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TETRAHEDRON: *ASYMMETRY*

Asymmetric synthesis of 3-amino-2-hydroxy-4-phenylbutanoate †

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Abstract

Asymmetric synthesis of 3-amino-2-hydroxy-4-phenylbutanoate, a key component of the natural product bestatin and HIV protease inhibitors of KNI-272 and R-87366, has been achieved from the stereoselective aldimine coupling reaction between 3-phenyl-2-aminopropanenitrile and (*Z*)-α-methoxy trimethylsilyl ketene acetal in the presence of Lewis acids.

1. Introduction

Bestatin is a dipeptide isolated from the culture filtrate of *Streptomyces olivoreticuli* with antitumor and antibacterial activities.[1] It is also known as a potent inhibitor of aminopeptidase B and of metalloenzyme leukotriene A4 hydrolase.[2] This dipeptide consists of the amino acid (*S*)-leucine and (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid **1** as the key component. Its diastereomer **2** with the (2*S*,3*S*)-configuration is also an important structural element of HIV-1 protease inhibitors represented by KNI 272 and R-87366.[3] Therefore, the stereoselective synthesis of 3-amino-2-hydroxy-4-phenylbutanoate has attracted a great deal of attention over recent years.

Most approaches toward the enantioselective synthesis of 3-amino-2-hydroxy-4-phenylbutanoate came from the chiral starting substrates such as phenylalanine,[4] sugars, or their derivatives.[5] Asymmetric syntheses were also reported based on the methods including stereoselective reduction, epoxidation, conjugate addition of amines, [2+2] cycloaddition of imines and ketene acetals, and aldol condensation of chiral enolates and aldehydes.[6] From the viewpoint of our recent success in the synthesis of *N*-benzoyl-(2*R*,3*S*)-phenylisoserine as the Taxol side chain, aldol type condensation of an imine with a ketene acetal may give easy access to the enantioselective synthesis of 3-amino-2-hydroxy-4-phenylbutanoic acid.[7]

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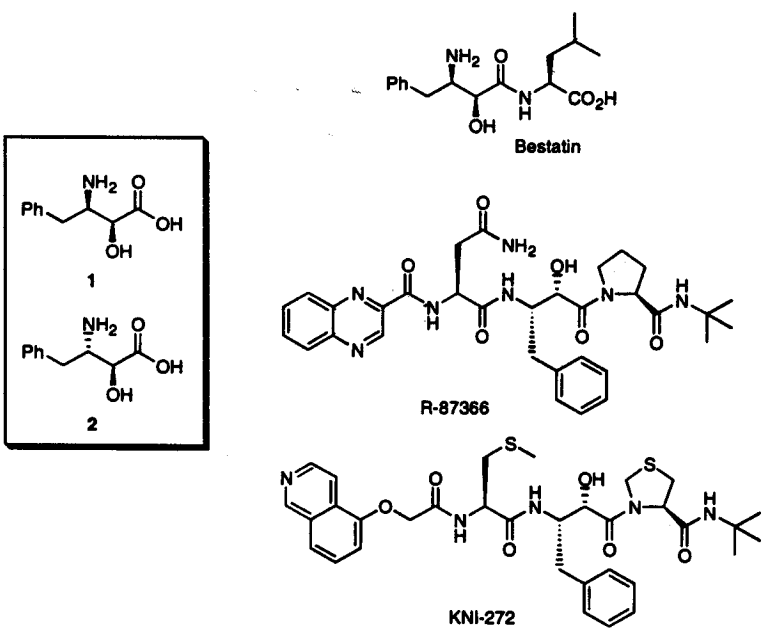
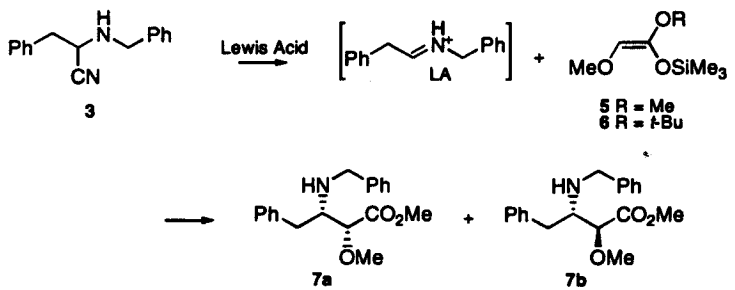


However, this method has not been reported to date because the corresponding imine phenylacetaldimine is not available due to possible conversion of the imine to eneamine 2-phenyletheneamine.[8] In this report the first practical aldimine route to the stereoselective synthesis of 3-amino-2-hydroxy-4-phenylbutanoate involving generation in situ of phenylacetaldimine equivalent and its coupling with ketene acetal is described.

2. Results and discussion

2-Benzylamino-3-phenylpropanenitrile **3** was used as a precursor of a phenylacetaldiminium ion based on the early observation[9] that the nitrile at the α-position of an amine could be easily removed with the assistance of Lewis acid. Initially, the crucial aldimine coupling reaction was studied between 2-benzylamino-3-phenylpropanenitrile **3** and the readily available nucleophile (*Z*)-1,2-dimethoxy-1-trimethylsilyloxyethene **5**,[10] in the presence of several different Lewis acids as shown in Scheme 1 and Table 1.



Scheme 1.

First $MgBr_2$, a good catalyst for the coupling between *N*-benzylbenzaldimine and the same nucleophile during the course of Taxol side chain synthesis, was tested.[7] The result was not satisfactory though the *syn* and *anti* stereoselectivities were as high as 78:22 at −15°C (entries 1–3). $TiCl_4$, $SnCl_4$, $AlCl_3$ and

Table 1
Reaction of 2-benzylamino-3-phenylpropanenitrile **3** and (*Z*)-1,2-dimethoxy-1-trimethylsilyloxy-ethene **5** in the presence of Lewis acids

Entry	Lewis acid	mole equiv.	Temp (°C)	Time (h)	Yield[a] (%)	*Syn* (**7a**) / *Anti* (**7b**)[b]
1	$MgBr_2$	1.0	-15	3	51	78 : 22
2	$MgBr_2$	1.0	rt	2	49	76 : 24
3	$MgBr_2$	0.1	rt	10	nr	
4	$TiCl_4$	1.0	rt	2	34	62 : 38
5	$SnCl_4$	1.0	rt	1	35	57 : 43
6	$AlCl_3$	1.0	rt	2	40	63 : 37
7	$Sc(OTf)_3$	1.0	rt	2	30	69 : 31
8	TMSOTf	1.0	rt	2	87	78 : 22
9	TMSOTf	0.1	rt	4	90	77 : 23
10	TMSOTf	0.1	0	5	85	77 : 23
11	TMSOTf	0.1	-20	5	60	79 : 21

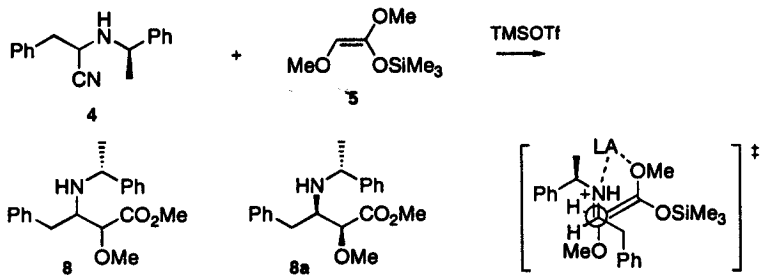
a. Isolated yield. b. Ratio was determined by either HPLC or ^1H NMR.

$Sc(OTf)_3$ were no good either for obtaining more than 40% yield (entries 4–7). All reactions proceeded in the *syn* fashion with ratios of 2:1–3:1. Other Lewis acids such as $BF_3 \cdot OEt_2$, TiF_4 and $Ti(OiPr)_4$ did not lead to any detectable amounts of the product; instead all starting substrates remained unreacted. The best result was obtained from the reaction with 1 mol equiv. of TMSOTf in 87% yield with the product with the desired stereochemistry being major with the *syn* **7a** to *anti* **7b** ratio of 78:22 at room temperature for 2 h (entry 8). The stereochemical outcome and the reaction yield were not changed much with catalytic amounts of Lewis acid or by lowering the reaction temperature (entries 9–11). Upon treatment of 2-benzylamino-3-phenylpropanenitrile **3** with 10 mol% of TMSOTf new peaks were observed in the ^1H and ^{13}C NMR at δ 5.45 and 167.8 ppm corresponding to the iminium ions with the removal of nitrile.

Thereafter, the reaction was performed at room temperature with 10 mol% of TMSOTf. The same reaction with (*Z*)-1-*t*-butoxy-2-methoxy-1-trimethylsilyloxyethene **6** as a nucleophile was expected to yield the product of *t*-butylester with better diastereoselectivity. However, the reaction did not proceed at all due to possible steric hindrance in the approach to the iminium ion.

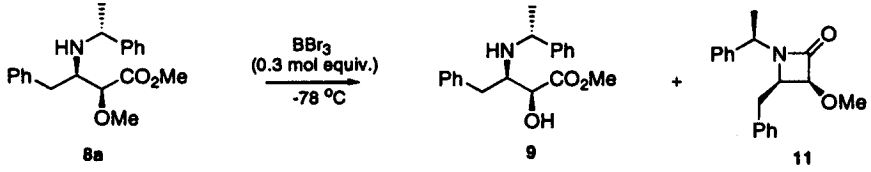
Once the reaction conditions were established, we carried out the reaction with the chiral substrate of 3-phenyl-2-[(*R*)-1-phenylethylamino]propanenitrile **4** considering the additional factor of diastereofacial selectivity. From the standard Strecker synthesis from phenylacetaldehyde and (*R*)-1-phenylethylamine was obtained 3-phenyl-2-[(*R*)-1-phenylethylamino]propanenitrile as a diastereomeric mixture of 2*R* and 2*S* with 4:1 ratio.[11] This diastereomeric mixture was used for the next coupling reaction without further purification or isolation because each isolated isomer yielded the same stereochemical outcome, possibly due to the same iminium ion intermediate. With 10 mol% of TMSOTf, the aldimine coupling yielded the expected product of methyl (2*S*,3*R*)-2-methoxy-4-phenyl-3-[(*R*)-1-phenylethylamino]butanoate **8a** as a major product among all four possible stereoisomers **8** in 59% isolated yield after flash column chromatography (*syn*:*anti*=79:21, diastereofacial ratio=84:16). The transition state of the reaction can be drawn, as shown in Scheme 2, with *synclinal* orientation of iminium ion activated by Lewis acid and ketene acetal approaching the less hindered face of the chiral iminium ion.[12]

The coupled product (2*S*,3*R*)-2-methoxy-4-phenyl-3-[(*R*)-1-phenylethylamino]butanoate **8a** was de-



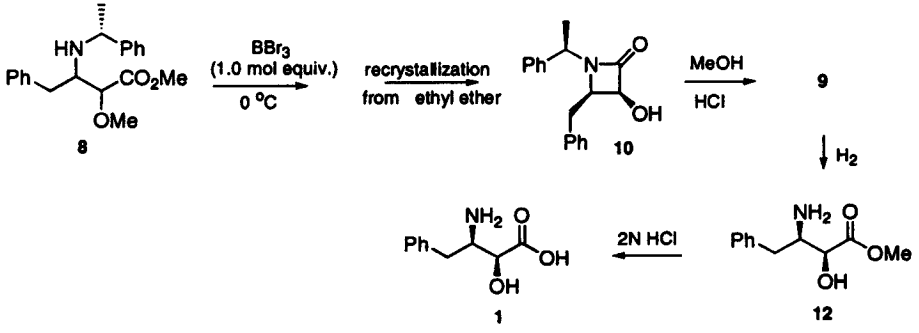
Scheme 2.

methylated with 0.3 mol equiv. of BBr_3 at −78°C to give free hydroxy compound **9** with the minor product of (3*S*,4*R*)-4-benzyl-3-methoxy-1-[(*R*)-1-phenylethyl]azetidin-2-one **11** in 81 and 16% isolated yields, respectively (Scheme 3). The minor product **11** was also obtained from lactamization of **8a** with LHMDS in THF in quantitative yield. Hydrogenolysis of **9** afforded methyl (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoate **12** in 79% yield. Treatment of (2*S*,3*R*)-2-methoxy-4-phenyl-3-[(*R*)-1-phenylethylamino]butanoate **8a** with 1.0 mol equiv. of BBr_3 at 0°C gave (3*S*,4*R*)-4-benzyl-3-hydroxy-1-[(*R*)-1-phenylethyl]azetidin-2-one **10** which could be obtained as a crystalline solid after recrystallization in diethyl ether.



Scheme 3.

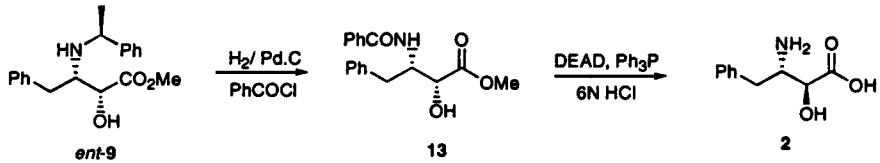
Once the reaction sequence had been established, we succeeded in getting **10** in enantiomerically pure form in 42% yield after two recrystallizations starting from a mixture of four stereoisomers **8** without chromatographic separation of the single isomer **8a** as shown in Scheme 4.



Scheme 4.

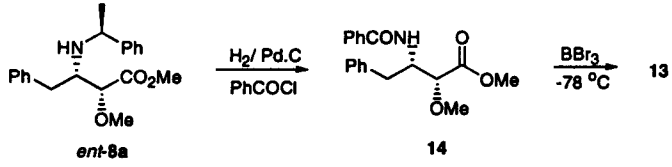
This afforded a practical route for getting a single enantiomerically pure 4-benzyl-3-hydroxyazetidin-2-one from chiral amine, aldehyde and subsequent aldimine coupling with ketene acetal without any tedious separation of diastereomers. Methanolysis and hydrogenolysis of azetidin-2-one **10** gave methyl (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoate **12** {$[\alpha]_D^{22}$=+19.4 (*c* 0.19, 1N HCl); lit.[4c] $[\alpha]_D^{24}$=+19.6 (*c* 0.84, 1N HCl)} in 61% yield. Free acid **1** {$[\alpha]_D^{24}$=+27.4 (*c* 0.43, 1N HCl)} was obtained by the known method of hydrolysis in 2N HCl.[13] Bestatin was readily prepared by coupling with (*S*)-leucine *tert*-butylester by the reported method.[4c] This reaction sequence was applied successfully to prepare several grams of (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoic acid **1** in good yield.

Preparation of its diastereomer (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid **2** was achieved as outlined in Scheme 5 utilizing the chiral amine (*S*)-1-phenylethylamine. The sequential reactions of aldimine coupling, demethylation and lactamization starting from 3-phenyl-2-[(*S*)-1-phenylethylamino]propanenitrile *ent*-**4** with (*Z*)-α-methoxy trimethylsilyl ketene acetal afforded (3*R*,4*S*)-4-benzyl-3-hydroxy-1-[(*S*)-1-phenylethyl]azetidin-2-one *ent*-**10** that is also a synthetic precursor of hydroxyethylene dipeptide isosteres.[14] The subsequent methanolysis of *ent*-**10** afforded (2*R*,3*S*)-2-hydroxy-4-phenyl-3-[(*S*)-1-phenylethylamino]butanoate (*ent*-**9**). Hydrogenation and benzoylation of *ent*-**9** yielded the amide **13**.



Scheme 5.

The same amide **13** was obtained from *ent*-**8a** separated from the diastereomeric mixture of the initially coupled products as shown in Scheme 6. Hydrogenation and benzoylation of *ent*-**8a** afforded methyl (2*R*,3*S*)-3-benzoylamino-2-methoxy-4-phenylbutanoate **14** which was readily converted to **13** by demethylation with BBr_3 in 90 and 79% yields, respectively. The target molecule (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid **2** {$[\alpha]_D^{22}$=–5.1 (*c* 0.19, 1N HCl); lit.[6c] $[\alpha]_D^{20}$=–5.4 (*c* 0.51, 1N HCl)} was obtained from **13** by the known literature procedure,[15] including cyclization to *cis*-oxazoline under Mitsunobu conditions with complete inversion of configuration at the α-position followed by hydrolysis in 6N HCl.



Scheme 6.

In conclusion, we have found that the reaction of chiral iminium ion generated in situ from 3-phenyl-2-[(*R*)-1-phenylethylamino]propanenitrile **4** with (*Z*)-α-methoxy trimethylsilyl ketene acetal in the presence of a catalytic amount of TMSOTf yielded (2*S*,3*R*)-2-methoxy-4-phenyl-3-[(*R*)-1-phenylethylamino]butanoate **8a** as the major component amongst all four possible stereoisomers. Demethylation and lactamization with BBr_3 from the aldimine coupled products without isolation of the major isomer were successfully achieved to afford (3*S*,4*R*)-4-benzyl-3-hydroxy-1-[(*R*)-1-phenylethyl]azetidin-2-one **10** in an enantiomerically pure form after recrystallization. The subsequent reactions of methanolysis, hydrogenolysis, and hydrolysis gave methyl (2*S*,3*R*)-3-amino-2-hydroxy-4-phenylbutanoate **1** as a key component of bestatin. Starting from the chiral amine (*S*)-1-phenylethylamine as a chiral auxiliary could afford (3*R*,4*S*)-4-benzyl-3-hydroxy-1-[(*S*)-1-phenylethyl]azetidin-2-one *ent*-**10** which leads to the synthetically valuable (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoic acid **2** by sequential transformations including inversion of the configuration at the α-position.

3. Experimental

3.1. General data

^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian 200 or 400 (200 and MHz for ^{1}H and 50.3 and 100.6 MHz for ^{13}C). Chemical shifts were given in ppm using TMS as internal standard. Mass spectra were obtained using a Hewlett Packard Model 5985B spectrometer or a Kratos Concept 1-S double focusing mass spectrometer. Elemental analyses were taken on a Perkin–Elmer 240 DS elemental analyzer. Melting points were measured by Mel-II capillary melting point apparatus. Optical rotations were measured with a Rudolph Research Autopole 3 polarimeter. The silica gel used for column chromatography was Merck 200–230 mesh. Thin layer chromatography was carried out with Merck 60F-254 plates with 0.25 mm thickness.

3.2. 2-Benzylamino-3-phenylpropanenitrile 3

Phenylacetaldehyde (3.23 g, 26.8 mmol) and $NaHSO_3$ (2.80 g, 26.9 mmol) were dissolved in H_2O (7 ml) and MeOH (22 ml). Into this was added benzylamine (3.71 g, 34.6 mmol) and KCN (2.25 g, 34.6 mmol). The resulting mixture was refluxed for 1 h for the completion and cooled down to room temperature before quenching by addition of H_2O (50 ml). The reaction product was extracted with EtOAc (50 ml) three times. The extracts were washed by 100 ml each of water and brine, dried by anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to give 6.20 g of the expected product that was used without further purification. ^{1}H NMR δ 1.58 (br s, 1H), 3.01 (d, 1H, J=5.4 Hz), 3.04 (d, 1H, J=4.2 Hz), 3.70 (t, 1H, J=6.1 Hz), 3.78 (d, 1H, J=13.2 Hz), 3.93 (d, 1H, J=13.2 Hz), 7.20–7.34 (m, 10H); ^{13}C NMR δ 39.1, 50.6, 51.3, 119.5, 127.5, 128.2, 128.5, 128.7, 129.5, 135.0, 138.1.

3.3. 3-Phenyl-2-[(R)-1-phenylethylamino]propanenitrile 4

This was prepared in the same manner to make 2-benzylamino-3-phenylpropanenitrile (**3**) utilizing (*R*)-phenylethylamine instead of benzylamine in 98% yield with the diastereomeric ratio of 4:1. Two diastereomers were separated by flash column chromatography with hexane and EtOAc (3:1, v/v) as eluent. However, for the next aldimine reaction the crude reaction product as a diastereomeric mixture was used without any further purification or isolation. (2*R*)-3-Benzyl-2-[(*R*)-1-phenylethylamino]propanenitrile **4**, ^{1}H NMR δ 1.19 (d, 3H, J=6.4 Hz), 1.44 (br s, 1H), 2.82–2.86 (m, 2H), 3.29 (t, 1H, J=6.1 Hz), 3.91 (q, 1H, J=6.6 Hz), 7.04–7.24 (m, 10H); ^{13}C NMR δ 24.6, 39.2, 49.1, 56.2, 119.7, 126.7, 127.3, 128.5, 128.6, 129.4, 135.1, 143.1. (2*S*)-3-Benzyl-2-[(*R*)-1-phenylethylamino]propanenitrile **4**, ^{1}H NMR δ 1.20 (d, 3H, J=6.4 Hz), 1.47 (br s, 1H), 2.90–2.92 (m, 2H), 3.29 (t, 1H, J=6.1 Hz), 3.47 (q, 1H, J=5.8 Hz), 7.04–7.24 (m, 10H); ^{13}C NMR δ 22.1, 39.2, 49.4, 55.8, 119.5, 126.6, 127.4, 128.6, 128.9, 129.2, 135.1, 144.4.

3.4. Methyl 3-benzylamino-2-methoxy-4-phenylbutanoate 7

Lewis acid TMSOTf (0.18 ml, 222 mg, 1 mmol) was added to the solution of 2-benzylamino-3-phenylpropanenitrile **3** (2.36 g, 10 mmol) in CH_2Cl_2 at room temperature. The resultant solution was stirred for 15 min before adding (*Z*)-1,2-dimethoxy-1-trimethylsilyloxyethene (1.76 g, 10 mmol) in drops. After 1 h for completion the reaction mixture was dumped into the H_2O. The reaction product was extracted with EtOAc (50 mL) three times. The organic layer was washed by 100 ml each of water and brine, dried by anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product

was purified by flash column chromatography to give 2.81 g of analytically pure products **7a** and **7b**. For **7a**: ^{1}H NMR δ 2.68 (dd, 1H, *J*=13.0, 9.0 Hz), 2.95 (dd, 1H, *J*=13.0, 5.4 Hz), 3.05–3.12 (m, 1H), 3.33 (s, 3H), 3.47 (d, 1H, *J*=2.8 Hz), 3.56 (s, 3H), 3.67 (1H, d, *J*=13.4 Hz), 3.81 (d, 1H, *J*=13.4 Hz), 4.21 (br s, 1H), 7.06–7.26 (m, 10H); ^{13}C NMR δ 37.0, 51.0, 51.5, 58.7, 60.5, 80.9, 126.3, 127.0, 128.2, 128.3, 128.6, 129.3, 139.2, 140.5, 172.5. For **7b**: ^{1}H NMR δ 2.71–2.77 (m, 2H), 3.12–3.27 (m, 1H), 3.33 (s, 3H), 3.49 (d, 1H, *J*=19.4 Hz), 3.62 (s, 3H), 3.66 (d, 1H, *J*=19.4 Hz), 3.69 (d, 1H, *J*=2.0 Hz), 4.23 (br s, 1H), 7.06–7.28 (m, 10H); ^{13}C NMR δ 36.2, 51.4, 51.7, 58.7, 60.2, 81.9, 126.3, 126.9, 128.1, 128.3, 128.4, 129.6, 138.5, 140.2, 172.3.

3.5. Methyl (2S,3R)-2-methoxy-4-phenyl-3-[(R)-1-phenylethylamino]butanoate 8a

This title compound was prepared in the same manner to make methyl 3-benzylamino-2-methoxy-4-phenylbutanoate **7** starting from 3-phenyl-2-[(*R*)-1-phenylethylamino]propanenitrile **4** (2.50 g, 10 mmol) instead of 2-benzylamino-3-phenylpropanenitrile **3**. ^{1}H NMR δ 1.15 (d, 3H, *J*=6.6 Hz), 1.58 (s, 1H), 2.63 (d, 2H, *J*=7.6 Hz), 3.08 (t, d, 1H, *J*=7.2, 2.0 Hz), 3.29 (s, 3H), 3.39–3.47 (m, 1H), 3.60 (s, 3H), 3.69 (q, 1H, *J*=6.3 Hz), 6.94–7.19 (m, 10H); ^{13}C NMR δ 23.9, 38.2, 51.2, 55.5, 58.4, 59.0, 80.2, 126.2, 126.4, 127.0, 128.2, 128.5, 129.2, 139.0, 145.7, 172.4. $[\alpha]_D^{22}$=+39.3 (*c* 0.19, CH_2Cl_2). MS *m/z*: 327 (M, 2), 312 (10), 236 (31), 224 (23), 120 (30), 105 (100). Anal. calcd for $C_{20}H_{25}NO_3$: C, 73.4; H, 7.70; N, 4.28. Found: C, 73.7; H, 7.45; N, 4.66. All other isomers were separated by flash column chromatography. Their stereochemistry was identified based on the coupling constants between α- and β-protons of β-lactams derived by the reaction with LHMDS as described in the part of compound **11**. Methyl (2*R*,3*R*)-2-methoxy-4-phenyl-3-[(*R*)-1-phenylethylamino]butanoate: ^{1}H NMR δ 1.21 (d, 3H, *J*=6.6 Hz), 1.58 (br s, 1H), 2.61 (d, 2H, *J*=7.2 Hz), 2.67–2.84 (m, 1H), 3.32 (s, 3H), 3.66 (d, 1H, *J*=7.2 Hz), 3.46 (s, 3H), 3.88 (q, 1H, *J*=6.5 Hz), 6.96–7.21 (m, 10H); methyl (2*S*,3*S*)-2-methoxy-4-phenyl-3-[(*R*)-1-phenylethylamino]butanoate: ^{1}H NMR δ 1.23 (d, 3H, *J*=6.6 Hz), 1.55 (s, 1H), 2.63–2.67 (m, 2H), 3.02 (ddd, 1H, *J*=8.2, 5.6, 3.8), 3.45 (s, 3H), 3.69 (s, 3H), 3.69 (q, 1H, *J*=6.6 Hz), 3.89 (d, 1H, *J*=3.8 Hz), 6.93–7.25 (m, 10H); methyl (2*R*,3*S*)-2-methoxy-4-phenyl-3-[(*R*)-1-phenylethylamino]butanoate: ^{1}H NMR δ 1.55 (d, 3H, *J*=6.6 Hz), 1.57 (s, 1H), 2.75 (d, 2H, *J*=6.0 Hz), 3.01 (q, 1H, *J*=5.8 Hz), 3.21 (s, 3H), 3.41 (d, 1H, *J*=5.6 Hz), 3.52 (s, 3H), 3.77 (q, 1H, *J*=6.4 Hz), 7.07–7.27 (m, 10H).

3.6. Methyl (2S,3R)-2-hydroxy-4-phenyl-3-[(R)-1-phenylethylamino]butanoate 9

BBr_3 (7.72 mg, 3.1 mmol) was added to the solution of methyl (2*S*,3*R*)-2-methoxy-4-phenyl-3-[(*R*)-1-phenylethylamino]butanoate **8a** (335 mg, 1.03 mmol) in CH_2Cl_2 (30 ml) at –78°C. The resultant reaction mixture was stirred for 2 h at –78°C before adding H_2O (30 ml). The solution was neutralized with 2N NaOH solution. The reaction product was extracted with EtOAc (50 ml) three times. The extracts were washed by 100 ml each of water and brine, dried by anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 261 mg of the title compound as major fraction. ^{1}H NMR δ 1.13 (d, 3H, *J*=6.6 Hz), 2.64–2.69 (m, 2H), 3.03–3.11 (m, 1H), 3.52 (q, 1H, *J*=6.5 Hz), 3.67 (s, 3H), 3.87 (d, 1H, *J*=1.6 Hz), 6.83–7.23 (m, 10H); ^{13}C NMR δ 23.9, 39.0, 52.0, 55.6, 58.3, 70.7, 126.3, 126.5, 127.0, 128.4, 128.6, 129.4, 138.2, 145.1, 175.2. $[\alpha]_D^{22}$=–13.3 (*c* 0.80, CH_2Cl_2). MS *m/z*: 295 (M–18, 2), 176 (2), 148 (100). Anal. calcd for $C_{19}H_{23}NO_3$: C, 72.8; H, 7.40; N, 4.47. Found: C, 72.6; H, 7.66; N, 4.38. (3*S*,4*R*)-4-Benzyl-3-methoxy-1-[(*R*)-1-phenylethyl]azetidin-2-one (48 mg, **11**) was also obtained as a minor product in 16% yield. ^{1}H NMR δ 1.52 (d, 3H, *J*=7.2 Hz), 2.71 (dd, 1H, *J*=14.4, 5.2 Hz), 2.91 (dd, 1H, *J*=14.4, 8.2 Hz), 3.31 (s, 3H), 3.68–3.78 (m, 1H), 4.28 (d, 1H, *J*=2.8 Hz), 4.47 (q, 1H, *J*=7.2 Hz), 6.92–7.30 (m, 10H); ^{13}C NMR δ 19.7,

35.2, 52.2, 59.2, 59.6, 83.4, 126.3, 127.0, 127.7, 128.3, 128.6, 129.0, 137.6, 140.0, 167.4. $[\alpha]_D^{22}$=–43.4 (*c* 0.80, CH_2Cl_2). Anal. calcd for $C_{19}H_{21}NO_2$: C, 77.3; H, 7.17; N, 4.74. Found: C, 77.4; H, 6.98; N, 4.54. (3*S*,4*R*)-4-Benzyl-3-methoxy-1-[(*R*)-1-phenylethyl]azetidin-2-one **11** was also obtained in 97% yield from the reaction of methyl (2*S*,3*R*)-2-methoxy-4-phenyl-3-[(*R*)-1-phenylethylamino]butanoate **8a**. Compound **8a** (50 mg 153 mmol) was added to LHMDS (153 mmol) solution in THF (15 ml) at –78°C. Then the cooling bath was removed and the resultant solution was stirred at 0°C for 2 h before adding the water. The reaction product was extracted with EtOAc (50 ml) twice. The extracts were washed by 50 ml each of water and brine, dried by anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 147 mg of the lactamized product **11**.

3.7. (3S,4R)-4-Benzyl-3-hydroxy-1-[(R)-1-phenylethyl]azetidin-2-one ***10***

BBr_3 (1.00 g, 4.0 mmol) was added at 0°C to the solution of the diastereomeric mixture of methyl 2-methoxy-4-phenyl-3-[(*R*)-1-phenylethylamino]butanoate **8** (1.31 g, 4.0 mmol) from the aldimine coupling reaction without any purification in CH_2Cl_2. Then the resultant reaction mixture was stirred for 10 h at room temperature before adding H_2O (30 ml). The solution was neutralized with 2N NaOH solution. The reaction product was extracted with EtOAc (50 ml) three times. The extracts were washed by 100 ml each of water and brine, dried by anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was dissolved in a minimum amount of ethyl ether and recrystallized at 4°C to give 517 mg of white crystalline solid in 46% overall yield. ^{1}H NMR δ 1.54 (d, 3H, *J*=7.2 Hz), 2.73 (dd, 1H, *J*=5.1, 4.8 Hz), 3.08 (dd, 1H, *J*=14.0, 8.3 Hz), 3.67–3.76 (m, 1H), 4.64–4.77 (m, 2H), 5.15 (br s, 1H), 6.99–7.31 (m, 10H); ^{13}C NMR δ 19.8, 34.9, 52.5, 60.8, 75.3, 126.4, 127.1, 127.8, 128.4, 128.7, 129.2, 137.8, 139.8, 170.2. $[\alpha]_D^{22}$=+52.1 (*c* 0.12, CH_2Cl_3). Anal. calcd for $C_{18}H_{19}NO_2$: C, 76.8; H, 6.81; N, 4.98. Found: C, 76.5; H, 6.62; N, 4.81.

3.8. Methyl (2S,3R)-3-amino-2-hydroxy-4-phenylbutanoate ***12***

In CH_3OH (20 ml) were dissolved methyl (2*S*,3*R*)-2-hydroxy-4-phenyl-3-[(*R*)-1-phenylethylamino]butanoate **9** (500 mg, 1.60 mmol) and Pd–C (30 mg). This solution was blanketed with H_2 gas in a balloon and the mixture was stirred at room temperature until all starting material was consumed on TLC for 15 h. The mixture was filtered and concentrated under reduced pressure. This crude reaction product was purified by flash column chromatography to give 264 mg of the title compound in 79% yield. $[\alpha]_D^{22}$=+19.4 (*c* 0.19, 1N HCl); lit,[9a] $[\alpha]_D^{24}$=+19.6 (*c* 0.84, 1N HCl).

3.9. Methyl (2R,3S)-2-methoxy-4-phenyl-3-[(S)-1-phenylethylamino]butanoate ent-***8a***

This was prepared in the same manner as for **8a** utilizing 3-phenyl-2-[(*S*)-1-phenylethylamino]propanenitrile *ent*-**4** instead of 3-phenyl-2-[(*R*)-1-phenylethylamino]propanenitrile **4**. $[\alpha]_D^{22}$=–38.7 (*c* 0.24, CH_2Cl_2).

3.10. (3R,4S)-4-Benzyl-3-hydroxy-1-[(S)-1-phenylethyl]azetidin-2-one ent-***10***

This was prepared in the same manner as for **10** starting from the diastereomeric mixture of methyl 2-methoxy-4-phenyl-3-[(*S*)-1-phenylethylamino]butanoate (*ent*-**8**). $[\alpha]_D^{22}$=–53.1 (*c* 0.18, CH_2Cl_2).

3.11. Methyl (2R,3S)-3-benzoylamino-2-hydroxy-4-phenylbutanoate 13

In CH_3OH (20 ml) was dissolved Pd–C (50 mg) and compound *ent*-**9** (190 mg, 0.61 mmol) that was prepared from *ent*-**10** by the same procedure for the molecule **10**. This solution, blanketed with H_2 gas in a balloon, was stirred at room temperature until all starting material was consumed on TLC for 15 h. The mixture was filtered and concentrated under reduced pressure. This crude reaction product was dissolved in a mixture of THF (5 mL) and water (5 mL). Benzoyl chloride (85 mg, 0.61 mmol) was added dropwise to this solution at 0°C maintaining pH 9–10 with NaOH solution. After addition was completed the resultant reaction mixture was stirred vigorously for 30 min. The reaction product was extracted with EtOAc (50 ml) three times. The extracts were washed by 100 ml each of water and brine, dried by anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 150 mg of the title compound in 79% yield. Mp 102–104°C; ^{1}H NMR δ 2.91–2.99 (m, 2H), 3.61 (s, 3H), 4.13 (s, 1H), 4.67 (br s, 1H), 4.72 (q, 1H, *J*=7.4 Hz), 6.64 (d, 1H, *J*=9.2 Hz), 7.11–8.01 (m, 10H); ^{13}C NMR δ 37.7, 52.9, 53.4, 70.1, 126.7, 126.9, 128.5, 128.6, 129.3, 131.6, 134.0, 137.2, 167.4, 174.1. $[\alpha]_D^{22}$=–19.8 (*c* 0.30, CH_2Cl_2). Anal. calcd for $C_{18}H_{19}NO_4$: C, 69.0; H, 6.11; N, 4.47. Found: C, 69.2; H, 6.31; N, 4.68.

3.12. Methyl (2R,3S)-3-benzoylamino-2-methoxy-4-phenylbutanoate 14

The same reaction as in compound **13** from *ent*-**9** was carried out with the starting material of *ent*-**8a** (1.27 g, 3.88 mmol) to yield the expected product in 90% yield as a white solid. Mp 148–150°C; ^{1}H NMR δ 2.91 (dd, 1H, *J*=13.6, 8.8 Hz), 3.08 (dd, 1H, *J*=13.2, 6.2 Hz), 3.41 (s, 3H), 3.62 (s, 3H), 3.70 (d, 1H, *J*=1.8 Hz), 4.78 (q, 1H, *J*=9.6 Hz), 6.65 (d, 1H, *J*=9.2 Hz), 7.17–7.74 (m, 10H); ^{13}C NMR δ 37.5, 51.9, 53.0, 58.3, 78.3, 126.5, 126.8, 128.2, 128.5, 129.1, 131.3, 134.1, 137.2, 166.8, 171.0. $[\alpha]_D^{22}$=–45.9 (*c* 0.21, CH_2Cl_2). Anal. calcd for $C_{19}H_{21}NO_4$: C, 69.7; H, 6.47; N, 4.28. Found: C, 69.4; H, 6.61; N, 4.59.

3.13. Methyl (2R,3S)-3-benzoylamino-2-hydroxy-4-phenylbutanoate 13 from 14

BBr_3 (152 mg, 0.61 mmol) was added into the solution of methyl (2*R*,3*S*)-3-benzoylamino-2-methoxy-4-phenylbutanoate **14** (200 mg, 0.61 mmol) in CH_2Cl_2 (30 ml) at –78°C. After 10 min the cooling bath was removed and the resultant reaction mixture was stirred for 2 h before adding H_2O (30 ml). The solution was neutralized with Na_2CO_3 solution. The reaction product was extracted with CH_2Cl_2 (30 ml) three times. The extracts were washed by 50 ml each of water and brine, dried by anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by flash column chromatography to give 151 mg of the title compound **13**.

3.14. (2S,3S)-3-Amino-2-hydroxy-4-phenylbutanoic acid 2

A solution of triphenylphosphine (289 mg) and diethyldiazodicarboxylate (191 mg, 1.10 mmol) in THF (20 ml) was added dropwise to methyl (2*R*,3*S*)-3-benzoylamino-2-hydroxy-4-phenylbutanoate **13** (150 mg, 0.479 mmol) dissolved in 20 mL of THF at 0°C under a N_2 atmosphere. The reaction mixture was allowed to warm to room temperature and stirred at this temperature for 28 h. The solution was concentrated under reduced pressure to give a brownish partial solid that was chromatographed by a short-path flash column with *n*-hexane and EtOAc (3:1, v/v). A solution of this solid in 6N HCl (20 ml) was refluxed for 6 h. After the reaction was completed, the mixture was cooled down. This was washed with 20 ml of diethyl ether. The aqueous layer was concentrated under reduced pressure. This

was adsorbed on Dowax 50W (250 ml) column and eluted with 2N NH_4OH to afford the product as a white solid (54 mg). $[\alpha]_D^{22}$=–5.1 (*c* 0.09, 1N HCl); lit.[6c] $[\alpha]_D^{20}$=–5.4 (*c* 0.51, 1N HCl).

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References

1. (a) Umezawa, H.; Aoyagi, T.; Suda, H.; Hamada, M.; Takeuchi, T. *J. Antibiot.* **1976**, *29*, 97. (b) Suda, H.; Takita, T.; Aoyagi, T.; Umezawa, H. *J. Antibiot.* **1976**, *29*, 100.
2. Orning, L.; Krivi, G.; Fitzpatrick, F. A. *J. Biol. Chem.* **1990**, *266*, 1375
3. (a) Mimoto, T.; Imai, J.; Tanaka, S.; Hattori, N.; Kisanuki, S.; Akaji, K.; Kiso, Y. *Chem. Pharm. Bull.* **1991**, *39*, 3088. (b) Mimoto, T.; Imai, J.; Kisanuki, S.; Enomoto, H.; Hattori, N.; Akaji, K. *Chem. Pharm. Bull.* **1992**, *40*, 2251. (c) Hormuth, S.; Reibig, H.-U.; Dorsch, D. *Liebigs Ann. Chem.* **1994**, 121.
4. (a) Herranz, R.; Castro-Pichel, J.; Vinuesa, S.; Garcia-Lopez, M. T. *J. Org. Chem.* **1990**, *55*, 2232. (b) Matsuda, F.; Matsumoto, T.; Ohsaki, M.; Ito, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 360. (c) Yuan, W.; Munoz, B.; Wong, C.-H.; Haeggstrom, J. Z.; Wetterholm, A.; Samuelsson, B. *J. Med. Chem.* **1993**, *36*, 211. (d) Harbeson, S. L.; Abelleira, S. M.; Akiyama, A.; Barrett III, R.; Carroll, R. M.; Straub, J. A.; Tkacz, J. N.; Wu, C.; Musso, G. F. *J. Med. Chem.* **1994**, *37*, 2918.
5. (a) Kang, S. H.; Ryu, D. H. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 2959. (b) Koseki, K.; Ebata, T.; Matsushita, H. *Biosci. Biotech. Biochem.* **1996**, *60*, 534. (c) Jefford, C. W.; McNulty, J.; Lu, Z.-H.; Wang, J. B. *Helv. Chim. Acta* **1996**, *79*, 1203. (d) Shibata, N.; Itoh, E.; Terashima, S. *Chem. Pharm. Bull.* **1998**, *46*, 733.
6. (a) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **1989**, *54*, 4235. (b) Kobayashi, Y.; Takemoto, Y.; Kamijo, T.; Harada, H.; Ito, Y.; Terashima, S. *Tetrahedron* **1992**, *48*, 1853. (c) Bunnage, M. E.; Davies, S. G.; Goodwin, C. J. *Synlett* **1993**, 731. (d) Blank, S.; Seebach, D. *Liebigs Ann. Chem.* **1993**, 889. (e) Hormuth, S.; Reibig, H.-U. Dorsche, D. *Liebigs Ann. Chem.* **1994**, 121. (f) Fuji, K.; Kawabata, T.; Kiryu, Y.; Sugiura, Y. *Heterocycles* **1996**, *42*, 701.
7. Ha, H.-J.; Park, G.-S.; Ahn, Y.-G.; Lee, G.-S. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1619.
8. A pure form of *N*-benzylphenylacetaldimine could not be obtained for synthetic purposes. In the literature there is one report using this imine for the reaction with 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one to give a product in less than 10% yield as an inseparable mixture. D'Annibale, A.; Pesce, A.; Resta, S.; Trogolo, C. *Tetrahedron Lett.* **1996**, *37*, 7429.
9. (a) Overman, L. E.; Okazaki, M. E.; Jacobsen, E. J. *J. Org. Chem.* **1985**, *50*, 2403. (b) Yue, C.; Royer, J.; Husson, H.-P. *J. Org. Chem.* **1992**, *57*, 4211. (c) Yue, C.; Nicolay, J. F.; Royer, J.; Husson, H.-P. *Tetrahedron* **1994**, *50*, 3139.
10. (a) Wissner, A. *J. Org. Chem.* **1979**, *44*, 4617. (b) Oesterle, T.; Simchen, G. *Liebigs Ann. Chem.* **1987**, 687.
11. (a) Weinges, K.; Gries, K.; Stemmle, B.; Schrank, W. *Chem. Ber.* **1977**, *110*, 2098. (b) Shafran, Y. M.; Bakulev, V. A.; Mokrushin, V. S. *Russ. Chem. Rev.* **1989**, *58*, 148.
12. For reviews, see: (a) Kleinman, E. F. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Heathcock, C. H., Eds.; Pergamon Press: New York, 1991; Vol. 2, Chapter 4.1. (b) *Stereoselective Synthesis*; Helmchen, G.; Hoffmann, R. W.; Mulzer, J.; Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1996; E 21 Vol. 3, Section 1.4.
13. Kato, K.; Saino, T.; Nishizawa, R.; Takita, T.; Umezawa, H. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1618.
14. Ojima, I.: Wang, H.; Wang, T.; Ng, E. W. *Tetrahedron Lett.* **1998**, *39*, 923.
15. (a) Bunnage, M. E.; Davies, S. G.; Goowin, C. J. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1375. (b) Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Goowin, C. J. *Tetrahedron: Asymmetry* **1995**, *6*, 165.