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Convenient Divergent Synthesis of a Library of Trehalosamine Analogues

Yu Hui and Cheng-Wei Tom Chang*

Department of Chemistry and Biochemistry, Utah State University, 0300 Old Main Hill, Logan, Utah 84322-0300

chang@cc.usu.edu

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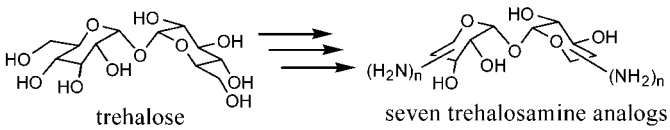
ABSTRACT



A library of seven trehalosamine analogues with various natural and non-natural binding motifs was synthesized through an expedient divergent synthetic approach. The final products were prepared in sufficient quantities and purities for different types of assay against various pathogens. Several stereo- and regioselective reactions on the trehalose scaffold were developed for rapid synthesis of all of the designed compounds.

Trehalosamine and other related aminotrehaloses derived from trehalose belong to a family of disaccharide aminoglycoside antibiotics bearing a 1,1′-glycosidic linkage (Figure 1).[1,2] These aminoglycoside antibiotics, which can be isolated from natural sources or synthesized chemically, have attracted interest for their potential as novel antibiotics. For example, α,α-trehalosamine isolated from Streptomyces is active against *Mycobacterium tuberculosis*.[1] The 4-amino-4-deoxy-α,α-trehalose is weakly active against *Escherichia coli* and *Bacillus subtilis*.[1] The 3,3′-neotrehalosdiamine, isolated from *Bacillus pumilis*, is the first example of the trehalosamine family with an α,β-linkage. Trehalose has been found ubiquitously in insects as the principal blood sugar. Trehalose has also been reported to participate in the germination of ascospores in fungi. Therefore, inhibitors of trehalase that mimic the trehalose scaffold can potentially be antifungal or plant-protection agents, such as trehazolin from *Amycolatopsis trehalostatica*[3,4] and salbastatin from *Streptomyces albus*.[5]

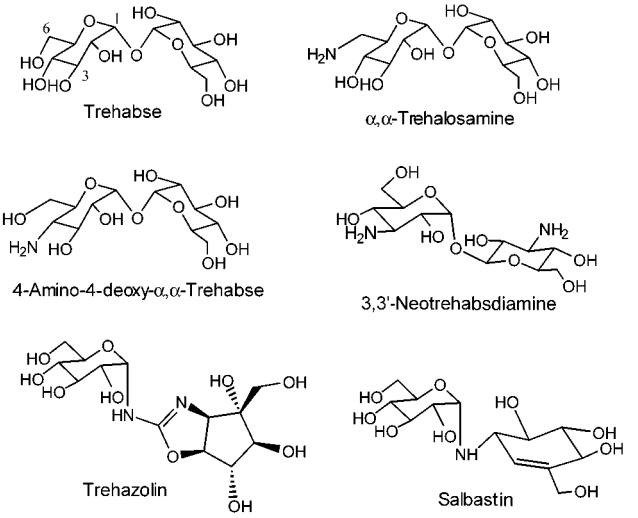


Figure 1. Trehalose and naturally occurring trehalosamines and trehalase inhibitors.

Aminoglycosides exert their antibacterial activity by entering into the cell via active transport and binding selectively to the bacterial ribosomal RNA, thereby inhibiting the protein synthesis of the microorganism. Many trehalosamine analogues have been synthesized. Examples include

(1) Hooper, I. R. *Aminoglycoside Antibiotics*; Springer-Verlag: New York, 1982.
(2) Haddad, J.; Kotra, L. P.; Mobashery, S. In *Glycochemistry Principles, Synthesis, and Applications*; Wang, P. G., Bertozzi, C. R., Ed.; Marcel Dekker: New York, 2001; p 307.
(3) Berecibar, A.; Grandjean, C.; Siriwardena, A. *Chem. Rev.* **1999**, *99*, 779−844.
(4) Kobayashi, Y. *Carbohydr. Res.* **1999**, *315*, 3.
(5) Vertesy, L.; Fehlhaber, H. W.; Shultz, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1844−1846.

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2,2′,6,6′-tetraazido-2,2′,6,6′-tetradeoxy-α,α-trehalose,[6] 6,6′-diamino-6,6′-dideoxy-α,α-trehalose,[7] 6-amino-6-deoxy-α,α-trehalose,[8] 3,3′-diamino-3,3′-dideoxy-α,α-trehalose,[9] 3-amino-3-deoxy-α,α-trehalose, and 3,3′-neotrehalosdiamine.[10] Most of the syntheses, however, have focused on the naturally occurring trehalosamines.[2]

On the basis of the common structural features of all aminoglycosides, Wong and co-workers have proposed several structural motifs including *cis*- or *trans*-1,2-hydroxyamines and *gluco*- and *galacto*-1,3-hydroxyamine substructures that are important for the molecular recognition of phosphodiester of RNA backbones.[11,12] Our group is interested in synthesizing various mono- or disaccharides with designed amino group substitution patterns that may serve as the probes for investigation of aminoglycoside−rRNA binding. Enlightened by the proposed binding motifs of aminoglycoside, we began to construct trehalosamine analogues with these binding motifs. In addition, we have proposed four additional natural and non-natural binding motifs, *gluco*- and *galacto*-1,3-diamino and *gluco*- and *galacto*-1,3-hydroxyamino with 4-NH_2 on the trehalose scaffold (Figure 2). The constructed aminosugar-containing

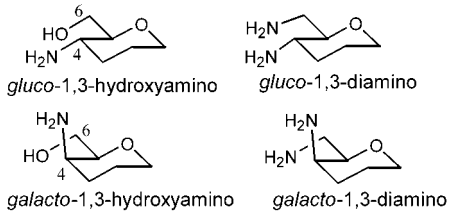


Figure 2. Proposed binding motifs of aminosugars.

trehalose or trehalosamine analogues can potentially lead to the development of novel antibiotics or trehalase inhibitors.

As part of our research, we would like to report the syntheses of a library of seven novel amino group-substituted trehalose derivatives bearing various *gluco*- and *galacto*-1,3-diamino and -hydroxyamino and *cis*- and *trans*-hydroxyamino binding motifs as shown in Figure 3. Compound **2** contains a reported *gluco*-1,3-hydroxyamine motif[11,12] and can be used as the control. Compounds **1** and **5** contain *gluco*- and *galacto*-1,3-diamino motifs, while compounds **6** and **7** have *gluco*- and *galacto*-1,3-hydroxyamino motifs. Compounds **3** and **4** will allow us to evaluate exclusively the *trans*- and *cis*-1,2-hydroxyamino binding motif.

Traditional synthetic methods often involve development of an individual route for the preparation of a single final product. For the preparation of a library of compounds, this approach is labor-intensive. To minimize the synthetic work while producing the optimal structural diversity in quantities

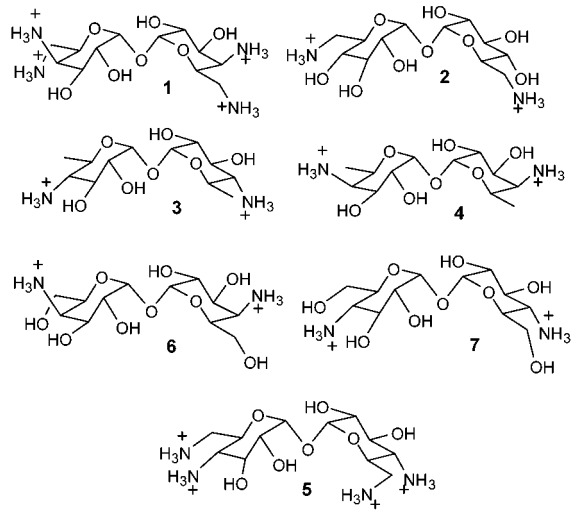
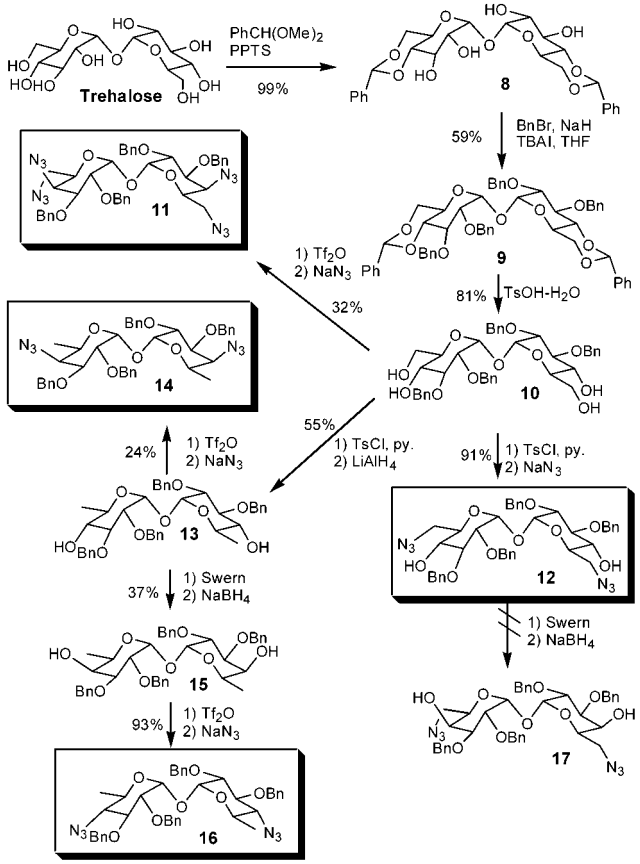


Figure 3. Designed trehalosamines.

sufficient for assays against various pathogens, we have developed a divergent synthetic approach for such purposes. Using commercially available trehalose as the starting material, a series of branching into different routes are used for adding the amino group substitution on the C-4 and/or C-6 positions (Scheme 1). The amino groups were introduced

Scheme 1. Synthesis of Trehalose-Based Aminoglycosides



(6) Paulsen, H.; Sumfleth, B. *Chem. Ber*. **1979**, 3203−3213.
(7) Umezawa, S.; Tsuchiya, T.; Nakada, S.; Tatsuta, K. *Bull. Chem. Soc. Jpn*. **1967**, *40*, 395−401.
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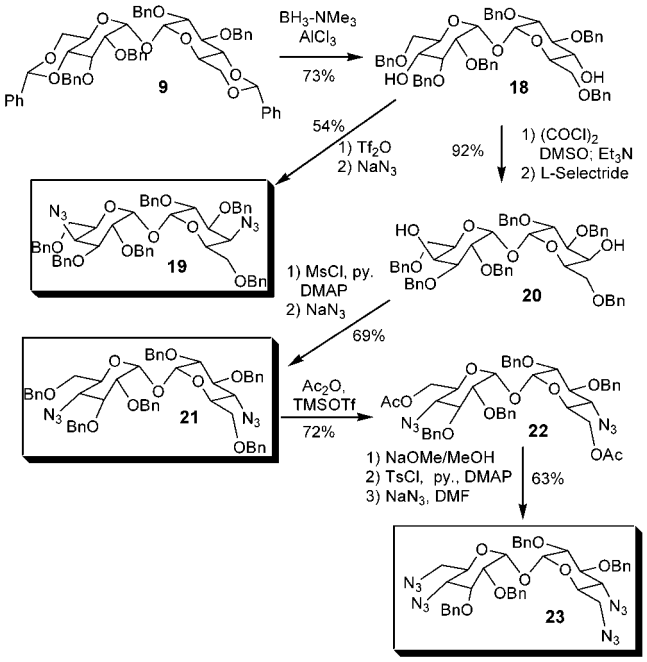
(9) Baer, H.; Bell, A. J. *Can. J. Chem*. **1978**, *56*, 2872−2878.

and masked as azido groups, which were converted into amino groups during the final stage of the synthesis.

Compound **8** was prepared from trehalose according to the literature procedures.[13] Perbenzylation of **8** provided compound **9**, which led to two distinct routes, one for the preparation of **10** (Scheme 1), the other for the preparation of **18** (Scheme 2). Compound **10** was obtained from

Scheme 2. Synthesis of Trehalose-Based Aminoglycosides



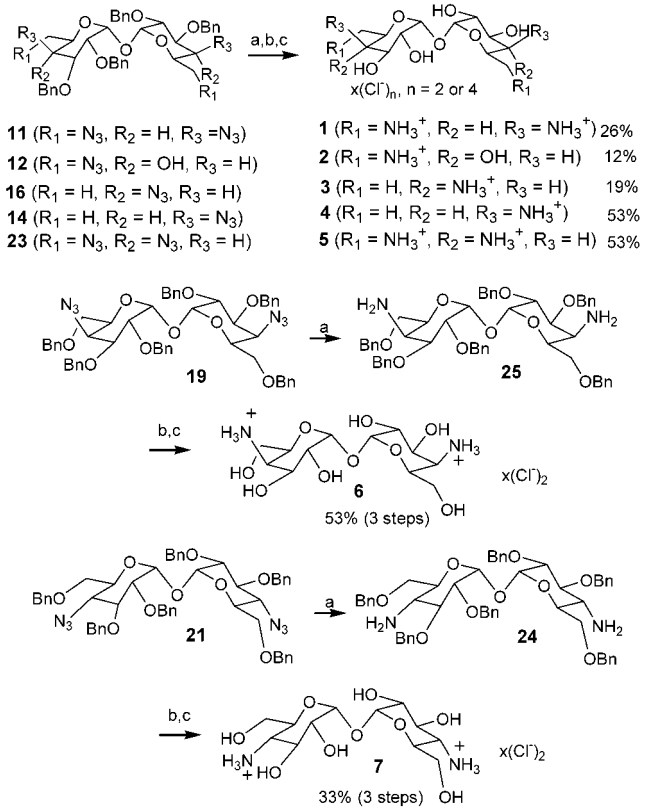
hydrolysis of the benzylidene groups of **9** using TsOH in MeOH. Triflation followed by an azido substitution on the 4,6-hydroxyl groups of each glucose component provided **11**, which has an intrinsically novel *galacto*-1,3-diamino binding motif. Alternately, deoxygenation of the 6-OH and 6′-OH of **10** was accomplished by reducing the tosylated derivatives with $LiAlH_4$ generating **13**. Direct incorporation of the azido groups on the 4-OH and 4′-OH of **13** yielded **14** with 4-N_3 and 4′-N_3 in the axial positions. A Swern oxidation followed by a $NaBH_4$ reduction converted the equatorial 4-OH and 4′-OH of **15** into axial positions, allowing the incorporation of azido groups in the equatorial positions, yielding **16** via an S_N2 azide substitution.

Originally, we intended to synthesize trehalosamine analogue **5**, bearing a novel *gluco*-diamino binding motif, from compound **12** based on our previous studies on the stereoselective reduction of ketosugars,[14] However, the 4- and 4′-hydroxyl groups of **12** could not be converted from equatorial to axial position at the same time in the employed conditions. A complex mixture was obtained with the *galacto*-glucoside as the major product when Swern oxidation/$NaBH_4$ reduction was used. Therefore, we have to develop a longer route for the preparation of **5**.

Compound **18** was synthesized from **9** using $BH_3-NMe_3/AlCl_3$ in THF (Scheme 2).[15] Direct azide substitution from **18** gave **19**. Compound **19** contains an intrinsically nonnatural *galacto*-1,3-hydroxyamino binding motif with C-4 and C-4′ amino groups. We were pleased to discover that the hydride reduction of the ketosugar from **18** using L-Selectride provided the desired product **20**, with the *galacto*-galactoside configuration. L-Selectride is expected to enhance the stereoselectivity in favor of the axial hydroxyl group. After the azide substitution, another novel trehalosamine analogue, precursor **21**, was made. The C-6/C-6′ benzyl groups of **21** were selectively displaced by acetyl groups using Ac_2O and TMSOTf generating **22**.[16,17] A three-step process involving hydrolysis of C-6/C-6′ acetyl groups, tosylation of C-6/C-6′ hydroxyl groups, and azide substitution, furnished the desired product **23,** with a novel and nonnatural *gluco*-1,3-diamino binding motif.[3]

It has been noted[18,19] that the attempts for the reduction of azido groups and the deprotection of benzyl groups under one-pot hydrogenation often provided a mixture with incomplete reaction. Therefore, a two-step procedure was used, in which all seven azido/benzyl trehalosamine analogues underwent a Staudinger reaction followed by hydrogenation (Scheme 3).[20] Generally, the final products were produced

Scheme 3. Final Synthesis of Trehalose-Based Aminoglycosides



(a) PMe_3, THF, (b) H_2, $Pd(OH)_2/C$, $HOAc/H_2O$, (c) Dowex 1X8 (Cl^-)

(10) Baer, H.; Bell, A. J. *Carbohydr. Res.* **1979**, *75*, 175−184.
(11) Wong, C.-H.; Hendrix, M.; Manning, D. D.; Rosenbohm, C.; Greenberg, W. A. *J. Am. Chem. Soc.* **1998**, *120*, 8319−8327.
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in good purity, requiring minimum purification, with the exception of compounds **19** and **21,** where column chromatography purifications were employed after the Staudinger reaction. The final products were obtained and characterized as acetate salts. After which, all of the analogues were converted into chloride salt by an ion-exchange column with Dowex 1X8-200 (Cl^- form) resin.

In summary, we have prepared seven trehalosamine analogues with natural and non-natural binding motifs. The non-natural binding motifs can be utilized for future drug development, which may potentially alleviate the problem of drug resistant microorganisms, since these microorganisms have never encountered the non-natural scaffolds. The philosophy of divergent synthesis allows us to expediently generate a library of compounds using traditional synthetic methods. All the analogues were obtained with high purity in significant amount, which permits us to pursue different types of assay against various agents. We are currently testing our trehalosamine analogues against *E. coli* and *S. aureus*.[4]

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Supporting Information Available: Experimental procedures, characterization data, and ^1H and ^{13}C NMR and mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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