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A rapid and convenient synthesis of β-proline

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Abstract—A short, reliable, and cheap synthesis of both enantiomers of β-proline, an efficient organocatalyst and an important building block in medicinal chemistry, has been developed in four steps (overall yield: 72%) from the diasteromeric adducts of methyl itaconate and (*R*)-α-methylbenzylamine. The key step involves the chemoselective reduction of a lactam group in the presence of a benzyl ester.

Pyrrolidine-3 carboxylic acid or β-proline **1** is a constrained β-aminoacid commonly used as a building block for the design of peptides with an enhanced stability toward hydrolysis by proteases.[1] However it is interesting to point out that no designed functional β-peptide has incorporated a β-proline residue, despite the obvious value and wide usage of proline in the conformational control of α-peptides. β-Proline could be exceptionally useful in increasing the structure and function of beta-peptides.[2] These applications have not been exploited significantly to date due to poor synthetic access. β-Proline **1** is also frequently used in the synthesis of ligands of receptors,[3] in compounds of medicinal interest[4] and in fluorescent agents.[5] Additionally, this analogue of proline **2** has recently displayed valuable properties as organocatalyst for *anti*-selective Mannich reactions between unmodified ketones and activated imines.[6] In our continuing interest for the use of 3-substituted pyrrolidines[7] we needed both enantiomers of β-proline **1** (see Fig. 1).

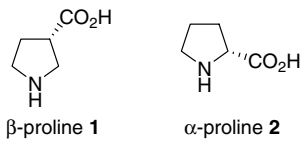

Figure 1. α- and β-prolines.

Few syntheses of the nonproteinogenic amino-acid **1** have been reported during the last decade. In the late nineties, an elegant synthesis starting from aspartic acid, easily transformed into alcohol **3**, used the rearrangement of an aziridinium intermediate.[8] However, the success of this route relied on a chromatography at low temperature (−20 °C). An enantiodivergent synthesis[9] from lactone **4** (produced by a biocatalyzed oxidation of a cyclobutanone) allowed the preparation of both enantiomers (*R*)- and (*S*)-**1**. Fmoc-protected β-proline has been synthesized in seven steps, including an initial decarboxylative step, from L-4-hydroxyproline **5**[10] (Fig. 2).

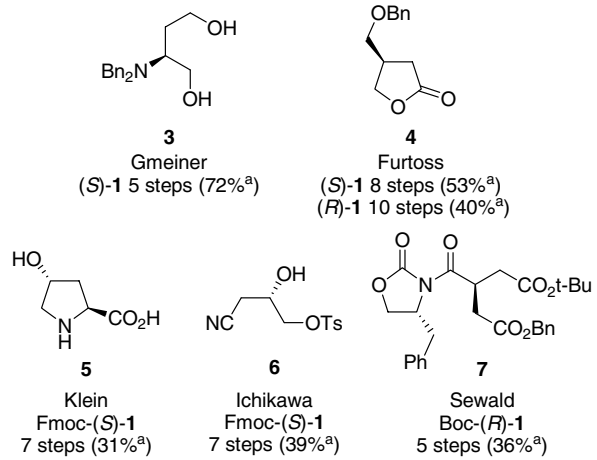

Figure 2. Previously reported precursors to β-proline 1. [a] Overall yield.

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It has also been prepared in seven steps from a (*R*)-glycidol derivative **6**.[11] Boc-β-proline was prepared from the diester **7** in a diastereoselective synthesis using Evans's oxazolidinone.[12]

All these methods used either advanced precursors or poorly available starting materials and required tedious multistep syntheses. Moreover, most of them lead to only one of the enantiomers. β-Proline **1** is commercially available, but its price is prohibitive with uses on large scale.[13] We herein wish to report a convenient, reliable, and cheap access to both enantiomers of β-proline **1** from a single synthesis.

The Michael addition of a primary amine on methyl itaconate **8** followed by a condensation is a powerful method for the rapid generation of pyrrolidin-2-ones.[14,15] When (*R*)-α-methylbenzylamine was used, a mixture of lactams **9** and **10** (d.r. 1.16:1 from ^{1}H NMR of the crude mixture, Scheme 1) was obtained in high yield.[16] These diastereoisomers were easily separated by column chromatography on silica gel.[17] The whole process can be conveniently carried out on a multigram scale.

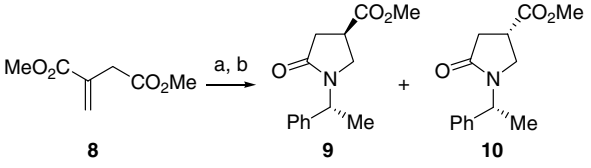
Attempts to reduce efficiently the lactam function of compound **9** or **10** were not satisfying using BH_3·DMS or 9-BBN according to a well-documented method[18] previously applied to closely related structures.[15,19] Such problematic selective reduction of lactam in the presence of an ester group by borane reagents has already been observed.[20] Pyrrolidine **11** was obtained from **10** in moderate 38–47% yields (Scheme 2).

Exhaustive reduction of both carbonyl functionalities by $LiAlH_4$ followed by the selective oxidation of the primary alcohol **12** to acid was next envisaged. Under the conditions described in Scheme 2 (a–e), β-proline **1** was prepared in five steps and an acceptable 59% overall yield from **10**. However, the synthesis required two distinct palladium catalysts for the hydrogenolysis steps, a deprotection–protection step before the oxidation and finally a stoechiometric amount of CrO_3.

In order to develop a shorter, more efficient, and eco-friendly synthesis of β-proline **1**, we decided to reinvestigate the reduction of the lactam ring using a chemoselective thionylation-desulfurization sequence. Thiolactam **13** was obtained from methyl ester **10** using a substoechiometric amount of Lawesson's reagent in toluene[21] (Scheme 3).

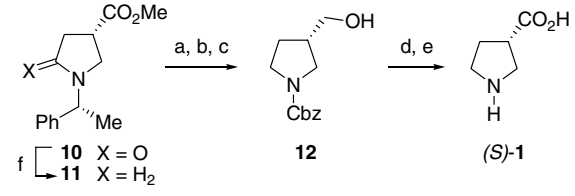
The reduction of the thiocarbonyl moiety of **13** using Raney nickel was next studied.[22] Erratic results obtained from commercially available Raney nickel led us to try different qualities of the reagent. The results are summarized in Table 1.

When using a large excess of Raney nickel from a commercially available source (quality 'A'), no reduction of the model thiolactam **14** occurred in EtOH at room temperature (Table 1, entry 1). Upon refluxing in ethanol, a complex mixture of unidentified products was obtained (entry 2). No reaction was observed in THF at room temperature or at 60 °C (entry 3). When the reagent was carefully washed (water, ethanol then THF) to eliminate any residual hydroxide ions, yields around 54–77% were reached. These yields were improved to 80% when using a freshly opened flask of Ra Ni (entry 5). The reduction of thiolactam **13** led to similar results in EtOH (entry 6) but lower yields in THF (45–31% entries 7 and 8) of the expected pyrrolidine **15**.

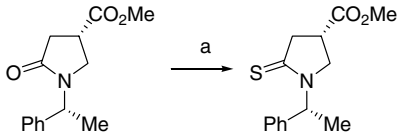


8 **9** **10**

Scheme 1. Reagents and conditions: (a) **8** (20 mmol, 1 equiv), (*R*)-α-methylbenzylamine (1.3 equiv), MeOH, 100 °C, 97%; (b) column chromatography (40–35% for **9** and 37–32% for **10**).



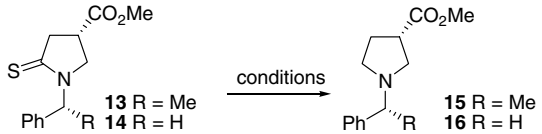
Scheme 2. Reagents and conditions: (a) $LiAlH_4$, THF, reflux, 87%; (b) $Pd(OH)_2$/C, H_2, MeOH, rt; (c) CbzCl, K_2CO_3, THF/H_2O, 0 °C, 76% for 2 steps; (d) Jones oxidation 89%; (e) Pd/C, H_2, MeOH, rt, 24 h, 100%; (f) BH_3·DMS, THF, rt 38–47%.



10 **13**

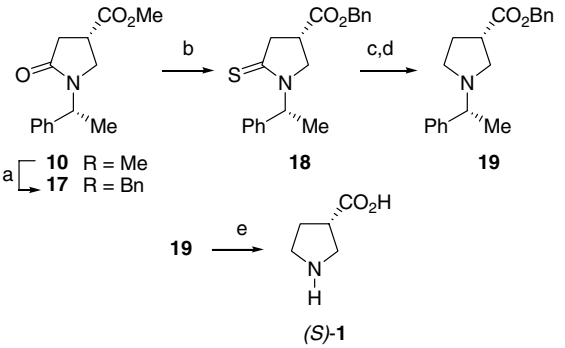
Scheme 3. Reagents and conditions: (a) Lawesson's reagent 0.8 equiv, toluene, 94 °C, 2 h, 98%.

Table 1. Reduction of lactams **13** and **14** using Raney nickel[a]



Entry	R	Conditions[a]	Isolated yield (%)
1	H	A, EtOH, rt	No reaction
2	H	A, EtOH, reflux	Complex mixture
3	H	A, THF, rt or 60 °C	No reaction
4	H	B, THF, rt	54–77
5	H	C, THF, rt	80
6	Me	A, EtOH, reflux	Complex mixture
7	Me	B, THF, reflux	45
8	Me	C, THF, rt	31

[a] Qualities: A = commercially available; B = Raney Ni washed with H_2O, EtOH and THF; C = Raney Ni from a freshly opened flask then washed with H_2O, EtOH and THF.



Scheme 4. Optimized method: (a) BnOH, APTS, toluene, reflux, 18 h, 98%; (b) Lawesson's reagent, toluene, 95 °C, 2 h, 98%; (c) MeI, CH_2Cl_2, rt, 24 h; (d) $NaBH_4$, MeOH, 0 °C, 1 h, 75% yields from **14**; (e) Pd/C, H_2, MeOH, rt, 24 h, 100%.

Previous results associated with the use of a large excess of a pyrophoric reagent, led us to envisage the reduction of the thiolactam via its methyl thioiminium salt.[23] Benzylic ester **17**[24] was prepared from **10** in order to release β-proline **1** after a single hydrogenolysis step in the final optimized route (Scheme 4). Thiolactam **18**[25] reacted with an excess methyl iodide in dichloromethane quantitatively to afford the thioiminium salt intermediate as a colorless foam, which was immediately treated with $NaBH_4$ in methanol to afford amino ester **19** with a reproducible 75% overall yield.[26] Finally, palladium mediated debenzylations released pure (*S*)-β-proline **1** quantitatively.[27] Under similar conditions, the lactam diasteromer **9** afforded (*R*)-**1** with comparable yields for each steps (72% overall yield from **9**).

In conclusion, we have reported the shortest synthesis of β-proline **1** starting from easily available lactams **9** or **10** prepared from the cheap methyl itaconate and (*R*)-α-methylbenzylamine. The key step involved the chemoselective reduction of a methyl thioiminium salt in the presence of a benzylic ester. This high yielding practical synthesis can be carried out on a multigram scale and provides in a single four step procedure both enantiomers of β-proline **1** in 72% overall yield.

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16. *Methyl-5-oxo-1-((R)-1-phenylethyl)pyrrolidine-3-carboxylate* **9** and **10**. To a solution of (*R*)-1-phenylethylamine (1.16 g, 9.57 mmol, 1.3 equiv) in methanol (1.5 mL) was added methyl itaconate **8** (1.16 g, 7.33 mmol). The mixture

was stirred at 80 °C for 1 h then at 100 °C for 16 h. Acidic aqueous workup (HCl 4 M) and extraction with CH_2Cl_2 yielded a colorless oil consisting of a 1.16/1.0 mixture of diastereoisomer **9** and **10** (1.76 g, 97%) which could be easily separated by chromatography over silica gel (pentane/EtOAc, 7:3).

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24. *(S)-Benzyl-5-oxo-1-((R)-1-phenylethyl)pyrrolidine-3-carboxylate* **17**. To a solution of lactam **10** (1.26 g, 5.11 mmol) in toluene (10 mL, 0.5 M) was added APTS (176 mg, 1.02 mmol, 20 mol %) and benzylic alcohol (830 mg, 7.66 mmol, 1.5 equiv). The mixture was heated under reflux for 18 h. After complete conversion (TLC, pentane/EtOAc, 1:1) of starting lactam, the volatile compounds were evaporated under vacuum and the residue was purified by chromatography over silica gel (pentane/EtOAc, 1:1) to give **17** as a colorless oil (1.59 g, 97%). $[\alpha]_D^{20}$ −87 (*c* 1.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.53 (d, 3H, $J = 7.2$ Hz), 2.71 (dd, 1H, $J = 17.1$, 9.6 Hz), 2.80 (dd, 1H, $J = 17.1$, 7.1 Hz), 3.18–3.30 (m, 2H), 3.52–3.59 (m, 1H), 5.08 (AB, 1H, $J = 12.2$ Hz), 5.11 (AB, 1H, $J = 12.2$ Hz), 5.50 (q, 1H, $J = 7.2$ Hz), 7.22–7.39 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 16.6 (CH_3), 34.8 (CH_2), 36.6 (CH), 45.0 (CH_2), 49.6 (CH), 67.5 (CH_2), 127.5 (CH), 128.1 (CH), 128.7 (CH), 128.9 (CH), 129.0 (CH), 129.1 (CH), 135.7 (C), 139.9 (C), 172.4 (C═O), 172.9 (C═O); IR (neat): *ν* 2976, 1733, 1683, 1423, 1269, 1174 cm^{-1}; HRMS calcd for $C_{20}H_{21}NO_3Na$ [MNa^+] 346.1419, found 346.1418.
25. *(S)-Benzyl-1-((R)-1-phenylethyl)-5-thioxopyrrolidine-3-carboxylate* **18**. To a solution of lactam **17** (1.42 g, 4.39 mmol) in toluene (27 mL, 0.16 M) was added Lawesson's reagent (1.42 g, 3.51 mmol, 0.8 equiv). The mixture was heated at 95 °C for 2 h. The volatile compounds were removed under vacuum to afford an oily residue. This crude material was purified by chromatography over silica gel (pentane/EtOAc, 8:2) to yield **18** as a colorless oil (1.46 g, 98%). $[\alpha]_D^{20}$ −315 (*c* 0.7, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.59 (d, 3H, $J = 7.1$ Hz), 3.21–3.29 (m, 1H), 3.38 (d, 1H, $J = 7.8$ Hz), 3.55 (dd, 1H, $J = 11.5$, 5.7 Hz), 3.79 (dd, 1H, $J = 11.5$, 8.6 Hz), 3.90 (d, 1H, $J = 6.3$ Hz), 5.05 (AB, 1H, $J = 12.2$ Hz), 5.09 (AB, 1H, $J = 12.2$ Hz), 6.38 (q, 1H, $J = 7.1$ Hz), 7.22–7.40 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.5 (CH_3), 38.0 (CH), 48.0 (CH_2), 51.7 (CH2), 54.5 (CH), 67.6 (CH_2), 127.5 (CH), 128.5 (CH), 128.6 (CH), 128.9 (CH), 129.1 (CH), 129.2 (CH), 135.5 (C), 138.5(C), 172.2 (C═O), 198.6 (C═S); IR (neat): *ν* 2961, 1718, 1496, 1444, 1312, 1273 cm^{-1}; HRMS calcd for $C_{20}H_{21}NO_2SNa$ [MNa^+] 362.1191, found 362.1182.
26. *(3S)-Benzyl-1-[(R)-1-phenylethyl]pyrrolidine-3-carboxylate* **19**. To a solution of thiolactam **18** (1.03 g, 3.04 mmol) in CH_2Cl_2 (15 mL) was added MeI (1.89 mL, 30.4 mmol., 10 equiv). The mixture was stirred at room temperature for 24 h. Removal of the volatile compounds under vacuum (room temperature bath) yielded a pale yellow foam. EtOH (5 mL) and $NaBH_4$ (1 g, 26.4 mmol) at 0 °C were added cautiously (H_2 evolution). The mixture was stirred for 1 h and quenched with water at 0 °C. The aqueous layer was extracted with CH_2Cl_2, the combined organic layers dried ($MgSO_4$) and evaporated under vacuum. The residue was purified by chromatography over silica gel (pentane/EtOAc, 8:2) to yield **19** as a colorless oil (705 mg, 75%). $[\alpha]_D^{20}$ −47 (*c* 2.5, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.42 (d, 3H, $J = 6.6$ Hz), 2.22 (m, 2H), 2.45 (dd, 1H, $J = 16.2$, 7.9 Hz), 2.62 (dd, 1H, $J = 9.1$, 7.7 Hz), 2.70 (t, 1H, $J = 9.1$ Hz), 2.85 (dd, 1H, $J = 13.1$, 6.5 Hz), 3.07 (td, 1H, $J = 16.2$, 8.0 Hz), 3.29 (dd, 1H, $J = 13.1$, 6.5 Hz), 5.11 (AB, 1H, $J = 12.4$ Hz), 5.16 (AB, 1H, $J = 12.4$ Hz), 7.21–7.41 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.5 (CH_3), 28.0 (CH_2), 42.5 (CH), 52.7 (CH_2), 56.2 (CH_2), 65.8 (CH), 66.8 (CH_2), 127.4 (CH), 127.6 (CH), 128.5 (CH), 128.6 (CH), 128.8 (CH), 129.0 (CH), 136.5 (C), 145.7 (C), 175.3 (C═O); IR (neat): *ν* 2972, 2787, 1731, 1453, 1164 cm^{-1}; HRMS calcd for $C_{20}H_{24}NO_2$ [MH^+] 310.1807, found 310.1820.
27. *(S)-β-Proline* **1.** To a solution of pyrrolidine **19** (375 mg, 1.27 mmol) in MeOH (10 mL) was added Pd/C (10% w/w, 134 mg, 10% mol). The reaction was stirred under a hydrogen atmosphere (balloon) for 18 h. Filtration over Celite (MeOH, CH_2Cl_2) and evaporation yielded colorless solid **1** (147 mg, 100%).