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Short asymmetric synthesis of (2*S*,3*S*)- and (2*S*,3*R*)-3-prolinoglutamic acids: 2-carboxy-3-pyrrolidine-acetic acids (CPAA)

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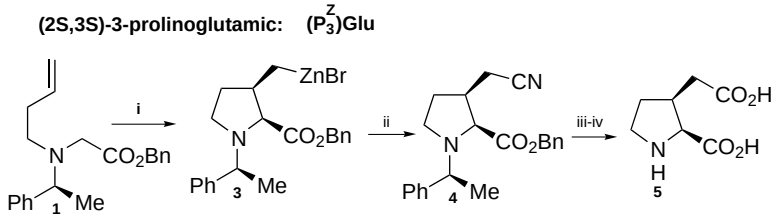
Abstract—The asymmetric synthesis of both *cis* and *trans* 3-prolinoglutamic acids can be easily achieved in a diastereoselective and enantioselective way via the amino–zinc–enolate cyclisation.

1. Introduction

L-Glutamic acid (L-Glu) is one of the major neurotransmitters in the mammalian central nervous system and the development of selective agonists and antagonists is a topic of current interest.[1–3] The use of both synthetic and naturally-occurring conformationally restricted glutamate analogs (α-kainic, dihydrokainic, domoic and acromelic acids for examples) has permitted the classification of excitatory amino acid receptors into at least two main types: the ionotropic and metabotropic receptors.[4–6] All of the aforementioned compounds contain a common amino acid moiety, 2-carboxy-3-pyrrolidine-acetic acid (CPAA) or 3-prolinoglutamic acid. Furthermore, 3-substituted prolines bearing the side chain of common α-amino acids are powerful tools for establishing the bioactive conformations of peptides.[7,8] Indeed, prolinomethionines have been used to determine the bioactive conformation of substance P.[8] Prolinoglutamic acids could be powerful tools in SAR studies of peptides containing glutamic acid. Thus, our goal is to prepare the different prolino-amino acids corresponding to the natural α-amino acids. *cis*/*trans* Racemic mixture syntheses of 3-prolinoglutamic acids have been reported.[9,10] Stereoselective racemic syntheses of *cis* and *trans* isomers have also been performed.[11,12] However, only the *trans* isomer (2*S*,3*R*) has been prepared optically active in eight steps starting from pyroglutamic acid.[13] We have described the amino–zinc–enolate cyclisation as a powerful and straightforward method for the synthesis of 3-substituted prolines.[14–16] We report here its application to a short and efficient asymmetric synthesis of both *cis* and *trans* 3-prolinoglutamic acids.

2. Results and discussion

The cyano derivative **4** was obtained in a 'one-pot' procedure starting from the previously described olefin



Scheme 1. (i) THF, LDA, −78°C, $ZnBr_2$, −78°C to rt; (ii) CuCN/2LiCl, 0°C, TsCN; (iii) H_2/Pd/C/MeOH; (iv) NaOH 3 equiv.; H_2O/reflux then Dowex 50-X8.

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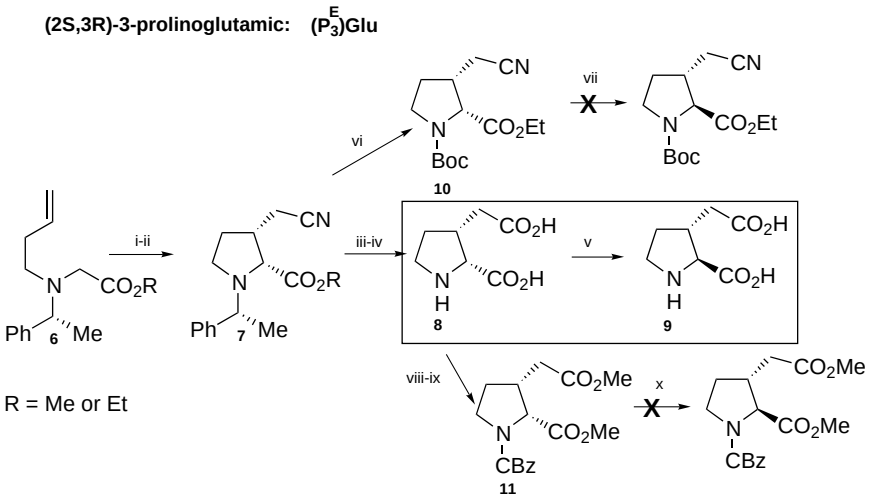

Scheme 2. (i) THF, LDA, −78°C, $ZnBr_2$, −78°C to rt; (ii) CuCN/2LiCl, 0°C, TsCN; (iii) HCl 6N, reflux; (iv) H_2/Pd/C then Dowex 50-X8; (v) H_2O, sealed tube, 190°C; (vi) H_2/Pd/C/MeOH/Boc_2O; (vii) THF/LDA, −78°C; (viii) $SOCl_2$, MeOH; (ix) CbzCl, $NaHCO_3$, toluene/MeOH; (x) refluxing MeONa/MeOH.

1.[15] This olefin was cyclised as described in Scheme 1. After deprotonation of **1** with LDA (1 equiv.) in THF at low temperature, the lithium enolate was transmetalated with zinc bromide (2.5 equiv. 1 M in ether). Warming up the reaction mixture to room temperature led to derivative **3** with a highly *cis* diastereoselective cyclisation, as previously demonstrated.[14] After a new transmetalation step with the THF soluble CuCN/2LiCl salts (1.1 equiv.),[17,18] the organozinccopper species were reacted with tosylcyanide (1 equiv.) leading to compound **4** as a single crystalline isomer[19] with (2*S*,3*S*) absolute configuration, according to the studies we have previously reported on the asymmetric induction of this reaction.[14] Hydrogenolysis over palladium charcoal followed by hydrolysis of the cyano group by refluxing aqueous sodium hydroxide and purification by ion-exchange chromatography led to *cis*-(2*S*,3*S*) prolinoglutamic acids **5**.[19]

The synthesis of the *trans* isomer **9** with (2*S*,3*R*) absolute configuration was achieved as described in Scheme 2. After the same sequence of reaction but starting with (+)-α-methylbenzylamine, the cyano derivative **7** was obtained. Hydrolysis of both methyl ester and cyano group by refluxing HCl 6N, hydrogenolysis of the chiral auxiliary over palladium charcoal and purification by ion-exchange chromatography led to compound **8**. As expected, compounds **5** and **8** have similar NMR spectra, showing that basic or acid hydrolysis of the nitrile occurred without epimerisation of C-2 chiral centre. Several attempts (Scheme 2) for inversion of the α-centre felt. However, heating at 190°C the *cis*-derivative **8** in a sealed tube as described by Osugi[9] resulted in a clean inversion of the α-centre with a *cis*/*trans* ratio (20/80) favouring the thermodynamically more stable *trans* crystalline isomer **9**.[19]

Conflicting NMR data have been reported in the literature for $J\alpha\beta$ coupling constant values for *cis* and *trans* prolinoglutamic acids: $J\alpha\beta$ (*trans*) = 8 Hz and $J\alpha\beta$ (*cis*) = 5.5 Hz,[11] $J\alpha\beta$ (*trans*) = 3.7 Hz and $J\alpha\beta$ (*cis*) = 8.8 Hz.[12] Our values: $J\alpha\beta$ (*trans*) = 7.5 Hz and $J\alpha\beta$ (*cis*) = 8.3 Hz demonstrate that the minor product described by Moss et al. was not the *cis* isomer[11] and that epimerisation of cisprolinoglutamic diester did not lead to the *trans* isomer in the work of Carpes et al.[12]

In conclusion, the syntheses of both *cis* (2*S*,3*R*) and *trans* (2*S*,3*S*) 3-prolino-glutamic acids have been achieved as an application of the amino–zinc–enolate cyclisation strategy. We are currently working on the preparation of the different prolinoamino acids of natural amino acids.

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19. Experimental part: All compounds had the expected analytical and spectroscopic properties.

3-Cyanomethyl-1(-1-phenyl-ethyl)-pyrrolidine-2-carboxylic-acid–benzyl ester 4.

According to general procedure for the cyclisation–transmetalation reaction.[14,15] From amine **1** (3.23 g, 10 mmol), THF (25 ml), LDA (6 ml, 12 mmol), $ZnBr_2$ (1.6 M, 19 ml), CuCN/2LiCl (1 M, 20 ml), yielding after purification by flash chromatography (cyclohexane/ethylacetate, 9/1), and crystallisation from cold ether/pentane pale yellow crystals (2.37 g, 68%). Mp: 51–53°C; $[\alpha]_D^{25}$ −70 (*c* 1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.24 (m, 5H), 7.15–7.14 (m, 3H), 7.07–7.05 (m, 2H), 5.05–4.97 (AB, 2H), 3.66–3.63 (q, 1H), 3.37–3.35 (d, 1H, $J^3=8$ Hz), 3–3.05 (m, 1H), 2.93–2.83 (m, 1H), 2.71–2.6 (m, 1H), 2.2–2 (m, 3H), 1.75–1.6 (m, 1H), 1.25–1.24 (d, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 144, 135.8, 129.3–129–128.8–127.7, 118.6, 66.7, 65.7, 61.2, 49.4, 38.6, 29.7, 22.9, 19.2. Anal. calcd for $C_{22}H_{24}N_2O_2$: C, 75.86; H, 6.89; N, 8.04. Found: C, 75.71; H, 7.05; N, 8.04.

3-Cyanomethyl-1(1-phenyl-ethyl)-pyrrolidine-2-carboxylic-acid-methyl ester 7.

Same protocol from amine **8** yielding after purification (flash chromatography, cyclohexane/ethylacetate, 9/1) and crystallisation (ether/pentane) colourless needles: $[\alpha]_D^{25}$ 76 (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz $CDCl_3$): δ 7.3 (m, 5H), 3.98 (q, 1H), 3.69 (s, 3H), 3.48 (d, 1H, $J^3=7.8$ Hz), 3.1 (m, 1H), 2.96 (m, 1H), 2.45–2.17 (m, 3H), 1.8 (m, 1H), 1.39 (d, 3H, $J^3=6.5$ Hz), 1.23–1.16 (tr, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$): δ 172.5, 143.5, 128, 127, 118, 65.4, 61, 51.5, 49, 38, 29.5, 22.4, 19. Anal. calcd for $C_{16}H_{20}N_2O_2$: C, 70.58; H, 7.35; N, 10.29. Found: C, 70.69; H, 7.69; N, 9.95.

(2*S*,3*S*)-3-Prolinoglutamic acid 5: 3-carboxymethyl-pyrrolidine-2-carboxylic acid.

White powder after ion-exchange chromatography and lyophilisation. ^{1}H NMR (250 MHz, D_2O): δ 4.33 (d, 1H, $J^3=8.25$ Hz), 3.73–3.65 (m, 1H), 3.53–3.42 (m, 1H), 3.1–3.06 (m, 1H), 2.71–2.60 (m, 1H), 2.42–2.30 (m, 2H), 2.00–1.92 (m, 1H). ^{13}C NMR (62.5 MHz, D_2O): δ 178.5, 172, 63.7, 44, 36.8, 36, 28.8. $[\alpha]_D^{25}$−32 (*c* 1, H_2O). MH^+: calcd: 174 (obtained: 174).

(2*S*,3*R*)-3-Prolinoglutamic acid 9: 3-Carboxymethyl-pyrrolidine-2-carboxylic acid.

White crystals from ethanol. ^{1}H NMR (250 MHz, D_2O): δ 3.79 (d, 1H, $J^3=7.5$ Hz), 3.44–3.36 (m, 2H), 2.85 (m, 1H), 2.7 (m, 1H), 2.55 (m, 1H), 2.3 (m, 1H), 1.8 (m, 1H). ^{13}C NMR (62.5 MHz, D_2O): δ 178, 173.5, 64.9, 44.7, 39.8, 39.2, 29.7. $[\alpha]_D^{25}$ 20 (*c* 0.1, H_2O). Mp: 242–244°C. MH^+: calcd: 174 (obtained: 174).