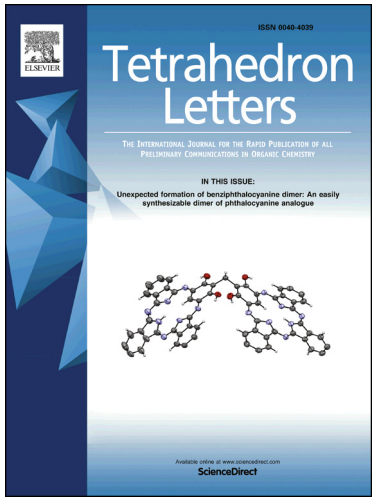

Highly Stereoselective Asymmetric Aldol Routes to *tert*-Butyl-2-(3,5-difluorophenyl)-1-oxiran-2-yl)ethyl)carbamates: Building Blocks for Novel Protease Inhibitors

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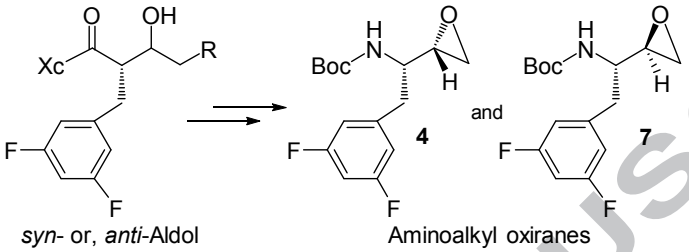

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ABSTRACT

Enantioselective syntheses of *tert*-butyl ((*S*)-2-(3,5-difluorophenyl)-1-((*S*)-oxiran-2-yl)ethyl)carbamate and ((*S*)-2-(3,5-difluorophenyl)-1-((*R*)-oxiran-2-yl)ethyl)carbamate are described. We utilized asymmetric *syn*- and *anti*-aldol reactions to set both stereogenic centers. We investigated ester-derived Ti-enolate aldol reactions as well as Evans' diastereoselective *syn*-aldol reaction for these syntheses. We have converted optically active ((*S*)-2-(3,5-difluorophenyl)-1-((*S*)-oxiran-2-yl)ethyl)carbamate to a potent β-secretase inhibitor.

The design of aspartic acid protease inhibitors continues to be an important area for drug development and discovery against a variety of human diseases.[1] These include renin inhibitors for hypertension, HIV protease inhibitors for HIV/AIDS and β- and γ-secretase inhibitors for Alzheimer's disease.[1-3] The β-secretase inhibitors are particularly receiving much attention due to their potential for the treatment of Alzheimer's disease (AD).[4] BACE1 is a membrane anchored aspartic acid protease, responsible for the initial cleavage of amyloid precursor protein to neurotoxic amyloid-β-peptides in the brain. The amyloid-β-peptide is the main component of amyloid plaques, the neuropathological hallmark of AD.[5,6] Since the discovery of BACE1 in 1999, extensive research efforts led to the evolution of a variety of small-molecule peptidomimetic and non-peptide BACE1 inhibitors with therapeutic potentials.[7,8] Over the years, many potent and selective peptidomimetic BACE1 inhibitors have been designed based upon incorporation of traditional hydroxyethylene and hydroxyethylamine transition-state isosteres at the cleavage site of BACE1.[4,9,10] The majority of early BACE1 inhibitors containing phenylalanine and leucine side chains as the P1 ligand showed low nanomolar BACE1 K_i values and they also exhibited good reduction of cellular Aβ production.[4,7,8] At present, there are at least three small molecule BACE1 inhibitors advanced to clinical trials.[11,12]

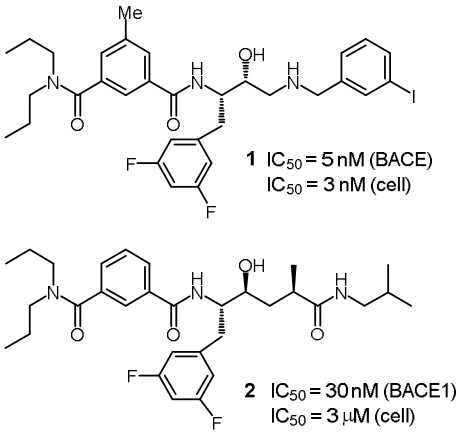

Figure 1. Structures of BACE-1 inhibitors **1** and **2**.

A clinically effective BACE1 inhibitor, however, needs to have the ability to cross the blood-brain barrier (BBB) and the neuronal membrane.[13] In this context, traditional transition-state isosteres were made more lipophilic by inserting fluorines in an effort to improve membrane permeability, metabolic stability, and enzyme-inhibitor interactions.[4,7,8] As exemplified in Figure 1,

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peptidomimetic inhibitors **1** (BACE1 IC_{50} = 5 nM; Cell IC_{50} = 3 nM) and **2** (BACE1 IC_{50} = 30 nM; Cell IC_{50} = 3 μM) incorporated hydroethylamine and hydroxyethylene dipeptide isosteres, respectively, with a 3,5-difluorophenylmethyl group as the P1 ligand.[14,15] These difluoro-dipeptide isosteres have been utilized in the design and synthesis of many other potent and selective BACE1 inhibitors with BBB permeability.[4,7,8]

In general, BACE1 inhibitors containing hydroxyethylamine isosteres show potent BACE1 inhibitory activity and cellular activity. The synthesis of inhibitors involves the opening of an aminoalkyl epoxide with an appropriate amine followed by the functionalization of the *N*-terminus with suitable P2 ligands.[2,4] As shown in Figure 2, BACE1 inhibitors containing a 3,5-difluorophenylmethyl side chain as the P1 ligand in a general inhibitor **3**, can be synthesized from *tert*-butyl-((*S*)-1-(*S*)-oxiran-2yl)-2-phenylethyl carbamate **4**. Enantioselective synthesis of such epoxide is typically carried out with optically active 3,5-difluorophenyl alanine **5**.[16,17] In our continuing interest in the design and synthesis of novel BACE1 inhibitors containing fluorines at P1-ligand, we have investigated the synthesis of difluoroepoxide **4** utilizing an asymmetric *syn*-aldol as the key step.[18,19] In principle, aldol product such as **6** would provide access to epoxide by removal of chiral auxiliary (X_C) followed by Curtius rearrangement of the resulting acid to install the amine functionality.[20,21] Furthermore, *anti*-aldol product such as **8**, obtained from a diastereoselective *anti*-aldol reaction,[22] could provide access to diastereomeric oxirane derivative **7** for the synthesis of BACE1 inhibitors with hydroxyethylene isosteres. Herein, we report a highly diastereoselective synthesis of (2*R*, 3*S*)-1,2-epoxy-3-(Boc-amino)-4-(3,5-difluorophenylmethyl) -butane **4** and (2*R*, 3*R*)-1,2-epoxy-3-(Boc-amino)-4-(3,5-difluorophenylmethyl)butane **7** (Figure 2) utilizing an asymmetric aldol reaction as the key step. The overall route is amenable to quantities of difluoroepoxide cores **4** and **7** in high optical purity.

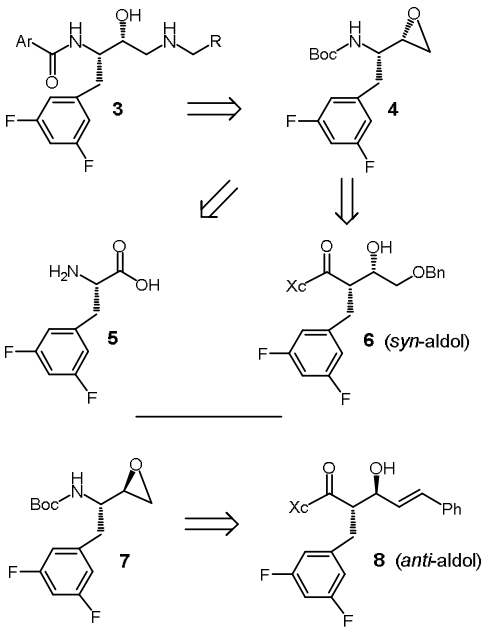
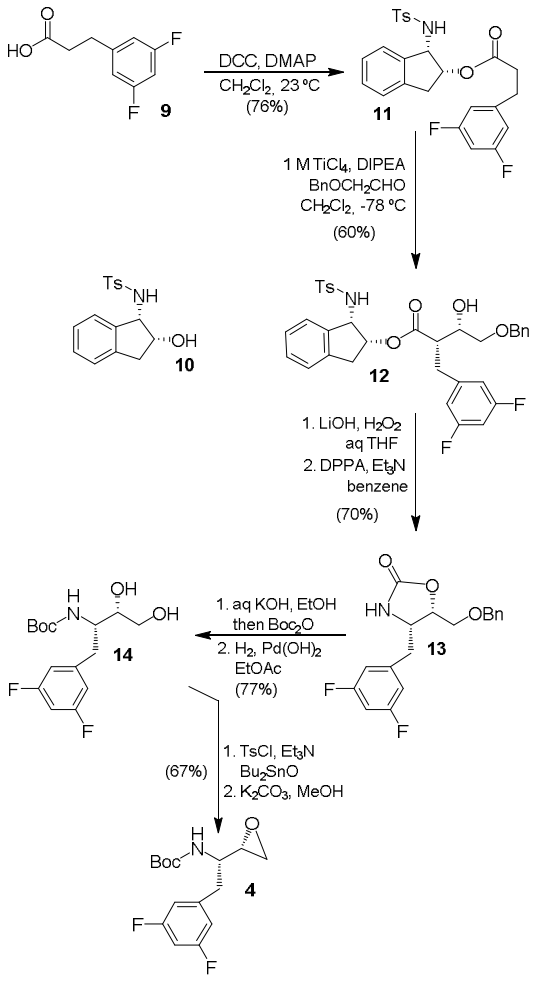


Figure 2. Structures of epoxides **4** and **8** and their respective aldol precursors

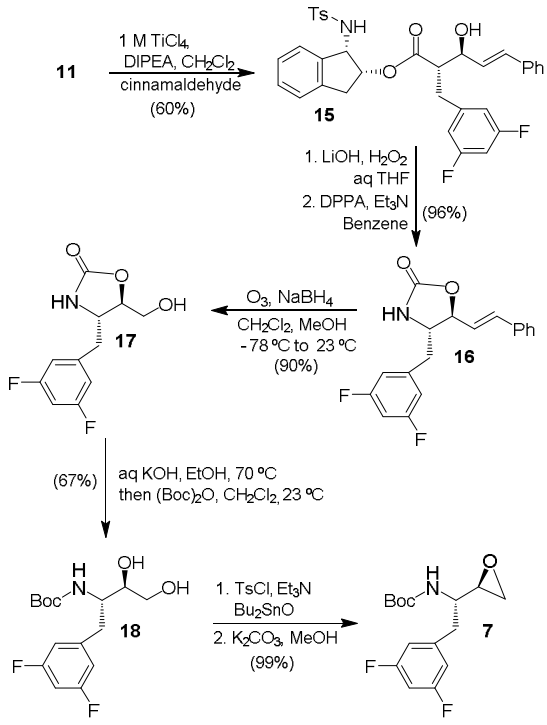
We first investigated ester-derived titanium-enolate based aldol reactions to afford both *syn*- and *anti*-aldol products for the stereoselective synthesis of aminoalkyl oxiranes **4** and **7**. These reactions have been utilized in the synthesis of a number of dipeptide isosteres.[19,20,23] The synthesis of oxirane **4** using *syn*-aldol reaction is shown in Scheme 1. 3,5-Difluorohydrocinnamic acid **9** was prepared in multigram scale as described in the literature.[24,25] Reaction of this acid with commercially available *N*-tosyl-1-aminoindan-2-ol **10** with DCC in the presence of DMAP in CH_2Cl_2 at 23 °C for 18 h afforded ester **11** in 76% yield. Treatment of ester **11** with 1M $TiCl_4$ in the presence of diisopropylethylamine (DIPEA) in CH_2Cl_2 at 0 °C to 23 °C for 2 h provided the corresponding Ti-enolate. Reaction of this Ti-enolate with (benzyloxy)acetaldehyde precomplexed with $TiCl_4$ in CH_2Cl_2 (1 M CH_2Cl_2) at -78 °C for 2 h provided the *syn*-aldol



Scheme 1. Synthesis of 3,5-difluorobenzyl epoxide **4**

product **12** in 60% yield. The ^{1}H-NMR analysis revealed the presence of a single diastereomer. Saponification of aldol product **12** with aqueous lithium hydroperoxide at 0 °C to 23 °C for 12 h provided the corresponding acid which was subjected to Curtius rearrangement[20,26] with diphenylphosphorazidate in the presence of triethylamine in dry benzene at 90 °C for 12 h to afford oxazolidinone derivative **13** in 70% yield over 2-steps. Oxazolidinone was converted to Boc-derivative **14** in a two-step sequence. Hydrolysis of **13** with aqueous KOH provided aminoalcohol which was reacted with di-*tert*-butyl dicarbonate in a mixture (1:1) of CH_2Cl_2 and water at 23 °C for 4 h to affod the Boc-derivative. Catalytic hydrogenation of benzyl ether over Pearlman's catalyst using a hydrogen-filled balloon in ethyl acetate removed the benzyl group and diol **14** was obtained in 77% yield over 2-steps. The diol **14** was converted to epoxide **4**

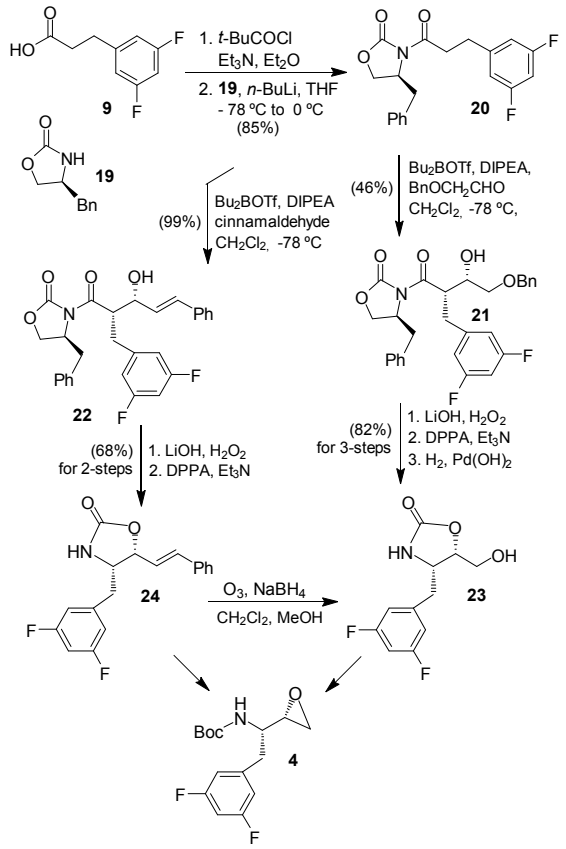
by a regioselective monotosylation of the primary alcohol with *p*-toluenesulfonylchloride and triethylamine in the presence of a catalytic amount (25 mol %) of dibutyltin oxide at 23 °C for 4 h to provide the corresponding tosylate. Exposure of this tosylate to K_2CO_3 in MeOH at 0 °C to 23 °C for 1 h afforded (*S*)-2-(3,5-difluorophenyl)-1(*S*)-oxiranyl ethyl carbamate **4** in 67% yield over two-steps. The overall route is straightforward and provided fluorine substituted chiral epoxide for the synthesis of BACE1 inhibitors.



Scheme 2. Synthesis of 3,5-difluorobenzyl epoxide **7**

For the synthesis of 3,5-difluorobenzyl oxirane **7**, we carried diastereoselective *anti*-aldol reaction of ester **11** with cinnamaldehyde as shown in Scheme 2. Ester **11** was converted to Ti-enolate with 1M $TiCl_4$ in CH_2Cl_2 in the presence of DIPEA as described above. This enolate was reacted with *trans*-cinnamaldehyde precomplexed with 1.3 equivalents of $TiCl_4$ at -78 °C for 3 h to provide *anti*-aldol product **15** as a single isomer (by ^{1}H-NMR and ^{13}C-NMR analysis). Saponification of ester **15** with aqueous lithium hydroperoxide followed by Curtius rearrangement of the resulting acid as described above resulted in oxazolidinone derivative **16** in 96% yield over 2-steps. Ozonolytic cleavage of the double bond in compound **16** was achieved by passing ozone in a mixture (4:1) of CH_2Cl_2 and MeOH at -78 °C followed by reduction with $NaBH_4$ providing alcohol **17** in 90% yield. Exposure of alcohol **17** to aqueous KOH followed by reaction of the resulting aminoalcohol with $(Boc)_2O$ in CH_2Cl_2 afforded Boc-derivative **18** in 67% yield. Diol derivative **18** was converted to (*S,R*)-3,5-difluorophenyl oxirane **7** by selective tosylation followed by treatment of the resulting tosylate with K_2CO_3 in MeOH as described for compound **14** in Scheme 1 to provide oxirane **7** in 67% yield over 2-steps.

The synthesis of (*S*)-2-(3,5-difluorophenyl)-1-(*S*)-(oxiran-2-yl)ethyl carbamate **4** using Evans' *syn*-aldol reaction is shown in Scheme 3. Difluorohydrocinnamic acid **9** was transformed into a mixed anhydride with pivaloyl chloride and triethylamine at -78 °C. The resulting mixed anhydride was reacted with lithio derivative of chiral oxazolidinone **19** to furnish carboximide **20**.[27,28] Treatment of this chiral carboximide derivative with dibutylboron trifluoromethanesulfonate (Bu_2BOTf) in the presence of *N,N*-diisopropylethylamine at -78 °C provided the boron enolate. Reaction of this boron enolate with benzyloxy acetaldehyde furnished aldol product **21** in 46% yield after standard work up and silica gel chromatography. The ^{1}H- and ^{13}C-NMR analysis showed the presence of a single diastereomer. In an effort to improve the overall efficiency of this asymmetric aldol route, we further explored the Evan's asymmetric aldol reaction of chiral carboximide **20** with relatively inexpensive cinnamaldehyde. As shown in Scheme 3, formation of boron enolate with Bu_2BOTf and aldol reaction with cinnamaldehyde proceeded very well providing *syn*-aldol product **22** in near quantitative yield. Aldol product **22** was obtained as a single diastereomer by ^{1}H- and ^{13}C-NMR analysis. This is a significant improvement over aldol reaction with benzyloxyacetaldehyde for aldol product **21**. Exposure of aldol product **21** to lithium hydroperoxide in aqueous THF at 0 °C to 23 °C for 10 h to provide the corresponding carboxylic acid. This acid was subjected to Curtius rearrangement[20,21] with diphenyl phosphorazidate in the presence of triethylamine in toluene at 90 °C for 16 h to provide the corresponding oxazolidinone derivative. Catalytic hydrogenation of benzyl ether over Pearlman's catalyst provided alcohol **23** in 82% yield over 3-steps. This was converted to epoxide **4** as described above.

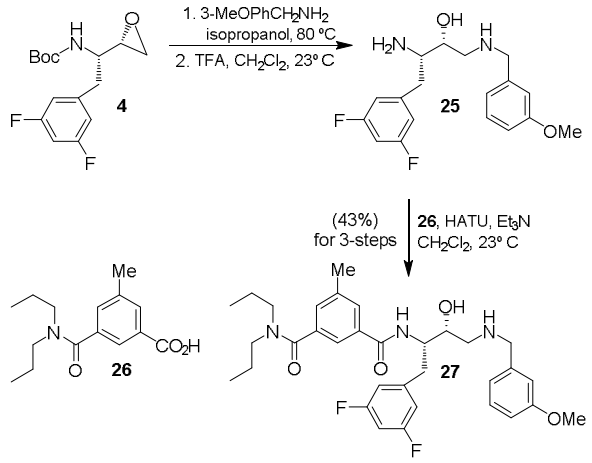


Scheme 3. Synthesis of 3,5-difluorobenzyl epoxide **4**

Aldol product **22** was also converted to epoxide **4**. The removal of the chiral auxiliary by exposure to lithium hydroperoxide followed by Curtius rearrangement of the resulting acid with DPPA as described above furnished oxazolidinone derivative **24** in 68% yield after silica gel chromatography. Ozonolysis of the double bond in a mixture

(4:1) of CH_2Cl_2 and methanol at -78 °C followed by a reductive workup with $NaBH_4$ furnished alcohol **23** in 90% yield. Alcohol **23** was readily converted to Boc-derivative **14** by exposure to aqueous KOH in ethanol followed by protection of the resulting crude amine as Boc derivative **14** as described previously.

We demonstrated the utility of difluorophenylethyl oxirane derivative **4** in the synthesis of known BACE1 inhibitor **27**.[14] As shown in Scheme 4, reaction of oxirane **4** with 3-methoxybenzylamine in isopropanol at 80 °C for 12 h provided the corresponding aminoalcohol. Deprotection of the Boc-group by exposure to trifluoroacetic acid (TFA) in CH_2Cl_2 at 23 °C for 2 h afforded aminoalcohol **25**. Coupling of the primary amine with known[14] isophthalic acid derivative **26** in the presence of HATU and triethylamine in CH_2Cl_2 at 23 °C for 16 h furnished inhibitor **27** in 43% yield over three steps.



Scheme 4. Synthesis of BACE1 inhibitor **27**

In conclusion, we accomplished convenient syntheses of aminoalkyl oxiranes **4** and **7** containing 3,5-difluorobenzyl side chain using an asymmetric aldol reaction as the key step. The stereochemistry of both stereogenic centers was set by highly diastereoselective *syn*- and *anti*-aldol reactions. The removal of the chiral auxiliary followed by Curtius rearrangement of the resulting acid installed the amine functionality. This was readily converted to epoxides **4** and **7** efficiently. These epoxides are important building blocks for the synthesis of a variety of BACE1 inhibitors incorporating hydroxyethylamine and hydroxyethylene isosteres. The overall route is quite efficient, scalable and provides facile access to diverse inhibitors. We have converted epoxide **4** to BACE1 inhibitor **27**. Further application of these epoxides in the synthesis of novel protease inhibitors is in progress in our laboratory.

Acknowledgments

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Supplementary Data

Supplementary data associated with this article can be found in the online version.

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Highlights

- Enantioselective syntheses of difluorinated aminoalkyl epoxides are reported.
- The synthesis utilized Ti-enolate and boron-enolate asymmetric aldol reactions.
- Aldol products were obtained with high diastereoselectivites and in good yields.
- Curtius rearrangement of β-hydroxy acids installed the amine functionalities.
- A fluorinated aminoalkyl oxirane was converted to a potent BACE1 inhibitor.