Stereocontrolled synthesis of (2*S**,3*R**,4*R**)-4-hydroxy-3-methylproline using a silicon assisted aza-[2,3]-Wittig sigmatropic rearrangement

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The first racemic synthesis of the non-proteinogenic amino acid (2*S*,3*R*,4*R*)-4-hydroxy-3-methylproline (**1**) has been achieved *via* iodolactonisation of an unnatural amino acid derivative **4**. The relative stereochemistry was derived from an efficient silicon assisted aza-[2,3]-Wittig sigmatropic rearrangement of **2**.

There is an evergrowing interest in the synthesis, pharmacology and conformational properties of non-proteinogenic amino acids. Amongst these, metabolites of proline can exert dramatic conformational changes in peptides,[1] and are valuable components of peptidomimetics.[2] Naturally occurring *trans*-4-hydroxyproline is found in various biologically active peptides.[3] A substituted derivative, (2*S*,3*R*,4*R*)-4-hydroxy-3-methylproline (HyMePro, **1**, Fig. 1), is an unusual proline derived amino acid which is a component of a potent calcium antagonist, the cyclic peptide scytonemin A, isolated from a *Scytonema* sp. (strain U-3-3) (Scytonemataceae).[4] The synthesis of **1** would be difficult to achieve *via* the standard methods used to synthesise 4-hydroxyproline derivatives.[5] In this paper we show that the silicon assisted aza-[2,3]-Wittig sigmatropic rearrangement we have developed,[6] can be used to provide an unnatural amino acid precursor which, by standard manipulations, can give **1** in high yield.

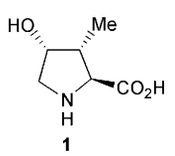

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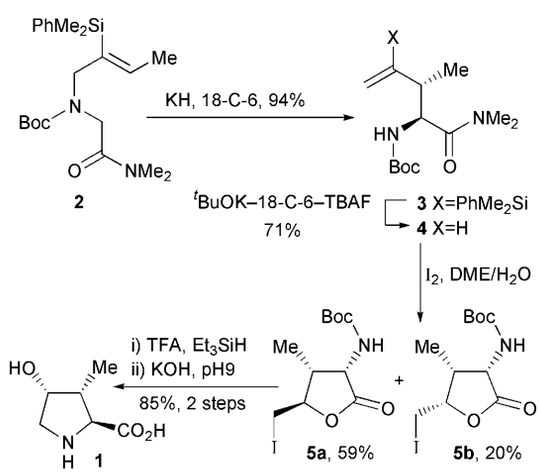
Fig. 1 HyMePro.

The rearrangement precursor **2** was prepared by the alkylation of the potassium anion of *N*-(*tert*-butoxycarbonyl)glycine *N*,*N*-dimethylamide, with (*Z*)-2-(phenyldimethylsilyl)but-2-enyl bromide in 97% yield. Treatment of **2** with KH and 0.5 equivalents of 18-crown-6 at 0 °C with warming to rt induced a [2,3]-sigmatropic rearrangement to furnish **3** in greater than 20 : 1 diastereoselectivity by ^{1}H NMR, in favour of the *anti* diastereoisomer drawn (Scheme 1). The sense of diastereoselectivity is in accord with our transition state model[13] and has been confirmed by single crystal X-ray crystallography.† Protodesilylation was achieved under optimised conditions[7] employing a combination of ^{t}BuOK–18-crown-6–TBAF to give alkene **4** with no loss of diastereoselectivity in a 71% yield. Partial hydrolysis of the amide by ^{t}BuOK may be diminishing this yield.[8] The *syn* diastereoisomer can be prepared in enantiomerically pure form by using Kazmaier's [3,3]-sigmatropic rearrangement of glycine ester enolates and has been manipulated in a similar fashion to give peptides containing the all-*cis* diastereoisomer of **1**.[9]

Iodolactonisation of **4** with I_2 in DME–H_2O gave a 3 : 1 mixture of **5a** : **5b** in 59% and 20% yield respectively (14% starting material). The two diastereoisomers were assigned based upon comparison of the Boc deprotected materials with literature data. Each diastereoisomer was deprotected with TFA–Et_3SiH and their ^{1}H NMR recorded. The C-4 stereochemistry was assigned by analogy to butyrolactones prepared by Yoshida[10] and other data.[11] It is proposed that in this ring system J_{trans} = 0–4.4 Hz and J_{cis} = 7.3–8.5 Hz. The primary amine resulting from deprotection of **5a** possesses $J_{H(2)–H(3)}$ = 8.0 Hz and $J_{H(3)–H(4)}$ = 3.0 Hz, to which we assign *trans* stereochemistry across the C3–C4 bond. The diastereomeric primary amine resulting from deprotection of **5b** possesses $J_{H(2)–H(3)}$ = 7.0 Hz and $J_{H(3)–H(4)}$ = 4.2 Hz, to which we assign *cis* stereochemistry across the C3–C4 bond. These assignments were confirmed by the conversion of **5a** into **1**. We expected to form diastereoisomer **5a** according to the work of Yoshida[10] (transition state **6**, Fig. 2). The alternate diastereoisomer **5b** could be formed due to the transannular stereoelectronically stabilised transition state structure **7** (Fig. 2), similar to those put forward by Ohfune[12] to account for the *cis* selectivity in the lactonisation of 2-aminopent-4-enoic acid derivatives.



Scheme 1

† Crystal data for **3**: $C_{21}H_{34}N_2O_3Si$, M = 390.59, monoclinic, space group: $P2(1)/c$, μ = 0.123 mm^{-1}, R_1 = 0.0407, wR_2 = 0.1140, a = 10.0044(6), b = 21.5554(13), c = 10.6645(7) Å, β = 91.963(1)°, U = 2298.4(2) Å^3, temperature of data collection 150(2) K, Z = 4, 5315 independent reflections (of 12413 measured), R(int) = 0.0370. We thank Dr C. Wilson, University of Nottingham, for this structure determination. CCDC reference number 148999. See http://www.rsc.org/suppdata/p1/b0/b007586h/ for crystallographic files in CIF or other electronic format.

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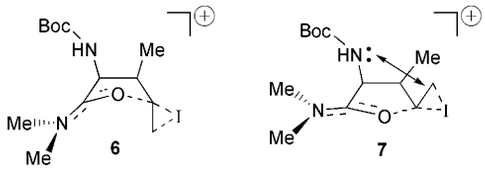

Fig. 2 Transition state models **6** and **7** to account for the formation of **5a** and **5b** respectively.

Deprotection of **5a** followed by treatment with 0.5 M KOH in THF until pH 9[12] and purification by Dowex®-50Wx4-100 ion exchange resin gave racemic HyMePro (**1**) in 85% yield over 2 steps (Scheme 1).‡

The silicon assisted aza-[2,3]-Wittig rearrangement is flexible enough to allow other substituted alkenes and migrating groups in precursors **2**.[6] This methodology can deliver unique allyl glycine derivatives which have the potential to become building blocks for more elaborate amino acids as demonstrated in this paper. Enantioselective variants are currently being investigated.

Experimental

General details

General experimental details are as published.[13]

(*Z*)-2-(Phenyldimethylsilyl)but-2-enyl bromide

To a solution of DIBAL (6.72 mL, 38.0 mmol, 1.1 equiv.) in Et_2O (18 mL) at 0 °C was added, *via* syringe, alkynyl silane **3** (6.0 g, 34 mmol). The mixture was warmed to rt, refluxed for 1 h and then cooled to 0 °C followed by the addition of MeLi (37.6 mL of a 1 M solution in THF, 38.0 mmol, 1.1 equiv.) *via* syringe. The mixture was stirred at rt for 1 h, cooled to 0 °C and added *via* cannula to a stirred suspension of paraformaldehyde (7.97 g, 0.272 mol, 8 equiv.) in Et_2O (18 mL) at 0 °C. After stirring at rt for 14 h, the mixture was poured into ice-cold 1 M HCl (50 mL), the mixture separated and the aqueous phase was extracted with Et_2O. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to give allylic alcohol (*Z*)-2-(phenyldimethylsilyl)but-2-en-1-ol as a colourless clear oil (92%, 6.44 g) which was judged >95% pure by ^{1}H NMR and used directly in the next step. IR ν_{max} (thin film) 3324, 2955, 1620 cm^{-1}; ^{1}H NMR δ 0.45 (6H, s), 1.45 (1H, br s), 1.66 (3H, dt, J = 7.0, 1.2), 4.15 (2H, quintet, J = 1.2), 6.42 (1H, qt, J = 7.0, 1.2), 7.30–7.61 (5H, m); ^{13}C NMR δ −1.4, 17.9, 69.3, 127.9, 128.9, 133.8, 138.2, 139.1, 140.6; MS (CI$^+$) 224 (MNH_4^+); Anal. Calcd. for $C_{12}H_{18}OSi$: C, 69.84; H, 8.74. Found C, 69.81; H, 8.85%. To a solution of PPh_3 (7.61 g, 29.0 mmol, 1.07 equiv.) in CH_2Cl_2 (25 mL) at −20 °C was added, *via* syringe, Br_2 (1.49 mL, 29.0 mmol, 1.07 equiv.). After 20 min Et_3N (2.93 g, 29.0 mmol, 1.07 equiv.) was added and after a further 20 min, (*Z*)-2-(phenyldimethylsilyl)but-2-en-1-ol (5.39 g, 27.1 mmol) was added also *via* syringe. After stirring for 10 min the mixture was warmed to rt and adsorbed onto silica. Silica gel filtration afforded allylic bromide (*Z*)-2-(phenyldimethylsilyl)but-2-enyl bromide as a colourless clear oil (6.53 g, 90%). IR ν_{max} (thin film) 2957, 1606 cm^{-1}; ^{1}H NMR δ 0.50 (6H, s), 1.62 (3H, d, J = 7.0), 4.15 (2H, m), 6.58 (1H, q, J = 7.0), 7.30–7.61 (5H, m); ^{13}C NMR δ −1.2, 17.7, 33.2, 127.7, 129.0, 134.2, 139.6, 139.9, 140.8; MS (EI$^+$) 270 (M^+, ^{81}Br); HRMS $C_{12}H_{17}BrSi$ calcd 270.0262, found 270.0259.

(*Z*)-*N*,*N*-Dimethyl-{*N*-*tert*-butoxycarbonyl-*N*-[2-(phenyldimethylsilyl)but-2-enyl]amino}acetamide (2)

A solution of *N*-(*tert*-butoxycarbonyl)glycine *N*,*N*-dimethylamide (1.51 g, 7.47 mmol)) in THF (5 mL + 5 mL wash) was added, *via* cannula, to a stirred suspension of KH (1.19 g, 8.94 mmol, 1.2 equiv. of a 35% dispersion in mineral oil, washed twice with hexane) in THF (15 mL) at 0 °C. After stirring for 1 h, (*Z*)-2-(phenyldimethylsilyl)but-2-enyl bromide (2.0 g, 7.47 mmol, 1.0 equiv.) in THF (5 mL + 5 mL wash) was added and the reaction stirred for a further 1 h followed by 14 h at rt. Saturated aq. $NaHCO_3$ was added, and the THF removed *in vacuo*. Saturated aq. $NaHCO_3$ was added, extracted with Et_2O, dried ($MgSO_4$) and concentrated *in vacuo* to give **2** as an off white powder (2.81 g, 97%), no further purification was necessary. Mp 71–73 °C; IR ν_{max} (thin film) 2973, 1698, 1666 cm^{-1}; ^{1}H NMR δ 0.27 (6H, s), 1.29 (9H, s), 1.54 (3H, br d, J = 6.1), 2.73 (3H, s), 2.75 (3H, s), 3.49–3.97 (4H, m), 5.92 (1H, q, J = 7.0), 7.15–7.21 (3H, m), 7.35–7.40 (2H, m); ^{13}C NMR δ −1.5, 17.8, 28.3, 35.6, 36.1, 46.3, 54.5, 79.9, 127.8, 128.8, 133.6, 133.9, 136.7, 139.5, 164.2, 172.1; MS (EI$^+$) 390 (M^+); Anal. Calcd. for $C_{21}H_{34}N_2O_3Si$: C, 64.58; H, 8.78; N, 7.18. Found C, 64.28; H, 8.79; N, 6.98%.

(2*S**,3*R**)-*N*,*N*-Dimethyl-2-(*tert*-butoxycarbonylamino)-3-methyl-4-(phenyldimethylsilyl)pent-4-enamide (3)

Precursor **2** (70 mg, 0.179 mmol) in THF (0.3 mL + 0.2 mL wash) and then 18-crown-6 (18-C-6) (23 mg, 0.089 mmol, 0.5 equiv.) were added to a stirred suspension of KH (50 mg, 0.43 mmol, 2.4 equiv. of a 35% dispersion in mineral oil washed twice with hexane) in THF (0.4 mL) at 0 °C. After 10 min the reaction was warmed to rt for 2 h before the reaction was cooled to 0 °C and quenched with pH 7 buffer (2 mL). The mixture was then extracted with Et_2O, the combined organics washed with H_2O, brine, dried ($MgSO_4$) and concentrated *in vacuo* to give a clear oil which was purified by flash-column chromatography (30% EtOAc–light petroleum) to give **3** (66 mg, 94%) as a clear oil which crystallised on standing as an inseparable ratio of diastereoisomers (>20 : 1 by ^{1}H NMR). Mp 52–54 °C; IR ν_{max} (thin film) 3299, 2966, 1705, 1641 cm^{-1}; ^{1}H NMR δ 0.34 (3H, s), 0.36 (3H, s), 0.84 (3H, d, J = 7.0), 1.33 (9H, s), 2.57 (1H, br dq, J = 7.0), 2.85 (3H, s), 2.97 (3H, s), 4.49 (1H, dd, J = 9.5, 9.2), 4.69 (1H, br d, J = 9.2), 5.50 (1H, d, J = 3.4), 5.78 (1H, d, J = 1.5), 7.27–7.29 (3H, m), 7.46–7.49 (2H, m); ^{13}C NMR δ −2.5, −2.4, 18.4, 28.4, 35.7, 37.5, 42.9, 52.7, 60.4, 79.2, 127.9, 128.1, 129.2, 134.2, 137.8, 151.3, 155.1, 172.5; MS (CI$^+$) 391 (MH^+). Anal. Calcd. for $C_{21}H_{34}N_2O_3Si$: C, 64.58; H, 8.78; N, 7.18. Found C, 64.13; H, 8.97; N, 7.21%.

(2*S**,3*R**)-*N*,*N*-Dimethyl-2-(*tert*-butoxycarbonylamino)-3-methylpent-4-enamide (4)

To a stirred solution of **3** (45 mg, 0.12 mmol) and 18-C-6 (43 mg, 0.16 mmol, 1.4 equiv.) in THF (0.25 mL) was added ^{t}BuOK (18.2 mg, 0.16 mmol, 1.4 equiv.). After 2 h at rt the mixture was cooled to 0 °C and quenched by the addition of NH_4Cl (0.3 mL). The aqueous phase was extracted with Et_2O; the combined organics washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was placed under nitrogen and treated with TBAF (0.6 mL of a 1 M solution, 0.6 mmol, 5 equiv.). After stirring for 24 h the reaction mixture was diluted with EtOAc, washed with H_2O, brine, dried ($MgSO_4$) and concentrated *in vacuo*. Purification by column chromatography (30% EtOAc–hexane) gave **4** (21 mg, 71%) as a crystalline solid, mp 43–45 °C; IR ν_{max} (thin film) 3304, 2974, 1704, 1642, 1252 cm^{-1}; ^{1}H NMR δ 1.06 (3H, d, J = 6.8), 1.42 (9H, s), 2.51–2.53 (1H, br m), 2.97 (3H, s), 3.12 (3H, s), 4.56 (1H, dd, J = 9.2, 6.4), 5.04 (1H, dt, J = 6.1, 1.2), 5.10 (1H, br s), 5.26 (1H br d, J = 8.8), 5.68 (1H, ddd, J = 7.6, 2.1, 1.2); ^{13}C NMR δ −16.5, 28.3, 35.7, 37.4, 41.1, 53.9, 79.4, 116.2, 138.6, 155.7, 171.5; MS (FAB$^+$) 257 (MH^+). Anal. Calcd. for $C_{13}H_{24}N_2O_3$: C, 60.89; H, 9.44; N, 10.93. Found C, 60.83; H, 9.75; N, 10.43%.

‡ The spectral data of **1** were identical to those reported for the natural product (ref. 4).

(2*S,3*R**,4*RS**)-2-(*tert*-Butoxycarbonylamino)-3-methyl-4-(iodomethyl)-γ-butyrolactone (5a and 5b)**

To a stirred solution of **4** (70 mg, 0.27 mmol) in DME–H_2O, 1:1 (1.0 ml), was added I_2 (76 mg, 0.3 mmol, 1.1 equiv.) at rt. After stirring for 2 h the mixture was diluted with Et_2O (2 mL) and washed with satd. aq. $Na_2S_2O_3$, $NaHCO_3$ and brine. The organics were dried ($MgSO_4$) and concentrated *in vacuo.* Purification by column chromatography (20% ethyl acetate–hexane) gave, in order of elution the 4*S** isomer **5b** (19 mg, 20%) as a white powder, mp 92–94 °C, IR ν_{max} (thin film) 3358, 2976, 1779, 1692, 1530 cm^{-1}; ^1H NMR δ 0.85 (3H, d, J = 7.1), 1.47 (9H, s), 3.09 (1H, t, J = 9.8), 3.14–3.15 (1H, br m), 3.44 (1H, dd, J = 9.9, 5.8), 4.63 (1H, br t, J = 5.7), 4.65–4.68 (1H, br m), 5.03 (1H, br s); ^{13}C NMR δ 6.5, 28.6, 37.9, 56.6, 80.2, 81.2; MS (FAB^+ or EI^+) unsatisfactory (see MS for deprotected **5b**); followed by the 4*R** isomer **5a** (57 mg, 59%) as a white powder, mp 101–103 °C; IR ν_{max} (thin film) 3334, 2976, 1783, 1693, 1518 cm^{-1}; ^1H NMR δ 1.05 (3H, d, J = 7.2), 1.46 (9H, s), 2.91 (1H, br m), 3.31 (1H, dd, J = 10.5, 8.2), 3.38 (1H, dd, J = 10.6, 5.2), 4.35–4.37 (1H, br m), 4.58–4.62 (1H, br m), 4.95 (1H, br s); ^{13}C NMR δ 4.3, 14.0, 28.3, 37.6, 52.8, 80.9, 84.8, 155.6, 174.3; MS (FAB^+) 356 (MH^+); HRMS $C_{11}H_{19}NO_4I$ calcd. 356.0359, found 356.0351; and **4** (10 mg, 14%).

Assignment of C-4 stereochemistry

The two diastereoisomers of **5** were Boc deprotected under standard conditions and their ^1H NMR spectra recorded.

Iodolactone **5a** (17 mg, 0.048 mmol) in DCM (0.25 mL) and Et_3SiH (1 drop) was treated with TFA (0.007 mL, 0.91 mmol, 1.9 equiv.) at rt. After stirring for 4 h at rt the reaction was diluted with DCM (3 mL) and washed with 1 M NaOH (2 mL). The organics were dried ($MgSO_4$) and concentrated *in vacuo* to give the 4*R** primary amine (10 mg, 82%); IR ν_{max} (thin film) 3379, 2920, 1777 cm^{-1}; ^1H NMR δ 1.14 (3H, d, J = 7.2), 1.58 (2H, s), 2.64 (1H, ddq, J = 7.8, 7.2, 3.0), 3.31 (1H, dd, J = 10.6, 7.3), 3.37 (1H, dd, J = 10.6, 5.2), 3.88 (1H, d, J = 8.0), 4.25 (1H, ddd, J = 7.4, 5.2, 3.0).

Iodolactone **5b** (10 mg, 0.028 mmol) in DCM (0.14 mL) and Et_3SiH (1 drop) was treated with TFA (3 drops) at rt. After stirring for 3 h the reaction was worked up as above to give the 4*S** primary amine (7 mg, 98%); IR ν_{max} (thin film) 3368, 2917, 1778; ^1H NMR δ 0.96 (3H, d, J = 7.2), 2.88 (1H, ddq, J = 7.2, 7.1, 4.5), 3.12 (1H, dd, J = 9.9, 9.8), 3.45 (1H, dd, J = 10.1, 5.8), 3.96 (1H, d, J = 7.0), 4.61 (1H, ddd, J = 9.9, 5.6, 4.3); MS (EI^+) 256 (MH^+), HRMS $C_6H_{11}NO_2I$ calcd. 255.9835, found 255.9926.

(2*S,3*R**,4*R**)-4-Hydroxy-3-methylproline (1)**

Iodolactone **5a** (35 mg, 0.099 mmol) in DCM (0.5 mL) and Et_3SiH (2 drops) was treated with TFA (0.023 mL, 0.295 mmol, 3 equiv.) at rt. After stirring for 2 h the reaction was concentrated *in vacuo* to remove the solvent and any excess TFA. The crude material was subsequently dissolved in THF (0.5 mL) and basified to pH 9 with 0.5 M KOH. After stirring at rt for 4 h the reaction mixture was washed with Et_2O (2 × 1 mL). The aqueous layer was separated and treated with Dowex®-50Wx4-100 ion exchange resin (0.5 × 10 cm column), eluting with 1 M NH_3 to give **1** (12.3 mg, 85%) as a white powder. Mp 259–262 °C (lit.[4] 255–260 °C); ^1H NMR (D_2O) δ 1.24 (3H, d, J = 6.9), 2.32 (1H, ddq, J = 10.8, 6.9, 3.7), 3.36 (1H, dd, J = 12.7, 0.8), 3.54 (1H, dd, J = 12.7, 3.7), 3.76 (1H, d, J = 10.9), 4.44 (1H, t, J = 3.6); ^{13}C NMR (D_2O) δ 11.6, 43.6, 52.8, 64.9, 73.1, 174.5; MS (EI^+) 146 (MH^+), HRMS $C_6H_{12}NO_3$ calcd. 146.0817, found 146.0815.

Acknowledgements

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