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Renin Inhibitors: C-Terminal Oxetanes as Potent Transition-State Mimics

Saul H. Rosenberg,* Kenneth P. Spina, Herman Stein, Jerome Cohen, William R. Baker and Hollis D. Kleinert

Aging and Degenerative Disease Research, Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL 60064, U.S.A.

Abstract—A novel transition-state mimic containing a C-terminal oxetane has been developed. Renin inhibitors incorporating this fragment exhibit enhanced potency against human plasma renin at physiological pH. The binding affinity of this new species has allowed size reductions at other sites.

Introduction

The allure of peptide-derived drugs rests in the assumption that it should be a straightforward enterprise to design agents that can either mimic or antagonize the actions of any of the numerous endogenous peptides possessing biological activity. In practice, however, *in vitro* potency has been readily attained while useful *in vivo* activity often remains elusive. There exist multiple barriers limiting both the oral absorption and *in vivo* half-lives of peptides. High molecular weight hinders intestinal absorption and enhances hepatic elimination, the presence of peptide bonds renders the compounds susceptible to degradative enzymes, and poor aqueous solubility can further restrict bioavailability and duration of action.[1]

The 25 year quest to develop novel antihypertensive agents that act through blockade of the renin–angiotensin system (RAS) illustrates both the problems associated with the development of peptide-based drugs and a variety of possible solutions. Angiotensin II (AII), an octapeptide, is the effector hormone of this cascade. While potent peptidic antagonists of the AII receptor have been known for over two decades, these compounds were structurally similar to AII and extensive structure–activity investigations failed to reduce their molecular size and peptide character.[2] Orally active AII antagonists were not achieved until the recent discovery, through random screening, of nonpeptide antagonists that did not possess obvious structural relationships to AII.[3] The development of inhibitors of angiotensin converting enzyme (ACE) followed a quite different path. ACE can accept substrates as small as tripeptides. Consequently, the report of the first ACE inhibitor in 1971[4] led to the development of captopril, an orally active, low molecular weight (M_r = 217), dipeptide analog by 1977.[5] The evolution of renin inhibitors has proceeded at a slower pace. Renin has a larger substrate requirement than ACE and screening has yet to yield a novel, nonpeptidic ligand. Consequently, the development of orally active renin inhibitors required directly confronting the obstacles associated with peptide-based drugs.

The design of tightly binding transition-state mimics such as the hydroxyethylene isostere, Sta, and ACHPA led quickly to potent renin inhibitors with molecular weights of 600–800.[6] Incorporation of features that protected certain amide bonds from proteolytic cleavage[7,8] and attachment of polar residues to either terminus[6] addressed the issues of both solubility and stability (Figure 1), yet renin inhibitors incorporating these features, such as enalkiren (A-64662, **1**),[9] exhibited only marginal oral bioavailability. It was only after a systematic evaluation of structure–absorption relationships that the parameters necessary for oral absorption were determined.[10] This study led to the discovery of zankiren (A-72517, **2**), the first peptide-based renin inhibitor to be both orally efficacious and significantly bioavailable in several species,[11,12] including man.[13,14] Improved bioavailability has also been demonstrated for a series of renin inhibitors with reduced peptide character, exemplified by A-74273 (**3**).[15]

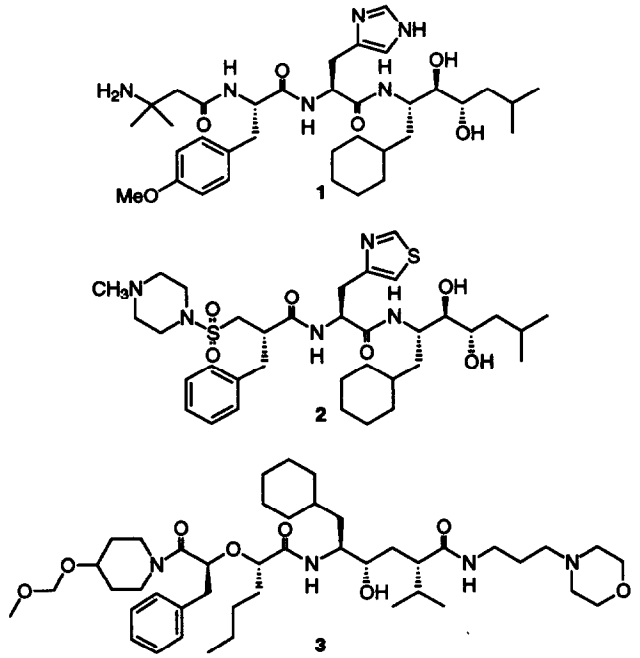
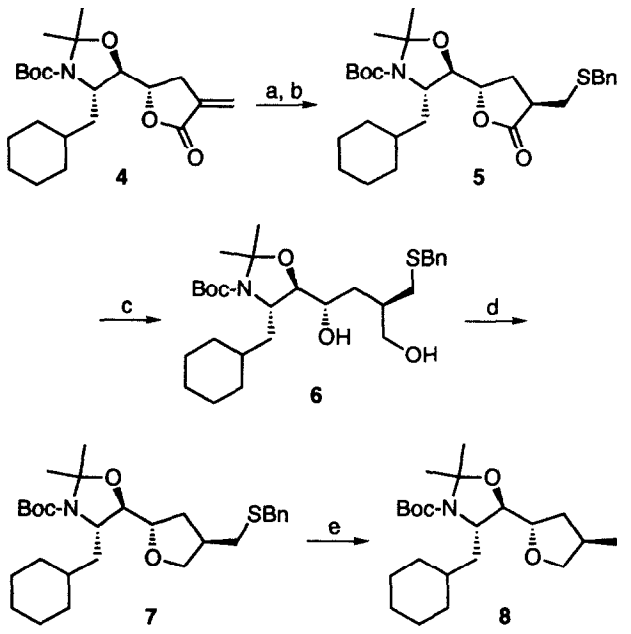


Figure 1. Renin inhibitors enalkiren, zankiren, and A-74273.

It is generally believed that hepatic extraction becomes problematic for compounds with molecular weights greater than 500.[1,16] Despite their unprecedented bioavailability, both zankiren and A-74273 (M_r = 707 and 787, respectively) fall within this molecular weight range. A smaller renin inhibitor might exhibit superior pharmacokinetic properties, however zankiren and A-74273 were highly optimized and smaller analogs were invariably less potent. We hypothesized that a transition-state mimic that bound more tightly to the active site of renin than the dihydroxyethylene isostere of zankiren would allow size reduction at other sites in the molecule. Previously, we have described a novel, highly potent transition-state mimic incorporating a (4*S*)-methyl-substituted tetrahydrofuran.[17] This fragment became the starting point for our structure–activity investigation.

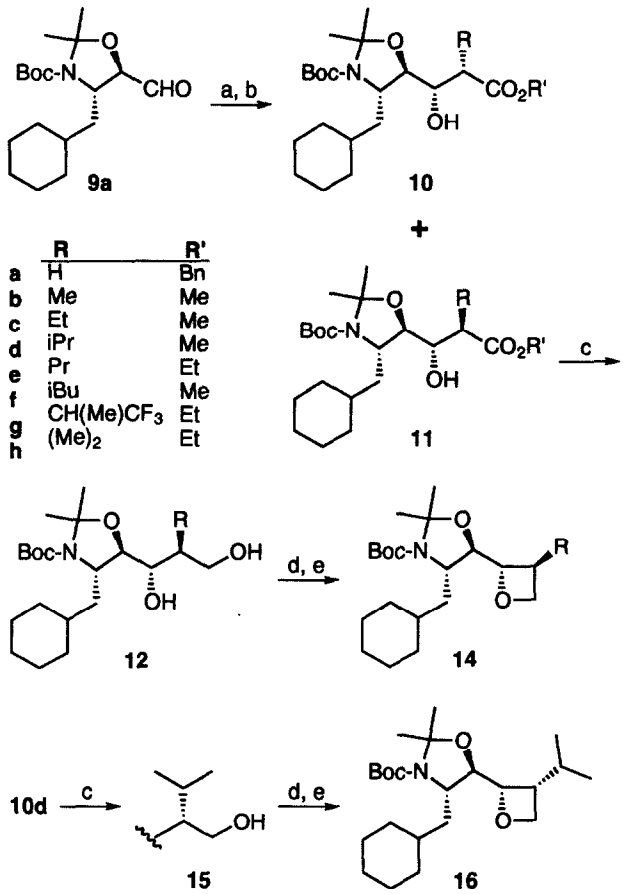
Chemistry

The synthesis of (4*R*)-methyl tetrahydrofuran **8** is outlined in Scheme I. Direct reduction of lactone **4** led exclusively to the (4*S*)-methyl configuration,[17] necessitating an alternate route. Michael addition of benzyl mercaptan afforded a separable 1:1.5 mixture of the (4*R*) and (4*S*) isomers of **5**. Reduction to **6** and ring closure under Mitsunobu conditions was followed by Raney nickel mediated desulfurization to provide **8**. Stereochemistry was confirmed through analogous conversion of the (4*S*) isomer of **5** to the known (4*S*)-methyl-substituted tetrahydrofuran[17] (results not shown).



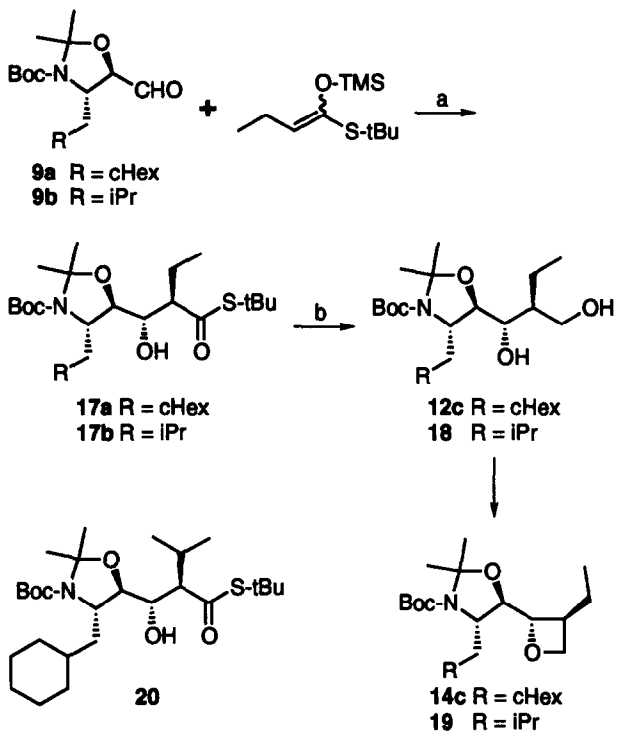
Scheme I. Reagents: (a) BnSH, TEA/DMF, 50 °C; (b) chromatographic diastereomer separation;(c) $NaBH_4$, $CaCl_2$/EtOH, THF; (d) $P(Ph)_3$, DEAD/THF; (e) RaNi/EtOH, reflux.

The original synthesis of the related oxetane derivatives was based upon a non-stereoselective Reformatsky reaction between a variety of 2-bromo esters and aldehyde **9a**.[17] This reaction provided an often difficult to separate mixture of β-hydroxy esters **10** and **11** (Scheme II). Formation of only the (1'*S*)-hydroxyl isomer is consistent with results from other zinc-mediated organometallic additions to **9a**.[17] Radical deoxygenation[18] of **11d** provided the des-hydroxy derivative (results not shown). This product was identical to material prepared via an alternative route[18] thereby confirming the (2'*R*)-stereochemistry at the isopropyl side-chain. The esters were reduced to the corresponding 1,3-diols **12a–h** and **15**, and cyclized to oxetanes **14a–h** and **16**. This synthesis, although inefficient, allowed the rapid preparation of a series of oxetanes incorporating various substituents at the 3-position.



Scheme II. Reagents: (a) $Br(R)CHCO_2R'$, Zn/THF, ultrasound; (b) chromatographic diastereomer separation; (c) $NaBH_4$, $CaCl_2$/EtOH, THF; (d) TsCl/pyridine; (e) $NaN(TMS)_2$/THF

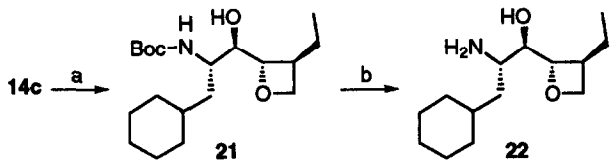
Once ethyl had been established as an optimum side chain, the requisite β-hydroxy ester **17a** was prepared through a stereoselective, Lewis acid-catalyzed aldol condensation[19] (Scheme III). Reduction and cyclization afforded the desired oxetane **14c** in 36 % yield from the starting aldehyde. Isopropyl derivative **20** has also been synthesized by this procedure.[19] As above, radical deoxygenation confirmed the assigned stereochemistry at the isopropyl side chain.[19] Conversion of **20** to the *n*-butyl amide[19] provided material different from the known derivative bearing a (1'*R*)-hydroxyl[18] thereby establishing stereochemistry at this site also. Aldehyde **9b**[20] was converted to oxetane **19** by this method.



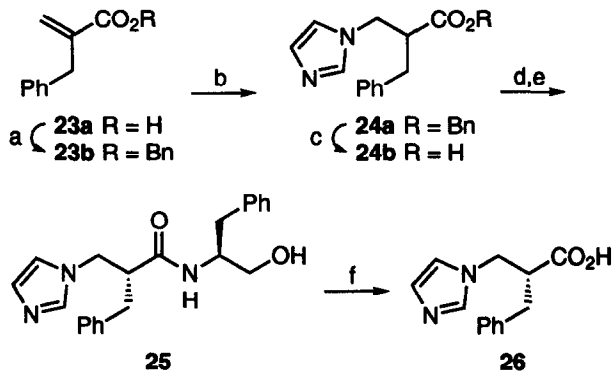
Scheme III. Reagents: (a) $BF_3{\cdot}Et_2O/CH_2Cl_2$, –78 °C; (b) $LiBH_4$/THF.

Protecting groups could be removed by sequential treatment of the Boc-acetonide derivatives with trifluoroacetic acid and water, however yields were capricious. Hydrolysis of the acetonide with warm acetic acid followed by cleavage of the carbamate provided fully deprotected oxetane **22** in consistently high yields (Scheme IV). Intact renin inhibitors **27–37** were obtained by coupling the various oxetane derivatives to Boc-Phe-His-OH. Alternately, other inhibitors were prepared via stepwise peptide couplings. The procedure for the synthesis of inhibitor **44e** is provided as an example.[21]

(Imidazolyl)methyl-substituted dihydrocinnamic acid **26** was prepared as outlined in Scheme V. The syntheses of the other N-terminal fragments[8,10,11] and of transition-state mimics **a–d** have been described.[17,18,22]



Scheme IV. Reagents: (a) AcOH/THF/H_2O, 45 °C. (b) TFA/CH_2Cl_2, 0 °C.

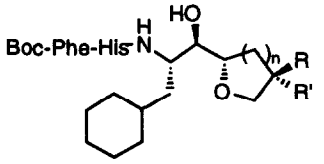


Scheme V. Reagents: (a) BnOH, DCC, DMAP/Et_2O; (b) imidazole/CH_3CN, reflux; (c) H_2, Pd/C, MeOH; (d) L-phenylalanol, HOBT, (*N*-Me)morpholine/DMF; (e) chromatographic diastereomer separation; (f) AcOH, HCl/H_2O, reflux.

Results and Discussion

The new transition-state mimics were first evaluated for renin inhibitory activity as the Boc-Phe-His derivatives (Table 1). *In vitro* activity was determined against either purified human renal renin at its pH optimum (pH = 6.0)[23] or human plasma renin at pH 7.4 (physiological pH).[8] Renin inhibition is generally lower in the plasma renin

Table 1. Effect of the C_3-substituent on the *in vitro* potency of renin inhibitors incorporating oxetane and tetrahydrofuran-derived transition state mimics



inhibitor	n	R	R'	IC_{50} (nM)[a] purified[a]	plasma[b]
27	0	H	H	1.2	17
28	0	Me	H	0.51	0.91
29	0	Et	H	0.47	0.79
30	0	iPr	H	0.61	1.0
31	0	H	iPr	30	n.d.[c]
32	0	Pr	H	0.58	1.2
33	0	iBu	H	1.1	3.8
34	0	CH(Me)CF_3	H	1.2	3.3
35	0	Me	Me	1.0	4.1
36	1	Me	H	0.93	1.7
37[17]	1	H	Me	1.2	1.7

[a] Purified human renal renin, pH 6.0.
[b] Human plasma renin, pH 7.4.
[c] not determined.

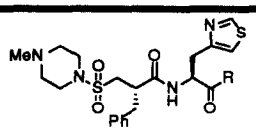
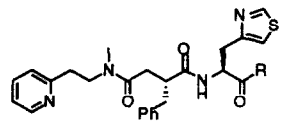
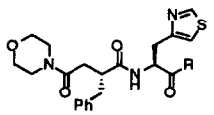
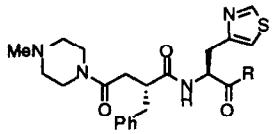
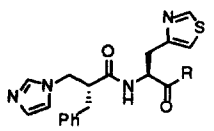
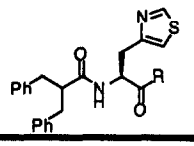
assay since plasma contains proteins that can bind to a renin inhibitor thereby reducing its effective concentration and consequently its observed potency. Since a renin inhibitor would encounter the various plasma components upon *in vivo* administration, the plasma renin assay at physiological pH is presumably the more relevant measurement.

Our initial synthesis of transition-state mimics derived from a C-terminal tetrahydrofuran was stereoselective, providing only the (4*S*)-methyl isomers.[17] Since we had been unable to establish the optimum stereochemistry at this site, our first strategy towards designing more potent analogs was to examine the effects of a (4*R*)-substituent. A new, non-stereoselective synthesis was developed (Scheme I) that provided access to (4*R*)-methyl derivative **8**, which was converted into renin inhibitor **36**. Surprisingly, both the (4*S*)-methyl (**37**) and (4*R*)-methyl (**36**) tetrahydrofuran derivatives were equipotent in both renin assays.

The effect of ring size was examined next. The 4-membered oxetane analogs were synthesized as outlined in Schemes II and III. In this series, an alkyl group at the 3-position proved essential for good *in vitro* activity against human plasma renin at physiological pH (compare **27** and **28**), and smaller groups (**28–30**, **32**) exhibited a modest superiority compared to the larger isobutyl analog (**33**). These differences were less pronounced when the compounds were assayed against purified human renal renin at its pH optimum. In contrast to the related tetrahydrofurans, a strong preference was observed for an alkyl group in the (*S*) configuration (compare **30** and **31**), and a (2*R*)-methyl was detrimental to potency even in the presence of a (2*S*) substituent (**35**). Gratifyingly, ethyl-substituted oxetane **29** was 2-fold more potent than tetrahydrofurans **36** and **37** in both renin assays.

The (3*S*)-ethyl oxetane (**e**) was compared to four other transition-state mimics that were among the most potent known: oxazolidinone **a**,[17] dipeptide glycol **b**,[22] hydroxyethylene isostere **c**,[18,24] and tetrahydrofuran **d**[17] (Table 2). When coupled to strongly binding N-terminal

Table 2. Comparison of the renin inhibitory activity of several transition-state mimics

	IC_{50} (nM, human plasma renin, pH 7.4)	R = **a**	R = **b**	R = **c**	R = **d**	R = **e**
38		1.1	1.1[11]	1.6	0.72	0.30
39		1.9	2.6[11]	1.8	1.3	0.44
40	Boc-Phe-His-R	2.8[17]	5.3[22]	1.6	1.7[17]	0.79
41		8.1[10]	8.3[10]	1.6	2.1	1.2
42		23	18[10]	7.8	5.2	1.6
43	EtO_2C-Phe-Leu-R	65	15[22]	9.8	7.5	1.9
44		37	22	6.1	9.8	1.2
45		92	54	10	20	4.4

fragments (**38–40**), oxetane **e** proved to be moderately more effective (2-fold to 7-fold) against human plasma renin at pH 7.4 compared to groups **a–d**. With more weakly binding N-terminal fragments (**42**, **43**), the oxetane-containing renin inhibitors maintained low nanomolar potency in sharp contrast to the other four transition-state mimics, which were 3-fold to 34-fold less active. Since modifications at the N-terminus were well tolerated, it appeared a reasonable initial site at which to attempt molecular weight reduction. Consequently, we examined the smaller dibenzylacetyl residue (**45**) in place of the substituted Phe or Phe mimics of **38–43**. Oxetane **45e** maintained potency against human plasma renin and was 12-fold more potent than dipeptide glycol **45b**. This inhibitor, however, did not contain a polar residue as was incorporated into zankiren (**2**) to enhance aqueous solubility. Replacement of one phenyl group with an imidazole (**44e**) provided this basic group and enhanced potency to 1.2 nM, equipotent to zankiren (IC_{50} = 1.1 nM, human plasma renin, pH 7.4[11]).

With **44e** as a lead structure, we investigated reducing the size of the P_1 and P_2-site side chains,[25] as well as further truncations at the N-terminus (Table 3). Replacing the P_1-site cyclohexyl with an isopropyl reduced activity more than 30-fold (**46**). Similarly, removing the N-terminal (imidazol-1-yl)methyl substituent (**47**) proved highly detrimental to *in vitro* potency. At the P_2-site, however, nanomolar potency was maintained when (4-thiazolyl)alanine was replaced with either norleucine (**48**) or leucine (**49**), thereby affording an additional modest reduction in molecular weight. Alanine at this site (**50**) proved significantly less active.

The C-terminal oxetane is the most potent known transition-state mimic. It was unexpected that this high binding affinity could be achieved without increasing the apparent number of contacts with the active site of renin. Inhibitors **48** and **49**, that incorporate this novel fragment, maintain nanomolar potency against human plasma renin. Furthermore, these inhibitors represent a 20 % molecular weight reduction compared to zankiren (**2**). It remains to be determined whether this size reduction is sufficient to affect *in vivo* pharmacokinetics. Presumably, maximum *in vivo* activity in the oxetane series will be achieved only after careful structural optimization as was necessary for the development of zankiren and A-74273. Significantly smaller renin inhibitors will most likely require the discovery of an entirely new class of compounds that, unlike all previous renin inhibitors, are not derived from the structure of the natural substrate.

Experimental Section

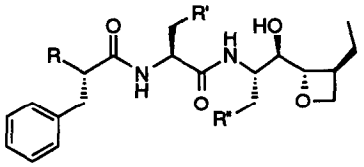
Solvents and other reagents were reagent grade and were used without further purification unless otherwise noted. Final product solutions were dried over anhydrous Na_2SO_4 (unless otherwise noted) prior to evaporation on a rotary evaporator. Tetrahydrofuran was distilled from sodium/benzophenone and dichloromethane was distilled from CaH_2. NMR spectra were recorded at 300 MHz and are expressed in ppm downfield from tetramethylsilane as an internal standard. Column chromatography was performed on silica gel 60, 0.04–0.063 mm (E. Merck) eluting with 5–10 psi air pressure. Thin-layer chromatography was done on silica gel plates (E. Merck) and components were visualized with ninhydrin or phosphomolybdic acid reagents.

(3S,5S,4'S,5'R and S)-5-[3'-(tert-Butyloxycarbonyl)-4'-(cyclohexylmethyl)-2',2'-(dimethyl)oxazolidin-5'-yl]-3-(benzylthiomethyl)dihydrofuran-2(3H)-one **5**

To olefin **4**[17] (905 mg, 2.30 mmol) in dimethylformamide (10 mL) was added triethylamine (0.42 mL, 3.0 mmol) and benzyl mercaptan (0.31 mL, 2.6 mmol). The mixture was heated at 50 °C for 48 h, cooled, and diluted with ether, which was washed with water and brine, and then was dried over $MgSO_4$ and evaporated. Chromatography of the residue on silica gel with 10 % ethyl acetate in hexane afforded 315 mg (26 %) of the 5*R*-isomer followed by 483 mg (41 %) of the 5*S*-isomer, both as solids.

5R-isomer. mp 144–146 °C; TLC (20 % ethyl acetate/80 % hexane) R_f = 0.36; ^{1}H NMR ($CDCl_3$) 7.37–7.22 (m,5H), 4.42 (ddd, 1H), 3.93 (br d, 1H), 3.76 (d, 2H), 2.95–2.81 (m, 2H), 2.44 (ddd, 1H), 2.15 (ddd, 1H), 1.90–0.90 (envelope, 14H), 1.55 (s, 3H), 1.51 (s, 3H), 1.48 (s, 9H). Anal. ($C_{29}H_{43}NO_5S$), calcd: C, 67.28; H, 8.37; N, 2.71; found: C, 66.89; H, 8.36; N, 2.62.

Table 3. Low molecular weight renin inhibitors: Truncations at the *N*-terminus and at the P_2 and P_1-sites.



inhibitor	R	R'	R"	MW	IC_{50} (nM)[a]
44e	(imidazol-1-yl)CH_2	(thiazol-4-yl)	cHex	608	1.2
46	(imidazol-1-yl)CH_2	(thiazol-4-yl)	iPr	568	40
47	H	(thiazol-4-yl)	cHex	529	100
48	(imidazol-1-yl)CH_2	Pr	cHex	567	6.6
49	(imidazol-1-yl)CH_2	iPr	cHex	567	8.7
50	(imidazol-1-yl)CH_2	H	cHex	525	100

[a]Human plasma renin, pH 7.4.

5S-isomer. mp 114–115 °C; TLC (20 % ethyl acetate/80 % hexane) R_f = 0.26; ^{1}H NMR ($CDCl_3$) 7.36–7.22 (m, 5H), 4.30 (ddd, 1H), 4.01 (br, 1H), 3.76 (s, 2H), 2.96 (dd, 1H), 2.87–2.73 (m, 1H), 2.59 (dd, 1H), 2.57–2.45 (m, 1H), 1.97–1.80 (m, 2H), 1.75–0.90 (envelope, 13H), 1.54 (s, 3H), 1.52 (s, 3H), 1.48 (s, 9H). Anal. ($C_{29}H_{43}NO_5S$), calcd: C, 67.28; H, 8.37; N, 2.71; found: C, 67.36; H, 8.45; N, 2.64.

*(4S,5R,1'S,3'R)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-5-[1',4'-dihydroxy-3'-(benzylthiomethyl)butyl]-2,2-(dimethyl)oxazolidine* **6**

Compound **5** (5*R*-isomer, 268 mg, 0.518 mmol) in ethanol (2 mL) was treated with $CaCl_2$ (105 mg, 1.04 mmol). After a homogeneous solution was obtained, tetrahydrofuran (1.2 mL) was added followed by $NaBH_4$ (78.0 mg, 2.06 mmol). After 20 h at ambient temperature the mixture was diluted with ether, washed with 0.5 M H_3PO_4, saturated aqueous $NaHCO_3$ solution, and brine, and then dried over $MgSO_4$ and evaporated. Chromatography of the residue on silica gel with 20 % ethyl acetate in hexane afforded 220 mg (81 %) of the desired product as a solid: mp 92–93 °C; ^{1}H NMR ($CDCl_3$) 7.35–7.22 (m, 5H), 4.05 (br d, 1H), 3.72 (s, 2H), 3.72–3.54 (m, 4H), 2.52 (dd, 1H), 2.41 (dd, 1H), 2.08–1.96 (m, 1H), 1.96–1.80 (m, 2H), 1.75–0.90 (envelope, 13H), 1.52 (s, 3H), 1.51 (s, 3H), 1.49 (s, 9H). Anal. ($C_{29}H_{47}NO_5S$), calcd: C, 66.76; H, 9.08; N, 2.68; found: C, 66.73; H, 9.06; N, 2.65.

*(4S,5R,2'S,4'R)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-dimethyl-5-[4'-(benzylthiomethyl)tetrahydrofuran-2'-yl]oxazolidine 7*

Compound **6** (211.6 mg, 0.406 mmol) and triphenylphosphine (248 mg, 0.946 mmol) in tetrahydrofuran (4 mL) at –10 °C were treated with diethyl azodicarboxylate (130 μL, 0.83 mmol). After 90 min at –10 °C and 18 h at ambient temperature the solvent was evaporated and the residue was chromatographed on silica gel with 4 % ethyl acetate in hexane to afford 205 mg (100 %) of a white solid: mp 69–70 °C; ^{1}H NMR ($CDCl_3$) 7.38–7.19 (m, 5H), 4.02–3.88 (m, 3H), 3.72 (s, 1H), 3.67–3.42 (m, 2H), 2.54–2.37 (m, 3H), 2.13–2.02 (m, 1H), 1.92–1.82 (m, 1H), 1.82–0.80 (envelope, 13H), 1.53 (s, 3H), 1.50 (s, 3H), 1.48 (s, 9H). Anal. ($C_{29}H_{45}NO_4S$), calcd: C, 69.15; H, 9.00; N, 2.78; found: C, 68.82; H, 8.94; N, 2.78.

*(4S,5R,2'S,4'R)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-dimethyl-5-[4'-(methyl)tetrahydrofuran-2'-yl]oxazolidine 8*

Compound **7** (64.0 mg, 0.127 mmol) in ethanol (2 mL) was treated with 7 drops of an aqueous suspension of Raney Ni (50 wt %). The mixture was heated at reflux for 48 h, filtered through celite, evaporated, and the residue was chromatographed on silica gel with 4 % ethyl acetate in hexane to afford 36.5 mg (75 %) of a solid: mp 79–81 °C; ^{1}H NMR ($CDCl_3$) 4.05–3.91 (m, 2H), 3.65–3.55 (br, 1H), 3.31 (dd, 1H), 2.32 (ddd, 1H), 2.12–1.80 (m, 2H), 1.75–0.80 (envelope, 14H), 1.55 (s, 3H), 1.51 (s, 3H), 1.48 (s, 9H), 1.04 (d, 3H). Anal. ($C_{22}H_{39}NO_4$), calcd: C, 69.25; H, 10.30; N, 3.67; found: C, 69.44; H, 10.32; N, 3.64.

*(4S,5R,1'S,2'*R and S*)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[1'-hydroxy-2'-methoxycarbonyl-3'-(methyl)butyl]oxazolidine* ***10d*** *and* ***11d***

To aldehyde **9a**[17] (0.800 g, 2.46 mmol) in tetrahydrofuran (10 mL) was added methyl 2-bromoisovalerate (0.720 g, 3.67 mmol) and zinc (0.400 g, 6.12 mmol). The reaction flask was placed in an ultrasonic cleaning bath for 1 h, and then was diluted with ethyl acetate and filtered. The mixture was washed with saturated $NaHCO_3$ solution, water, and brine, and then was dried over Na_2SO_4 and evaporated. Chromatography of the residue on silica gel with 10–15 % ethyl acetate in hexane provided 0.324 g (30 %) of the 2'*R*-isomer (**11d**) as an oil followed by 0.464 g (43 %) of the 2'*S*-isomer (**10d**) as a solid.

10d. mp 109–110 °C; TLC (20 % ethyl acetate/80 % hexane) R_f = 0.46; ^{1}H NMR ($CDCl_3$) 4.16–4.05 (m, 1H), 3.95–3.88 (m, 1H), 3.80 (dd, 1H), 3.70 (s, 3H), 2.90–2.80 (m, 1H), 2.67 (dd, 1H), 2.33–2.21 (m, 1H), 1.51 (s, 3H), 1.50 (s, 3H), 1.47 (s, 9H), 1.07 (dd, 3H), 0.99 (dd, 3H). Anal. ($C_{24}H_{43}NO_6$), calcd: C, 65.28; H, 9.81; N, 3.17; found: C, 65.18; H, 9.73; N, 3.13.

11d. TLC (20 % ethyl acetate/80 % hexane) R_f = 0.55; ^{1}H NMR ($CDCl_3$) 4.20–4.10 (m, 1H), 3.76 (s, 3H), 3.73–3.62 (m, 2H), 3.53–3.43 (m, 1H), 2.65–2.55 (m, 1H), 2.23–2.18 (m, 1H), 1.53 (br s, 6H), 1.48 (s, 9H), 1.04 (d, 3H), 0.98 (d, 3H).

The following compounds were prepared using the same procedure as for **11d**:

*(4S,5R,1'S)-5-[2'-Benzyloxycarbonyl-1'-(hydroxy)ethyl]-3-(*tert*-butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)oxazolidine* ***11a***

mp 91–93 °C; ^{1}H NMR ($CDCl_3$) 7.42–7.33 (m, 5H), 5.17 (s, 2H), 4.17–4.03 (m, 1H), 4.00–3.88 (m, 1H), 3.67 (d, 1H), 3.30–3.20 (br, 1H), 2.90 (dd, 1H), 2.54 (dd, 1H), 1.52 (s, 3H), 1.51 (s, 3H), 1.48 (s, 9H). Anal. ($C_{27}H_{41}NO_6$), calcd: C, 68.18; H, 8.69; N, 2.94; found: C, 67.83; H, 8.57; N, 2.86.

*(4S,5R,1'S,2'*R,*)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[1'-hydroxy-2'-(methoxycarbonyl)propyl]oxazolidine* ***11b***

mp 88–91 °C; ^{1}H NMR ($CDCl_3$) 4.23–4.06 (m, 1H), 3.80–3.62 (m, 1H), 3.73 (s, 3H), 3.50–3.34 (m, 1H), 3.08–2.94 (m, 1H), 1.52 (s, 6H), 1.47 (s, 9H), 1.38 (d, 3H). Anal. ($C_{22}H_{39}NO_6$), calcd: C, 63.90; H, 9.50; N, 3.39; found: C, 64.18; H, 9.80; N, 3.46.

*(4S,5R,1'S,2'*R*)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[1'-hydroxy-2'-(methoxycarbonyl)butyl]oxazolidine* ***11c***

mp 88–90°C; ^{1}H NMR ($CDCl_3$) 4.22–4.10 (m, 1H), 3.75 (m, 3H), 3.70–3.50 (m, 2H), 2.82 (br t, 1H), 1.52 (s, 6H), 1.48 (s, 9H), 1.00 (t, 3H). Anal. ($C_{23}H_{41}NO_6$), calcd: C, 64.61; H, 9.66; N, 3.28; found: C, 64.55; H, 9.65; N, 3.23.

*(4S,5R,1'S,2'R)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[2'-ethoxycarbonyl-1'-(hydroxy)pentyl]oxazolidine* ***11e***

^{1}H NMR ($CDCl_3$) 4.32–4.18 (m, 3H), 3.70–3.60 (m, 2H), 3.55–3.46 (m, 1H), 2.93–2.83 (m, 1H), 1.52 (br s, 6H), 1.47 (s, 9H), 1.31 (t, 3H), 0.94 (t, 3H).

*(4S,5R,1'S,2'R)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[1'-hydroxy-2'-methoxycarbonyl-4-(methyl)pentyl]oxazolidine* ***11f***

mp 95–97 °C; ^{1}H NMR ($CDCl_3$) 4.20–4.10 (m, 1H), 3.74 (s, 3H), 3.65–3.53 (m, 2H), 3.53–3.42 (m, 1H), 3.05–2.95 (m, 1H), 1.52 (br s, 6H), 1.48 (s, 9H), 0.95 (d, 3H), 0.92 (d, 3H). Anal. ($C_{25}H_{45}NO_6$), calcd: C, 65.90; H, 9.95; N, 3.07; found: C, 65.99; H, 10.03; N, 3.10.

*(4S,5R,1'S,2'R,3'RS)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[2'-ethoxycarbonyl-1'-hydroxy-3'-(trifluoromethyl)butyl]oxazolidine* ***11g***

mp 86–89 °C; ^{1}H NMR ($CDCl_3$) 4.37–4.08 (m, 3H), 3.74–3.63 (m, 1H), 3.60–3.45 (m, 1H), 3.08–2.98 (m, 1H), 2.96–2.77 (m, 1H), 1.52 (br s, 6H), 1.48 (s, 9H). Anal. ($C_{25}H_{42}NO_6F_3$), calcd: C, 58.92; H, 8.31; N, 2.75; found: C, 59,24; H, 8.54; N, 2.73.

*(4S,5R,1'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[2'-ethoxycarbonyl-1'-hydroxy-2'-(methyl)propyl]oxazolidine* ***11h***

^{1}H NMR ($CDCl_3$) 4.30–4.08 (m, 3H), 3.83 (dd, 1H), 3.63 (dd, 1H), 2.78–2.88 (br, 1H), 1.48 (s, 15H), 1.35–1.22 (m, 9H).

*(4S,5R,1'S,2'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[1'-hydroxy-2'-hydroxymethyl-3'-(methyl)butyl]oxazolidine* ***12d***

To **11d** (185 mg, 0.419 mmol) in ethanol (0.8 mL) was added $CaCl_2$ (85.0 mg, 0.842 mmol). After the mixture became homogeneous, tetrahydrofuran (0.5 mL) and $NaBH_4$ (63.0 mg, 0.842 mmol) were added. After 24 h, the mixture was poured into ether which was washed sequentially with 0.5 M H_3PO_4, saturated $NaHCO_3$ solution, and brine, and then dried over $MgSO_4$ and evaporated. Chromatography of the residue on silica gel with 15 % ethyl acetate in hexane provided 122.2 mg (71 %) of the desired product as a foam: ^{1}H NMR ($CDCl_3$) 4.20–4.06 (m, 2H), 4.04–3.96 (m, 1H), 3.91 (d, 1H), 3.85–3.75 (m, 1H), 3.22–3.05 (br, 1H), 2.19–2.04 (m, 1H), 1.52 (s, 6H), 1.48 (s, 9H), 1.05 (d, 3H), 1.04 (d, 3H).

The following compounds were prepared using the same procedure as for **12d**:

*(4S,5R,1'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-5-[1',3'-(dihydroxy)propyl]-2,2-(dimethyl)oxazolidine* ***12a***

mp 130–131 °C; ^{1}H NMR ($CDCl_3$) 4.15–3.95 (m, 2H), 3.95–3.77 (m, 2H), 3.68 (dd, 1H), 3.00–2.85 (br, 1H), 1.54 (s, 3H), 1.52 (s, 3H), 1.48 (s, 9H).

*(4S,5R,1'S,2'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[1'-hydroxy-2'-(hydroxymethyl)propyl]oxazolidine* ***12b***

mp 101–103 °C; ^{1}H NMR ($CDCl_3$) 4.17–3.98 (m, 2H), 3.86 (dd, 1H), 3.77–3.67 (m, 1H), 3.58–3.48 (m, 1H), 2.90–2.75 (br, 1H), 1.53 (s, 3H), 1.52 (s, 3H), 1.47(s, 9H), 1.16 (d, 3H). Anal. ($C_{21}H_{39}NO_5$), calcd: C, 65.42; H, 10.20; N, 3.63; found: C, 65.46; H, 10.38; N, 3.66.

*(4S,5R,1'S,2'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[1'-hydroxy-2'-(hydroxymethyl)butyl]oxazolidine* ***12c***

^{1}H NMR ($CDCl_3$) 4.18–4.07 (m, 2H), 3.90 (d, 1H), 3.86–3.77 (m, 1H), 3.68–3.59 (m, 1H), 3.05–2.87 (br, 1H), 1.52 (s, 6H), 1.48 (s, 9H), 1.01 (t, 3H).

*(4S,5R,1'S,2'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[1'-hydroxy-2'-(hydroxymethyl)pentyl]oxazolidine* ***12e***

^{1}H NMR ($CDCl_3$) 4.17–4.07 (m, 2H), 3.89 (d, 1H), 3.83–3.74 (m, 1H), 3.65–3.57 (m, 1H), 3.10–2.95 (br, 1H), 1.51 (s, 6H), 1.48 (s, 9H), 0.95 (t, 3H).

*(4S,5R,1'S,2'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[1'-hydroxy-2'-hydroxymethyl-4'-(methyl)pentyl]oxazolidine* ***12f***

^{1}H NMR ($CDCl_3$) 4.18–4.07 (m, 2H), 3.89 (d, 1H), 3.80–3.70 (m, 1H), 3.60–3.50 (m, 1H), 3.10–3.00 (br, 1H), 1.52 (s, 6H), 1.48 (s, 9H), 0.92 (d, 6H).

*(4S,5R,1'S,2'S,3'RS)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[1'-hydroxy-2'-hydroxymethyl-3'-(trifluoromethyl)butyl]oxazolidine* ***12g***

mp 145–146 °C; ^{1}H NMR ($CDCl_3$) 4.30–3.95 (m, 3H), 3.92 (d, 1H), 3.84–3.69 (m, 1H), 3.45–3.24 (br, 1H), 2.92–2.70 (m, 1H), 1.52 (br s, 6H), 1.48 (s, 9H), 1.33 (dd, 3H). Anal. ($C_{23}H_{40}NO_5F_3$), calcd: C, 59.08; H, 8.62; N, 3.00; found: C, 59.03; H, 8.76; N, 2.99.

*(4S,5R,1'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[1'-hydroxy-2'-hydroxymethyl-2'-(methyl)propyl]oxazolidine* ***12h***

mp 140–142 °C; ^{1}H NMR ($CDCl_3$) 4.33–4.25 (m, 1H), 3.90 (dd, 1H), 3.72–3.62 (m, 1H), 3.53–3.38 (m, 2H), 2.80–2.50 (br, 2H), 1.60 (s, 3H), 1.52 (s, 3H), 1.48 (s, 9H), 1.05 (s, 3H), 1.00 (s, 3H).

*(4S,5R,1'S,2'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[1'-hydroxy-3'-methyl-2'-[(p-toluenesulfonyloxy)methyl]butyl]oxazolidine* ***15***

^{1}H NMR ($CDCl_3$) 7.82 (d, 2H), 7.37 (d, 2H), 4.34–4.25 (m, 2H), 4.13–4.02 (m, 1H), 3.73–3.67 (m, 2H), 2.47 (s, 3H), 1.54 (s, 6H), 1.47 (s, 9H), 0.97 (d, 3H), 0.88 (d, 3H).

*(4S,5R,2'S,3'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[3'-(ethyl)oxetan-2'-yl]oxazolidine* ***14c***

Alcohol **12c** (1.395 g, 3.491 mmol) in pyridine (4 mL) at 0 °C was treated with *p*-toluenesulfonyl chloride (0.730 g, 3.83 mmol). After 24 h at 0 °C and 36 h at ambient temperature, the mixture was diluted with ether and washed sequentially with 0.5 M H_3PO_4, water, and brine, and then dried over $MgSO_4$ and evaporated to afford 1.883 g (97 %) of the desired product as a foam: ^{1}H NMR ($CDCl_3$) 7.81 (d, 2H), 7.37 (d, 2H), 4.30–4.15 (m, 2H), 4.12–4.01 (m, 1H), 3.72 (d, 1H), 3.64–3.54 (m, 1H), 2.47 (s, 3H), 1.52 (s, 3H), 1.48 (s, 3H), 1.47 (s, 9H), 0.88 (t, 3H).

To this tosylate (1.883 g, 3.400 mmol) in tetrahydrofuran (30 mL) at 0 °C was added sodium bis(trimethylsilyl)-amide in tetrahydrofuran (4.5 mL, 4.5 mmol, 1.0 M). After 45 min, the reaction was quenched with 0.5 M H_3PO_4. The mixture was concentrated, diluted with ether, washed sequentially with 0.5 M H_3PO_4, water, and brine, and then dried over $MgSO_4$ and evaporated. Chromatography of the residue on silica gel with 10 % ethyl acetate in hexane afforded 1.139 g (88 %) of the desired product as a solid: mp 40–41 °C; ^{1}H NMR ($CDCl_3$) 4.62 (dd, 1H), 4.37–4.28 (m, 1H), 4.27 (dd, 1H), 4.01 (dd, 1H), 3.90–3.78 (br m, 1H), 2.73–2.59 (m, 1H), 1.56 (s, 3H), 1.53 (s, 3H), 1.47 (s, 9H), 0.89 (t, 3H). Anal. ($C_{22}H_{39}NO_4$), calcd: C, 69.25; H, 10.30; N, 3.67; found: C, 69.10; H, 10.10; N, 3.49.

The following compounds were prepared using the same procedure as for **14c**:

*(4S,5R,2'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-(oxetan-2'-yl)oxazolidine* ***14a***

mp 70–72 °C; ^{1}H NMR ($CDCl_3$) 4.78–4.62 (m, 2H), 4.56 (dd, 1H), 4.03 (dd, 1H), 3.79 (br d, 1H), 2.77–2.62 (m, 1H), 2.62–2.47 (m, 1H), 1.56 (s, 3H), 1.52 (s, 3H), 1.47 (s, 9H). Anal. ($C_{20}H_{35}NO_4$), calcd: C, 67.95; H, 9.98; N, 3.96; found: C, 67.80; H, 9.96; N, 3.91.

*(4S,5R,2'S,3'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[3'-(methyl)oxetan-2'-yl]oxazolidine* ***14b***

mp 73–74 °C; ^{1}H NMR ($CDCl_3$) 4.64 (dd, 1H), 4.34–4.26 (m, 1H), 4.23 (dd, 1H), 4.00 (dd, 1H), 3.87–3.73 (br, 1H), 2.94–2.78 (m, 1H), 1.55 (s, 3H), 1.52 (s, 3H), 1.47 (s, 9H), 1.28 (d, 3H). Anal. ($C_{21}H_{37}NO_4$), calcd: C, 68.63; H, 10.15; N, 3.98; found: C, 68.68; H, 9.93; N, 3.78.

*(4S,5R,2'S,3'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[3'-(isopropyl)oxetan-2'-yl]oxazolidine* ***14d***

^{1}H NMR ($CDCl_3$) 4.58 (dd, 1H), 4.42–4.30 (m, 1H), 4.30 (dd, 1H), 4.01 (dd, 1H), 4.00–3.84 (br m, 1H), 2.46–2.32 (m, 1H), 1.58 (s, 3H), 1.52 (s, 3H), 1.46 (s, 9H), 0.92 (d, 3H), 0.88 (d, 3H). Anal. ($C_{23}H_{41}NO_4$), calcd: C, 69.83; H, 10.45; N, 3.54; found: C, 70.10; H, 10.84; N, 3.55.

*(4S,5R,2'S,3'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[3'-(propyl)oxetan-2'-yl]oxazolidine* ***14e***

mp 76–77 °C; ^{1}H NMR ($CDCl_3$) 4.62 (dd, 1H), 4.37–4.28 (m, 1H), 4.27 (dd, 1H), 4.00 (dd, 1H), 3.95–3.75 (br m, 1H), 2.82–2.67 (m, 1H), 1.55 (s, 3H), 1.52 (s, 3H), 1.47 (s, 9H), 0.90 (t, 3H). Anal. ($C_{23}H_{41}NO_4$), calcd: C, 69.83; H, 10.45; N, 3.54; found: C, 70.24; H, 10.45; N, 3.56.

*(4S,5R,2'S,3'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[3'-(isobutyl)oxetan-2'-yl]oxazolidine* ***14f***

mp 77–78 °C; ^{1}H NMR ($CDCl_3$) 4.62 (dd, 1H), 4.38–4.28 (m, 1H), 4.27 (dd, 1H), 4.00 (dd, 1H), 3.95–3.73 (br m, 1H), 2.90–2.73 (m, 1H), 1.55 (s, 3H), 1.52 (s, 3H), 1.47 (s, 9H), 0.88 (d, 3H), 0.86 (d, 3H). Anal. ($C_{24}H_{43}NO_4$), calcd: C, 70.38; H, 10.58; N, 3.42; found: C, 70.65; H, 10.91; N, 3.37.

*(4S,5R,2'S,3'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[3'-(1,1,1-trifluoroisopropyl)-oxetan-2'-yl]oxazolidine* ***14g***

mp 102–104 °C; ^{1}H NMR ($CDCl_3$) 4.63 (dd, 1H), 4.51–4.37 (m, 2H), 4.10–3.80 (br, 1H), 4.02 (dd, 1H), 2.93–2.78 (m, 1H), 2.69–2.51 (m, 1H), 1.58 (s, 1H), 1.53 (s, 1H), 1.47 (s, 9H), 1.16 (d, 3H). Anal. ($C_{23}H_{38}NO_4F_3 \cdot 0.25H_2O$), calcd: C, 60.84; H, 8.55; N, 3.08; found: C, 61.04; H, 8.71; N, 3.05.

*(4S,5R,2'S)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[3',3'-(dimethyl)oxetan-2'-yl]oxazolidine* ***14h***

Alcohol **12h** (57.5 mg, 0.144 mmol) in dichloromethane (1 mL) at −10 °C was treated with methanesulfonyl chloride (0.011 mL, 0.14 mmol) and triethylamine (0.022 mL, 0.16 mmol). After 1 h, the mixture was warmed to ambient temperature and stirred for an additional hour. The solvent was evaporated and the residue was taken up in ether which was washed sequentially with 0.5 M H_3PO_4, saturated $NaHCO_3$ solution, and brine, and then dried over $MgSO_4$ and evaporated to afford 0.0666 g (97 %) of the methanesulfonate [^{1}H NMR ($CDCl_3$) 4.38 (d, 1H), 4.23–4.12 (m, 1H), 3.90–3.83 (m, 2H), 3.52–3.46 (m, 1H), 3.03 (s, 3H), 1.58 (s, 3H), 1.51 (s, 3H), 1.49 (s, 9H), 1.15 (s, 3H), 1.02 (s, 3H)]. Treatment of this material in the same manner as the above tosylates provided the desired oxetane: mp 96.0–96.5 °C; ^{1}H NMR ($CDCl_3$) 4.36–4.22 (m, 2H), 4.18–4.03 (m, 2H), 3.87–3.72 (br m, 1H), 1.51 (s, 6H), 1.47 (s, 9H), 1.30 (s, 3H), 1.29 (s, 3H).

*(4S,5R,2'S,3'R)-3-(*tert*-Butyloxycarbonyl)-4-(cyclohexylmethyl)-2,2-(dimethyl)-5-[3'-(isopropyl)oxetan-2'-yl]oxazolidine* ***16***

mp 99–100 °C; ^{1}H NMR ($CDCl_3$) 4.62–4.50 (m, 2H), 4.37–4.28 (m, 2H), 3.94–3.81 (br m, 1H), 2.94–2.78 (m, 1H), 2.20–2.03 (m, 1H), 1.53 (s, 3H), 1.52 (s, 3H), 1.46 (s, 9H), 1.00 (d, 3H), 0.76 (d, 3H). Anal. ($C_{23}H_{41}NO_4$), calcd:

C, 69.83; H, 10.45; N, 3.54; found: C, 69.91; H, 10.48; N, 3.53.

*(4S,5R,2'S,3'S)-3-(*tert*-Butyloxycarbonyl)-4-(isobutyl)-2,2-(dimethyl)-5-[3'-(ethyl)oxetan-2'-yl]oxazolidine* ***19***

^{1}H NMR ($CDCl_3$) 4.62 (dd, 1H), 4.36–4.28 (m, 1H), 4.26 (dd, 1H), 4.02 (dd, 1H), 3.88–3.73 (br, 1H), 2.73–2.58 (m, 1H), 1.58 (s, 6H), 1.47 (s, 9H), 0.97 (d, 3H), 0.95 (d, 3H), 0.89 (t, 3H).

*1-(*tert*-Butylthio)-1-(trimethylsilyloxy)but-1-ene*

To *tert*-butylthiobutyrate (4.99 g, 31.2 mmol) in dichloromethane (30 mL) at 0 °C was added trimethylsilyl trifluoromethanesulfonate (6.10 mL, 31 mmol) and triethylamine (5.2 mL, 37 mmol). The cooling bath was removed and the mixture was stirred at ambient temperature for 45 min. After evaporation of the solvent, the lower layer was separated and discarded and the upper layer was distilled to afford 6.116 g (84 %) of the desired product: bp 95–96 °C (11 mm); ^{1}H NMR ($CDCl_3$) 5.21 (t, 1H), 2.18 (dq, 2H), 1.37 (s, 9H), 0.94 (t, 3H), 0.21 (s, 9H).

*(4S,5R,1'S,2'R)-3-(*tert*-Butyloxycarbonyl)-5-[2'-*tert*-butylthiocarbonyl-1'-(hydroxy)butyl]-4-(cyclohexylmethyl)-2,2-(dimethyl)oxazolidine* ***17a***

To aldehyde **9a**[17] (5.827 g, 17.90 mmol) was added 1-(*tert*-butylthio)-1-(trimethylsilyloxy)but-1-ene (6.116 g, 26.30 mmol) in dichloromethane (60 mL). The mixture was cooled to –78 °C and was treated with borontrifluoride etherate (2.30 mL, 18.7 mmol). After 1 h, the mixture was transferred via cannula into a rapidly stirring solution of pH 7 phosphate buffer (120 mL) at 0 °C. The mixture was partitioned, the aqueous phase was extracted with dichloromethane, and the combined organic layers were dried over $MgSO_4$ and evaporated. Chromatography of the residue on silica gel with 3–5 % ethyl acetate in hexane afforded 4.463 g (51 %) of the desired product as a solid: mp 89–90 °C; ^{1}H NMR ($CDCl_3$) 4.23–4.10 (m, 1H), 3.69–3.59 (m, 1H), 3.57–3.47 (m, 2H), 2.93–2.85 (m, 1H), 1.53 (s, 3H), 1.52 (s, 3H), 1.48 (s, 9H), 1.46 (s, 9H), 1.01 (t, 3H). Anal. ($C_{26}H_{47}NO_5S \cdot 0.25H_2O$), calcd: C, 63.70; H, 9.77; N, 2.86; found: C, 63.88; H, 9.56; N, 2.90.

*(4S,5R,1'S,2'R)-3-(*tert*-Butyloxycarbonyl)-5-[2'-*tert*-butylthiocarbonyl-1'-(hydroxy)butyl]-4-(isobutyl)-2,2-(dimethyl)oxazolidine* ***17b***

This compound was prepared from aldehyde **9b**[20] in an analogous fashion: mp 76–78 °C; ^{1}H NMR ($CDCl_3$) 4.20–4.05 (m, 1H), 3.70–3.46 (m, 2H), 2.96–2.83 (m, 1H), 1.49 (s, 9H), 1.48 (s, 9H), 1.02 (t, 3H), 1.00–0.87 (m, 6H). Anal. ($C_{23}H_{43}NO_5S$), calcd: C, 61.99; H, 9.72; N, 3.14; found: C, 62.22; H, 9.50; N, 3.19.

12c (from 17a)

Thiol ester **17a** (2.0015 g, 4.121 mmol) in tetrahydrofuran (40 mL) at 0 °C was treated with $LiBH_4$ in tetrahydrofuran (5.0 mL, 10 mmol, 2.0 M). After 4 h at 0 °C and 12 h at ambient temperature, the reaction was concentrated and quenched with 0.5 M H_3PO_4. The mixture was diluted with ether and washed with water, saturated $NaHCO_3$ solution and brine, and then was dried over Na_2SO_4 and evaporated. Chromatography of the residue on silica gel with 15 % ethyl acetate in hexane afforded 1.3949 g (85 %) of the desired product as a foam.

*(4S,5R,1'S,2'S)-3-(*tert*-Butyloxycarbonyl)-4-(isobutyl)-2,2-(dimethyl)-5-[1'-hydroxy-2'-(hydroxymethyl)butyl]oxazolidine* ***18***

Compound **17b** was reduced in an analogous fashion to **17a**: ^{1}H NMR ($CDCl_3$) 4.22-4.02 (m, 2H), 3.95–3.74 (m, 2H), 3.70–3.58 (m, 1H), 1.52 (s, 6H), 1.49 (s, 9H), 1.01 (t, 3H), 1.02–0.90 (m, 6H).

*(1R,2S,2'S,3'S)-2-[(*tert*-Butyloxycarbonyl)amino]-3-cyclohexyl-1-[3'-(ethyl)oxetan-2'-yl]-1-(hydroxy)propane* ***21***

Compound **14c** (0.522 g, 1.37 mmol) was treated with 3:1:1 acetic acid:tetrahydrofuran:water (15 mL) at 45 °C for 27 h. After evaporation of the solvent, the mixture was diluted with ether, washed with saturated $NaHCO_3$ solution, water, and brine, and then was dried over Na_2SO_4 and evaporated to afford 0.44 g (94 %) of a solid: mp 82–87 °C; ^{1}H NMR ($CDCl_3$) 4.80–4.68 (m, 1H), 4.60 (dd, 1H), 4.39 (dd, 1H), 4.29 (dd, 1H), 3.74–3.61 (m, 2H), 3.01–2.85 (m, 2H), 1.43 (s, 9H), 0.84 (t, 3H). Anal. ($C_{19}H_{35}NO_4$), calcd: C, 66.83; H, 10.33; N, 4.10; found: C, 66.84; H, 10.48; N, 4.09.

(1R,2S,2'S,3'S)-2-Amino-3-cyclohexyl-1-[3'-(ethyl)oxetan-2'-yl]-1-(hydroxy)propane ***22***

Trifluoroacetic acid (15 mL) was chilled in an ice–water bath and poured into a solution of compound **21** (0.430 g, 1.26 mmol) in dichloromethane (15 mL) at 0 °C. After 1 h at 0 °C, the solvent was evaporated and the residue was diluted with water, basified with Na_2CO_3, and extracted into chloroform which was dried over Na_2SO_4 and evaporated to afford 0.318 g (100 %) of a solid: mp 66–70 °C; ^{1}H NMR ($CDCl_3$) 4.52 (dd, 1H), 4.36 (dd, 1H), 4.28 (dd, 1H), 3.44 (dd, 1H), 3.02–2.92 (m, 1H), 2.90–2.73 (m, 1H), 0.87 (t, 3H). Anal. ($C_{14}H_{27}NO_2$), calcd: C, 66.83; H, 10.33; N, 4.10; found: C, 66.84; H, 10.48; N, 4.09.

Benzyl 2-benzylacrylate ***23b***

2-Benzylacrylic acid (2.20 g, 13.6 mmol) in dry ether (40 mL) was treated with dicyclohexylcarbodiimide (2.60 g, 12.6 mmol), benzyl alcohol (1.30 mL, 12.6 mmol) and 4-dimethylaminopyridine (0.310 g, 2.54 mmol). After stirring at room temperature for 44 h, the mixture was filtered and evaporated. Chromatography of the residue on silica with 5 % ethyl acetate in hexane afforded 2.70 g (85 %) of a colorless oil: bp 150 °C (0.2 mm); ^{1}H NMR ($CDCl_3$) 7.15–7.40 (m, 10H), 6.28 (m, 1H), 5.49 (m, 1H), 5.17 (2H, s), 3.67 (s, 2H). Anal. ($C_{17}H_{16}O_2 \cdot 0.15H_2O$), calcd: C, 80.07; H, 6.44; found: C, 80.17; H, 6.47.

Benzyl (2RS)-2-benzyl-3-(imidazol-1-yl)propionate **24a**

Acrylate **23b** (10.00 g, 36.93 mmol) and imidazole (5.40 g, 79.3 mmol) in acetonitrile (10 mL) were heated at reflux for 44 h. The mixture was evaporated and the residue was chromatographed on silica gel with 2 % methanol in chloroform to afford 11.20 g (88 %) of the desired product as an oil: ^{1}H NMR ($CDCl_3$) 7.38 (s, 1H), 7.38–7.05 (m, 10H), 7.00 (dd, 1H), 6.80 (dd, 1H), 5.03 (d, 1H), 4.99 (d, 1H), 4.25 (dd, 1H), 4.03 (dd, 1H), 3.22–3.09 (m, 1H), 3.02 (dd, 1H), 2.78 (dd, 1H).

(2RS)-2-Benzyl-3-(imidazol-1-yl)propionic acid **24b**

Ester **24a** (11.20 g, 35.0 mmol) and 10 % palladium on carbon (3.00 g) in methanol (250 mL) were stirred under a hydrogen atmosphere for 16 h. The mixture was filtered and evaporated to afford 7.90 g (98 %) of the desired product as a solid: mp 159–163 °C. Anal. ($C_{13}H_{14}N_2O_2 \cdot 0.5H_2O$), calcd: C, 66.51; H, 6.23; N, 11.93; found: C, 66.81; H, 6.03; N, 11.93.

(2R)-2-Benzyl-3-(imidazol-1-yl)propionic acid amide of L-phenylalaninol **25**

To a solution of racemic acid **24b** (484 mg, 2.10 mmol), L-phenylalaninol (325 mg, 2.15 mmol), 1-hydroxybenzotriazole (770 mg, 5.70 mmol), and 4-methylmorpholine (0.250 mL, 2.27 mmol) in *N,N*-dimethylformamide (10 mL) at –23 °C was added 1-(3,3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (575 mg, 3.00 mmol). After stirring for 2 h at –23 °C and then for 18 h at room temperature, the mixture was taken up in saturated $NaHCO_3$ solution and extracted into ethyl acetate. The organic extracts were washed with water and brine, and then were dried over Na_2SO_4 and evaporated to a foam. Chromatography on silica gel with 3–4 % methanol in chloroform afforded the desired (2*R*)-isomer (335 mg, 44 %) followed by the (2*S*)-isomer (292 mg, 38 %), both as solids.

(2R)-isomer. mp 139–141 °C; TLC (15 % methanol/85 % chloroform) R_f = 0.44; ^{1}H NMR ($CDCl_3$) 7.40 (s, 1H), 6.82 (s, 1H), 5.42 (d, 1H), 4.31 (dd, 1H), 4.06–3.91 (m, 2H), 3.26 (d, 2H), 2.97–2.72 (m, 2H). Anal. ($C_{22}H_{25}N_3O_2$), calcd: C, 72.70; H, 6.93; N, 11.56; found: C, 72.34; H, 6.88; N, 11.46.

(2S)-isomer. mp 116–118 °C; TLC (15 % methanol/85 % chloroform) R_f = 0.37; ^{1}H NMR ($CDCl_3$) 7.42 (s, 1H), 6.39 (s, 1H), 5.53 (d, 1H), 4.30 (dd, 1H), 4.10–3.93 (m, 2H), 3.43–3.24 (m, 2H), 2.93 (dd, 1H). Anal. ($C_{22}H_{25}N_3O_2$), calcd: C, 72.70; H, 6.93; N, 11.56; found: C, 72.65; H, 6.93; N, 11.50.

(2R)-2-Benzyl-3-(imidazol-1-yl)propionic acid **26**

Compound **25** (316 mg, 0.87 mmol) was heated to reflux in 1:3 (v/v) acetic acid/6 N HCl for 4 h. The solution was then concentrated to an oil, taken up in water, and adjusted to pH 11 by dropwise addition of 3 M aqueous NaOH. After saturating with NaCl, the aqueous layer was extracted with 85 % chloroform/15 % isopropanol (total volume = 100 mL) to remove the amino alcohol. The aqueous layer was then adjusted to pH 6 by dropwise addition of 2 M aqueous HCl and the desired product was removed by repeated extractions with 75 % chloroform/25 % isopropanol (total volume = 400 mL). The extracts were dried over Na_2SO_4, filtered, and evaporated to a solid which was taken up in 94 % chloroform/6 % methanol, filtered through Celite, and then concentrated giving 153 mg (76 %) of a pale-yellow crystalline solid: mp 140–145 °C; ^{1}H NMR (DMSO-d_6) 7.57 (s, 1H), 6.87 (s, 1H), 4.25–4.01 (m, 2H), 3.20–3.04 (m, 1H), 2.88–2.66 (m, 2H). Anal. ($C_{13}H_{14}N_2O_2 \cdot 0.1\ H_2O$), calcd: C, 67.28; H, 6.17; N, 12.07; found: C, 67.27; H, 6.14; N, 12.03.

Boc-L-(4-thiazolyl)alanine amide of **22**

To a mixture of amine **22** (4.278 g, 17.72 mmol), 1-hydroxybenzotriazole (6.4708 g, 47.89 mmol) and Boc-L-(4-thiazolyl)Ala-OH[26] (5.076 g, 18.64 mmol) in dimethylformamide (40 mL) at –23 °C was added *N*-methylmorpholine (2.00 mL, 18.2 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.85 mg, 25.3 mmol). After stirring at –23 °C for 2 h and at ambient temperature overnight, the mixture was poured into saturated $NaHCO_3$ solution and extracted into ethyl acetate which was washed with water and brine, and then was dried over Na_2SO_4 and evaporated. Chromatography of the residue on silica gel with 1.2–1.4 % methanol in chloroform afforded 7.340 g (84 %) a foam: ^{1}H NMR ($CDCl_3$) 8.78 (d, 1H), 7.13 (d, 1H), 6.55 (d, 1H), 6.31 (br d, 1H), 4.56 (dd, 1H), 4.53–4.44 (m, 1H), 4.22 (dd, 1H), 4.05 (dd, 1H), 3.92–3.79 (m, 1H), 3.67–3.60 (m, 1H), 3.45 (dd, 1H), 3.18 (dd, 1H), 2.84–2.72 (m, 1H), 1.47 (s, 9H), 0.85 (t, 3H). Anal. ($C_{25}H_{41}N_3O_5S$), calcd: C, 60.58; H, 8.34; N, 8.48; found: C, 60.33; H, 8.33; N, 8.24.

H-*L-(4-Thiazolyl)alanine amide of* **22**

The Boc-L-(4-thiazolyl)alanine amide of **22** (442.4 mg, 0.893 mmol) in dichloromethane (12.5 mL) at –10 °C was treated with trifluoroacetic acid (12.5 mL), and was stirred at –10 °C for 4.5 h. While cold, the solvent was distilled under reduced pressure and the residue was taken up in water. The mixture was made basic with Na_2CO_3 and extracted into chloroform which was dried over Na_2SO_4 and evaporated. Chromatography of the residue on silica gel with 3 % methanol in chloroform afforded 292 mg (83 %) of a foam: ^{1}H NMR ($CDCl_3$) 8.78 (d, 1H), 7.70 (d, 1H), 7.12 (d, 1H), 4.59 (dd, 1H), 4.24 (dd, 1H), 4.18 (dd, 1H), 3.92–3.78 (m, 2H), 3.75–3.65 (m, 2H), 3.31 (dd, 1H), 3.18 (dd, 1H), 2.90–2.75 (m, 1H), 0.85 (t, 3H). Anal. ($C_{20}H_{33}N_3O_3S$), calcd: C, 60.73; H, 8.41; N, 10.62; found: C, 60.85; H, 8.42; N, 10.58.

(2R)-2-Benzyl-3-(imidazol-1-yl)propionyl-L-(4-thiazolyl)-alanine amide of (1R,2S,2'S,3'S)-2-amino-3-cyclohexyl-1-[3'-(ethyl)oxetan-2'-yl]-1-(hydroxy)propane **44e**

To a mixture of *H*-L-(4-thiazolyl)alanine amide of **22** (4.002 g, 10.12 mmol), 1-hydroxybenzotriazole (3.700 g, 27.38 mmol) and acid **26** (2.419 g, 10.51 mmol) in

dimethylformamide (25 mL) at –23 °C was added *N*-methylmorpholine (1.20 mL, 10.9 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.77 mg, 14.5 mmol). After stirring at –23 °C for 2 h and at ambient temperature overnight, the mixture was poured into saturated $NaHCO_3$ solution and extracted into ethyl acetate which was washed with water and brine, and then was dried over Na_2SO_4 and evaporated. Chromatography of the residue on silica gel with 2–3 % methanol in chloroform afforded 5.277 g (88 %) a foam: ^1H NMR ($CDCl_3$) 8.68 (d, 1H), 7.47 (s, 1H), 7.38–7.10 (m, 5H), 7.12 (br d, 1H), 6.98 (s, 1H), 6.93 (d, 1H), 6.87 (s, 1H), 6.13 (br d, 1H), 4.63–4.50 (m, 2H), 4.32 (dd, 1H), 4.22 (dd, 1H), 4.03 (dd, 1H), 3.98 (dd, 1H), 3.92–3.77 (m, 1H), 3.59 (dd, 1H), 3.18 (dd, 1H), 3.02 (dd, 1H), 2.98–2.66 (m, 4H), 0.83 (t, 3H). Anal. ($C_{33}H_{45}N_5O_4S \cdot 0.25H_2O$), calcd: C, 64.73; H, 7.49; N, 11.44; found: C, 64.59; H, 7.59; N, 11.16.

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