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Synthesis of thienamycin-like 2-*iso*-oxacephems with optional stereochemistry

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Abstract—All four *trans*-stereoisomers of 7-(1-hydroxyethyl)-2-*iso*-oxacephem-4-carboxylic acids, which are the 2-*iso*-oxacephem analogues of *Thienamycin*, have been synthesized. (α*R*,6*R*,7*R*)- and (α*S*,6*S*,7*S*)-7-(1-hydroxyethyl)-3-methyl-2-*iso*-oxacephem-4-carboxylic acids have been prepared starting from L- and D-threonine, the configuration at the α-position was inverted by using *Mitsunobu* reactions providing the (α*S*,6*R*,7*R*)- and (α*R*,6*S*,7*S*)-diastereomers of the compounds above. A synthetic route to the *cis*-annelated analogues was also worked out.

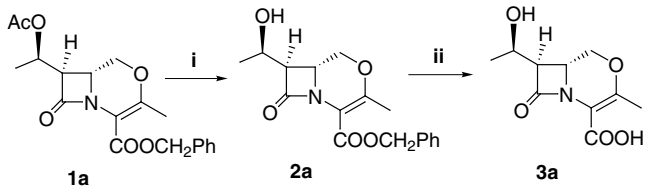
1. Introduction

Due to the developed resistance of bacteria against β-lactam antibiotics, the search for novel antibiotics remains a challenging problem.[1] Although a broad range of resistance mechanisms exists,[2] the production of β-lactamase enzymes is the most important mechanism through which bacteria have become resistant to β-lactam antibiotics.[3,4] Thienamycin, the first representative of carbapenem derivatives,[5,6] exhibits a broad antibacterial spectrum and is stable against β-lactamases due to the hydroxyethyl side chain. This fact, together with the known antibacterial activity of some 2-*iso*-oxacephems,[7] led us to the combination of these structural elements. Although it turned out that the type B β-lactamases (zinc-metalloenzymes) catalyze the hydrolysis of carbapenem derivatives as well,[8] our aim to synthesize enantiomerically pure thienamycin-like 2-*iso*-oxacephems with three stereogenic centres remains a synthetic chemical challenge.

2. Results and discussion

The aim of this research was to synthesize all eight stereoisomers of 7-(1-hydroxyethyl)-3-methyl-2-*iso*-oxacephem-4-carboxylic acids. In a recent paper, we have already reported the stereoselective synthesis of precursors **1a** and **1b**. The syntheses were carried out enantioselectively in the sequences marked with a and b. Only one of the enantiomer sequences is depicted in the schemes. Letters a and b mean compounds prepared from L- or D-threonine, respectively. Starting from L- and D-threonine, which in turn led to (α*R*,6*R*,7*R*)- and (α*S*,6*S*,7*S*)-**3a** and **3b**.[9] The only remaining problem to be solved was to remove the *O*-acetyl group without destroying the β-lactam moiety. Treatment of compounds **1a** and **1b** with methanolic sodium methoxide at ambient temperature provided the 7-(1-hydroxyethyl) derivatives **2a** and **2b** which, after hydrogenolysis, yielded the desired products **3a** and **3b**. Under the circumstances of atmospheric hydrogenolysis, the tetrasubstituted double bond in the 2-*iso*-oxacephem ring remains intact (Scheme 1).

As we have shown in our previous paper, D-*allo*-threonine is an appropriate starting material for 7-(1-hydroxyethyl)-2-*iso*-oxacephem-4-carboxylic acid with *Thienamycin*-like configuration.[9] Starting with this compound was not feasible due to its high cost. Starting with D-threonine meant



Scheme 1. Reagents: (i) NaOMe/MeOH; (ii) H_2/Pd/C, MeOH.

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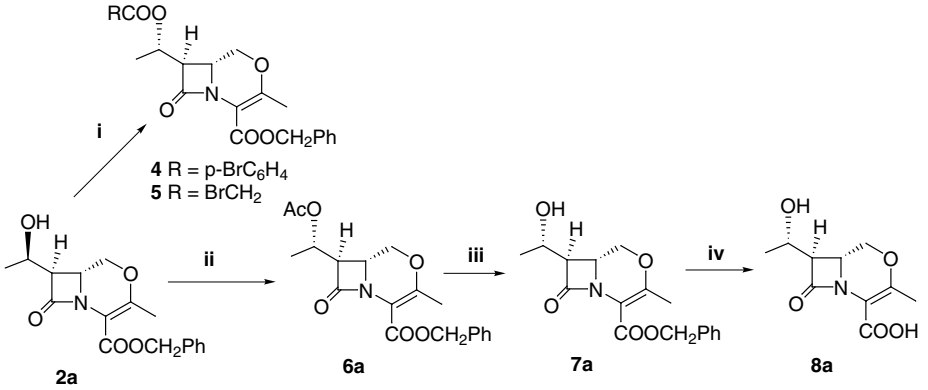
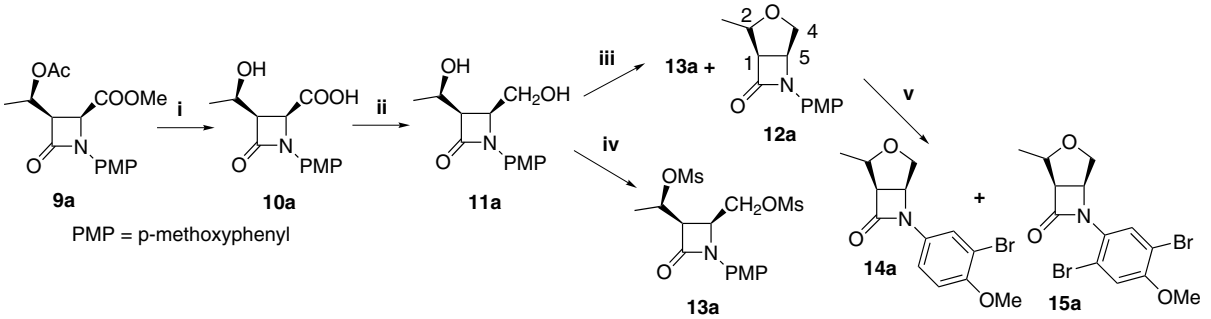
that the configuration must be inverted at the α-hydroxy carbon atom. Preliminary experiments were carried out using Mitsunobu reactions on model compound **2a** for inversion on the α-carbon atom. Acids containing a heavy atom (4-bromobenzoic acid: **4a**; bromoacetic acid: **5a**) were used in order to obtain derivatives for X-ray investigations. Unfortunately, these compounds could not be crystallized. The corresponding inverted 7-(1-acetoxyethyl) derivatives **6a** and **6b** were formed in good yields. Because they are crystalline at rt, unlike **1a** and **1b**, and the NMR spectra and specific rotations are different, the configuration of the α-carbon atom of **6a** and **6b** must differ from that of **1a** and **1b**. The deacetylation and hydrogenolysis furnished the corresponding 7-(1-hydroxyethyl)-2-*iso*-oxacephem-4-carboxylic acids **8a** and **8b**. The latter exhibits the same stereochemical pattern (α*R*,6*S*,7*S*) as thienamycin (α*R*,5*R*,6*S*). The spatial arrangement on the bridgehead carbon is the same in the two compounds; the non-equivalent stereodescriptors (6*S* and 5*R*, respectively) are due to the Cahn–Ingold–Prelog convention (Scheme 2).

After our success in the synthesis of the four stereoisomers **3a** and **3b** and **8a** and **8b** of the *trans*-2-*iso*-oxacephem skeleton, we turned our attention to the synthesis of the *cis*-isomers. Over the course of the synthetic route leading to these compounds, the *cis*-acetoxy ester **9a**,[10] which was derived from dimethyl malonate and L-threonine, could be reduced via the hydroxy carboxylic acid **10a** to the dihydroxy compound **11a**.[9] Depending on reaction conditions, two different compounds were formed by mesylation. Compound **11a**, reacting with mesyl chloride in pyridine, furnished a 1:1 mixture of 2-methyl-3-oxa-6-azabicyclo[3.2.0]heptan-7-one **12a** and the desired dimesylate **13a**. The configuration of carbon 2 in **12a** might be questionable. Our efforts in preparing the bromo derivative **14a** were successful (a by-product, dibromo derivative **15a** was also formed). Unfortunately, since the single crystal of **14a** decomposed on X-ray irradiation, the X-ray crystallographic measurement did not provide direct evidence of the configuration of the carbon atoms at positions 1, 2 and 5. The fact that in its ^{1}H NMR spectrum there was a coupling between 2-H and 1-H but none between 4-H and 5-H makes it likely that the ring closure did not effect the configuration on C-2, similar to our previous experience[9] (Scheme 3).

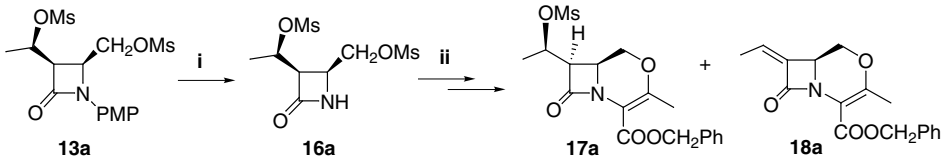
Dimesylate **13a** was also formed from **11a** with mesyl chloride in THF by adding triethylamine at 0 °C. This compound was deprotected on the nitrogen to **16a**, which we hoped would transform easily using our method[11,12] to the corresponding 2-*iso*-oxacephem **17a**. Unfortunately, this compound did not prove to be suitable for the transformation, because during the ring closure step (boiling in chloroform in the presence of NEt_3) elimination of the mesylate occurred, resulting in **17a** and the unsaturated derivative **18a** in poor yields (Scheme 4).



Scheme 2. Reagents and conditions: (i) RCOOH, DEAD or DIAD, PPh_3, THF; R *p*-BrC_6H_4 or $BrCH_2$; (ii) AcOH, DEAD, PPh_3, THF, 0 °C; (iii) NaOMe/MeOH; (iv) H_2/Pd/C, MeOH.



Scheme 3. Reagents and conditions: (i) 1 M HCl, reflux; (ii) (a) ClCOOEt, NEt_3, THF, −20 °C; (b) $NaBH_4$; (iii) MsCl, pyridine; (iv) MsCl, NEt_3, THF; (v) Br_2, acetic acid.

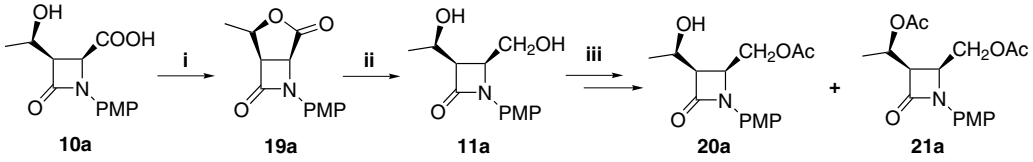


Scheme 4. Reagents and conditions: (i) CAN, acetonitrile/water, −10 °C; (ii) (a) benzyl 2,3-dioxobutyrate, NEt_3, THF; (b) $SOCl_2$, pyridine, −20 °C; (c) Zn, acetic acid, 5 °C; (d) NEt_3, $CHCl_3$, reflux.

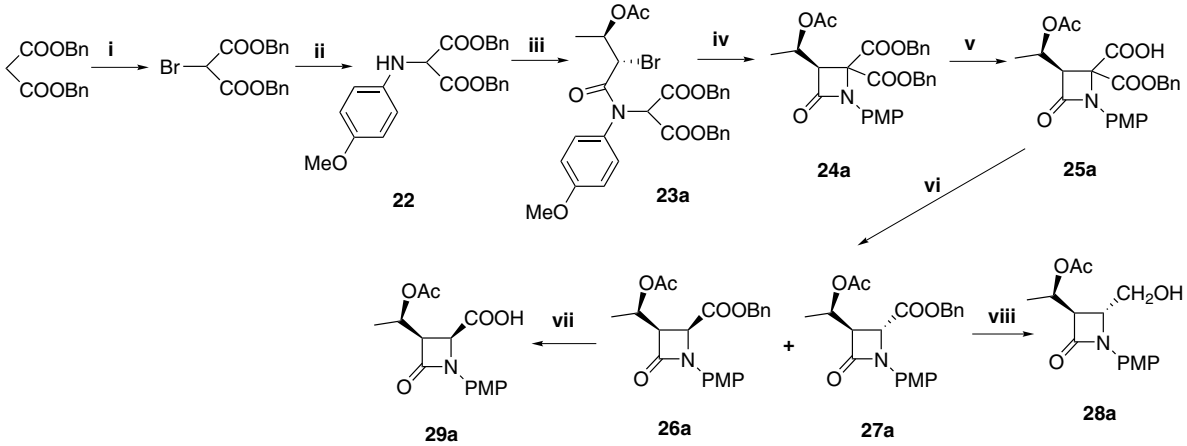
Due to the side reaction leading to **18a**, we tried to selectively re-acetylate the hydroxy carboxylic acid **10a** on the side chain hydroxyl group. On treatment with acetyl chloride, a ring closure occurred instead of acetylation, furnishing the corresponding lactone **19a**. This compound could be reduced with sodium borohydride to diol **11a** in a very good yield (Scheme 5).

It is very common in carbohydrate chemistry that primary and secondary hydroxyl groups can be distinguished by a tritylation/acetylation/detritylation sequence. In our case, this method did not provide satisfactory results. When the detritylation was carried out in acetic acid, the reaction surprisingly provided the acetylated derivative on the primary hydroxyl group **20a** (and not on the secondary) and the diacetyl derivative **21a**. The formation of **20a** could be explained by an intramolecular transacetylation as a consequence of the spatial proximity of the hydroxyl groups. Compounds **20a** and **21a** were also formed by direct acetylation of **11a**, the physical properties of which were the same as those of the products of the previous reaction sequence. The question, as to which regioisomer is **20a** from the two possible ones, was answered based on its ^1H NMR spectrum, in which the chemical shift of the α-carbon is always about 4 ppm if it bears a free hydroxyl group and about 5.5 ppm, if it bears an acetoxy group. In the case of detritylation carried out in 1 M HCl/dioxane, compound **11a** was regained. Atmospheric hydrogenolysis of the tritylated/acetylated intermediate did not bring about any reaction (Scheme 5).

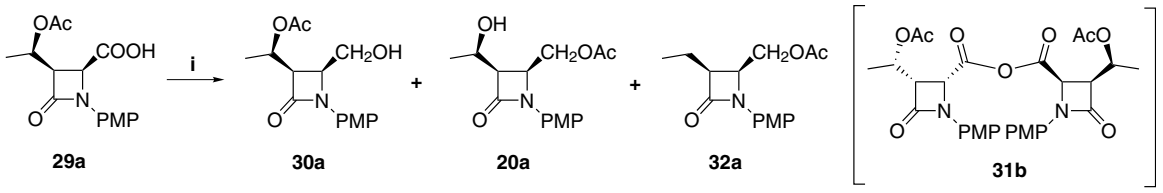
These unsuccessful attempts prompted us to find a new orthogonal protecting group strategy for the synthesis of the *cis*-annelated ring systems. The benzyl group was considered as a good candidate for that role, with it being a protecting group removable by a non-hydrolytic route. Starting with dibenzyl malonate and using the same route described for the methyl esters[10,11] via intermediates **22**, **23a** and **23b**→**25a** and **25b** afforded the diastereomeric mixtures of acetoxy benzyl esters **26a** and **26b** and **27a** and **27b**, respectively (the configuration of these compounds was determined based on the coupling constants between 2-H and 3-H, which are different and typical in the *cis* and *trans* derivatives) (Scheme 6).



Scheme 5. Reagents and conditions: (i) AcCl, pyridine, THF; (ii) $NaBH_4$, MeOH; (iii) (a) TrCl, pyridine, reflux; (b) AcCl, pyridine, THF; (c) acetic acid, reflux.



Scheme 6. Reagents and conditions: (i) Br_2, CCl_4; (ii) *p*-anisidine, ether; (iii) (2*R**,3*S**)-3-acetoxy-2-bromobutyryl chloride, toluene, 80 °C; (iv) DBU, toluene; (v) 1 N NaOH, pyridine, 0 °C; (vi) 2-picoline, 140 °C; (vii) H_2/Pd/C, DMF; (viii) $NaBH_4$, *tert*-butyl alcohol.



Scheme 7. Reagents and conditions: (i) (a) ClCOOEt, NEt_3, THF, −20°C; (b) $NaBH_4$.

Compounds **28a** and **28b** are the same intermediates, which could be transformed to the known *trans-iso*-oxacephems as described earlier.[9] The free carboxylic acids **29a** and **29b** can be obtained by hydrogenolysis without the loss of the acetyl protecting group. The reduction to the corresponding alcohol acetates **30a** and **30b** was carried out by using the mixed anhydride method.[13] It is worth mentioning that the isolated intermediate of this reaction proved to be an anhydride (**31b** isolated from the **b** series). The isomeric alcohol acetates **20a** and **20b** (as a result of transacetylation) also appeared in the reaction mixtures. Compounds **30a** and **30b** and **20a** and **20b** could not be separated, their mixture was used in the next reaction, their ratio was determined from the NMR spectra, as compound **20a** had been previously synthesized (see above). A by-product, which is the result of reduction in the side chain, was also isolated in trace amounts (**32a** isolated from the **a** series) (Scheme 7).

The mesylation of the mixtures **30a** and **30b** and **20a** and **20b** provided only the desired compounds **33a** and **33b**. The further transformations were carried out similarly as described for the *trans*-series.[9] Unfortunately, the deacetylation of **35a** and **35b** with catalytic sodium methoxide furnished again the mixture of the elimination products **18a** and **18b** and the desired **36a** and **36b**. The isomeric unsaturated compound **37a** could also be isolated and characterized. The configuration of the double bond in **18** and **37** was determined from their ^1H NMR spectra based on the magnetic anisotropy of the neighbouring β-lactam carbonyl group. Our assignment is in accordance with the literature data.[14] Various methods were tried for deacetylation of **35a** and **35b**, but the results were the same. These observations can be explained by the fact that the H-7 is more accessible for the alkoxide base in the *cis*-series than that in the *trans*-series.

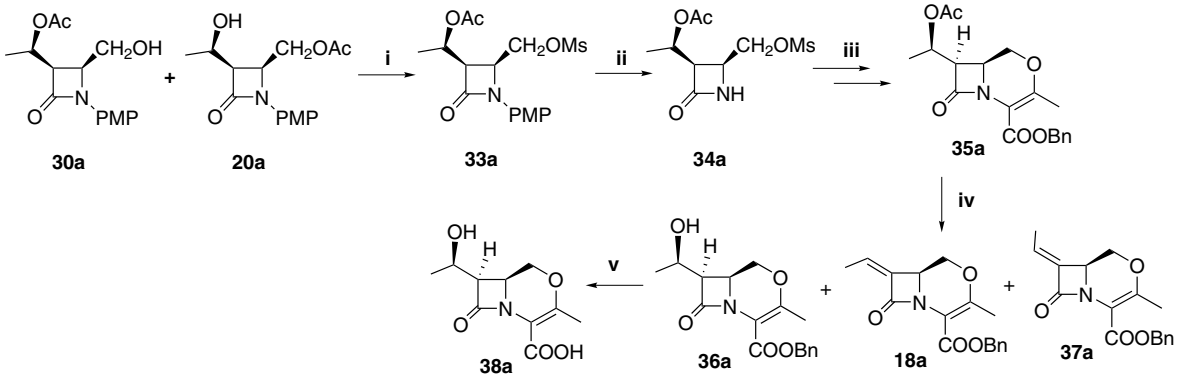
The hydrogenolysis of **18a** and **18b** did not lead to the corresponding unsaturated carboxylic acids because they decomposed during this procedure. Compounds **36a** and **36b** were debenzylated with catalytic hydrogenolysis to **38a** and **38b** (Scheme 8).

Compounds **36a** and **36b** could be transformed to the epimers at the α-C atom by the Mitsunobu reaction similarly to the *trans*-series.

3. Conclusion

A general synthetic route has been developed for all stereoisomers of 7-(1-hydroxyethyl)-3-methyl-2-*iso*-oxacephem-4-carboxylic acids. In the case of *cis*-2-*iso*-oxacephem series, the acetoxy compounds **35** and **35b** get out of the synthetic pathway providing mainly 7-ethylidene derivatives **18a** and **18b** and the yield, of the hydroxyethyl esters **36a** and **36b** were not high enough to carry out the Mitsunobu reaction to produce the corresponding diastereomers (α*S*,6*S*,7*R* and α*R*,6*R*,7*S*).

All of the bicyclic β-lactams were sent to two laboratories for antibacterial screening. These compounds were tested twice on *Staphylococcus aureus ATCC* 25923 up to 100 mg/L (in liquid medium), but none of them showed any antibacterial activity. Ampicillin was used as a positive control (*Laboratoire de Biochimie UMR CNRS 7573* École *Nationale Superieure de Chimie de Paris*). The same compounds were tested on 26 species by using Neomycin as control substance in *Novartis/Vienna*, but none of them showed any activity. The beta-lactamase assays were carried out at *Nabriva Therapeutics/Vienna* without any positive results.



Scheme 8. Reagents and conditions: (i) MsCl, NEt_3, THF, 0 °C; (ii) CAN, acetonitrile/water, −10 °C; (iii) (a) benzyl 2,3-dioxobutyrate, NEt_3, THF; (b) $SOCl_2$, pyridine, −20 °C; (c) Zn, acetic acid, 5 °C; (d) NEt_3, $CHCl_3$, reflux; (iv) NaOMe/MeOH, 0 °C; (v) H_2/Pd/C, MeOH.

4. Experimental

4.1. General

Melting points were determined on a hot stage melting point apparatus and are uncorrected. Optical rotations (*c* 1.0 g/100 cm^3 in CH_2Cl_2) unless stated otherwise, $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1} and were taken on a Perkin–Elmer 241 polarimeter 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) or a Bruker 300 spectrometer (^1H 300.13, ^{13}C 75.48 MHz), respectively, at 298 K in $CDCl_3$ as a solvent, unless stated otherwise. The digital resolution of both spectrometers is 0.3 Hz. Chemical shifts were given on the delta scale as parts per million (ppm) with tetramethylsilane (TMS) as the internal standard. The IR spectra were recorded on a Zeiss Specord M80 spectrophotometer. High resolution FABMS was measured on a MAT 312 instrument equipped with a Maspec II32 data system using V/E scan or on a Waters-Micromass LCT apparatus using ESI+ method (**8a**,**b**). 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 (±0.4%) 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 phosphomolybdic acid (PMA). All solvents were distilled and dried before use.

4.2. Benzyl (6*R*,7*R*)-7-[(1*R*)-1-hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 2a

NaOMe/MeOH solution (0.2 M, 0.8 mL; 0.16 mmol) was added to a solution of benzyl (6*R*,7*R*)-7-[(1*R*)-1-acetoxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate **1a**[9] (0.5 g; 1.4 mmol) in methanol (30 mL) and stirred for 2 h at rt (TLC: CH_2Cl_2–EtOAc 1:1, UV + PMA, Rf_1 0.75, Rf_2 0.28). After completion the mixture was neutralized with 1 M HCl, and the methanol was evaporated under reduced pressure. The residue was taken up in 10 mL EtOAc, washed with water, brine and dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give **2a** (0.42 g, 95%) as a yellow oil. It was pure enough for further reactions, but purified by prep. TLC (CH_2Cl_2–EtOAc 6:9) for analytical investigations. $[\alpha]_D^{23.5} = -184.3$. IR (film): *v* 3448 (OH), 2976 (CH), 1752 (br, CON, COO), 1616 (Ar), 1392, 1208, 1132, 1084, 1024, 700 cm^{-1}. ^1H NMR (500 MHz): δ 1.38 (3H, d, $J = 6.2$ Hz, β-Me), 2.25 (3H, s, 3-Me), 3.00 (1H, dd, $J_{\alpha H} = 5.7$ Hz, $J_{trans} = 1.7$ Hz, 7-H), 3.48 (1H, ddd, $J_{1HA} = 9.5$ Hz, $J_{1HB} = 3.6$ Hz, $J_{trans} = 1.7$ Hz, 6-H), 3.69 (1H, m ∼ t, 1-H_A), 3.75 (1H, s, OH), 4.27 (1H, m ∼ qui, α-H), 4.67 (1H, dd, $J_{gem} = 10.7$ Hz, $J_{6H} = 3.5$ Hz, 1-H_B), 5.28 (2H, s, CH_2Ph), 7.30–7.46 (5H, m, ArH). ^{13}C NMR (75 MHz): δ 18.21 (β-Me), 21.44 (3-Me), 44.04 (6-C), 63.37 (7-C), 65.68 (α-C), 66.94 (CH_2Ph), 69.55 (1-C), 107.03 (4-C), 128.26, 128.35 and 128.66 (Ar-2′,3′,4′-C), 136.23 (Ar-1′-C), 154.94 (3-C), 163.33 (COOBn), 166.04 (CON). HRMS *m*/*z* 317.1272 ($C_{17}H_{19}O_5N$ calcd 317.1263).

4.3. Benzyl (6*S*,7*S*)-7-[(1*S*)-1-hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 2b

Prepared analogously to **2a** from **1b**[9] (0.48 g; 1.34 mmol) and gave **2b** (0.40 g, 95%) as a yellow oil. It was pure enough for further reactions, but was purified by prep. TLC (CH_2Cl_2–EtOAc 6:9) for analytical investigations. $[\alpha]_D^{22.5} = +184.2$. IR (film): *v* 3448 (OH), 2976 (CH), 1752 (br, CON, COO), 1616 (Ar), 1392, 1208, 1128, 1080, 1024, 696 cm^{-1}. ^1H NMR (500 MHz): δ 1.37 (3H, d, $J = 6.2$ Hz, β-Me), 2.23 (3H, s, 3-Me), 2.97 (1H, dd, $J_{\alpha H} = 5.6$ Hz, $J_{trans} = 1.7$ Hz, 7-H), 3.45 (1H, ddd, $J_{1HA} = 9.5$ Hz, $J_{1HB} = 3.7$ Hz, $J_{trans} = 1.7$ Hz, 6-H), 3.69 (1H, m ∼ t, 1-H_A), 4.25 (1H, m ∼ qui, α-H), 4.65 (1H, dd, $J_{gem} = 10.7$ Hz, $J_{6H} = 3.7$ Hz, 1-H_B), 5.27 (2H, s, CH_2Ph), 7.30–7.46 (5H, m, ArH). ^{13}C NMR (75 MHz): δ 18.21 (β-Me), 21.31 (3-Me), 43.94 (6-C), 63.40 (7-C), 65.52 (α-C), 66.92 (CH_2Ph), 69.57 (1-C), 106.99 (4-C), 128.25, 128.32 and 128.65 (Ar-2′,3′,4′-C), 136.20 (Ar-1′-C), 154.95 (3-C), 163.35 (COOBn), 166.09 (CON). HRMS: 317.1270 ($C_{17}H_{19}O_5N$ calcd 317.1263).

4.4. (6*R*,7*R*)-7-[(1*R*)-1-Hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylic acid 3a

Compound **2a** (70 mg; 0.2 mmol) was hydrogenated under normal pressure in the presence of 10% Pd/C catalyst (10 mg) in methanol (20 mL) for an hour (TLC: CH_2Cl_2–EtOAc 1:1, UV, Rf_2 0.3, Rf_3 0; CH_2Cl_2–MeOH 10:3, UV, Rf_3 0.4). The catalyst was filtered off and washed with methanol. The filtrate was evaporated under reduced pressure. The resulting colourless oil solidifies on ether to give **3a** (35 mg, 78%) as a white solid. Mp 117–119 °C. $[\alpha]_D^{20} = -220.8$ (MeOH). IR (KBr): *v* 3416 (br, COOH), 1744 (CON), 1192, 1120, 720, 696, 540 cm^{-1}. ^1H NMR (500 MHz, MeOD-d_4): δ 1.35 (3H, d, $J = 6.5$ Hz, β-Me), 2.19 (3H, s, 3-Me), 3.03 (1H, m, 7-H), 3.47 (1H, m, 6-H), 3.69 (1H, m ∼ t, 1-H_A), 4.12 (1H, m ∼ qui, α-H), 4.64 (1H, dd, $J_{gem} = 10.6$ Hz, $J_{6H} = 3.6$ Hz, 1-H_B). ^{13}C NMR (75 MHz, MeOD-d_4): δ 17.90 (β-Me), 21.48 (3-Me), 45.51 (6-C), 64.11 (7-C), 65.85 (α-C), 70.30 (1-C), 110.66 (4-C), 152.70 (3-C), 168.72 (CON).[†] HRMS *m*/*z* 227.0787 ($C_{10}H_{13}NO_5$ calcd 227.0794).

4.5. (6*S*,7*S*)-7-[(1*S*)-1-Hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylic acid 3b

Prepared analogously to **3a** from **2b** (120 mg; 0.38 mmol) and gave **3b** (70 mg, 81%) as a white hygroscopic solid. Mp 117–119 °C. $[\alpha]_D^{19} = +220.4$ (MeOH). IR (KBr): *v* 3432 (br, COOH), 1752 (br, CON, COO), 1624, 1208, 1120, 720, 696, 540 cm^{-1}. ^1H NMR (500 MHz, MeOD-d_4): δ 1.35 (3H, d, $J = 6.5$ Hz, β-Me), 2.19 (3H, s, 3-Me), 3.03 (1H, m, 7-H), 3.47 (1H, m, 6-H), 3.69 (1H, m ∼ t,

[†] In all of the hydroxy-2-*iso*-oxacephem-4-carboxylic acids, the carboxylic acid CO signal in the ^{13}C NMR spectra is missing due to its diffuse shape.

1-H_A), 4.12 (1H, m ~ qui, α-H), 4.64 (1H, dd, J_{gem} = 10.6 Hz, J_{6H} = 3.6 Hz, 1-H_B). ^{13}C NMR (75 MHz, MeOD-d_4): δ 17.97 (β-Me), 21.48 (3-Me), 45.52 (6-C), 64.13 (7-C), 65.81 (α-C), 70.37 (1-C), 110.28 (4-C), 153.25 (3-C), 168.88 (CON). HRMS *m/z* 227.0777 ($C_{10}H_{13}NO_5$ calcd 227.0794).

4.6. Benzyl (6*R*,7*R*)-7-{(1*S*)-1-[(4-bromobenzoyl)oxy]-ethyl}-3-methyl-2-*iso*-oxacephem-4-carboxylate 4a

PPh_3 (0.08 g; 0.35 mmol) and 4-bromobenzoic acid (0.06 g; 0.35 mmol) were added to a solution of **2a** (0.1 g; 0.31 mmol) in THF (5 mL). A solution of DEAD (0.05 mL; 0.35 mmol) in THF (1 mL) was added dropwise to it at rt. The mixture was stirred for a day (TLC: CH_2Cl_2–EtOAc 10:1, UV + PMA, Rf_2 0.05, Rf_4 0.45). The solvent was removed under reduced pressure and the product was isolated by prep. TLC (CH_2Cl_2–EtOAc 10:1) to give **4a** (60 mg, 40%) as a yellow oil. $[\alpha]_D^{22} = -59.8$. IR (film) *v* 2936 (CH), 1768 (CON), 1720 (COO), 1616 (Ar), 1592 (Ar), 1392, 1360, 1272, 1104, 760, 696 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.52 (3H, d, *J* = 6.3 Hz, β-Me), 2.26 (3H, s, 3-Me), 3.14 (1H, d, $J_{\alpha H}$ = 6.2 Hz, 7-H), 3.61 (1H, d, J_{1HA} = 9.5 Hz, 6-H), 3.72 (1H, m ~ t, 1-H_A), 4.66 (1H, dd, J_{gem} = 10.5 Hz, J_{6H} = 3.5 Hz, 1-H_B), 5.23 (2H, AB, J_{gem} = 12.5 Hz, CH_2Ph), 5.56 (1H, qui, *J* = 6.3 Hz, α-H), 7.22–7.40 (5H, m, ArH), 7.45 (2H, d, J_{ortho} = 8.2 Hz, Ar-3′,5′-H), 7.81 (2H, d, J_{ortho} = 8.2 Hz, Ar-2′, 6′-H). ^{13}C NMR (125 MHz): δ 17.80 (β-Me), 18.60 (3-Me), 44.60 (6-C), 61.52 (7-C), 66.62 (α-C), 68.32 (CH_2Ph), 69.06 (1-C), 106.36 (4-C), 127.52, 127.65, 127.75, 127.98, 128.29, 130.74, 131.34 and 135.36 (Ar–C), 154.33 (3-C), 162.52 (COOBn), 164.48 (CON), 176.43 (ArCOO).

4.7. Benzyl (6*R*,7*R*)-7-[(1*S*)-1-(bromoacetoxy)ethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 5a

PPh_3 (0.09 g; 0.33 mmol) and bromoacetic acid (and 0.05 g; 0.33 mmol) were added to a solution of **2a** (0.09 g; 0.3 mmol) in THF (5 mL). A solution of DIAD (0.05 mL; 0.33 mmol) in THF (1 mL) was added dropwise to it at rt. The mixture was stirred overnight (TLC: CH_2Cl_2–EtOAc 10:1, UV + PMA, Rf_2 0.05, Rf_5 0.5). The solvent was removed under reduced pressure and the product was isolated by prep. TLC (CH_2Cl_2–EtOAc 15:1) to give **5a** (40 mg, 31%) as a yellow oil and 60 mg (66%) of starting material was also recovered. $[\alpha]_D^{21} = -117.5$. IR (film): *v* 2960 (CH), 1768 (CON), 1712 (COO), 1620 (Ar), 1392, 1356, 1276, 1132, 1088 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.45 (3H, d, *J* = 6.3 Hz, β-Me), 2.25 (3H, s, 3-Me), 3.01 (1H, dd, $J_{\alpha H}$ = 7.5 Hz, J_{trans} = 1.9 Hz, 7-H), 3.48 (1H, ddd, J_{1HA} = 9.5 Hz, J_{1HB} = 3.7 Hz, J_{trans} = 1.9 Hz, 6-H), 3.68 (2H, s, CH_2Br), 3.68 (1H, m ~ t, 1-H_A), 4.66 (1H, dd, J_{gem} = 10.7 Hz, J_{1HB} = 3.7 Hz, 1-H_B), 5.25 (2H, AB, J_{gem} = 12.5 Hz, CH_2Ph), 5.42 (1H, m ~ qui, α-H), 7.27–7.45 (5H, m, ArH). ^{13}C NMR (75 MHz): δ 18.04 (β-Me), 18.67 (3-Me), 25.74 (CH_2Br), 44.99 (6-C), 61.51 (7-C), 66.95 (α-C), 69.37 (CH_2Ph), 70.06 (1-C), 106.78 (4-C), 128.29, 128.44 and 128.63 (Ar-2′,3′,4′-C), 136.06 (Ar-1′-C), 155.01 (3-C), 163.04 (COOBn), 163.46 (CON), 166.65 (BrCH_2*C*OO).

4.8. Benzyl (6*R*,7*R*)-7-[(1*S*)-1-acetoxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 6a

PPh_3 (0.4 g; 1.5 mmol) and abs. acetic acid (0.4 mL; 6.3 mmol) were added to a solution of **2a** (0.2 g; 0.63 mmol) in THF (20 mL). A solution of 40% DEAD/toluene (0.5 mL; 1.25 mmol) in THF (5 mL) was added to it dropwise at 0 °C. The solution was stirred for an hour (TLC: CH_2Cl_2–EtOAc 10:1, UV + PMA, Rf_2 0.05, Rf_6 0.5). The product was isolated after evaporation of the solvent by flash chromatography (CH_2Cl_2→CH_2Cl_2–EtOAc 10:0.5). The white solid crystalline material was triturated with ether to give **6a** (0.15 g, 68%) as white crystals. Mp 132 °C. $[\alpha]_D^{21} = -190.0$. IR (KBr): *v* 1780 (COO), 1744 (CON), 1704 (COO), 1624 (Ar), 1376, 1296, 1248, 1208, 1136, 768, 752 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.40 (3H, d, *J* = 6.5 Hz, β-Me), 1.95 (3H, s, MeCO), 2.25 (3H, s, 3-Me), 2.98 (1H, dd, $J_{\alpha H}$ = 7.1 Hz, J_{trans} = 1.9 Hz, 7-H), 3.47 (1H, ddd, J_{1HA} = 9.4 Hz, J_{1HB} = 3.7 Hz, J_{trans} = 1.9 Hz, 6-H), 3.67 (1H, m ~ t, 1-H_A), 4.64 (1H, dd, J_{gem} = 10.6 Hz, J_{6H} = 3.7 Hz, 1-H_B), 5.25 (2H, AB, J_{gem} = 12.5 Hz, CH_2Ph), 5.35 (1H, m ~ qui, α-H), 7.27–7.40 (5H, m, ArH). ^{13}C NMR (75 MHz): δ 18.01 (β-Me), 18.85 (3-Me), 21.18 (*Me*CO), 45.01 (6-C), 61.80 (7-C), 66.93 (α-C), 67.88 (CH_2Ph), 69.48 (1-C), 106.85 (4-C), 128.23, 128.38 and 128.62 (Ar-2′,3′,4′-C), 136.11 (Ar-1′-C), 154.87 (3-C), 163.15 (COOBn), 164.09 (CON), 170.30 (Me*C*OO). $C_{19}H_{21}NO_6$ requires C 63.5; H 5.9; N 3.9; found C 63.7; H 5.8; N 3.85.

4.9. Benzyl (6*S*,7*S*)-7-[(1*R*)-1-acetoxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 6b

Prepared analogously to **6a** from **2b** (0.4 g; 1.27 mmol) and gave **6b** (0.36 g, 80%) as white crystals. Mp 132 °C. $[\alpha]_D^{21} = +191.1$. IR (KBr): *v* 1784 (COO), 1744 (CON), 1704 (COO), 1624 (Ar), 1376, 1296, 1248, 1208, 1136, 768, 752 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.40 (3H, d, *J* = 6.5 Hz, β-Me), 1.95 (3H, s, MeCO), 2.24 (3H, s, 3-Me), 2.98 (1H, dd, $J_{\alpha H}$ = 7.1 Hz, J_{trans} = 1.9 Hz, 7-H), 3.47 (1H, ddd, J_{1HA} = 9.4 Hz, J_{1HB} = 3.7 Hz, J_{trans} = 1.9 Hz, 6-H), 3.67 (1H, m ~ t, 1-H_A), 4.64 (1H, dd, J_{gem} = 10.6 Hz, J_{6H} = 3.7 Hz, 1-H_B), 5.25 (2H, AB, J_{gem} = 12.5 Hz, CH_2Ph), 5.35 (1H, m ~ qui, α-H), 7.29–7.45 (5H, m, ArH). ^{13}C NMR (125 MHz): δ 18.04 (β-Me), 18.88 (3-Me), 21.20 (*Me*CO), 45.07 (6-C), 61.86 (7-C), 66.96 (α-C), 67.95 (CH_2Ph), 69.50 (1-C), 106.91 (4-C), 128.26, 128.42 and 128.65 (Ar-2′,3′,4′-C), 136.16 (Ar-1′-C), 154.86 (3-C), 163.17 (COOBn), 164.07 (CON), 170.31 (Me*C*OO). $C_{19}H_{21}NO_6$ requires C 63.5; H 5.9; N 3.9; found C 63.5; H 5.7; N 3.85.

4.10. Benzyl (6*R*,7*R*)-7-[(1*S*)-1-hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 7a

NaOMe/MeOH (0.1 M, 0.4 mL; 0.04 mmol) was added to a solution of **6a** (0.1 g; 0.28 mmol) in methanol (10 mL) and stirred for 2 h at rt (TLC: CH_2Cl_2–EtOAc 1:1, UV + PMA, Rf_6 0.75, Rf_7 0.28). After completion the mixture was neutralized with 1 M HCl and the methanol was evaporated under reduced pressure. The residue was dissolved in 10 mL EtOAc, washed with water, with brine

and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give **7a** (70 mg, 80%) as a yellow oil. This was pure enough for further reactions, but purified by prep. TLC (CH_2Cl_2–EtOAc 6:9) for analytical investigations, the resulting white solid was recrystallized from ether/hexane to give needle-like white crystals. Mp 94–95 °C. $[\alpha]_D^{23} = -190.7$. IR (KBr): ν 3360 (OH), 2952 (CH), 1756 (CON), 1712 (COO), 1612 (Ar), 1392, 1216, 1136, 1088, 1064, 696 cm^{-1}. ^1H NMR (500 MHz): δ 1.34 (3H, d, $J = 6.3$ Hz, β-Me), 2.13 (1H, br s, OH), 2.23 (3H, s, 3-Me), 2.86 (1H, dd, $J_{\alpha H} = 6.3$ Hz, $J_{trans} = 1.6$ Hz, 7-H), 3.54 (1H, ddd, $J_{1HA} = 9.5$ Hz, $J_{1HB} = 3.6$ Hz, $J_{trans} = 1.7$ Hz, 6-H), 3.68 (1H, m ~ t, 1-H_A), 4.30 (1H, qui, $J = 6.3$ Hz, α-H), 4.67 (1H, dd, $J_{gem} = 10.7$ Hz, $J_{6H} = 3.6$ Hz, 1-H_B), 5.27 (2H, s, $ArCH_2$), 7.30–7.46 (5H, m, ArH). ^{13}C NMR (125 MHz): δ 18.28 (β-Me), 22.12 (3-Me), 44.50 (6-C), 64.35 (7-C), 65.40 (α-C), 66.95 (CH_2–Ph), 69.69 (1-C), 107.01 (4-C), 128.27, 128.37 and 128.66 (Ar-2′,3′,4′-C), 136.19 (Ar-1′-C), 154.98 (3-C), 163.42 (COOBn), 165.82 (CON). HRMS m/z 317.1275 ($C_{17}H_{19}O_5N$ calcd 317.1263).

4.11. Benzyl (6*S*,7*S*)-7-[(1*R*)-1-hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 7b

Prepared analogously to **7a** from **6b** (0.1 g; 0.28 mmol) and gave **7b** (80 mg, 91%) as needle-like white crystals. Mp 95 °C. $[\alpha]_D^{31} = +190.4$. IR (KBr): ν 3360 (OH), 2952 (CH), 1756 (CON), 1712 (COO), 1616 (Ar), 1392, 1216, 1136, 1088, 1064, 696 cm^{-1}. ^1H NMR (300 MHz): δ 1.34 (3H, d, $J = 6$ Hz, β-Me), 2.23 (3H, s, 3-Me), 2.86 (1H, d, $J_{\alpha H} = 6$ Hz, 7-H), 3.53 (1H, m, 6-H), 3.68 (1H, m ~ t, 1-H_A), 4.30 (1H, qui, $J = 6$ Hz, α-H), 4.67 (1H, dd, $J_{gem} = 10.6$ Hz, $J_{6H} = 3.5$ Hz, 1-H_B), 5.27 (2H, s, CH_2Ph), 7.30–7.46 (5H, m, ArH). ^{13}C NMR (75 MHz): δ 18.09 (β-Me), 21.96 (3-Me), 44.36 (6-C), 64.18 (7-C), 65.26 (α-C), 66.77 (CH_2Ph), 69.53 (1-C), 106.86 (4-C), 128.09, 128.20 and 128.49 (Ar-2′,3′,4′-C), 136.04 (Ar-1′-C), 154.79 (3-C), 163.24 (COOBn), 165.64 (CON). HRMS m/z 317.1253 ($C_{17}H_{19}O_5N$ calcd 317.1263).

4.12. (6*R*,7*R*)-7-[(1*S*)-1-Hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylic acid 8a

Compound **7a** (70 mg; 0.2 mmol) was hydrogenated under normal pressure in the presence of 10% Pd/C catalyst (10 mg) in methanol (20 mL) for an hour (TLC: CH_2Cl_2–EtOAc 1:1, UV, Rf_7 0.3, Rf_8 0, CH_2Cl_2–MeOH 10:3, UV, Rf_8 0.4). The catalyst was filtered off and washed with methanol. The solvent was evaporated under reduced pressure. The resulting colourless oil solidified on ether to give **8a** (40 mg, 88%) as a white solid. Mp 139–140 °C. $[\alpha]_D^{20} = -232.3$ (MeOH). IR (KBr): ν 3432 (br, COOH), 1736 (br, CON, COO), 1628, 1576, 1400, 1152, 792 cm^{-1}. ^1H NMR (500 MHz, MeOD-d_4): δ 1.28 (3H, d, $J = 6.5$ Hz, β-Me), 2.16 (3H, s, 3-Me), 2.84 (1H, m, 6-H), 3.48 (1H, m, 7-H), 3.66 (1H, m ~ t, 1-H_A), 4.21 (1H, m ~ qui, α-H), 4.60 (1H, dd, $J_{gem} = 10.7$ Hz, $J_{1HB} = 3.7$ Hz, 1-H_B). ^{13}C NMR (75 MHz, MeOD-d_4): δ 17.71 (β-Me), 22.08 (3-Me), 46.28 (6-C), 64.84 (7-C), 66.16 (α-C), 70.16 (1-C), 112.12 (4-C), 150.63 (3-C), 168.49 (CON). HRMS m/z measured as Na/K adduct 250.0695 ($C_{10}H_{13}NO_5Na^+$ calcd 250.0691) and 266.0427 ($C_{10}H_{13}NO_5K^+$ calcd 266.0431).

4.13. (6*S*,7*S*)-7-[(1*R*)-1-Hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylic acid 8b

Prepared analogously to **8a** from **7b** (70 mg; 0.2 mmol) and gave **8b** (40 mg, 88%) as a white solid. Mp 139–140 °C. $[\alpha]_D^{20} = +231.8$ (MeOH). IR (KBr): ν 3440 (br, COOH), 1736 (br, CON, COO), 1628, 1576, 1400, 1148, 792 cm^{-1}. ^1H NMR (500 MHz, MeOD-d_4): δ 1.27 (3H, d, $J = 6.5$ Hz, β-Me), 2.16 (3H, s, 3-Me), 2.84 (1H, m, 6-H), 3.48 (1H, m, 7-H), 3.67 (1H, m ~ t, 1-H_A), 4.21 (1H, m ~ qui, α-H), 4.60 (1H, dd, $J_{gem} = 10.7$ Hz, $J_{6H} = 3.7$ Hz, 1-H_B). ^{13}C NMR (75 MHz, MeOD-d_4): δ 17.76 (β-Me), 22.08 (3-Me), 46.28 (6-C), 64.82 (7-C), 66.15 (α-C), 70.20 (1-C), 111.85 (4-C), 151.05 (3-C), 168.60 (CON). HRMS m/z measured as Na/K adduct 250.0699 ($C_{10}H_{13}NO_5Na^+$ calcd 250.0691) and 266.0439 ($C_{10}H_{13}NO_5K^+$ calcd 266.0431).

4.14. (3*R*,4*S*)-3-[(1*R*)-1-(Methanesulfonyloxy)ethyl]-4-[(methanesulfonyloxy)methyl]-1-(4-methoxyphenyl)-azetidin-2-one 13a

Mesyl chloride (0.5 mL; 6.5 mmol) was added to a solution of (3*R*,4*S*)-3-[(1*R*)-1-hydroxyethyl]-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidin-2-one **11a**[9] (0.5 g; 2 mmol) in THF (15 mL) at −5 °C, and then NEt_3 (0.7 mL; 5 mmol) was added to it dropwise. After 1 h of stirring at the same temperature (TLC: CH_2Cl_2–EtOAc 10:1, UV, Rf_{11} 0.05, Rf_{13} 0.19), the white precipitate was dissolved by adding water, the mixture was extracted with 3×30 mL EtOAC. The organic phase was washed with brine, dried over $MgSO_4$, and the solvent removed under reduced pressure. The light yellow oil was triturated with ether and the precipitating white crystals were filtered to give **13a** (0.69 g, 85%). Mp 129–130 °C. $[\alpha]_D^{20} = -87.5$. IR (KBr): ν 1756 (CON), 1516 (Ar), 1352, 1336 (Ms), 1248, 1168 (Ms), 892, 840 cm^{-1}. ^1H NMR (500 MHz): δ 1.74 (3H, d, $J = 6.5$ Hz, β-Me), 3.05 + 3.13 ($2 \times 3H$, $2 \times s$, $2 \times SMe$), 3.64 (1H, dd, $J_{\alpha H} = 3.5$ Hz, $J_{4H} = 5.5$ Hz, 3-H), 3.80 (3H, s, OMe), 4.51 (1H, q, $J = 5.5$ Hz, 4-H), 4.72 (2H, dAB, $J_{gem} = 11$ Hz, $J_{4H} = 5.5$ Hz, CH_2), 5.30 (1H, qd, $J_{3H} = 3.5$ Hz, $J_{CH_3} = 6.5$ Hz, α-H), 6.90 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-3′,5′-H), 7.35 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-2′,6′-H). ^{13}C NMR (125 MHz): δ 20.56 (β-Me), 37.62 and 40.12 ($2 \times SMe$), 53.33, 55.59 and 56.12 (3-C, 4-C, OMe), 66.96 (CH_2), 74.25 (α-C), 114.66 (Ar-3′,5′-C), 119.07 (Ar-2′,6′-C), 130.04 (Ar-1′-C), 156.84 (Ar-4′-C), 162.03 (CON). $C_{15}H_{21}NO_8S_2$ requires C 44.2; H 5.2; N 3.44; S 15.7; found C 44.3; H 5.1; N 3.3; S 15.8.

4.15. (1*R*,2*R*,5*S*)-6-(4-Methoxyphenyl)-2-methyl-3-oxa-6-azabicyclo[3.2.0]heptan-7-one 12a

Mesyl chloride (0.25 mL; 3 mmol) was added dropwise to a solution of **11a** (0.5 g; 2 mmol) in pyridine (15 mL). After 3 h of stirring at rt (TLC: CH_2Cl_2–EtOAc 10:1, UV, Rf_{11} 0.05, Rf_{12} 0.42, Rf_{13} 0.19), pyridine was removed under reduced pressure. The oily residue was dissolved in dichloromethane, washed with water, then with 10% HCl and then

with water again. After it was dried over $MgSO_4$, the oily residue obtained after evaporation of solvent was triturated with ether, the precipitating white crystals were filtered to afford **13a** (0.26 g; 32%). The mother liquor was purified with prep. TLC (CH_2Cl_2–EtOAc 15:1, run twice) to give **12a** (0.20 g, 43%) as white crystals. Mp 161 °C. $[\alpha]_D^{28} = -197.2$. IR (KBr): *v* 1720 (CON), 1520 (Ar), 1400, 1384, 1248, 824 cm^{-1}. ^1H NMR (300 MHz): δ 1.54 (3H, d, $J = 6.3$ Hz, 2-Me), 3.49 (1H, dd, $J_{gem} = 10.8$ Hz, $J_{5H} = 3.0$ Hz, 4-H_A), 3.67 (1H, dd, $J_{2H} = 5.5$ Hz, $J_{5H} = 4.0$ Hz, 1-H), 3.79 (3H, s, OMe), 3.85 (1H, m ~ qui, 2-H), 4.22 (1H, d, $J_{gem} = 10.8$ Hz, 4-H_B), 4.53 (1H, dd, $J_{4HA} = 3.0$ Hz, $J_{1H} = 4.0$ Hz, 5-H), 6.87 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-3′,5′-H), 7.31 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-2′,6′-H). ^{13}C NMR (75 MHz): δ 15.84 (2-Me), 55.74, 57.54 and 58.25 (1-C, 5-C, OMe), 67.45 (4-C), 74.19 (2-C), 114.76 (Ar-3′,5′-C), 118.10 (Ar-2′,6′-C), 131.00 (Ar-1′-C), 156.37 (Ar-4′-C), 162.79 (CON). $C_{13}H_{15}NO_3$ requires C 66.9; H 6.5; N 6.0; found C 66.8; H 6.5; N 6.0.

4.16. (1*R*,2*R*,5*S*)-6-(3-Bromo-4-methoxyphenyl)-2-methyl-3-oxa-6-azabicyclo[3.2.0]heptan-7-one 14a and (1*R*,2*R*,5*S*)-6-(2,5-Dibromo-4-methoxyphenyl)-2-methyl-3-oxa-6-azabicyclo[3.2.0]heptan-7-one 15a

Bromine (0.04 mL; 0.8 mmol) was added dropwise to a solution of **12a** (0.18 g; 0.77 mmol) in acetic acid (2 mL) and then stirred at rt for a day (TLC: CH_2Cl_2–EtOAc 10:2, UV, Rf_{12} 0.45, Rf_{14} 0.50). Because the reaction was not completed, another 0.04 mL of bromine was added and stirred again for a day. It was then poured onto the mixture of ice (5 g) and $Na_2S_2O_5$ (0.15 g; 0.8 mmol). The precipitating yellowish crystals were filtered, dried and purified with prep. TLC (CH_2Cl_2–EtOAc 10:2), resulting in 0.15 g (62%) of **14a** and 60 mg (20%) of **15a** as white solids.

4.16.1. (1*R*,2*R*,5*S*)-6-(3-Bromo-4-methoxyphenyl)-2-methyl-3-oxa-6-azabicyclo[3.2.0]heptan-7-one 14a. Mp 163–165 °C (MeOH). $[\alpha]_D^{28} = -169.2$. IR (KBr): *v* 1744, (CON), 1504 (Ar), 1448, 1404, 1384, 1296, 1280, 1248, 1228, 1184, 1096, 1048, 1012, 872, 812, 672 cm^{-1}. ^1H NMR (500 MHz): δ 1.53 (3H, d, $J = 6.5$ Hz, 2-Me), 3.49 (1H, dd, $J_{gem} = 10.9$ Hz, $J_{5H} = 2.9$ Hz, 4-H_A), 3.68 (1H, dd, $J_{2H} = 5.5$ Hz, $J_{5H} = 4.1$ Hz, 1-H), 3.84 (1H, m ~ qui, 2-H), 3.87 (3H, s, OMe), 4.20 (1H, d, $J_{gem} = 10.9$ Hz, 4-H_B), 4.52 (1H, dd, $J_{4HA} = 2.9$ Hz, $J_{1H} = 4.1$ Hz, 5-H), 6.87 (1H, d, $J_{ortho} = 8.8$ Hz, Ar-5′-H), 7.35 (1H, dd, $J_{ortho} = 8.8$ Hz, $J_{meta} = 2.5$ Hz, Ar-3′-H), 7.51 (1H, d, $J_{meta} = 2.5$ Hz, Ar-6′-H). ^{13}C NMR (125 MHz): δ 15.78 (2-Me), 56.79, 57.73 and 58.53 (1-C, 5-C, OMe), 67.40 (4-C), 74.23 (α-C), 112.39 and 112.77 (Ar-3′-C, Ar-5′-C), 117.13 (Ar-6′-C), 121.61(Ar-2′-C), 131.62 (Ar-1′-C), 152.82 (Ar-4′-C), 162.94 (CON). $C_{13}H_{14}BrNO_3$ requires C 50.0; H 4.5; N 4.5; Br 25.6; found C 49.9; H 4.4; N 4.4; Br 25.65.

4.16.2. (1*R*,2*R*,5*S*)-6-(2,5-Dibromo-4-methoxyphenyl)-2-methyl-3-oxa-6-azabicyclo[3.2.0]heptan-7-one 15a. Rf_{15} 0.64. Mp 193–195 °C (MeOH, recrystallises at 190 °C). $[\alpha]_D^{28} = -109.3$. IR (KBr): *v* 1744 (CON), 1492 (Ar), 1380, 1256, 1056, 1024, 840 cm^{-1}. ^1H NMR (500 MHz): δ 1.58 (3H, d, $J = 6.5$ Hz, 2-Me), 3.47 (1H, dd, $J_{gem} = 11$ Hz, $J_{5H} = 3$ Hz, 4-H_A), 3.69 (1H, dd, $J_{2H} = 5.5$ Hz, $J_{5H} = 4$ Hz, 1-H), 3.88 (3H, s, OMe), 3.91 (1H, m ~ qui, 2-H), 3.96 (1H, d, $J_{gem} = 11$ Hz, 4-H_B), 5.01 (1H, m ~ t, 5-H), 7.04 (1H, s, Ar-3′-H), 7.84 (1H, s, Ar-6′-H). ^{13}C NMR (75 MHz): δ 15.84 (2-Me), 56.94, 59.04 and 61.50 (1-C, 5-C, OMe), 67.90 (4-C), 75.36 (α-C), 111.33 (Ar-5′-C), 115.97 (Ar-2′-C), 116.42 (Ar-3′-C), 128.29 (Ar-6′-C), 131.57 (Ar-1′-C), 152.22 (Ar-4′-C), 165.69 (CON). $C_{13}H_{13}Br_2NO_3$ requires C 39.9; H 3.3; N 3.6; Br 40.9; found C 39.9; H 3.3; N 3.4; Br 40.8.

4.17. (3*R*,4*S*)-3-[(1*R*)-1-(Methanesulfonyloxy)ethyl]-4-[(methanesulfonyloxy)methyl]azetidin-2-one 16a

A solution of CAN (1.64 g; 3 mmol) in water (15 mL) was added dropwise to a solution of **13a** (0.41 g; 1 mmol) in acetonitrile (10 mL) while the temperature was kept between −10 and 0 °C during the addition and the mixture was stirred at this temperature for an additional hour (TLC: CH_2Cl_2–EtOAc 1:1, UV + PMA, Rf_{13} 0.7, Rf_{16} 0.2 only PMA). Water (10 mL) was added and the mixture was extracted with EtOAc (5 × 20 mL). The combined organic layers were washed subsequently with 10% $NaHCO_3$ (15 mL), 10% $NaHSO_3$ (15 mL), with 10% $NaHCO_3$ (15 mL) and with brine. All the aqueous phases were extracted with EtOAc. The combined organic layers were dried ($MgSO_4$). The solvent was removed under reduced pressure. The resulting white solid was triturated with EtOAc to give **16a** (0.20 g, 66%). Mp 143–145 °C. IR (KBr): *v* 3328 (NH), 1764 (CON), 1384, 1352 (Ms), 1168 (Ms), 984, 968, 904, 824, 524 cm^{-1}. ^1H NMR (500 MHz, DMSO): δ 1.46 (3H, d, $J = 6.2$ Hz, β-Me), 3.21 + 3.22 (2 × 3H, 2 × s, 2 × SMe), 3.61 (1H, m ~ t, 3-H), 3.93 (1H, m, 4-H), 4.40 (1H, m ~ t, CH_{2A}), 4.51 (1H, dd, $J_{gem} = 10.5$ Hz, $J_{4H} = 3.5$ Hz, CH_{2B}), 5.07 (1H, m ~ qui, α-H), 7.35 (1H, s, NH). ^{13}C NMR (125 MHz, DMSO): δ 20.71 (β-Me), 36.83 and 38.78 (2 × SMe), 48.58 (3-C), 56.66 (4-C), 70.49 (CH_2), 74.93 (α-C), 166.03 (CON). $C_8H_{15}NO_7S_2$ requires C 31.9; H 5.0; N 4.65; S 21.3; found C 32.1; H 4.9; N 4.6; S 21.0.

4.18. Benzyl (6*S*,7*R*)-7-[(1*R*)-1-(methanesulfonyloxy)-ethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 17a and benzyl (6*S*,7*Z*)-7-ethylidene-3-methyl-2-*iso*-oxacephem-4-carboxylate 18a

Benzyl 2,3-dioxobutyrate[11] (0.41 g) and NEt_3 (0.05 mL) were added to the solution of **16a** (0.4 g; 1.3 mmol) in THF (15 mL). The mixture was stirred at rt for 3 h, then cooled down to −25 °C. Pyridine (0.4 mL), then a solution of thionyl chloride (0.27 mL) in 5 mL THF were added dropwise. After 1 h of stirring the white precipitate was filtered off and the solvent was removed under reduced pressure. Zinc (0.45 g) was slowly added at 5 °C to the solution of the yellow oily residue in the mixture of acetic acid (15 mL) and water (3 mL). After 2 h of stirring the insoluble materials were filtered off, and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane, washed with water, dried over $MgSO_4$, and the solvent was evaporated. The resulting oil was purified by flash chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$–EtOAc

1:1), and the fractions having an Rf 0.5 (TLC: CH_2Cl_2–EtOAc 10:2) were collected. Starting material (0.05 g) was also recovered. The aqueous layer of the extraction was extracted with EtOAc. The organic phase was dried over $MgSO_4$, the solvent was evaporated and resulted in 0.05 g of starting material (total 25%). NEt_3 (0.05 mL) was added to the solution of the material with Rf 0.5 of the above mentioned chromatography in chloroform (10 mL) and refluxed for 2 h (TLC: CH_2Cl_2–EtOAc 10:2, UV, Rf_{18} 0.6, Rf_{19} 0.85). The mixture was washed with water, dried over $MgSO_4$, the solvent was evaporated and the residue was purified with flash chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$–EtOAc 10:0.3) to give 80 mg (15%) of **17a** and 40 mg (10%) of **18a**.

4.18.1. Benzyl (6*S*,7*R*)-7-[(1*R*)-1-(methanesulfonyloxy)ethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 17a. Yellow oil. IR (film): ν 1768 (CON), 1712 (COO), 1620 (Ar), 1356 (Ms), 1176 (Ms), 920 cm^{-1}. ^1H NMR (500 MHz): δ 1.55 (3H, d, $J = 6.5$ Hz, β-Me), 2.27 (3H, s, 3-Me), 3.15 (3H, s, SMe), 3.75 (1H, ddd, $J_{1HA} = 10$ Hz, $J_{1HB} = 3.5$ Hz, $J_{cis} = 5.5$ Hz, 6-H), 3.92 (1H, dd, $J_{cis} = 5.5$ Hz, $J_{\alpha H} = 8.0$ Hz, 7-H), 4.07 (1H, m ~ t, 1-H_A), 4.58 (1H, dd, $J_{gem} = 10.5$ Hz, $J_{1HB} = 3.5$ Hz, 1-H_B), 5.03 (1H, qd, $J_{7H} = 8.0$ Hz, $J_{CH_3} = 6.5$ Hz, α-H), 5.27 (2H, AB, $J_{gem} = 12.5$ Hz, CH_2Ph), 7.32–7.40 (3H, m, Ar-3′,4′,5′-H), 7.45 (2H, d, $J_{ortho} = 7.2$ Hz, Ar-2′,6′-H). ^{13}C NMR (125 MHz): δ 18.17 (β-Me), 21.90 (3-Me), 39.62 (SMe), 45.32 (6-C), 58.43 (7-C), 66.71, 67.03 and 73.31 (α-C, CH_2Ph, 1-C), 106.56 (4-C), 128.34, 128.50 and 128.67 (Ar-2′,3′,4′-C), 135.95 (Ar-1′-C), 155.65 (3-C), 162.94 (COOBn), 164.21 (CON).

4.18.2. Benzyl (6*S*,7*Z*)-7-ethylidene-3-methyl-2-*iso*-oxacephem-4-carboxylate 18a. Yellow oil. IR (film): ν 1752 (CON), 1720 (COO), 1612 (Ar), 1352, 1212, 1120, 1080, 1032, 736, 696 cm^{-1}. ^1H NMR (500 MHz): δ 2.06 (3H, d, $J = 7.2$ Hz, β-Me), 2.25 (3H, s, 3-Me), 3.55 (1H, m ~ t, 1-H_A), 3.86 (1H, dd, $J_{1HA} = 9$ Hz, $J_{1HB} = 3.7$ Hz, 6-H), 4.60 (1H, dd, $J_{gem} = 10.6$ Hz, $J_{6H} = 3.7$ Hz, 1-H_B), 5.29 (2H, AB, $J_{gem} = 12.5$ Hz, CH_2Ph), 5.81 (1H, q, $J = 7.2$ Hz, α-H), 7.30–7.46 (5H, m, ArH). ^{13}C NMR (125 MHz): δ 15.16 (β-Me), 18.12 (3-Me), 49.39 (6-C), 66.96 and 69.06 (CH_2Ph, 1-C), 107.47 (4-C), 128.20, 128.45 and 128.65 (Ar-2′,3′,4′-C), 129.29 (α-C), 136.27 (Ar-1′-C), 139.45 (7-C), 153.85 (3-C), 163.22 and 163.65 (COOBn, CON).

4.19. (1*R*,2*R*,5*S*)-6-(4-Methoxyphenyl)-2-methyl-3-oxa-6-azabicyclo[3.2.0]heptane-4,7-dione 19a

A solution of AcCl (0.65 mL; 9 mmol) in THF (5 mL) was added dropwise to a suspension of (2*S*,3*R*)-3-[(1*R*)-1-hydroxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylic acid **10a**[9] (1.6 g; 6 mmol) in THF (30 mL) under salt-ice cooling. Then a solution of pyridine (1.2 mL; 15 mmol) in THF (5 mL) was added dropwise to it. The suspension was stirred at −5 °C for 2 h, then at rt for another 2 h (TLC: CH_2Cl_2–EtOAc 10:2, UV, Rf_{19} 0.5). The insoluble material was dissolved in water and the mixture was extracted with EtOAc (3 × 30 mL). The organic phase was washed with 1 M HCl, then with brine and then dried over $MgSO_4$, the solvent was evaporated to give **19a** (1.4 g, 95%) as a beige solid material, which was pure enough for further reactions. Mp 148–149 °C. $[\alpha]_D^{30} = -60.4$. IR (KBr): ν 1744 (br, CON, COO), 1516 (Ar), 1384, 1248, 1024, 904, 828 cm^{-1}. ^1H NMR (500 MHz): δ 1.65 (3H, d, $J = 6.8$ Hz, 2-Me), 3.79 (3H, s, OMe), 4.04 (1H, dd, $J_{2H} = 7.5$ Hz, $J_{5H} = 4.5$ Hz, 1-H), 4.62 (1H, d, $J = 4.5$ Hz, 5-H), 4.83 (1H, m ~ qui, 2-H), 6.88 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-3′,5′-H), 7.84 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-2′,6′-H). ^{13}C NMR (125 MHz): δ 18.18 (2-Me), 53.96, 54.77 and 55.71 (1-C, 5-C, OMe), 75.27 (2-C), 114.69 (3′,5′-C), 118.54 (2′,6′-C), 130.78 (1′-C), 156.99 (4′-C), 160.95 (CON), 170.62 (COO). $C_{13}H_{13}NO_4$ requires C 63.15; H 5.3; N 5.7; found C 62.9; H 5.4; N 5.2.

4.20. (3*R*,4*S*)-3-[(1*R*)-1-Hydroxyethyl]-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidin-2-one 11a

$NaBH_4$ (0.75 g; 0.02 mol) was added in small portions under ice cooling to a solution of **19a** (1.4 g; 5.7 mmol) in methanol (25 mL) (gas generation). The suspension was stirred at rt overnight (TLC: CH_2Cl_2–EtOAc 1:1, UV, Rf_{11} 0.15, Rf_{19} 0.7). The solvent was evaporated under reduced pressure. The remaining solid material was suspended in water and neutralized with 1 M HCl. The white insoluble solid material was filtered and then suspended in CH_2Cl_2, the insoluble material was filtered to give 1.2 g (84%) of **11a** as a white solid material, which was pure enough for further reactions. Its physical properties are the same as those previously described.[9]

4.21. (3*R*,4*S*)-4-(Acetoxymethyl)-3-[(1*R*)-1-hydroxyethyl]-1-(4-methoxyphenyl)azetidin-2-one 20a and (3*R*,4*S*)-3-[(1*R*)-1-acetoxyethyl]-4-(acetoxymethyl)-1-(4-methoxyphenyl)azetidin-2-one 21a

AcCl (0.28 mL; 4 mmol), then NEt_3 (0.32 mL, 4 mmol) were added dropwise at 0 °C to a suspension of compound **11a** (0.4 g; 1.6 mmol) in THF (15 mL). The mixture was stirred for 2 h at that temperature, then for an additional day (TLC: CH_2Cl_2–EtOAc 10:2, UV, Rf_{11} 0.05, Rf_{20} 0.15, Rf_{21} 0.55) at rt. It was diluted with water, neutralized with 1 M HCl, then extracted with EtOAc (3 × 15 mL). It was washed with brine, dried over $MgSO_4$ and the solvent evaporated under reduced pressure. The remaining solid was triturated with ether, the insoluble white solid was filtered off to give 0.2 g of **20a**. The ethereal mother liquor was purified by prep. TLC (CH_2Cl_2–EtOAc 10:2) to give **21a** (0.15 g, 28%) and an additional 0.05 g of **20a** (total 53%).

4.21.1. (3*R*,4*S*)-4-(Acetoxymethyl)-3-[(1*R*)-1-hydroxyethyl]-1-(4-methoxyphenyl)-azetidin-2-one 20a. White solid. Mp 125 °C. $[\alpha]_D^{28} = -77.8$. IR (KBr): ν 3472 (OH), 1736 (br, CON, COO), 1520 (Ar), 1384, 1252, 1224, 1036, 824 cm^{-1}. ^1H NMR (500 MHz): δ 1.46 (3H, d, $J = 6.5$ Hz, β-Me), 1.68 (1H, br s, OH), 2.09 (3H, s, MeCO), 3.42 (1H, m ~ t, 3-H), 3.79 (3H, s, OMe), 4.28 (1H, m, α-H), 4.33 (1H, m ~ q, 4-H), 4.60 (2H, dAB, $J_{gem} = 10$ Hz, $J_{4H} = 5.5$ Hz, CH_2), 6.87 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-3′,5′-H), 7.40 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-2′,6′-H). ^{13}C NMR (75 MHz): δ 21.08 (β-Me), 23.24

(*Me*CO), 53.62, 55.72 and 58.07 (2-C, 3-C, OMe), 62.32 and 64.66 (CH_2, α-C), 114.60 (Ar-3′,5′-C), 119.21 (Ar-2′,6′-C), 130.76 (Ar-1′-C), 156.63 (Ar-4′-C), 165.25 (CON), 170.66 (Me*C*O). $C_{15}H_{19}NO_5$ requires C 61.4; H 6.5, N 4.8; found C 61.3; H 6.4; N 4.7.

4.21.2. (3*R*,4*S*)-3-[(1*R*)-1-Acetoxyethyl]-4-(acetoxymethyl)-1-(4-methoxyphenyl)azetidin-2-one 21a. White solid. Mp 114–115 °C. $[\alpha]_D^{24} = -58.5$. IR (KBr): *v* 1732 (br, CON, COO), 1516 (Ar), 1400, 1384, 1252, 1028, 832 cm^{-1}. ^1H NMR (500 MHz): δ 1.51 (3H, d, $J = 6.5$ Hz, β-Me), 2.09 (6H, s, 2 × MeCO), 3.53 (1H, m ∼ t, 3-H), 3.79 (3H, s, OMe), 4.30 (1H, dd, $J_{gem} = 11.5$ Hz, $J_{4H} = 6.5$ Hz, CH_{2A}), 4.36 (1H, m ∼ q, 4-H), 4.53 (1H, dd, $J_{gem} = 11.5$ Hz, $J_{4H} = 5.5$, CH_{2B}), 5.33 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 4$ Hz, α-H), 6.88 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-3′,5′-H), 7.38 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-2′,6′-H). ^{13}C NMR (125 MHz): δ 19.80 (β-Me), 20.91 and 21.56 (2 × *Me*CO), 53.06, 55.75 and 55.83 (2-C, 3-C, OMe), 62.35 and 66.68 (CH_2, α-C), 114.66 (Ar-3′,5′-C), 119.00 (Ar-2′,6′-C), 130.83 (Ar-1′-C), 156.65 (Ar-4′-C), 163.64 (CON), 170.44 and 170.57 (2 × Me*C*O). $C_{17}H_{21}NO_6$ requires C 60.9; H 6.3; N 4.2; found C 61.1; H 6.1; N 4.0.

4.22. Tritylation/acetylation/detrytilation of 11a

A solution of trityl chloride (0.3 g; 1.1 mmol) and **11a** (0.2 g, 0.8 mmol) in pyridine (2 mL) was boiled for 4 h (TLC: CH_2Cl_2–acetone 10:0.5, UV, Rf 0.4, Rf_{11} 0.05). It was then concentrated under reduced pressure and dissolved in CH_2Cl_2. If it consisted of an insoluble material, then it was filtered off. The filtrate was washed with water and dried ($MgSO_4$). AcCl (0.07 mL, 1 mmol) and pyridine (0.07 mL, 1 mmol) were added to the solution of the residue obtained after evaporation of the solvent in THF (5 mL) at 0 °C. The mixture was stirred for 2 h (TLC: CH_2Cl_2–acetone 10:0.5, UV, Rf 0.85), concentrated under reduced pressure and the residue dissolved in CH_2Cl_2. It was washed with water, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The residue was purified by flash chromatography (CH_2Cl_2) to give 0.3 g white solid material. Mp 158 °C. 0.1 g of it was refluxed for 3 h in 90% acetic acid. The residue obtained after concentration under reduced pressure was dissolved in EtOAc, washed with water, dried over $MgSO_4$, the solvent was evaporated under reduced pressure. The residue was purified by prep. TLC (CH_2Cl_2–acetone 10:2) to give 30 mg of white solid material with an Rf 0.2, with all of its physical properties being the same as **20a**, and 30 mg of white solid material with an Rf 0.5, with all of its physical properties the same as **21a**.

4.23. Dibenzyl malonate

Diethyl malonate (25 mL; 0.16 mol), benzyl alcohol (35 mL; 0.34 mol) and a catalytic amount of DMAP were heated in a 150 °C oil bath by using a Dean–Stark trap. The amount of the ethanol distillating out of the reaction was measured. After 1 day of heating, another 5 mL (0.05 mol) of benzyl alcohol was added, then after another day another 5 mL was added. When the distillation speed of the outdistillating ethanol slowed down (after 4–5 days of heating), the mixture was distilled through a column at 0.1 mmHg. All the fractions boiling below 160 °C were collected and used again for the next charge. The fraction having a boiling point of 165–173 °C consisted of the title compound and gave 19.2 g (42%) of the title compound as a colourless liquid. n_D 1.5542. IR (film): *v* 1736 (COO), 1456, 1332, 1272, 1148 (COC), 1008, 748, 696 cm^{-1}. ^1H NMR (300 MHz): δ 3.46 (2H, s, CCH_2C), 5.16 (4H, s, CH_2Ar), 7.32 (10H, ∼s, ArH).

4.24. Dibenzyl bromomalonate

Bromine (7.3 mL; 0.142 mol) was added dropwise to the solution of dibenzyl malonate (38 g; 0.135 mol) in CCl_4 (100 mL), always waiting for its colour to disappear. It was stirred for 2 h, then washed with water, 2 × 50 mL saturated Na_2CO_3, then with brine. It was then dried over Na_2SO_4, and the solvent was evaporated under reduced pressure to give 45 g light yellow oil, which was distilled at 0.1 mmHg. The fraction boiling under 60 °C was discarded and the remaining material (37 g) was used without further purification (at this pressure it cannot be distilled without decomposition). *Caution*: the compound is very lachrymatory, all of the glassware should be washed with alcoholic ammonia. n_D 1.5590. IR (film): *v* 1744 (COO), 1456, 1376, 1232, 1140 (COC), 1004, 748, 696 cm^{-1}. ^1H NMR (300 MHz): δ 4.46 (1H, s, CHBr), 5.19 (4H, s, CH_2), 7.31 (10H, ∼s, ArH).

4.25. Dibenzyl [(4-methoxyphenyl)amino]malonate 22

The solution of dibenzyl bromomalonate (37 g; 0.1 mol) and freshly distilled *p*-anisidine (25 g; 0.2 mol) in 100 mL ether was stirred for two 2 days at rt under an N_2 atmosphere. The precipitation was filtered off (*p*-anisidine·HBr) and washed with ether. The filtrate was concentrated under reduced pressure and the dark brown-black solid recrystallized from ethanol to give **22** (25.1 g, 46% calcd for dibenzyl malonate) as a white crystalline solid. Mp 92 °C. IR (KBr): *v* 3376 (NH), 1752 (CO), 1728 (CO), 1520, 1320, 1280, 1240, 1224, 1160 (COC), 824, 744, 696 cm^{-1}. ^1H NMR (500 MHz): δ 3.35 (1H, br s, NH), 3.73 (3H, s, OMe), 4.82 (1H, s, NCH), 5.17 (4H, s, CH_2O), 6.63 (2H, d, $J_{ortho} = 8.7$ Hz, PMP-3′,5′-H), 6.74 (2H, d, $J_{ortho} = 8.6$ Hz, PMP-2′,6′-H), 7.22–7.31 (10H, m, benzyl-ArH). ^{13}C NMR (75 MHz): δ 55.87 (OMe), 62.22 (CHN), 68.14 (CH_2Ph), 115.13 and 115.76 (PMP-2′,3′,5′,6′-C), 128.47 and 128.80 (benzyl-2′,3′,5′,6′-C), 128.74 (benzyl-4′-C), 135.00 (benzyl-1′-C), 139.15 (PMP-1′-C), 153.64 (PMP-4′-C), 167.70 (COO). $C_{24}H_{23}NO_5$ requires C 71.1; H 5.7; N 3.45; found C 71.1; H 5.7; N 3.2.

4.26. Dibenzyl {[(2*S*,3*R*)-3-acetoxy-2-bromobutyryl](4-methoxyphenyl)amino}malonate 23a

The solution of **22** (14.4 g; 36 mmol) and (2*S*,3*R*)-3-acetoxy-3-bromobutyryl chloride[11] (8.7 g; 36 mmol) in toluene (40 mL) was stirred at 80 °C for 2.5 days (till the evolution of HCl gas ceased). TLC: toluene–acetone 10:0.5, UV, Rf_{22} 0.9, Rf_{23} 0.5. The mixture was washed with water, dried over Na_2SO_4 and the solvent was evaporated under reduced pressure to give 22 g brown oil (99%), which was used without further purification, but was purified by prep. TLC (tol-

uene–EtOAc 15:2) for analytical investigations resulting in a yellow oil. $[\alpha]_D^{30.5} = +54$. IR (film): ν 2936 (CH), 1748 (br, CON, COO), 1672, 1512 (Ar), 1456, 1376, 1236, 1168, 748, 696 cm^{-1}. ^1H NMR (500 MHz): δ 1.25 (3H, d, $J = 6.5$ Hz, 4-Me), 1.98 (3H, s, MeCO), 3.80 (3H, s, OMe), 4.08 (1H, d, $J_{CHOAc} = 9.5$ Hz, CHBr), 5.02 + 5.08 and 5.15 + 5.20 ($2 \times 2H$, $2 \times AB$, $J_{gem} = 12$ Hz, $2 \times CH_2$), 5.34 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{CHBr} = 9.5$ Hz, CHOAc), 5.43 (1H, s, CHN), 6.81 (2H, br, PMP-3′,5′-H), 7.21–7.31 (12H, m, PMP-2′,6′-H, benzyl-ArH). ^{13}C NMR (125 MHz): δ 17.66 (4-Me), 21.01 (*Me*CO), 44.98 (CHBr), 55.54 (OMe), 65.31 (CHN), 68.13 (CH_2), 71.15 (CHOAc), 114.84 and 115.13 (PMP-3′,5′-C), 128.58 and 128.63 (benzyl-2′,3′,4′,5′,6′-C), 130.09 and 130.41 (PMP-2′,6′-C), 131.42 (PMP-1′-C), 134.65 and 134.85 (benzyl-1′-C), 160.23 (PMP-4′-C), 164.88, 165.24 168.04 and 169.65 (CON, Me*C*O, $2 \times$ COOBn). $C_{30}H_{30}NO_8Br$ requires C 58.8; H 4.9; N 2.3; Br 13.05; found C 58.9; H 4.8; N 2.1; Br, 13.5.

4.27. Dibenzyl {[(2*R*,3*S*)-3-acetoxy-2-bromobutyryl]-(4-methoxyphenyl)amino}malonate 23b

Prepared analogously to **23a** from (2*R*,3*S*)-3-acetoxy-3-bromobutyryl chloride[11] (14.8 g; 61 mmol) and **22** (24.6 g; 61 mmol) and gave a brown oil (36 g, 97%), which was used without further purification, but was purified with prep. TLC (toluene–acetone 10:0.5) for analytical investigations resulting in a yellow oil. $[\alpha]_D^{24} = -54.9$. IR (film): ν 2940 (CH), 1752 (br, CON, COO), 1676, 1512 (Ar), 1456, 1376, 1232, 1184, 1168, 748, 696 cm^{-1}. ^1H NMR (500 MHz): δ 1.25 (3H, d, $J = 6.4$ Hz, 4-Me), 2.00 (3H, s, MeCO), 3.81 (3H, s, OMe), 4.06 (1H, d, $J_{CHOAc} = 9.5$ Hz, CHBr), 5.03 + 5.09 and 5.16 + 5.21 ($2 \times 2H$, $2 \times AB$, $J_{gem} = 12$ Hz, $2 \times CH_2$), 5.33 (1H, qd, $J_{CH_3} = 6.4$ Hz, $J_{CHBr} = 9.4$ Hz, CHOAc), 5.43 (1H, s, CHN), 6.81 (2H, br, PMP-3′,5′-H), 7.21–7.31 (12H, m, PMP-2′,6′-H, benzyl-ArH). ^{13}C NMR (125 MHz): δ 17.78 (4-Me), 21.14 (*Me*CO), 45.06 (CHBr), 55.66 (OMe), 65.40 (CHN), 68.26 (CH_2), 71.29 (CHOAc), 114.87 and 115.24 (PMP-3′,5′-C), 128.70 and 128.75 (benzyl-2′,3′,4′,5′,6′-C), 130.25 and 130.57 (PMP-2′,6′-C), 131.54 (PMP-1′-C), 134.76 and 134.98 ($2 \times$ benzyl-1′-C), 160.33 (PMP-4′-C), 165.01, 165.39, 168.17 and 169.79 (CON, Me*C*O, $2 \times$ COOBn). $C_{30}H_{30}NO_8Br$ requires C 58.8; H 4.9; N 2.3; Br 13.05; found C 58.7; H 4.9; N 2.1; Br 12.9.

4.28. Dibenzyl (3*R*)-3-[(1*R*)-1-acetoxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidine-2,2-dicarboxylate 24a

A solution of DBU (8.2 mL; 54 mmol) in toluene (30 mL) was added dropwise under an ice bath cooling to a solution of **23a** (33 g; 54 mmol) in toluene (200 mL). The mixture was stirred for a day at rt (TLC: CH_2Cl_2–EtOAc 10:2, UV, Rf_{24} 0.75, Rf_{23} 0.57). The precipitate (DBU·HBr) was filtered off and washed with EtOAc. The filtrate was washed subsequently with 10% HCl, with satd $NaHCO_3$, water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure to give 24.8 g brown oil, which was purified by flash chromatography (CH_2Cl_2) and gave **24a** (20.0 g, 70%) as a yellow oil. $[\alpha]_D^{30} = -48.0$. IR (film): ν 1770 (COO), 1744 (CON), 1512 (Ar), 1456, 1376, 1248, 1188, 1128, 1036, 952, 832, 752, 696 cm^{-1}. ^1H NMR (500 MHz): δ 1.48 (3H, d, $J = 6.5$ Hz, β-Me), 1.98 (3H, s, MeCO), 3.75 (3H, s, OMe), 3.99 (1H, d, $J_{\alpha H} = 2.4$ Hz, 3-H), 4.93 + 5.29 and 5.05 + 5.13 ($2 \times 2H$, $2 \times AB$, $J_{gem} = 12$ Hz, $2 \times CH_2$), 5.33 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 2.4$ Hz, α-H), 6.73 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-3′,5′-H), 7.07 (2H, d, $J_{ortho} = 7.2$ Hz, benzyl-2′-H), 7.23–7.34 (8H, m, benzyl-ArH), 7.39 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-2′,6′-H). ^{13}C NMR (125 MHz): δ 18.50 (β-Me), 21.05 (MeCO), 55.54 (OMe), 62.26, 66.63, 67.69, 68.46 and 68.82 (3-C, 2-C, $2 \times CH_2$, α-C), 114.19 (PMP-3′,5′-C), 121.02 (PMP-2′,6′-C), 128.68, 128.76, 128.78, 128.89, 128.93, 129.11 (benzyl-2′,3′,4′,5′,6′-C), 129.99 (PMP-1′-C), 134.15 and 134.31 ($2 \times$ benzyl-1′-C), 157.16 (PMP-4′-C), 163.28 (CON), 165.82 and 166.90 ($2 \times$ COOBn), 170.31 (MeCO). $C_{30}H_{29}NO_8$ requires C 67.8; H 5.5; N 2.6; found C 67.6; H 5.4; N 2.6.

4.29. Dibenzyl (3*S*)-3-[(1*S*)-1-acetoxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidine-2,2-dicarboxylate 24b

Prepared analogously to **24a** from **23b** (36 g; 59 mmol) gave 30.6 g brown oil, which was purified by flash chromatography (CH_2Cl_2) to give **24b** (25.2 g, 79%) as a yellow oil. $[\alpha]_D^{22} = +48.6$. IR (film): ν 1770 (COO), 1744 (CON), 1512 (Ar), 1456, 1376, 1240, 1128, 1036, 952, 832, 736, 696 cm^{-1}. ^1H NMR (500 MHz): δ 1.49 (3H, d, $J = 6.5$ Hz, β-Me), 1.99 (3H, s, MeCO), 3.77 (3H, s, OMe), 3.98 (1H, d, $J_{\alpha H} = 2.4$ Hz, 3-H), 4.93 + 5.29 and 5.05 + 5.13 ($2 \times 2H$, $2 \times AB$, $J_{gem} = 12$ Hz, $2 \times CH_2$), 5.34 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 2.4$ Hz, α-H), 6.73 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-3′,5′-H), 7.08 (2H, d, $J_{ortho} = 7.3$ Hz, benzyl-2′-H), 7.23–7.34 (8H, m, benzyl-ArH), 7.39 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-2′,6′-H). ^{13}C NMR (75 MHz): δ 18.58 (β-Me), 21.16 (*Me*CO), 55.64 (OMe), 62.31, 66.70, 67.73, 68.53 and 68.91 (3-C, 2-C, $2 \times CH_2$, α-C), 114.25 (PMP-3′,5′-C), 121.06 (PMP-2′,6′-C), 128.67, 128.77, 128.85, 128.97, 129.01, 129.19 (benzyl-2′,3′,4′,5′,6′-C), 130.06 (PMP-1′-C), 134.19 and 134.35 ($2 \times$ benzyl-1′-C), 157.21 (PMP-4′-C), 163.35 (CON), 165.89 and 165.98 ($2 \times$ COOBn), 170.42 (Me*C*O). $C_{30}H_{29}NO_8$ requires C 67.8; H 5.5; N 2.6; found C 67.7; H 5.7; N 2.3.

4.30. (3*R*)-3-[(1*R*)-1-Acetoxyethyl]-2-(benzyloxycarbonyl)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylic acid 25a

NaOH (1 M, 16 mL) was added dropwise at 5 °C to a solution of **24a** (8.5 g; 16 mmol) in pyridine (6 mL). The mixture was stirred at this temperature for 3 h (TLC: CH_2Cl_2–EtOAc 10:2, UV, Rf_{24} 0.75, Rf_{25} 0.05), then diluted with 10% HCl (10 mL) and extracted with EtOAc. The organic phase was washed with 10% HCl again, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure to give 7.2 g of a brown oil (containing also some benzyl alcohol). The aqueous phase was cooled down, saturated with NaCl, and acidified with cc. HCl to pH 2–3. The separating oil was extracted with EtOAc and dried over $MgSO_4$. The solvent was evaporated under reduced pressure to give a light brown oil (0.7 g). The two fractions were collected and used without further purification. IR (film): ν 3500–3300 (COOH), 1770 (COO), 1752 (CON), 1512 (Ar), 1456, 1376, 1248, 1128, 1032, 832, 748, 700 cm^{-1}.

4.31. (3*S*)-3-[(1*S*)-1-Acetoxyethyl]-2-(benzyloxycarbonyl)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylic acid 25b

Prepared analogously to **25a** from **24b** (25.2 g; 47 mmol). The evaporation of the solvent from the organic phase resulted in 23.7 g of a brown oil, the acidification of the aqueous phase resulted in 2.3 g of **25b**, as a light brown oil. The two fractions were collected. IR (film): *v* 3500–3300 (COOH), 1770 (COO), 1752 (CON), 1512 (Ar), 1456, 1376, 1248, 1128, 1032, 832, 752, 700 cm^{-1}. ^1H NMR (500 MHz): δ 1.45 (3H, d, $J = 6.5$ Hz, β-Me), 1.96 (3H, s, MeCO), 3.76 (3H, s, OMe), 3.91 (1H, d, $J_{\alpha H} = 2.5$ Hz, 3-H), 4.97 + 5.31 (2H, AB, $J_{gem} = 12$ Hz, CH_2), 5.30 (1H, m, α-H), 6.80 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-3′,5′-H), 7.33 (5H, ~s, benzyl-ArH), 7.47 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-2′,6′-H). ^{13}C NMR (75 MHz): δ 18.50 (β-Me), 21.11 (*Me*CO), 55.67 (OMe), 62.47, 66.84, 67.22, 68.69 (3-C, 2-C, CH_2, α-C), 114.35 (PMP-3′,5′-C), 120.85 (PMP-2′,6′-C), 128.84, 128.99, 129.02 (benzyl-2′,3′,4′,5′,6′-C), 130.10 (PMP-1′-C), 134.26 (benzyl-1′-C), 157.20 (PMP-4′-C), 163.48 (CON), 165.87 and 169.43 (COOH, COOBn), 170.69 (Me*C*O).

4.32. *cis*/*trans* Benzyl (3*R*)-3-[(1*R*)-1-acetoxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate 26a, 27a

The solution of **25a** (7.9 g) in α-picoline (30 mL) was heated in an 140 °C oil bath for 3 h (TLC: CH_2Cl_2–EtOAc 10:0.5, UV, $Rf_{26,27}$ 0.5, Rf_{25} 0.05). The picoline was removed by distillation at 15 mmHg. The remaining material was dissolved in EtOAc (150 mL), washed with 10% HCl (20 mL), with 10% $NaHCO_3$ (20 mL), then with brine. The organic phase was dried over Na_2SO_4 and concentrated till about 30 mL solvent remained. The precipitating white solid was filtered to give 1.2 g of pure **26a** as a white solid, which was recrystallized from MeOH. The filtrate was concentrated under reduced pressure; the benzyl alcohol was removed by distillation at 0.1 mmHg to give a brown oil (3.2 g), which was purified by flash chromatography. The fractions (2.5 g) containing the title compounds were triturated with *tert*-butyl alcohol. The insoluble white crystals were filtered to give 0.2 g of **26a**. The mother liquor containing **27a** was used without further purification in the next step.

4.32.1. Benzyl (2*S*,3*R*)-3-[(1*R*)-1-acetoxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate 26a. Yield: 1.4 g (22% from **24a**) of a white solid. Mp 164 °C (MeOH). $[\alpha]_D^{23} = -74.8$. IR (KBr): *v* 1740 (br, CON, COO), 1520 (Ar), 1248, 1212, 1152, 1032, 832, 736 cm^{-1}. ^1H NMR (500 MHz): δ 1.46 (3H, d, $J = 6.5$ Hz, β-Me), 2.00 (3H, s, MeCO), 3.69 (1H, dd, $J_{\alpha H} = 3.1$ Hz, $J_{cis} = 6.5$ Hz, 3-H), 3.79 (3H, s, OMe), 4.60 (1H, d, $J_{cis} = 6.5$ Hz, 2-H), 4.99 + 5.21 (2H, AB, $J_{gem} = 12$ Hz, CH_2), 5.30 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 3.1$ Hz, α-H), 6.86 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-3′,5′-H), 7.30 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-2′,6′-H), 7.35 (5H, m, benzyl-ArH). ^{13}C NMR (75 MHz): δ 18.91 (β-Me), 21.21 (*Me*CO), 54.12, 55.73 and 57.11 (3-C, 2-C, OMe), 66.27 and 67.95 (CH_2, α-C), 114.55 (PMP-3′,5′-C), 118.66 (PMP-2′,6′-C), 128.94, 129.03, 129.13 (benzyl-2′,3′,4′,5′,6′-C), 131.08 (PMP-1′-C), 134.73 (benzyl-1′-C), 156.73 (PMP-4′-C), 162.59 (CON), 167.86 (COO), 170.60 (Me*C*O). $C_{22}H_{23}NO_6$ requires C 66.5; H 5.8; N 3.5; found C 66.5; H 5.8; N 3.4.

4.32.2. Benzyl (2*R*,3*R*)-3-[(1*R*)-1-acetoxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate 27a. A sample was purified from the *tert*-butyl alcoholic mother liquor for analytical investigations with prep. TLC (CH_2Cl_2–EtOAc 10:1), then crystallized from hexane/EtOAc to give pure **27a** as a white solid. Mp 67–68 °C (hexane/EtOAc). $[\alpha]_D^{26} = +60.8$. IR (KBr): *v* 1770 (COO), 1752 (CON), 1516 (Ar), 1456, 1400, 1376, 1240, 1176, 1048, 1024, 912, 824, 760, 704 cm^{-1}. ^1H NMR (500 MHz): δ 1.42 (3H, d, $J = 6.5$ Hz, β-Me), 1.98 (3H, s, MeCO), 3.57 (1H, dd, $J_{\alpha H} = 4.5$ Hz, $J_{trans} = 2.5$ Hz, 3-H), 3.78 (3H, s, OMe), 4.32 (1H, d, $J_{trans} = 2.5$ Hz, 2-H), 5.21 (2H, AB, $J_{gem} = 12$ Hz, CH_2), 5.30 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 4.5$ Hz, α-H), 6.82 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-3′,5′-H), 7.21 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-2′,6′-H), 7.33 (5H, m, benzyl-ArH). ^{13}C NMR (75 MHz): δ 17.54 (β-Me), 21.15 (*Me*CO), 53.68, 55.70 and 58.71 (3-C, 2-C, OMe), 67.19 and 67.83 (CH_2, α-C), 114.65 (PMP-3′,5′-C), 118.36 (PMP-2′,6′-C), 128.59, 128.87, 129.01 (benzyl-2′,3′,4′,5′,6′-C), 130.78 (PMP-1′-C), 134.97 (benzyl-1′-C), 156.81 (PMP-4′-C), 162.26 (CON), 169.60 (COOBn), 170.52 (Me*C*O). $C_{22}H_{23}NO_6$ requires C 66.5; H 5.8; N 3.5; found C 66.2; H 5.75; N 3.4.

4.33. *cis*/*trans* Benzyl (3*S*)-3-[(1*S*)-1-acetoxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate 26b, 27b

Prepared analogously to **26a**, **27a** from **25b** (26 g), and gave 8 g material, containing **27b,** and 6.3 g (34% from **24b**) of **26b**.

4.33.1. Benzyl (2*R*,3*S*)-3-[(1*S*)-1-acetoxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate 26b. White solid. Mp 164 °C (MeOH). $[\alpha]_D^{23.5} = +73.4$. IR (KBr): *v* 1740 (br, CON, COO), 1520 (Ar), 1248, 1212, 1152, 11032, 832, 736 cm^{-1}. ^1H NMR (500 MHz): δ 1.46 (3H, d, $J = 6.5$ Hz, β-Me), 2.00 (3H, s, MeCO), 3.69 (1H, dd, $J_{\alpha H} = 3$ Hz, $J_{cis} = 6.5$ Hz, 3-H), 3.79 (3H, s, OMe), 4.60 (1H, d, $J_{cis} = 6.5$ Hz, 2-H), 4.99 + 5.21 (2H, AB, $J_{gem} = 12$ Hz, CH_2), 5.30 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 3$ Hz, α-H), 6.86 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-3′,5′-H), 7.30 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-2′,6′-H), 7.25–7.35 (5H, m, benzyl-ArH). ^{13}C NMR (75 MHz): δ 18.72 (β-Me), 21.04 (*Me*CO), 53.89, 55.54 and 56.89 (3-C, 2-C, OMe), 66.09 and 67.78 (CH_2, α-C), 114.35 (PMP-3′,5′-C), 118.45 (PMP-2′,6′-C), 128.76, 128.86, 128.97 (benzyl-2′,3′,4′,5′,6′-C), 130.87 (PMP-1′-C), 134.50 (benzyl-1′-C), 156.52 (PMP-4′-C), 162.41 (CON), 167.66 (COOBn), 170.46 (Me*C*O). $C_{22}H_{23}NO_6$ requires C 66.5; H 5.8; N 3.5; found C 66.5, H 5.9, N 3.7.

4.33.2. Benzyl (2*S*,3*S*)-3-[(1*S*)-1-acetoxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate 27b. White solid. Mp 68–69 °C (hexane/EtOAc). $[\alpha]_D^{21.5} = -61.3$. IR (KBr): *v* 1770 (COO), 1752 (CON), 1516 (Ar), 1456, 1400, 1380, 1240, 1176, 1048, 1024, 912, 824, 760, 704 cm^{-1}. ^1H NMR (500 MHz): δ 1.42 (3H, d, $J = 6.5$ Hz, β-Me), 1.98 (3H, s, MeCO), 3.57 (1H, dd, $J_{\alpha H} = 4.5$ Hz, $J_{trans} = 2.5$ Hz, 3-H), 3.78 (3H, s, OMe), 4.32 (1H, d, $J_{trans} = 2.5$ Hz, 2-H), 5.21 (2H, AB, $J_{gem} = 12$ Hz, CH_2), 5.31 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 4.5$ Hz, α-H), 6.82 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-

3′,5′-H), 7.21 (2H, d, $J_{ortho} = 9.0$ Hz, PMP-2′,6′-H), 7.26–7.34 (5H, m, benzyl–ArH). ^{13}C NMR (75 MHz): δ 17.59 (β-Me), 21.21 (*Me*CO), 53.66, 55.72 and 58.74 (3-C, 2-C, OMe), 67.18 and 67.84 (CH_2, α-C), 114.65 (PMP-3′,5′-C), 118.33 (PMP-2′,6′-C), 128.63, 128.90, 129.01 (benzyl-2′,3′,4′,5′,6′-C), 130.82 (PMP-1′-C), 134.99 (benzyl-1′-C), 156.80 (PMP-4′-C), 162.21 (CON), 169.62 (COOBn), 170.48 (Me*C*O). $C_{22}H_{23}NO_6$ requires C 66.5; H 5.8; N 3.5; found C 66.3; H 5.5, N 3.4.

4.34. (3*R*,4*R*)-3-[(1*R*)-1-Acetoxyethyl]-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidine-2-one 28a

$NaBH_4$ (0.38 g; 10 mmol) was added to a solution of **27a** (1.6 g; 4 mmol) in *tert*-butyl alcohol (30 mL) under cooling with cold water. After 2 h of stirring (TLC: CH_2Cl_2–EtOAc 10:0.5, UV, $Rf_{26,27}$ 0.5, Rf_{28} 0.1), the insoluble inorganics were filtered off on a G4 filter and washed several times with EtOAc. The first filtrate (containing only *tert*-butyl alcohol) was concentrated at 50 mmHg. The residue was dissolved in the EtOAc used for washing the inorganics. It was washed with brine, dried ($MgSO_4$) and the residue obtained after evaporation of the solvent was purified by flash chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$–EtOAc 10:2) to give **28a** (0.45 g, 14% from **24a**) as a light yellow oil. All of its physical properties were the same as those previously described.[9,11] If the starting material contains *cis* impurity, it can be recovered unreacted during chromatography.

4.35. (3*S*,4*S*)-3-[(1*S*)-1-Acetoxyethyl]-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidine-2-one 28b

Prepared analogously to **28a** from **27b** (8 g; 20 mmol) and gave **28b** (2.2 g, 14% from **24b**) as a light yellow oil. All of its physical properties are the same as those previously described.[9,11]

4.36. (2*S*,3*R*)-3-[(1*R*)-1-Acetoxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylic acid 29a

Compound **26a** (1.93 g; 4.9 mmol) dissolved in DMF (120 mL) was hydrogenolyzed at normal pressure in the presence of 10% Pd/C (0.5 g). After 20 min the reaction was completed. The catalyst was filtered off and the resulting white solid obtained after removal of the solvent by distillation at 0.1 mmHg was triturated with ether. The insoluble white solid was filtered and gave **29a** (1.34 g, 90%). Mp 233 °C. IR (KBr): *v* 3500–3300 (COOH), 1740 (br, CON, COO), 1696, 1512 (Ar), 1392, 1292, 1248, 1176, 1028, 832 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ 1.33 (3H, d, $J = 6.5$ Hz, β-Me), 1.90 (3H, s, MeCO), 3.72 (3H, s, OMe), 3.83 (1H, dd, $J_{\alpha H} = 3.7$ Hz, $J_{cis} = 6.5$ Hz, 3-H), 4.72 (1H, d, $J_{cis} = 6.5$ Hz, 2-H), 5.08 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 4$ Hz, α-H), 6.91 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-3′,5′-H), 7.29 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-2′,6′-H). ^{13}C NMR (75 MHz, DMSO): δ 18.25 (β-Me), 20.64 (*Me*CO), 53.63, 55.25 and 55.49 (3-C, 2-C, OMe), 66.24 (α-C), 114.03 (Ar-3′,5′-C), 117.98 (Ar-2′,6′-C), 131.27 (Ar-1′-C), 155.45 (Ar-4′-C), 163.26 (CON), 169.44 and 169.59 (COOH, Me*C*O). $C_{15}H_{17}NO_6$ requires C 58.6; H 5.5; N 4.6; found C 58.4; H 5.3; N 4.4.

4.37. (2*R*,3*S*)-3-[(1*S*)-1-Acetoxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylic acid 29b

Prepared analogously to **29a** from **26b** (2.15 g; 5.4 mmol) and gave **29b** (1.6 g, 96%) as a white solid. Mp 233 °C. IR (KBr): *v* 3500–3300 (COOH), 1740 (br, CON, COO), 1696, 1512 (Ar), 1392, 1288, 1248, 1176, 1028, 832 cm^{-1}. ^{1}H NMR (500 MHz, DMSO): δ 1.34 (3H, d, $J = 6.5$ Hz, β-Me), 1.90 (3H, s, MeCO), 3.72 (3H, s, OMe), 3.87 (1H, dd, $J_{\alpha H} = 3.7$ Hz, $J_{cis} = 6.5$ Hz, 3-H), 4.76 (1H, d, $J_{cis} = 6.5$ Hz, 2-H), 5.07 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 3.5$ Hz, α-H), 6.92 (2H, d, $J_{ortho} = 8.9$ Hz, Ar-3′,5′-H), 7.30 (2H, d, $J_{ortho} = 8.9$ Hz, Ar-2′,6′-H). ^{13}C NMR (125 MHz, DMSO): δ 19.08 (β-Me), 21.55 (*Me*CO), 54.30, 56.15 and 56.44 (3-C, 2-C, OMe), 67.11 (α-C), 114.94 (Ar-3′,5′-C), 118.92 (Ar-2′,6′-C), 132.10 (Ar-1′-C), 156.38 (Ar-4′-C), 164.14 (CON), 170.38 and 170.56 (COOH, Me*C*O). $C_{15}H_{17}NO_6$ requires C 58.6; H 5.5; N 4.6; found C 58.2; H 5.1; N 4.4.

4.38. (3*R*,4*S*)-3-[(1*R*)-1-Acetoxyethyl]-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidine-2-one 30a

NEt_3 (0.75 mL; 5.5 mmol) was added to a suspension of **29a** (0.9 g; 2.9 mmol) in THF (150 mL). Then a solution of ethyl chloroformate (0.55 mL; 5.5 mmol) in THF (5 mL) was added to it dropwise at −20 °C. The mixture was stirred for 1.5 h at this temperature (TLC: CH_2Cl_2–MeOH 10:3, UV, Rf_{29} 0.3, Rf_{31} 0.9), then an additional 0.75 mL (5.5 mmol) of triethylamine and a 0.55 mL (5.5 mmol) of ethyl chloroformate were added. It was stirred for 1 h at this temperature. $NaBH_4$ (0.6 g; 16 mmol) was added to it, then a solution of MeOH (2 mL) and THF (10 mL) was added dropwise at −20 °C (gas generation) (TLC: CH_2Cl_2–EtOAc 10:2, UV, Rf_{31} 0.6, Rf_{30} 0.2). Because the reaction was not complete, an additional 0.3 g (8 mmol) of $NaBH_4$ and a solution of 1 mL of MeOH and 5 mL of THF were added dropwise at the same temperature. After the reaction was complete, the mixture was neutralized with 1 M HCl. The residue obtained after evaporation of the solvent was taken up in a mixture of water and EtOAc. The two phases were separated. The aqueous phase was extracted with EtOAc, and the combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was evaporated under reduced pressure. The remaining material was triturated first with CH_2Cl_2, then the insoluble material was filtered off. The remaining solid obtained after evaporation of the solvent was triturated with ether to give a white crystalline solid (0.78 g), which proved to be (NMR) the 10:1 mixture of the title compound **30a** and its regioisomer **20a**. The ether mother liquor was purified by flash chromatography ($CH_2Cl_2 \rightarrow CH_2Cl_2$–EtOAc 10:0.2) to give an additional 0.05 g (total 97%) of the title compound (and its isomer). Mp 147–150 °C. IR (KBr): *v* 3488 (OH), 1732 (br, CON, COO), 1512 (Ar), 1456, 1392, 1296, 1280, 1248, 1164, 1136, 1112, 1064, 1028, 832 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.46 (3H, d, $J = 6.5$ Hz, β-Me), 2.08 (3H, s, MeCO), 3.49 (1H, m ∼ t, 3-H), 3.78 (3H, s, OMe), 3.97 + 4.03 (2H, dAB, $J_{gem} = 12$ Hz, $J_{4H} = 5$ Hz, CH_2), 4.27 (1H, m ∼ q, 4-H), 5.41 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 5.5$ Hz, α-H), 6.86 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-3′,5′-H), 7.44 (2H,

d, $J_{ortho} = 9.0$ Hz, Ar-2′,6′-H). ^{13}C NMR (75 MHz): δ 20.14 (β-Me), 21.60 (*Me*CO), 55.67, 55.71 and 56.19 (3-C, 4-C, OMe), 60.77 (CH_2), 66.63 (α-C), 114.59 (Ar-3′,5′-C), 119.04 (Ar-2′,6′-C), 131.20 (Ar-1′-C), 156.47 (Ar-4′-C), 164.15 (CON), 170.81 (Me*C*O).

4.38.1. (3*S*,4*S*)-3-Ethyl-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidine-2-one 32a. From the chromatography, 20 mg (1.3%) of **32a** was also isolated. TLC: CH_2Cl_2–EtOAc 7:4, UV, Rf_{32} 0.48, Rf_{30} 0.38. Mp 108–110 °C (hexane), white, needle like crystals. IR (KBr): *v* 3424 (OH), 1708 (CON), 1520 (Ar), 1252, 1024, 824 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.14 (3H, t, $J = 7.4$ Hz, β-Me), 1.74 + 1.91 (2 × 1H, 2 × m, CH_2Me), 1.94 (1H, s, OH), 3.26 (1H, m ∼ q, 3-H), 3.78 (3H, s, OMe), 3.97 + 4.04 (2H, dAB, $J_{gem} = 12$ Hz, $J_{4H} = 4.8$ Hz, CH_2O), 4.21 (1H, m ∼ q, 4-H), 6.85 (2H, d, $J_{ortho} = 8.9$ Hz, Ar-3′,5′-H), 7.42 (2H, d, $J_{ortho} = 8.9$ Hz, Ar-2′,6′-H). ^{13}C NMR (125 MHz): δ 13.02 (β-Me), 18.44 (CH_2Me), 53.32, 55.70 and 56.19 (3-C, 4-C, OMe), 60.86 (CH_2O), 114.58 (Ar-3′,5′-C), 118.91 (Ar-2′,6′-C), 131.52 (Ar-1′-C), 156.28 (Ar-4′-C), 168.27 (CON). HRMS *m*/*z* 235.1210 ($C_{13}H_{17}NO_3$ calcd 235.1208).

4.39. (3*S*,4*R*)-3-[(1*S*)-1-Acetoxyethyl]-4-(hydroxymethyl)-1-(4-methoxyphenyl)azetidine-2-one 30b

Prepared analogously to **30a** from **29b** (1.6 g; 5.2 mmol) and gave a mixture of the title compound and its regioisomer (10:1) (1.4 g, 92%) as a white solid. Mp 148–150 °C. IR (KBr): *v* 3488 (OH), 1736 (CON), 1712 (COO), 1704, 1512 (Ar), 1456, 1392, 1296, 1280, 1252, 1164, 1136, 1112, 1064, 1028, 832 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.47 (3H, d, $J = 6.5$ Hz, β-Me), 2.09 (3H, s, MeCO), 3.49 (1H, m ∼ t, 3-H), 3.79 (3H, s, OMe), 3.97 + 4.04 (2H, m ∼ AB, CH_2), 4.27 (1H, m ∼ q, 4-H), 5.42 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 5.5$ Hz, α-H), 6.87 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-3′,5′-H), 7.45 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-2′,6′-H). ^{13}C NMR (125 MHz): δ 19.95 (β-Me), 21.40 (*Me*CO), 55.50, 55.52 and 55.96 (3-C, 4-C, OMe), 60.61 (CH_2), 66.42 (α-C), 114.41 (Ar-3′,5′-C), 118.85 (Ar-2′,6′-C), 131.00 (Ar-1′-C), 156.29 (Ar-4′-C), 163.90 (CON), 170.58 (Me*C*O).

4.39.1. (2*R*,3*S*)-3-[(1*S*)-1-Acetoxyethyl]-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylic anhydride 31b. A small sample was taken out of the reaction mixture before the addition of $NaBH_4$. The solvent was evaporated under reduced pressure. The remaining material was solved in CH_2Cl_2, washed with water, dried over $MgSO_4$ and provided **31b** after evaporation of the solvent. Mp: decomposes at 220 °C. IR (KBr): *v* 1832 (COanh), 1768 (COO), 1736 (CON), 1516 (Ar), 1456, 1396, 1376, 1248, 1240, 1200, 1184, 1160, 1064, 1040, 960, 944, 824 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.57 (6H, d, $J = 6.5$ Hz, β-Me), 2.00 (6H, s, MeCO), 3.80 (6H, s, OMe), 3.82 (2H, dd, $J_{\alpha H} = 2.5$ Hz, $J_{cis} = 6.5$ Hz, 3-H), 4.27 (2H, d, $J_{cis} = 6.5$ Hz, 2-H), 5.37 (2H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 2.5$ Hz, α-H), 6.90 (4H, d, $J_{ortho} = 9.0$ Hz, Ar-3′,5′-H), 7.40 (4H, d, $J_{ortho} = 9.0$ Hz, Ar-2′,6′-H). ^{13}C NMR (75 MHz): δ 18.62 (β-Me), 21.26 (*Me*CO), 53.77, 55.73 and 57.17 (3-C, 2-C, OMe), 66.10 (α-C), 114.60 (Ar-3′,5′-C), 118.53 (Ar-2′, 6′-C), 130.67 (Ar-1′-C), 156.91 (Ar-4′-C), 161.67 and 161.97 (CON, COOCO), 171.64 (Me*C*O).

4.40. (3*R*,4*S*)-3-[(1*R*)-1-Acetoxyethyl]-4-[(methanesulfonyloxy)methyl]-1-(4-methoxyphenyl)azetidine-2-one 33a

Mesyl chloride (0.55 mL; 7.4 mmol) was added to a solution of the mixture of **30a** and **20a** (1.4 g; 4.8 mmol) in THF (50 mL) at −5 °C. A solution of triethylamine (1 mL; 7.5 mmol) in THF (5 mL) was added to the reaction mixture at this temperature. It was stirred for 1 h (TLC: CH_2Cl_2–EtOAc 10:2, Rf_{30} 0.2, Rf_{33} 0.55), then neutralized with 1 M HCl, the solvent was evaporated under reduced pressure. The residue was taken up in EtOAc and water. The two phases were separated and the aqueous phase was extracted with EtOAc. The combined organic layers were washed with brine, dried over $MgSO_4$ and the residue obtained after evaporation of the solvent was triturated with ether to give **33a** (1.5 g, 85%) as white crystals. Mp 121 °C. $[\alpha]_D^{25.5} = -67.2$. IR (KBr): *v* 1752 (COO), 1736 (CON), 1520 (Ar), 1384, 1352, 1296, 1236, 1176, 1152, 1032, 976, 960, 848, 832, 528 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.51 (3H, d, $J = 6.4$ Hz, β-Me), 2.10 (3H, s, MeCO), 3.00 (3H, s, SMe), 3.59 (1H, dd, $J_{\alpha H} = 3.7$ Hz, $J_{cis} = 5.5$ Hz, 3-H), 3.80 (3H, s, OMe), 4.46 (2H, m, 4-H + CH_{2A}), 4.62 (1H, dd, $J_{gem} = 10$ Hz, $J_{4H} = 5$ Hz, CH_{2B}), 5.32 (1H, qd, $J_{CH_3} = 6.4$ Hz, $J_{3H} = 3.7$ Hz, α-H), 6.90 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-3′,5′-H), 7.36 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-2′,6′-H). ^{13}C NMR (75 MHz): δ 19.79 (β-Me), 21.64 (*Me*CO), 37.92 (SMe), 53.10, 55.76 and 56.00 (3-C, 4-C, OMe), 66.41 and 66.61 (CH_2, α-C), 114.80 (Ar-3′,5′-C), 119.10 (Ar-2′,6′-C), 130.40 (Ar-1′-C), 156.88 (Ar-4′-C), 163.21 (CON), 170.50 (Me*C*O). $C_{16}H_{21}NO_7S$ requires C 51.7; H 5.7; N 3.8; S 8.6; found C 51.5; H 5.6; N 3.6; S 8.85.

4.41. (3*S*,4*R*)-3-[(1*S*)-1-Acetoxyethyl]-4-[(methanesulfonyloxy)methyl]-1-(4-methoxyphenyl)azetidine-2-one 33b

Prepared analogously to **33a** from the mixture of **30b** and **20b** (1.2 g; 4 mmol) and gave **33b** (1.24 g, 84%) as white crystals. Mp 121 °C. $[\alpha]_D^{25.5} = +66.6$. IR (KBr): *v* 1752 (COO), 1736 (CON), 1516 (Ar), 1384, 1352, 1296, 1236, 1176, 1152, 1032, 976, 960, 848, 832 cm^{-1}. ^{1}H NMR (500 MHz): δ 1.52 (3H, d, $J = 6.4$ Hz, β-Me), 2.11 (3H, s, MeCO), 3.00 (3H, s, SMe), 3.59 (1H, dd, $J_{\alpha H} = 3.6$ Hz, $J_{cis} = 5.5$ Hz, 3-H), 3.80 (3H, s, OMe), 4.46 (2H, m, 4-H + CH_{2A}), 4.63 (1H, dd, $J_{gem} = 10.5$ Hz, $J_{4H} = 5$ Hz, CH_{2B}), 5.32 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 3.6$ Hz, α-H), 6.89 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-3′,5′-H), 7.36 (2H, d, $J_{ortho} = 9.0$ Hz, Ar-2′,6′-H). ^{13}C NMR (75 MHz): δ 19.76 (β-Me), 21.59 (*Me*CO), 37.88 (SMe), 53.11, 55.73 and 55.99 (3-C, 4-C, OMe), 66.41 66.58 (CH_2, α-C), 114.78 (Ar-3′,5′-C), 119.10 (Ar-2′,6′-C), 130.39 (Ar-1′-C), 156.87 (Ar-4′-C), 163.20 (CON), 170.45 (Me*C*O). $C_{16}H_{21}NO_7S$ requires C 51.7; H 5.7; N 3.8; S 8.6; found C 51.7; H 5.85; N 4.1; S 8.65.

4.42. (3*R*,4*S*)-3-[(1*R*)-1-Acetoxyethyl]-4-[(methanesulfonyloxy)methyl]azetidine-2-one 34a

A solution of CAN (7.6 g; 14 mmol) in water (80 mL) was added dropwise to the solution of **33a** (1.64 g; 4.6 mmol) in acetonitrile (60 mL), while the temperature was kept between −10 and 0 °C. It was stirred at this temperature

for two h (TLC: CH_2Cl_2–EtOAc 1:1, UV + PMA, Rf_{34} 0.2 (only PMA), Rf_{33} 0.7). The reaction mixture was diluted with water (80 mL) and extracted with 5 × 100 mL EtOAc. The combined organic layers were washed subsequently with 10% $NaHCO_3$, 10% $NaHSO_3$, again with 10% $NaHCO_3$ and brine. All of the aqueous phases were extracted back with EtOAc and these were combined with the organic phase. It was then dried over Na_2SO_4. Evaporation of the solvent followed by flash chromatography (CH_2Cl_2→CH_2Cl_2–EtOAc 10:1) gave a yellowish solid that was triturated with ether and provided **34a** (0.95 g, 83%) as a white solid. Mp 104 °C. $[\alpha]_D^{22.5} = -31.0$. IR (KBr): *v* 3320 (NH), 1764 (COO), 1736 (CON), 1384, 1352, 1248, 1172, 1136, 1033, 984, 976, 968, 824 cm^{-1}. ^1H NMR (500 MHz): δ 1.44 (3H, d, $J = 6.5$ Hz, β-Me), 2.11 (3H, s, MeCO), 3.07 (3H, s, SMe), 3.51 (1H, m ∼ t, 3-H), 4.06 (1H, m, 4-H), 4.35 (1H, dAB, $J_{gem} = 11$ Hz, $J_{4H} = 4.5$ Hz, CH_{2A}), 4.43 (1H, dAB, $J_{gem} = 11$ Hz, $J_{4H} = 8$ Hz, CH_{2B}), 5.20 (1H, qd, $J_{CH_3} = 6.5$ Hz, $J_{3H} = 4$ Hz, α-H), 6.18 (1H, s, NH). ^{13}C NMR (75 MHz): δ 19.62 (β-Me), 21.58 (*Me*CO), 37.98 (SMe), 50.01 and 57.27 (3-C, 4-C), 66.19 (CH_2), 68.61 (α-C), 166.27 (CON), 170.42 (Me*C*O). $C_9H_{15}NO_6S$ requires C 40.75; H 5.7; N 5.3; S 12.1; found C 40.6; H 5.6; N 5.1; S 12.1.

4.43. (3*S*,4*R*)-3-[(1*S*)-1-Acetoxyethyl]-4-[(methanesulfonyloxy)methyl]azetidine-2-one 34b

Prepared analogously to **34a** from **33b** (2.5 g; 7 mmol) and gave **34b** (1.33 g, 72%) as a white solid. Mp 105 °C. $[\alpha]_D^{24.5} = +31.4$. IR (KBr): *v* 3320 (NH), 1764 (AcO), 1736 (CON), 1384, 1352, 1248, 1172, 1136, 1032, 984, 976, 968, 824 cm^{-1}. ^1H NMR (500 MHz): δ 1.44 (3H, d, $J = 6.4$ Hz, β-Me), 2.11 (3H, s, MeCO), 3.07 (3H, s, SMe), 3.51 (1H, m ∼ t, 3-H), 4.06 (1H, m, 4-H), 4.35 (1H, dAB, $J_{gem} = 10.6$ Hz, $J_{4H} = 4.2$ Hz, CH_{2A}), 4.43 (1H, dAB, $J_{gem} = 10.5$ Hz, $J_{4H} = 8.1$ Hz, CH_{2B}), 5.20 (1H, qd, $J_{CH_3} = 6.4$ Hz, $J_{3H} = 4.1$ Hz, α-H), 6.33 (1H, s, NH). ^{13}C NMR (75 MHz): δ 19.63 (β-Me), 21.57 (*Me*CO), 37.95 (SMe), 49.97 and 57.24 (3-C, 4-C), 66.19 (CH_2), 68.64 (α-C), 166.44 (CON), 170.43 (Me*C*O). $C_9H_{15}NO_6S$ requires C 40.75; H 5.7; N 5.3; S 12.1; found C 40.7, H 5.5; N 5.1; S 12.25.

4.44. Benzyl (6*S*,7*R*)-7-[(1*R*)-1-acetoxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 35a

Benzyl 2,3-dioxobutyrate (1.15 g; 5 mmol) and NEt_3 (0.3 mL; 2 mmol) were added to the solution of **34a** (0.93 g; 3.5 mmol) in THF (50 mL). The mixture was stirred at rt for 3 h, then cooled down to −25 °C. Pyridine (1.0 mL; 12 mmol), then a solution of thionyl chloride (0.7 mL; 10 mmol) in 5 mL dry THF were added dropwise. After 1 h stirring, the white precipitate (Py*HCl) was filtered off and the filtrate was evaporated under reduced pressure. Zinc (1.0 g; 15 mmol) was added slowly at 5 °C to a solution of the yellow oily residue in a mixture of acetic acid (40 mL) and water (6 mL). After 2 h of stirring, the insoluble materials were filtered off. The residue obtained after evaporation of the solvent was dissolved in CH_2Cl_2, washed with water, dried over $MgSO_4$ and the resulting oil obtained after evaporation of the solvent was purified by flash chromatography (CH_2Cl_2→CH_2Cl_2–EtOAc 1:1). Fractions having an Rf 0.5 (TLC: CH_2Cl_2–EtOAc 10:2) were collected. Starting material (0.15 g) was also recovered. The aqueous layer was extracted with EtOAc, dried over $MgSO_4$. The solvent was evaporated, and resulted in 0.15 g of starting material (total 30%). NEt_3 (0.3 mL) was added to the solution of the material with Rf 0.5 in chloroform (30 mL) and it was refluxed for 4 h (TLC: CH_2Cl_2–EtOAc 10:2, UV, Rf_{17} 0.5, Rf_{35} 0.7). The mixture was washed with water and dried over $MgSO_4$. The residue obtained after evaporation of the solvent was purified by flash chromatography (CH_2Cl_2→CH_2Cl_2–EtOAc 10:0.3) to give **35a** (0.6 g, 48%) as a yellow oil. $[\alpha]_D^{28} = +96.6$ (*c* 3). IR (film): *v* 1772 (COO), 1740 (CON), 1710 (COO), 1616 (Ar), 1456, 1392, 1240, 1188, 1144, 1072, 1040, 952, 740, 696 cm^{-1}. ^1H NMR (500 MHz): δ 1.35 (3H, d, $J = 6.4$ Hz, β-Me), 2.08 (3H, s, MeCO), 2.23 (3H, s, 3-Me), 3.68 (1H, m, 6-H), 3.82 (1H, dd, $J_{\alpha H} = 6.7$ Hz, $J_{cis} = 5.8$ Hz, 7-H), 4.04 (1H, m ∼ t, 1-H_A), 4.49 (1H, dd, $J_{gem} = 10.4$ Hz, $J_{6H} = 3.6$ Hz, 1-H_B), 5.25 (3H, m, α-H+CH_2Ph), 7.29 (1H, m ∼ t, Ar-4′-H), 7.36 (2H, m ∼ t, Ar-3′,5′-H), 7.45 (2H, d, $J_{ortho} = 7.1$ Hz, Ar-2′,6′-H). ^{13}C NMR (125 MHz): δ 18.12 (β-Me), 20.39 (3-Me), 21.51 (*Me*CO), 45.60 (6-C), 58.34 (7-C), 65.30 (α-C), 66.69 (CH_2Ph), 67.00 (1-C), 106.75 (4-C), 128.28 (Ar-4′-C), 128.53 and 128.67 (Ar-2′,3′,5′,6′-C), 136.08 (Ar-1′-C), 155.25 (3-C), 163.18 and 164.80 (CON, COOBn), 170.30 (Me*C*O). $C_{19}H_{21}NO_6$ requires C 63.5; H 5.9; N 3.9; found C 63.4; H 5.9; N 3.85.

4.45. Benzyl (6*R*,7*S*)-7-[(1*S*)-1-acetoxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 35b

Prepared analogously to **35a** from **34b** (1.3 g; 4.9 mmol) and gave **35b** (0.7 g, 40%) as a yellow oil. $[\alpha]_D^{28} = -97.8$. IR (film): *v* 1772 (COO), 1740 (CON), 1712 (COO), 1620 (Ar), 1456, 1392, 1352, 1304, 1240, 1188, 1144, 1072, 1040, 740, 696 cm^{-1}. ^1H NMR (500 MHz): δ 1.35 (3H, d, $J = 6.4$ Hz, β-Me), 2.08 (3H, s, MeCO), 2.23 (3H, s, 3-Me), 3.68 (1H, m, 6-H), 3.82 (1H, dd, $J_{\alpha H} = 6.7$ Hz, $J_{cis} = 5.8$ Hz, 7-H), 4.04 (1H, m ∼ t, 1-H_A), 4.49 (1H, dd, $J_{gem} = 10.4$ Hz, $J_{6H} = 3.6$ Hz, 1-H_B), 5.25 (3H, m, α-H + CH_2Ph), 7.29 (1H, m ∼ t, Ar-4′-H), 7.36 (2H, m ∼ t, Ar-3′,5′-H), 7.45 (2H, d, $J_{ortho} = 7.1$ Hz, Ar-2′,6′-H). ^{13}C NMR (125 MHz): δ 18.12 (β-Me), 20.39 (3-Me), 21.51 (*Me*CO), 45.62 (6-C), 58.35 (7-C), 65.31 (α-C), 66.70 (CH_2Ph), 67.00 (1-C), 106.76 (4-C), 128.28 (Ar-4′-C), 128.53 and 128.67 (Ar-2′,3′,5′,6′-C), 136.09 (Ar-1′-C), 155.24 (3-C), 163.17 and 164.80 (CON, COOBn), 170.29 (Me*C*O). HRMS *m*/*z* 359.1397 ($C_{19}H_{21}NO_6$ calcd 359.13957).

4.46. Benzyl (6*S*,7*R*)-7-[(1*R*)-1-hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 36a and benzyl (6*S*,7*Z*)-7-ethylidene-3-methyl-2-*iso*-oxacephem-4-carboxylate 18a

NaOMe/MeOH (0.2 M) was added hourly in 1 mL portions at 0 °C to a solution of **35a** (0.45 g; 1.25 mmol) in methanol (30 mL) until the starting material disappeared (4 h) (TLC: CH_2Cl_2–EtOAc 10:2, UV + PMA, Rf_{18} 0.7, Rf_{36} 0.15). After completion, the mixture was neutralized

with 1 M HCl and the methanol was evaporated under reduced pressure. The residue was dissolved in EtOAc (30 mL), washed with water and brine and dried over $MgSO_4$. The yellow crude oil (0.37 g) obtained after evaporation of the solvent was purified by prep. TLC (CH_2Cl_2–EtOAc 10:1.5) to give **36a** (160 mg, 40%), **18a** (90 mg, 24%) and **37a** (15 mg, 4%).

4.46.1. Benzyl (6*S*,7*R*)-7-[(1*R*)-1-hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 36a. Yellow oil. $[\alpha]_D^{26} = +103.5$. IR (film): ν 3448 (OH), 2976 (CH), 1752 (CON), 1708, 1616 (Ar), 1456, 1392, 1308, 1224, 1152, 1072, 1048, 740, 696 cm^{-1}. ^1H NMR (500 MHz): δ 1.30 (3H, d, $J = 6.5$ Hz, β-Me), 2.24 (3H, s, 3-Me), 2.36 (1H, br s, OH), 3.63 (1H, m, 7-H), 3.70 (1H, m, 6-H), 4.15 (1H, m ~ qui, α-H), 4.24 (1H, m ~ t, 1-H_A), 4.51 (1H, dd, $J_{gem} = 10.7$ Hz, $J_{6H} = 3.7$ Hz, 1-H_B), 5.26 (2H, AB, $J_{gem} = 12.5$ Hz, CH_2Ph), 7.30–7.46 (5H, m, ArH). ^{13}C NMR (125 MHz): δ 18.17 (β-Me), 23.17 (3-Me), 45.54 (6-C), 60.79 (7-C), 63.66 (α-C), 66.76 and 66.98 (CH_2Ph, 1-C), 106.52 (4-C), 128.30 (Ar-4′-C), 128.50 and 128.67 (Ar-2′,3′,5′,6′-C), 136.08 (Ar-1′-C), 155.66 (3-C), 163.18 (CON), 167.22 (COOBn). HRMS m/z 317.1281 ($C_{17}H_{19}O_5N$ calcd 317.1263).

4.46.2. Benzyl (6*S*,7*Z*)-7-ethylidene-3-methyl-2-*iso*-oxacephem-4-carboxylate 18a. Yellow oil. $[\alpha]_D^{25.5} = +121.0$. HRMS m/z 299.1139 ($C_{17}H_{17}NO_4$ calcd 299.1158), the spectra were the same as cited above (see Section 4.19.2).

4.46.3. Benzyl (6*S*,7*E*)-7-ethylidene-3-methyl-2-*iso*-oxacephem-4-carboxylate 37a. Needle-like white crystals. Rf_{37a} 0.65. $[\alpha]_D^{34} = +196.1$ (c 0.4). Mp 119–120 °C. IR (KBr): ν 1752 (CON), 1712 (COO), 1608 (Ar), 1456, 1384, 1348, 1320, 1288, 1204, 1116, 1080, 1048, 992, 748, 700 cm^{-1}. ^1H NMR (500 MHz): δ 1.80 (3H, d, $J = 6.7$ Hz, β-Me), 2.26 (3H, s, 3-Me), 3.60 (1H, m ~ t, 1-H_A), 4.00 (1H, dd, $J_{1HA} = 9$ Hz, $J_{1HB} = 3.6$ Hz, 6-H), 4.69 (1H, dd, $J_{gem} = 10.7$ Hz, $J_{6H} = 3.6$ Hz, 1-H_B), 5.28 (2H, AB, $J_{gem} = 12.5$ Hz, CH_2Ph), 6.33 (1H, q, $J = 6.7$ Hz, α-H), 7.30 (1H, t, $J_{ortho} = 7.1$ Hz, Ar-4′-H), 7.36 (2H, t, $J_{ortho} = 7.1$ Hz, Ar-3′,5′-H), 7.48 (2H, d, $J_{ortho} = 7.1$ Hz, Ar-2′,6′-H). ^{13}C NMR (125 MHz): δ 15.31 (β-Me), 18.17 (3-Me), 49.21 (6-C), 67.06 and 68.70 (CH_2Ph, 1-C), 107.51 (4-C), 125.94 (α-C), 128.25 (Ar-4′-C), 128.53 and 128.66 (Ar-2′,3′,5′,6′-C), 136.17 (Ar-1′-C), 140.78 (7-C), 153.91 (3-C), 162.71 and 163.60 (COOBn, CON). HRMS m/z 299.1143 ($C_{17}H_{17}NO_4$ calcd 299.1158).

4.47. Benzyl (6*R*,7*S*)-7-[(1*S*)-1-hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 36b and benzyl (6*R*,7*Z*)-7-ethylidene-3-methyl-2-*iso*-oxacephem-4-carboxylate 18b

Prepared analogously to **36a** and **18a** from **35b** (0.35 g; 1 mmol) and gave **36b** (120 mg, 38%) and **18b** (80 mg, 27%).

4.47.1. Benzyl (6*R*,7*S*)-7-[(1*S*)-1-hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylate 36b. Yellow oil. $[\alpha]_D^{25.5} = -102.7$. IR (film): ν 3448 (OH), 2976 (CH), 1752 (CON), 1712, 1616 (Ar), 1456, 1392, 1304, 1224, 1152, 1072, 1048, 740, 696 cm^{-1}. ^1H NMR (500 MHz): δ 1.30 (3H, d, $J = 6.5$ Hz, β-Me), 2.24 (3H, s, 3-Me), 2.40 (1H, br s, OH), 3.63 (1H, m, 7-H), 3.70 (1H, m, 6-H), 4.14 (1H, m ~ qui, α-H), 4.24 (1H, m ~ t, 1-H_A), 4.51 (1H, dd, $J_{gem} = 10.7$ Hz, $J_{6H} = 3.8$ Hz, 1-H_B), 5.26 (2H, AB, $J_{gem} = 12.5$ Hz, CH_2Ph), 7.30 (1H, t, $J_{ortho} = 7.3$ Hz, Ar-4′-H), 7.36 (2H, t, $J_{ortho} = 7.3$ Hz, Ar-3′,5′-H), 7.45 (2H, d, $J_{ortho} = 7.2$ Hz, Ar-2′,6′-H). ^{13}C NMR (125 MHz): δ 18.18 (β-Me), 23.18 (3-Me), 45.55 (6-C), 60.80 (7-C), 63.69 (α-C), 66.75 and 66.99 (CH_2Ph, 1-C), 106.55 (4-C), 128.31 (Ar-4′-C), 128.51 and 128.68 (Ar-2′,3′,5′,6′-C), 136.08 (Ar-1′-C), 155.65 (3-C), 163.17 (CON), 167.21 (COOBn). HRMS m/z 317.1271 ($C_{17}H_{19}O_5N$ calcd 317.1263).

4.47.2. Benzyl (6*S*,7*Z*)-7-ethylidene-3-methyl-2-*iso*-oxacephem-4-carboxylate 18b. Yellow oil. $[\alpha]_D^{24.5} = -121.2$. IR (film): ν 1752 (CON), 1712, 1612 (Ar), 1456, 1384, 1352, 1292, 1208, 1120, 1080, 1028, 736, 696 cm^{-1}. ^1H NMR (500 MHz): δ 2.07 (3H, d, $J = 7.2$ Hz, β-Me), 2.25 (3H, s, 3-Me), 3.55 (1H, dd, $J_{6H} = 9.3$ Hz, $J_{gem} = 10.6$ Hz, 1-H_A), 3.86 (1H, dd, $J_{1HA} = 9.3$ Hz, $J_{1HB} = 3.8$ Hz, 6-H), 4.60 (1H, dd, $J_{gem} = 10.6$ Hz, $J_{6H} = 3.8$ Hz, 1-H_B), 5.29 (2H, AB, $J_{gem} = 12.5$ Hz, CH_2Ph), 5.81 (1H, q, $J = 7.1$ Hz, α-H), 7.30–7.41 (3H, m, Ar-3′,4′,5′-H), 7.48 (2H, d, $J_{ortho} = 7.2$ Hz, Ar-2′,6′-H). ^{13}C NMR (125 MHz): δ 15.17 (β-Me), 18.12 (3-Me), 49.40 (6-C), 66.98 and 69.07 (CH_2Ph, 1-C), 107.49 (4-C), 128.21 (Ar-4′-C), 128.46 and 128.65 (Ar-2′,3′,5′,6′-C), 129.29 (α-C), 136.28 (Ar-1′-C), 139.47 (7-C), 153.86 (3-C), 163.23 and 163.65 (COOBn, CON). HRMS m/z 299.1168 ($C_{17}H_{17}NO_4$ calcd 299.1158).

4.48. (6*S*,7*R*)-7-[(1*R*)-1-Hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylic acid 38a

Compound **36a** (150 mg; 0.47 mmol) was hydrogenated under normal pressure in the presence of 10% Pd/C catalyst (20 mg) in methanol (40 mL) for an hour (TLC: CH_2Cl_2–EtOAc 1:1, UV, Rf_{36} 0.3, Rf_{38} 0; CH_2Cl_2–MeOH 10:3, UV, Rf_{37} 0.3). The catalyst was filtered off and washed with methanol. The filtrate was evaporated under reduced pressure. The resulting colourless oil solidified on ether to give **38a** (75 mg, 70%) as a white solid. $[\alpha]_D^{25.5} = +175.8$ (MeOH). IR (KBr): ν 3500–3400 (br, OH, COOH), 1748 (CON), 1628, 1396, 1228, 1160, 1048 cm^{-1}. ^1H NMR (300 MHz, MeOD-d_4): δ 1.26 (3H, d, $J = 6.5$ Hz, β-Me), 2.15 (3H, s, 3-Me), 3.30 (1H, s, OH), 3.65 (2H, m, 6-H+7-H), 4.11 (1H, m ~ qui, α-H), 4.26 (1H, m ~ t, 1-H_A), 4.50 (1H, dd, $J_{gem} = 10.8$ Hz, $J_{6H} = 3.5$ Hz, 1-H_B). ^{13}C NMR (75 MHz, MeOD-d_4): δ 17.89 (β-Me), 23.81 (3-Me), 47.29 (6-C), 61.73 (7-C), 64.31 (α-C), 67.77 (1-C), 111.25 (4-C), 151.94 (3-C), 169.10 (CON). HRMS m/z 227.0810 ($C_{10}H_{13}NO_5$ calcd 227.0794).

4.49. (6*R*,7*S*)-7-[(1*S*)-1-Hydroxyethyl]-3-methyl-2-*iso*-oxacephem-4-carboxylic acid 38b

Prepared analogously to **38a** from **36b** (60 mg; 0.19 mmol) and gave **38b** (30 mg, 70%) as white solid. $[\alpha]_D^{27} = -176.7$ (MeOH). IR (KBr): ν 3500–3400 (br, OH, COOH), 1748 (CON), 1628, 1576, 1376, 1228, 1160, 1048, 788 cm^{-1}. ^1H

NMR (300 MHz, MeOD-d_4): δ 1.26 (3H, d, $J = 6.5$ Hz, β-Me), 2.15 (3H, s, 3-Me), 3.30 (1H, s, OH), 3.65 (2H, m, 6-H+7-H), 4.11 (1H, m ~ qui, α-H), 4.28 (1H, m ~ t, 1-H_A), 4.50 (1H, dd, $J_{gem} = 11$ Hz, $J_{6H} = 3.4$ Hz, 1-H_B). ^{13}C NMR (75 MHz, MeOD-d_4): δ 17.90 (β-Me), 23.78 (3-Me), 47.29 (6-C), 61.79 (7-C), 64.34 (α-C), 67.82 (1-C), 110.93 (4-C), 152.23 (3-C), 169.09 (CON). HRMS m/z 227.0812 ($C_{10}H_{13}NO_5$ calcd 227.0794).

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References

1. Davies, J. *Science* **1994**, *264*, 375–382.
2. Niccolai, D.; Tarsi, L.; Thomas, R. J. *Chem. Commun.* **1997**, 2333–2342.
3. Wash, C. *Nature* **2000**, *406*, 775–781.
4. Wright, G. D. *Chem. Biol.* **2000**, *7*, 127–132.
5. Albers-Schönberg, G.; Arison, B. H.; Hensens, O. D.; Hirschfield, J.; Hoogsten, K.; Kaczka, E. A.; Rhodes, R. E.; Kahan, J. S.; Kahan, F. M.; Ratcliffe, R. W.; Walton, E.; Ruswinkle, J. J.; Morin, R. B.; Christensen, B. G. *J. Am. Chem. Soc.* **1978**, *100*, 6491–6499.
6. Neu, H. C.; Labthavikul, P. *Antimicrob. Agents Chemother.* **1982**, *21*, 180–187.
7. Doyle, T. W.; Belleau, B.; Luh, B. Y.; Conway, T. T.; Menard, M.; Dougles, J. L.; Chu, D. T. W.; Lim, G.; Morris, L. R.; Rivest, P.; Case, M. *Can. J. Chem.* **1977**, *57*, 484–507.
8. Diaz, N.; Suarez, D.; Merz, K. M., Jr.; Sordo, T. L. *J. Med. Chem.* **2005**, *48*, 780–791.
9. Sánta, Z.; Nagy, J.; Párkányi, L.; Nyitrai, J. *Monatsh. Chem./ Chem. Monthly* **2004**, *135*, 671–684.
10. Madarász, Z.; Németh, I.; Toscano, P.; Welch, J.; Nyitrai, J. *Tetrahedron Lett.* **1995**, *36*, 8303–8306.
11. Sánta, Z.; Párkányi, L.; Németh, I.; Nagy, J.; Nyitrai, J. *Tetrahedron: Asymmetry* **2001**, *12*, 89–94.
12. Greff, Z.; Horváth, Z.; Nyitrai, J.; Kajtár-Peredy, M.; Brlik, J. *J. Chem. Res. (S)* **1990**, 170–171; Greff, Z.; Horváth, Z.; Nyitrai, J.; Kajtár-Peredy, M.; Brlik, J. *J. Chem. Res. (M)* **1990**, 120l–1258.
13. Soai, K.; Yokoyama, S.; Mochida, K. *Synthesis* **1978**, 647–648.
14. Nagao, Y.; Kumagai, T.; Kobayashi, S.; Tamai, S.; Ohta, K.; Inoue, Y.; Kishi, I. *Heterocycles* **1997**, *46*, 193–198.