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Efficient Synthesis of an Enantiopure β-Lactam as an Advanced Precursor of Thrombin and Tryptase Inhibitors

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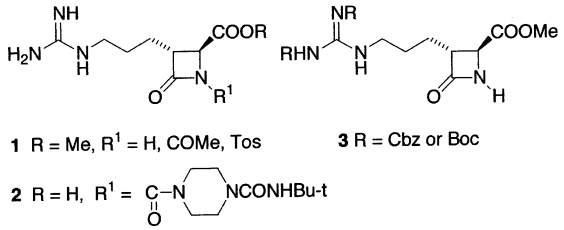
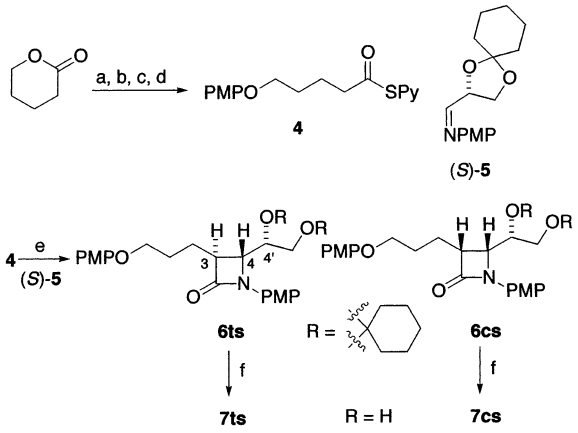
Abstract: A new and efficient synthesis of a β-lactam that is an advanced precursor of inhibitors of thrombin and tryptase is reported. The reaction sequence is based on the use of an inexpensive enantiomerically pure starting material and is designed to allow access to both enantiomers of the target molecules by epimerization of a side-product obtained along the synthesis. An improved procedure for the epimerization step that takes advantage of the use of a polymer-supported and recyclable phase-transfer catalyst is described.

The synthesis of β-lactams has witnessed a resurgence of interest since the discovery that several representatives of this class of compounds can effectively inhibit proteases.[1,2] In particular, azetidinone **1** (Chart 1) was identified[3] as a powerful and selective inhibitor of thrombin, a serine protease involved in both venous and arterial thrombotic episodes.[4] More recently, β-lactam **2** (Chart 1) was found to display inhibition of tryptase at the subnanomolar level and suppress induced inflammation in animal lungs.[5] These compounds featured an ω-guanidyl-substituted *n*-propyl side chain at C-3 and a carboxylic residue at C-4, both essential for biological activity. The thrombin inhibitor **1** was prepared in racemic form by assembling the β-lactam ring via the condensation between the enolate of methyl 5-[*N*′,*N*″-bis-(carbobenzyloxy)guanidino]pentanoate and the *N*-trimethylsilylimine derived from cinnamaldehyde, followed by oxidative degradation of the styryl residue to establish the carboxy function at C-4.[3] The tryptase inhibitor **2** was prepared in enantiopure form starting from unnatural and relatively expensive D-ornithine, which was transformed into a *N*-protected α-bromoacid to be used in an intramolecular α-bromoamide/aminomalonate condensation as the crucial β-lactam forming reaction.[5] We reasoned that the stereoisomerically pure trans compound

CHART 1. Structures of Thrombin and Tryptase Inhibitors 1 and 2 and of Common Precursor 3



SCHEME 1. Synthesis of β-Lactams 6ts and 6cs and of Diols 7ts and 7cs



3 (Chart 1) could represent a convenient, advanced precursor of **1** and **2** and differently N-substituted derivatives thereof. Here, we report a concise, new synthesis of **3** (R = Boc) by a route that starts from readily available and inexpensive D-glyceraldehyde and opens access to both enantiomers of the target molecules in enantiopure form.

The synthetic plan was centered on the condensation between *S*-2-pyridylthio 5-(4-methoxyphenoxy)pentanoate **4** and the *N*-4-methoxyphenylimine derived from *O*,*O*-cyclohexylidene D-glyceraldehyde, (*S*)-**5** (Scheme 1). Compound **4** was readily obtained in four steps from δ-valerolactone by methanolysis (MeOH, catalytic pTSA, reflux, 18 h, 100% yield based on the crude product), etherification (4-methoxyphenol, PPh_3, diisopropylazodicarboxylate, DCM, rt, 48 h, 90% yield), basic hydrolysis to the acid (1 M KOH, 1:1 MeOH/water, rt, 24 h, 100% yield based on the crude product), and thioester formation (2,2′-dipyridyl disulfide, PPh_3, DCM, rt, 15 h, 97.5% yield). The overall isolated yield for **4** was 87.8% from δ-valerolactone.

Reaction of the titanium enolate of this thioester ($TiCl_4$, TEA, DCM, −78 °C)[6] with imine (*S*)-**5** (from −78 °C to rt, 18 h) afforded a 1:1 mixture of β-lactams 3,4-trans-4,4′-syn **6ts** and 3,4-cis-4,4′-syn **6cs** in 55% yield (see Scheme 1 for numbering). The trans/cis stereochemical assignment was based on the value of the HC-3/HC-4 coupling constant values (J_{cis} = 5.0−6.0 Hz; J_{trans} = 2.0−

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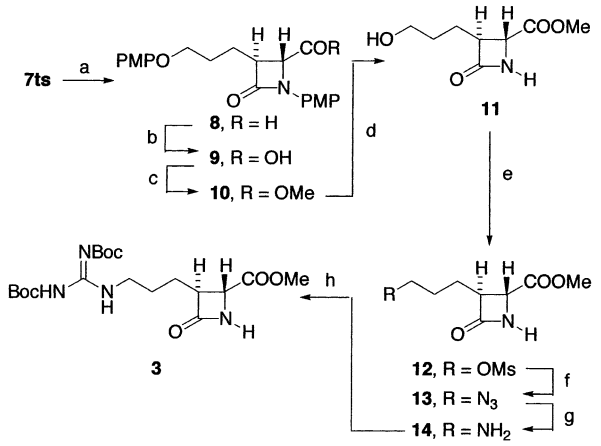
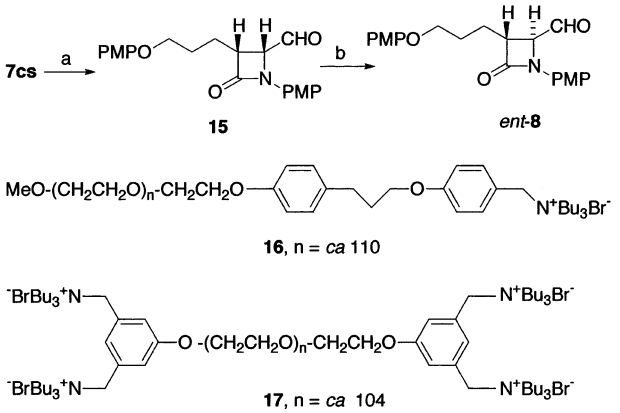
SCHEME 2. Synthesis of Precursor 3 from Diol 7ts



SCHEME 3. Epimerization of Aldehyde 15 to *ent*-8 in the Presence of Supported Catalysts 16 and 17



2.5 Hz); the complete syn stereoselectivity at C-4/C-4′, expected on the basis of our previous experience in analogous condensations involving a variety of thioesters and imine **5**,[6−10] was suggested by comparison of NMR chemical shift trends for diagnostic protons in similar products[7−10] and confirmed by the conversion of **6ts** to adduct **3** (see below). To obtain stereochemically pure compounds, β-lactams **6ts** and **6cs** were deprotected (1:1 TFA/water, from 0 °C to rt, 55 min) and readily separated by flash chromatography ($\Delta R_f \geq 0.2$ in 6:4 hexane/AcOEt) to afford diol **7ts** (39%) and **7cs** (39%).

The conversion of pure **7ts** into the target molecule **3** was performed as described in Scheme 2. Stepwise oxidation of the diol function afforded first aldehyde **8** ($NaIO_4$, 1:1 AcOEt/water, rt, 1 h, 90% yield) and then acid **9** ($KMnO_4$, 1:1 acetone/water, rt, 50 min), which was isolated as its methyl ester **10** (diazomethane, diethyl ether, 1.5 h, 85% overall yield from **8**). Alternatively, direct conversion of diol **7ts** to acid **9** was performed in 72% yield by reaction with $NaIO_4$ and $KMnO_4$ in 1:1 acetone/water at rt for 1 h. The 4-methoxyphenyl protecting groups were then simultaneously removed (CAN, 3:1 acetonitrile/water, from −45 to −15 °C, 45 min) to afford alcohol **11** in 66% yield. Standard manipulation of the hydroxy function, involving formation of mesylate **12** (MsCl, TEA, DCM, from 0 °C to rt, 15 h), synthesis of azide **13** (NaN_3, DMF, rt, 20 h), and hydrogenation (10% Pd/C, H_2, MeOH, rt, 5 h), afforded amine **14** in 62% overall yield from **11**. The introduction of the protected guanidino group was performed following a procedure recently developed by Goodman et al.[11] by reaction of **14** with *N*,*N*′-di-Boc-*N*″-trifylguanidine[12] and TEA (DCM, rt, 4 h) that afforded **3** (R = Boc) in 91% yield. The overall yield of stereoisomerically pure adduct **3** from thioester **4** and imine **5** was 6.1% after 10 steps requiring 6 chromatographic purifications.

As mentioned above, the thrombin inhibitor **2** has been described so far only in the racemic form and, to the best of our knowledge, no stereochemistry/activity relationship has been reported. Therefore, the possibility of obtaining both enantiomers of **3** was worth investigating. Among the precursors of β-lactam **3**, it was anticipated that the "useless" cis isomer **7cs** could provide an easy entry to the required compound. In this line, oxidation of **7cs** afforded aldehyde cis-**15** (95% yield, Scheme 3) featuring a stereocenter at C-4 that should be readily epimerized under basic conditions[13] to afford the more stable trans-configurated β-lactam *ent*-**8**. Unfortunately, neither the described procedure (40% aqueous dimethylamine, 5% benzyl tributylammonium bromide, benzene, rt, 18−48 h)[13] nor modification of solvent, reaction temperature, or reaction time produced appreciable epimerization in **15**, which was recovered in 30−75% yield. However, replacement of the phase-transfer catalyst with its poly(ethylene glycol)-supported analogue **16**[14] (10% of catalyst, DCM, rt, 18 h) improved the trans/cis *ent*-**8**/**15** ratio to 90:10 and the recovery yield to 94%. Eventually, the use of the poly(ethylene glycol)-supported tetrakis ammonium catalyst **17**[15] (2.5% catalyst, DCM, rt, 18 h) in the same process resulted in the isolation of the pure trans-configurated aldehyde *ent*-**8** in 95% yield. Remarkably, catalyst **17** was readily recovered by precipitation and filtration[15] and recycled for two additional epimerization reactions (*ent*-**8**/**15** ratio = 90:10, ≥90% yield). Conversion of aldehyde *ent*-**8** to amine *ent*-**14** was then accomplished in an overall yield very similar to that reported in Scheme 2.

In conclusion, both enantiomers of a β-lactam that is an advanced precursor of powerful inhibitors of thrombin and tryptase have been synthesized by a new approach based on the use of an inexpensive enantiomerically pure starting material. The stereodivergency of the synthesis is made possible by an improved procedure that allows complete epimerization of one of the azetidinone stereocenters by the use of a recyclable polymer-supported

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catalyst. Extension of this chemistry to the synthesis of other β-lactams endowed with protease inhibition properties is under investigation in our laboratories.

Experimental Section

General. ^{1}H NMR spectra were recorded at 300 MHz in chloroform-*d* ($CDCl_3$) unless otherwise stated and were referenced to tetramethylsilane (TMS) at 0.00 ppm; peak assignments were based on direct and long-range C−H correlations as well as on two-dimensional experiments. ^{13}C NMR spectra were recorded at 75 MHz and were referenced to 77.0 ppm in $CDCl_3$. Optical rotations were measured at the Na D-line in a 1 dm cell at 22 °C. IR spectra were recorded on thin film or as solutions in DCM. 5-(4-Methoxyphenoxy)pentanoic acid[16] and imine (*S*)-**5**[8] were known compounds.

***S*-2-Pyridylthio 5-(4-Methoxyphenoxy)pentanoate 4.** This compound was prepared according to a described procedure.[17] To a stirred solution of 5-(4-methoxyphenoxy)pentanoic acid (0.628 g, 2.8 mmol) in dry DCM (10 mL) were added 2-pyridyl disulfide (0.801 g, 3.64 mmol) and PPh_3 (1.027 g, 3.92 mmol), each in 5 mL of dry DCM. The yellow solution was stirred for 15 h at rt. The reaction was quenched by the addition of water (10 mL). The organic phase was separated, and the aqueous phase was extracted three times with DCM. The combined organic phases were dried over sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography with a 1:1 hexane/EtOAc mixture as the eluant to give the title compound in 97.5% yield (0.866 g) as a yellow thick oil that solidified upon standing in the freezer. IR (thin film): 1695 cm^{-1}. ^{1}H NMR: δ 8.62 (dd, 1H, *J* = 3.6, 2.0 Hz, H−C6 of pyridine), 7.74 (dt, 1H, *J* = 5.7, 2.0 Hz, H−C4 of pyridine), 7.62 (dd, 1H, *J* = 5.8, 1.0 Hz, H−C3 of pyridine), 7.29 (m, 1H, H−C5 of pyridine), 6.84 (s, 4H, C_6H_4), 3.95 (t, 2H, *J* = 6.0 Hz, OCH_2), 3.78 (s, 3H, OMe), 2.81 (t, 2H, *J* = 7.3 Hz, CH_2C=O), 1.90 (m, 4H, CH_2−CH_2). ^{13}C NMR: δ 196.4, 153.9, 153.2, 151.7, 150.5, 137.2, 130.2, 123.6, 115.6, 114.8, 68.0, 55.8, 43.8, 28.7, 22.3. Anal. Calcd for $C_{17}H_{19}NO_3S$: C, 64.33; H, 6.03; N, 4.41. Found: C, 64.08; H, 6.13; N, 4.33.

(3*S*,4*R*,4′*S*)- and (3*R*,4*R*,4′*S*)-1-(4-Methoxyphenyl)-3-[3-(4-methoxyphenoxy)prop-1-yl]-4-(1,4-dioxaspiro[4.5]dec-2-yl)azetidin-2-one 6. To a stirred solution of thioester **4** (0.100 g, 0.315 mmol) in dry DCM (2 mL) cooled at −78 °C and kept under nitrogen was added dropwise a 1 M DCM solution of titanium tetrachloride (0.347 mL, 0.347 mmol). After 5 min of stirring, TEA (0.052 mL, 0.378 mmol) was added dropwise and stirring was continued for 20 min. A DCM (2 mL) solution of imine **5** (0.043 g, 0.158 mmol) was then added, and the reaction mixture was allowed to slowly warm to room temperature. After a total reaction time of 18 h, the reaction was quenched by addition of a saturated aqueous solution of sodium bicarbonate (5 mL). The resulting mixture was filtered through a Celite cake; the organic phase was separated, and the aqueous phase was extracted with DCM (2 × 10 mL). The combined organic phases were concentrated under vacuum, and the residue was dissolved in THF (5 mL) and treated with 5 mL of a 1 M aqueous solution of KOH (2 mL) to hydrolyze the unreacted thioster. After 1 h stirring at room temperature, EtOAc (5 mL) was added and the organic phase was separated, washed with water, dried over sodium sulfate, filtered, and concentrated under vacuum. ^{1}H NMR analysis of the crude reaction mixture revealed the presence of a 1:1 mixture of diastereoisomers. The mixture was purified by flash chromatography with a 6:4 hexane/EtOAc mixture as the eluant to afford the title compounds (0.083 g) in 55% yield as a thick pale yellow oil. IR (thin film): 1742, 1510, 1231 cm^{-1}. **Compound 6cs.** ^{1}H NMR: δ 7.65 (B part of an AB system, 2H, *J* = 9.0 Hz, H *ortho* to N in N−PMP), 6.86 (m, 6H, remaining aromatic protons), 4.36 (t, 1H, *J* = 6.0 Hz, H−C4′), 4.22 (dd, 1H, *J* = 6.7, 6.0 Hz, one H of CH−CH_2−O), 4.15 (dd, 1H, *J* = 6.0, 5.5 Hz, H−C4), 4.00 (m, 2H, Ar−O−CH_2), 3.82 (s, 3H, one of two MeO), 3.79 (s, 3H, one of two MeO), 3.72 (dd, 1H, *J* = 6.7, 6.0 Hz, one H of CH−CH_2−O), 3.40 (m, 1H, H−C3),1.33−2.00 (m, 14H, CH_2−CH_2 of the side chain at C-3 and cyclohexyl protons). ^{13}C NMR: δ 167.6, 156.3, 153.2, 153.1, 131.6, 120.2, 114.9, 114.8, 113.8, 110.8, 76.6, 67.9, 66.6, 58.9, 55.9, 55.6, 50.4, 36.6, 34.6, 27.8, 25.2, 24.1, 23.9, 22.7. **Compound 6ts.** ^{1}H NMR: δ 7.57 (B part of an AB system, 2H, *J* = 9.0 Hz, H *ortho* to N in N−PMP), 6.86 (m, 6H, remaining aromatic protons), 4.43 (t, 1H, *J* = 6.7 Hz, H−C4′), 4.08 (dd, 1H, *J* = 8.7, 6.5 Hz, one H of CH−CH_2−O), 4.00 (m, 2H, Ar−O−CH_2), 3.88 (dd, 1H, *J* = 6.5, 2.4 Hz, H−C4), 3.82 (s, 3H, one of two MeO), 3.78 (s, 3H, one of two MeO), 3.76 (dd, 1H, *J* = 6.7, 6.0 Hz, one H of CH−CH_2−O), 3.00 (m, 1H, H−C3),1.33−2.00 (m, 14H, CH_2−CH_2 of side chain at C-3 and cyclohexyl protons). ^{13}C NMR: δ 166.8, 156.3, 154.2, 154.0, 131.7, 119.3, 115.5, 115.4, 114.0, 111.3, 76.7, 68.0, 65.5, 60.3, 55.9, 55.6, 51.3, 36.7, 34.5, 27.8, 27.1, 25.2, 24.1, 23.9. Anal. Calcd for $C_{28}H_{35}NO_6$: C, 69.83; H, 7.33; N, 2.91. Found: C, 70.12; H, 7.44; N, 2.76.

(3*S*,4*R*,4′*S*)- and (3*R*,4*R*,4′*S*)-1-(4-Methoxyphenyl)-3-[3-(4-methoxyphenoxy)prop-1-yl]-4-(1,2-dihydroxyethyl)azetidin-2-one 7. To a stirred suspension of the diastereoisomeric mixture of compounds **6cs** and **6ts** (0.200 g, 0.415 mmol) in water (5 mL) cooled to 0 °C was slowly added TFA (5 mL). The resulting solution was allowed to warm to room temperature, and the reaction was monitored by TLC. After disappearance of the starting material (ca. 55 min), the reaction was quenched by the cautious addition of a saturated aqueous solution of potassium carbonate (10 mL). The aqueous phase was extracted with DCM (3 × 15 mL), dried over a mixture of potassium carbonate and sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography with hexane/EtOAc mixtures of increasing polarity (from 6:4 to 1:1 to 1:9) as the eluants. Diol **7cs**, mp 115−117 °C, was obtained in 39% yield (0.065 g). $[\alpha]_D$ 33.3 (*c* 0.3, DCM). IR (DCM): 3400, 1719, 1510 cm^{-1}. ^{1}H NMR: δ 7.40 (B part of an AB system, 2H, *J* = 9.0 Hz, H *ortho* to N in N−PMP), 6.89 (A part of an AB system, 2H, *J* = 9.0 Hz, H *meta* to N in N−PMP), 6.85 (s, 4H, O−*Ar*−O), 4.30 (t, 1H, *J* = 5.7 Hz, H−C4), 4.04 (m, 3H, C*H*-OH and CH_2−OAr), 3.80 (s, 3H, one MeO), 3.78 (s, 3H, one MeO), 3.67 (m, 2H, CH_2−OH), 3.42 (dt, 1H, *J* = 7.0, 5.7 Hz, H−C3), 2.40 (bs, 2H, OH), 1.92−2.25 (m, 4H, CH_2- CH_2). ^{13}C NMR: δ 167.5, 156.4, 153.7, 152.9, 131.1, 120.4, 115.3, 114.6, 114.0, 71.6, 67.9, 64.5, 55.6, 55.5, 55.3, 50.6, 27.7, 22.0. Diol **7ts**, a low-melting material, was obtained in 39% yield (0.065 g). $[\alpha]_D$ 29.8 (*c* 0.5, DCM). IR (DCM): 3430, 1720, 1510 cm^{-1}. ^{1}H NMR: δ 7.45 (B part of an AB system, 2H, *J* = 8.9 Hz, H *ortho* to N in N−PMP), 6.88 (A part of an AB system, 2H, *J* = 8.9 Hz, H *meta* to N in N−PMP), 6.85 (s, 4H, O−*Ar*−O), 4.03 (m, 1H, C*H*−OH), 3.97 (m, 3H, H−C4 and CH_2−OAr), 3.79 (s, 3H, one MeO), 3.77 (s, 3H, one MeO), 3.69 (m, 2H, CH_2−OH), 3.17 (dt, 1H, *J* = 6.7, 2.0 Hz, H−C3), 2.40 (bs, 2H, OH), 1.88−2.10 (m, 4H, CH_2−CH_2). ^{13}C NMR: δ 167.5, 156.4, 153.6, 152.9, 131.2, 119.7, 115.5, 114.7, 114.3, 73.4, 68.2, 63.3, 59.9, 55.7, 55.5, 50.6, 26.9, 25.7. Anal. Calcd for $C_{22}H_{27}NO_6$: C, 65.82; H, 6.78; N, 3.49. Found: C, 65.52; H, 6.54; N, 3.65.

(3*S*,4*R*)-1-(4-Methoxyphenyl)-3-[3-(4-methoxyphenoxy)-prop-1-yl]-4-formyl-azetidin-2-one 8. To a solution of compound **7ts** (0.020 g, 0.05 mmol) in a mixture of EtOAc (2 mL) and water (2 mL) cooled to 0 °C was added sodium metaperiodate (0.042 g, 0.2 mmol) in one portion. The reaction was monitored by TLC. After the mixture was stirred for 1.5 h, the phases were separated, and the aqueous phase was extracted with EtOAc (2 × 10 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated under vacuum to afford the crude product (0.017 g, 90% yield) as a low-melting material that was used without further purification. $[\alpha]_D$ 47.3 (*c* 0.9, DCM). IR (DCM): 1740, 1690, 1510 cm^{-1}. ^{1}H NMR: δ 9.75 (d, 1H, *J* = 4.3 Hz, CHO), 7.26 (B part of an AB system, 2H, *J* = 9.0 Hz, H *ortho* to N in N−PMP), 6.88 (A part of an AB system, 2H, *J* = 9.0 Hz, H *meta* to N in N−PMP), 6.83 (s, 4H, O−*Ar*−O), 4.17 (dd, 1H, *J* = 4.3, 2.5 Hz, H−C4), 3.96 (t,

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2H, J = 6.8 Hz, CH_2−OAr), 3.79 (s, 3H, one MeO), 3.65 (s, 3H, one MeO), 3.43 (m, 1H, H−C3), 1.83−2.08 (m, 4H, CH_2−CH_2). ^{13}C NMR: δ 198.5, 165.1, 156.6, 154.0, 152.9, 131.2, 117.6, 115.4, 114.7, 114.6, 70.5, 62.9, 55.7, 55.5, 52.7, 26.9, 25.2. Anal. Calcd for $C_{21}H_{23}NO_5$: C, 68.28; H, 6.28; N, 3.79. Found: C, 68.53; H, 6.47; N, 3.58.

(3*R*,4*R*)-1-(4-Methoxyphenyl)-3-[3-(4-methoxyphenoxy)-prop-1-yl]-4-formyl-azetidin-2-one 15 was similarly obtained in 95% yield from **7cs**. Mp: 98−100 °C. $[\alpha]_D$ 92.2 (*c* 1.3, DCM). IR (DCM): 1731, 1691, 1509 cm^{-1}. ^{1}H NMR: δ 9.88 (d, 1H, J = 3.4 Hz, CHO), 7.25 (B part of an AB system, 2H, J = 9.0 Hz, H *ortho* to N in N−PMP), 6.87 (A part of an AB system, 2H, J = 9.0 Hz, H *meta* to N in N−PMP), 6.84 (s, 4H, O−*Ar*−O), 4.52 (dd, 1H, J = 6.0, 3.4 Hz, H−C4), 3.96 (t, 2H, J = 6.8 Hz, CH_2−OAr), 3.80 (s, 3H, one MeO), 3.78 (s, 3H, one MeO), 3.72 (m, 1H, J = 6.0, 4.0 Hz, H−C3), 1.83−2.10 (m, 4H, CH_2−CH_2). ^{13}C NMR: δ 199.9, 165.6, 156.6, 153.0, 152.9, 131.1, 117.3, 115.4, 114.7, 114.6, 67.5, 60.3, 55.7, 55.5, 53.6, 27.4, 22.6.

(3*S*,4*R*)-1-(4-Methoxyphenyl)-3-[3-(4-methoxyphenoxy)-prop-1-yl]-4-carbomethoxy-azetidin-2-one 10: Aldehyde Oxidation. To a stirred solution of aldehyde **8** (0.097 g, 0.242 mmol) in acetone (2 mL) was added potassium permanganate (0.020 g, 0.126 mmol) in water (2 mL). The reaction was monitored by TLC analysis, which showed complete disappearance of the starting material after 50 min. The reaction was quenched by the addition of solid sodium sulfite. The resulting slurry was filtered through a Celite cake that was repeatedly washed with 5 mL portions of DCM, chloroform, and EtOAc. The resulting mixture was concentrated as such under vacuum, and the residue was washed several times with DCM (5 mL portions). The combined organic phases were dried over sodium sulfate, filtered, and concentrated under vacuum to afford the crude acid **9** as a low-melting solid. This was used as such for the conversion to the ester. **Esterification.** To a stirred suspension of the acid in diethyl ether (5 mL) was added dropwise an ethereal solution of diazomethane. After the mixture was stirred for 1.5 h, the excess diazomethane was decomposed by addition of a few drops of acetic acid. The residue obtained by evaporation of the solvent under vacuum was purified by flash chromatography with a 1:1 hexane/EtOAc mixture as the eluant to afford the product (0.082 g) as a thick oil in 85% overall yield from the aldehyde. $[\alpha]_D$ 33.6 (*c* 0.7, DCM). IR (DCM): 1749, 1740, 1509 cm^{-1}. ^{1}H NMR: δ 7.27 (B part of an AB system, 2H, J = 9.0 Hz, H *ortho* to N in N−PMP), 6.88 (A part of an AB system, 2H, J = 9.0 Hz, H *meta* to N in N−PMP), 6.85 (s, 4H, O−*Ar*−O), 4.23 (d, 1H, J = 2.4 Hz, H−C4), 3.99 (t, 2H, J = 5.6 Hz, CH_2−OAr), 3.80 (s, 6H, two MeO), 3.78 (s, 3H, one MeO), 3.43 (m, 1H, H−C3), 1.88−2.18 (m, 4H, CH_2−CH_2).^{13}C NMR: δ 170.4, 165.3, 156.4, 153.9, 153.0, 131.0, 117.8, 115.4, 114.7, 114.4, 67.7, 66.9, 55.7, 55.5, 55.3, 52.7, 26.9, 25.5. Anal. Calcd for $C_{22}H_{25}NO_6$: C, 66.15; H, 6.31; N, 3.51. Found: C, 66.44; H, 6.57; N, 3.68.

(3*S*,4*R*)-3-Hydroxyprop-1-yl-4-carbomethoxy-azetidin-2-one 11. To a stirred solution of ester **10** (0.050 g, 0.125 mmol) in acetonitrile (6 mL) cooled to −40 °C was added a solution of CAN (0.548 g, 1 mmol) in water (2 mL). The reaction temperature is allowed to slowly rise to −15 °C. After the mixture was stirred for 45 min, the reaction was quenched by the addition of saturated aqueous solutions of sodium sulfite and sodium bicarbonate. The resulting slurry, warmed to room temperature, was filtered through a Celite cake, and the filter was washed with EtOAc (25 mL). The organic phase was separated, and the aqueous phase was extracted with AcOEt (2 × 10 mL) and DCM (2 × 10 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography with EtOAc as the eluant to afford the product (0.016 g) in 66% yield. Mp: 98−100 °C. $[\alpha]_D$ −13.5 (*c* 0.4, DCM). IR (DCM): 3450,1746, 1741 cm^{-1}. ^{1}H NMR: δ 6.10 (bs, 1H, NH), 3.83 (d, 1H, J = 2.5 Hz, H−C4), 3.70 (s, 3H, OMe), 3.61 (t, 2H, J = 6.0 Hz, CH_2−OH), 3.24 (m, 1H, H−C3), 1.65−2.00 (m, 4H, CH_2−CH_2).^{13}C NMR: δ 171.4, 166.1, 60.3, 58.1, 54.2, 51.6, 27.9, 24.4. Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48. Found: C, 51.55; H, 6.87; N, 7.61.

(3*S*,4*R*)-3-Aminoprop-1-yl-4-carbomethoxy-azetidin-2-one 14: Synthesis of Mesylate 12. To a stirred solution of alcohol **11** (0.038 g, 0.2 mmol) and TEA (0.033 mL, 0.24 mmol) in DCM (2 mL) cooled at 0 °C was added mesyl chloride (0.017 mL, 0.22 mmol) in DCM (2 mL). Stirring was continued for 6 h at 0 °C and then for 12 h at rt. The reaction mixture was then transferred to a separatory funnel and washed with cold water (5 mL). The aqueous phase was extracted with DCM (2 × 5 mL), and the combined organic phases were dried over sodium sulfate, filtered, and concentrated under vacuum. ^{1}H NMR analysis of the crude product was consistent with the formation of mesylate **12**, which was used as such. **Synthesis of Azide 13.** To a stirred solution of the crude mesylate in DMF (1 mL) was added sodium azide (0.026 g, 0.4 mmol) in one portion. The mixture was stirred 24 h at rt, and water (1 mL) was added. This mixture was then transferred to a distillation apparatus with DCM (5 mL), and the organic solvents and water were removed by evaporation under vacuum to afford a pale yellow residue. ^{1}H NMR analysis of the crude product was consistent with the formation of azide **13**, which was used as such. **Hydrogenation.** A suspension of the crude azide and 10% Pd/C (0.010 g) in EtOH (5 mL) was stirred under a hydrogen atmosphere for 6 h at rt. The catalyst was removed by filtration on Celite, and the filtrate was concentrated under vacuum. The resulting residue was dissolved in AcOEt and purified by filtration on a short plug of silica gel with a 98:2 AcOEt/MeOH mixture as the eluant. The product (0.023 g) was obtained in 62% overall yield from alcohol **11**. Mp: 64−66 °C. $[\alpha]_D$ −12.1 (*c* 0.3, DCM). IR (DCM): 3350,1745, 1740 cm^{-1}. ^{1}H NMR: δ 6.00 (bs, 1H, NH), 3.83 (d, 1H, J = 2.5 Hz, H−C4), 3.78 (s, 3H, OMe), 3.38 (m, 2H, CH_2−NH_2), 3.29 (m, 1H, H−C3), 1.72−1.93 (m, 4H, CH_2−CH_2). ^{13}C NMR: δ 173.1, 165.4, 55.7, 52.2, 50.6, 39.3, 26.8, 25.1. Anal. Calcd for $C_8H_{14}N_2O_3$: C, 51.60; H, 7.58; N, 15.04. Found: C, 51.29; H, 7.75; N, 14.89.

(3*S*,4*R*)-3-(*N*′,*N*″-Di-*tert*-butyloxycarbonylguanidino)-prop-1-yl-4-carbomethoxy-azetidin-2-one 3. To a stirred solution of amine **14** (0.016 g, 0.086 mmol) and TEA (0.015 mL, 0.107 mmol) in DCM (2 mL) was added *N*,*N*′-di-Boc-*N*″-trifylguanidine[12] (0.038 g, 0.1 mmol) in DCM (1 mL). The mixture was stirred at room temperature for 4 h, and the reaction was quenched by the addition of a saturated aqueous solution of sodium bicarbonate (2 mL). The organic phase was eparated, and the aqueous phase was extracted with DCM (3 × 5 mL). The combined organic phases were dried over sodium sulfate, filtered, and concentrated under vacuum. The residue was purified by flash chromatography with EtOAc as the eluant to afford the product (0.034 g) in 91% yield. Mp: 135−137 °C. $[\alpha]_D$ −6.5 (*c* 0.1, DCM). IR (DCM): 3340,1755, 1736, 1660 cm^{-1}. ^{1}H NMR: δ 11.50 (s, 1H, BocN*H*), 8.37 (t, 1H, J = 5.0 Hz, N*H*−CH$_2$), 6.17 (bs, 1H, lactam NH), 3.88 (d, 1H, J = 2.5 Hz, H−C4), 3.77 (s, 3H, OMe), 3.58 (m, 2H, CH_2−NH), 3.33 (m, 1H, H−C3), 1.82−2.05 (m, 4H, CH_2−CH_2). ^{13}C NMR: δ 174.2, 168.7, 166.6, 166.1, 156.3, 79.3, 78.1, 55.0, 51.1, 50.5, 42.7, 28.2, 27.8, 26.0, 25.1. Anal. Calcd for $C_{19}H_{32}N_4O_7$: C, 53.26; H, 7.53; N, 13.08. Found: C, 53.51; H, 7.69; N, 12.86.

Epimerization of (3*R*,4*R*)-15 to (3*R*,4*S*)-8. To a stirred solution of aldehyde **15** (0.037 g, 0.1 mmol) and dimethylamine (0.4 mL of a 40% solution in water) in DCM (2 mL) was added catalyst **17** (0.014 g, 0.0025 mmol). After the mixture was stirred for 48 h at room temperature, the solvent was evaporated under vacuum, and to the residue was added diethyl ether (10 mL). The catalyst was filtered off, and the solvent was evaporated to afford the pure trans title aldehyde in 95% yield (0.035 g). The product had $[\alpha]_D$ −48.3 (*c* 0.2, DCM) and was identical by ^{1}H NMR to (3*S*,4*R*)-**8**.

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Supporting Information Available: Spectra and experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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