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Synthesis of Enantiomerically Pure 2-Isoxacephems

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Summary. (αR,6*R*,7*R*)-7-(1-Acetoxyethyl)-3-methyl-2-isoxacephem-4-carboxylic acid and its enantiomer have been prepared. The ring systems were formed from the corresponding enantiomerically pure *N*-unsubstituted β-lactams. The reduction of methyl [(αR,2*S*,3*R*)-3-(1-acetoxyethyl)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate] has been solved *via* a hemi-acetal. The structure and the configuration of a new stereogenic center in this intermediate was predicted by using 2D NMR technique and unambiguously proven by x-ray.

Keywords. Antibiotics; β-Lactams; Chiral building block; Enantioselectivity.

Introduction

Mono- and bicyclic β-lactams play a distinctive role in the therapy of bacterial infections [1]. After the discovery of penicillins and cephalosporins, interest turned to their nuclear analogues, such as carbapenems, oxacephems, and 2-isocephems [2]. The research activity is still high owing to the growing number of resistant strains of bacteria [3]. An excellent review was published in the late nineties showing the growing spectra of resistant bacteria and the broad variations of their resistance mechanism [4]. The first carbapenem, thienamycin **1a** and its formamidine derivative **1b** have been a great breakthrough in the antibacterial chemotherapy for years owing to their broad spectra and β-lactamase stability due to the 2-hydroxyethyl side chain.

The more stable **1b** is used under the trade name *Imipenem* with cilastatin sodium, which prevents renal metabolism of penem and carbapenem antibiotics

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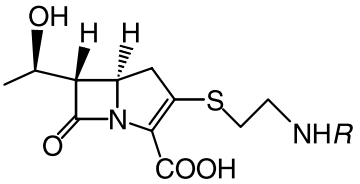
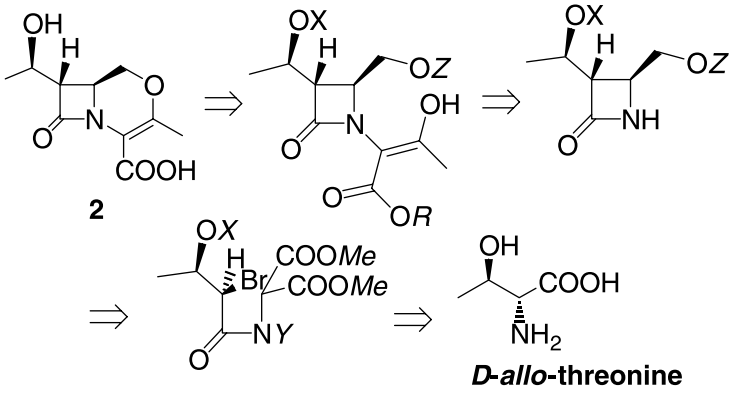


1a $R = H$
1b $R = -CH{=}NH$

Fig. 1. Thienamycin (**1a**) and its formamidine **1b**



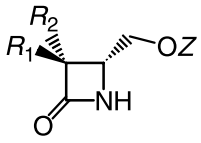
Scheme 1

by specific and reversible dehydropeptidase I inhibition. It makes thienamycin a very expensive agent.

Among the 2-isoxa- and 2-isocephems some exhibited rather high antibacterial activity [5]. Now, we decided to introduce the 1-hydroxyethyl group with proper stereochemistry into position 7 of the 2-isoxacephem structure as shown in compound **2**. The retrosynthetic analysis of **2** shown in Scheme 1 led us to *D-allo*-threonine as a chiral building block for the total synthesis of the target compound **2**. The synthetic methods leading to 2-isoxacephems have been worked out by using the cheapest threonine (*L*) and extended to the *D*-series. So, we have used these amino acids first in order to see, whether our synthetic pathway is feasible or not.

Results and Discussion

In recent papers we have described the stereoselective synthesis of monocyclic β-lactams [6, 7] which has unambiguously shown the possibility of preparation of the target *trans*-2-isoxacephems with optional stereochemistry. Before starting with the properly substituted monocyclic compounds, the scope and limitation of two methods leading to 2-isoxacephems have been studied. We first report the extension and comparison of these methods starting from **3** and **4** as model compounds (Scheme 2) in order to find the most effective route (for further examples see Ref. [8]).



3 - 4

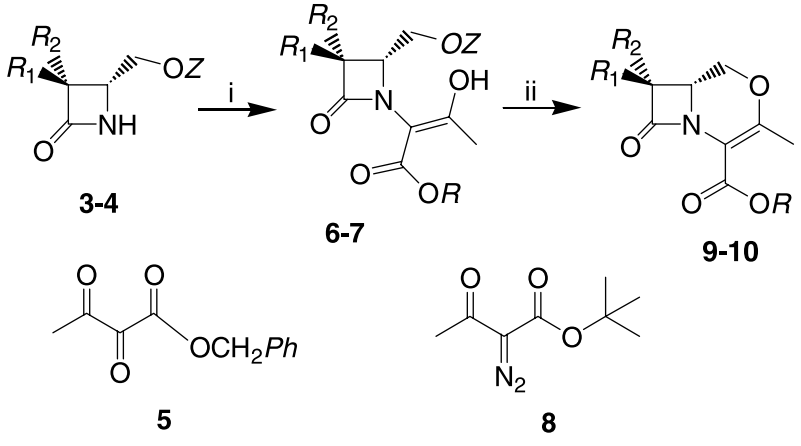
3 R_1=R_2=H, *Z*=*Ts* (racemic)
4 R_1=*i-Pr*, R_2=H, *Z*=*Ms* (racemic)

Scheme 2

Compound **3** is unsubstituted in position 3; compound **4** and the molecule to be synthesized have sterically very similar substituents.

The first procedure (Method A) developed by us starts with the reaction of *N*-unsubstituted β-lactams with benzyl 2,3-dioxobutyrate **5** [9] and the adducts are converted without isolation into the corresponding 2-(2-oxo-3,4-disubstituted-azetidin-1-yl)acetoacetates **6a** and **7a**. The second method (Method B) was described by *Durst* [10]. It is based on an intermolecular carbene (generated from the corresponding diazo ester **8**) insertion reaction into the β-lactam N–H group providing the acetoacetates **6b** and **7b**. In both methods cyclizations are carried out with triethylamine in chloroform (**9a**, **10a**, **9b**, **10b**). In all cases, the ''dioxobutyrate'' method gave better yields than the carbene insertion one.

A benzyl group was used in the ''dioxobutyrate'' method, a *tert*-butyl group in the carbene insertion method as carboxyl protecting group. According to our earlier results the *tert*-butyl ester protecting group can be removed easily by using $AlCl_3$ in anisole [11] but the yields depend very much on substituents in position 7. Benzyl and allyl protecting groups cannot be used in carbene insertion reactions [12]. Similarly to other carbene insertion reactions, they are also very substrate



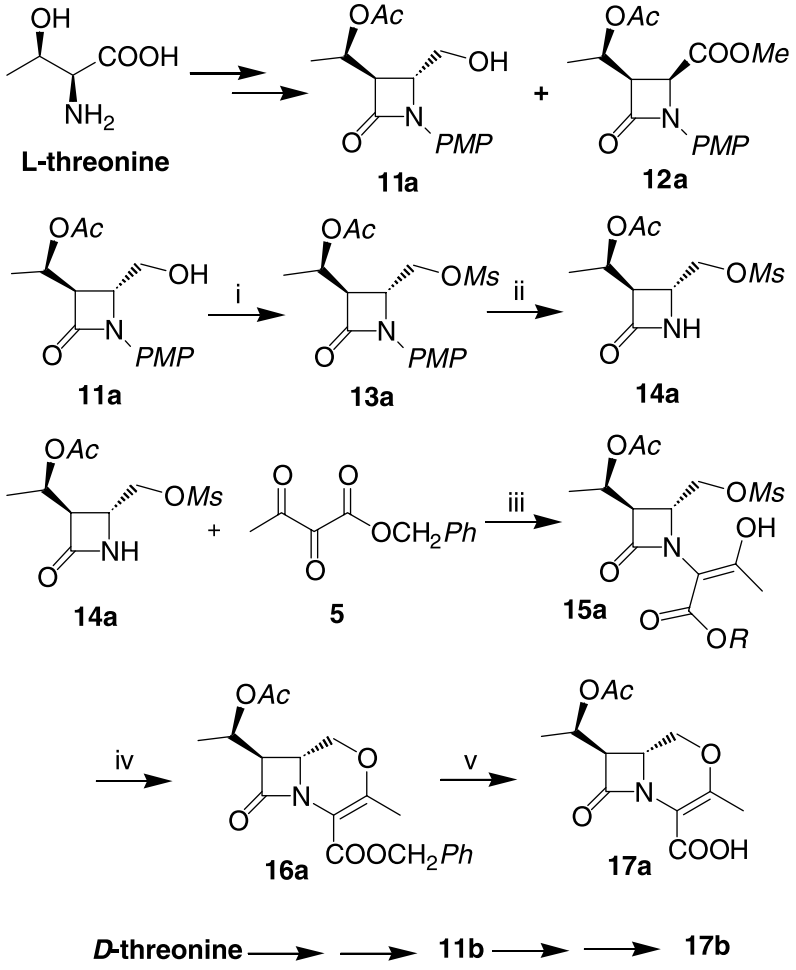
3, **6, 9** R_1=R_2=H, *Z*=*Ts* (racemic)
4,7,10 R_1=*i-Pr*, R_2=H, *Z*=*Ms* (racemic)

Scheme 3. i: **A** *R* = benzyl: a) **5**, Et_3N/THF/rt, b) $SOCl_2/Py/THF/-25°C$, c) $Zn/AcOH/4°C$; **B** (R = *tert*-butyl): 6 equiv. **8**, 5 mol-% $Rh_2(OAc)_4$/benzene/reflux; ii: $CHCl_3/Et_3N$/reflux

Table 1. Overall yields of the products **9** and **10**

Starting materials	Method **A**		Method **B**	
3 $R^1 = R^2 = H$; $Z = Ts$ **4** $R^1 = i\text{-}Pr$; $R^2 = H$; $Z = Ms$	$R = Bn$		$R = t\text{-}Bu$	
	Product	Yield	Product	Yield
	9a	42%	**9b**	25%
	10a	46%	**10b**	10%

dependent in our cases as well. In model compounds containing a 3-acylamino group in monocyclic β-lactams the yields are satisfactory or good [10, 11] but in the reactions of the compounds studied in this paper they are rather low. We think that the $Rh_2(OAc)_4$ catalyst must form a complex with the β-lactam substrate and with the diazoacetoacetate, which brings the carbene close to the β-lactam N–H

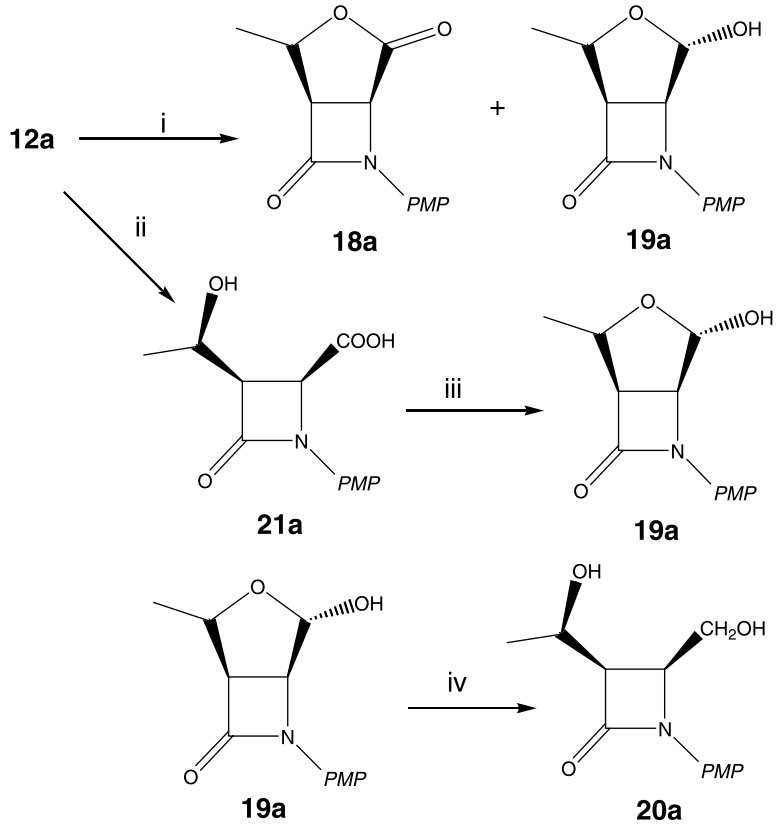


Scheme 4. i: mesyl chloride/*Py*/0–25°C; ii: ammonium cerium(IV) nitrate/acetonitrile/water/0°C; iii: a) Et_3N/*THF*/25°C, b) $SOCl_2$/*Py*/−25°C, c) Zn/*Ac*OH/4°C; iv: $Et_3N/CHCl_3$/reflux; v: H_2/10% Pd/C/*Et*O*Ac*

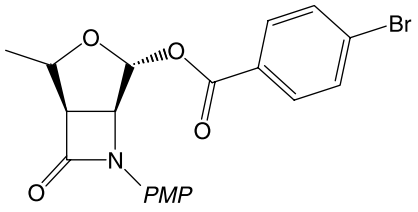
group. Changing the catalyst from Rh to Cu will not improve the results, because *O*-alkylation will be preferred instead of carbene insertion into the N–H bond in case of lactams [13]. In spite of these results the carbene insertion reaction has been tried on compound **14a** as well, but the expected enol ester could not be detected.

These preliminary experiences have convinced us about the only suitable way, which might provide the target compounds **17a** and **17b** with satisfactory yield and excellent optical purity. We have already proven the absolute configuration in compound **12a** (αR,2*S*,3*R*), which determines the absolute configuration in compound **11a** (αR,3*R*,4*R*) [7]. The following steps towards the target product **17a** do not affect the stereogenic centers, which means that the ''dioxobutyrate''-method furnishes the enantiomerically pure benzyl ester that after hydrogenolyses provides the (αR,6*R*,7*R*)-7-(2-acetoxyethyl)-3-methyl-2-isoxacephem-4-carboxylic acid (**17a**). Similarly, starting from D-threonine the enantiomer 2-isoxacephem-4-carboxylic acid (**17b**) could be obtained.

The reduction of *cis*-esters **12a** and **12b** should be solved in order to prepare *cis*-annelated-2-isoxacephems. The ester **12a** was used for preliminary investigations. In the first experiments di(isobutyl)aluminum hydride in toluene or *THF* was chosen as reduction agent. The reactions were carried out at −78°C. Two products



Scheme 5. i: *DIBAL*/*THF*/−78°C; ii: 1 *N* HCl/reflux; iii: a) ClCOOEt/Et_3N/*THF*/−20°C, b) $NaBH_4$/*Me*OH/−20°C; iv: $NaBH_4$/*Me*OH/rt



22a

Scheme 6

were formed in low yield, a bicyclic lactone **18a** and a bicyclic hemi-acetal **19a**. The reduction of **19a** with sodium borohydride provided the *cis*-diol **20a** in very good yield. The ester **12a** could be hydrolyzed with diluted hydrochloric acid at surprisingly high temperature to the hydroxyacid **21a** in good yield without destroying the β-lactam ring. The reduction of **21a** provided the hemi-acetal **19a** in excellent yield by using the mixed anhydride method [14]. Although **19a** has a new stereogenic center, it proved to be diastereomerically pure according its NMR spectra.

The dihedral angle of hydrogen atoms in position 4 and 5 of **19a** is approximately 90°. That is the reason, why there is no coupling between them in the ^{1}H NMR spectrum. Knowing the absolute configuration in position 5 (*S*), the absolute configuration in position 4 must be (*S*). Compound **19a** was *O*-acylated by 4-bromobenzoyl chloride and the product **22a** crystallized from dichloromethane.

Its Ortep plot is depicted in Fig. 2 showing that our prediction has been correct.

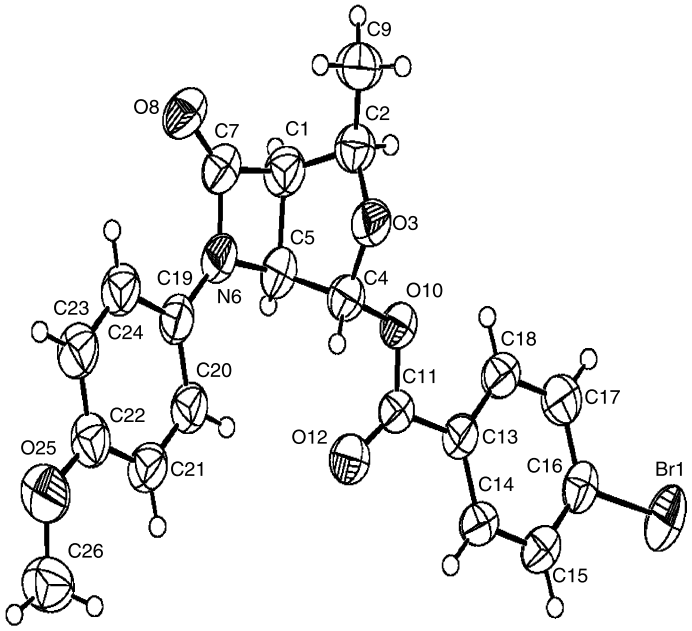


Fig. 2. Molecular structure of **22a**; atomic displacement ellipsoids represent 50% probabilities

Conclusion

Starting with building block threonine all stereoisomers of 2-isoxacephem can be prepared in principle by stereoselective reactions. Two of the isomers (**17a** and **17b**) have been successfully synthesized and the route leading to *cis*-annelated 2-isoxacephems has also been opened.

Experimental

Melting points were determined on a hot stage melting point apparatus and are uncorrected. Optical rotations ($c = 1.0\,g/100\,cm^3$, CH_2Cl_2) were taken on a Perkin-Elmer 241 polarimeter, that was calibrated by measuring the optical rotations of both enantiomers of menthol. The ^1H and ^{13}C NMR spectra were obtained using a Bruker DRX 500 spectrometer (^1H 500.33 MHz, ^{13}C 125.75 MHz) at 298 K in $CDCl_3$ as solvent, unless stated otherwise. The IR spectra were recorded on a Specord M80 spectrophotometer. Mass spectra were measured with a Fisons Trio 1000 spectrometer at 70 eV, unless stated otherwise. Elemental analyses (C, H, N, S) were conducted using the Elemental Analyser VARIO EL III (Elementar Analysensysteme Gmbh), their results were found to be in good agreement ($\pm 0.2\%$) with the calculated values. Column and thin-layer chromatography were carried out on Merck Kieselgel 60 (0.063–0.2 mm) and Merck Kieselgel 60 F_{254} Alufolien, respectively. For preparative TLC Merck PSC ready-for-use plates (Kieselgel 60 F_{254}, 20×20 cm, 2 mm) were used. TLC spots were detected by UV, and/or phosphomolybdenic acid (*PMA*). All of the known compounds (**9a** [11], **9b** [11], **10a** [9]) were identified by their spectra. They are given in the experimental part, if the resolution of their NMR spectra is higher, than those in the earlier papers.

Method A

N-Unsubstituted β-lactams **3**–**4** (10.0 mmol) and benzyl 2,3-dioxobutyrate **5** [9] (11.0 mmol) were dissolved in 100 cm^3 of *THF* containing triethylamine (0.14 cm^3). This solution was stirred at ambient temperature until the starting material had practically disappeared (0.5 h). The solution was cooled to $-25°C$ and pyridine (1.33 cm^3, 13.0 mmol) was added to the mixture. Thionyl chloride (0.9 cm^3, 12.5 mmol) in *THF* (30 cm^3) was added dropwise at the same temperature and the mixture was stirred for 1 h. It was allowed to warm up to room temperature, and the insoluble material was removed by filtration. The solution was evaporated to dryness and the residue was taken up in a mixture of acetic acid (200 cm^3) and water (30 cm^3). This solution was cooled to 4°C and stirred with Zn powder (3.3 g) for 1 h. Inorganic material was filtered off, and the filtrate was concentrated in vacuum to dryness. The residue was taken up in a mixture of CH_2Cl_2 and water (160 cm^3 each). The organic layer was separated, dried ($MgSO_4$), and the solution was concentrated to give an oily crude product as a mixture of **6a** and **7a** (TLC, *n*-hexane:ethyl acetate = 6:5, R_f(**6a**): 0.3, R_f(**7a**): 0.5). This crude product was dissolved in 60 cm^3 of $CHCl_3$ and was refluxed in the presence of Et_3N (2.0 cm^3, 14.4 mmol) for 2 h. The concentrated solution was purified by column chromatography (R^1 = H or *i-Pr*, *n*-hexane:ethyl acetate = 10:0.1 → 10:2, TLC: *n*-hexane:ethyl acetate = 6:5, R_f(**9a**): 0.6, R_f(**10a**): 0.8). Fractions with appropriate R_f values were collected and evaporated to give **9a** (42%) and **10a** (46%).

Method B

N-Unsubstituted β-lactams **3**–**4** (10.0 mmol) were dissolved in hot benzene (75 cm^3) and rhodium acetate (0.5 mmol) was added to this mixture. This solution was heated to reflux temperature. *t*-Butyl 2-diazo-3-oxobutyrate **8** (60.0 mmol) was dissolved in 30 cm^3 of benzene and this solution was dropped into the reaction mixture. The solution was cooled to room temperature after 30 min refluxing. Rhodium acetate was filtered off, and the filtrate was clarified with charcoal, and concentrated in

vacuum. The residue was purified by column chromatography ($R^1 = H$ or *i-Pr*, *n*-hexane:ethyl acetate = 10:0.1 → 1:1, TLC: *n*-hexane:ethyl acetate = 6:5, R_f(**6b**): 0.3, R_f(**7b**): 0.4. The oily product was refluxed in $CHCl_3$ (25 cm^3) in the presence of Et_3N (1.4 eq.) for 2 h. The solution was concentrated to dryness and the crude product was purified by column chromatography ($R^1 = H$ or *i-Pr*, *n*-hexane:ethyl acetate = 10:0.1 → 1:1, TLC: *n*-hexane:ethyl acetate = 6:5, R_f(**9b**): 0.6, R_f(**10b**): 0.8) to give **9b** (25%), **10b** (10%).

tert-Butyl (+/−)-3-Methyl-2-isoxacephem-4-carboxylate
(**9b**, $C_{12}H_{17}NO_4$, $R^1 = R^2 = H$, $R = t\text{-}Bu$) [11]

Mp 94–96°C (ethyl acetate); IR (KBr): $\bar{\nu} = 3000$, 1760, 1690, 1210, 1100, 1050 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.54$ (s, $C(CH_3)_3$), 2.22 (s, 3-CH_3), 2.63 and 3.45 (ABX, $J_{gem} = 15.2$, $J_{trans,H6} = 1.9$, $J_{cis,H6} = 4.8$ Hz, 7-CH_2), 3.53 (dddd, $J_{trans,H7_A} = 1.9$, $J_{cis,H7_B} = 4.8$, $J_{H6,1-CH_2} = 9.5$ and 3.2 Hz, H6), 3.59 and 4.62 (ABX, $J_{gem} = 10.0$, $J_{1-CH_2,H6} = 9.5$ and 3.2 Hz, 1-CH_2) ppm.

Benzyl (+/−)-trans-7-Isopropyl-3-methyl-2-isoxacephem-4-carboxylate
(**10a**, $C_{17}H_{19}NO_4$, $R^1 = i\text{-}Pr$, $R^2 = H$, $R = Bn$) [9]

Mp 78°C (diisopropyl ether); IR (KBr): $\bar{\nu} = 1770$, 1700 (CO) cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.03$ and 1.10 (2d, $J_{vic} = 6.6$ Hz, $CH(CH_3)_2$), 2.19 (m, $J_{vic} = 6.6$, $J_{H\alpha,H7} = 7.5$ Hz, $CH(CH_3)_2$), 2.23 (s, 3-CH_3), 2.64 (dd, $J_{H7,H\alpha} = 7.5$, $J_{trans,H6} = 2.0$ Hz, H7), 3.27 (ddd, $J_{H6,1-CH_2} = 9.5$ and 3.5, $J_{trans,H7} = 2.0$ Hz, H6), 3.64 (dd, $J_{gem} = 10.5$, $J_{H1_A,H6} = 9.5$ Hz, $H1_A$), 4.60 (dd, $J_{gem} = 10.5$, $J_{H1_B,H6} = 3.5$ Hz, $H1_B$), 5.28 (s, CH_2Ph), 7.25–7.55 (m, 5 ArH) ppm.

tert-Butyl (+/−)-trans-7-Isopropyl-3-methyl-2-isoxacephem-4-carboxylate
(**10b**, $C_{15}H_{23}NO_4$, $R^1 = i\text{-}Pr$, $R^2 = H$, $R = t\text{-}Bu$)

Mp 82–85°C (ethyl acetate); IR (KBr): $\bar{\nu} = 2990$, 2972, 1760, 1720, 1250, 1050 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.04$ and 1.10 (2d, $J_{vic} = 7$ Hz, $CH(CH_3)_2$), 1.53 (s, $C(CH_3)_3$), 2.17 [m, $J_{H\alpha,H7} = 7.5$, $J_{vic} = 7$ Hz, $CH(CH_3)_2$], 2.19 (s, 3-CH_3), 2.64 (dd, $J_{H\alpha,H7} = 7.5$, $J_{trans,H6} = 1.9$ Hz, H7), 3.27 (ddd, $J_{H6,1\text{-}CH_2} = 10.0$ and 3.6, $J_{trans,7\text{-}H} = 1.9$ Hz, H6), 3.59 (dd, $J_{gem} = 10.0$, $J_{H1_A,H6} = 10.0$ Hz, 1H, $H1_A$), 4.58 (dd, $J_{gem} = 10.0$, $J_{H1_B,H6} = 3.6$ Hz, 1H, $H1_B$) ppm.

(αR, 3R, 4R)-3-(1-Acetoxyethyl)-4-hydroxymethyl-N-(4-methoxyphenyl)-azetidin-2-one
(**11a**, $C_{15}H_{19}NO_5$)[a]

Oil; $[\alpha]_D^{23.5} = +48.6°\ g^{-1}\ cm^3\ dm^{-1}$; IR (neat): $\bar{\nu} = 3600$–3200 (OH), 1740 (CON), 1710 (CO), 1230 and 1010 (COC) cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.43$ (d, $J_{CH_3,H\alpha} = 6.5$ Hz, β-CH_3), 1.9 (brs, OH), 2.03 (s, CH_3CO), 3.46 (dd, $J_{H3,H\alpha} = 4.6$, $J_{trans,H4} = 2.5$ Hz, H3), 3.79 (s, OCH_3), 3.90 (dd, $J_{gem} = 12$, $J_{CH_{2A},H4} = 3.5$ Hz, 1H, $CH_{2A}O$), 3.98 (td, $J_{trans,H3} = 2.6$, $J_{H4,CH_2} = 3.6$ Hz, 1H, H4), 4.02 (dd, $J_{gem} = 12$, $J_{CH_{2B},H4} = 3.75$ Hz, 1H, $CH_{2B}O$), 5.31 (m, $J_{H\alpha,CH_3} = 6.5$, $J_{H\alpha,H3} = 4.6$ Hz, Hα), 6.89 (d, $J_{ortho} = 9$ Hz, H3′, H5′), 7.35 (d, $J_{ortho} = 9$ Hz, H2′, H6′) ppm.

(αR, 3R, 4R)-3-(1-Acetoxyethyl)-4-(mesyloxymethyl)-N-(4-methoxyphenyl)-azetidin-2-one (**13a**, $C_{16}H_{21}NO_7S$)

Mesyl chloride (1.2 cm^3, 12 mmol) was added under stirring and cooling (−5–0°C) to compound **11a** (3.0 g, 10 mmol) dissolved in pyridine (20 cm^3). The stirring was continued for 2.5 h (TLC:

[a] The stereodescriptors given in Ref. [7] for compound **11a** are wrong

CH_2Cl_2:*Et*OA*c* = 8:5, R_f(**11a**): 0.5, R_f(**13a**): 0.6). The reaction mixture was diluted with water (20 cm^3) and dichloromethane (60 cm^3). The organic layer was washed with 10% HCl (3 × 20 cm^3), then with water (3 × 20 cm^3). The solution was dried ($MgSO_4$) and concentrated to dryness. The crude oil was purified by column chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$:*Et*OA*c* = 10:1) to give the title compound (2.9 g, 76%). Brownish oil; $[\alpha]_D^{20} = +57.6^\circ\ g^{-1}\ cm^3\ dm^{-1}$; IR (neat): $\bar{\nu} = 1740$ (CON), 1710 (CO), 1516, 1360 and 1176 (SO_2), 1240 and 1028 (COC) cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 1.43$ (d, $J_{CH_3,H\alpha} = 7.0$ Hz, β-CH_3), 2.04 (s, CH_3CO), 2.92 (s, SO_2CH_3), 3.46 (dd, $J_{H3,H\alpha} = 4.0$, $J_{trans,H4} = 2.0$ Hz, H3), 3.79 (s, OCH_3), 4.17 (m, H4), 4.51 (d, $J_{CH_2O,H4} = 4.5$ Hz, CH_2O), 5.32 (m, Hα), 6.89 (d, $J_{ortho} = 8.8$ Hz, H3′, H5′), 7.32 (d, $J_{ortho} = 8.8$ Hz, H2′, H6′) ppm; ^{13}C NMR (125 MHz): $\delta = 18.22$ (β-CH_3), 21.81 (*C*H_3CO), 38.26 (SO_2CH_3), 52.75, 56.12, 57.12, 67.18, and 67.62 (Cα, C3, C4, CH_2O, CH_3O), 115.12 (C3′, C5′), 119.26 (C2′, C6′), 130.27 (C1′), 157.02 (C4′), 162.95 (CON), 170.70 (CH_3*C*O) ppm; MS: m/z (%) = 371 (M^+, 23), 311 (13), 243 (13), 202 (17), 149 (100), 134 (82), 43 (61).

(αS, 3S, 4S)-3-(1-Acetoxyethyl)-4-(mesyloxymethyl)-N-(4-methoxyphenyl)-azetidin-2-one (**13b**, $C_{16}H_{21}NO_7S$)

Prepared analogously as **13a**. Yield: 75%; $[\alpha]_D^{22.5} = -51.7^\circ\ g^{-1}\ cm^3\ dm^{-1}$; IR (neat): $\bar{\nu} = 1740$ (CON), 1516, 1366, and 1176 (SO_2), 1248 and 1028 (COC) cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 1.45$ (d, $J_{CH_3,H\alpha} = 6.6$ Hz, β-CH_3), 2.06 (s, CH_3CO), 2.93 (s, SO_2CH_3), 3.47 (dd, $J_{H3,H\alpha} = 4.3$, $J_{trans,H4} = 2.4$ Hz, H3), 3.80 (s, OCH_3), 4.18 (m, H4), 4.46 (d, $J_{CH_2O,H4} = 4.1$ Hz, CH_2O), 5.33 (m, Hα), 6.90 (d, $J_{ortho} = 8.9$ Hz, H3′, H5′), 7.32 (d, $J_{ortho} = 9.0$ Hz, H2′, H6′) ppm; ^{13}C NMR (125 MHz): $\delta = 18.22$ (β-CH_3), 21.83 (*C*H_3CO), 38.29 (SO_2CH_3), 52.75, 56.13, 57.16, 67.18, and 67.62 (C-α, C-3, C-4, CH_2O, CH_3O), 115.12 (C3′, C5′), 119.25 (C2′, C6′), 130.33 (C1′), 157.03 (C4′), 162.92 (CON), 170.70 (CH_3*C*O) ppm; MS: m/z (%) = 371 (M^+, 20), 311 (13), 243 (13), 202 (15), 149 (100), 134 (85), 43 (62).

(αR, 3R, 4R)-3-(1-Acetoxyethyl)-4-(mesyloxymethyl)azetidin-2-one (**14a**, $C_9H_{15}NO_6S$)

Ammonium cerium(IV) nitrate (11 g, 20 mmol) dissolved in water (120 cm^3) was added to the solution of compound **13a** (2.5 g, 6.7 mmol) in acetonitrile (70 cm^3) under cooling (−10–0°C) and stirring. The starting material was consumed after 2 h (TLC: CH_2Cl_2:*Et*OA*c* = 1:1, R_f(**13a**): 0.5, R_f(**14a**): 0.15). The reaction mixture was diluted with water (200 cm^3) and extracted with *Et*OA*c* (3 × 150 cm^3). The combined organic layers were washed with 10% $NaHCO_3$ solution (85 cm^3), then the aqueous layer was extracted with *Et*OA*c* (40 cm^3). The combined organic layers were washed with 10% $NaHSO_3$ solutions until they became colorless and the aqueous layer was extracted with *Et*OA*c*. The combined organic layers were washed with 10% Na_2CO_3 solutions, dried (Na_2SO_4), and concentrated to dryness. The crude oil was purified by column chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$:*Et*OA*c* = 1:1) to give the title compound (1.30 g, 73%). Slowly crystallizing oil; mp 70°C; $[\alpha]_D^{22.5} = -21.5^\circ\ g^{-1}\ cm^3\ dm^{-1}$; IR (KBr): $\bar{\nu} = 3700$–3400 (NH), 1750 and 1720 (CO), 1330 and 1160 (SO_2), 1230 and 1020 (COC) cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 1.41$ (d, $J_{CH_3,H\alpha} = 6.45$ Hz, β-CH_3), 2.08 (s, CH_3CO), 3.08 (s, SO_2CH_3), 3.24 (m, H3), 3.81 (m, H4), 4.27 (dd, $J_{CH_{2A},H4} = 6.5$, $J_{gem} = 11$ Hz, 1H, $CH_{2A}O$), 4.40 (dd, $J_{CH_{2B},H4} = 3.5$, $J_{gem} = 11$ Hz, 1H, $CH_{2B}O$), 5.25 (qui, $J_{vic} = 6.2$ Hz, Hα), 6.14 (brs, NH) ppm; ^{13}C NMR (125 MHz): $\delta = 17.39$ (β-CH_3), 21.15 (*C*H_3CO), 37.80 (SO_2CH_3), 48.92, 57.66, 66.63, and 69.35 (Cα, C3, C4, CH_2O), 165.64 (CON), 170.5 (CH_3*C*O) ppm; MS (18 eV): m/z (%) = 266 (M^++H, 0.7), 222 (0.7), 113 (37), 84 (100), 43 (92).

(αS, 3S, 4S)-3-(1-Acetoxyethyl)-4-(mesyloxymethyl)azetidin-2-one (**14b**, $C_9H_{15}NO_6S$)

Prepared analogously as **14a**. Yield: 75%; mp 72°C; $[\alpha]_D^{24} = +20.5^\circ\ g^{-1}\ cm^3\ dm^{-1}$; IR (KBr): $\bar{\nu} = 3500$–3300 (NH), 1760 and 1740 (CO), 1356 and 1176 (SO_2), 1244 and 1028 (COC) cm^{-1}; ^{1}H

NMR (500 MHz): $\delta = 1.41$ (d, $J_{CH_3,H\alpha} = 6.5$ Hz, β-CH_3), 2.09 (s, CH_3CO), 3.09 (s, SO_2CH_3), 3.25 (dd, $J_{H3,H\alpha} = 3.6$, $J_{trans,H4} = 2.6$ Hz, H3), 3.81 (AB*X*, H4), 4.28 (*A*B*X*, $J_{CH_{2A},H4} = 6.5$, $J_{gem} = 10.9$ Hz, 1H, $CH_{2A}O$), 4.41 (A*B*X, $J_{CH_{2B},4\text{-}H} = 3.7$, $J_{gem} = 10.9$ Hz, 1H, $CH_{2B}O$), 5.25 (qd, $J_{H\alpha,CH_3} = 6.4$, $J_{H\alpha,H3} = 4.6$ Hz, Hα), 6.43 (brs, NH) ppm; ^{13}C NMR (125 MHz): $\delta = 18.11$ (β-CH_3), 21.85 (*C*H_3CO), 38.38 (SO_2CH_3), 49.49, 58.17, 67.23, and 70.03 (Cα, C3, C4, CH_2O), 166.24 (CON), 170.72 (CH_3*C*O) ppm; MS (18 eV): m/z (%) = 266 (M^++H, 0.7), 222 (0.7), 113 (36), 84 (100), 43 (93).

Benzyl (αR, 6R, 7R)-7-(1-Acetoxyethyl)-3-methyl-2-isoxacephem-4-carboxylate (**16a**, $C_{19}H_{21}NO_6$)

Compound **16a** was prepared according to *Method A* starting with **14a** (1.25 g, 4.7 mmol) and benzyl 2,3-dioxobutyrate [9] (1.5 g, 7 mmol). The oily crude intermediate (2.5 g) (TLC: CH_2Cl_2:*Et*O*Ac* = 10:2, R_f(**14a**): 0.05 PMA, R_f(**15a**): 0.35) was purified by column chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$:*Et*O*Ac* = 1:1) provided **15a** (1.0 g, 47%) and the starting material **11a** (0.4 g, 32%). Crude **15a** (0.9 g, 2 mmol) was dissolved in $CHCl_3$ (15 cm^3) and in the presence of Et_3N (0.1 cm^3, 7.2 mmol) it was refluxed for 1 h (TLC: CH_2Cl_2:*Et*O*Ac* = 10:2, R_f(**16a**): 0.5). The concentrated solution was washed with water and purified by column chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$: *Et*O*Ac* = 10:2) to give the title compound **16a** (0.38 g, 53%). Colorless oil; $[\alpha]_D^{22} = -121.0^\circ\ g^{-1}\ cm^3\ dm^{-1}$; IR (film): $\bar{\nu} = 1770$, 1744 and 1710 (CO), 1616 (Ar), 1456, 1376, 1240, 1136, 1084 and 1028 (COC) cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 1.42$ (d, $J_{CH_3,H\alpha} = 6.5$ Hz, β-CH_3), 1.99 (s, CH_3CO), 2.24 (s, 3-CH_3), 3.09 (dd, $J_{trans,H6} = 1.8$, $J_{H7,H\alpha} = 4$ Hz, H7), 3.39 (ddd, $J_{trans,H7} = 1.8$, $J_{H6,H1_A} = 9.4$, $J_{H6,H1_B} = 3$ Hz, H6), 3.67 (t, $J = 10.0$ Hz, 1H, H1$_A$), 4.64 (dd, $J_{H1_B,H6} = 3.7$, $J_{gem} = 10.7$ Hz, 1H, H1$_B$), 5.23 + 5.30 (AB, $J_{gem} = 12.7$ Hz, ArCH_2), 5.33 (qd, $J_{H\alpha,H7} = 4.3$, $J_{H\alpha,CH_3} = 6.5$ Hz, Hα), 7.29 (t, $J_{ortho} = 7.5$ Hz, H4′), 7.34 (t, $J_{ortho} = 7.3$ Hz, H3′, H5′), 7.44 (d, $J_{ortho} = 7.4$ Hz, H2′, H6′) ppm; ^{13}C NMR (125 MHz): $\delta = 17.76$ (3-CH_3, β-CH_3), 21.06 (*C*H_3CO), 43.60 (C6), 60.69 (C7), 66.55 and 66.76 (Cα, ArCH_2), 69.27 (C1), 106.69 (C4), 127.94, 127.97, 128.38, and 136.07 (Ar–C), 154.53 (C3), 162.94 and 164.18 (CON, *C*O*O*CH_2), 170.47 (CH_3*C*O) ppm; MS: m/z (%) = 359 (M^+, 8), 317 (6), 226 (8), 125 (6), 91 (100), 43 (55).

Benzyl (αS, 6S, 7S)-7-(1-Acetoxyethyl)-3-methyl-2-isoxacephem-4-carboxylate (**16b**, $C_{19}H_{21}NO_6$)

Prepared analogously as **16a**. Yield: 28%; oil; $[\alpha]_D^{20.5} = +130.0^\circ\ g^{-1}\ cm^3\ dm^{-1}$; IR (film): $\bar{\nu} = 1780$, 1736, 1720 (CO), 1620 (Ar), 1456, 1392, 1375, 1355, 1240, 1136, 1084 and 1028 (COC) cm^{-1}; ^{1}H NMR (500 MHz): $\delta = 1.45$ (d, $J_{CH_3,H\alpha} = 6.5$ Hz, β-CH_3), 2.02 (s, CH_3CO), 2.26 (s, 3-CH_3), 3.12 (dd, $J_{trans,H6} = 1.8$, $J_{H7,H\alpha} = 4$ Hz, H7), 3.42 (ddd, $J_{trans,H7} = 1.8$, $J_{H6,H1_A} = 9.4$, $J_{H6,H1_B} = 3.5$ Hz, H6), 3.69 (t, $J = 9.7$ Hz, 1H, H1$_A$), 4.66 (dd, $J_{H1_B,H6} = 3.7$, $J_{gem} = 10.7$ Hz, 1H, H1$_B$), 5.25 + 5.31 (AB, $J_{gem} = 12.6$ Hz, ArCH_2), 5.33 (qd, $J_{H\alpha,H7} = 4.3$, $J_{H\alpha,CH_3} = 6.5$ Hz, Hα), 7.31 (t, $J_{ortho} = 7.3$ Hz, H4′), 7.36 (t, $J_{ortho} = 7.3$ Hz, H3′, H5′), 7.46 (d, $J_{ortho} = 7.3$ Hz, H2′, H6′) ppm; ^{13}C NMR (125 MHz): $\delta = 18.48$ (3-CH_3, β-CH_3), 21.76 (*C*H_3CO), 44.24 (C6), 61.29 (C7), 67.13 and 67.32 (Cα, ArCH_2), 69.83 (C1), 107.16 (C4), 128.34, 128.37, 128.77, and 136.43 (Ar–C), 154.84 (C3), 163.21, 164.44 (CON, *C*O*O*CH_2), 170.74 (CH_3*C*O) ppm.

(αR, 6R, 7R)-7-(1-Acetoxyethyl)-3-methyl-2-isoxacephem-4-carboxylic acid (**17a**, $C_{12}H_{15}NO_6$)

The benzyl ester **16a** (0.35 g, 0.97 mmol) was hydrogenated in ethyl acetate (15 cm^3) in the presence of 10% Pd/C catalyst (0.05 g) under atmospheric pressure for 2 h (TLC: CH_2Cl_2:*Et*O*Ac* = 10:2, R_f(**17a**): 0.1; CH_2Cl_2:*Me*OH = 10:1, R_f(**17a**): 0.3). The catalyst was filtered off, washed with ethyl acetate and concentrated to dryness to give the title compound (0.24 g, 92%). Colorless oil; $[\alpha]_D^{24.5} =$

$-193.0°\ g^{-1}\ cm^3\ dm^{-1}$; IR (film): $\bar{\nu} = 3000–3300$ (COOH), 1780 and 1736 (CO), 1612 (Ar), 1244 and 1028 (COC) cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.44$ (d, $J_{CH_3,H\alpha} = 6.5$ Hz, β-CH_3), 2.09 (s, CH_3CO), 2.29 (s, 3-CH_3), 3.19 (dd, $J_{trans,H6} = 2.0$, $J_{H7,H\alpha} = 4.0$ Hz, H7), 3.49 (ddd, $J_{trans,H7} = 2.0$, $J_{H6,H1_A} = 7.5$, $J_{H6,H1_B} = 3.0$ Hz, H6), 3.73 (t, $J = 10.0$ Hz, 1H, $H1_A$), 4.69 (dd, $J_{H1_B,H6} = 3.7$, $J_{gem} = 10.7$ Hz, 1H, $H1_B$), 5.32 (qd, $J_{H\alpha,H7} = 4.3$, $J_{H\alpha,CH_3} = 6.5$ Hz, Hα) ppm; ^{13}C NMR (125 MHz): $\delta = 17.78$ (β-CH_3), 18.06 (3-CH_3), 21.18 (CH_3CO), 44.35 (C6), 60.07 (C7), 66.59 (Cα), 69.09 (C1), 106.54 (C4), 156.54 (C3), 165.05 (COOH), 165.47 (CON), 170.60 (CH_3CO) ppm; MS: m/z (%) = 269 (M^+, 3), 227 (8), 183 (6), 141 (6), 123 (5), 98 (10), 69 (9), 54 (9), 43 (100).

(αS, 6S, 7S)-7-(1-Acetoxyethyl)-3-methyl-2-isoxacephem-4-carboxylic acid (**17b**, $C_{12}H_{15}NO_6$)

Prepared analogously as **17a**. Yield: 28%; colorless oil; $[\alpha]_D^{22.5} = +193.3°\ g^{-1}\ cm^3\ dm^{-1}$; IR (film): $\bar{\nu} = 3000–3300$ (COOH), 1780, 1740, and 1725 (CO), 1608 (Ar), 1244 and 1028 (COC) cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.45$ (d, $J_{CH_3,H\alpha} = 6.5$ Hz, β-CH_3), 2.11 (s, CH_3CO), 2.31 (s, 3-CH_3), 3.20 (d, $J_{trans,H6} = 2.0$ Hz, H7), 3.48 (d, $J_{H6,H1_A} = 7.5$ Hz, H6), 3.74 (t, $J = 9.9$ Hz, 1H, $H1_A$), 4.70 (dd, $J_{H1_B,H6} = 3.7$, $J_{gem} = 10.7$ Hz, 1H, $H1_B$), 5.33 (qd, $J_{H\alpha,H7} = 4.4$, $J_{H\alpha,CH_3} = 6.5$ Hz, Hα), 9.22 (brs, COOH) ppm; ^{13}C NMR (125 MHz): $\delta = 18.46$ and 18.76 (β-CH_3, 3-CH_3), 21.88 (CH_3CO), 44.94 (C6), 60.65 (C7), 67.14 (Cα), 69.64 (C1), 106.99 (C4), 156.83 (C3), 165.52 and 165.65 (CON, COOH), 170.82 (CH_3CO) ppm; MS: m/z (%) = 269 (M^+, 3), 227 (7), 183 (6), 141 (6), 123 (5), 98 (9), 69 (9), 54 (9), 43 (100).

(1R, 2R, 5S)-6-(4-Methoxyphenyl)-2-methyl-3-oxa-6-azabicyclo[3.2.0]heptane-4,7-dione (**18a**, $C_{13}H_{13}NO_4$)

The *cis*-ester **12a** (1.60 g, 5.0 mmol) was suspended in dry *THF* (25 cm^3) and 1 *M DIBAL* in *THF* (15.0 cm^3, 15.0 mmol) was added under nitrogen at $-70°C$ in such a rate, that the temperature did not rise above $-65°C$. Stirring was continued for 2 h (TLC: CH_2Cl_2:*EtOAc* = 10:2, R_f(**12a**): 0.70, R_f(**18a**): 0.50, R_f(**19a**): 0.20). A further amount of 1 *M DIBAL* in *THF* (7.0 cm^3, 7.0 mmol) was added under nitrogen at $-70°C$ and after 0.5 h stirring the excess of the reagent was decomposed by addition of methanol (5 cm^3). The mixture was allowed to warm up to rt, acidified by 10% HCl (50 cm^3), and extracted with ethyl acetate (2×100 cm^3). The combined organic phases were washed subsequently with saturated $NaHCO_3$ solution, water, and dried ($MgSO_4$). The crude product (1.20 g) was purified by column chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$:*EtOAc* = 1:1) to give unreacted **12a** (0.50 g, 31%), **19a** (0.24 g, 20%), and **18a** (50.0 mg, 3%). Mp 145°C (*Me*OH); IR (KBr): $\bar{\nu} = 1744$ (CO), 1516 (Ar), 1248 and 1044 (COC) cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.64$ (d, $J_{H2,CH_3} = 6.0$ Hz, CH_3), 3.79 (s, $ArOCH_3$), 4.04 (dd, $J_{H5,H1} = 4.6$, $J_{H2,H1} = 7.5$ Hz, H1), 4.64 (d, $J_{H1,H5} = 4.7$ Hz, H5), 4.83 (qui, $J = 6.8$ Hz, H2), 6.88 (d, $J_{ortho} = 8.9$ Hz, H3′, H5′), 7.50 (d, $J_{ortho} = 8.9$ Hz, H2′, H6′) ppm; ^{13}C NMR (125 MHz): $\delta = 18.18$ (CH_3), 53.96, 54.78, and 55.71 (CH_3OAr, C1, C5), 75.26 (C2), 114.69 (C3′, C5′), 118.54 (C2′, C6′), 130.78 (C1′), 156.99 (C4′), 160.95 (CON), 170.62 (C4) ppm.

(1R, 2R, 4S, 5S)-4-Hydroxy-6-(4-methoxyphenyl)-2-methyl-3-oxa-6-azabicyclo[3.2.0]heptan-7-one (**19a**, $C_{13}H_{15}NO_4$)

Ethyl chloroformate (1.6 cm^3, 15.0 mmol) dissolved in *THF* (6 cm^3) was added to the mixture of *cis*-hydroxyacid **21a** (1.94 g, 6.0 mmol) and triethylamine (2.2 cm^3, 15.0 mmol) in *THF* (23 cm^3) at $-20°C$ under stirring. After consumption of the acid **21a** (TLC: CH_2Cl_2:*EtOAc* = 10:2, R_f(**21a**): 0.10, R_f(anhydride): 0.50) $NaBH_4$ (1.75 g, 46.0 mmol) was added to the solution. A mixture of methanol (15 cm^3) and *THF* (10 cm^3) was dropped into the reaction mixture within 2 h at the same temperature. The reaction was monitored by TLC (CH_2Cl_2:*EtOAc* = 10:2, R_f(**19a**): 0.10). The *THF*/*Me*OH solution was

concentrated to dryness, the residue was diluted with saturated NaCl solution (25 cm^3), extracted with *EtOAc* (2 × 40 cm^3), washed with brine, and dried ($MgSO_4$). Evaporation provided an oily crude product (1.80 g) which was purified by column chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$:*EtOAc* = 1:1) to give besides **20a** (8%), the ethoxyformyl derivative of **19a** (10%), and the title compound (1.26 g, 84%). Mp 184°C; $[\alpha]_D^{21.5} = -98.8°\ g^{-1}\ cm^3\ dm^{-1}$; IR (KBr): $\bar{\nu} = 1720$ (CO), 1516 (Ar), 1244 (COC), 968, 832 cm^{-1}; ^{1}H NMR (500 MHz, *DMSO*-d_6, COSY): $\delta = 1.35$ (d, $J_{H2,CH_3} = 6.5$ Hz, CH_3), 3.73 (s, $ArOCH_3$), 3.78 (dd, $J_{H5,H1} = 4.4$, $J_{H2,H1} = 5.3$ Hz, H1), 4.23 (qui, $J = 6.0$ Hz, H2), 4.38 (d, $J_{H1,H5} = 4.0$ Hz, H5), 5.30 (d, $J_{H4,OH} = 4.3$ Hz, OH), 6.61 (d, $J_{OH,H4} = 4.3$ Hz, H4), 6.95 (d, $J_{ortho} = 8.9$ Hz, H3′, H5′), 7.29 (d, $J_{ortho} = 8.9$ Hz, H2′, H6′) ppm; ^{13}C NMR (125 MHz, *DMSO*-d_6): 15.66 (CH_3), 55.28, 56.34, 61.19, and 69.71 (CH_3OAr, C1, C5, C2), 94.03 (C4), 114.62 (C3′, C5′), 117.24 (C2′, C6′), 130.87 (C1′), 155.50 (C4′), 162.82 (CON) ppm.

(αR, 3R, 4S)-3-(1-Hydroxyethyl)-4-(hydroxymethyl)-1-(4-methoxyphenyl)-azetidin-2-one (**20a**, $C_{13}H_{17}NO_4$)

Sodium borohydride (1.90 g, 50.0 mmol) was added in small portions to the solution (*Me*OH, 150 cm^3) of cyclic hemi-acetal **19a** (3.10 g, 12.0 mmol) at 0°C under stirring. The reaction was monitored by TLC (CH_2Cl_2:*EtOAc* = 1:1, R_f(**19a**): 0.5, R_f(**20a**): 0.2). The mixture was stirred 1 h at rt, concentrated to dryness the residue was suspended in water (30 cm^3), and it was acidified with 1 *N* HCl to *pH* = 6.0. The precipitated product was filtered off and proved to be the title compound **20a** (2.40 g, 80%). A second crop (0.80 g) could be isolated from the aqueous solution by extraction with *EtOAc*. This was triturated with methanol to give 0.60 g (20%) of **20a**. Mp 198–201°C; IR (KBr): $\bar{\nu} = 3200$, 3288 (OH), 1728 (CO), 1512 (Ar), 1248 and 1024 (COC), 832 cm^{-1}; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 1.28$ (d, $J_{H\alpha,CH_3} = 5.8$ Hz, β-CH_3), 3.4 (m, H3), 3.72 (s, $ArOCH_3$), 3.88 + 3.98 (AB, $J_{gem} = 9$ Hz, CH_2), 4.07 and 4.12 (2m, H4, Hα), 5.03 and 5.15 (2brs, 2OH), 6.91 (d, $J_{ortho} = 8.2$ Hz, H3′, H5′), 7.46 (d, $J_{ortho} = 8.2$ Hz, H2′, H6′) ppm; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 23.18$ (β-CH_3), 55.41, 56.90, 57.86, 59.12, and 62.61 (C3, C4, Cα, CH_2, $ArOCH_3$), 114.31 (C3′, C5′), 118.38 (C2′, C6′), 131.96 (C1′), 155.30 (C4′), 165.66 (CON) ppm.

(αR, 2S, 3R)-3-(1-Hydroxyethyl)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylic acid (**21a**, $C_{13}H_{15}NO_5$)

The *cis*-ester **12a** (3.20 g, 10.0 mmol) was suspended in 1 *N* HCl (30 cm^3) and the suspension was refluxed for 20 h. The insoluble material was filtered off and triturated with CH_2Cl_2 (30 cm^3) at rt. The insoluble material was filtered off and proved to be **21a** (2.0 g, 77%). Unreacted **12a** could be recovered from the CH_2Cl_2 solution (0.1 g, 3%).

21a: Mp 169°C; IR (KBr): $\bar{\nu} = 3368$ (OH), 1736, 1712 (CO), 1512 (Ar), 1248 and 1024 (COC), 832 cm^{-1}; ^{1}H NMR (500 MHz, *DMSO*-d_6): $\delta = 1.26$ (d, $J_{H\alpha,CH_3} = 6.4$ Hz, β-CH_3), 3.59 (dd, $J_{H\alpha,H3} = 4.1$, $J_{H2,H3} = 6.2$ Hz, H3), 3.72 (s, $ArOCH_3$), 4.02 (qd, $J_{H3,H\alpha} = 4.3$, $J_{CH_3,H\alpha} = 6.0$ Hz, α-H), 4.66 (d, $J_{H3,H2} = 6.4$ Hz, H2), 4.85 (brs, OH), 6.91 (d, $J_{ortho} = 8.9$ Hz, H3′, H5′), 7.28 (d, $J_{ortho} = 8.8$ Hz, H2′, H6′), 12.85 (brs, COOH) ppm; ^{13}C NMR (125 MHz, *DMSO*-d_6): $\delta = 22.27$ (β-CH_3), 53.43, 55.43, 58.90, and 62.69 (C3, C4, Cα, $ArOCH_3$), 114.20 (C3′, C5′), 118.08 (C2′, C6′), 131.66 (C1′), 155.47 (C4′), 164.68 (CON), 170.21 (COOH) ppm.

(1R, 2R, 4R, 5S)-6-(4-Methoxyphenyl)-2-methyl-7-oxo-3-oxa-6-azabicyclo[3.2.0]hept-4-yl 4-Bromobenzoate (**22a**, $C_{20}H_{18}BrNO_5$)

4-Bromobenzoyl chloride (80.0 mg, 0.36 mmol) was added to the solution of compound **19a** (80.0 mg, 0.32 mmol) in pyridine (0.4 cm^3) in the presence of a catalytic amount of *DMAP*. The mixture was stirred for 1 d, diluted with water (2 cm^3), the precipitate was dissolved in ether (5 cm^3), and the

aqueous pyridine solution was extracted with ether ($3 \times 2\,cm^3$). The ethereal phases were combined, washed with brine, and dried ($MgSO_4$).

The ethereal solution was concentrated to dryness (0.16 g oil), purified by preparative TLC (CH_2Cl_2:*EtOAc* = 10:2.5, R_f(**22a**): 0.80) to give **22a** (90.0 mg, 65%). Mp 152–153°C (CH_2Cl_2); $[\alpha]_D^{32} = 286.3°\ g^{-1}\ cm^3\ dm^{-1}$; IR (KBr): $\bar{\nu} = 1736$ (CO), 1720 (CO), 1594, 1512 (Ar), 1400, 1360, 1272, 1244 and 1140 (COC), 1096, 944, 832 cm^{-1}; ^1H NMR (500 MHz): $\delta = 1.61$ (d, $J_{H2,CH_3} = 6.2$ Hz, CH_3), 3.81 (s, $ArOCH_3$), 3.84 (dd, $J_{H5,H1} = 4.4$, $J_{H2,H1} = 5.3$ Hz, H1), 4.54 (qui, $J = 6.0$ Hz, H2), 4.61 (d, $J_{H1,H5} = 4.0$ Hz, H5), 6.92 (d, $J_{ortho} = 8.9$ Hz, H3′, H5′), 7.51 (d, $J_{ortho} = 8.9$ Hz, H3′, H5′), 7.63 (d, $J_{ortho} = 8.0$ Hz, H3″, H5″), 7.92 ($J_{ortho} = 8.0$ Hz, H3″, H5″) ppm; ^{13}C NMR (125 MHz): $\delta = 15.81$ (CH_3), 55.43, 56.12, 60.94, and 74.21 (CH_3OAr, C1, C5, C2), 97.11 (C4), 114.71 (C3′, C5′), 117.73 (C2′, C6′), 128.19 (C4″), 129.01 (C1″), 130.83 (C1′), 131.27 (C3″, C5″), 131.99 (C2″, C6″), 155.48 (C4′), 161.47 (CON), 164.96 (COO) ppm.

X-Ray Structure Determination of **22a**

Formula: $C_{20}H_{17}BrNO_5$, formula weight: 431.26, crystal system: monoclinic, space group: $P2_1$, $a = 7.323(1)$, $b = 12.428(1)$, $c = 10.803(2)$ Å, $\beta = 109.04(3)°$, $V = 929.4(2)$ $Å^3$. 4235 reflections (including a full set of *Friedel* opposites) were collected on an Enraf-Nonius CAD4 diffractometer of which 3690 were unique and the intenisty of 3645 were greater than 2s (*I*). An empirical absorption correction [15] was applied to the data (max. and min. transmission factors were 0.8757 and 0.7973). The structure was solved by direct methods [16] and refined by anisotropic full matrix least-squares [17] on F^2. Final *R*2, *wR*2 values were 0.0623, 0.1513 for all and 0.0620, 0.1506 for $I = 2s$ (*I*). The absolute structure parameter was −0.01(2) [18]. The structure plot was prepared using the PLATON [19] program. Data have been deposited with the Cambridge Crystallographic Data Centre, deposition number CCDC 220364.

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