A catalytic asymmetric synthesis of 5,5-dimethylproline

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Received 8 April 2005; accepted 2 May 2005

Abstract—The methyl ester derivative of commercially available N-acetyl-allylglycine readily undergoes cross-metathesis with 2-methylbut-2-ene and ruthenium–alkylidene catalyst to afford the prenylglycine derivative. Acid-catalysed cyclisation then affords 5,5-dimethylproline in near quantitative yield and enantioselectivity.

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1. Introduction

In folded proteins only 0.03% of Xaa\textsubscript{i−1}-nonPro\textsubscript{i} bonds are in the cis-conformation.\(^1\) The inclusion of the cyclic amino acid proline 1, however, increases the prevalence of cis-configured Xaa\textsubscript{i−1}-Pro\textsubscript{i} bonds to 5.2%.\(^2\) Despite its low occurrence, the cis-peptide bond is an important structural feature in a multitude of naturally occurring peptides and proteins where it can induce a turn in the peptide backbone, decrease intermolecular aggregation and ultimately influence the protein folding and stability.\(^3\) Attempts to constrain peptide bonds into the cis-conformation have involved replacement of constituent proline residues with nonproteinaceous analogues. For example, reversible pseudoproline (ΨPro) residues 2 derived from cysteine, serine and threonine have been used to increase the percentage of Xaa\textsubscript{i−1}-ΨPro\textsubscript{i} bonds in the cis-conformation (Fig. 1).\(^4\) Although the pseudoproline derivatives possess varying stability, their acid sensitivity does not facilitate long term incorporation into peptides.\(^5\) A structurally similar analogue, 5,5-dimethylproline (dmP) 3, locks the imidic Xaa\textsubscript{i−1}-dmP\textsubscript{i} bond exclusively in the cis-conformation.\(^5,6\) The irreversible formation, stability and conformational properties of this nonproteinaceous amino acid render it useful in peptidimimetic studies. For example, replacement of a proline residue with 5,5-dimethylproline in ribonuclease A was recently shown to accelerate protein folding and enhance conformational stability.\(^7\) To date, nontrivial syntheses of this unnatural chiral amino acid have limited its use in peptidomimetics. Current routes involve the formation of the racemate of 3 followed by chemical resolution.\(^5,6,8\) Herein, we report a convenient catalytic asymmetric synthesis of 5,5-dimethylproline 3 from commercially available starting materials.

2. Results and discussion

Our interest in asymmetric hydrogenation firstly led us to investigate the synthesis of a prenylglycine derivative 4 as a precursor to 5,5-dimethylproline 3. Rh(I)–Et–DuPHOS catalysed hydrogenation of dienamide precursor 5 proceeded in a highly regioselective and stereoselective manner (>99% ee) to afford the prenylglycine derivative 4 in excellent yield (98%). Acid-catalysed hydrolysis and cyclisation of amido ester 4 gave 5,5-dimethylproline hydrochloride 6 in a single step (Scheme 1). A minor by-product, alcohol 7, was readily removed via chromatography to give 5,5-dimethylproline 3 in 60% yield. No epimerisation was observed and the enantiomeric excess was determined to be 98% ee by specific rotation determination.

Although asymmetric hydrogenation enables expedient and equal access to both isomers of 4, and hence...
Metathesis of the N-acetyl-protected allylglycine methyl ester 8a was complete after 4 h, however reaction of the corresponding free carboxylic acid derivative 8b proceeded at a slower rate (3 days for completion). Complete conversion of 8b to 4b was achieved in 12 h using 2-methylbut-2-ene. Similarly, cross-metathesis of N-Boc-protected allylglycine methyl ester 8c proceeded smoothly to give the prenylglucose derivative 4c in quantitative yield after 5 h. Interestingly, cross-metathesis of the free acid 8d with isobutylene failed to go to completion even after 3 days (58% conversion). The use of 2-methylbut-2-ene, however led to 4d with 95% conversion in 12 h. In our experiments, the generation of the prenyl group via cross-metathesis was found to be more expedient when the potential for Ru–methylidene intermediate formation was reduced. Hence, the use of 2-methylbut-2-ene favours the catalytic cycling through the more stable ruthenium ethylidene species. Attempts to cross-metathesis the hydrochloride salt of allylglycine with isobutylene and 2-methylbut-2-ene were unsuccessful and gave only poor conversions (<25%) to the desired prenylglycine derivative.

Interestingly, exposure of Boc-protected prenylglycine methyl ester 4c to the same cyclisation conditions failed to yield the desired proline analogue 6 and gave only a mixture of prenylglycine hydrochloride and alcohol 7. This result suggests that the acid-catalysed transformation of 4 into 6 follows a mechanism involving initial amide protonation followed by cyclisation and hydrolysis of the N-acetyl protecting group.

3. Conclusion

In conclusion, we have developed an expeditious procedure for the synthesis of enantiomerically pure 5,5-dimethylproline 3 from commercially available starting materials. A ruthenium-catalysed cross-metathesis reaction of N-acetyl-protected allylglycine 8b, or its methyl ester 8a, with isobutylene or 2-methylbut-2-ene, followed by an acid catalysed cyclisation of the resultant chiral prenylglycine analogues afforded the cyclic amino acid 3 in 90% yield and 98% ee.

Scheme 1. Asymmetric hydrogenation route to pseudoproline 6.
4. Experimental

4.1. General experimental methods

Melting points were determined using a hot-stage melting point apparatus and are uncorrected. Infrared spectra were recorded on a FT-IR spectrophotometer as potassium bromide disks of solids (KBr) or as thin films of liquids (neat) between sodium chloride plates. Nuclear magnetic resonance spectra (1H and 13C NMR) were recorded on either 300 or 400 MHz spectrometers. Low resolution electrospray ionisation (ESI) were recorded on a QMS-quadrupole mass spectrometer. Accurate mass measurements were obtained at high resolution with a FTMS and a 4.7 T superconducting magnet. The instrument was externally calibrated with FC5311. Analytical thin-layer chromatography (TLC) was performed on plastic slides coated with silica gel (Polygram SIL g/uv254) and preparative chromatography was performed on C18 reverse phase silica gel. Flash chromatography was performed using standard procedures. Chloroform used for optical rotation experiments were measured with a polarimeter (in a cell length of 1 dm) at a wavelength of 589 nm (sodium D line) at a temperature of 22 °C.

4.2. Preparation of dienamide

4.2.1. (2Z)-Methyl 2N-acetamidino-5-methylhexa-2,4-dienoate 5. Dienamide 5 was prepared according to modified literature procedures. Tetramethylguanidine (7.0 mL, 55.8 mmol) was added to a solution of methyl 2N-acetamido-2-(dimethoxyphosphinyl)acetaet (10.08 g, 42.2 mmol) in distilled tetrahydrofuran (100 mL) at −78 °C. After 15 min, 3-methyl-2-butenal (5.0 mL, 51.8 mmol) was added and the mixture stirred for 2 h at −78 °C. The mixture was warmed to 25 °C using a warm water bath and stirred at this temperature for an additional 14 h. The reaction mixture was then diluted with dichloromethane (150 mL) and washed with dilute hydrochloric acid solution (1 M, 2 × 100 mL), copper sulfate solution (1 M, 2 × 100 mL), saturated sodium bicarbonate solution (2 × 100 mL) and saturated sodium chloride solution (1 × 100 mL). The organic layer was dried over MgSO4 and evaporated under reduced pressure to give an off-white solid (7.50 g). Purification by flash chromatography (SiO2, dichloromethane–ethyl acetate–light petroleum, 2:2:1) gave dienoate 5 (6.10 g, 73%) as a pale brown solid, mp 115–116 °C. tR = 6.3 min (GC column 30QC5/BPX5, 150 °C for 1 min, 10 °C min−1 to 280 °C for 6 min) vmax (neat): 3258, 3099, 2956, 1729, 1663, 1610, 1560, 1522, 1440, 1374, 1338, 1286, 1255, 1208, 1156, 1123, 1041W, 1016, 687, 896W, 868, 768, 716, 658, 603, 581, 603, 561W cm−1. 1H NMR (400 MHz, CDCl3): δ 1.89 (s, 6H, (CH3)2), 2.13 (s, 3H, CH3CO), 3.77 (s, 3H, OCH3), 3.95 (d, J 11.8 Hz, 1H, H4), 6.97 (br s, 1H, NH), 7.24 (br d, J 11.8 Hz, 1H, H3). 13C NMR (100 MHz, CDCl3): δ 19.3, 23.6 ((CH3)2), 27.1 (CH3CO), 52.4 (OCH3), 120.8 (C4), 121.1 (C5), 130.5 (C3), 147.2 (C2), 166.0, 168.0 (Cl, CONH), HRMS (ESI†, MeOH): m/z calecd for C10H15N2O3Na [M+Na]+ 220.0950. Found 220.0947.

4.3. General asymmetric hydrogenation procedure

In a drybox, a Fischer–Porter tube was charged with catalyst (1–3 mg), deoxygenated solvent (~5 mL) and substrate (28–108 mg). Three vacuum/argon cycles to purge the gas line of any oxygen followed by three vacuum/argon cycles of the vessel were carried out before the tube was pressurised with hydrogen to the specified pressure (psi). The reaction mixture was then stirred at room temperature for the specified period of time. The pressure in the vessel was then released, and the contents evaporated under reduced pressure. The crude product was passed through a short plug of silica (elucent = ethyl acetate) prior to spectroscopic and chromatographic analysis. The hydrogenation experiment is described using the following format: substrate, solvent, catalyst, hydrogen pressure, reaction time, isolated yield, enantiomeric excess (assigned configuration), retention time (GC conditions).

4.3.1. (2S)-Methyl 2N-acetamidino-5-methylhexa-4-enooate 4a. (2Z)-Methyl 2N-acetamidino-5-methylhexa-2,4-dienoate 5 (74.0 mg, 0.38 mmol), methanol (5 mL), [(COD)Rh(S,S)-Et–DuPHOS]OTf (2 mg), 75 psi H2, 2 h, 100% yield, 100% ee (2S)-4a, tR = 24.2 min (GC chiral column QCM-C024, 100 °C for 1 min, 5 °C min−1 to 210 °C for 7 min). [α]22D = +58.2 (c 0.79, CHCl3), mp 46–48 °C. vmax (neat): 3288m, 2955w, 1746s, 1660s, 1538m, 1436m, 1377m, 1274w, 1210w, 1126w, 1030w, 736w cm−1. 1H NMR (300 MHz, CDCl3): δ 1.59 (s, 3H, H6a), 1.69 (d, J 0.9 Hz, 3H, H6b), 2.00 (s, 3H, CH3CO), 2.39–2.60 (m, 2H, H3), 3.72 (s, 3H, OCH3), 4.63 (dt, J 7.9, 5.6 Hz, 1H, H2), 4.99 (t, J 7.5 Hz, 1H, H4), 6.02 (br s, 1H, NH). 13C NMR (100 MHz, CDCl3): δ 18.0, 26.0, ((CH3)2), 23.3 (CH3CO), 30.8 (C3), 52.2,
52.4 (C2, OCH3), 117.6 (C4), 136.6 (C5), 169.8, 172.8 (C1, CONH). HRMS (ESI+, MeOH): m/z calculated for C10H17NO3Na [M+Na]+ 222.1106. Found 222.1105.

4.3.2. 5,5-Dimethylproline 3,5,6,8 Hydrochloric acid (5 mL) was added to enamide 4a (160 mg, 0.80 mmol) and the mixture heated at reflux for 90 min. The reaction mixture was then evaporated under reduced pressure to afford the crude hydrochloride 6 as a dark yellow oil. Purification by preparative reverse phase thin layer chromatography (ethyl acetate-methanol, 1:1) gave 5,5-dimethylproline 3 (68.8 mg, 60%) as a colourless oil. vmax (neat): 3333bs, 2975s, 1737s, 1591w, 1453w, 1382m, 1248m, 1154w, 1125w, 1089s, 1048s, 926w, 880s, 805w, 736w cm⁻¹. 1H NMR (300 MHz, CDCl3): δ 1.45 (s, 3H, CH3), 1.47 (s, 3H, CH3), 1.89 (t, J 7.2 Hz, 2H, H4), 2.16–2.28 (m, 1H, H3a), 2.38–2.50 (m, 1H, H3b), 4.04 (dd, J 9.1, 6.4 Hz, 1H, H2). 13C NMR (100 MHz, CDCl3): δ 28.0 (C2), 28.3 (C4), 38.4 (C3), 60.0 (C2), 67.3 (C5), 171.6 (COOMe, NCOMe). HRMS (ESI+, MeOH): m/z calculated for C7H14NO2 [M+H]+ 144.1025. Found 144.1021. [x]D⁰₂₅ = −49.7 (c 0.75, H2O), 98% ee. Purification by preparative reverse phase thin layer chromatography (ethyl acetate-methanol, 1:1) gave 5,5-dimethylproline 3 (58.9 mg, 90%) as a colourless oil. Spectral data was consistent with that previously reported. [x]D⁰₂₅ = −50.2 (c 1.01, H2O) [lit.5 [x]D⁰₂₅ = −51.2 (c 1, H2O)], 98% ee.

4.4. General metathesis procedure
A Schlenk flask was charged with a catalyst (5–20 mol %), deoxygenated solvent (~5 mL) and substrate (10–60 mg). The reaction mixture was left to stir at 50 °C for a specified period of time. Metathesis reactions were terminated upon exposure to oxygen and volatile species removed under reduced pressure. The crude product was purified by flash chromatography. Metathesis experiments are described using the following format: substrate, solvent, catalyst, reaction time, reaction temperature, percent conversion. Chromatographic purification conditions (isolation yield).

4.4.1. (2S)-Methyl 2-(N-acetylaminopent-4-enoic acid 4a. (2S)-Methyl 2-N-acetylamino-5-methylhex-4-enoate 8a (30.3 mg, 0.18 mmol), dichloromethane (4 mL), second generation Grubbs’ catalyst (7.5 mg, 0.01 mmol, 5 mol %), isobutylene (5 psi), 72 h, 50 °C, 100% conversion. Purification by flash chromatography (SiO2, dichloromethane–light petroleum–ethyl acetate, 1:1:1) furnished prenylglycine derivative 4a (29.9 mg, 85%) as a brown oil. tf = 24.2 min (GC column 30QC5/BPX5, 150 °C for 1 min, 10 °C min⁻¹ to 280 °C for 6 min). [x]D⁰₂₅ = +58.1 (c 1.50, CHCl3). Spectral data was consistent with that previously reported.

4.4.2. (2S)-2-N-Acetylamino-5-methylhex-4-enic acid 4b. Method A: (2S)-2-N-Acetylamino-5-methylhex-4-enic acid 8b (78.0 mg, 0.50 mmol), dichloromethane (7 mL), second generation Grubbs’ catalyst (21.2 mg, 0.02 mmol, 5 mol %), isobutylene (5 psi), 72 h, 50 °C, 74% conversion into 4b.

Method B: (2S)-2-N-Acetylamino-5-methylhex-4-enic acid 8b (78.0 mg, 0.50 mmol), dichloromethane (7 mL), second generation Grubbs’ catalyst (21.2 mg, 0.02 mmol, 5 mol %), 2-methylbut-2-ene (1 mL), 12 h, 50 °C, 100% conversion. Trituration with diethyl ether afforded the prenylglycine derivative 4b as a colourless solid, mp 107–110 °C. vmax (neat): 3421bs, 3324w, 3055m, 2971w, 2932m, 1728s, 1671s, 1526m, 1438m, 1386m, 1266s, 1103w, 910w, 737s, 704m cm⁻¹. 1H NMR (200 MHz, CDCl3): δ 1.55 (s, 3H, H6a), 1.64 (s, 3H, H6b), 1.96 (s, 3H, CH3CO), 2.32–2.58 (m, 2H, H3), 4.51 (q, J 6.2 Hz, 1H, H2), 5.02 (t, J 6.8 Hz, 1H, H4), 6.48 (br d, J 7.3 Hz, 1H, NH), 8.34 (br s, 1H, OH).
13C NMR (100 MHz, CDCl3): δ 18.0, 23.0 ((CH3)2), 25.9 (CH2CO), 30.4 (C3), 52.7 (C2), 118.0 (C4), 136.2 (C5), 171.1, 174.9 (C1, CONH). HRMS (ESI\(^+\), MeOH): m/z calec for C9H13NO3Na [(M+Na\(^+\)] 208.0950. Found 208.0931.

4.4.3. (2S)-Methyl 2-n-tert-butoxycarbonylamino-5-methylhex-4-enoate 4c.\(^{16}\) (2S)-Methyl 2-n-tert-butoxycarbonylamino-pent-4-enoate 8c (182 mg, 0.80 mmol), dichloromethane (7 mL), second generation Grubbs’ catalyst (31.0 mg, 0.04 mmol, 5 mol %), isobutylene (5 psi), 4 h, 50 °C, 100% conversion. The crude product was used in the subsequent acid catalysed cyclisation reaction.

**Method B:** (2S)-2-n-tert-Butoxycarbonylamino-5-methylhex-4-enoic acid 4d.\(^{17}\) **Method A:** (2S)-2-n-tert-Butoxycarbonylamino-pentanoic acid 8d (65.1 mg, 0.30 mmol), dichloromethane (4 mL), second generation Grubbs’ catalyst (13.2 mg, 0.02 mmol, 5 mol %), isobutylene (5 psi), 42 h, 50 °C, 58% conversion into 4d.

**Method B:** (2S)-2-n-tert-Butoxycarbonylamino-pentanoic acid 8d (65.1 mg, 0.30 mmol), dichloromethane (4 mL), second generation Grubbs’ catalyst (13.2 mg, 0.02 mmol, 5 mol %), 2-methylbut-2-ene (1 mL), 12 h, 50 °C, 95% conversion into 4d.

v\(_{\text{max}}\) (neat): 3434, 3057, 2982, 2934, 2857, 1810s, 1750s, 1715s, 1633w, 1499m, 1456w, 1418s, 1396w, 1372s, 1310w, 1266s, 1218s, 1167m, 1120s, 1074s, 952w, 844m, 746m, 704m cm\(^{-1}\). \(^{1}\)H NMR (400 MHz, CDCl3): δ 1.41 (s, 9H, (CH3)), 1.58 (s, 3H, H6a), 1.68 (s, 3H, H6b), 2.34–2.54 (m, 2H, H3), 3.70 (s, 3H, OCH3), 4.29–4.31 (m, 1H, H2), 4.99 (apparent t, J 7.4 Hz, 2H, H4, NH). 13C NMR (100 MHz, CDCl3): δ 17.8 (C6a), 25.9 (C6b), 28.3 ((CH3)2), 31.0 (C5), 52.2 (OCH3), 53.3 (C2), 85.1 (OC(CH3)), 117.7 (C4), 136.2 (C5), 155.3 (CONH), 172.9 (C1). HRMS (ESI\(^+\), MeOH): m/z calec for C13H23NO4Na [(M+Na\(^+\)] 280.1525. Found 280.1520.

Acknowledgements

The authors gratefully acknowledge the financial assistance of the Australian Research Council and the provision of an Australian Postgraduate Research Award (to J.E.).

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