Tetrahedron 74 (2018) 2440–2446

Contents lists available at ScienceDirect

Tetrahedron

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

Comparing of endocyclic and exocyclic cleavage reactions using mycothiol synthesis as an example

Shino Manabe*, Yukishige Ito**

RIKEN, Synthetic Cellular Chemistry Laboratory, Hirosawa, Wako, Saitama 351-0198, Japan

ARTICLE INFO

Article history:
Received 30 December 2017
Received in revised form
20 March 2018
Accepted 29 March 2018
Available online 30 March 2018

Keywords:
Anomerization
Glycosylation
Cyclitols
Glycosides
Mycothiol

ABSTRACT

Glycosides can be cleaved in either an exo- or endocyclic fashion. Specifically, the former pathway is used during conventional glycosylation; whereas the latter pathway has not been the subject of attention. Endocyclic cleavage reaction enable the anomerization of β-glycosides to α-glycosides. Herein, we compared the efficacies of endo- and exocyclic cleavage reactions during the synthesis of mycothiol, a potential drug development target for tuberculosis treatment, in terms of selectivity and product yield. In addition, the direct resolution of benzyl-protected inositol by a highly stereoselective glycosylation reaction was investigated.

1. Introduction

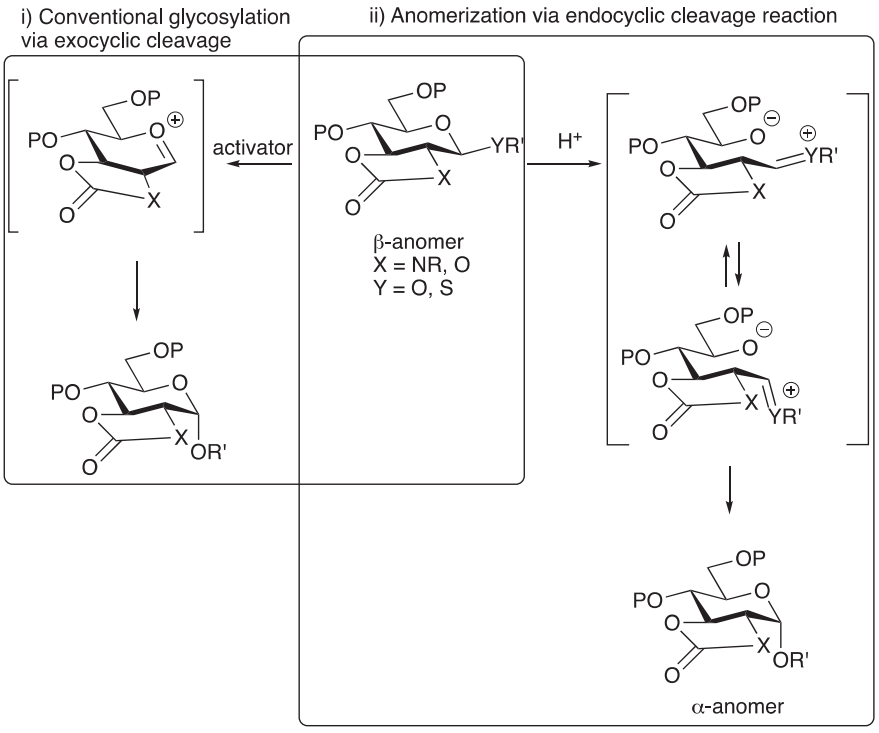
The glycosylation reaction is the most important transformation in glycoside and glycoconjugate synthesis. In a typical glycosylation reaction, the configuration of the anomeric stereocenter is determined when the glycosyl bond is formed (Scheme 1(i)). In this case, the glycoside is produced by nucleophilic attack on the cyclic oxacarbenium ion generated through exocyclic cleavage, with the stereochemistry at the anomeric position determined by the direction of the approaching nucleophile. The completely stereoselective formation of 1,2-*cis*-glycosides remains a challenge for conventional glycosylation, despite the significant progress achieved in this field.[1–3] In contrast to conventional glycosylation, the bond between the anomeric position and the O-5 oxygen can also be cleaved in an endocyclic fashion (Scheme 1(ii)).[4,5] We have clearly shown evidence of endocyclic cleavage reaction by capturing linear cation.[4] Building on our previous reports on endocyclic-cleavage-promoted anomerization as a powerful tool for the stereoselective formation of 1,2-*cis*-aminoglycosides,[6,7] we synthesized mycothiol **1** (Fig. 1) using an endocyclic cleavage reaction.[8]

Mycothiol is the major low-molecular-weight thiol found in most actinomycetes, including *Mycobacteria* and *Streptomycetes*,[9,10] and is required for maintaining a reducing intracellular environment for protection against foreign electrophilic agents (e.g., oxidants, radicals, and drugs) in Gram-positive bacteria. Because mycothiol-based metabolic pathways are not found in eukaryotes, this thiol is expected to be an effective drug target for tuberculosis treatment.[11] Mycothiol is also involved in the biosynthesis of lincomycin A, a sulfur-containing lincosamide antibiotic.[12] However, the limited availability of mycothiol, commonly obtained from *M. smegmatis* cell cultures (<1.5 mg of mycothiol from 1 L of culture),[13] necessitates the development of an approach based purely on chemical synthesis.

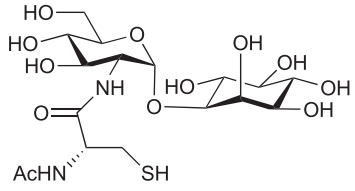
From a structural viewpoint, mycothiol contains *N*-acetylcysteine, α-D-glucosamine, and D-*myo*-inositol residues and has already been synthesized by several groups, including our own.[8,14–18] Our approach was based on an endocyclic cleavage reaction (Scheme 2).[6–8] In the first step, β-glycoside **4** was stereoselectively prepared from phthaloyl-protected glycosyl donor **2**, followed by the introduction of the *N*-acetyl-2,3-*trans*-carbamate group and the quantitative anomerization to the α-anomer **5a** (58% yield from **3**). Finally, deprotection and the introduction of an *N*-acetylcysteine moiety afforded mycothiol. Importantly, intermediate **5a**, an α-glycoside, can be directly prepared by conventional glycosylation using compound **6** as a glycosyl donor, which raises the question of whether the direct preparation of a 1,2-*cis*-glycoside

* Corresponding author. Tel.: +81 48 467 9432; fax: +81 48 462 4680.
** Corresponding author.
E-mail addresses: smanabe@riken.jp (S. Manabe), yukito@riken.jp (Y. Ito).

https://doi.org/10.1016/j.tet.2018.03.069
0040-4020/



Scheme 1. Endocyclic cleavage reaction and exocyclic cleavage reaction.



1

Fig. 1. Structure of mycothiol **1**.

from a suitable donor is more effective than the anomerization approach. Herein, we compare the efficiencies of both anomerization and direct glycosylation approaches using the synthesis of mycothiol as an illustrative example.

2. Results and discussion

Glycosyl donors bearing 2,3-*trans*-carbamate groups (i.e., **6**[19] and **7**[20]) and protected resolved inositol acceptors (i.e., **3**[16] and **8**[17]) were reacted under a variety of conditions, with the results summarized in Table 1. Donor **6** was activated using typical reagents, i.e., *N*-iodosuccinimide/trimethylsilyl trifluoromethanesulfonate (NIS/TMSOTf) and benzenesulfinyl chloride/silver trifluoromethanesulfonate (PhSCl/AgOTf). When a catalytic amount of TMSOTf was used (entries 1–3), β-glycoside **10b** was obtained as the only product. The yield of β-glycoside **10b** increased only slightly (from 51 to 60%) when the loading of donor **6** was increased from 1.5 equiv. (entry 1) to 2.4 equiv. (entry 2). On the other hand, only the α-product **10a** was obtained in 35% when the amount of TMSOTf was increased to 2.4 equiv. (entry 4). Only the β-glycoside **5b** was isolated in 53% yield, and 22% of acceptor **3** was recovered when PhSCl/AgOTf was employed in the presence of di-*tert*-butylmethylpyridine (DTBMP) (entry 5); however, only α-product **5a** was obtained (entries 6–8) in the absence of DTBMP. For instance, entry 6 shows that only **5a** was obtained in 61% yield after 30 min of reaction, with the yield increasing to 74% and acceptor recovery decreasing to 2% when the reaction time was increased to 10 h (entry 8). The addition of molecular sieves did not increase the yields in ether the NIS-TMSOTf or PhSCl-AgOTf system (entries 4 and 10). On the basis of these results, we conclude that the observed α-selectivity originates from *in situ* anomerization. The data in entries 1–3 suggest that a catalytic amount of acid was insufficient to elicit the anomerization of β-glycoside **5b**; however, anomerization was possible when more than a stoichiometric amount of TMSOTf or AgOTf was used, which is consistent with Oscarson's report.[21] Furthermore, DTBMP neutralized reaction acidity and suppressed anomerization (entry 5). The sum of acceptor recovery yield and the yield of **5a** decreased with increasing reaction time, which probably reflects the decomposition of **5a** by endocyclic cleavage, as shown in Scheme 3. Under these conditions, excess donor **6** was anomerized to the corresponding α-thioglycoside **12**, which was not activated under the same conditions and recovered.

When donor **7** was employed in the reaction, α-product **9a** was obtained as the major kinetic product (entries 11, 14, and 15). We previously reported that *N*-benzyl-2,3-*trans*-glycosides do not anomerize under glycosylation reaction conditions.[22] A similar phenomenon was observed when acceptor **8** was used, although the product yields were lower compared to those obtained with acceptor **3** (entries 12–15). Specifically, the β-product **10b** and the α-product **10a** were obtained in yields of 40 and 44% when NIS/TMSOTf and AgOTf/PhSCl were used, respectively (entries 12 and 13). Donor **7** exhibited high α-selectivity in the presence of either AgOTf/PhSCl or NIS/TMSOTf (entries 14 and 15).