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Amino-zinc-ene-enolate cyclisation: a short access to (2*S*,3*R*)- and (2*S*,3*S*)-3-benzylprolines (3-benzylpyrrolidine-2-carboxylic acids)

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Abstract—The synthesis of 3-benzylprolines can be easily achieved in a diastereoselective and enantioselective way via amino-zinc-ene-enolate cyclisation. Transmetalation of the cyclic zinc intermediate with $Pd_2(dba)_3$/P(*o*-Tolyl)$_3$ allowed functionalisation with an aromatic ring. One-pot hydrogenolysis and Boc-protection led to the *cis*-isomer readily usable for peptide synthesis. The *trans*-isomer was obtained by epimerisation of the α-centre in a sealed tube at 200 °C.

Proline chimeras that combine amino acid side-chain functionality with conformational rigidity are potentially valuable for a wide field of biological applications. For example, in SAR studies of biologically active peptides, these proline analogues are used to replace native residues with the aim of probing both the information brought by the side chain and the conformation (around the peptide backbone and the side chain) of the native residue.[1] Functionalised prolines have also been viewed as templates for the introduction of chemical diversity into polyproline oligomers (e.g., polyproline II helix) allowing inhibition of protein–protein interactions.[2] Moreover, we have recently demonstrated that 3-substituted prolines with the appropriate side-chain represent valuable tools to mimic natural β-turns of types I, II and II′ found in proteins.[3]

Several approaches have been reported for the synthesis of these compounds but these lead however to *cis*/*trans* mixtures or to racemates.[4,5] We have reported the amino-zinc-ene-enolate cyclisation as a straightforward method for the asymmetric synthesis of *cis*-3-substituted prolines.[6] *Trans*-isomers can be obtained by simple epimerisation of the α-centre. The value of this approach is linked to the relative stability of zinc intermediates, which can be transmetalated into a variety of new organometallics[7] allowing reaction pathways not available for the zinc derivative. This point was demonstrated in the case of the amino-zinc-ene-enolate cyclisation by the synthesis of various prolinoamino acids after transmetalation of the zinc intermediate with copper salts (e.g., prolinomethionines,[8] prolinoglutamics[9] and prolinoleucines[10,11]). Transmetalation of organozinc compounds with Pd(0) (first reported by Negishi)[12] allows coupling with an aryl iodide. We report here its application to the short synthesis of Boc-protected (2*S*,3*R*)- and (2*S*,3*S*)-3-benzyl-pyrrolidine-2-carboxylic acids for which only long and racemic syntheses have been proposed.[13,14]

The commercially available olefin **1**[15] was converted in a one-pot procedure to the 3-benzyl derivative **2** as described in Scheme 1: after deprotonation with LDA in THF at −78 °C, the lithium enolate of amino ester **1** was transmetalated with zinc bromide (3 equiv, 1 M in ether). Warming up to room temperature led to a cyclic organozinc intermediate presenting a *cis* relative stereochemistry as previously demonstrated.[6] This intermediate was then submitted to a subsequent transmetalation with the active Pd(0) catalyst generated in situ from $Pd_2(dba)_3$ and tri-*o*-tolylphosphine.[16] Coupling with iodo-benzene was performed at room temperature to give **2** in reasonable yield (50%).[17]

One-pot hydrogenolysis over palladium charcoal and Boc protection led to optically pure (2*S*,3*R*)-3-benzyl-1-(*tert*-butyloxycarbonyl)-pyrrolidine-2-carboxylic acid **3**

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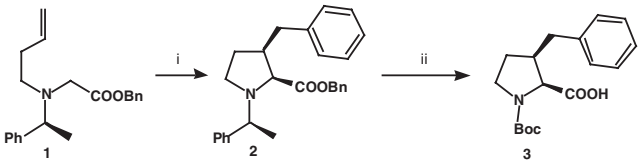
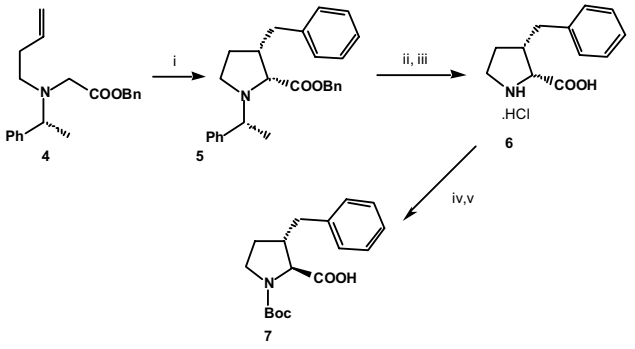


Scheme 1. (i) THF, LDA, −78 °C, $ZnBr_2$, −78 °C to rt, then $Pd_2(dba)_3$/P(*o*-Tolyl)$_3$, Ph–I, rt, 50% (ii) H_2, Pd/C, Boc_2O, MeOH, 80%.



Scheme 2. (i) THF, LDA, −78 °C, $ZnBr_2$, −78 °C to rt, then $Pd_2(dba)_3$/P(*o*-Tolyl)$_3$, Ph–I, rt, 50%, (ii) H_2, Pd/C, MeOH, (iii) 1M HCl, 90%, (iv) H_2O, sealed tube, 200 °C, (v) Boc_2O, K_2CO_3, H_2O/dioxane (1:1).

in 80% yield.[17] The synthesis of the *trans*-isomer **7** was performed as described in Scheme 2. After the same reaction sequence starting form the enantiomer **4**, compound **5** was obtained.[17] The hydrogenolysis over palladium charcoal followed by acidification with 1 M HCl led to compound **6**, which was isolated as a white solid.[17] The epimerisation of the α-centre was performed by heating derivative **6** at 200 °C in a sealed tube.[9] No side-product was detected, and a *cis*/*trans* ratio (28/72) was obtained in favour of the thermodynamically more stable *trans* isomer. The value of the *cis*/*trans* ratio is a result of the steric hindrance existing between both substituents of the pyrrolidine ring. Indeed, under the same conditions, complete epimerisation of the α-centre was observed in the case of prolinoleucine (unpublished results).

After Boc-protection, a sequence of recrystallisations (ether/pentane) gave optically pure (2*S*,3*S*)-3-benzyl-1-(*tert*-butyloxycarbonyl)-pyrrolidine-2-carboxylic acid **7**. [17]

In conclusion, a short and efficient synthesis of both diastereoisomers of *cis* (2*S*,3*R*)- and *trans* (2*S*,3*S*)-3-benzyl-1-(*tert*-butyloxycarbonyl)-pyrrolidine-2-carboxylic acids has been achieved using the amino-zinc-enolate cyclisation reaction and a cross-coupling reaction with Pd(0). The *cis* isomer was obtained in two steps whereas four steps were required for the *trans* isomer. This strategy is to be applied to other aromatic substituents in order to obtain a library of 3-benzylproline derivatives.

References and notes

1. Quancard, J.; Karoyan, P.; Sagan, S.; Convert, O.; Lavielle, S.; Chassaing, G.; Lequin, O. *Eur. J. Biochem.* **2003**, *270*, 2869, and references cited therein.
2. Ragin, A. D.; Morgan, R. A.; Chmielewski, J. *Chem. Biol.* **2002**, *8*, 943.
3. Quancard, J.; Karoyan, P.; Lequin, O.; Wenger, E.; Aubry, A.; Lavielle, S.; Chassaing, G.; *Tetrahedron Lett.*; **2004**, *45*, 623.
4. Kamenacka, T. M.; Park, Y.-J.; Lin, L. S.; Lanza, T. J.; Hagmann, W. K. *Tetrahedron Lett.* **2001**, *42*, 8571.
5. Pellegrini, N.; Schmitt, M.; Guery, S.; Bourguignon, J.-J. *Tetrahedron Lett.* **2002**, *43*, 3243.
6. (a) Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **1997**, *38*, 85; (b) Lorthiois, E.; Marek, I.; Normant, J. *Tetrahedron Lett*. **1997**, *38*, 39.
7. Knochel, P.; Perea, J. J. A.; Jones, P. *Tetrahedron* **1998**, *54*, 8275.
8. Karoyan, P.; Chassaing, G. *Tetrahedron: Asymmetry* **1997**, *8*, 2025.
9. Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **2002**, *43*, 253.
10. Karoyan, P.; Quancard, J.; Vaissermann, J.; Chassaing, G. *J. Org. Chem.* **2003**, *68*, 2256.
11. Karoyan, P.; Chassaing, G. *Tetrahedron Lett.* **2002**, *43*, 1221.
12. Negishi, E. *Acc. Chem. Res.* **1982**, *15*, 340.
13. Lavielle, S.; Brunissen, A.; Carruette, A.; Garret, C.; Chassaing, G. *Eur. J. Pharm.* **1994**, *258*, 273.
14. Moss, W. O.; Jones, A. C.; Wisedale, R.; Mahon, M. F.; Molloy, K. C.; Bradbury, R. H.; Hales, N. J.; Gallagher, T. *J. Chem. Soc., Perkin Trans. 1* **1992**, *20*, 2615.
15. Both enantiomers are commercially available from Senn Chemicals AG, Switzerland.
16. Dexter, C. S.; Jackson, R. F. W. *J. Chem. Soc., Chem. Commun.* **1998**, 75.
17. (2*S*,3*R*)-3-benzyl-1(-1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid benzyl ester **2**. LDA (2.5 mL, 5 mmol) was added to a solution of amine **1** (5 mmol) in dry THF (10 mL) at −78 °C followed by $ZnBr_2$ (1 M, 15 mL). The mixture was allowed to warm up slowly to rt and stirred for 4 h. Iodobenzene (6.5 mmol), $Pd(dba)_2$ (0.162 mmol) and P(*o*-Tolyl)$_3$ (0.65 mmol) were then successively added and the mixture was stirred for 30 min. Et_2O was added and the organic layer was washed with NH_4Cl, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by flash chromatography (cyclohexane/ethyl acetate, 97:3) to give a yellow oil (50%). $[\alpha]_D^{20}$ −44.5° (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 7.35–7.04, (m, 15H), 5.17–5.02 (AB, 2H), 3.71 (q, 1H, $^3J = 6.8$ Hz), 3.50 (d, 1H, $^3J = 8.0$ Hz), 3.10–3.02 (m, 1H), 2.92–2.82 (m, 1H), 2.80–2.73 (m, 1H), 2.66–2.56 (m, 1H), 2.27–2.18 (m, 1H), 1.81–1.67 (m, 2H), 1.33 (d, 3H, $^3J = 6.8$ Hz). ^{13}C NMR (68.5 MHz, $CDCl_3$) δ: 173.2, 144.5, 140.4, 135.8, 128.7, 128.6, 128.5, 128.3, 127.4, 127.0, 126.0, 66.6, 65.9, 61.6, 50.1, 43.8, 37.0, 29.6, 22.8. Anal. Calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.04; H, 7.41; N, 3.66.
(2*S*,3*R*)-3-benzyl-1-(*tert*-butyloxycarbonyl)-pyrrolidine-2-carboxylic acid 3: mp: 103–105 °C, $[\alpha]_D^{20}$ 14° (*c* 1, $CHCl_3$); ^{1}H NMR (250 MHz, $CDCl_3$) δ: 9.33 (br s, 1H), 7.31–7.15 (m, 5H), 4.43 and 4.35 (2d, Boc *cis*/*trans* isomerisation, 1H, $^3J = 8.0$ and 8.3 Hz), 3.76–3.55 (m, 1H), 3.33–3.17 (m, 1H), 3.14–2.99 (m, 1H), 2.75–2.50 (m, 1H), 2.45–2.36 (m, 1H), 1.92–1.71 (m, 2H), 1.46–1.43 (2s, Boc *cis*/*trans* isomerisation, 9H). ^{13}C NMR (68.5 MHz, $CDCl_3$): δ 177.5, 176.4, 154.8, 153.9, 139.8, 139.5, 128.7, 128.5, 126.4, 80.4, 62.6, 62.2, 46.1, 45.7, 44.3, 43.5, 36.3, 29.6, 28.8, 28.3 Anal. Calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.74; H, 7.70; N, 4.75.

(2*R*,3*S*)-3-benzyl-1(-1-phenyl-ethyl)-pyrrolidine-2-carboxylic acid benzyl ester **5**. Same protocol starting from amine **4** yielding a yellow oil. $[\alpha]_D^{20}$ 44.3° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ: 7.35–7.04, (m, 15H), 5.17–5.02 (AB, 2H), 3.71 (q, 1H, $^3J = 6.8$ Hz), 3.50 (d, 1H, $^3J = 8$ Hz), 3.10–3.02 (m, 1H), 2.92–2.82 (m, 1H), 2.80–2.73 (m, 1H), 2.66–2.56 (m, 1H), 2.27–2.18 (m, 1H), 1.81–1.67 (m, 2H), 1.33 (d, 3H, $^3J = 6.8$ Hz). ^{13}C NMR (68.5 MHz, $CDCl_3$) δ: 173.2, 144.5, 140.4, 135.8, 128.7, 128.6, 128.5, 128.3, 127.4, 127.0, 126.0, 66.6, 65.9, 61.6, 50.1, 43.8, 37.0, 29.6, 22.8. Anal. Calcd for $C_{27}H_{29}NO_2$: C, 81.17; H, 7.32; N, 3.51. Found: C, 81.12; H, 7.30; N, 3.56.

(2*R*,3*S*)-3-benzyl-pyrrolidine-2-carboxylic acid hydrochloride **6**. White powder after washing with CH_2Cl_2. mp: 180–183 °C, $[\alpha]_D^{20}$ 12.7° (*c* 1, MeOH); ^1H NMR (250 MHz, D_2O) δ: 7.38–7.27, (m, 5H), 4.44 (d, 1H, $^3J = 7.1$ Hz), 3.62–3.53 (m, 1H), 3.39–3.28 (m, 1H), 3.01–2.91 (m, 2H), 2.52–2.41 (m, 1H), 2.08–1.95 (m, 1H), 1.88–1.74 (m, 1H). ^{13}C NMR (68.5 MHz, D_2O) δ: 171.0, 139.5, 129.3, 129.1, 127.1, 63.4, 44.8, 42.2, 34.6, 28.5.

(2*S*,3*S*)-3-benzyl-1-(*tert*-butyloxycarbonyl)-pyrrolidine-2-carboxylic acid **7**: mp: 90–92 °C, $[\alpha]_D^{20}$ −34.9° (*c* 1, $CHCl_3$); ^1H NMR (250 MHz, $CDCl_3$) δ: 9.65 (br s, 1H), 7.31–7.17 (m, 5H), 4.09 and 3.97 (2d, Boc *cis*–*trans* isomerisation, 1H, $^3J = 4.3$ and 4.6 Hz), 3.67–3.32 (m, 2H), 3.03–2.94 (m, 1H), 2.80–2.52 (m, 2H), 2.01–1.88 (m, 1H), 1.73–1.55 (m, 1H), 1.48–1.43 (2s, Boc *cis*/*trans* isomerisation, 9H). ^{13}C NMR (68.5 MHz, $CDCl_3$) δ: 178.6, 176.3, 155.6, 154.0, 138.9, 129.0, 128.6, 126.5, 81.0, 80.5, 64.0, 45.9, 45.8, 45.4, 44.0, 38.9, 29.2, 29.0, 28.4, 28.3 Anal. calcd for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.89; H, 7.49; N, 4.74.