Tetrahedron Letters 51 (2010) 6542–6544

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

A synthesis of the γ-secretase inhibitor BMS-708163

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ARTICLE INFO

Article history:
Received 21 July 2010
Revised 28 September 2010
Accepted 6 October 2010
Available online 14 October 2010

ABSTRACT

A concise, convergent racemic synthesis of BMS-708163 is reported. Two fragments consisting of *N*-4-chlorophenylsulfonyl-3,3,3-trifluorpropylglycine and a 1,2,4-oxadiazole derivative of 2-fluorobenzyl alcohol were prepared in separate pots and then coupled together via a Mitsunobu reaction. Since a convenient chiral synthesis of optically pure (D)-3,3,3-trifluoropropyl glycine methyl ester was developed using Schöllkopf reagent alkylation, this methodology can also be adopted for the enantioselective synthesis of BMS-708163.

Alzheimer's disease (AD) claims more than 4 million lives in the United States alone and many more in the world every year.[1a,b] One of the hallmarks of this debilitating disease is the presence of amyloid-β-containing peptide plaques in the brain. There is considerable evidence that Aβ-42, the longer form of the two Aβ-peptides shows stronger tendency to cause deposition of extracellular insoluble plaques in the AD brain.[1c,2] Other genetic, biophysical, and toxicological data emerging from studies of familial forms of AD and transgenic animal modeling of amyloid β-protein precursor (APP) and presenilin (PS) mutants have also implicated Aβ42 in the pathogenesis of this senile disease.[3] Therefore, an immediate possibility to treat AD may suggest itself in developing drugs for AD that may target Aβ42. A key APP-processing aspartic protease enzyme in the biogenetic pathway leading to the generation of the 1–42 Aβ-peptide is the γ-secretase complex.[4] However, this enzyme complex is known to endoproteolyze APP as well as several other transmembrane proteins, including Notch.[5] Most of these γ-secretase inhibitors developed over the years show no significant desired selectivity toward APP-processing over the undesired Notch processing. Recently, Bristol-Myers Squibb has developed an orally bioavailable, Notch-sparing γ-secretase inhibitor, BMS-708169[6] (Fig. 1) that is currently undergoing clinical trials.[7]

To the best of our knowledge, BMS-708163 is not available commercially. However, details of its chemical synthesis have recently been reported.[6,8] The main features of the reported synthesis are: (1) preparation of the optically pure (D)-α-3,3,3-trifluoropropylglycinamide **a** (Fig. 1) which was obtained by employing an asymmetric Strecker synthesis as a key step, and, (2) *N*-sulfonylation of the glycinamide **a** with 4-chlorobenzenelsolfonyl chloride to give a sulfonamide, (3) coupling of the sulfonamide with 4-bromomethyl-3-fluorobenzonitrile to give **b**, and finally, (4) conversion of the cyano function of **b** to a *N*-hydroxyamidine followed by ring closure to BMS-808163.

For our ongoing pharmacological studies, an efficient method for generating racemic version of BMS-708163 was considered sufficient. Therefore racemic 3,3,3-trifluoromethylglycine ethyl ester **3** (Scheme 1) was prepared utilizing acetamidomalonic ester synthesis.[9] The use of 3,3,3-trifluoropropyl iodide electrophile in the S_N2-reaction with the anion derived from diethyl acetamidomalonate gave the desired α-substituted diester in poor yield. However, the same reaction with a trifluoromethanesulfonyl derivative of the 3,3,3-trifluoropropyl alcohol **1** produced the diester **2** in 63% yield. Standard decarboxylation of the diester followed by Fischer esterification furnished 3,3,3-trifluorpropylglycine ethyl

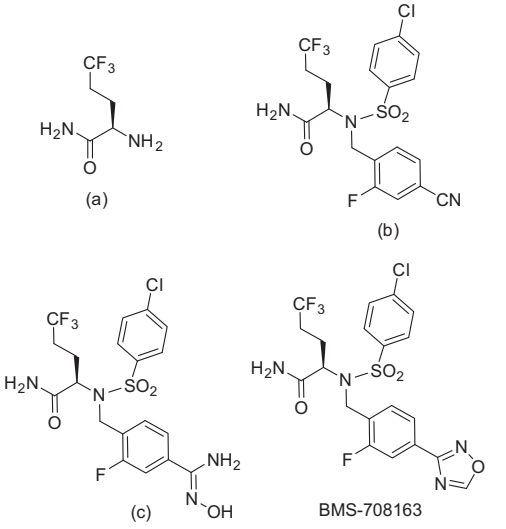

Figure 1. BMS-708163 and reported synthetic intermediates.[6,8]

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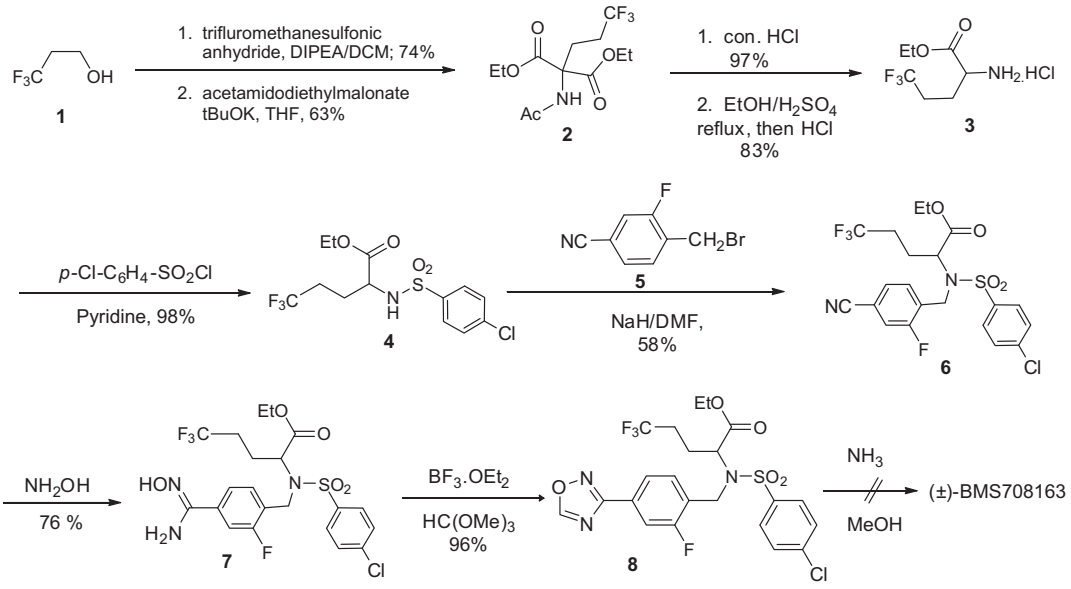
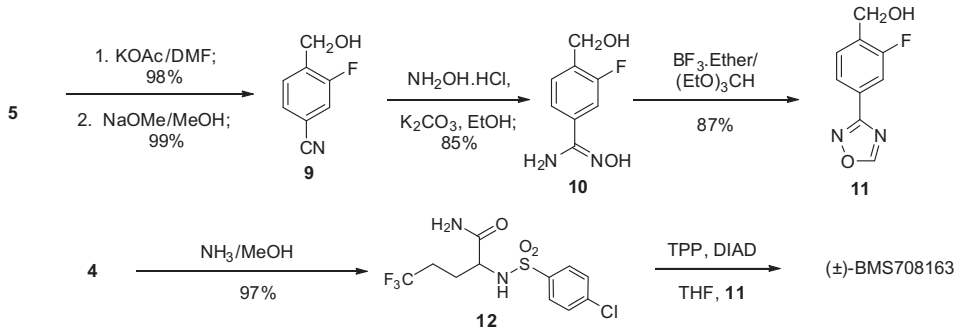
doi:10.1016/j.tetlet.2010.10.025



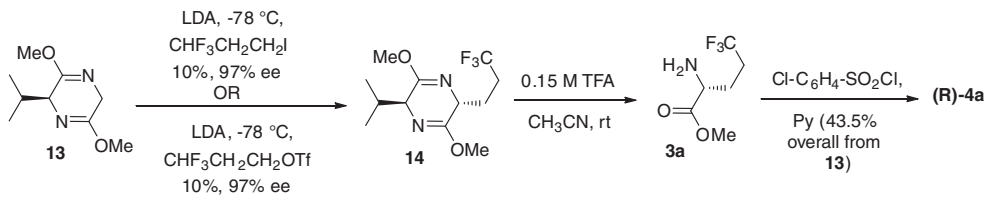
Scheme 1. Plan A: Synthesis of racemic BMS-708163.



Scheme 2. Plan B: Synthesis of racemic BMS-708163.

ester hydrochloride **3** in 81% combined yield. The aminoester **3** underwent *N*-sulfonylation with 4-chlorobenezesulfonyl chloride in pyridine at ambient temperature to give the sulfonamide **4** in high yield. The reaction of the sodio anion of **4** with 4-bromomethyl-3-fluoro-benzononitrile **5** produced the tertiary sulfonamide **6** in moderate (58%) yield. Controlled reaction of hydroxylamine with **6** in ethanol proceeded without incident to give the *N*-hydroxyamidine **7** (76%). A ring closure of the *N*-hydroxyamidine **7** with triethyl orthoformate under boron trifluoride etherate catalysis gave 1,2,4-oxadiazole **8** in 96% yield. However, attempted ammonolysis of the ester **8** in methanol under various conditions to the final BMS-708163 failed because of competing reaction of ammonia with the 1,2,4-oxadiazole ring. Therefore, this route was abandoned in favor of a plan that called for installing the required carboxamide function earlier in the synthetic sequence prior to conversion of a nitrile function to 1,2,4-oxadiazole ring. This amounted to adopting a convergent route to BMS-708163.

Since the S_N2-reaction of 4-bromomethyl-3-fluorobenzonitrile **5** with the sulfonamide anion derived from **4** (Scheme 1) had resulted in moderate yield, we decided to make use of a Mitsunobu reaction[10] instead. To this end, the bromide function of **5** was converted to a hydroxyl group by first displacing it with an acetate anion, then saponifying the resulting acetate. The two steps resulted in 99% yield of the 3-fluoro-4-hydroxymethylbenzonitrile **9** (Scheme 2). Addition of hydroxylamine to the nitrile function occurred smoothly to give the *N*-hydroxyamidine **10** (85%) that could be cyclized to 1.2,4-oxadiazole **11** with triethyl orthoformate



Scheme 3. Chiral synthesis of the amino ester **4a**.

under a Lewis acid catalysis in high yield.[11] In another pot, the sulfonamide ester **12** was generated by treating the amino ester **3** with a saturated solution of ammonia in methanol. The alcohol **11** was then coupled with the *N*-4-chlolrobenzenesulfonyl carboxamide **12** using a Mitsunobu protocol that furnished BMS-708163 in 66% isolated yield after silica gel purification.

The synthesis of enantiomeric forms of **3** is known.[6,8,12] We attempted an alternative, shorter, and more convenient method to generate **3**, based on Schöllkopf reagent diastereoselective alkylation.[13] Thus, the lithio anion derived from the reagent **13** (Scheme 2) was alkylated at −78 °C in tetrahydrofuran with 1-iodo-3,3,3-trifluoropropane to give diastereomerically enriched product **14** in low (10%) but with 97% de (Scheme 3). The yield was considerably improved (61%) by using 3,3,3-trifluoropropyl trifluormethanesulfonate as an electrophile, but the diastereomeric induction dropped to 74% de and the diastereomers could not be separated by silica gel chromatography. We hoped to separate the desired *R*-isomer of 3,3,3-trifluoropropylglycinamide **3a** at a later stage. Therefore, the enriched diastereomeric mixture **14** was hydrolyzed with 0.15 M aqueous TFA in acetonitrile to afford the desired enantiomerically-enriched (*R*)-methyl 3,3,3-trifluorpropyl glycinate **3a** admixed with the (*S*)-valine methyl ester. Unfortunately, valine ester impurity could not be effectively separated from the **3a**. However, when this scalemic mixture of the two esters was subjected to *N*-sulfonylation, the enantiomerically-enriched methyl sulfonamide derivative (*R*)-**4a** could be readily separated from the corresponding (*S*)-enantiomer of methyl valine sulfonamide (overall yield of (*R*)-**4a** in three steps from Schöllkopf alkylation was 43.5%).

In sum, a concise, convergent racemic synthesis of the APP-selective, Notch-sparing γ-secretase BMS-708163 has been achieved in overall reasonable yield. Since the optically pure (D)-3,3,3-trifluoropropylglycinamide is known in the literature,[6,8,12] this synthesis of BMS-708163 constitutes a formal chiral synthesis as well.

Acknowledgments

The internal financial support provided for this synthetic project by Mayo Foundation is gratefully acknowledged.

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