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Glucose-based Chiral Auxiliary Strategy for the Synthesis of GABA Derivatives

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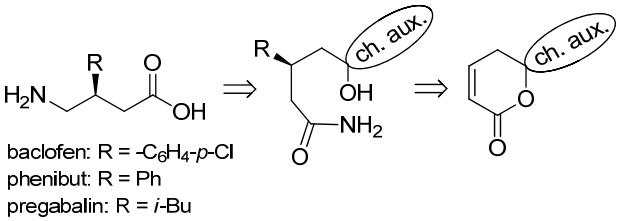
Nowadays carbohydrates receive a lot of attention from chemists owing to their availability and versatility in terms of stereoselective synthesis. Although a large variety of synthetic methods employing sugars as chiral scaffolds are described, there is a vast selection of compounds that can benefit from novel chiral pool synthesis strategies. Present research is directed towards the use of commercially available and inexpensive diacetone-α-D-glucose (**1**, DAG) as a chiral auxiliary.

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



Scheme 1. Retrosynthetic analysis of 3-substituted 4-aminobutyric acids

The proposed key reaction is diastereoselective Michael addition [1] on α,β-unsaturated lactone **2** that contains sugar moiety as a chiral auxiliary [2]. The latter is obtained in a four-step synthesis from DAG. Synthetic transformations include oxidation [3], allylmagnesium chloride addition, acylation with trans-crotonyl chloride and ring-closing metathesis (Scheme 2).

At this stage, the addition products **3a** and **3b** 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 **3a** with ammonia in methanol affords amide **4** that, upon removal of protecting groups and subsequent oxidative cleavage of sugar moiety with sodium periodate, is converted into 3-substituted glutaric acid monoamide **5**. After Hofmann rearrangement of the latter, the target molecule **6** is obtained in enantiomerically pure form.

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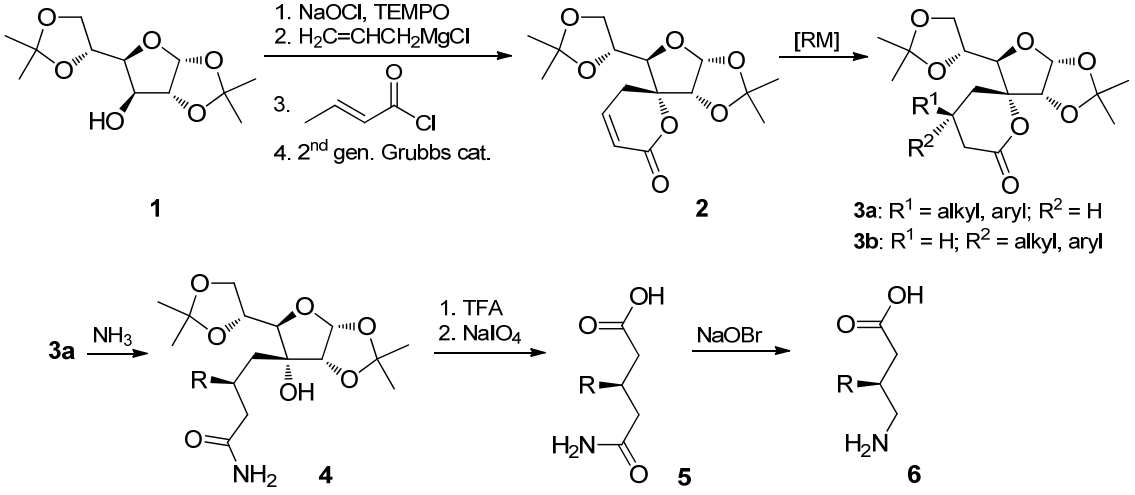
REFERENCES

[1] Rossiter, B.E.; Swingle, N.M. *Chem. Rev.* **1992**, *92*, 771-808.
[2] Kishida, M.; Yamauchi, N.; Sawada, K.; Ohashi, Y.; Eguchi, T.; Kakinuma, K. *J. Chem. Soc., Perkin Trans. 1*. **1997**, *6*, 891-896.
[3] Ostrovskis, P.; Mackeviča, J.; Kumpiņš, V.; Turks, M. In: *Carbohydrate Chemistry: Proven Synthetic Methods, Volume 2*; van der Marel, G.; Codee, J., Eds.; CRC Press, 2013 (in press).



Scheme 2. Synthetic route towards GABA analogues **6**