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# Non-Proteinogenic Amino Acid Synthesis. The β-Anion Derived from Aspartic Acid, and its Application to α-Amino Acid Synthesis.

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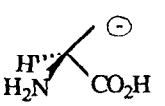
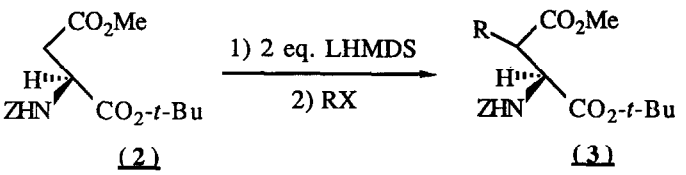
**Abstract:** Treatment of α-t-Butyl β-methyl N-Z-(S)-aspartate (2) with lithium amide bases generates the corresponding β-ester enolate, which can be alkylated with suitable electrophiles. The application of this strategy for synthesis of optically active amino acids has been investigated.

The non-proteinogenic α-amino acids represent an important group of natural products because of their varied biological and biochemical properties,[1] and the asymmetric synthesis of α-amino acids continues to be an active area of research.[2] One approach to these compounds, that of elaboration of the chiral pool, has been widely used, and in this paper we describe the synthesis and utility of a synthetic equivalent for the β-anion (1).[3] Although a number of β-anion synthons have been reported, derived from serine[4] or aspartic acid,[5,6] it seemed by analogy with some previous work[4-8] that suitably protected aspartic acid could be readily elaborated to non-proteinogenic amino acids. The synthesis of α-t-butyl β-methyl N-benzyloxycarbonyl-(S)-aspartate (2) was therefore undertaken; differential protection of the two carboxyl groups allowed subsequent selective deprotection, and the nitrogen function was blocked as the benzyloxycarbonyl derivative, since N-trityl aspartic acid derivatives have been reported to be difficult to handle and purify.[9,10]



(1)

(S)-Aspartic acid was converted into β-methyl (S)-aspartate hydrochloride in 95% yield by the method of Coleman,[11] as has been previously reported for the corresponding β-methyl glutamate derivative.[7] Treatment of this ester with benzyl-chloroformate and potassium carbonate gave β-methyl N-benzyloxycarbonyl-(S)-aspartate[12] in 91% yield, which was converted into the required diester (2) in 91% yield by treatment with isobutene and sulphuric acid[13,14] (Scheme 1). The optical rotation of diester (2) was identical to that previously reported.[15] The high overall yield of diester (2) (79%), and the easy purification of each of the intermediates made this synthesis particularly attractive.

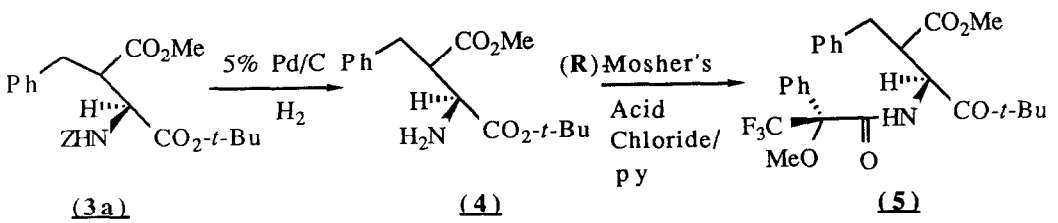



(2) (3)

a, R= $PhCH_2$ -

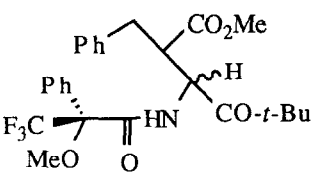
b, R= $CH_2$=$CHCH_2$- Z = $PhCH_2OC(=O)$-

Scheme 1




(3a) (4) (5)

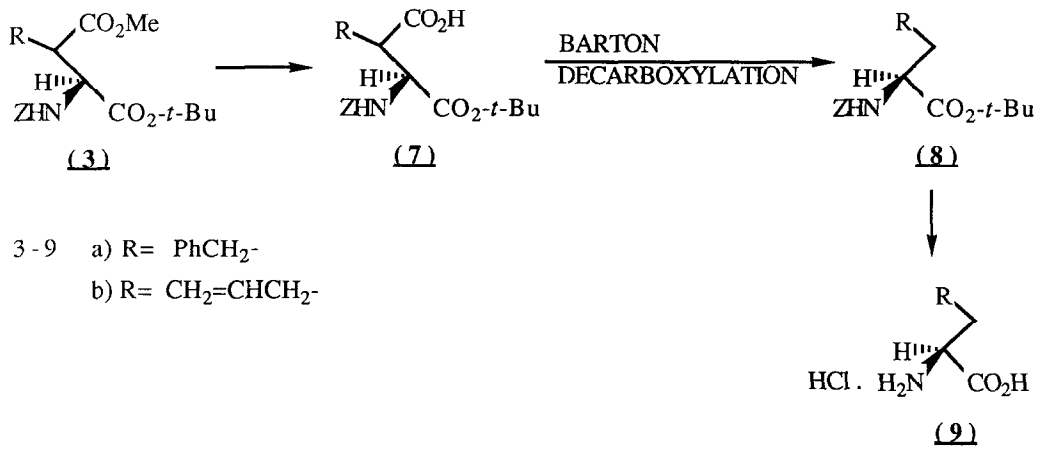
Scheme 2




(6)

Treatment of diester (2) with two equivalents of lithium di-isopropylamide (LDA), or lithium hexamethyldisilazide (LHMDS) in tetrahydrofuran (THF), at -78°C, followed by warming to -30°C, recooling to -78°C, and addition of an alkylating agent, resulted in formation of the β-alkylated adducts (3a and 3b) in 50-60% yield (Scheme 1). No products resulting from α-deprotonation were observed in these reactions, and the products (3a and 3b) were obtained as a mixture of diastereomers (5:1 and 3:1 respectively) at the β-carbon atom. Attempts to extend this reaction to less reactive alkylating agents (e.g. n-BuI, n-BuBr, and PrI) were unsuccessful, and resulted in recovered diester (2), or decomposition. Reaction of methyl iodide with the ester enolate of (2), generated using either LDA or LHMDS, gave a mixture of C and N alkylated products, and the addition of HMPA to any of these reactions had no beneficial effect.

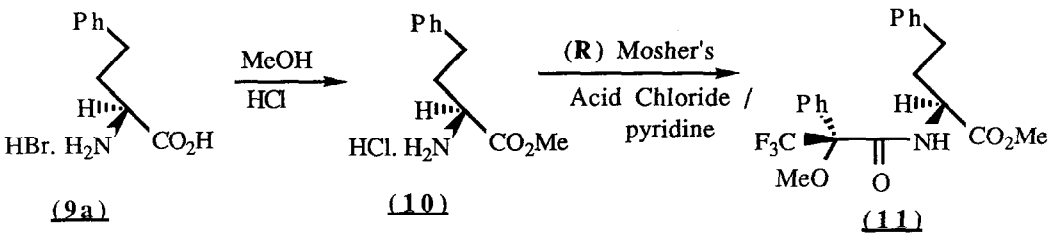
The optical purity at the α-centre of the products derived from the sequence shown in Scheme 1 was determined by the following method. Hydrogenolysis of diester (3a) gave amine (4), which was converted to the amide (5) by reaction with (R)-Mosher's acid chloride[16] (Scheme 2). The corresponding amide (6) derived from racemic aspartic acid was also prepared exactly as described for (S)-amide (6). The $^{19}F$ nmr spectrum of amide (6) contained two peaks of equal intensity for each epimer at the β-position, showing that the stereoisomers at the α-centre were being resolved. The corresponding spectrum of amide (5), which had been prepared from aspartate (2) using LDA as the base, also showed two peaks for each β-stereoisomer, and by integration of these peaks the enantiomeric excess (at the α-centre) was calculated as 85%. This indicated that partial racemisation had occurred at the α-centre during the alkylation reaction. However the $^{19}F$ nmr spectrum of amide (5), which had been prepared from aspartate (2) using LHMDS as the base, contained only one peak for each β-stereoisomer, showing that the adducts (3) were enantiomerically pure within the n.m.r. detection limits.



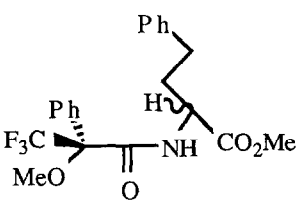

Scheme 3

The potential of diester (2) for subsequent elaboration to other optically pure amino acids was then investigated. Thus, treatment of diesters (3a and 3a) with lithium hydroxide in aqueous methanol[17] gave β-acids (7a and 7b), but attempted decarboxylation of acid (7a) under the reported conditions for similar aspartate derivatives[18] was unsuccessful, resulting in decomposition or recovery of unreacted acid (7a). Although similar difficulty with the decarboxylation of secondary acids has been reported,[19] by treating acid (7a or 7b) with 1-oxa-2-oxo-3-thiaindolizinium chloride[19] and using simultaneous reflux and irradiation in the presence of t-butyl thiol, a moderate yield of protected amino acids (8a and 8b) was obtained (38% and 28% respectively) (Scheme 3).

Amino ester (8a) was deprotected with HBr in acetic acid, giving homophenylalanine hydrobromide (9a) in good yield, but the optical rotation of (9a) was +36.2° (2% solution in 1.0M HCl), compared to the literature value[20] of +44.0° (2% solution in 1.0M HCl). This indicated an enantiomeric excess of 80%, and this result was confirmed by re-esterification with methanolic HCl; treatment of this ester (10) with (R)-Mosher's acid chloride[16] gave amide (11) as shown in Scheme 4. The $^{19}F$ nmr spectrum of amide (12), prepared from racemic homophenylalanine,[23] showed two peaks of equal intensity, corresponding to the two stereoisomers at the α-centre, and indicated that the




(9a) (10) (11)




(12)

Scheme 4

stereoisomers were resolved. The $^{19}F$ nmr spectrum of amide (10) showed the same two peaks, and by integration, the enantiomeric excess was calculated as 80%, in good agreement with the value obtained by optical rotation. Control experiments, in which α-t-butyl N-benzyloxycarbonyl-(S)-aspartate[21] was subjected to identical saponification conditions[17] (LiOH/MeOH/$H_2O$), and in which t-butyl N-benzyloxycarbonyl (S)-phenylalanine[22] was treated with HBr in acetic acid, indicated that racemisation was unlikely to occur in either of these two steps. From these results, it appeared that the partial racemisation observed in the formation of (9) occurred during the Barton decarboxylation reaction and this may well be due to the vigorous conditions which were required in order to obtain the desired product.

Thus, alkylation of the β-carbon of protected aspartic acid has been achieved, without disruption of the optical purity of the α-centre provided LHMDS is used to generate the intermediate ester enolate. The application of this chemistry to the synthesis of other amino acids is currently in progress.

## EXPERIMENTAL

General experimental procedures have been described.[7]

t-Butyl 2-benzyloxycarbonylamino-3-carbomethoxy-4-phenyl-(2S)-butanoate (3a)

To bis(trimethylsilyl)amine (12 ml, excess) in THF (100 ml) at 0°C under argon was added BuLi (0.9 M; 35 ml, 32 mMol). After stirring at RT for 10 minutes, the solution was cooled to -78°C and a solution of α-t-butyl β-methyl N-Z-(S)-aspartate[11-14] (2) (5.0, 15.0 mMol) in THF (50 ml) was added. The resulting red solution was allowed to warm to -30°C, and stirred at between -30°C and - 40°C for 45 minutes. The solution was recooled to -78°C, and benzyl bromide (5 ml, excess) was added. The resulting yellow solution was allowed to warm to room temperature over a period of 1 hour, then poured into 1 M hydrochloric acid (100 ml). The products were extracted with ether (3 x 100 ml), the combined organic phases were dried ($MgSO_4$) and evaporated in vacuo to give an orange oil which was subjected to flash chromatography (30% $Et_2O$/hexane) to give (3a) as a colourless oil which slowly crystallised. Yield 3.8 g (60%); (Found: C, 67.45; H, 6.8; N, 3.3. $C_{24}H_{29}NO_6$ requires: C, 67.4; H, 6.8; N, 3.3%); $\nu_{max}$ (neat) 3380 m, 3036 w, 2980 m, 1735 s and 1710 $cm^{-1}$ s; $\delta_H$ 1.43 and 1.45 (2 x 9H, s, $OC(CH_3)_3$), 2.7 -3.2 (2H, m, $PhCH_2$), 3.25 - 3.55 (1H, m, $CHCO_2Me$), 3.63 and 3.64 (2 x 3H, s, $OCH_3$), 4.46 (1H, dd, J 9.5 and 3.7 Hz, NCH major diastereomer), 4.5 - 4.65 (1H, m, NCH minor diastereomer), 5.11 and 5.17 (2 x 2H, s, $PhCH_2O$), 5.58 and 5.76 (2 x 1H, d, J 7.3 and 9.5 Hz, NH), 7.0 - 7.5 (10H, m, ArH); $\delta_C$ (DEPT) 27.76 and 27.93 (2 x q, $OC(CH_3)_3$), 34.04 and 34.44 (2 x t, $PhCH_2CH$), 48.74 and 50.22 (2 x d, $CHCO_2Me$), 51.45 and 51.77 (2 x q, $OCH_3$), 54.71 and 55.30 (2 x d, NCH), 66.98 (t, $PhCH_2O$), 82.47 and 82.97 (2 x s, $OCMe_3$), 126.56, 126.64, 126.96, 128.04, 128.44, 128.51, 128.93 and 130.08 (8 x d, ArCH), 136.39 and 138.12 (2 x s, ArC), 156.36 (s, $NCO_2$), 169.58, 169.63, 172.11 and 173.07 (4 x s, $CO_2$); m/z (DCI) 445 ($M+NH_4^+$, 100%), 428 ($MH^+$, 21), 389 (58).

t-Butyl 2-benzyloxycarbonylamino-3-carbomethoxy-(2S)-5-hexenoate (3b)

Compound (3b) was prepared in an identical manner to (3a) above, using diester (2)[11-14] (1.0 g, 3.0 mMol) and quenching the reaction with allyl bromide (1 ml, excess). The reaction mixture was then allowed to warm to RT over a period of 1 hour before being worked up as above. Flash chromatography (30% $Et_2O$/Hexane) gave (3b) as a colourless oil. Yield 440 mg (40%); $\nu_{max}$ (neat) 3390 m, 2980 m and 1725 $cm^{-1}$ s; $\delta_H$ 1.44 and 1.46 (2 x 9H, s, $OC(CH_3)_3$), 2.2 - 2.6 (2H, m, $=CHCH_2$), 3.0 - 3.2 (1H, m, $CHCO_2Me$), 3.62 and

3.68 (2 x 3H, s, $OCH_3$), 4.4 - 4.6 (1H, m, NCH), 5.0 - 5.2 (3H, m, $PhCH_2O$ and C=CH), 5.4 - 6.0 (3H, m, $C=CH_2$ and NH), 7.2 - 7.4 (5H, m, ArH). These peak assignments were confirmed by a proton COSY experiment. $\delta_C$ (DEPT) 27.78 and 27.98 (2 x q, $OC(CH_3)_3$), 37.84 and 39.85 (2 x t, $=CHCH_2$), 46.65 and 48.14 (2 x d, $CHCO_2Me$), 51.44 and 51.74 (2 x q, $OCH_3$), 54.60 and 54.93 (2 x d, NCH), 66.88 and 66.97 (2 x t, $OCH_2Ph$), 82.41 and 82.88 (2 x s, $OCMe_3$), 117.83 and 119.29 (2 x t, $CH_2=C$, 127.73, 127.96 and 128.42 (3 x d, ArCH), 131.31 and 134.32 (2 x d, C=CH), 136.32 and 136.58 (2 x s, ArC), 155.89 and 156.40 (2 x s, $NCO_2$), 169.53, 169.68, 170.45 and 170.70 (4 x s, $CO_2$); m/z (DCI) 378 ($MH^+$, 5%), 322 (78), 108 (34), 91 (100).

t-Butyl 2-amino-3-carbomethoxy-4-phenyl-(2S)-butanoate (4)

To N-Z compound (3a) (250 mg, 0.6 mMol) in degassed ethanol (10 ml) was added 5% Pd/C (100 mg). The mixture was stirred under a hydrogen atmosphere for 2.5 hours, diluted with ether (100 ml), filtered through celite, and the solvent evaporated *in vacuo* to give (4) as a colourless oil. Yield 170 mg (99%); $\nu_{max}$ (neat) 3394 w, 2980 m, 1735 s and 1155 $cm^{-1}$ s; $\delta_H$ 1.42 and 1.46 (2 x 9H, s, $OC(CH_3)_3$), 2.22 (2H, br, $NH_2$), 2.8 - 3.3 (3H, m, $PhCH_2$ and $CHCO_2$), 3.61 and 3.64 (2 x 3H, s, $OCH_3$), 3.6 - 3.8 (1H, m, NCH), 7.1 - 7.4 (5H, m, ArH); $\delta_C$ (DEPT) 27.38 and 27.74 (2 x q, $OC(CH_3)_3$), 33.58 and 34.37 (2 x t, $PhCH_2$), 50.29 and 50.46 (2 x d, $CHCO_2Me^*$), 51.26 and 51.43 (2 x q, $OCH_3$), 55.26 (d, $NCH^*$), 81.84 (s, $OCMe_3$), 127.39, 128.19, 128.27, 128.44, 128.63 and 129.11 (6 x d, ArCH), 137.69 and 138.90 (2 x s, ArC), 173.15 and 173.33 (2 x s, $CO_2$); m/z (CI) 294 ($MH^+$, 100%), 238 (40), 192 (36), 91 (16).

t-Butyl N-(2-methoxy-2-phenyl-3,3,3-trifluoro-(R)-propionoyl)-2-amino-3-carbomethoxy-4-phenyl-(2S)-butanoate (5)

To amine (4) (20 mg, 0.07 mMol) dissolved in $CDCl_3$ (0.5 ml) was added (R)-Mosher's acid chloride[16] (20 mg, 0.08 mMol) and pyridine (1 drop, excess). The solution was kept at RT for 30 minutes, then analysed by $^{19}F$ nmr spectroscopy, without purification. $\delta_F$ -71.00 and -70.90, for material prepared using LHMDS as the base; for material prepared using LDA as the base, two additional peaks at -70.50 and -70.80 ppm were observed (ratio 25:2).

α-t-Butyl β-methyl N-Z-(RS)-aspartate

This was prepared from (RS)-aspartic acid in three steps by the literature procedure for the corresponding (S)-isomer.[11-14] The overall yield was 79%, and the product was identical to the (S)-isomer (2) by t.l.c. and $^1H$ n.m.r. spectroscopy.

t-Butyl 2-benzyloxycarbonylamino-3-carbomethoxy-4-phenyl-(2RS)-butanoate

This compound was prepared according to the method described above for the corresponding (S)-isomer (3a), using racemic α-t-butyl β-methyl N-Z-aspartate. The product was obtained in 58% yield, and was identical to the optically pure (S)-isomer (3a) by t.l.c. and $^1H$ n.m.r. spectroscopy.

t-Butyl 2-amino-3-carbomethoxy-4-phenyl-(2RS)-butanoate

This compound was prepared according to the method described above for the corresponding (S)-isomer (4), using racemic diester. The product was obtained in 97% yield, and was identical to the optically pure (S)-isomer (4) by t.l.c. and $^1H$ n.m.r. spectroscopy.

t-Butyl N-(2-methoxy-2-phenyl-3,3,3-trifluoro-(R)-propionoyl)-2-amino-3-carbomethoxy-4-phenyl-(2RS)-butanoate (6)

This compound was prepared according to the method described above for the corresponding (S)-isomer (5), using racemic amine. $\delta_F$ -71.00 and -70.50 (ratio 1:1), and -70.90 and -70.80 (ratio 1:1).

t-Butyl 2-benzyloxycarbonylamino-3-carboxy-4-phenyl-(2S)-butanoate (7a)

To diester (3a) (3.2 g, 7.5 mMol) in MeOH (50 ml) was added a saturated solution of LiOH in $MeOH/H_2O$ (9:1) (50 ml), followed by sufficient MeOH to obtain an homogeneous solution. The resulting solution was stirred at RT for 18 hours, and the MeOH was evaporated *in vacuo*. The residue was partitioned between ether and 10% aqueous citric acid, and the product extracted with ether (3 x 100 ml). The combined organic phases

were dried ($MgSO_4$) and evaporated in vacuo, to give (7a) as a white foam. An analytical sample was obtained by flash chromatography (30% $Et_2O/CH_2Cl_2$). Yield 2.4 g (78%); (Found: C, 66.6; H, 6.3; N, 3.2. $C_{23}H_{27}NO_6$ requires: C, 66.8; H, 6.5; N, 3.4%); $\nu_{max}$ (nujol) 3000 br and 1720 $cm^{-1}$ s; $\delta_H$ 1.41 and 1.43 (2 x 9H, s, $OC(CH_3)_3$), 2.7 - 3.8 (3H, m, $PhCH_2CH$), 4.2 - 4.3 (1H, m, NCH minor diastereomer), 4.47 (1H, dd, J 9.7 and 3.4 Hz, NCH major diastereomer), 5.14 and 5.17 (2 x 2H, s, $PhCH_2O$), 5.80 and 5.91 (2 x 1H, d, J 9.5 and 9.7 Hz, NH), 7.1 - 7.5 (10H, m, ArH), 8.42 (1H, br, $CO_2H$); $\delta_C$ (DEPT) 27.62 and 27.76 (2 x q, $OC(CH_3)_3$), 40.16 and 40.86 (2 x t, $PhCH_2CH$), 48.58 and 49.94 (2 x d, $CHCO_2H$), 54.20 and 54.47 (2 x d, NCH), 66.31 and 67.06 (2 x t, $PhCH_2O$), 82.67 and 83.47 (2 x s, $OCMe_3$), 126.62, 126.96, 127.94, 128.36, 128.49, 128.88 and 129.99 (7 x d, ArCH), 134.86, 136.19 and 137.84 (3 x s, ArC), 154.51 and 156.55 (2 x s, $NCO_2$), 169.67, 169.77, 175.33 and 177.48 (4 x s, $CO_2$); m/z (DCI) 431 ($M+ NH_4^+$, 9%), 414 ($MH^+$, 18), 375 (64), 358 (100), 314 (43), 108 (51), 91 (86).

t-Butyl 2-benzyloxycarbonylamino-3-carboxy-(2S)-5-hexenoate (7b)

Compound (7b) was prepared in an identical manner to (7a) above using diester (3b) (330 mg, 0.9 mMol). Flash chromatography (30% $Et_2O/CH_2Cl_2$) gave (7b) as a colourless oil. Yield 180 mg (57%); $\nu_{max}$ (neat) 320 br, 1724 s and 1505 $cm^{-1}$ m; $\delta_H$ 1.41 and 1.47 (2 x 9H, s, $OC(CH_3)_3$), 2.2 - 2.7 (1H, m, $CHCO_2$), 2.8 - 3.3 (2H, m, $C=CHCH_2$), 4.4 - 4.7 (1H, m, NCH), 5.0 - 5.3 (4H, m, $PhCH_2O$ and C=CH and NH), 5.5 - 5.9 (2H, m, $C=CH_2$), 7.3 - 7.5 (5H, m, ArH), 8.35 (1H, br, $CO_2H$); $\delta_C$ (DEPT) 27.78 and 27.94 (2 x q, $OC(CH_3)_3$), 32.41 and 36.69 (2 x t, $C=CHCH_2$), 46.63 (d, $CHCO_2H^*$), 50.87 and 54.39 (2 x d, $NCH^*$), 66.41 and 67.14 (2 x t, $PhCH_2O$), 82.82 and 83.17 (2 x s, $OCMe_3$), 118.08 and 119.52 (2 x t, $C=CH_2$), 127.79, 128.03, 128.13, 128.41 and 128.47 (5 x d, ArCH), 131.13 and 134.17 (2 x d, C=CH), 136.17 and 136.82 (2 x s, ArC), 156.05 and 156.58 (2 x s, $NCO_2$), 169.37, 169.67, 175.30 and 175.74 (4 x s, $CO_2$); m/z (DCI) 381 ($M+ NH_4^+$, 84%), 364 ($MH^+$, 22), 325 (100), 308 (28), 285 (71), 91 (38).

t-Butyl N-Z-(S)-homophenylalanine (8a)

To acid (7a) (400 mg, 1.0 mMol) dissolved in sodium dried benzene (5 ml) under argon, was added 1-oxa-2-oxo-3-thiaindolizinium chloride[19] (400 mg, excess), followed by t-butyl thiol (0.5 ml, excess). The mixture was refluxed and irradiated with a 250 W tungsten lamp for 4 hours. The cooled mixture was evaporated in vacuo, the residue redissolved in ether (20 ml), washed with 1M hydrochloric acid (3 x 50 ml), and water (2 x 50 ml). The organic phase was dried ($MgSO_4$) and evaporated in vacuo. Flash chromatography ($CH_2Cl_2$ then 1% $Et_2O/CH_2Cl_2$) gave (12a), which was contaminated with t-butyl-pyridine disulphide. The crude product was dissolved in ether (50 ml) and washed with 1M hydrochloric acid (3 x 50 ml) to remove the disulphide. The ether layer was dried ($MgSO_4$) and evaporated in vacuo to give (8a) as a colourless oil which slowly crystallised. Yield 135 mg (38%); (Found: C, 71.3; H, 7.5; N, 4.0. $C_{22}H_{27}NO_4$ requires C, 71.5; H, 7.3; N, 3.8%); $[\alpha]_D^{\delta}$° + 12.0° (c 0.5 in $CHCl_3$); $\nu_{max}$ (neat) 3340 w, 3030 w, 2988 m and 1720 $cm^{-1}$ s; $\delta_H$ 1.48 (9H, s, $OC(CH_3)_3$), 1.8 - 2.3 (2H, m, $CHCH_2$), 2.6 - 2.8 (2H, m, $PhCH_2CH_2$), 4.34 (1H, dd, J 12.7 and 7.1 Hz, NCH), 5.13 (2H, s, $OCH_2Ph$), 5.36 (1H, d, J 7.7 Hz, NH), 7.0 - 7.4 (10H, m, ArH); $\delta_C$ 27.95 (q, $OC(CH_3)_3$), 31.41 and 34.65 (2 x t, $CH_2CH_2Ph$), 54.22 (d, NCH), 82.14 (s, $OCMe_3$), 126.05, 128.02, 128.07, 128.29 and 128.43 (5 x d, ArCH), 136.32 and 140.92 (2 x s, ArC), 156.62 (s, $NCO_2$), 171.30 (s, $CO_2$); m/z (CI) 370 ($MH^+$, 0.5%), 220 (40), 200 (100).

t-Butyl 2-benzyloxycarbonylamino-(2S)-5-hexenoate (8b)

Compound (8b) was prepared in an identical manner to (8a) above using acid (7b) (200 mg, 0.6 mMol). Flash chromatography (1% $Et_2O/CH_2Cl_2$) gave (8b) as a colourless oil. Yield 50 mg (28%), $\nu_{max}$ ($CHCl_3$) 3435 m, 2982 m and 1720 $cm^{-1}$ s; $\delta_H$ 1.47 (9H, s, $OC(CH_3)_3$), 1.6 - 2.2 (4H, m, $CH_2CH_2$), 4.2 - 4.4 (1H, m, NCH), 4.9 - 5.2 (2H, m, $C=CH_2$), 5.12 (2H, s, $OCH_2Ph$), 5.31 (1H, d, J 8.3 Hz, NH), 5.6 - 5.9 (1H, m, C=CH), 7.36 (5H, s, ArH); $\delta_C$ 28.04 (q, $OC(CH_3)_3$), 29.34 and 32.27 (2 x t, $CH_2CH_2$), 54.11 (d, NCH), 66.92 (t, $OCH_2Ph$), 82.11 (s, $OCMe_3$), 115.55 (t, $C=CH_2$), 128.09, 128.13 and 128.52 (3 x d, ArCH), 136.45 (s, ArC), 137.18 (d, C=CH), 155.92 (s, $NCO_2$), 171.14 (s, $CO_2$); m/z (CI) 337 ($M+ NH_4^+$, 7%), 320 ($MH^+$, 16), 281 (56), 264 (100), 220 (36), 108 (30), 91 (70).

(S)-Homophenylalanine hydrobromide (9a)

Protected amino acid (8a) (600 mg, 1.6 mMol) was dissolved in a solution of 40% hydrogen bromide in glacial acetic acid (12 ml). The resulting solution was stirred at RT for 45 minutes, and the solvents were evaporated *in vacuo* as an azeotrope with toluene. The resulting yellow solid was thoroughly washed with $CH_2Cl_2$ giving (9a) as a white solid. Yield 300 mg (71%); $[\alpha]_D^{20}$ +36.2° (2% solution in 1M hydrochloric acid) (lit.,[20] +44.0° 2% solution in 1M hydrochloric acid); $\nu_{max}$ (KBr) 3000 br and 1740 $cm^{-1}$ s; $\delta_H$ ($D_2O$) 2.0 - 2.2 (2H, m, $PhCH_2$), 2.5 - 2.7 (2H, m, $CHCH_2$), 3.90 (1H, t, J 6.2 Hz, NCH), 7.1 - 7.3 (5H, m, ArH); m/z (DCI) 180 ($MH^+$, 100%), 134 (26), 91 (17).

Methyl (S)-homophenylalanine hydrochloride (10)

Amino acid (9a) (150 mg, 0.6 mMol) was dissolved in methanol saturated with anhydrous HCl (5 ml), and the resulting solution stirred at RT for 18 hours. The solvent was evaporated *in vacuo*, giving (10) as a white solid. Yield 126 mg (95%); $\nu_{max}$ (KBr) 2950 br, and 1750 $cm^{-1}$ s; $\delta_H$ 1.80 (3H, br, $NH_3$), 2.3 - 2.5 (2H, m, $PhCH_2$), 2.8 - 3.0 (2H, m, $CHCH_2$), 3.70 (3H, s, $OCH_3$), 4.0 - 4.3 (1H, m, NCH), 7.1 - 7.3 (5H, m, ArH); m/z (CI) 194 ($MH^+$, 100%), 134 (30), 91 (12).

Methyl (RS)-homophenylalanine hydrochloride

This compound was prepared according to the method described above for amino ester (10) using racemic homophenylalanine[23] (250 mg, 1.4 mMol). Evaporation of the solvents gave methyl (RS)-homophenylalanine hydrochloride as a white solid. The product was obtained in 98% yield, and was identical to the (S)-isomer (10) by $^1H$ n.m.r. spectroscopy.

Methyl N-(2-methoxy-2-phenyl-3,3,3-trifluoro-(R)-propionoyl)-2-amino-4-phenyl-(S)-butanoate (11)

Compound (11) was prepared in an identical manner to (5) above using amine (10) (25 mg, 0.1 mMol). $\delta_F$ -70.88 and -70.57 ppm; ratio 5:1 for material obtained using LDA as base and 9:1 for material obtained using LHMDS as base.

Methyl N-(2-methoxy-2-phenyl-3,3,3-trifluoro-(R)-propionoyl)-2-amino-4-phenyl-(RS)-butanoate (12)

Compound (12) was prepared in an identical manner to (5) above using racemic methyl homophenylalanine hydrochloride (20 mg, 0.09 mMol). $\delta_F$ -70.88 and -70.57 (ratio 1:1).

α-t-Butyl N-Z-(S)-aspartate from α-t-butyl β-methyl N-Z-(S)-aspartate (2)

This compound was subjected to hydrolysis conditions in an identical manner to (3a) above using diester (2) (400 mg, 1.2 mMol). Flash chromatography (30% $Et_2O/CH_2Cl_2$) gave the product as a colourless oil. Yield 280 mg (70%); $[\alpha]_D^{25}$ +11.2° (c 0.8 in $CHCl_3$) (lit.,[24] -7.6° c 0.8 in $CHCl_3$); $\nu_{max}$ (neat) 3600-2400 br, and 1720 $cm^{-1}$ s; $\delta_H$ 1.44 (9H, s, $OC(CH_3)_3$), 2.85 (1H, dd, J 17.2 and 4.6 Hz, $CH_2CO_2$), 3.05 (1H, dd, J 17.2, and 4.3 Hz, $CH_2CO_2$), 4.53 (1H, dt, J 8.1 and 4.2 Hz, NCH), 5.12 (2H, s, $CH_2Ph$), 5.78 (1H, d, J 8.1 Hz, NH), 7.35 (5H, s, ArH), 8.44 (1H, br, $CO_2H$); m/z (DCI) 341 ($M+NH_4^+$, 100%), 324 ($MH^+$, 67), 285 (15), 268 (32), 224 (18), 178 (28), 108 (12), 91 (30).

α-t-Butyl β-methyl N-Z-(S)-aspartate (2) from α-t- butyl N-Z-(S)-aspartate

To the acid (50 mg, 0.15 mMol) dissolved in ether (10 ml) was added diazomethane dissolved in ether (excess). The resulting yellow solution was stirred at RT for 1 hour, the solvents were evaporated *in vacuo*, and the residue subjected to flash chromatography (4% $Et_2O/CH_2Cl_2$), giving (3) as a colourless oil. Yield 36 mg (69%); $[\alpha]_D^{23}$ -19.0° (c 1.5 in EtOH) (lit.,[15] -18.8° c 1.2 in EtOH); $\nu_{max}$ (neat) 3350 m, 2980 s and 1725 $cm^{-1}$ s; $\delta_H$ 1.42 (9H, s, $O(CH_3)_3$), 2.79 (1H, dd, J 16.5 and 4.5 Hz, $CHCO_2Me$), 2.96 (1H, dd, J 16.5, and 4.2 Hz, $CHCO_2Me$), 3.69 (3H, s, $OCH_3$), 4.4 - 4.6 (1H, m, NCH), 5.10 (2H, s, $CH_2Ph$), 5.77 (1H, d, J 8.4 Hz, NH), 7.2 - 7.4 (5H, m, ArH); m/z (CI) 355 ($M+NH_4^+$, 4%), 338 ($MH^+$, 20), 299 (30), 282 (100), 238 (42), 206 (44), 148 (64), 108 (40), 102 (46), 91 (87). This indicated that no racemisation occurred during the previous saponification step.

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References


1. P.J. Lea, R.M. Wallsgrove and B.J. Miflin, 'Chemistry and Biochemistry of the Amino Acids', G.C. Barrett (Ed.), Chapman and Hall, London, 1985, 207; M.A. Rogawski and J.L. Barker (Eds.), 'Neurotransmitter Actions in the Vertebrate Nervous System', Plenum, London, 1985, part 1; A. Osol (Ed.), 'Remington's Pharmaceutical Sciences 16th Ed.', Mack Publishing, Easton PA, 1980, 1170; J.E. Baldwin, 'Proceedings of the 3rd International Symposium on Recent Advances in the Chemistry of β-Lactam Antibiotics', A.G. Brown and S.M. Roberts (Eds.), The Royal Society of Chemistry, London, 1985, 62.

2. See for example: K.E. Koenig, 'Asymmetric Synthesis Vol. 5', J.D. Morrison (Ed.), Academic, London, 1985, Chapter 3; W. Oppolzer, R. Pedrosa and R. Moretti, Tetrahedron Lett., 1986, 27, 831; H. Kunz and W. Sager, Angew.Chem.,Int.Ed.Engl., 1987, 26, 557; C. Gennari, L. Colombo and G. Bertolini J.Am.Chem.Soc., 1986, 108, 6394; D.A. Evans, T.C. Britton, R.L. Dorow and J.F. Dellaria, J.Am.Chem.Soc., 1986, 108, 6395; L.A. Trimble and J.C. Vederas, J.Am.Chem.soc., 1986, 108, 6397; D.A. Evans and T.C. Britton, J.Am.Chem.Soc., 1987, 109, 6881; K. Weinges and H. Blackholm, Chem.Ber., 1980, 113, 3098; D. Seebach, M. Boes, R. Naef and W.B. Schweizer, J.Am.Chem.Soc., 1983, 105, 5390; D. Seeback, D.D. Miller, S. Muller and T. Weber, Helv.Chim.Acta, 1985, 68, 949; J.D. Aebi and D.Seebach, Helv.Chim.Acta, 1985, 68, 1507; R. Fitzi and D. Seebach, Angew.Chem., Int.Ed.Engl., 1986, 25, 345; D. Seebach, E. Juaristi, D.D. Miller, C. Schickli and T. Weber, Helv.Chim.Acta, 1987, 70, 237; U. Schollkopf, Top.Curr.Chem., 1983, 109, 66; U. Schollkopf, Pure Appl.Chem., 1983, 55, 1799; U. Schollkopf, H.J. Neubauer and M. Hauptreif, Angew.Chem., Int.Ed.Engl., 1985, 24, 1066; P.J. Sinclair, D. Zhai, J. Reibenspies and R.M. Williams, J.Am.Chem.Soc., 1986, 108, 1103; R.M. Williams, P.J. Sinclair, D. Zhai and D. Chen, J.Am.Chem.Soc., 1988, 110, 1547; L.D. Arnold, T.H. Kalantar and J.C. Vederas, J.Am.Chem.Soc., 1985, 107, 7105; L.D. Arnold, J.C.G. Drover and J.C. Vederas, J.Am.Chem.Soc., 1987, 109, 4649; L.D. Arnold, R.G. May and J.C. Vederas, J.Am.Chem.Soc., 1988, 110, 2237; J.A. Bajgrowicz, A. El Hallaoui, R. Jacquier, C. Pigiere and P. Viallefont, Tetrahedron Lett., 1984, 25, 2231.

3. For a preliminary account of some of this work, see J.E. Baldwin, M.G. Moloney and M. North, J.Chem.Soc.,Perkin Trans.1,1989, 833

4. N.A. Sasaki, C. Hashimoto and P. Potier, Tetrahedron lett., 1987, 28, 6069.

5. P.L. Feldman and H. Rapoport, J.Org.Chem., 1986, 51, 3882.

6. D. Seebach and D. Wasmuth, Angew.Chem., Int.Ed.Engl., 1981, 20, 971.

7. J.E. Baldwin, M. North, A. Flinn and M.G. Moloney, J.Chem.Soc., Chem.Commun., 1988, 828; J.E. Baldwin, M. North, A. Flinn and M.G. Moloney Tetrahedron, 1989, 1453; J.E. Baldwin, M. North, A. Flinn and M.G. Moloney, Tetrahedron, 1989, 1465.

8. G.J. McGarvey, R.N. Hiner, Y. Matsubara, and T. Oh, Tetrahedron Lett., 1983, 24, 2733; G.J. McGarvey, J.M. Williams, R.N. Hiner, Y. Matsubara and T. Oh, J.Am.Chem.Soc., 1986, 108, 4943.

9. B.D. Christie and H. Rapoport, J.Org.Chem., 1985, 50, 1239.

10. J.E. Baldwin, M. North and A. Flinn, Tetrahedron, 1988, 44, 637.

11. D. Coleman, J.Chem.Soc., 1951, 2294.

12. H. Schwarz, F.M. Bumpus and I.H. Page, J.Am.Chem.Soc., 1957, 79, 5697.

13. J. Tomasz, Acta.Chim.Acad.Sci.Hung., 1971, 70, 255;

14. P.M. Hardy, J.C. Haylock and H.N. Rydon, J.Chem.Soc., Perkin Trans. 1, 1972, 605.

15. I. Schon, T. Szirtes, T. Uberhardt, A. Rill, A. Csehi and B. Hegedus, Int.J.Pept.Protein Res., 1983, 22, 92.

16. J.A. Dale, D.L. Dull and H.S. Mosher, J.Org.Chem., 1969, 34, 2543.

17. T.W. Greene, 'Protective Groups in Organic Synthesis', Wiley, Chichester, 1981, 158.

18 D.H.R. Barton, D. Crich, Y. Herve, P. Potier and J. Thierry, Tetrahedron, 1985, 41, 4347; D.H.R. Barton, D. Bridon, Y. Herve, P. Potier, J. Thierry and S.Z. Zard, Tetrahedron, 1986, 42, 4983; D.H.R. Barton, J. Guilhem, Y. Herve, P. Potier and J. Thierry, Tetrahedron Lett., 1987, 28, 1413; D.H.R. Barton, Y. Herve, P. Potier and J. Thierry, Tetrahedron, 1987, 43 4297; D.H.R. Barton, Y. Herve, P. Potier and J. Thierry, J.Chem.Soc.,Chem.Commun., 1984, 1298.

19. D.H.R. Barton, D. Crich and W.B. Motherwell, Tetrahedron, 1985, 41, 3901.

20. H.N. Weller and E.M. Gordon, J.Org.Chem., 1982, 47, 4160.

21. M.R. Attwood, C.H. Hassall, A. Krohn, G. Lawton and S. Redshaw, J.Chem.Soc.,Perkin Trans. 1, 1986, 1011.

22. P.A. Stadler, Helv.Chim.Acta, 1978, 61, 1675.

23. Purchased from Sigma Chemical Company.

24. A. Vasella, R. Voeffray, J. Pless, and R. Huguenin, Helv.Chim.Acta., 1983, 66, 1241.