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Efficient enantioconvergent synthesis of (*S*)-α-benzyl-α-methyl-β-alanine from (*R*)- and (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid

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Abstract—An efficient synthesis of (*S*)-α-benzyl-α-methyl-β-alanine in 59% overall yield from benzaldehyde and methyl cyanoacetate has been developed. Enantioconvergent approaches to the synthesis of the target α,α-disubstituted β-amino acid from both enantiomers of previously resolved 2-cyano-2-methyl-3-phenylpropanoic acid constitute the key steps in the proposed methodology. The use of inexpensive and readily available reagents and the simplicity of the experimental procedures make the present protocol synthetically attractive and of great potential for scale up.

1. Introduction

The synthesis of enantiopure β-amino acids has long been of interest,[1] partly due to their presence in a number of biologically active compounds[2] (antibiotics, antitumoural agents, enzyme inhibitors, etc.) and their use as intermediates in the synthesis of β-lactam antibiotics. A currently active area of research is the conformational study of oligomers of β-amino acids, which are also known as β-peptides. It has been reported that short-chain β-peptides fold into turns, helices, and sheet-like structures[3] analogous to the secondary structures of proteins. Moreover, β-peptides are chemically stable and resistant to enzymatic degradation,[3g,4] suggesting that they might provide an attractive tool for the construction of peptidomimetics. These compounds are therefore intriguing candidates for the development of novel drugs.[5]

Structural investigations have recently been carried out with β-peptides constituted by achiral α,α-disubstituted β-amino acids and, as predicted, these oligomers provide exciting new secondary structures.[6] In order to be able to identify structurally other β-peptides containing such residues and to establish the handness of secondary structures they may form, it is important to have access to procedures that provide homochiral α,α-disubstituted β-amino acids. Preparation of this kind of β-amino acid in its enantiomerically pure form has already been extensively reviewed by Seebach.[7] Numerous methodologies have been described for the synthesis of such systems and each approach has its own advantages and limitations. Today the development of an efficient process that is suitable for large-scale preparations, which as well as being easy to operate, practical and inexpensive, remains a significant challenge.

In the preceding paper,[8] we reported an efficient, large scale laboratory preparation of enantiomerically pure α,α-disubstituted α-amino acid (*S*)-methylphenylalanine from benzaldehyde and methyl cyanoacetate. The synthetic methodology described involves the synthesis and resolution of racemic 2-cyano-2-methyl-3-phenylpropanoic acid and the subsequent transformation of each isolated enantiomer via independent pathways into the enantiomerically pure target amino acid. The simplicity of the experimental procedure and its use of inexpensive and readily available reagents make this methodology interesting from an economic point of view.

We envisioned that (*R*)- and (*S*)-α,α-disubstituted α-cyanoacetic acids would also act as precursors for chiral α,α-disubstituted β-amino acids of determinate configuration in enantiomerically pure form if we were

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able to develop efficient enantioconvergent syntheses using both enantiomers of the cyanoacetic acid as starting materials. Such an approach would be possible if both the cyano and the acid functional groups in the starting compound could be independently transformed into the carboxylic and the aminomethyl groups of the target α,α-disubstituted-β-amino acid (Fig. 1).

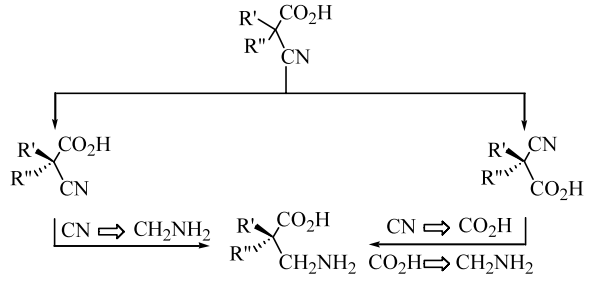


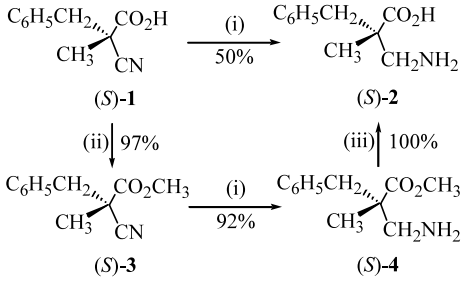
Figure 1. Enantioconvergent approach to the synthesis of (*R*)- or (*S*)-α,α-disubstituted-β-amino acids from both enantiomers of a chiral α,α-dialkylcyanoacetate

As a model for establishing the methodology, the enantioconvergent synthesis of (*S*)-α-benzyl-α-methyl-β-alanine from (*R*)- and (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid was selected.

2. Results and discussion

Racemic 2-cyano-2-methyl-3-phenylpropanoic acid was prepared in 92% overall yield from benzaldehyde and methyl cyanoacetate. The mixture was resolved into (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid (*S*)-**1** [(ee >96%, 41% yield)] and (*R*)-2-cyano-2-methyl-3-phenylpropanoic acid (*R*)-**1** [(ee >96%, 38% yield)] by crystallisation of its diastereomeric norephedrine salts as described in the preceding paper.[8]

Transformation of (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid (*S*)-**1** into (*S*)-α-benzyl-α-methyl-β-alanine (*S*)-**2** was conveniently performed as shown in Scheme 1.



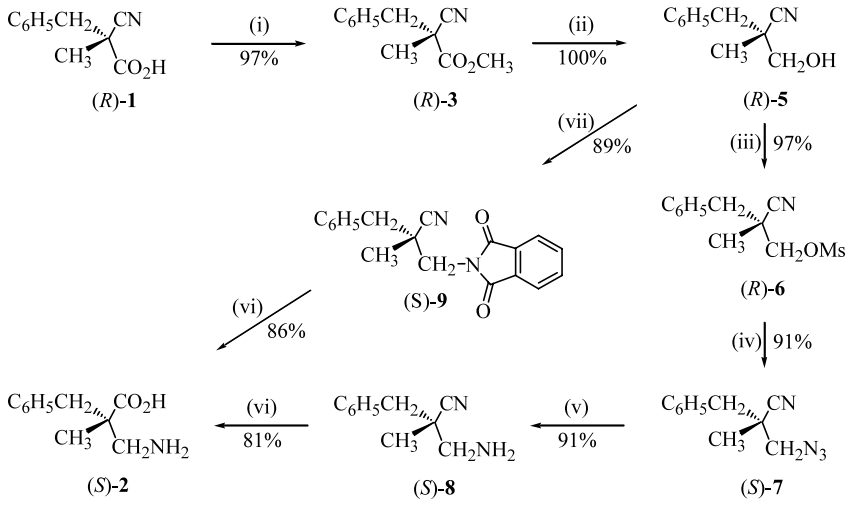
Scheme 1. *Reagents and conditions*: (i) H_2, Ni(Raney), 1% ammonia/methanol; (ii) Cs_2CO_3, CH_3I, acetone; (iii) KOH, methanol, Δ.

Hydrogenation of the cyano group in compound (*S*)-**1** was cleanly achieved at atmospheric pressure at 35°C by using Raney nickel as the catalyst and a solution of 1% ammonia in methanol as the solvent. This procedure afforded the target amino acid (*S*)-**2**, albeit only in moderate yield (50%). In an attempt to improve on this result, various catalysts (Rh/Al_2O_3, PtO_2, Pd/C) were tested in this hydrogenation reaction but none of these worked efficiently under mild conditions. Finally, compound (*S*)-**2** was obtained with a considerably increased yield through an alternative multi-step procedure consisting of hydrogenation with Raney nickel of methyl (*S*)-2-cyano-2-methyl-3-phenylpropanoate (*S*)-**3**, obtained from (*S*)-**1** and methyl iodide in the presence of Cs_2CO_3 and hydrolysis of the resulting amino ester (*S*)-**4** with 10% KOH/MeOH at room temperature. Enantiomerically pure (*S*)-α-benzyl-α-methyl-β-alanine (*S*)-**2** can easily be isolated by ion-exchange chromatography in 88% overall yield from (*S*)-**1**. Although all compounds were isolated for characterisation purposes, it is worth mentioning that all crude intermediates were pure enough to carry out subsequent steps without the need for purification—a factor that is advantageous for use on a large scale.

Conversion of enantiopure (*R*)-2-cyano-2-methyl-3-phenylpropanoic acid (*R*)-**1** into (*S*)-α-benzyl-α-methyl-β-alanine (*S*)-**2** was conveniently performed by two alternative routes, both of which are shown in Scheme 2.

Crude methyl ester (*R*)-**3**, obtained from (*R*)-**1** by reaction with methyl iodide and Cs_2CO_3, was quantitatively reduced with sodium borohydride at room temperature in a mixture of THF/H_2O. The subsequent reaction of the crude cyano alcohol (*R*)-**5** with methanesulfonyl chloride at room temperature gave the corresponding mesylate (*R*)-**6** in a nearly quantitative yield. This compound was submitted to a substitution process using sodium azide as a nucleophile in DMF at reflux. Cyano azide (*R*)-**7** was smoothly hydrogenated using Pd/C as catalyst to afford cyano amine (*S*)-**8**, which was hydrolysed, without purification, by refluxing with 20% aqueous HCl. Elution of the amino acid hydrochloride through an ion-exchange column yielded enantiomerically pure (*S*)-α-benzyl-α-methyl-β-alanine (*S*)-**2** in 65% overall yield from (*R*)-**1**. Although all compounds were isolated for characterisation purposes, it is again noteworthy that all crude intermediates were sufficiently pure to carry out to next step without any purification.

As an alternative, we assessed the possibility of substitution of the hydroxy group in cyano alcohol (*R*)-**5** without prior activation and this was achieved using Mitsunobu reaction conditions. Thus, treatment of alcohol (*R*)-**5** with an excess of phthalimide, triphenylphosphine and diethyl azodicarboxylate (DEAD) led to the phthalimido derivative (S)-**9** in 89% yield. This compound was purified by column chromatography and subsequently hydrolysed with hydrochloric acid under reflux. Ion-exchange chromatography of the resulting material gave enantiomerically pure (*S*)-α-benzyl-α-methyl-β-alanine (*S*)-**2** in 74% overall yield based on the starting cyano acid (*R*)-**2**.



Scheme 2. *Reagents and conditions*: (i) Cs_2CO_3, CH_3I, acetone; (ii) $NaBH_4$, THF/H_2O; (iii) MsCl, Et_3N, CH_2Cl_2; (iv) NaN_3, DMF; (v) H_2, Pd/C, methanol; (vi) 20% HCl, Δ; ion-exchange chromatography; (vii) Phthalimide, PPh_3, THF, DEAD.

The methodology described here also constitutes a formal synthesis (*R*)-α-benzyl-α-methyl-β-alanine on the basis that (*R*)-2-cyano-2-methyl-3-phenylpropanoic acid and its enantiomer, (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid, can be used as starting materials in synthetic routes depicted in Schemes 1 and 2, respectively, with similar results to those described above.

3. Conclusion

We have developed a practical and efficient procedure for the enantioconvergent synthesis of (*S*)-α-benzyl-α-methyl-β-alanine in 59% overall yield from benzaldehyde and methyl 2-cyanoacetate. The apparent synthetic advantages of the methodology described include the ready availability of the starting materials and the extremely simple experimental procedure. The synthesis avoids low temperature reactions and difficult purifications, thus making it amenable to large-scale synthesis. Extension of this method to the synthesis of other important α,α-disubstituted β-amino acids is currently under way.

4. Experimental

4.1. General

Melting points were determined using a Gallenkamp apparatus and are uncorrected. IR spectra were registered on a Mattson Genesis FTIR spectrophotometer; ν_{max} is given for the main absorption bands. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity-300 or a Bruker ARX-300 apparatus at room temperature, using the residual solvent signal as the internal standard; chemical shifts (δ) are quoted in ppm, and coupling constants (J) are measured in hertz. Optical rotations were measured in a cell with a 10 cm pathlength at 25°C using a JASCO P-1020 polarimeter. TLC was performed on Polygram® sil G/UV_{254} precoated silica gel polyester plates and products were visualised under UV light (254 nm) or using ninhydrin, anisaldehyde or phosphomolybdic acid developers. Column chromatography was performed using silica gel (Kieselgel 60). (*R*)- and (*S*)-2-Cyano-2-methyl-3-phenylpropanoic acid were obtained as described in the preceding paper.[8]

4.2. Synthesis of methyl (*S*)-2-cyano-2-methyl-3-phenylpropanoate, (*S*)-3

Cs_2CO_3 (3.59 g, 11 mmol) was added to a solution of (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid (*S*)-**1** (1.89 g, 10 mmol) in methanol (30 mL). The resulting mixture was stirred at room temperature for 30 min and then evaporated to dryness. The resulting residue was dissolved in DMF (30 mL), methyl iodide (1.70 g, 12 mmol) was added and the reaction mixture stirred at room temperature for 32 h. When the reaction was complete, ether (50 mL) was added and the resulting solution washed with saturated aqueous NaCl solution (4×20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford 1.97 g (97% yield) of crude methyl (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid (*S*)-**3**. This material was pure enough to be used in the next step without further purification. An analytically pure sample of (*S*)-**3** was obtained by purification of the crude product by column chromatography on silica gel (ether/hexane 1:3). Oil; $[\alpha]_D^{25}=+31.2$ (*c* 1, in $CHCl_3$), {lit.[9] $[\alpha]_D^{25}=+2.9$ (neat)}; IR (Nujol) 2243, 1743 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.61 (s, 3H), 3.04 (d, 1H, $J=13.5$ Hz), 3.22 (d, 1H, $J=13.5$ Hz), 3.73 (s, 3H), 7.26–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.1, 43.7, 45.3, 53.4, 119.6, 127.9, 128.6, 129.9, 134.0, 169.5.

4.3. Synthesis of (*S*)-α-benzyl-α-methyl-β-alanine methyl ester, (*S*)-4

A solution of crude methyl (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid (*S*)-**3** (1.97 g) in 0.5% ammonia/

methanol (50 mL) was hydrogenated at room temperature and atmospheric pressure using Raney nickel (5 mL) as a catalyst. The reaction was monitored by TLC and, on completion (2 h), the catalyst was filtered off and washed with several portions of methylene chloride. The filtrate was evaporated to dryness in vacuo to afford 1.84 g (92% yield) of crude (*S*)-α-benzyl-α-methyl-β-alanine methyl ester (*S*)-**4**, which was pure enough to be used in the next step without further purification. An analytically pure sample of (*S*)-**4** was obtained by filtration of the crude product through a short pad of silica gel (methylene chloride/ethanol 9:1). Oil; $[\alpha]_D^{25}=-18.0$ (*c* 1, in $CHCl_3$); IR (Nujol)) 3397, 3335, 1727 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10 (s, 3H), 1.31 (brs, 2H), 2.65 (bd, $J=12$ Hz), 2.74 (d, 1H, $J=13.2$ Hz), 2.95 (d, 1H, $J=13.5$ Hz), 2.95 (bd, 1H, $J=12$ Hz), 3.65 (s, 3H), 7.05–7.10 (m, 2H), 7.16–7.27 (m, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 19.6, 42.7, 49.6, 49.7, 51.7, 126.5, 128.1, 130.0, 137.2, 176.6

4.4. Final step in the synthesis of (*S*)-α-benzyl-α-methyl-β-alanine, (*S*)-2, using (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid (*S*)-1 as the precursor

Method a. A solution of crude (*S*)-α-benzyl-α-methyl-β-alanine methyl ester (*S*)-**4** (1.84 g) in 10% KOH in methanol (30 mL) was stirred at room temperature for 1 h. On completion of the reaction the solvent was evaporated in vacuo and the residue diluted with water (100 mL) and washed with ether. The aqueous layer was acidified with concentrated aqueous HCl, washed with ether and evaporated in vacuo to give the crude amino acid hydrochloride, which was submitted to ion-exchange column chromatography on Dowex 50Wx8 to afford 1.72 g [quantitative yield, 89% overall yield form (*S*)-**1**] of (*S*)-α-benzyl-α-methyl-β-alanine (*S*)-**2** as a white powder.

Method b. A solution of (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid (*S*)-**1** (1.13 g, 6 mmol) in 1% ammonia/methanol (40 mL) was hydrogenated at 35°C and atmospheric pressure using Raney nickel (4 mL) as a catalyst. The reaction was monitored by TLC and, on completion (6 h), the catalyst was filtered off and washed with several portions of water. The filtrate was evaporated to dryness in vacuo and the residue was dissolved in 1N HCl. The solution was purified by ion-exchange column chromatography on Dowex 50Wx8 to afford 579 mg (50% yield) of (*S*)-α-benzyl-α-methyl-β-alanine (*S*)-**2** as a white solid. Mp = 246°C, (lit.[10] mp = 205–206°C); $[\alpha]_D^{25}=+20.7$ (*c* 1, in H_2O), {lit.[10] $[\alpha]_D^{25}=+17.8$ (*c* 1, in H_2O)}; IR (Nujol)) 3550–2500, 1658 cm^{-1}; ^1H NMR (D_2O, 300 MHz) δ 1.07 (s, 3H); 2.67 (d, 1H, $J=13.5$ Hz); 2.75 (d, 1H, $J=12.9$ Hz); 2.85 (d, 1H, $J=13.5$ Hz); 2.95 (d, 1H, $J=12.9$ Hz); 7.09–7.23 (m, 5H); ^{13}C NMR (D_2O, 75 MHz) δ 21.0, 43.5, 46.1, 46.2, 127.0, 128.5, 130.0, 137.1, 181.7.

4.5. Synthesis of methyl (*R*)-2-cyano-2-methyl-3-phenylpropanoate, (*R*)-3

Cs_2CO_3 (3.59 g, 11 mmol) was added to a solution of (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid (*S*)-**1** (1.89 g, 10 mmol) in methanol (30 mL). The resulting mixture was stirred at room temperature for 30 min and then evaporated to dryness. The resulting residue was dissolved in DMF (30 mL), methyl iodide (1.70 g, 12 mmol) was added and the reaction mixture stirred at room temperature for 32 h. When the reaction was complete, ether (50 mL) was added and the resulting solution washed with saturated aqueous NaCl solution (4×20 mL), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford 1.97 g (97% yield) of crude methyl (*R*)-2-cyano-2-methyl-3-phenylpropanoic acid (*R*)-**3**. This material was pure enough to be used in the next step without further purification. An analytically pure sample of (*R*)-**3** was obtained by purification of the crude product by column chromatography on silica gel (ether/hexane 1:3). Oil; $[\alpha]_D^{25}=-30.9$ (*c* 1, in $CHCl_3$); IR (neat) 2243, 1743 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.61 (s, 3H), 3.05 (d, 1H, $J=13.5$ Hz), 3.22 (d, 1H, $J=13.5$ Hz), 3.72 (s, 3H), 7.26–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.1, 43.6, 45.3, 53.3, 119.6, 127.9, 128.7, 129.9, 134.0, 169.3.

4.6. Synthesis of (*R*)-2-hydroxymethyl-2-methyl-3-phenylpropionitrile, (*R*)-5

To a solution of crude methyl (*R*)-2-cyano-2-methyl-3-phenylpropanoic acid (*R*)-**3** (1.97 g) in THF (40 mL) was added a solution of $NaBH_4$ (3.8 g, 0.1 mol) in THF/H_2O (5:1, 30 mL). The reaction mixture was stirred at room temperature for 1 h. The solution was quenched with 10% HCl and THF was removed by evaporation in vacuo. The aqueous solution was extracted with ether and the combined organic layers washed with saturated aqueous $NaHCO_3$ and water. The organic layer was dried over anhydrous $MgSO_4$ and the solvent evaporated in vacuo to give 1.70 g (quantitative yield) of (*R*)-2-hydroxymethyl-2-methyl-3-phenylpropionitrile (*R*)-**5**. This material was pure enough to be used in the next step without further purification. An analytically pure sample of (*R*)-**5** was obtained by purification of the crude product by column chromatography on silica gel (ether/hexane 1:1). Oil; $[\alpha]_D^{25}=-9.9$ (*c* 1, in $CHCl_3$); IR (neat) 3550–3450, 2239 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.29 (s, 3H), 2.33 (s, 1H), 2.80 (d, 1H, $J=13.4$ Hz), 3.01 (d, 1H, $J=13.4$ Hz), 3.62 (s, 2H), 7.26–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 20.5, 40.6, 41.2, 67.2, 123.0, 127.3, 128.4, 130.2, 134.8.

4.7. Synthesis of (*R*)-2-mesyloxymethyl-2-methyl-3-phenylpropionitrile, (*R*)-6

Methanesulfonyl chloride (1.37 g, 12 mmol) was added dropwise to a solution of crude (*R*)-2-hydroxymethyl-2-methyl-3-phenylpropionitrile (*R*)-**5** (1.70 g) and triethylamine (1.21 g, 12 mmol) in methylene chloride (50 mL) at 0°C and the resulting solution was stirred at this temperature for 30 min. Upon completion of the reaction, the mixture was washed with brine, dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to afford 2.38 g (97% yield) crude mesylate (*R*)-**6**. This material was pure enough to be used in the next step without further purification. An analytically pure sam-

ple of (*R*)-**6** was obtained by purification of the crude product by column chromatography on silica gel (ether/hexane 4:1). Oil; $[\alpha]_D^{25}=-3.3$ (*c* 1, in $CHCl_3$); IR (neat) 2241, 1359, 1178 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.38 (s, 3H), 2.87 (d, 1H, $J=13.5$ Hz), 2.99 (d, 1H, $J=13.5$ Hz), 3.10 (s, 3H), 4.12 (s, 2H), 7.24–7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.0, 37.9, 38.3, 41.5, 71.3, 121.0, 127.9, 128.8, 130.2, 133.4.

4.8. Synthesis of (*S*)-3-azido-2-benzyl-2-methylpropionitrile, (*S*)-7

To a solution of sodium azide (1.3 g, 20 mmol) in DMF (30 mL) was added crude (*R*)-2-mesyloxymethyl-2-methyl-3-phenylpropionitrile (*R*)-**6** (2.38 g) and the mixture stirred under reflux for 12 h. The reaction mixture was allowed to cool, dissolved in ether (50 mL) and the resulting solution was washed with saturated aqueous NaCl solution (4×20 mL), dried over anhydrous $MgSO_4$, filtered and evaporated in vacuo to afford 1.70 g (91% yield) of (*S*)-3-azido-2-benzyl-2-methylpropionitrile, (*S*)-**7**. An analytically pure sample of (*S*)-**7** was obtained by filtration of the crude product through a short pad of silica gel (ether/hexane 4:1). Oil; $[\alpha]_D^{25}=-9.2$ (*c* 1, in $CHCl_3$); IR (neat) 2236, 2107 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.34 (s, 3H), 2.83 (d, 1H, $J=13.7$ Hz), 2.95 (d, 1H, $J=13.7$ Hz), 3.37 (d, 1H, $J=12.2$ Hz), 3.42 (d, 1H, $J=12.2$ Hz), 7.24–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.0, 38.8, 42.1, 57.0, 121.9, 127.7, 128.6, 130.2, 134.2.

4.9. Synthesis of (*S*)-3-amino-2-benzyl-2-methylpropionitrile, (*S*)-8

A solution of crude (*S*)-3-azido-2-benzyl-2-methylpropionitrile (*S*)-**7** (1.70 g) in methanol (40 mL) was hydrogenated at room temperature and atmospheric pressure using 10% Pd/C (300 mg) as a catalyst. The reaction was monitored by TLC and, on completion (4 h), the catalyst filtered off and the filtrate evaporated to dryness in vacuo to afford 1.34 g (91% yield) of pure (*S*)-3-azido-2-benzyl-2-methylpropionitrile (*S*)-**8**. Oil; $[\alpha]_D^{25}=-11.8$ (*c* 1, in $CHCl_3$); IR (neat) 3500–3300, 2233 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25 (s, 3H), 1.40 (brs, 2H), 2.71 (d, 1H, $J=13.4$ Hz), 2.75 (d, 1H, $J=13.2$ Hz), 2.85 (d, 1H, $J=13.2$ Hz), 2.97 (d, 1H, $J=13.4$ Hz), 7.24–7.33 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 41.1, 42.4, 50.0, 123.4, 127.3, 128.4, 130.2, 135.2.

4.10. Synthesis of (*S*)-2-benzyl-3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-2-methylpropionitrile, (*S*)-9

A 100 mL round-bottomed flask was charged with phthalimide (1.47 g, 10 mmol), dry THF (30 mL), PPh_3 (2.63 g, 10 mmol), and (*R*)-2-hydroxymethyl-2-methyl-3-phenylpropionitrile (*R*)-**5** (0.7 g, 4 mmol) (obtained as described above) in the order stated. The resulting solution was cooled to 0°C and kept under an argon atmosphere. DEAD (1.74 g, 10 mmol) was added dropwise to the stirred reaction mixture. After completion of the addition, the resulting yellow solution was stirred at 40°C for 7 d. The reaction mixture was then concentrated in vacuo and the crude product purified by column chromatography on silica (methylene chloride/hexane 4:1) to give 1.08 g (89% yield) of (*S*)-2-benzyl-3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-2-methylpropionitrile (*S*)-**9** as a white solid. Mp = 132°C; $[\alpha]_D^{25}=+2.8$ (*c* 1, in $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.32 (s, 3H), 2.79 (d, 1H, $J=13.5$ Hz), 3.09 (d, 1H, $J=13.5$ Hz), 3.86 (d, 1H, $J=13.8$ Hz), 3.99 (d, 1H, $J=13.8$ Hz), 7.24–7.33 (m, 5H), 7.74–7.90 (m, 4H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.6, 39.7, 43.7, 45.1, 122.0, 123.8, 127.6, 128.5, 130.3, 131.7, 134.4, 134.5, 168.1.

4.11. Final step in the synthesis of (*S*)-α-benzyl-α-methyl-β-alanine, (*S*)-2, using (*R*)-2-cyano-2-methyl-3-phenylpropanoic acid (*R*)-1 as the precursor

Method a. Crude (*S*)-3-azido-2-benzyl-2-methylpropionitrile (*S*)-**8** (1.34 g) in 20% aqueous HCl (50 mL) was heated under reflux for 7 d. The solvent was removed under reduced pressure to afford a solid, which was dissolved in water, washed with ether and evaporated in vacuo to give the crude amino acid hydrochloride. This material was submitted to ion-exchange column chromatography on Dowex 50Wx8 to afford 1.25 g [81% yield, 65% overall yield from (*R*)-**1**] of (*S*)-α-benzyl-α-methyl-β-alanine (*S*)-**2** as a white powder.

Method b. Crude (*S*)-2-benzyl-3-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-2-methylpropionitrile (*S*)-**9** (1.08 g) in 20% aqueous HCl (25 mL) and acetic acid (25 mL) was heated under reflux conditions for 7 d. The solvent was removed under reduced pressure to afford a solid, which was dissolved in water, washed with methylene chloride and evaporated in vacuo to give the crude amino acid hydrochloride. This material was submitted to ion-exchange column chromatography on Dowex 50Wx8 to afford 589 mg [86% yield, 75% overall yield form (*R*)-**1**] of (*S*)-α-benzyl-α-methyl-β-alanine (*S*)-**2** as a white powder.

The physical and spectroscopic data of the compound obtained were in complete agreement with those of (*S*)-α-benzyl-α-methyl-β-alanine (*S*)-**2** obtained using (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid (*S*)-**1** as the precursor.

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