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A new synthetic approach to 5-dethia-4-methyl-5-oxacephems

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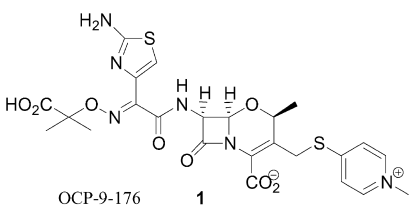
Abstract—Starting from L-ethyl lactate and 4-vinyloxy-azetidin-2-one the diastereomeric (4*S*,6*R*)- and (4*S*,6*S*)-4-methyl-5-oxa-3-methylene and 3-oxo-cephams were obtained. The formation of the cepham skeleton proceeds with a diastereomeric excess up to 80%, depending on catalyst and reaction conditions. For comparison, the corresponding racemic cephams lacking a methyl at C-4 or with a *gem*-dimethyl group at C-4 were synthesized.

The synthesis of 5-oxacephalotin[1] and 5-oxacephamandol,[2] characterized by a higher activity than their natural congeners containing sulfur, as well as the isolation of clavulanic acid,[3] a potent inhibitor of β-lactamase enzymes, directed attention of academic and industrial laboratories to the synthesis of oxygen analogs of penicillins and cephalosporins.[4–6] There are four different synthetic methods proposed for construction of the basic skeleton of these compounds. Two of these involve nucleophilic substitution at C-4 of the azetidin-2-one, carried out as an inter- or intramolecular process[4,6] and the remaining two methods involve cycloaddition reactions between ketenes and iminoethers,[7] or between vinyl ethers and isocyanates.[5]

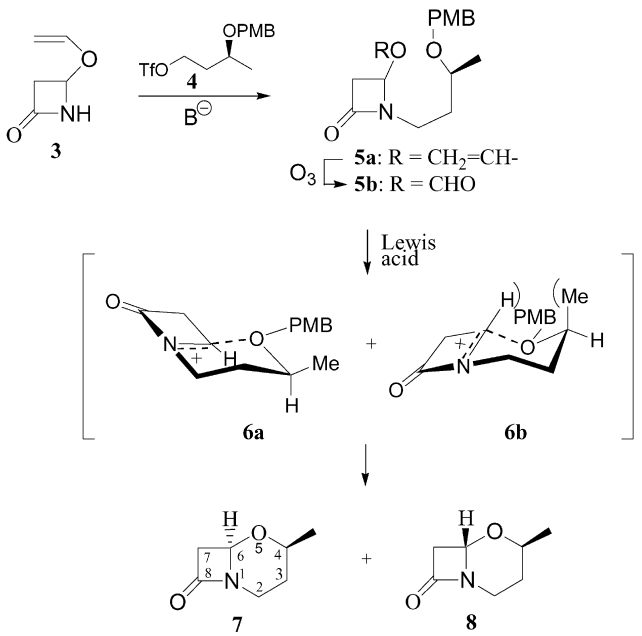
During 1988, the Merck and Meiji groups[8] reported a new oxacepham OCP-9-176 (**1**) with a 4β-methyl substituent. Introduction of the 4β-methyl substituent to the oxacephem skeleton apparently increases the stability of the antibiotics to β-lactamases without significant change of the activity.



In the course of our studies on the syntheses of clavams and 5-oxacephams we have proposed two new methodologies.[5,9]

The first one is based on the [2+2]cycloaddition of isocyanates to the chiral vinyl ethers resulting in a formation of 4-alkoxy-azetidin-2-ones, suitable for further transformations.[5] For example, the oxacephem **2** [structurally related to OCP-9-176 (**1**)] was obtained in a few step synthesis from L-rhamnal.[10]

The alternative methodology, shown in Scheme 1, employed 4-vinyloxyazetidin-2-one **3** which can be easily *N*-alkylated with a chiral *p*-methoxybenzyl ether **4** containing a suitable leaving group.[9] Subsequently, the vinyloxy



Scheme 1.

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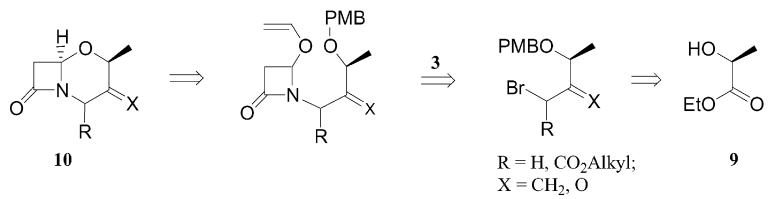
substituent can be oxidized to a 4-acyloxy residue. The Lewis acid-promoted cyclization of **5** via nucleophilic displacement of the 4-vinyloxy or 4-acyloxy group by the oxygen atom of the *p*-methoxybenzyl ether led to the mixture of oxacephams **7** and **8** (5:1 ratio, respectively).[9] The favored geometry of the transition state of the cyclization is probably closer to structure **6a**, which does not show an interaction between an axial methyl and the iminium cation, than to structure **6b**. The diastereoselectivity of the intramolecular substitution at C-4 of the β-lactam ring in **5b** is much better than that observed for the intermolecular condensation of 4-acetoxy-azetidin-2-one with chiral alcohols.[11] In the present work we report studies toward a stereo-controlled approach to the 4-methyl-5-oxacephems bearing functional groups at the C-2, C-3 carbon atoms, amenable to further transformations.

Retrosynthetic analysis depicted in Scheme 2 shows that starting with ethyl L-lactate **9** and using methodology involving the intermediary azetidinone **3** should provide an attractive approach to the oxacepham **10**. We assume that the crucial step of the planned synthesis should proceed via a low-energy transition state, like structure **6a**. Consequently, the (6*R*) configuration of compound **10** should be expected.

Bearing in mind the above presented speculation, we synthesized compound **13** from ethyl lactate **9** in a three-step sequence. (Scheme 3). The *p*-methoxybenzylation of **9**, following the known procedure[12] (NaH, PMB-Cl, DMF, THF, RT), unexpectedly gave the racemic ether ±**11**, in contrast with the published results. The optically pure compound **11** was obtained via benzylation with the *p*-methoxybenzyl imidate in the presence of an acid catalyst, according to Shimano et al.[13] procedure. The Claisen condensation of *t*-butyl acetate and lactate **11** according to Pastor et al.[14] led to β-ketoester **12** in 92% yield. The bromination of **12** using copper (II) bromide in the presence of a Koser's reagent[15] gave a mixture of starting ketoester **12**, mono-bromide **13**, and dibromide **14** in a 1:9:1 ratio, respectively. Purification of the products by flash chromatography on silica gel afforded unexpectedly compounds **13** and **14** in 37 and 34% yield respectively.

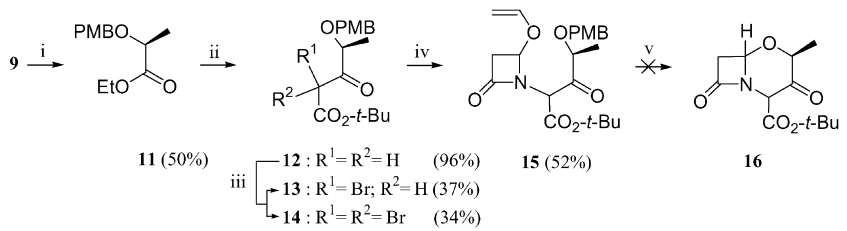
The ^{1}H NMR spectra of equimolar amounts of **12** and **14** in $CDCl_3$ solution, recorded after 24 h, indicated the presence of a mixture of **12**, **13** and **14** in the same proportion as in the crude bromination product. This experiment indicated that the state of equilibrium exists between mono-bromide **13**, β-ketoester **12** and dibromide **14**. The chromatographic separation of the less-polar dibromide **14** shifts the equilibrium of the reaction product back to the original mixture. Therefore, the crude bromide **13** was used in the next step. The alkylation of **3** with crude **13** proceeded smoothly under phase-transfer conditions (K_2CO_3, Bu_4NBr, acetonitrile, RT) to give **15** in 52% yield as a mixture of two diastereomers. The mixture **15** was not separated and configurations of components were not assigned.

Based on our earlier results,[10,11] we assumed that the cyclization of **15** could proceed with a relatively high stereoselectivity to give a mixture of oxacephams **16**. Since the nucleophilic substitution proceeds via iminium cation,[16] the configuration at C-4 of the azetidin-2-one ring in the

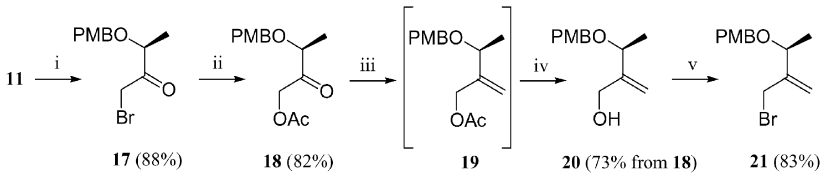


10 **9**

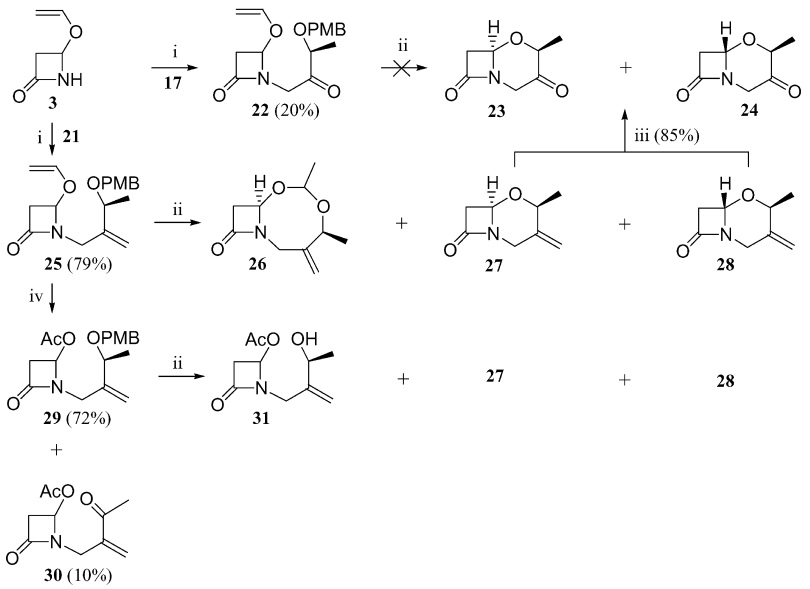
Scheme 2.



Scheme 3. *Reagents and conditions*: (i) *p*-methoxybenzyl 2,2,2-trichloroacetimidate, 10-camphor-sulphonic acid, CH_2Cl_2, overnight at rt; (ii) HMDS-Li, THF, −50°C, 15 min, *t*-butyl acetate then 0°C and acetic acid; (iii) $CuBr_2$, hydroxy(tosyloxy)iodobenzene, CH_3CN, 0°C, 5 min; (iv) comp. **3**, K_2CO_3, Bu_4NBr, CH_3CN, 24 h, rt; (v) $BF_3{\cdot}Et_2O$, CH_2Cl_2.



Scheme 4. *Reagents and conditions*: (i) CH_2Br_2, MeLi, THF, −78°C; (ii) AcONa, DMF, 2 h, rt; (iii) $MePPh_3^+I^-$, THF, BuLi, −78°C; (iv) K_2CO_3, MeOH, 3 h, rt; (v) imidazole, $Ph_3P{\cdot}Br_2$, CH_2Cl_2, 10 min, 0°C.



Scheme 5. *Reagents and conditions*: (i) $Bu_4N^+HSO_4^-$, BuLi, THF, 30 min at −78°C then gradually to rt; (ii) various Levis acids and conditions, see Table 1; (iii) CH_2Cl_2/MeOH, O_3, 10 min at −78°C then Me_2S; (iv) PCC/silica gel, CH_2Cl_2, 6 h, reflux.

substrate should not influence the stereoselectivity of cyclization. We expected that the major compound should have the (*R*)-configuration at C-6 (Scheme 1). Unfortunately, the mixture of **15** when treated with the $BF_3{\cdot}Et_2O$ underwent decomposition, probably due to the instability of either the easy enolizable substrate **15** or product **16**, under the reaction conditions. This assumption led us to revise our original plan and to propose use of compound **22**, lacking, in comparison to the **15**, the *t*-butyloxycarbonyl group.

The bromoketone **17** was prepared from lactate **11** in 88% yield, employing the one-step general procedure (Scheme 4).[17] The alkylation of **3** with **17** under the PTC conditions (K_2CO_3, Bu_4NBr, acetonitrile), or in the presence of common bases such as triethylamine, DBU or diisopropylethylamine failed. Fortunately, treatment of an equimolar mixture of β-lactam **3** and tetrabutylammonium hydrogen sulfate with two equivalents of butyllithium in THF at −78°C, followed by the addition of **17** in one portion, resulted in the formation of the *N*-alkylated product **22** in 20% yield (Scheme 5).

The isolated compound **22**, during attempted cyclization in the presence of $BF_3{\cdot}Et_2O$ did not furnish the expected oxacephams **23**, **24** and only tarry products were obtained.

The well-documented examples of the synthesis of oxacephems or oxacephams with an exocyclic C-3 methylene substituent via acid-catalyzed nucleophilic substitution at the β-lactam C-4 carbon, allowed us to expect that replacement of the carbonyl group in the side chain by a double bond should provide Lewis acid-stable substrates (and products, as well).[4] In particular, the literature example[4] directed our attention to a new substrate **25**, that should be suitable for cyclization. The compound **25** was obtained by a standard reaction sequence. The bromoketone **17** was transformed into the acetate **18**, which was subsequently subjected to a Wittig olefination (Scheme 4). The crude olefin **19** was hydrolyzed to give allyl alcohol **20**. The bromination of **20** with triphenylphosphine dibromide in a presence of imidazole yielded **21**. The alkylation of **3** with the bromide **21** provided **25** as an equimolar mixture of diastereomers in 79% yield (Scheme 5). The vinyloxy group in **25** was oxidized with PCC on silica gel to give a mixture of respective 4-acetates **29** in 72% yield. The acetate **29** was accompanied by a

Table 1. Catalysts and reaction conditions of cyclizations of **25**, **29** and **31**.

Substrate	Lewis acid	Amount (equiv.)	Reaction time, temperature (°C)	Yield of **27** and **28** (%)	dr **27**:**28**	By-products and comments
25	$BF_3{\cdot}Et_2O$	1	15 min; rt	30	4:1	
	$SnCl_2$	1	50 min; rt	20	9:1	
	TMS-Cl	4				
	$SnCl_4$ 0.5	0.5	50 min; rt	14	2.8:1	**26** (12%)
29	$SnCl_4$	1	2.5 h; rt	50	4:1	
	$SnCl_4$	1	10 min; −45			**31** (60%)
	$TiCl_4$	1	5 min; 0			**31** (52%)
	$BF_3{\cdot}Et_2O$	1	1.5 h; 0	50	4:1	
	$SnCl_2$	1	50 min; rt	50	8.8:1	
	TMS-Cl	4				
31	$SnCl_4$	0.5	20 min; rt	50	9:1	
	$TiCl_4$	1	12 h; rt			Decomposition
	$BF_3{\cdot}Et_2O$	1	30 min; rt	20	7:1	

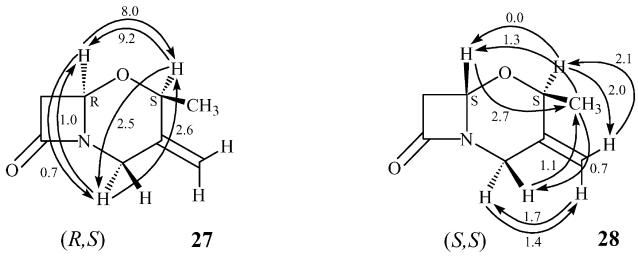


Figure 1. The NOE effects in ^{1}H NMR spectra of **27** and **28**.

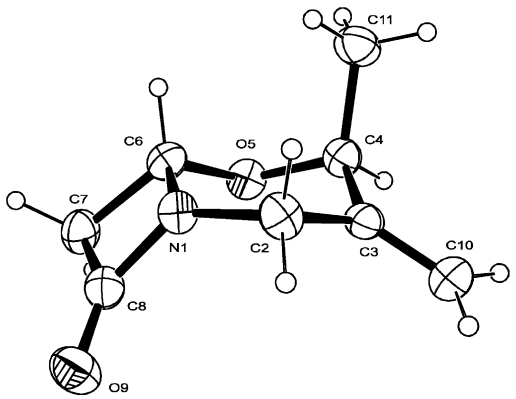


Figure 2. ORTEP diagram of compound **28**.

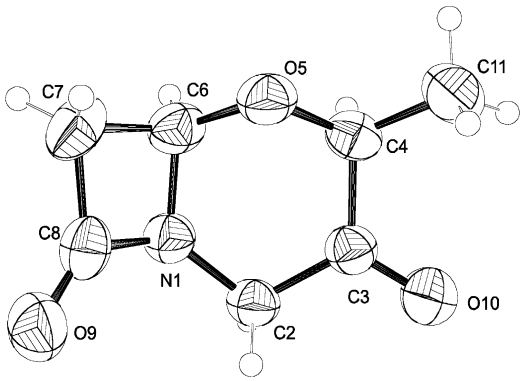


Figure 3. ORTEP diagram of compound **23**.

minute amount of a ketone **30**. The compounds **25** and **29** were subjected to the cyclization in the presence of a Lewis acid.

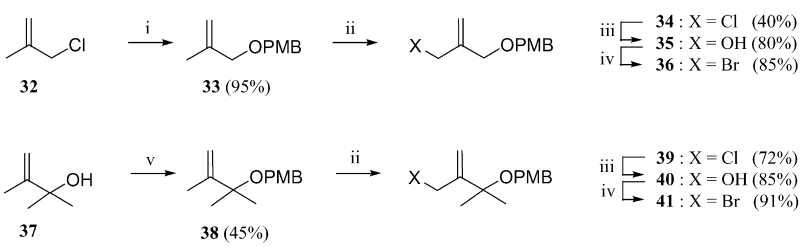
Table 1 shows that the 4-acetoxy group reacts more readily than the 4-vinyloxy one. Moreover, the compound **25** in the presence of $SnCl_4$ gave a mixture of acetals **26** together with cephams **27** and **28**. The acetate **29** treated with an equimolar amount of $SnCl_4$ or $TiCl_4$ formed the corresponding complexes immediately, which in the presence of moisture underwent subsequent debenzylation to provide alcohol **31**. The effective cyclization required about 1 h but did not proceed beyond approx. 50% conversion. The best yield and selectivity were obtained for the acetate **29** and $SnCl_2$/TMS-Cl mixture. As we expected, in all cases the desired diastereomer (6*R*)-**27** prevails. The configurations of both diastereomers **27** and **28** were assigned by analysis and comparison of respective NOEs (Fig. 1). The assignments made by ^{1}H NMR were corroborated by the X-ray structure analysis made for **28** (Fig. 2).[18] Since the isomers **27** and **28** were not easy to separate, for the next step they were used as a mixture.

The double bonds in **27** and **28** can be easily oxidized to the carbonyl groups providing ketones **23** and **24**, respectively. The compounds **23** and **24** were separated into the pure individual components that offer a convenient starting point for further transformations leading to the substituted 5-oxacephems. The structure and configuration of **23** was proved by the X-ray structure analysis (Fig. 3).[18]

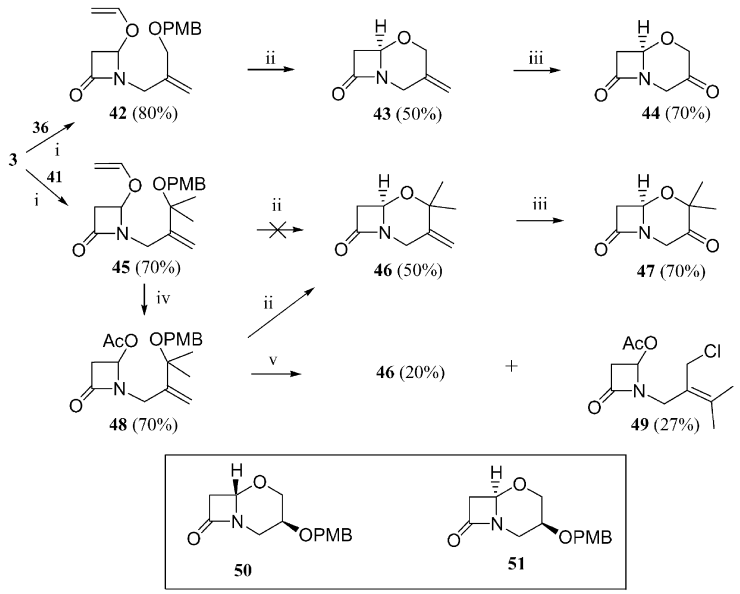
It was of interest to compare the results found for cyclization of **25**, **29** and **31** with the corresponding reactions leading to their congeners that are not chiral: unsubstituted at C-4 **43** and **44**, and 4,4-dimethyl substituted **46** and **47**. As a starting material, ether **33**[19] and alcohol **37**[20] were selected. Both compounds **33** and **37** were transformed into the respective bromo-ethers **36** and **41** using a standard reaction sequence (Scheme 6).

The *N*-alkylation of **3** with **36** and **41** gave compounds **42** and **45** (Scheme 7). The β-lactam **42** treated with $BF_3{\cdot}Et_2O$ afforded oxacepham **43** in 50% yield. The cyclization of **45**, however, was not successful under those conditions. The successful formation of oxacepham **46** required prior oxidation of the vinyloxy group to the acetate **48**, which was subjected to the cyclization in the presence of $BF_3{\cdot}Et_2O$ to give **46** in 50% yield. When the **48** was treated with $SnCl_2$/TMS-Cl, the product **46** was obtained in 20% yield only and it was accompanied by 30% of chloride **49**. Ozonolysis of **43** and **46** led to corresponding ketones **44** and **47** in a good yield. Compounds **50** and **51**, which are related to the ketone **44**, have recently been obtained (in a 7:3 ratio) by us from glyceraldehyde using three other methodologies.[11]

It was shown that 5-oxacephams with an 3-exo-methylene



Scheme 6. *Reagents and conditions*: (i) PMB-OH, NaH, DMF, 1 h rt; (ii) $LiClO_4$, pyridine, SO_2Cl_2, CH_2Cl_2, 10 min at −78°C; (iii) THF/H_2O, K_2CO_3, reflux, 6 h; (iv) imidazole, $Ph_3P{\cdot}Br_2$, CH_2Cl_2, 10 min 0°C; (v) PMB-Cl, NaH, DMF, 40°C.



Scheme 7. *Reagents and conditions*: (i) $Bu_4N^+HSO_4^-$, BuLi, THF, −78°C gradually to 0°C; (ii) $BF_3{\cdot}Et_2O$, CH_2Cl_2; (iii) CH_2Cl_2/MeOH, O_3, 10 min at −78°C then Me_2S; (iv) PCC/silica gel, CH_2Cl_2 6 h, reflux; (v) $SnCl_2$, TMS-Cl, CH_2Cl_2.

group or a 3-carbonyl group (suitable for further functionalization) can be easily obtained starting from 4-vinyloxy-azetidin-2-one **3**. The introduction of a methyl group to C-4 of the cepham skeleton with good stereoselectivity can be performed using ethyl lactate **9** as a chiral starting material.

1. Experimental

1.1. General

The melting points are uncorrected. The optical rotations were measured using JASCO Dip-360 and P-1020 digital polarimeters. The IR spectra were obtained using FT-IR-1600 Perkin–Elmer spectrophotometer. The ^1H NMR and ^{13}C NMR spectra were recorded using Bruker AM 500 spectrometer. The mass spectra were recorded using AMD 604 mass spectrometer. The column chromatography was performed on Merck Kiesel gel (230–400 mesh). The ozonolysis was carried out using Buchi Ozone Generator OZI.

All reactions were carried out under argon atmosphere using anhydrous solvents. The reagents were purchased from commercial supplies and used without further purification, unless noted. The tetrahydrofuran was distilled from Na and benzophenone ketyl, the ethylene chloride and toluene were distilled from CaH_2.

1.1.1. (2*S*) Ethyl 2-(*p*-methoxybenzyloxy)-propanoate (11). The compound **11** was obtained according to Shimano et al.[13] procedure.

1.1.2. (4*S*) *tert*-Butyl 4-(*p*-methoxybenzyloxy)-3-oxo-pentanoate (12). To a solution of HMDS-Li (12 mL 1 M solution in hexane, 12 mmol) in THF (40 mL), at −50°C, the *tert*-butyl acetate (1.4 g, 12 mmol) was added dropwise. The reaction mixture was stirred vigorously for 15 min, and the (*S*) ethyl 2-(*p*-methoxybenzyloxy)-propionate **11** (1.2 g, 5 mmol) was added. The temperature was allowed to rise to room temperature then the mixture was cooled to 0°C and acetic acid (0.72 g) was added dropwise. Subsequently, the reaction mixture was diluted with *t*-BuOMe (80 mL), washed with saturated $NaHCO_3$ aq. solution (80 mL), brine (80 mL), dried and evaporated. The crude product was purified by chromatography using *t*-BuOMe/hexane/toluene (3:17:80 v/v/v) as an eluant to give **12** (1.47 g; 96%). Oil; $[\alpha]_D=-6.2$ (*c* 0.92, CH_2Cl_2); IR (film) 1742, 1716, 1514, 1456, 1249 cm^{-1}; ^1H NMR ($CDCl_3$): 1.34 (d, 3H, *J*=6.5 Hz, CH_3), 1.45 (bs, 9H, *t*-Bu), 3.51 (s, 2H, H-2,2), 3.81 (s, 3H, OMe), 3.99 (q, 1H, *J*=6.5 Hz, H-4), 4.49 (bs, 2H, Bn), 7.27, 6.89 (2m, 4H, Aryl); ^{13}C NMR δ 16.8, 27.9, 45.8 (t), 55.3, 71.6 (t), 79.9, 81.8 (s), 113.8, 129.1 (s), 129.6, 159.5 (s), 166.6 (s), 205.8 (s); MS (HR-ESI) *m/z*: $(M+Na)^+$ requires for $C_{17}H_{24}O_5Na$: 331.1516. Found: 331.1528; Anal. calcd for $C_{17}H_{24}O_5$ (308.37): C, 66.21; H, 7.84. Found: C, 66.08; H, 7.67.

1.1.3. (2*R*,4*S*) and (2*S*,4*S*) *tert*-Butyl 2-bromo-4-(*p*-methoxybenzyloxy)-3-oxo-pentanoates (13) and (4*S*) *tert*-butyl 2,2-dibromo-4-(*p*-methoxybenzyloxy)-3-oxo-pentanoate (14). To the vigorously stirred solution of compound **12** (7.7 g, 25 mmol) in acetonitrile (250 mL), at 0°C, the copper (II) bromide (7.26 g, 35.5 mmol), and hydroxy(tosyloxy)iodobenzene (9.8 g, 25 mmol) was added and the mixture was stirred at 0°C for 5 min. Subsequently, it was poured into cold water, extracted with CH_2Cl_2, dried, and concentrated. The crude products were purified by flash chromatography using toluene/AcOEt (97:3 v/v) as an eluant to give **13** (3.57 g, 37%) and **14** (3.96 g, 34%).

^1H NMR spectrum of a crude mixture shows compounds **12**, **13** and **14** in a ratio 1:9:1.

Compound **13**. Oil; IR (film) 1731, 1613, 1514, 1370,

1249 cm^{-1}; ^1H NMR (selected signals for the mixture of diastereomers; $CDCl_3$): 1.52–1.33 (m, 24H, *t*-Bu and H-5), 3.81 (bs, 6H, OMe), 4.32–4.13 (m, 2H, H-4), 4.61–4.43 (m, 4H, Bn), 5.27, 5.22 (2s, 2H, H-2), 7.27, 6.88 (2 m, 8H, Aryl); Anal. calcd for $C_{17}H_{23}BrO_5$ (387.27): C, 66.21; H, 7.84. Found: C, 66.08; H, 7.67.

Compound **14**. Mp 53–54°C; IR (CH_2Cl_2) 1761, 1742, 1515, 1248 cm^{-1}; ^1H NMR ($CDCl_3$): 1.34 (s, 9H, *t*-Bu), 1.41 (d, 3H, *J*=6.6 Hz, CH_3), 3.81 (s, 3H, OMe), 4.62–4.43 (m, 3H, H-4, Bn), 7.28, 6.86 (2 m, 4H, Aryl); Anal. calcd for $C_{17}H_{22}Br_2O_5$ (466.16): C, 43.80; Br, 34.28; H, 4.76. Found: C, 42.59; Br, 34.42; H, 4.85.

1.1.4. (2*R*,4*S*,4′*R*), (2*R*,4*S*,4′*S*), (2*S*,4*S*,4′*R*), (2*S*,4*S*,4′*S*) *tert*-Butyl 4-(*p*-methoxybenzyloxy)-3-oxo-2-(4′-vinyloxy-azetidin-2′-on-1′-yl)-pentanoates (15). To a stirred suspension of K_2CO_3 (1.66 g, 12 mmol) and Bu_4NBr (0.65 g, 2 mmol) in CH_3CN (10 mL), the crude compound **13** (0.93 g, 2.4 mmol) and 4-vinyloxy-azetidin-2-one (0.22 g, 1.9 mmol) were added. The mixture was stirred at room temperature for 24 h. Subsequently, it was diluted with toluene (10 mL), the precipitate was filtered off, the filtrate was poured into water (50 mL), extracted with toluene (3×20 mL), dried, and evaporated. The crude product was purified by flash chromatography using hexane/*t*-BuOMe (75:25 v/v) as an eluant to afford a mixture of two diastereomers (0.42 g, 52%). Oil; IR (CH_2Cl_2) 1780, 1740, 1613, 1514, 1371 cm^{-1}; ^1H NMR (selected signals for the mixture of two diastereomers in a ratio of about 2.3:1): major component 1.30 (d, *J*=6.5 Hz, Me), 1.48 (s, *t*-Bu), 2.87 (dd, *J*=15.2, 1.6 Hz, H-3a), 3.03 (dd, *J*=15.2, 4.2 Hz, H-3b), 3.80 (s, OMe), 5.61 (dd, 1H, *J*=4.2, 1.6 Hz, H-4), 6.46 (dd, 1H, *J*=14.1, 6.5 Hz, =CH–O); minor component 1.35 (d, *J*=6.5 Hz, Me), 1.47 (s, *t*-Bu), 2.88 (dd, *J*=15.2, 1.7 Hz, H-3a), 3.06 (dd, *J*=15.2, 4.3 Hz, H-3b), 3.79 (s, OMe), 5.57 (dd, 1H, *J*=4.3, 1.7 Hz, H-4), 6.456 (dd, 1H, *J*=14.1, 6.6 Hz, =CH–O); MS (EI-HR) *m/z*: $(M+Na)^+$ requires for $C_{22}H_{29}O_7NaN$: 442.1842. Found: 442.1838.

1.1.5. (3*S*) 1-Bromo-3-(*p*-methoxybenzyloxy)-butan-2-one (17). To a stirred solution of compound **11** (2.4 g, 10 mmol) and CH_2Br_2 (3.45 g, 1.39 mL, 20 mmol) in THF (40 mL) upon cooling to −78°C, MeLi (20 mL, 1 M solution in THF/cumene 1:9, 20 mmol) was added dropwise. Stirring and cooling was continued for 30 min and then acetic acid (2.4 g, 2.3 mL, 40 mmol) was added. The temperature was allowed to rise to 0°C. The solution was poured into an ice-water mixture (~150 mL), extracted with *t*-BuOMe (3×50 mL), extracts were dried over $MgSO_4$ and evaporated. The product was purified by chromatography using hexane/AcOEt (85:15 v/v) as an eluant to give **17** (2.5 g; 88 %). Oil; $[\alpha]_D=-15.4$ (*c* 1, CH_2Cl_2); IR (CH_2Cl_2) 1737 cm^{-1}; ^1H NMR ($CDCl_3$): 1.39 (d, 3H, *J*=6.8 Hz, CH_3), 3.81 (s, 3H, OMe), 4.15 (bs, 2H, CH_2Br), 4.17 (q, 1H, *J*=6.8 Hz, H-3), 4.49, 4.54 (2d, 2H, *J*=11.3 Hz, Bn), 6.89, 7.27 (2 m, 4H, Aryl); ^{13}C NMR δ 17.2, 31.8 (t), 55.3, 71.8 (t), 78.6, 114.0, 129.1 (s), 129.6, 159.6 (s), 203.3 (s); MS (HR-LSIMS) *m/z*: $(M+Na)^+$ requires for $C_{12}H_{15}O_3^{79}BrNa$: 309.0107. Found: 309.0102; Anal. calcd for $C_{12}H_{15}BrO_3$ (287.15): C, 50.19; H, 5.26; Br, 27.83. Found: C, 50.33; H, 5.35; Br, 27.78.

1.1.6. (3*S*) 1-Acetoxy-3-(*p*-methoxybenzyloxy)-butan-2-one (18). To a solution of compound **17** (1.44 g, 5 mmol) in DMF (20 mL), the AcONa (2 g, 25 mmol) was added and the mixture was stirred at room temperature for 2 h. Subsequently, it was poured into cold water, extracted with *t*-BuOMe, dried, and concentrated. The crude product was purified by chromatography using hexane/*t*-BuOMe (70:30 v/v) as an eluant to give **18** (7.2 g; 82 %). Oil; $[\alpha]_D=-10.2$ (*c* 0.59, CH_2Cl_2); IR (film) 1738, 1752 cm^{-1}; ^1H NMR ($CDCl_3$): 1.37 (d, 3H, *J*=6.8 Hz, CH_3), 2.16 (s, 3H, Ac), 3.81 (s, 3H, OMe), 4.03 (q, 1H, *J*=6.8 Hz, H-3), 4.49, 4.54 (2d, 2H, *J*=11.3 Hz, Bn), 4.91, 4.97 (2d, 2H, *J*=17.6 Hz, H-1), 6.89, 7.27 (2 m, 4H, Aryl); ^{13}C NMR δ 17.0, 20.4, 55.3, 65.9 (t), 71.6 (t), 79.1, 114, 129.2 (s), 129.5, 159.5 (s), 170.3 (s), 205.2 (s); MS (HR-LSIMS) *m/z*: $(M+Na)^+$ requires for $C_{14}H_{18}O_5Na$: 289.1052. Found: 289.1054; Anal. calcd for $C_{14}H_{18}O_5$ (266.29): C, 63.15; H, 6.81. Found: C, 63.25; H, 6.75.

1.1.7. (3*S*) 2-Hydroxymethyl-3-(*p*-methoxybenzyloxy)-but-1-ene (20). To a stirred suspension of finely pulverized methyltriphenylphosphonium iodide (12.4 g, 30.6 mmol) in THF (250 mL), at −78°C, BuLi (15.3 mL 2 M solution in cyclohexane, 30.6 mmol) was added dropwise. The temperature was allowed to rise until the mixture became clear (about 0°C). The mixture was cooled again to −78°C and treated with **18** (7 g, 26.5 mmol). The temperature was allowed to rise to room temperature and the mixture was stirred for 0.5 h. Subsequently it was diluted with *t*-BuOMe (100 mL), filtered through Celite and concentrated. The crude **19** was dissolved in MeOH (200 mL), catalytic amount of K_2CO_3 was added and the mixture was stirred at room temperature for 3 h. Subsequently it was filtered through Celite and concentrated. The crude product was purified by chromatography using hexane/AcOEt (70:30 v/v) as an eluant to give **20** (4.3 g; 73 %). Oil; $[\alpha]_D=-29.9$ (*c* 0.59, CH_2Cl_2); IR (CH_2Cl_2) 3512, 1613, 1514 cm^{-1}; ^1H NMR ($CDCl_3$): 1.34 (d, 3H, *J*=6.6 Hz, CH_3), 3.79 (s, 3H, OMe), 4.08 (q, 1H, *J*=6.5 Hz, H-3), 4.15, 4.26 (2d, 2H, *J*=13.5 Hz, CH_2OH), 4.34, 4.47 (2d, 2H, *J*=11.3 Hz, Bn), 5.11, 5.20 (2bs, 2H, $=CH_{2a,b}$); ^{13}C NMR δ 20.2, 55.2, 63.1 (t), 69.9 (t), 77.1, 112.6 (t), 113.8, 129.3, 130.4 (s), 148.8 (s), 159.2 (s); MS (HR-EI) *m/z*: M^+ requires for $C_{13}H_{18}O_3$: 222.1256. Found: 222.1266; Anal. calcd for $C_{13}H_{18}O_3$ (222.28): C, 70.24; H, 8.16. Found: C, 69.88; H, 8.18.

1.1.8. (3*S*) 2-Bromomethyl-3-(*p*-methoxybenzyloxy)-but-1-ene (21). To a solution of imidazole (1.52 g, 22.4 mmol) in CH_2Cl_2 (120 mL) the compound **20** (4.14 g, 18.64 mmol) was added and the mixture was cooled to 0°C. Separately, the Ph_3P (5.37 g, 20.5 mmol) and bromine (3.28 g; 1 mL, 20.5 mmol) were added to CH_2Cl_2 (70 mL) at 0°C. The resulted suspension was added via cannula to the solution containing compound **20**. The mixture was stirred at 0°C for 10 min. Subsequently, it was poured into an ice-water mixture and extracted with *t*-BuOMe. The extract was dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography using hexane/*t*-BuOMe (94:6 v/v) as an eluant to give **21** (4.4 g; 83 %). Oil; $[\alpha]_D=-30.0$ (*c* 0.66, CH_2Cl_2); IR (CH_2Cl_2) 1613, 1514 cm^{-1}; ^1H NMR ($CDCl_3$): 1.35 (d, 3H, *J*=6.5 Hz, CH_3), 3.80 (s, 3H, OMe), 3.97, 4.07 (2d, 2H, *J*=10.6 Hz, CH_2OH), 4.16 (q, 1H, *J*=6.4, H-3), 4.47, 4.32 (2d, 2H, *J*=11.3, Bn), 5.33, 5.39

(2bs, 2H, =CH_2), 6.88, 7.27 (2 m, 4H, Aryl); ^{13}C NMR δ 20.5, 32.2 (t), 55.3, 70.1 (t), 75.2, 113.8, 116.6 (t), 129.3, 130.5 (s), 146.6 (s), 159.2 (s); MS (HR-EI) *m/z*: M^+ requires for $C_{13}H_{17}O_2^{79}Br$: 284.0412. Found: 284.0414; Anal. calcd for $C_{13}H_{17}BrO_2$ (285.18): C, 54.75; H, 6.01; Br, 28.02. Found: C, 54.61; H, 6.00; Br, 28.12.

1.1.9. (4*R*,3′*S*) and (4*S*,3′*S*) 1-[3′-(*p*-Methoxybenzyloxy)-2′-oxo-butyl]-4-vinyloxy-azetidin-2-one (22). To a stirred suspension of finely powdered tetrabutylammonium hydrogen sulfate (390 mg, 1.1 mmol) in THF (15 mL) was added 4-vinyloxy-azetidin-2-one (113 mg, 1.0 mmol). Upon cooling to −78°C, BuLi (1.1 mL, 2 M solution in cyclohexane, 2.2 mmol) was added. The temperature was allowed to rise until the mixture became clear (about −30°C). Subsequently, it was cooled again to −78°C and treated with **17** (290 mg, 1.0 mmol). After 30 min the temperature was allowed to rise 0°C and the mixture was poured into cold water containing citric acid and extracted with AcOEt. The extract was dried and concentrated. The crude product was purified by chromatography using AcOEt/hexane (40:60 v/v) as an eluant to give **22** (63 mg; 20%). Oil; $[\alpha]_D$=−11.2 (*c* 0.96, CH_2Cl_2); IR (CH_2Cl_2) 1774, 1731 cm^{-1}; ^{1}H NMR (selected signals for two diastereomers in a ratio 1:1; $CDCl_3$): 1.38 (d, 3H, *J*=6.8 Hz, Me), 3.27, 3.29 (2dd, 2H, *J*=15.0, 3.8 Hz, H-3), 3.81 (2s, 3H, OMe), 3.98, 3.99 (2q, 2H, *J*=6.8 Hz, H-3′), 4.16, 4.17 (2dd, 1H, *J*=6.7, 2.0 Hz, OCH=C*H*H), 4.33, 4.35 (2dd, 1H, *J*=14.3, 2.0 Hz, OCH=CH*H*), 5.54, 5.56 (2dd, 2H, *J*=1.2, 3.8 Hz, H-4), 6.34, 6.37 (dd, 2H, *J*=14.3, 6.7 Hz, OC*H*=CH_2); MS (HR-LSIMS) *m/z*: $(M+H)^+$ requires for $C_{17}H_{22}O_5N$: 320.1498. Found: 320.1489; Anal. calcd for $C_{17}H_{21}NO_5$ (319.35): C, 63.94; H, 6.63. Found: C, 63.73; H, 6.93.

1.1.10. (4*R*,3′*S*) and (4*S*,3′*S*) 1-[3′-(4-methoxy-benzyloxy)-2′-methylene-butyl]-4-vinyloxy-azetidin-2-one (25). Compound **25** was prepared from **21** (280 mg, 1.0 mmol) and 4-vinyloxy-azetidin-2-one (135 mg, 1.2 mmol) according to the procedure described for **22**. The crude product was purified by chromatography using AcOEt/hexane (40:60 v/v) as an eluant to give **25**, (250 mg, 79%). Oil; $[\alpha]_D$=−17.6 (*c* 0.65, CH_2Cl_2); IR (CH_2Cl_2) 1768 cm^{-1}; ^{1}H NMR (selected signals taken from the mixture of two diastereomers in a ratio of about 1:1; $CDCl_3$): 1.31, 1.30 (2d, 3H, *J*=6.5 Hz, Me), 2.89, 2.90 (2bd, 2H, *J*=14.9 Hz H-3), 3.10, 3.11 (2dd, 2H, *J*=14.9, 3.7 Hz, H-3), 3.73, 3.75 (2d, H, *J*=16.6 Hz, NC*H*H), 3.97, 4.00 (2q, 1H, *J*=6.5 Hz, H-3′), 4.04 (d, 1H, *J*=16.6, NCH*H*), 4.17 (2dd, 1H, *J*=6.7, 2.0 Hz, OCH=CH*H*), 4.34 (2dd, 1H, *J*=14.3, 2.0 Hz, OCH=C*H*H), 4.41, 4.44 (2d, 2H, *J*=11.0 Hz, Bn), 5.10, 5.12 (2d, 1H, *J*=1.2 Hz, =C*H*H), 5.20, 5.23 (2 bs, 1H, =CH*H*), 5.25 (2dd, 2H, *J*=3.7, 1.2 Hz, H-4), 6.35, 6.36 (2dd, 1H, *J*=14.3, 6.7 Hz, OC*H*=CH_2); MS (HR-LSIMS) *m/z*: $(M+Na)^+$ requires for $C_{18}H_{23}O_4NaN$: 340.1525. Found: 340.1524; Anal. calcd for: $C_{18}H_{23}NO_4$ (319.36): C, 68.12; H, 7.3; N, 4.41. Found: C, 68.14; H, 7.21; N, 4.38.

1.1.11. (4*R*,3′*S*) and (4*S*,3′*S*) 1-[3′-(*p*-Methoxy-benzyloxy)-2′-methylene-butyl]-4-acetoxy-azetidin-2-one (29) and (4*R*), and (4*S*) 1-[2′-methylene-but-3′-one-1′-yl]-4-acetoxy-azetidin-2-one (30). To a solution of compound **25** (340 mg, 1 mmol) in CH_2Cl_2 (30 mL) the mixture of PCC (650 mg, 3 mmol) and silica gel (800 mg Merck Kiesel gel) was added. The suspension was stirred under reflux for 6 h, then filtered through Celite. The Celite pad was washed several times with AcOEt and the combined filtrates were concentrated. The crude product was purified by chromatography using hexane/AcOEt (60:40 v/v) as an eluant to give **29** (250 mg; 72 %) and **30** (35 mg, 10%).

Compound **29**. Oil; $[\alpha]_D$=−26.8 (*c* 1.0, CH_2Cl_2); IR (CH_2Cl_2) 1772, 1752 cm^{-1}; ^{1}H NMR (selected signals taken for the mixture of diastereomers in a ratio of about 1:1; $CDCl_3$): 1.31, 1.30 (2d, 3H, *J*=6.5 Hz, CH_3), 2.06, 2.07 (2s, 3H, Ac), 2.95, 2.96 (2bd, 1H, *J*=15.0 Hz, H-3), 3.23 (dd, 1H, *J*=15.0, 3.8 Hz, H-3), 3.80 (s, 3H, OMe), 5.08, 5.09, 5.17, 5.18 (4bs, 2H, =CH_2), 6.01, 6.02 (2dd, 1H, *J*=3.8, 1.2 Hz, H-4); MS (HR-LSIMS) *m/z*: $(M+H)^+$ requires for $C_{18}H_{24}NO_5$: 334.1654. Found: 334.1654; Anal. calcd for: $C_{18}H_{23}NO_5$ (333.38): C, 64.85; H, 6.95; N, 4.20. Found: C, 64.89; H, 6.78; N, 4.30.

Compound **30**. Oil; IR (CH_2Cl_2) 1774, 1753, 1680 cm^{-1}; ^{1}H NMR ($CDCl_3$): 2.09 (s, 3H, Ac), 2.36 (s, 3H, CH_3), 2.94 (bd, 1H, *J*=15.0 Hz, H-3), 3.27 (dd, 1H, *J*=15.0, 3.9 Hz, H-3′), 4.08, 4.02 (2d, 2H, *J*=16.3 Hz, NCH_2), 5.98 (dd, 2H, *J*=3.9, 1.2 Hz, H-4), 6.00, 6.17 (2bs, 2H, =CH_2); ^{13}C NMR δ 20.8 (t), 25.7 (t), 41.4, 44.9, 76.6 (t), 126.9, 143.0 (s), 165.5 (s), 170.5 (s), 198.1 (s); MS (HR-LSIMS) *m/z*: $(M+H)^+$ requires for $C_{10}H_{14}NO_4$: 212.0923. Found: 212.0924; Anal. calcd for: $C_{10}H_{13}NO_4$ (211.22): C, 56.87; H, 6.20; N, 6.63. Found: C, 56.73; H, 6.17; N, 6.78.

1.2. General procedure for preparation of 5-oxacephams 27 and 28 (see Table 1). To a stirred solution of N-substituted β-lactam (**25**, **29** or **31**, 0.3 mmol) in dry CH_2Cl_2 (3 mL) the Lewis acid was added. The mixture was stirred until disappearance of the substrate (TLC monitoring). The saturated solution of $NaHCO_3$ (2 mL) was added and stirring was continued for 10 min. The organic phase was separated, dried ($MgSO_4$) and evaporated. The analytical samples of pure diastereoisomers **27** and **28** were obtained using HPLC (*t*-BuOMe/hexane 40:60). For the subsequent synthesis of **23** and **24** a crude mixture of **27** and **28** was used.

1.2.1. (4*S*,6*R*) 4-Methyl-3-methylene-5-oxa-cepham (27). Mp 52–53°C; $[\alpha]_D$=+100.8 (*c* 0.51, CH_2Cl_2); IR (CH_2Cl_2) 1765 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.42 (d, 3H, *J*=6.3 Hz, Me), 2.80 (dd, 1H, *J*=14.9, 0.7 Hz, H-7), 3.16 (ddd, 1H, *J*=15.0, 3.3, 1.9 Hz, H-7′), 3.63 (dd, 1H, *J*=15.0, 1.9 Hz, H-2), 4.18 (bq, 1H, *J*=6.3 Hz, H-4), 4.32 (bd, 1H, *J*=15.0 Hz, H-2′), 5.01, 5.06 (2 m, 2H, C=CH_2), 5.10 (dd, 1H, *J*=3.3, 0.7 Hz, H-6);); ^{13}C NMR δ 17.5, 44.6 (t), 45.5 (t), 72.6, 77.6, 110.7 (t), 139.7 (s), 167.5 (s); MS (EI-HR) *m/z*: M^+ requires for $C_8H_{11}NO_2$: 153.0790. Found: 153.0793; Anal. calcd for $C_8H_{11}NO_2$ (153.18): C, 62.73; H, 7.24; N, 9.14. Found: C, 62.72; H, 7.20; N, 9.08.

1.2.2. (4*S*,6*S*) 4-Methyl-3-methylene-5-oxa-cepham (28). Mp 75°C; $[\alpha]_D$=−248.8 (*c* 0.18, CH_2Cl_2); IR (CH_2Cl_2) 1763 cm^{-1}; ^{1}H NMR ($CDCl_3$): 1.41 (d, 3H, *J*=6.9 Hz, Me), 2.75 (bd, 1H, *J*=15.0 Hz, H-7), 3.11 (ddd, 1H, *J*=15.0, 3.2, 1.8 Hz, H-7′), 3.72 (dd, 1H, *J*=15.5, 1.8 Hz, H-2), 4.24 (bd, 1H, *J*=15.5 Hz, H-2′), 4.47 (q, 1H, *J*=6.9 Hz, H-4), 4.93, 4.88 (2bs, 2H, =CH_2), 5.16 (d, 1H, *J*=3.2 Hz, H-6).

1.2.3. (4*S*) 1-Aza-3-methylene-4,6-dimethyl-5,7-dioxa-bicyclo[6.2.0]decan-8-ones (26). Compound **26** was obtained from **25** in the presence $SnCl_4$ (0.5 equiv.) in a 12% yield, as a by-product during preparation of 5-oxa-cephams **27** and **28** (see Table 1).

Compound **26**. Oil; $[\alpha]_D$=+5.5 (*c* 0.4, CH_2Cl_2); IR (CH_2Cl_2) 1757 cm^{-1}; ^1H NMR (selected signals taken for the mixture of diastereomers; $CDCl_3$): 1.32, 1.33, 1.41, 1.42 (4d, 6H, C_4-Me and C_6-Me), 2.62, 2.87 (2bd, 1H, *J*=14.7 Hz, H-9), 4.33, 4.56 (2bq, 1H, H-4), 4.92, 4.98, 5.29 (3dd, 1H, H-6); MS (EI-HR) *m/z*: $(M)^+$ requires for $C_{10}H_{15}NO_3$: 197.1052. Found: 197.1021.

1.2.4. (4*R*,3′*S*) i (4*S*,3′*S*) 4-Acetoxy-1-[3′-hydroxy-2′-methylene-but-1′-yl]-azetidin-2-one (31). The compound **31** was obtained from **29** in the presence $SnCl_4$ or $TiCl_4$ (1 equiv. in each case) in 60% and 52% respectively, if the reaction time was 10 and 5 min, respectively (Table 1). Oil; $[\alpha]_D$=−24.2 (*c* 1.58, CH_2Cl_2); IR (CH_2Cl_2) 1771, 1751 cm^{-1}; ^1H NMR (taken for the mixture of diastereomers; $CDCl_3$+D_2O): 1.31, 1.32 (2d, 3H, *J*=6.5 Hz, CH_3), 2.09 (s, 3H, Ac), 2.98 (bd, 1H, *J*=15.0 Hz, H-3_a), 3.27 (dd, 1H, *J*=15.0, 4.0 Hz, H-3_b), 3.92, 3.91 (2dd, 2H, *J*=16.0 Hz, NCH_2), 4.30, 4.32 (2q, 1H, *J*=6.6 Hz, H-3′), 6.00, 6.02 (2dd, 1H, H-4); MS (HR-LSIMS) *m/z*: $(M+H)^+$ requires for $C_{10}H_{16}NO_4$: 214.1079. Found: 214.1089; Anal. calcd for $C_{10}H_{15}NO_4$ (213.23): C, 56.33; H, 7.09; N, 6.57. Found: C, 56.12; H, 7.10; N, 6.67.

1.3. Preparation of compounds 23 and 24

The solution of diastereoisomers **27** and **28** (92 mg, 0.6 mmol) in CH_2Cl_2 (20 mL) and methanol (1 mL) was placed in a three-necked flask, equipped with thermometer, bubbling tube and ozone outlet. The solution was stirred and upon cooling to −78°C ozone was bubbled in. After about 10 min, the TLC showed the disappearance of the substrate, and the solution turned light-blue. The ozone generation was turned off, and oxygen was passed through the solution for 5 min to remove the excess of ozone. Subsequently, dimethyl sulfide (0.4 mL) was added in one portion, and stirring was continued at −78°C for 10 min. The reaction mixture was brought to room temperature and solvent evaporated. Purification on silica gel using AcOEt/hexane (60:40 v/v) as an eluant gave **23** and **24** in 85% yield. The ratio of diastereomers **23** and **24** depended on the corresponding ratio of the substrate **27**/**28**.

1.3.1. (4*S*,6*R*) 4-Methyl-5-oxa-3-oxo-cepham (23). Mp 46–47°C; $[\alpha]_D$=+35.6 (*c* 0.55, CH_2Cl_2); IR (CH_2Cl_2) 1777, 1738 cm^{-1}; ^1H NMR ($CDCl_3$): 1.43 (d, 3H, *J*=6.7 Hz, Me), 2.94 (d, 1H, *J*=15.3 Hz, H-7), 3.31 (ddd, 1H, *J*=15.3, 3.4, 1.9 Hz, H-7′), 3.70 (ddd, 1H, *J*=19.2, 1.8, 0.7 Hz, H-2), 4.22 (bq, 1H, *J*=6.7 Hz, H-4), 4.33 (d, 1H, *J*=19.2 Hz, H-2′), 5.28 (dd, 1H, *J*=3.4, 0.7 Hz, H-6); ^{13}C NMR δ 15.4, 45.1 (t), 48.4 (t), 77.4, 78.7, 168.5 (s), 200.6 (s); Anal. calcd for $C_7H_9NO_3$ (155.15): C, 54.19; H, 5.85; N, 9.03. Found: C, 54.20; H, 6.03; N, 9.05.

1.3.2. (4*S*,6*S*) 4-Methyl-5-oxa-3-oxo-cepham (24). Oil; $[\alpha]_D$=−269.2 (*c* 0.46, CH_2Cl_2); IR (CH_2Cl_2) 1776, 1748 cm^{-1}; ^1H NMR ($CDCl_3$): 1.40 (d, 3H, *J*=6.7 Hz, Me), 3.11 (dd, 1H, *J*=16.0, 0.9 Hz, H-7), 3.36 (ddd, 1H, *J*=16.0, 3.3, 1.6 Hz, H-7′), 3.72 (ddd, 1H, *J*=19.2, 1.6, 0.9 Hz, H-2), 4.38 (bq, 1H, *J*=6.7 Hz, H-4), 4.43 (d, 1H, *J*=19.2 Hz, H-2′), 5.41 (d, 1H, *J*=3.3 Hz, H-6);); ^{13}C NMR δ 14.3, 44.53 (t), 48.9 (t), 72.6, 76.1, 169.7 (s), 202.9 (s); MS (EI-HR) *m/z*: M^+ requires for $C_7H_9NO_3$: 155.0582. Found: 155.0572.

1.3.3. 3-(*p*-Methoxybenzyloxy)-2-methyl-prop-1-ene (33). The compound **33** was obtained according to Wallace et al.[19] procedure.

1.3.4. 2-Chloromethyl-3-(*p*-methoxybenzyloxy)-prop-1-ene (34). To the solution of compound **33** (87 mg, 0.45 mmol) in CH_2Cl_2 (5 mL), $LiClO_4$ (9.5 mg, 0.09 mmol) and pyridine (43 mg, 44 μL, 0.54 mmol) was added. The mixture was cooled to −78°C and sulfuryl chloride (72.9 mg, 44 μL, 0.54 mmol) was added. Stirring and cooling was continued for 10 min, then the temperature was allowed to rise to 0°C. The mixture was poured into cold water containing $NaHCO_3$, extracted with hexane and extract was dried and concentrated. The crude product was purified by chromatography using hexane/*t*-BuOMe (95:5 v/v) as an eluant to give **34** (41 mg, 40%). Oil; IR (CH_2Cl_2) 2960, 1613 cm^{-1}; ^1H NMR ($CDCl_3$): 3.81 (s, 3H, OMe), 4.09 (bs, 2H, CH_2Cl), 4.12 (bs, 2H, Bn), 4.45 (s, 2H, CH_2OPMB), 5.25, 5.31 (2 m, 2H, =CH_2), 6.88, 7.26 (2 m, 4H, Aryl); ^{13}C NMR δ 45.3 (t), 55.3 (q), 70.0 (t), 72.1 (t), 113.8 (d), 116.7 (t), 129.3 (d), 130.1 (s), 142.1 (s), 159.3 (s); MS (HR-ESI) *m/z*: $(M+Na)^+$ requires for $C_{12}H_{15}O_2Na^{35}Cl$: 249.0653. Found: 249.0670; Anal. calcd for $C_{12}H_{15}ClO_2$ (226.70): C, 63.58; H, 6.67; Cl, 15.64. Found: C, 62.57; H, 6.97.

1.3.5. 2-Hydroxymethyl-3-(*p*-methoxybenzyloxy)-prop-1-ene (35). To the solution of compound **34** (88 mg, 0.39 mmol) in THF (5 mL), water (20 mL) and K_2CO_3 (110 mg, 0.78 mmol) were added. The mixture was heated under reflux until the substrate has disappeared (~6 h). After cooling, the mixture was extracted with AcOEt (3×10 mL), dried and concentrated. The crude product was purified by chromatography using hexane/*t*-BuOMe (50:50 v/v) as an eluant to give **35** (65 mg, 80%). Oil; IR (CH_2Cl_2) 3419, 2924, 1614 cm^{-1}; ^1H NMR ($CDCl_3$): 3.81 (s, 3H, OMe), 4.07 (s, 2H, Bn), 4.19 (bs, 2H, CH_2OH), 4.46 (s, 2H, CH_2OPMB), 5.14, 5.20 (2bs, 2H, =CH_2), 6.88, 7.76 (2 m, 4H, Aryl); ^{13}C NMR δ 55.3, 64.8 (t), 71.6 (t), 72.0 (t), 113.5 (t), 113.9, 129.4, 130.0 (s), 145.1 (s), 159.3 (s); MS (EI-HR) *m/z*: $(M)^+$ requires for $C_{12}H_{16}O_3$: 208.1099. Found: 208.1105; Anal. calcd for $C_{12}H_{16}O_3$ (208.25): C, 69.21; H, 7.74. Found: C, 69.63; H, 7.87.

1.3.6. 2-Bromomethyl-3-(*p*-methoxybenzyloxy)-prop-1-ene (36). The compound **36** was obtained from **35** (4 g, 19.2 mmol) according to the procedure described for compound **21**. The crude product was purified by chromatography using hexane/*t*-BuOMe (95:5 v/v) as an eluant to give **36** (4.4 g, 85%). Oil; IR (film) 2954, 1612 cm^{-1}; ^1H NMR ($CDCl_3$): 3.81 (s, 3H, OMe), 4.04 (s, 2H, CH_2Br), 4.12 (s, 2H, Bn), 4.47 (s, 2H, CH_2OPMB), 5.25, 5.35 (bs, 1H, =CH_2), 7.28, 6.89 (2 m, 4H, Aryl); ^{13}C NMR δ 33.1 (t), 55.3, 70.1 (t), 72.1 (t), 113.8, 117.2 (t), 129.4, 130.1 (s),

142.5 (s), 159.3 (s); MS (HR-EI) *m/z*: $(M)^+$ requires for $C_{12}H_{15}^{79}BrO_2$: 270.0255. Found: 270.0264; Anal. calcd for $C_{12}H_{15}BrO_2$ (271.15): C, 53.16; H, 5.58; Br, 29.47. Found: C, 52.90; H, 5.68; Br, 29.34.

1.3.7. 3-(*p*-Methoxybenzyloxy)-2,3-dimethyl-but-1-ene (38). To the suspension of NaH (washed with hexane) (216 mg, 9 mmol) in DMF (10 mL) the 2,3-dimethyl-but-1-en-3-ol **37**[20] (600 mg, 6 mmol) was added dropwise. After 30 min, *p*-methoxy-benzyl chloride (780 mg, 680 μL, 5 mmol) was added. Subsequently, the reaction mixture was stirred and heated to 40°C until the *p*-methoxy-benzyl chloride disappeared. The reaction mixture was poured into cold water, extracted with hexane, dried and concentrated. The crude product was purified by chromatography using hexane/*t*-BuOMe (95:5 v/v) as an eluant to give **38** (490 mg, 45%). Oil; IR (CH_2Cl_2) 2985, 1613 cm^{-1}; ^1H NMR ($CDCl_3$); 1.38 (s, 6H, 2Me), 1.80 (bs, 3H, Me), 3.78 (s, 3H, OMe), 4.19 (s, 2H, Bn), 4.97 (m, 2H, $=CH_2$), 7.25, 6.85 (2 m, 4H, Aryl); ^{13}C NMR δ 18.5, 25.9, 55.3, 64.4 (t), 77.3 (s), 112.0 (t), 113.8, 128.9, 131.7 (s), 148.9 (s), 158.9 (s); MS (HR-LSIMS) *m/z*: $(M+Na)^+$ requires for $C_{14}H_{20}O_2Na$: 243.1361. Found: 243.1350; Anal. calcd for $C_{14}H_{20}O_2$ (220.31): C, 76.33; H, 9.15. Found: C, 76.48; H, 8.89.

1.3.8. 2-Chloromethyl-3-(*p*-methoxybenzyloxy)-3-methyl-but-1-ene (39). The compound **39** was obtained from **38** (2.3 g, 10.4 mmol) according to the procedure described for compound **34**. The crude product was purified by chromatography using hexane/*t*-BuOMe (95:5 v/v) as an eluant to give **39** (1.9 g, 72%). Oil; IR (CH_2Cl_2) 2984, 1613 cm^{-1}; ^1H NMR ($CDCl_3$): 1.45 (s, 6H, 2Me), 3.80 (s, 3H, OMe), 4.19 (bs, 2H, CH_2Cl), 4.21 (s, 2H, Bn), 5.39, 5.54 (2s, 2H, $=CH_2$), 6.87, 7.24 (2 m, 4H, Aryl); ^{13}C NMR δ 26.3, 43.4 (t), 55.3, 64.6 (t), 77.1 (s), 113.8, 116.4 (t), 128.9, 131.1 (s), 148.6 (s), 159.0 (s); MS (HR-LSIMS) *m/z*: $(M+Na)^+$ requires for $C_{14}H_{19}O_2Na^{35}Cl$: 277.0971. Found: 277.0970.

1.3.9. 2-Hydroxymethyl-3-(*p*-methoxybenzyloxy)-3-methyl-but-1-ene (40). The compound **40** was obtained from **39** (76 mg, 0.3 mmol) according to the procedure described for compound **35**. The crude product was purified by chromatography using hexane/*t*-BuOMe (60:40 v/v) as an eluant to give **40** (60 mg, 85%). Oil; IR (CH_2Cl_2) 3506, 2984, 1614 cm^{-1}; ^1H NMR ($CDCl_3$): 1.45 (s, 6H, 2Me), 3.78 (s, 3H, OMe), 4.25 (bs, 2H, CH_2OH), 4.28 (s, 2H, Bn), 5.17, 5.28 (2s, 2H, $=CH_2$), 6.86, 7.23 (2 m, 4H, Aryl); ^{13}C NMR δ 26.1, 55.3, 63.5 (t), 64.4 (t), 77.5 (s), 111.7 (t), 113.9, 128.9, 131.1 (s), 151.7 (s), 159.0 (s); MS (HR-LSIMS) *m/z*: $(M+Na)^+$ requires for $C_{14}H_{20}O_3Na$: 259.1310. Found: 259.1304; Anal. calcd for $C_{14}H_{20}O_3$ (236.31): C, 71.16; H, 8.53. Found: C, 71.10; H, 8.60.

1.3.10. 2-Bromomethyl-3-(*p*-methoxybenzyloxy)-3-methyl-but-1-ene (41). The compound **41** was obtained from **40** (1.6 g, 6.6 mmol) according to the procedure described for **21**. The crude product was purified by chromatography using hexane/*t*-BuOMe (95:5 v/v) as an eluant to give **41** (1.8 g, 91%). Oil; IR (CH_2Cl_2) 2985, 1614 cm^{-1}; ^1H NMR ($CDCl_3$): 1.47 (s, 6H, 2Me), 3.79 (s, 3H, OMe), 4.10 (bs, 2H, CH_2Br), 4.20 (s, 2H, Bn), 5.43, 5.57 (2s, 2H, $=CH_2$), 6.86, 7.23 (2 m, 4H, Aryl); ^{13}C NMR δ 26.5, 30.9 (t), 55.3, 64.6 (t), 77.1 (s), 113.8, 118.6 (t), 128.9, 131.1 (s), 148.9 (s), 159.0 (s); MS (HR-LSIMS) *m/z*: $(M+Na)^+$ requires for $C_{14}H_{19}O_2Na^{79}Br$: 321.0466. Found: 321.0458; Anal. calcd for $C_{14}H_{19}BrO_2$ (299.20): C, 56.20; H, 6.40; Br, 26.71. Found: C, 56.22; H, 6.52; Br, 26.78.

1.3.11. (±) 1-[3′-(*p*-Methoxybenzyloxy)-2′-methylene-propyl]-4-vinyloxy-azetidin-2-one (42). Compound **42** was obtained from **36** (59 mg, 0.22 mmol) and 4-vinyl-oxy-azetidin-2-one (32 mg, 0.28 mmol) according to the procedure described for **22**. The crude product was purified by chromatography using hexane/*t*-BuOMe (30:70 v/v) as an eluant to give **42** (54 mg, 80%). Oil; IR (CH_2Cl_2) 1768 cm^{-1}; ^1H NMR ($CDCl_3$): 2.86 (d, 1H, *J*=14.8 Hz, H-3), 3.08 (dd, 1H, *J*=14.8, 3.7 Hz, H-3), 3.72 (d, 1H, *J*=15.8 Hz, NC*H*H), 3.81 (s, 3H, OMe), 3.96 (s, 2H, CH_2OPMB), 4.04 (d, 2H, *J*=15.8 Hz, NCH*H*), 4.16 (dd, 1H, *J*=6.7, 2.2 Hz, OCH=C*H*H), 4.33 (dd, 1H, *J*=14.2, 2.2 Hz, OCH=CH*H*), 4.43 (s, 2H, *J*=10.7 Hz, Bn), 5.14, 5.24 (d, 2H, $=CH_2$), 5.23 (bd, 1H, *J*=3.7 Hz, C-4), 6.35 (dd, 1H, *J*=14.2, 6.7 Hz, OC*H*=CH_2), 6.88, 7.26 (2 m, 4H, Aryl); ^{13}C NMR δ 43.3 (t), 44.8 (t), 55.3, 71.2 (t), 72.2 (t), 77.2, 80.2, 96.1 (t), 113.8, 116.0 (t), 129.5, 140.2 (s), 148.2 (s), 159.3 (s), 165.6 (s); MS (HR-LSIMS) *m/z*: $(M+Na)^+$ requires for $C_{17}H_{21}NO_4Na$: 326.1368. Found: 326.1385; Anal. calcd for $C_{17}H_{21}NO_4$ (303.36): C, 67.31; H, 6.98; N, 4.62. Found: C, 67.07; H, 7.11; N, 4.48.

1.3.12. (±) 3-Methylene-5-oxa-cepham (43). To the stirred solution of compound **42** (58 mg, 0.19 mmol) in CH_2Cl_2 (2 mL) at 0°C, the $BF_3{\cdot}Et_2O$ (27 mg, 24 μL, 0.18 mmol) was added. The mixture was stirred at 0°C until disappearance of the substrate (~0.5 h). Subsequently, the saturated solution of $NaHCO_3$ (3 mL) was added and stirring was continued for 5 min. The mixture was poured into cold water and extracted with ethyl acetate (3×). The combined extracts were dried and concentrated. The crude product was purified by chromatography using hexane/*t*-BuOMe (25:75 v/v) as an eluant, followed by the kugelrohr vacuum distillation (oven temp. 80°C, 0.2 mm Hg) to give **43** (13 mg, 50%). Oil; IR (CH_2Cl_2) 1767 cm^{-1}; ^1H NMR ($CDCl_3$): 2.81 (d, 1H, *J*=15.0 Hz, H-7), 3.17 (ddd, 1H, *J*=15.0, 3.3, 1.9 Hz, H-7′), 3.67 (bd, 1H, *J*=15.4 Hz, H-2), 4.20, 4.33 (2d, 2H, *J*=13.0 Hz, H-4,4′), 4.34 (d, 1H, *J*=15.4 Hz, H-2′), 5.00, 5.05 (2 m, 2H, $=CH_2$), 5.02 (d, 1H, *J*=3.3 Hz, H-6); ^{13}C NMR δ 43.4 (t), 45.3 (t), 69.8 (t), 77.3 (d), 113.2 (t), 135.3 (s), 167.3 (s); MS (LSIMS-HR) *m/z*: $(M+H)^+$ requires for $C_7H_{10}NO_2$: 140.0712. Found: 140.0705; Anal. calcd for $C_7H_9NO_2$ (139.15): C, 60.42; H, 6.52; N, 10.07. Found: C, 59.90; H, 6.78; N, 9.68.

1.3.13. (±) 5-Oxa-3-oxo-cepham (44). The compound **44** was obtained from **43** (220 mg, 1.58 mmol) according to the procedure described for **23** and **24**. The crude product was purified by chromatography using hexane/AcOEt (20:80 v/v) as an eluant to give **44** (190 mg, 85%). Oil; IR (CH_2Cl_2) 1777, 1744 cm^{-1}; ^1H NMR ($CDCl_3$): 2.99 (d, 1H, *J*=15.4 Hz, H-7), 3.32 (ddd, 1H, *J*=15.4, 3.3, 1.8 Hz, H-7′), 3.74 (dt, 1H, *J*=19.5, 1.8 Hz, H-2), 4.20, 4.38 (2bd, 2H, *J*=17.4 Hz, H-4,4′), 4.41 (d, 1H, *J*=19.5 Hz, H-2′), 5.26 (d, 1H, *J*=3.3 Hz, H-6); ^{13}C NMR δ 44.6 (t), 48.9 (t), 71.8 (t), 77.2 (d), 168.7 (s), 199.3 (s); MS (EI-HR) *m/z*: M^+ requires for $C_6H_7NO_3$: 141.0426. Found:141.0419; Anal.

calcd for $C_6H_7NO_3$ (141.12): C, 51.06; H, 5.00; N, 9.92. Found: C, 49.02; H, 5.27; N, 9.14.

1.3.14. (±) 1-[3′-(*p*-Methoxybenzyloxy)-2′-methylene-3′-methyl-butyl]-4-vinyloxy-azetidin-2-one (45). The compound **45** was obtained from **41** (299 mg, 1.0 mmol) and 4-vinyloxy-azetidin-2-one (135 mg, 1.2 mmol) according to the procedure described for **22**. The crude product was purified by chromatography using hexane/*t*-BuOMe (40:60 v/v) as an eluant to give **45** (230 mg, 70%). Oil; IR (CH_2Cl_2) 1768 cm^{-1}; ^1H NMR ($CDCl_3$): 1.43, 1.44 (2s, 6H, 2Me), 2.93 (d, 1H, *J*=14.8 Hz, H-3), 3.16 (dd, 1H, *J*=14.8, 3.6 Hz, H-3′), 3.82 (s, 3H, OMe), 3.88 (d, 1H, *J*=17.0 Hz, NC*H*H), 4.12 (d, 1H, *J*=17.0 Hz, NCH*H*), 4.17 (dd, 1H, *J*=6.7, 2.2 Hz, OCH=C*H*H), 4.22, 4.25 (d, 2H, *J*=10.7 Hz, Bn), 4.33 (dd, 1H, *J*=14.3, 2.2 Hz, OCH=CH*H*), 5.18, 5.28 (s, 2H, $=CH_2$), 5.30 (bd, 1H, *J*=3.5 Hz, C–4), 6.35 (dd, 1H, *J*=14.3, 6.7 Hz, OC*H*=CH_2), 6.88, 7.27 (2 m, 4H, Aryl); ^{13}C NMR δ 25.7, 26.0, 40.8 (t), 44.9 (t), 55.3, 64.5 (t), 76.5 (s), 80.1, 91.1 (t), 112.9 (t), 113.8, 129.0, 131.0 (s), 146.7 (s), 147.9, 159 (s), 165.8 (s); MS (HR-LSIMS) *m*/*z*: $(M+Na)^+$ requires for $C_{19}H_{25}O_4NaN$: 354.1681. Found: 354.1695; Anal. calcd for $C_{19}H_{25}NO_4$ (331.41): C, 68.86; H, 7.60; N, 4.23. Found: C, 68.75; H, 7.60; N, 4.16.

1.3.15. (±) 4,4-Dimethyl-3-methylene-5-oxa-cepham (46). Compound **46** was obtained from **48** (230 mg, 0.66 mmol) according to the procedure described for **43** using $BF_3{\cdot}Et_2O$ (46 mg, 42 μL, 0.33 mmol). The reaction mixture was quenched with saturated $NaHCO_3$ after 1 h. The crude product was purified by chromatography using hexane/AcOEt (60:40 v/v) as an eluant to give **46** (55 mg, 50%). Oil; IR (CH_2Cl_2) 1766 cm^{-1}; ^1H NMR ($CDCl_3$): 1.47, 1.52 (2s, 6H, 2Me), 2.79 (bd, 1H, *J*=14.9 Hz, H-7), 3.19 (ddd, 1H, *J*=14.9, 3.2, 1.7 Hz, H-7′), 3.80 (bd, 1H, *J*=15.0 Hz, NC*H*H), 4.26 (d, 1H, *J*=15.0 Hz, NCH*H*), 5.07, 4.95 (2 m, 2H, $=CH_2$), 5.22 (d, 1H, *J*=3.2 Hz, H-6); ^{13}C NMR δ 23.7, 27.4, 42.6 (t), 45.9 (t), 72.9, 76.0 (s), 110.4 (t), 142.9 (s), 168.5 (s); MS (EI-HR) *m*/*z*: M^+ requires for $C_9H_{13}NO_2$: 167.0946. Found:167.0959.

1.3.16. (±) 4,4-Dimethyl-5-oxa-3-oxo-cepham (47). The compound **47** was obtained from **46** (30 mg, 0.18 mmol) according to the procedure described for **23** and **24**. The crude product was purified by chromatography using hexane/AcOEt (60:40 v/v) as an eluant to give **47** (21 mg, 70%). Oil; IR (CH_2Cl_2) 1776, 1733 cm^{-1}; ^1H NMR ($CDCl_3$): 1.49, 1.42 (2s, 6H, 2Me), 2.92 (d, 1H, *J*=15.2 Hz, H-7), 3.30 (ddd, 1H, *J*=15.2, 3.3, 1.9 Hz, H-7′), 3.74 (dd, 1H, *J*=19.2, 1.9 Hz, H-2), 4.31 (d, 1H, *J*=19.2 Hz, H-2′), 5.39 (d, 1H, *J*=3.3 Hz, H-6); ^{13}C NMR δ 22.2, 25.0, 45.5 (t), 46.9 (t), 72.5, 81.6 (s), 168.9 (s), 203.3 (s); MS (EI-HR) *m*/*z*: M^+ requires for $C_8H_{11}NO_3$: 169.0739. Found:169.0735.

1.3.17. (±) 1-[3′-(*p*-Methoxybenzyloxy)-2′-methylene-3′-methyl-butyl]-4-acetoxy-azetidin-2-one (48). The compound **48** was obtained from **45** (2.6 g, 7.8 mmol) according to the procedure described for **29**. The crude product was purified by chromatography using hexane/*t*-BuOMe (40:60 v/v) as an eluant to give **48** (1.9 g, 70%). Colourless crystals mp 56–57°C; IR (CH_2Cl_2) 1772, 1752 cm^{-1}; ^1H NMR ($CDCl_3$): 1.40, 1.41 (2s, 6H, 2Me), 2.02 (s, 3H, Ac) 2.96 (bd, 1H, *J*=15.1 Hz, H-3), 3.27 (dd, 1H, *J*=15.1, 3.9 Hz, H-3′), 3.79 (s, 3H, OMe), 3.88 (d, 1H, *J*=17.2 Hz, NC*H*H), 4.03 (bd, 1H, *J*=17.2 Hz, NCH*H*), 4.19, 4.22 (2d, 2H, *J*=10.8 Hz, Bn), 5.11, 5.20 (2s, 2H, $=CH_2$), 6.02 (dd, 1H, *J*=3.9, 1.2 Hz, C-4), 6.86, 7.26 (2m, 4H, Aryl); ^{13}C NMR δ 20.7, 25.9, 26.2, 41.6 (t), 44.8 (t), 55.3, 64.4 (t), 76.4, 76.5 (s), 111.8 (t), 113.8, 128.9, 131.1 (s), 147.1 (s), 158.9 (s), 165.6 (s), 170.5 (s); MS (HR-LSIMS) *m*/*z*: $(M+H)^+$ requires for $C_{19}H_{26}O_5N$: 348.1811. Found: 348.1820; Anal. calcd for $C_{19}H_{25}NO_5$ (347.41): C, 65.69; H, 7.25; N, 4.03. Found: C, 65.66; H, 7.17; N, 4.10.

1.3.18. (±) 1-[2′-Chloromethyl-3′-methyl-but-2′-enyl]-4-acetoxy-azetidin-2-one (49). To the suspension of $SnCl_2$ (57 mg, 0.3 mmol) in CH_2Cl_2 (1 mL), the TMS-Cl (130 mg, 152 μL, 1.2 mmol) was added. The mixture was stirred for 15 min and the solution of **48** (104 mg, 0.3 mmol) in CH_2Cl_2 (0.5 mL) was added. Stirring was continued at room temperature until disappearance of the substrate (~1 h). The mixture was cooled to 0°C and saturated solution of $NaHCO_3$ (2 mL) was added. The reaction mixture was stirred for 5 min, poured into cold water and extracted with CH_2Cl_2 (3×). The combined extracts were dried over $MgSO_4$ and concentrated. The crude product was purified by chromatography using CH_2Cl_2: *t*-BuOMe (95:5 v/v) as an eluant to give **49** (20 mg, 27%) and **46** (10 mg, 20%).

Compound **49**. Oil; IR (CH_2Cl_2) 1769, 1753 cm^{-1}; ^1H NMR ($CDCl_3$): 1.82, 1.85 (2s, 6H, 2Me), 2.10 (s, 3H, Ac) 2.89 (bd, 1H, *J*=15.0 Hz, H-3), 3.25 (dd, 1H, *J*=15.0, 3.9 Hz, H-3′), 3.88 (d, 1H, *J*=15.0 Hz, NC*H*H), 4.05 (d, 1H, *J*=15.0 Hz, NCH*H*), 4.19, 4.15 (2d, 2H, *J*=11.4 Hz, CH_2Cl), 5.99 (dd, 1H, *J*=3.9, 1.2 Hz, H-4); ^{13}C NMR δ 20.8, 20.8, 41.1 (t), 43.6 (t), 44.9 (t), 76.1, 76.9, 123.6 (s), 139.7 (s), 165.5 (s), 170.4 (s); MS (LR-ESI) *m*/*z*: $(M+Na)^+$ requires for $C_{11}H_{16}ClO_3NNa$: 245.1. Found: 245.1; Anal. calcd for $C_{11}H_{16}ClNO_3$ (245.70): C, 53.77; H, 6.56; N, 14.43; Cl, 14.43. Found: C, 56.80; H, 7.03; N, 5.46; Cl, 13.14.

References

1. Cama, L. D.; Christensen, B. G. *J. Am. Chem. Soc.* **1974**, *96*, 7582.
2. Firestone, R. A.; Fahey, J. L.; Maciejewicz, N. S.; Patel, G. S.; Christensen, B. G. *J. Med. Chem.* **1977**, *20*, 551.
3. (a) Brown, A. G.; Butlerworth, D.; Cole, M.; Hanscomb, G.; Hood, J. D.; Reading, C.; Robinson, G. N. *J. Antibiot.* **1976**, *29*, 668. (b) Brown, A. G.; Corbet, D. F.; Goodacre, J.; Harbridge, J. B.; Howarth, T. T.; Ponsford, R. J.; Stirling, I.; King, T. I. *J. Chem. Soc. Perkin Trans. 1* **1984**, 635.
4. Nagata, W.; Narisada, M.; Yoshida, T. *Chemistry and Biology of β-Lactam Antibiotics*; Morin, R. B., Gorman, M., Eds.; Academic: New York, 1982; vol. 2, p 1. (b) Nagata, W. In *Current Trends in Organic Synthesis*; Nozaki, H., Ed.; Pergamon: Oxford, 1983; p 83.
5. (a) Chmielewski, M.; Kałuża, Z.; Grodner, J.; Urbański, R. In *Cycloaddition Reaction in Carbohydrate Chemistry*. *ACS Symposium Series*; Giuliano, R. M., Ed.;, 1992; vol. 494, p 50. (b) Chmielewski, M.; Kałuża, Z.; Furman, B. *J. Chem. Soc., Chem. Commun.* **1996**, 2689.

6. (a) Pfaendler, H. R.; Neumann, T.; Bartsch, R. *Synthesis* **1992**, 1179. (b) Wild, H.; Metzger, K.-G. *Biorg. Med. Chem. Lett.* **1993**, *3*, 2211.
7. (a) Antonini, I.; Cardellini, M.; Claudi, F.; Moracci, F. M. *Synthesis* **1986**, 379. (b) Hegedus, L. S.; Montgomery, J.; Narukawa, Y.; Snustad, D. S. *J. Am. Chem. Soc.* **1991**, *113*, 5784.
8. Shibahara, S.; Okonogi, T.; Murai, Y.; Kudo, K.; Yoshida, T.; Kondo, S.; Christensen, B. G. *J. Antibiot.* **1988**, *41*, 1154.
9. (a) Kałuża, Z.; Park, H.-S. *Synlett* **1996**, 895. (b) Kałuża, Z.; Łysek, R. *Tetrahedron: Asymmetry* **1997**, *8*, 2553. (c) Kałuża, Z.; Łysek, R. *Tetrahedron Lett.* **1998**, *39*, 8349. (d) Kałuża, Z. *Tetrahedron Lett.* **1999**, *40*, 1025.
10. Bełżecki, C.; Urbański, R.; Urbańczyk-Lipkowska, Z.; Chmielewski, M. *Tetrahedron* **1997**, *53*, 14153.
11. Kałuża, Z.; Furman, B.; Krajewski, P.; Chmielewski, M. *Tetrahedron* **2000**, *56*, 5553.
12. Carr, K.; Greener, A. N.; Mullah, K. B.; Somerville, F. M.; Sutherland, J. K. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1975.
13. Shimano, M.; Kamei, N.; Shibata, T.; Inoguchi, K.; Itoh, N.; Ikari, T.; Senda, H. *Tetrahedron* **1998**, *54*, 12745.
14. Pastor, S. D.; Nelson, A. L. *J. Heterocycl. Chem.* **1984**, *21*, 657.
15. Coats, S. J.; Wasserman, H. H. *Tetrahedron Lett.* **1995**, *36*, 7739.
16. Borsuk, K.; Suwińska, K.; Chmielewski, M. *Tetrahedron: Asymmetry* **2001**, *12*, 979.
17. Kowalski, C. J.; Haque, M. S. *J. Org. Chem.* **1985**, *50*, 5140.
18. The crystallographic data for compounds **28** and **24** have been deposit with the Cambridge Crystallographic Data Center as a supplementary publications number CCDC 204498 and CCDC 203736, respectively. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].
19. Wallace, G. A.; Scott, R. W.; Heathcock, C. H. *J. Org. Chem.* **2000**, *65*, 4145.
20. Rozhkov, I. N.; Makin, S. M. *Zh. Obshch. Khim.* **1964**, *34*, 59.