NJC

PAPER

View Article Online
View Journal

A new approach to the stereoselective synthesis of *trans*-3-carbamoyl-β-lactam moieties†

Anna Zakaszewska, Ewelina Najda-Mocarska and Sławomir Makowiec*

Cite this: DOI: 10.1039/c7nj00445a

Received 7th February 2017,
Accepted 14th February 2017

DOI: 10.1039/c7nj00445a

rsc.li/njc

One-pot synthesis of optically active 1,4-disubstituted-3-carbamoyl-azetidinones from 5-[(*N*-arylamino)-(hydroxyl)methylene]-2,2-dimethyl-1,3-dioxa-4,6-diones and chiral aldimines is achieved *via* thermal generation of carbamoyl ketenes and subsequent [2+2] cycloaddition. Three possible chiral induction approaches were tested and (*R*)-(+)-1-phenylethylamine was confirmed as the best chiral auxiliary. Among the four possible diastereoisomers, only two with significant excess of one were formed.

Introduction

Cardiovascular diseases are still the leading cause of death in developed countries.[1] Atherosclerosis associated with the pathological metabolism of fats and cholesterol plays a significant role in the development of these diseases. Among the many methods of treating this type of disorder, the therapy that aims at reducing the level of plasma cholesterol is one of the newest and the most promising methods.[2] Ezetimibe, the first NPC1L1 inhibitor, is a drug used alone or in combination with statins to treat hypercholesterolemia.[3] Despite some suspicions of carcinogenicity, its effectiveness is not to be doubted. Since the discovery of ezetimibe,[4] NPC1L1 inhibitors with various similar structures have been developed, such as AZD 4121 (Astra Zeneca),[5] AVE5530 (Sanofi-Aventis),[6] and SCH-48461[7] (Fig. 1). Formation of an azetidinone ring along with appropriate stereocenters is crucial to the synthesis of such inhibitors. As widely known, β-lactam antibiotics have a *cis* configuration, whereas known inhibitors of cholesterol transport should exhibit a *trans* configuration.

In 1980, Watanabe proposed an unconventional method for the construction of β-lactam rings, based on the thermal decomposition of 5-acyl-2,2-dimethyl-1,3-dioxa-4,6-diones to 2-oxo-ketenes and their subsequent reaction with aldimine.[8] Recently, we have focused our research efforts on the formation of β-lactams during [2+2] cycloaddition of aldimines to β-oxo-ketenes generated from 5-carbamoyl-2,2-dimethyl-1,3-dioxadiones (**1**) under pyrolytic conditions.[9] On a representative series of models, we have observed the exclusive formation of *trans* β-lactam rings.

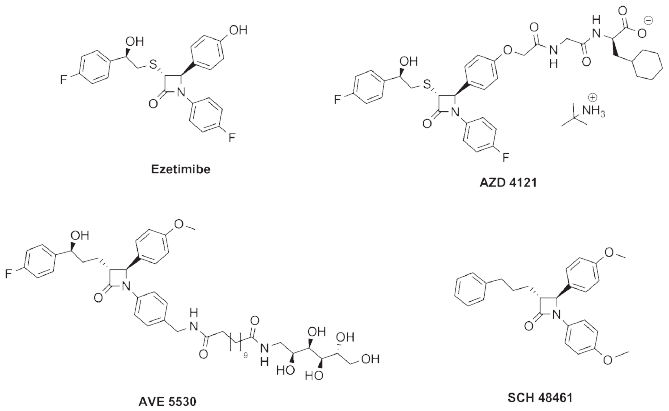

Fig. 1 NPC1L1 inhibitors.

However, the presence of a *trans* configuration is not the only necessary criterion that increases the potential of cholesterol absorption inhibitors, since only one from a pair of enantiomers can exhibit biological activity.[10] Therefore, we hypothesize that the application of a recently developed method along with suitable chiral induction would lead to the formation of only one diastereoisomer of 3-carbamoyl β-lactam. Such a method could be a simple one-pot procedure for the formation of ezetimibe-like scaffolds.

Our previous research carried out with 5-acyl-2,2-dimethyl-1,3-dioxadiones as a source of ketenes and chiral aldimines confirmed our hypothesis. However, yields of azetidinones obtained with chiral induction compared to those obtained by experiments conducted without chiral induction were worse.[11]

Results and discussion

Our study discusses a methodology for synthesizing diastereoisomerically enriched 3-carbamoyl-β-lactams and proposes an exhaustive study on the relationship between the type and position

Department of Organic Chemistry, Faculty of Chemistry, Gdansk University of Technology, Narutowicza 11/12, 80-233 Gdansk, Poland. E-mail: mak@pg.gda.pl; Fax: +48-58-347-2694; Tel: +48-58-347-2883

† Electronic supplementary information (ESI) available: Spectroscopic characterization data for compounds **1e**, **g**, **h**, and **i**, **5**, **7aaa-ahd**, **8aaa-ahd**, and **9**. See DOI: 10.1039/c7nj00445a