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A New Entry for the Controlled Synthesis of 2,6-Dideoxy Oligosaccharides

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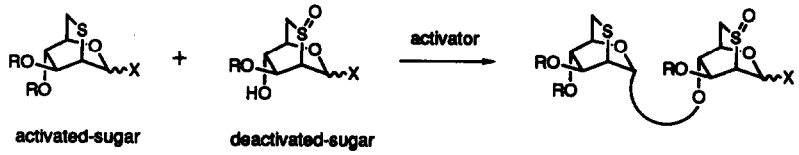
Key Words: oligosaccharide, glycosylation, 2,6-anhydro-2-thio sugar, 2,6-anhydro-2-sulfinyl sugar, avermectins.

Abstract: A novel methodology for the controlled synthesis of 2,6-dideoxy oligosaccharides by combinational use of an activated 2,6-anhydro-2-thio sugar and a deactivated 2,6-anhydro-2-sulfinyl sugar, both of which have a same leaving group at anomeric position, has been demonstrated.

Over recent years oligosaccharides have been the subject of considerable interest in carbohydrate chemistry and biochemistry, as well as in organic synthesis.[1] Therefore, stereoselective block synthesis of oligosaccharides is one of the most challenging task for organic chemists and a suitable demonstration to show the efficiency of a glycosylation protocol.[2] We have recently reported a highly stereocontrolled glycosylation method by using several 2,6-anhydro-2-thio sugars for the synthesis of both 2,6-dideoxy α- and β-glycosides.[3] Since several 2,6-dideoxy oligosaccharides frequently appear in naturally occurring bioactive substances such as aureolic acid antibiotics, anthracycline antibiotics, cardiac glycosides and avermectins,[4] we have applied our glycosylation protocol to the block synthesis of 2,6-dideoxy oligosaccharides. In this article, we wish to report a novel methodology for the controlled synthesis of 2,6-dideoxy oligosaccharides by combinational use of an activated 2,6-anhydro-2-thio sugar and a deactivated 2,6-anhydro-2-sulfinyl sugar, both of which possess a same leaving group at anomeric center.



In the course of investigating the chemistry of 2,6-anhydro-2-thio glycosides, we found that the high reactivity of 2,6-anhydro-2-thio glycosyl donor under the variety of glycosylation conditions resulted from the electron donating nature of the sulfur at C-2 position in the 2,6-anhydro-2-thio sugar and the rate of the glycosylation reaction was strongly affected by the oxidation state of the sulfur. Indeed, the glycosylations of 2,6-anhydro-2-sulfinyl fluorides **2**[5] and **3**[5] and 2,6-anhydro-2-sulfonyl fluoride **4**[5] with cyclohexanol under the conditions[3b], in which the glycosylation of 2,6-anhydro-2-thio fluoride **1**[3b] exclusively gave the α-glycoside **5**[3b], did not proceed and each unchanged glycosyl donor was recovered in almost quantitative yield. Since the both 2,6-anhydro-2-sulfinyl glycosyl donors showed the same low reactivity in the glycosylation conditions, the armed-disarmed phenomenon[6] in this glycosylation reaction would come from the electronic effect of the C-2-substituent as Fraser-Reid's explanation[6c], not from the effect of neighboring participation of the C-2-substituent to the anomeric center.

To enhance the synthetic utility of this reaction, other pairs of activated and deactivated sugars were examined. The 2,6-anhydro-2-thio sugar **6**[5,7] possessing an acetoxy group as a leaving group was coupled with the corresponding 2,6-anhydro-2-sulfinyl sugar **7**[5] in the presence of TMSOTf in CH_2Cl_2 to afford the deactivated oligosaccharide **8**[5] in 81% yield. Also, the glycosylation of the 2,6-anhydro-2-thio sugar **9**[5,7] possessing a thiophenyl group at anomeric center with the corresponding 2,6-anhydro-2-sulfinyl sugar **10**[5] having a same leaving group by NIS-TMSOTf[6c,8] in CH_2Cl_2 proceeded nicely to give the oligosaccharide **11**[5] in 89% yield. Notably, the self-coupling products of the deactivated sugars were not detected and the stereoselectivity of these glycosylations was highly α-selective[9]. Further, the obtained deactivated oligosaccharide **11**[5] was easily converted into the activated oligosaccharide **12**[5] by simple reduction of the sulfoxide moiety using LAH in THF. After the protection of hydroxy group of **12**, the resulting **13**[5] was found to smoothly glycosylate with a model alcohol, cyclohexanol, by NBS in CH_2Cl_2 under the mild conditions to stereospecifically[9] produce the α-glycoside **14**[5] which was transformed into the desired 2,6-dideoxy oligosaccharide **15**[5] by hydrogenolysis using a catalytic amount of Raney-Ni.[3a] Although D-sugars were employed as the starting materials and *tert*-butyldiphenylsilyl (TPS) groups were used as the protecting groups in this synthesis considering synthetic generality, the disaccharide **15** was corresponding to the glycon of biologically important antibiotic, avermectins, including the configuration of both anomeric centers.

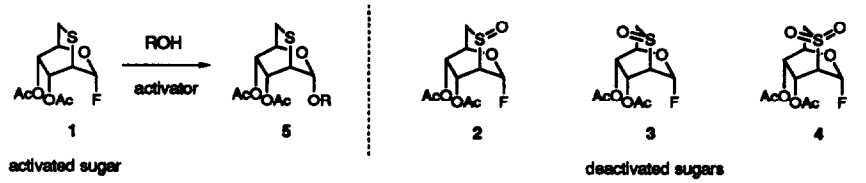
In conclusion, the present glycosylation method by using an activated 2,6-anhydro-2-thio sugar and a deactivated 2,6-anhydro-2-sulfinyl sugar offered a new entry for the controlled synthesis of 2,6-dideoxy oligosaccharides which were often found in useful antibiotics. Synthetic studies on the trisaccharide moiety of antitumor antibiotic, olivomycin A, along this line are now in progress and the results will be published elsewhere.

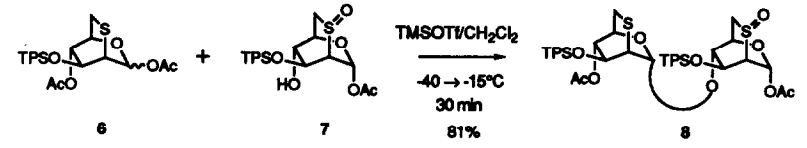
Acknowledgment

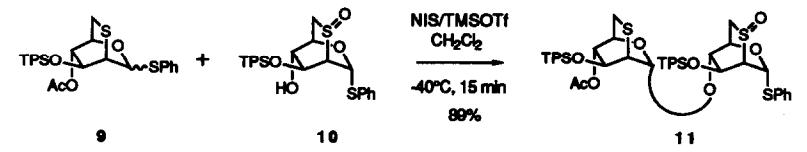
We are grateful to the Institute of Microbial Chemistry for the generous support of our program. Financial support by the Ministry of Education, Science and Culture (Grant-in-Aid Scientific Research) is gratefully acknowledged.

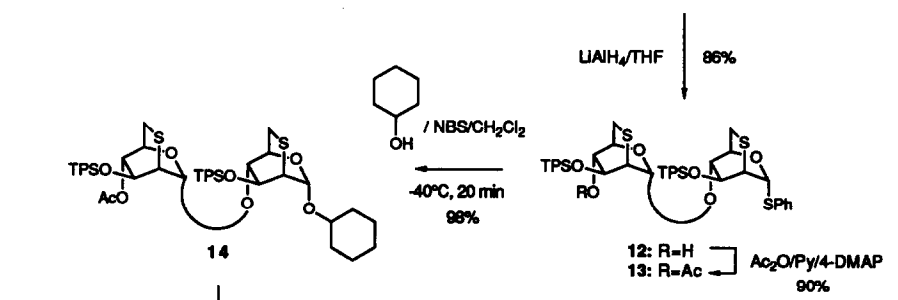
References and Notes

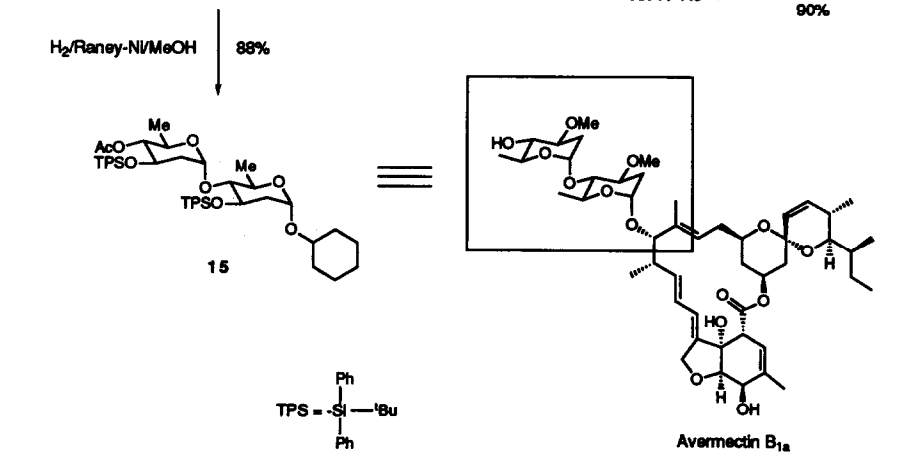
1) J. F. Kennedy, C. A. White, *Bioactive Carbohydrates in Chemistry, Biochemistry and Biology*, Halsted Press, New York, 1983.


ROH
activator
1
activated sugar
5
2
3
4
deactivated sugars


TMSOTf/CH2Cl2
-40 → -15°C
30 min
81%
6
7
8


NIS/TMSOTf
CH2Cl2
-40°C, 15 min
89%
9
10
11


LiAlH4/THF
86%
/ NBS/CH2Cl2
-40°C, 20 min
98%
14
12: R=H
13: R=Ac
Ac2O/Py/4-DMAP
90%


H2/Raney-Ni/MeOH
88%
15
TPS = -Si(Ph)2-tBu
Avermectin B1a

2) For four recent reviews of *O*-glycosylation, see: (a) H. Paulsen, *Angew. Chem. Int. Ed. Engl.*, 1982, **21**, 155; (b) R. R. Schmidt, *Angew. Chem. Int. Ed. Engl.*, 1986, **25**, 212; (c) R. R. Schmidt, *Comprehensive Organic Synthesis*, Pargamon Press, Oxford, 1991, **6**, 33; (d) K. Suzuki, T. Nagasawa, *J. Synth. Org. Chem. Jpn.*, 1992, **50**, 378.

3) (a) K. Toshima, S. Mukaiyama, T. Ishiyama and K. Tatsuta, *Tetrahedron Lett.*, 1990, **31**, 3339; (b) K. Toshima, S. Mukaiyama, T. Ishiyama and K. Tatsuta, *Tetrahedron Lett.*, 1990, **31**, 6361; (c) K. Toshima, S. Mukaiyama, T. Yoshida, T. Tamai and K. Tatsuta, *Tetrahedron Lett.*, 1991, **32**, 6155; (d) K. Toshima, Y. Nozaki, S. Mukaiyama and K. Tatsuta, *Tetrahedron Lett.*, 1992, **33**, 1491.

4) B. W. Bycraft, "*Dictionary of Antibiotics and Related Substances*", Chapman and Hall, London, 1988.

5) All new compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means. Selected ^{1}H-NMR ($CDCl_3$/270 MHz) data for compounds **9**, **10**, **11**, and **15** follow; **9**-α: δ 1.11 (s, 9H, t-Bu), 1.95 (S, 3H, OAc), 2.76 (dd, 1H, J=3.2 and 1.8Hz, H-2), 3.00 (dd, 1H, J=14.0 and 2.4Hz, H-6), 3.15 (dd, 1H, J=14.0 and 3.7Hz, H-6), 4.20 (dd, 1H, J=3.7 and 2.4Hz, H-5), 4.74 (dd, 1H, J=3.6 and 3.2Hz, H-3), 4.94 (d, 1H, J=3.6Hz, H-4), 5.57 (d, 1H, J=1.8Hz, H-1), 7.25-7.8 (15H, Ph X 3); **9**-β: δ 1.10 (s, 9H, t-Bu), 1.89 (S, 3H, OAc), 2.86 (dd, 1H, J=3.6 and 2.2Hz, H-2), 2.98 (dd, 1H, J=14.0 and 3.0Hz, H-6), 3.58 (dd, 1H, J=14.0 and 2.9Hz, H-6), 4.18 (dd, 1H, J=3.0 and 2.9Hz, H-5), 4.22 (dd, 1H, J=4.0 and 2.2Hz, H-3), 5.03 (d, 1H, J=4.0Hz, H-4), 5.30 (d, 1H, J=3.6Hz, H-1), 7.25-7.8 (15H, Ph X 3); **10**: δ 1.11 (s, 9H, t-Bu), 2.85 (ddd, 1H, J=14.4, 5.6 and 1.0Hz, H-6), 3.16 (d, 1H, J=12.0Hz, OH), 3.35 (dd, 1H, J=14.4 and 0.8Hz, H-6), 3.52 (dd, 1H, J=5.8 and 2.0Hz, H-2), 3.68 (dd, 1H, J=12.0 and 2.2Hz, H-4), 4.42 (ddd, 1H, J=5.6, 2.2 and 0.8Hz, H-5), 4.51 (d, 1H, J=5.8Hz, H-3), 5.96 (d, 1H, J=2.0Hz, H-1), 7.25-7.8 (15H, Ph X 3); **11**: δ 1.02 (s, 9H, t-Bu), 1.06 (s, 9H, t-Bu), 1.81 (s, 3H, OAc), 2.25 (dd, 1H, J=3.8 and 2.0Hz, H-2'), 2.72 (dd, 1H, J=14.4 and 5.6Hz, H-6 or H-6'), 2.75-2.9 (m, 2H, H-6 or H-6'), 3.30 (br s, 1H, H-2), 3.33 (dd, 1H, J=14.4 and 1.4Hz, H-6 or H-6'), 3.66 (dd, 1H, J=4.8 and 1.5Hz, H-4), 4.09 (br m, 1H, H-5 or H-5'), 4.43 (br m, 1H, H-5 or H-5'), 4.47 (d, 1H, J=2.0Hz, H-1'), 4.53 (d, 1H, J=4.8Hz, H-3), 4.64 (dd, 1H, J=2.3 and 1.9Hz, H-4'), 4.77 (dd, 1H, J=3.8 and 2.3Hz, H-3'), 5.86 (d, 1H, J=2.0Hz, H-1), 7.25-7.8 (25H, Ph X 5); **15**: δ 0.93 (s, 9H, t-Bu), 1.02 (s, 9H, t-Bu), 1.0-2.0 (13H, cyclohexyl, H-2 or H-2' X 3), 1.10 (d, 6H, J=6.2Hz, Me X 2), 1.84 (s, 3H, OAc), 2.04 (dd, 1H, J=12.6 and 5.0Hz, H-2 or H-2'), 3.27 (dd, 1H, J=8.4 and 8.4Hz, H-4), 3.3-3.4 (m, 1H, cyclohexyl), 3.50 (dq, 1H, J=8.4 and 6.2Hz, H-5), 3.70 (dq, 1H, J=8.6 and 6.2Hz, H-5'), 4.05-4.25 (m, 2H, H-3 and H-3'), 4.63 (dd, 1H, J=3.8 and 2.0Hz, H-1 or H-1'), 4.79 (dd, 1H, J=8.6 and 8.6Hz, H-4'), 5.45 (d, 1H, J=3.8Hz, H-1 or H-1'), 7.25-7.8 (20H, Ph X 4).

6) (a) D. R. Mootoo, P. Konradsson, U. Udodong and B. Fraser-Reid, *J. Am. Chem. Soc.*, 1989, **111**, 8540: (b) P. Konradsson, D. R. Mootoo, R. E. McDevitt and B. Fraser-Reid, J. Chem. Soc., Chem. Commun., **1990**, 631; (c) B. Fraser-Reid, Z. Wu, U. Udodong and H. Ottosson, *J. Org. Chem.*, 1990, **55**, 6068.

7) The α/β ratio of the configuration of anomeric center did not affect the glycosylation reaction at all.

8) G. H. Veeneman, S. H. van Leeuwen and J. H. van Boom, *Tetrahedron Lett.*, 1990, **31**, 1331.

9) β-Anomers of **8**, **11** and **14** were not detected by both TLC and ^{1}H-NMR (270MHz) analyses at all.

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