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SYNTHESIS OF A PROTECTED MONODEHYDRO Leu-ENKEPHALIN AND ITS HYDROGENATION CATALYZED BY CHIRAL RHODIUM COMPLEXES

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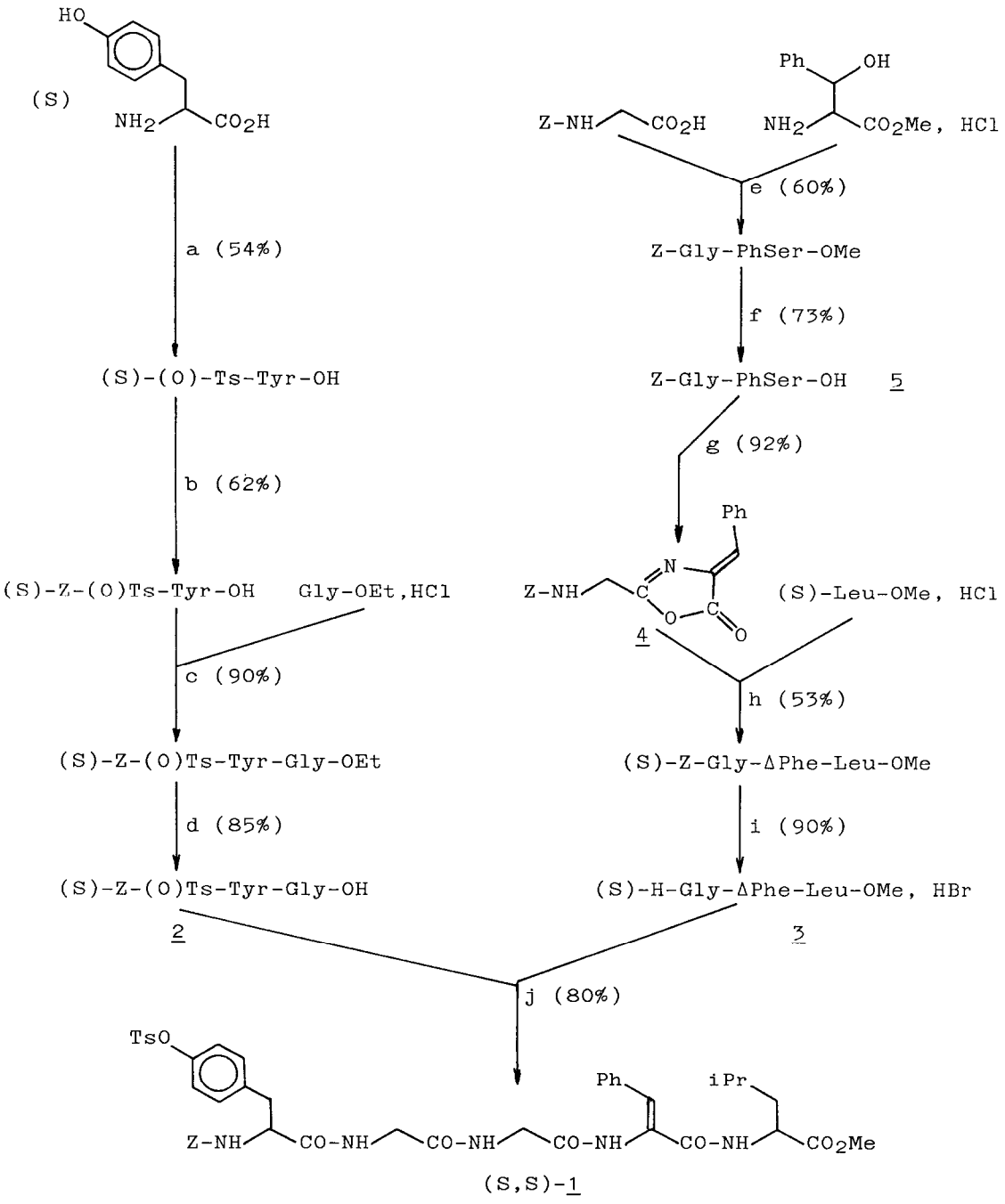
Abstract

(S,S)-Z-(O)Ts-Tyr-Gly_2-ΔPhe-Leu-OMe was synthesized. Some chiral rhodium complexes catalyze the reduction of the C=C bond. The stereochemistry of reduction of the ΔPhe moiety was investigated, 93 % de could be achieved with dipamp as ligand in the catalyst.

The progresses of asymmetric hydrogenation were particularly spectacular with dehydroaminoacids as substrates. Some chiral diphosphines had frequently allowed asymmetric synthesis of α-aminoacids with ee's in the range of 90-99 % (for some reviews see ref[1-4]). It is also possible to control to a good extent the asymmetric reduction of monodehydrodipeptides by the proper choice of the chiral catalyst[5-10]. Bistritiated dipeptides were obtained by this method[11], as well as some building blocks for synthesis of a protected (R)-Ala-^{5}Leu-enkephalin[12]. In regard to the biological importance of enkephalin we studied the use of asymmetric hydrogenation as a potential tool for the stereoselective labelling of the Phe or Tyr fragment. We wish to describe here the synthesis of a protected monodehydro Leu-enkephalin as well as the preliminary results in its homogeneous hydrogenation in presence of some chiral catalysts.

Synthesis of (S,S)-Z-(O)Ts-Tyr-Gly_2-ΔPhe-Leu-OMe 1 was carried out as



(S,S)-1

a) i: OH^-, $CuSO_4$; ii: TsCl, Et_2O ; iii: 12N HCl ; iiii: NH_3, H_2O
b) NaOH, ZCl - c) BOP, iPr_2EtN, CH_2Cl_2
d) i: NaOH, acetone ; ii: HCl - e) BOP, iPr_2EtN, CH_2Cl_2
f) i: NaOH, acetone ; ii: HCl - g) Ac_2O, AcONa
h) N-Me morpholine, CH_2Cl_2 - i) HBr, AcOH 33% - j) DCCI, NEt_3, CH_2Cl_2

Scheme 1

described in Scheme 1. The compound was obtained by a coupling reaction between (S)-Z-(O)Ts-Tyr-Gly-OH 2 and (S)-Gly-ΔPhe-Leu-OMe,HBr 3 in presence of DCCI and triethylamine.

Dehydropeptide 1, recrystallised in ethyl acetate, was isolated as a white crystalline compound (mp = 127-130°C, $|\alpha|_D^{20}$ = 18.2° (C= 1 in MeOH), analysis ($C_{44}H_{49}N_5O_{11}S$ = 856): C= 60.52 (61.60), H= 5.92 (5.76), N= 8.10 (8.16), S= 3.72 (3.74)).The purity of 1 has been checked by tlc (ethyl acetate-methanol) and by hplc on a reversed phase column (water-methanol). The ^1H NMR spectrum of 1 (400 MHz) is in agreement with the proposed structure.

The chosen strategy allows the synthesis of stereochemically pure (S,S)-1. The use of BOP[13] as coupling reagent and the protection of the amino function of tyrosine by a carbobenzoxy group (Z) prevents the racemization of this aminoacid in fragment 2. The leucine residue is never subject to racemization during the synthesis of fragment 3. The formation of the oxazolone 4 from dipeptide 5 is known to produce a C=C bond with Z configuration, as shown by the NMR spectrum of compound 4.

Asymmetric hydrogenation of 1 (2.0 mmol) was achieved in 10 ml methanol at 15°C during 48 h with a catalytic ratio 4:1. (Rh dipamp COD)$^+BF_4^-$ and hydrogen pressure of 10 bar lead to a complete reduction giving a large excess of the (S) configuration (93 % de). With RhCl(-)bppm under 1 bar the reduction is quantitative, a predominent (R) configuration was observed, although with a lower stereoselectivity (68 % de). The stereochemistry and stereoselectivity were easily obtained by the following procedure (already described in ref. 14) : degradation of the polypeptide by acidic hydrolysis, derivatization of the aminoacids into N-trifluoroacetyl isopropyl esters and analysis by glc on a chiral stationary phase. In both hydrogenations it appears that a "catalyst control"[15] overcomes the asymmetric induction due to the two chiral aminoacids already present in the substrate. This "catalyst control" is especially efficient with dipamp.

This gives hope to introduce stereoselectively tritium in various enkephalin-related compounds[16-17].

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(17) We also recently[18] prepared and reduced (S,S)-Z-(O)Ts-ΔTyr-$(Gly)_2$-Phe-Leu-OMe, the results will be soon reported.

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