Structure-Based Design and Synthesis of Macroheterocyclic Peptidomimetic Inhibitors of the Aspartic Protease β-Site Amyloid Precursor Protein Cleaving Enzyme (BACE)

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Based on the X-ray cocrystal structure of the Tang−Ghosh heptapeptide inhibitor 1 (OM00-3), a series of macroheterocyclic analogues were designed and synthesized. Analogues containing dithia, dioxa, oxathia, and carbathia macrocycles were synthesized by methods relying on ring-closing olefin metathesis for the dioxa analogues and by alkylation of thiolates or bisthiolates for the others. Molecular modeling suggested that the incorporation of piperidine units appended to the macrocycles improved interactions through additional H-bonds and introduced further rigidity. These were synthesized in enantiomerically pure form using enzyme-catalyzed desymmetrization and diastereomer separation. Inhibitory activity on β-site amyloid precursor protein cleaving enzyme (BACE) was observed with several macroheterocyclic inhibitors and structure−activity relationship (SAR) correlations were deduced. Cocrystal structures of two synthetic analogues revealed interesting and unexpected binding interactions.

Introduction

There is substantial evidence that β-amyloid plays an important role in the pathogenesis of Alzheimer's Disease. The generation of this short peptide is initiated by cleavage of a larger precursor protein by the aspartic protease BACE (β-site amyloid precursor protein cleaving enzyme, β-secretase). BACE is therefore recognized as one of the most promising targets for a disease-modifying treatment of Alzheimer's Disease and many research efforts are aiming at the identification of suitable inhibitors as drug candidates.[1]

Although in drug discovery the ultimate goal usually is to identify non-peptidic inhibitors, very often the first step in the process toward such a compound is through substrate analogues. It is well established that protease substrates have to adopt an extended β-strand conformation to be recognized and cleaved by the enzyme.[2] Accordingly, such protease inhibitors are designed to mimic essential features of peptides in β-strand conformations. Macrocyclization is an established method to pre-organize and stabilize this bioactive conformation.[3] It has been applied successfully for a number of proteases, in particular aspartic proteases. In many cases, the activity, cell permeability, oral availability, or proteolytic stability could be improved considerably compared with the open chain analogues.[4]

Only a limited number of macrocyclic inhibitors of BACE have been reported in the literature so far. A first paper reports on cycloamide−urethane-derived compounds linking the P_2 and P_4 moieties of a hydroxyethylene peptidomimetic inhibitor.[5] The compounds were synthesized by ring-closing olefin metathesis, and in the best case, a gain in activity of approximately an order of magnitude was achieved by going from the open precursor to the ring-closed inhibitor. In addition, increased cellular activity was observed when compared with similar open-chain analogues. In a more recent publication, macrocyclic inhibitors linking P_1 with either P_3 or the nitrogen of the amide bond between P_2 and P_3 are presented.[6] In contrast to the first examples with linkers between functional groups in the hydrophilic S_2 and S_4 pockets, in this latter case, the linker consists of a pure carbon chain located in the hydrophobic S_1 and S_3 environment. Again, compared with similar open-chain analogues a slight improvement in activity was observed. In addition, cellular activity was achieved with the compounds linking the nitrogen of the amide bond between P_2 and P_3. This is most likely due to better permeability gained by the elimination of a H-bond donor.

In this paper, we report on the design and synthesis of 15- to 17-membered macrocyclic hydroxyethylene inhibitors where P_1 and P_3 are connected through thioether or ether linkages, as well as on novel bicyclic macrocycles encompassing a piperidine ring. Statin-derived bis-thioether macrocycles have been studied already as inhibitors of pepsin and penicillopepsin.[7] Modeling and overlays with the published X-ray structure of **1** (OM00-3) suggested that this principle should also be applicable for inhibitors of BACE (Figure 1). Furthermore, novel bicyclic macrocycles containing a basic piperidine ring have been designed to pick up additional interactions with the enzyme.

Results and Discussion

Chemistry. For the synthesis of the dioxa *O*/*O* macrocycles, we relied on the now venerable Grubbs olefin metathesis reaction[8] of appropriately spaced bis-*O*-allyl intermediates as shown in a disconnective analysis in Figure 2. We had also hoped that the mixed oxathia macrocycles could be prepared by such a carbocyclization. However, after initial exploratory studies, it became evident that the synthesis of the dithia variants would require a different methodology due to the incompatibility of the Grubbs reagent with the presence of two thioether-type groups. The bis-*O*-allyl and bis-*O*,*S*-allyl ether intermediates would be generated from appropriate hydroxymethyl amino acids such as serine or cysteine for the P_2 site, and a new δ-hydroxymethyl-δ-amino acid. The latter would originate from the versatile Garner's aldehyde.[9]

Addition of the organozinc acetylide, prepared from methyl propiolate to **1** at −78 °C afforded the desired **2** (57%) and its

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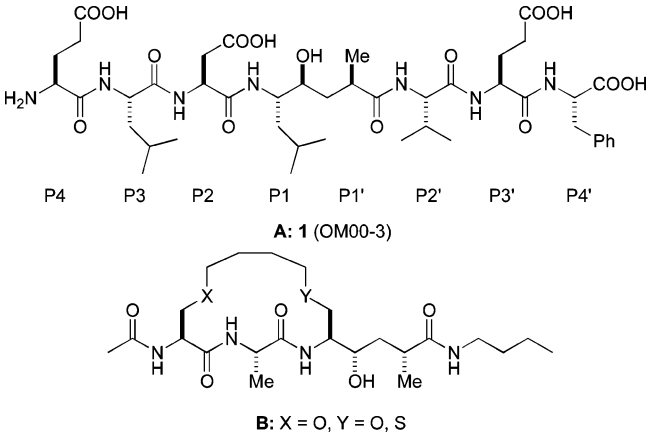


Figure 1. (A) Tang−Ghosh BACE inhibitors **1** (OM00-3) and (B) proposed heteromacrocyclic pseudopeptidomimetic.

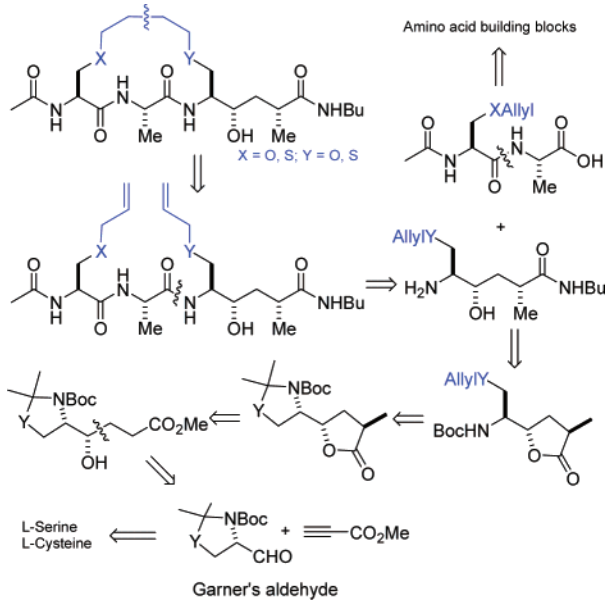
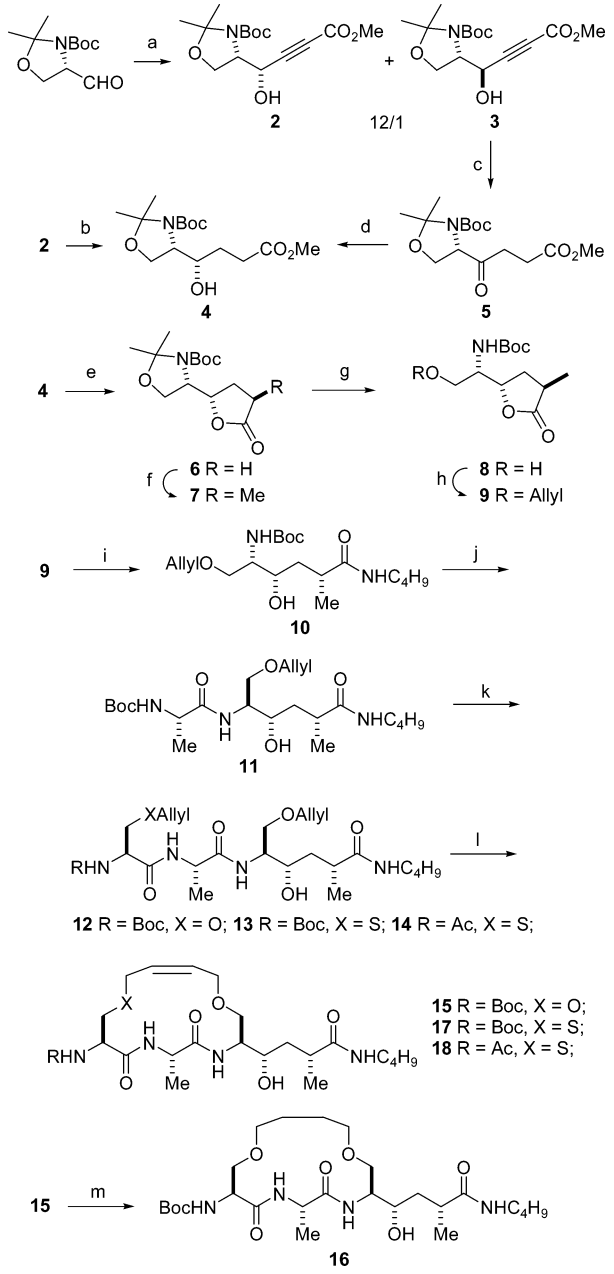


Figure 2. Disconnective analysis of the heteromacrocyclic pseudopeptides.

4-epimer **3** (5%) (Scheme 1). Although zinc acetylides have been added to Garner's aldehyde and the corresponding L-cysteine variant, the analogous reaction with methyl propiolate with a favorable stereochemical ratio is, to the best of our knowledge, unprecedented. After a number of conditions involving bases and additives were explored, the best ratio of 12:1 in favor of **2** was obtained with *n*-BuLi/$ZnBr_2$ (or $ZnCl_2$) in ether. Catalytic reduction of **2** led to the saturated ester **4**. The minor isomer **3** could be oxidized to the acetylenic ketone, the triple bond could be reduced to **5**, and the resulting compound could be subsequently treated with sodium borohydride in methanol to give **4**. Treatment of **4** with AcOH in toluene at reflux temperature afforded the lactone **6**, which was alkylated via the lithium enolate to give **7** in 70% yield as a single isomer. Cleavage of the acetal to **8** and *O*-allylation using allyltrichloroacetimidate and triflic acid[10,11] gave the lactone **9** in excellent overall yield. Treatment of **9** with butylamine effected ring opening to give the butylamide **10**.

Cleavage of the *N*-Boc group and coupling with Boc-Ala-OH in the presence of PyBOP gave the dipeptide **11** in 85% yield. Further extension with Boc-Ser(allyl)-OH led to the bis-*O*-allyl precursor **12** in 67% yield. Attempted carbocyclization with the Grubbs first generation catalyst[12] did not lead to any

Scheme 1[a]

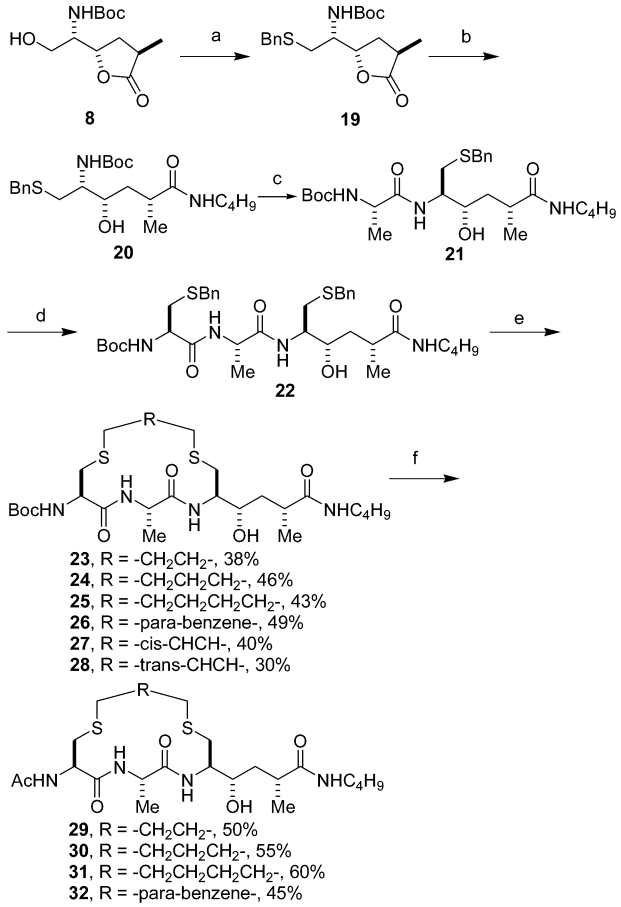


[a] Reagents and conditions: (a) BuLi, methyl propiolate, Et_2O, −78 °C, then $ZnBr_2$, Et_2O, −78−0 °C, then Garner's aldehyde, 62%; (b) Pd/C/$BaSO_4$, H_2, AcOEt, 95%; (c) (i) Dess−Martin periodinane, 75%, (ii) Pd/C, H_2, 96%; (d) $NaBH_4$, MeOH, 85%; (e) AcOH, toluene, 95%; (f) LiHMDS, THF, then MeI, 70%, (g) TsOH, THF−H_2O, 75%; (h) allyl trichloroacetimidate, TfOH, CH_2Cl_2, 80%; (i) $C_4H_9NH_2$, 40%; (j) (i) TFA, CH_2Cl_2, (ii) *N*-Boc-Ala, PyBOP, DIEA, CH_2Cl_2, 85%; (k) (i) TFA, CH_2Cl_2, (ii) *N*-Boc-*O*-allyl-SerOH, PyBOP, DIEA, CH_2Cl_2, 67% for **12**; *N*-Boc-*S*-allyl-Cys, PyBOP, DIEA, CH_2Cl_2, 75% for **13**; *N*-Ac-*S*-allyl-Cys, HOBt, EDC, DCM-H_2O, 27% for **14**; (l) Grubbs second generation catalyst 20−30 mol %, CH_2Cl_2, 34% for **15**, 25% for **17**, 23% for **18**; (m) Pd/C, H_2, 91%.

desired product. However, using the second generation catalyst[13,14] (20 mol % in CH_2Cl_2) gave the dioxa-*O*/*O* macrocycle **15** as an inseparable mixture of cis and trans isomers in 34% yield. Catalytic reduction led to the saturated macrocycle **16** in 91% yield.

The oxathia macrocycle was synthesized via the same protocol (Scheme 1). Thus, coupling of the amine from **11** with Boc-Cys(allyl)-OH proceeded smoothly to give the bis-*O*,*S*-allyl dipeptide **13** in 75% yield. Carbocyclization via ring closure

Scheme 2[a]

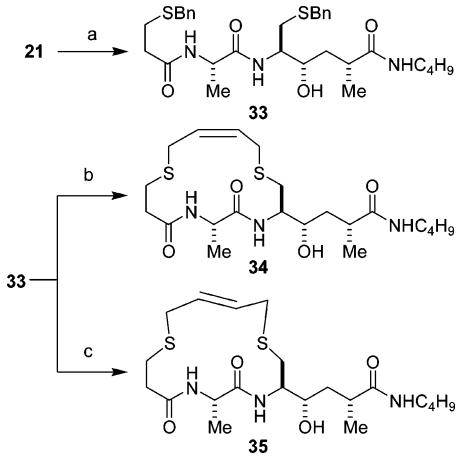


[a] Reagents and conditions: (a) BnSH, PMe_3, ADDP, CH_2Cl_2, 66%; (b) $C_4H_9NH_2$, $AlMe_3$, CH_2Cl_2, 88%; (c) (i) TFA, CH_2Cl_2, (ii) *N*-Boc-Ala, PyBOP, DIEA, CH_2Cl_2, 90%; (d) (i) TFA, CH_2Cl_2, (ii) *N*-Boc-*S*-Bn-Cys, PyBOP, DIEA, CH_2Cl_2, 57%; (e) Na−NH_3 (liq), then $BrCH_2$−R−CH_2Br; (f) (i) TFA, CH_2Cl_2, (ii) Ac_2O, DMF, $NaHCO_3$.

metathesis of **13** using the second generation Grubbs catalyst (30 mol % in CH_2Cl_2)[13,14] afforded the desired oxathia macrocycle **17** as a mixture of cis and trans isomers in 25% yield. To explore the influence of the *N*-terminal group, we also prepared the *N*-acetyl macrocycle **18** from acyclic precursor **14**. Attempts to improve the yields of these carbocyclizations by variation of catalyst load or concentration were not successful.

We next turned our attention to the dithia macrocycles. Since the Grubbs macrocylization of bis-*S*-allyl precursors corresponding to **13** was not possible, presumably due to the strong coordination with the catalyst, we adopted a macrocyclization protocol based on an intramolecular bis-thioetherification with appropriate dibromides and a bis-thiolate.[7,15−17] By varying the length of the dibromoalkenes and alkanes, we envisaged the preparation of dithia macrocycles having 15−17-membered pseudopeptide rings. Rather than utilize the L-cysteine equivalent of the Garner aldehyde[18] and to reinvestigate stereocontrolled routes to the corresponding acetylenic ester similar to **2**, we chose to use the advanced intermediate from the previous route (Scheme 1) and to introduce a benzylthio group via a Mitsunobu reaction (Scheme 2).[19] Thus, treatment of **8** with benzyl mercaptan, in the presence of trimethylphosphine and ADDP (azodicarbonyldipiperidine),[20] led to the corresponding benzylthio analogue **19** in 66% yield. Ring opening to the acyclic butylamide **20**, followed by peptide coupling with Boc-Cys-(Bn)-OH gave the bis-benzylthio dipeptide **22** in 57% yield. Reductive cleavage with Na/NH_3 (liquid),[21] and treatment of

Scheme 3[a]



[a] Reagents and conditions: (a) (i) TFA, CH_2Cl_2, (ii) 3-benzylsulfanyl propionic acid, PyBOP, DIEA, CH_2Cl_2, 70%; (b) Na−NH_3 (liq), *cis*-1,4-dibromobutene, 51%; (c) Na−NH_3 (liq), *trans*-1,4-dibromobutene, 45%.

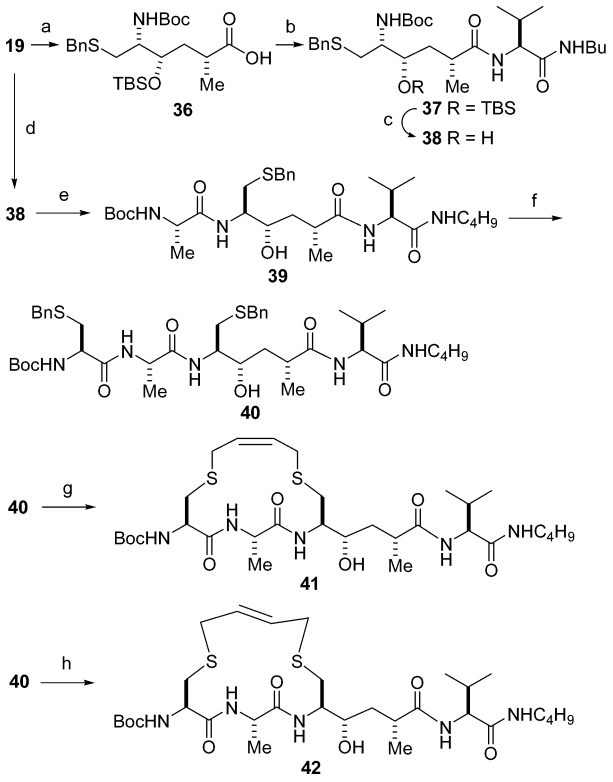
the resulting bis-thiolate with a variety of dibromides gave the corresponding dithia macrocycles **23**−**28** in modest to good yields depending on the nature of the products. Four analogues were also deprotected to the amines, which were converted to the corresponding *N*-acetyl variants **29**−**32** by acetylation with acetic anhydride.

To probe the interactions of the P_3−P_4 amide, we deemed it necessary to synthesize dithia macrocycles with *cis*- and *trans*-alkene bridges but lacking the terminal *N*-Boc or *N*-Ac group (Scheme 3). The common intermediate **19** was cleaved to the amine then coupled with Boc-Ala-OH as usual. Further extension with 3-*S*-benzylpropionic acid gave the bis-*S*-benzyl dipeptide **33**. Reductive cleavage of the benzyl groups and bis-alkylation with *cis*-1,4-dibromobutene and *trans*-1,4-dibromobutene gave the corresponding dithia macrocycles **34** and **35** in 51% and 45% yields, respectively.

Previous SAR data[5,22−26] and preliminary results from our laboratory[27−29] had shown a beneficial effect of a valine residue at P_2' in inhibition experiments on BACE. We decided to synthesize an extended variant of **27** and **28**, incorporating a valine residue and capping with a butylamide (Scheme 4). Thus, **19** was treated with aq LiOH, and the resulting Li^+ carboxylate was carefully acidified to give the free carboxylic acid **36** in 91% overall yield. Coupling with H-Val-*n*-butyl in the presence of PyBOP gave the peptide **37** in 86% yield. Cleavage of the *t*-butyldimethylsilyl (TBS) group afforded the corresponding hydroxyl compound **38**. A more expedient route was to treat the lactone **19** directly with H-Val-*n*-butyl in the presence of 2-hydroxypyridine and refluxing toluene[30,31] to afford **38** in 66% yield. Extension to **39** and coupling with Boc-Cys(Bn)-OH gave **40** in excellent overall yield. Reductive cleavage and bis-alkylation as described above gave the *cis*- and *trans*-dithia macrocycles **41** and **42** in 24% and 22% yields, respectively. Various attempts to increase the yields of bis-alkylations in this and related cases were unsuccessful.

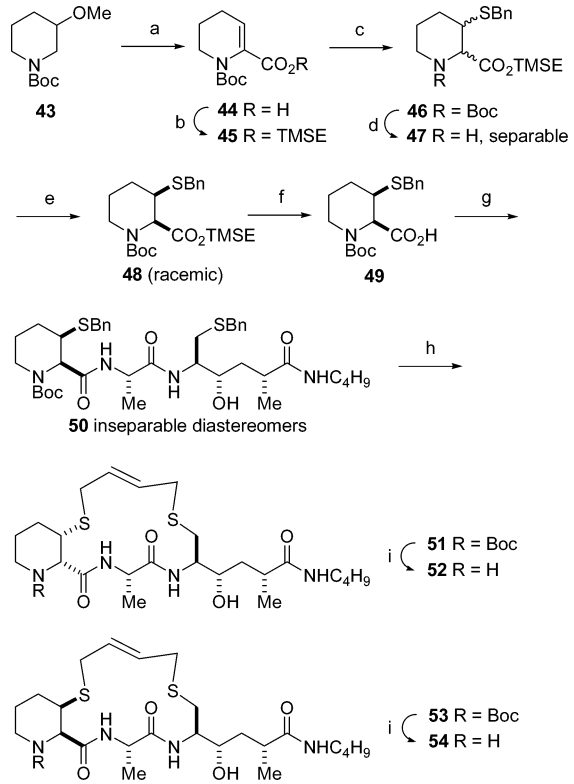
The series of oxathia macrocycles and dithia macrocycles described above was tested for inhibition of BACE under standard conditions.[32] Although little or only marginal inhibition was observed for the majority of the analogues, we found that the *trans*-dithia macrocycle **42** exhibited an IC_{50} of 156 nM against BACE. However, the isomeric *cis* macrocycle **41** showed 10-fold weaker activity. The X-ray structure of **42** in a complex with human BACE was solved at a resolution of 2.10 Å (see Discussion).

Scheme 4[a]



[a] Reagents and conditions: (a) (i) LiOH, DME−H_2O, (ii) TBSCl, imidazole, THF, 91% for two steps; (b) Val-*N*-^{n}Bu, PyBOP, DIEA, CH_2Cl_2, 86%; (c) TsOH, MeOH, 50%; (d) Val-*N*-^{n}Bu, 2-hydroxypyridine, toluene, 66%; (e) (i) TFA, CH_2Cl_2, (ii) *N*-Boc-Ala, PyBOP, DIEA, CH_2Cl_2, 82%; (f) (i) TFA, CH_2Cl_2, (ii) *N*-Boc-*S*-Bn-Cys, PyBOP, DIEA, CH_2Cl_2, 61%; (g) Na−NH_3 (liq), *cis*-1,4-dibromobutene, 24%; (h) Na−NH_3 (liq), *trans*-1,4-dibromobutene, 22%.

Scheme 5[a]



[a] Reagents and conditions: (a) (i) TMEDA, *sec*-BuLi, THF, (ii) CO_2, HCl, 80%; (b) TMSEOH, DEAD, Ph_3P, THF, 72%; (c) BnSH, NaOMe, MeOH, 78%; (d) TFA, DCM, 75%; (e) $(Boc)_2O$, $NaHCO_3$, MeOH, 90%; (f) TBAF, THF, quant; (g) **21**, PyBOP, DIEA, CH_2Cl_2, 62%; (h) (i) Na−NH_3 (liq), (ii) *trans*-dibromobutene, 54%; (i) TFA/DCM, quant.

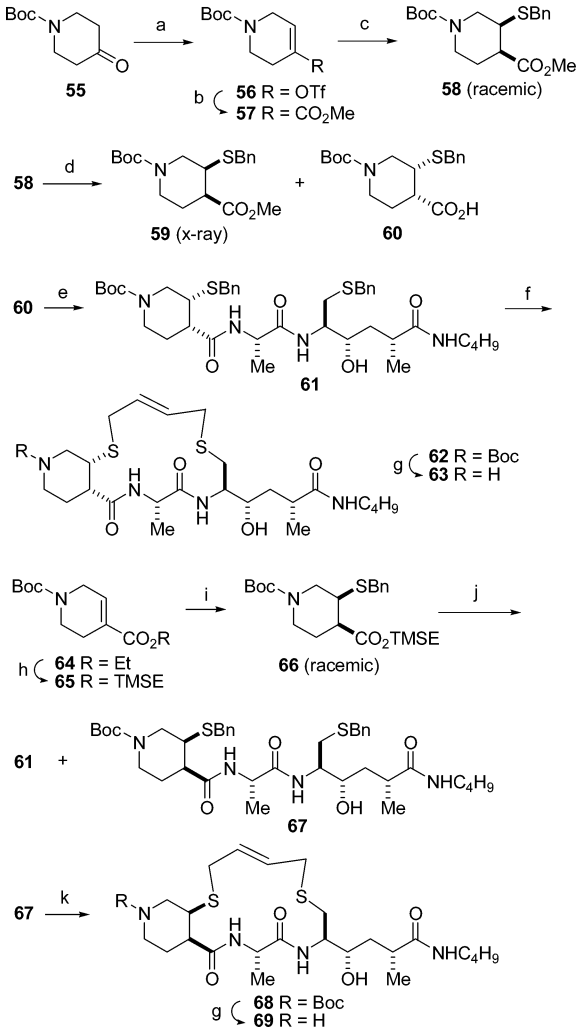
In addition to the above-described inhibitors, modeling studies also suggested bicyclic piperidine macrocycles as potential inhibitors so as to benefit from specific interactions with individual amino acid residues in the P_3 pocket, such as Gly11 and Thr232 (see Discussion). We synthesized 2,3-disubstituted and 3,4-disubstituted piperidine dithia macrocycles **52**, **54**, **63**, and **69** ,respectively, in diastereomerically pure form (Schemes 5 and 6).

The synthesis of these bicyclic macrocycles presented significant challenges. Modeling studies suggested the need for a (2*R*,3*R)* absolute configuration for the piperidine moiety as in **54**. Our synthetic route allowed us to prepare both diastereomeric final products with either (2*S*,3*S*) or (2*R*,3*R*) configuration as in **52** and **54**, respectively. Results later showed that unexpectedly the (2*S*,3*S*)-diastereomer **52** had higher activity compared with **54** (see Discussion).

Racemic *N*-Boc-3-methoxy piperidine **43** was treated with *sec*-BuLi in the presence of tetramethylethylenediamine (TMEDA) to generate the corresponding α-lithiated heterocycle[33] (Scheme 5). Quenching with CO_2 and workup led to the α,*β*-unsaturated acid **44** in excellent yield. Esterification to the trimethylsilylethyl ester **45** and treatment with benzyl mercaptan in methanolic sodium methoxide[34,35] gave a 78% yield of a 1:1 mixture of diastereomeric *N*-Boc-3-*S*-benzyl pipecolic acid esters **46**. Cleavage of the Boc group allowed the separation of the racemic cis and trans isomers. The cis isomer of **47** was transformed again to the *N*-Boc ester **48**, and the (trimethylsilyl)-ethyl (TMSE) ester was cleaved leading to free acid **49**. Peptide coupling with the amine derived from **21** gave amides **50** as a 1:1 inseparable mixture of diastereomers. Treatment with Na/NH_3(liquid) generated the corresponding sodium thiolates, which upon alkylation with *trans*-1,4-dibromobutene gave the desired bicyclic dithia macrocycles **51** and **53** in 54% yield after separation by column chromatography. Cleavage of the *N*-Boc group gave the corresponding piperidine dithia macrocycles **52** and **54**, respectively. The stereochemical identity of **52** was deduced from the X-ray structure of a cocrystal complex with BACE (see below). While the (2*R*,3*R*)-isomer **54** showed only weak inhibitory activity against BACE (45% inhibition at 10 μM), the (2*S*,3*S*)-isomer **52** showed an IC_{50} of 190 nM, which was in contradiction to the modeling study (see Discussion).

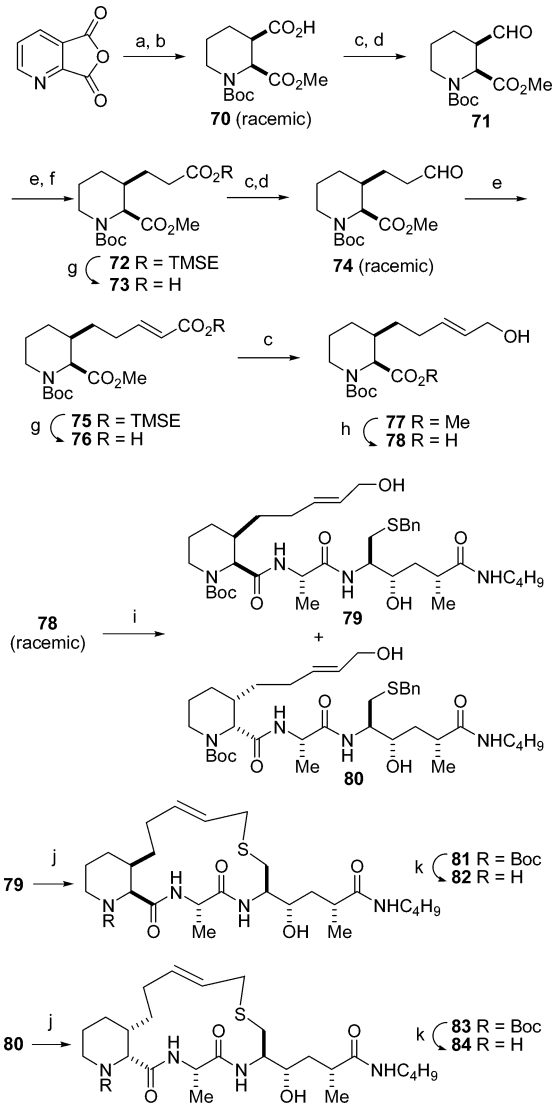
The isomeric (3*R*,4*S)*-bicyclic piperidine dithia macrocycle corresponding to **63** (and its 3*S*,4*R*-diastereomer **69**) were synthesized starting with *N*-Boc-4-ketopiperidine **55** (Scheme 6). Treatment with lithium diisopropylamide (LDA) and trapping the enolate with Comins's reagent[36,37] gave the enol triflate **56**, which was transformed to the corresponding methyl ester **57** using a Pd-catalyzed carbonylation reaction.[38] Conjugate addition of benzyl mercaptan in methanolic sodium methoxide gave a racemic mixture of *cis*-3-benzylthioethers **58**. Treatment of the mixture with pig liver esterase in phosphate buffer (pH 7.2) afforded the ester **59** and acid **60** in quantitative yield. The identity of the ester **59** was ascertained from a single-crystal X-ray structure.[32] Coupling of the amine derived from **21** with **60** afforded the (3*R*,4*S*)-piperidine linear peptide **61** in 68% yield. Reductive cleavage of the benzyl groups and bis-alkylation with *trans*-1,4-dibromobutene gave the intended macrocycle **62** in 39% isolated yield. Cleavage of the *N*-Boc group gave the corresponding piperidine dithia macrocycle **63** in quantitative yield. A similar protocol was followed for the synthesis of the diastereoisomeric (3*S*,4*R)*-piperidine dithia macrocycles **68** and

Scheme 6[a]



[a] Reagents and conditions: (a) (i) LDA, THF, (ii) Comins's reagent, THF, 81%; (b) $Pd(OAc)_2$, Ph_3P, CO, DMF, MeOH, 77%; (c) BnSH, NaOMe, MeOH, 89%; (d) PLE, buffer, pH 7.2, 49%; (e) **21**, PyBOP, DIEA, CH_2Cl_2, 68%; (f) (i) Na−NH_3 (liq), (ii) *trans*-dibromobutene, 39%; (g) TFA, CH_2Cl_2, quant; (h) (i) LiOH, THF, H_2O, (ii) TMSEOH, EDCI, DMAP, 74% for two steps; (i) BnSH, NaOMe, MeOH, 82%; (j) (i) TBAF, (ii) **21**, PyBOP, DIEA, $CH2Cl_2$, 68%; (k) Na−NH_3 (liq), then *trans*-1,4-dibromobutene, 48%.

Scheme 7[a]



[a] Reagents and conditions: (a) MeOH, reflux, 50%; (b) (i) Pd/C, H_2, HOAc, (ii) $(Boc)_2O$, MeOH, $NaHCO_3$ 76%; (c) (i) $(COCl)_2$, toluene, (ii) $NaBH_4$, THF, 78%; (d) Dess−Martin periodinane, 90%; (e) $Ph_3P{=}CHCO_2$-TMSE, CH_2Cl_2, 93%; (f) Pd/C, H_2, AcOEt, 98%; (g) TBAF, THF, 93%; (h) LiOH, THF−H_2O, quant; (i) **21**, PyBOP, DIEA, CH_2Cl_2, 64%; (j) (i) Na−NH_3 (liq), (ii) ADDP, PMe_3, CH_2Cl_2, 42% for two steps; (k) TFA, CH_2Cl_2, quant.

69 starting from **64**, which was prepared from 3-keto-4-carbomethoxy *N*-benzylpiperidine.[39,40] In this case, it was more practical to separate the diastereomeric macrocycles **61** and **67**, rather than to use enantiopure **59**.

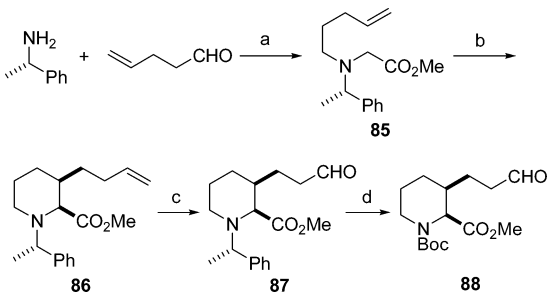
Our modeling studies also suggested that the carba/thia analogues **82** and **84** of the two 2,3-disubstituted piperidine bicyclic macrocycles would be potential inhibitors of the enzyme (Scheme 7). We therefore in parallel also developed methods for the stereocontrolled synthesis of macrocycles in this new series. For practical reasons, we utilized sequences that would give both diastereomers to maximize information with regard to stereochemical differences.

The commercially available 2,3-pyridinedicarboxylic anhydride was subjected to methanolysis, and the resulting acid **70** was converted through well-precedented steps to the extended α,β-unsaturated ester **72**, then aldehyde **74**, which was extended to the allylic alcohol **77** (Scheme 7). Coupling of the corresponding carboxylic acid **78** with the amine derived from **21** afforded a separable mixture of dipeptides **79** and **80**. Cleavage of the *S*-benzyl group, followed by intramolecular Mitsunobu thioetherification, gave the bicyclic piperidine carba/thia macrocycles **81** and **83**, respectively. Cleavage of the *N*-Boc group by acidic treatment gave the free piperidine bicyclic macrocycles **82** and **84**, respectively.

An enantio-enriched version was also achieved to assign absolute stereochemistry to the separated diastereomers **82** and **84** and to eventually secure their synthesis as pure diastereomers. Thus, *S*-1-phenylethylamine was transformed to the bis-alkylated enantiopure glycine ester **85** following Normant's procedure[41,42] (Scheme 8). Base-catalyzed cyclization in the presence of CuCN and allyl bromide gave the chain-extended piperidine **86** in 65% yield. Oxidative cleavage of the terminal olefin with OsO_4 in the presence of $NaIO_4$ afforded the aldehyde **87**. Reductive cleavage of the α-methylbenzyl group and further protection as *N*-Boc derivative afforded **88,** which corresponds to the enantiopure form of **74**. Thus, access to enantiopure **82** could be achieved via an asymmetric synthesis.

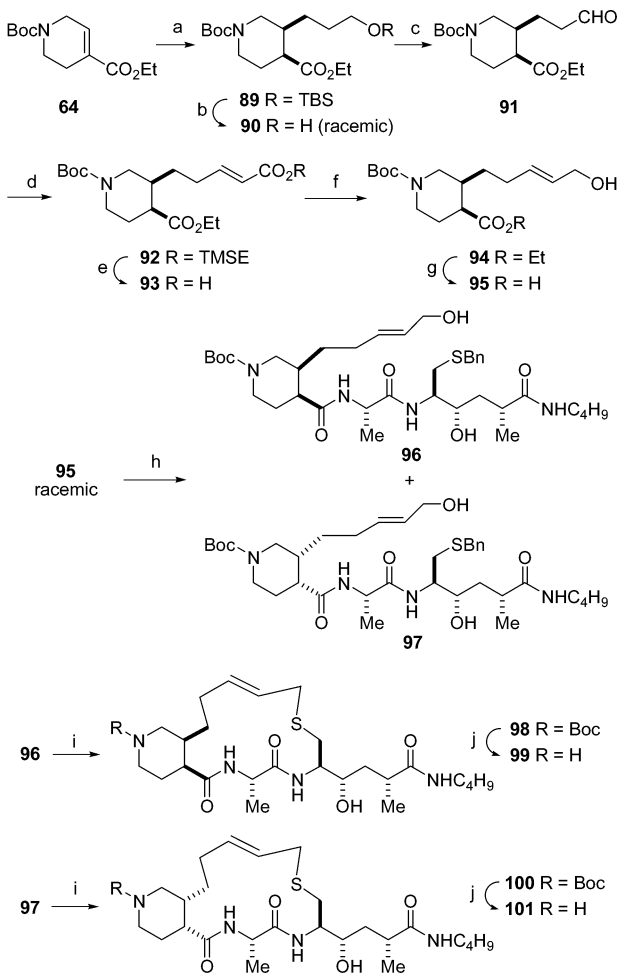
Finally, the diastereomeric 3,4-disubstituted piperidine carba/thia variants **99** and **101** were synthesized from the previously

Scheme 8[a]



[a] Reagents and conditions: (a) (i) DCM, 4 Å MS, rt, (ii) $NaBH_4$, MeOH, (iii) $BrCH_2CO_2Me$, Et_3N, DMSO, 80% for three steps; (b) (i) LDA, $ZnBr_2$, Et_2O, (ii) CuCN, AllylBr, THF, 65%; (c) OsO_4, dioxane−H_2O, $NaIO_4$, 61%; (d) Pd/C, H_2, $(Boc)_2O$, MeOH, 54%.

Scheme 9[a]



[a] Reagents and conditions: (a) (i) Mg, $BrCH_2CH_2CH_2OTBS$, THF, then CuI, (ii) **64**, TMSCl, HMPA, 68%; (b) TBAF, THF, 90%; (c) Dess−Martin periodinane, 80%; (d) $Ph_3P{=}CHCO_2TMSE$, CH_2Cl_2, 75%; (e) TBAF, THF, 63%; (f) (i) $ClCO_2Et$, Et_3N, THF, (ii) $NaBH_4$, MeOH, 60%; (g) LiOH, THF−H_2O, 96%; (h) **21**, PyBOP, DIEA, CH_2Cl_2, 70%; (i) (i) Na−NH_3 (liq), (ii) ADDP, PMe_3, imidazole, CH_2Cl_2, 30%; (j) TFA, DCM, quant.

described ester **64** (Scheme 9). A mixed cuprate reagent prepared from 3-*tert*-butyldimethylsilyloxy propyl bromide[43] was added to **64** to give an 8:1 cis/trans mixture of adducts **89**. Cleavage of the TBS group led to the corresponding alcohols, which were separable by flash column chromatography. Oxidation of the racemic cis isomer **90** with the Dess−Martin periodinane reagent,[44,45] followed by Wittig homologation, gave α,β-unsaturated ester **92**, which was selectively transformed to the corresponding allylic alcohol **94**. Hydrolysis of the ethyl ester and coupling of the resulting acid **95** with the amine derived from **21** gave a 1:1 mixture of the dipeptides **96** and **97**, which were easily separated by flash column chromatography. Cleavage of the benzylthioether and intramolecular Mitsunobu thioetherification, as previously described in Scheme 6, gave the isomeric macrocycles **98** and **100**, which were individually converted to the bicyclic piperidine carbathio macrocycles **99** and **101**, respectively (relative cis stereochemistry).

Biological Data and Structure−Activity Relationships. SAR of Dithia Macrocycles. Statin-derived bis-thioether macrocycles have been shown to have similar activity on pepsin compared with their open chain analogues.[7] Hydroxyethylene-type open-chain inhibitors **103** and **104**, spanning P_3 to P_2', were available from previous unpublished studies in our laboratory. These showed submicromolar activity on BACE and nanomolar activity on pepsin (Table 1). We prepared a number of closely related *N*-Ac dithia macrocycles linking P_1 and P_3 side chains (Table 1, **29**−**31**). A dramatic loss of activity was found (IC_{50} > 10 μM) against BACE, while a less pronounced loss in activity was observed for pepsin and cathepsin D (Table 1). These two enzymes were chosen for comparison because they are the most similar structurally known aspartic proteases (except for the almost identical BACE2).

The 15- and 16-membered *N*-Boc saturated macrocycles were found to have about equal potency for BACE, while the 17-membered ring had clearly lower activity (Table 1, **23** and **24** compared with **25**). For pepsin, the ring size does not seem to affect the activity, while for cathepsin D, the larger rings are preferred over the smaller 15-membered ring.

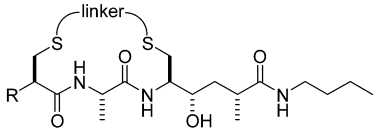
Compared with the saturated inhibitor **23**, the conformationally restricted *trans*-olefin **28** in the 15-membered series showed increased activity on BACE, while the corresponding *cis*-olefin **27** was only slightly weaker. Molecular modeling could not reveal any clear differences between the saturated linker and the two olefinic counterparts. The data suggests that in the *trans*-olefin, the flexibility of the chain is restricted in a favorable conformation, leading to better binding and increased activity compared with the saturated analogue. As predicted in the model, the aromatic linker in compounds **26** and **32** is too bulky to fit in the pocket, and the activity is therefore lost.

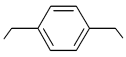
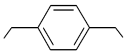
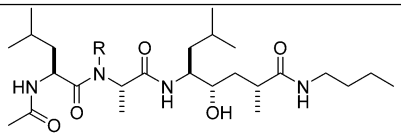
The replacement of the Boc group by an acetyl consistently results in lower activity against BACE, as well as cathepsin D and pepsin (Table 1, **23**−**26** compared with **29**−**32**) as reported by other groups.[46] The S_4 pocket is substantially more hydrophobic in cathepsin D (e.g., Leu236, Leu 292, Leu303, and Met307 in cathepsin D correspond to Asn233, Arg307, Lys321, and Ser325 in BACE, respectively), which may explain the larger contribution of the Boc group to binding potency. The small beneficial effect observed with BACE compared with cathepsin D suggests that in this case, the *tert*-butyl moiety of the Boc group cannot make good hydrophobic contacts due to the more hydrophilic nature of the S_4 pocket. This inference is supported by the X-ray analysis of the BACE complex with **42** (see below).

While both *N*-Boc and *N*-acetyl groups allow for the positive interaction of the NH with Thr232, the loss of this interaction results in considerably lower activity as seen in the corresponding amino analogues compounds **34** and **35** (compared with **27** and **28**).

SAR of Oxygen-Linked Macrocycles. In a limited program, we also explored the dioxa and mixed oxa/thia analogues of the dithia macrocycles (Table 2). For the interpretation of the results, it has to be considered that these compounds were

Table 1. SAR of Dithia Macrocycles and Open-Chain References

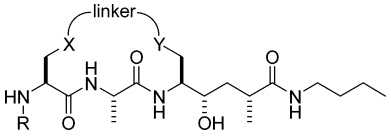


Compound no.	R =	Linker	IC_{50} BACE (μM)	IC_{50} CathD (μM)	IC_{50} Pepsin (μM)
23	BocNH	$(CH_2)_4$	20.0	0.18	0.025
24	BocNH	$(CH_2)_5$	16.9	0.020	0.030
25	BocNH	$(CH_2)_6$	>10	0.025	0.060
26	BocNH		>10	0.195	0.385
27	BocNH	*cis*-CH_2-CH=CH-CH_2	9.0	0.46	<0.01
28	BocNH	*trans*-CH_2-CH=CH-CH_2	1.3	0.19	<0.01
29	AcNH	$(CH_2)_4$	>10	9.7	0.74
30	AcNH	$(CH_2)_5$	>10	1.7	0.29
31	AcNH	$(CH_2)_6$	>10	1.25	0.27
32	AcNH		>10	3.6	1.7
34	H	*cis*-CH_2-CH=CH-CH_2	>10	>10	79%@ 10μM[a]
35	H	*trans*-CH_2-CH=CH-CH_2	>10	3.9	0.8
102	H_2N	*trans*-CH_2-CH=CH-CH_2	>10	0.15	<0.01
					
103	H		0.12	0.26	0.015
104	Me		0.10	0.19	0.046

[a] IC_{50} not determined.

obtained as undefined mixtures of *cis*- and *trans*-olefins. Nevertheless, we can conclude that the dioxa analogues are weaker on all three enzymes compared with the dithia macrocycle (Table 2, **15** and **16** compared with **23**, **27**, and **28**). In the case of BACE, this seems to be due to unfavorable interactions of the oxygen in this specific position in P_3. The properties of this position are determined by the closely located lipophilic Ile110 and the proximity of the carbonyl oxygen of Gly11. The detrimental effect of an oxygen atom at this particular position was also observed in other peptidomimetic macrocyclic series (unpublished results). The mixed analogue **17** showed improved activity on BACE compared with the dithia analogues **27** and **28**, indicating a slightly positive effect of the replacement of sulfur by an oxygen in the P_1 linker. The effect

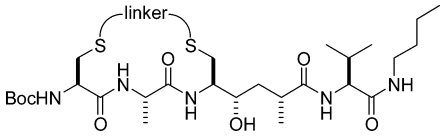
Table 2. SAR of Oxygen-Linked Macrocycles



compd no.	R, X, Y	linker	IC_{50} BACE (μM)	IC_{50} CathD (μM)	IC_{50} pepsin (μM)
16	Boc, O, O	$(CH_2)_4$	>10	1.11	0.325
15	Boc, O, O	CH_2—CH═CH—CH_2[a]	20.3	0.91	0.060
17	Boc, S, O	CH_2—CH═CH—CH_2[a]	0.51	0.11	<0.01
18	Ac, S, O	CH_2—CH═CH—CH_2[a]	1.12	6.0	0.17

[a] Olefins were mixtures of cis and trans isomers.

Table 3. Elongation in P′



compd no.	linker	IC_{50} BACE (μM)	IC_{50} CathD (μM)	IC_{50} pepsin (μM)
41	cis-CH_2—CH═CH—CH_2	1.97	0.050	<0.01
42	trans-CH_2—CH═CH—CH_2	0.156	0.011	<0.01

on inhibition of cathepsin D and pepsin was marginal. The replacement of the *N*-Boc group by *N*-acetyl resulted in the same small effect as seen before (Table 2, **17** compared with **18**). Due to the difficulty to control the geometry of the olefins, further studies were continued only in the dithia series (despite the tendency for higher potency of the mixed analogues).

Effect of Elongation in P′. The compounds described so far do not contain an amino acid residue in P_2' but rather a butylamide capping group filling the respective pocket. As already demonstrated in other series,[27] the elongation of the P′ side by a capped P_2' amino acid increases the activity. In the present case, the introduction of an additional valine in P_2' resulted in an increase of activity by about one order of magnitude (Table 3). This is true for BACE as well as cathepsin D and comparable to the effect found in previous series.[27] The effect on pepsin could not be quantified by our assay system, but the high activity (<10 nM) is well in line with the activity reported by Szewczuk et al.[7] for an analogous statin-derived *trans*-butene-linked 15-membered dithia macrocycle (<1 nM). Against BACE, the *trans*-dithia macrocycle **42** exhibited an IC_{50} of 156 nM and was submitted for cocrystallization. The structure of the complex was solved to a resolution of 2.10 Å (Figure 3) and supported our original hypothesis, showing a very good match of the experimental structure to the one predicted by the model.

In particular, a structural overlay of the **1** (OM00-3) complex (Figure 3) with the macrocyclic compound **42** demonstrated that the peptide backbones of both compounds superimpose remarkably well. All important binding interactions originally observed in the complex with the linear peptidomimetic inhibitor were in fact nicely mimicked by the macrocyclic inhibitor. Critical hydrogen-bonded interactions to the BACE active site, including those to Gly34, Pro70, Thr72, Gln73, Gly230, and Thr232, are also observed with **42**, further confirming that the binding of the hydroxyethylene transition state isostere is not altered as a consequence of the incorporation of the macrocyclic motif **42**. Furthermore, and in comparison to the **1** complex, only a few structural changes affecting the enzyme active site are observed,

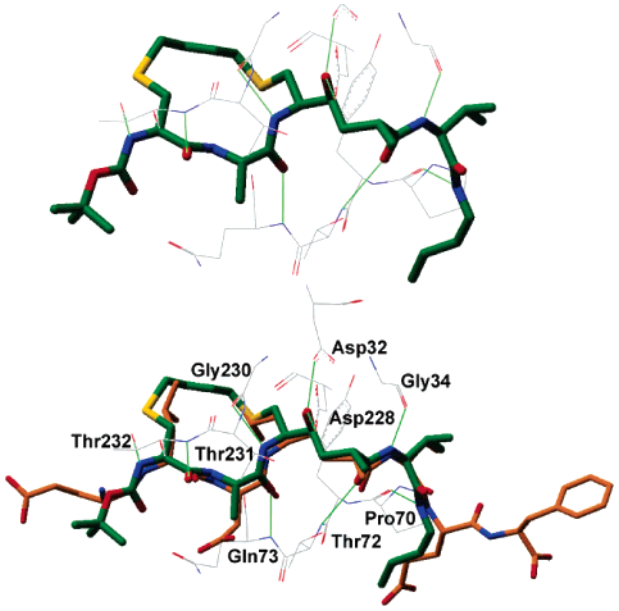


Figure 3. X-ray structure of **42** (dark green)−BACE complex (top) and overlay of the X-ray structures of BACE complexes with **42** (this work, dark green) and **1** (PDB 1M4H, orange) (bottom).

the main difference between the two complexes being a small induced fit of the enzyme flap, which can be rationalized by the presence of smaller substituents at P_2 and the leaner substituent at P_1 in **42**. The butylamide cap binds to the S_3' subsite and appears to be a good replacement for the P_3' glutamic acid of **1**, contributing similar hydrophobic contacts to the enzyme flap as well as to the H-bonded interaction to the Pro70 oxygen. Surprisingly, the N-terminal Boc protecting group was not visible in the electron density maps, suggesting that this part of the molecule remains mobile in the complex or adopts several binding modes. This observation is consistent with the fact that the S_4 pocket of BACE is large, very hydrophilic, and highly exposed to solvent. Also, our in vitro inhibition data show that an N-terminal Boc group is only marginally better than the corresponding *N*-acetyl derivative against BACE but clearly more active than the free amine **102** as reported for other cases.[6] The electron density for the *trans*-butene linker in the macrocycle was weak, leaving the position of the double bond undefined, indicating that conformational disorder is also affecting this region of the molecule, although to a lesser extent. This observation suggests that the *trans*-dithia bridge could be present in more than one tight fitting conformation in the S_1 and S_3 subpockets, which are both large enough to accommodate a branched alkyl side chain such as leucine, as in OM00-3 for instance. Indeed, flexible docking calculations indicate that several conformations in the area of the double bond are possible without affecting the overall position of the ligand.

Bicyclic Scaffolds. In addition to the above-described macrocycles, we also explored two bicyclic piperidine scaffolds with a positively charged nitrogen represented by 2,3- and 3,4-disubstituted **54** and **69**, respectively. They were designed in the model to each pick up one of two possible interactions, either with the Thr232 OH (as in **1** and other peptidomimetic inhibitors) or with the Gly11 CO (Figure 4). These interactions were intended to replace and compensate for the interactions of the P_3-P_4 amide or carbamate group in the former structures.

To our disappointment, the designed compound **69** was found to be inactive against BACE, while compound **54** showed weak activity (Table 4). In comparison with compound **35** (lacking the piperidine ring), there was no gain in activity for **69** but a

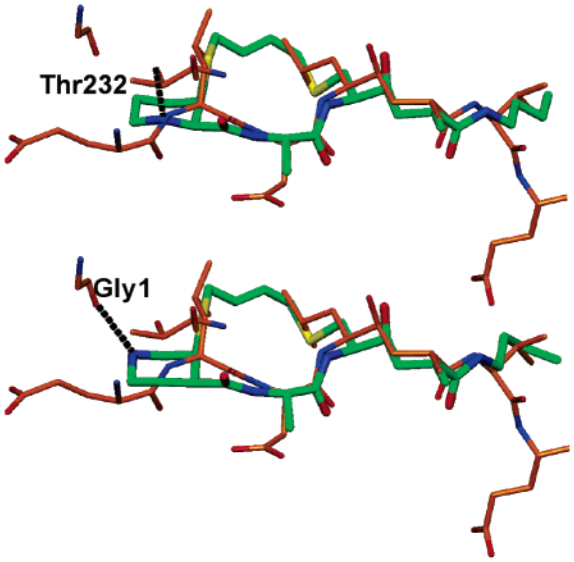
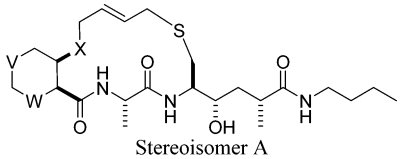
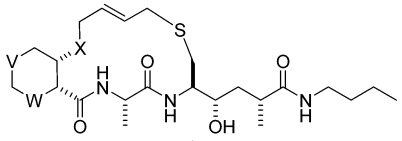


Figure 4. Overlay of OM00-3 (orange) with models of bicyclic inhibitors (**54**, top, and **69**, bottom) showing the intended interactions and expected conformation.

Table 4. SAR of Bicyclic Macrocycles





compd no.	stereoisomer	X	V	W	IC_{50} BACE (μM)	IC_{50} CathD (μM)	IC_{50} pepsin (μM)
69	A	S	NH	CH_2	>10	>10	~2
63	B	S	NH	CH_2	>10	~9	~10
54	A	S	CH_2	NH	~12	~0.2	~0.01
52	B	S	CH_2	NH	0.19	0.01	<0.01
99	A	CH_2	NH	CH_2	>10	>10	>10
101	B	CH_2	NH	CH_2	>10	>10	>10
82	A	CH_2	CH_2	NH	>10	>10	0.092
84	B	CH_2	CH_2	NH	>10	6.9	0.51

slight gain for **54**, indicating that the interaction with Thr232 is more feasible than the interaction with Gly11. The observed parallel gain in activity for **54** compared with **35** in cathepsin D and pepsin can be attributed to a similar positive interaction of the piperidine nitrogen with the Ser235 residue in the position corresponding to Thr232 in BACE. Since the syntheses for both bicyclic scaffolds started from racemic materials and involved a separation of isomers in a later step, we also had access to diastereomers **52** and **63**. As for **69**, the diastereomeric compound **63** was inactive against BACE and compared with **35**, which does not have a piperidine ring, did not show improvement for cathepsin D and pepsin either. However, compound **52** (the diastereomer of the weak inhibitor **54**) showed surprisingly good activity (Table 4). Compared with the elongated macrocycle **42**, **52** lacks the P_4 and P_3' moieties. Nevertheless, the two compounds are equipotent against all enzymes. This was difficult to understand on the basis of the model, and the compound was therefore submitted for cocrys-

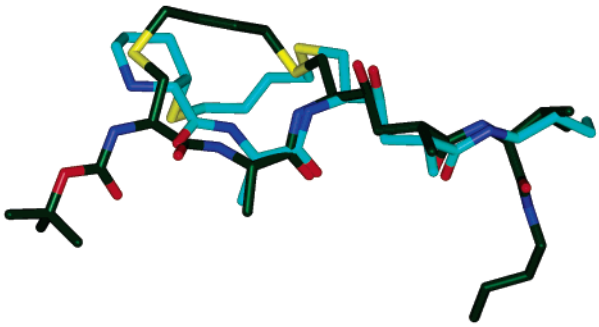


Figure 5. Overlay of the X-ray conformations of the BACE complexes with **42** (dark green) and **52** (cyan).

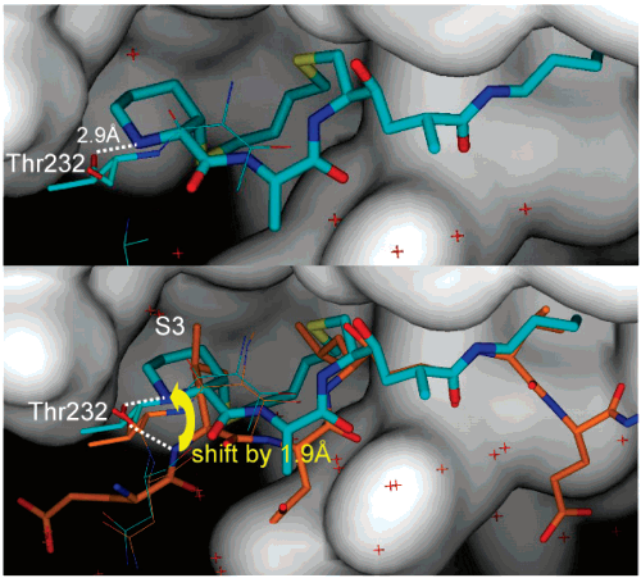


Figure 6. X-ray crystal structure of **52** (cyan)−BACE complex (top) and overlay of crystal structures of **52** (cyan) and **1** (orange) (partial surface to show S_3 pocket) (bottom).

tallization. The structure could be solved to a resolution of 2.3 Å, and in contrast to the crystal structure of **42** with the enzyme, it revealed some unexpected surprises.

A comparison of the BACE complexes with **42** and **52** is presented in Figure 5. The structure of the active site and the conformation of the enzyme flap are similar in the two complexes. However, the binding modes of these two *trans*-dithia macrocyclic compounds differ substantially in several respects. As expected, the butylamine group of **52** binds in S_2' and acts as a replacement of the valine side chain of **42**, while maintaining the key H-bonded interaction to Gly34. Modeling of the originally suggested (2*R*,3*R*) isomer **54** predicted an interaction of the piperidine nitrogen with Thr232. The active diastereomer **52** indeed forms such a hydrogen bond of 2.9 Å length. However, the position of the nitrogen is not as seen in most cocrystal structures (e.g., **1**) but instead is shifted by 1.5−2 Å toward the S_3 pocket (Figure 6). Because of this shift, the piperidine carbon chain fills nicely the hydrophobic S_3 pocket. As an additional striking difference, the *trans*-dithia bridge of **52** follows a completely different path in comparison to that observed in the complex with **42**. It seems surprising that such good activity is exhibited by a compound with such an unusual conformation of the macrocyclic chain, in particular because the space usually occupied by P_1 and P_3, as seen in **1**, is not filled (see Figure 6). We speculate that this is due to the positive interaction of the piperidine moiety in the S_3 pocket as described above. Interestingly, although the electron density was well defined for most inhibitor atoms, it was again weaker for the *trans*-butene linker, with an undefined position of the double bond. This observation suggests that the conformational flexibility already observed for the *trans*-dithia linker of compound **42** is also exhibited by the bicyclic piperidine macrocyclic compound **52**.

In an attempt to better understand the discrepancy between the model and the results for the bicyclic compounds we tried a functional modification in the macrocycle by replacing one sulfur atom by carbon. Unexpectedly, all the diastereomeric carbathia bicyclic macrocycles (**82**, **84**, **99**, and **101**), were inactive against BACE, including the carbon analogue **84** of the active inhibitor **52**. The activities were found to be lower than the respective dithia analogues for cathepsin D (Table 4). Curiously, only the two carbathia analogues **82** and **84** showed inhibition against pepsin (Table 4).

Conclusion

The primary objective of this study was to demonstrate the feasibility of linking P_1 and P_3 residues in acyclic BACE inhibitors, which would result in macrocyclic structures. Beside other advantages, these compounds were expected to show improved activity through pre-organization of the bioactive conformation. However, our expectations for activity on BACE were not fulfilled, especially in comparison with the high activity on pepsin. A cocrystal structure of one of the inhibitors in BACE showed that despite the macrocyclization, the molecule still seems to be relatively flexible, as could be concluded, for example, from the weak electron density for the chain positioned in the S_1-S_3 pockets. To improve interactions through additional hydrogen bonds and to introduce further rigidity, novel bicyclic macrocycles incorporating a piperidine moiety were designed. Synthetic approaches for all possible diastereoisomers of the piperidine moiety were developed. Surprisingly, the biological results did not match the predictions from the model with respect to the preferred stereochemistry. A cocrystal structure of the most active inhibitor revealed a shift of the molecule that unexpectedly placed the piperidine ring in the S_3 pocket, while forcing the P_1-P_3 chain into an unusual conformation and orientation.

Experimental Section

Solvents were distilled under positive pressure of dry argon before use and dried by standard methods: THF and ether from Na/benzophenone; CH_2Cl_2 and toluene from CaH_2. All commercially available reagents were used without further purification. All reactions were performed under argon atmosphere. NMR (^1H, ^{13}C) spectra were recorded on Bruker AMX-300 and ARX-400 spectrometers in $CDCl_3$, CD_3OD, or D_2O with solvent resonance as the internal standard. Low- and high-resolution mass spectra were recorded on VG Micromass, AEIMS 902, or Kratos MS-50 spectrometers using fast atom bombardment (FAB). The purity of the macrocyclic target compounds was determined to be >95% by LC/MS obtained on a Finnigan Surveyor MSQ spectrometer. Purity of the compounds was determined by method A, Alltech Prevail C18 column (250 mm × 4.6 mm) at 0.5 mL/min flow rate using a gradient of 20−90% acetonitrile−water (0.1% trifluoroacetic acid), and method B, Alltech Prevail C18 column (250 mm × 4.6 mm) at 0.5 mL/min flow rate using 65% methanol−water (0.1% trifluoroacetic acid). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter in a 1 dm cell at ambient temperature. Analytical thin-layer chromatography was performed on Merck 60F 254 precoated silica gel plates. Flash column chromatography was performed using 40−60 micron silica gel at increased pressure. All melting points are uncorrected.

(4*S*,1′*S*)-4-(1-Hydroxy-3-methoxycarbonyl-prop-2-ynyl)-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (2) and

(4*S*,1′*R*)-4-(1-Hydroxy-3-methoxycarbonyl-prop-2-ynyl)-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (3). Butyl lithium (1.6 M in hexane, 28 mL, 44.8 mmol) was added dropwise into a solution of methyl propiolate (4.1 mL, 49.1 mmol) in Et_2O (200 mL) at −78 °C, the solution was stirred at the same temperature for 1 h, and then a pre-prepared and pre-cooled solution of zinc bromide (12.4 g, 55 mmol) in diethyl ether (100 mL) was added through a cannula. The mixture was stirred at −78 °C to room temperature for 2 h, then cooled to −20 °C, and a pre-cooled solution of Garner's aldehyde[9] (4.1 g, 17.9 mmol) in Et_2O (40 mL) was added by a cannula. The mixture was stirred at −20 °C to room temperature for 6 h, then cooled to −20 °C, and saturated NH_4Cl (50 mL) was added to quench the reaction. The mixture was extracted with Et_2O (3 × 100 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Flash chromatography (hexane/AcOEt 3/1) of the residue gave **2** (3.2 g, 57%) and **3** (0.27 g, 5%). For **2**: $[\alpha]_D$ −79.3 (*c* 0.85, $CHCl_3$), ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ 4.69 (dd, 1H, J = 8.4, 6.0 Hz), 4.32 (b, 1H), 4.15 (b, 1H), 4.05 (m, 2H), 3.74 (s, 3H), 1.64 (s, 3H), 1.49 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.3, 154.0, 95.2, 86.4, 82.4, 77.2, 71.4, 65.6, 61.9, 53.2, 28.7, 26.7, 24.5; MS (FAB) *m*/*z* 314 (M + H$^+$), 258, 240, 214, 200; HRMS calcd for $C_{15}H_{23}NO_6$ (M + H$^+$) 314.1617, found 314.1613. For **3**: $[\alpha]_D$ −68.8 (*c* 1.29, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ 5.44 (b, 1H), 4.57 (b, 1H), 4.08 (b, 1H), 4.07−3.82 (m, 2H), 3.72 (s, 3H), 1.56 (s, 3H), 1.47 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.8, 153.9, 95.6, 85.8, 82.3, 77.7, 65.3, 64.8, 62.6, 53.1, 28.6, 26.1, 25.5; MS (FAB) *m*/*z* 314 (M + H$^+$), 258, 240, 214, 200; HRMS calcd for $C_{15}H_{23}NO_6$ (M + H$^+$) 314.1617, found 314.1613.

(4*S*,1′*S*)-4-(1-Hydroxy-3-methoxycarbonyl-propyl)-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (4). In procedure 1, a mixture of **2** (0.82 g, 2.6 mmol) and palladium (5% on barium sulfate, 0.25 g) in AcOEt (10 mL) was charged with H_2 to 50 psi and stirred for 3 h, then filtered through a pad of Celite and washed with AcOEt. The combined filtrate was concentrated to give product **4** (0.78 g, 95%). In procedure 2, into a solution of **5** (0.71 g, 2.3 mmol) in MeOH (20 mL) was added $NaBH_4$ (0.18 g, 4.6 mmol) portionwise at −15 °C. The mixture was stirred at −15 to 0 °C for 5 h, saturated NH_4Cl (5 mL) was added, MeOH was removed, the aqueous solution was extracted with AcOEt, and the organic layer was dried and concentrated. Flash chromatography (hexane/AcOEt 2/1) of the residue gave **4** (0.6 g, 85%): $[\alpha]_D$ −50.3 (*c* 0.64, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.14 (m, 1H), 4.09 (m, 1H), 3.98 (m, 1H), 3.94 (m, 1H), 3.80 (m, 1H), 3.65 (s, 3H), 2.52−2.42 (m, 2H), 1.82 (m, 1H), 1.62 (m, 1H), 1.56 (s, 3H), 1.47 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.5, 154.6, 94.8, 82.2, 77.6, 72.3, 65.1, 62.1, 51.9, 30.9, 28.7, 26.8, 24.5; MS (FAB) *m*/*z* 318 (M + H$^+$).

(4*S*)-4-(3-Methoxycarbonyl-propionyl)-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (5). Into a solution of Dess−Martin periodinane reagent (5 g, 12 mmol) in CH_2Cl_2 (50 mL), **3** (2.7 g, 8.6 mmol) in CH_2Cl_2 (25 mL) was added. The mixture was stirred at room temperature for 3 h, saturated $NaHCO_3$ and Na_2SO_3 were added, and then 1 N NaOH was added to get a clear solution. The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL); the combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography (hexane/AcOEt 5/1) of the residue gave the ketone (2.0 g, 75%). A mixture of the ketone (0.41 g, 1.3 mmol) and palladium (5% on barium sulfate, 0.1 g) in AcOEt (6 mL) was charged with H_2 to 50 psi and stirred for 3 h, then filtered through a pad of Celite and washed with AcOEt. The combined filtrate was concentrated to give **5** (0.4 g, 96%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.31 (b, 1H), 4.13−3.96 (m, 2H), 3.64 (s, 3H), 2.78 (m, 2H), 2.58 (m, 2H), 1.67 (s, 3H), 1.45 (s, 9H), 1.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 206.4, 172.7, 152.3, 94.4, 80.6, 76.9, 65.1, 51.7, 33.7, 33.3, 28.1, 25.3, 24.6; MS (FAB) *m*/*z* 316 (M + H$^+$), 260, 216, 202.

(4*S*,2′*S*)-2,2-Dimethyl-4-(5-oxo-tetrahydro-furan-2-yl)-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (6). Compound **4** (0.32 g, 1 mmol) was dissolved in toluene (5 mL), acetic acid (18 μL) was added, the mixture was heated to reflux for 5 h and then cooled to room temperature, and the solvent was removed under reduced pressure. Flash chromatography of the residue gave the product **6** (0.27 g, 95%): $[\alpha]_D$ −21.7 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz, 50 °C) δ 4.82 (b, 1H), 4.25 (b, 1H), 4.0 (dd, 1H, J = 10.0, 6.3 Hz), 3.87 (d, 1H, J = 10.0 Hz), 2.54 (m, 2H), 2.18 (m, 2H), 1.60 (s, 3H), 1.51 (s, 3H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.1, 153.6, 95.1, 81.2, 80.3, 79.2, 65.2, 59.5, 28.7, 26.8, 25.5, 23.6; MS (FAB) *m*/*z* 286 (M + H$^+$), 230, 186, 172, 154; HRMS calcd for $C_{14}H_{23}NO_5$ (M + H$^+$) 286.1654, found 286.1649.

(4*S*,2′*S*,4′*R*)-2,2-Dimethyl-4-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (7). To a stirred solution of **6** (0.8 g, 3.16 mmol) in THF (30 mL) at −78 °C under argon was added LiHMDS (1 M in THF, 4.7 mL) dropwise. The mixture was stirred at −78 °C for 30 min, then methyl iodide (0.39 mL, 6.4 mmol) was added dropwise, and the mixture was stirred at −78 °C for 40 min. The reaction mixture was quenched with saturated NH_4Cl and extracted with AcOEt (3 × 100 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography to give **7** as an amorphous solid (0.5 g, 70%): $[\alpha]_D$ −1.6 (*c* 0.73, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.75 (b, 1H), 4.21 (b, 1H), 3.94 (dd, 1H, J = 9.6, 6.2 Hz), 3.82 (m, 1H), 2.72 (b, 1H), 2.45(b, 1H), 2.33 (b, 1H), 1.93 (b, 1H), 1.63 (s, 3H), 1.57 (s, 3H), 1.49(s, 9H), 1.30 (d, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.2, 179.8, 153.5, 152.3, 95.2, 94.8, 81.4, 81.1, 77.2, 64.4, 58.5, 34.6, 34.4, 31.9, 28.7, 27.4, 27.1, 24.5, 23.2, 16.6, 16.4; MS (FAB) *m*/*z* 300 (M + H$^+$), 244, 200, 186, 154; HRMS calcd for $C_{15}H_{25}NO_5$ (M + H$^+$) 300.1810, found 300.1806.

(1*S*,2′*S*,4′*R*)-[2-Hydroxy-1-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic Acid *tert*-Butyl Ester (8). To a stirred solution of **7** (0.67 g, 2.2 mmol) in THF−H_2O (1/1, 26 mL) was added *p*-toluenesulfonic acid (0.85 g, 4.4 mmol). The mixture was stirred at room temperature for 2 days, saturated $NaHCO_3$ solution was added to pH 8, the mixture was extracted with AcOEt (3 × 60 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (hexane/AcOEt 1/2) to give **8** (0.43 g, 75%): $[\alpha]_D$ +4.6 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.92 (d, 1H, J = 8.2 Hz), 4.78 (b, 1H), 3.80−3.69 (m, 3H), 2.73 (m, 1H), 2.41 (m, 1H), 1.99 (m, 1H), s, 3H), 1.45 (s, 9H), 1.29 (d, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.5, 156.5, 80.8, 78.2, 63.5, 54.9, 34.6, 32.7, 28.7, 16.9; MS (FAB) *m*/*z* 260 (M + H$^+$), 204, 160, 136; HRMS calcd for $C_{12}H_{21}NO_5$ (M + H$^+$) 260.1511, found 260.1506.

(1*S*,2′*S*,4′*R*)-[2-Allyloxy-1-(4-methyl-5-oxo-tetrahydro-furan-2-yl)-ethyl]-carbamic Acid *tert*-Butyl Ester (9). Into a solution of **8** (0.2 g, 0.77 mmol) in CH_2Cl_2 (5 mL) and cyclohexane (10 mL) was added 2,2,2-trichloro-acetimidic acid allyl ester (0.33 g, 1.54 mmol) dropwise at 0 °C, followed by trifluoromethanesulfonic acid (12 μL). The mixture was warmed to room temperature and stirred for 5 h. The precipitate was filtered off, and the filtrate was washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt 2/1) of the residue gave **9** (0.18 g, 80%): $[\alpha]_D$ +7.8 (*c* 0.85, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.95 (b, 1H), 5.90 (m, 1H), 5.25 (m, 2H), 4.8 (m, 1H), 4.63 (m, 1H), 4.0 (m, 1H), 3.5 (m, 2H), 2.74 (m, 1H), 2.39 (m, 1H), 1.96 (m, 1H), 1.45 (s, 9H), 1.30 (d, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.4, 156.7, 134.5, 117.9, 81.0, 80.7, 72.6, 69.6, 66.4, 34.8, 32.5, 28.7, 16.9; MS (FAB) *m*/*z* 300 (M + H$^+$), 244, 200, 154; HRMS calcd for $C_{15}H_{25}NO_5$ (M + H$^+$) 300.1810, found 300.1816.

(1*S*,2*S*,4*R*)-(1-Allyloxymethyl-4-butylcarbamoyl-2-hydroxy-pentyl)-carbamic Acid *tert*-Butyl Ester (10). A mixture of **9** (0.26 g, 86 μmol) and butylamine (1.8 mL) was stirred at room temperature for 4 h. Excess butylamine was removed under reduced pressure. The residue was purified by flash chromatography (hexane/AcOEt 2/1) to give **10** (0.13 g, 40%): $[\alpha]_D$ −14 (*c* 0.25, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.86 (m, 2H), 5.20 (m, 3H), 3.98 (m, 2H), 3.91 (m, 1H), 3.65 (m, 2H), 3.62 (m, 2H), 3.24 (m, 2H), 2.49 (m, 1H), 1.65 (m, 2H), 1.45 (s, 9H), 1.48−1.32 (m,

4H), 1.16 (d, 3H, $J = 7.0$ Hz), 0.92 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8, 156.7, 134.3, 118.0, 80.0, 77.6, 73.3, 72.9, 70.6, 53.4, 39.5, 38.5, 37.7, 32.1, 28.8, 20.5, 14.2; MS (FAB) *m/z* 373 ($M + H^+$), 273, 200, 154; HRMS calcd for $C_{19}H_{36}N_2O_5$ ($M + H^+$) 373.2702, found 373.2690.

(1*S*,1′*S*,2′*S*,4′*R*)-[1-(1-Allyloxymethyl-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (11). Into a solution of **10** (0.17 g, 0.46 mmol) in CH_2Cl_2 (6 mL) was added TFA (1 mL). The solution was stirred at room temperature for 30 min and then concentrated. The residue was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 °C, and *N*-Boc alanine (0.14 g, 0.7 mmol), PyBOP (0.36 g, 0.7 mmol), and diisopropylethylamine (DIEA) (0.32 mL, 1.85 mmol) were added consecutively. The mixture was stirred at 0 °C to room temperature for 2 h and concentrated, and the residue was treated with 10% citric acid (2 mL), then extracted with AcOEt (3 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated. Flash chromatography (AcOEt) of the residue gave **11** (0.17 g, 85%): $[\alpha]_D$ −25.1 (*c* 0.55, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.67 (d, 1H, $J = 8.8$ Hz), 5.9−5.82 (m, 2H), 5.28−5.19 (m, 2H), 4.92 (b, 1H), 4.13 (b, 1H), 3.99−3.92 (m, 4H), 3.62 (d, 2H, $J = 4.0$ Hz), 3.24 (dd, 2H, $J = 12.9$, 6.7 Hz), 2.48 (m, 1H), 1.66 (m, 2H), 1.55 (m, 2H), 1.45 (s, 9H), 1.38 (d, 3H, $J = 7.1$ HZ), 1.35 (m, 2H), 1.15 (d, 3H, $J = 7.0$ Hz), 0.93 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8, 173.4, 154.7, 134.3, 118.2, 80.5, 77.6, 72.9, 72.5, 70.1, 52.4, 39.6, 38.4, 37.8, 32.1, 28.7, 20.5, 19.1, 17.9, 14.2; MS (FAB) *m/z* 444 ($M + H^+$), 370, 326, 307, 154; HRMS calcd for $C_{22}H_{41}N_3O_6$ ($M + H^+$) 444.3087, found 444.3084.

(1*S*,1′*S*,1″*S*,2″*S*,4″*R*)-{2-Allyloxy-1-[1-(1-allyloxymethyl-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl)-ethylcarbamoyl]-ethyl}-carbamic Acid *tert*-Butyl Ester (12). Into a solution of **11** (33 mg, 0.074 mmol) in CH_2Cl_2 (2.0 mL) was added TFA (0.33 mL). The mixture was stirred for 30 min and then concentrated in a vacuum. The amine salt was dissolved in CH_2Cl_2 (4 mL) and cooled to 0 °C, and *N*-Boc *O*-allyl serine (37 mg, 0.15 mmol) and PyBOP (77 mg, 0.15 mmol), followed by DIEA (70 μL, 0.37 mmol), were added. The mixture was stirred at 0 °C to room temperature for 2 h, then processed as described above. Flash chromatography (4% MeOH in AcOEt) of the residue gave pure **12** (28 mg, 67%): $[\alpha]_D$ −21 (*c* 1.3, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.0 (d, 1H, $J = 4.8$ Hz), 6.67 (b, 1H), 6.1 (b, 1H), 5.85 (m, 2H), 5.49 (d, 1H, $J = 5.6$ Hz), 5.28−5.16 (m, 4H), 4.36 (b, 1H), 3.98−3.81 (m, 6H), 3.55 (m, 3H), 3.22 (m, 4H), 2.50 (m, 1H), 1.60 (m, 3H), 1.45 (s, 9H), 1.41 (d, 3H, $J = 7.0$ Hz), 1.35 (m, 2H), 1.14 (d, 3H, $J = 7.0$ Hz), 0.91 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8, 172.7, 170.5, 156.1, 134.5, 134.3, 118.1, 117.9, 81.0, 72.7, 72.5, 69.8, 54.7, 52.3, 46.8, 39.5, 38.5, 37.7, 32.1, 28.7, 27.7, 26.7, 20.5, 19.1, 14.2; MS (FAB) *m/z* 593 ($M + Na^+$), 571 ($M + H^+$); HRMS calcd for $C_{28}H_{50}N_4O_8$ ($M + H^+$) 571.3693, found 571.3699.

(1*S*,1′*S*,1″*S*,2″*S*,4″*R*)-{1-[1-(1-Allyloxymethyl-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl)-ethylcarbamoyl]-2-allylsulfanyl-ethyl}-carbamic Acid *tert*-Butyl Ester (13). Into a solution of **11** (120 mg, 0.27 mmol) in CH_2Cl_2 (6.0 mL) was added TFA (1.0 mL). The mixture was stirred at room temperature for 30 min and then concentrated in a vacuum. The amine salt was dissolved in CH_2Cl_2 (7 mL) and cooled to 0 °C, and *N*-Boc *S*-allyl cysteine (130 mg, 0.0.47 mmol) and PyBOP (0.21 g, 0.45 mmol), followed by DIEA (230 μL, 1.35 mmol), were added. The mixture was processed as described above. Flash chromatography (2% MeOH in AcOEt) of the residue gave pure **13** (0.12 g, 75%): $[\alpha]_D$ −62.7 (*c* 0.4, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.0 (d, 1H, $J = 8.0$ Hz), 6.85 (b, 1H), 6.08 (b, 1H), 5.86−5.73 (m, 2H), 5.45 (s, 1H), 5.26−5.12 (m, 4H), 4.52 (m, 1H), 4.24 (m, 1H), 4.0−3.92 (m, 4H), 3.59 (d, 2H, $J = 4.6$ Hz), 3.23 (dd, 2H, $J = 13.0$, 6.9), 3.15 (d, 2H, $J = 7.2$ Hz), 2.83 (m, 2H), 2.57 (m, 1H), 1.68−1.50 (m, 2H), 1.48−1.41 (m, 2H), 1.46 (s, 9H), 1.42 (d, 3H, $J = 7.0$ Hz), 1.35 (m, 2H), 1.14 (d, 3H, $J = 7.0$ Hz), 0.92 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.6, 172.6, 170.9, 156.2, 134.5, 134.0, 118.6, 117.9, 81.2, 80.2, 72.7, 71.9, 70.0, 55.9, 54.3, 49.9, 49.1, 39.6, 38.5, 37.7, 33.2, 31.9, 28.7, 20.5, 18.1, 14.2; MS (FAB) *m/z* 587 ($M + H^+$), 513, 414, 154; HRMS calcd for $C_{28}H_{50}N_4O_7S$ ($M + H^+$) 587.3492, found 587.3495.

(2*R*,4*S*,5*S*,2′*S*,2″*S*)-5-[2-(2-Acetylamino-3-allylsulfanyl-propionylamino)-propionylamino]-6-allyloxy-4-hydroxy-2-methyl-hexanoic Acid Butylamide (14). Into a solution of **11** (74 mg, 0.16 mmol) in CH_2Cl_2 (2.4 mL) was added TFA (0.4 mL). The mixture was stirred at room temperature for 30 min and then concentrated in a vacuum. The residue was treated with AcOEt (10 mL), washed with 1 N $NaHCO_3$, dried, and concentrated in a vacuum. The residue was dissolved in CH_2Cl_2−H_2O (1/1, 6 mL) and cooled to 0 °C. *N*-Ac *S*-allyl cysteine (49 mg, 0.32 mmol) and 1-hydroxybenzotriazole (HOBt) (33 mg, 0.32 mmol), followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCI; 46 mg, 0.32 mmol), were added. The mixture was stirred at 0−5 °C for 2 days, and then diluted with AcOEt (5 mL). 1 N HCl was added to pH 5, and the mixture was extracted with AcOEt (3 × 10 mL), then processed as described above. Flash chromatography (8% MeOH in AcOEt) of the residue gave **14** (23 mg, 27%): $[\alpha]_D$ −31.2 (*c* 0.5, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 7.48 (d, 1H, $J = 8.8$ Hz), 5.91−5.76 (m, 2H), 5.29−5.10 (m, 4H), 4.44 (m, 1H), 4.36 (m, 1H), 3.98 (m, 3H), 3.74 (m, 1H), 3.53 (m, 1H), 3.45 (m, 1H), 3.19 (m, 4H), 2.86 (m, 1H), 2.71 (m, 1H), 2.56 (b, 1H), 2.0 (s, 3H), 1.86 (m, 1H), 1.69 (m, 1H), 1.48 (m, 2H), 1.38 (d, 3H, $J = 7.0$ Hz), 1.33 (m, 2H), 1.11 (d, 3H, $J = 6.8$ Hz), 0.94 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 173.8, 172.5, 171.8, 135.1, 134.3, 117.1, 116.2, 71.9, 69.4, 67.8, 53.5, 49.8, 49.6, 39.1, 38.1, 37.6, 34.4, 32.0, 21.4, 20.1, 17.8, 17.1, 13.2; MS (FAB) *m/z* 529 ($M + H^+$), 511, 307, 154; HRMS calcd for $C_{25}H_{44}N_4O_6S$ ($M + H^+$) 529.3069, found 529.3066.

(3*S*,6*S*,9*S*,1′*S*,3′*R*)-[3-(3-Butylcarbamoyl-1-hydroxy-butyl)-6-methyl-5,8-dioxo-1,11-dioxa-4,7-diaza-cyclopentadec-13-en-9-yl]-carbamic Acid *tert*-Butyl Ester (15). Into a solution of **12** (25 mg, 0.044 mmol) in CH_2Cl_2 (18 mL) was added a solution of second generation Grubbs catalyst[14] (4 mg, 4.5 μmol) in CH_2Cl_2 (4 mL). The mixture was stirred at room temperature overnight and then concentrated. The residue was purified by flash chromatography (4% MeOH in AcOEt) to give **15** (8 mg, 34%): $[\alpha]_D$ −29 (*c* 0.4, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.65 (m, 2H), 4.61 (m, 1H), 4.27 (m, 1H), 4.02−3.90 (m, 5H), 3.69−3.50 (m, 5H), 3.18−3.13 (m, 2H), 2.59 (m, 1H), 1.98−1.71 (m, 5H), 1.44 (s, 9H), 1.34 (d, 3H, $J = 6.8$ Hz), 1.36 (m, 2H), 1.12 (d, 3H, $J = 7.0$ Hz), 0.94 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (MeOD, 100 MHz) δ 176.4, 172.1, 170.8, 155.1, 127.5, 126.6, 79.2, 68.3, 68.1, 67.8, 67.2, 52.6, 52.0, 47.8, 37.5, 36.6, 36.0, 33.8, 30.1, 26.1, 25.2, 24.6, 18.5, 11.6; MS (FAB) *m/z* 543 ($M + H^+$), 469, 425, 297, 154; HRMS calcd for $C_{26}H_{46}N_4O_8$ ($M + H^+$) 543.3394, found 543.3396; LC/MS retention time [A] 5.15 min, [B] 7.20 min.

(3*S*,6*S*,9*S*,1′*S*,3′*R*)-[3-(3-Butylcarbamoyl-1-hydroxy-butyl)-6-methyl-5,8-dioxo-1,11-dioxa-4,7-diaza-cyclopentadec-9-yl]-carbamic Acid *tert*-Butyl Ester (16). A mixture of **15** (9 mg, 0.016 mmol) and 10% Pd/C (16 mg) in AcOEt (2 mL) was charged with H_2 (balloon) and stirred overnight. The suspension was filtered through a pad of Celite washed with AcOEt, the combined filtrate was concentrated, and the residue was purified by flash chromatography (8% MeOH in AcOEt) to give **16** (8.2 mg, 91%): $[\alpha]_D$ −38.5 (*c* 0.4, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 4.64 (m, 1H), 4.39 (m, 1H), 4.24 (m, 1H), 4.01 (m, 1H), 3.64−3.39 (m, 7H), 3.16 (m, 2H), 2.58 (m, 2H), 2.02−1.86 (m, 3H), 1.73 (m, 2H), 1.60 (m, 2H), 1.45 (s, 9H), 1.46−1.32 (m, 6H), 1.34 (d, 3H, $J = 6.9$ Hz), 1.36 (m, 2H), 1.12 (d, 3H, $J = 6.8$ Hz), 0.94 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR (MeOD, 100 MHz) δ 176.3, 172.1, 170.1, 154.9, 78.2, 69.8, 69.3, 69.0, 68.0, 67.6, 52.6, 52.1, 37.5, 363, 36.0, 26.1, 25.3, 25.1, 24.5, 18.5, 16.4, 15.7, 11.6; MS (FAB) *m/z* 545 ($M + H^+$), 3.7, 289, 154; HRMS calcd for $C_{26}H_{48}N_4O_8$ ($M + H^+$) 545.3550, found 545.3546; LC/MS retention time [A] 5.23 min, [B] 7.39 min.

(3*S*,6*S*,9*S*,1′*S*,3′*R*)-[3-(3-Butylcarbamoyl-1-hydroxy-butyl)-6-methyl-5,8-dioxo-1-oxa-11-thia-4,7-diaza-cyclopentadec-13-en-9-yl]-carbamic Acid *tert*-Butyl Ester (17). Into a solution of **13** (16 mg, 0.023 mmol) in CH_2Cl_2 (12 mL) was added second

generation Grubbs catalyst[14] (4 mg, 4.5 μmol). The mixture was stirred at room temperature overnight, additional catalyst (2 mg, 2.25 μmol) was added, and the mixture was stirred for 6 h. A few drops of MeOH was added, the mixture was concentrated, and the residue was purified by flash chromatography (4% MeOH in AcOEt) to give **17** (3.1 mg, 25%): $[\alpha]_D$ −58.5 (c 0.4, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.68 (m, 1H), 5.55 (m, 1H), 4.57 (m, 1H), 4.0 (m, 1H), 3.99−3.89 (m, 3H), 3.63−3.55 (m, 3H), 3.22−3.11 (m, 4H), 2.85 (m, 2H), 2.62 (m, 2H), 1.76 (m, 2H), 1.48−1.35 (m, 2H), 1.46 (s, 9H), 1.34 (d, 3H, J = 7.0 Hz), 1.12 (d, 3H, J = 7.0 Hz), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.9, 173.0, 172.7, 156.8, 130.5, 129.5, 79.6, 70.4, 70.2, 69.0, 54.1, 54.0, 50.7, 39.0, 38.0, 37.6, 32.5, 31.6, 27.7, 26.5, 20.1, 18.0, 13.2; MS (FAB) m/z 559 (M + H$^+$), 485, 307, 154; HRMS calcd for $C_{26}H_{46}N_4O_7S$ (M + H$^+$) 559.3165, found 559.3166; LC/MS retention time [A] 19.43 min, [B] 27.15 min.

(3*S*,6*S*,9*S*,1′*S*,3′*R*)-4-(9-Acetylamino-6-methyl-5,8-dioxo-1-oxa-11-thia-4,7-diaza-cyclopentadec-13-en-3-yl)-*N*-butyl-4-hydroxy-2-methyl-butyramide (18). Into a solution of **14** (21 mg, 0.04 mmol) in CH_2Cl_2 (20 mL) was added second generation Grubbs catalyst[14] (7 mg, 8 μmol). The mixture was stirred at room temperature overnight, additional catalyst (3.5 mg, 4 μmol) was added, and the mixture was stirred for 6 h. A few drops of MeOH was added, and the mixture was concentrated. The residue was flash purified by flash chromatography (10% MeOH in AcOEt) to give **18** (4.5 mg, 23%): ^{1}H NMR (MeOD, 400 MHz) δ 7.84 (b, 1H), 7.2 (d, 1H, J = 8.4 Hz), 5.65 (m, 1H), 5.56 (m, 1H), 4.55 (m, 1H), 4.36 (m, 1H), 3.97−3.90 (m, 3H), 3.60−3.54 (m, 3H), 3.21−2.87 (m, 3H), 2.66 (m, 1H), 2.59 (m, 3H), 2.02 (m, 1H), 2.0 (s, 3H), 1.74 (m, 1H), 1.48−1.32 (m, 8H), 1.12 (d, 3H, J = 6.9 Hz), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 125 MHz) δ 177.6, 172.7, 172.1, 171.8, 130.4, 128.9, 70.1, 69.9, 68.7, 60.2, 53.6, 52.7, 48.5, 38.7, 37.6, 31.8, 31.3, 29.4, 20.9, 19.7, 17.6, 15.4, 13.1; MS (FAB) m/z 501 (M + H$^+$); HRMS calcd for $C_{23}H_{40}N_4O_6S$ (M + H)$^+$ 500.2741, found 500.2734; LC/MS retention time [A] 3.98 min, [B] 6.51 min.

(1*S*,2′*S*,4′*R*)-[2-Benzylsulfanyl-1-(4-methyl-5-oxo-tetrahydrofuran-2-yl)-ethyl]-carbamic Acid *tert*-Butyl Ester (19). Into a solution of **8** (0.2 g, 0.77 mmol) in CH_2Cl_2 (12 mL) were added imidazole (0.11 g, 1.5 mmol), 1,1′-(azodicarbonyl)dipiperidine (ADDP) (0.39 g, 1.5 mmol), and benzyl mercaptan (0.4 mL, 3.0 mmol), followed by PMe_3 (1 M in toluene, 1.54 mL) dropwise. The mixture was stirred at room temperature for 1 day, hexane (12 mL) was added, and the precipitate was removed by filtration. The filtrate was concentrated, and the residue was purified by flash chromatography (hexane/AcOEt 3/1) to give the product **19** (0.19 g, 66%): $[\alpha]_D$ +9.2 (c 0.9, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33−7.23 (m, 5H), 4.77 (t, 1H, J = 6.6 Hz), 4.69 (d, 1H, J = 12.3), 3.87(dd, 1H, J = 16.3, 8.1 Hz), 3.73 (s, 2H), 2.70 (dd, 1H, J = 9.5, 7.1 Hz), 2.58 (m, 2H), 2.36 (m, 1H), 1.92 (m, 1H), 1.45 (s, 9H), 1.26 (d, 3H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 180.5, 156.4, 138.1, 129.5, 128.9, 127.6, 80.6, 78.1, 52.8, 36.4, 34.8, 33.9, 32.7, 28.7, 16.9; MS (FAB) m/z 366 (M + H$^+$), 310, 266, 186; HRMS calcd for $C_{19}H_{27}NO_4S$ (M) 364.1569, found 364.1563.

(1*S*,2*S*,4*R*)-(1-Benzylsulfanylmethyl-4-butylcarbamoyl-2-hydroxy-pentyl)-carbamic Acid *tert*-Butyl Ester (20). Trimethyl aluminum (1.0 M in toluene, 0.22 mL) was added to a solution of butylamine (0.088 mL, 0.88 mmol) in CH_2Cl_2 (2.5 mL) and stirred for 15 min. A solution of **19** (82 mg, 0.22 mmol) in CH_2Cl_2 (2.5 mL) was added, and the stirring was continued for 15 min. The mixture was heated to 45 °C until TLC indicated completion of reaction. After cooling, 5% HCl was added, and the clear solution was extracted with CH_2Cl_2 (3 × 20 mL); the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried, and concentrated. Flash chromatography (hexane/AcOEt 1/1) of the residue gave pure **20** (85 mg, 88%): $[\alpha]_D$ +3.3 (c 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.23 (m, 5H), 6.04 (b, 1H), 5.04 (d, 1H, J = 9.2 Hz), 3.88 (m, 1H), 3.73 (s, 2H), 3.59 (m, 1H), 3.22 (m, 2H), 2.60 (m, 3H), 1.68 (m, 1H), 1.48 (m, 3H), 1.45 (s, 9H), 1.34 (m, 2H), 1.20 (d, 3H, J = 7.0 Hz), 0.91 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.5, 156.7, 138.7, 129.5, 128.9, 127.4, 79.9, 68.4, 54.1, 39.7, 38.6, 38.2, 36.7, 34.2, 32.1, 28.8, 20.5, 17.5, 14.2; MS (FAB) m/z 439 (M + H$^+$), 339, 230, 172, 154; HRMS calcd for $C_{23}H_{38}N_2O_4S$ (M + H$^+$) 439.2637, found 439.2642.

(1*S*,1′*S*,2′*S*,4′*R*)-[1-(1-Benzylsulfanylmethyl-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl)-ethyl]-carbamic Acid *tert*-Butyl Ester (21). Into a solution of **20** (0.084 g, 0.19 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.5 mL). The mixture was stirred at room temperature for 30 min and then concentrated in a vacuum. The residue was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. *N*-Boc alanine (0.079 g, 0.38 mmol), PyBOP (0.21 g, 0.38 mmol), and DIEA (0.18 mL, 0.9 mmol) were added consecutively. The mixture was stirred at 0 °C to room temperature for 3 h and then concentrated. The residue was treated with 10% citric acid (2 mL) and extracted with AcOEt (3 × 20 mL); the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (AcOEt/hexane 4/1) of the residue gave pure **21** (88 mg, 90%): $[\alpha]_D$ −53.1 (c 0.96, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30−7.20 (m, 5H), 6.80 (d, 1H, J = 8.6 Hz), 6.41 (bs, 1H), 5.26 (bs, 1H), 4.12 (m, 1H), 3.88 (m, 2H), 3.70 (s, 2H), 3.23−3.13 (m, 2H), 2.64−2.51 (m, 3H), 1.57 (m, 2H), 1.46−1.29 (m, 5H), 1.40 (s, 9H), 1.36 (d, 3H, J = 7.1 Hz), 1.13 (d, 3H, J = 6.9 Hz), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.6, 174.0, 155.7, 138.6, 129.4, 128.9, 127.4, 80.6, 68.5, 60.9, 52.6, 51.2, 39.8, 38.6, 38.0, 36.7, 33.8, 31.9, 28.7, 20.5, 17.6, 14.6, 14.2; MS (FAB) m/z 510 (M + H$^+$), 492, 436, 392, 307, 154; HRMS calcd for $C_{26}H_{43}N_3O_5S$ (M + H$^+$) 510.2975, found 510.2979.

(1*S*,1′*S*,1″*S*,2″*S*,4″*R*)-{2-Benzylsulfanyl-1-[1-(1-benzylsulfanylmethyl-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl)-ethylcarbamoyl]-ethyl}-carbamic Acid *tert*-Butyl Ester (22). Into a solution of **21** (0.09 g, 0.176 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.5 mL). The mixture was stirred at room temperature for 30 min and then concentrated in a vacuum. The residue was dissolved in CH_2Cl_2 (5 mL) and cooled to 0 °C. *N*-Boc *S*-benzyl cysteine (0.1 g, 0.36 mmol), PyBOP (0.19 g, 0.36 mmol), and DIEA (0.17 mL, 0.82 mmol) were added consecutively. The mixture was stirred at 0 °C to room temperature for 3 h and concentrated, the residue was treated with 10% citric acid (2 mL) and extracted with AcOEt (3 × 20 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (AcOEt) of the residue gave **22** (70 mg, 57%): $[\alpha]_D$ −31.8 (c 0.76, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 7.34−7.19 (m, 10H), 4.27 (m, 1H), 4.18 (m, 1H), 3.95 (m, 1H), 3.76 (s, 2H), 3.72 (m, 1H), 3.69 (s, 2H), 3.16 (m, 2H), 2.83 (m, 1H), 2.64−2.48 (m, 4H), 1.49 (m, 2H), 1.47−1.32 (m, 6H), 1.45 (s, 9H), 1.40 (d, 3H, J = 7.1 Hz), 1.10 (d, 3H, J = 7.0 Hz), 0.92 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 178.0, 177.8, 172.3, 156.1, 138.7, 138.5, 129.2, 128.5, 127.4, 126.9, 126.3, 79.9, 68.9, 54.3, 52.9, 49.9, 39.2, 39.1, 38.3, 37.7, 37.6, 36.0, 35.7, 33.4, 32.6, 31.6, 27.7, 20.1, 17.7, 17.3, 13.2; MS (FAB) m/z 704 (M + H$^+$), 629, 307, 154; HRMS calcd for $C_{36}H_{54}N_4O_6S_2$ (M + H$^+$) 703.3556, found 703.3555.

(3*S*,6*S*,9*S*,1′*S*,3′*R*)-[3-(3-Butylcarbamoyl-1-hydroxy-butyl)-6-methyl-5,8-dioxo-1,11-dithia-4,7-diaza-cyclopentadec-9-yl]-carbamic Acid *tert*-Butyl Ester (23). Into a solution of **22** (42 mg, 0.06 mmol) in liquid ammonia (300 mL) was added sodium until a blue color persisted for about 10 min. 1,4-Dibromobutane (0.016 mL, 0.12 mmol) was added, and the mixture was warmed at reflux for 2 h. Ammonia was removed under a stream of argon; the residue was dissolved in AcOEt, washed with 10% citric acid, saturated $NaHCO_3$, and brine, dried over Na_2SO_4, and concentrated. Flash chromatography of the residue gave pure **23** (13 mg, 38%): $[\alpha]_D$ −17.5 (c 0.4, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 4.55 (m, 1H), 4.36 (bs, 1H), 3.99 (m, 1H), 3.54 (d, 1H, J = 9.9 Hz), 3.18 (m, 4H), 2.91−2.81 (m, 3H), 2.62−2.53 (m, 6H), 1.91 (m, 2H), 1.71 (m, 4H), 1.45 (s, 9H), 1.42 (m, 2H), 1.38 (d, 3H, J = 7.0 Hz), 1.12 (d, 3H, J = 7.0 Hz), 0.94 (t, 3H, J = 7.2 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 178.0, 174.1, 171.5, 156.8, 80.1, 70.4, 62.4, 61.1, 54.3, 53.6, 39.0, 38.0, 37.8, 35.2, 31.6, 31.6, 30.6, 29.8, 27.9,

27.6, 20.1, 17.9, 13.2; MS (FAB) *m*/*z* 577 (M + H$^+$), 503, 307, 154; HRMS calcd for $C_{26}H_{48}N_4O_6S_2$ (M + H$^+$) 577.3105, found 577.3106; LC/MS retention time [A] 19.94 min, [B] 7.84 min.

(3*S*,6*S*,9*S*,1′*S*,3′*R*)-[3-(3-Butylcarbamoyl-1-hydroxy-butyl)-6-methyl-5,8-dioxo-1,11-dithia-4,7-diaza-cyclohexadec-9-yl]-carbamic Acid *tert*-Butyl Ester (24). Compound **24** (14 mg, 46%) was prepared from **22** (36 mg, 0.051 mmol) and 1,5-dibromopentane (0.017 mL, 0.1 mmol) according to the general procedure for the preparation of **23**: $[\alpha]_D$ −31.8 (*c* 0.68, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 4.48 (m, 1H), 4.28 (m, 1H), 3.97 (m, 1H), 3.66 (m, 1H), 3.23−3.15 (m, 4H), 2.88−2.75 (m, 3H), 2.66−2.45 (m, 6H), 1.72−1.60 (m, 4H), 1.49−1.35 (m, 6H), 1.45 (s, 9H), 1.38 (d, 3H, *J* = 7.0 Hz), 1.12 (d, 3H, *J* = 7.0 Hz), 0.94 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 173.6, 171.7, 156.2, 79.8, 69.3, 57.8, 53.9, 53.1, 49.3, 46.5, 46.4, 39.0, 37.8, 34.4, 31.6, 28.1, 27.9, 27.6, 26.8, 26.4, 26.3, 20.1, 13.2; MS (FAB) *m*/*z* 591 (M + H$^+$), 563,542; HRMS calcd for $C_{27}H_{50}N_4O_6S_2$ (M + H$^+$) 591.3257, found 591.3257; LC/MS retention time [A] 22.80 min, [B] 8.11 min.

(3*S*,6*S*,9*S*,1′*S*,3′*R*)-[3-(3-Butylcarbamoyl-1-hydroxy-butyl)-6-methyl-5,8-dioxo-1,11-dithia-4,7-diaza-cycloheptadec-9-yl]-carbamic Acid *tert*-Butyl Ester (25). Compound **25** (14 mg, 43%) was prepared from **22** (38 mg, 0.054 mmol) and 1,6-dibromohexane (0.014 mL, 0.1 mmol) according to the general procedure for the preparation of **23**: $[\alpha]_D$ −26 (*c* 0.6, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 4.46 (m, 1H), 4.34 (m, 1H), 3.94 (m, 1H), 3.71 (m, 1H), 3.18 (m, 2H), 2.87−2.72 (m, 3H), 2.65−2.49 (m, 6H), 1.70−1.50 (m, 5H), 1.49−1.35 (m, 10H), 1.45 (s, 9H), 1.38 (d, 3H, *J* = 7.1 Hz), 1.12 (d, 3H, *J* = 7.0 Hz), 0.94 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.0, 173.4, 171.8, 156.3, 79.8, 69.0, 54.3, 53.7, 49.4, 39.0, 38.0, 37.7, 34.5, 33.1, 31.9, 31.6, 30.8, 29.1, 28.9, 27.6, 27.1, 26.5, 20.1, 17.9, 17.8, 13.2; MS (FAB) *m*/*z* 605 (M + H$^+$), 531, 307, 154; HRMS calcd for $C_{28}H_{52}N_4O_6S_2$ (M + H$^+$) 605.3420, found 605.3421; LC/MS retention time [A] 23.03 min, [B] 31.21 min.

(5*S*,8*S*,11*S*,1′*S*,3′*R*)-[5-(3-Butylcarbamoyl-1-hydroxy-butyl)-8-methyl-7,10-dioxo-3,13-dithia-6,9-diaza-bicyclo[13.2.2]nonadeca-1(18),15(19),16-trien-11-yl]-carbamic Acid *tert*-Butyl Ester (26). Compound **26** (20 mg, 49%) was prepared from **22** (46 mg, 0.065 mmol) and 1,4-bis-bromomethyl-benzene (35 mg, 0.12 mmol) according to the general procedure for the preparation of **23**: $[\alpha]_D$ −25.9 (*c* 0.5, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 7.37−7.24 (m, 4H), 4.37 (m, 1H), 4.28 (m, 1H), 4.06 (m, 1H), 3.94−3.57 (m, 5H), 3.18 (m, 2H), 2.76 (m, 1H), 2.50 (m, 3H), 2.30 (m, 1H), 1.68 (m, 2H), 1.55−1.30 (m, 4H), 1.46 (s, 9H), 1.33 (d, 3H, *J* = 6.8 Hz), 1.14 (d, 3H, *J* = 7.0 Hz), 0.95 (t, 3H, *J* = 7.4 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 179.5, 173.8, 172.1, 156.5, 137.8, 131.6, 131.3, 130.7, 81.0, 68.5, 62.1, 54.4, 52.9, 40.5, 40.1, 39.1, 34.9, 34.8, 33.1, 31.1, 29.1, 21.6, 19.0, 14.6; MS (ESI) *m*/*z* 625 (M + H$^+$), 607, 507, 452; HRMS calcd for $C_{30}H_{48}N_4O_6S_2$ (M + H$^+$) 625.3094, found 625.3121; LC/MS retention time [A] 23.58 min, [B] 8.47 min.

(3*S*,6*S*,9*S*,1′*S*,3′*R*)-[3-(3-Butylcarbamoyl-1-hydroxy-butyl)-6-methyl-5,8-dioxo-1,11-dithia-4,7-diaza-cyclopentadec-13-en(*cis*)-9-yl]-carbamic Acid *tert*-Butyl Ester (27). Compound **27** (15 mg, 40%) was prepared from **22** (46 mg, 0.065 mmol) and *cis*-1,4-dibromo-2-butene (28 mg, 0.13 mmol) according to the general procedure for the preparation of **23**: $[\alpha]_D$ −56.1 (*c* 0.34, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.65 (m, 1H), 5.52 (m, 1H), 4.51 (m, 1H), 4.31 (m, 1H), 3.96 (m, 1H), 3.58 (m, 2H), 3.47 (m, 1H), 3.17 (m, 2H), 3.07 (m, 2H), 2.85 (m, 2H), 2.70 (m, 1H), 2.57 (m, 2H), 1.74 (m, 4H), 1.52−1.32 (m, 5H), 1.45 (s, 9H), 1.36 (d, 3H, *J* = 7.0 Hz), 1.11 (d, 3H, *J* = 7.0 Hz), 0.94 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 173.5, 172.5, 156.6, 130.4, 126.9, 80.2, 70.4, 56.3, 54.1, 49.5, 39.1, 38.1, 37.7, 35.0, 31.6, 30.9, 29.2, 28.4, 27.6, 20.1, 17.9, 16.5, 13.2; MS (FAB) *m*/*z* 575 (M + H$^+$), 557, 457, 402; HRMS calcd for $C_{26}H_{46}N_4O_6S_2$ (M + H$^+$) 575.2937, found 575.2947; LC/MS retention time [A] 5.79 min, [B] 7.60 min.

(3*S*,6*S*,9*S*,1′*S*,3′*R*)-[3-(3-Butylcarbamoyl-1-hydroxy-butyl)-6-methyl-5,8-dioxo-1,11-dithia-4,7-diaza-cyclopentadec-13-en(*trans*)-9-yl]-carbamic Acid *tert*-Butyl Ester (28). Compound **28** (10 mg, 30%) was prepared from **22** (42 mg, 0.06 mmol) and *trans*-1,4-dibromo-2-butene (30 mg, 0.14 mmol) according to the general procedure for the preparation of **23**: $[\alpha]_D$ −42.5 (*c* 0.24, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 6.74 (d, 1H, *J* = 7.3 Hz), 5.55 (m, 2H), 4.50 (dd, 1H, *J* = 14.6, 7.5 Hz), 4.28 (m, 1H), 3.80 (m, 1H), 3.67 (m, 2H), 3.20−3.06 (m, 5H), 2.89−2.77 (m, 3H), 2.56 (m, 1H), 2.43 (dd, 1H, *J* = 13.4, 7.0 Hz), 1.70 (m, 2H), 1.49−1.31 (m, 4H), 1.45 (s, 9H), 1.38 (d, 3H, *J* = 7.0 Hz), 1.12 (d, 3H, *J* = 7.0 Hz), 0.94 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 178.0, 173.6, 172.2, 156.4, 129.6, 121.4, 80.1, 69.6, 54.6, 53.2, 48.8, 39.1, 38.2, 37.7, 33.5, 32.7, 31.6, 29.2, 27.6, 27.2, 20.1, 17.8, 16.3, 13.2; MS (FAB) *m*/*z* 575 (M + H$^+$), 557, 457, 402; HRMS calcd for $C_{26}H_{46}N_4O_6S_2$ (M + H$^+$) 575.2937, found 575.2953; LC/MS retention time [A] 5.75 min, [B] 7.61 min.

(3*S*,6*S*,9*S*,1′*S*,3′*R*)-4-(9-Acetylamino-6-methyl-5,8-dioxo-1,11-dithia-4,7-diaza-cyclopentadec-3-yl)-*N*-butyl-4-hydroxy-2-methyl-butyramide (29). Into a solution of **23** (12 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) was added TFA (0.33 mL); the mixture was stirred at room temperature for 30 min and then concentrated in a vacuum. The residue was dissolved in DMF (2 mL) and cooled to 0 °C, Ac_2O (0.03 mL, 0.2 mmol) and $NaHCO_3$ (30 mg, 0.35 mmol) were added consecutively, and the mixture was stirred at 0 °C to room temperature for 3 h. Solvent was removed under reduced pressure, the residue was treated with 10% citric acid and extracted with AcOEt, and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Flash chromatography of the residue gave pure **29** (5.4 mg, 50%): $[\alpha]_D$ −17.5 (*c* 0.4, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 4.56 (m, 1H), 4.50 (m, 1H), 3.94 (m, 1H), 3.62 (m, 1H), 3.16 (m, 2H), 2.95−2.76 (m, 4H), 2.62−2.50 (m, 6H), 2.01 (s, 3H), 1.67 (m, 4H), 1.42−1.35 (m, 6H), 1.37 (d, 3H, *J* = 7.1 Hz), 1.11 (d, 3H, *J* = 7.0 Hz), 0.94 (t, 3H, *J* = 7.2 Hz); MS (ESI) *m*/*z* 519 (M + H$^+$), 338, 258; HRMS calcd for $C_{23}H_{42}N_4O_5S_2$ (M + H$^+$) 519.2669, found 519.2670; LC/MS retention time [A] 4.38 min, [B] 6.83 min.

(3*S*,6*S*,9*S*,1′*S*,3′*R*)-4-(9-Acetylamino-6-methyl-5,8-dioxo-1,11-dithia-4,7-diaza-cyclohexadec-3-yl)-*N*-butyl-4-hydroxy-2-methyl-butyramide (30). Compound **30** (2 mg, 55%) was prepared from **24** (4 mg, 0.007 mmol) and acetic anhydride (0.01 mL, 0.07 mmol) according to the general procedure for the preparation of **29**: $[\alpha]_D$ −28.3 (*c* 0.3, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 4.55 (m, 1H), 4.48 (m, 1H), 3.97 (m, 1H), 3.65 (m, 1H), 3.18 (m, 2H), 2.93−2.80 (m, 4H), 2.67−2.46 (m, 6H), 1.98 (s, 3H), 1.69−1.56 (m, 4H), 1.52−1.41 (m, 8H), 1.38 (d, 3H, *J* = 7.0 Hz), 1.13 (d, 3H, *J* = 6.9 Hz), 0.94 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 179.8, 173.5, 171.8, 171.2, 69.4, 63.1, 53.2, 53.0, 49.3, 46.4, 38.1, 37.7, 33.8, 32.7, 31.9, 31.6, 30.6, 28.0, 26.7, 21.4, 20.1, 17.9, 17.8, 13.2; MS (ESI) *m*/*z* 533 (M + H$^+$), 515, 460; HRMS calcd for $C_{24}H_{44}N_4O_5S_2$ (M + H$^+$) 533.2831, found 533.2850; LC/MS retention time [A] 16.90 min, [B] 7.19 min.

(3*S*,6*S*,9*S*,1′*S*,3′*R*)-4-(9-Acetylamino-6-methyl-5,8-dioxo-1,11-dithia-4,7-diaza-cycloheptadec-3-yl)-*N*-butyl-4-hydroxy-2-methyl-butyramide (31). Compound **31** (5 mg, 60%) was prepared from **25** (9 mg, 0.013 mmol) and acetic anhydride (0.016 mL, 0.13 mmol) according to the general procedure for the preparation of **29**: $[\alpha]_D$ −37.1 (*c* 0.35, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 4.52 (m, 1H), 4.46 (m, 1H), 3.92 (m, 1H), 3.66 (m, 1H), 3.18 (m, 2H), 2.90−2.74 (m, 3H), 2.65−2.50 (m, 6H), 1.98 (s, 3H), 1.63−1.50 (m, 5H), 1.49−1.35 (m, 8H), 1.38 (d, 3H, *J* = 7.0 Hz), 1.12 (d, 3H, *J* = 7.0 Hz), 0.94 (t, 3H, *J* = 7.2 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 173.4, 171.9, 171.2, 69.1, 64.6, 53.7, 53.6, 49.4, 39.0, 37.7, 34.1, 31.9, 31.6, 29.1, 28.9, 27.0, 26.5, 21.4, 20.1, 17.9, 17.8, 13.2; MS (ESI) *m*/*z* 547 (M + H$^+$), 529, 474; HRMS calcd for $C_{25}H_{46}N_4O_5S_2$ (M + H$^+$) 547.2987, found 547.2975; LC/MS retention time [A] 18.59 min, [B] 27.39 min.

(2*R*,4*S*,5′*S*,8′*S*,11′S)-4-(11-Acetylamino-8-methyl-7,10-dioxo-3,13-dithia-6,9-diaza-bicyclo[13.2.2]nonadeca-1(18),15(19),16-trien-5-yl)-*N*-butyl-4-hydroxy-2-methyl-butyramide (32). Compound **32** (4 mg, 45%) was prepared from **26** (10 mg, 0.016 mmol) and acetic anhydride (0.015 mL, 0.16 mmol) according to the

general procedure for the preparation of **29**: $[\alpha]_D$ −41 (*c* 0.3, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 7.38−7.30 (m, 4H), 4.34-(m, 2H), 3.86 (m, 2H), 3.70 (m, 4H), 3.18 (m, 3H), 2.54 (m, 3H), 2.32 (m, 2H), 1.99 (s, 3H), 1.68 (m, 2H), 1.53−1.35 (m, 4H), 1.32 (d, 3H, J = 7.0 Hz), 1.14 (d, 3H, J = 7.0 Hz), 0.95 (t, 3H, J = 7.3 Hz); MS (ESI) *m*/*z* 567 (M + H$^+$); HRMS calcd for $C_{27}H_{42}N_4O_5S_2$ (M + H$^+$) 567.2669, found 567.2669; LC/MS retention time [A] 5.26 min, [B] 7.60 min.

(2*R*,4*S*,5*S*,2′*S*)-6-Benzylsulfanyl-5-[2-(3-benzylsulfanyl-propionylamino)-propionylamino]-4-hydroxy-2-methyl-hexanoic Acid Butylamide (33). Into a solution of **21** (0.15 g, 0.29 mmol) in CH_2Cl_2 (4.5 mL) was added TFA (0.75 mL). The mixture was stirred at room temperature for 30 min and concentrated, and the residue was dissolved in CH_2Cl_2 (8 mL), cooled to 0 °C, then treated with 3-benzylsulfanyl propionic acid (0.11 g, 0.58 mmol), PyBOP (0.23 g, 0.44 mmol), and DIEA (0.28 mL, 1.45 mmol) successively. The mixture was stirred at 0 °C to room temperature for 3 h and concentrated, the residue was treated with 10% citric acid (2 mL) and extracted with AcOEt (3 × 30 mL), and the combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (4% MeOH in AcOEt) of the residue gave pure **33** (120 mg, 70%): ^{1}H NMR (MeOD, 400 MHz) δ 7.41−7.22 (m, 10H), 4.36 (m, 1H), 3.92 (m, 1H), 3.74 (m, 5H), 3.21 (m, 4H), 2.66 (m, 3H), 2.51 (m, 4H), 1.64 (m, 1H), 1.47 (m, 2H), 1.42−1.31 (m, 2H), 1.36 (d, 3H, J = 7.0 Hz), 1.10 (d, 3H, J = 7.1 Hz), 0.92 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 174.1, 173.3, 138.9, 129.2, 129.0, 128.5, 128.4, 126.9, 126.1, 125.5, 68.7, 64.2, 54.8, 52.8, 49.8, 46.9, 39.1, 38.3, 37.7, 35.9, 35.7, 31.6, 26.9, 20.1, 17.7, 17.3, 13.2; MS (FAB) *m*/*z* 588 (M + H$^+$), 570, 460, 307; HRMS calcd for $C_{31}H_{45}N_3O_4S_2$ (M + H$^+$) 588.2929, found 588.2922.

(3*S*,6*S*,1′*S*,3′*R*)-*N*-Butyl-4-hydroxy-2-methyl-4-(6-methyl-5,8-dioxo-1,11-dithia-4,7-diaza-cyclopentadec-13-en-3-yl)-butyramide (34). Compound **34** (11 mg, 51%) was prepared from **33** (28 mg, 0.047 mmol) and *cis*-1,4-dibromo-2-butene (0.025 mL, 0.15 mmol) according to the general procedure for the preparation of **23**: $[\alpha]_D$ −30 (*c* 0.1, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 7.78 (b, 1H), 7.60 (d, 1H, J = 9.1), 5.69 (m, 1H), 5.51 (m, 1H), 4.47 (dd, 1H, J = 14.5, 7.2 Hz), 3.96 (m, 1H), 3.54 (m, 3H), 3.16 (dd, 1H, J = 12.6, 7.0 Hz), 3.02 (m, 2H), 2.86 (m, 2H), 2.72−2.54 (m, 4H), 1.72 (m, 1H), 1.53−1.29 (m, 4H), 1.43 (d, 3H, J = 7.1 Hz), 1.12 (d, 3H, J = 7.0 Hz), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (DMSO, 100 MHz) δ 176.1, 172.8, 172.1, 130.0, 128.5, 70.2, 56.5, 49.0, 39.0, 38.2, 37.7, 36.7, 32.2, 32.0, 29.6, 29.3, 27.8, 20.4, 19.7, 18.1, 14.6; MS (FAB) *m*/*z* 460 (M + H$^+$), 307, 154; HRMS calcd for $C_{21}H_{37}N_3O_4S_2$ (M + H$^+$) 460.2304, found 460.2301; LC/MS retention time [A] 16.14 min, [B] 6.83 min.

(3*S*,6*S*,1′*S*,3′*R*)-*N*-Butyl-4-hydroxy-2-methyl-4-(6-methyl-5,8-dioxo-1,11-dithia-4,7-diaza-cyclopentadec-13-en-3-yl)-butyramide (35). Compound **35** (8 mg, 45%) was prepared from **33** (23 mg, 0.039 mmol) and *trans*-1,4-dibromo-2-butene (30 mg, 0.14 mmol) according to the general procedure for the preparation of **23**: $[\alpha]_D$ −24 (*c* 0.1, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.56 (m, 2H), 4.44 (dd, 1H, J = 14.2, 7.1 Hz), 3.74 (m, 1H), 3.68 (m, 1H), 3.22−3.02 (m, 6H), 2.84 (m, 3H), 2.60 (m, 2H), 2.46 (m, 2H), 1.72 (m, 1H), 1.53−1.39 (m, 4H), 1.37 (d, 3H, J = 7.1 Hz), 1.12 (d, 3H, J = 7.0 Hz), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 173.6, 173.5, 130.4, 128.7, 69.2, 54.3, 49.3, 39.0, 38.4, 37.8, 35.5, 32.9, 32.8, 31.6, 31.1, 28.0, 20.1, 17.9, 16.0, 13.2; MS (FAB) *m*/*z* 460 (M + H$^+$), 338, 307, 154; HRMS calcd for $C_{21}H_{37}N_3O_4S_2$ (M + H$^+$) 460.2304, found 460.2307; LC/MS retention time [A] 15.96 min, [B] 6.95 min.

(2*R*,4*S*,5*S*)-6-Benzylsulfanyl-5-*tert*-butoxycarbonylamino-4-(*tert*-butyl-dimethyl-silanyloxy)-2-methyl-hexanoic Acid (36). Into a solution of **19** (0.11 g, 0.3 mmol) in 1,2-dimethoxyethane (1.8 mL) was added 1 N LiOH (1.8 mL). The mixture was stirred at room temperature for 3 h and then partitioned between 10% citric acid (2 mL) and AcOEt (20 mL). The organic layers were washed with brine, dried over $MgSO_4$, and concentrated. The residue was dissolved in DMF (2 mL), and then TBSCl (0.27 g, 1.8 mmol) and imidazole (0.25 g, 3.6 mmol) were added. The mixture was stirred at room temperature for 24 h, and then MeOH (2 mL) was added. After being stirred for 2 h, the solution was concentrated, and the residue was treated with 10% citric acid (2 mL) and extracted with AcOEt (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (hexane/AcOEt 2/1) of the residue gave **36** (0.1 g, 91%), and **19** (30 mg) was also recovered: $[\alpha]_D$ +28.1 (*c* 1.4, $CHCl_3$); ^{1}H NMR ($CHCl_3$, 400 MHz) δ 7.34−7.23 (m, 5H), 4.80 (d, 1H, J = 7.6 Hz), 4.08 (m, 1H), 3.73 (s, 2H), 3.71 (m, 1H), 2.52 (m, 3H), 1.96 (m, 1H), 1.49 (s, 9H), 1.24 (d, 3H, J = 7.0 Hz), 0.88 (s, 9H), 0.05 (s, 3H), −0.06 (s, 3H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ 180.8, 156.5, 138.5, 129.5, 128.9, 127.5, 80.3, 69.9, 51.9, 38.0, 36.6, 36.1, 33.8, 28.8, 26.3, 18.4, 16.9, −3.9, −4.2; MS (FAB) *m*/*z* 498 (M + H$^+$), 398, 154; HRMS calcd for $C_{30}H_{52}NO_6SSi$ (M + H$^+$) 498.2709, found 498.2708.

(1*S*,2*S*,4*R*,1′*S*)-[1-Benzylsulfanylmethyl-4-(1-butylcarbamoyl-2-methyl-propylcarbamoyl)-2-(*tert*-butyldimethylsilanyloxy)-pentyl]-carbamic Acid *tert*-Butyl Ester (37). Into a solution of **36** (0.22 g, 0.44 mmol) and Val *N*-*n*-Bu (0.12 g, 0.52 mmol) in CH_2Cl_2 (6 mL) was added PyBOP (0.28 g, 0.53 mmol) at 0 °C, followed by DIEA (0.38 mL, 2.2 mmol). The mixture was stirred at 0 °C to room temperature for 3 h, then 10% citric acid (2 mL) was added, and the mixture was extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (hexane/AcOEt 3/1) of the residue gave **37** (0.2 g, 86%): $[\alpha]_D$ +4.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR ($CHCl_3$, 400 MHz) δ 7.34−7.23 (m, 5H), 6.74 (m, 1H), 6.45 (d, 1H, J = 8.9 Hz), 4.72 (d, 1H, J = 9.6 Hz), 4.2 (m, 1H), 3.96 (m, 1H), 3.73 (s, 2H), 3.28 (m, 1H), 3.14 (m, 1H), 2.45 (d, 2H, J = 7.2 Hz), 2.28 (m, 1H), 2.02 (m, 1H), 1.81 (m, 1H), 1.76 (m, 2H), 1.45 (s, 9H), 1.32 (m, 2H), 1.08 (d, 3H, J = 6.7 Hz), 0.95 (m, 9H), 0.88 (s, 9H), 0.02 (s, 3H), −0.01 (s, 3H); ^{13}C NMR ($CHCl_3$, 100 MHz) δ 176.5, 171.6, 156.4, 138.6, 129.5, 128.9, 127.5, 80.0, 69.7, 59.1, 51.4, 39.5, 38.7, 37.6, 36.5, 34.1, 32.0, 31.2, 28.8, 28.7, 26.2, 20.5, 19.7, 19.0, 18.4, 16.7, 14.1, −3.7, −4.3; MS (FAB) *m*/*z* 652 (M + H$^+$), 552; HRMS calcd for $C_{34}H_{61}N_3O_5SSi$ (M + H$^+$) 652.4188, found 652.4188.

(1*S*,2*S*,4*R*,1′*S*)-[1-Benzylsulfanylmethyl-4-(1-butylcarbamoyl-2-methyl-propylcarbamoyl)-2-hydroxy-pentyl]-carbamic Acid *tert*-Butyl Ester (38). In procedure 1, into a solution of **37** (0.2 g, 0.3 mmol) in MeOH (12 mL) was added *p*-toluenesulfonic acid (91 mg, 0.33 mmol). The mixture was stirred at room temperature for 3 h, then saturated aqueous $NaHCO_3$ (2 mL) was added, and the mixture was extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated. Flash chromatography (hexane/AcOEt 3/1) of the residue gave **38** (80 mg, 50%). In procedure 2, into a solution of **19** (56 mg, 0.15 mmol) in toluene (1.2 mL) was added Val *N*-*n*-Bu (87 mg, 0.3 mmol) and 2-hydroxypyridine (16 mg, 0.17 mmol). The mixture was heated to reflux for 3 days. After cooling, the solvent was evaporated; the residue was purified by flash chromatography (hexane/AcOEt 3/1, 1/2) to give **38** (53 mg, 66%): $[\alpha]_D$ −28.2 (*c* 0.9, MeOD); ^{1}H NMR (MeOD, 400 MHz) δ 7.34−7.23 (m, 5H), 6.14 (d, 1H, J = 9.5 Hz), 4.12 (d, 1H, J = 7.8 Hz), 3.74 (s, 2H), 3.63 (m, 2H), 3.16 (m, 2H), 2.65 (m, 1H), 2.59 (dd, 1H, J = 13.9, 7.0 Hz), 2.45 (dd, 2H, J = 13.7, 7.5 Hz), 2.01 (m, 1H), 1.75 (m, 1H), 1.49 (m, 2H), 1.46 (s, 9H), 1.35 (m, 2H), 1.12 (d, 3H, J = 6.9 Hz), 0.94 (m, 9H); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 172.6, 157.4, 138.8, 129.2, 128.4, 126.9, 79.2, 69.2, 59.4, 54.2, 39.0, 38.3, 37.5, 35.5, 32.9, 31.5, 31.0, 27.8, 20.1, 18.9, 18.2, 17.7, 13.1; MS (FAB) *m*/*z* 538 (M + H$^+$), 438, 307, 154; HRMS calcd for $C_{28}H_{47}N_3O_5S$ (M + H$^+$) 538.3301, found 538.3307.

(1*S*,2*S*,4*R*,1′*S*,1″*S*)-{1-[1-Benzylsulfanylmethyl-4-(1-butylcarbamoyl-2-methyl-propylcarbamoyl)-2-hydroxy-pentylcarbamoyl]-ethyl}-carbamic Acid *tert*-Butyl Ester (39). Into a solution of **38** (70 mg, 0.13 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.5 mL). The mixture was stirred at room temperature for 30 min and then concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C, and *N*-Boc alanine (0.05 g, 0.26 mmol), PyBOP (0.1 g, 0.2 mmol), and DIEA (0.11 mL, 0.65 mmol) were added consecutively. The mixture was stirred at 0 °C to room

temperature for 3 h and then concentrated. The residue was treated with 10% citric acid (2 mL) and extracted with AcOEt (3 × 20 mL). The combined organic layers were washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (AcOEt/hexane 2/1) of the residue gave pure **39** (65 mg, 82%): $[\alpha]_D$ −49.2 (*c* 0.9, MeOD); ^{1}H NMR (MeOD, 400 MHz) δ 8.01 (b, 1H), 7.69 (d, 1H, J = 8.2 Hz), 7.47 (d, 1H, J = 9.2 Hz), 7.34−7.19 (m, 5H), 4.10 (m, 2H), 3.93 (m, 1H), 3.80 (m, 1H), 3.73 (s, 2H), 3.26−3.13 (m, 2H), 2.64 (m, 1H), 2.61 (dd, 1H, J = 13.7, 7.4 Hz), 2.50 (dd, 2H, J = 13.8, 7.2 Hz), 2.03 (m, 1H), 1.67 (m, 1H), 1.49 (m, 4H), 1.44 (s, 9H), 1.38−1.29 (m, 6H), 1.11 (d, 3H, J = 6.9 Hz), 0.94 (m, 9H); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 175.1, 172.7, 156.4, 138.7, 129.2, 128.5, 126.9, 79.6, 68.5, 59.6, 52.6, 51.1, 39.2, 38.6, 37.5, 35.5, 32.7, 31.5, 31.0, 27.8, 20.1, 18.9, 18.2, 17.5, 16.9, 13.1; MS (FAB) *m*/*z* 609 (M + H$^+$), 536, 436, 307, 154; HRMS calcd for $C_{31}H_{52}N_4O_6S$ (M + H$^+$) 609.3686, found 609.3682.

(1*S*,1′*S*,1″*S*,2″*S*,4″*R*,1‴*S*)-(2-Benzylsulfanyl-1-{1-[1-benzylsulfanylmethyl-4-(1-butylcarbamoyl-2-methyl-propylcarbamoyl)-2-hydroxy-pentylcarbamoyl]-ethylcarbamoyl}-ethyl)-carbamic Acid *tert*-Butyl Ester (40). Into a solution of **39** (0.065 g, 0.11 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.5 mL). The mixture was stirred at room temperature for 30 min and then concentrated under vacuum. The residue was dissolved in CH_2Cl_2 (3 mL) and cooled to 0 °C. *N*-Boc *S*-benzyl cysteine (0.067 g, 0.22 mmol), PyBOP (0.083 g, 0.17 mmol), and DIEA (0.093 mL, 0.55 mmol) were added consecutively. The mixture was stirred at 0 °C to room temperature for 3 h and then concentrated. Processing as described for **39** gave a residue, which was purified by flash chromatography (AcOEt) to give pure **40** (52 mg, 61%): $[\alpha]_D$ −53.8 (*c* 0.9, MeOD); ^{1}H NMR (MeOD, 400 MHz) δ 8.05 (b, 1H), 7.71 (d, 1H, J = 8.2 Hz), 7.56 (d, 1H, J = 9.0 Hz), 7.34−7.19 (m, 10H), 4.41 (m, 1H), 4.29 (m, 1H), 4.12 (m, 1H), 3.97 (m, 1H), 3.77 (s, 4H), 3.69 (m, 2H), 3.25−3.13 (m, 2H), 2.86−2.69 (m, 4H), 2.58 (m, 2H), 2.03 (m, 1H), 1.69 (m, 1H), 1.46 (s, 9H), 1.40 (d, 3H, J = 7.0 Hz), 1.48−1.34 (m, 6H), 1.10 (d, 3H, J = 6.9 Hz), 0.94 (m, 9H); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 173.6, 172.7, 172.2, 156.7, 138.7, 138.5, 129.2, 128.5, 128.4, 127.1, 127.0, 126.9, 79.9, 76.6, 68.9, 59.5, 53.9, 52.6, 39.2, 38.5, 36.1, 36.0, 35.6, 33.3, 32.5, 31.5, 31.0, 27.7, 20.1, 18.9, 18.2, 17.3, 13.1; MS (FAB) *m*/*z* 801 (M + H$^+$), 729, 530, 266, 173; HRMS calcd for $C_{41}H_{63}N_5O_7S_2$ (M + H$^+$) 802.4247, found 802.4245.

(3*S*,6*S*,9*S*,1′*S*,3′*R*,1″*S*)-{3-[3-(1-Butylcarbamoyl-2-methyl-propylcarbamoyl)-1-hydroxy-butyl]-6-methyl-5,8-dioxo-1,11-dithia-4,7-diaza-cyclopentadec-13-en-9-yl}-carbamic Acid *tert*-Butyl Ester (41). Compound **41** (5.5 mg, 24%) was prepared from **40** (28 mg, 0.035 mmol) and *cis*-1,4-dibromo-2-butene (15 mg, 0.07 mmol) according to the general procedure for the preparation of **23**: $[\alpha]_D$ −22 (*c* 0.1, MeOD); ^{1}H NMR (MeOD, 400 MHz) δ 5.65 (m, 1H), 5.52 (m, 1H), 4.54 (d, 1H, J = 7.1 Hz), 4.31 (m, 1H), 3.98 (m, 1H), 3.60 (m, 1H), 3.48 (m, 1H), 3.24−3.05 (m, 6H), 2.92−2.79 (m, 2H), 2.68 (m, 2H), 2.54 (m, 2H), 1.76 (m, 1H), 1.60−1.38 (m, 5H), 1.45 (s, 9H), 1.40 (d, 3H, J = 7.0 Hz), 1.12 (d, 3H, J = 6.9 Hz), 0.94 (m, 9H); MS (ESI) *m*/*z* 674 (M + H$^+$); HRMS calcd for $C_{31}H_{55}N_5O_7S_2$ (M + H$^+$) 674.3616, found 674.3612; LC/MS retention time [A] 6.06 min, [B] 7.89 min.

(3*S*,6*S*,9*S*,1′*S*,3′*R*,1″*S*)-{3-[3-(1-Butylcarbamoyl-2-methyl-propylcarbamoyl)-1-hydroxy-butyl]-6-methyl-5,8-dioxo-1,11-dithia-4,7-diaza-cyclopentadec-13-en-9-yl}-carbamic Acid *tert*-Butyl Ester (42). Compound **42** (3 mg, 22%) was prepared from **40** (17 mg, 0.02 mmol) and *trans*-1,4-dibromo-2-butene (14 mg, 0.06 mmol) according to the general procedure for the preparation of **23**: $[\alpha]_D$ −35.2 (*c* 0.11, MeOD); ^{1}H NMR (MeOD, 400 MHz) δ 8.04 (bs, 1H), 7.74 (d, 1H, J = 8.7 Hz), 5.59 (m, 2H), 4.51 (m, 1H), 4.34 (m, 1H), 4.10 (m, 1H), 3.85 (m, 1H), 3.70 (m, 1H), 3.24−3.03 (m, 4H), 2.95−2.82 (m, 4H), 2.69 (m, 1H), 2.04 (m, 1H), 1.73 (m, 1H), 1.61−1.28 (m, 6H), 1.46 (s, 9H), 1.38 (d, 3H, J = 7.2 Hz), 1.12 (d, 3H, J = 7.1 Hz), 0.94 (m, 9H); ^{13}C NMR (MeOD, 100 MHz); MS (FAB) *m*/*z* 675 (M + H$^+$), 613, 460, 307; HRMS calcd for $C_{31}H_{55}N_5O_7S_2$ (M + H$^+$) 674.3616, found 674.3616; LC/MS retention time [A] 5.97 min, [B] 7.97 min.

5,6-Dihydro-4*H*-pyridine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-(2-Trimethylsilanyl-ethyl) Ester (45). Into a solution of **44** (1.23 g, 5.4 mmol) in THF (27 mL) was added PPh_3 (3.4 g, 13.4 mmol) and trimethylsilyl ethanol (1.2 mL, 8.1 mmol). The mixture was cooled to 0 °C, and diethylazodicarboxylate (DEAD) (1.9 mL, 12.0 mmol) was added dropwise. The mixture was stirred at 0 °C to room temperature for 2 h until the reaction was complete. The solution was partitioned between Et_2O (100 mL) and saturated $NaHCO_3$ (60 mL) and extracted with Et_2O twice, and the combined organic layers were dried over Na_2SO_4 and concentrated. Flash chromatography (hexane/AcOEt 8/1) of the residue gave **45** (1.26 g, 72%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.98 (t, 1H, J = 3.8 Hz), 4.26 (t, 2H, J = 8.64 Hz), 3.59 (t, 2H, J = 5.5 Hz), 2.22 (m, 2H), 1.81 (m, 2H), 1.45 (s, 9H), 1.05 (t, 2H, J = 8.6 Hz), 0.06 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.8, 153.5, 133.7, 121.9, 81.7, 63.6, 43.5, 28.5, 23.4, 23.1, 17.7, −1.1; MS (ESI) *m*/*z* 328 (M + H$^+$); HRMS calcd for $C_{16}H_{29}NO_4Si$ (M + H$^+$) 328.1939, found 328.1928.

3-Benzylsulfanyl-piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-(2-Trimethylsilanyl-ethyl) Ester (46). Into a solution of **45** (1.0 g, 3.05 mmol) in MeOH (22 mL) was added benzyl mercaptan (1.36 mL, 10.7 mmol); then a freshly prepared solution of NaOMe in MeOH (0.5 M, 18 mL) was added dropwise at room temperature. The mixture was stirred at room temperature for 7 h until the reaction was complete; then Amberlite IR 120(+) was added to pH 7, the resin was filtered and washed with MeOH, and the filtrate was concentrated. Flash chromatography (hexane/AcOEt 8/1) of the residue gave **46** (1.08 g, 78%): ^{1}H NMR ($CDCl_3$, 400 MHz, 55 °C) δ 7.36−7.23 (m, 5H), 4.94 (b, 1H), 4.26−4.18 (m, 2H), 4.04, 3.94 (b, 1H), 3.84 (m, 2H), 3.16, 2.95 (b, 1H), 1.92−1.82 (m, 1H), 1.77−1.64 (m, 2H), 1.51−1.30 (m, 2H), 1.48, 1.46 (s, 9H), 1.08−0.96 (m, 2H), 0.06, 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz, 55 °C) δ 170.3, 156.4, 137.9, 137.8, 128.7, 128.6, 128.3, 126.9, 80.1, 79.9, 63.4, 62.8, 41.8, 36.1, 35.7, 28.2, 28.1, 26.4, 26.2, 19.8, 17.5, 17.4, −1.7; MS (ESI) *m*/*z* 474 (M + Na$^+$), 352 (M-Boc)$^+$. HRMS calcd for $C_{23}H_{37}NO_4SSi$ (M + H$^+$) 452.2285, found 452.2295.

***cis*-3-Benzylsulfanyl-piperidine-2-carboxylic Acid 2-Trimethylsilanyl-ethyl Ester (47).** Into a solution of **46** (0.36 g, 0.8 mmol) in CH_2Cl_2 (18 mL) was added TFA (3 mL). The mixture was stirred at room temperature for 40 min. The solvent and excess TFA were removed under reduced pressure. The residue was treated with AcOEt (20 mL), washed with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt 2/1) of the residue gave the desired cis product **47** (0.11 g, 39%) and the trans isomer (0.10 g, 36%), which was discarded: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.24 (m, 5H), 4.26 (dd, 1H, J = 11.1, 6.8 Hz), 4.16 (dd, 1H, J = 11.0, 6.6 Hz), 3.72 (ab, 2H, J = 13.3 Hz), 3.61 (d, 1H, J = 2.8 Hz), 3.14 (m, 1H), 2.59 (m, 1H), 1.85 (m, 5H), 1.44 (m, 1H), 1.0 (m, 2H), 0.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.6, 139.2, 129.3, 128.6, 127.3, 63.6, 63.3, 46.1, 44.8, 37.1, 31.4, 22.1, 17.8, −1.1; MS (ESI) *m*/*z* 352 (M + H$^+$).

***cis*-3-Benzylsulfanyl-piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-(2-Trimethylsilanyl-ethyl) Ester (48).** Into a solution of **47** (80 mg, 0.21 mmol) in MeOH (4 mL) was added $NaHCO_3$ (46 mg, 0.53 mmol) and $(Boc)_2O$ (60 mg, 0.23 mmol). The mixture was stirred in an ultrasonic bath for 3 h. After cooling, the excess $NaHCO_3$ was filtered off, and the filtrate was evaporated. The residue was treated with Et_2O (30 mL) and filtered again, the filtrate was concentrated, and the residue was purified by flash chromatography (hexane/AcOEt 8/1) to give **48** (90 mg, 90%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.26 (m, 5H), 5.09, 4.84 (b, 1H), 4.24 (m, 2H), 3.94−3.78 (m, 31H), 3.26 (m, 2H), 2.68 (m, 1H), 1.89 (m, 1H), 1.73 (m, 2H), 1.46 (s, 9H), 1.37 (m, 1H), 1.06 (m, 2H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.6, 156.4, 138.2, 129.1, 128.9, 127.0, 80.1, 63.4, 57.6, 41.7, 40.5, 36.1, 28.2, 27.0, 26.5, 19.8, −1.7; MS (ESI) *m*/*z* 452 (M + H$^+$); HRMS calcd for $C_{23}H_{37}NO_4SSi$ (M + H$^+$) 452.2285, found 452.2295.

***cis*-3-Benzylsulfanyl-piperidine-1,2-dicarboxylic acid 1-*tert*-butyl ester (49).** Into a suspension of **48** (105 mg, 0.23 mmol)

and molecular sieves 4 Å in THF (1.9 mL) was added tetrabutyl ammonium fluoride (TBAF; 1 N in THF, 0.5 mL) at 0 °C. The mixture was stirred at 0 °C to room temperature for 5 h; then 10% citric acid was added to pH 3.0, and the mixture was extracted with AcOEt (3 × 20 mL). The combined organic layers were sequentially washed with 10% citric acid, then with brine, dried over Na_2SO_4, and concentrated to give the acid **49** (80 mg, quant): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.2 (b, 1H), 7.36−7.26 (m, 5H), 5.15, 4.87 (b, 1H), 3.96 (b, 1H), 3.86 (m, 2H), 3.28 (m, 1H), 2.68 (b, 1H), 1.74 (m, 4H), 1.47 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.6, 156.5, 138.1, 129.3, 128.9, 127.6, 81.1, 59.2, 41.6, 36.3, 28.7, 27.0, 25.5, 24.4, 20.3; MS (ESI) *m*/*z* 352 (M + H^+).

3-Benzylsulfanyl-2-[1-(1-benzylsulfanylmethyl-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl)-ethylcarbamoyl]-piperidine-1-carboxylic Acid *tert*-Butyl Ester (50). Into a solution of **49** (90 mg, 0.26 mmol) and 5-(2-amino-propionylamino)-6-benzylsulfanyl-4-hydroxy-2-methyl-hexanoic acid butylamide (prepared separately, 0.13 g, 0.26 mmol) in CH_2Cl_2 (8 mL) was added PyBOP (0.2 g, 0.38 mmol) and DIEA (96 μL, 0.52 mmol) at 0 °C. The mixture was stirred at 0 °C to room temperature for 4 h, and then 10% citric acid (2 mL) was added. The mixture was extracted with AcOEt (3 × 30 mL). The combined organic layers were sequentially washed with saturated $NaHCO_3$, then with brine, dried over Na_2SO_4, and concentrated to give a mixture of two diastereoisomers **50** (120 mg, 62%), which were inseparable; ^{1}H NMR (MeOD, 400 MHz) δ 7.76 (b, 1H), 7.37−7.20 (m, 10H), 4.40 (b, 1H), 3.98 (m, 1H), 3.83 (m, 3H), 3.71 (m, 3H), 3.18 (m, 3H), 2.73 (m, 1H), 2.73 (m, 1H), 2.61 (m, 1H), 2.52 (m, 2H), 1.68 (m, 4H), 1.49 (m, 3H), 1.46 (s, 9H), 1.38 (m, 6H), 1.12 (d, 3H, J = 6.9 HZ), 0.93 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 173.7, 172.1, 155.3, 138.8, 129.1, 129.0, 128.7, 128.5, 127.4, 127.3, 126.9, 126.4, 81.2, 68.9, 68.8, 64.5, 60.6, 53.3, 53.2, 52.9, 49.6, 42.9, 39.1, 38.2, 37.8, 37.7, 35.8, 32.7, 31.7, 31.7, 27.7, 20.1, 19.9, 17.7, 13.5, 13.2; MS (ESI) *m*/*z* 765 (M + Na^+), 643 (M-Boc)$^+$. HRMS calcd for $C_{39}H_{58}N_4O_6S_2$ (M + H^+) 743.3871, found 743.3870.

(11*S*,15*R*,17*R*,17a*R*,1′*R*,3′*S*)-12-(3-Butylcarbamoyl-1-hydroxy-butyl)-15-methyl-14,17-dioxo-2,3,4,4a,6,9,11,12,13,14,15,16,17,-17a-tetradecahydro-5,10-dithia-1,13,16-triaza-benzocyclopentadecene-1-carboxylic Acid *tert*-Butyl Ester (51) and (11*S*,15*R*,-17*S*,17a*S*,1′*R*,3′*S*)-12-(3-Butylcarbamoyl-1-hydroxy-butyl)-15-methyl-14,17-dioxo-2,3,4,4a,6,9,11,12,13,14,15,16,17,17a-tetradecahydro-5,10-dithia-1,13,16-triaza-benzocyclopentadecene-1-carboxylic Acid *tert*-Butyl Ester (53). Into a solution of dry liquid ammonia (300 mL) was added **50** (36 mg, 0.048 mmol); then sodium was added portionwise until a blue color persisted for more than 15 min. *trans*-1,4-Dibromo-2-butene was added. The mixture was allowed to reflux for 2 h, and then ammonia was removed with a stream of argon. The residue was dissolved in AcOEt, sequentially washed with 10% citric acid, then with brine, dried over $NaSO_4$, and concentrated. Flash chromatography (4% MeOH in AcOEt) of the residue gave a mixture of **51** and **53**, which were separated by preparative HPLC to give **51** (8 mg, 27%) and **53** (8 mg, 27%). For **51**: $[\alpha]_D$ +112 (*c* 0.8, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.81 (m, 1H), 5.66 (m, 1H), 4.87 (d, 1H, J = 4.5 Hz), 4.58 (q, 1H, J = 6.8 Hz), 3.94 (m, 1H), 3.87 (m, 1H), 3.61 (dt, 1H, J = 9.7, 3.2 Hz), 3.50 (dd, 1H, J = 14.7, 5.7 Hz), 3.36 (m, 1H), 3.33 (m, 1H), 3.22 (dd, 1H, J = 13.6, 7.8 Hz), 3.19 (t, 2H, J = 7.0 Hz), 3.11 (dd, 1H, J = 13.5, 7.9 Hz), 3.02 (m, 1H), 2.91 (dd, 1H, J = 14.2, 6.1 Hz), 2.61 (m, 1H), 2.52 (dd, 1H, J = 14.2, 7.9 Hz), 1.87 (m, 1H), 1.74 (m, 4H), 1.52−1.43 (m, 2H), 1.49 (s, 9H), 1.41 (d, 3H, J = 6.9 HZ), 1.36 (m, 3H), 1.14 (d, 3H, J = 7.0 Hz), 0.96 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 173.5, 169.9, 156.0, 131.0, 128.8, 80.9, 69.5, 53.5, 49.7, 49.1, 45.9, 39.1, 38.8, 37.7, 33.9, 32.8, 32.7, 31.6, 27.7, 27.0, 24.2, 20.1, 18.0, 16.6, 13.1; MS (ESI) *m*/*z* 637 (M + Na^+); HRMS calcd for $C_{29}H_{50}N_4O_6S_2$ (M + H^+) 615.3244, found 615.3241; LC/MS retention time [A] 23.52 min, [B] 8.38 min. For **53**: $[\alpha]_D$ −90.5 (*c* 0.4, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.6 (m, 2H), 4.33 (m, 2H), 4.22 (b, 1H), 3.90 (m, 1H), 3.81 (m, 1H), 3.68 (m, 1H), 3.49 (m, 3H), 3.19 (t, 2H, J = 7.0 Hz), 3.07 (m, 2H), 3.0 (m, 1H), 2.92 (m, 1H), 2.62 (m, 1H), 2.34 (m, 1H), 2.06 (m, 1H), 1.78 (m, 3H), 1.56 (m, 2H), 1.49 (s, 9H), 1.44 (d, 3H, J = 7.1 HZ), 1.38 (m, 4H), 1.14 (d, 3H, J = 7.0 Hz), 0.95 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 173.4, 171.1, 155.7, 129.6, 129.2, 81.0, 54.2, 49.7, 48.8, 43.5, 40.6, 39.1, 38.0, 37.5, 33.7, 32.8, 32.4, 31.6, 28.9, 27.7, 26.1, 20.1, 18.0, 16.8, 13.2; MS (ESI) *m*/*z* 637 (M + Na^+); HRMS calcd for $C_{29}H_{50}N_4O_6S_2$ (M + H^+) 615.3245, found 615.3256; LC/MS retention time [A] 23.77 min, [B] 31.36 min.

(2*S*,4*R*,11′*S*,15′*R*,17′*R*,17a′*R*)-*N*-Butyl-4-hydroxy-2-methyl-4-(15-methyl-14,17-dioxo-2,3,4,4a,6,9,11,12,13,14,15,16,17,17a-tetradecahydro-1*H*-5,10-dithia-1,13,16-triaza-benzocyclopentadecen-12-yl)-butyramide (52). Into a solution of **51** (6 mg, 0.01 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.5 mL) dropwise. The mixture was stirred at room temperature for 40 min and then evaporated. The residue was dissolved in AcOEt (10 mL), washed sequentially with saturated $NaHCO_3$ (1 mL) and then with brine, dried over $NaSO_4$, and concentrated to give **52** (5 mg, quant): $[\alpha]_D$ +21 (*c* 0.3, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.63 (ddd, 1H, J = 14.5, 8.9, 5.4 Hz), 5.47 (m, 1H), 4.36 (q, 1H, J = 7.1 Hz), 3.78 (dt, 1H, J = 9.7, 3.1 Hz), 3.62 (m, 2H), 3.49 (m, 1H), 3.27 (m, 2H), 3.20 (m, 2H), 3.01 (dd, 1H, J = 14.2, 7.9 Hz), 2.71 (m, 1H), 2.61 (m, 1H), 2.41 (dd, 1H, J = 14.1, 3.4 Hz), 2.11 (m, 1H), 1.94 (m, 2H), 1.71 (ddd, 1H, J = 13.6, 9.8, 3.4 Hz), 1.52 (m, 3H), 1.41 (d, 3H, J = 7.1 Hz), 1.32 (m, 3H), 1.14 (d, 3H, J = 7.0 Hz), 0.96 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 174.0, 172.4, 131.5, 126.8, 68.0, 64.0, 55.8, 49.9, 48.8, 46.1, 45.3, 39.1, 39.0, 37.8, 33.4, 31.7, 30.9, 30.6, 20.9, 20.1, 17.9, 16.5, 13.1; MS (ESI) *m*/*z* 515 (M + H^+); HRMS calcd for $C_{24}H_{42}N_4O_4S_2$ (M + H^+) 515.2720, found 515.2723; LC/MS retention time [A] 11.33 min, [B] 22.16 min.

(2*S*,4*R*,11′*S*,15′*R*,17′*S*,17a′*S*,)-*N*-Butyl-4-hydroxy-2-methyl-4-(15-methyl-14,17-dioxo-2,3,4,4a,6,9,11,12,13,14,15,16,17,17a-tetradecahydro-1*H*-5,10-dithia-1,13,16-triaza-benzocyclopentadecen-12-yl)-butyramide (54). Compound **54** (5.6 mg, quant) was prepared from **53** (7 mg, 0.011 mmol) according to the procedure for the preparation of **52**: $[\alpha]_D$ −102 (*c* 0.25, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.73 (m, 1H), 5.36 (m, 1H), 4.55 (q, 1H, J = 7.0 Hz), 3.86 (m, 1H), 3.77 (m, 1H), 3.19 (m, 4H), 2.97 (td, 1H, J = 13.0, 4.0 Hz), 2.70 (m, 2H), 2.60 (m, 1H), 2.50 (dd, 1H, J = 14.3, 3.6 Hz), 2.04 (m, 2H), 1.94 (m, 1H), 1.70 (ddd, 1H, J = 13.5, 9.2, 3.8 Hz), 1.50 (m, 4H), 1.37 (d, 3H, J = 7.0 Hz), 1.15 (d, 3H, J = 6.9 Hz), 0.96 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 173.5, 171.2, 132.6, 126.1, 67.7, 61.5, 53.1, 48.6, 45.5, 44.8, 39.1, 38.6, 37.8, 32.6, 31.7, 31.3, 29.7, 29.0, 20.1, 19.8, 17.73, 17.4, 13.2; MS (ESI) *m*/*z* 515 (M + H^+); HRMS calcd for $C_{24}H_{42}N_4O_4S_2$ (M + H^+) 515.2720, found 515.2723; LC/MS retention time [A] 11.88 min, [B] 22.65 min.

4-Trifluoromethanesulfonyloxy-3,6-dihydro-2*H*-pyridine-1-carboxylic Acid *tert*-Butyl Ester (56). Into a solution of diisopropylamine (0.78 mL, 5.6 mmol) in THF (15 mL) was added *n*-BuLi (1.6 M in hexane, 3.5 mL, 5.4 mmol) at −10 °C. The mixture was stirred at −10 to 0 °C for 30 min to get a LDA solution, which was added dropwise to a solution of *N*-Boc-4-oxo-piperidine **55** (1.0 g, 4.9 mmol) in THF (5 mL) at −78 °C. After the mixture was stirred for 2 h, *N*-(5-chloro-2-pyridyl)triflimide (2.17 g, 5.1 mmol) in THF (5 mL) was added dropwise. The mixture was stirred at −78 °C for 12 h, then warmed to room temperature and concentrated. Flash chromatography (hexane/AcOEt 2/1) of the residue gave **56** (1.2 g, 81%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.75 (b, 1H), 4.03 (b, 2H), 3.62 (m, 2H), 2.43 (b, 2H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.7, 149.8, 139.8, 80.9, 60.7, 41.8, 28.7, 28.5, 21.4.

3,6-Dihydro-2*H*-pyridine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester 4-Methyl Ester (57). Into a solution of **56** (0.26 g, 0.78 mmol) in DMF (3.2 mL) and MeOH (1.5 mL) were added palladium acetate (5 mg, 0.03 mmol), triphenylphosphine (13 mg, 0.06 mmol), and triethylamine (0.22 mL, 1.56 mmol). The mixture was purged with CO for 5 min and then stirred under CO atmosphere (with a balloon) at room temperature for 12 h. Ether (20 mL) and H_2O (5 mL) were added; the organic layer was washed with H_2O until neutral, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt 5/1) of the residue gave **57** (146

mg, 77%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.82 (b, 1H), 4.01 (b, 2H), 3.45 (t, 2H, J = 5.55 Hz), 2.33 (b, 2H), 1.41 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 164.5, 154.6, 134.5, 131.1, 80.652.1, 43.8, 40.5, 28.7, 24.6.

***cis*-3-Benzylsulfanyl-piperidine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester 4-Methyl Ester (58).** Into a solution of **57** (96 mg, 0.37 mmol) in MeOH (2.8 mL) was added benzyl mercaptan (0.14 mL, 1.1 mmol). A solution of NaOMe in MeOH (0.5 M, 2.0 mL) was added dropwise. The mixture was stirred at room temperature for 2 h until the reaction was complete, then Amberlite IR 120(+) was added to pH 7, the resin was filtered and washed with MeOH, and the filtrate was concentrated. Flash chromatography (hexane/AcOEt 5/1) of the residue gave **58** (0.12 g, 89%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.23 (m, 5H), 4.02 (m, 2H), 3.74 (ab, 2H, J = 13.5 Hz), 3.63 (s, 3H), 3.12 (dd, 1H, J = 13.6, 2.55 Hz), 3.05 (m, 1H), 2.85 (td, 1H, J = 13.4, 3.0 Hz), 2.72 (dt, 1H, J = 10.6, 4.1 Hz), 1.86 (m, 1H), 1.70 (m, 1H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 155.4, 138.3, 129.4, 128.8, 127.5, 80.1, 52.2, 47.4, 45.7, 43.0, 42.7, 36.3, 28.9, 24.5; MS (FAB) *m*/*z* 365 (M + H^+); HRMS calcd for $C_{19}H_{27}NO_4S$ (M + H^+) 365.1647, found 365.1645.

(3*S*,4*R*)-3-Benzylsulfanyl-piperidine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester 4-Methyl Ester (59) and (3*R*,4*S*)-3-Benzylsulfanyl-piperidine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester (60). Compound **58** (72 mg, 0.4 mmol) was dissolved in acetone (0.2 mL), and then phosphate buffer (pH 7.2, 4.0 mL) was added. To this solution were added pig liver esterase (14 mg) and 0.1 N NaOH to pH 8. The mixture was stirred at room temperature for 4 days with occasionally addition of 0.1 N NaOH to maintain pH 8. HCl (1 N) was added to pH 2, the mixture was extracted with AcOEt (3 × 20 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt 5/1, pure AcOEt) of the residue gave **59** (35 mg, 49%) and **60** (32 mg, 49%). For **59**: $[\alpha]_D$ −92.2 (*c* 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.23 (m, 5H), 4.02 (m, 2H), 3.74 (ab, 2H, J = 13.5 Hz), 3.63 (s, 3H), 3.12 (dd, 1H, J = 13.6, 2.55 Hz), 3.05 (m, 1H), 2.85 (td, 1H, J = 13.4, 3.0 Hz), 2.72 (dt, 1H, J = 10.6, 4.1 Hz), 1.86 (m, 1H), 1.70 (m, 1H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.8, 155.4, 138.3, 129.4, 128.8, 127.5, 80.1, 52.2, 47.4, 45.7, 43.0, 42.7, 36.3, 28.9, 24.5; MS (FAB) *m*/*z* 365 (M + H^+); HRMS calcd for $C_{19}H_{27}NO_4S$ (M + H^+) 365.1647, found 365.1645. For **60**: $[\alpha]_D$ +65.4 (*c* 1.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.23 (m, 5H), 4.08 (m, 2H), 3.81 (ab, 2H, J = 13.1 Hz), 3.14 (m, 2H), 3.08 (bs, 1H), 2.80 (m, 2H), 1.65 (m, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.5, 156.4, 138.2, 129.4, 128.9, 127.5, 80.3, 47.6, 45.7, 43.1, 42.9, 36.8, 28.8, 24.3; MS (FAB) *m*/*z* 352 (M + H^+); IR ($CHCl_3$) 2975, 1736, 1695, 1427, 1163.

(3*S*,4*R*,1′*R*,1″*S*,2″*R*,4″*S*)-3-Benzylsulfanyl-4-[1-(1-benzylsulfanylmethyl-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl)-ethylcarbamoyl]-piperidine-1-carboxylic Acid *tert*-Butyl Ester (61). Into a solution of **60** (22 mg, 0.063 mmol) and 5-(2-amino-propionylamino)-6-benzylsulfanyl-4-hydroxy-2-methyl-hexanoic acid butylamide (prepared separately, 26 mg, 0.063 mmol) in CH_2Cl_2 (2.5 mL) were added PyBOP (49 mg, 0.095 mmol) and DIEA (24 μL, 0.13 mmol) at 0 °C. The mixture was stirred at 0 °C to room temperature for 4 h, and then 10% citric acid (1 mL) was added. The mixture was extracted with AcOEt (3 × 10 mL), and the combined organic layers were sequentially washed with saturated $NaHCO_3$, then with brine, dried over Na_2SO_4, and concentrated to give a mixture of two diastereoisomers, which were separated by flash chromatography (4% MeOH in AcOEt), giving **61** (32 mg, 68%): $[\alpha]_D$ −7.5 (*c* 0.5, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 7.36−7.19 (m, 10H), 4.36 (m, 1H), 3.96 (m, 3H), 3.77 (m, 3H), 3.69 (ab, 2H, J = 13.1 Hz), 3.25 (m, 1H), 3.17 (m, 3H), 2.90 (m, 1H), 2.79 (m, 1H), 2.62 (dd, 1H, J = 13.6, 7.0 Hz), 2.55 (m, 1H), 2.47 (dd, 1H, J = 13.6, 7.6 Hz), 1.90 (m, 1H), 1.68 (m, 2H), 1.50 (m, 2H), 1.47 (s, 9H), 1.38 (d, 3H, J = 7.1 HZ), 1.32 (m, 4H), 1.11 (d, 3H, J = 7.0 Hz), 0.93 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.4, 173.4, 1732.3, 155.2, 138.3, 128.8, 128.1, 127.9, 126.7, 126.4, 79.7, 68.3, 62.5, 60.0, 52.6, 49.3, 38.6, 37.7, 37.2, 36.8, 35.3, 32.2, 31.2, 27.2, 24.0, 19.6, 17.1, 16.9, 12.9, 12.7; MS (FAB) *m*/*z* 743 (M + H^+), 643, 154; HRMS calcd for $C_{39}H_{58}N_4O_6S_2$ (M + H^+) 743.3876, found 743.3872.

(4*R*,7*R*,10*S*,18*S*,1′*R*,3′*S*)-10-(3-Butylcarbamoyl-1-hydroxy-butyl)-7-methyl-5,8-dioxo-1,3,4,4a,5,6,7,8,9,10,11,13,16,17a-tetradecahydro-12,17-dithia-2,6,9-triaza-benzocyclopentadecene-2-carboxylic Acid *tert*-Butyl Ester (62). Compound **62** (9 mg, 39%) was prepared from **61** (28 mg, 0.038 mmol) and *trans*-1,4-dibromo-2-butene (32 mg, 0.1 mmol) according to the procedure for the preparation of **23**: $[\alpha]_D$ +133.3 (*c* 0.45, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.72 (m, 1H), 5.33 (m, 1H), 4.53 (m, 1H), 4.20 (m, 2H), 3.85 (m, 2H), 3.45 (m, 2H), 3.17 (m, 5H), 2.92 (m, 3H), 2.66 (dd, 1H, J = 14.4, 10.2 Hz), 2.57 (m, 1H), 2.49 (dd, 1H, J = 14.4, 3.2 Hz), 1.67 (m, 2H), 1.51 (m, 2H), 1.47 (s, 9H), 1.37 (m, 2H), 1.348 (d, 3H, J = 7.0 Hz), 1.13 (d, 3H, J = 7.0 Hz), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 178.0, 176.4, 173.7, 156.0, 132.7, 126.0, 80.0, 67.4, 53.0, 47.1, 45.9, 42.4, 39.2, 39.1, 38.7, 37.9, 32.4, 31.7, 31.2, 29.3, 27.7, 22.4, 20.1, 17.7, 17.4, 13.5, 13.1; MS (FAB) *m*/*z* 615 (M + H^+), 515, 442, 307; IR ($CHCl_3$) 3299, 1734, 1634, 1536; HRMS calcd for $C_{29}H_{50}N_4O_6S_2$ (M + H^+) 615.3250, found 615.3227; LC/MS retention time [A] 22.77 min.

(2*S*,4*R*,4′*R*,7′*R*,10′*S*,18′*S*)-*N*-Butyl-4-hydroxy-2-methyl-4-(7-methyl-5,8-dioxo-1,3,4,4a,5,6,7,8,9,10,11,13,16,17a-tetradecahydro-2*H*-12,17-dithia-2,6,9-triaza-benzocyclopentadecen-10-yl)-butyramide (63). Compound **63** (6.6 mg, quant) was prepared from **62** (8 mg, 0.013 mmol) according to the procedure for the preparation of **52**: $[\alpha]_D$ +190 (*c* 0.3, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.69 (m, 1H), 5.49 (m, 1H), 4.51 (m, 1H), 4.35 (dd, 1H, J = 14.2, 7.2 Hz), 3.79 (m, 1H), 3.58 (m, 1H), 3.48 (m, 1H), 3.23−3.08 (m, 6H), 2.96 (dd, 1H, J = 13.7, 10.3 Hz), 2.86 (dt, 1H, J = 12.8, 3.4 Hz), 2.77 (td, 1H, J = 12.9, 3.4 Hz), 2.59 (m, 1H), 2.43 (dd, 1H, J = 13.6, 3.8 Hz), 1.94 (m, 1H), 1.82 (m, 1H), 1.68 (m, 1H), 1.52 (m, 2H), 1.46−1.26 (m, 5H), 1.38 (d, 3H, J = 7.1 Hz), 1.12 (d, 3H, J = 7.0 Hz), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 174.0, 173.5, 130.4, 128.0, 67.8, 55.7, 50.4, 49.2, 46.8, 44.4, 43.5, 39.1, 39.0, 37.8, 33.5, 32.2, 31.7, 30.9, 22.6, 20.1, 18.0, 15.8, 13.1; MS (ESI) *m*/*z* 515 (M + H^+); HRMS calcd for $C_{24}H_{42}N_4O_4S_2$ (M + H^+) 515.2726, found 515.2743; LC/MS retention time [A] 12.65 min, [B] 20.72 min.

3,6-Dihydro-2*H*-pyridine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester 4-Ethyl Ester (64). 1-Benzyl-3-oxo-piperidine-4-carboxylic acid ethyl ester hydrochloric salt (3.0 g, 10 mmol) was dissolved in an aqueous solution of EtOH−H_2O (1/1, 20 mL). Pd/C (10%, 0.5 g) was added, and the mixture was charged with H_2 to 50 psi, stirred for 20 h, then filtered through a pad of Celite, and washed with EtOH. The filtrate was concentrated under reduced pressure to give a pale yellowish solid, which was dissolved in $CHCl_3$ (15 mL). A solution of $NaHCO_3$ (0.84 g, 10 mmol) in H_2O (7.5 mL) was added, followed by NaCl (1.71 g). The mixture was heated to 70 °C, and a solution of $(Boc)_2O$ in $CHCl_3$ (6 mL) was added slowly by a syringe pump during a period of 3 h. The stirring was continued for 8 h at 70 °C, then 2 h at room temperature. The organic layer was separated, and the aqueous layer was extracted twice with $CHCl_3$. The combined organic layers were dried over $MgSO_4$ and concentrated. Flash chromatography (hexane/AcOEt 5/1) of the residue gave 3-oxo-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester (2.2 g, 81%). Into a solution of the former ester (0.27 g, 1 mmol) in EtOH (5 mL), $NaBH_4$ (25 mg, 0.6 mmol) was added portionwise. The mixture was stirred at room temperature for 3 h, and the solvent was removed. The residue was diluted with AcOEt, washed sequentially with 1 N HCl, then with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt 2/1) of the residue gave 3-hydroxy-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester 4-ethyl ester as a mixture of cis and trans isomers with a ratio of 4/1 (0.26 g, 96%). Into this mixture (0.16 g, 0.6 mmol) in CH_2Cl_2 (9 mL) was added ADDP (0.3 g, 0.9 mmol) and imidazole (84 mg, 0.9 mmol). PMe_3 (1 M in toluene, 1.2 mL) was then added dropwise. The mixture was stirred at room temperature for 1 day, and hexane (9 mL) was added. The solid was filtered off, and the residue was washed once with hexane.

The filtrate was concentrated, and the residue was purified by flash chromatography (hexane/AcOEt 5/1, 2/1) to give **64** (0.12 g, 80%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.89 (s, 1H), 4.21 (q, 2H, J = 7.1 Hz), 4.06 (d, 2H, J = 2.8 Hz), 3.51 (t, 2H, J = 5.6 Hz), 2.39 (bs, 2H), 1.46 (s, 9H), 1.29 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.74, 155.1, 135.5, 129.6, 80.4, 61.0, 43.9, 40.8, 28.8, 24.8, 14.7; MS (FAB$^+$) m/z 255 (M + H$^+$); IR ($CHCl_3$) ν (cm^{-1}) 2973, 1701, 1418, 1247, 1168; HRMS calcd for $C_{13}H_{21}NO_4$ (M + H$^+$) 255.1471, found 255.1480.

3,6-Dihydro-2*H*-pyridine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester 4-(2-Trimethylsilanyl-ethyl) Ester (65). Into a solution of **64** (85 mg, 0.33 mmol) in THF (0.5 mL) was added 1 N LiOH (0.4 mL) at room temperature. The mixture was stirred overnight; then 1 N HCl was added to pH 2, and the mixture was extracted with AcOEt (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give an acid (74 mg, 98%). Into a solution of this acid (52 mg, 0.23 mmol) in CH_2Cl_2 (3 mL) were added EDCI (66 mg, 0.34 mmol), trimethylsilyl ethanol (50 μL, 0.34 mmol), and 4-dimethylaminopyridine (DMAP; 42 mg, 0.34 mmol) at 0 °C. The mixture was stirred at 0 °C to room temperature for 6 h until the reaction was complete and then filtered through a pad of Celite and washed with AcOEt, and the filtrate was concentrated. Flash chromatography (hexane/AcOEt 7/1) of the residue gave pure **65** (55 mg, 74%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.86 (bs, 1H), 4.24 (t, 2H, J = 8.4 Hz), 4.06 (m, 2H), 3.51 (t, 2H, J = 5.6 Hz), 3.50 (t, 2H, J = 5.6 Hz), 2.38 (m, 2H), 1.47 (s, 9H), 1.02 (t, 2H, J = 8.4 Hz), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.8, 155.1, 135.3, 129.8, 80.4, 63.3, 44.0, 39.7, 28.8, 24.8, 17.7, −1.0; MS (FAB) m/z 328 (M + H$^+$); HRMS calcd for $C_{16}H_{30}NO_4Si$ (M + H$^+$) 328.1944, found 328.1939.

***cis*-3-Benzylsulfanyl-piperidine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester 4-(2-Trimethylsilanyl-ethyl) Ester (66).** Into a solution of **65** (140 mg, 0.43 mmol) in MeOH (3 mL) was added benzyl mercaptan (0.17 mL, 1.72 mmol), followed by a solution of NaOMe in MeOH (0.5 M, 2.15 mL) added dropwise at 0 °C. The mixture was stirred at 0 °C to room temperature for 2 h until the reaction was complete; then Amberlite IR 120(+) was added to pH 7, and the mixture was filtered and washed with MeOH. The filtrate was concentrated, and the residue was purified by flash chromatography (hexane/AcOEt 5/1) to give **66** (0.16 g, 82%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.23 (m, 5H), 4.21−4.02 (m, 4H), 3.76 (ab, 2H, J = 13.46 Hz), 3.14 (dd, 1H, J = 13.6, 2.65 Hz), 3.08 (bs, 1H), 1.73 (m, 1H), 1.49 (s, 9H), 0.94 (t, 2H, J = 8.6 Hz), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 172.6, 155.4, 138.4, 129.4, 128.9, 127.5, 80.1, 63.4, 45.8, 43.0, 36.3, 28.9, 24.5, 17.7, −1.0; MS (FAB) m/z 452 (M + H$^+$), 396, 368, 324, 278; HRMS calcd for $C_{23}H_{37}NO_4$ (M + H$^+$) 452.2290, found 452.2268.

(3*R*,4*S*,1′*R*,1″*S*,2″*R*,4″*S*)-3-Benzylsulfanyl-4-[1-(1-benzylsulfanylmethyl-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl)-ethylcarbamoyl]-piperidine-1-carboxylic Acid *tert*-Butyl Ester (67). Into a solution of **66** (30 mg, 0.066 mmol) in THF (0.4 mL) were added TBAF (1 N in THF, 0.1 mL) and molecular sieves 4 Å at 0 °C. The mixture was stirred at 0 °C to room temperature for 3 h, then 10% citric acid was added to pH 3.0, and the mixture was extracted with AcOEt (3 × 10 mL). The combined organic layers were washed sequentially with 10% citric acid, then with brine, dried over Na_2SO_4, and concentrated to give 3-benzylsulfanyl-piperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester (23 mg, quant): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34−7.23 (m, 5H), 4.08 (m, 2H), 3.81 (ab, 2H, J = 13.1 Hz), 3.14 (m, 2H), 3.08 (bs, 1H), 2.80 (m, 2H), 1.65 (m, 2H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.5, 156.4, 138.2, 129.4, 128.9, 127.5, 80.3, 47.6, 45.7, 43.1, 42.9, 36.8, 28.8, 24.3; MS (FAB$^+$) m/z 352 (M + H$^+$); IR ($CHCl_3$) 2975, 1736, 1695, 1427, 1163; MS (ESI) m/z 352 (M + H$^+$). Into a solution of the above acid (22 mg, 0.063 mmol) and the amine derived from **21** (26 mg, 0.063 mmol) in CH_2Cl_2 (2.5 mL) were added PyBOP (49 mg, 0.095 mmol) and DIEA (24 μL, 0.13 mmol) at 0 °C. The mixture was stirred at 0 °C to room temperature for 4 h, and then 10% citric acid (1 mL) was added. The mixture was extracted with AcOEt (3 × 10 mL); the combined organic layers were washed sequentially with saturated $NaHCO_3$, then with brine, dried over Na_2SO_4, and concentrated to give a mixture of two diastereoisomers, which were separated by flash chromatography (4% MeOH in AcOEt) to give **67** (16 mg, 34%): $[\alpha]_D$ −22.8 (*c* 0.9, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 7.36−7.20 (m, 10H), 4.30 (dd, 1H, J = 14.3, 7.1 Hz), 4.05 (m, 1H), 3.92 (m, 2H), 3.77 (s, 2H), 3.74 (m, 1H), 3.72 (s, 2H), 3.25 (d, 1H, J = 12.8 Hz), 3.16 (t, 2H, J = 6.6 Hz), 2.93 (m, 2H), 2.77 (m, 1H), 2.60 (dd, 1H, J = 13.8, 7.1 Hz), 2.53 (m, 1H), 2.47 (dd, 1H, J = 13.7, 7.6 Hz), 2.0 (m, 1H), 1.64 (m, 2H), 1.49 (s, 9H), 1.36 (m, 4H), 1.30 (d, 3H, J = 7.0 HZ), 1.10 (d, 3H, J = 7.0 Hz), 0.93 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 178.0, 174.2, 173.7, 155.8, 138.8, 138.6, 129.4, 129.2, 128.6, 128.4, 127.2, 126.9, 80.2, 71.9, 68.7, 60.5, 52.6, 49.7, 45.9, 43.7, 39.2, 39.0, 38.3, 37.7, 35.7, 32.6, 31.7, 27.7, 24.3, 20.1, 19.9, 17.7, 17.2, 13.5, 13.2; MS (FAB) m/z 743 (M + H$^+$), 643, 154; IR ($CHCl_3$) 2968, 1710, 1654, 14367, 942; HRMS calcd for $C_{39}H_{58}N_4O_6S_2$ (M + H$^+$) 743.3876, found 743.3872.

(4*S*,7*R*,10*S*,18*R*,1′*R*,3′*S*)-10-(3-Butylcarbamoyl-1-hydroxy-butyl)-7-methyl-5,8-dioxo-1,3,4,4a,5,6,7,8,9,10,11,13,16,17a-tetradecahydro-12,17-dithia-2,6,9-triaza-benzocyclopentadecene-2-carboxylic Acid *tert*-Butyl Ester (68). Into a solution of dry liquid ammonia (300 mL) was added **67** (36 mg, 0.048 mmol); then sodium was added portionwise until a blue color persisted for 5−10 min. *trans*-1,4-Dibromo-2-butene (35 mg, 0.16 mmol) was added. The mixture was allowed to reflux for 2 h, and then ammonia was removed with a stream of argon. The residue was dissolved in AcOEt, sequentially washed with 10% citric acid and with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (4% MeOH in AcOEt) of the residue gave **68** (12 mg, 48%): $[\alpha]_D$ −80 (*c* 0.11, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 7.87 (m, 1H), 7.71 (bs, 1H), 5.71 (m, 1H), 5.51 (m, 1H), 4.33 (m, 2H), 4.24 (m, 2H), 3.80 (m, 1H), 3.45 (m, 2H), 3.22−3.03 (m, 7H), 2.83 (m, 2H), 2.59 (m, 1H), 2.36 (d, 1H, J = 8.23 Hz), 1.90 (m, 1H), 1.67 (m, 2H), 1.52 (m, 2H), 1.47 (s, 9H), 1.38 (d, 3H, J = 7.1 HZ), 1.33 (m, 2H), 1.11 (d, 3H, J = 7.0 Hz), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 178.0, 174.2, 174.0, 156.0, 130.0, 123.8, 80.2, 67.7, 60.2, 56.3, 50.5, 45.3, 44.5, 39.8, 39.3, 37.8, 33.7, 32.1, 31.7, 27.7, 22.7, 20.1, 18.1, 15.8, 13.2; MS (FAB) m/z 615 (M + H$^+$); IR ($CHCl_3$) 3286, 1644, 1623, 1542; HRMS calcd for $C_{29}H_{50}N_4O_6S_2$ (M + H$^+$) 615.3250, found 615.3246; LC/MS retention time [A] 21.57 min, [B] 29.00 min.

(2*S*,4*R*,4′*S*,7′*R*,10′*S*,18′*R*)-*N*-Butyl-4-hydroxy-2-methyl-4-(7-methyl-5,8-dioxo-1,3,4,4a,5,6,7,8,9,10,11,13,16,17a-tetradecahydro-2*H*-12,17-dithia-2,6,9-triaza-benzocyclopentadecen-10-yl)-butyramide (69). Into a solution of **68** (6 mg, 0.009 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.6 mL). The mixture was stirred at room temperature for 30 min and concentrated under vacuum. The residue was treated with AcOEt (10 mL), washed with saturated $NaHCO_3$ (1 mL), dried over Na_2SO_4, and concentrated to give **69** (4.2 mg, quant): $[\alpha]_D$ −58.7 (*c* 0.3, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.74 (m, 1H), 5.34 (m, 1H), 4.51 (m, 1H), 4.34 (m, 1H), 4.22 (m, 2H), 3.86 (m, 2H), 3.17 (m, 3H), 2.96 (m, 2H), 2.70−2.34 (m, 3H), 1.71 (m, 3H), 1.54−1.34 (m, 12H), 1.14 (d, 3H, J = 6.9 Hz), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 178.6, 177.9, 168.3, 131.4, 128.9, 68.1, 67.5, 45.0, 39.2, 39.1, 31.7, 30.6, 29.4, 29.1, 23.9, 23.0, 20.1, 17.3, 13.4, 13.1; MS (ESI) m/z 515 (M + H$^+$); HRMS calcd for $C_{24}H_{42}N_4O_4S_2$ (M + H$^+$) 515.2726, found 515.2743; LC/MS retention time [A] 12.77 min, [B] 6.08 min.

***cis*-Piperidine-1,2,3-tricarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (70).** Furo[3,4-*b*]pyridine-5,7-dione (12 g, 80.4 mmol) was dissolved in boiling methanol (60 mL), and the mixture was refluxed for 2 h. After cooling, the solvent was removed, and the solid was recrystallized in ethyl acetate to give pyridine-2,3-dicarboxylic acid 2-methyl ester (7 g, 50%). Into a flask with this ester (3 g, 16.6 mmol) were added acetic acid (30 mL) and 10% Pd/C (0.9 g); then H_2 was charged in to 50 psi, and the mixture was stirred for 16 h and then filtered through a pad of Celite. The filtrate was concentrated to dryness under reduced pressure. The

residue was dissolved in methanol (60 mL); then $NaHCO_3$ (3.5 g, 44.4 mmol) and Boc_2O (4 g, 18.3 mmol) were added consecutively. The mixture was placed into an ultrasonic bath for 3 h. The solid was filtered off, the filtrate was concentrated, and the residue was purified by flash chromatography (hexane/AcOEt 2/1) to give racemic **70** (3.6 g, 76%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.9 (s, 1H), 5.6, 5.3 (b, 1H), 4.13−3.94 (m, 1H), 3.72 (s, 3H), 2.66 (m, 2H), 1.68 (m, 4H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.6, 170.7, 156.6, 80.7, 52.8, 43.4, 28.7, 24.4, 22.6; MS (ESI) *m*/*z* 288 (M + H^+); HRMS calcd for $C_{13}H_{21}NO_6$ (M + H^+) 288.1442, found 288.1435.

***cis*-3-Formyl-piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (71).** Into a solution of **70** (1.3 g, 4.5 mmol) in toluene (25 mL) was added oxalyl chloride (0.41 mL, 4.5 mmol), followed by DMF (8 μL) at 0 °C. The mixture was stirred at 0 °C for 1 h and then concentrated to dryness. The residue was dissolved in THF (25 mL), and sodium borohydride (0.17 g, 4.5 mmol) was added portionwise at 0 °C. After the mixture was stirred for another 30 min, water (7 mL) was added carefully, followed by AcOEt (20 mL). The organic phase was separated, and the aqueous layer was extracted once again with AcOEt (20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt 1/2) of the residue gave the alcohol (0.96 g, 78%). Into a solution of this alcohol (0.83 g, 3.0 mmol) in CH_2Cl_2 (30 mL) was added Dess−Martin periodinane (1.6 g, 3.6 mmol) portionwise at 5 °C. The mixture was stirred at room temperature overnight; then saturated $NaHCO_3$ (5 mL) and $Na_2S_2O_3$ (10 mL) were added. The mixture was then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography of the residue (hexane/AcOEt 1/1) gave racemic **71** (0.73 g, 90%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.71 (s, 1H), 5.56, 5.30 (d, 1H, J = 4.4 Hz), 4.0 (m, 1H), 3.68 (s, 3H), 2.81 (m, 1H), 2.47 (m, 1H), 2.11 (m, 1H), 1.75 (m, 1H), 1.45 (s, 9H), 1.44−1.28 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 199.1, 170.2, 155.2, 80.6, 55.7, 52.3, 41.9, 28.1, 23.8, 20.5; MS (ESI) *m*/*z* 272 (M + H^+); HRMS calcd for $C_{13}H_{21}NO_5$ (M + H^+) 272.1493, found 272.1497.

***cis*-3-[2-(2-Trimethylsilanyl-ethoxycarbonyl)-ethyl]-piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (72).** Into a solution of **71** (1.4 g, 5.2 mmol) in CH_2Cl_2 (40 mL) was added $Ph_3P{=}CHCO_2TMSE$ (3.45 g, 8.2 mmol). The mixture was stirred at room temperature overnight and then concentrated. Flash chromatography of the residue (hexane/AcOEt 5/1) gave a pure ester (2.0 g, 93%). Into a flask containing this ester (1.9 g, 4.5 mmol), AcOEt (40 mL), and 10% Pd/C (0.5 g), H_2 was filled in to 50 psi; then the suspension was stirred for 2 h and filtered through a pad of Celite. The filtrate was concentrated, and the residue was purified by flash chromatography (hexane/AcOEt 5/1) to give racemic **72** (1.84 g, 98%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.87, 4.67 (s, 1H), 4.17 (t, 2H, J = 8.4 Hz), 3.94 (m, 1H), 3.70 (s, 3H), 3.27 (m, 1H), 2.42 (m, 2H), 1.78−1.62 (m, 5H), 1.45 (s, 9H), 1.40 (m, 2H), 1.0 (t, 2H, J = 8.4 Hz), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.9, 172.0, 156.5, 80.6, 63.0, 58.2, 56.6, 51.9, 40.9, 32.5, 28.8, 26.0, 25.1, 17.7, −1.0; MS (ESI) *m*/*z* 416 (M + H^+); HRMS calcd for $C_{20}H_{37}NO_6Si$ (M + H^+) 416.2463, found 416.2451.

***cis*-3-(2-Carboxy-ethyl)-piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (73).** To a solution of **72** (1.8 g, 4.3 mmol) in THF (26 mL) containing molecular sieves was added TBAF (1 M in THF, 7 mL, 7 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C to room temperature for 5 h, 1 N HCl was added to pH 2, and the mixture was extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated, and the residue was purified by flash chromatography (hexane/AcOEt 1/2) to give racemic **73** (1.3 g, 93%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.6 (b, 1H), 4.85, 4.66 (s, 1H), 3.92 (m, 1H), 3.68 (s, 3H), 3.24 (m, 1H), 2.45 (m, 2H), 1.80−1.61 (m, 5H), 1.42 (s, 9H), 1.33 (m, 2H); MS (ESI) *m*/*z* 316 (M + H^+); HRMS calcd for $C_{15}H_{25}NO_6$ (M + H^+) 316.1755, found 316.1748.

***cis*-3-(3-Oxo-propyl)-piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (74).** Racemic **74** (0.9 g, 86%) was prepared from **73** (1.25 g, 3.9 mmol) as described for the preparation of **71**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.8 (s, 1H), 4.86, 4.66 (s, 1H), 3.92 (m, 1H), 3.70 (s, 3H), 3.16 (m, 1H), 2.49 (m, 2H), 1.80−1.60 (m, 5H), 1.44 (s, 9H), 1.32 (m, 2H); MS (ESI) *m*/*z* 322 (M + Na^+); HRMS calcd for $C_{15}H_{25}NO_5$ (M + Na^+) 322.1615, found 322.1625.

***cis*-3-[4-(2-Trimethylsilanyl-ethoxycarbonyl)-but-3-enyl]-piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (75).** Racemic **75** (1.08 g, 85%) was prepared from **74** (0.86 g, 2.88 mmol) according to the procedure for the preparation of **72**: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.93 (dt, 1H, J = 15.4, 6.9 Hz), 5.82 (d, 1H, J = 15.4 Hz), 4.86, 4.66 (s, 1H), 4.23 (t, 2H, J = 8.5 Hz), 3.88 (m, 1H), 3.70 (s, 3H), 3.16 (m, 1H), 2.32 (m, 2H), 1.70 (m, 5H), 1.44 (s, 9H), 1.37 (m, 2H), 1.02 (t, 2H, J = 8.5 Hz), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 166.3, 155.4, 147.9, 121.5, 79.9, 62.1, 55.9, 51.1, 41.1, 37.8, 31.1, 29.3, 28.0, 25.6, 24.7, 16.9, −1.8; MS (ESI) *m*/*z* 442 (M + H^+); HRMS calcd for $C_{22}H_{39}NO_6Si$ (M + H^+) 442.2619, found 442.2640.

***cis*-3-(4-Carboxy-but-3-enyl)-piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (76).** To a solution of **75** (1.06 g, 2.4 mmol) in THF (20 mL) containing molecular sieves was added TBAF (1 M in THF, 5 mL, 5 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C to room temperature for 5 h, 1 N HCl was added to pH 2, and the mixture was extracted with AcOEt (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (hexane/AcOEt 1/2) to give racemic **76** (0.74 g, 90%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.0 (b, 1H), 7.06 (dt, 1H, J = 15.5, 7.0 Hz), 5.85 (d, 1H, J = 15.7 Hz), 4.86, 4.67 (s, 1H), 3.90 (m, 1H), 3.70 (s, 3H), 3.14 (m, 1H), 2.34 (m, 2H), 1.68 (m, 5H), 1.45 (s, 9H), 1.33 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 170.9, 155.4, 150.9, 120.6, 79.9, 60.1, 57.3, 51.2, 41.1, 37.8, 31.0, 28.0, 25.7, 24.7, 20.7; MS (ESI) *m*/*z* 342 (M + H^+); HRMS calcd for $C_{17}H_{27}NO_6$ (M + H^+) 342.1911, found 342.1923.

***cis*-3-(5-Hydroxy-pent-3-enyl)-piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (77).** Racemic **77** (0.14 g, 60%) was prepared from **76** (0.245 g, 0.72 mmol) via reduction with oxalyl chloride and $NaBH_4$ following the preparation of **71**, but stopping at the alcohol stage: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.64 (m, 2H), 4.86, 4.61 (s, 1H), 4.05 (m, 2H), 3.85 (m, 1H), 3.66 (s, 3H), 3.21 (m, 1H), 2.15 (m, 3H), 1.63 (m, 5H), 1.42 (s, 9H), 1.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.4, 155.3, 131.8, 129.4, 79.9, 63.1, 57.5, 51.0, 41.1, 37.8, 31.7, 28.0, 25.7, 24.7; MS (ESI) *m*/*z* 328 (M + H^+).

***cis*-3-(5-Hydroxy-pent-3-enyl)-piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester (78).** Into a solution of **77** (50 mg, 0.15 mmol) in THF (1 mL) was added 1 N LiOH (0.7 mL, 0.7 mmol). The mixture was stirred at room temperature for 40 h, and then 10% citric acid was added to pH 2. The mixture was extracted with AcOEt (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give racemic **78** (48 mg, quant); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.0 (b, 2H), 5.69 (m, 2H), 4.92, 4.66 (s, 1H), 4.11 (m, 2H), 3.89 (m, 1H), 3.21 (m, 1H), 2.11 (m, 23H), 1.68 (m, 5H), 1.46 (s, 9H), 1.29 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.1, 156.5, 133.1, 129.9, 81.0, 64.1, 56.5, 42.1, 32.4, 30.3, 28.8, 26.2, 25.5; MS (ESI) *m*/*z* 314 (M + H^+).

(2*R*,3*S*,1′*R*,1″*S*,2″*R*,4″*S*)-2-[1-(1-Benzylsulfanylmethyl-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl)-ethylcarbamoyl]-3-(5-hydroxy-pent-3-enyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (79) and (2*S*,3*R*,1′*R*,1″*S*,2″*R*,4″*S*)-2-[1-(1-Benzylsulfanyl-methyl-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl)-ethyl-carbamoyl]-3-(5-hydroxy-pent-3-enyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (80). Into a solution of **78** (48 mg, 0.15 mmol) and 5-(2-amino-propionylamino)-6-benzylsulfanyl-4-hydroxy-2-methyl-hexanoic acid butylamide (prepared separately, 74 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) were added PyBOP (0.12 mg, 0.23 mmol) and DIEA (58 μL, 0.3 mmol) at 0 °C. The mixture was stirred at 0 °C to room temperature for 4 h; then 10% citric

acid (1 mL) was added. The mixture was extracted with AcOEt (3 × 20 mL), and the combined organic layers were sequentially washed with saturated $NaHCO_3$, then with brine, dried over Na_2SO_4, and concentrated to give a mixture of two diastereoisomers **79** (34 mg, 32%) and **80** (34 mg, 32%), which were separated by flash chromatography (4% MeOH in AcOEt). For **79**: $[\alpha]_D$ −47.5 (*c* 0.75, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.23 (m, 5H), 5.66 (m, 2H), 4.62 (b, 1H), 4.41 (m, 2H), 4.0 (m, 2H), 3.94 (m, 2H), 3.88 (m, 1H), 3.78 (s, 2H), 3.18 (m, 2H), 2.60 (m, 3H), 2.20 (m, 2H), 1.69 (m, 6H), 1.53 (m, 4H), 1.48 (s, 9H), 1.39 (m, 8H), 1.12 (d, 3H, J = 6.9 Hz), 0.95 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.1, 173.6, 172.4, 156.3, 138.0, 128.4, 127.7, 126.2, 80.1, 67.0, 61.9, 57.5, 51.0, 49.0, 38.3, 37.6, 37.2, 36.9, 34.9, 32.4, 31.8, 30.9, 29.0, 27.0, 26.6, 24.4, 19.4, 17.6, 17.4, 12.4; MS (ESI) *m*/*z* 705 (M + H$^+$); HRMS calcd for $C_{37}H_{60}N_4O_7S$ (M + H$^+$) 705.4256, found 705.4253. For **80**: $[\alpha]_D$ −36.3 (*c* 0.95, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.36−7.22 (m, 5H), 5.66 (m, 2H), 4.62 (b, 1H), 4.38 (m, 2H), 4.02 (m, 2H), 3.94 (m, 2H), 3.76 (m, 3H), 3.33 (m, 2H), 3.18 (t, 2H, J = 7.0 Hz), 2.65−2.50 (m, 3H), 2.15 (m, 2H), 1.67 (m, 6H), 1.50 (m, 4H), 1.47 (s, 9H), 1.40 (m, 3H), 1.38 (d, 3H, J = 7.0 Hz), 1.12 (d, 3H, J = 6.9 Hz), 0.94 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.1, 173.4, 172.1, 156.2, 138.0, 130.8, 129.2, 128.4, 127.7, 126.2, 80.5, 67.2, 61.8, 59.5, 52.0, 38.3, 37.6, 37.2, 36.9, 34.9, 31.7, 30.9, 29.5, 29.0, 27.0, 26.9, 25.2, 24.6, 19.4, 16.9, 12.4; MS (ESI) *m*/*z* 705 (M + H$^+$); HRMS calcd for $C_{37}H_{60}N_4O_7S$ (M + H$^+$) 705.4256, found 705.4259.

(12*S*,15*R*,17*R*,17a*S*,1′*R*,3′*S*)-12-(3-Butylcarbamoyl-1-hydroxybutyl)-15-methyl-14,17-dioxo-3,4,4a,5,6,9,11,12,13,14,15,16,17,-17a-tetradecahydro-2*H*-10-thia-1,13,16-triaza-benzocyclopentadecene-1-carboxylic Acid *tert*-Butyl Ester (81). Sodium was added portionwise to **79** (25 mg, 0.035 mmol) in liquid ammonia (60 mL) at −78 °C until a permanent blue coloration was established. After the mixture was stirred for another 15 min, the color was discharged by addition of the minimum quantity of solid NH_4Cl, and the solvent was evaporated under a stream of argon. The residue was dissolved in AcOEt (40 mL), washed sequentially with 1 N HCl (3 mL) and then with brine, dried over Na_2SO_4, and concentrated to give the free thiol (22 mg). Into a solution of this thiol in CH_2Cl_2 (7 mL) were added 1,1′-(azodicarbonyl)dipiperidine (ADDP) (18.5 mg, 0.07 mmol) and imidazole (5.0 mg, 0.07 mmol). Trimethylphosphine (1 M in toluene, 73 μL, 0.073 mmol) was then added dropwise. The mixture was stirred at room temperature for 40 h and evaporated. Flash chromatography (4% MeOH in AcOEt) of the residue gave **81** (8.4 mg, 42%): $[\alpha]_D$ −46.5 (*c* 0.4, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.58 (m, 1H), 5.30 (m, 1H), 4.64−4.43 (m, 3H), 3.91 (m, 2H), 3.78 (m, 1H), 3.48 (m, 1H), 3.19 (m, 3H), 3.0 (dd, 1H, J = 12.7, 5.5 Hz), 2.60 (m, 3H), 2.15 (m, 2H), 1.73 (m, 5H), 1.48 (s, 9H), 1.53−1.37 (m, 6H), 1.34 (d, 3H, J = 6.8 Hz), 1.14 (d, 3H, J = 6.9 Hz), 0.97 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.2, 173.9, 173.6, 157.3, 137.4, 126.6, 80.2, 68.4, 59.7, 52.9, 49.0, 42.7, 39.8, 38.9, 38.7, 37.2, 32.8, 32.7, 30.9, 30.4, 28.8, 26.7, 26.0, 21.3, 18.7, 14.3; MS (ESI) *m*/*z* 597 (M + H$^+$); HRMS calcd for $C_{30}H_{52}N_4O_6S$ (M + H$^+$) 597.3680, found 597.3687; LC/MS retention time [A] 14.45 min, [B] 32.46 min.

(2*S*,4*R*,12′*S*,15′*R*,17′*R*,17a′*S*)-*N*-Butyl-4-hydroxy-2-methyl-4-(15-methyl-14,17-dioxo-1,2,3,4,4a,5,6,9,11,12,13,14,15,16,17,17a-hexadecahydro-10-thia-1,13,16-triaza-benzocyclopentadecen-12-yl)-butyramide (82). Into a solution of **81** (8 mg, 0.013 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.5 mL), and the mixture was stirred at room temperature for 40 min. The solvent and excess TFA were removed under reduced pressure, and the residue was treated with AcOEt (20 mL), washed sequentially with saturated $NaHCO_3$, then with brine, dried over Na_2SO_4, and concentrated to give **82** (6.5 mg, quant): $[\alpha]_D$ +5.5 (*c* 0.4, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.56 (m, 1H), 5.27 (m, 1H), 4.54 (dd, 1H, J = 13.8, 6.8 Hz), 3.85 (m, 1H), 3.79 (m, 1H), 3.60 (d, 1H, J = 3.2 Hz), 3.19 (m, 4H), 3.0 (m, 1H), 2.60 (m, 4H), 2.34 (m, 1H), 2.18 (m, 1H), 1.92 (m, 4H), 1.75 (m, 2H), 1.68 (m, 3H), 1.50 (m, 3H), 1.40 (m, 2H), 1.33 (d, 3H, J = 7.0 Hz), 1.14 (d, 3H, J = 6.9 Hz), 0.96 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2, 172.9, 171.2, 134.9, 124.6, 66.6, 61.2, 52.9, 44.1, 43.2, 38.3, 38.1, 37.0, 34.8, 31.7, 30.9, 28.8, 28.4, 25.7, 24.8, 19.4, 18.7, 16.8, 16.3; MS (ESI) *m*/*z* 497 (M + H$^+$); HRMS calcd for $C_{25}H_{44}N_4O_4S$ (M + H$^+$) 497.3156, found 497.3161; LC/MS retention time [A] 8.59 min, [B] 23.41min.

(12*S*,15*R*,17*S*,17a*R*,1′*R*,3′*S*)-12-(3-Butylcarbamoyl-1-hydroxybutyl)-15-methyl-14,17-dioxo-3,4,4a,5,6,9,11,12,13,14,15,16,17,-17a-tetradecahydro-2*H*-10-thia-1,13,16-triaza-benzocyclopentadecene-1-carboxylic Acid *tert*-Butyl Ester (83). Compound **83** was obtained from **80** following the procedure for the preparation of **81**: $[\alpha]_D$ +36 (*c* 0.2, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.56 (m, 1H), 5.33 (m, 1H), 4.34 (m, 2H), 3.86 (m, 3H), 3.37 (m, 1H), 3.25−3.01 (m, 5H), 2.69 (dd, 1H, J = 13.1, 10.3 Hz), 2.58 (m, 2H), 2.18 (m, 1H), 1.92 (m, 2H), 1.78−1.62 (m, 6H), 1.52−1.30 (m, 8H), 1.47 (s, 9H),1.14 (d, 3H, J = 7.0 Hz), 0.96 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.1, 174.2, 173.6, 157.5, 137.0, 126.5, 81.9, 68.9, 61.4, 54.2, 51.2, 47.6, 40.3, 40.2, 39.9, 38.8, 37.6, 34.6, 34.1, 32.8, 31.1, 30.9, 28.8, 21.3, 18.7, 17.2, 14.3; MS (ESI) *m*/*z* 597 (M + H$^+$); HRMS calcd for $C_{30}H_{52}N_4O_6S$ (M + H$^+$) 597.3680, found 597.3679; LC/MS retention time [A] 13.72 min, [B] 31.69 min.

(2*R*,4*S*,12′*S*,15′*R*,17′*S*,17a′*R*)-*N*-Butyl-4-hydroxy-2-methyl-4-(15-methyl-14,17-dioxo-1,2,3,4,4a,5,6,9,11,12,13,14,15,16,17,17a-hexadecahydro-10-thia-1,13,16-triaza-benzocyclopentadecen-12-yl)-butyramide (84). Compound **84** was obtained from **83** following the procedure for the preparation of **82**: $[\alpha]_D$ +18 (*c* 0.2, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.42 (m, 1H), 5.30 (m, 1H), 4.24 (m, 2H), 4.02 (m, 1H), 3.90 (m, 1H), 3.20 (m, 2H), 3.03 (m, 2H), 2.74 (m, 1H), 2.58 (m, 1H), 2.30 (m, 2H), 2.17 (m, 1H), 2.01 (m, 3H), 1.74 (m, 4H), 1.64 (m, 2H), 1.51 (m, 3H), 1.46 (d, 3H, J = 7.1 Hz), 1.40 (m, 3H), 1.15 (d, 3H, J = 7.0 Hz), 0.96 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 179.1, 176.5, 174.4, 137.1, 125.9, 68.3, 65.2, 61.2, 53.9, 49.9, 47.3, 40.2, 39.9, 38.9, 37.2, 33.8, 32.7, 31.1, 30.7, 28.5, 27.9, 21.3, 18.7, 18.0, 14.3; MS (ESI) *m*/*z* 497 (M + H$^+$); HRMS calcd for $C_{25}H_{44}N_4O_4S$ (M + H$^+$) 497.3156, found 497.3161.

(1′*S*)-[Pent-4-enyl-(1-phenyl-ethyl)-amino]-acetic Acid Methyl Ester (85). Pent-4-enal (0.84 g, 10 mmol) was added to a solution of (*S*)-1-phenyl-ethylamine (1.21 g, 10 mmol) and 4 Å molecular sieves in CH_2Cl_2 (20 mL). The mixture was stirred at room temperature for 3 h and then concentrated to dryness. The residue was dissolved in methanol (40 mL) and cooled to 0 °C, $NaBH_4$ (0.49 g, 13 mmol) was added portionwise, and the suspension was stirred at 0 °C to room temperature for 30 min, then concentrated. The residue was triturated with CH_2Cl_2, the solvent was removed to give crude (*S*)-pent-4-enyl-(1-phenyl-ethyl)-amine, which was dissolved in DMSO (200 mL), and methyl bromoformate (0.95 mL, 10 mmol) and triethylamine (1.66 mL, 12 mmol) were then added consecutively. The mixture was stirred at room temperature for 40 h, then treated with a solution of saturated NH_4Cl and NH_4OH (2/1, 50 mL) and extracted with ether (2 × 100 mL). The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt, 8/1) of the residue gave **85** (0.74 g, 80%): $[\alpha]_D$ −32.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.40−7.24 (m, 5H), 5.79 (m, 1H), 4.95 (m, 2H), 4.05 (q, 1H, J = 6.7 Hz), 3.69 (s, 3H), 3.38 (ab, 2H, J = 17.2 Hz), 2.63 (m, 2H), 2.05 (m, 2H), 1.55 (m, 2H), 1.37 (d, 3H, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ. 172.4, 144.2, 138.3, 127.8, 127.2, 126.5, 114.1, 60.0, 50.9, 50.2, 30.9, 26.6; MS (ESI) *m*/*z* 262 (M + H$^+$); HRMS calcd for $C_{16}H_{23}NO_2$ (M + H$^+$) 262.1802, found 262.1810.

(2*R*,3*S*,1′*S*)-3-But-3-enyl-1-(1-phenyl-ethyl)-piperidine-2-carboxylic Acid Methyl Ester (86). Into a solution of **85** (0.34 g, 1.3 mmol) in Et_2O (15 mL) was added LDA (1 M in THF and hexane, 1.55 mL) at −70 °C. The mixture was stirred at −70 to −50 °C for 40 min; then $ZnBr_2$ (1 M in Et_2O, 4.6 mL) was added. The mixture was stirred at −40 °C to room temperature for 5 h and cooled to −40 °C; then a suspension of CuCN (0.54 g, 6 mmol) in THF (10 mL) was added. The mixture was stirred at −40 to −5 °C for 1 h and cooled to −40 °C, and then allylbromide (0.4 mL,

4.7 mmol) was added. The mixture was stirred at −40 °C to room-temperature overnight, treated with a solution of saturated NH_4Cl and NH_4OH (2/1, 20 mL), and extracted with AcOEt (3 × 30 mL). The combined organic layers were sequentially washed with saturated NH_4Cl, then with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt, 15/1) of the residue gave **86** (0.26 g, 65%): $[\alpha]_D$ −9.5 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 7.35−7.24 (m, 5H), 5.72 (m, 1H), 4.89 (m, 2H), 3.66 (q, 1H, J = 6.6 Hz), 3.63 (s, 3H), 3.42 (d, 1H, J = 5.1 Hz), 3.10 (td, 1H, J = 11.7, 3.1 Hz), 2.91 (m, 1H), 2.01 (m, 2H), 1.80 (m, 2H), 1.58 (m, 2H), 1.48 (td, 1H, J = 12.8, 3.9 Hz), 1.33 (d, 3H, J = 6.6 Hz), 1.31−1.11 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ. 173.1, 145.0, 138.1, 127.8, 127.6, 127.4, 126.8, 126.4, 114.3, 62.4, 61.7, 49.8, 42.2, 37.8, 31.7, 30.8, 25.4, 24.9, 20.7; MS (ESI) *m*/*z* 302 (M + H^+); HRMS calcd for $C_{19}H_{27}NO_2$ (M + H^+) 302.2115, found 302.2115.

(2*R*,3*S*,1′*S*)-3-(3-Oxo-propyl)-1-(1-phenyl-ethyl)-piperidine-2-carboxylic Acid Methyl Ester (87). Into a solution of **86** (0.11 g, 0.37 mmol) in dioxane−H_2O (3/1, 3.5 mL) were added 2,6-lutidine (87 μL, 0.74 mmol), osmium tetroxide (2.5% in *tert*-butyl alcohol, 96 μL), and sodium metaperiodate (0.3 g, 1.36 mmol). The mixture was stirred at room temperature for 3 h; then water (5 mL) and CH_2Cl_2 (10 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt, 5/1) of the residue gave **87** (68 mg, 61%): $[\alpha]_D$ −32.1 (*c* 1.4, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.7 (s, 1H), 7.33−7.24 (m, 5H), 3.65 (q, 1H, J = 6.6 Hz), 3.63 (s, 3H), 3.40 (d, 1H, J = 5.0 Hz), 3.10 (m, 1H), 2.91 (m, 1H), 2.42 (m, 2H), 1.78 (m, 2H), 1.53 (m, 4H), 1.33 (d, 3H, J = 6.6 Hz)); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 201.8, 200.7, 172.7, 172.6, 144.8, 144.3, 127.9, 127.8, 126.8, 126.7, 126.6, 126.5, 62.3, 62.1, 61.7, 61.4, 50.2, 50.0, 46.7, 42.0, 41.2, 38.1, 32.7, 25.6, 25.3, 25.2, 25.0, 24.9, 24.7, 20.6; MS (ESI) *m*/*z* 304 (M + H^+); HRMS calcd for $C_{18}H_{25}NO_3$ (M + H^+) 304.1907, found 304.1918.

(2*R*,3*S*)-3-(3-Oxo-propyl)-piperidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester 2-Methyl Ester (88). Into a flask were added **87** (0.34 g, 1.12 mmol), methanol (40 mL), Boc_2O (0.5 g, 2.3 mmol), and 10% Pd/C (0.12 g). The mixture was stirred for 16 h under an atmosphere of H_2 (balloon), then filtered through a pad of Celite. The filtrate was concentrated to dryness under reduced pressure, and the residue was purified by flash chromatography (hexane/AcOEt 2/1) to give **88** (0.18 g, 54%): $[\alpha]_D$ −10.2 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 9.74 (s, 1H), 4.86, 4.66 (s, 1H), 3.90 (m, 1H), 3.66 (s, 3H), 3.16 (m, 1H), 2.49 (m, 2H), 1.80−1.60 (m, 5H), 1.44 (s, 9H), 1.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.2, 200.9, 171.8, 156.1, 155.5, 80.6, 58.1, 56.5, 52.0, 51.9, 41.9, 28.7, 26.7, 26.2, 25.5, 25.0; MS (ESI) *m*/*z* 300 (M + H^+).

***cis*-3-[3-(*tert*-Butyl-dimethyl-silanyloxy)-propyl]-piperidine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester 4-Ethyl Ester (89).** To a suspension of Mg (0.45 g, 18.5 mmol) in THF (20 mL) was added dropwise 3-*tert*-butyldimethylsilanyloxypropyl bromide (3.0 mL, 13 mmol). The mixture was stirred at room temperature for 2 h to form the Grignard reagent. Into another 100 mL flask were added CuI (1.2 g, 6.5 mmol) and THF (10 mL). The stirring solution was cooled to −78 °C, and the previously prepared Grignard reagent was added dropwise through a cannula. The mixture was stirred at −78 °C for 1 h; then a solution of **64** (0.45 g, 1.74 mmol), trimethylsilyl chloride (TMSCl; 1.63 mL, 13.5 mmol), and hexamethylphosphoramide (HMPA) (2.25 mL, 13.5 mmol) in THF (7 mL) was added slowly through a syringe pump over a period of 2 h. The mixture was stirred at −78 °C for another 3 h and then gradually warmed to −20 °C for 2 h. The reaction was quenched by adding saturated NH_4Cl and NH_4OH (4/1, 30 mL). The mixture was extracted with Et_2O (3 × 50 mL), and the combined organic layers were washed with brine (3 × 50 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Flash chromatography (hexane/AcOEt 5/1) of the residue gave **89** (0.4 g, 68%), and **64** (0.14 g) was also recovered: ^1H NMR ($CDCl_3$, 400 MHz) δ 4.15 (m, 2H), 3.85 (m, 2H), 3.60 (m, 2H), 3.10 (m, 2H), 2.64 (m, 1H), 1.97 (m, 1H), 1.80 (m, 1H), 1.66 (m, 2H), 1.51 (m, 1H), 1.46 (s, 9H), 1.32 (m, 1H), 1.27 (t, 3H, J = 7.1 Hz), 1.12 (m, 1H), 0.89 (s, 9H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.2, 155.4, 80.0, 63.6, 60.6, 46.6, 44.7, 42.7, 37.1, 31.2, 28.8, 26.3, 24.3, 18.7, 14.7, −4.7; MS (ESI) *m*/*z* 430 (M + H^+).

***cis*-3-(3-Hydroxy-propyl)-piperidine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester 4-Ethyl Ester (90).** Into a solution of **89** (100 mg, 0.23 mmol) in THF (2.3 mL) was added TBAF (1 N in THF, 0.4 mL) at 0 °C. The mixture was stirred at 0 °C to room temperature for 3 h, then saturated NH_4Cl (2 mL) was added, and the mixture was extracted with AcOEt (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt 1/1) of the residue gave racemic **90** (65 mg, 90%): ^1H NMR ($CDCl_3$, 400 MHz) δ 4.17 (m, 2H), 3.97 (m, 2H), 3.66 (m, 2H), 3.04 (dd, 1H, J = 13.3, 2.4 Hz), 2.96 (ddd, 1H, J = 13.6, 10.0, 4.0 Hz), 2.65 (dt, 1H, J = 9.9, 4.5 Hz), 2.02 (m, 1H), 1.87−1.67 (m, 4H), 1.58 (m, 1H), 1.47 (s, 9H), 1.40 (m, 1H), 1.28 (t, 3H, J = 7.1 Hz), 1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.2, 155.6, 80.1, 62.9, 60.8, 46.3, 45.2, 43.1, 36.8, 31.1, 28.8, 24.3, 23.4, 14.7; MS (ESI) *m*/*z* 315 (M + H^+); HRMS (FAB) calcd for $C_{16}H_{29}NO_5$ (M + H^+) 315.2046, found 315.2047.

***cis*-3-(3-Oxo-propyl)-piperidine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester 4-Ethyl Ester (91).** Into a solution of **90** (54 mg, 0.17 mmol) in CH_2Cl_2 (2 mL) was added Dess−Martin periodinane (0.1 g, 0.24 mmol) portionwise at 10 °C. The mixture was stirred at room temperature overnight, then saturated $NaHCO_3$ (1.5 mL) and $Na_2S_2O_3$ (2 mL) were added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt 2/1) of the residue gave racemic **91** (42 mg, 80%): ^1H NMR ($CDCl_3$, 400 MHz) δ 9.73 (s, 1H), 4.12 (q, 2H, J = 7.1 Hz), 4.0 (b, 1H), 3.83 (dd, 1H, J = 13.5, 4.3 Hz), 3.01 (dd, 1H, J = 13.6, 2.7 Hz), 2.85 (b, 1H), 2.61 (dt, 1H, J = 10.0, 4.4 Hz), 2.48 (m, 2H), 1.96 (m, 1H), 1.83−1.59 (m, 3H), 1.46 (m, 1H), 1.43 (s, 9H), 1.23 (t, 3H, J = 7.1 Hz), 1.20 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 202.1, 173.8, 155.4, 80.1, 60.9, 46.3, 45.3, 44.7, 42.3, 41.5, 36.4, 32.2, 28.8, 24.1, 19.9, 14.6; MS (ESI) *m*/*z* 314 (M + H^+).

***cis*-3-[4-(2-Trimethylsilanyl-ethoxycarbonyl)-but-3-enyl]-piperidine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester 4-Ethyl Ester (92).** Into a solution of **91** (110 mg, 0.35 mmol) in CH_2Cl_2 (5 mL) was added $Ph_3P{=}CHCO_2TMSE$ (0.28 g, 0.7 mmol). The mixture was stirred at room temperature overnight and then concentrated. Flash chromatography (hexane/AcOEt 5/1) of the residue gave racemic **92** (120 mg, 75%): ^1H NMR ($CDCl_3$, 400 MHz) δ 6.9 (dt, 1H, J = 15.6, 7.2 Hz), 5.82 (d, 1H, J = 15.6 Hz), 4.22 (t, 2H, J = 8.4 Hz), 4.13 (q, 2H, J = 7.0 Hz), 4.09 (m, 1H), 3.89 (dd, 1H, J = 13.6, 4.1 Hz), 3.04 (m, 1H), 2.63 (dt, 1H, J = 9.7, 4.6 Hz), 2.36 (m, 1H), 2.21 (m, 1H), 1.99 (m, 1H), 1.80−1.59 (m, 3H), 1.49 (m, 1H), 1.45 (s, 9H), 1.27 (t, 3H, J = 7.0 Hz), 1.10 (t, 2H, J = 8.4 Hz), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.9, 167.1, 156.2, 144.4, 122.4, 80.0, 62.9, 60.9, 45.0, 44.4, 36.4, 30.2, 28.8, 26.2, 25.4, 19.7, 14.7, −1.3; MS (ESI) *m*/*z* 456 (M + H^+); HRMS calcd for $C_{23}H_{41}NO_6Si$ (M + H^+) 456.2776, found 456.2777.

***cis*-3-(4-Carboxy-but-3-enyl)-piperidine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester 4-Ethyl Ester (93).** Into a solution of **92** (150 mg, 0.33 mmol) in THF (2.6 mL) were added TBAF (1 N in THF, 0.66 mL) and 4 Å molecular sieves at 0 °C. The mixture was stirred at 0 °C to room temperature for 3 h, then 10% citric acid was added to pH 3.0, and the mixture was extracted with AcOEt (3 × 20 mL). The combined organic layers were sequentially washed with 10% citric acid, then with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt 1/1 and 1/2) of the residue gave racemic **93** (72 mg, 63%): ^1H NMR ($CDCl_3$, 400 MHz) δ 7.03 (dt, 1H, J = 15.5, 6.8 Hz), 5.84 (d, 1H, J = 15.6 Hz), 4.15 (m, 2H), 4.04 (m, 1H), 3.90 (dd, 1H, J = 13.6, 4.3 Hz), 3.02 (d, 1H, J = 11.7 Hz), 2.90 (b, 1H), 2.63 (m, 1H), 2.39 (m, 1H), 2.24 (m, 1H), 2.03 (m, 1H), 1.79−1.61 (m, 2H), 1.54 (m, 1H), 1.46 (s, 9H), 1.30 (m, 2H), 1.26 (t, 3H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$,

100 MHz) δ 173.9, 171.8, 155.2, 151.2, 121.6, 80.2, 60.9, 46.3, 44.9, 42.5, 36.3, 30.4, 28.8, 25.4, 23.8, 14.6; MS (ESI) *m*/*z* 356 ($M + H^+$).

***cis*-3-(5-Hydroxy-pent-3-enyl)-piperidine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester 4-Ethyl Ester (94).** Into a solution of **93** (40 mg, 0.11 mmol) and triethylamine (0.019 mL, 0.14 mmol) in THF (3.2 mL) was added ethyl chloroformate (0.13 mL, 0.14 mmol) at −5 °C. The mixture was stirred for 20 min, and then sodium borohydride (17.2 mg, 0.44 mmol) and methanol (0.32 mL) were added consecutively. The mixture was stirred for 30 min at −5 °C, and then saturated NH_4Cl was added to quench the reaction. The mixture was extracted with Et_2O (3 × 10 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Flash chromatography (hexane/AcOEt 1/1) of the residue gave racemic **94** (24 mg, 60%): ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.62 (m, 2H), 4.28 (m, 1H), 4.15 (m, 4H), 3.76 (m, 2H), 3.05−2.82 (m, 2H), 2.62 (m, 1H), 2.26 (b, 1H), 2.0 (m, 2H), 1.82−1.70 (m, 3H), 1.46 (s, 9H), 1.26 (t, 3H, J = 7.0 Hz), 1.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.2, 155.4, 132.9, 130.2, 80.0, 77.6, 64.1, 60.9, 44.9, 42.6, 36.4, 30.5, 30.1, 28.8, 14.7; MS (FAB) *m*/*z* 342 ($M + H^+$).

***cis*-3-(5-Hydroxy-pent-3-enyl)-piperidine-1,4-dicarboxylic Acid 1-*tert*-Butyl Ester (95).** Into a solution of **94** (25 mg, 0.073 mmol) in THF (0.4 mL) was added 1 N LiOH (0.3 mL, 0.3 mmol) at room temperature. The mixture was stirred overnight, then 10% citric acid was added to pH 2, and the mixture was extracted with AcOEt (3 × 20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give racemic **95** (22 mg, 96%): ^{1}H NMR (MeOD, 400 MHz) δ 5.65 (m, 2H), 4.01 (m, 4H), 3.05 (dd, 1H, J = 13.6, 2.7 Hz), 2.88 (m, 1H), 2.68 (dt, 1H, J = 10.2, 4.4 Hz), 2.17 (m, 1H), 2.05 (m, 2H), 1.72 (m, 2H), 1.48 (s, 9H), 1.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.7, 155.7, 131.5, 130.0, 80.1, 62.6, 46.2, 44.8, 43.6, 42.4, 36.3, 30.2, 27.7, 26.1; MS (ESI) *m*/*z* 336 ($M + Na^+$), 314 ($M + H^+$).

(3*R*,4*R*,1′*R*,1″*S*,2″*R*,4″*S*)-4-[1-(1-Benzylsulfanylmethyl-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl)-ethyl carbamoyl]-3-(5-hydroxy-pent-3-enyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (96) and (3*S*,4*S*,1′*R*,1″*S*,2″*R*,4″*S*)-4-[1-(1-Benzylsulfanylmethyl-4-butylcarbamoyl-2-hydroxy-pentylcarbamoyl)-ethyl carbamoyl]-3-(5-hydroxy-pent-3-enyl)-piperidine-1-carboxylic Acid *tert*-Butyl Ester (97). Into a solution of **95** (25 mg, 0.073 mmol) and 5-(2-amino-propionylamino)-6-benzylsulfanyl-4-hydroxy-2-methyl-hexanoic acid butylamide (prepared separately, 36 mg, 0.088 mmol) in CH_2Cl_2 (3 mL) were added PyBOP (57 mg, 0.11 mmol) and DIEA (30 μL, 0.16 mmol) at 0 °C. The mixture was stirred at 0 °C to room temperature for 4 h, and then 10% citric acid (1 mL) was added. The mixture was extracted with AcOEt (3 × 20 mL). The combined organic layers were sequentially washed with saturated $NaHCO_3$ and with brine, then dried over Na_2SO_4, and concentrated to give a mixture of two diastereoisomers, **96** (18 mg, 35%) and **97** (18 mg 35%), which were separated by flash chromatography (4% MeOH in AcOEt). For **96**: $[\alpha]_D$ −38 (*c* 0.3, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 7.34−7.20 (m, 5H), 5.62 (m, 2H), 4.39 (m, 1H), 4.01−3.94 (m, 5H), 3.76 (m, 1H), 3.74 (s, 2H), 3.16 (m, 3H), 2.61 (m, 2H), 2.51 (m, 2H), 2.22 (m, 1H), 2.06 (m, 1H), 1.92 (m, 1H), 1.84 (m, 1H), 1.62 (m, 2H), 1.51 (m, 2H), 1.46 (s, 9H), 1.35 (m, 7H), 1.11 (d, 3H, J = 6.9 Hz), 0.93 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 175.2, 174.1, 155.7, 138.8, 129.9, 129.2, 128.5, 126.9, 80.0, 68.6, 62.7, 62.6, 52.8, 49.5, 49.3, 39.1, 38.4, 37.6, 37.1, 35.7, 35.6, 32.6, 31.7, 30.1, 27.7, 20.1, 17.7, 17.4, 17.2, 13.2; MS (FAB) *m*/*z* 704 ($M + H^+$); HRMS calcd for $C_{37}H_{60}N_4O_7S$ ($M + H^+$) 705.4256, found 705.4265. For **97**: $[\alpha]_D$ −47 (*c* 0.6, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 7.35−7.25 (m, 5H), 5.62 (m, 2H), 4.40 (m, 1H), 4.01−3.94 (m, 4H), 3.80 (m, 1H), 3.75 (s, 2H), 3.19 (m, 3H), 2.89 (m, 1H), 2.64 (m, 2H), 2.53 (m, 2H), 2.20 (m, 1H), 2.05 (m, 1H), 1.92 (m, 1H), 1.82 (m, 1H), 1.61 (m, 2H), 1.52 (m, 2H), 1.47 (s, 9H), 1.39 (m, 8H), 1.12 (d, 3H, J = 6.9 Hz), 0.95 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 175.0, 174.3, 155.7, 138.8, 130.1, 129.2, 128.4, 126.9, 80.0, 68.6, 62.6, 52.8, 52.6, 49.6, 49.3, 39.1, 38.3, 37.6, 37.1, 35.7, 32.7, 32.6, 31.7, 30.0, 27.7, 20.1, 17.7, 17.6, 17.4, 17.2, 13.2; MS (FAB) *m*/*z* 704 ($M + H^+$); HRMS calcd for $C_{37}H_{60}N_4O_7S$ ($M + H^+$) 705.4256, found 705.4259.

(4*R*,7*R*,10*S*,18*R*,1′*R*,3′*S*)-10-(3-Butylcarbamoyl-1-hydroxy-butyl)-7-methyl-5,8-dioxo-3,4,4a,5,6,7,8,9,10,11,13,16,17,17a-tetradecahydro-1*H*-12-thia-2,6,9-triaza-benzocyclopentadecene-2-carboxylic Acid *tert*-Butyl Ester (98). Na was added portionwise to **96** (47 mg, 0.68 mmol) in liquid ammonia (80 mL) at −78 °C until a permanent blue coloration persisted. After the mixture was stirred for another 15 min, the color was then discharged by addition of the minimum quantity of solid NH_4Cl. Liquid ammonia was evaporated under a stream of argon. The residue was dissolved in AcOEt (40 mL), washed sequentially with 1 N HCl (3 mL) and then with brine, dried over Na_2SO_4, and concentrated to give a thiol (42 mg). To a solution of this thiol (42 mg, 0.068 mmol) in CH_2Cl_2 (12 mL) were added 1,1′-(azodicarbonyl)dipiperidine (ADDP) (33.6 mg, 0.14 mmol) and imidazole (9.0 mg, 0.14 mmol). Trimethylphosphine (1 M in toluene, 0.14 mL) was then added dropwise. The mixture was stirred at room temperature for 20 h and evaporated. Flash chromatography (10% MeOH in AcOEt) of the residue gave product **98** (12 mg, 30%): $[\alpha]_D$ −9.1 (*c* 0.35, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 7.81 (b, 1H), 5.58 (m, 1H), 5.28 (m, 1H), 4.46 (dt, 1H, J = 6.9, 4.0 Hz), 4.10 (m, 2H), 3.86(d, 1H, J = 6.8 Hz), 3.77 (t, 1H, J = 9.6 Hz), 3.19 (m, 3H), 2.98 (m, 2H), 2.68 (m, 3H), 2.56 (m, 1H), 2.33 (m, 1H), 2.17 (m, 1H), 1.99 (m, 2H), 1.75 (m, 2H), 1.52 (m, 2H), 1.46 (s, 9H), 1.39 (m, 3H), 1.33 (d, 1H, J = 7.0 Hz), 1.14 (d, 3H, J = 6.9 Hz), 0.95 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 178.0, 174.1, 172.7, 155.6, 135.5, 125.5, 80.0, 69.4, 53.7, 49.8, 46.1, 39.0, 38.9, 37.8, 36.8, 32.1, 31.7, 29.7, 29.5, 27.7, 25.6, 20.1, 17.7, 17.0, 13.2; MS (ESI) *m*/*z* 597 ($M + H^+$), 497 $(M\text{-Boc})^+$. HRMS calcd for $C_{30}H_{52}N_4O_6S$ ($M + H^+$) 597.3680, found 597.3691; LC/MS retention time [A] 6.16 min, [B] 8.15 min.

(2*S*,4*R*,4′*R*,7′*R*,10′*S*,18′*R*)-*N*-Butyl-4-hydroxy-2-methyl-4-(7-methyl-5,8-dioxo-1,2,3,4,4a,5,6,7,8,9,10,11,13,16,17,17a-hexadecahydro-12-thia-2,6,9-triaza-benzocyclopentadecen-10-yl)-butyramide (99). Into a solution of **98** (7 mg, 0.012 mmol) in CH_2Cl_2 (3 mL) was added TFA (0.5 mL), and the mixture was stirred at room temperature for 30 min. The solvent and excess TFA were removed under reduced pressure. The residue was dissolved in AcOEt (20 mL), washed sequentially with saturated $NaHCO_3$ and with brine, dried over Na_2SO_4, and concentrated to give **99** (6 mg, quant): $[\alpha]_D$ −3.3 (*c* 0.3, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.58 (m, 1H), 5.32 (m, 1H), 4.64 (b, 1h), 4.47 (q, 1H, J = 7.1 Hz), 4.36 (q, 1H, J = 7.1 Hz), 3.81 (m, 2H), 3.19 (m, 3H), 2.98 (m, 3H), 2.75 (m, 2H), 2.61 (m, 1H), 2.40 (dd, 1H, J = 14.2, 4.0 Hz), 2.15 (m, 1H), 2.03 (m, 2H), 1.68 (m, 3H), 1.49 (m, 3H), 1.40−1.24 (m, 8H), 1.14 (d, 3H, J = 7.0 Hz), 0.96 (t, 3H, J = 7.3 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 178.0, 175.2, 173.7, 134.8, 125.9, 67.8, 53.4, 45.8, 42.6, 42.2, 39.1, 38.6, 37.7, 35.2, 32.4, 31.7, 29.7, 28.9, 26.3, 22.4, 20.1, 17.7, 17.1, 13.1; MS (ESI) *m*/*z* 497 ($M + H^+$); HRMS calcd for $C_{25}H_{44}N_4O_4S$ ($M + H^+$) 497.3156, found 497.3157; LC/MS retention time [A] 16.95 min, [B] 21.50 min.

(4*S*,7*R*,10*S*,18*S*,1′*R*,3′*S*)-10-(3-Butylcarbamoyl-1-hydroxy-butyl)-7-methyl-5,8-dioxo-3,4,4a,5,6,7,8,9,10,11,13,16,17,17a-tetradecahydro-1*H*-12-thia-2,6,9-triaza-benzocyclopentadecene-2-carboxylic Acid *tert*-Butyl Ester (100). Compound **100** (12 mg, 46%) was prepared from **97** (27 mg, 0.038 mmol) according to the procedure for the preparation of **98**: $[\alpha]_D$ +21 (*c* 0.3, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.56 (m, 1H), 5.27 (m, 1H), 4.33 (dt, 1H, J = 7.3, 6.9 Hz), 4.13 (m, 2H), 3.84 (m, 1H), 3.74 (m, 1H), 3.40 (m, 1H), 3.17 (td, 1H, J = 6.9, 2.8 Hz), 3.10 (d, 1H, J = 7.0 Hz), 2.98 (m, 2H), 2.69 (m, 2H), 2.50 (m, 2H), 2.23 (m, 1H), 2.16 (m, 1H), 1.89 (m, 2H), 1.62 (m, 3H), 1.56 (m, 3H), 1.46 (s, 9H), 1.37 (m, 3H), 1.32 (d, 1H, J = 7.0 Hz), 1.142 (d, 3H, J = 6.9 Hz), 0.95 (t, 3H, J = 7.2 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 177.9, 176.0, 174.2, 155.8, 135.3, 121.6, 80.1, 67.4, 53.8, 50.3, 45.0, 39.0, 38.8, 37.8, 36.6, 33.1, 31.7, 29.8, 27.7, 25.7, 24.5, 20.1, 17.7, 15.5, 13.2; MS (ESI) *m*/*z* 619 ($M + Na^+$), 497 $(M\text{-Boc})^+$; HRMS calcd for $C_{30}H_{52}N_4O_6S$ ($M + H^+$) 597.3680, found 597.3678; LC/MS retention time [A] 22.11 min, [B] 30.18 min.

(2*S*,4*R*,4′*S*,7′*R*,10′*S*,18′*S*)-*N*-Butyl-4-hydroxy-2-methyl-4-(7-methyl-5,8-dioxo-1,2,3,4,4a,5,6,7,8,9,10,11,13,16,17,17a-hexadecahydro-12-thia-2,6,9-triaza-benzocyclopentadecen-10-yl)-butyramide (101). Compound **101** (6 mg, quant) was prepared from **100** (7 mg, 0.012 mmol) according to the procedure described for the preparation of **99**: $[\alpha]_D$ +34.4 (*c* 0.25, MeOH); ^{1}H NMR (MeOD, 400 MHz) δ 5.55 (m, 1H), 5.28 (m, 1H), 4.65 (b, 1H), 4.35 (q, 1H, J = 6.6 Hz), 3.84 (m, 1H), 3.77 (m, 1H), 3.42 (m, 1H), 3.19 (q, 1H, J = 7.0 Hz), 3.13 (t, 1H, J = 7.8 Hz), 3.0 (m, 2H), 2.85 (m, 1H), 2.71 (m, 1H), 2.62 (m, 1H), 2.51 (dd, 1H, J = 13.0, 3.3 Hz), 2.25 (m, 2H), 2.05 (m, 2H), 1.85 (m, 2H), 1.63 (m, 4H), 1.51 (m, 2H), 1.47−1.28 (m, 6H), 1.14 (d, 3H, J = 6.9 Hz), 0.96 (t, 3H, J = 7.2 Hz); ^{13}C NMR (MeOD, 100 MHz) δ 178.0, 175.1, 174.2, 134.3, 125.8, 67.0, 54.0, 50.4, 46.2, 44.9, 43.8, 39.0, 38.8, 37.8, 36.6, 33.1, 31.7, 29.8, 29.2, 25.7, 20.1, 17.8, 15.6, 13.2; MS (ESI) *m*/*z* 497 (M + H$^+$); HRMS calcd for $C_{25}H_{44}N_4O_4S$ (M + H$^+$) 497.3156, found 497.3154; LC/MS retention time [A] 15.88 min, [B] 21.18 min.

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Supporting Information Available: Experimental details for enzyme inhibition measurements, modeling of compounds in BACE, and crystallization, as well as crystal structure data. This material is available free of charge via the Internet at http://pubs.acs.org. The X-ray structures of the BACE complexes with compounds **42** and **52** have been deposited with the Protein Data Bank (PDB identifier 2F3E and 2F3F, respectively).

References

(1) Thompson, L. A.; Brown, J. J.; Zusi, F. C. Progress in the discovery of BACE inhibitors. *Curr. Pharm. Des.* **2005**, *11*, 3383−3404.
(2) Tyndall, J. D. A.; Nall, T.; Fairlie, D. P. Proteases Universally Recognize Beta Strands in their Active Sites. *Chem. Rev.* **2005**, *105*, 973−1000.
(3) Tyndall, J. D. A.; Fairlie, D. P. Macrocycles Mimic the Extended Peptide Conformation Recognized by Aspartic, Serine, Cysteine, and Metalloproteases. *Curr. Med. Chem.* **2001**, *8*, 893−907.
(4) Loughlin, W. A.; Tyndall, J. D. A.; Glenn, M. P.; Fairlie, D. P. Beta Strand Mimetics. *Chem. Rev.* **2004**, *104*, 6085−6118.
(5) Ghosh, A. K.; Devasamudram, T.; Hong, L.; Dezutter, C.; Xu, X.; Weerasena, V.; Koelsch, G.; Bilcer, G.; Tang, J. Structure-based design of cycloamide-urethane-derived novel inhibitors of human brain memapsin 2 (β-secretase). *Bioorg. Med. Chem. Lett.* **2005**, *15*, 15−20.
(6) Rojo, I.; Martin, J. A.; Broughton, H.; Timm, D.; Erickson, J.; Yang, H.-Ch.; McCarthy, J. R. Macrocyclic peptidomimetic inhibitors of β-secretases (BACE): First X-ray structure of a macrocyclic peptidomimetic-BACE complex. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 191−195.
(7) Szewczuk, Z.; Lebholz, K. L.; Rich, D. H. Synthesis and biological activity of new conformationally restricted analogs of pepstatin. *Int. J. Pept. Protein Res.* **1992**, *40*, 233−242.
(8) Grubbs, R. H.; Chang, S. Recent advances in olefin metathesis and its application in organic synthesis. *Tetrahedron* **1998**, *54*, 4413−4450.
(9) Garner, P.; Ramakanth, J. Stereodivergent synthesis of threo and erythro 6-amino-6-deoxyheptosulose derivatives via an optically active oxazolidine aldehyde. *J. Org. Chem.* **1986**, *51*, 2609−2612.
(10) Kokotos, C.; Chiou, A. Convenient Synthesis of Benzyl and Allyl Esters Using Benzyl and Allyl 2,2,2-Trichloroacetimidate. *Synthesis* **1997**, 168−170.
(11) Sasmal, S.; Geyer, A.; Maier, M. E. Synthesis of Cyclic Peptidomimetics from Aldol Building Blocks. *J. Org. Chem.* **2002**, *67*, 6260−6263.
(12) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. Application of Ring-Closing Metathesis to the Synthesis of Rigidified Amino Acids and Peptides. *J. Am. Chem. Soc.* **1996**, *118*, 9606−9614.
(13) Lee, C. W.; Grubbs, R. H. Stereoselectivity of Macrocyclic Ring-Closing Olefin Metathesis. *Org. Lett.* **2000**, *2*, 2145−2147.
(14) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. Synthesis and Activity of a New Generation of Ruthenium-Based Olefin Metathesis Catalysts Coordinated with 1,3-Dimesityl-4,5-dihydroimidazol-2-ylidene Ligands. *Org. Lett.* **1999**, *1*, 953−956.
(15) Walker, M. A.; Johnson, T. General method for the synthesis of cyclic peptidomimetic compounds. *Tetrahedron Lett.* **2001**, *42*, 5801−5804.
(16) Lambert, J. N.; Mitchell, J. P.: Roberts, K. D. The synthesis of cyclic peptides. *J. Chem. Soc., Perkin I* **2001**, 471−484.
(17) Mosberg, H. I.; Omnaas, J. R. Dithioether-containing cyclic peptide. *J. Am. Chem. Soc.* **1985**, *107*, 2986−2987.
(18) Kemp, D. S.; Carey, R. I. Boc-l-Dmt-OH as a fully *N*,*S*-blocked cysteine derivative for peptide synthesis by prior thiol capture. Facile conversion of *N*-terminal Boc-l-Dmt-peptides to H-Cys(Scm)-peptides. *J. Org. Chem.* **1989**, *54*, 3640−3646.
(19) Mitsunobu, O. The Use of Diethyl Azodicarboxylate and Triphenylphosphine in synthesis and transformation of natural products. *Synthesis* **1981**, 1−28.
(20) Tsunoda, T.; Yamamiya, Y.; Ito, S. 1,1′-(Azodicarbonyl)dipiperidine-tributylphosphine, a new reagent system for Mitsunobu reaction. *Tetrahedron Lett.* **1993**, *34*, 1639−1642.
(21) Corrie, J. E. T.; Hlubucek, J. R.; Lowe, G. Synthesis of a cephalosporin analogue. *J. Chem. Soc., Perkin Trans. I* **1977**, 1421−1425.
(22) Hong, L.; Turner, R. T.; Koelsch, G.; Shin, D.; Ghosh, A. K.; Tang, J. Crystal structure of memapsin 2 (β-secretase) in complex with an inhibitor OM00-3. *Biochemistry* **2002**, *41*, 10963−10967.
(23) Turner, R. T.; Koelsch, G.; Hong, L.; Castaheira, P.; Ghosh, A. K.; Tang, J. Subsite specificity of memapsin 2 (β-secretase): implications in inhibitor design. *Biochemistry* **2001**, *40*, 10001−10006.
(24) Ghosh, A. K.; Bilcer, G.; Harewood, C.; Kawahama, R.; Shin, D.; Hussain, K. A.; Hong, L.; Loy, J. A.; Nguyen, C.; Koelsch, G.; Ermolieff, J.; Tang, J. Structure-based design: potent inhibitors of human brain memapsin 2 (β-secretase). *J. Med. Chem.* **2001**, *44*, 2865−2868.
(25) Tang, J.; Ghosh, A. K.; Hong, L.; Koelsch, G.; Turner, R. T. III; Chang, W. Study of memapsin 2 (β-Secretase) and Strategy of Inhibitor Design. *J. Mol. Neurosci.* **2003**, *20*, 299−304.
(26) Turner, R. T., III; Hong, L.; Koelsch, G.; Ghosh, A. K.; Tang, J. Structural locations and functional roles of new subsites S_5, S_6, and S_7 in memapsin 2 (β-secretase). *Biochemistry* **2005**, *44*, 105−112.
(27) Hanessian, S.; Yun, H.; Hou, Y.; Yang, G.; Bayrakdarian, M.; Therrien, E.; Moitessier, N.; Roggo, S.; Veenstra, S.; Tintelnot-Blomley, M.; Rondeau, J. M.; Paganetti, P.; Neumann, U.; Betschart, C. Structure-based design, synthesis, and BACE inhibitory activity of carbocyclic and heterocyclic peptidomimetics. *J. Med.* Chem. **2005**, *48*, 5175−5190.
(28) Hanessian, S.; Hou, Y.; Bayrakdarian, M.; Tintelnot-Blomley, M. Stereoselective synthesis of constrained oxacyclic hydroxyethylene isosteres of aspartic protease inhibitors: Aldol and Mukaiyama aldol methodologies for branched tetrahydrofuran 2-carboxylic acids. *J. Org. Chem.* **2005**, *70*, 6735−6745.
(29) Hanessian, S.; Yun, H.; Hou, Y. Stereoselective synthesis of constrained azacyclic hydroxyethylene isosteres as aspartic protease inhibitors—Dipolar cycloaddition and related methodologies toward branched pyrrolidine and pyrrolidinone carboxylic acids. *J. Org. Chem.* **2005**, *70*, 6746−6756.
(30) Fernandez, M. M.; Diez, A.; Rubiralta, M.; Montenegro, E.; Casamitjana, N.;Kogan, M. J.; Giralt, E. Spirolactams as conformationally restricted pseudopeptides: Synthesis and conformational analysis. *J. Org. Chem.* **2002**, *67*, 7587−7599.
(31) Strekowski, L.; Visnick, M.; Battiste, M. A. Resolution and assignment of absolute configuration to the enantiomers of anastrephin and epianastrephin and their analogs. *J. Org. Chem.* **1986**, *51*, 4836−4839.
(32) See Supporting Information.
(33) Wilkinson, T. J.; Stehle, N. W.; Beak, P. Enantioselective syntheses of 2-alkyl- and 2,6-dialkylpiperidine alkaloids: Preparations of the hydrochlorides of (−)-coniine, (−)-solenopsin A, and (−)-dihydropinidine. *Org. Lett.* **2000**, *2*, 155−158.
(34) Schuster, M. C.; Mann, D. A.; Buchholz, T. J.; Johnson, K. M.; Thomas, W. D.; Kiessling, L. L. Parallel synthesis of glycomimetic libraries: Targeting a C-type lectin. *Org. Lett.* **2003**, *5*, 1407−1410.
(35) Larsen, P. K.; Jacobsen, P.; Brehm, L.; Larsen, J. J.; Schaumburg, K. GABA agonists and uptake inhibitors designed as agents with irreversible actions. *Eur. J. Med. Chem.* **1980**, *15*, 529−535.
(36) Foti, C. J.; Comins, D. J. Synthesis and reactions of α-(trifluoromethanesulfonyloxy) enecarbamates prepared from *n*-acyllactams. *J. Org. Chem.* **1995**, *60*, 2656−2657.

(37) Luker, T.; Hiemstra, H.; Speckamp, W. N. Total synthesis of desoxoprosophylline: Application of a lactam-derived enol triflate to natural product synthesis. *J. Org. Chem*. **1997**, *62*, 3592−3596.
(38) Rohr, M.; Chayer, S.; Carrido, F.; Mann, A.; Taddei, M.; Wermuth, C. G. Synthesis of 2- and/or 6-methylated analogues of isoguvacine (1,2,3,6-tetrahydropyridine-4-carboxylic acid), a $GABA_A$ agonist. *Heterocycles* **1996**, *43*, 2131−2138.
(39) Ueda, T.; Irie, T.; Fukushi, K.; Ikota, N.; Namba, H.; Shinotoh, H.; Iyo, M.; Tanada, S.; Maeda, M.; Takatoku, K.; Yomoda, I.; Nagatsuka, S. Synthesis of *N*-methyl-3-acetoxy-4-(1-hydroxy-3-[^{123}I]-iodopro-2-enyl) piperidine, a novel acetylchlorine analogue. *J. Labelled Compd. Radiopharm*. **1999**, *42* (Suppl. 1), s762−s764.
(40) Moreno-Manas, M.; Perez, M.; Pleeixats, R. Palladium-catalyzed allylation of 3-hydroxyisoxazole, 5-isoxazolone and 5-pyrazolone systems. *Tetrahedron* **1994**, *50*, 515−528.
(41) Lorthiois, E.; Marek, I.; Normant, J. F. Amino zinc enolate carbocyclization reactions. New access to polysubstituted piperidine derivatives. *J. Org. Chem*. **1998**, *63*, 566−574.
(42) Karoyan, P.; Chassaing, G. New strategy for the synthesis of 3-substituted prolines. *Tetrahedron Lett.* **1997**, *38*, 85−88.
(43) Khiari, J.; Hassine, B. B.; Gravel, D. Méthodologie de synthèse des analogues à chaines ouvertes de l′huperzine A. *C. R. Acad. Sci. Paris, Chim.* **2001**, *4*, 705−710.
(44) Dess, D. B.; Martin, J. C. Readily accessible 12-I-5 oxidant for the conversion of primary and secondary alcohols to aldehydes and ketones. *J. Org. Chem.* **1983**, *48*, 4155−4156.
(45) Sato, Y.; Takimoto, M.; Mori, M. Total synthesis of prostaglandin $F_2\alpha$ via nickel-promoted stereoselective cyclization of 1,3-diene and aldehyde. *Synlett* **1997**, 734−736.
(46) Gosh, A. K.; Tang, J. J.; Bilcer, G.; Chang, W.; Hong, L.; Koelsch, G. E.; Loy, J. A.; Turner, R. T., III; Devasumadran, T. Compounds which inhibit beta-secretase activity and methods of use thereof. U.S. Pat. Appl. 20040121947, 2004.

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