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Faculty of Material Science and Applied Chemistry

ABSTRACTS

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Synthesis of 4-Aminobutyric Acid Derivatives: a Sugar-Based Chiral Auxiliary Approach

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Keywords – **Chiral auxiliaries, diacetone-α-D-glucose, diastereoselective Michael addition, 4-aminobutyric acid**

I. INTRODUCTION

Carbohydrates and their derivatives are compounds of great versatility in terms of stereoselective synthesis. Although a large variety of synthetic methods employing sugars as chiral scaffolds has been described, there is a vast selection of compounds which could benefit from novel chiral pool synthesis strategies. Our work is directed towards applications of commercially available and inexpensive diacetone-α-D-glucose (**1**, DAG) as a chiral auxiliary.

II. RESULTS AND DISCUSSIONS

Here we report our approach towards synthesis of enantiomerically enriched 3-aryl- or 3-alkyl-4-aminobutyric acids. This class of compounds includes well known CNS drugs baclofen, phenibut and pregabalin.

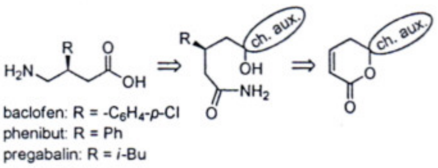

Fig.1. Retrosynthetic analysis of 3-aryl- or 3-alkyl-4-aminobutyric acids.

The proposed key reaction is diastereoselective Michael addition[1] on α,β-unsaturated lactone **4** which contains sugar moiety as chiral auxiliary[2]. The latter is obtained in a three-step synthesis. In the first step, DAG is oxidized[3] using sodium hypochlorite and TEMPO as a catalyst to afford ketone **2**, which is then subjected to addition of allylmagnesium chloride followed by acylation with *trans*-crotonyl chloride. The obtained diene **3** is converted into the desired lactone **4** by ring-closing metathesis reaction. Cuprate addition to lactone **4** affords products **5a** and **5b**.

To the date, we have observed a partially diastereoselective conjugate addition of nucleophilic reagents on α,β-unsaturated lactone moiety of **4**. Product **5a** is obtained in slight excess over **5b**. A screening of catalytic systems which could modify the product ratio is currently in progress.

At this stage, the addition products **5a** and **5b** can be separated by chromatography or recrystallization. Compounds are readily distinguished by ^{1}H-NOESY NMR spectra: both molecules show characteristic NOE interactions.

Further, treatment of pure diastereomer **5a** with ammonia in methanol affords amide **6** which, upon removal of protecting groups and subsequent oxidative cleavage of sugar moiety with sodium periodate, is converted into 3-substituted glutaric acid monoamide **7**. After Hofmann rearrangement of the latter, the target molecule **8** is obtained in enantiomerically pure form.

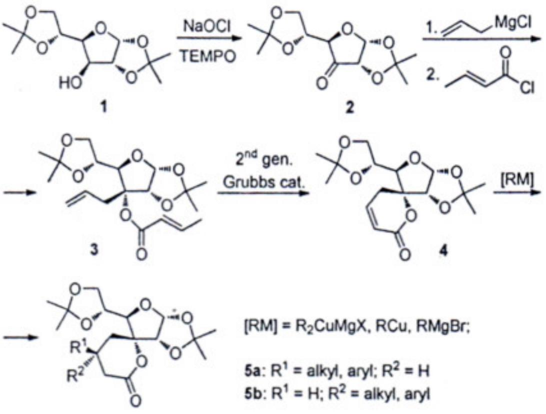

Fig.2. Synthesis of sugar-functionalized lactone **4** followed by diastereoselective Michael addition reaction.

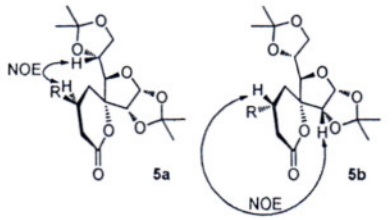

Fig.3. NOE interactions characteristic for **5a** and **5b**.

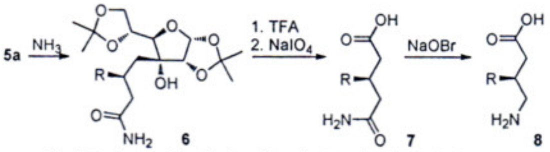

Fig.4. Synthesis of 3-substituted 4-aminobutyric acid derivatives.

The potential application of current results is not limited to the particular 4-aminobytyric acid derivatives and can be used as a general method.

Diastereoselectivity of the process **4** → **5a** + **5b** and its optimization will be discussed.

III. REFERENCES

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