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SOLUTION SYNTHESIS OF N-METHYLATED PEPTIDES BY THE DIPHENYL PHOSPHINIC MIXED ANHYDRIDE PROCEDURE.

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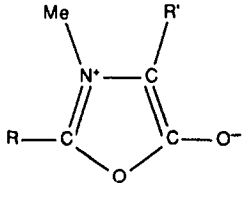
Abstract - A proton n.m.r. method has been used to monitor racemisation during the coupling of N-methylated amino acids by the diphenylphosphinic mixed anhydride procedure. No racemisation was observed when urethane protection was employed, but use of the benzoyl group led to extensive racemisation. The reagent was subsequently used for the assembly of several extensively N-methylated peptides.

The stability of the diphenylphosphinic (Dpp) mixed anhydrides towards disproportionation has been studied in detail[1] and ^{31}P n.m.r. spectroscopy shows that both mixed anhydride formation and the subsequent acylation is instantaneous. The shift in the ^{31}P signal representing the diphenylphosphinic carboxylic mixed anhydride, to that of the diphenylphosphinate anion was observed within the time needed to mix the reagents and place the sample in the spectrometer.[2]

There is little evidence in the literature, however, concerning the racemisation of N-methylated amino acids during diphenylphosphinic mixed anhydride activation, although in a standard Izumiya test on unmethylated amino-acids, it was found that 5.7% racemisation was encountered in the coupling of Z-Gly-Ala-OH to H-Leu-OBzl using this means of activation.[1] N-Methylated amino acids are particularly susceptible to racemisation during coupling using DCCI,[3,4] but the use of N-hydroxybenzotriazole (HOBt) or N-hydroxysuccinimide (HONSu) as additives has been found to be useful in the minimisation of the formation of the oxazolonium ion (1) which is the racemisation intermediate.



(1)

The work reported in this paper investigates the extent of racemisation observed during Dpp mixed anhydride coupling of N-methylated amino acids using a ^{1}H n.m.r. racemisation test.[4,5]

All amino acids are of the L-configuration unless otherwise specified; nomenclature and abbreviations follow the IUPAC-IUB Joint Commission on Biochemical Nomenclature (JCBN), 1983.

The formation of diastereoisomeric benzyloxycarbonyl dipeptide methyl esters during the coupling of Z-D,L-(Me)Leu-OH (2) or Z-L-(Me)Leu-OH (3) with the $Br^{-}H_2^{+}$-Ala-OMe (4) using DppCl

Standard conditions were used, viz, the formation of the mixed anhydride was allowed to was monitored by ^1H n.m.r. spectroscopy at 220 MHz and 250 MHz.

take place at -20°C using two equivalents of N-methylmorpholine (NMM) as base; the $Cl^{-}H_2^{+}$-Ala-OMe (4) was added to (2) and (3) respectively after twenty minutes activation. The reaction mixture was kept at this temperature for one hour and overnight at ambient temperature. Simple work-up of the reaction mixture afforded (A) Z-D,L-(Me)Leu-L-Ala-OMe (5) and (B) Z-X-(Me)Leu-L-Ala-OMe (6) (where X = L or partially D,L depending upon the extent of racemisation). The total residue from each coupling was analysed by ^1H n.m.r. spectroscopy at 220 MHz and 250 MHz in deuteriochloroform (The latter spectra are shown in Figure 1).

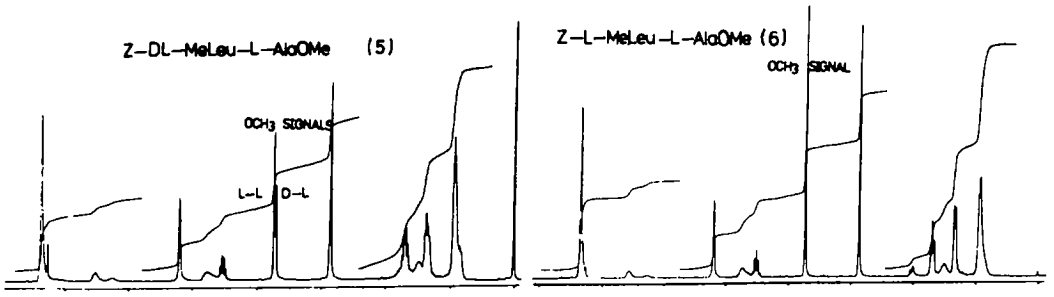


FIGURE 1 ^1H n.m.r. spectrum (250 MHz) of reaction mixtures A and B, Z-D,L-(Me)Leu-Ala-OMe (5) and Z-X-(Me)Leu-Ala-OMe (6) where X = D or L depending on the extent of racemisation.

The ^1H n.m.r. spectra of compound (5) showed two methyl ester signals at δ 3.73 and 3.70 (250 MHz), for the L-L and D-L diastereoisomers respectively, whereas the product of (B) gave one methyl ester signal at δ 3.73 (250 MHz), corresponding to the L-L form.

Separation of the diastereoisomeric methyl ester signals in the n.m.r. spectra at 220 MHz and 250 MHz was thus obtained. This result proved to be of interest as previously, it had been found[6] that a mixture of the benzyloxycarbonyl protected dipeptide methyl esters, Z-L-Val-L-Val-OMe and Z-D-Val-L-Val-OMe, gave methyl ester signals in the ^1H n.m.r. spectra (at 100 MHz) which were not separable. This suggested that the influence of the benzene ring might be of importance and that the low nucleophilic character of the urethane carbonyl group may reduce the ease of formation of the suggested hydrogen bonded seven-membered structure of the dipeptide methyl ester (see Figure 2). The extent of separation between the methyl ester signals, therefore, depends on the strength of the magnetic field, the bulkiness of the N-terminal amino acid side chain which gives rise to a larger separation due to steric interaction, and N-terminal substituents which would contribute differently by their shielding effects on the methyl ester groups of the L-L and D-L forms. In the proposed[6] seven-membered ring model conformation of a hydrogen-bonded N-benzoyl dipeptide methyl ester (Figure 2), the more packed conformation appears to be the D-L form.

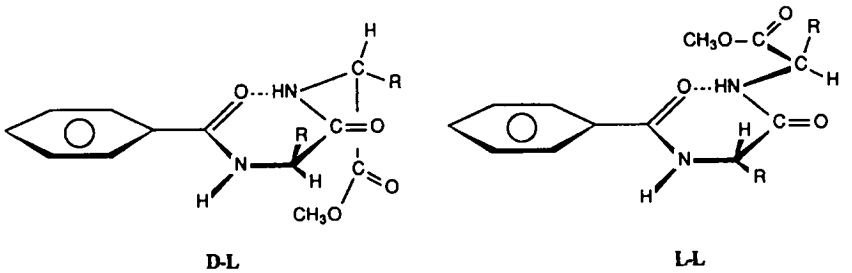


FIGURE 2 Conformation of the benzoyl dipeptide methyl ester in the D-L and L-L forms.

If the shielding effect exhibited by the N-terminal substituent (within the seven-membered cyclic hydrogen-bonded structure) on the methyl ester signals of the D-L form is increased, a greater separation of the methyl ester signals would be predicted. This would be possible if the benzyloxycarbonyl substituent was replaced by a group which provides more efficient shielding. Such an increased separation was accomplished by the removal of the benzyloxycarbonyl group from (5) and (6) by treatment with 36% HBr/AcOH, followed by subsequent replacement by a benzoyl group employing a modified Schotten-Baumann[7] procedure, using benzoyl chloride in the presence of triethylamine. The crude products Bz-D,L-(Me)Leu-L-Ala-OMe (7) and Bz-X-(Me)Leu-L-Ala-OMe (8) were analysed by ^{1}H n.m.r. in deuteriochloroform (Figure 3). The ^{1}H n.m.r. spectra of compound (7) showed two symmetrical methyl ester signals at δ 3.75 and 3.69 (250 MHz), for the L-L and D-L diasteriomeric forms respectively. The ^{1}H n.m.r. spectra of compound (8) showed only one methyl ester signal at 3.75 (250 MHz) corresponding to the L-L form. The benzoyl group of the diastereomeric methyl esters thus gave rise to an increased separation of 6.8 Hz when compared to the corresponding benzyloxycarbonyl compounds.

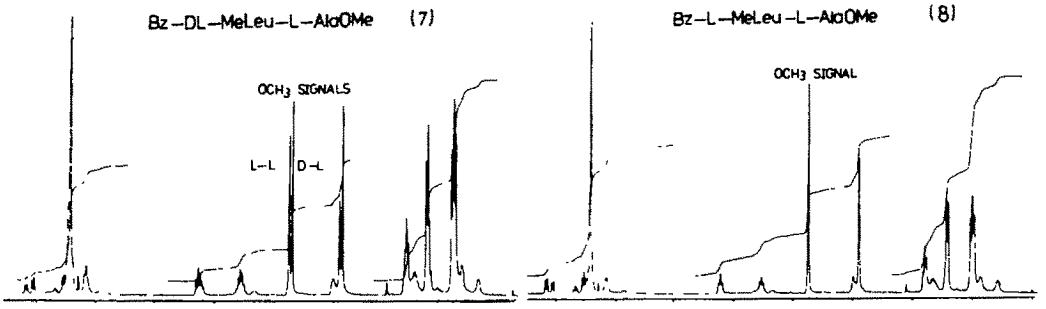


FIGURE 3 ^{1}H n.m.r. spectrum (250 MHz) of Bz-D,L-(Me)Leu-Ala-OMe (7) and Bz-X-(Me)Leu-Ala-OMe (8); where X = D or L depending on the extent of racemisation.

These results confirm that no racemisation occurs during Dpp mixed anhydride activation of benzyloxycarbonyl N-methylated amino acids within the limits of the n.m.r. method, and that the above benzyloxycarbonyl derivatives are chirally stable towards this type of activation.

The chiral stability of N-methylamino acids protected by non-urethane groups towards DppCl activation was then considered as the nature of the amino protecting group is known to influence racemisation as discussed earlier, by either increasing or decreasing the electron density on the nitrogen atom. In the case of urethane protecting groups, the reduction of electron density on nitrogen would result in an electron withdrawing effect. The benzoyl group was therefore, used as a typical non-urethane protecting group which would give information on the extent of racemisation which might be encountered in fragment condensation, where racemisation would be mediated by oxazolone formation.

Bz-X-(Me)Ala-L-Ala-OMe (9) (where X = L or D-L form depending on the extent of racemisation) was synthesised by coupling Bz-L-(Me)Ala-OH (10) with $Cl^-H_2^+$-Ala-OMe (4) using the DppCl, and DCCI/HOBt/-5°C[4] methods. The crude product from each coupling was analysed by ^{1}H n.m.r. (220 MHz). The DCCI/HOBt/-5°C method gave the benzoyl dipeptide methyl esters showing only one methyl ester signal at δ 3.72 corresponding to the L-L form. With the DppCl method, two symmetrical signals at δ 3.72 and 3.68 corresponding to the L-L and D-L forms respectively were observed. The addition of the amino component during coupling using DppCl, was made after periods of activation of one minute and twenty minutes, and in both cases the ratio of the methyl ester signals observed was 1:1 indicating that racemisation was very fast. The immediate observation of a yellow colour after the addition of DppCl to the solution of Bz-(Me)Ala-OH (10) indicated the formation of an oxazolonium intermediate,[4] which is assumed to be the racemisation source.

A series of experiments were then undertaken in order to study the optimum coupling conditions for the formation of N-methylated peptides. The results which are summarised in Table 1 showed that most of the conventional coupling methods afforded a mixture of products and laborious purification on silica gel or gel filtration columns was required. The exception to this was the Dpp mixed anhydride method which gave high yields of homogeneous, optically pure protected peptides; the only impurity being diphenylphosphinic acid which could be easily removed by chromatography on a short silica gel column.

COMPOUND	COUPLING METHOD[a]	ACTIVATION T°/time(h)	YIELD %	$[\alpha]_D^{20}$
Z-Val-(Me)Leu-OBu^t	DCCI/HOBt/THF[b]	- 5*	50	
	DCCI/HOBt/THF[b]	20/20	52	
	DCCI/HONSu/THF[b]	- 5*	10	
	ONSu ester/THF[b]	20/20	2	
	Piv.Cl/THF[b]	-20/1	57	-66.1 (c 2.3, MeOH)
	DppCl/THF	-20/1	93	-66.5 (c 1.1,MeOH)
Z-Abu-Sar-OBu^t	Piv.Cl/THF	-20/1	59	
	DppCl/THF	-20/1	69	
Z-(Me)Leu-(Me)Val-OBu^t	Piv.Cl/EtOAc	-20/1		
	DppCl/THF	-20/1	91	-141.8 (c 1, MeOH)
Z-(Me)Thr(Bu^t)-Abu-Sar-OBu^t	DCCI/HOBt/DCM	0/1	25	-23.4 (c 1, MeOH)
	DppCl/THF	-20/1	69	-44.7 (c 1.2, MeOH)
Z-(Me)Leu-(Me)Leu-(Me)Val-OBu^t	DCCI/HOBt/DCM	0/1	49	-173.5 (c 1, MeOH)
	DppCl/THF	-20/1	83	-167.2 (c 1.4, $CHCl_3$)
Z-(Me)Leu-Val-(Me)Leu-OBu^t	DCCI/HOBt/THF	0/2	38	-85.4 (c 1, MeOH)
	DppCl/THF	-20/1	85	-93.4 (c 1.2, MeOH)
Z-D-Ala(Me)Leu-(Me)Leu-(Me)Val-OBu^t	DCCI/HOBt/THF	0/2	40	
	DppCl/THF	-20/1	83	-131.7 (c 1, MeOH)
Z-Ala-D-Ala-(Me)Leu-Me(Leu)-(Me)Val-OBu^t	DCCI/HOBt/THF[b]	- 5/1*	60	-140.7 (c 1, MeOH).
	DppCl/THF	-20/1	88	-168.6 (c 1.1, $CHCl_3$

TABLE 1 Comparison of methods for the preparation of fully protected N-methylated peptides. After activation the reaction mixtures were allowed to attain room temperature except in the cases indicated (*) where the reaction was maintained at -5° throughout.
[a] Reaction time was 24h except where indicated, [b] 12h reaction.

Thus the diphenylphosphinic mixed anhydride method provides an excellent procedure for the synthesis of peptides containing N-methylated residues. When urethane protecting groups are used, racemisation is very low or non-existent, and yields of optically homogeneous products are high. Similar to other mixed anhydride methods, the diphenylphosphinic mixed anhydride procedure cannot be used for fragment couplings or couplings in which non-urethane amino group protection is employed.

Acknowledgements

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EXPERIMENTAL

Product purity was routinely checked using t.l.c. on Merck aluminium-backed plates with 0.2 mm layers of Kieselgel 60 F254 eluting with (1) DCM/EtOAc (A, 4:1; B, 3:1; C, 2:1; D, 1:1; E, 1:2; F, 1:3; G, 1:4), (2) $CHCl_3$/MeOH (99:1), (3) DCM/Petroleum ether (9:1), (4) $CHCl_3$/MeOH/AcOH (17:2:1) or (5) n-butanol/glacial acetic acid/water (4:1:1); detection was achieved using I_2 vapour, absorbance of U.V. light at 254 nm, bromocresol green or chlorine/starch/potassium iodide. Optical rotations were measured on a Bendix type 153 automatic polarimeter (1 cm cell) using the sodium D line. I.R. spectra were determined using sodium chloride cells or rock salt flat plates on Perkin Elmer 1320 spectrometer. ^{1}H N.m.r. spectra were recorded either on a Perkin Elmer R34 (220MHz) or a Bruker WM250 (250 MHz) spectrometer. Mass spectra were recorded on a VG 7070E spectrometer using E.I., C.I., DCI and FAB as ionisation systems. M.p.s. were recorded on a Koffer block and are uncorrected. Liquid chromatography separation was performed on a silica gel column using Kieselgel (60 - 230 mesh ASTM) with a variety of solvent systems.

Solvents were dried and distilled prior to use, THF and DMF dried over CaH_2, the latter being distilled in vacuo, and stored over molecular sieves type 5A.

General Procedures

Coupling using the diphenylphosphinic mixed anhydride method.

A solution of the N-protected amino acid (1.1 equiv.) and NMM (2 equiv.) in THF (2.4 mM/ml) was cooled to -20°C. DppCl (1.1 equiv.) in THF (2.4 mM/ml) was cooled to -20°C and added to this solution. The reaction mixture was stirred for ten to twenty minutes at -20°C, and the cooled amino component at -20° (1 equiv.) in THF (2.4 mM/ml) added. The suspension was stirred for one to two hours at -20°C and 24 - 48 hours at ambient temperature. The solvent was evaporated and the residue taken up into ethyl acetate, washed successively with brine, 1M $KHSO_4$, 1M $NaHCO_3$ and water. The organic phase was dried over Na_2SO_4 and evaporated to give a residual oil or solid containing trace amounts of diphenylphosphinic acid. Products were generally purified by silica gel chromatography using various solvent systems. The dipeptide-methyl esters used for the racemisation test were subjected to ^1H n.m.r. as crude products.

Coupling using the DCCI/HOBt/-5°C method.

DCCI (1 equiv) in THF (1 mM/2.5 ml) was added to a mixture of the N-protected amino acid (1 equiv.), the amino component (1 equiv.), HOBt (1 equiv.) and NMM (1 equiv.) in THF at -5°C and the mixture was stirred at -5°C for twelve hours. The precipitated urea was filtered and the filtrate was washed successively with 1M $KHSO_4$, 1M $NaHCO_3$ brine and water. The organic phase was dried over Na_2SO_4 and evaporation of the solvent gave an oil or solid, which was purified by silica gel chromatography, except for the dipeptide methyl esters, used in the racemisation test, which were analysed by ^1H n.m.r. as crude products.

Coupling, using the pivalic mixed anhydride method.

Pivaloyl chloride (1 equiv.) was added to a solution of the N-protected amino acid (1 equiv.) and NMM (1 - 2 equiv.) in THF at -20°C. The reaction mixture was stirred (2 - 5 min.) at -20°C followed by the addition of the amino component (1 equiv.). The suspension was stirred for two hours at -15°C and overnight at ambient temperature. The reaction mixture was evaporated to dryness and the residue extracted into ethyl acetate, washed successively with 1M $KHSO_4$, 1M $NaHCO_3$, brine and water, then dried over Na_2SO_4 and evaporated. The residue was subjected to chromatographic purification as required.

Z-D,L-(Me)Leu-OH (2) and Z-(Me)Leu-OH (3)

These compounds were prepared from the corresponding benzyloxycarbonyl amino acids using the method of Coggins and Benoiton.[8] Z-D,L-(Me)Leu-OH (2) 84%, oil, (lit.,[8] oil), $[\alpha]_D^{25}$ 0 (c 1, EtOH); Z-(Me)Leu-OH (3) 85%, m.p., 74 - 75°C, (lit.,[10] 73 - 74°C), $[\alpha]_D^{25}$ -25.8° (c 1, EtOH), (lit.,[10] $[\alpha]_D^{25}$ -23° (c 1, EtOH). Calculated for $C_{14}H_{21}NO_4$; C, 64.46; H, 7.58; N, 5.01. Found: C, 64.61; H, 7.51; N, 5.01%; δ_H (220 MHz, $CDCl_3$), 1.06 (6H, m, $CH(CH_3)_2$), 1.58 (1H, m, $-CH(CH_3)_2$), 1.74 (2H, m, β-CH_2-CH), 2.81, 2.78 (3H, 2s, N-CH_3, cis- and trans-rotamers), 4.79, 4.97 (1H, 2t, α-C-H, cis- and trans-rotamers), 5.19 (2H, s, $PhCH_2$-), 7.33, 7.31 (5H, 2s, ArH, cis- and trans-rotamers), and 11.56 (1H, s, COOH), m/z 279 (M^+, DCI).

Cl H_2^+-Ala-OMe (4).

The compound was prepared using the method of Zahn[9] by reaction of a methanolic solution of alanine with thionyl chloride, (79% yield), m.p., 106 - 108° (lit.,[9] m.p., 108°), $[\alpha]_D^{25}$ + 8.63° (c 1.75, MeOH), (lit.,[9] $[\alpha]_D^{25}$ + 9.0°, (c 2, MeOH),) δ_H (220 MHz, D_2O), 1.56 (3H, d, $CH.CH_3$), 3.81 (3H, s, OCH_3), and 4.2 (1H, q, $CH.CH_3$).

Preparation of Z-D,L-(Me)Leu-Ala-OMe (5) and Z-(Me)Ala.OMe (6).

Experiments A and B were carried out by coupling Z-D,L-(Me)Leu-OH (2) in the case of A, and Z-(Me)Leu-OH (3) in the case of B, to Cl H_2^+-Ala-OMe (4) by the Dpp mixed anhydride procedure which is described above. The total product was examined by ^1H n.m.r. at 220 and 250 MHz in $CDCl_3$; (2) δ_H (220 MHz), 0.90 (6H, m, $CH(CH_3)_2$Leu), 1.25 (3H, d, $CHCH_3$Ala), 1.63 (3H, m, $CHCH_2$), 2.84 (3H, s, N-CH_3), 3.71 and 3.74 (3H, 2s, OCH_3 L-L and D-L diastereoisomers), 4.47 (1H, t, αCH-(Me)Leu), 4.72 (1H, m, αCH-Ala), 5.16 (2H, s, $PhCH_2$), 6.57 (1H, br., NH), and 7.36 (5H, s, ArH); (3) δ_H (220 MHz), 0.91 (6H, m, $CH(CH_3)_2$Leu), 1.24 (3H, d, $CHCH_3$Ala), 1.64 (3H, m, $CHCH_2$), 2.84 (3H, s, N-CH_3), 3.71 (3H, s, OCH_3, L-L diastereoisomers), 4.48 (1H, t, αCH-(Me)Leu), 4.71 (1H, m, αCH-Ala), 5.17 (2H, s, $PhCH_2$), 6.57 (1H, br., NH), and 7.35 (5H, s, ArH).

Subsequently, compounds prepared in both experiments were purified by silica gel chromatography using EtOAc/DCM (1:3) as eluant; this afforded Z-D,L-(Me)Leu-Ala-OMe (2) as an oil (77%), $[\alpha]_D^{25}$ - 4.2° (c 1, MeOH), m/z 365 (M^+, DCI) and Z-X-(Me)Leu-Ala-OMe (3) (where X = L or D, depending on the extent of racemisation) also as an oil (90%), $[\alpha]_D^{25}$ - 52.8° (c 1, MeOH), m/z 365 (M^+, DCI).

Conversion to the benzoylated derivatives (7) and (8).

The dipeptide hydrobromides were first prepared by treating compounds (2) and (3) prepared in experiments A and B above with 36% HBr in acetic acid.

Compounds (2) and (3) (2.1g, 6 mM) were treated with 36% HBr/acetic acid (6g) under anhydrous conditions. Each reaction mixture was stirred at room temperature for two hours, the solvent was then evaporated under vacuum and the residues decanted several times with ether.

The hydrobromides were then benzoylated using a modified Schotten Baumann procedure. The hydrobromides (622 mg, 2 mM) were each dissolved in dichloromethane (10 ml) and treated

separately with triethylamine (0.27 ml, 2 mmol). The mixture was cooled to 0°C and treated with cold solutions of benzoyl chloride (250 mg, 2 mmol) followed by the addition of further triethylamine (0.27 ml, 2 mmol). The reaction mixtures were stirred at ambient temperature for twelve hours. Triethylammonium hydrochloride was then filtered and the solvent evaporated in vacuo. The residues were taken into ethyl acetate, washed successively with 1M HCl, 1M $NaHCO_3$, water, dried over Na_2SO_4 and evaporated to give oils (7) and (8) which were analysed directly by ^1H n.m.r. (220 and 250 MHz) in $CDCl_3$ solution; Bz-D,L-(Me)Leu-Ala-OMe (7), δ_H ($CDCl_3$), 0.98 (6H, m, $CH(CH_3)_2$), 1.42 (3H, d, $CHCH_3$), 1.75 (3H, m, CH_2CH), 3.13 (3H, s, NCH_3), 3.70 and 3.76 (3H, 2s, OCH_3 L,L and D,L diastereoisomers), 4.55 (1H, t, αCH-Ala), 5.20 (1H, m, αCH-(Me)Leu), 7.04 (1H, br., CONH), and 7.46 (5H, s, ArH); Bz-(Me)Leu-Ala-OMe (8), δ_H ($CDCl_3$), 0.98 (6H, m, $CH(CH_3)_2$), 1.42 (3H, d, $CHCH_3$), 1.76 (3H, m, CH_2CH), 3.13 (3H, s, NCH_3), 3.76 (3H, s, OCH_3, L,L form), 4.55 (1H, t, αCH-Ala), 5.20 (1H, m, αCH-(Me)Leu), 7.04 (1H, br., CONH), and 7.46 (5H, s, ArH).

The compounds were then purified by silica gel chromatography EtOAc/DCM (1:1). (7) Was obtained as an oil (76%), $[\alpha]_D^{24}$ +0.98° (c 1.8, MeOH), m/z 335 (M+, DCI); (8) also obtained as an oil (75%), $[\alpha]_D^{25}$ - 61.6° (c 1, MeOH), m/z 335 (M+, DCI).

Assessment of racemisation in the formation of Bz-X-(Me)Ala-Ala-OMe (9)

(a) By the DCCI/HOBt/-5° method.

Compound (9) was synthesised from Bz-(Me)Ala-OH (10) and $Cl^-H_2^+$-Ala-OMe (4) using the general DCCI/HOBt/-5° procedure described above. The reaction afforded the protected dipeptide (9) as an oil which was analysed directly by ^1H n.m.r. (220 MHz) in $CDCl_3$ giving; δ_H ($CDCl_3$), 1.44 (6H, dd, 2 x $CHCH_3$), 2.90 (3H, s, NCH_3), 3.74 (3H, s, OCH_3, L,L form), 4.54 (1H, q, αCH-(Me)Ala), 5.16 (1H, m, αCH-Ala), 7.05 (1H, br., NH), and 7.32 (5H, s, ArH). Subsequent purification of this compound on a silica gel column gave crystalline Bz-(Me)Ala-L-Ala-OMe (9), m.p., 106 - 107°C (from ether/petroleum ether), $[\alpha]_D^{25}$ - 128.4° (c 1, $CHCl_3$), m/z 293 (M+, DCI).

(b) By the diphenyl phosphinic mixed anhydride method.

Bz-(Me)Ala-OH (10) and $Cl^-H_2^+$-Ala-OMe (4) were coupled using the general DppCl procedure already described. This gave (9) as an oil which was analysed directly by ^1H n.m.r. (220 MHz) in $CDCl_3$, giving; δ_H ($CDCl_3$), 1.44 (6H, dd, 2 x $CHCH_3$), 2.91 (3H, s, NCH_3), 3.70 - 3.74 (3H, 2s, OCH_3, D,L and L,L diastereoisomers), 4.54 (H, q, αCH-(Me)Ala), 5.16 (1H, m, αCH-Ala), 7.05 (1H, br., NH) and 7.32 (5H, s, ArH).

Bz-(Me)Ala-OH (10)

This compound was prepared by the method of Coggins and Benoiton[8] having m.p., 120 - 122° (from ether) (lit.,[4] 120-122°), $[\alpha]_D^{28}$ - 62.5 (c 1.3, $CHCl_3$), (lit.,[4] $[\alpha]_D^{24}$ -62.5° (c 1.3, $CHCl_3$); δ_H ($CDCl_3$); 1.46 (3H, 2d, overlapping rotational isomers $CHCH_3$, 2.93 (3H, s, NCH_3), 4.44 - 5.23 (1H, 2m, and, 7.37 (5H, s, ArH).

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