Carbohydrate Chemistry

Hybrid Solution/Solid-Phase Synthesis of Oligosaccharides by Using Trichloroacetyl Isocyanate as Sequestration-Enabling Reagent of Sugar Alcohols

Alessandro Dondoni, Alberto Marra,* and Alessandro Massi**

In recent years there has been a steady increase in interest in glycoscience with particular emphasis toward programs at the chemistry/biology interface. Current studies are mainly directed toward the understanding at molecular level of the key role exerted by glycoconjugate-derived oligosaccharides in beneficial or detrimental events that occur in living organisms.[1] In most, if not all, of these studies, organic synthesis is required to provide meaningful quantities of native oligosaccharides and their analogues in a pure state with well-defined structures to be used as biological, biochemical, and biophysical probes. Pure oligosaccharides are very difficult to access from natural sources owing to the complexity and microheterogeneity of glycosylated proteins[2] and their instability to many isolation procedures. Enormous progress has been made in the area of oligosaccharide synthesis especially in the last decade, and a plethora of synthetic methods in either the solution or solid phase have been reported.[3,4] However both techniques present their own limitations. For instance, solution-phase reactions require a laborious workup and time-consuming product isolation by chromatography after each glycosidation trail. On the other hand, the solid-phase approach does not entail the above problems and lends itself to automation, however, the polymer-bound substrate suffers an attenuated reactivity for entropic and steric reasons, and monitoring the progress of the reaction and estimating the yield of coupled product by TLC or standard NMR and MS analyses is more difficult. A number of sophisticated analytical methods have therefore been developed as a result.[5] Another serious concern in the solid-phase approach is the need for robust linkers that tolerate various reaction conditions but can be easily cleaved to retrieve the product without affecting its functionalities, especially the labile and stereomutable *O*-glycosidic bond. Even in the face of spectacular advances in the field of automated solid-phase synthesis of oligosaccharides up to nine-member constructs,[4l] the main way to access complex oligosaccharides that feature a great structural diversity still appears to be the convergent solution-phase approach by coupling tri- or tetrasaccharide building blocks.[6]

Hence the search for innovative and practical methods based on recent synthetic techniques is actively pursued. Notable is the tag-assisted solution-phase strategy developed by Hindsgaul and co-workers,[7] Pozgay,[8] and Ito and co-workers[9] in which a suitable group (tag) installed in one of the reactants serves to selectively remove the coupled product from the complex reaction mixture. An oligosaccharide synthesis centered on the use of a highly fluorinated tag was reported by Inazu and co-workers [10] following an earlier approach by Curran et al. based on the fluorous-tag method[11] which, however, was quite limited in scope. We envisaged a novel approach to oligosaccharide synthesis based on a solid-supported sequestering or scavenging technique,[12] which involves executing the reaction in solution in the presence of an excess of one reactant and then removing the residue with a polymer-bound reagent. This approach is referred to as polymer-assisted solution-phase (PASP) synthesis and offers all the advantages associated with solution-phase chemistry and those which are intrinsic to classical solid-phase techniques, such as the use of a large excess of one reagent to drive the reaction to completion followed by a simple filtration step for the isolation of the product. Quite surprisingly there are few examples of the PASP technique applied to oligosaccharide synthesis, and unfortunately the reported methods are not free of substantial shortcomings. In one instance Kirschning et al. reported a route that was limited to the preparation of 2-deoxy-glycoconjugates,[13] while Ley and co-workers developed a method that operated only with primary sugar alcohols as acceptors.[14] Herein we report our own strategy in which the coupling of the sugar is carried out by the use of a twofold excess of a primary or secondary sugar alcohol. Once the reaction is completed, as shown by the total consumption of the glycosyl donor, the unreacted acceptor is selectively derivatized by trichloroacetyl isocyanate, which is a powerful detecting reagent of alcohols and is widely employed as an analytical tool in NMR spectroscopy.[15] The resultant trichloroacetyl urethane is removed from the solution mixture by a suitable solid-supported base. The free sugar alcohol is recovered from the sequestered material and reused as an acceptor in a subsequent glycosylation cycle.

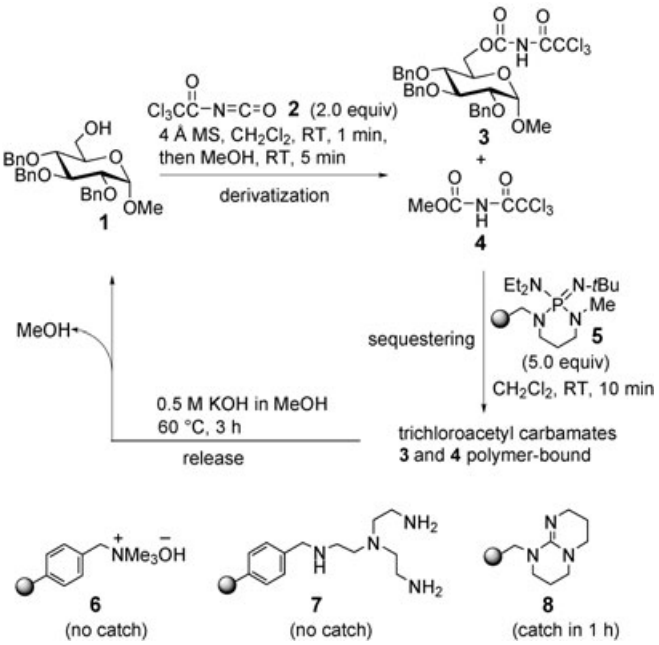
Before developing our method, we made several (unsuccessful) attempts to sequester the model secondary sugar alcohol **9** (Scheme 2) with commercially available polymer-supported reagents such as PS-benzenesulfonyl chloride (PS = polystyrene), PS-phenylisocyanate, and the dichlorotriazine developed by Masala and Taddei.[16] Discouraging results were also obtained in an attempt to modify the capture strategy of **9** by the use of tetrafluorophthalic anhydride as a sequestration-enabling reagent (SER).[17] This anhydride failed to provide the expected ester (see Supporting Information). To develop an efficient strategy for sequestering both primary and secondary sugar alcohols in a PASP synthesis of oligosaccharides, our study commenced by examining the capture–release sequence of the primary sugar alcohol **1** using trichloroacetyl isocyanate (**2**, TAI) as the hitherto unemployed SER.[18] Thus treatment of **1** with **2**

[*] Prof. A. Dondoni, Prof. A. Marra, Dr. A. Massi
Laboratorio di Chimica Organica
Dipartimento di Chimica
Università di Ferrara
Via L. Borsari 46, 44100 Ferrara (Italy)
Fax: (+39) 0532-291-167
E-mail: adn@dns.unife.it
mra@dns.unife.it
msslsn@dns.unife.it

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

  DOI: 10.1002/ange.200462422

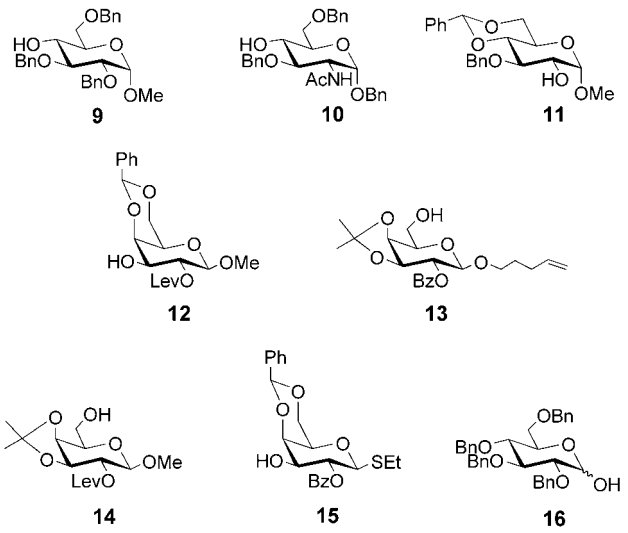
(ratio 1:2) under neutral conditions afforded the sugar urethane **3** almost instantaneously as shown by TLC analysis (Scheme 1, derivatization step). Then, the reaction mixture was quenched with a large excess of MeOH that transformed



Scheme 1. Use of trichloroacetyl isocyanate (**2**, TAI) as a new sequestration-enabling reagent (SER). Also shown are other polymer-supported bases (**6**–**8**) tested in the sequestering step. Bn = benzyl.[19]

unconverted TAI **2** into methyl urethane **4**. The exclusion of water in this operation is recommended to avoid the decomposition of **2** into trichloroacetamide whose removal would require purification by column chromatography. The solid-phase sequestering of **3** and **4** was carried out using the highly basic, non-nucleophilic polymer-supported BEMP (2-*tert*-butylimino-2-diethylamino-1,3-dimethyl-perhydro-1,3,2-diazaphosphorine on polystyrene, **5**) to give urethanes bound to the polymer as ion pairs.[19] Filtration of the resin and subsequent treatment with KOH in MeOH followed by neutral aqueous workup released the starting sugar alcohol **1** in high yield (95%) and purity (95%).

The wide scope of this derivatization–sequestering–release (DSR) sequence was demonstrated by successful application to primary and secondary sugar alcohols **9**—**15**, which feature diverse protecting groups of the hydroxy group (Scheme 2). In all cases the starting compound or a partially deprotected derivative was recovered in high yield (95%) and purity (>95%) with unaltered anomeric configuration. Note that the methodology was compatible with the presence of the NHAc group (see compound **10**) which allowed *N*-acetyl amino sugars to be included as substrates in the TAI-mediated capture–release sequence.[20] Efficient sequestering of the sugar hemiacetal **16** was also demonstrated, although in this case the polymer-bound product decomposed under the strongly basic conditions of the release step. Nevertheless, a means for removing hemiacetal side products from glycosidation mixtures is a useful tool, as these compounds may be

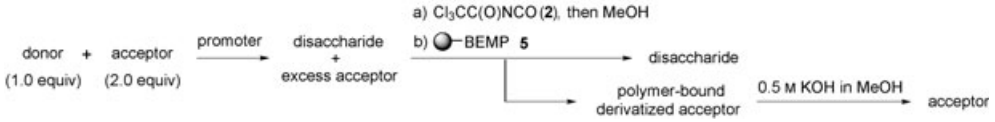


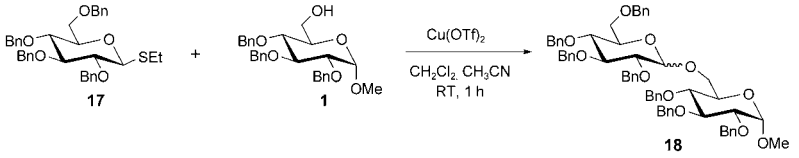
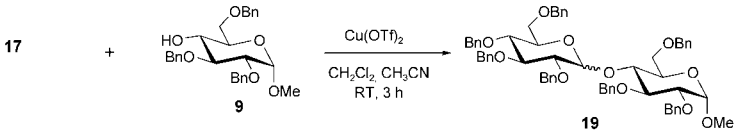
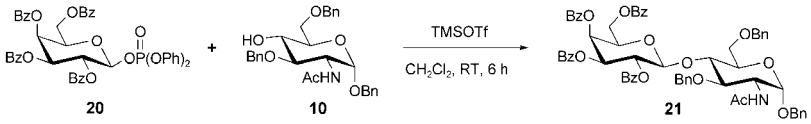
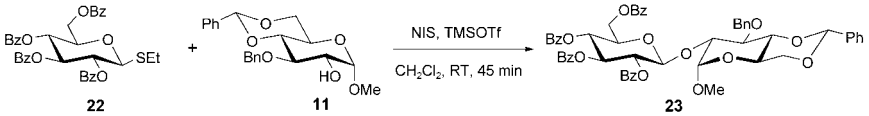
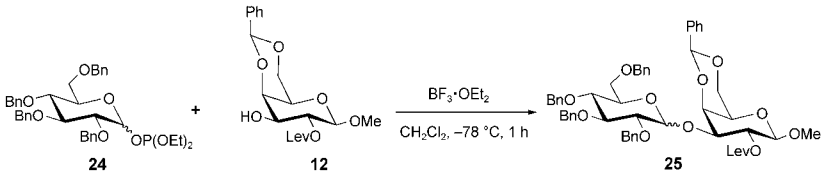
Scheme 2. Other representative sugar alcohols and a hemiacetal subjected to the derivatization–sequestering–release (DSR) sequence. Note compounds **12**–**15** were recovered as deacylated derivatives. Bz = benzoyl, Lev = levulinoyl (4-oxopentanoyl).

easily formed by the hydrolysis of a large variety of activated glycosyl donors.

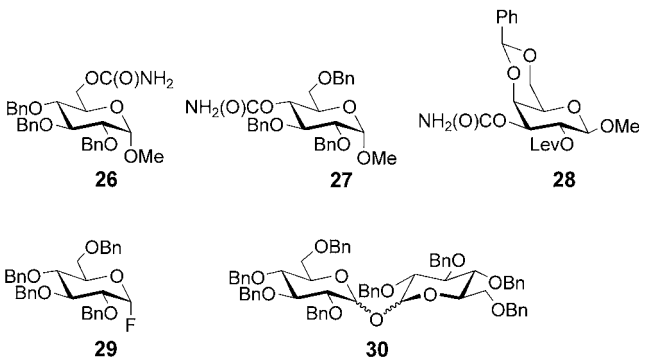
With an efficient solid-phase sequestering methodology of sugar alcohols in hand, the solution-phase synthesis of various disaccharides and their isolation was conducted as outlined in Table 1. Once the glycosidation of the donor was completed in the presence of a twofold excess of acceptor, filtration of the reaction mixture was followed by aqueous workup and evaporation of the solvent to afford the target disaccharide along with the unconverted acceptor and other carbohydrate-containing byproducts. This reaction mixture was essentially free of impurities arising from the glycosyl donor-activation system. In fact, the accurate choice of anomeric leaving groups (thioethyl, pentenyl, phosphates, and phosphites; see Table 1 and Scheme 5) and the relevant promoters ($Cu(OTf)_2$ (OTf = trifluoromethanesulfonate), MeOTf, NIS (*N*-iodosuccinimide), TMSOTf (TMS = trimethylsilyl), $BF_3{\cdot}OEt_2$) led to byproducts that could be removed by filtration, evaporation, or by aqueous workup.[21] Only in the case of succinimide, which formed in the NIS activation system, did removal of this byproduct take place in the next step upon treatment of the reaction mixture with polymer-supported BEMP (**5**). The unconverted acceptor was scavenged and recovered by the above DSR sequence, and the desired disaccharide was isolated as a mixture of anomers. Excellent yields and high purities were registered for all crude products **18**, **19**, **21**, and **23** obtained in this way. The purities estimated in the ^1H NMR spectra were confirmed by means of chromatographic purification, which also allowed the identification of the residual (4–5%) sugar carbamates **26** and **27** byproducts (Scheme 3). The yields of the two analytically pure products **18** and **19** were much higher than those obtained when equimolar amounts of reaction partners were used in the same solution-phase synthesis, thus substantiating the effectiveness of the glycosidation reaction under the conditions employed. Nevertheless, we observed that our improved glycosidation con-

Table 1: Application of the proposed methodology to the synthesis of disaccharides.



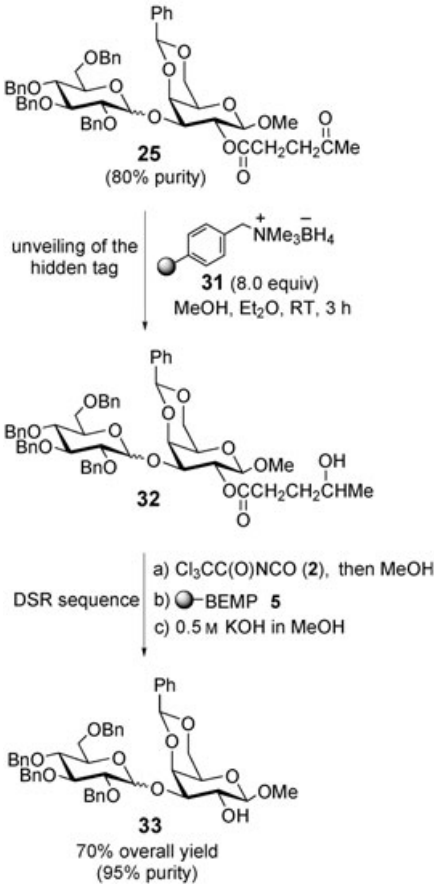
Glycosidation	Yield [%]	Purity [%][a]	Isolated yield [%][b]	Ratio α/β	Recovered excess acceptor [%]
	quant.	95	96 (83)[c]	1:2	92
	98	95	91 (59)[c]	1:1	95
	92	95	87	0:1	97
	quant.	95	96	0:1	92
	94[d]	80[d]	73	1:3	98[e]

[a] From ^{1}H NMR analysis. [b] After column chromatography on silica gel. [c] Yield of isolated disaccharide when the glycosidation reaction is carried out with an equimolar ratio of donor and acceptor. [d] Disaccharide **25** was obtained in 88% yield with 90% purity using TMSOTf (trimethylsilyl trifluoromethanesulfonate) as the promoter under the same reaction conditions. [e] Acceptor recovered as deacylated derivative.

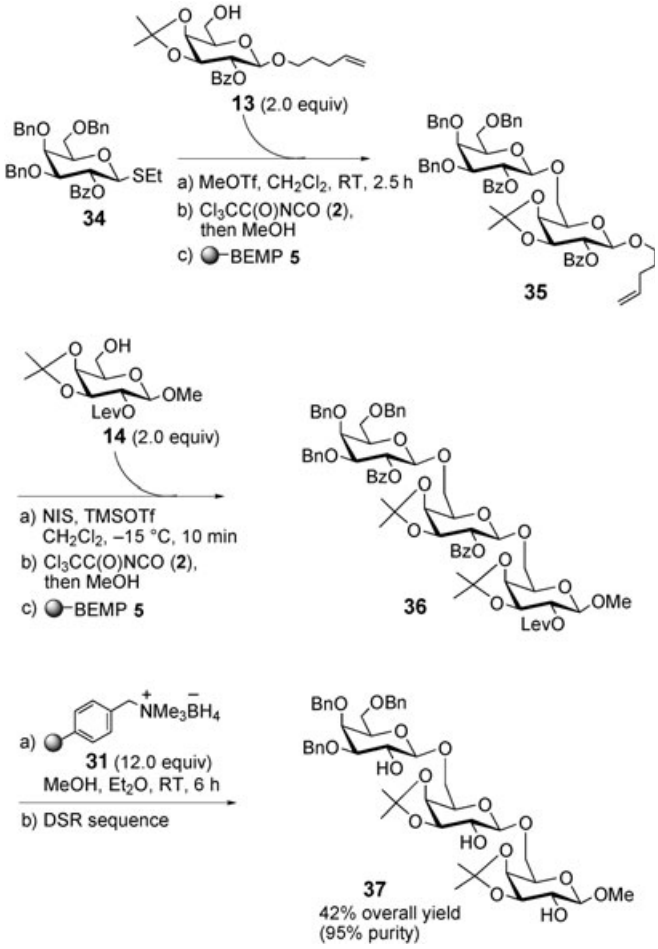


Scheme 3. Sugar byproducts formed during the glycosidations described in Table 1.

ditions did not always protect the donor from its partial degradation, thus giving unsatisfactory results especially in terms of purity of the isolated target glycoconjugate. This was the case with disaccharide **25**, which was obtained in good yield (94%) but with quite low purity (80%), as confirmed by isolation of its contaminants—the carbamate **28**, glycosyl fluoride **29**, and trehaloses **30**—by chromatography (Scheme 3). Evidently, the side products **29** and **30** arise from the initial decomposition of the phosphite-activated donor **24**. To overcome this limitation, we refined the proposed methodology by considering a second cycle of purification for disaccharide **25** which exploits the benefits of both a tag-assisted and a "resin-capture–release" purification strategy.[22] The key element in this improved protocol was the levulinoyl (4-oxopentanoyl) ester group which serves as a hidden tag (Scheme 4) and was earlier installed on the glycosyl acceptor **12**. Thus, the crude disaccharide **25**, which results from the first TAI-based purification sequence (80% purity, Table 1), was treated with polymer-supported borohydride **31** to unveil the C2 hydroxy group.[23] Instead, the γ-hydroxyester **32** was obtained as a single product. This product was derivatized with TAI (**2**), trapped as an activated polymer intermediate onto PS-BEMP, and finally, after washing to remove soluble byproducts **28**–**30**, was released in solution by means of KOH in MeOH (Scheme 4). This new hybrid solution/solid-phase approach afforded the disaccharide **33** in 70% overall yield (starting from **24**) and with 95%



Scheme 4. Use of the levulinoyl group as a hidden tag in the "resin-capture–release" purification strategy.



Scheme 5. Synthesis of a trisaccharide; chromatographic purification not required.

purity (determined by chromatography and ^{1}H NMR spectroscopy).

As a demonstration of the power of our strategy, the assembly of trisaccharide **37** was conducted by iterative glycosidation (Scheme 5). Efficiency relied on the nontrivial task to select reaction partners with suitable hydroxy group protection and anomeric activation to ensure good reactivity and stereo- and chemoselectivity in each cycle. Thus, under methyl triflate activation, the 2-benzoyl-directed β glycosidation of thioethyl galactoside **34** with an excess of primary alcohol **13** followed by derivatization with TAI (**2**) and sequestration of the urethane with PS-BEMP (**5**) afforded β-D-(1,6)-disaccharide **35**. This crude compound under *O*-pentenyl activation by NIS–TMSOTf was subjected to glycosidation by the sugar alcohol **14**, which bears the levulinoyl ester group at C2. The trisaccharide **36** obtained was isolated by workup of the reaction mixture with the standard TAI-based sequestering technique. The crude trisaccharide **36** was finally purified by reduction of the levulinate carbonyl group using the polymer-supported borohydride **31** followed by sequestration with the DSR sequence as described in Scheme 4. The benzoyl- and levulinoyl-free trisaccharide **37** was isolated in 42% yield and 95% purity according to NMR spectral analysis. In two separate experiments, the coupled products **35** and **36** were isolated (89 and 55% yield, respectively) by column chromatography and were duly characterized by NMR spectroscopy, thus confirming the formation of the β-D-glycosidic linkage in both solution-phase glycosidations.

Overall, the efforts made herein were directed to find conditions that would allow an automated synthesis of oligosaccharides by the merging of the polymer-support technology with solution-phase chemistry. The results obtained so far are quite promising and indicate that this goal can be pursued. The effectiveness of TAI as a new SER for scavenging both primary and secondary sugar alcohols and the exploitation of the levulinoyl group as a hidden tag for hybrid solution/solid-phase synthesis represent the major novelties and key operations in this new strategy. However, more research is required to provide examples that allow the scope of this strategy to be extended to the synthesis of more-complex oligosaccharides than those described above. This work is currently underway in our laboratory.

Received: October 25, 2004
Revised: December 10, 2004
Published online: February 3, 2005

Keywords: chemoselectivity · glycosylation · solid-phase synthesis · synthetic methods

[1] a) A. Varki, *Glycobiology* **1993**, *3*, 97; b) A. Kobata, *Acc. Chem. Res.* **1993**, *26*, 319; c) R. A. Dwek, *Chem. Rev.* **1996**, *96*, 683; d) *Essentials of Glycobiology* (Eds: A. Varki, R. Cummings, J. Esko, H. Freeze, G. Hart, J. Marth), Cold Spring Harbor, Plainview, New York, **1999**.

[2] a) T. W. Rademacher, R. B. Parekh, R. A. Dwek, *Annu. Rev. Biochem.* **1988**, *57*, 785; b) R. S. Rush, P. L. Derby, D. M. Smith, C. Merry, G. Rogers, M. F. Rhode, V. Katta, *Anal. Chem.* **1995**, *67*, 1442.

[3] For recent reviews, see: a) *Modern Methods in Carbohydrate Synthesis* (Eds: S. H. Khan, R. A. O'Neil), Harwood, Amsterdam, **1996**; b) *Preparative Carbohydrate Chemistry* (Ed.: S. Hanessian), Marcel Dekker, New York, **1997**; c) *Carbohydrates in Chemistry and Biology* (Eds.: B. Ernst, G. W. Hart, P. Sinaÿ), Wiley-VCH, Weinheim, **2000**; d) *Solid Support Oligosaccharide Synthesis and Combinatorial Libraries* (Ed.: P. H. Seeberger), Wiley-Interscience, New York, **2001**; e) G.-J. Boons, *Tetrahedron* **1996**, *52*, 1095; f) H. M. I. Osborn, T. Q. Khan, *Tetrahedron* **1999**, *55*, 1807; g) F. Schweizer, O. Hindsgaul, *Curr. Opin. Chem. Biol.* **1999**, *3*, 291; h) P. M. St. Hilaire, M. Meldal, *Angew. Chem.* **2000**, *112*, 1210; *Angew. Chem. Int. Ed.* **2000**, *39*, 1162; i) P. H. Seeberger, W.-C. Haase, *Chem. Rev.* **2000**, *100*, 4349; j) K. M. Koeller, C.-H. Wong, *Chem. Rev.* **2000**, *100*, 4465; k) H. Herzner, T. Reipen, M. Schultz, H. Kunz, *Chem. Rev.* **2000**, *100*, 4495; l) P. Sears, C.-H. Wong, *Science* **2001**, *291*, 2344; m) K. C. Nicolaou, H. J. Mitchell, *Angew. Chem.* **2001**, *113*, 1624; *Angew. Chem. Int. Ed.* **2001**, *40*, 1576; n) A. V. Demchenko, *Synlett* **2003**, 1225; o) P. H. Seeberger, *Chem. Commun.* **2003**, 1115; p) D. Crich, L. B. L. Lim, *Org. React.* **2004**, *64*, 115.

[4] For selected recent papers (2000–2004), see: a) X.-S. Ye, C.-H. Wong, *J. Org. Chem.* **2000**, *65*, 2410; b) K. Egusa, K. Fukase, Y. Nakai, S. Kusumoto, *Synlett* **2000**, 27; c) F. Burkhart, Z. Zhang, S. Wacowich-Sgarbi, C.-H. Wong, *Angew. Chem.* **2001**, *113*, 1314; *Angew. Chem. Int. Ed.* **2001**, *40*, 1274; d) O. J. Plante, E. R. Palmacci, P. H. Seeberger, *Science* **2001**, *291*, 1523; e) T. Zhu, G.-J. Boons, *Org. Lett.* **2001**, *3*, 4201; f) H. M. Nguyen, J. L. Poole, D. Y. Gin, *Angew. Chem.* **2001**, *113*, 428; *Angew. Chem. Int. Ed.* **2001**, *40*, 414; g) S. Yamago, T. Yamada, O. Hara, H. Ito, Y. Mino, J. Yoshida, *Org. Lett.* **2001**, *3*, 3867; h) F. Roussel, M. Takhi, R. R. Schmidt, *J. Org. Chem.* **2001**, *66*, 8540; i) J. D. C. Codée, L. J. van den Bos, R. E. J. N. Litjens, H. S. Overkleeft, J. H. van-Boom, G. A. van der Marel, *Org. Lett.* **2003**, *5*, 1947; j) T. K. Ritter, K.-K. T. Mong, H. Liu, T. Nakatani, C.-H. Wong, *Angew. Chem.* **2003**, *115*, 4805; *Angew. Chem. Int. Ed.* **2003**, *42*, 4657; k) D. Majumdar, T. Zhu, G.-J. Boons, *Org. Lett.* **2003**, *5*, 3591; l) K. Routenberg, P. H. Seeberger, *Angew. Chem.* **2004**, *116*, 612; *Angew. Chem. Int. Ed.* **2004**, *43*, 602; m) S. Yamago, T. Yamada, T. Maruyama, J. Yoshida, *Angew. Chem.* **2004**, *116*, 2197; *Angew. Chem. Int. Ed.* **2004**, *43*, 2145; n) X. Huang, L. Huang, H. Wang, X.-S. Ye, *Angew. Chem.* **2004**, *116*, 5333; *Angew. Chem. Int. Ed.* **2004**, *43*, 5221; o) X. Wu, R. R. Schmidt, *J. Org. Chem.* **2004**, *69*, 1853.

[5] a) T. Kanemitsu, C.-H. Wong, O. Kanie, *J. Am. Chem. Soc.* **2002**, *124*, 3591; b) M. Mogemark, M. Elofsson, J. Kihlberg, *J. Org. Chem.* **2003**, *68*, 7281; c) M. Mogemark, F. Gårdmo, T. Tengel, J. Kihlberg, M. Elofsson, *Org. Biomol. Chem.* **2004**, *2*, 1770.

[6] Among the numerous examples which can be cited, the most convincing case is the work recently reported by Danishefsky and co-workers targeted to carbohydrate-based HIV vaccines. See: a) M. Mandal, V. Y. Dudkin, X. Geng, S. J. Danishefsky, *Angew. Chem.* **2004**, *116*, 2611; *Angew. Chem. Int. Ed.* **2004**, *43*, 2557; b) X. Geng, V. Y. Dudkin, M. Mandal, S. J. Danishefsky, *Angew. Chem.* **2004**, *116*, 2616; *Angew. Chem. Int. Ed.* **2004**, *43*, 2562.

[7] a) M. M. Palcic, L. D. Heeze, M. Pierce, O. Hindsgaul, *Glycoconjugate J.* **1988**, *5*, 49; b) Y. Ding, J. Labbe, O. Kanie, O. Hindsgaul, *Bioorg. Med. Chem.* **1996**, *4*, 683; c) U. J. Nilsson, E. J.-L. Fournier, O. Hindsgaul, *Bioorg. Med. Chem.* **1998**, *6*, 1563.

[8] a) V. Pozsgay, *Org. Lett.* **1999**, *1*, 477; b) V. Pozsgay, *Tetrahedron: Asymmetry* **2000**, *11*, 151.

[9] a) H. Ando, S. Manabe, Y. Nakahara, Y. Ito, *J. Am. Chem. Soc.* **2001**, *123*, 3848; b) Y. Ito, S. Manabe, *Chem. Eur. J.* **2002**, *8*, 3077.

[10] a) T. Miura, Y. Hirose, M. Ohmae, T. Inazu, *Org. Lett.* **2001**, *3*, 3947; b) T. Miura, K. Goto, H. Varagai, H. Matsumoto, Y. Hirose, M. Ohmae, H. Ishida, A. Satoh, T. Inazu, *J. Org. Chem.* **2004**, *69*, 5348.

[11] D. P. Curran, R. Ferritto, Y. Hua, *Tetrahedron Lett.* **1998**, *39*, 4937.

[12] a) J. J. Parlow, R. V. Devraj, M. S. South, *Curr. Opin. Chem. Biol.* **1999**, *3*, 320; b) S. J. Shuttleworth, S. M. Allin, R. D. Wilson, D. Nasturica, *Synthesis* **2000**, 1035; c) L. A. Thompson, *Curr. Opin. Chem. Biol.* **2000**, *4*, 324; d) S. V. Ley, I. R. Baxendale, R. N. Bream, P. S. Jackson, A. G. Lezach, D. A. Langbottom, M. Nesi, J. S. Scott, R. I. Storer, S. J. Taylor, *J. Chem. Soc. Perkin Trans. 1* **2000**, *23*, 3815; e) A. Kirschning, H. Monenschein, R. Wittenberg, *Angew. Chem.* **2001**, *113*, 670; *Angew. Chem. Int. Ed.* **2001**, *40*, 650.

[13] a) A. Kirschning, M. Jesberger, A. Schönberger, *Org. Lett.* **2001**, *3*, 3623; b) J. Jaunzems, D. Kashin, A. Schönberger, A. Kirschning, *Eur. J. Org. Chem.* **2004**, 3435.

[14] R. N. MacCoss, P. E. Brennan, S. V. Ley, *Org. Biomol. Chem.* **2003**, *1*, 2029.

[15] a) V. W. Goodlett, *Anal. Chem.* **1965**, *37*, 431; b) M. Meyer zur-Heyde, *Fresenius Z. Anal. Chem.* **1979**, *295*, 125; c) G. H. P. Roos, M. C. Watson, *S. Afr. J. Chem.* **1991**, *44*, 95.

[16] S. Masala, M. Taddei, *Org. Lett.* **1999**, *1*, 1355.

[17] J. J. Parlow, W. Naing, M. S. South, D. L. Flynn, *Tetrahedron Lett.* **1997**, *38*, 7959.

[18] To the best of our knoweledge TAI (**2**) has not been used so far in PASP synthetic strategies. However, the use of benzenesulfonyl isocyanate as a SER was announced, see: W. Naing, S. Yang, J. J. Parlow, D. L. Flynn, R. V. Devras in *Book of Abstracts*, 216th ACS National Meeting, Boston, August 23–27, **1998**. We are not aware of any article in follow-up to that communication.

[19] The sequestering of urethanes **3** and **4** failed with other polymer-supported bases, namely Ambersep 900 OH **6** and trisamine **7**, whereas the rigidified guanidine-type compound **8** was quite effective but required a much longer reaction time than the diazaphosphorine **5**.

[20] The DSR sequence shown in Scheme 1 was successfully applied to a sugar primary amine and, with some limitations, to an anomeric sugar thiol (see Supporting Information). Work in this area is in progress.

[21] In earlier PASP glycosidation approaches, Kirschning and Ley and their co-workers used thiophenyl and selenophenyl glycosides, respectively, as donors. The removal of sulphur- and selenium-containing byproducts required suitable scavenging procedures. See: a) J. Jaunzems, G. Sourkouni-Argirusi, M. Jesberger, A. Kirschning, *Tetrahedron Lett.* **2003**, *44*, 637; b) J. Jaunzems, E. Hofer, M. Jesberger, G. Sourkouni-Argirusi, A. Kirschning, *Angew. Chem.* **2003**, *115*, 1198; *Angew. Chem. Int. Ed.* **2003**, *42*, 1166, and ref. [14].

[22] For a definition of "resin-capture–release" hybrid technique, see: A. Kirschning, H. Monenschein, R. Wittenberg, *Chem. Eur. J.* **2000**, *6*, 4445.

[23] It is well known that the reduction by $NaBH_4$ of sugars protected as *O*-levulinates induces the cleavage of the ester group by removal of methyl γ-butyrolactone.

