Organic LETTERS
Cite This: Org. Lett. XXXX, XXX, XXX−XXX
Letter
pubs.acs.org/OrgLett

Regioselective One-Pot Benzoylation of Triol and Tetraol Arrays in Carbohydrates

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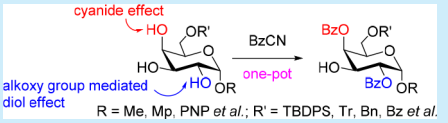
Supporting Information

ABSTRACT: Protection of 2,3,4-*O*-unprotected α-galacto- and α-fucopyranosides with BzCN and DMAP/DIPEA as the base afforded directly and regioselectively the 3-*O*-unprotected derivatives. The rationale for these studies was to take advantage of the eventual cooperativity of the "cyanide effect" and "the alkoxy group mediated diol effect". This way, even the totally unprotected α-galactopyranosides could be regioselectively transformed into the corresponding 2,4,6-*O*-protected derivatives. The great utility of these building blocks was demonstrated in efficient trisaccharide syntheses.



The density of functional groups in carbohydrates is not found in any other class of natural products. Nature uses this enormous possibility for structural diversity in oligosaccharide and glycoconjugate synthesis as well as for carbohydrate modification and molecular recognition. Therefore, selective access to these functional groups via regioselective protection or masking of the other functional groups is a necessity for chemical synthesis.[1−5] As this task often demands a multistep, time-consuming, and tedious endeavor, there are strong incentives to develop efficient one-pot procedures.[4−6] To this end, the distinctness of each of the functional groups has to be evaluated in order to take advantage of eventually only minor differences in their reactivities or, alternatively, to find clues to change the reactivity order.

A particularly important carbohydrate is galactopyranose, as it serves often not only for linear carbohydrate chain extension but also as a branching point, for instance, via the 3- and the 6-hydroxy groups. Regioselective protection of the primary 6-hydroxy group is generally performed with sterically demanding groups, thus permitting via orthogonal protection also selective access to this group. However, selective access to the secondary 3-hydroxy group is quite challenging, as this group is mostly found to be more reactive than the 2- and the 4-hydroxy groups, though not sufficiently more reactive for regioselective 3-*O*-reaction. Therefore, temporary protection of the 3-hydroxy group, for instance, with the help of organotin[7−9] or organoboron[10] reagents, is performed. After protection of the other hydroxy groups, the temporary protection is removed, thus liberating the 3-hydroxy group. Obviously, such indirect protection procedures are neither time nor cost-effective. Additionally, due to the low atom-economy, such procedures are not so desirable considering the added-up expense of the disposal of the waste. Hence, developing direct and simple methods for the synthesis of partially protected carbohydrates, as for instance, the often required 3-*O*-unprotected galactopyranosides and related compounds, is of great importance.

Benzoyl cyanide (BzCN) is frequently used for partial protection of carbohydrates.[11−14] However, the influence of the released cyanide anion on the regioselectivity of 1,2-*cis*-diol systems has remained unnoticed. We found recently that BzCN in the presence of catalytic amounts of 4-(dimethylamino)pyridine (DMAP)[15] leads to preferential axial benzoylation.[16] This "cyanide effect" is based on dual hydrogen bonding to the axial oxygen. Thus, acidity differences are generated that can be successfully employed to allow the kinetically controlled 4-*O*-benzoylation of 3,4-*O*-unprotected galactopyranosides and the structurally related 1,2-*cis*-diols present in fuco- and manopyranosides or myo-inositols. Additionally, we observed that equatorial 1,2-*trans*-diols vicinal to an axial alkoxy group, under basic conditions, preferentially *O*-acylate at the hydroxy group next to the axial alkoxy group,[17] as this arrangement leads, due to accumulation of lone pair orbitals, to an increase in the oxygen nucleophilicity. This "alkoxy group mediated diol effect" is particularly strong when the alkoxy group is the anomeric group, as present in α-gluco- and α- galactopyranosides.

These observations provide a rationale for how 2,3,4-*O*-unprotected α-galactopyranosides and structurally related systems permit a direct transformation into 3-*O*-unprotected derivatives. The "cyanide effect" with BzCN as the reagent and DMAP as the catalyst apparently favors 4-*O*-benzoylation, while the "alkoxy group mediated diol effect" with BzCN as the

Received: May 8, 2018

DOI: 10.1021/acs.orglett.8b01446
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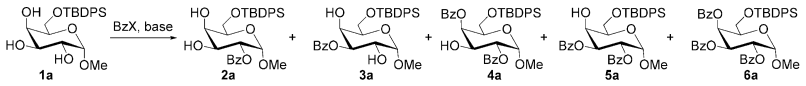
Table 1. Regioselectivity of the Benzoylation of 2,3,4-*O*-Unprotected Galactopyranoside 1a[a]



						product (%)				
entry	BzX (equiv)	base (equiv)	solvent	temp (°C)	time (h)	**2a**	**3a**	**4a**	**5a**	**6a**
1	BzCN (2.1)	DMAP (0.1)	DCM	rt	1	<3	9	10	17	37
2				−78	10	7	10	60	10	10
3		PPY (0.1)				9	11	52	12	17
4		DBU(0.1)				<3	18	42	16	20
5		DABCO(0.1)				67	<3	15	15	<3
6		DMAP (0.1)	DCM/MeCN (3:1)			5	8	51	12	15
7			DCM/DMF (4:1)			<3	26	31	28	14
8			DCM/THF(1:1)			19	20	40	9	11
9			DCM/$CHCl_3$(1:3)			10	5	70	7	<3
10			$CHCl_3$(1:3)	−60		5	5	69	6	12
11		DMAP (0.1) DIPEA (2.0)	DCM	rt	1	10	18	47	13	10
12				−78	10	<3	10	59	8	20
13			DCM/$CHCl_3$(1:3)			<3	10	76	6	5
14		DIPEA (2.0)				17	17	38	22	6
15	BzF (2.1)	DMAP (0.1) DIPEA (2.0)	DCM	−78 to rt	48	<3	25	<3	54	19
16	Bz_20 (2.1)		DCM	−78 to rt		<3	21	<3	42	34
17	BzCl (2.1)		DCM	−78 to rt		<3	15	<3	44	21

[a]All of the reactions were performed with 30 mg of substrate in 3 mL of solvent (~0.03 M).

reagent and a base generally favors 2-*O*-benzoylation. This way, due to a change of the reactivity order of the galactopyranoside hydroxy groups, the generally kinetically and thermodynamically favored 3-*O*-benzoylation, particularly in the presence of fluoride and benzoate counterions,[16] should be disfavored. Thus, under kinetic reaction control the desired 3-*O*-unprotected derivative should be accessible.

For our exploratory studies, readily available 6-*O*-*tert*-butyldiphenylsilyl (TBDPS) protected methyl α-D-galactopyranoside **1a**[18] was selected. Reaction of **1a** with 2.1 equiv of BzCN in the presence of DMAP as catalyst (0.1 equiv) at room temperature (rt) in dichloromethane (DCM) revealed low selectivity (Table 1, entry 1). However, carrying out this reaction at −78 °C led to a dramatic change: the rationale for our studies was confirmed; the 2,4-di-*O*-benzoyl-protected derivative **4a** was by far the major product (entry 2). TLC monitoring during the reaction course indicated that the kinetic reaction control strongly favored 2-*O*-benzoylation to **2a** and thereafter 4-*O*-benzoylation furnishing **4a**. Competitive benzoylation of the 3-hydroxy group in **1a**, leading to **3a**, was much slower than the 2-*O*-benzoylation. The 4-*O*-benzoylated derivative of **1a** was not observed at all. Formation of the 2,3-di-*O*-benzoylated byproduct **5a** seemed to originate mainly from **3a**. Due to the high reactivity of the 2-hydroxy group, the 3,4-di-*O*-benzoyl derivative was not found at all.

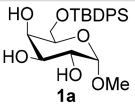
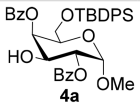
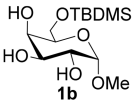
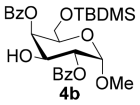
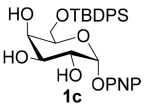
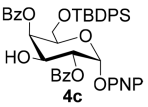
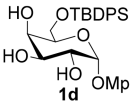
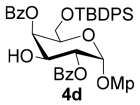
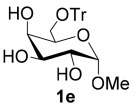
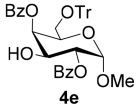
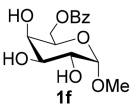
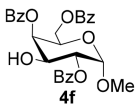
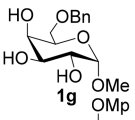
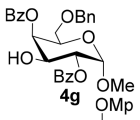
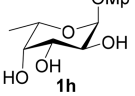
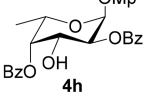
Studies to further improve the regioselective formation of **4a** were performed with other catalysts, as for instance, 4-pyrrolidinopyridine (PPY, entry 3), 1,8-diazabicyclo(5.4.0) undec-7-ene (DBU, entry 4), and 1,4-diazabicyclo(2.2.2)-octane (DABCO, entry 5). However, no improvement in the regioselective formation of **4a** was observed. Interestingly, the DABCO-catalyzed reaction became very slow after generation of the 2-*O*-benzoylated product **2a**, which is of practical usefulness. The studies of the solvent influence on the DMAP catalyzed reaction (entries 6−10) showed that chloroform addition to DCM (entry 9) or chloroform alone (entry 10) improved the regioselective formation of **4a**. More polar solvents and, particularly, DMF had a negative effect on the regioselectivity (entry 7), which may due to the strong interference of this solvent with internal hydrogen bonding. Next, we studied the influence of auxiliary bases (entries 11−14), as neutralization of some of the acid released could have a positive effect on the reaction course. Indeed, comparison of the results with addition of diisopropylethylamine (DIPEA, 2.0 equiv; entry 11) with the results in entry 1 showed an increase in regioselectivity that could be further improved by lowering the temperature (entry 12) and by the addition of chloroform to the DCM solvent (entry 13). DIPEA alone, without DMAP (entry 14) led to a very different result. With benzoyl fluoride and chloride and benzoic acid anhydride as acylating agents (entries 15−17), the 2,3-di-*O*-benzoylated product **5a** was preferentially obtained, as was previously observed.[16]

These results indicate that under the conditions of entry 13 the relative benzoylation rates of **1a** are 2-O > 3-O ≫ 4-O, of **2a** are 4-O ≫ 3-O and of **3a** are 2-O > 4-O, as derived from the appearance of the intermediates and the final products (for details see the SI). Once intermediate **2a** is generated, it is by far faster transformed into **4a** than into **5a**. Hence, the alkoxy group mediated diol effect is stronger than the cyanide effect. However, both effects cooperatively permit the preferential one-pot formation of the valuable 3-*O*-unprotected galactopyranoside **4a**.

To demonstrate the scope of this method for regioselective 2,4-di-*O*-protection, different substrates with varying groups at C-1 and C-6, repectively, were investigated (Table 2). Replacing the silyl protecting group in **1a** by the *tert*-butyldimethylsilyl (TBDMS) group (compound **1b**) or changing the methyl group at the anomeric oxygen to *p*-

DOI: 10.1021/acs.orglett.8b01446
Org. Lett. XXXX, XXX, XXX−XXX

Table 2. Regioselectivity of the Benzoylation of Triols

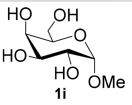
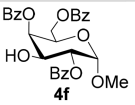
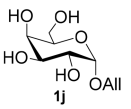
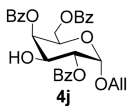
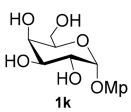
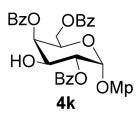
entry	substrate	product	yield (%)	procedure[a]
1	 **1a**	 **4a**	76[b]	A
2	 **1b**	 **4b**	72	A
3	 **1c**	 **4c**	70	A
4	 **1d**	 **4d**	70	A
5	 **1e**	 **4e**	72	A
6	 **1f**	 **4f**	73	B
7	 **1g**	 **4g**	71	B
8	 **1h**	 **4h**	75	B

[a]Procedure A: The reactions were performed with 30 mg of substrate, BzCN (2.1 equiv), DMAP (0.1 equiv), and DIPEA (2.1 equiv) in 3 mL of $CHCl_3/CH_2Cl_2$ (3:1) at −78 °C for 10 h. Procedure B: The reactions were performed with 30 mg of substrate, BzCN (2.1 equiv), DMAP (0.2 equiv), and DIPEA (2.1 equiv) in 30 mL of $CHCl_3$ from −10 °C to rt for 8 h. [b]72% was obtained in 1 mmol scale reaction; no improvement was observed with the dropwise addition (30 min) of BzCN.

nitrophenyl (PNP, **1c**) or to 4-methoxyphenyl (Mp, **1d**) had no effect on the regioselectivity (formation of compounds **4b**–**d**, entries 2–4). In addition, replacement of the 6-*O*-silyl protection by 6-*O*-trityl protection led to the same regioselectivity (entry 5, transformation of **1e** into **4e**). As replacement of the bulky 6-*O*-protection by 6-*O*-benzoyl protection (compound **1f**) or by 6-*O*-benzyl protection (compound **1g**) led to a solubility decrease, the reactions with these compounds had to be performed at lower concentration and at higher temperature (procedure B); however, the regioselectivities were not affected (entries 6 and 7). Even with fucopyranoside **1h**, having hydrogen instead of a substituted oxy group at C-6, the regioselectivity remained the same (entry 8). Hence, independent of the size and the electronic effect of the substituents at C-6 and C-1 high regioselectivity is obtained.

In our previous studies, we found that under the conditions of the cyanide effect for 3,4,6-*O*-unprotected galactopyranosides the *O*-acylation rates are 4-O > 6-O > 3-O.[16] As for 2,3,4-*O*-unprotected α-galactopyranosides, the *O*-acylation rates are found to be 2-O > 3-O ≫ 4-O and, once 2-*O*-benzoylation has occurred, 4-*O*-benzoylation is much faster than 3-*O*-benzoylation (see above), 2,3,4,6-*O*-unprotected α-galactopyranosides and structurally related compounds should permit also regioselective 2,4,6-*O*-protection. This way, from readily available precursors in a one-pot reaction directly the valuable 3-*O*-unprotected galactopyranosides should become available. To our satisfaction, the unprotected α-galactopyranoside **1i** furnished with 3.1 equiv of BzCN, DMAP as catalyst (0.2 equiv), and DIPEA (3.1 equiv) as auxiliary base the desired 3-*O*-unprotected derivative in 62% yield (Table 3, entry 1).

Table 3. Regioselectivity of the Benzoylation of 2,3,4,6-*O*-Unprotected Galactopyranosides

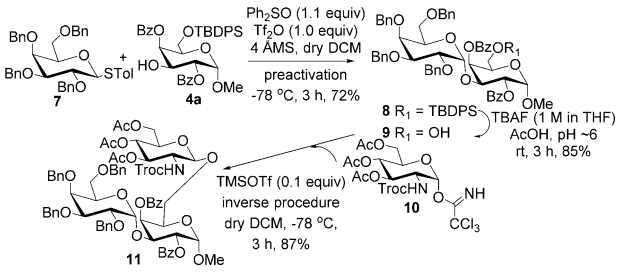
entry	substrate	product	yield (%)
1	 **1i**	 **4f**	62
2	 **1j**	 **4j**	67
3	 **1k**	 **4k**	61

[a]The reactions were performed with 20 mg of substrate, BzCN (3.1 equiv), DMAP (0.2 equiv), and DIPEA (3.1 equiv) in 30 mL of $CHCl_3$ from −10 °C to rt over 8 h.

Replacement of the methyl group by the allyl group (**1j**, entry 2) or the Mp group (**1k**, entry 3) did not affect the regioselective formation of **4j** and **4k**, respectively. These studies confirmed that 2-*O*-benzoylation is the fastest reaction; thereafter the 2,4-di-*O*-benzoylated derivative appears, and, finally, the 2,4,6-tri-*O*-benzoyl derivative is the main product. Benzoyl migration under the reaction conditions was not observed.

With the 3-*O*-unprotected galactopyranosides **4a**–**k** in hand, the convenient and efficient synthesis of branched and chain extended oligosaccharides could be demonstrated. With **4a** as acceptor and *O*-benzyl protected thiogalactopyranoside **7**[19] as glycosyl donor using the preactivation procedure,[20,21] the α-(1–3)-linked disaccharide **8** was obtained in good yield (Scheme 1). 6-*O*-Desilylation with TBAF in the presence of

Scheme 1. Synthesis of Trisaccharide 11



acetic acid afforded 6-*O*-unprotected acceptor **9**, which was glycosylated with glucosamine derived trichloroacetimidate **10** as donor[22] in the presence of TMSOTf as a catalyst which furnished the β(1–6)-linkage in very good yield. This way, the branched trisaccharide **11** was obtained from galactose and glycosyl donors **7** and **10** in only five steps.

DOI: 10.1021/acs.orglett.8b01446
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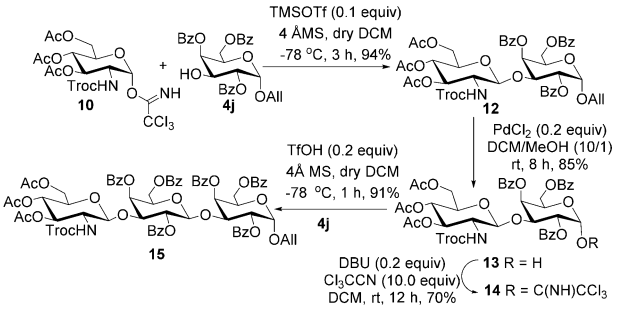
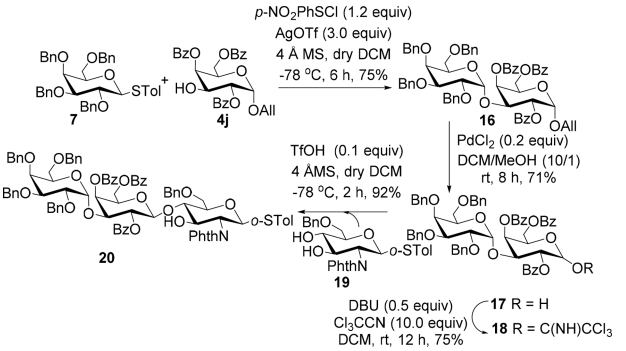
Chain extension in both directions could be demonstrated, for instance, with compound **4j** (Scheme 2). Reaction with

Scheme 2. Synthesis of Trisaccharide 15



glycosyl donor **10** in the presence of TMSOTf as catalyst afforded the $\beta(1-3)$-linked disaccharide **12**. Anomeric *O*-deallylation with $PdCl_2$ in DCM/MeOH leading to **13** and then reaction with Cl_3CCN in the presence of DBU as catalyst afforded disaccharide donor **14**. Reaction again with **4j** as acceptor led to trisaccharide **15** in very high yield. Similarly, from glycosyl donor **7** and acceptor **4j** under 4-nitrobenzenesulfenyl chloride/silver triflate[23,24] promoted condition the $\alpha(1-3)$-linked disaccharide **16** was obtained (Scheme 3).

Scheme 3. Synthesis of α-Gal Trisaccharide 20



Anomeric *O*-deallylation (leading to **17**) and transformation into the trichloroacetimidate **18** as glycosyl donor gave with glucosamine derivative **19**[21] as acceptor under TfOH catalysis the linear trisaccharide **20** that provides access to an important cellular epitope.[25]

The cooperation of two effects, the "alkoxy group mediated diol effect" and the "cyanide effect", permits the direct and regioselective one-pot transformation of 6-*O*-protected and completely *O*-unprotected α-galactopyranosides into their 3-*O*-unprotected derivatives. Such valuable compounds are now readily available and will help improve the efficiency of various oligosaccharide syntheses. This has been demonstrated in efficient branched and linear trisaccharide syntheses.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01446.

Experimental details and NMR spectra of compounds **4a–k**, **8**, **9**, **11**, **12**, **14–16**, **18**, and **20** (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by National Natural Science Foundation of China (21702125) and the Natural Science Foundation of Shandong Province, China (ZR2017BB045), and the Young Scholars Program of Shandong University. Dedicated to Professor Chi-Huey Wong on the occasion of his 70th birthday.

■ REFERENCES

(1) Wang, C.-C.; Lee, J.-C.; Luo, S.-Y.; Kulkarni, S. S.; Huang, Y.-W.; Lee, C.-C.; Chang, K.-L.; Hung, S.-C. *Nature* **2007**, *446*, 896.
(2) Français, A.; Urban, D.; Beau, J.-M. *Angew. Chem., Int. Ed.* **2007**, *46*, 8662.
(3) Witschi, M. A.; Gervay-Hague, J. *Org. Lett.* **2010**, *12*, 4312.
(4) Zhu, X.; Schmidt, R. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 1900.
(5) Boltje, T. J.; Buskas, T.; Boons, G.-J. *Nat. Chem.* **2009**, *1*, 611.
(6) Zulueta, M. M. L.; Janreddy, D.; Hung, S. C. *Isr. J. Chem.* **2015**, *55*, 347.
(7) Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.* **1998**, *53*, 17.
(8) Xu, H.; Lu, Y.; Zhou, Y.; Ren, B.; Pei, Y.; Dong, H.; Pei, Z. *Adv. Synth. Catal.* **2014**, *356*, 1735.
(9) Muramatsu, W.; Takemoto, Y. *J. Org. Chem.* **2013**, *78*, 2336.
(10) Lee, D.; Williamson, C. L.; Chan, L.; Taylor, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 8260.
(11) Abbas, S. A.; Haines, A. H. *Carbohydr. Res.* **1975**, *39*, 358.
(12) Paulsen, H.; Paal, M.; Schultz, M. *Tetrahedron Lett.* **1983**, *24*, 1759.
(13) Gege, C.; Vogel, J.; Bendas, G.; Rothe, U.; Schmidt, R. R. *Chem. - Eur. J.* **2000**, *6*, 111.
(14) Jacquinet, J.-C. *Carbohydr. Res.* **2004**, *339*, 349.
(15) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.
(16) Peng, P.; Linseis, M.; Winter, R. F.; Schmidt, R. R. *J. Am. Chem. Soc.* **2016**, *138*, 6002.
(17) Kumar, A.; Geng, Y.; Schmidt, R. R. *Eur. J. Org. Chem.* **2012**, *2012*, 6846.
(18) Fleet, G. W. J.; Seymour, L. C. *Tetrahedron Lett.* **1987**, *28*, 3015.
(19) Zhang, Z.; Ollmann, I. R.; Ye, X.-S.; Wischnat, R.; Baasov, T.; Wong, C.-H. *J. Am. Chem. Soc.* **1999**, *121*, 734.
(20) Huang, X.; Huang, L.; Wang, H.; Ye, X. S. *Angew. Chem., Int. Ed.* **2004**, *43*, 5221.
(21) Peng, P.; Xiong, D.-C.; Ye, X.-S. *Carbohydr. Res.* **2014**, *384*, 1.
(22) Roehrig, C. H.; Retz, O. A.; Hareng, L.; Hartung, T.; Schmidt, R. R. *ChemBioChem* **2005**, *6*, 1805.
(23) Crich, D.; Cai, F.; Yang, F. *Carbohydr. Res.* **2008**, *343*, 1858.
(24) Peng, P.; Geng, Y.; Göttker-Schnetmann, I.; Schmidt, R. R. *Org. Lett.* **2015**, *17*, 1421.
(25) Eto, T.; Ichikawa, Y.; Nishimura, K.; Ando, S.; Yamakawa, T. *J. Biochem.* **1968**, *64*, 205.

DOI: 10.1021/acs.orglett.8b01446
Org. Lett. XXXX, XXX, XXX–XXX