Studies of Unusual Amino Acids and Their Peptides. XIV. The Asymmetric Hydrogenation of the Phenylhydrazone of Methyl *N*-(3,3-Dimethyl-2-oxobutanoyl)-L-valinate

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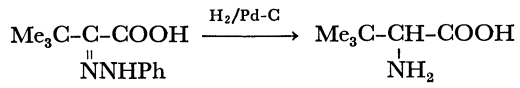
Synopsis. The asymmetric hydrogenation of the phenylhydrazone of methyl *N*-(3,3-dimethyl-2-oxobutanoyl)-L-valinate was investigated using palladium catalysts. The configuration of the newly formed *t*-leucine moiety was found to be L.

In the previous papers,[1,2] the present authors have reported on the convenient syntheses and the optical resolution of *t*-leucine (2-amino-3,3-dimethylbutanoic acid). One of our attempts at preparing racemic *t*-leucine on a large scale consisted in the reductive cleavage of the phenylhydrazone (**1**) of 3,3-dimethyl-2-oxobutanoic acid by hydrogenation (Scheme 1).



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Scheme 1.

The success of this method prompted us to examine the asymmetric synthesis of this amino acid through the hydrogenation of the condensation product between the phenylhydrazone (**1**) and an amino-acid ester as the source of chirality. Methyl L-valinate was chosen in the present investigation, as in our previous study of the kinetic resolution of *t*-leucine.[3] The diastereomeric ratio of the resulting dipeptide, after conversion to the *N*-pivaloyl derivative, can easily be estimated by means of GLC analysis.[3,4]

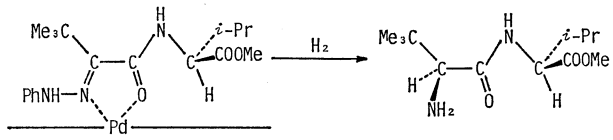
Thus, the phenylhydrazone (**1**) was coupled with methyl L-valinate by means of the DCC[5] method. The resulting phenylhydrazone (**2**) of methyl *N*-(3,3-dimethyl-2-oxobutanoyl)-L-valinate was hydrogenated in methanol in the presence of a double molar amount of *p*-toluenesulfonic acid, using a palladium catalyst. For estimating the diastereomeric ratio of the resulting dipeptide, the crude product was pivaloylated in the usual manner.[4] The results are summarized in Table 1. The authentic samples were prepared by condensing *N*-Z-L- or *N*-Z-D-*t*-leucine with methyl L-valinate by means of the DCC method, followed by debenzyloxycarbonylation and the subsequent pivaloylation.

When palladium on carbon was used as a catalyst, the configuration of the newly formed *t*-leucine moiety was L (L-Tle–L-Val:D-Tle–L-Val=67:33). The reaction temperature, as far as we examined it, had little influence on the diastereomeric ratio. In a series of studies[6] of the asymmetric amino-acid syntheses through the hydrogenation of oximes or Schiff bases of α-keto esters or amides, Harada *et al.* postulated an intermediate substrate-catalyst complex for explaining the configurations and the optical yields of the products. According to this hypothesis, the present results could be explained by assuming the preferred conformation of the intermediate complex formed prior to hydrogenation to be as is shown in Scheme 2.[7] The choice of catalyst was found to have a significant influence on the present asymmetric hydrogenation. Thus, the use of palladium black or palladium oxide resulted in a higher optical purity of the *t*-leucine moiety than in the case of palladium on carbon.

TABLE 1. *t*-LEUCYL DIPEPTIDE PREPARED VIA THE ASYMMETRIC HYDROGENATION[a] OF THE PHENYLHYDRAZONE (**2**) OF METHYL *N*-(3,3-DIMETHYL-2-OXOBUTANOYL)-L-VALINATE

Catalyst	Temp °C	Yield[b] %	Ratio of diastereomers L-L %	D-L %
Pd-C	10	43	66	34
Pd-C	50	45	67	33
Pd-C	60	52	66	34
Pd-C	100	52	64	36
Pd black	50	44	77	23
PdO	50	48	78	22

a) Under an initial pressure of 100 kg/cm². b) Overall yield of the pivaloylated derivative isolated by preparative TLC on silica gel (see Experimental).



Scheme 2.

Experimental

All the melting points are uncorrected. The optical rotations were measured with a JASCO DIP-4 polarimeter. The ^1H NMR spectra (in $CDCl_3$) were recorded on a Hitachi R-24B spectrometer, with TMS as the internal standard. The GLC analyses were performed on a Hitachi 063 gas chromatograph equipped with a flame-ionization detector, using a column packed with 0.5% FFAP on Chromosorb G (φ 3 mm×2 m; column temp 150 °C; carrier gas, N_2 11 ml/min; injector temp, 250 °C). Merck Kieselgel 60 and Kieselgel GF_{254} (Type 60) were used for the column chromatography and the preparative TLC respectively.

Phenylhydrazone (2) of Methyl N-(3,3-Dimethyl-2-oxobutanoyl)-L-valinate. Into a chilled mixture of the phenylhydrazone (**1**) of 3,3-dimethyl-2-oxobutanoic acid (17.6 g), L-Val-OMe·HCl (14.1 g), and triethylamine (8.5 g) in THF (240 ml), a solution of DCC (16.5 g) in THF (40 ml) was stirred.

Stirring was continued at 0 °C for 2 h and then at room temperature overnight. After *N,N'*-dicyclohexylurea had been removed by filtration, the filtrate was evaporated under reduced pressure. The residue was dissolved in EtOAc, washed successively with water, 0.5 M HCl, water, 0.5 M $NaHCO_3$, and water, and dried over $MgSO_4$. After the removal of the solvent, the residue was chromatographed on a silica-gel column with $CHCl_3$–EtOAc (1:1). The first colored fraction gave the desired product (**2**) as pale yellow needles: yield, 20.5 g (77%); mp 110—112 °C (from MeOH aq); $[\alpha]_D^{20}$ −16.9° (*c* 1.0, MeOH). Found: C, 64.78; H, 8.35; N, 12.34%. Calcd for $C_{18}H_{27}N_3O_3$: C, 64.84; H, 8.16; N, 12.60%.

The phenylhydrazone of ethyl *N*-(3,3-dimethyl-2-oxobutanoyl)-L-valinate was prepared in the same manner as above: mp 99—100 °C (from EtOH aq); $[\alpha]_D^{20}$ −20.9° (*c* 1.0, MeOH). Found: C, 65.71; H, 8.70; N, 11.86%. Calcd for $C_{19}H_{29}N_3O_3$: C, 65.68; H, 8.41; N, 12.09%.

Hydrogenation of the Phenylhydrazone **2**. The phenylhydrazone **2** (1.00 g) and *p*-toluenesulfonic acid monohydrate (1.26 g) were dissolved in MeOH (50 ml), after which the mixture was hydrogenated overnight in the presence of a palladium catalyst (0.5 g) under the conditions shown in Table 1. The reaction mixture was freed from the catalyst and evaporated to dryness under reduced pressure. The residue was dissolved in CH_2Cl_2 (30 ml) and acylated with Piv–Cl (0.94 g) in the presence of *N,N*-diisopropylethylamine (1.86 g) in the usual manner.[4] A part of the crude product was used without purification for the GLC analysis in order to estimate the diastereomeric ratio. The *N*-pivaloyl derivative was isolated as a mixture of diastereomers by preparative TLC on silica gel using benzene–EtOAc (9:1). The results are summarized in Table 1.

Preparation of Authentic Samples. Z-L-Tle-L-Val-OMe: Into a chilled mixture of Z-L-Tle[1] (398 mg), L-Val-OMe·HCl (252 mg), *N*-ethylmorpholine (173 mg), and THF (3.5 ml), DCC (340 mg) was stirred. The mixture was stirred at 0 °C for 2 h and then at room temperature overnight. The usual work-up afforded white crystals; yield, 457 mg (81%). The analytical sample was obtained by recrystallization from EtOAc–Et_2O–petroleum ether: mp 71—72.5 °C; $[\alpha]_D^{25}$ −21.2° (*c* 1.0, MeOH); ^1H NMR δ=0.91 (6H, d, J=7 Hz), 1.00 (9H, s), 2.11 (1H, m), 3.67 (3H, s), 4.05 (1H, d, J=9 Hz), 4.47 (1H, dd, J=5 Hz and 8.5 Hz), 5.05 (2H, s), 5.54 (1H, bd, J=9 Hz), 6.48 (1H, bd, J=8.5 Hz), and 7.23 (5H, s). Found: C, 63.40; H, 8.16; N, 7.42%. Calcd for $C_{20}H_{30}N_2O_5$: C, 63.47; H, 7.99; N, 7.40%.

Piv-L-Tle-L-Val-OMe: A solution of Z-L-Tle-L-Val-OMe (182 mg) in MeOH (5 ml) was hydrogenated in the presence of concd HCl (53 mg), using 5% Pd–C (50 mg). The catalyst was then filtered off, and the filtrate was evaporated under reduced pressure, followed by the successive addition and the evaporation of MeOH. The residual solid (125 mg) was dissolved in CH_2Cl_2 (3 ml), and the mixture was treated with Piv–Cl (71 mg) in the presence of *N,N*-diisopropylethylamine (134 mg); yield, 125 mg (85%). The analytical sample was obtained by recrystallization from EtOAc–hexane: mp 138.5—139.5 °C; $[\alpha]_D^{25}$ −39.4° (*c* 1.0, MeOH); GLC t_R=62.3 min; ^1H NMR δ=0.90 (6H, d, J=7 Hz), 0.99 (9H, s), 1.20 (9H, s), around 2.15 (1H, m), 3.69 (3H, s), 4.23 (1H, d, J=9.5 Hz), 4.37 (1H, dd, J=5.5 Hz and 8.5 Hz), and 6.0—6.45 (2H, b). Found: C, 62.31; H, 9.83; N, 8.63%. Calcd for $C_{17}H_{32}N_2O_4$: C, 62.16; H, 9.82; N, 8.53%.

The corresponding D-L-isomer was obtained, starting from Z-D-Tle,[1] in the same manner as above.

Z-D-Tle-L-Val-OMe: mp 78—79 °C (from hexane); $[\alpha]_{25}^{D}$ −7.8°(*c* 1.0, MeOH); ^1H NMR δ=0.91 (6H, d, J=7 Hz), 1.01 (9H, s), 2.13 (1H, m), 3.65 (3H, s), 4.06 (1H, d, J=9.5 Hz), 4.49 (1H, dd, J=5 Hz and 8.5 Hz), 5.05 (2H, s), 5.65 (1H, bd, J=9.5 Hz), 6.61 (1H, bd, J=8.5 Hz), and 7.25 (5H, s). Found: C, 63.35; H, 8.04; N, 7.66%.

Piv-D-Tle-L-Val-OMe: mp 129—130 °C (from hexane); $[\alpha]_D^{25}$ +0.6° (*c* 1.0, MeOH); GLC t_R=58.3 min; ^1H NMR δ=0.94 (6H, d, J=6.5 Hz), 1.01 (9H, s), 1.21 (9H, s), 2.15 (1H, m), 3.68 (3H, s), 4.35 (1H, d, J=9 Hz), 4.45 (1H, dd, J=5 Hz and 8.5 Hz), 6.32 (1H, bd, J=9 Hz), and 6.61 (1H, bd, J=8.5 Hz). Found: C, 62.35; H, 9.75; N, 8.59%.

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2) T. Miyazawa, T. Nagai, T. Yamada, S. Kuwata, and H. Watanabe, *Memoirs of Kōnan University, Science Series*, No. 23 (1979), p. 51.

3) T. Miyazawa, K. Takashima, T. Yamada, S. Kuwata, and H. Watanabe, *Chem. Lett.*, **1978**, 873.

4) The asymmetric synthesis of this dipeptide sequence by the oxazolone method has been reported; E. Frauendorfer, W. Steglich, and F. Weygand, *Chem. Ber.*, **106**, 1019 (1973).

5) The following abbreviations are used throughout: DCC, dicyclohexylcarbodiimide; Z, benzyloxycarbonyl; THF, tetrahydrofuran; Piv–Cl, pivaloyl chloride; Tle, *t*-leucine; Piv, pivaloyl.

6) K. Harada, T. Munegumi, and S. Nomoto, *Tetrahedron Lett.*, **22**, 111 (1981), and the references cited therein.

7) The formation of an L-alanyl dipeptide in the catalytic hydrogenation of the benzylamine Schiff base of *N*-(2-oxopropanoyl)-L-valine methyl or isobutyl ester has been reported: K. Harada and K. Matsumoto, *J. Org. Chem.*, **32**, 1794 (1967); *Bull. Chem. Soc. Jpn.*, **44**, 1068 (1971).