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AN APPROACH TO THE PYRANONAPHTHOQUINONES*†

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ABSTRACT

Reaction of levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-*glycero*-hex-3-enopyranos-2-ulose) with *o*-xylylene generated from *o*-bis(bromomethyl)benzene by treatment with zinc under ultrasonic irradiation gave 53% of the *exo*-adduct (1*S*,3*R*,4a*R*,10a*S*)-3,11-anhydro-3-hydroxy-1-hydroxymethyl-4-oxo-3,4,5,10-tetrahydronaphtho[2,3-*c*]pyran (**11**) together with small proportions of the tertiary alcohols (1*S*,3*R*,4a*R*,10a*S*)-3,11-anhydro-3,4-dihydroxy-1-hydroxymethyl-4-*C*-(*o*-methylbenzyl)-3,4,5,10-tetrahydronaphtho[2,3-*c*]pyran (**12**) and 1,6-anhydro-3,4-dideoxy-2-*C*-(*o*-methylbenzyl)-β-D-*erythro,threo*-hex-3-enopyranose (**13**). Reduction of **11** afforded the epimeric alcohols **14** and **15** which, on conversion into their xanthates **18** and **19** and treatment with tributyltin hydride, gave the deoxy compound (1*S*,3*R*,4a*R*,10a*S*)-3,11-anhydro-3-hydroxy-1-hydroxymethyl-3,4,5,10-tetrahydronaphtho[2,3-*c*]pyran (**20**), which affords potential access to the pyranonaphthoquinones.

INTRODUCTION

Considerable attention has been paid to annelations of unsaturated carbohydrate derivatives, particularly 2,3-unsaturated pyranosyl compounds bearing carbonyl groups at C-1 (unsaturated lactones)[1] or at C-4 (4-ulosides)[2–6]. In most of the reports, the Diels–Alder reaction has been applied, buta-1,3-diene or substituted derivatives have been used as dienes, and new alicyclic systems have been produced. In one instance[6], benzannelation was achieved by use of 1-(trimethylsilyloxy)butadiene, but only occasional advantage has been taken to produce polycyclic systems containing aromatic rings by this approach. Addition of cyanobenzo-

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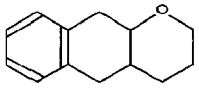
cyclobutene (a source of a reactive *o*-xylylene diene to a glycal derivative, however, gave[7] several isomeric products containing the 3,4,5,10-tetrahydronaphtho[2,3-*b*]-pyran ring system (**1**), and we have reported briefly the synthesis of compounds with the ring systems **2** and **3** which resulted from the additions of appropriate *o*-xylylenes to a 2,3-dideoxyhex-2-enopyranosid-4-ulose[8].



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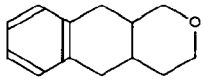

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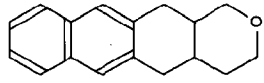

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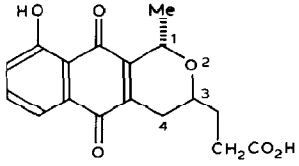
The pyranonaphthoquinones are a family of compounds containing the naphtho[2,3-*c*]pyran ring system **2**, which exhibit antifungal, anti-Gram-negative bacterial, and anticancer activity[9]. The best known member is nanaomycin A (**4**), the Diels–Alder, carbohydrate-based synthesis of which is best planned from a hex-3-enopyranosid-2-ulose derivative since this results in C-6 of the hexose occupying position 1 of the tricyclic system and the anomeric centre taking position 3. In the reaction referred to above, involving the addition of *o*-xylylene to the 2,3-double bond of a hexose derivative[8], the anomeric centre and C-6 take positions 1 and 3, respectively, of the ring system **2**.



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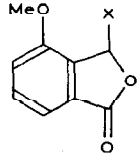
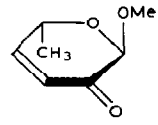


5 X = SO_2Ph
6 X = CN



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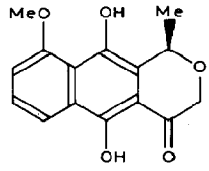

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The merit of hex-3-enopyranos-2-ulose derivatives as starting materials has been recognised by others and, following several syntheses of racemic nanaomycin A (**4**), those of the enantiomers of this and related substances were completed subsequent to the condensation of the carbanion derived from 4-methoxy-3-(phenylsulphonyl)-1(3*H*)-isobenzofuranone (**5**) and methyl 3,4,6-trideoxy-α-D-*glycero*-hex-3-enopyranosid-2-ulose (**7**), which was available in 5 steps from L-

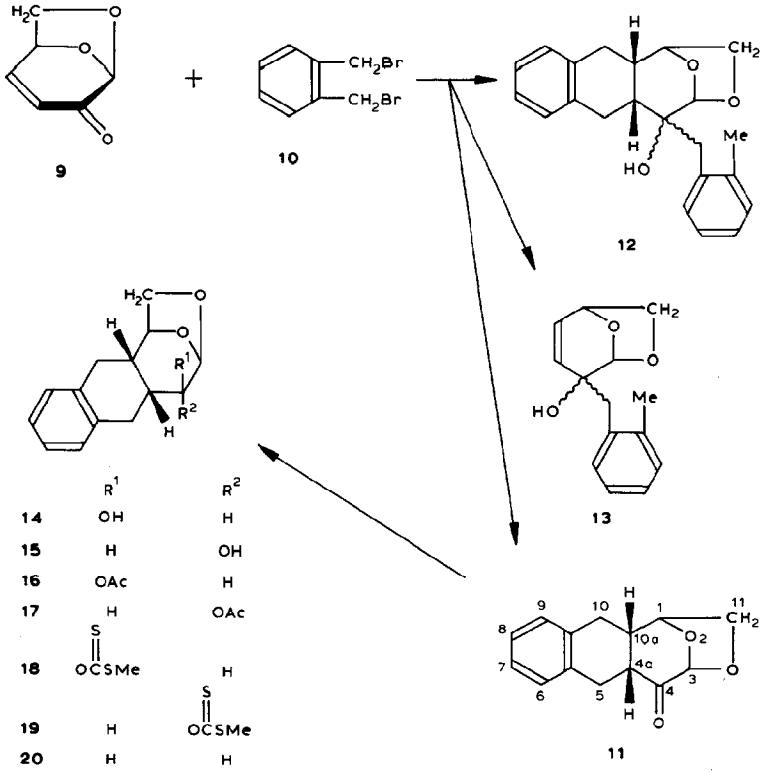
rhamnose[10]. In related vein, and since we reported that the cellulose-degradation product levoglucosenone (**9**) can be annelated with *o*-xylylene to give a crystalline adduct with the correct ring structure[8], Freskos and Swenton[11] have reported making highly oxygenated products (*e.g.*, **8**), which are related to the natural pyranonaphthoquinones, by reaction between **9** and the anion of the 3-cyano-analogue **6**.

We now report details of the reaction between **9** and *o*-xylylene, and conversion of the major product into a compound of potential value for the synthesis of pyranonaphthoquinones.

RESULTS AND DISCUSSION

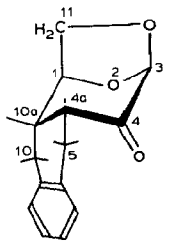
When levoglucosenone (**9**), which was prepared by pyrolysis of cellulose under nitrogen[12], was treated with the dibromide **10** in 1,4-dioxane over zinc powder for 2 h at 25° in an ultrasonic bath[13], it was converted into **11–13** isolated in yields of 53, 3, and 14%, respectively.

The 400-MHz ^{1}H- and ^{13}C-n.m.r. spectra of the major product (**11**) were consistent with the assigned structure; the aromatic and benzylic resonances in



addition to appropriate carbohydrate-derived signals confirmed that a cycloaddition process had occurred. Reduction of **11** with sodium borohydride afforded the epimeric alcohols **14** and **15** isolated in yields of 35 and 50%, respectively, and characterised as their acetates **16** and **17**. Since the epimers **14** and **16** had $J_{4,4a}$ values of 9.8 and 10.6 Hz, respectively, H-4 and H-4a are axial, and the compounds therefore have the D-*altro* configuration. Thus, the cycloaddition reaction to give **11** occurred from the "α" or *exo*-face of the double bond in keeping with the direction of addition of buta-1,3-diene[14], cyclopentadiene[14–16], cyclohexa-1,3-diene, 1,3-diphenylisobenzofuran[14], and 1,2,3,4-tetrachloro-5,5-dimethoxycyclopentadiene[15] to levoglucosenone.

The ^{1}H-n.m.r. spectrum of **11** further indicated that the new ring fused to the carbohydrate moiety adopts the conformation **11a** close to $^{10a}S_{4a}$, with H-10 and H-10a antiperiplanar, and having the carbonyl group exposed in such a way that nucleophilic attack from either direction is not greatly favoured. Reduction, therefore, gave similar proportions of the epimeric alcohols, as occurs also with related ketones derived from levoglucosenone[16].



11a

It is proposed that the by-products **12** and **13** were formed *via* a Reformatsky-like organo-zinc intermediate, the formation of which may have been promoted by the ultrasonic irradiation used in the reaction[17], and which attacked the carbonyl groups of the main product and of levoglucosenone. The minor by-product **12** is taken to have the same stereochemistry at the ring junction as does **11**, on the basis of the close similarity between their respective H-1 and H-10a signals (notably the occurrence of ~12 Hz coupling in the latter), but the configuration at C-4 is undetermined. On the basis of its dextrorotation, the D-*allo* configuration for **12** is favoured; **15** and **17** are dextrorotatory, and the epimers **14** and **16** are levorotatory in keeping with relevant empiricisms[18] and with observations with related compounds[16].

The ^{1}H-n.m.r. spectrum of the major by-product **13** showed that 1,2-addition had occurred at the carbonyl centre, the vinylic protons being intact. Since levoglucosenone normally undergoes carbonyl reaction from the *exo*-direction[15,19], the *threo* configuration is favoured, but no direct evidence is available at present.

Several products were obtained when the ketone **11** was subjected to Wolff–

TABLE I

^{1}H-N.M.R. DATA FOR COMPOUNDS **11, 14–17**[a]

Compound	*Chemical shifts (δ) with coupling constants (Hz) in parentheses*											
	H-1 ($J_{1,10a}$)	*H-3* ($J_{3,4}$)	*H-4* ($J_{4,4a}$)	*H-4a* ($J_{4a,5}$)	*H-5* ($J_{5,5'}$)	*H-5'* ($J_{4a,5'}$)	*H-10* ($J_{10,10a}$)	*H-10'* ($J_{10,10'}$)	*H-10a* ($J_{4a,10a}$) ($J_{10',10a}$)	*H-11* ($J_{1,11}$)	*H-11'* ($J_{1,11'}$) ($J_{11,11'}$)	*Others*
11	4.65 dt (1.6)	5.17 s	—	3.19 dt (4.8)	3.28 dd (16.6)	2.88 dd (8.2)	2.92 dd (11.6)	2.73 dd (15.4)	2.38 m (8.2) (4.7)	4.10 dd (1.2)	4.03 dd (5.0) (7.4)	7.08 m (ArH)
14	4.45 d (<1)	5.32 bs (~1)	3.31 d (9.8)	2.15 m (1.6)	3.05 d (17.2)	2.91 dd (6.6)	3.10 dd (10.8)	2.79 dd (17.0)	2.07 m (~8) (7.0)	3.93 d (0)	3.85 dd (5.0) (7.2)	7.09 m (ArH); 1.67 bs (OH)
15	4.50 dd (1.4)	5.43 d (2.4)	3.59 m (~3)	2.50 m (2.2)	2.92 dd (17.6)	3.09 dd (8.8)	3.22 dd (12.2)	2.84 dd (16.6)	1.92 ddd (6.2) (6.2)	4.00 dd (0)	3.92 ddd (5.1) (7.3)	7.09 m (ArH) 1.0 bs (OH)
16	4.46 dd (2.0)	5.44 d (1.6)	4.61 dd (10.6)	2.55 m (2.1)	2.72 dd (17.3)	2.92 dd (6.9)	3.17 dd (11.1)	2.81 dd (17.0)	2.1 m (~8) (6.6)	4.04 d (0)	3.92 dd (5.1) (7.2)	7.0 m (ArH); 2.1 s (OAc)
17	4.50 dd (2.1)	5.33 d (2.4)	4.90 m (3.2)	2.60 m (1.4)	2.67 dd (17.4)	2.98 dd (8.0)	3.38 dd (11.6)	2.80 dd (16.8)	1.98 ddd (6.0) (6.6)	4.15 dd (0)	3.88 dd (5.0) (7.2)	7.0 m (ArH); 1.37 s (OAc)

[a]Measured at 400 MHz for solutions in $CDCl_3$ (internal $SiMe_4$).

Kishner reduction, and therefore deoxygenation was effected by conversion of the mixed alcohols **14** and **15** into their methyl xanthates which were reductively cleaved by treatment with tributyltin hydride in refluxing toluene to afford compound **20**, which has potential as a synthetic precursor of members of the pyranonaphthoquinone series.

EXPERIMENTAL

General methods. — ^{1}H-N.m.r. spectra were recorded for solutions in $CDCl_3$ with a Bruker WM400 or Varian FT80A instrument as indicated, and ^{13}C-n.m.r. spectra were recorded with the latter. Optical rotations were determined for 0.5–1% solutions in chloroform, using a 1-dm cell and a Perkin–Elmer 241 polarimeter.

Ultrasound irradiation was generated using a Branson laboratory ultrasonic cleaning bath (80 W, 50 kHz) with cooling to maintain 25°. The chromatographic solvent used was light petroleum–ethyl acetate (3:1) unless otherwise indicated.

*Reaction of 1,6-anhydro-3,4-dideoxy-β-*D-glycero-*hex-3-enopyranos-2-ulose* (**9**) *with* o-*xylylene.* — A solution of 1,2-bis(bromomethyl)benzene (10.5 g, 2 mol) in 1,4-dioxane (15 mL) was added to a solution of **9** (2.5 g) in the same volume of solvent over acid-washed zinc powder (6.0 g), and the mixture was maintained for 2 h in the ultrasonic bath at 25°. Only traces of the enone (R_F 0.25) remained, and a major product (R_F 0.50) and two minor products (R_F 0.63 and 0.42) had been formed. Filtration was carried out using Celite, and the filtrate was diluted with dichloromethane (100 mL), washed with water (2 × 100 mL), dried, and concentrated under reduced pressure, to give a syrup which was fractionated on a column of silica gel to afford **11**–**13**.

(1*S*,3*R*,4a*R*,10a*S*)-3,11-Anhydro-3,4-dihydroxy-1-hydroxymethyl-4-*C*-(*o*-methylbenzyl)-3,4,5,10-tetrahydronaphtho[2,3-*c*]pyran (**12**; 0.12 g, 3%) had R_F 0.63, m.p. 133–134° (from ethanol), $[\alpha]_D$ +74°. N.m.r. data: ^{1}H (80 MHz), δ 1.58 (s, 1 H, OH), 1.80 (m, 1 H, H-10a), 2.38 (s, 3 H, Me), 2.7–3.2 (m, 7 H, H-4a,5,5′,10,10′, CH_2-4), 3.8–3.9 (m, 2 H, CH_2-1), 4.45 (m, 1 H, H-1), 5.01 (s, 1 H, H-3), 7.0–7.2 (m, 8 H, ArH); ^{13}C, δ 20.2 (Me), 27.2, 32.1, 32.9 (C-5,10, CH_2-4), 37.9, 38.4 (C-4a,10a), 68.2 (C-11), 74.7 (C-4), 77.0 (C-1), 103.1 (C-3), 125.4–138.2 (ArC).

Anal. Calc. for $C_{22}H_{24}O_3$: C, 78.6; H, 7.2. Found: C, 78.4; H, 7.3.

(1*S*,3*R*,4a*R*,10a*S*)-3,11-Anhydro-3-hydroxy-1-hydroxymethyl-4-oxo-3,4,5,10-tetrahydronaphtho[2,3-*c*]pyran (**11**; 2.42 g, 53%) had R_F 0.50, m.p. 70–71° (from ethanol), $[\alpha]_D$ −50°. N.m.r. data: ^{1}H (see Table I); ^{13}C, δ 26.1, 31.1 (C-5,10), 38.8, 42.2 (C-4a,10a), 68.0 (C-11), 77.5 (C-1), 101.2 (C-3), 201.6 (C-4), 126.0–136.5 (ArC).

Anal. Calc. for $C_{14}H_{14}O_3$: C, 73.0; H, 6.1. Found: C, 72.8; H, 6.0.

1,6-Anhydro-3,4-dideoxy-2-*C*-(*o*-methylbenzyl)-β-D-*erythro,threo*-hex-3-enopyranose (**13**; 0.65 g, 14%) had R_F 0.42, $[\alpha]_D$ −90° (dichloromethane). N.m.r. data: ^{1}H (80 MHz), δ 2.36 (s, 3 H, Me), 2.44 (s, 1 H, OH), 2.94, 2.98 (2s, 2 H,

CH_2-2), 3.75 (s, 2 H, H-6,6'), 4.68 (t, 1 H, H-5), 5.25 (d, 1 H, $J_{1,3}$ 2, H-1), 5.43 (dd, 1 H, $J_{3,4}$ 10 Hz, H-3), 5.97 (dd, 1 H, $J_{4,5}$ 3.4 Hz, H-4), 7.05-7.25 (m, 4 H, ArH).

Anal. Calc. for $C_{14}H_{16}O_3$: C, 72.4; H, 6.9. Found: C, 72.7; H, 6.9.

Reduction of **11**. — A solution of **11** (0.4 g) in ethanol (20 mL) containing acetic acid (0.1 mL) and sodium acetate (0.16 g) was stirred with sodium borohydride for 0.5 h, after which two chromatographically less-mobile products had been formed. Solids were removed and the filtrate was concentrated to a small volume under reduced pressure. Chloroform (60 mL) was added and the solution was washed with aqueous sodium hydrogencarbonate and then water, and dried. Removal of the solvent gave a syrup which was fractionated by preparative t.l.c. (light petroleum–ethyl acetate, 2:1) to give **14** and **15**.

(1*S*,3*R*,4*S*,4a*R*,10a*S*)-3,11-Anhydro-3,4-dihydroxy-1-hydroxymethyl-3,4,5,10-tetrahydronaphtho[2,3-*c*]pyran (**14**; 0.14 g, 35%) had R_F 0.20, m.p. 131–132° (from ether–light petroleum), $[\alpha]_D$ −61°. The ^{1}H-n.m.r. data are given in Table I.

Anal. Calc. for $C_{14}H_{16}O_3$: C, 72.4; H, 6.9. Found: C, 72.6; H, 7.2.

(1*S*,3*R*,4*R*,4a*R*,10a*S*)-3,11-Anhydro-3,4-dihydroxy-1-hydroxymethyl-3,4,5,10-tetrahydronaphtho[2,3-*c*]pyran (**15**; 0.20 g, 50%) had R_F 0.37, m.p. 102–103° (from ether–light petroleum), $[\alpha]_D$ +24°. The ^{1}H-n.m.r. data are given in Table I.

Anal. Found: C, 72.6; H, 7.0.

The 4-acetate (**16**) of **14** had m.p. 155–156° (from ethanol), $[\alpha]_D$ −84°. The ^{1}H-n.m.r. data are given in Table I.

Anal. Calc. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6. Found: C, 70.2; H, 6.8.

The 4-acetate (**17**) of **15** had m.p. 103–104° (from ethanol), $[\alpha]_D$ 0°. The ^{1}H-n.m.r. data are given in Table I.

Anal. Found: C, 69.8; H, 6.8.

(1S,3R/S,4R/S,4aR,10aS)-3,11-Anhydro-3-hydroxy-1-hydroxymethyl-4-[methylthio(thiocarbonyl)oxy]-3,4,5,10-tetrahydronaphtho[2,3-c]pyran (**18,19**). — A mixture (3.8 g) of **14** and **15**, sodium hydride (4.0 g), and imidazole (1.3 g) was stirred for 12 h in tetrahydrofuran (50 mL). Carbon disulphide (3.2 mL) was added, the mixture was stirred for 1 h, water (100 mL) was added, the mixture was extracted with dichloromethane (3 × 30 mL), and the combined extracts were washed with dilute hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and then water, dried, and concentrated. Flash column chromatography (light petroleum–ethyl acetate, 3:1) of the resulting dark syrup gave the mixture of xanthates as a yellow syrup (3.5 g, 63%), $[\alpha]_D$ −50°. ^{1}H-N.m.r. data (80 MHz): δ 1.96 (s, 1.5 H, CH_3), 2.25 (m, 1 H, H-10a), 2.56 (s, 1.5 H, CH_3), 2.60–3.5 (m, 6 H, H-4,4a,5,5',10,10'), 3.8–4.0 (m, 2 H, CH_2-1), 4.45 (m, 1 H, H-1), 5.3–5.75 (m, 1 H, H-3), 6.9–7.1 (m, 4 H, ArH).

Anal. Calc. for $C_{16}H_{18}O_3S_2$: C, 59.7; H, 5.6; S, 19.9. Found: C, 60.1; H, 5.8; S, 18.7.

(1S,3R,4aR,10aS)-3,11-Anhydro-3-hydroxy-1-hydroxymethyl-3,4,5,10-tetrahydronaphtho[2,3-c]pyran (**20**). — A solution of the above mixture of xanthates (2.0 g) in dry toluene (50 mL) was added dropwise to a refluxing solution of tri-

butyltin hydride (2.5 mL) in toluene (40 mL). Boiling under reflux was continued for 18 h, during which time t.l.c. indicated that the starting materials had reacted to give a slightly more mobile product. The solvent was removed under reduced pressure and the residue was subjected to flash chromatography (light petroleum–ethyl acetate, 4:1) to give **20** (0.67 g, 50%), m.p. 101–103°, $[\alpha]_D$ −12°. ^{1}H-N.m.r. data (80 MHz): δ 1.15–1.65 (m, 3 H, H-10a, benzylic CH_2), 1.90 (m, 1 H, H-4a), 2.2–3.25 (m, 4 H, H-4,4′, benzylic CH_2), 3.7–4.0 (m, 2 H, CH_2-1), 4.35 (bs, 1 H, $W_{1/2}$ 10 Hz, H-1), 5.49 (bs, 1 H, $W_{1/2}$ 5 Hz, H-3), 7.1 (m, 4 H, ArH).

Anal. Calc. for $C_{14}H_{16}O_2$: C, 77.8; H, 7.5. Found: C, 78.1; H, 7.6.

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