (23). A solution of **22** (599 mg, 1.44 mmol), 1 N NaOH (2.9 mL, 2.9 mmol) in THF (4.0 mL) and MeOH (4.2 mL) was stirred at 0 °C for 3.2 h. 1 N HCl (1.2 mL) was added and the mixture was concentrated under reduced pressure. The residue was suspended in benzene and concentrated (4×). TBSOTf (5.70 g, 21.6 mmol) was added to an ice-cold solution of the residue and 2,6-lutidine (4.62 g, 43.1 mmol) in DMF (7.2 mL). The mixture was stirred at 0 °C for 1 h and ambient temperature for 14 h. The mixture was poured into a cold 10% citric acid solution (150 mL) and extracted with EtOAc (3×75 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$) and concentrated. A mixture of the residue and K_2CO_3 (796 mg, 5.76 mmol) in MeOH (6.0 mL), H_2O (7.7 mL) and THF (20 mL) was stirred at room temperature for 2.5 h. The mixture was poured into H_2O (175 mL), acidified by addition of 10% citric acid solution (pH < 3) and extracted with EtOAc (3×75 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated. The residue was partially purified by flash chromatography (Hex/EtOAc, 4/1) to give the acid (649 mg). BOP·PF_6 (575 mg, 1.30 mmol) was added to a solution of the acid, *i*-Pr_2NEt (382 mg, 2.95 mmol) and **7**·HCl (364 mg, 1.30 mmol) in CH_2Cl_2 (6.5 mL). The mixture was stirred at room temperature for 3 h, then diluted with EtOAc (125 mL) and washed with 1 N HCl solution (30 mL), saturated $NaHCO_3$ solution (30 mL), H_2O (30 mL) and brine (30 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex/EtOAc, 6/1) gave **23** (582 mg, 52%) as a white solid: $[\alpha]_D^{25}$ −67.0° (*c* 0.54, MeOH); IR (KBr) ν_{max} 3410 (br), 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.27–7.14 (m, 6H), 6.93 (dd, *J* = 3.5, 5.1 Hz, 1H), 6.86 (br d, *J* = 3.5 Hz, 1H), 5.13 (d, *J* = 8.6 Hz, 1H), 4.20 (q, *J* = 7.8 Hz, 1H), 3.74 (ddd, *J* = 1.6, 4.1, 10.3 Hz, 1H), 3.63 (ddd, *J* = 1.9, 4.1, 9.7 Hz, 1H), 3.21 (dd, *J* = 10.8, 15.0 Hz, 1H), 2.98–3.08 (m, 3H), 2.89 (td, *J* = 3.1, 9.0 Hz, 1H), 2.71–2.66 (m, 1H), 2.47–2.41 (m, 2H), 1.90–1.87 (m, 1H), 1.72–1.11 (m, 14H), 1.00 (s, 9H), 0.95 (d, *J* = 6.7 Hz, 3H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.96–0.79 (m, 2H), 0.78 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H), −0.19 (s, 3H), −0.60 (s, 3H); MS (FAB) *m/z* 774 (MH^+); Anal. calcd for $C_{43}H_{75}NO_5SSi_2$: C, 66.70; H, 9.76; N, 1.81. Found: C, 66.45; H, 9.97; N, 1.74.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-4(*S*),5(*S*)-dihydroxy-6-phenyl-2(*S*)-(2-thienylmethyl)hexanamide (1e).** Compound **23** (577 mg, 0.74 mmol) was dissolved in acetonitrile containing 5% of aqueous HF 40% solution (total volume of 15 mL). After stirring at room temperature for 4 h, the reaction mixture was poured into a saturated $NaHCO_3$ solution (125 mL) and extracted with EtOAc (3×75 mL). The combined organic layers were washed with brine (40 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex/EtOAc, 3/2 then 1/1) gave **1e** (254 mg, 62%) as a white solid (R_f 0.41; EtOAc/Hex, 1/1) along with a small amount of the corresponding hydroxylactone (55 mg, 25%) (R_f 0.6; EtOAc/Hex, 1/1): $[\alpha]_D^{25}$ −35.3° (*c* 1.03, MeOH); IR (KBr) ν_{max} 3390 (br), 1625 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.20 (m, 5H), 7.16 (dd, *J* = 1.0, 5.1 Hz, 1H), 6.91 (dd, *J* = 3.5, 5.1 Hz, 1H), 6.84 (br d, *J* = 3.5 Hz, 1H), 5.69 (d, *J* = 8.6 Hz, 1H), 4.32 (d, *J* = 4.4 Hz, 1H), 4.24 (td, *J* = 3.6, 9.1 Hz, 1H), 3.64–3.59 (m, 1H), 3.49–3.47 (m, 1H), 3.26–3.20 (m, 1H), 3.05 (t, *J* = 8.4 Hz, 1H), 2.96–2.84 (m, 5H), 2.81 (d, *J* = 5.1 Hz, 1H), 2.70 (dd, *J* = 9.2, 13.7 Hz, 1H), 1.98–1.60 (m, 9H), 1.53–1.48 (m, 1H), 1.38–1.11 (m, 8H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.94–0.79 (m, 2H); MS (FAB) *m/z* 546 (MH^+); Anal. calcd for $C_{31}H_{47}NO_5S$: C, 68.22; H, 8.68; N, 2.57. Found: C, 67.92; H, 8.82; N, 2.51.

1-(Triphenylmethyl)-1*H*-imidazole-4-propanoic acid (25). Et_3N (26.73 g, 36.8 mL, 0.26 mol) was added dropwise (12 min) to a solution of **24**[28] (32.58 g, 0.21 mol) and triphenylmethyl chloride (64.80 g, 0.23 mol) in CH_2Cl_2 (350 mL) and the reaction mixture was then stirred at room temperature for 63 h. After dilution with CH_2Cl_2 (total volume of 900 mL), the solution was washed with

H_2O (2×200 mL), saturated $NaHCO_3$ solution (200 mL) and brine (150 mL), then dried ($MgSO_4$), filtered and concentrated. To the oily residue so obtained (102.0 g) in a mixture of THF and H_2O (630 mL, 210 ml) was added $LiOH \cdot H_2O$ (22.03 g, 0.52 mol). The reaction mixture was stirred at ambient temperature for 3 h after which time most of the THF was removed in vacuo. The residue was poured into water (1 L) and the solution acidified to pH 2–3 by addition of 10% citric acid solution. The mixture was extracted with CH_2Cl_2 (3×500 mL) and the combined organic extracts were washed with 10% citric acid solution (250 mL), and brine (250 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was triturated with ether (300 mL). Upon filtration **25** was obtained as a white solid (77.14 g, 96%): IR (KBr) ν_{max} 3400, 3130–2460, 1715 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.58 (s, 1H), 7.45–7.36 (m, 9H), 7.10–7.07 (m, 6H), 6.77 (s, 1H), 2.69 (t, J=7.3 Hz, 2H), 2.51 (t, J=7.3 Hz, 2H); MS (CI) m/z 383 (MH^+); Anal. calcd for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.19; H, 5.85; N, 7.39.

4(*S*)-(1-Methylethyl)-3-[[1-oxo-3-(1-triphenylmethyl)-1*H*-imidazol-4-yl]propyl]-2-oxazolidinone (26). To mechanically stirred suspension of **25** (11.5 g, 30.1 mmol) in THF (120 mL) was added Et_3N (3.59 g, 35.5 mmol). The solution was cooled to −78 °C and pivaloyl chloride (3.79 g, 31.4 mmol) was added dropwise (4 min). The reaction mixture was allowed to warm to 0 °C and maintained at this temperature for 75 min before being re-cooled to −78 °C. Meanwhile, a 1.6 M solution of *n*-BuLi in hexane (17.1 mL, 27.3 mmol) was added over a 10 min period to a cold (−78 °C) solution of 4(*S*)-(1-methylethyl)-2-oxazolidinone (3.53 g, 27.3 mmol) in THF (110 mL). After 30 min at −78 °C, the solution was quickly added via cannula to the cold (−78 °C) solution of the mixed anhydride prepared previously. The reaction mixture was stirred at −78 °C for 40 min, then allowed to warm to 0 °C (25 min) and stirred at 0 °C for 30 min. A saturated NH_4Cl solution (50 mL) was added. The mixture was poured into H_2O (500 mL) and extracted with EtOAc (3×250 mL). The combined organic extracts were washed with $NaHCO_3$ solution (125 mL), and brine (125 mL), then dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by flash chromatography (Hex/EtOAc, 3/1) gave **26** (11.38 g, 84%) as a pale yellow solid: $[\alpha]_D^{25}$ +44.8° (*c* 1.04, MeOH); IR (KBr) ν_{max} 1780, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.30 (m, 10H), 7.15–7.10 (m, 6H), 6.58 (s, 1H), 4.40 (dt, J=3.6, 8.7 Hz, 1H), 4.23 (t, J=8.7 Hz, 1H), 4.17 (dd, J=3.6, 8.7 Hz, 1H), 3.34–3.20 (m, 2H), 2.98–2.86 (m, 2H), 2.33 (td, J=3.6, 7.0 Hz, 1H), 0.89 (d, J=7.3 Hz, 3H), 0.82 (d, J=7.0 Hz, 3H); MS (FAB) m/z 494 (MH^+); Anal. calcd for $C_{31}H_{31}N_3O_3$: C, 75.43; H, 6.33; N, 8.51. Found: C, 75.45; H, 6.46; N, 8.45.

4(*S*)-(1-Methylethyl)-3-[1-oxo-6-phenyl-2(*S*)-[[(1-triphenylmethyl)-1*H*-imidazol-4-yl]methyl]-4-hexenyl]-2-oxazolidinone (27). A solution of **26** (9.52 g, 19.3 mmol) in THF (20 mL) was added (10 min) to a cold (−78 °C) solution of NaHMDS (19.5 mL of 1.09 M solution in THF, 21.2 mmol) in THF (85 mL). The mixture was stirred at −78 °C for 1 h, before a solution of **4** (6.11 g, 28.9 mmol) in THF (5 mL) was added (10 min). After stirring at −78 °C for 3.5 h, a saturated NH_4Cl solution (25 mL) was introduced and the mixture allowed to warm to 0 °C. The mixture was poured into H_2O (600 mL) and extracted with EtOAc (3×200 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (150 mL) and brine (150 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (Hex/EtOAc, 1/1) gave **27** (5.75 g, 48%) contaminated with traces of chiral auxiliary (77 mg) as well as starting material **26** (3.44 g, 36%). An analytical sample of **27** was obtained by flash chromatography ($CHCl_3$/EtOH, 15/1): $[\alpha]_D^{25}$ +27.4° (*c* 1.00, MeOH); IR (KBr) ν_{max} 1780, 1700, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.20 (d, J=1.4 Hz, 1H), 7.42–7.36 (m, 9H), 7.21 (t, J=7.3 Hz, 1H), 7.14–7.06 (m, 10H), 6.61 (d, J=1.4 Hz, 1H), 5.50–5.36 (m, 2H), 4.45–4.41 (m, 1H), 4.31 (t, J=8.9 Hz, 1H), 4.21–4.17 (m, 1H), 4.13 (dd, J=2.9, 8.9 Hz, 1H), 3.25 (d, J=6.0 Hz, 2H), 3.08 (dd, J=6.8, 15.3 Hz, 1H), 3.0 (dd, J=5.4, 15.3 Hz, 1H), 2.44–2.37 (m, 1H), 2.26–2.18 (m, 2H), 0.85 (d, J=7.0 Hz, 3H), 0.77 (d, J=7.0 Hz, 3H); MS (FAB) m/z 624 (MH^+); Anal. calcd for $C_{41}H_{41}N_3O_3$: C, 78.94; H, 6.62; N, 6.74. Found: C, 78.58; H, 6.64; N, 6.65.

5(*S*)-[1(*S*)- and 5(*R*)-[1(*R*)-Hydroxy-2-phenylethyl]-3(*R*)-[[1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]dihydrofuran-2(3*H*)-one (28a,b). A solution of OsO_4 (109 mg, 0.43 mmol) in THF (2.2 mL) was added to a solution of **27** (5.41 g, 8.67 mmol) and $NMMO \cdot H_2O$ (1.47 g, 10.8 mmol) in THF (87 mL) and H_2O (3.5 mL). The reaction mixture was stirred at room temperature for 60 min. 10% $NaHSO_3$ solution (10 mL) was added and the mixture stirred for 15 min. The mixture was poured into H_2O (600 mL) and extracted with EtOAc (3×200 mL). The combined organic extracts were washed with brine (150 mL), dried ($MgSO_4$), filtered and concentrated to afford a gummy residue. To a solution of this residue (6.1 g) in THF (130 mL) and H_2O (43 mL) at 0 °C was added a 30% H_2O_2 solution (4.9 mL, 43.3 mmol) followed by $LiOH \cdot H_2O$ (728 mg, 17.3 mmol). The reaction mixture was stirred at 0 °C for 45 min. Water (5 mL) and solid Na_2SO_3 were added until complete disappearance of peroxide (monitored with KI paper). Most of the THF was then removed under reduced pressure. The residual aqueous solution was diluted with H_2O (250 mL) and a 10% citric acid solution (~150 mL) and the resulting was extracted with EtOAc (3×200 mL). The combined organic extracts were washed with brine

(75 mL), dried ($MgSO_4$), filtered and concentrated. A solution of the residue (6.5 g) in THF (175 mL) was treated with TFA (5.2 mL) at 0 °C for 3.75 h. The reaction mixture was then poured into H_2O (1.2 L) and extracted with EtOAc (2×300 mL). The combined organic extracts were washed with saturated $NaHCO_3$ solution (2×200 mL), brine (150 mL) then dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography (EtOAc/Hex, 4/1) gave **28** (1/1 mixture of diastereomers) as a white solid (2.74 g, 60%): IR (KBr) ν_{max} 3150 (br), 1765 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.35–7.19 (m, 30H), 7.12–7.10 (m, 12H), 6.61 (s, 1H), 6.60 (s, 1H), 4.33 (ddd, J = 3.5, 6.7, 9.8 Hz, 1H), 4.23 (ddd, J = 3.5, 4.8, 8.3 Hz, 1H), 3.78–3.71 (m, 2H), 3.18–2.97, 2.90–2.82 (m, 9H), 2.77 (dd, J = 7.9, 14.6 Hz, 1H), 2.32–2.12 (m, 4H), 1.76 (br, 2H); MS (FAB) m/z 529 (MH^+).

5(*S*)-[1(*S*)-(Benzoyloxy)-2-phenylethyl]-3(*R*)-[[1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]dihydrofuran-2(3*H*)-one (29a) and 5(*R*)-[1(*R*)-(benzoyloxy)-2-phenylethyl]-3-(*R*)-[[1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]dihydrofuran-2(3*H*)-one (29b). Benzoyl chloride (1.02 g, 7.26 mmol) was added (10 min) to an ice-cold solution of **28a,b** (2.56 g, 4.84 mmol), Et_3N (1.96 g, 19.4 mmol) and DMAP (296 mg, 2.42 mmol) in CH_2Cl_2 (81 mL). The reaction mixture was stirred at 0 °C for 2 h. H_2O (5 mL) was added, the mixture was taken up in EtOAc (400 mL) and washed successively with 1 N HCl solution (100 mL), $NaHCO_3$ solution (100 mL) and brine (100 mL) then dried ($MgSO_4$), filtered and concentrated. Purification and separation by flash chromatography (Hex/EtOAc, 1/1 then 1/3) afforded a mixture of **29a** (R_f 0.21; EtOAc/Hex, 1/1) and **29b** (R_f 0.14; EtOAc/Hex, 1/1). A second purification by flash chromatography (CH_2Cl_2/EtOAc, 4/1) delivered pure **29a** (1.04 g, 34%) and **29b** (1.17 g, 38%) both as white solids along with a small mixed fraction (0.44 g). **29a**: $[\alpha]_D^{25}$ +4.4° (*c* 1.01, MeOH); IR (KBr) ν_{max} 1775, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.98 (dd, J = 1.3, 7.8 Hz, 2H), 7.57 (tt, J = 1.3, 7.8 Hz, 1H), 7.43 (t, J = 7.8 Hz, 2H), 7.31–7.20 (m, 15H), 7.10–7.06 (m, 6H), 6.53 (d, J = 1.3 Hz, 1H), 5.31 (td, J = 2.2, 7.3 Hz, 1′-H), 4.45 (ddd, J = 2.2, 4.1, 8.9 Hz, 5-H), 3.12 (d, J = 7.3 Hz, 2H), 3.02–2.94 (m, 1H), 2.94 (dd, J = 4.5, 14.4 Hz, 1H), 2.80 (dd, J = 7.5, 14.4 Hz, 1H), 2.25 (d~t, J = 8.0, 8.9, 13.5 Hz, 4-H), 2.11 (ddd, J = 4.1, 9.6, 13.5 Hz, 4-H); MS (FAB) m/z 633 (MH^+); Anal. calcd for $C_{42}H_{36}N_2O_4$: C, 79.72; H, 5.73; N, 4.43. Found: C, 80.13; H, 5.81; N, 4.39. **29b**: $[\alpha]_D^{25}$ −8.8° (*c* 1.01 MeOH); IR (KBr) ν_{max} 1775, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.97 (dd, J = 1.3, 7.8 Hz, 2H), 7.51 (tt, J = 1.3, 7.8 Hz, 1H), 7.35 (t, J = 7.8 Hz, 2H), 7.32–7.19 (m, 15H), 7.09–7.04 (m, 6H), 6.47 (d, J = 1.3 Hz, 1H), 5.34 (td, J = 3.4, 7.1 Hz, 1′-H), 4.50 (ddd, J = 3.4, 6.4, 9.9 Hz, 5-H), 3.19–3.03 (m, 4H), 2.60 (dd, J = 8.6, 14.0 Hz, 1H), 2.31 (ddd, J = 6.4, 8.9, 12.7 Hz, 4-H), 1.92–1.83 (m, 4-H); MS (FAB) m/z 633 (MH^+); Anal. calcd for $C_{42}H_{36}N_2O_4$: C, 79.72; H, 5.73; N, 4.43. Found: C, 79.40; H, 5.82; N, 4.44.

4(*S*),5(*S*)-Bis[(*tert*-butyldimethylsilyl)oxy]-*N*-[1(*S*)-(cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-6-phenyl-2(*R*)-[[1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]hexanamide (30). A solution of **29a** (0.80 g, 1.26 mmol) and $LiOH \cdot H_2O$ (318 mg, 7.59 mmol) in THF and H_2O (19 mL and 6.3 mL) was stirred at ambient temperature for 15 h. The mixture was concentrated under reduced pressure, and residual solvent removed by azeotropic distillation with benzene. TBSOTf (4.05 g, 37.8 mmol) was added to an ice-cold solution of the residue and 2,6-lutidine (6.66 g, 25.2 mmol) in DMF (12.6 mL). The mixture was stirred at 0 °C for 1.5 h before being poured into a saturated $NaHCO_3$ solution (250 mL) and extracted with ether (3×125 mL). The combined organic extracts were successively washed with 1 N HCl solution (2×125 mL), H_2O (2×125 mL), brine (125 mL), then dried ($MgSO_4$), filtered and concentrated. A mixture of the residue and 1 N NaOH solution (5 mL) in THF (25 mL) was stirred at 0 °C for 1 h. Thereafter, the mixture was poured into a 0.1 N HCl solution (250 mL) and extracted with ether (3×125 mL). The combined etherial layers were washed with a saturated $NaHCO_3$ solution (70 mL), 0.1 N HCl (100 mL), brine (100 mL), then dried ($MgSO_4$), filtered and concentrated. The residue was partially purified by flash chromatography (Hex/EtOAc, 1/1) to give the desired acid (0.80 g). BOP·PF_6 (479 mg, 1.08 mmol) was added to a solution of this acid, *i*-Pr_2NEt (227 mg, 1.75 mmol) and **7** (264 mg, 1.08 mmol) in CH_2Cl_2 (5.2 mL). The mixture was stirred at room temperature for 1.7 h. The reaction mixture was diluted with EtOAc (150 mL) and the solution washed successively with a 1 N HCl solution (50 mL), a saturated $NaHCO_3$ solution (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered and concentrated. The residue was purified by flash chromatography (Hex/EtOAc, 2/1) to give **30** (0.76 g, 60%) as a white solid: $[\alpha]_D^{25}$ −43.5° (*c* 1.02, MeOH); IR (KBr) ν_{max} 3400 (br), 1675, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.15 (d, J = 1.6 Hz, 1H), 7.41–7.37 (m, 9H), 7.29 (t, J = 7.2 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.14 (d, J = 7.2 Hz, 2H), 7.11–7.08 (m, 6H), 7.03 (d, J = 9.5 Hz, 1H), 6.84 (d, J = 1.6 Hz, 1H), 4.35 (br q, J = 8.0 Hz, 1H), 3.69 (dd, J = 4.1, 9.2 Hz, 1H), 3.53 (dd, J = 4.4, 10.2 Hz, 1H), 3.33–3.23 (m, 3H), 2.79–2.73 (m, 2H), 2.40–2.34 (m, 1H), 2.23 (dd, J = 10.8, 13.0 Hz, 1H), 1.87–1.05 (m, 15H), 0.92 (d, J = 6.7 Hz, 3H), 0.84 (s, 9H), 0.83 (d, J = 6.4 Hz, 3H), 0.93–0.82 (m, 2H), 0.74 (s, 9H), 0.15, 0.10, −0.21, −0.63 (4s, 12H); MS (FAB) m/z 1000 (MH^+).

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-4(*S*),5(*S*)-dihydroxy-6-phenyl-2(*R*)-[[1-(triphenylmethyl)-1*H*-imidazol-4-yl]methyl]hexanamide (31).** Compound **30** (0.52 g, 0.52 mmol) was dissolved in acetonitrile

containing 10% of aqueous solution of HF 40% (total volume of 10 mL). The reaction mixture was stirred at room temperature for 1.8 h then quenched by addition of a saturated $NaHCO_3$ solution (100 mL). The mixture was extracted with EtOAc (150 mL). The organic layer was washed with brine (50 mL), dried ($MgSO_4$), filtered and concentrated. Purification by flash chromatography ($CHCl_3$/EtOH, 15/1) gave **31** (316 mg, 79%) as a white solid: $[\alpha]_D^{25}$ −26.9° (*c* 0.90, MeOH); IR (KBr) ν_{max} 3380 (br), 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39 (d, *J* = 7.3 Hz, 1H), 7.35–7.30 (m, 9H), 7.27 (t, *J* = 7.3 Hz, 2H), 7.21–7.17 (m, 3H), 7.11–7.07 (m, 6H), 6.68 (d, *J* = 9.4 Hz, 1H), 6.57 (d, *J* = 1.3 Hz, 1H), 4.38 (br td, *J* = 5.3, 9.4 Hz, 1H), 3.60 (dt, *J* = 4.3, 8.9 Hz, 1H), 3.53 (dt, *J* = 3.7, 10.2 Hz, 1H), 3.30 (td, *J* = 1.9, 9.1 Hz, 1H), 3.15 (d, *J* = 8.3 Hz, 1H), 2.96–2.89 (m, 2H), 2.85 (dd, *J* = 4.3, 13.8 Hz, 1H), 2.74 (dd, *J* = 8.8, 13.8 Hz, 1H), 2.62 (dd, *J* = 3.2, 14.6 Hz, 1H), 2.01–1.94 (m, 1H), 1.87–1.13 (m, 15H), 0.97–0.80 (m, 2H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H); MS (FAB) *m/z* 772 (MH^+); Anal. calcd for $C_{49}H_{61}N_3O_5$: C, 76.23; H, 7.96; N, 5.44. Found: C, 76.32; H, 8.04; N, 5.45.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-4(*S*),5(*S*)-dihydroxy-2(*R*)-[(1*H*-imidazol-4-yl)methyl]-6-phenylhexanamide (1f).** A solution of **31** (257 mg, 0.33 mmol) in MeOH (6.6 mL) was stirred under an atmosphere of H_2 in presence of moist 20% $Pd(OH)_2/C$ (103 mg) at room temperature for 54 h. The reaction mixture was filtered through a pad of Celite® and the resulting solution was concentrated under reduced pressure. The residue was purified by flash chromatography (EtOAc/MeOH, 4/1) to give **1f** (154 mg, 88%) as a white solid: $[\alpha]_D^{25}$ −39.6° (*c* 0.83, MeOH); IR (KBr) ν_{max} 3350 (br), 1630 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.54 (d, *J* = 8.7 Hz, 1H), 7.45 (s, 1H), 7.24–7.15 (m, 5H), 6.76 (br s, 1H), 4.70 (d, *J* = 6.9 Hz, 1H), 4.38 (d, *J* = 6.0 Hz, 1H), 4.30 (d, *J* = 5.4 Hz, 1H), 4.11 (dt, *J* = 4.8, 9.0 Hz, 1H), 3.44–3.39 (m, 1H), 3.02–2.74 (m, 4H), 2.70 (dd, *J* = 3.6, 13.4 Hz, 1H), 2.55 (dd, *J* = 8.8, 13.4 Hz, 1H), 1.77–1.06 (m, 17H), 0.94–0.70 (m, 2H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H); MS (FAB) *m/z* 530 (MH^+); Anal. calcd for $C_{30}H_{47}N_3O_5$: C, 68.02; H, 8.94; N, 7.93. Found: C, 67.11; H, 8.98; N, 7.82.

3-[2(*R*)-(Cyclopropylmethyl)-1,3-dioxobutyl]-4(*S*)-(phenylmethyl)-2-oxazolidinone (32). To a solution of *i*-Pr_2NH (1.24 mL, 9.43 mmol) in THF (15 mL) at 0 °C was added 1.1 M *n*-BuLi in hexanes (8.57 mL, 9.43 mmol). The solution so obtained was stirred for 30 min at 0 °C and then cooled to −78 °C before being transferred via cannula to a cooled (−78 °C) solution of oxazolidinone **3** (2.35 g, 8.58 mmol) in THF (10 mL). The resulting enolate was stirred for 45 min at that temperature and was then cannulated into acetyl chloride (0.73 mL, 10.3 mmol). This solution was then allowed to warm to room temperature and stirred 15 min. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. EtOAc was added, the organic phase was separated, washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (Hex/EtOAc, 4/1) afforded the desired product **32** (1.386 g, 51%) as a 49/1 mixture of diastereomers: $[\alpha]_D^{25}$ −19.2° (*c* 1.54, $CHCl_3$); IR (neat) ν_{max} 3000, 1775, 1720, 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39–7.20 (m, 5H), 4.68 (m, 2H), 4.19 (m, 2H), 3.42 (dd, *J* = 3.2, 13.5 Hz, 1H), 2.77 (dd, *J* = 9.9, 13.3 Hz, 1H), 2.35 (s, 3H), 2.08 (m, 1H), 1.55 (m, 1H), 0.88 (m, 1H), 0.52 (m, 2H), 0.24–0.08 (m, 2H); MS (CI) *m/z* 333 (MNH_4^+), 316 (MH^+); Anal. calcd for $C_{18}H_{21}NO_4$: C, 68.55; H, 6.71, N, 4.44. Found: C, 68.69; H, 6.72; N, 4.47.

3-[2(*R*)-(Cyclopropylmethyl)-1,3-dioxo-5(*S* and *R*)-hydroxy-6-phenylhexyl]-4(*S*)-(phenylmethyl)-2-oxazolidinone (33 and 34). To a cooled (−15 °C) solution of the β-ketoimide **32** (1.00 g, 3.17 mmol) in CH_2Cl_2 (25 mL) were added a 1.0 M solution of $TiCl_4$ (4.2 mL, 4.19 mmol) followed by *i*-Pr_2NEt (0.73 mL, 4.19 mmol). The solution was stirred 1 h at −15 °C then cooled to −78 °C. Phenylacetaldehyde (0.50 mL, 4.19 mmol) in CH_2Cl_2 (2 mL) was then added and the mixture was warmed to −10 °C and stirred for 1 h. The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl. The aqueous phase was extracted with CH_2Cl_2 and the combined organic extracts were washed with brine and then dried ($MgSO_4$). Removal of the solvent gave the β-hydroxyketones **33** and **34** (1.13 g, 82%) as a 2/1 mixture of isomers after purification by flash chromatography (Hex/EtOAc, 4/1). Analytical samples of **33** and **34** were obtained from a second chromatographic separation. **33** (3*S*, major): $[\alpha]_D^{25}$ +30.8° (*c* 1.28, MeOH); IR (film) ν_{max} 3540 (br), 3040, 1775, 1725, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.39–7.18 (m, 10H), 4.69 (m, 1H), 4.59 (dd, *J* = 4.4, 9.0 Hz, 1H), 4.41 (m, 1H), 4.20 (m, 2H), 3.39 (dd, *J* = 3.5, 13.5 Hz, 1H), 2.92 (dd, *J* = 2.9, 17.5 Hz, 1H), 2.82–2.71 (m, 4H), 2.08 (m, 1H), 1.51 (m, 1H), 0.85 (m, 1H), 0.55–0.41 (m, 2H), 0.22–0.05 (m, 2H); MS (CI) *m/z* 436 (MH^+); HRMS (EI) calcd for $C_{26}H_{27}NO_4$ ($MH^+ - H_2O$) 417.1940. Found: 417.1935. **34** (3*R*, minor): IR (film) ν_{max} 3530, 1775, 1715, 1690, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.35–7.17 (m, 10H), 4.70–4.65 (m, 1H), 4.63 (dd, *J* = 8.6, 4.8 Hz, 1H), 4.35–4.31 (m, 1H), 4.20–4.16 (m, 2H), 3.37 (dd, *J* = 13.7, 3.2 Hz, 1H), 2.99 (d, *J* = 2.9 Hz, 1H), 2.90 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.88 (dd, *J* = 17.2, 8.6 Hz, 1H), 2.78 (dd, *J* = 4.1, 3.2 Hz, 1H), 2.75–2.72 (m, 2H), 2.03–1.96 (m, 1H), 1.50 (ddd, *J* = 14.0, 7.6, 4.8 Hz, 1H), 0.76–0.72 (m, 1H), 0.44–0.37 (m, 2H), 0.13–0.07 (m, 1H), 0.05–0.01 (m, 1H); MS (FAB) *m/z* 436 (MH^+); Anal. calcd for $C_{26}H_{29}NO_5$: C, 71.70; H, 6.71; N, 3.22. Found: C, 71.90; H, 6.79; N, 3.30.

3-[2(*R*)-(Cyclopropylmethyl)-3(*R*),5(*S*)-dihydroxy-3,5-*O*-isopropylidene-6-phenyl-1-oxohexyl]-4(*S*)-(phenylmethyl)-2-oxazolidinone (35). A solution of **33** (110 mg, 0.25 mmol) and $NaBH(OAc)_3$ (80.5 mg, 0.38 mmol) in AcOH (3 mL) was stirred at room temperature for 1 h. The reaction was quenched by addition of saturated $NaHCO_3$ and extracted with EtOAc. The combined organic extracts were washed with brine, dried ($MgSO_4$), filtered and concentrated. The crude diol obtained was dissolved in DMF (1 mL) and 2,2-dimethoxypropane (1 mL), a catalytic amount of *p*-TsOH was added and the mixture was stirred at room temperature for 1 h. 0.5 N HCl was added and the solution was extracted with ether. The organic phase was washed with brine, dried ($MgSO_4$) and concentrated. Flash chromatography (Hex/EtOAc, 9/1) gave the desired acetonide **35** (81 mg, 69%): $[\alpha]_D^{25}$ +125.3° (*c* 0.81, MeOH); IR (CCl_4) ν_{max} 1785, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.18 (m, 10H), 4.78 (m, 1H), 4.28 (dt, *J* = 3.7, 10.1 Hz, 1H), 4.21–4.07 (m, 4H), 3.15 (dd, *J* = 3.2, 13.6 Hz, 1H), 2.94 (dd, *J* = 7.2, 13.9 Hz, 1H), 2.85 (dd, *J* = 8.3, 13.6 Hz, 1H), 2.70 (dd, *J* = 6.3, 13.9 Hz, 1H), 1.80–1.60 (m, 3H), 1.21 (s, 3H), 1.28 (s, 3H), 0.71 (m, 1H), 0.41–0.29 (m, 2H), 0.00 (m, 2H); MS (FAB) *m/z* 478 (MH^+); Anal. calcd for $C_{29}H_{35}NO_5$: C, 72.93; H, 7.39; N, 2.93. Found: C, 73.23; H, 7.49; N, 2.84.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-3(*R*),5(*S*)-dihydroxy-3,5-*O*-isopropylidene-6-phenylhexanamide (37).** Oxazolidinone **35** (686 mg, 1.43 mmol) was dissolved in a cooled (0 °C) mixture of THF/H_2O (3/1, 28 mL) and was treated with 30% H_2O_2 (1.30 mL, 11.5 mmol) followed by LiOH (70 mg, 2.92 mmol). The reaction was stirred at 0 °C for 7 h then at room temperature overnight. Na_2SO_3 was added to destroy the excess peroxide. The THF was removed and the solution was acidified with 0.1 N HCl and quickly extracted with EtOAc. The combined EtOAc extracts were washed with brine, dried ($MgSO_4$) and concentrated to give **36** in quantitative yield. To a solution of a portion of the crude acid **36** (389 mg, 1.22 mmol) and *i*-Pr_2NEt (0.64 mL, 3.7 mmol) in CH_3CN (30 mL) at 25 °C was added a solution of **7** (HCl salt, 374 mg, 1.34 mmol) in CH_3CN (10 mL + 0.1 mL *i*-Pr_2NEt to aid dissolution) and BOP·PF_6 (600 mg, 1.34 mmol). After 1 h of stirring at room temperature, the solution was filtered and the resulting solid was purified by flash chromatography (Hex/EtOAc, 3/1) to give the desired pure product **37** (180 mg, 27% from **35**) as a white solid: $[\alpha]_D^{25}$ +2.8° (*c* 0.50, MeOH); IR ($CHCl_3$) ν_{max} 3640, 3340, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.18 (m, 5H), 6.52 (d, *J* = 9.2 Hz, 1H), 4.59 (d, *J* = 3.5 Hz, 1H), 4.29 (m, 1H), 4.05 (m, 2H), 3.21 (m, 2H), 2.84 (dd, *J* = 7.6, 14.3 Hz, 1H), 2.70 (dd, *J* = 5.1, 14.0 Hz, 1H), 2.36 (dd, *J* = 2.2, 5.4 Hz, 1H), 1.95–1.09 (m, 24H), 0.93 (d, *J* = 6.7 Hz, 3H), 1.00–0.80 (m, 3H), 0.82 (d, *J* = 6.7 Hz, 3H), 0.52 (m, 1H), 0.51–0.41 (m, 2H), 0.12–0.00 (m, 2H); HRMS (FAB) calcd for $C_{33}H_{54}NO_5$ (MH^+) 544.4002. Found: 544.3985.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-3(*R*),5(*S*)-dihydroxy-6-phenylhexanamide (2a).** A solution of acetonide **37** (18 mg, 0.033 mmol) in MeOH (10 mL + 2 drops of water) was treated with a trace of Amberlite® acidic ion exchange resin (IR-120, prewashed with MeOH). The solution was stirred for 2 h at room temperature and then heated for 3 h at 50 °C. The resin was removed by filtration and the filtrate stripped of solvent under reduced pressure. Flash chromatography (CH_2Cl_2/MeOH, 20/1) afforded the desired product **2a** (11 mg, 66%) as a white solid: $[\alpha]_D^{25}$ −15.9° (*c* 0.55, MeOH); IR (KBr) ν_{max} 3500, 3400, 3290, 1680, 1620 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (d, *J* = 9.0 Hz, 1H), 7.27–7.14 (m, 5H), 4.73 (d, *J* = 6.3 Hz, 1H), 4.65 (d, *J* = 3.9 Hz, 1H), 4.42 (d, *J* = 6.0 Hz, 1H), 4.32 (d, *J* = 7.2 Hz, 1H), 4.15 (m, 1H), 3.87–3.80 (m, 2H), 3.30 (s, 2H), 3.14 (m, 1H), 2.93 (m, 1H), 2.63 (m, 2H), 2.50 (m, 1H), 2.38 (m, 1H), 1.82–1.05 (m, 20H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.74 (d, *J* = 6.6 Hz, 3H), 0.96–0.70 (m, 3H), 0.70–0.60 (m, 1H), 0.40–0.30 (m, 2H), 0.10–0.00 (m, 2H); MS (FAB) *m/z* 504 (MH^+); Anal. calcd for $C_{30}H_{49}NO_5 \cdot H_2O$: C, 69.06; H, 9.85; N, 2.68. Found: C, 69.28; H, 9.67; N, 2.78.

3-[2(*R*)-(Cyclopropylmethyl)-3(*S*),5(*S*)-dihydroxy-3,5-*O*-isopropylidene-6-phenyl-1-oxohexyl]-4(*S*)-(phenylmethyl)-2-oxazolidinone (38). To a cooled (−78 °C) solution of β-hydroxyketone **33** (100 mg, 0.23 mmol) in THF (3 mL) was added a 1.0 M solution of DIBAL in hexane (0.25 mL, 0.25 mmol). A small amount of DIBAL (0.1 mL, 0.1 mmol) was then added every 10 min until the reaction was determined to be complete by TLC. The reaction was then stopped by the addition of MeOH and allowed to warm to room temperature. The solution was diluted with EtOAc, washed with a saturated solution of NH_4Cl, and filtered through a pad of Celite®. The filtrate was washed with brine, dried ($MgSO_4$) and concentrated to give a residue which was dissolved in a 1/1 mixture of DMF/2,2-dimethoxypropane (4 mL) and treated with a catalytic amount of *p*-TsOH. After stirring for 2 h at room temperature, the reaction was stopped by the addition of NH_4Cl. The solution was then extracted with ether and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. Purification by flash chromatography (Hex/EtOAc, 10/1) afforded the desired *syn* acetonide **38** (25 mg, 23% from **33**): $[\alpha]_D^{25}$ +54.3° (*c* 0.56, $CHCl_3$); IR ($CHCl_3$) ν_{max} 1785, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.38–7.09 (m, 10 H), 4.66 (m, 1H), 4.24–4.01 (m, 5H), 3.17 (dd, *J* = 2.5, 13.4 Hz, 1H), 2.94 (dd, *J* = 5.7, 13.3 Hz, 1H), 2.60 (dd, *J* = 7.3, 13.5 Hz, 1H), 2.54 (dd, *J* = 10.2,

13.0 Hz, 1H), 1.80 (m, 1H), 1.55–1.41 (m, 3H), 1.43 (s, 3H), 1.41 (s, 3H), 0.72–0.61 (m, 1H), 0.41–0.30 (m, 2H), 0.10–0.00 (m, 2H); MS (FAB) *m/z* 500 (MNa^+); Anal. calcd for $C_{29}H_{35}NO_5$: C, 72.93; H, 7.39; N, 2.93. Found: C, 73.08; H, 7.58; N, 3.01.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-3(*S*),5(*S*)-dihydroxy-3,5-*O*-isopropylidene-6-phenylhexanamide (40).** Compound **38** (430 mg, 0.90 mmol) was converted to acid **39** using a procedure similar to that described above for **36**. Acid **39** (258 mg, 0.65 mmol) was then immediately coupled to **7** as described for compound **37** to give **40**. Compound **40** (237 mg, 68% from **38**) was isolated as a white solid after flash chromatography (Hex/EtOAc, 4/1): $[\alpha]_D^{25}$ −18.7° (*c* 0.70, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3400, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31–7.14 (m, 5H), 6.21 (d, *J* = 9.2 Hz, 1H), 4.40 (m, 2H), 3.99 (m, 2H), 3.23 (m, 2H), 2.89 (dd, *J* = 6.7, 13.6 Hz, 1H), 2.63 (dd, *J* = 6.4, 13.8 Hz, 1H), 2.43 (m, 1H), 1.98–0.80 (m, 26H), 0.94 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.78–0.68 (m, 1H), 0.50–0.38 (m, 2H), 0.15–0.02 (m, 2H); MS (FAB) *m/z* 544 (MH^+); Anal. calcd for $C_{33}H_{53}NO_5$: C, 73.02; H, 9.66; N, 2.58. Found: C, 72.73; H, 10.01; N, 2.47.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-3(*S*),5(*S*)-dihydroxy-6-phenylhexanamide (2b).** Acetonide **40** (120 mg, 0.22 mmol) was dissolved in MeOH (8 mL) to which was added a small amount of Amberlite® acidic resin and H_2O (6 drops). The solution was stirred at 60 °C overnight. After filtration to remove solids and evaporation of the solvent, the desired diol **2b** (112 mg, 100%) was obtained as a white solid: $[\alpha]_D^{25}$ −15.4° (*c* 0.68, MeOH); IR (KBr) ν_{max} 3400, (br), 1620, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.18 (m, 5H), 6.14 (d, *J* = 8.6 Hz, 1H), 4.38 (m, 2H), 4.04 (m, 2H), 3.24 (m, 2H), 2.82 (dd *J* = 4.5, 13.5 Hz, 1H), 2.69 (dd, *J* = 8.6, 13.7 Hz, 1H), 2.46 (m, 2H), 0.84–2.0 (m, 21H), 0.94 (d, *J* = 6.6 Hz, 3H), 0.84 (d, 3H, *J* = 6.7 Hz), 0.73 (m, 1H), 0.52–0.41 (m, 2H), 0.21–0.00 (m, 2H); HRMS (FAB) calcd for $C_{30}H_{49}NO_5$ (MH^+): 503.3611. Found: 503.3595.

3-[2(*R*)-(Cyclopropylmethyl)-3(*S*),5(*R*)-dihydroxy-3,5-*O*-isopropylidene-6-phenyl-1-oxohexyl]-4(*S*)-(phenylmethyl)-2-oxazolidinone (41). The β-hydroxyketone **34** (208 mg, 0.48 mmol) was reduced to the desired diol **41** using similar reaction conditions to those described for **35**. The crude material was immediately converted to the acetonide using the procedure described for compound **35**. The desired compound **41** (93 mg, 41%) was obtained in pure form after flash chromatography (Hex/EtOAc, 9/1): $[\alpha]_D^{25}$ +55.5° (*c* 0.355, MeOH); IR (KBr) ν_{max} 1760, 1690, 1605 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.39–7.15 (m, 10H), 4.67 (m, 1H), 4.25 (m, 1H), 4.13 (m, 4H), 3.22 (dd, *J* = 3.3, 13.3 Hz, 1H), 2.92 (dd, *J* = 7.6, 13.7 Hz, 1H), 2.65 (dd, *J* = 6.6, 13.7 Hz, 1H), 2.50 (dd, *J* = 10.1, 13.2 Hz, 1H), 1.81 (m, 1H), 1.69 (m, 2H), 1.50 (m, 1H), 1.38 (s, 3H), 1.31 (s, 3H), 0.70 (m, 1H), 0.42–0.32 (m, 2H), 0.11–0.00 (m, 2H); MS (FAB) *m/z* 478 (MH^+); Anal. calcd for $C_{29}H_{35}NO_5$: C, 72.93; H, 7.39; N, 2.93. Found: C, 72.89; H, 7.52; N, 2.90.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-3(*R*),5(*S*)-dihydroxy-3,5-*O*-isopropylidene-6-phenylhexanamide (43).** Compound **41** (244 mg, 0.51 mmol) was converted to acid **42** using a procedure similar to that described above for **36**. Acid **42** (20.0 mg, 0.063 mmol) was then immediately coupled to **7** as described for compound **37** to give **43**. Compound **43** (24 mg, 70% from **41**) was isolated as a white solid after flash chromatography (Hex/EtOAc, 4/1): $[\alpha]_D^{25}$ −24.5° (*c* 0.103, MeOH); IR ($CHCl_3$) 3380, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.15 (m, 5H), 6.17 (d, *J* = 9.2 Hz, 1H), 4.37 (m, 2H), 4.00 (m, 2H), 3.26–3.18 (m, 2H), 2.85 (dd, *J* = 7.6, 14.0 Hz, 1H), 2.68 (dd, *J* = 5.4, 14.0 Hz, 1H), 2.61 (d, *J* = 9.2 Hz, 1H), 2.44 (m, 1H), 2.20 (s, 1H, br), 1.36 (s, 3H), 1.25 (s, 3H), 1.98–0.78 (m, 20H), 0.92 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H), 0.78–0.68 (m, 1H), 0.50–0.39 (m, 2H), 0.17–0.01 (m, 2H); HRMS (FAB) calcd for $C_{33}H_{54}NO_5$ (MH^+): 544.4002. Found: 544.3979.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-3(*R*),5(*S*)-dihydroxy-6-phenylhexanamide (2c).** Acetonide **43** (30 mg, 0.055 mmol) was dissolved in MeOH (4 mL) containing a small amount of Amberlite® acidic resin and water (10 drops) and was stirred at 60 °C for 3 h. The desired diol **2c** (27 mg, 95%) was obtained in pure form as a white solid after filtration and removal of solvent under reduced pressure: $[\alpha]_D^{25}$ −28.8° (*c* 0.565, MeOH); IR (KBr) ν_{max} 3350 (broad), 1670, 1640, 1610 cm^{-1}; ^1H NMR (DMSO-d_6) δ 7.67 (d, *J* = 9.0 Hz, 1H), 7.27–7.15 (m, 5H), 4.77 (m, 1H), 4.72 (d, *J* = 6.3 Hz, 1H), 4.46 (d, *J* = 5.4 Hz, 1H), 4.38 (d, *J* = 5.7 Hz, 1H), 4.16 (m, 1H), 3.89 (m, 1H), 3.70 (m, 1H), 2.92 (m, 1H), 2.71–2.51 (m, 2H), 2.30 (m, 1H), 1.82–0.07 (m, 22H), 0.85 (d, *J* = 6.9 Hz, 3H), 0.72 (d, *J* = 6.3 Hz, 3H), 0.64 (m, 1H), 0.34 (m, 2H), 0.10–0.10 (m, 2H); HRMS (FAB) calcd for $C_{30}H_{50}NO_5$ (MH^+): 504.3689. Found: 504.3699.

3-[2(*R*)-(Cyclopropylmethyl)-3(*R*),5(*R*)-dihydroxy-3,5-*O*-isopropylidene-6-phenyl-1-oxohexyl]-4(*S*)-(phenylmethyl)-2-oxazolidinone (44). Using the reaction conditions described above for the preparation of **38**, **34** (131 mg, 0.30 mmol) was converted to **44** (50 mg, 35%), the major *syn* diastereomer which were each obtained in pure form after flash chromatography (Hex/EtOAc, 10/1): IR ($CHCl_3$) ν_{max} 1780, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.40 (m, 10H), 4.78 (m, 1H), 4.35–4.00 (m, 5H), 3.18 (dd, *J* = 3.3, 13.5 Hz, 1H), 2.95 (dd, *J* = 5.8, 13.5 Hz, 1H),

2.78 (dd, J=8.9, 13.7 Hz, 1H), 2.65 (dd, J=7.3, 13.7 Hz, 1H), 1.68–1.20 (m, 10H), 0.69 (m, 1H), 0.35 (m, 2H), 0.00 (m, 2H); HRMS (FAB) calcd for $C_{29}H_{36}NO_5$: 478.2593. Found: 478.2576.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-3(*R*),5(*R*)-dihydroxy-3,5-*O*-isopropylidene-6-phenylhexanamide (46).** The removal of the chiral auxiliary from **43** (38.0 mg, 0.080 mmol) was done using the same reaction conditions described for the preparation of **36**. The crude acid **45** (17.1 mg, 68%) so obtained was used in the next step without further purification. Acid **45** (17.1 mg, 0.054 mmol) was transformed to compound **46** using the procedure described for the preparation of **37**. Purification by flash chromatography yielded the acetonide **46** (9.3 mg, 32%): $[\alpha]_D^{25}$ −47.0° (c 0.455, $CHCl_3$); IR ($CHCl_3$) ν_{max} 3700–3040 (br), 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.30–7.17 (m, 5H), 6.63 (d, J=8.9 Hz, 1H), 4.55 (d, J=4.1 Hz, 1H), 4.37–4.26 (m, 1H), 4.10–4.00 (m, 2H), 3.36–3.30 (m, 1H), 3.23–3.19 (m, 1H), 2.91 (dd, J=5.7, 13.4 Hz, 1H), 2.59 (dd, J=7.3, 13.4 Hz, 1H), 2.33 (ddd, J=4.1, 7.5, 7.5 Hz, 1H), 1.96 (ddd, J=6.7, 13.4, 20.3 Hz, 1H), 1.76–1.12 (m, 18H), 1.44 (s, 3H), 1.43 (s, 3H), 0.98–0.81 (m, 2H), 0.97 (d, J=6.7 Hz, 3H), 0.94 (d, J=6.4 Hz, 3H), 0.71–0.61 (m, 1H), 0.51–0.38 (m, 2H), 0.09–0.03 (m, 2H); HRMS (FAB) calcd for $C_{33}H_{54}NO_5$ (MH^+): 544.4002. Found: 544.3967.

***N*-[1(*S*)-(Cyclohexylmethyl)-2(*R*),3(*S*)-dihydroxy-5-methylhexyl]-2(*R*)-(cyclopropylmethyl)-3(*R*),5(*R*)-dihydroxy-6-phenylhexanamide (2d).** Diol **2d** was prepared from acetonide **46** (9.0 mg, 0.017 mmol) using the reaction conditions described for the preparation of **2a**. Diol **2d** (7.0 mg, 84%) was obtained after purification by flash chromatography (Hex/EtOAc, 1/1) as a white solid: $[\alpha]_D^{25}$ −1.15° (c 0.26, MeOH); IR ($CHCl_3$) ν_{max} 3700–3040 (br), 1640, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34–7.18 (m, 5H), 6.30 (d, J=8.9 Hz, 1H), 4.43 (d, J=4.1 Hz, 1H), 4.35 (d, J=4.1 Hz, 1H), 4.36–4.32 (m, 1H), 4.14–4.08 (m, 1H), 4.04 (ddd, J=3.5, 7.0, 13.0 Hz, 1H), 3.33 (ddd, J=4.5, 8.3, 12.4 Hz, 1H), 3.25–3.22 (m, 1H), 2.94 (d, J=1.9 Hz, 1H), 2.77–2.75 (m, 2H), 2.30 (ddd, J=3.2, 6.7, 8.3 Hz, 1H), 1.86–1.82 (m, 1H), 1.80–1.60 (m, 10H), 1.46–1.14 (m, 8H), 1.02–0.83 (m, 2H), 0.96 (d, J=6.7 Hz, 3H), 0.90 (d, J=6.7 Hz, 3H), 0.75–0.69 (m, 1H), 0.51–0.44 (m, 2H), 0.15–0.05 (m, 2H); MS (CI) m/z 504 (MH^+); Anal. calcd for $C_{30}H_{49}NO_5 \cdot H_2O$: C, 69.20; H, 9.62; N, 2.79. Found: C, 69.40, H, 9.68, N, 2.93.

Human plasma renin assay pH 6.0

Human plasma (Biological Specialty Corporation, Lansdale, PA) was used as the source of both the enzyme, renin, and the substrate, angiotensinogen. Angiotensin I was quantified using a commercially available radioimmunoassay kit from NEN–Dupont (Cat. No. NEA-105). The assay was performed in 0.27 M MES (4-morpholineethanesulfonic acid), 1% HSA (human serum albumin), pH 5.85 containing 13 μL/mL dimercaprol solution, 13 μL/mL 8-hydroxyquinoline sulfate solution and 1% DMSO. The dimercaprol and 8-hydroxyquinoline sulfate solutions were added just before use and were provided with the radioimmunoassay kit. The assay was carried out in a final volume of 100 μL in 1.0 mL polypropylene mini tubes. To 50 μL of serial dilution of the test compounds in assay buffer or 50 μL of assay buffer only (37 °C and 4 °C controls) was added 50 μL of human plasma to initiate the reaction. After addition of the human plasma, the assay mixture was incubated at 37 °C for 60 to 90 min in order to achieve an angiotensin I generation of 2–3 ng/mL. In 37 °C controls, no inhibitor was added in order to determine the maximum angiotensin I level generated with the human plasma pool used. In 4 °C controls, no angiotensin I was generated, tubes being kept on ice-cold water during the incubation. These served to determine the background level of angiotensin I. When the incubation was completed, tubes were quickly returned to ice-cold water. The generation of angiotensin I was then quantified using the radioimmunoassay kit from NEN–Dupont according to the manufacturer instructions except that 2% PEG 8000 was added to the angiotensin I second antibody solution. IC_{50} values were generated from the inhibition curves using the SAS statistical software system (SAS Institute Inc., Cary, NC) and a non linear curve fit using the Hill model. Diastereomers **1a–d, 2a–d** and P_2 analogues **1e** and **1f** were tested in parallel in the assay in order to make sure that the observed differences of IC_{50} values were real ($n \geq 4$). The variability was about 10 to 15% for IC_{50} values smaller than 100 nM and from 15 to 50% for the IC_{50} values larger than 100 nM.

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