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Strategies for the Formation of 1-Dethia-1-oxa-cephams

Z. Kałuża, B. Furman, P. Krajewski and M. Chmielewski*

Institute of Organic Chemistry of the Polish Academy of Sciences, 01-224 Warsaw, Poland

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Abstract—The paper describes three possible routes for the formation of 1-dethia-1-oxa-cephams. The first two routes: (a) [2+2]cycloaddition to chiral vinyl ethers and (b) condensation of 4-acetoxyazetidin-2-one to chiral alcohols, are followed by the ring closure step involving *N*-alkylation. The third route (c) consists of *N*-alkylation prior to the cyclization step. In order to compare routes (a), (b) and (c), diastereomeric 1-dethia-3-(4-methoxybenzyloxy)-1-oxacephams were synthesized using three possible strategies. While the comparison of stereoselectivities of the [2+2]cycloaddition method (a) and the condensation (b) shows unequivocally the advantage of the former, the route (c) leads to the reverse direction of asymmetric induction relative to the first two steps and offers the highest asymmetric induction. © 2000 Elsevier Science Ltd. All rights reserved.

Introduction

1-Dethia-1-oxacephems, 1-oxapenems, and clavams represent interesting groups of β-lactam antibiotics and inhibitors of β-lactamase enzymes.[1,2,3,4] All these compounds have one structural feature in common which is an alkoxy fragment present at C-4 of the azetidin-2-one ring. Therefore the synthesis of these 1-oxabicyclic β-lactam antibiotics requires introduction of the 4-alkoxy fragment to the azetidin-2-one ring at a certain stage of the synthetic plan.

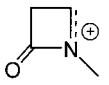
The most common strategy for the synthesis of 1-oxabicyclic β-lactams involves nucleophilic substitution at C-4 of the azetidin-2-one ring, which can constitute the ring closure step, or which can be followed by formation of the five- or six-membered ring. The weak point of such a strategy lies in a low asymmetric induction if C-3 of the azetidin-2-one ring stays unsubstituted, or in exclusive formation of the 3,4-*trans*-functionalized β-lactam ring if C-3 bears a substituent.

[2+2]Cycloaddition of chlorosulfonyl isocyanate (CSI) to chiral vinyl ethers, having a chiral center next to the oxygen atom (Scheme 1, route a),[5] offers an alternative way for the synthesis of 3-unsubstituted 4-alkoxyazetidin-2-ones to the commonly used one which is based on the condensation of commercially available 4-acetoxyazetidin-2-one (**1**) with chiral alcohols (Scheme 1, route b).[4] The latter methodology provides low asymmetric induction,[4] although an easy nucleophilic substitution of the acyloxy group[6] makes **1** a very attractive intermediate for the synthesis of a variety of clavams.[4]

Recently, a new strategy for 1-dethia-1-oxacephams synthesis, employing readily available 4-benzyloxy- and 4-vinyloxyazetidin-2-ones (**2** and **3**), has been reported in our laboratory.[7] The strategy consisted of *N*-alkylation of **2** or **3** with a specially prepared chiral fragment prior to the cyclization step (Scheme 1, route c). The idea of this strategy is based on the common observation that a ring closure reaction usually affords better stereodifferentiation than an intermolecular condensation. New building blocks **2** and **3** offer substantial advantage over 4-acetoxyazetidin-2-one (**1**) owing to their stability under basic conditions, which allow *N*-alkylation. The ring closure reaction proceeds after transformation of the 4-benzyloxy or 4-vinyloxy substituent into the 4-acyloxy group followed by a nucleophilic displacement of the latter in the presence of a Lewis acid catalyst.[7] The vinyloxy substituent can also be displaced by nucleophiles in certain cases.[8]

So far, the strategy involving the azetidin-2-ones **2** and **3** has been successfully performed for the 1-oxacepham synthesis only.[7,8] Three possible routes (a), (b) and (c) leading to the 1-oxabicyclic β-lactams **4** are presented in Scheme 1.

Nucleophilic displacement at C-4 of the azetidin-2-one ring proceeds via a flat intermediate which is supposed to have a mesomeric cation structure **5**. It should be noted, however, that displacements performed on *N*-unsubstituted or *N*-silylated azetidin-2-ones proceed more readily.[9]



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Keywords: azetidinones; oxacephams; stereocontrol.

* Corresponding author. E-mail: chmiel@ichf.edu.pl

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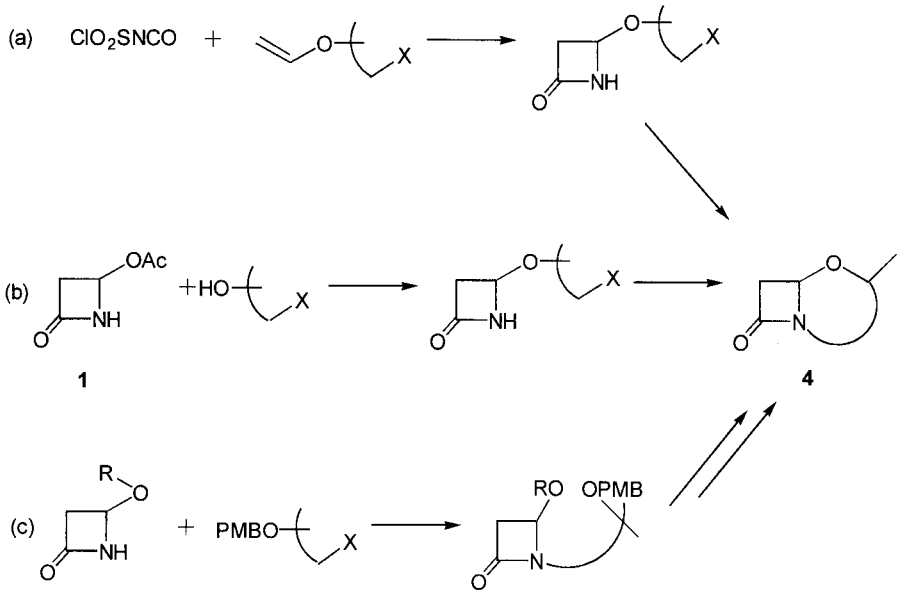


Scheme 1.

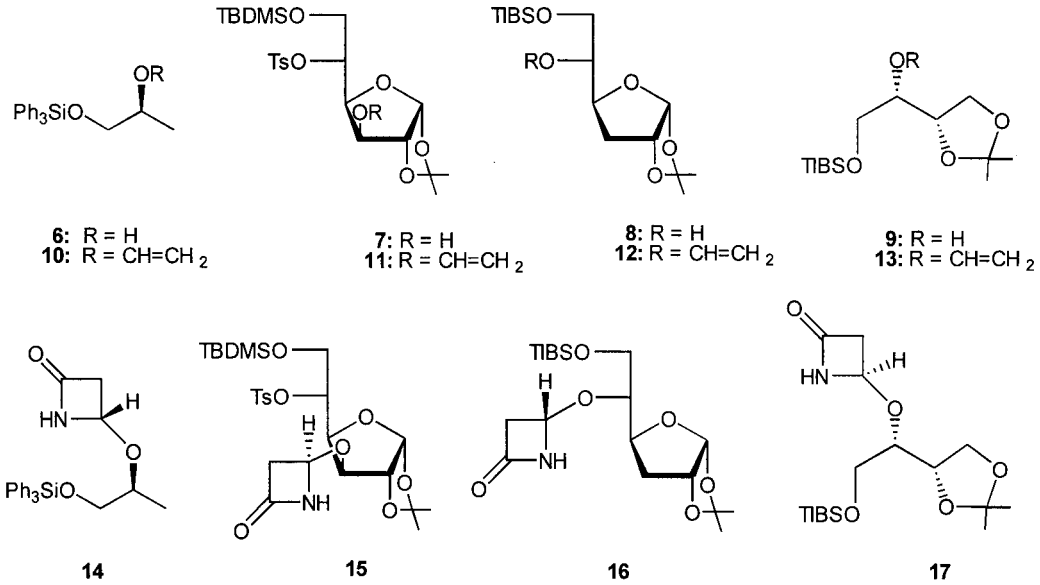
Facial differentiation in the reaction of the small, flat intermediate **5** with chiral alcohols (route b) cannot be significant. It has been shown,[7b,8] however, that trapping an *O*-protected chiral alcohol, having an sp^3 electrophilic center, by *N*-alkylation of **2** or **3** and subsequent ring closure via nucleophilic substitution (route c), offers much better stereoselectivity.

In the present paper we intend to compare routes (a), (b) and (c).

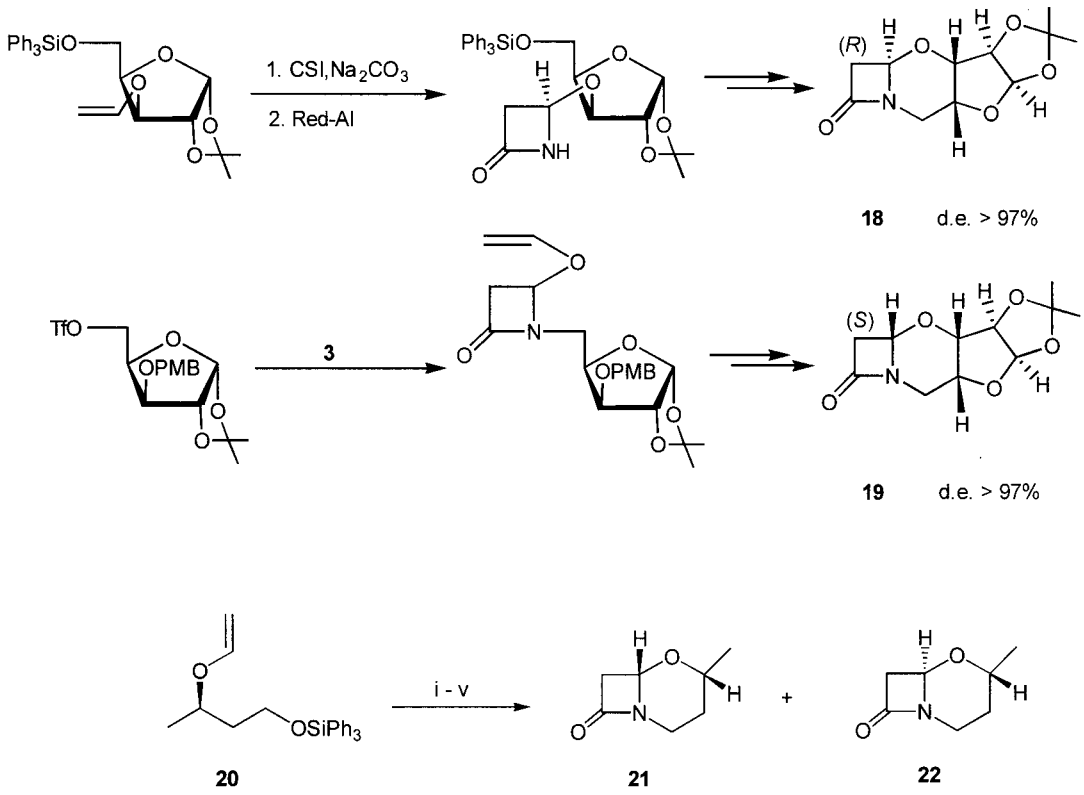
Results and Discussion

To demonstrate advantages offered by the [2+2]cycloaddition method (route a) over the condensation method (route b), we selected four alcohols **6**–**9** which, when transformed into vinyl ethers **10**–**13**, afforded high asymmetric induction with chlorosulfonyl isocyanate (Scheme 2).[5b,d,10,11]

Alcohols **6**–**9** subjected to the condensation with **1** under standard conditions[4] furnished the corresponding



Scheme 2.



Scheme 3. i: CSI, Na_2CO_3 toluene, −78°; ii: Red-Al; iii: HF/Py; iv: TsCl; v: Bu_4NBr, Na_2CO_3, CH_3CN.

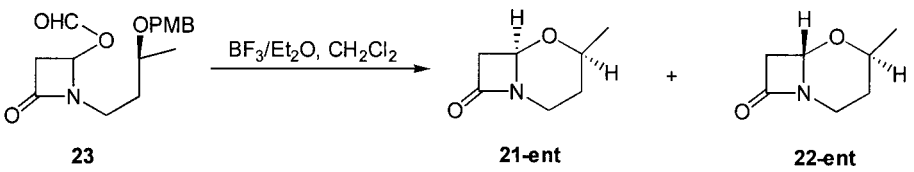
4-alkoxyazetidinones **14**–**17** with 9, 82, 20, and 44% d.e., respectively, whereas [2+2]cycloaddition of CSI to the vinyl ethers **10**–**13** gave the same compounds **14**–**17** with 75, >97, >97 and 91% d.e., respectively (Scheme 2). Both of the methods [2+2]cycloaddition (a) and condensation (b) showed the same direction of asymmetric induction and comparable yields which varied from 30 to 60%.

Owing to the rigid geometry of the transition state of the [2+2]cycloaddition and defined conformation of vinyl ethers, [2+2]cycloaddition offers excellent asymmetric induction in certain cases.[5,10,11] Recently we have proposed a stereochemical model of the transition state for the [2+2]cycloaddition of CSI to vinyl ethers, which allowed us to predict the direction of asymmetric induction.[12]

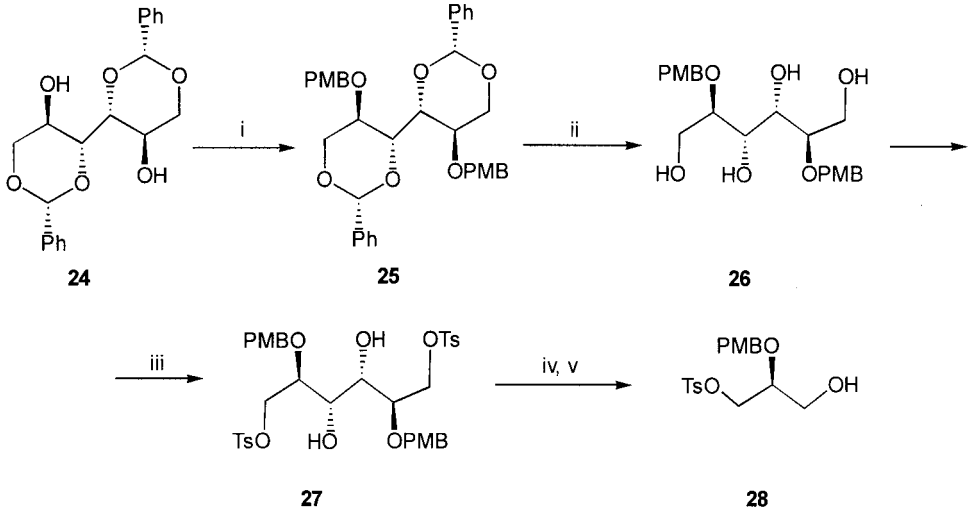
The high asymmetric induction and the control of the absolute configuration of the bridge-head carbon atom of the antibiotic are particularly important for the synthesis of the β-lactamase inhibitors and natural clavams since they do not have a substituent at the carbon atom next to the β-lactam carbonyl group. The route (c) which, similarly to the cycloaddition, proceeds via the well defined transition state, usually provides high asymmetric inductions.[7]

Directions of asymmetric induction in routes (a) and (b) compared to route (c) are opposite, providing alternative diastereomers. This is well illustrated in the formation of tetracyclic β-lactams **18** and **19** (Scheme 3).[5a,7b] The cycloaddition route (a) provides, after intramolecular *N*-alkylation, the diastereomer **18** having the (*R*)-configuration at the C-4 of the azetidinone ring,[5a] whereas the route (c) gives, after intramolecular nucleophilic substitution, diastereomer **19** having the (*S*)-configuration at the same carbon atom.[7b] Another example illustrates well the complementary direction of the asymmetric induction in routes (a) and (c). [2+2]Cycloaddition of CSI to the vinyl ether **20** followed by intramolecular *N*-alkylation afforded the cephams **21** and **22** in a ratio of 1:3, respectively.[5d] On the other hand, a ring closure in **23** gave a corresponding mixture of **21-ent** and **22-ent** in a ratio of 5:1 (Scheme 4).[7b] In other words, the [2+2]cycloaddition provides the stereoisomer having *anti* H-2 and H-6 protons as the main product, whereas the ring closure affords mainly the corresponding stereoisomer having *syn* located H-2 and H-6 protons.

In order to compare routes (a), (b) and (c), we synthesized cephams **33** and **34**. Alcohol **28**, the starting material for the



Scheme 4.

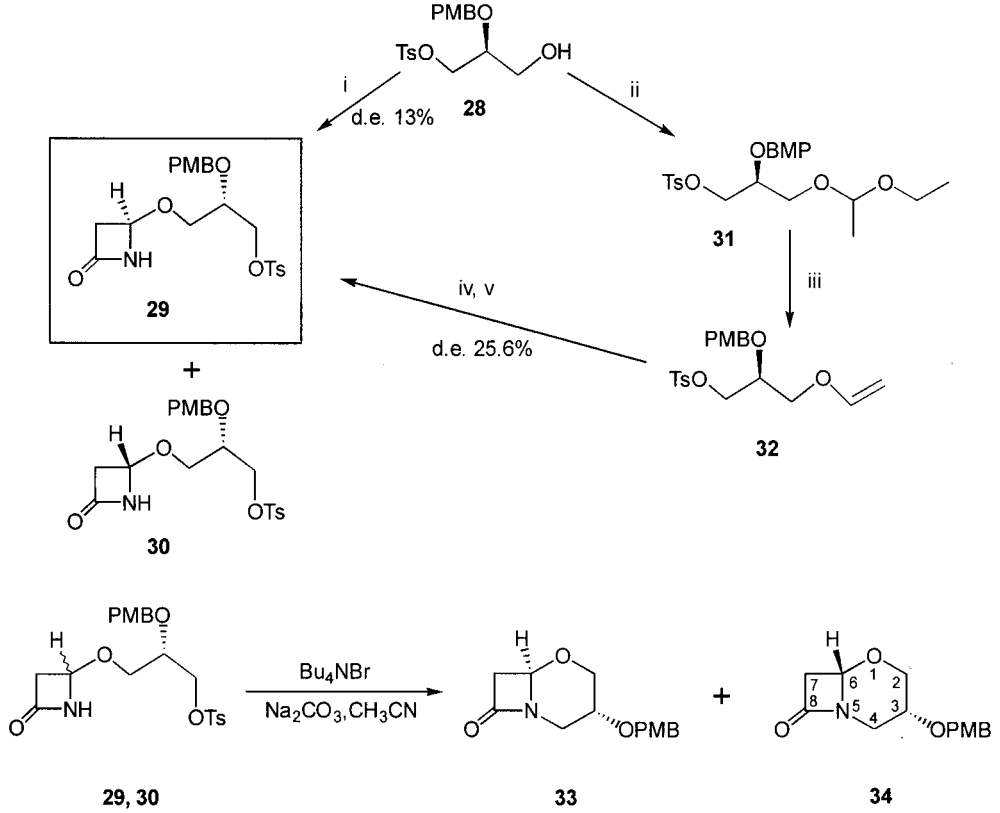


Scheme 5. i: PMBCl, NaH, DMF; ii: Bu_4NHSO_4, MeOH H_2O, reflux; iii: TsCl, Py, CH_2Cl_2; iv: $NaIO_4$, MeOH, H_2O; v: $NaBH_4$.

routes (a) and (b) was prepared from commercially available 1,3:4,6-di-*O*-benzylidene-D-mannitol (**24**) by a five step reaction sequence which is shown in Scheme 5. In both routes (a) and (b), **28** was transformed into a mixture of two diastereomeric products **29** and **30**.

The alcohol **28** treated with 4-acetoxyazetidinone (**1**) under standard reaction conditions[4] afforded 4-alkoxyazetidinone **29** in a 68% yield with d.e. 13.0%. On the other hand, **28** was transformed into the vinyl ether **32** via a two step procedure involving formation of the mixed acetal **31** followed by its degradation in the presence of a TMS-triflate–triethylamine mixture.[13] [2+2]Cycloaddition of CSI to **32** in the presence of sodium carbonate gave **29** in 52% yield with 25.6% d.e. (Scheme 6).

In order to prove the configurations of **29** and **30**, the epimeric mixtures obtained via route (a) and (b) were subjected to intramolecular *N*-alkylation to afford respective mixtures of **33** and **34** which were separated into pure components. The ratios of **33** and **34** reflected those of **29** and **30** in the substrate of the intramolecular alkylation. The



Scheme 6. i: **1**, $Pd(OAc)_2$, PhMe, Et_3N; ii: ethyl vinyl ether, TFA; iii: TMSOTf, Et_3N, CH_2Cl_2; iv: CSI, Na_2CO_3, PhMe; v: Red-Al.

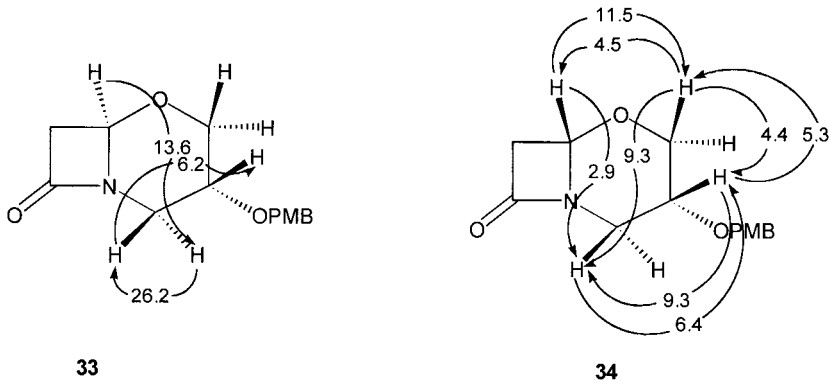
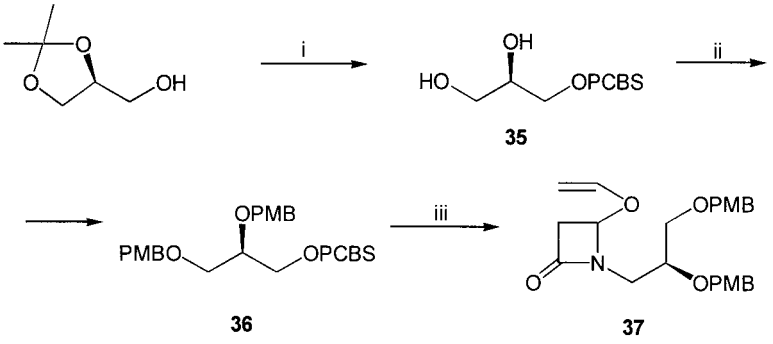


Figure 1. NOEs (%) proving the relative configurations of **33** and **34**.

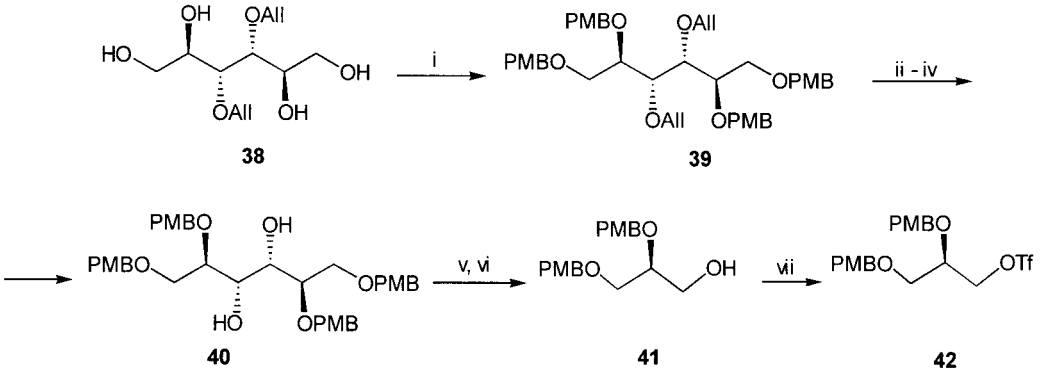
absolute configuration at C-6 of the cephams **33** and **34** was proved by NOE measurements (Cf. Experimental). In the case of **34**, irradiation of the signal due to H-6 (δ 4.96) was found to enhance the intensity of the signal due to H-2β (δ 3.71) by 11.5% and H-4β (δ 3.02) by 2.9%. Conversely, the signal due to H-6 was enhanced by 4.5% when H-2β was irradiated. The irradiation of the signal due to H-2β enhanced the signal of H-3 by 4.4% and H-4β by 9.3%. In the case of **33**, the picture is more complicated due to overlapping of the H-2β and H-7β signals. Irradiation of the signal due to H-6 (δ 4.89) enhanced the intensity of H-4α (δ 4.07) by 13.6% whereas it did not show any spin interaction with H-4β (δ 3.35). Spin interaction was found between the H-4β and H-3 protons; irradiation of H-4β enhanced the intensity of H-3 (δ 3.57) by 6.2% (Fig. 1).

For the route (c) we synthesized 1-*O*-(*p*-chlorophenylsulfonyl)-2,3-di-*O*-(*p*-methoxybenzyl)-D-glycerol **36** from 2,3-*O*-isopropylidene-D-glycerol (Scheme 7).[14] Compound **36** was used for *N*-alkylation of azetidinone **3** followed by the cyclization step (route c). This reaction sequence should eventually provide enantiomeric forms of cephams **33** and **34**. Formation of **33-ent** and **34-ent** does not affect, however, the comparison of stereochemical pathways of routes (a), (b) and (c).

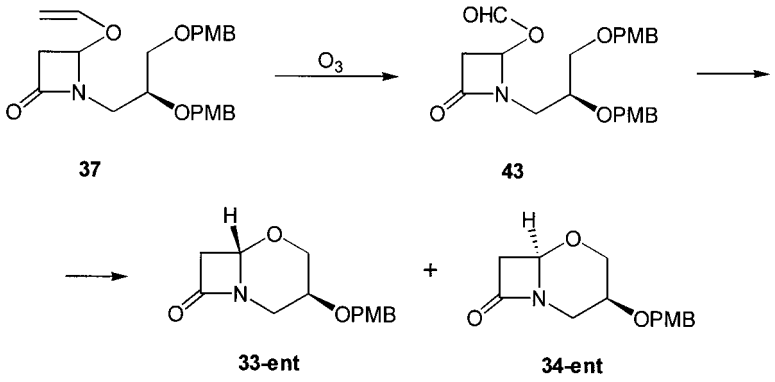
N-alkylation of azetidinone **3** by compound **36** afforded **37** as a mixture of two diastereomers in 24% yield only. Due to the low yield of formation of **37** from **36**, we prepared the triflate **42** from the known **38**[15] by a seven step transformation (Scheme 8). The reaction sequence shown in Scheme 8 is different from the known literature procedure.[16] Due to the sensitivity of *p*-methoxybenzyl protection to acidic conditions, allyl groups were removed using a three



Scheme 7. i: Ref. 14; ii: 4-methoxybenzyl 2,2,2-trichloroacetimidate, CSA, CH_2Cl_2; iii: **3**, Bu_4NHSO_4, BuLi.



Scheme 8. i: PMBCl, NaH, DMF; ii: KO*t*-Bu, DMSO; iii: O_3/Me_2S; iv: MeONa, MeOH; v: $NaIO_4$, H_2O, MeOH; vi: $NaBH_4$; vii: Tf_2O, lutidine, CH_2Cl_2.



Scheme 9.

step reaction sequence to give a good overall yield. *N*-alkylation of **3** by **42** afforded **37** in 78% yield. Ozonolysis of the vinyl group in **37** yielded the 4-formyloxy derivative **43** which was subjected to ring closure in the presence of a Lewis acid catalyst to give a mixture of **33-ent** and **34-ent** in the proportion 3:7, respectively (Scheme 9). The direction of asymmetric induction was found to be opposite to that noticed for formation of a mixture of **33/34** using routes (a) and (b).

The geometry of the transition state of the nucleophilic substitution at C-4 of the azetidin-2-one ring in the route (c) is probably like that of the product. Examination of the coupling constants between the protons of the six-membered ring in the cephams **33** and **34** (**33-ent** and **34-ent**) provide evidence that both, due to the introduction of a four-membered ring, exist in distorted chair conformations; consequently the transition state of the ring closure should be chair-like (Fig. 2).

It has been shown by X-ray crystallography that the nitrogen atoms in 1-oxacephams displays a flat sp^2 hybridization[17] contrary to that in 1-oxacephems which is shown to be slightly pyramidal.[18] Bearing in mind the chair-like transition state of the ring closure, the preference of the **34-ent** formation testifies that the quasi-axial position of the *p*-methoxybenzyloxy group at C-2 is preferred. The preference of the axial position of many substituents at C-5 of 1,3-oxazines has been reported in the past.[19]

While the comparison of diastereoselectivities of the [2+2]cycloaddition method (a) and the condensation (b) shows unequivocally the advantage of the former, the route (c) which leads to the reverse direction of asymmetric induction than (a) and (b), looks to be the most attractive one. The application of the route (c) is likely to be limited, however, to the synthesis of 1-oxacephams. So far, the formation of clavams using route (c) has been unsuccessful.

Experimental

Optical rotations were measured with a JASCO Dip-360 digital polarimeter. IR spectra were obtained with a FT-IR-1600 Perkin–Elmer spectrophotometer. ^{1}H NMR spectra were recorded with a Bruker AM 500 spectrometer. Mass spectra were recorded with a AMD 604 mass spectrometer. Column chromatography was performed on Merck Kiesel gel (230–400 mesh). Ozonolysis was performed on Büchi Ozone-Generator OZI.

Compounds **6**–**9** were obtained according to known procedures.[5b,d,10,11]

The 4-alkoxyazetidin-2-ones **14**–**17** were obtained from the respective alcohols (**6**–**9**) according to the procedure described below.

A solution of alcohol **6**–**9** (0.1 mmol) and palladium acetate (0.005 g, 0.02 mmol) in toluene (5 mL) was treated under argon with a solution of 4-acetoxy-2-azetidinone (**1**) (0.026 g, 0.2 mmol) and triethylamine (28 μL, 0.2 mmol) in dry toluene 1 mL. After 24 h of stirring, the brown residue was filtered and washed with ethyl acetate. The organic

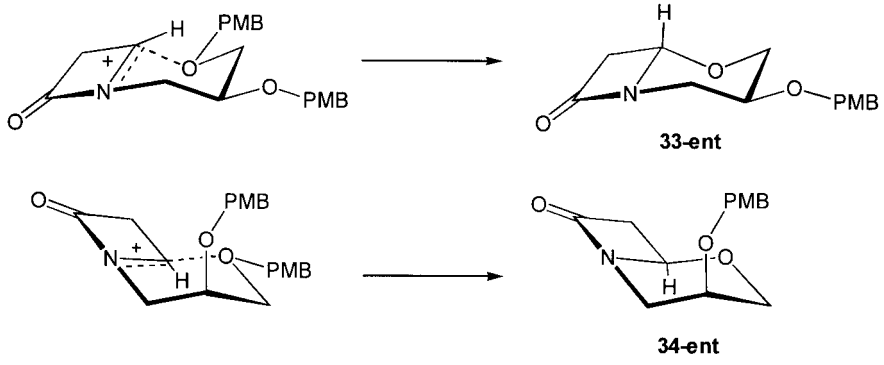


Figure 2. Stereochemical models of transition states of the ring closure reactions.

solution was washed with water, dried and evaporated. The yellow oils were purified by chromatography using hexane: ethyl acetate 7:3 v/v as an eluent to afford corresponding products **14**–**17**. The spectroscopic and analytical data of the β-lactams **14**–**17** were published before.[5e,5d,10,11]

1,3:4,6-Di-*O*-benzylidene-2,5-bis-*O*-(*p*-methoxybenzyl)-D-mannitol (25). A suspension of sodium hydride (60% oil dispersion, 1.60 g, 40.0 mmol) in dry DMF (70 mL) was cooled to 0°C and 1,3:4,6-di-*O*-benzylidene-D-mannitol (5.38 g, 15.0 mmol) dissolved in DMF (20 mL) was added slowly. The reaction was stirred for 30 min and *p*-methoxybenzyl chloride (3.64 mL, 36.0 mmol) was added. The mixture was stirred for 1.5 h at room temperature, diluted with ether, washed, dried ($MgSO_4$), and evaporated. The residue was purified on a silica gel column using hexane: ethyl acetate 8:2 v/v as an eluent to afford **25** (7.9 g, 85%). $[\alpha]_D=-30.4$ ($c=1.0$, CH_2Cl_2); IR (CH_2Cl_2): 1260, 1554 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.45–6.70 (m, 16H, Ar-H); 5.36 (s, 2H, acetal); 4.52 (2d, 4H, benzyl, $J=11.6$ Hz); 4.25 (dd, H-1a, H-6a); 3.67 (s, 6H, OMe); Anal. calcd for $C_{36}H_{38}O_8$: C, 72.22; H, 6.40. Found: C, 72.21; H, 6.53.

2,5-Di-*O*-(*p*-methoxybenzyl)-D-mannitol (26). A solution of **25** (5.94 g, 10.0 mmol) in methanol/water (10:1) (20 mL) was stirred in the presence of Bu_4NHSO_4 (0.80 g, 2.0 mmol) at 60°C. Stirring and heating were continued until disappearance of the substrate (8 h). After neutralization with sodium hydrogen carbonate, evaporation of the solvent, the crude product was purified by chromatography to afford **26** (1.63 g, 40%). $[\alpha]_D=-9.0$ ($c=1.9$, methanol); IR (CH_2Cl_2): 1264, 1533 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.23 and 6.86 (m, 8H, Ar-H); 4.55 (2d, 4H, benzyl, $J=11.1$ Hz); 3.89 (t, 2H, H-3, H-4, $J=6.1$ Hz); 3.79 (s, 6H, OMe); 3.82–3.75 (m, 4H, H-1a,1b, H-6a,6b); 3.61–3.52 (m, 2H, H-2, H-5); 2.84 (d, 2H, OH); 2.31 (t, 2H, OH). Anal. calcd for $C_{22}H_{30}O_8$: C, 62.55; H, 7.16. Found: C, 62.32; H, 6.90.

2,5-Di-*O*-(*p*-methoxybenzyl)-1,6-di-*O*-(*p*-toluenesulfonyl)-D-mannitol (27). Compound **26** (1.59 g, 4.0 mmol) in dry pyridine (40 mL) was cooled to 0°C and treated with *p*-toluenesulfonyl chloride (1.64 g, 8.6 mmol). The temperature of reaction was allowed to rise to room temperature and mixture was left until disappearance of the substrate (TLC, 24 h). Subsequently, the solution was poured into ice-water (100 mL) and extracted with *t*-butyl methyl ether (3×50 mL). Combine extracts were dried and evaporated. The crude product was purified by chromatography to afford **27** (2.60 g, 90%). $[\alpha]_D=-24.9$ ($c=1.2$, CH_2Cl_2); IR (CH_2Cl_2): 1176, 1250, 1514 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.77, 7.31 and 7.16, 6.85 (4×m, 16 H, Ar-H); 4.45 (2d, 4H, benzyl, $J=11.3$ Hz); 4.25 (dd, H-1a, H-6a, $J=2.7$ Hz); 3.79 (s, 6H, OMe); 3.77 (m, 4H, H-1a,1b, H-6a,6b); 3.58 (m, 2H, H-2, H-5); 2.84 (d, 2H, OH); 2.31 (t, 2H, OH). MS (HR, LSIMS) *m/z* $(M+Na)^+$, calcd for $C_{22}H_{30}O_7NaS$: 753.20154. Found: 753.19712.

(2*S*)-2-*O*-(*p*-Methoxybenzyl)-3-*O*-(*p*-toluenesulfonyl)-glycerol (28). A solution of $NaIO_4$ (0.86 g, 4.0 mmol) in water (30 mL) was added to an ice-cooled solution of **27** (2.20 g, 3.0 mmol) in methanol/water 1:1 (20 mL). After being stirred for 10 min, the mixture was filtered. While cooling (ice-water), the filtrate was treated with $NaBH_4$ (0.23 g, 6.0 mmol) and the mixture was stirred for 2 h. Subsequently, the mixture was adjusted to pH 8 by the careful addition of AcOH at 0°C, and it was extracted 4 times with ethyl acetate. The extract was dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel to afford **28** (1.65 g, 75%) as an oil. $[\alpha]_D=-20.4$ ($c=0.5$, CH_2Cl_2); IR (CH_2Cl_2): 1176, 1365, 1514, 2955 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.79 and 7.34 (m, 4H, Ar-H); 7.21 and 6.86 (m, 4H, Ar-H); 4.52 (2d, 2H, benzyl, $J=11.3$ Hz); 4.11 (d, 2H, H-3a,3b); 3.80 (s, 3H, OMe); 3.75–3.60 (m, 2H, H-1a,1b); 3.58 (m, 1H, H-2); 2.45 (s, 3H, Me); 1.82 (t, 1H, OH). MS (HR, LSIMS) *m/z* $(M+Na)^+$, calcd for $C_{18}H_{22}O_6NaS$: 389.10349. Found: 389.10372.

(2*S*)-1-*O*-(1′-Ethoxyethyl)-2-*O*-(*p*-methoxybenzyl)-3-*O*-(*p*-toluenesulfonyl)glycerol (31). A solution of alcohol **28** (1.10 g, 3.0 mmol) in ethyl vinyl ether (10 mL) was cooled to 0°C and treated with trifluoroacetic acid (2 μL). The mixture was left at room temperature until disappearance of the substrate (48 h). Subsequently, with stirring, pulverized sodium carbonate (0.10 g) was added. After 1 h the solution was filtered and the ether was evaporated. The crude product was purified on a silica gel column using hexane:*t*-butyl methyl ether 9:1 v/v as an eluent to afford **31** as a 1:1 diastereomeric mixture (1.27 g, 97%). IR ($CHCl_3$): 1177, 1362, 1456, 1612 cm^{-1}; ^1H NMR ($CDCl_3$): δ signals due to acetal protons of two diastereomers 4.66, 4.61 (2q, 1H, O–C**H**(CH_3)–O, $J=5.3$ Hz); MS (HR, LSIMS) *m/z* $(M+Na)^+$, calcd for $C_{22}H_{30}O_7NaS$: 461.16098. Found: 461.16412.

(2*S*)-2-*O*-(*p*-Methoxybenzyl)-3-*O*-(*p*-toluenesulfonyl)-1-*O*-vinylglycerol (32). A solution of **31** (0.88 g, 2.0 mmol) in dichloromethane (2 mL) was treated with triethylamine (0.42 mL, 3.0 mmol) under nitrogen. Upon cooling to 0°C, the mixture was stirred and treated dropwise with TMS-triflate (0.50 mL, 2.6 mmol). Stirring and cooling were continued until disappearance of the substrate (3 h). Subsequently, the mixture was treated with 10% sodium hydroxide (1 mL) and hexane (20 mL). Organic layer was separated, dried and evaporated. The crude product was purified on a silica gel column using hexane:*t*-butyl methyl ether 9.5:0.5 v/v as an eluent to give **32** (0.58 g, 75%). $[\alpha]_D=-17.0$ ($c=1.0$, CH_2Cl_2); IR (CH_2Cl_2): 1362, 1615, 1637 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.78 and 7.31 (m, 4H, Ar-H); 7.21 and 6.85 (m, 4H, Ar-H); 6.37 (dd, 1H, H-1′, $J=6.8$, 14.3 Hz), 4.52 (s, 2H, benzyl); 4.16 (dd, 1H, H-3a, $J=4.7$, 10.4 Hz); 4.12 (dd, 1H, H-2′*trans*, $J=2.3$, 14.5 Hz); 4.07 (dd, 1H, H-3b, $J=5.3$, 10.4 Hz); 4.01 (dd, 1H, H-2′*cis*, $J=2.3$, 6.8 Hz); 3.83 (m, 1H, H-2); 3.80 (s, 3H, OMe); 3.69 (d, 2H, H-1a,1b); 2.44 (s, 3H, Me). MS (HR, LSIMS) *m/z* $(M+Na)^+$, calcd for $C_{20}H_{24}O_6NaS$: 415.11914. Found: 415.12294.

(2*R*, 4′*S*)- and (2*R*, 4′*R*)-2-*O*-(Azetidin-2′-onyl-4′)-2-*O*-(*p*-methoxybenzyl)-3-*O*-(*p*-toluenesulfonyl)glycerol. (29 and 30). *Method A:* To a solution of CSI (61 μL, 0.7 mmol) in toluene (1 mL) anhydrous Na_2CO_3 (0.08 g) was added. The mixture was cooled to −78°C and upon stirring was treated dropwise with vinyl ether **32** (0.20 g, 0.5 mmol) in toluene (1 mL). Stirring and cooling were maintained for 1.5 h. Subsequently the mixture was diluted

with toluene (5 mL) and treated at −78°C with 1 M Red-Al in toluene. After 30 min temperature was allowed to rise to room temperature and water (0.4 mL) was added. The mixture was stirred for additional 30 min. Subsequently it was filtered through Celite and evaporated. Purification on a silica gel column using hexane:ethyl acetate 7:3 v/v as an eluent gave a mixture of **29** and **30** (0.12 g, 52%, d.e. 25.6%). IR ($CHCl_3$): 1768, 3425 cm^{-1}; ^1H NMR ($CDCl_3$) signals due to **29** inter alia: 4.95 (dd, 1H, H-4′, J=1.5, 4.0 Hz); 3.04 (ddd, 1H, H-3′b, J=2.6, 5.2, 15.1 Hz); 2.73 (ddd, 1H, H-3′a, J=0.6, 1.5, 15.1 Hz), signals due to **30** inter alia: 5.01 (dd, 1H, H-4′, J=1.5, 3.9 Hz); 3.02 (ddd, 1H, H-3′b, J=2.7, 5.2, 15.1 Hz); 2.79 (ddd, 1H, H-3′a, J=0.6, 1.5, 15.1 Hz). MS (HR, LSIMS) m/z $(M+H)^+$, calcd for $C_{21}H_{26}O_7NS$: 436.14300. Found: 436.14166.

Method B: The title compounds **29** and **30** (68%, d.e. 13.0%) were prepared from 4-acetoxy-2-azetidinone (**1**) and **28** according to the procedure described for compounds **14**–**17**.

(3*S*, 6*S*)- and (3*S*, 6*R*)-3-(*p*-Methoxybenzyloxy)-1-oxacephams (33 and 34). A mixture of **33** and **34** was obtained from a mixture of **29** and **30** according to the procedure described earlier (87%).[5a] Compounds **33** and **34** were separated on a silica gel column using CH_2Cl_2: toluene:*t*-butyl methyl ether 6:2:2 v/v as an eluent.

*Major product **33**, less polar (TLC):* $[\alpha]_D$=−54.0 (c=0.2, CH_2Cl_2); IR (CH_2Cl_2): 1758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.89 (d, 1H, H-6, J=3.2 Hz); 4.49 (2d, 2H, benzyl, J=11.4 Hz); 4.14 (ddd, 1H, H-2a, J=1.7, 5.9, 12.9 Hz); 4.07 (ddd, 1H, H-4a, J=1.7, 4.5, 11.4 Hz); 3.57 (m, 1H, H-3); 3.35 (dd, 1H, H-4b, J=11.4 Hz); 3.10 (ddd, 1H, H-7a, J=1.8, 3.3, 14.9 Hz); 2.77 (ddd, 1H, H-2b, J=1.7, 9.6, 12.9 Hz); 2.76 (dd, 1H, H-7b, J=0.5, 14.9 Hz); MS (HR, LSIMS) m/z $(M+H)^+$, calcd for $C_{14}H_{18}O_4N$: 264.12360. Found: 264.12184.

*Minor product **34**, more polar (TLC):* $[\alpha]_D$=70.3 (c=0.2, CH_2Cl_2); IR (CH_2Cl_2): 1766 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.96 (d, 1H, H-6, J=3.2 Hz); 4.55 (2d, 2H, benzyl, J=11.3 Hz); 4.17 (dt, 1H, H-2a, J=2.4, 12.7 Hz); 4.04 (ddd, 1H, H-4a, J=1.4, 2.4, 14.4 Hz); 3.71 (dd, 1H, H-2b, J=1.2, 12.7 Hz); 3.34 (m, 1H, H-3); 3.17 (ddd, 1H, H-7a, J=1.2, 3.3, 14.9 Hz); 3.02 (ddd, 1H, H-4b, J=1.6, 2.8, 14.4 Hz); 2.96 (dd, 1H, H-7b, J=0.5, 14.9 Hz); MS (HR, LSIMS) m/z $(M+H)^+$, calcd for $C_{14}H_{18}O_4N$: 264.12360. Found: 264.12162.

Steady-state NOE experiments

Steady-state NOEs for **33** (ca. 10 mg in 0.7 ml C_6D_6) and **34** (ca. 10 mg in 0.7 ml C_6D_6) were measured at room temperature on a Varian INOVA 500 spectrometer using a routine program for multiplet irradiation (Fig. 1). The samples were degassed to minimize external relaxation. The longest ^1H T_1 determined for the samples were used for setting up the total irradiation time necessary to produce steady-state NOEs. The experimental conditions used were: 15 s total irradiation, 4 s acquisition, 5000 Hz spectral width. NOE intensities were calibrated by using a reference signal that was unaffected by the irradiation, and the same phase parameters were used for reference and irradiated spectra. The estimated precision of the experimental NOE values is 1% of NOE.

(*R*)-1-*O*-*p*-Chlorobenzenesulfonyl-2,3-di-*O*-*p*-methoxybenzyl glycerol (36). To a solution of compound **35**[14] (10 mmol, 2.66 g) in dry methylene chloride (50 mL) was added *p*-methoxybenzyl-2,2,2-trichloroacetimidate (40 mmol, 11.3 g) and 10-camphorosulfonic acid (1 mmol, 0.232 g). After stirring for 24 h at r.t., the precipitate was filtered off, washed with hexane–methylene chloride 1:1 mixture, filtrates were combined, and concentrated. Crude product was purified on silica gel using hexane:*t*-butylmethyl ether 4:1, v/v as an eluent to afford **36** as a white crystals 2.96 g (58 %), mp. 85.5–86.5°C; $[\alpha]_D$=1.4 (c=1.0, CH_2Cl_2); IR (CH_2Cl_2): 1623, 1514 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.48 and 4.39 (2×bs, 4H, benzyl); 4.22 (dd, 1H, H-1a, J=10.4, 4.0 Hz); 4.11 (dd, 1H, H-1b, J=10.4, 5.7 Hz); 3.81 (s, 6H, OMe); 3.80–3.69 (m, 1H, H-2); 3.47 (d, 1H, H-3a, J=0.8 Hz); 3.44 (d, 1H, H-3b, J=1.8 Hz);. MS (LSIMS, HR) m/z: $(M+Na)^+$ calcd for $C_{25}H_{27}O_7ClNaS$: 529.10637. Found: 529.10779. Anal. calcd for $C_{25}H_{27}O_7ClS$: C, 59.23; H, 5.37; Cl, 6.99; S, 6.32. Found: C, 59.15; H, 5.43; Cl, 7.04; S, 6.37.

3,4-Di-*O*-allilo-1,2,5,6-tetra-*O*-*p*-methoxybenzyl-D-mannitol (39). Sodium hydride (130 mmol, 5.2 g 60% in oil) was washed with hexane and suspended in dry DMF (150 mL) under argon atmosphere. Into this mixture mannitol **38**[15] (25 mmol, 6.54 g) in DMF (50 mL) was added dropwise with stirring at rt. After 20 min PMB chloride (110 mmol, ~15 mL) was added dropwise during 30 min. Stirring was continued for 2 h. Subsequently the mixture was poured into cold water and extracted with toluene (3×200 mL). The extract was washed with water, dried ($MgSO_4$), and evaporated. The crude product was purified on silica gel using hexane:ethyl acetate 4:1, v/v as an eluent to afford **39** as an oil, (15.5 g, 84%).$[\alpha]_D$=12.7 (c=0.5, CH_2Cl_2); IR (CH_2Cl_2): 2864, 1613, 1514 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.23–6.83 (m, 16H,): 5.84 (ddt, 2H, –C**H**=, J=17.2, 10.4, 5.7 Hz); 5.15 (ddd, 2H, =CH_a**H_b**, J=17.2, 3.4, 1.6 Hz); 5.05 (ddd, 2H, =**CH_a**H_b, J=10.4, 3.4, 1.2 Hz); 4.50 (dd, 4H, benzyl, J=11.3 Hz); 4.43 (2d, 4H, PMB, J=11.3 Hz); 4.10 (ddt, 2H, **CH_a**H_bCH=, J=12.5, 5.7, 1.6 Hz); 4.02 (ddt, 2H, CH_a**H_b**CH=, J=12.5, 5.7, 1.2 Hz); 3.78 (bs, 12H, OMe); 3.82–3.76 (m, 6H, H-1a, H-2, H-3, H-4, H-5, H-6a); 3.62 (dd, 2H, H-1b, H-6b, J=11.4, 5.0 Hz). MS (LSIMS, HR) m/z: $(M+Na)^+$ calcd for $C_{44}H_{56}O_{10}Na$: 765.36147. Found: 765.36495. Anal. calcd for $C_{44}H_{56}O_{10}$: C, 71.14; H, 7.33. Found: C, 70.28; H, 7.14.

1,2,5,6-Tetra-*O*-*p*-methoxybenzyl-D-mannitol (40). A solution of **39** (11.02 g, 14.8 mmol) in DMSO (100 mL) was treated with potassium *t*-butoxide (8.32 g, 74.3 mmol) under nitrogen. The mixture was stirred at 60°C until disappearance of the substrate (2 h). Subsequently it was poured into ice-water (500 mL) and extracted with *t*-butyl methyl ether (3×100 mL). Combine extracts were dried and evaporated. The crude product was dissolved in CH_2Cl_2 (150 mL) and 3 mL of ethanolic saturated solution of ozonizable dye (Sudan red 7B)[20] was placed in the three-necked flask, equipped with thermometer, bubbling tube and ozone outlet. The solution was stirred and upon cooling

to −78°C, ozone was bubbled through. After about 20 min, the deep red color of the reaction mixture turned to light yellowish. The ozone generator was switched off, and oxygen was passed through the solution for 2 min. Dimethyl sulfide (9.5 ml) was added in one portion, and stirring was continued at −78°C for 20 min. The reaction mixture was brought to r.t. and the solvent was evaporated. The crude mixture was dissolved in methanol and treated with triethylamine (5 mL) and mixture was left for (24 h), until disappearance of the substrate (TLC). After 24 h the solution was evaporated to dryness. The yellow oil was chromatographed using hexane:ethyl acetate 1:1, v/v as an eluent to give a **40** (7.8 g). Oil, $[\alpha]_D=-12.4$ (c=0.7, CH_2Cl_2); IR (CH_2Cl_2): 3473, 2934, 1613, 1514 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.25–6.81 (m, 16H, Ar-H); 4.63 and 4.50 (2×d, 4H, PMB, J=11.2 Hz); 4.47 (s, 4H, PMB); 3.90 (t, 2H, H-3, H-4, J=5.8 Hz); 3.79, 3.78 (2×s, 12H, OMe); 3.79–3.69 (m, 2H, H-2, H-5); 3.69 (dd, 2H, H-1a, H-6a, J=10.0, 4.3 Hz); 3.61 (dd, 2H, H-1b, H-6b, J=10.0, 4.8 Hz); 3.03 (d, 2H, OH, J=5.8 Hz). MS (LSIMS, HR) m/z: $(M+Na)^+$ calcd for $C_{38}H_{46}O_{10}Na$: 685.29887. Found: 685.30309. Anal. calcd for $C_{38}H_{46}O_{10:}$ C, 68.84; H, 7.00. Found: C, 68.59; H, 7.03.

(2*S*)-2,3-Di-*p*-methoxybenzyl glycerol (41). A solution of $NaIO_4$ (7.6 g, 13.0 mmol) in water (100 mL) was added to an ice-cooled solution of **40** (7.6 g, 11.5 mmol) in methanol/water 1:1 (200 mL). After being stirred for 30 min, the mixture was filtered. The filtrate, was treated with $NaBH_4$ (0.378 g, 10.0 mmol) under ice-cooling, and the mixture was stirred at 0°C for 2 h. The mixture was adjusted to pH 8 by the careful addition of AcOH at 0°C and extracted 4 times with ethyl acetate. The extracts were dried over Na_2SO_4, and the solvent was evaporated. The residue was chromatographed on silica gel using hexane:ethyl acetate 3:2, v/v as an eluent to afford **41** (5.5 g, 72%) as an oil. $[\alpha]_D=-21.0°$ (c=1.2, $CHCl_3$), Lit. $[\alpha]_D=-21.3°$ (c=1.0, $CHCl_3$).[21]

(*R*)-2,3-Di-*p*-methoxybenzyl-1-*O*-trifluoromethanesulfonyl glycerol (42). 2,6-Lutidine (12 mmol, ~1.4 ml) was dissolved under argon in dry CH_2Cl_2 (20 ml) and after cooling was added dropwise to −20°C triflic anhydride (10 mmol, ~1.7 ml). The mixture was stirred for 5 min and then a solution of hydroxy compound **41** (3.0 g, 9 mmol) in CH_2Cl_2 (15 ml) was added dropwise. Stirring and temperature were maintained for ~30 min (TLC control). Subsequently the solution was warmed up to 0° and poured into ice-water (100 ml). The organic phase was separated, washed with cold water (3×50 ml), dried ($MgSO_4$) and evaporated. The crude oil was dissolved in *t*-butyl-methyl ether (~10 ml) and titrated with hexane (~30 ml). The precipitate was filtered off through Celite and the filtrate was concentrated to give crude triflate **42**, which was promptly used for the next step without any further purification.

(4*S*,2′*S*)- and (4*R*,2′*S*)-1-[2′,3′-Di-(*p*-methoxybenzyloxy)propan-1′-yl]-4-vinyloxyazetidin-2-one (37). Alkylation of 3 with 4-chlorobenzenesulfonate (36). To a stirred suspension of fine powdered tetrabutylammonium hydrogen sulfate (3.57 g, 10.5 mmol) in dry THF (70 ml) under argon was added 3 (10 mmol, 1.13 g). Into this mixture, upon cooling to −78°C, butyllithium (21 mmol, 8.4 ml of 2.5 M/hexane) was added and after 20 min sulfonate **36** (1.673 g, 3.3 mmol) in a THF solution (10 ml) was added. Stirring was continued at −78°C for 15 min and subsequently the mixture was allowed to warm to rt. Stirring was maintained for additional 24 h and then the reaction mixture was poured into water (300 ml) and extracted with *t*-butyl-methyl ether (3×150 ml). Combined extracts were washed with water, dried ($MgSO_4$) and evaporated. Crude product was purified on silica gel using hexane:*t*-butylmethyl ether 2:3, v/v as an eluent to afford **37** as an oil, 0.325 g (23%). IR (CH_2Cl_2): 1766, 1641, 1613 cm^{-1}; ^1H NMR ($CDCl_3$) selected data for the 1:1 mixture of diastereomers: δ 6.33 and 6.32 (2×dd, 2H, OCH=, J=14.3, 6.8); 5.23 and 5.13 (2 dd, 2H, H-4, J=3.6, 1.1 Hz); 3.02 and 2.98 (2 dd, 2H, H-3a, J=14.8, 3.6 Hz); 2.79, 2.78 (2 bd, 2H, H-3b, J=14.8 Hz); MS (LSIMS, HR) m/z: $(M+Na)^+$ calcd for $C_{24}H_{29}O_6NNa$: 450.189258. Found: 450.190706. Anal. calcd for $C_{24}H_{29}O_6N$: C, 67.43; H, 6.84; N, 3.28. Found: C,67.40; H, 6.88; N, 2.99.

Alkylation of 3 with crude triflate 42. Alkylation of **3** (1.356 g, 12 mmol) with crude triflate **42** (~9 mmol) was performed as describe above. Reaction was completed after 1 h to afford **37** (3.02 g, 78%).

(4*S*,2′*S*)- and (4*R*,2′*S*)-1-[2′,3′-Di-(*p*-methoxybenzyloxy)propan-1′-yl]-4-formyloxyazetidin-2-one (43). The solution of **37** (2.99 g, 7 mmol) in CH_2Cl_2 (100 mL) and 3 mL of ethanolic saturated solution of ozonizable dye (Sudan red 7B)[20] was placed in the three-necked flask, equipped with thermometer, bubbling tube and ozone outlet. The solution was stirred and upon cooling to −78°, ozone was bubbling. After about 15 min, the deep red color of the reaction mixture turned to light yellowish. The ozone generator was switched off, and oxygen was passed through the solution for 2 min. Dimethyl sulfide (2 ml) was added in one portion, and stirring was continued at −78°C for 20 min. The reaction mixture was brought to rt and the solvent was evaporated. Crude product was purified on silica gel using hexane:*t*-butylmethyl ether 1:4, v/v) to afford **43** as an oil, (2.01 g, 67%). IR (CH_2Cl_2): 1774, 1731, 1612 cm^{-1}; ^1H NMR ($CDCl_3$) selected data for the 1:1 mixture of diastereomers: δ 7.94 and 7.92 (2 d, 2H, C**H**O, J=0.5 Hz); 6.03 and 5.86 (2 bd, 2H, H-4, J=3.6 Hz); 3.15 and 3.14 (2 dd, 2H, H-3a, J=15.0, 3.6 Hz), 2.86 and 2.84 (2 bd, 2H, H-3b J=15.0 Hz), MS (LSIMS, HR) m/z: $(M+Na)^+$ calcd for $C_{23}H_{27}O_7NNa$: 452.16852. Found: 452.16789. Anal. calcd for $C_{23}H_{27}O_7N$: C, 64.32; H, 6.34; N, 3.26. Found: C, 64.33; H, 6.60; N, 3.07.

(3*S*,6*R*)- and (3*S*,6*S*)-1-Dethia-3-(4-methoxybenzyloxy)-1-oxacephams 33-ent and 34-ent. To a stirred suspension of molecular sieves A-4 (~0.3 g) in CH_2Cl_2 (40 mL) 4-formyloxy-β-lactam **43** (2.5 mmol, 1.074 g) in 5 mL of CH_2Cl_2 was added. After 5 min $BF_3{\cdot}Et_2O$ (1.0 mmol, 126 μL) was added in one portion. The mixture was stirred for ~40 min (TLC control). The saturated solution of $NaHCO_3$ (10 mL) was added and stirring was continued for 10 min. The organic phase was separated, washed with water, dried ($MgSO_4$) and evaporated. ^1H NMR spectra of

crude product showed that reaction mixture was consisted of oxacephams (**33-ent**) and (**34-ent**), in the proportion of 3:7 (NMR). Purification on silica gel (eluent: hexane:ethyl acetate 3:1→2:3, v/v) gave two fractions: first fraction contained **33-ent**, oil 0.11 g (17%) $[\alpha]_D$=53.3 (c=0.5, CH_2Cl_2), second fraction (210 mg, 31%) consisted of oxacepham **34-ent**, $[\alpha]_D$=−70.9 (c=0.4, CH_2Cl_2).

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