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Formal Total Synthesis of the Potent Renin Inhibitor Aliskiren: Application of a SmI_2-Promoted Acyl-like Radical Coupling

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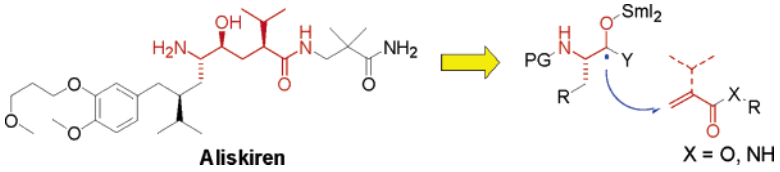

A formal total synthesis of the potent renin inhibitor aliskiren is disclosed exploiting an alternative coupling strategy recently developed by this laboratory for the preparation of the hydroxyethylene isostere-based class of protease inhibitors. The thioester derivative of the amino acid representing the C5−C9 fragment of the aliskiren carbon skeleton underwent a carbon chain extension via a SmI_2-promoted radical addition to *n*-butyl acrylate. Introduction of the C3-isopropyl group with the correct relative configuration was accomplished via stereoselective reduction of the obtained ketone with concomitant lactonization, followed by an aldol reaction with acetone. Further functional group and protecting group manipulation culminated in a formal total synthesis of aliskiren in 10 steps from the corresponding fully protected non-natural amino acid.

Introduction

Aspartic proteases (aspartic endopeptidases) comprise one of the four primary classes of peptide cleaving enzymes, exploiting two aspartic acid residues for their catalytic activity with the direct participation of a lytic water molecule.[1−6] These enzymes play an important role in the regulation of a variety of physiological processes such as digestion (pepsin),[7] the control of blood pressure (plasma renin),[8] and the degradation of endocytosed peptides (lysosomal cathepsin D).[9] Furthermore, they are responsible for acute disease propagation caused either by parasites such as malaria (plasmepsin),[10] viruses, including HIV (HIV protease),[11] opportunistic fungi infections in AIDS patients (secreted aspartic protease from *Candida albicans*),[12] or neurodegenerative disorders such as Alzheimer's disease (β- and γ-secretase).[13] Enormous efforts have therefore been undertaken to develop selective inhibitors as therapeutic agents for the treatment of disorders linked to the involvement of aspartic proteases.[14,15] As illustrated by compounds **1**−**4** in Figure 1, the hydroxyethylene isostere constitutes an important structural entity of many successful and potent aspartic protease inhibitors,[16−20] replacing the scissile bond in the specific dipeptide portion of the substrate undergoing amide hydrolysis. This subunit mimics the tetrahedral intermediate in the enzyme-

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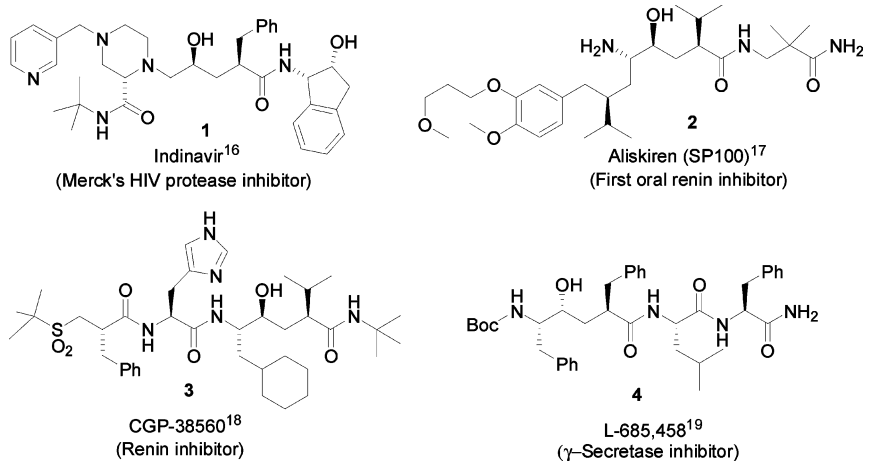

FIGURE 1. Some prominent protease inhibitors featuring the hydroxyethylene isostere moiety.

mediated cleavage with the hydroxyl group interacting with the aspartic acid side chains through hydrogen bonding.[14,15]

While renin represents a key player in the renin−angiotensin system for controlling blood volume, arterial pressure, and cardiac and vascular function, its manipulation also provides a means for the therapeutic treatment of hypertension and heart failure.[21,22] Renin is secreted by the kidney in response to a decrease in circulating volume and blood pressure and cleaves the substrate angiotensinogen to form the inactive angiotensin I. Angiotensin I is converted to the active angiotensin II by angiotensin converting enzyme (ACE). Interestingly, the first inhibitors containing a hydroxyethylene isostere reported were developed in 1982 for the purpose of inhibiting renin.[23] While many drug candidates in the subsequent years were identified displaying potent in vitro and in vivo activity, their application as new antihypertensive agents was abandoned due to inadequate oral bioavailability properties (low stability, poor solubility).[24] Furthermore, compared to the ACE targeting drugs, renin inhibitors require interaction with additional subsites for tight binding resulting in the requirement of higher molecular weight compounds and hence non-cost-effective syntheses. Nevertheless, in contrast to renin, ACE is implicated in alternative pathways and its inhibition therefore results in side effects (cough, angioneurotic edema).[25]

To improve the unfavorable pharmacokinetic behavior of earlier peptide-like renin inhibitors, a combination of molecular modeling and crystallographic structural analyses were employed by a team of Novartis chemists to design a new class of hydroxyethylene-based renin inhibitors lacking the peptide backbone.[18] Out of this intensive study, the nonpeptidic compound, aliskiren (Figure 1), successfully emerged as a potent renin modulator, exhibiting sub-nanomolar binding affinity to human renin and oral administration properties.[26] This compound is now

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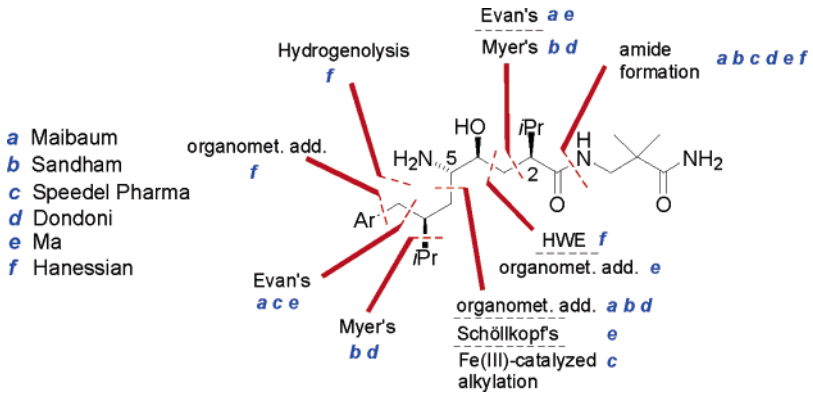
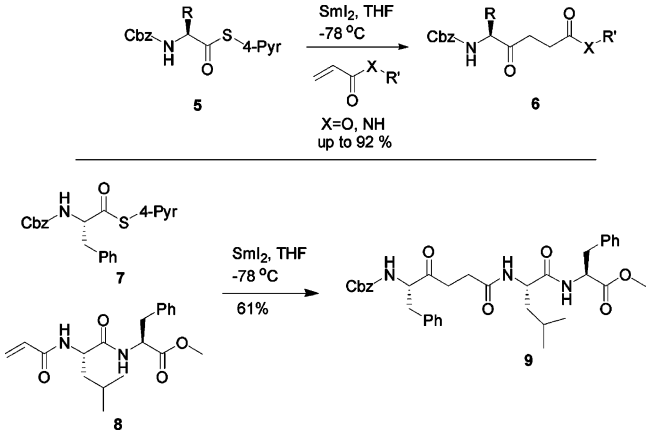


FIGURE 2. Previous coupling strategies employed for the synthesis of aliskiren.

nearing completion of Phase III clinical studies and holds great promise as the first marketable renin inhibitor. Since its discovery a number of synthetic approaches to the preparation of aliskiren or the generic structure represented by its tetrasubstituted 8-aryloctanoic acid amide framework have been undertaken. The key bond disconnections and coupling reactions for each of these syntheses are depicted in Figure 2. Three of these originate from Novartis, of which two led by Maibaum[27] and Sandham[28] rely on asymmetric enolate alkylations for the installation of the appropriate alkyl appendages at C2 and C7 and an ensuing organometallic addition step to secure the 8-aryloctanoic acid backbone. An alternative approach from Speedel Pharma exploits two asymmetric catalytic transformations and an Fe(III)-mediated C−C bond-forming reaction.[29] From academia, Dondoni[30] and Ma[31] have separately reported modified versions of the Maibaum and Sandham syntheses. A conceptionally different route to the generic structure of aliskiren was published by Hanessian and co-workers relying on the use of L-pyroglutamate as a chiral template and exploiting internal induction to install stereoselectively the required functionality.[32] Herein, we report full details of our synthetic endeavors directed to accessing aliskiren via an alternative coupling strategy which assembles the carbon backbone of the hydroxyethylene isostere unit in a unique two step protocol involving our recently disclosed SmI_2-mediated radical addition reaction followed by a simple diastereoselective reduction step.[33−37] Our interest in

SCHEME 1. Example of a Coupling Reaction with SmI_2 and 4-Pyridylthioesters



examining the generality of this synthetic approach to accessing a variety of the hydroxyethylene-based class of protease inhibitors (Figure 1) coupled with the structural complexity of aliskiren suggested this compound would represent a worthy opponent to evaluate the efficacy and flexibility of the synthesis plan.

Results and Discussion

Synthesis Plan. In 2003, we reported the ability of thioester-functionalized amino acids to effectively undergo a samarium diiodide promoted radical addition to activated alkenes such as acrylamides and acrylates affording products akin to a formal acyl radical addition (Scheme 1).[33] As rapid decarbonylation of acyl radical generated from amino acid precursors precedes the radical addition step, this unexpected observation suggested that an alternative mechanism involving a ketyl-like radical anion is operating for the low-valent lanthanide-mediated C−C bond-forming reactions. The γ-keto amides and esters generated from this coupling step represent products of high synthetic value requiring only a simple stereoselective reduction of the ketone functionality in order to access the targeted hydroxyethylene dipeptide isosteres. We have demonstrated the adaptability of such a synthetic route to structures acquainted with many aspartic protease inhibitors.[35] For example, Scheme 1 illustrates rapid access to **9**, a compound possessing a similar structure to the γ-secretase inhibitor **4**.[33] This pivotal C−C bond forming reaction therefore represents a potential key synthetic step for accessing the entire carbon skeleton of aliskiren.

A truncated retrosynthetic analysis of aliskiren with the above considerations is illustrated in Scheme 2. The C3−C4 bond of

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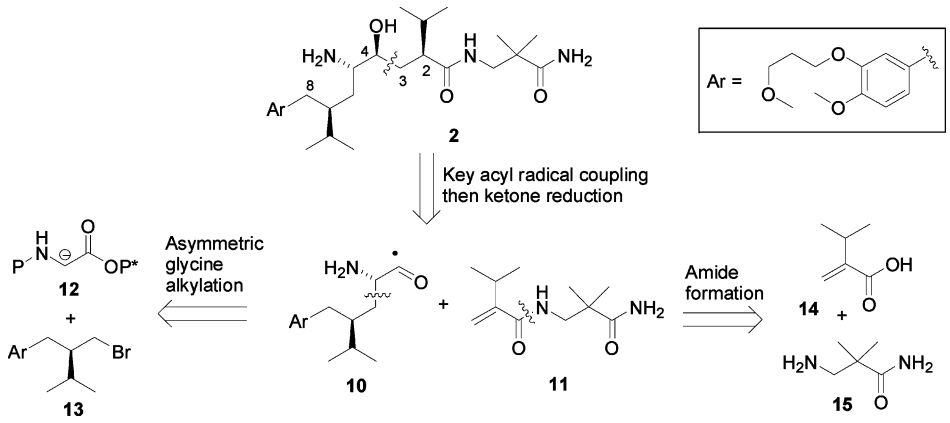
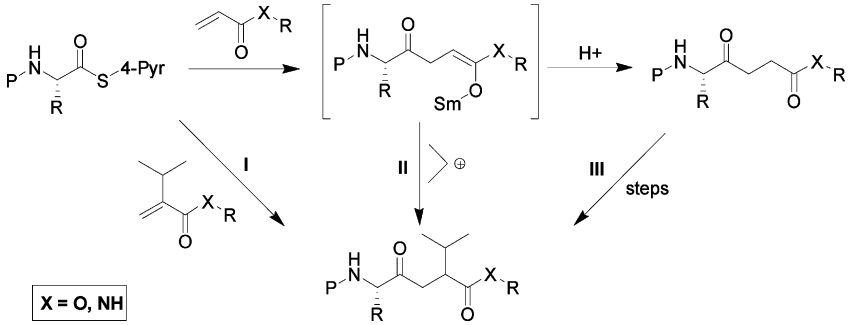
SCHEME 2. Retrosynthetic Considerations of Aliskiren



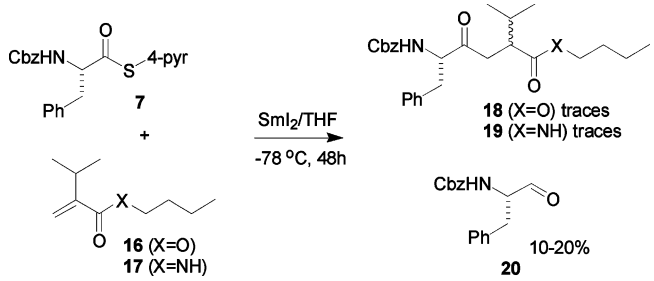
SCHEME 3. Possible Approaches to Installing the α-Isopropyl Group



the 8-aryloctanoic acid skeleton was envisaged to be assembled in a highly convergent fashion by the addition of two fully functionalized subunits, the acyl radical **10** and the acrylamide **11**. Alternatively, an acrylate derivative could also operate as the radical acceptor with the amide moiety installed later in the synthesis. Placing our major disconnection at the common hydroxyethylene unit should introduce flexibility into the synthesis, which would in turn facilitate access to new analogues. The acyl radical equivalent **10** required from this disconnection could be prepared from the corresponding non-natural amino acid, itself synthesized by asymmetric alkylation of a chiral glycine equivalent **12** with the known alkyl bromide **13**. The application of this non-natural amino acid was expected to complement our earlier studies with naturally occurring amino acids. Achieving high stereochemical control at C2 was nevertheless a major concern which was addressed from the outset of this synthetic project. In our earlier work with the thioester addition reactions, the influence of α-methyl substitution on the acrylamide was examined, but 1,4-stereocontrol in those cases was only modest.[33] Although the steric bulk of the isopropyl side group could reinforce any stereochemical preferences in the enolate protonation step (Scheme 3, approach **I**), options were nevertheless required in the event of an unsuccessful outcome such as low or incorrect selectivity. Theoretically, the stereoselective introduction of the C2-alkyl appendage could also be accomplished at two other stages, namely during the radical addition step (approach **II**) through the trapping of the putative enolate intermediate resulting from the second electron transfer or after (approach **III**) via internal induction from a cyclic lactone enolate intermediate.[38]

Model Studies. The model study for approach **I**, whereby the isopropyl side chain had already been installed prior to the coupling reaction, is shown in Scheme 4. Acrylate **16** was prepared in two steps from *n*-butyl acetoacetate using published

SCHEME 4. Approach I Model Study



procedures[39] and was converted to acrylamide **17** via basic hydrolysis followed by an EDCI promoted amide coupling with *n*-butylamine. The key coupling reactions were then carried out according to earlier work by subjecting a THF solution of the acrylate or acrylamide combined with the 4-pyridylthioester of Cbz-protected phenylalanine **5** (1.5 equiv) to 3.3 equiv of SmI_2 for 3 days at −78 °C. Regrettably, concerns about the stereoselectivity of this reaction were unwarranted as the coupling products were not observed. Instead significant amounts of unreacted starting materials were obtained together with a

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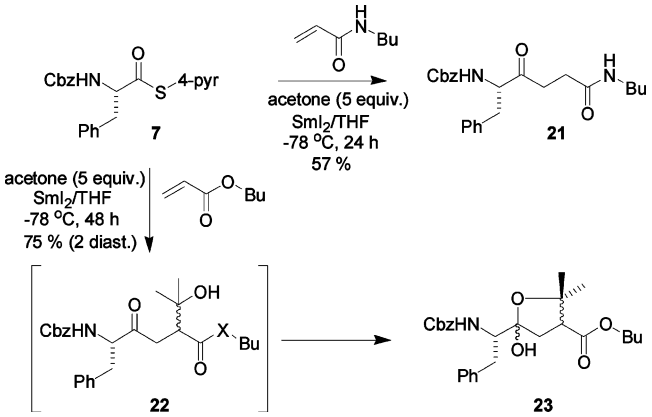
SCHEME 5. Approach II Model Study



10−20% yield of the aldehyde **20**. Increasing the number of equivalents of the radical acceptor or the reaction time did not improve the outcome.[40] Thus, the normal addition pathway appears to be critically slowed by steric hindrance of the isopropyl group. As such, the proposed ketyl radical intermediate may resort to alternative routes including either a hydrogen abstraction step or reduction by SmI_2 followed by protonation with the formation of the aldehyde as the end result.

Turning to approach **II** (Scheme 5), we explored the possibility of introducing the isopropyl side chain during the coupling reaction by trapping the proposed samarium(III) enolate intermediate with acetone followed by a deoxygenation step. Such sequential radical-anionic reactions promoted by SmI_2 have literature precedence including the use of acetone as the coupling reagent.[37] Hence, attempts were performed to couple the thioester **7** to *n*-butyl acrylamide in the presence of 5 equiv of acetone. Although the radical reactions proceeded as planned, quite unexpectedly none of the desired alkylated product could be isolated, and only the unalkylated product **21** was formed. Internal protonation from the amide group was likely the culprit, yet we have previously trapped samarium(III) glycine enolates with either ketones or aldehydes without major intervention of this protonation pathway.[41] In stark contrast, when *n*-butyl acrylate was used the enolate intermediate could be trapped, prompting the suggestion that an internal proton transfer was indeed the problem with the reactions featuring the acrylamide. The resulting alkylated product **22** undergoes ring closure and was isolated as its hemiacetal form **23** in a good 74% yield. This structure represents a ring constrained γ-hydroxyester and may therefore be a useful precursor to a new class of potential protease inhibitors. It was interesting to note that only two isomers dominated from the possible four, though unfortunately we have been unable to establish which of these has formed, due to problems regarding separation of the isomers. Attempts to react hemiacetal **23** further by accessing its ketone form were unsuccessful. For example, subjecting the hemiacetal to reduction in order to produce the corresponding diol was unsuccessful when using either (*S*)-Alpine Hydride or $NaBH_4$. We attribute the low reactivity of **23** to a *gem*-dimethyl effect bestowing a marked stability to the hemiacetal form. Therefore, we were prompted to explore approach **III**, introducing the isopropyl group at a later stage in the synthesis.

In approach **III**, a diastereoselective ketone reduction step is required with concomitant lactone formation. Other researchers have demonstrated the ability of chiral γ-butyrolactones to undergo stereoselective α-alkylation with good 1,4-asymmetric induction,[38] making these compounds common precursors to the hydroxyethylene isosteres.[20,38] To this end, we next initiated a short study regarding the stereoselective reduction of γ-keto esters **24a**−**e** with concomitant cyclization to γ-butyrolactones as shown in Table 1. A series of γ-keto esters were synthesized as recently reported by us,[36] via reaction of the 4-pyridylthioesters of Cbz-protected amino acids **5** with SmI_2, in the presence of *tert*-butyl alcohol and either methyl or *n*-butyl acrylate at −78 °C in yields ranging from 40 to 80%.

Ketone reduction with (*S*)-Alpine Hydride[42a] (entries 1, 3, 4, 5, and 7) generally proceeded rapidly at −78 °C in THF affording excellent stereoselectivity for the (*S*)-stereoisomer, and the intermediates then slowly reacted further overnight at −78 °C to give the desired lactones **26**. Generally, the methyl esters (entries 3, 5, and 7) underwent conversion to the lactone faster than the corresponding *n*-butyl esters (entries 1 and 4). To gain access to the complementary (*R*)-stereoisomer, Luche reduction conditions ($NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH) were also examined (entries 2, 6, and 8).[42b] The selectivities were lower and, with the exception of the γ-ketone derived from alanine (entry 6), reactions ceased at the alcohol stage. In all cases the intermediate alcohol could be separated from the more polar lactone upon purification by column chromatography. Conversion of any intermediate alcohols **25** to the desired lactones could be readily promoted by treatment with NaH in THF in excellent yields (entries 2 and 6). Assignment of stereochemistry is based on the extensive reduction results obtained by other researchers.[38c, 42]

With these successful reduction studies terminated, we then proceeded to complete the model study as planned in approach III (Scheme 6). Introduction of the C2-isopropyl group proceeded by deprotonation of lactone **26a** with LiHMDS, and then reaction with excess acetone generated the alkylated product **27** in excellent yield and diastereoselectivity (91%, dr 20:1), which is expected to favor the least hindered side of the lactone ring affording the trans product.[38e] Removal of the unwanted hydroxyl group was achieved by its initial elimination, easily accomplished by reaction with PCl_5, giving an 8:1 mixture of regioisomers in favor of the terminal isomer **28**. Finally, completion of the hydroxyethylene isostere core was realized, by first ring opening the lactone using *n*-butylamine and $AlMe_3$[20d,43] providing amide **29** in a 55% yield, followed by a simultaneous reduction of the double bond and removal of the Cbz protection group affording **30** upon subjection to hydrogenation conditions. The unoptimized yield of 55% for the ring opening step, was attributed to two undesired, though not surprising, competing reactions. Evidence of rearrangement of the double bond into conjugation with the amide carbonyl, and of further reaction of the product alcohol with the Cbz protecting group furnishing an oxazolidinone, were both observed within the minor byproducts formed under the conditions required for the reaction.

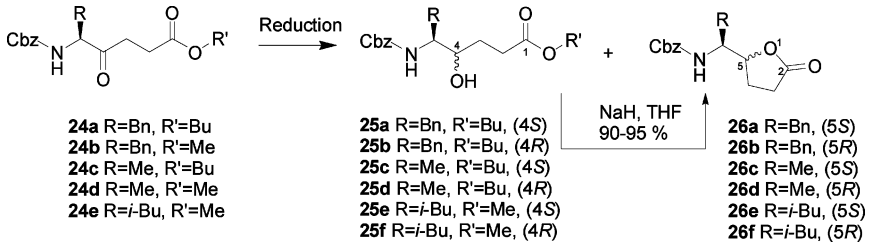
(40) We have previously observed the formation of aldehyde products in attempts to couple amino acid thioesters with more sterically demanding side chains (ref 36).

(41) (a) Ricci, M.; Madariaga, L.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 242. (b) Ricci, M.; Blakskjær, P.; Skrydstrup, T. *J. Am. Chem. Soc.* **2000**, *122*, 12413. (c) Blakskjær, P.; Gavrila, A.; Andersen, L.; Skrydstrup, T. *Tetrahedron Lett.* **2004**, *45*, 9091.

(42) Asymmetric reduction of α-amino ketones is comprehensively covered in: (a) Våbenø, J.; Brisander, M.; Lejon, T.; Luthman, K. *J. Org. Chem.* **2002**, *67*, 9186. (b) Hoffman, R. V.; Maslouh, N.; Cervantes-Lee, F.; *J. Org. Chem.* **2002**, *67*, 1045.

(43) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *18*, 4171.

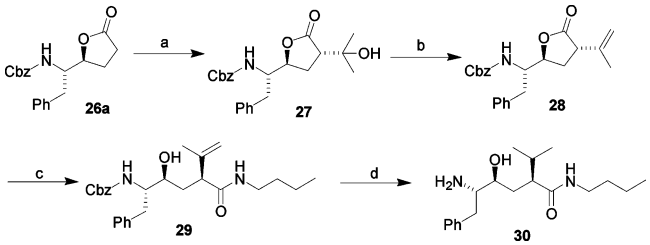
TABLE 1. Ketone Reduction Studies



entry	substrate	reductant	*S*/*R*	alcohol (yield, %)	lactone (yield, %)
1	**24a**	(*S*)-Alpine Hydride	10:1	**25a** (19)	**26a** (79)
2	**24a**	$NaBH_4$, $CeCl_3$	1:4	**25a** (13), **25b** (81)	**26b** (91)[a]
3	**24b**	(*S*)-Alpine Hydride	10:1		**26a** (95)
4	**24c**	(*S*)-Alpine Hydride	10:1	**25c** (15)	**26c** (59)[b]
5	**24d**	(*S*)-Alpine Hydride	10:1		**26c** (93)
6	**24d**	$NaBH_4$, $CeCl_3$	1:4		**26c** + **26d** (87)
7	**24e**	(*S*)-Alpine Hydride	10:1		**26e** (88)
8	**24e**	$NaBH_4$, $CeCl_3$	2:5	**25e** + **25f** (84)	**26f** (66),[a] **26e** (25)[a]

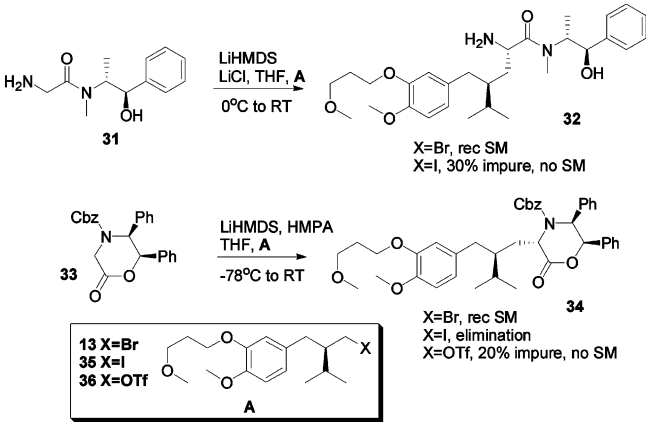
[a] Lactone derived from reaction of alcohol **25** with NaH. [b] Unoptimized yield.

SCHEME 6. Approach III Model Study[a]



[a] Reagents and conditions: (a) LiHMDS, THF, −78 °C, 2 h, then acetone, 91%, dr = 20:1; (b) PCl_5, CH_2Cl_2, −78 °C, 88%, term/conj = 8:1; (c) *n*-$BuNH_2$, $Al(CH_3)_3$, CH_2Cl_2, 20 °C, 55%; (d) Pd/C/H_2, EtOH, 94%.

SCHEME 7. Asymmetric Alkylation of Glycine Enolates



Formal Total Synthesis of Aliskiren. With our successful model study in hand, we next moved toward the total synthesis of aliskiren. For this the corresponding non-natural amino acid was required, envisaged to be prepared by asymmetric alkylation of a chiral glycine equivalent with the bromide **13** previously prepared by Maibaum and co-workers in eight steps.[44] Although the same researchers converted the bromide to the requisite amino acid exploiting Schöllkopf's methodology, we chose to initially examine other perhaps more direct alternatives described by Williams and Myers (Scheme 7).

Initially, the pseudoephedrine amide of glycine **31** was reacted according to procedures outlined by Myers et al.[45] While repeating Myers' chemistry was effective in our hands with reactive bromides such as BnBr, bromide **13** was recovered unreacted under identical conditions even after prolonged reaction times. When the corresponding iodide **35** was examined, alkylation did proceed in 38% yield; however, the product **32** was difficult to purify which subsequently interfered with the establishment of the stereoselectivity of this reaction. Furthermore, reduction of the iodide was a major competing reaction furnishing the corresponding alkane in 56% yield. As an alternative, the cyclic glycine auxiliary **33** developed by Williams et al.[46] was also studied. Once again, good results could only be obtained when using reactive electrophiles. When unactivated electrophiles, such as bromide **13**, iodide **35**, or triflate **36** were used, the coupling step proved unrewarding. Thus we reasoned it was necessary to apply the Schöllkopf methodology[47] as reported by the Novartis group,[44] suspecting that they may have reached this conclusion in a similar manner (Scheme 8). Coupling of the bis-lactim **37** with bromide **13** then afforded **38** in an excellent yield (90%) and with a high diastereomeric ratio (98:2). Acidic hydrolysis of the bis-lactim auxiliary followed by Cbz protection under standard conditions afforded the fully protected nonnatural amino acid **40**.[48] Ester hydrolysis provided the free acid **41**, which was then coupled with 4-mercaptopyridine using EDCI to give the required thioester **42** in excellent yield, with no evidence of any α-epimerization. Reaction of the thioester with either methyl or *n*-butyl acrylate in the presence of SmI_2 and *t*-BuOH proceeded slowly, but gave the methyl and butyl γ-keto esters **43** and **44** respectively in satisfactory yields of 60−70% after

(44) Goeschke, R.; Stutz, S.; Heinzelmann, W.; Maibaum, J. *Helv. Chim. Acta* **2003**, *86*, 2848.

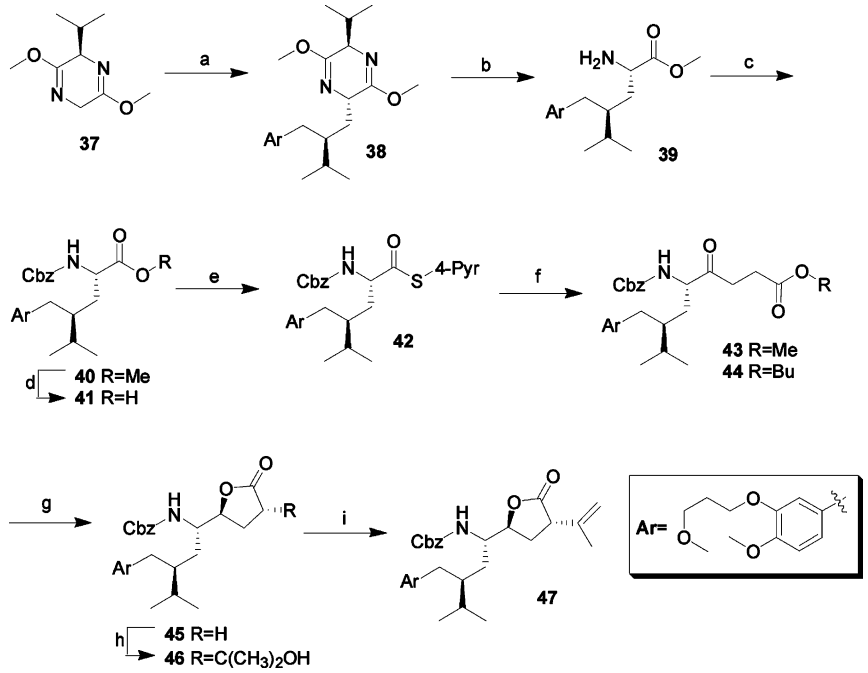
(45) (a) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656. (b) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496. (c) Myers, A. G.; Schnider, P.; Kwon, S.; Kung, D. W. *J. Org. Chem.* **1999**, *64*, 3322.

(46) (a) Williams, R. M.; Im, M. N. *J. Am. Chem. Soc.* **1991**, *113*, 9276. (b) Williams, R. M. *Aldrichim. Acta* **1992**, *25*, 15.

(47) (a) Schoellkopf, U.; Westphalen, K. O.; Schroeder, J.; Horn, K. *Liebigs Ann. Chem.* **1988**, 781. (b) Schoellkopf, U.; Groth, U.; Deng, C. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 798. (c) Bull, S. D.; Davies, S. G.; Moss, W. O. *Tetrahedron: Asymmetry* **1998**, *9*, 321.

(48) Previous experience within this group has shown that the Cbz group is sterically better tolerated in the SmI_2 coupling reaction than the corresponding Boc group thus dictating its choice here (refs 33 and 36).

SCHEME 8. Synthesis of Advanced Lactone Intermediate[a]



[a] Reagents and conditions: (a) *n*-BuLi, THF, −75 °C, then **9** −75 to −18 °C, 90%; (b) HCl, H_2O, CH_3CN, 99%; (c) CbzCl, pyridine, CH_2Cl_2, 88%; (d) NaOH (2 M), THF, MeOH, 100%; (e) EDCI, 4-mercaptopyridine, CH_2Cl_2, 0 °C, 97%; (f) SmI_2, *t*-BuOH, −78 °C, 6 d, methyl acrylate, 67%, or butyl acrylate, 60%; (g) (*S*)-Alpine Hydride, THF −78 °C, 91%, dr = 4:1; (h) LiHMDS, THF, −78 °C, 2 h, then acetone, 97%, dr = 5:1; (i) PCl_5, CH_2Cl_2, −78 °C, 99%, term/conj = 8:1.

6 days at −78 °C. It was gratifying that such a large amino acid side chain was tolerated in this radical coupling step, as we earlier had found that sometimes even small steric hindrances (such as with the 4-pyridylthioesters of Cbz-valine or Boc-leucine, for example) can halt the reaction completely.[36] Reduction of compound **43** to lactone **45** using (*S*)-Alpine Hydride proceeded in high yield; however, the diastereoselectivity was somewhat lower (4:1) when compared with the model study starting from phenylalanine, which we have tentatively assigned a (5*S*) stereochemistry based on earlier results. This is consistent with a mismatched case, where the substrate directs reduction toward the undesired face and the larger side chain exacerbates that effect. Nevertheless, separation of isomers could be achieved by careful column chromatography on silica gel. Alkylation with LiHMDS and acetone as before gave **46** in excellent yield, but with a decreased selectivity (5:1) as an inseparable mixture of isomers. Finally elimination of the tertiary alcohol with PCl_5 as described above supplied us with the advanced intermediate **47** displaying a selectivity of 8:1 for the terminal/conjugated regioisomers. Completion of the formal total synthesis of **2** is illustrated in Scheme 9. Attempts to ring open lactone **47** directly with amines as per the model study were met with failure, leading instead to rearrangement of the double bond into conjugation and/or product decomposition. For this reason, the same lactone was subjected to Pd/C under H_2 which both reduced the double bond and removed the Cbz protecting group providing the free amine **48**. Reprotection of the amine as the more stable Boc carbamate then gave a readily separable 4:1 mixture of lactones **49** and **54**. The major isomer **49** responded to ring opening conditions more predictably, for example reaction with *n*-butylamine and $AlMe_3$ in dichloromethane at 20 °C produced the simplified aliskiren analogue **50** in a 58% yield. Lactone **49** has been previously converted to aliskiren by Ma et al.[31] via lactone amidation and deprotection thereby completing a formal total synthesis of the renin inhibitor. Amine **48** is also readily transformed into the known lactone **52** through a reductive alkylation with benzaldehyde and $NaBH_4$. This same lactone represents a late stage intermediate in the total synthesis of the aliskiren reported by Dondoni et al.[30]

Access to the C2-epimer of the simple aliskiren analogue **50** was likewise possible by base-catalyzed isomerization of the double bond of lactone **47** into conjugation. The corresponding conjugated alkene in **51** can thus be reduced selectively[38e] affording lactone **54** after Boc protection, with inverted stereochemistry at C2. Ring opening with *n*-butylamine and $AlMe_3$ proceeded as with the lactone **49** generating C2-epimer **55**.

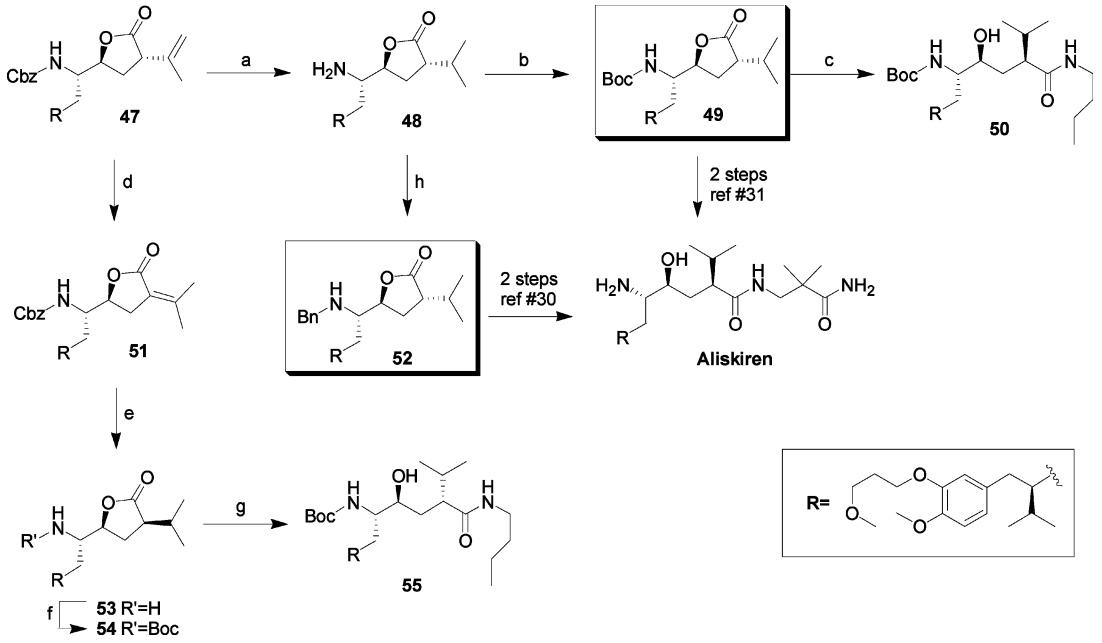
Conclusions

We have achieved our objective of applying a SmI_2-promoted acyl-like radical addition reaction between an amino acid thioester and an activated alkene as a key step to the formal synthesis of the potent renin inhibitor, aliskiren. Although this synthesis does not compete with the industrial preparation of aliskiren, it does provide a relevant example on the use of this coupling methodology for accessing an important intermediate in the synthesis of hydroxyethylene isosteres, the functionalized γ-lactone, in only two steps from an amino acid thioester. Work is now underway to identify conditions which permit the radical-based C−C bond-forming step to be performed with α-branched acrylates and acrylamides as well as studying stereochemical issues. A successful venture in this direction would provide a rapid and general approach to this class of hydroxyethylene dipeptide isosteres.

Experimental Section

Butyl 5-((1*S*)-1-Benzyloxycarbonylamino-2-phenylethyl)-5-hydroxy-2,2-dimethyltetrahydrofurancarboxylate (23). The thioester **7** (177 mg, 0.45 mmol) was dissolved in anhydrous THF

SCHEME 9. Formal Total Synthesis of Aliskiren[a]



[a] Reagents and conditions: (a) Pd/C/H_2, EtOH, 99%; (b) Boc_2O, NEt_3, THF, 83%; (c) $AlMe_3$, *n*-$BuNH_2$, CH_2Cl_2, 58%; (d) pyridine, NEt_3, 80 °C, CH_2Cl_2, 89%; (e) Pd/C/H_2, EtOH, 90%, dr = 10:1; (f) Boc_2O, NEt_3, THF, 81%; (g) $AlMe_3$, *n*-$BuNH_2$, CH_2Cl_2, 48%.

(5 mL) and the flask flushed with argon for 10 min. *n*-Butyl acrylate (144 μL, 1.35 mmol) and acetone (165 μL, 2.25 mmol) were added, and then the mixture was cooled to −78 °C before a 0.1 M solution of SmI_2 (15 mL, 1.50 mmol) was added via syringe. The mixture was stirred at −78 °C for 2 d, the flask flushed with O_2 before satd NH_4Cl solution (2 mL) was added, and the mixture warmed to rt. The mixture was poured into 0.5 M HCl (40 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (10−50% EtOAc in pentane as eluant), which gave **23** (R_f = 0.50−0.60, 30% EtOAc in pentane) (156 mg, 0.332 mmol, 74%) as a colorless oil as an inseparable 1:1 mixture of diastereoisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.10−7.40 (m, 10H), 5.87 (br s, $^1/_2$H), 5.56 (br s, $^1/_2$H), 4.85−5.09 (m, 3H), 3.93−4.18 (m, 3H), 3.10−3.37 (m, 2H), 2.09−2.89 (m, 3H), (m, 2H), 1.67−1.60 (m, 2H), 1.54 (s, $1^1/_2$H), 1.26−1.43 (m, 2H), 1.35 (s, $1^1/_2$H), 1.35 (s, $1^1/_2$H), 1.10 (s, $1^1/_2$H), 0.95 (t, J = 7.2 Hz, $1^1/_2$H), 0.94 (t, J = 7.2 Hz, $1^1/_2$H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.3, 171.6, 156.4, 138.9−126.2 (multiple peaks, 24C), 106.8, 105.4, 85.0, 84.2, 66.8, 66.5, 65.7, 64.8, 60.7, 59.2, 52.9, 52.3, 39.9, 38.5, 37.9, 37.1, 30.9, 30.8, 30.7, 30.6, 25.9, 24.4, 19.3, 19.2, 13.8, 13.7; HRMS $C_{27}H_{35}NO_6$ [M + Na^+] calcd 492.2362, found 492.2362.

Phenylmethyl [(1*S*)-2-Phenyl-1-[(2*S*)-tetrahydro-5-oxo-2-furanyl]ethyl]carbamate (26a).[38c] The γ-keto ester **24a** (40 mg, 0.0972 mmol) was dissolved in THF (10 mL), and then the solution was cooled to −78 °C before the addition of (*S*)-Alpine Hydride (0.5 mL, 0.25 mmol, 0.5 M in THF). The mixture was stirred at −78 °C for 3 h, en satd NH_4Cl solution (5 mL) was added, and the mixture was warmed to rt before being poured into water (30 mL) and extracted with EtOAc (3 × 15 mL). The combined organics were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (10−40% EtOAc in pentane as eluant), which gave lactone **26a** (R_f = 0.45, 35% EtOAc in pentane) (26 mg, 0.0766 mmol, 79%) as an oil, and the intermediate alcohol **25a** (R_f = 0.60, 35% EtOAc in pentane) (8 mg, 0.019 mmol, 20%) as a white solid. **26a**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.20−7.40 (m, 10H), 5.07 (AB system, J = 12.0 Hz, 2H), 4.98 (d, J = 9.6 Hz, 1H), 4.48 (t, J = 7.2 Hz, 1H), 4.08 (q, J = 8.8 Hz, 1H), 2.95 (AB system d, J = 15.2, 7.2 Hz, 2H), 2.47 (t, J = 8.4 Hz, 2H), 2.03−2.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 177.0, 156.5, 136.9, 136.2, 129.3 (2C), 128.7 (2C), 128.5 (2C), 128.1, 127.9 (2C), 126.8, 79.7, 67.0, 54.7, 39.2, 28.6, 24.0; HRMS $C_{20}H_{21}NO_4$ [M + Na^+] calcd 362.1368, found 362.1361.

Phenylmethyl [(1*S*)-2-Phenyl-1-[(2*S*,4*R*)-tetrahydro-4-(1-hydroxy-1-methylethyl)-5-oxo-2-furanyl]ethyl]carbamate (27). The lactone **26a** (59 mg, 0.174 mmol) was dissolved in THF (7.5 mL) and the mixture cooled to −78 °C. LiHMDS (0.40 mL, 0.40 mmol, 1.0 M in hexanes) was added and the mixture stirred for 80 min before the addition of acetone (0.15 mL, 2.04 mmol). The mixture was stirred for an additional 90 min, then satd NH_4Cl (aq) (5 mL) was added and the mixture allowed to warm to rt. The mixture was poured into water (30 mL) and extracted with EtOAc (3 × 15 mL), and then the combined organics were dried (Na_2SO_4), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (5:5:2−0:1:1 pentane/CH_2Cl_2/Et_2O as eluant), which gave compound **27** (R_f = 0.20, 1:1:1 pentane/CH_2Cl_2/Et_2O) (60 mg, 0.151 mmol, 87%) as an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.18−7.40 (m, 10H), 5.05 (s, 2H), 5.00 (d, J = 9.6 Hz, 1H), 4.50 (dd, J = 8.4, 4.4 Hz, 1H), 4.05−4.15 (m, 1H), 3.08 (br s, 1H), 2.91 (d, J = 8.0 Hz, 2H), 2.66 (dd, J = 10.4, 8.0 Hz, 1H), 2.27 (td, J = 12.4, 4.8 Hz, 1H), 2.05−2.17 (m, 1H), 1.24 (s, 3H), 1.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 178.6, 156.6, 136.8, 136.1, 129.2 (2C), 128.7 (2C), 128.5 (2C), 128.2, 127.9 (2C), 126.8, 78.3, 71.4, 67.0, 55.7, 49.9, 38.8, 27.6, 27.2, 22.8; HRMS $C_{23}H_{27}NO_5$ [M + Na^+] calcd 420.1787, found 420.1782.

Phenylmethyl [(1*S*)-2-Phenyl-1-[(2*S*,4*R*)-tetrahydro-4-isopropenyl-5-oxo-2-furanyl]ethyl]carbamate (28). The alcohol **27** (55 mg, 0.138 mmol) was dissolved in CH_2Cl_2 (10 mL) and the mixture cooled to −78 °C before PCl_5 (70 mg, 0.336 mmol) in CH_2Cl_2 (3 mL) was added via syringe. The mixture was stirred at −78 °C for 40 min, satd $NaHCO_3$(aq) (5 mL) was added, and the mixture was allowed to warm to rt. The mixture was poured into water (30 mL) and extracted with CH_2Cl_2 (3 × 15 mL), and then the combined organic portions were dried (Na_2SO_4), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (10−20% EtOAc in pentane as eluant), which gave compound **28** (R_f = 0.50, 20% EtOAc in pentane) (46 mg, 0.121 mmol, 88%) as white solid. An 8:1 mixture of terminal:conjugated regioisomers

was evident from ^{1}H NMR spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) terminal regioisomer 7.15−7.38 (m, 10H), 5.07 (s, 2H), 4.93 (s, 1H), 4.90 (br s, 1H), 4.82 (s, 1H), 4.52 (t, J = 7.2 Hz, 1H), 4.10 (q, J = 8.4 Hz, 1H), 3.24 (dd, J = 10.0, 5.6 Hz, 1H), 2.94 (d, J = 7.6 Hz, 2H), 2.28−2.38 (m, 1H), 2.10−2.22 (m, 1H), 1.76 (s, 3H) conjugated regioisomer inter alia 2.21 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.7, 156.5, 140.1, 136.9, 136.2, 129.2 (2C), 128.7 (2C), 128.5 (2C), 128.2, 127.9 (2C), 126.8, 114.0, 78.4, 67.0, 55.0, 47.6, 39.2, 29.8, 20.6; HRMS $C_{23}H_{25}NO_4$ [M + Na^+] calcd 402.1681, found 402.1670.

(2*R*,4*S*,5*S*)-(1-Methyl-2-ethenyl)hydroxy[(phenylmethoxy)-carbonyl]amino-6-phenylhexanoic Acid *N*-Butylamide (29). *n*-Butylamine was dissolved in CH_2Cl_2 (2 mL), and then trimethylaluminum (0.4 mL, 0.80 mmol) was added. The mixture was stirred at rt for 15 min and then transferred via syringe to a solution of the lactone **28** (46 mg, 0.121 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at rt for 3 h, poured directly into 0.5 M HCl (30 mL), and extracted with CH_2Cl_2 (3 × 15 mL), and then the combined organics were dried (Na_2SO_4), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (1:2:2−1:1:0 Et_2O/CH_2Cl_2/pentane as eluant), which gave compound **29** (R_f = 0.35, 1:1:1 pentane/CH_2Cl_2/Et_2O) (30 mg, 0.0663 mmol, 55%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.10−7.35 (m, 10H), 5.75 (br s, 1H), 5.25 (d, J = 9.2 Hz, 1H), 5.05 (AB system, J = 13.6 Hz, 2H), 4.90 (s, 1H), 4.85 (s, 1H), 3.88 (br s, $^1/_2$H), 3.79 (q, J = 8.0 Hz, 1H), 3.66 (br s, 1H), 3.06−3.25 (m, 3H), 2.91 (d, J = 7.6 Hz, 2H), 1.75−1.90 (m, 2H), 1.68 (s, 3H), 1.32−1.45 (m, 2$^1/_2$H), 1.20−1.32 (m, 2H), 0.89 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.3, 156.6, 143.7, 138.3, 136.8, 129.3 (2C), 128.5 (2C), 128.4 (2C), 128.0, 127.8 (2C), 126.3, 114.0, 68.6, 66.5, 56.5, 50.9, 39.3, 38.9, 34.7, 31.4, 21.1, 20.0, 13.7; HRMS $C_{27}H_{36}N_2O_4$ [M + Na^+] calcd 475.2573, found 475.2585.

(2*R*,4*S*,5*S*)-Isopropylhydroxyamino-6-phenylhexanoic Acid *N*-Butylamide (30). The alkene **29** (15 mg, 0.0331 mmol) was dissolved in MeOH (2 mL), and then $PdCl_2$ (6 mg, 0.338 mmol) was added. The mixture was stirred under an atmosphere of H_2 for 18 h, and then the flask was flushed with N_2 before the mixture was filtered through Celite and the solids were washed with MeOH (3 × 3 mL). The filtrates were evaporated to dryness in vacuo, dissolved in CH_2Cl_2, poured into satd $NaHCO_3$ (25 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organics were dried (Na_2SO_4), filtered, and evaporated in vacuo to give compound **30** (R_f = 0.10−0.35, 20% MeOH in CH_2Cl_2) (10 mg, 0.0312 mmol, 94%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.05−7.26 (m, 5H), 5.74 (br s, 1H), 3.09−3.30 (m, 3H), 2.86 (dd, J = 13.2, 4.0 Hz, 1H), 2.74 (dt, J = 10.0, 4.4 Hz, 1H), 2.39 (dd, J = 13.2, 9.6 Hz, 1H), 2.05 (ddd, J = 11.2, 8.4, 3.2 Hz, 1H), 1.72−1.86 (m, 3H), 1.50 (ddd, J = 13.6, 10.8, 2.8 Hz, 1H), 1.15−1.33 (m, 6H), 0.82−0.90 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.3, 138.8, 129.3 (2C), 128.6 (2C), 126.4, 71.3, 57.2, 51.3, 40.8, 39.0, 35.2, 31.7, 30.5, 21.1, 20.4, 20.1, 13.7; HRMS $C_{19}H_{32}N_2O_2$ [M + Na^+] calcd 321.2542, found 321.2544.

4-(2*S*-Iodomethyl-3-methylbutyl)-1-methoxy-2-(3-methoxypropoxy)benzene (35). Method 1. (2*S*)-2-[4-Methoxy-3-(3-methoxypropoxy)benzyl]-3-methylbutan-1-ol[44] (153 mg, 0.516 mmol) was dissolved in CH_2Cl_2 (16 mL), and then PPh_3 (444 mg, 1.168 mmol) and imidazole (112 mg, 1.168 mmol) were added. After 5 min, iodine (348 mg, 1.32 mmol) was added, and then the mixture was stirred at rt for 16 h before it was poured into satd $Na_2S_2O_3$ solution (30 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (5−20% EtOAc in pentane as eluant), which gave iodide **35** (R_f = 0.5, 10% EtOAc in pentane) (161 mg, 0.396 mmol, 77%) as a white solid. **Method 2.** Bromide **13**[44] (80 mg, 0.223 mmol) was dissolved in acetone, and then NaI (200 mg, 1.334 mmol) was added. The mixture was stirred at rt for 20 h, then poured into water (30 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered and evaporated, which gave iodide **35** (86 mg, 0.212 mmol, 95%) as a white solid requiring no further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.71 (d, J = 8.4 Hz, 1H), 6.68 (d, J = 1.6 Hz, 1H), 6.66 (dd, J = 8.4, 1.6 Hz, 1H), 4.03 (t, J = 6.4 Hz, 2H), 3.76 (s, 3H), 3.50 (t, J = 6.5 Hz, 2H), 3.28 (s, 3H), 3.14 (dd, J = 10.0, 4.8 Hz, 1H), 3.02 (dd, J = 10.0, 4.4 Hz, 1H), 2.69 (dd, J = 13.6, 4.8 Hz, 1H), 2.28 (dd, J = 13.6, 9.6 Hz, 1H), 2.02 (quin., J = 6.4 Hz, 2H), 1.64 (oct., J = 6.8 Hz, 1H), 1.07 (dddt, J = 9.6, 6.8, 4.8, 4.8 Hz, 1H), 0.93 (d, J = 6.8 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.3, 147.8, 132.9, 121.1, 114.1, 111.8, 69.3, 66.0, 58.6, 56.0, 47.5, 36.6, 30.5, 29.5, 19.8, 19.5, 14.3; HRMS $C_{17}H_{27}O_3I$ [M + Na^+] calcd 429.0903, found 429.0906.

Methyl (2*S*,4*S*)-2-[[(Phenylmethoxy)carbonyl]amino]-4-methoxy-3-(3-methoxypropoxy)-γ-(1-methylethyl)benzene pentanoate (40). The free amine **39**[44] (2.043 g, 5.56 mmol) was dissolved in CH_2Cl_2 (35 mL), and then benzyl chloroformate (1.65 mL, 11.59 mmol) was added. Pyridine (0.94 mL) was then added carefully (modest exotherm), before the mixture was stirred at rt for 2 h. The mixture was poured into 0.5 M HCl (100 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo to give an oil. Pure product was obtained by column chromatography (increasing polarity from 10% to 40% EtOAc in pentane as eluant), which gave compound **40** (R_f = 0.45, 35% EtOAc in pentane) (2.468 g, 4.92 mmol, 89%) as a colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.25−7.35 (m, 5H), 6.73−6.77 (m, 2H), 6.66 (d, J = 7.6 Hz, 1H), 5.26 (d, J = 6.4 Hz, 1H), 5.10 (s, 2H), 4.41 (app q, J = 7.2 Hz, 1H), 4.09 (t, J = 6,4 Hz, 2H), 3.81 (s, 3H), 3.69 (s, 3H), 3.55 (t, J = 6.4 Hz, 2H), 3.31 (s, 3H), 2.60 (dd, J = 13.6, 4.8 Hz, 1H), 2.46 (dd, J = 13.6, 7.2 Hz, 1H), 2.0 (p, J = 6.4 Hz, 2H), 1.71 (h, J = 6.4 Hz, 1H), 1.56−1.66 (m, 3H), 0.84 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 173.2, 155.9, 148.1, 147.5, 136.2, 133.4, 128.3 (2C), 127.9, 127.8 (2C), 121.1, 114.3, 111.6, 69.2, 66.7, 65.8, 58.4, 55.9, 52.3, 52.1, 41.8, 36.4, 33.1, 29.5, 27.8, 19.7, 171.1; HRMS $C_{28}H_{39}NO_7$ [M + Na^+] calcd 524.2624, found 524.2603.

(2*S*,4*S*)-2-[[(Phenylmethoxy)carbonyl]amino]-4-methoxy-3-(3-methoxypropoxy)-γ-(1-methylethyl)benzenepentanoic Acid (41). The methyl ester **40** (273 mg, 0.544 mmol) was dissolved in THF (5.6 mL), and then MeOH (5.6 mL) and 2 M NaOH solution (0.7 mL) were added. The mixture was stirred at rt for 3.5 h and then poured into 0.2 M HCl (40 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo giving the crude **41** (264 mg, 0.541 mmol, 99%) as a colorless gum that required no further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.95 (br s, 1H), 7.25−7.36 (m, 5H), 6.65−6.80 (m, 3H), 5.33 (d, J = 8.8 Hz, 1H), 5.11 (s, 5H), 4.40 (td, J = 8.8, 5.2 Hz, 1H), 4.04−4.15 (m, 2H), 3.81 (s, 3H), 3.58 (t, J = 6.4 Hz, 2H), 3.33 (s, 3H), 2.60 (dd, J = 13.6, 5.2 Hz, 1H), 2.48 (dd, J = 13.6, 7.2 Hz, 1H), 2.07 (p, J = 6.4 Hz, 2H), 1.58−1.80 (m, 4H), 0.85 (d, J = 7.2 Hz, 3H), 0.83 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.2, 156.0, 148.1, 147.7, 136.2, 133.4, 128.5 (2C), 128.1 (2C), 127.9, 121.6, 114.4, 111.7, 69.4, 66.9, 65.9, 58.4, 56.0, 52.3, 41.8, 36.2, 33.4, 29.2, 28.2, 19.5, 17.8; HRMS $C_{27}H_{37}NO_7$ [M + Na^+] calcd 510.2468, found 510.2468.

Pyridin-4-yl (2*S*,4*S*)-2-[[(Phenylmethoxy)carbonyl]amino]-4-methoxy-3-(3-methoxypropoxy)-γ-(1-methylethyl)benzenepentanethioate (42). The acid **41** (264 mg, 0.541 mmol) was dissolved in CH_2Cl_2 (10 mL), and then the solution cooled to 0 °C before mercaptopyridine (79 mg, 0.707 mmol) and EDCI (156 mg, 0.816 mmol) were added. The mixture was stirred at 0 °C for 3.5 h, and then the mixture was poured into water (40 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (50−100% EtOAc in pentane as eluant) which gave compound **42** (R_f = 0.25, 50% EtOAc in

pentane) (294 mg, 0.506 mmol, 94%) as a colorless gum: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.52 (d, J = 5.6 Hz, 2H), 7.16−7.32 (m, 7H), 6.68 (d, J = 8.0 Hz, 1H), 6.64 (d, J = 2.0 Hz, 1H), 6.58 (dd, J = 8.0, 2.0 Hz, 1H), 5.43 (d, J = 8.8 Hz, 1H), 5.09 (AB system, J = 12.4 Hz, 2H), 4.35−4.43 (m, 1H), 4.00 (t, J = 6.4 Hz, 2H), 3.74 (s, 3H), 3.47 (t, J = 6.4 Hz,. 2H), 3.24 (s, 3H), 2.39−2.50 (m, 2H), 1.99 (p, J = 6.4 Hz, 2H), 1.50−1.74 (m, 4H), 0.81 (d, J = 6.8 Hz, 3H), 0.76 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 197,2, 155.8, 149.9 (2C), 148.3, 147.7, 138.3, 136.0, 133.0, 128.5 (2C), 128.2, 128.0 (2C), 128.0 (2C), 121.1, 114.3, 111.8, 69.3, 67.2, 65.9, 59.9, 58.5, 55.9, 42.0, 36.5, 33.0, 29.5, 28.6, 19.6, 17.5; HRMS $C_{32}H_{40}N_2O_6S$ [M + Na^+] calcd 603.2505, found 603.2520.

γ-Ketoester 43. The thioester **42** (271 mg, 0.470 mmol) was dissolved in anhydrous THF (7.5 mL) and the flask flushed with argon for 10 min. Methyl acrylate (455 μL, 5.06 mmol) and *tert*-butyl alcohol (112 μL, 1.52 mmol) were added, and then the mixture cooled to −78 °C before a 0.1 M solution of SmI_2 (20 mL, 2.00 mmol) was added via syringe. The mixture was stirred at −78 °C for 2 d and then the flask flushed with O_2 before satd NH_4Cl (aq) (5 mL) was added and the mixture warmed to rt. The mixture was poured into 0.5 M HCl (30 mL) and extracted with EtOAc (3 × 15 mL). The combined organics were washed with satd $Na_2S_2O_3$ solution (20 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (20−50% EtOAc in pentane as eluant), which gave compound **43** (R_f = 0.55, 50% EtOAc in pentane) (167 mg, 0.299 mmol, 64%) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26−7.36 (m, 5H), 6.80 (s, 1H), 6.76 (d, J = 8.0 Hz, 1H), 6.69 (d, J = 8.0 Hz, 1H), 5.30 (d, J = 8.0 Hz, 1H), 5.09 (AB system, J = 12.4 Hz, 2H), 4.33 (t, J = 8.0 Hz, 1H), 4.09 (t, J = 6.8 Hz, 2H), 3.81 (s, 3H), 3.64 (s, 3H), 3.55 (t, J = 6.4 Hz), 3.31 (s, 3H), 2.79 (dt, J = 17.6, 7.6 Hz, 1H), 2.07 (p, J = 6.4, 2H), 2.43−2.70 (m 5H), 1.44−1.74 (m, 3H), 1.39 (t, J = 11.2 Hz, 1H), 0.76−0.86 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 207.8, 172.7, 156.1, 148.3, 147.6, 136.3, 133.3, 128.4 (2C), 128.0, 127.8 (2C), 121.2, 114.3, 111.7, 69.3, 66.8, 65.9, 58.5, 58.1, 55.9, 51.7, 42.0, 37.0, 34.3, 32.1, 29.5, 28.3, 27.4, 20.1, 16.5; HRMS $C_{31}H_{43}NO_8$ [M + Na^+] calcd 580.2886, found 580.2867.

γ-Ketoester 44. The thioester **42** (275 mg, 0.473 mmol) was dissolved in THF (7.5 mL), and then *n*-butyl acrylate (372 μL, 2.59 mmol) and *tert*-butyl alcohol (106 μL, 1.43 mmol) were added. The mixture was cooled to −78 °C, and then SmI_2 (0.1 M, 20 mL, 2.00 mmol) was added slowly via syringe. The mixture was stirred at −78 °C for 3 d and then the flask flushed with O_2 before satd NH_4Cl (aq) (5 mL) was added and the mixture warmed to rt. The mixture was poured into 0.5 M HCl (40 mL) and extracted with EtOAc (3 × 15 mL). The combined organics were washed with satd $Na_2S_2O_3$ solution (20 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (10−40% EtOAc in pentane as eluant), which gave compound **44** (R_f = 0.40, 30% EtOAc in pentane) (170 mg, 0.283 mmol, 60%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27−7.37 (m, 5H), 6.81 (d, J = 1.6 Hz 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.70 (dd, J = 8.0, 1.6 Hz, 1H), 5.19 (1H, d, J = 8.4 Hz, 1H), 5.03 (s, 2H), 4.28 (app br t, J = 8.4 Hz, 1H), 3.94−4.06 (m, 4H), 3.75 (s, 3H), 3.49 (t, J = 6.4 Hz, 2H), 3.25 (s, 3H), 2.68−2.78 (m, 1H), 2.36−2.64 (m, 5H), 2.01 (p, 6.4 Hz, 2H), 1.48−1.67 (m, 5H), 1.24−1−37 (m, 3H), 0.85 (t, J = 7.2 Hz, 3H), 0.76 (d, J = 7.2 Hz, 3H), 0.74 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 207.9, 172.4, 156.2, 148.3, 147.7, 136.3, 133.4, 128.5 (2C), 128.1, 127.9 (2C), 121.2, 114.4, 111.7, 69.4, 66.8, 65.9, 64.6, 58.6, 58.1, 56.0, 42.0, 37.1, 34.4, 32.2, 30.5, 29.6, 28.3, 27.7, 20.2, 19.0, 16.9, 13.6; HRMS $C_{34}H_{49}NO_8$ [M + Na^+] calcd 622.3356, found 622.3354.

Phenylmethyl [(1*S*,3*S*)-3-[[4-Methoxy-3-(3-methoxypropoxy)-phenyl]methyl]-4-methyl-1-[(2*S*)-tetrahydro-5-oxo-2-furanyl]-pentyl]carbamate (45). The γ-keto methyl ester **43** (144 mg, 0.257 mmol) was dissolved in THF (25 mL), and then the solution was cooled to −78 °C before the addition of (*S*)-Alpine Hydride (1.1 mL, 0.55 mmol, 0.5 M in THF). The mixture was stirred at −78 °C for 24 h, satd NH_4Cl solution (5 mL) was added carefully, and the mixture was warmed to rt before being poured into water (40 mL) and extracted with EtOAc (3 × 20 mL). The combined organics were dried ($MgSO_4$), filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (15−70% EtOAc in pentane as eluant), which gave compound **45** (R_f = 0.25, 50% EtOAc) (124 mg, 0.235 mmol, 91%) as a 4:1 mixture of isomers as determined by ^{1}H NMR. These were separable by careful column chromatography (20−50% Et_2O in 1:1 CH_2Cl_2/pentane as eluant), which gave isomerically pure **45** (R_f = 0.45, 25% Et_2O in CH_2Cl_2) (85 mg) and the corresponding epimer (R_f = 0.35, 25% Et_2O in CH_2Cl_2) (21 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.26−7.36 (m, 5H), 6.72−6.77 (m, 2H), 6.64 (dd, J = 8.4, 2.0 Hz, 1H), 5.13 (s, 2H), 4.82 (d, J = 10.0 Hz, 1H), 4.42 (td, J = 7.2, 1.6 Hz, 1H), 4.09 (t, J = 6.4 Hz, 2H), 3.78−3−88 (m, 1H), 3.82 (s, 3H), 3.55 (t, J = 6.4 Hz, 2H), 3.31 (s, 3H), 2.60 (dd, J = 13.6, 5.6 Hz, 1H), 2.36−2.48 (m, 3H), 2.12−2.23 (m, 1H), 2.07 (p, J = 6.4 Hz, 2H), 1.95−2.05 (m, 1H), 1.61−1.73 (m, 2H), 1.49−1.58 (m, 1H), 1.30 (dd, J = 13.6, 9.2, 3.2 Hz, 1H), 0.82 (d, J = 6.8 Hz, 3H), 0.81 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.9, 156.8, 148.2, 147.6, 136.3, 133.6, 128.5 (2C), 128.1, 127.8 (2C), 121.2, 114.4, 111.7, 82.6, 69.3, 66.8, 65.9, 58.5, 56.0, 51.9, 42.4, 37.1, 33.4, 29.6, 28.4, 27.9, 28.4, 27.9, 24.3, 20.2, 16.7; HRMS $C_{30}H_{41}NO_7$ [M + Na^+] calcd 550.2781, found 550.2781.

Lactone 46. The lactone **45** (137 mg, 0.258 mmol) was dissolved in THF (15 mL) and the mixture cooled to −78 °C. LiHMDS (0.70 mL, 0.70 mmol, 1 M in hexanes) was added and the mixture stirred for 2 h before dropwise addition of acetone (0.70 mL, 9.54 mmol). The mixture was stirred for an additional 2 h, and then satd NH_4Cl(aq) (5 mL) was added and the mixture allowed to warm to rt. The mixture was poured into water (30 mL) and extracted with EtOAc (3 × 20 mL), and then the combined organics were dried (Na_2SO_4) filtered, and evaporated in vacuo. The pure product was obtained by column chromatography (5:5:2−0:1:1 pentane/CH_2Cl_2/Et_2O as eluant), which gave compound **46** (R_f = 0.30, 50% Et_2O in CH_2Cl_2) (133 mg, 0.234 mmol, 91%) an inseparable 5:1 mixture of isomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27−7.37 (m, 5H), 6.71−6.78 (m, 2H), 6.64 (d, J = 8.0 Hz, 1H), 5.13 (AB system, J = 12.8 Hz, 2H), 4.70 (d, J = 9.6 Hz, 1H), 4.42 (t, J = 6.0 Hz, 1H), 4.09 (t, J = 6.4 Hz, 2H), 3.75−3.85 (m, 1H), 3.83 (s, 3H), 3.56 (t, J = 6.4 Hz, 2H), 3.32 (s, 3H), 3.04 (brs, 1H), 2.51 (m, 4H), 2.44 (dd, J = 12.8, 8.0 Hz, 1H), 2.03−2.25 (m, 2H), 1.46−1.63 (m, 3H), 1.31 (ddd, J = 12.8, 9.2, 3.2 Hz, 1H), 1.25 (s, 3H), 1.20 (s, 3H), 0.83 (d, J = 7.2 Hz, 3H), 0.81 (d, J = 8.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 178.4, 156.8, 148.2, 147.6, 136.3, 133.5, 128.5 (2C), 128.2, 127.8 (2C), 121.2, 114.4, 111.8, 81.0, 71.4, 69.4, 66.9, 66.0, 58.5, 56.0, 52.8, 49.9, 42.4, 37.1, 33.1, 29.6, 28.2, 27.6, 27.5, 26.1, 20.2, 16.9; HRMS $C_{33}H_{47}NO_8$ [M + Na^+] calcd 608.3199, found 608.3201.

Lactone 47. Alcohol **51** (133 mg, 0.234 mmol) was dissolved in CH_2Cl_2 (15 mL) and then the mixture cooled to 0 °C. PCl_5 (210 mg, 1.01 mmol) dissolved in CH_2Cl_2 (5 mL) was added over 5 min via syringe then the mixture stirred for 2.5 h. Saturated $NaHCO_3$ solution (5 mL) was added, and then the mixture was warmed to rt, poured into water (30 mL), and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated. The pure product was obtained by column chromatography (20−50% EtOAc in pentane as eluant) which gave compound **47** (R_f = 0.60, 40% EtOAc in pentane) (132 mg, 0.233 mmol, 99%) as an inseparable 40:8:6 mixture of **47a**, **47b,** and **51**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.28−7.37 (m, 5H), 6.72−6.77 (m, 2H), 6.64 (dd, J = 8.4, 1.6 Hz, 1H), 5.14 (AB system, J = 12.0 Hz, 2H), 4.96 (s, 1H), 4.84 (s, 1H), 4.68 (d, J = 10.0 Hz, 1H), 4.45 (td, J = 7.2, 1.6 Hz, 1H), 4.09 (t, J = 6.8 Hz, 2H), 3.80−3.90 (m, 1H), 3.83 (s, 3H), 3.36 (t, J = 6.4 Hz, 2H), 3.32 (s, 3H), 3.19 (dd, J = 10.0, 5.2 Hz, 1H), 2.60 (dd, J = 13.6,

5.2 Hz, 1H), 2.40 (dd, J = 13.6, 8.8 Hz, 1H), 2.12−2.30 (m, 2H), 2.09 (p, J = 6.4 Hz, 2H), 1.79 (s, 3H), 1.60−1.72 (m, 3H), 1.47−1.57 (, 1H), 1.31 (ddd, J = 13.6, 8.8, 3.6 Hz, 1H), 0.82 (d, J = 7.2 Hz, 3H), 0.81 (3H, d, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.6, 156.8, 148.1, 147.7, 140.1, 136.2, 133.6, 128.6 (2C), 128.2, 127.9 (2C), 121.2, 114.4, 113.9, 111.8, 81.2, 69.4, 67.0, 66.0, 58.6, 56.1, 52.1, 47.6, 42.5, 37.2, 33.5, 30.1, 29.6, 28.0, 20.7, 20.3, 16.8; HRMS $C_{33}H_{45}NO_7$ [M + Na^+] calcd 590.3094, found 590.3098.

(3*S*,5*S*)-Dihydro-5-[(1*S*,3*S*)-3-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl]-4-methyl-1-amino-pentyl]-3-(1-methylethyl)-2-(3*H*)-furanone (48). Alkene **47** (51 mg, 0.0898 mmol) was dissolved in EtOH (5 mL), and then 10% Pd/C (10 mg) was added. The mixture was stirred under an atmosphere of H_2 for 2 d, and then the flask was flushed with N_2 before it was filtered through Celite. The solids were washed with EtOH, and then the combined filtrates were evaporated to dryness giving compound **48** (R_f = 0.20, 5% MeOH in CH_2Cl_2) (39 mg, 0.0895 mmol 99%) as a 4:1 mixture of diastereoisomers that was not purified any further: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.76 (d, J = 8.0 Hz, 1H), 6.66−6.73 (m, 2H), 4.08 (t, J = 6.4 Hz, 2H), 3.99 (dt, J = 10.0, 6.4 Hz, 1H), 3.82 (s, 3H), 3.56 (t, J = 6.0 Hz, 2H) 3.45 (s, 3H), 2.40−2.60 (m, 4H), 1.90−2.02 (m, 4H), 1.16−1.82 (m, 7H), 1.02 (d, J = 6.4 Hz, 3H), 0.82−0.92 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 178.0, 148.3, 147.7, 132.8, 121.4, 114.6, 111.9, 77.8, 69.4, 66.1, 58.5, 56.0, 53.4, 45.0, 40.6, 37.0, 30.6, 29.5, 29.2, 28.8, 26.5, 20.1, 19.5, 18.6, 17.5; HRMS $C_{25}H_{41}NO_5$ [M + Na^+] calcd 458.2882, found 458.2896.

1,1-Dimethylethyl [(1*S*,3*S*)-3-[[4-Methoxy-3-(3-methoxypropoxy)phenyl]methyl]-4-methyl-1-[(2*S*,4*S*)-tetrahydro-4-(1-methylethyl)-5-oxo-2-furanyl]pentyl]carbamate (49).[31] Amine **48** (39 mg, 0.0895 mmol) was dissolved in THF (1.0 mL), and then NEt_3 (51 mg, 0.10 mmol) and di-*tert*-butyl dicarbonate (51 mg, 0.10 mmol) were added. The mixture was stirred at rt for 18 h, and then all volatiles were removed in vacuo. The pure products were obtained by careful column chromatography (5−40% EtOAc in pentane as eluant), which gave isomerically pure **49** (R_f = 0.60, 40% EtOAc in pentane) (30 mg, 0.0560 mmol, 63%) and a mixture of **49** and **53** (R_f = 0.55, 40% EtOAc in pentane) (10 mg, 0.0187 mmol, 21%). **49**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.76 (d, J = 8.0 Hz, 1H), 6.73 (s, 1H), 6.68 (d, J = 8.0 Hz, 1H), 4.33−4.40 (m, 2H), 4.09 (t, J = 6.4 Hz, 2H), 3.82 (s, 3H), 3.75−3.85 (m, 1H), 3.57 (t, J = 6.4 Hz, 2H), 3.35 (s, 3H), 2.62 (dd, J = 13.6, 5.6 Hz, 1H), 2.54 (td, J = 10.0, 6.0 Hz,), 2.38 (dd, J = 14.0, 9.6 Hz, 1H), 2.00−2.20 (m, 5H), 1.33−1.70 (m, 3H), 1.45 (s, 9H), 1.22−1.32 (m, 1H), 1.00 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H), 0.82 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 179.2, 156.4, 148.4, 147.8, 133.9, 121.5, 114.5, 111.9, 81.6, 79.9, 69.6, 66.2, 58.8, 56.2, 52.1, 46.0, 42.6, 37.6, 33.5, 29.8, 29.4, 28.5 (3C), 27.9, 26.8, 20.6, 20.5, 18.6, 16.7; HRMS $C_{30}H_{49}NO_7$ [M + Na^+] calcd 558.3407, found 558.3406.

(2*R*,4*S*,5*S*,7*S*)-Isopropylhydroxy(*N*-butoxycarbamoyl)aminoisopropyl-8-(4-methoxy-3-(3-methoxypropoxy)benzenoctanoic Acid *n*-Butylamide (50).[49,50] *n*-Butylamine (120 mg, 1.641 mmol) was dissolved in CH_2Cl_2 (2 mL), and then trimethylaluminum (0.8 mL, 2 M solution in toluene, 1.60 mmol) was added. The mixture was stirred at rt for 30 min and then transferred via syringe to a solution of lactone **49** (14 mg, 0.0261 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at rt for 20 h, and then the reaction was quenched by careful addition of satd NH_4Cl solution (3 mL). The mixture was poured into 1 M $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated. The pure product was obtained by column chromatography (15−60% EtOAc in pentane as eluant) which gave compound **50** (R_f = 0.30, 50% EtOAc in pentane) (9 mg, 0.0152 mmol, 58%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.72−6.82 (m, 2H), 6.69 (d, J = 8.0 Hz, 1H), 5.70 (br s, 1H), 4.67 (d, J = 8.8 Hz, 1H), 4.10 (t, J = 5.6 Hz, 2H), 3.82 (s, 3H), 3.74 (br s, 1H), 3.57 (t, J = 6.4 Hz, 2H), 3.48−3.55 (m, 1H), 3.38−3.46 (m, 1H), 3.35 (s, 3H), 3.27−3.37 (m, 1H), 3.12−3.23 (m, 1H), 2.61 (dd, J = 13.2, 4.4 Hz, 1H), 2.38 (dd, J = 14.0, 8.8 Hz, 1H), 2.08 (p, J = 6.4 Hz, 2H), 1.98 (td, J = 8.8, 3.2 Hz, 1H), 1.80−1.94 (m, 4H), 1.44 (s, 9H), 1.16−1.80 (m, 7H), 0.89−0.95 (m, 9H), 0.82 (d, J = 7.2 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 176.2, 156.9, 148.4, 147.7, 134.5, 121.5, 114.7, 111.8, 79.3, 71.3, 69.6, 66.2, 58.8, 56.2, 54.1, 51.7, 42.4, 39.3, 37.6, 34.7, 32.8, 31.8, 29.8, 29.8, 28.6 (3C), 28.3, 21.4, 2p0.6, 20.5, 20.3, 17.0, 13.9; HRMS $C_{34}H_{60}N_2O_7$ [M + Na^+] calcd 631.4298, found 631.4294.

Lactone 51. Lactone **47** (36 mg, 0.0634 mmol) was dissolved in CH_3CN (1.0 mL), and then NEt_3 (0.5 mL) and 2-hydroxypyridine (10 mg, 0.104 mmol) were added. The mixture was heated at 80 °C for 2 d, and then all volatiles were removed in vacuo. The pure product was obtained by column chromatography (15−50% EtOAc in pentane as eluant) which gave compound **51** (R_f = 0.55, 1:1:1 pentane/CH_2Cl_2/Et_2O) (32 mg, 0.0564 mmol, 89%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.27−7.36 (m, 5H), 6.73−6.78 (m 2H), 6.65 (dd, J = 8.0, 1.2 Hz, 1H), 5.11 (AB system, J = 12.4 Hz, 2H), 4.68 (d, J = 12.4 Hz, 1H), 4.37 (t, J = 6.8 Hz, 1H), 4.09 (t, J = 6.4 Hz, 2H), 3.80−3.90 (m, 1H), 3.83 (s, 3H), 3.56 (t, J = 6.4 Hz, 2H), 3.32 (s, 3H), 2.82 (dd, J = 16.4, 8.0 Hz, 1H), 2.58−2.68 (m, 2H), 2.41 (dd, J = 13.6, 9.2 Hz, 1H), 2.20 (s, 3H), 2.08 (p, J = 6.4, 2H), 1.77 (s, 3H), 1.63−1.74 (m, 2H), 1.48−1−58 (m, 1H), 1.30 (ddd, J = 14.0, 9.6, 3.2 Hz, 1H), 0.83 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 170.1, 157.0, 150.6, 148.4, 147.7, 136.6, 133.9, 128.6 (2C), 128.2, 127.9 (2C), 121.4, 119.0, 114.6, 111.9, 78.2, 69.9, 66.1, 58.8, 56.2, 52.6, 42.6, 37.3, 33.4, 31.0, 29.8, 28.0, 24.6, 20.5, 20.0, 16.8; HRMS $C_{33}H_{45}NO_7$ [M + Na^+] calcd 590.3094, found 590.3097.

(3*S*,5*S*)-Dihydro-5-[(1*S*,3*S*)-3-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl]-4-methyl-1-[(phenylmethyl)amino]pentyl]-3-(1-methylethyl)-2(3*H*)-furanone (52).[30] Amine **48** (29 mg, 0.0669 mmol) was dissolved in ethanol (1.0 mL) and then the solution cooled to 0 °C before benzaldehyde (20 μL, 0.197 mmol) was added. The mixture was stirred at 0 °C for 90 min. $NaBH_4$ (10 mg, 0.264 mmol) was then added quickly and stirring continued at rt for a further 40 min. The mixture was poured into water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated. The pure product was obtained by column chromatography (5:5:1−0:1:1 pentane/CH_2Cl_2/Et_2O as eluant), which gave **52** (R_f = 0.45, 1:1:1 pentane/CH_2Cl_2/Et_2O) (24 mg, 0.0457 mmol, 68%) and the diastereoisomer (R_f 0.25, 1:1:1 pentane/CH_2Cl_2/Et_2O) (6 mg, 0.0114 mmol, 17%) as colorless oils. **52**: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.14−7.27 (m, 5H), 6.70 (d, J = 8.4 Hz 1H), 6.62 (d, J = 2.0 Hz, 1H), 6.56 (dd, J = 8.4, 2.0 Hz, 1H), 4.23 (ddd, J = 8.0, 6.0, 4.8 Hz, 1H), 4.00 (t, J = 6.4 Hz, 2H), 3.77 (d, J = 12.8 Hz, 1H), 3.76 (s, 3H), 3.67 (d, J = 12.8 Hz, 1H), 3.49 (t, J = 6.0 Hz, 2H), 3.27 (s, 3H), 2.38−2.47 (m, 3H), 2.33 (dd, J = 13.6, 6.8 Hz, 1H), 1.98−2.10 (m, 3H), 1.77−1.89 (m, 2H), 1.58−1−69 (m, 2H), 1.30−1.40 (br s, 1H), 1.43 (ddd, J = 14.0, 7.6, 4.8 Hz, 1H), 1.22 (ddd, J = 14.0, 7.2, 5.6 Hz, 1H), 0.91 (d, J = 6.8 Hz, 3H), 0.79−0.84 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 179.4, 148.4, 147.9, 140.7, 134.0, 128.5 (2C), 128.3 (2C), 127.1, 121.3, 114.3, 111.8, 80.9, 69.5, 66.2, 58.8, 58.8, 56.1, 51.9, 46.0, 42.5, 37.3, 31.7, 29.7, 29.1, 26.6, 20.5, 19.2, 18.4, 18.3; HRMS $C_{32}H_{47}NO_5$ [M + Na^+] calcd 548.3351, found 548.3373.

(3*S*,5*S*)-Dihydro-5-[(1*R*,3*S*)-3-[[4-methoxy-3-(3-methoxypropoxy)phenyl]methyl]-4-methyl-1-aminopentyl]-3-(1-methylethyl)-2-(3*H*)-furanone (53). Alkene **51** (32 mg, 0.0564 mmol) was dissolved in EtOH (5 mL), and then 10% Pd/C (15 mg) was added. The mixture was stirred under an atmosphere of H_2 for 18 h, and

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then the flask was flushed with N_2 before it was filtered through Celite. The solids were washed with EtOH and then the combined filtrates evaporated to dryness giving compound **53** (23 mg, 0.0528 mmol, 94%) as a 10:1 mixture of diastereoisomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.76 (d, J = 8.0 Hz, 1H), 6.66−6.74 (m, 2H), 4.08 (t, J = 6.4 Hz, 2H), 3.99 (dt, J = 10.0, 6.4 Hz, 1H), 3.82 (s, 3H), 3.56 (t, J = 6.0 Hz, 2H), 3.45 (s, 3H), 2.40−2.60 (m, 4H), 2.00−2.02 (m, 4H), 1.16−1.82 (m 7H), 1.02 (d, J = 6.4 Hz, 3H), 0.82−0.92 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 177.7, 148.3, 147.7, 133.9, 121.1, 114.3, 111.7, 82.9, 69.3, 66.1, 58.6, 56.0, 53.6, 46.9, 41.9, 37.7, 34.0, 29.8, 29.6, 27.5, 27.0, 20.6, 19.9, 18.2, 17.5; HRMS $C_{25}H_{41}NO_5$ [M + Na^+] calcd 458.2882, found 458.2896.

1,1-Dimethylethyl [(1*S*,3*S*)-3-[[4-Methoxy-3-(3-methoxypropoxy)-phenyl]methyl]-4-methyl-1-[(2*S*,4*R*)-tetrahydro-4-(1-methylethyl)-5-oxo-2-furanyl]pentyl]carbamate (54). Amine **53** (16 mg, 0.0369 mmol) was dissolved in THF (0.4 mL), and then NEt_3 (21 mg, 0.10 mmol) and di-*tert*-butyl dicarbonate (21 mg, 0.10 mmol) were added. The mixture was stirred at rt for 18 h, and then all volatiles were removed in vacuo. The pure product was obtained by column chromatography (10−40% EtOAc in pentane as eluant) which gave compound **54** (R_f = 0.60, 40% EtOAc in pentane) (16 mg, 0.0299 mmol, 81%) as a gum: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.72−6.78 (m, 2H), 6.69 (dd, J = 8.4, 2.0 Hz, 1H), 4.47 (d, J = 10.4 Hz, 1H), 4.30 (dd, J = 9.6, 6.4 Hz, 1H), 4.09 (t, J = 6.4 Hz, 2H), 3.76−3.85 (m, 1H), 3.82 (s, 3H), 3.57 (t, J = 6.4 Hz, 2H), 3.34 (s, 3H), 2.64 (dd, J = 14.0, 5.6 Hz, 1H), 2.58 (ddd, J = 12.4, 9.2, 4.8 Hz, 1H), 2.38 (dd, J = 14.0, 9.6 Hz, 1H), 2.03−2.26 (m, 4H), 1.84 (td, J = 12.0, 10.8 Hz, 1H), 1.50−1.72 (m, 3H), 1.44 (s, 9H), 1.27 (ddd, J = 14.4, 9.6, 3.6 Hz, 1H), 1.01 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 0.82 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 178.0, 156.2, 148.3, 147.7, 133.8, 121.4, 114.5, 80.4, 79.5, 69.5, 66.0, 58.6, 56.1, 50.5, 46.3, 42.4, 37.1, 33.6, 29.6, 28.3 (3C), 27.7, 27.5, 26.1, 20.5, 20.4, 17.9, 16.6; HRMS $C_{30}H_{49}NO_7$ [M + Na^+] calcd 558.3407, found 558.3406.

(2*S*,4*S*,5*S*,7*S*)-Isopropylhydroxy-(*N*-butoxycarbamoyl)aminoisopropyl-8-(4-methoxy-3-(3-methoxypropoxy)benzenoctanoic Acid *n*-Butylamide (55).[49,50] *n*-Butylamine (120 mg, 1.641 mmol) was dissolved in CH_2Cl_2 (2 mL) and then trimethylaluminum (0.8 mL, 2 M solution in toluene, 1.60 mmol) was added. The mixture was stirred at rt for 30 min and then transferred via syringe to a solution of lactone **47** (15 mg, 0.0280 mmol) in CH_2Cl_2 (1 mL). The mixture was stirred at rt for 2 d and then the reaction quenched by careful addition of satd NH_4Cl solution (3 mL). The mixture was poured into 1 M $NaHCO_3$ solution (20 mL) and extracted with CH_2Cl_2 (4 × 15 mL). The combined organic portions were dried ($MgSO_4$), filtered, and evaporated. The pure product was obtained by column chromatography (1−5% MeOH in CH_2Cl_2 as eluant) which gave compound **55** (R_f = 0.33, 5% MeOH in CH_2Cl_2) (8 mg, 0.0135 mmol, 48%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.72−6.80 (m, 2H), 6.71 (d, J = 8.0 Hz, 1H), 5.77 (t, J = 5.6 Hz, 1H), 4.76 (d, J = 10.0 Hz, 1H), 4.05−4.15 (m, 2H), 3.82 (s, 3H), 3.58−3.67 (m, 1H), 3.57 (t, J = 6.4 Hz, 2H), 3.45−3.52 (m, 1H), 3.45 (s, 3H), 3.24−3.34 (m, 1H), 3.10−3.24 (m, 1H), 2.61 (dd, J = 13.2, 6.4 Hz, 1H), 2.53 (d, J = 4.0 Hz, 1H), 2.38 (dd, J = 14.0, 9.2 Hz, 1H), 2.08 (p, J = 6.4 Hz, 2H), 1.73−1.94 (m, 4H), 1.40−1−70 (m, 5H), 1.45 (s, 9H), 1.25−1.40 (m, 2H), 1.14 (ddd, J = 13.6, 8.8, 4.8 Hz, 1H), 0.87−0−94 (m, 9H), 0.83 (d, J = 2.8 Hz, 3H), 0.82 (d, J = 2.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 175.6, 156.6, 148.4, 147.7, 134.5, 121.6, 114.8, 111.9, 79.1, 73.0, 69.6, 66.2, 58.8, 56.2, 51.6, 51.4, 42.2, 39.4, 37.3, 34.4, 33.2, 31.9, 31.6, 29.8, 28.6 (3C), 28.1, 20.9, 20.3, 20.3, 20.2, 17.2, 13.9; HRMS $C_{34}H_{60}N_2O_7$ [M + Na^+] calcd 631.4298, found 631.4089.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra for all new compounds and experimental protocols for preparation of compounds **25a**,**b**,**e**,**f** and **26b**−**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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