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AN APPROACH TO LANKACIDIN SYNTHESIS: CONTROL OF STEREOCHEMISTRY USING Δ^2-ISOXAZOLINES

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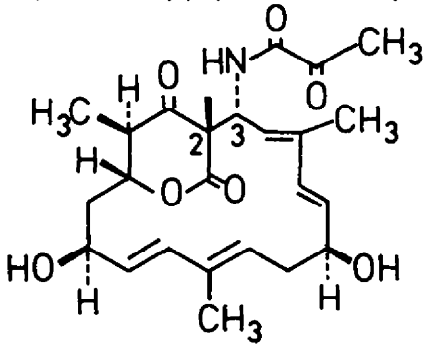
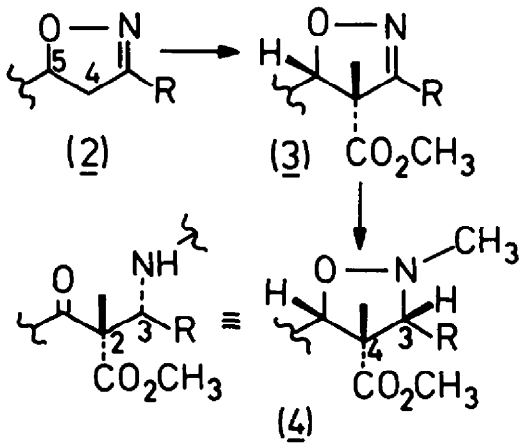
Abstract - A procedure is developed for the 'one-pot' acylation and methylation of isoxazolines at C(4). Thus the 5-substituted isoxazolines (8), (9), and (18) were converted into their cis-4-methoxycarbonyl-trans-4-methyl derivatives (10), (11), and (19), by deprotonation using lithium diisopropylamide, followed by the sequential addition of methyl chloroformate and methyl iodide. The reduction of these substituted isoxazolines was then investigated. N-Methylation using Meerwein's salt, and reduction of the derived N-methylisoxazolinium salt using sodium borohydride gave isoxazolidines (14) and (20), but only in modest yields. The analogous N-methylation - reduction of the lactone-isoxazoline (12) was not stereoselective. The isoxazolidines (14) and (20) have the correct relative configurations at C(3) and C(4) for conversion into lankacidin analogues.

The lankacidins, e.g. lankacidin C(1), comprise an interesting group of macrocyclic antibiotics which show anti-tumour activity.[1] The novel structures of these compounds, together with their biological activity, make them attractive synthetic targets. One problem in any proposed lankacidin synthesis, concerns the control of stereochemistry at the six chiral centres. We here describe attempts to establish the desired configurations at C(2) and C(3) using isoxazolines as templates.



(1)

It was decided to investigate the route outlined in Scheme 1. Thus as addition of nitrile oxides to

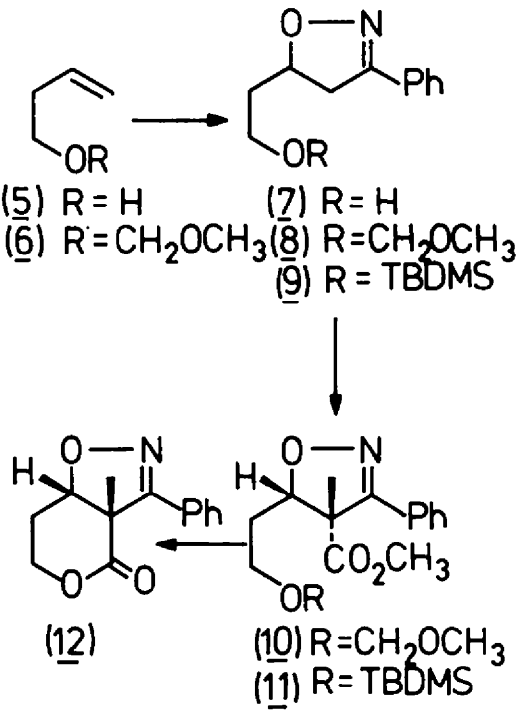


Scheme 1

terminal alkenes is known to be regioselective,[2] and as alkylation of 5-monosubstituted isoxazolines at C(4) is known to occur stereoselectively cis to the hydrogen at C(5),[3] it was hoped that a stereoselective procedure for the sequential acylation and methylation of a 5-substituted isoxazoline (2) could be developed. This approach would avoid the regiochemical problems associated with the cycloaddition of nitrile oxides to α β-unsaturated esters.[4] Moreover if a subsequent reduction of the derived isoxazoline (3) was stereoselective, being subject to 1,3-asymmetric induction,[5] the isoxazolidine (4) so obtained would have the correct stereochemistry to serve as a precursor of the C(1) - C(4) fragment of lankacidin C(1).

RESULTS AND DISCUSSION

Isoxazolines (7) and (8) were prepared by the addition of benzonitrile oxide, generated from α-chlorobenzaldoxime and triethylamine, to but-3-enol (5) and its methoxymethyl ether (6), in yields of ca. 54%.[6] Silylation of the hydroxyalkylisoxazoline (7) using t-butyldimethylsilyl chloride gave the silyl ether (9) in quantitative yield. The hydroxyl protected isoxazolines (8) and (9) were then treated at -78°C with two equivalents of lithium diisopropylamide in THF/HMPA[3] or THF/N,N'-dimethyl-1,3-imidazolidin-2-one (DMI), followed by the sequential addition of methyl chloroformate and methyl iodide. Flash chromatography gave the 4-methoxycarbonyl-4-methylisoxazolines (10) and (11) in yields of 58% and 66-77%, respectively, as shown in Scheme 2.



Scheme 2

Structures were assigned to these isoxazoline products on the basis of spectroscopic data. In particular the change in chemical shift of H(5) on acylation and methylation, from ca. δ 4.9 to δ 4.58, is consistent with the shielding effect expected of a cis vicinal methyl substituent.[7] Moreover on irradiation of the C(4) methyl substituent of isoxazoline (10), a nuclear Overhauser enhancement of 8.3% was observed for H(5) which also supports the stereochemistry shown. Finally treatment of the silylated isoxazoline (11) with tetra-n-butylammonium fluoride initiated desilylation and lactonization to give the lactone-isoxazoline (12) (40%). The structure and stereochemistry of this lactone were established by an extensive series of ^{1}H n.m.r. spin-decoupling experiments. Figure 1 shows the conformation which is consistent with the data. Of note is the long-range coupling (2Hz) between H(4β) and H(6). In cis-fused bicyclo [4.3.0] systems the six-membered ring frequently adopts the boat conformation found here.

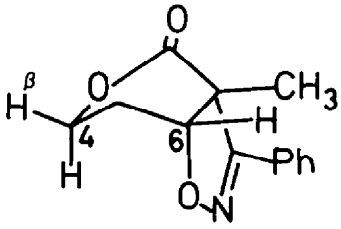


Figure 1

The selective formation of the 4-methoxycarbonyl-4-methylisoxazolines (10) and (11) is consistent with methylation of an intermediate enolate anion taking place from the less hindered side (see Figure 2). This procedure would appear to be quite stereoselective since none of the alternative diastereoisomer was isolated in either case, although a small amount may have been lost during the work-up and purification.

Next the selective reduction of isoxazolines (10)-(12) to isoxazolidines was investigated. Since

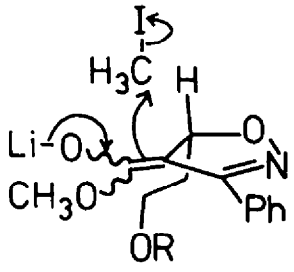


Figure 2

powerful hydride reducing agents would be expected to reduce the ester moiety, the use of mild reducing agents was required. One procedure in the literature for the reduction of isoxazolines to isoxazolidines involves N-methylation using Meerwein's salt followed by reduction of the derived isoxazolinium salt using sodium borohydride.[8] Although this procedure would introduce an unwanted N-methyl group, its stereoselectivity was studied as a guide for later work. The results of this investigation are given in the Table.

Firstly the reduction of the lactone-isoxazoline (12) was studied. When sodium borohydride was added to an ethanol solution of the crude N-methyl isoxazolinium salt, prepared by treatment of the isoxazoline (12) with trimethyloxonium tetrafluoroborate in nitromethane (2 days, 20°C) and evaporation of the solvent, effervescence was observed, and after flash chromatography, only the over-reduced isoxazolidine (15) was isolated. If an excess of sodium hydrogen carbonate was added to the isoxazolinium salt solution before the sodium borohydride, the major product was an approximately 1:1 mixture of the lactone-isoxazolidines (13) (48%), although some over-reduced product (15) was still obtained. In contrast reduction of the monocyclic isoxazolines (10) and (11) was more stereoselective. Thus reduction of the silylated isoxazoline (11) in the presence of sodium hydrogen carbonate gave the desilylated hydroxyalkylisoxazolidine (14)(36%) as the major product together with isoxazolines (16) and (17); reduction of the methoxymethyl isoxazoline (10) without the addition of base, gave the hydroxyalkylisoxazolidine (14)(27%), together with isoxazolidine (15)(11%) and isoxazoline (16)(12%).

Structures were assigned to products (13)-(17) on the basis of spectroscopic data. The ^{1}H n.m.r. chemical shift of the C-methyl substituent was used

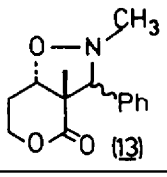
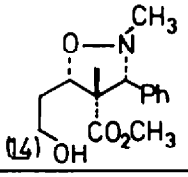
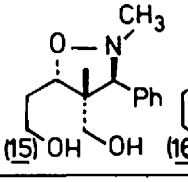
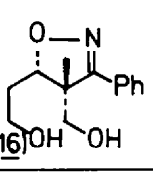
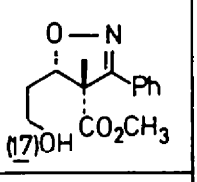
S.M.	$NaHCO_3$	Products; % Yields				
		 (13)	 (14)	 (15)	 (16)	 (17)
(12)[a]	no	-	-	46	-	-
(12)[a]	yes	48	-	33	-	-
(11)[a]	yes	-	36	-	10	17
(10)[b]	no	-	27	11	12	-

TABLE: REDUCTION OF Δ^2-ISOXAZOLINES

[a] Yields are of isolated chromatographed products.

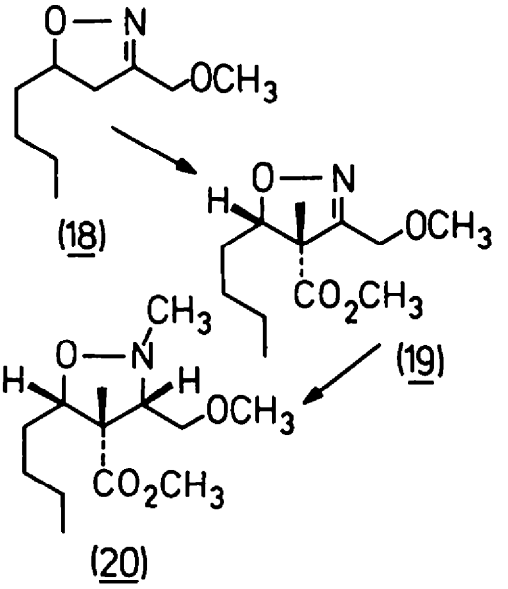
[b] Product mixture not separated; components identified by comparison of the mixture with authentic samples.

to assign the configuration of the phenyl substituent in isoxazolidines (13)–(15) on the basis of the shielding effect of a cis vicinal phenyl group.[7] Thus the ^{1}H n.m.r. chemical shift of the 4-methyl substituent was 1.40 and 0.63 δ, respectively, for isoxazolidines (14) and (15), and 1.52 and 1.03 δ for the isomeric lactone-isoxazolidines (13).

Although only modest yields of products were isolated it would appear that the reduction of the 'open-chain' isoxazolines (10) and (11) was more stereoselective than reduction of the lactone-isoxazoline (12).[5] Also better yields of ester-isoxazolidines (13) and (14) were obtained when the reduction was carried out in the presence of base. In fact the configuration of isoxazolidine (15), obtained from reduction of the lactone-isoxazoline (12) in the absence of base, suggests that lactone reduction occurred first, being followed by an intramolecular hydride delivery by the 4-hydroxymethyl group.[9] The cause of the influence of base on the reduction is not clear, however from the point of view of the proposed synthesis, the stereoselective reduction of isoxazoline (11) is promising, although incomplete N-methylation would appear to be a problem.

Finally, to see whether this route was applicable to isoxazolines derived from aliphatic nitrile oxides, it was repeated using the 3-methoxymethyl-isoxazoline (18) prepared from methoxyacetonitrile oxide and 1-hexene. In this case the 'one pot' acylation and methylation was less successful giving the desired product (19) in only 34% yield. The N-methylation and sodium borohydride reduction, in the presence of sodium hydrogen carbonate, gave the desired isoxazoline (20) (28%).

Thus it would appear that the route outlined in Scheme I is a viable route to N-methylated isoxazolidines which have the same stereochemistry at C(3) and C(4) as the lankacidins have at C(2) and C(3). Reductive cleavage of the N-O bond, N-acylation, and alcohol oxidation would give rise to fragments corresponding to C(1) - C(4) of the lankacidins. However an isoxazoline reduction procedure not involving prior N-methylation will need to be developed before this approach can be used in a synthesis of the lankacidins themselves. Although the yields of the 'one-pot' acylation-methylation, and



and the isoxazoline reduction steps were rather variable, the stereoselectivities of both these procedures were quite high. Of note is the 1,3-asymmetric induction observed in the isoxazoline N-methylation-reduction step.[5]

EXPERIMENTAL

Melting points were determined on a Buchi 510 apparatus, and are uncorrected. I.r. spectra were measured on Perkin Elmer 257 and 297 spectrophotometers, and ^{1}H n.m.r. spectra on a Bruker WH-300 spectrometer (300MHz). Mass specta were measured on a VG-micromass ZAB-16F spectrometer using either electron impact (EI) or chemical ionization (CI) modes.

T.l.c. was carried out using glass plates coated with silica gel blend 41 and Merck aluminium sheets, precoated with silica gel $60F_{254}$. Flash chromatography was on Merck silica gel 60, and short column chromatography on Merck Keiselgel 60H.

All solvents were dried and distilled before use. Ether refers to diethyl ether.

5-(2-Hydroxyethyl)-3-phenyl-Δ^2-isoxazoline(7). Triethylamine (4.33 ml, 31 mmol) was added to a solution of but-3-en-1-ol (1.33 ml, 15.5 mmol) and α-chlorobenzaldoxime (4.83 g, 31 mmol)[6] in dichloromethane (60 ml). After 15h at 20°C, the mixture was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. Flash

chromatography (ether) gave 5-(2-hydroxyethyl)-3-phenyl-Δ^2-isoxazoline (7) (1.92 g, 54%), m.p. 78°C (light petroleum-dichloromethane). IR ($CHCl_3$) $\nu_{max.}$ 3 620, 3 450br, 3 000, 1 595, 1 565, 1 447, 1 357, 1 040, 900, and 688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.99 (3 H, m, $HOCH_2CH_2$-), 3.08 (1 H, dd, J 8, 16.5 Hz, 4-H), 3.49 (1 H, dd, J 10, 16.5 Hz, 4-H), 3.88 (2 H, t, J 6Hz, $HOCH_2$), 4.96 (1 H, m, 5-H), 7.42 (3 H, m, aromatic H), and 7.67 (2 H, m, aromatic H); MS (CI) m/z 192 (M^++H, base peak) and 120 (M^+- 71) (Found: C, 69.0; H, 6.85; N, 7.45. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%).

5-(2-Methoxymethoxyethyl)-3-phenyl-Δ^2-ixoxazoline (8). Chloromethyl methyl ether (5.7 ml, 75 mmol) was added to a solution of but-3-en-1-ol (3.6 g, 50 mmol) and diisopropyl-ethylamine (17.4 ml, 100 mmol) in anhydrous dichloromethane (125 ml) at 0 °C under nitrogen. After 1h, the solution was washed with ice-cold aqueous HCl (150ml, 0.5 M), with water (100 ml), dried ($MgSO_4$) and filtered. To the filtrate was added a solution of α-chlorobenzaldoxime (11.63 g, 75 mmol) in dichloromethane (170 ml), followed by Et_3N (10.4 ml, 75 mmol) at 0°C under nitrogen. After 5 min, the mixture was allowed to warm to 20°C, and was stirred for 15h. After washing with water, the dried ($MgSO_4$) organic phase was concentrated under reduced pressure, and the product isolated after flash chromatography (light petroleum -ether, 1:1) was identified as 5-(2-methoxymethoxyethyl)-3-phenyl- Δ^2-isoxazoline (8) (6.32 g, 54%),m.p. 39-40°C (light petroleum-ether). IR ($CHCl_3$) $\nu_{max.}$ 3 005, 1 595, 1 445, 1 355, 1 145, 1 108, 1 042, 912 and 688 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.0 (2 H, m, OCH_2CH_2CH), 3.08 (1 H, dd, J 7.5, 16.5 Hz, 4-H), 3.38 (3 H, s, CH_3O), 3.46 (1 H, dd, J 10.5, 16.5Hz, 4-H), 3.74 (2 H, m, OCH_2CH_2), 4.64 (2 H, s, OCH_2O), 4.92 (1 H, m, 5-H), 7.42 (3 H, m, aromatic H), and 7.68 (2 H, m, aromatic H); MS (CI) m/z 236 (M^++H), 204 (M^+-31), and 190 (M^+-45) (Found: C, 66.15; H, 7.15; N, 6.11. $C_{13}H_{17}NO_3$ requires C, 66.35; H, 7.3; N, 5.95%)

5-(2-Hydroxyethyl)-3-phenyl- Δ^2-isoxazoline t-butyldimethyl-silyl ether (9). Isoxazoline (7) (1.878 g, 9.8 mmol), t-butyl-dimethylsilylchloride (1.63 g, 10.8 mmol), and imidazole (1.671 g, 24.6 mmol), in dry DMF (4 ml) were stirred at 20°C for 15h. Ether (150 ml) was added, and the mixture washed with water (6 x 30 ml), dried ($MgSO_4$), and concentrated under reduced pressure to give the silyl ether (9) (2.98 g). IR (film) $\nu_{max.}$ 1 595, 1 357, 1 253, 1 096, 907, 833, 775, 758, and 692 cm^{-1}; ^1H NMR ($CDCl_3$)δ 0.07 and 0.08 (each 3 H, s, SiMe), 0.91 (9 H, s, Me_3C), 1.82 and 1.99 (each 1H, m, OCH_2CH_2) 3.08 (1 H, dd, J 8, 16 Hz, 4-H), 3.43 (1 H, dd, J 10, 16 Hz, 4-H), 3.81 (2 H, m, OCH_2), 4.88 (1 H, m, 5-H), 7.42 (3 H, m, aromatic H), and 7.67 (2 H, m, aromatic H); MS (CI) m/z 306 (M^+ + H, base peak) and 131 (M^+-174).

(4 RS, 5 RS)-4-Methoxycarbonyl-5-(2-methoxymethoxyethyl)-4-methyl-3-phenyl- Δ^2-isoxazoline (10). Isoxazoline (8) (1.175 g, 5 mmol) in THF (3 ml) was added to lithium diisopropylamide (11 mmol) in either THF (30 ml) - HMPA (1.74 ml, 10 mmol) or THF (30 ml) - DMI (10 mmol) at -78°C under argon. After 90 min, methyl chloroformate (0.46 ml, 6 mmol) was added to the red solution. After a further 2h, methyl iodide (1.56 ml, 25 mmol) was added, and the mixture was stirred for 1h before being allowed to warm to 20°C. Aqueous NH_4Cl (40 ml) was added, and the product extracted into dichloromethane (4 x 30 ml). After drying ($MgSO_4$), concentration under reduced pressure gave an oil which on flash chromatography (light petroleum-ether 1:1)gave (4RS, 5RS)-4-methoxycarbonyl-5-(2-methoxymethoxy-ethyl)-4-methyl-3-phenyl- Δ^2-isoxazoline (10) (885 mg, 58%), as an oil, IR (film) $\nu_{max.}$ 1 733, 1 590, 1 560, 1 230, 1 150, 1 107, 1 040, 920, 762, and 693 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.59 (3 H, s, C-CH_3), 1.95 (2 H, m, OCH_2CH_2), 3.38 (3 H, s, OCH_3), 3.74 (2 H, m, OCH_2), 3.76 (3 H, s, CO_2CH_3), 4.58 (1 H, t, J 7.5 Hz, 5-H), 4.65 (2 H, s, OCH_2O), 7.39 (3 H, m, aromatic H), and 7.51 (2 H, m, aromatic H); MS (CI) m/z 308 (M^++H).

(4 RS, 5 RS)-5-(2-Hydroxyethyl)-4-methoxy-carbonyl-4-methyl-3-phenyl- Δ^2-isoxazoline t-butyldimethylsilyl ether (11). Isoxazoline (9) (610 mg, 2 mmol) was treated with LDA-HMPA, methyl chloroformate, and methyl iodide as described above to give, after flash chromatography (light petroleum-ether, 8:1), isoxazoline (11) (497 mg, 66%) as an oil. Using DMI as cosolvent, the yield was 77%. IR

(film)$\nu_{max.}$ 1 737, 1 252, 1 217, 1 100, 910, 835, 775, 733, and 694 cm^{-1}; ^1H NMR ($CDCl_3$)δ 0.07 and 0.08 (each 3 H, s, SiMe), 0.90 (9 H, s, CMe_3), 1.57 (3 H, s, C-CH_3), 1·84 (2 H, m, $OCH_2\underline{CH_2}$), 3.75 (3 H, s, CO_2CH_3), 3.83 (2 H, m, OCH_2), 4.58 (1 H, dd, J 4.5, 9.5 Hz, 5-H), 7.4 (3 H, m, aromatic H), and 7.52 (2 H, m, aromatic H); MS (CI) 378 ($\underline{M}^+$+H), and 192 ($\underline{M}^+$- 185)

cis-1-Methyl-9-phenyl-3,7-dioxa-8-azabicyclo-[4.3.0]non-8-en-2-one (12). Tetra-n-butylammonium fluoride (0.76 ml of a 1M solution in THF) was added to isoxazoline (11) (144 mg, 0.38 mmol) in THF (4 ml) at -20°C. The mixture was allowed to warm to 20°C, and was stirred for 20 min. After washing with brine, and extraction into dichloromethane, the organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure to give after flash chromatography (light petroleum-ethyl acetate, 8:1), cis-1-methyl-9-phenyl-3,7-dioxa-8-azabicyclo[4.3.0]non-8-en-2-one(12)(35 mg, 40%) as in oil. IR ($CHCl_3$) $\nu_{max.}$ 3 050, 1 740, 1 390, 1 268, 1 175, 1 122, 1 031, and 692 cm^{-1}; ^1H NMR (C_6D_6)δ1.05 (1 H, ddt, J 15.5, 12, 4Hz, 5β-H), 1.30 (1 H, dq, J 15.5, 2 Hz, 5α-H), 1.4 (3 H, s, C-CH_3), 3.43 (1 H, ddt, J 11.5, 4, 2 Hz, 4β-H), 3.92 (1 H, ddd, J 12, 11.5, 2 Hz, 4α-H), 3.99 (1 H, dt, J 4, 2 Hz, 6-H), 7.00 (3 H, m, aromatic H), and 8.1 (2 H, m, aromatic H); MS (EI) m/z 231 ($\underline{M}^+$) and 130 ($\underline{M}^+$-101, base peak) (Found: $\underline{M}^+$231.0895. $C_{13}H_{13}NO_3$ requires M 231.0895)

N-Methylation-reduction of Δ^2-Isoxazolines.

a) Of lactone-isoxazoline (12), no $NaHCO_3$. A solution of trimethyloxonium tetrafluoroborate (151 mg, 1.02 mmol), and isoxazoline (12) (34 mg, 0.15 mmol) in anhydrous nitromethane (1.5 ml), was stirred for 48h at 20°C. The solvent was removed under reduced pressure, and the residue dissolved in anhydrous ethanol (2 ml). Sodium borohydride (72 mg, 1.89 mmol) was added in portions with ice cooling, and the mixture was then stirred for 60 min at 20°C. Water (5 ml) was added, and the product extracted into dichloromethane (3 x 10 ml). The combined extracts were dried (Na_2SO_4), concentrated under reduced pressure, and the product isolated by flash chromatography (chloroform-ethanol, 20:1) followed by prep. t.l.c. to give (3 RS, 4 SR, 5 RS)-2,4-dimethyl-5-(2-hydroxyethyl)-4-hydroxymethyl-3-phenylisoxazolidine (15) (17 mg, 46%), m.p. 97-99°C (ethyl acetate-light petroleum). IR ($CHCl_3$)$\nu_{max.}$ 3 635, 3 420br, 3 020, 1 460, 1 060, 915, and 710 cm^{-1}; ^1H NMR ($CDCl_3$)δ0.63 (3 H, s, C-CH_3), 1.96 (2 H, m, $OCH_2\underline{CH_2}$), 2.33 (2 H, br. s, 2xOH), 2.67 (3 H, s, NCH_3), 3.50 (1 H, s, 3-H), 3.62 and 3.67 (each 1 H, d, J 11Hz, $\underline{CH_2}OH$), 3.85 (3 H, m, 5-H + $OCH_2\underline{CH_2}$), and 7.30 (5 H, m, aromatic H); MS (EI) m/z 251 ($\underline{M}^+$) and 134 ($\underline{M}^+$-117, base peak) (Found: C, 67.2; H, 8.3; N, 5.7. $C_{14}H_{21}NO_3$ requires C, 66.9; H, 8.4; N, 5.6%).

b) Of lactone-isoxazoline (12), with $NaHCO_3$. Crude isoxazolinium salt prepared as above from isoxazoline (12) (70 mg, 0.3 mmol) and trimethyloxonium tetrafluoroborate (178 mg, 1.2 mmol) was dissolved in anhydrous ethanol (5 ml). $NaHCO_3$ (101 mg) followed by sodium borohydride (58 mg, 1.53 mmol) were added, and the mixture was stirred for 60 min at 20°C. Work-up as described above gave a residue which was chromatographed on silica gel (light petroleum-ethyl acetate-ethanol, gradient elution) to give two fractions. The first fraction was identified as a 1:1 mixture of cis-1,8-dimethyl-9-phenyl-3,7-dioxa-8-aza-bicyclo[4.3.0]nonan-2-ones(13) (32 mg, 48%), m.p. 78-80°C (ether-light petroleum). IR ($CHCl_3$)$\nu_{max.}$ 3 000, 1 725, 1 268, 1 254, 1 165, 1 117, 1 027, and 695 cm^{-1}; ^1H NMR ($CDCl_3$)δ1.03 and 1.52 (each 3 H, s, C-CH_3 of each isomer), 2.13 (4 H, m, $OCH_2\underline{CH_2}$ of both isomers), 2.58 and 2.67 (each 3 H, s, N-CH_3 of each isomer), 3.50 and 3.68 (each 1 H, s, 9-H of each isomer), 4.17 (1 H, m, 6-H of one isomer), 4.35 (3 H, m, 6-H of one isomer + 2 x 4-H), 4.70 and 5.20 (each 1 H, m, 4-H), and 7.32 (10 H, m, aromatic H); MS (EI) m/z 247 ($\underline{M}^+$) and 134 ($\underline{M}^+$-113, base peak) (Found: C, 68.1; H, 6.85; N, 5.65. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.95; N, 5.65%). The second fraction was identified as diol (15) (25 mg, 33%).

c) Of isoxazoline (11), with $NaHCO_3$. The isoxazolinium salt prepared from isoxazoline (11) (310 mg, 0.82 mmol) and trimethyloxonium tetrafluoroborate (146 mg, 0.99 mmol) as described above was dissolved in ethanol (3 ml) together with $NaHCO_3$ (82 mg). Sodium borohydride (156 mg, 4.11 mmol) was added, and after 60 min at 20°C,

work-up as outlined above gave a mixture of three products separated by flash chromatography (ethyl acetate-light petroleum, gradient elution). The first eluted product was identified as (4 RS, 5 RS)-5-(2-hydroxyethyl)-4-methoxycarbonyl-4-methyl-3-phenyl-Δ^2-isoxazoline (17) (36 mg, 17%), an oil. IR ($CHCl_3$) $\nu_{max.}$ 3 620, 3 520, 3 000, 1 733, 1 215, 1 050, 910, and 694 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.56 (3 H, s, C-CH_3), 1.94 (2 H, m, OCH_2CH_2), 2.03 (1 H, br. s, OH), 3.77 (3 H, s, OCH_3), 3.88 (2 H, t, J 6 Hz, OCH_2), 4.57 (1 H, dd, J 5, 8 Hz, 5-H), and 7.5 (5 H, m, aromatic H); MS (EI) m/z 263 (M^+), 231 (M^+ - 32), 130 (M^+ - 103), and 77 (base peak) (Found: M^+ 263.1157. $C_{14}H_{17}NO_4$ requires M 263.1157. Repeated chromatography (ethyl acetate-chloroform, 2:1) separated the second and third eluted products to give firstly (3 RS, 4 SR, 5SR)- 2,4-dimethyl-5-(2-hydroxyethyl)-4-methoxycarbonyl-3-phenylisoxazolidine (14) (81 mg, 36%), an oil. IR ($CHCl_3$)$\nu_{max.}$ 3 620, 3 500, 3 000, 1 725, 1 452, 1 434, 1 220, 1 066, 1 050, and 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ1.40 (3 H, s, C-CH_3), 1.84 and 1.96 (each 1 H, m, OCH_2HCH), 1.87 (1 H, br.s, OH), 2.8 (3 H, s, NCH_3), 3.49 (3 H, s, OCH_3), 3.74 (1 H, s, 3-H) 3.82 (2 H, t, J 7.5 Hz, OCH_2), 4.37 (1 H, dd, J 7.5, 10 Hz, 5-H), and 7.43 (5 H, m, aromatic H); MS (EI) m/z 279 (M^+) and 134 (M^+ - 145, base peak) (Found: M^+ 279.1471. $C_{15}H_{21}NO_4$ requires M 279.1470). The third eluted product was identified as (4RS, 5SR)-5-(2-hydroxyethyl)-4-hydroxymethyl-4-methyl-3-phenyl-Δ^2-1,2-isoxazoline (16) (20mg, 10%), an oil. IR ($CHCl_3$)$\nu_{max.}$ 3 620, 3 400br, 3 000, 1 045, 905, and 690 cm^{-1}; ^1H NMR ($CDCl_3$)δ 1.33 (3 H, s, C-CH_3), 2.02 and 2.19 (each 1 H, m, OCH_2HCH), 2.67 (2 H, br. s, 2x OH), 3.78 and 3.80 (each 1 H, d J 13 Hz, $HOCH_2$), 3.88 (2 H, m, OCH_2CH_2), 4.35 (1 H, dd, J 6, 10 Hz, 5-H), 7.42 (3 H, m, aromatic H), and 7.65 (2 H, m, aromatic H); MS (CI) m/z 236 (M^++H) and 160 (M^+ - 75, base peak)

d) Of isoxazoline (10), no $NaHCO_3$. The isoxazolinium salt from isoxazoline (10) (1.082 g, 3.52 mmol) and trimethyloxonium tetrafluoroborate (1.044 g, 7.05 mmol) in ethanol (25 ml) was treated with sodium borohydride (666 mg, 17.5 mmol) at 20°C. Work-up and purification as above gave an oil (471 mg) shown to be a mixture of isoxazolidines (14) and (15), and isoxazoline (16) by ^1H n.m.r. and t.l.c. The yields shown in the table were estimated from the integration of the ^1H n.m.r. spectrum.

5-Butyl-3-methoxymethyl-Δ^2-isoxazoline (18).[10] Triethylamine (5 ml) was added to a mixture of 2-methoxy-1-nitroethane (6.6 g, 63 mmol),[11] phenylisocyanate (13.8 ml, 126 mmol), and hexene (23.6 ml, 189 mmol), in anhydrous benzene (400 ml), and the mixture heated under reflux for 20h. The mixture was cooled, filtered, and concentrated under reduced pressure to give, after flash chromatography (ether-light petroleum, 1:2) 5-butyl-3-methoxymethyl-Δ^2-isoxazoline (18), (8.82 g, 82%), an oil. IR (film)$\nu_{max.}$ 1 332, 1 190, 1 108, 1 089, and 870 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (3 H, t, J 7 Hz, CH_3CH_2), 1.38 (3 H, m, $HCHCH_2$), 1.56 (1 H, m, HCH), 1.74 (2 H, m, CH_2), 2.65 (1 H, dd, J 8, 17Hz, 4-H), 3.07 (1 H, dd, J 10, 17 Hz, 4-H), 3.35 (3 H, s, OCH_3), 4.19 (2 H, s, CH_3OCH_2), and 4.61 (1 H, m, 5-H); MS (CI) m/z 172 (M^++ H, base peak).

(4RS, 5RS)-5-Butyl-4-methoxycarbonyl-3-methoxymethyl-4-methyl-Δ^2-isoxazoline (19). Isoxazoline (18) (1.54 g, 9.02 mmol) in THF (3 ml) was added to LDA (19.8 mmol) and HMPA (4.7 ml, 27.1 mmol) in THF (70 ml) at -78° under argon. After 2h, methyl chloroformate (0.84 ml, 10.8 mmol) was added, and after a further 2h, methyl iodide (2.81 ml, 45.3 mmol) was also added. After 1h at -78°C, the mixture was allowed to warm to 20°C. Work-up as before gave a crude product which was filtered through a plug of silica gel (ethyl acetate-light petroleum, 1:5), and chromatographed, to give (4RS, 5RS)-5-butyl-4-methoxycarbonyl-3-methoxymethyl-4-methyl-Δ^2-isoxazoline (19) (738 mg, 34%) as an oil. IR ($CHCl_3$)$\nu_{max.}$ 1 738, 1 450, 1 260, 1 225, 1 155, 1 101, and 900 cm^{-1}; ^1H NMR (C_6D_6)δ0.79 (3 H, t, J 7 Hz, CH_3CH_2), 1.21 (4 H, m, CH_2CH_2), 1.35 (3 H, s, C-CH_3), 1.51 (2 H, m, CH_2), 2.97 (3 H, s, OCH_3), 3.26 (3 H, s, CO_2CH_3), 3.98 and 4.10 (each 1 H, d, J 12.5 Hz, CH_3OCH_2), and 4.03 (1 H, dd, J 4, 10 Hz, 5-H); MS (CI) m/z 244 (M^++ H) (Found: M^+ 243.1470. $C_{12}H_{21}NO_4$ requires 243.1470).

(3RS, 4RS, 5RS)-5-Butyl-2,4-dimethyl-4-methoxycarbonyl-3-methoxymethylisoxazolidine (20). The crude isoxazolinium salt prepared from isoxazoline

(19) (176 mg, 0.72 mmol) and trimethyloxonium tetrafluoroborate (215 mg, 1.45 mmol) as described above, was dissolved in anhydrous ethanol (3 ml) containing $NaHCO_3$ (300 mg), and sodium borohydride (276 mg, 7.26 mmol) was added. Work-up as above and flash chromatography (ethyl acetate-light petroleum) gave (3 RS, 4 RS, 5 RS)-5-butyl-2,4-dimethyl-4-methoxycarbonyl-3-methoxymethylisoxazolidine (20) (53 mg, 28%) as an oil; IR ($CHCl_3$) $\nu_{max.}$ 1725, 1218, 1112, and 990 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.87 (3 H, t, J 7 Hz, $C\underline{H}_3CH_2$), 1.4 (6 H, m, $CH_2C\underline{H}_2C\underline{H}_2$), 1.36 (3 H, s, C-$CH_3$), 2.81 (3 H, s, N-$CH_3$), 2.86 (1 H dd, J 5, 7 Hz, 3-H), 3.31 (3 H, s, CH_3O), 3.53 (1 H, dd, J 5, 10 Hz, OCHCH), 3.57 (1 H, dd, 7, 10 Hz, OCHCH), 3.73 (3 H, s, CO_2CH_3), and 3.90 (1 H, dd, J 3, 9 Hz, 5-H); MS (EI) m/z 259 (M^+) and 214 (M^+-45, base peak) (Found: 259.1783; $C_{13}H_{25}NO_4$ requires 259.1783).

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