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Synthesis of pure methyl [(2*S*,3*R*,α*R*)-1-(3-bromo-4-methoxyphenyl)-3-(α-acetoxy)ethyl-4-oxoazetidin-2-carboxylate] and its enantiomer

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Abstract—Synthesis of key intermediates leading to 2-*iso*-oxacephems was carried out starting from L- and D-threonine. As predicted in our previous paper (*Tetrahedron Lett*. **1995**, *36*, 8303–8306) all diastereomers of 2-*iso*-oxacephems can be prepared from the appropriate enantiomers of the amino acid threonine. The absolute configuration of the 2,3- and α-carbon atoms in the β-lactam structure was determined by X-ray crystallographic studies.

1. Introduction

Bicyclic β-lactams and their nuclear analogues[2] are still of great interest as a result of both their antibacterial activity and the continuing need for novel β-lactamase inhibitors. It is widely known that the configuration in positions 6 and 7 in bicyclic β-lactams is a determining factor in their biological activity. Our aim to synthesize *Thienamycin* analogues in the 2-*iso*-oxacephem series makes obtaining the correct configuration of the α-carbon atom in the hydroxyethyl side chain a key challenge in this synthesis.

2. Discussion

Herein, we report the total synthesis of the monocyclic β-lactam enantiomers **9a** and **9b**. The key intermediates leading to the 2-*iso*-oxa- and 2-*iso*-cephems were synthesized in four steps.[3] At the start of the synthesis bromide **3a** was synthesized from L-threonine using literature procedures. Upon treatment with thionyl chloride in dichloromethane at elevated temperature, **3a** was cleanly converted to the acid chloride **4a.** The β-lactam precursor **6a** was then formed by amination of acid chloride **4a** with the malonate and 4-methoxyphenyl functionalized secondary amine **5**.

Treatment of a benzene solution of **6a** with DBU effected ring closure at room temperature to form the lactam **7a**, which was then subjected to basic hydrolysis and mono-decarboxylation of the malonate residue to give the mono-ester **8a**. Treatment of **8a** with sodium borohydride in *tert*-butanol led to chemoselective reduction, allowing the *cis*-mono-ester **9a** to be isolated from the *trans* isomer. The above steps towards **9a** were carried out as was described in our preliminary paper[1] (Scheme 1). (For detailed conditions see Section 4.) The same methods were used in the synthesis of the enantiomeric analogues from D-threonine, to ultimately form **9b**.

With the exceptions of α-hydroxy, α-amino or α-acylamino esters,[4,5] sodium borohydride does not usually reduce esters. Use of this reducing agent was extended to β-lactam esters[6] where interesting chemoselectivity was observed. Of the diastereomeric mixture of esters **8a** only the *trans* isomer reacted with sodium borohydride at ambient temperature; this is because the carbonyl group in the *cis*-ester is in a hindered position, being crowded by the α-acetoxyethyl and 4-methoxyphenyl groups. The reduction product, *trans*-alcohol **11a**, could then be easily isolated chromatographically from the desired *cis* isomer **9a**. It is also notable that, at elevated reaction temperature, the *cis*-ester **9a** partially isomerized into the corresponding *trans*-ester due to the basicity of sodium borohydride. The reduction of β-lactam *cis*-esters has previously been carried out via hydrolysis and subse-

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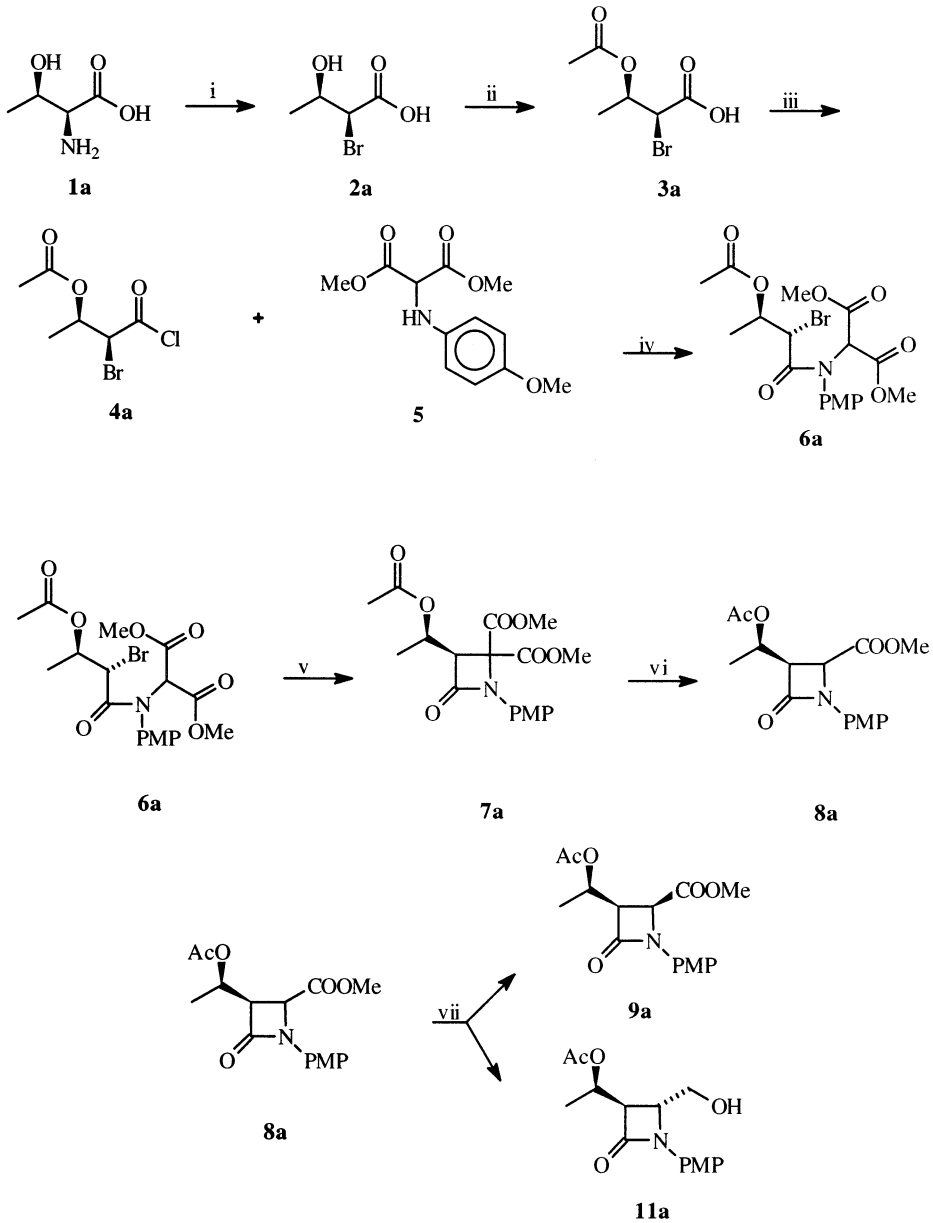
quently using the mixed anhydride method,[6] which was unsuccessful in the case of compound **9a**.

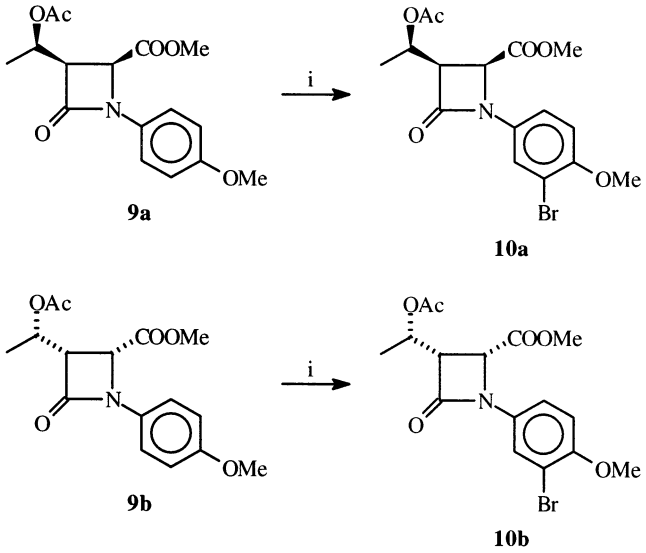
For unambiguous determination of the absolute configuration of all carbon atoms, a heavy atom was needed in the enantiomers **9a** and **9b**. Bromination at the aromatic center of **9a** and **9b** with bromine in acetic acid was regioselective in both cases, with one isomer resulting from bromination at the 3-position on the aromatic ring to afford **10a** and **10b**, respectively, in good yield (Scheme 2). Single-crystal X-ray analysis, as shown on an ORTEP diagram (Fig. 1), proved that the first reaction (step i in Scheme 1) proceeded with complete retention of configuration, whilst in the ring closure step (step v in Scheme 1) complete inversion took place on the C-2 stereocenter of threonine.

3. Conclusion

Two enantiomeric β-lactams **9a** and **9b** have been formed starting from L- and D-threonine. The introduction of a bromo-substituent into the aromatic ring had no effect on the configuration in positions α, 2 and 3, as could be expected. It was also unambiguously proven that our method for the synthesis of enantiomerically pure 3-(1-acetoxyethyl)-β-lactams is a general one; the stereochemistry of the product depends only on the stereogenicity of the starting threonine. The carbon atom in position 2 in the chain of threonine reacts in the amino-bromine exchange step with retention, and the ring closure takes place with inversion (S_N2_i). This study indicates that starting from D-*allo*-threonine will allow *Thienamycin*-like stereochemistry to be reached.



Scheme 1. Synthesis of one enantiomer **9a** (α*R*,2*S*,3*R*) is shown only. i: $NaNO_2$, KBr, 1.25 M H_2SO_4, 0→25°C; ii: AcCl, CH_2Cl_2, Py, 5°C; iii: $SOCl_2$, CH_2Cl_2, 60°C; iv: toluene, 80°C; v: DBU, benzene, rt; vi: (a) 1N NaOH, Py, 5°C; (b) α-picoline, 150°C, 80 min; vii: $NaBH_4$, *tert*-BuOH, rt. Abbr.: PMP = 4-methoxyphenyl.



Scheme 2. i: Bromine, acetic acid, rt.

4. Experimental

4.1. General

IR spectra were obtained on a Zeiss Specord IR 75 spectrometer. Optical rotations ($T=22.0$°C, unless stated otherwise, $c=1.0$ g/100 cm^3, CH_2Cl_2) were taken on a Perkin–Elmer 241 polarimeter, that was calibrated by measuring the optical rotations of both enantiomers of menthol. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were measured on a Bruker DRX-500 spectrometer. Elemental analyses were performed in the Microanalytical Laboratory of the Department of Organic Chemistry, L. Eötvös University, Budapest, Hungary. Melting points were measured on a hot plate melting point apparatus and are uncorrected. Chromatographic work up was carried out by using Merck silica gel 60 (0.2–0.063) for column chromatography and PF_{254} ready plates for TLC, unless otherwise stated.

4.2. Dimethyl {*N*-[(2*S*,3*R*)-3-acetoxy-2-bromobutyryl]-*N*-(4-methoxyphenyl)aminomalonate} 6a

A mixture of (2*S*,3*R*)-3-acetoxy-2-bromobutyryl chloride[7] **4a** (7.3 g, 30.0 mmol) and dimethyl [*N*-(4-methoxyphenyl)aminomalonate] (7.6 g, 30.0 mmol) was stirred at 80°C in toluene (25 ml) for 2 days, filtered off, and the filtrate was washed with water (3×10 ml) and dried over $MgSO_4$. The solution was concentrated to dryness. The crude oil (13.2 g, 95%) was used for the following step: 1.0 g was purified on 15 g of Kieselgel G by using $CH_2Cl_2 \rightarrow CH_2Cl_2$:EtOAc 10:1 as eluent to give the pure oily product. $[\alpha]_D=+90$. IR (neat): ν 1720 (CO), 1640 (CON), 1200 and 1000 (COC) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.30 (3H, d, $J=6.25$ Hz, CH_3), 2.0 (3H, s, CH_3CO), 3.64, 3.75, and 3.81 (9H, 3s, 3×OCH_3), 4.07 (1H, d, $J=9.4$ Hz, CHBr), 5.30–5.33 (1H, m, C*H*OAc), 5.32 [1H, s, C*H*(COOMe)$_2$], 6.91 (2H, d, $J=8.25$ Hz, ArH), 7.42 (2H, brd, ArH) ppm.

4.3. Dimethyl {*N*-[(2*R*,3*S*)-3-acetoxy-2-bromobutyryl]-*N*-(4-methoxyphenyl)aminomalonate} 6b

D-Threonine (11.9 g, 0.1 mol) and KBr (41.8 g, 0.35 mol) were dissolved under cooling in 1.25 M sulfuric acid (210 ml). Sodium nitrite (11.16 g, 0.16 mol) was added in small portions to this solution at 0°C. After 1 h the solution was stirred for another 1 h at 25°C. The reaction mixture was extracted with ether (5×50 ml). The combined organic extract was washed with brine then dried ($MgSO_4$). After evaporation of the solvent, the residue was distilled at 0.1 torr. The crude product **2b** (11.9 g, 65%) was pure enough for use in the following step. $[\alpha]_D=+21.2$. IR (neat): ν 3600–3200 br (OH), 1710 (CO) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.36 (3H, d, $J=6.25$ Hz, CH_3), 4.19 (1H, qd, $J=6.25$ Hz, $J=4.3$ Hz, C*H*OH), 4.31 (1H, d, $J=4.3$, CHBr), 6.08 (1H, brs, OH) ppm. ^{13}C NMR ($CDCl_3$): δ 20.34 (CH_3), 52.91 (CHBr), 67.67 (CHOH), 172.89 (CO) ppm.

Freshly distilled acetyl chloride (8.0 ml, 0.11 mol) was added to a stirred solution of (2*R*,3*S*)-2-bromo-3-hydroxybutyric acid **2b** (7.9 g, 43.2 mmol) in CH_2Cl_2 (50 ml) at 5°C. A mixture of pyridine (8.0 ml, 7.82 g, 99

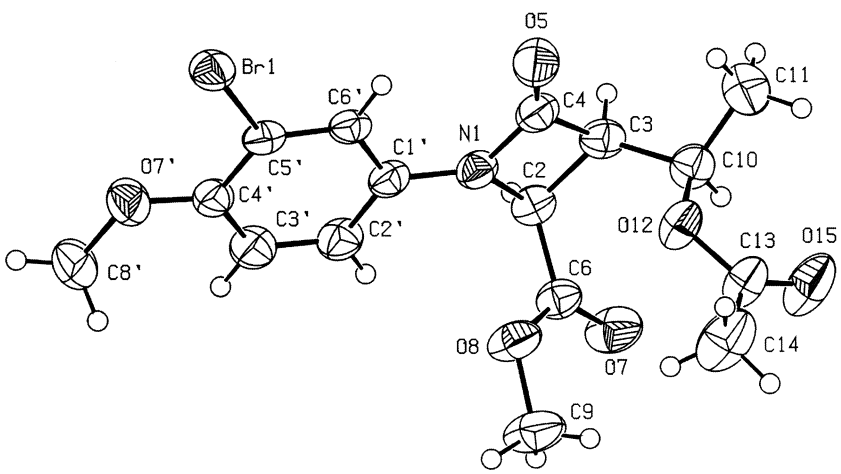


Figure 1. The molecular diagram of **10a** with the numbering of atoms. Atomic displacement ellipsoids represent 50% probabilities.

mmol) and CH_2Cl_2 (50 ml) was also added at the same temperature. After stirring for 1.5 h water was added to the mixture. The solution was acidified with HCl to pH 2–3, extracted with ether (3×30 ml) and the organic solution was concentrated to an oily residue, which was stirred with a mixture of THF and water (1:1; 100 ml) for 4 h at ambient temperature in order to remove the anhydride. After extraction with ether (3×30 ml) the combined organic layers were dried ($MgSO_4$) and concentrated to dryness. The solvent impurities were removed in vacuo (0.1 torr) to give 9.52 g (98%) oily product **3b**. $[\alpha]_D = +3.8$. IR (neat): ν 1720 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.42 (3H, d, $J = 6.35$ Hz, CH_3), 2.11 (3H, s, CH_3CO), 4.36 (1H, d, $J = 6.35$, CHBr), 5.31–5.37 (1H, m, C*H*OAc) ppm. ^{13}C NMR ($CDCl_3$): δ 17.79 (CH_3), 20.97 (*C*H_3CO), 47.91 (CHBr), 69.42 (*C*HOAc), 170.19 and 171.87 (*C*OO's) ppm.

(2*R*,3*S*)-3-Acetoxy-2-bromobutyryl chloride **4b** was prepared analogously to its (2*S*,3*R*)-enantiomer.[8] Thionyl chloride (11.15 ml, 0.15 mol) was added dropwise to a solution of (2*R*,3*S*)-3-acetoxy-2-bromobutyric acid **3b** (9.4 g, 41.9 mmol) in CH_2Cl_2 (40 ml) at 0°C. The mixture was stirred at 60°C for 8 h. The solution was concentrated to dryness. Benzene (2×50 ml) was added and distilled from the crude oil to give **4b** (8.05 g, 79%). The residue was pure enough to use directly in the following step.

Analogously to **6a**, 8.05 g (33.0 mmol) of **4b** and dimethyl [*N*-(4-methoxyphenyl)aminomalonate] (8.37 g, 33.0 mmol) gave 13.4 g (88%) of **6b**. $[\alpha]_D^{23.5} = -78.3$. IR (neat): ν 1720 (CO) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.29 (3H, d, $J = 6.25$ Hz, CH_3), 1.99 (3H, s, CH_3CO), 3.66, 3.76, and 3.82 (3×3H, 3s, 3×CH_3O), 4.09 (1H, d, $J = 9.4$ Hz, CHBr), 5.30–5.33 (1H, m, C*H*OAc), 5.32 [1H, s, C*H*(COOMe)$_2$], 6.91 (2H, d, $J = 8.25$ Hz, ArH), 7.42 (2H, brd, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 17.70 (CH_3), 21.04 (*C*H_3CO), 45.05 (CHBr), 53.12 and 53.18 (2×CH_3O), 55.64 (*C*H_3OAr), 65.08 [*C*H(COOMe)$_2$], 71.13 (*C*HOAc), 114.96, 115.25, 130.14, 130.32, 131.62, and 160.36 (Ar-Cs), 165.56, 165.88, 168.05, and 169.70 (COs) ppm.

4.4. Dimethyl [(α*R*,3*R*)-3-(1-acetoxyethyl)-1-(4-methoxyphenyl)-4-oxoazetidine-2,2-dicarboxylate] 7a

The bromoester **6a** (4.61 g, 10 mmol) was dissolved in benzene (30 ml). DBU (1.57 ml, 10.5 mmol) in benzene (4.2 ml) was dropped to this solution under cooling (15–20°C). The mixture was stirred overnight, and the DBU salt was filtered off and washed with ethyl acetate. The combined organic filtrates were washed subsequently with 10% HCl, saturated $NaHCO_3$ solution, water and then with brine. It was evaporated after drying ($MgSO_4$) to give crude product (3.49 g, 92%) which was used without purification for the following step. The analytically pure product was obtained similarly as mentioned above. Oil. $[\alpha]_D = -97$. IR (neat): ν 1750 (CON), 1720 (CO), 1200 and 1000 (COC) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.47 (3H, d, $J = 6.6$ Hz, CH_3), 1.95 (3H, s, CH_3CO), 3.72 (9H, s, 3×OCH_3), 3.92 (1H, d, $J = 2.7$ Hz, 3-H), 5.0–5.4 (1H, m, C*H*OAc), 6.80 and 7.48 (4H, AA′BB′, $J = 8.8$ Hz, ArH) ppm. Anal. calcd for $C_{18}H_{21}NO_8$ C, 56.99; H, 5.58; N, 3.69; found C, 56.89; H, 5.56; N, 3.77.

4.5. Dimethyl [(α*S*,3*S*)-3-(1-acetoxyethyl)-1-(4-methoxyphenyl)-4-oxoazetidine-2,2-dicarboxylate] 7b

Prepared analogously to **7a** in 86% yield. Oil. $[\alpha]_D = +95$. IR (neat): ν 1750 (CON), 1720 (CO), 1200 and 1000 (COC) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.51 (3H, d, $J = 6.6$ Hz, CH_3), 1.98 (3H, s, CH_3CO), 3.78–3.80 (9H, s, 3×OCH_3), 3.99 (1H, d, $J = 2.3$ Hz, 3-H), 5.28–5.32 (1H, m, C*H*OAc), 6.85 and 7.46 (4H, dd, $J_{ortho} = 7.15$ Hz, $J_{meta} = 1.8$ Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 18.49 (CH_3), 21.00 (*C*H_3CO), 53.09 and 53.93 (2×CH_3O), 55.59 (*C*H_3OAr), 62.28 (*C*HOAc), 66.58 (C-3), 67.36 (C-2), 114.30, 120.7, 130.17, and 157.18 (Ar-Cs), 163.17 (C-4), 166.33 and 167.63 (*C*OOMe), 170.26 (CH_3CO) ppm. Anal. calcd for $C_{18}H_{21}NO_8$ C, 56.99; H, 5.58; N, 3.69; found N, 3.82.

4.6. (α*R*,3*R*)-3-(1-Acetoxyethyl)-2-methoxycarbonyl-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylic acid

1N NaOH (20 ml) was added to a stirred solution of the diester **7a** (8.0 g, 21 mmol) in pyridine (10 ml) at 5°C. The mixture was maintained at this temperature overnight, then diluted with saturated $NaHCO_3$ (12 ml) and extracted with ethyl acetate (2×20 ml). The aqueous solution was saturated with NaCl, acidified with concentrated HCl and extracted with ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$) and evaporated. The crude product (4.5 g, 59%) was purified for analysis by TLC using CH_2Cl_2:EtOAc 10:3 as eluent. Mp: 103°C. $[\alpha]_D = -20.9$. IR (KBr): ν 3700–3400 (OH), 1750 (CON), 1720 (CO), 1700 (COOH), 1220 and 1000 (COC) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.45 (3H, d, $J = 6.6$ Hz, CH_3), 1.93 (3H, s, CH_3CO), 3.72 (6H, s, 2×OCH_3), 3.90 (1H, d, $J = 3.0$ Hz, 3-H), 5.0–5.4 (1H, m, C*H*OAc), 6.65 and 7.45 (4H, AA′BB′, $J = 9$ Hz, ArH), 9.67 (1H, brs, OH) ppm. Anal. calcd for $C_{17}H_{19}NO_8$ (365.34) C, 55.88; H, 5.24; N, 3.83; found C, 55.62; H, 4.98; N, 3.53.

4.7. (α*S*,3*S*)-3-(1-Acetoxyethyl)-2-methoxycarbonyl-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylic acid

Prepared analogously to Section 4.6 in 58% yield.

4.8. Methyl [(α*R*,2*RS*,3*R*)-3-(1-acetoxyethyl)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate] 8a

The compound from Section 4.6 (3.6 g, 10.0 mmol) was stirred under reflux with 2-picoline (10 ml) for 80 min. The solution was concentrated to dryness and dissolved in EtOAc. The organic solution was washed subsequently with 10% HCl, saturated $NaHCO_3$ and brine, dried ($MgSO_4$) and evaporated to give 2.32 g (72%) crude mixture of esters **8a**.

4.9. Methyl [(α*S*,2*RS*,3*S*)-3-(1-acetoxyethyl)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate] 8b

Prepared analogously to **8a** in 67% yield.

4.10. Methyl [(αR,2S,3R)-3-(1-acetoxyethyl)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate] 9a

A solution of **8a** (15 g, 46 mmol) in *tert*-butyl alcohol was treated with $NaBH_4$ (8.75 g, 230 mmol) at ambient temperature. The reaction mixture was concentrated to dryness in vacuo. The residue was triturated with EtOAc, the insoluble inorganic compounds were filtered off, and washed thoroughly with EtOAc. The combined organic filtrates were washed three times with brine, and the aqueous layers were extracted with EtOAc. The organic solution was dried ($MgSO_4$) and evaporated. The residue was separated from a single product by column chromatography to give the title compound (10.5 g, 68%). R_f=0.7 (TLC, CH_2Cl_2:EtOAc 10:2). Mp: 179°C. $[\alpha]_D$=−141.5. IR (KBr): *v* 2936, 2880, 2840 (CH), 1750 (CON), 1720 (CO), 1248 and 1032 (COC) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.49 (3H, d, J=6.5 Hz, CH_3), 1.99 (3H, s, CH_3CO), 3.70 (1H, dd, $J_{\alpha\text{-}H}$=3.0 Hz, J_{cis}=6.4 Hz, 3-H), 3.73 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.59 (1H, d, J_{cis}=6.4 Hz, 2-H), 5.26 (1H, qd, J=6.5 Hz, $J_{3\text{-}H}$=3.0 Hz, α-H), 6.87 (2H, d, J_{ortho}=8.8 Hz, ArH), 7.31 (2H, d, J_{ortho}=8.8 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 18.88 (CH_3), 21.17 (CH_3CO), 52.60 (CH_3OOC), 53.92 (C-2), 55.72 (CH_3-OAr), 56.98 (C-3), 66.23 (C-α), 114.53, 118.55, 131.10 and 156.68 (Ar-Cs), 162.60 (C-4), 168.40 (*C*OOMe), 170.58 (CH_3CO) ppm. Anal. calcd for $C_{16}H_{19}NO_6$ (321.33) C, 59.81; H, 5.96; N, 4.36; found C, 59.85; H, 5.86; N, 4.43.

The side product proved to be the corresponding alcohol **11a**.

4.11. Methyl [(αS,2R,3S)-3-(1-acetoxyethyl)-1-(4-methoxyphenyl)-4-oxoazetidine-2-carboxylate] 9b

Compound **9b** was similarly prepared as **9a**, starting with the corresponding diester **7b** via the diastereomeric monoester **8b**, without purification of the intermediate αS,3S-2-methoxycarbonyl-2-carboxylic acid. This was immediately reduced with sodium borohydride in *tert*-butyl alcohol to **11b** in 11.5% yield, and separated by column chromatography from the unreacted **9b** in 65% yield. R_f=0.7 (TLC, CH_2Cl_2:EtOAc 10:2). Mp: 178°C. $[\alpha]_D$=+143.1. IR (KBr): *v* 2990, 2956, 2936 (CH),1750, 1736 (CO), 1516 (Ar), 1248 and 1050 (COC) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.50 (3H, d, J=6.4 Hz, CH_3), 2.01 (3H, s, CH_3CO), 3.71 (1H, dd, $J_{\alpha\text{-}H}$=2.9 Hz, J_{cis}=6.4 Hz, 3-H), 3.75 (3H, s, OCH_3), 3.80 (3H, s, OCH_3), 4.60 (1H, d, J_{cis}=6.4 Hz, 2-H), 5.26 (1H, qd, J=6.4 Hz, $J_{3\text{-}H}$=2.9 Hz, α-H), 6.89 (2H, d, J_{ortho}=8.9 Hz, ArH), 7.32 (2H, d, J_{ortho}=8.9 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$): δ 18.91 (CH_3), 21.19 (CH_3CO), 52.63 (CH_3OOC), 53.94 (C-3), 55.74 (CH_3OAr), 57.01 (C-2), 66.25 (C-α), 114.56, 118.57, 131.12, and 156.71 (Ar-Cs), 162.61 (C-4), 168.40 (*C*OOMe), 170.61 (CH_3CO) ppm. Anal. calcd for $C_{16}H_{19}NO_6$ (321.33) C, 59.81; H, 5.96; N, 4.36; found C, 59.75; H, 5.53; N, 4.46.

4.12. (αR,2R,3R)-3-(1-Acetoxyethyl)-4-hydroxymethyl-1-(4-methoxyphenyl)azetidine-2-one 11a

Oil. R_f=0.15 (TLC, CH_2Cl_2:EtOAc 10:2). $[\alpha]_D$=+43.7. IR (neat): *v* 3600–3200 (OH), 1740 (CON), 1710 (CO), 1230 and 1010 (COC) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.43 (3H, d, J=6.5 Hz, CH_3), 1.9 (1H, brs, OH), 2.03 (3H, s, CH_3CO), 3.46 (1H, m, J_{vic}=4.6 Hz, J_{trans}=2.5 Hz, 3-H), 3.79 (3H, s, OCH_3), 3.98 (3H, m, 4-CH_2+4-H), 5.31 (1H, m, J=6.5 Hz, J=4.6 Hz, α-H), 6.89 (2H, m, J_{ortho}=9 Hz, ArH), 7.35 (2H, m, J_{ortho}=9 Hz, ArH) ppm. Anal. calcd for $C_{15}H_{19}NO_5$ (293.32) C, 61.42; H, 6.53; N, 4.48; found C, 61.23; H, 6.50; N, 4.67.

4.13. (αS,2S,3S)-3-(1-Acetoxyethyl)-4-hydroxymethyl-1-(4-methoxyphenyl)azetidine-2-one 11b

Prepared by the reduction of **8b** in 12% yield as described above. Oil. R_f=0.15 (TLC, CH_2Cl_2:EtOAc 10:2). $[\alpha]_D^{24.5}$=−49.0. IR (neat): *v* 3600–3200 (OH), 1740 (CON), 1710 (CO), 1230 and 1010 (COC) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.44 (3H, d, J=6.45 Hz, CH_3), 1.83 (1H, brs, OH), 2.04 (3H, s, CH_3CO), 3.46 (1H, dd, J_{vic}=4.5 Hz, J_{trans}=2.4 Hz, 3-H), 3.79 (3H, s, OCH_3), 3.92 (1H, dd, $J_{CH_2,4H}$=3.5 Hz, J_{gem}=12 Hz, CH_2), 3.99 (1H, ddd, $J_{CH_2,4H}$=3.5 Hz, $J_{CH_2,4H}$=3.7 Hz, $J_{3H,4H}$=2.4 Hz, 4H), 4.06 (1H, dd, $J_{CH_2,4H}$=3.7 Hz, J_{gem}=12 Hz, CH_2), 5.32 (1H, qd, $J_{CH_3,\alpha H}$=6.6 Hz, $J_{4H,\alpha H}$=4.6 Hz, α-H), 6.89 and 7.37 (4H, AA′BB′, J=9 Hz, ArH) ppm. ^{13}C NMR ($CDCl_3$) δ 17.93 (CH_3), 21.40 (CH_3CO), 55.39 (C-3), 55.67 (C-4), 55.75 (CH_3OAr), 61.13 (CH_2OH), 67.64 (C-α), 114.76, 118.85 (C-2′ and C-3′), 130.95 (C-1′), 156.58 (C-4′), 163.95 (C-2), 170.80 (Me*C*O) ppm.

4.14. Methyl [(αR,2S,3R)-3-(1-acetoxyethyl)-1-(3-bromo-4-methoxyphenyl)-4-oxoazetidine-2-carboxylate] 10a

A solution of bromine (0.1 ml; 2 mmol) in acetic acid (3 ml) was added to a solution of **9a** (0.20 g; 0.6 mmol) in acetic acid (7 ml), and the mixture was stirred for 1 day at ambient temperature. The solution was poured onto a mixture of crushed ice (100 g) and $Na_2S_2O_5$ (0.20 g; 1 mmol). The product which crystallized immediately as a white powder, collected by filtration and dissolved in CH_2Cl_2. The resultant dichloromethane solution was washed with cold water and 5% Na_2CO_3 solution, then dried (Mg_2SO_4), and evaporated to provide pure product (0.17 g, 71%). Using a stoichiometric amount of bromine give a mixture of unreacted starting material (R_f 0.6) and product (R_f 0.65) using CH_2Cl_2:EtOAc 10:2 as eluent. $[\alpha]_D^{24.5}$=−127.3. Mp: 166°C. IR (KBr): *v* 1744 (CON), 1720 (CO), 1240 and 1048 (COC) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.47 (3H, d, J=7.0 Hz, CH_3), 1.98 (3H, s, CH_3CO), 3.71 (1H, m, $J_{3H,2H}$=6.5 Hz, $J_{3H,\alpha H}$=2.8 Hz, 3-H), 3.73 (3H, s, OCH_3), 3.85 (3H, s, $ArOCH_3$), 4.59 (1H, $J_{3H,2H}$=6.5 Hz, 2-H), 5.23 (1H, qd, $J_{CH_3,\alpha H}$=7 Hz, $J_{3\text{-}H,\alpha H}$=2.8 Hz, α-H), 6.84 (1H, d, J_{ortho}=8.9 Hz, Ar-5′-H), 7.29 (1H, dd, J_{ortho}=8.9 Hz, J_{meta}=2.5 Hz, Ar-6′-H), 7.58 (1H, d, J_{meta}=2.5 Hz, Ar-2′-H) ppm. ^{13}C NMR ($CDCl_3$): δ 18.76 (CH_3), 21.08 (CH_3CO), 52.65 (CH_3OOC), 53.98 (C-2), 56.69 (CH_3OAr), 57.14 (C-3), 66.16 (C-α), 112.07 (C-3′), 112.34 (C-5′), 117.34 (C-6′), 122.33 (C-2′), 131.62 (C-1′), 153.05 (C-4′), 162.69 (C-4), 168.10 (*C*OOMe), 170.44 (C-4) ppm. Anal. calcd for $C_{15}H_{18}BrNO_5$ (400.23) C, 48.02; H, 4.53; Br, 19.96; N, 3.50; found C, 48.30; H, 4.68; Br, 19.87; N, 3.74.

4.15. Methyl [(αS,2R,3S)-3-(1-acetoxyethyl)-1-(3-bromo-4-methoxyphenyl)-4-oxoazetidine-2-carboxylate] 10b

Prepared analogously to its enantiomer **10a** starting from **9b**. $[\alpha]_D^{24.5} = +127.2$. Mp: 166°C. IR (KBr): ν 1756 (CON), 1728 (CO), 1244 and 1048 (COC) cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.49 (3H, d, $J_{CH_3,\alpha} = 6.5$ Hz, CH_3), 1.99 (3H, s, CH_3CO), 3.72 (1H, m, $J_{3H,2H} = 6.5$ Hz, $J_{3H,\alpha H} = 2.8$ Hz, 3-H), 3.75 (3H, s, OCH_3), 3.87 (3H, s, $ArOCH_3$), 4.59 (1H, $J_{3H,2H} = 6.5$ Hz, 2-H), 5.25 (1H, qd, $J_{CH_3,\alpha H} = 6.5$ Hz, $J_{3\text{-}H,\alpha H} = 2.8$ Hz, α-H), 6.86 (1H, d, $J_{ortho} = 8.9$ Hz, Ar-5′-H), 7.32 (1H, dd, $J_{ortho} = 8.9$ Hz, $J_{meta} = 2.5$ Hz, Ar-6′-H), 7.59 (1H, $J_{meta} = 2.5$ Hz, Ar-2′-H) ppm. ^{13}C NMR ($CDCl_3$): δ 18.82 (CH_3), 21.13 (CH_3CO), 52.71 (CH_3O), 54.03 (C-2), 56.75 (CH_3OAr), 57.21 (C-3), 66.20 (C-α), 112.17 (C-3′), 112.38 (C-5′), 117.42 (C-6′), 122.40 (C-2′), 131.66 (C-1′), 153.14 (C-4′), 162.70 (C-4), 168.12 (*C*OOMe), 170.52 (CH_3CO) ppm. Anal. calcd for $C_{15}H_{18}BrNO_5$ (400.23) C, 48.02; H, 4.53; Br, 19.96; N, 3.50; found C, 48.00; H, 4.79; Br, 19.92; N, 3.61.

4.16. Crystallography

The two enantiomers were recrystallized from CH_2Cl_2–hexane to furnish suitable single crystals for X-ray analyses. Intensity data were collected on an Enraf–Nonius CAD4 diffractometer (graphite-monochromated Mo Kα radiation, $\lambda = 0.710730$ Å). The structures were solved by direct methods and refined[9] against F^2. Crystal data for **10a**, **10b**. $C_{16}H_{18}BrNO_6$, Fwt = 400.22, $T = 293(2)$ K, $F(000) = 408$, monoclinic, space group $P2_1$, $Z = 2$, **10a:** $a = 7.940(1)$, $b = 5.566(1)$, $c = 19.977(2)$ Å, $\beta = 97.38(1)°$, $V = 875.6(2)$ Å^3, $D_{calcd} = 1.518$ Mg/m^3, $\mu = 2.378$ mm^{-1}, number of independent reflections = 8275, $R_1 = 0.0339$, $wR_2 = 0.0797$, goodness-of-fit = 0.845, absolute structure parameter = −0.001(6). **10b**: $a = 7.940(1)$, $b = 5.565(1)$, $c = 19.966(2)$ Å, $\beta = 97.40(1)°$, $V = 874.9(2)$ Å^3, $D_{calcd} = 1.519$ Mg/m^3, $\mu = 2.380$ mm^{-1}, number of independent reflections = 5436, $R_1 = 0.0341$, $wR_2 = 0.0761$, goodness-of-fit = 0.855, absolute structure parameter = −0.013(8). A molecular diagram[10] of **10a** with the numbering of atoms is depicted in Fig. 1.

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