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Cyclic sulfates as useful tools in the asymmetric synthesis of 1-aminocyclopropane-1-carboxylic acid derivatives

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ABSTRACT

The enantiomers of 4-(2-methoxyethyl)-1,3,2-dioxathiolane-2,2-dioxide and 4-(methoxymethyl)-1,3,2-dioxathiolane-2,2-dioxide have been used as 'epoxide-like' synthons during the asymmetric alkylation of oxazinone-derived glycine equivalents. Using a fully stereoselective synthesis, eight stereoisomers of the *spiro* derivatives of the glycine equivalents were obtained. The relative configurations of the *spiro* compounds obtained were easily determined using nuclear magnetic resonance spectroscopy and two dimensional nuclear Overhauser effect experiments. Additionally, one of the *spiro* derivatives obtained was hydrolyzed to its corresponding amino acid, which was a derivative of 1-aminocyclopropano-1-carboxylic acid, a very important building block that is present in many compounds, which have interesting biological activity.

1. Introduction

In 2004, according to the literature, more than 20% of drugs belonging to the top 200 sales were based on compounds that possess a peptidic nature.[1] In addition, more than 200 peptides, proteins, and antibodies were launched for sale in 2010.[2] At the same time 40% of failures in clinical trials are caused by the low bioavailability and poor pharmacokinetics of the test compounds.[2] In particular, compounds that possess a peptidic nature have several drawbacks due to their rapid proteolysis and measures have to be taken to modify their structure in order to improve their pharmacokinetic properties, for example, the introduction of unnatural amino acids into their structure.[1–3]

1-Aminocyclopropane-1-carboxylic acid building blocks are present in many compounds, which have interesting biological activity (Fig. 1). The first example of a compound containing the 1-aminocyclopropane-1-carboxylic acid building block was cytotrienin A, an ansamycin-type anticancer drug, which was isolated from a species of *Steptomyces*.[4] Cytotrienin A induces apoptosis in human promyelocytic leukemia HL-60 cell line.[5] Another important example is the modification of the antiviral agent, Valacyclovir, which is an ester derivative of Acyclovir. Valacylovir is the L-valine ester of Acyclovir (prodrug) and has an oral bioavailability that is 5-fold higher than the original drug as a result of this modification. Using 1-aminocyclopropane-1-carboxylic acid instead of L-valine has allowed even better pharmacokinetic properties to be obtained.[6] 1-Aminocyclopropane-1-carboxylic acid is also found as a part of Simeprevir, an inhibitor of NS3/4A protease inhibitors, which was registered in 2014 as a new drug to treat hepatitis C.[7–9] 1-Aminocyclopropane-1-carboxylic acid was also used in investigations to improve the biological activity in factor Xa inhibitors[10] and atypical retinoids (anti-tumor activity).[11]

Therefore, it is necessary to search for new synthetic methods and various derivatives of 1-aminocyclopropane-1-carboxylic acid, which may be used as building blocks to improve the pharmacokinetic properties of biologically active compounds.

This work is a continuation of our efforts directed toward methods for the asymmetric synthesis of aminocycloalkane carboxylic acid derivatives.[12,13] The synthesis of the stereoisomers of 1-aminocyclopropane-1-carboxylic acid derivatives were based on glycine equivalent **1**, which was developed by Wanner et al.[14] Herein, we have focused our attention on cyclic sulfates **2** and **3** as they are emerging as important 'epoxide-like' synthons and should lead us to obtain the target compounds **4** and **5** with excellent diastereoselectivity. Compounds **4** and **5** can be hydrolyzed to their corresponding amino acids **6** and **7** (Scheme 1).

2. Results and discussion

2-(2,2-Dimethyl-1,3-dioxolan-4-yl)ethanol **8** and (2,2-dimethyl-1,3-dioxolan-4-yl)methanol **9** were selected as starting materials

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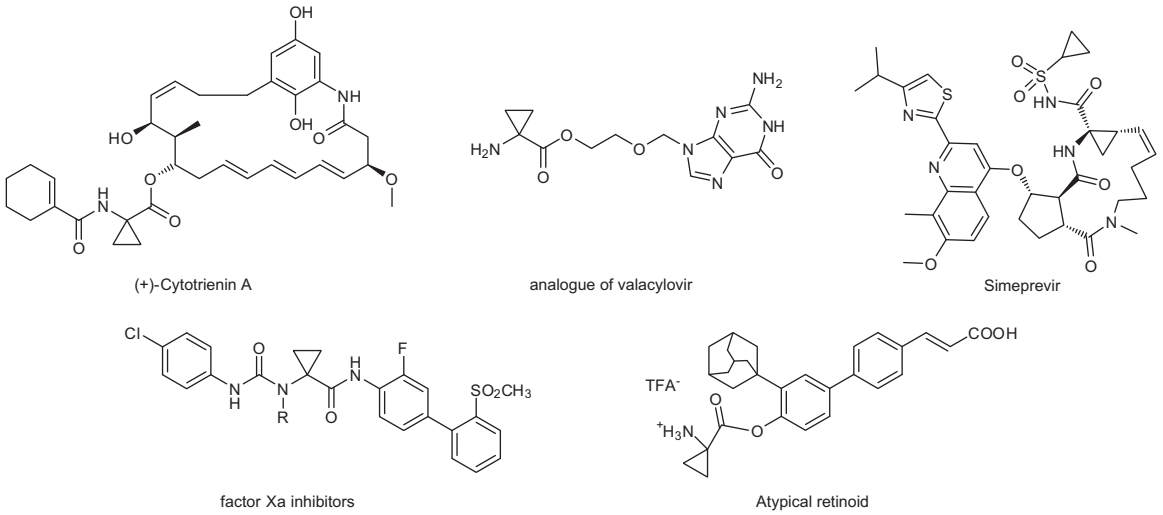
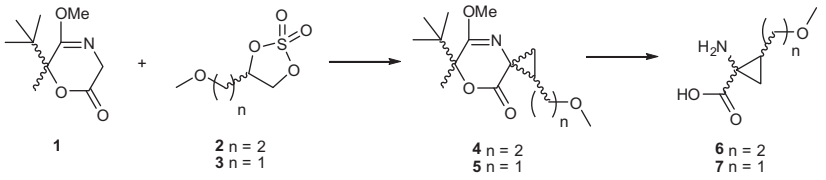


Figure 1. Examples of using 1-aminocyclopropane-1-carboxylic acids derivatives as a building block.



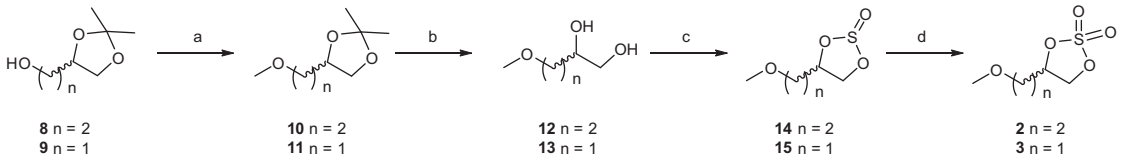
Scheme 1. Scheme of planned synthesis.

to prepare sulfates **2** and **3**, since they are both easily available in a single enantiomeric form. Firstly, **8** and **9** were converted into their methoxy derivatives **10** and **11** using methyl iodine and potassium hydroxide in dimethyl sulfoxide as a solvent.[15] The deprotection to give compounds **12** and **13** was carried out in a mixture of 1 M hydrochloric acid and acetone.[16] Compounds **12** and **13** were reacted with thionyl chloride to give cyclic sulfites **14** and **15**, which were further oxidized using sodium periodate and a catalytic amount of ruthenium trichloride to their corresponding cyclic sulfates **2** and **3**.[17,18] In this way a racemic mixture and two enantiomers of compound **2**, and a racemic mixture of compound **3** and enantiomer (*S*)-**3** were obtained.

The as-prepared cyclic sulfates **2** and **3** were used as the alkylating agents of glycine equivalents (*S*)-**1** and (*R*)-**1**. The deprotonation agent, sodium *bis*(trimethylsilyl)amide (NaHMDS) was used. The enantiomer of the glycine equivalent **1** was deprotonated at −30 °C for 30 min, the cyclic sulfate **2** or **3** was added and the reaction mixture stirred for 2 h. The last portion of NaHMDS was added dropwise for 1 h after which the mixture was stirred overnight and purified (Scheme 2).

When a racemic mixture of compound **2** was used, two stereoisomers of compound **4** were obtained (as determined by proton nuclear magnetic resonance ^{1}H NMR spectroscopy). The separation of these stereoisomers was not easy to carry out and so we decided to use the single enantiomers of compound **2**, which were easily obtained from the enantiomers of 2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol **8**. This led us to obtain four stereoisomers of the *spiro*-derivatives **4** as single diastereoisomers in good yields (44–51%) (Scheme 3).

The relative configurations within compound **4** were determined using NMR spectroscopy based on the nuclear Overhauser effects (NOEs) experiments with the absolute configurations determined by the absolute configuration of **1**.[12,13,19] The most important interaction observed was between the protons of the *tert*-butyl group with methoxyethyl group (compounds **4a** and **4d**) or the absence of these interactions (compounds **4b** and **4c**) (Fig. 2). In each reaction only one stereoisomer of compound **4** was formed and its stereoselectivity was dependent on the absolute configuration of the cyclic sulfate. We obtained two pairs of enantiomers of compound **4** in series I: from glycine equivalent



a: MeI, KOH; DMSO, RT; 24 h
b: 1 M HCl; acetone; reflux; 1 h
c: $SOCl_2$; $CHCl_3$; 0°C-reflux; 1 h
d: $NaIO_4$, $RuCl_3xH_2O$; $CHCl_3$; MeCN, H_2O; 0°C-RT; 3 h

Scheme 2. Synthesis of cyclic sulfate **2** and **3**.