Stereospecific Synthesis of *N*-(Diphenylmethylene)-α,β-didehydroamino Acid Methyl Esters from β-Hydroxy-α-amino Acids

Cesarino Balsamini,*[a] Ermanno Duranti,[a] Leonardo Mariani,[b] Americo Salvatori,[a] Gilberto Spadoni[a]

[a] Istituto di Chimica Farmaceutica, Università di Urbino, Piazza del Rinascimento 6, I-61029 Urbino, Italy
[b] Istituto di Scienze Chimiche, Università di Urbino, Piazza del Rinascimento 6, I-61029 Urbino, Italy

N-(Diphenylmethylene)-α,β-didehydroamino acid methyl esters **2b–d** are prepared with absolute geometric selectivity from inexpensive β-hydroxyamino acids through the intermediates *N*-(diphenylmethylene)-β-hydroxyamino acid methyl esters **1b–d**. Besides, an easy conversion from *E* isomers to the corresponding *Z* isomers was performed, thus avoiding the use of the uncommon *allo*-β-hydroxyamino acids as starting materials.

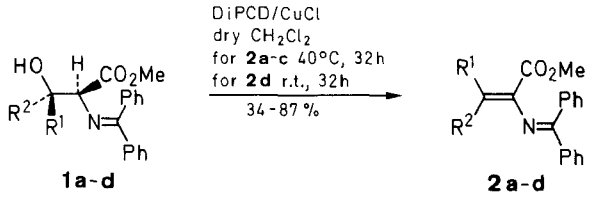
Protected α,β-didehydroamino acids are valuable intermediates in the synthesis of bioactive didehydropeptides and uncommon or optically pure amino acids.[1-3] Among these intermediates, the recently introduced *N*-(arylmethylene)-α,β-didehydroamino acids[4] are a[3] synthons of increasing interest, as implemented by the following examples.

- The *N*-benzylidene protection has been used to activate the α,β-double bond of didehydroamino esters in the nucleophilic addition of organometallics to yield β-substituted alanines.[5]
- A similar but more general synthesis involving Michael-type reaction on methyl *N*-(DPM)-didehydroalaninate (**2a**) was recently reported,[6] (DPM = diphenylmethylene); the DPM group can be easily removed by dilute protic acids.[7]
- The double bond of the *N*-(DPM)-didehydroalanine is the reactive functionality of a nickel complex which is the chiral building block of an asymmetric synthesis of amino acids.[8]

In the course of a research program on the reactivity and new synthetic applications of *N*-(DPM)-α,β-didehydroamino acids, e.g. for the stereospecific synthesis of β,β-disubstituted amino acids, we needed the *E* and *Z* isomers of alkyl *N*-(DPM)-α,β-didehydro-β-methylalaninates **2b,c** and *N*-(DPM)-α,β-didehydro-β-phenylalaninates **2d,e**. Here we describe the synthesis of these compounds.

Methods useful for the above-mentioned synthesis have been recently and authoritatively examined.[2] The authors of this review observed that the procedures involving both direct or indirect β-elimination of water are noteworthy when the starting β-hydroxyamino acids are easily available, as the commercial serine, threonine and phenylserine. The direct elimination has been performed in mild reaction conditions by a number of different reagents, as DAST (diethylaminosulfur trifluoride)/pyridine,[9] triphenylphosphine/diethyl azodicarboxylate,[10] and DiPCD (diisopropyl carbodiimide/copper(I) chloride).[11] While DAST is reported to behave stereospecifically, the others gave *E*, *Z* mixtures. In general, the synthesis of didehydroamino acids leads to isomeric mixtures or to the thermodynamically more stable *Z* isomer.

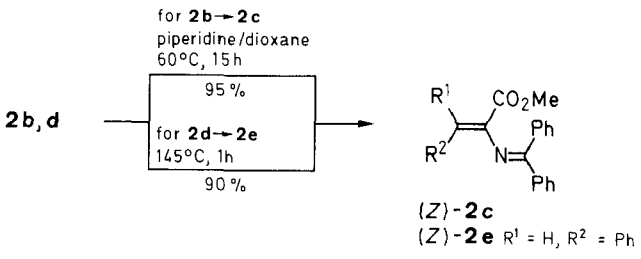
We investigated these reagents with the *N*-(DPM)-β-hydroxyamino acid methyl esters **1a–d**, which are readily prepared from the corresponding amino acids. The triphenylphosphine/diethyl azodicarboxylate system was found ineffective. The DAST method gave compound **2c** from **1b** with the expected *Z* geometry although in very poor yield (< 10%); **1d** surprisingly did not produce **2e**. Finally, the DiPCD/copper(I) chloride system, a dehydrating agent for β-hydroxy ketones formerly proposed by Corey[12] and later used on *N*-(benzyloxycarbonyl)-L-threonine by Miller,[11] stereospecifically gave **2a–d** in satisfactory yield (Scheme **A**).



Starting Material	Substrate	R^1	R^2	Product	Yield (%)
D,L-Ser	(±) **1a**	H	H	**2a**	87
L-Thr	**1b**	Me	H	(*E*)-**2b**	84
L-a-Thr	**1c**	H	Me	(*Z*)-**2c**	81
D,L-PhSer	(±) **1d**	Ph	H	(*E*)-**2d**	34

Scheme **A**

These results appear interesting since the *E* isomers, which have now been prepared with high selectivity, are not easily accessible. However, the preparation of (*Z*)-**2c** and (*Z*)-**2e** implies the use of the expensive L-allothreonine and the commercially unavailable allophenylserine as starting materials, respectively. To avoid this drawback, and supposing a kinetic control in the formation of the *E* isomers, we also investigated the *E* → *Z* isomerization of **2b** and **2d**.



Scheme **B**

The best conditions for the highest yield of conversion were defined: the **2d** → **2e** conversion occurs thermally, while the **2b** → **2c** conversion occurs in dioxane and is catalyzed by piperidine (Scheme **B**). Similar base-catalyzed *E* → *Z* isomerization has been observed; a mechanism, admitting a reversible Michael-type addition of the base and an α-carbanion intermediate, has

Table. Compounds **1** and **2** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula	IR (Nujol) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)	MS (70 eV) m/z (%)
(±)-**1a**	83	96–97 (Et_2O/ hexane)	$C_{17}H_{17}NO_3$ (283.3)	3300, 1735	3.17 (br s, 1H, OH), 3.77 (s, 3H, CH_3), 3.95 (m, 3H, CH–CH_2), 7.20–7.70 (m, 10H$_{arom}$)	283 (M^+, 5), 206 (100), 105
1b	78	78–80 (hexane)	$C_{18}H_{19}NO_3$ (297.4)	3310, 1740, 1660	1.34 (d, 3H, ^3J = 6.1, CH–C$\underline{H}_3$), 3.20 (br s, 1H, OH), 3.35 (br d, 1H, H$_\alpha$), 3.76 (s, 3H, OCH_3), 4.12 (dq, 1H, H$_\beta$, $^3J_{\alpha,\beta}$ = 7.9, ^3J = 6.1), 7.10–7.70 (m, 10H$_{arom}$)	297 (M^+, 2), 220 (100), 105
1c	75	76 (hexane)	$C_{18}H_{19}NO_3$ (297.4)	3300, 1740, 1660	1.23 (d, 3H, ^3J = 6.3, CH–C$\underline{H}_3$), 3.20 (br s, 1H, OH), 3.77 (s, 3H, OCH_3), 3.85–4.05 (br s, 1H, H$_\alpha$), 4.24 (dq, 1H, H$_\beta$, $^3J_{\alpha,\beta}$ = 8.4, ^3J = 6.3), 7.10–7.80 (m, 10H$_{arom}$)	297 (M^+, 2), 105 (100), 220
(±)-**1d**	84	81–82 (Et_2O/ hexane)	$C_{23}H_{21}NO_3$ (359.4)	3350, 1730, 1630	3.20 (br d, 1H, OH), 3.70 (s, 3H, OCH_3), 3.85 (br s, 1H, H$_\beta$), 5.01 (d, 1H, ^3J = 8.05, H$_\alpha$), 7.10–7.90 (m, 15H$_{arom}$)	195, 165, 105, 91 (100)
2a	87	oil[6]		–	–	
2b	84	53 (hexane)	$C_{18}H_{17}NO_2$ (279.3)	1720, 1630	1.91 (d, 3H, ^3J = 7.57, CH–C$\underline{H}_3$), 3.55 (s, 3H, OCH_3), 5.60 (q, 1H, ^3J = 7.57, H$_\beta$), 7.17–7.78 (m, 10H$_{arom}$)	279 (M^+, 99), 165 (100), 105
2c	81 95[b]	oil	$C_{18}H_{17}NO_2$ (279.3)	1720,[a] 1640, 1620	1.59 (d, 3H, ^3J = 7.21, CH–C$\underline{H}_3$), 3.65 (s, 3H, OCH_3), 6.10 (q, 1H, ^3J = 7.21, H$_\beta$), 7.15–7.77 (m, 10H$_{arom}$)	279 (M^+, 95), 165 (100), 105
2d	34	88 (hexane)	$C_{23}H_{19}NO_2$ (341.4)	1720, 1660, 1620	3.50 (s, 3H, OCH_3), 6.35 (s, 1H, H$_\beta$), 7.20–7.82 (m, 15H$_{arom}$)	341 (M^+, 100), 282, 179, 165, 105
2e	90[c]	147 (Et_2O/ hexane)	$C_{23}H_{19}NO_2$ (341.4)	1715, 1625	3.57 (s, 3H, OCH_3), 6.95 (s, 1H, H$_\beta$), 7.16–7.90 (m, 15H$_{arom}$)	341 (M^+, 100), 282, 179, 165

[a] Neat.
[b] From **2b**.
[c] From **2d**.

been also proposed.[13] The reaction conditions of the more widely studied hydrogen chloride catalyzed isomerizations[14] are incompatible with our substrates.

The high stereospecificity of the DiPCD β-elimination has a mechanistic relevance besides being synthetically useful. Our results are consistent with the mechanism previously proposed for this reaction, which implies a concerted *syn*-elimination of an *O*-alkylisourea intermediate.[12] The absence of stereospecificity, otherwise observed in the reaction of *N*-(benzyloxycarbonyl)-L-threonine with DiPCD,[11] suggests that the structure of the *N*-substituent could have an influence on the mechanism of these reactions.

The new compounds were characterized by ^{1}H-NMR spectroscopy and mass spectrometry. The structures of **2b,c** were determinated by ROESY experiments.[15] Furthermore, the ^{13}C-NMR data (**2b**, $\delta_{C=O}$ = 164.7, $^3J_{C=O,H}$ = 10.77 Hz, and **2c**, $\delta_{C=O}$ = 164.4, $^3J_{C=O,H}$ = 4.65 Hz) correspond to those reported respectively for *E* and *Z* isomers of similar didehydroamino acid esters.[16] With regard to the geometry of **2d** and **2e**, the ^{1}H-NMR signal of the **2e** vinyl proton shows a downfield shift of 0.6 ppm with respect to **2d**. This shift value corresponds to that observed for (*Z*)-**2c** and (*E*)-**2b** (0.5 ppm). These NMR data and the occurrence of the $E \rightarrow Z$ isomerization of **2d** and of **2b** support the geometry proposed for (*E*)-**2d** and (*Z*)-**2e**.

Melting points were determined on a Buchi SMP-510 capillary apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 257 spectrometer. NMR measurements were taken by a Bruker AC 200 spectrometer. The ROESY experiments were performed by a Varian VXR 300 spectrometer and MS spectra by VG ZAB 2F (70 eV) instrument. Satisfactory elemental analysis (C, H, N ± 0.4 from the theoretical value) were obtained for the new compounds.

***N*-(Diphenylmethylene)-β-hydroxyamino Acid Methyl Esters 1a–d:**
The compounds are prepared from the commercial β-hydroxyamino acids, which are esterified by conventional procedures and *N*-(DPM) protected according to the literature[7] (Table).

***N*-(Diphenylmethylene)-α,β-didehydroamino Acid Methyl Esters 2a–d; General Procedure:**
The substrate **1a–d** (10 mmol), 1,3-diisopropylcarbodiimide (2.525 g, 20 mmol) and CuCl (0.297 g, 3 mmol) in dry CH_2Cl_2 (50 mL) are stirred for 32 h at 40 °C (r.t. for **2d**) with exclusion of moisture. The mixture is filtered on Celite by suction, washed with H_2O (3 × 20 mL), dried (Na_2SO_4) and evaporated. Flash column chromatography (silica gel; benzene/EtOAc, 98:2) is used to obtain pure samples of compounds **2a–d** (Table).

Methyl (*Z*)-*N*-(Diphenylmethylene)-α,β-didehydro-β-methylalaninate (2c):
A solution of methyl (*E*)-*N*-(DPM)-α,β-didehydro-β-methylalaninate (**2b**, 2.79 g, 10 mmol) and piperidine (0.5 mmol) in dioxane (20 mL) is heated at 60 °C for 15 h. The reaction is followed by ^{1}H-NMR. The solvent is evaporated *in vacuo* to give **2c** practically pure by ^{1}H-NMR (Table); yield: 2.70 g (95%).

Methyl (*Z*)-*N*-(Diphenylmethylene)-α,β-didehydro-β-phenylalaninate (2e):
Methyl (*E*)-*N*-(DPM)-α,β-didehydro-β-phenylalaninate (**2d**, 3.41 g, 10 mmol) is heated at 145°C for 1 h in a sealed vessel to give **2e**. ^{1}H-NMR control reveals an almost complete isomerization (Table); yield. 3.20 g (90%).

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