The Highly Diastereoselective, Heterogeneous Hydrogenation of Didehydrodipeptides. Synthesis of Optically Active Amino Acids

Ulrich Schmidt*, Siegfried Kumpf and Karin Neumann

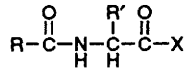
Institut für Organische Chemie und Isotopenforschung der Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany

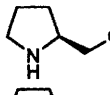
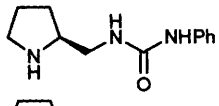
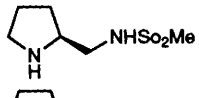
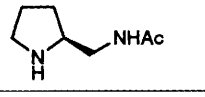
Didehydrodipeptides containing proline amides are hydrogenated with high diastereoselectivity.

The catalytic hydrogenation of didehydroamino acid derivatives containing an attached chiral auxiliary has been investigated[1] frequently but, with only a few exceptions,[2] the optical inductions achieved were mostly small.

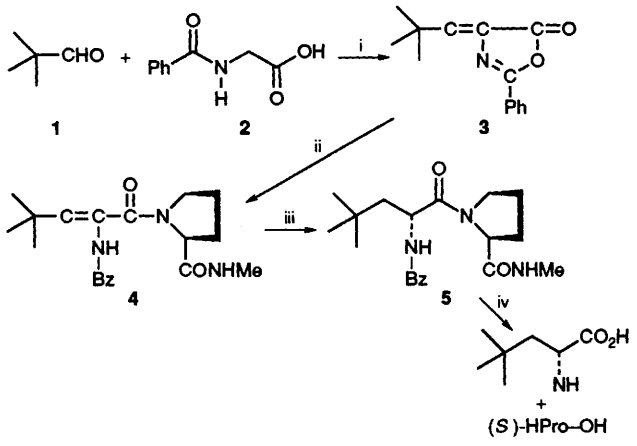
In 1973, Poisel and Schmidt[3] obtained de values of ≥ 80% for the hydrogenation of proline-containing aralkylidenedioxopiperazines. This report, however, has mostly been ignored[1a] or the high diastereoselectivity erroneously attributed to a recrystallization.[1b] Further successful, diastereoselective hydrogenations of unsaturated dioxopiperazines were described later.[4] Even so, the preparation of the starting material is rather tedious and, therefore, their hydrogenations are of little value for the synthesis of optically active α-amino acids. This is also valid for the hydrogenation of alkylideneimidazolidinones[5] since the latter substrates must be prepared from an expensive, optically active material (dialkoxyphosphorylimidazolidinone) which is then lost in the process. The hydrogenation does indeed proceed with high

Table 1 Dipeptides obtained by heterogeneous catalytic hydrogenation of α,β-didehydrodipeptides



Run	R	R′	X	Conf.	Cat. Pd/y	f/bar	t/h	T/°C	Solvent	Conc.	R,S : S,S
1	Ph	Bn	(*S*)-Pro–NH_2	*Z*	C	30	48	50	Toluene	1 : 40	75 : 25[a]
2	Ph	Bn	(*S*)-Pro–NMe_2	*Z*	C	45	20	50	EtOAc	1 : 40	71 : 29[b]
3	Ph	Bn	(*S*)-Pro–NHMe	*Z*	C	50	48	50	Toluene	1 : 40	93 : 7[c]
4	Ph	Bn	(*S*)-Pro–NHMe	*Z*	C	50	48	50	Toluene	1 : 10	92 : 8[c]
5	Ph	Bn	(*S*)-Pro–NHMe	*Z*	C	50	48	50	Toluene	1 : 5	90 : 10[c]
6	Ph	Bn	(*S*)-Pro–NHMe	*Z*	C	50	48	100	Toluene	1 : 40	90 : 10[c]
7	Ph	Bn	(*S*)-Pro–NHMe	*Z*	C	100	96	room temp.	Toluene	1 : 40	92 : 8[c]
8	Ph	Bn	(*S*)-Pro–NHMe	*E*	C	50	48	50	Toluene	1 : 40	73 : 27[d]
9	Ph	Bn	(*S*)-Pro–NHMe	*Z*	$CaCO_3$	3	20	room temp.	MeOH	1 : 40	87 : 13[c]
10	Ph	Bn	(*S*)-Pro–NHMe	*Z*	$CaCO_3$	50	48	50	Toluene	1 : 40	94 : 6[c]
11	Ph	$CH_2C_6H_3(OMe)_2$-3,4	(*S*)-Pro–NHMe	*Z*	C	50	48	50	Toluene	1 : 40	90 : 10[b]
12	Ph	$CH_2C_6H_4OMe$-3	(*S*)-Pro–NHMe	*Z*	C	50	48	50	Toluene	1 : 40	94 : 6[c]
13	Ph	$CH_2C_6H_4OMe$-4	(*S*)-Pro–NHMe	*Z*	C	50	48	50	Toluene	1 : 40	92 : 8[c]
14	Me	Bn	(*S*)-Pro–NHMe	*Z*	C	50	48	50	Toluene	1 : 40	94 : 6[d]
15	C_6H_{11}	Bn	(*S*)-Pro–NHMe	*Z*	C	50	48	50	Toluene	1 : 40	92 : 8[a]
16	Me	Bn	(*S*)-Pro–NHPh	*Z*	C	50	48	50	Toluene	1 : 40	95 : 5[d]
17	Me	CH_2CMe_3	(*S*)-Pro–NHMe	*Z*	C	50	48	50	Toluene	1 : 40	94 : 6[c]
18	Me	CH_2CMe_3	(*S*)-Pro–NHMe	*Z*	$CaCO_3$	50	48	50	Toluene	1 : 40	97 : 3[c]
19	Me	CH_2CMe_3	(*S*)-Pro–NHMe	*Z*	C	50	48	50	Bu^tOH	1 : 40	80 : 20[c]
20	Me	CH_2CMe_3	(*S*)-Pro–NHMe	*Z*	$CaCO_3$	50	48	50	Bu^tOH	1 : 40	90 : 10[c]
21	Me	Pr^i	(*S*)-Pro–NHMe	*Z*	C	40	72	100	EtOAc	1 : 40	90 : 10[d]
22	Me	Bu^n	(*S*)-Pro–NHMe	*Z*	C	40	48	50	Benzene	1 : 40	95 : 5[a]
23	Me	Pr^i	(*S*)-Pro–NHMe	*Z*	C	50	48	50	Toluene	1 : 40	97 : 3[d]
24	Me	Bu^i	(*S*)-Pro–NHMe	*Z*	C	50	48	50	Toluene	1 : 40	95 : 5[d]
25	Ph	Bn		*Z*	C	50	48	50	Toluene	1 : 40	75 : 25[c]
26	Ph	Bn		*Z*	C	50	48	50	Toluene	1 : 40	77 : 23[d]
27	Ph	Bn		*Z*	C	50	48	50	Toluene	1 : 40	76 : 24[d]
28	Ph	Bn		*Z*	C	50	48	50	Toluene	1 : 40	76 : 24[d]

[a] Ratio of diastereoisomers (rd) was determined by HPLC on a silica gel column (Merck Hibar, LiChrosorb Si 60, 7μ; eluent Hexene–propan-2-ol (runs 1, 2, 22); eluent CH_2Cl_2–MeOH (run 15). [b] rd was determined by ^{13}C NMR spectroscopy recorded on a Bruker AC-F 250 (62.5 MHz). [c] rd was determined by reverse-phase HPLC on a silica gel column (Merck LiChrospher RP-18, 5 μm, 250 × 4 mm; eluent MeCN–H_2O (runs 3–7, 9, 10, 17–20, 25); eluent MeOH–H_2O (runs 12, 13). [d] Hydrolysis [conc. HCl–AcOH–H_2O (2 : 1 : 1); 100 °C; 24 h]. Transformation into the *N*-pivaloylamino acid methyl ester and determination of the optical purity by GC (Carlo Erba Fractovap GI, PT Programmer) on glass capillary columns (7% bornylamide, 4% permethyl-β-cyclodextrine, 30 m) prepared in the GC department of our institute.



Scheme 1 *Reagents and conditions*: i, $Pb(OAc)_2$, Ac_2O, 72 h, reflux, 81%; ii, (*S*)-Pro-NHMe, $CHCl_3$, from 0 °C to 20 °C over 14 h, 50 °C, 1 h, 74%; iii, Pd/C, H_2, toluene, 50 °C, 48 h, quantitative; iv, conc. HCl–AcOH–H_2O (2 : 1 : 1), 100 °C, 24 h, *quantitative*

diastereoselectivity but the subsequent hydrolysis to furnish the desired amino acid is difficult and provides only modest yields.

In the hydrogenations of didehydrotripeptides and tetradehydrotripeptides containing *C*-terminal proline *tert*-butylamide units, high optical inductions (81–93% de) were observed at the internal didehydroalanine position. However, a substantially lower degree of asymmetric induction was realised at the didehydrobutyrine residue with 54% de being the best result achieved.[6]

We have now developed a method for the smooth hydrogenation of didehydrodipeptides containing proline amides which proceeds with high diastereoselectivities (90 : 10–95 : 5). The starting point for the process is the conversion of an (*S*)-didehydrodipeptide to the (*R*,*S*)-dipeptide. The scope of the reaction encompasses both aliphatic and aromatic didehydroamino acid derivatives. The preferred methylamides are prepared from azlactones and proline methylamide and are therefore, much more accessible than the above-mentioned didehydrotripeptides bearing a *C*-terminal proline *tert*-butylamide.

The results of our investigations are summarised in Table 1. Proline methylamide is the auxiliary of choice (runs 3–15 and 17–24). Proline anilide (run 16) could also be used with good results but was not further investigated because of the more complicated preparation of the anilide. A ten-membered, hydrogen-bonded ring between the amide nitrogen and the carbonyl group of the *N*-acyl part of the didehydroamino acid is responsible for the high diastereoselectivity. Accordingly the induction is low in the hydrogenation of the *N*-dimethylamide (run 2) and the use of solvents that weaken the hydrogen bridging bond (alcohols, dmf) is disadvantageous (runs 9 and 19). Pressure, temperature, and concentration have little effect (runs 4–7) and the solvent of choice is toluene.

This diastereoselective hydrogenation is applicable for both aromatic and aliphatic substrates (runs 17–24). Palladium on calcium carbonate (run 19) is superior to palladium on carbon (run 20).

The *Z*-didehydrodipeptides derived from the corresponding azlactones and (*S*)-proline methylamide contain about 2% of the *E*-diastereomers which can be removed easily by flash chromatography. The pure *E*-compounds react with lower diastereoselectivities (run 8). Other optically active auxiliaries are not so efficient as the proline amides (runs 25–28).

This diastereoselective hydrogenation step can be incorporated into a reaction sequence for the production of optically active amino acids, as illustrated below for neopentylglycine (Scheme 1).

Pivalaldehyde **1** condensed with hippuric acid **2** in an Erlenmeyer reaction[7] to furnish the alkylideneoxazolinone **3** which combined with (*S*)-proline methylamide to give the didehydrodipeptide **4**. Catalytic hydrogenation of the latter gave rise to the crystalline (*R*,*S*)-dipeptide **5**† containing only 5% of the (*S*,*S*)-diastereoisomer, which can be removed easily by recrystallization. Hydrolysis of this product gave a mixture of (*R*)-neopentylglycine and (*S*)-proline which could be separated by ion-exchange chromatography. Alternatively on a laboratory scale, the amino acids can be converted to the corresponding *N*-benzyloxycarbonyl methyl esters which are separated by MPLC on a silica gel column.

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Footnote

† Mp 97–98 °C, ^1H NMR [250 MHz, $(CD_3)_2SO$, rotamers], δ 8.70–8.65 (m, 1H), 8.1 (q, *J* 4.6 Hz, 0.5H), 7.92–7.88 (m, 2H), 7.58–7.41 (m, 3.5H), [4.99 (d, *J* 6.8 Hz), 4.25 (d, *J* 6.0 Hz), 1H], [4.75 (t, *J* 7.1 Hz), 4.6 (t, *J* 8.8 Hz), 1H], [3.89–3.86 (m), 3.59–3.32 (m), 2H], [2.61 (d, *J* 4.6 Hz), 2.57 (d, *J* 4.6 Hz), 3H], 2.31–1.76 (m, 5H), [1.6 (dd, *J* 14.4, 2.5 Hz), 1.46 (dd, *J* 14.4, 2.5 Hz), 1H], [0.97 (s), 0.87 (s), 9H].

References

1 (*a*) R. M. Williams, *Synthesis Of Optically Active α-Amino Acids*, Pergamon, Oxford, 1989; (*b*) K. Harada, in *Asymmetric Synthesis*, ed. J. D. Morrison, Academic, London, 1985, vol. 5, p. 346.
2 J. P. Vigneron, H. Kagan and H. Horeau, *Tetrahedron Lett.*, 1986, 5681.
3 H., Poisel and U. Schmidt, *Chem. Ber.*, 1973, **106**, 3408.
4 Lit. 23–27 in ref. 1(*b*).
5 Ch. P. Schickli and D. Seebach, *Liebigs Ann. Chem.*, 1991, 655; D. Seebach, H. M. Bürger and Ch. P. Schickli, *Liebigs Ann. Chem.*, 1991, 669.
6 Lit. 14 and 15 in ref. 1(*b*).
7 I. L. Finar and D. D. Libman, *J. Chem. Soc.*, 1949, 2726; M. Crawford and W. T. Little, *J. Chem. Soc.*, 1959, 729.