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C6 Picoloyl Protection: a Remote Stereodirecting Group for 2-Deoxy-β-Glycoside Formation

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We reported a remote control glycosylation method using the picoloyl protecting group for 2-deoxy-β-glycosidic bond formation. The method is applicable to various 2-deoxythioglycosyl donors and the utility is illustrated by synthesis of a deoxytrisaccharide component of landomycins.

β-2,6-Dideoxyglycosides are common carbohydrate components of many bioactive natural products, including landomycins, olivomycins, digoxin, and anthracyclines. Removal or modification of the deoxyglycoside components usually changes the biological properties of the natural products. These findings have inspired the use of glycosylation for modification of the pharmacokinetic and medicinal properties of some natural products and lead compounds in the drug industry. A point in case is the diolivosyl modified urdamycins, which are potent inhibitors of xanthine oxidase.

Most glycosidic linkages in 2-deoxysugar-containing oligosaccharides are of a β-configuration. However, the construction of β-glycosidic bonds with 2-deoxysugar donors is conceived a difficult task. The absence of a 2-hydroxy substituent not only excludes the use of the neighbouring group participation mechanism (NGP), but it also promotes glycal formation. In addition, the anomic effect of 2-deoxyglycoside favours the formation of the undesired α-anomer. Recently, Bennett and Zhu explored the use of S_N2 substitution strategy for the preparation of 2-deoxy-β-glycosides. Despite such progress in glycosylation chemistry, there remain concerns over the practicability and scope of these methods.

It is known that an ester protecting group at a remote location can confer α-selectivity in glycosidic bond formation. Such remote control concept has been extended to picoloyl (Pico) and 2-quinoilonecarbonyl protecting groups, that presumably provide a stereodirecting effect through hydrogen-bond mediated aglycone delivery (HAD) mechanism. Although the HAD mechanism has not been vigorously confirmed, the idea offers new avenues to tackle stereochemistry problems in glycosidic bond formation.

As 2-deoxysugars have no substituent at C2 position, it is rational to explore the stereodirecting effect of the Pico function for β-selective glycosylation. In addition, the Pico protecting group can be selectively removed without hampering common protecting functions. Such property paves ways for dideoxyglycoside formation. Herein, we report a new glycosylation method for construction of 2-deoxy-β-glycosides and explore its utility for synthesis of the deoxytrisaccharide component of Landomycins 1a-h (Figure 1), isolated from Streptomyces.

To identify suitable conditions for glycosylation, 6-O-Pico-2-deoxythioalloside 2a (1.2 equiv.) was selected as a model donor to react with galactosyl acceptor 3 (1.0 equiv.). The final concentrations of donor 2a and acceptor 3 in the reaction mixture were 10 and 12 mM, respectively; and such low concentration was beneficial to the HAD mechanism. In present procedure, donor, acceptor, and activated molecular sieve (AW300) were mixed before addition of promoters. At first, N-iodosuccinimide...
(NIS, 1.2 equiv.) and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 1.2 equiv.) were used as promoters.\textsuperscript{18} Although the reaction furnished desired disaccharide 4a, some glycal formation occurred (Table 1, entry 1). Therefore, a lower −50 °C temperature was applied, though the yield was even worse due to sluggish reaction (Entry 2). Dimethyldisulfide and triflic anhydride ($\text{Me}_2\text{S}_2\text{TF}_2\text{O}$) were then employed as promoters.\textsuperscript{19} Under this condition, the disaccharide 4a was produced in high yield (90%), but the $\alpha:\beta$ ratio was 1:3 (Entry 3). The modest selectivity may be due to an acid byproduct derived from the Pico protecting function was studied (Figure 2, Table 2). At 0.1 equiv of the acid, the reaction yield was moderate (50%) due to sluggish glycosylation (Entry 4). To increase the rate of the reaction, the amounts of TFOH were raised to 0.2, 0.6 and 1.2 equiv of the acid, the reaction yield was moderate (50%) due to the strong H-bonding association of the Pico group with the stationary phase of the separation column, the selectivity. Due to the strong H-bonding association of the Pico group with the stationary phase of the separation column, the $\alpha:\beta$ ratio was determined by HPLC after removal of the Pico function in 4a. Confirmation of the $\beta$-configuration of 4a was based on the $3J_{\text{H-H}}$ coupling constant (9.5 Hz) of the anomeric proton (5.13 ppm in $^1\text{H}$NMR).\textsuperscript{21}

It was unclear if the axial 3-O-benzoyl (Bz) function of 2a also plays some role in the selectivity of the reaction.\textsuperscript{22} For clarification, 3,6-di-O-benzyl-2-deoxythioalloside 2b that substituting the C6 Pico with a Bz function was coupled with acceptor 3 (Entry 8),\textsuperscript{23} but the $\alpha:\beta$ ratio of the product 4b was 1:1, confirming the stereo-directing effect of the C6 Pico group glycosylation.

With the optimised conditions in hand, the scope of application of the Pico protecting function was studied (Figure 2, Table 2). At first, 4-O-Pico-2-deoxythiogalatoside 5 and 6-O-Pico-2-deoxythiogalatoside 6 were coupled with glycosyl acceptors 3, 11, 12, 13, and/or 14. Glycosylation of acceptors 3, 11, and 13 with 4-O-Pico protected donor 5 furnished the desired disaccharides 16–18 in high yields, with the $\alpha:\beta$ ratios from 1:6 to 1:11 (Table 2, entries 1–3).

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| Table 1: Development of a $\beta$-selective glycosylation method for 2-deoxythioalloside donors 2a and 2b |
|-----------------|-----------------|-----------------|-----------------|
| Entry | Donor, acceptor | Promoters (equiv.) | $^\circ$C, time (h) | Yield (%), $\alpha:\beta$ |
| 1 | 2a, 3 | NIS (1.2), TMSOTf (1.2) | −30, 20 | 50, 1:10<sup>a</sup> |
| 2 | 2a, 3 | NIS (1.2), TMSOTf (1.2) | −50, 20 | 30, ND<sup>a</sup> |
| 3 | 2a, 3 | $\text{Me}_2\text{S}_2\text{TF}_2\text{O}$ (1.2) | −50, 1 | 90, 1:3<sup>a</sup> |
| 4 | 2a, 3 | NIS (1.2), TFOH (0.1) | −50, 48 | 50, ND |
| 5 | 2a, 3 | NIS (1.2), TFOH (0.2) | −50, 27 | 95, 1:16<sup>a</sup> |
| 6 | 2a, 3 | NIS (1.2), TFOH (0.6) | −50, 24 | 93, 1:8<sup>a</sup> |
| 7 | 2a, 3 | NIS (1.2), TFOH (1.2) | −50, 20 | 95, 1:1<sup>a</sup> |
| 8 | 2b, 3 | NIS (1.2), TFOH (0.2) | −50, 1 | 70, 1:1<sup>a</sup> |

<sup>a</sup>Some acceptor 3 was silylated. The $\alpha:\beta$ ratio was estimated from TLC or $^1\text{H}$NMR. ND: not determined. The $\alpha:\beta$ ratio was determined by HPLC analysis after deprotection of the picrolycol in 4a.

[Refer to Figure 2 and Table 2 for details.]
results of entries 1-6 together indicates the C6 Pico function provides a better stereoselective control in present context. Then 6-O-Bz-2-deoxyhexitooligosaccharidyl donor 6 was used as a control element to couple with acceptor 3 (Entry 7). In sharp contrast, the donor 6 provided a moderate α-selectivity of glycosylation. Noted that 21 can be converted to oliose-β-(1→3)-olivose, which is the dideoxydisaccharide component in chromomycycin and durhamycin A.16

After studying donors 5 and 6, 6-O-Pico-2-deoxythioallose 2a and 6-O-Pico-2-deoxythigalactoside 7 were examined. Glycosylation of acceptors 10 and 11 with donor 2 gave the desired disaccharides 22 and 23 in ~50-54% yield and with considerable good β-selectivity (~1:8 α:β ratio) (Table 2, entries 8 and 9). Moderate yield of the reactions may be caused by the disarming effect of the Bz group that affects the coupling efficiency. Furthermore, glycosylation of acceptors 3 and 11 with 6-O-Pico-2-deoxythigalactoside 7 provided the expected disaccharides 24 and 25 in 64-70% yields and their α:β ratios are 1:12 and 1:9, respectively (Entries 10 and 11). When a control donor, namely 6-O-Bz-2-deoxythigalactose, 7 that lacking the Pico function, was used for glycosylation of 3, a modest α-selectivity was observed (Entry 12). Of noted is that some variation of the protecting group pattern in donor is tolerated, as witnessed in the glycosylation of 15 with donor 8 (Entry 13). To examine the effect of the electron-withdrawing Pico group at C4 position, 14-4-O-Pico protected donor 8 was coupled with 15 (Entry 14). Interestingly, a dramatic change in selectivity of glycosylation was observed and α:anomer of 26 was the major product. The result implicates that the effect of the stereochemical control of the Pico function can be tuned by its position, which is in agreement with finding of Demchenoko et al.14a Encouraged by the β-selectivity of 2-deoxythioglycosyl donors 2a, 6, 7, and 8, a 2,3-dideoxy-D-erythro-hexopyranosyl donor 9 was investigated, which is presumably more reactive than mono-deoxy donors. Glycosylation of primary acceptor 3 with 9 still produced β-linked 2,3-dideoxydisaccharide 27 as a sole isomer (Entry 15). Unfortunately, very modest β-selectivity was given in glycosylation of secondary acceptor 11 (Entry 16).

The utility of the β-glycosylation method was demonstrated by synthesis of a deoxytrisaccharide target 29 from building blocks 6-O-Pico-2-deoxythigalactose 7, 2,6-dideoxyoligoside 12, and L-rhodinosyl acetate 30 (Scheme 1a). Deoxytrisaccharide 29 is the carbohydrate component of landmycins E, G, P, and Q (1a-1d in Fig 1). Reducing end disaccharide unit 31 was first constructed by the glycosylation of olivoside acceptor 12 with Pico protected 2-deoxythiogalactosyl donor 7 using the glycosylation protocol established in Table 1. Disaccharide 31 was obtained in 75% yield as an inseparable 1:1 α:β mixture. Subsequent oxidative removal of the 2-naphthylmethyl (Nap) group furnished disaccharide 32. At this stage, the β-isomer of 32 was isolated and used as the acceptor for glycosylation with L-rhodinosyl acetate 30 to give expected trisaccharide 33 as a single isomer in excellent yield (92%).24 Subsequent deprotection of the Pico function in 33 followed by Barton-McCombie deoxygenation concluded the synthesis of target trisaccharide 29.25

In summary, a β-selective glycosylation method was developed for direct synthesis of 2-deoxyglycosides and further application for preparation of deoxyoligosaccharide was demonstrated.

Notes and references

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(a) L-rhodinosyl acetate

(b) Deoxytrisaccharide target

Scheme 1. Stereoselective synthesis of deoxytrisaccharide 29.

Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x.


3. (a) M. G. Brazhnikova, E. B. Kruglik, I. N. Kovasharova, N. V. Konstantinovna, V. V. Proshiahkova, Antibiotiki, 1962, 7, 39-44; (b) Yu.


16. Acid washed AW300 molecular sieve (MS) (from Aldrich) was used and detailed activation procedure of MS was given in SI.

17. Takahashi reported that an electron-withdrawing sulfonyl protection at C4 hydroxyl was found to increase the β-selectivity of glycosylation for 2,6-dideoxy glycosyl imidate donor. Tanaka, A. Yoshizawa, T. Takahashi, Angew. Chem., Int. Ed. 2007, 46, 2505–2507.


27. Acid washed AW300 molecular sieve (MS) (from Aldrich) was used and detailed activation procedure of MS was given in SI.

