Transformation of Glutamic Acid into (*S*)-Benzyl 2-(dibenzylamino)-6-(dimethoxyphosphoryl)-5-oxohexanoate for a Convenient Access to 5-Substituted Prolines

Elena Cini,[a] Gianluca Giorgi,[b] Manuela Rodriquez,[c] Maurizio Taddei*[a]

[a] Dipartimento Farmaco Chimico Tecnologico, Università degli Studi di Siena, Via A. Moro, 53100 Siena, Italy
Fax +39(0577)234333; E-mail: taddei.m@unisi.it

[b] Dipartimento di Chimica, Università degli Studi di Siena, Via A. Moro, 53100 Siena, Italy

[c] Dipartimento di Scienze Farmaceutiche, Università degli Studi di Salerno, Via Ponte don Melillo, 84084 Fisciano, Salerno, Italy

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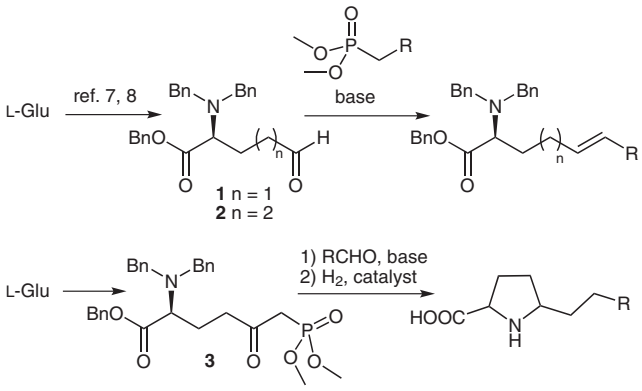
Abstract: L-Glutamic acid was transformed into β-keto-phosphonate in two steps. This compound was employed in the stereocontrolled synthesis of *cis*-5-substituted prolines through a Woodward–Horner–Emmons (WHE) reaction with different aldehydes followed by hydrogenolysis/hydrogenation-mediated ring closure. We found also that a one-pot sequential hydroformylation–WHE reaction was possible with *cis*-5-substituted prolines. In addition to differently functionalised prolines, an indolizidine amino acid with a structure related to constrained peptidomimetics was obtained.

Key words: amimo acids, hydrogenation, peptidomimetics, microwaves

The importance of proline derivatives in peptide and natural product chemistry and in organic synthesis is well evidenced by the high number of reviews and scientific literature on the subject.[1] Substituted prolines are considered as conformationally constrained amino acids[2] and they have been introduced in peptidomimetics and peptide analogues with successful results.[3] Many natural products containing heterocyclic rings related to proline have been isolated and some of them show very interesting properties.[4] Consequently, proline has been considered as a privileged structure in the search for new hits in drug discovery.[5] Moreover, proline and substituted prolines have found a broad application as organocatalysts in asymmetric synthesis.[6]

In the search of new simple approaches to biologically relevant natural and non-natural amino acids, we described recently the synthesis of aldehydes **1** and **2** starting from L-glutamic acid.[7,8] These aldehydes, after reaction with phosphonium ylides[7] or phosphonates,[8] could provide an useful entry to lipophilic or long-chain-substituted enantiomerically pure α-amino acids. We envisaged the possibility to invert this reactivity sequence, installing the phosphonate on the glutamic moiety (**3** in Scheme 1) and permitting it to react with different aldehydes to produce, after hydrogenation, different 5-substituted prolines (Scheme 1). This class of amino acids has been previously prepared by reaction of protected pyroglutamic acid with organometallic reagents followed by intramolecular cyclisation.[9] Other approaches include cyclisation of sulfonamides,[10] sulfinimines,[11] acetylenic-derived amino acids[12] or stereoselective hydrogenation of pyrrolines,[13] and five-membered iminium ions.[14] Phosphonates structurally related to **3** have been prepared by Lubell and co-workers in 3–5 steps starting from glutamic or pyroglutamic acid.[15,16]



Scheme 1

We considered a simpler sequence starting from tetrabenzyl glutamic acid **4** and using the hindrance of the benzyl protection at the α-nitrogen to force the phosphonomethylene anion to discriminate between the two benzyl ester groups. Different variables such as the solvent, the nature, and the concentration of the base employed to generate the anion, the temperature and the order of the addition of the reagents were addressed in order to obtain a higher ratio in favour of the desired (*S*)-benzyl 2-(dibenzylamino)-6-(dimethoxyphosphoryl)-5-oxohexanoate (**5**) with respect to the other possible products (**6** and **7**) formed in the reaction (Table 1). First attempts carried out with stoichiometric amounts of $(MeO)_2POMe$ and BuLi in THF gave a mixture of the two regioisomers **5** and **6** in 50:50 ratio in 42% yields together with 40% of unreacted starting material. Keeping the reaction mixture to –78 °C and quenching at this temperature improved the **5/6** ratio but decreased the yields. Then, the nature of the base was changed trying LDA, $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, $KN(SiMe_3)_2$, without any improvement in the amount of **5** isolated (entries 4–8 in Table 1). Changes in the solvent from THF to DME or toluene did not improve yields or se-

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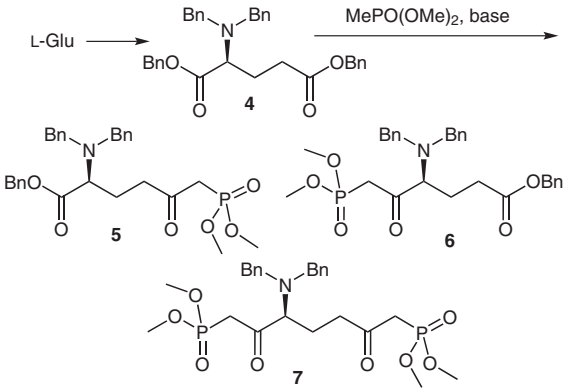
Table 1 Optimisation of the Procedure for the Selective Formation of the β-Keto Phosphonate **5**



Entry	Base	Solvent, temperature, reaction conditions[a]	Ratio of **5/6/7**	Yield (%)[b]
1	BuLi	THF, –78 °C to r.t., A.	50:50:0	42
2	BuLI	THF, –78 °C, A	70:30:0	22
3	LDA	THF, –78 °C to r.t., A	60:40:0	35
4	NaHDMS	THF, –78 °C to r.t., A	55:40:5	43
5	NaHDMS	toluene, –78 °C to r.t., A	30:55:15	40
6	NaHDMS	DME, –78 °C to r.t., A	65:35:0	50
7	LiHDMS	THF, –78 °C to r.t., A	65:35:0	33
8	KHDMS	THF, –78 °C to r.t., A	60:30:10	45
9	KO*t*-Bu	THF, –78 °C to r.t., A	–	–[c]
10	*i*-PrMgBr	THF, 0 °C, A	–	–[c]
11	*t*-BuLi	Et_2O, –78 °C to r.t., A	–	–[d]
12	BuLi	THF, –78 °C to r.t., B	60:20:20	76
13	BuLi	THF, –78 °C, C	75:25:0	82

[a] Conditions A: $MePO(OMe)_2$ (1 equiv), base (1.3 equiv). Conditions B: $MePO(OMe)_2$ (3 equiv), base (3 equiv). Conditions C: 0.1 M soln $MePO(OMe)_2$ (3 equiv), base (3 equiv).
[b] Yields of isolated **4**, **5**, and **6**.
[c] Decomposition of **4** observed.
[d] Starting material recovered.

lectivity. Surprisingly, in toluene the phosphonate **6** was the major isomer formed. Finally, an increase of the amount of the phosphonomethylene anion gave an improvement of the yields, although with concomitant increase of the diphosphonate **7**.

Better yields and selectivity were observed by slow addition of a solution of **4** in THF to the lithium anion. The best result was achieved by slow addition of a diluted solution of **4** in THF to the lithium phosphonate in THF at –78 °C and carrying out the aqueous workup at this temperature after four hours of stirring. However, **5** could be obtained in pure form in 65% yield exclusively after flash chromatography separation from **6**.[17]

Compound **5** was then reacted with different aldehydes under standard neutral Horner–Wadsworth–Emmons conditions to give compounds **8**–**17** in good yields, mainly as the *E*-isomer as revealed by ^{1}H NMR analysis ($^3J_{CH=CH}$ >15 Hz). It is noteworthy that the aldehydes employed for preparing compounds **12**–**14** were obtained by microwave-assisted hydroformylation[18] of the corresponding alkenes, in a sort of tandem hydroformylation–Horner–Wadsworth–Emmons reaction.[19]

Compounds **8**–**17** were then submitted to hydrogenolysis in a Parr bottle at 4.8 bar in MeOH and in the presence of $Pd(OH)_2$/C at room temperature for 12–48 hours depending on the substrate, giving prolines **18**–**28** in good to acceptable yields (see Table 2).[20] Boc_2O was added to the reaction mixture, in order to isolate *N*-Boc prolines as the reaction products. The presence of the Boc group facilitates the isolation and purification of the product especially with smaller substituents in position 5. However, without Boc_2O, unprotected prolines could be isolated, as in the case of compounds **18**, **20**, **22**, and **28** whose lipophilicity allowed purification by simple column chromatography on silica gel. Unfortunately, the hydrogenolysis conditions led to a complete reduction of the phenyl ring in product **26**; although, by monitoring the conversion of the reaction every hour, it was possible to isolate compound **27** in acceptable yields after six hours at room temperature. In the case of compound **14**, the bromine atom was removed during cyclisation, giving the simple alkyl proline **25**. The hydrogenolysis/hydrogenation cyclisation of **8**–**17** can be carried out also in less than one hour under microwave dielectric heating at 80 °C and under 4.8 bar of H_2 in the presence of $Pd(OH)_2$.[21] However, the yields of the products obtained were lower than working at room temperature for a longer time. All compounds **18**–**28** were obtained in diastereomeric ratio higher than 90% (^{1}H NMR analysis, 400 MHz). NOE experiments showed a significant effect between the proton in position 2 and protons in position 3 and 4, and analogously an effect was observed on these protons when CH(5) was irradiated. No effects were observed between CH(2) and CH(5), suggesting a 2,5-*trans* relationship. However, X-ray crystal-structure analysis of compound **20**[22] revealed a *cis* relationship between the substituents of the pyrrolidinium

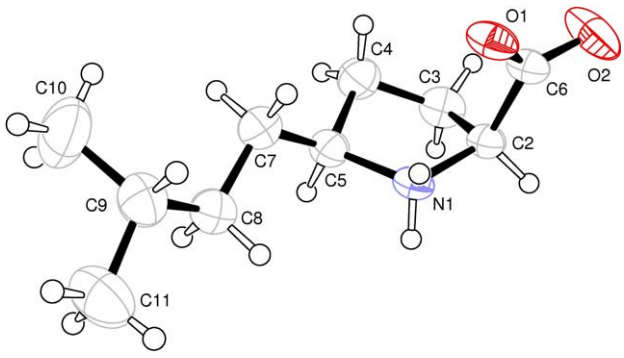
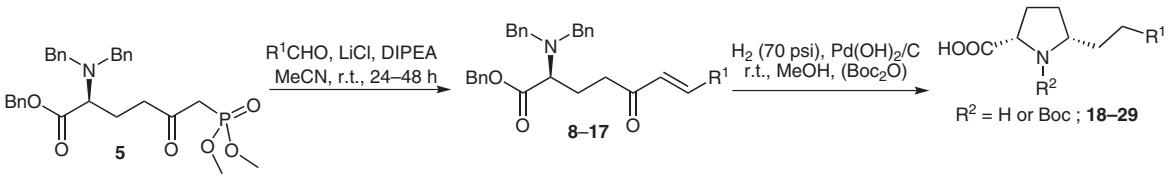


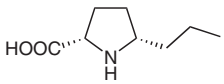
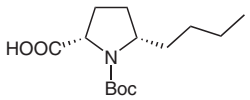
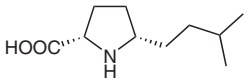
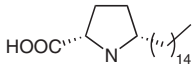
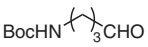
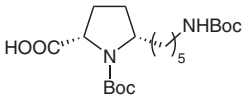
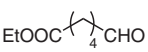
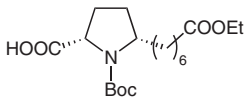
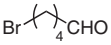
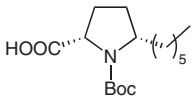
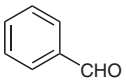
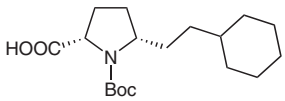
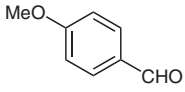
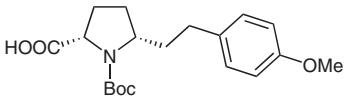
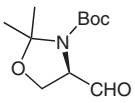
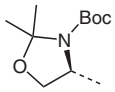
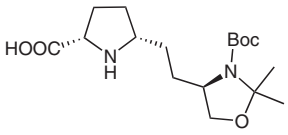
Figure 1 X-ray crystal structure of compound **20**; ellipsoids for nonhydrogen atoms enclose 50% probability

ring and an *R*-configuration for the stereocentre at C(5) (Figure 1).

As with other analogues,[23] **20** crystallises as 5-isopentylpyrrolidinium-2-carboxylate with the N(1)–C(2) and N(1)–C(5) distances equal to 1.503(2) and 1.522(2) Å, re-

Table 2 Synthesis of Different 5-Substituted Prolines



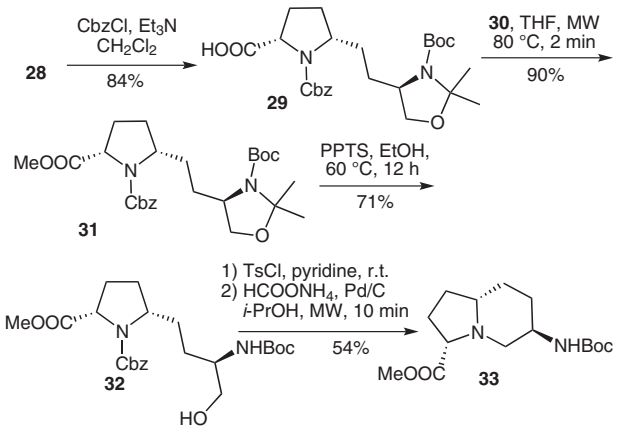
Entry	Aldehyde	Benzyl 2-dibenzylamino-5-oxa-enoic acid (R^1)	Proline	Yields (%)[a]
1	MeCHO	Me **8** (77%)	 **18**	75
2		$MeCH_2$ **9** (76%)[a]	 **19**	75
3		Me_2CH **10** (69%)	 **20**	68
4		$Me(CH_2)_{12}$ **11** (85%)	 **21** R^2 = Boc **22** R^2 = H	75 60
5		$BocNH(CH_2)_3$ **12** (75%)[a]	 **23**	56
6		$EtOOC(CH_2)_4$ **13** (70%)[a]	 **24**	78
7		$Br(CH_2)_4$ **14** (81%)[a]	 **25**	70
8		Ph **15** (85%)[a]	 **26**	67
9		4-$MeOC_6H_4$ **16** (81%)[a]	 **27**	56
10		 **17** (76%)[a]	 **28**	66

[a] Isolated yields.

spectively. The pyrrolidinium ring shows an envelope conformation with N(1), C(2), C(4), C(5) defining the best least-squares plane while C(3) is out-of-plane with a deviation of 0.59 Å from it. The two substituents, that is, the carboxylate and the isopentyl chain are in axial and bisectional position, respectively (Figure 1).

The crystal structure is stabilised by strong intermolecular hydrogen bonds involving the pyrrolidinium NH_2 and both the oxygen atoms of the carboxylate group.

Starting from compound **28** we designed a convenient synthetic scheme to prepare the indolizidine amino acid **33**, having a structure related to other indolizidines that have applications as peptidomimetics in medicinal chemistry.[24] Proline **28** was first protected as the Cbz derivative and then methylated at the carboxylic group. *O*-Methylisourea **30**, prepared through reaction of commercially available PS-supported microporous DCC in dry methanol under microwave heating,[25] was used for methylation of the COOH group. Addition of **29** to resin **30** at 60 °C in dichloromethane gave compound **31** in 75% overall yield (Scheme 2). The oxazolidine acetonide was then removed using PPTS in hot ethanol[26] to give the proline derivative **32**. The terminal OH was transformed into the tosylate and the product submitted to microwave-assisted transfer hydrogenation.[27] The Cbz group was removed and the free proline NH underwent intramolecular nucleophilic substitution at the carbon carrying the tosylate to give the indolizidine amino acid **33** as a single diasteromer as revealed by ^{1}H NMR (400 MHz) and HPLC analyses.



Scheme 2 Preparation of indolizidine amino acid **31**

Compound **33** has the two functional groups orthogonally protected and it is in a suitable form to be inserted into a peptide sequence.

In conclusion we have developed a convenient approach to enantiomerically pure *cis*-5-substituted prolines that can be applied to differently functionalised substrates (apart alkenes or alkyl halides). The resulting prolines can be used as modified amino acids, potential organocatalysts soluble in low polarity organic solvents or as starting material for the preparation of indolizidine alkaloids or peptidomimetics.

Acknowledgment

This work was financially supported by MIUR (Rome, Progetto PRIN 2006) and the University of Siena (Progetto PAR 2005).

Reference and Notes

(1) For example, search for 'proline' in ISI Web of Knowledge™ of Thomson Reuters) gives more than 200 reviews in 'chemistry' between 2000 and 2008.
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(17) **(*S*)-2-Dibenzylamino-6-(dimethoxyphosphoryl)-5-oxohexanoic Acid Benzyl Ester (5)**
To a soln of dimethyl methylphosphonate (0.191 g, 1.54 mmol) in dry THF (17 mL) cooled at –78 °C, BuLi (0.62 mL of a 2.5 M soln in hexane) was added dropwise. After 40 min, a soln of **4** (0.390 g, 7.7 mmol) in dry THF (14 mL) was added. After stirring for 4 h at –78 °C, a sat. soln of NH_4Cl (6 mL) was added followed by EtOAc (30 mL). After warming to r.t., the organic phase was separated. The aqueous phase was extracted with EtOAc, all the organic fractions were collected and dried over Na_2SO_4. The solvent was removed in vacuo, and the crude material was purified by column chromatography (PE–EtOAc, 1:3) to give compound **5** as colourless oil (0.26 g, 65% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95–2.02 (m, 2 H, H-3), 2.41–2.78 (m, 2 H, H-4), 2.79–2.97 (m, 2 H, H-6), 3.29 (t, *J* = 6.8 Hz, 1 H, H-2), 3.67 (AB system, 4 H, NCH_2Ph), 3.68 (d, *J* = 2.8 Hz, 3 H, OCH_3), 3.71 (d, *J* = 2.8 Hz, 3 H, OCH_3), 5.19 (AB system, 2 H, OCH_2Ph), 7.19–7.36 (m, 15 H, ArH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 22.6, 40.0, 40.4, 42.5, 52.8, 53.0, 54.4, 59.8, 66.1, 127.1 54.5, 59.8, 66.2, 127,1, 128.2, 128.3, 128.5, 128.6, 128.9, 135.9 (2 C), 139.21, 172.13, 200.7, 200.8. HRMS (ES): *m/z* calcd for $C_{29}H_{35}NO_6P$ $[M + H]^+$: 524.2202; found: 524.2180.
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(20) **(*S*,*E*) 2-Dibenzylamino-5-oxoicos-6-enoic Acid Benzyl Ester (11) – General Procedure**

To a soln of **5** (0.900 g, 1.7 mmol) in dry MeCN (18 mL), dry LiCl (72.0 mg, 1.7 mmol) was added followed by DIPEA (180 mg, 239 μL, 1.4 mmol). After stirring for 2 h at r.t., tetradecanal (0.276 g, 1.3 mmol) in MeCN was added and the mixture stirred at r.t. for 72 h. Brine was added and the organic layer separated. The aqueous phase was extracted with EtOAc, all the organic fractions were collected and dried over Na_2SO_4. The solvent was removed under vacuum and the crude mixture was purified by column chromatography (PE–EtOAc, 5:1) to give compound **11** as a colourless oil (0.673 g, 85% yield); $[\alpha]_D^{25}$ –55.5 (*c* 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 6.6 Hz, 3 H), 1.24–1.47 (m, 20 H), 1.45 (m, 2 H), 2.07–2.19 (m, 4 H), 2.41–2.69 (m, 2 H), 3.39 (dd, *J* = 8.4, 6.2 Hz, 1 H), 3.73 (AB system, 4 H), 5.23 (AB system, 2 H), 6.00 (d, *J* = 15.6 Hz, 1 H), 6.71 (dt, *J* = 15.6, 7.0 Hz, 1 H), 7.22–7.43 (m, 15 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 20.8, 22.6, 23.3, 28.0, 29.1, 29.2, 29.3 (3 C), 29.4, 29.5, 31.8 (2 C), 32.3, 36.3, 54.4, 60.1, 65.9, 126.9 (3 C), 128.1 (4 C), 128.2 (2 C), 128.4 (4 C), 128.7 (2 C), 130.1, 135.9, 139.2 (2 C), 147.2, 172.2, 199.3. MS (ES): *m/z* = 632 $[M + Na]^+$.

(2*S*,5*R*)-5-Pentadecylpyrrolidine-1,2-dicarboxylic Acid 1-*tert*-Butyl Ester (21) – General Procedure

To a soln of **11** (100 mg, 0.16 mmol) in CH_2Cl_2–MeOH (1:9, 5 mL) placed in the bottle connected with a Parr apparatus, Boc_2O (54 mg, 0.25 mmol) and $Pd(OH)_2$/C (20%, 9 mg, 0.012 mmol) were added. The bottle was filled with H_2 at 4.8 bar and shaken at r.t. for 8 h. The bottle was degassed, the catalyst filtered (**attention**: the residue Pd may be pyrophoric) and washed several times with MeOH. The solvent was removed under vacuum and the crude mixture was purified by column chromatography ($CHCl_3$–MeOH, 98:2) to give compound **21** as white gel (51 mg, 75% yield); $[\alpha]_D^{25}$ –20.7 (*c* 0.1, $CDCl_3$). ^{1}H NMR (400 MHz, $CHCl_3$): δ = 0.84 (t, *J* = 7.2 Hz, 3 H), 1.09–1.43 (m, 26 H), 1.47 (s, 9 H), 1.59–1.67 (m, 2 H), 1.82–1.94 (m, 2 H), 1.95–2.28 (m, 2 H), 3.71–3.83 (m, 1 H), 4.18–4.26 (m, 1 H), 9.91 (br s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 22.7, 26.6, 28.3 (3 C), 29.3 (2 C), 29.7 (10 C), 31.9, 34.3, 58.9, 60.0, 67.0, 173.7, 179.4. MS (ES): *m/z* = 424 $[M - H]^-$.

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(22) Crystallographic data (excluding structure factors) for X-ray crystal structure of **18** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 710555. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 (1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

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