Tetrahedron Letters,Vol.27,No.11,pp 1293-1296,1986 0040-4039/86 $3.00 + .00
Printed in Great Britain

TOTAL SYNTHESIS OF THE ANTIVIRAL (±) VIRANTMYCIN

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Summary: A total synthesis of the antiviral metabolite virantmycin is described.

The unusual metabolite virantmycin (1), isolated by Japanese workers[1] from Streptomyces nitrosporeus has been found to possess potent antiviral activity. Its novel structure was elucidated[2] mainly by n.m.r. studies, but the relative and absolute stereochemistry at the two chiral centres remain unknown pending the results of an X-ray crystallographic determination. We have synthesised the racemic form of virantmycin from p-aminobenzoic acid by the following route.

Direct iodination of p-aminobenzoic acid has been reported as proceeding very poorly but iodine monochloride treatment of the methyl ester in acetic acid gave 77% of the mono-iodo derivative (2) m.p. 84-87 °C. The second key component of the synthesis, the acetylenic alcohol (3) was readily obtained (68%) by interaction of lithium acetylide-ethylenediamine complex with ketone (4). The preparation of this ketone from the corresponding β-ketoester (5) proved unexpectedly difficult, the best process (65%) involving the elegant propane-1,2-diol/alkoxide method recently described.[3] The β-ketoester (5) was readily (91%) obtained by alkylation of methyl 4-methoxyacetoacetate with sodium hydride and 1-bromo-2,3-dimethylbut-2-ene. Direct coupling of the iodoester (2) and the acetylenic alcohol (3) was carried out very effectively without the necessity for functional group protection to give (6; 94%) m.p. 72-74 °C by treatment in diethylamine with a catalytic quantity of bis(triphenylphosphine)palladium (II) chloride in the presence of cuprous iodide at room temperature.[4] This intermediate (6) comprises in its structure the entire carbon framework of virantmycin. Meyer-Schuster rearrangement[5] of the amino-alcohol (6) was carried out ($MeSO_3H$/THF/40 °C) to yield the bicyclic ketone (8; 63%) m.p. 122-125 °C obviously produced by intramolecular cyclisation of the initially formed conjugated ketone (7). Borohydride reduction of (6) followed by dehydration with triphenylphosphine/carbon tetrachloride then gave the bicyclic diene (9; 66%). This product proved to be thermally unstable and

readily lost the elements of dimethyl ether to give the corresponding quinoline. Accordingly the synthesis was continued with the stable N-formyl derivative prepared using acetic formic anhydride.

Initial attempts to functionalise regioselectively the endocyclic double bond of (9) in the presence of the more electron-rich side-chain double bond were abortive. The following procedure proved to be successful. Bis-epoxidation of the N-formyl derivative of (9) with excess m-chloroperbenzoic acid gave a mixture of diastereoisomeric bis-epoxides (10; 86%). This product, without separation, was subjected to hydrogenolysis (10% Pd-C/H_2; dioxan) to cleave the sole benzylic carbon-oxygen bond at C-4 to yield the hydroxy-epoxide (11; 60%). De-epoxidation of (11) was carried out (45%) by treatment with WCl_6-n-BuLi[6] the product of which, after deformylation ($NaOH/H_2O$/MeOH; room temperature) surprisingly gave a single pure diastereoisomer (80%) m.p. 151-153 °C of the amino-alcohol (12) pointing to stereoselectivity in the endocyclic epoxidation.

Treatment of the amino-alcohol (12) with thionyl chloride in dichloromethane yielded a homogeneous crystalline chloro-ester (13; 45%) m.p. 134-137 °C. Hydrolysis of this ester with lithium hydroxide in refluxing aqueous acetonitrile gave a racemic chloro-acid (73%) m.p. 133-139 °C identical in all chromatographic and spectroscopic respects[7] with natural virantmycin.[8] Unfortunately, the spectroscopic properties gave no unambiguous indication of the relative stereochemistry of the two centres in the synthetic chloro-acid (1), the chloro-ester (13) or the hydroxy-ester (12). Oxidation (Me_2SO; $(COCl)_2$) of the N-formyl derivative of (12) gave a low yield of the keto-ester (14) which by borohydride reduction and deformylation gave predominantly the other diastereoisomer of (12). By procedures similar to those described above this was converted to the second racemic diastereoisomer of (13). The proton n.m.r. spectrum of this product was significantly different from that of virantmycin methyl ester but again gave no clue as to the relative stereochemistry. We are currently attempting to solve the problem by growing suitable crystals of chloro-ester (13) for X-ray examination. The (±)-virantmycin obtained as above showed significant *in vitro* activity against herpes simplex types 1 and 2.[9]

We thank Dr R F Newton and Dr D I C Scopes of Glaxo Group Research for their helpful interest and support and for their participation in an SERC CASE studentship (MLH).

References and Notes

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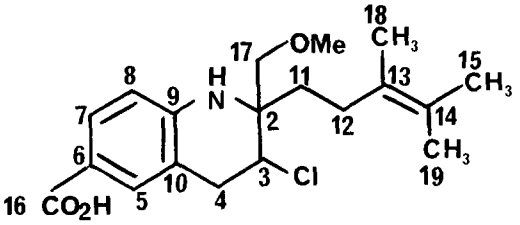

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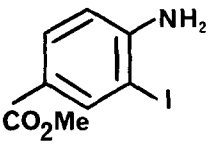

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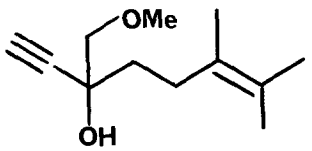

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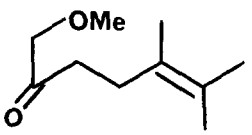

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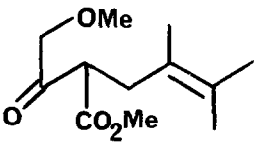

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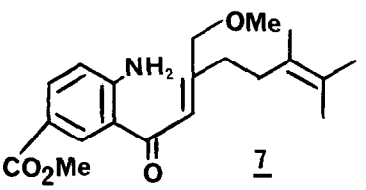

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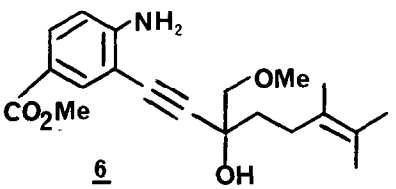

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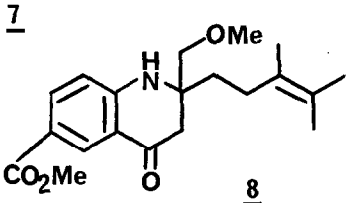

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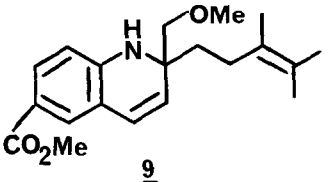

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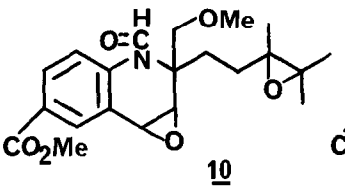

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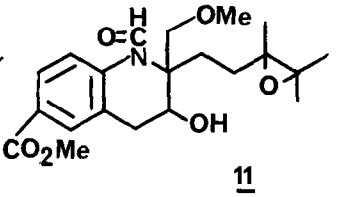

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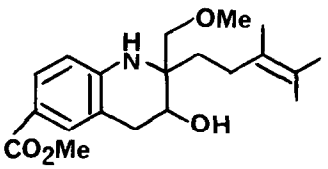

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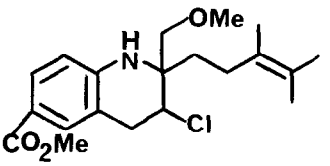

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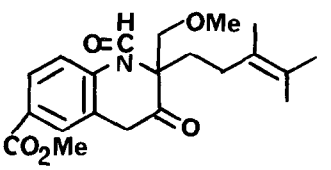

14

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7. Decoupled ^{13}C chemical shifts of synthetic (±)-virantmycin (corresponding reported[2] chemical shifts of natural virantmycin in brackets) ($CDCl_3$). δC-2, 58.1 (58.0); C-3, 56.2 (56.2); C-4, 33.6 (33.5); C-5, 132.4 (132.4); C-6, 117.6 (117.7); C-7, 130.4 (130.4); C-8, 113.5 (113.5); C-9, 147.2 (147.2); C-10, 116.0 (116.0); C-11, 33.5 (33.5); C-12, 27.8 (27.8); C-13, 124.8 (124.8); C-14, 126.5 (126.5); C-15, 19.9 (18.8); C-16, 171.9 (171.9); C-17, 74.1 (74.1); C-18, 18.4 (18.4); C-19, 20.5 (20.6); OMe, 59.4 (59.4).

   Decoupled ^{13}C chemical shifts of synthetic (±)-virantmycin methyl ester (corresponding reported[2] chemical shifts of naturally derived ester in brackets) ($CDCl_3$). δC-2, 58.1 (57.9); C-3, 56.5 (56.4); C-4, 33.6 (33.4); C-5, 131.7 (131.6); C-6, 119.0 (118.6); C-7, 129.7 (129.6); C-8, 113.6 (113.5); C-9, 146.4 (146.5); C-10, 116.2 (115.9); C-11, 33.8 (33.6); C-12, 27.9 (27.8); C-13, 124.7 (124.6); C-14, 126.7 (126.5); C-15, 19.9 (19.9); C-16, 167.2 (167.2); C-17, 74.2 (73.9); C-18, 18.4 (18.4); C-19, 20.5 (20.6); OMe, 59.4 (73.9?); ester OMe, 51.4 (51.5).

8. We are grateful to Professor S Omura for generously providing a sample.

9. We thank Glaxo Group Research for carrying out the bioassays.

(Received in UK 6 January 1986)