Proceedings of the 37th European Peptide Symposium
Michal Lebl, Editor
European Peptide Society, 2024
http://doi.org/10.17952/37EPS.2024.P2247

Synthesis and application of β-amino γ-lactam (Bgl) residues

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Introduction

α-Amino γ-lactam (Agl), so-called Freidinger-Veber lactam residues have garnered significant interest in the realm of peptide mimicry due to ability to introduce backbone constraint (Figure 1)[1,2]. In peptides, the Agl residue prefers the *i*+1 position of β-turn conformers and can thereby stabilize a bioactive conformation that is commonly found in natural peptides[1,2]. Compared to Agl residues, β-amino γ-lactam (Bgl) analogs have been less frequently explored in spite potential to favor turn geometry. For example, Bgl residues have been utilized in the study of growth hormone-releasing peptide-6 (GHRP-6, H-His-D-Trp-Ala-Trp-D-Phe-Lys-NH_2) to gain insight into a turn conformer about the Ala[3] residue[3]. Moreover, a Bgl scan of 101.10 (H-D-Arg-D-Tyr-D-Thr-D-Val-D-Glu-D-Leu-D-Ala-NH_2) illustrated the relevance of turn conformers for interleukin-1 receptor modulation[4]. Highlighting utility for stabilizing biologically active peptide conformers, such studies spur interest in synthetic methods for making Bgl residues. Previously, Bgl peptides have been synthesized using aspartate-derived cyclic sulfamidates as bis-electrophiles[4]. Towards an alternative method for Bgl peptide synthesis, commercially available (*S*)-(–)-β-hydroxy-γ-butyrolactone has now been employed as precursor.

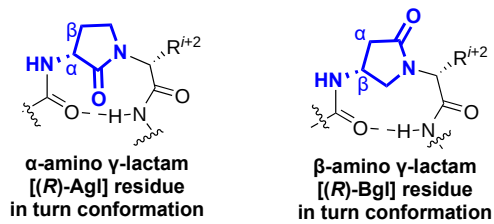

Figure 1. Agl and Bgl residues at i+1 position of β-turn conformations

Results and Discussion

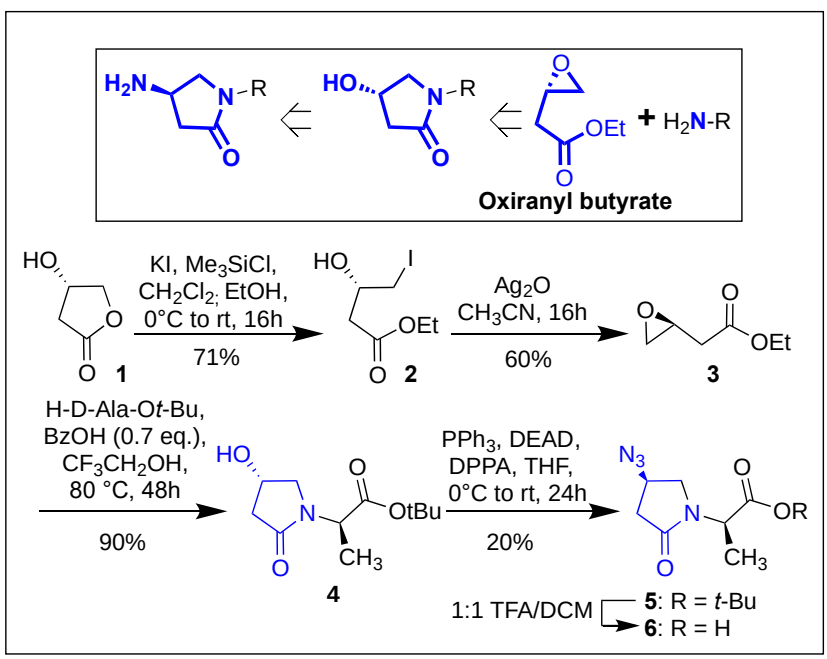

Figure 2. Conceptual and actual applications of oxiranyl butyrate in Bgl residue synthesis.

(*S*)-(–)-β-Hydroxy-γ-butyrolactone undergoes a ring-opening reaction in the presence of potassium iodide, trimethylsilyl chloride and ethanol to provide iodo ester **2** in 71% yield[5] (Figure 2). Oxiranyl butyrate **3** is prepared from iodo alcohol **2** on treatment with silver oxide in acetonitrile in 60% yield[5]. In proof-of-concept studies, oxiranyl butyrate **3** was employed as a bis-electrophile in the alkylation and acylation of D-alanine *tert*-butyl ester. Employing benzoic acid as catalyst in trifluoroethanol at 80°C for 48 h gave β-hydroxy lactam **4** in 90% yield[6]. An initial attempt to displace the alcohol by azide using diethyl azo dicarboxylate (DEAD), diphenyl phosphoryl azide (DPPA) and triphenyl phosphine in THF provided Bgl analog **5** (20% unoptimized), which after removal of the *tert*-butyl ester with trifluoroacetic acid in dichloromethane is suitable for incorporation into peptides. The scope of this approach is currently being developed with interest in expanding the synthesis of Bgl analogs in peptides including GHRP-6 and 101.10 to study further biological activities.

Acknowledgments

We thank the Canadian Institutes of Health Research (CIHR) for project PJT-190158, the Natural Sciences and Engineering Research Council of Canada (NSERC) for funding Discovery Research Project RGPIN-2019-04079, and the Fonds de Recherche du Québec - Nature et Technologie (FRQNT) for support of the Centre in Green Chemistry and Catalysis (CGCC, FRQNT-2020-RS4-265155-CCVC). The authors acknowledge the assistance of members of the Université de Montréal facilities: Dr. P. Aguiar (NMR spectroscopy) and Dr. A. Fürtös (mass spectrometry). CYL is grateful for a doctoral fellowship from the FRQNT.

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