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Efficient resolution of *rac*-2-cyano-2-methyl-3-phenylpropanoic acid. An appropriate starting material for the enantioconvergent synthesis of (*S*)-α-methylphenylalanine on a large laboratory scale

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Abstract—A large laboratory scale synthesis of (*S*)-α-methylphenylalanine from benzaldehyde and methyl cyanoacetate has been developed. The synthesis is based on the following sequence: (i) preparation of racemic 2-cyano-2-methyl-3-phenylpropanoic acid, (ii) resolution of the enantiomers by crystallisation using norephedrine, and (iii) development of an efficient enantioconvergent synthesis of (*S*)-α-methylphenylalanine from enantiopure (*S*)- and (*R*)-2-cyano-2-methyl-3-phenylpropanoic acid. The simplicity of the experimental procedures, which avoid low temperature reactions, the need for an inert atmosphere and column chromatography, combined with the use of inexpensive and readily available reagents make this method synthetically very attractive.

1. Introduction

Optically active α,α-disubstituted α-amino acids have generated ever-increasing interest in biology and pharmacology as well as in chemistry. Some of these compounds are naturally occurring or are structural components of natural products that have interesting properties, e.g. as antibiotics.[1] The presence of the tetrasubstituted stereogenic carbon atom means that the incorporation of these compounds into peptides leads to restricted conformational flexibility,[2] to stabilisation of defined secondary structures in small peptides,[3] and to higher resistance towards both enzymatic and chemical hydrolysis.[4] These compounds can therefore be used for the investigation of 3D structure–bioactivity relationships and in the development of new pharmaceutical agents with prolonged action and/or more selective properties. Some enantiopure α,α-disubstituted α-amino acids have also become of significant medicinal and biochemical interest as they are powerful enzyme inhibitors.[5] For example, (*S*)-α-methyl-DOPA, an inhibitor of DOPA decarboxylase, is an important commercial antihypertensive (Aldomet™).[6] Moreover, these substances have been used as building blocks for the synthesis of more elaborate compounds.[7] An illustrative example is the hydantoin BIRT-377,[8] derived from α-methyl-*p*-bromophenylalanine, which has recently been identified as a potent inhibitor of the interaction between intercellular adhesion molecule-1 and lymphocyte function-associated antigen-1 and has potential application for the treatment of inflammatory and immune disorders.

The extensive use of chiral α,α-disubstituted α-amino acids is only limited by their availability in enantiopure form and in large quantities. Various methods have been devised to obtain chiral α,α-disubstituted α-amino acids in enantiomerically pure form[9] and, among these, the most noteworthy are asymmetric synthesis, which is mainly based on stereoselective synthesis using chiral auxiliaries, and enzymatic resolution of racemic compounds.

The most successful diastereoselective syntheses involve the alkylation of chiral, nonracemic enolates that are commonly derived from proteinogenic amino acids.[9a] This reaction normally requires the use of very strong and sensitive bases and it is therefore usually carried

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out under anhydrous conditions and at low temperature. These reaction conditions do not allow this methodology to be applied to economical and/or large-scale synthesis. Recently the use of iminic substrates has allowed diastereoselective alkylation under mild conditions[10] and application of asymmetric phase transfer catalysis and other enantioselective processes to the synthesis of α,α-dialkylamino acids in enantiomerically pure form.[11]

There are also several enzymatic processes and, of these, the chemo-enzymatic synthesis developed by DSM Research,[12] which involves a combination of Strecker synthesis (to gain access to a racemic aminoamide) and kinetic resolution (using a broadly specific amino acid amidase), is the most general approach to the synthesis of α,α-disubstituted α-amino acids in enantiomerically pure form. The only drawback associated with this procedure is that the maximum theoretical yield is 50%, which is dependent on the enzyme specificity, as the undesired enantiomer can not be racemised.

As a part of our research programme aimed at establishing the conformational preferences of acyclic α,α-disubstituted α-amino acids,[13] we needed to prepare several of these amino acids in enantiomerically pure form and on a multi-gram scale. In an attempt to achieve this goal we became interested in developing a new, practical and efficient synthetic route. In recent years we have described the preparation of several α,α-disubstituted α-amino acids using a synthetic methodology based on the diastereoselective alkylation of α-cyanoesters derived from (1*S*,2*R*,4*R*)-10-dicyclohexylsulfamoylisoborneol.[14] The most attractive features of our methodology are:

1) It allows the synthesis of new enantiomerically pure α,α-dialkylamino acids combining two side chains of proteinogenic or non-proteinogenic amino acids at the same alpha-carbon.
2) Both enantiomers of the same amino acid can be obtained in enantiomerically pure form using different synthetic variants. (i) In the alkylation step, chiral 2-alkylcyanoacetate and alkyl halide can be appropriately combined to provide the same α,α-dialkylcyanoacetate with the (*R*)- or (*S*)-configuration (Fig. 1). (ii) A particular enantiopure α,α-dialkyl cyanoacetate can be conveniently elaborated to afford both enantiomers of the same amino acid. The stereodivergent synthesis is possible because both the carboxylate and the cyano groups are immediate precursors, through hydrolysis or rearrangement processes, of both the carboxylic acid and the amino groups of the final amino acid (Fig. 2).

However, due to the high molecular weight of the chiral auxiliary used in the synthesis, this methodology can hardly be applied to obtain α,α-disubstituted α-amino acids on a large scale.

Despite its 'low technology' image, classical resolution by crystallisation of diastereomeric compounds is

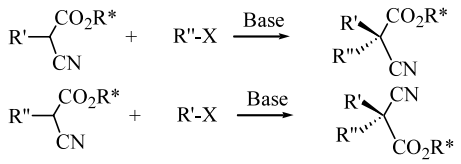


Figure 1. Complementary synthesis of (*R*)- and (*S*)-α,α-dialkylcyanoacetates.

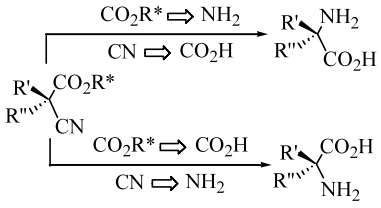


Figure 2. Enantiodivergent synthesis of (*R*)- and (*S*)-α,α-dialkylamino acids from an enantiomerically pure α,α-dialkylcyanoacetate.

widely used in industry and furnishes a large proportion of those optically active drugs that are not derived from natural products.[15] The maximum theoretical yield of 50% for each enantiomer sets a low ceiling on the productivity of such processes. For this reason, easy racemisation of the undesired isomer is a prerequisite for the economic success of this technology. When racemisation is not possible, as is the case in compounds with a quaternary stereogenic centre, the development of enantioconvergent processes is an attractive alternative. In an enantioconvergent synthesis, an enantiomerically pure product is formed in 100% theoretical yield from a racemate because each enantiomer reacts via an independent and complementary stereochemical pathway.

With this idea in mind, we envisaged a new synthetic approach for the preparation of enantiomerically pure α,α-disubstituted-α-amino acids on a large laboratory scale from inexpensive aldehydes and methyl cyanoacetate. This new approach involves the synthesis of a specific *rac*-α,α-disubstituted α-cyanoacetic acid, its resolution and the development of an efficient enantioconvergent synthesis from the two isolated enantiomers (Fig. 3). In order to demonstrate the feasibility of the proposed methodology, we decided to apply it to the synthesis of (*S*)-α-methylphenylalanine. This compound

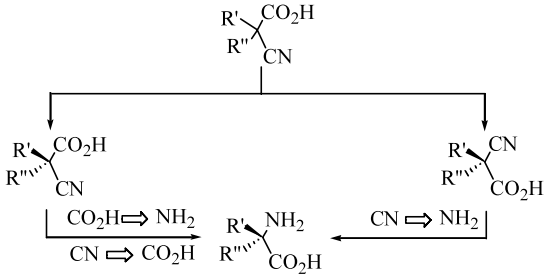
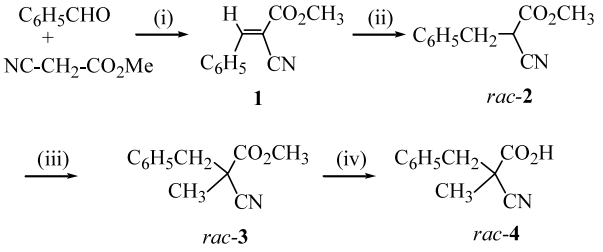


Figure 3. Enantioconvergent approach to the synthesis of (*R*)- or (*S*)-α,α-dialkylamino acids from both enantiomers of a chiral α,α-dialkylcyanoacetate.

has been used, amongst other things, in the preparation of an analogue of a commercial sweetener (aspartame) possessing the same sweetness but superior stability.[16] In this paper we describe the results obtained in the practical preparation of this amino acid on ca. 15 g scale.

2. Results and discussion

Racemic 2-cyano-2-methyl-3-phenylpropanoic acid *rac*-**4** was efficiently prepared by the four-step procedure outlined in Scheme 1.



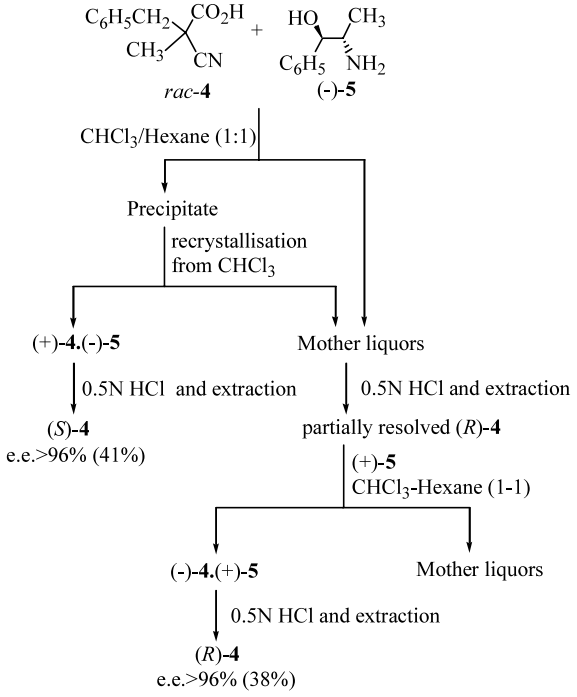
Scheme 1. *Reagents and conditions*: (i) NH_4AcO, AcOH; (ii) H_2, Pd/C, THF; (iii) K_2CO_3, CH_3I, acetone; (iv) KOH, methanol.

The Knoevenagel condensation of inexpensive and commercially available benzaldehyde and methyl cyanoacetate afforded methyl (*E*)-2-cyanocinnamate **1** as a solid, which was filtered off and submitted to hydrogenation using palladium on carbon as a catalyst. In the next step, crude 2-cyano-3-phenylpropanoate *rac*-**2** was deprotonated under mild conditions employing potassium carbonate in acetone and the resulting enolate was alkylated with methyl iodide to give methyl 2-cyano-2-methyl-3-phenylpropanoate *rac*-**3**, which was sufficiently pure for use in the next step. Finally, hydrolysis of cyano ester *rac*-**3** was accomplished with KOH in methanol and the resulting carboxylate salt was purified by a standard acid-base extraction to provide 2-cyano-2-methyl-3-phenylpropanoic acid *rac*-**4** as a yellowish powder in 92% overall yield from the starting materials. All reactions in this synthesis were carried out at room temperature and strictly anhydrous conditions were not required.

The resolution of *rac*-**4** was investigated by crystallisation of the diastereomeric salts formed with chiral amines. Owing to the well-documented lack of predictability in identifying a successful resolving agent for classical resolutions, the selection was made by trial and error.[17] The following components were included in the study: (i) resolving agents: (*R*)-(+)-1-phenylethylamine, (1*R*,2*S*)-(−)-norephedrine and (*R*)-(−)-2-amino-2-phenylethanol, (ii) solvents: ethanol, butanone, ethyl acetate, diisopropyl ether, chloroform, toluene and hexane.

Moreover, an alternative combinatorial approach recently proposed by Vries et al.[18] was also tested. This approach is based on the addition of a 'family' of resolving agents to a solution of a racemate, a treatment that generally causes very rapid precipitation of the crystalline diastereomeric salt in high diastereomeric purity and yield. Unfortunately, in our case a 'family' of resolving agents composed of an equimolecular mixture of (*R*)-1-phenylethylamine, (*R*)-1-(4-nitrophenyl)ethylamine and (*R*)-1-(4-methylphenyl)ethylamine led to unsatisfactory results.

Among the three commercially available optically active amines tested, (1*R*,2*S*)-(−)-norephedrine (−)-**5** gave the best results and of the solvents examined for improving the efficiency of the resolution, a mixture of chloroform and hexane (1:1) was found to be the most effective. The resolution was therefore carried out on multi-gram scale as depicted in Scheme 2.



Scheme 2. Chemical resolution of *rac*-**4**.

Resolving agent (−)-**5** was added to a solution of *rac*-**4** in chloroform/hexane (1:1) and the resulting mixture was stirred for 5 min under reflux. On cooling to room temperature an almost pure diastereomeric salt precipitated. The composition of the mixture could be directly determined by ^1H NMR spectroscopy,[19] which indicated a diastereomeric ratio (+)-**4**(−)-**5**/(−)-**4**(−)-**5** of 95/5. A further recrystallisation in chloroform afforded the diastereomerically pure salt (+)-**4**(−)-**5**. Enantiomerically pure (+)-2-cyano-2-methyl-3-phenylpropanoic acid (+)-**4** was recovered in 41% yield (maximum theoretical yield = 50%) upon hydrolysis of the salt with aqueous HCl and dichloromethane extraction. The measured specific rotation of (+)-**4** $\{[\alpha]_D^{25} = 27.2$ (*c* 2 in $CHCl_3)\}$ is in good agreement with the literature value for the (*S*)-enantiomer[20] and confirmed both the high enantiomeric excess and absolute configuration of compound (*S*)-**4**. The opposite enantiomer was obtained by

evaporation of the combined mother liquors, followed by decomposition of the salt by the addition of 0.5N hydrochloric acid and dichloromethane extraction. The enantiomeric purity of (*R*)-**4** could be increased to e.e.>96% by reaction with an equimolecular amount of (1*S*,2*R*)-(+)-norephedrine (+)-**5** and precipitation of the diastereomeric salt (−)-**4**(+)-**5** from a chloroform/hexane (1:1) mixture. Hydrolysis of (−)-**4**(+)-**5** provided (*R*)-**4** with a chemical yield of 38% {$[\alpha]_D^{25} = -27.8$ (*c* 2, $CHCl_3$)}.

Having obtained both enantiomers of **4**, we proceeded to study the development of an efficient and practical enantioconvergent synthesis of (*S*)-α-methylphenylalanine. Compound (*S*)-**4** was transformed successfully into the target amino acid via the synthetic route shown in Scheme 3. The acid chloride prepared by treatment of (*S*)-**4** with thionyl chloride was reacted with sodium azide in aqueous acetone to afford crude acyl azide (*S*)-**5**. This compound was immediately rearranged by refluxing in a mixture of toluene/methanol and the resulting cyano urethane (*S*)-**6** was hydrolysed with 20% hydrochloric acid under reflux. Elution of the crude amino acid hydrochloride salt through an ion exchange column yielded enantiomerically pure (*S*)-α-methylphenylalanine (*S*)-**7** in 90% overall yield from (*S*)-**4**. The specific rotation value {$[\alpha]_D^{25} = -21.8$ (*c* 1, H_2O), lit.[12a] $[\alpha]_D^{25} = -22$ (*c* 1, H_2O)} allowed us to confirm the enantiomeric purity of the final product. It should be noted that crude intermediates were used directly in all steps of the synthetic scheme and a purification step was *not* required in the entire sequence. Furthermore, the course of all reactions could be easily monitored by IR spectroscopy. Finally, the physical and spectroscopic data of an isolated analytically pure sample of compound (*S*)-**6** are fully consistent with those previously reported in the literature.[14e]

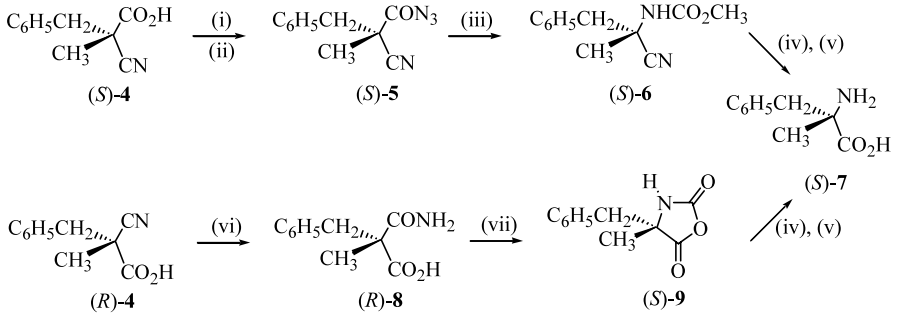
Alternatively, (*R*)-**4** was converted successfully into (*S*)-**7** as shown in the synthetic route in Scheme 3. Compound (*R*)-**8** was prepared by treatment of (*R*)-**4** with sodium hydroxide and H_2O_2, with the resulting product submitted to a Hofmann-type rearrangement to afford the *N*-carboxyanhydride (*S*)-**9**. This material was hydrolysed, without purification, by refluxing with aqueous hydrochloric acid. The next step involved the usual treatment using an ion exchange column to give enantiomerically pure (*S*)-α-methylphenylalanine {$[\alpha]_D^{25} = -21.6$ (*c* 1, H_2O)} in 89% overall yield based on starting cyano acid (*R*)-**4**. It is worth mentioning that all crude intermediate products were pure enough to be used in the next step without purification—a fact that would be advantageous on a large scale—and that the physical and spectroscopic data of isolated analytically pure samples of compounds (*R*)-**8**[21] and (*S*)-**9**[22] are fully consistent with those previously reported in the literature.

The specific rotation values for samples of (*S*)-**7**, obtained through both synthetic routes, demonstrated that both Curtius and Hofmann rearrangements proceeded with retention of configuration, as reported in the literature.[23]

The methodology described here also constitutes a formal synthesis of (*R*)-α-methylphenylalanine on the basis that (*R*)-2-cyano-2-methyl-3-phenylpropanoic acid and its enantiomer, (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid, could be used as starting materials for a complementary enantioconvergent synthesis of the amino acid of *R* configuration, with similar results expected to those described above.

3. Conclusion

We have developed a practical and efficient procedure for the synthesis of (*S*)-α-methylphenylalanine on a large laboratory scale starting from readily available and inexpensive reagents. The most remarkable characteristic of this methodology is the high overall yield (63% from benzaldehyde and methyl 2-cyanoacetate) obtained using simple and mild reaction conditions that avoid the use of difficult purification procedures. This sequence may be easily scaled up, meaning that this methodology is very promising for the preparation of α,α-disubstituted α-amino acids that are now very important on an industrial scale.



Scheme 3. *Reagents and conditions*: (i) $SOCl_2$; (ii) NaN_3, acetone/H_2O; (iii) Δ, toluene/methanol; (iv) 20% HCl, reflux; (v) ion-exchange chromatography; (vi) NaOH, H_2O_2; (vii) $C_6H_5I(OAc)_2$, methanol.

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. ^{1}H 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. Elemental analyses were carried out on a Perkin–Elmer 200 C, H, N, S analyser. 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.

4.2. Synthesis of *rac*-2-cyano-2-methyl-3-phenylpropanoic acid, *rac*-4

A mixture of methyl cyanoacetate (9.9 g, 0.1 mol), benzaldehyde (10.6 g, 0.1 mol), glacial acetic acid (4.8 g, 0.08 mol) and ammonium acetate (1.54 g, 0.02 mol) was stirred at room temperature for several minutes until it solidified. The resulting paste was allowed to stand at room temperature overnight and the solid was filtered off and washed with hexane. The solid was dissolved in ethyl acetate and washed successively with saturated aqueous $NaHCO_3$ and water. The organic phase was dried over anhydrous $MgSO_4$, filtered and the solvent removed in vacuo to afford crude methyl (*E*)-2-cyanocinnamate **1**. The crude material was dissolved in THF (75 mL) and hydrogenated at atmospheric pressure and room temperature using 10% palladium on charcoal (300 mg) as the catalyst. The reaction was monitored by TLC and, on completion (1 day), the catalyst was filtered off and the filtrate was evaporated to dryness to provide crude methyl 2-cyano-3-phenylpropanoate *rac*-**2**. Potassium carbonate (13.8 g, 0.1 mol) was added to a well-stirred solution of crude *rac*-**2** and methyl iodide (17.03 g, 7.5 mL, 0.12 mol) in acetone (75 mL) and the resulting mixture was stirred at room temperature for 12 h. After the reaction was complete, the solvent was evaporated and the residue dissolved in ether. The solution was filtered and concentrated in vacuo to afford crude methyl 2-cyano-2-methyl-3-phenylpropanoate *rac*-**3**. Crude *rac*-**3** was dissolved in a 10% solution of KOH in methanol (125 mL) and the reaction mixture was stirred at room temperature for 1 h. The solvent was evaporated in vacuo, the residue diluted with water (100 mL) and the solution washed with ether. The aqueous layer was acidified with concentrated aqueous HCl and extracted several times with ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford 17.4 g of 2-cyano-2-methyl-3-phenylpropanoic acid *rac*-**4** as a white solid (92% overall yield from methyl cyanoacetate and benzaldehyde. Mp = 93°C, (lit.[20] mp = 93–94°C); IR (Nujol) 2262, 1747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.64 (s, 3H), 3.06 (d, 1H, J = 13.5 Hz), 3.26 (d, 1H, J = 13.5 Hz), 7.26–7.34 (m, 5H), 10.25 (brs, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.8, 43.2, 44.3, 118.9, 128.0, 128.7, 130.0, 133.6, 174.1

4.3. Resolution of *rac*-4 by crystallisation of its (1*R*,2*S*)-(−)-norephedrine and (1*S*,2*R*)-(+)-norephedrine salts

(1*R*,2*S*)-(−)-Norephedrine (15.1 g, 0.1 mol) was added to a solution of racemic 2-cyano-2-methyl-3-phenylpropanoic acid *rac*-**4** (18.9 g, 0.1 mmol) in a 1/1 mixture of chloroform/hexane (1 L). The mixture was stirred and heated under reflux for 5 min, the resulting solution was allowed to cool to room temperature and a white solid began to precipitate. The mixture was kept overnight at room temperature to complete the precipitation. The solid was filtered off and recrystallised from hot chloroform. The product was dissolved in 0.5N aq. HCl (150 mL) and extracted three times with ether. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and evaporated under reduced pressure, to afford 7.78 g of the enantiomerically pure cyano acid (*S*)-**4** [mp 88°C, $[\alpha]_D^{25}$ = +27.2 (*c* 2, in $CHCl_3$)] as colourless crystals (yield 41%). The physical[14e,20] and spectroscopic data[14e] for the product agree with those described in the literature for (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid.

Evaporation of the mother liquors furnished a beige paste, which was acidified with 0.5N HCl and extracted three times with ether. The combined organic layers were dried over anhydrous magnesium sulfate and evaporated under reduced pressure to afford 11.1 g of partially resolved cyano acid (*R*)-**4**, which was dissolved in a 1/1 mixture of chloroform/hexane (600 mL). (1*S*,2*R*)-(+)-Norephedrine (8.88 g, 58.8 mmol) was added and the mixture was refluxed until all of the solid had dissolved. The resulting solution was allowed to cool to room temperature and, after 12 h, the resulting colourless precipitate was filtered off. The solid was dissolved in 0.5N aq. HCl (150 mL) and extracted three times with ether. The combined organic layers were dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure to afford 7.2 g of the enantiomerically pure cyano acid (*R*)-**4** {mp 88°C, $[\alpha]_D^{25}$ = −27.8 (*c* 2, in $CHCl_3$)} as colourless crystals (yield 38%). The physical[20] data for the product agree with those reported in the literature for (*R*)-2-cyano-2-methyl-3-phenylpropanoic acid. IR (Nujol) 2267, 1743 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.64 (s, 3H), 3.06 (d, 1H, J = 13.5 Hz), 3.26 (d, 1H, J = 13.5 Hz), 6.25 (brs, 1H), 7.26–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.9, 43.2, 44.5, 118.9, 128.1, 128.7, 130.0, 133.6, 174.2.

4.4. Synthesis of (*S*)-α-methylphenylalanine (*S*)-7 from (*S*)-4

Thionyl chloride (75 mL) was added to (*S*)-2-cyano-2-methyl-3-phenylpropanoic acid (*S*)-**4** (9.45 g, 50 mmol)

and the mixture was heated under reflux for 12 h. The excess thionyl chloride was removed in vacuo, the residue was dissolved in acetone (18 mL) and this solution was added to a solution of NaN_3 (3.93 g, 60 mmol) in water (18 mL). The mixture was stirred for 40 min at room temperature, the acetone was evaporated in vacuo at room temperature and the resulting aqueous solution was extracted with ether. The organic layer was dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The residue was dissolved in a mixture of toluene (75 mL) and methanol (25 mL) and the solution was stirred and heated under reflux for 4 h. The solvents were evaporated in vacuo to afford crude cyano urethane (*S*)-**6**. This compound was hydrolysed with 20% aqueous HCl (180 mL) under reflux for 36 h. The liquids were removed in vacuo and the residue was dissolved in water, washed with ether and introduced into an ion exchange column (Dowex 50 W×8). Elution of the column with 5% aqueous ammonia and subsequent solvent evaporation in vacuo afforded 8.06 g of (*S*)-α-methylphenylalanine **7** [90% overall yield from (*S*)-**4**]. The physical[12a,14e] and spectroscopic data[14e] of the product agree with those reported in the literature for (*S*)-α-methylphenylalanine.

4.5. Synthesis of (*S*)-α-methylphenylalanine (*S*)-7 from (*R*)-4

1N Aqueous NaOH (63 mL) was added to (*R*)-2-cyano-2-methyl-3-phenylpropanoic acid (*R*)-**4** (9.45 g, 50 mmol) until all of the solid had dissolved. 35% H_2O_2 (116 mL) was added with caution and 10% aqueous NaOH (90 mL) was then added slowly. The reaction mixture was stirred at room temperature overnight and then acidified with concentrated aqueous HCl until pH 2. This mixture was extracted with CH_2Cl_2 (4×50 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to afford 9.75 g (94%) of crude (*R*)-2-benzyl-2-methylmalonic acid monoamide (*R*)-**8**. Iodobenzene diacetate (17.4 g, 54 mmol) was added to a solution of crude (*R*)-2-benzyl-2-methylmalonic acid monoamide (*R*)-**8** (9.31 g, 45 mmol) in methanol (150 mL). The resulting mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue partitioned between CH_2Cl_2 and water. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. Crude (*S*)-4-benzyl-4-methyloxazolidin-2,5-dione (*S*)-**9** was hydrolysed with 20% aqueous HCl (200 mL) under reflux for 5 h. The liquids were removed in vacuo and the residue was dissolved in water, washed with CH_2Cl_2 and introduced into an ion exchange column (Dowex 50 W×8). Elution of the column with 5% aqueous ammonia followed by solvent evaporation in vacuo afforded 7.17 g of (*S*)-α-methylphenylalanine (*S*)-**7** [89% overall yield from (*R*)-**4**]. The physical[12a,14e] and spectroscopic data[14e] of the product agree with those reported in the literature for (*S*)-α-methylphenylalanine.

Acknowledgements

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