STEREOCONTROLLED SYNTHESES OF ASPARTAME [(S)-Asp-(S)-PhOMe] AND ITS (R)-ASPARTYL CONGENER [(R)-Asp-(S)-PhOMe] VIA NITRONE CYCLOADDITION

David Keirs and Karl Overton*

Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, Scotland

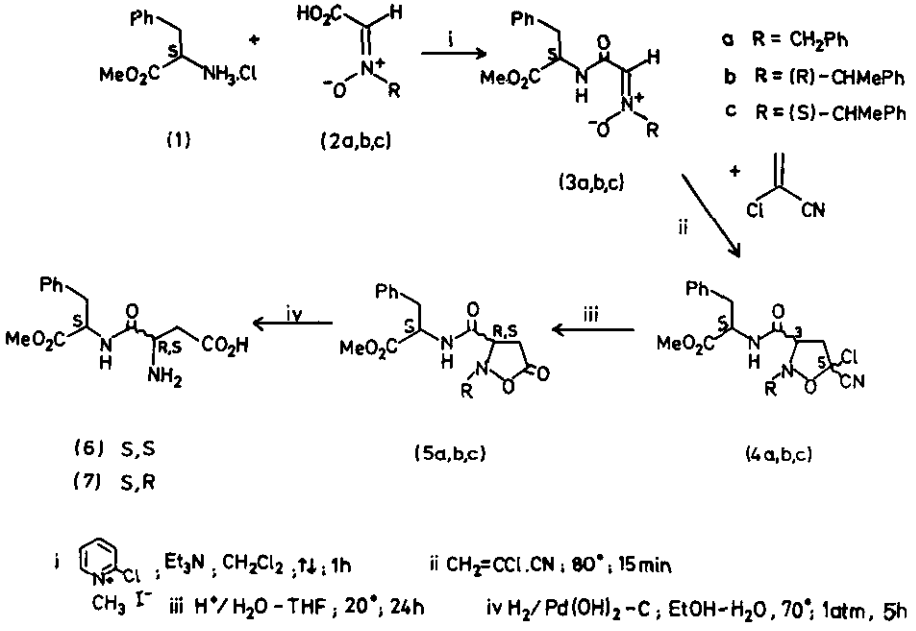
Abstract—The title compounds have been synthesised *via* cycloaddition of nitrones (3a,b,c) to 2-chloroacrylonitrile.

The low-calorie dipeptide sweetener aspartame [(S)-Asp-(S)-PhOMe] has about 180 times the sweetness of sucrose.[1] The first synthesis was reported[2] in 1966 but its sweetness was discovered accidentally[3] two years later during work on the synthesis of the C-terminal tetrapeptide sequence of gastrin, Try.Met.Asp.Phe.NH_2. The commercial importance of aspartame as a non-toxic, low-calorie artificial sweetener (Canderel; Equal; Nutra-Sweet; Tri-Sweet) has resulted in continued synthetic effort and additions to the patent literature.[4]

The principal difficulty with conventional syntheses based on simple peptide coupling is the problem of differentiating between the α- and β-carboxyl groups of (S)-aspartic acid and the consequent need to separate mixtures of regioisomeric dipeptides.[5] Resourceful chemical[6,7,8] and enzymological[9] solutions have to some extent overcome this problem. Two recent syntheses do not depend on a protocol for coupling the natural amino acids but instead elaborate synthetic dipeptide precursors. Thus, Fuganti[10] employed a chiral rhodium catalyst to generate aspartame (80% d,e) *via* hydrogenation of N-protected dehydroaspartame. Another inventive but hardly practical recent synthesis[11] features as key step the photochemical oxazıridine-amide rearrangement of a dipeptide precursor.

We now present a different approach to aspartame, in which the aspartyl moiety was assembled *via* 1,3-dipolar cycloaddition of nitrones (3) to the ketene equivalent 2-chloroacrylonitrile*.[12] Our reason for embarking on this synthesis was to see whether the sequence we had successfully used to synthesise stereoselectively the natural β-amino acids β-leucine, β-phenylalanine, β-tyrosine[13] and β-lysine[14] could be applied to make α-aspartyl dipeptides, and whether chirality could be efficiently transferred to the newly generated α-aspartyl chiral centre by the second

* We have found this to be much superior to vinyl acetate,[14] since it avoids the low-yield oxidation step needed to transform the initial adducts into isoxazolidinones.



amino acid [in this case (S)-phenylalanine] already incorporated into nitrone (3).

The nitrones (2a,b,c) were readily obtained by reacting glyoxylic acid hydrate with the appropriate alkyl hydroxylamine. Nitrone (2a) was crystalline, nitrones (2b) and (2c) were oils. ^{1}H Nmr showed each of the nitrones was the single Z-isomer. The methyl ester of nitrone (2b) [from methyl glyoxylate] exists in solution as a 1:1 mixture of Z and E isomers and is probably useless for asymmetric cycloaddition with chloroacrylonitrile (see Experimental). Coupling with (S)-phenylalanine methyl ester hydrochloride (1) was effected in dichloromethane with N-methyl-2-chloropyridinium iodide in presence of triethylamine, affording crystalline (3a) and (3b) and oily (3c) (55-60%). Again, ^{1}H nmr showed each nitrone (3a,b,c) was the single Z-isomer. Cycloaddition of each of the nitrones (3a,b,c) with excess α-chloroacrylonitrile at 80°C led regiospecifically to the adducts (4a,b,c), obtained as mixtures of diastereoisomers at C-3 and C-5 in virtually quantitative yields. They were hydrolysed directly at 20°C in aqueous THF containing 0.2-0.4 equivalents of HCl. Purification by flash chromatography over silica gel afforded the isoxazolidinones (5a,b,c) in 75-85% yields as either a mixture of two diastereomers (5a,b) or a single diastereomer (5c). The proportion of diastereomers in each mixture was obtained from their ^{1}H nmr spectra at 200 MHz (see Experimental) and the stereochemical assignments follow from

conversion into either (S)-Asp-(S)-PhOMe or (R)-Asp-(S)-PhOMe on hydrogenolysis as below.

Most striking is the fact that nitrone (3c) leads to a single diastereomer (5c) [3R]. Thus, introduction of a second chiral centre, (S)-CHMePh, reinforces the directing effect[15] of (S)-PheOMe and ensures cyclo addition of chloroacrylonitrile exclusively to the re,re-face of nitrone (3c). By contrast, in nitrone (3b) [R = (R)-CHMePh], the two chiral directing groups are in conflict, and cyclo addition is less diastereoselective [(3R):(3S) = 2:3] than with nitrone (3a) [R = CH_2Ph] [(3R):(3S) = 5:2]. Unfortunately, the single isomer (5c) leads not to aspartame, but to the tasteless (R)-aspartyl epimer as the sole product (see below).

Hydrogenolysis of the isoxazolidinones (5a,b,c) with Pearlman's catalyst in aqueous ethanol under atmospheric pressure at either 20°C (5a) or 70°C (5b,c) afforded the dipeptides in near-quantitative yields on filtration of catalyst and removal of solvent in vacuo. Thus, the major (3S)-isomer of (5b), separable from the minor (3R)-isomer by flash chromatography, afforded the sweet-tasting aspartame (S)-Asp-(S)-PhOMe (6), identical (mp, $[\alpha]_D$, ^1H and ^{13}C nmr and ir) with an authentic specimen. Similarly, hydrogenolysis of the single isomer (5c) afforded the tasteless (R)-Asp-(S)-PheOMe (7), identified by mp, $[\alpha]_D$,[3] and the very close correspondence of its spectroscopic properties (ms, ir, ^1H and ^{13}C nmr) with those of aspartame.

EXPERIMENTAL

The following instruments were used: Nmr : Perkin-Elmer R32 (90 MHz) or Bruker WP200SY (200 MHz). ^1H and ^{13}C nmr spectra are for $CDCl_3$ solutions at 200 MHz (^1H) or 50 MHz (^{13}C) unless otherwise indicated. Ms : VG/Kratos MS 9025. Ir : Perkin Elmer 983. Optical Rotations: Optical Activity AA-100.

Nitrones (2a,b,c)

To glyoxylic acid hydrate (Aldrich; 40 mmol), suspended in CH_2Cl_2 (50 ml) was added the appropriate hydroxylamine (or its oxalate and 1 equ. Et_3N) (40 mmol) and the solution stirred 5 h at 20°C. More CH_2Cl_2 (50 ml) was added, the CH_2Cl_2 solution washed with water (50 ml), dried (Na_2SO_4), and the solvent removed in vacuo to leave the crude nitrones (2a,b,c).

Thus N-benzylhydroxylamine afforded nitrone (2a) as a yellow paste which, crystallised from $Et_2O/CHCl_3$ (62%), had mp 92-93°. m/z (C_8H_9ON, $M^+ - CO_2$) 135.0685 (135.0684). ^1H Nmr (90 MHz) δ 5.06 (2H, s, $PhCH_2N$), 7.28 (1H, s, H-C=N), 7.45 (5H, s, C_6H_5); ^{13}C nmr δ 70.48 (CH_2Ph), 129.4-130.3 (C=N + C_6H_5), 161.21 (CO_2H).

N-(R)-Phenethylhydroxylamine oxalate,[16] mp 181-183°, afforded the oily nitrone (2b) (61%). m/z ($C_9H_{11}ON$, $M^+ - CO_2$) 149.0850 (149.0787). ^1H Nmr (90 MHz) δ 1.82 (3H, d, J = 6.0 Hz, CH_3),

5.21 (1H, q, J = 7.0 Hz, $C\underline{H}CH_3$), 7.39 (5H, s, $C_6\underline{H}_5$), 7.45 (1H, s, $\underline{H}$-C=N); ^{13}C nmr 17.68 ($\underline{C}H_3$), 74.74 ($\underline{C}H.CH_3$), 127.0-128.9 ($\underline{C}_6H_5$), 135.45 ($\underline{C}$=N), 161.13 ($\underline{C}O_2H$).

N-(S)-Phenethylhydroxylamine oxalate,[16] mp 177-180°C afforded the oily nitrone (2c) (74%). ^{1}H Nmr (90 MHz) δ 1.85 (3H, d, J = 6.0 Hz, $C\underline{H}_3$), 5.23 (1H, q, J = 7.0 Hz, $C\underline{H}CH_3$), 7.35 (5H, m, $C_6\underline{H}_5$), 7.53 (1H, s, $\underline{H}$-C=N).

Methyl ester of nitrone (2b). Methyl glyoxylate[17] (11.4 mmol) condensed as above with N-(R)-phenethylhydroxylamine oxalate afforded the methyl ester of nitrone (2b) which, crystallised from $Et_2O/CHCl_3$ (82%), had mp 84-85°. ^{1}H Nmr (90 MHz) δ 3.75 and 3.79 (1:1.1) (3H, s, $C\underline{H}_3OCO$), 5.16 and 7.07 (1:1.2) (1H, q, J = 7.0 Hz, $C\underline{H}CH_3$).

Nitrones (3a,b,c)

Nitrone (2a,b or c) (20 mmol), (S)-phenylalanine methyl ester hydrochloride (20 mmol), N-methyl-2-chloropyridinium iodide[18] (24 mmol) and Et_3N (70 mmol) in dry CH_2Cl_2 (100 ml) were refluxed for 1 h (t.l.c.). The clear solution was washed three times with HCl (5%; 40 ml) and once with water (40 ml), dried and solvent removed in vacuo. The nitrones (3a,b,c) were eluted from silica gel with ethyl acetate-hexane (45:55).

Nitrone (3a) (48%), mp 98-100°C [EtOAc/light petroleum (40-60°C)], $[\alpha]_D$ -8.1° (c = 0.1 in $CHCl_3$); m/z ($C_{19}H_{20}O_4N_2$, M^+) 340.1437 (340.1423); ir (KBr disc) 1234, 1645, 1742 cm^{-1}; ^{1}H nmr δ 3.08 (1H, dd, J = 6.0, 14.0 Hz, $CHC\underline{H}_A\underline{H}_BPh$), 3.18 (1H, dd, J = 7.0, 14.0 Hz, $CHCH_A\underline{H}_BPh$), 3.67 (3H, s, $CO_2C\underline{H}_3$), 4.88 (1H, m, $CH_2C\underline{H}N$), 4.92 (2H, s, $C\underline{H}_2Ph$), 7.05 (1H, s, $\underline{H}$-C=N), 7.22 (5H, m, $C_6\underline{H}_5$), 7.40 (5H, s, $C_6\underline{H}_5$), 10.22 (1H, d, J = 7.0 Hz, N$\underline{H}$); ^{13}C nmr δ 37.68 ($C\underline{C}H_2Ph$), 52.13 ($\underline{C}H_3OCO$), 53.39 ($\underline{C}H$-N=), 71.43 ($\underline{C}H_2$-N=), 126.9-135.7 (2 x $\underline{C}_6H_5$), 160.1 (NH$\underline{C}$O), 171.0 ($\underline{C}O_2CH_3$).

Nitrone (3b) (58%), mp 102-104°C from Et_2O; $[\alpha]_D$ -28.3° (c = 0.12 in $CHCl_3$); m/z ($C_{20}H_{22}O_4N_2$, M^+) 354.1577 (354.1580); (M^+-OH) 337.1538 (337.1552); ir (KBr disc) 1218, 1239, 1258, 1648, 1742 cm^{-1}; ^{1}H nmr δ 1.79 (3H, d, J = 7 Hz, $C\underline{H}_3CH$), 3.07 (1H, dd, J = 6.0, 14.0 Hz, $CHC\underline{H}_A\underline{H}_BPh$), 3.20 (1H, dd, J = 7.0, 14.0 Hz, $CHCH_A\underline{H}_BPh$), 3.66 (3H, s, $CO_2C\underline{H}_3$), 4.86 (1H, m, $CH_2C\underline{H}N$), 5.09 (1H, q, J = 7.0 Hz, PhC$\underline{H}$N), 7.14 (1H, s, $\underline{H}$-C=N), 7.23 (5H, m, $C_6\underline{H}_5$), 7.40 (5H, s, $C_6\underline{H}_5$), 10.27 (1H, d, J = 7.0 Hz, N$\underline{H}$); ^{13}C nmr δ 18.67 ($\underline{C}H_3CH$), 37.82 ($\underline{C}H_2Ph$), 52.11 ($\underline{C}H_3OCO$), 53.53 ($\underline{C}H$-N), 76.28 ($\underline{C}H$-N=), 126.9-136.5 (2 x $\underline{C}_6H_5$), 160.35 (NH$\underline{C}$O), 171.08 ($\underline{C}O_2CH_3$).

Nitrone (3c) (54%), oil, $[\alpha]_D$ +10.5° (c = 0.07 in $CHCl_3$); m/z ($C_{20}H_{21}O_3N_2$, M^+-OH) 337.1560 (337.1552); ir ($CHCl_3$) 1650, 1735 cm^{-1}; ^{1}H nmr δ 1.82 (3H, d, J = 7.0 Hz, $C\underline{H}_3CH$), 3.07 (1H, dd, J = 6.0, 14.0 Hz, $CHC\underline{H}_A\underline{H}_BPh$), 3.18 (1H, dd, J = 7.0, 14.0 Hz, $CHCH_A\underline{H}_BPh$), 3.70 (3H, s, $CO_2C\underline{H}_3$), 4.86 (1H, m, $CH_2C\underline{H}N$), 5.09 (1H, q, J = 7.0 Hz, PhC$\underline{H}$N), 7.14 (1H, s, $\underline{H}$-C=N), 7.13-7.28 (5H, m, $C_6\underline{H}_5$), 7.42 (5H, s, $C_6\underline{H}_5$), 10.27 (1H, d, J = 7.0 Hz, N$\underline{H}$); ^{13}C nmr δ 18.76 ($\underline{C}H_3CH$), 37.93 ($\underline{C}H_2Ph$),

52.22 ($\underline{C}H_3OCO$), 53.57 ($\underline{C}H$-N-), 76.39 ($\underline{C}H$-N=), 126.96-136.78 (2 x $\underline{C}_6H_5$), 160.37 (NH$\underline{C}O$), 171.19 ($\underline{C}O_2CH_3$).

Cycloadducts (4a,b,c)

Nitrones (3a,b,c) (1.5 mmol) in 2-chloroacrylonitrile (10 ml) were heated at 80°C (oil bath) under Ar for 15 min. Excess 2-chloroacrylonitrile was removed *in vacuo*, affording the crude adducts (4a,b,c) in 95-100% yield. Flash chromatography of (4a) (EtOAc/hexane 25:75) afforded the cycloadduct(s) (93%) with unchanged ^{1}H nmr spectrum, which had complex continuous absorption (11H) between δ3 and δ5 and a complex multiplet (10H) at δ7.0-7.5. The $\underline{C}H_3OCO$ signal at δ 3.74 was split in two. *m/z* 392 (M^+-Cl). Ir ν_{max} ($CHCl_3$) 1520, 1685 and 1745 cm^{-1}; band for CN (2200-2260 cm^{-1}) absent.

The spectroscopic properties of adducts (4b) and (4c) were analogous to those of (4a), with the changes to be expected for replacement of CH_2Ph by (R)- or (S)-CHMePh. In particular, in the ^{1}H nmr spectra, the $\underline{C}H_3CH$ and $\underline{C}H_3OCO$ signals indicated formation of two (3c) or more than two (3b) diastereomeric adducts. The crude cycloadducts were used for hydrolysis.

Isoxazolidin-5-ones (5a,b,c)

Cycloadduct (4a,b,c) (1.5 mmol), dissolved in a minimum volume of THF was diluted with H_2O (10 ml) and sufficient THF added to produce a single phase. Aqueous HCl (0.2-0.4 equ. of 1N) was added, the solution was stirred at 20°C for 16-24 h then neutralised (1N NaOH, congo red), concentrated to 1/3 volume and extracted with EtOAc (5 x 10 ml). Drying (Na_2SO_4), removal of solvent *in vacuo*, and flash chromatography over silica gel (35-40% EtOAc/hexane) afforded the isoxazolidinones (5a, b,c) in 75-85% yield.

Hydrolysis of adduct (4a) afforded the oily (5a) (82%) consisting of a mixture of C-3 epimers [(3R):(3S) = 5:2 from $\underline{C}H_3OCO$ signals in ^{1}H nmr spectrum at 200 MHz]. They were inseparable by glc (SE-54 capillary, R.I. = 2555) and by preparative flash chromatography on silica. ^{1}H Nmr δ 2.75-3.23 (4H, m, $\underline{C}H_2CO$ + $PhC\underline{H}_2CH$), 3.68 and 3.78 (3H, 2 x s, $\underline{C}H_3OCO$), 3.84-4.23 (3H, m, $PhC\underline{H}_2$-N + $\underline{C}H$-N), 4.71-4.88 (1H, m, $\underline{C}H$-N), 6.95-7.35 (10H, m, 2 x $\underline{C}_6H_5$), 7.60 and 7.71 (1H, 2 x d, N$\underline{H}$). ^{13}C Nmr δ 31.35 ($\underline{C}CH_2Ph$), 37.101† + 37.578† ($\underline{C}H_2CO$), 52.19 + 52.13 ($\underline{C}H_3OCO$), 52.87 + 52.51 (N-$\underline{C}H$-CONH), 62.45 + 62.39 ($Ph\underline{C}H_2N$-), 64.03 ($\underline{C}HCO_2Me$), 126.87 - 129.33 (2 x $\underline{C}_6H_5$), 168.38 + 168.14 ($\underline{C}ONH$), 170.92 + 170.89 ($\underline{C}O_2CH_3$), 173.59 + 173.90 ($\underline{C}OCH_2$).

Hydrolysis of adduct (4b) and chromatography afforded the mixture of C-3 epimers (5b; 83%;

†Major followed by minor.

(3R):(3S) = 2:3 from $CHC\underline{H}_3$ signals in ^{1}H nmr at 200 MHz]. m/z ($C_{22}H_{24}O_5N_2$, M^+) 396.1700 (396.1685). The mixture was resolved by flash chromatography: 35% EtOAc-hexane eluted (3S)-(5b) mp 112-113°. m/z (M^+) 396.1667. ir ($CHCl_3$) ν_{max} 1782, 1735, 1673 cm^{-1}. $[\alpha]_D$ = -40° (c = 0.064 in $CHCl_3$). ^{1}H Nmr δ 1.54 (3H, d, J = 6.0 Hz, $C\underline{H}_3CH$), 2.75 (2H, m, $C\underline{H}_2CO$), 3.05 (1H, dd, J = 6.0, 15.0 Hz, $CHC\underline{H}_A\underline{H}_B$Ph), 3.17 (1H, dd, J = 5.0, 15.0 Hz, $CHCH_A\underline{H}_B$Ph), 3.74 (3H, s, $CO_2C\underline{H}_3$), 3.87 (1H, dd, J = 5.5, 9.0 Hz, COC<u>H</u>N), 4.11 (1H, q, J = 6.0 Hz, PhC<u>H</u>N), 4.81 (1H, m, $CH_2C\underline{H}N$), 7.10-7.40 (10H, m, 2 x $C_6\underline{H}_5$), 7.84 (1H, d, J = 10.0 Hz, N<u>H</u>); ^{13}C nmr δ 20.08 ($C\underline{H}_3CH$), 30.29 (Ph$C\underline{H}_2$), 38.12 (CO$C\underline{H}_2$), 52.72 (COO$C\underline{H}_3$), 52.96 (<u>C</u>H-NHCO), 61.81 (Ph<u>C</u>H-N), 67.12 (NHCO<u>C</u>H-N), 116.03-138.79 (2 x $\underline{C}_6H_5$), 168.51 (<u>C</u>ONH), 171.22 ($\underline{C}O_2CH_3$), 175.13 (<u>C</u>OCH_2). 40% EtOAc-hexane eluted (3R)-(5b), oil, m/z (M^+) 396.1692 (396.1685); ir ν_{max} ($CHCl_3$) 1780, 1735, 1670 cm^{-1}. $[\alpha]_D$ +51.9° (c = 0.053, $CHCl_3$). ^{1}H Nmr δ 1.47 (3H, d, J = 8.0 Hz, $C\underline{H}_3CH$), 2.29 (1H, dd, J = 10.0, 17.5 Hz, $C\underline{H}_A\underline{H}_B$CO), 2.77 (1H, dd, J = 5.0, 17.5 Hz, $CH_A\underline{H}_B$CO), 3.09 (1H, dd, J = 7.5, 14.5 Hz, $CHC\underline{H}_A\underline{H}_B$Ph), 3.25 (1H, dd, J = 5.0, 14.5 Hz, $CHCH_A\underline{H}_B$Ph), 3.74 (3H, s, $CO_2C\underline{H}_3$), 3.88 (1H, q, J = 8.0 Hz, PhC<u>H</u>N), 3.88 (1H, dd, J = 4.0, 17.0 Hz, COC<u>H</u>N), 4.82 (1H, m, $CH_2C\underline{H}N$), 7.10-7.30 (10H, m, 2 x $C_6\underline{H}_5$), 7.58 (1H, d, J = 8.0 Hz, N<u>H</u>); ^{13}C nmr δ 19.01 ($C\underline{H}_3CH$), 32.67 (Ph$C\underline{H}_2$), 37.50 (CO$C\underline{H}_2$), 52.57 (COO$C\underline{H}_3$), 52.95 (<u>C</u>H-NHCO), 63.44 (Ph<u>C</u>H-N), 67.14 (NHCO<u>C</u>H-N), 127.36-137.22 (2 x $\underline{C}_6H_5$), 168.97 (<u>C</u>ONH), 171.23 ($\underline{C}O_2CH_3$), 173.73 (<u>C</u>OCH_2).

Hydrolysis of adduct (4c) and chromatography furnished a single isoxazolidinone (5c) (77%), mp 92-94°. m/z (M^+) 396.1693 (396.1685); ir ν_{max} (KBr disc) 1678, 1787, 1790 cm^{-1}. $[\alpha]_D$ + 45° (c = 0.04, $CHCl_3$). ^{1}H Nmr δ 1.52 (3H, d, J = 6.0 Hz, $C\underline{H}_3CH$), 2.73 (1H, dd, J = 14.0, 20.0 Hz, $C\underline{H}_A\underline{H}_B$CO), 2.90 (1H, dd, J = 3.0, 20.0 Hz, $CH_A\underline{H}_B$CO), 3.01 (1H, dd, J = 5.0, 15.0 Hz, $CHC\underline{H}_A\underline{H}_B$Ph), 3.21 (1H, dd, J = 4.5, 15.0 Hz, $CHCH_A\underline{H}_B$Ph), 3.74 (3H, s, $CO_2C\underline{H}_3$), 3.88 (1H, dd, J = 2.5, 15.0 Hz, COC<u>H</u>N), 4.12 (1H, q, J = 6.0 Hz, PhC<u>H</u>N), 4.72 (1H, m, $CH_2C\underline{H}N$), 7.4 (10H, m, 2 x $C_6\underline{H}_5$), 7.78(1H, d, J = 8.0 Hz, N<u>H</u>); ^{13}C nmr δ 19.92 ($C\underline{H}_3CH$), 30.09 (Ph$C\underline{H}_2$), 37.36 (CO$C\underline{H}_2$), 52.36 ($C\underline{H}_3OCO$), 53.23 (<u>C</u>HCO$_2$Me), 61.64 (Ph<u>C</u>H-N-), 66.74 (NHCO<u>C</u>H-N-), 126.17-138.66 (2 x $\underline{C}_6H_5$), 169.01 (<u>C</u>ONH), 171.04 (<u>C</u>OOCH$_3$), 174.99 (<u>C</u>OCH_2).

<u>Isoxazolidinone [5b; OMe in place of (S)-PhOMe]</u>. Cycloaddition of the methyl ester of nitrone (2b) with chloroacrylonitrile and hydrolysis, as before, afforded the oily <u>isoxazolidinone</u> of the <u>title</u> (59%). m/z ($C_{13}H_{15}NO_4$, M^+) 249.1005 (249.1001). ^{1}H Nmr (90 MHz) δ 3.56 and 3.80 (1.23:1) (3H, s, $C\underline{H}_3OCO$). Ir ν_{max} ($CHCl_3$) 1740, 1780 cm^{-1}.

<u>Hydrogenolysis of Isoxazolidinones (5a,b,c)</u>

Isoxazolidinone (3S)-(5b) obtained as above (100 mg, 0.25 mmol) in EtOH/H_2O (25 ml, 3:2) was hydrogenated over $Pd(OH)_2$ on charcoal (20 mg, 20%) at 70°C and 1 Torr. for 5 h. Filtration and

removal of solvent in vacuo left a white solid (74 mg; 100%). Washing with chilled water afforded the sweet (S)-Asp-(S)-PhOMe (Aspartame) (6) (65 mg), mp 243-247°, $[\alpha]_D$ +29.8° (c = 0.05, acetic acid) [Lit.[10] mp 248-250°C, $[\alpha]_D$ +30.3° (c = 0.1, acetic acid)]. Comparison of ^1H and ^{13}C nmr at 200 MHz with those of commercial aspartame (Aldrich) proved identical.

Isoxazolidinone (3R)-(5b) (100 mg), hydrogenated under the same conditions, afforded the tasteless (R)-Asp-(S)-PhOMe (7) (75 mg), mp 154-157°C, $[\alpha]_D$ -17.4° (c = 0.05, H_2O) [Lit.[3] mp 159°C, $[\alpha]_D$ -18° (c = 0.1, H_2O)].

Hydrogenation of the single isomer (5c) (100 mg) likewise afforded (R)-Asp-(S)-PhOMe (100%).

Hydrogenation of the inseparable mixture of diastereomers (5a) (100 mg) under the above conditions but at 20°C afforded (100%) a mixture of (R)-Asp-(S)-PhOMe and (S)-Asp-(S)-PhOMe in a 5:2 ratio from the relative intensities of CH_3COO signals (δ 3.61 and 3.59) (d_6-DMSO, 200 MHz).

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