Solid-Phase [2+2] Cycloadditions between Chlorosulfonyl Isocyanate and Chiral Vinyl Ethers

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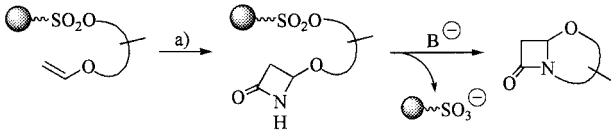
Vinyl ethers **10**, **23**, and **33** were attached to Wang resin through the *p*-oxyphenylsulfonyl linker. The [2+2] cycloadditions between chlorosulfonyl isocyanate and the polymer-bound vinyl ethers **12**, **24**, and **34**, followed by intramolecular alkylation of the β-lactam nitrogen atom, gave mixtures of the corresponding diastereomeric clavams **8/9** and **21/22** or the oxacephams **31/32**, accompanied by the oxirane **7** or the oxetane **30**, respectively. This cyclization/cleavage step was performed in the presence of the strong organic bases BEMP and DBU. The corresponding reaction sequences performed in solution provided the oxabicyclic β-lactams without the accompanying anhydrosugars.

Introduction

Solid-phase organic synthesis (SPOS) enables a large number of structurally akin molecules to be prepared in a short time, and provides a valuable tool for lead discovery in the search for new therapeutics.[1] Thanks to the importance of β-lactam antibiotics, a number of SPOS approaches to this class of compounds have recently been reported.[2,3] In particular, [2+2] cycloadditions between ketenes and resin-bound imines have attracted the attention of many laboratories.[3] Alternative to the [2+2] cycloaddition of ketenes to imines [2+2] cycloadditions between isocyanates and olefins by SPOS methodology, however, have not so far been reported.

We have shown that [2+2] cycloadditions between chlorosulfonyl isocyanate (CSI) and chiral vinyl ethers proceed in many cases with excellent stereoselectivity and allow control of the configuration at C-4 of the 4-alkoxyazetidin-2-one.[4] The cycloadducts offer a route to 5-oxacephams and clavams through suitable transformation of a chiral auxiliary.[4] The experience we have gained in [2+2] cycloaddition reactions between CSI and vinyl ethers has prompted us to investigate these reactions under solid-phase conditions. When undertaking this task, we were aware that simple transfer of reaction conditions from solution to solid-phase may not always provide the expected results.

For this study we selected 5-*O*-vinyl[5] and (*Z*)-5-*O*-propenyl ethers of 1,2-*O*-isopropylidene-α-D-glucofuranose and (*Z*)-3-*O*-propenyl ethers of 1,2-*O*-isopropylidene-α-D-xylofuranose.[6] In reactions performed in solution, these afforded high stereoselectivity, providing the (*S*) and the (*R*) configuration, respectively, at C-4 of the azetidin-2-one. Binding of the vinyl ether to the polymer support through a sulfonyl linker seemed to be the most attractive approach, since the intramolecular alkylation of the nitrogen atom after the cycloaddition step, to form the bicyclic structure, would remove the product from the resin by a cyclization/cleavage methodology (Scheme 1).[7]



Scheme 1. a) i. CSI, Na_2CO_3; ii. Red-Al

Results and Discussion

We have recently reported a procedure for the polymer-bound sulfonylation of alcohols based on *p*-pivaloyloxyphenylsulfonate esters.[8] After deprotection, the phenolic group of the sulfonate ester is suitable for attachment to the hydroxymethyl terminals of the Wang resin by the Mitsunobu procedure.[9] This procedure does not leave any free sulfonyl acid group on the resin. This could be critical, since [2+2] cycloaddition reactions carried out on sugar vinyl ethers bound to a polymer using chlorosulfonylated resins followed by the cyclization/cleavage methodology did not produce any β-lactam.[10]

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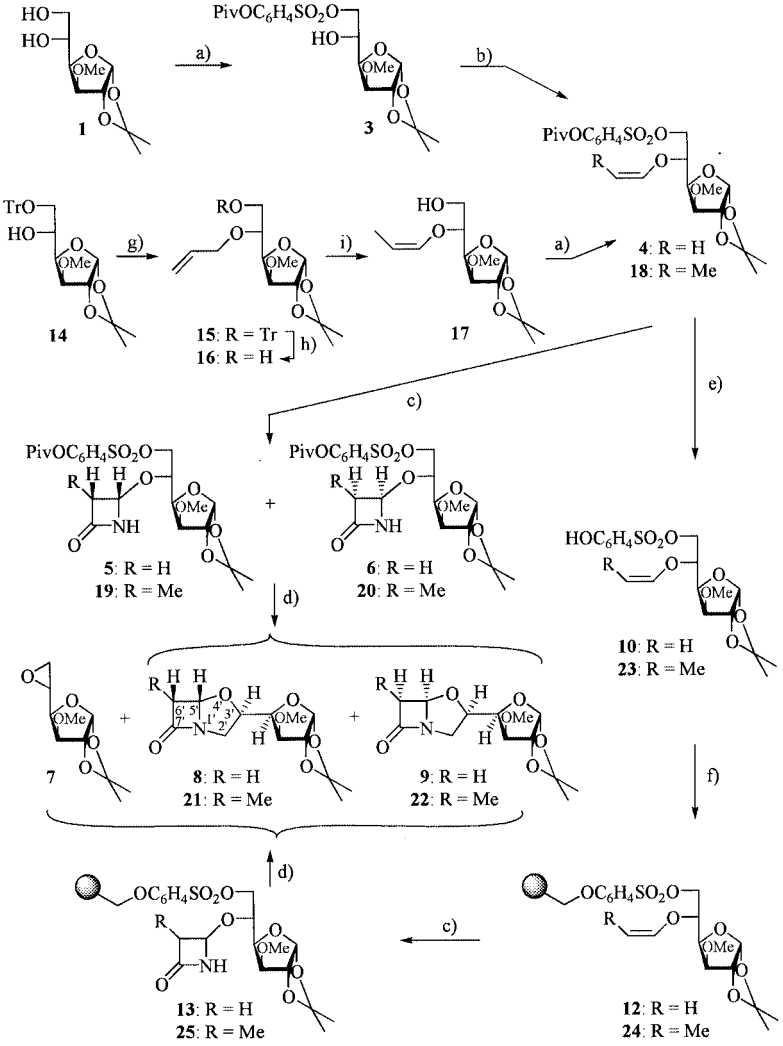
Sulfonylation of **1** with *p*-pivaloyloxybenzenesulfonyl chloride (**2**)[11] gave compound **3**, which was transformed into the vinyl ether **4** by transetherification.[12] Subsequent treatment of **4** with CSI in toluene under standard conditions[13] afforded a mixture of the β-lactams **5** and **6** in relatively low yield (26%) and with 60% *de*. The intramolecular alkylation of the nitrogen atom in the **5/6** mixture provided the known clavams **8** and **9** in a ratio of ca. 4.7:1, respectively.

On the other hand, the pivaloyl residue in **4** was removed with sodium in methanol and the resulting phenol **10** was then attached to the Wang resin **11** by the Mitsunobu reaction procedure.[9] The [2+2] cycloaddition between CSI and the solid-phase-bound vinyl ether **12** gave a mixture of adducts **13**, which was subjected to the cyclization/cleavage methodology in the presence of 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) or DBU to furnish a mixture of the known compounds **7**,[14] **8**, and **9**[5] in a ratio of about 0.1:3:1.

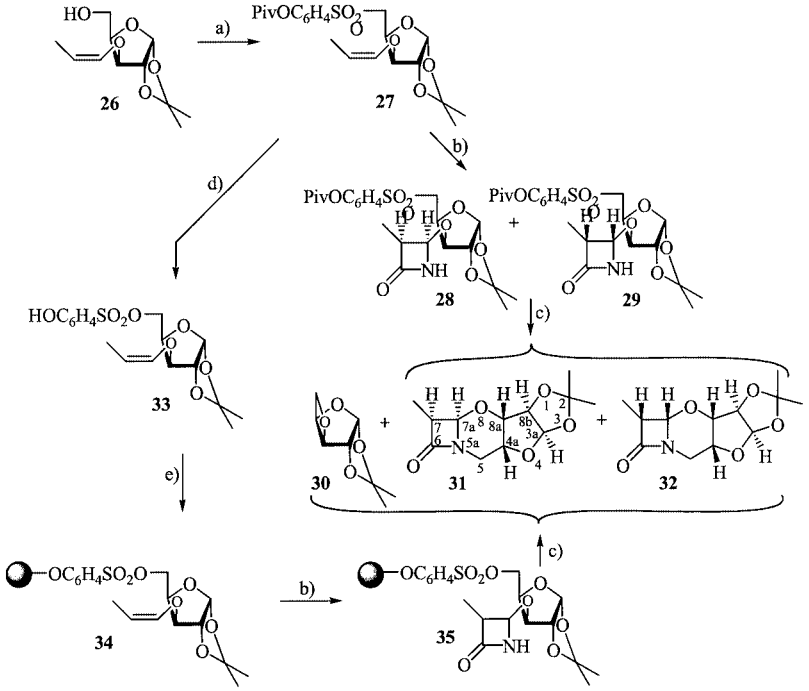
It has been shown that cycloadditions between CSI and (*E*)- and (*Z*)-alkenyl ethers are stereospecific, affording *trans*-3,4-disubstituted azetidin-2-ones from the former and the *cis* counterparts from the latter.[15] In the cases of the two chiral propenyl ethers, the direction of asymmetric induction at C-4 of each *cis* diastereomeric azetidin-2-one was the same as that found for the corresponding unsubstituted vinyl ether. Since (*Z*)-propenyl ethers can be obtained in high yield by potassium *tert*-butoxide rearrangement of the corresponding allyl ethers,[16] we decided to use propenyl ethers rather than vinyl ethers for model studies.

As was expected, [2+2] cycloadditions performed on **4** and on (*Z*)-5-*O*-propenyl ether **18** in solution gave similar proportions of diastereomers **5/6** and **19/20**, amounting to ca. 4:1 and 5:1, respectively (Scheme 2).

Vinyl ether **17** was bound to the Wang resin **11** through the phenol **23**, by the procedure used for **4**. Subsequent cycloaddition with CSI, followed by reduction of the adduct **25** and the cyclization/cleavage step in the presence of



Scheme 2. a) $PivOC_6H_4SO_2Cl$ (**2**), Py, DMAP; b) $Hg(OAc)_2$, Δ*T*; c) i. CSI, Na_2CO_3, CH_2Cl_2/toluene, −78 to −30 °C, 2−0 h, ii. Red-Al; d) BEMP or DBU, CH_3CN, Δ*T*; e) Na/MeOH; f) Wang resin (**11**), DEAD, TPP, CH_2Cl_2, 48 h; g) 60% NaH in mineral oil, DMF, AllBr; h) 1% *p*-TsOH, MeOH; i) *t*BuOK, DMSO, 50 °C



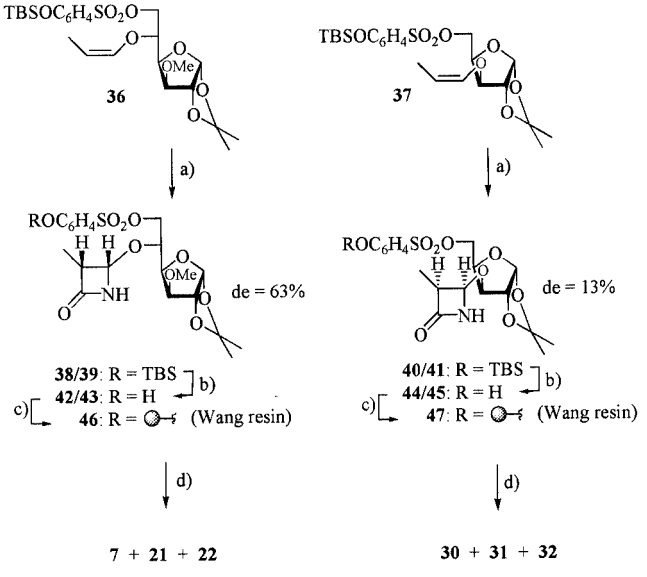
Scheme 3. a) $PivOC_6H_4SO_2Cl$ (**2**), Py, DMAP; b) i. CSI, Na_2CO_3, CH_2Cl_2/toluene, −78 to −30 °C, 2−10 h, ii. Red-Al; c) BEMP or DBU, Δ*T*, CH_3CN; d) Na/MeOH; e) Wang resin (**11**), DEAD, TPP, CH_2Cl_2, 48 h

BEMP or DBU, provided the clavams **21** and **22** and the oxirane **7** in a ratio of about 5:1:9. Prolongation of heating (24 h) of **25** in the presence of BEMP resulted in partial epimerization of the resulting clavams **21/22** at the C-6′ atom.

A similar reaction pattern was observed for 3-*O*-propenyl ether **27**, obtained from the known compound **26**. Cycloaddition between CSI and the ether **27** afforded a mixture of cycloadducts **28** and **29** (26% *de*), which were subjected to the intramolecular alkylation to provide the known cephams **31** and **32** in a ratio of about 1.5:1.0 (Scheme 3). Cycloaddition with the resin-bound vinyl ether **34** and subsequent cyclization/cleavage gave a mixture of **31** and **32**, accompanied by the oxetane **30**,[17] in a ratio of about 1.2:1.1:1.0.

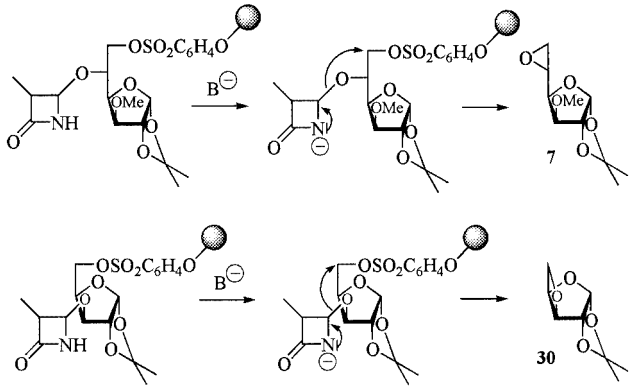
The formation of the oxirane **7** in the case of the cycloaddition/cyclization sequence involving **24**, and that of the oxetane **30** in that of the same process involving **34**, require explanation. The corresponding reactions performed in solution did not show any evidence either of **7** or of **30**. The formation of both compounds might have been caused by the presence of moisture, which might have hydrolyzed either the vinyl ether or the cycloadduct with simultaneous liberation of the corresponding hydroxy group. The basic conditions of the cycloaddition/cleavage step would subsequently result in formation of the epoxide or oxetane. Careful drying of **24** and **34**, however, did not change the proportion of the corresponding anhydrosugar. In order to clarify the reaction pathway, CSI cycloadditions to both ethers **36** and **37** were performed in solution to afford the cycloadducts **38/39** and **40/41** with *de* values of 63 and 13%, respectively (Scheme 4). Desilylation of both diastereomeric mixtures **38/39** and **40/41** allowed them to be attached to the resin by a Mitsunobu procedure.

In the case of **46**, the cycloaddition/cleavage sequence provided a mixture of **7** and **21/22** in a ratio of about 2:9:1, whereas in the case of **47**, the same reaction sequence gave a mixture of **30**, **31**, and **32** in a ratio of about 3:2:6. In each case, the proportion of products was significantly different from that obtained from the [2+2] cycloaddition step performed under solid-phase conditions. The experiments



Scheme 4. a) $PivOC_6H_4SO_2Cl$ (**2**), Py, DMAP; b) TBAB, THF, room temp., 15 min; c) Wang resin (**11**), DEAD, TPP, CH_2Cl_2, 48 h; d) BEMP or DBU, CH_3CN, Δ*T*, 1.5 h

shown in Scheme 5 testify to the formation of anhydrosugars **7** and **30** as an innate feature of the cyclization/cleavage step performed on the resin. This suggests that, on the resin, the adoption of geometries giving rise to the epoxide **7** or oxetane **30** competes with those affording the clavams **21** and **22** or cephams **31** and **32**, respectively. This correlates well with the change in the proportions of the diastereomeric β-lactams during the cyclization/cleavage step. No such difference in the rates of reaction of both diastereomers was observed in solution; in all cases investigated the proportions of diastereomeric β-lactams and the corresponding clavams[5] or cephams[4c] were similar. This clearly points to different energies of the transition states of the cyclization reactions in solution and on solid support.



Scheme 5

Conclusion

It should be stressed that numerous attempts to perform the cycloaddition/cyclization sequence under solid-phase conditions with better overall yield failed. Neither careful drying of the vinyl ether bound to the polymer, nor protection of remaining free hydroxy groups on the resin by acetylation or silylation prior to cycloaddition raised the yields of diastereomeric clavams **8/9** and **21/22** or cephams **31/32**, nor did they eliminate formation of the corresponding anhydrosugars **7** and **30**. The low yield of the cycloaddition/cyclization sequence and the noticeable difference in the rates of reaction of the two diastereomers during the cyclization step did not allow us to assign asymmetric induction in the reactions investigated. It should, however, be reasonable to assume that stereoselectivity in the [2+2] cycloaddition step was in the same range as observed for us for reactions performed in solution.[4c,5] Finally, it is worth noting that in all investigated cases the cyclization/cleavage step could be performed with either BEMP or DBU. The standard basic conditions used by us previously[4−6,13] failed, providing only the anhydrosugars **7** and **30**.

Experimental Section

General: Melting points were determined with a Boetius micromelting point apparatus and are uncorrected. Optical rotations were measured at ambient temperature with a JASCO P 3010 polarimeter. IR spectra were recorded with a Perkin−Elmer FT-IR Spectrum 2000 spectrophotometer. ^{1}H and ^{13}C NMR spectra were obtained with Varian Gemini AC 200 and Bruker Avance 500 spectrometers at ambient temperature with solutions in $CDCl_3$. Mass spectra were determined with an AMD 604 Inectra GmbH spectrometer. All reactions were performed under argon in anhydrous solvents, distilled from the following desiccants: CH_2Cl_2 and pyridine from CaH_2, and THF from Na/benzophenone. The progress of the reactions performed in solution was monitored by thin layer chromatography (TLC) on Merck 60-F_{254} silica gel plates. Column flash chromatography was performed with Merck 60 silica gel (230−400 mesh).

Sources of Compounds: Wang resin **11** (Rapp Polymere; capacity: 1.13 mmol/g, 200−400 mesh) was reagent grade and used as purchased without further purification. *p*-Pivaloyloxybenzenesulfonyl chloride (**2**) was obtained from the commercially available sodium salt of *p*-hydroxybenzenesulfonic acid by the known procedure.[11] Compounds **1**,[18] **14**,[19] and **26**[6] were obtained by literature procedure. The syntheses and spectral and analytical data of compounds **3**, **15**, **16**, and **17** are provided in the Supporting Information.[20]

Synthesis of Compounds 3, 18 and 27. General Procedure: Compounds **3**, **18**, and **27** were obtained from the respective alcohols **1**, **17**,[20] and **26** (10 mmol) by treatment with *p*-pivaloyloxybenzenesulfonyl chloride (**2**) (14 mmol) in pyridine solution (20 mL) at 0 °C overnight. The standard workup, followed by chromatographic purification, afforded compounds **3**, **18**, and **27** in good yield.

1,2-*O*-Isopropylidene-3-*O*-methyl-6-*O*-(*p*-pivaloyloxyphenylsulfonyl)-5-*O*-vinyl-α-D-glucofuranose (4): Compound **4** was obtained from **3** by the known mercury acetate catalyzed transetherification method[12] (82%). Oil. $[\alpha]_D^{22} = -28.8$ (c = 0.72, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32, 1.48 (2 s, 6 H, 2 × Me), 1.38 [s, 9 H, $(CH_3)_3CC(O)-$], 3.37 (s, 3 H, CH_3O-), 3.73 (d, J = 3.1 Hz, 1 H, H-3), 4.03 (dd, J = 1.8 Hz, 1 H and J = 6.4 Hz, H-2′a), 4.10−4.18 (m, 2 H, H-4, H-6a), 4.25−4.29 (m, 1 H, H-5), 4.33 (dd, J = 1.8 Hz, 1 H and J = 13.9 Hz, H-2′b), 4.46 (dd, J = 2.0 Hz, 1 H and J = 10.7 Hz, H-6b), 4.55 (d, J = 3.7 Hz, 1 H, H-2), 5.83 (d, J = 3.7 Hz, 1 H, H-1), 6.23 (dd, J = 6.4 Hz, 1 H and J = 13.9 Hz, H-1′), 7.20−7.26, 7.93−7.97 (2 m, 4 H, phenyl) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.18, 26.69, 26.91, 39.16, 57.43, 70.40, 74.47, 77.83, 81.10, 82.86, 89.72, 105.12, 111.93, 122.28, 129.65, 132.74, 151.02, 155.17, 176.01 ppm. IR (film): $\tilde{\nu}$ = 1759, 1638, 1594, 1370, 1104, 1028 cm^{-1}. HRMS (LSIMS): calcd. for $[M + H]^+$ ($C_{23}H_{33}O_{10}S$) 501.17944, found 501.17777. $C_{23}H_{32}O_{10}S$ (500.58): calcd. C 55.19, H 6.44; found C 55.46, H 6.88. [2+2] Cycloadditions between chlorosulfonyl isocyanate and the vinyl ethers **4**, **18**, and **27** were performed according to the known procedure.[5,6,13]

(4′*S*)- and (4′*R*)-1,2-*O*-Isopropylidene-3-*O*-methyl-5-*O*-(2′-oxoazetidin-4′-yl)-6-*O*-(*p*-pivaloyloxyphenylsulfonyl)-α-D-glucofuranose (5 and 6): A mixture of compounds **5/6** in a ratio of ca. 4:1 was obtained from **4** by the known procedure.[5,6,13] Purification by flash chromatography on silica gel (65% EtOAc in hexane) furnished a mixture of **5/6** as a solid foam (26%). **5:** ^{1}H NMR (500 MHz, $CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 2.85 (dd, J = 0.7 Hz, 1 H and J = 15.2 Hz, H-3′a), 3.77 (d,

J = 2.7 Hz, 1 H, H-3), 4.57 (d, J = 3.7 Hz, 1 H, H-2), 5.28 (dd, J = 1.4 Hz, 1 H and J = 4.0 Hz, H-4′), 5.80 (d, J = 3.7 Hz, 1 H, H-1), 6.29 (br. s, 1 H, NH) ppm. **6:** ^{1}H NMR ($CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 2.79 (dd, J = 0.7 Hz, 1 H and J = 15.0 Hz, H-3′a), 3.75 (d, J = 2.8 Hz, 1 H, H-3), 4.55 (d, J = 3.7 Hz, 1 H, H-2), 5.14 (dd, J = 1.4 Hz, 1 H and J = 4.0 Hz, H-4′), 5.82 (d, J = 3.7 Hz, 1 H, H-1), 6.52 (br. s, 1 H, NH) ppm. IR (CH_2Cl_2): $\tilde{\nu}$ = 3418, 1759, 1736, 1365, 1178, 1082, 1026 cm^{-1}. HRMS (LSIMS): calcd. for $[M + H]^+$ ($C_{24}H_{34}O_{11}NS$) 544.18526, found 544.18485. $C_{24}H_{33}NO_{11}S$ (543.60): calcd. C 53.02, H 6.10, N 2.57; found C 52.69, H 6.43, N 2.47.

(4*S*,3′*R*,5′*S*)- and (4*S*,3′*R*,5′*R*)-4-*C*-(4′-Dethia-4′-oxapenam-3′-yl)-1,2-*O*-isopropylidene-3-*O*-methoxy-β-L-threofuranose (8 and 9): The mixture of **5** and **6** (0.24 g, 0.44 mmol) was dissolved in anhydrous CH_3CN (12 mL) and treated with Bu_4NBr (0.18 g, 0.57 mmol) and pulverized K_2CO_3 (0.6 g). The mixture was stirred and kept under reflux for ca. 1 h (TLC). Subsequently, toluene (10 mL) was added, the residue was filtered, washed with water, and dried (Na_2SO_4), and the solvents were evaporated. The crude product was separated by flash chromatography on silica gel with an ethyl acetate/hexane mixture (1:5, v/v) as eluent to give **8** (0.076 g, 61%) and **9** (0.010 g, 8%). The spectral and analytical data of compound **8** are identical to those reported in the literature.[5] **9:** Oil. $[\alpha]_D^{22}$ = +30.3 (c = 0.1, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32, 1.49 (2 s, 6 H, 2 × Me), 2.87 (d, J = 15.9 Hz, 1 H, H-6′a), 3.13 (dd, J = 7.1 Hz, 1 H and J = 11.5 Hz, H-2′a), 3.23 (dd, J = 2.5 Hz, 1 H and J = 15.9 Hz, H-6′b), 3.43 (s, 3 H, CH_3O−), 3.75 (d, J = 3.3 Hz, 1 H, H-3), 3.90 (dd, J = 5.4 Hz, 1 H and J = 11.5 Hz, H-2′b), 4.13 (dd, J = 3.3 Hz, 1 H and J = 6.8 Hz, H-4), 4.51 (q, J = 6.8 Hz, 1 H, H-3′), 4.56 (d, J = 3.7 Hz, 1 H, H-2), 5.19 (d, J = 2.5 Hz, 1 H, H-5′), 5.87 (d, J = 3.7 Hz, 1 H, H-1) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.30, 26.87, 44.69, 48.68, 57.99, 80.31, 81.38, 81.64, 83.82, 84.63, 105.17, 112.01, 177.01 ppm. IR (film): $\tilde{\nu}$ = 1784 cm^{-1}. HRMS (LSIMS): calcd. for $[M + H]^+$ ($C_{13}H_{20}O_6N$) 286.12906, found 286.12765.

Synthesis of Compounds 10, 23, and 33. General Procedure: Compounds **10**, **23**, and **33** were obtained from the corresponding *p*-pivaloyloxyphenylsulfonates **4**, **18**, and **27** (6 mmol) by treatment with sodium (10 mmol) in MeOH solution (10 mL) at room temperature. After 1−2 h, the reaction mixtures were treated with solid carbon dioxide and extracted with CH_2Cl_2. The extracts were washed with water and dried ($MgSO_4$), and the solvents were evaporated to give crude products. Chromatographic purification afforded compounds **10**, **23**, and **33**, respectively.

6-*O*-(*p*-Hydroxyphenylsulfonyl)-1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-vinyl-α-D-glucofuranose (10): Compound **10** was obtained from **4** by the procedure described above (87%). Oil. $[\alpha]_D^{22}$ = −27.9 (c = 0.7, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31, 1.46 (2 s, 6 H, 2 × Me), 3.36 (s, 3 H, CH_3O−), 3.73 (d, J = 3.1 Hz, 1 H, H-3), 4.02 (dd, J = 1.7 Hz, 1 H and J = 6.3 Hz, H-2′a), 4.08 (dd, J = 6.8 Hz, 1 H and J = 10.7 Hz, H-6a), 4.09−4.16 (m, 1 H, H-4), 4.22−4.27 (m, 1 H, H-5), 4.32 (dd, J = 1.7 Hz, 1 H and J = 13.9 Hz, H-2′b), 4.38 (dd, J = 2.0 Hz, 1 H and J = 10.7 Hz, H-6b), 4.55 (d, J = 3.7 Hz, 1 H, H-2), 5.82 (d, J = 3.7 Hz, 1 H, H-1), 6.24 (dd, J = 6.3 Hz, 1 H and J = 13.9 Hz, H-1′), 6.89−6.93, 7.75−7.79 (2 m, 4 H, phenyl) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 26.18, 26.72, 57.57, 70.14, 74.67, 78.02, 81.20, 82.94, 89.86, 105.18, 112.14, 115.95, 126.87, 130.51, 151.17, 160.69 ppm. IR (film): $\tilde{\nu}$ = 3403, 1638, 1603, 1589, 1355, 1165, 1080, 841 cm^{-1}. HRMS (LSIMS): calcd. for $[M + H]^+$ ($C_{18}H_{25}O_9S$) 417.12193, found 417.12239. $C_{18}H_{24}O_9S$ (416.45): calcd. C 51.90, H 5.81; found C 52.25, H 6.72.

Preparation of Polymer-Bound Sulfonate Esters 12, 24, and 34 by the Mitsunobu Reaction. General Procedure: Phenol **10** (0.63 g, 1.5 mmol) and PPh_3 (0.39 g, 1.5 mmol) were added to a suspension of Wang resin **11** (0.38 g, 0.43 mmol) in CH_2Cl_2 (5 mL). The mixture was cooled to 0 °C, DEAD (diethyl azodicarboxylate, 0.24 mL, 1.5 mmol) was added dropwise over 10 min, and the reaction mixture was allowed to warm to room temperature. The suspension was stirred for 48 h, it was then filtered and washed [2 × 10 mL each CH_2Cl_2, MeOH, THF, THF/water (2:1), THF, MeOH, CH_2Cl_2, and Et_2O], and then dried for 6 h under vacuum to give resin **12**. IR (KBr disk): $\tilde{\nu}$ = 1636, 1599, 1373, 1167, 1079, 756 cm^{-1}. **12**: calcd. S 2.49; found S 2.27. Elemental analysis indicating 2.27% S corresponds to a 91% yield. Capacity of **12**: 0.71 mmol/g.

[2+2] Cycloadditions between CSI and Resin-Bound Vinyl Ethers 12, 24, and 34. General Procedure: CSI (0.24 mL, 2.8 mmol) was added at −78 °C to a suspension of anhydrous Na_2CO_3 (0.2 g) and resin **12** (0.4 g, 0.28 mmol) in a CH_2Cl_2/toluene mixture (1:1, v/v; 12 mL). The reaction mixture was stirred at −78 °C for 30 min, and then at −30 °C for another 10 h. Subsequently, the suspension was cooled to −78 °C, diluted with the CH_2Cl_2/toluene mixture (14 mL), treated with Red-Al (1 M solution in toluene, 2.8 mL), and left for 30 min, whilst the temperature of the reaction mixture was maintained. The temperature was then allowed to rise to 0 °C, and water (2.8 mL) was added. The mixture was stirred for 30 min, and then filtered and washed (3 × 10 mL) with 10% aqueous potassium sodium tartrate, H_2O, DMF, H_2O, MeOH, THF, MeOH, CH_2Cl_2, and Et_2O, and then dried for 16 h under vacuum to give β-lactam bound to the resin. **13**: IR (KBr disk): $\tilde{\nu}$ = 3370, 1778, 1599, 1492, 1364, 1164, 1075, 747 cm^{-1}. calcd. N 0.96; found N 0.87. Elemental analysis indicating 0.87% N corresponds to a 91% yield. Capacity of **13**: 0.62 mmol/g.

Synthesis of Clavams 8, 9, 21, and 22 and 5-Oxacephams 31 and 32 by the Cyclization/Cleavage Step. General Procedure: The resin **13** (0.1 g, 0.062 mmol) was suspended in anhydrous CH_3CN (3 mL) and treated with BEMP (0.036 mL, 0.124 mmol) or DBU (0.018 mL, 0.124 mmol). The mixture was stirred and kept under reflux for ca. 3 h. The resin was filtered and washed (3 × 5 mL each) with THF and Et_2O. The organic layer was separated and the solvents were evaporated. The residue was diluted with CH_2Cl_2 (15 mL), washed with 10% citric acid and water, dried ($MgSO_4$), and concentrated. The crude mixture was separated on a silica gel column with an ethyl acetate/hexane mixture (1:5, v/v) as eluent to give **8**, **9**, and the anhydrosugar **7**.

5,6-Anhydro-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (7): Compound **7**, obtained from **13**, **25**, and **46**, displayed spectral and analytical data identical to those reported in the literature.[14]

1,2-*O*-Isopropylidene-3-*O*-methyl-6-*O*-(*p*-pivaloyloxyphenylsulfonyl)-5-*O*-(prop-1′-enyl)-α-D-glucofuranose (18): Compound **18** was obtained from **17** by the general procedure described earlier[6] (74%). Oil. $[\alpha]_D^{22}$ = −25.1 (c = 0.42, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31, 1.47 (2 s, 6 H, 2 × Me), 1.37 [s, 9 H, $(CH_3)_3CC(O)$−], 1.52 (dd, 3 H, J = 1.6 Hz and J = 6.8 Hz, CH_3-3′), 3.35 (s, 3 H, CH_3O−), 3.71 (d, J = 2.7 Hz, 1 H, H-3), 4.07−4.14, 4.35−4.43 (2 m, 5 H, H-2, H-4, H-5, H-6a, H-6b), 4.53 (d, J = 3.7 Hz, 1 H, H-2), 5.81 (d, J = 3.7 Hz, 1 H, H-1), 5.95 (dq, J = 6.1 Hz, 1 H and J = 1.7 Hz, H-1′), 7.23−7.26, 7.92−7.95 (2 m, 4 H, phenyl) ppm. IR (film): $\tilde{\nu}$ = 1759, 1669, 1370, 1106 cm^{-1}. HRMS (EI): calcd. for $[M]^+$ ($C_{24}H_{34}O_{10}S$) 514.18727, found 514.18716. $C_{24}H_{34}O_{10}S$ (514.61): calcd. C, 56.02, H 6.66; found C 55.95, H 6.67.

(3′*R*,4′*S*)- and (3′*S*,4′*R*)-1,2-*O*-Isopropylidene-3-*O*-methyl-5-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-6-*O*-(*p*-pivaloyloxyphenylsulfonyl)-α-D-

glucofuranose (19 and 20): Compounds **19/20** were obtained in a ratio of ca. 5:1 from **18** by the known procedure.[5,6,13] Chromatographic separation on silica gel with a hexane/ethyl acetate mixture (4:6, v/v) as eluent gave **19/20** (69%). Solid foam. **19:** ^{1}H NMR (500 MHz, $CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 1.20 (d, *J* = 7.5 Hz, 3 H, CH_3-3′), 3.29−3.35 (m, 1 H, H-3′), 3.40 (s, 3 H, CH_3O−), 3.77 (d, *J* = 2.6 Hz, 1 H, H-3), 4.57 (d, *J* = 3.7 Hz, 1 H, H-2), 5.27 (d, *J* = 4.3 Hz, 1 H, H-4′), 5.81 (d, *J* = 3.7 Hz, 1 H, H-1), 6.24 (br. s, 1 H, NH) ppm. **20:** ^{1}H NMR (500 MHz, $CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 1.19 (d, *J* = 7.5 Hz, 3 H, CH_3-3′), 3.25−3.28 (m, 1 H, H-3′), 3.39 (s, 3 H, CH_3O−), 3.75 (d, *J* = 3.0 Hz, 1 H, H-3), 4.56 (d, *J* = 3.7 Hz, 1 H, H-2), 5.09 (d, *J* = 4.4 Hz, 1 H, H-4′), 5.82 (d, *J* = 3.7 Hz, 1 H, H-1), 6.53 (br. s, 1 H, NH) ppm. IR (film): ṽ = 3355, 1761, 1367, 1107 cm^{-1}. HRMS (LSIMS): calcd. for $[M + H]^+$ ($C_{25}H_{36}O_{11}NS$) 558.20091, found 558.20224.

(4*S*,3′*R*,5′*S*,6′*R*)- and (4*S*,3′*R*,5′*R*,6′*S*)-4-*C*-(4′-Dethia-6′-methyl-4′-oxapenam-3′-yl)-1,2-*O*-isopropylidene-3-*O*-methoxy-β-L-threofuranose (21 and 22): Compounds **21/22** were obtained from the **19/20** mixture by the procedure described for **8/9**. After chromatographic separation with a hexane/ethyl acetate mixture (8.5:1.5, v/v) as eluent, the pure components were obtained. **21:** Oil. $[\alpha]_D^{22}$ = −124.2 (*c* = 0.49, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (d, *J* = 7.6 Hz, 3 H, CH_3-6′), 1.32, 1.49 (2 s, 6 H, 2 × Me), 2.98 (ddd, 1 H, *J* = 0.6 Hz, *J* = 7.2 Hz and *J* = 12.0 Hz, H-2′a), 3.39 (ddd, 1 H, *J* = 0.5 Hz, *J* = 3.2 Hz and *J* = 15.0 Hz, H-6′), 3.42 (s, 3 H, CH_3O−), 3.77 (d, *J* = 3.3 Hz, 1 H, H-3), 3.91 (dd, *J* = 6.4 Hz, 1 H and *J* = 12.0 Hz, H-2′b), 4.30 (dd, *J* = 3.3 Hz, 1 H and *J* = 5.7 Hz, H-4), 4.32−4.34 (m, 1 H, H-3′), 4.55 (d, *J* = 3.7 Hz, 1 H, H-2), 5.30 (d, *J* = 3.2 Hz, 1 H, H-5′), 5.87 (d, *J* = 3.7 Hz, 1 H, H-1) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.71, 26.23, 26.86, 47.29, 48.97, 58.09, 78.90, 80.96, 81.71, 84.10, 87.10, 105.28, 111.92, 182.56 ppm. IR (film): ṽ = 1783 cm^{-1}. HRMS (EI): calcd. for $[M]^+$ ($C_{14}H_{21}NO_6$) 299.13689, found 299.13655. $C_{14}H_{21}NO_6$ (299.33): calcd. C 56.18, H 7.07, N 4.68; found C 55.92, H 6.97, N 4.62. **22:** White solid. M.p. 68−71 °C. $[\alpha]_D^{22}$ = +42.9 (*c* = 0.43, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.19 (d, *J* = 7.6 Hz, 3 H, CH_3-6′), 1.32, 1.48 (2 s, 6 H, 2 × Me), 3.11 (ddd, 1 H, *J* = 0.7 Hz, *J* = 7.2 Hz and *J* = 11.6 Hz, H-2′a), 3.37−3.42 (m, 1 H, H-6′), 3.43 (s, 3 H, CH_3O−), 3.75 (d, *J* = 3.2 Hz, 1 H, H-3), 3.83 (dd, *J* = 5.4 Hz, 1 H and *J* = 11.6 Hz, H-2′b), 4.09 (dd, *J* = 3.3 Hz, 1 H and *J* = 7.1 Hz, H-4), 4.52−4.56 (m, 1 H, H-3′), 4.54 (d, *J* = 3.7 Hz, 1 H, H-2), 5.17 (d, *J* = 3.0 Hz, 1 H, H-5′), 5.87 (d, *J* = 3.7 Hz, 1 H, H-1) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 7.74, 26.34, 26.86, 47.90, 48.27, 58.02, 79.84, 81.19, 81.66, 83.97, 87.42, 105.15, 111.99, 181.69 ppm. IR (CH_2Cl_2): ṽ = 1780 cm^{-1}. HRMS (EI): calcd. for $[M]^+$ ($C_{14}H_{21}NO_6$) 299.13689, found 299.13661. $C_{14}H_{21}NO_6$ (299.33): calcd. C 56.18, H 7.07, N 4.68; found C 56.24, H 7.21, N 4.52.

6-*O*-(*p*-Hydroxyphenylsulfonyl)-1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-(prop-1′-enyl)-α-D-glucofuranose (23): Compound **23** was obtained from **18** by the procedure described above (86%). Oil. $[\alpha]_D^{22}$ = −25.5 (*c* = 0.4, CH_2Cl_2). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31, 1.48 (2 s, 6 H, 2 × Me), 1.52 (dd, 3 H, *J* = 1.6 Hz and *J* = 6.8 Hz, CH_3−3′), 1.64 (br. s, 1 H, −OH), 3.36 (s, 3 H, CH_3O−), 3.72 (d, *J* = 2.4 Hz, 1 H, H-3), 4.03−4.15, 4.33−4.42 (2 m, 5 H, H-2′, H-4, H-5, H-6a, H-6b), 4.54 (d, *J* = 3.7 Hz, 1 H, H-2), 5.81 (d, *J* = 3.7 Hz, 1 H, H-1), 5.97 (dq, *J* = 6.1 Hz, 1 H and *J* = 1.6 Hz, H-1′), 6.89−6.93, 7.76−7.79 (2 m, 4 H, phenyl) ppm. IR (film): ṽ = 3411, 1669, 1589, 1357, 1081 cm^{-1}. HRMS (EI): calcd. for $[M]^+$ ($C_{19}H_{26}O_9S$) 430.12975, found 430.12740. $C_{19}H_{26}O_9S$ (430.48): calcd. C 53.01, H 6.09.found C 52.57, H 6.22.

Resin 24: Resin **24** was obtained according to the Mitsunobu procedure described above. IR (KBr disk): ṽ = 3487, 1669, 1599, 1373, 1166, 1079, 692 cm^{-1}. calcd. S 2.47; found S 2.08. Elemental analysis indicating 2.08% S corresponds to an 84% yield. Capacity of **24**: 0.65 mmol/g.

Resin 25: Resin **25** was obtained according to the general procedure described above. IR (KBr disk): ṽ = 3468, 1748, 1600, 1374, 1241, 1025, 827 cm^{-1}. calcd. N 0.87; found N 0.99. Elemental analysis indicating 0.99% N corresponds to a 99% yield. Capacity of **25**: 0.65 mmol/g. Compounds **7**, **21**, and **22** were obtained from the resin **25** according to the general procedure described above to provide a mixture in a ratio of about 5:1:9, respectively

1,2-*O*-Isopropylidene-5-*O*-(*p*-pivaloyloxyphenylsulfonyl)-3-*O*-(prop-1′-enyl)-α-D-xylofuranose (27): Compound **27** was obtained from **26** according to the procedure described above (93%). Oil. $[\alpha]_D^{22}$ = −7.1 (*c* = 0.61, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30, 1.48 (2 s, 6 H, 2 × Me), 1.44 [s, 9 H, $(CH_3)_3CC(O)$−], 1.47 (dd, 3 H, *J* = 1.7 Hz and *J* = 6.9 Hz, CH_3-3′), 4.15 (d, *J* = 3.0 Hz, 1 H, H-3), 4.24 (dd, *J* = 6.2 Hz, 1 H and *J* = 10.1 Hz, H-5a), 4.31 (dd, *J* = 5.3 Hz, 1 H and *J* = 10.1 Hz, H-5b), 4.41−4.59 (m, 3 H, H-2′, H-2, H-4), 5.88 (d, *J* = 3.7 Hz, 1 H, H-1), 5.89 (dq, *J* = 6.1 Hz, 1 H and *J* = 1.7 Hz, H-1′), 7.23−7.30, 7.90−7.98 (2 m, 4 H, phenyl) ppm. IR ($CHCl_3$): ṽ = 1757, 1670, 1376, 1108, 979 cm^{-1}. HRMS (LSIMS): calcd. for $[M + Na]^+$ ($C_{22}H_{30}NaO_9S$) 493.15082, found 493.15203. $C_{22}H_{30}O_9S$ (470.55): calcd. C 56.16, H 6.43; found C 56.41, H 6.78

(3′*S*,4′*R*)- and (3′*R*,4′*S*)-1,2-*O*-Isopropylidene-3-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-5-*O*-(*p*-pivaloyloxyphenylsulfonyl)-α-D-xylofuranose (28 and 29): A **28/29** mixture in a ratio of ca. 1.7:1 was obtained from **27** according to the general procedure described earlier above (52%). Oil. **28:** ^{1}H NMR (500 MHz, $CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 1.16 (d, *J* = 6.7 Hz, 3 H, CH_3-3′), 1.31, 1.47 (s, 3 H, 2 × Me), 4.16 (dd, *J* = 5.5 Hz, 1 H and *J* = 9.8 Hz, H-5a), 4.28 (dd, *J* = 7.3 Hz, 1 H and *J* = 9.8 Hz, H-5b), 4.57 (d, *J* = 3.7 Hz, 1 H, H-2), 5.10 (d, *J* = 4.4 Hz, 1 H, H-4′), 5.88 (d, *J* = 3.7 Hz, 1 H, H-1), 6.43 (br. s, 1 H, NH) ppm. **29:** ^{1}H NMR (500 MHz, $CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 1.14 (d, *J* = 6.7 Hz, 3 H, CH_3−3′), 1.32, 1.48 (s, 3 H, 2 × Me), 4.15 (dd, *J* = 5.2 Hz, 1 H and *J* = 9.7 Hz, H-5a), 4.29 (dd, *J* = 7.7 Hz, 1 H and *J* = 9.7 Hz, H-5b), 4.51 (d, *J* = 3.6 Hz, 1 H, H-2), 5.13 (d, *J* = 4.2 Hz, 1 H, H-4′), 5.87 (d, *J* = 3.6 Hz, 1 H, H-1), 6.57 (br. s, 1 H, NH) ppm. IR (film): ṽ = 3341, 1761 cm^{-1}. HRMS (LSIMS): calcd. for $[M + H]^+$ ($C_{23}H_{32}NO_{10}S$) 514.17469, found 514.17593. $C_{23}H_{31}NO_{10}S$ (513.58): calcd. C 53.79, H 6.08, N 2.73; found C 53.40, H 6.57, N 2.58.

(3a*R*,4a*R*,7*S*,7a*R*,8a*S*,8b*R*)- and (3a*R*,4a*R*,7*R*,7a*S*,8a*S*,8b*R*)-2,2-Dimethyl-hexahydro-1,3,4,8-tetraoxa-5a-aza-cyclobuta[*f*]indeno-[*b*]cyclopentan-6-one[21] (31 and 32): A mixture of **31** and **32** was obtained from the **28/29** mixture according to the procedure described above. Chromatographic separation on silica gel with a hexane/ethyl acetate mixture (3:7, v/v) as eluent gave compounds **31** and **32**, with spectral and analytical data identical to those reported in the literature.[6]

5-*O*-(*p*-Hydroxyphenylsulfonyl)-1,2-*O*-isopropylidene-3-*O*-(prop-1′-enyl)-α-D-xylofuranose (33): Compound **33** was obtained from **27** by the procedure described above (72%). Oil. $[\alpha]_D^{22}$ = −8.6 (*c* = 1.17, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.30, 1.48 (2 s, 6 H, 2 × Me), 1.47 (dd, 3 H, *J* = 1.7 Hz and *J* = 6.8 Hz, CH_3-3′), 4.16 (d, *J* = 3.3 Hz, 1 H, H-3), 4.20 (dd, *J* = 6.6 Hz, 1 H and *J* = 10.2 Hz, H-5a), 4.31 (dd, *J* = 5.5 Hz, 1 H and *J* = 10.2 Hz, H-5b),

4.42−4.60 (m, 2 H, H-2′, H-4), 4.54 (d, J = 3.6 Hz, 1 H, H-2), 5.87−5.93 (m, 2 H, H-1, H-1′), 6.87−6.93, 7.73−7.80 (2 m, 4 H, phenyl) ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 3582, 1670, 1376, 1168, 1082 cm^{-1}. HRMS (LSIMS): calcd. for $[M + H]^+$ ($C_{17}H_{23}O_8S$) 387.11136, found 387.11053. $C_{17}H_{22}O_8S$ (386.43): calcd. C 52.84, H 5.74; found C 53.09, H 6.14.

Resin 34: Resin **34** was obtained by the Mitsunobu procedure as described above. IR (KBr disk): $\tilde{\nu}$ = 3341, 1669, 1597, 1512, 1493, 1374, 1166, 1078, 976, 692 cm^{-1}. calcd. S 2.55; found S 2.05. Elemental analysis indicating 2.05% S corresponds to an 80% yield. Capacity of **34**: 0.65 mmol/g.

Resin 35: Resin **35** was obtained according to the general procedure described above. IR (KBr disk): $\tilde{\nu}$ = 1778, 1595, 1512, 1493, 1373, 1163, 1067 cm^{-1}. calcd. N 1.03; found N 1.00. Elemental analysis indicating 1.00% N corresponds to a 97% yield. Capacity of **35**: 0.64 mmol/g. Compounds **30**, **31**, and **32** were obtained from the resin **35** by the procedure described above.

3,5-Anhydro-1,2-*O*-isopropylidene-α-D-xylofuranose (30): Compound **30**, obtained from **35** and **47**, displayed spectral and analytical data identical to those reported in the literature.[17]

6-*O*-(*p*-*tert*-Butyldimethylsilyloxyphenylsulfonyl)-1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-(prop-1′-enyl)-α-D-glucofuranose (36): A solution of *tert*-butyldimethylsilyl chloride (0.88 g, 5.86 mmol) in CH_3CN (5 mL) was added dropwise at 0 °C to a stirred solution of **23** (2.1 g, 4.88 mmol) and imidazole (0.8 g, 11.7 mmol) in dry CH_3CN (20 mL). The temperature of the reaction mixture was allowed to rise to room temperature. After 2 h, the solvent was removed, the mixture was poured into water, extracted with Et_2O, and dried ($MgSO_4$), and the solvents were evaporated. The crude product was purified on silica gel with an ethyl acetate/hexane mixture (1:1, v/v) as eluent to yield **36** (2.3 g, 86%) as an oil. $[\alpha]_D^{22}$ = −22.8 (c = 1.17, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.25 (s, 6 H, *t*Bu*Me*$_2$Si−), 0.99 (s, 9 H, *t*BuMe$_2$Si−), 1.31, 1.47 (2 s, 6 H, 2 × Me), 1.53 (dd, 3 H, J = 1.7 Hz and J = 6.8 Hz, CH_3-3′), 3.35 (s, 3 H, CH_3O−), 3.71 (d, J = 2.3 Hz, 1 H, H-3), 4.05−4.13, 4.34−4.41 (2 m, 5 H, H-2′, H-4, H-5, H-6a, H-6b), 4.53 (d, J = 3.7 Hz, 1 H, H-2), 5.80 (d, J = 3.7 Hz, 1 H, H-1), 5.96 (dq, J = 6.0 Hz, 1 H and J = 1.6 Hz, H-1′), 6.89−6.93, 7.76−7.79 (2 m, 4 H, phenyl) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.42, 9.14, 18.20, 25.52, 26.21, 26.79, 57.53, 70.77, 75.74, 78.22, 81.23, 83.07, 101.82, 105.25, 111.98, 120.40, 127.94, 130.21, 145.10, 160.51 ppm. IR (film): $\tilde{\nu}$ = 1670, 1496, 1365, 1082, 907 cm^{-1}. HRMS (LSIMS): calcd. for $[M + Na]^+$ ($C_{25}H_{40}NaO_9SSi$) 567.20600, found 567.20757. $C_{25}H_{40}O_9SSi$ (544.74): calcd. C 55.12, H 7.4; found C 55.08, H 7.66.

5-*O*-(*p*-*tert*-Butyldimethylsilyloxyphenylsulfonyl)-1,2-*O*-isopropylidene-3-*O*-(prop-1′-enyl)-α-D-xylofuranose (37): Compound **37** was obtained from **33** by the procedure described above (89%). Oil. $[\alpha]_D^{22}$ = −11.9 (c = 0.46, CH_2Cl_2). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.24 (s, 6 H, *t*Bu*Me*$_2$Si−), 0.99 (s, 9 H, *t*BuMe$_2$Si−), 1.29, 1.47 (2 s, 6 H, 2 × Me), 1.46 (dd, 3 H, J = 1.7 Hz and J = 6.9 Hz, CH_3-3′), 4.15 (d, J = 3.1 Hz, 1 H, H-3), 4.20 (dd, J = 6.2 Hz, 1 H and J = 10.2 Hz, H-5a), 4.27 (dd, J = 6.1 Hz, 1 H and J = 10.2 Hz, H-5b), 4.42−4.54 (m, 2 H, H-2′, H-4), 4.51 (d, J = 3.6 Hz, 1 H, H-2), 5.87 (d, J = 3.6 Hz, 1 H, H-2), 5.90 (dq, J = 6.0 Hz, 1 H and J = 1.7 Hz, H-1′), 6.87−6.93, 7.73−7.80 (2 m, 4 H, phenyl) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = −4.42, 9.13, 18.19, 25.50, 26.25, 26.79, 66.35, 77.40, 82.67, 82.87, 104.36, 105.08, 112.31, 120.47, 127.64, 130.22, 143.21, 160.75 ppm. IR ($CHCl_3$): $\tilde{\nu}$ = 1670, 1496, 1371, 1083, 908 cm^{-1}. HRMS (LSIMS): calcd. for $[M + Na]^+$ ($C_{23}H_{36}NaO_8SSi$) 523.17979, found 523.18033. $C_{23}H_{36}O_8SSi$ (500.69): calcd. C 55.17, H 7.45; found C 54.83, H 7.42.

(3′*R*,4′*S*)- and (3′*S*,4′*R*)-6-*O*-(*p*-*tert*-Butyldimethylsilyloxyphenylsulfonyl)-1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-α-D-glucofuranose (38 and 39): Compounds **38/39** were obtained from **36**, in a ratio of ca. 5.1:1, by the known procedure.[5,6,13] Purification by flash chromatography on silica gel (40% EtOAc in hexane) furnished **38/39** as an oil (77%). **38:** ^1H NMR (500 MHz, $CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 1.19 (d, J = 7.5 Hz, 3 H, Me), 3.77 (d, J = 2.3 Hz, 1 H, H-3), 4.57 (d, J = 3.7 Hz, 1 H, H-2), 5.31 (d, J = 4.3 Hz, 1 H, H-4′), 5.80 (d, J = 3.7 Hz, 1 H, H-1), 6.25 (br. s, 1 H, NH) ppm. **39:** ^1H NMR ($CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 1.18 (d, J = 7.5 Hz, 3 H, Me), 3.75 (d, J = 3.0 Hz, 1 H, H-3), 4.56 (d, J = 3.7 Hz, 1 H, H-2), 5.09 (d, J = 4.4 Hz, 1 H, H-4′), 5.82 (d, J = 3.7 Hz, 1 H, H-1), 6.55 (br. s, 1 H, NH) ppm. IR (film): $\tilde{\nu}$ = 3297, 1773, 1363, 1281, 1022, 905 cm^{-1}. HRMS (LSIMS): calcd. for $[M + H]^+$ ($C_{26}H_{42}NO_{10}SSi$) 588.22987, found 588.23078. $C_{26}H_{41}NO_{10}SSi$ (583.78): calcd. C 53.13, H 7.03, N 2.38; found C 52.92, H 7.35, N 2.39.

(3′*S*,4′*R*)- and (3′*R*,4′*S*)-5-*O*-(*p*-*tert*-Butyldimethylsilyloxyphenylsulfonyl)-1,2-*O*-isopropylidene-3-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-α-D-xylofuranose (40 and 41): Compounds **40/41**, in a ratio of ca. 1.3:1, were obtained from **37** by the procedure described above. Purification by flash chromatography on silica gel (25% EtOAc in hexane) furnished **40/41** as an oil (67%). **40:** ^1H NMR (500 MHz, $CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 1.15 (d, J = 7.5 Hz, 3 H, Me), 1.30, 1.46 (2 s, 6 H, 2 × Me), 4.57 (d, J = 3.7 Hz, 1 H, H-2), 5.12 (d, J = 4.4 Hz, 1 H, H-4′), 5.88 (d, J = 3.7 Hz, 1 H, H-1), 6.39 (br. s, 1 H, NH) ppm. **41**: ^1H NMR ($CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 1.16 (d, J = 7.5 Hz, 3 H, Me), 1.31, 1.47 (2 s, 6 H, 2 × Me), 4.51 (d, J = 3.6 Hz, 1 H, H-2), 5.15 (d, J = 4.2 Hz, 1 H, H-4′), 5.86 (d, J = 3.6 Hz, 1 H, H-1), 6.59 (br. s, 1 H, NH) ppm. IR (film):$\tilde{\nu}$ = 3340, 1770, 1591, 1363, 1176, 908 cm^{-1}. HRMS (LSIMS): calcd. for $[M + H]^+$ ($C_{24}H_{38}NO_9SSi$) 544.20366, found 544.20194. $C_{24}H_{37}NO_9SSi$ (543.72): calcd. C 53.02, H 6.86, N 2.57; found C 52.81, H 7.02, N 2.84.

(3′*R*,4′*S*)- and (3′*S*,4′*R*)-6-*O*-(*p*-Hydroxyphenylsulfonyl)-1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-α-D-glucofuranose (42 and 43): The mixture of **38** and **39** (1.75 g, 2.98 mmol) was dissolved in THF (40 mL), and TBAF·3H_2O (0.47 g, 1.49 mmol) was added. The mixture was stirred for ca. 10 min (TLC), the solvent was then evaporated, and the crude product was separated on a silica gel column with a hexane/EtOAc mixture (1:4, v/v) as eluent to give a mixture of stereoisomers **42/43** in a ratio of ca. 5.2:1 (1.15 g, 94%). **42:** ^1H NMR (500 MHz, $CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 3.77 (d, J = 2.0 Hz, 1 H, H-3), 4.58 (d, J = 3.7 Hz, 1 H, H-2), 5.30 (d, J = 4.3 Hz, 1 H, H-4′), 5.82 (d, J = 3.7 Hz, 1 H, H-1), 6.41 (br. s, 1 H, NH) ppm. **43:** ^1H NMR ($CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 3.74 (d, J = 2.7 Hz, 1 H, H-3), 4.57 (d, J = 3.7 Hz, 1 H, H-2), 5.11 (d, J = 4.4 Hz, 1 H, H-4′), 5.84 (d, J = 3.7 Hz, 1 H, H-1), 6.66 (br. s, 1 H, NH) ppm. IR (film): $\tilde{\nu}$ = 3342, 1749, 1588, 1360, 1022, 842 cm^{-1}. HRMS (LSIMS): calcd. for $[M + H]^+$ ($C_{20}H_{28}NO_{10}S$) 474.14339, found 474.14369. $C_{20}H_{27}NO_{10}S$ (473.51): calcd. C, 50.73, H 5.74, N 2.95; found C 50.62, H 6.11, N 2.79.

(3′*S*,4′*R*)- and (3′*R*,4′*S*)-5-*O*-(*p*-Hydroxyphenylsulfonyl)-1,2-*O*-isopropylidene-3-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-α-D-xylofuranose (44 and 45): Compounds **44/45** were obtained, in a ratio of ca.

1.1:1, from **40/41** according to the procedure described for **42/43** (94%). **44:** ^{1}H NMR (500 MHz, $CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 1.10 (d, *J* = 7.5 Hz, 3 H, Me), 1.29, 1.46 (2 s, 6 H, 2 × Me), 4.05 (d, *J* = 3.3 Hz, 1 H, H-3), 4.57 (d, *J* = 3.7 Hz, 1 H, H-2), 5.15 (d, *J* = 4.4 Hz, 1 H, H-4′), 6.81 (br. s, 1 H, NH) ppm. **45:** ^{1}H NMR ($CDCl_3$, selected signals taken from the spectrum of the mixture): δ = 1.09 (d, *J* = 7.5 Hz, 3 H, Me), 1.31, 1.48 (2 s, 6 H, 2 × Me), 4.07 (d, *J* = 3.1 Hz, 1 H, H-3), 4.51 (d, *J* = 3.6 Hz, 1 H, H-2), 5.16 (d, *J* = 4.2 Hz, 1 H, H-4′), 6.93 (br. s, 1 H, NH) ppm. IR (film): ν̃ = 3334, 1749, 1351, 1076, 978 cm^{-1}. HRMS (LSIMS): calcd. for $[M + H]^+$ ($C_{18}H_{24}NO_9S$) 430.11718, found 430.11740. $C_{18}H_{23}NO_9S$ (429.46): calcd. C 50.34, H 5.39, N 3.26; found C 49.96, H 5.76, N 3.08.

Resin 46: Resin **46** was obtained by the Mitsunobu procedure described above. IR (KBr disk) ν̃ = 3469, 1775, 1596, 1374, 1077, 1019 cm^{-1}. calcd. N 1.04, S 2.34; found N 0.81, S 2.32. Elemental analysis indicating 0.81% N corresponds to a 78% yield. Capacity of **46**: 0.88 mmol/g.

Resin 47: Resin **47** was obtained according to the Mitsunobu procedure described above. IR (KBr disk): ν̃ = 3469, 1775, 1596, 1374, 1165, 1070, 968, 689 cm^{-1}. calcd. N 1.08, S 2.47 found N 0.99, S 2.39. Elemental analysis indicating 0.99% N corresponds to a 92% yield. Capacity of **47**: 1.03 mmol/g.

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[1] [1a] E. M. Gordon, M. A. Gallop, D. V. Patel, *Acc. Chem. Res.* **1996**, *29*, 144−154. [1b] J. S. Früchtel, G. Jung, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 17−42. [1c] L. A. Thompson, J. A. Ellman, *Chem. Rev.* **1996**, *96*, 555−600. [1d] P. H. H. Hermkens, H. C. J. Ottenheijm, D. C. Rees, *Tetrahedron* **1996**, *52*, 4527−4554. [1e] F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2288−2337. [1f] P. H. H. Hermkens, H. C. J. Ottenheijm, D. C. Rees, *Tetrahedron* **1997**, *53*, 5643−5678. [1g] S. Booth, P. H. H. Hermkens, H. C. J. Ottenheijm, D. C. Rees, *Tetrahedron* **1998**, *54*, 15385−15443. [1h] R. C. D. Brown, *J. Chem. Soc., Perkin Trans. 1* **1998**, 3293−3320. [1i] F. Zaragoza Dörwald, *Organic Synthesis on Solid Phase*, Wiley-VCH, Weinheim, New York, **2000**. [1j] P. Seneci, *Solid-Phase Synthesis and Combinatorial Technologies*, Wiley-VCH, Weinheim, New York, **2000**.

[2] [2a] A. K. Bose, M. S. Manhas, A. Mathur, D. R. Wagle, in *Recent Progress in the Chemical Synthesis of Antibiotics and Related Microbial Products*, (Ed.:G. Lukacs), Springer-Verlag, Berlin, **1993**, vol. 2, p. 551. [2b] S. Kobayashi, M. Moriwaki, R. Akiyama, S. Suzuki, I. Hachiya, *Tetrahedron Lett.* **1996**, *37*, 7783−7786. [2c] J. Pitlik, C. A. Townsend, *Bioorg. Med. Chem. Lett.* **1997**, *7*, 3129−3134. [2d] E. G. Mata, *Tetrahedron Lett.* **1997**, *38*, 6335−6338. [2e] E. G. Mata, *Curr. Pharm. Design* **1999**, *5*, 955−964. [2f] B. Furman, R. Thürmer, Z. Kałuża, R. Łysek, W. Voelter, M. Chmielewski, *Angew. Chem. Int. Ed.* **1999**, *38*, 1121−1123. [2g] B. Furman, R. Thürmer, Z. Kałuża, W. Voelter, M. Chmielewski, *Tetrahedron Lett.* **1999**, *40*, 5909−5912. [2h] M. Massimiliano, M. Taddei, *Org. Lett.* **2001**, *3*, 337−340.

[3] [3a] B. Ruhland, A. Bhandari, E. M. Gordon, M. A. Gallop, *J. Am. Chem. Soc.* **1996**, *118*, 253−254. [3b] Z.-J. Ni, D. Maclean, C. P. Holmes, M. M. Murphy, B. Ruhland, J. W. Jacobs, E. M. Gordon, M. A. Gallop, *J. Med. Chem.* **1996**, *39*, 1601−1608. [3c] B. Ruhland, A. Bombrun, M. A. Gallop, *J. Org. Chem.* **1997**, *62*, 7820−7826. [3d] Y. Pei, R. A. Houghten, J. S. Kiely, *Tetrahedron Lett.* **1997**, *38*, 3349−3352. [3e] V. Molteni, R. Annunziata, M. Cinquini, F. Cozzi, M. Benaglia, *Tetrahedron Lett.* **1998**, *39*, 1257−1260. [3f] R. Singh, J. M. Nuss, *Tetrahedron Lett.* **1999**, *40*, 1249−1252. [3g] S. Schunk, D. Enders, *Org. Lett.* **2000**, *2*, 907−910. [3h] K. H. Gordon, S. Balasubramanian, *Org. Lett.* **2001**, *3*, 53−56.

[4] [4a] M. Chmielewski, Z. Kałuża, B. Furman, *Chem. Commun.* **1996**, 2689−2696. [4b] B. Furman, Z. Kałuża, R. Łysek, M. Chmielewski, *Polish J. Chem.* **1999**, *73*, 43−54. [4c] Z. Kałuża, B. Furman, M. Patel, M. Chmielewski, *Tetrahedron: Asymmetry* **1994**, *5*, 2179−2186. [4d] K. Borsuk, K. Suwińska, M. Chmielewski, *Tetrahedron: Asymmetry* **2001**, *12*, 979−981.

[5] Z. Kałuża, B. Furman, M. Chmielewski, *Tetrahedron: Asymmetry* **1995**, *6*, 1719−1730.

[6] R. Łysek, B. Furman, Z. Kałuża, M. Chmielewski, *Pol. J. Chem.* **2000**, *74*, 51−60.

[7] J. H. van Maarseveen, *Comb. Chem. High Throughput Screening* **1998**, *1*, 185−214.

[8] B. Furman, R. Łysek, M. Łatyjasek, W. Wojtkielewicz, M. Chmielewski, *Synth. Commun.* **2001**, *31*, 2795−2802.

[9] [9a] O. Mitsunobu, *Synthesis* **1981**, 1−28. [9b] D. L. Hughes, *Org. React.* **1992**, *42*, 335−656. [9c] T. A. Rano, K. T. Chapman, *Tetrahedron Lett.* **1995**, *36*, 3789−3792.

[10] We used chlorosulfonylated polystyrene Ps-TsCl (Argonaut Technologies) and Wang resin elongated with the trimethylenechlorosulfonyl Ps-$CH_2OC_6H_4CH_2OCH_2CH_2CH_2SO_2Cl$ linker.

[11] K. Imaki, T. Okada, Y. Nakayama, Y. Nagao, K. Kobayashi, Y. Sakai, T. Mohri, T. Amino, H. Nakai, M. Kawamura, *Bioorg. Med. Chem.* **1996**, *4*, 2115−2134.

[12] W. H. Watanabe, L. E. Conlon, *J. Am. Chem. Soc.* **1957**, *79*, 2828−2833.

[13] Z. Kałuża, W. Abramski, C. Bełżecki, J. Grodner, D. Mostowicz, R. Urbański, M. Chmielewski, *Synlett* **1994**, 539−541.

[14] [14a] R. B. Duff, E. G. V. Percival, *J. Chem. Soc.* **1949**, 1675. [14b] D. H. R. Barton, W. B. Motherwell, *J. Chem. Soc., Perkin Trans. 1* **1980**, 1124−1131.

[15] B. Furman, Z. Kałuża, M. Chmielewski, *Tetrahedron* **1996**, *53*, 6019−6024.

[16] T. J. Prosser, *J. Am. Chem. Soc.* **1961**, *83*, 1701−1704.

[17] N. G. Cooke, A. D. Jones, A. Whiting, *Tetrahedron* **1992**, *48*, 9553−9560.

[18] M. K. Gurjar, S. K. Das, U. K. Saha, *Tetrahedron Lett.* **1994**, *35*, 2241−2244.

[19] K. Kefurt, Z. Kefurtova, J. Jary, I. Horakova, M. Marek, *Carbohydr. Res.* **1992**, *223*, 137−146.

[20] Supporting Information for this article, including preparative procedures and spectral and analytical data for compounds **3**, **15**, **16**, and **17**, is available (see footnote on the first page of this article).

[21] In a previous paper[6] we used sugar nomenclature for compounds **31** and **32**: (3′*S*,4′*R*)-and (3′*R*,4′*S*)-5-deoxy-1,2-*O*-isopropylidene-3-*O*:5-*C*-(3′-methyl-2-oxoazetidine-1′,4′-diyl)-α-D-xylofuranose.

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