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STUDIES TOWARDS FUNICULOSIN. SYNTHESIS OF THE UNIQUE ALL-*CIS* CYCLOPENTANETETROL MOIETY

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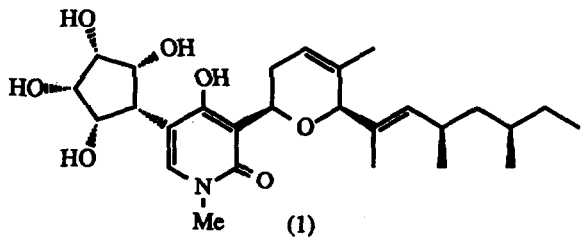
Summary : A total synthesis of the all-*cis* cyclopentanetetrol moiety (19) present in funiculosin (1), featuring the Claisen-Ireland rearrangement (8) → (9), iodolactonisation (9) → (10*a*), and the intramolecular oxygen nucleophile displacement (14) → (16), as key steps, is described.

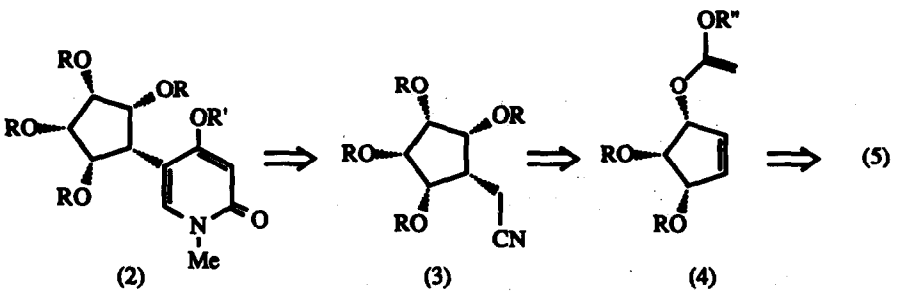
The antibiotic funiculosin (1) is a very novel and unusual secondary metabolite produced by *Penicillium funiculosum*.[1] Structurally the molecule is tricyclic, and is made up of a 3- dihydropyran - substituted 4-hydroxy-2-pyridone which is further substituted at C-5 in the pyridone ring by a unique all-*cis* cyclopentanetetrol moiety. In addition, the antibiotic accommodates nine chiral centres, five of which are contiguous and associated with the cyclopentanetetrol, the remainder being associated with the *cis*-substituted dihydropyran residue. Although both pyridone and dihydropyran structural units are found quite commonly within natural products, funiculosin is the only natural compound to contain the interesting and unusual all-*cis* substituted cyclopentanetetrol moiety.



(1)

Funiculosin exhibits antiviral properties and shows antifungal activity against a wide variety of pathogenic fungi; it also exhibits antitumoral activity.[2] The novel and unusual structure of funiculosin, together with its interesting biological profile attracted us towards synthetic studies with this new antibiotic substance. In this *Letter* we describe our preliminary studies, and outline a concise and stereocontrolled synthesis of the unique all-*cis* cyclopentanetetrol moiety (19) found in funiculosin.

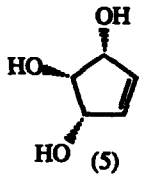
Our general strategy for a total synthesis of funiculosin relied on access to a protected form of the C-5 cyclopentanetetrol substituted 2-pyridone (2). Model studies had established that this system could be produced from condensation between an appropriate cyclopentaneacetonitrile and a C_3 unit such as malonyl dichloride.[3] Hence the cyclopentanetetrol acetonitrile (3) became a key intermediate in our projected synthesis. Analysis of a number of complementary synthetic routes led us to design a route to (3) which incorporated an Ireland-Claisen rearrangement of the ester enol ether (4), derived in two steps from the readily available cyclopentenetriol (5), as a key stage (Scheme 1).



Scheme 1

Thus, optimisation of literature methods first allowed us to prepare the cyclopentenetriol (5) in five steps starting from cyclopentadiene.[4] Protection of (5) as the corresponding methylenedioxy derivative (6) [$(CH_2O)_n$, HCl, 60°C, 6h; 89%] followed by treatment of (6) with Ac_2O-C_6H_5N then provided the acetate (7; 92%).[5] Deprotonation of (7) using lithium *bis*- (trimethylsilyl) amide at -78°C, and quenching the resulting enolate with *t*-butyldimethylsilyl chloride in 1,3,-dimethyl - 3,4,5,6,-tetrahydro-2(1H) pyrimidone (-78°C, then -20°C) next led to the ester enol ether (8; 98%), which was immediately heated in xylene in a sealed tube at 175°C for 18h. Work-up of the Claisen-Ireland rearrangement product, in the presence of tetra-*n*-butylammonium fluoride (18°C for 1h) then gave the key intermediate cyclopenteneacetic acid (9) which was produced as colourless rectangular prisms m.p. 56-8°C in 90% yield from (8).[6]

Iodolactonisation of (9) in the presence of KI-I_2-$NaHCO_3$ next lead to the iodolactone (10*α*; m.p. 134-5°C; 92%), which was then converted into the acetonitrile (13) following reduction (*i*-Bu_2AlH in CH_2Cl_2,-78°C, 62%) to (11), oxime (12) formation, and dehydration of (12) using 1,1'-carbonyl-diimidazole in refluxing dichloromethane. With the iodohydrin acetonitrile (13) in hand we were now in a position to introduce the final oxygen centre into the substituted cyclopentane. To achieve this aim and at the same time incorporate the required all-*cis* stereochemistry of the substituents in the target cyclopentanetetrol (19), we elected to use the intramolecular oxygen nucleophile displacement strategy highlighted by Corey and his colleagues.[7,8] Thus, the iodohydrin (13) was first reacted with methyl malonyl chloride in THF in the presence of DMAP at -78°C to produce the mixed ester (14), which was then treated with sodium hydride leading the ketene acetal (15; 92%). Hydrolysis of (15) in the presence of 1M HCl next led to a mixture of positional isomers of the substituted malonate (16) which on saponification gave the all-*cis* cyclopentane substituted acetonitrile (17; 84%) as a colourless solid, m.p. 110°C. The structure and stereochemistry of (17) were confirmed by a single crystal X-ray analysis.[9] When a solution of the methylenedioxy derivative (17) in methanol was treated with ozone[10] at -78°C for 1.5h, work-up produced a mixture of positional isomers of the anticipated formate (18) which on saponification (MeOH-$KHCO_3$, 25°C, 0.5h) gave rise to the target all-*cis* cyclopentanetetrol acetonitrile (19) which was produced as a viscous oil.[5] Work is now in progress to incorporate this strategy for the synthesis of (19) into a total synthesis of funiculosin.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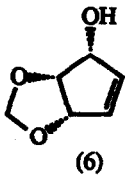
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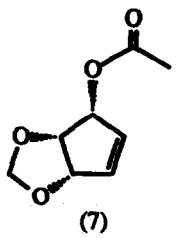
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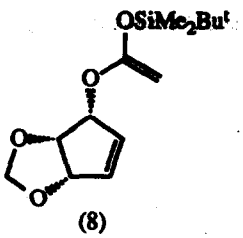
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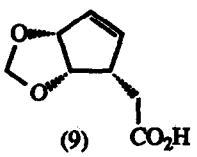
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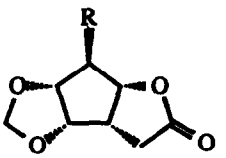
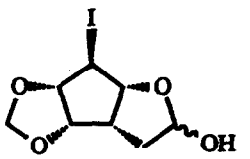

(10)
a, R=I; *b*, R=OH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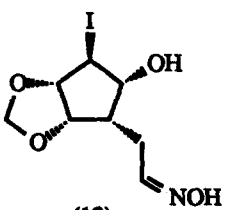
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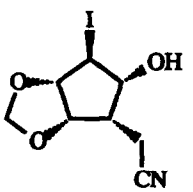
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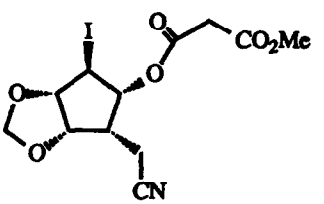
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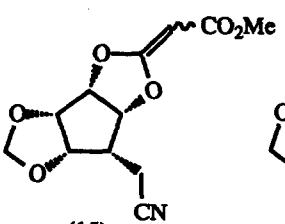
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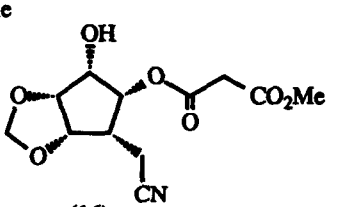
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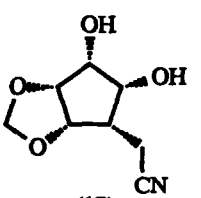
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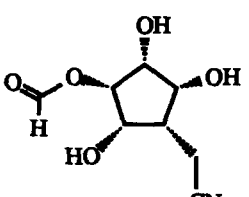
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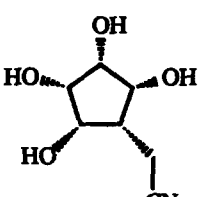
(19)

Acknowledgement. We thank J. Paul Madeley for some preliminary work, and Dr P.J. Whittle (Pfizer Central Research) for his interest in this study. We also thank Pfizer Central Research for generous finanical support.

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2. K. Ando, I. Matsuura, Y. Nawata, H. Endo, H. Sasaki, T. Okytomi, T. Saehi and G. Tamura, *J. Antibiotics*, **1978**, *31*, 533.
3. S.J. Davis, J.A. Elvidge and A.B. Foster, *J. Chem. Soc.*, **1962**, 3638; J.P. Madeley, PhD thesis, University of Nottingham, **1988**.
4. See F.G. Cocu, T. Posternak and G. Wolczunowicz, *Helv. Chim. Acta*, **1970**, *53*, 2275, and references cited therein.
5. All new compounds showed satisfactory spectroscopic data together with microanalytical or mass spectrometry data. Acetate (7) had m.p. 47-9°C, b.p. 170-2°C at 10mmHg and showed υ_{max} 1740 cm.$^{-1}$, δ_H 2.1 (OAc), 4.6 (C<u>H</u>HO$_2$), 4.8 (app.t, *J*~5.6Hz, C<u>H</u>O), 5.0 (CH<u>H</u>O$_2$), 5.1 (dd, *J* 5.4 and 1.8Hz, C<u>H</u>O), 5.9 (app.dt, *J* 5.9 and 1.8Hz, :C<u>H</u>), 6.1 (dd, *J* 5.9 and 1.9Hz,:C<u>H</u>) p.p.m.; the cyclopenteneacetic acid (9) showed δ_H 2.5 (dd, *J* 17.3 and 7.0Hz, C<u>H</u>HCO$_2$H), 2.6 (dd, *J* 17.3 and 8.8Hz, CH<u>H</u>CO$_2$H), 3.15 (m, C<u>H</u>CH:), 4.6 (C<u>H</u>HO$_2$), 4.7 (app.t, *J*~5.8Hz, C<u>H</u>O), 5.0 (CH<u>H</u>O$_2$), 5.2 (d, *J* 5.4Hz, C<u>H</u>O), 5.7 (app.dt, *J* 5.8 and 2.1Hz,:C<u>H</u>), 6.0 (d, *J* 5.8Hz, :C<u>H</u>) p.p.m., δ_C 33.8 (t), 44.0 (d), 77.8 (d), 84.9 (d), 93.4 (t), 127.4 (d), 138.6 (d), 177.4 p.p.m; the iodohydrin acetonitrile (13) had m.p. 106-8°C and showed υ_{max} 2252 cm^{-1}, δ_C 17.9 (t), 29.8 (d), 41.7 (d), 80.8 (d), 81.8 (d), 89.9 (d), 95.9 (t), 118.8 p.p.m.; the all-*cis* acetonitrile (17) showed δ_H 2.1-2.2 (m, C<u>H</u>.CH$_2$CN), 2.25 (O<u>H</u>), 2.75 (app.d, *J* 8.5Hz, C<u>H</u>$_2$CN), 3.0 (O<u>H</u>), 3.9 (dd, *J* 6.6 and 4.6Hz, C<u>H</u>OH), 4.0 (dd, *J* 4.5 and 4.3Hz, C<u>H</u>OH), 4.55 (app.t, *J*~5.8Hz, C<u>H</u>O), 4.6 (dd, *J* 5.8 and 5.6Hz, C<u>H</u>O), 4.9 (C<u>H</u>HO$_2$), 5.2 (CH<u>H</u>O$_2$) p.p.m.; the tetrol (19) showed δ_H 2.3 (m, C<u>H</u>CH$_2$CN), 2.6 (d, *J* 8.0Hz, CH$_2$CN), 3.9 (br.d, *J* 6.4Hz, 2 x CHO<u>H</u>), 4.0 (br, 2 x C<u>H</u>OH and 2 x C<u>H</u>OH), 4.1 (br, 2 x C<u>H</u>OH) p.p.m.
6. Use of the acetonide derivative corresponding to (8) in the Claisen-Ireland rearrangement led to much poorer yields (<5%) of the acetonide cyclopenteneacetic acid corresponding to (9) (J.P. Madeley, Ph.D thesis, University of Nottingham, **1988**).
7. See E.J. Corey and J. Das, *Tetrahedron Lett.*, **1982**, *41*, 4217.
8. Direct nucleophilic displacement of (10*a*) using potassium superoxide (18-crown-6, DMSO, 0°C, 3h), led to the corresponding alcohol (10*b*) (*i.e.* with the "wrong" stereochemistry), whose structure and stereochemistry were determined by X-ray analysis.[9]
9. We thank Dr M.J. Begley of this department for these data which will be published in the full paper.
10. P. Deslongchamps and C. Moreau, *Can. J. Chem.*, **1971**, *49*, 2465.

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