Tetrahedron Letters 54 (2013) 5541–5543

Contents lists available at ScienceDirect

Tetrahedron Letters

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

4-CF_3-ezetimibe analogs: design, synthesis, and biological evaluation of cholesterol absorption inhibitions

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ARTICLE INFO

Article history:
Received 13 June 2013
Revised 19 July 2013
Accepted 6 August 2013
Available online 13 August 2013

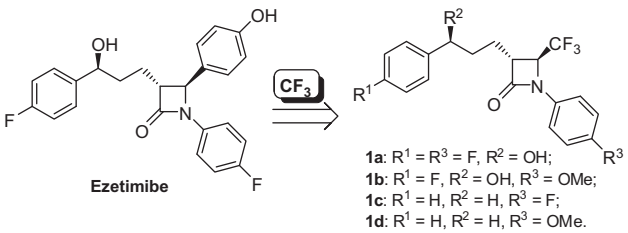
Keywords:
Ezetimibe
Cholesterol
β-Lactam
Trifluoromethyl
Asymmetric hydrogention

ABSTRACT

On the purpose of looking for better cholesterol absorption inhibitors, several trifluoromethyl substituted ezetimibe analogs **1a–d** were designed and synthesized. The key steps in the synthesis of these optically pure *trans*-4-CF_3-β-lactams include chiral auxiliary induced asymmetric hydrogenation and substrate controlled stereoselective alkylation. The inhibitory activities of these target compounds were evaluated on the cholesterol absorption in Caco-2 cells. The result showed that the inhibitory activity of compound **1a** was comparable to ezetimibe.

Ezetimibe is a strong cholesterol absorption inhibitor that reduces plasma low-density lipoprotein fraction (LDL-C). It was approved as the first drug for the treatment of high cholesterol in 2002.[1] Last year, annual worldwide sales for ZETIA (ezetimibe) were $2.57 billion, which puts ezetimibe high on the list of valuable drugs. So the development of new synthetic methods for ezetimibe has become interesting targets for many academic and industrial laboratories.[2] At the same time, a lot of research interests have been put in the synthesis of new ezetimibe derivatives,[3] as the inhibition mechanism of ezetimibe was not fully elucidated at a molecular level.[4] The structure–activity relationship (SAR) studies of ezetimibe analogs are still necessary to develop new cholesterol absorption inhibitors, which might ultimately be useful in preventing cardiovascular disease.[5]

It is well known that the incorporation of fluorine atom and/or fluorine-containing groups into an organic molecule often changes the chemical, physical, and biological properties of the parent compound.[6] Introduction of fluorine atom and/or fluorine-containing groups into biologically active molecules has become an important strategy in the design of pharmaceuticals and agrochemicals.[7] For example, the *p*-fluorine substitution in the N1-phenyl and C3-pendent phenyl rings of ezetimibe was found to block the undesired metabolic transformations,[1b] because of the higher strength of the C–F bond compared to C–H bond. In continuity of our research interest in fluorine-containing biologically active molecules,[8] we designed a series of new 4-CF_3-ezetimibe analogs **1a–d** (Scheme 1), mainly considering from two aspects. First, the C4-position of ezetimibe is the most frequently modified position, and some successful examples have been reported.[3a,9] Secondly, the trifluoromethyl group (CF_3) enjoys a privileged role in the realm of medicinal chemistry because its incorporation into small molecules often enhances the efficacy by promoting electrostatic interactions with targets, improving cellular membrane permeability, and increasing robustness toward oxidative metabolism of the drug. It was also suggested in the literature that introducing the trifluoromethyl group on the β-lactam ring would have a good effect on antibacterial activity.[10] We hope that our target molecules **1** will contribute to the SAR studies of ezetimibe analogs. What is more, the synthesis of **1** is the first example for preparing optically pure 4-trifluormethyl substituted *trans*-β-lactams, which



Scheme 1. Design of target molecules **1a–d**.

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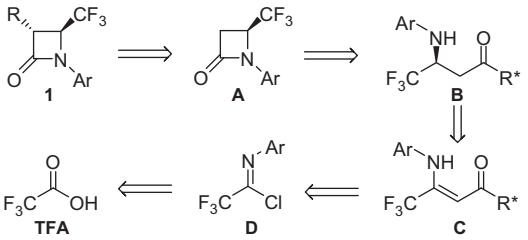
http://dx.doi.org/10.1016/j.tetlet.2013.08.027



Scheme 2. Retrosynthetic analysis of compound **1**.

might be important precursors to other chiral fluorinated compounds.[11]

The retrosynthetic analysis of target molecules **1** is shown in Scheme 2. Compounds **1** can be prepared by alkylation of 4-trifluormethylated β-lactams **A**. Although construction of chiral 4-trifluormethylated β-lactams have been reported by several groups,[11b,d,12] none of them were interested in *N*-aryl derivatives. Herein we proposed a new synthetic route to intermediate **A**. The key step is auxiliary induced asymmetric hydrogenation of enamine **C** to chiral α-trifluoromethyl amine **B**, which can be easily converted to **A** by some transformations. Enamine **C** can be prepared from a simple staring material trifluoroacetic acid (TFA) via the intermediate **D** according to the reported work.[13,14]

The synthesis of target molecules **1** began with TFA, which reacted with 4-substituted anilines in carbon tetrachloride in the presence of triphenylphosphine and triethylamine to give *N*-aryl trifluoroacetimidoyl chlorides **2**, according to the Uneyama's method[13] (Scheme 3). Then, treatment of commercially available chiral amide **3** with lithium diisopropylamide (LDA, 2.0 equiv) at −78 °C in THF generated the corresponding lithium enolate, which reacted with imidoyl chlorides **2** to provide the enamines **4** in good yields and high *Z*/*E* selectivities.[14] After that, we turned our attention to the reduction of enamines **4**, but no reduction product was obtained under the reported reaction condition of $ZnI_2/NaBH_4$.[14] To our delight, Pd/C catalyzed hydrogenation of enamines **4a** and **4b** gave the desired products **5a** and **5b** in high yields and good diastereoselectives (**5a**: 87% yield, dr = 91:9; **5b**: 94% yield, dr = 87:13), respectively. What was more, enantiomerically pure compounds **5a** and **5b** (>99:1 dr) can be obtained in moderate yields via recrystallization of the crude products. From the X-ray crystallographic analysis of compound **5b** (see ESI), the newly formed stereocenter

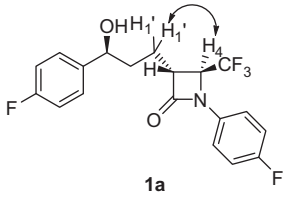
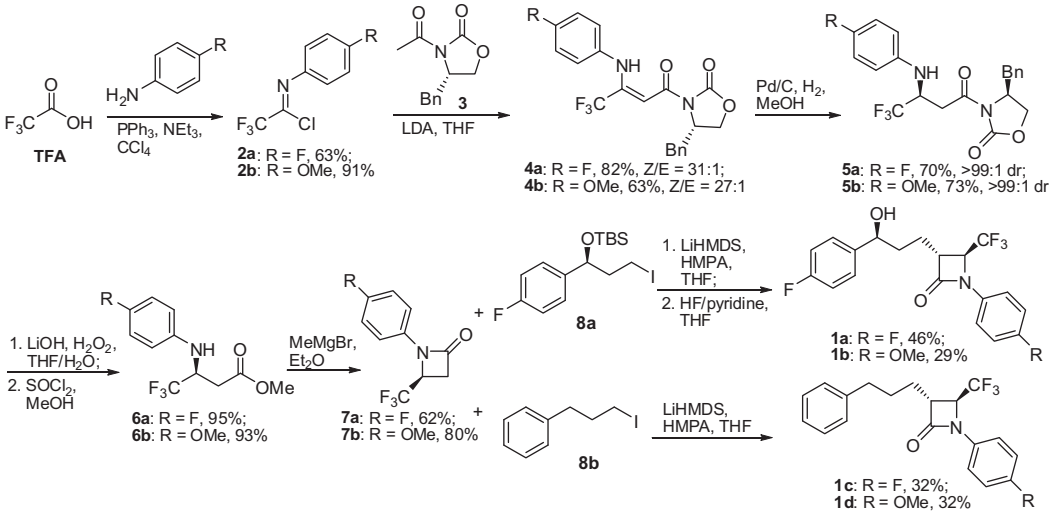


Figure 1. NOE correlation of compound **1a**.

Table 1
Inhibitory effect on the cholesterol absorption in Caco-2 cells

Entry	Compound	Inhibitory rate of ^{3}H cholesterol absorption (%)		
		25 μM	50 μM	100 μM
1	Ezetimibe	15.6 ± 1.6	46.1 ± 1.8	92.9 ± 0.2
2	**1a**	18.6 ± 0.7	30.5 ± 2.8	72.6 ± 1.0
3	**1b**	11.6 ± 1.5	30.0 ± 0.0	45.6 ± 1.1
4	**1c**	23.0 ± 4.0	23.5 ± 0.5	31.4 ± 3.9
5	**1d**	10.8 ± 0.6	18.3 ± 1.1	28.3 ± 0.2

in compounds **5** was confirmed to be (*S*)-configuration, just the same as our desired configuration. With these chiral α-trifluoromethyl amines **5** in hand, the preparation of optically active 4-trifluormethylated β-lactams **7** was operated in general steps. Removing the chiral auxiliary of compounds **5** by treatment with hydrogen peroxide and lithium hydroxide, followed by esterification, gave chiral β-trifluoromethyl-β-amino esters **6** in excellent yields. The β-lactams **7** were obtained by intramolecular cyclization of esters **6** using methyl magnesium bromide as the base.[12b] The final step was to assemble β-lactams **7** with alkyl chains. Coupling of β-lactams **7a** and **7b** with alkyl iodides **8a**[3h] under the condition of LiHMDS/HMPA in THF gave the coupling products, which were then deprotected to afford the final products **1a** and **1b**, respectively. The other two target molecules **1c** and **1d** were obtained by coupling of β-lactams **7a** and **7b** with alkyl iodides **8b**[15] under the same coupling conditions. It was noteworthy that all the coupling reactions exclusively produced the *trans*-isomers. This *trans*/*cis* stereoselectivity is consistent with previous similar alkylation reactions of β-lactams.[16] The absolute configuration of final products **1** was further confirmed by 2D NMR NOESY experiment. As show in Figure 1, correlation between H_4 and H_1' was clearly observed in compounds **1a**.



Scheme 3. Synthesis of target molecules **1a–d**.

Finally, the new trifluoromethylated analogs **1a–d** were subjected to cholesterol absorption experiment in Caco-2 cells, with ezetimibe as the reference. The results are summarized in Table 1. The inhibitory activity of compound **1a** was close to ezetimibe (entries 1 and 2). This result showed that the C4-aryl group of ezetimibe could be replaced by trifluoromethyl group. However, the changes of other position groups of ezetimibe resulted in lower biological activities (entries 3–5).

In conclusion, several trifluoromethyl substituted ezetimibe analogs, optically pure *trans*-4-CF_3-β-lactams **1a–d**, were synthesized in convenient synthetic methods. The inhibitory activities of these analogs were evaluated and compound **1a** showed a good inhibitory activity.

Acknowledgments

We thank the National Natural Science Foundation of China (21072028, 21272036) and the National Basic Research Program of China (2012CB21600) for funding this work.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.08.027.

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