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Formation of 1,1-α,α-Glycosidic Bonds By Intramolecular Aglycone Delivery. A Convergent Synthesis of Trehalose

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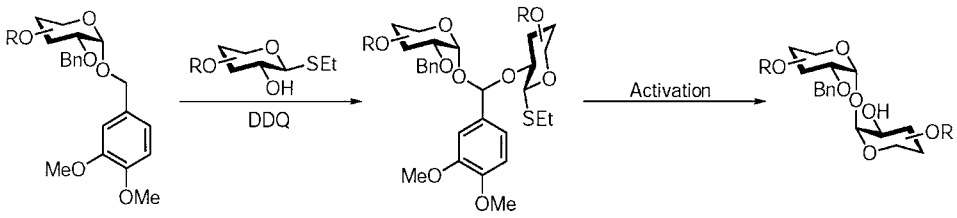
ABSTRACT



We report a new synthesis of trehalose analogs that involves the use of intramolecular aglycone delivery for stereoselective formation of the 1,1-α,α-glycosidic bond. The glycosylation reaction afforded the desired isomer exclusively and in good yield.

Mycobaterial infection, including tuberculosis, has been reemerging as a public health risk due to synergy with the human immunodeficiency virus, overcrowded populations, and drug resistance. An unusual feature of mycobacteria is their outer envelope, which comprises unique polysaccharides and glycolipids thought to participate in host−pathogen interactions.[1] Even more intriguing are the large quantities of certain glycolipids in many virulent strains of *Mycobacterium tuberculosis*.[2] Over three decades ago, Goren elucidated the partial structures of some of these molecules and demonstrated that they possess a common trehalose core (**1**, Figure 1).[3] Examples of these glycolipids include sulfolipid-1 (SL-1, **2**), trehalose 6,6′-dimycolate (**3**), and more complex structures such as **4**. Several of these glycolipids have been shown to affect host−bacterium interactions, including immune system evasion and the infection process. Sulfolipid-1 was administered to both neutrophils and macrophages and modulated activation of both cell types.[4] Trehalose 6,6′-dimycolate can induce lung and liver granulomas in both rabbits and mice.[5] Both of these events are highly relevant to mycobacterial virulence.[6] The synthesis of these glycolipids and possible biosynthetic intermediates is important for elucidation of their biological properties.

To maximize the convergence of our synthesis, a method for the formation of the critical 1,1-α,α-glycosidic bond was needed. Methodologies for constructing 1,1-α,α-glycosidic linkages have been limited by the poor anomeric selectivity of the glycosylation step where not one but two anomeric linkages are formed simultaneously.[7]

Furthermore, only a few strategies allow for the synthesis of desymmetrized derivatives necessary for the synthesis of

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(1) Goren, M. B. *Bacteriol. Rev.* **1972**, *36*, 33−63.

(2) (a) Middlebrook, G.; Coleman, C. M.; Schaefer, W. B. *Proc. Natl. Acad. Sci. U.S.A.* **1959**, *45*, 1801−1804. (b) Elbion, A. D.; Pan, Y. T.; Pastuszak, I.; Carroll, D. *Glycobiology* **2003**, *13*, 17R-27R.

(3) (a) Goren, M. B. *Biochim. Biophys. Acta* **1970**, *120*, 116−126. (b) Goren, M. B. *Biochim. Biophys. Acta* **1970**, *120*, 127−138.

(4) (a) Zhang, L.; English, D.; Andersen, B. R. *J. Immunol.* **1991**, *146*, 2730−2736 (b) Pabst, M. J.; Gross, J. M.; Bronza, J. P.; Goren, M. B. *J. Immunol.* **1988**, *140*, 634−640.

(5) Hamasaki, N.; Isowa, K.; Kamada, K.; Terano, Y.; Matsumoto, T.; Arakawa, T.; Kobayashi, K.; Yano, I. *Infect. Immun.* **2000**, *68*, 3704−3709.

(6) O'Brien, L.; Roberts, B.; Andrew, P. W. *Curr. Top. Microbiol. Immunol.* **1996**, *215*, 97−130.

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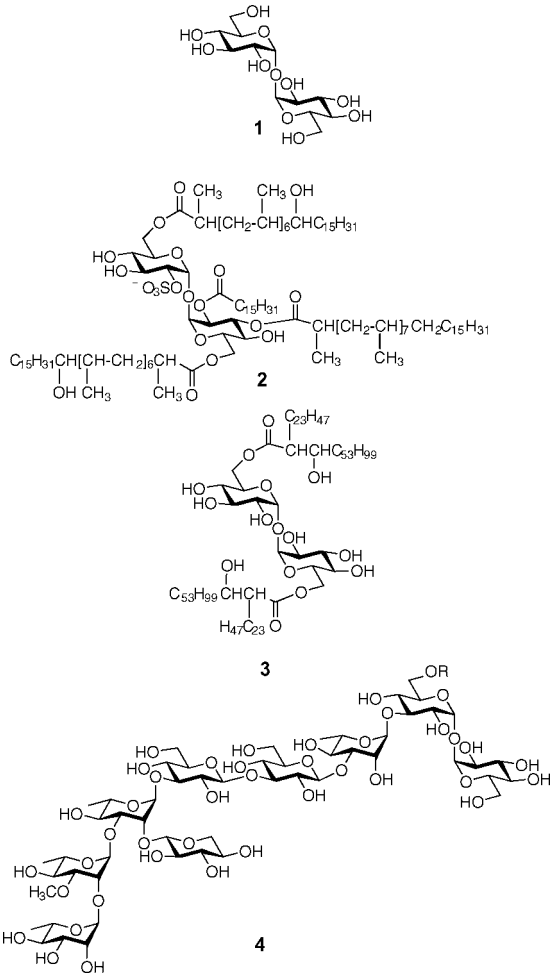


Figure 1. Trehalose (**1**), sulfolipid-1 (**2**), trehalose 6,6′-dimycolate (**3**), and oligosaccharide **4**.

molecules such as SL-1.[7c−f] Indeed, the best of these methods only produced α,α-trehalose in a yield of 39% with appreciable formation of α,*β* and *β*,α side products.[7c] Therefore, a high-yielding, stereoselective method for the formation of 1,1-α,α-glycosidic linkages remains an important goal. Thus, we turned our attention to the intramolecular aglycone delivery (IAD) methodology developed for the synthesis of *β*-mannosides.[8] Using IAD, the donor and acceptor molecules are oriented with a linker prior to activation such that only one stereoisomer can be formed. Reviewing the *β*-mannoside literature, we felt the most promising avenue to explore was the methodology developed by Ito: the oxidation of methoxy-substituted benzyl ethers by agency of 2,3-dichloro-4,5-dicyanoquinone (DDQ) to form mixed acetals (Figure 2A).[8d]

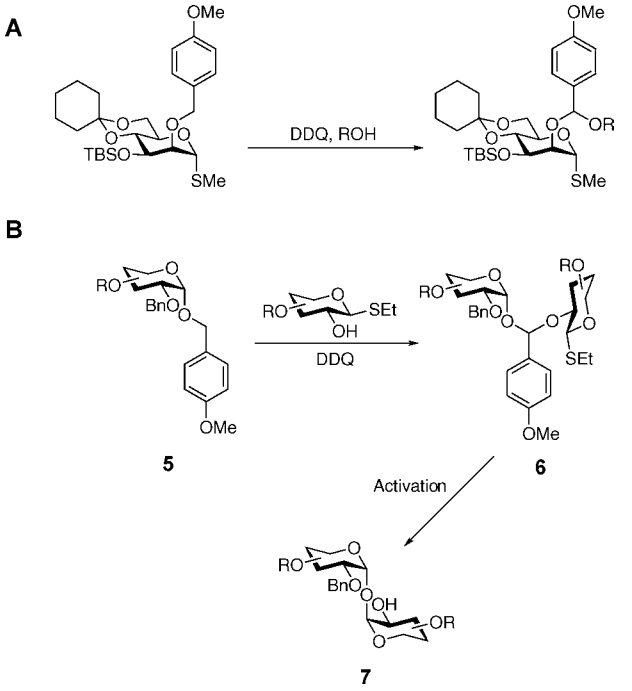


Figure 2. (A) Ito's mixed acetal methodology for the formation of *β*-mannosides. (B) General IAD scheme for formation of a 1,1-α,α-glycosidic linkage.

In our case, the anomeric configuration of intermediate mixed acetal **6** will be guaranteed by the use of acceptor monosaccharide **5**, in which the α-anomer is fixed (Figure 2B). Upon activation of the glycosyl donor by alkylation, the intermolecular tether will deliver the acceptor to the α-face of the donor, thus ensuring the formation of the second α-anomer, yielding trehalose derivative **7**.

Toward this goal, known selectively protected glucose derivative **8**[9] was glycosylated with 4-methoxybenzyl alcohol (PMBOH), involving a glycosyl iodide intermediate developed by Gervay and Hadd,[9] to give **9** with complete anomeric selectivity (Scheme 1). Compound **9** was then oxidized with DDQ under strict anhydrous conditions and the resulting benzylic cation was trapped by known thioglucoside **10**[10] in a one-pot procedure. The crude reaction mixture containing mixed acetal **11** was activated with methyl trifluoromethanesulfonate (MeOTf) to give desymmetrized trehalose derivative **12** as one stereoisomer in 40% yield. The remainder of the material was mostly starting materials due to incomplete oxidation of **9**. Niether α,*β* nor *β*,α products were observed.

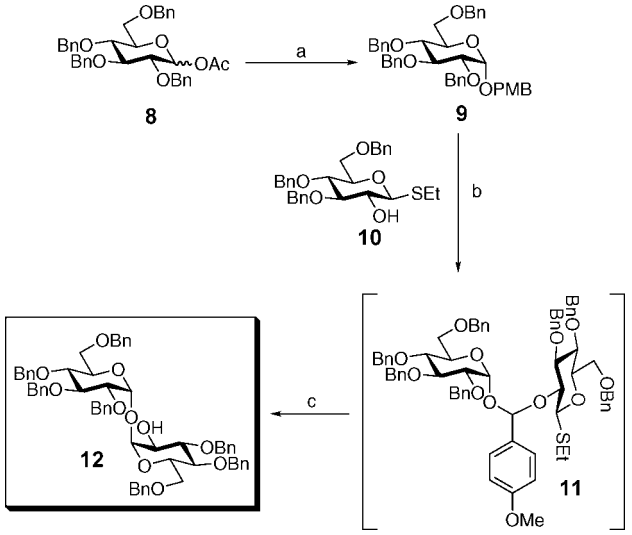
(7) (a) Yoshimura, J.; Hara, K.; Sato, T.; Hashimoto, H. *Chem. Lett.* **1983**, 319−320. (b) Nishizawa, M.; Garcia, D. M.; Noguchi, Y.; Komatsu K.; Hatakeyama, S.; Yamada, H. *Chem. Pharm. Bull.* **1994**, *42*, 2400−2402. (c) Ronnow, T.; Meldal, M.; Bock, K. *Tetrahedron*: *Asymmetry* **1994**, *5*, 2109−2122. (d) Cipolla, L.; Lay, L.; Nicotra, F.; Panza, L.; Russo, G. *Tetrahedron Lett.* **1994**, *35*, 8669−8670. (e) Posner, G. H.; Bull, D. S. *Tetrahedron Lett.* **1996**, *37*, 6279−6282. (f) Nicolau, K. C.; van Delft, F. L.; Conley, S. R.; Mitchell, H. J.; Jin, Z.; Rodriguez, R. M. *J. Am. Chem. Soc.* **1997**, *119*, 9057−9058.

(8) (a) Barresi, F.; Hindsgaul, O. *Synlett* **1992**, 759−761. (b) Stork, G.; Kim, G. *J. Am. Chem. Soc.* **1992**, *114*, 1087−1088. (c) Ennis, S. C.; Fairbanks, A. J.; Tennant-Eyles, R. J.; Yates, H. S. *Synlett* **1999**, *9*, 1387−1390. (d) Ito, Y.; Ando, H.; Wada, M.; Kawai, T.; Ohnish, Y.; Nakahara, Y. *Tetrahedron* **2001**, *57*, 4123−4132. (e) Abdel-Rahman, A. A.-H.; El Ashry, E. S. H.; Schmidt, R. R. *Carbohydr. Res.* **2002**, *337*, 195. (f) Aloui, M.; Chambers, D. J.; Cumpstey, I.; Fairbanks, A. J.; Redgrave, A. J.; Seward, C. M. P. *Chem. Eur. J.* **2002**, *8*, 2608.

(9) Hadd, M. J.; Gervay, J. *Carbohydr. Res.* **1999**, *320*, 61−69.

(10) Danishefsky, S. J.; Hu, S.; Cirillo, P. F.; Eckhardt, M.; Seeberger, P. H. *Chem. Eur. J.* **1997**, *3*, 1617−1628.

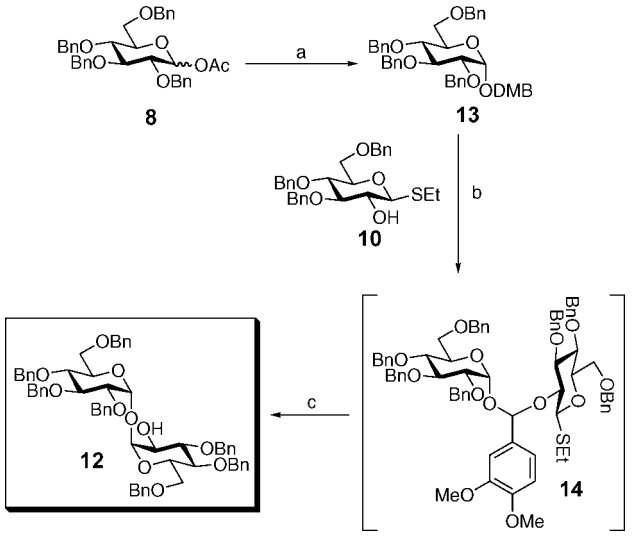
Scheme 1. Synthesis Using *p*-Methoxybenzyl Glycoside[a]



[a] Reaction conditions: (a) (i) TMSI, CH_2Cl_2, 0 °C, 1 h; (ii) Bu_4NI, PMBOH, CH_2Cl_2, reflux, 16 h, 76%. (b) DDQ, 4 Å MS, CH_2Cl_2, 4 h. (c) MeOTf, DTBMP, ClH_2CCH_2Cl, 4 Å MS, 40 °C, 16 h, 40%.

To address the problem of incomplete oxidation, **8** was reacted with 3,4-dimethoxybenzyl alcohol (DMBOH) under the same conditions as above to give **13** (Scheme 2). Indeed,

Scheme 2. Synthesis Using 3,4-Dimethoxybenzyl Glycoside[a]

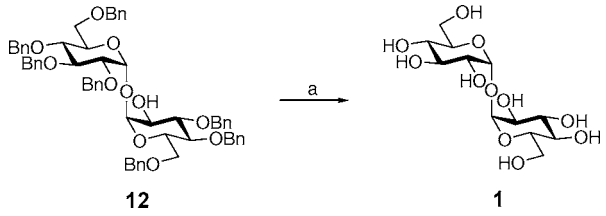


[a] Reaction conditions: (a) (i) TMSI, CH_2Cl_2, 0 °C, 1 h; (ii) Bu_4NI, DMBOH, CH_2Cl_2, reflux, 16 h, 80%. (b) DDQ, 4 Å MS, CH_2Cl_2, 4 h. (c) MeOTf, DTBMP, ClH_2CCH_2Cl, 4 Å MS, 40 °C, 16 h, 68%.

when **13** was used with donor **10** under identical conditions, the yield improved to an excellent 68%. Again, neither α,*β* nor *β*,α products were isolated from the reaction mixture.

To confirm the identity of **12**, the benzyl ether protecting groups were removed by catalytic hydrogenolysis to give **1**

Scheme 3. Final Deprotection[a]

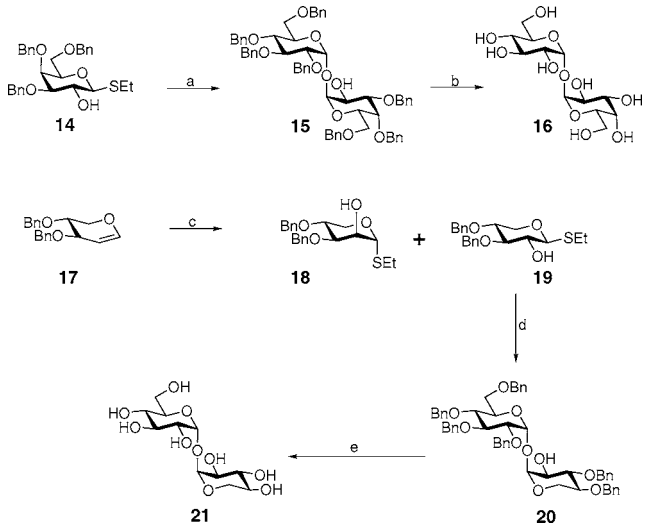


[a] Reaction conditions: (a) H_2, Pd/C, MeOH, 24 h, 95%.

(Scheme 3). The ^1H NMR spectrum of **1** was identical to that of an authentic sample.

To examine the scope of this reaction, we next synthesized the asymmetric galactose and xylose derivatives of trehalose, **16**[11] and **21**, respectively (Scheme 4). Known thioglycoside

Scheme 4. Asymmetric Derivatives[a]



[a] Reaction conditions: (a) (i) **13**, DDQ, 4 Å MS, CH_2Cl_2, 4 h; (ii) MeOTf, DTBMP, ClH_2CCH_2Cl, 4 Å MS, 40 °C, 16 h, 93%. (b) H_2, Pd/C, MeOH, 24 h, 95%. (c) (i) DMDO, CH_2Cl_2, 0 °C, 1 h; (ii) EtSH, TFAA, CH_2Cl_2, 0 °C to rt, 16 h, 95%. (d) (i) **13**, DDQ, 4 Å MS, CH_2Cl_2, 4 h; (ii) MeOTf, DTBMP, ClH_2CCH_2Cl, 4 Å MS, 40 °C, 16 h, 65%. (e) H_2, Pd/C, MeOH, 24 h, 95%.

14[12] was subjected to the same IAD conditions with acceptor **13** to provide **15** in excellent yield as a single 1,1-α,α stereoisomer. Disaccharide **15** was then deprotected to provide galactosyl-trehalose derivative **16**. Toward xylosyl-trehalose, known xylal **17**[13] was oxidized with dimethyl dioxirane (DMDO) followed by nucleophilic opening of the resulting epoxide with EtSH and catalytic trifluoroacetic anhydride (TFAA) to give **18** and **19** in a 1:1 ratio.

(11) Ronnow, T.; Meldal, M.; Bock, K. *J. Carbohydr. Chem.* **1995**, *14*, 197−211.

(12) Ziegler, T.; Dettmann, R.; Zettl, A.; Zettl, U. *J. Carbohydr. Chem.* **1999**, *18*, 1079−1095.

(13) Fischer, S.; Hamann, C. H. *J. Carbohydr. Chem.* **1995**, *14*, 327−339.

Compound **19** was separated from **18** and subjected to the IAD conditions. The resulting disaccharide **20** was obtained in good yield again as one stereoisomer. Deprotection then gave derivative **21**.

In conclusion, we have demonstrated that IAD can be used to form the difficult 1,1-α,α-glycosidic linkage of trehalose. Desymmetrized derivative **12** was formed with complete stereoselectivity at both anomeric centers and in excellent yield. Other monosaccharides also performed well in this reaction, allowing high-yielding syntheses of galactosyl- and xylosyl-trehalose derivatives. Furthermore, because of the highly convergent nature of this route, the synthesis of other complex unsymmetrical disaccharides can be readily accomplished. We are currently exploring the extension of this methodology to the synthesis of natural products with trehalose core structures including SL-1.

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Supporting Information Available: Synthetic procedures and full characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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