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TOTAL SYNTHESIS OF THE ANTIVIRAL (±)-VIRANTMYCIN†

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Abstract: The total synthesis of the racemic modification of the antiviral metabolite virantmycin is described starting from *p*-aminobenzoic acid and utilising acetylenic precursors.

The unusual metabolite (-)-virantmycin (1), isolated by Japanese workers[1] from *Streptomyces nitrosporeus* was found to possess high antiviral activity. Its novel structure was elucidated[2] by a combination of chemical transformations and spectroscopic studies, but the relative and absolute stereochemistry of the two chiral centres at C-2 and C-3 were unknown at the time of our preliminary synthetic communication[3] More recently however investigations at Hokkaido[4] and Cambridge[5] have indicated the stereochemistry at these centres to be 2R, 3R as shown in the enantiomer (1). We now report the full details of our synthesis of (±)-virantmycin.

The key intermediate in the synthesis was the acetylenic alcohol (3), produced in high yield by the action of lithium acetylide on the methoxyketone (2). This latter was obtained by the alkylation of methyl 4-methoxy-3-oxobutanoate with sodium hydride and 1-bromo-2,3-dimethylbut-2-ene followed by decarbomethoxylation by the elegant propane-1,2-diol/alkoxide method.[6] Iodination of methyl 4-aminobenzoate with iodine monochloride furnished the second component of the synthesis, methyl 4-amino-3-iodobenzoate (4). This product was then coupled[7] very efficiently at room temperature with the acetylenic alcohol (3) in the presence of a palladium (II)/copper(I) catalyst to give a 94% yield of a product (5) comprising in its structure the entire carbon framework of virantmycin. We had hoped to produce the heterocycle (7; R=H) by partial catalytic hydrogenation of the triple bond of (5) and subsequent cyclisation of the resulting Z-hydroxyamine. However all attempts to achieve this were fruitless but an indirect process proved successful. Acid-catalysed Meyer-Schuster rearrangement[8] of the hydroxyacetylene (5) presumably first produced the isomeric αβ-unsaturated ketone but this intermediate underwent an intramolecular Michael reaction involving the primary amino group to give a good overall yield of the bicyclic aminoketone (6). Reduction of (6) with sodium borohydride and dehydration of the resulting two diastereoisomeric alcohols by means of triphenylphosphine/carbon tetrachloride then furnished the required bicyclic diene (7; R=H). This product was found to be thermally unstable and was readily aromatised with loss of the elements of dimethyl ether to give the quinoline (8). However the stable N-formyl derivative (7; R=HCO) was readily prepared with formic acetic anhydride and was used in the succeeding steps. The next problem was to devise a method of functionalisation at C-3 involving the less nucleophilic ring double bond. Epoxidation of the diene (7; R=HCO) with an excess of m-chloroperbenzoic acid produced a diastereoisomeric mixture of bis-epoxides (9). This was then subjected to palladium-catalysed hydrogenolysis which affected only the sole benzylic carbon-oxygen bond at C-4 to produce a corresponding mixture of hydroxyepoxides (10). Treatment of (10) with tungsten hexachloride-n-butyl-lithium[9] resulted in de-epoxidation to regenerate the tetra-substituted side-chain double bond; deformylation then gave the crystalline hydroxyamine (11; R=H). Surprisingly this secondary alcohol was found to be a single homogeneous racemic diastereoisomer. This implies that the epoxidation of the ring double bond had taken place stereoselectively and

† Dedicated to Professor W. D. Ollis on the occasion of his 65th birthday.

of course the resulting stereochemistry at C-3 is retained during the hydrogenolysis procedure. The *cis* relationship between the resulting hydroxyl group and the neighbouring methoxymethyl group in the racemate (11; one enantiomer shown) has been established by NOE difference spectroscopy.[5] The hydroxyamine (11) was treated with thionyl chloride in dichloromethane to give the methyl ester of (±)-virantmycin (12; one enantiomer shown). The retention of configuration at C-3 is rationalised by the initial formation of an aziridine with inversion (probably via the chlorosulphite) followed by nucleophilic cleavage of the aziridine ring by chloride ion, again with inversion. The double inversion thus results in overall retention. This has been borne out by the isolation of the intermediate aziridine and its reaction with chloride.[10] Finally hydrolysis of the methyl ester (12) with lithium hydroxide gave racemic virantmycin (1; one enantiomer shown) m.p. 133-139 °C identical in all chromatographic and spectroscopic properties with natural (-)-virantmycin m.p. 59 °C. This large difference in the melting points of an enantiomer and the corresponding racemic compound is unusual but examples have been reported previously.[11]

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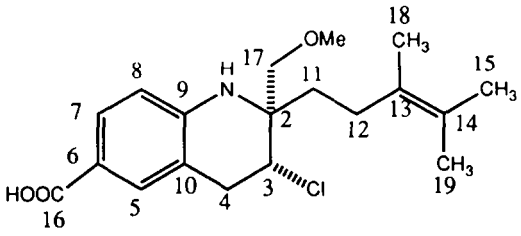
EXPERIMENTAL

Melting points were taken on a Kofler hot stage and are uncorrected. N.m.r. spectra were recorded on a Bruker WM-250 spectrometer (250 MHz for ^1H and 63 MHz for ^{13}C) in deuterochloroform with tetramethylsilane as internal standard. I.r. spectra were recorded in chloroform on a Perkin-Elmer 297 spectrometer. U.v. spectra were recorded in methanol on a Pye-Unicam SP8-100 instrument. Mass spectra were determined on AEI MS902 and MS30 instruments. Analytical and preparative t.l.c. was carried out on Merck Kieselgel 60 F_{254}. Flash chromatography was carried out on Merck Kieselgel 60 Art 9385 230-400 mesh and gravity elution column chromatography on Merck Kieselgel 60 Art 7734 70-230 mesh.

5,6-Dimethyl-1-methoxyhept-5-en-2-one (2). - A solution of methyl 4-methoxy-3-oxobutanoate (9.92 g, 69 mmol) in THF (80 ml) was added to a suspension of sodium hydride (1.66 g, 69 mmol) in THF (80 ml) under nitrogen. To the resulting anion solution 1-bromo-2,3-dimethylbut-2-ene[12] (11.25 g, 69 mmol) was added dropwise and the reaction mixture heated with stirring at 45 °C for 1.25 h. Stirring was continued for 20 h at room temperature. Filtration through celite, washing with hexane (100 ml), shaking the combined organic solutions with water (100 ml), drying ($MgSO_4$) evaporation and distillation (Kugelrohr) b.p. 90-95 °C/0.8 mm gave the liquid mono-alkylated β-ketoester (4.47 g; 91%) (Found: C, 63.05; H, 8.8; M^+ 228.1348. $C_{12}H_{20}O_4$ requires C, 63.14; H, 8.85%; M 228.1362).

This β-ketoester (167.4 g, 0.733 mol) was added neat to a solution prepared by treating propane-1,2-diol (1800 ml) with sodium (51.1 g, 2.22 mol) and the mixture heated at 83-85 °C for 30 min. The cooled mixture was then treated with water (500 ml) and the aqueous solution continuously extracted with light petroleum (b.p. 40-60 °C) for 148 h. Evaporation of the petroleum and distillation gave the *ketone* (2) (82.1 g, 65%) b.p. 82-85 °C/10 mm (Found: C, 70.35; H, 10.75; M^+ 170.1309. $C_{10}H_{18}O_2$ requires C, 70.55; H, 10.66%; M 170.1306). ν_{max} 1720, 1635 cm^{-1}. δ_H 3.99 (2H, s, OCH_2CO), 3.4 (3H, s, CH_3O), 2.49-2.43 (2H, t, J=8Hz, $COCH_2CH_2$), 2.33-2.27 (2H, t, J=8Hz, $COCH_2CH_2$), 1.61 (9H, s, 3 x CH_3). The *2,4-dinitrophenylhydrazone* crystallised from methanol in yellow needles m.p. 116.5-119 °C (Found: C, 54.65; H, 6.05; N, 15.7. $C_{16}H_{22}N_4O_5$ requires C, 54.85; H, 6.33; N, 15.99%).



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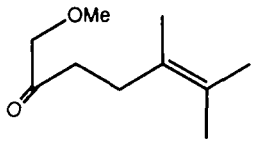

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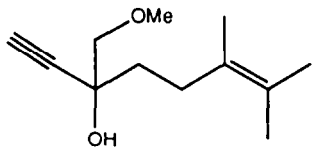

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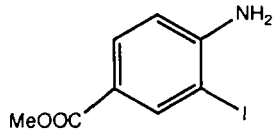

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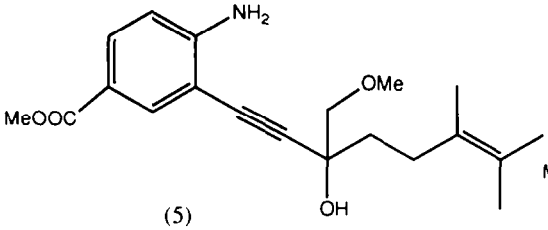

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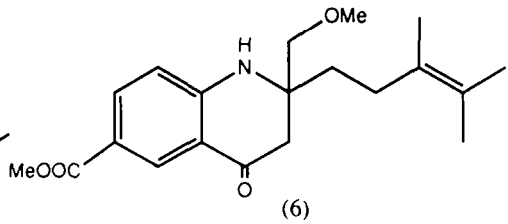

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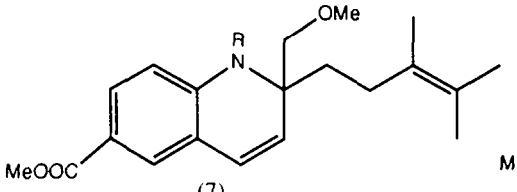

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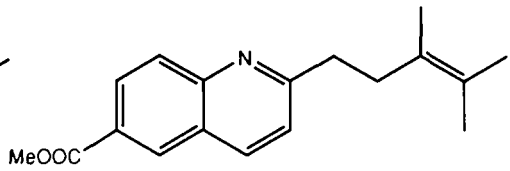

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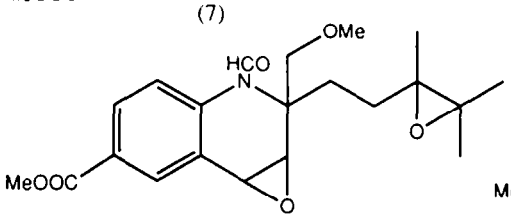

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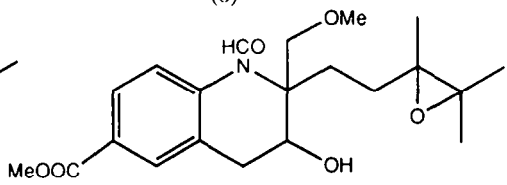

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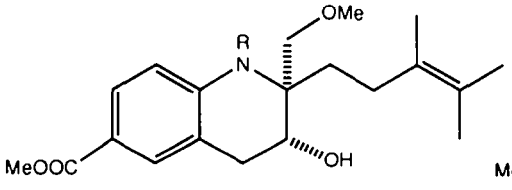

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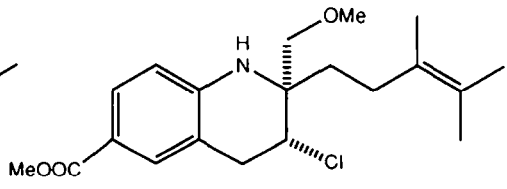

(12)

6,7-Dimethyl-3-methoxymethyloct-6-en-1-yn-3-ol (3). - A mixture of THF (310 ml) and benzene (310 ml) was saturated with acetylene at room temperature. Lithium acetylide-ethylenediamine complex (97.5 g, 1.06 mol) was added rapidly with the acetylene stream maintained followed by a solution of ketone (2) (82.1 g, 0.48 mol) in THF/benzene (1:1, 60 ml) dropwise over 15 min. The reaction mixture was heated at 35 °C for 4 h, the first hour in an acetylene atmosphere, the remainder in a nitrogen atmosphere, followed by heating at 50 ° C for 1.5 h. Water (50 ml) was then added and the mixture heated at 70 °C for 1 h to remove excess acetylene. Water (350 ml) was then added and the aqueous layer further extracted with ether (2 x 300 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The resulting brown oil was divided into two portions and each portion purified by flash chromatography using 550 g silica gel and hexane/ethyl acetate (10:1) as eluant. This yielded the pure *alcohol* (3) (64.2 g, 68%) together with recovery of the starting ketone (14.5 g, 18%). (Found: C, 72.7; H, 10.35. $C_{12}H_{20}O_2$ requires C, 73.43; H, 10.27%). ν_{max} 3550, 3300, 1680 cm^{-1} δ_H (90 MHz) 3.60-3.50 (5H, 2 x s, CH_3O, OCH_2C), 2.78 (1H, br s, OH), 2.48 (1H, s, C≡CH), 2.40-2.15 (2H, m, $C(OH)CH_2CH_2$), 1.80-1.60 (11 H, s + m, 3 x CH_3, $C(OH)CH_2CH_2$).

Methyl 3-Iodo-4-aminobenzoate (4). - Methyl 4-aminobenzoate (10.4 g, 68.5 mmol) dissolved in acetic acid (110 ml) was treated with a solution of iodine monochloride (11.1 g, 68.5 mmol) in acetic acid (110 ml) dropwise over 15 min at room temperature followed by stirring for 1 h. Evaporation of the solvent gave a brown solid which was suspended in dichloromethane (200 ml) and neutralised with solid sodium bicarbonate. After addition of water (200 ml) the organic layer was washed with sodium bicarbonate solution and water and dried ($MgSO_4$). The organic layer was evaporated on to silica gel (20 g) and the impregnated silica applied as a plug to a silica column. Flash elution using hexane/ethyl acetate (5:1) gave starting material (0.74 g, R_f 0.27) and *methyl 3-iodo-4-aminobenzoate* (4) (14.6 g, R_f 0.41, 77%) crystallising from ethyl acetate in pale orange needles m.p. 84-87 °C. (Found: C, 34.9; H, 3.1; N, 4.8. M^+276.9610. $C_8H_8INO_2$ requires C, 34.68; H, 2.91; N, 5.06%. M 276.9600). ν_{max} 3495, 3390, 1705, 1615 cm^{-1}. λ_{max} (ε) 281 nm (21 200). δ_H (80 MHz) 8.34 (1H, d, J = 1.8 Hz, H-2), 7.82 (1H, dd, J = 1.9 and 8.4 Hz, H-6), 6.70 (1H, d, J = 8.4 Hz, H-5), 3.86 (3H, s, CO_2CH_3). δ_C 150.8 (C=O), 141.1 (C-2), 131.2 (C-6), 113.9 (C-5), 51.7 (OCH_3). Also isolated was *methyl 3,4-diiodo-4-aminobenzoate* (2.09 g, R_f 0.55) as pale yellow needles m.p. 163-164 °C. (Found: C, 24.2; H, 1.6; N, 3.45. M^+ 402.8567. $C_8H_7I_2NO_2$ required C, 23.85; H, 1.75; N, 3.48%. M 402.8567).

Methyl 3-(6,7-dimethyl-3-hydroxy-3-methoxymethyloct-6-en-1-ynyl)-4-aminobenzoate (5). - Methyl 3-iodo-4-aminobenzoate (4) (6.19 g, 22.4 mmol) the hydroxyacetylene (3) (8.77 g, 44.7 mmol) and bis(triphenylphosphine) palladium dichloride (157 mg, 1 mol%) were dissolved in diethylamine (140 ml) in a nitrogen atmosphere. Cuprous iodide (85 mg, 2 mol%) was added and the mixture was stirred for 16 h at room temperature. Evaporation under reduced pressure, addition of water, extraction with ethyl acetate and drying ($MgSO_4$) was followed by evaporation on to silica. The impregnated silica was applied as a plug to a silica column and flash elution using hexane/ethyl acetate (3:2) gave the above-titled coupled *product* (5) (7.31 g, 94%) crystallising from ethyl acetate as an off-white powder m.p. 72.5-74.5 °C. (Found: C, 69.6; H, 7.7; N, 4.0. M^+ 345.1966. $C_{20}H_{27}NO_4$ requires C, 69.54; H, 7.88; N, 4.06%. M 345.1940). ν_{max} 3550, 3495, 3395, 2220, 1700, 1615 cm^{-1}. λ_{max} (ε) 293 (17400), 242 (30,700) nm. δ_H 7.96 (1H, d, J = 2.0 Hz, H-2), 7.80 (1H, dd, J = 2.0 Hz, J = 8.6 Hz, H-6), 6.66 (1H, d, J = 8.6 Hz, H-5), 4.77 (2H, br s, NH_2), 3.85 (3H, s, CO_2CH_3), 3.62-3.49 (5H, merged t + s, CH_2OMe), 2.93 (1H, s, OH), 2.5-2.3 (2H, m, CH_2-C=), 1.9-1.6 (11H, m, CH_2CH_2C=, 3 x CH_3). δ_C 166.5 (C=O), 152.0 (C-4), 134.3 (C-2), 131.5 (C-6), 126.9, 124.9 (C=C), 119.4 (C-1), 113.1 (C-5), 106.6 (C-3), 96.6, 80.6 (C≡C), 79.6, (C-OH), 71.4 (CH_2O), 59.6 (CH_2OCH_3), 51.6 (CO_2CH_3), 36.9 (CH_2C=), 29.3 (CH_2CH_2C=), 20.6, 20.1, 18.3 (3 x CH_3).

Methyl 2-(3,4-dimethylpent-3-enyl)-2-(methoxymethyl)-4-oxo-1,2,3,4-tetrahydroquinoline-6-carboxylate (6). - To a solution of the hydroxyaminoacetylene (5) (1 g, 2.9 mmol) in THF (6 ml) was added aqueous methanesulphonic acid (50%, 5 drops) and the reaction mixture heated at 40 °C for 20 h. The cold solution was diluted with ether (5 ml) and washed with saturated sodium bicarbonate solution (5 ml). The dried ($MgSO_4$) organic layer was evaporated to give a red oil which was chromatographed on a silica column using hexane/ethyl acetate (3:1) to give the above *tetrahydroquinoline ketone* (6) (0.634 g, 63%, R_f 0.53) crystallising from ether in pale yellow prisms m.p. 122-125 °C. (Found: C, 69.7; H, 7.9; N, 3.9. M^+ 345.1951. $C_{20}H_{27}NO_4$ requires C, 69.54; H, 7.88; N, 4.05% M 345.1940). ν_{max} (ε) 373 (3 600), 296 (25 800), 244 (25 000) nm. δ_H 8.49 (1H, d, J = 2.1 Hz, H-5), 7.96 (1H, dd, J = 2.1 Hz, J = 8.6 Hz, H-7), 6.66 (1H, d, J = 8.6 Hz, H-8), 5.00 (1H, br s, NH), 3.86 (3H, s, CO_2CH_3), 3.40, 3.36 (5H, AB + s, CH_2OCH_3), 2.65 (2H, AB, H-3), 2.05-1.95 (2H, m, CH_2CH_2C=), 1.77-1.67 (2H, m, CH_2CH_2C=), 1.60 (9H, s, 3 x CH_3). δ_C 192.1 (C-4), 166.6 (ester C=O), 152.6 (C-9), 136.0 (C-7), 129.8 (C-5), 126.4, 124.8 (C=C), 119.0 (C-6), 117.1 (C-10), 115.5 (C-8), 75.9 (CH_2OMe), 59.3 (CH_2OCH_3), 58.4 (C-2), 51.6 (CO_2CH_3), 43.5 (C-3), 33.7 (CH_2C=), 28.6 (CH_2CH_2C=), 20.5, 19.9, 18.3 (3 x CH_3). Also isolated was a by-product (97 mg, 10%) which crystallised as an orange powder m.p. 60-70 °C from hexane. It was formulated as *2-(2'-amino-5'-carbomethoxyphenyl)-4-(3,4-dimethylpent-3-enyl)furan* on the basis of the following properties. (Found: C, 72.85; H, 7.2; N, 4.55. M^+ 313.1680. $C_{19}H_{23}NO_3$ requires C, 72.82; H, 7.40; N, 4.47%. M 313.1678). ν_{max} 3495, 3405, 1710, 1620, 1580 cm^{-1}. λ_{max} (ε) 296 (13 400), 265 (27,500) nm. δ_H 8.12 (1H, d, J = 2.0 Hz, H-6'), 7.75 (1H, dd, J = 2.0 Hz, J = 8.5 Hz, H-4'), 7.27 (1H, d, J = 0.8 Hz, H-5), 6.79 (1H, d, J = 8.4 Hz, H-3'), 6.53 (1H, br s, H-3), 3.86 (3H, s, CO_2CH_3), 2.52-2.46 (2H, m, CH_2-C=), 2.33-2.26 (2H, m, CH_2CH_2C=), 1.68, 1.65, 1.63 (9H, 3 x s, 3 x CH_3).

Methyl N-formyl-1,2-dihydro-2-(3,4-dimethylpent-3-enyl)-2-(methoxymethyl)quinoline-6-carboxylate (7; R=HCO). - A solution of the tetrahydroquinoline ketone (6) (4.74 g, 13.7 mmol) in methanol (110 ml) was treated at room temperature with an excess of sodium borohydride (monitored by t.l.c.). Water (10 ml) was added and the solvent evaporated under reduced pressure. The resulting alcohol was dissolved in carbon tetrachloride (50 ml) and triphenylphosphine (3.59 g, 13.7 mmol) was added. The reaction mixture was heated at 54 °C for 5 h and was evaporated under reduced pressure on to silica gel. The impregnated silica was applied as a plug to a silica column and eluted with hexane/ethyl acetate (2:1). Crystallisation from hexane gave the *diene* (7; R=H) (3.46 g, 76%) as a white powder m.p. 81.5-84.5 °C. (Found: C, 73.15; H, 8.3; N, 4.1. M^+ 329.1982. $C_{20}H_{27}NO_3$ requires C, 72.92; H, 8.26; N, 4.25%. M 329.1991). ν_{max} 3410, 1695. λ_{max} (ε) 326 (14 900), 260 (23 200), 230 (21 800) nm. δ_H 7.66 (1H, dd, J = 2.0 Hz, J = 8.5 Hz, H-7), 7.54 (1H, d, J = 2.0 Hz, H-5), 6.44 (1H, d, J = 9.7 Hz, H-4), 6.38 (1H, d, J = 8.5 Hz, H-8), 5.33 (1H, dd, J = 2.0 Hz, J = 9.7 Hz, on shaking with D_2O, d, J = 9.7 Hz, H-3), 4.46 (1H, br s, NH), 3.86 (3H, s, CO_2CH_3), 3.50 (1H, d, J = 9 Hz, one CH_2O), 3.38 (3H, s, OMe), 3.22 (1H, d, J = 9 Hz, one CH_2O), 2.12 (2H, m, CH_2CH_2C=), 1.83-1.38 (11H, m + 1.61 s, 3 x CH_3, CH_2CH_2C=). δ_C 167.1 (ester C=O), 147.8 (C-9), 131.3 (C-7), 128.8 (C-5), 127.3 (C=C), 126.5 (C-3), 124.8 (C-4), 124.1 (C=C), 118.4 (C-6), 118.2 (C-10), 111.5 (C-8), 79.5 (CH_2O), 59.3 (CH_2OCH_3), 59.1 (C-2), 51.3 (CO_2CH_3), 37.9 (CH_2C=), 29.1 (CH_2CH_2C=), 20.4, 19.9, 18.3 (3 x CH_3). The diene (7; R=H) (830 mg, 2.52 mmol) was treated with formic-acetic anhydride prepared from formic acid (0.49 g, 10.7 mmol) and acetic anhydride (1.06 g, 10.4 mmol) for 12 h at room temperatue. After evaporation the residue was dissolved in ether (25 ml) washed with sodium bicarbonate solution and dried ($MgSO_4$). Evaporation followed by flash chromatography on silica using hexane/ethyl acetate (5:1) gave the *N-formyldiene* (7; R=HCO) (816 mg, 90%) as a gum. (Found: C, 70.4; H, 7.35; N, 4.15. M^+ 357.1940.

$C_{21}H_{27}NO_4$ requires C, 70.56; H, 7.61; N, 3.92%. M 357.1940) ν_{max} 1710, 1680, 1600, 1580 cm^{-1}. λ_{max} (ε) 304 (7000), 250 (31 000) nm. δ_H 8.77 (br, H-8), 7.87 (1H, dd, J = 1.8 Hz, J = 8.6 Hz, H-7), 7.72 (1H, d, J = 1.9 Hz, H-5), 6.57 (1H, d, J = 10.1 Hz, H-4), 5.72 (1H, d, J = 10.1 Hz, H-3), 3.90 (4H, br s, CO_2CH_3 + one CH_2O), 3.54 (1H, d, J = 10 Hz, one CH_2O), 3.36 (3H, s, OCH_3), 2.04 (2H, m, CH_2C=), 1.56 (11H, br s, 3 x CH_3, CH_2CH_2C=). δ_C 166.3 (ester C=O), 162.4 (amide C=O), 131.9, 129.8, 128.1, 126.2, 125.2, 124.9, 120.0 (aromatics + alkenes, 3 signals not visible), 75.5 (CH_2O), 64.2 (CH_2OCH_3), 59.2 (C-2), 51.9 (CO_2CH_3), 34.1 (CH_2C=), 28.6 (CH_2CH_2C=), 20.4, 19.9, 18.3 (3 x CH_3).

Methyl 2-(3,4-dimethylpent-3-enyl)quinoline-6-carboxylate (8). - The diene (7; R=H) (36 mg) in hexane (3 ml) was heated at 70 °C for 20 h. Evaporation and flash chromatography on silica using hexane/ethyl acetate (5:1) gave the *quinoline* (8) (27 mg, 87%) which crystallised from hexane in rods m.p. 70-70.5 °C. (Found: C, 76.45; H, 7.3; N, 4.75. M^+ 283.1574. $C_{18}H_{21}NO_2$ requires C, 76.29; H, 7.47; N, 4.94%. M 283.1572). ν_{max} 1715, 1620, 1600 cm^{-1}. λ_{max} (ε) 324 (4 700), 311 (4 700), 279 (6 600), 241 (45 300) nm. δ_H 8.54 (1H, d, J = 1.8 Hz, H-5), 8.26 (1H, dd, J = 1.9 Hz, J = 8.9 Hz, H-7), 8.13 (1H, d J = 8.5 Hz, H-4), 8.05 (1H, d, J = 8.8 Hz, H-8), 7.32 (1H, d, J = 8.5 Hz, H-3), 3.97 (3H, s, CO_2CH_3), 3.06-3.00 (2H, m, CH_2CH_2C=), 2.53 (2H, br t, CH_2CH_2C=), 1.72, 1.62, 1.55 (9H, 3 x s, 3 x CH_3).

Methyl N-formyl-2-(3,4-dimethyl-3,4-epoxypentyl)-3,4-epoxy-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline-6-carboxylate diastereoisomers (9). - The N-formyldiene (7; R=HCO) (183 mg) was dissolved in dichloromethane (2 ml) and *m*-chloroperbenzoic acid (80%, 239 mg) and sodium bicarbonate (116 mg) were added. The mixture was stirred at room temperature for 72 h, diluted with dichloromethane (5 ml) and then washed with saturated sodium bicarbonate solution and water. Drying ($MgSO_4$) and evaporation gave a gum which was purified by flash chromatography on silica using hexane/ethyl acetate (7:4) as solvent. Evaporation gave the *bis-epoxide* (9) as a foam (172 mg, 86%, Rf 0.14). (Found: C, 64.55; H, 7.15; N, 3.75. M^+ 389.1851. $C_{21}H_{27}NO_6$ requires C, 64.77; H, 6.99; N, 3.59%. M 389.1838). ν_{max} 1720, 1690, 1615, 1580 cm^{-1}. λ_{max} (ε) 274 (11 300) nm. δ_H 8.43 (1H, br s, CHO), 8.11 (1H, br s, H-5), 8.01 (1H, br m, H-7), 3.92 (~5 H, m, CO_2CH_3, CH_2O, H-4) 3.46 (3H, 2 x s, OCH_3), 3.22 (1H, br s, H-3), 1.84-1.33 (-4H, m, CH_2CH_2), 1.21-1.03 (9H, m, 3 x CH_3). A diastereoisomeric mixture is indicated. The side-chain mono-epoxide (23 mg 12%, R_f 0.23) was also isolated.

Methyl N-formyl-2-(3,4-dimethyl-3,4-epoxypentyl)-3-hydroxy-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline-6-carboxylate (10). - A solution of the bis-epoxide (9) (400 mg) in dioxan (5 ml) was stirred with Raney nickel (W-4, ~100 mg) for 30 min. The suspension was filtered through celite and the pad washed with ether. The ether was evaporated under reduced presssure and the dioxan solution stirred with palladium on carbon (10%, 60 mg) under 1 atm. of hydrogen for 21 h. Filtration through celite, evaporation and flash chromatography on silica using hexane/ethyl acetate (1:1) gave the *hydroxyepoxide* (10) (260 mg, 64%) as a foam. (Found: C, 64.5; H, 7.4; N, 3.55. M^+ 391.1991. $C_{21}H_{29}NO_6$ requires C, 64.43; H, 7.41; N, 3.58%. M 391.1995). ν_{max} 3600-3200, 1720, 1685, 1615, 1585 cm^{-1}. λ_{max} (ε) 274 (13 200). δ_H 8.67 (1H, br s, CHO), 7.86 (2H, m, H-5,7), 4.1 (~1H, m, H-3), 3.92 (H, s, part of one CH_2O), 3.89 (3 H, s, CO_2CH_3 + part of one CH_2O), 3.47 (1H, m, one CH_2O), 3.38 (3H, br s, OCH_3), 3.02 (~2H, br, H-4), 1.9-1.5 (br m, CH_2CH_2), 1.27-1.15 (9H, m, 3 x CH_3). Deformylation by the method described below gave the parent *amine* crystallising from hexane/ethyl acetate as a powder m.p. 130.5-132 °C. (Found: C, 65.85; H, 8.05; N, 3.65. M^+ 363.2051. $C_{20}H_{29}NO_5$ requires C, 66.09; H, 8.04; N, 3.85%. M 363.2046). ν_{max} 3430, 3600-3300, 1700, 1610, 1580 cm^{-1}. λ_{max} (ε) 302 (22 400), 220 (12 700) nm. δ_H 7.69 (2H, m, H-5-7), 6.49 (1H, d, J = 8.3 Hz, H-8), 4.39 (1H, br s, NH), 3.89 (1H, m, H-3), 3.83 (3H, s, CO_2CH_3), 3.62,

3.41 (2H, 2 x d, J = 9.3 Hz, CH_2O), 3.36 (3H, s, OCH_3), 3.06, 2.83 (2H, 2 x dd, $J_{4,4}$ = 16.8 Hz, $J_{3,4}$ (1) = 4.3 Hz, $J_{3,4}$ (2) = 6.4 Hz, H-4), 2.0-1.6 (4H, br m, CH_2CH_2), 1.32-1.25 (9H, m, 3 x CH_3).

Methyl N-formyl-2-(3,4-dimethylpent-3-enyl)-3-hydroxy-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline-6-carboxylate (11, R = HCO). - A hexane solution of *n*-butyllithium (1.55 M, 2.15 ml) was added dropwise to a cooled (-78 °C) mixture of tungsten hexachloride (661 mg) and THF (20 ml) under nitrogen and the mixture warmed to room temperature to give a clear brown solution. It was then cooled again (-78 °C) and treated with a solution of the hydroxyepoxide (10) (445 mg) in THF (5 ml). The reaction mixture was stirred at 3 ° C for 30 min then at room temperature for 1 h and then poured into a solution of sodium tartrate (1.5N) and sodium hydroxide (2N, 20 ml). The organic layer was dried ($MgSO_4$), evaporated and the residue purified by flash chromatography on silica using hexane/ethyl acetate (1:1) to give starting material (99 mg) and the *hydroxyamide* (11, R = HCO) (192 mg, 45%) as a foam. (Found: C, 66.95; H, 7.95; N, 3.65. M^+ 375.2046. $C_{21}H_{29}NO_5$ requires C, 67.18; H, 7.79; N, 3.73%. M 375.2056). ν_{max} (CCl_4) 3470, 1725, 1690, 1610 cm^{-1}. λ_{max} (ε) 275 (14 000). δ_H 8.68 (1H, br s, CHO), 7.89-7.84 (2H, m, H-5,7), 4.18 (1H, m, H-3), 3.95 (1H, br s, one CH_2O), 3.89 (3H, s, CO_2CH_3), 3.44 (1H, br s, one CH_2O), 3.41 (3H, br s, OCH_3), 3.01 (2H, br d, H-4), 1.97-1.94 (~2H, m, CH_2CH_2=), 1.79-1.80 (br m, CH_2CH_2C=), 1.56, 1.55, 1.49 (9H, 3 x s, 3 x CH_3).

Methyl 2-(3,4-dimethylpent-3-enyl)-3-hydroxy-2-(methoxymethyl)-1,2,3,4-tetrahydroquinoline-6-carboxylate (11, R = H). - To a solution of the hydroxyamide (11, R = HCO) (0.947 g) in methanol (40 ml) was added sodium hydroxide (0.2 g) and the mixture stirred at room temperature for 20 h. Evaporation of the solvent was followed by addition of ethyl acetate and water. The organic layer was dried ($MgSO_4$), evaporated and the residue purified by flash chromatography on silica using hexane/ethyl acetate (2:1) to give the hydroxyamine (11, R = H) (0.704, 80%) crystallising from hexane/ethyl acetate as a powder m.p. 150.5-153 °C. (Found: C, 69.35; H, 8.4; N, 4.1. M^+ 347.2090. $C_{20}H_{29}NO_4$ requires C, 69.14; H, 8.41; N, 4.03%. M 347.2097). ν_{max} (CCl_4) 3525, 3420, 1710, 1610 cm^{-1}. λ_{max} (ε) 310 (25 800), 231 (9 300) nm. δ_H 7.71-7.69 (1H, m, H-5, half H-7), 7.66 (H, d, J = 2.0 Hz, half H-7), 6.48 (1H, d, J = 8.4 Hz, H-8), 4.38 (1H, br s, NH), 3.98-3.93 (1H, m, H-3), 3.83 (3H, s, CO_2CH_3), 3.65, 3.44 (2H, 2 x d, J = 9.2 Hz, CH_2O), 3.39 (3H, s, OCH_3), 3.09 (1H, dd, J = 4.4 Hz, J = 16.7 Hz, one H-4), 2.83 (1H, dd, J = 5.9 Hz, J = 16.7 Hz, one H-4), 2.65 (1H, br d, J = 9.0 Hz, OH), 2.09-2.00 (2H, m, CH_2C=), 1.86-1.70 (2H, m, CH_2CH_2C=), 1.61, 1.60 (9H, 2 x s, 3 x CH_3).

(±)-Virantmycin methyl ester (12). - The hydroxyamine (11, R = H) (200 mg) was dissolved in dichloromethane. A solution of thionyl chloride (76 µl) in dichloromethane was added dropwise under nitrogen and the mixture heated at 40 °C for 5.5 h. The cooled reaction mixture was passed through a silica column using hexane/ethyl acetate (1:1) as eluant. Evaporation and rechromatography on silica with hexane/ethyl acetate (2:1) gave *(±)-virantmycin methyl ester* (12) (95 mg, 45%) crystallising from hexane/ethyl acetate as rods m.p. 134-137 ° C. (Found: C, 65.9; H, 7.7; N, 3.8. M^+ 367.1743. $C_{20}H_{28}ClNO_2$ requires C, 65.65; H, 7.71; N, 3.83%. M 367.1758), ν_{max} 3420, 1700, 1610 cm^{-1}. λ_{max} (ε) 309 (12 500), 232 (2 700) nm. δ_H 7.71-7.69 (2H, m, H-5,7), 6.51 (1H, d, J = 9.0 Hz, H-8), 4.54 (1H, br s, NH, disappears on addition of D_2O), 4.34 (1H, br t, H-3), 3.83 (3H, s, CO_2CH_3), 3.54, 3.53 (2H, 2 x s, CH_2O), 3.37 (3 H, s, OCH_3 + half of one H-4), 3.31 (H, d, J = 4.8 Hz, half of one H-4), 3.08 (1H, dd, J = 6.1 Hz, J = 17.2 Hz, one H-4), 2.16-1.94 (2H, m, CH_2C=), 1.84-1.72 (2H, m, CH_2CH_2C=), 1.59 (9H, s, 3 x CH_3). δ_C 167.2 (ester C=0), 146.6 (C-9), 131.7 (C-5), 129.7 (C-7), 126.7, 124.7 (C=C), 119.0 (C-6), 116.2 (C-10), 113.6 (C-8), 74.2 (CH_2O),

59.4 (OCH_3), 58.1 (C-2), 56.5 (C-3), 51.4 (CO_2CH_3), 33.8 (CH_2C=), 33.6 (C-4), 27.9 (CH_2CH_2C=), 20.5, 19.9, 18.4 (3 x CH_3).

(±)-Virantmycin (1). - The methyl ester (12) (69 mg) was dissolved in acetonitrile (3.2 ml) and water (1.2 ml), lithium hydroxide monohydrate (16 mg) added and the mixture heated at 70 °C for 4 h. The cooled reaction mixture was carefully neutralised with dilute HCl, the solvent evaporated and the residue treated with ethyl acetate and water. The organic layer was separated, dried (Na_2SO_4) and evaporated to give a gum which was chromatgraphed on a silica column using hexane/ethyl acetate as eluate. Evaporation gave a solid (49 mg, 73%) which crystallised from ethyl acetate as a fine crystalline powder m.p. 133-139 °C (unsharp). The natural and synthetic virantmycins gave identical t.l.c. R_f values with the following ten developing solvents: CH_2Cl_2(R_f 0.015), hexane/ethyl acetate (5:1) + trace of acetic acid (R_f 0.048), hexane/ethyl acetate (3:1) (R_f 0.11), hexane/ethyl acetate (1:1) (R_f 0.34), CH_2Cl_2/methanol (10:1) (R_f 0.41), benzene/acetone (2:1) (R_f 0.49), hexane/ethyl acetate (1:3) (R_f 0.54), benzene/acetone (1:1) (R_f 0.60), ethyl acetate/ethanol (9:1) (R_f 0.65), CH_2Cl_2/methanol (1:1) (R_f0.78). (Found: C, 65.05; H, 7.4; N, 3.9; Cl, 10.35. M^+ 351.1593. $C_{19}H_{26}ClNO_3$ requires C, 64.86; H, 7.45; N, 3.78; Cl, 10.08%. M 351.1601). ν_{max} 3435, 3300-2300, 1680, 1615, 1585 cm^{-1} λ_{max} (ε) 307 (19 800), 229 (8 100). δ_H [values reported for the natural product in square brackets] 7.78-7.75 (2H, m, H-5,7) [7.78d, 7.82dd], 6.53 (1H, d, J = 9.0 Hz, H-8) [6.56, d, J = 8.5 Hz], 4.65 (1H, s, NH), 4.36 (1H, dd, H-3) [4.36, t], 3.56 (2H, s, CH_2O) [3.58 s], 3.39 (3H, s, OCH_3), [3.46 s], 3.35 (1H, dd, J = 17.1, 6.1 Hz, H-4) [3.40 dd, J = 16.4, 6.0], 3.10 (1H, dd, J = 4.9 Hz, H-4) [3.08 dd], 2.07-1.98 (2H, m, CH_2C=) [2.0 m], 1.80-1.66 (2H, m, $CHCH_2C$=) [1.6 m], 1.62, 1.60 (9H, s, 2 x s, 3 x CH_3) [1.60 s]. δ_C 171.9 (C-16) [171.9], 147.2 (C-9) [147.2], 132.4 (C-5) [132.4], 130.4 (C-7) [130.4], 126.5 (C-14) [126.5], 124.8 (C-13) [124.8], 117.6 (C-6) [117.7], 116.0 (C-10) [116.0], 113.5 (C-8) [113.5], 74.1 (C-17) [74.1], 59.4 (OCH_3) [59.4], 58.1 (C-2) [58.0], 56.2 (C-3) [56.2], 33.6 (C-4) [33.5], 33.5 (C-11) [33.5], 27.8 (C-12) [27.8], 19.9 (C-17) [18.8], 18.4 (C-18) [18.4], 20.5 (C-19) [20.6].

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