Optimized Synthesis of an Orthogonally Protected Glucosamine

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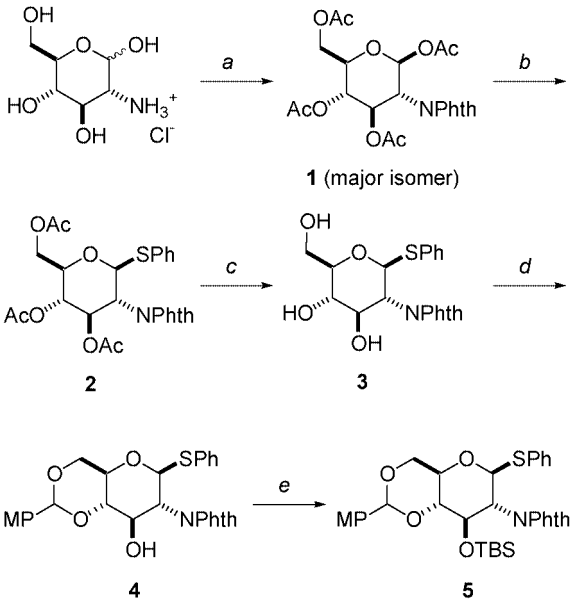
Abstract: Glucosamine hydrochloride was transformed into an orthogonally protected intermediate in seven steps and 34% overall yield. The synthesis includes an optimized preparation of *N*-phthaloyl-β-D-glucosamine tetraacetate, a commonly used precursor in carbohydrate chemistry.

Keywords: carbohydrates, glucosamine, glycosides, orthogonal protecting groups

Glucosamine derivatives are important intermediates in the synthesis of oligosaccharides and glycoconjugates.[1] Both natural and synthetic glucosamine-containing compounds have demonstrated potent anticoagulation and immunomodulatory activity[2] and are used clinically to treat heart disease,[3] arthritis,[4] and kidney disorders.[5] Recent methodological advances in the solid-state synthesis of complex carbohydrates[6] are likely to increase demand for the scalable preparation of monosaccharide precursors with orthogonal protecting group systems. Although numerous synthetic procedures exist, few are truly appropriate for economic scale-up. Here we report an efficient and scalable synthetic sequence of an orthogonally protected glucosamine derivative (Scheme 1). Of particular note is the efficient conversion of glucosamine to *N*-phthaloyl-β-D-glucosamine tetraacetate (**1**), a popular intermediate first introduced by Baker in 1954.[7]



Scheme 1 *Reagents and conditions*: (a) (i) NaOMe, MeOH (ii) $Phth_2O$, Et_3N (iii) Ac_2O, pyridine (77%); (b) PhSH, TMSOTf, CH_2Cl_2 (76%); (c) NaOMe, 3:2 MeOH–CH_2Cl_2, –10 °C; (d) *p*-anisaldehyde dimethyl acetal, CSA, toluene, 90 °C (80% yield over two steps); (e) *t*-$BuMe_2SiCl$, $AgNO_3$, Et_3N, CH_2Cl_2 (88%). MP = *p*-methoxyphenyl, Phth = phthaloyl, TBS = *tert*-butyldimethylsilyl, CSA = camphorsulfonic acid

The preparation of **1** was adapted from a procedure described by Lemieux and coworkers.[8] Glucosamine hydrochloride was neutralized with one equivalent of freshly prepared NaOMe, then treated directly with finely powdered phthalic anhydride added in two portions with subsequent addition of triethylamine and methanol to reduce viscosity. A filtration step for removing sodium chloride was deemed unnecessary and even undesirable, as the neutral glucosamine itself was only partially soluble under these conditions. However, efficient mechanical stirring was found to be essential for complete conversion of the amine to the intermediate phthalamate, to accelerate the exchange rate of the reactants between the solid and solution states and to maintain a small grain size to prevent unreacted materials from being trapped in particulate form. The crude product and salts were cooled and collected by filtration and carefully dried under reduced pressure, then resuspended in pyridine and treated with acetic anhydride and stirred at room temperature, again with mechanical stirring. Pyridine was efficiently removed from the reaction mixture by azeotropic distillation with toluene prior to aqueous extraction of the inorganic by-products, minimizing problems associated with waste remediation and loss of product by inefficient partitioning between the aqueous and organic phases. Recrystallization from a binary (20:80) mixture of EtOAc and hexanes yielded the desired tetraacetate in 77% yield as an 8:1 mixture of anomers, with **1** as the predominant isomer.

The anomeric mixture of glycosyl tetraacetates were most efficiently converted to β-thiophenyl glycoside **2** using trimethylsilyl triflate (TMSOTf) as a Lewis acid.[9] Less expensive Lewis acids such as $BF_3{\cdot}Et_2O$ have also been used as catalysts for glycosylation[10] but the reaction times are much slower. Dissolution of the tetraacetates in anhydrous CH_2Cl_2 and treatment with 1.2 equivalents of TMSOTf at ambient temperature produced the desired compound **2** in 7 hours. It is worth mentioning that the β-acetate **1** is considerably more reactive than the α-anomer; we have observed that glycosyl tetraacetates with lower β/α ratios can require 1–3 days for complete conversion. Re-

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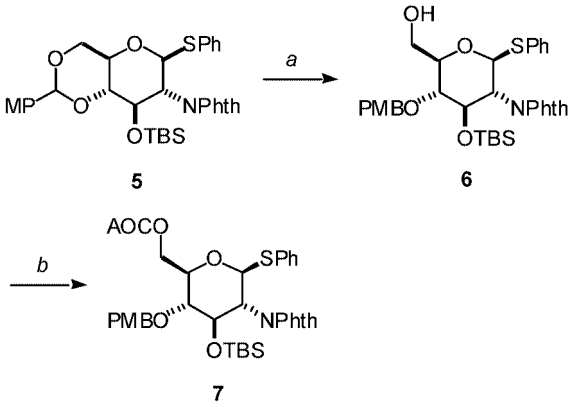
crystallization after aqueous workup was again accomplished using a binary mixture of EtOAc and hexanes to yield compound **2** in 76% yield.

Triacetate **2** could be chemoselectively saponified to triol **3** by treatment with NaOMe in a 60:40 mixture of MeOH–CH_2Cl_2 at –20 to –10 °C.[11] Methanolysis did not proceed at an appreciable rate for temperatures below –20 °C, whereas the phthalimide group was susceptible to partial cleavage for reaction temperatures above 0 °C. The reaction mixture was neutralized by passage through an ion-exchange resin packed in methanol. The crude triol was dried under reduced pressure, then resuspended in anhydrous toluene and treated with *p*-anisaldehyde dimethyl acetal and a catalytic amount of camphorsulfonic acid at reflux with azeotropic removal of methanol.[12] Attempts to recrystallize the product from aqueous ethanol at –20 °C were inefficient and yielded crystalline solids which melted below room temperature.[13] Therefore, the product was purified by silica gel chromatography to yield the desired anisylidene acetal **4** in 80% yield over two steps. Protection of the sterically hindered O-3 as a *tert*-butyldimethylsilyl (TBS) ether was achieved most economically with the corresponding chloride assisted by $AgNO_3$.[14] The reaction was conducted in CH_2Cl_2 at room temperature using Et_3N as a base and protected from light to prevent photoactivated degradation. The silver salts were removed by filtration through Celite prior to aqueous workup, and crystallization was accomplished using a binary mixture of EtOAc and hexanes to yield the fully protected intermediate **5** in 88% yield.

Glucosamine derivative **5** is a versatile intermediate; it can be directly activated for glycosylation[15] or converted to the C-4 or C-6 *p*-methoxybenzyl (PMB) ether by regioselective cleavage of the 4,6-anisylidene (Scheme 2). Treatment of **5** with BH_3·THF and TMSOTf in CH_2Cl_2[16] yielded the C-4 ether **6** in 96% yield after silica gel chromatography. The primary alcohol was then protected as an allyloxycarbonate (AOC) using allyl chloroformate and Et_3N assisted by 4-dimethylaminopyridine in CH_2Cl_2;[17] purification by silica gel chromatography yielded the orthogonally protected glucosamine **7** in 87% yield.

In summary, we have reported a scalable, seven-step synthesis of an orthogonally protected glucosamine, with an overall yield of 34% or an average yield of 86% per step. We anticipate that efficient synthetic routes to carbohydrate precursors such as the one reported here will be important for the large-scale synthesis of complex carbohydrates and glycoconjugates.



Scheme 2 *Reagents and conditions*: (a) (i) BH_3·THF, TMSOTf, CH_2Cl_2, –25 to 0 °C (96%); (b) allyl chloroformate, Et_3N, DMAP, CH_2Cl_2 (87%) AOC = allyloxycarbonyl, MP = *p*-methoxyphenyl, Phth = phthaloyl, PMB = *p*-methoxybenzyl, TBS = *tert*-butyldimethylsilyl

All starting materials and reagents were obtained from commercial sources and used as received unless otherwise noted. Hexanes were purified by fractional distillation; CH_2Cl_2 and toluene were freshly distilled from CaH_2; THF was freshly distilled from sodium benzophenone ketyl. Silica gel chromatography was performed with ICN SiliTech 32-63 D. Melting points were determined using a capillary tube apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained using a Varian spectrometer operating at 300 MHz and 75 MHz, respectively. Chemical shifts are reported in ppm with the residual solvent peak as an internal reference. IR spectra were acquired from thin films on NaCl plates using a Nicolet Nexus 670 spectrometer. Optical rotations were obtained at r.t. with a Rudolph AUTOPOL III polarimeter. Mass spectra were obtained using a Hewlett-Packard 5989B or a Finnigan 4000 mass spectrometer. Elemental analyses were performed in the Department of Chemistry, Purdue University.

1,3,4,6-Tetra-*O*-acetyl-2-phthalimido-2-deoxy-β-D-glucopyranoside (1)

A 1 M NaOMe solution was prepared by adding Na metal (5.33 g, 0.232 mol) in small pieces to MeOH (Mallinckrodt, ChromAR HPLC, 232 mL) at –5 °C in a 500 mL round-bottomed flask equipped with a reflux condensor, which was swirled until the metal had been completely consumed. This was slowly added at 0 °C to a 1 L round-bottomed flask containing glucosamine hydrochloride (50 g, 0.232 mol). The reaction mixture was mechanically agitated for 2 h at r.t. using a stirring rod with a tapered Teflon blade, then treated with finely ground phthalic anhydride (19 g, 0.128 mol) and mechanically stirred for another 45 min. The mixture was charged with a second portion of phthalic anhydride (19 g, 0.128 mol), Et_3N (35.5 mL, 0.255 mol), and MeOH (230 mL) and vigorously stirred for another 24 h, during which it slowly changed from a milky white solution to a thick yellow paste. The intermediate phthalamate (and salts) were precipitated as a white solid by cooling the mixture to –20 °C for 4 h. These were filtered and thoroughly washed with cold MeOH, then dried overnight under reduced pressure. The solid was redispersed in pyridine (Mallinckrodt, 500 mL) with vigorous mechanical stirring and cooled to –5 °C, followed by treatment with Ac_2O (Mallinckrodt, 330 mL). The mixture was mechanically stirred at r.t. for 48 h, during which it slowly changed from a translucent white to an opaque yellow solution. Cold EtOH (100 mL) was slowly added to the mixture to quench the excess Ac_2O, which was then reduced by rotary evaporation. This was redispersed in toluene (3 × 100 mL) and concentrated several times for the azeotropic removal of pyridine. The remaining slurry was redissolved in $CHCl_3$ (1 L) and washed with distilled H_2O (4 × 250 mL) and brine (250 mL), then dried (Na_2SO_4) and evaporated to dryness. The crude product was dissolved in minimal amount of hot EtOAc (100 mL), then diluted with hexanes (400 mL) and left to cool at –5 °C. The recrystallized product was collected by filtration, washed with cold hexanes, and dried to yield the desired tetraacetate as an 8:1 mixture of anomers (85.3 g, 77%). Comparison of the ^1H NMR signals ($CDCl_3$, 300 MHz) with the values in the literature[18] confirmed **1** as the major β-isomer; mp 94–95 °C.

Phenyl 3,4,6-Tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (2)

An oven-dried 1 L round-bottomed flask was charged with tetraacetate **1** (43.25 g, 90.9 mmol), thiophenol (Aldrich, 28 mL, 272.8 mmol), and anhyd CH_2Cl_2 (430 mL). The mixture was treated with freshly distilled TMSOTf (20 mL, 109.2 mmol) at r.t. and stirred for 7 h under argon. The mixture was then quenched with a sat. aq solution of $NaHCO_3$ (400 mL) and separated. The aqueous layer was extracted with additional CH_2Cl_2 (2 × 100 mL); the combined organic phases were then washed with brine (250 mL), dried (Na_2SO_4), and concentrated by rotary evaporation equipped with a bleach trap. The crude product was dissolved in a minimum amount of hot EtOAc (65 mL), then diluted with hexanes (200 mL) and cooled to 0 °C. The recrystallized product was collected by filtration, washed with cold 10% EtOAc in hexanes, and dried to yield the desired thiophenyl glycoside **2** (36.5 g, 76%). Comparison of the ^{1}H NMR signals ($CDCl_3$, 300 MHz) with the values in the literature[19] confirmed the identity of **2**; mp 145.0 ± 0.5 °C.

Phenyl 4,6-*O*-(*p*-Methoxybenzylidene)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (4)

To a 100 mL round-bottomed flask was added the triacetate **2** (8.5 g, 16.1 mmol) and a 3:2 mixture of MeOH–CH_2Cl_2 (Mallinckrodt, 80.0 mL). The mixture was cooled to –20 °C, treated with a 0.3 M NaOMe solution in MeOH (21.3 mL, 6.4 mmol) and stirred for 10 min, then warmed to –10 °C and stirred for 2 h. The reaction mixture was warmed to 0 ºC and passed through an ion-exchange resin (Dowex 50WX8-100) packed with MeOH. The crude triol was concentrated by rotary evaporation and dried under vacuum overnight in a 250 mL round-bottomed flask, then suspended in anhyd toluene (Mallinckrodt, 80 mL). *p*-Anisaldehyde dimethyl acetal (Avocado, 3.3 mL, 19.4 mmol) and camphorsulfonic acid (0.86 g, 3.7 mmol) were also added and the mixture was stirred at 90 °C for 3 h in a flask equipped with a Dean–Stark apparatus. The temperature was increased to 120 °C and refluxed until 2 mL of MeOH–toluene azeotrope had been collected, then cooled to r.t. The mixture was quenched with a sat. aq solution of $NaHCO_3$ (100 mL) and diluted with EtOAc (60 mL). The aqueous layer was separated and extracted with additional EtOAc (2 × 50 mL). The combined organic phases were then washed with brine (50 mL), dried (Na_2SO_4), and concentrated by rotary evaporation. The product was purified by silica gel chromatography using a 10–50% EtOAc–hexanes gradient to yield the desired anisylidene acetal **4** as a white solid (6.75 g, 80% overall yield); mp 182.0 ± 0.5 °C; $[\alpha]_D$ +32.9 (*c* = 1.02, $CHCl_3$).

IR (film): 3474, 1774, 1713, 1614, 1519, 1387, 1250, 1091, 752, 720, 688 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.89 (m, 4 H, ArH), 7.36–7.42 (m, 7 H, ArH), 6.90 (d, 2 H, *J* = 8.7 Hz, ArH), 5.70 (d, 1 H, *J* = 10.5 Hz, H-1), 5.52 (s, 1 H, C*H*-PMP), 4.65 (dd, 1 H, *J* = 2.9, 9.8 Hz, H-3), 4.39 (dd, 1 H, *J* = 4.6, 10.2 Hz, H-6a), 4.32 (t, 1 H, *J* = 10.2 Hz, H-2), 3.77–3.84 (m, 4 H, H-6e, OCH_3), 3.70 (ddd, 1 H, *J* = 4.5, 9.3, 9.8 Hz, H-5), 3.58 (t, 1 H, *J* = 9.0 Hz, H-4), 2.54 (d, 1 H, *J* = 3.3 Hz, OH).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.29 (1 C, C_{arom}–OCH_3), 134.20, 132.59, 131.78, 131.57, 129.34, 128.93, 128.07, 127.62, 123.81, 123.34, 113.72 (17 C, C and CH arom), 101.86 (1 C, C_{acetal}), 84.25 (1 C, C-1), 81.81, 70.27, 69.68, 68.51, 55.49, 55.28 (6 C, C-2,3,4,5,6, OCH_3).

ESI-MS: *m*/*z* = 520 (M + H).

Anal. Calcd for $C_{28}H_{25}NO_7S$: C, 64.73; H, 4.85; N, 2.70. Found: C, 64.68; H, 4.88; N, 2.64.

Phenyl 3-*O*-(*tert*-Butyldimethylsilyl)-4,6-*O*-(*p*-methoxybenzylidene)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (5)

Anisylidene acetal **4** (1.5 g, 2.9 mmol) was dissolved in anhyd CH_2Cl_2 (10 mL) in an oven-dried 25 mL round-bottomed flask. Et_3N (0.69 mL, 4.9 mmol) was added and the reaction mixture was stirred for 10 min at r.t., under argon. $AgNO_3$ (0.74 g, 4.3 mmol) was added and the reaction flask was covered with aluminum foil (to prevent photoactivated degradation) and stirred for 15 min, then treated with *tert*-butyldimethylchlorosilane (TBSCl, 0.66 g, 4.3 mmol). A white precipitate of AgCl was observed immediately. The mixture was stirred at r.t. for 18 h, then filtered through Celite into a sat. aq solution of $NaHCO_3$ (10 mL). The aqueous phase was separated and extracted with additional CH_2Cl_2 (2 × 7 mL). The combined organic phases were then washed with brine (7 mL), dried (Na_2SO_4), and concentrated by rotary evaporation. The crude product was dissolved in a minimum amount of hot EtOAc (5 mL), then diluted with hexanes (20 mL) and cooled to 0 °C overnight. The recrystallized product was collected by filtration, washed with cold 10% EtOAc in hexanes and dried to yield the desired compound **5** as white crystals (1.62 g, 88%); mp 176.0 ± 0.5 °C; $[\alpha]_D$ +26.8 (*c* = 0.81, $CHCl_3$).

IR (film): 1772, 1711, 1617, 1515, 1472, 1385, 1247, 1171, 1142, 1117, 1092, 856, 722 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.73–7.88 (m, 4 H, ArH), 7.23–7.41 (m, 7 H, ArH), 6.89 (d, 2 H, *J* = 8.7 Hz, ArH), 5.67 (d, 1 H, *J* = 10.7 Hz, H-1), 5.48 (s, 1 H, C*H*PMP), 4.63 (t, 1 H, *J* = 9.3 Hz, H-3), 4.37 (dd, 1 H, *J* = 4.4, 9.9 Hz, H-6a), 4.32 (t, 1 H, *J* = 9.9 Hz, H-2), 3.77–3.83 (m, 4 H, H-6e, OCH_3), 3.71 (ddd, 1 H, *J* = 4.4, 9.2, 9.8 Hz, H-5), 3.56 (t, 1 H, *J* = 8.9 Hz, H-4), 0.57 [s, 9 H, $C(CH_3)_3$], –0.14 (s, 3 H, $SiCH_3$), –0.30 (s, 3 H, $SiCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.05 (1 C, C_{arom}–OCH_3), 134.22, 132.28, 132.14, 131.68, 129.59, 128.90, 127.88, 127.64, 123.61, 123.22, 113.46 (17 C, C and CH arom), 101.89 (1C, C_{acetal}), 84.37 (1C, C-1), 82.39, 70.66, 70.58, 68.60, 56.66, 55.21 (6 C, C-2,3,4,5,6, OCH_3), 25.36 [3 C, $C(CH_3)_3$], 17.69 [1 C, $C(CH_3)_3$], –4.16 (1 C, $SiCH_3$), –5.39 (1 C, $SiCH_3$).

ESI-MS: *m*/*z* = 634 (M + H).

Anal. Calcd for $C_{34}H_{39}NO_7SSi$: C, 64.43; H, 6.20; N, 2.21. Found: C, 64.28; H, 6.15; N, 2.19.

Phenyl 3-*O*-(*tert*-Butyldimethylsilyl)-4-*O*-(*p*-methoxybenzyl)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (6)

Compound **5** (151 mg, 0.24 mmol) was dissolved in anhyd CH_2Cl_2 (1.0 mL) in an oven-dried 25 mL round-bottomed flask. The reaction mixture was cooled to –20 °C under argon and treated with borane–THF (2.4 mL of a 1 M solution in THF). The mixture was stirred at –20 °C for 15 min, then treated with TMSOTf (0.07 mL of a 2 M solution in CH_2Cl_2) and warmed to 0 °C over a period of 30 min. The mixture was stirred at 0 °C for an additional 4 h, cooled to –15 °C and treated with Et_3N (0.2 mL), then quenched by the dropwise addition of MeOH (3 mL) until effervescence ceased. The mixture was warmed to r.t. and concentrated by rotary evaporation to dryness. The product was purified by silica gel chromatography using a 20–40% EtOAc–hexanes gradient to yield the desired O-6 alcohol **6** as a white crystalline solid (145 mg, 96%); mp 166.0 ± 0.5 °C; $[\alpha]_D$ +48.0 (*c* = 1.03, $CHCl_3$).

IR (film): 3479, 1776, 1711, 1613, 1514, 1387, 1249, 1109, 1087, 1034, 838, 754, 720 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.69–7.82 (m, 4 H, ArH), 7.18–7.31 (m, 7 H, ArH), 6.84 (d, 2 H, *J* = 8.54 Hz, ArH), 5.61 (d, 1 H, *J* = 10.5 Hz, H1), 4.74 (d, 1 H, *J* = 11.3 Hz, benzyl-H), 4.55 (d, 1 H, *J* = 11.4 Hz, benzyl-H), 4.45 (t, 1 H, *J* = 9.5 Hz, H-3), 4.21 (t, 1 H, *J* = 10.2 Hz, H-2), 3.80–3.86 (m, 1 H, H-6a), 3.75 (s, 3 H, OCH_3), 3.59–3.67 (m, 1 H, H-5), 3.50–3.58 (m, 1 H, H-6e), 3.46 (t, 1 H,

J = 9.6 Hz, H-4), 1.89 (t, 1 H, *J* = 6.8 Hz, OH), 0.69 [s, 9 H, $C(CH_3)_3$], –0.05 (s, 3 H, $SiCH_3$), –0.47 (s, 3 H, $SiCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 159.11 (1 C, C_{arom}–OCH_3), 134.24, 132.20, 132.12, 130.08, 128.92, 128.90, 127.83, 123.54, 113.76 (17 C, C and CH arom), 83.39 (1 C, C-1), 79.61, 79.37, 74.46, 73.30, 62.01, 56.74, 55.21 (7 C, C-2,3,4,5,6, OCH_3, C benzyl), 25.63 [3 C, $C(CH_3)_3$], 17.60 [1 C, $C(CH_3)_3$], –4.11 (1 C, $SiCH_3$), –4.68 (1 C, $SiCH_3$).

ESI–MS: *m*/*z* = 658 (M + Na).

Anal. Calcd for $C_{34}H_{41}NO_7SSi$: C, 64.22; H, 6.50; N, 2.20. Found: C, 64.36; H, 6.52; N, 2.18.

Phenyl 3-*O*-(*tert*-Butyldimethylsilyl)-6-alloxycarbonyl-4-*O*-(*p*-methoxybenzyl)-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (7)

Compound **6** (89.6 mg, 0.14 mmol) was dissolved in anhyd CH_2Cl_2 (1.5 mL) in an oven-dried 5 mL pear-shape flask. 4-Dimethylaminopyridine (DMAP, 171 mg, 1.4 mmol) and Et_3N (0.18 mL, 1.8 mmol) were added and the reaction mixture was cooled to 0 °C with stirring under argon. Allyl chloroformate (0.22 mL, 2.1 mmol) was added and the mixture was warmed to r.t. and stirred for 3 h. The mixture was quenched with a sat. aq solution of $NaHCO_3$ (4 mL) and diluted with CH_2Cl_2 (1 mL). The aqueous phase was extracted with additional CH_2Cl_2 (2 × 2 mL). The combined organic phases were then washed with brine (4 mL), dried (Na_2SO_4), and concentrated by rotary evaporation. The product was purified by silica gel chromatography using a 20–40% EtOAc–hexanes gradient to afford the desired compound **7** as a yellow oil (87.8 mg, 87%); $[\alpha]_D$ +53.5 (*c* = 0.99, $CHCl_3$).

IR (film): 1750, 1715, 1613, 1514, 1387, 1250, 1090, 961, 839, 721 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.75–7.90 (m, 4 H, ArH), 7.21–7.41 (m, 7 H, ArH), 6.93 (d, 2 H, *J* = 8.7 Hz, ArH), 5.92–6.05 (m, 1 H, H_2C=C*H*CH_2) 5.61 (d, 1 H, *J* = 10.5 Hz, H-1), 5.41 (dq, 1 H, *J* = 1.4, 17.1 Hz, HC*H*=CHCH_2), 5.32 (dq, 1 H, *J* = 1.2, 10.4 Hz, *H*CH=CHCH_2), 4.84 (d, 1 H, *J* = 11.3 Hz, benzyl-H), 4.67 (d, 2 H, *J* = 5.7 Hz, C=CHCH_2O) 4.48–4.54 (m, 3 H, benzyl-H, H-3, H-6a), 4.28 (t, 1 H, *J* = 10.1 Hz, H-2), 4.21 (t, 1 H, *J* = 6.5 Hz, H-6e), 3.83 (s, 3 H, OCH_3), 3.73–3.78 (m, 1 H, H-5), 3.54 (t, 1 H, *J* = 9.8 Hz, H-4), 0.77 [s, 9 H, $C(CH_3)_3$], 0.02 (s, 3 H, $SiCH_3$), –0.41 (s, 3 H, $SiCH_3$).

^{13}C NMR (75 MHz, $CDCl_3$): δ= 159.22 (1 C, C_{arom}–OCH_3), 154.69 [1 C, O–*C*(O)–O], 134.22, 132.41, 132.19, 131.50, 129.75, 128.99, 128.76, 127.77, 123.27, 118.97, 113.83 (19 C, C and CH arom, $C_{allylic}$), 83.38 (1 C, C-1), 79.47, 77.07, 74.72, 73.54, 68.58, 66.44, 56.46, 55.23 (8 C, C-2,3,4,5,6, OCH_3, =CHCH_2O, C_{benzyl}), 29.66, 25.65 [3 C, $C(CH_3)_3$], 17.60 [1 C, $C(CH_3)_3$], –4.14 (1 C, $SiCH_3$), –4.58 (1 C, $SiCH_3$). ESI–MS: *m*/*z* = 742 (M + Na).

Anal. Calcd for $C_{38}H_{45}NO_9SSi$: C, 63.40; H, 6.30; N, 1.95. Found: C, 63.72; H, 6.48; N, 1.87.

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