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A Novel Neoglycopeptide Building Block

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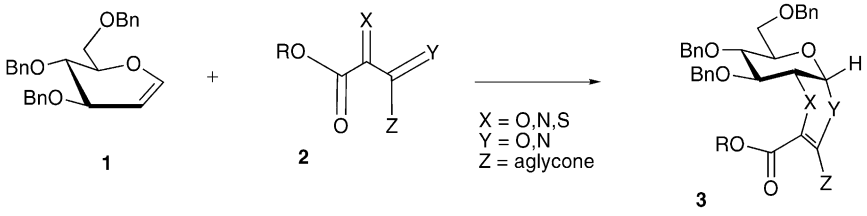
Abstract—The synthesis of a neoglycopeptide building block is described. The key step is a cycloaddition where the chemistry is orthogonal to standard glycosyl transfer methodology. Also described is some exploratory chemistry of the building block.

The synthesis of *N*-linked glycopeptides is an important activity in present-day glycoscience.[1] There are a variety of methods for introducing the anomeric primary amino group which, in the native *N*-glycopeptides, serves as the link to the aspartic acid γ carboxyl and thence to the peptide or protein via the aspartic acid α-amino acid functionality. Interestingly, except for the method to be described below, there is only one other approach that introduces a pre-functionalized amino group at the anomeric carbon, namely the modified Ritter reaction reported by Fraser-Reid.[2] There is also great interest in 'neo' glycopeptides where the link between carbohydrate and peptide is not *N*-aspartyl, but is *N*-other or where even the *N* is omitted.[3] Our method is based on the general concept of heterocycloaddition (Scheme 1) to glycals (represented by **1**) with a diene that contains both the functionality desired in the aglycone (peptide) and the required hetero atoms which make up the diene framework (shown as **2**) and thus merge the sugar and the aglycone in one step, for example, when Y = N and Z = 'peptide component' for the specific example of a glycopeptide (depicted as **3**).[4] Our approach requires some preliminary synthetic construction of the necessary diene, but avoids manipulations of the anomeric functionality (other than deprotection). We describe in detail the case where X = S, Y = N and Z = 'aspartate residue'.[5]

In order to prepare an N-linked aspartic acid by our method it was necessary to prepare heterodiene **4**. The precursor to diene **4** was prepared as shown in Scheme 2 by first applying our version[6] of the *C*-acetylation of amino acids to the BOC benzyl ester of aspartic acid **5** to produce keto diesters **8a**,**b**. This transformation routinely takes place in >90% yield. Preparation of the oximes **9a**,**b** under conditions carefully defined to avoid oxazolidinone formation was then followed by application of the Hudson rearrangement to afford heterodiene precursors **4a** and **4b**.[7]

Sulfonimines **4a,b** were then phthalimidosulfenylated to produce the ultimate heterodiene precursors **11a**,**b**. It



Scheme 1.

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[†]Taken in part from the PhD thesis of A.B., 2000, Universita di Firenze; the experiments described were done while A.B. was at Hunter College as a visiting researcher sponsored by Dipartimento di Chimica Organica, Universita di Firenze, Firenze, Italy.
[‡]Taken in part from the PhD thesis of B.L., 1999, City University of New York.

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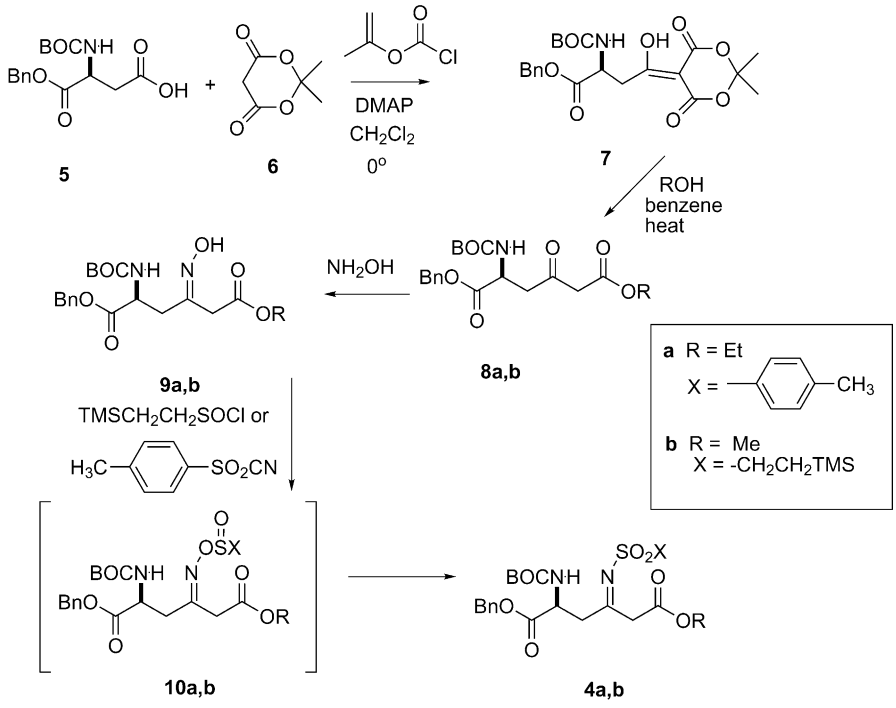
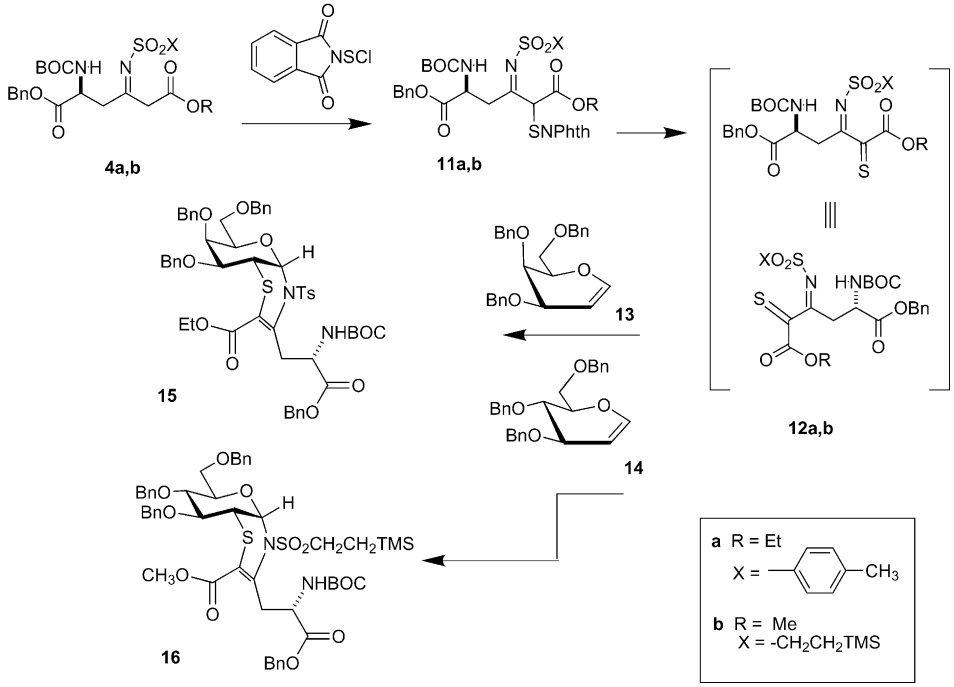


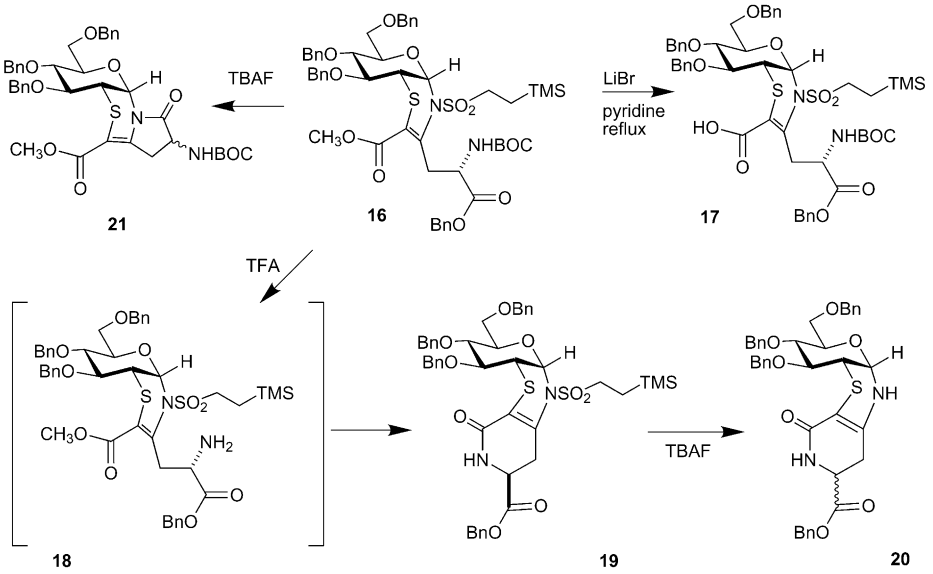
Scheme 2.

should be noted that the four-step sequence from **5** to **4a**,**b** is tolerated by the BOC group and causes no epimerization of the α-amino carbon. The dienes **12a** and **12b** were then generated in the presence of tribenzyl galactal **13** and glucal **14** by addition of lutidine and pyridine, respectively. The cycloadditions proceeded smoothly over a period of 12 h at room temperature to afford the adduct **15** in 75% yield and for the same time at 40 °C to afford adduct **16** in 66% yield (88% yield based on recovered glucal) after purification by flash chromatography (Scheme 3). Again, it should be noted that the α-amino carbon is tolerant of the conditions for the conversions of Scheme 3.

At this point, we had in hand a masked galactoaspartate and a masked glucoaspartate mimic, each with two differentiated carboxyls, a protected α-amino function and a protected anomeric vinylogous amide. Since the toluenesulfonyl group in the galacto series was very robust and not selectively cleavable in the presence of



Scheme 3.



Scheme 4.

the other protecting groups, we chose to carry out our exploratory chemistry with the TMS-ethylsulfonyl protecting group in the gluco series, as follows (Scheme 4).

The ω carboxyl was subjected to LiI and LiBr in DMF and pyridine at several temperatures; and the demethylation was successfully achieved with lithium bromide and refluxing pyridine to afford **17** in 70% yield. The BOC-protected α-amino function of **16** was easily deprotected by TFA/CH_2Cl_2 to afford **18** which then spontaneously cyclized with the ω ester carbonyl to afford lactam **19** in >95% yield. This tricyclic derivative permitted the simple deprotection of the TMS-ethylsulfonyl group by TBAF in THF to produce **20** in 96% yield as a 3/1 mixture of epimers. In the more flexible material **16**, fluoride catalyzed liberation of the anomeric N with either TBAF or CsF resulted in lactam formation (**21**) with the α-ester carbonyl, even when acetic acid was used with the fluoride reagent so as to protonate the supposed anionic N intermediate. Lactam **21** was obtained as a 1.5/1 mixture of epimers.

In conclusion, we have demonstrated that a 'neo' glycopeptide building block can be constructed by a novel heterocycloaddition. The rigid structure of this sugar-peptide-type molecule represents a novel and versatile scaffold for the construction of glycopeptides through peptide chain elongation at either the N- or C-terminal functions of **17**, **20** and **21**.[8] However, it is our belief that the most promising future development will be to elaborate our synthesis of **4b** and **11b** to an aspartate already incorporated into a small peptide since small peptides should be inert to all the chemical steps required. Then, a cycloadduct analogous to **16** would have the amino function and the acid carboxyl of aspartate embedded in a robust peptide linkage. Thus the adverse ring-formations and epimerizations, which are due to the ester functions in our model, should be minimized.

Experimental

All reactions were carried out under a dry argon or nitrogen atmosphere at ambient temperature unless otherwise stated. Low temperatures were recorded as bath temperatures. Chromatography was carried out on silica gel 60, 230–400 mesh, using flash chromatography techniques. Analytical thin-layer chromatography (TLC) was performed on E. Merck precoated silica 60 F_{254} plates. Petroleum ether, hexane, pentane, dichloromethane, and ethyl acetate used as eluants were ACS reagent grade solvent. The following reaction solvents were purified by distillation: dichloromethane and chloroform (from P_2O_5), diethyl ether (from benzophenone and sodium, N_2), benzene (from CaH_2, N_2) and THF (from benzophenone and sodium, N_2), triethylamine (from CaH_2, N_2), acetonitrile (from P_2O_5). NMR spectra were measured with a GE QE 300 MHz instrument. Chemical shifts are reported in δ units, coupling constants in Hz. TMS (δ = 0.0) was used as internal reference for spectra measured in $CDCl_3$. Infrared spectra were recorded on a Perkin–Elmer 1310 spectrophotometer and a BOMEM FTIR.

Benzyl 2-NHBOC-5-carbomethoxy-4-oxopentanoate (8). A solution of benzyl *N*-BOC aspartate (150 mg, 0.46 mmol), Meldrum's acid (74 mg, 0.51 mmol) and DMAP (125 mg, 1.02 mmol) in 2.5 mL of anhydrous CH_2Cl_2 was cooled at −5 °C. A solution of isopropenyl chloroformate (64 mg, 0.53 mmol) in 1.2 mL of anhydrous CH_2Cl_2 was added very slowly to the reaction mixture under vigorous magnetic stirring. After the addition was complete, stirring was continued for 1 h at −5 °C until the complete disappearance of the starting material was detected. Then, 1.0 mL of 10% aq solution of $KHSO_4$ was added to the solution, the cooling bath was removed and an additional 1.0 mL of the $KHSO_4$ solution was added. After dilution with CH_2Cl_2, the two phases were separated and the organic phase was washed with brine and then dried over anhydrous

sodium sulfate. The evaporation of the solvent gave the Meldrum's acid adduct (petroleum ether/ethyl acetate 1/4, $R_f = 0.5$) that was used for the following reaction without any purification.

A solution of the Meldrum adduct in 4.0 mL of benzene and 1.0 mL of anhydrous MeOH was heated under reflux for 9 h. After evaporation of the solvent the crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 2/1, $R_f = 0.4$) to afford **8b** (169 mg, 96%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.31 (m, 5H, Ph), 5.48 (bd, $J = 8.4$ Hz, 1H, NH), 5.151 (s, 2H, $\underline{CH_2}$Ph), 4.59–4.53 (m, 1H, $\underline{CH}$NH), 3.706 (s, 3H, OCH_3), 3.432 (s, 2H, CO$\underline{CH_2}$CO), 3.31–3.23 (A part of an ABX system, $J_{AB} = 18.3$ Hz, $J_{AX} = 4.4$ Hz, 1H of $\underline{CH_2}$CH), 3.14–3.06 (B part of an ABX system, $J_{AB} = 18.3$ Hz, $J_{BX} = 4.4$ Hz, 1H of $\underline{CH_2}$CH), 1.417 (s, 9H, *ter*-but). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 201.2 (CO); 171.4, 167.5 (C_q esters); 156.0 (Cq *t*-Boc); 135.9 (C_q arom); 129.2, 129.0, 128.8 (CH arom); 80.8 (C_q *ter*-but); 68.1 ($\underline{CH_2}$Ph); 53.1, 50.3, 49.6, 45.5 (OCH_3, CO$\underline{CH_2}$CO, $\underline{CH_2}$CH, $CH_2\underline{CH}$); 29.0 (*ter*-but).MS (ES): calcd for $C_{19}H_{25}NO_7$ + Na, 402; found *m*/*z* 402.2 $[M + Na]^+$); 280.1 ; 248.1.

Similarly, **8a** was produced by using ethanol in place of methanol. Yield: 92%; mp: 53–56 °C (lit.[113] 54–57 °C); FTIR (film): 3374, 2979, 1738, 1713, 1501, 1367, 1164; ^{1}H NMR ($CDCl_3$), δ ppm 7.32 (m, 5H), 5.43 (d, $J = 8.9$, 1H), 5.18 (s, 2H), 4.60 (m, 1H), 4.2 (q, $J = 7.2$, 2H), 3.41 (s, 2H), 3.20 (m, 2H), 1.42 (s, 9H), 1.23 (t, $J = 7.2$, 3H). ^{13}C NMR ($CDCl_3$), δ ppm: 201.2, 171.3, 166.8, 155.8, 135.6, 128.9, 128.7, 128.5, 80.5, 67.8, 61.2, 49.9, 49.5, 45.1, 28.6, 14.4.

Benzyl 2-NHBoc-5-carbomethoxy-4-(trimethylsilylethylsulfonamido)-3-pentenoate (4b). The crude oximes **9a**,**b** were synthesized from **8a**,**b** as follows. A solution of $NH_2OH{\cdot}HCl$ (2.0 equiv) and Na_2CO_3 (2.0 equiv) in EtOH (20 mL) was heated under reflux. After 1 h, 1.14 g (3.0 mmol) of keto compound **8** was added at room temperature. The resulting solution was heated under reflux until the disappearance of the starting material was detected. The solvent was evaporated, the mixture was diluted with ethyl acetate (10 mL) and washed twice with brine (2×8.0 mL). Drying of the organic phase over anhydrous sodium sulfate followed by evaporation of the solvent gave the crude product as a mixture of *syn–anti* isomers (dichloromethane/methanol 70/1, $R_f = 0.2$, 95%) which was pure enough to be used in the following step. Attempts to further purify the product by silica gel column and florosil column chromatography showed that the product was not stable during purification and the yield of the chromatographed product was very low. Spectral data of one of the two **9b** oximes: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 8.46 (bs, 1H, OH), 7.42–7.27 (m, 5H, Ph), 5.44 (bd, $J = 8.1$ Hz, 1H, NH), 5.204 (s, 2H, $\underline{CH_2}$Ph), 4.65–4.57 (m, 1H of $\underline{CH}CH_2$), 3.71 (s, 3H, $\underline{OCH_3}$), 3.31–3.26 (A part of an AB system, $J_{AB} = 16.1$ Hz, 1H of CO$\underline{CH_2}$CO), 3.24–3.18 (B part of an AB system, $J_{AB} = 16.1$ Hz, 1H of CO$\underline{CH_2}$CO), 3.04–2.96 (A part of an ABX system, $J_{AB} = 13.5$ Hz, $J_{AX} = 9.1$ Hz, 1H of $\underline{CH_2}$CH), 2.89–2.83 (B part of an ABX system, $J_{AB} = 13.5$ Hz), 1.413 (s, 9H, *ter*-but). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.0, 170.4 (C_q esters); 155.9, 151.5 (C_q *t*-Boc + C_q oxime); 135.8 (C_q arom); 129.2, 129.0, 128.9, 128.8 (CH arom.); 80.8 (C_q *ter*-but); 68.1 ($\underline{CH_2}$Ph); 52.9 (OCH_3); 51.7 ($\underline{CH}CH_2$); 40.3 (CH_2); 30.9 ($CH\underline{CH_2}$); 29.0 (*ter*-but). Spectral data for oxime **9a,** crude yield 92% from **8a**: ^{1}H NMR ($CDCl_3$), δ ppm 8.04 (br, 1H), 7.33 (m, 5H), 5.62 (d, $J = 9.0$ Hz, 1H), 5.16 (s, 2H), 4.60 (m, 1H), 4.11 (q, $J = 7.2$ Hz, 2H), 3.34 (m, 2H), 2.84 (m, 2H), 1.28 (s, 9H), 1.20 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$), δ ppm 172.0, 168.9, 155.9, 150.5, 135.6, 128.8, 128.5, 80.3, 67.5, 61.4, 51.2, 36.8, 33.9, 28.5, 14.4, 14.3.

The crude oxime **9a** was converted to the title compound **4a** as follows using material prepared from 200 mg (0.49 mmol) of **8a.** A solution of oxime (3 mmol, 1 equiv) in anhydrous CCl_4 (30 mL, 0.10 M) was cooled to 0 °C and treated with triethylamine (4.5 equiv). The solution was stirred for 5 min at such temperature before a suspension of *p*-toluenesulfonyl cyanide (2.5 equiv) in 1 mL of CCl_4 was added. The resulting reaction mixture was stirred at 0 °C for 1 h, allowed to warm to room temperature over 30 min and further stirred at room temperature for 10 h. Concentration of the reaction mixture afforded the crude product. Purification by a silica column afforded the product. Yield: 56%; ^{1}H NMR ($CDCl_3$), δ ppm 10.96 (br, 1H), 7.84 (d, $J = 8.1$ Hz, 2H), 7.70 (d, 7.9, 1H), 7.38 (m, 6H), 5.64 (d, $J = 8.1$, 1H), 5.20 (m, 3H), 4.8 (m, 1H), 4.14 (m, 2H), 3.65 (m, 1H), 2.40 (s, 3H), 2.30 (m, 3H), 1.42 (s, 9H), 1.32 (m, 3H). ^{13}C NMR ($CDCl_3$), δ ppm 171.2, 169.0, 152.3, 144.7, 137.5, 135.7, 130.4, 130.2, 129.0, 128.8, 128.7, 127.5, 100.5, 67.8, 60.8, 53.1, 35.0, 30.1, 28.6, 22.0, 14.5.

The crude oxime **9b** was converted to the title compound **4b** as follows using material prepared from 815 mg (2.07 mmol) of **8b**. A solution of the oxime (approx. 2 mmol) and triethylamine (2 mmol) in anhydrous ether (4 mL) was cooled to −30 °C and a solution of the TMSethylsulfinyl chloride in diethyl ether (2 mmol in 4.0 mL) was added. The reaction mixture was stirred for 1 h at −30 °C and then at room temperature for 45 min. The crude product was purified by silica gel column chromatoghraphy with petroleum ether/ethyl acetate 5/1, $R_f = 0.48$) to obtain **4b** (792 mg, 70%) as a pale yellow oil. The ^{1}H NMR spectrum revealed the presence of two compounds. One of these two (possibly an isomer at the nitrogen center) was present only in traces and was not separable from the major product. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 10.590 (s, 1H, NH), 7.42–7.34 (m, 5H, Ph), 5.29–5.10 (m, 4H, $\underline{CH}$COOMe + $\underline{NH}$t−Boc + $\underline{CH_2}$Ph), 4.61–4.55 (m, 1H, $\underline{CH}CH_2$), 3.700 (s, 3H, OCH_3), 3.24–3.09 (m, 3H, CH_2SO_2 + 1H of $\underline{CH_2}$CH), 2.84–2.76 (m, 1H of $\underline{CH_2}$CH), 1.395 (s, 9H, *ter*-but), 1.08–1.02 (m, 2H, $\underline{CH_2}Si(CH_3)_3$), 0.031 (s, 9H, $Si(CH_3)_3$).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.4, 169.6 (C_q esters); 155.7, 152.9 (C_q enam. + C_q *t*-Boc); 135.9 (C_q arom); 129.3, 128.9 (CH arom.); 100.2 ($\underline{CH}$COOMe); 81.2 (C_q *ter*-but); 68.3 ($\underline{CH_2}$Ph); 53.5, 52.5, 52.3 ($OCH_3 + CH_2SO_2 + \underline{CH}CH_2$); 37.6 ($CH\underline{CH_2}$); 29.3 (*ter*-but); 10.8 ($CH_2Si(CH_3)_3$);−0.88 ($Si(CH_3)_3$).

Synthesis of galactal cycloadduct **15**. First, the tosyl imine **4a** is phthalimidosulfenylated as follows. To a solution of sulfonyl imine 76 mg (0.15 mmol) in dichloromethane was added PhthN-S-Cl (38 mg, 1.2 equiv) in portions at 0 °C during a period of 15 min. The reaction mixture was stirred at such temperature for an additional 20 min, allowed to warm up to room temperature in 30 min. Cold *n*-pentane was added. A white precipitate formed which was filtered and then washed with cold *n*-pentane to afford the desired product. To a solution of the phthalimidosulfenyl imine and tri-*O*-benzyl-D-galactal (54 mg, 0.13 mmol, 1 equiv) in chloroform was added a catalytic amount of 2,6-lutidine (2 mol%). The resulting solution was stirred at room temperature until the reaction was complete as monitored by TLC. The solution was dissolved in dichloromethane and washed with saturated ammonium chloride and brine, dried over Na_2SO_4. The organic solvent was removed under reduced pressure. The crude materials were purified by a silica gel column to give the desired product (50 mg, 0.09 mmol). Yield: 75%; ^{1}H NMR ($CDCl_3$), δ ppm 7.83 (d, J = 11.1 Hz, 2H), 7.35 (m, 20H), 6.87 (d, J = 11.1 Hz, 2H), 6.13 (d, J = 6.9 Hz, 1H), 6.22 (m, 1H), 5.15 (m, 1H), 4.97 (d, 12.9, 1H), 4.85 (d, J = 13.2 Hz, 1H), 4.53 (m, 5H), 4.21 (m, 2H), 4.0–3.7 (m, 5H), 3.54 (m, 2H), 3.28 (m, 2H), 2.21 (s, 3H), 1.29 (s, 9H), 1.20 (m, 3H). ^{13}C NMR ($CDCl_3$), δ ppm 173.1, 167.0, 155.7, 144.2, 138.1, 138.0, 135.6, 129.8, 128.6, 128.3, 128.2, 128.0, 127.8, 127.6, 127.5, 127.2, 119.2, 86.6, 77.7, 77.6, 77.5, 77.2, 74.5, 73.4, 72.7, 67.0, 62.3, 44.7, 44.6, 33.6, 29.7, 28.4, 21.5, 13.9.

Synthesis of glucal cycloadduct 16

To an ice-cooled solution of **4b** (350 mg, 0.646 mmol) in $CHCl_3$ (3.0 mL), propylene oxide (45 mg, 0.77 mmol) and phthalimidosulphenyl chloride, 98% (154 mg, 0.71 mmol) were added slowly. After 20 min, the ice bath was removed and the mixture was stirred for 90 min at room temperature. After an ^{1}H NMR of the reaction mixture showed the total disappearance of the starting material, 3,4,6-tri-*O*-benzyl glucal **14** (269 mg, 0.65 mmol), and pyridine (41 μL, 0.52 mmol) were added and the solution was heated to 40 °C overnight. After evaporation of the solvent the crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 9/1; with petroleum ether/ethyl acetate 4/1, R_f = 0.3) to obtain **16** (421 mg, 66%) as a pale yellow oil and recovering 66 mg (conversion yield: 88%) of starting material. The ^{1}H NMR shows traces of an isomer, probably the β-cycloadduct, not separable from the major product. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.34–7.01 (m, 20H, Ph), 6.453 (d, J = 8.0 Hz, 1H, NH), 6.371 (d, $J_{1,2}$ = 7.5 Hz, 1H, H_1), 5.31–5.29 (A part of an AB system, J_{AB} = 12.5 Hz, 1H of $\underline{CH_2}$Ph), 5.05–5.03 (B part of an AB system, J_{AB} = 12.5 Hz, 1H of $\underline{CH_2}$Ph), 4.78–4.76 (A part of an AB system, J_{AB} = 10.5 Hz, 1H of $\underline{CH_2}$Ph), 4.72–4.70 (A part of an AB system, J_{AB} = 11.0 Hz, 1H of $\underline{CH_2}$Ph), 4.63–4.61 (B part of an AB system, J_{AB} = 10.5 Hz, 1H of $\underline{CH_2}$Ph), 4.51–4.49 (B part of an AB system, J_{AB} = 11.0 Hz, 1H of $\underline{CH_2}$Ph), 4.48–4.46 (A part of an AB system, J_{AB} = 12.5 Hz, 1H of $\underline{CH_2}$Ph), 4.43–4.40 (B part of an AB system, J_{AB} = 12.5 Hz, 1H of$\underline{CH_2}$Ph), 4.39–4.36 (m, 1H, $\underline{CH}CH_2$), 3.79–3.74 (m, 4H, $OCH_3 + H_3$), 3.60–3.57 (m, 1H, H_5), 3.35–3.31 (m, 8H, $CH_2SO_2 + CH\underline{CH_2} + H_{6a} + H_{6b} + H_2 + H_4$), 1.198 (s, 9H, *ter*-but), 1.16–1.07 (m, 2H, $\underline{CH_2}Si(CH_3)_3$), −0.045 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 171.5, 166.9, 155.9, 145.1 (C_q esters + C_q *t*-Boc + C_q olef); 138.0, 137.7, 135.4 (C_q arom); 128.5, 128.4, 128.3, 128.1, 128.0, 127.9, 127.7, 127.6, 127.5 (CH arom); 118.6 (C_q olef); 80.0 (C_q *ter*-but); 86.0, 78.7, 78.2, 77.2 ($C_1 + C_3 + C_4 + C_5$); 76.2, 75.1, 73.3, 68.6, 67.2 (4 $\underline{CH_2}$Ph + C_6); 73.4 ($CH_2\underline{CH}$); 54.4 ($\underline{CH_2}CH$); 53.0 (OCH_3); 48.1(C_2); 33.4 (CH_2SO_2); 28.3 (*ter*-but); 9.8 ($\underline{CH_2}Si(CH_3)_3$);−2.0 ($Si(CH_3)_3$). IR: 3360, 2950, 1718, 1595, 1497, 1453, 1352, 1253, 1153, 1072 cm^{-1}. MS (ES): m/z 1006 (100%, $[M + NH_4^+]^+$). Anal. calcd: (%) for $C_{51}H_{64}N_2O_{12}S_2Si$ (989.28): C, 61.92; H, 6.52; N, 2.83; S, 6.48. Found: C, 61.65; H, 6.54; N, 2.70; S, 6.45. $[\alpha]_D^{23}$ + 189° (c 0.28, $CHCl_3$).

Synthesis of carboxylic acid 17

A solution of **16** (100 mg, 0.10 mmol) and LiBr (35 mg, 0.40 mmol) in anhydrous pyridine (3.0 mL) was refluxed for 3.5 h. The solvent was evaporated and silica gel column cromatography (dichloromethane/methanol 9/1; with dichloromethane/methanol 9/1, R_f = 0.4) gave **17** (68 mg, 70%) as a pale yellow oil. The ^{1}H NMR is characterized by very broad signals. ^{1}H NMR ($CDCl_3$, 300 MHz): 7.43–7.04 (m, 20H); 6.16–6.13 (m, 1H); 5.03–4.96 (m); 4.97–4.70 (m); 4.53–4.43 (m); 3.61–3.01 (m); 1.2–0.86 (m); 0.025–0.014 (s, 9H, *t*-but) δ. MS (ES): calcd for $C_{50}H_{62}N_2O_{12}S_2Si$: 974 found m/z 875.4 (100%, $[M - t\text{-Boc} + H]^+$), 997.3 (25%, $[M + Na]^+$).

Synthesis of lactam 21

TBAF (0.24 mmol) was added to an ice-cooled solution of **16** (120 mg, 0.12 mmol) in THF (2.0 mL). The ice bath was immediately removed and the solution was stirred at room temperature until the complete disappearance of the starting material was observed (about 6 h). The solution was diluted with CH_2Cl_2 and washed with saturated solution of NH_4Cl (3×3.0 mL). The organic phase was dried over anhydrous sodium sulfate and after evaporation of the solvent silica gel column chromatography of the crude product (petroleum ether/ethyl acetate 2.5/1) gave **21** (75 mg, 80%) as a yellow oil as a mixture of isomers (1.5/1, isomer with higher R_f/isomer with lower R_f).

Spectral data of the first isomer (higher R_f): ^{1}H NMR spectra at different temperatures show sharpening of the peaks.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.16 (m, 15H, Ph); 5.97 (bm, 1H, H_1); 5.13–5.09 (bm, 1H, $\underline{CH}CH_2$); 4.68–4.51 (m, 6H, 3 $\underline{CH_2}$Ph); 4.18–4.11 (m, 1H, $\underline{CH}CH_2$); 4.02–3.98 (m, 1H, H_5); 3.86–3.70 (m, 8H, $H_{6a} + H_{6b} + OCH_3 + H_3 + H_4 + 1H$ of $CH\underline{CH_2}$); 3.28 (bm, 1H, H_2); 3.153 (m, 1H); 1.430 (s, 9H, *ter*-but). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 172.9 (C_q lact); 164.4 (C_q esters); 155.0, 145.1 (C_q *t*-Boc + C_q olef); 138.0, 137.6, 137.1 (C_q arom); 128.4, 128.3, 128.2, 128.1, 127.9, 127.7, 127.6, 127.5 (CH arom); 96.8 (C_q olef); 80.7; 77.2; 74.6;

74.0, 73.8, 73.6, 73.5 (broad signals); 68.4; 68.2; 53.4; 52.1; 50.1; 41.1; 34.0; 28.3.MS (ES): calcd for $C_{39}H_{44}N_2O_9S$: 716 Found: *m/z* 717.3 (35%, $[M+H]^+$), 734.3 (100%, $[M+NH_4^+]^+$), 739.2 (30%, $[M+Na]^+$).

Spectral data of the second isomer (lower R_f): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.36–7.15 (m, 15H, Ph); 5.866 (bd, $J=3.3$ Hz, 1H, H_1); 5.12–5.10 (m, 1H, NH); 4.74–4.49 (m, 6H, 3 $\underline{CH_2}$Ph); 4.19–4.12 (m, 1H, $\underline{CH}CH_2$); 4.06–4.03 (m, 1H, H_5); 3.99–3.69 (m, 8H, $H_{6a}+H_{6b}+OCH_3+H_3+H_4+1H$ of $CH\underline{CH_2}$); 3.259 (bdd, $J_{2,1}=4.0$ Hz, $J_{2,3}=6.6$ Hz, 1H, H_2); 3.10–3.07 (A part of an ABX system, $J_{AB}=16.8$ Hz, $J_{AX}=7.3$ Hz, 1H of $CH\underline{CH_2}$); 3.04–3.02 (B part of an ABX system, $J_{AB}=16.8$ Hz, $J_{BX}=7.3$ Hz, 1H of $CH\underline{CH_2}$); 1.426 (s, 9H, *ter*-but). MS (ES): calcd for $C_{39}H_{44}N_2O_9S$: 716. Found: *m/z* 717.3 (35%, $[M+H]^+$), 734.3 (100%, $[M+NH_4^+]^+$), 739.2 (30%, $[M+Na]^+$).

Synthesis of lactam 19

Compound **16** (51 mg, 0.05 mmol) was dissolved at 0 °C in 0.8 mL of a 10% solution of CF_3COOH in anhydrous CH_2Cl_2. Ten min after the addition the ice bath was removed and the solution was left for 2 h at room temperature with magnetic stirring. The solvent was evaporated and Et_2O was added to the crude product to precipitate the salt of the amine as a white solid. After evaporation of the solvent the product was dissolved in anhydrous DMF (2.0 mL) and NEt_3 (8.5 μL, 0.06 mmol) was added. The solution was left at room temperature for 4 h and the solvent was removed by evaporation and silica gel column chromatography of the crude product (petroleum ether/ethyl acetate 1/1, visualized with UV and phosphomolibdic acid) gave **19** (44 mg, quantitative yield) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.14 (m, 20H, Ph); 6.38 (bs, 1H, NH); 6.152 (d, $J_{1,2}=5.9$ Hz, 1H, H_1); 5.27–5.29 (A part of an AB system, $J_{AB}=12.1$ Hz, 1H of CH_2 of COOBn); 5.17–5.13 (B part of an AB system, $J_{AB}=12.1$ Hz, 1H of CH_2 of COOBn); 4.88–4.82 (A part of an AB system, $J_{AB}=10.0$ Hz, 1H of $\underline{CH_2}$Ph); 4.85-4.78 (m, 1H of $\underline{CH_2}$Ph); 4.73–4.70 (B part of an AB system, $J_{AB}=10.0$ Hz, 1H of $\underline{CH_2}$Ph); 4.58–4.51 (m, 3H); 4.24–4.19 (m, 1H, $\underline{CH}CH_2$); 3.78–3.26 (m, 8H, $H_2+H_3+H_4+H_5+H_{6a}+H_{6b}+1H$ of CH_2SO_2+1H of $CH\underline{CH_2}$); 3.05–2.92 (m, 2H, 1H of CH_2SO_2+1H of $CH\underline{CH_2}$); 1.11–1.05 (m, 2H, $CH_2Si(CH_3)_3$); 0.00 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.2, 163.2 (C_q est. + C_q lact); 143.4 (C_q olef); 137.5, 137.4, 137.3 (C_q arom); 134.5 (C_q arom); 128.6, 128.4, 128.3, 128.1, 127.9, 127.8, 127.7, 127.6 (CH arom); 116.3 (C_q olef); 85.8 (CH); 78.2, 77.9 (2 CH); 76.0, 75.2, 73.6 (3 CH_2); 72.4 (CH); 68.4, 68.1 (2 CH_2); 52.6 (CH_2); 52.2 (CH); 46.3 (CH); 32.0 (CH_2SO_2); 9.9 ($\underline{CH_2}Si(CH_3)_3$); −1.92 ($Si(CH_3)_3$).

Synthesis of desulfonylated lactam 20

TBAF (0.16 mmol) was added to a solution of **19** (140 mg, 0.16 mmol) in anhydrous THF (2.5 mL) and the solution was stirred until the complete disappearance of the starting material was detected (about 4 h). After dilution with CH_2Cl_2 the solution was washed with saturated solution of NH_4Cl (3×3.0 mL). The organic phase was dried over anhydrous sodium sulfate and after evaporation of the solvent the crude product was purified by silica gel column chromatography (petroleum ether/ethyl acetate 1/2, $R_f=0.30$, $R_f=0.22$ visualized with UV and phosphomolybdic acid) to afford **20** (109 mg, 96%) as a yellow oil as a mixture of isomers (3/1, isomer with $R_f=0.30$/isomer with $R_f=0.22$).

Spectral data of the first isomer ($R_f=0.30$): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.14 (m, 20H, Ph); 5.79 (bs, 1H, NH); 5.334 (d, $J_{1,2}=4.4$ Hz, 1H, H_1); 5.25–5.21 (A part of an AB system, $J_{AB}=12.1$ Hz, 1H of CH_2 of COOBn); 5.19–5.15 (B part of an AB system, $J_{AB}=12.1$ Hz, 1H of CH_2 of COOBn); 5.03–5.00 (A part of an AB system, $J_{AB}=10.2$ Hz, 1H of $\underline{CH_2}$Ph); 4.88–4.84 (A part of an AB system, $J_{AB}=10.6$ Hz, 1H of $\underline{CH_2}$Ph); 4.77–4.74 (B part of an AB system, $J_{AB}=10.2$ Hz, 1H of $\underline{CH_2}$Ph); 4.59–4.51 (m, 2H, $\underline{CH_2}$Ph); 4.51–4.47 (B part of an AB system, $J_{AB}=10.6$ Hz, 1H of $\underline{CH_2}$Ph); 4.43 (bs, 1H, NH); 4.18–4.11 (m, 1H,$\underline{CH}CH_2$); 3.94–3.91 (m, 1H); 3.65–3.63 (m, 2H, $H_{6a}+H_{6b}$); 3.62–3.51 (m, 2H); 3.162 (dd, $J_{2,1}=4.0$ Hz, $J_{2,3}=9.2$ Hz, H_2); 2.70–2.67 (m, 2H, $CH\underline{CH_2}$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.6, 165.2 (C_q esters + C_q lact); 144.7 (C_q olef); 137.9, 137.8, 137.7, 134.8 (C_q arom); 128.9, 128.8, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 127.9, 127.8, 127.7 (CH arom); 88.0 (C_q olef.); 78.9; 78.7; 78.0; 77.2; 75.3; 73.6; 72.2; 69.2; 67.7; 51.9; 41.7; 31.3. MS (ES): calcd for $C_{40}H_{40}N_2O_7S$: 692. Found *m/z* 693.5 (100%, $[M+H]^+$), 715.5 (30%, $[M+Na]^+$).$[\alpha]_D^{23}$ +214° (*c* 0.13, $CHCl_3$).

Spectral data of the second isomer ($R_f=0.22$): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.39–7.14 (m, 20H, Ph); 5.796 (bd, $J=1.8$ Hz, 1H, NH); 5.384 (d, $J_{1,2}=4.8$ Hz, 1H, H_1); 5.22–5.18 (A part of an AB system, $J_{AB}=12.1$ Hz, 1H of CH_2 of COOBn); 5.16–5.12 (B part of an AB system, $J_{AB}=12.1$ Hz, 1H of CH_2 of COOBn); 4.99–4.95 (A part of an AB system, $J_{AB}=9.9$ Hz, 1H of $\underline{CH_2}$Ph); 4.88–4.84 (A part of an AB system, $J_{AB}=10.6$ Hz, 1H of $\underline{CH_2}$Ph); 4.69–4.66 (B part of an AB system, $J_{AB}=9.9$ Hz, 1H of $\underline{CH_2}$Ph); 4.57–4.52 (m, 2H); 4.50–4.47 (B part of an AB system, $J_{AB}=10.6$ Hz, 1H of $\underline{CH_2}$Ph); 4.17–4.12 (m, 1H, $\underline{CH}CH_2$); 3.69–3.60 (m, 2H); 3.54–3.43 (m, 2H); 2.84–2.76 (A part of an ABX system, $J_{AB}=15.7$ Hz, $J_{AX}=8.4$ Hz, 1H of $CH\underline{CH_2}$); 2.74–2.66 (B part of an ABX system, $J_{AB}=15.7$ Hz, $J_{BX}=5.9$ Hz, 1H of $CH\underline{CH_2}$). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.1, 165.7 (C_q esters + C_q lact); 145.6 (C_q olef); 138.1, 137.9, 137.8; 134.7 (C_q arom); 128.7, 128.6, 128.5, 128.3, 128.2, 128.0, 127.9, 127.8, 127.7, 127.6 (CH arom); 87.6 (C_q olef); 79.2, 78.7, 78.4, 76.8, 75.1, 73.6, 72.1, 69.3, 67.7, 51.2, 41.3, 31.3. MS (ES): calcd for $C_{40}H_{40}N_2O_7S$: 692. Found *m/z* 693.5 (100%, $[M+H]^+$), 715.5 (30%, $[M+Na]^+$).

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