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SYNTHESIS OF CHIRAL OLIGOPEPTIDES BY MEANS OF CATALYTIC ASYMMETRIC HYDROGENATION OF DEHYDROPEPTIDES

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Abstract—Asymmetric hydrogenations of Ac-ΔTyr(Ac)-(*S*)-Ala-Gly-OMe (**6**), Ac-ΔTyr(Ac)-(*R*)-Ala-Gly-(*S*)-Phe-OMe (**7**), Ac-ΔPhe-NH-CH(*R*)-CH_2-OCH_2Ph (**10**), HCO-ΔPhe-(*S*)-Leu-OMe (**16**), X-AA-ΔPhe-AA′-OMe (**5**: X = ^{t}BOC, CBZ, CF_3CO; AA, AA′ = α-amino acid), and ^{t}BOC-AA-ΔPhe-AA′-NH-Y (**21**: Y = H, NH-AA′-ΔPhe-AA-^{t}BOC, NHPh), catalyzed by cationic Rh complexes, $[L^*Rh(NBD)]^+ClO_4$ (L^* = chiral diphosphine), were performed to give the corresponding chiral oligopeptides with high stereoselectivities. It was found that the nature of the N-protecting group of dehydrotripeptides (**5**) exerted a significant influence on the asymmetric induction as well as catalyst efficiency. The chiral centers in AA and AA′ amino acid residues in **5** were also found to have some influence on the catalytic asymmetric induction. Possible mechanism which can accommodate these effects are discussed. Asymmetric reduction of RCOCO-AA-OMe (**13**) via hydrosilylation was carried out to give chiral depsipeptide units. The asymmetric hydrogenation of dehydropeptides was successfully applied to the synthesis of enkephalin analogs, Ac-(*R*)-Tyr-(*R*)-Ala-Gly-(*S*)-Phe-(*S*)-Leu-OMe (**23**) and Ac-(*S*)-Tyr-(*R*)-Ala-Gly-(*S*)-Phe-(*S*)-Leu-OMe (**29**).

Recently it has been shown that the asymmetric hydrogenations of dehydrodipeptides of type **1** or **2** catalyzed by chiral Rh complexes give the corresponding optically active dipeptides with desired configurations, where the type **1** dehydrodipeptides are very good substrates achieving quite high stereoselectivities[1] while the type 2 dehydrodipeptides realize only moderate to good selectivities.[2] Kagan *et al.* have succeeded in "double" asymmetric hydrogenation of N-acetyldehydrophenylalanyldehydrophenylalanine methyl ester (**3**) with high diastereo- and enantioselectivities.[3] We also have reported the preliminary results on the effective asymmetric hydrogenations of dehydrodipeptide derivatives (**4**),[4] dehydrotripeptides of the type **5**,[5] and their application to the synthesis of peptide hormone analogs.[6] As it has recently been shown that significant modifications of physiological activities can be effected through introduction of one or more "unnatural" amino acid residues instead of "natural" ones in a biologically active peptide such as enkephalin, vasopressin,, angiotensin II, gonadoliberin and other hormones,[7] the asymmetric hydrogenation of dehydropeptides may furnish effective new device for the synthesis of such peptides. We will describe here a full account of our research on the asymmetric hydrogenation of dehydrooligopeptides including depsipeptide unit synthesis via asymmetric hydrosilylation, and its application to the synthesis of enkephalin analogs.

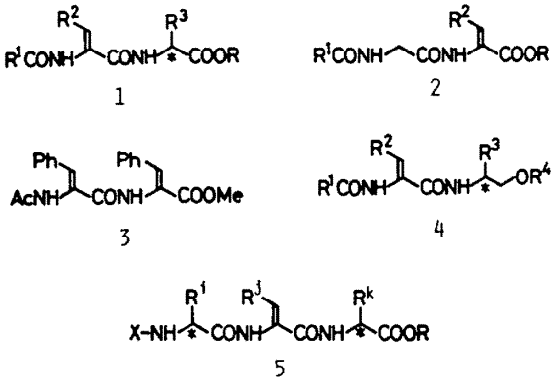

Chart 1.

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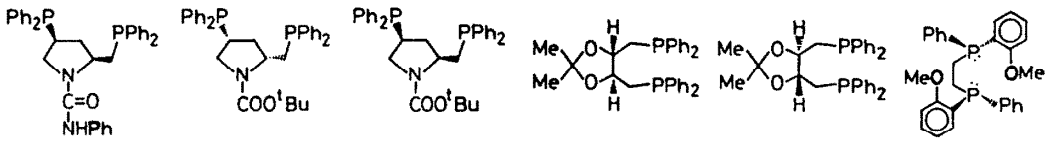


Chart 2.

RESULTS AND DISCUSSION

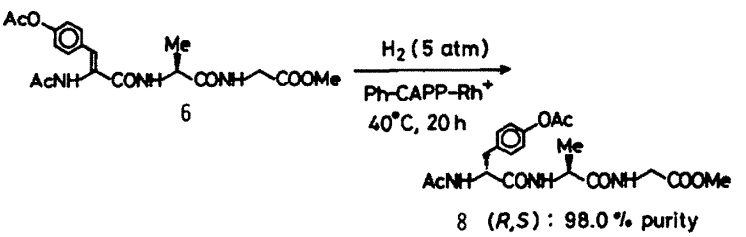
Asymmetric hydrogenation of dehydrotripeptide and dehydrotetrapeptide bearing dehydroamino acid residues at N-*termini*

As an extension of the asymmetric hydrogenation of dehydrodipeptides of the type **1**, we carried out the reaction of Ac-ΔTyr(Ac)-(*S*)-Ala-Gly-OMe (**6**) and Ac-ΔTyr(Ac)-(*R*)-Ala-Gly-(*S*)-Phe-OMe (**7**) with the use of a cationic Rh(I) complex with Ph-CAPP[31] as chiral ligand (Ph-CAPP-Rh^+) in ethanol at 40° and 5 atm of hydrogen for 20 hr. The reactions proceeded smoothly to give the corresponding tripeptide (**8**) [(*R*,*S*)/(*S*,*S*) = 98.0/2.0] and tetrapeptide (**9**) [(*R*,*R*,*S*)/(*S*,*R*,*S*) = 99.6/0.4] in quantitative yields, respectively (eqns 1,2).

Asymmetric hydrogenation of N-(N-*acetyldehydro-α-aminoacyl*)-*β-amino ethers*

In order to look at the effects of functional group other than ester group at the C-terminus of N-acetyldehydrodipeptide on catalytic asymmetric induction, we employed N-(N-acetyldehydrophenylalanyl)-*β*-amino alcohol benzyl ethers (**10**) as substrates.

The asymmetric hydrogenation of **10** catalysed by chiral Rh complexes proceeded smoothly at 40° and 5–10 atm of hydrogen to give the corresponding dipeptide analog (**11**) in quantitative yield, which was further converted to N-(N-acetylphenylalanyl)-*β*-amino alcohol (**12**) through hydrogenolysis of benzyl protecting group on 10% Pd-C (eqn 3): For the transformation of **11d** to **12d**, treatment with HBr–AcOH followed by 1N NaOH was employed (eqn 4). The results on using Ph-CAPP, (+)BPPM,[1a] (+)DIOP[32] and (−)DIOP[32] as chiral ligands are summarized in Table 1. As Table 1 shows, a large double asymmetric induction was observed in the case of **10b–d**, the formation of (*S*,*S*)-isomer being preferred, while it was found that the effect of chiral center in **10a** was virtually negligible. Despite the unfavorable opposing double asymmetric induction, (*R*,*S*)-isomers with high optical purities were obtained by the entry of Ph-CAPP. Consequently, it turns out that desired configurations can be introduced with high stereoselectivity by the proper choice of chiral ligands.



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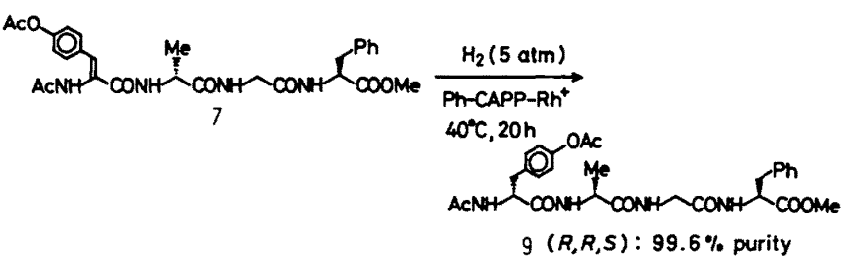

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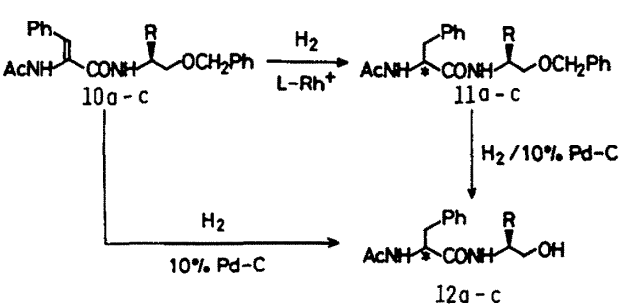

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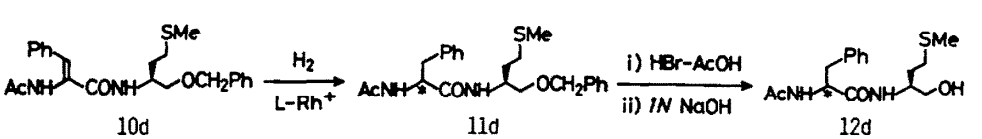

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Table 1. Asymmetric hydrogenation of N-(N-acetyldehydrophenylalanyl)-β-amino alcohol benzyl ethers (**10**) catalyzed by chiral rhodium complexes[a]

Substrate	R	Chiral Ligand	Conditions H_2 press., Temp., Time	(*R*,*S*) / (*S*,*S*)[b]	% Asymmetric Induction
10a	CH_2Ph	Ph-CAPP	5 atm, 40°C, 40 h	97.4 / 2.6	94.8 (*R*)
		(+)BPPM	5 atm, 40°C, 40 h	0.9 / 99.1	98.2 (*S*)
		(+)DIOP	5 atm, 40°C, 68 h	11.3 / 88.7	77.4 (*S*)
		(-)DIOP	5 atm, 40°C, 68 h	87.7 / 12.3	75.4 (*R*)
10b	$CH_2CH(CH_3)_2$	Ph-CAPP	5 atm, 40°C, 42 h	98.7 / 1.3	97.4 (*R*)
		(+)BPPM	5 atm, 40°C, 42 h	0.9 / 99.1	98.2 (*S*)
		(+)DIOP	5 atm, 40°C, 48 h	5.5 / 94.5	89.0 (*S*)
		(-)DIOP	5 atm, 40°C, 48 h	84.2 / 15.8	68.4 (*R*)
10c	$CH(CH_3)_2$	Ph-CAPP	5 atm, 40°C, 43 h	94.4 / 5.6	88.8 (*R*)
		(+)BPPM	5 atm, 40°C, 40 h	1.4 / 98.6	97.2 (*S*)
		(+)DIOP	5 atm, 40°C, 43 h	6.7 / 93.3	86.6 (*S*)
		(-)DIOP	5 atm, 40°C, 43 h	75.1 / 24.9	50.2 (*R*)
10d	$CH_2CH_2SCH_3$	Ph-CAPP[c]	5 atm, 40°C, 46 h	90.7 / 9.3	81.4 (*R*)
		(+)BPPM[c]	5 atm, 40°C, 46 h	4.5 / 95.5	91.0 (*S*)
		(+)DIOP[c]	10 atm, 40°C, 48 h	10.6 / 89.4	78.8 (*S*)
		(-)DIOP[c]	10 atm, 40°C, 48 h	82.5 / 17.5	65.0 (*R*)

[a] All reactions were run with 0.30 mmol of substrate and 3.0×10^{-3} mmol of chiral catalyst in ethanol unless otherwise noted. Chemical yields were quantitative in all cases.
[b] Determined by HPLC analysis. [c] 6.0×10^{-3} mmol of chiral catalyst was used.

Table 2. Asymmetric hydrogenation of N-(N-acetyldehydrophenylalanyl)-β-amino alcohol benzyl ethers (**10**) catalyzed by 10% Pd-C or dppb-Rh^+[a]

Substrate	R	Catalyst[b]	Conditions H_2 press., Temp., Time	(*R*,*S*) / (*S*,*S*)[c]	% Asymmetric Induction
10a	CH_2Ph	10% Pd-C	1 atm, 25°C, 40 h	43.0 / 57.0	14.0 (*S*)
		dppb-Rh^+	5 atm, 40°C, 40 h	39.6 / 60.4	20.8 (*S*)
10b	$CH_2CH(CH_3)_2$	10% Pd-C	1 atm, 25°C, 40 h	28.8 / 71.2	42.4 (*S*)
		10% Pd-C	1 atm, 2°C, 17 h	28.3 / 71.7	43.4 (*S*)
		10% Pd-C	1 atm, -15°C, 17 h	27.0 / 73.0	46.0 (*S*)
		dppb-Rh^+	5 atm, 40°C, 40 h	41.3 / 58.7	17.4 (*S*)
10c	$CH(CH_3)_2$	10% Pd-C	1 atm, 25°C, 40 h	29.3 / 70.7	41.4 (*S*)
		10% Pd-C[d]	1 atm, 2°C, 20 h	24.5 / 75.7	51.0 (*S*)
		10% Pd-C[d]	1 atm, -15°C, 20 h	23.8 / 76.2	52.4 (*S*)
		dppb-Rh^+	5 atm, 40°C, 40 h	27.1 / 72.9	45.8 (*S*)
10d	$CH_2CH_2SCH_3$	10% Pd-C	1 atm, 25°C, 20 h	78.2 / 21.8[e]	56.4 (*R*)
		10% Pd-C[d]	1 atm, 2°C, 48 h	80.6 / 19.4[e]	61.2 (*R*)
		dppb-Rh^+[f]	10 atm, 40°C, 46 h	50.8 / 49.2[e]	1.6 (*R*)

[a] All reactions were run with 0.30 mmol of substrate and 100-120 mg (0.10-0.12 mmol) of 10% Pd-C or 3.0×10^{-3} mmol of dppb-Rh^+ in ethanol unless otherwise noted. Chemical yields were quantitative in all cases. [b] dppb-Rh^+ was prepared in situ by mixing dppb (3.0×10^{-3} mmol) and $[Rh(NBD)_2]^+ClO_4^-$ (3.0×10^{-3} mmol) in degassed ethanol. [c] The diastereomer ratios were determined for **12** by HPLC analysis unless otherwise noted. [d] 300 mg (0.30 mmol) of 10% Pd-C was used. [e] The diastereomer ratios were determined for **11d**. [f] 6.0×10^{-3} mmol of the catalyst was used.

As considerably large effects of chiral centers in **10** on the asymmetric induction by chiral Rh catalysts were observed, we estimated the simple asymmetric induction caused by the chiral center in the substrate with the use of achiral catalysts, dppb-Rh^+ and 10% Pd-C.

The asymmetric hydrogenation of **10a–c** on 10% Pd-C proceeded at 25° and 1 atm of hydrogen to give **12** directly in quantitative yield. When the reaction was carried out at lower temperatures, it was revealed on the basis of HPLC analysis of the mixture that the reaction proceeded stepwise, i.e. **11** was detected as primary product, which was further converted to **12a–c**. As the hydrogenolysis of **11d** did not proceed at all even at 50°, **11d** was treated with HBr-AcOH followed by 1N NaOH to give **12d** in high yield. Results are summarized in Table 2.

As Table 2 shows, the steric and electronic character of substituents in chiral β-amino alcohol benzyl ether moiety exerts a large influence on stereoselectivity. Namely, the formation of (*S,S*)-isomer is predominant in the case of **3d**, especially on using Pd catalyst, which strongly suggests a significant attractive interaction between sulfur in methionine moiety and Pd. The results clearly indicate that Pd catalyst is more sensitive to the steric and electronic effect of the substituents than dppb-Rh^+ in these systems.

As for the asymmetric hydrogenation of *cyclic* dehydrodipeptides on Pd–C, Izumiya *et al.* reported extremely high asymmetric inductions.[8] However, only low stereoselectivities (0–20% asymmetric induction) have been realized in the *open-chain* dehydrodipeptides as far as the reported data and our experiments are concerned.† Accordingly, it can be said that the asymmetric inductions of 46.0–61.2% achieved in the reactions of **10b–d** are remarkably good values for simple *open-chain* systems.

†For example, Ac-ΔPhe-(*S*)-Phe-OMe: 10% Pd-C, 1 atm of H_2, 25°, (*R,S*)/(*S,S*) = 60.2/39.8 [see also Ref. 1*c*]; Ac-ΔPhe-(*S*)-Phe-OH: 10% Pd-C, 1 atm of H_2, 25°, (*R,S*)/(*S,S*) = 60/40 [see ref. 1*c*]; Ac-ΔPhe-(*S*)-Val-OMe: 10% Pd-C, 1 atm of H_2, 25°, (*R,S*)/(*S,S*) = 44.1/55.9, −15°, (*R,S*)/(*S,S*) = 47.8/52.2; Ac-ΔPhe-(*S*)-Val-OH: 10% Pd-C, 1 atm of H_2, 25°, (*R,S*)/(*S,S*) = 47.6/52.4; ^{t}BOC-(*S*)-Leu-ΔAla-OMe: Pd black, 1 atm of H_2, 25°, (*R,S*)/(*S,S*) = 50/50 [see ref. 8*b*].

Asymmetric reduction of N-(α-*ketoacyl*)-α-*amino esters*

As there are many naturally occurring depsipeptides which have interesting biological activities such as actinomycins,[9] triostin C,[10] and AM-toxins,[11] the asymmetric synthesis of depsipeptide building blocks is of considerable synthetic value. Accordingly, we carried out the asymmetric reduction of N-(α-ketoacyl)-α-amino esters (**13**) via hydrosilylation, which gave chiral depsipeptide building block, N-(α-hydroxyacyl)-α-amino esters (**14**) (eqn 5).

The asymmetric hydrosilylation of **13** followed by acidic methanolysis was carried out by using α-naphthylphenylsilane as reducing agent and neutral Rh complexes with (+)DIOP, (−)DIOP and PPh_3 (L-Rh^N) as catalysts. Attempted determination of the optical purity of the product (**14**) by ^{1}H NMR analysis using shift reagent resulted in unsatisfactory separation of key signals. Thus, all α-hydroxyacylamino esters (**14**) were transformed to the corresponding trifluoroacetates (**15**) by treating with trifluoroacetic anhydride in the presence of N-methylmorpholine (NMM). The trifluoroacetates (**15**) were submitted to ^{19}F NMR analysis using $Eu(fod)_3$ as the shift reagent, and the optical purities of **15** were successfully determined. The absolute configurations of **1** thus obtained were determined by the comparison with authentic samples based on ^{19}F NMR analysis. Results are summarized in Table 3.

On the other hand, the attempted asymmetric hydrogenation of **13** catalyzed by neutral Rh(I) complexes with (+)DIOP, (−)DIOP, (−)BPPM, *p*-Br-C_6H_4-CAPP,[31] and PPh_3, resulted in bringing about almost the same extent of asymmetric induction (20–28%) in the same direction as shown in Table 4. This means that only a simple asymmetric induction arising from the chiral center in **13** takes place, and the Rh complex bearing chiral ligand does not act as chiral catalyst at all. These results form a sharp contrast to those for the asymmetric hydrogenation of α-keto esters catalyzed by the same chiral Rh complexes.[12] The results may indicate that chiral diphosphines only act as mono-dentate ligand because of the strong coordination of the substrate (**13**) with the Rh center of the catalyst. Accordingly, the exploitation of effective chiral ligands for asymmetric hydrogenation is necessary to achieve high stereoselectivities in this system.

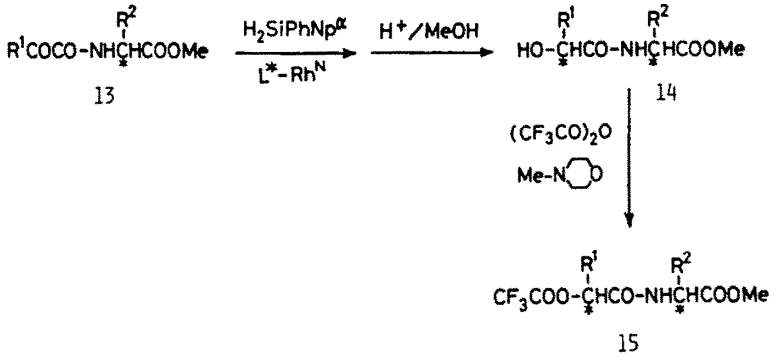

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Table 3. Asymmetric reduction of N-(α-ketoacyl)-α-amino esters (**13**) via hydrosilylation[a]

Product	Catalyst	Isolated Yield(%)	(*R*,*S*) / (*S*,*S*)[b]	% excess diastereomer
Me HO-CH-CO-Phe-OMe * 14a	(+)DIOP-Rh^N	75	17 / 83	66
	(-)DIOP-Rh^N	78	84 / 16	68
	$Rh(PPh_3)_3Cl$[c]	64	33 / 67	34
Me HO-CH-CO-Val-OMe * 14b	(+)DIOP-Rh^N	70	16 / 84	68
	(-)DIOP-Rh^N	78	86 / 14	72
	$Rh(PPh_3)_3Cl$[c]	71	29 / 71	42
Ph HO-CH-CO-Phe-OMe * 14c	(+)DIOP-Rh^N	79	9 / 91	82
	(-)DIOP-Rh^N	83	71 / 29	42
	$Rh(PPh_3)_3Cl$[c]	62	22 / 78	56
Ph HO-CH-CO-Ala-OMe * 14d	(+)DIOP-Rh^N	72	15 / 85	70
	(-)DIOP-Rh^N	71	81 / 19	62
	$Rh(PPh_3)_3Cl$[c]	50	49 / 51	2

[a] Reactions were run with 5 mmol of substrate, 7.5 mmol of $H_2SiPhNp^\alpha$ and 0.025 mmol of catalyst in 5 ml of benzene at 20°C for 24 h and at 40°C for 12 h unless otherwise noted. [b] Determined by ^{19}F NMR analysis of 15. [c] Reaction was run with 0.1 mmol of catalyst at 20°C for 24 h and at 40°C for 4 days.

Table 4. Asymmetric hydrogenation of N-(α-ketoacyl)-α-amino ester (**13a**)[a]

Product	Catalyst	Conditions H_2 press., Temp., Time	Yield (%)	(*R*,*S*) / (*S*,*S*)[b]	% excess diastereomer
Me HO-CH-CO-Phe-OMe * 14a	(+)DIOP-Rh^N	50 atm, 40°C, 20 h	100	37 / 63	26
	(-)DIOP-Rh^N	50 atm, 40°C, 20 h	100	37 / 63	26
	(-)BPPM-Rh^N	50 atm, 25°C, 64 h	100	36 / 64	28
	p-Br-C_6H_4-CAPP-Rh^N	50 atm, 25°C, 64 h	100	37 / 63	26
	$Rh(PPh_3)_3Cl$	50 atm, 25°C, 64 h	100	40 /60	20
	10% Pd-C[c]	1 atm, 20°C, 24 h	100	58 / 42	16

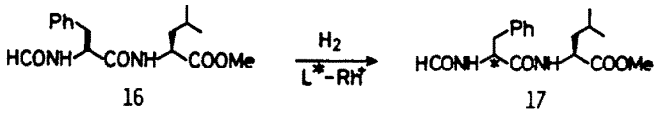
[a] Reactions were run with 1.0 mmol of substrate and 1.0×10^{-2} mmol of catalyst in 5 ml of benzene. [b] Determined by ^{19}F NMR analysis of 15a. [c] 500 mg of 10% Pd-C was used.

Asymmetric hydrogenation of N-*formyldehydrodipeptide*

Although the results on the asymmetric hydrogenations of N-acyldehydrodipeptides of the type **1–4**, where acyl stands for acetyl or benzoyl, provide interesting and significant information about the applicability of homogeneous asymmetric hydrogenation to peptide synthesis, the chiral N-acyldipeptides so far obtained in these reactions have only a limited use for peptide synthesis as fragments since it is hard to remove the acetyl or benzoyl protecting group. Accordingly, we prepared an N-formyldehydrodipeptide (**16**), which could provide a versatile dipeptide fragment after the asymmetric hydrogenation because of the easy deprotection of formyl group.[13]

N-Formyldehydrophenylalanyl-(*S*)-leucine methyl ester (**16**) was prepared by the condensation of (*S*)-leucine methyl ester with (*Z*)-N-formyldehydrophenylalanine which was obtained by the reaction of methyl isocyanoacetate with benzaldehyde followed by hydrolysis,[14] with the use of N,N-bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (BOP-Cl) as condensation reagent.[15] For this condensation, DCC–HOBT method (DCC = dicyclohexylcarbodiimide; HOBT = 1-hydroxybenzotriazole) and mixed anhydride method by using isobutyl chloroformate turned out to be ineffective.

The asymmetric hydrogenation of **16** catalyzed by cationic Rh complexes with Ph–CAPP and diPAMP was carried out at 40° and 10 atm of hydrogen in ethanol for 12 hr, which gave N-formylphenylalanyl-(*S*)-leucine methyl ester (**17**) with excellent stereoselectivity in quantitative yield: Ph-CAPP-Rh$^+$, (*R*,*S*)/(*S*,*S*) = 96.4/3.6; diPAMP-Rh$^+$,[33] (*R*,*S*)/(*S*,*S*) = 1.6/98.4.



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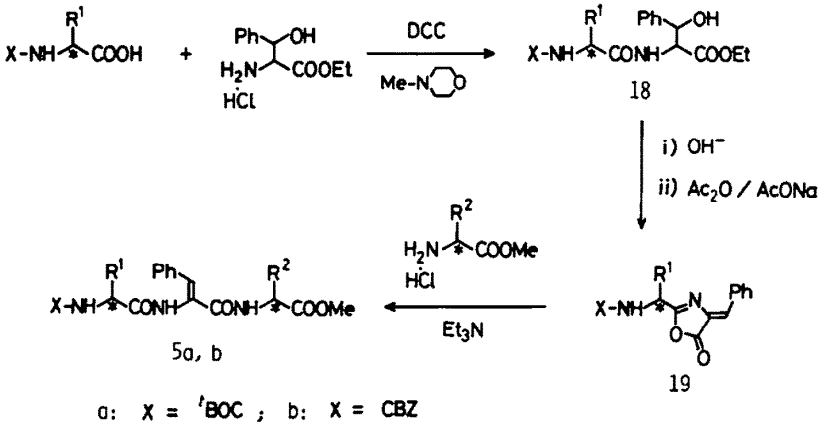
Asymmetric hydrogenation of dehydrotripeptides

As a general model for dehydropolypeptides, we prepared dehydropeptides of the type **5** in which a dehydroamino acid residue is sandwiched between two amino acid residues. As N-protecting group for **5**, we employed t-butoxycarbonyl (^{t}BOC), benzyloxycarbonyl (CBZ), and trifluoroacetyl so that the chiral tripeptides (**20**) obtained by the asymmetric hydrogenation could be used as versatile tripeptide building blocks for polypeptide synthesis.

The dehydrotripeptides (**5a, b**) were readily prepared by a synthetic route illustrated in eqn (7). **5c** ($X = CF_3$) was prepared from **5a** through acidic deblocking and trifluoroacetylation.

For comparison purpose, N_3CH_2CO-ΔPhe-(*S*)-Leu-OMe (**5d**) which is equivalent to Gly-ΔPhe-(*S*)-Leu-OMe, was prepared from azidoacetyl chloride, phenylserine ethyl ester and (*S*)-leucine methyl ester in a similar manner.

The asymmetric hydrogenation of X′-Gly-ΔPhe-(*S*)-Leu-OMe (**5a-1, 5b–d**) was carried out by using Ph-CAPP-Rh$^+$ as chiral catalyst. The results are listed in Table 5. As typically exemplified in Table 5, **5** bearing ^{t}BOC group (**5a-1**) brings about saliently the best stereoselectivity as well as catalyst efficiency. As for the asymmetric hydrogenation of **5b**, we further carried out the reaction with higher concentration of chiral catalysts (10 atm of hydrogen, 40° for 40–42 hr in ethanol) and found that high stereoselectivities could be realized by using 5.0 mol% of the chiral catalyst, and in the case of diPAMP-Rh$^+$, 2.0 mol% concentration was enough to attain high stereoselectivity: Typical results are as follows (conversion is 100% in every case). (+)BPPM-Rh$^+$ (5.0 mol%): (*R,S*)/(*S,S*) = 8.0/92.0; (−)BPPM-Rh$^+$ (5.0 mol%): (*R,S*)/(*S,S*) = 93.0/7.0; Ph-CAPP-Rh$^+$ (5.0 mol%): (*R,S*)/(*S,S*) = 94.1/5.9; diPAMP-Rh$^+$ (2.0 mol%): (*R,S*)/(*S,S*) = 3.3/96.7. The lower stereoselectivities at lower catalyst concentration might be due to non-stereoselective hydrogenation on metallic Rh which would be generated by the decomposition of chiral catalysts.



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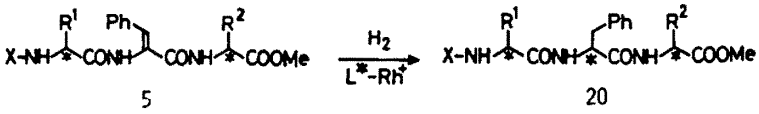

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Table 5. Asymmetric hydrogenation of 5 by using Ph-CAPP-Rh$^+$ as catalyst[a]

Entry	Substrate	Catalyst (mol%)	H_2 press. (atm)	Conversion[b] (%)	(*R,S*) / (*S,S*)[b]
1	^{t}BOC-Gly-ΔPhe-(*S*)-Leu-OMe (5a-1)	1.0	10	100	96.9 / 3.1
2	CBZ-Gly-ΔPhe-(*S*)-Leu-OMe (5b)	2.0	10	82	86.4 / 13.6
3	TFA-Gly-ΔPhe-(*S*)-Leu-OMe (5c)	5.0	50	93	61.5 / 38.5
4	N_3CH_2CO-ΔPhe-(*S*)-Leu-OMe (5d)	5.0	50	0	—

[a] Reactions were run with 0.30 mmol of substrate in ethanol at 40°C for 40 h. [b] Determined by HPLC analysis.

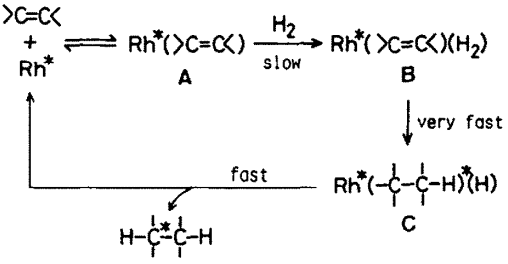
As it turned out that **5a-1** could realize the same level of stereoselectivity and catalyst efficiency as N-acyldehydrodipeptides (**1**) did,[1] we fixed on 'BOC as the protecting group at N-terminus and prepared several dehydrotripeptides, 'BOC-AA-ΔPhe-AA'-OMe (**5a**) (AA = amino acid residue), to look at the effects of chiral centers on the asymmetric induction by chiral catalysts. The asymmetric hydrogenation of **5a** series proceeded smoothly by using 1.0 mol% of chiral catalysts at 40° and 10 atm of hydrogen to give the corresponding tripeptides (**20a**) in quantitative yields. Results are listed in Table 6.

As Table 6 shows, both the amino acid residues sandwiching dehydroamino acid moiety exert a considerable influence on asymmetric induction. The results indicate that (i) (*S*)-Leu-OMe or (*S*)-Met-OMe at the C-terminus has only a slight effect on the asymmetric induction (Entries 2, 3; 5; 31, 32), (ii) 'BOC-(*S*)-Ala or 'BOC-(*S*)-Phe at the N-terminus considerably favors the creation of *R* configuration (Entries 26, 27; 8, 9; 20, 21), which is supported by the results on using achiral catalyst, dppb-Rh$^+$ (Entries 11, 23, 29), and (iii) (*R*)-Leu-OMe at the C-terminus favors the creation of *S* configuration, which contradicts the effect of 'BOC-(*S*)-Ala at the N-terminus (Entries 14, 15; 17).

Table 6. Asymmetric hydrogenation of 'BOC-AA-ΔPhe-AA'-OMe (**5a**)[a]

Entry	Substrate	Catalyst	Tripeptide (20a)
1	^{t}BOC-Gly-ΔPhe-(*S*)-Leu-OMe	Ph-CAPP-Rh$^+$	(*R*,*S*) / (*S*,*S*)[b] = 96.9 / 3.1
2	5a-1	(-)BPPM-Rh$^+$	94.0 / 6.0
3		(+)BPPM-Rh$^+$	8.0 / 92.0
4		diPAMP-Rh$^+$	1.1 / 98.9
5		dppb-Rh$^+$	49.1 / 50.9
6		10% Pd-C[c]	54.7 / 45.3
7	^{t}BOC-(*S*)-Ala-ΔPhe-(*S*)-Leu-OMe	Ph-CAPP-Rh$^+$	(*S*,*R*,*S*) / (*S*,*S*,*S*)[b] = 92.5 / 7.5
8	5a-2	(-)BPPM-Rh$^+$	90.8 / 9.2
9		(+)BPPM-Rh$^+$	17.9 / 82.1
10		diPAMP-Rh$^+$	5.0 / 95.0
11		dppb-Rh$^+$	69.9 / 30.1
12		10% Pd-C[c]	43.5 / 56.5
13	^{t}BOC-(*S*)-Ala-ΔPhe-(*R*)-Leu-OMe	Ph-CAPP-Rh$^+$	(*S*,*R*,*R*) / (*S*,*S*,*R*)[b] = 79.9 / 20.1
14	5a-3	(-)BPPM-Rh$^+$	85.9 / 14.1
15		(+)BPPM-Rh$^+$	14.0 / 86.0
16		diPAMP-Rh$^+$	3.0 / 97.0
17		dppb-Rh$^+$	44.9 / 55.1
18		10% Pd-C[c]	32.6 / 67.4
19	^{t}BOC-(*S*)-Phe-ΔPhe-(*S*)-Leu-OMe	Ph-CAPP-Rh$^+$	(*S*,*R*,*S*) / (*S*,*S*,*S*)[b] = 94.4 / 5.6
20	5a-4	(-)BPPM-Rh$^+$	89.7 / 10.3
21		(+)BPPM-Rh$^+$	24.9 / 75.1
22		diPAMP-Rh$^+$	4.1 / 95.9
23		dppb-Rh$^+$	76.2 / 23.8
24		10% Pd-C[c]	39.8 / 60.2
25	^{t}BOC-(*S*)-Phe-ΔPhe-Gly-OMe	Ph-CAPP-Rh$^+$	(*S*,*R*) / (*S*,*S*)[b] = 92.6 / 7.4
26	5a-5	(-)BPPM-Rh$^+$	92.4 / 7.6
27		(+)BPPM-Rh$^+$	12.1 / 87.9
28		diPAMP-Rh$^+$	3.3 / 96.7
29		dppb-Rh$^+$	74.9 / 25.1
30		10% Pd-C[c]	43.7 / 56.3
31	^{t}BOC-Gly-ΔPhe-(*S*)-Met-OMe	Ph-CAPP-Rh$^+$	(*R*,*S*) / (*S*,*S*)[b] = 93.7 / 6.3
32	5a-6	diPAMP-Rh$^+$	3.8 / 96.2
33		10% Pd-C[c]	65.4 / 34.6

[a] All reactions were run with 0.30 mmol of substrate and 3.0×10^{-3} mmol of catalyst in ethanol at 40°C and 10 atm of hydrogen for 18 h unless otherwise noted. [b] Determined by HPLC analysis. [c] 100 mg of 10% Pd-C was used.



(9)

According to the well-established mechanism of the asymmetric hydrogenation of dehydroamino acid catalyzed by cationic Rh complex with *cis*-chelating diphosphine,[16] (i) the rate determining step is the oxidative addition of molecular hydrogen to substrate-Rh complex (A) (eqn 9) and (ii) the favorable diastereomer in substrate-Rh dihydride complex (B) leads to the formation of major enantiomer in hydrogenated products. Consequently, the ratio of the enantiomers is given by the following equation,

$$[R]/[S] = [\mathrm{Rh}^*(\rangle C{=}C\langle)_R(\mathrm{H}_2)]/[\mathrm{Rh}^*(\rangle C{=}C\langle)_S(\mathrm{H}_2)]$$

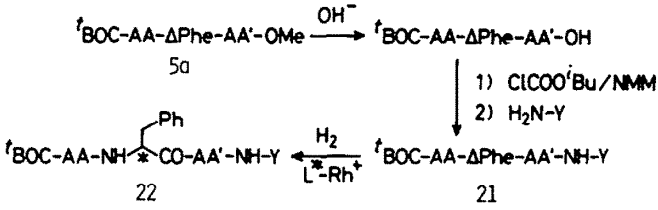
$$= k^R_{\mathrm{H}_2}/k^S_{\mathrm{H}_2} \cdot [\mathrm{Rh}^*(\rangle C{=}C\langle)_R]/[\mathrm{Rh}^*(\rangle C{=}C\langle)_S] \quad (10)$$

where $k^R_{\mathrm{H}_2}$ or $k^S_{\mathrm{H}_2}$ is the rate constant for the oxidative addition of molecular hydrogen.

Provided that this mechanism is also operative in the asymmetric hydrogenation of dehydropeptides, the modes of the coordination of dehydropeptides should have significant influence on either the concentration of the substrate-Rh complex (A) or the rate constant, k_{H_2}, and the influence is finally reflected in the enantioselectivity following eqn (10). Although a detailed understanding of the effects of chiral centers as well as N-protecting groups on the asymmetric induction by chiral Rh catalysts must await further mechanistic studies, the observed large effects of chiral amino acid residue at the N-terminus on the asymmetric induction can be explained by assuming the quasi-5-membered ring chelate formation with Rh using enamide structure, which is well-documented for the complexes of simple N-acyldehydroamino acids,[16,17] as shown in Fig. 1.

Namely, the ^{t}BOC–AA residue at the N-terminus is most likely to occupy the position close to the phenyl group(s) of a chiral diphosphine ligand in both the substrate-Rh complex (A) and the substrate-Rh dihydride complex (B), and thus the absolute configuration at the chiral center and the bulkiness of the substituent (R^1) should affect the mode of the enantio-face selection of olefinic moiety by the chiral Rh complex. While the AA-OMe residue at the C-terminus may have much weaker effect since this coordination by using ester CO oxygen should be broken by the oxidative addition of molecular hydrogen.

Next, we carried out the asymmetric hydrogenation of dehydrotripeptide amide, hydrazide and phenylhydrazide, ^{t}BOC-AA-ΔPhe-AA′-NH-Y (21: Y = H, NH-AA′-ΔPhe-AA-^{t}BOC, NHPh; AA′ = (*S*)-Leu) to look at the effects of the nitrogen functionalities at C-terminus on the asymmetric induction. Results are listed in Table 7. Dehydrotripeptides (**21**) were prepared from **5a** through mixed anhydrides with isobutyl chloroformate.



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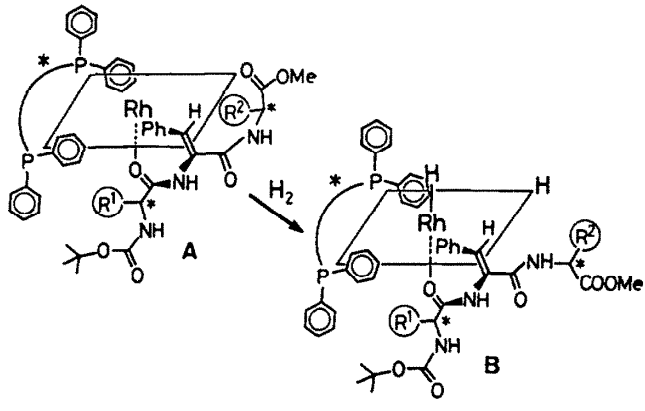


Fig. 1.

Table 7. Asymmetric hydrogenation of 'BOC-AA-ΔPhe-AA'-NH-Y (21)[a]

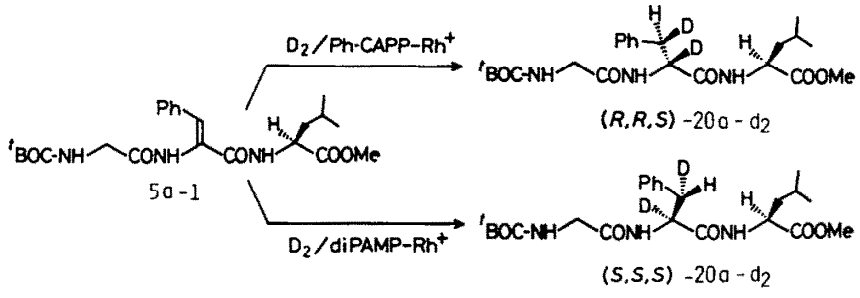
Entry	Substrate	Catalyst	Tripeptide (22)
1	^{t}BOC-Gly-ΔPhe-(*S*)-Leu-NH_2	(+)BPPM-Rh^+	(*R*,*S*) / (*S*,*S*)[b] = 7.4 / 92.6
2	21a	diPAMP-Rh^+	9.5 / 90.5
3		(-)BPPM-Rh^+	80.6 / 19.4
4		dppb-Rh^+	47.7 / 52.3
5		10% Pd-C[c]	48.4 / 51.6
6	^{t}BOC-(*S*)-Ala-ΔPhe-(*S*)-Leu-NH_2	(+)BPPM-Rh^+	(*S*,*R*,*S*) / (*S*,*S*,*S*)[b] = 16.8 / 83.2
7	21b	diPAMP-Rh^+	2.5 / 97.5
8		(-)BPPM-Rh^+	73.3 / 26.7
9		dppb-Rh^+	70.4 / 29.6
10		10% Pd-C[c]	37.8 / 62.2
11	(^{t}BOC-Gly-ΔPhe-(*S*)-Leu-NH)$_2$	(+)BPPM-Rh^+	(*R*,*S*) / (*S*,*S*)[b] = 1.2 / 98.8
12	21c	diPAMP-Rh^+	3.8 / 96.2
13		(-)BPPM-Rh^+	81.2 / 18.8
14		dppb-Rh^+	59.2 / 40.8
15		10% Pd-C[c]	66.2 / 33.8
16	^{t}BOC-Gly-ΔPhe-(*S*)-Leu-NHNHPh	(+)BPPM-Rh^+	(*R*,*S*) / (*S*,*S*)[b] = 7.1 / 92.9
17	21d	diPAMP-Rh^+	8.3 / 91.7
18		(-)BPPM-Rh^+	85.3 / 14.7
19		dppb-Rh^+	53.3 / 46.9
20		10% Pd-C[c]	57.2 / 42.8

[a] All reactions were run with 0.10 mmol of substrate and 2.0×10^{-2} mmol of catalyst in ethanol at 40°C and 10 atm of hydrogen for 24-36 h unless otherwise noted. [b] Determined by HPLC analysis. [c] 50 mg of 10% Pd-C was used.

As Table 7 shows, the nitrogen functionalities at the C-terminus of 21 exert considerable influence on the asymmetric induction by chiral catalysts in contrast with the methyl ester terminus of **5a**, viz. (*S*,*S*)- or (*S*,*S*,*S*)-isomer is produced with high diastereomeric purity by using (+)BPPM-Rh^+ or diPAMP-Rh^+ whereas considerably lower stereoselectivity is observed for (*R*,*S*)- or (*S*,*R*,*S*)-isomer formation. It should be noted that dppb-Rh^+ cannot be a good achiral model catalyst any longer for looking at the double asymmetric induction in this system, which also forms a sharp contrast to the case of **5a**. The results may imply a relatively strong coordination of nitrogen functionality to chiral Rh complex, which could bring about a significant change in either the rate constant k_{H_2} or the relative concentration of the two diastereomeric substrate-Rh complexes (**A**) (*vide supra*).

In connection with the regiospecific and stereoselective labeling of polypeptides, we carried out the dideuteration of **5a-1** as a model system by using Ph-CAPP-Rh^+ and diPAMP-Rh^+ as catalysts. The reactions were run with 1.0 mol% of the chiral catalyst in ethanol at 40° and 10 atm of dideuterium for 18 hr and the corresponding dideuteriotripeptides (**20a-d_2**) were obtained in quantitative yields without any scrambling of deuterium (eqn 12); Ph-CAPP-Rh^+: (*R*,*R*,*S*)/(*S*,*S*,*S*) = 93.0/7.0; diPAMP-Rh^+: (*R*,*R*,*S*)/(*S*,*S*,*S*) = 2.6/97.4.

As for the highly stereoselective labeling of N-acyldipeptides, we reported the dideuteration of Ac-ΔPhe-(*S*)-Ala-OMe[1a] and Levine–Pinto *et al.* re-



(12)

ported the ditritiation of Ac-ΔPhe-(*S*)-Phe-OMe,[18] but the present system may provide a better model for the specific labeling of a certain amino acid residue in a polypeptide. As it has been shown that the introduction of deuterium to the chiral center of certain amino acids, e.g. 3-fluoro-2-deuterio-(*R*)-alanine, increases the metabolic stability remarkably,[19] the stereoselective dideuteration may provide a convenient device for this kind of modification of biological activity. Tritiation of peptides is, of course, very important for the study on metabolism, and if tritium could be introduced into polypeptides specifically in the very late stage of polypeptide synthesis, such a method would give us big benefits since the method can keep the amounts of radioactive side products at minimum level in sharp contrast with the stepwise synthesis of the labeled polypeptides starting from tritiated amino acids. In this respect, the catalytic asymmetric ditritiation of dehydropeptides may provide a potentially useful method for this problem.

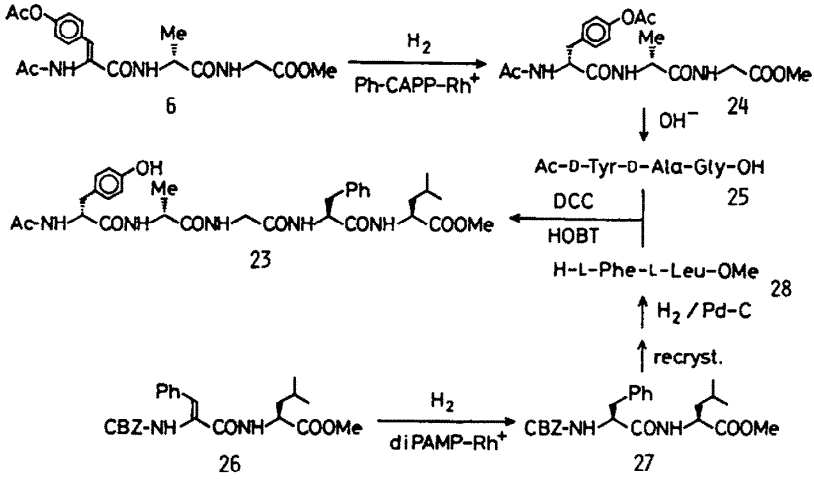
Asymmetric synthesis of enkephalin analogs†

We applied the asymmetric hydrogenation of dehydropeptides to the synthesis of the analogs of enkephalin[20] which is an opioid hormone isolated from brain through fragment condensation.

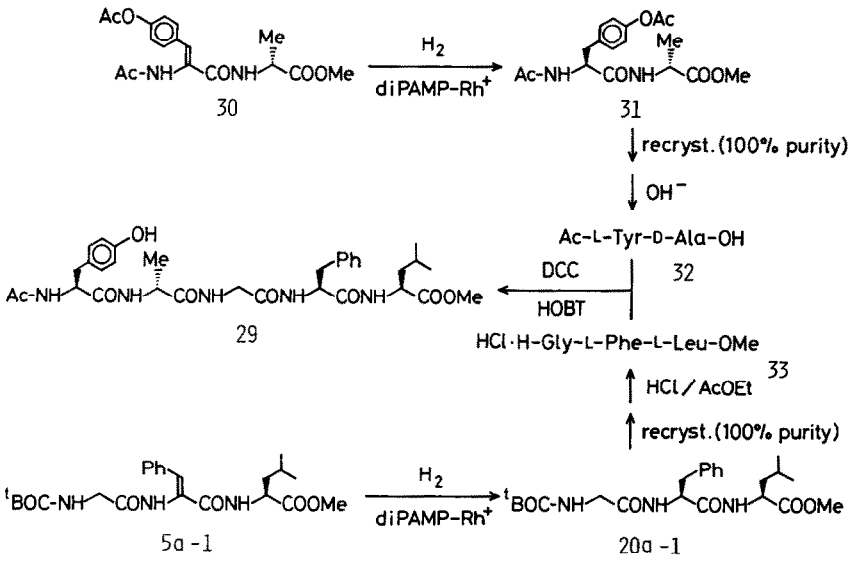
Scheme 1 shows the synthetic route to [Ac-D-Tyr[1], D-Ala[2], Leu[5]-OMe]enkephalin (**23**). The tripeptide fragment, Ac-D-Tyr-D-Ala-Gly was synthesized via the asymmetric hydrogenation of Ac-ΔTyr(Ac)-D-Ala-Gly-OMe (**6**) catalyzed by Ph-CAPP-Rh$^+$ (1.0 mol%) in ethanol at 40° and 5 atm of hydrogen, which gave Ac-D-Tyr(Ac)-D-Ala-Gly-OMe (**24**) with 99.4% diastereomer excess [(D,D)/(L,D) = 99.7/0.3] in quantitative yield. **24** thus obtained was saponified with 1N NaOH in methanol at 0° for 30 min to give Ac-D-Tyr-D-Ala-Gly-OH (**25**) in 93% yield. On the other hand, the dipeptide fragment, L-Phe-L-Leu-OMe, was synthesized via the asymmetric hydrogenation of CBZ-ΔPhe-L-Leu-OMe (**26**) catalyzed by diPAMP-Rh$^+$ (2.0 mol%) in ethanol at 50° and 20 atm of hydrogen, which gave CBZ-L-Phe-L-Leu-OMe (**27**) with 95.6% diastereomer excess[(D,L)/(L,L) = 2.2/97.8] in quantitative yield. **26** was prepared in good yield by the coupling of CBZ-ΔPhe-OH with HCl·Leu-OMe using DCC, HOBT and NMM in dimethylformamide (DMF). The optically pure **27** was obtained by the purification on silica gel column (90% recovery), which was submitted to hydrogenolysis on 10% Pd-C in methanol in the presence of hydrochloric acid (1.0 eq) to give HCl·Phe-Leu-OMe (**28**) in nearly quantitative yield. Then, the two fragments, **25** and **28**, were coupled by using DCC, HOBT and NMM in DMF at 0° to give Ac-D-Tyr-D-Ala-Gly-L-Phe-L-Leu-OMe (**23**) in 85% yield.

Scheme 2 shows the synthetic route to [Ac-Tyr[1], D-Ala[2], Leu[5]-OMe]enkephalin (**29**)[20b,21] via the coupling of Ac-L-Tyr-D-Ala with Gly-L-Phe-L-Leu-OMe. The asymmetric hydrogenation of Ac-ΔTyr(Ac)-D-Ala-OMe (**30**) catalyzed by diPAMP-Rh$^+$ (1.0 mol%) in ethanol at 40° and 10 atm of hydrogen gave Ac-L-Tyr(Ac)-D-Ala-OMe (**31**) with 96.8% diastereomer excess [(D,D)/(L,D) = 1.6/98.4] in quantitative yield. After recrystallization from ethyl acetate (88% recovery), optically pure **31** thus obtained was saponified by 1N NaOH at 0° to give Ac-L-Tyr-D-Ala-OH(**32**) in 94% yield. ^{t}BOC-Gly-L-Phe-L-Leu-OMe (**20a-1**) with 97.8% diastereomer excess[(D,L)/(L,L) = 1.1/98.9] was obtained quantitatively by the asymmetric hydrogenation of ^{t}BOC-Gly-ΔPhe-L-Leu-OMe (**5a-1**) with the use of diPAMP-Rh$^+$ (1.0 mol%) in ethanol at 40° and 10 atm of hydrogen, which was further recrystallized to give the optically pure **20a-1** (92% recovery). Then, ^{t}BOC group was removed by treating with hydrogen chloride in ethyl acetate to give HCl·Gly-L-Phe-L-Leu-OMe (**33**) in 96% yield. The coupling of **32** and **33** was carried out by using DCC, HOBT and NMM in DMF at 0° to give Ac-L-Tyr-D-Ala-Gly-L-Phe-L-Leu-OMe (**29**) in 89% yield.

†As for the expression of absolute configurations in peptides, D or L is used rather than *R* or *S*. Thus, D, L expression is employed in this section: D and L correspond to *R* and *S*, respectively in amino acids.



Scheme 1. Synthesis of [Ac-D-Tyr[1], D-Ala[2], Leu[5]-OMe]enkephalin.



Scheme 2. Synthesis of [Ac-Tyr[1], D-Ala[2], Leu[5]-OMe]enkephalin.

EXPERIMENTAL

M.p. are uncorrected. IR spectra were recorded on a Hitachi 285 spectrophotometer by using samples as KBr disks. ^{1}H NMR spectra were measured with a Varian XL-100-15A or EM-390 spectrometer with Me_4Si as the internal standard. ^{19}F NMR spectra were recorded on a Varian XL-100-15A spectrometer with FCl_3C as the internal standard. Optical rotations were measured with a Union PM 201 polarimeter. HPLC analysis was carried out with TOYO SODA HLC-803A apparatus using a column packed with LS 410K (ODS SIL).

Materials. N,N-Dicyclohexylcarbodiimide(DCC), 1-hydroxybenzotriazole (HOBT) and N-methylmorpholine (NMM) were used as purchased. α-Amino acids and HCl salts of their methyl esters were purchased and used without purification. N,N-Bis[2-oxo-3-oxazolidinyl]phosphorodiamidic chloride (BOP-Cl) was commercially available from Chemical Dynamics Corp. Compound **26** was prepared by the condensation of (*S*)-Leu-OMe with CBZ-ΔPhe-OH using DCC and HOBT, which was obtained from benzyl carbamate and phenylpyruvic acid in accordance with the method reported by Shin *et al.*[22] Compound **30** was prepared by the reaction of the azlactone of N,O-diacetyltyrosine with (*S*)-Ala-OMe by following the previously reported procedure.[1a,23] The azlactones of N-acyldehydro-α-amino acids were prepared by a reported method.[24] $[Rh(NBD)_2]^+ClO_4^-$ (NBD = norbornadiene),[25] $[Rh(COD)Cl]_2$ (COD = 1,5-cyclooctadiene)[26] and $RhCl(PPh_3)_3$ were prepared by the literature methods. (+)DIOP,[32] (−)DIOP,[32] and 1,4-bis-(diphenylphosphino)butane (dppb) were commercially available from Strem Chemicals Inc. (−)BPPM,[27,17d] (+)BPPM,[1a,28] PhCAPP,[31] were prepared by following the reported methods. α-Naphthylphenylsilane was prepared from phenyltrichlorosilane by known method. A shift reagent for NMR measurements, tris[6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octadionato]europium(III), Eu(fod)$_3$, was commercially available from Aldrich Chemical Co.

Preparation of dehydropeptides. Compound **6** was prepared by the reaction of **31** with (*S*)-alanylglycine methyl ester hydrochloride in the presence of Et_3N in $CHCl_3$ in a manner similar to the reported synthesis of dehydrodipeptides[1a]; **6**: 163–165°, $[\alpha]_D^{20}$ + 40.00° (*c* 1.025, MeOH). Compound **7** was prepared by the coupling of Ac-ΔTyr(Ac)-(*R*)-Ala-OH, which was obtained from **31** and (*R*)-Ala-OH in the presence of NaOH, with Gly-(*S*)-Phe-OMe in a usual manner by using DCC-HOBT method; **7**: m.p. 105–108°,$[\alpha]_D^{20}$ + 13.63° (*c* 0.719, MeOH).

Dehydrotripeptides (**5a, b**) were prepared from N-protected α-amino acids, phenylserine ethyl ester, and α-amino acid methyl esters by following the route shown in eqn (7).[29] The preparation of **5a-2** is typically described.

^{t}BOC-(S)-Ala-ΔPhe-(S)-Leu-OMe (**5a-2**). To a mixture of ^{t}BOC-(*S*)-alanine (11.35 g, 60 mmol), (*d,l*)-phenylserine hydrochloride (14.74 g, 60 mmol), and HOBT (8.51 g, 63 mmol) in DMF (180 ml) was added NMM (6.07 g, 60 mmol) at 0° with stirring for 30 min. Then, DCC (12.38 g, 60 mmol) was added to the mixture and stirred for 2 hr at 0° and 12 hr at 25°, ppts were filtered off and the solvent was removed under reduced pressure. The residue was dissolved in $CHCl_3$ (300 ml), washed with 10% aqueous citric acid, sat NaClaq, 5% $NaHCO_3$aq and sat NaClaq, and dried over $MgSO_4$. After the removal of solvent, resulted crude product was dried overnight in a vacuum desiccator to give **18a-2** (20.00 g, 96%) as colorless viscous oil.

Compound **18a-2** thus obtained (19.22 g, 50.5 mmol) was added to a mixed soln of 1N NaOHaq (66 ml) and MeOH (120 ml) at 0° and stirred for 2 hr. Then, the soln was neutralized by adding 10% aqueous citric acid and the solvent was removed. To the residue was added EtOAc (300 ml), and organic layer was washed with sat NaClaq, dried over $MgSO_4$, and the solvent was evaporated to give ^{t}BOC-(*S*)-Ala-Ser(Ph)-OH (17.02 g, 96%) as colorless solid.

A mixture of ^{t}BOC-(*S*)-Ala-Ser(Ph)-OH (16.41 g, 46.6 mmol), NaOAc (20.9 g, 22.5 mmol) and Ac_2O (75 ml) was stirred for 1 hr at 0° and 12 hr at 25°. Then, chilled water (80 ml) was added to the mixture and the precipitated pale yellow crystals of **19a-2** were collected on a glass filter (13.45 g, 89%): m.p. 107.5–109°.

A mixture of **19a-2** (3.93 g, 12.4 mmol), (*S*)-leucine methyl ester hydrochloride (2.25 g, 12.4 mmol) and Et_3N (1.26 g, 12.4 mmol) in $CHCl_3$ (80 ml) was stirred for 1 hr at 0° and 40 hr at 25°. Then, $CHCl_3$ (100 ml) was added to the mixture and the soln was washed with 10% aqueous citric acid, sat NaClaq, dried over $MgSO_4$, and concentrated to give crude product. The crude product thus obtained was recrystallized from EtOAc to afford **5a-2** (4.62 g, 81%) as colorless crystals: m.p. 163–164°; $[\alpha]_D^{20}$ − 50.0° (*c* 1.001, MeOH); NMR ($CDCl_3$) δ 0.93 (d, J = 6 Hz, 6H), 1.38 (d, J = 6 Hz, 3H), 1.40 (s, 9H), 1.56–1.90 (m, 3H), 3.70 (s, 3H),

4.18 (quintet, J = 6.5 Hz, 1H), 4.65 (q, J = 7 Hz, 1H), 5.23–5.43 (d, J = 6.5 Hz, 1H), 7.12–7.53 (m, 7H), 8.87 (bs, 1H) ppm; IR (KBr disk) 3400, 3250 (ν_{NH}), 1730, 1695 ($\nu_{C=O}$), 1530 (δ_{NH}) cm^{-1}. (Found: C, 62.23; H, 7.67; N, 8.90%; $C_{24}H_{35}N_3O_6$. Requires: C, 62.45; H, 7.64; N, 9.10%.)

Physical properties, spectral and microanalytical data for other **5a** series and **5b** are as follows.

Compound **5a-1**: m.p. 192–193°; $[\alpha]_D^{20} - 25.3°$ (*c* 1.002, MeOH); NMR ($CHCl_3/CD_3OD$) δ 0.93 (d, J = 6 Hz, 6H), 1.43 (s, 9H), 1.60–1.83 (m, 3H), 3.75 (s, 3H), 3.83 (bs, 2H), 4.64 (t, J = 7 Hz, 1H), 7.25–7.60 (m, 6H) ppm; IR (KBr disk) 3400, 3300, 3260, 3180 (ν_{NH}), 1738, 1682 ($\nu_{C=O}$), 1538 (δ_{NH}) cm^{-1}. (Found: C, 61.62; H, 7.52; N, 9.34%; $C_{23}H_{33}N_3O_6$ Requires: C, 61.73; H, 7.43; N, 9.39%.)

Compound **5a-3**: m.p. 145–146°; $[\alpha]_D^{20} + 27.87°$ (*c* 1.008, MeOH); NMR ($CDCl_3$) δ 0.93 (d, J = 6 Hz, 6H), 1.38 (d, J = 6 Hz, 3H), 1.47 (s, 9H), 1.61–1.83 (m, 3H), 3.64 (s, 3H), 4.10 (octet, J = 6 Hz, 5.5 Hz, 1H), 4.58 (q, J = 7 Hz, 1H), 5.29 (d, J = 5.5 Hz, 1H), 7.10–7.45 (m, 6H), 7.81 (bs, 1H) ppm; IR (KBr disk) 3220 (ν_{NH}), 1750, 1720, 1690 ($\nu_{C=O}$), 1535 (δ_{NH}) cm^{-1}. (Found: C, 61.46; H, 7.72; N, 8.76%; $C_{24}H_{35}N_3O_6 \cdot 0.5\ H_2O$ Requires: C, 61.26; H, 7.71; N, 8.93%.)

Compound **5a-4**: m.p. 162.5–163°; $[\alpha]_D^{20} - 77.24°$ (*c* 1.002, MeOH); NMR ($CDCl_3$) δ 0.96 (d, J = 5.5 Hz, 6H), 1.38 (s, 9H), 1.55–1.81 (m, 3H), 3.13 (d of ABq, J = 15 Hz, 9 Hz, 4.5 Hz, 2H), 3.67 (s, 3H), 4.30 (sextet, J = 9 Hz, 4.5 Hz, 7 Hz, 1H), 4.67 (q, J = 7 Hz, 1H), 5.10 (d, J = 7 Hz, 1H), 7.06–7.50 (m, 12H), 7.92 (bs, 1H) ppm; IR (KBr disk) 3370 (ν_{NH}), 1749, 1730, 1695, 1648 ($\nu_{C=O}$), 1502 (δ_{NH}) cm^{-1}. (Found: C, 67.04; H, 7.44; N, 7.57%; $C_{30}H_{39}N_3O_6$ Requires: C, 67.02; H, 7.31; N, 7.82%.)

Compound **5a-5**: m.p. 130.5–131°; $[\alpha]_D^{20} - 52.68°$ (*c* 1.004, MeOH); NMR ($CDCl_3$) δ 1.33 (s, 9H), 3.05 (d of ABq, J = 13.5 Hz, 9 Hz, 6 Hz, 2H), 3.62 (s, 3H), 3.95 (quintet, J = 4 Hz, 2H), 4.41 (sextet, J = 9 Hz, 6 Hz, 7 Hz, 1H), 5.32 (d, J = 4 Hz, 1H), 6.90–7.38 (m, 12H), 8.27 (bs, 1H) ppm; IR (MBr disk) 3390 (ν_{NH}), 1755, 1740, 1680, 1660 ($\nu_{C=O}$), 1530 (δ_{NH}) cm^{-1}. (Found: C, 65.12; H, 6.60; N, 8.62%; $C_{26}H_{31}N_3O_6$ Requires: C, 64.85; H, 6.49; N, 8.73%.)

Compound **5a-6**: m.p. 163.5–164.5°; $[\alpha]_D^{20} - 50.84°$ (*c* 1.009, MeOH); NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.12 (s, 3H), 2.00–2.37 (m, 2H), 2.43–2.50 (m, 2H), 3.72 (s, 3H), 3.88 (d, J = 5.5 Hz, 2H), 4.74 (q, J = 7 Hz, 1H), 5.59 (t, J = 5.5 Hz, 1H), 7.12–7.57 (m, 7H), 8.24 (bs, 1H) ppm; IR (KBr disk) 3380, 3270, 3230, 3170 (ν_{NH}), 1742, 1680 ($\nu_{C=O}$), 1540 (δ_{NH}) cm^{-1}. (Found: C, 56.51; H, 6.77; N, 8.90; S, 6.77%; $C_{22}H_{31}N_3O_6S$ Requires: C, 56.76; H, 6.71; N, 9.03; S, 6.89%.)

Compound **5b**: m.p. 133.5–135.5°; $[\alpha]_D^{20} - 16.3°$ (*c* 1.003, MeOH); NMR ($CDCl_3$) δ 0.99 (d, J = 6 Hz, 6H), 1.43–1.87 (m, 3H), 3.67 (s, 3H), 3.93 (d, J = 6 Hz, 2H), 4.68 (q, J = 7 Hz, 1H), 5.02 (s, 2H), 5.95 (t, J = 6 Hz, 1H), 7.03–7.50 (m, 12H), 8.07–8.40 (m, 1H) ppm; IR (KBr disk) 3270 (ν_{NH}), 1736, 1705, 1675, 1655 ($\nu_{C=O}$), 1610, 1540 (δ_{NH}) cm^{-1}. (Found: C, 64.59; H, 6.72; N, 8.63%; $C_{26}H_{31}N_3O_6$ Requires: C, 64.85; H, 6.49; N, 8.73%.)

Compound **5c** was prepared from **5a-1** as follows. To a suspension of **5a-1** (2.24 g, 5.00 mmol) in EtOAc (20 ml) was added a HCl–EtOAc soln (20 ml) at 0° with stirring for 1 hr. Then, the solvent was removed to give HCl·Gly-ΔPhe-(*S*)-Leu-OMe as white powder (2.02 g, 100%). To a mixture of HCl·Gly-ΔPhe-(*S*)-Leu-OMe thus obtained (1.92 g, 5.00 mmol) and Et_3N (1.01 g, 10 mmol) in $CHCl_3$ (25 ml) was added trifluoroacetic anhydride (1.26 g, 6.00 mmol) at 0° with stirring and temp was allowed to gradually rise to room temp for 6 hr. Then, the mixture was washed with 10% aqueous citric acid, sat NaClaq, dried over $MgSO_4$, and the solvent was evaporated to give crude product, which was recrystallized from EtOAc–hexane to afford **5c** (1.55 g, 71%) as colorless crystals: m.p. 188–189.5°; $[\alpha]_D^{20} - 18.9°$ (*c* 1.005, MeOH); NMR ($CDCl_3/CD_3OD$) δ 0.96 (d, J = 7 Hz, 6H), 1.52–1.78 (m, 3H), 3.68 (s, 3H), 3.95 (s, 2H), 4.58 (m, 2H), 6.98 (s, 1H), 7.28 (m, 5H) ppm; IR (KBr disk) 3420, 3230, (ν_{NH}), 1740, 1720, 1677, 1658 ($\nu_{C=O}$), 1535 (δ_{NH}) cm^{-1}. (Found: C, 54.05; H, 5.71; N, 9.25%; $C_{20}H_{24}N_3O_5F_3$ Requires: C, 54.17; H, 5.46; N, 9.48%.)

Compound **5d** was prepared from 2-azidomethyl-4-benzylidene-2-oxazolin-5-one, which was obtained from N-azidoacetyl-(*d,l*)-phenylserine ethyl ester, and (*S*)-leucine methyl ester in a manner similar to the preparation of **5a**.

Compound **5d**: m.p. 152–153.5°; $[\alpha]_D^{20} - 5.7°$ (*c* 1.001, MeOH); NMR ($CDCl_3$) δ 0.97 (d, J = 6 Hz, 6H), 1.40–2.06 (m, 3H), 3.72 (s, 3H), 3.93 (s, 2H), 4.66 (q, J = 7 Hz, 1H), 7.00 (s, 1H), 7.05 (d, J = 7 Hz, 1H), 7.20–7.56 (m, 5H), 8.15 (bs, 1H) ppm; IR (KBr disk) 3230 (ν_{NH}), 2120 (ν_{N_3}), 1755, 1658, 1628 ($\nu_{C=O}$), 1554, 1528 (δ_{NH}) cm^{-1}. (Found: C, 58.27; H, 6.34; N, 18.53%; $C_{18}H_{23}N_5O_4$ Requires: C, 57.90; H, 6.21; N, 18.76%.)

Compound **16** was prepared by the coupling of N-formyldehydrophenylalanine, which was obtained from methyl isocyanoacetate and benzaldehyde by Schöllkopf's method,[14] with (*S*)-leucine methyl ester hydrochloride by using BOP–Cl as the coupling reagent[15] in the presence of Et_3N in CH_2Cl_2 at 10°.

Compound **16**: Colorless crystals; m.p. 92.5–94.5°; $[\alpha]_D^{20} - 11.40°$ (*c* 1.000, MeOH); NMR ($CDCl_3/CD_3OD$) δ 0.98 (d, J = 6 Hz, 6H), 1.48–1.87 (m, 3H), 3.72 (s, 3H), 4.65 (m, 1H), 7.10–7.60 (m, 6H), 8.20 (s, 1H) ppm; IR (KBr disk) 3240 (ν_{NH}), 1750, 1680, 1655 ($\nu_{C=O}$), 1540 (δ_{NH}) cm^{-1}. (Found: C, 63.87; H, 6.74; N, 8.55%; $C_{17}H_{22}N_2O_4$ Requires: C, 64.13; H, 6.97; N, 8.80%.)

Dehydropeptide amide (**21a, b**) hydrazide (**21c**) and phenylhydrazide (**21d**) were prepared from the corresponding **5a** by conventional method through saponification of **5a** using 2N NaOHaq in MeOH at 5°, and mixed anhydride formation with isobutyl chloroformate in THF in the presence of NMM at −15° followed by the addition of ammonia, hydrazine hydrate or phenylhydrazine.

Compound **21a**: Colorless crystals; m.p. 195.5–197°; $[\alpha]_D^{20} + 76.94°$ (*c* 1.002, MeOH). (Found: C, 61.16; H, 7.70; N, 13.10%; $C_{22}H_{32}N_4O_5$ Requires: C, 61.09; H, 7.46; N, 12.95%.)

Compound **21b**: Colorless crystals; m.p. 116–118°; $[\alpha]_D^{20} + 46.56°$ (*c* 1.005, MeOH). (Found: C, 61.19; H, 7.63, N, 11.71%; $C_{23}H_{34}N_4O_5 \cdot 0.5\ CH_3CO_2C_2H_5$ Requires: C, 61.20; H, 7.81, N, 11.42%.)

Compound **21c**: Colorless crystals; m.p. 148–150°; $[\alpha]_D^{20} + 33.30°$ (*c* 1.003, MeOH). (Found: C, 59.35; H, 7.32; N, 15.32%; $C_{22}H_{33}N_5O_5$ Requires: C, 59.04; H, 7.43; N, 15.65%.)

Compound **21d**: Colorless crystals; m.p. 129.5–131°; $[\alpha]_D^{20} + 33.30°$ (*c* 1.003, MeOH). (Found: C, 60.52, H, 7.44; N, 11.79%; $C_{44}H_{64}N_8O_{10} \cdot CH_3CO_2C_2H_5$ Requires: C, 60.62; H, 7.42, N, 11.78%.)

Preparation of N-(N-*acetyldehydrophenylalanyl*)-β-*amino alcohol benzyl ethers* (**10**)

Compounds **10a–d** were prepared by the reaction of 2-methyl-4-benzylidene-2-oxazolin-5-one with β-amino alcohol benzyl ethers in $CHCl_3$ at room temp in a manner similar to the preparation of dehydropeptides (*vide supra*). β-Amino alcohol benzyl ethers were prepared by following the reported procedure for the corresponding methyl ethers with the use of benzyl bromide instead of MeI.[30] (*S*)-Phenylalaninol benzyl ether: b.p. 143°/0.3 mm Hg; $[\alpha]_D^{20} + 2.1°$ (*c* 1.01, $CHCl_3$). (*S*)-Leucinol benzyl ether: b.p. 97°/0.4 mm Hg; $[\alpha]_D^{20} + 6.7°$ (*c* 1.28, $CHCl_3$). (*S*)-Valinol benzyl ether: b.p. 79°/0.2 mm Hg; $[\alpha]_D^{20} + 16.4°$ (*c* 1.48, $CHCl_3$). (*S*)-Methioninol benzyl ether: b.p. 137°/0.5 mm Hg; $[\alpha]_D^{20} - 2.73°$ (*c* 1.537, $ChCl_3$).

Compound **10a**: Colorless crystals; m.p. 114.5–115.5°; $[\alpha]_D^{20} - 63.57°$ (*c* 1.01, MeOH); NMR ($CDCl_3$) δ 1.97 (bs, 3H), 2.90 (d, J = 7.5 Hz, 2H), 3.42 (d, J = 4 Hz, 2H), 4.34 (m, 1H), 4.45 (s, 2H), 6.63 (bs, 1H), 6.83 (d, J = 8 Hz, 1H), 7.00–7.55 (m, 15H), 8.00 (bs, 1H) ppm; IR (KBr disk) 3250 (ν_{NH}), 1650, 1620 ($\nu_{C=O}$, $\nu_{C=C}$), 1540 (δ_{NH}) cm^{-1}. (Found: C, 75.40; H, 6.49; N, 6.36%; $C_{27}H_{28}N_2O_3$ Requires: C, 75.68; H, 6.59; N, 6.54%.)

Compound **10b**: Colorless crystals; m.p. 137–138; $[\alpha]_D^{20} - 7.34°$ (*c* 0.994, MeOH); NMR ($CDCl_3$) δ 0.92 (d, J = 6 Hz, 6H), 1.20–1.80 (m, 3H), 2.00 (bs, 3H), 4.45 (d,

J = 5 Hz, 2H), 4.20 (m, 1H), 4.46 (s, 2H), 6.65 (d, J = 9 Hz, 1H), 6.70 (bs, 1H), 7.10–7.50 (m, 10H), 7.86 (bs, 1H) ppm; IR (KBr disk) 3250 (ν_{NH}), 1650, 1630 (ν_{C-O}, $\nu_{C=C}$), 1555 (δ_{NH}) cm^{-1}. (Found: C, 72.83; H, 7.64; N, 7.06%; $C_{24}H_{30}N_2O_3$ Requires: C, 73.07; H, 7.66; N, 7.10%.)

Compound **10c**: Colorless crystals; m.p. 135–136.5°; $[\alpha]_D^{20}$ − 9.96° (*c* 1.064, MeOH); NMR ($CDCl_3$) δ 0.94 (d, J = 7 Hz, 6H), 1.75–2.10 (m, 1H), 2.01 (bs, 3H), 3.54 (d of ABq, J = 10.5 Hz, 4.5 Hz, 7 Hz, 2H), 3.90 (m, 1H), 4.43 (bs, 2H), 6.58 (bs, 1H), 6.72 (bs, J = 7 Hz, 1H), 7.18–7.40 (m, 10H), 7.88 (bs, 1H) ppm; IR (KBr disk) 3250 (ν_{NH}), 1655, 1630 (ν_{C-O}, ν_{C-C}), 1555 (δ_{NH}) cm^{-1}. (Found: C, 72.34; H, 7.42; N, 7.31%; $C_{23}H_{28}N_2O_3$ Requires: C, 72.61; H, 7.42; N, 7.36%.)

Compound **10d**: Colorless crystals; m.p. 130–131°; $[\alpha]_D^{20}$ − 14.95° (*c* 1.010, MeOH); NMR ($CDCl_3$) δ 1.60–2.00 (m, 2H), 1.86 (bs, 3H). 2.00 (s, 3H), 2.20–2.65 (m, 2H), 3.20–3.60 (m, 2H), 4.06 (m, 1H), 4.35 (bs, 2H), 6.36 (bs, 1H), 7.03 (bs, 5H), 7.25 (s, 5H), 7.68 (bd, J = 8 Hz, 1H), 8.65 (bs, 1H) ppm; IR (KBr disk) 3250 (ν_{NH}), 1655, 1630 (ν_{C-O}, ν_{C-C}), 1560 (δ_{NH}) cm^{-1}. (Found: C, 66.46; H, 6.77; N, 6.58; S, 7.61%; $C_{23}H_{28}N_2O_3S$ Requires: C, 66.96; H, 6.84; N, 6.79; S, 7.77%.)

Preparation of N-(α-*ketoacyl*)-α-*amino esters* (**13**)

Compounds **13a–d** were prepared by the reaction of α-ketoacyl chloride (1.1 eq) with HCl salts of α-amino acid methyl esters (1.0 eq) in the presence of NMM (2.2 eq) in CH_2Cl_2 at 0° for 2–3 hr. Pyruvoyl chloride and phenylglyoxyloyl chloride were obtained in high yields by reacting dichloromethyl methyl ether with pyruvic acid and phenylglyoxylic acid, respectively by following the reported procedure.[15]

Compound **13a**: 88% yield; viscous oil; $[\alpha]_D^{20}$ + 22.38° (*c* 1.695, $CHCl_3$); NMR ($CDCl_3$) δ 2.38 (s, 3H), 3.09 (d, J = 6 Hz, 2H), 3.66 (s, 3H), 4.76 (d of t, J = 6 Hz, 9 Hz, 1H), 7.00–7.50 (m, 6H) ppm; IR (neat) 3410, 3350 (ν_{NH}), 1745, 1690 ($\nu_{C=O}$), 1520 (δ_{NH}) cm^{-1}.

Compound **13b**: 80% yield; viscous oil; $[\alpha]_D^{20}$ − 5.75° (*c* 1.476, $CHCl_3$); NMR ($CDCl_3$) δ 0.95 (d, J = 7 Hz, 6H), 2.23 (m, 1H), 2.49 (s, 3H), 3.76 (s, 3H), 4.55 (d of d, J = 9 Hz, 5 Hz, 1H), 7.45 (m, 1H) ppm; IR (neat) 3300 (ν_{NH}), 1740, 1690 (ν_{C-O}), 1520 (δ_{NH}) cm^{-1}.

Compound **13c**: 99% yield; viscous oil; $[\alpha]_D^{20}$ + 57.30° (*c* 1.438, $CHCl_3$); NMR ($CDCl_3$) δ 3.25 (d, J = 6 Hz, 2H), 3.76 (s, 3H), 5.00 (d of t, J = 6 Hz, 8 Hz, 1H), 7.30 (s, 5H), 7.35–7.96 (m, 4H), 8.32 (m, 2H) ppm; IR (neat) 3300 (ν_{NH}). 1745, 1670 (ν_{C-O}), 1520 (δ_{NH}) cm^{-1}.

Compound **13d**: 98% yield; viscous oil; $[\alpha]_D^{20}$ + 7.41° (*c* 1.254, $CHCl_3$); NMR ($CDCl_3$) δ 1.56 (d, J = 7 Hz, 3H), 3.80 (s, 3H), 4.70 (quintet, J = 7 Hz, 1H), 7.30–7.94 (m, 4H), 8.37 (m, 2H) ppm; IR (neat) 3300 (ν_{NH}), 1745, 1670 (ν_{C-O}), 1530 (δ_{NH}) cm^{-1}.

Preparation of chiral catalyst solution

The cationic chiral Rh catalysts were prepared *in situ* by the reaction of $[Rh(NBD)_2]^+ClO_4^-$ with chiral diphosphine in degassed solvent. Typically, 3.87 mg (1.0×10^{-5} mol) of $[Rh(NBD)_2]^+$–ClO_4^- and 6.30 mg (1.1×10^{-5} mol) of Ph-CAPP were dissolved in 5 ml of degassed EtOH under argon, and the soln was stirred for 15 min. The neutral chiral Rh catalysts were also prepared *in situ* by the reaction of $[Rh(COD)Cl]_2$ with chiral diphosphine in degassed solvent. Typically, 6.1 mg (1.25×10^{-5} mol) of $[Rh(COD)Cl]_2$ and 15.2 mg (2.75×10^{-5} mol) of BPPM were mixed in 5 ml of degassed benzene under argon, and the mixture was stirred for 15 min. The complexes of other chiral diphosphine ligands were prepared in a similar manner.

Hydrogenation procedure

Typically, **5a-1** (895 mg, 2.00 mmol) was hydrogenated in the presence of $[(diPAMP)Rh(NBD)]^+ClO_4^-$ *in situ* prepared (2.00×10^{-2} mmol) in 30 ml of degassed EtOH at 40° and 10 atm of hydrogen in a stainless steel autoclave using a glass reaction tube for 18 hr. Then, Bosnich's workup[25a] was employed to remove the catalyst, and the soln was further treated with a small amount of Norit. In order to determine the optical purity, the soln was submitted to HPLC analysis with a reversed-phase column packed with TOYO SODA LS 410K (ODS SIL) and MeOH–H_2O (68/32) as the eluent, which indicated that the (*R,S*)/(*S,S*) ratio of the produced tripeptide was 1.1/98.9. After simple evaporation of the solvent, **20a-1** (898 mg) was obtained in 99.9% yield. Recrystallization of **20a-1** thus obtained from EtOAc–hexane gave optically pure tripeptide as colorless crystals (828 mg, 92% recovery): m.p. 115–116°; HPLC analysis, (*R,S*)/(*S,S*) = 0.0/100.0; $[\alpha]_D^{20}$ − 20.65° (*c* 1.002, MeOH).

Hydrosilylation procedure

Typically, a mixture of **13c** (1.55 g, 4.98 mmol) and α-naphthylphenylsilane (1.76 g, 7.51 mmol) in 5 ml of degassed benzene was added to the soln of [(+)DIOP]Rh(COD)Cl (2.6×10^{-2} mmol) *in situ* prepared in 3 ml of degassed benzene at ice-cooled temp, and the soln was stirred for 24 hr at 20° and 12 hr at 40°. The completion of the reaction was checked by TLC. Then, a MeOH soln (50 ml) of *p*-toluenesulfonic acid (TsOH) (100 mg) was added to the mixture and stirred at 40° for 1 hr. After the solvent was removed, the residue was submitted to a short column chromatography on silica gel, which was done carefully to avoid resolution, to give **14c** in 79% yield (1.23 g) from hexane–ether elute: $[\alpha]_D^{20}$ + 84.1° (*c* 1.02, $CHCl_3$).

Compound **14c** thus obtained was allowed to react with trifluoroacetic anhydride (910 mg, 4.33 mmol) in the presence of NMM (440 mg, 4.35 mmol) in 15 ml of CH_2Cl_2 at 0° for 1 hr. The mixture was washed with water, dried over $MgSO_4$, solvent evaporated, and dried in a vacuum to give **15c**. ^{19}F NMR measurement of this sample by using Eu(fod)$_3$ as the shift reagent in $CDCl_3$ revealed that the (*R,S*)/(*S,S*) ratio was 91/9. The absolute configuration was determined by the comparison with authentically prepared (*S,S*)-**15c** through the coupling of (*S*)-mandelic acid with (*S*)-phenylalanine methyl ester by using DCC followed by trifluoroacetylation.

Compound **14c** obtained via hydrosilylation of **13c** was purified by recrystallization from EtOH to give optically pure (*R,S*)-**14c**: $[\alpha]_D^{20}$ + 99.2° (*c* 1.00, $CHCl_3$). (Found: C, 69.03; H, 6.15; N, 4.43%; $C_{18}H_{19}NO_4$ Requires: C, 69.00; H, 6.11; N, 4.47%.)

Synthesis of enkephalin analogs

The synthesis of **29** is typically described.

Compound **31** (696 mg, 98.4% diastereomeric purity) was obtained by the asymmetric hydrogenation of **30** (697 mg, 2.00 mmol) by using $[(diPAMP)Rh(NBD)]^+ClO_4^-$ (6.0×10^{-2} mmol) *in situ* prepared, at 40° and 10 atm of hydrogen for 24 hr in EtOH. **31** thus obtained was recrystallized from EtOAc to give the optically pure compound in 88% recovery (612 mg). Then, optically pure **31** (508 mg, 1.45 mmol) was saponified by 1N NaOHaq (3.2 ml) in MeOH (6 ml) at 0° for 1 hr. After usual workup, **32** was obtained as colorless crystals (401 mg, 94%).

Compound **20a-1** (787 mg, 1.75 mmol) prepared by the asymmetric hydrogenation of **5a-1** followed by recrystallization (*vide supra*), was deblocked by treating with HCl in dry EtOAc (15 ml) at 0° for 1 hr and at 25° for additional 1 hr. After removal of solvent and washing with ether, **33** was obtained as colorless crystals (648 mg, 96%).

The coupling of **32** (353 mg, 1.20 mmol) and **33** (463 mg, 1.20 mmol) was carried out by using DCC (248 mg, 1.20 mmol), HOBT (170 mg, 1.26 mmol) and NMM (121 mg, 1.20 mmol) in DMF (8 ml) at 0° for 2 hr and at 25° for 12 hr. After usual workup, **29** was obtained as colorless powder (671 mg, 89%).

Compound **29**: m.p. 259–261° (dec); $[\alpha]_D^{20}$ − 13.4° (*c* 1.001, DMF); NMR (dimethylsulfoxide-d_6) δ 0.88 (d of d, J = 6 Hz, 6H), 1.11 (d, J = 7 Hz, 3H), 1.43–1.70 (m, 3H), 1.78 (s, 3H), 2.57–3.05 (m, 4H), 3.50–3.77 (m, 2H), 3.60 (s, 3H), 3.99–4.78 (m, 4H), 6.62 (d, J = 8.5 Hz, 2H), 6.99 (d,

J = 8.5 Hz, 2H), 7.24 (s, 5H), 7.80–8.42 (m, 5H), 9.11 (s, 1H) ppm; IR (KBr disk) 3500s, 3290 (ν_{NH}, ν_{OH}), 1730, 1700s, 1667, 1630 ($\nu_{C=O}$), 1540, 1520 (δ_{NH}). (Found: C, 61.31; H, 7.08; N, 11.34%; $C_{32}H_{43}N_5O_8$ Requires: C, 61.43; H, 6.93; N, 11.19%.) HPLC analysis revealed that the diastereomeric purity was ≥96.6%. Slight racemization could take place at the coupling of the two fragments in the last step and the saponification step.

In a similar manner, **23** was synthesized by the coupling of **25** with **28**.

Compound **23**: Colorless crystals; m.p. 207–210°; $[\alpha]_D^{20}$ – 18.9° (*c* 1.044, DMF); NMR (dimethylsulfoxide-d_6) δ 0.85 (d of d, J = 6 Hz, 6H), 1.19 (d, J = 7 Hz, 3H), 1.55 (m, 3H), 1.74 (s, 3H), 2.50–3.20 (m, 4H), 3.50–3.80 (m, 2H), 3.58 (s, 3H), 3.90–4.80 (m, 4H), 6.60 (d, J = 8 Hz, 2H), 7.02 (d, J = 8 Hz, 2H), 7.20 (s, 5H), 7.65–8.40 (m, 5H), 9.07 (s, 1H) ppm; IR (KBr disk) 3300 (n_{NH}, ν_{OH}), 1755, 1695s, 1660, 1620 ($\nu_{C=O}$), 1550, 1520 (δ_{NH}). (Found: C, 58.59; H, 6.94; N, 10.75%; $C_{32}H_{43}N_5O_8 \cdot 1.5\ H_2O$ Requires: C, 58.88; H, 7.10; N, 10.73%.) HPLC analysis revealed that the diastereomeric purity was ≥99.6%.

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