Tetrahedron 74 (2018) 4857–4867

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A new approach to the synthesis of lactams of muramic, isomuramic and normuramic acids via intramolecular *O*-alkylation: Stereochemical features of the intramolecular nucleophilic substitution

Sergey S. Pertel*, Sergey A. Seryi, Elena S. Kakayan

V.I. Vernadsky Crimean Federal University, 4, Vernadsky Ave., 295007, Simferopol, Russian Federation

ARTICLE INFO

Article history:
Received 7 June 2018
Received in revised form
24 July 2018
Accepted 27 July 2018
Available online 30 July 2018

Keywords:
Intramolecular nucleophilic substitution
Williamson alkylation
Stereoselectivity
Inversion
Retention of configuration
Neighboring group participation
δ-lactam
Muramic
Isomuramic and normuramic acid

ABSTRACT

The title compounds were synthesized from the selectively protected *N*-acylated D-glucosamine derivatives, containing α-halo carboxylic acid moieties, via intramolecular 3-*O*-alkylation. It was found that if the starting compound contains asymmetric electrophilic center, isomuramic acid derivatives were mainly formed, regardless of the configuration of the electrophilic carbon atom. An explanation for the observed stereochemical results was proposed on the basis of the analysis of steric interactions in the molecules of the starting compounds, as well as using the concept of anchimeric assistance. It was shown that *N*-acetylation of the obtained lactam derivatives and subsequent methanolysis under mild conditions led to the selective cleavage of δ-lactam ring resulting in the formation of the corresponding ester derivatives of *N*-acetylmuramic acid or its analogues in high yields.

1. Introduction

Muramic acid is a naturally occurring sugar amino acid containing the residues of (*R*)-lactic acid which is linked to C-3 of D-glucosamine through an ether linkage. *N*-Acetylmuramic acid is a constituent of the repeating unit of peptidoglycan of bacterial cell wall, so-called murein [1]. Three-dimensional structure of murein, which is composed of the network of linear polysaccharide chains cross-linked by short peptide bridges via carboxyl groups of the muramic acid moieties, confers rigidity to the cell wall and resistance to an outer exposure.

The structure of the bacterial peptidoglycan undergoes significant changes during sporulation. A substantial part of the peptide fragments and *N*-acetyl substituents are cleaved and intramolecular *N*-acylation occurs in muramic acid constituents resulting in the formation of δ-lactam derivatives [2–4]. The structure of muramic acid δ-lactam is unique to the peptidoglycan of bacterial spore or spore cortex. If the cortex does not contain the repeating units of muramic δ-lactam, the germination of bacterial spores becomes impossible [5–8].

The low molecular-weight glycopeptide fragments of the bacterial peptidoglycan, so-called muramyl peptides, as well as their numerous synthetic analogues, possess a wide spectrum of biological activity, including immunomodulatory and somnogenic effects [9,10]. Certain muramyl peptides have already been approved for medical applications and are used as drugs for therapies of cancer and other diseases [10]. In addition to muramyl peptides, muramic acid derivatives, which are the substrates of the enzymes involved in the biosynthesis of murein, are of significant interest [11–17]. Such compounds are necessary for creating the inhibitors of the bacterial peptidoglycan biosynthesis, which can be used as new efficient antibacterial agents [18–20].

In addition to muramic acid and its lactam, the epimer of muramic acid at the lactyl residue, so-called isomuramic acid, occurs in nature. In particular, it was found in *O*-specific polysaccharides of

* Corresponding author.
E-mail address: sergepertel@yahoo.com (S.S. Pertel).

https://doi.org/10.1016/j.tet.2018.07.051
0040-4020/

Proteus penneri 62 [21] and *Providencia alcalifaciens 032* [22]. Synthetic normuramic acid, which contains glycolic acid residue instead of lactyl moiety, is the constituent of normuramyl peptides – biologically active analogues of natural muramyl peptides [23].

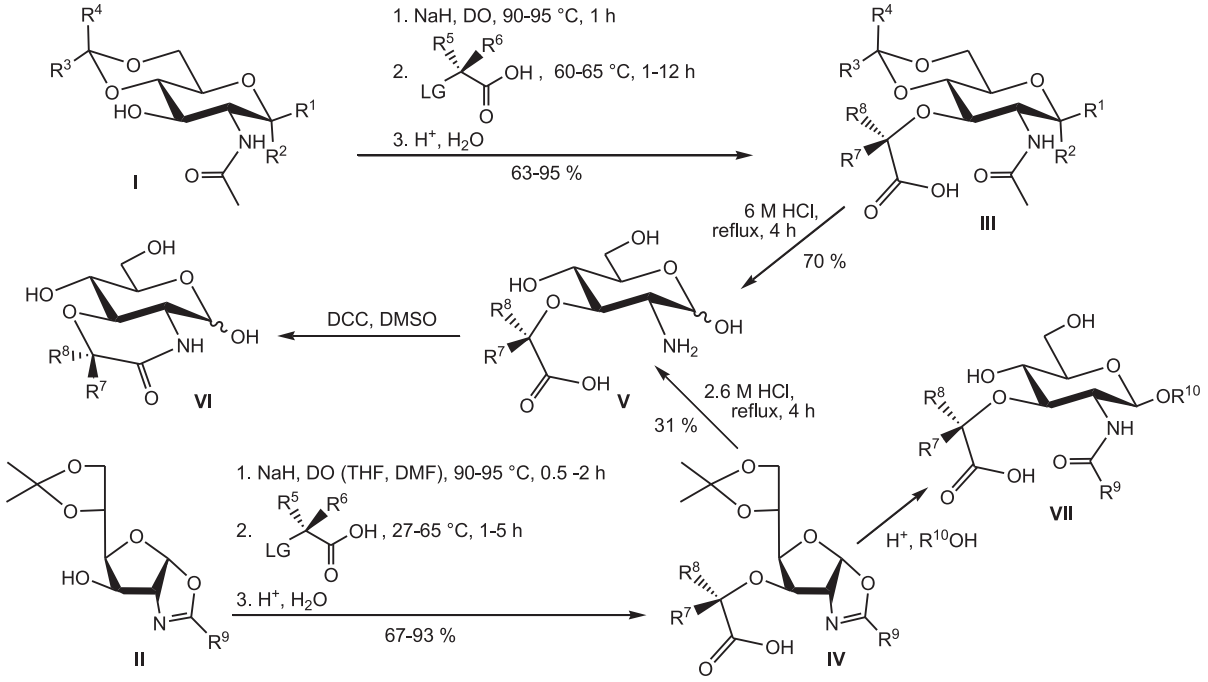
The preparation of muramic acid, its analogues and derivatives **V-VII** is a cumbersome task. The key step of this synthesis consists in the Williamson *O*-alkylation at C-3 of the suitably protected D-glucosamine derivative **I** or **II** with α-halo carboxylic acid or its synthetic equivalent, which is accompanied by the inversion of configuration [13,24–37] (Scheme 1).

The synthesis of muramic acid lactam and its analogues **VI** requires the removal of *N*-protecting group in the products **III-IV** under rather harsh conditions followed by intramolecular acylation, which, in contrast to the previous steps, proceeds smoothly leading to the corresponding lactam derivative [25,38,39].

Several transformations used in this approach to the synthesis of the derivatives of muramic acid and its analogues proceed under quite harsh conditions (e.g. Williamson alkylation and *N*-deacylation). It is an obvious drawback of the method since it limits considerably the choice of protecting groups and may facilitate racemization of the products. A complete separation of the resulting mixture of diastereomers is a time-consuming and tedious process [29]. At the same time, the presence of stereoisomeric impurities in the target products is highly undesirable since, as it has been shown, the biological activity of muramic acid derivatives crucially depends on their stereochemical purity [40]. However, the complete inversion of the configuration is not generally achieved even under relatively mild conditions and when using the enantiomerically pure alkylating reagents [41–43]. It is explained by the fact that alkylating reagents, which contain carboxyl function adjacent to an asymmetric electrophilic center, tend to retain the configuration due to neighboring group participation (anchimeric assistance), accompanied by the formation of the intermediary α-lactone [44–46].

We aimed to study the possibility of performing an alternative and more efficient approach, in terms of stereoselectivity and the reaction conditions, to the synthesis of the title compounds, which is based on intramolecular *O*-alkylation. In this case, the nucleophilic and electrophilic centers are spatially close to each other, which should facilitate their interaction due to the entropy factor, and are arranged in a certain position relative to each other, which should affect the stereochemistry of the process.

In order to implement this approach, the electrophilic moiety, i.e. the residue of α-halo carboxylic acid or its synthetic equivalent should be first introduced into the D-glucosamine molecule. The selective *N*-acylation is suitable for this purpose. Thus, the compounds, which are designed for such an intramolecular *O*-alkylation, should correspond to the structure **1** and the reaction should directly provide the corresponding lactam derivatives (Fig. 1).



R^1 = O-PG, R^2 = H or R^1 = H, R^2 = O-PG
PG – protecting group, e.g. Alkyl, TBDMS
R^3 = R^4 = CH_3 or R^3 = Ph, R^4 = H
R^5 = H, R^6 = CH_3 or R^5 = CH_3, R^6 = H or R^5 = R^6 = H
LG – leaving group, e.g. Cl, Br
R^8 = H, R^7 = CH_3 (muramic acid and its derivatives) or R^8 = CH_3, R^7 = H (isomuramic acid and its derivatives) or R^8 = R^7 = H (normuramic acid and its derivatives)
R^9 = CH_3 or Ph
R^{10} = CH_3 or H

Scheme 1. Synthesis of muramic acid, its analogues and derivatives via intermolecular 3-*O*-alkylation.