Letters to the Editor

Glysosylation of nucleophiles on ion-exchange resin: a new synthesis of dibenzyl glycosyl phosphates*

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One of fundamental problems in the modern carbohydrate chemistry is the development of efficient methods for the synthesis of oligosaccharides which are fragments of the oligosaccharide chains of natural glycolipids, glycoproteins, and polysaccharides of biomedical significance.[1—8] At the present time, along with the purely chemical synthesis of oligosaccharides[9—11] which is suitable in principle for the preparation of variety of structures, the application of enzymes for the intersaccharide glysoside bond formation (enzymic and chemical enzymic syntehsis)[12—14] is becoming increasingly important. Glycosyltransferases,[12] isolated from the natural sources or (in recent times, increasingly frequently) obtained by genetic engineering methods, are most widely used. The use of glycosyltrasferases implies the availability of the corresponding activated glysosyl donors, *viz.*, nucleotide sugars (nucleoside monophosphate sugars or nucleoside diphosphate sugars),[15] which, in turn, can be obtained from glycosyl phosphates.[15,16] Note that glycosyl phosphates not only are building blocks for the synthesis of nucleotide sugars, but are also used as glycosyl donors in the chemical glycosylation reactions.[17] In particular, dibutyl glycosyl phosphates have been applied with success for the synthesis of earlier unavailable oligosialic acids[18] and are used in automated oligosaccharide synthesizers.[19,20] A series of known approaches to the chemical synthesis of glycosyl phosphates is based on glycosylation as the key step (for more details, see Refs 15 and 16).

In the present communication, we propose a new approach for the synthesis of glycosyl phosphates based on the reaction between a glycosyl donor and phosphate anions immobilized on anion-exchange resin as counterions. This approach is based on esterification of orthophosphoric acid and its derivatives ("phosphoric acids") by alkylation (glycosylation) of the polymeric salt of a phosphoric acid salt (phosphate form of ion-exchange resin). Formation of carboxylic esters by alkylation of the carboxylate form of anion-exchange resin is known for a long time.[21] The analogous reaction for the preparation of phosphoric esters by alkylation (including glycosylation) of the phosphate forms of anion-exchange resin has not been described in the literature (according to the REAXYS database).

To demonstrate the applicability of this approach in the synthesis of glycosyl phosphates, we chosed glycosylation of an Amberlyst A-26 macroporous anion-exchange resin in the dibenzyl phosphate form using acetobromosugars. The dibenzyl phosphate form of the resin was

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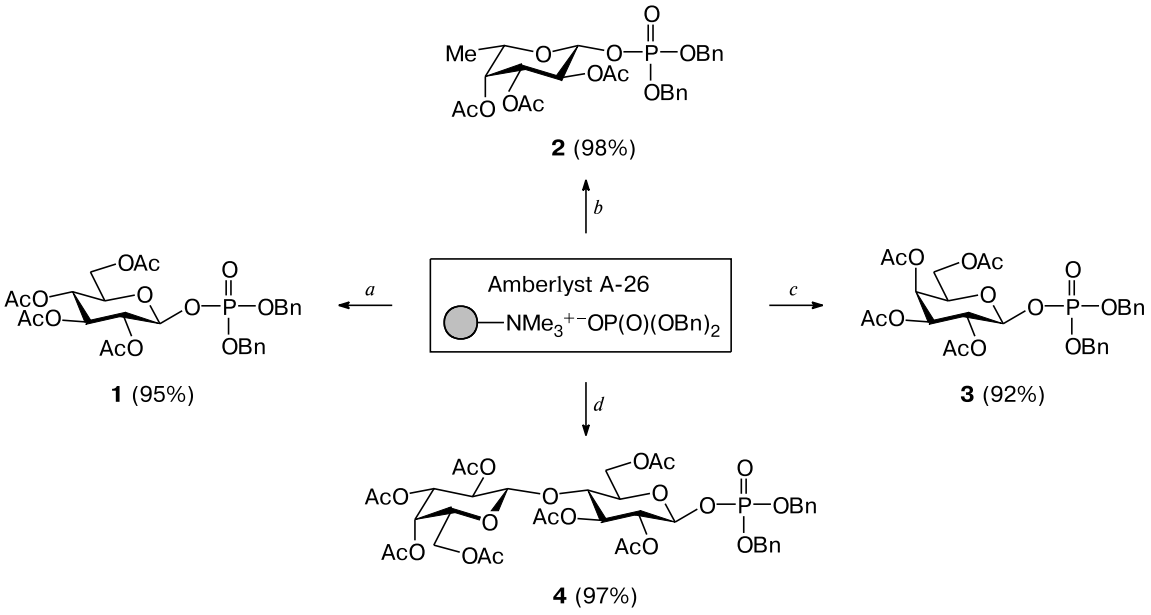
Scheme 1



Reagents and conditions: (*a*) acetobromoglucose,[22,23] MeCN; (*b*) acetobromofucose,[25] MeCN; (*c*) acetobromogalactose,[24] MeCN; and (*d*) acetobromolactose,[26,27] MeCN.

obtained from the resin in the hydrocarbonate form (prepared by treatment of the commercially available Amberlyst A-26 hydroxyl form with aqueous $NaHCO_3$) under the action of the excess of a solution of dibenzyl phosphoric acid $(BnO)_2P(O)OH$ in a MeCN—H_2O (1 : 1) mixture followed by washing with acetonitrile and vacuum drying of the resin.

The resulted polymeric phosphate-containing reagent underwent reaction with a series of acetobromosugars (derivatives of glucose,[22,23] galactose,[24] fucose,[25] and lactose[26,27]) in anhydrous acetonitrile (Scheme 1). The reactions proceeded unambiguously to result in the formation of expected dibenzyl glycosyl phosphates **1**—**4** which were isolated in high yields (92—99%) as single diastereomers with equatorial aglycon (inversion of configuration of the sugar anomeric center was observed in all cases).

Note exceptionally mild conditions of the reaction and product isolation excluding anomerization of the kinetically formed equatorial phosphates which are known[28—30] for their tendency to transform into the thermodynamically more stable axial isomers. Of special notice is virtually quantitative isolation of the equatorial fucose phosphate **2** having β-configuration[25,31] whose preparation as the single anomer frequently presents difficulties due to its configurational instability. The method proposed for the synthesis of glycosyl phosphates supplements well the known approaches.[15,16] Note that this reaction is the first example of using the ion-exchange resin as the source of nucleophile (glycosyl acceptor) in the glycosylation reactions.

Synthesis of dibenzyl glycosyl phosphates using an Amberlyst A-26 ion-exchange resin in the dibenzyl phosphate form (general procedure). A suspension of dried Amberlyst A-26 ion-exchange resin ($(BnO)_2P(O)O^-$ form, 8 g of the resin per 1 mmol of the glycosyl donor) in a solution of glycosyl halide (0.1—0.3 mmol) in anhydrous CH_3CN (20 mL per 1 mmol of the glycosyl donor) was stirred using a shaker at room temperature (25—30 °C). After complete consumption of the glycosyl donor (24—120 h, TLC control: AcOEt—toluene, 2 : 1 or AcOEt—petroleum ether, 2 : 1), the reaciton mixture was filtered through a cartridge with silica gel (PrepSep-Si, Fisher); the resin and the cartridge were washed with AcOEt (100 mL). The filtrate was concentrated (25 °C) and the residue was dried *in vacuo* to yield pure glycosyl phosphates **1**—**4** whose ^1H, ^{13}C, and ^{31}P NMR spectra coincided with literature data (for **1** (see Ref. 32) the reaction time (τ) was 96 h and the yield was 95%; for **2** (see Ref. 31) τ was 24 h and the yield was 98%; for **3** (see Ref. 32) τ was 96 h and the yield was 92%; for **4** (see Ref. 32) τ was 120 h and the yield was 97%).

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References

1. A. Varki, R. D. Cummings, J. D. Esko, H. H. Freeze, P. Stanley, C. R. Bertozzi, G. W. Hart, M. E. Etzler, *Essentials of Glycobiology*, 2nd ed., Cold Spring Harbor Laboratory Press, New York, 2008, 784 pp.
2. G. W. Hart, R. J. Copeland, *Cell*, 2010, **143**, 672.
3. H.-J. Gabius, S. André, J. Jiménez-Barbero, A. Romero, D. Solís, *Trends Biochem. Sci.*, 2011, **36**, 298.
4. R. D. Astronomo, D. R. Burton, *Nature Rev. Drug Discov.*, 2010, **9**, 308.

5. R. Roy, T. C. Shiao, *Chimia*, 2011, **65**, 24.
6. M. C. Galan, D. Benito-Alifonso, G. M. Watt, *Org. Biomol. Chem.*, 2011, **9**, 3598.
7. L. Cipolla, F. Peri, *Mini Rev. Med. Chem.*, 2011, **11**, 39.
8. A. Bernardi, J. Jiménez-Barbero, A. Casnati, C. De Castro, T. Darbre, F. Fieschi, J. Finne, H. Funken, K.-E. Jaeger, M. Lahmann, T. K. Lindhorst, M. Marradi, P. Messner, A. Molinaro, P. V. Murphy, C. Nativi, S. Oscarson, S. Penadés, F. Peri, R. J. Pieters, O. Renaudet, J.-L. Reymond, B. Richichi, J. Rojo, F. Sansone, C. Schäffer, W. B. Turnbull, T. Velasco-Torrijos, S. Vidal, S. Vincent, T. Wennekes, H. Zuilhof, A. Imberty, *Chem. Soc. Rev.*, 2013, **42**, 4709.
9. *Handbook of Chemical Glycosylation: Advances in Stereoselectivity and Therapeutic Relevance*, Ed. A. V. Demchenko, Wiley-VCH, Weinheim, 2008, 501 pp.
10. J. T. Smoot, A. V. Demchenko, *Adv. Carbohydr. Chem. Biochem.*, 2009, **62**, 161.
11. S. Kaeothip, A. V. Demchenko, *Carbohydr. Res.*, 2011, **346**, 1371.
12. O. Blixt, N. Razi, in *Glycoscience: Chemistry and Chemical Biology*, Eds B. Fraser-Reid, K. Tatsuta, J. Thiem, Springer-Verlag, Heidelberg, 2nd ed., 2008, p. 1361.
13. S. Muthana, H. Cao, X. Chen, *Curr. Opin. Chem. Biol.*, 2009, **13**, 573.
14. A. Homann, J. Seibel, *Appl. Microbiol. Biotechnol.*, 2009, **83**, 209.
15. G. K. Wagner, T. Pesnot, R. A. Field, *Nat. Prod. Rep.*, 2009, **26**, 1172.
16. N. Oka, K. Sato, T. Wada, *Trends Glycosci. Glycotechnol.*, 2012, **24**, No. 138, 152.
17. C. H. Hsu, K. C. Chu, Y. S. Lin, J. L. Han, Y. S. Peng, C. T. Ren, C. Y. Wu, C.-H. Wong, *Chem.-Eur. J.*, 2010, **16**, 1754.
18. K.-C. Chu, C.-T. Ren, C.-P. Lu, C.-H. Hsu, T.-H. Sun, J.-L. Han, B. Pal, T.-A. Chao, Y.-F. Lin, S.-H. Wu, C.-H. Wong, C.-Y. Wu, *Angew. Chem., Int. Ed. Engl.*, 2011, **50**, 9391.
19. P. H. Seeberger, *Carbohydr. Res.*, 2008, **343**, 1889.
20. C. H. Hsu, S. C. Hung, C. Y. Wu, C.-H. Wong, *Angew. Chem., Int. Ed. Engl.*, 2011, **50**, 11872.
21. G. Cainelli, F. Manescalchi, *Synthesis*, 1975, 723.
22. R. U. Lemieux, in *Methods in Carbohydrate Chemistry*, Eds R. L. Whistler, M. L. Wolfrom, Academic Press, New York—London, 1963, Vol. **2**, p. 221.
23. X. Nie, G. Wang, *J. Org. Chem.*, 2005, **70**, 8687.
24. S. Liu, R. N. Ben, *Org. Lett.*, 2005, **7**, 2385.
25. G. Baisch, R. Öhrlein, *Bioorg. Med. Chem.*, 1997, **5**, 383, and references cited therein.
26. L. O. Kononov, A. V. Kornilov, A. A. Sherman, E. V. Zyryanov, G. V. Zatonskii, A. S. Shashkov, and N. E. Nifant´ev, *Russ. J. Biorg. Chem.*, 1998, **24**, 537 (*Engl. Transl.*) [*Bioorg. Khim.*, 1998, **24**, 608].
27. W. Seebacher, R. Weis, J. Jurenitsch, K. Rauchensteiner, E. Haslinger, *Monatsh. Chem.*, 2000, **131**, 985.
28. V. N. Shibaev, L. L. Danilov, in *Studies in Natural Products Chemistry*, *Stereoselective synthesis*, Ed. Atta-ur-Rahman, Elsevier, Amsterdam, 1991, Vol. **8**, Part E, p. 63.
29. P. A. Illarionov, V. I. Torgov, V. N. Shibaev, *Russ. Chem. Bull.* (*Int. Ed.*), 2000, **49**, 1895 [*Izv. Akad. Nauk*, *Ser. Khim.*, 2000, 1924].
30. A. V. Orlova, A. M. Shpirt, N. Y. Kulikova, L. O. Kononov, *Carbohydr. Res.*, 2010, **345**, 721.
31. R. R. Schmidt, B. Wegmann, K.-H. Jung, *Liebigs Ann. Chem.*, 1991, 121.
32. R. Roy, F. Tropper, C. Grand-Maitre, *Can. J. Chem.*, 1991, **69**, 1462.

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