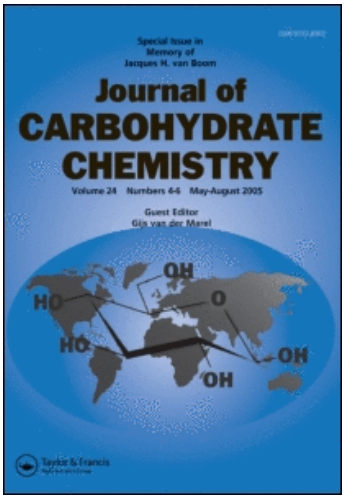


Journal of Carbohydrate Chemistry

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713617200

d-Glucose as a Regioselectively Addressable Scaffold for Combinatorial Chemistry on Solid Phase

Francesco Peri[a]; Francesco Nicotra[a]; Colin P. Leslie[b]; Fabrizio Micheli[b]; Pierfausto Seneci[b]; Carla Marchioro[b]

[a] Department of Biotechnology and Biosciences, University of Milano-Bicocca, Piazza Della Scienza, 2, Italy [b] Medicines Research Centre, GlaxoSmithKline SpA, Verona, Italy

Online publication date: 27 February 2003

To cite this Article Peri, Francesco , Nicotra, Francesco , Leslie, Colin P. , Micheli, Fabrizio , Seneci, Pierfausto and Marchioro, Carla(2003) 'd-Glucose as a Regioselectively Addressable Scaffold for Combinatorial Chemistry on Solid Phase', Journal of Carbohydrate Chemistry, 22: 1, 57 — 71

To link to this Article: DOI: 10.1081/CAR-120019014

URL: http://dx.doi.org/10.1081/CAR-120019014

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

JOURNAL OF CARBOHYDRATE CHEMISTRY
Vol. 22, No. 1, pp. 57–71, 2003

D-Glucose as a Regioselectively Addressable Scaffold for Combinatorial Chemistry on Solid Phase

Francesco Peri,[1,*] Francesco Nicotra,[1,*] Colin P. Leslie,[2] Fabrizio Micheli,[2] Pierfausto Seneci,[2] and Carla Marchioro[2]

[1]Department of Biotechnology and Biosciences, University of Milano–Bicocca, Piazza Della Scienza,
[2]GlaxoSmithKline SpA, Medicines Research Centre, Verona, Italy

ABSTRACT

D-Glucose derivatives bearing an anomeric thiophenyl group and orthogonally protections on secondary hydroxyl groups were linked to solid supports (PS/DV polymer, tentagel resin) through an ester bond on C-6. It was investigated the possibility to remove orthogonally protecting groups and functionalize selectively the free hydroxyls groups and the anomeric carbon of sugars in solid phase.

Key Words: Combinatorial chemistry; Sugars; Solid phase; Scaffolds.

INTRODUCTION

D-Glucose is a readily available, chiral and highly functionalized compound which displays, in the pyranose form, conformational rigidity and five different hydroxyl groups in a well defined spatial arrangement. These characteristics make glucose an attractive scaffold for designing primary screening libraries. Following this observation,

*Correspondence: Dr. Francesco Peri and Dr. Francesco Nicotra, Department of Biotechnology and Biosciences, University of Milano–Bicocca, Piazza Della Scienza, 2; I-20126, Italy; E-mail: francesco.peri@unimib.it and francesco.nicotra@unimib.it.

DOI: 10.1081/CAR-120019014
0732-8303 (Print); 1532-2327 (Online)

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

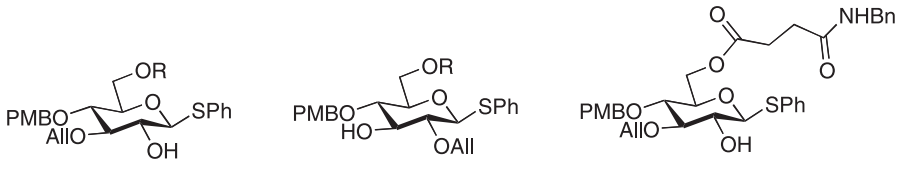
nonpeptidal peptidomimetics derived from glucose have been developed as efficient antagonists of the hormone somatostatin,[1,2] and as β-adrenergic and NK-1 antagonists.[3]

The decoration of monosaccharides by differential derivatization of the hydroxyl groups is particularly suitable for developing libraries by a combinatorial approach, once the protected sugar is linked to a polymer through the C-1 or C-6 hydroxyl groups.[4] The regioselective functionalization of the hydroxyl groups in solid phase must be accomplished by a sequence of selective deprotection-coupling steps.

To efficiently carry out such combinatorial syntheses, the choice of a convenient set of mutually orthogonal protecting groups, selectively removable without affecting the resin linker and resistant to the reaction conditions commonly employed during organic synthesis, is of crucial importance. Such requirements represent a real synthetic challenge, considering that only a fraction of the known hydroxyl protecting groups are compatible with solid phase chemistry. Several orthogonal protection schemes have been adapted from the solid phase strategies developed for the synthesis of oligosaccharides[4] and improved in order to maximize the number of diversity sites. Up to three orthogonal hydroxyl protecting groups for D-glucose[5] and five for D-galactose,[6] bound to resin through a thioglycoside anchor, have been employed. Orthogonally protected D-glucose was linked with four different glycosyl donors, using an efficient deprotection–glycosylation procedure in solution, affording a library of branched oligosaccharides.[7] Synthetic strategies compatible with solid phase chemistry have been validated in solution for D-glucose scaffolds presenting a high degree of diversity.[8] The problem of extensive orthogonalities has been partially circumvented by using aminoglucuronic acids.[9] The carboxylic group of the sugar can be exploited to link the solid support, and the amino group of the sugar allows an enlarged choice of orthogonal protecting groups.

The flexible strategy of glycal assembly for solid phase glycosidation developed by Danishefsky[10] and co-workers inspired the use of monosaccharide scaffolds with oxirane rings. An anhydrosugar with an oxirane ring was anchored to the polymer, and two sites of diversity were accessed on solid phase by epoxide-opening reactions.[11] Despite the remarkable progresses recently achieved in this field, the complete orthogonality between identical functional groups is a major problem in combinatorial syntheses and the efficient extension of solution protection/deprotection techniques to polymer-bound sugars still represents a frontier for the organic chemist.

In this context, we planned to develop a system in which β-D-glucopyranose platforms are linked to a polymer through an ester bond involving the OH-6 group, ortho-



1: R = H
1a: R = CO-Tentagel
1b: R = $COCH_2CH_2CONH$-PS/DV

2: **R** = H
2a: R = CO-Tentagel
2b: R = $COCH_2CH_2CONH$-PS/DV

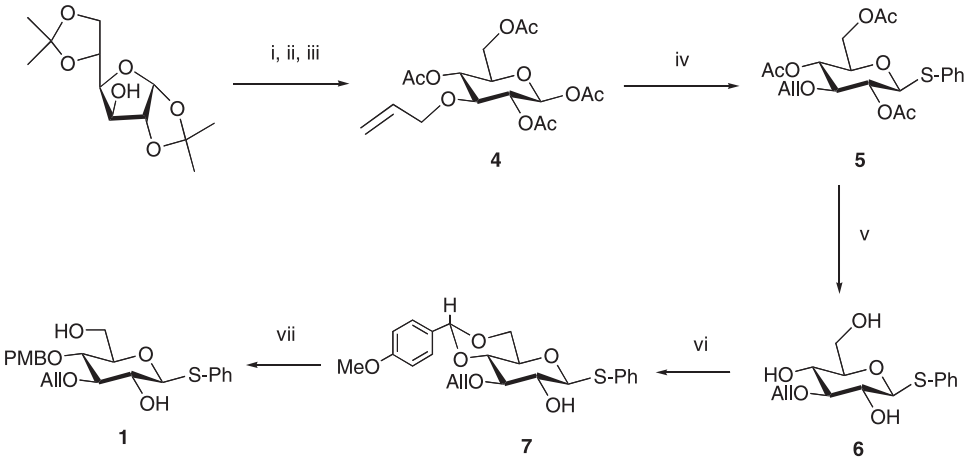
3

Figure 1. Thioglucosides **1**, **2** and **3** and their polymer-bound analogues.

gonally protected on the secondary hydroxyls and activated as thioglucosides at the anomeric position. We tested the efficiency of the orthogonal set chosen and of the functionalisation reactions on a model compound in solution, then we extended the reactivity study to the same scaffold bound to PEG and polystyrene/divinylbenzene resins.

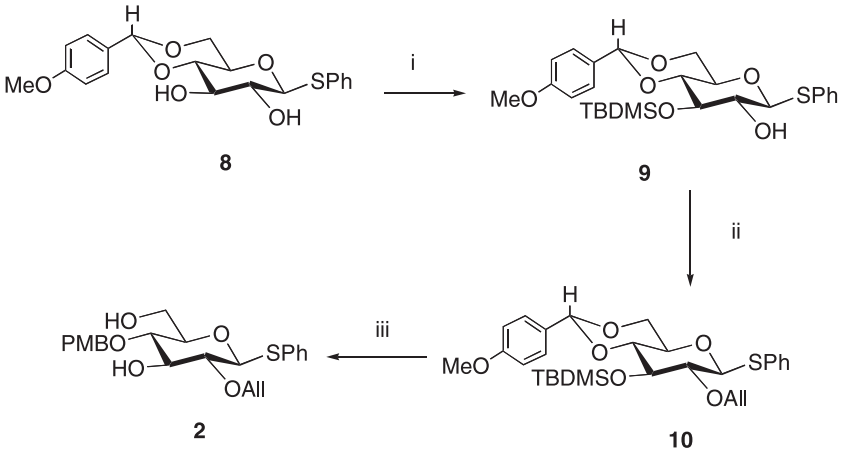
RESULTS AND DISCUSSION

Thioglucosides **1** and **2** were prepared, having the same set of orthogonal groups but with different regiochemistry (Figure 1). Both monosaccharides were bound to the Tentagel resin (**1a** and **2a**) through an ester linkage, and to the PS/DV polymer through a succinamide linkage (**1b** and **2b**). Compound **1** was functionalized with an *N*-benzylamidosuccinyl appendage at C-6, to give the model compound **3** which mimics the sugar-linker system of **1b** and **2b**. The hydroxyl protecting groups chosen for this study, the *p*-methoxybenzyl (PMB) and the allyl (All) group, can be removed, respectively, by oxidative cleavage (DDQ) and double bond isomerisation followed by acid hydrolysis of the enol ether. In addition to these two groups, a free hydroxyl group is present in both glucosides (at C-2 in **1** and C-3 in **2**) as a third functionalizable site. Finally, both thioglucosides can be activated as sulfoxides and a fourth group can be introduced at the anomeric position. We verified the orthogonality efficiency under the experimental conditions employed for deprotection and functionalisation of the four hydroxyl groups of the sugars (at C-1, C-2, C-3, C-4), and for anchoring/cleavage to/from solid supports through an ester linkage. We also compared the reactivity of model compound **3** in solution with that of compounds **1a** and **1b** on solid phase. Thioglucoside **1** was prepared according to the synthetic strategy shown in Scheme 1. 1,2,4,6-Tetra-*O*-acetyl-3-*O*-allyl-β-D-glucopyranose **4** was obtained from the commercially available 1,2,5,6-diisopropylidene-D-glucofuranose by allylation at C-3 (93%),

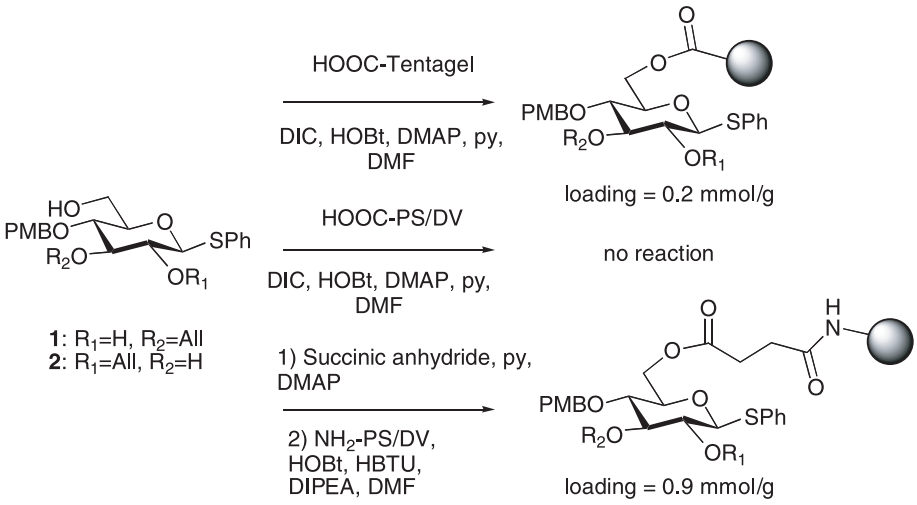


Scheme 1. i: Allyl bromide, NaH, DMF; ii: Amberlite IR-120 H^+, MeOH–H_2O; iii: Ac_2O, py, DMAP; iv: PhSH, BF_3–Et_2O, CH_2Cl_2; v: MeONa, MeOH; vi: Anisaldehyde dimethyl acetal, *p*-TSA, CH_3CN; vii: $LiAlH_4$–$AlCl_3$, CH_2Cl_2/Et_2O.

followed by acid hydrolysis of the acetonide groups (98%) and acetylation (98%).[12] Compound **4** was transformed into phenyl 2,4,6-tri-*O*-acetyl-3-*O*-allyl-1-thio-β-D-glucopyranoside (**5**) by BF_3-Et_2O catalysed reaction with thiophenol in dry CH_2Cl_2 (82%). Treatment of **5** with MeONa in dry MeOH afforded compound **6** (97%), which upon reaction with anisaldehyde dimethyl acetal in dry MeCN with a catalytic amount of *p*-TSA gave compound **7** (94%), in which both the C-4 and C-6 hydroxyl groups are protected as a *p*-methoxybenzylidene (PMB) acetal. Several attempts to protect the free C-2 hydroxyl group of compound **7** as ether, silyl ether or ester, employing different experimental conditions, were unsuccessful and indicated the very low reactivity of this hydroxyl group. As a consequence we decided to maintain this hydroxyl group unprotected in the subsequent solid-phase approach. The *p*-methoxybenzylidene acetal of **7** was finally reduced with $LiAlH_4-AlCl_3$ in dry CH_2Cl_2/Et_2O, to install regioselectively a PMB ether at C-4 and to liberate the primary hydroxyl group at C-6, yielding phenyl 3-*O*-allyl-4-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (**1**) (98% yield). Phenyl 2-*O*-allyl-4-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (**2**) was obtained using a similar synthetic pathway (Scheme 2). Phenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[13,14] was deacetylated (MeONa in MeOH, 97%) to furnish phenyl 1-thio-β-D-glucopyranoside, which was converted into its PMB acetal **8**[15] (90%). Reaction of **8** with *tert*-butyldimethylsilyl (TBDMS) chloride in the presence of imidazole resulted in a totally regioselective silylation at C-3 affording compound **9** in 94% yield. This result is consistent with the very low reactivity of the hydroxyl group at C-2 observed in derivative **7**. Compound **9** was then allylated to give compound **10** (70%), treatment of which with $LiAlH_4-AlCl_3$ in dry CH_2Cl_2/Et_2O led to regioselective reductive opening of the acetal and concomitant hydrolysis of the silyl ether to afford phenyl 2-*O*-allyl-4-*O*-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (**2**) (82%). In a first screening of the best resin-linker system to support compounds **1** and **2** for solid phase transformations, we excluded the possibility of linking the sugars to resins through an acid-labile bond, because acid conditions (due to the use of Lewis acid promoters) are

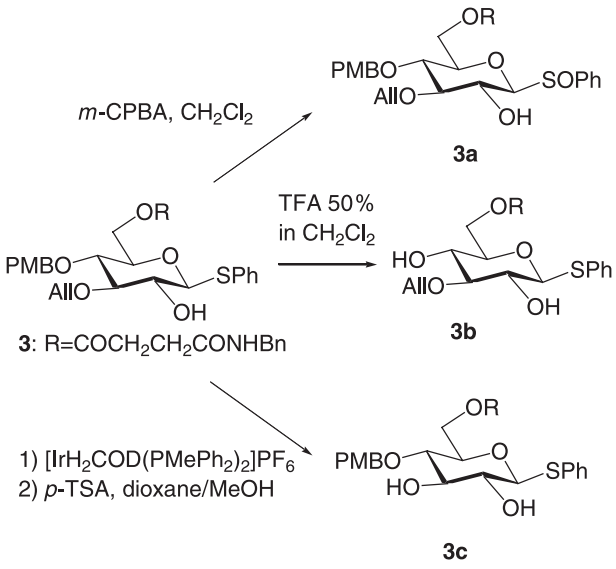


Scheme 2. i: TBDMS–Cl, Imidazole, CH_2Cl_2; ii: Allyl bromide, NaH, DMF; iii: $LiAlH_4-AlCl_3$, CH_2Cl_2/Et_2O.

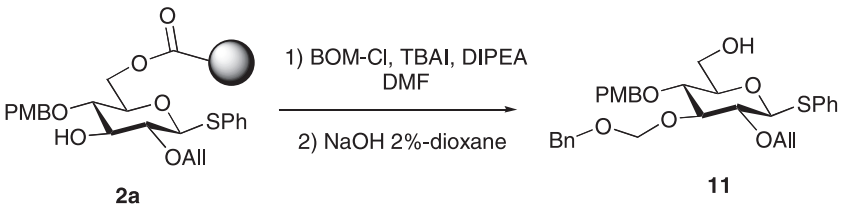


Scheme 3. Loading on PS/DV and Tentagel resins of thioglucosides **1** and **2**.

required in the most common methods for solid phase glycosylations.[4] Moreover, both allyl and PMB groups are acid-labile, but resistant to basic conditions. For this reason, we investigated the loading of substrates **1** and **2** onto carboxylic Tentagel and polystyrene-divinylbenzene resins through a base-labile ester linker. Compounds **1** and **2**, DIC, HOBt, DMAP and pyridine were reacted with carboxy-Tentagel (Novabiochem, 0.27 mmol/g) or carboxy-polystyrene (Novabiochem, 1.24 mmol/g) resins in dry DMF



Scheme 4. Orthogonal deprotection of secondary xydroxyl groups on model compound **3**.



Scheme 5. Functionalization as BOM ether of polymer-bound substrate **2a.**

under an argon atmosphere. A loading value of about 0.2 mmol/g for both **1** and **2** was found for Tentagel resin (calculated gravimetrically on crude sugars cleaved from resins with a mixture of 2% aqueous NaOH and dioxane), while a negligible amount of both sugars loaded onto polystyrene resin even when employing longer reaction times or repeating the loading procedure (Scheme 3). The very low reactivity of the carboxy-PS/DV resin with compounds **1** and **2** is probably due to the absence of a spacer between the reactive carboxylic group and the polymer bulk of the resin. To overcome this problem, compounds **1** and **2** were functionalised at C-6 with a succinate linker and then reacted with an amino-polystyrene resin (Novabiochem, 1.13 mmol/g) in the presence of HBTU, HOBt and DIPEA in dry DMF, thus yielding resins **1b** and **2b** with acceptable loading values (about 0.9 mmol/g). The low reactivity of free hydroxyl groups at C-2 or C-3 in **1** and **2**, respectively, ensured the selective attachment of sugar to polymer through the C-6 position. This was confirmed, in the case of the Tentagel resin derivatives, by the observation that MAS ^{1}H NMR spectra of solids **1a** and **2a** correspond to homogeneous C-6 linked sugars. Model compound **3** was submitted to orthogonal deprotection at positions C-4 (affording **3b**) and C-2 (affording **3c**) and activation of the anomeric position as sulfoxide (affording **3a**) as depicted in Scheme 4. The very low reactivity of the free hydroxyl group at C-2 was once more confirmed by the failure of **3** to undergo acetylation (Ac_2O, pyridine and DMAP, rt) or carbamate formation (phenyl isocyanate, DMAP, rt). Etherification at C-2 by using benzyl bromide and NaH turned out to be incompatible with the succinate linker, the ester bond being hydrolyzed affording a mixture of mono- and dialkylated products. Unfortunately, the ester bond of **3** was also cleaved when benzyl trichloroacetimidate was used as alkylating agent in the presence of Lewis acids TMSOTf or BF_3-Et_2O. In this case a complex mixture of products was formed. The oxidation of **3** to the sulfoxide **3a** was carried out in good yield using *m*-CPBA in dry CH_2Cl_2 (82% yield). As an example of solid phase derivatization on Tentagel resin, compound **2a** was functionalised at C-3 as its benzyloxymethyl (BOM) ether (Scheme 5). Resin **2a** was reacted with BOM chloride, TBAI and DIPEA in dry DMF, giving, after cleavage from the resin (2% NaOH/dioxane), compound **11** in 98% yield. Alkyloxy halides are more reactive than the corresponding alkyl halides and alkylation proceeds on the free OH in the presence of weak bases (such as DIPEA). Under these conditions it is possible to form the ether at C-3 avoiding the hydrolysis of the ester linker. The regioisomer **1a** did not react under the same reaction conditions, thus indicating that the reactivity of the free hydroxyl group at C-2 in this compound is lower than that of C-3 hydroxyl group in **2a**. The experimental data collected on compounds **1a** and **2a** bound to Tentagel resin, suggested

exploring the possibility of functionalizing **1b** and **2b** on solid phase as BOM ethers. Only **2b** reacted forming the BOM ether at C-2 in high yield (92% yield), while **1b** did not react under the same conditions, mirroring the results obtained with Tentagel-bound glucosides **1a** and **2a**.

CONCLUSIONS

In summary we reported the efficient loading of two phenyl thioglucosides, protected with the same set of orthogonal groups, onto Tentagel and PS/DV resins. The base-labile ester linker, used to anchor the thioglucosides to the resin through the C-6 position, allowed the use of acidic conditions for hydroxyl group deprotection. *p*-Methoxybenzyl and allyl protecting groups were found to be completely orthogonal, and the derivatization of the free hydroxyl groups of the sugars via alkoxymethyl ethers was carried out on solid phase with good yields. Despite the elevated number of known hydroxyl protecting groups, the development of polymer-bound sugars presenting three or four really independent functionalisation sites, is still a challenging task. Both glucosides **1** and **2**, were planned to have four orthogonal sites once linked to a polymer through C-6. The deprotection–functionalization experiments showed that sugar **1** in polymer-bound **1a** and **1b** presents three effective orthogonal sites including the anomeric position. Glucoside **2**, in derivatives **2a** and **2b**, was first derivatized at C-3 as a BOM ether. The C-2 and C-4 positions offer two other orthogonal sites, so that including the anomeric C-1, compound **2** presents four diversity sites on solid phase.

The reactivity of the anomeric positions of **1** and **2** on solid phase and the development of libraries based on these scaffolds, are currently being investigated and will be reported in due course.

EXPERIMENTAL

General procedures. All solvents were dried over molecular sieves (Fluka), for at least 24 h prior to use. Resins for solid phase synthesis were purchased from Novabiochem (Laufelfingen, CH). Thin-layer chromatography (TLC) was performed on Silica Gel 60 F_{254} plates (Merck) with detection with UV light when possible, or charring with a solution containing conc. H_2SO_4/MeOH/H_2O in a ratio of 5/45/45. Flash column chromatography was performed on silica gel 230–400 mesh (Merck). Usual workup refers to dilution with an organic solvent, washing with water to neutrality (pH test paper), drying with Na_2SO_4, filtration, and evaporation of solvent under reduced pressure. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 (400 MHz for ^{1}H and 100.62 MHz for ^{13}C) and Bruker AC300 (300 MHz for ^{1}H and 75.47 MHz for ^{13}C) spectrometers, using TMS as the internal standard. Aromatic carbons are omitted in the description of ^{13}C spectra. $[\alpha]_D$ values were measured at 20°C on a Perkin Elmer 241 digital polarimeter and are given in units of 10^{-1} deg cm^2 g^{-1}. Mass spectra were recorded on a MALDI 2 Kompakt Kratos instrument, using gentisic acid (DHB) as matrix. Elemental analyses were performed with a Perkin–Elmer Series II Analyzer 2400.

Phenyl 2,4,6-Tri-*O*-acetyl-3-*O*-allyl-1-thio-β-D-glucopyranoside (5). To a solution of 1,2,4,6-tetra-*O*-acetyl-3-*O*-allyl-β-D-glucopyranose **4** (1 g, 2.58 mmol) in dry CH_2Cl_2 (20 mL), thiophenol (3.87 mmol, 394 μL) and BF_3-Et_2O (3.87 mmol, 483 μL) were added under an argon atmosphere. The reaction mixture was stirred for 12 h at rt (monitoring by TLC, AcOEt/petroleum ether 1:1). The crude product was then diluted with dichloromethane, and after usual workup purified by FC (AcOEt/petroleum ether 1:1), affording compound **5** as a white solid (0.96 g, 82% yield).

$[\alpha]_D^{25°}$ + 49.7 (*c* 1, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) 7.50–7.20 (m, 5H, H_{arom}), 5.75 (ddd, 1H, $J_{1'-2'}$ = 6.5 Hz, $J_{2'-3'cis}$ = 10.8 Hz, $J_{2'-3'trans}$ = 15.95 Hz, H-2′), 5.17 (bd, 1H, $J_{2'-3'trans}$ = 15.9 Hz, H-3′), 5.10 (bd, 1H, $J_{2'-3'cis}$ = 10.8 Hz, H-3′), 5.00 (t, 1H, $J_{1-2} = J_{2-3}$ = 9.6 Hz, H-2), 4.98 (t, 1H, $J_{3-4} = J_{4-5}$ = 9.3 Hz, H-4), 4.61 (d, 1H, J_{1-2} = 10.4 Hz, H-1), 4.20–4.00 (m, 4H, 2H-6 and 2H-1′), 3.59 (t, 1H, $J_{3-4} = J_{2-3}$ = 9.3 Hz, H-3), 3.58 (m, 1H, H5), 2.10–2.00 (3s, 9H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 171.2, 168.1, 167.9, 134.3, 117.2, 86.4, 81.5,76.3, 73.4, 71.6, 69.8, 62.9, 21.4, 21.3, 21.2. MS (MALDI-TOF): 439.2 (M + H), 478.6 (M + K).

Anal. Calcd for $C_{21}H_{26}O_8S$: C, 57.52; H, 5.98; S, 7.31. Found: C, 58.09; H, 5.77; S, 7.88.

Phenyl 3-*O*-Allyl-1-thio-β-D-glucopyranoside (6). To a vigorously stirred solution of compound **5** (3 g, 6.85 mmol) in dry MeOH (50 mL), a catalytic amount of metallic sodium was added under an argon atmosphere. After 12 h at rt hydrolysis of all acetates was complete as assessed by TLC (AcOEt/petroleum ether 4:6). Amberlite IR 120 H^+ was then added and stirring continued until the solution reached a neutral pH. The resin was then removed by filtering, the solvent evaporated, and pure compound **6** was recovered as a colourless oil (2.09 g, 98% yield). $[\alpha]_D^{25°}$ + 21.1 (*c* 0.8, MeOH).^{1}H NMR (300 MHz, d-MeOH): δ(ppm) 7.60–7.30 (m, 5H, H_{arom}), 5.94 (ddd, 1H, $J_{1'-2'}$ = 5.8 Hz, $J_{2'-3'cis}$ = 11.1 Hz, $J_{2'-3'trans}$ = 16.4 Hz, H-2′), 5.29 (bd, 1H, $J_{2'-3'trans}$ = 16.6 Hz, H-3′), 5.19 (bd, 1H, $J_{2'-3'cis}$ = 10.9 Hz, H-3′), 4.54 (d, 1H, J_{1-2} = 9.2 Hz, H-1), 4.46 (dd, 1H, $J_{1'a-2'}$ = 5.1 Hz, $J_{1'a-1'b}$ = 12.7 Hz, H-1′a), 4.24 (dd, 1H, $J_{1'b-2'}$ = 5.9 Hz, $J_{1'a-1'b}$ = 12.7 Hz, H-1′b), 3.93 (dd, 1H, J_{6a-5} = 3.6 Hz, J_{6a-6b} = 11.8 Hz, H6a), 3.78 (dd, 1H, J_{6b-5} = 6.9 Hz, J_{6a-6b} = 11.8 Hz, H6b), 3.52 (t, 1H, $J_{3-4} = J_{2-3}$ = 9.0 Hz, H-3), 3.42 (t, 1H, $J_{1-2} = J_{2-3}$ = 9.0 Hz, H-2), 3.41 (m, 1H, H5,), 3.35 (t, 1H, $J_{3-4} = J_{4-5}$ = 8.7 Hz, H-4). ^{13}C NMR (100 MHz, d-MeOH): δ(ppm) 139.6, 119.5, 92.2, 90.2, 84.8, 78.1, 76.6, 73.9, 65.6. MS (MALDI-TOF): 335.7 (M + Na), 351.6 (M + K).

Anal. Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45; S, 10.26. Found: C, 57.11; H, 6.78; S, 10.48.

Phenyl 3-*O*-Allyl-4,6-*p*-methoxybenzyliden-1-thio-β-D-glucopyranoside (7). To a stirred solution of compound **6** (3 g, 9.6 mmol) in dry MeCN (50 mL), anisaldehyde dimethyl acetal (14.4 mmol, 2.45 mL) and a catalytic amount of *p*-TSA were added under an argon atmosphere. The product precipitates immediately as a white solid from the dark red solution. The mixture was stirred 30 min at rt, then cooled to 0°C for 30 min to promote the crystallisation of the product.

Pure compound **7** was recovered as white needles by filtration of the crude. The mother liquors were concentrated and crystallization from cold acetonitrile was repeated to recover a second crop of the product (3.88 g in total, 94% yield). $[\alpha]_D^{25°}$ + 7.8 (*c* 1,

$CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ(ppm) 7.50–7.30 (m, 5H, H_{arom}), 6.88 (m, 4H, H_{arom}), 5.83 (ddd, 1H, $J_{1'-2'}$ = 6.4 Hz, $J_{2'-3'cis}$ = 10.7 Hz, $J_{2'-3'trans}$ = 17.1 Hz, H-2′), 5.49 (s, 1H, H_{PMB}), 5.28 (bd, 1H, $J_{2'-3'trans}$ = 17.1 Hz, H-3′), 5.19 (bd, 1H, $J_{2'-3'cis}$ = 10.7 Hz, H-3′), 4.63 (d, 1H, J_{1-2} = 9.6 Hz, H-1), 4.40 (dd, 1H, $J_{1'a-2'}$ = 6.2 Hz, $J_{1'a-1'b}$ = 12.7 Hz, H-1′a), 4.35 (dd, 1H, J_{4-5} = 4.7, J_{3-4} = 9.9 Hz, H-4), 4.25 (dd, 1H, $J_{1'b-2'}$ = 5.9 Hz, $J_{1'a-1'b}$ = 12.7 Hz, H-1′b), 3.80 (s, 3H, OCH_3), 3.75 (t, 1H, J_{3-4} = J_{2-3} = 9.9 Hz, H-3), 3.60–3.40 (m, 3H, H-2, H-5 and 2 H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 117.7, 113.8, 101.4, 88.7, 81.6, 81.3, 74.0, 72.4, 71.0, 68.8, 55.6. MS (MALDI-TOF): 454.3 (M + Na), 470.7 (M + K).

Anal. Calcd for $C_{15}H_{20}O_5S$: C, 57.67; H, 6.45; S, 10.26. Found: C, 57.11; H, 6.78; S, 10.48.

Phenyl 3-*O*-Allyl-4-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (1). To a solution of compound **7** (0.81 g, 1.89 mmol) in dry CH_2Cl_2/Et_2O (2:1, 15 mL), a 1 M solution of $LiAlH_4$ in THF (8.7 mL, 8.7 mmol) was added under an argon atmosphere and the mixture was refluxed for 4 h. After cooling the mixture to rt, $AlCl_3$ (1 g, 9.2 mmol) in dry Et_2O (10 mL) was added dropwise and the solution was then refluxed for a further 4 h. The crude was then diluted with AcOEt (50 mL) and, after standard workup, pure compound **1** was recovered as a white solid (0.80 g, 98% yield).

$[\alpha]_D^{25°}$(*c* 1, $CHCl_3$) + 28.8. ^1H NMR (300 MHz, $CDCl_3$): δ(ppm) 7.60–7.30 (m, 5H, H_{arom}), 6.85–7.35 (m, 4H, H_{arom}), 5.99 (ddd, 1H, $J_{1'-2'}$ = 5.6 Hz, $J_{2'-3'cis}$ = 10.0 Hz, $J_{2'-3'trans}$ = 16.7 Hz, H-2′), 5.31 (bd, 1H, $J_{2'-3'trans}$ = 16.7 Hz, H-3′), 5.19 (bd, 1H, $J_{2'-3'cis}$ = 10.0 Hz, H-3′), 4.66 (AB_q, 2H, CH_2–PMB), 4.52 (d, 1H, J_{1-2} = 8.2 Hz, H-1), 4.43–4.30 (m, 2H, H-1′a, H-1′b), 3.82 (bd, 1H, H-6a), 3.80 (s, 3H, OCH_3), 3.67 (bd, 1H, H-6b), 3.50–3.30 (m, 4H, H-2, H-3, H-4 and H-5). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 117.3, 114.1, 88.4, 85.7, 79.8, 77.0, 75.0, 74.5, 73.0, 62.5, 55.6. MS (MALDI-TOF): 455.3 (M + Na), 470.4 (M + K).

Anal. Calcd for $C_{23}H_{28}O_6S$: C, 63.87; H, 6.52; S, 7.41. Found: C, 64.01; H, 6.58; S, 7.48.

Phenyl 3-*O*-^{t}butyldimethylsilyl-4,6-*p*-methoxybenzylidene-1-thio-β-D-glucopyranoside (9). To a solution of compound **8** (1 g, 2.56 mmol) in dry CH_2Cl_2 (20 mL), TBDMS chloride (0.57 g, 3.84 mmol) and imidazole (0.35 g, 5.12 mmol) were added under an argon atmosphere and the mixture was refluxed for 24 h. After dilution with AcOEt (50 mL), the crude was submitted to standard work-up and purified by column FC (AcOEt/petroleum ether with 1% triethylamine), affording **9** as a colorless oil (1.2 g, 94%). $[\alpha]_D^{25°}$(*c* 1, $CHCl_3$) + 22.8. ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.60–7.20 (m, 5H, H_{arom}), 6.85 (m, 4H, H_{arom}), 5.46 (s, 1H, H_{PMB}), 4.64 (d, 1H, J_{1-2} = 9.8 Hz, H-1), 4.40 (dd, 1H, $J_{1'a-2'}$ = 6.2 Hz, $J_{1'a-1'b}$ = 12.7 Hz, H-1′a), 4.31 (dd, 1H, J_{4-5} = 4.7, J_{3-4} = 9.9 Hz, H-4), 4.25 (dd, 1H, $J_{1'b-2'}$ = 5.9 Hz, $J_{1'a-1'b}$ = 12.7 Hz, H-1′b), 3.80 (s, 3H, OCH_3), 3.75 (t, 1H, J_{3-4} = J_{2-3} = 9.9 Hz, H-3), 3.60–3.40 (m, 3H, H-2, H-5 and 2 H-6). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 113.6, 101.8, 89.1, 81.1, 76.3, 73.9, 71.1, 68.9, 55.6, 26.2. MS (MALDI-TOF): 527.6 (M + Na), 543.8 (M + K).

Anal. Calcd for $C_{26}H_{36}O_6SSi$: C, 61.87; H, 7.19; S, 6.35; Si, 5.56. Found: C, 61.91; H, 7.58; S, 6.48; Si, 5.32.

Phenyl 2-*O*-Allyl-3-*O*-*tert*-butyldimethylsilyl-4,6-*p*-methoxybenzyliden-1-thio-β-D-glucopyranoside (10). A vigorously stirred solution of compound **9** (500 mg, 1 mmol) in dry DMF (20 mL) was cooled to 0°C. Sodium hydride (80 mg of a 60% suspension in oil, 2 mmol) and allyl bromide (170 μL, 2 mmol) were added portionwise over 15 min, then the reaction mixture was allowed to warm to rt and stirred at this temperature for 2 hrs. Methanol was carefully added to the mixture to hydrolyze residual sodium hydride, and solvents were evaporated in vacuo. After usual work-up and column chromatography (AcOEt/petroleum ether 0.5:9.5, 1% triethylamine), compound **10** was recovered as a colorless oil (380 mg, 70%). $[\alpha]_D^{25°}$(*c* 1, $CHCl_3$) + 17.3. ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.40 (m, 5H, H_{arom}), 6.85 (m, 4H, H_{arom}), 5.98 (m, 1H, H-2′), 5.45 (s, 1H, H_{PMB}), 5.31 (dd, 1H, $J_{3'a-3'b}$ = 17.2 Hz, $J_{3'a-2'}$ = 1.5 Hz, H-3′a), 5.19 (dd, 1H, $J_{3'b-3'a}$ = 10.4 Hz, $J_{3'b-2'}$ = 1.4 Hz, H-3′b), 4.70 (d, 1H, J_{1-2} = 9.9 Hz, H-1), 4.39 (dd, 1H, $J_{1'a-1'b}$ = 11.4 Hz, $J_{1'a-2}$ = 5.7 Hz, H-1′a), 4.30 (m, 2H), 3.82 (s, 3H, OCH_3), 3.82 (m, 1H), 3.73 (t, 1 H, J = 10.3 Hz), 3.45 (m, 2H), 3.27 (t, 1H, J = 9.8 Hz), 0.85 (s, 9H, H_{tBu}), 0.22 (s, 1H, H_{Me}), 0.00 (s, 3H, H_{Me}). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 117.6, 113.6, 102.6, 88.9, 81.8, 81.5, 76.4, 75.0, 70.6, 68.9, 55.6, 26.2, − 3.7, − 4.0. MS (MALDI-TOF): 567.4 (M + Na), 583.6 (M + K).

Anal. Calcd for $C_{29}H_{40}O_6SSi$: C, 63.94; H, 7.40; S, 5.89; Si, 5.16. Found: C, 63.71; H, 7.38; S, 5.58; Si, 5.12.

Phenyl-2-*O*-allyl-4-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (2). Compound **10** (540 mg, 1 mmol), was reacted according to the same procedure used to transform **7** in **1**. After usual workup, pure compound **2** was recovered as a white solid (0.80 g, 98% yield). $[\alpha]_D^{25°}$(*c*.1, $CHCl_3$) + 34.2. ^{1}H NMR (300 MHz, $CDCl_3$): δ(ppm) 7.60–7.30 (m, 5H, H_{arom}), 6.85–7.35 (m, 4H, H_{arom}), 5.98 (ddd, 1H, $J_{1'-2'}$ = 5.8 Hz, $J_{2'-3'cis}$ = 10.8 Hz, $J_{2'-3'trans}$ = 17.7 Hz, H-2′), 5.31 (bd, 1H, $J_{2'-3'trans}$ = 17.7 Hz, H-3′a), 5.21 (bd, 1H, $J_{2'-3'cis}$ = 10.9 Hz, H-3′b), 4.70 (AB_q, 2H, CH_2–PMB), 4.62 (d, 1H, J_{1-2} = 9.7 Hz, H-1), 4.41 (dd, 1H, J = 11.7, 5.8 Hz, H-1′a), 4.23 (dd, 1H, J = 12.6, 5.8 Hz, H-1′b), 3.90–3.60 (m, 3H, H-6a, H-6b, H-3), 3.78 (s, 3H, OCH_3), 3.43 (t, 1H, H-4, J = 9.2 Hz), 3.35 (m, 1H, H-5), 3.22 (t, 1H, H-2, J = 9.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 118.0, 114.1, 87.3, 80.9, 79.3, 78.7, 77.1, 74.6, 74.4, 62.6, 55.6. MS (MALDI-TOF): 456.6 (M + Na + H), 472.4 (M + K + H).

Anal. Calcd for $C_{23}H_{28}O_6S$: C, 63.87; H, 6.52; S, 7.41. Found: C, 64.01; H, 6.58; S, 7.48.

Loading of 1 and 2 onto solid supports. The direct attachment of **1** and **2** to carboxy-polystyrene resin was carried out according to the following procedure. Tentagel carboxy resin (Novabiochem, 0.27 mmol/g, 0.4 g, 0.10 mmol) was allowed to swell by shaking for 30 min in CH_2Cl_2 (5 mL), then was shaken for 30 min in dry THF (5 mL) to remove moisture. Compound **1** (232 mg, 0.54 mmol), DIC (83 μL, 0.54 mmol), HOBt (4 mg, 0.02 mmol), DMAP (2.5 mg, 0.02 mmol) and pyridine (43 μL, 0.54 mmol) were dissolved under an argon atmosphere in dry DMF (4 mL) and the mixture was added to the resin. The suspension was shaken under an argon atmosphere for 72 h, then solvents and reactants were removed by filtration and the resin was washed with CH_2Cl_2 (5 mL, 30 min × 2), acetone (5 mL, 30 min × 2), MeOH (5 mL, 30 min × 2) and CH_2Cl_2 (5 mL, 30 min × 2) and finally dried in vacuo for 12 h.

In order to determine the loading, 200.5 mg of resin were suspended in dioxane (1 mL) and aqueous 2% NaOH (1.5 mL) and shaken for 24 h at rt. The solvents were filtered and the resin was washed with Et_2O (5 mL, 30 min × 2), water (5 mL, 30 min × 2) and Et_2O (5 mL, 30 min × 2) collecting all the effluents. HCl 0.1 N was added under stirring until pH 5 was reached. The product was extracted with AcOEt (3 × 10 mL). The organic phase was dried over sodium sulfate, filtered and the solvents evaporated in vacuo; 17.5 mg of pure **1** were recovered, corresponding to a loading of 0.2 mmol/g. Compound **2** was loaded using an identical procedure and gave similar loading values.

The loading of **1** and **2** to amino polystyrene HL resin was performed by reacting the sugars previously functionalised with a succinate linker on C-6 with resin. To a solution of sugar **1** (100 mg, 0.232 mmol) in dry CH_2Cl_2 (1.5 mL), succinic anhydride (46 mg, 0.46 mmol), dry pyridine (56 μL, 0.696 mmol) and DMAP (catalytic amount) were added under an argon atmosphere and the reaction mixture was cooled to 0°C. After 30 min at 0°C, EtOH (3 mL) was added and the reaction mixture was stirred for 15 min at rt to eliminate the excess anhydride. Then the solvents were evaporated and the product purified by FC (eluent: AcOEt/$CHCl_3$ 1:1). Pure C-6 succinate derivative was obtained as a white solid (104 mg, 85% yield).

To a solution of C-6 succinate derivative (232 mg, 0.44 mmol) in dry DMF (1.5 mL), HBTU (159 mg, 0.418 mmol), HOBt (65 mg, 0.44 mmol) and DIPEA (112 μL, 0.66 mmol) were added and the mixture was stirred at rt for 10 min. Then this solution was transferred into a solid phase reactor in which aminomethylated polystyrene HL resin (100 mg, 0.11 mmol) was previously swelled in dry CH_2Cl_2. The suspension was shaken at rt for 1 h, then the resin was drained and washed with DMF (2 mL, 30 min × 2), THF (2 mL, 30 min × 2) and CH_2Cl_2 (2 mL, 30 min × 2). In order to determine the loading gravimetrically the resin was suspended in dioxane (1 mL) and aqueous 2% NaOH (1.5 mL) and shaken overnight at rt. The mixture was filtered and the resin was washed with Et_2O (2 mL, 30 min × 2), water (2 mL, 30 min × 2) and Et_2O (2 mL, 30 min × 2) collecting all the effluents. HCl (0.1 N) was added under stirring until pH 5 was reached. The mixture was extracted with AcOEt (3 × 2 mL). Pure compound **1** was recovered (39 mg, corresponding to a loading of 0.9 mmol/g).

Phenyl 3-*O*-allyl-6-benzamidosuccinyl-4-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (3). Compound **1** was converted into the corresponding C-6 succinic ester derivative as described in the previous section. To a solution of C-6 succinic ester derivative (500 mg, 0.94 mmol) in dry DMF (10 mL), benzylamine (123 μL, 1.13 mmol), HBTU (430 mg, 1.13 mmol) and DIPEA (390 μL, 2.26 mmol) were added under an argon atmosphere and the reaction mixture was stirred at rt for 2 h.

After this time, the solvent was evaporated, the residue dissolved in AcOEt and the organic layer washed with water, aqueous HCl (0.1 N), aqueous $NaHCO_3$ and water. After usual work-up, the product was purified by FC (eluent: AcOEt/petroleum ether 7:3). Pure compound **3** was obtained as a colourless oil (553 mg, 95% yield). $[\alpha]_D^{25°}$(*c* 1, $CHCl_3$) + 12.7. ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.40–7.20 (m, 5 H, H_{arom}), 7.35–6.85 (4H, H_{arom}), 5.95 (m, 2H, H-2′, NH), 5.32 (dd, 1H, J = 17.0, 1.5 Hz, H-3′a), 5.19 (bd, 1H, J = 11.5 Hz, H-3′b), 4.63 (AB_q, 2H, CH_2–PMB), 4.45–4.30 (m, 6H, H-1, H-6a, 2 Ph–CH_2–NH, 2 H-1′), 4.19 (dd, 1H, J = 11.7, 5.3 Hz, H-6b), 3.78 (s, 3H, OCH_3), 3.50–3.30 (m, 4H, H-2, H-3, H-4, H-5), 2.65 (m, 2H, CO–CH_2), 2.45

(m, 2H, CO−CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 172.4, 171.1, 117.4, 114.1, 88.2, 85.8, 77.3, 76.7, 74.9, 74.5, 72.7, 63.6, 55.6, 40.0, 31.4, 30.0. MS (MALDI-TOF): 642.7 (M + Na), 658.7 (M + K).

3-*O*-Allyl-6-benzamidosuccinyl-4-*p*-methoxybenzyl-β-D-glucopyranosyl sulfoxide (3a). To a solution of compound **3** (500 mg, 0.81 mmol) in dry CH_2Cl_2 (5 mL) cooled at − 78°C, *m*-CPBA (123 μL, 1.13 mmol) dissolved in dry CH_2Cl_2 (5 mL) was added and the mixture was stirred at this temperature, and TLC (AcOEt/petroleum ether, 6:4) was used to monitor the reaction. Upon completion, a saturated aqueous solution of $FeSO_4$ (20 mL) was added, the organic layer was diluted with CH_2Cl_2 (10 mL) and the biphasic mixture vigorously stirred at rt for 10 min. After usual workup, the product was purified by FC (eluent: AcOEt/petroleum ether 7:3). Pure compound **3a** was obtained as a mixture of diastereomers **3a′** and **3a″** in almost equimolar amounts (colourless oil, 343 mg, 82% yield). **3a′**: $[\alpha]_D^{25^\circ}$(*c* 0.1, $CHCl_3$) + 35.5. ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.0−7.0 (m, 14 H, H_{arom}), 6.12 (bt, 1H, NH), 6.01 (m, 1H, H-2′), 5.33 (dd, 1H, J = 17.1, 1.5 Hz, H-3′a), 5.20 (dd, 1H, J = 10.4, 1.2 Hz, H-3′b), 4.63 (AB_q, 2H, CH_2−PMB), 4.55−4.40 (m, 3H, H-1′a, Ph−CH_2−NH), 4.34 (m, 2 H, H-6a and H-1′b), 4.20 (t, 1H, J_{1-2} = 9.5 Hz, H-2), 4.12 (dd, 1H, J_{6a-6b} = 11.9 Hz, J_{5-6b} = 5.4 Hz, H-6b), 3.95 (d, 1H, J = 9.5 Hz, H-1), 3.79 (s, 3H, OCH_3), 3.49 (t, 1H, J = 8.6 Hz, H-3), 3.41 (t, 1H, J = 8.6 Hz, H-4), 3.37 (m, 1H, H-5), 2.69 (m, 2H, $COCH_2$), 2.52 (m, 2H, $COCH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 172.5, 171.3, 117.3, 114.1, 93.0, 85.3, 77.7, 75.7, 75.1, 74.7, 73.9, 63.1, 55.6, 44.1, 31.3, 29.8. MS (MALDI-TOF): 661.2 (M + Na), 677.4 (M + K). (M + K).

Anal. Calcd for $C_{34}H_{39}NO_9S$: C, 64.03; H, 6.16; S, 5.03. Found: C, 64.09; H, 6.77; S, 4.98.

3a″: $[\alpha]_D^{25^\circ}$(*c* 0.1, $CHCl_3$) + 25.6. ^{1}H NMR (400 MHz, $CDCl_3$): δ(ppm) 8.0−7.0 (m, 14 H, H_{arom}), 6.08 (bt, 1H, NH), 5.97 (m, 1H, H-2′), 5.32 (dd, 1H, J = 17.2, 1.4 Hz, H-3′a), 5.20 (dd, 1H, J = 10.5, 1.4 Hz, H-3′b), 4.59 (AB_q, 2H, CH_2−PMB), 4.50−4.40 (m, 3H, Ph−CH_2−NH, H-1′a), 4.30 (m, 2 H, H-6a, H-1′b), 4.09 (dd, 1H, J_{6a-6b} = 11.9 Hz, J_{5-6b} = 4.8 Hz, H-6b), 3.83 (t, 1H, J = 8.7 Hz, H-2), 3.79 (m, 4H, H-1 and OCH_3), 3.53 (t, 1H, J = 8.8 Hz, H-3), 3.45 (m, 1H, H-5), 3.18 (t, 1H, J = 9.4 Hz, H-4), 2.59 (m, 2H, $COCH_2$), 2.48 (m, 2H, $COCH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 172.4, 171.1, 117.5, 114.1, 88.4, 85.7, 77.9, 75.6, 75.0, 74.8, 71.01, 62.7, 55.6, 44.1, 31.3, 29.7. MS (MALDI-TOF): 661.5 (M + Na), 677.4 (M + K).

Anal. Calcd for $C_{31}H_{35}NO_8S$: C, 64.01; H, 6.06; S, 5.51. Found: C, 64.18; H, 6.08; S, 5.53.

Phenyl 3-*O*-allyl-6-benzamidosuccinyl-1-thio-β-D-glucopyranoside (3b). A solution of compound **3** (100 mg, 0.16 mmol) in TFA/CH_2Cl_2 (1:1) was stirred 1 h at rt until the hydrolysis was complete. Solvents were evaporated and crude purified by flash chromatography (AcOEt/petroleum ether, 4:6). Pure compound **3b** was recovered as a colorless oil (73.6 mg, 92% yield). $[\alpha]_D^{25^\circ}$(*c* 0.1, $CHCl_3$) − 18.5. ^{1}H-NMR (400 MHz, $CDCl_3$): δ(ppm) 7.5−7.2 (m, 14 H, H_{arom}), 6.20 (bt, 1H, NH), 5.95 (m, 1H, H-2′), 5.35 (dd, 1H, J = 17.5, 1.3 Hz, H-3′a), 5.15 (dd, 1H, J = 10.7, 1.6 Hz, H-3′b), 4.45 (AB_q, 2H, Ph−CH_2−NH), 4.40−4.20 (m, 3H, H-1′a, H-1, 2 H-6), 4.10 (m, 1H,

H1′b), 3.50 (m, 2H, H-2 and H-4), 3.39 (t, 1H, J = 9.0 Hz, H-3), 3.35 (m, 1H, H-5), 2.80 (bs, 1H, OH), 2.70 (m, 2H, $COCH_2$), 2.50 (m, 2H, $COCH_2$). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 173.1, 171.5, 117.6, 88.5, 85.0, 77.9, 74.2, 72.4, 69.7, 63.9, 44.1, 31.3, 30.1, 29.9. MS (MALDI-TOF): 524.5 (M + Na), 540.6 (M + K).

Anal. Calcd for $C_{26}H_{31}NO_7S$: C, 62.26; H, 6.23; S, 6.39. Found: C, 62.29; H, 6.34; S, 6.23.

Phenyl 6-benzamidosuccinyl-4-*p*-methoxybenzyl-1-thio-β-D-glucopyranoside (3c). To a solution of **3** (100 mg, 0.16 mmol) in dry THF (5 mL), degassed with several vacuum/argon cycles, $Ir[COD(PPh_2Me_2)_2]PF_6$ was added in catalytic amount and the solution turned to a light red color. Then the suspension was treated with cycles of vacuum/hydrogen and turned to a pale yellow color, indicating the formation of $IrH_2[COD(PPh_2Me_2)_2]PF_6$. The suspension was then stirred for 24 h at rt. After this time, *p*-TsOH (catalytic) dissolved in MeOH/dioxane (1:9, 5 mL), was added and the solution was stirred 24 h at rt. Solvents were evaporated and crude purified by flash chromatography (AcOEt/petroleum ether, 3:7). Pure compound **3c** was recovered as a colorless oil (60 mg, 65% yield). $[\alpha]_D^{25^\circ}$(*c* 0.1, $CHCl_3$) + 12.5. ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.40–7.20 (m, 5 H, H_{arom}), 7.30–6.90 (4H, H_{arom}), 5.97 (bs, 1H, NH), 4.65 (AB_q, 2H, CH_2–PMB), 4.50–4.35 (m, 5H, H-6a, 2 Ph–CH_2–NH, 2 H-1′), 4.23 (dd, 1H, J = 11.4, 4.7 Hz, H-6b), 3.78 (m, 4H, H-1 and OCH_3), 3.53 (t, 1H, J = 8.7 Hz, H-2), 3.30 (m, 3H, H-3, H-4, H-5), 2.74 (m, 2H, CO–CH_2), 2.51 (m, 2H, CO–CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ(ppm) 172.4, 171.1, 117.4, 87.11, 84.5, 79.3, 77.4, 75.6, 74.5, 72.7, 63.6, 55.6, 40.0, 30.7, 29.4. MS (MALDI-TOF): 604.7 (M + Na), 620.5 (M + K).

Anal. Calcd for $C_{31}H_{35}NO_8S$: C, 64.01; H, 6.06; N, 2.41; S, 5.51. Found: C, 64.29; H, 6.04; S, 5.23.

Phenyl 3-*O*-allyl-4-*p*-methoxybenzyl-3-benzyloxymethyl-1-thio-β-D-glucopyranoside (11). To a suspension of Tentagel resins **2a** (0.15 mmol) in dry DMF (2 mL), benzyloxymethyl chloride (200 μL, 1.5 mmol, *CAUTION*: toxic, carcinogenic), DIPEA (384 μL, 2.25 mmol) and TBAI (110 mg, 0.30 mmol) were added under argon atmosphere and the mixture was shaken 4 h at rt. Resin was then drained, washed with CH_2Cl_2 (2 × 2 mL), THF (2 × 2 mL), CH_2Cl_2 (2 × 2 mL) and product cleaved by suspending the resin in dioxane (1 mL) and aqueous 2% NaOH (1.5 mL) and shaking overnight at rt. After usual washings of the resin and workup, crude was purified by flash chromatography (AcOEt/petroleum ether, 1:9) affording pure compound **11** as a colourless oil (82 mg, 98% yield). $[\alpha]_D^{25^\circ}$(*c* 0.1, $CHCl_3$) + 23.4. ^1H NMR (400 MHz, $CDCl_3$): δ(ppm) 7.30 (m, 10H, H_{arom}), 7.0 (AXq, 4H, H_{arom}), 5.99 (m, 1H, H-2′), 5.27 (dd, 1H, J = 15.8, 1.8 Hz, H-3′a), 5.17 (bd, 1H, J = 11.2 Hz, H-3′b), 5.03 (s, 1H, O–CH_2–O), 4.80–4.60 ($2AB_q$, 4H, CH_2–PMB and O–CH_2–Ph), 4.62 (d, 1H, J = 9.6 Hz, H-1), 4.40 (dd, 1H, J = 12.5, 5.8 Hz, H-1′a), 4.26 (dd, 1H, J = 11.7, 5.8 Hz, H-1′b), 3.82 (dd, 1H, J = 11.8, 2.8 Hz, H-6a), 3.79 (t, 1H, J = 8.8 Hz, H-3), 3.77 (s, 1H, OCH_3), 3.64 (dd, 1H, J = 11.9, 4.8 Hz, H-6b), 3.49 (t, 1H, J = 9.6 Hz), 3.35 (m, 1H, H-5), 3.32 (t, 1H, J = 9.1 Hz, H-2). MS (MALDI-TOF): 575.7 (M + Na), 591.2 (M + K).

Anal. Calcd for $C_{31}H_{36}O_7S$: C, 67.37; H, 6.57; S, 5.80. Found: C, 67.29; H, 6.54; S, 5.73.

ABBREVIATIONS

m-CPBA	*m*-chloroperbenzoic acid
DDQ	dichlorodicyanoquinone
DBMP	2,6-di-*tert*-butyl-4-methylpyridine
DIC	diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DMAP	*N,N*-dimethyl-4-aminopyridine
DMF	dimethylformamide
FC	flash chromatography
HBTU	*O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate
HOBt	*N*-hydroxybenzotriazole
NIS	*N*-iodosuccinimide
PMB	*p*-methoxybenzyl
PS/DV	polystyrene/divinylbenzene (resin)
TBDMS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
TIS	*tris*-isopropylsilane
p-TSA	*p*-toluenesulfonic acid
TMSOTf	trimethylsilyl trifluoromethanesulfonate

ACKNOWLEDGMENTS

We gratefully acknowledge Raffaella Rossini, Stefano Vignando and Ilaria Fossati for their contribution to the experimental work and GlaxoSmithKline and MIUR for financial support.

REFERENCES

1. Hirschmann, R.; Nicolau, K.C.; Pietranico, S.; Salvino, J.; Leathy, E.M.; Sprengler, P.A.; Furst, G.; Smith, A.B., III; Strader, C.D.; Cascieri, M.A.; Candelore, M.R. Nonpeptidal peptidomimetics with a β-D-glucose scaffolding. A partial somatostatin agonist bearing a close structural relationship to a potent, selective, substance P antagonist. J. Am. Chem. Soc. **1992**, *114*, 9217, 9218.
2. Hischmann, R.; Yao, W.; Cascieri, M.A.; Strader, C.D.; Maechler, L.; Cichy-Knight, M.A.; Hines, J., Jr.; van Rijn, R.D.; Sprengeler, P.A.; Smith, A.B., III. Synthesis of potent cyclic hexapeptide NK-1 antagonists. Use of a mini-library in transforming a peptidal somatostatin receptor ligand into an NK-1 receptor ligand via a polyvalent peptidomimetic. J. Med. Chem. **1996**, *39*, 2441–2448.
3. Hischmann, R.; Hines, J., Jr.; Cichy-Knight, M.A.; Van Rijn, R.D.; Sprengeler, P.A.; Spoors, P.G.; Sheakespeare, W.C.; Pietranico-Cole, S.; Barbosa, J.; Liu, J.; Yao, W.; Rohrer, S.; Smith, A.B., III. Modulation of receptor and receptor subtype affinities using diastereomeric and enantiomeric monosaccharide

scaffolds as a means to structural and biological diversity. J. Med. Chem. **1998**, *41*, 1382–1391.
4. Seeberger, P.H.; Haase, W.-C. Solid-phase oligosaccharide synthesis and combinatorial carbohydrate libraries. Chem. Rev. **2000**, *100*, 4349–4393.
5. Wunberg, T.; Kallus, C.; Opatz, T.; Henke, S.; Schmidt, W.; Kunz, H. Carbohydrates as multifunctional chiral scaffolds in combinatorial synthesis. Angew. Chem. Int. Ed. **1998**, *37*, 2503–2505.
6. Kallus, C.; Opatz, T.; Wunberg, T.; Schmidt, W.; Henke, S.; Kunz, H. Combinatorial solid-phase synthesis using D-galactose as a chiral five-dimension-diversity scaffold. Tetrahedron Lett. **1999**, *40*, 7783–7786.
7. Wong, C.-H.; Ye, X.-S.; Zhang, Z. Assembly of oligosaccharide libraries with a designed building block and an efficient orthogonal protection–deprotection strategy. J. Am. Chem. Soc. **1999**, *40*, 7783–7786.
8. Hirschmann, R.; Ducry, L.; Smith, A.B., III. Development of an efficient, regio- and stereoselective route to libraries based on the β-D-Glucose scaffold. J. Org. Chem. **2000**, *65*, 8307–8316.
9. Sofia, M.J.; Hunter, R.; Chan, T.V.; Vaughan, A.; Dulina, R.; Wang, H.; Gange, D. Carbohydrate-based small-molecule scaffolds for the construction of universal pharmacophore mapping libraries. J. Org. Chem. **1998**, *63*, 2802, 2803.
10. Danishefsky, S.J.; Bilodeau, M.T. Glycals in organic synthesis: the evolution of comprehensive strategies for the assembly of oligosaccharides and glycoconjugates of biological consequence. Angew. Chem. Int. Ed. **1996**, *35* (13, 14), 1380–1419.
11. Wendeborn, S.; De Mesmaeker, A.; Brill, W.K.D.; Berteina, S. Synthesis of diverse and complex molecules on the solid phase. Acc. Chem. Res. **2000**, *33* (4), 215–224.
12. Takeo, K.; Nakaji, T.; Shinmitsu, K. Synthesis of lycotetraose. Carbohydr. Res. **1984**, *133*, 275–287.
13. Gridley, J.J.; Hacking, A.J.; Osborn, H.M.I.; Spackman, D.G. Regioselective lipase-catalysed acylation of 4,6-*O*-benzylidene-β-D-pyranoside derivatives displaying a range of anomeric substituents. Synlett **1997**, *12*, 1397–1399.
14. Gridley, J.J.; Hacking, A.J.; Osborn, H.M.I.; Spackman, D.G. Regioselective lipase-catalysed acylation of 4,6-*O*-benzylidene-α- and β-D-pyranoside derivatives displaying a range of anomeric substituents. Tetrahedron **1998**, *54* (49), 14925–14946.
15. Yeung, B.K.S.; Hill, D.C.; Janicka, M.; Petillo, P.A. Synthesis of two hyaluronan trisaccharides. Org. Lett. **2000**, *2* (9), 1279–1282.

Received May 9, 2002
Accepted December 3, 2002