Synthesis of 2-Amino-5-hydroxycaprolactam Derivatives Mediated by *E*-Selective Olefination and Asymmetric Oxidation of the Enol Ether

Hong Li,[a,c] Yingxue Liu,[a] Qijun Liu,[a,c] Wenhui Hu,[a] Guo-Chun Zhou*[a,b]

[a] Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou 510530, P. R. of China

[b] College of Biotechnology and Pharmaceutical Engineering and College of Pharmaceutical Sciences, Nanjing University of Technology, Nanjing 210009, P. R. of China
Fax +86(20)32015351; E-mail: allspringzhou@yahoo.com

[c] Graduate School of Chinese Academy of Sciences, Beijing 100039, P. R. of China

Received 5 August 2010; revised 6 September 2010

Abstract: The asymmetric synthesis of 2-amino-5-hydroxycaprolactam derivatives is essential for exploring the antitumor properties of ester-bearing bengamides. In this study, chiral caprolactam isomers were achieved on the basis of highly *E*-selective Wittig olefination, asymmetric oxidations of the *E*-enol ethers, reductive amination of the aldehyde derivatives, cyclization of the 5-hydroxylysine analogues or/and deprotection.

Key words: caprolactam, *E*-selective olefination, asymmetric oxidation, enol ether, reductive amination

Bengamides (**1**, Figure 1) are classified as fused ketide–amino acid derivatives, which were first isolated by Crews and co-workers from *Jaspis* sponges.[1] It was demonstrated that natural and synthetic bengamides target type 1 and type 2 methionine aminopeptidases (MetAP1 and MetAP2)[2] and act as potent cancer cell growth inhibitors[3] and anti-angiogenesis agents.[2,4] The seven-membered caprolactam rings of (2*S*)-aminocaprolactam, (2*S*,5*S*)-**2** and (2*S*,5*R*)-**2** (Figure 1) are the basic building scaffolds of bengamides. (2*S*)-Aminocaprolactam and (2*S*,5*S*)-**2**, being the cyclized products of lysine and the unnatural amino acid (2*S*,5*S*)-5-hydroxylysine, respectively, have been found in natural bengamides, while (2*S*,5*R*)-**2**, which is a derivative of the natural amino acid (2*S*,5*R*)-5-hydroxylysine, has been used for synthetic bengamides. Bengamides with a lipophilic ester substituent at the 5-position of the caprolactam (Figure 1, R = natural linear acyloxy and R = synthetic cyclic acyloxy) are generally more potent than their non-ester-bearing counterparts (Figure 1, R = H) in inhibiting cancer cell growth[4,5] and HUVEC proliferation.[5] Therefore, the asymmetric synthesis of **2** and its analogues is essential for exploring the antitumor properties of ester-bearing bengamide analogues. 5-Hydroxycaprolactams of **2** can be cyclized from their corresponding 5-hydroxylysines,[5] however, a continued supply of 5-hydroxylysine from natural sources or commercial agents was not a practical option since (2*S*,5*R*)-5-hydroxylysine is limited in Nature and (2*S*,5*S*)-5-hydroxylysine is also difficult to obtain. The development of an efficient synthetic approach capable of producing large quantities of **2** and its analogues that meets the need for diverse ester-bearing bengamides was thus required. Although there are some reports on the synthesis of 5-hydroxylysine[6] and 5-hydroxycaprolactam **2**,[7] we report herein an alternative asymmetric synthesis of **2** and its analogues.

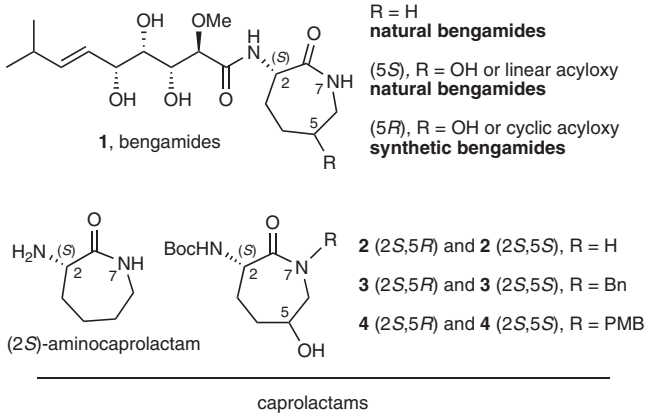
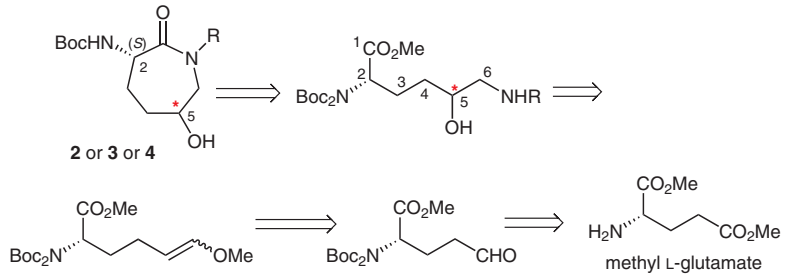


Figure 1 Structures of bengamides and caprolactams

As shown in Scheme 1, we envisioned a new strategy for the asymmetric synthesis of **2**, **3** and **4** that relied on olefination and then asymmetric epoxidation or dihydroxylation of an intermediate enol ether. We wanted to prepare the *E* or *Z* form of the 1,2-disubstituted olefin of the enol ether from dimethyl L-glutamate, and then introduce the stereogenic center (red asterisk) by means of either Jacobsen epoxidation[8] of the *Z*-olefin, or Sharpless asymmetric dihydroxylation[9] and Shi asymmetric epoxidation[10] of the *E*-olefin. Finally, the α-hydroxy aldehyde intermediates could be transformed into the corresponding amine by reductive amination to stereoselectively construct the (5*S*) or (5*R*)-hydroxylysine analogues, which can be cyclized into **2**, **3** or **4**, respectively.

Starting from commercially available dimethyl L-glutamate, bis-*tert*-butyl carbamate protection of the α-amine of dimethyl L-glutamate was conducted and then the δ-carboxylic ester was selectively reduced to aldehyde **5** with diisobutylaluminum hydride (DIBAL-H) through a modified literature procedure.[11] Although the use of (methoxymethyl)triphenylphosphonium chloride to construct enol ether olefins is common, in most circumstanc-

SYNTHESIS 2010, No. 23, pp 4068–4074
Advanced online publication: 30.09.2010
DOI: 10.1055/s-0030-1258275; Art ID: F13710SS



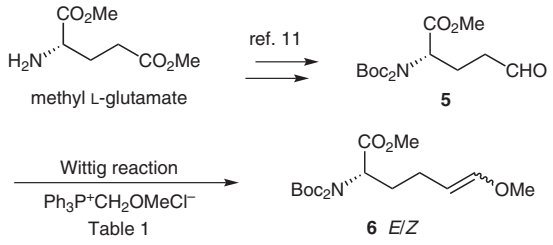
Scheme 1 Synthetic strategy for **2**, **3** and **4** (red asterisk indicates chiral center) from methyl L-glutamate

Table 1 Wittig Reaction of Aldehyde **5** with (Methoxymethyl)triphenylphosphonium Chloride (Scheme 2)

Base	Additive	Result[a]	Solvent				
	–		THF	Et_2O	Dioxane	DME	Toluene
n-BuLi	–	Yield (%)	33	30	50	45	<10.0
		E/*Z*	80:20	76:24	77:23	87:13	78:12
i-BuLi	–	Yield (%)	31	19	18	70	31
		E/*Z*	86:14	83:17	76:24	84:16	62:38
LiHMDS	–	Yield (%)	31	11	28	70	19
		E/*Z*	92:8	92:8	77:23	84:16	89:11
NaHMDS	–	Yield (%)	82	63	56	74	82
		E/*Z*	89:11	83:17	77:23	87:13	89:11
	15-crown-5	Yield (%)	77	68	28	77	50
		E/*Z*	86:14	91:9	74:26	88:12	88:12
KHMDS	–	Yield (%)	19	79	trace	69	72
		E/*Z*	87:13	89:11	NA	88:12	90:10
	18-crown-6	Yield (%)	32	70	trace	82	23
		E/*Z*	89:11	89:11	NA	88:12	88:12

[a] The ratios of *E*/*Z* were determined by ^{1}H NMR spectroscopic analysis.

es these enol ether olefins have simply been used for elongation of the aldehyde molecule without considering the *E*/*Z* geometry of olefins. Moreover, from the limited number of reports available, the *E*/*Z* ratio of the enol ether olefin formed from the Wittig reaction is not consistent. For example, aromatic aldehydes with similar structural properties produced quite different *E*/*Z* ratios (from 52:48[12] and 56:44[13] to 95:5[12]) using the same base (PhLi) in tetrahydrofuran to generate the ylide; meanwhile, alkyl aldehydes generated the *Z*-form as the predominant isomer in some cases,[14,15] but with only a slight excess in others,[16] when the ylide was generated with lithium hexamethyldisilazide (LiHMDS)[14,16] or butyllithium[15] in tetrahydrofuran. Since substrate **5** is structurally similar to the those used in the last references,[14–16] we initially expected *Z* selectivity for olefin **6** in the Wittig reaction. Undaunted, we explored the Wittig olefination of **5** with (methoxymethyl)triphenylphosphonium chloride by employing potassium hexamethyldisilazide (KHMDS) as a base to generate the ylide in toluene (Scheme 2). The reaction furnished an *E*/*Z* mixture, however, the *E*-isomer was produced as the predominant methyl enol ether product **6** [*E*/*Z* ratio 91:9, determined by ^{1}H NMR integration of enol proton signals for the *E*-isomer (δ = 6.30 ppm, J ~ 12.6 Hz) and for *Z*-isomer (δ = 5.88 ppm, J ~ 6.4 Hz)].



Scheme 2 Preparation of enol ether olefin **6**

We further investigated the Wittig reaction of **5** with a range of common bases, solvents and additives (Scheme 2). The reaction yields and *E*/*Z* ratios of olefin **6** are shown in Table 1. It was found that NaHMDS and KHMDS were both suitable bases that facilitated the Wittig reaction to produce acceptable yields (~80%) and good *E*/*Z* ratios (~91:9); toluene was found to be a good solvent for both bases, as was 1,2-dimethoxyethane. Dioxane was not a good solvent and *n*-butyllithium and isobutyllithium were not suitable bases in that they generally gave lower yields of **6** and poor geometrical selectiv-

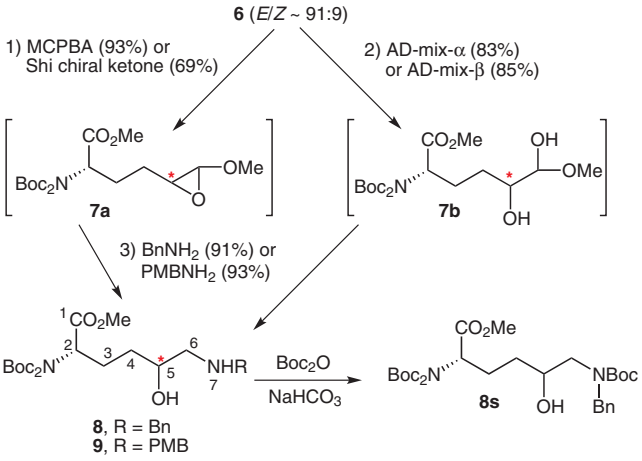
Table 2 Conversion of **6** into **2**, **3** and **4** by Oxidation and Reductive Amination (Scheme 3), Cyclization and Deprotection (Scheme 4)

Oxidant			MCPBA	AD-mix-α	AD-mix-β	Shi reagent
6 to **2** and **3** *via* **8** and **10**	**2**	(2*S*,5*R*)/(2*S*,5*S*)[a]	50:50	18:82	94:6	82:18
		Yield (%)[b]/isomer	NA[d]	12/(2*S*,5*S*)	18/(2*S*,5*R*)	9/(2*S*,5*R*)
	3	(2*S*,5*R*)/(2*S*,5*S*)	57:43	20:80	395:5	79:21
	8	(2*S*,5*R*)/(2*S*,5*S*)	50:50	15:85	395:5	79:21
	8s	(2*S*,5*R*)/(2*S*,5*S*)[c]	50:50	20:80	92:8	80:20
6 to **2** *via* **9**, **11** and **4**	**2**	(2*S*,5*R*)/(2*S*,5*S*)[a]	49:51	15:85	94:6	80:20
		Yield (%)[b]/isomer	NA[d]	18/(2*S*,5*S*)	29/(2*S*,5*R*)	14/(2*S*,5*R*)
	4		50:50	20:80	395:5	80:20
	9		50:50	19:81	395:5	81:19

[a] Before recrystallization.
[b] Total yield based on **6** after the 1st batch recrystallization.
[c] HPLC analysis data are available (see Supporting Information).
[d] Not applicable.

ity for the olefin. Moreover, adding 18-crown-6 (for K^+) or 15-crown-5 (for Na^+) did not significantly affect either the reaction yields or *E*/*Z* ratios. Thus, we chose either NaHMDS or KHMDS as a base in toluene to generate the ylide for the Wittig olefination.

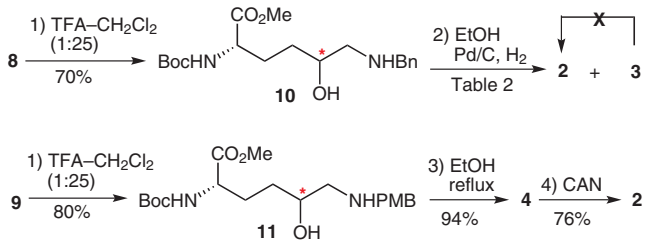
Since the *E*-configuration of the disubstituted enol ether **6** (*E*/*Z*, ~91:9) was ideal for both Sharpless asymmetric dihydroxylation[9] and Shi asymmetric epoxidation,[10] the C-5 diastereomeric excess of the possible intermediate of **7a** or **7b**, respectively, could be achieved by applying the Shi chiral reagent, AD-mix-α or AD-mix-β (Scheme 3). However, because intermediates **7a** and **7b** were not stable, they were directly transformed into the corresponding amine **8** or **9** by reductive amination with either benzylamine or 4-methoxybenzylamine by treatment with sodium cyanoborohydride. Two diastereomeric products of **8** could be distinguished by ^{1}H NMR spectroscopic analysis, in which characteristic proton resonances of the (2*S*,5*R*)- and the (2*S*,5*S*)-isomers could be identified at δ = ~1.92, ~2.30 ppm and at δ ~ 2.00, ~ 2.21 ppm, respectively. Similarly, the corresponding ^{1}H NMR chemical shifts of the (2*S*,5*R*)- and (2*S*,5*S*)-isomer of **9** were differentiated at δ = ~1.88, ~2.27 ppm and at δ = ~1.98, ~2.18 ppm. The results summarized in Table 2 indicated that application of *m*-chloroperoxybenzoic acid produced **8** or **9** in almost 50:50 diastereomeric ratios of (2*S*,5*R*)/(2*S*,2*S*); in contrast, the (2*S*,5*S*)-isomer of **8** or **9** formed as the predominant product upon use of the AD-mix-α, while the (2*S*,5*R*)-isomer of **8** or **9** was formed as the major product by application of either AD-mix-β or the Shi chiral reagent. To verify the ^{1}H NMR spectroscopic determinations of the stereoselectivity of these oxidations, the two isomers of **8** were converted into the corresponding (2*S*,5*R*)- and (2*S*,5*S*)-7-*N*-Boc carbamoylated products **8s**, which were analyzed by reverse-phase HPLC; the results were used to determine the diastereomer ratios of (2*S*,5*R*)/(2*S*,5*S*) (see Supporting Information). To our delight, HPLC analysis data (Table 2) revealed that the diastereomeric ratios of (2*S*,5*R*)/(2*S*,5*S*) were 50:50 by *m*-chloroperoxybenzoic acid, 20:80 by AD-mix-α, 92:8 by AD-mix-β, and 80:20 by use of Shi's chiral reagent, which were very close to the values determined by ^{1}H NMR spectroscopic analysis.



Scheme 3 Asymmetric epoxidation or dihydroxylation of *E*-rich disubstituted enol ether **6** and reductive amination of aldehyde intermediates **7** (red asterisk indicates chiral center)

We found (data not shown) that bis-Boc protection of the α-amine hampered the cyclization and that, although **8** and **9** can be hydrogenated, the resulting products with free primary amines at the 7-position were difficult to purify and gave low yields. Removal of one protected carbamate was therefore conducted by treatment with trifluoroacetic acid in dichloromethane (1:25; Scheme 4). However, the mono-Boc protected intermediates **10** and **11** were too unstable to isolate due to their tendency to cyclize to **3** and **4**, respectively, at room temperature. Upon heating to reflux temperature in ethanol for 48 hours, **10** and **11** both completely cyclized to **3** or **4**, respectively, in high yield. Furthermore, hydrogenation of **10** in refluxing

ethanol in the presence of Pd/C/H_2 or $Pd(OH)_2/H_2$ afforded a mixture of **2** (~60%) and **3** (~40%), which were easily separated by silica gel chromatography, while hydrogenation of **11** under the same conditions produced **4** as the dominant product together with a very low yield of **2** (generally less than 10%). Neither **3** nor **4** underwent deprotection of the Bn or PMB group, respectively, upon treatment with Pd/C/H_2 or $Pd(OH)_2/H_2$, however, the PMB group of **4** was successfully removed by treatment with cerium(IV) ammonium nitrate[17] to afford **2**.



Scheme 4 Synthesis of **2**, **3** and **4** (red asterisk indicates chiral center)

The diastereomeric ratios of compounds **2**, **3** and **4** were determined by ^{1}H NMR spectroscopic analysis and are listed in Table 2. The (2*S*,5*R*)- and (2*S*,5*S*)-isomers of **2** were assigned according to the proton signals identified at δ = 4.60 (m, 5-H) and δ = 7.40 (s, 7-NH) ppm or at δ = 4.92 (m, 5-H) and 7.76 (s, 7-NH) ppm; the (2*S*,5*R*)-and (2*S*,5*S*)-isomers of **3** were characterized by the respective signals at δ = 4.35 (m, 5-H), 4.21 (d, *J* = 14.4 Hz, 7-N-CH_2-Ph) and 5.21 (d, *J* = 14.4 Hz, 7-N-CH_2-Ph) ppm, and at δ = 4.44 (m, 5-*H*), 4.51 (d, *J* = 14.4 Hz, 7-N-CH_2-Ph) and 4.78 (d, *J* = 14.4 Hz, 7-N-CH_2-Ph) ppm; and the (2*S*,5*R*)- and (2*S*,5*S*)-isomers of **4** were determined on the basis of signals at δ = 4.32 (m, 5-H), 4.22 (d, *J* = 14.4 Hz, 7-N-CH_2-Ar-*p*-OMe) and 5.04 (d, *J* = 14.4 Hz, 7-N-CH_2-Ph-*p*-OMe) ppm, and at δ = 4.36 (m, 5-*H*), 4.42 (d, *J* = 14.4 Hz, 7-N-CH_2-Ar-*p*-OMe) and 4.61 (d, *J* = 14.4 Hz, 7-N-CH_2-Ar-*p*-OMe) ppm. It is worth mentioning that the diastereomeric ratio of compounds **2**, **3** and **4** were consistent with those of compounds **8** and **9**, respectively, and that the diastereomeric ratios of the (2*S*,5*R*)- and (2*S*,5*S*)-isomers of **2** were the same as those of the corresponding isomers of **4** upon CAN-mediated deprotection.

The diastereomeric purity of the (2*S*,5*R*)- and (2*S*,5*S*)-isomers of **2** reached more than 95% after recrystalization[7b] (MeOH–EtOAc, ~1:1) of the products from either the AD-mix-β dihydroxylation, Shi asymmetric epoxidation or from the AD-mix-α-mediated dihydroxylation, and the ^{1}H- and ^{13}C NMR spectra of both isomers were identical to the corresponding reported data.[5,7b] The (2*S*,5*R*)-**3** or (2*S*,5*R*)-**4** isomers originating from AD-mix-β-mediated dihydroxylation were easily purified to more than 95% diastereomeric purity by silica gel column chromatography, however, only ~90% diastereomeric purity for the (2*S*,5*R*)- and (2*S*,5*S*)-**3** isomers, or the (2*S*,5*R*)- and (2*S*,5*S*)-**4** isomers could be achieved after Shi asymmetric epoxidation or AD-mix-α-mediated dihydroxylation, respectively, and only after repeated silica gel column chromatography.

As discussed above and shown in Table 2, the synthetic route to **2** from **6** via **4** could afford the pure (2*S*,5*R*)-**2** isomer in higher than 29% total yield from AD-mix-β-mediated dihydroxylation, and the pure (2*S*,5*S*)-**2** isomer in higher than 18% total yield from AD-mix-α-mediated dihydroxylation after one recrystallization; recrystallization yields could be significantly increased by recycling the mixtures. It is noted that our present synthesis is a general method to synthesize diverse N-substituted derivatives of caprolactam.

In summary, the asymmetric synthesis of different isomers of **2**, **3** and **4** was achieved on the basis of highly *E*-selective olefination, asymmetric oxidation of the enol ether, reductive amination of the aldehyde derivatives, cyclization of 5-hydroxylysine analogues or/and deprotection. We have found in the present work that both NaHMDS and KHMDS in toluene provide excellent conditions for *E*-selective olefination. The use of AD-mix-α was found the be the best choice for generating the (2*S*,5*S*)-isomers, and AD-mix-β was the best oxidant for the (2*S*,5*R*)-isomers. The synthetic route to **2** from **6** via **4** could be an ideal and practical method for achieving the synthesis of **2**. In addition, it would be possible to synthesize further derivatives of N-substituted caprolactams by using the present method.

^{1}H and ^{13}C NMR spectra were recorded with a Bruker AV-400 instrument operating at 400 and 100 MHz, respectively, in $CDCl_3$ unless otherwise mentioned. Coupling constants (*J*) are expressed in hertz (Hz). Chemical shifts (δ) for the NMR spectral data are reported in parts per million (ppm) relative to the solvent. Low- and high-resolution MS (ESI) were recorded with an Agilent 1200 HPLC-MSD mass spectrometer or Applied Biosystems Q-STAR Elite ESI-LC-MS/MS mass spectrometer. Scanned copies of the ^{1}H and ^{13}C NMR spectra and the HPLC analytical data are included in the Supporting Information.

(2*S*)-Methyl 2-[Bis(*tert*-butoxycarbonyl)amino]-6-methoxyhex-5-enoate (6) Using KHMDS in Toluene

(Methoxymethyl)triphenyl phosphonium chloride (8.47 g, 25.5 mmol) was suspended in anhydrous toluene (100 mL) under a nitrogen atmosphere and then cooled into 0 °C before the addition of KHMDS (48 mL, 0.5 M in toluene, 24.0 mmol). The reaction was stirred at 0 °C for 30 min, then cooled to –80 °C and a solution of (2*S*)-methyl-2-[bis(*tert*-butoxycarbonyl)amino]-5-oxopentanoate (**5**; 8.0 g, 23.2 mmol) in toluene (50 mL) was added dropwise. The reaction was stirred for 90 min at the same temperature and at r.t. for 60 min. Sat. NH_4Cl (50 mL) was added at –80 °C and the mixture was warmed to r.t. and extracted with EtOAc (3 × 150 mL), dried over anhydrous Na_2SO_4 and purified by column silica gel chromatography (petroleum ether–EtOAc, 98:2→95:5) to give **6**.

Yield: 6.2 g (72%); *E*/*Z* ratio 91:9.

Pure (*E*)-6

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.29 (d, *J* = 12.8 Hz, 1 H), 4.86 (m, 1 H), 4.67 (m, 1 H), 3.72 (s, 3 H), 3.49 (s, 3 H), 2.16 (m, 1 H), 1.98 (m, 3 H), 1.49 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.5, 152.1 (2C), 147.9, 101.4, 83.0 (2C), 57.4, 55.8, 52.1, 31.1, 28.0 (6C), 24.5.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{31}NNaO_7$: 396.1993; found: 396.2002.

(2*S*,5*R*)/(2*S*,5*S*)-Methyl 2-[Bis-(*tert*-butoxycarbonyl)amino]-5-hydroxy-6-oxopentanoate (7)

Preparation of 7a by Shi Epoxidation

To a solution of **6** (2.1 g, 5.7 mmol; *E*/*Z* ratio ~91:9) in dimethoxymethane (30 mL) and MeCN (15 mL), 30 mL of 0.05 M $Na_2B_2O_4$/0.4 mM EDTA, Bu_4NHSO_4 (77.0 mg, 0.23 mmol) and fructose-derived chiral ketone (436 mg, 1.7 mmol) were added and the reaction was stirred at 0 °C for 15 min. A solution of Oxone (3.85 g, 0.57 mmol) in aq EDTA (0.4 mM, 18 mL) and aq K_2CO_3 (3.9 g in 18 mL) were added dropwise over 3 h. The reaction was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (4 × 100 mL), washed with brine (2 × 100 mL), and dried over anhydrous Na_2SO_4. After filtration and concentrated, the residue was quickly purified by flash chromatography to afford **7a** (69% yield).

Preparation of 7b by AD-Mix Dihydroxylation

AD-mix-α or AD-mix-β (280 mg) was dissolved in *t*-BuOH (1.5 mL) and H_2O (1.5 mL) at r.t. and the solution was cooled to 0 °C. A solution of **6** (74.6 mg, 0.2 mmol; *E*/*Z* ratio ~91:9) in *t*-BuOH (1.0 mL) and H_2O (1.0 mL) was added and the reaction was stir at 0 °C until **6** was completely consumed (reaction monitored by TLC). Na_2SO_3 (300 mg) was added at 0 °C to r.t. for 30 min and the mixture was extracted with CH_2Cl_2 (4 × 15 mL). The combined organic phase was washed with brine (2 × 15 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude product was quickly purified by silica gel column chromatography (CH_2Cl_2–MeOH, 98:2) to give **7b** (83% yield for AD-mix-α dihydroxylation and 85% yield for AD-mix-β dihydroxylation).

Compounds **7a** and **7b** were not stable and were therefore used for further reductive amination as soon as possible after purification.

(2*S*,5*R*)/(2*S*,5*S*)-Methyl 6-(Benzylamino)-2-[bis(*tert*-butoxycarbonyl)amino]-5-hydroxyhexanoate (8)

To a solution of **7** (300 mg, 0.8 mmol) in MeOH (20 mL), benzylamine ($BnNH_2$; 0.8 mmol) or 4-methoxybenzylamine ($PMBNH_2$; 0.8 mmol) was added at 0 °C. The reaction was stirred at 0 °C for 10 min and then at r.t. for 3 h, $NaCNBH_3$ (75 mg, 1.2 mmol) was added to the reaction, which was then stirred for a further 2 h and then diluted with H_2O (10 mL). Extraction with CH_2Cl_2 (3 × 60 mL) and usual workup gave the crude product, which was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 98:2) to afford **8** (340 mg, 91%). The (2*S*,5*R*)- and (2*S*,5*S*)-isomers of **8** were characterized by ^{1}H NMR signals at δ = ~1.92, ~2.30 ppm and at δ = ~2.00, ~2.21 ppm, respectively.

Pure (2*S*,5*R*)-8 from AD-Mix-β Dihydroxylation

^{1}H NMR (400 MHz, $CDCl_3$ + D_2O): δ = 7.23–7.35 (m, 5 H), 4.86 (dd, *J* = 5.2, 9.2 Hz, 1 H), 3.78 (dd, *J* = 13.2, 22.0 Hz, 2 H), 3.70 (s, 3 H), 3.63 (m, 1 H), 2.74 (dd, *J* = 3.2, 12.0 Hz, 1 H), 2.48 (m, 1 H), 2.45 (m, 1 H), 1.90 (m, 1 H), 1.40–1.60 (m, 2 H), 1.49 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2, 151.1 (2C), 138.1, 128.6 (2C), 128.5 (2C), 127.5, 83.1 (2C), 68.8, 58.2, 54.1, 53.2, 52.1, 31.6, 28.0 (6C), 26.2.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{24}H_{38}N_2NaO_7$: 489.2571; found: 489.2570.

(2*S*,5*R*)/(2*S*,5*S*)-Methyl 6-[(*tert*-Butoxycarbonyl)benzylamino]-2-[bis(*tert*-butoxycarbonyl)amino]-5-hydroxyhexanoate (8s)

To a solution of **8** (30 mg, 0.064 mmol) in dioxane (4 mL), sat. $NaHCO_3$ (4 mL) and di-*tert*-butyl dicarbonate (70 mg, 0.32 mmol) were added. The reaction was stirred at r.t. for 3 h and then extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude product was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 98:2) to give **8s** (82%).

(2*S*,5*R*)/(2*S*,5*S*)-Methyl 6-(4-Methoxybenzylamino)-2-[bis(*tert*-butoxycarbonyl)amino]-5-hydroxyhexanoate (9)

Prepared as described for compound **8** to afford **9** (93% yield). The (2*S*,5*R*)- and (2*S*,5*S*)-isomers of **9** were differentiated at δ = ~1.88, ~2.27 ppm and at δ = ~1.98, ~2.18 ppm.

Pure (2*S*,5*R*)-9 from AD-Mix-β Dihydroxylation

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 4.82 (m, 1 H), 3.78–3.53 (m, 3 H), 3.75 (s, 3 H), 3.63 (s, 3 H), 2.67 (dd, *J* = 2.8, 12.0 Hz, 1 H), 2.44 (dd, *J* = 2.8, 12.0 Hz, 1 H), 2.27 (m, 1 H), 1.88 (m, 1 H), 1.59–1.34 (m, 4 H), 1.45 (s, 18 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 158.8, 152.2 (2C), 132.3, 129.2 (2C), 113.9 (2C), 83.0 (2C), 69.4, 58.3, 55.2, 54.6, 53.1, 51.7, 31.7, 27.9 (6C), 26.2.

HRMS (ESI): *m*/*z* [M + H]$^+$ calcd for $C_{25}H_{41}N_2O_8$: 497.2863; found: 497.2853.

(2*S*,5*R*)/(2*S*,5*S*)-Methyl 6-(Benzylamino)-2-[(*tert*-butoxycarbonyl)amino]-5-hydroxyhexanoate (10) and (2*S*,5*R*)/(2*S*,5*S*)-Methyl 6-(4-Methoxybenzylamino)-2-[(*tert*-butoxycarbonyl)amino]-5-hydroxyhexanoate (11)

Compound **8** or **9** (~1.0 mmol) was dissolved in CH_2Cl_2 (20 mL) and treated with TFA (0.8 mL) at r.t. for 15 min. The reaction was quenched with sat. aq $NaHCO_3$ (50 mL) and extracted with CH_2Cl_2 (3 × 60 mL). The combined organic phase was washed with brine (50 mL) and dried over anhydrous Na_2SO_4. After filtration and concentration, the crude product was quickly purified by silica gel column chromatography (CH_2Cl_2–MeOH, 98:2) to give **10** (70% yield) or **11** (80% yield). Compounds **10** and **11** were used for further reactions as soon as possible after purification.

(2*S*,5*R*)/(2*S*,5*S*)-2-[(*tert*-Butoxycarbonyl)amino]-5-hydroxy-*N*-benzylcaprolactam (3) and (2*S*,5*R*)/(2*S*,5*S*)-2-[(*tert*-Butoxycarbonyl)amino]-5-hydroxy-*N*-(4-methoxybenzyl)caprolactam (4)

Compound **10** or **11** (~1.0 mmol) was dissolved in EtOH (20 mL) and the solution was heated at reflux for 48 h. After evaporation, the residue was purified by silica gel chromatography (CH_2Cl_2–MeOH, 98:2) to give **3** (92% yield) or **4** (94% yield).

(2*S*,5*R*)-**3** and (2*S*,5*S*)-**3** were characterized by the respective signals at δ = 4.35 (m, 5-H), 4.21 (d, *J* = 14.4 Hz, 7-N-CH_2-Ph) and 5.21 (d, *J* = 14.4 Hz, 7-N-CH_2-Ph) ppm, or at δ = 4.44 (m, 5-H), 4.51 (d, *J* = 14.4 Hz, 7-N-CH_2-Ph) and 4.78 (d, *J* = 14.4 Hz, 7-N-CH_2-Ph) ppm.

(2*S*,5*R*)-3 from AD-Mix-β Dihydroxylation or from Shi Epoxidation

Purified by repeated silica gel chromatography (CH_2Cl_2–MeOH, 100:0→98:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.40 (m, 5 H), 6.06 (d, *J* = 5.6 Hz, 1 H), 5.21 (d, *J* = 14.4 Hz, 1 H), 4.35 (m,1 H), 4.21 (d, *J* = 14.4 Hz, 1 H), 3.99 (m, 1 H), 3.55 (d, *J* = 15.6 Hz, 1 H), 3.39 (m,1 H), 1.94 (m, 2 H), 1.83 (m, 1 H), 1.67 (m, 1 H), 1.61 (m, 1 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 173.0, 155.3, 137.0, 128.7 (2C), 128.1 (2C), 127.6, 79.6, 65.4, 53.1, 51.5, 34.9, 29.7, 29.4 (3C), 26.7.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{26}N_2NaO_4$: 357.1790; found: 357.1799.

(2*S*,5*S*)-3 from AD-Mix-α Dihydroxylation

Purified by repeated silica gel chromatography (CH_2Cl_2–MeOH, 100:0→98:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.20–7.50 (m, 5 H), 6.08 (d, *J* = 5.6 Hz, 1 H), 4.78 (d, *J* = 14.4 Hz, 1 H), 4.51 (d, *J* = 14.4 Hz, 1 H), 4.44 (m, 1 H), 3.50 (m, 1 H), 3.38 (m, 1 H), 3.25 (d, *J* = 14.4 Hz, 1 H), 2.16 (m, 2 H), 2.11 (m, 1 H), 1.80 (m, 1 H), 1.60 (m, 1 H), 1.47 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 155.2, 136.7, 128.8 (2C), 128.2 (2C), 127.8, 79.6, 68.5, 54.1, 53.0, 51.9, 36.9, 30.4, 28.4 (3C).

MS (ESI): *m*/*z* (%) = 707 (8) $[2M + K]^+$, 335 (90) $[M + H]^+$.

(2*S*,5*R*)-**4** or (2*S*,5*S*)-**4** isomers were determined on the basis of ^{1}H NMR signals at δ = 4.32 (m, 5-H), 4.22 (d, *J* = 14.4 Hz, 7-N-C*H*$_2$-Ar-*p*-OMe) and 5.04 (d, *J* = 14.4 Hz, 7-N-C*H*$_2$-Ar-*p*-OMe) ppm or at δ = 4.36 (m, 5-H), 4.42 (d, *J* = 14.4 Hz, 7-N-C*H*$_2$-Ar-*p*-OMe) and 4.61 (d, *J* = 14.4 Hz, 7-N-C*H*$_2$-Ar-*p*-OMe) ppm.

(2*S*,5*R*)-4 from AD-Mix-β Dihydroxylation or from Shi Epoxidation

Purified by repeated silica gel chromatography (CH_2Cl_2–MeOH, 100:0→98:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, *J* = 8.8 Hz, 2 H), 6.85 (d, *J* = 8.8 Hz, 2 H), 6.06 (m, 1 H), 5.04 (d, *J* = 14.4 Hz, 1 H), 4.32 (m, 1 H), 4.22 (d, *J* = 14.4 Hz, 1 H), 3.97 (m, 1 H), 3.79 (s, 3 H), 3.54 (d, *J* = 15.2 Hz, 1 H), 3.39 (dd, *J* = 5.2, 15.6 Hz, 1 H), 1.94 (m, 2 H), 1.82 (m, 1 H), 1.67 (m, 1 H), 1.54 (m, 1 H), 1.45 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 159.3, 155.2, 129.6 (2C), 129.2, 114.2 (2C), 79.5, 65.6, 55.2, 53.2, 52.5, 51.4, 34.9, 28.4 (3C), 26.7.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{19}H_{29}N_2O_5$: 365.2076; found: 365.2075.

(2*S*,5*S*)-4 from AD-Mix-α Dihydroxylation

Purified by repeated silica gel chromatography (CH_2Cl_2–MeOH, 100:0→98:2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.15 (d, *J* = 8.4 Hz, 2 H), 6.82 (d, *J* = 8.4 Hz, 2 H), 6.03 (m, 1 H), 4.61 (d, *J* = 14.4 Hz, 1 H), 4.42 (d, *J* = 14.4 Hz, 1 H), 4.36 (m, 1 H), 3.76 (s, 3 H), 3.44–3.19 (m, 3 H), ~2.60 (br s, 1 H), 2.09 (m, 2 H), 1.72 (m, 1 H), 1.56 (m, 1 H), 1.42 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 159.3, 155.2, 129.6 (2C), 128.9, 114.2 (2C), 79.5, 68.4, 55.2, 54.1, 53.0, 51.3, 36.8, 30.3, 28.4 (3C).

MS (ESI): *m*/*z* (%) = 751.3 (20) $[2M + Na]^+$, 629.3 (70) $[2M + H – Boc]^+$, 387.1 (75) $[M + Na]^+$, 465.1 (75) $[M + H]^+$, 265.1 (100) $[M + H – Boc]^+$.

(2*S*,5*R*)/(2*S*,5*S*)-2-[(*tert*-Butoxycarbonyl)amino]-5-hydroxycaprolactam (2) and (2*S*,5*R*)/(2*S*,5*S*)-2-[(*tert*-Butoxycarbonyl)amino]-5-hydroxy-*N*-benzylcaprolactam (3)

Compound **10** (300 mg, 0.82 mmol) was dissolved in EtOH (50 mL) and treated with 10% Pd/C (86 mg) under H_2. The reaction was heated at reflux overnight and then cooled to r.t., filtered and evaporated. The crude product was purified by gradient silica gel column chromatography (CH_2Cl_2–MeOH, 98:2→95:5) to afford **2** (110 mg, 55.0%) and **3** (100 mg, 37%). The (2*S*,5*R*)-**2** and (2*S*,5*S*)-**2** isomers were assigned according to the ^{1}H NMR signals at δ = 4.60 (m, 5-H) and 7.40 (s, 7-NH) ppm, or at δ = 4.92 (m, 5-H) and 7.76 (s, 7-NH) ppm. All the spectroscopic data for pure (2*S*,5*R*)-**2** and pure (2*S*,5*S*)-**2** were in accord with their corresponding reported data.[5,7b]

Pure (2*S*,5*R*)-2

Obtained from AD-mix-β dihydroxylation (33% total yield) or Shi epoxidation (20% total yield) after the 1st batch recrystallization (MeOH–EtOAc; recrystallization yield of the 1st batch: 60% and ~37%, respectively).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.40 (m, 1 H), 6.37 (d, *J* = 6.4 Hz, 1 H), 4.58 (d, *J* = 4.4 Hz, 1 H), 4.06 (m, 1 H), 3.72 (m, 1 H), 3.29 (m, 1 H, overlapped with DMSO), 3.01 (m, 1 H), 1.45–1.99 (m, 4 H), 1.38 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.3, 155.0, 78.4, 64.1, 52.9, 45.6, 34.7, 28.6 (3C), 25.4.

MS (ESI): *m*/*z* (%) = 389 (100) $[2M + H – Boc]^+$, 267 (50) $[M + Na]^+$.

Pure (2*S*,5*S*)-2

Obtained from AD-mix-α dihydroxylation (22% total yield) after the 1st batch recrystallization (MeOH–EtOAc; recrystallization yield of the 1st batch: ~40%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.73 (m, 1 H), 6.37 (d, *J* = 6.8 Hz, 1 H), 4.92 (d, *J* = 4.4 Hz, 1 H), 4.01 (m, 1 H), 3.25 (m, 1 H), 3.07 (m, 1 H), 2.97 (m, 1 H), 1.99 (m, 1 H), 1.75 (m, 1 H), 1.50 (m, 2 H), 1.37 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 174.5, 154.9, 78.7, 69.5, 53.2, 48.0, 36.9, 29.9, 28.7 (3C).

MS (ESI): *m*/*z* (%) = 389 (100) $[2M + H – Boc]^+$, 267 (15) $[M + Na]^+$, 245 (10) $[M + H]^+$.

2 from 4 by CAN

Compound **4** (100 mg, 0.275 mmol) was dissolved in MeCN–H_2O (9:1, 15 mL) and the solution was cooled to –10 °C. CAN (603 mg, 1.1 mmol) was added and the reaction was stirred at –10 °C for 30 min and then at 0 °C overnight. When the reaction was complete, sat. aq $NaHCO_3$ (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 20 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified by silica gel chromatography (MeOH–EtOAc, 98:2→90:10) to afford **2** (51 mg, 76%), in which the diastereomeric ratio of the (2*S*,5*R*)-**2** and (2*S*,5*S*)-**2** isomers were the same as those of the (2*S*,5*R*)-**4** and (2*S*,5*S*)-**4** isomers. Pure (2*S*,5*R*)-**2** and (2*S*,5*S*)-**2** isomers were recrystallized (MeOH–EtOAc) as above (the 1st batch recrystallization yields from AD-mix-α dihydroxylation, AD-mix-β dihydroxylation, and Shi epoxidation were ~40%, 60% and ~37%, respectively).

Supporting Information

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

Acknowledgment

This work was supported by the National Basic Research Program of China (2007CB914504).

References

(1) (a) Quinoa, E.; Adamczeski, M.; Crews, P.; Bakus, G. J. *J. Org. Chem.* **1986**, *51*, 4494. (b) Adamczeski, M.; Quinoa, E.; Crews, P. *J. Am. Chem. Soc.* **1989**, *111*, 647.

(2) Towbin, H.; Bair, K. W.; DeCaprio, J. A.; Eck, M. J.; Kim, S.; Kinder, F. R.; Morollo, A.; Mueller, D. R.; Schindler, P.; Song, H. K.; van Oostrum, J.; Versace, R. W.; Voshol, H.; Wood, J.; Zabludoff, S.; Phillips, P. E. *J. Biol. Chem.* **2003**, *278*, 52964.

(3) (a) Thale, Z.; Kinder, F. R.; Bair, K. W.; Bontempo, J.; Czuchta, A. M.; Versace, R. W.; Phillips, P. E.; Sanders, M. L.; Wattanasin, S.; Crews, P. *J. Org. Chem.* **2001**, *66*, 1733. (b) Kinder, F. R.; Versace, R. W.; Bair, K. W.; Bontempo, J. M.; Cesarz, D.; Chen, S.; Crews, P.; Czuchta, A. M.; Jagoe, C. T.; Mou, Y.; Nemzek, R.; Phillips, P. E.; Tran, L. D.; Wang, R. M.; Weltchek, S.; Zabludoff, S. *J. Med. Chem.* **2001**, *44*, 3692.

(4) Kim, S.; LaMontagne, K.; Sabio, M.; Sharma, S.; Versace, R. W.; Yusuff, N.; Phillips, P. E. *Cancer Res.* **2004**, *64*, 2984.
(5) Kinder, F. R.; Wattanasin, S.; Versace, R. W.; Bair, K. W.; Bontempo, J.; Green, M. A.; Lu, Y. J.; Marepalli, H. R.; Phillips, P. E.; Roche, D.; Tran, L. D.; Wang, R. M.; Waykole, L.; Xu, D. D.; Zabludoff, S. *J. Org. Chem.* **2001**, *66*, 118; and references therein.
(6) (a) Löhr, B.; Orlich, S.; Kunz, H. *Synlett* **1999**, 139. (b) Adamczyk, M.; Reddy, R. E.; Rege, S. D. *J. Labelled Compd. Radiopharm.* **2001**, *44*, 185. (c) van den Nieuwendijk, A. M. C. H.; Kriek, N. M. A. J.; Brussee, J.; van Boom, J. H.; van der Gen, A. *Eur. J. Org. Chem.* **2000**, 3683.
(7) (a) Broka, C. A.; Ehrler, J. *Tetrahedron Lett.* **1991**, *32*, 5907. (b) Roche, D.; Prasad, K.; Repic, O.; Blacklock, T. J. *Tetrahedron Lett.* **2001**, *42*, 1459; and references therein. (c) Boeckman, R. K.; Clark, T. J.; Shook, B. C. *Org. Lett.* **2002**, *4*, 2109. (d) Liu, G.; Tai, W.-Y.; Li, Y.-L.; Nan, F.-J. *Tetrahedron Lett.* **2006**, *47*, 3295.
(8) Jacobsen, E. N.; Zhang, W.; Muci, A. R.; Ecker, J. R.; Deng, L. *J. Am. Chem. Soc.* **1991**, *113*, 7063.
(9) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K. S.; Kwong, H. L.; Morikawa, K.; Wang, Z. M.; Xu, D.; Zhang, X. L. *J. Org. Chem.* **1992**, *57*, 2768.
(10) Frohn, M.; Dalkiewicz, M.; Tu, Y.; Wang, Z. X.; Shi, Y. *J. Org. Chem.* **1998**, *63*, 2948.
(11) (a) Padron, J. M.; Kokotos, G.; Mart, T.; Markidis, T.; Gibbons, W. A.; Mart, V. S. *Tetrahedron: Asymmetry* **1998**, *9*, 3381. (b) Adamczyk, M.; Johnson, D. D.; Reddy, R. E. *Tetrahedron: Asymmetry* **1999**, *10*, 775.
(12) Desai, D.; Sharma, A. K.; Lin, J.-M.; Krzeminski, J.; Pimentel, M.; El-Bayoumy, K.; Nesnow, S.; Amin, S. *Chem. Res. Toxicol.* **2002**, *15*, 64.
(13) Sharma, A. K.; Gowdahalli, K.; Gimbor, M.; Amin, S. *Chem. Res. Toxicol.* **2008**, *21*, 154.
(14) O'Sullivan, T. P.; Zhang, H.; Mander, L. N. *Org. Biomol. Chem.* **2007**, *5*, 2627.
(15) Liu, G.; Romo, D. *Org. Lett.* **2008**, *11*, 1143.
(16) Srikrishna, A.; Babu, R. R. *Tetrahedron* **2008**, *64*, 10501.
(17) Brouillette, Y.; Martinez, J.; Lisowski, V. *J. Org. Chem.* **2009**, *74*, 4975.