JOC Article

Stereoselective Synthesis of Constrained Oxacyclic Hydroxyethylene Isosteres of Aspartic Protease Inhibitors: Aldol and Mukaiyama Aldol Methodologies for Branched Tetrahydrofuran 2-Carboxylic Acids

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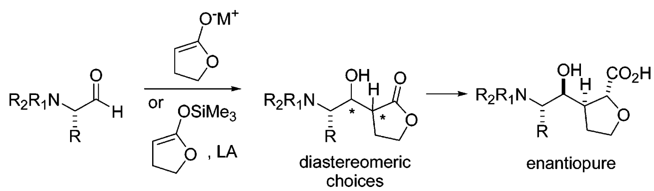

The synthesis of diastereomeric 3-substituted-tetrahydrofuran 2-carboxylic acids in enantiopure form was achieved relying on aldol condensations of N-substituted α-amino aldehydes with enolates and enol silyl ethers of γ-butyrolactone. Catalytic YbFOD leads to a high yield of a *syn/syn*-α-amino alcohol isomer. This was used as a constrained THF subunit in the synthesis of a peptidomimetic intended as an inhibitor of the enzyme BACE1, which is implicated in the cascade of events leading to plaque formation in Alzheimer's disease.

Introduction

The advent of structure-based design of enzyme inhibitors has instigated extensive studies on conceptually novel approaches to peptidomimetic motifs.[1] One of the more commonly used replacements for a scissile bond in a specific dipeptide portion of a peptidic inhibitor is the hydroxyethylene isostere, especially in conjunction with aspartic proteases.[2] For example, the potent synthetic heptapeptide inhibitor of β-secretase (BACE1, memapsin-2) OM99-2[3] has such a hydroxyethylene subunit as part of its structure (Figure 1). The length of this subunit corresponds to that of a Leu-Ala dipeptide, in which the central amide bond is replaced by an S-hydroxyethylene isostere. Thus, OM99-2 can be considered as a pseudo-octapeptide encompassing a central unnatural γ-amino acid. BACE1 is an important membrane-bound enzyme that initiates the formation of β-amyloid peptide from the amyloid precursor protein. A cascade of events follow, ultimately leading to plaque formation in the brain.[4] The enzyme has been considered as an ideal target for small

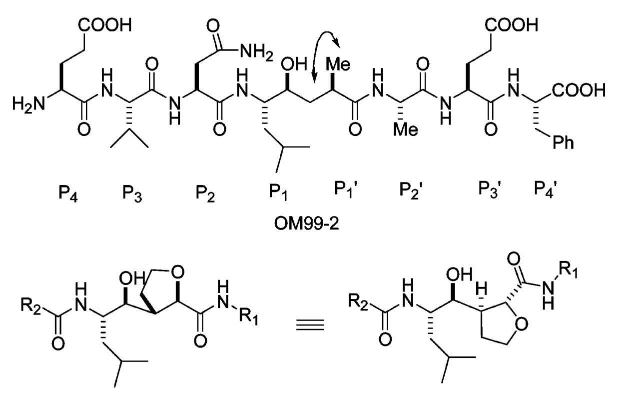

FIGURE 1. Tang–Ghosh inhibitor OM99-2 of β-secretase (BACE1) and proposed P_1' constrained oxacyclic hydroxyethylene isosteres.

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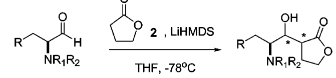
molecule inhibitors, with the objective of developing a drug for Alzheimer's disease.[5] X-ray crystal structures of OM99-2 and close derivatives thereof bound to BACE1[3,6] show the critical role of the hydroxyl group at the P_1 site for interaction with the two Asp residues at the catalytic site. Extensive SAR studies on OM99-2 has instigated much interest in the synthesis of smaller, nonpeptidic inhibitors of the enzyme.[6,7]

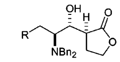
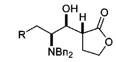
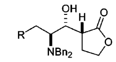
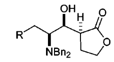
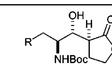
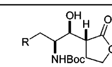
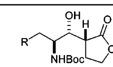
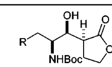
We have previously reported on the design and synthesis of a number of prototypical enzyme inhibitors in therapeutically relevant areas.[8] Herein we report on our results of the stereoselective synthesis of P_1' constrained oxacyclic variants[9] of the hydroxyethylene isostere present in the Tang–Ghosh pseudo-octapeptide OM99-2.[3]

Molecular modeling suggested that such a P_1' constrained oxacycle bridging the *C*-methyl group with the adjacent methylene carbon shown as a stereochemically defined structure in Figure 1 would not unduly affect the conformation of OM99-2 seen in the X-ray structure. On the basis of this premise, we set out to study methods for the stereoselective synthesis of a 2,3-trans-substituted tetrahydrofuranyl δ-amino acid motif as an integral part of a truncated version of OM99-2 (Figure 1).

TABLE 1. Stereoselective Aldol Additions



1a-d

Entry	R	 3a-c	 4a-c	 5a-c	 6a-c
1[a]	*i*-Pr, **1a**	85 (X-ray)	7	8	0
2[a]	H, **1b**	76	2	13	6
3[a]	Ph, **1c**	62	12	13	13
		 3d	 4d	 5d	 6d
4[b]	*i*-Pr, **1d**	45	48	7	0

[a] Ratios of isomers determined from HPLC analysis. [b] Ratios of isomers determined from isolated weights of individual products.

Results and Discussion

Our initial studies focused on the aldol condensation of a series of aldehydes readily prepared from *N*,*N*-dibenzyl L-amino acids[10] with the lithium enolate of γ-butyrolactone **2**.[11,12] As seen in Table 1, the major products derived from *N*,*N*-dibenzyl derivatives of L-leucinal **1a**, L-alaninal **1b**, and L-phenylalaninal **1c** were the corresponding *anti*/*anti*-aldol 3-furanone products **3a**–**c**, obtained in excellent to good yields. Only minor amounts of the diastereomers **4a** and **5a** were formed (Table 1, entry 1). Minor quantities of the other diastereomers **4b**,**c**, **5b**,**c**, and **6b**,**c** were formed in the case of **1b** and **1c**, respectively. (Table 1, entries 2 and 3). The relative stereochemistry of several aldol products was confirmed by single-crystal X-ray analysis.

With the *N*-Boc L-leucinal **1d**, equal amounts of the adducts **3d** and **4d** with only a minor amount of **5d** were isolated. The desired 3-furanone derivative **6d** was not formed under the lithium enolate conditions described above. The relative stereochemistry of the adduct **3d** was determined by transformation to the corresponding pyrrolidinone **7** and correlated with **3a** of known configuration (X-ray) as shown in Scheme 1.

We next explored the Mukaiyama aldol reaction[13] of the same aldehydes with the trimethylsilyl enol ether of

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SCHEME 1

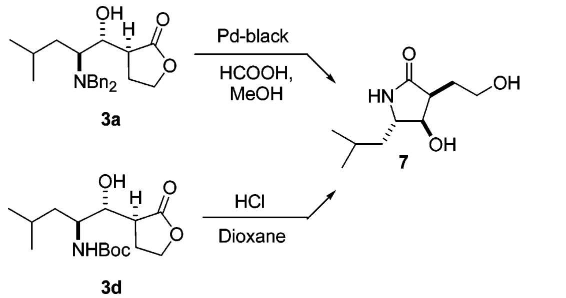
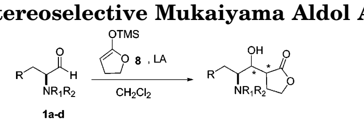
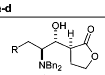
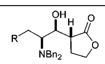
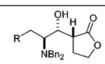
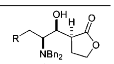
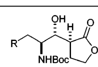
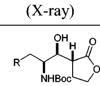
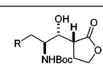
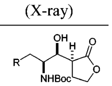


TABLE 2. Stereoselective Mukaiyama Aldol Additions

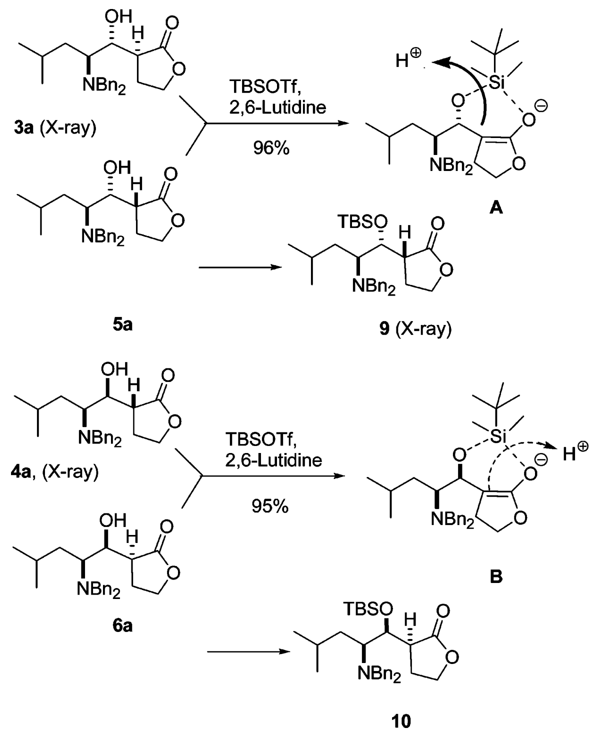


Entry	R	Lewis acid	 **3a-c**	 **4a-c**	 **5a-c**	 **6a-c**
1 [a]	*i*-Pr, **1a**	$EtAlCl_2$ [c]	10	0	90	0
2 [a]	*i*-Pr, **1a**	BF_3 etherate [c]	0	0	91	9
3 [a]	*i*-Pr, **1a**	$ZnBr_2$ [c]	3	0	91	6
4 [a]	*i*-Pr, **1a**	$MgBr_2$ [d]	0	0	78	22
5 [a]	*i*-Pr, **1a**	YbFOD [d]	0	23	45	32
6 [a]	*i*-Pr, **1a**	$Cu(OTf)_2$ [d]	0	0	21	79
7 [a]	H, **1b**	YbFOD [d]	14	11	63 (X-ray)	12
8 [a]	H, **1b**	$Cu(OTf)_2$ [d]	5	10	8	77 (X-ray)
9 [a]	Ph, **1c**	YbFOD [d]	2	27	42	29
10 [a]	Ph, **1c**	$Cu(OTf)_2$ [d]	0	14 (X-ray)	8	78 (X-ray)
			 **3d**	 **4d**	 **5d**	 **6d**
11 [b]	*i*-Pr, **1d**	YbFOD [d]	0	7	0	93

[a] Ratios of isomers determined from HPLC analysis. [b] Ratios of isomers determined from isolated weights of individual products. [c] The reaction was done at −78 °C. [d] The reaction was done at room temperature with a catalytic quantity (5 mol %) of reagent.

γ-butyrolactone **8** in the presence of a variety of Lewis acids in stoichiometric or catalytic quantities.[14] The distribution of diastereomeric adducts was drastically changed compared to that of the lithium enolates, as seen in Table 2. Thus, with $EtAlCl_2$, $BF_3{\cdot}Et_2O$, $MgBr_2$, and $ZnBr_2$, the *syn*/*anti*-aldol product **5a** was the major isomer (Table 2, entries 1−4). A reversal in favor of the desired *syn*/*syn*-aldol **6a** was observed with $Cu(OTf)_2$ (Table 2, entry 6). This trend was also evident in the case of **1b** (Table 2, entry 8) and **1c** (Table 2, entry 10). Using catalytic quantities of YbFOD[15] diminished the diastereoselectivity with all three aldehydes to give mixtures

SCHEME 2



of the *anti*/*syn*-, *syn*/*anti*-, and *syn*/*syn*-isomers **4a**−**c**, **5a**−**c**, and **6a**−**c**, respectively, in good yields. On the other hand, YbFOD was the preferred catalyst for the synthesis of the desired isomer **6d** in the case of the *N*-Boc L-leucinal.

We observed an interesting interconversion of diastereomers in our attempts to convert the isomeric **3a**−**c** adducts into the corresponding O-TBS ethers (Scheme 2). Thus, treatment of **3a** (or **5a**) with TBS triflate in the presence of 2,6-lutidine afforded the *syn*/*anti*-isomer **9** in 96% yield (X-ray). Similarly, treatment of **4a** (or **6a**) under the same conditions gave the *syn*/*syn*-isomer **10** in 95% yield. In each case, complete epimerization at the furanone (C-3) branching site had taken place with isomers **3a** and **4a**. This can be rationalized on the basis of initial formation of a TBS silyl ether, followed by enolate formation and concomitant participation of the enolate hydroxyl group to give a transient hypervalent dioxasilicon intermediate.[16] Protonation from the least hindered face affords the respective products **9** and **10**, as illustrated in the perspective drawings A and B (Scheme 2). The same trend was observed in the case of the TBS ethers of **3b** and **3c**, which were converted to the diastereoimeric TBS ethers **5b** and **5c**, respectively. Similarly, **4b** and **4c** afforded **6b** and **6c** (as TBS ethers).

The stereoselective formation of the major products **3a**−**c** in the Li enolate aldol reaction with the *N*,*N*-dibenzyl aldehydes **1a**−**c** can be explained on the basis of a preferred *Re*-face attack by the enolate in a Zimmerman−Traxler-type transition state (Figure 2A). The observed *anti*/*anti*-aldol products **3a**−**c** (Table 1, entries 1−3) may be explained by considering a Felkin−Anh model with a "pseudoequatorial" orientation of the large *N*,*N*-dibenzylamino group in A (as compared to a *Si*-face

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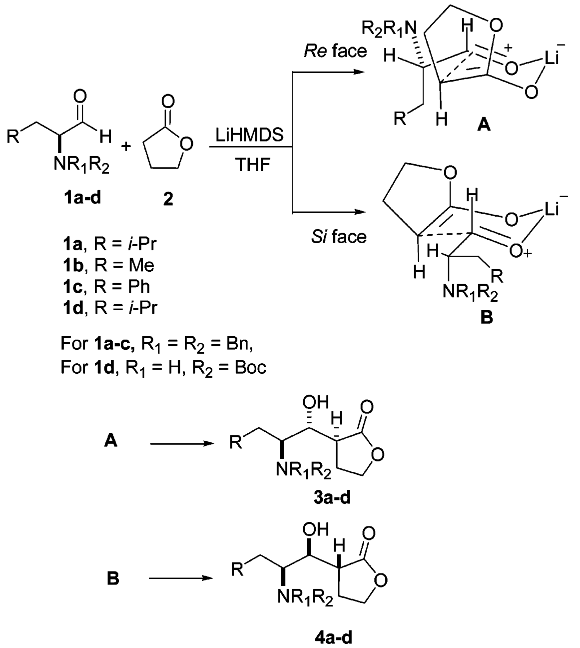

FIGURE 2. Possible transition state models for aldol additions.

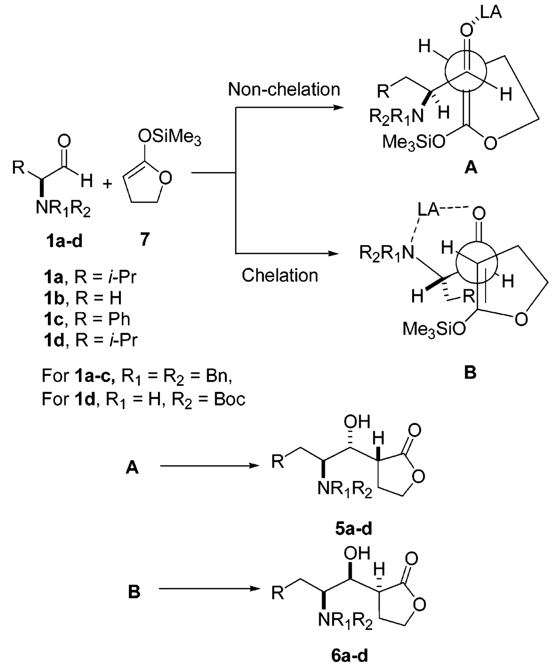

FIGURE 3. Possible chelated and nonchelated transition state models for Mukaiyama aldol condensations.

attack B). The nature of the side chain does not have a significant stereodirecting influence, since the major isomer is the *anti*/*anti*-aldol product from **1a**−**c**, albeit with some differences in the case of phenyl analogue **1c**. The equal amounts of diastereomers **3d** and **4d** in the case of the *N*-Boc-protected aldehydes (Table 1, entry 4) may be due to loss of stereodifferentiation caused by internally chelated intermediates involving the *N*-Boc group. The same trend has been observed in related cases by Reetz and co-workers.[17]

The Mukaiyama aldol product favoring the *syn*/*anti*- and *syn*/*syn*-aldol isomers **5a**−**c** or **6a**−**c** can be rationalized based on whether nonchelated or chelated transition states are involved, respectively.[14,15] Thus, with the *N*,*N*-dibenzyl aldehydes **1a**−**c** and monodentate Lewis acids such as $EtAlCl_2$ and BF_3 etherate, the major product **5a** can arise from nonchelated intermediate A (Figure 3). The bidentate $MgBr_2$ gave a ca. 3:1 ratio of **5a** and **6a**, reflecting a contribution from the chelated transition state, leading to intermediate B (Figure 3, Table 2, entry 4). Curiously, $ZnBr_2$ led to a preponderance of **5a**, although a chelated transition state may be expected (Figure 3, Table 2, entry 3).[10c] In the presence of $Cu(OTf)_2$, the *syn*-aldol isomer **6a** was formed, regardless of the nature of the aldehyde, presumably arising from a chelated transition state (Table 2, entries 6, 8, and 10).

Using catalytic quantities of the lanthanide YbFOD led to mixtures of **4a**−**c**, **5a**−**c**, and **6a**−**c** (Table 2, entries 5, 7, and 9). The nature of the side chain seems not to have a significant effect on the ratio of isomers, although a preference for **5b** was observed compared to the larger aldehyde precursors (Table 2, entries 5, 7, and 9). On the other hand, catalytic YbFOD led to an excellent stereoselectivity in favor of the desired *syn*/*syn*-aldol isomer **6d** in the case of the *N*-Boc L-leucinal **1d**, presumably arising from a kinetically controlled addition proceeding via B (Figure 3).

From a practical standpoint, we were pleased that, depending on the type of catalyst or method used, each of the four possible diastereomers of the adducts **3**−**6** could be obtained in preparatively significant amounts. More rewarding, however, was the success of the Mukaiyama aldol reaction in the presence of a catalytic quantity of YbFOD to furnish the desired *syn*/*syn*-*N*-Boc lactone **6d** in high yield.

For the purposes of obtaining the intended P_1' constrained motif (Figure 1), we opted to proceed with the *syn*/*syn*-*N*,*N*-dibenzyl lactone **10**, obtained from **6a** and **4a** via TBS ether formation in excellent overall yield. Treatment of **10** with lithio dithiane[18] at −78 °C led to a mixture of ketone **11a** and the hemiacetals **11b**,**c** (Scheme 3). Reduction of this mixture with $NaBH_4$ gave essentially a single isomer **12**. Intramolecular cycloetherification under Mitsunobu[19] conditions led to **13** in 87% yield, whose structure and absolute configuration were ascertained from a single-crystal X-ray analysis. It follows that the reduction of the ketone with $NaBH_4$ had given the 2*S*-alcohol stereoselectively and that the cycloetherification had proceeded without inversion of configuration, as would be expected from the activation of a primary alcohol. An alternative route involving cycloetherification by tosylation of the primary alcohol in **12** and intramolecular displacement gave **13** in only 50% yield even after 24 h. Treatment of **13** with $HgCl_2/CaCO_3$ or CH_3I/Na_2CO_3 did not give the desired aldehyde. However, a mixture of HgO and BF_3 etherate[20] cleaved the dithianyl

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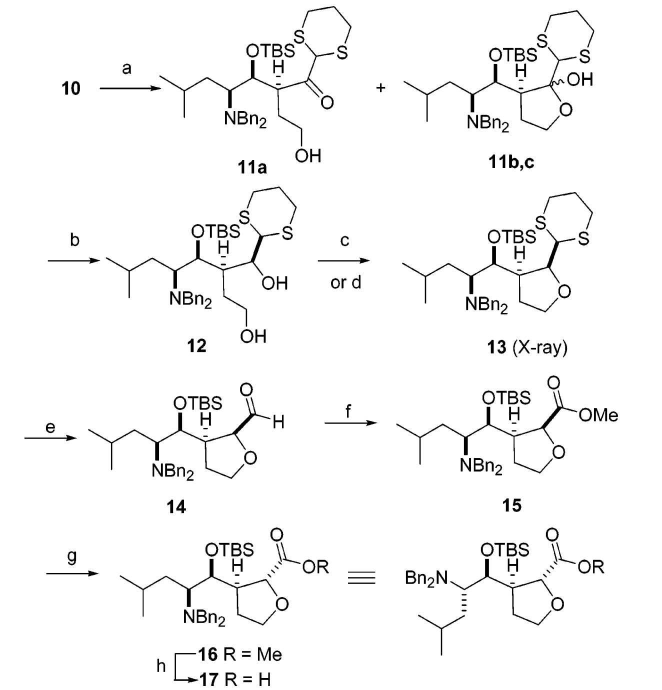
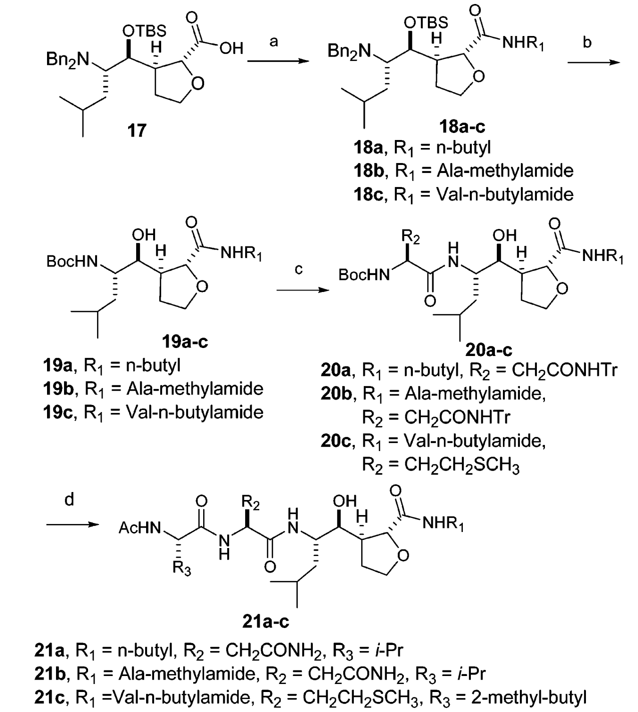
SCHEME 3[a]



[a] Reagents and conditions: (a) 1,3-Dithiane, *n*-BuLi, THF, −78 to 0 °C; (b) $NaBH_4$, MeOH, room temperature, 58%, two steps; (c) PPh_3, DEAD, THF, room temperature, 87%; (d) TsCl, pyridine, 0 °C to room temperature 50%; (e) HgO, BF_3 etherate, CH_3CN/H_2O, room temperature, 84%; (f) (i) $NaOCl_2$, 2-methyl-2-butene, buffer, CH_3CN/H_2O, room temperature, 52%; (ii) CH_2N_2; (g) NaOMe/MeOH, reflux; (h) NaOH, $MeOH/H_2O$, 80% for two steps.

SCHEME 4[a]



[a] Reagents and conditions: (a) *n*-Butylamine or L-Ala-methylamide or L-Val-*n*-butylamide, PyBop, *i*-Pr_2NEt, DCM, 0 °C to room temperature; (b) (i) Pd-black, HCOOH/MeOH; (ii) Boc_2O, $NaHCO_3$, MeOH; (iii) TBAF; (c) (i) HCl in dioxane (4 M); (ii) *N'*-Tr-L-AspOH or *N*-Boc-MetOH, PyBOP, DIEA, DCM, 0 °C to room temperature; (d) Ac-L-ValOH or Ac-L-LeuOH, HOBT, EDC, DCM/H_2O, 0 to 5 °C; for **20a**,**b**, TFA/H_2O, room temperature.

group and produced **14** in high yield. Oxidation to the acid with $NaClO_2$,[21] and esterification with CH_2N_2 gave **15**, which was epimerized to **16** with NaOMe and MeOH. The desired acid **17** was obtained by alkaline hydrolysis and separated from the minor unepimerized isomer by column chromatography. An alternative synthesis of a precursor to **16** using nitroaldol methodology under Shibasaki catalytic conditions[22] was recently reported by us.[23]

With a preparative route to the P_1/P_1' constrained tetrahydrofuran amino acid **17** in hand, we proceeded to prepare three prototypical truncated mimics of OM99-2. Extensive SAR studies on OM99-2 in conjunction with X-ray crystallography of complexes with BACE1 have shown that certain amino acid components of the heptapeptide can be changed without significant loss of activity.[6c] For example, the P2′−P4′ units can be truncated and replaced by a simple alkylamide chain. The Asp subunit has also been changed to Met in an effort to decrease the polar nature of the inhibitor. We therefore adapted these changes to our constrained oxacyclic variant of OM99-2 to ultimately have three prototypical and diversely substituted mimics. Thus, the free acid **17** was coupled with *n*-butylamine, with L-Ala methylamide, and L-Val *n*-butylamide to give **18a**−**c**, respectively (Scheme 4). Catalytic transfer hydrogenation removed the *N*,*N*-dibenzyl group, and the resulting amine was protected as the *N*-Boc derivative before treatment with TBAF to cleave the silyl ether group, to afford **19a**−**c** in excellent overall yield. Removal of the *N*-Boc group and coupling with *N'*-Tr-BocAspOH, mediated by PyBop, afforded **20a** and **20b**. In the case of **19c**, coupling was done with BocMetOH to give **20c**. Further extension of **20a** and **20b** with AcValOH, followed by acid treatment, gave the pseudopeptides **21a** and **21b**, respectively (Scheme 4). Similarly, extension of **20c** with AcLeuOH gave **21c**, thus completing the intended series of oxacyclic analogues of OM99-2. To avoid epimerization, we found EDC/HOBT in a two-phase system (CH_2Cl_2/H_2O) to be advantageous in the preparation of **21a**−**c**.

Compounds **21a**−**c** were tested for their ability to inhibit BACE1. Weak inhibitory activity was observed only with **21c** (IC_{50} = 8.5 μM).[24] Although **21a** was inactive against BACE1, it showed inhibition against pepsin and cathepsin D with IC_{50} values of 0.17 and 0.28 μM, respectively. Compound **21b** was devoid of activity with all three enzymes. The carbocyclic analogue of **21c** in which the tetrahydrofuran ring is replaced by a cyclopentane and a cyclopentanone are low nanomolar inhibitors of BACE1.[24] The substantial loss of activity

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when a cyclopentane is replaced by an oxacyclic analogue might be the result of repulsive interactions of the ring oxygen atom with amide carbonyls in the active site, thus deviating from optimal conformations for binding. Further studies aimed at the modification of the acyclic backbone with azacyclic constrained isosteres OM99-2 are reported in the companion article.[25]

Experimental Section

(3*S*)-3-[(1*R*,2*S*)-2-Dibenzylamino-1-hydroxy-4-methyl-pentyl]-dihydro-furan-2-one (3a). Method A, LiHMDS: To a dry flask containing LiHMDS (1.4 mL, 1.0 M in THF) was added THF (5 mL), and the solution was cooled to −78 °C. γ-Butyrolactone (100 μL, 1.30 mmol) was added dropwise, and the reaction mixture was stirred for 0.5 h. A cold solution of **1a** (265 mg, 0.90 mmol) in THF (10 mL) was added dropwise by cannula, and the reaction mixture was stirred for a further 2 h at −78 °C before quenching with saturated aqueous NH_4Cl (10 mL). The reaction mixture was extracted with EtOAc (15 mL × 3), and the organic phase was dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography (20% EtOAc in hexanes) to afford **3a** (252 mg, 66%) as a white solid; mp 114−115 °C; $[\alpha]_D$ −27.5 (*c* 1.1, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.55 (3H, d, J = 6.4 Hz), 0.96 (3H, d, J = 6.7 Hz), 1.04 (1H, m), 1.90 (2H, m), 2.02 (2H, m), 2.00 (1H, m), 2.58 (2H, m), 3.55 (2H, d, J = 14.0 Hz), 4.02 (2H, d, J = 14.0 Hz), 4.08 (1H, s), 4.12 (1H, m), 4.28 (1H, d, J = 9.5 Hz), 4.34 (1H, m), 7.31 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 22.1, 24.5, 24.6, 26.1, 34.5, 42.9, 54.9, 56.4, 67.1, 70.4, 127.3, 128.6, 129.3, 141.1, 181.0; IR (film) 3499, 3028, 2953, 1753; MS (FAB) *m/z* 382 [M + 1]$^+$; HRMS calcd for $C_{24}H_{32}NO_3$ [M + 1]$^+$ 382.2382; found 382.2373.

(3*S*)-3-[(1*R*,2*S*)-2-Dibenzylamino-1-hydroxy-propyl]-dihydro-furan-2-one (3b). The compound was prepared from **1b** as described above (Method A, LiHMDS). Purification by column chromatography (20% EtOAc in hexanes) gave **3b** as a colorless oil (52%); $[\alpha]_D$ +28.3 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.18 (3H, d, J = 6.8 Hz), 1.72 (1H, m), 1.88 (1H, m), 2.75 (1H, m), 2.90 (1H, m), 3.60 (2H, d, J = 13.8 Hz), 3.82 (1H, s), 3.84 (2H, d, J = 13.8 Hz), 3.90 (1H, dd, J = 7.2 and 4.5 Hz), 4.07 (1H, m), 4.27 (1H, td, J = 8.8 and 1.5 Hz), 7.20−7.37 (10 H, m); ^{13}C NMR ($CDCl_3$): δ 8.3, 26.3, 42.5, 55.1, 55.3, 67.1, 74.5, 127.3, 128.6, 128.9, 129.2, 140.8, 179.8; IR (film) 3495, 3027, 2934, 1754; MS (FAB) *m/z* [M + 1]$^+$; HRMS calcd for $C_{21}H_{26}NO_3$ [M + 1]$^+$ 340.1912; found 340.1872.

(3*R*)-3-[(1*S*,2*S*)-2-Dibenzylamino-1-hydroxy-propyl]-dihydro-furan-2-one (4b). The compound was isolated as the second isomer in the preparation of **3b**. Purification by column chromatography (20% EtOAc in hexanes) gave **4b** as a colorless oil (19%); $[\alpha]_D$ +18.8 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.15 (3H, d, J = 6.7), 2.05 (2H, m), 2.73 (1H, td, J = 8.3 and 3.6 Hz), 3.24 (1H, m), 3.36 (2H, d, J = 13.2 Hz), 3.66 (1H, dd, J = 8.2 and 3.6 Hz), 3.86 (2H, d, J = 13.2 Hz), 4.13 (1H, dd, J = 15.7 and 7.2 Hz), 4.31 (1H, dd, J = 15.5 and 7.2 Hz), 4.58 (1H, br), 7.23−7.33 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 9.1, 26.9, 41.3, 54.2, 54.9, 67.7, 74.1, 127.7, 128.9, 129.6, 139.4, 178.1; R (film) 3500, 3028, 2918, 1766; MS (EI) *m/z* 339.1 [M + 1]$^+$; HRMS calcd for $C_{21}H_{25}NO_3$ [M + 1]$^+$ 339.1834; found 339.1834.

(3*S*)-3-[(1*R*,2*S*)-2-Dibenzylamino-1-hydroxy-3-phenyl-propyl]-dihydro-furan-2-one (3c). The compound was prepared from **1c** as described above (Method A, LiHMDS). Purification by column chromatography (20% EtOAc in hexanes) gave **3c** as a colorless oil (46%); $[\alpha]_D$ +23.2 (*c* 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.50 (2H, m), 2.24 (1H, m), 2.92 (1H, m), 3.08 (2H, m), 3.83 (4H, s), 3.89 (1H, m), 4.13 (1H, s), 4.20 (1H, d, J = 9.04), 4.62 (1H, m), 7.15−7.28 (15 H, m); ^{13}C NMR ($CDCl_3$) δ 26.0, 30.9, 43.2, 55.1, 61.0, 67.0, 73.5, 126.5, 127.2, 128.6, 128.7, 129.0, 130.0, 140.7, 141.0, 180.6; IR (film) 3506, 3062, 3026, 2916, 1751; MS (FAB) *m/z* 416.2 [M + 1]$^+$; HRMS calcd for $C_{27}H_{29}NO_3$ [M + 1]$^+$ 416.2225; found 416.2216.

(3*R*)-3-[(1*S*,2*S*)-2-Dibenzylamino-1-hydroxy-3-phenyl-propyl]-dihydro-furan-2-one (4c). The compound was isolated as the second isomer in the preparation of **3c**. Purification by column chromatography (20% EtOAc in hexanes) gave **4c** as a colorless oil (10%); mp 147−148 °C; $[\alpha]_D$ +18.2 (*c* 0.4, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.07 (1H, m), 1.59 (2H, m), 2.14 (1H, m), 2.59 (1H, dd, J = 14.3 and 8.8 Hz), 2.85 (1H, m), 3.28 (1H, dd, J = 14.2 and 3.9 Hz), 3.42 (2H, d, J = 13.0 Hz), 3.80 (1H, m), 4.04 (3H, m), 4.24 (1H, dd, J = 8.95 and 1.6 Hz), 4.71 (1H, s), 7.13−7.39 (15 H, m); ^{13}C NMR ($CDCl_3$) δ 20.9, 32.3, 43.1, 53.9, 62.0, 67.5, 69.5, 127.1, 128.0, 129.1, 129.3, 129.3, 129.6, 138.6, 139.9, 178.8; IR (film) 1770; MS (FAB) *m/z* 416.2 [M + 1]$^+$; HRMS calcd for $C_{27}H_{29}NO_3$ [M + 1]$^+$ 416.2225; found 416.2223.

(3*S*)-3-[(1*R*,2*S*)-2-*tert*-Butoxycarbonylamino-1-hydroxy-4-methyl-pentyl]-dihydro-furan-2-one (3d). The compound was prepared from **1d** as described above (Method A, LiHMDS). Purification by column chromatography (30% EtOAc in hexanes) gave **3d** as a colorless oil (24%); $[\alpha]_D$ −24.1 (*c* 0.3, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.92 (3H, d, J = 6.6 Hz), 0.94 (3H, d, J = 6.7 Hz), 1.13 (1H, m), 1.43 (9H, s), 1.54 (1H, m), 1.69 (1H, m), 2.28 (2H, m), 2.49 (1H, m), 2.60 (1H, m), 3.67 (1H, t, J = 9.6 Hz), 3.85 (1H, m), 4.24 (1H, m), 4.35 (1H, t, J = 7.0 Hz), 4.43 (1H, t, J = 8.8 Hz), 4.95 (1H, d, J = 9.4 Hz); ^{13}C NMR ($CDCl_3$) δ 180.4, 156.3, 79.8, 74.8, 67.6, 50.9, 42.2, 37.3, 28.8, 25.6, 24.9, 24.3, 21.9; IR (film) 3391, 2958, 2871, 1759, 1698, 1512; MS (FAB) *m/z* 302.1 [M + 1]$^+$; HRMS calcd for $C_{15}H_{28}NO_5$ [M + 1]$^+$ 302.1967; found 302.1954.

(3*R*)-3-[(1*S*,2*S*)-2-*tert*-Butoxycarbonylamino-1-hydroxy-4-methyl-pentyl]-dihydro-furan-2-one (4d). The compound was isolated as the second isomer in the preparation of **3d**. Purification by column chromatography (30% EtOAc in hexanes) gave **4d** as a colorless oil (27%); $[\alpha]_D$ −37.3 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.93 (3H, d, J = 2.6 Hz), 0.94 (3H, d, J = 2.6 Hz), 1.34 (1H, m), 1.44 (9H, s), 1.64 (2H, m), 1.98 (1H, m), 2.61 (1H, m), 2.64 (1H, m), 3.68 (2H, m), 4.24 (1H, m), 4.43 (2H, m), 4.79 (1H, d, J = 10.2 Hz); ^{13}C NMR ($CDCl_3$) δ 22.71, 23.3, 25.2, 26.3, 28.7, 42.1, 50.4, 67.7, 74.2, 79.7, 81.6, 156.5; IR (film) 3453, 3360, 2960, 2871, 1755, 1707, 1503, 1455; MS (EI) *m/z* 301.2 [M]$^+$; HRMS calcd for $C_{15}H_{27}NO_5$ [M]$^+$ 301.1889; found 301.1901.

(3*R*)-3-[(1*R*,2*S*)-2-*tert*-Butoxycarbonylamino-1-hydroxy-4-methyl-pentyl]-dihydro-furan-2-one (5d). The compound was isolated as the third isomer in the preparation of **3d**. Purification by column chromatography (30% EtOAc in hexanes) gave **5d** as a white solid (4%); $[\alpha]_D$ −4.2 (*c* 0.7, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.95 (3H, d, J = 6.5 Hz), 0.98 (3H, d, J = 6.6 Hz), 1.27 (1H, m), 1.45 (9H, s), 1.60 (1H, m), 1.71 (1H, m), 2.40 (1H, m), 2.50 (1H, m), 2.81 (1H, m), 3.74 (1H, m), 3.99 (1H, dd, J = 7.4 and 2.2 Hz), 4.22 (1H, dd, J = 16.4 and 9.1 Hz), 4.38 (1H, m), 4.41 (1H, m); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.7, 24.1, 25.2, 28.7, 41.1, 43.3, 52.3, 67.8, 73.6, 80.3, 156.7, 179.8; IR (film) 3354, 2958, 1758, 1607, 1524, 1367; MS (FAB) *m/z* 302.2 [M + 1]$^+$; HRMS calcd for $C_{15}H_{28}NO_5$ [M + 1]$^+$ 302.1967; found 302.1968.

(3*R*)-3-[(1*R*,2*S*)-2-Dibenzylamino-1-hydroxy-4-methyl-pentyl]-dihydro-furan-2-one (5a). Method B, $EtAlCl_2$: To a solution of the aldehyde **1a** (162 mg, 0.55 mmol) in CH_2Cl_2 (5 mL) at −78 °C was added $EtAlCl_2$ (1.0 M in hexanes, 0.55 mL), and the reaction mixture was stirred for 10 min. (4,5-Dihydro-furan-2-yloxy)-trimethylsilane (**7**) (130 mg, 0.82 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the reaction mixture was stirred at −78 °C for 2 h, after which it was quenched by adding saturated aqueous NH_4Cl (10 mL), then warmed to room temperature. Extraction with EtOAc (15 mL × 3) and concentration gave an oil that was redissolved in THF (10 mL), aqueous HCl (1%, 1.0 mL) was added, and the solution was stirred for 30 min before it was neutralized with saturated $NaHCO_3$ and extracted with EtOAc (3 × 10 mL).

(25) Hanessian, S.; Yun, H.; Hou, Y.; Tintelnot-Blomley, M. *J. Org. Chem.* **2005**, *70*, 6746.

Concentration and purification by column chromatography (20% EtOAc in hexanes) gave **5a** as a colorless oil (162 mg, 78%); $[\alpha]_D$ +26.2 (*c* 0.50, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.84 (1H, m), 0.98 (6H, m), 1.55 (2H, m), 1.93 (2H, m), 2.40 (1H, m), 2.51 (1H, m), 3.23 (1H, t, J = 9.4), 3.40 (2H, d, J = 13.2 Hz), 3.70 (2H, d, J = 13.2 Hz), 3.90 (1H, dd, J = 8.7 and 16.7 Hz), 4.16 (1H, m), 4.25 (1H, m), 7.30 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 21.0, 23.3, 24.0, 26.7, 36.7, 44.2, 54.6, 57.2, 67.7, 71.9, 127.5, 128.7, 129.9, 140.4, 181.0; IR (film) 3509, 3028, 2956, 1753. MS (FAB) *m/z* 382 [M + 1]$^+$; HRMS calcd for $C_{24}H_{32}NO_3$ [M + 1]$^+$ 382.2382; found 382.2392.

(3*S*)-3-[(1*S*,2*S*)-2-Dibenzylamino-1-hydroxy-4-methyl-pentyl]-dihydro-furan-2-one (6a). Method C, Cu(OTf)$_2$: To a solution of the aldehyde **1a** (26 mg, 0.087 mmol) in CH_2Cl_2 (1 mL) was added Cu(OTf)$_2$ (35 mg, 0.087 mmol) at room temperature, and the reaction mixture was stirred for 15 min. (4,5-Dihydro-furan-2-yloxy)-trimethyl-silane (**7**) (25 mg, 0.174 mmol) was added in one portion, and the reaction mixture was stirred at room temperature until full consumption of the starting aldehyde (5 h). Saturated $NaHCO_3$ (2 mL) was added, and the reaction mixture was extracted with EtOAc (3 × 5 mL). The organic phase was concentrated, the residue was redissolved in THF (10 mL), aqueous HCl (1%, 1.0 mL) was added, and the solution was stirred for 30 min before it was neutralized with $NaHCO_3$, extracted with EtOAc (3 × 10 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated, and the residue was purified by column chromatography (20% EtOAc in hexanes) to afford **6a** as a colorless oil (16 mg, 50%); $[\alpha]_D$ +0.8 (*c* 0.5, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.96 (6H, m), 1.25 (2H, m), 1.68 (3H, m), 2.58 (2H, m), 3.45 (2H, d, J = 13.2 Hz), 3.90 (2H, d, J = 13.2 Hz), 4.04 (1H, m), 4.23 (1H, m), 4.71 (1H, m), 7.30 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 21.3, 23.4, 23.7, 27.1, 36.3, 42.9, 54.6, 57.8, 67.6, 70.1, 127.9, 129.0, 129.7, 179.1; IR (film) 3400, 2957, 1769, 1453; MS (FAB) *m/z* [M + 1]$^+$; HRMS calcd for $C_{24}H_{32}NO_3$ [M + 1]$^+$ 382.2382; found 382.2372.

(3*S*)-3-[(1*S*,2*S*)-2-Dibenzylamino-1-hydroxy-propyl]-dihydro-furan-2-one (6b). The compound was prepared from **1b** as described above (Method C, Cu(OTf)$_2$). Purification by column chromatography (20% EtOAc in hexanes) gave **6b** as a white solid (29%); mp 121−122 °C; $[\alpha]_D$ +20.1 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.08 (3H, d, J = 6.6 Hz), 1.83 (2H, m), 2.54 (2H, m), 3.30 (2H, d, J = 13.1 Hz), 3.86 (2H, d, J = 13.1 Hz), 4.13 (2H, m), 4.22 (1H, m), 4.45 (1H, br), 7.26−7.38 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 8.3, 20.8, 39.7, 42.4, 53.6, 55.8, 67.6, 69.8, 127.9, 129.0, 129.5, 130.2, 138.8, 179.1; IR (film) 3370, 3028, 2968, 1770; MS (EI) *m/z* 339.1 [M + 1]$^+$; HRMS calcd for $C_{21}H_{25}NO_3$ [M + 1]$^+$ 339.1834; found 339.184723.

(3*R*)-3-[(1*S*,*S*)-2-Dibenzylamino-1-hydroxy-4-methyl-pentyl]-dihydro-furan-2-one (4a). Method D, YbFOD: To a solution of aldehyde **1a** (2.7 g, 9.11 mmol) in CH_2Cl_2 (100 mL) was added YbFOD (482 mg, 0.46 mmol, 5 mol %). After 5 min, (4,5-dihydro-furan-2-yloxy)-trimethyl-silane (**7**) (2.88 g, 18.22 mmol) was added in one portion. The reaction mixture was stirred under Ar until full consumption of the starting material (6 h), after which it was quenched with 10 mL of water, and the organic phase was dried with Na_2SO_4 and concentrated under reduced pressure. The residue was redissolved in THF (100 mL), aqueous HCl (1%, 10 mL) was added, and the solution was stirred for 30 min before it was neutralized with saturated $NaHCO_3$, extracted with EtOAc (3 × 100 mL), and dried with Na_2SO_4. The combined organic phase was concentrated, and the residue was purifed by column chromatography (20% EtOAc in hexanes) to afford **4a** as a white crystalline solid (798 mg, 23%); mp 143−144 °C; $[\alpha]_D$ +27.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.91 (1H, s), 0.95 (3H, d, J = 6.4 Hz), 1.05 (3H, d, J = 6.4 Hz), 1.44 (1H, m), 1.55 (1H, m), 1.73 (1H, m), 1.80 (1H, m), 2.65 (1H, m), 3.00 (1H, m), 3.35 (2H, d, J = 13.2 Hz), 3.66 (1H, dd, J = 4.04 and 7.58 Hz), 3.93 (1H, m), 4.00 (1H, b), 4.16 (1H, m), 4.67 (1H, s), 7.29 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 22.5, 24.4, 25.9, 26.2, 33.5, 41.2, 55.8, 56.2, 67.4, 74.2, 127.4, 128.6, 129.8, 140.9, 181.1; IR (film) 3469, 3028, 2955, 1748; MS (FAB) *m/z* 382.2 [M + 1]$^+$; HRMS calcd for $C_{24}H_{32}NO_3$ [M + 1]$^+$ 382.2382; found 382.2362.

(3*R*)-3-[(1*R*,2*S*)-2-Dibenzylamino-1-hydroxy-propyl]-dihydro-furan-2-one (5b). The compound was prepared from **1b** as described above (Method D, YbFOD). Purification by column chromatography (20% EtOAc in hexanes) gave **5b** as a white solid (55%); mp 158−159 °C; $[\alpha]_D$ +35.9 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.91 (1H, m), 1.21 (3H, d, J = 6.6 Hz), 1.80 (1H, m), 2.21 (1H, m), 2.62 (1H, m), 3.26 (1H, m), 3.30 (2H, d, J = 12.8 Hz), 3.71 (2H, d, J = 12.8 Hz), 3.96 (1H, dd, J = 16.3 and 9.2 Hz), 4.14 (2H, m), 7.26−7.33 (10 H, m); ^{13}C NMR ($CDCl_3$) δ 8.8, 20.6, 43.5, 54.5, 55.0, 67.7, 71.7, 127.6, 128.7, 128.8, 129.2, 129.6, 129.8, 140.1, 180.9; IR (film) 3469, 3028, 2917, 2807, 1753; MS (FAB) *m/z* 340.2 [M + 1]$^+$; HRMS calcd for $C_{21}H_{26}NO_3$ [M + 1]$^+$ 340.1912; found 340.1916.

(3*R*)-3-[(1*R*,2*S*)-2-Dibenzylamino-1-hydroxy-3-phenyl-propyl]-dihydro-furan-2-one (5c). The compound was prepared from **1c** as described above (Method D, YbFOD). Purification by column chromatography (20% EtOAc in hexanes) gave **5c** as a white solid (33%); mp 125−126 °C; $[\alpha]_D$ +35.7 (*c* 0.4, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.88 (1H, m), 1.61 (1H, m), 1.80 (1H, s), 2.93 (1H, m), 3.13 (1H, m), 3.24 (1H, m), 3.40 (2H, d, J = 12.9 Hz), 3.78 (2H, d, J = 11.64 Hz), 3.92 (1H, dd, J = 8.94 and 7.47 Hz), 4.13 (1H, td, J = 8.70 and 2.28 Hz), 4.39 (1H, d, J = 9.4 Hz), 7.14−7.39 (15 H, m); ^{13}C NMR ($CDCl_3$) δ 20.8, 31.4, 33.2, 43.8, 54.7, 61.8, 67.6, 71.9, 126.6, 127.6, 128.0, 128.7, 129.1, 129.3, 129.6, 129.8, 129.8, 139.9, 141.8, 180.6; IR (film) 3488, 3027, 2915, 1752; MS (FAB) *m/z* 416.2 [M + 1]$^+$; HRMS calcd for $C_{27}H_{28}NO_3$ [M + 1]$^+$ 416.2225; found 416.2229.

(3*S*)-3-[(1*S*,2*S*)-2-Dibenzylamino-1-hydroxy-3-phenyl-propyl]-dihydro-furan-2-one (6c). The compound was isolated as the second isomer in the preparation of **5c**. Purification by column chromatography (20% EtOAc in hexanes) gave **6c** as a white solid (20%); mp 140−141 °C; $[\alpha]_D$ +51.7 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.77 (1H, m), 1.09 (1H, m), 1.64 (1H, s), 2.75 (1H, m), 2.94 (1H, dd, J = 9.8 and 1.9 Hz), 3.17 (1H, m), 3.45 (2H, d, J = 13.1 Hz), 3.50 (1H, dd, J = 8.3 and 3.5 Hz), 3.84 (1H, m), 4.04 (1H, m), 4.23 (2H, m), 4.62 (1H, m), 7.19−7.36 (15 H, m); ^{13}C NMR ($CDCl_3$) δ 25.6, 30.5, 41.2, 56.0, 60.7, 67.3, 73.1, 126.5, 127.5, 128.7, 128.8, 129.0, 129.8, 129.9, 140.5, 140.7, 181.5; IR (film) 3471, 3026, 1748; MS (FAB) *m/z* 416.2 [M + 1]$^+$; HRMS calcd for $C_{27}H_{29}NO_3$ [M + 1]$^+$ 416.2225; found 416.2223.

(3*S*)-3-[(1*S*,2*S*)-2-tert-Butoxycarbonylamino-1-hydroxy-4-methyl-pentyl]-dihydro-furan-2-one (6d). The compound was prepared from **1d** as described above (Method D, YbFOD). Purification by column chromatography (30% EtOAc in hexanes) gave **6d** as a white solid (71%); mp 96−97 °C; $[\alpha]_D$ −48.9 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.93 (3H, d, J = 2.4 Hz), 0.94 (3H, d, J = 2.4 Hz), 1.34 (1H, m), 1.44 (9H, s), 1.64 (2H, m), 2.26 (1H, m), 2.53 (1H, m), 2.75 (1H, td, J = 6.0 and 3.4 Hz), 3.10 (1H, b), 3.75 (1H, m), 4.05 (1H, s), 4.21 (1H, m), 4.39 (1H, td, J = 7.5 and 2.3 Hz), 4.66 (1H, d, J = 8.6 Hz); ^{13}C NMR ($CDCl_3$) δ 22.4, 22.8, 23.6, 25.1, 28.7, 42.1, 44.7, 52.6, 67.7, 71.8, 80.0, 156.7, 179.3; IR (film) 3446, 2958, 2872, 1767, 1689, 1515; MS (EI) *m/z* 301.2 [M]$^+$; HRMS calcd for $C_{15}H_{27}NO_5$ [M]$^+$ 301.1889; found 301.1898.

(4*S*)-4-Hydroxy-(3*R*)-(2-hydroxy-ethyl)-(5*S*)-5-isobutyl-pyrrolidin-2-one (7). To a solution of **3a** (43 mg, 0.11 mmol) in MeOH (1.0 mL) was added HCOOH (100 μL). Pd-black (30 mg) was added, and the suspension was stirred at room temperature for 1.5 h. The catalyst was removed by filtration, and the filtrate was concentrated. The residue was dissolved in EtOAc, and the solution was washed with saturated $NaHCO_3$ and dried with Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (10% MeOH in CH_2Cl_2) to afford **7** as a colorless oil (15 mg, 70%): $[\alpha]_D$ −15.1 (*c* 0.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.96 (6H, d, J = 6.1 Hz), 1.37 (1H, m), 1.69 (1H, m), 2.00 (1H, m), 2.62 (1H, m), 3.56 (1H, m), 3.75 (1H, m), 3.86 (1H, m), 3.93 (1H, m), 4.15 (1H, d, J = 16.1 Hz); ^{13}C

NMR ($CDCl_3$) δ 22.3, 23.6, 25.5, 26.9, 43.2, 45.9, 60.4, 62.0, 74.6, 178.6; IR (film); HRMS (FAB) calcd for $C_{10}H_{19}NO_3$ [M + 1] 201.14; found 201.14.

(3*R*)-3-[(1*R*,2*S*)-1-(*tert*-Butyl-dimethyl-silanyloxy-2-dibenzylamino-4-methyl- pentyl)]-dihydro-furan-2-one (9). To a solution of the alcohol **3a** (312 mg, 0.82 mmol) in anhydrous CH_2Cl_2 (2 mL) at 0 °C was added 2,6-lutidine (202 μL, 2.05 mmol) followed by TBSOTf (282 μL, 1.23 mmol). The mixture was stirred at 0 °C for 1 h before it was quenched with aqueous NH_4Cl. The mixture was extracted with EtOAc (3 × 10 mL), and the combined organic phase was dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography (10% EtOAc in hexanes) to afford **9** as a crystalline solid (390 mg, 96%); mp 93−94 °C; $[\alpha]_D$ +9.4 (*c* 0.8, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.00 (3H, s), 0.10 (3H, s), 0.60 (1H, m), 0.85 (9H, s), 1.02 (6H, m), 1.58 (3H, m), 1.98 (1H, m), 2.52 (2H, m), 3.33 (1H, t, *J* = 10.2 Hz), 3.48 (2H, d, *J* = 13.0 Hz), 3.77 (2H, d, *J* = 13.6 Hz), 3.79 (1H, m), 4.13 (2H, m), 7.27 (10 H, m); ^{13}C NMR ($CDCl_3$) δ −3.8, −3.6, 18.6, 20.4, 23.0, 24.1, 26.3, 26.6, 37.3, 43.7, 54.8, 58.1, 67.3, 72.7, 127.5, 128.7, 130.1, 140.4, 180.6; IR (film) 3064, 2956, 2858, 1770; MS (FAB) *m/z* 496.3 $[M + 1]^+$; HRMS calcd for $C_{30}H_{44}NO_3Si$ $[M + 1]^+$ 496.3246; found 496.3251.

(3*S*)-3-[(1*S*,2*S*)-1-(*tert*-Butyl-dimethyl-silanyloxy-2-dibenzylamino-4-methyl-pentyl)]-dihydro-furan-2-one (10). The compound was prepared from **4a** or **6a** as a colorless oil (95%); $[\alpha]_D$ −34.2 (*c* 0.95, $CHCl_3$); ^1H NMR ($CDCl_3$): δ −0.10 (3H, s), −0.07 (3H, s), 0.82 (9H, s), 0.95 (6H, m), 1.49 (1H, m), 1.61 (2H, m), 1.77 (1H, m), 2.32 (1H, m), 2.36 (1H, m), 2.59 (1H, m), 2.68 (1H, m), 3.48 (2H, d, *J* = 13.4 Hz), 3.98 (2H,, d, *J* = 13.4 Hz), 4.10 (1H, m), 4.28 (1H, m), 4.33 (1H, m), 7.30 (10 H, m); ^{13}C NMR ($CDCl_3$): δ −4.8, −4.1, 14.6, 18.6, 23.1, 23.5, 23.5, 24.2, 25.7, 26.1, 26.4, 26.6, 32.0, 34.1, 44.6, 55.8, 60.4, 67.3, 72.3, 127.4, 128.5, 128.7, 129.4, 130.1, 140.7, 180.0; IR (film) 3028, 2930, 2857, 1770; MS (FAB) *m/z* 496.2 $[M + 1]^+$; HRMS calcd for $C_{30}H_{46}NO_3Si$ $[M + 1]^+$ 496.3246; found 496.3247.

(2*S*)-2-[(1*S*,2*S*)-1-(*tert*-butyl-dimethyl-silanyloxy)-2-dibenzylamino-4-methyl-pentyl]-(1*S*)-1-[1,3]dithian-2-yl-butane-1,4-diol (12). To a solution of 1,3-dithiane (92 mg, 0.76 mmol) in anhydrous THF (4 mL) was added *n*-butyllithium (2.5 M in hexane) (278 μL, 0.70 mmol) under Ar at −78 °C. After 30 min, the solution was transferred by cannula to a solution of lactone **10** (156 mg, 0.32 mmol) in THF (4 mL) at −78 °C. The reaction mixture was stirred at −78 °C for a further 40 min before it was quenched with saturated NH_4Cl and allowed to warm to room temperature. The mixture was extracted with EtOAc (3 × 10 mL), the combined organic phase was dried by Na_2SO_4 and concentrated under reduced pressure, and the residue was purified by column chromatography (10% EtOAc in hexanes) to afford a mixture of ketone **11a** and lactols **11b**,**c** (131 mg). The mixture of products was dissolved in anhydrous methanol, and $NaBH_4$ (21 mg, 0.53 mmol) was added in small portions at room temperature. The solution was stirred until the disappearance of starting material by TLC (about 1 h) and quenched with water. The solvent was removed under reduced pressure, and the residue was extracted by EtOAc (3 × 10 mL). Purification by column chromatography (20% EtOAc in hexanes) gave diol **12** as a foamy white solid (113 mg, 58%); mp 48−50 °C; $[\alpha]_D$ −19.5 (*c* 0.4, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.04 (3H, s), 0.17 (3H, s), 0.82 (2H, m), 0.87 (9H, s), 0.98 (3H, d, *J* = 6.0), 1.02 (3H, d, *J* = 6.0), 1.50 (2H, m), 1.74 (2H, m), 2.02 (2H, m), 2.20 (1H, m), 2.69 (2H, m), 2.90 (3H, m), 3.28 (2H, d, *J* = 13.08), 3.51 (2H, m), 3.83 (1H, d, *J* = 2.55), 3.91 (1H, d, *J* = 2.13), 4.16 (1H, b), 4.41 (2H, d, *J* = 8.34), 4.80 (1H, b), 7.30 (10 H, m); ^{13}C NMR ($CDCl_3$) δ −4.6, −3.3, 14.1, 14.6, 18.6, 19.5, 21.5, 22.5, 24.6, 25.8, 26.5, 26.5, 26.7, 30.2, 31.0, 31.2, 33.5, 42.5, 53.1, 56.2, 61.5, 64.8, 75.2, 76.3, 77.6, 127.3, 127.5, 128.7, 129.4, 130.6, 139.7, 139.9; IR (film) 3469, 3028, 2954, 2857, 1453; MS (FAB) *m/z* 618.3 $[M + 1]^+$; HRMS calcd for $C_{34}H_{56}NO_3S_2Si$ $[M + 1]^+$ 618.3470; found 618.3482.

(*S*)-Dibenzyl-(3*S*)-[(1*S*)-1-*tert*-butyl-dimethyl-silanyloxy)-(2*S*)-2-[1,3]dithian-2-yl-tetrahydro-furan-3-yl)-methyl]-3-methyl-butyl]-amine (13). To a solution of diol **12** (12 mg, 0.020 mmol) in anhydrous THF (1 mL), PPh_3 (21 mg, 0.076 mmol) was added, and a solution of DEAD (12 mg, 1.006 mmol) in THF (1 mL) was added dropwise. The reaction mixture was stirred at room temperature for 3 h, the solvent was removed under reduced pressure, and the residue was purified by column chromatography (10% EtOAc in hexanes) to give **13** as white crystals (12 mg, 87%); $[\alpha]_D$ +16.3 (*c* 0.6, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.08 (3 H, s), 0.09 (3 H, s), 0.80 (9 H, s,), 1.03 (3 H, d, *J* = 6.5 Hz), 1.08 (3 H, d, *J* = 6.3 Hz), 1.45 (1 H, m), 1.65 (1 H, m), 1.81 (2 H, m), 1.96 (3 H, m), 2.35 (2 H, d, *J* = 8.7 Hz), 2.47 (1 H, m), 2.68 (2 H, m), 2.77 (2 H, m), 3.19 (1 H, m), 3.27 (2 H, d, *J* = 12.9 Hz), 3.58 (1 H, m), 3.63 (1 H, m), 4.00 (2 H, m), 4.11 (2 H, d, *J* = 9.5 Hz), 7.26 (10 H, m); ^{13}C NMR ($CDCl_3$) δ −2.9, −2.7, 18.9, 22.9, 24.6, 25.7, 25.9, 26.7, 30.6, 31.0, 31.5, 33.6, 46.1, 51.5, 56.4, 57.7, 69.0, 73.8, 77.6, 80.6, 127.4, 128.6, 129.7, 141.1; IR (film) 3028, 2954, 2857, 1454; MS (FAB) *m/z* 600 $[M + 1]^+$; HRMS calcd for $C_{34}H_{54}NO_2S_2Si$ $[M + 1]^+$ 600.3365; found 600.3391.

(3*S*)-3-[(1*S*)-1-*tert*-Butyl-dimethyl-silanyloxy)-(2*S*)-2-dibenzylamino-4-methyl-pentyl]-tetrahydro-furan-(2*S*)-2-carbaldehyde (14). An amount of **13** (55 mg, 0.092 mmol) was dissolved in a mixture of THF−H_2O (9:1, 2 mL), a mixture of red HgO (40 mg, 0.184 mmol) and BF_3 etherate (23.2 μL, 0.184 mmol) in THF (1 mL) were added, and the resulting mixture was stirred at room temperature for 24 h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 × 10 mL), and the organic phase was dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography (10% EtOAc in hexanes) to afford **14** as a colorless oil (38 mg, 84%); $[\alpha]_D$ +8.0 (*c* 0.9, CH_2Cl_2); ^1H NMR ($CDCl_3$): δ 0.00 (3 H, s), 0.06 (3 H, s), 0.81 (9 H, s), 0.93 (2H, m), 1.03 (6 H, q, *J* = 4.4 and 6.2 Hz), 1.45 (2 H, m), 1.66 (2 H, m), 2.11 (1 H, m), 2.41 (1 H, m), 2.56 (1 H, m, *J* = 9.8 Hz), 3.23 (1 H, m), 3.30 (2 H, d, *J* = 13.1 Hz), 3.75 (1 H, dd, *J* = 10.0 and 1.6 Hz), 3.86 (2 H, m), 4.11 (2 H, m), 7.28 (10 H, m), 9.31 (1 H, d, *J* = 2.0 Hz); ^{13}C NMR ($CDCl_3$): δ −3.3, −2.9, 18.9, 22.7, 24.5, 25.3, 26.6, 31.1, 33.3, 47.8, 56.2, 57.3, 69.2, 73.8, 76.9, 82.2, 127.4, 128.6, 129.2, 129.4, 129.9, 130.2, 134.8, 141.2, 203.8; IR (film) 3085, 3063, 3028, 2955, 2928, 2857, 1730; MS (FAB) *m/z* 510 $[M + 1]^+$; HRMS calcd for $C_{31}H_{48}NO_3Si$ $[M + 1]^+$ 510.3403; found 510.3389.

(3*S*)-3-[(1*S*)-1-*tert*-Butyl-dimethyl-silanyloxy)-(2*S*)-2-dibenzylamino-4-methyl-pentyl]-tetrahydro-furan-(2*S*)-2-carboxylic acid methyl ester (15). To a solution of the aldehyde **14** (34 mg, 0.067 mmol) and 2-methyl-2-butene (86 μL, 0.80 mmol) in a mixture of *t*-BuOH/CH_3CN (0.8 mL 5:3) was added dropwise a solution of $NaClO_2$ (45 mg, 0.34 mmol), and NaH_2PO_4 dihydrate (64 mg, 0.34 mmol) in water (0.67 mL) was added dropwise at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h and quenched with 5% aqueous $Na_2S_2O_3$ (0.67 mL), and a few drops of 1% HCl were added to pH 6. The mixture was extracted with EtOAc (3 × 5 mL). The combined organic phase was dried with Na_2SO_4 and concentrated, and the crude acid was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. An ethereal solution of CH_2N_2 was added until the yellow color of the solution persisted. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (10% EtOAc in hexanes) to give ester **15** as a colorless oil (18 mg, 52%); $[\alpha]_D$ +57.86 (*c* 0.8, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 0.04 (3 H, s), 0.08 (3 H, s,), 0.82 (9H, s), 1.00 (1 H, d, *J* = 4.3 Hz), 1.05 (1 H, d, *J* = 4.5 Hz), 1.47 (2 H, m), 1.72 (1 H, m), 1.92 (1 H, m), 2.09 (1 H, m), 2.49 (1 H, d, *J* = 9.9 Hz), 2.56 (1 H, d, *J* = 7.5 Hz), 3.26 (2 H, d, *J* = 13.0 Hz), 3.33 (1H, m), 3.48 (1 H, d, *J* = 10.1 Hz), 3.54 (3H, s), 3.82 (1 H, m), 4.12 (1 H, m), 7.30 (10 H, m); ^{13}C NMR ($CDCl_3$) δ −3.2, −2.9, 18.9, 22.5, 24.5, 25.4, 26.6, 29.7, 33.4, 46.8, 51.5, 56.3, 57.3, 69.1, 74.9, 127.3, 128.5, 129.9, 173.3; IR (film): 3063, 3028, 2954, 2858, 1738; MS (FAB) *m/z* 540.3 [M + 1]$^+$; HRMS calcd for $C_{32}H_{50}NO_4Si$ [M + 1]$^+$ 540.3509; found 540.3488.

(3*S*)-3-[(1*S*)-1-*tert*-Butyl-dimethyl-silanyloxy)-(2*S*)-2-dibenzylamino-4-methyl-pentyl] -tetrahydro-furan-(2*S*)-2-carboxylic Acid (17). A solution of **15** (190 mg, 0.35 mmol) in NaOMe (25% in weight in MeOH, 1 mL) was refluxed at 70 °C for 6 h. Water (100 μL) was added, and the mixture was stirred at room temperature 12 h. The reaction mixture was acidified with HCl (5N, 3.5 mL) to pH 3 and extracted with EtOAc (3 × 20 mL), and the organic phase was dried with Na_2SO_4 and concentrated. The residue was purified by column chromatography (75% of EtOAc in hexanes) to afford **17** as a colorless oil (82 mg, 80%); $[\alpha]_D$ −15.1 (*c* 0.6, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ −0.36 (3 H, s), −0.03 (3H, s,), 0.83 (9H, s), 0.91 (6H, d, J = 6.4 Hz), 1.54 (2H, m), 1.85 (1H, m), 2.05 (1H, m), 2.16 (1H, m), 2.56 (1H, m), 2.91 (1H, m), 3.65 (2H, d, J = 13.6 Hz), 3.94 (2H, d, J = 13.6 Hz), 4.08 (1H, d, J = 8.16 Hz, 8.2 Hz), 7.19−7.42 (10 H, m); ^{13}C NMR ($CDCl_3$) δ −4.6, −3.9, 18.5, 22.6, 24.0, 25.7, 25.9, 26.4, 28.4, 34.8, 47.7, 55.7, 59.5, 70.1, 72.2, 79.5, 127.6, 128.8, 129.4, 139.6, 176.8; IR (film) 3583 (b), 3063, 3028, 2954, 2856, 1722; MS (FAB) *m/z* 525 [M + 1]$^+$; HRMS calcd for $C_{31}H_{47}NO_4Si$ [M + 1]$^+$ 525.3274; found 525.3282.

(3*S*)-3-[(1*S*)-1-*tert*-Butyl-dimethyl-silanyloxy)-(2*S*)-2-dibenzylamino-4-methyl-pentyl]-tetrahydro-furan-(2*R*)-2-carboxylic Acid Butylamide (18a). To a solution of acid **17** (30 mg, 0.057 mmol) and *n*-butylamine (15 μL, 0.152 mmol) in CH_2Cl_2 (2 mL) was added PyBop (30 mg, 0.057 mmol) at 0 °C followed by *i*-Pr_2NEt (39 μL, 0.23 mmol). The reaction mixture was stirred at 0 °C to room temperature for 14 h, and then it was diluted with EtOAc (5 mL) and washed with aqueous 1 N HCl and saturated $NaHCO_3$. The organic phase was dried with Na_2SO_4 and concentrated, and the residue was purified by column chromatography (10% EtOAc in hexanes) to afford **18a** as a colorless oil (28 mg, 80%); $[\alpha]_D$ −41.4 (*c* 1.15, CH_2Cl_2); ^{1}H NMR ($CDCl_3$): δ −0.42 (3 H, s), 0.00 (3 H, s), 0.82 (9 H, s), 0.86 (3 H, d, J = 5.9 Hz), 0.95 (6 H, m), 1.37 (2 H, m), 1.52 (4 H, m), 1.65 (1 H, m), 1.92 (2 H, m), 2.30 (2 H, m), 2.84 (1 H, m), 3.30 (1 H, m), 3.69 (2 H, d, J = 13.8 Hz), 3.81 (2 H, m), 3.86 (2 H, d, J = 13.8 Hz), 3.96 (1 H, d, J = 8.4 Hz), 4.46 (1 H, m), 6.59 (1 H, m), 7.21 (2 H, m), 7.31 (4 H, m), 7.43 (4 H, m);^{13}C NMR ($CDCl_3$): δ −4.5, −4.0, 14.2, 18.5, 20.5, 22.4, 24.6, 25.6, 26.4, 27.5, 32.2, 35.6, 38.7, 47.8, 55.4, 59.6, 69.7, 71.4, 78.3, 80.7, 127.2, 128.6, 129.2, 140.9, 173.2; IR (film) 3424, 3063, 2955, 2929, 2857, 1675, 1524; MS (FAB) *m/z* 581.4 [M + 1]$^+$; HRMS calcd for $C_{35}H_{57}N_2O_3Si$ [M + 1]$^+$ 581.4131; found 581.4138.

(3*S*)-3-[(1*S*)-1-*tert*-Butyl-dimethyl-silanyloxy)-(2*S*)-2-dibenzylamino-4-methyl-pentyl]-tetrahydro-furan-(2*R*)-2-carboxylic Acid *N*-Methyl-L-ala Amide (18b). Boc-L-alanine methylamide (17 mg, 0.085 mmol) was stirred with HCl in dioxane (4M, 1 mL) for 0.5 h and was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (2 mL). To the solution, acid **17** (30 mg, 0.057 mmol), PyBop (30 mg, 0.057 mmol), and *i*-Pr_2NEt (39 μL, 0.23 mmol) were added at 0 °C. The reaction mixture was stirred at 0 °C to room temperature for 14 h, and then it was diluted with EtOAc (10 mL). The organic phase was washed with aqueous 1 N HCl and saturated $NaHCO_3$. The organic phase was dried and concentrated. The residue was purified with column chromatography (20% EtOAc in hexanes) to afford **18b** as a colorless oil (22 mg, 63%); $[\alpha]_D$ −40.4 (*c* 0.9 in $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ −0.04 (3H, s), 0.01 (3H, s), 0.82 (9H, s), 0.86 (2H, m), 0.93 (3 H, d, J = 6.0 Hz), 1.26 (1H, m), 1.42 (3 H, d, J = 6.8 Hz), 1.50 (1 H, m), 1.93 (2 H, m), 2.29 (2 H, m), 2.69 (2 H, d, J = 4.6 Hz), 2.84 (1 H, m), 3.70 (2 H, d, J = 13.7 Hz), 3.81 (2 H, d, J = 13.7 Hz), 3.91 (1 H, m), 4.01 (1H, m), 4.46 (1H, m), 6.19 (1 H, m), 7.02 (1 H, m), 7.21 (2 H, m), 7.29 (4 H, m), 7.43 (4 H, m); ^{13}C NMR ($CDCl_3$) δ −4.5, −4.0, 14.2, 18.5, 20.6, 22.4, 24.6, 25.7, 26.4, 27.5, 32.2, 35.6, 38.7, 47.8, 55.4, 59.6, 69.7, 71.4, 78.3, 80.7, 127.2, 128.6, 129.2, 140.9, 173.2; IR (film) 3324, 3063, 2954, 2931, 2858, 1655, 1513; MS (FAB) *m/z* 610.4 [M + 1]$^+$; HRMS calcd for $C_{35}H_{56}N_3O_4Si$ [M + 1]$^+$ 610.4040; found 610.4024.

(3*S*)-3-[(1*S*)-1-*tert*-Butyl-dimethyl-silanyloxy)-(2*S*)-2-dibenzylamino-4-methyl-pentyl]-tetrahydro-furan-(2*R*)-2-carboxylic Acid *N*-Butyl-L-Val Amide (18c). Boc-L-valine *n*-butylamide (49 mg, 0.18 mmol) was stirred with HCl in dioxane (4 M, 1 mL) for 1 h. After removing the solvent under reduced pressure, the compound was dissolved in CH_2Cl_2 (2 mL) and cooled to 0 °C. The acid **17** (63 mg, 0.12 mmol) was added followed by PyBOP (65 mg, 0.12 mmol) and *i*-Pr_2NEt (65 μL, 0.375 mmol). The reaction mixture was stirred from 0 °C to room temperature for 3 h before it was diluted with EtOAc (10 mL) and washed with aqueous 1 N HCl and saturated $NaHCO_3$. The organic phase was dried and concentrated, and the residue was purified by column chromatography (20% EtOAc in hexanes) to afford **18c** as a colorless oil (64 mg, 79%); $[\alpha]_D$ −37.9 (*c* 0.42, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 0.83 (3H, t, J = 7.2 Hz), 1.23 (2H, m), 1.28 (3H, d, J = 7.0 Hz), 1.37 (9H, s), 1.41 (2H, m), 3.15 (2H, m), 4.14 (1H, m), 5.44 (1H, d, J = 7.7 Hz), 6.72 (1H, b); ^{13}C NMR ($CDCl_3$) δ −4.6, −3.9, 14.0, 18.5, 18.8, 19.7, 20.4, 22.3, 24.6, 25.4, 26.3, 27.4, 30.9, 31.9, 35.4, 39.6, 48.2, 54.9, 58.8, 59.5, 69.9, 71.0, 80.7, 127.2, 128.6, 129.1, 140.9, 171.2, 173.8; IR (film) 3308, 2964, 2956, 2859, 16519, 1515; MS (FAB) *m/z* 680.5 [M + 1]$^+$; HRMS calcd for $C_{40}H_{66}N_3O_4Si$ [M + 1]$^+$ 680.4822; found 680.4791.

(3*S*)-3-[(1*S*)-1-Hydroxyl)-(2*S*)-2-*tert*-butoxycarbonylamino]-tetrahydro-furan-(2*R*)-2-carboxylic Acid Butylamide (19a). To a solution of **18a** (28 mg, 0.048 mmol) in HCOOH/MeOH (5%) (1 mL) at room temperature was added Pd-black (28 mg), and the suspension was stirred for 1 h. The solid was filtered, and the solution was concentrated to dryness. The residue was dissolved in MeOH (2.0 mL), and Boc_2O (52.3 mg, 0.24 mmol) and $NaHCO_3$ (200 mg) were added. The mixture was stirred at room temperature for 14 h, the solid was filtered, and the solution was concentrated to dryness. The residue was treated with TBAF (1.0 M in THF, 0.5 mL) at 0 °C for 0.5 h before it was taken up by EtOAc (10 mL). The EtOAc solution was washed with water and concentrated. The residue was purified by column chromatography (50% EtOAc in hexanes) to give **19a** as a colorless oil (14 mg, 77%); $[\alpha]_D$ +3.02 (*c* 0.4, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 0.92 (9 H, m), 1.33 (3 H, m), 1.43 (9 H, s), 1.51 (2H, m), 1.67 (3H, m), 2.00 (1 H, m), 2.10 (1 H, m), 2.40 (1 H, m), 3.26 (2 H, m), 3.64 (1 H, m), 3.77 (1 H, m), 3.83 (1 H, m), 3.98 (1 H, m), 4.10 (1 H, d, J = 5.7 Hz), 4.18 (1 H, d, J = 7.7 Hz), 5.11 (1 H, d, J = 8.3 Hz), 6.74 (1 H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.4, 22.4, 23.7, 25.2, 28.2, 28.8, 31.9, 38.9, 41.7, 48.5, 52.4, 69.2, 74.3, 79.8, 79.8, 157.4, 173.8; IR (film) 3329, 2957, 2871, 1688, 1661, 1531; MS (FAB) *m/z* 387.2 [M + 1]$^+$; HRMS calcd for $C_{20}H_{39}N_2O_3Si$ [M + 1]$^+$ 387.2858; found 387.2840.

(3*S*)-3-[(1*S*)-1-*tert*-Butyl-dimethyl-silanyloxy)-(2*S*)-2-*tert*-butoxycarbonylamino-4-methyl-pentyl]-tetrahydro-furan-(2*R*)-2-carboxylic Acid *N*-Methyl-L-ala Amide (19b). By a similar procedure **19b** was prepared and purified by column chromatography to give a colorless oil (10% hexanes in EtOAc) (13 mg, 91%); $[\alpha]_D$ −33.0 (*c* 0.40, $CHCl_3$); ^{1}H NMR (MeOD) δ 0.91 (6H, m), 1.39 (2H, m), 1.40 (3 H, d, J = 7.0 Hz), 1.42 (9H, s), 1.62 (3 H, m), 1.97 (1 H, m), 2.10 (1 H, m), 2.37 (1 H, m), 2.82 (2 H, d, J = 4.7 Hz), 3.62 (2 H, m), 3.75 (1 H, m), 3.88 (2H, m), 3.98 (1H, m), 4.21 (2 H, d, J = 7.8 Hz), 4.41 (1 H, m), 4.99 (2 H, d, J = 8.9 Hz), 6.18 (1 H, m), 7.23 (2 H, d, J = 7.2 Hz); ^{13}C NMR (MeOD) δ 14.2, 18.4, 20.8, 22.3, 23.7, 25.2, 26.7, 27.5, 28.7, 41.5, 48.4, 48.7, 52.7, 52.9, 69.5, 74.1, 79.7, 80.0, 157.3, 172.8, 174.0; IR (film) 3324, 2956, 1652, 1520; MS (FAB) calcd for $C_{20}H_{38}N_3O_6$ *m/z* 416.2 [M + 1]$^+$; HRMS found, 416.28.

Compound 20a. Compound **19a** (14 mg, 0.036 mmol) was stirred with HCl in dioxane (4 M, 0.5 mL) for 1 h at room temperature. The mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in CH_2Cl_2 (1.0 mL). The solution was cooled to 0 °C, and *N*′-trityl-BocAspOH

(25.6 mg, 0.054 mmol) was added followed by PyBop (18.8 mg, 0.036 mmol) and i-Pr_2NEt (23 μL, 0.14 mmol). The mixture was stirred at 0 °C to room temperature for 2 h before it was diluted with EtOAc (5 mL), and the organic phase was washed with aqueous 1 N HCl and $NaHCO_3$. The organic phase was dried and concentrated, and the residue was purified by column chromatography (30% hexanes in EtOAc) to give **20a** as a white solid (27 mg, 99%); $[\alpha]_D$ −9.04 (c 0.8, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.88 (6H, dd, J = 0.3 and 0.5 Hz), 0.92 (3 H, t, J = 7.3 Hz), 1.34 (3H, m), 1.43 (9 H, s), 1.48 (2 H, m), 1.58 (2 H, m), 1.85 (1 H, m), 2.02 (1 H, m), 2.38 (1 H, m), 2.62 (1 H m), 2.90 (1 H, s), 3.00 (1 H, m), 3.10 (1 H, m), 3.27 (1 H, m), 3.66 (2 H, m), 3.83 (1 H, m), 3.90 (1 H, m), 4.08 (1 H, d, J = 7.3 Hz), 4.14 (1 H, d, J = 6.3 Hz), 4.36 (1 H, m), 6.08 (1 H, d, J = 7.8 Hz), 6.64 (1 H, t, J = 5.6 Hz), 6.99 (1 H, m), 7.07 (1 H, d, J = 8.4 Hz), 7.17−7.31 (15H, m); ^{13}C NMR ($CDCl_3$) δ 14.1, 20.4, 21.5, 22.4, 23.6, 25.2, 28.4, 28.6, 31.9, 38.3, 38.8, 40.3, 47.9, 52.0, 52.9, 60.8, 69.3, 71.1, 74.8, 127.5, 128.4, 129.1, 144.8, 156.3, 170.6, 172.9, 173.5; IR (film) 3326, 2958, 1657, 1526; MS (FAB) m/z 743.9 $[M + 1]^+$; HRMS calcd for $C_{43}H_{58}N_4O_7$ $[M + 1]^+$ 743.4364; found 743.4383.

Compound 20b. By a similar procedure **20b** was prepared from **19b**. Purification by column chromatography (10% MeOH in EtOAc) gave **20b** as a white solid (17 mg, 71%); $[\alpha]_D$ −28.4 (c 0.7, $CHCl_3$); ^1H NMR (MeOD) δ 0.88 (6H, m), 1.25−1.49 (4 H, m), 1.32 (3H, d, J = 6.6 Hz), 1.42 (9 H, s), 1.61 (2 H, m), 1.84 (1 H, m), 1.99 (1 H, m), 2.33 (1 H, m), 2.62 (3 H, d, J = 3.8 Hz), 2.69 (1 H, m), 2.95 (1 H, m), 3.62 (1 H, m), 3.84 (3 H, m), 4.06 (1 H, m), 4.36 (2 H, m), 6.14 (1 H, b), 6.29 (1 H, b), 6.96 (1 H, b), 7.26 (15 H, m); ^{13}C NMR (MeOD) δ 18.6, 22.3, 23.7, 25.1, 26.6, 27.8, 28.6, 38.5, 40.4, 47.9, 48.7, 52.2, 52.6, 69.3, 71.1, 74.4, 77.6, 79.7, 80.7, 127.5, 128.4, 129.1, 144.7, 156.2, 170.7, 172.7, 172.9, 173.9; IR (film) 3318, 2956, 1651, 1519; MS (FAB) m/z 772.4 $[M + 1]^+$; HRMS calcd for $C_{43}H_{58}N_5O_8$ $[M + 1]^+$ 772.4298; found 772.4285.

Compound 20c. Compound **18c** (56 mg, 0.082 mmol) was dissolved in HCOOH/MeOH (5%) (4 mL), Pd-black (56 mg) was added, and the suspension was stirred for 1 h. The catalyst was filtered, the solvent was removed under reduced pressure, and the residue was redissolved in EtOAc and washed with 1 N NaHCO. The organic phase was dried and concentrated, and the residue was stirred with Boc_2O (89.38 mg, 0.41 mmol) and $NaHCO_3$ (300 mg) in MeOH (3 mL) overnight. After removal of the solid and the solvent, the residue was treated with TBAF (1.0 M in THF, 1.5 mL, predried with molecular seives) at 0 °C for 1.5 h. The reaction mixture was diluted with EtOAc (10 mL), washed with water, and dried with Na_2SO_4. After concentration, the residue was purified by column chromatography (50% EtOAc in hexanes) to give **19c** (34 mg, 83%). The compound was stirred with HCl in dioxane (4 M, 1 mL) at room temperature for 1 h. After removing the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (1.5 mL) and cooled to 0 °C. N-Boc-L-MetOH (20.3 mg, 0.082 mmol) was added, followed by PyBOP (42.4 mg, 0.082 mmol) and i-Pr_2-NEt (35 μL, 0.204 mmol). The reaction mixture was stirred from 0 °C to room temperature for 3 h before it was diluted with EtOAc (10 mL) and washed with aqueous 1 N HCl and saturated $NaHCO_3$. The organic phase was dried and concentrated, and the residue was purified by column chromatography (40% hexanes in EtOAc) to give **20c** was as a colorless oil (18 mg, 43%); $[\alpha]_D$ −38.4 (c 0.69, MeOH); ^1H NMR ($CDCl_3$) δ 0.92 (9H, m), 1.33 (3H, m), 1.36 (3H, d, J = 6.9 Hz), 1.45 (12H, s), 1.48 (2H, m), 1.58 (3H, s), 1.64 (4H, m), 1.67 (2H, m), 1.72 (1H, m), 1.88 (1H, m), 2.37 (1H, m), 2.47 (1H, m), 3.24 (2H, dd, J = 6.7 and 13.1 Hz), 3.63 (1H, m), 3.74 (1H, m), 4.52 (1H, t, J = 7.0 Hz), 6.40 (1H, t, J = 6.8 Hz), 6.63 (1H, b); ^{13}C NMR ($CDCl_3$) δ 13.1, 13.3, 14.2, 17.7, 18.7, 20.1, 20.6, 21.3, 22.9, 24.7, 26.2, 27.7, 27.8, 30.3, 31.4, 31.5, 31.6, 39.1, 41.4, 51.6, 53.6, 54.5, 58.5, 69.1, 71.8, 79.7, 80.1, 156.8, 172.1, 173.7, 174.4; IR (film) 3304, 2960, 2932, 2872, 1651, 1525; MS (FAB) calcd for $C_{30}H_{56}N_4O_7S$ m/z $[M + 1]^+$ 617.4; found 617.42.

Compound 21a. Compound **20a** (12 mg, 0.017 mmol) was stirred with HCl in dioxane (4 M, 0.5 mL) for 1 h at room temperature. The mixture was concentrated to dryness under reduced pressure, and the residue was dissolved in a mixture of CH_2Cl_2 (0.5 mL) and water (0.5 mL). The solution was cooled to 0 °C, and N-Ac-L-ValOH (2.7 mg, 0.017 mmol) was added followed by HOBt (2.3 mg, 0.017 mmol) and EDC (3.8 mg 0.018 mmol). The reaction mixture was stirred at 0 to 5 °C for 24 h, and then it was diluted with EtOAc (5 mL). The organic phase was washed with aqueous 1 N HCl, aqueous 1 N $NaHCO_3$, and brine. The organic phase was dried and concentrated, and the residue was purified by column chromatography (20% MeOH in CH_2Cl_2) to give the peptide product (14 mg). This was stirred with TFA/water (95:5, 0.5 mL) at room temperature for 1 h, MeOH (3 mL) was added, and the reaction mixture was concentrated at room temperature to dryness under reduced pressure. The residue was taken up with EtOAc (5 mL) and washed with aqueous $NaHCO_3$ and brine. The organic phase was dried and concentrated, and the residue was purified by column chromatography (20% MeOH in CH_2Cl_2) to give **21a** as a white solid (8 mg, 61%); $[\alpha]_D$ −24.1 (c 0.34, MeOH); ^1H NMR ($CDCl_3$) δ 0.87−1.02 (15H, m), 1.38 (3 H, m), 1.50 (3H, m), 1.60 (3 H, m), 1.85 (1 H, m), 2.02 (3 H, s), 2.09 (1 H, m), 2.33 (1 H, m), 2.74 (1 H, m), 3.20 (2 H, t, J = 7.1 Hz), 3.77 (1 H, m), 3.93 (2 H, m), 4.14 (2 H, dd, J = 6.8 Hz), 4.66 (1 H, t, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 13.1, 17.6, 18.6, 20.1, 21.2, 21.4, 22.9, 24.6, 25.9, 30.4, 31.6, 36.4, 38.6, 41.1, 48.3, 50.9, 52.1, 59.9, 69.1, 72.2, 80.3, 171.6, 172.6, 172.8, 174.2, 174.7; IR (film) 3308, 2959, 1635, 1451; MS (FAB) m/z 542.3 $[M + 1]^+$; HRMS calcd for $C_{26}H_{47}N_5O_7$ $[M + 1]^+$ 542.3553; found 542.3542.

Compound 21b. By a similar procedure **21b** was prepared from **20b**. Purification by column chromatography gave **21b** as an white solid (5.2 mg, 66%); $[\alpha]_D$ −34.0 (c 0.20, MeOH); ^1H NMR ($CDCl_3$): δ 0.88 (3 H, d, J = 6.5 Hz), 0.91 (3 H, d, J = 6.5 Hz), 0.97 (6 H, d, J = 6.3 Hz), 1.29 (2 H, m), 1.36 (3 H, d, J = 7.1 Hz), 1.54 (1H, m), 1.61 (1 H, m), 1.90 (1 H, m), 2.02 (3 H, s), 2.09 (1 H, m), 2.39 (1 H, m), 2.74 (3 H, s), 2.75 (1 H, m), 3.71 (1 H, t, J = 4.4 Hz), 3.95 (2 H, m), 4.00 (1 H, m), 4.10 (1 H, d, J = 6.4 Hz), 4.23 (1 H, d, J = 6.4 Hz), 4.35 (1 H, q, J = 7.1 Hz), 4.66 (1 H, t, J = 6.5 Hz); ^{13}C NMR ($CDCl_3$) δ 13.4, 17.7, 18.6, 21.2, 21.4, 22.9, 24.6, 25.4, 26.1, 30.4, 36.4, 40.8, 48.9, 50.1, 50.9, 51.8, 59.9, 69.1, 72.3, 80.1, 171.7, 172.6, 172.9, 174.1, 174.3, 174.4; IR (film) 3307, 2964, 1673, 1536. MS (FAB) m/z 571.1 $[M + 1]^+$, 593.1 $[M + 23]^+$; HRMS calcd for $C_{26}H_{47}N_6O_8$ $[M + 1]^+$ 571.3455; found 571.3436.

Compound 21c. Compound **20c** (13 mg, 0.021 mmol) was treated with HCl in dioxane (4 M, 1 mL) for 1 h. After removing the solvent under reduced pressure, the residue was dissolved in EtOAc and washed with 1 N $NaHCO_3$ and water. The solvent was evaporated, and the residue was dissolved in CH_2Cl_2/water (1:1) (1.0 mL) and cooled to 0 °C. N-Ac-LeuOH (7.23 mg, 0.042 mmol) was added, followed by EDC (9 mg, 0.042 mmol) and HOBT (5.6 mg, 0.042 mmol). The reaction mixture was stirred from 0 to 5 °C for 24 h. The reaction mixture was diluted with EtOAc (5 mL) and washed with aqueous 1 N HCl and 1 N $NaHCO_3$. The organic phase was dried and concentrated, and the residue was purified by column chromatography (10% MeOH in CH_2Cl_2) to give **21c** as a white solid (13 mg, 92%). $[\alpha]_D$ −49.1 (c 0.6, MeOH); ^1H NMR ($CDCl_3$) δ 0.91 (9H, m), 1.34 (3H, m), 1.37 (3H, d, J = 7.2 Hz), 1.43 (9H, s), 1.47 (2H, m), 1.63 (4H, m), 1.74 (2H, m), 1.88 (2H, m), 1.91 (2H, m), 2.10 (3H, s), 2.36 (1H, m), 2.38 (1H, m), 2.57 (2H, m), 3.21 (2H, m), 3.28 (1H, m), 3.40 (1H, m), 4.22 (1H, q, J = 7.0 Hz), 4.31 (1H, t, J = 6.4 Hz), 5.0 (1H, b), 5.26 (1H, d, J = 6.9 Hz), 6.58 (1H, b), 7.27 (1H, b), 8.28 (1H, b); ^{13}C NMR ($CDCl_3$) δ 14.0, 15.2, 18.7, 19.6, 21.1, 22.1, 22.2, 22.3, 22.6, 23.3, 23.9, 24.9, 25.7, 25.9, 26.5, 27.0, 31.2, 32.2, 32.4, 32.5, 40.0, 41.7, 42.4, 46.8, 52.5, 53.5, 53.9, 59.5, 70.0, 72.7, 81.0, 173.1, 173.4, 173.4, 175.0, 175.3; IR (film)

3288, 3081, 2958, 2872, 1644, 1538; MS (FAB) *m/z* 672 [M + 1]$^+$; HRMS calcd for $C_{33}H_{62}N_5O_7S$ [M + 1]$^+$ 672.4371; found 672.4362.

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[26] (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.

(26) McMartin, C.; Bohacek, R. S. *J. Comput.-Aided Mol. Des.* **1997**, *11*, 333.

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Supporting Information Available: NMR spectra for the synthetic molecules and CIF files of X-ray structures **3a**, **4a**, **4c**, **5b**, **6c**, **9**, and **13**. 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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