Design and Synthesis of Highly Potent Benzodiazepine γ-Secretase Inhibitors: Preparation of (2*S*,3*R*)-3-(3,4-Difluorophenyl)-2-(4-fluorophenyl)-4-hydroxy-*N*-((3*S*)-1-methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]-diazepin-3-yl)butyramide by Use of an Asymmetric Ireland−Claisen Rearrangement

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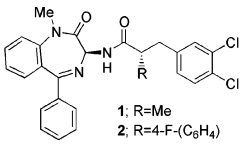
Abstract: Novel benzodiazepine-containing γ-secretase inhibitors for potential use in Alzheimer's disease have been designed that incorporate a substituted hydrocinnamide C-3 side chain. A syn combination of α-alkyl or aryl and β-hydroxy or hydroxymethyl substituents was shown to give highly potent compounds. In particular, (2*S*,3*R*)-3-(3,4-difluorophenyl)-2-(4-fluorophenyl)-4-hydroxy-*N*-((3*S*)-2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepin-3-yl)butyramide (**34**) demonstrated excellent in vitro potency (IC_{50} = 0.06nM). **34** could also be selectively methylated to give [^{3}H]-**28**, which is of use in radioligand binding assays.

Introduction. The 40−42 amino acid amyloid-β (Aβ) peptide is the major component of the extracellular proteinaceous plaques seen in Alzheimer's disease (AD), and much evidence suggests a pivotal role for Aβ in the disease process.[1,2] In particular, individuals possessing autosomal dominant mutations in the genes encoding for amyloid-β precursor protein (βAPP) or the membrane-bound protein homologues presenilin 1 and 2 have elevated Aβ levels and suffer from aggressive forms of early onset AD.[3−6] These observations have led to the hypothesis that Aβ, in its soluble form or when aggregated into oligomers, fibrils, and subsequently plaques, is responsible for neuronal toxicity and cell death.[7] Inhibition of Aβ synthesis is thus an attractive target for therapeutic intervention in AD.

Aβ is derived by processing of the 695−770 residue, type I transmembrane protein βAPP.[8] The major metabolic pathway of βAPP involves sequential cleavage by the proteases α-secretase and γ-secretase, leading to non-amyloidogenic fragments. Alternative processing by stepwise cleavage mediated by β-secretase and γ-secretase leads to the production of Aβ, and it is inhibitors of the latter enzyme that were targeted in the current work.[9−19]

A whole-cell γ-secretase inhibition assay using SH-SY5Y neuroblastoma cells in which human γ-secretase catalyzes the breakdown of the overexpressed exogenous substrate A4CTF has been developed.[20] We have previously disclosed[21,22] benzodiazepines **1** and **2**, which have demonstrated in vitro inhibition of



1; R=Me
2; R=4-F-(C_6H_4)

Aβ(1−40) secretion in this assay. Here, we describe the subsequent optimization of these leads resulting in the identification of novel, hydroxy-functionalized derivatives possessing picomolar levels of potency for the in vitro inhibition of Aβ peptide synthesis.

Chemistry. Initially the introduction of a hydroxyl group into the β-position of the hydrocinnamide side chain was investigated. In the case where the α-substituent was methyl, this was carried out using the Evans oxazolidinone chiral auxiliary methodology[23] to yield the *syn*- or *anti*-aldol adduct with either absolute stereochemistry. Coupling to the known, homochiral benzodiazepine[24] **7** yielded the desired amides **3**−**6** as shown in Scheme 1.

Functionalization of *syn*-aldol **3** was possible to yield adducts **8**−**11**; alternatively, oxidation of **3** gave the β-keto amide **12** (exclusively in the keto form in $CDCl_3$ solution) as a mixture of diastereomers. Treatment with the appropriate hydroxylamine yielded the oximes **13** and **14**, again as mixtures of isomers.

When the above route was applied to the preparation of α-(4-fluorophenyl)-substituted aldol analogues, significant retro-aldol reaction was observed at the LiOH/H_2O_2-mediated auxiliary cleavage step, necessitating the use of a silyl protecting group. This modification allowed the preparation of the desired syn isomers **15**−**18** as outlined in Scheme 2.

The synthesis of β-hydroxymethyl analogue **22** proceeded via carbene addition to methyl methacrylate, yielding after saponification the dibromocyclopropane **19**[25] (Scheme 3). Subsequent silver-mediated ring expansion[26] gave the 4-bromofuran-2-one **20**, which was subjected to Suzuki coupling[27] and hydrogenation to yield the *syn*-lactone **21**. When this racemic lactone was opened with benzodiazepine **7** under aluminum catalysis,[28] a kinetic resolution occurred to yield adduct **22** as a single diastereomer together with recovered lactone. Prolonged reaction times failed to give conversion of the slower-reacting enantiomer of the lactone. Attempts to determine the relative stereochemistry of adduct **22** were unsuccessful.

The lactone-opening route used above was deemed unsuitable for the preparation of α-(4-fluorophenyl)-

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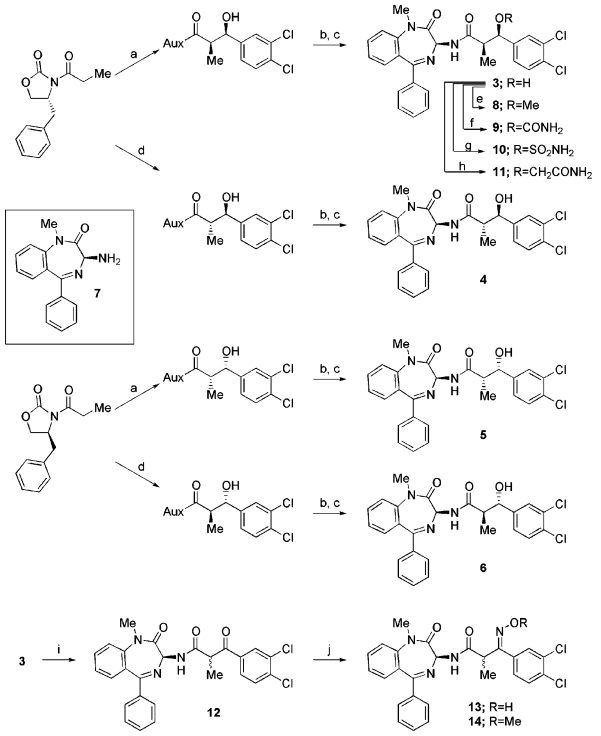
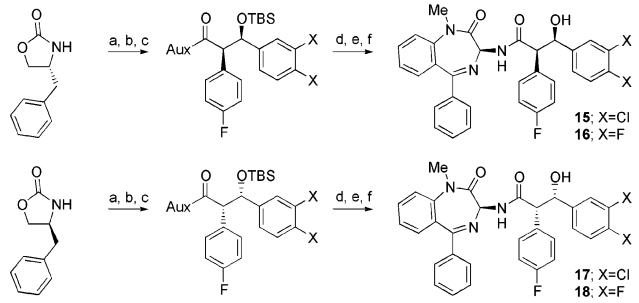
Scheme 1. Synthesis of Aldol Isomers and Derivatives[a]



[a] Reagents: (a) 3,4-dichlorobenzaldehyde, Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C; (b) H_2O_2, LiOH, THF/H_2O; (c) **7**, HBTU, CH_3CN; (d) 3,4-dichlorobenzaldehyde, 2 equiv of Bu_2BOTf, $^iPr_2NEt$, Et_2O, −78 °C; (e) Me_2SO_4, NaH, DMF/THF; (f) $ClSO_2NCO$, THF then $Na_2S_2O_5$; (g) $ClSO_2NH_2$, pyridine, CH_2Cl_2; (h) ICH_2CONH_2, NaH, DMF/THF; (i) Dess−Martin periodinane, CH_2Cl_2; (j) $H_2NOR.HCl$, pyridine, EtOH.

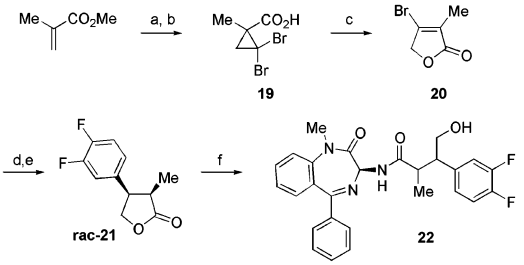
Scheme 2. Preparation of *syn*-α-(4-Fluorophenyl)aldol Analogues[a]



[a] Reagents: (a) 4-fluorophenylacetyl chloride, ^{n}BuLi, THF, −78 °C; (b) 3,4-dichlorobenzaldehyde or 3,4-difluorobenzaldehyde, Bu_2BOTf, Et_3N, CH_2Cl_2, −78 °C; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; (d) H_2O_2, LiOH, THF/H_2O; (e) TBAF, THF; (f) **7**, EDC, HOBt, CH_2Cl_2.

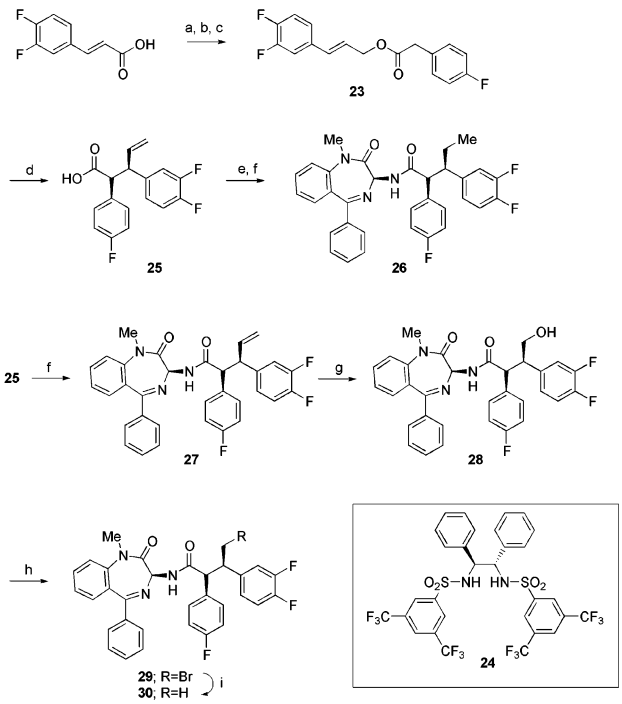
substituted adducts analogous to **22** because of the likelihood of epimerization of the *syn*-3,4-bis-aryllactone analogous to **21** and its potentially low reactivity toward aminolysis. This, coupled with the desire for a flexible, enantioselective route prompted us to investigate the use of an asymmetric Ireland−Claisen reaction.[29,30] The appropriate substrate **23** for this rearrangement was easily accessible from 3,4-difluorocinnamic acid as shown in Scheme 4. Use of the standard Corey protocol[29] (rearrangement at −78 °C/24h then +4 °C/48h) gave the desired syn pentenoic acid derivative **25** in good (63%) yield. The enantiomeric excess (ee) was determined to be >99% by coupling to excess, homochiral (>99% ee)

Scheme 3. Synthesis of β-Hydroxymethyl Analogue **22**[a]



[a] Reagents (a) $CHBr_3$, NaOH, $BnEt_3N^+Cl^-$, H_2O; (b) LiOH, THF/H_2O; (c) AgO_2CCF_3, CF_3CH_2OH, reflux; (d) 3,4-difluorophenylboronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME/H_2O, 90 °C; (e) 40 psi of H_2, Pd/C, EtOAc; (f) **7**, $AlMe_3$, CH_2Cl_2, reflux.

Scheme 4. Preparation of Alternative β-Substituted Analogues by Use of an Asymmetric Ireland−Claisen Rearrangement[a]



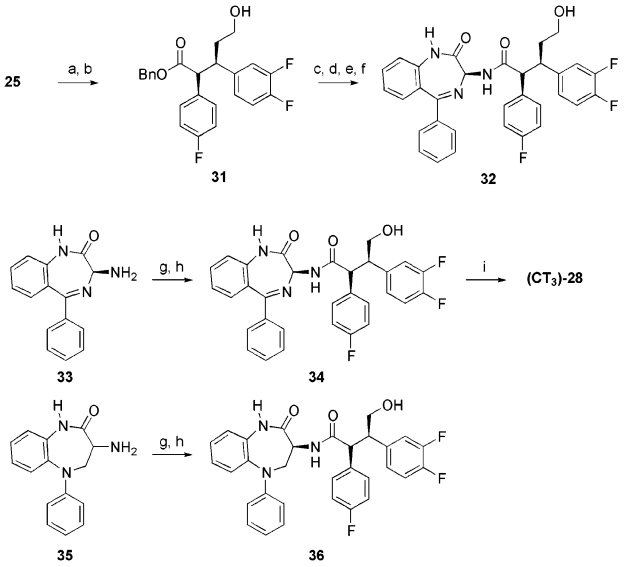
[a] Reagents: (a) MeI, K_2CO_3, DMF; (b) DIBAL−H, THF, −10 °C; (c) 4-fluorophenylacetyl chloride, Et_3N, CH_2Cl_2, 0 °C; (d) **24**, BBr_3, Et_3N, PhMe (see text for details); (e) 40 psi of H_2, Pd/C, EtOH; (f) **7**, EDC, HOBt, CH_2Cl_2; (g) O_3, MeOH, CH_2Cl_2, −78 °C, then $NaBH_4$, −78 °C to room temp; (h) PPh_3, CBr_4, CH_2Cl_2; (i) Bu_3SnH, AIBN, PhH, reflux.

benzodiazepine **7** to give complete conversion to a single diastereomer by NMR and HPLC analysis.

An improvement in the yield and ease of reaction was observed by modifying the reaction conditions (for the full procedure, see Supporting Information). Addition of the ester to the bromoborane catalyst derived from bis-sulfonamide **24**[29] was carried out at −78 °C, and stirring was maintained at this temperature for 1 h. Subsequent slow warming to ambient temperature over 16 h afforded, after purification, a 79% yield of the desired isomer with the ee undiminished. This reaction protocol was amenable to scale (>5 g) with the chiral ligand routinely reisolated and reused after recrystallization (dichloromethane/isohexane).

The substituted pentenoic acid **25** was hydrogenated and coupled to benzodiazepine **7** to yield the β-ethyl compound **26**. Alternatively, direct coupling to give **27**,

Scheme 5. Preparation of Alternative Hydroxylated Derivatives and Tritiated **28**[a]



[a] Reagents: (a) BnBr, K_2CO_3, DMF; (b) BH_3·THF, THF, then H_2O_2; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C; (d) 40 psi of H_2, Pd/C, MeOH; (e) **33**, EDC, HOBt, CH_2Cl_2; (f) TBAF, AcOH, THF, 40 °C; (g) **25**, EDC, HOBt, CH_2Cl_2; (h) O_3, MeOH, CH_2Cl_2, −78 °C, then $NaBH_4$, −78 °C to room temp; (i) CT_3I, NaH, THF, 40 °C, 2 h.

followed by ozonolysis with in situ reduction yielded alcohol **28**. This was deoxygenated by conversion to the bromide **29** followed by radical debromination (Bu_3SnH) to afford the *β*-methyl analogue **30**.

To investigate the effect of increasing further the length of the linking chain to the hydroxyl group, the *β*-hydroxyethyl compound **32** was prepared as shown in Scheme 5. Ireland−Claisen product **25** was benzyl-protected and hydroborated to give alcohol **31**. Subsequent manipulation of protecting groups and coupling to benzodiazepine **33**[24] yielded the desired analogue **32**.

The *β*-hydroxymethyl side chain was also coupled to the N(1)−H benzodiazepine **33** and racemic 1,5-benzodiazepine **35**[31] to yield the analogues **34** and **36** (after isomer separation), respectively. Selective N-methylation of **34** was also possible, and by use of CT_3I, this procedure proved to be amenable to the preparation of the radioligand (CT_3)-**28**.

Results and Discussion. Previous work within our group had identified 1-methyl-2-oxo-5-phenyl-2,3-dihydro-1*H*-benzo[*e*][1,4]diazepines bearing an *N*-hydrocinnamide side chain at the 3-position to be a novel class of *γ*-secretase inhibitors.[21] Introduction of a substituent at the α-position of the side chain as in **1** (320 nM) or **2** (15 nM) was found to greatly increase potency.

Further development focused on introduction of a *β*-substituent, and the inhibitory activities of a range of such compounds are summarized in Table 1. Preparation of the four aldol stereoisomers (**3**−**6**) demonstrated an increase in potency with the (2*R*,3*R*) isomer only (**3**, 19 nM), the other isomers being at best equipotent to analogue **1**. The preference for the (2*R*) configuration is opposite that seen with non-*β*-substituted derivatives.[8] Hydroxyl derivatization was generally poorly tolerated (**8**−**11**) with only the *β*-methoxy analogue **8** (59 nM) retaining moderate potency.

Table 1. Inhibitory Activities of Aldol Adducts and Derivatives **1**−**6** and **8**−**18**

compd	IC_{50} [a] ± SD (nM)	compd	IC_{50} [a] ± SD (nM)
1	320 ± 200	**11**	4750 ± 2700
2	15 ± 8	**12**	930 ± 700
3	19 ± 6	**13**	35 ± 19
4	1340 ± 540	**14**	>10000
5	880 ± 310	**15**	1.2 ± 0.9
6	380 ± 190	**16**	0.8 ± 0.7
8	59 ± 25	**17**	67 ± 50
9	2450 ± 55	**18**	9.6 ± 6
10	450 ± 290		

[a] IC_{50} values were determined over the range of 0.3 nM to 10 *μ*M and are the mean of at least three determinations.

Table 2. Inhibitory Activities of Further *β*-Functionalized Analogues

compd	IC_{50} [a] ± SD (nM)	compd	IC_{50} [a] ± SD (nM)
22	6.9 ± 4	**30**	1.5 ± 0.9
26	212 ± 160	**32**	35 ± 23
27	100 ± 70	**34**	0.06 ± 0.03
28	0.07 ± 0.04	**36**	0.07 ± 0.03
29	6.7 ± 4		

[a] IC_{50} values were determined over the range of 0.3 nM to 10 *μ*M or 0.003−100 nM as appropriate and are the mean of at least three determinations.

Oxidation to the *β*-keto amide **12** (927 nM) was attended by a large reduction in potency relative to **3**, although formation of the oxime **13** (35 nM as a diastereomeric mixture) allowed activity to be regained. The inactivity of methyl oxime **14** may suggest an important role for the hydroxyl function in the binding of these side chains.

Previous studies had shown that use of an α-(4-fluorophenyl) substituent allowed preparation of more potent analogues (cf. **1** vs **2**), and this was also the case in the current *β*-hydroxy series of compounds. Thus, **15** (1.2 nM) showed an increase in potency relative to methyl-substituted **3** with the (2*R*,3*R*) stereochemistry again preferred (2*S*,3*S* isomer **17**, 67 nM). Exchange of the chlorine substituents for fluorine, a modification that had previously been shown to improve potency,[21] gave **16** (IC_{50} = 0.8 nM).

Although the initial investigation of substituents at the *β*-position had suggested a limited degree of steric tolerance (cf. **8**−**11**), the increase in potency observed on going from ketone **12** to oxime **13** suggested that introduction of a homologated alcohol moiety may be advantageous. Thus, we next prepared compounds bearing a *β*-hydroxymethyl function, and activities of representative compounds are summarized in Table 2.

Initial synthesis of the chemically more tractable α-methyl analogue **22** (6.9 nM) as a single, undefined syn isomer demonstrated an increase in potency relative to the corresponding *β*-hydroxy compound **3**.

By use of a modified asymmetric Ireland−Claisen rearrangement, the corresponding α-(4-fluorophenyl)-*β*-hydroxymethyl analogue was next prepared with the syn (now 2*S*,3*R*) stereochemistry (corresponding to **16**) targeted. Use of the Lewis acid catalyst derived from (*S*,*S*)-bis-sulfonamide **24** in the key rearrangement yielded desired **28**, which demonstrated greatly enhanced potency (IC_{50} = 0.07 nM). Analogues bearing a lipophilic *β*-substituent (**26**, **27**, **29**, **30**) all showed reduced levels of potency with only the *β*-methyl analogue **30** retaining moderate activity, suggesting an

interaction of the hydroxyl group to be important in the binding of these analogues.

Further hydroxyl homologation to the β-hydroxylethyl analogue **32** led to a large reduction in potency. The optimal C-3 amide side chain could also be introduced onto other benzodiazepine cores to yield, for example, **34** or **36** with maintenance of excellent levels of potency. Selective N-methylation of **34** was also possible, and this transformation using CT_3I was utilized in the synthesis of radiolabel (CT_3)-**28**, which has found use in in vitro binding studies.[32]

Conclusions. A series of benzodiazepine γ-secretase inhibitors bearing a C-3 hydrocinnamide side chain has been developed and yielded highly potent compounds (e.g., **34**, 0.06 nM) resulting from systematic optimization of hydroxylated derivatives. This compound was prepared using a modified Corey asymmetric Ireland−Claisen rearrangement. The N(1)−H analogue **34** could also be radiolabeled by N-methylation to yield the useful radioligand (CT_3)-**28**.

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Supporting Information Available: Spectral data for all new compounds, experimental protocols for the asymmetric Ireland−Claisen reaction and radiolabeling process and details of the biological assay protocol. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Jhee, S.; Shiovitz, T.; Crawford, A. W.; Cutler, N. R. Beta-amyloid therapies in Alzheimer's Disease. *Expert Opin. Invest. Drugs* **2001**, *10*, 593−605.
(2) Sambamurti, K.; Grieg, N. H.; Lahiri, D. K. Advances in the cellular and molecular biology of the β-amyloid protein in Alzheimer's disease. *NeuroMol. Med.* **2002**, *1*, 1−31.
(3) Rogaeva, E. The solved and unsolved mysteries of the genetics of early-onset Alzheimer's disease. *NeuroMol. Med.* **2002**, *2*, 1−10.
(4) Wolfe, M. S. Presenilin and gamma-secretase: structure meets function. *J. Neurochem.* **2001**, *76*, 1615−1620.
(5) Checler, F. The multiple paradoxes of presenilins. *J. Neurochem.* **2001**, *76*, 1621−1627.
(6) Selkoe, D. J. Alzheimer's disease: genes, proteins, and therapy. *Physiol. Rev.* **2001**, *81*, 741−766.
(7) Hardy, J.; Higgins, G. A. Alzheimer's disease: the amyloid cascade hypothesis. *Science* **1992**, *256*, 184−185.
(8) Selkoe, D. J.; Podlisny, M. B.; Joachim, C. L.; Vickers, E. A.; Lee, G.; Fritz, L. C.; Oltersdorf, T. β-Amyloid precursor protein of Alzheimer disease occurs as 110- to 135-kD membrane-associated proteins in neural and nonneural tissues. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 7341−7345.
(9) Tsai, J.-Y.; Wolfe, M. S.; Xia, W. The search for γ-secretase and development of inhibitors. *Curr. Med. Chem.* **2002**, *9*, 1087−1106.
(10) Several other substrates for γ-secretase are now known, most notably Notch. For a review, see the following. Sisodia, S. S.; St. George-Hyslop, P. H. γ-Secretase, Notch, Aβ and Alzheimer's disease: Where do the presenilins fit in? *Nat. Rev. Neurosci.* **2002**, *3*, 281−290.
(11) Felsenstein, K.; Smith, D. W.; Poss, M. A.; Chaturvedula, P.; Sloan, C. P. 5-Amino-6-cyclohexyl-4-hydroxy-hexanamide derivatives as inhibitors of β-amyloid protein production. U.S. Patent 5,703,129, 1997.
(12) Wolfe, M. S.; Citron, M.; Diehl, T. S.; Xia, W.; Donkor, I. O.; Selkoe, D. J. A Substrate-based difluoro ketone selectively inhibits Alzheimer's γ-secretase activity. *J. Med. Chem.* **1998**, *41*, 6−9.
(13) Higaki, J. N.; Chakravarty, S.; Bryant, C. M.; Cowart, L. R.; Harden, P.; Scardina, J. M.; Mavunkel, B.; Luedtke, G. R.; Cordell, B. A combinatorial approach to the identification of dipeptide aldehyde inhibitors of β-amyloid production. *J. Med. Chem.* **1999**, *42*, 3889−3898.
(14) Thompson, R. C.; Wilkie, S.; Stack, D. R.; Vanmeter, E. E.; Shi, Q.; Britton, T. C.; Audia, J. E.; Reel, J. K.; Mabry, T. E.; Dressman, B. A.; Cwi, C. L.; Henry, S. S.; McDaniel, S. L.; Stucky, R. D.; Porter, W. J. Preparation of cyclic amino acid compounds for inhibiting β-amyloid peptide release and/or its synthesis. Patent WO 9967221, 1999.
(15) Olson, R. E.; Liu, H.; Thompson, L. A., III. Preparation and use of hydroxyalkanoyl aminolactams and related structures as inhibitors of Aβ protein production. Patent WO 0119797, 2001.
(16) Rishton, G. M.; Retz, D. M.; Tempest, P. A.; Novotny, J.; Kahn, S.; Treanor, J. J. S.; Lile, J. D.; Citron, M. Fenchylamine sulfonamide inhibitors of amyloid β peptide production by the γ-secretase proteolytic pathway: potential small-molecule therapeutic agents for the treatment of Alzheimer's disease. *J. Med. Chem.* **2000**, *43*, 2297−2299.
(17) Seiffert, D.; et al. Presenilin-1 and -2 are molecular targets for γ-secretase inhibitors. *J. Biol. Chem.* **2000**, *275*, 34086−34091.
(18) Belanger, P. C.; Collins, I. J.; Hannam, J. C.; Harrison, T.; Lewis, S. J.; Madin, A.; McIver, E. G.; Nadin, A. J.; Neduvelil, J. G.; Shearman, M. S.; Smith, A. L.; Sparey, T. J.; Stevenson, G. I.; Teall, M. R. Synthesis of sulfonamido-substituted bridged bicycloalkyl derivatives as γ-secretase inhibitors. Patent WO 0170677, 2001.
(19) Dovey, H. F.; et al. Functional gamma-secretase inhibitors reduce beta-amyloid peptide levels in brain. *J. Neurochem.* **2001**, *76*, 173−181.
(20) Clarke, E. E.; Shearman, M. S. Quantitation of amyloid-β peptides in biological milieu using a novel homogeneous time-resolved fluorescence (HTRF) assay. *J. Neurosci. Methods* **2000**, *102*, 61−68.
(21) Churcher, I.; Ashton, K.; Butcher, J. W.; Clarke, E. E.; Harrison, T.; Owens, A. P.; Teall, M. R.; Williams, S.; Wrigley, J. D. J. A new series of potent benzodiazepine γ-secretase inhibitors. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 179−183.
(22) Castro Pineiro, J. L.; Churcher, I.; Guiblin, A. R.; Harrison, T.; Kerrad, S.; Madin, A.; Nadin, A. J.; Owens, A. P.; Sparey, T. J.; Teall, M. R.; Williams, S. Benzodiazepine derivatives as amyloid precursor protein modulators. Patent WO 0190084, 2001.
(23) Evans, D. A.; Ennis, M. D.; Mathre, D. J. Asymmetric alkylation reactions of chiral imide enolates. A practical approach to the enantioselective synthesis of α-substituted carboxylic acid derivatives. *J. Am. Chem. Soc.* **1982**, *104*, 1737−1739.
(24) Reider, P. J.; Davis, P.; Hughes, D. L.; Grabowski, E. J. J. Crystallization-induced asymmetric transformation: stereospecific synthesis of a potent peripheral CCK antagonist. *J. Org. Chem.* **1987**, *52*, 955−957.
(25) Sydnes, L. K. Chemistry of gem-dihalocyclopropanes. XII. Preparation of gem-dibromocyclopropyl ketones and alkyl gem-dibromocyclopropanecarboxylates under phase transfer conditions. *Acta Chem. Scand., Ser. B* **1977**, *31*, 823−825.
(26) Svendsen, J. S.; Sydnes, L. K. Selective formation of 4-bromo-3-methyl-2-(5*H*)-furanone by solvolysis of 2,2-dibromo-1-methyl cyclopropanecarboxylic acid. *Acta Chem. Scand.* **1990**, *44*, 202−204.
(27) Miyaura, N.; Yanagi, T.; Suzuki, A. The palladium-catalyzed cross-coupling reaction of phenylboronic acid with haloarenes in the presence of bases. *Synth. Commun.* **1981**, *11*, 513−519.
(28) Heitz, M.-P.; Overman, L. E. Complementary use of iminium ion and *N*-acyl iminium ion cyclization initiators for asymmetric synthesis of both enantiomers of hydroxylated indolizidines. *J. Org. Chem.* **1989**, *54*, 2591−2596.
(29) Corey, E. J.; Lee, D.-H. Highly enantioselective and diastereoselective Ireland−Claisen rearrangement of achiral allylic esters. *J. Am. Chem. Soc.* **1991**, *113*, 4026−4028.
(30) For a review of asymmetric Claisen rearrangements, see the following. Enders, D.; Knopp, M.; Schiffers, R. Asymmetric [3.3]-sigmatropic rearrangements in organic synthesis. *Tetrahedron, Asymmetry* **1996**, *7*, 1847−1882.
(31) Claremon, D. A.; Liverton, N.; Selnick, H. G.; Smith, G. R. Preparation of novel *N*-(1-alkyl-5-phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-3-yl)acetamides for treatment of arrhythmia. Patent WO 9640653, 1996.
(32) Clarke, E. E.; Churcher, I.; Wrigley, J. D. J.; Harrison, T.; Shearman, M. S.; Beher, D. Manuscript in preparation.

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