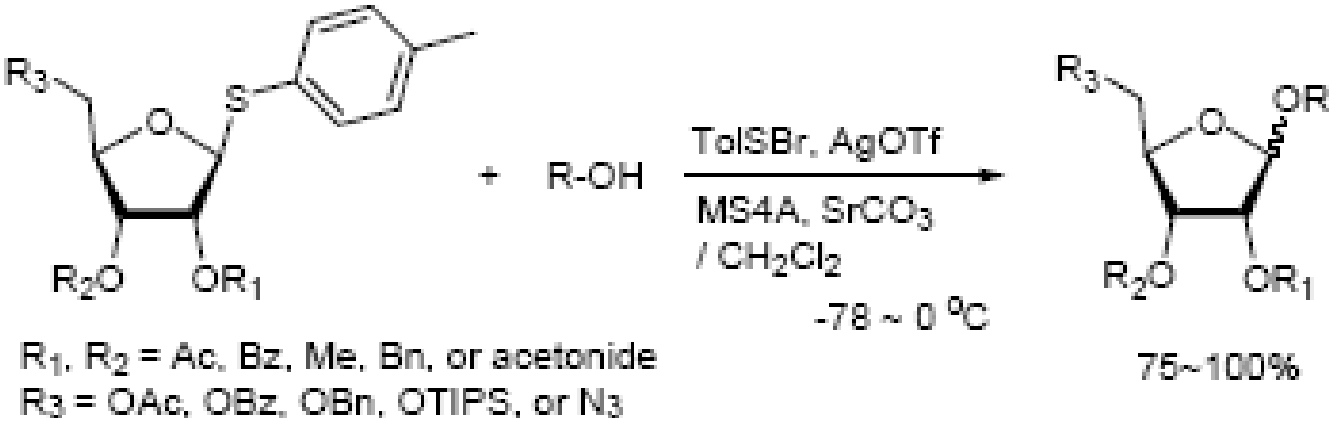
NIH Public Access
Author Manuscript
J Org Chem. Author manuscript; available in PMC 2009 December 19.

Published in final edited form as:
J Org Chem. 2008 December 19; 73(24): 9767–9770. doi:10.1021/jo801408x.

Highly Efficient *O*-Glycosylations with *p*-Tolyl Thioribosides and *p*-TolSOTf

Michio Kurosu* and **Kai Li**
Department of Microbiology, Immunology, and Pathology, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, 1682 Campus Delivery, Fort Collins, CO 80523-1682

Abstract



A wide variety of *p*-tolyl thioriboside donors are examined for *O*-ribosylations of *primary* and *secondary* alcohols. *p*-Tolylsulfenyl trifluoromethanesulfonate (*p*-TolSOTf) is very effective in promoting *O*-ribosylations with *p*-tolyl thioriboside; all reactions are completed within 1~15 min. to provide the desired products in good yield with reliable α/β selectivity. A wide range of functional groups are tolerated under these conditions. The described *O*-ribosylation conditions are very useful for the generation of ribosamino-uridine library molecules in solution or on polymer-support.

The 5-deoxy-5-aminoribose moiety of ribosamino-uridine antibiotics (i.e. muraymycin, liposidomycin, caprazamycin, and FR-900493) has been considered as an important functional group to exhibit excellent antibacterial activities.[1] These antibiotics are known to interfere with the enzyme involved in the committed step of peptidoglycan biosynthesis, MraY which catalyzes the transformation of UDP-*N*-acylmuramyl-L-alanyl-γ-D-glutamyl-*meso*-diaminopimelyl-D-alanyl-D-alanine (Park's nucleotide) to prenylpyrophosphoryl-*N*-acylmuramyl-L-Ala-γ-D-glu-*meso*-DAP[2]-D-Ala-D-Ala (lipid I), and are non-toxic or less toxic *in vivo*. Thus, MraY has been a target of interest for the discovery of novel antimycobacterial agents.[3] However, medicinal chemistry programs of these natural products with an aim to improve the efficacy including pharmacokinetics are hampered by a limited number of modification reactions which can selectively modify the desired positions of such complex molecules.[4] In addition, one of the drawbacks of performing medicinal chemistry with these complex antibiotics is the requirement for the fermentation of the natural product starting materials.[5]

michio.kurosu@colostate.edu.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

In our ongoing effort to define the minimum structure requirement of ribosamino-uridine MraY inhibitors of natural product origin to exhibit equal biological activity,[6] we envisioned synthesizing a library of ribosamino-uridine molecules in solution or on polymer-support.[7] Because structural diversity of ribosamino-uridine antibiotics are observed not only in the lipid moiety (R group in Figure 1) but also at the 2-position of aminoribose moiety (i.e. methyl or sulfonyl group), it is desired to develop a versatile and robust ribosylation method which also amenable to glycosylations on polymer-support.[8]

Although numerous examples of *N*-glycosylations of purine or pyrimidine bases with furanose derivatives have been reported,[9] *O*-ribosylation has rarely discussed in literatures. Recently, Merrer and co-workers reported *O*-ribosylations of *primary* alcohols using bromo- or fluoro-ribosides with the established promoters such as AgOTf or $SnCl_2/AgClO_4$.[10] Reaction rates for *O*-ribosylations with 1-halo riboside are very slow (6~36h), and in our hands under these conditions *O*-ribosylations of the *secondary* alcohols resulted in unsatisfactory yields of 15~65%. In addition, because of the limited accessibility of 1-halo ribosides it is difficult to diversify ribosamino-uridine library molecules by *O*-ribosylations with these methods. In this note, we wish to report expeditious *O*-ribosylations of *primary* and *secondary* alcohols with a wide variety of *p*-tolyl thioriboside donors and *p*-TolSOTf that would be very useful to synthesize a library of ribosamino-uridine molecules.[11]

Because thioglycosides 1) can conveniently be synthesized *via* acid catalyzed thioglycosylations of 1-*O*-acetylglycoside, and 2) exhibit excellent chemical stabilities against acids and bases, the anomeric thioethers have widely been utilized as a temporary protecting group of anomeric positions as well as glycosyl donors.[12] However, a choice of promoter requires careful consideration when use less electrophilic thioglycosides; in some cases no activation or very slow reaction rate was observed using conventional thiophilic reagents.[13] In order to identify an effective thiophilic reagent for *O*-ribosylations, we first screened thiophilic reagents using an anomeric mixture (α/β = 1/6.6) of *p*-tolyl tribenzoyl thioglycosides **1a** and the immobilized propargyl alcohol on the polymer-resin **i**[14]. As a result of extensive reaction screenings it was found that *p*-TolSOTf in-situ generated from *p*-TolSBr[15] and AgOTf provided the β-*O*-ribosylated product **ii** in near quantitative yield within 15 min. at 0 °C;[16] **ii** was characterized after cleavage from the polymer-resin with 20% TFA. Significantly, even in the presence of a large excess of the promoters (>10 equiv) all functional groups (acetal, alkyne, alkene, and BOM protecting group) were intact. It is worthy while mentioning that the other conditions tested (i.e. NIS, NIS/TfOH, NIS/AgOTf, and $NIS/AgBF_4$)[17] provided **ii** in 0~15 % yields together with a significant amount of byproducts.[18]

To investigate how effectively *p*-TolSOTf can promote glycosylations of a wide range of *p*-tolyl thioribosides we synthesized the donor ribosides **1b**~**n** and the conditions developed for an *O*-ribosylation on the polymer-resin (Scheme 1) were applied to *primary* and *secondary* alcohols in solution. All reactions were conducted with donor (2 equiv against acceptor), *p*-TolSOTf (1 equiv against donor), and MS4Å (2 times the weight of donor)[19] in CH_2Cl_2 in the presence or absence of $SrCO_3$[20]. The representative *O*-ribosylations using these conditions were summarized in Table 1. The reactions of the *primary* alcohols **2a**~**e** with tri-*O*-acyl riboside **1a** or **1b** at 0 °C provided the corresponding β-glycosides **3a**~**f** exclusively with greater than 85% yield within 1~5 min. (entries 1~6). It was realized that *p*-TolSOTf, which colours blue in CH_2Cl_2, could be generated even at -78 °C[21] and could also activate **1a** and **1b** at the same temperature without noticeable decrease in the reaction rate. Because chemical modifications of the 5-position of 5-deoxy-5-aminoribose in ribosamino-uridine antibiotics is important to improve *in vitro* and *in vivo* efficacy, glycosylations of the acceptor **2e** with the 5-TIPS-protected thioribose **1c** and 5-azido-5-deoxy-thioriboside **1d**, whose 5-positions can easily be diversified after glycosylations, were evaluated. Under the buffered conditions (condition B in Table 1) the azide and silyl groups in the ribosyl donors were intact (entries

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

7~8). The *primary* and *secondary* donor alcohols (i.e. alkanols, alkynols, and homoallylic alcohols)[22] were ribosylated with the donors **1a**~**d** to furnish the β-glycosides in greater than 80% yield; limited examples of the reactions of the *secondary* alcohols (i.e **2f**) were shown in Table 1 (entries 19~21).[22] However, *primary* and *secondary* allylic alcohols (i.e. 5-phenylpent-1-en-3-ol) were not applicable to these conditions due probably to its low nucleophilicity. Ribosylations of propargyl alcohol with the ether protected thioribosides **1e**~**g** (entries 9~11) provided a mixture of α/β glycosides (5~6.6/1) in 75~90% yield. Thus, synthetically useful level of α-selectivity in *O*-ribosylations was observed by using the ether protecting groups. Glycosylations of propargyl alcohol with the acetonide protected thioribosides **1h**~**j** (entries 12~14) provided a 1:1.1 (α/β) mixture of the corresponding products regardless of structure of the 5-position of **1h**~**j**. As seen in muraymycins (Figure 1), an alkylation is observed at the 2-position of aminoribose unit. To study the effect of 3-*O*-acyl group in the 2-*O*-methylated thioglycosides, glycosylations of propargyl alcohol with **1k**~**n** (entries 15~18) were examined. The 3-*O*-acetyl group in **1k**~**n** were effective in reversing the selectivity; the reactions with **1k** or **1l** gave a 1:3 mixture of the α- and β-ribosides. The 3-*O*-benzoyl protected donors **1m** or **1n** improved α/β -selectivity (α/β = 1:5.5). These selectivities observed at 0 °C were not dramatically enhanced by lowering the reaction temperatures (i.e. -78 °C); the α/β selectivity was increased to 1:6.5 for **1m**. The glycosylations of **2f**, a versatile intermediate for the generation of ribosamino-uridine libraries, with **1m** or **1n** gave identical selectivities (α/β = 1:5.5) observed for the *primary* alcohol. Similarly, the reactions of **2f** with the 3-*O*-acetate, **1k** or **1l**, provided an anomeric mixture (α/β = 1:2.5) of the glycosides (Scheme 2). Mechanistically, the ribosyl carbenium ion generated by *p*-TolSOTf would first be stabilized by the formation of an intimate ion pair[23] with triflate ion, and undergoes a pseudo 5-membered ring formation when 2-*O*-acyl ribosyl donor is applied. These processes must proceed prior to the glycosylation step. Although an anchimeric assistance by the 3-*O*-acyl group to form a pseudo 6-membered ring (**iii** in Scheme 2) has not been proven theoretically, the data summarized in Table 1 (e.g. Entry 11 vs. 17) clearly indicate that the 3-*O*-acyl carbonyl group is responsible for β-selective glycosylations. It is speculated that the formation of a pseudo 6-membered ring is a slower process than that of a 5-membered ring. Thus, non-selective glycosylation of an intermediate **iv** may compete with β-selective glycosylation (through **iii**) to provide an α/β anomeric mixture. The 3-*O*-benzoyl group seems to be stereoelectronically more favoured than the 3-*O*-acetyl group to participate in anchimeric assistance in ribosylations (Scheme 2).[24]

In conclusion, thioribosides were, for the first time, generalized for *O*-ribosylations using *p*-TolSOTf.[25] *p*-TolSOTf can be generated by a mixing *p*-TolSBr and AgOTf in CH_2Cl_2 at -78~0 °C, and has a short half-life (ca. 15 min.) at 0 °C. However, the reaction rate of *O*-ribosylations under these conditions is very fast; all reactions summarized in Table 1 were completed within 1~15 min. The 2-*O*-acyl group is an important factor to obtain β-selective ribosylation product exclusively. The anchimeric assistance of 3-*O*-acyl group may attribute to furnish β-selective ribosylations with 2-*O*-alkyl thioribosides. The ether protected thioglycosides provided useful level of α-selectivities (i.e. α/β = 6.6/1 for benzyl ether). The 2,3-acetonide protected thioglycosides give rise to a 1:1.1 (α/β) anomeric mixture of ribosides. Most importantly, *p*-TolSOTf is applicable to substrates possessing a wide variety of functional groups such as alkyne, alkene, and commonly utilized protecting groups in multiple step syntheses (i.e. silyl, ketal, and ether protecting groups, and N_3 group). Moreover, the conditions reported here are applicable to *O*-ribosylations on the polymer-supported resin (Scheme 1). The 2- and 5-positions of aminoribose moiety of ribosamino-uridine library molecules can be diversified by using the thioriboside donors summarized in Table 1 and their related structure of molecules. The generation of diverse structures of ribosamino-uridine libraries and biological evaluations of these library molecules will be reported elsewhere.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Experimental Section

Typical Procedure for *O*-Ribosylation with 1a

A mixture of **1a** (2.0 equiv), alcohols (1.0 equiv), MS4Å, AgOTf (2.0 equiv), and $SrCO_3$ (4.0 equiv; Condition B) in CH_2Cl_2 (0.1~0.2 M) was stirred at rt for 15 min. The reaction mixture was cooled 0 °C and *p*-TolSBr (2.0 M in $ClCH_2CH_2Cl$, 2.0 equiv) was added. After 1~15 min. the reaction mixture was quenched with Et_3N (5.0 equiv), and the resulting mixture was filtered through a SiO_2 plug. Purification by silica gel chromoatography (hexanes:EtOAc) provided the desired products. $SrCO_3$ was excluded for Condition A.

Propargyl 5-azido-5-deoxyl-2,3-*O*-isopropylidene-β-D-ribofuranoside (3n and 4n)

3n (β isomer):$[\alpha]^{20}_D$ = +78.4 (*c* 0.5 in $CHCl_3$); IR (film) 2102, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 1H), 4.65 (dd, *J* = 6.0 Hz, 18.9 Hz, 2H), 4.32 (t, *J* = 7.2 Hz, 1H), 4.26 (dd, *J* = 1.2, 2.4 Hz, 1H), 4.24 (dd, *J* = 1.2, 2.1 Hz, 1H), 3.46 (dd, *J* = 7.8, 12.6 Hz, 1H), 3.30 (dd, *J* = 6.9, 12.6 Hz, 1H), 2.46 (m, 1H), 1.50 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.1, 107.1, 85.9, 85.4, 82.2, 75.2, 54.8, 53.8, 26.6, 25.1; HRMS (ESI) Calcd. for $C_{11}H_{15}N_3NaO_4$ $(M+Na)^+$. 276.0960; found: 276.0960. **4n** (α isomer): $[\alpha]^{20}_D$ = −16.0 (*c* 0.1 in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 5.23 (d, *J* = 4.8 Hz, 1H), 4.73 (dd, *J* = 4.8, 7.2 Hz, 1H), 4.55 (dd, *J* = 3.6 Hz, 7.2 Hz, 1H), 4.32 (dd, *J* = 2.4, 4.2 Hz, 2H), 4.27 (m, 1H), 3.55 (dd, *J* = 4.0, 13.2 Hz, 1H), 3.36 (dd, *J* = 4.4, 16.0 Hz, 1H), 2.39 (t, *J* = 2.4 Hz, 1H), 1.55 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ116.2, 99.8, 81.2, 81.2, 80.7, 75.0, 55.1, 52.6, 26.2, 26.1; HRMS (ESI) Calcd. for $C_{11}H_{15}N_3NaO_4$ $(M+Na)^+$. 276.0960; found: 276.0962.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This paper is dedicated to the memory of Professor Albert I. Meyers, an inspirational scientist. We thank the National Institutes of Health and Colorado State University for generous financial supports.

REFERENCES AND NOTES

1. Dini C. Curr Top Med Chem 2005;5:1221. [PubMed: 16305528]
2. DAP: (2*R*,6*S*)-2,6-diaminoheptanedioic acid.
3. van Heijenoort J. Glycobiology 2001;11:25R.
4. a) Corre LL, Gravier-Pelletier C, Merrer YL. Eur J Org Chem 2007:5386. b) Hirano S, Ichikawa S, Matsuda A. Angew Chem Int Ed 2005;44:1854. c) Hotoda H, Daigo M, Furukawa M, Murayama K, Hasegawa CA, Kaneko M, Muramatsu Y, Ishii MM, Miyakoshi S, Takatsu T, Inukai M, Kakuta M, Abe T, Fukuoka T, Utsui Y, Ohya S. Bioorg Med Chem lett 2003;13:2833. [PubMed: 14611839]
5. No efficient chemical synthesis of ribosamino-uridine natural products which can be performed medicinal chemistry has been reported.
6. For synthetic effort towards identification of the minimum structure requirement of liposidomycins. see, Dini C, Drochon N, Feteanu S, Guillot JC, Peixoto C, Aszodi J. Bioorg Med Chem Lett 2001;11:529. [PubMed: 11229763]
7. Kurosu M, Narayanasamy P, Crick DC. Heterocycles 2007;72:339.
8. In mycobacterial growth inhibitory and enzymatic assays against MraY of representative uridine-β-hydroxyaminocarboxilic acid derivative, it was realized that the molecules which do not possess the aminoribose group significantly lowered mycobacterial growth inhibitory activity. Thus, it is important to retain the aminoribose (highlighted in Figure 1) or its equivalent in MraY inhibitors of uridine-β-hydroxyaminocaroxylic acid analogs.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

9. (a) Ferrero M, Gotor V. Chem Rev 2000;100:4319. [PubMed: 11749350]Townsend, LB. Nucleoside Analogues Chemistry Biology and Medical Applications. Walker, RT.; De Clercq, E.; Eckstein, F., editors. Plenum Press; New York: 1979. p. 193 (c) Reese CB. Tetrahedron 1978;34:3143.
10. Ginistry M, Gravier-Pelletier C, Merrer YL. Tetrahedron Asymmetry 2006;17:142.
11. Other potential glycosylations with ribose derivatives, see. Garcia BA, Poole JA, Gin DY. J Am Chem Soc 1997;119:7597.(b)Knapp S, Shieh W-C. 1991;32:3627.
12. a) Ekelof K, Garegg PJ, Olsson L, Oscarson S. Pure and Appl Chem 1997;69:1847. b) Garegg PJ. Advances in Carbohyd Chem and Biochem 1997;52:179.
13. For an example of the nonsusceptible thioglycoside against NIS/TfOH, see. Li K, Kurosu M. Heterocycles. 2007 in press.
14. Kurosu M, Biswas K, Crick DC. Org Lett 2007;9:1141. [PubMed: 17311394]
15. *P*-TolSBr was generated by mixing a 1:1 ratio of $(p\text{-TolS})_2$ and Br_2 in $ClCH_2CH_2Cl$, and this was stable over a month at rt.
16. The utility of *p*-TolSCl/AgOTf for glycosylations with the thiopyranosides, see. Huang X, Huang L, Wang H, Ye X-S. Angew Chem Int Ed 2004;43:5221.
17. Kaeothip S, Pornsuriyasak P, Demchenko AV. Tetrahedron Lett 2008;49:1542. [PubMed: 18438466]
18. We also examined the effect of MeSOTf for this reaction. However, trace amounts of the desired product were isolated. see, a)Kurosu M, Kitagawa I. J Carbohydr Chem 2006;25:427.b)Dasgupta F, Garegg PJ. Carbohydr Res 1988;177:C13.
19. 4Å MS is not indispensable for these reactions. In order not to obtain inconsistent results caused by adventitious water, two times weight of MS was added in all reactions.
20. $SrCO_3$ was applied as a buffer of the reactions. Addition of $SrCO_3$ was effective especially in the reaction with the silyl group containing donors. 2,6-Di-*ter*-butylpyridine was also effective, but reaction rate was diminished.
21. There is a short half-life (ca. 5~15 min) of *p*-TolSOTf at rt.
22. For other examples of ribosylations with *primary* and *secondary* alcohols, see, Supporting Information.
23. Winstein S, Clippinger E, Fainberg AH, Heck R, Robinson GC. J Am Chem Soc 1956;78:328.
24. For the other mechanistic considerations, see. Smith DM, Woerpel KA. Org Biomol Chem 2006;4:1195. [PubMed: 16557303]
25. For applications of thiohlycoside for arabinosylation and galactofuranosylation reactions. see, a) Pathak AK, Pathak V, Seitz L, Gurcha SS, Besra GS, Riordan JM, Reynolds RC. Bioorg Med Chem 2007;15:5629. [PubMed: 17544276]b)Joe M, Nacario RC, Lowary TL. J Am Chem Soc 2007;129:9885. [PubMed: 17655235]

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

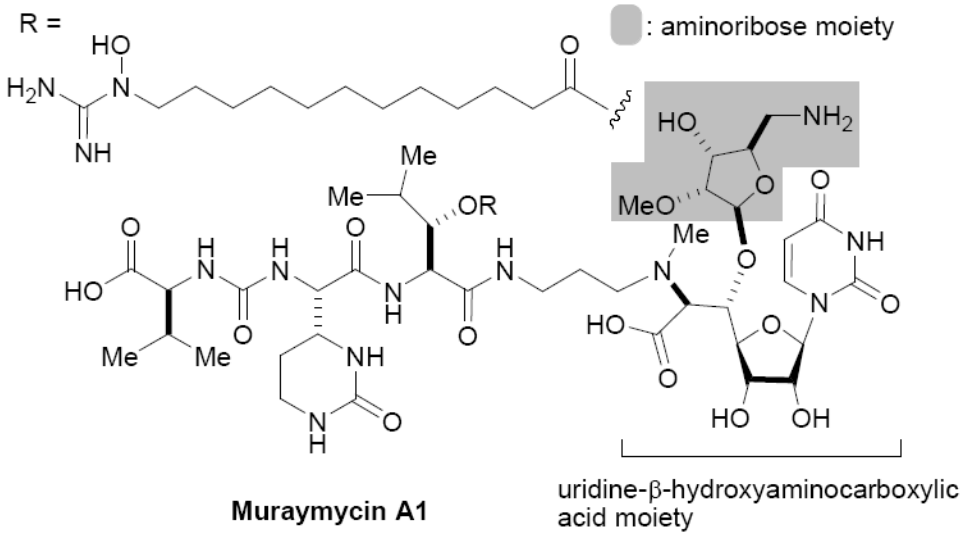
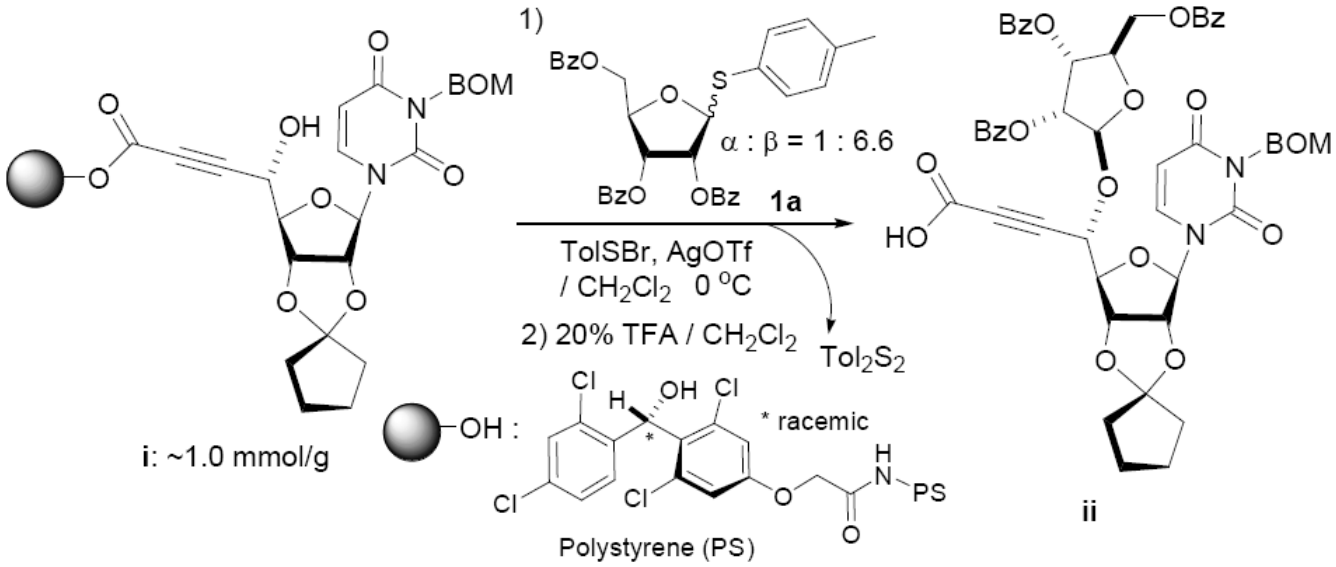


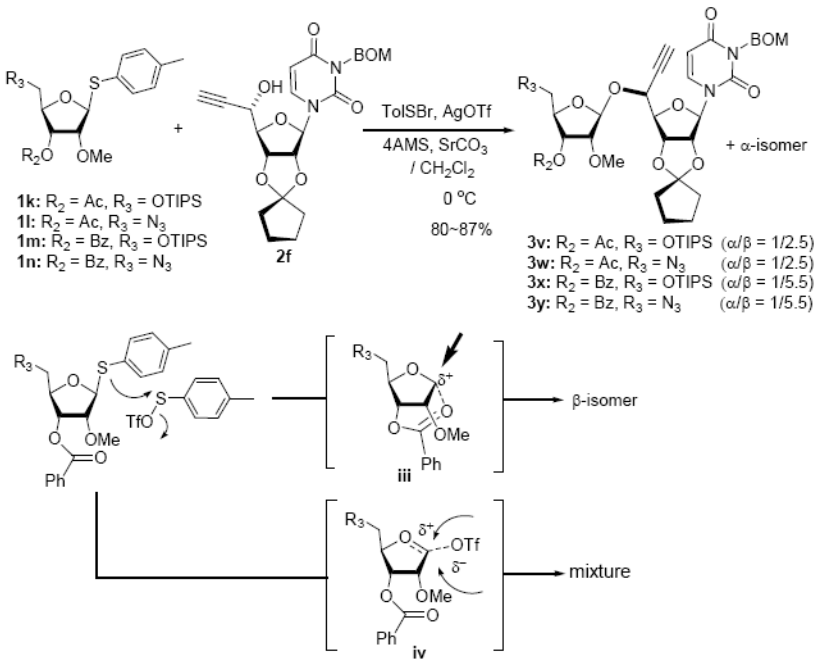
FIGURE 1.
Representative Structure of Ribosamino-uridine Antibiotics.



SCHEME 1.

Screening of a Promoter for 1 Using the Immobilized Propargyl Alcohol on the Polymer Resin i.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript



SCHEME 2.
Glycosylations of 2f with the thioribosides 1k~n.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

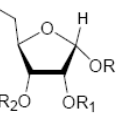
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

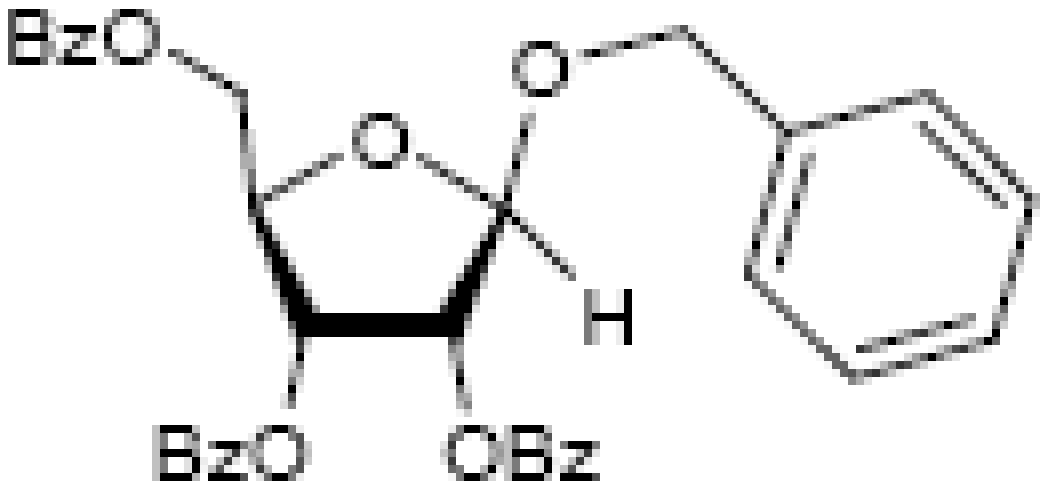
TABLE 1

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript



4a~x

emperature (°C)	Condition	Major Product	Yield(%)	α/β Selectivity (4/3)[b]
			98	0/1
			98	0/1



3a: R_1, R_2 = Bz, R_3 = OBz

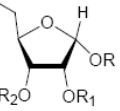
3b: R_1, R_2 = Ac, R_3 = OAc

8~0

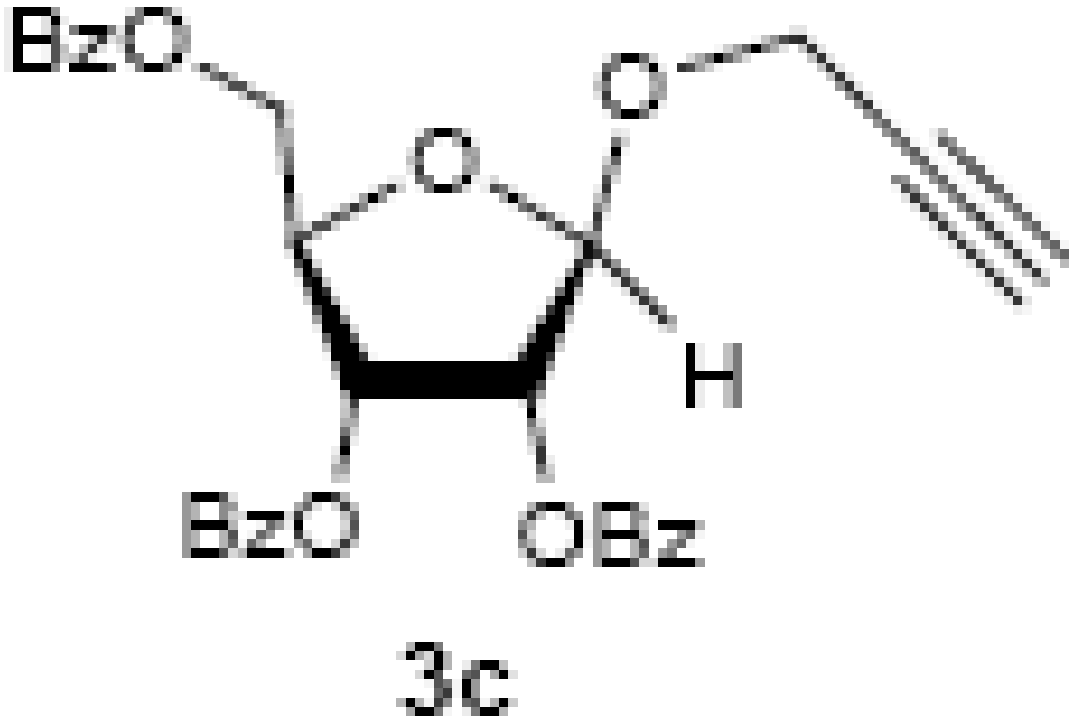
A

J Org Chem. Author manuscript; available in PMC 2009 December 19.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript



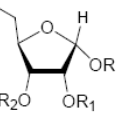
4a~x

emperature (°C)	Condition	Major Product	Yield(%)	α/β Selectivity (4/3)[b]
8~0			100	0/1

3c

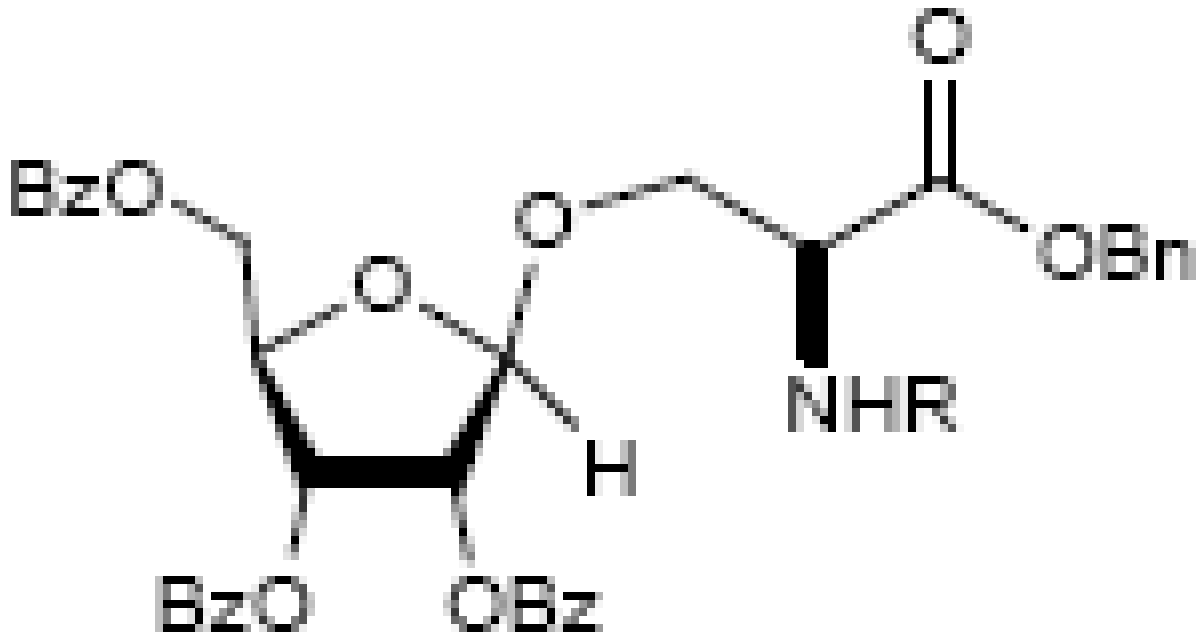
J Org Chem. Author manuscript; available in PMC 2009 December 19.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript



4a~x

emperature (°C)	Condition	Major Product	Yield(%)	α/β Selectivity (4/3)[b]
			95	0/1
			98	0/1



3d: R= Boc
3e: R= Fomc

8~0

J Org Chem. Author manuscript; available in PMC 2009 December 19.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

4a–x

Temperature (°C)	Condition	Major Product	Yield(%)	α/β Selectivity (4/3)[b]
			98	0/1
			95	0/1
			85	0/1

B

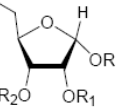
NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

4a–x

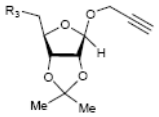
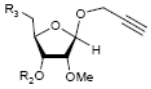
Temperature (°C)	Condition	Major Product	Yield(%)	α/β Selectivity (4/3)[b]
			90	6.6/1
			75	6.0/1
			78	5.0/1

4i: R_1, R_2 = Bn, R_3 = OBn
4j: R_1, R_2 = Bn, R_3 = OTIPS
4k: R_1, R_2 = Me, R_3 = OTIPS

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript



4a~x

emperature (°C)	Condition	Major Product	Yield(%)	α/β Selectivity (4/3)[b]
		 **3l:** R_3 = OBz **3m:** R_3 = OTIPS **3n:** R_3 = N_3	95	1/1.1
			85	1/1.1
			80	1/1.1
		 **3o:** R_2 = Ac, R_3 = OTIPS **3p:** R_2 = Ac, R_3 = N_3 **3q:** R_2 = Bz, R_3 = OTIPS **3r:** R_2 = Bz, R_3 = N_3	85	1/3.0
			90	1/3.0
			85	1/5.5
			90	1/5.5

J Org Chem. Author manuscript; available in PMC 2009 December 19.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

4a–x

Temperature (°C)	Condition	Major Product	Yield(%)	α/β Selectivity (4/3)[b]
			90	0/1
			80	0/1
			90	0/1

B

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

4a–x	Condition	Major Product	Yield(%)	α/β Selectivity (4/3)[b]
Temperature (°C)				