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SYNTHESIS OF ENKEPHALIN ANALOGS VIA ASYMMETRIC HYDROGENATION OF DEHYDROPEPTIDE BUILDING BLOCKS

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Summary [Ac-D-Tyr^1, D-Ala^2, Leu^5-OMe]Enkephalin and [Ac-Tyr^1, D-Ala^2, Leu^5-OMe]Enkephalin were successfully synthesized by the coupling of dipeptide units and tripeptide units which were readily obtained by the asymmetric hydrogenation of the corresponding dehydropeptide building blocks

Recently, it has been shown that significant modifications of physiological activities can be effected through inversion of configuration at one or more chiral centers, or through replacement of one or more "natural" amino acid residues by "unnatural" amino acid components in a biologically active peptide such as Enkephalin, Vasopressin, Angiotensin II, Gonadoliberin and other hormones [1] As reported in the previous papers,[2,3] we found that the homogeneous asymmetric hydrogenation of dehydrodipeptides and dehydrotripeptides with chiral rhodium catalysts could bring about quite high stereoselectivities inducing desired configurations at the places originated from the dehydroamino acid residues Now, we would like to describe here successful applications of the asymmetric hydrogenation to the asymmetric syntheses of analogs of Leucine-Enkephalin which is an opioid hormone isolated from brain[4,5,6] we have synthesized [Ac-D-Tyr^1, D-Ala^2, Leu^5-OMe]Enkephalin and [Ac-Tyr^1, D-Ala^2, Leu^5-OMe]Enkephalin by the coupling of dipeptide fragments and tripeptide fragments, where all fragments were obtained by the asymmetric hydrogenation of the corresponding dehydropeptides

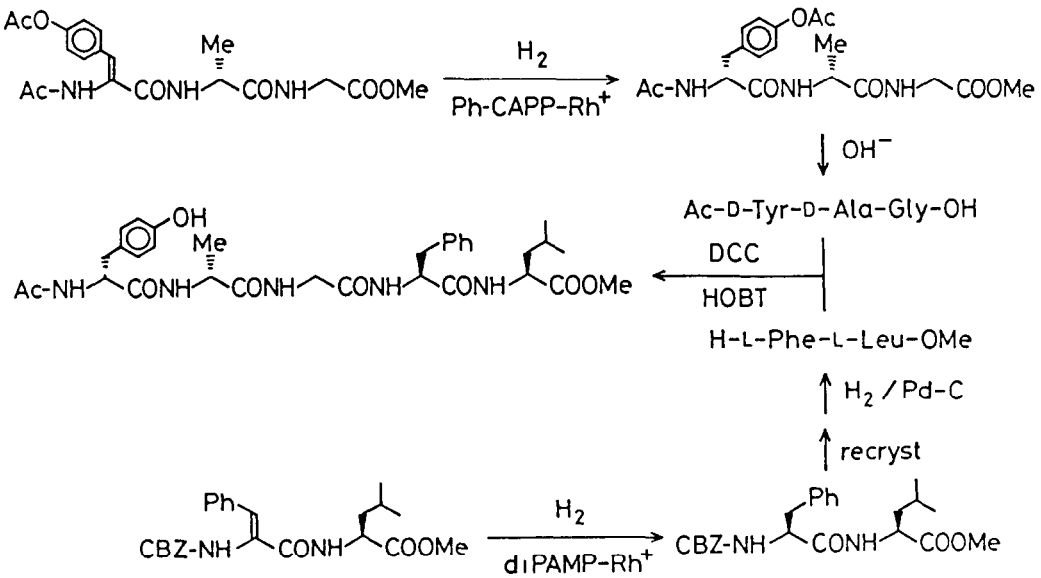
1 Asymmetric Synthesis of [Ac-D-Tyr^1, D-Ala^2, Leu^5-OMe]Enkephalin (Scheme 1)

The tripeptide fragment, Ac-D-Tyr-D-Ala-Gly, was synthesized via the asymmetric hydrogenation of Ac-ΔTyr(Ac)-D-Ala-Gly-OMe catalyzed by [(Ph-CAPP)Rh(COD)]ClO_4 (COD = 1,5-cyclooctadiene)[7] (1 0 mol%) in ethanol at 40°C and 5 atm of hydrogen quantitative yield, (D,D)/(L,D) = 99 7/0 3 (HPLC analysis) [8] Ac-ΔTyr(Ac)-D-Ala-OMe was readily prepared in good yield by reacting the azlactone of N,O-diacetyldehydrotyrosine with HCl D-Ala-Gly-OMe in chloroform at room temperature in the presence of N-methylmorpholine Ac-D-Tyr(Ac)-D-Ala-Gly-OMe thus obtained was saponified with 1N sodium hydroxide in methanol at 0°C for 30 min to give Ac-D-Tyr-D-Ala-Gly-OH in 93% yield On the other hand, the dipeptide fragment, Phe-Leu-OMe, was synthesized via the asymmetric hydrogenation of CBZ-ΔPhe-Leu-OMe (CBZ = benzyloxycarbonyl) catalyzed by [(diPAMP)Rh-(NBD)]ClO_4 (NBD = norbornadiene)[9] (2 0 mol%) in ethanol at 50°C and 20 atm of hydrogen quantitative yield, (D,L)/(L,L) = 2 2/97 8 (HPLC analysis) [8] CBZ-ΔPhe-Leu-OMe was prepared in good yield by the coupling of CBZ-ΔPhe-OH with HCl Leu-OMe using dicyclohexylcarbodiimide (DCC), 1-

hydroxybenzotriazole (HOBT) and N-methylmorpholine (NMM) in dimethylformamide (DMF) The optically pure CBZ-Phe-Leu-OMe was obtained by the purification on silica gel column (n-hexane-AcOEt) (90%), 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 in nearly quantitative yield

Then, the two fragments were coupled by using DCC, HOBT and NMM in DMF at 0°C to give [Ac-D-Tyr^1, D-Ala^2, Leu-OMe]Enkephalin in 85% yield [10]

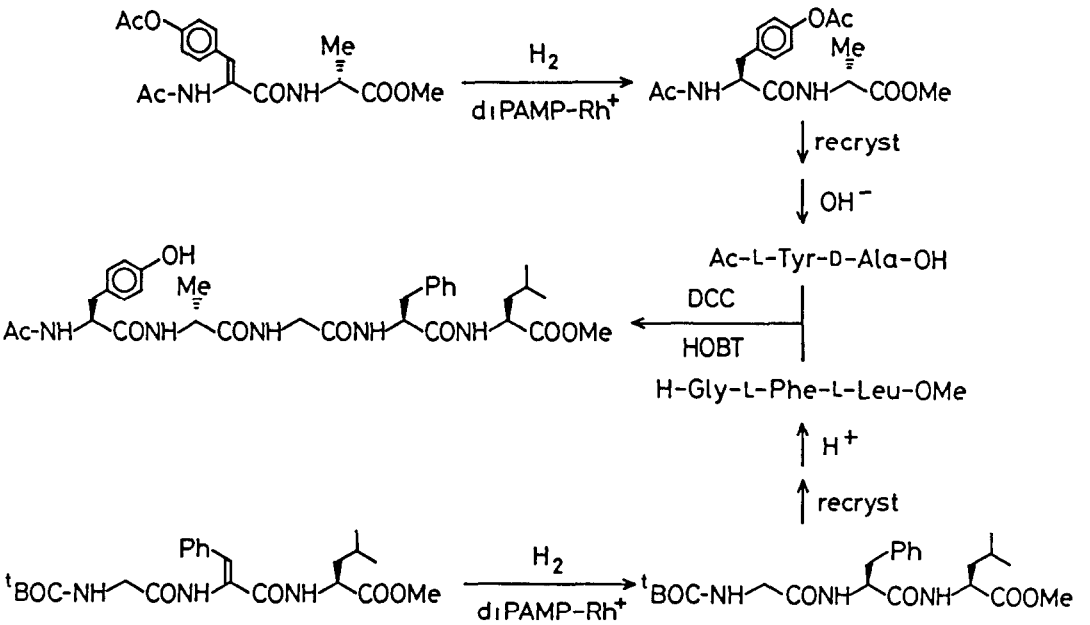
Scheme 1 Synthesis of [Ac-D-Tyr^1, D-Ala^2, Leu^5-OMe]Enkephalin



2 Asymmetric Synthesis of [Ac-Tyr^1, D-Ala^2, Leu-OMe]Enkephalin (Scheme 2)

This highly active Leucine-Enkephalin analog[5,11] was synthesized by the coupling of Ac-Tyr-D-Ala with Gly-Phe-Leu-OMe The asymmetric hydrogenation of Ac-ΔTyr(Ac)-D-Ala-OMe[12] catalyzed by [(diPAMP)Rh(NBD)]ClO_4 (1 0 mol%) in ethanol at 40°C and 10 atm of hydrogen gave Ac-Tyr(Ac)-D-Ala-OMe in quantitative yield (D,D)/(L,D) = 1 6/98 4 (HPLC analysis) [8] After recrystallization from ethyl acetate (88% recovery), optically pure Ac-Tyr(Ac)-D-Ala-OMe was saponified by 1N sodium hydroxide at 0°C to give Ac-Tyr-D-Ala-OH in 94% yield ^{t}BOC-Gly-Phe-Leu-OMe (^{t}BOC = t-butoxycarbonyl) with 98 9% diastereomeric purity was obtained quantitatively by the asymmetric hydrogenation of ^{t}BOC-Gly-ΔPhe-Leu-OMe with the use of [(diPAMP)Rh(NBD)]ClO_4 (1 0 mol%) in ethanol at 40°C and 10 atm of hydrogen, which was further recrystallized from n-hexane-AcOEt to give the optically pure tripeptide (92% recovery) Then, ^{t}BOC protecting group was removed by treating with hydrogen chloride in ethyl acetate to give HCl Gly-Phe-Leu-OMe in 96% yield The coupling of Ac-Tyr-D-Ala-OH and HCl Gly-Phe-Leu-OMe was carried out by using DCC, HOBT and NMM in DMF at 0°C to give [Ac-Tyr^1, D-Ala^2, Leu^5-OMe]Enkephalin in 89% yield [13]

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



Although we simply describe here, as typical example, straightforward applications of asymmetric hydrogenation to the synthesis of the fragments of Enkephalin analogs which only have amino acid residues with natural or unnatural configurations, this method is readily applicable to the asymmetric synthesis of peptide building blocks which involve amino acid residues bearing unnatural substituents as well as being labeled with deuterium or tritium as exemplified in the preceding paper, these chemical modifications have been shown to be very important for obtaining unique and significant biological activities and for the studies on metabolism Further investigation is currently in progress along this line

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10 Ac-D-Tyr-D-Ala-Gly-Phe-Leu-OMe mp 207-210°C, $[\alpha]_D^{20}$ -18 9° (c 1 044, DMF), NMR (dimethylsulfoxide-d_6) δ 0 85 (dd, J=6Hz, 6H), 1 19 (d, J=7Hz, 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=8Hz, 2H), 7 02 (d, J=8Hz, 2H), 7 20 (s, 5H), 7 65-8 40 (m, 5H), 9 07 (s, 1H) HPLC analysis[7] revealed that the diastereomeric purity was ≥ 99 6% Slight racemization could take place at the saponification step

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12 Ac-ΔTyr(Ac)-D-Ala-OMe was easily prepared by reacting the azlactone of N,O-diacetyldehydrotyrosine with HCl D-Ala-OMe in chloroform at room temperature in the presence of NMM.

13 Ac-Tyr-D-Ala-Gly-Phe-Leu-OMe mp 259-261°C (decomp), $[\alpha]_D^{20}$ -13 4° (c 1 001, DMF), NMR (dimethylsulfoxide-d_6) δ 0 88 (dd, J=6Hz, 6H), 1 11 (d, J=7Hz, 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 5Hz, 2H), 6 99 (d, J=8 5Hz, 2H), 7 24 (s, 5H), 7 80-8 42 (m, 5H), 9 11 (s, 1H) HPLC analysis[7] 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

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