Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 7049–7052

N-Dimethylphosphoryl-protection in the efficient synthesis of glucosamine-containing oligosaccharides with alternate *N*-acyl substitutions

You Yang[a,b] and Biao Yu[a,*]

[a]*State Key Laboratory of Bio-organic and Natural Products Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032, China*
[b]*Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China*

Received 20 June 2007; revised 14 July 2007; accepted 16 July 2007
Available online 27 July 2007

Abstract—Ready transformation of *N*-dimethylphosphoryl-protection into the corresponding *N*-acyl derivatives (in the presence of acyl chlorides and DMAP in pyridine) provided an effective approach to the synthesis of glucosamine-containing oligosaccharides with alternate *N*-acyl substitutions.

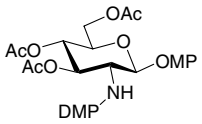
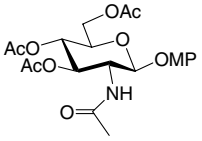
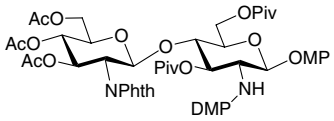
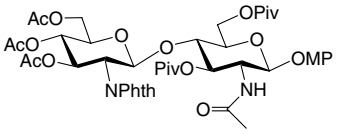
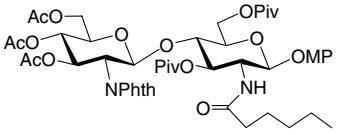
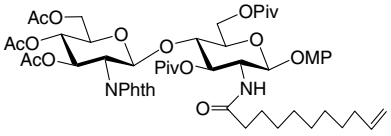
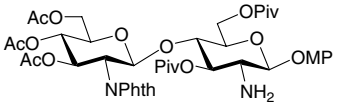
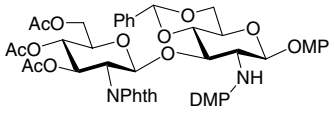
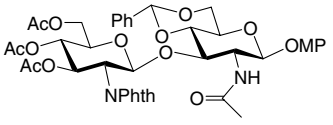
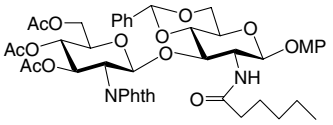
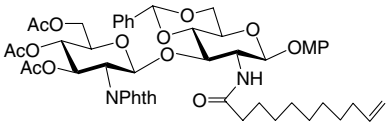
2-Amino-2-deoxy-D-glucopyranose (D-glucosamine) exists as an integral component of numerous biologically important prokaryotic and eukaryotic carbohydrates, including chitin, peptidoglycans, mucopolycharides, lipopolysaccharides, and nodulation factors.[1–3] The 2-amino-group of the D-glucosamine residues is mostly substituted with an acetyl group; while replacement of the *N*-acetate with long chain acyl groups occurs in the lipopolysaccharides[2] and nodulation factors,[3] where the fatty acid moieties are crucial to their biological functions. It is also noted that a variety of the synthetic N- and O-acylated glucosamine derivatives show immuno-modulating and antitumor effects of potentially clinical usefulness.[4,5] Nevertheless, introduction of the glucosamine residue into oligosaccharides and glycoconjugates has been a long-standing problem in preparative carbohydrate chemistry.[6] The 2-N-protecting groups always play a key role in glycosidic coupling with glucosamine derivatives as both donors and acceptors.[6,7] While the *N*-acyl-glucosamine derivatives are usually not the choice for glycosylation due to the involvement of the 2-amide function in side reactions.[6,7] Thus, the required *N*-acyl residues have to be introduced at the final stage of synthesis after N-deprotection. Recently, we have shown that 2-*N*-dimethylphosphoryl(DMP)-glucosamine derivatives could be effective glycosyl donors and acceptors in the synthesis of glucosamine-containing oligosaccharides.[8] However, deprotection of the 2-*N*-DMP-group afterwards remains problematic; the literature protocols, which require strong hydrolytic conditions (NaOH, EtOH/H_2O, reflux or $NH_2NH_2{\cdot}H_2O$, EtOH, reflux), jeopardize the multifunctional groups in the saccharide substrates and lead to low yields of the hydrolyzed products.[9] Herein, we report the ready transformation of the 2-*N*-DMP-protection into *N*-acyl substitution under mild conditions in excellent yields.

We have found that N-transacylation could take place on the 2-*N*-acetyl-α-D-glucosamine derivatives under the action of an excess amount of acyl chlorides in refluxing pyridine.[10] Acyl replacement of the 2-*N*-phosphoryl group might also be feasible under similar conditions, via *N*-acylphosphoramidates formation and the subsequent P–N bond cleavage,[11] thus applicable to the sophisticated saccharide substrates. Expectedly, treatment of *p*-methoxyphenyl 3,4,6-tri-*O*-acetyl-2-*N*-DMP-2-deoxy-β-D-glucopyranoside (**1**)[8] with acetyl chloride (10 equiv) in the presence of DMAP in refluxing pyridine overnight provided the desired 2-*N*-acetyl-glucosamine derivative **2** in an excellent 91% yield (Table 1, entry 1). To test the scope of this transformation, two disaccharides of glucosamine (**7** and **8**) with

Keywords: Dimethylphosphoryl; Protecting group; Glucosamine; Acylation; Oligosaccharide.
* Corresponding author. E-mail: byu@mail.sioc.ac.cn

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.07.108

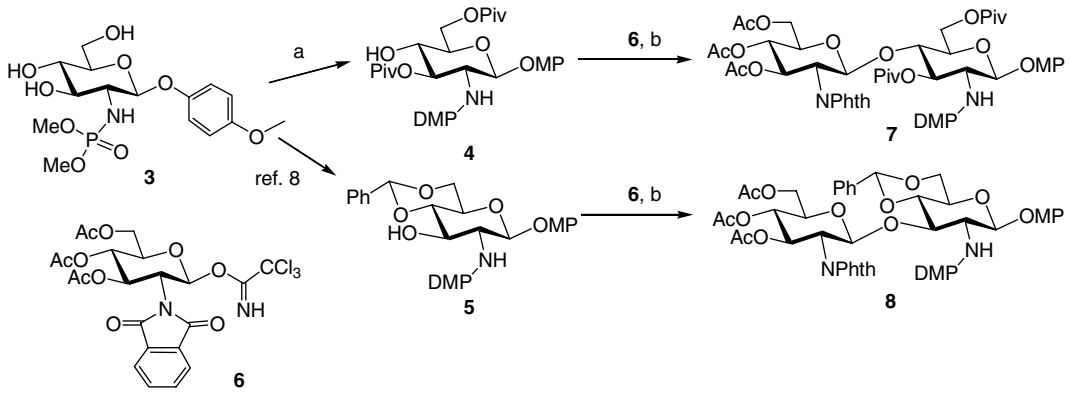
Table 1. Ready transformation of the *N*-DMP-protected saccharides into the corresponding *N*-acyl derivatives[a]

Entry	Substrates	Acyl chloride	Products	Yield (%)
1	 **1**	CH_3COCl	 **2**	91
2	 **7**	CH_3COCl	 **9a**	87
3	**7**	$C_5H_{11}COCl$	 **9b**	99
4	**7**	Undec-10-enoyl chloride	 **9c**	88
5	**7**	FmocCl	 **9d**	78
6	 **8**	CH_3COCl	 **10a**	93
7	**8**	$C_5H_{11}COCl$	 **10b**	98
8	**8**	Undec-10-enoyl chloride	 **10c**	79

[a] For a typical procedure for this transformation: To a stirred mixture of **7** (39 mg, 0.04 mmol) and DMAP (3 mg, 0.025 mmol) in pyridine (2.5 mL) at room temperature, was added dropwise undec-10-enoyl chloride (89 μl, 0.4 mmol) under the atmosphere of Ar. The temperature was allowed to increase naturally to 120 °C to reflux and the stirring continued overnight. The mixture was then concentrated in vacuo. The residue was purified by silica gel column chromatography (petroleum ether–EtOAc 3:1) to afford **9c** (36 mg, 88%) as a white solid.

alternate *N*-phthalimido(Phth)- and DMP-protection were readily prepared (Scheme 1)[8] and applied to the present selective *N*-acyl substitution reaction. The results are listed in Table 1 (entries 2–8).

Under similar conditions (10 equiv of acyl chloride, 0.5 equiv of DMAP, pyridine, reflux, overnight), the *N*-DMP-group (in saccharides **1**, **7**, and **8**) was cleanly replaced with *N*-acyl (acetyl, hexanoyl, and undec-10-



Scheme 1. Reagents and conditions: (a) PivCl (6 equiv), pyridine, −4 °C, 65%; (b) TMSOTf (0.3 equiv), 4 Å MS, CH_2Cl_2, −15 °C to rt, 49% (for **7**; 49% **4** recovered); 64% (for **8**).

enoyl) substitutions, affording the corresponding *N*-acyl derivatives (**2**, **9a**–**c**, and **10a**–**c**) in 79–99% isolated yields. The *O*-acyl (acetyl, pivaloyl) groups, the *O*-acetal group, the 2-*N*-Phth group, and the glycosidic linkages stayed intact in this transformation. Interestingly, when FmocCl (9-fluorenylmethoxycarbonyl chloride) was used in the treatment of disaccharide **7**, compound **9d** with a free 2-amino-group was obtained exclusively in 78% yield (entry 5), where the corresponding 2-*N*-Fmoc group could not survive in the presence of DMAP in refluxing pyridine. This result provides an easy entry to the selective deprotection of the 2-*N*-DMP-group.

Subsequent removal of the *N*-Phth, *O*-acyl, and *O*-acetal protections in disaccharides **9a/b** and **10a/b** under conventional acidic and basic conditions provided the corresponding disaccharides **11a/b** and **12a/b** in satisfactory yields (60–92%, Scheme 2), where the two 2-amino-groups of the glucosamine residues could be distinguished with different substitutions.

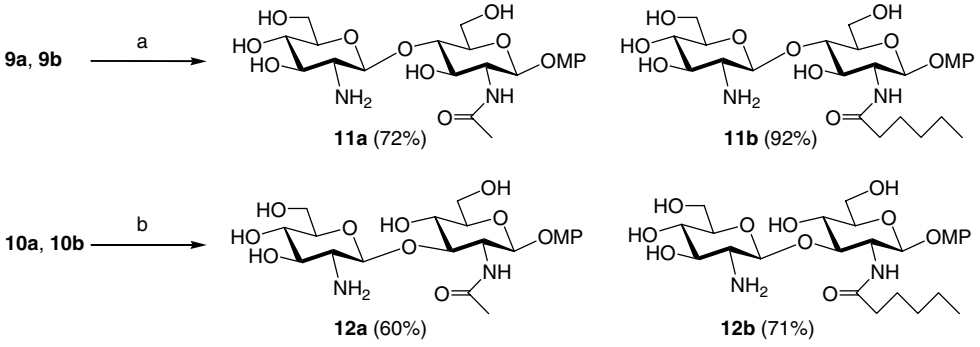
Given the efficiency of the present transformation of the 2-*N*-DMP-protection of glucosamines into the corresponding *N*-acyl (and $-NH_2$) derivatives (in the presence of acyl chlorides and DMAP in pyridine), we can foresee the further application of the 2-*N*-DMP-protection in the synthesis of glucosamine-containing oligosaccharides and glycoconjugates of biological and pharmacological significance.[12]

Acknowledgments

Financial support from the National Natural Science Foundation of China (20572122, 20321202) and the Committee of Science and Technology of Shanghai (06XD14026) is gratefully acknowledged.

References and notes

1. (a) Dwek, R. A. *Chem. Rev.* **1996**, *96*, 683–720; (b) Zachara, N. E.; Hart, G. W. *Chem. Rev.* **2002**, *102*, 431–438.
2. Kusumoto, S.; Fukase, K.; Oikawa, M.; Suda, Y. *J. Chin. Chem. Soc.* **2002**, *49*, 453–458.
3. D'Haeze, W.; Holsters, M. *Glycobiology* **2002**, *12*, 79R–105R.
4. (a) Johnson, D. A.; Baldridge, J. R.; Sowell, C. G.; Cluff, C. W. U.S. Patent 65,25,028 B1, 2003; *Chem. Abstr. 138*, 153772; (b) Anastassiades, T. P. WO Patent 2,002,017,890 A2, 2002; *Chem. Abstr. 136*, 210563; (c) West, M.; Meutermans, W.; Adamson, G.; Schafer, K.; Schliebs, D. WO Patent 2,002,032,915 A1, 2002; *Chem. Abstr. 136*, 325779.



Scheme 2. Reagents and conditions: (a) $NH_2NH_2{\cdot}H_2O$, MeOH, reflux, overnight; then 1 M MeONa in MeOH, rt, overnight; (b) $TsOH{\cdot}H_2O$ (6 equiv), MeOH, rt, overnight; then $NH_2NH_2{\cdot}H_2O$, MeOH, reflux, overnight.

5. García-Álvarez, I.; Corrales, G.; Doncel-Pérez, E.; Muñoz, A.; Nieto-Sampedro, M.; Fernández-Mayoralas, A. *J. Med. Chem.* **2007**, *50*, 364–373.
6. (a) Banoub, J.; Boullanger, P.; Lafont, D. *Chem. Rev.* **1992**, *92*, 1167–1195; (b) Debenham, J.; Rodebaugh, R.; Fraser-Raid, B. *Liebigs Ann.* **1997**, 791–802.
7. (a) Crich, D.; Dudkin, V. *J. Am. Chem. Soc.* **2001**, *123*, 6819–6825; (b) Lucas, R.; Hamza, D.; Lubineau, A.; Bonnaffe, D. *Eur. J. Org. Chem.* **2004**, 2107–2117; (c) Liao, L.; Auzanneau, F.-I. *J. Org. Chem.* **2005**, *70*, 6265–6273.
8. Yang, Y.; Yu, B. *Tetrahedron Lett.* **2007**, *48*, 4557–4560.
9. (a) Zervas, L.; Konstas, S. *Chem. Ber.* **1960**, *93*, 435–446; (b) Heyns, K.; Harrison, R.; Propp, K.; Paulsen, H. *J. Chem. Soc., Chem. Commun.* **1966**, 671–672; (c) Iwamoto, R.; Imanaga, Y. *Carbohydr. Res.* **1972**, *24*, 133–139; (d) Merser, C.; Sinay, P. *Tetrahedron Lett.* **1973**, *13*, 1029–1032; (e) Sarfati, R. S.; Szabo, L. *Carbohydr. Res.* **1978**, *65*, 11–22; (f) Lafont, D.; Descotes, G. *Carbohydr. Res.* **1988**, *175*, 35–48.
10. Li, Y.; Li, C.; Wang, P.; Chu, S.; Guan, H.; Yu, B. *Tetrahedron Lett.* **2004**, *45*, 611–613.
11. (a) Symes, J.; Modro, T. A. *Can. J. Chem.* **1986**, *64*, 1702–1707; (b) Challis, B. C.; Iley, J. N. *J. Chem. Soc., Perkin Trans. 2* **1987**, 1489–1495.
12. All the new compounds in this work give satisfactory analytical data; some selected data are shown below. **2**: $[\alpha]_D^{28}$ −10.1 (*c* 1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 6.92 (d, 2H, $J = 9.0$ Hz), 6.77 (d, 2H, $J = 9.0$ Hz), 5.97 (d, 1H, $J = 9.0$ Hz), 5.39 (t, 1H, $J = 9.6$ Hz), 5.08–5.15 (m, 2H), 4.27 (dd, 1H, $J = 5.4$, 12.6 Hz), 4.07–4.15 (m, 2H), 3.79–3.83 (m, 1H), 3.75 (s, 3H), 2.06 (s, 3H), 2.04 (s, 3H), 2.02 (s, 3H), 1.95 (s, 3H). MALDI-MS: *m/z* $C_{21}H_{27}NO_{10}$ $[M+Na]^+$ calcd 476.2, found 476.2. Compound **9b**: $[\alpha]_D^{28}$ −25.8 (*c* 0.52, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.83–7.86 (m, 2H), 7.74–7.78 (m, 2H), 6.77 (d, 2H, $J = 9.0$ Hz), 6.69 (d, 2H, $J = 9.0$ Hz), 5.89 (d, 1H, $J = 9.6$ Hz), 5.79 (t, 1H, $J = 9.9$ Hz), 5.46 (d, 1H, $J = 7.8$ Hz), 5.09–5.15 (m, 2H), 4.82 (d, 1H, $J = 5.1$ Hz), 4.25–4.45 (m, 4H), 4.18 (t, 1H, $J = 12.3$ Hz), 3.88–3.99 (m, 3H), 3.71 (s, 3H), 3.62–3.64 (m, 1H), 2.19 (t, 2H, $J = 7.5$ Hz), 2.11 (s, 3H), 2.03 (s, 3H), 1.85 (s, 3H), 1.60–1.63 (m, 2H), 1.31–1.34 (m, 4H), 1.24 (s, 9H), 1.23 (s, 9H), 0.89 (t, 3H, $J = 6.3$ Hz). MALDI-HRMS: *m/z* $C_{49}H_{64}N_2O_{18}$ $[M+Na]^+$ calcd 991.4044, found 991.4046. Compound **9d**: $[\alpha]_D^{28}$ −9.2 (*c* 0.85, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.83–7.86 (m, 2H), 7.72–7.75 (m, 2H), 6.85 (d, 2H, $J = 8.7$ Hz), 6.69 (d, 2H, $J = 8.7$ Hz), 5.85 (d, 1H, $J = 7.2$ Hz), 5.79 (t, 1H, $J = 9.3$ Hz), 5.50 (d, 1H, $J = 8.4$ Hz), 5.22 (d, 1H, $J = 8.1$ Hz), 5.11 (t, 1H, $J = 9.6$ Hz), 4.34 (t, 1H, $J = 9.6$ Hz), 4.14–4.28 (m, 3H), 3.92–4.03 (m, 2H), 3.71 (s, 3H), 3.44–3.57 (m, 4H), 2.11 (s, 3H), 2.04 (s, 3H), 1.85 (s, 3H), 1.19 (s, 9H), 1.04 (s, 9H). MALDI-HRMS: *m/z* $C_{43}H_{54}N_2O_{17}$ $[M+Na]^+$ calcd 893.3307, found 893.3315. Compound **10b**: $[\alpha]_D^{28}$ −5.7 (*c* 0.62, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.12–7.68 (m, 9H), 6.87 (d, 2H, $J = 9.3$ Hz), 6.77 (d, 2H, $J = 9.0$ Hz), 6.11 (d, 1H, $J = 6.6$ Hz), 5.66–5.82 (m, 3H), 5.41 (s, 1H), 5.12 (t, 1H,$J = 9.6$ Hz), 4.87 (t, 1H, $J = 10.2$ Hz), 4.35 (dd, 1H, $J = 8.4$, 10.8 Hz), 4.23–4.28 (m, 2H), 4.11 (dd, 1H, $J = 5.7$, 12.3 Hz), 3.69–3.82 (m, 6H), 3.51–3.57 (m, 1H), 3.19–3.27 (m, 1H), 2.13 (s, 3H), 1.99–2.06 (m, 5H), 1.81 (s, 3H), 1.43–1.54 (m, 2H), 1.19–1.34 (m, 4H), 0.87 (t, 3H, $J = 6.9$ Hz). MALDI-HRMS: *m/z* $C_{46}H_{52}N_2O_{16}$ $[M+Na]^+$ calcd 911.3214, found 911.3209. Compound **11b**: $[\alpha]_D^{28}$ −13.5 (*c* 0.83, MeOH); ^1H NMR (300 MHz, pyridine-d_5): δ 9.03 (d, 1H, $J = 7.8$ Hz), 7.32 (d, 2H, $J = 9.3$ Hz), 6.92 (d, 2H, $J = 9.0$ Hz), 5.80 (d, 1H, $J = 7.5$ Hz), 5.04 (d, 1H, $J = 7.8$ Hz), 4.64–4.66 (m, 2H), 4.48–4.52 (m, 1H), 4.28–4.41 (m, 4H), 4.18 (t, 1H, $J = 9.0$ Hz), 3.94–4.01 (m, 3H), 3.62 (s, 3H), 3.31 (t, 1H, $J = 7.8$ Hz), 2.41 (t, 2H, $J = 7.5$ Hz), 1.76–1.82 (m, 2H), 1.13–1.34 (m, 4H), 0.73 (t, 3H, $J = 7.2$ Hz). ^{13}C NMR (75 MHz, pyridine-d_5): δ 173.9, 155.6, 152.8, 118.6, 115.2, 105.3, 101.0, 81.3, 78.8, 78.1, 76.9, 73.5, 71.7, 62.4, 61.8, 58.6, 57.5, 55.7, 37.2, 31.8, 26.2, 22.8, 14.2. MALDI-HRMS: *m/z* $C_{25}H_{40}N_2O_{11}$ $[M+Na]^+$ calcd 567.2538, found 567.2524.