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Stereospecific synthesis of α-methylated amino acids

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Summary. Both 2,5-trans and 2,5-cis disubstituted 2-tert-butyl-5-(indol-3-yl)methylimidazolidin-4-ones were synthesised and their enolates were prepared using LDA. While the enolate of the 2,5-trans disubstituted derivative could not be methylated, the enolate of the cis-2,5-disubstituted derivative was successfully methylated with methyl iodide to a product which on hydrolysis gave enantiomerically pure α-methyl-L-tryptophan.

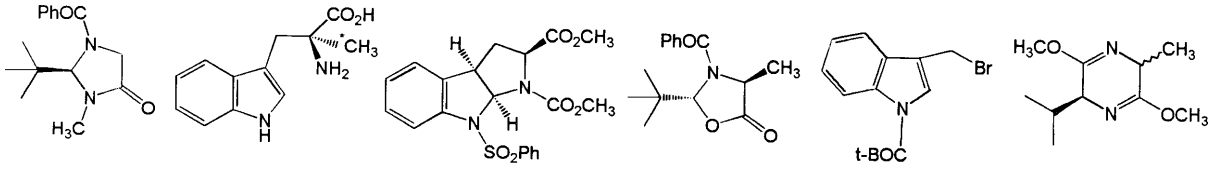
Keywords: Amino acids – α-Methyl-L-tryptophan – Stereospecific synthesis – α-Methyl-L-phenylalanine – 2-tert-butylimidazolidin-4-one

Introduction

The synthesis of α-methylated amino acids has received a lot of attention, due largely to their apparent importants as enzyme inhibitors (Saari et al., 1978) and as conformational modifiers in physiologically active peptides (Paul et al., 1986). A wide variety of methods (Williams et al., 1991) have been developed for their synthesis. We have been interested in the asymmetric synthesis of radiolabelled α-methyl-L-tryptophan (Mzengeza et al., 1995) and α-methyl-L-tyrosine (Rajagopal et al., 1993), in which the label is on the α-methyl group. These compounds are useful as tracers for either positron emission tomography (PET) or autoradiography depending on the half-life of the isotope used (Diksic, 1991). Therefore methods which involve stereoselective introduction of the radiolabelled methyl group are most suitable. We have explored the use of the chiral glycine equivalents such as the imidazolidinone **1** (Williams, 1989).

We were interested in the asymmetric synthesis of radiolabelled α-methyl-L-tryptophan **2** because this is a useful tracer for the study of the biosynthesis of the neurotransmitter serotonin. Crich et al. (1989) have reported a synthesis of α-methyl-L-tryptophan by the enantioselective methylation of hexahydropyrrolo[2,3-b]indole-2-carboxylate **3**, a cyclic tautomer of tryptophan. We (Mzengeza et al., 1995; Venkatachalam et al., 1993) and others (Plenevaux et al., 1994; Chakraborty et al., 1996) have successfully adapted

this method for the enantioselective radiosynthesis of α-[^{11}C]methyl and α-[^{14}C]methyl-L-tryptophan. We, however, required a method that could also be applied to the synthesis of a wide variety of other labelled α-methyl amino acids. Seebach et al. (1988) has also reported the asymmetric synthesis of α-methyl-L-tryptophan using the chiral oxazolidin-5-one **4** prepared from alanine, by alkylating its enolate with N-tert-butyloxycarbonylindol-3-ylmethyl bromide **5**. Similarly, Schöllkopf et al. (1985) synthesized α-methyl-D-tryptophan methyl ester also by alkylating the enolate of the bislactim ether **6** with the indolylmethyl bromide **5**. Although both these methods furnish α-methyltryptophan, they are obviously not suitable for radiosynthesis of α-methyl labelled compounds because in both methods the methyl group comes from alanine.



1 **2** **3** **4** **5** **6**

Materials and methods

n-Butyllithium, diisopropylamine, hexamethylphosphoramide (HMPA), hexamethylphosphorotriamide (HMPT), 1,3-dimethyl-2-imidazolidinone (DMEU), (R)-(−)-1-benzoyl-2-*tert*-butyl-3-methyl-4-imidazolidinone, benzoyl chloride, L-tryptophan, α-methyl-D,L-phenylalanine, CaH_2 were obtained from Aldrich Chemical Company. α-Methyl-L-tryptophan was purchased from Bis Chem Inc., Montreal, Canada. α-Methyl-L-phenylalanine and α-methyl-D,L-tryptophan were purchased from Sigma Chemical Company. (2R)-(−)-2,5-Dihydro-3,6-dimethoxy-2-isopropylpyrazine and (2S)-(+)-2,5-dihydro-3,6-dimethoxy-2-isopropylpyrazine were from Merck. Solvents such as anhydrous THF, CH_2Cl_2, hexanes, EtOAc, ether were obtained from Aldrich and purified before use. Diisopropylamine was freshly distilled over CaH_2 under argon before use. HPLC analysis was conducted using Bio-Rad model 1350 HPLC pump, multiple wave length detector and recorder. Enantiomeric purity of the final product after synthesis was determined using a Diacel chiralpak WH analytical column (24 × 0.4 cm) and 5.0 mm $CuSO_4$:MeOH (90:10) as eluent at 1.5 mL/min flow rate and UV detector (Bio-Rad) set at 254 nm and the temperature of the column being maintained at 49°C. TLC's were carried out on Analtech uniplate TLC plates (Cat No. 47521). The NMR spectra were obtained using 400 MHz Varian instrument using $CDCl_3$/TMS as solvent. The low temperatures (−78°C) during reactions are bath temperatures of acetone cooled and maintained by a Flexicool cooling probe immersed in acetone.

*(2R,5R)-1-Benzoyl-2-(*tert*-butyl)-5-[(2R,5S)-1-benzoyl-2-(*tert*-butyl)-5-[1-(*tert*-butyloxycarbonyl)indol-3-yl]methyl-3-methylimidazolidin-4-one (**9**)*

To a stirred solution of anhydrous diisopropylamine (0.2 mL, 1.4 mmol) and DMPU (1 mL) in anhydrous THF (5 mL) cooled to −78°C was added nBuLi (0.56 mL of 2.5 M solution, 1.4 mmol). The reaction mixture was stirred at −78°C for a further 40 min. To

the resulting LDA was slowly added a solution of (2R)-1-benzoyl-2-(*tert*-butyl)-3-methylimidazolidin-4-one **7** (0.130 g, 0.5 mmol) in anhydrous THF (5 mL) using a dry syringe. A deep red solution of the enolate **8** was formed which was stirred at −78°C for a further 40 minutes after which time methyl iodide (1 mL) was added. The reaction mixture was left stirring overnight at −78°C. A TLC (EtOAc : hexanes, 2 : 1) of the reaction mixture showed unreacted starting material and the formation of a product at rf 0.45. The mixture was then rotary evaporated and saturated NH_4Cl (3 mL) was added and the mixture was extracted with ether (6 × 10 mL). The ether extracts were combined, dried over anhydrous $MgSO_4$, filtered and evaporated to give an oily residue (0.268 g). Column chromatographic purification over silica eluting with EtOAc : hexanes (2 : 1) gave the pure **9**; H-NMR $\delta(CDCl_3)$: 1.05 (s, 9H, t-Bu-C2), 1.67 (s, 9H, tBOC), 3.06 (s, 3H, CH_3-N), 3.20 (m, 2H, CH_2 indolylmethyl), 4.69 (d, 1H, H-C5), 5.60 (s, 1H, H-C2), 7.05–8.06 (m, 9H, arom).

*(2R,5S)-1-Benzoyl-2-(*tert*-butyl)-5-(indol-3-yl)methyl-3-methylimidazolidin-4-one (**12b**)*

A mixture of freshly prepared crude N-(2′,2′-dimethylpropylidene)-L-tryptophan monomethylamide **11b** (Naef, 1985) (8.5 g, 25 mmol) and benzoic anydride (6.6 g, 30 mmol) was heated in an oil bath at 150°C for 1 hour. The reaction was cooled, then dissolved in CH_2Cl_2 (50 mL) and washed with Na_2CO_3 (2 × 25 mL) followed by water (50 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to yield a brown residue which solified to a powder after trituration with ether. Column chromatography with silica gel using CH_2Cl_2/MeOH (98 : 2) gave pure **12b** (2.2 g, 28%); H-NMR: $\delta(CDCl_3)$: 1.20 (9H, s, tBu), 3.06 (3H, s, N-CH_3), 3.28–3.30 (2H, d, 14 Hz), 4.23–4.28 (1H, t, H-C5), 5.61 (1H, s, H-C2), 6.69–6.71 (1H, d, arom), 6.83–6.92 (2H, m, arom), 7.06–7.11 (1H, m, arom), 7.21–7.38 (5H, m, arom), 8.08 (1H, br s, NH).

*(2R,5S)-1-Benzoyl-2-(*tert*-butyl)-5-[1-(*tert*-butyloxycarbonyl)indol-3-yl] methyl-3-methylimidazolidin-4-one (**12c**)*

To a solution of compound **11b** (1.946, 5 mmol) in anhydrous THF (25 mL) under argon was added 4-dimethylaminopyridine (60 mg) followed by di-*tert*-butyl dicarbonate (1.4 g, 6.4 mmol) and the mixture was stirred at room temperature for 48 h. A clear solution resulted and TLC (silica, AcOEt : hexanes, 2 : 1) showed a single product with rf 0.43. The solution was evaporated and triturated with ether (2 × 20 mL) to a white solid. Chromatography over silica with AcOEt : hexanes (2 : 1) as eluent gave the pure product (2.20 g, 90%); H-NMR $\delta(CDCl_3)$: 1.20 (s, 9H, t-Bu), 1.64 (s, 9H, t-BOC), 3.05 (s, 3H, N-CH_3), 3.28–3.29 (d, 2H, CH_2), 4.23–4.28 (t, 1H, H-C5), 5.42 (s, 1H, H-C2), 6.69–6.72 (d, 1H, arom), 7.0 (m, 2H, arom), 7.0–7.1 (m, 1H, arom), 7.2–7.3 (m, 5H, arom).

*(2R,5S)-1-Benzoyl-2-(*tert*-butyl)-5-[1-(*tert*-butyloxycarbonyl)indol-3-yl] methyl-3,5-dimethylimidazolidin-4-one (**13c**)*

To a stirred solution of anhydrous diisopropylamine (0.2 mL, 1.4 mmol) and HMPA (1 mL) in anhydrous THF 5 mL) cooled to −78°C was added nBuLi (0.56 mL of 2.5 M solution, 1.4 mmol). The reaction mixture was stirred at −78°C for a further 40 min. To the resulting LDA was slowly added a solution of (2R,5S)-1-benzoyl-2-(*tert*-butyl)-5-[1-(*tert*-butyloxycarbonyl)indol-3-yl]methyl-3-methylimidazolidin-4-one **12c** (0.250 g,

0.5 mmol) in anhydrous THF (5 mL) using a dry syringe. A deep red solution of the enolate was formed which was stirred at −78°C for a further 40 minutes after which time methyl iodide (1 mL) was added. The reaction mixture was stirred for a further 48 h at −78°C. A TLC (EtOAc:hexanes, 2:1) of the reaction mixture showed unreacted starting material and the formation of a product at rf 0.45. The mixture was then rotary evaporated and saturated NH_4Cl (3 mL) was added and the mixture was extracted with ether (6×10 mL). The ether extracts were combined, dried over anhydrous $MgSO_4$, filtered and evaporated to give an oily residue (0.268 g). Column chromatographic purification over silica eluting with EtOAc:hexanes (2:1) gave the pure **13c**; H-NMR $\delta(CDCl_3)$: (mixture of 2 rotamers): 0.67, 1.33 (s/s, 9H, t-Bu-C2), 1.42/1.60 (s/s, 9H, tBOC), 1.75/1.97 (s/s, 3H, CH_3-C5), 2.82/3.02 (s/s, 3H, CH_3 CH_3-C5-N), 3.37/3.94 (d, 2H, CH_2 indolylmethyl), 4.86/5.73 (s/s, 1H, H-C2), 6.71–7.60 (m, 8H, arom), 8.02–8.14 (m, 1H, arom).

*Hydrolysis of (2R,5S)-1-benzoyl-2-(*tert*-butyl)-5-[1-(*tert*-butyloxycarbonyl)indol-3-yl]methyl-3,5-dimethylimidazolidin-4-one 13c to α-methyl-L-tryptophan (**14b**)*

In a sealed tube was placed (2R,5S)-1-benzoyl-2-(*tert*-butyl)-5-[1-(*tert*-butyloxycarbonyl)indol-3-yl]methyl-3-methylimidazolidin-4-one (40 mg, 0.08 mmol) and freshly prepared NaOMe/MeOH (0.5 g Na metal in 5 mL dry MeOH) and mixture was heated in an oil bath at 210°C for 4 h. The mixture was allowed to cool to room temperature, quenched with H_2O (2 mL) and evaporated to dryness. The resulting solid was acidified with 10 N HCl (5 mL) and MeOH (1 mL) added. The resulting solution was again heated in a sealed tube at 210°C for 3 h. The mixture was allowed to cool to room temperature, then evaporated to dryness and treated with 10 N KOH (6 mL) and MeOH (1 mL). The resulting mixture was again heated in a sealed tube at 210°C for 4 h. After which time the mixture was allowed to cool to room temperature and then evaporated to dryness. The resulting solid was dissolved in water (5 mL) and neutralized with concentrated HCl. HPLC of the resulting solution using a chiral analytical column showed formation of α-methyl-L-tryptophan **14b**; H-NMR $\delta(D_2O)$: 1.43 (s, 3H, αCH_3), 3.11 (d, J = 15 Hz, 1H, CH_2), 3.27 (d, J = 15 Hz, 1H, CH_2), 7.07 (m, 1H, arom), 7.10 (m, 2H, arom), 7.34 (d, J = 8.1 Hz, arom), 7.52 (d, J = 7.9 Hz, 1H, arom).

*N-(2′,2′-Dimethylpropylidene)-L-phenylalanine, monomethyl amide (**11a**)*

L-Phenylalanine methyl ester hydrochloride (5.4 g, 25 mmol) was added portionwise to a stirred 8 M solution of anhydrous methylamine in anhydrous methanol (30 mL) at 0°C. The clear solution was kept at 0°C for 1 h and at 25°C for an additional 24 h. The resulting L-phenylalanine monomethyl amide was evaporated on the rotavapor to give a yellowish sticky oil which solidified on standing. A vigorously stirred suspension of the solid (5.2 g, 25 mmol) in pentane (50 mL) containing pivalaldehyde (4.5 mL, 1.5 eq.) was heated at reflux using a Dean-Stark apparatus to separate the H_2O formed. The sticky residue was completely dissolved after 2 h except for the finely powdered precipitate of methylammonium chloride. After filtration and evaporation the product was obtained as a clear oil which solidified on standing was obtained (5.3 g, 85%); rf 0.3 (hexane-EtOAc-Et_3N, 60:40:1).

*(2S,5R)-1-Benzoyl-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one (**12a**)*

A mixture of N-(2′,2′-Dimethylpropylidene)-L-Phenylalanine, monomethyl amide **11a** (5.0 g, 20 mmol) and benzoic anhydride (5.6 g, mmol) was heated in an oil bath at 150°C

for 1 h. The resulting dark yellow mixture was dissolved in CH_2Cl_2 (50 mL) and washed with 2 N Na_2CO_3 (2 × 25 mL) followed by H_2O (50 mL) and then dried over anydrous Na_2SO_4 and filtered. A precitate formed from the filtrate on standing which was removed by filtration. The second filtrate was evaporated to dryness and the residence was triturated with ether. The resulting solid was dissolved in hot CH_2Cl_2 and diluted with hexane to turbidity and the cooled. The crystals formed were collected by filtration, washed with hexane and air-dried to give the product, 5.6 g (80%); m.p. 182–7°C (lit.(ref) m.p. 193°C); H-NMR δ($CDCl_3$): 1.16 (s, 9H, t-Bu), 3.04 (s, 3H, N-CH_3), 3.06–3.10 (m, 2H, CH_2), 4.07–4.12 (q, 1H, H-C5), 5.57 (s, 1H, H-C2), 6.70–6.73 (q, 2H, arom), 7.10–7.14 (m, 3H, arom), 7.33–7.50 (m, 5H, arom).

*(2S,5R)-1-Benzoyl-5-benzyl-2-*tert*-butyl-3,5-dimethyl-imidazolidin-4-one (**13a**)*

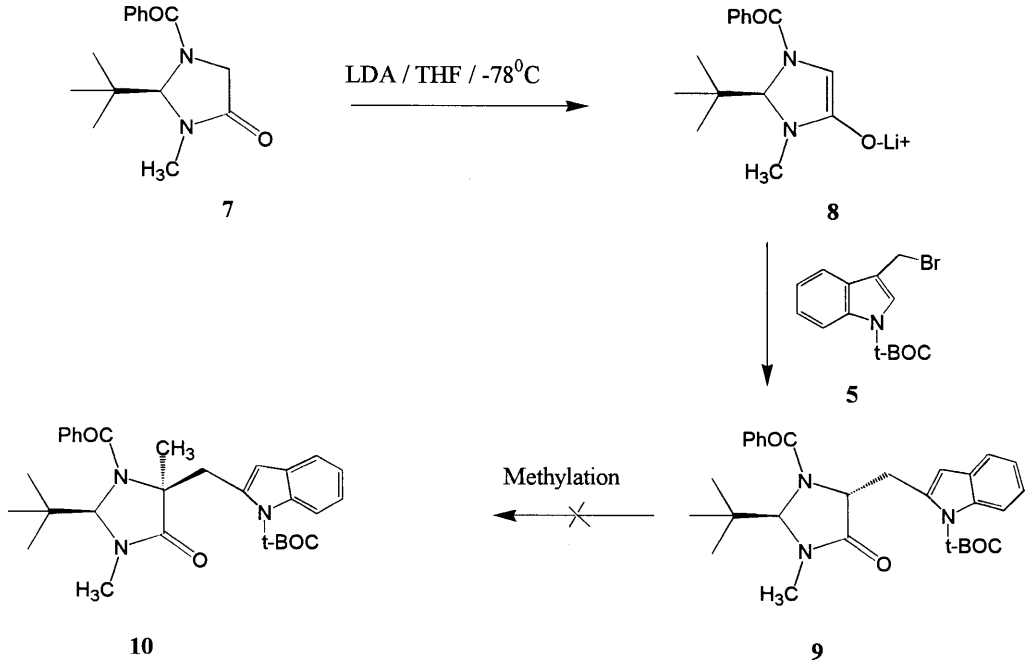
To a stirred solution of anhydrous diisopropylamine (0.100 mL, 0.7 mmol) and HMPA (1 mL) in anhydrous THF (5 mL) cooled to −78°C was added nBuLi (0.25 mL of 2.5 M solution, 0.625 mmol). The reaction mixture was stirred at −78°C for a further 40 min and to the resulting LDA was slowly added a solution of (2S,5R)-1-benzoyl-5-benzyl-2-*tert*-butyl-3-methyl-imidazolidin-4-one **12a** (0.105 g, 0.3 mmol) in anhydrous THF (5 mL) using a dry syringe. A deep red solution of the enolate was formed which was stirred at −78°C for a further 40 minutes after which time methyl iodide (1 mL) was added. The reaction mixture was stirred for a further 5 h at −78°C and then allowed to warm to room temperature. A TLC (EtOAc : hexanes, 1 : 1) of the reaction mixture showed the formation of a product at rf 0.61. The mixture was then rotary evaporated and saturated NH_4Cl (5 mL) was added and this was extracted with ether (6 × 10 mL). The ether extracts were combined, dried over anhydrous $MgSO_4$, filtered and evaporated to give the product. Column chromatographic purification over silica eluting with EtOAc : hexanes (1 : 1) gave the pure product (0.092 g, 84%); H-NMR δ($CDCl_3$): 0.69, 1.00 (s, H-C5), 2.90, 3.08 (s, NCH_3), 4.85, 5.24 (s, H-C2), 6.70–7.80 (m, arom).

*Hydrolysis of (2S,5R)-1-benzoyl-5-benzyl-2-*tert*-butyl-3,5-dimethyl-imidazolidin-4-one (**13a**) to α-methyl-L-phenylalanine (**14a**)*

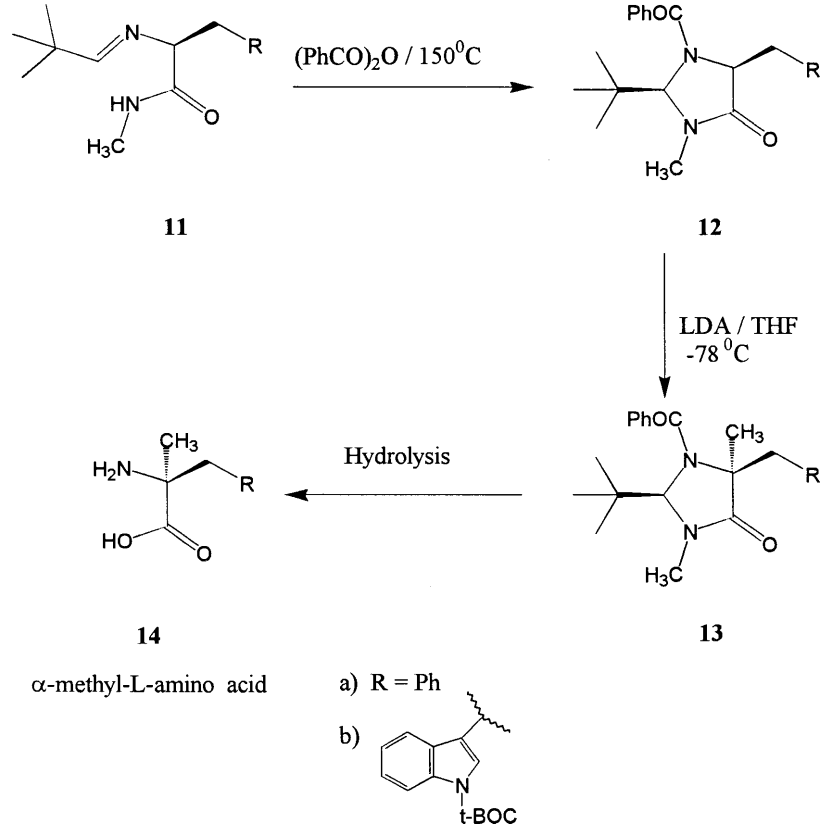
(2S,5R)-1-Benzoyl-5-benzyl-2-*tert*-Butyl-3,5-dimethyl-imidazolidin-4-one **13a** (0.092 g, 0.25 mmol) was treated with 10 N HCl (4 mL) and heated in a sealed tube at 210°C for 4 h. The resulting solution was cooled in ice and then rotary evaporated to dryness to give a white solid which redissolved in water (5 mL) and re-evaporated to dryness. Analysis of the solid, using chiral HPLC utilizing a WH chiral analytical column at 49°C and eluting with 10% methanol in aqueous 5 mM $CuSO_4$ as the mobile phase (1.5 mL/min flow rate), showed a-methyl-L-phenylalanine **14a** with retention time of 21.03 minutes.

Results and discussion

We decided to start with the readily available chiral glycine equivalent, (2R)-1-benzoyl-2-(tert-butyl)-3-methylimidazolidin-4-one **7** (Scheme 1). The reaction of **7** in tetrahydrofuran (THF) with lithium diisopropylamide (LDA) at −78°C gave a reddish-orange solution of the enolate of **8** which was alkylated with N-(tert-butyloxycarbonyl)indol-3-ylmethyl bromide **5** to give the 2,5-trans substituted product **9**. The incoming alkylating group approaches stereoselectively from the face trans to the bulky 2-*tert*-butyl group (Williams,



Scheme 1



Scheme 2

1989). Thus methylation of **9** should give compound **10** in which the 5-(N-tert-butyloxycarbonyl)indol-3-ylmethyl is cis to the 2-tert-butyl group. All our attempts at methylating compound **9** were unsuccessful. The reason for the failure to achieve methylation is not entirely clear but we reasoned that it could be due to the indolylmethyl group which would not invert into the position *cis* to the 2-*tert*-butyl largely because of steric hindrance.

We therefore pursued a different approach in which we prepared the chiral imidazolidin-4-one already containing 2,5-cis substituents **12** (Scheme 2). Alkylation of this should proceed with retention of configuration. Both the 5-benzyl **12a** and 5-indol-3-ylmethyl **12b** substituted 2,5-cis imidazolidin-4-ones were prepared following the procedure by Seebach (Naef et al., 1985). The Schiff base of the L-amino acid N-methyl amide and pivalaldehyde **11** was reacted with benzoic acid anhydride at 150°C to give the imidazolidin-4-ones **12**. In case of the 5-benzyl substituted 2,5-cis imidazolidin-4-one **12a**, the enolate was easily methylated with methyl iodide give **13a** which was hydrolysed by 10N hydrochloric acid in a sealed tube at 210°C gave α-methyl-L-phenylalanine as shown by chiral HPLC. Similarly, 5-indol-3-ylmethyl 2,5-cis disubstituted imidazolidin-4-one **12b** (Scheme 2) upon reaction with LDA at -78°C gave a deep reddish-orange solution of the enolate which was then reacted with methyl iodide to give the methylated product **13b**. However, compound **13b** could not be easily hydrolysed (Gander-Coquoz and Seebach, 1988) to the free amino acid. Hydrolysis was achieved by first converting **13b** into α-methyl-N-benzoyltryptophan methyl ester by reaction with sodium methoxide in methanol followed by partial hydrolysis with 10N hydrochloric acid in a sealed tube at 210°C for 3h to give α-methyl-L-tryptophan methyl ester hydrohydrochloride. Hydrolysis of the ester with 10N KOH at 210°C following by neutralization with hydrochloric acid gave α-methyl-L-tryptophan **14b**.

We are now in the process of trying to adapt this method for the synthesis of radiolabelled α-methyl-L-tryptophan.

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