[2+2]-Cycloaddition of Chlorosulfonyl Isocyanate to (*Z*)-Propenyl Ethers Bound to Polystyrene Resins by Alkylsulfonyl Linkers

Robert Łysek,[a] Barbara Grzeszczyk,[a] Bartłomiej Furman,[a] and Marek Chmielewski*[a]

Keywords: [2+2]-Cycloaddition / Chlorosulfonyl isocyanate / Solid-phase organic synthesis / Clavams / 5-Oxacephams

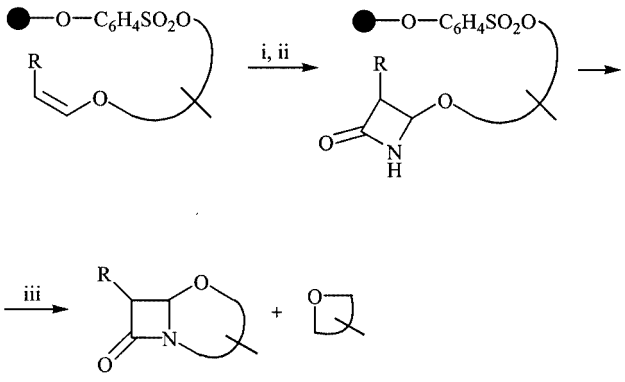
The 3-*O*- and 5-*O*-(Z)-propenyl ethers derived from 1,2-*O*-isopropylidene-α-D-xylo- and glucofuranoses, respectively, were attached to the Merrifield, MPPC and NCPSC resins using alkylsulfonyl linkers. The [2+2]-cycloaddition of chlorosulfonyl isocyanate to the polymer-bound vinyl ethers followed by the intramolecular alkylation of the β-lactam nitrogen led to the formation of mixtures of the corresponding diastereomeric oxacephams or clavams with a low stereoselectivity. In the case of Merrifield and MPP resins, the β-lactams were accompanied by the corresponding oxetanes or oxiranes. Reactions performed using soluble polymer proceeded similarly to those carried out in solution.

Introduction

Solid-phase organic synthesis (SPOS) of nonoligomeric small organic molecules is quite different from automated oligomer synthesis since it requires the use of a whole arsenal of organic reactions.[1,2] Solid phase approaches to the β-lactam antibiotics have been reviewed[3] because of the importance of this class of compounds. However, the application of SPOS methodologies to the generation of β-lactam combinatorial libraries has been barely reported.[3]

Recently, we showed that the [2+2]-cycloaddition reaction between chlorosulfonyl isocyanate (CSI) and sugar vinyl ether bound to the Wang resin by the *p*-oxyphenylsulfonyl linker followed by the intramolecular alkylation of the β-lactam nitrogen atom, gave mixtures of the corresponding clavams or 5-oxacephams accompanied by the oxirane or oxetane, respectively (Scheme 1).[4] The corresponding reaction sequences performed in solution provided the oxabicyclic β-lactams without the accompanying anhydrosugars.[5−7]

We were able to demonstrate that the formation of anhydrosugars is an intrinsic feature of the cyclization/cleavage step[8] performed on the resin.[4] The relatively low yield of the cycloaddition/cyclization sequence and the noticeably different stereoselectivity in the formation of the two diastereomeric clavams or cephams, have not allowed assignment of asymmetric induction in the [2+2]-cycloaddition step. It should be stressed that, in solution, we have not noticed any significant change of the primary ratio of diastereomers obtained in the course of the [2+2]-cycloaddition step during the subsequent intramolecular alkylation



R = H, CH_3
i: CSI, Na_2CO_3; ii: Red-Al; iii: BEMP or DBU

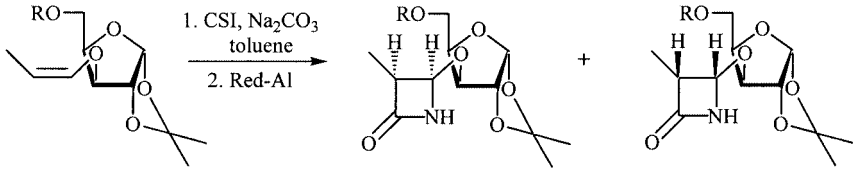
Scheme 1

of the β-lactam nitrogen atom.[5−7] The aim of the work presented here was to determine whether the reported results could be attributed specifically to the *p*-oxyphenylsulfonyl linker, or perhaps to others that bind vinyl ether to the resin. In addition, we were interested to see whether any change of the linker or even the resin, may eliminate or diminish formation of anhydrosugars. We were also interested to see whether it is possible to influence the stereoselectivity of the reaction sequence by changing the size of the sulfonyl group.

Results and Discussion

Recently, following the Musicki and Widlanski alkylation of α-lithio sulfonates,[9] we reported on a useful procedure

[a] Institute of Organic Chemistry PAN,
Kasprzaka 44/52, 01−224 Warsaw, Poland
Fax: (internat.) + 48-22-6326681
E-mail: chmiel@icho.edu.pl



1: R = H
2: R = Ms
3: R = *i*-PrSO$_2$-
4: R = Ph⟩SO$_2$-

	5 (55%)	**6** (45%)
	7 (65%)	**8** (35%)
	9 (83%)	**10** (17%)

Scheme 2

to immobilize sulfonate esters on the Merrifield resin.[10] The *p*-oxyphenylsulfonyl linker (Scheme 1)[4] which we previously used, did not allow any control over the selectivity of cycloaddition by variation of the size of the sulfonyl group. The Musicki and Widlanski method[9] offers an easy method for enlargement of the sulfonyl group by use of an isopropylsulfonate ester.[11] This was demonstrated by the formation of the isopropyl sulfonate **3** and *C*-benzylation of its corresponding lithium salt, affording **4**. Both (*Z*)-propenyl ethers **3** and **4** were subjected to the [2+2]-cycloaddition using CSI. The stereoselectivities of both reactions were compared to the related data reported previously for the mesyl derivative **2** (Scheme 2).[5−7,11]

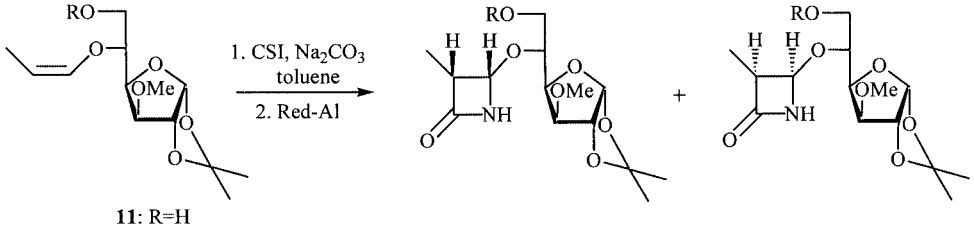
A similar comparison was made for the (*Z*)-propenyl ethers **12**−**15** (Scheme 3).[6] In those cases, it is evident that the introduction of the benzyl group to the isopropylsulfonyl group increases the stereoselectivity of the cycloaddition.

Vinyl ethers **2** and **3** were attached to the Merrifield resin by the Musicki and Widlanski[9] procedure to afford ethers **24** and **25**, respectively. The [2+2]-cycloaddition between CSI and the polymer bound vinyl ethers **24** and **25** provided the corresponding mixtures of cycloadducts **26** and **27**, which were then subjected to a cyclization/cleavage promoted by 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP). This resulted in mixtures of known cephams **28** and **29**[7] accompanied by the oxetane **30**[12] (Scheme 4), which were separated into pure components by chromatography.

In the case of **24**, the ratio of products **28**:**29**:**30** in the mixture was 1.0:1.0:3.1, respectively. The more bulky sulfonyl residue in **25** changed the ratio to 1.1:1.0:1.8. Since it can be assumed that the stereoselectivity in the [2+2]-cycloaddition step is in the same range as for reactions performed in solution, the above results testify to the crucial role of the cyclization step, which has a stronger effect on the ratio of the products than the [2+2]-cycloaddition. It is also evident that the amount of anhydrosugar **30** depends to some extent on the type of linker; the results resemble those observed for the *p*-oxyphenylsulfonyl linker.[4] One can speculate that the (4′*R*)-cycloadduct bound to the resin does prefer to form the oxetane **30** rather than the cepham **28**.

Introduction of the longer, benzyl type linker {5-[4-(methyl)phenyl]pentyl}polystyrene, (MPP) to **3** and formation of the vinyl ether **31**, afforded a similar result of [2+2]-cycloaddition through the cycloadduct stage **32**. The ratio of products **28**:**29**:**30** was 3.5:3.0:1.0, respectively. This shows that a longer linker brings the final result of cycloaddition closer to that observed when the corresponding reaction is performed in solution.[5]

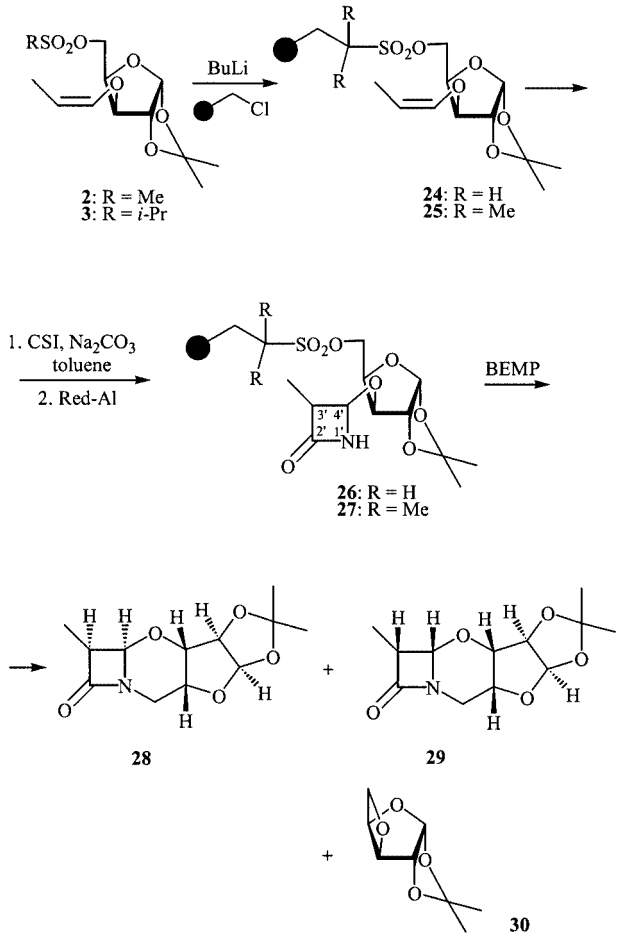
Similar results to those presented above were also observed for the clavam formation using the 5-*O*-propenyl ethers bound to Merrifield and MPP resins **33**−**35**. The



11: R=H
12: R = Ms
13: R = TIBS
14: R = ⟩SO$_2$-
15: R = Ph⟩SO$_2$-

	16 (79%)	**17** (21%)
	18 (95%)	**19** (5%)
	20 (89%)	**21** (11%)
	22 (95%)	**23** (5%)

Scheme 3



Scheme 4

cyclization/cleavage performed on **36**−**38** provided the corresponding known clavams **39**, **40**[4] and the oxirane **41**[13] in a ratio of 3.3:1:2.5 for **33**, 2.8:1:1.4 for **34** and 1.4:1:4.6 for **35**, respectively.

Since in all cases the cyclization/cleavage step performed on the resin proceeded at different rates for the diastereomeric cycloadducts, we decided to carry out the cycloaddition/cyclization sequence using the simplest, nonchiral, commercially available vinyl ether.

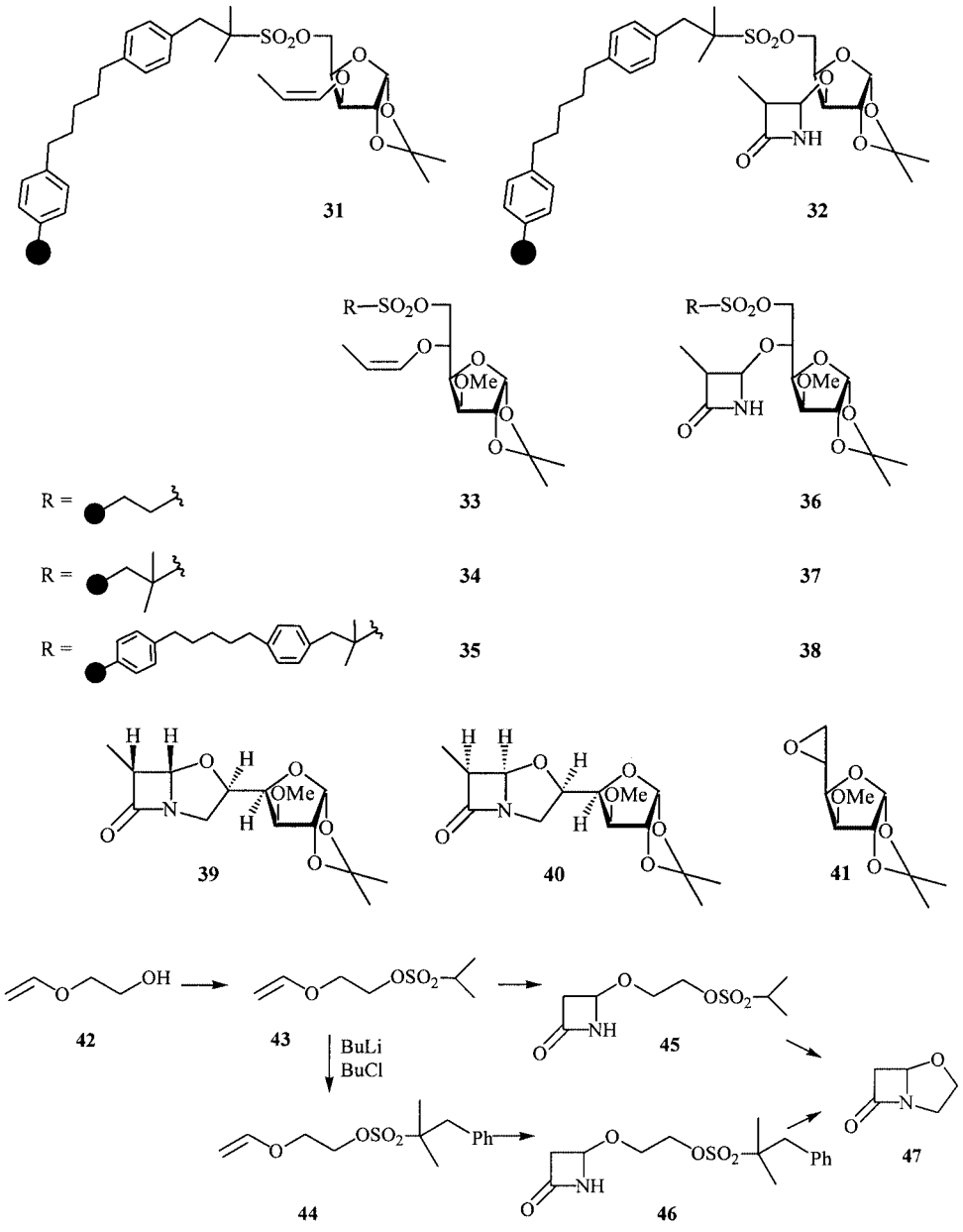
Vinyl ether **42** was sulfonylated with isopropylsulfonyl chloride to afford **43**, which was used directly for the cycloaddition or was first transformed into **44** by benzylation of the lithium salt of **43**.[9] The cycloaddition of CSI to **43** and **44** led to the corresponding cycloadducts **45** and **46** which were converted into clavam **47** by a standard PTC method (Scheme 5).[5−7]

Subsequently, the sulfonate **43** was alkylated using Merrifield or MPP resin to give the corresponding polymer-bound vinyl ethers **48** and **49**, respectively. Following the standard procedure, the [2+2]-cycloaddition of CSI to both **48** and **49** provided β-lactams **50** and **51**, which were subsequently subjected to the cyclization/cleavage using BEMP in acetonitrile. In both cases, we did not observe any β-lactam product. These results might indicate (in both cases) the formation of ethylene oxide as the preferred reaction pathway. However, ethylene oxide was not detected in the post-reaction mixture (Scheme 6).

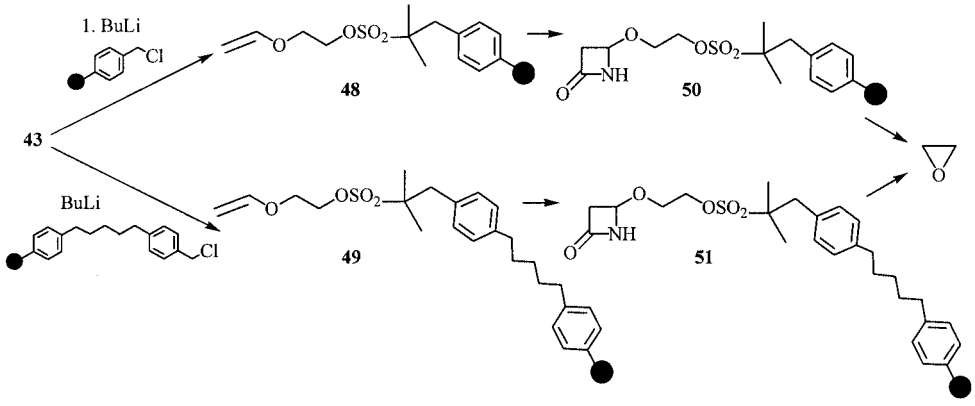
Since the experiments performed using simple, nonchiral vinyl ethers **48** and **49** bound to the polymer corroborated our earlier observations on preferred formation of anhydrosugars, we decided to run the cycloadditions on a soluble polymer, noncrosslinked chloromethylated polystyrene (NCPS), prepared by the known procedure.[14]

Vinyl ether **2** was attached to the soluble polymer by the Musicki and Widlanski[9] procedure to give **52**, which yielded a mixture of cycloadducts **53** when treated with CSI. The ratio of diastereomeric cycloadducts was estimated using ^{1}H NMR of the polymer-bound cycloadducts to be 1.6:1. The mixture **53** subjected to the cyclization/cleavage step under standard BEMP/CH_3CN conditions provided a mixture of cephams **28** and **29** in a ratio of about 1.3:1, respectively, without anhydrosugar **30** (Scheme 7). In contrast to the β-lactams bound to Wang[4] or Merrifield resins, the cyclization/cleavage step on **53** can also be performed employing conditions commonly used in solution (TBABr, K_2CO_3 anh., CH_3CN/CH_2Cl_2) to provide **28** and **29** in a ratio of about 1.2:1, respectively. It should be recalled that under such reaction conditions the cyclization/cleavage procedure produced anhydrosugars exclusively. A mixture of **28** and **29** in a ratio 1.2:1, respectively, can be obtained also if **53** dissolved in DMF is treated with cesium carbonate. It is also possible to apply a two step procedure which involves cleavage of cycloadducts from the NCPS resin by the iodide ion (TBAI) to afford a mixture of iodides **54** and **55** in the proportion 1.5:1, respectively, which in turn is subjected to cyclization by treatment with TBABr, K_2CO_3 anh., CH_3CN yielding cephams **28** and **29** in a ratio of about 1.3:1, respectively. The mixture of **54/55** was partly separated by chromatography. The absolute configurations of **54** and **55** were assigned by CD spectroscopy. According to the Rehling and Jensen rule,[15] a negative Cotton Effect should be associated with a (4′*R*)-configuration, whereas a positive one is associated with a (4′*S*)-configuration (cf. Exp. Sect.).

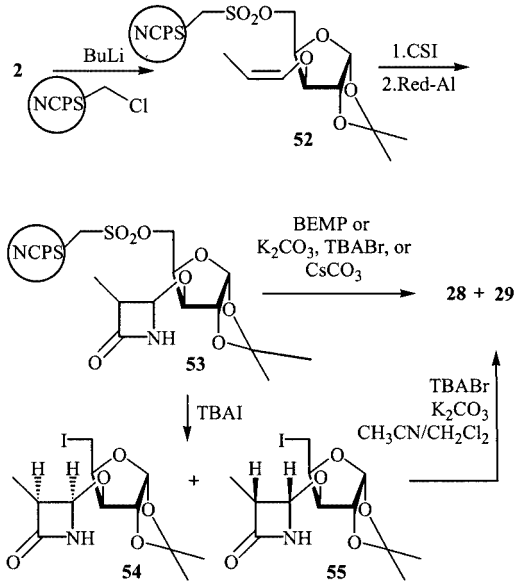
It is reasonable to assume that the stereoselectivity in the [2+2]-cycloaddition step performed on **52** is in the same range as observed by us for the corresponding reactions performed in solution. The cyclization/cleavage step proceeds with different rates for each of the diastereomeric β-lactams and consequently the proportion of cephams/clavams formed changes in favor of the stereoisomer that undergoes cyclization more readily while the other one is subjected to a partial decomposition. In the case of the two step procedure, the cleavage from the resin by iodide ion does not change significantly the ratio of diastereomeric cycloadducts, whereas during the cyclization step the proportion of products becomes different from that originally formed. This is illustrated well by the nucleophilic substitution performed in solution on the 1.8:1 mixture of diastereomers **7/8** obtained by cycloaddition. Sulfonates **7/8** treated with Bu_4NI in DMF at 100 °C yielded readily the corresponding mixture of iodides **54/55** in a ratio of about 1.8:1, respectively. This means that the ratio of dia-



Scheme 5



Scheme 6



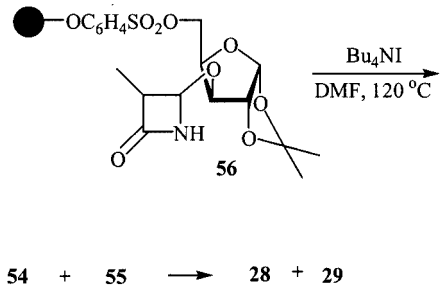
Scheme 7

stereomers during nucleophilic substitution does not vary. The subsequent cyclization performed on **54/55** under standard phase-transfer conditions yielded a mixture **28**:**29** in a ratio 1.5:1, respectively. This means that the final proportion of cephams **28** and **29** originates from two steps: the [2+2]-cycloaddition of CSI to **52** and the cyclization reaction performed on the resin or in solution. It is worth noting that the cyclization conditions influence the ratio of cephams formed.

Stereochemical analysis of the *N*-alkylation reaction pathway suggests a more sterically crowded transition state for both the more abundant cycloadducts: one resulting in the cepham skeleton and the other resulting in that of the clavam (Figure 1). In both these transition states, one of the two substituents on either side of the oxygen atom in the quasi five- or six-membered ring occupies an axial position causing a 1,3-interaction with the bridgehead β-lactam hydrogen atom. In the case of the less abundant cycloadducts, both substituents in question are located in an equatorial position and consequently the transition states of both cyclizations are free from such an interaction (Figure 1).

Although the cyclization step carried out on the NCPS resin under both conditions afforded cephams **28** and **29** without the oxetane **30**, only the two step procedure seemed promising for reactions performed on Merrifield or Wang type resins.

The modified two step procedure applied to the cycloadduct bound to the Wang resin **56** allowed us to remove both diastereomeric β-lactams **54** and **55** in a ratio of about 1.7:1, respectively, and their subsequent treatment with iodide anion under standard phase-transfer conditions afforded cephams **28** and **29** (Scheme 8).



Scheme 8

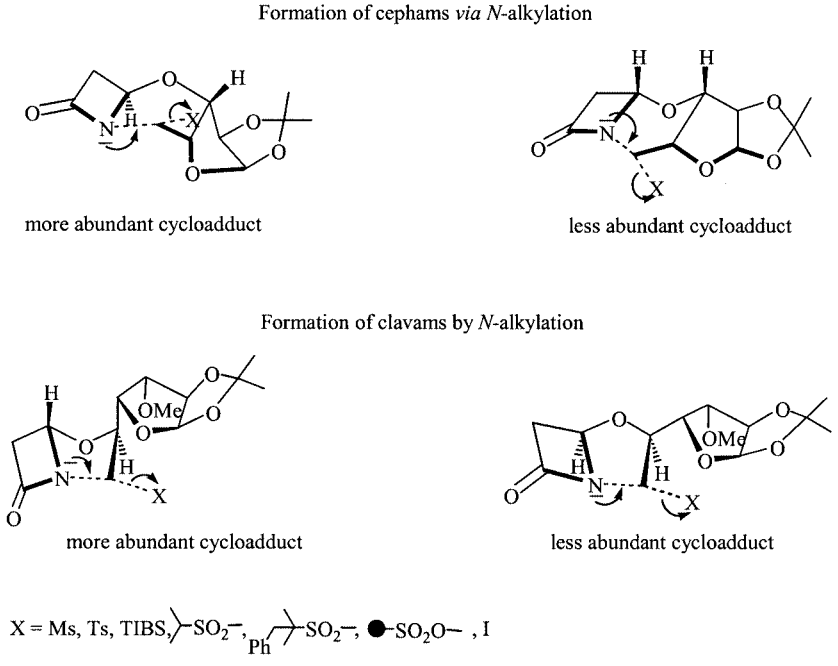
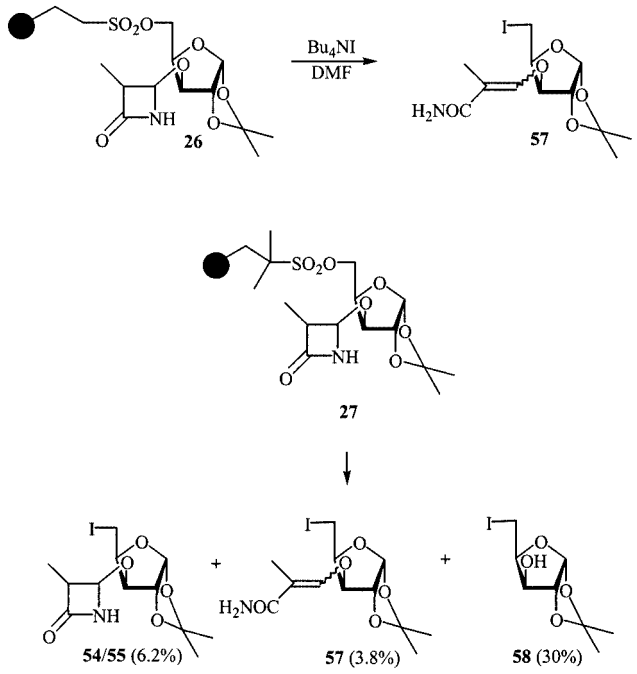


Figure 1. Stereochemical pathway of intramolecular *N*-alkylation

However, the same two step procedure performed on cycloadducts bound to the Merrifield resin by the methylsulfonyl **26** or the (dimethyl)methylsulfonyl linker **27** failed. In both cases, the cleavage of adduct from the resin by treatment with iodide ion required heating in DMF solution for an extended period. Under such conditions the β-lactam ring decomposed to provide many products. Some of these were isolated and characterized as **54**, **55**, **57** and **58**[16] and are shown in Scheme 9.



Scheme 9

Conclusion

The [2+2]-cycloaddition of chlorosulfonyl isocyanate to sugar vinyl ethers bound to polystyrene resins by alkylsulfonyl linkers, followed by a cyclization/cleavage step, provides the corresponding clavams or 5-oxacephams in low yield, accompanied by oxirane or oxetane, respectively. This reaction pathway resembles the one involving the *p*-oxyphenylsulfonyl linker[4] and is different from the corresponding processes carried out in solution. An attempt to increase the stereoselectivity of the process by introduction of the (dimethyl)methylsulfonyl linker in place of the mesyl group failed since the cleavage of products from the resin significantly changes the ratio of diastereomers obtained during the cycloaddition step.

When performed on a vinyl ether bound to NCPS, the same reaction sequence proceeds similarly to that carried out in solution. The cyclization/cleavage methodology[8] can be replaced by the two step procedure involving a cleavage of the adduct from the resin by the nucleophilic substitution against iodide anion followed by the standard cyclization of resulting iodides in solution. This two step procedure was successfully performed for the β-lactams bound to the Wang resin by *p*-oxyphenylsulfonyl linker whereas it failed for the corresponding β-lactams bound to Merrifield or CMPP resin by the alkylsulfonyl linkers. However, it should be pointed out that in the case of the two step procedure, the advantage of the cyclization/cleavage methodology in providing the high yield and purity of the detached product[8] is lost since all side products are disconnected simultaneously.

Experimental Section

General Remarks: ^{1}H and ^{13}C NMR spectra of the compounds were obtained from $CDCl_3$ solutions using Varian Gemini AC-200 and Bruker Avance 500 spectrometers at ambient temperature. Mass spectra were determined with an AMD 604 Inectra GmbH and HPLC-MS with Mariner and API 356 detectors, spectrometers. Optical rotation was measured at ambient temperature with a JASCO P 3010 polarimeter. IR spectra were recorded with a Perkin−Elmer FT-IR Spectrum 2000 spectrophotometer. Melting points were determined with a Boetius micromelting point apparatus and are uncorrected. Flash column chromatography was performed on silica gel Merck Kieselgel 60 (230−400 mesh). Thin layer chromatography (TLC) was performed on silica gel plates (60-F_{254}, Merck). Zones were detected visually by ultraviolet irradiation (254 nm) or spraying with $H_2MoO_4{\cdot}H_2O/Ce(SO_4)_2{\cdot}4H_2O$ in 15% H_2SO_4, followed by heating at 100 °C. 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.

Starting Material: Merrifield resin (Aldrich) and {5-[4-(chloromethyl)phenyl]pentyl}polystyrene (CMPP resin; Aldrich) were reagent grade and used as purchased without further purification. Noncrosslinked chloromethylated polystyrene was obtained following a known procedure.[14] Compounds **1**,[7] **11**,[4] were obtained according to the known procedure. Compounds **28**,[7] **29**,[7] **39**[4] and **40**[4] were characterized earlier. Anhydrosugars **30**[12] and **41**[13] were reported previously. Polymer bound sulfonate ether **56** was obtained following a known procedure.[4]

Synthesis of Compounds 2, 3, 12−14. General Procedure: A solution of the appropriate sulfonyl chloride (12 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of the respective alcohols **1** and **11** (10 mmol) and pyridine (15 mmol) in dry CH_2Cl_2 (20 mL), at 0 °C. The mixture was stirred for 30 min at the same temperature and then the reaction temperature warmed to room temperature. After 10 h, the mixture was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), the solvents were evaporated, and the residue was purified on silica gel to give the respective products **2**, **3**, **12**−**14** in good yield. Compositions of the post-reaction mixtures were assigned by ^{1}H NMR spectra.

1,2-*O*-Isopropylidene-5-*O*-methylsulfonyl-3-*O*-(prop-1′-enyl)-α-D-xylofuranose (2): Compound **2** was obtained from **1** using methanesulfonyl chloride. White solid; yield: 90%. $[\alpha]_D^{22} = +2.3$ (c = 1.0, CH_2Cl_2). IR ($CHCl_3$): $\tilde{\nu}$ = 1670 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.33, 1.51 (2s, 6 H, 2 × Me), 1.55 (dd, J = 1.7, 6.9 Hz, 3 H, CH_3), 3.07 (s, 3 H, Ms), 4.21 (d, J = 3.0 Hz, 1 H, H-3), 4.42−4.65 (m, 4 H, H-2′, H-4, H-5a, H-5b), 4.57 (d, J = 3.7 Hz, 1 H, H-2), 5.96 (dq, J = 6.1, 1.7 Hz, 1 H, H-1′), 5.97 (d, J = 3.7 Hz, 1 H, H-2) ppm. MS (EI, HR): [M$^+$] ($C_{12}H_{20}O_7S$) calcd.

308.09298; found 308.09209. $C_{12}H_{20}O_7S$ (308.35): calcd. C 46.74, H 6.54, S 10.40; found C 46.65, H 6.51, S 10.38.

1,2-*O*-Isopropylidene-5-*O*-isopropylsulfonyl-3-*O*-(prop-1′-enyl)-α-D-xylofuranose (3): Compound **3** was obtained from **1** using 1-methylethanesulfonyl chloride. Oil; yield: 90%. $[\alpha]_D^{22} = -7.2$ (*c* = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1670 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.33, 1.51 (2s, 6 H, 2 × Me), 1.44 (dd, *J* = 1.9, 6.9 Hz, 6 H, $(CH_3)_2CH-$), 1.55 (dd, *J* = 1.7, 6.9 Hz, 6 H, CH_3), 3.37 [sept, *J* = 6.9 Hz, 1 H, $(CH_3)_2CH-$], 4.20 (d, *J* = 3.1 Hz, 1 H, H-3), 4.41 (dd, *J* = 7.0, 10.8 Hz, 1 H, H-5a), 4.46 (dd, *J* = 4.9, 10.8 Hz, 1 H, H-5b), 4.50−4.61 (m, 3 H, H-2′, H-2, H-4), 5.96 (d, *J* = 3.8 Hz, 1 H, H-1), 5.95 (dq, *J* = 6.1, 1.7 Hz, 1 H, H-1′) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.2, 16.5, 16.6, 26.3, 26.8, 52.3, 66.5, 77.8, 82.7, 83.2, 104.6, 105.2, 112.3, 143.1 ppm. HRMS (LSIMS): $[M^+]$ ($C_{14}H_{24}O_7S$): calcd. 336.12428; found 336.12394. $C_{14}H_{24}O_7S$ (336.41): calcd. C 49.99, H 7.19, S 9.53; found C 50.09, H 7.11, S 9.39.

5-*O*-(1′′,1′′-Dimethyl-2′′-phenyl)ethylsulfonyl-1,2-*O*-isopropylidene-3-*O*-(prop-1′-enyl)-α-D-xylofuranose (4): *n*BuLi (2.5 M. in hexane, 1.1 mL, 2.74 mmol) was added with stirring to a mixture of compound **3** (0.70 g, 2.1 mmol), *N*,*N*′-dimethylpropyleneurea (DMPU; 5 mL) and dry THF (20 mL) under argon at −70 °C. The mixture was then warmed up slowly to −50 °C (15−30 min) and treated with BnCl (0.27 mL, 2.13 mmol). Stirring was continued for 1.5 h while warming up to room temperature. The excess reagents were decomposed by addition of isopropyl alcohol (3 mL). The reaction mixture was poured into saturated NaCl solution and extracted with diethyl ether (3 × 50 mL). The combined extracts were washed with water, dried (Na_2SO_4), filtered and concentrated. The residue was purified on a silica gel column using hexane/ethyl acetate (4:1, v/v) as eluent to give **4** (1.072 g, 63%). $[\alpha]_D^{22} = -16.9$ (*c* = 1.3, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1670 1346, 1128, 1082, 981 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.32, 1.51 (2s, 6 H, 2 × Me), 1.368, 1.371 [2s, 6 H, $-(CH_3)_2C-$], 1.55 (dd, *J* = 1.7, 6.9 Hz, 3 H, CH_3-3′), 3.14 (s, 2 H, Bn), 4.20 (d, *J* = 2.8 Hz, 1 H, H-3), 4.47 (dd, *J* = 8.4, 11.9 Hz, 1 H, H-5a), 4.50−4.63 (m, 4 H, H-2′, H-2, H-4, H-5b), 5.95−5.97 (m, 2 H, H-1, H-1′) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.2, 21.1, 21.2, 26.3, 26.8, 41.4, 66.4, 77.9, 82.7, 83.2, 104.6, 105.3, 127.1, 128.2, 131.0, 143.2 ppm. HRMS (LSIMS): $[M^+ + Na]$ ($C_{21}H_{30}O_7SNa$): calcd. 449.16100; found 449.16288. $C_{21}H_{30}O_7S$ (426.53): calcd. C 59.13, H 7.09, S 7.52; found C 59.01, H 6.89, S 7.44.

1,2-*O*-Isopropylidene-3-*O*-methyl-6-*O*-methylsulfonyl-5-*O*-(prop-1′-enyl)-α-D-glucofuranose (12): Compound **12** was obtained from **11** using methanesulfonyl chloride; 85%; oil. $[\alpha]_D^{22} = -40.4$ (*c* = 0.7, CH_2Cl_2). IR ($CHCl_3$): $\tilde{\nu}$ = 1669 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.31, 1.50 (2s, 6 H, 2 × Me), 1.58 (dd, *J* = 1.7, 6.8 Hz, 3 H, CH_3-3′), 3.03 (s, 3 H, Ms), 3.39 (s, 3 H, CH_3O-), 3.76 (d, *J* = 2.8 Hz, 1 H, H-3), 4.14−4.57 (m, 5 H, H-2′, H-4, H-5, H-6a, H-6b), 4.59 (d, *J* = 3.7 Hz, 1 H, H-2), 5.86 (d, *J* = 3.7 Hz, 1 H, H-1), 6.00 (dq, *J* = 6.1, 1.7 Hz, 1 H, H-1′) ppm. $C_{14}H_{24}O_8S$ (352.41): calcd. C 47.72, H 6.86; found C 48.25, H 7.07.

1,2-*O*-Isopropylidene-3-*O*-methyl-6-*O*-(2′′,4′′,6′′-triisopropylphenylsulfonyl)-5-*O*-(prop-1′-enyl)-α-D-glucofuranose (13): Compound **13** was obtained from **11** using 2,4,6-triisopropylbenzenesulfonyl chloride; 81%; oil. $[\alpha]_D^{22} = -41.5$ (*c* = 0.6, CH_2Cl_2). IR (CH_2Cl_2): $\tilde{\nu}$ = 1669 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.30, 1.50 (2s, 6 H, 2 × Me), 1.52 (dd, *J* = 1.7, 6.8 Hz, 3 H, CH_3-3′), 2.89 [sept, *J* = 6.9 Hz, 1 H, $(CH_3)_2CH-$], 3.35 (s, 3 H, CH_3O-), 3.71 (d, *J* = 3.1 Hz, 1 H, H-3), 4.07−4.21 [m, 4 H, H-4, H-2′, 2 × $(CH_3)_2CH-$], 4.13 (dd, *J* = 7.4, 10.6 Hz, 1 H, H-6a), 4.37 (m, 1 H, H-5), 4.43 (dd, *J* = 1.8, 10.6 Hz, 1 H, H-6b), 4.53 (d, *J* = 3.7 Hz, 1 H, H-2), 5.82 (d, *J* = 3.7 Hz, 1 H, H-1), 6.00 (dq, *J* = 6.1, 1.7 Hz, 1 H, H-1′), 7.20 (s, 2 H, aryl) ppm. MS (EI, HR): $[M^+]$ ($C_{28}H_{44}O_8S$): calcd. 540.27569; found 540.27692. $C_{28}H_{44}O_8S$ (540.69): calcd. C 62.19, H 8.20; found C 62.28, H 8.31.

1,2-*O*-Isopropylidene-6-*O*-isopropylsulfonyl-3-*O*-methyl-5-*O*-(prop-1′-enyl)-α-D-glucofuranose (14): Compound **14** was obtained from **11** using 1-methylethanesulfonyl chloride; 79%; oil. $[\alpha]_D^{22} = -29.8$ (*c* = 1.5, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 1669 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.32, 1.49 (2s, 6 H, 2 × Me), 1.426, 1.432 [2d, 2 × *J* = 6.9 Hz, 6 H, $(CH_3)_2CH-$], 1.58 (dd, *J* = 1.7, 6.8 Hz, 3 H, CH_3-3′), 3.32 [sept, *J* = 6.9 Hz, 1 H, $(CH_3)_2CH-$], 3.39 (s, 3 H, CH_3O-), 3.76 (d, *J* = 2.9 Hz, 1 H, H-3), 4.12−4.19 (m, 2 H, H-4, H-2′), 4.30 (dd, *J* = 5.9, 11.0 Hz, 3 H, H-6a), 4.44 (m, 1 H, H-5), 4.54−4.58 (m, 2 H, H-2, H-6b), 5.86 (d, *J* = 3.7 Hz, 1 H, H-1), 6.01 (dq, *J* = 6.1, 1.7 Hz, 1 H, H-1′) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.2, 16.6, 16.7, 26.2, 26.8, 52.1, 57.5, 70.0, 76.0, 78.1, 81.2, 83.07, 102.1, 105.2, 144.9 ppm. HRMS (LSIMS): $[M^+ + Na]$ ($C_{16}H_{28}O_8SNa$): calcd. 403.14026; found 403.14079. $C_{16}H_{28}O_8S$ (380.46): calcd. C 50.52, H 7.42, S 8.43; found C 50.33, H 7.67, S 8.37.

6-*O*-(1′′,1′′-Dimethyl-2′′-phenyl)ethylsulfonyl-1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-(prop-1′-enyl)-α-D-glucofuranose (15): Compound **15** was obtained from **14** according to the procedure described for compound **4**; 54%; oil. $[\alpha]_D^{22} = -17.1$ (*c* = 1.1, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1669 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.32, 1.48 (2s, 6 H, 2 × Me), 1.35 [s, 6 H, $Bn(CH_3)_2C-$], 1.59 (dd, *J* = 1.7, 6.8 Hz, 3 H, CH_3-3′), 3.15 (s, 2 H, Bn), 3.40 (s, 3 H, CH_3O-), 3.77 (d, *J* = 2.4 Hz, 1 H, H-3), 4.16−4.21, 4.33−4.37 (2m, 3 H, H-2′, H-4, H-6a), 4.45 (m, 1 H, H-5), 4.58 (d, *J* = 3.7 Hz, 1 H, H-2), 4.64 (dd, *J* = 1.7, 11.5 Hz, 1 H, H-6b), 5.88 (d, *J* = 3.7 Hz, 1 H, H-1), 6.03 (dq, *J* = 6.1, 1.7 Hz, 1 H, H-1′), 7.16−7.32 (m, 5 H, Ph) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 9.2, 21.0, 21.0, 26.2, 26.8, 41.2, 57.5, 70.0, 76.1, 78.2, 81.2, 83.1, 101.9, 105.3, 127.0, 128.1, 131.0, 145.1 ppm. HRMS (LSIMS): $[M^+ + Na]$ ($C_{23}H_{34}O_8SNa$): calcd. 493.18721; found 493.18643. $C_{23}H_{34}O_8S$ (470.59): calcd. C 58.70, H 7.28; found C 58.58, H 7.38.

[2+2]-Cycloaddition of Chlorosulfonyl Isocyanate to Vinyl Ethers 2−4, 12−15 was performed according to the procedure described in the literature.[5,6,7]

(3′*R*,4′*S*)- and (3′*S*,4′*R*)-1,2-*O*-Isopropylidene-3-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-5-*O*-methylsulfonyl-α-D-xylofuranose (5/6): A mixture of stereoisomers **5** and **6**, in a ratio of 1.2:1, respectively, was obtained from **2**, 30%; solid foam. IR (KBr): $\tilde{\nu}$ = 3193, 1775 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) selected data taken for the mixture of diastereomers: δ = 1.14, 1.16 (2d, 2 × *J* = 6.7 Hz, 6 H, CH_3), 4.15 (dd, *J* = 5.2, 9.7 Hz, 1 H, H-5a), 4.16 (dd, *J* = 5.5, 9.8 Hz, 1 H, H-5a), 4.28 (dd, *J* = 7.3, 9.8 Hz, 1 H, H-5b), 4.29 (dd, *J* = 7.7, 9.7 Hz, 1 H, H-5b), 4.51 and 4.57 (2d, *J* = 3.7 Hz, 2 H, H-2), 5.10 (d, *J* = 4.4 Hz, 1 H, H-4′), 5.13 (d, *J* = 4.2 Hz, 1 H, H-4′), 5.87 and 5.88 (2d, *J* = 3.6 Hz, 2 H, H-1), 6.43 and 6.57 (2 br. s, 2 H, NH) ppm. MS (LSIMS, HR): $[M^+ + H]$ ($C_{13}H_{21}NO_8S$): calcd. 352.10741; found 352.10661. Analytical data taken for the mixture: $C_{13}H_{21}NO_8S$ (351.36): calcd. C 44.44, H 6.02, N 3.99; found C 44.85, H 6.59, N 3.76.

(3′*R*,4′*S*)- and (3′*S*,4′*R*)-1,2-*O*-Isopropylidene-5-*O*-isopropylsulfonyl-3-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-α-D-xylofuranose (7/8): A mixture of stereoisomers **7** and **8**, in a ratio of 1.8:1, respectively, was obtained from **3**, 66%; solid foam. IR (KBr): $\tilde{\nu}$ = 3336, 1776 cm^{-1}; Compound **7** (major isomer): ^1H NMR (500 MHz, $CDCl_3$) selected signals taken for the mixture: δ = 4.60 (d, *J* = 3.7 Hz, 1 H, H-2),

5.16 (d, J = 4.4 Hz, 1 H, H-4′), 5.95 (d, J = 3.7 Hz, 1 H, H-1), 6.55 (br. s, 1 H, NH) ppm. **Compound 8 (minor isomer):** ^{1}H NMR (500 MHz, $CDCl_3$) selective signals taken for the mixture: δ = 4.53 (d, J = 3.6 Hz, 1 H, H-2), 5.14 (d, J = 4.3 Hz, 1 H, H-4′), 5.92 (d, J = 3.6 Hz, 1 H, H-1), 6.71 (br. s, 1 H, NH) ppm. MS (LSIMS, HR): [M^+ + Na] ($C_{15}H_{25}NO_8SNa$): calcd. 402.1193; found 402.1213. Analytical data taken for the mixture: $C_{15}H_{25}NO_8S$ (379.43): calcd. C 47.48, H 6.64, N 3.69; found C 47.43, H 6.77, N 3.59.

(3′*R*,4′*S*)- and (3′*S*,4′*R*)-5-*O*-(1′′,1′′-Dimethyl-2′′-phenyl)-ethylsulfonyl-1,2-*O*-isopropylidene-3-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-α-D-xylofuranose (9/10): A mixture of stereoisomers **9** and **10**, in a ratio of 5:1, respectively, was obtained from **4**; 69%; solid foam. IR (KBr): ṽ = 3329, 1773 cm^{-1}. **Compound 9 (major isomer):** ^{1}H NMR (500 MHz, $CDCl_3$) selected signals taken for the mixture: δ = 1.25 (d, J = 7.5 Hz, 3 H, CH_3-3′), 4.33 (dd, J = 5.5, 10.2 Hz, 1 H, H-5b), 4.61 (d, J = 3.7 Hz, 1 H, H-2), 5.16 (d, J = 4.4 Hz, 1 H, H-4′), 5.96 (d, J = 3.7 Hz, 1 H, H-1), 6.59 (br. s, 1 H, NH) ppm. **Compound 10 (minor isomer):** ^{1}H NMR (500 MHz, $CDCl_3$) selected signals taken for the mixture: δ = 1.22 (d, J = 7.5 Hz, 3 H, CH_3-3′), 4.53 (d, J = 3.6 Hz, 1 H, H-2), 5.14 (d, J = 4.2 Hz, 1 H, H-4′), 5.92 (d, J = 3.6 Hz, 1 H, H-1), 6.75 (br. s, 1 H, NH) ppm. MS (LSIMS, HR): [M^+ + H] ($C_{22}H_{32}NO_8S$): calcd. 470.18486; found 470.18504. Analytical data taken for the mixture: calcd. for $C_{22}H_{31}NO_8S$ (469.56): calcd. C 56.28, H 6.65, N 2.98, S 6.83; found C 55.47, H 6.87, N 3.65, S 7.09.

(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*-methylsulfonyl-α-D-glucofuranose (16/17): Compounds **16** and **17** were obtained from **12** in a ratio of ca. 3.4:1, respectively; 30%; oil. IR (film): ṽ = 3347, 1770 cm^{-1}. Compound **16** (major isomer): ^{1}H NMR (500 MHz, $CDCl_3$) selected signals taken for the mixture: δ = 1.25 (d, J = 7.5 Hz, 3 H, CH_3), 3.04 (s, 3 H, Ms), 3.37 (qdd, J = 7.5, 2.3, 4.3 Hz, 1 H, H-3′), 5.32 (d, J = 4.3 Hz, 1 H, H-4′), 5.86 (d, J = 3.8 Hz, 1 H, H-1), 6.30 (br. s, 1 H, NH) ppm. **Compound 17 (minor isomer):** ^{1}H NMR (500 MHz, $CDCl_3$) selected signals taken for the mixture: δ = 1.22 (d, J = 7.5 Hz, 3 H, CH_3), 3.05 (s, 3 H, Ms), 3.30 (qdd, J = 7.5, 2.1, 4.4 Hz, 1 H, H-3′), 5.11 (d, J = 4.4 Hz, 1 H, H-4′), 5.87 (d, J = 3.8 Hz, 1 H, H-1), 6.59 (br. s, 1 H, NH) ppm. MS (EI, HR): [M^+] ($C_{15}H_{25}NO_9S$): calcd. 395.12500; found 395.12543.

(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*-(2′′,4′′,6′′-triisopropylphenyl-sulfonyl)-α-D-glucofuranose (18/19): Compounds **18/19** were obtained from **13** in a ratio of 21:1, respectively; 66%; solid foam. IR (film): ṽ = 1771, 3306 cm^{-1}. **Compound 18 (major isomer):** ^{1}H NMR (500 MHz, $CDCl_3$) selected signals taken for the mixture: δ = 2.89 [sept, J = 6.9 Hz, 1 H, $(CH_3)_2CH-$], 3.35 (qdd, J = 7.5, 2.3, 4.3 Hz, 1 H, H-3′), 3.42 (s, 3 H, CH_3O), 3.78 (d, J = 3.2 Hz, 1 H, H-3), 4.00−4.42 [m, 6 H, H-4, H-5, H-6a, H-6b, 2 × $(CH_3)_2CH-$], 4.57 (d, J = 3.7 Hz, 1 H, H-2), 5.43 (d, J = 4.3 Hz, 1 H, H-4′), 5.81 (d, J = 3.7 Hz, 1 H, H-1), 6.29 (br. s, 1 H, NH), 7.18 (s, 2 H, aryl) ppm. **Compound 19 (minor isomer):** ^{1}H NMR (500 MHz, $CDCl_3$) selected signals taken for the mixture: δ = 3.76 (d, J = 3.1 Hz, 1 H, H-3), 5.16 (d, J = 4.4 Hz, 1 H, H-4′), 6.61 (br. s, 1 H, NH) ppm. MS (EI, HR): [M^+] ($C_{29}H_{45}NO_9S$): calcd. 583.28150; found 583.28404. Analytical data taken for the mixture: $C_{29}H_{45}NO_9S$ (583.74): calcd. C 59.67, H 7.77, N 2.40; found C 59.37, H 7.76, N 2.34.

(3′*R*,4′*S*)- and (3′*S*,4′*R*)-1,2-*O*-Isopropylidene-6-*O*-isopropylsulfonyl-3-*O*-methyl-5-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-α-D-glucofuranose (20/21): Compounds **20** and **21** were obtained from **14** in a ratio of 8:1, respectively; 71%; solid foam. IR (film): ṽ = 3338, 1771 cm^{-1}. **Compound 20 (major isomer):** ^{1}H NMR (500 MHz, $CDCl_3$) selected signals taken for the mixture: δ = 1.26 (d, J = 7.5 Hz, 3 H, CH_3), 1.33, 1.49 (2s, 6 H, 2 × Me), 1.42 [d, J = 6.9 Hz, 6 H, $(CH_3)_2CH-$], 3.32 [sept 1 H, $(CH_3)_2CH-$], 3.35 (qdd, J -7.5, 2.22, 4.3 Hz, 1 H, H-3′), 3.43 (s, 3 H, OCH_3), 3.80 (d, J = 3.1 Hz, 1 H, H-3), 4.60 (d, J = 3.7 Hz, 1 H, H-2), 5.33 (d, J = 4.4 Hz, 1 H, H-1′), 5.85 (d, J = 3.7 Hz, 1 H, H-1), 6.33 (br. s, 1 H, NH) ppm. **Compound 21 (minor isomer):** ^{1}H NMR 500 MHz, $CDCl_3$ selected signals taken for the mixture: δ = 1.22 (d, J = 7.5 Hz, 3 H, CH_3-3′), 1.32, 1.61 (2s, 6 H, 2 × Me), 3.42 (s, 3 H, OCH_3), 5.11 (d, J = 4.4 Hz, 1 H, H-1′), 6.69 (br. s, 1 H, NH) ppm. HRMS (LSIMS): [M^+ + H] ($C_{17}H_{30}NO_9S$): calcd. 424.16413; found 424.16578. Analytical data taken for the mixture: $C_{17}H_{29}NO_9S$ (423.49): calcd. C 48.22, H 6.90, N 3.31, S 7.57; found C 48.11, H 6.91, N 3.34, S 7.50.

(3′*R*,4′*S*)- and (3′*S*,4′*R*)-6-*O*-(1′′,1′′-Dimethyl-2′′-phenyl)-ethylsulfonyl-1,2-*O*-isopropylidene-3-*O*-methyl-5-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-α-D-glucofuranose (22/23): Compounds **22** and **23** were obtained from **15** in a ratio of 22:1; 70%; solid foam. IR (film): ṽ = 3340, 1772 cm^{-1}. **Compound 22:** ^{1}H NMR (500 MHz, $CDCl_3$) selected signals taken for the mixture: δ = 1.26 (d, J = 7.5 Hz, 3 H, CH_3), 1.32, 1.48 (2s, 6 H, 2 × Me), 1.358, 1.360 [2s, 6 H, $Bn(CH_3)_2C-$], 3.12 (br. s, 2 H, Bn), 3.36 (qdd, J = 7.5, 2.3, 4.4 Hz, 1 H, H-3′), 3.44 (s, 3 H, CH_3O), 3.81 (d, J = 3.2 Hz, 1 H, H-3), 4.05 (ddd, J = 2.0, 6.4, 9.0 Hz, 1 H, H-5), 4.16 (dd, J = 3.2, 9.0 Hz, 1 H, H-4), 4.35 (dd, J = 6.4, 11.4 Hz, 1 H, H-6a), 4.61 (d, J = 3.7 Hz, 1 H, H-2), 4.68 (dd, J = 2.0, 11.4 Hz, 1 H, H-6b), 5.33 (d, J = 4.4 Hz, 1 H, H-4′), 5.88 (d, J = 3.7 Hz, 1 H, H-1), 6.50 (br. s, 1 H, NH) ppm. **Compound 23 (minor isomer):** ^{1}H NMR (500 MHz, $CDCl_3$) selected signals taken for the mixture: δ = 1.23 (d, J = 7.5 Hz, 3 H, CH_3), 3.79 (bd, J = 3.1 Hz, 1 H, H-3), 4.60 (d, J = 3.7 Hz, 1 H, H-2), 6.81 (br. s, 1 H, NH) ppm. HRMS (LSIMS): [M^+ + Na] ($C_{24}H_{35}NO_9SNa$): calcd. 536.19302; found 536.19451. Analytical data taken for the mixture: $C_{24}H_{35}NO_9S$ (513.61): calcd. C 56.13, H 6.87, N 2.73; found C 55.25, H 7.21, N 2.49.

Alkylation of α-Lithiosulfonate Esters 2, 3, 12, 14 and 43 with Merrifield or CMPP Resins. General Procedure: A solution of *n*BuLi in hexane (2.5 M, 2 mL, 5 mmol) was added dropwise to a solution of **2** (1.48 g, 4.8 mmol) in THF (12 mL) and DMPU (4 mL) at −70 °C. After 15 min, the Merrifield or CMPP resin (1 g, 1.2 mmol) was added in one portion. The stirring was continued at the same temperature for 20 min and then at −25 °C for 10 h. The reaction was quenched at −25 °C by addition of 5 mL of MeOH, then filtered and washed (2 × 20 mL each) with MeOH, THF/water (2:1), water, THF/water (2:1), THF, MeOH, CH_2Cl_2 and Et_2O then dried for 6 h under vacuum to give resin **24**. IR (KBr disk): ṽ = 1669 cm^{-1}. Anal.: calcd. S 2.90; found S 2.45. Elemental analysis indicating 2.45% S, gives 84.5% yield. Other vinyl ethers bound to the resin **25**, **31**, **33**−**35**, **48** and **49** gave IR (KBr disk): ṽ ≈ 1670 cm^{-1}, while elemental analyses indicate the yields to be within the range of 70−90% except for **48** and **49** for which corresponding analyses indicate 63 and 33% yields, respectively.

[2+2]-Cycloaddition of CSI to Resin 24, 25, 31, 33−35, 48, 49. General Procedure: Chlorosulfonyl isocyanate (5 mmol) was added to a suspension of anhydrous Na_2CO_3 (0.25 g) and resin **24**, **25**, **31**, **33**−**35**, **48**, **49** (0.5 g) in a 1:1 mixture of CH_2Cl_2/toluene (12 mL) at −78 °C. The reaction mixture was stirred at −78 °C for 30 min, and then at −30 °C for another 10 h. The suspension was cooled to −78 °C, diluted with CH_2Cl_2/toluene mixture (1:1, v/v) (14 mL), treated with Red-Al (1 M solution in toluene, 5 mL), and left for 30 min whilst the temperature of reaction was maintained. Sub-

sequently, the temperature was allowed to rise to 0 °C and water (5 mL) and 10% aqueous potassium sodium tartrate (5 mL) were added. The mixture was stirred for 30 min then filtered and washed (3 × 10 mL each) with 10% aqueous potassium sodium tartrate, H_2O, DMF, H_2O, MeOH, THF, MeOH, CH_2Cl_2 and Et_2O then dried for 16 h under vacuum to give resins **26**, **27**, **32**, **36**, **37**, **38**, **50** and **51**. IR (KBr disk) $\tilde{\nu}$ in the range of 3440 and 1780 cm^{-1}. Elemental analyses indicate yields in the range 90−100%.

Synthesis of 5-Oxacephams 28, 29 and Clavams 39, 40 by the Cyclization/Cleavage Step. General Procedure: The β-lactam resin **26** (0.2 g, 0.17 mmol) was suspended in anhydrous CH_3CN (3 mL) and treated with BEMP (0.98 mL, 0.34 mmol) or DBU. The mixture was stirred and kept under reflux for about 1.5 h. The resin was filtered and washed (3 × 5 mL each) with THF and Et_2O. The organic layer was separated and the solvents 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 into pure components on a silica gel column[4] to give the products **28**, **29** and anhydrosugar **30** in a ratio of about 1.0:1.0:3.1, respectively. Compound **27** under the same conditions provided products **28**, **29** and **30** in ratio 1.1:1.0:1.8. Compound **32** under the same conditions provided products **28**, **29** and **30** in ratio 3.5:3.0:1.0. The same procedure applied to polymer bound clavams **36**, **37** and **38** afforded mixtures **39**, **40** and **41** in ratios 3.3:1:2.5, 2.8:1:1.4, and 1.4:1:4.6, respectively. Products were separated by chromatography.[4]

2-Vinyloxyethyl Propane-2-sulfonate (43): A solution of 1-methylethanesulfonyl chloride (4.32 mL, 38.5 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred solution of the alcohol **42** (3.08 g, 35 mmol) and triethylamine (7.3 mL, 52.5 mmol) in dry CH_2Cl_2 (35 mL) at 0 °C. The mixture was stirred for 30 min at the same temperature and then the reaction was allowed to warm up to room temperature. After 2 h, the mixture was diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), filtered and solvents were evaporated. Column chromatography of the residue with hexane/ethyl acetate (3:1) gave **43** (6.64 g, 97.7%). Oil. IR (film): $\tilde{\nu}$ = 1622 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.7 Hz, 6 H, 2 × Me), 3.349 [sept, *J* = 6.7 Hz, 1 H, $(CH_3)_2CH-$], 3.96 (m, 2 H, CH_2), 4.09 (dd, *J* = 6.8, 2.4 Hz, 1 H, C*H*H=), 4.25 (dd, *J* = 14.3, 2.4 Hz, 1 H, CH*H*=), 4.43 (m, 2 H, CH_2), 6.47 (dd, *J* = 14.3, 6.8 Hz, 1 H, =C*H*O−) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 16.6, 52.4, 65.8, 67.3, 87.6, 151.1 ppm. HRMS (LSIMS) [M^+] ($C_7H_{14}O_4S$): calcd. 194.06128; found 194.06208. $C_7H_{14}O_4S$ (194.24): calcd. C 43.28, H 7.26, S 16.5; found C 42.84, H 7.15, S 16.33.

1-Vinyloxyethyl 1,1-Dimethyl-2-phenylethanesulfonate (44): *n*BuLi (2.5 M. in hexane, 1.08 mL, 5.2 mmol) was added with stirring to a mixture of compound **43** (0.779 g, 4.0 mmol), DMPU (4 mL) and dry THF (16 mL) under argon at −70 °C. The mixture was stirred for 30 min and then a solution of BnCl (0.51 mL, 4.4 mmol) in THF (1 mL) was added dropwise. After 3 h isopropanol (5 mL) was added and the residue was poured into saturated NaCl solution and extracted with diethyl ether (3 × 50 mL). The extract was washed with water, dried ($MgSO_4$), filtered and concentrated. Column chromatography of the residue with hexane/ethyl acetate (3:1) gave **44** (0.864 g, 76%).Oil. IR (film): $\tilde{\nu}$ = 1621 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.40, (s, 6 H, 2 × Me), 3.184 (s, 2 H, Bn), 4.01(m, 2 H, CH_2), 4.12 (dd, *J* = 2.4, 14.3 Hz, 1 H, C*H*H=), 4.27 (dd, *J* = 6.7, 2.2 Hz, 1 H, CH*H*=), 4.52 (m, 2 H, CH_2), 6.50 (dd, *J* = 14.3, 6.7 Hz, 1 H, =C*H*O−) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.1, 22.3, 41.3, 63.7, 65.9, 67.2, 87.5, 127.1, 128.2, 131.0, 151.2 ppm. HRMS (LSIMS) [M^+ + H] ($C_{14}H_{21}O_4S$): calcd. 285.11606; found 285.11562. $C_{14}H_{20}O_4S$ (284.36): calcd. C 59.13, H 7.09, S 11.27; found C 59.17, H 7.13, S 11.31.

2-[(2′-Oxoazetidin-4′-yl)oxy]ethyl Propane-2-sulfonate (45): CSI (1.08 mL, 12.43 mmol) was added to a suspension of anhydrous Na_2CO_3 (1.5 g) and **43** in toluene (30 mL) at −70 °C. The reaction mixture was stirred for 1 h. Red-Al (1 M solution in toluene 12.5 mL) was added dropwise to the mixture and it was left for 30 min. The temperature was then allowed to rise to 0 °C and water (1 mL) was added. The mixture was stirred for 30 min filtered and solvents evaporated to yield **45**. Oil. IR (film): $\tilde{\nu}$ = 3343, 1768 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.44 (d, *J* = 6.9 Hz, 6 H, 2 × Me), 2.91 (dd, *J* = 1.0, 15.1 Hz, 1 H, H-3′a), 3.13 (ddd, *J* = 15.4, 2.9 Hz, 1 H, H-3′b), 3.35 [sept, 1 H, C*H*$(CH_3)_2$], 3.82 (m, 2 H, CH_2), 4.37 (m, 2 H, CH_2), 5.15 (dd, *J* = 3.9, 1.3 Hz, 1 H, H-4′), 6.66 (br. s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 45.4, 66.0, 68.2, 52.5, 78.5 ppm. HRMS (LSIMS): [M^+ + H] ($C_8H_{16}NO_5S$): calcd. 238.07492; found 238.07539. $C_8H_{15}NO_5S$ (237.28): calcd. C 40.50, H 6.37; N 5.90, S 13.51; found C 40.50, H 6.49, N 5.84, S 13.45.

2-[(2′-Oxoazetidin-4′-yl)oxy]ethyl 1,1-Dimethyl-2-phenylethanesulfonate (46): CSI (0.1 mL, 1.1 mmol) was added to a suspension of anhydrous Na_2CO_3 (0.133 g, 1.25 mmol) and **44** in toluene (5 mL) at −70 °C. The reaction mixture was stirred for 1.5 h. Red-Al (1 M solution in toluene 1.1 mL) was added dropwise to the mixture and it was left for 30 min. The temperature was then allowed to rise to 0 °C and water (1 mL) was added. The mixture was stirred for 30 min, filtered and the solvents evaporated. Column chromatography of the residue with hexane/ethyl acetate (1:4) gave **46** (0.12, 50%). Oil. IR (film): $\tilde{\nu}$ = 3342, 1770 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 6 H, 2 × Me), 2.92 (dd, *J* = 1.4, 14.8 Hz, 1 H, H-3), 3.13(d, 2 H, Bn), 3.13 (ddd, *J* = 2.8, 4.0, 14.8 Hz, 1 H, H-3), 3.82 (m, 2 H, CH_2OMs) 4.42(m, 2 H, CH_2), 5.14 (dd, *J* = 4.0, 1.4 Hz, 1 H, H-4′), 6.54 (br. s, 1 H, NH) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 21.2, 41.4, 45.4, 66.2, 68.4, 78.6, 127.3, 128.3, 130.9 ppm. HRMS (LSIMS): [M^+ + H] ($C_{15}H_{22}NO_5S$): calcd. 328.12187; found 328.12069. $C_{15}H_{21}NO_5S$ (327.39): calcd. C 55.03, H 6.47, N 4.28, S 9.79; found C 54.92, H 6.58, N 4.39, S 9.98.

(±)-Clavam (47): Compound **45** (0.136 g, 5.8 mmol) was dissolved in anhydrous CH_3CN (7 mL) and treated with Bu_4NBr (0.203 g, 0.630 mmol) and pulverized K_2CO_3 (0.610 g). The mixture was stirred and kept under reflux for about 1 h (TLC). Subsequently, diethyl ether was added, the residue was filtered, washed with water and dried ($Mg SO_4$). The solvents were evaporated at 17 °C. The crude product was purified by flash chromatography on silica gel with methylene chloride/ diethyl ether (95:5, v/v) as eluent to give **47** (0.047 g, 67%). ^1H NMR (500 MHz, $CDCl_3$): δ = 2.83 (d, *J* = 16.2 Hz, 1 H, H-6a), 3.02 (m, 1 H, H-2a), 3.26 (ddd, *J* = 0.8, 2.8, 16.2 Hz, 1 H, H-6b), 3.81 (ddd, *J* = 5.7, 7.3, 10.9 Hz, 1 H H-2b), 4.06 (ddd, *J* = 5.7, 7.2, 8.4 Hz, 1 H, H-3a), 4.16 (ddd, *J* = 5.8, 7.3, 8.4 Hz, 1 H, H-3b), 5.17 (d, *J* = 2.7 Hz, 1 H, H-5) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 44.1, 45.9, 70.1, 84.3, 178.1 ppm. HRMS (ESI): [M^+ + Na] ($C_5H_7NO_2Na$): calcd. 136.0369; found 136.0371. Compound **47** can be obtained from **46** by the same procedure to afford the final product in a similar yield.

Alkylation of (*Z*)-1,2-*O*-Isopropylidene-5-*O*-methylsulfonyl-3-*O*-(prop-1′-enyl)-α-D-xylofuranose (2) with Soluble Chloromethylated Polystyrene: BuLi (2.5 solution in hexane, 1.7 mL. 4.2 mmol) was added to a mixture of compound **2** (1.079 g, 3.5 mmol), DMPU (2 mL) and dry THF (8 mL) under argon at −70 °C. The mixture was stirred for 30 min and then added dropwise via cannula to a

cold solution of polymer (3 g) in THF (15 mL) at − 70 °C. The product-bound polymer **52** was obtained using the standard workup procedure.[14]

[2+2]-Cycloaddition of CSI to 52: CSI (0.087 mL) was added to a suspension of anhydrous Na_2CO_3 and the product-bound polymer **52** (1.0 g) at −70 °C. The reaction mixture was stirred for 6 h, then diluted with toluene (13 mL). Red-Al (1 M solution in toluene 1.2 mL) was added dropwise to the mixture. Stirring was continued for 1 h while warming up to room temperature. The excess reagents were decomposed by addition of water (1 mL). The mixture was stirred for 30 min, filtered through Celite and evaporated with toluene. The β-lactam-bound polymer **53** (1.076 g) was obtained as a solid using the standard workup procedure. The approximate proportion of diastereomers was obtained from the ^{1}H NMR spectrum of the resin as 1.7:1.

Formation of Cephams 28 and 29 from the Polymer-bound β-Lactam 53: The polymer-bound cycloadduct **53** (0.12 g, 0.036 mmol) was dissolved in anhydrous DMF (2 mL) and Cs_2CO_3 (0.024 g, 0.072 mmol). The mixture was stirred at 60 °C for 1 h (TLC). Subsequently, diethyl ether was added, the residue was filtered through Celite and the solvents evaporated. This resulting residue was dissolved in a small amount of CH_2Cl_2 and the polymer was precipitated by adding the CH_2Cl_2 solution to a cooled solution of methanol (−30 °C). After removal of the polymer, the filtrate was concentrated to give the crude product. The crude residue was purified by silica gel chromatography (hexane/ethyl acetate, 1:1) to give (0.012 g) a mixture of oxacephams **28** and **29** in a ratio of about 1.2:1, respectively.

(3′*R*,4′*S*)- and (3′*S*,4′*R*)-5-Deoxy-5-*O*-iodo-1,2-*O*-isopropylidene--3-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-α-D-xylofuranose (54 and 55): A mixture of **7** and **8** (0.181 g, 0.477 mmol) was dissolved in anhydrous DMF (9 mL) and treated with Bu_4NI (0.352 g, 0.954 mmol). The mixture was stirred overnight at 120 °C (TLC). Subsequently, this mixture was diluted with diethyl ether and washed with water, dried ($MgSO_4$), filtered and concentrated. The crude residue was purified by silica gel chromatography (hexane/ethyl acetate, 1:9) to give **54** and **55** (0.093 g, 51%) in a ratio of about 1.8:1, respectively. A sample of iodides **54/55** was separated by chromatography (hexane/ethyl acetate, 1:9) into almost pure diastereomers (both samples contained up to 10% of the other diastereomer).

54: $[\alpha]_D = -47$ (c = 0.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.32, 1.51 (2s, 6 H, isopr.), 1.26 (d, J = 7.5 Hz, 3 H, CH_3), 3.20 (dd, J = 9.2, 10.3 Hz, 1 H, H-5), 3.30 (dd, J = 4.7, 9.2 Hz, 1 H, H-5′), 3.43 (ddq, J = 2.7, 4.5, 7.5 Hz, 1 H, H-3′), 4.16 (d, J = 3.1 Hz, 1 H, H-3), 4.49 (ddd, J = 3.1, 4.7, 10.3 Hz, 1 H, H-4), 4.59 (d, J = 3.7 Hz, 1 H, H-2), 5.22 (d, J = 4.5 Hz, 1 H, H-4′), 5.98 (d, J = 3.7 Hz, 1 H, H-1), 6.52(br. s, 1 H, NH) ppm. CD: Δε ($\lambda_{max.}$) = 6.00 (219.0), 0.087 (257.5).

55: $[\alpha]_D = -82$ (c = 0.7, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.23 (d, J = 7.5 Hz, 3 H, CH_3), 1.32, 1.51 (2s, 6 H, isopr.), 3.24 (dd, J = 9.3, 10.3 Hz, 1 H, H-5), 3.31 (dd, J = 4.7, 9.3 Hz, 1 H, H-5′), 3.37 (ddq, J = 2.2, 4.3, 7.5 Hz, 1 H, H-3′), 4.15 (d, J = 3.0 Hz, 1 H, H-3), 4.50 (ddd, J = 3.0, 4.7, 10.3 Hz, 1 H, H-4), 4.54 (d, J = 3.7 Hz, 1 H, H-2), 5.20 (d, J = 4.3 Hz, 1 H, H-4′), 5.96 (d, J = 3.7 Hz, 1 H, H-1′), 6.52 (br. s, 1 H, NH) ppm. CD: Δε ($\lambda_{max.}$) = 2.02 (221.0), 0.099 (278.5). HRMS (ESI) taken for the mixture of **54/55**: $[M^+ + Na]$ ($C_{12}H_{18}NO_5NaI$): calcd. 406.0122; found 406.0145.

(3′*R*,4′*S*)- and (3′*S*,4′*R*)-5-Deoxy-5-iodo-1,2-*O*-isopropylidene-3-*O*-(3′-methyl-2′-oxoazetidin-4′-yl)-α-D-xylofuranose (54 and 55): The product-bound polymer **56** obtained according to the procedure described earlier,[4] (0.100 g, 0.113 mmol) was dissolved in anhydrous DMF (2 mL) and treated with Bu_4NI (0.083, 0.226 mmol) then stirred at 120 °C overnight. (TLC). Subsequently, the mixture was diluted with diethyl ether washed with water, dried ($MgSO_4$) filtered and concentrated. The crude residue was purified by silica-gel chromatography (hexane/ethyl acetate, 1:2) to give (0.007 g) of **54** and **55** in a ratio about 1.7:1.

(*Z* and *E*)-3-*O*-(2′-Carbamoylpropenyl)-5-deoxy-5-iodo-1,2-di-*O*-isopropylidene-D-xylofuranoses (57): β-Lactam bound resin **26** (0,200 g, 0.153 mmol) was dissolved in anhydrous DMF (1.5 mL) and treated with Bu_4NI (0.113, 0.307 mmol) then stirred at 120 °C overnight (TLC). Subsequently, the mixture was diluted with diethyl ether, washed with water, dried ($MgSO_4$) filtered and concentrated. The crude residue was purified by silica-gel chromatography (hexane/ethyl acetate, 1:1) to give (0.009 g) of **57**. $[\alpha]_D^{17} = -28.3$ (c = 0.2, $CHCl_3$). IR (film): $\tilde{\nu}$ = 1679, 1589, 1376, 1197, 1160, 1074, 1018 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.31, 1.52 (2s, 6 H, 2 × CH_3), 1.80 (d, J = 1.3 Hz, 3 H, CH_3-3′), 3.21−3.34 (m, 2 H, H-5b, H-4), 4.52−4.56 (m, 2 H, H-5a, H-3), 4.61 (d, J = 3.7 Hz, 1 H, H-2), 5.45 (br. s, 2 H, NH_2), 5.98 (d, J = 3.7 Hz, 1 H, H-1), 7.37 (q, J = 1.3 Hz, 3.8 Hz, 1 H, H-4′) ppm. HRMS (ESI) $[M^+ + Na]$ ($C_{12}H_{18}INO_5Na$): calcd. 406.0122; found 406.01243..

Reaction of 27 with Bu_4NI: β-Lactam-bound resin **27** (0.200 g, 0.173 mmol) was dissolved in anhydrous DMF (1.5 mL) and treated with Bu_4NI (0.128 g, 0.347 mmol) then stirred at 120 °C overnight. (TLC). Subsequently, the mixture was diluted with diethyl ether, washed with water, dried ($MgSO_4$) filtered and concentrated. The crude residue was purified by silica-gel chromatography (hexane/ethyl acetate, 1:2) to give (19.8 mg, 30%) of **58**,[16] (4.1 mg, 6.2%) of **54/55**, (2.5 mg, 3.8%) of **57**.

Acknowledgments

This work was partially supported by the Polish State Committee for Scientific Research (KBN), grant no. T 09/PBZ.6.04. R. L. thanks the Foundation for Polish Science for the FNP 2001 scholarship. The authors are kindly indebted to Dr. J. Frelek and Ms. P. Szczukiewicz for carrying out the CD measurements.

[1] F. Zaragoza Dörwald, in *Organic Synthesis on Solid Phase*, Wiley-VCH, Weinheim, New York, **2000**.
[2] P. Seneci, in *Solid-Phase Synthesis and Combinatorial Technologies*, Wiley-VCH, Weinheim, New York, **2000**.
[3] I. G. Mata, *Curr. Pharm. Design.* **1999**, *5*, 955−964.
[4] R. Łysek, B. Furman, M. Cierpucha, B. Grzeszczyk, L. Matyjasek, M. Chmielewski, *Eur. J. Org. Chem.* **2002**, 2377−2384.
[5] Z. Kałuża, B. Furman, M. Patel, M. Chmielewski, *Tetrahedron: Asymmetry* **1994**, *5*, 2179−2186.
[6] Z. Kałuża, B. Furman, M. Chmielewski, *Tetrahedron: Asymmetry* **1995**, *6*, 1719−1730.
[7] R. Łysek, B. Furman, Z. Kałuża, M. Chmielewski, *Polish. J. Chem.* **2000**, *74*, 51−60.
[8] J. H. van Maarseveen, *Comb. Chem. High Throughput Screening* **1988**, *1*, 185−214.
[9] B. Musicki, T. S. Widlanski, *J. Org. Chem.* **1990**, *55*, 4231−4233.
[10] B. Furman, R. Łysek, L. Matyjasek, W. Wojtkielewicz, M. Chmielewski, *Synth. Commun.* **2001**, *31*, 2795−2802.

[11] M. Cierpucha, J. Solecka, J. Frelek, P. Szczukiewicz, M. Chmielewski, *Biorg. Med. Chem.* **2004**, *12*, 405−416.
[12] N. G. Cooke, A. D. Jones, A. Whiting, *Tetrahedron* **1992**, *48*, 9553−9560.
[13] [13a] R. B. Duff, E. G. V. Percival, *J. Chem. Soc.* **1949**, 1675. [13b] D. H. A. Barton, W. B. Motherwell, *J. Chem. Soc., Perkin Trans. 1* **1980**, 1124−1131.
[14] Sh. Chen, K. D. Janda, *J. Am. Chem. Soc.* **1997**, *119*, 8724−8725.
[15] H. Rehling, H. Jensen, *Tetrahedron Lett.* **1972**, 2793−2796.
[16] J. R. Bearder, M. L. Dewis, D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1* **1995**, 227−233.

Received April 5, 2004

