C-Nucleoside Studies. Part 7.[1,2] A New Synthesis of Showdomycin, 2-β-D-Ribofuranosylmaleimide

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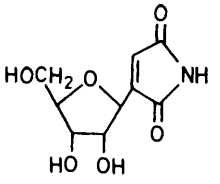
Showdomycin, 2-β-D-ribofuranosylmaleimide (1), has been prepared in six stages from 2,3,5-tri-*O*-benzyl-β-D-ribofuranosylethyne (2) in 23% overall yield (8% from D-ribose). Dimethoxycarbonylation of (2) afforded the substituted maleic ester (4) which was converted, in two stages, into the crystalline anhydride (10). Ammonolysis followed by ring-closure gave the crystalline maleimide (13), which was debenzylated with boron trichloride to give showdomycin.

SHOWDOMYCIN, 2-β-D-ribofuranosylmaleimide (1), was first isolated from *Streptomyces showdoensis* by Nishimura

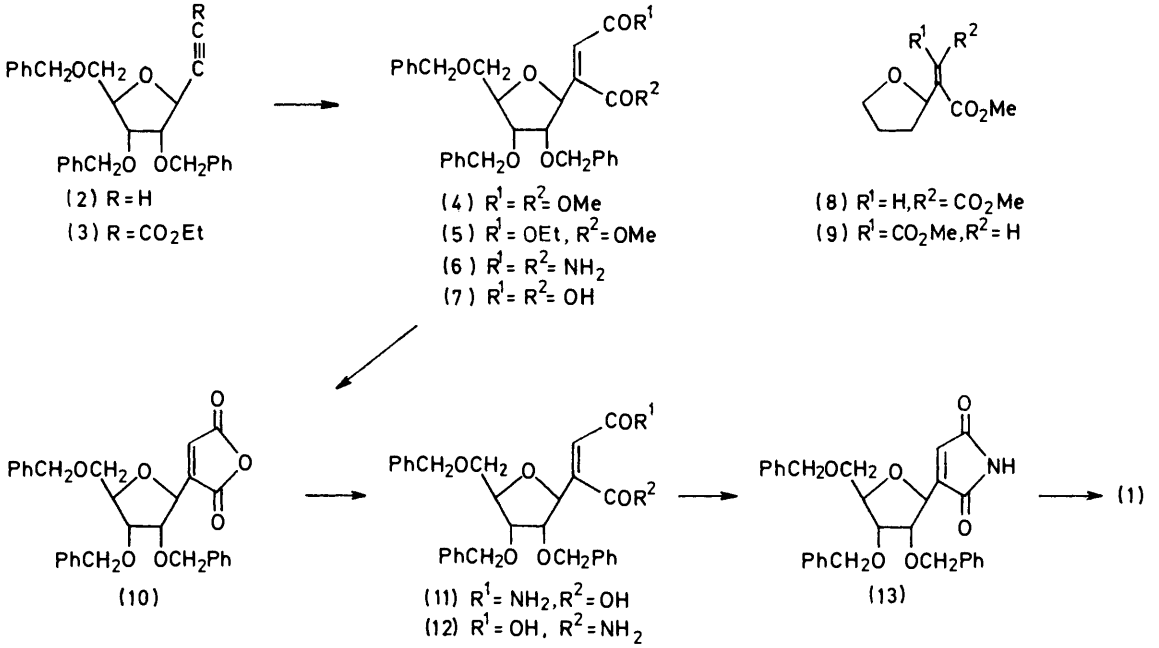


(1)

et al.[3] and shown to have antibiotic [3] and antitumour [4] activity. The structure of showdomycin was established in 1967 [5-7] and was shown to belong to the group of *C*-nucleoside antibiotics.[8-10]

(2), and to study the conjugate addition of cyanide ion [21] or an alkyl isocyanide [22,23] to the triple bond. We experienced great difficulty in obtaining the acetylenic ester (3) and although this problem has now been solved [1,24-27] we have achieved our objective in a different way.

In 1972 Heck described the conversion of terminal acetylenes into maleic esters using carbon monoxide under mild conditions.[28] When the ethyne (2) was treated, in methanol solution, with carbon monoxide (2 atm.) in the presence of palladium chloride and mercuric chloride the diester (4) could be isolated as a pure syrup in 80% yield after chromatography.[2] The structure was assigned unambiguously by analysis and spectroscopic data. In particular, the ^{1}H n.m.r. spectrum was



(2) R = H
(3) R = CO_2Et
(4) $R^1 = R^2 = OMe$
(5) $R^1 = OEt$, $R^2 = OMe$
(6) $R^1 = R^2 = NH_2$
(7) $R^1 = R^2 = OH$
(8) $R^1 = H$, $R^2 = CO_2Me$
(9) $R^1 = CO_2Me$, $R^2 = H$
(10)
(11) $R^1 = NH_2$, $R^2 = OH$
(12) $R^1 = OH$, $R^2 = NH_2$
(13)

The synthesis of showdomycin [2,11-15] and some closely related analogues [16-18] has attracted several groups of investigators.[19] In the three successful syntheses of showdomycin itself [11-13] a stabilised Wittig reagent was used to complete the maleic acid portion of the molecule. Our own approach has been to utilise the protected ribofuranosylethyne (2),[2,20] and to construct the remainder of the maleimide ring by addition to the triple bond.

Originally we intended to prepare the ester (3), by conventional carboxylation reactions from the ethyne

very similar to that reported [12] for the ester (5). The maleate stereochemistry was expected,[28] and was confirmed by comparison of the allylic coupling constant $J_{1',3}$ (1.5 Hz) in (4) with those quoted for (5),[12] (8),[29] and (9) [29] (2.0, 2.0, and 0.5 Hz, respectively).

Attempts were made to convert the diester (4) into the diamide (6) or even, hopefully, into the maleimide (13) by treatment with ammonia [30] in methanol or ether. In both cases, the reaction was complex and several products could be detected by t.l.c. It seems clear that

Michael addition to the double bond took place in preference to amide formation, followed by more complex reactions.

The diester (4) was converted into the maleic acid (7) by hydrolysis with potassium hydroxide in aqueous dioxan. The diacid was not purified, and was directly converted into the crystalline anhydride (10) by treatment with either trifluoroacetic anhydride or acetic anhydride. The yield of (10) based on diester (4) was 81%. The ^{1}H n.m.r. spectrum of the anhydride (10) showed a marked similarity to that of the imide (13),[12] as expected.

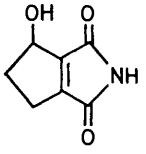
The anhydride (10) reacted readily with ammonia in ether to produce the maleamic acid [(11) and/or (12)] whose precise structure was not determined (see later). Of the methods employed to effect ring closure (Table)

Yield of crystalline imide (13) by cyclisation of maleamic acid [(11) or (12)]

Reagent	Reaction conditions	Yield (%)
Ethyl polyphosphate [a] (20% in DMF)	DMF; 80°; 3 h	26
MeCOCl [b]	DMF; room temp.; 20 h	55
P_2O_5 [a,b]	DMF; 80°; 2 h	very low (t.l.c.)
$(CF_3CO)_2O$ [c]	room temp.; 20 h	30 [d]
Me_3CCOCl	DMF; room temp.; 20 h	36
$MeSO_2Cl$	DMF; room temp.; 20 h	27

[a] Ref. 11. [b] Ref. 31. [c] Ref. 32. [d] Another major product was also formed, possibly a trifluoroacetate.

the best (55% yield) was treatment with acetyl chloride (30 mol. equiv.) in *NN*-dimethylformamide (DMF).[31] Trifluoroacetic anhydride, used in the synthesis [32] of



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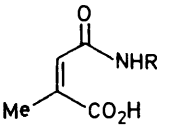

(15) R = Pr^n

(16) R = $NHOCH_2Ph$

maleimycin (14), gave promising results but appeared to cause partial debenzylation.

Removal of the protecting groups using boron trichloride in dichloromethane [12,16] gave showdomycin (1) in 65% yield, identified by direct comparison with a sample provided by Dr. J. Farkaš. The overall yield of showdomycin from the ethyne (2) was 23% (8% from D-ribose [20]).

Although the regioselectivity of the ammonolysis of (10) is probably unimportant for synthesis of showdomycin it is likely that the maleamic acid intermediate is (11) rather than (12). 2-Methylmaleic anhydride is known to react with primary amines in ether to give mainly the isomer with the amide group remote from the methyl substituent [as in (15) [33] and (16) [34]]. It is interesting that the opposite regioselectivity is shown by alkoxides,[35] hydride reagents,[36] trimethylsilyl azide,[37] and certain carbanions [38] in reactions with 2-methylmaleic anhydride, but that stabilised Wittig reagents [36] behave with the same regioselectivity as amines. Dunitz [39] has pointed out the nature of steric effects in similar cyclic systems.

EXPERIMENTAL

General methods are outlined in Parts 2 and 6.[1] Light petroleum refers to the fraction of b.p. 40—60°.

Dimethyl 2-(2,3,5-Tri-O-benzyl-β-D-ribofuranosyl)maleate (4).—The ethyne (2) [20] (350 mg), palladium chloride (147 mg, 1.01 mol. equiv.), and mercuric chloride (223 mg, 1.01 mol. equiv.) were suspended in dry methanol (30 ml) in a Schlenk tube (100 ml capacity). The tube was evacuated, filled with carbon monoxide (2 atm.), and the mixture stirred vigorously overnight. The carbon monoxide was displaced with air, the precipitated palladium removed by filtration using Celite, and the filtrate evaporated. The syrupy residue was dissolved in ether (50 ml) and extracted with saturated aqueous potassium hydrogen carbonate (2 × 25 ml) followed by water (3 × 25 ml). The ether layer was dried (Na_2SO_4) and evaporated to leave a pale yellow syrup (404 mg). Chromatography on silica gel (12 g) and elution with light petroleum–ether (3 : 1) gave the *diester* (4) (357 mg, 80%), $[\alpha]_D^{20}$ +6.23° (*c* 1.92 in $CHCl_3$), as a homogeneous syrup; $\nu_{max.}$ (film) 1 735 cm^{-1} (C=O); δ(100 MHz; $CDCl_3$), 3.56 (2 H, t), 3.68 and 3.72 (both 3 H, s, OMe), 3.88—4.12 (2 H, m), 4.2—4.4 (1 H, m), 4.49 (4 H, s, CH_2Ph), 4.56 (2 H, s, CH_2Ph), 4.75 (1 H, dd, $J_{1',2'}$ 4.5 Hz, $J_{1',3}$ 1.5 Hz), 6.33 (1 H, d, $J_{1',3}$ 1.5 Hz, H-3), and 7.3 (15 H, m, Ph); *m/e* 546w (*M*), 515w (*M* − OCH_3), and 455s (*M* − C_7H_7) (Found: C, 70.3; H, 6.1. $C_{32}H_{34}O_8$ requires C, 70.3; H, 6.3%).

2-(2,3,5-Tri-O-benzyl-β-D-ribofuranosyl)maleic Anhydride (10).—To a solution of the dimethyl ester (4) (462 mg) in pure 1,4-dioxan (20 ml) was added solid potassium hydroxide (188 mg, 4 mol. equiv.) and water (4 ml). The mixture was stirred for 1.5 h, solid potassium hydroxide (188 mg, 4 mol. equiv.) added, and stirring continued for a further 22.5 h. After acidification with hydrochloric acid (2M; 5 ml) the product was extracted with chloroform (2 × 25 ml). Evaporation followed by drying of the residue by co-evaporation with dry benzene, afforded the crude diacid (7) (438 mg, 100%); $\nu_{max.}$ (film) 1 720 cm^{-1} (C=O); δ(100 MHz; $CDCl_3$) 3.90—4.94 (12 H, m), 6.68 (1 H, s, H-3), 7.32 (15 H, s, Ph), and 7.84 (2 H, br s, exchangeable, CO_2H); *m/e* 500m (*M* − H_2O), 456m (*M* − H_2O − CO_2), and 409s (*M* − H_2O − C_7H_7).

When the crude dicarboxylic acid (7) (60 mg) was stirred with trifluoroacetic anhydride (10 ml) at room temperature for 0.25 h a crystalline precipitate separated. Excess of reagent and trifluoroacetic acid were removed by evaporation and the residue was recrystallised from ether–light petroleum to give the *anhydride* (10) (45 mg, 77%), m.p. 95—96°, $[\alpha]_D^{20}$ +69° (*c* 0.07 in ethanol-free $CHCl_3$); $\nu_{max.}$ (KBr) 1 850 and 1 795 cm^{-1} (C=O); δ(100 MHz; $CDCl_3$) 3.55 (1 H, dd, $J_{5'a,5'b}$ 11 Hz, $J_{4',5'a}$ 3 Hz, H-5'a), 3.8 (1 H, dd, $J_{5'a,5'b}$ 11 Hz, $J_{4',5'b}$ 3 Hz, H-5'b), 3.90—4.05 (2 H, m, H-2', H-3'), 4.25—4.75 (7 H, m, $PhCH_2$, H-4'), 5.15 (1 H, dd, $J_{1',2'} = J_{1',3} = 2.5$ Hz, H-1'), 6.9 (H-1, d, $J_{1',3}$ 2.5 Hz, H-3), and 7.25 (15 H, m, Ph); *m/e* 409s (*M* − C_7H_7) (Found: C, 72.0; H, 5.7. $C_{30}H_{28}O_7$ requires C, 72.0; H, 5.6%).

Treatment of the crude dicarboxylic acid (7) (767 mg) with freshly distilled acetic anhydride (15 ml) for 20 h at room temperature, followed by evaporation of the acetic acid and anhydride, afforded the pure maleic anhydride (10) (597 mg,

81%) when crystallised from ether–light petroleum using a seed crystal from the earlier preparation.

2-(2,3,5-*Tri*-O-*benzyl*-β-D-*ribofuranosyl*)*maleimide* (13).—The anhydride (10) (124 mg) was dissolved in dry ether (25 ml) and dry ammonia was bubbled through the solution at 0 °C for 10 min, during which time a white precipitate formed. Evaporation left the crude maleamic acid(s) [(11) and/or (12)] (128 mg), apparently as the free acid(s).

The crude maleamic acid (517 mg) was dissolved in dry *NN*-dimethylformamide (15 ml), acetyl chloride (2.1 ml, *ca.* 30 mol. equiv.) was added, and the mixture stirred at room temperature for 20 h. Water (40 ml) was added and the solution extracted with chloroform (2 × 30 ml). The combined chloroform extracts were evaporated, and the residue was azeotroped with dry xylene to remove the dimethylformamide. The residue was chromatographed on silica gel using a gradient of light petroleum–ether (9 : 1 ⟶ 3 : 1) for elution. Crystallisation of the major product from ether–light petroleum gave the maleimide (13) (275 mg, 55% from the anhydride), m.p. 63—64° (lit.,[12] 64—65°), $[\alpha]_D^{20}$ +93.4° (*c* 0.91 in $CHCl_3$) [lit.,[12] +96° ($CHCl_3$)]; $\nu_{max.}$ (KBr) 3 250, 1 775, 1 725, and 1 637 cm^{-1}; δ (100 MHz; $CDCl_3$) 3.50 (1 H, dd, $J_{5'a,5'b}$ 11 Hz, $J_{4',5'a}$ 3 Hz, H-5'a), 3.70 (1 H, dd, $J_{5'a,5'b}$ 11 Hz, $J_{4',5'b}$ 3 Hz, H-5'b), 3.96 (2 H ,m, H-2' and H-3'), 4.22—4.70 (1 H, dd, $J_{1',2'} = J_{1',3} = 2$ Hz, H-1'), 6.54 (1 H, dd, $J_{1',3} = J_{3,NH} = 2$ Hz, H-3), 7.24 (15 H, m, Ph), and 7.66 (1 H, br s, exchangeable, NH); *m/e* 499m (*M*) and 408s ($M - C_7H_7$) (Found: C, 72.35; H, 6.1; N, 3.1. Calc. for $C_{30}H_{29}NO_6$: C, 72.1; H, 5.8; N, 2.8%).

Yields of (13) from other ring closures are given in the Table.

2-β-D-*Ribofuranosylmaleimide* (1) (*Showdomycin*).—A solution of boron trichloride (*ca.* 6 g, 50 mmol) in dry dichloromethane (15 ml) was cooled to −78 °C (acetone–CO_2 bath) and a chilled solution of the tribenzyl ether (13) (280 mg, 0.56 mmol) in dry dichloromethane (15 ml) was added slowly through a septum. The reaction was stirred at −78 °C for 5 h, when the cooling bath was removed and methanol–dichloromethane (1 : 1; 35 ml) was added dropwise. The mixture was stirred at room temperature for 0.5 h, solvents were removed under reduced pressure, and the residue was coevaporated four times with methanol (30 ml).

The crude product was dissolved in methanol and silica gel was added. After evaporation of the methanol, the silica was made into a slurry with light petroleum and added to the top of a chromatography column of silica gel prepared in light petroleum. Elution with light petroleum–ethyl acetate (5 : 1 ⟶ 1 : 1) removed the less polar impurities. Ethyl acetate–acetone (100 : 1 ⟶ 30 : 1) eluted the major component which crystallised from acetone–ether to give showdomycin (1) (84 mg, 65%), m.p. 152—154° (lit.,[3] 153—154°), $[\alpha]_D^{20}$ +47.1° (*c* 0.425 in H_2O) [lit.,[3] +49.9° (H_2O), indistinguishable (i.r., t.l.c., mixed m.p.) from a sample provided by Dr. J. Farkaš. The ^1H n.m.r. spectrum (100 MHz; CD_3CO_2D–D_2O) closely resembled the published spectrum;[5] *m/e* 211s (*M* − H_2O), 140m (*M* − 89), 126s (base +30) (lit.,[40]) (Found: C, 47.2; H, 4.9; N, 6.0. Calc. for $C_9H_{11}CO_6$: C, 47.2; H, 4.8; N, 6.1%).

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