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TETRAHEDRON: *ASYMMETRY*

[2+2] Cycloaddition of chlorosulfonyl isocyanate to allenyl-sugar ethers

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Abstract

The direction and magnitude of asymmetric induction in the [2+2] cycloaddition of chlorosulfonyl isocyanate to 3-*O*-allenyl-α-D-xylofuranoses was investigated. It is shown that *gem* terminal dimethylallenes react more readily than methyl free congeners. The configuration of adducts was established by X-ray and CD-spectroscopy of alkylidene cephams. A stereochemical model of the transition state for the [2+2] cycloaddition of chlorosulfonyl isocyanate and allenyl ethers is proposed, based on the lowest energy conformation of the cumulene.

1. Introduction

β-Lactam antibiotics with an *exo*-methylene double bond, such as asparenomycins A, B, C **1**–**3**, 6643-X **4**,[1] Ro 15-1903 **5**,[2] 6-(*Z*)-methoxymethylene-penicillanic acid **6**,[3] and 7-alkylidene-cephalosporins **7**[4] display high activities as β-lactamase inhibitors (Fig. 1).

In 1985 Buynak et al.[5] reported on the synthesis of (±)-asparenomycin C via 3-isopropylidene-4-acetoxy-azetidin-2-one **9** which in turn has been obtained by [2+2] cycloaddition of chlorosulfonyl isocyanate (CSI) to acetoxyallene **8** (Scheme 1).[6] Other allenes have also been shown to react with CSI to form β-lactams with an *exo* double bond next to the carbonyl group.[7,8]

Recently, we have initiated a synthetic project aimed at transforming sugar-derived chiral vinyl ethers into 5-dethia-5-oxacephams and clavams.[9,10] The crucial step of the synthesis involved the [2+2] cycloaddition of vinyl ethers and CSI, which has been shown to display an excellent diastereoselectivity in many cases.[9,10] It was of interest to examine alkoxyallenes in these reactions and to demonstrate that the [2+2] cycloaddition strategy offers an entry to 5-oxacephams and clavams featuring an *exo* double bond.

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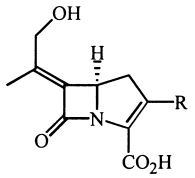
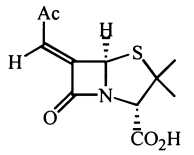
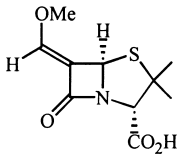


Asparenomycin A; R = SOCH=CHNHAc: **1**
Asparenomycin B; R = $SOCH_2CH_2NHAc$: **2**
Asparenomycin C; R = SCH=CHNHAc: **3**
6643-X ; R = SCH_2CH_2NHAc: **4**



Ro 15-1903: **5**



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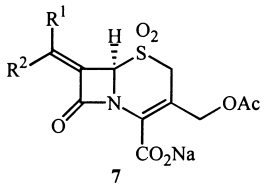

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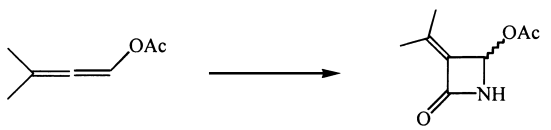
R^1, R^2 = H, Halogen, Aryl, CO_2t-Bu, CHO, $COCH_3$, *t*-Bu

Figure 1.



8 **9**

Scheme 1.

The search for new β-lactam antibiotics has shown that the carbon atom next to the carbonyl group can be substituted by a variety of groups while keeping the desired biological activity.[11] Introduction of the *exo*-alkylidene fragment to the β-lactam ring provides an easy access to other antibiotics via synthetic transformations of the double bond.

2. Results and discussion

For the present studies we selected five allenes **10**–**14**. Compound **10** was obtained from **16** by the standard method,[12,13] whereas **12** was obtained from **17** via a but-2-yne ether stage **19**. The synthesis of *gem* dimethyl-substituted allenes **11**, **13** and **14** has been reported recently.[13] An attempt to isomerize the propargyl ether **15** led to the formation of a bicyclic compound **18** (Fig. 2).

[2+2] Cycloaddition of CSI/Na_2CO_3[14] to **10** in toluene at –60°C, followed by the reduction of the *N*-chlorosulfonyl group with Red-Al,[15] gave β-lactam **20** as a 1:1 mixture of two diastereomers in ca. 6% yield only. The post-reaction mixture contained substantial amounts of unreacted allene **10**. All attempts to increase the yield of the reaction by raising the temperature, changing the solvent, etc. were unsuccessful; we only observed a decomposition of the substrate **10**.

[2+2] Cycloaddition of CSI to **11** under standard conditions afforded a mixture of β-lactams **21** and **22** in a ratio 2.3:1 (de = 39%), respectively, in 65% yield. An acid catalyzed detritylation of

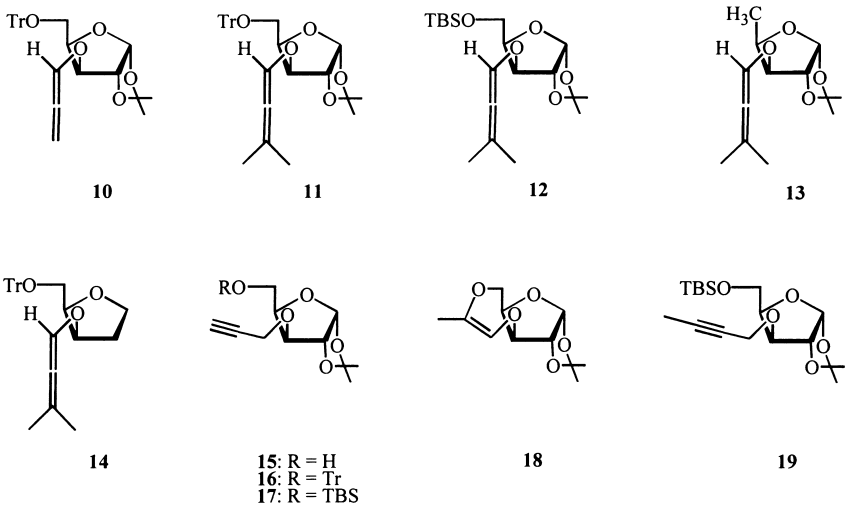


Figure 2.

21/**22** gave a mixture **23**/**24**, which was subjected to tosylation of terminal hydroxymethyl groups followed by intramolecular *N*-alkylation to afford a mixture of cephams **27** and **28**[†] which were separated into the pure components.

The absolute configuration of the stereogenic center at C-4′ in **27** and **28** was proved by NOE experiments. In the case of diastereomer **28** an irradiation of the signal H-4′ (δ 5.17) showed the enhancement of H-3 (δ 4.14) by 6.6%. Conversely, the signal due to H-4′ was enhanced by 3.7% when H-3 was irradiated. Cepham **27** did not demonstrate any spin–spin interaction between H-3 (δ 4.16) and H-4′ (δ 5.41). X-Ray structure analyses of compound **28** (Table 3, Fig. 9) and diacetate **31** (Table 3, Fig. 10) obtained from a mixture of compounds **23**/**24**, unequivocally proved the configuration at C-4′ to be (*S*) in the former and (*R*) in the latter. Thus, the configuration of related compounds **21**–**27** was also established.

[2+2] Cycloaddition of CSI to **12** offers higher stereoselectivity (de = 55%) in the formation of (4′*R*) stereoisomer **29** than the corresponding cycloaddition to **11** (Fig. 3).

Diminution of the size of the terminal sugar substituent by transforming a trityloxymethyl into a methyl group **13** leads to the decrease in the face-differentiation of the double bond in the cycloaddition. Under the standard reaction conditions the mixture of two diastereomers **32** and **33** was obtained in a ratio of about 1.3:1 (de = 13%), respectively.

The absolute configurations of compounds **32** and **33** were assigned by comparison of their CD spectrum with corresponding data of mixtures **21**/**22**, **23**/**24**, **25**/**26** and **29**/**30**. All CD and UV data for mixtures of **21**/**22**, **23**/**24**, **25**/**26**, **29**/**30** and **32**/**33** are provided in Table 1. CD spectra of mixtures **21**/**22**, **23**/**24**, **25**/**26** and **29**/**30** showed the same positive sign of the long wavelength CD band at ca. 250 nm and of the short wavelength CD band around 210 nm (Fig. 5). In all cases, an additional CD band around 230 nm of opposite sign to the first two was present. The positive sign of the 250 nm CD band can be assigned to the same configuration at C-4′ of the azetidin-2-one ring. The absolute stereochemistry assignment could be done empirically based on the combined analysis of the NMR, CD, X-ray data as well as chemical correlation of synthetic steps. According to the NOE experiments for compounds **27** and **28**, we were able to describe the

[†] For the sake of simplicity, numbering of cephams refer to sugar nomenclature.

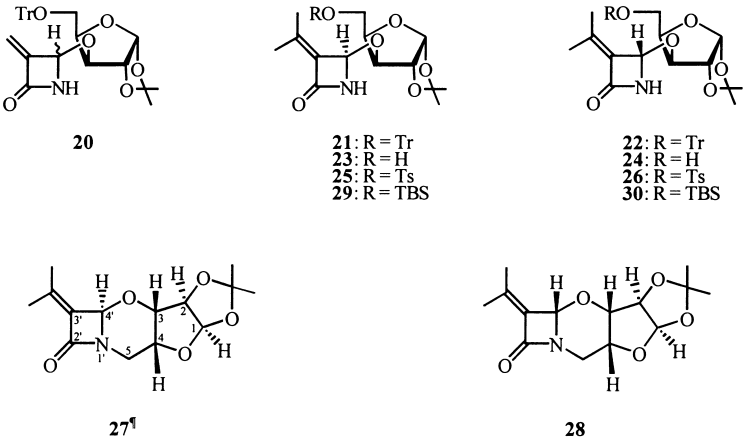


Figure 3.

absolute configuration of minor diastereomers in the mixtures of **21**/**22** and **23**/**24** to be (4′*S*). The reliability of this assignment was confirmed by X-ray analysis of **28**. Thus, the absolute configuration at C-4′ in the major diastereomers in the mixtures **21**/**22**, **23**/**24**, **25**/**26** and **29**/**30** should be (*R*) owing to the same shape of the CD curves. In the case of mixture **32**/**33** (Fig. 5) there was only one positive CD band visible at 207 nm in its spectrum. This can be explained on the basis of the low diastereocontrol in this reaction leading to the mixture of **32**:**33** in a ratio of 1.3:1 only. However, the positive sign of the 207 nm CD band allows us to describe the (4′*R*) absolute configuration to the major diastereomer in this case too.

Table 1
UV and CD data of β-lactams **21**–**26**, **29**, **30**, **32**–**35** measured in acetonitrile

Compounds	UVε (λ_{max}/nm)			CD Δε (λ_{max}/nm)		
21/22	48950 (202)	24640 (220^{sh})	1040 (258^{sh})	+ 1.23 (222)	– 0.1 (231)	+ 0.42 (248)
23/24	–	13780 (215)	–	+ 1.40 (210)	–	+ 0.35 (250)
29/30	–	15790 (215)	–	+ 1.83 (209)	– 0.58 (228)	+ 0.65 (250)
23/24*	–	14080 (215)	–	+ 2.73 (209)	–	+ 0.89 (249)
25/26	34750 (196)	24180 (220)	1090 (255^{sh})	+ 2.07 (209)	– 1.25 (228)	+ 0.76 (251)
32/33	–	15480 (215)	–	+ 0.59 (212)	–	–
34	49080 (195)	17270 (220^{sh})	2030 (257^{sh})	– 5.26 (208^{sh})	+ 3.75 (223)	– 0.77 (252)
35	50510 (200)	24230 (220^{sh})	1320 (258^{sh})	+1.28 (208)	–1.07 (230)	+1.43 (251)

*the mixture of compounds obtained from **29/30**

^{sh}- shoulder

It should be mentioned at this stage that a comparison of the bond lengths in the azetidin-2-one ring of diacetate **31** with the respective bond lengths of the (4*R*)-methylazetidin-2-one model compound shows a difference in the C-2′–C-3′ bond length equal to 0.17 Å[16] (cf. Experimental).

The shortening of the C-2′–C-3′ bond in compound **31** unequivocally indicates a participation of the *exo* double bond with the β-lactam chromophoric system. Therefore, the β-lactam octant rule is not applicable to the investigated compounds and cannot be used for determination of their absolute configuration.

The lower asymmetric induction found for **13** versus that found for **11** and **12** was not fully understood, therefore we decided to investigate the stereoselectivity in the addition of CSI to **14** which, compared to **11**, did not contain a dioxolane ring. Due to the instability of **14** under the reaction conditions, a mixture of compounds **34** and **35** was obtained in a low yield and a ratio of about 2.6:1 (de = 44%), respectively. Compounds **34** and **35** were separated and purified. The absolute configurations of **34** and **35** were proved, as for the mixture **32**/**33**, by CD spectroscopy (Fig. 4). As shown in Table 1 and Fig. 5, the CD spectra of both epimers fell under two different patterns of sign sequence. In the case of compound **34**, the negative long wavelength CD band was followed by the positive and by the negative short wavelength ones. For compound **35** the opposite relation of sign pattern was observed, i.e. the positive long wavelength CD band was followed by the negative and positive ones. Hence, according to the aforementioned discussion, the prevailing diastereomer **34** had an (*S*) configuration at the C′-4 carbon atom whereas its epimer **35** had an (*R*) configuration at the same carbon of the azetidin-2-one ring.

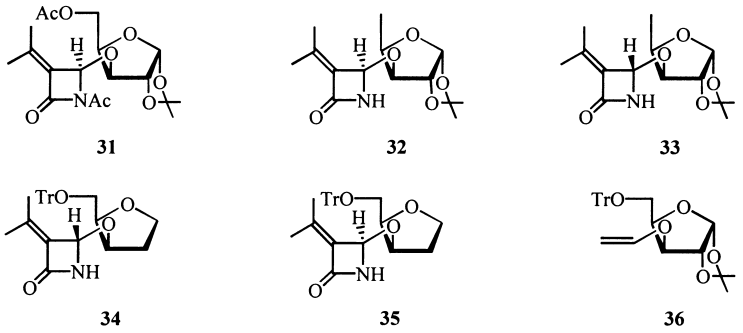


Figure 4.

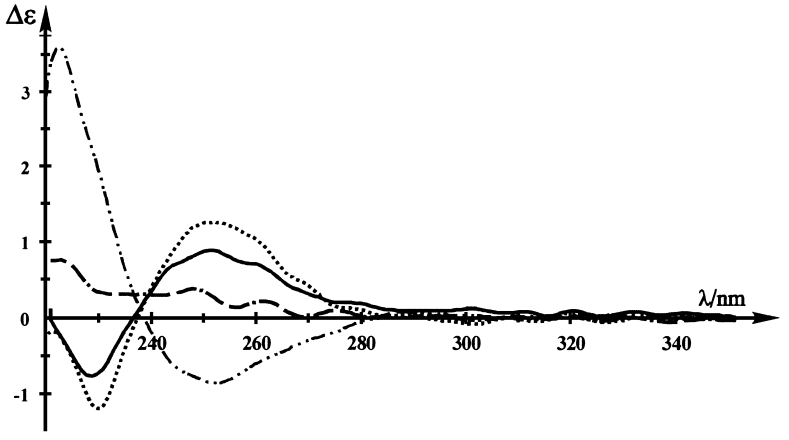


Figure 5. CD spectra of **29**/**30** (—), **32**/**33** (-·-·-), **34** (-···-), **35** (····) in acetonitrile

According to the Hammond postulate, the transition states of exothermic reactions resemble the starting materials, in energy and geometry. It would therefore be reasonable to use the ground-state conformation of olefins to reflect the geometry in the transition state of [2+2] cycloadditions with CSI. Recently, using NOE coefficients, we have assigned the most favorable ground state conformation of sugar derived alkoxyallenes.[13] The NOE studies on compounds **11**, **13** and **14** have shown with high confidence that the *s-cis* conformation should dominate in a solution and the presence of *s-trans* conformer in solution is negligible in modelling ground-state conformations of the investigated molecules. Consequently, conformation of the alkoxyallene fragment and configuration of the main diastereomer testify to the preferred *si*-entry of CSI to allenes **11**–**13** and the *re*-entry to **14** (Fig. 6).

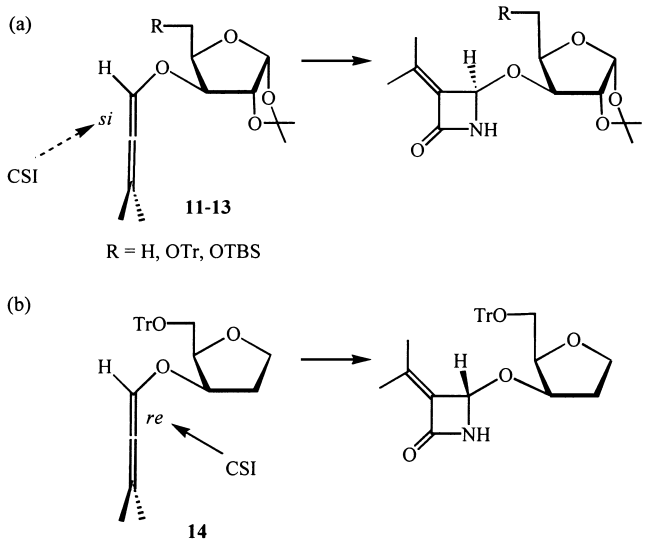


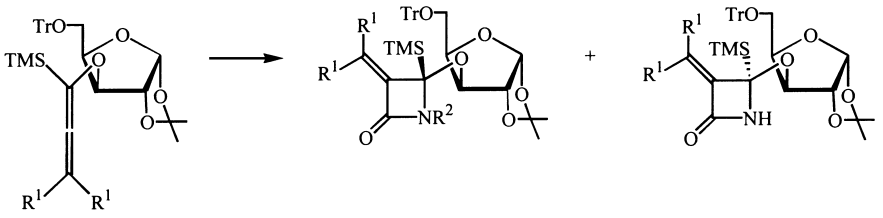
Figure 6. Stereochemical model of the CSI addition to allenes: (a) **11**–**13** and (b) **14**

The comparison of the face-discrimination found for addition of CSI to **11**–**13** and to the vinyl ether **36**[9] is particularly interesting. The lower face-discrimination found for **11**–**13** is a consequence of the *s-cis* conformation of the alkoxyallene, which makes both sides of the double bond similarly accessible. The role of both methyl groups perpendicular to the vinyloxy double bond in the stereoselectivity of [2+2] cycloaddition deserves, however, further elucidation.

In order to explain the contribution of *gem* methyl groups of allene, we synthesized two cumulenes **37** and **38**. Introduction of trimethylsilyl groups to **10** and **11** was accomplished by the standard procedure involving lithiation followed by silylation with TMSCl.[17]

We expected that an introduction of the trimethylsilyl group to the diastereo-zeroplane should not influence the face-discrimination, whereas allenes **37** and **38** should react more readily and be more resistant to the cycloaddition conditions.

[2+2] Cycloaddition of CSI to **37** proceeded with high face-discrimination to afford the corresponding β-lactams **39** and **41** in a ratio of about 18:1 (de = 89%), respectively (Scheme 2). Compound **38** afforded a lower asymmetric induction but a better yield of cycloaddition. A mixture of compounds **40** and **42** was obtained in a ratio of 3.2:1 (de = 52%), respectively (Scheme 2). In both reactions the total yields were increased by 30% as compared to the additions



37: $R^1 = H$
38: $R^1 = CH_3$

39: $R^1 = H$, $R^2 = H$,
40: $R^1 = CH_3$, $R^2 = H$,
43: $R^1 = CH_3$, $R^2 = Ac$

41: $R^1 = H$
42: $R^1 = CH_3$

Scheme 2.

involving the silyl-free allenes **10** and **11**, respectively. The mixtures **39**/**41** and **40**/**42** were separated into the pure components.

Absolute configurations of compounds **39**–**42** were assigned by a combination of X-ray crystallography and CD spectroscopy. We were able to obtain a crystalline β-lactam **43** by *N*-acetylation of compound **40** (Table 3, Fig. 10). The known configuration of **40** and a comparison of CD spectra of β-lactams **39**–**42** (Fig. 7, Table 2) provided the proof of their configuration. As can be seen in Table 2 and Fig. 7, compounds **39** and **40** display the same shape of their CD curves, whereas compounds **41** and **42** display the opposite pattern of sign sequence. Taking into account the known absolute configuration of compound **40** (4′*R*) and the same negative sign of the long wavelength CD band, the configuration of compound **39** also has to be (4′*R*). Consequently, configuration at C-4′ of compounds **41** and **42** has to be (*S*).

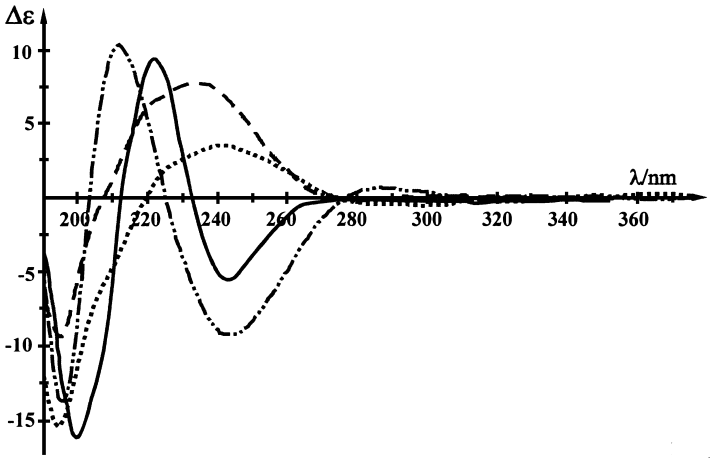


Figure 7. CD spectra of **39** (····), **40** (—), **41** (····), **42** (- - -) in acetonitrile

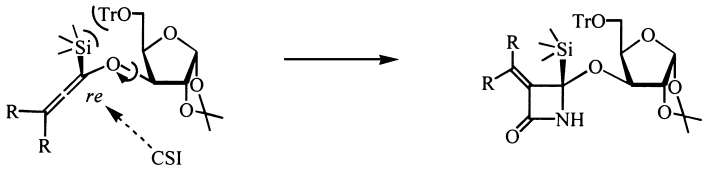
Unexpectedly, the preferred direction of asymmetric induction in **37** and **38** differed from that predicted by the analogy to the cycloaddition involving **11**. We were not able to assign the preferred ground-state conformation of **37** and **38** either by X-ray or by NOE coefficients.[13,18] It could be assumed, however, that the two bulky lipophilic substituents, trityl and trimethylsilyl interact with the repulsive force causing the C(3)–C(4) bond of the furanoid ring to become

perpendicular to the diastereo-zero plane which consists of the vinyloxy double bond, O(3) oxygen atom and C(3) carbon atom (Fig. 8). Such a geometry of allenes allows, as postulated by us earlier,[13,18] stereoelectronic interaction between the π-electrons of the vinyloxy fragment and the σ^* orbital of the C(3)–C(4) bond. If the proposed ground-state conformation of the allenes **37** and **38** (Fig. 8) reflects the transition-state conformation, then the *si* side of the double bond is blocked by a trityloxymethyl substituent and consequently the attack of the isocyanate occurs from the *re* side, affording preferentially (*R*) configurations of the products **39** and **40**.

Table 2
UV and CD data of β-lactams **39**–**42** measured in acetonitrile

Compounds	UVε (λ_{max}/nm)			CD Δε (λ_{max}/nm)		
39	93400 (192)	11080 (230^{sh})	1930 (257^{sh})	−13.7 (196)	+ 10.28 (212)	− 9.29 (245)
40	73880 (192)	17420 (223^{sh})	1230 (257^{sh})	−17.0 (200)	+ 8.49 (222)	− 6.34 (244)
41	129270 (192)	15110 (230^{sh})	2590 (257^{sh})	−15.4 (195)	−	+ 3.41 (241)
42	75190 (192)	24310 (222^{sh})	1430 (257^{sh})	−9.4 (195)	−	+7.08 (232)

^{sh}- shoulder



R = H, CH_3

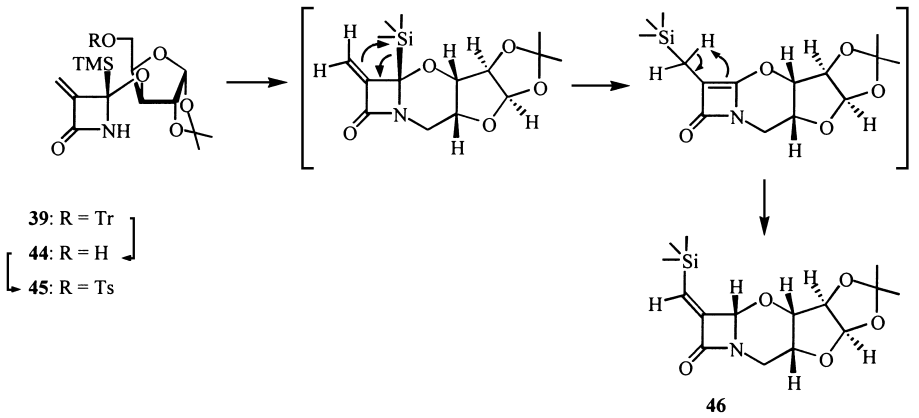
Figure 8. Stereochemical model of the CSI addition to allenes **33** and **34**

The experiments performed on **37** and **38** demonstrate the decisive role of the *gem*-methyl groups in the allene fragment, which certainly activate a vinyloxy double bond of the allenes for cycloaddition. This was proved by the experiment performed on the mixture of **37** and **38** and 0.5 equiv. of CSI. It resulted in exclusive formation of cephams **40** and **42**.

The lower stereoselectivity found for **38** versus **37** can be explained by the increased reaction rate in the case of dimethylallene **38**.

An attempt to perform an intramolecular cyclization of **45**, readily available by the standard detritylation–tosylation sequence was unsuccessful. Both reaction conditions,[9,19] usually applied by us, gave compound **46** as the only isolated product in the yield not exceeding 18% (Scheme 3). The structure and configuration of **46** was proved by X-ray crystallography (Table 3, Fig. 11).

In summary, we have demonstrated that the [2+2] cycloaddition of CSI to alkoxyallene provides β-lactams with a moderate stereoselectivity. Assuming that the transition state of the cycloaddition resembles the ground-state conformation of alkoxyallene, we were able to explain the direction and magnitude of the asymmetric induction.



Scheme 3.

Table 3
Crystal data and structure refinement for compounds **28**, **31**, **43**, and **46**

Identification code	**28**	**31**	**43**	**46**
Empirical formula	$C_{14}H_{19}NO_5$	$C_{18}H_{25}NO_8$	$C_{38}H_{45}NO_7Si$	$C_{15}H_{23}NO_5Si$
Formula weight	281.30	383.39	655.84	325.44
Temperature (K)	293(2)	293(2)	293(2)	293(2)
Wavelength (Å)	1.54178	1.54178	0.71073	0.71073 A
Crystal system,	monoclinic	orthorhombic	monoclinic	orthorhombic
Space group	$P2_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
Unit cell dimensions (Å, °) a:	9.821(2)	6.0470(10)	9.6650(5)	5.6200(8)
b:	5.4810(10)	18.128(4)	15.8530(9)	16.601(2)
c:	13.768(3)	18.578(4)	12.1910(8)	18.380(4)
β:	100.27(3)	---------	100.411(2)	----------
Volume ($Å^3$)	729.2(3)	2036.5(7)	1837.1(6)	1714.8(5)
Z, Calculated density (Mg . m^{-3})	2, 1.281	4, 1.250	2, 1.180	4, 1.268
Absorption coefficient (mm^{-1})	0.813	0.833	0.111	0.159
F(000)	300	816	694	704
Crystal size (mm)	0.14x0.21x0.56	072x0.14x0.14	0.45x0.20x0.05	0.75x0.04x0.03
θ-range for data collection (°)	3.26 to 73.85	3.41 to 63.59	2.48 to 27.43	3.31 to 19.99
Reflections collected / unique	1829/1083]	2040/822	7574/7531	5680/1532
R(int)	0.1100	0.0000	0.039	0.075]
Refinement method	full-matrix least-squares on F^2			
Data / restraints / parameters	1083 / 1 / 182	822 / 0 / 245	7531 / 0 / 431	1532 / 0 / 205
Goodness-of-fit on F^2	1.074	0.785	1.780	0.925
Final R indices [I>2σ (I)]				
R_1	0.066	0.092	0.044	0.049
wR_2	0.139	0.253	0.082	0.085
Absolute struct. param.	0.6(9)	-4.2(11)	-0.01(12)	0.0(3)
Extinction coefficient	0.046(7)	0.008(4)	0.018(1)	0.007(1)
Δρ (e. $Å^{-3}$)	0.22 and -0.21	0.38 and -0.36	0.27 and -0.14	0.12 and -0.14

3. Experimental

Melting points were determined on a Kofler hot-stage apparatus with microscope and are uncorrected. ^{1}H NMR spectra were obtained on Bruker Avance 500 and Varian Gemini AC-200 spectrometers for solutions in $CDCl_3$ or benzene-d_6 with tetramethylsilane as an internal standard and are expressed as δ values. Signals for aromatic protons (phenyls) were not characteristic and therefore they were not included in spectral data. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum 2000 spectrophotometer. Mass spectra were determined with an AMD 604 Inectra GmbH spectrometer. Optical rotations were measured using a JASCO P 3010 polarimeter at ambient temperature. CD spectra were recorded on a J-715 spectropolarimeter in acetonitrile. Column chromatography was performed on Merck silica gel (230–400 mesh).

3.1. 1,2-O-*Isopropylidene-3*-O-*propargyl-α-D-xylofuranose* **15**

Compound **15** was obtained from 1,2:5,6-di-*O*-isopropylidene-3-*O*-propargyl-α-D-glucofuranose[12] by the standard reaction sequence[13] involving deprotection of the isopropylidene grouping, glycolic cleavage of a terminal diol and a reduction of the aldehyde to the alcohol. The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate, 7:3 v/v, as an eluent to give **15** (83%): oil; $[\alpha]_D^{22} = -66.1$ (0.9, CH_2Cl_2); IR (film) 2117, 3275, 3486 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.33, 1.51 (2s, 6H, 2×Me), 2.51 (t, 1H, $J = 2.4$ Hz, ≡CH), 3.84 (dd, 1H, $J = 5.5$ and 12.0 Hz, H-5a), 3.93 (dd, 1H, $J = 5.3$ and 12.0 Hz, H-5b), 4.01–4.20 (m, 2H, –OCH_2–), 4.19 (d, 1H, $J = 3.4$ Hz, H-3), 4.14–4.34 (m, 3H, H-4, –OCH_2–), 4.62 (d, 1H, $J = 3.8$ Hz, H-2), 5.95 (d, 1H, $J = 3.8$ Hz, H-1); anal. calcd for $C_{11}H_{16}O_5$ (228.25): C, 57.88; H, 7.06. Found: C, 57.64; H, 7.26.

3.2. 5-O-t-*Butyldimethylsilyl-3*-O-*propargyl-1,2*-O-*isopropylidene-α-D-xylofuranose* **17**

To a stirred solution of **16** (6 g, 26.3 mmol) and imidazole (3.76 g, 55.2 mmol) in dry CH_3CN (40 mL) at 0°C, a solution of *t*-butyldimethylsilyl chloride (4.36 g, 28.9 mmol) in CH_3CN (15 mL) was added dropwise. The temperature of the reaction was allowed to rise to room temperature. After 2 h, the solvent was removed and the mixture was poured into water, extracted with Et_2O, dried ($MgSO_4$) and evaporated. The crude product was purified by column chromatography on silica gel using hexane:ethyl acetate, 94:6 v/v, as an eluent to give **17** (8.1 g, 90%): syrup; $[\alpha]_D = -39.0$ (*c* 1.9, $CHCl_3$); IR (film) 2119, 3271, 3312 cm^{-1} (lit.,[12] oil, $[\alpha]_D^{22} = -37.6$ (*c* 1.9, $CHCl_3$); IR (KBr) 1100, 1200, 1380, 2100, 3300 cm^{-1}).

3.3. 1,2-O-*Isopropylidene-3*-O-*(prop-1′,2′-dienyl)-5*-O-*trityl-α-D-xylofuranose* **10**

To a solution of **15** (4.70 g, 10 mmol) in a 1:1 v/v mixture of *t*-BuOH:DMSO (30 mL) freshly sublimated *t*-BuOK (1.12 g, 10 mmol) was added. The solution was heated at 55°C for 1.5 h (TLC monitoring), cooled to room temperature, and water (50 mL) and *t*-butyl methyl ether (50 mL) were added. The aqueous phase was extracted with *t*-butyl methyl ether (3×60 mL). The combined ether extracts were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography to give **10** (85%): oil; $[\alpha]_D^{22} = -6.6$ (*c* 1.1, CH_2Cl_2); IR (film) 1954 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: 1.32, 1.54 (2s, 6H, 2×Me), 3.32 (dd, 1H, $J = 6.8$ and 9.3 Hz, H-5a), 3.42 (dd, 1H, $J = 5.8$ and 9.3 Hz, H-5b), 4.28 (d, 1H, $J = 3.0$ Hz, H-3), 4.38 (ddd, 1H, $J = 3.0$,

5.8 and 6.8 Hz, H-4), 4.55 (d, 1H, $J=3.8$ Hz, H-2), 5.44 (dd, 1H, $J=6.0$ and 8.5 Hz, $H_AH_BC=$), 5.55 (dd, 1H, $J=6.0$ and 8.5 Hz, $H_AH_BC=$), 5.86 (d, 1H, $J=3.8$ Hz, H-1), 6.58 (t, 1H, $J=6.0$ Hz, $=CHO-$); MS (EI, HR) m/z: M^+ calcd for $C_{30}H_{30}O_5$: 470.20932. Found: 470.20818; anal. calcd for $C_{30}H_{30}O_5$ (470.58): C, 76.57; H, 6.42. Found C, 76.50; H, 6.54.

3.4. 1,2-O-*Isopropylidene*-3-O:5-O-(prop-1′-en-1′,2′-diyl)-α-D-xylofuranose **18**

Compound **15** under the isomerization conditions (see procedure described for **10**) afforded **18** (74%): oil; $[\alpha]_D^{22}=+67.0$ (c 1.5, CH_2Cl_2); IR (film) 1677 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 1.32, 1.54 (2s, 6H, 2×Me), 1.60 (d, 3H, $J=1.2$ Hz, Me), 4.18 (dd, 1H, $J=9.5$, 11.5 Hz, H-5a), 4.29 (dd, 1H, $J=6.2$, 11.5 Hz, H-5b), 4.51 (d, 1H, $J=3.2$ Hz, H-3), 4.56 (d, 1H, $J=3.7$, H-2), 4.60–4.64 (m, 1H, H-4), 5.62 (d, 1H, $J=1.2$ Hz, $-OCH=$), 5.85 (d, 1H, $J=3.7$, H-1); MS (EI, HR) m/z: M^+ calcd for $C_{11}H_{16}O_5$: 228.0998. Found: 228.1008; anal. calcd for $C_{11}H_{16}O_5$ (228.25): C, 57.88; H, 7.06. Found: C, 57.75; H, 7.22.

3.5. 3-O-(But-2′-ynyl)-5-O-t-butyldimethylsilyl-1,2-O-isopropylidene-α-D-xylofuranose **19**

To a solution of *n*-BuLi (2.5 M in hexane, 9.56 mL, 23.9 mmol) and a mixture of dry THF:HMPA (9:1 v/v, 40 mL) under argon was added **17** (6.3 g, 18.4 mmol) in THF (10 mL) at –60°C with stirring. The mixture was allowed to slowly warm up to –20°C and then treated with MeI (1.48 mL, 23.9 mmol). Stirring was continued for 1 h while warming up to room temperature. The mixture was diluted with *t*-butyl methyl ether:hexane, 1:1 v/v, washed with brine, dried ($MgSO_4$), and concentrated. The residue was purified on a silica gel column using hexane:ethyl acetate, 94:6 v/v, as an eluent to give **19** (3.8 g, 58%): oil; $[\alpha]_D^{22}=-40.0$ (c 0.48, CH_2Cl_2); IR (CH_2Cl_2) 2226 cm^{-1}; ^1H NMR (200 MHz, benzene-d_6) δ: 0.07 (s, 6H, *t*-BuMe_2Si–), 0.95 (s, 9H, *t*-*Bu*Me_2Si–), 1.11, 1.41 (2s, 6H, 2×Me), 1.46 (t, 3H, $J=2.3$ Hz, Me–C≡), 3.91–4.15 (m, 4H, H-5a, H-5b, H-1′a, H-1′b), 4.22 (d, 1H, $J=3.4$ Hz, H-3), 4.41 (d, 1H, $J=3.8$ Hz, H-2), 4.51–4.60 (m, 1H, H-4), 5.88 (d, 1H, $J=3.8$ Hz, H-1); MS (EI, HR) m/z: $(M-CH_3)^+$ calcd for $C_{17}H_{29}O_5Si$: 341.1784. Found: 341.1788.

3.6. 5-O-t-Butyldimethylsilyl-1,2-O-isopropylidene-3-O-(3′-methyl-buta-1′,2′-dienyl)-α-D-xylofuranose **12**

To a solution of **19** (2.7 g, 7.57 mmol) in dry THF (20 mL) at –45°C was added *n*-BuLi (2.2 M in hexane, 4.13 mL, 9.1 mmol). After 25 min at –45°C, MeI (0.56 mL, 9.1 mmol) was added, then the solution was warmed to 25°C over 20 min. Subsequently, *t*-butyl methyl ether (100 mL) and saturated aqueous NaCl solution (50 mL) were added. The organic layer was separated, washed with water, dried ($MgSO_4$), and concentrated. The residue was purified on a silica gel column, using hexane:ethyl acetate, 95:5 v/v, as an eluent to give **12** (1.4 g, 50%): oil; $[\alpha]_D^{22}=-30.2$ (c 0.5, CH_2Cl_2); IR (film) 1959 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: 0.07 (s, 6H, *t*-BuMe_2Si–), 0.89 (s, 9H, *t*-*Bu*Me_2Si–), 1.30, 1.51 (2s, 6H, 2×Me), 1.82 (d, 3H, $J=2.1$ Hz, Me), 1.85 (d, 3H, $J=2.1$ Hz, Me), 3.82 (dd, 1H, $J=6.0$ and 10.0 Hz, H-5a), 3.88 (dd, 1H, $J=6.9$ and 10.0 Hz, H-5b), 4.16 (d, 1H, $J=3.0$ Hz, H-3), 4.30 (ddd, 1H, $J=3.0$, 6.0 and 6.9 Hz, H-4), 4.54 (d, 1H, $J=3.7$ Hz, H-2), 5.86 (d, 1H, $J=3.7$ Hz, H-1), 6.40 (sept., 1H, $J=2.1$ Hz, H-1′); MS (HR, LSIMS) m/z: $(M+H)^+$ calcd for $C_{19}H_{35}O_5Si$: 371.2254. Found: 371.2227; anal. calcd for $C_{19}H_{34}O_5Si$ (370.57): C, 61.58; H, 9.23. Found: C, 61.02; H, 9.37.

3.7. [2+2]Cycloaddition of chlorosulfonyl isocyanate to alkoxyallenes **10–14**. General procedure

To a suspension of anhydrous Na_2CO_3 (0.15 g) in dry toluene (2 mL) chlorosulfonyl isocyanate (0.114 mL, 1.3 mmol) was added. The mixture was stirred and upon cooling to –70°C a solution of alkoxyallenes **10–14** (1 mmol) in dry toluene (2 mL) was added dropwise. The temperature of the mixture was allowed to rise to –30°C and it was maintained for 1.5 h. The mixture was then cooled to –70°C, diluted with toluene (6 mL), treated with Red-Al (1 M solution in toluene, 1.3 mL), and left for 30 min while maintaining the temperature. The cooling bath was removed and water (0.2 mL) was added at 0°C. After 15 min of an intensive stirring the suspension was filtered through Celite, the solvent was evaporated and the residue was purified by chromatography on silica gel to give the respective products.

3.8. (4′R) and (4′S) 1,2-O-Isopropylidene-3-O-(3′-methyleneazetidin-2′-on-4′-yl)-5-O-trityl-α-D-xylofuranoses **20**

In a ratio of ca. ~1:1 (6%): oil; IR (film) 1772, 3296 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) selective signals taken for the mixture: major isomer ~52%: δ 4.23 (d, 1H, $J=3.0$ Hz, H-3), 4.46 (d, 1H, $J=3.8$ Hz, H-2), 5.15 (d, 1H, $J=1.9$ Hz, $H_AH_BC=$), 5.42 (s, 1H, H-4′), 5.73 (m, 1H, $H_AH_BC=$), 6.52 (br s, 1H, NH). Minor isomer ~48%: 4.19 (d, 1H, $J=3.0$ Hz, H-3), 4.51 (d, 1H, $J=3.8$ Hz, H-2), 5.20 (d, 1H, $J=1.9$ Hz, $H_AH_BC=$), 5.40 (s, 1H, H-4′), 5.68 (m, 1H, $H_AH_BC=$), 6.34 (br s, 1H, NH); MS (HR, LSIMS) m/z: $(M+Na)^+$ calcd for $C_{31}H_{31}O_6NNa$: 536.2049. Found: 536.2037.

3.9. (4′R) and (4′S) 1,2-O-Isopropylidene-3-O-[3′-(1-methylethylidene)azetidin-2′-on-4′-yl]-5-O-trityl-α-D-xylofuranose **21** and **22**

In a ratio of ca. 2.3:1 (60%): oil; IR (film) 1729, 1763, 3408 cm^{-1}. Compound **21**: ^1H NMR (500 MHz, benzene-d_6) selective signals taken for the mixture: δ 1.44 (s, 3H, Me), 1.81 (s, 3H, Me), 3.35 (dd, 1H, $J=5.0$ and 9.9 Hz, H-5a), 3.81 (d, 1H, $J=3.0$ Hz, H-3), 4.33 (d, 1H, $J=3.7$ Hz, H-2), 4.58–4.61 (m, 1H, H-4), 4.76 (s, 1H, H-4′), 5.85 (br s, 1H, NH), 5.90 (d, 1H, $J=3.8$ Hz, H-1). Compound **22**: ^1H NMR (500 MHz, benzene-d_6) selective signals taken for the mixture: δ 1.46 (s, 3H, Me), 1.80 (s, 3H, Me), 3.34 (dd, 1H, $J=5.0$ and 9.9 Hz, H-5a), 3.94 (d, 1H, $J=3.0$ Hz, H-3), 4.34 (d, 1H, $J=3.7$ Hz, H-2), 4.63–4.66 (m, 1H, H-4), 4.85 (s, 1H, H-4′), 5.75 (br s, 1H, NH), 5.94 (d, 1H, $J=3.8$ Hz, H-1); MS (HR, LSIMS) m/z: $(M+Na)^+$ calcd for $C_{33}H_{35}O_6NNa$: 564.2362. Found: 564.2390; anal. taken for the mixture calcd for $C_{33}H_{35}O_6N$ (541.66): C, 73.18; H, 6.98; N, 2.58. Found: C, 72.98; H, 6.77; N, 2.41.

3.10. (4′R) and (4′S) 1,2-O-Isopropylidene-3-O-[3′-(1-methylethylidene)azetidin-2′-on-4′-yl]-α-D-xylofuranose **23** and **24**

The mixture **21**/**22** was detritylated with 0.2% of *p*-TsOH in MeOH at room temperature (~2 h, TLC monitoring). The crude product was purified by column chromatography using hexane:ethyl acetate, 2.5:7.5 v/v, as an eluent to give a mixture of compounds **23** and **24**, in a ratio ca. 2:1 (75%): oil; IR (film) 1746, 3307, 3459 cm^{-1}. Compound **23**: ^1H NMR (500 MHz, $CDCl_3$) selective signals taken for the mixture: δ 1.31, 1.49 (2s, 6H, 2×Me), 1.87 (s, 3H, Me), 2.08 (s, 3H, Me), 4.22 (d, 1H, $J=3.4$ Hz, H-3), 4.51 (d, 1H, $J=3.8$ Hz, H-2), 5.94 (d, 1H, $J=3.8$ Hz, H-1), 6.66 (br s, 1H, NH). Compound **24**: ^1H NMR (500 MHz, $CDCl_3$) selective signals taken for the

mixture: δ 1.32, 1.50 (2s, 6H, 2×Me), 1.84 (s, 3H, Me), 2.07 (s, 3H, Me), 4.17 (d, 1H, $J=3.3$ Hz, H-3), 4.59 (d, 1H, $J=3.7$ Hz, H-2), 5.93 (d, 1H, $J=3.7$ Hz, H-1), 6.82 (br s, 1H, NH); MS (HR, LSIMS) m/z: $(M+H)^+$ calcd for $C_{14}H_{22}O_6N$: 300.1447. Found: 300.1427; anal. taken for the mixture calcd for $C_{14}H_{21}O_6N$ (299.33): C, 56.18; H, 7.07; N, 4.68. Found: C, 56.09; H, 7.33; N, 4.41.

*3.11. (4′R) and (4′S) 1,2-*O*-Isopropylidene-3-*O*-[3′-(1-methylethylidene)azetidin-2′-on-4′-yl]-5-*O*-tosyl-α-D-xylofuranose **25** and **26***

The mixture of **25**/**26** was obtained from **23**/**24** by a standard tosylation procedure (82%): oil; IR (film) 1730, 1759, 3323 cm^{-1}. Compound **25**: ^1H NMR (200 MHz, $CDCl_3$) selective signals taken for the mixture: δ 2.46 (s, 3H, tosyl), 4.43 (d, 1H, $J=3.8$ Hz, H-2), 5.59 (s, 1H, H-4′), 5.85 (d, 1H, $J=3.8$ Hz, H-1), 6.61 (br s, 1H, NH). Compound **26**: ^1H NMR (200 MHz, $CDCl_3$) selective signals taken for the mixture: δ 2.46 (s, 3H, tosyl), 4.57 (d, 1H, $J=3.7$ Hz, H-2), 5.57 (s, 1H, H-4′), 5.86 (d, 1H, $J=3.7$ Hz, H-1), 6.52 (br s, 1H, NH); MS (HR, LSIMS) m/z: $(M+H)^+$ calcd for $C_{21}H_{28}O_8NS$: 454.1536. Found: 454.1531; anal. calcd for $C_{21}H_{27}O_8NS$ (453.52): C, 55.62; H, 6.00; N, 3.08. Found: C, 55.79; H, 6.15; N, 3.05.

*3.12. (4′R) and (4′S) 5-Deoxy-1,2-*O*-isopropylidene-3-*O*:5-*C*-[3′-(1-methylethylidene)azetidin-2′-on-1′,4′-diyl)-α-D-xylofuranose **27** and **28***

A mixture of compounds **25**/**26** (1.1 g, 2.42 mmol) was dissolved in anhydrous CH_3CN (45 mL) and treated with Bu_4NBr (0.92 g, 2.90 mmol) and pulverized K_2CO_3 (3.0 g). The mixture was stirred under reflux for 45 min (TLC). Subsequently, toluene (50 mL) was added, the mixture was filtered, washed with water, dried (Na_2SO_4) and evaporated. The crude product was separated by flash chromatography on a silica gel (25–40% ethyl acetate–hexane) to give **27** (0.35 g, 51%) and **28** (0.20 g, 30%). Compound **27**: colorless crystals; mp 64.5–67°C; $[\alpha]_D^{22}=+136.1$ (0.28, $CHCl_3$); IR (film) 1759 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.33, 1.48 (2s, 6H, 2×Me), 1.84 (s, 3H, Me), 2.06 (s, 3H, Me), 3.36 (dd, 1H, $J=3.3$ and 14.4 Hz, H-5a), 4.06 (dd, 1H, $J=6.9$ and 14.4 Hz, H-5b), 4.16 (d, 1H, $J=3.0$ Hz, H-3), 4.50 (m, 1H, H-4), 4.61 (d, 1H, $J=3.8$ Hz, H-2), 5.41 (s, 1H, H-4′), 5.99 (d, 1H, $J=3.8$ Hz, H-1); MS (EI, HR) m/z: M^+ calcd for $C_{14}H_{19}O_5N$: 281.1263. Found: 281.1266; anal. calcd for $C_{14}H_{19}O_5N$ (281.31): C, 59.78; H, 6.81; N, 4.98. Found: C, 60.20; H, 7.06; N, 4.92. Compound **28**: colorless crystals; mp 186–191°C; $[\alpha]_D^{22}=-44.2$ (0.53, CH_2Cl_2); IR (film) 1748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.31, 1.49 (2s, 6H, 2×Me), 1.82 (s, 3H, Me), 2.03 (s, 3H, Me), 3.36 (dd, 1H, $J=4.0$ and 15.2 Hz, H-5a), 4.05 (dd, 1H, $J=1.7$ and 4.0 Hz, H-4), 4.13 (d, 1H, $J=15.2$ Hz, H-5b), 4.14 (d, 1H, $J=1.7$ Hz, H-3), 4.51 (d, 1H, $J=3.7$ Hz, H-2), 5.17 (s, 1H, H-4′), 5.89 (d, 1H, $J=3.7$ Hz, H-1); MS (EI, HR) m/z: $(M-CH_3)^+$ calcd for $C_{13}H_{16}O_5N$: 266.1028. Found: 266.1030; anal. calcd for $C_{14}H_{19}O_5N$ (281.32): C, 59.78; H, 6.81; N, 4.98. Found: C, 59.53; H, 7.03; N, 4.83.

*3.13. X-Ray structure analysis of compounds **28**, **31**, **43** and **46***

X-ray data for crystals of compounds **28** (Fig. 9) and **31** (Fig. 10) were collected on a Nonius MACH3 four-circle diffractometer using EXPRESS procedure.[20] ω–2θ Scanning mode was applied. Unit cell parameters were obtained by refinement of 15 reflections in the θ-range 14.2–19.4 and 16.8–21.4°, for compounds **28** and **31**, respectively. Data reduction was performed with the use of an OpenMoleN system of programs.[21]

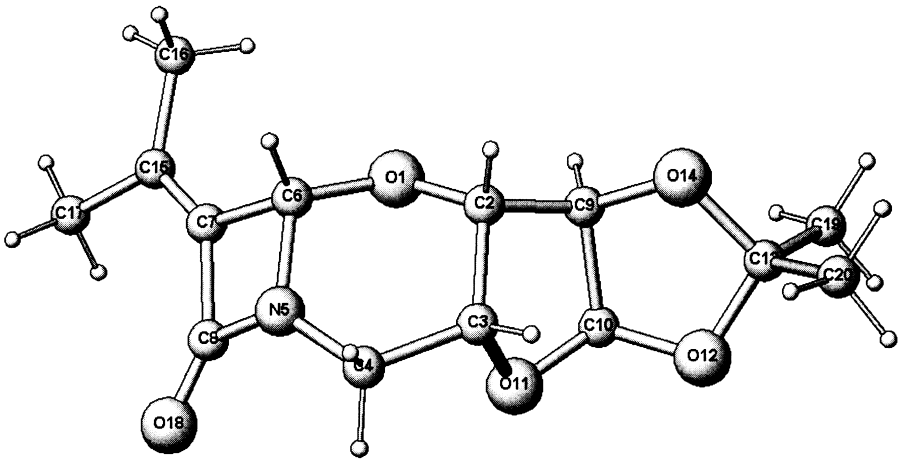


Figure 9. Molecular structure of the compound **28** with the crystallographic numbering scheme

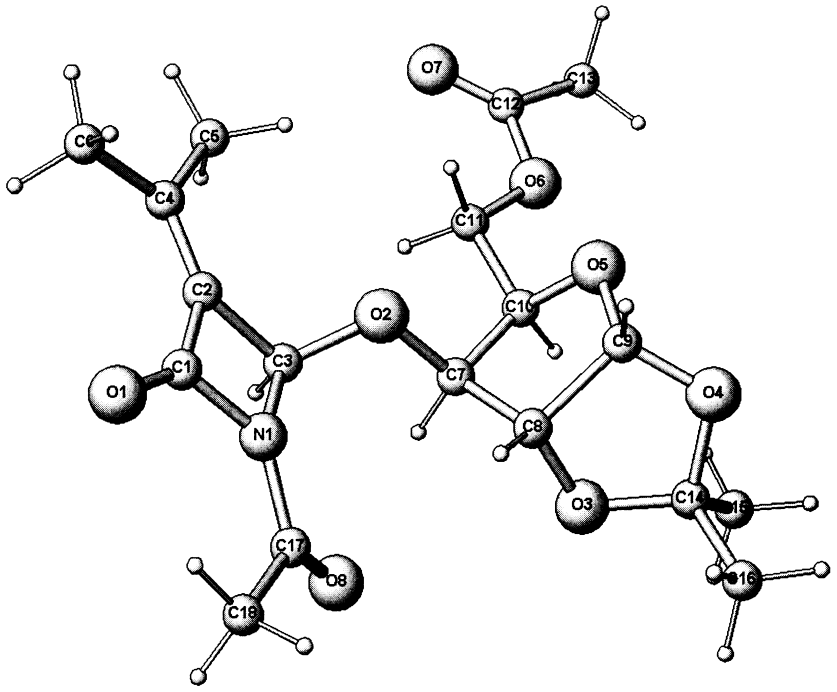


Figure 10. Molecular structure of the compound **31** with the crystallographic numbering scheme

X-Ray data for crystals of compounds **43** (Fig. 11) and **46** (Fig. 12) were collected on a Nonius KappaCCD diffractometer.[22] Detector: 1242 (horizontal)×1152 (vertical) pixels, CCD pixel size is 22.5×22.5 mm which gives at the input a pixel of 110×110 mm (with 2×2 binning). Compound **43**: 99 frames with pfi scan and 27 frames with ω scan were collected, scan angle 2°, scan time 40 s/frame. Compound **46**: 132 frames with η scan were collected, scan angle 1.5°, scan time 450 s/frame. Unit cell parameters and data reduction with Denzo and Scalepak,[23] structures were

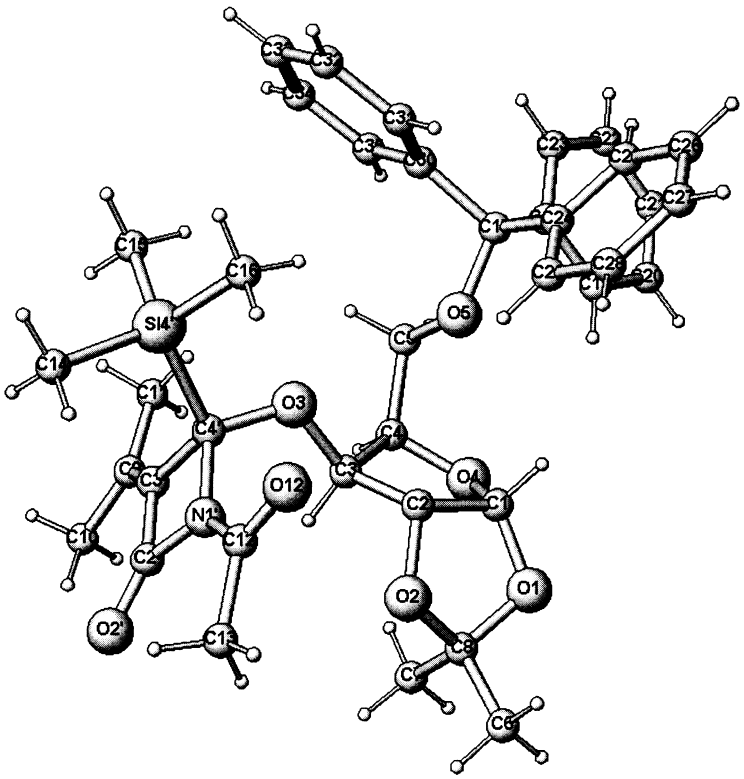


Figure 11. Molecular structure of the compound **43** with the crystallographic numbering scheme

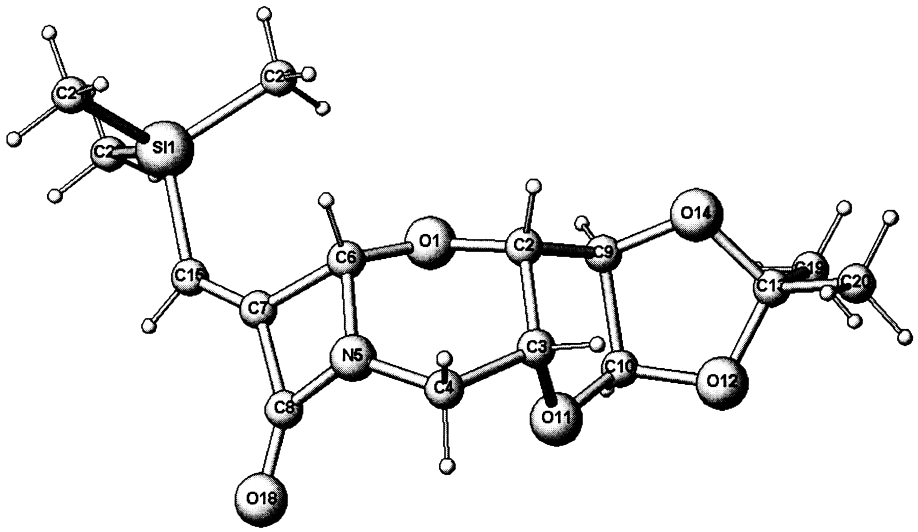


Figure 12. Molecular structure of the compound **46** with the crystallographic numbering scheme

solved with direct methods SHELXS-86[24] and refined with SHELXL-97,[25] molecular diagrams with ATOMS.[26] Crystal data and details of structure solution and refinement are shown in Table 3.[27]

3.14. (4′R) and (4′S) 5-O-t-Butyldimethylsilyl-3-O-[3′-(1-methylethylidene)azetidin-2′-on-4′-yl]-1,2-O-isopropylidene-α-D-xylofuranose **29** and **30**

In a ratio of ca. 3:1, compounds **29** and **30** were obtained from **12** according to the general procedure described earlier. Chromatographic separation on silica gel, using hexane:ethyl acetate, 7.5:2.5 v/v, as an eluent, gave **29**/**30** (48%): oil; IR (film) 1755, 3296 cm^{-1}. Compound **29**: ^1H NMR (200 MHz, $CDCl_3$) selective signals taken for the mixture: δ 1.31, 1.51 (2s, 6H, 2×Me), 1.86 (s, 3H, Me), 2.06 (s, 3H, Me), 4.12 (d, 1H, $J=3.2$ Hz, H-3), 4.52 (d, 1H, $J=3.7$ Hz, H-2), 5.56 (s, 1H, H-4′), 5.90 (d, 1H, $J=3.7$ Hz, H-1), 6.65 (br s, 1H, NH). Compound **30**: ^1H NMR ($CDCl_3$) selective signals taken for the mixture: 1.33, 1.52 (2s, 6H, 2×Me), 1.83 (s, 3H, Me), 2.05 (s, 3H, Me), 4.57 (d, 1H, $J=3.8$ Hz, H-2), 5.46 (s, 1H, H-4′), 5.89 (d, 1H, $J=3.8$ Hz, H-1), 6.87 (br s, 1H, NH); MS (EI, HR) m/z: $(M–CH_3)^+$ calcd for $C_{19}H_{32}O_6NSi$: 398.1999. Found: 398.2018; anal. taken for the mixture calcd for $C_{20}H_{35}O_6NSi$ (413.60): C, 58.08; H, 8.53; N, 3.39. Found: C, 58.19; H, 8.77; N, 3.44.

3.15. (4′R) 5-O-Acetyl-3-O-[N-acetyl-3′-(1-methylethylidene)azetidin-2′-on-4′-yl]-1,2-O-isopropylidene-α-D-xylofuranose **31**

A solution of **23**/**24** (0.05 g, 0.167 mmol) and DMAP (0.01g) in acetic anhydride and pyridine 1:2 v/v (2 mL) was stirred at room temperature until the reaction was complete (TLC). After 1 h, the mixture was poured into water, extracted with CH_2Cl_2, dried (Na_2SO_4), and evaporated. The residue was purified by flash chromatography using ethyl acetate:hexane, 3:7 v/v, as an eluent to give a mixture of 4′-stereoisomers in a ratio of ca. 2:1 (0.057 g, 89%).

The major compound **31** was isolated in pure form by crystallization from a Et_2O–hexane mixture: colorless crystals; mp 125–127°C; $[\alpha]_D^{22}=-48.2$ (0.8, CH_2Cl_2); IR (CH_2Cl_2) 1701, 1744, 1784 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 1.31, 1.51 (2s, 6H, 2×Me), 1.93 (s, 3H, Me), 2.15 (s, 3H, Me), 2.09 (s, 3H,$CH_3C(O)$–), 2.45 (s, 3H, $CH_3C(O)$–), 4.29 (dd, 1H, $J=6.0$ and 11.3 Hz, H-5a), 4.33 (dd, 1H, $J=6.5$ and 11.3 Hz, H-5b), 4.43 (ddd, 1H, $J=2.9$, 6.0 and 6.5 Hz, H-3), 4.53 (d, 1H, $J=3.7$ Hz, H-2), 4.59 (d, 1H, $J=2.9$ Hz, H-3), 5.73 (s, 1H, H-4′), 5.90 (d, 1H, $J=3.8$ Hz, H-1); MS (LSIMS, HR) m/z: $(M+Na)^+$ calcd for $C_{18}H_{25}O_8NNa$: 406.14779. Found: 406.14847; anal. calcd. for $C_{18}H_{25}O_8N$ (383.41): C, 56.39; H, 6.57; N, 3.65. Found: C, 56.67; H, 6.87; N, 3.35.

3.16. (4′R) and (4′S) 1,2-O-Isopropylidene-3-O-[3′-(1-methylethylidene)azetidin-2′-on-4′-yl]-α-D-xylofuranose **23**/**24**

A mixture of compounds **29**/**30** (1.3 g, 3.14 mmol) was dissolved in THF (40 mL) and TBAF·$3H_2O$ (0.99 g, 3.14 mmol) was added. The mixture was stirred for 15 min (TLC), then the solvent was evaporated and a crude product was separated on silica gel column, using hexane:ethyl acetate, 2.5:7.5 v/v, as an eluent, to give a mixture of stereoisomers **23**/**24** in a ratio of ca. 3:1 (0.87 g, 92%).

3.17. (4′R) and (4′S) 5-O-Deoxy-1,2-O-isopropylidene-3-O-(3′-(1-methylethylidene)-azetidin-2′-on-4′-yl)-D-xylofuranose **32** and **33**

A mixture of compounds **32**/**33** in a ratio of ~1.3:1, was obtained from **13** according to the procedure described earlier (40%): oil; IR (CH_2Cl_2) 1728, 1762, 3411 cm^{-1}; compound **32**: ^1H NMR

(200 MHz, $CDCl_3$) taken for the mixture: δ 3.96 (d, 1H, $J=3.0$ Hz, H-3), 4.51 (d, 1H, $J=3.8$ Hz, H-2), 5.56 (s, 1H, H-4′), 6.68 (br s, 1H, NH). Compound **33**: ^{1}H NMR (200 MHz, $CDCl_3$) taken for the mixture: δ 3.96 (d, 1H, $J=3.0$ Hz, H-3), 4.58 (d, 1H, $J=3.8$ Hz, H-2), 5.68 (s, 1H, H-4′), 6.65 (br s, 1H, NH); MS (HR, LSIMS) m/z: $(M+H)^+$ calcd for $C_{14}H_{22}O_5N$: 284.1498. Found: 284.1471; anal. taken for the mixture calcd for $C_{14}H_{21}O_5N$ (283.33): C, 59.35; H, 7.47; N, 4.94. Found: C, 58.97; H, 7.56; N, 4.76.

*3.18. (4′S) and (4′R) 1,4-Anhydro-2-deoxy-3-*O*-[3′-(1-methylethylidene)azetidin-2′-on-4′-yl]-5-*O*-trityl-D-*threo*-pentitol **34**/**35***

A mixture of compounds **34**/**35**, in a ratio of ~2.6:1, was obtained from **14** according to the procedure described earlier (17%). Products were separated into the pure components by chromatography. Compound **34**: oil; $[\alpha]_D^{22}=+23.5$ (c 0.15, CH_2Cl_2); IR (CH_2Cl_2) 1727, 1759, 3412 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.61 (s, 3H, Me), 1.87–1.93 (m, 1H, H-2a), 2.00 (s, 3H, Me), 2.03–2.10 (m, 1H, H-2b), 3.14 (dd, 1H, $J=5.8$ and 9.6 Hz, H-5a), 3.45 (dd, 1H, $J=6.1$ and 9.6 Hz, H-5b), 3.78–3.83 (m, 1H, H-1a), 3.88–3.92 (m, 1H, H-1b), 4.00 (ddd, 1H, $J=4.3$, 4.8 and 6.8 Hz, H-4), 4.34–4.37 (m, 1H, H-3), 5.36 (s, 1H, H-4′), 6.11 (br s, 1H, NH); MS (HR, LSIMS) m/z: $(M+Na)^+$ calcd for $C_{30}H_{31}O_4NNa$: 492.2151. Found: 492.2162. Compound **35**: oil; $[\alpha]_D^{22}=-9.2$ (c 0.35, CH_2Cl_2); IR (CH_2Cl_2) 1728, 1759, 3413 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.55 (s, 3H, Me), 1.98 (s, 3H, Me), 1.99–2.04 (m, 1H, H-2a), 2.12–2.20 (m, 1H, H-2b), 3.15 (dd, 1H, $J=5.4$ and 9.8 Hz, H-5a), 3.46 (dd, 1H, $J=6.4$ and 9.8 Hz, H-5b), 3.82–3.87 (m, 1H, H-4), 3.95–4.01 (m, 2H, H-1a, H-1b), 4.28 (m, 1H, H-3), 5.41 (s, 1H, H-4′), 6.12 (br s, 1H, NH); MS (HR, LSIMS) m/z: $(M+Na)^+$ calcd for $C_{30}H_{31}O_4NNa$: 492.2151. Found: 492.2140; anal. calcd for $C_{30}H_{31}O_4N$ (469.60): C, 76.73; H, 6.65; N, 2.98. Found: C, 76.50; H, 6.48; N, 2.83.

*3.19. 1,2-*O*-Isopropylidene-3-*O*-(1′-trimethylsilylpropa-1′,2′-dienyl)-5-*O*-trityl-α-D-xylo-furanose **37***

To a solution of **10** (2.65 g, 5.63 mmol) in dry THF (25 mL) at –50°C, *n*-BuLi (2.5 M in hexane, 2.7 mL, 6.75 mmol) was added. After 30 min at –30°C, trimethylsilyl chloride (0.86 mL, 6.75 mmol) was added. Stirring was continued for 45 min while warming up to room temperature. The mixture was diluted with 1:1 *t*-butyl methyl ether:hexane, washed with brine, dried ($MgSO_4$), and the solvent evaporated. The residue was purified on a silica gel column using hexane:ethyl acetate, 94:6 v/v, as an eluent to give **37** (2.35 g, 77%): oil; $[\alpha]_D^{22}=-9.4$ (c 0.65, CH_2Cl_2); IR (film) 1925 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: –0.04 (s, 9H, –$SiMe_3$), 1.32, 1.54 (2s, 6H, 2×Me), 3.29 (dd, 3H, $J=5.3$ and 9.8 Hz, H-5a), 3.39 (dd, 3H, $J=6.4$ and 9.8 Hz, H-5b), 4.30 (d, 1H, $J=3.2$ Hz, H-3), 4.37–4.45 (m, 1H, H-4), 4.47 (d, 1H, $J=3.8$ Hz, H-2), 5.11 (d, 1H, $J=8.8$ Hz, H_AH_BC=), 5.24 (d, 1H, $J=8.8$ Hz, H_AH_BC=), 5.86 (d, 1H, $J=3.8$ Hz, H-1); MS (EI, HR) m/z: M^+ calcd for $C_{33}H_{38}O_5Si$: 542.2488. Found: 542.2496.

3.20. 1,2-O-Isopropylidene-3-O-(3′-methyl-1′-trimethylsilylbuta-1′,2′-dienyl)-5-O-trityl-α-D-xylo-furanose **38**

Compound **38** was obtained from **11** according to the procedure described above (87%): oil; $[\alpha]_D=+8.6$ (c 0.51, CH_2Cl_2); IR (film) 1934 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ: –0.06 (s, 9H, –$SiMe_3$), 1.31, 1.53 (2s, 6H, 2×Me), 1.70 (s, 3H, Me), 1.78 (s, 3H, Me), 3.35 (d, 2H, $J=16.9$ Hz, H-5a, H-5b), 4.26 (d, 1H, $J=3.2$ Hz, H-3), 4.35–4.47 (m, 1H, H-4), 4.45 (d, 1H, $J=3.8$ Hz, H-2),

5.83 (d, 1H, $J=3.7$ Hz, H-1); MS (EI, HR) m/z: M^+ calcd for $C_{35}H_{42}O_5Si$: 570.28015. Found: 570.27947; anal. calcd for $C_{35}H_{42}O_5Si$ (570.82): C, 73.65; H, 7.42. Found: C, 73.64; H, 7.60.

*3.21. (4′R) and (4′S) 1,2-*O*-Isopropylidene-3-*O*-[3′-methylene-4′-trimethylsilylazetidin-2′-on-4′-yl]-5-*O*-trityl-α-D-xylofuranose **39** and **41***

In a ratio of ~18:1, compounds **39** and **41** were obtained from **37** according to the general procedure described earlier. Chromatographic separation on silica gel, using hexane:ethyl acetate, 7:3 v/v, as an eluent, gave **39** (28%) and **41** (2%). Compound **39**: oil; $[\alpha]_D^{22}=-38.9$ (c 0.65, CH_2Cl_2); IR (film) 1757, 3237 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: –0.08 (s, 9H, –$SiMe_3$), 1.31, 1.53 (2s, 6H, 2×Me), 2.99 (dd, 1H, $J=3.6$ and 10.2 Hz, H-5a), 3.47 (dd, 1H, $J=6.9$ and 10.2 Hz, H-5b), 4.16 (d, 1H, $J=3.4$ Hz, H-3), 4.29 (d, 1H, $J=3.8$ Hz, H-2), 4.42–4.49 (m, 1H, H-4), 4.60 (d, 1H, $J=1.8$ Hz, H_AH_BC=), 5.58 (d, 1H, $J=1.8$ Hz, H_AH_BC=), 5.88 (d, 1H, $J=3.8$ Hz, H-1), 6.60 (br s, 1H, NH); MS (HR, LSIMS) m/z: $(M+Na)^+$ calcd for $C_{34}H_{39}O_6NSiNa$: 608.2444. Found: 608.2454. Compound **41**: oil; $[\alpha]_D^{22}=-2.4$ (c 0.4, CH_2Cl_2); IR (film) 1759, 3201 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: –0.11 (s, 9H, –$SiMe_3$), 1.31, 1.53 (2s, 6H, 2×Me), 3.02 (dd, 1H, $J=6.8$ and 9.4 Hz, H-5a), 3.50 (dd, 1H, $J=5.3$ and 9.4 Hz, H-5b); 4.25 (d, 1H, $J=3.7$ Hz, H-2), 4.31 (d, 1H, $J=3.0$ Hz, H-3), 4.33–4.43 (m, 1H, H-4), 5.28 (d, 1H, $J=1.7$ Hz, H_AH_BC=), 5.84 (d, 1H, $J=3.7$ Hz, H-1), 5.87 (br s, 1H, NH), 5.91 (d, 1H, $J=1.7$ Hz, H_AH_BC=); MS (HR, LSIMS) m/z: $(M+Na)^+$ calcd for $C_{34}H_{39}O_6NSiNa$: 608.2444. Found: 608.2453; anal. calcd for $C_{34}H_{39}O_6NSi$ (585.79): C, 69.72; H, 6.70; N, 2.39. Found: C, 69.43; H, 6.91; N, 2.27.

*3.22. (4′R) and (4′S) 1,2-*O*-Isopropylidene-3-*O*-[3′-(1-methylethylidene)-4′-trimethylsilylazetidin-2′-on-4′-yl]-5-*O*-trityl-α-D-xylofuranose **40** and **42***

In a ratio of ~3:1, compounds **40** and **42** were obtained from **38** according to the general procedure described earlier. Chromatographic separation on silica gel, using hexane:ethyl acetate, 8:2 v/v, as an eluent, gave **40** (62%) and **42** (21%). Compound **40**: oil; $[\alpha]_D^{22}=-15.0$ (c 0.63, CH_2Cl_2); IR (film) 1737, 3216 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: –0.06 (s, 9H, –$SiMe_3$), 1.18 (s, 3H, Me), 1.30, 1.53 (2s, 6H, 2×Me), 1.98 (s, 3H, Me), 3.10 (dd, 1H, $J=2.2$ and 10.6 Hz, H-5a), 3.43 (dd, 1H, $J=7.8$ and 10.6 Hz, H-5b), 4.07 (d, 1H, $J=3.6$ Hz, H-3), 4.44 (d, 1H, $J=3.8$ Hz, H-2), 4.48 (ddd, 1H, $J=2.2$, 3.6 and 7.8 Hz, H-4), 5.89 (d, 1H, $J=3.8$ Hz, H-1), 6.13 (br s, 1H, NH); MS (HR, LSIMS) m/z: $(M+Na)^+$ calcd for $C_{36}H_{43}O_6NSiNa$: 636.27576. Found: 636.27641; anal. calcd for $C_{36}H_{43}O_6Si$ (613.84): C, 70.44; H, 7.06; N, 2.28. Found: C, 70.29; H, 7.10; N, 2.17. Compound **42**: oil; $[\alpha]_D=+30.3$ (c 0.65, CH_2Cl_2); IR (film) 1738, 3168 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ: –0.11 (s, 9H, –$SiMe_3$), 1.29, 1.52 (2s, 6H, 2×Me), 1.80 (s, 3H, Me), 2.10 (s, 3H, Me), 3.04 (dd, 1H, $J=5.2$ and 9.9 Hz, H-5a), 3.42 (dd, 1H, $J=6.2$ and 9.9 Hz, H-5b), 4.24 (d, 1H, $J=3.3$ Hz, H-3), 4.27 (d, 1H, $J=3.7$ Hz, H-2), 4.35 (ddd, 1H, $J=3.2$, 5.2 and 6.2 Hz, H-4), 5.55 (br s, 1H, NH), 5.86 (d, 1H, $J=3.7$ Hz, H-1); MS (HR, LSIMS) m/z: $(M+Na)^+$ calcd for $C_{36}H_{43}O_6NSiNa$: 636.27576. Found: 636.27452; anal. calcd for $C_{36}H_{43}O_6Si$ (613.84): C, 70.44; H, 7.06; N, 2.28. Found: C, 69.91; H, 7.17; N, 2.30.

*3.23. (4′R) 3-*O*-[*N*-Acetyl-3′-(1-methylethylidene)-4′-trimethylsilylazetidin-2′-on-4′-yl]-1,2-*O*-isopropylidene-5-*O*-trityl-α-D-xylofuranose **43***

Compound **43** was obtained from **40** according to the procedure described for **31** (76%): colorless crystals; mp 190–192°C; $[\alpha]_D^{22}=+25.9$ (c 0.42, CH_2Cl_2); IR (CH_2Cl_2) 1692, 1766 cm^{-1}; ^1H

NMR (500 MHz, $CDCl_3$) δ: –0.01 (s, 9H, $-SiMe_3$), 1.28, 1.50 (2s, 6H, 2×Me), 1.34 (s, 3H, Me), 2.12 (s, 3H, Me), 2.38 (s, 3H, acetyl), 3.11 (dd, 1H, J = 2.4 and 10.4 Hz, H-5a), 3.42 (dd, 1H, J = 7.4 and 10.4 Hz, H-5b), 4.07 (d, 1H, J = 4.7 Hz, H-3), 4.40 (d, 1H, J = 4.0 Hz, H-2), 4.48 (ddd, 1H, J = 2.4, 4.6 and 7.4 Hz, H-4), 5.91 (d, 1H, J = 4.0 Hz, H-1); MS (HR, EI) m/z: M^+ calcd for $C_{38}H_{45}O_7NSi$: 655.2965. Found: 655.2969; anal. calcd for $C_{38}H_{45}O_7NSi$ (655.89): C, 69.59; H, 6.91; N, 2.13. Found: C, 69.57; H, 6.86; N, 2.21.

*3.24. (4′R) 1,2-*O*-Isopropylidene-3-*O*-[3′-methylene-4′-trimethylsilylazetidin-2′-on-4′-yl]-α-D-xylofuranose **44***

Compound **44** was obtained from **39** according to the procedure described for **23**/**24** (78%); oil, $[\alpha]_D^{22}$ = –62.0 (c 0.47, CH_2Cl_2); IR (film) 1734, 1769, 3396, 3601 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.14 (s, 9H, $-SiMe_3$), 1.30, 1.47 (2s, 6H, 2×Me), 1.87 (br s, 1H, –OH), 3.69–3.75 (m, 1H, H-5a), 3.84–3.89 (m, 1H, H-5b), 4.29–4.33 (m, 2H, H-3, H-4), 4.39 (d, 1H, J = 3.7 Hz, H-2), 5.35 (d, 1H, J = 1.6 Hz, H_AH_BC=), 5.89 (d, 1H, J = 3.7 Hz, H-1), 5.91 (d, 1H, J = 1.6 Hz, H_AH_BC=), 6.76 (br s, 1H, NH); MS (EI, HR) m/z: M^+ calcd for $C_{14}H_{22}O_6NSi$: 328.1216. Found: 328.1227.

*3.25. (4′R) 1,2-*O*-Isopropylidene-3-*O*-[3′-methylene-4′-trimethylsilylazetidin-2′-on-4′-yl]-5-*O*-tosyl-α-D-xylofuranose **45***

Compound **45** was obtained from **44** by the standard tosylation procedure (82%): oil, $[\alpha]_D^{22}$ = –40.7 (c 0.21, CH_2Cl_2); IR (film) 1761, 3267 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.12 (s, 9H, $-SiMe_3$), 1.27, 1.39 (2s, 6H, 2×Me), 2.45 (s, 3H, tosyl), 4.08 (dd, 1H, J = 5.6 and 9.8 Hz, H-5a), 4.18 (dd, 1H, J = 6.9 and 9.8 Hz, H-5b), 4.26 (m, 1H, H-4), 4.30 (d, 1H, J = 3.3 Hz, H-3), 4.39 (d, 1H, J = 3.6 Hz, H-2), 5.47 (d, 1H, J = 1.9 Hz, H_AH_BC=), 5.78 (d, 1H, J = 3.6 Hz, H-1), 5.94 (d, 1H, J = 1.9 Hz, H_AH_BC=), 6.76 (br s, 1H, NH), 7.35, 7.78 (2m, 4H, tosyl); MS (EI, HR) m/z: M^+ calcd for $C_{21}H_{28}O_8NSi$: 482.1305. Found: 482.1318.

*3.26. (4′S) 5-Deoxy-1,2-*O*-isopropylidene-3-*O*:5-*C*-[E-3′-(trimethylsilylmethylene)azetidin-2′-on-1′,4′-diyl)-α-D-xylofuranose **46** (Fig. 12)*

Compound **46** was obtained from **45** according to the procedure described for **27**/**28** (18%): colorless crystals; mp 157–158°C (from AcOEt–hexane); $[\alpha]_D^{22}$ = –75.2 (c 0.3, CH_2Cl_2); IR (CH_2Cl_2) 1765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 0.17 (s, 9H, $-SiMe_3$), 1.31, 1.49 (2s, 6H, 2×Me), 3.43 (dd, 1H, J = 4.0 and 15.2 Hz, H-5a); 4.06 (m, 1H, H-4), 4.17 (m, 1H, H-3), 4.18 (d, 1H, J = 15.2 Hz, H-5b), 4.50 (d, 1H, J = 3.7 Hz, H-2), 5.19 (d, 1H, J = 1.0 Hz, H-4′), 5.88 (d, 1H, J = 3.7 Hz, H-1), 6.32 (d, 1H, J = 1.0 Hz, TMSHC=); MS (EI, HR) m/z: M^+ calcd for $C_{15}H_{23}O_5NSi$: 325.1345. Found: 325.1354.

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27. Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre, Cambridge, UK, as a supplementary publication.