Total Synthesis of (±)-Citreoviral

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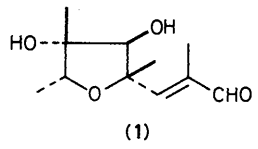
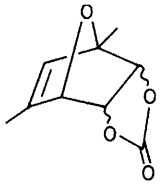
Citreoviral, a novel metabolite of *Penicillium citreoviride* B., has been synthesized in racemic form starting from 2,4-dimethylfuran.

In connection with our work on citreoviridin, a potent inhibitor of ATP-synthesis and ATP-hydrolysis catalysed by mitochondrial enzyme systems, we have isolated citreoviral (**1**), a novel metabolite of *Penicillium citreoviride* B. (IFO 6050).[1] In view of a recent publication[2] on the synthesis of citreoviridin we now describe the total synthesis of citreoviral in racemic form from 2,4-dimethylfuran; there are similarities in the intermediate.[2]

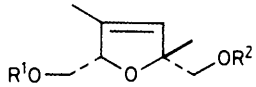
Diels–Alder reaction of 2,4-dimethylfuran with vinylene carbonate was carried out in a sealed tube under argon (130—140 °C; 22 h) to give a 7:5 mixture of the two adducts (**2**) and (**3**)† in 65% yield, both of which could be obtained pure: δ ($CDCl_3$) (**2**), 4.83 (1H, d, *J* 4 Hz); (**3**), 4.60 (1H, br.s). This mixture could be converted directly into the diol (**4**),† however, in 93% overall yield, in 3 steps [i, 1 M NaOH (1.5 equiv.) in MeOH (room temp.; 1 h); ii, $NaIO_4$ (1.1 equiv.) in dioxane–H_2O (1:1) (room temp.; 40 min); iii, $NaBH_3CN$ (3.5 equiv.) in dioxane–H_2O–AcOH (1:1:3) (room temp.; 1 day)]. This diol was treated with t-butylchlorodiphenylsilane (1.2 equiv.)–imidazole (2.4 equiv.) in benzene (room temp.; 1 day) to afford the desired silyl ether (**5**),† m.p. 99—100 °C (from MeOH), in 54% yield, in addition to the silyl ethers (**6**) and (**7**),† both of which were quantitatively converted into the original diol (**4**) on treatment with Bu^n_4NF in tetrahydrofuran (THF) (room temp., 2 h). The silyl ether (**5**) could thus be obtained from (**4**) in almost quantitative yield. Compound (**5**) was quantitatively acetylated with Ac_2O–pyridine and then osmylated with OsO_4 (1.3 equiv.) and pyridine (2.0 equiv.) in dioxane (room temp.; overnight) followed by decomposition with aqueous $NaHSO_3$ to give the diol (**8**)† in 32% yield.‡ The diol (**8**) was converted into the monohydroxyacetal (**9**),† m.p. 76—76.5 °C (from hexane–EtOAc), in 88% overall yield, in 6 steps [i, 2,2-dimethoxypropane (2 equiv.)–*p*-$MeC_6H_4SO_3H$ in acetone (room temp.; 8 h); ii, Bu^n_4NF in THF (room temp.; 2 h); iii, $MeSO_2Cl$ (3 equiv.)–pyridine (3 equiv.)–4-*N*,*N*-dimethylaminopyridine (DMAP) (2 equiv.) in CH_2Cl_2 under argon (room temp.; 13 h); iv, NaI (10 equiv.) in dimethylformamide under argon (100 °C; 2 days); v, H_2/Raney Ni–NaOAc (2 equiv.) in EtOH (room temp.; 10 h); vi, K_2CO_3 in MeOH (room temp.; 13 h)]. In 2 steps [i, Me_2SO (20 equiv.)–dicyclohexylcarbodi-imide (DCC) (10 equiv.) in benzene containing a few drops of pyridine and CF_3CO_2H (room temp.; 2 h); ii, $Ph_3P{=}C(Me)CO_2Me$ (1.5 equiv.) in benzene under argon (80 °C; 14 h)] compound (**9**) was converted into the corresponding α,β-unsaturated ester (**10**),† in 64% overall yield, treatment of which with Amberlite IR-120 resin (H^+ form) in H_2O–MeOH (1:1) (60 °C; overnight) afforded the diol (**11**),† m.p. 122—123 °C (from hexane–EtOAc), in 63% yield. Reversal of the configuration of the secondary OH group in (**11**) and conversion of the ester group into aldehyde would then lead to citreoviral (**1**).



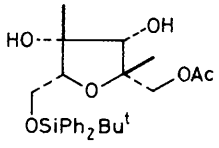
(**1**)



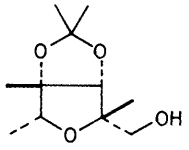
(**2**) (*endo*)
(**3**) (*exo*)



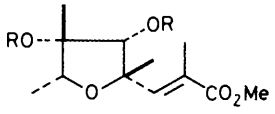
(**4**) $R^1 = R^2 = H$
(**5**) $R^1 = SiPh_2Bu^t$, $R^2 = H$
(**6**) $R^1 = R^2 = SiPh_2Bu^t$
(**7**) $R^1 = H$, $R^2 = SiPh_2Bu^t$



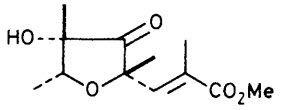
(**8**)



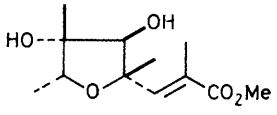
(**9**)



(**10**) R,R = CMe_2
(**11**) R = H



(**12**)



(**13**)

Oxidation of compound (**11**) with Me_2SO (20 equiv.)–DCC (10 equiv.) in benzene containing a few drops of pyridine and CF_3CO_2H (room temp.; 4.5 h) gave the ketone (**12**),† i.r. (film) 1770 cm^{-1}, in 77% yield, reduction of which with $NaBH_4$ in THF under argon (−50 °C—room temp.; 1 h) afforded the *trans*-diol (**13**),† m.p. 133—134 °C (from hexane–EtOAc), in 68% yield, in addition to the original *cis*-diol (**11**) in 28% yield. The *trans*-diol (**13**) was readily converted into (±)-citreoviral (**1**) in *ca.* 40% yield, in 2 steps [i, Bu^i_2AlH (5 equiv.) in THF (−78 °C; 1 h); ii, active MnO_2 in CH_2Cl_2 (room temp.; 13 h)]; the synthetic sample was identical to

† The i.r., n.m.r., and high-resolution mass spectral data for the new compounds were in accord with the structures assigned.

‡ The unwanted isomer was obtained in moderate yield, in which the stereochemistry of the newly formed OH groups was different from that in (**8**). Although osmylation of (**5**) was also attempted, satisfactory results were not obtained.

natural citreoviral (**1**) in all respects (i.r., n.m.r., and mass spectra, and chromatographic behaviour).

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References

1 Y. Shizuri, S. Nishiyama, D. Imai, S. Yamamura, H. Furukawa, K. Kawai, and N. Okada, *Tetrahedron Lett.*, 1984, **25**, 4771, and references cited therein.
2 C. S. Wilcox, G. W. Long, and H. Suh, *Tetrahedron Lett.*, 1984, **25**, 395.