the latter is practically of 3+ and hence the charge carriers are dominantly created by interband thermal activation like in the former. This result also indicates that the structural difference of 2H and 3R does not apparently have any significant influence on the electronic transport properties. The enhanced conduction observed in $Ag_{0.75}CoO_{2-\delta}$ can be attributted to the presence of charge carriers induced by the mixed-valence state. But they are obviously localized, probably due to the partial absence of Ag^+ ions and the increase of non-crystallinity in Ag sublattice, that should cause the localization of the charge carriers. The transport process in this phase should occur through the mobility activation of carriers.

In conclusion, Ag-delafossites prepared by cation-exchange reation at low temperature are considered to have the structures pre-determined by the structural type of precursor. Ag-deficient delafossite-type oxides $Ag_xCoO_{2-\delta}$ (x= 0.95, 0.75) obtained from nonstoichiometric $Na_{0.7}CoO_{2-\delta}$ crystallize in 2H-type structure, and exhibit semiconductivity even in the presence of mixed-valency.

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Synthesis of Enkephalin Degrading Peptidase Inhibitors

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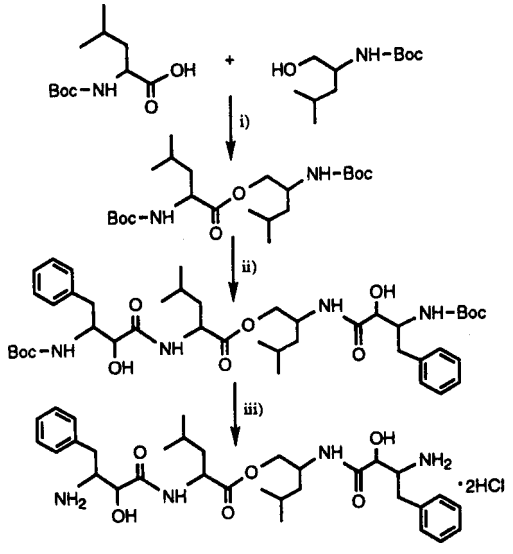
Since their isolation from pig brain,[1] enkephalins (Tyr-Gly-Gly-Phe-Leu and Tyr-Gly-Gly-Phe-Met) have come under intensive study because they may afford an alternative potential method of pain relief. In addition to their opiate-like properties they are known to have roles as neurotransmitters or neuromodulators in the central nerve system.[2] One of the major difficulties associated with use of these compounds as analgesic is their short half life.[3] Both Leu- and Met-enkephalin are rapidly inactivated by enzymes in serum and in brain. Three mechanisms for inactivation of enkephalins in brain have been observed: (a) cleavage at the Tyr-Gly bond by enkephalin aminopeptidase; (b) cleavage at the Gly-Phe bond by enkephalinase; (c) cleavage at the Phe-Met or Phe-Leu bond by carboxypeptidase. Most efforts directed at obtaining longer acting enkephalins have centered on the synthesis of enkephalin analogous resistant to enzymatic degradation. For example, a simple substitution of with D- has been resulted in a compound which is active via intracerebral or vascular administration.[3] Recently, by synthetic combinational library containing tens of millions of D-amino acid hexapeptides, the peptide, Ac-D-Arg-D-Phe-D-Trp-D-Ile-D-Asn-D-Lys-NH_2 which bears no resemblance to any known opioid peptide was reported to show strong analgesic effect.[4] Another approach to increase the effective action of enkephalins would be to limit their rate of degradation by blocking enzymatic pathways associated with catabolism. A variety of aminopeptidase or enkephalinase inhibitors with Zn-chelating function consisting of a thiol, carboxyl, phosphoryl, or hydroxamate group have been studied. Recently, Nishimura and Hazato isolated endogenous inhibitor of enkephalin degrading enzymes from bovine spinal cord. This new substance, designated spinorphin, is composed of a heptapeptide (Leu-Val-Val-Tyr-Pro-Trp-Thr).[5] In order to obtain longer acting enkephalins, it seems to be necessary to block the activities of enkephalin aminopeptidase and enkephalinase simultaneously. Therefore, simultaneous administration of thiophan, an inhibitor of enkephalinase and bestatin, an inhibitor of membrane-bound aminopeptidase, induced stronger analgegesic effects than thiophan alone.[6] In a continuing search for inhibitors, we have synthesized a new type of inhibitor, that can inhibit enkephalin am-

inopeptidase and enkephalinase simultaneously. Enkephalin degrading peptidases, enkephalin aminopeptidase and enkephalinase are known to be zinc-metalloenzymes.[7,8] Inhibition of aminopeptidase by bestatin proceeds to act *via* chelation of zinc with the hydroxyl group and amino group.[9] It is also known that thiorphan interacts with enkephalinase by the chelation between thiol group of thiorphan and a zinc atom at the active site of enkephalinase.[10] Considering the inhibition pattern of bestatin and thiorphan and the substrate recognition by aminopeptidase and enkephalinase, it has been suggested that if a compound has two binding sites for zinc atoms at the active sites of aminopeptidase and enkephalinase, it could be a strong inhibitor of both aminopeptidase and enkephalinase. The fact that aminopeptidase is strongly inhibited by bestatin led us to design a depsipepde, (2S,3R)-AHPBA-leucine-(2S,3R)-AHPBA-leucinol ester (Scheme 1), that is an analog of bestatin, as a inhibitor of aminopeptidase and enkephalinase.

The depsipeptide could in priciple be synthesized in three ways. One way to achieve this is to couple Boc-AHPBA-Leu with Boc-AHPBA-leucinol. Since AHPBA has a secondary hydroxyl group, the two primary hydroxyl groups of leucinol must be protected before coupling in order to avoid competition between the secondary alcohol of AHPBA and the primary alcohol of leucinol in the esterification reaction. The protecting groups should then be removable under mild conditions. Another way is to synthesize depsipeptide by a stepwise procedure from AHPBA and leucinol. In this Scheme, however, the protection and the deprotection of one of the secondary alcohol of AHPBA is still necessary. Finally, the compound could be prepared by coupling between one molecule of diamine ester and two moecules of Boc-AHPBA as shown in Scheme 1. Minimum protection could be especially important in the synthesis of this kind of compound containing many functional groups. Therefore, the synthesis of the depsipeptide was achieved by the procedure described in Scheme 1. Ester was prepared from Boc-Leu and Boc-leucinol using DCC/DMAP as coupling reagent in excellent yield (96%). After removal



Scheme 1. Synthesis of depsipeptide i) DCC/DMAP, ii) 4N-HCl/Dioxane, 2 Boc-AHPBA, DCC/HOBt, iii) 4N-HCl/Doxane.

Table 1. Inhibition of EAP and enkephalinase by synthesized inhibitors

no.	compound[a]	EAP, $IC_{50}\times10^{-5}$ M	enkephalinse, $IC_{50}\times10^{-5}$ M
1	(2R,3R)-depsipeptide	0.02	4
2	(2R,3R)-depsipeptide	1.0	10

[a](2S,3R)-depsipeptide and (2S,3R)-depsipeptide represent (2S, 3R)-3-amino-2-hydroxy-4-phenylbutanoyl-L-leucine-(2S,3R)-3-amino-2-hydroxy-4-phenyl-butanoy-leucinol ester and (2R,3R)-3-amino-2-hydroxy-4-phenylbutanoyl-L-leucine-(2R,3R)-3-amino-2-hydroxy-4-phenylbutanoyl-leucinol ester, respectively.

of Boc groups, followed by neutralization of the hydrochloride salt, diamine ester was coupled to two equivalents of Boc-AHPBA in methlene chloride by DCC/HOBt procedure. The product was obtained in 72% yield after column chromatography. Deprotection of Boc groups with 4 N HCl in dioxane gave the desired depsipeptide.

Depsipeptide synthesized inhibits both aminopeptidase ($IC_{50}=2\times10^{-7}$ M) and enkephalinase ($IC_{50}=4\times10^{-5}$ M). The inhibition for aminopeptidase was much more strong than that of enkephalinase (Table 1). The inhibitor is almost as strong as bstatin for aminopeptidase, but regarding inhibition of enkephalinase it is not strong as thiorphan. The weak inhibition of enkephalinase shown by the inhibitor was due to lack of carboxyl group that is known to have a significant role in substrate recognition by enkephalinase.[11] But it still showed moderately strong inhibition of enkephalinase. The chiral requirement of the hydroxyl group of the inhibitor was observed for enkephalin aminopeptidase. The diastereomer, (2R,3R)-AHPBA-leucine-(2R,3R)-AHPBA-leucinol ester whose chirality of the hydroxyl group was changed from (S) to (R), as in epibestatin, the activity was decreased 50-fold. Similar chiral requirement of the hydroxyl group for enkephalinase was seen. But the difference in activity between diastereomers for enkephalinase was much smaller than that of diastereomers for enkephaline aminopeptidase. Considering the fact that both enzymes bind the same substrate, enkephaline, but cut different sites of substrate, they might presumably have similar binding sites, but they have different catalytic sites. Therefore, the inhibitor seems to bind the active site of enkephaline aminopeptidase or enkephalinase as shown in Figure 1.

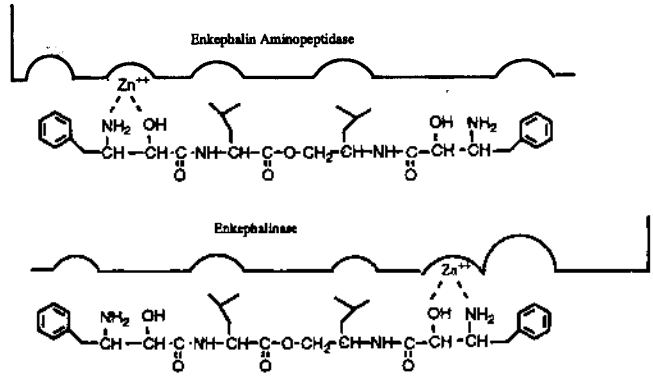


Figure 1. Schematic model of the inhibition of enkephalin aminopeptidase and enkephalinase by depsipeptide inhibitor.

In conclusion, the inhibitor showed very strong inhibition for aminopeptidase and also showed moderately strong inhibition for enkephalinase. The first attempt to inhibit aminopeptidase and enkephalinase simultaneously by a single compound seemed successful and applications of this novel approach to development of therapeutically useful inhibitors are in progress.

Experimentals

Melting points were determined on a Fisher-John's melting point apparatus and are corrected. The ^{1}H NMR spectra were recorded on a Bruker 300-MHz. Optical rotation measured at sodium D line by a Perkin Elmer 241 polaimeter. Silica gel 60 was used for column chromatography. Thin-layer chromatography (TLC) was performed on silica gel G plates. TLC solvent system used were: A, ethyl acetate-benzene (50 : 50); B, methanol-chloroform (5 : 95); C, butanol-acetic acid-water (4 : 1 : 1).

(2RS,3R)-N-(tert-Butyloxycarbonyl)-3-amino-2-hydroxy-4-phenyl-butanoic acid. The title compound was prepared in 74% yield from Boc-D-Phe-OMe using the reported procedure.[12] Separation of diastereomers of the title compound was achieved by converting the amino acid to methyl ester and chromatographing over silica gel, eluting with gradient of 20-30% ethyl acetate in toluene. R_f 0.40 (C), 0.31 (C), ^{1}H NMR (d_6-Acetone) δ 1.33 (s, 9H). 3.70-4.03 (m, 2H), 5.33-6.03 (bm, 3H), 7.1-7.4 (m, 5H)

N-(tert-Butyloxycarbonyl)-leucinol. Leucinol hydrochloride (2.523 g, 16.42 mmol) was dissolved in water (10 mL) and dioxane (10 mL), neutralized with triethylamine (3.5 mL, 24.6 mmol) and reacted with BOC-ON (4.85 g, 24.6 mmol) at room temperature overnight. After addition of water (15 mL) and ethyl acetate (30 mL), the aqueous layer was separated, acidified with cold 1 N HCl, and extracted with ethyl acetate. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound. R_f 0.35 (A), ^{1}H NMR ($CDCl_3$) δ 0.93 (d, *J*=Hz, 6H), 1.45 (s, 9H), 1.13-1.86 (s+m, 12H), 3.33 (bd, 1H), 3.40-3.86 (m, 2H), 4.90 (bd, 1H).

N-(tert-Butyloxycarbonyl)-L-leucine-N-(tert-Butyloxycarbonyl)-leucinol ester. A solution of Boc-Leu-OH (0.15 g, 0.6 mmol), Boc-L-leucinol (0.109 g, 0.5 mmol), DCC (0.165 g, 0.8 mmol), and 4-dimethylaminopyridine (6.1 mg, 0.05 mmol) in methylene chloride (3 mL) was stirred at room temperature overnight. The DCU was removed by filteration and the filtrate washed with water, saturated $NaHCO_3$, cold 1 N HCl and brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* (95% yield): mp 97-99 °C R_f 0.65 (A), ^{1}H NMR ($CDCl_3$) 0.93 (d, *J*=6 Hz, 12H), 1.43 (s, 18H), 1.43-2.12 (m, 6H), 4.10 (d, *J*=4.5 Hz, 2H). 3.72-4.40 (m, 2H), 4.52 (d, *J*=8 Hz, 1H), 4.90 (d, *J*=8 Hz, 1H).

(2S,3R)-[N-(tert-Butyloxycarbonyl)-3-amino-2-hydroxy-4-phenyl-butanoyl]-L-leucine-(2S,3R)-[N-(tert-Butyloxycarbonyl)-3-amino-2-hydroxy-4-phenylbutanoyl]-leucinol ester. N-(tert-Butyloxycarbonyl)-L-leucine-N-(tert-Butyloxycarbonyl)-leucinol ester (0.146 g, 0.37 mmol) was deprotected in 4 N HCl in dioxane (10 mL). The salt was dissolved in methyene chloride (3 mL), neutralized with triethylamine (0.14 mL, 0.99 mmol), and coupled with (2S,3R)-Boc-AHPBA-OH (0.218 g, 0.74 mmol) by using HOBt (0.152 g, 0.99 mmol) and DCC (0.204 g, 0.99 mmol) at 5 °C overnight. The reaction mixture was filtered and the methyene chloride layer was washed with distilled water, saturated sodium bicarbonate, and 1 N HCl. The solution was dried ($MgSO_4$) and the solvent evaporated in vacuo to give the protected depsipeptide. The compound was purified by chromatography over silica gel eluting with 1% methanol in chloroform (72% yield): mp 154-156 °C. R_f 0.50(B). ^{1}H NMR ($CDCl_3$) δ 0.78-1.04 (m, 12H), 1.20-2.15 (s+m, 24H), 2.98 (bd, *J*=7 Hz, 4H), 3.84-4.73 (m, 8H), 5.04 (bd, *J*=7 Hz, 2H), 6.76 (d, *J*=8 Hz, 1H), 7.02 (d, *J*=10 Hz, 1H), 7.22 (s, 10H). Anal. Calcd for $C_{42}H_{64}N_4O_{10}$: C, 64.26; H, 8.22; N, 7.20. Found: C, 64.27; H, 8.05; N, 7.07.

(2S,3R)-3-amino-2-hydroxy-4-phenylbutanoyl-L-leucine-(2S,3R)-3-amino-2-hydroxy-4-phenylbutanoyl-leucinol ester. Removal of N-Boc group of the protected depsipeptide (0.079 g, 0.1 mmol) was carried out using 4 N HCl in dioxane (30 min, 25 °C) to give the title compound in quantitative yield. mp 213-215 °C. R_f 0.31 (C). $[\alpha]_D^{24}$=10.57° (c=0.38, DMF). ^{1}H NMR (DMSO-d_6) 0.71-0.93 (m, 18H), D 1.02-1.78 (m, 6H), 2.82-3.02 (AB, 4H), 3.91-4.04 (m, 4H), 4.13-4.38 (m, 2H), 6.82 (bs, 2H), 7.33 (s, 10H), 7.93-8.46 (m, 6H). Anal. Calcd for $C_{32}H_{50}N_4O_6Cl_2$: C, 58.44; H, 7.66; N, 8.52. Found: C, 58.29; H, 7.73; N, 8.50.

Determination of Enzyme Activity. Enkephalin aminopeptidase was purified from rat brain by the reported procedure.[13] The enzyme activity was measured by colorimetric determination of the hydrolysis L-Tyr-β-naphthylamide after converting the liberated naphthylamine to a red dye as described the reported procedure.[13] Enkephalinase was prified from porcine kidney by the modification of the reported procedure.[14] Enkephaline activity was determined with Cbz-Tyr-Gly-Gly-Phe-p-NA as the substrate in a coupled enzyme assay in the presence of aminopeptidae M[15]. The appearance of *p*-nitroanilide was monitored at 380 nm with Gilford 250 spectrophotometer at 25 °C.

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16. Abbreviations used are as follows: AHPBA, 3-amino-2-hydroxy-4-phenylbutanoic acid; DCC, dicyclohexylcarbodiimide; DMAP, 4-dimethylaminopyridine; HOBt, 1-hydroxybenzotriazole; Cbz, benzyloxycarbonyl; Boc, tertiary-butyloxycarbonyl; PA, p-nitroaniline.

[4+4] Photocycloaddition of Methyl 1-Naphthoate to Furan

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The photocycloaddition of naphthalene derivatives to alkenes is still of substantial interest, although it has been extensively studied for the elucidation of the role of exciplex and for the exploitation of synthetic potentials.[1] Several photocycloaddition modes of naphthalenes, including 1,2-addition,[2] 1,4-addition,[3] and 1,8-addition,[4] have been reported. Many investigations on the 1,4-photocycloaddition have been conducted with naphthalene and cyanonaphthalenes. It was reported that the irradiations of naphthalene with 1,3-dienes yielded [4+4] cycloadducts as major products,[5] while those of cyanonaphthalenes with 1,3-dienes yielded [2+2] cycloadducts as major products.[6] The irradiation of 1-cyanonaphthalene with furan gave the *endo*-[4+4] cycloadduct,[7] while that of 2-cyanonaphthalene with furan yielded the cage cycloadduct.[8] The photoreaction of 1-cyanonaphthalene and furan has been recently reinvestigated, and the product composition of a photostationary state was explained by secondary orbital interaction and secondary processes.[9] However, the photocycloaddition of dienes to naphthalene derivatives other than cyanonaphthalenes seems to be rather limited. For methyl 1-naphthoate (**1**), the irradiation with an enol of β-ketone induced 1,2-photocycloaddition.[10] While several simple arenecarboxylic acid esters were reported to undergo [2+2] photocycloaddition at the carbonyl group to furan,[11] the photoreaction of **1** and furan has not been studied. In this study, we examined the temperature effect on the photoreaction of **1** and furan and elucidated the mechanism for this reaction.

Experimental

Irradiation of 1 and Furan at Ambient Temperature. Compound **1** (1.938 g, 10.41 mmol) and furan (excess, about 20 mL) were dissolved in distilled dichloromethane. After purging with nitrogen for 20 minutes, the solution at ambient temperature was irradiated through a cylindrical Pyrex glass filter with a 450 watt Hanovia medium pressure mercury lamp for 11 hours. A gentle stream of nitrogen was maintained during the irradiation, and the reaction was followed with either TLC or ^{1}H NMR analysis. The reaction mixture was separated by a silica gel column chromatography eluting with *n*-hexane and dichloromethane mixtures of increasing polarity to afford 1.471 g (7.900 mmol) of unreacted **1**, 343 mg (1.35 mmol) of **2**, 153 mg (0.602 mmol) of the **3**, and 75.3 mg (0.296 mmol) of **4**. The yields of **2**, **3**, and **4** based on the consumed **1** were 53.8%, 24.0% and 11.8%, respectively. **2**: mp 75.0-76.0 °C (dichloromethane/*n*-hexane); ^{1}H NMR (200 MHz, $CDCl_3$) 7.79-7.74 (1H, m, aromatic H), 7.18-7.09 (2H, m, aromatic H), 6.93-6.86 (1H, m, aromatic H), 6.43 (1H, d, *J*=5.4 Hz, CO_2-C=CH), 6.04 (1H, dd, *J*=2.7, 1.5 Hz, O-CH=C), 5.37 (1H, dd, *J*=7.2, 7.2 Hz, O-CH-C_2), 4.98 (1H, dd, *J*=2.8, 2.8 Hz, O-C=CH), 4.17-4.06 (1H, m, Ar-CH-C_2), 4.02-3.91 (1H, m, O-C-CH-C_2), 3.83 (3H, s, CO_2-CH), 3.68-3.55 (1H, m, CO_2-C=C-CH); ^{13}C NMR (50 MHz, $CDCl_3$) 167.64, 148.40, 133.73, 130.87, 130.59, 129.39, 129.24, 127.44, 126.44, 125.95, 102.19, 83.68, 52.42, 51.75, 41.30, 36.34; IR ($CHCl_3$) 3025, 2950, 1715, 1600, 1491, 1435 cm^{-1}; UV ($CHCl_3$) λ_{max} (ε) 291.6 (2460); MS (CI^+, methane) m/e 255 (M+1), 215, 195, 187 (100), 186, 155, 69. **3**: mp 89.0-90.0 °C (dichloromethane/*n*-hexane); ^{1}H NMR (200 MHz, $CDCl_3$) 7.03-6.93 (3H, m, aromatic H), 6.83-6.69 (3H, m, aromatic H, CH=C-C-CO_2, C=CH-C-CO_2), 5.86 (1H, dd, *J*=5.9, 1.5 Hz, olefinic H), 5.79 (1H, dd, *J*=5.9, 1.7 Hz, olefinic H), 4.69 (1H, d, *J*=1.7 Hz, C=C-CH-O), 4.47 (1H, dd, *J*=6.6, 1.5 Hz, C=C-CH-O), 3.91 (3H, s, CO_2-CH), 3.61 (1H, ddd, *J*=6.5, 6.5, 1.7 Hz, CH-C=C-C-CO_2); IR ($CHCl_3$) 3018, 2958, 1730, 1658, 1612, 1266, 1248 cm^{-1}; UV (CH_3CN) λ_{max} (ε) 278.2 (591), 270.4 (622), 262.8 (544); MS (CI^+, methane) m/e 255 (M+1), 187, 186 (100), 155, 69. **4**: mp