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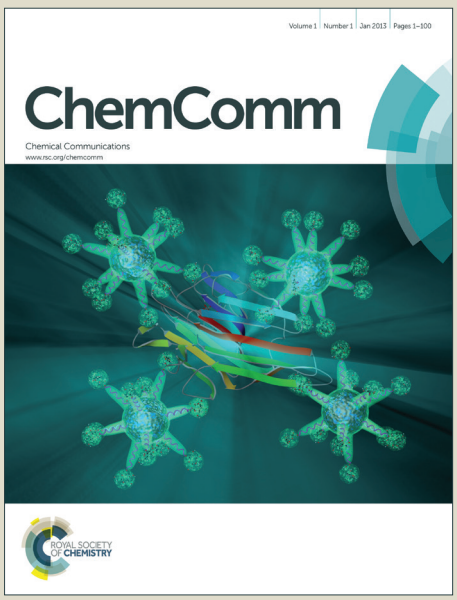

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C6 Picoloyl Protection: a Remote Stereodirecting Group for 2-Deoxy-β-Glycoside Formation

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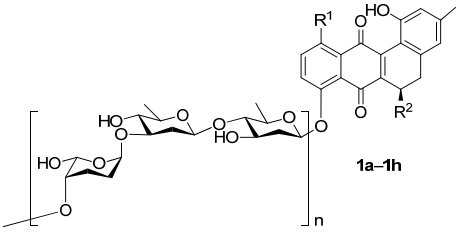
We reported a remote control glycosylation method using the picoloyl protecting group for 2-deoxy-β-glycosidic bond formation. The method is applicable to various 2-deoxythioglycosyl donors and the utility is illustrated by synthesis of a deoxytrisaccharide component of landomycins.

β-2,6-Dideoxyglycosides are common carbohydrate components of many bioactive natural products,[1] including landomycins,[2] olivomycins,[3] digoxin,[4] and anthracyclines.[5] Removal or modification of the deoxyglycoside components usually changes the biological properties of the natural products.[6] 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.[7]

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.[8] The absence of a 2-hydroxyl substituent not only excludes the use of the neighbouring group participation mechanism (NGP), but it also promotes glycal formation. In addition, the anomeric effect of 2-deoxyglycoside favours the formation of the undesired α-anomer.[9-11] Recently, Bennett and Zhu explored the use of S_N2 substitution strategy for the preparation of 2-deoxy-β-glycosides.[12] 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.[13] Such remote control concept has been extended to picoloyl (Pico)[14] and 2-quinolonecarbonyl[15] 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.[14b,15] 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*.[2,16]



n = 1, R^1 = OH, R^2 = OH; Landomycin E (**1a**) n = 2, R^1 = OH, R^2 = OH; Landomycin A (**1e**)
n = 1, R^1 = H, R^2 = OH; Landomycin G (**1b**) n = 2, R^1 = H, R^2 = OH; Landomycin S (**1f**)
n = 1, R^1 = H, R^2 = H; Landomycin P (**1c**) n = 2, R^1 = H, R^2 = H; Landomycin T (**1g**)
n = 1, R^1 = OH, R^2 = H; Landomycin Q (**1d**) n = 2, R^1 = OH, R^2 = H; Landomycin U (**1h**)

Figure 1. Landomycins **1a-h**.

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.[14a] In present procedure, donor, acceptor, and activated molecular sieve (AW300) were mixed before addition of promoters.[17] At first, *N*-iodosuccinimide

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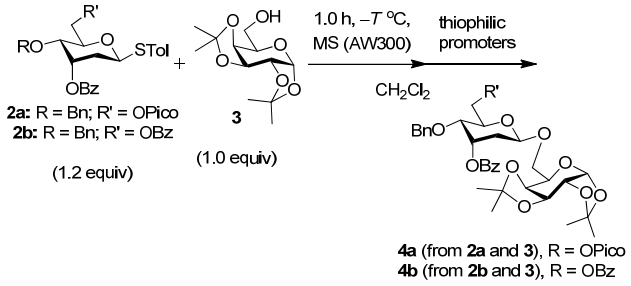
(NIS, 1.2 equiv.) and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 1.2 equiv.) were used as promoters.[18] Although the reaction furnished desired disaccharide **4a**, some glycal formation occurred (Table 1, entry 1). Therefore, a lower –50 ˚C temperature was applied, though the yield was even worse due to sluggish reaction (Entry 2). Dimethyldisulfide and triflic anhydride (Me_2S_2-Tf_2O) were then employed as promoters.[19] Under this condition, the disaccharide **4a** was produced in high yield (90%), but the α:β ratio was 1:3 (Entry 3). The modest selectivity may be due to an acid byproduct derived from the promoter. Thus, the glycosylation employed NIS (1.2 equiv.) and trifluoromethanesulfonic acid (TfOH) as the promoters.[20] 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. (Entries 5-7). The best result was achieved at 0.2 equiv. of the acid; in such conditions, the α:β ratio of **4a** was 1:16 (Entry 5). However, higher acid concentration diminished the glycosylation selectivity. Due to the strong H-bonding association of the Pico group with the stationary phase of the separation column, the α:β ratio was determined by HPLC after removal of the Pico function in **4a** Confirmation of the β-configuration of **4a** was based on the $^3J_{H1\text{-}H2}$ coupling constant (9.5 Hz) of the anomeric proton (5.13 ppm in ^{1}H NMR).[21]

Table 1: Development of a β-selective glycosylation method for 2-deoxythioalloside donors **2a** and **2b**



Entry	Donor, acceptor	Promoters (equiv.)	T °C, time (h)	**4**, (%, α:β)
1	**2a**, **3**	NIS (1.2), TMSOTf (1.2)	–30, 20	50, 1:1[a,b]
2	**2a**, **3**	NIS (1.2), TMSOTf (1.2)	–50, 20	30, ND[a,c]
3	**2a**, **3**	Me_2S_2-Tf_2O (1.2)	–50, 1	90, 1:3[d]
4	**2a**, **3**	NIS (1.2), TfOH (0.1)	–50, 48	50, ND[c]
5	**2a**, **3**	NIS (1.2), TfOH (0.2)	–50, 27	95, 1:16[d]
6	**2a**, **3**	NIS (1.2), TfOH (0.6)	–50, 24	93, 1:8[d]
7	**2a**, **3**	NIS (1.2), TfOH (1.2)	–50, 20	95, 1:1[b]
8	**2b**, **3**	NIS (1.2), TfOH (0.2)	–50, 1	70, 1:1[b]

[a] Some acceptor **3** was silylated. [b]The α:β ratio was estimated from TLC or ^{1}H NMR. [c]ND: not determined. [d]The α:β ratio was determined by HPLC analysis after deprotection of the picoloyl group in **4a**.

It was unclear if the axial 3-O-benzoyl (Bz) function of **2a** also plays some role in the selectivity of the reaction.[22] For clarification, 3,6-di-*O*-Bz-2-deoxythioalloside **2b** that substituting the C6 Pico with a Bz function was coupled with acceptor **3** (Entry 8),[23] but the α:β 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-deoxythiogalactoside **5** and 6-*O*-Pico-2-deoxy-thiogalactoside **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 α:β ratios from 1:6 to 1:11 (Table 2, entries1-3).

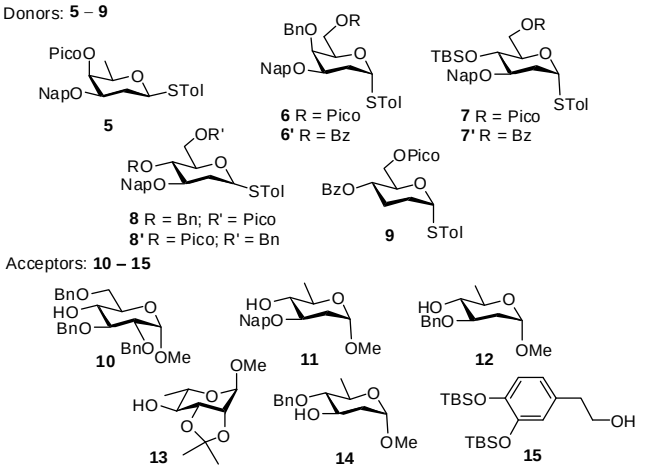
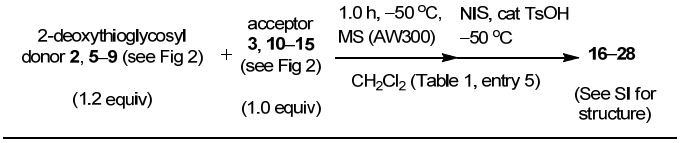


Figure 2. Deoxythioglycosyl donors **5**–**9** and acceptors **10–15** for glycosylation studies.

Table 2. Scope and limitation of the β-selective glycosylation protocol



Entry	Donor/ acceptor	Time (h)	Product		
			No.	Yield (%)	α:β
1	**5** / **3**	20	**16**	80	1:7.0[a]
2	**5** / **11**	21	**17**	83	1:11[a]
3	**5** / **13**	24	**18**	84	1:6.0[a]
4	**6** / **3**	24	**19**	79	1:19[b]
5	**6** / **12**	48	**20**	63	1:19[b]
6	**6** / **14**	24	**21**	60	1:19[b]
7	**6'** / **3**	1	**19'**	79	6:1[c]
8	**2a** / **10**	40	**22**	50	1:8.0[a]
9	**2a** / **11**	24	**23**	54	1:7.6[a]
10	**7** / **3**	16	**24**	70	1:12[a]
11	**7** / **11**	27	**25**	64	1:9[a]
12	**7'** / **3**	1	**24'**	90	2:1[c]
13	**8** / **15**	21	**26**	79	1:19[b]
14	**8'** / **15**	22	**26'**	94	10:1[c]
15	**9** / **3**	3	**27**	60	1:19[b]
16	**9** / **11**	22	**28**	55	1:2[c]

[a]The α:β ratio was determined by HPLC analysis after removal of the Pico function. [b]The α-anomer was not detectable by TLC and ^{1}H NMR; thus a conservative estimate of the α/β ratio (1:19) was given. [c]The α/β-anomer ratio was estimated by ^{1}H-NMR spectra (for **19'** and **24'**) or isolated yields (for **26'**).

Remarkably, glycosylation of acceptors **3**, **12**, and **14** with 6-*O*-Pico protected donor **6** produced disaccharides **19**, **20**, and **21** with excellent β-selectivity (Entries 4, 5, and 6). Putting the

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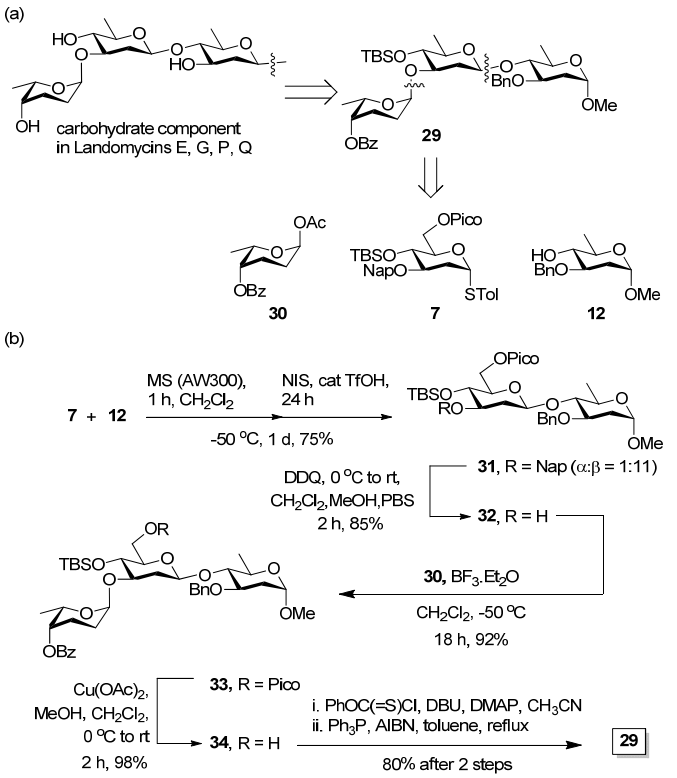
results of entries 1-6 together indicates the C6 Pico function provides a better stereochemical control in present context. Then 6-O-Bz-2-deoxythiogalactosyl donor **6'** was used as a control element to couple with acceptor **3** (Entry 7). In sharp contrast, the donor **6'** provided a moderate α-selectivity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

After studying donors **5** and **6**, 6-*O*-Pico-2-deoxythioalloside **2a** and 6-*O*-Pico-2-deoxythioglucoside **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-deoxythioglucoside **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-deoxythioglucoside, **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,[23] 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 stereo-chemical 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-*erytho*-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-deoxythioglucoside **7**, 2,6-dideoxyolivoside **12**, and L-rhodinosyl acetate **30** (Scheme 1a). Deoxytrisaccharide **29** is the carbohydrate component of landomycins 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-deoxythioglycosyl donor **7** using the glycosylation protocol established in Table 1. Disaccharide **31** was obtained in 75% yield as an inseparable 1:11 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.



Scheme 1. Stereoselective synthesis of deoxytrisaccharide **29**.

Notes and references

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