Studies on the Syntheses of Heterocyclic Compounds containing Benzopyrone. Part 6.[1] Biomimetic Total Synthesis of Citromycetin

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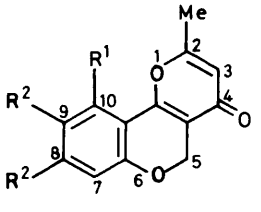
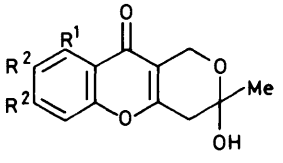
Biomimetic total synthesis of citromycetin (**1a**) is described. Regioselective cyclization of the enetrione (**5**), chosen as a common intermediate for the syntheses of citromycetin (**1a**) and fulvic acid (**2a**), with conc. HCl–AcOH (1:30) gave the chloromethylpyrone (**7b**). Oxidation, followed by demethylation of the substituents of the pyranobenzopyranone obtained by debenzylation and cyclization of the reactive intermediate (**5**), yielded citromycetin (**1a**).

Citromycetin, an antibiotic active on gram-postive bacteria,[2] was first isolated from various strains of *Citromyces* in 1931.[3] About 20 years after its first isolation, Robertson and co-workers[4] determined its structure as (**1a**), but its total synthesis has not been accomplished.[5] There are many reports[6] on the biosynthesis of citromycetin (**1a**), and Hutchinson and co-workers[6b] have proposed that the enetrione (**3a**) is an important intermediate for citromycetin (**1a**). We chose this biogenetic intermediate (**3a**) as the synthetic intermediate for our attempted routes to citromycetin (**1a**) and fulvic acid (**2a**). The β-carbon of the α,α-diacylethylene system (**3a**) is highly electron-deficient because of the two α electron-withdrawing groups, and Michael-type reaction at this β-carbon must occur easily. Futhermore, proper choice of reaction conditions may well result in some selectivity in the cyclization. We have reported that the syntheses of 2-methylpyrano[3,2-*c*][1]-benzopyran-4(5*H*)-one (**1b**)[7] [basic skeleton of citromycetin (**1a**)] and 3,4-dihydro-3-hydroxy-3-methylpyrano[4,3-*b*][1]-benzopyran-10(1*H*)-one (**2b**)[8] [basic skeleton of fulvic acid (**2a**)] were achieved by acid treatment of the enetrione (**3b**), which was regarded as an equivalent of (**3a**), and that regioselective cyclization was dependent on the solvent used. In the preceding paper we have also described the total synthesis of fulvic acid (**2a**)[9] *via* regioselective cyclization of the enedione (**4**) (whose propenyl and methoxy group substituents were chosen so as to be ultimately convertible into carboxy and hydroxy groups) with 5% aqueous HCl–tetrahydrofuran (THF) (1:2). In this paper we report the biomimetic total synthesis of citromycetin (**1a**) *via* highly regioselective cyclization of compound (**4**).[10]



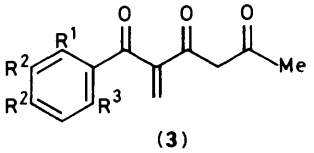
(**1**)

a; $R^1 = CO_2H$, $R^2 = OH$
b; $R^1 = R^2 = H$
c; $R^1 = CH{=}CHMe$, $R^2 = OMe$
d; $R^1 = CHO$, $R^2 = OMe$
e; $R^1 = CO_2H$, $R^2 = OMe$
f; $R^1 = CO_2Me$, $R^2 = OMe$



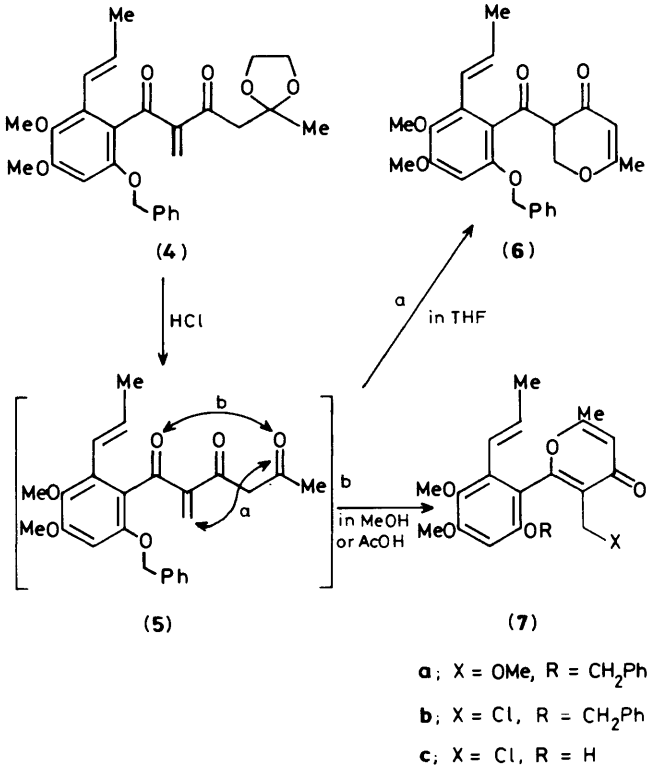
(**2**)

a; $R^1 = CO_2H$, $R^2 = OH$
b; $R^1 = R^2 = H$



(**3**)

a; $R^1 = CO_2H$, $R^2 = R^3 = OH$
b; $R^1 = R^2 = H$, $R^3 = OCH_2Ph$

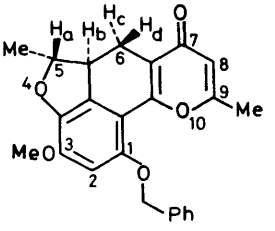


a; X = OMe, R = CH_2Ph
b; X = Cl, R = CH_2Ph
c; X = Cl, R = H

Scheme 1.

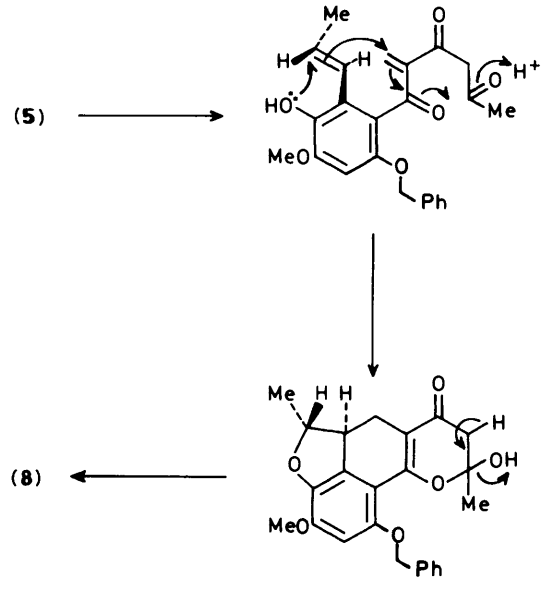
The enedione (**4**) was treated with conc. HCl–MeOH (1:30) to give the expected methoxymethylpyrone (**7a**) in 85% yield (Scheme 1). The structure (**7a**) was confirmed by a dienone olefinic proton signal (δ 6.12).[11] Thus in addition to the result[1] reported in the preceding paper, perfect regioselective cyclization was established in the acid-catalysed cyclization of dione (**4**) in a similar manner to that of (**3b**).[7,8] Of course, under these conditions prior hydrolysis of the acetal group in (**4**) must take place. Condensation between the ene and the terminal acetyl ketone in intermediate (**5**) takes place in a relatively weak nucleophilic solvent, such as THF, to form the benzoylpyrone

(6). In contrast, in methanol, a relatively strong nucleophilic solvent, the cyclization is initiated by the Michael-type addition of methanol to the ene, followed by condensation between the benzoyl and the acetyl ketones to afford compound (**7a**). These results show that alternative enzymic-type selectivities can be achieved with simple laboratory reagents. Use of a more labile phenol-protecting group would be expected to lead to spontaneous double cyclization to afford the tricyclic pyranobenzopyrone (**1c**). However, attempts to introduce an *exo*-methylene group to the dione having a methoxyethoxymethyl group instead of a benzyl group into (**4**) (no *exo*-methylene group) were unsuccessful. In order to use the methoxymethylpyrone (**7a**) for the total synthesis of citromycetin, the chloro compound (**7b**) was required to be formed.[7] Hence, nucleophilic halide attack to the ene was considered worthy of investigation. Fortunately, treatment of enedione (**4**) with conc. HCl–AcOH (1:10) gave the chloromethylpyrone (**7b**) in 68% yield,



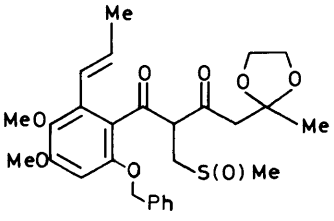
(**8**)

accompanied by the tetracyclic furan (**8**) (19%). The structure (**7b**) was determined by exact mass ^{1}H n.m.r. signals due to chloromethyl group (δ 4.23) and a dienone olefinic proton (δ 6.23).[11] Since nuclear Overhauser effect (n.O.e.) are observed between furan-Me and H_b in the ^{1}H n.m.r. spectrum of compound (**8**), two protons, H_b and H_a, are in a *trans*

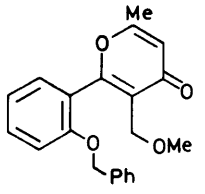


Scheme 2.

configuration. The formation of compound (**8**) is explained as shown in Scheme 2. Under these conditions demethylation of the methoxy group *ortho* to the propenyl group competes with chloride attack on the methylene group by hydrochloric acid, and the hydroxy group in the resulting phenol condenses with the methylene group through the (*E*)-propenyl (*J* 15.9 Hz) in a concerted manner to give product (**8**). More conveniently, the sulphinyl compound (**9**),[1] the precursor of compound (**4**), was treated under the same conditions to yield compounds (**7b**) (73%) and (**8**) (22%). In both cases the ratio of the products is similar and the cyclizations result from condensation between the benzoyl and acetyl ketones. The fact that demethylation occurs by mild acid treatment led to the conclusion that demethylation might take place under conditions similar to



(**9**)



(**10**)

those for the conversion of the methoxy group in compound (**10**) into a bromo substituent. Thus debenzylation of compound (**7b**) with BF_3·OEt_2Me_2S[12] gave the phenol (**7c**), which on base treatment afforded tricyclic pyranobenzopyran (**1c**) in 61% yield from (**7b**). Conversion of the substituents on the benzene ring was accomplished in a somewhat more straightforward manner than in the synthesis of fulvic acid (**2a**).[1] Ozonolysis of compound (**1c**) in the presence of a dye (Oil Violet)[13] gave the aldehyde (**1d**) in 64% yield. The aldehyde (**1d**) was converted into the carboxylic acid (**1e**) by treatment with sulphamic acid and sodium chlorite.[14] Methylation of acid (**1e**) with diazomethane led to the methyl ester (**1f**), whose spectral data were identical with those reported for methyl *O,O*-dimethylcitromycetin (dimethylcitromycetin methyl ester).[15] Finally demethylation of the acid (**1e**) with $AlCl_3$–Me_2S[16] afforded citromycetin (**1a**). Thus the total synthesis of citromycetin (**1a**) was achieved *via* biomimetic cyclization of enetrione (**5**). The physical and spectral data for synthetic citromycetin (**1a**) were identical with those of natural citromycetin.

Experimental

M.p.s were measured on a Yanako micro-melting-point apparatus and are uncorrected. All extracts were dried over anhydrous magnesium sulphate. Column chromatography was carried out on Silicic Acid (100 mesh; Mallinckrodt). I.r. spectra were recorded on a JASCO IR-810 spectrophotometer. U.v. spectra were recorded with a Hitachi Model 200-10 spectrophotometer. Mass spectra were taken on a Shimazu LKB-9000 mass spectrometer and high-resolution mass spectra with a JEOL JMS-01SG instrument. N.m.r. spectra were obtained with a JEOL JMN-GX 270 spectrometer (tetramethylsilane as internal reference).

2-[6-*Benzyloxy*-3,4-*dimethoxy*-2-(*prop*-1-*enyl*)*phenyl*]-3-*methoxymethyl*-6-*methyl*-4H-*pyran*-4-*one* (**7a**).—To a solution of 1-[6′-benzyloxy-3′,4′-dimethoxy-2′-(prop-1-enyl)phenyl]-4-(2-methyl-1,3-dioxolan-2-yl)-2-methylenebutane-1,3-dione (**4**) (307 mg, 0.66 mmol) in MeOH (30 ml) was added conc. HCl (1.0 ml) dropwise and the resulting solution was stirred for 20 h at ambient temperature. The reaction mixture was poured into saturated aqueous NaCl (30 ml), and extracted with AcOEt (60 ml × 2).The extract was washed with saturated aqueous NaCl (20 ml × 3), dried, and evaporated to give the title pyran-4-one (**7a**) (245 mg, 85%), *m/z* 436 (M^+); δ($CDCl_3$) 1.73 (3 H, d, *J* 6.0 Hz, =CMe), 2.11 (3 H, s, 6-Me), 3.10 (3 H, s, CH_2OMe), 3.68 (3 H, s, OMe), 3.81 (3 H, s, OMe), 4.05 (2 H, s, CH_2OMe), 5.01 (2 H, s, CH_2Ph), 6.00—6.24 (2 H, m, CH=CH), 6.12 (1 H, s, 5-H), 6.56 (1 H, s, ArH), and 7.19 (5 H, s, Ph).

2-[6-*Benzyloxy*-3,4-*dimethoxy*-2-(*prop*-1-*enyl*)*phenyl*]-3-*chloromethyl*-6-*methyl*-4H-*pyran*-4-*one* (**7b**).—*Method A*. A solution of compound (**4**) (135 mg, 0.29 mmol) and conc. HCl (0.1 ml) in AcOH (1 ml) was stirred for 24 h at ambient temperature. The reaction mixture was poured into ice–water (10 ml), and extracted with AcOEt (20 ml × 2). The extract was washed with water (10 ml × 3), dried, and evaporated. The resulting residue was subjected to column chromatography. The first fraction eluted with $CHCl_3$ gave the *title pyran*-4-*one* (**7b**), whose recrystallization from benzene–hexane afforded needles (87 mg, 68%), m.p. 137—139 °C (Found: C, 67.6; H, 5.8%; M^+, 440.1399. $C_{25}H_{25}ClO_5$ requires C, 68.10; H, 5.72% *M*, 440.1389); $\nu_{max.}$(KBr) 1 670, 1 625, and 1 602 cm^{-1}; δ($CDCl_3$) 1.76 (3 H, d, *J* 6.3 Hz, =CMe), 2.23 (3 H, s, 6-Me), 3.73 (3 H, s, OMe), 3.87 (3 H, s, OMe), 4.23 (2 H, s, CH_2Cl), 5.05 (2 H, s, CH_2Ph), 6.09 (1 H, dq, *J* 15.9 and 6.3 Hz, =C*H*Me), 6.23 (1 H, s, 5-H), 6.25 (1 H, d, *J* 15.9 Hz, =C*H*Ar), 6.52 (1 H, s, ArH), and 7.27—7.33 (5 H, m, Ph); δ_C($CDCl_3$) 19.5 (=C*Me*), 19.8 (6-Me), 37.3 (CH_2Cl), 56.0 (OMe), 60.4 (OMe), 71.2 (CH_2O), 97.3 (arom. C-5), 113.9 (C-5), 123.5 (=CAr), 126.8, 128.0, 128.6 (arom. Cs), 133.2 (=*C*Me), 141.1, 153.1, 155.2 (arom. C-3, -4, -6), and 162.3, 166.0, 178.1 (C-2, -6, -4).

Further elution with AcOEt–$CHCl_3$ (5:95 v/v) gave 1-*benzyloxy*-5a,b-*dihydro*-3-*methoxy*-5,9-*dimethylbenzofuro*[3,4-gh]-[1]*benzopyran*-7(5H)-*one* (**8**) (22 mg, 19%), m.p. 220—223 °C (from benzene) (Found: C, 73.5; H, 5.7%; M^+, 390.1504. $C_{24}H_{22}O_5$ requires C, 73.83; H, 5.68%; *M*, 390.1466); $\nu_{max.}$(KBr) 1 655, 1 638, and 1 600 cm^{-1}; δ($CDCl_3$) 1.62 (3 H, d, *J* 6.0 Hz, CH*Me*, 10% n.O.e. with H_b), 2.15 (3 H, s, =CMe), 2.23 (1 H, dd, *J* 14.8 and 14.8 Hz, H_d, 14% n.O.e. with H_a), 3.21 (1 H, ddd, *J* 14.8, 10.3, and 7.1 Hz, H_b), 3.40 (1 H, dd, *J* 14.8 and 7.1 Hz, H_c), 3.93 (3 H, s, OMe), 4.70 (1 H, dq, *J* 10.3 and 6.0 Hz, H_a), 5.06 (2 H, ABq, *J* 11.5 Hz, CH_2O), 6.11 (1 H, s, =CH), 6.41 (1 H, s, ArH), and 7.34—7.50 (5 H, m, Ph); δ_C($CDCl_3$) 19.4 (CH*Me*), 19.6 (=C*Me*), 23.4 ($CHCH_2$), 44.3 (*C*HCH_2), 56.6 (OMe), 72.1 (*C*H_2Ph), 90.6 (O*C*HMe), 100.0 (arom. C), 113.3 (=CH), 127.4, 128.1, 128.4 (arom. Cs), and 178.7 (CO).

Method B. A solution of 1-[6-benzyloxy-3,4-dimethoxy-2-(prop-1-enyl)phenyl]-4-(2-methyl-1,3-dioxolan-2-yl)-2-(methylsulphinylmethyl)butane-1,3-dione (**9**) (5.012 g, 9.46 mmol) and conc. HCl (2 ml) in AcOH (50 ml) was stirred for 24 h at ambient temperature. Work-up as above gave compounds (**7b**) (3.02 g, 73%) and (**8**) (0.81 g, 22%).

3-*Chloromethyl*-2-[6-*hydroxy*-3,4-*dimethoxy*-2-(*prop*-1-*enyl*)-*phenyl*]-6-*methyl*-4H-*pyran*-4-*one* (**7c**).—To a solution of the protected phenol (**7b**) (3.00 g, 6.79 mmol) in CH_2Cl_2 (100 ml) at −40 °C were added Me_2S (40 ml) and BF_3·OEt_2 (5 ml). The reaction mixture was stirred for 42 h at ambient temperature, poured into saturated aqueous NaCl (100 ml), and extracted with AcOEt (100 ml × 2). The extract was washed with saturated aqueous NaCl (20 ml × 3), dried, and evaporated. Recrystallization of the resulting crystalline residue from pentane–Et_2O gave the *title pyran*-4-*one* (**7c**) (2.12 g, 89%) as yellow needles, m.p. 187—190 °C; *m*/*z* (M^+) 350.9018 ($C_{18}H_{19}ClO_5$ requires *M*, 350.0920); $\nu_{max.}$(KBr) 3 000, 1 660, and 1 590 cm^{-1}; δ($CDCl_3$) 1.75 (3 H, dd, *J* 6.4 and 1.5 Hz, (=CH*Me*), 2.28 (3 H, s, 6-Me), 3.73 (3 H, s, OMe), 3.88 (3 H, s, OMe), 4.31 (2 H, s, CH_2Cl), 6.03 (1 H, dq, *J* 16.3 and 6.4 Hz, =C*H*Me), 6.23 (1 H, dq, *J* 16.3 and 1.5 Hz, =C*H*Ar), 6.26 (1 H, s, 5-H), and 6.56 (1 H, s, ArH).

8,9-*Dimethoxy*-2-*methyl*-10-(*prop*-1-*enyl*)*pyrano*[3,2-c][1]-*benzopyran*-4(5H)-*one* (**1c**).—To a solution of the phenol (**7c**) (1.65 g, 4.71 mmol) in MeOH (100 ml) at 0 °C was added saturated aqueous $NaHCO_3$ (20 ml). The reaction mixture was stirred for 6 h at ambient temperature, and concentrated to one-quarter of its original volume and extracted with Et_2O (50 ml × 2). The extract was washed with water (30 ml × 3), dried, and evaporated. The residue was subjected to column chromatography ($CHCl_3$ as eluant) to give crystalline material, whose recrystallization from n-hexane–benzene gave the *title compound* (**1c**) (1.20 g, 69%) as needles, m.p. 119—122 °C (Found: C, 68.6; H, 5.9. $C_{18}H_{18}O_5$ requires C, 68.78; H, 5.77%); *m*/*z* 314 (M^+); $\nu_{max.}$(KBr) 1 670 and 1 620 cm^{-1}; δ($CDCl_3$) 1.92 (3 H, dd, *J* 6.3 and 1.5 Hz, =CH*Me*), 2.27 (3 H, s, 2-Me), 3.70 (3 H, s, OMe), 3.88 (3 H, s, OMe), 5.06 (2 H, s, 5-H_2), 5.98 (1 H, dq, *J* 15.0 and 6.3 Hz, =C*H*Me), 6.14 (1 H, s, 3-H), 6.46 (1 H, s, 7-H), and 6.58 (1 H, dq, *J* 15.0 and 1.5 Hz, =C*H*Ar); δ_C($CDCl_3$) 19.1 (=C*Me*), 19.8 (2-Me), 56.0 (OMe), 60.3 (OMe),62.5 (C-5), 99.6 (C-7), 113.9 (=*C*Ar), 124.3 (C-3), 131.7 (=*C*Me), 142.2, 155.7, 156.7, 157.3, 164.0 (C-6a, -8, -9, -2, -10b), and 176.3 (C-4).

8,9-*Dimethoxy*-2-*methyl*-4-*oxo*-4H,5H-*pyrano*[3,2-c][1]-*benzopyran*-10-*carbaldehyde* (**1d**).—A stirred solution of compound (**1c**) (960 mg, 2.87 mmol) and Oil Violet (3 mg) in ethanol (200 ml) was ozonolysed at −75 °C. When the red colour of the reaction mixture had been discharged, the flow of ozone was stopped and nitrogen was flushed into the mixture. Dimethyl sulphide (30 ml) was added to the mixture, which was stirred for a further 30 min. The solvent was distilled off, water (30 ml) was added to the resulting residue, and the mixture was extracted with AcOEt (100 ml × 2). The extract was washed with water (20 ml × 3), dried, and evaporated. Application to column chromatography ($CHCl_3$ as eluant) and recrystallization (from benzene) of the residue gave the *title aldehyde* (**1d**) (555 mg, 64%) as needles, m.p. 215—216.5 °C; *m*/*z* (M^+) 302.0803 ($C_{16}H_{14}O_6$ requires *M*, 302.0789); $\nu_{max.}$(KBr) 3 080, 2 960, 1 700, and 1 680 cm^{-1}; δ($CDCl_3$) 2.26 (3 H, s, 2-Me), 3.88 (3 H, s, OMe), 3.92 (3 H, s, OMe), 5.14 (2 H, s, 5-H_2), 6.14 (1 H, s, 3-H), 6.67 (1 H, s, 7-H), and 10.49 (1 H, s, CHO).

O,O-*Dimethylcitromycetin* (**1e**).—To a solution of the aldehyde (**1d**) (555 mg, 1.84 mmol) in THF (80 ml) was added a solution of sulphamic acid (400 mg) and sodium chlorite (400 mg) in water (20 ml). The reaction mixture was stirred for 24 h at ambient temperature, poured into saturated aqueous NaCl (40 ml), and extracted with AcOEt (80 ml × 2). The extract was washed with water (20 ml × 3), dried, and evaporated. Column chromatography (AcOEt–$CHCl_3$ as eluant) and recrystallization (from ethanol) of the residue gave O,O-*dimethylcitromycetin* (**1e**) (387 mg, 66%) as prisms, m.p. 289—292 °C (decomp.); *m*/*z* (M^+) 318.0742 ($C_{16}H_{14}O_7$ requires *M*, 318.0739); $\nu_{max.}$(KBr) 3 700—2 500, 1 715, 1 660, and 1 600 cm^{-1}; δ([$^2H_5$]pyridine) 2.01 (3 H, s, 2-Me), 3.75 (3 H, s, OMe), 3.97 (3 H, s, OMe), 5.20 (2 H, s, 5-H_2), 6.07 (1 H, s, 3-H), and 6.59 (1 H, s, 7-H); δ_C ([$^2H_5$]pyridine–$CDCl_3$ 1:1) 18.8 (2-Me), 56.0 (OMe), 61.8 (OMe), 63.2 (C-5), 101.8 (C-7), 114.1 (C-3), 104.9, 112.3, 128.4 (C-4a, -10, -10a), 141.4, 154.8, 155.0, 156.9, 164.3 (C-6a, -8, -9, -10b, -2), 168.9 (CO_2H), and 175.7 (C-4).

O,O-*Dimethylcitromycetin Methyl Ester* (**1f**).—A solution of *O*,*O*-dimethylcitromycetin (**1e**) (73 mg, 0.23 mmol) in MeOH (8 ml) was added to a ethereal solution of diazomethane (50 ml) and the mixture was stirred for 2 h at ambient temperature. Excess of diazomethane was decomposed with AcOH, and the resulting mixture was distilled to dryness. The residue was dissolved in AcOEt (20 ml), and the solution was washed with saturated aqueous NaCl (10 ml × 3). The organic layer was dried and evaporated, and the crystalline residue was recrystallized from EtOH–Et_2O to give O,O-*dimethylcitromycetin methyl ester* (**1f**) (62 mg, 81%) as plates, m.p. 174—176 °C (lit.,[3] 178 °C) (Found: C, 61.2, H, 4.8. $C_{17}H_{16}O_7$ requires, C, 61.44, H, 4.86%); *m*/*z* 332 (M^+); $\nu_{max.}$(KBr) 1 737, 1 666, 1 625, and 1 595 cm^{-1}; $\lambda_{max.}$(EtOH) 251 log ε (4.22), 294 (3.93), and 353 nm (4.16); δ($CDCl_3$) 2.27 (3 H, s, Me), 3.83 (3 H, s, OMe), 3.89 (3 H,

s, OMe), 3.96 (3 H, s, OMe), 5.16 (2 H, s, 5-H_2), 6.12 (1 H, s, 3-H), and 6.56 (1 H, s, 7-H).

Citromycetin (**1a**).—To a solution of *O,O*-dimethylcitromycetin (**1e**) (40 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (50 ml) at −25 °C were added Me_2S (5 ml) and then $AlCl_3$ (310 mg). The reaction mixture was stirred for 15 h at ambient temperature. Water (50 ml) was added to the reaction mixture, and the separated aqueous layer was washed with Et_2O (80 ml × 3), treated with 5% HCl (15 ml), and extracted with AcOEt (90 ml × 2). The extract was washed with saturated aqueous NaCl (30 ml × 3), dried, and evaporated. The resulting yellow crystalline material was recrystallized from Et_2O-EtOH to give *citromycetin* (**1a**) (25 mg, 69%) as yellow needles, m.p. 271—273 °C (lit.,[3] 283—285 °C decomp.) (Found: C, 57.8; H, 3.6%; M^+, 290.0422. Calc. for $C_{14}H_{10}O_7$: C, 57.93; H, 3.48%; *M*, 290.0425); $\nu_{max.}$(KBr) 3 650—2 400, 1 703, and 1 660 cm^{-1}; $\lambda_{max.}$(EtOH) 257 log ε (3.97), 304 (3.83), and 379 nm (4.03); δ(CD_3OD) 2.33 (3 H, s, 2-Me), 5.00 (2 H, s, 5-H_2), 6.20 (1 H, s, 3-H), and 6.51 (1 H, s, 7-H); δ_C(CD_3OD) 19.2 (2-Me), 63.3 (C-5), 105.3 (C-10a), 105.7 (C-7), 112.5 (C-4a), 114.2 (C-3), 118.1 (C-10), 141.7 (C-9), 153.0 (C-8), 153.7 (C-6a), 158.4 (C-10b), 167.4 (C-2), 171.2 (CO_2H), and 178.4 (C-4).

Acknowledgements

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