

STEREOCONTROLLED SYNTHESSES 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 reported² in 1966 but its sweetness was discovered accidentally³ two years later during work on the synthesis of the C-terminal tetrapeptide sequence of gastrin, Try.Met.Asp.Phe.NH₂. 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 enzymological⁹ 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, Fuganti¹⁰ employed a chiral rhodium catalyst to generate aspartame (80% d,e) via hydrogenation of N-protected dehydroaspartame. Another inventive but hardly practical recent synthesis¹¹ features as key step the photochemical oxaziridine-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 -tyrosine¹³ and β -lysine¹⁴ 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.

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 effect¹⁵ 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 = CH₂Ph] [(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 ¹³C 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 ¹³C nmr) with those of aspartame.

EXPERIMENTAL

The following instruments were used: Nmr : Perkin-Elmer R32 (90 MHz) or Bruker WP200SY (200 MHz). ¹H and ¹³C nmr spectra are for CDCl₃ solutions at 200 MHz (¹H) or 50 MHz (¹³C) 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 CH₂Cl₂ (50 ml) was added the appropriate hydroxylamine (or its oxalate and 1 equ. Et₃N) (40 mmol) and the solution stirred 5 h at 20°C. More CH₂Cl₂ (50 ml) was added, the CH₂Cl₂ solution washed with water (50 ml), dried (Na₂SO₄), 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 Et₂O/CHCl₃ (62%), had mp 92-93°. m/z (C₈H₉ON, M⁺ -CO₂) 135.0685 (135.0684). ¹H Nmr (90 MHz) δ 5.06 (2H, s, PhCH₂N), 7.28 (1H, s, H-C=N), 7.45 (5H, s, C₆H₅); ¹³C nmr δ 70.48 (CH₂Ph), 129.4-130.3 (C=N + C₆H₅), 161.21 (CO₂H).

N-(R)-Phenethylhydroxylamine oxalate,¹⁶ mp 181-183°, afforded the oily nitrone (2b) (61%). m/z (C₉H₁₁ON, M⁺ -CO₂) 149.0850 (149.0787). ¹H Nmr (90 MHz) δ 1.82 (3H, d, J = 6.0 Hz, CH₃),

5.21 (1H, q, J = 7.0 Hz, CHCH₃), 7.39 (5H, s, C₆H₅), 7.45 (1H, s, H-C=N); ¹³C nmr 17.68 (CH₃), 74.74 (CH₂CH₃), 127.0-128.9 (C₆H₅), 135.45 (C=N), 161.13 (CO₂H).

N-(S)-Phenethylhydroxylamine oxalate,¹⁶ mp 177-180°C afforded the oily nitron (2c) (74%).

¹H Nmr (90 MHz) δ 1.85 (3H, d, J = 6.0 Hz, CH₃), 5.23 (1H, q, J = 7.0 Hz, CHCH₃), 7.35 (5H, m, C₆H₅), 7.53 (1H, s, H-C=N).

Methyl ester of nitron (2b). Methyl glyoxylate¹⁷ (11.4 mmol) condensed as above with

N-(R)-phenethylhydroxylamine oxalate afforded the methyl ester of nitron (2b) which, crystallised from Et₂O/CHCl₃ (82%), had mp 84-85°. ¹H Nmr (90 MHz) δ 3.75 and 3.79 (1:1.1) (3H, s, CH₃OCO), 5.16 and 7.07 (1:1.2) (1H, q, J = 7.0 Hz, CHCH₃).

Nitrones (3a,b,c)

Nitron (2a,b or c) (20 mmol), (S)-phenylalanine methyl ester hydrochloride (20 mmol), N-methyl-2-chloropyridinium iodide¹⁸ (24 mmol) and Et₃N (70 mmol) in dry CH₂Cl₂ (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).

Nitron (3a) (48%), mp 98-100°C [EtOAc/light petroleum (40-60°C)], [α]_D -8.1° (c = 0.1 in CHCl₃); m/z (C₁₉H₂₀O₄N₂, M⁺) 340.1437 (340.1423); ir (KBr disc) 1234, 1645, 1742 cm⁻¹; ¹H nmr δ 3.08 (1H, dd, J = 6.0, 14.0 Hz, CHCH_AH_BPh), 3.18 (1H, dd, J = 7.0, 14.0 Hz, CHCH_AH_BPh), 3.67 (3H, s, CO₂CH₃), 4.88 (1H, m, CH₂CHN), 4.92 (2H, s, CH₂Ph), 7.05 (1H, s, H-C=N), 7.22 (5H, m, C₆H₅), 7.40 (5H, s, C₆H₅), 10.22 (1H, d, J = 7.0 Hz, NH); ¹³C nmr δ 37.68 (CCH₂Ph), 52.13 (CH₃OCO), 53.39 (CH-N-), 71.43 (CH₂-N=), 126.9-135.7 (2 x C₆H₅), 160.1 (NHCO), 171.0 (CO₂CH₃).

Nitron (3b) (58%), mp 102-104°C from Et₂O; [α]_D -28.3° (c = 0.12 in CHCl₃); m/z (C₂₀H₂₂O₄N₂, M⁺) 354.1577 (354.1580); (M⁺-OH) 337.1538 (337.1552); ir (KBr disc) 1218, 1239, 1258, 1648, 1742 cm⁻¹; ¹H nmr δ 1.79 (3H, d, J = 7 Hz, CH₃CH), 3.07 (1H, dd, J = 6.0, 14.0 Hz, CHCH_AH_BPh), 3.20 (1H, dd, J = 7.0, 14.0 Hz, CHCH_AH_BPh), 3.66 (3H, s, CO₂CH₃), 4.86 (1H, m, CH₂CHN), 5.09 (1H, q, J = 7.0 Hz, PhCHN), 7.14 (1H, s, H-C=N), 7.23 (5H, m, C₆H₅), 7.40 (5H, s, C₆H₅), 10.27 (1H, d, J = 7.0 Hz, NH); ¹³C nmr δ 18.67 (CH₃CH), 37.82 (CH₂Ph), 52.11 (CH₃OCO), 53.53 (CH-N), 76.28 (CH-N=), 126.9-136.5 (2 x C₆H₅), 160.35 (NHCO), 171.08 (CO₂CH₃).

Nitron (3c) (54%), oil, [α]_D +10.5° (c = 0.07 in CHCl₃); m/z (C₂₀H₂₁O₃N₂, M⁺-OH) 337.1560 (337.1552); ir (CHCl₃) 1650, 1735 cm⁻¹; ¹H nmr δ 1.82 (3H, d, J = 7.0 Hz, CH₃CH), 3.07 (1H, dd, J = 6.0, 14.0 Hz, CHCH_AH_BPh), 3.18 (1H, dd, J = 7.0, 14.0 Hz, CHCH_AH_BPh), 3.70 (3H, s, CO₂CH₃), 4.86 (1H, m, CH₂CHN), 5.09 (1H, q, J = 7.0 Hz, PhCHN), 7.14 (1H, s, H-C=N), 7.13-7.28 (5H, m, C₆H₅), 7.42 (5H, s, C₆H₅), 10.27 (1H, d, J = 7.0 Hz, NH); ¹³C nmr δ 18.76 (CH₃CH), 37.93 (CH₂Ph),

52.22 ($\underline{\text{CH}_3\text{OCO}}$), 53.57 ($\underline{\text{CH-N}}$), 76.39 ($\underline{\text{CH-N}}$), 126.96-136.78 ($2 \times \underline{\text{C}_6\text{H}_5}$), 160.37 ($\underline{\text{NHCO}}$), 171.19 ($\underline{\text{CO}_2\text{CH}_3}$).

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 ^1H nmr spectrum, which had complex continuous absorption (11H) between $\delta 3$ and $\delta 5$ and a complex multiplet (10H) at $\delta 7.0-7.5$. The $\underline{\text{CH}_3\text{OCO}}$ signal at $\delta 3.74$ was split in two. $\underline{m/z}$ 392 ($\text{M}^+ - \text{Cl}$). Ir ν_{max} (CHCl_3) 1520, 1685 and 1745 cm^{-1} ; band for CN ($2200-2260 \text{ cm}^{-1}$) 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 ^1H nmr spectra, the $\underline{\text{CH}_3\text{CH}}$ and $\underline{\text{CH}_3\text{OCO}}$ 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 $\underline{\text{CH}_3\text{OCO}}$ signals in ^1H nmr spectrum at 200 MHz]. They were inseparable by glc (SE-54 capillary, R.I. = 2555) and by preparative flash chromatography on silica. ^1H Nmr δ 2.75-3.23 (4H, m, $\underline{\text{CH}_2\text{CO}}$ + PhCH_2CH), 3.68 and 3.78 (3H, $2 \times \underline{s}$, $\underline{\text{CH}_3\text{OCO}}$), 3.84-4.23 (3H, m, $\text{PhCH}_2\text{-N}$ + $\underline{\text{CH-N}}$), 4.71-4.88 (1H, m, $\underline{\text{CH-N}}$), 6.95-7.35 (10H, m, $2 \times \underline{\text{C}_6\text{H}_5}$), 7.60 and 7.71 (1H, $2 \times \underline{d}$, NH). ^{13}C Nmr δ 31.35 ($\underline{\text{CCH}_2\text{Ph}}$), 37.101[†] + 37.578[†] ($\underline{\text{CH}_2\text{CO}}$), 52.19 + 52.13 ($\underline{\text{CH}_3\text{OCO}}$), 52.87 + 52.51 ($\underline{\text{N-CH-CONH}}$), 62.45 + 62.39 ($\text{PhCH}_2\text{-N}$), 64.03 ($\underline{\text{CHCO}_2\text{Me}}$), 126.87 - 129.33 ($2 \times \underline{\text{C}_6\text{H}_5}$), 168.38 + 168.14 ($\underline{\text{CONH}}$), 170.92 + 170.89 ($\underline{\text{CO}_2\text{CH}_3}$), 173.59 + 173.90 ($\underline{\text{COCH}_2}$).

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

[†]Major followed by minor.

(3R):(3S) = 2:3 from CHCH_3 signals in ^1H nmr at 200 MHz]. m/z ($\text{C}_{22}\text{H}_{24}\text{O}_5\text{N}_2$, 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} . $[\alpha]_D = -40^\circ$ ($c = 0.064$ in CHCl_3). ^1H Nmr δ 1.54 (3H, $\underline{d}$, $J = 6.0$ Hz, CH_3CH), 2.75 (2H, $\underline{m}$, CH_2CO), 3.05 (1H, $\underline{dd}$, $J = 6.0$, 15.0 Hz, $\text{CHCH}_{\text{A-B}}\text{Ph}$), 3.17 (1H, $\underline{dd}$, $J = 5.0$, 15.0 Hz, $\text{CHCH}_{\text{A-B}}\text{Ph}$), 3.74 (3H, $\underline{s}$, CO_2CH_3), 3.87 (1H, $\underline{dd}$, $J = 5.5$, 9.0 Hz, COCHN), 4.11 (1H, $\underline{q}$, $J = 6.0$ Hz, PhCHN), 4.81 (1H, $\underline{m}$, CH_2CHN), 7.10-7.40 (10H, $\underline{m}$, $2 \times \text{C}_6\text{H}_5$), 7.84 (1H, $\underline{d}$, $J = 10.0$ Hz, NH); ^{13}C nmr δ 20.08 (CH_3CH), 30.29 (PhCH_2), 38.12 (COCH_2), 52.72 (COOCH_3), 52.96 (CH-NHCO), 61.81 (PhCH-N), 67.12 (NHCOCH-N), 116.03-138.79 ($2 \times \text{C}_6\text{H}_5$), 168.51 (CONH), 171.22 (CO_2CH_3), 175.13 (COCH_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} . $[\alpha]_D +51.9^\circ$ ($c = 0.053$, CHCl_3). ^1H Nmr δ 1.47 (3H, $\underline{d}$, $J = 8.0$ Hz, CH_3CH), 2.29 (1H, $\underline{dd}$, $J = 10.0$, 17.5 Hz, $\text{CH}_{\text{A-B}}\text{CO}$), 2.77 (1H, $\underline{dd}$, $J = 5.0$, 17.5 Hz, $\text{CH}_{\text{A-B}}\text{CO}$), 3.09 (1H, $\underline{dd}$, $J = 7.5$, 14.5 Hz, $\text{CHCH}_{\text{A-B}}\text{Ph}$), 3.25 (1H, $\underline{dd}$, $J = 5.0$, 14.5 Hz, $\text{CHCH}_{\text{A-B}}\text{Ph}$), 3.74 (3H, $\underline{s}$, CO_2CH_3), 3.88 (1H, $\underline{q}$, $J = 8.0$ Hz, PhCHN), 3.88 (1H, $\underline{dd}$, $J = 4.0$, 17.0 Hz, COCHN), 4.82 (1H, $\underline{m}$, CH_2CHN), 7.10-7.30 (10H, $\underline{m}$, $2 \times \text{C}_6\text{H}_5$), 7.58 (1H, $\underline{d}$, $J = 8.0$ Hz, NH); ^{13}C nmr δ 19.01 (CH_3CH), 32.67 (PhCH_2), 37.50 (COCH_2), 52.57 (COOCH_3), 52.95 (CH-NHCO), 63.44 (PhCH-N), 67.14 (NHCOCH-N), 127.36-137.22 ($2 \times \text{C}_6\text{H}_5$), 168.97 (CONH), 171.23 (CO_2CH_3), 173.73 (COCH_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} . $[\alpha]_D +45^\circ$ ($c = 0.04$, CHCl_3). ^1H Nmr δ 1.52 (3H, $\underline{d}$, $J = 6.0$ Hz, CH_3CH), 2.73 (1H, $\underline{dd}$, $J = 14.0$, 20.0 Hz, $\text{CH}_{\text{A-B}}\text{CO}$), 2.90 (1H, $\underline{dd}$, $J = 3.0$, 20.0 Hz, $\text{CH}_{\text{A-B}}\text{CO}$), 3.01 (1H, $\underline{dd}$, $J = 5.0$, 15.0 Hz, $\text{CHCH}_{\text{A-B}}\text{Ph}$), 3.21 (1H, $\underline{dd}$, $J = 4.5$, 15.0 Hz, $\text{CHCH}_{\text{A-B}}\text{Ph}$), 3.74 (3H, $\underline{s}$, CO_2CH_3), 3.88 (1H, $\underline{dd}$, $J = 2.5$, 15.0 Hz, COCHN), 4.12 (1H, $\underline{q}$, $J = 6.0$ Hz, PhCHN), 4.72 (1H, $\underline{m}$, CH_2CHN), 7.4 (10H, $\underline{m}$, $2 \times \text{C}_6\text{H}_5$), 7.78 (1H, $\underline{d}$, $J = 8.0$ Hz, NH); ^{13}C nmr δ 19.92 (CH_3CH), 30.09 (PhCH_2), 37.36 (COCH_2), 52.36 (CH_3OCO), 53.23 (CHCO_2Me), 61.64 (PhCH-N), 66.74 (NHCOCH-N), 126.17-138.66 ($2 \times \text{C}_6\text{H}_5$), 169.01 (CONH), 171.04 (COOCH_3), 174.99 (COCH_2).

Isoxazolidinone [5b; OMe in place of (S)-PhOMe]. Cycloaddition of the methyl ester of nitron (2b) with chloroacrylonitrile and hydrolysis, as before, afforded the oily isoxazolidinone of the title (59%). m/z ($\text{C}_{13}\text{H}_{15}\text{NO}_4$, M^+) 249.1005 (249.1001). ^1H Nmr (90 MHz) δ 3.56 and 3.80 (1.23:1) (3H, $\underline{s}$, CH_3OCO). ir ν_{max} (CHCl_3) 1740, 1780 cm^{-1} .

Hydrogenolysis of Isoxazolidinones (5a,b,c)

Isoxazolidinone (3S)-(5b) obtained as above (100 mg, 0.25 mmol) in EtOH/ H_2O (25 ml, 3:2) was hydrogenated over $\text{Pd}(\text{OH})_2$ 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°, $[\alpha]_D +29.8^\circ$ (c = 0.05, acetic acid) [Lit.¹⁰ mp 248-250°C, $[\alpha]_D +30.3^\circ$ (c = 0.1, acetic acid)]. Comparison of ¹H and ¹³C 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, $[\alpha]_D -17.4^\circ$ (c = 0.05, H₂O) [Lit.³ mp 159°C, $[\alpha]_D -18^\circ$ (c = 0.1, H₂O)].

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 CH₃COO signals (δ 3.61 and 3.59) (d₆-DMSO, 200 MHz).

ACKNOWLEDGEMENT

We thank the S.E.R.C. for studentship support.

REFERENCES

1. M.R. Cloninger and R.E. Baldwin, Science, 1970, **170**, 81; J.A. Oppermann, E. Muldoon, and R.E. Ranney, J. Nutr., 1973, **103**, 1454.
2. J.M. Davey, A.H. Laird, and J.S. Morley, J. Chem. Soc. (C), 1966, 555.
3. R.H. Mazur, J.M. Schlatter, and A.H. Goldkamp, J. Am. Chem. Soc., 1969, **91**, 2684.
4. U.S. 3,492,131 (1968, 1970); B.P. 1,243,169 (1971); U.S. 3,879,372 (1972); U.S. 3,933,781 (1976); U.S. 4,173,562 (1979).
5. Y. Ariyoshi and N. Sato, Bull. Chem. Soc. Japan, 1972, **45**, 942; Y. Ariyoshi, T. Yamatani, N. Uchiyama, and N. Sato, ibid., 1972, **45**, 2208; Y. Ariyoshi, T. Yamatani, N. Uchiyama, Y. Adachi, and N. Sato, ibid., 1973, **46**, 1893; Y. Ariyoshi, T. Yamatani and Y. Adachi, ibid., 1973, **46**, 2611.
6. J.S. Tou and B.D. Vineyard, J. Org. Chem., 1985, **50**, 4982.
7. F.C. Vinick and S. Jung, Tetrahedron Lett., 1982, **23**, 1315.
8. H. Pietsch, Tetrahedron Lett., 1976, 4053.
9. Y. Isowa, M. Ohmori, T. Ichikawa, and K. Mori, Tetrahedron Lett., 1979, 2611; K. Oyama, K. Kihara, and Y. Nonaka, J. Chem. Soc., Perkin Trans. 2, 1981, 356; K. Oyama, S. Nishimura, Y. Nonaka, K. Kihara, and T. Hashimoto, J. Org. Chem., 1981, **46**, 5242.
10. C. Fuganti, P. Grasselli, L. Malpezzi, and P. Casati, J. Org. Chem., 1986, **51**, 1126.
11. P. Duhamel, B. Goument, and J.-C. Plaquevent, Tetrahedron Lett., 1987, **28**, 2595.

12. H. Schneider, Helv. Chim. Acta, 1982, 65, 726; S. Ranganathan, D. Ranganathan, and A.K. Mehrotra, Synthesis, 1977, 289.
13. D.F.C. Moffat, Ph.D. Thesis, Glasgow 1986; R. Tomanek, Ph.D. Thesis, Glasgow, 1988.
14. D. Keirs, D. Moffat, and K. Overton, J. Chem. Soc., Chem. Comm., 1988, 654.
15. S. Masamune, W. Choy, J.S. Petersen, and L.R. Sita, Angew. Chem. Int. Ed. Engl., 1985, 24, 1.
16. P.M. Wovkulich and M.R. Uskokovic, Tetrahedron, 1985, 41, 3455.
17. T.R. Kelly, T.E. Schmidt, and T.G. Haggerty, Synthesis, 1972, 544.
18. E. Bald, K. Saigo, and T. Mukaiyama, Chem. Lett., 1975, 1163.

Received, 22nd August, 1988