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Synthesis, biological, and chiroptical activity of 3-phenyl-clavams

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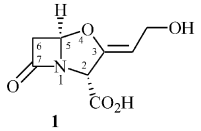
Abstract—The [2 + 2]cycloaddition of chlorosulfonyl isocyanate to simple vinyl ethers derived from the 2-*O*-sulfonylated (*R*) and (*S*) 1-phenyl-1,2-ethanediol leads to 4-alkoxy-azetidin-2-ones with a moderate stereoselectivity. The cycloaddition to analogous (*Z*)-propenyl ethers proceeds stereospecifically with the retention of the olefin configuration. The intramolecular alkylation of β-lactam nitrogen atom furnished all possible stereoisomers of 3-phenyl- and 6-methyl-3-phenyl-clavams. The biological and chiroptical activity of synthesized clavams was investigated. The (3*R*,5*R*)-diastereomer **30** showed higher inhibition of bacterial enzymes than other related compounds.

1. Introduction

While a number of different clavams were isolated,[1–5] only clavulanic acid **1**[1] and its simple *O*-acyl derivatives with the (5*R*)-configuration at the ring junction offer the strong β-lactamase inhibition and a weak antibacterial activity. Certain other clavams, represented by the family **2**–**5,** with (*S*)-configuration at C-5, exhibit activity against a number species of fungi.[2–5]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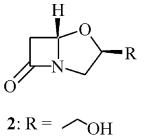
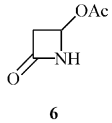

2: R = OH
3: R = OH
4: R = CO$_2$H, NH$_2$
5: R = HO$_2$C, O, N, H, HO, NH$_2$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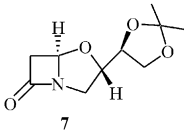
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Compounds **1**–**5** lack substituent at C-6 carbon atom and, consequently, their syntheses usually begin with the commercially available 4-acetoxy-azetidinone **6** as a convenient starting material.[6–9] The condensation of **6** with a separately prepared chiral alcohol has been followed by the intramolecular alkylation of the nitrogen atom in the intermediary 4-alkoxy-azetidinone. The drawback of such a strategy is related to a low asymmetric induction at C-4 of the azetidin-2-one ring.[6–10]

The [2 + 2]cycloaddition of chlorosulfonyl isocyanate (CSI) to chiral vinyl ethers, having a stereogenic center located next to the oxygen atom, offers an alternative to that which is based on the condensation of **6** with chiral alcohols.[10–13] It has been demonstrated that the [2 + 2]cycloaddition method is stereospecific and provides the excellent stereoselectivity even in the case of open-chain vinyl ethers.[14,15]

A few years ago we synthesized, starting from (*L*)-tartaric acid, clavam **13**, structurally related to the clavulanic acid **1** missing the C-2 carboxylic function.[15] Compound **13** displayed marked *anti* β-lactamase activity.

Since the 1-phenyl-1,2-ethanediol (**14**) is commercially available in both enantiomeric forms, it was of interest to investigate the [2 + 2]cycloaddition to its 1-*O*-vinyl and (*Z*) 1-*O*-propenyl ethers and to synthesize the corresponding 3-phenyl-clavams via intramolecular alkylation of the nitrogen atom in intermediary adducts, as well as examine the biological activity of all possible stereoisomeric clavams formed.

2. Results and discussion

Our previous studies performed on the vinyl ethers **8**[14] and **9**,[15] substituted at C-1 with a five-membered ring

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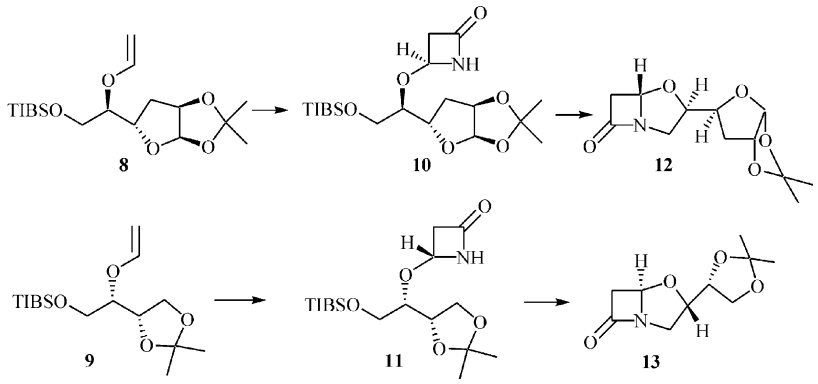


Scheme 1.

and protected at the primary hydroxyl group with the triisopropylbenzenesulfonyl (TIBS) group, demonstrated the high stereoselectivity of [2+2]cycloaddition (Scheme 1). We have established the existence of opposite (*S*) and (*R*) configurations at C-4′ in products **10** and **11**, respectively, depending on the (*R*) and (*S*) configuration at the carbon atom bearing vinyloxy group in the starting material. Therefore, we expected that the replacement of five-membered ring (furanoid or dioxolane) with the phenyl ring should not change the high asymmetric induction. The primary hydroxyl group was protected by formation of the sulfonyl group. In order to compare the influence of bulkiness of sulfonyl groups on the diastereoselectivity of cycloaddition, we tested the mesyl, isopropanesulfonyl (IPS), 1,1-dimethyl-2-phenyl-ethanesulfonyl (BIPS) and triisopropylbenzenesulfonyl (TIBS) protective groups. The BIPS group was obtained according to the procedure developed by Musicki and Widlanski[16] for the *C*-alkylation of mesylates. The experimental protocol consisted of lithiation of the isopropyl group of the sulfonate followed by alkylation of the resulting salt with benzyl chloride.

The enantiomers **14** (*R*) and **14** (*S*) were independently transformed into corresponding vinyl ethers **18**, **19** and **21** using standard reaction sequence. The sequence consisted of sulfonylation at the primary hydroxy group followed by the *trans*-etherification procedure with vinyl *n*-butyl ether in the presence of mercury acetate.[17] The vinyl ether **20** was obtained from **19** using Musicki and Widlanski method.[16]

Table 1. Proportions of stereisomers **22**/**23**, **24**/**25**, **26**/**27**, **28**/**29** and **42**/**43**, **44**/**45**, **46**/**47**, **48**/**49** obtained by [2+2]cycloaddition of CSI to vinyl ethers **18**–**21** and (*Z*)-propenyl ethers **38**–**41**[18]

Substrate	Proportions of diastereomers (1*R*,4′*S*) versus (1*R*,4′*R*) or (1*S*,4′*R*) versus (1*S*,4′*S*)
18	1.9:1
19	2:1
20	3:1
21	1:2.4
38	1:1
39	1:1.35
40	1:1.15
41	1:10

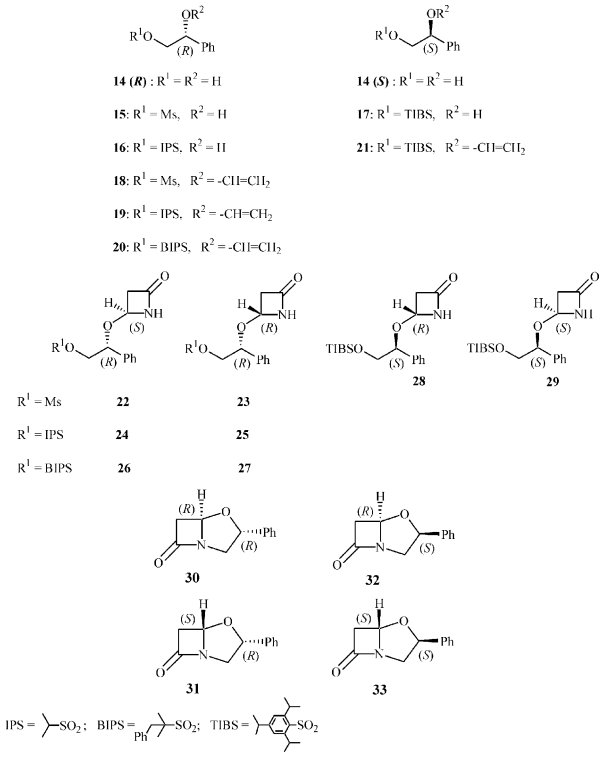
The [2+2]cycloaddition of CSI to the vinyl ethers **18**–**20**[18] proceeds with a moderate diastereoselectivity yielding **22**, **24** and **26** as the main components of the corresponding post-reaction mixtures (Table 1); in other words, the defined absolute configuration (*R* or *S*) of the vinyl ether generates opposite absolute configuration at C-4′ of the azetidin-2-one ring (*S* or *R*, respectively). In the case of addition to **21**, the direction of asymmetric induction was changed. In this case the compound **29** become the main product (Table 1); it means that defined absolute configuration of the vinyl ether generates the same absolute configuration at C-4′ of the azetidin-2-one ring.

Mixtures **22**/**23** and **28**/**29** (*SR* and *SS*) were not separated into pure components and were used directly in the next step, whereas analogous mixtures **24**/**25** and **26**/**27** were successfully separated into pure diastereomers by chromatography prior to subsequent transformations.

The intramolecular *N*-alkylation in **22**–**29** proceeds under standard the PTC conditions to provide corresponding mixture of clavams **30** and **31**, or pure diastereomers **32** and **33**. Mixture of **30** and **31** was separated into pure components by chromatography. The configuration of stereoisomers **30**–**33** was established analysing NOE's in ^{1}H NMR spectra[11–15,19] (protons H-3 and H-5 display spin–spin interaction in the case of 3*R*5*S* or 3*S*5*R* diastereomers whereas for 3*R*5*R* or 3*S*5*S* analogous spin–spin interactions were not detected) and circular dichroism spectra (see over).

The (*Z*)-propenyl ethers **38**, **39** and **41** were obtained following the standard reaction sequence (Scheme 2). Following tritylation of the primary hydroxy group and alkylation of the secondary one, the trityl substituent was removed and allyl ether **36** was rearranged to the (*Z*)-propenyl **37** by treatment with *t*-BuOK in DMSO.[20] The free hydroxy group was subsequently sulfonylated using the same methodology as employed during preparation of compounds **15**, **16** and **18**. Compound **40** was obtained from **39** by the method used for **20**.[16]

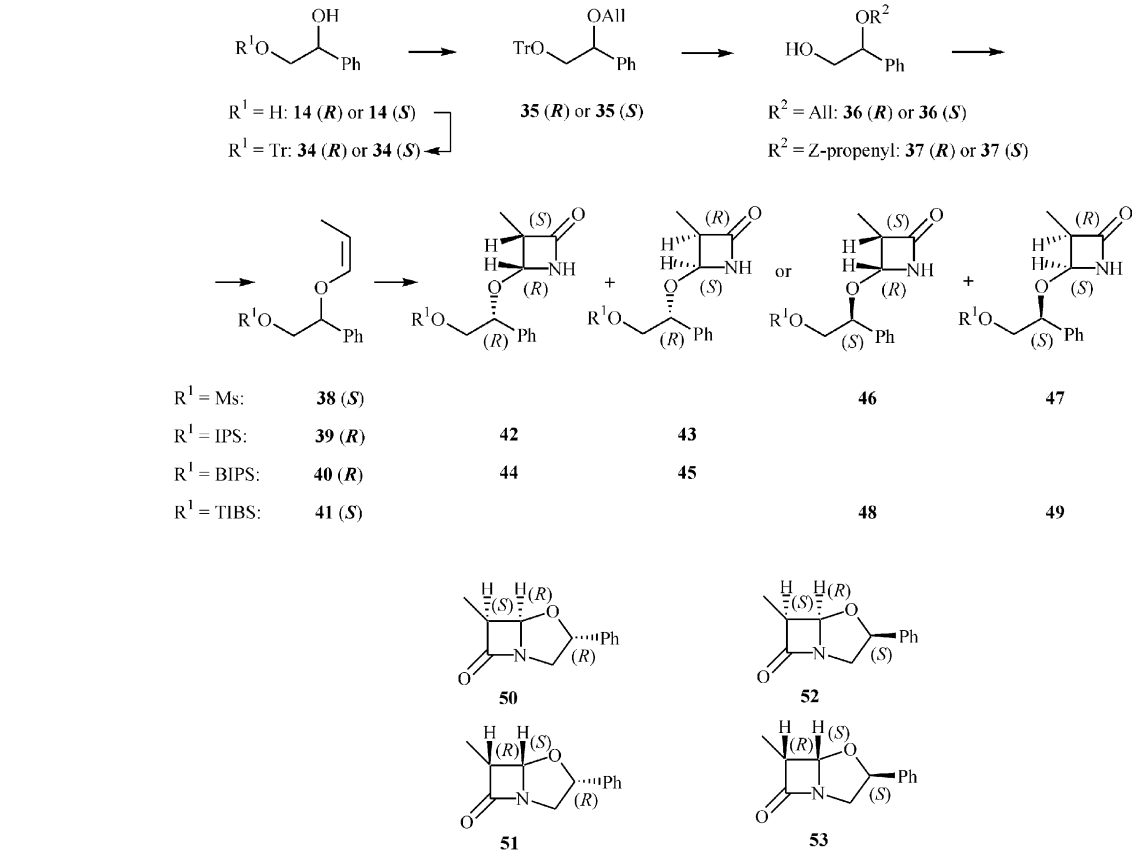
The comparison of CSI [2+2]cycloaddition to vinyl ethers **18**–**20** with analogous addition to (*Z*)-propenyl ethers **38**–**40** shows that the direction of asymmetric induction in both sets of reactions is opposite.[18] The



diastereomers with the same absolute configuration at C-1 and C-4′ carbon atoms (1*R*4′*R*: **42**, **44** and 1*S*4′*S*: **47**, **49**) are found as a main components of the post-reaction mixtures. The diastereomeric excess in the case of addition to **38**–**40** is low, in contrast to the case of TIBS substituted ether **41**, where it was found to be excellent.[18] The diastereomeric mixtures **42**/**43**, **44**/**45**, **46**/**47** and **48**/**49** were separated into pure components using chromatography.

To confirm assignment of the absolute configuration at C-4 in 4-alkoxy-azetidinones **24**–**27** and **38**–**49**, the CD spectroscopy was used. The assignment of absolute configuration was based on the β-lactam sector rule.[21] Recently, the β-lactam sector rule was applied successfully to the configurational assignments of monobactams, that are differently substituted at C-3 and C-4 atoms.[22] According to the rule, a negative sign of the CD band occurring around 220 nm corresponds to the (4*R*) and a positive sign of the same band to the (4*S*) configuration. Following this finding, the absolute configuration at C-4 can be established as (*R*) for azetidinones **25**, **27**, **42**, **44**, **46**, and **48** displaying a negative long-wavelength CD band, whereas a positive Cotton effect (CE) around 220 nm in compounds **24**, **26**, **43**, **45**, **47**, and **49** indicates the (*S*) absolute configuration at the same carbon atom (see Experimental). This assignment nicely corroborates the prediction made by analysis of the NMR data. To illustrate, the CD spectra of representative 4-alkoxy-azetidinones are presented in Figure 1. These spectra appear almost enantiomeric for local enantiomers **24**, **25** and **46**, **47**.

The intramolecular alkylation of β-lactam nitrogen atom in compounds **42**–**49** led to the corresponding clavams **50**–



Scheme 2.

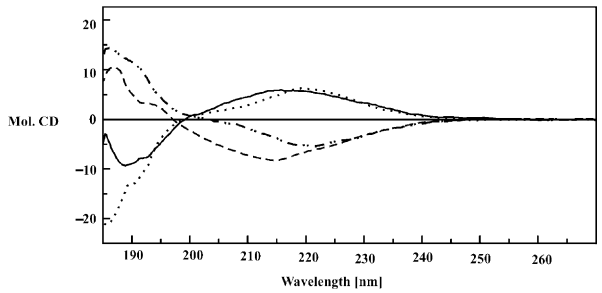


Figure 1. CD spectra of azetidinones **24** (·····), **25** (- - -), **46** (–···–···–), and **47** (—) recorded in acetonitrile.

53. The configuration of all stereoisomeric clavams **50–53** was established analogously as for compounds **30–33**.

The absolute configuration of clavams **30–33** and **50–53** was also determined by the analysis of their respective circular dichroic spectra. It was previously shown that the absolute configuration at the bridge-head carbon atom determines the sign of the CD of penicillins, cephalosphorins, penams and clavams.[23] Very recently, a simple helicity rule for the assignment of absolute configuration at the ring junction carbon atom by correlation with the sign of the CD band associated with the *n*–π* transition was proposed for clavams and 5-oxacephams.[24]

The application of the aforementioned helicity rule to clavams **30–33** and **50–53** leads to the conclusion that the absolute configuration at C-5 atom in compounds **30**, **32**, **50**, and **52**, characterized by a positive CD band attributed to the *n*–π* β-lactam amide transition, is (*R*) (see Experimental). The negative sign of the same CE indicates the (5*S*) absolute configuration for clavams **31**, **33**, **51**, and **53** (see Experimental). Such assignment is consistent with the stereochemical conclusions based on application of other spectroscopic methods, for example, NMR spectroscopy. As an example, two pairs of representative diastereomers **32**, **33** and **50**, **51** are shown in Figure 2.

The analysis of results of cycloaddition may suggest the change of the preferred conformation of the ether group in the transition state when the simple vinyl ether is replaced by the (*Z*)-propenyl moiety. In the past we have not noticed such a phenomenon.[13,25] In the case of a simple vinyl ether the preferred conformation of the transition state is probably s-*trans* with the H-1 proton located within the diastereozero-plane, anti-periplanar

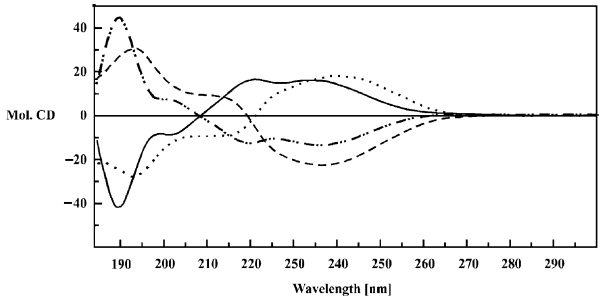


Figure 2. CD spectra of clavams **32** (—), **33** (– - - -), **50** (·····), and **51** (–···–···–) recorded in acetonitrile.

to C-1′ of the olefin (Fig. 3a). A streochemical model of the transition state for [2 + 2]cycloaddition of CSI and vinyl ethers based on the conformation depicted in Figure 3a has been recently proposed by us.[26] The CSI molecule approaches the double bond *syn* to the phenyl group. This directional preference is not very large and is amplified if the size of the sulfonyl group is increased. In the case of (*Z*)-propenyl ethers, the rationalization of the experimental findings is not fully consistent. One can postulate a change of the preferred conformation of the transition state to the *s-trans* with H-1 proton located in diastereozero-plane, syn-periplanar to C-1′ of the olefin (compare Fig. 3a with Fig. 3c). The chirality center rotates around the C–O bond by 180°. The preferred approach of CSI molecule is the same as in the case of simple vinyl ether. This leads to the reverse direction of asymmetric induction and consequently to the lower diastereomeric excess, since the double bond is at a greater distance to both large substituents. In the case of TIBS substituent (ethers **21** and **41**), the complexation of both aromatic rings changes geometry of the transition state; both large substituents are closer each other (Fig. 3b and 3c). It could be assumed that the preferred conformation of the transition state for both simple vinyl ether and (*Z*)-propenyl ether, in such case, is similar. This assumption can explain the change of direction of asymmetric induction in the case of the vinyl ether **21** (Fig. 3b) in comparison with related ethers **18–20** (Fig. 3a). Similar conformation of the transition state for the ether **21** and **41**, however, does not explain a significant difference in asymmetric induction of cycloaddition between simple vinyl ether **21** (1:2.4) versus *Z*-propenyl **41** (1:10) (Table 1).

Clavams **30–33** and **50–53** were evaluated for their biological activity. An inhibition of the DD-carboxy-

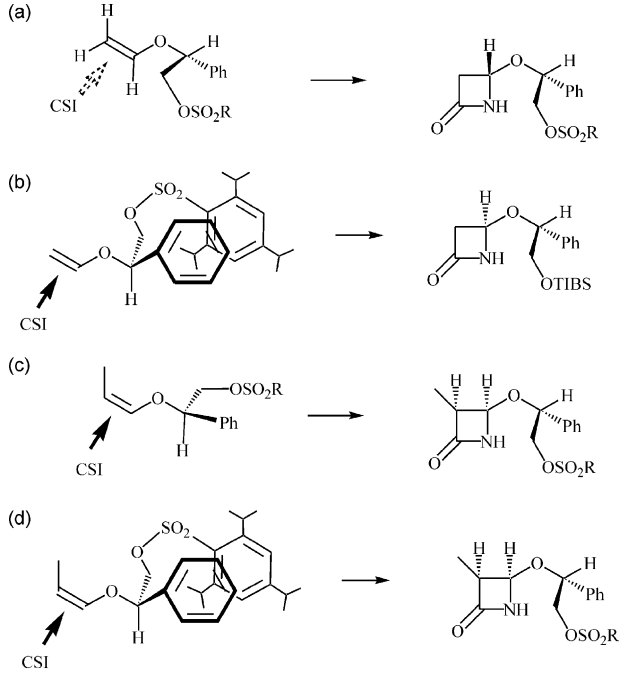


Figure 3. Preferred stereochemical pathway for cycloaddition of CSI to vinyl ethers and Z-propenyl ethers. For the sake of simplicity, configuration of substrates refer to (*R*) series only..[18]

Table 2. Biological activity of 3-phenyl-clavams **30**, **31** and **50–53**

Compd	Inhibition of DD-peptidase ID_{50} (M)	Inhibition of β-lactamase IC_{50} (M)
30	$0.18 \cdot 10^{-3}$	$0.88 \cdot 10^{-2}$
31	—	$0.80 \cdot 10^{-1}$
50	$0.42 \cdot 10^{-2}$	$0.95 \cdot 10^{-2}$
51	—	$0.76 \cdot 10^{-1}$
52	—	$0.69 \cdot 10^{-1}$
53	—	$0.26 \cdot 10^{-1}$

peptidase activity and, separately, an inhibition of β-lactamase were measured (Table 2).[27–29] Compounds **31–33** and **51–53** showed only a trace of DD-peptidase inhibition. Within studied series only compound **30** (*R,R*) showed inhibition of DD-peptidase, whereas its 6-methyl congener **50** (*R,R*) showed significantly lower activity. Clavams not placed in Table 2, **32** and **33**, exhibited lack of β-lactamase inhibition (**32**) or a min only (**33**). All tested clavams were not soluble in water, so enzymatic tests were done in 25% of methanol. In higher concentration of methanol in reaction mixture both enzymes lost of activity.

3. Conclusion

It was shown that the [2 + 2]cycloaddition of CSI to ethers **18–21** and **38–41** proceeds with a low stereoselectivity. Analogous cyclo-additions to **38–41** are stereospecific. Vinyl ethers **18–20** and (*Z*)-propenyl ethers **38–41** displayed opposite directions of asymmetric induction. Interaction between phenyl and arylsulfonyl groups causes that ether **21** exhibits the same direction of asymmetric induction as (*Z*)-propenyl ethers. We demonstrated that the circular dichroism spectroscopy is a very useful tool for the assignment of the absolute configuration of clavams bearing a phenyl group at C-3. Only one clavam, with the (3*R*,5*R*) configuration shows an interesting inhibition of DD-peptidase, but lower than known inhibitors sulbactam (ID_{50} (M) = $5.5 \cdot 10^{-4}$), or clavulanic acid (ID_{50} (M) = $2.0 \cdot 10^{-5}$).[30]

4. Experimental

Melting points were determined on a Koefler hot-stage apparatus. NMR spectra were recorded using Brucker Avance 500 and Varian Mercury 400 instruments. IR spectra were recorded on a Perkin–Elmer FTIR Spectrum 200 spectrophotometer. UV spectra were measured on a Cary 100 spectrophotometer in acetonitrile. CD spectra were recorded between 180–400 nm at room temperature with a JASCO J-715 spectropolarimeter using acetonitrile solutions. Solutions with concentrations in the range 0.8×10^{-4} to 1.2×10^{-3} mol·dm^{-3} were examined in cells with path length 0.1 or 1 cm. Optical rotations were measured using a JASCO P 3010 polarimeter at 22 ± 3 °C. Mass spectra were recorded using AMD-604 Inectra GmbH and HPLC-MS with Mariner and API 356 detectors. Column chromatography was performed using E. Merck Kiesel Gel (230–400 mesh).

4.1. General procedure of sulfonylation

To a solution of (1*S*) or (1*R*) 1-phenyl-1,2-ethanediol (**14**) (0.5 g, 3.62 mmol) and Et_3N (0.75 mL, 5.43 mmol) in CH_2Cl_2 (10 mL) the sulfonyl chloride (3.98 mmol) was added at 0 °C. After 13 h at 10 °C the reaction mixture was diluted with water (50 mL). The solution was extracted with diethyl ether (3×40 mL). The combined organic extracts were dried with magnesium sulfate, filtered and concentrated to dryness. The residue was purified by a column chromatography on silica gel using hexane–ethyl acetate 19:1 (v/v) as eluent, to give corresponding sulfonate.

4.1.1. (1*R*) 2-*O*-Methanesulfonyl-1-phenyl-1,2-ethanediol (15). Yield: 88%; R_f (hexane–ethyl acetate v/v 1:1) 0.5; $[\alpha]_D$ −62.0 (*c* 0.9, CH_2Cl_2); IR (film): 1352 cm^{-1} (S=O), 3524 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$): δ 3.03 (s, 3H, Ms), 4.28 (dd, 1H, *J* = 10.9, 8.2 Hz, H-2), 4.34 (dd, 1H, *J* = 10.9, 3.4 Hz, H-2′), 5.05 (dd, 1H, *J* = 8.2, 3.4 Hz, H-1), 7.31–7.47 (m, 5H, Aryl); ^{13}C NMR ($CDCl_3$): δ 37.62, 72.13, 73.91, 126.18, 128.68, 128.77, 138.33. ESIHRMS, *m*/*z*; $(M + Na)^+$ calcd for $C_9H_{12}O_4SNa$: 239.0349. Found: 239.0339.

4.1.2. (1*R*) 2-*O*-Isopropanesulfonyl-1-phenyl-1,2-ethanediol (16). Yield: 74%; mp 45.5–46.7 °C; R_f (hexane–ethyl acetate v/v 1:1) 0.8; $[\alpha]_D$ −50.1 (*c* 0.7, CH_2Cl_2); IR (film): 1346 cm^{-1} (S=O), 3518 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$): δ 1.42, 1.43 (2xd, 6H, *J* = 6.9 Hz, isopr.), 3.34 (sept., 1H, *J* = 6.9 Hz, isopr.), 4.27 (dd, 1H, *J* = 11.0, 8.4 Hz, H-2), 4.34 (dd, 1H, *J* = 11.0, 3.4 Hz, H-2′), 5.05 (dd, 1H, *J* = 8.4, 3.4 Hz, H-1), 7.31–7.42 (m, 5H, Aryl); ^{13}C NMR (400 MHz, $CDCl_3$): δ 16.53, 16.62, 52.45, 72.33, 73.51, 126.20, 128.58, 128.71, 138.45; ESIHRMS, *m*/*z*; $(M + Na)^+$ calcd for $C_{11}H_{16}O_4SNa$: 267.0662. Found: 267.0661. Anal. calcd for $C_{11}H_{16}O_4S$: C, 54.08; H, 6.60; S, 13.12. Found: C, 54.18; H, 6.81; S, 13.04.

4.1.3. (1*S*) 1-Phenyl-2-*O*-(2,4,6-triisopropylbenzenesulfonyl)-1,2-ethanediol (17). Yield: 83%; R_f (hexane–ethyl acetate v/v 9:1) 0.25; mp 193–195 °C; $[\alpha]_D$ +35.2 (*c* 1.2, CH_2Cl_2); IR (film): 3527 cm^{-1} (OH); ^{1}H NMR ($CDCl_3$): δ 1.25 (bd, 18H, *J* = 6.9 Hz, TIBS), 2.91 (sept., 1H, *J* = 6.9 Hz, TIBS), 4.10 (dd, 1H, *J* = 10.7, 8.7 Hz, H-2), 4.14 (sept., 2H, *J* = 6.9 Hz, TIBS), 4.17 (dd, 1H, *J* = 3.2, 10.7 Hz, H-2), 5.06 (dd, 1H, *J* = 8.7, 3.2 Hz, H-1), 7.18 (s, 2H, TIBS), 7.30–7.35 (m, 5H, Aryl); ^{13}C NMR ($CDCl_3$): δ 23.50, 24.68, 24.72, 29.69, 34.25, 72.21, 73.63, 123.86, 126.22, 128.50, 128.68, 129.17, 138.42, 150.89, 153.98; ESIHRMS, *m*/*z*; $(M + Na)^+$ calcd for $C_{23}H_{32}O_4SNa$: 427.1914. Found: 427.1935.

4.2. General procedure of *trans*-vinylation

A solution of sulfonate (**15**, **16** or **17**, 2.28 mmol) and mercury(II) acetate (0.03 g) in butyl vinyl ether (30 mL) was refluxed for 1 h. The solution was cooled, washed with saturated aqueous sodium carbonate (2×), dried with magnesium sulfate, filtered and concentrated to dryness. The residue was purified by a column chromatography on silica gel using hexane–ethyl acetate 9:1 (v/v) as an eluent, to give corresponding vinyl ether (**18**, **19**, **21**).

4.2.1. (1*R*) 2-*O*-Methanesulfonyl-1-phenyl-1-*O*-vinyl-1,2-ethanediol (18). Yield: 69%; R_f (hexane–ethyl acetate v/v 3:1) 0.5; $[\alpha]_D$ −52.5 (*c* 1.5, CH_2Cl_2); IR (film): 1357 cm^{-1} (S=O), 1639 cm^{-1}, 1624 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 3.03 (s, 3H, Ms), 4.10 (dd, 1H, *J* = 6.7, 2.2 Hz, H-2′a), 4.30 (dd, 1H, *J* = 14.1, 2.2 Hz, H-2′b), 4.34 (dd, 1H, *J* = 11.2, 3.7 Hz, H-2a), 4.44 (dd, 1H, *J* = 11.2, 7.8 Hz, H-2b), 5.10 (dd, 1H, *J* = 7.8, 3.7 Hz, 1H, H-1), 5.37 (dd, 1H, *J* = 14.1, 6.7 Hz, 1H, H-1′), 7.31–7.49 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 37.78, 71.99, 78.78, 90.64, 126.54, 2x128.90, 135.83, 149.83; ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{11}H_{14}O_4SNa$: 265.0505. Found: 265.0519

4.2.2. (1*R*) 2-*O*-Isopropanesulfonyl-1-phenyl-1-*O*-vinyl-1,2-ethanediol (19). Yield: 72%; R_f (hexane–ethyl acetate v/v 3:1) 0.5; $[\alpha]_D$ −55.5 (*c* 1.9, CH_2Cl_2); IR (film): 1350 cm^{-1} (S=O), 1623 cm^{-1}, 1640 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 1.41 (2×d, 6H, *J* = 6.9, 1.5 Hz, isopr.), 3.33 (sept, 1H, *J* = 6.9 Hz, isopr.), 4.06 (dd, 1H, *J* = 6.6, 2.2 Hz, H-2′a), 4.27 (dd, 1H, *J* = 14.2, 2.2 Hz, H-2′b), 4.32 (dd, 1H, *J* = 11.3, 3.8 Hz, H-2a), 4.37 (dd, 1H, *J* = 11.3, 7.9 Hz, H-2b), 5.08 (dd, 1H, *J* = 7.9, 3.8 Hz, H-1), 6.36 (dd, 1H, *J* = 14.2, 6.6 Hz, H-1′), 7.30–7.42 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 16.46, 16.62, 52.46, 71.31, 78.89, 90.40, 125.53, 128.80, 128.83, 136.03, 149.94; ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{13}H_{18}O_4SNa$: 293.0818. Found: 293.0830. Anal. calcd for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71; S, 11.86. Found: C, 57.70; H, 6.80; S, 11.92.

4.2.3. (1*S*) 1-Phenyl-2-*O*-(2,4,6-triisopropylbenzenesulfonyl)-1-*O*-vinyl-1,2-ethanediol (21). Yield: 73%; R_f (2× hexane–*tert*-butyl-methyl ether v/v 19:1) 0.5; $[\alpha]_D$ +57.6 (*c* 1.0, CH_2Cl_2); IR (film): 1622 cm^{-1}, 1639 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 1.24 (d, 6H, *J* = 6.8 Hz, TIBS), 1.26 (d, 12H, *J* = 6.8 Hz, TIBS), 2.90 (sept, 1H, *J* = 6.8 Hz, TIBS), 3.98 (dd, 1H, *J* = 6.7, 2.1 Hz, H-2′a), 4.14 (sept, 2H, *J* = 6.8 Hz, TIBS), 4.16 (dd, 1H, *J* = 14.2, 2.1 Hz, H-2′b), 4.19 (dd, 1H, *J* = 11.1, 4.3 Hz, H-2a), 4.22 (dd, 1H, *J* = 11.1, 7.5 Hz, H-2b), 5.05 (dd, 1H, *J* = 7.5, 4.3 Hz, H-1), 6.23 (dd, 1H, *J* = 14.2, 6.7 Hz, H-1′), 7.18 (s, 2H, Aryl), 7.27–7.37 (m, 5H, aryl); ^{13}C NMR (500 MHz, $CDCl_3$): δ 23.34, 24.49, 24.54, 29.47, 34.07, 71.07, 78.58, 90.03, 123.58, 126.35, 128.50, 128.62, 129.40, 136.21, 149.7, 150.64, 153.54; LSIMSHRMS *m*/*z*; $(M+Na)^+$: calcd for $C_{25}H_{34}O_4SNa$: 453.2075 Found: 453.2092.

4.2.4. (1*R*) 2-*O*-(1′,1′-Dimethyl-2′-phenyl-ethanesulfonyl)-1-phenyl-1-*O*-vinyl-1,2-ethanediol (20). Compound **19** (0.394 g, 1.46 mmol) was dissolved in THF/DMPU mixture [5 mL; 5:1 (v/v)] and cooled to −78 °C. The *n*-BuLi (2.7 M; 0.81 mL, 2.19 mmol) was added dropwise under argon atmosphere. Solution was stirred for 10 min until a pale red color developed, then benzyl bromide (0.31 mL, 2.63 mmol) was added. The temperature was allowed rise up to −20 °C. After 1 h reaction was quenched with MeOH (1 mL). The solution was extracted with *t*-butyl-methyl ether (3×). The combined organic extracts were dried with magnesium sulfate, filtered and concentrated to dryness. The residue was purified by a column chromatography on silica gel using hexane–ethyl acetate 3:1 (v/v) as eluent to obtain **20** (0.384 g, 73%); R_f (hexane–ethyl acetate v/v 3:1) 0.6; $[\alpha]_D$ −38.9 (*c* 1.8, CH_2Cl_2); IR (film): 1344 cm^{-1} (S=O), 1623 cm^{-1}, 1638 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 1.33 (s, 6H, 2×CH_3), 3.10 (s, 2H, CH_2Ph), 4.07 (dd, 1H, *J* = 6.6, 2.2 Hz, H-2′a), 4.30 (dd, 1H, *J* = 14.1, 2.2 Hz, H-2′), 4.40 (m, 2H, H-2a,2b), 5.10 (dd, 1H, *J* = 5.4, 6.3 Hz, H-1), 6.38 (dd, 1H, *J* = 14.1, 6.7 Hz, H-1′), 7.11–7.20 (m, 2H, aryl), 7.23–7.45 (m, 8H, aryl); ^{13}C NMR ($CDCl_3$): δ 20.97, 41.21, 63.41, 71.11, 78.97, 90.33, 126.59, 127.12, 128.21, 128.79, 128.82, 130.99, 134.82, 136.21, 150.11; ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{20}H_{24}O_4SNa$: 383.1288. Found: 383.1305. Anal. calcd for $C_{20}H_{24}O_4S$: C, 66.64; H, 6.7; S, 8.89. Found: C, 66.58; H, 6.72; S, 8.94.

4.3. General procedure of cycloaddition

To a well stirred suspension of anhydrous sodium carbonate (0.2 g) in solution of vinyl ether (**18**–**21**, 1.23 mmol) in dry toluene (5 mL), the chlorosulfonyl isocyanate (139 μL, 1.6 mmol) was added within 5 min, under an argon atmosphere at −50 °C. The mixture was stirred at the same temperature for another 25 min and was diluted with toluene (5 mL) and cooled to −70 °C. The Red-Al solution in toluene (1M; 1.24 mL) was slowly added and the reaction mixture was stirred for 15 min. The cooling bath was removed and water (0.2 mL) was added at 0 °C. Stirring was continued for additional 10 min. The suspension was filtered and solvent was evaporated. The residue was purified by a column chromatography on silica gel using hexane–ethyl acetate 1:1 (v/v) as eluent, to give a mixture of corresponding diastereomers.

4.3.1. (1*R*,4′*S*) and (1*R*,4′*R*) 1-*O*-(Azetidin-2′-on-4′-yl)-2-*O*-methanesulfonyl-1-phenyl-1,2-ethanediol (22 and 23). Yield: 46%; R_f (hexane–ethyl acetate v/v 1:4) 0.3; IR (film): 1352 cm^{-1} (S=O), 1768 cm^{-1} (C=O), 3352 cm^{-1} (NH); ^1H NMR ($CDCl_3$) selected signals: δ 3.00 (s, 1H, Ms of minor component), 3.03 (s, 2H, Ms of major component), 5.11 (dd, 0.66H, *J* = 11.5, 3.8 Hz, H-4′ of major component), 5.17 (dd, 0.33H, *J* = 1.5, 3.8 Hz, H-4′ of minor component); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{12}H_{15}NO_5SNa$: 308.0563. Found: 308.0555.

4.3.2. (1*R*,4′*S*) 1-*O*-(Azetidin-2′-on-4′-yl)-2-*O*-isopropane-sulfonyl-1-phenyl-1,2-ethanediol (24). R_f (hexane–ethyl acetate v/v 3:7) 0.4; $[\alpha]_D$ −72.3 (*c* 0.8, CH_2Cl_2); IR (film): 1347 cm^{-1} (S=O), 1770 cm^{-1} (C=O), 3340 cm^{-1} (NH); IR (film): 1347 cm^{-1} (S=O), 1770 cm^{-1} (C=O), 3340 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.41, 1.43 (2×d, 6H, *J* = 6.8 Hz, isopr.), 2.88 (ddd, 1H, *J* = 15.1, 1.6, 0.6 Hz, H-3′a), 3.06 (ddd, 1H, *J* = 15.1, 3.8, 2.5 Hz, H-3′b), 3.33 (sept, 1H, *J* = 6.8 Hz, isopr), 4.27 (dd, 1H, *J* = 11.3, 7.2 Hz, H-2a), 4.32 (dd, 1H, *J* = 11.3, 4.9 Hz, H-2b), 4.79 (dd, 1H, *J* = 7.2, 4.9 Hz, H-1), 5.11 (dd, 1H, *J* = 3.8, 1.6 Hz, H-4′), 7.15–7.48 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 16.48, 16.57, 45.85, 52.71, 71.50, 78.20, 79.09, 126.74, 128.98, 129.16, 135.96, 171.01; UV ε (λ_{max}): 9200 (205^{sh}), 4200 (216^{sh}); CD Δε (λ_{max}): −12.8 (190.4) +6.3 (219.8); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{14}H_{19}NO_5SNa$: 336.0876. Found: 336.0885.

4.3.3. (1*R*,4′*R*) 1-*O*-(Azetidin-2′-on-4′-yl)-2-*O*-isopropane-sulfonyl-1-phenyl-1,2-ethanediol (25). R_f (hexane–ethyl acetate v/v 3:7) 0.35; $[\alpha]_D$ −48.2 (*c* 0.5, CH_2Cl_2); IR (film): 1347 cm^{-1} (S=O), 1772 cm^{-1} (C=O), 3338 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.40, 1.41 (2×d, 6H, *J* = 6.8 Hz, isopr.), 2.93 (ddd, 1H, *J* = 15.1, 1.6, 0.8 Hz, H-1′a), 3.12 (ddd, 1H, *J* = 15.1, 3.8, 2.5 Hz, H-1′b), 3.31 (sept, 1H, *J* = 7.0 Hz, isopr.), 4.25 (dd, 1H, *J* = 11.3, 4.1 Hz, H-2a), 4.33 (dd, 1H, *J* = 11.3, 7.9 Hz, H-2b), 4.80 (dd, 1H, *J* = 7.9, 4.1 Hz, H-1), 5.17 (dd, 1H, *J* = 3.8, 1.6 Hz, H-4′), 5.85 (bs, 1H, NH), 7.33–7.44 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$) δ: 16.47, 16.63, 45.99, 52.54, 71.50, 78.30, 79.05, 126.98, 129.06, 129.35, 136.24, 165.76; UV ε (λ_{max}): 8800 (205), 4940 (214^{sh}); CD Δε (λ_{max}): +10.9 (187.0), −7.0 (217.0); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{14}H_{19}NO_5SNa$: 336.0876. Found: 336.0884.

4.3.4. (1*R*,4′*S*) 1-*O*-(Azetidin-2′-on-4′-yl)-2-*O*-(1″,1″-dimethyl-2″-phenyl-ethanesulfonyl)-1-phenyl-1,2-ethanediol (26). R_f (hexane–ethyl acetate v/v 3:7) 0.6; $[\alpha]_D$ −63.1 (*c* 0.6, CH_2Cl_2); IR (film): 1342 cm^{-1} (S=O), 1774 cm^{-1} (C=O), 3340 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.35 (s, 6H, 2×CH_3), 2.91 (ddd, 1H, *J* 1 = 5.1, 1.6, 0.8 Hz, H-3′a), 3.08 (ddd, 1H, *J* = 15.1, 4.0, 2.5 Hz, H-3′b), 3.10 (s, 2H, 1H, CH_2Ph), 4.30 (dd, 1H, *J* = 11.4, 8.0 Hz, H-2a), 4.37 (dd, 1H, *J* = 11.4, 4.2 Hz, H-2b), 4.82 (dd, 1H, *J* = 8.0, 4.2 Hz, H-1), 5.13 (dd, 1H, *J* = 4.0, 1.6 Hz, H-4′), 6.81 (bs, 1H, NH), 7.02–7.56 (m, 10H, 2×aryl); ^{13}C NMR ($CDCl_3$): δ 21.05, 21.09, 41.27, 45.88, 63.59, 72.02, 77.87, 79.37, 126.71, 127.24, 128.28, 128.98, 129.13, 130.96, 134.52, 136.08, 166.20; UV ε (λ_{max}): 18300 (207), 10800 (215^{sh}); CD Δε (λ_{max}):−15.9 (189.4), +5.7 (220.0); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{21}H_{25}NO_5SNa$: 426.1346. Found: 426.1366.

4.3.5. (1*R*,4′*R*) 1-*O*-(Azetidin-2′-on-4′-yl)-2-*O*-(1″,1″-dimethyl-2″-phenyl-ethanesulfonyl)-1-phenyl-1,2-ethanediol (27). R_f (hexane–ethyl acetate v/v 3:7) 0.55; $[\alpha]_D$ −42.1 (*c* 0.4, CH_2Cl_2); IR (film): 1342 cm^{-1} (S=O), 1774 cm^{-1} (C=O), 3343 cm^{-} (NH); ^1H NMR ($CDCl_3$): δ 1.33 (s, 6H, 2×CH_3), 2.95 (ddd, 1H, *J* = 15.1, 1.6, 0.8 Hz, H-4′a), 3.09 (s, 2H, CH_2Ph), 3.13 (ddd, 1H, *J* = 15.1, 3.8, 2.5 Hz, H-4′b), 4.31 (dd, 1H, *J* = 11.3, 4.3 Hz, H-2a), 4.39 (dd, 1H, *J* = 11.3, 7.9 Hz, H-2b), 4.83 (dd, 1H, *J* = 7.9, 4.3 Hz, H-1), 5.20 (dd, 1H, *J* = 3.8, 1.6 Hz, H-4′), 5.82 (bs, 1H, NH), 7.10–7.45 (m, 10H, 2×aryl); ^{13}C NMR ($CDCl_3$): δ 21.08, 21.10, 41.33, 45.99, 63.50, 71.63, 78.31, 79.00, 127.02, 127.23, 128.27, 129.06, 129.34, 130.94, 134.63, 136.40, 165.72; ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{21}H_{25}NO_5SNa$: 426.1346. Found: 426.1367.

4.3.6. (1*S*,4′*R*) and (1*S*,4′*S*) 1-*O*-(Azetidin-2′-on-4′-yl)-2-*O*-(2,4,6-triisopropylbenzenesulfonyl)-1-phenyl-1,2-ethanediol (28 and 29). Yield: 43%; R_f (hexane–ethyl acetate v/v 7:3) 0.2; IR (film): 1776 cm^{-1} (C=O), 3269 cm^{-1} (NH); ^1H NMR ($CDCl_3$) selected signals taken for the mixture of **28** and **29**; **29**: δ 2.85 (ddd, 1H, *J* = 15.1, 1.5, 0.8 Hz, H-3′a), 3.06 (ddd, 1H, *J* = 15.1, 4.0, 2.6 Hz, H-3′b), 4.81 (dd, 1H, *J* = 3.7, 8.4 Hz, H-1), 5.10 (dd, 1H, *J* = 4.0, 1.5 Hz, H-4′), 5.64 (bs, 1H, NH); **28**: 2.82 (ddd, 1H, *J* = 15.1, 1.5, 0.7 Hz, H-3′a), 3.00 (ddd, 1H, *J* = 15.1, 4.0, 2.7 Hz, H-3′b), 4.83 (dd, 1H, *J* = 3.8, 8.1 Hz, H-1), 5.09 (dd, 1H, *J* = 4.0, 1.4 Hz, H-4′), 6.32 (bs, 1H, NH). LSIMSHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{26}H_{35}NO_5SNa$: 453.2133. Found: 496.2121.

4.4. General procedure for clavams formation

To a solution of 4-alkoxyazetidinone **22–29** and **42–49** (0.21 mmol) in acetonitrile (5 mL) were added the tetrabutylammonium bromide (0.07 g, 0.21 mmol) and potassium carbonate (0.31 g, 3.15 mmol). The mixture was heated under reflux for 1 h, cooled, diluted with toluene (5 mL) and filtered. The colorless solution was washed with water (5 mL), dried with magnesium sulfate, filtered and concentrated to dryness. The residue was purified on a silica gel using hexane–ethyl acetate 7:3 (v/v) as an eluent, to give corresponding clavams.

4.4.1. (3*R*,5*R*) 3-Phenyl-clavam (30). Mp 49.5-51.0 °C; R_f (hexane–ethyl acetate v/v 7:1) 0.6; $[\alpha]_D$ +106.4 (*c* 1.9, CH_2Cl_2); IR (film): 1783 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 2.83 (ddd, 1H, *J* = 11.9, 8.2, 0.9 Hz, H-2a), 2.99 (dd, 1H, *J* = 16.5, 0.9 Hz, H-6a), 3.40 (ddd, 1H, *J* = 16.5, 2.9, 0.9 Hz, H-6b), 4.24 (ddd, 1H, *J* = 11.9, 6.2, 0.5 Hz, H-2b), 5.18 (dd, 1H, *J* = 8.2, 6.2 Hz, H-3), 5.57 (d, 1H, *J* = 2.9 Hz, H-5), 7.33–7.41 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 46.03, 53.23, 82.40, 85.12, 125.95, 128.43, 128.74, 138.35, 177.71; UV ε (λ_{max}): 14900 (208^{sh}), 12800 (214^{sh}), 970 (234^{sh}); CD Δε (λ_{max}): −24.0 (197.0), −9.4 (213.5), +20.1 (228.5^{sh}), +23.7 (236.5); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{11}H_{11}NO_2SNa$: 212.0682. Found: 212.0691.

4.4.2. (3*R*,5*S*) 3-Phenyl-clavam (31). R_f (hexane–ethyl acetate v/v 7:6) 0.4; $[\alpha]_D$ −259.8 (*c* 0.7, CH_2Cl_2); IR (film): 1784 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 3.04 (d, 1H, *J* = 16.1 Hz, H-6a), 3.35 (ddd, 1H, *J* = 16.1, 2.6, 0.9 Hz, H-6b), 3.46 (ddd, 1H, *J* = 10.6, 7.1, 0.9 Hz, H-2a), 3.62 (dd, 1H, *J* = 10.6, 7.6 Hz, H-2b), 5.27 (dd, 1H, *J* = 7.1, 7.6 Hz, H-3), 5.32 (dd, 1H, *J* = 2.9, 0.5 Hz, H-5), 7.31–7.40 (m, 5H, aryl); ^{13}C NMR (400 MHz, $CDCl_3$): δ 43.75, 53.82, 84.92, 85.34, 126.08, 128.62, 128.74, 138.31, 177.45; UV ε (λ_{max}): 8800 (209^{sh}), 7300 (215^{sh}), 440 (237^{sh}); CD Δε (λ_{max}): +40.9 (189.0), +8.0 (200.5), −12.5 (224.0), −13.7 (233.0); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{11}H_{11}NO_2SNa$: 212.0682. Found: 212.0688.

4.4.3. (3*S*,5*R*) 3-Phenyl-clavam (32). $[\alpha]_D$ +256,5 (*c* 3.6, CH_2Cl_2); UV ε (λ_{max}): 9760 (208^{sh}), 7900 (215^{sh}), 490 (236^{sh}); CD Δε (λ_{max}): −47.8 (189.0), −11.7 (198.5), +16.4 (220.5), +15.8 (233.0).

4.4.4. (3*S*,5*S*) 3-Phenyl-clavam (33). $[\alpha]_D$ −104.8 (*c* 1.6, CH_2Cl_2); UV ε (λ_{max}): 12100 (208^{sh}), 10300 (215^{sh}), 750 (236^{sh}); CD Δε (λ_{max}): +30.9 (193.5), +8.6 (213.0), −14.5 (225.0^{sh}), −21.4 (236.5). Anal. calcd for $C_{11}H_{11}NO_2S$ taken for the mixture of **32** and **33**: C, 69.83; H, 5.86; N, 7.40. Found: C, 69.32; H, 5.80; N, 7.23.

4.4.5. (1*R*) 1-Phenyl-2-*O*-triphenylmethyl-1,2-ethanediol (34*R*). To a solution of **14*R*** (0.52 g, 3.76 mmol) in a dry CH_2Cl_2 (10 mL) the TrCl (1.15 g, 4.14 mmol) was

added. The reaction was stirred for 3 h, diluted with water and extracted ethyl ether. The combined organic layers were dried with magnesium sulfate, filtered and concentrated to dryness. The residue was purified by a column chromatography on silica gel using hexane–ethyl acetate 9:1 (v/v) as eluent, to give **34*R*** (1.24 g, 87%). Yield: 87%; R_f (hexane–ethyl acetate v/v 7:3) 0.65; $[\alpha]_D$ −10.9 (*c* 0.7, CH_2Cl_2); IR (film): 3445 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 3.28 (dd, 1H, *J* = 9.7, 8.3 Hz, H-2a), 3.35 (dd, 1H, *J* = 9.7, 3.7 Hz, H-2b), 4.76 (dd, 1H, *J* = 8.3, 3.7 Hz, H-1), 7.21–7.33 (m, 14H aryl), 7.39–7.44 (m, 6H, aryl); ^{13}C NMR ($CDCl_3$): δ 69.28, 73.30, 87.07, 126.21, 127.14, 127.72, 127.88, 128.24, 128.63, 140.47, 143.74; ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{27}H_{24}O_2Na$: 403.1669. Found: 403.1692. Anal. calcd for $C_{27}H_{24}O_2$: C, 85.23; H, 6.36. Found: C, 85.30; H, 6.26.

4.4.6. (1*S*) 1-Phenyl-2-*O*-triphenylmethyl-1,2-ethanediol (34*S*). $[\alpha]_D$ +11.5 (*c* 1.4, CH_2Cl_2). Anal. calcd for $C_{27}H_{24}O_2$: C, 85.23; H, 6.36. Found: C, 84.95; H, 6.38.

4.4.7. (1*R*) 1-*O*-Allyl-1-phenyl-2-*O*-triphenylmethyl-1,2-ethanediol (35*R*). To a cold solution (at 0 °C) of **34*R*** (1.20 g, 3.16 mmol) in dry DMF (20 mL) the NaH suspension in mineral oil (60%; 0.15 g, 3.79 mmol) was added. The solution was stirred at 0 °C for 0.5 h and allyl bromide (0.35 g, 3.79 mmol) was added dropwise. Cooling bath was removed and reaction mixture was stirred for 2 h (TLC monitoring) at room temperature. The excess of NaH was decomposed with MeOH (1 mL). The reaction mixture was diluted with sat. aq NaCl (50 mL). The solution was extracted with *t*-butyl-methyl ether (3×). The combined organic extracts were dried with magnesium sulfate, filtered and concentrated to dryness. The residue was purified by a column chromatography on silica gel using hexane–ethyl acetate 5:1 (v/v) as eluent to obtain **35*R*** (1.27 g, 96%); R_f (hexane–ethyl acetate v/v 3:1) 0.75; mp 82–84 °C; $[\alpha]_D$ −11.0 (*c* 1.1, CH_2Cl_2); IR (film): absence of hydroxyl group; ^1H NMR ($CDCl_3$): δ 3.17 (dd, 1H, *J* = 9.6, 5.0 Hz, H-2a), 3.44 (dd, *J* = 6.9, 9.6 Hz, H-2b), 3.90 (m, 1H, Allyl), 4.02 (m, 1H, Allyl), 4.45 (dd, 1H, *J* = 6.9, 5.0 Hz, H-1), 5.16 (dm, 1H, Allyl), 5.29 (dm, 1H, Allyl), 5.92 (dddd, 1H, Allyl), 7.11–7.49 (m, 20H, Ph + Tr); ^{13}C NMR ($CDCl_3$): δ 68.47, 69.91, 80.63, 86.68, 116.52, 126.84, 127.16, 127.69, 128.20, 128.74, 134.98, 140.04, 144.05; ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{30}H_{28}O_2Na$: 443.1982. Found: 443.2003. Anal. calcd for $C_{30}H_{28}O_2$: C, 85.68; H, 6.71. Found: C, 85.72; H, 6.75.

4.4.8. (1*S*) 1-*O*-Allyl-1-phenyl-2-*O*-triphenylmethyl-1,2-ethanediol (35*S*). $[\alpha]_D$ +11.3 (c 0.7, CH_2Cl_2). Anal. calcd for $C_{30}H_{28}O_2$: C, 85.68; H, 6.71. Found: C, 85.68; H, 6.61.

4.4.9. (1*R*) 1-*O*-Allyl-1-phenyl-1,2-ethanediol (36*R*). Compound **35*R*** (1.22 g, 2.90 mmol) was dissolved in a methanolic solution of *p*-TsOH (5%; 60 mL). The reaction was complete after 1 h (TLC monitoring). The reaction mixture was concentrated, diluted with water (50 mL) and extracted with *t*-butyl-methyl ether (3×). The combined organic extracts were dried with magnesium sulfate, filtered and concentrated. The residue was purified by a column chromatography on silica gel using hexane–ethyl acetate 7:3 (v/v) as eluent, to give **36*R*** (0.496 g, 96%); R_f (hexane–ethyl acetate v/v 3:1) 0.35; $[\alpha]_D$ −102.5 (*c* 1.3, CH_2Cl_2); IR (film): 3436 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 3.63 (dd, 1H, *J* = 11.7, 3.7 Hz, H-2a), 3.71 (dd, 1H, *J* = 11.7, 8.5 Hz, H-2b), 3.86 (m, 1H, Allyl), 4.04 (m, 1H, Allyl), 4.45 (dd, 1H, *J* = 6.9, 5.0 Hz, H-1), 5.16 (dm, 1H, Allyl), 5.29 (m, 1H, Allyl), 5.92 (dddd, 1H, *J* = 17.2, 10.4, 6.2, 5.3 Hz, Allyl),7.28–7.40 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 67.34, 69.75, 82.13, 117.19, 126.86, 128.12, 128.52, 134.46, 138.46; ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{11}H_{14}O_2Na$: 201.0910. Found: 201.0897. Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.91; H, 7.83.

4.4.10. (1*S*) 1-*O*-Allyl-1-phenyl-1,2-ethanediol (36*S*). $[\alpha]_D$ +95.5 (*c* 1.3, CH_2Cl_2). Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.62; H, 8.06.

4.4.11. (1*R*) 1-Phenyl-1-*O*-(*Z*-prop-1′-en-1′-yl)-1,2-ethanediol (37*R*). A solution of allyl ether **36*R*** (0.44 g, 2.47 mmol) and freshly sublimed *t*-BuOK (0.69 g, 6.18 mmol) in DMSO (30 mL), was stirred at 55 °C for 1.5 h. The reaction mixture was diluted with a satd aq NaCl (30 mL). The solution was extracted with *t*-butyl-methyl ether (3×). The combined organic extracts were dried with magnesium sulfate, filtered and concentrated to dryness. The residue was purified by a column chromatography on silica gel using hexane–ethyl acetate 17:3 (v/v) as eluent, to give **37*R*** (0.392 g, 89%); R_f (hexane–ethyl acetate v/v 3:1) 0.40; mp 65–66.5 °C; $[\alpha]_D$ +92.1 (*c* 0.7, CH_2Cl_2); IR (film): 1665 cm^{-1} (C=C), 3239 cm^{-1} (OH); ^1H NMR ($CDCl_3$): δ 1.67 (dd, 1H, *J* = 8.0, 4.0 Hz, H-1), 3.76 (m, 2H, H-2), 4.46 (dq, 1H, *J* = 6.2, 6.8 Hz, H-2′), 4.75 (dd, 1H, *J* = 6.8, 1.7 Hz, CH_3), 5.95 (dq, 1H, *J* = 6.2, 1.7 Hz, H-1′), 7.28–7.43 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 9.40, 67.19, 84.11, 102.63, 126.54, 128.23, 128.54, 138.12, 144.16; ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{11}H_{14}O_2Na$: 201.0886. Found: 201.0894. Anal. calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 74.11; H, 7.91.

4.4.12. (1*S*) 1-Phenyl-1-*O*-(*Z*-prop-1′-en-1′-yl)-1,2-ethanediol (37*S*). $[\alpha]_D$ −81.3 (*c* 0.8, CH_2Cl_2).

4.4.13. (1*S*) 2-*O*-Methanesulfonyl-1-*O*-(*Z*-prop-1′-en-1′-yl)-1-phenyl-1,2-ethanediol (38*S*). Yield: 96%; R_f (hexane–ethyl acetate v/v 3:1) 0.4; $[\alpha]_D$ −15.5 (*c* 0.9, CH_2Cl_2); IR (film): 1350 cm^{-1} (S=O), 1668 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 1.65 (dd, 3H, *J* = 6.9, 1.8 Hz, CH_3), 3.01 (s, 3H, Ms), 4.34 (dd, 1H, *J* = 11.3, 3.7 Hz, H-2a), 4.45 (dd, 1H, *J* = 11.3, 8.0 Hz, H-2), 4.48 (dq, 1H, *J* = 6.2, 6.9 Hz, H-2′), 4.92 (dd, 1H, *J* = 8.0, 3.7 Hz, H-1), 5.93 (dq, 1H, *J* = 6.2, 1.9 Hz, H-1′), 7.28–7.46 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 9.40, 37.70, 72.37, 80.82, 103.21, 126.67, 128.90, 128.92, 136.39, 143.69; ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{12}H_{16}O_4SNa$: 279.0662. Found: 279.0654. Anal. calcd for $C_{12}H_{16}O_4S$: C, 56.23; H, 6.29; S 12.51. Found: C, 56.35; H, 6.18; S 12.39.

4.4.14. (1*R*) 2-*O*-Isopropanesulfonyl-1-phenyl-1-*O*-(Z-prop-1′-en-1′-yl)-1,2-ethanediol (39*R*). Yield: 94%; R_f

(hexane–ethyl acetate v/v 3:1) 0.5; $[\alpha]_D$ +12.2 (*c* 0.9, CH_2Cl_2); IR (film): 1670 cm^{-1} (C=C); ^1H NMR ($CDCl_3$): δ 1.41, 1.42 (2×d, 3H, *J* = 6.8 Hz, isopr.), 1.65 (dd, 3H, *J* = 6.9, 1.8 Hz, CH_3), 3.33 (sept, 1H, *J* = 6.8 Hz, isopr.), 4.32 (dd, 1H, *J* = 11.1, 3.7 Hz, H-2a), 4.39 (dd, 1H, *J* = 11.1, 8.0 Hz, H-2b), 4.46 (dq, 1H, *J* = 6.2, 6.9 Hz, H-2′), 4.92 (dd, 1H, *J* = 8.0, 3.7 Hz, H-1), 3.93 (dq, 1H, *J* = 6.2, 1.8 Hz, H-1′), 7.31–7.41 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 9.34, 16.45, 16.59, 52.44, 71.63, 80.89, 102.91, 126.66, 128.75, 128.78, 136.59, 143.77; ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{14}H_{20}O_4SNa$: 307.0975. Found: 307.0992. Anal. calcd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09; S, 11.28. Found: C, 59.25; H, 6.99; S, 11.06.

4.4.15. (1*S*) 1-Phenyl-1-*O*-(*Z*-prop-1′-en-1′-yl)-2-*O*-(2,4,6-triisopropyl-benzenesulfonyl)-1,2-ethanediol (41*S*). Yield: 86%; R_f (hexane–ethyl acetate v/v 3:1) 0.35; mp 57.5–58.5 °C; $[\alpha]_D$ −11.5 (*c* 1.1, CH_2Cl_2); IR (film): 1671 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.25 (d, 6H, *J* = 6.8 Hz, TIBS), 1.27 (d, 12H, *J* = 7.0 Hz, TIBS), 1.59 (dd, 3H, *J* = 6.8, 1.7 Hz, CH_3), 2.92 (sept, 1H, *J* = .8 Hz, TIBS), 4.16 (sept, 2H, *J* = 7.0 Hz, TIBS), 4.21 (dd, 1H, *J* = 11.9, 5.5 Hz, H-2a), 4.23 (dd, 1H, *J* = 11.9, 6.4 Hz, 2a), 4.41 (dq, 1H, *J* = 6.2, 6.8 Hz, H-2′), 4.92 (dd, 1H, *J* = 6.4, 5.5 Hz, H-1), 5.85 (dq, 1H, *J* = 6.2, 1.7 Hz, H-1′), 7.23-7.45 (m, 7H, aryl); ^{13}C NMR ($CDCl_3$): δ 9.33, 23.51, 24.65, 24.69, 29.63, 34.22, 71.50, 80.82, 102.87, 123.73, 126.63, 128.68, 129.48, 136.95, 143.76, 150.79, 153.70; ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{26}H_{36}O_4SNa$: 467.2227. Found: 467.2241. Anal. calcd for $C_{26}H_{36}O_4S$: C, 70.23; H, 8.16; N, 7.21. Found: C, 70.16; H, 8.05; N, 7.10.

4.4.16. (1*R*) 2-*O*-(1″,1″-Dimethyl-2″-phenyl-ethanesulfonyl)-1-phenyl-1-*O*-(*Z*-prop-1′-en-1′-yl)-1,2-ethanediol (40*R*). Yield: 58%; R_f (hexane–ethyl acetate v/v 3:1) 0.65; $[\alpha]_D$ −4.1 (*c* 0.8, CH_2Cl_2); IR (film): 1345 cm^{-1} (S=O), 1669 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.33 (s, 6H, 2×CH_3), 1.66 (dd, 3H, *J* = 6.8, 1.7 Hz, CH_3), 3.11 (s, 2H, CH_2Ph), 4.41 (m, 2H, H-2a, 2b), 4.51 (dq, 1H, *J* = 6.2, 6.8 Hz, H-1′), 4.95 (dd, 1H, *J* = 6.5, 5.2 Hz, H-1), 5.96 (dq, 1H, *J* = 6.2, 1.7 Hz, H-2′), 7.11–7.21 (m, 2H, aryl), 7.27–7.43 (m, 8H, aryl); ^{13}C NMR ($CDCl_3$): δ 9.40, 20.93, 20.95, 41.18, 63.38, 71.40, 80.91, 102.87, 126.71, 127.11, 128.19, 128.73, 128.77, 130.98, 134.84, 136.73, 143.92; ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{21}H_{26}O_4SNa$: 397.1444. Found: 397.1462. Anal. calcd for $C_{21}H_{26}O_4S$: C, 67.39; H, 7.00; S 8.56. Found: C, 67.37; H, 7.21; S 8.63.

4.4.17. (1*R*,3′*S*,4′*R*) 2-*O*-Isopropanesulfonyl-1-*O*-(3′-methyl-azetidin-2′-on-4′-yl)-1-phenyl-1,2-ethanediol (42). R_f (hexane–ethyl acetate v/v 1:1) 0.30; mp 79.1–81 °C; $[\alpha]_D$ −42.9 (*c* 0.5, CH_2Cl_2); IR (film): 1348 cm^{-1} (S=O), 1770 cm^{-1} (C=O), 3339 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.33 (d, 3H, *J* = 7.5 Hz, CH_3), 1.39, 1.40 (2×d, 6H, *J* = 6.8 Hz, isopr.), 3.28 (sept, 1H, *J* = 6.8 Hz, isopr.), 3.33 (ddq, 1H, *J* = 3.7, 2.1, 7.5 Hz, H-3′), 4.25 (dd, 1H, *J* = 11.2, 4.1 Hz, H-2a), 4.35 (dd, 1H, *J* = 11.2, 8.0 Hz, H-2b), 4.76 (dd, 1H, *J* = 8.0, 4.1 Hz, H-1), 5.10 (d, 1H, *J* = 3.7 Hz, H-4′), 5.78 (bs, 1H, NH), 7.30–7.49 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 8.62, 16.53, 16.62, 51.13, 52.49, 71.39, 80.28, 80.93, 126.99, 128.97, 129.28, 136.37, 170.41; UV ε (λ_{max}): 4850 (207^{sh}), 2800 (215^{sh}); CD Δε (λ_{max}): +13.0 (189.8), −5.7 (217.8); MS (ESI), *m*/*z*; $(M+Na)^+$ calcd for $C_{15}H_{21}NO_5SNa$: 350.1033. Found: 350.1. Anal. calcd for $C_{15}H_{21}NO_5S$: C, 55.03; H, 6.47; N, 4.28; S, 9.79. Found: C, 54.97; H, 6.37; N, 4.18; S, 9.61.

4.4.18. (1*R*,3′*R*,4′*S*) 2-*O*-Isopropanesulfonyl-1-*O*-(3′-methyl-azetidin-2′-on-4′-yl)-1-phenyl-1,2-ethanediol (43). R_f (hexane–ethyl acetate v/v 1:1) 0.35; $[\alpha]_D$ −78.5 (*c* 0.5, CH_2Cl_2); IR (film): 1347 cm^{-1} (S=O), 1771 cm^{-1} (C=O), 3341 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.26 (d, 3H, *J* = 7.7 Hz, CH_3), 1.41, 1.42 (2×d, 6H, *J* = 6.8 Hz, isopr.), 3.28 (ddq, 1H, *J* = 2.2, 4.4, 7.7 Hz, H-3′), 3.33 (sept, 1H, *J* = 6.8 Hz, isopr), 4.28 (dd, 1H, *J* = 11.4, 7.5 Hz, H-2a), 4.32 (dd, 1H, *J* = 11.4, 4.4 Hz, H-2b), 4.82 (dd, 1H, *J* = 7.5, 4.4 Hz, H-3′), 4.98 (d, 1H, *J* = 4.4 Hz, H-4′), 6.78 (bs, 1H, NH), 7.28–7.46 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 8.67, 16.54, 16.61, 50.39, 52.72, 72.11, 79.47, 80.19, 126.65, 128.84, 128.97, 136.00, 171.10; UV ε (λ_{max}): 4500 (207^{sh}), 2400 (216^{sh}); CD Δε (λ_{max}): −11.0 (190.2), +5.3 (220.0); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{15}H_{21}NO_5SNa$: 350.1033. Found: 350.1050. Anal. calcd for $C_{15}H_{21}NO_5S$: C, 55.03; H, 6.47; N, 4.28; S, 9.79. Found: C, 54.93; H, 6.47; N, 4.20; S, 9.87.

4.4.19. (1*R*,3′*S*,4′*R*) 2-*O*-(1″,1″-Dimethyl-2″-phenyl-ethanesulfonyl)-1-*O*-(3′-methyl-azetidin-2′-on-4′-yl)-1-phenyl-1,2-ethanediol (44). R_f (hexane–ethyl acetate v/v 1:1) 0.3; $[\alpha]_D$ −22.6 (*c* 0.7, CH_2Cl_2); IR (film): 1343 cm^{-1} (S=O), 1771 cm^{-1} (C=O), 3340 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.32 (s, 6H, 2×CH_3), 1.35 (d, 3H, *J* = 7.5, Hz, CH_3), 3.08 (s, 2H, CH_2Ph), 3.35 (ddq, 1H, *J* = 4.2, 2.0, 7.5 Hz, H-3′), 4.32 (dd, 1H, *J* = 11.1, 4.3 Hz, H-2a), 4.42 (dd, 1H, *J* = 11.1, 7.9 Hz, H-2b), 4.78 (dd, 1H, *J* = 7.9, 4.3 Hz, H-1), 5.11 (d, 1H, *J* = 4.2 Hz, H-4′), 5.75 (bs, 1H, NH), 7.10–7.19 (m, 2H, aryl), 7.27–7.44 (m, 8H, aryl); ^{13}C NMR ($CDCl_3$): δ 8.63, 21.03, 41.26, 51.14, 63.39, 71.41, 80.44, 80.98, 127.11, 127.21, 128.26, 129.03, 129.35, 130.92, 134.60, 136.55, 170.46; UV ε (λ_{max}): 17300 (207), 9000 (216^{sh}); CD Δε (λ_{max}): +10.0 (189.5), −3.5 (220.5); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{22}H_{27}NO_5SNa$: 440.1502. Found: 440.1510.

4.4.20. (1*R*,3′*R*,4′*S*) 2-*O*-(1″,1″-Dimethyl-2″-phenyl-ethanesulfonyl)-1-*O*-(3′-methyl-azetidin-2′-on-4′-yl)-1-phenyl-1,2-ethanediol (45). R_f (hexane–ethyl acetate v/v 1:1) 0.35; $[\alpha]_D$ −40.9 (*c* 0.6, CH_2Cl_2); IR (film): 1331 cm^{-1} (S=O), 1771 cm^{-1} (C=O), 3336 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.29 (d, 3H, *J* = 7.5 Hz, CH_3), 1.35 (s, 6H, 2×CH_3), 3.10 (s, 2H, CH_2Ph), 3.31 (ddq, 1H, *J* = 4.3, 2.0, 7.5 Hz, H-3′), 4.30 (dd, 1H, *J* = 11.3, 7.9 Hz, H-2a), 4.38 (dd, 1H, *J* = 11.3, 4.1 Hz, H-2b), 4.82 (dd, 1H, *J* = 7.9, 4.1 Hz, H-1), 5.19 (d, 1H, *J* = 4.3 Hz, H-4′), 6.64 (bs, 1H, NH), 7.11-7.22 (m, 2H, aryl), 7.27-7.46 (m, 8H, aryl); ^{13}C NMR ($CDCl_3$): δ 10.99, 21.07, 21.10, 41.30, 53.59, 63.58, 71.87, 79.38, 84.93, 126.79, 127.23, 128.28, 129.00, 129.17, 130.95, 134.58, 136.30, 169.71; UV ε (λ_{max}): 19400 (207), 11200 (215^{sh}); CD Δε (λ_{max}): −11.6 (192.5), +3.6 (220.5); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{22}H_{27}NO_5SNa$: 440.1502. Found: 440.1525.

4.4.21. (1*S*,3′*S*,4′*R*) 2-*O*-Methanesulfonyl-1-*O*-(3′-methyl-azetidin-2′-on-4′-yl)-1-phenyl-1,2-ethanediol (46). R_f (hexane–ethyl acetate v/v 3:7) 0.25; $[\alpha]_D$ +71.1 (*c* 0.6, CH_2Cl_2); IR (film): 1353 cm^{-1} (S=O), 1769 cm^{-1} (C=O), 3354 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.26 (d, 1H, *J* = 7.6 Hz, CH_3), 3.03 (s, 3H, Ms), 3.27 (ddq, 1H, *J* = 4.4, 2.2, 7.6 Hz, H-3′), 4.32 (d, 2H, H-2a,2b), 4.80 (t, 1H, H-1), 5.03 (d, 1H, *J* = 4.4 Hz, H-4′), 6.87 (bs, 1H, NH), 7.30–7.44 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 8.65, 37.87, 50.44, 72.46, 79.10, 80.08, 126.79, 126.99, 129.15, 135.94, 171.31; UV ε (λ_{max}): 8800 (206), 4900 (215^{sh}); CD Δε (λ_{max}): +13.5 (186.4), −5.4 (220.2); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{13}H_{17}NO_5SNa$: 322.0720. Found: 322.0739.

4.4.22. (1*S*,3′*R*,4′*S*) 2-*O*-Methanesulfonyl-1-*O*-(3′-methyl-azetidin-2′-on-4′-yl)-1-phenyl-1,2-ethanediol (47). R_f (hexane–ethyl acetate v/v 3:7) 0.20; $[\alpha]_D$ +49.6 (*c* 0.8, CH_2Cl_2); IR (film): 1353 cm^{-1} (S=O), 1769 cm^{-1} (C=O), 3354 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.39 (d, 1H, *J* = 7.4 Hz, CH_3), 3.00 (s, 3H, Ms), 3.36 (ddq, 1H, *J* = 4.3, 2.2, 7.4 Hz, H-3′), 4.26 (dd, 1H, *J* = 11.1, 3.8 Hz, H-2a), 4.38 (dd, 1H, *J* = 11.1, 8.1 Hz, H-2b), 4.75 (dd, 1H, *J* = 8.1, 3.8 Hz, H-1), 5.10 (d, *J* = 4.3 Hz, H-4′), 5.68 (bs, 1H, NH), 7.35–7.49 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 8.59, 37.59, 51.20, 71.82, 80.07, 80.95, 127.06, 129.12, 129.48, 136.27, 170.30; UV ε (λ_{max}): 8900 (205), 5000 (214^{sh}); CD Δε (λ_{max}): −9.4 (189.0), +5.3 (219.2); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{13}H_{17}NO_5SNa$: 322.0720. Found: 322.0704.

4.4.23. (1*S*,3′*S*,4′*R*) 1-*O*-(3′-Methyl-azetidin-2′-on-4′-yl)-1-phenyl-2-*O*-(2,4,6-triisopropylbenzenesulfonyl)-1,2-ethanediol (48). R_f (hexane–ethyl acetate v/v 1:1) 0.50; mp 104–107 °C; $[\alpha]_D$ +46.1 (*c* 0.5, CH_2Cl_2); IR (film): 1347 cm^{-1} (S=O), 1774 cm^{-1} (C=O), 3271 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.23 (d, 3H, *J* = 7.7 Hz, CH_3), 1.26 (d, 18H, *J* = 6.8 Hz, TIBS), 2.91 (sept, 1H, *J* = 6.8 Hz, TIBS), 3.26 (ddq, 1H, *J* = 4.4, 2.2, 7.7 Hz, H-3′), 4.12 (sept, 2H, *J* = 6.8 Hz, TIBS), 4.14 (dd, 1H, *J* = 11.4, 8.1 Hz, H-2a), 4.20 (dd, 1H, *J* = 11.4, 3.8 Hz, H-2b), 4.88 (dd, 1H, *J* = 8.1, 3.8 Hz, H-1), 5.11 (d, 1H, *J* = 4.4 Hz, H-4′), 6.40 (bs, 1H, NH), 7.19 (s, 2H, aryl TIBS), 7.27–7.44 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 8.61, 23.49, 24.70, 29.72, 34.24, 50.52, 72.31, 79.98, 80.88, 123.90, 126.59, 126.91, 128.88, 129.29, 136.49, 150.77, 154.09, 170.74; UV ε (λ_{max}): 59750 (204), 11100 (230^{sh}); CD Δε (λ_{max}): +6.4 (191.8), −4.5 (219.6); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{27}H_{37}NO_5SNa$: 510.2285. Found: 510.2276.

4.4.24. (1*S*,3′*R*,4′*S*) 1-*O*-(3′-Methyl-azetidin-2′-on-4′-yl)-1-phenyl-2-*O*-(2,4,6-triisopropylbenzenesulfonyl)-1,2-ethanediol (49). R_f (hexane–ethyl acetate v/v 1:1) 0.45; mp 119–121 °C; $[\alpha]_D$ +31.5 (*c* 0.7, CH_2Cl_2); IR (film): 1347 cm^{-1} (S=O), 1774 cm^{-1} (C=O), 3257 cm^{-1} (NH); ^1H NMR ($CDCl_3$): δ 1.22, 1.24, 1.25 (3×d, 18H, *J* = 6.8 Hz, TIBS), 1.29 (d, 3H, *J* = 6.7 Hz, CH_3), 2.90 (sept, 1H, *J* = 6.8 Hz, TIBS), 3.32 (ddq, 1H, *J* = 4.3, 2.2, 7.6 Hz, H-3′), 4.09 (dd, 1H, *J* = 11.1, 3.8 Hz, H-2a), 4.11 (sept, 1H, *J* = 6.8 Hz, TIBS), 4.20 (dd, 1H, *J* = 11.1, 8.1 Hz, H-2a), 4.79 (dd, 1H, *J* = 8.1, 3.8 Hz, H-1), 5.09 (d, 1H, *J* = 4.3 Hz, H-4′), 5.68 (bs, 1H, NH), 7.17 (s, 2H, aryl TIBS), 7.28–7.40 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 8.49, 23.50, 24.71, 24.69, 34.22, 51.17, 71.58, 80.26, 81.00, 123.82, 126.97, 128.98, 129.21, 136.76, 150.73, 153.91, 170.50; UV ε (λ_{max}): 64,040 (204), 11,900 (230^{sh}); CD Δε (λ_{max}): −19.9 (188.6), +7.0 (216.2); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{27}H_{37}NO_5SNa$: 510.2285. Found: 510.2306.

4.4.25. (3*R*,5*R*,6*S*) 6-Methyl-3-phenyl-clavam (50). Yield: 62%; R_f (hexane–ethyl acetate v/v 3:7) 0.35; $[\alpha]_D$ +58.9 (*c* 0.9 CH_2Cl_2); IR (film): 1771 cm^{-1} (C=O); ^1H NMR ($CDCl_3$): δ 1.23 (d, 3H, *J* = 7.7 Hz, CH_3), 2.76 (ddd, 1H, *J* = 12.0, 8.7, 0.5 Hz, H-2), 3.51 (dq, 1H, *J* = 3.3, 7.7 Hz, 1 Hz, H-6), 4.19 (ddd, 1H, *J* = 12.0, 6.0, 0.5 Hz, H-2′), 5.03 (dd, 1H, *J* = 8.4, 6.0 Hz, H-3), 5.56 (bd, 1H, *J* = 3.3 Hz, H-5), 7.27–7.44 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 7.82, 49.69, 52.48, 83.13, 88.11, 125.99, 128.44, 128.72, 138.30, 182.53; UV ε (λ_{max}): 11,600 (208^{sh}), 10,300 (215^{sh}), 760 (238^{sh}); CD Δε (λ_{max}): −27.8 (193.2), −9.6 (214.0), +10.4 (226.0^{sh}), +18.7 (240.2); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{12}H_{13}NO_2Na$: 226.0839. Found: 226.0849.

4.4.26. (3*R*,5*S*,6*R*) 6-Methyl-3-phenyl-clavam (51). Yield: 59%; R_f (hexane–ethyl acetate v/v 3:7) 0.25; $[\alpha]_D$ −236.2 (c 0.9, CH_2Cl_2); IR (film): 1779 cm^{-1} (C=O); ^1H NMR (C_6D_6): δ 1.12 (d, 3H, *J* = 7.6 Hz, CH_3), 2.84 (ddd, 1H, *J* = 10.5, 7.3, 0.7 Hz, H-2′), 3.90 (ddq, 1H, *J* = 3.1, 0.7, 7.6 Hz, 1 Hz, H-6), 3.42 (dd, 1H, *J* = 10.4, 8.0 Hz, H-2), 4.64 (bt, 1H, H-3), 4.68 (d, 1H, *J* = 3.1 Hz, H-5), 7.02–7.14 (m, 5H, aryl); ^{13}C NMR ($CDCl_3$): δ 7.80, 47.77, 53.19, 84.93, 87.46, 126.25, 128.66, 128.79, 138.26, 182.39; UV ε (λ_{max}): 9500 (208^{sh}), 8040 (220^{sh}), 490 (236^{sh}); CD Δε (λ_{max}): +44.5 (189.4), +7.4 (201.0), −11.2 (222.8), −14.6 (236.0); ESIHRMS, *m*/*z*; $(M+Na)^+$ calcd for $C_{12}H_{13}NO_2Na$: 226.0839. Found: 226.0848.

4.4.27. (3*S*,5*R*,6*S*) 6-Methyl-3-phenyl-clavam (52). $[\alpha]_D$ +244,3 (c 0.8, CH_2Cl_2). UV ε (λ_{max}): 9200 (209^{sh}), 7700 (215^{sh}), 450 (237^{sh}); CD Δε (λ_{max}): −43.9 (189.5), −6.8 (201.5), +13.8 (219.5), +14.9 (236.0). Anal. calcd $C_{12}H_{13}NO_2S$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.53; H, 6.56; N, 6.75.

4.4.28. (3*S*,5*S*,6*R*) 6-Methyl-3-phenyl-clavam (53). Yield: 59%; $[\alpha]_D$ −58.3 (*c* 0.7, CH_2Cl_2); UV ε (λ_{max}): 14500 (209^{sh}), 11,600 (215^{sh}), 880 (238^{sh}); CD Δε (λ_{max}): +28.7 (193.0), +10.6 (213.0), −11.0 (226.4^{sh}), −19.9 (240.2). Anal. calcd for $C_{12}H_{13}NO_2S$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.85; H, 6.50; N, 6.85.

4.5. Assay of DD-carboxypeptidase activity

The enzyme activity was measured as described previously.[27,28] Samples for assay of the DD-carboxypeptidase activity consisted of 10 μL of DD-carboxypeptidase from *Saccharopolyspora erythraea* PZH TZ 64-575 (40 units/mg), 20 μL of substrate solution containing 4.52 mg/mL Nα, Nε-diacetyl-L-lysyl-D-alanyl-D-alanine in 0.1 M phosphate buffer, pH 8.0 and 10 μL of 0.1 M phosphate buffer, pH 8.0. Standard sample contained 20 μL of D-alanine in distilled water.

Reaction mixture for assay of the DD-carboxypeptidase activity consisted of 60 μL of 0.05 mg/mL flavin adenine dinucleotide in 0.1 M phosphate buffer, pH 8.0, 10 μL of 0.05 mg/mL horseradish peroxidase (1230 units/mg) in distilled water, 5 μL of 5 mg/mL *o*-dianisidine in methanol, and 2 μL of 11.77 mg/mL D-amino acid oxidase from porcine kidney (6.7 units/mg) in 0.1 M phosphate buffer, pH 8.0.

Samples were incubated for 30 min at 37 °C and then boiled for 2 min. After cooling, 77 μL of the reaction mixture was added, and all samples were incubated for 10 min at 37 °C. Next, to each sample was added 350 μL of mixture consisting of methanol, distilled water and sulfuric acid (5:5:6 by volume). Absorption of resulted solution was measured at 540 nm.

The inhibition of DD-peptidase 640-575 by the discussed above clavams was evaluated.[31] Mixtures of 10 μL of DD-peptidase 64-575 (40 units/mg), 5 μL solution of a clavam in methanol and 5 μL of 0.1 M phosphate buffer, pH 8.0 were incubated for 45 min. at 37 °C. The concentration of a clavam in the mixture was from 0.1 to 0.000055 M. Following the incubation, 20 μL of substrate solution was added to 20 μL of each sample and resulted mixtures were incubated again. The inhibition of DD-peptidase is given as ID_{50} (M).

The inhibition of penicillinase was evaluated following literature method.[29] The samples for the assay of inhibition of β-lactamase consisted of 10 mm^3 of penicillinase (Penase, $5{\cdot}10^6$ IU/mL, Bacto), 20 mm^3 0.1 M phosphate buffer, pH 7.0, 10 mm^3 solution of clavams in methanol. The samples were incubated for 30 min at 37 °C, then 30 mm^3 of nitrocephin, 430 mm^3 0.1 M phosphate buffer pH 7.0 were added and all the samples were incubated for 10 min at 37 °C. Absorption was measured at 482 nm. The inhibition of β-lactamase is expressed as IC_{50} (M).

The following clavams were tested for both activities: **30**–**33** and **50**–**53** (Table 2).

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