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NEW APPROACHES TO THE ASYMMETRIC SYNTHESIS OF NON-PROTEINOGENIC α-AMINO ACIDS AND DIPEPTIDES THROUGH CHIRAL β-LACTAM INTERMEDIATES

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Summary: Novel and effective routes to optically pure aromatic α-amino acids, α-methyl-α-amino acids and their derivatives including dipeptides are developed via homochiral β-lactams which are obtained through asymmetric [2+2] cycloadditions of ketenes to imines.

In recent years, β-lactam skeleton has been recognized as providing useful synthetic building blocks by exploiting its strain energy besides its use in the synthesis of a variety of β-lactam antibiotics.[1,2] We have been exploring such new aspects of β-lactam chemistry using homochiral, i.e., optically pure, β-lactams as versatile intermediates for the synthesis of aromatic α-amino acids and their derivatives,[3] oligopeptides,[4] labeled peptides,[5] and azetidines which are further converted to polyamines, polyamino alcohols and polyamino ethers.[6] Based on the hydrogenolysis of chiral 4-aryl-β-lactam intermediates on palladium catalyst, we have developed the "**β-Lactam Synthon Method**" for peptide synthesis and successfully applied it to the synthesis of potent enkephalin analogues.[7]

However, our previous syntheses of those compounds were based on homochiral diastereomeric β-lactams which were obtained through chromatographic separations of two diastereomers since only cycloadditions of achiral ketenes such as azidoketene, phenoxyketene and benzyloxyketene to chiral imines were employed. Recently, it has been shown that the asymmetric cycloaddition of chiral ketenes to achiral imines can yield chiral β-lactams with good to excellent stereoselectivity by Ikota and Hanaki,[8] and Evans and Sjogren.[9] Those reports inspired us to examine the applicability of those chiral ketenes to the reaction with chiral imines in which it is necessary to take into account both favorable and unfavorable double asymmetric inductions. If the asymmetric cycloaddition

can achieve excellent stereoselectivity regardless of the chiral centers in imines, the process will provide extremely effective routes to the direct precursors of homochiral dipeptides and azetidines with desired configurations. Actually, this approach was successful and thus we describe here new and effective asymmetric synthesis of peptides through homochiral β-lactams as a basic methodology to our goals.

On the other hand, the significance of non-proteinogenic amino acids has recently been recognized in connection with design and synthesis of enzyme inhibitors as potential pharmaceutical drugs and also for the study of enzymic reaction mechanisms.[10-13] Among those non-proteinogenic amino acids, α-alkyl-α-amino acids have been attracting medicinal and biochemical interests, i.e., (a) those amino acids are known to be powerful enzyme inhibitors for e.g., dopa,[10] ornithine,[11] glutamate,[11] S-adenosylmethionine (SAM) decarboxylases[12] and aspartate aminotransferase[13] and (b) those amino acids act as conformational modifier for physiologically active peptides.[14] Some of α-alkyl-α-amino acids have been found in the metabolites of bacteria and act as antibiotics such as amicetin[15] and antiamoebin I[16]. α-Alkyl-α-amino acids also provide a challenging synthetic problem for chemists since the α-alkyl-α-amino acids have chiral quaternary carbons and thus conventional enzymic optical resolution technology cannot be applied effectively, viz., no racemization can take place at the chiral α-carbons and thus D-isomers cannot be recycled to the optical resolution process. Therefore, the asymmetric synthesis of optically pure α-alkyl-α-amino acids is the method of choice. Schöllkopf et al.[17] has been developing a general method based on bis(lactim) ethers and Seebach et al.[18] reported a method based on chiral proline derivatives using "self-reproduction of chirality". Karady[19], Williams[20], and Georg[21] developed effective methods based on oxazolidinone, aza-δ-lactone, and Schmidt rearrangement, respectively. We have successfully been working on this important problem through extremely stereoselective alkylations of homochiral β-lactams followed by the reductive cleavage of the alkylated β-lactams.[22-25] Thus, we describe here effective new methods for the asymmetric synthesis of α-alkyl-α-amino acids and their derivatives including dipeptides as an application of the "β-Lactam Synthon Method".

RESULTS AND DISCUSSION

Asymmetric Synthesis of α-Amino Acids, Dipeptides and Their Derivatives by The "β-Lactam Synthon Method"

First, we looked at the effectiveness of asymmetric induction by homochiral ketenes (2) generated in situ from homochiral 4-phenyloxazolidinylacetyl

chloride (1a: S, 1b:R) in the [2+2] cycloaddition to homochiral imines (3) derived from esters of alanine, valine, phenylalanine, and methionine (Scheme 1). As shown in Table 1, it is very fortunate to find that the chiral centers in the imines (3) do not have any significant influence on the asymmetric induction and no appreciable double asymmetric induction is observed, viz., the chiral center in the ketene (2) plays a key role in this asymmetric synthesis. In each case, the reaction gave only one of the two possible diastereomers: In spite of an an extensive search by HPLC and ^{1}H NMR spectroscopy, the other diastereomer of 4 could not be detected in any case examined.[22]

Scheme 1.

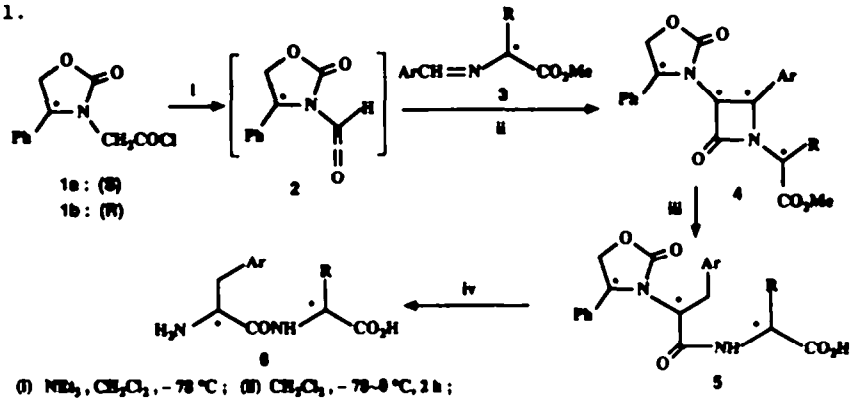


Table 1. Asymmetric [2+2] Cycloadditions of Homochiral Ketenes (2) to Homochiral Imines (3)

Entry	Ketene	Imine (3)		β-Lactam 4		
		Ar	R	Yield(%)	Config.	% d.e.[a]
a	2a	Ph	Me (R)	82	(3S,4R)	>99
b	2a	Ph	Me (S)	76	(3S,4R)	>99
c	2b	Ph	^{i}Pr (S)	92	(3R,4S)	>99
d	2b	Ph	^{i}Pr (R)	86	(3R,4S)	>99
e	2b	Ph	$PhCH_2$ (S)	91	(3R,4S)	>99
f	2b	Ph	$MeS(CH_2)_2$ (S)	79	(3R,4S)	>99

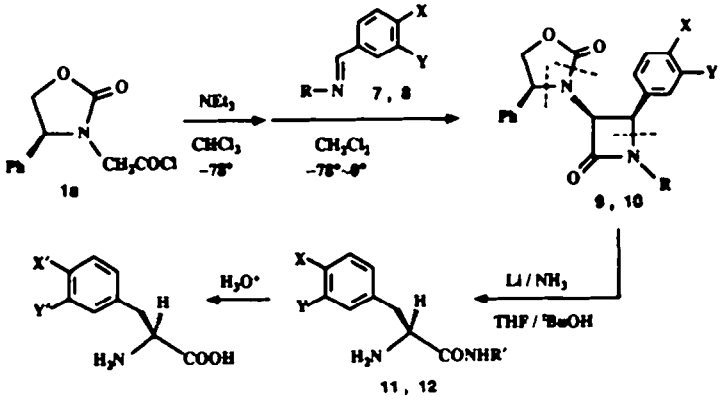
[a] Determined by HPLC analysis (see Experimental Section).

The β-lactams (4) thus obtained were saponified and then converted to the corresponding N-protected dipeptides (5) quantitatively through hydrogenolysis over Pd/C in MeOH: The N-protected dipeptides (6) can be used for fragment condensation with other N-terminus-free peptide units. The modified Birch reduction[9] of 5 with Li in liquid NH_3/THF/t-BuOH gave the corresponding homo-

chiral dipeptides (6) in excellent yields (Scheme 1).[22]

The simple asymmetric synthesis of homochiral α-amino acids is achieved by the asymmetric [2+2] cycloaddition followed by reductive cleavage as well. For example, the amides of phenylalanine (11: X=Y=H, R'=Me) and O,O-dimethyldopa (12: X=Y=MeO, R'=H) with >99.5% e.e. were synthesized via β-lactams, 9 (X=Y=H, R=Me) and 10 (X=Y=MeO, R=$PhCH_2$), which were obtained through the asymmetric [2+2] cycloadditions of the homochiral ketene (2) generated from 1 to imines, 7 and 8, respectively, in high yields (Scheme 2).

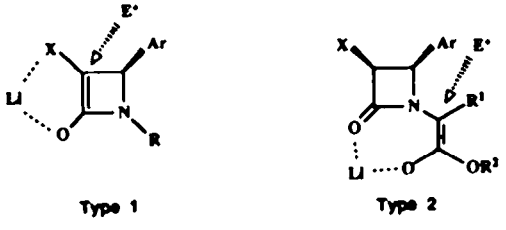
Scheme 2



The asymmetric cycloaddition-reductive cleavage process will open an effective route to homochiral peptides since it is demonstrated that the desirable absolute configurations can be introduced to the chiral β-lactams 4 regardless of the chiral centers in the imines and no racemization is observed during the modified Birch reduction. This new method is particularly useful for the introduction of unnatural amino acid residues with desired absolute configurations into physiologically active peptides.

Asymmetric Synthesis of α-Alkyl-α-Amino Acids, Dipeptides and Their Derivatives

We have studied two types of asymmetric alkylations, (i) the alkylation of the C-3 carbon of a β-lactam (Type 1)[23,24] and (ii) the alkylation of a side chain carbon bonding to the β-lactam nitrogen (Type 2).[25,24]



Type 1 Type 2

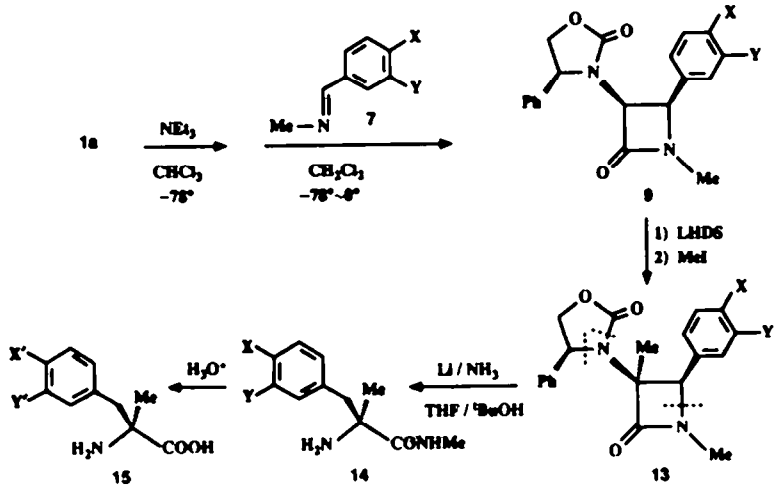
In the Type 1 alkylation, an electrophile should attack the C-3 from the opposite side of the bulky 4-aryl group of the β-lactam enolate to avoid steric conflict. In the Type 2 alkylation, the enolate is supposed to form a chelate

with the β-lactam oxygen and then an electrophile should attack from the back side of the 4-aryl group.

If the reactions proceed following our hypotheses, chiral quaternary carbons should be created in a highly predictable manner, which is very beneficial for the synthesis of a series of new α-substituted α-amino acids and their derivatives.

We applied the **Type** 1 alkylation to the asymmetric synthesis of the amides of (S)-α-methylphenylalanine (**14a**: X=Y=H) and (S)-α-methyl-dopa (**14b**: X=Y=MeO) (**Scheme** 3). (S)-α-Methyl-dopa (**15b**: X'=Y'=OH) is an inhibitor of dopa decarboxylase and being widely used as antihypertensive drug.[10]

Scheme 3.



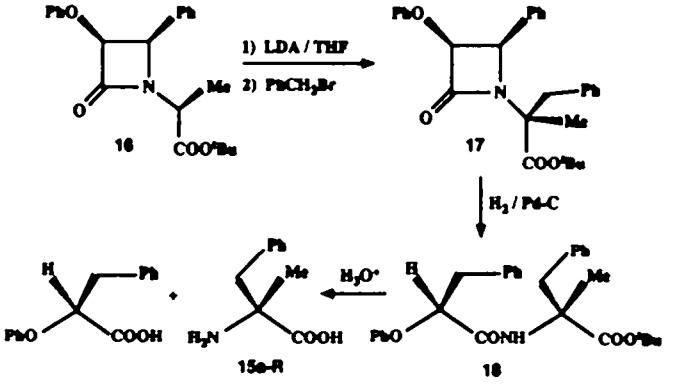
First, homochiral β-lactams (**9a,b**: >99.5% d.e.) were synthesized through the asymmetric [2+2] cycloadditions of the homochiral ketene (**2a**) generated *in situ* from **1a** and triethylamine to arylmethylidene-N-methylamines (**7a,b**). Second, to a β-lactam (**9**) in THF was added LHDS (1.3 eq.) in THF at -78 °C in order to generate the **Type** 1 chiral β-lactam enolate. Methyl iodide (3 eq.) was then added to the enolate and the mixture was stirred overnight at -78°C ∿ room temperature. A usual work-up and purification on a short silica gel column gave a (3S)-3-methyl-3-oxazolidinyl-β-lactam (**13**: >99.5% d.e.) in excellent yield. The 3-methyl-β-lactams (**13a,b**) thus obtained were submitted to the modified Birch reduction to give the corresponding N-methylamides of α-methyl-α-amino acids (**14**) in excellent yields, which are the direct precursors of (S)-α-methyl-phenylalanine (**15a**) and (S)-α-methyl-dopa (**15b**).

The **Type** 2 alkylation was applied to the asymmetric synthesis of (S)-α-methylphenylalanine (**Scheme** 4) and (R)-phenylalanyl-(S)-α-methylphenylalanine (**Scheme** 5).[25]

A β-lactam enolate was generated by treating a β-lactam (**16**) with LDA (1.0

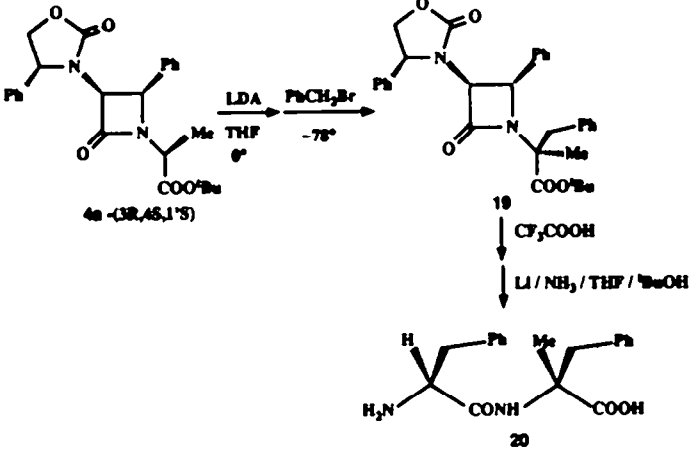
eq.) in THF at 0 ∿ 5°C and the solution was cooled to -78 ∿ -90°C. The asymmetric alkylation was carried out by adding benzyl bromide to the enolate to give an alkylated β-lactam ester (17) with >98 % d.e. The hydrogenolysis of 17 on Pd-C gave the corresponding dipeptide derivative (18) in nearly quantitative yield. The hydrolysis of 17 with 6N hydrochloric acid in aqueous THF at 110 °C gave optically pure (R)-α-methylphenylalanine (15a-R) in high yield.

Scheme 4



The asymmetric alkylation of a homochiral β-lactam ester [4a-(3R,4S,1'S)] prepared via the asymmetric ketene addition (vide supra) in which the 3-amino group of the β-lactam was protected as an oxazolidinone structure, proceeded with extremely high stereoselectivity (>99% d.e.) to give the methylated β-lactam ester (19) in excellent yield (Scheme 5). Deprotection of 19 with TFA and the dissolving metal reduction gave (R)-phenylalanyl-(S)-α-methylphenylalanine (20: >99% d.e.) in good yield.

Scheme 5



Consequently, it is demonstrated that the Type 1 and Type 2 asymmetric alkylations of chiral β-lactams provide unique and effective routes to a variety of α-substituted aromatic α-amino acids and their derivatives which have chiral quaternary centers. Further studies on the applications of these methods to new double and triple asymmetric alkylations are actively in progress and the results will be published elsewhere shortly.

EXPERIMENTAL SECTION

General Methods

Melting points are not corrected. Microanalyses were performed by M-H-W Laboratories, Phoenix, Arizona. ^{1}H-NMR spectra (chemical shifts in parts per million from the internal Me_4Si) were recorded on a Nicolet NT-300 or a General Electric QE-300 spectrometer. IR spectra were measured with a Perkin-Elmer Model 1310 or Model 1430 spectrometer using samples as neat liquid or KBr disks. Optical rotations were measured with Perkin-Elmer Model 241 polarimeter. HPLC analyses were carried out with a Waters HPLC assembly with a Waters Model 440 UV detector with a Spectra-Physics SP4270 integrator using a column packed with a Waters Resolve 5μ-Spherical Silica (normal phase), a 5μ-Spherical C18 or a μ-Bondapak C18 (reversed phase).

Materials

All amino acids were used as purchased. Benzaldehyde, 1,1,1,3,3,3-hexamethyldisilazane (HMDS) and t-butanol were purchased and distilled over activated 4A molecular sieves before use. Tetrahydrofuran (THF) used in this work was freshly distilled under nitrogen in the presence of sodium and benzophenone. Palladium on carbon (5% and 10%) was purchased from Aldrich Chemical Co. (4S)- and (4R)-Phenyloxazolidinylacetyl chloride were obtained by the reported method.[9] (3S,4R)-1-Benzyl-3-[(4S)-phenyloxazolidinyl]-4-(3,4-dimethoxyphenyl)azetidin-2-one (10) was prepared following the procedure reported by us.[23] Silica gel used for chromatography, MN-Kieselgel 60 (Silica Gel 60) was purchased from Brinkmann Instruments, Inc.

Synthesis of β-Lactams (4) Through Asymmetric [2+2] Cycloaddition

Typically, the synthesis of the (3R,4S)-β-lactam 4a from 1b and 2a (R=$PhCH_2$) is described: To 1a (1.0 mmol) in CH_2Cl_2 (10 ml) was added Et_3N (1.8 mmol) at -78 °C. After stirring for 15 min, 3a (1.2 mmol) in CH_2Cl_2 was added to the solution. The reaction system was allowed to warm to 0 °C for 2 h. Then, the reaction mixture was quenched with water. After the usual workup and chromatographic purification, 4a was obtained as colorless solid (91% yield, 100% d.e. by HPLC).

4a: m.p. 150-152°C; $[\alpha]_D^{20}$ +22.1° (c 1.0, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.21 (d, J=7.6 Hz, 3H), 3.66 (s, 3H), 3.94 (m, 2H), 4.20 (t, J=8.8 Hz, 1H), 4.34 (t, J=8.1 Hz, 1H), 4.57 (d, J=5.1 Hz, 1H), 4.85 (d, J=5.1 Hz, 1H), 7.1-7.5 (m, 10H); IR (KBr disk) 1780, 1760, 1735 (νC=O) cm^{-1}. Anal. Calcd. for $C_{22}H_{22}N_2O_5$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.75; H, 5.54; N, 7.00.

4b: m.p. 174-175°C; $[\alpha]_D^{20}$ +29.5° (c 2.7, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.21 (d, J=7.5 Hz, 3H), 3.70 (s, 3H), 3.90 (m, 1H), 4.10 (m, 2H), 4.48 (d, J=5.1 Hz, 1H), 4.72 (q, J=7.5 Hz, 1H), 5.02 (d, J=5.1 Hz, 1H), 7.2-7.6 (m, 10H); IR (KBr disk) 1780, 1760, 1735 (νC=O) cm^{-1}. Calcd. for $C_{22}H_{22}N_2O$: C, 66.99; H, 5.62; N, 7.10. Found: C, 66.87; H, 5.46; N, 7.00.

4c: m.p. 161-162°C; $[\alpha]_D^{20}$ -58.89° (c 1.6, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 0.76 (d, J=6.7 Hz, 3H), 0.97 (d, J=6.7 Hz, 3H), 1.95 (m, 1H), 3.68 (s, 3H), 4.0 (m, 3H), 4.28 (d, J=7.1 Hz, 1H), 4.45 (d, J=5.2 Hz, 1H), 5.02 (d, J=5.2 Hz, 1H), 7.0-7.5 (m, 10H); IR (KBr disk) 1770, 1740 (νC=O) cm^{-1}. Anal. Calcd for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.30; H, 6.28; N, 6.55.

4d: m.p. 159-160°C; $[\alpha]_D^{20}$ -16.9° (c 1.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 0.94 (d, J=6.7 Hz, 3H), 1.18 (d, J=6.7 Hz, 3H), 2.72 (m, 1H), 3.57 (s, 3H), 3.62 (d, J=9.9 Hz, 1H), 3.91 (dd, J=8.1, 7.2 Hz, 1H), 4.16 (dd, J=8.8, 8.1 Hz, 1H), 4.21 (dd, J=8.8, 7.2 Hz, 1H), 4.50 (d, J=5.2 Hz, 1H), 4.67 (d, J=5.2 Hz, 1H), 7.1-7.5 (m, 10H); IR (KBr disk) 1770, 1740 (νC=O) cm^{-1}. Anal. Calcd. for $C_{24}H_{26}N_2O_5$: C, 68.23; H, 6.20; N, 6.63. Found: C, 68.45; H, 6.29; N, 6.87.

4e: m.p. 170-172°C; $[\alpha]_D^{20}$ -48.4° (c 1.8, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.97 (dd, J=8, 14 Hz, 1H), 3.06 (dd, J=8, 14 Hz, 1H), 3.63 (s, 3H), 3.91 (dd, J=2.7, 0.7 Hz, 1H), 4.12 (dd, J=2.7, 8.4 Hz, 1H), 4.16 (dd, J=0.7, 8.4 Hz, 1H), 4.43 (d, J=5.1 Hz, 1H), 4.62 (t, J=8 Hz, 1H), 4.66 (d, J=5.1 Hz, 1H), 7.0-7.4 (m, 15H); IR (KBr disk) 1775, 1730 (νC=O) cm^{-1}. Anal. calcd. for $C_{28}H_{26}N_2O_5$: C, 71.47; H, 5.57; N, 5.96. Found: C, 71.30; H, 5.49; N, 5.95.

4f: m.p. 120-122°C; $[\alpha]_D^{20}$ -37.1° (c 2.3, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 1.90 (s, 3H), 1.72-2.02 (m, 2H), 2.36-2.56 (m, 2H), 3.71 (s, 3H), 3.92 (dd, J=7.8, 7.1 Hz, 1H), 4.02 (dd, J=8.2, 7.1 Hz, 1H), 4.13 (dd, J=8.2, 7.8 Hz, 1H), 4.49 (d, J=5.2 Hz, 1H), 4.74 (dd, J=8.7, 5.1 Hz, 1H), 5.03 (d, J=5.2 Hz, 1H), 7.10-7.90 (m, 10H); IR (KBr disk) 1760, 1730 (νC=O) cm^{-1}. Anal. Calcd. for $C_{24}H_{26}N_2O_5S$: C, 63.41; H, 5.77; N, 6.17; S, 7.06. Found: C, 63.25; H, 5.78; N, 6.19; S, 7.00.

Synthesis of Homochiral Dipeptides (6) from β-Lactams (4)

Typically, 4c (0.44 mmol) was saponified with 1N NaOH followed by hydrogenolysis (1 atm H_2) over 5% Pd/C (0.44 mmol) in MeOH (10 ml) at 50 °C for 5 h to give 5c in 95% yield. The Birch reduction of 5c (0.44 mmol) was carried out with Li (3.5 mmol) in liquid NH_3 (15 ml), THF (5 ml), and t-BuOH (3.5 mmol) at -78 °C for 15 min. The reaction was quenched with solid NH_4Cl. After usual workup, (R)-Phe-(S)-Val-OH (6c) was obtained in 97% yield (HPLC).

The HPLC analysis (Waters μ-Bondapak C18 column, MeOH/0.1N NH_4OAc, pH 5) of the dipeptide thus obtained showed single peak (>99.5% d.e.) corresponding to that of the authentic sample in every case examined, which clearly indicated that no racemization took place during the process.

Synthesis of (3S,4R)-1-Methyl-3-[(4S)-phenyloxazolidinyl]-4-arylazetidin-2-ones (9)

Typically, to a solution of (4S)-phenyloxazolidinylacetic acid (1.73 g, 7.83 mmol) in toluene (40 mL) was added oxalyl chloride (3.41 mL, 39.2 mmol) and two drops of dimethylformamide at room temperature with stirring, and the mixture was heated at 60°C for 5 h. The removal of the solvents and excess oxalyl chloride under a vacuum to gave the corresponding acid chloride quantitatively. The acid chloride thus obtained was dissolved in methylene chloride (50 mL) and the solution was cooled to -78°C. Triethylamine (2.0 mL, 14.1 mmol) was added to the acid chloride solution and the mixture was stirred at -78°C for 30 min. Then, a solution of 3,4-Dimethoxybenzylidene-N-methylamine (1.61 g, 9.0 mmol) in methylene chloride (20 mL) was added to the mixture at -78°C with stirring. The reaction mixture was allowed to stir overnight with gradual increase of temperature to room temperature. The reaction was quenched with water (10 mL) followed by the addition of citric acid (3.8 g) and the reaction mixture was stirred for 1.5 h to decompose the excess Schiff base. The methylene chloride layer was separated, washed with water, washed with brine, dried over anhydrous sodium sulfate and concentrated to dryness. The crude product thus obtained was purified on a silica gel column (eluent: $CHCl_3$/AcOEt = 1) to give 9b (2.84 g, 95%) as colorless solid.

9a: 85% yield; m.p. 236-238°C; $[\alpha]_D^{20}$ +54.1° (c 1.1, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.89 (s, 3H), 3.94 (dd, J=7.7, 7.3 Hz, 1H), 4.22 (dd, J=8.8, 7.7 Hz, 1H), 4.42 (dd, J=8.8, 7.3 Hz, 1H), 4.58 (d, J=4.8 Hz, 1H), 4.69 (d, J=4.8 Hz, 1H), 7.0-7.5 (m,10H); IR (KBr disk) 1745, 1730 (νC=O) cm-1. Anal. Calcd. for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.63; H, 5.61; N, 8.61.

9b: 95% yield; m.p. 114-117°C; $[\alpha]_D^{20}$ +7.10° (c 6.2, $CHCl_3$); ^{1}H-NMR ($CDCl_3$) δ 2.86 (s, 3H), 3.90 (s, 3H), 3.93 (s, 3H), 3.85-4.05 (m, 1H), 4.22 (dd, J=8.8, 8.0 Hz, 1H), 4.28 (dd, J=8.8, 6.7 Hz, 1H), 4.45 (d, J=4.6 Hz, 1H), 4.63 (d, J=4.6 Hz, 1H), 6.8-7.5 (m, 8H); IR (KBr disk) 1770, 1755, 1740 (νC=O) cm^{-1}. Anal. Calcd for $C_{21}H_{22}N_2O_5$: C, 65.95; H, 5.80; N, 7.33. Found: C, 65.91; H, 5.78; N, 7.39.

Synthesis of 2-Amino-3-aryl-N-methylpropionamides (11, 12)

In a typical run, ammonia is condensed (30 mL) to a reaction flask, equipped with a dry ice/acetone condenser, containing a solution of 9 or 10 (0.50 mmol) in THF (35 mL), t-butanol (4 mL), and lithium (5.0 mmol) at -78°C for 5-7 min with stirring: For the reaction of 10, HMDS (mmol) was used as an additive. The reaction is quenched with solid ammonium chloride (600 mg). After the usual work-up and purification on a silica gel column, 11 or 12 is obtained as colorless oil.

11: $[\alpha]_D^{20}$ -6.8° (c 1.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 1.38 (broad s, 2H), 2.68 (dd, J=13.7, 9.5 Hz, 1H), 2.82 (d, J=5.0 Hz, 3H), 3.29 (dd, J=13.7, 4.0 Hz, 1H), 3.61 (dd, J=9.5, 4.0 Hz, 1H), 7.1-7.6 (m, 6H); IR (neat) 3350, 3320, 3270 (νNH), 1640 (νC=O), 1515 (δNH) cm^{-1}. Anal. Calcd. for

$C_{10}H_{14}N_2O \cdot 0.25H_2O$: C, 65.72; H, 8.00; N, 15.33. Found: C, 65.72; H, 8.14; N, 15.08.

12: $[\alpha]_D^{20}$ -3.94° (c 0.94, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.90 (broad s, 2H), 2.69 (dd, J=13.7, 9.4 Hz, 1H), 3.20 (dd, J=13.7, 4.0 Hz, 1H), 3.60 (dd, J=9.4, 4.0 Hz, 1H), 3.89 (s, 6H), 5.79 (broad s, 1H), 6.84-6.75 (m, 3H), 7.14 (broad s, 1H); IR (KBr disk) 3330, 3300, 3240, 3180 (νNH), 1640 (νC=O), 1510 (δNH) cm^{-1}. Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.91; H, 7.19; N, 12.49. Found: C 58.96; H, 7.14; N, 12.37.

Synthesis of (3S,4R)-1-Methyl-3-methyl-3-[(4S)-phenyloxazolidinyl]-4-arylazetidin-2-ones (13)

The synthesis of 13b (X = Y = MeO) is typically described. Lithium hexamethyldisilazide (LHDS, 2.90 mmol) in THF (15 mL) was added to 9b (853 mg, 2.23 mmol) in THF (35 mL) at -78 °C and the mixture was stirred for 1 h. Methyl iodide (0.36 mL, 5.80 mmol) was then added to the enolate at the same temperature and the mixture was stirred for overnight: The reaction system was allowed to warm gradually to room temperature. The reaction was quenched with 10% ammonium chloride, and the reaction mixture was acidified to pH 7 by 1N HCl, THF removed, and extracted with methylene dichloride. After usual work-up and purification on a short silica gel column, (3S)-3-methyl-3-oxazolidinyl-β-lactam (13b) was obtained in 95% yield (713 mg, >99.5% d.e. by HPLC; hexane/AcOEt = 1/3) as colorless solid.

13a: 95% yield; m.p. 214-216°C; $[\alpha]_D^{20}$ +22.8° (c 1.2, $CHCl_3$); ^1H-NMR ($CDCl_3$) δ 1.58 (s, 3H), 2.82 (s, 3H), 3.77 (m, 1H), 3.83 (m, 1H), 4.50 (m, 1H), 4.51 (s, 1H), 7.1-7.5 (m, 10H); IR (KBr disk) 1750, 1730 (νC=O) cm^{-1}. Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.46; H, 6.07; N, 8.33.

13b: 93% yield; m.p. 249-250°C; $[\alpha]_D^{20}$ +47.2° (c 8.0, $CHCl_3$); ^1H-NMR ($CDCl_3$) δ 1.51 (s, 3H), 2.85 (s, 3H), 3.79 (m, 2H), 3.91 (s, 3H), 3.92 (s, 3H), 4.40 (m, 1H), 4.43 (s, 1H), 6.6-7.4 (m, 8H); IR (KBr disk) 1760, 1745, 1735 (νC=O) cm^{-1}. Anal. Calcd. for $C_{22}H_{24}N_2O_5 \cdot 0.25H_2O$: C, 65.90; H, 6.16; N, 6.99. Found: C, 65.83; H, 6.17; N, 6.92.

Synthesis of (S)-2-Amino-3-aryl-2-methyl-N-methylpropionamides (14)

The methylated β-lactams (13) were converted to the corresponding N-methylamides of α-methyl-α-amino acids (14) through the modified Birch reduction in the same manner as described for the synthesis of 11 and 12.

14a: colorless liquid; $[\alpha]_D^{20}$ +50.5° (c 0.5, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.35 (broad s, 2H), 1.37 (s, 3H), 2.63 (d, J=13.2 Hz, 1H), 2.73 (d, J=4.9 Hz, 3H), 3.36 (d, J=13.2 Hz, 1H), 7.1-7.5 (m, 6H); IR (neat) 3325, 3300(s), 3200(s) (νNH), 1645 (νC=O), 1530 (δNH) cm^{-1}. Anal. Calcd. for $C_{11}H_{16}N_2O$: C, 68.71; H, 8.39; N, 14.57. Found: C, 68.83; H, 8.40; N, 14.66.

14b: colorless liquid; $[\alpha]_D^{20}$ -4.68° (c 4.2, $CHCl_3$); ^1H-NMR ($CDCl_3$) δ 1.38 (s, 3H), 1.40 (broad s, 2H), 2.48 (d, J=13.3 Hz, 1H), 2.74 (d, J=4.5 Hz, 3H), 3.40 (d, J=13.3 Hz, 1H), 3.83 (s, 3H), 3.95 (m, 3H), 6.67-6.92 (m, 3H), 7.47 (broad d, J=4.5 Hz, 1H); IR (neat) 3325, 3300(s), 3200(s) (νNH), 1645 (νC=O), 1505 (δNH) cm-1. Anal. Calcd. for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.11. Found: C, 61.77; H, 7.89; N, 11.30.

Preparation of 1-[(S)-1-(t-butoxycarbonyl)ethyl]-(3S,4R)-3-phenoxy-4-phenylazetidin-2-one (16)

A mixture of t-butyl benzylidene-(S)-alaninate (8.25 g, 35.5 mmol) and triethylamine (7.35 g, 72.0 mmol) in dichloromethane (50 mL) was added dropwise a solution of phenoxyacetyl chloride (12.1 g, 71.0 mmol) in dichloromethane (50 mL) at -78°C over a period of 30 min with stirring. The reaction mixture was allowed to warm gradually to room temperature with stirring for 12 h. The reaction was quenched by adding methanol (10 mL). A usual work-up followed by chromatography on silica gel (eluent; AcOEt/hexane = 1/10) gave (3S,4R,1'S)-β-lactam (16; 5.22 g, 40.1%) and (3R,4S,1'S)-β-lactam (16'; 5.20 g, 39.9%).

16: colorless crystals; m.p. 110-111°C; $[\alpha]_D^{20}$ -20.9° (c 1.0, $CHCl_3$) ; ^1H NMR ($CDCl_3$) δ 1.42 (s, 9H), 1.70 (d, J=7.5 Hz, 3H), 3.85 (q, J=7.5 Hz, 1H), 5.02 (d, J=4.6 Hz, 1H), 5.43 (d, J=4.6 Hz, 1H), 6.5-7.5 (m, 10H); IR (KBr disk) 1755 (νC=O), 1735 (νC=O) cm^{-1}.

16': colorless crystals; m.p. 114.5-115.5°C; $[\alpha]_D^{25}$ +4.7° (c 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.11 (d, J=7.4 Hz, 3H), 1.49 (s, 9H), 4.56 (q, J=7.4 Hz, 1H), 5.25 (d, J=4.7 Hz, 1H), 5.49 (d, J=4.7 Hz, 1H), 6.5-7.5 (m, 10H); IR (KBr disk) 1750 (νC=O), 1730 (νC=O) cm^{-1}.

Although we used 16 for the synthesis of (R)-α-methylphenylalanine via the asymmetric alkylation here, 16' gives (S)-α-methylphenylalanine through the same procedure.

Synthesis of a Dipeptide Derivative (18) and (R)-α-methylphenylalanine (15a-H) Through the Type 2 Asymmetric Alkylation

To a solution of β-lactam ester 16 (200 mg, 0.545 mmol) in THF (15 mL) was added 1.0 equivalent of LDA (1.53 mL of 0.355 M solution in n-hexane/THF) at 0-5 °C and the mixture was stirred for 5 min at the same temperature. The reaction system was cooled to -78 °C and 3.0 equivalent of benzyl bromide (280 mg, 1.63 mmol) was added. The reaction mixture was stirred at -78 °C for 5 h and quenched with a saturated methanol solution of ammonium chloride (2 mL). After the solvent was evaporated, the residue was extracted with ethyl acetate, washed with brine and water, dried over anhydrous sodium sulfate, and solvent removed to give crude alkylation product. The ^1H NMR using toluene as the internal standard showed the formation of 17 in 96% yield. The ^1H NMR showed the formation of only one diastereomer, the other isomer was not detected. After purification on a silica gel column, analytically as well as optically pure 17 (203 mg, 82% yield) was obtained.

17: colorless solid; m.p. 101-102 °C; $[\alpha]_D$ -1.7° (c 2.78, CH_2Cl_2); ^1H- NMR ($CDCl_3$) δ 1.19 (s, 3H), 1.53 (s, 9H), 3.01 (d, J = 13.5 Hz, 1H), 3.45 (d, J = 13.5 Hz, 1H), 4.27 (d, J = 4.7 Hz, 1H), 5.19 (d, J = 4.7 Hz, 1H), 6.60-7.50 (m, 15H); IR (KBr disk) 1750, 1730 (νC=O) cm^{-1}. Anal. Calcd for $C_{29}H_{31}NO_4$: C, 76.14; H, 6.78; N, 3.06. Found: C, 75.96; H, 6.70; N, 3.08.

A solution of 17 (230 mg, 0.5 mmol) in MeOH (10 mL) was added to 10% Pd-C (60 mg) in a standard hydrogenolysis apparatus and the mixture was heated at 50 °C for 8 h with stirring. The progress of the reaction was monitored by TLC. After the reaction was completed, the catalyst was filtered and the solvent was evaporated to give the corresponding dipeptide derivative (18) in nearly quantitative yield (229 mg, 99%): colorless viscous oil; $[\alpha]_D^{25}$ -13° (c 0.81, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.39 (s, 9H), 1.55 (s, 3H), 3.11 (d, J=13.6 Hz, 1H), 3.12 (dd, J=14.2, 8.0 Hz, 1H), 3.33 (dd, J=14.2, 3.3 Hz, 1H), 3.56 (d, J=13.6 Hz, 1H), 4.62 (dd, J=8.0, 3.3 Hz, 1H), 6.6-7.4 (m, 16H); IR (neat) 3360 (νNH), 1715 (νC=O), 1665 (νC=O) cm^{-1}.

A suspension of 18 (150 mg, mmol) in 6N HCl (mL) in a Pyrex ampoule was heated at 120°C for 48 h. Hydrochloric acid was removed *in vacuo*. Water (5 mL) was added to the solid residue and extracted with ether (5 mL x 2) to remove the resulting 2-phenoxy-3-phenylpropanoic acid. The aqueous layer was concentrated *in vacuo* to dryness yielding white powder which gave a positive ninhydrin test. The white powder, i.e., (R)-α-methylphenylalanine hydrochloride (nearly quantitative yield), was dissolved in water and passed through an ion exchange column (Dowex-3) to give free (R)-α-methylphenylalanine (50 mg, 85.5%) as white solid: $[\alpha]_D^{20}$ +20.5 ± 1° (c 1.0, H_2O) [lit.[26] $[\alpha]_D^{20}$ -20.7° (c 0.805, H_2O) for S isomer]; ^1H NMR (D_2O) δ 1.90 (s, 3H), 3.30 (d, J=14 Hz, 1H), 3.7 (d, J=14 Hz, 1H), 7.6-7.8 (m, 5H).

Synthesis of (R)-Phenylalanyl-(S)-α-methylphenylalanine (20)

In a manner similar to that described for the asymmetric alkylation of 16, 4a-(3R,4S,1'S) was deprotonated by LDA (1.0 eq.) at 0°C in THF followed by the addition of benzyl bromide (3 eq.) at -78°C to give 19 (>99% d.e.) in 90% yield.

19: colorless needles; m.p. 200-200.5 °C; $[\alpha]_D^{20}$-40° (c 1.0, CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 1.31 (s, 3H), 1.51 (s, 9H), 2.93 (d, J = 13.4 Hz, 1H), 3.29 (d, J = 13.4 Hz, 1H), 3.90 (m, 1H), 4.10 (m, 2H), 4.23 (s, 2H), 6.90-7.70 (m, 15H); IR (KBr disk) 1780, 1755, 1740 (νC=O) cm^{-1}. Anal. Calcd for $C_{32}H_{34}N_2O_5$: C, 73.00; H, 6.46; N, 5.32. Found: C, 73.00; H, 6.60; N, 5.32.

The deprotection of t-butyl ester moiety of **19** was carried out by reacting **19** (400 mg) with trifluoroacetic acid (TFA, 2.0 mL) in dichloromethane (10 mL) at room temperature with stirring for 1 h. The removal of TFA and the solvent in vacuo gave C-terminus free **19** in quantitative yield. The reductive cleavage of the β-lactam ring as well as the deprotection of N-terminus were carried out by using the modified Birch reduction in essentially the same manner as that described for the synthesis of **14** from **13**. Thus, to a dark blue solution of lithium (13.8 mg, 2.0 mmol) in liquid ammonia (20 mL) was added a solution of C-terminus free **19** (200 mg, 0.43 mmol) and t-BuOH (150 mg, 2.0 mmol) in THF (8 mL) at -78 °C and the mixture was stirred for 5 min. The reaction was quenched by adding solid ammonium chloride (100 mg) at -78 °C. After the solvent was removed the residue was dissolved in water (5 mL), acidified to pH3 and washed with ether (10 mL X 3). The aqueous layer was neutralized with 0.1N ammonium hydroxide and charged to an ion exchange column packed with Dowex 50-X8. After inorganic salts were washed out with water, **20** was obtained from 0.1 ammonium hydroxide elute, which was monitored by HPLC (Waters 5μ-Spherical C18 column, MeOH/0.1N NH_4OAc = 1/1 v/v; pH was adjusted to 5.0 with AcOH). Recrystallization from hot water gave 106 mg (76.3%) of pure **20** (>99.5% d.e.).

20: m.p. >250°C; colorless needles; $[\alpha]_D^{20}$ +45° (c 1.5, MeOH); ^1H NMR (CD_3OD) δ 1.56 (s, 3H), 2.77 (dd, J=8.9, 14.2 Hz, 1H), 2.18 (dd, J=8.5, 10.7 Hz, 1H), 2.87 (dd, J=5.8, 14.2 Hz, 1H), 3.26 (d, J=13.3 Hz, 1H), 3.35 (d, J=13.3 Hz, 1H), 3.99 (dd, J=5.8, 8.9 Hz, 1H), 7.0-7.5 (m, 10H) (HOD appears at δ 4.92 as a broad singlet); ^{13}C NMR (CD_3OD) δ 24.32, 38.85, 42.72, 56.24, 63.78, 127.44, 128.57, 128.96, 130.02, 130.39, 131.15, 136.29, 139.23, 168.53, 179.07.

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