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Efficient Asymmetric Synthesis of Amino Acids through Hydrogenation of the Didehydroamino Acid Residue in Cyclic Imino-Ester Derivatives

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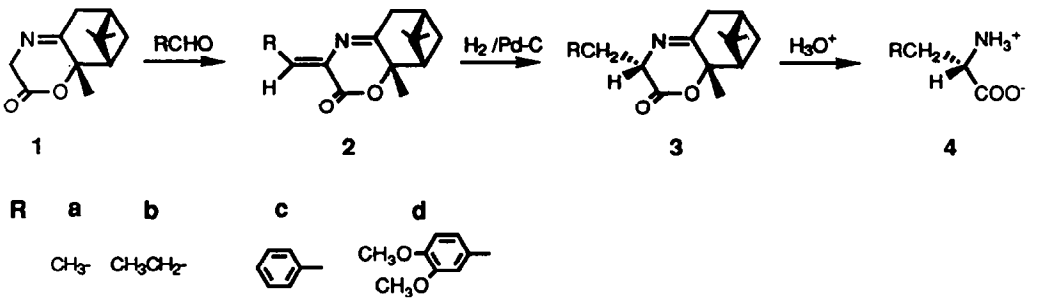
Abstract: The trisubstituted olefinic bond of chiral cyclic α,β-didehydroamino acid derivatives was hydrogenated in the presence of Pd/C with >95% diastereoface discrimination to give, after hydrolysis, the corresponding S-amino acids. The reduction of the double bond with L-selectride® does not change the orientation of diastereoface discrimination and the diastereoselectivity is still high.

Several studies have been carried out with the heterogeneous asymmetric hydrogenation of α,β-didehydroamino acid derivatives yielding amino acids in order to make the most of the benefits of heterogeneous catalysis. However, efficient asymmetric inductions were only performed by catalytic hydrogenation of tripeptides containing didehydroalanine residues[1] or diketopiperazines, cyclic derivatives containing a didehydroamino acid residue.[2]

We now wish to report our studies of the use of 2-hydroxypinan-3-one as a chiral auxiliary in heterogeneous asymmetric hydrogenation to obtain enantiomerically pure α-amino acids. This chiral auxiliary is very attractive because it is easily obtained by permanganate oxidation of α-pinene,[3] and allows us to obtain cyclic derivatives of α,β-didehydroamino acids whose structures have the right architectural features to give rise to high induction on diastereoface-differentiating processes as has been proved with enolate-trapping reactions[4] and 1,3-dipolar cycloadditions.[5]

The starting α,β-didehydroamino acid derivatives **2** were prepared from lactone **1** and the corresponding aldehyde by a modification of the previously-described procedure.[4] Thus lactone **1**, in the presence of t-BuOK, reacted with a series of aldehydes to furnish the corresponding didehydrocompound as a single stereoisomer in 60% to 85% yield after flash chromatography. In order to establish unambiguously the stereochemistry of compounds **2** vicinal CH spin coupling in the proton coupled ^{13}C NMR spectra of **2** were measured since it has been reported[6] that unambiguous stereochemical assignments in trisubstituted alkenes can be obtained from vicinal CH spin coupling in proton coupled ^{13}C NMR spectra, specially in the case of α,β-unsaturated carboxylic acids in which the ranges of *trans* and *cis* couplings are $^{1,3}J^{t}_{C\text{-}H}$ = 14.5 to 12.8 Hz and $^{1,3}J^{c}_{C\text{-}H}$ = 7.5 to 6.5 Hz. The small recorded values (4.2 - 4.9 Hz) confirm a *cis* stereochemistry for the hydrogen and carbonyl group in compounds **2**.



Scheme 1

Hydrogenation of **2** at 1 atm pressure of H_2 with Pd/C in methanol at room temperature provided the corresponding S-amino acid derivative in high yield and with virtually quantitative topological control (Scheme 1, Table 1).

Table 1

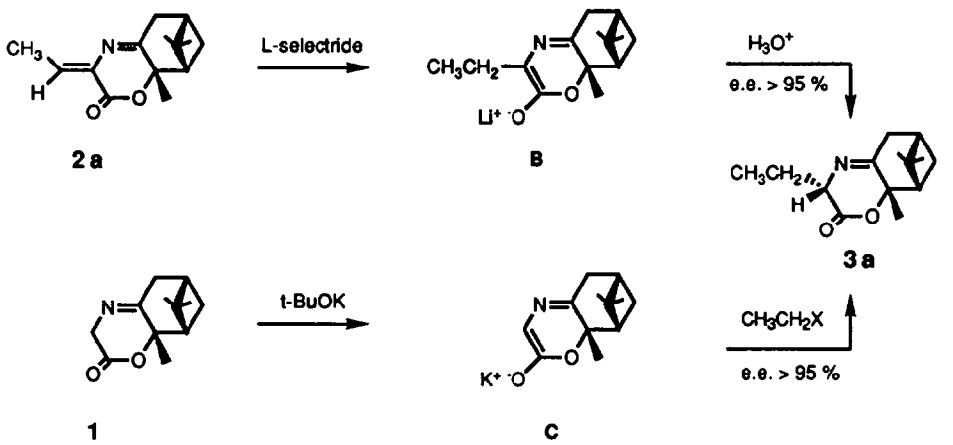
Entry	R	Yield 3	d.e.	Yield 4	e.e.(Abs. Conf)
1	methyl	75	>95 (S)	93	>95 (S)
1	ethyl	73	>95 (S)	92	>95 (S)
1	phenyl	68	>95 (S)	93	>95 (S)
1	3,4-dimethoxyphenyl	63	>95 (S)	85	>95 (S)

The extent of chiral induction was conveniently determined in the ^{1}H-NMR and ^{13}C-NMR spectra of the crude reaction mixtures. In the ^{1}H-NMR spectra splitting of the proton α to the alkyl or benzyl group demonstrates that the hydrogen entered the same face to the gem dimethyl group, since this proton shows homoallylic coupling. This was confirmed after acidic cleavage with THF-6N HCl (70° C, 3h) since starting from the lactones **3** optically pure S-amino acids, 2-aminobutiric acid, norvaline, phenylalanine and 3,4-dimethoxyphenylalanine were prepared whose absolute configurations and enantiomeric excesses were determined according to their chiroptic properties.

Next L-selectride®-promoted hydrogenation of the olefinic double bond through an enolate intermediate was tested in order to reverse the topicity of the reaction since it has been described[4] that in the alkylation of the enolate derived from the lactone **1** the electrophile entered the face opposite to the gem dimethyl group.

Nevertheless, surprising results were obtained with this reagent as protonation of the enolate intermediate **B** showed the same topicity as the heterogeneous Pd catalysed

hydrogenation and amino acid derivatives of S-configuration were obtained also with virtually quantitative topological control. That is to say, the electrophile entered the same face to the gem dimethyl group and amino acids of the same configuration were obtained from the enolate **C** derived from lactone **1** derived from glycine and introducing an ethyl substituent and starting from enolate **B** derived from compound **2a** and introducing a hydrogen.(Scheme 2)



2a **B** **3a**

1 **C**

Scheme 2

Recently Roumestant[7] obtained a similar result during the alkylation of chiral Schiff bases derived from amino esters and 2-hydroxypinan-3-one since amino acids of the same configuration were obtained from the Schiff base of phenylalanine methyl ester introducing a methyl substituent as starting from the Schiff base of alanine methyl ester and introducing a benzyl substituent.

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EXPERIMENTAL

Apparatus: ^1H NMR and ^{13}C-NMR spectra were recorded on a Varian Unity 300 MHz spectrometer in deuteriochloroform using tetramethylsilane as internal standard, chemical shifts are expressed in ppm. IR spectra were recorded on a Perkin-Elmer 1600 FTIR infrared spectrophotometer. Optical rotations were measured on a Perkin-Elmer 241-C polarimeter at 25° C. Melting points were determined on a Büchi 510 capillary melting point apparatus and are uncorrected. Routine analyses agree with calculated values within ± 0.3%.

Chemicals: All reactions were carried out under Ar with magnetic stirring. Solvents were dried prior to use. Chiral lactone **1** was prepared according to the previously described procedure[4] L-selectride® 1.0 M solution in T.H.F. was purchased from Aldrich. TLC plates were visualised using

UV light and anisaldehyde/sulphuric acid/ethanol (2/1/100). Sep-pak C_{18} (reverse phase) cartridge were purchased from Waters.

Preparation of chiral cyclic α,β-didehydroamino acid derivatives **2a-e**

General method. A solution of lactone **1** (3 mmol) in dry THF (30 ml) was added under argon at -78° C to a stirred suspension of t-BuOK (3mmol) in dry THF (30 ml). The mixture was stirred for 45 min. After the addition of the carbonyl compound (3.5 mmol) in dry THF (30 ml) the mixture was stirred at - 80° C and the reaction was followed by TLC (kiesegel Merck 60 F_{254}). The solvent was evaporated and the residue chromatographed by flash chromatography (silicagel 60, eluent: chloroform/ether 1/1) to afford analytically pure samples of compounds **2a-e**.

Products **2** have the following characteristics:
2a (85%); mp = 58° C (lit.[4] 59° C); IR 1725 cm^{-1}; $[\alpha]_D$ 609.8 (c = 1.08, $CHCl_3$); ^{1}H-NMR δ 1.05 (3H, s), 1.26 (1H, d, J = 11.4Hz), 1.38 (3H, s), 1.52 (3H, s), 2.00 (3H, d, J = 7.2Hz), 2.12-2.15 (2H, m), 2.34-2.43 (1H, m), 2.76-2.83 (1H, m), 2.92-2.98 (1H, m), 6.70 (1H, q, J = 7.2Hz); ^{13}C NMR δ 12.64, 22.71, 23.29, 27.19, 27.65, 36.58, 38.92, 39.44, 49.21, 84.09, 131.11, 133.76, 164.53, 170.76.
2b (87%); yellow oil; IR 1730 cm^{-1}; $[\alpha]_D$ 475.3 (c = 1.02, $CHCl_3$); ^{1}H-NMR δ 1.04 (3H, s), 1.08 (3H, t, J = 7.8Hz), 1.10 (1H, d, J = 11.4Hz), 1.37 (3H, s), 1.52 (3H, s), 2.11-2.14 (2H, m), 2.32-2.42 (2H, m), 2.50-2.61 (1H, m), 2.75-2.82 (1H, m), 2.90-2.96 (1H, m), 6.60 (1H, t, J = 7.8Hz); ^{13}C NMR δ 12.66, 20.12, 22.68, 23.14, 27.16, 27.62, 36.53, 38.90, 39.42, 49.18, 84.06, 132.40, 137.22, 164.72, 170.84.
2c (61%); mp = 90° C (lit.[4] 92° C); IR 1720 cm^{-1}; $[\alpha]_D$ 944.8 (c = 9.57, $CHCl_3$); ^{1}H-NMR δ 1.08 (3H, s), 1.32 (1H, d, J = 11.4Hz), 1.40 (3H, s), 1.60 (3H, s), 2.16-2.22 (2H, m), 2.40-2.45 (1H, m), 2.88-2.97 (1H, m), 3.03-3.08 (1H, m), 7.30 (1H, s), 7.37-7.40 (3H, m), 7,84-7.88 (2H, m); ^{13}C NMR δ 22.96, 23.58, 27.33, 27.94. 37.07, 39.09, 39.65, 49.28, 84.66, 128.45, 128.59, 129.62, 130.94, 132.00, 134.01, 165.48, 172.63.
2d (66%); mp = 147° C; IR 1715 cm^{-1}; $[\alpha]_D$ 1428.8 (c = 0.89, $CHCl_3$); ^{1}H-NMR δ 1.07 (3H, s), 1.32 (1H, d, J = 11.4Hz), 1.39 (3H, s), 1.58 (3H, s), 2.14-2.18 (2H, m), 2.37-2.44 (1H, m), 2.86-2.93 (1H, m), 2.97-3.04 (1H, m), 3.90 (6H, s), 6.88 (1H, d, J = 8.4Hz), 7.25 (1H, s), 7.38 (1H, dd, J = 7.8Hz, J = 1.8 Hz), 7,69 (1H, d, J = 1.8Hz); ^{13}C NMR δ 23.05, 23.65, 27.47, 28.03, 37.08, 39.25, 39.76, 49.51, 55.83, 55.92, 84.47, 110.97, 114.65, 126.59, 127.39, 129.06, 129.38, 148.91, 150.82, 165.63, 171.31.

Hydrogenation of chiral cyclic α,β-didehydroamino acid derivatives **2a-e**

General method for Pd catalysed hydrogenation. A solution of compound **2a-e** (2 mmol) in methanol (10 ml) was hydrogenated with 5% palladium on charcoal (100 mg) and the reaction was followed by TLC (kiesegel Merck 60 F_{254}). When the reaction was finished, the catalyst was removed by filtration and the filtrate was evaporated to dryness to afford the corresponding α-amino acid derivative **3a-e** as a single diastereoisomer (measured by ^{1}H-NMR) in nearly

quantitative yield. Purification of the residue by flash chromatography (silicagel 60, eluent: ether/hexane 7/3) gave analytically pure samples of compounds **3a-e**.

General method for L-selectride® promoted hydrogenation. A 1.0M solution of L-selectride® in dry THF (0.44 mmol, 0.44 ml) was added under argon at -78° c to a stirred solution of compound **2a-e** (0.4 mmol) in dry ether (20 ml). After 1h the low temperature bath was replaced by an ice bath and stirring was continued for 1h. After recooling to -78° C the mixture was quenched with saturated aqueous NH_4Cl solution (3ml). The cold bath was removed after 5 min and the mixture allowed to warm to room temperature. An ether extraction, washing by water, drying on $MgSO_4$ and concentration in vacuo yielded the corresponding α-amino acid derivative **3a-e** as a single diastereoisomer (measured by ^{1}H-NMR). Purification of the residue by flash chromatography (silicagel 60, eluent: ether/hexane 7/3) gave analytically pure samples of compounds **3a-e**.

Products **3** have the following characteristics:
3a (75%); yellow oil; IR 1745 cm^{-1}; $[\alpha]_D$ - 220.4 (c = 1.04, $CHCl_3$); ^{1}H-NMR δ 1.04 (3H, s),1.08 (3H, t, J = 7.2Hz), 1.15 (1H, d, J = 11.4Hz), 1.38 (3H, s), 1.62 (3H, s), 1.93-2.22 (4H, m), 2.31-2.40 (1H, m), 2.70-2.78 (1H, m), 2.83-2.92 (1H, m), 3.92-3.98 (1H, m); ^{13}C NMR δ 10.08, 22.11, 22.93, 25.19, 27.38, 27.55, 36.94, 39.31, 39.52, 50.36, 59.91, 85.00, 171.74, 172,80.
3b (73%); yellow oil; IR 1745 cm^{-1}; $[\alpha]_D$ -176.8 (c = 1.07, $CHCl_3$); ^{1}H-NMR δ 0.96 (3H, t, 7.5Hz), 1.00 (3H, s), 1.11 (1H, d, J = 11.4Hz), 1.34 (3H, s), 1.41-1.53 (2H, m), 1.58 (3H, s), 1.81-2.16 (4H, m), 2.27-2.35 (1H, m), 2.65-2.73 (1H, m), 2.78-2.86 (1H, m), 3.90-3.97 (1H, m); ^{13}C NMR δ 13.92, 18.99, 22.07, 22.92, 27.37, 27.54, 34.15, 36.92, 39.27, 39.51, 50.35, 58.78, 84.95, 171.93, 172.67.
3c (68%); yellow oil; IR 1740 cm^{-1}; $[\alpha]_D$ - 154.8 (c = 0.98, $CHCl_3$); ^{1}H-NMR δ 1.01 (3H, s), 1.11 (1H, d, J = 11.4Hz), 1.37 (3H, s), 1.59 (3H, s), 2.04-2.20 (2H, m), 2.30-2.38 (1H, m), 2.68-2.77 (1H, m), 2.79-2.88 (1H, m), 3.18 (1H, dd, J =8.4Hz, J = 14.1 Hz), 3.48 (1H, dd, J = 4.5Hz, J = 14.1Hz), 4.22-4.29 (1H, m), 7.22-7.41 (5H, m); ^{13}C NMR δ 22.05, 22.85, 27.30, 27.45, 36.94, 38.08, 39.22, 39.48, 50.30, 60.55, 85.19, 126.33, 128.12, 129.72, 138.70, 171.54, 172.51.
3d (63%); yellow oil; IR 1740 cm^{-1}; $[\alpha]_D$ - 134 (c = 1.02, $CHCl_3$); ^{1}H-NMR δ 0.99 (3H, s), 1.07 (1H, d, J = 11.4Hz), 1.35 (3H, s), 1.57 (3H, s), 2.04-2.17 (2H, m), 2.27-2.36 (1H, m), 2.65-2.73 (1H, m), 2.79-2.87 (1H, m), 3.11 (1H, dd, J =7.8Hz, J = 14.1 Hz), 3.49 (1H, dd, J = 4.5Hz, J = 14.1Hz), 3.83 (3H, s), 3.86 (3H, s) 4.16-4.22 (1H, m), 6.78 (1H, d, J = 8.4Hz), 6.90 (1H, dd, J = 8.4Hz, J = 2.1Hz) 6.95 (1H, d, J = 2.1Hz); ^{13}C NMR δ 22.19, 22.92, 27.40, 27.55, 37.11, 37.83, 39.35, 39.58, 50.43, 55.86, 60.81, 85.22, 111.10, 113.50, 121.87, 131.33, 147.70, 148.60, 171.59, 172.38.

Hydrolysis of chiral cyclic α,β-didehydroamino acid derivatives **3a-e**

General method. Compound **3a-e** (2 mmol) was dissolved in THF and 10 ml of 6N HCl were then added. The mixture was stirred at 70° C for 3h. The solution was extracted with ether, the aqueous layer was dried and to the crystalline residue was added anhydrous ethanol 6 mL and a large excess of propylene oxide. The mixture was refluxed for 20 min and the free amino acid partially precipitated. After removal of the ethanol, the white residue was dissolved in distilled water (2 mL)

and eluted through a C_{18} reverse-phase Sep-pak cartridge, which after removal of water gave rise to the corresponding amino acid.

Products **4** have the following characteristics:

4a (93%); S-2-aminobutiric acid, mp = 293° C (lit.[8] 292-303° C);$[\alpha]_D$ + 18.6 (c = 4.8 in 6N HCl) (lit. + 18.65, c = 4.8 in 6N HCl).

4b (92%); S-norvaline, mp = 304° C (lit.[8] 307° C);$[\alpha]_D$ + 22.8 (c = 10 in 20% HCl) (lit. + 23.0, c = 10 in 20% HCl).

4c (93%); S-phenylalanine mp = 283° C (lit. 283° C);$[\alpha]_D$ - 35.2 (c = 1.94) (lit. - 35.1 c = 1.94 in water)

4d (85%); S-2-amino-3-[3,4-dimethoxyphenyl]propanoic, acid mp = 207° C (lit.[9] 207° C);$[\alpha]_D$ - 5.50 (c = 3.30 in 1 N HCl) (lit. - 5.75, c = 3.30 in 1 N HCl).

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