Horner–Wadsworth–Emmons reaction for the synthesis of unusual α,β-didehydroamino acids with a chiral axis

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Dedicated to Prof. Enrique Meléndez on the occasion of his 70th birthday
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Abstract
The Horner–Wadsworth–Emmons reaction of *N*-benzyloxycarbonyl(dimethoxyphosphinyl) glycine esters with σ-symmetric prochiral 4-substituted-cyclohexanones under basic conditions is described. This reaction gives unusual α,β-didehydroamino acids with a chiral axis in their racemic form. The methodology has been extended to the synthesis of dipeptides containing a phenylalanine residue and these unusual new α,β-didehydroamino acids at the i+2 position.

Keywords: Amino acids, olefination

Introduction

The α,β-didehydroamino acids[1] have received considerable attention following their discovery in several naturally occurring oligopeptides.[2] Furthermore, the incorporation of these systems into peptide sequences introduces unique conformational constraints, leading to the application of these peptides as mechanistic probes in the study of enzyme mechanisms and binding.[3] Accordingly, the development of synthetic strategies to gain access to natural and unnatural α,β-didehydroamino acids is desirable.

During the course of our work on the synthesis of unusual α-amino acids, we envisioned the synthesis of axially chiral α,β-didehydroamino acid derivatives with the general structure depicted in Figure 1.

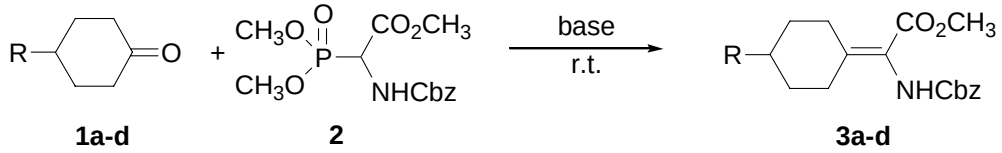
Figure 1

In this context we reported details of the synthesis, resolution and characterization of model dipeptides containing R_a and S_a (4-methylcyclohexylidene)glycine[4] in the i+1 position by the oxazolone method developed by Obrecht.[5] We present here our results on the synthesis of this class of axially chiral amino acid through a different approach that gives new and conveniently protected derivatives in racemic form.

Results and Discussion

A number of different procedures have been described in the literature for the synthesis of α,β-didehydroamino acid derivatives[1a] and for this study we chose the Horner–Wadsworth–Emmons reaction of 4-substituted cyclohexanones with *N*-acyl(dialkoxyphosphinyl)glycine esters[6] in the presence of a base.

The coupling reactions between various 4-substituted cyclohexanones **1a–1d** and commercially available *N*-benzyloxycarbonyl(dimethoxyphosphinyl)glycine methyl ester under basic conditions were examined (Scheme 1) and the results are summarized in Table 1.



1a-d **2** **3a-d**

a: R = CH_3, **b**: R = ^{t}Bu, **c**: R = Ph, **d**: R = EtO_2C

Scheme 1

In the first instance, compound **1a** was treated with an equimolecular amount of *N*-benzyloxycarbonyl(dimethoxyphosphinyl)glycine methyl ester **2** in the presence of equimolecular amounts of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane at room temperature. This reaction afforded the desired compound **3a** – albeit in low yield (25%) – after 3 days.

The use of an excess of the carbonyl compound (i.e. 1.5 molar amounts) under the same reaction conditions furnished **3a** in 52% yield. Other solvents or bases gave comparable or slightly worse yields of compound **3a**. A further increase in the amount of carbonyl compound

led to increased yields and the use of 4 molar equivalents of 4-methylcyclohexanone gave compound **3a** in 75% yield.

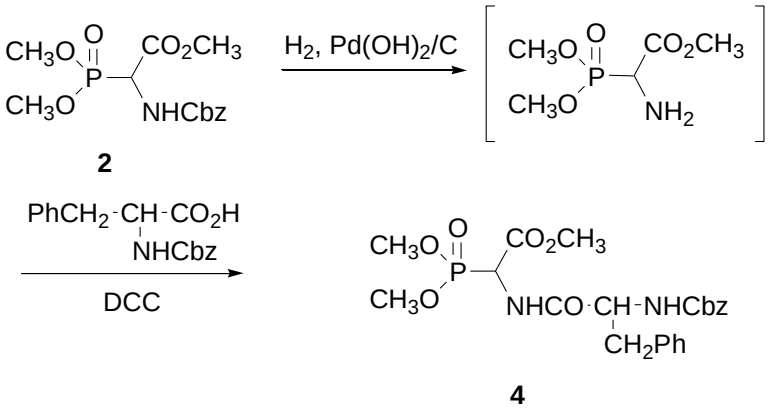
The reaction was extended to other 4-substituted cyclohexanones, namely 4-*tert*-butyl-, 4-phenyl- and 4-carboxyethylcyclohexanones **1b**, **1c** and **1d**. In all cases the reaction involving 4 molar equivalents of 4-substituted cyclohexanone and *N*-benzyloxycarbonyl-(dimethoxyphosphinyl)glycine methyl ester **2** in the presence of equimolecular amounts of DBU in dichloromethane at room temperature provided the corresponding α,β-didehydroamino esters **3b–3d** in moderate to good yields. Longer reaction times were required to reach an acceptable yield in the case of 4-*tert*-butylcyclohexanone.

Table 1. α,β-Didehydroamino acid esters **3** prepared by the Horner–Wadsworth–Emmons reaction

Entry	Carbonyl compound	Base	**1/2**	Solvent	Time	Yield (%)
1	**1a**	DBU	1/1	CH_2Cl_2	3 d	25
2	**1a**	DBU	1.5/1	CH_2Cl_2	3 d	52
3	**1a**	DBU	1.5/1	THF	3 d	50
4	**1a**	DBU	1.5/1	CH_3CN	3 d	47
5	**1a**	TMG	1.5/1	THF	3 d	44
6	**1a**	DBU	2/1	CH_2Cl_2	3 d	56
7	**1a**	DBU	3/1	CH_2Cl_2	3 d	65
8	**1a**	DBU	4/1	CH_2Cl_2	3 d	75
9	**1b**	DBU	4/1	CH_2Cl_2	3 d	42
10	**1b**	DBU	4/1	CH_2Cl_2	5 d	60
11	**1c**	DBU	4/1	CH_2Cl_2	3 d	68
12	**1d**	DBU	4/1	CH_2Cl_2	3 d	85

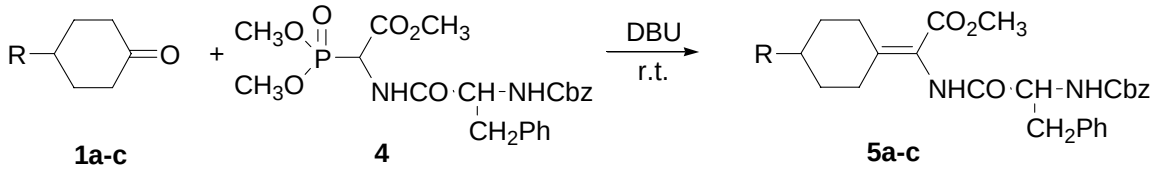
TMG = 1,1,3,3-tetramethylguanidine.

The promising results described above led us to study Horner–Wadsworth–Emmons reactions of other *N*-acyl(dimethoxyphosphinyl)glycine methyl esters in an attempt to obtain model dipeptides containing an axially chiral α,β-didehydroamino acid moiety in the i+2 position. To perform this study dipeptide **4**, which contains a phosphoglycinate unit, was obtained according to Scheme 2.



Scheme 2

Hydrogenolysis of the benzyloxycarbonyl group in compound **2** using $Pd(OH)_2$ as a catalyst provided an intermediate amino ester, which was coupled with *N*-benzyloxycarbonylphenylalanine in the presence of dicyclohexylcarbodiimide (DCC) to give compound **4**. Condensation of this phosphoglycinate with 4-substituted cyclohexanones **1a–1c** under the previously established reaction conditions gave didehydrodipeptide esters **5a–5c** in moderate yields (32–45% after 9 days) (Scheme 3).



a: R = CH_3, **b**: R = ^{t}Bu, **c**: R = Ph

5a, 45%
5b, 32%
5c, 38%

Scheme 3

Conclusions

The method described here proved to be very useful and convenient for the preparation of axially chiral α,β-didehydroamino acid derivatives in racemic form. Moreover, the condensation between 4-substituted cyclohexanones and dipeptides containing the phosphoglycinate moiety allowed the synthesis of dipeptides containing axially chiral α,β-didehydroamino acids. Studies into the use of chiral bases to perform the reaction in enantioselective fashion, the resolution of racemic compounds into enantiomers and the synthesis of other model dipeptides containing this intriguing class of chiral amino acid are underway and will be published in due course.

Experimental Section

General Procedures. Melting points were determined using a Gallenkamp apparatus and are uncorrected. Column chromatography was performed on silica gel (70–230 mesh). IR spectra were registered on a Mattson Genesis FTIR spectrophotometer; ν_{max} is given for the main absorption bands. ^{1}H, ^{13}C and ^{31}P NMR spectra were recorded on a Bruker Advance 400 apparatus, using the residual solvent signal as the internal standard; chemical shifts (□) are quoted in ppm and coupling constants (*J*) are measured in Hertz. TLC was performed on Polygram® sil G/UV_{254} precoated silica gel polyester plates and products were visualized under UV light (254 nm) or using ninhydrin, anisaldehyde or phosphomolybdic acid developers. Column chromatography was performed using silica gel (Kieselgel 60). All starting materials were commercially available research-grade chemicals and were used without further purification. Elemental Analyses were carried out on a Perkin-Elmer 200 H, C, N, S analyzer and were in satisfactory agreement with calculated values; C, ± 0.27; H, ± 0.16; N, ± 0.21.

General procedure for the synthesis of 2-(4-alkylcyclohexylidene)-2-benzyloxycarbonylamino acetic acid methyl esters (3a–3d)

To a stirred solution of *N*-benzyloxycarbonyl-2-(dimethoxyphosphinyl)glycine methyl ester **2** (332 mg, 1 mmol) in dichloromethane (10 mL) was added DBU (160 mg, 1.05 mmol) and stirring was continued for 10 min. The corresponding 4-alkylcyclohexanone (4 mmol) was added and the reaction mixture was stirred at room temperature for the reaction time listed in Table 1. On completion of the reaction ethyl acetate (20 mL) was added and the solution was washed with 1N H_2SO_4 (5 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was purified by column chromatography to give the corresponding 2-(4-alkylcyclohexylidene)-2-benzyloxycarbonylamino acetic acid methyl ester **3**.

(3a). 75% yield; eluent hexane/ethyl acetate 7:1; mp 98.3–98.5 °C; IR (nujol) 3302, 1717, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 ºC, 400 MHz) δ 0.89 (d, 3H, *J* = 6.8 Hz), 1.03–1.20 (m, 2H), 1.54–1.67 (m, 1H), 1.74–1.85 (m, 2H), 1.86–1.98 (m, 1H), 1.98–2.10 (m, 1H), 2.61–2.71 (m, 1H), 3.34–3.41 (m, 1H), 3.68 (s, 3H), 5.12 (s, 2H), 5.90 (brs, 1H), 7.29–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 ºC, 100 MHz) δ 21.4, 29.7, 30.6, 32.1, 35.3, 35.7, 51.7, 67.2, 118.4, 128.0, 128.1, 128.5, 136.2, 151.0, 154.9, 165.5.

(3b). 60% yield; eluent hexane/ethyl acetate 7:1; mp 126.9–127.2 °C; IR (nujol) 3309, 1709, 1648 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 ºC, 400 MHz) δ 0.84 (s, 9H), 1.10–1.29 (m, 3H), 1.85–1.96–2.01 (m, 4H), 2.72–2.78 (m, 1H), 3.46–3.52 (m, 1H), 3.68 (s, 3H), 5.12 (s, 2H), 5.84 (brs, 1H), 7.26–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 50 ºC, 100 MHz) δ 27.5, 28.0, 28.4, 30.2, 31.2, 32.4, 47.7, 51.8, 67.2, 118.1, 128.1, 128.2, 128.5, 136.3, 151.4, 154.9, 165.6.

(3c). 68% yield; eluent hexane/ethyl acetate 4:1; mp 153.3–153.6 °C; IR (nujol) 3320, 1705 cm^{-1}; ^{1}H NMR ($CDCl_3$, 50 ºC, 400 MHz) δ 1.58–1.74 (m, 2H), 2.03–2.25 (m, 4H), 2.75–2.85 (m, 1H), 2.85–2.93 (m, 1H), 3.61–3.69 (m, 1H), 3.79 (s, 3H), 5.18 (s, 2H), 5.99 (brs, 1H), 7.18–7.22 (m, 3H), 7.26–7.35 (m, 7H); ^{13}C NMR ($CDCl_3$, 50 ºC, 100 MHz) δ 30.2, 31.1, 34.4, 34.8,

38.2, 44.0, 51.9, 67.3, 119.0, 126.2, 126.8, 128.1, 128.2, 128.4, 128.5, 136.2, 145.9, 149.8, 154.9, 165.5.

(3d). 85% yield; eluent hexane/ethyl acetate 4:1; mp 83.5–83.7 °C; IR (nujol) 3288, 1725, 1693 cm^{-1}; ^1H NMR ($CDCl_3$, 60 ºC, 400 MHz) δ 1.22 (t, 3H, *J* = 7.2 Hz), 1.65–1.75 (m, 2H), 1.95–2.10 (m, 3H), 2.19–2.29 (m, 1H), 2.47–2.54 (m, 1H), 2.59–2.68 (m, 1H), 3.23–3.31 (m, 1H), 3.71 (s, 3H), 4.10 (q, 2H, *J* = 7.2 Hz), 5.11 (s, 2H), 5.99 (brs, 1H), 7.26–7.31 (m, 5H); ^{13}C NMR ($CDCl_3$, 60 ºC, 100 MHz) δ 14.2, 28.6, 28.8, 29.3, 29.4, 42.1, 51.9, 60.4, 67.2, 119.2, 128.1, 128.2, 128.5, 136.1, 148.9, 154.8, 165.3, 174.7.

(*RS*)-*N*-[*N*-Benzyloxycarbonyl-(*S*)-phenylalanyl]-2-(dimethoxyphosphinyl)glycine methyl ester (4). *N*-Benzyloxycarbonyl-2-(dimethoxyphosphinyl)glycine methyl ester **2** (3.3 g, 10 mmol) in ethanol (40 mL) was hydrogenated at room temperature and atmospheric pressure using 20% palladium hydroxide on charcoal (150 mg) as a catalyst. The reaction was monitored by TLC and, on completion (15 h), the catalyst was filtered off and washed with several portions of methanol. The solvent was removed *in vacuo* and the residue dissolved in dichloromethane (15 mL), cooled to –10 ºC and a solution of *N*-benzyloxycarbonyl-(*S*)-phenylalanine (4 g, 10 mmol) in dichloromethane (15 mL) was added dropwise at this temperature. After 10 min a solution of dicyclohexylcarbodiimide (2.27 g, 11 mmol) in dichloromethane (15 mL) was added at –10 ºC, and the reaction mixture was allowed to warm up to room temperature and stirred overnight. The precipitated urea was filtered off and the filtrate was washed with 1M potassium hydrogen sulfate (15 mL) and saturated aqueous sodium hydrogen carbonate (15 mL). The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (first eluent ethyl acetate/ethanol 20:1, second eluent ethyl acetate/ethanol 15:1) to give (*RS*)-*N*-[*N*-benzyloxycarbonyl-(*S*)-phenylalanyl]-2-(dimethoxyphosphinyl)glycine methyl ester **4** (4.54 g, 95%) as an equimolecular mixture of diastereoisomers. ^1H NMR ($CDCl_3$, 60 ºC, 400 MHz) δ 2.97–3.17 (m, 2H), 3.69 and 3.75 (d, 3H, *J* = 11.1 Hz), 3.72 and 3.75 (d, 3H, *J* = 11.1 Hz), 3.75 and 3.77 (s, 3H), 4.47–4.58 (m, 1H), 5.05 (s, 2H), 5.13 (dd, 1H, *J* = 22 Hz, *J* = 9.0 Hz), 5.25 and 5.31 (bd, 1H, *J* = 8.4 Hz and *J* = 7.5 Hz), 6.84 and 6.91 (bd, 1H, *J* = 8.7 Hz and *J* = 8.1 Hz), 7.15–7.33 (m, 10H); ^{13}C NMR ($CDCl_3$, 60 ºC, 100 MHz) δ 38.2 and 38.3, 49.3, 51.3, 53.0, 53.8 and 53.9, 56.0 and 56.1, 67.0 and 67.1, 127.0, 127.9, 128.0, 128.4, 128.6, 129.3, 136.1, 136.2, 155.8, 166.5 and 166.6, 170.7 and 170.8; ^{31}P NMR ($CDCl_3$, 60 ºC, 161 MHz) δ 18.30 and 18.37.

General procedure for the synthesis of (*RS*)-2-(4-alkylcyclohexylidene)-2-[*N*-benzyloxycarbonyl-(*S*)-phenylalanylamino] acetic acid methyl esters (5a–5c)

To a stirred solution of (*RS*)-*N*-[*N*-benzyloxycarbonyl-(*S*)-phenylalanyl]-2-(dimethoxyphosphinyl) glycine methyl ester **4** (1.9 g, 4 mmol) in dichloromethane (15 mL) was added DBU (790 mg, 5.2 mmol) and stirring was continued for 10 min. The corresponding 2-alkylcyclohexanone (16 mmol) was added and the reaction mixture was stirred at room temperature for 9 d. On completion of the reaction ethyl acetate (20 mL) was added and the solution was washed with 1N H_2SO_4 (5 mL) and dried over anhydrous $MgSO_4$. The solvent was evaporated *in vacuo* and the

residue was purified by column chromatography on silica gel (eluent ethyl acetate/ethanol 20:1) to give the corresponding (*RS*)-2-(4-alkylcyclohexylidene)-2-[*N*-benzyloxycarbonyl-(*S*)-phenylalanylamino] acetic acid methyl ester **5** as an almost equimolecular mixture of diastereoisomers.

(5a). 45% yield; IR (nujol) 3304, 3272, 1719, 1683 cm^{-1}; ^1H NMR ($CDCl_3$, 28 ºC, 400 MHz) δ 0.82 and 0.83 (d, 3H, *J* = 6.4 Hz), 0.86–1.10 (m, 2H), 1.45–1.58 (m, 1H), 1.60–1.78 (m, 3H), 1.87–1.98 (m, 1H), 2.10–2.19 (m, 1H), 2.98–3.10 (m, 2H), 3.20–3.30 (m, 1H), 3.60 (s, 3H), 4.38–4.46 (m, 1H), 4.99–5.07 (m, 2H), 5.20 (brs, 1H), 6.91 (brs, 1H), 7.14–7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 28 ºC, 100 MHz) δ 21.3, 29.7, 30.6, 32.0 and 32.1, 35.3 and 35.4, 35.7, 38.2, 51.6, 56.4, 67.3, 118.0, 127.1, 128.0, 128.3, 128.6, 128.8, 129.4, 136.3 and 136.5, 150.9 and 151.2, 156.1, 165.0, 169.8.

(5b). 32% yield; IR (nujol) 3318, 3260, 1717, 1695, 1663 cm^{-1}; ^1H NMR ($CDCl_3$, 28 ºC, 400 MHz) δ 0.76 and 0.77 (s, 9H), 0.90–1.16 (m, 3H), 1.60–1.75 (m, 2H), 1.78–1.90 (m, 2H), 1.98–2.28 (m, 1H), 3.03–3.17 (m, 2H), 3.31–3.40 (m, 1H), 3.60 (s, 3H), 4.40–4.48 (m, 1H), 4.97–5.06 (m, 2H), 5.25 (brs, 1H), 7.03 (brs, 1H), 7.14–7.30 (m, 10H); ^{13}C NMR ($CDCl_3$, 28 ºC, 100 MHz) δ 27.5, 27.9 and 28.0, 28.3 and 28.3, 30.1 and 30.2, 31.1 and 31.2, 32.4, 38.90, 47.5 and 47.6, 51.8, 56.1, 67.2, 117.5, 127.0, 128.0 ans 128.0, 128.3, 128.5, 128.7, 129.3 and 129.4, 136.0 and 136.3, 150.9 and 151.3, 156.0, 165.1, 169.8.

(5c). 38% yield; IR (nujol) 3290, 1720, 1687, 1657 cm^{-1}; ^1H NMR ($CDCl_3$, 28 ºC, 400 MHz) δ 1.40–1.70 (m, 2H), 1.75–1.88 (m, 2H), 1.90–2.10 (m, 2H), 2.22–2.34 (m, 1H), 2.60–2.70 (m, 1H), 3.01–3.12 (m, 2H), 3.42–3.50 (m, 1H), 3.62 (s, 3H), 4.42–4.51 (m, 1H), 4.95–5.05 (m, 2H), 5.28 (brs, 1H), 7.01 (brs, 1H), 7.16–7.32 (m, 15H); ^{13}C NMR ($CDCl_3$, 28 ºC, 100 MHz) δ 30.1, 30.9 and 31.0, 34.4 and 34.4, 34.7 and 34.8, 38.0, 43.9 and 44.0, 51.9, 56.1, 67.2, 118.3, 126.2, 126.8, 127.1, 128.0, 128.3, 128.4, 128.5, 128.7, 129.3 and 129.4, 136.0 and 136.2, 145.8 and 145.8, 149.7, 156.1, 165.0, 169.9.

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