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Stereoselective Synthesis of Constrained Azacyclic Hydroxyethylene Isosteres as Aspartic Protease Inhibitors: Dipolar Cycloaddition and Related Methodologies toward Branched Pyrrolidine and Pyrrolidinone Carboxylic Acids

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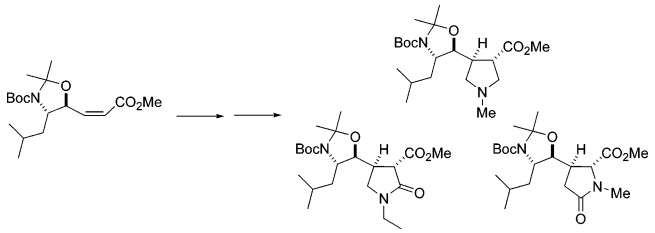

The synthesis of three vicinally substituted azacyclic carboxylic acids in enantiopure form was achieved from a common α-amino aldehyde originating from L-leucine. Pyrrolidines and pyrrolidinones were elaborated from α,β-unsaturated γ-hydroxy-δ-amino acids via azomethine ylide 1,3-dipolar addition and conjugate addition/cyclization strategies, respectively. The azacyclic amino acids were incorporated in a pseudopeptide now encompassing a hydroxyethylene isostere. Low nanomolar inhibition of BACE1, an enzyme implicated in the cascade of events leading to plaque formation in Alzheimer's disease, was found with a pyrrolidinone analogue.

Introduction

In the preceding article,[1] we described the methodology for the synthesis of oxacyclic hydroxyethylene isosteres that encompass a δ-amino-γ-hydroxy carboxylic acid motif as a constrained unnatural amino acid. Hydroxyethylene isosteres of peptidic substrates have gained popularity in conjunction with the design and synthesis of aspartic protease inhibitors.[2] Tang, Ghosh, and coworkers[3] have described the synthesis of a pseudooctapeptide (OM99-2) that is a potent inhibitor of β-secretase, memapsin-2 (BACE1) (Figure 1A). The unnatural 2-alkyl-4-hydroxy-5-amino-7-methyl octanoic acid formally replaces a central Leu-Ala dipeptide in which the amide bond corresponds to an *S*-hydroxyethylene isostere (Figure 1B). X-ray crystallographic studies[3,4] further demonstrated the specific interactions of P_4-P_4' subsites with corresponding S−S′ sites in the enzyme. In particular, two Asp residues at the catalytic site of the enzyme interact with the *S*-hydroxyl group in the P_1-P_1' 4-hydroxy-5-amino octanoic acid subunit. Extensive analogue work aimed at understanding the role of individual amino acids at the P′ and P sites has greatly advanced our knowledge of functional prerequisites for inhibitory activity.[5] These studies have also been validated by X-ray cocrystal structures of new analogues.[4,5] On the basis of this valuable structural information, several groups have contributed toward the design and synthesis of inhibitors

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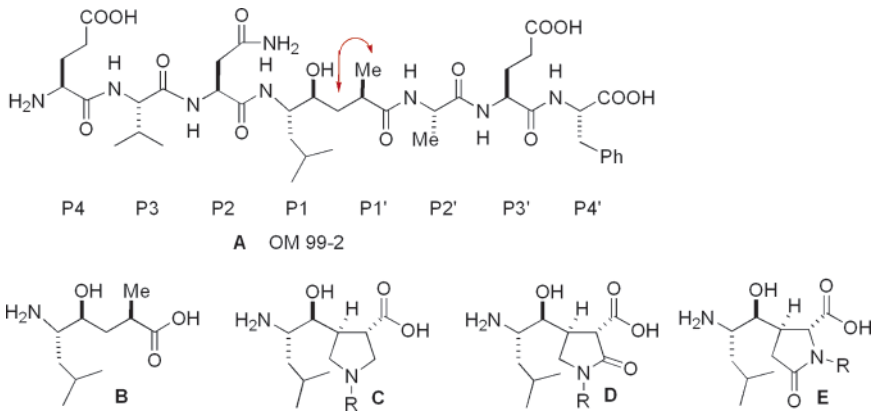

FIGURE 1. (A) Tang−Ghosh inhibitor of BACE1. (B) δ-Amino-γ-hydroxyoctanoic acid hydroxyethylene isostere. (C, D, E) P_1−P_1' constrained azacyclic hydroxyethylene isosteres.

of BACE1[6] in the quest of a therapeutic agent for Alzheimer's disease.[7] We have recently investigated the backbone replacement of the P_1' Ala subunit in OM99-2 with a rigid variant by introducing a cyclopentane ring spanning the Ala methyl group and the adjacent methylene in the chain.[8]

Herein, we report on the synthesis of azacyclic constrained hydroxyethylene isosteres encompassed in the 4-hydroxy-5-amino-7-methyl octanoic acid structure (Figure 1C,D,E) of OM99-2. Relying on the available X-ray parameters,[4] we envisaged a ligation of the P_1' *C*-methyl group with the adjacent methylene to form an *N*-alkyl pyrrolidine or pyrrolidinone. Preliminary molecular modeling of an energy-minimized hypothetical azacyclic structure did not show adverse interactions with the enzyme. It was also hoped that the basic nitrogen in the pyrrolidine and the lactam carbonyl in the corresponding azacycles would be favorably positioned for productive interactions with suitable donor/acceptor sites in the enzyme. We therefore embarked on the stereoselective synthesis of the three azacyclic disubstituted amino acids shown in Figure 1, in which the absolute configurations of three of the four stereogenic centers in the hydroxyethylene substructure correspond to the original Tang−Ghosh motif.[3]

There are ample methods for the construction of vicinally substituted pyrrolidines and pyrrolidinones.[9] However, the intended novel azacyclic targets presented several challenges, not the least of which was controlling the relative stereochemistry of four contiguous stereogenic centers. In considering various approaches to the vicinally substituted pyrrolidine and pyrrolidinone carboxylic acid motifs such as C, D, and E (Figure 1), we explored various heterocyclization methods relying on asymmetric induction by resident chirality from a common intermediate. Dipolar [3 + 2] cycloaddition reactions[10] and stereocontrolled conjugate addition of suitable carbon nucleophiles[11] were considered to be logical synthetic strategies.

Results

Treatment of *N*-Boc-leucinal **1** with the Li salt of methyl propiolate, as described by Fray and Kleinman,[12] gave a 25−30% yield of a mixture in which the desired 4*S*-hydroxy isomer **2** was the major product (Scheme 1). Using the less basic and more oxophilic Ce salt of methyl propiolate[13] resulted in a significant improvement in yield without affecting the ratio of epimeric products (72%). Protection as the *N*,*O*-cyclic acetonide, followed by sepa-

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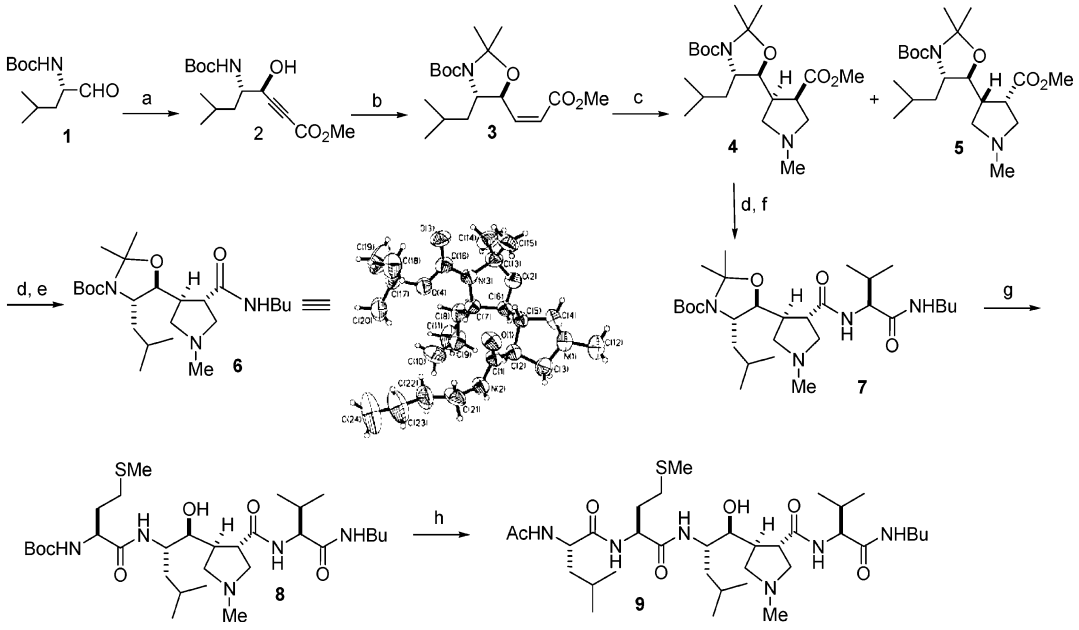
SCHEME 1[a]



[a] Reagents and conditions: (a) i. LDA, methyl propiolate, THF, −78 °C; ii. $CeCl_3$, −78 °C then aldehyde, 72% (ratio of epimers is 5:1); (b) i. DMP, TsOH (cat.), acetone, 64% (yield of the separable major isomer); ii. Lindlar Pd, quinoline, C_6H_6, H_2 (1 atm), 90%; (c) $MeNHCH_2COOH$, $(HCHO)_n$, 4 Å MS, C_6H_6, reflux, 96% (**4/5** = 4:1); (d) , NaOMe, MeOH, 99%; (e) i. $Ba(OH)_2$, EtOH−H_2O; H_2SO_4; ii. $BuNH_2$, EDC, HOBt, DMAP, DCM, 88%; (f) i. $Ba(OH)_2$, MeOH−H_2O and then H_2SO_4; ii. PyBOP, DIEA, DCM, H-Val-NHBu, 76%; (g) i. 4 M HCl in dioxane; ii. Boc-Met-OH, PyBOP, DIEA, DCM, 44%; (h) i. 4 M HCl in dioxane; ii. Ac-Leu-OH, EDC, HOBt, DCM-H_2O, 40%.

ration of the desired major isomer, and Lindlar catalytic hydrogenation led to the *cis*-ester **3** in excellent yield. Treatment with *N*-methyl glycine in the presence of formaldehyde[14] and molecular sieves afforded the azomethine ylide cyclization product **4** and its diastereomer **5** as a 4:1 mixture, respectively, in 96% yield. The easily separable *cis*-isomer **4** was equilibrated with NaOMe to the desired *trans*-ester in quantitative yield. Hydrolysis of the corresponding ester to the acid and coupling with *n*-butylamine gave the amide **6**. A single-crystal X-ray analysis provided definitive evidence for the structural and configurational assignments of diastereomer **5** produced in the cycloaddition reaction (Scheme 1). Previous reports have shown that $P_2'-P_4'$ truncated pseudopeptides containing the acyclic hydroxyethylene isostere unit exhibited good inhibitory activity against BACE 1.[4] Furthermore, the replacement of the asparagine subunit with methionine was found to be acceptable. We therefore continued with the synthesis of a prototype inhibitor that took advantage of these structural simplifications. Coupling of the acid from **5** with L-Val *n*-butyramide gave **7**, which was subsequently treated with TFA in CH_2Cl_2 to cleave the *N*,*O*-acetal. Peptide coupling with Boc-Met-OH gave **8**, which was further elaborated to the intended prototype pseudopeptide inhibitor **9**.

The synthesis of the 2-pyrrolidinone analogue D (Figure 1) was initiated from the common precursor **3** (Scheme 2). Treatment with vinylmagnesio cuprate in the presence of TMSCl[11a,b] led to a >9:1 mixture of vinyl adducts **10** and **11**. On the basis of our previous results with γ-*N*-Boc α,β-unsaturated esters[11a,b] and corresponding *N*,*N*-dibenzyl esters,[11c] we had anticipated a preponderance of the *syn*-adduct **11**. Instead, the major product was found to be the undesired *anti*-isomer **10** as confirmed by a single-crystal X-ray structure of an *n*-butylamide derivative (Scheme 2). In the event, the mixture of vinyl adducts **10** and **11** was subjected to ozonolysis to give the corresponding aldehydes **12**. Reductive amination with ethylamine resulted in concomitant lactam formation to afford **13a** and its epimer **13b** in a ratio of >9:1 after chromatographic separation. Treatment of **13a** with LDA and acylation of the enolate with methyl chloroformate afforded the *trans*-isomer **14**. Hydrolysis of the ester group in a suspension of barium hydroxide, followed by amide formation with *n*-butylamine, gave the crystalline amide **15** (Scheme 2).

We sought an alternative synthesis of the desired *trans*-3,4 disubstituted 2-pyrrolidinone motif D (Figure 1). Thus, conjugate addition of nitromethane to **3** in the presence of a bulky bicyclic guanidine base[15] led to the corresponding 3-nitromethyl adduct **16** in quantitative yield. Reduction of the nitro group with Raney-Ni in the presence of H_2PtCl_6[16] afforded the lactam **17**, which was *N*-ethylated with NaH and ethyl iodide to give **18**.

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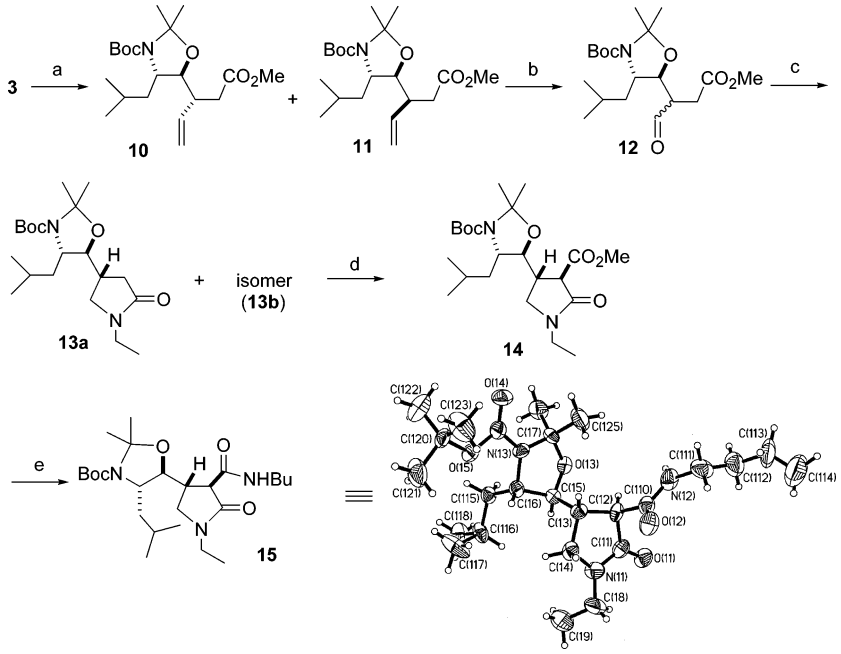
SCHEME 2[a]



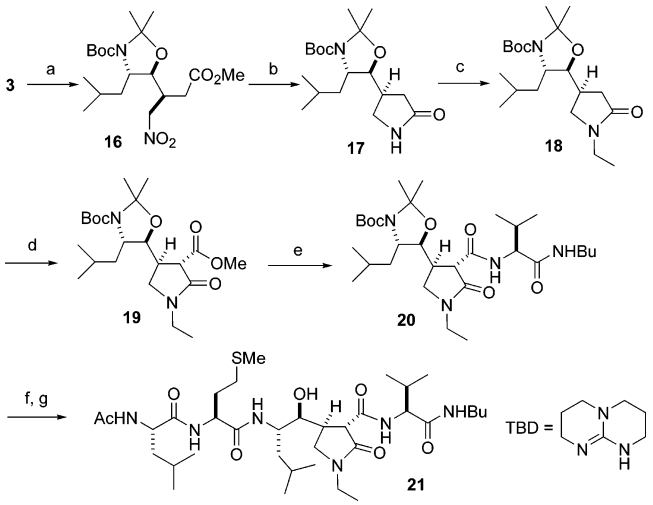
[a] Reagents and conditions: (a) i. $CH_2CHMgBr$, CuI, TMSCl, THF, −78 °C; ii. aqueous NH_4Cl, 91%; (b) O_3, DCM, −78 °C and then PPh_3, 99%; (c) i. $EtNH_2$, Na_2SO_4; ii. $NaBH(OAc)_3$ and then aqueous $NaHCO_3$, separate **13a** from diastereomer (**13a/13b** = 9:1), 91%; (d) i. LDA, THF, −78 °C; ii. ClCOOMe, 85%; (e) i. $Ba(OH)_2$, H_2O−EtOH then H_2SO_4; ii. EDC, HOBt, DMAP, $BuNH_2$, DCM, 70%.

Introduction of a methoxycarbonyl group via enolate chemistry followed the same protocol as described above to give **19**. Elaboration to the intended P_1'−P_1 motif was accomplished by peptide coupling of **20** as previously described[1] to give the prototypical azacyclic pseudopeptide **21** (Scheme 3).

The synthesis of the last pyrrolidinone carboxylic acid motif E (Figure 1) is shown in Scheme 4. The common precursor **3** was oxidatively cleaved to the aldehyde **22**, and the latter was subjected to a Wittig olefination to give the bromo ester **23**. Michael addition and concomitant lactam formation with tolysulfonyl *N*-methylacetamide[17] in the presence of sodium hydride in THF led to an inseparable 1.3:1 mixture of the tosyl lactams **24a** and **24b**. Cleavage of the tosyl group with sodium amalgam in sodium dihydrogen phosphate led to a mixture of the corresponding lactams **25a**,**b**.

Cleavage of the methyl ester and peptide coupling with H-Val-NHBu, gave the two amides **26** and **27**, which could be separated by column chromatography. Chain extension of **26** and **27** as described above gave the respective lactams **28** and **29**. We did not secure chemical proof for their configurational identity due to the difficulty of distinguishing between the precursor diastereomeric adducts **24a** and **24b** resulting from the original addition/cyclization. However, potent inhibition of BACE1 by compound **29** by analogy with a carbocyclic analogue[8] (see below) argued heavily in favor of its configurational assignment, since the isomeric **28** was inactive.

SCHEME 3[a]



[a] Reagents and conditions: (a) $MeNO_2$, TBD, 99%; (b) H_2PtCl_6, Raney-Ni, MeOH, H_2, 72%; (c) NaH, THF; EtI, 80%; (d) LDA, THF, −78 °C and then $ClCO_2Me$, 98%; (e) NaOH, MeOH−H_2O, 65 °C; then 1 N HCl; and then H-Val-NHBu, PyBOP, DIEA, DCM, 86%; (f) TFA, DCM; then $NaHCO_3$; and then Boc-Met-OH, PyBOP, DIEA, DCM, 63%; (g) TMSI, DCM; then $Na_2S_2O_3$, $NaHCO_3$; and then Ac-Leu-OH EDC, HOBt, DCM/H_2O, 83%.

Discussion

The addition of propiolate esters to *N*-Boc aldehydes derived from amino acids has many precedents.[12,13] In general, selectivities in favor of the *syn*-amino alcohols are good, although the basicity of the Li propiolates can lead to side reactions and racemization in some cases. Imamoto and co-workers[12a] have shown that addition of $CeCl_3$ to Grignard and organolithium reagents greatly improves yields. Indeed, inclusion of $CeCl_3$ effectively

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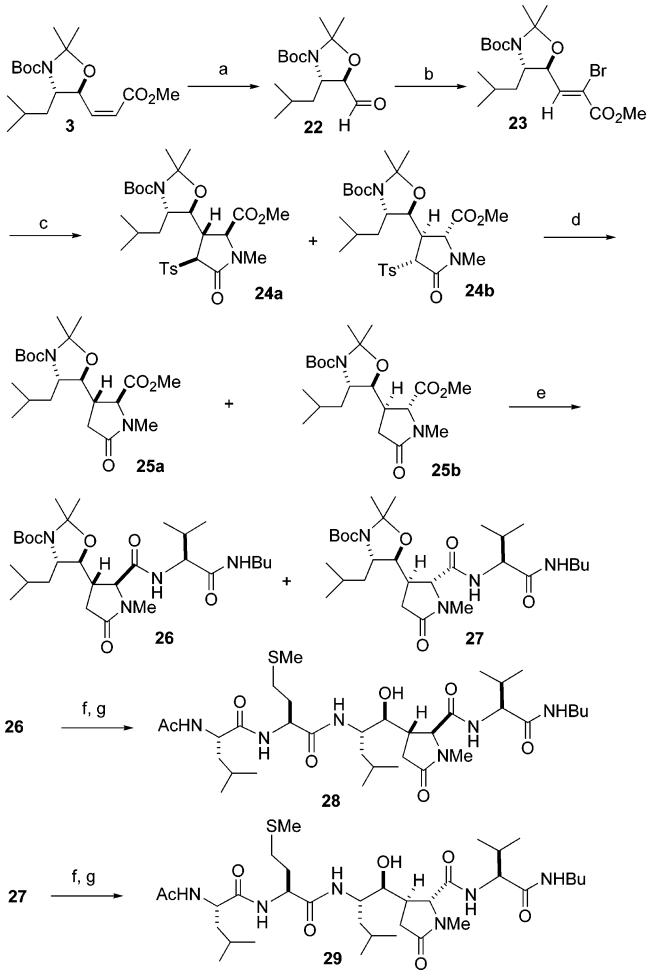
SCHEME 4[a]



[a] Reagents and conditions: (a) O_3, DCM, −78 °C; and then PPh_3, 99%; (b) $Ph_3PC(Br)CO_2Me$, toluene, DCE, 80 °C, 3h, 94% (*Z*-isomer, Z/E > 14:1); (c) $TsCH_2CONHMe$, NaH, THF, 20 min; and then **23**, room temperature 12h, 81%; (d) Na amalgam, Na_2HPO_4, MeOH, 0 °C, 1 h, 99%; (e) NaOH, MeOH−H_2O, 65 °C; then 1 N HCl; and then H-Val-NHBu, PyBOP, DIEA, DCM, 50% (**26/27** = 1.3:1); (f) TFA, DCM; then $NaHCO_3$; and then Boc-Met-OH, PyBOP, DIEA, DCM, 73% from **26** and 73% from **27**; (g) TMSI, DCM; then $Na_2S_2O_3$, $NaHCO_3$; then Ac-Leu-OH, EDC, HOBt, DCM/H_2O, **28** (75%) and **29** (68%).

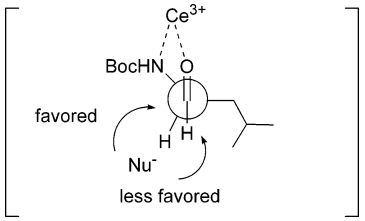


FIGURE 2. Transition state model of a Ce^{3+} coordinated intermediate.

improved the efficiency and selectivity of the addition, affording **2** in 72% yield (5:1 ratio). A proposed transition state model in which a chelation-controlled addition of Ce methyl propiolate may be operative as shown in Figure 2.

The azomethine ylide cycloaddition reaction is a versatile method for the synthesis of 3,4-substituted pyrrolidines from an olefin and a suitable nitrogen dipole

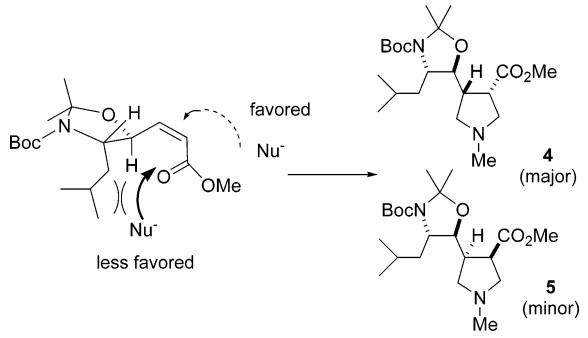


FIGURE 3. Transition state model for azomethine ylide cycloaddition.

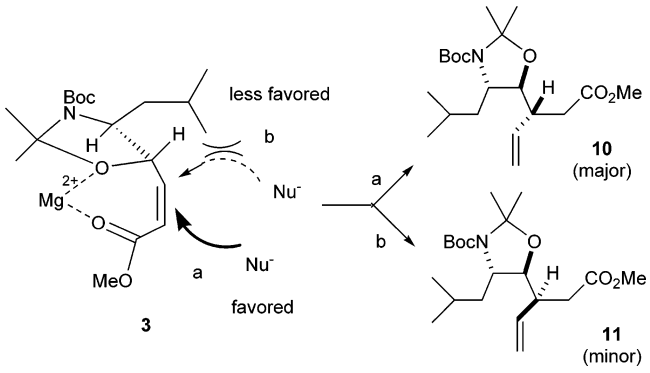


FIGURE 4. Transition state model for cuprate addition.

precursor.[10] The *N*-ylides can be generated in situ with *N*-alkylamino glycine and formaldehyde as shown in preparatively useful examples by Joucla and Mortier.[14] Alternatively, *N*-alkyl-*N*-trimethylsilylmethyl methoxymethylamines[14b] can be direct precursors of the azomethine. Usually electron poor or activated alkene dipolarophiles harboring functional groups on stereogenic carbons react with high facial selectivity, due to internal induction (resident chirality).[14b] It has been reported that a *cis*-α,*β*-unsaturated *γ*-alkoxy ester gives much higher facial selectivity compared to the *trans*-isomer.[14a] To the best of our knowledge, azomethine ylide 1,3-dipolar cycloaddition with α,*β*-unsaturated *γ*-amino acid esters have little if any precedent. The facial selectivity found in the case of **3** can be rationalized based on a transition state model where the $A^{1,3}$ strain is minimized,[18] as depicted in Figure 3. Thus, cycloaddition is more likely to occur from the least hindered face of the enoate leading to **5** as the major isomer.

Addition of vinyl cuprates to *γ*-ureido *trans*-enoates leads to the *syn*-adducts as major isomers.[11a,b] However, in the case of the *cis*-enoate **3**, the major product was in fact the *anti*-isomer **10**. Considering the effect of the $A^{1,3}$ strain in the transition state of the conjugate addition, the syn-product **11** should have predominated. The results can be rationalized on the basis of a chelated intermediate of **3**, where the normally preferred facial attack due to minimization of the $A^{1,3}$ strain is counterbalanced by the steric bulk of the chelate, leading to the *anti*-isomer **10** as the major product (Figure 4).

The exclusive formation of the desired *syn*-nitromethyl isomer **16** in the conjugate addition to **3** can be rational-

(18) For a review, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841.

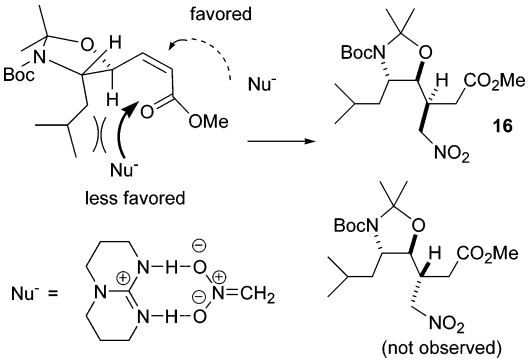


FIGURE 5. Transition state model for Michael addition with nitromethane.

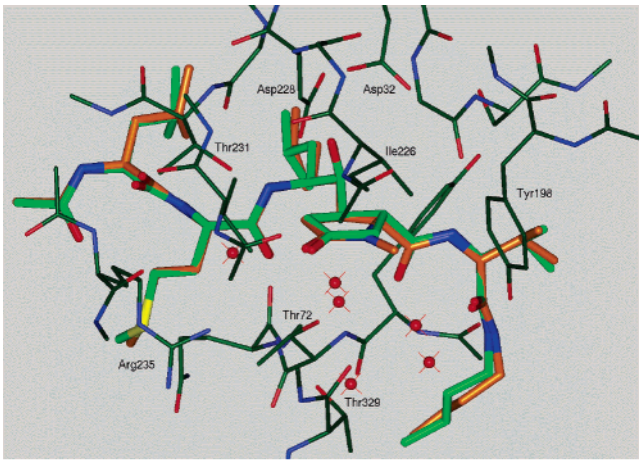
ized based on the minimization of the $A^{1,3}$ strain in the transition state and the approach of the bulky nitromethyl anion from the more favored *Si* face of the enoate to give **16** (Figure 5).

In conclusion, we have described methods for the synthesis of 3,4-substituted pyrrolidine, 2-pyrrolidinone 3-carboxylic acids as well as 5-pyrrolidine 2,3-substituted-3-carboxylic acids utilizing internal asymmetric induction in cycloaddition and Michael addition reactions from a common precursor **3**. The azacyclic motifs were used as constrained replacements of a hydroxyethylene dipeptide mimic found in OM99-2. The latter is a potent inhibitor of BACE1 and is a pivotal enzyme in the formation of plaque, a hallmark event in the progression of Alzheimer's disease. The azacyclic motifs were elaborated to prototypical inhibitor-type molecules and tested for activity against BACE1, which uncovered a low nanomolar inhibitor (IC_{50} < 10 nM, 79% inhibition at 10 μM) for compound **29**. In contrast, the diastereomeric **28** and the pyrrolidine **9** or positional lactam isomer, **21**, respectively, were considerably less active.[8] The potent activity of **29** follows a similar level of inhibition by an analogous cyclopentanone analogue[8] **30**, where the carbonyl group points in the same direction in the enzyme as the lactam carbonyl in **29** and interacts with two water molecules as evidenced by a cocrystal structure. Figure 6 depicts the superposition of the modeled structure of **29** on the cocrystal structure of the cyclopentanone analogue in the presence of BACE1.

Experimental Section

(5*S*)-*tert*-Butoxycarbonylamino-(4*S*,*R*)-hydroxy-7-methyl-oct-2-ynoic Acid Methyl Ester (2).[13] To a solution of *i*-Pr_2NEt (2.55 g, 25.2 mmol) in 20 mL of THF at −78 °C was added butyllithium (2.5 M in hexanes, 8.4 mL, 21 mmol), and the solution was warmed to 0 °C for 0.5 h and then cooled to −78 °C. To the LDA solution was added methyl propiolate (2.55 g, 25.2 mmol) dropwise, and the reaction mixture was stirred at −78 °C for 0.5 h (solution A).

To a 250-mL flame-dried flask was added anhydrous $CeCl_3$ (5.16 g, 21 mmol) and THF (40 mL). The reaction mixture was vigorously stirred at room temperature for 2 h and then cooled to −78 °C. To this suspension was added solution A (−78 °C) in one portion. The reaction mixture was stirred at the same temperature for 1 h, and then a solution of Boc-leucinal (3.0 g, 14 mmol) in THF (12 mL) was added. The resulting mixture was stirred at −78 °C for 3 h, quenched by addition of a solution of acetic acid (4 mL) in THF (16 mL) at −78 °C, and allowed to warm to room temperature. The mixture was



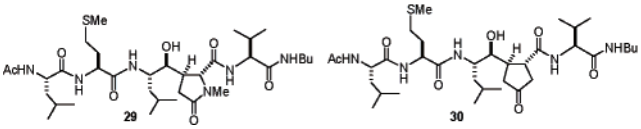


FIGURE 6. Superposition of docked structure of **29** (orange) on the X-ray cocrystal structure of a cyclopentanone analogue[8] (green). Red circles correspond to water molecules.

extracted with Et_2O (100 mL) and washed with 10% citric acid (2 × 40 mL), and the separated organic layer was washed with saturated $NaHCO_3$ (3 × 50 mL) and brine (50 mL), dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (30% EtOAc in hexanes) to afford **2** and its epimer (5:1) (3.1 g, 72%) as a yellow oil; ^{1}H NMR ($CDCl_3$) δ 4.74 (m, 1H), 4.50 (m, 1H), 3.84−3.70 (m, 1H), 3.76 (s, 3H), 1.67 (m, 1H), 1.58−1.20 (m, 2H), 1.43 (s, 9H), 0.93 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 156.6, 153.0, 86.2, 80.0, 65.1, 52.9, 52.7, 38.6, 28.1, 24.6, 23.2, 21.7, 21.5.

(4*S*)-Isobutyl-(5*S*)-(2-methoxycarbonyl-vinyl)-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (3). A solution of **2** (1.27 g, 3.74 mmol), 2,2-dimethoxypropane (15 mL, 0.12 mol), and dry acetone (70 mL) was heated to reflux for 5 min under argon atmosphere. Then TsOH was added until a permanent dark red solution was obtained. The reaction mixture was refluxed for an additional 2 h, cooled to room temperature, and concentrated. Saturated $NaHCO_3$ (20 mL) was added to the residue and extracted with EtOAc (3 × 60 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated to give a crude product as a yellow oil, which was purified by column chromatography (4% EtOAc in hexanes) to afford a yellow oil (0.92 g, 64%); $[\alpha]_D$ −25.6 (*c* 1.5, $CHCl_3$); IR (neat) 2960, 2874, 2238, 1723, 1703, 1457, 1436, 1381, 1254, 1175, 1128, 1089, 1068, 1027, 851, 752; ^{1}H NMR ($CDCl_3$) δ 4.58 (s, 1H), 4.28−3.90 (m, 1H), 3.77 (s, 3H), 1.73 (s, 3H), 1.62−1.30 (m, 6H), 1.48 (s, 9H), 0.95 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 153.9, 151.6, 118.1, 96.4, 91.0, 86.6, 68.8, 62.5, 53.1, 43.4, 42.5, 28.8, 28.0, 26.3, 24.0, 21.9; MS (FAB): *m/z* 340 [M + 1]$^+$; HRMS calcd for $C_{18}H_{30}NO_5$ [M + 1]$^+$ 340.4325; found 340.2124.

Benzene (30 mL), Lindlar catalyst (60 mg, 5 wt %), and quinoline (0.24 mL) were placed in a 100-mL round-bottom flask, and the suspension was stirred for 20 min at room temperature. A solution of the yellow oil (1.2 g, 3.54 mmol) in benzene (20 mL) was added to the flask, and the mixture was stirred for an additional 20 min at room temperature. The flask was then charged with H_2 (balloon) and stirred vigorously overnight. The catalyst was removed by filtration through a pad of Celite, washed with EtOAc, and filtered. The filtrate was concentrated, and the residual yellow oil was purified by column chromatography (5% Et_2O in CH_2Cl_2) to give **3** (1.1 g, 90%) as a yellow oil; $[\alpha]_D$ +24.0 (*c* 1.2, $CHCl_3$); IR (neat) 2959,

2873, 1743, 1700, 1388, 1367, 1256, 1175, 1092, 922, 870, 770 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.28 (m, 1H), 5.84 (m, 1H), 5.47 (m, 1H), 3.80−3.62 (m, 1H), 3.68 (s, 3H), 1.70−1.47 (m, 9H), 1.44 (s, 9H), 0.89 (d, J = 5.9 Hz, 3H), 0.85 (d, J = 6.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 166.2, 152.1, 147.6, 121.5, 80.3, 75.6, 61.9, 53.3, 51.9, 43.6, 28.9, 28.0, 26.3, 25.4, 24.3, 21.9; MS (FAB): *m/z* 342 $[M + 1]^+$; HRMS calcd for $C_{18}H_{32}NO_5$ $[M + 1]^+$ 342.2281; found 342.2281.

(4*S*)-Isobutyl-(5*S*)-((4*R*)-methoxycarbonyl-1-methyl-pyrrolidin-(3*S*)-yl)-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (4) and (4*S*)-Isobutyl-(5*S*)-((4*S*)-methoxycarbonyl-1-methyl-pyrrolidin-(3*R*)-yl)-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (5). Compound **3** (175.1 mg, 0.51 mmol), sarcosine (0.2 g, 1.12 mmol), paraformaldehyde (3.42 mmol), and 0.8 of activated molecular sieves 4 Å powder were dissolved in dry benzene (14 mL) and refluxed gently under the argon atmosphere overnight. The reaction mixture was cooled and filtered, the filtrate was concentrated, and the residual yellow oil was purified by column chromatography (10% MeOH in EtOAc) to give **4** (160 mg, 78%) and **5** (38 mg, 18%) as light yellow oils; For **4** $[\alpha]_D$ +12.0 (*c* 0.95, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 4.07 (m, 1H), 3.66 (s, 3H), 3.60−3.82 (br, 1H), 3.13 (m, 1H), 3.03 (m, 1H), 2.58−2.75 (m, 2H), 2.51 (br, 1H), 2.40 (s, 3H), 1.48−1.72 (m, 4H), 1.46 (S, 9H), 1.20−1.43 (m, 5H), 0.93 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 6.3 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.7, 152.4, 80.1, 59.5, 57.8, 51.9, 45.2, 44.2, 42.5, 28.8, 27.9, 25.0, 24.0, 22.4, 14.0; MS (EI): *m/z* 398.3, $[M^+]$; HRMS calcd for $C_{21}H_{38}N_2O_5$ 398.2781, found 398.2814. For **5** $[\alpha]_D$ −35.8 (*c* 0.54, $CHCl_3$), ^1H NMR ($CDCl_3$) δ 4.09 (m, 1H), 3.65 (s, 3H), 3.56 (m, 1H), 3.10 (m, 2H), 2.88 (m, 1H), 2.75 (m, 1H), 2.56 (m, 1H), 2.33 (s, 3H), 2.10 (m, 1H), 1.50−1.61 (m, 7H), 1.45 (s, 9H), 1.20−1.38 (m, 2H), 0.86 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 175.1, 152.2, 80.1, 60.8, 60.0, 52.0, 47.0, 44.9, 43.4, 42.3, 28.9, 28.5, 28.3, 25.9, 24.4, 21.5; MS (EI) *m/z* 398.3, $[M]^+$; HRMS calcd for $C_{21}H_{38}N_2O_5$ $[M]^+$ 398.2781; found 398.2790.

(5*S*)-((4*S*)-Butylcarbamoyl-1-methyl-pyrrolidin-(3*S*)-yl)-(4*S*)-isobutyl-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (6). To the solution of **4** (50 mg, 0.13 mmol) in MeOH (1 mL) was added freshly prepared NaOMe (0.5 M, 0.5 mL in methanol). The reaction mixture was refluxed under an argon atmosphere for 5 h, cooled, and quenched by addition of 5 mL of aqueous saturated ammonium chloride solution. The aqueous layer was extracted by ethyl acetate (3 × 30 mL), and the combined organic layers were dried anhydrous sodium sulfate, filtered, and evaporated under reduced pressure to a yellow syrup. The syrup was purified by column chromatography (10% MeOH in EtOAc) to afford a colorless syrup; $[\alpha]_D$ −10.9 (*c* 1.0, MeOH), ^1H NMR ($CDCl_3$) δ 3.83 (m, 1H), 3.66 (s, 3H), 3.60−3.75 (m, 1H), 2.72 (d, J = 6.9 Hz, 2H), 2.61 (br, 3H), 2.47 (br, 1H), 2.26 (s, 3H), 1.48−1.60 (m, 4H), 1.42−1.48 (m, 3H), 1.41 (s, 9H), 1.21−1.40 (m, 2H), 0.88 (d, J = 6.3 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 174.2, 151.4, 93.7, 82.9, 79.3, 59.0, 58.7, 58.5, 51.9, 46.1, 43.3, 42.2, 41.6, 28.3, 27.7, 25.4, 24.0, 20.8; MS (EI) *m/z* 398.2, $[M]^+$; HRMS calcd for $C_{21}H_{38}N_2O_5$ $[M + 1]^+$ 398.2780; found 398.2790.

To a solution of the colorless syrup (40 mg, 0.1 mmol) in ethanol (1 mL) was added 1 mL of 0.1 M aqueous barium hydroxide. The resulting suspension was stirred for 1 h and then heated to 50 °C for 3 h. The mixture was quenched by addition of 2 mL of 0.1 N sulfuric acid dropwise at −5 °C, stirred for 30 min, and filtered, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (2 mL), the solution was cooled to 0 °C, and *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDC) (43 mg, 0.22 mmol) was added, followed by hydroxybenzotriazole (HOBt) (30 mg, 0.22 mmol). *n*-Butylamine (22 μL, 0.22 mmol) and 4-(dimethylamino)-pyridine (27 mg, 0.22 mmol) were added, and the reaction mixture was stirred at 0 °C for 0.5 h, allowed to warm to room temperature overnight, quenched by addition of saturated $NaHCO_3$ (10 mL), and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated. The residue was purified by column chromatography (20% MeOH in EtOAc) to afford **6** as a colorless oil; ^1H NMR ($CDCl_3$) δ 6.83 (br s, 1H), 3.83 (br s, 1H), 3.67 (br s, 1H), 3.21 (q, J = 6.9 Hz, 2H), 3.02 (br, 1H), 2.86 (m, 1H), 2.58−2.46 (m, 1H), 2.34 (s, 3H), 2.46−2.17 (m, 4H), 1.48 (s, 9H), 1.2−1.72 (m, 14H), 1.27 (m, 2H), 0.92 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 175.0, 94.9, 84.4, 79.7, 59.6, 59.2, 48.9, 41.5, 38.7, 31.6, 28.4, 27.5, 25.4, 24.1, 19.9, 13.6; MS (FAB): *m/z* 440 $[M + 1]^+$; HRMS calcd for $C_{24}H_{46}N_3O_4$ $[M + 1]^+$ 440.3489; found 440.3476.

Compound 7. Boc-Val-NHBu (52 mg, 0.19 mmol) was treated with HCl in dioxane (4 M, 1.5 mL) at room temperature for 1 h. After the solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. The acid (from epimerization and hydrolysis of methyl ester **4**, 40 mg, 0.10 mmol) was added followed by PyBOP (54 mg, 0.10 mmol) and *i*-Pr_2NEt (74 μL, 0.42 mmol). The reaction mixture was stirred from 0 °C to room temperature for 3 h before it was diluted with EtOAc (10 mL), washed with 1 N aqueous HCl and saturated $NaHCO_3$. The organic phase was dried and concentrated, and the residue was purified by column chromatography (10% MeOH in EtOAc) to afford **7** (43 mg, 76%) as a white solid; $[\alpha]_D$ −28.0 (*c* 0.50, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.28 (br, 1H), 7.27 (br, 1H), 6.58 (br, 1H), 5.26 (d, J = 6.9 Hz, 1H), 5.0 (br, 1H), 4.31 (t, J = 6.4 Hz, 1H), 4.22 (q, J = 7.0 Hz, 1H), 3.40 (m, 1H), 3.28 (m, 1H), 3.21 (m, 2H), 2.57 (m, 2H), 2.38 (m, 1H), 2.36 (m, 1H), 2.10 (s, 3H), 1.91 (m, 2H), 1.88 (m, 2H), 1.74 (m, 2H), 1.63 (m, 4H), 1.47 (m, 2H), 1.43 (s, 9H), 1.37 (d, J = 7.2 Hz, 3H), 1.34 (m, 3H), 0.91 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 175.7, 171.4, 152.0, 83.4, 80.2, 59.9, 59.7, 58.9, 49.1, 47.6, 46.7, 41.9, 39.5, 32.0, 30.6, 28.9, 28.0, 26.9, 26.8, 25.9, 24.6, 21.5, 20.4, 20.0, 18.5, 14.05; IR (film) 3285, 2960, 2776, 1701, 1638, 1547; MS (FAB): *m/z* 539.3 $[M + 1]^+$; HRMS calcd for $C_{29}H_{55}N_4O_5$ $[M + 1]^+$ 539.4172; found 539.4131.

Compound 8. A solution of **7** (31 mg, 0.06 mmol) in HCl (4 M in dioxane, 1 mL) was stirred at room temperature for 1 h. After removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (1.5 mL) and cooled to 0 °C. Boc-methionine (14 mg, 0.06 mmol) was added followed by PyBOP (30 mg, 0.06 mmol) and *i*-Pr_2NEt (39.7 μL, 0.23 mmol). The solution was stirred from 0 °C to room temperature for 2 h and diluted with EtOAc to 3 mL. The reaction mixture was kept in the cold room (5 °C) overnight before it was diluted with EtOAc (10 mL) and washed with 1 N aqueous HCl and saturated $NaHCO_3$. The organic phase was dried and concentrated, and the residue was purified by column chromatography (10% MeOH in CH_2Cl_2) to afford **8** (13 mg, 33%) as a colorless oil; $[\alpha]_D$ −20.75 (*c* 1.60, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 8.28 (br, 1H), 7.27 (br, 1H), 6.58 (br, 1H), 5.26 (d, J = 6.9 Hz, 1H), 5.0 (br, 1H), 4.31 (t, J = 6.4 Hz, 1H), 4.22 (q, J = 7.0 Hz, 1H), 3.40 (m, 1H), 3.28 (m, 1H), 3.21 (m, 2H), 2.57 (m, 2H), 2.38 (m, 1H), 2.36 (m, 1H), 2.10 (s, 3H), 1.91 (m, 2H), 1.88 (m, 2H), 1.74 (m, 4H), 1.63 (m, 4H), 1.47 (m, 2H), 1.43 (s, 9H), 1.37 (d, J = 7.2 Hz, 3H), 1.34 (m, 3H), 0.91 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 175.0, 173.8, 156.2, 80.7, 60.5, 57.9, 54.8, 49.2, 47.3, 40.0, 39.7, 32.0, 31.7, 30.8, 30.7, 28.7, 25.3, 23.6, 22.3, 20.5, 19.9, 19.3, 15.8, 14.2; MS (FAB): *m/z* $[M + 1]^+$ 630.3; HRMS calcd for $C_{31}H_{60}N_5O_6S$ $[M + 1]^+$ 630.4219; found 630.4251.

Compound 9. A solution of **8** (10 mg, 0.02 mmol) in HCl (4 M in dioxane, 1 mL) was stirred at room temperature for 1 h. After removal of the solvent under reduced pressure, the residue was dissolved in EtOAc (10 mL) and washed with $NaHCO_3$ (1 N, 5 mL) and brine (5 mL). The solvent was evaporated, and the residue was dissolved in CH_2Cl_2/H_2O (1:1) (1.0 mL) and cooled to 0 °C. Ac-Leu-OH (5.42 mg, 0.03 mmol) was added, followed by EDC (7 mg, 0.03 mmol) and HOBt (4 mg, 0.03 mmol). The reaction mixture was stirred from 0 to 5 °C for 24 h. The reaction mixture was extracted with EtOAc (3 × 5 mL). The organic phase was dried and concentrated, and the residue was purified by column chromatography (20% MeOH in CH_2Cl_2) to afford **9** (4 mg, 40%) as a white solid; $[\alpha]_D$ −19.56 (*c* 0.23, MeOH); ^1H NMR (CD_3OD) δ 7.69 (m, 1H),

7.27 (m, 1H), 4.46 (q, J = 4.7 Hz, 1H), 4.30 (t, J = 6.5 Hz, 1H), 4.09 (d, J = 7.5 Hz, 1H), 3.97 (m, 1H), 3.61 (t, J = 3.9 1H), 3.35 (s, 3H), 3.30 (s, 3H), 3.22 (m, 1H), 3.13 (m, 2H), 3.08 (m, 2H), 2.65 (s, 3H), 2.61 (m, 1H), 2.51 (m, 1H), 2.10 (s, 3H), 2.08 (m, 1H), 2.00 (s. 3H), 1.58 (m, 1H), 1.48 (m, 4H), 1.35 (m, 2H), 1.27 (m, 7H), 0.91 (m, 16H); ^{13}C NMR (CD_3OD) δ 174.7, 174.2, 172.6, 172.3, 172.2, 73.2, 59.8, 59.3, 56.6, 52.7, 48.6, 48.4, 46.3, 40.8, 39.1, 31.5, 30.2, 24.9, 24.8, 22.8, 22.4, 21.4, 21.1, 20.1, 18.8, 18.2, 13.1; MS (FAB): m/z [M + 1]$^+$ 685.4; HRMS calcd for $C_{34}H_{65}N_6O_6S$ [M + 1]$^+$ 685.4686; found 685.4688.

(4*S*)-Isobutyl-(5*S*)-((1*R*,*S*)-methoxycarbonylmethyl-allyl)-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (10 and 11). To a suspension of cuprous iodide (1.1 g, 6 mmol) in THF (25 mL) was added vinylmagnesium bromide (1 M in THF, 12 mL, 12 mmol), followed by addition of **3** (683 mg, 2 mmol) in THF (2 mL) at −78 °C, and the mixture was stirred for 2 h. The reaction mixture was treated with concentrated NH_4OH and saturated NH_4Cl (v/v, 1:1) at −78 °C, then warmed to room temperature. The aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (10% EtOAc in hexanes) to afford **10** and **11** as light yellow oil (0.6 g, 80%, inseparable diastereomers: 10, 11; 9:1); ^{1}H NMR ($CDCl_3$) δ 5.56 (m, 1H), 5.17 (m, 2H), 3.86 (m, 1H), 3.63 (m, 4H), 2.85 (m, 1H), 2.69 (m, 1H), 2.31 (m, 1H), 1.80−1.20 (m, 9H), 1.46 (S, 9H), 0.90 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 173.2, 152.0, 137.8, 119.1, 94.9, 94.3, 82.7, 80.0, 59.1, 51.8, 46.3, 44.0, 43.0, 36.3, 31.9, 28.9, 28.5, 25.7, 24.4, 23.0, 21.4, 14.4; MS (FAB): m/z 370.2 [M + 1]$^+$; HRMS calcd for $C_{20}H_{36}NO_5$ [M + 1]$^+$ 370.2593; found 370.2586.

(5*S*)-((1*R*,*S*)-Formyl-2-methoxycarbonyl-ethyl)-(4*S*)-isobutyl-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (12). To a solution of **10** and **11** (0.55 g, 1.49 mmol) in CH_2Cl_2 (30 mL) was bubbled ozone (0.8 mL/s) at −78 °C until a permanent blue color was obtained. The reaction mixture was stirred for 15 min at −78 °C, and then the flask was charged with argon to remove excess ozone. The mixture was quenched by addition of PPh_3 (1.95 g, 9.5 mmol) at −78 °C and stirred for 12 h at room temperature, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (66% EtOAc in hexanes) to afford **12** as a colorless solid (534 mg, 99%); ^{1}H NMR ($CDCl_3$) δ 9.73 (s, 1 H), 4.08 (br, 1 H), 3.85 (br, 1 H), 3.62 (s, 3 H), 2.99 (m, 1 H), 2.74 (d, J = 7.2 Hz, 1 H), 1.80−1.25 (m, 10 H), 1.42 (s, 9 H), 0.87 (d, J = 6.0 Hz, 6 H); ^{13}C NMR ($CDCl_3$) δ 201.8, 200.9, 172.1, 151.3, 106.7, 94.2, 79.9, 76.9, 76.6, 59.2, 58.9, 56.8, 51.8, 51.5, 43.6, 42.4, 41.8, 29.9, 28.2, 27.4, 25.2, 25.0, 24.8, 23.9, 21.0; MS (FAB): m/z 372.4 [M + 1]$^+$; HRMS calcd for $C_{19}H_{34}NO_6$ [M + 1]$^+$ 372.2386; found 372.2380.

(5*S*)-(1-Ethyl-5-oxo-pyrrolidin-(3*R*)-yl)-(4*S*)-isobutyl-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (13a) and (5*S*)-(1-Ethyl-5-oxo-pyrrolidin-(3*S*)-yl)-(4*S*)-isobutyl-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (13b). To the solution of **12** (387 mg, 1.04 mmol) in 1,2-dichloroethane (30 mL) was added anhydrous Na_2SO_4 powder (1.0 g, 7.5 mmol). The reaction mixture was cooled to 0 °C, ethylamine (84 μL, 1.113 mmol) was added, and the solution was stirred for 12 h at 0 °C. Sodium triacetoxyborohydride (300 mg, 1.225 mmol) was added, and the whole mixture was stirred for 72 h at room temperature. The mixture was treated with saturated $NaHCO_3$ (15 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (50% EtOAc in hexanes) to afford **13a** (312 mg, 82%) and **13b** (35 mg, 9%) as colorless syrups; For **13a** $[\alpha]_D$ −5.9 (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.82−3.50 (br, 1H) 3.68 (q, J = 8.6 Hz, J = 1.8 Hz, 1H), 3.43 (q, J = 9.4 Hz, J = 8.1 Hz, 1H), 3.30 (m, 2H), 2.98 (m, 1H), 2.56 (m, 1H), 2.46 (m, 2H), 1.75−1.30 (m, 8H), 1.46 (s, 9H), 1.09 (t, J = 7.2 Hz, 3H), 0.93 (d, J = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 173.2, 81.5, 80.0, 59.5, 48.6, 42.0, 36.8, 35.3, 33.6, 28.3, 27.4, 25.4, 23.9, 21.0, 12.3; MS (FAB): m/z 368.3 [M]$^+$; HRMS calcd for $C_{20}H_{36}N_2O_4$ [M]$^+$ 368.2675; found 368.2663. For **13b** $[\alpha]_D$ −32.2 (c 3.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.83−3.55 (m, 2H), 3.41 (m, 2H), 3.32 (m, 2H), 2.53 (m, 2H), 1.98 (m, 1H), 1.70−1.35 (m, 9H), 1.46 (s, 9H), 1.10 (t, J = 7.3 Hz, 3H), 0.92 (d, J = 5.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 172.4, 82.8, 59.8, 48.5, 43.0, 41.9, 37.0, 35.3, 34.7, 29.0, 28.3, 27.7, 25.3, 24.0, 20.8, 12.3; MS (FAB): m/z 369.26 [M + 1]$^+$; HRMS calcd for $C_{19}H_{36}N_2O_4$ [M]$^+$ 368.2675; found 368.2663.

(5*S*)-(1-Ethyl-(4*R*)-methoxycarbonyl-5-oxo-pyrrolidin-(3*R*)-yl)-(4*S*)-isobutyl-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (14). To the solution of **13a** (300 mg, 0.81 mmol) in THF (9 mL) was added LDA (3.66 mL, 0.5 M, 1.83 mmol) at −78 °C. The reaction mixture was stirred for 10 min at −78 °C, then methyl chloroformate (0.54 mL, 3.31 mmol) was added and stirred for 4 h at −78 °C. The reaction was quenched by addition of saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (50% EtOAc in hexanes) to afford **14** as a colorless oil (336 mg, 97%); $[\alpha]_D$ +12.4 (c 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 3.85−3.45 (m, 2H), 3.37 (s 3H), 2.90 (m, 3H), 2.76 (br, 1H), 2.40 (br, 1H), 1.86−1.10 (m, 8H), 1.37 (s, 9H), 0.89 (br, 3H), 0.81 (d, J = 6.6 Hz, 3H), 0.66 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 168.2, 165.5, 148.7, 79.1, 76.9, 56.6, 49.3, 44.1, 37.8, 34.5, 25.6, 22.8, 21.4, 18.3, 9.5; MS (FAB): m/z 427.3 [M + 1]$^+$.

(5*S*),((4*S*)-Butylcarbamoyl-1-ethyl-5-oxo-pyrrolidin-(3*R*)-yl)-(4*S*)-isobutyl-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (15). To the solution of **14** (280 mg, 0.66 mmol) in 5 mL of ethanol and 3 mL of water was added $Ba(OH)_2{\cdot}8H_2O$ (0.19 g, 0.6 mmol). The reaction mixture was stirred for 3 h at 65 °C, then overnight at room temperature. Sulfuric acid (0.1 N, 12 mL, 6 mmol) was added, and the suspension was stirred for 0.5 h at 0 °C. The solvent was evaporated, and the residue was directly used in the following reaction without further purification.

To the solution of the above residue in CH_2Cl_2 (15 mL) was added EDC (132 mg, 0.69 mmol) at 0 °C, followed by HOBt (93.2 mg, 0.69 mmol), and then butylamine (66 μL, 0.69 mmol) and DMAP (84.3 mg, 0.11 mmol). The reaction mixture was stirred for 0.5 h at 0 °C and then overnight at 0 °C, quenched by addition of saturated $NaHCO_3$ (10 mL), and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (50% EtOAc in hexanes) to afford **15** as a colorless oil (228 mg, 74%); $[\alpha]_D$ +20.3 (c 1.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.14 (br, 1H), 3.63 (m, 2H), 3.54 (t, J = 8.9 Hz, 1H), 3.40−3.00 (m, 6H), 2.83 (d, J = 9.8 Hz, 1H), 1.70−1.28 (m, 9H), 1.25 (m, 2H), 1.02 (t, J = 7.1 Hz, 3H), 0.91 (d, J = 5.8 Hz, 3H), 0.87 (d, J = 6.0 Hz, 3H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.3, 167.6, 151.8, 94.5, 81.4, 80.3, 59.8, 51.1, 48.6, 48.5, 44.1, 42.8, 39.9, 37.8, 37.3, 31.8, 28.8, 28.0, 25.8, 24.5, 21.6, 20.3, 14.0, 12.6; MS (FAB): m/z 467.3 [M + 1]$^+$; HRMS calcd for $C_{25}H_{45}N_3O_5$ [M + 1]$^+$ 467.3359; found 467.3367.

(4*S*)-Isobutyl-(5*S*)-(2-methoxycarbonyl-(1*R*)-nitromethyl-ethyl)-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (16). A solution of **3** (340 mg, 1 mmol) and 1,3,4,6,7,8-hexahydro-2*H*-pyrimido[1,2-a]pyrimidine (TBD) (55 mg, 0.4 mmol) in nitromethane (1 mL) was stirred at 0 °C for 48 h. The reaction mixture was directly purified by column chromatography (16% EtOAc in hexanes) to afford **16** as a colorless oil (398 mg, 99%); $[\alpha]_D$ +19.4 (c 3.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ: 4.70 (dd, J = 13.2 Hz, J = 3.6 Hz, 1H), 4.62 (dd, J = 13.2 Hz, J = 7.6 Hz, 1H), 3.90 (d, J = 8.2 Hz, 1H), 3.75 (br, 1H), 3.68 (s, 3H), 2.73 (br, 1H), 2.50 (d, J = 6.0 Hz, 2H), 1.80−1.25 (m, 7H), 1.46 (d, J = 5.0 Hz, 9H), 0.92 (d, J = 6.4 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ: 172.5, 171.6, 151.8, 95.2, 80.7, 75.4, 59.0, 58.5, 52.4, 44.2, 42.9, 38.5, 33.7, 28.8, 28.1, 25.6, 24.5,

21.6, 21.5; MS (FAB): *m/z* 425.2 $[M + 23]^+$; HRMS calcd for $C_{19}H_{34}N_2O_7Na$ $[M + 23]^+$ 425.2264; found 425.2258.

(4*S*)-Isobutyl-2,2-dimethyl-(5*S*)-(5-oxo-pyrrolidin-(3*S*)-yl)-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (17). A solution of **16** (398 mg, 0.99 mmol), Raney-Ni (200 mg), and H_2PtCl_6 (20 mg) in methanol was hydrogenated under 60 psi H_2 at room temperature overnight. The solvent was removed under reduced pressure, and the residue was partitioned between CH_2Cl_2 (10 mL) and NH_4OH-NH_4Cl (10 mL, 1:1, v/v). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was purified by column chromatography (14% EtOAc in hexanes) to afford **17** as a white solid (240 mg, 72%); $[\alpha]_D$ +5.5 (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.30 (br, 1H), 3.82−3.51 (m, 2H), 3.48 (m, 1H), 3.40 (dd, J = 10.1 Hz, J = 6.0 Hz, 1H), 2.45 (m, 1H), 2.43 (dd, J = 16.8 Hz, J = 9.0 Hz, 1H), 1.96 (m, 1H), 1.70−1.25 (m, 9H), 1.47 (s, 9H), 0.94 (d, J = 5.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ: 178.5, 177.6, 151.9, 94.6, 93.9, 83.1, 82.4, 80.4, 60.3, 45.0, 43.6, 42.6, 39.2, 34.2, 28.9, 28.5, 28.2, 25.9, 24.5, 21.4; MS (FAB): *m/z* 363.2 $[M + 23]^+$; HRMS calcd for $C_{18}H_{32}N_2O_4Na$ $[M + 23]^+$ 363.2260; found 363.2254.

(5*S*)-(1-Ethyl-5-oxo-pyrrolidin-(3*S*)-yl)-(4*S*)-isobutyl-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (18). To a solution of **17** (54 mg, 0.16 mmol) in DMF (1 mL) was added NaH (7 mg, 60% dispersion in mineral oil). The reaction mixture was stirred at room temperature for 1.5 h until the evolution of gas had ceased, and then a solution of EtI (25.4 μL, 0.32 mmol) was added. The mixture was poured into saturated NH_4Cl (10 mL) and extracted with EtOAc (5 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography (EtOAc/hexanes, 4:1) to afford **18** as a white solid (47 mg, 80%); $[\alpha]_D$ −32.2 (*c* 3.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 3.83−3.55 (m, 2H), 3.41 (m, 2H), 3.32 (m, 2H), 2.53 (m, 2H), 1.98 (m, 1H), 1.70−1.35 (m, 9H), 1.46 (s, 9H), 1.10 (t, J = 7.3 Hz, 3H), 0.92 (d, J = 5.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 172.4, 82.8, 59.8, 48.5, 43.0, 41.9, 37.0, 35.3, 34.7, 29.0, 28.3, 27.7, 25.3, 24.0, 20.8, 12.3; MS (FAB): *m/z* 369.3 $[M + 1]^+$.

(5*S*)-(1-Ethyl-(4*S*)-methoxycarbonyl-5-oxo-pyrrolidin-(3*S*)-yl)-(4*S*)-isobutyl-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (19). To the solution of **18** (63 mg, 0.17 mmol) in THF (1.9 mL) was added LDA (0.75 mL, 0.5 M, 0.38 mmol) at −78 °C. The reaction mixture was stirred for 10 min at −78 °C. Methyl chloroformate (114 μL, 0.684 mmol) was added and stirred for 4 h at −78 °C. The reaction was quenched by addition of saturated NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (50% EtOAc in hexanes) to afford **19** as a colorless oil (72 mg, 99%); ^1H NMR ($CDCl_3$) δ 3.85−3.45 (m, 2H), 3.77 (s 3H), 3.67 (m, 2H), 3.50 (t, J = 9.3 Hz, 1H), 3.38 (m, 3H), 3.13 (br, 1H), 2.92 (m, 1H), 1.75−1.25 (m, 8H), 1.44 (s, 9H), 1.11 (t, J = 7.3 Hz, 3H), 0.91 (d, J = 5.9 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 170.4, 168.2, 151.9, 94.6, 82.6, 80.4, 59.6, 53.2, 52.6, 47.6, 43.7, 42.7, 39.9, 38.1, 28.8, 28.4, 28.1, 25.9, 24.5, 21.4, 12.7; MS (FAB): *m/z* 427.2 $[M + 1]^+$.

Compound 20. A solution of **19** (146 mg, 0.34 mmol) and NaOH (27 mg, 0.68 mmol) in MeOH (1.2 mL) and H_2O (0.6 mL) was stirred at 65 °C for 1 h at room temperature overnight. The solution was treated with 1 N HCl (4 mL), extracted with EtOAc (3 × 10 mL), and washed with brine (10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated. The crude acid was dissolved in CH_2Cl_2 (2 mL) and treated with H-Val-NHBu (from Boc-Val-NHBu 93 mg, 0.34 mmol), followed by addition of PyBOP (164 mg, 0.51 mmol) and *i*-Pr_2NEt (141 μL, 1.03 mmol). The reaction mixture was stirred for 0.5 h at 0 °C, then at room temperature overnight, CH_2Cl_2 (30 mL) was added, and the solution was washed with 5% $NaHSO_4$ (3 × 20 mL), followed by saturated $NaHCO_3$ (3 × 20 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (66% EtOAc in hexanes) to afford **20** as a white solid (99 mg, 86%); $[\alpha]_D$ −56.5 (*c* 4.0, $CHCl_3$); ^1H NMR (MeOD) δ 8.38 (d, J = 8.3 Hz, 1H), 4.33 (br, 1H), 3.92 (d, J = 5.2 Hz, 1H), 3.76 (d, J = 5.6 Hz, 1H), 3.58 (t, J = 8.3 Hz, 1H), 3.52−3.27 (m, 4H), 3.20 (m, 3H), 2.38 (br, 1H), 1.68−1.41 (m, 6H), 1.66 (s, 3H), 1.49 (d, J = 7.0 Hz, 9H), 1.34 (m, 2H), 1.17 (t, J = 7.2 Hz, 3H), 1.02 (d, J = 7.0 Hz, 3H), 1.00−0.90 (m, 11H); ^{13}C NMR (MeOD) δ 172.3, 170.9, 169.6, 152.2, 94.2, 83.1, 80.4, 59.6, 59.8, 59.5, 52.2, 41.5, 39.3, 37.9, 37.4, 31.4, 29.8, 27.8, 27.5, 27.1, 25.7, 23.6, 21.5, 20.1, 19.2, 16.6, 13.2, 11.6; MS (FAB): *m/z* 567.3 $[M + 1]^+$; HRMS calcd for $C_{30}H_{55}N_4O_6$ $[M + 1]^+$ 567.4122; found 567.4117.

Compound 21. To the solution of **20** (91 mg, 0.16 mmol) in 2.5 mL of CH_2Cl_2 was added 0.5 mL of TFA, and the solution was stirred for 0.5 h at room temperature. The solvent was removed under reduced pressure. To the residue and Boc-Met-OH (80 mg, 0.32 mmol) dissolved in 4 mL of CH_2Cl_2 and cooled to 0 °C were added PyBOP (170 mg, 0.32 mmol) and *i*-Pr_2NEt (111 μL, 0.64 mmol). The reaction mixture was stirred for 4 h at 0 °C, EtOAc (30 mL) was added, and the solution was washed with 1 N HCl (3 × 15 mL), followed by saturated $NaHCO_3$ (3 × 15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (80% EtOAc in hexanes) to afford a white solid (67 mg, 63%); $[\alpha]_D$ −83.7 (*c* 1.3, MeOH); ^1H NMR ($CDCl_3$) δ 7.50 (br, 1H), 5.34 (d, J = 5.9 Hz, 1H), 4.26 (m, 2H), 3.63−3.11 (m, 10H), 2.98 (m, 1H), 2.62 (br, 2H), 2.35 (m, 1H), 2.25−2.00 (br, 1H), 2.08 (s, 3H), 1.92 (m, 1H), 1.80−1.39 (m, 4H), 1.41 (s, 9H), 1.38−1.19 (m, 4H), 1.10 (t, J = 7.2 Hz, 3H), 1.00−0.75 (m, 15 H); ^{13}C NMR ($CDCl_3$) δ 173.1, 171.4, 170.4, 168.6, 155.7, 80.2, 74.1, 59.7, 54.1, 52.4, 51.5, 45.8, 40.0, 39.2, 38.3, 37.8, 31.1, 30.0, 29.2, 28.1, 24.6, 23.6, 23.2, 21.5, 19.9, 19.4, 17.8, 15.1, 13.5, 12.2; MS (FAB): *m/z* 658.2 $[M + 1]^+$; HRMS calcd for $C_{32}H_{60}N_5O_7S$ $[M + 1]^+$ 658.4213; found 658.4220.

To a solution of the above solid (16 mg, 0.02 mmol) in CH_2Cl_2 (0.3 mL) was added TMSI (12 μL) and stirred at room temperature for 0.5 h. MeOH (0.5 mL) was added, and after 10 min the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (0.5 mL) and H_2O (0.5 mL) and followed by addition of Ac-leucine (5 mg, 0.03 mmol), EDC (6 mg, 0.03 mmol), and HOBt (4 mg, 0.03 mmol). The reaction mixture was stirred at 0 °C for 24 h, and another portion of EDC (6 mg, 0.03 mmol) was added. The solution was stirred for at 0 °C for 24 h, then diluted by addition of EtOAc (30 mL), $NaHCO_3$ (3 × 10 mL), and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by column chromatography (10% MeOH in EtOAc) to afford **21** as a white solid (14 mg, 83%); $[\alpha]_D$ −83.7 (*c* 1.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.45 (d, J = 9.4 Hz, 1H), 4.49 (q, J = 4.8 Hz, 1H), 4.35 (t, J = 7.5 Hz, 1H), 4.29 (d, J = 5.1 Hz, 1H), 3.98 (m, 1H), 3.57 (m, 4H), 3.33 (m, 4H), 3.19 (m, 2H), 2.98 (m, 1H), 2.48 (m, 1H), 2.41 (m, 1H), 2.22 (m, 1H), 2.15 (m, 1H), 2.11 (s, 3H), 2.00 (s, 3H), 1.96 (m, 1H), 1.70 (m, 1H), 1.59 (t, J = 7.4 Hz, 3H), 1.51 (m, 3H), 1.34 (m, 4H), 1.17 (t, J = 7.2 Hz, 3H), 1.03 (d, J = 6.9 Hz, 3H), 0.95 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 174.2, 172.9, 172.5, 171.4, 171.2, 75.3, 59.5, 53.3, 52.3, 52.1, 49.9, 41.4, 40.7, 39.3, 39.1, 37.7, 31.6, 31.3, 31.0, 30.3, 24.9, 24.7, 22.8, 22.5, 21.4, 21.3, 21.0, 20.2, 18.8, 17.0, 14.3, 13.1, 11.5; MS (FAB): *m/z* 735.4 $[M + 23]^+$; HRMS calcd for $C_{35}H_{64}N_6O_7SNa$ $[M + 23]^+$ 735.4455; found 735.4450.

(5*R*)-Formyl-(4*S*)-isobutyl-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (22). Into a solution of **3** (0.341 g, 1.0 mmol) in CH_2Cl_2 (20 mL) was bubbled ozone (0.8 mL/s) at −78 °C until a permanent blue color was obtained. The reaction mixture was stirred for 15 min at −78 °C, and the flask was purged with argon to remove excess ozone. The mixture was quenched by addition of PPh_3 (0.79 g, 3.0 mmol) at −78 °C and allowed to stir at room temperature overnight. The solvent was evaporated under reduced pressure, and the residue was purified by column chromatography (66% EtOAc

in hexanes) to afford **22** as a colorless solid (284 mg, 99%); $[\alpha]_D$ +29.5 (*c* 1.2, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 9.85 (s, 1H), 4.15 (br, 2H), 1.80−1.49 (m, 9H), 1.48 (s, 9H), 0.97 (t, J = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 203.2, 151.6, 85.0, 80.7, 71.6, 57.2, 43.5, 28.8, 28.0, 27.1, 26.2, 25.9, 24.2, 21.6; MS (FAB): *m/z* 369.0 $[M]^+$.

(5*S*)-((*Z*)-2-Bromo-2-methoxycarbonyl-vinyl)-(4*S*)-isobutyl-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (23). To a solution of **22** (414 mg, 1.4 mmol) in toluene (3.8 mL) and CH_2Cl_2 (1.9 mL) was added $Ph_3PC(Br)CO_2Me$ (752 mg, 1.82 mmol). The reaction mixture was stirred at 80 °C for 4 h. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (14% EtOAc in hexanes) to afford **23** as a colorless oil (524 mg, 89%) and an isomer (as a colorless oil 50 mg, 9%); For **23**; $[\alpha]_D$ −2.5 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.32 (d, J = 8.4 Hz, 1H), 4.69 (dd, J = 8.4 Hz, J = 1.7 Hz, 1H), 4.00−3.60 (br, 1H), 3.79 (s, 3H), 1.75−1.49 (m, 9H), 1.42 (s, 9H), 0.88 (d, J = 7.3 Hz, 3H), 0.84 (d, J = 8.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 162.8, 151.7, 143.8, 140.3, 117.6, 96.3, 80.5, 79.6, 61.4, 53.9, 53.7, 43.5, 42.6, 28.8, 28.0, 25.9, 24.2, 21.8; MS (FAB): *m/z* 442.1 $[M + 23]^+$; HRMS calcd for $C_{18}H_{30}BrNO_5Na$ $[M + 23]^+$ 442.1205; found 442.1199. For isomer; $[\alpha]_D$ −36.6 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.38 (d, J = 6.8 Hz, 1H), 5.16 (dd, J = 9.0 Hz, J = 1.5 Hz, 1H), 4.00−3.60 (m, 1H), 3.84 (s, 3H), 1.75−1.30 (m, 9H), 1.50 (s, 9H), 0.94 (t, J = 6.7 Hz, 6H); ^{13}C NMR ($CDCl_3$) δ 163.1, 146.4, 114.5, 80.6, 61.7, 53.9, 53.7, 28.9, 25.7, 25.6, 24.2, 22.0; MS (FAB): *m/z* 442.1 $[M + 23]^+$; HRMS calcd for $C_{18}H_{30}BrNO_5Na$ $[M + 23]^+$ 442.1205; found 442.1199.

(4*S*)-Isobutyl-(5*S*)-[(2*S*)-methoxycarbonyl-1-methyl-5-oxo-(4*S*)-(toluene-4-sulfonyl)-pyrrolidin-(3*S*)-yl]-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (24a) and (4*S*)-Isobutyl-(5*S*)-[(2*R*)-methoxycarbonyl-1-methyl-5-oxo-(4*R*)-(toluene-4-sulfonyl)-pyrrolidin-(3*R*)-yl]-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (24b). To a suspension of NaH (104 mg, 2.6 mmol, dispersed in mineral oil and washed three times with dry pentane) in THF (8 mL) was added 2-tolylsulfonyl *N*-methylacetamide (196 mg, 0.86 mmol) in portions. After being stirred at room temperature for 20 min, a solution of **23** (363 mmol, 0.86 mmol) was added to the suspension mixture during a period of 30 min. The reaction mixture was stirred overnight at room temperature and quenched by addition of saturated NH_4Cl (10 mL) and 1 N HCl (2 mL). The aqueous layer was extracted with EtOAc (5 × 15 mL), and the combined organic layers were dried (Na_2SO_4), filtered, and evaporated. The residue was purified by column chromatography (50% EtOAc in hexanes) to afford a mixture of **24a** and **24b** (397 mg, 81%) as an inseparable colorless oil; ^1H NMR ($CDCl_3$) δ 7.81 (d, J = 8.1 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 4.14 (m, 1H), 4.03 (m, 1H), 4.01−3.75 (m, 4H), 3.61 (m, 1H), 3.36 (m, 1H), 3.00 (d, 3H), 2.47 (d, 3H), 1.68−1.32 (m, 18H), 0.96 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 171.1, 170.8, 152.6, 152.5, 146.5, 146.5, 134.2, 133.2, 130.1, 130.0, 129.7, 82.2, 80.6, 69.0, 68.1, 67.0, 63.7, 62.0, 61.2, 59.5, 58.3, 53.2, 53.1, 42.3, 30.9, 30.8, 28.9, 28.8, 27.5, 26.1, 26.0, 25.9, 24.7, 22.1, 21.7, 21.1; MS (FAB): *m/z* 589.3 $[M + 23]^+$; HRMS calcd for $C_{28}H_{42}N_2O_8SNa$ $[M + 23]^+$ 589.2560; found 589.2556.

(4*S*)-Isobutyl-(5*S*)-((2*S*)-methoxycarbonyl-1-methyl-5-oxo-pyrrolidin-(3*S*)-yl)-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (25a) and (4*S*)-Isobutyl-(5*S*)-((2*R*)-methoxycarbonyl-1-methyl-5-oxo-pyrrolidin-(3*R*)-yl)-2,2-dimethyl-oxazolidine-3-carboxylic Acid *tert*-Butyl Ester (25b). A solution of **24a** and **24b** (283 mg, 0.5 mmol), dibasic sodium phosphate (235 mg, 2 mmol), and sodium amalgam (10%, 450 mg) in methanol (12 mL) was vigorously stirred at 0 °C for 1 h. To the reaction mixture was added saturated NH_4Cl (20 mL), the solvent was evaporated under reduced pressure, and the residue was dissolved in H_2O (20 mL) and extracted with EtOAc (5 × 15 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated in vacuo. The residue was purified by column chromatography (50% EtOAc in hexanes) to afford **25a** and **25b** (204 mg, 99%) as an inseparable colorless oil; ^1H NMR ($CDCl_3$) δ 3.85−3.51 (m, 4H), 2.85 (m, 3H), 2.75−2.32 (m, 2H), 1.70−1.30 (m, 6H), 1.48 (s, 9H), 0.95 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.3, 173.7, 172.2, 171.9, 151.9, 95.3, 81.8, 80.8, 65.0, 63.9, 60.0, 59.6, 53.1, 52.9, 43.8, 43.4, 40.6, 40.1, 33.6, 31.5, 29.3, 28.9, 28.2, 26.0, 25.8, 24.6, 21.6, 21.4; MS (FAB): *m/z* 435.2 $[M + 23]^+$; HRMS calcd for $C_{21}H_{36}N_2O_6Na$ $[M + 23]^+$ 435.2471; found 435.2468.

Compounds 26 and 27. A solution of **25a** and **25b** (120 mg, 0.29 mmol) and NaOH (23.3 mg, 0.58 mmol) in MeOH (4.0 mL) and H_2O (2.0 mL) was stirred at 65 °C for 1 h at room temperature overnight. The solution was treated with 1 N HCl (7 mL), extracted with EtOAc (3 × 10 mL), and washed with brine (10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The mixture of crude acid was dissolved in CH_2Cl_2 (4.8 mL) and treated with H-Val-NHBu (from Boc-Val-NHBu, 118 mg, 0.44 mmol), followed by addition of PyBOP (233 mg, 0.44 mmol) and *i*-Pr_2-NEt (202 μL, 1.16 mmol). The reaction mixture was stirred for 0.5 h at 0 °C and then at room temperature overnight. EtOAc (30 mL) was added, and the solution was washed with 1 N HCl (3 × 15 mL), followed by saturated $NaHCO_3$ (3 × 15 mL) and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated in vacuo. The residue was purified by column chromatography (EtOAc) to afford **26** (41 mg, 27%) and **27** (35 mg, 23%); For **26**; $[\alpha]_D$ −6.4 (*c* 2.0, MeOH); ^1H NMR (MeOD) δ 4.28 (d, J = 3.3 Hz, 1H), 4.19 (d, J = 8.4 Hz, 1H), 3.79 (m, 2H), 3.34 (d, J = 15.5 Hz, 1H), 3.33 (m, 1H), 2.82−2.65 (m, 1H), 2.78 (s, 3H), 2.60 (m, 1H), 2.04 (m, 2H), 1.63−1.54 (m, 11H), 1.49 (s, 9H), 1.40 (m, 3H), 0.96 (m, 15H); ^{13}C NMR (MeOD) δ 175.2, 171.5, 171.4, 82.8, 80.4, 66.1, 59.8, 59.6, 43.8, 40.1, 39.2, 39.1, 33.7, 31.4, 31.3, 27.8, 27.7, 25.5, 23.6, 20.6, 20.2, 18.7, 18.2, 13.1; MS (FAB): *m/z* 553.3 $[M + 1]^+$; For **27**; $[\alpha]_D$ −31.8 (*c* 1.6, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 6.83 (d, J = 8.6 Hz, 1H), 6.26 (br, 1H), 4.24 (t, J = 8.0 Hz, 1H), 3.90 (br, 1H), 3.81 (br, 1H), 3.68 (br, 1H), 3.30 (m, 1H), 3.19 (m, 1H), 2.80 (s, 3H), 2.48 (m, 3H), 2.06 (m, 1H), 1.60−1.44 (m, 13H), 1.46 (s, 9H), 1.33 (m, 3H), 0.96 (m, 18H); ^{13}C NMR ($CDCl_3$) δ 171.1, 170.5, 167.6, 152.0, 94.4, 82.5, 80.4, 59.4, 58.8, 51.6, 47.3, 43.8, 39.6, 38.3, 36.4, 31.7, 29.8, 28.8, 28.2, 27.6, 25.8, 24.6, 21.6, 20.4, 20.1, 17.2, 14.1, 12.6; MS (FAB): *m/z* 553.3 $[M + 1]^+$.

Compound 28. To the solution of **26** (40 mg, 0.07 mmol) in 0.4 mL of CH_2Cl_2 was added 0.1 mL of TFA, and the solution was stirred for 1 h at room temperature. The solvent was evaporated under reduced pressure. The residue and Boc-Met-OH (36 mg, 0.15 mmol) were dissolved in 2 mL of CH_2Cl_2 and cooled to 0 °C. PyBOP (77 mg, 0.15 mmol) and *i*-Pr_2NEt (50 μL, 0.29 mmol) were added. The reaction mixture was stirred for 0.5 h at 0 °C overnight. EtOAc (20 mL) was added, and the solution was washed with 1 N HCl (3 × 10 mL), followed by saturated $NaHCO_3$ (3 × 10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (10% MeOH in EtOAc) to afford a white solid (34 mg, 73%); $[\alpha]_D$ −16.2 (*c* 1.7, $CHCl_3$). To a solution of the solid (32 mg, 0.05 mmol) in CH_2Cl_2 (1.5 mL) was added TMSI (50 μL) and stirred at room temperature for 0.5 h. MeOH (0.5 mL) was added and stirred for 10 min. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (0.9 mL) and H_2O (0.6 mL), followed by addition of Ac-leucine (10.4 mg, 0.06 mmol), EDC (13 mg, 0.07 mmol), and HOBt (9 mg, 0.07 mmol). The reaction mixture was stirred at 0 °C for 24 h, another portion of EDC (13 mg, 0.07 mmol) was added, and the solution was stirred for at 0 °C for 24 h, then diluted by addition of EtOAc (30 mL), $NaHCO_3$ (3 × 10 mL), and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by column chromatography (20% MeOH in EtOAc) to afford **28** as a white solid (26 mg, 75%); $[\alpha]_D$ −49.3 (*c* 1.4, MeOH); ^1H NMR (MeOD) δ 8.05 (t, J = 5.6 Hz, 1H), 7.54 (d, J = 9.5 Hz, 1H), 4.48 (dd, J = 8.9 Hz, J = 5.4 Hz, 1H), 4.37 (t, J = 7.6 Hz, 1H), 4.27 (d,

J = 5.0 Hz, 1H), 4.25 (d, J = 6.0 Hz, 1H), 4.03 (m, 1H), 3.53 (d, J = 8.8 Hz, 1H), 3.30 (m, 1H), 3.19 (m, 1H), 2.79 (s, 3H), 2.66 (m, 2H), 2.49 (m, 2H), 2.25 (m, 2H), 2.15−1.85 (m, 2H), 2.08 (s, 3H), 2.00 (s, 3H), 1.65 (m, 7H), 1.48−1.20 (m, 3H), 0.96 (m, 21H); ^{13}C NMR (MeOD) δ 175.8, 174.1, 172.8, 172.7, 172.6, 172.6, 172.5, 172.1, 172.0, 75.8, 66.0, 59.3, 59.2, 52.5, 40.7, 30.9, 30.3, 28.0, 24.9, 24.7, 22.8, 22.4, 21.4, 21.3, 21.1, 20.2, 18.9, 17.2, 14.4, 13.2; MS (FAB): *m/z* 721.4 $[M + 23]^+$; HRMS calcd for $C_{34}H_{62}N_6O_7SNa$ $[M + 23]^+$ 721.4299; found 721.4292.

Compound 29. To the solution of **27** (34 mg, 0.06 mmol) in 0.4 mL of CH_2Cl_2 was added 0.1 mL of TFA, the solution was stirred for 1 h at room temperature, and the solvent was evaporated under reduced pressure. The residue and Boc-Met-OH (31 mg, 0.12 mmol) were dissolved in 1.8 mL of CH_2Cl_2 and cooled to 0 °C. PyBOP (65 mg, 0.12 mmol) and *i*-Pr_2NEt (43 μL, 0.25 mmol) were added. The reaction mixture was stirred for 0.5 h at 0 °C overnight, EtOAc (20 mL) was added, and the solution was washed with 1 N HCl (3 × 10 mL), followed by saturated $NaHCO_3$ (3 × 10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated, and the residue was purified by column chromatography (10% MeOH in EtOAc) to afford a white solid (29 mg, 73%); $[\alpha]_D$ −40.0 (*c* 1.5, $CHCl_3$). To a solution of the white solid (27 mg, 0.04 mmol) in CH_2Cl_2 (1.2 mL) was added TMSI (40 μL) and stirred at room temperature for 0.5 h. MeOH (0.5 mL) was added and stirred for 10 min. The solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (0.9 mL) and H_2O (0.5 mL), followed by addition of Ac-leucine (9 mg, 0.05 mmol), EDC (11 mg, 0.05 mmol), and HOBt (7 mg, 0.05 mmol). The reaction mixture was stirred at 0 °C for 24 h, another portion of EDC (11 mg, 0.05 mmol) was added, and the solution was stirred for at 0 °C for 24 h, then diluted by addition of EtOAc (30 mL), $NaHCO_3$ (3 × 10 mL), and brine (15 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography (20% MeOH in EtOAc) to afford **29** as a white solid (20 mg, 68%); $[\alpha]_D$ −75.0 (*c* 1.0, MeOH); ^{1}H NMR (MeOD) δ 8.18 (t, J = 5.2 Hz, 1H), 7.54 (d, J = 9.3 Hz, 1H), 4.49 (dd, J = 9.6 Hz, J = 4.6 Hz, 1H), 4.36 (t, J = 7.5 Hz, 1H), 4.18 (d, J = 3.3 Hz, 1H), 4.14 (d, J = 11.7 Hz, 2H), 3.47 (dd, J = 6.3 Hz, J = 2.6 Hz, 1H), 3.31 (m, 1H), 3.24 (m, 1H), 2.75 (s, 3H), 2.73−2.50 (m, 4H), 2.38 (m, 1H), 2.26−1.92 (m, 3H), 2.10 (s, 3H), 2.01 (s, 3H), 1.75 (m, 1H), 1.65 (m, 4H), 1.60 (m, 2H), 1.42−1.24 (m, 3H), 0.96 (m, 21H); ^{13}C NMR (MeOD) δ 176.6, 174.3, 172.6, 172.2, 172.1, 171.5, 72.5, 65.9, 60.0, 52.7, 31.5, 31.0, 30.4, 28.0, 24.9, 24.8, 22.9, 22.4, 21.5, 21.2, 21.1, 20.1, 18.7, 18.5, 14.3, 13.1; MS (FAB): *m/z* 721.4 $[M + 23]^+$; HRMS calcd for $C_{34}H_{62}N_6O_7SNa$ $[M + 23]^+$ 721.4299; found 721.4292.

Modeling of Compounds in BACE1. A 10 Å shell around the inhibitor in the BACE1 OM99-2 cocrystal structure (PDB ref 1FKN) was used for calculations. In this binding site model, the Monte Carlo docking/energy minimization protocol of the MCDOCK routine in the QXP program[19] (within the Flow96 package) was applied. Depending on the size and flexibility of the ligands, 1000 or 2000 search and energy minimization cycles were performed to ensure an in-depth conformational search and the exploration of different possible binding modes.

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Supporting Information Available: NMR spectra for the synthetic molecules and CIF files of X-ray structures **6** and **15**. X-ray crystallographic data have been deposited in the Cambridge Crystallographic Database. This material is available free of charge via the Internet at http://pubs.acs.org.

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