A New Polymer Support Silylene Linking Method for Hindered Hydroxyl-Bearing Systems

Kenneth A. Savin,[†] Jonathan C. G. Woo,[†] and Samuel J. Danishefsky*[,†,‡]

Laboratory for Bioorganic Chemistry, Sloan-Kettering Institute for Cancer Research, 1275 York Avenue, New York, New York 10021, and Department of Chemistry, Columbia University, Havemeyer Hall, New York, New York 10027

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In 1993 we described a new strategy for the synthesis of oligosaccharides on solid support.[1] The scheme called for fashioning the first covalent attachment to the solid phase through a silicon−oxygen bond at the nonreducing end of the sugar. The polymer-bound silyl chloride was synthesized from polystyrene. The carbohydrate glycosyl "donor" entity would be on the support. The oligomer would grow through reiterative glycosylation reactions at its reducing end. Obviously, the success of the method is significantly dependent on the ability to load the monomer through the silylation reaction, and on the robustness of the silyl ether linkage during the coupling events. Significant improvement in the stability factor was achieved through the use of a diisopropyl linker in place of the previously used diphenylsilyl arrangement. Through this modification, the solid-phase method has been adapted to an increasing number of glycosylation protocols. Among the total syntheses which have been accomplished through our methodology were the Lewis Y determinant[2] and the Lewis B determinant (as a hexasaccharide).[3] Moreover, solid-state methodology has been adapted to the synthesis of a network for β-1,4 linkages.[4] The need for the chemistry we describe in this publication arose from recognition of limitations in the first silylation event which serves to "load" the polymer. We found efficiencies were poor when we attempted to conduct the loading at positions which bear relatively hindered hydroxyl centers.

To deal with this problem, we substantially modified the existing technology.[1−5] We have developed a general method where even sterically encumbered alcohols can be attached to a solid support with little or no prior manipulation of a commercially available polymer.[6] The process requires inexpensive materials, and the linker is compatible with a variety of reaction conditions. Furthermore, as part of our studies directed toward the automation of glycal-based carbohydrate synthesis, the linker can, if necessary, be cleaved quickly, without damaging the original polymer support. This capability allows, in principle, for facile recycling of the polymer support for further use (vide infra).

The approach described here utilizes a two-stage linking procedure. The core of our modified logic takes advantage of the enhanced reactivity of a dialkyldihalosilane relative to its monohalogenated counterpart.[7] This differential in reactivity allows for a single linkage of more sterically demanding systems in the first stage, while discouraging 2-fold silylation (see **1** → **2**). With this subgoal accomplished, a more reactive nucleophilic site, such as a sterically unhindered primary alcohol, even if polymer bound, can join to the less active remaining silylating site. The commercially available hydroxymethyl-modified Merrifield or Wang resins[6] performed well in the second stage silylation which constitutes the loading step.

An example of the working of this method starts with 3,6-dibenzyl glucal.[8] The 4-position, being sterically shielded, is relatively unreactive. However, exposure of **1** to the action of dichlorodiisopropylsilane in methylene chloride containing 5 equiv of imidazole led to intermediate **2**. An attractive feature of the method is that **2** is not formally isolated and purified. Rather, this product was exposed to the swelled benzyl hydroxy polymer **3**[6] in CH_2Cl_2 for 20 h, thereby producing the linked glycal, **4**. The unreacted sites on **3** were capped by reversing the order of reagent addition (imidazole and diisopropyldichlorosilane are added to the polymer followed by methanol). The new loading method was applied to a variety of other glycals bearing hindered free alcohols, including those which are sterically demanding and showed similarly good results (see Experimental Section) (Scheme 1).

To test the range of reaction conditions to which this type of polymer-bound system could be exposed, we focused on one of the most labile systems **8**, where the polymer is linked through the primary 6-position of a galactal cyclic carbonate. We set as our goal the synthesis of the known glycopeptide **16**.[9]

Linked galactal **8** was exposed to the action of dimethyldioxirane (Scheme 2). Subsequent treatment of the β-epoxide with 6-*O*-TIPS-glucal **9** provided the linked disaccharide **10**.[1c] Acetylation of the diol was followed by addition with iodonium bis-*sym*-collidine perchlorate and anthracenesulfonamide to afford the presumed iodosulfonamide (**11**). Treatment of intermediate **11** with tetra-*n*-butylamonium azide was followed by acetylation of the sulfonamide group (see compound **12**). At this stage, the system was well disposed for cleavage of the sulfonamide

[†] Sloan-Kettering Institute for Cancer Research.
[‡] Columbia University.

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(6) The hydroxy-modified Merrifield and Wang resins (hydroxymethyl resin) were purchased from Bachem Bioscience Inc. and used without further manipulation.

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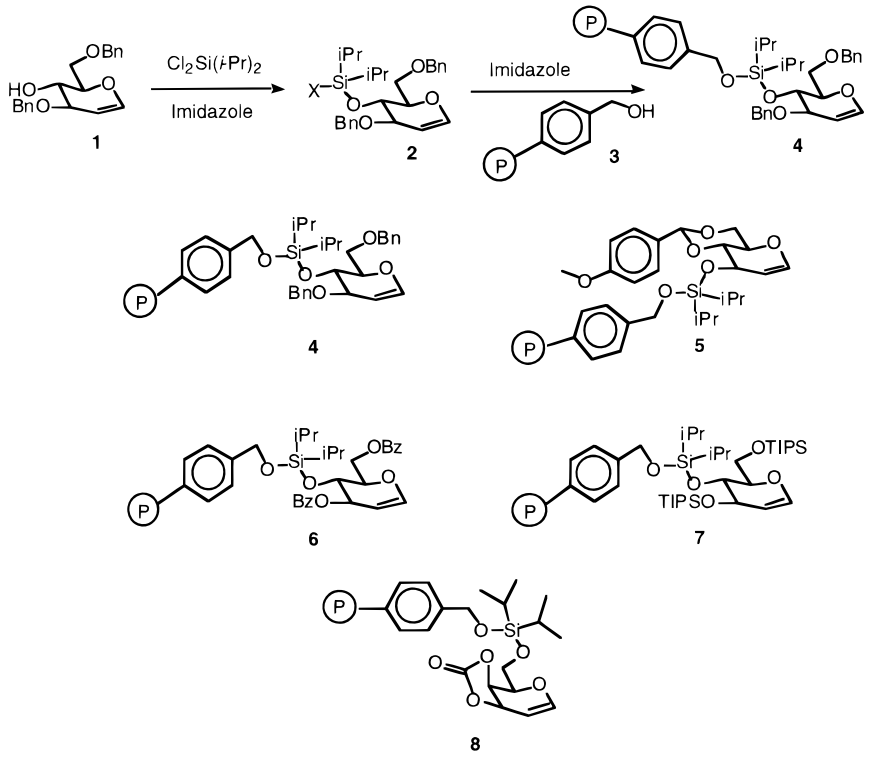
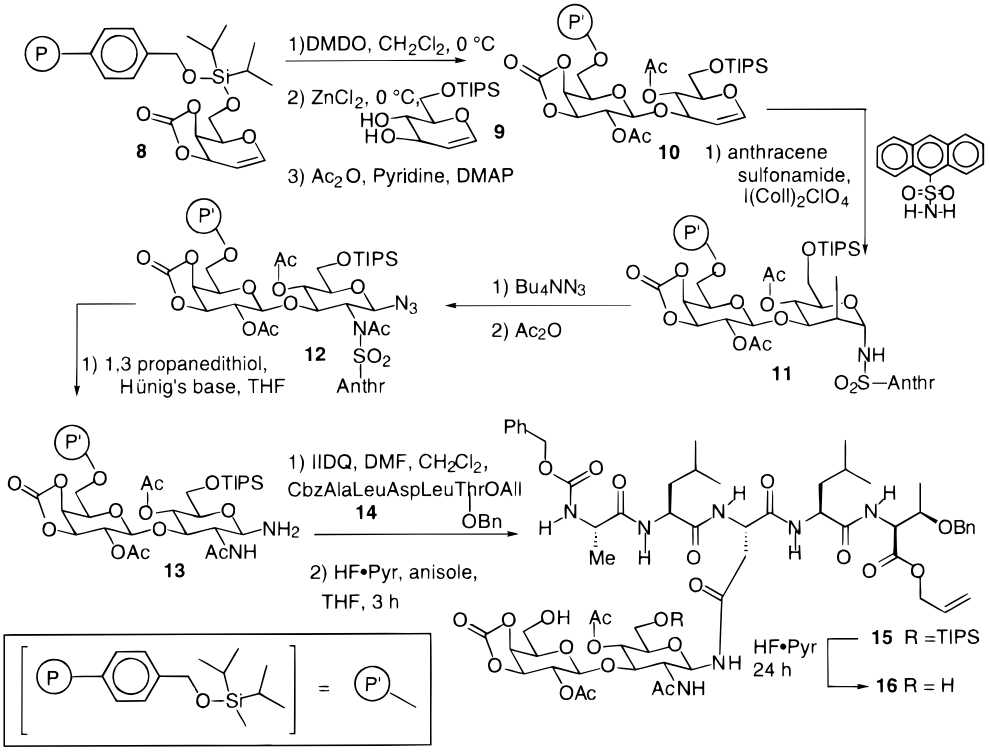
Scheme 1



Scheme 2



protecting group. In the event, treatment of polymer bound **12** resulted, as shown, in both the exposure of the *N*-acetyl function and also in reduction of the anomeric azide to the amine (see **13**). Reaction of **13** with a solution of the pentapetide **14** and 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (IIDQ)[10] in DMF and methylene chloride gave the linked disaccharide pentapeptide which was readily disengaged from the support via HF·Pyr and anisole[11] in THF at 0 °C for 3 h.[9] With the 6-*O*-TIPS-protected glycopeptide **15** in hand, it was necessary to reveal the other primary hydroxyl group. Indeed, removal of the TIPS group, again utilizing HF·Pyr at room temperature for 24 h, allowed access to the glycopeptide

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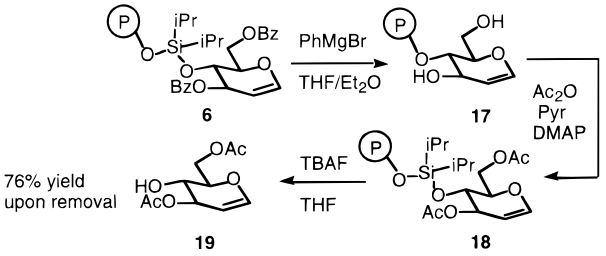
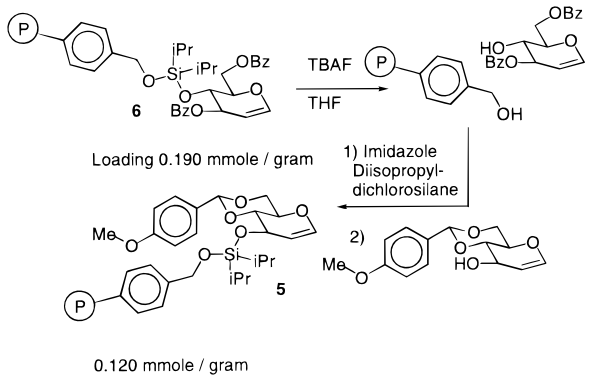
Scheme 3



Scheme 4



16 in 44% overall yield from the loaded galactal carbonate **8**. This compound was identical both spectroscopically and chromatographically with material previously prepared through the original linkage strategy using a polystyrene resin (see Experimental Section).

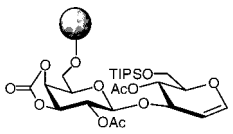
The chemical properties of the new polymer-bound constructs were assessed. The transformation of **6** to **19** demonstrates that de-benzoylation can be achieved through the agency of phenylmagnesium bromide—without cleavage of the glycal from the support. After gaining access to both flanking hydroxyls (Scheme 3), we further manipulated the polymer-bound substrate. Exhaustive acetylation and cleavage from the support via TBAF led to unbound diacetate **19** in greater than 75% yield from loaded **6**. The system was readily cleaved using TBAF at room temperature, in only a few minutes. This capability allows for ready access to material on the polymer and easy evaluation of reaction progress (Scheme 4). Further, use of the recovered polymer allowed for a modest loading of a second glycal, thereby demonstrating that the solid support can be recovered. We continue to investigate the limitations and extensions of this new polymer support linker and will report our results in due course.

Experimental Section

Synthesis of Polymer-Bound Glucal (General Procedure). 6. Into a 25 mL round-bottom flask with a stir bar was weighed the imidazole (2.21 g, 32.45 mmol), and to this was added 10 mL of CH_2Cl_2. To the imidazole solution was added diisopropyldichlorosilane ($DIPSiCl_2$) (1.20 g, 1.18 mL, 6.49 mmol) dropwise, and this was stirred for 5 min before 3,6-dibenzoyl-D-glucal (2.3 g, 6.49 mmol) in 7 mL of methylene chloride was added dropwise via cannula. The mixture was stirred for 30 min at room temperature. To an oven-dried 100 mL polymer flask with a coarse filter was weighed 1.62 g of Wang resin (approximately 1.62 mmol). The polymer was diluted with 2 mL of dry CH_2Cl_2 and allowed to swell. The mixture of glucal, imidazole, and $DIPSiCl_2$ was then added to the polymer dropwise via cannula and washed in with 2 mL of CH_2Cl_2. The mixture was stirred for 24 h and then filtered, washed with 1 × 20 mL of DMF, 3 × 20 mL of THF, and 3 × 20 mL of CH_2Cl_2, and dried in vacuo to provide a faintly yellow polymer. The unreacted polymer sites were then capped by exposing the polymer to imidazole (2.21 g, 32.45 mmol) and $DIPSiCl_2$ (1.20 g, 1.18 mL, 6.49 mmol) in 20 mL of CH_2Cl_2 for 24 h followed by methanol (0.291 mg, 368 μL, 9.09 mmol). The mixture was then stirred for 48 h. This material was washed as described above to yield 2.28 g of faintly yellow polymer **6**.

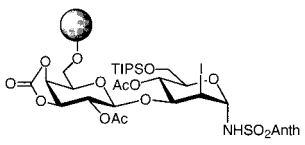
Polymer-Supported Synthesis of Glyco Pentapeptide 16. To 2.2 g (approximately 0.6 mmol) of polymer-loaded 3,4-galactal carbonate **8** (prepared as above) in a 100 mL polymer flask was added 20 mL of methylene chloride, and this was cooled to 0 °C. Dimethyldioxirane (25 mL of a 0.6 M solution in acetone, 15.0 mmol) was added dropwise via cannula stirred for 1 h at 0 °C, and then the liquid was filtered and the process repeated. The polymer was then washed with 20 mL of CH_2Cl_2, 20 mL of a 50/50 mixture of CH_2Cl_2:THF, and once with THF (20 mL). The polymer was then exposed to high vacuum for 18 h. To the yellow polymer was then added 15 mL of THF, the solution was cooled to 0 °C, and the 6-*O*-TIPS glucal was then added dropwise as a solution in 5 mL of THF via cannula and washed in with 2 mL of THF. To this mixture was added $ZnCl_2$ (4 mL of a 1.0 M solution in Et_2O, 4.0 mmol), and this was allowed to stir and come to room temperature over the next 28 h. The liquid was then filtered away, and the polymer was washed with 2 × 20 mL of THF, 1 × 20 mL of a 50/50 mixture of CH_2Cl_2:THF (20 mL) ,and 1 × 20 mL of CH_2Cl_2 and was then exposed to high vacuum for 18 h, providing 2.4 g of a faintly yellow polymer (**8a**).

10. To a mixture of the polymer-supported disaccharide **8a** (750.0 mg) swollen in 15 mL of CH_2Cl_2 was added Ac_2O (1 mL) followed by pyridine (2 mL). After 36 h, the reaction was filtered and washed with THF (3 × 10 mL) and CH_2Cl_2 (3 × 10 mL) and then dried under vacuum to give 930.0 mg of polymer-bound diacetate **10**: FTIR (KBr pellet) 1820, 1761, 1647, 1370 cm^{-1}.



10

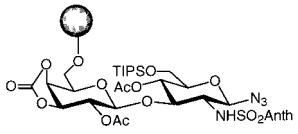
11. The anthracene sulfonamide (650 mg) and polymer-supported disaccharide glycal **10** (650 mg) were combined and dried under vacuum overnight. To a solution/suspension of this cooled (0 °C) mixture in 6.0 mL of THF was added the iodonium bis-*sym*-collidine perchlorate (1.12 g, 2.39 mmol) in one portion as a solution in 3 mL of THF via cannula, and this was washed in with 2 mL of THF. The reaction was protected from light, stirred at 0 °C for 6.5 h, and then quenched with a solution of ascorbic acid (5 g) in THF/water (22 mL/3 mL). The polymer was filtered and washed with THF/water (1:1, 3 × 20 mL), THF (3 × 20 mL), and CH_2Cl_2 (3 × 20 mL), and the resin was dried under reduced pressure to give 645 mg of resin **11**: FTIR (KBr pellet) 3482, 1820, 1752, 1370 cm^{-1}.



11

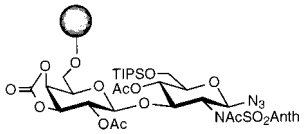
11a. To the polymer-supported iodosulfonamide **11** (645 mg) was added the tetrabutylammonium azide (690 mg, 2.907 mmol) in one portion in the glovebag under N_2. The resin was swollen in 18 mL of THF, and after 14 h, the reaction was filtered and washed with THF (3 × 20 mL) and CH_2Cl_2 (3 × 20 mL) and was dried under reduced pressure to give 580 mg of resin **11a** as an orange resin that emitted at a deep blue color when exposed to short-wave *hv* at 254 nm.

12. To the polymer-supported azide **11a** (580 mg) swollen in 7.0 mL of THF was added Ac_2O (1.184 g, 1.097 mL, 11.6 mmol) followed by DMAP (977.4 mg, 8.0 mmol) dissolved in 3 mL of



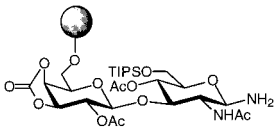
11a

THF and 400 μL of pyridine. The reaction was protected from light. After 24 h, the reaction was filtered and washed with THF (3 × 20 mL) and CH_2Cl_2 (3 × 20 mL) and the red orange resin was dried under reduced pressure to give 580 mg of resin **12** that emitted at a deep blue-green color when exposed to short-wave *hν* at 254 nm: FTIR (KBr pellet) 2116, 1820, 1752, 1370 cm^{-1}.



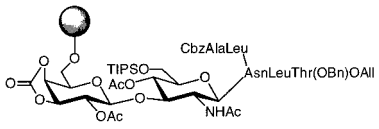
12

13. In a polymer synthesis flask, the polymer-bound disaccharide azide **12** (580 mg) was swollen in 10 mL of DMF. To this mixture (6.6 g, 6.0 mL, 60.99 mmol) were added 1,3-propanedithiol and 4.5 g (6.0 mL, 34.8 mmol) of diisopropylethylamine successively. The reaction lightened in color, and after 16 h the solvent was filtered, the resin was washed with DMF (3 × 20 mL), and 1.5 mL (14.9 mmol) of 1,3-propanedithiol and 1.5 mL (8.6 mmol) of diisopropylethylamine were successively added. The reaction was stirred for an additional 24 h and then was filtered and washed with DMF (4 × 20 mL), THF (4 × 20 mL), and CH_2Cl_2 (2 × 5 mL), and the resin was dried under reduced pressure to give 509.5 mg of an orange brown resin **13**: FTIR (KBr pellet) 1820, 1752, 1370 cm^{-1}.



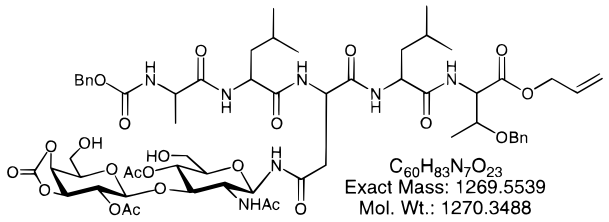
13

13a. In a polymer synthesis flask, the polymer-bound trisaccharide **13** (105.0 mg) was swollen in 1.0 mL of CH_2Cl_2 for 1 h at room temperature. To this mixture were added the pentapeptide CbzAlaLeuAspLeuThr(OBn)OAll (237.3 mg, 0.260 mmol) in 5 mL of CH_2Cl_2 and 1.0 mL of DMF followed by IIDQ (Aldrich, 80 μL, 0.253 mmol), and the solution was washed in with 0.5 mL of CH_2Cl_2 and 0.5 mL of DMF. After 48 h, the solvent was filtered, the resin was washed with CH_2Cl_2 (5 × 5 mL), THF (1 × 5 mL), and CH_2Cl_2 (3 × 5 mL), and the resin was dried under reduced pressure to give 98 mg of resin **13a**: FTIR (KBr pellet) 1820, 1752, 1370 cm^{-1}.



13a

16. In a Teflon flask, the polymer-bound trisaccharide−pentapeptide **13a** (98 mg) and anisole (5.0 μL, 0.46 mmol) were suspended in 3 mL of CH_2Cl_2 for 1 h at room temperature. The mixture was cooled to −10 °C (acetone/ice), and HF·pyridine (50 μL, 1.7 mmol) was slowly added. After 4 h the reaction was warmed to room temperature for 24 h. Water (5 mL) was added at −10 °C, and the mixture was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were washed twice with a mixture of brine (10 mL) and saturated $NaHCO_3$ (1−2 mL, pH 7). The organic extracts were dried over sodium sulfate, filtered over a medium porosity glass filter, and concentrated. The residue was purified over RP-18 silica, gradient elution 7:3 → 9:1 MeOH:H_2O (0.1% TFA) to give trisaccharide−pentapeptide **16** (5.9 mg): $[\alpha]^{24}_D$ −14.4 (*c* 0.65, CH_2Cl_2); FTIR (neat) 3289, 2955, 1807, 1745, 1639, 1537, 1454, 1371, 1230, 1167, 1050 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 7.38−7.26 (10H, m), 5.88 (1H, ddd, J = 5.7, 10.5, 17.2 Hz), 5.31 (1H, dd, J = 1.5, 17.2 Hz), 5.19 (1H, dd, J = 1.5, 10.5 Hz), 5.13−5.00 (3H, m), 4.88−4.80 (2H, m), 4.71 (1H, t apparent, J = 6.0 Hz), 4.64−4.58 (3H, m), 4.55 (1H, dd, J = 5.7, 13.2 Hz), 4.48 (1H, m), 4.42−4.36 (2H, m), 4.17−4.10 (2H, m), 3.97 (1H, t apparent, J = 9.5 Hz), 3.92 (1H, m), 3.77 (2H, m), 3.57 (1H, m), 3.49 (2H, m), 2.74 (1H, dd, J = 5.7, 15.7 Hz), 2.63 (1H, dd, J = 6.9, 15.7 Hz), 2.10 (3H, s), 2.07 (3H, s), 1.96 (3H, s), 1.72−1.58 (6H, m), 1.35 (3H, d, J = 7.2 Hz), 1.22 (3H, d, J = 6.3 Hz), 0.94 (6H, d, J = 6.4 Hz), 0.89 (6H, d, J = 6.4 Hz); ^{13}C NMR (125 MHz, CD_3OD) δ 175.9, 175.1, 174.5, 173.9, 172.8, 172.6, 172.5, 171.8, 171.3, 170.8, 158.5, 155.5, 139.5, 138.2, 133.2, 129.5, 129.4, 129.3, 129.1, 129.0, 128.7, 101.4, 80.9, 79.9, 77.5, 77.3, 76.8, 75.8, 75.6, 75.5, 73.6, 73.5, 72.0, 70.3, 67.8, 67.0, 62.2, 61.3, 58.3, 55.5, 53.3, 52.2, 52.2, 51.2, 42.0, 41.5, 38.1, 25.9, 25.7, 23.6, 23.5, 23.3, 22.1, 21.8, 21.1, 20.8, 18.2, 16.4; HRMS (FAB) calcd for $C_{60}H_{83}N_7O_{23}Na$ 1292.5490, found 1292.5493.



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