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SYNTHESIS OF NOVEL α-AMINO-ACIDS AND DERIVATIVES USING RADICAL CHEMISTRY: SYNTHESIS OF L- AND D-α-AMINO-ADIPIC ACIDS, L-α-AMINOPIMELIC ACID AND APPROPRIATE UNSATURATED DERIVATIVES

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Abstract - *Radicals generated by photolysis (W light) of suitably protected amino-acid derivatives of N-hydroxy-2-thiopyridone add efficiently to activated olefins to afford satisfactory yields of adducts. Oxidation of the thiopyridyl residue to sulphoxide and thermal elimination afford excellent yields of the corresponding α,β-unsaturated derivatives. Lateral chain decarboxylation of suitably protected aspartic and glutamic acids provides convenient syntheses of L-α- and D-α-aminoadipic acids, of L-α-aminopimelic acid and of L-α-amino-δ-trans-dehydropimelic acid.*

INTRODUCTION

The presence of α-aminoadipic and α-aminopimelic acids, has been shown in plants and microorganisms[1,2]. α-Aminoadipic acid is a known product of lysine metabolism[3]. In its D form, it is also a constituant of the Arnstein tripeptide, the acyclic precursor of penicillin N. Because of its importance as a constituent of this antibiotic, α-aminoadipic acid has been the target of several synthetic studies. Rosowsky et al.[4] have used L-α-aminoadipic acid as well as L-α-aminopimelic acids in the synthesis of methotrexate analogous. Another study has shown that α-aminopimelic acid can replace diaminopimelic acid in bacterial metabolism[5]. Diaminopimelic acid is an essential constituent of the bacterial membrane and the inhibition of its biosynthesis from aspartic acid has been shown to lead to an antibiotic[5] when coupled with alanine or proline; α-Aminopimelic acid alone is not transported into the cell.

Since Dieckmann in 1894,[6] many syntheses of α-aminoadipic and α-aminopimelic acids have been described[3,7,8]. A summary of the early syntheses of aminopolycarboxylic acids has been given by Greenstein and Winitz[9]. However, in all these syntheses, the products were racemates and required enzymatic resolution[10,11]. More recently, L-α-aminoadipic and L-α-aminopimelic acids have been prepared from L-glutamic acid and its higher homologue, respectively, using the Arndt-Eistert reaction.[12,13] In 1980, Scott and Wilkinson prepared L-α-aminoadipic acid by degradation of lysine with sodium hypochlorite.[14]

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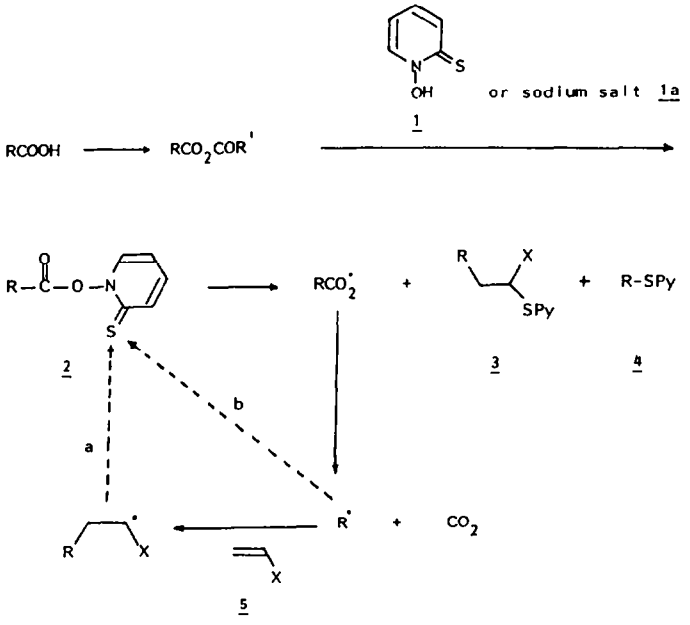
Recently this reaction has been improved using t-butylhypochlorite.[15] In 1982, Baldwin et al. obtained L-α-aminoadipic acid, selectively protected, also from a derivative of lysine.[16] Buckley and Rapoport transformed L-Z-lysine into L-Z-α-aminoadipic in an original biomimetic reaction.[17] However, Sklavounos considered all these syntheses unsuitable for large scale work and made[18] D-α-aminoadipic acid in large quantities by hydrolysis of cephalosporin C. L-α-Aminopimelic acid was obtained in 1983 by Rosowsky et al., by condensation of Meldrum's acid with glutamic acid.[4] One year after, the D-isomer was prepared by Maurer et al. from L-serine.[19]

Much less has been reported for the unsaturated analogs of these amno acids. Allan realised[20] a synthesis of racemic unsaturated analogous of α-aminoadipic acid, resolution being effected with lysine. In addition, racemic γ,δ-unsaturated iminoesters can be obtained from the reaction of 4-bromo-2-butenoates with the anions of the imines of the α-aminoesters.[21] To our knowledge, the only synthesis which permits one to obtain directly L-5-amino-2-hexenedioic acid is the one of Ramsamy et al.[22] in which the carboxyl of protected L-glutamic acid is reduced to alcohol, then oxidised to aldehyde and condensed with the appropriate Wittig reagent.

In summary, the classical methods for the preparation of these important amino acids require resolution of the racemate mixture and the other syntheses described involve multistage reactions.

The syntheses we wish to report here are generally high yielding, clean and yield, when the radical is not based on an asymetric centre, optically pure compounds. The approach is based upon our recent free radical generation using O-ester 2 of the thiohydroxamic acid 1 for the decarboxylative functionalisation[23] of a variety of carboxylic acids. This method is particularly well adapted to the modification of amino acids and peptides and especially the side chain of aspartic and glutamic acids.[24] The olefins chosen for the functionalisation are activated by an electron withdrawing substituent.[33] For each case, optimum conditions have been chosen to avoid polymerisation of the olefin.[26] The reaction proceeds by the simple radical chain mechanism depicted in Scheme 1 (path a) involving the intermediacy of disciplined carbon radicals.

Scheme 1. Mechanism involved in trapping of radicals.



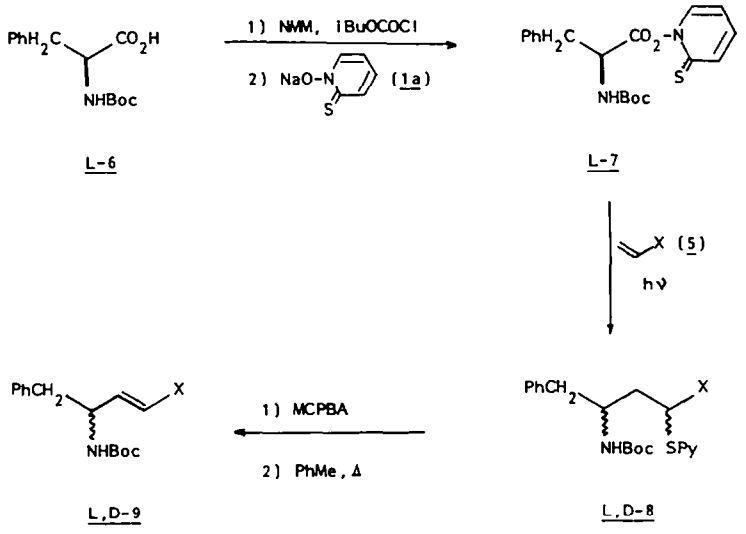
RESULTS

I. Synthesis of Unsaturated Amino Acid Derivatives.

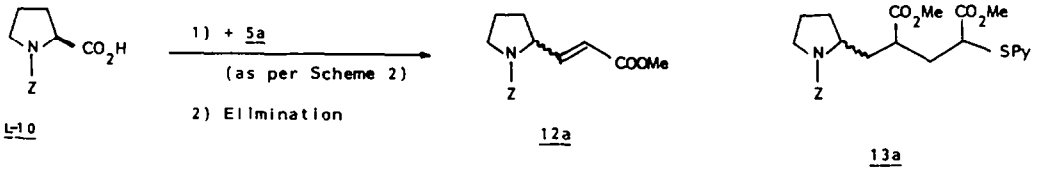
A. α-Carboxyl decarboxylation.

The decarboxylation reaction was first studied with N-Boc-L-phenylalanine 6 (Scheme 2). The ester 7 was formed in situ by reaction of the mixed anhydride of the aminoacid and the sodium salt of the N-hydroxy-2-thiopyridone. Irradiation in the presence of 5 equivalents of the appropriate olefin gave the racemic adduct. For the addition of radicals to nitroethylene 5c, camphosulfonic acid was added to minimise base-catalysed side reaction.[26] The experiments were also performed with methyl acrylate 5a and acrylonitrile 5b. The addition products 8a, 8b and 8c were obtained in good yields (see Table 1), as a mixture of stereoisomers. Then these adducts were transformed into unsaturated compounds 9a and 9b by oxidation with m-chloroperbenzoic acid followed by heating under reflux in toluene (see Experimental). The stereochemistry of the double bond is always E, as determined by NMR. The coupling constant of the two vinylic protons being 16 Hz in all cases. Elimination from compound 8c, led to a complexe mixture which was not investigated further. As expected, adducts formed by α-decarboxylation were racemic, showing no optical rotation.

Scheme 2. α-Decarboxylation Leading to Racemic β, γ-unsaturated Amino Acid Derivatives (see Table 1).

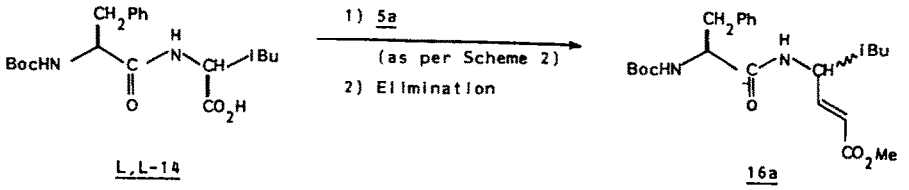


In a related study the proline derivative 10 was converted to the addition product 11a, as a mixture of isomers in 60% yield. The product 13a of double addition to olefin 5a was also



isolated in 17% yield. Oxidation and elimination converted the adduct 11a in good yield (87%) into the racemic E-olefin 12a.

It was of interest to see if a dipeptide would permit some degree of asymmetric synthesis. The L, L-dipeptide 14 was converted (62%) into the mixed isomers 15a. Oxidation and elimination afforded the E-isomer mixture 16a (86%). This could be separated into two isomers in approximately equal amounts. There was, therefore, little asymmetric induction.



L,L-14 16a

Table 1. α-Decarboxylation of N-Boc-L-Phenylalanine with Various Olefins (see Scheme 2).

CH_2=CHZ (5 eq.)	Addn. Prod. (Yield)	Elim. Prod. (Yield)
CH_2=$CHCO_2Me$ (5a)	8a (83%)	9a (92%)
CH_2=CHCN (5b)	8b (78%)	9b (76%)
CH_2=$CHNO_2$ (5c)	8c (63%)	-

B. Side chain decarboxylation.

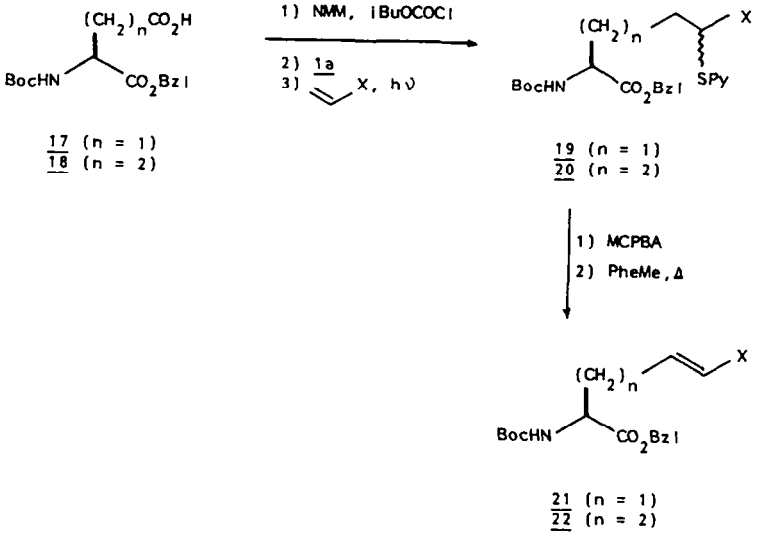
The decarboxylation reaction was also used to modify the side chain of protected aspartic 17 and glutamic 18 acids (Scheme 3). Although the yields of addition products are slightly lower in this case, the overall yields following elimination are still very good (38-65%) (see Table 2). All the unsaturated amino acid derivatives prepared were optically pure and showed E double bond stereochemistry (J = 16 Hz). In all cases the rearrangement product R-SPy 4 (see Scheme 1) is also produced in <20%.

Table 2. Side Chain Decarboxylation of Asp. and Glu. Derivatives with Various Olefins.

Acid	CH_2=CHX (5 eq.)	Addn. Prod. (Yield)	Elim. Prod. (Yield)
17	CH_2=$CHCO_2Me$ (5a)	19a (62%)[a]	21a (86%)[a]
	CH_2=CHCN (5b)	19b (56%)	21b (67%)
	CH_2=$CHNO_2$ (5c)	19c (74%)	-
	CH_2=$CHSO_2Ph$ (5d)	19d (62%)	21d (85%)
18	5a	20a (60%)[a]	22a (91%)[a]
	5c	20c (73%)	-

a) Diadduct also formed. See Text.

Scheme 3. Side Chain Decarboxylation Leading to Optically Pure Unsaturated Amino Acid Derivatives (see Table 2).

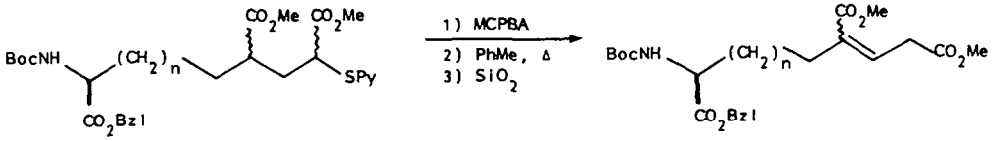


17 (n = 1)
18 (n = 2)

19 (n = 1)
20 (n = 2)

21 (n = 1)
22 (n = 2)

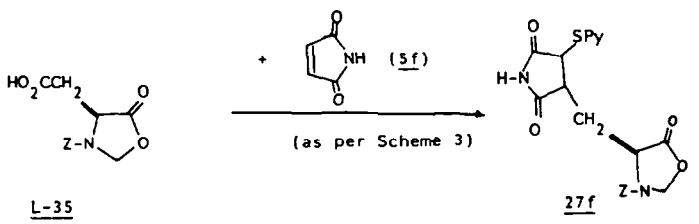
With methyl acrylate 5a, diaddition products 23a and 24a were obtained in minor amounts. Oxidation and elimination afforded products 25a and 26a. The migration of the double bond from the initial disubstituted to a more stable trisubstituted position occurred during the elution from silica gel.



L-23a (n = 1)
L-24a (n = 2)

L-25a (n = 1)
L-26a (n = 2)

The addition compounds 27f was obtained with a 52% yield but the elimination was unsatisfactory (see below). On the other hand, the same reaction performed with palmitic acid ($nC_{15}H_{31}CO_2H$) 36 afforded addition and elimination products 31f and 32f in respectively 69%

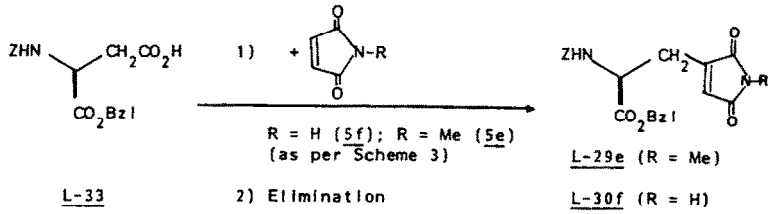


L-35

27f

and 79% yield. Similarly, the acid 33 gave addition product 34f (59%) and elimination product 30f (79%). Thus the difficulty with 27f was in the nature of the α-carboxyl protecting group.

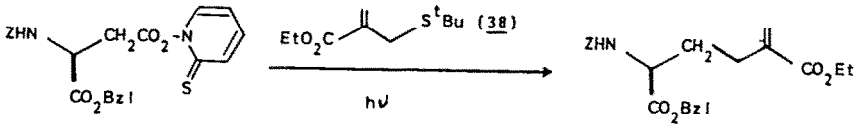
Addition products from nitroethylene 5c and vinyl sulfone 5d could be transformed (Table 2) as previously described.[26,27]



L-33 L-29e (R = Me) L-30f (R = H)

C. Allylic Derivatives via in situ Addition-Elimination.

Another interesting application of this reaction of addition to an olefin is the synthesis of allylic derivatives. This can be achieved with the olefin 38 (Scheme 4). In the case of aliphatic and alicyclic acids, the yield of the adduct is increased because the reaction of addition is concerted with the elimination of a thiyl radical which is an excellent chain carrier in this system.[28] Disappointingly, when this reaction was performed with 33 the expected product 37 was obtained in only 34% yield.

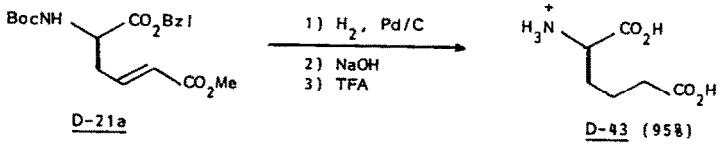


L-37

II. Conversion of Addition and Elimination Products to Amino Acids.

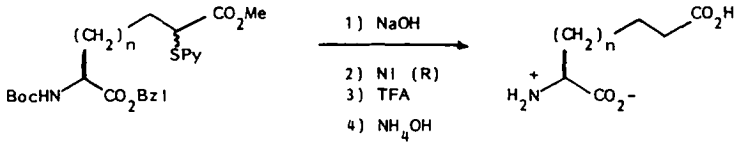
The addition products 19a and 20a from methyl acrylate were subjected to successive deprotection of ester, thioether and amino group to yield free amino acids (Scheme 4). The thiopyridyl group was reduced with Raney nickel (50% in water) after saponification of the two ester groups. The amino deprotection was achieved by trifluoroacetic acid. The N-Boc diacid 39 (92%) crystallised in ethyl acetate whereas the N-Boc diacid 40 (88%) was an oil. The two free amino acids 41 and 42 have physical characteristics identical to those given in literature.[5,10,11]

D-α-aminoadipic acid 43 was prepared in a different manner, from the D-isomer (enantiomer of 21a), and was obtained in the same way as the L isomer in a 86% yield. Raney nickel reduction was replaced by elimination and hydrogenation over palladium on carbon to obtain larger quantities of this amino acid.



D-21a D-43 (95%)

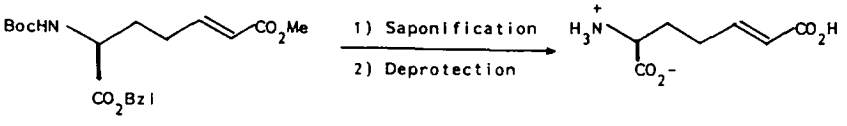
Scheme 4. Conversions to L-α-Aminoadipic and L-α-Aminopimelic Acids.



19a (n = 1) 41 (n = 1) (76%)

20a (n = 2) 42 (n = 2) (81%)

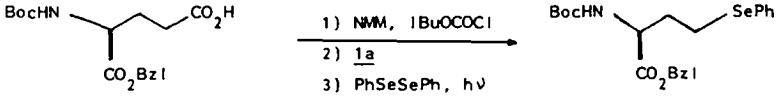
To our knowledge, there is no reference to α-aminodehydropimelic acids in an optically pure form. For this reason we wish to report the synthesis of the α-amino-δ-dehydropimelic



L-22a L-45

acid 45, optically pure obtained by saponification of 22a to yield 44 and then deprotection in a very good overall yield (92%).

Recently we described several methods for the synthesis of L-vinylglycine based on our radical generating system.[24] Also we have recently shown[29,30] that photolysis of N-hydroxy-2-thiopyridone esters at room temperature is a much more efficient system than is



L-18 L-48

an earlier thermal method.[29] Application of this new procedure to the protected glutamic acid 18 in the presence of diphenyl diselenide afforded in good yields (86%) the corresponding seleno-compound 48 which can be readily transformed into vinylglycine.[24]. This represents a significant improvement in our synthesis of vinylglycine.

EXPERIMENTAL

General

Melting points were determined using a Ernst Leitz Wetzmar apparatus and are uncorrected. Optical rotation measurements were conducted using the Perkin Elmer 141 MC and 241 MC polarimeters at ambient temperature. ^{1}H NMR spectra were recorded on a Varian T-60 (60 MHz), EM-360L (60 MHz) and Brucker WP-200 (200 MHz) and WM-400 (400 MHz) in $CDCl_3$ unless otherwise specified, with TMS as internal standard. I.R. spectra were recorded with a Perkin Elmer 257 spectrometer using nujol, CH_2Cl_2 solution or a film as appropriate. Mass spectra were run on

AEI MS-9 and on AEI MS-50 spectrometers. Thin layer chromatography (t.l.c.) was performed with Merck silica gel $60F_{254}$ and the compounds were visualised by spraying with Ninhydrin and Pataki[34] reagents or by examination under u.v. light. Column chromatography was performed with SDS 60A 35-70μ and Merck 60A 40-63μ silica gel under slight pressure.

The protected L and D-Aspartic acids were prepared according to known procedures[32] or were purchased.

General Procedure for Addition to an Olefin

To a solution of the protected amino acid (1 mmol) in anhydrous THF (5 ml) at -15°C was added N-methyl morpholine (1 mmol) and isobutyl chloroformate (1 mmol) under nitrogen or argon. The solution was allowed to stir at -15°C for five minutes and then was added a solution of N-hydroxy-2-thiopyridone (1.2 mmol) and triethylamine (1.2 mmol) in THF (3 ml) cooled to -15°C (the sodium salt of 1 (1.2 mmol) could also be used)). The mixture was stirred at -15°C under an inert atmosphere for 45 minutes in the dark. The reaction was followed by t.l.c. The solution was then rapidly filtered and the yellow filtrate was irradiated in the presence of the olefin (5 mmol) with two tungsten lamps of 100W for 20 minutes at ambient temperature under an inert atmosphere. The mixture was extracted with ether and washed successively with $NaHCO_3$ (0.1N), H_2O, HCl (0.5N), H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography to give the adduct.

General Procedure for the Oxidation-Elimination of Addition Product

To a solution of adduct (1 mmol) in chloroform (5 ml) was added a solution of metachloroperbenzoic acid (1.05 mmol) in chloroform (2 ml) at 0°C. The solution was allowed to stir at room temperature for one hour. The mixture was extracted with methylene chloride and washed successively with $NaHCO_3$ (1N), H_2O, HCl (0.5N), H_2O and brine. The organic layer was dried over Na_2SO_4 and concentrated. The residue was taken up in anhydrous toluene (10 ml) and heated at reflux (110°C) for one hour. The solvent was then removed under reduced pressure and the residue chromatographed on a column.

The Methyl Ester Mixture 8a. - This was obtained as an oil (83%), ν_{max} 1725 cm^{-1}; δ_H: 1.40 (9H, s), 2.2 (2H, m), 2.80 (2H, d, J = 10 Hz), 3.63 (3H, s), 3.80 (1H, m), 4.76 (1H, m), 5.08 (1H, m), 7.17 (5H, s), 6.90-8.45 (4H, m); m/e: 416 (M^+), 316 (M^+-Boc), 305 (M^+-SPy).

The Olefin 9a. - This was obtained (92%) as the E isomer and had m.p. 90-91°c (pentane:ether); $[\alpha]_D^0$° (c = 2.0, CH_3OH or $CHCl_3$); ν_{max} : 1730, 1690 cm^{-1}; δ_H: 1.40 (9H, s), 2.87 (2H, d, J = 6.6 Hz), 3.67 (3H, s), 4.60 (2H, m), 5.83 (1H, d, J = 16.7 Hz), 6.87 (1H, dd, J_1 = 16.7 Hz, J_2 = 4.7 Hz), 7.21 (5H, s); m/e: 305 (M^+), 205 (M^+-Boc) (Found: C, 66.86; H, 7.37; N, 4.69; O, 20.94. Calc. for $C_{17}H_{23}NO_4$: C, 66.86; H, 7.59; N, 4.59; O, 20.96%).

The Nitrile Mixture 8b. - This was obtained as an oil (78%); ν_{max} 2240 cm^{-1}; δ_H: 1.43 (9H, s), 2.13 (2H, t, J = 7Hz), 2.77 (2H, d, J = 6 Hz), 4.03 (1H, m), 4.73 (2H, m), 7.00 (5H, s), 6.67-8.33 (4H, m); m/e: 383 (M^+), 283 (M^+-Boc), 220 (M^+-$CH_2CH(CN)SPy$).

The Olefin 9b. - This was obtained (86%) as the E-isomer. It had m.p. 141-143°C (ether:pentane); $[\alpha]_D^0$° (c = 2,0, $CHCl_3$ and CH_3OH); ν_{max} (nujol) 2220, 1690 cm^{-1}; δ_H: 1.40 (9H, s), 2.87 (2H, d, J = 6Hz), 4.03 (2H, m), 5.43 (1H, d, J = 16,7 Hz), 6.73 (1H, dd, J_1 = 16,7 Hz, J_2 = 4 Hz), 7.30 (5H, m) (Found: C, 70.26; H, 7.18; N, 10.19; O, 11.75. Calc. for $C_{16}H_{20}N_2O_2$: C,70.56; H, 7.40; N, 10.29; O, 11.75%).

The Nitro-derivative Mixture 8c. - This was obtained as an oil (63%); ν_{max} 1710 cm^{-1}; δ_H: 1.36 (9H, s), 2.30 (2H, m), 2.80 (2H, d, J = 6 Hz), 3.92 (1H, m), 4.65 (1H, m), 6.43 (1H, m), 7.03 (9H, m); m/e: 403 (M^+), 357 (M^+-NO_2); 220 (M^+-CH_2-$CH(NO_2)SPy$).

The Methyl Ester 11a. - This was obtained as an oil (60%); ν_{max} 1745, 1705 cm^{-1}; δ_H: 1.86 (6H, m), 3.42 (2H, m), 3.65 (3H, s), 4.12 (1H, m), 4.65 (1H, m), 5.12 (2H, s), 6.85-7.65 (3H, m), 7,33 (5H, m), 8.4 (1H, d, J = 5 Hz); m/e: 400 (M^+), 289 (M^+-SPy), 265 (M^+-Z).

The Olefin 12a. - This was obtained as an oil (87%) (E isomer); $[\alpha]_D^0$° (c = 2, CH_3OH); δ_{max} 1740, 1700, 1665 cm^{-1}; δ_H: 1.85-2.08 (4H, 2m), 3.50 (2H, m), 3.71 (3H, 2s), 4.52 (1H, m), 5.13 (2H, s), 5.80 (0.5 H, d, J = 16.7 Hz), 5.90 (0.5 H, d, J = 16,7 Hz), 6.85 (1H, dt, J_1 = 16.7 Hz, J_2 = 5.3 Hz), 7.33 (5H, m); m/e: 289 (M^+), 154 (M^+-Z).

The Dimethyl Ester Mixture 13a. - This was obtained as an oil (17%); ν_{max} 1745, 1705 cm^{-1}; δ_H: 1.85-2.65 (8H, m), 3.42 (2H, m), 3.60 (1H, m), 3.64-3.66 (3H, 2s), 3.74 (3H, s), 3.97 (1H, m), 4.7 (1H, m), 5.15 (2H, s), 7.41 (5H, s), 6.92-7,67 (3H, m), 8.45 (1H, m); m/e: 486 (M^+), 375 (M^+-SPy), 351 (M^+-Z).

The Methyl Ester Mixture 15a. - This was obtained as an oil (62%); ν_{max} 1740, 1690 cm^{-1}; δ_H: 0.82 (6H, m), 1.33 (3H, m), 1.40 (9H, s), 2.05 (2H, m), 3.05 (2H, t, J = 6.6 Hz), 3.67 (3H, s), 4.30 (3H, m), 5.06 (1H, m), 6.05 (1H, m), 7.20 (9H, m); m/e: 529 (M^+), 429 (M^+-Boc), 418 (M^+-SPy).

The Olefin Mixture 16a. - This (86%) had m.p. 122-123°C (ether-pentane); $[\alpha]_D$0° (c = 1, CH_3OH); ν_{max} (nujol): 1735, 1690 cm^{-1}; δ_H: 0.85 (6H, m), 1.32 (3H, m), 1.42 (9H, s), 3.07 (2H, m), 3.71 + 3.72 (3H, 2s), 4.31 (1H, m), 4.57 (1H, m), 5.07 (1H, m), 5.87 (2H, m), 6.77 (1H, dd, J_1 = 5 Hz, J_2 = 16 Hz), 7.25 (5H, m) (Found: C, 65.79; H, 8.15; O, 18.99. Calc. for $C_{23}H_{34}N_2O_5$: C, 65.98; H, 8.19; O, 19.10%). The two diastereoisomers were separated by HPLC on semi-preparative Ultrasphere Column (N°1494, ODS 5µm) with normal phase silica gel. 16a', the less polar derivative, had m.p. 138-139°C; δ_H: 0.87 (6H, m), 1.32 (3H, m), 1.43 (9H, s), 3.07 (2H, m), 3.72 (3H, s), 4.27 (1H, q, J = 6.7 Hz), 4.60 (1H, m), 5.05 (1H, m), 5.65 (1H, m), 5.81 (1H, d, J = 16 Hz), 6.66 (1H, m), 7.25 (5H, m) and 16a had m.p. 108-109°C; δ_H: 0.82 (6H, m), 1.30 (3H, m), 1.43 (9H, s), 3.07 (2H, m), 3.71 (3H, s), 4.29 (1H, m), 4.55 (1H, m), 5.04 (1H, m), 5.83 (2H, m), 6.74 (1H, dd, J_1 = 16 Hz, J_2 = 5 Hz), 7.25 (5H, m).

The Adipic Acid Derivative Mixture 19a. - This was obtained as an oil (62%); ν_{max}: 1740, 1720 cm^{-1}; δ_H: 1.40 (9H, s), 1.92 (4H, m), 3.58 (3H, s), 4.20 (1H, m), 4.50 (1H, t, J = 6 Hz), 4.97 (2H, s), 5.23 (1H, m), 7.03 (5H, s), 6.57-8.16 (4H, m); m/e: 474 (M^+), 374 (M^+-Boc), 339 (M^+-COOBzl).

The Olefin 21a L-isomer. - This (86%, E-isomer) had m.p. 71°C (pentane); $[\alpha]_D$ -14.9° (c = 1.0, CH_3OH); ν_{max}: 1720, 1665 cm^{-1}; δ_H: 1.40 (9H, s), 2.61 (2H, t, J = 7 Hz), 3.63 (3H, s), 4.37 (1H, q, J = 6.9 Hz), 5.07 (2H, s), 5.30 (1H, m), 5.70 (1H, d, J = 16 Hz), 6.63 (1H, dt, J_1 = 16 Hz, J_2 = 5.9 Hz), 7.17 (5H, s) (Found: C, 62.53; H, 6.80; O, 26.48. Calc. for $C_{19}H_{25}NO_6$: C, 62.79; H, 6.93; O, 26.42%).

The Nitrile Mixture 19b. - This was obtained as an oil (56%); ν_{max}: 2240 cm^{-1}; δ_H: 1.39 (9H, s), 2.00 (4H, m), 4.35 (1H, m), 4.77 (1H, m), 5.12 (2H, s), 5.26 (1H, m), 7.28 (5H, s), 6.88-7,42 (3H, m), 8.40 (1H, d, J = 6 Hz); m/e: 441 (M^+), 341 (M^+-Boc).

The Olefin 21b. - This was obtained (67%, E-isomer) as an white solid; $[\alpha]_D$ -15.6° (c = 0.58; CH_3OH);
ν_{max}: 2225, 1750, 1715 cm^{-1}; δ_H: 1.43 (9H, s), 2.59 (1H, m), 2.78 (1H, m), 4.48 (1H, m), 5.15 (2H, s), 5.22 (1H, d, J = 16 Hz), 5.28 (1H, m), 6.55 (1H, dt, J_1 = 16 Hz, J_2 = 8 Hz), 7,38 (5H, m) (Found: C, 65.37; H, 6.78; N, 8.65; O, 19.05. Calc. for $C_{18}H_{22}N_2O_4$: C, 65.43; H, 6.71; N, 8.48; O, 19.37%).

The Sulfone 19d. - This compound (62%) had m.p. 130-131°C (ether:pentane); $[\alpha]_D$ + 119° (c = 0.70, CH_3OH); ν_{max} (Nujol) : 1750, 1715 cm^{-1}; δ_H: 1.47 (9H, s), 2.00-2.52 (4H, m), 4.43 (1H, m), 5.23 (2H, s), 5.42 (1H, m), 5.80 (1H, dd, J_1 = 12 Hz, J_2 = 4 Hz), 7.45 (5H, s), 7.00-8.58 (9H, m); m/e= 557 (M^+), 457 (M^+-Boc), 415 (M^+ - SO_2Ph) (Found: C, 60.52; H, 5.74; N, 5.15; O, 17.20. Calc. for $C_{28}H_{32}N_2O_6S_2$: C, 60.41; H, 5.79; N, 5.03; O, 17.24%).

The Unsaturated Sulfone 21d. - This was obtained (E-isomer) as an oil (85%); $[\alpha]_D$ -2.4° (c = 1.0, CH_3OH); ν_{max}: 1750, 1715, 1630 cm^{-1}; δ_H: 1.41 (9H, s), 2.65 (2H, q, J = 6 Hz), 4.47 (1H, m), 5.10 (2H, s), 5.25 (1H, m), 6.35 (1H, d, J = 16 Hz), 6.86 (1H, m), 7,32-8.00 (10H, m) (Found: C, 61.69; H, 5.99; N, 3.01; O, 21.36. Calc. for $C_{23}H_{27}NO_6S$: C, 61.99; H, 6.11; N, 3.16; O, 21.54%).

The Nitro Derivative 19c. - This (74%) had m.p. 79°C; $[\alpha]_D$ -18.2° (c = 1.0, CH_3OH), ν_{max} (nujol): 1750, 1690 cm^{-1}; δ_H: 1.43 (9H, s), 1.85-2.37 (4H, m), 4.42 (1H, m), 5.14 (1H, m), 5.16 (2H, s), 6.53 (1H, dt, J_1 = 7.5 Hz, J_2 = 4 Hz), 7.35 (5H, s), 7.09 (1H, m), 7.21 (1H, m), 7.55 (1H, m), 8.42 (1H, m); m/e: 462 (M^+), 415 (M^+-NO_2), 362 (M^+-Boc) (Found: C, 57.18; H,5.99; N, 9.09; O, 20.63. Calc. for $C_{22}H_{27}N_3O_6S$: C, 57.25; H, 5.90; N, 9.10; O, 20.80%).

The Pimelic Acid Derivative Mixture 20a. - This was obtained as an oil (60%); $[\alpha]_D$ -11.8° (c = 1.0, CH_3OH); ν_{max}: 1740, 1715 cm^{-1}; δ_H: 1.34 (9H, s), 1.72 (6H, m), 3.65 (3H, s), 4.23 (1H, m), 4.55 (1H, t, J = 8 Hz), 4.89 (1H, m), 5.10 (2H, s), 7.35 (5H, s), 6.63-6.86 (3H, m), 8.38 (1H, d, J = 5.4 Hz); m/e: 488 (M^+), 388 (M^+-Boc) (Found: C, 61.26; H, 6.76; N, 5.53;O, 19.88. Calc. for $C_{25}H_{32}N_2O_6S$: C, 61.45; H, 6.60; N, 5.73; O, 19.65%).

The Olefin 22a. - This (91%), (E-isomer) had m.p. 50-51°C (pentane); $[\alpha]_D$ -14° (c = 1.0, CH_3OH); ν_{max}: 1750, 1725, 1675 cm^{-1}; δ_H: 1.44 (9H, s), 1.87 (2H, m), 2.20 (2H, dt, J_1 = 7 Hz, J_2 = 1 Hz), 3.71 (3H, s), 4.36 (1H, m), 5.17 (2H, s), 5.25 (1H, m), 5.72 (1H, d, J = 16 Hz), 6.90 (1H, dt, J_1 = 16 Hz, J_2 = 7 Hz), 7.35 (5H, s); m/e: 377 (M^+), 277 (M^+-Boc), 242 (M^+-COOBzl) (Found: C, 63.45; H, 7.32; O, 25.33. Calc. for $C_{20}H_{27}NO_6$: C, 63.63; H, 7.21; O, 25.43%).

The Nitro Compound Mixture 20c. - This was obtained as an oil (73%); $[\alpha]_D$ -19.0° (c = 1.0, CH_3OH); ν_{max} : 1750, 1720 cm^{-1}; δ_H: 1,40 (9H, s), 1.67 (4H, m), 2.17 (2H, dt, J_1 = 5.9 Hz, J_2 = 6,9 Hz), 4.07 (1H, m), 4.93 (1H, m), 5.00 (2H, s), 6.30 (1H, t, J = 6.9 Hz), 7.13 (5H, s), 6.60-8.23 (4H, m); m/e: 429 (M^+-NO_2), 375 (M^+-Boc), 340 (M^+-CO_2Bzl) (Found: C, 57.95; H, 6.19; N, 8.59; O, 20.04. Calc. for $C_{23}H_{29}N_3O_6S$: C, 58.09; H, 6.15; N, 8.84; O, 20.19%).

The Dimethyl Ester Mixture 23a. - This was obtained from 17 D-isomer as an oil (11%); ν_{max} 1740, 1700 cm^{-1}; δ_H: 1.45 (9H, s), 1.7-2.66 (7H, 2m), 3.6 and 3.65 (3H, 2s), 3.71 (3H, s), 4.35 (1H, m), 4.46 (1H, m), 5.08 (1H, m), 5.17 (2H, s), 7.36 (5H, s), 6.89-7.67 (3H, m), 8.42 (1H, d, J = 7 Hz); m/e: 560 (M^+), 460(M^+-Boc), 425 (M^+-CO_2Bzl).

The Olefin Mixture 25a. - This was obtained from 23a as an oil (78%); $[\alpha]_D$ +7.8° (c = 1.0, CH_3OH); ν_{max} : 1750, 1720, 1650 cm^{-1}; δ_H: 1,40 (9H, s), 1.90 (2H, m), 2.30 (2H, q, J = 7 Hz), 3.19 (2H, d, J = 8 Hz), 3.69 (3H, s), 3.75 (3H, s), 4.39 (1H), 5.18 (2H, s), 5.2 (1H, m), 6.92 (1H, t, J = 8 Hz), 7.37 (5H, s); m/e: 449 (M^+), 349 (M^+-Boc), 314 (M^+-CO_2Bzl) (Found: C, 61.50; H, 6.99; O, 28.22. Calc. for $C_{23}H_{31}NO_8$: C, 61.45; H, 6.95; O, 28.47%).

The Dimethyl Ester Mixture 24a. - This was obtained as an oil (14%); ν_{max} 1740, 1705 cm^{-1}; δ_H: 1.45 (9H, s), 1.79-2.56 (9H, 2m), 3.62 and 3.67 (3H, 2s), 3.72 (3H, s), 4.31 (1H, m), 4.69 (1H, m), 5.06 (1H, m), 5.16 (2H, s), 7.35 (5H, s), 6.87-7.78 (3H, m), 8.45 (1H, d, J = 7 Hz); m/e: 574 (M^+), 474(M^+-Boc), 439 (M^+-CO_2Bzl).

The Olefin Mixture 26a. - This was obtained as an oil (80%); $[\alpha]_D$ -17.3° (c = 1.1, CH_3OH); ν_{max} : 1750, 1720 cm^{-1}; δ_H: 1,42 (9H, s), 1.70 (4H, m), 2.27 (2H, t, J = 7 Hz), 3.17 (2H, d, J = 7.5 Hz), 3.70 (3H, s), 3.75 (3H, s), 4.30 (1H, m), 5.00 (1H, m), 5.13 (2H, s), 6.85 (1H, t, J = 7.5 Hz), 7.29 (5H, s); m/e: 464 (MH^+), 408 (M^+-=<), 364 (MH^+-Boc) (Found: C, 62.05; H, 7.12; O, 27.48. Calc. for $C_{24}H_{33}NO_8$: C, 62.19; H, 7.17; O, 27.61%).

The Compound 27f. - This was obtained as a gum (52%); $[\alpha]_D$ +66.7° (c = 0.5, CH_3OH), ν_{max} (Nujol): 1795, 1700 cm^{-1}; δ_H: 2.46 (2H, m), 3.50 (1H, m), 4.26 (1H, m), 4.71 (1H, m), 5.13 (2H, s), 5.25 (1H, t, J = 4 Hz), 5.47 (1H, t, J = 4 Hz), 7.35 (5H, s), 6.86-7.63 (3H, m), 8.25 (1H, d, J = 6 Hz), 9.00 (1H, m) (Found: C, 56.95; H,4.52; O, 22.00. Calc. for $C_{21}H_{19}N_3O_6S$: C, 57.13; H, 4.34; O, 21.75%).

The Mixed N-Methylsuccipimide Derivatives 28e. - This was a foam (71%); $[\alpha]_D$ -26.7° (c = 1.0, CH_3OH), ν_{max} : 1690 cm^{-1}; δ_H: 2.35 (2H, m), 2.96 (3H, s), 3.24 (1H, m), 4.18 (1H, m), 4.75 (1H, m), 5.05 (4H, 2s), 5.94 (1H, m), 7.30 (10H, 2s), 6.79-7.62 (3H, m), 8.15 (1H, d, J = 6 Hz); m/e: 534 (M^+), 399 (M^+-Z) (Found: C, 62.80; H, 4.93; N, 7.88; O, 18.20. Calc. for $C_{28}H_{27}N_3O_6S$: C, 63.02; H, 5.10; N, 7.87; O, 17.99%).

The N-Methylmaleimide Derivative 29e. - This (91%) had m.p. 122°C (ether:pentane); $[\alpha]_D$ +2.1° (c = 1.0, $CHCl_3$); ν_{max} (CH_2Cl_2): 1700 cm^{-1}; δ_H: 2.95 (5H, 1 m + 1 s), 4.7 (1H, m), 5.10 (2H, s), 5.16 (2H, s), 5.66 (1H, m), 6.26 (1H, s), 7.32 (10H, s) (Found: C, 65.35; H, 5.05; N, 6.83; O, 22.80. Calc. for $C_{23}H_{21}N_2O_6$: C, 65.53; H, 5.02; N, 6.68; O, 22.77%).

The Mixed Succinimide Derivative 34f. - This was obtained as an oil (59%), ν_{max} : 1770, 1700 cm^{-1}; δ_H: 2.33 (2H, m), 3.22 (1H, m), 4.15-4.27 (1H, 2d, J = 7 Hz), 4.80 (1H, m), 5.20 (4H, s), 6.17 (1H, m), 6.92-8.29 (14H, m), 9.43 (1H, m); m/e: 408 (M^+ - SPy).

The Maleimide Derivative 30f. - This (79%) had m.p. 79-80°C (ethylacetate:pentane); $[\alpha]_D$ -40.0° (c = 1,2, CH_3OH); ν_{max} (nujol): 1780, 1710 cm^{-1}; δ_H: 2.89 (2H, m), 4.62 (1H, m), 5.04 (2H, s), 5.11 (2H, s), 5.84 (1H, d, J = 9 Hz), 6.17 (1H, s), 7.27 (10H, s); 8.25 (1H, m) (Found: C, 64.97; H, 4.82; O, 23.31. Calc. for $C_{22}H_{20}N_2O_6$: C, 64.70; H, 4.96; O, 23.51%).

The Succinimide Derivative 31f. - This (69%) had m.p. 94-95°C (ether:pentane); ν_{max} 1780, 1720 cm^{-1}; δ_H: 0.80 (3H, t, J = 5 Hz), 1.30 (28H, m)), 3.11 (1H, q, J = 6 Hz), 3.97 (1H, d, J = 6 Hz), 6.82-7.61 (3H, m), 8.27 (2H, m) (Found: C, 68.61; H, 9.26; N, 6.89; O, 7.40. Calc. for $C_{24}H_{38}N_2O_2S$: C, 68.85; H, 9.15; N, 6.69; O,7.64%).

The Maleimide Derivative 32f. - This (79%) had m.p. 85-86°C (ether:pentane); ν_{max} : 1770, 1730 cm^{-1}; δ_H: 0.89 (3H, m), 1.27 (26H, m), 2.39 (2H, t, J = 6 Hz), 6.22 (1H, s), 7.95 (1H, m) (Found: C, 74.15; H, 10.74; O, 10.24. Calc. for $C_{19}H_{33}NO_2$: C, 74.20; H, 10.82; O, 10.40%).

The Unsaturated Ester 37. - This was an oil (34%); $[\alpha]_D$ -17.9° (c = 1.6, CH_3OH); ν_{max} 1720, 1620 cm^{-1}; δ_H: 1.27 (3H, t, J = 6.6 Hz), 1.98 (2H, m), 2.36 (2H, t, J = 8 Hz), 4.22 (2H, q, J = 6.6 Hz), 4.48 (1H, m), 5.16 (2H, s), 5.21 (2H, s), 5.48 (1H, m), 5.55 (1H, s), 6.22 (1H, s), 7.43 (10H, s); m/e: 425 (M^+), 290 (M^+-Z) (Found: C, 67.29; H, 6.50. Calc. for $C_{24}H_{27}NO_6$: C, 67.75; H, 6.40%).

General Procedure for the Saponification and Desulphurisation of Some Adducts.

To a solution of the amino-acid derivative (1 mmol) in dioxane (5 ml) was added a solution of 1N aqueous sodium hydroxide 1N (2 mmol) and the mixture was allowed to stir at room temperature for one hour. The dioxane was then removed under reduced pressure, the aqueous layer was washed with ether and acidified to pH 4 with solid citric acid. The acidic aqueous layer was then extracted with ethyl acetate. The extract was washed with brine, dried over Na_2SO_4 and evaporated. The residue was dissolved in absolute ethanol (3 ml) and a small amount of Merck Raney Nickel (50% in water) was added. The mixture was allowed to stir overnight at room temperature. The Raney Nickel was filtered and washed with an ethanol-water solution. The solvent was concentrated and the residue acifified with a 5% solution of citric acid. The diacide was extracted with ethyl acetate.

2-L-N-Boc Aminoadipic Acid 39. - This (90%) had m.p. 121-122°C (ethyl acetate), $[\alpha]_D$ -10.67° (c = 1.0, CH_3OH) (lit.[31]); m.p. 121-122°C, $[\alpha]_D$ +10.6° (c = 1, $CHCl_3$); ν_{max} : 1730 cm^{-1}; ^1H NMR (CD_3OD) δ: 1.49 (9H, s), 1.74 (4H, m), 2.33 (2H, m), 4.09 (1H, m) (Found: C, 50.58; H, 7.23. Calc. for $C_{11}H_{19}NO_6$: C, 50.55; H, 7.33%). We found that this compound is insoluble in $CHCl_3$, the solvent formerly[31] used for the $[\alpha]_D$.

2-L-N-Boc Aminopimelic Acid 40. - This was an oil (90%); $[\alpha]_D$ -4.56° (c = 3.0, CH_3OH); ν_{max} : 1730 cm^{-1}; ^1H NMR (CD_3OD) δ: 1.45 (9H, s), 1.8 (6H, m), 2.30 (2H, t, J = 8 Hz), 4.08 (1H, m); m/e: 275 (M^+), 175 (M^+-Boc).

L-α-Aminoadipic Acid 41. - The Boc derivative 39 (0.57 mmol) and trifluoroacetic acid (5.7 mmol) were stirred in methylene chloride (0.6 ml) for one hour at room temperature. The solution was concentrated and the residue dissolved in a 2N NH_4OH aqueous solution to pH 3.5. The water was removed under reduced pressure and the residue washed with anhydrous ether and absolute ethanol. The amino acid was dried in a dessicator. The solid so obtained (83%) had m.p. 201-202°C; $[\alpha]_D$ +24.6° (c = 0.7 in 5N HCl) (lit.[10], m.p. 200-202°C, $[\alpha]_D$ +24.6° (c = 2.0 in 5N HCl)) ; ^1H NMR (D_2O) δ: 1.26 (2H, m), 1.42 (2H, m), 1.77 (2H, m), 2.28 (1H, m).

L-α-Aminopimelic Acid 42. - This was obtained from 40, following the same procedure as above (93%), had m.p. 203-205°C; $[\alpha]_D$ +21,1° (c = 1,1, HCl 5N) (lit.[5,11]); $[\alpha]_D$ +20.4° (c = 1.0, HCl 5N) and $[\alpha]_D$ + 21.5° (c = 1.0 in HCL 5N).

The Boc protecting group was removed as for the L-isomer to give D-α-aminoadipic acid 43 (95%); m.p. 199-201°; $[\alpha]_D$ -23.2° (c = 1.0 in 5N HCl) (lit.[10], $[\alpha]_D$ -24.9° (c = 1.0 in 6N HCl).

D-α-Aminoadipic Acid 43. - A solution of the derivative D-21a (1.65 mmol), obtained as above D-Boc-Asp-O-Bzl in methanol (12 ml) was hydrogenated over a small amount of 10% palladium on carbon for 30 minutes. The mixture was filtered and the palladium washed with methanol and water. The solvents were evaporated under reduced pressure and the methyl ester acid 46 was crystallised as the dicyclohexylamine salt in ethyl acetate-light petroleum. The salt had m.p. 105-106°C; $[\alpha]_D$ -8.3° (c = 1.1, CH_3OH) (Found: C, 63.16; H, 9.50; N, 5.92; O, 20.85. Calc. for $C_{24}H_{44}N_2O_6$: C, 63.13; H, 9.71; N, 6.14; O, 21.02%).

Saponification as specified in the general procedure afforded D-N-Boc-aminoadipic acid 47 (93%); m.p. (ethyl acetate) 122-123°; $[\alpha]_D$ +10.1° (c = 1.0, MeOH). The infra-red and N.M.R. spectra were identical to those of the L-isomer 39.

The Boc protecting group was removed as for the L-isomer to give D-α-aminoadipic acid 43 (95%); m.p. 199-201°; $[\alpha]_D$ -23.2° (c = 1.0 in 5N HCl) (lit.[10], $[\alpha]_D$ -24.9° (c = 1.0 in 6N HCl).

2-L-N-Boc-amino-δ-trans-dehydropimelic Acid 44. - The compound 22a was saponified using the above procedure with 1N NaOH affording the diacid 44 (96%) as an oil; ν_{max} : 1700, 1660 cm^{-1}; ^1H NMR (CD_3OD) δ: 1.49 (9H, s), 1.90 (2H, m), 2.25 (2H, m), 4.10 (1H, m), 5.81 (1H, d, J = 16 Hz), 6.92 (1H, dt, J_1 = 16 Hz, J_2 = 6 Hz).

L-α-amino-δ-trans-dehydropimelic Acid 45. - Diacid 44 was deprotected using the above procedure with trifluoroacetic acid, affording the title compound 45 (92%) which had m.p. 208-209°C (d); $[\alpha]_D$ +39.6° (c = 1,0 5N HCl); ^1H NMR (D_2O) δ: 2.55 (2H, m), 2.80 (2H, m), 3.87 (1H, t, J = 6 Hz), 5.50 (1H, d, J = 16 Hz), 6.41 (1H, dt, J_1 = 16 Hz, J_2 = 8 Hz).

The Seleno Compound 48. - To a solution of the acid 18 (7 mmol) in anhydrous THF (35 ml) were added N-methylmorpholine (7 mmol) and isobutylchloroformate (7 mmol) at -15°C under argon. After five minutes there was added the sodium salt of thiohydroxamic acid 1 (9.1 mmol). The mixture was rapidly stirred for one hour at -15°C and then irradiated in the presence of diphenyldiselenide (14 mmol) at ambient temperature for 25 minutes. The mixture was then extracted with ether, washed with water, dried, concentrated and purified on column chromatography (hexane:ether 4:1). The product 48 (yield 86%) was an oil; $[\alpha]_D$ -39.7° (c = 1.2, CH_3OH); ν_{max} : 1740, 1710 cm^{-1}; δ_H: 1.42 (9H, s), 2.12 (2H, m), 2.85 (2H, t, J = 6.4 Hz), 4.47 (1H, m), 5.05 (1H, m), 5.15 (2H, s), 7.12-7.97 (10H, m) (Found: C, 58.77; H, 5.95; N, 2.93; O, 14.43. Calc. for $C_{22}H_{27}NO_4Se$: C, 58.92; H, 6.07; N, 3.12; O, 14.27%).

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