Pyranonaphthoquinone Antibiotics. Part 2.[1] Syntheses of (±)-Nanaomycin A and (±)-Eleutherins

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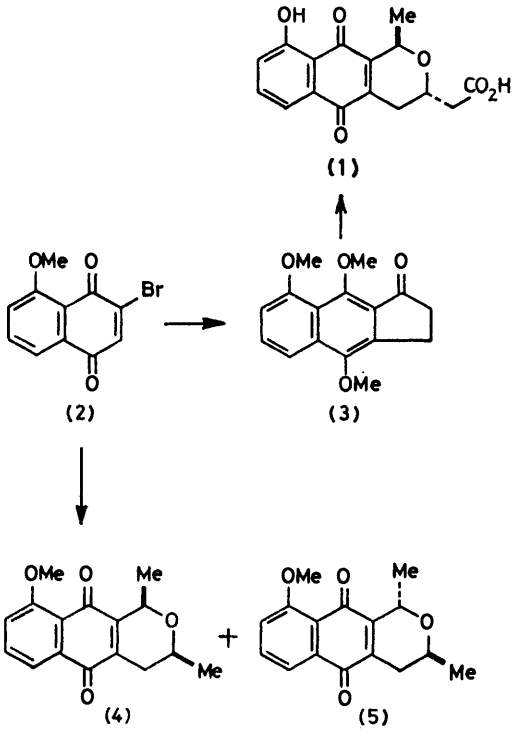
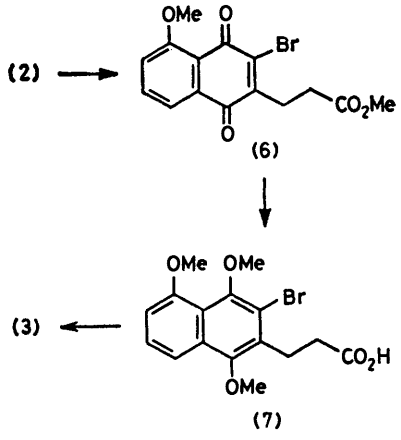
Two routes for the synthesis of (±)-nanaomycin A (1) starting with 2-bromo-8-methoxy-1,4-naphthoquinone (2) are described. The benzindanone (3) prepared from (2) in three steps was treated with methylmagnesium iodide and then with hydrochloric acid to afford the benzindene (8). Lemieux–Johnson oxidation of (8) gave the keto-aldehyde (9), which was converted into the conjugated ester (10) by reaction with methoxycarbonylmethylene-triphenylphosphorane. Reductive cyclisation of (10) with sodium borohydride afforded a *ca.* 1 : 1.9 mixture of the *cis*-naphthopyran (11) and its *trans*-isomer (12). Oxidative demethylation of (11) and (12) with cerium(IV) followed by treatment with aluminium chloride yielded the corresponding quinones (15) and (16). Ester hydrolysis of (16) formed (±)-nanaomycin A (1). Reductive methylation of the 2-allyl derivative of (2) afforded the bromonaphthalene (18), which was treated with butyl-lithium followed by acetaldehyde to give the naphthylcarbinol (19). The lactol (20) obtained by Lemieux–Johnson oxidation of (19) was treated with trimethyl phosphonoacetate–sodium hydride to yield a *ca.* 2.1 : 1 mixture of the naphthopyrans (11) and (12). Cyclisation of (19) with mercury(II) acetate–sodium borohydride yielded a *ca.* 1 : 0.9 mixture of the *cis*-naphthopyran (21) and its *trans*-isomer (22), which were oxidatively demethylated to give (±)-eleutherin (4) and (±)-isoeleutherin (5) respectively.

In the preceding paper,[1] we presented a new synthetic approach to the basic framework of pyranonaphthoquinone antibiotics which employs indan-1-one derivatives as precursors for the pyranobenzoquinone structure. We have now extended this method to a new



synthesis of racemic nanaomycin A (1), starting with 2-bromo-8-methoxy-1,4-naphthoquinone (2) *via* the benzindanone intermediate (3). Furthermore, an alternative and more straightforward route to (1) from (2), as well as a short access to racemic eleutherin (4) and isoeleutherin (5), are described.

The benzindanone (3) was prepared by the steps in Scheme 1, starting with 2-bromo-8-methoxy-1,4-naphthoquinone (2) which was derived from 1,5-dihydroxynaphthalene by the recently reported method[2] of Rapoport. The bromonaphthoquinone (2) was treated with methyl hydrogen succinate[3] in the presence of ammonium persulphate and silver nitrate to introduce[4] the propionate side chain at C-2. The product (6) obtained in 54% yield was subjected to conventional



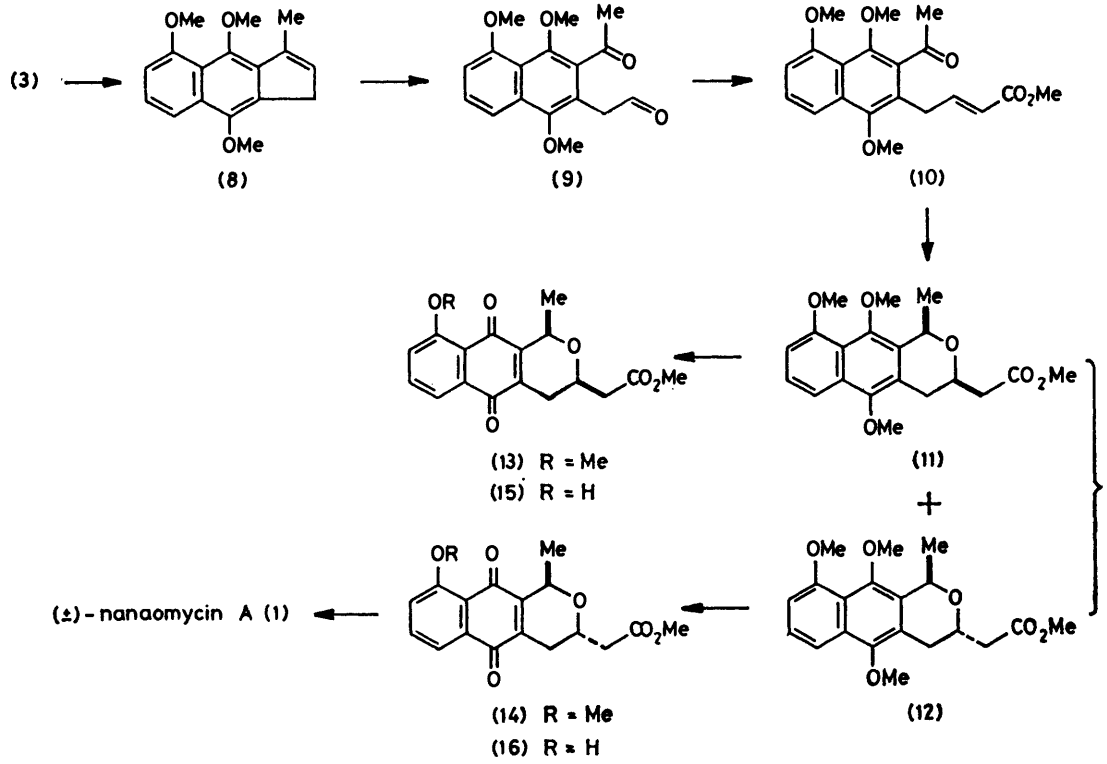
Scheme 1

reductive methylation to give the bromo-acid (7) in 87% yield. Compound (7) was then treated with 2.2 mol. equiv. of butyl-lithium[5] in tetrahydrofuran at −78 °C to lead to the benzindanone (3) in an overall yield of 30% from (2).

Construction of the pyran ring of the target molecule, nanaomycin A (1), from (3) was achieved by the sequence of reactions described in Part 1.[1] Reaction of the benzindanone (3) with methylmagnesium iodide in ether followed by brief treatment of the resulting carbinol with hydrochloric acid produced the benzindene

(8) in 82% yield. The latter compound was oxidised with osmium tetraoxide–sodium metaperiodate and the intermediate keto-aldehyde (9) produced was immediately treated with methoxycarbonylmethylenetriphenylphosphorane to yield the conjugated ester (10) in an overall yield of 31% from (8). The olefinic geometry of the ester (10) was determined to be *E* by n.m.r. analysis (J_{vic} 16 Hz), as shown in the preceding paper [1] for an analogous compound. Formation of the pyran ring from (10) was carried out by reductive cyclisation with sodium borohydride to give a mixture of which was confirmed by comparison of its m.p.[7] and spectral data [8] (n.m.r., i.r., and m.s.) with those reported (Scheme 2).

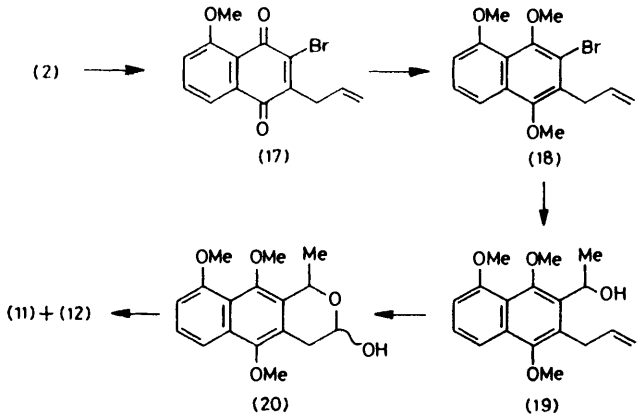
An alternative route for the synthesis of nanaomycin A from 2-bromo-8-methoxy-1,4-naphthoquinone (2) is outlined in Scheme 3, which started with the oxidative alkylation of (2) with vinylacetic acid in the presence of persulphate and silver nitrate. The 2-allyl derivative (17) obtained in 65% yield was reduced with sodium hydrosulphite and then alkylated with dimethyl sulphate and potassium hydroxide giving 2-allyl-3-



SCHEME 2

of naphthopyrans (11) and (12) in 81% yield. The *cis*-isomer (11) and the *trans*-isomer (12) were formed in a ratio of *ca.* 1 : 1.9 (by g.l.c.) and were separable by silica gel chromatography. The stereochemistry of the isomers was determined by oxidation of both isomers to the corresponding naphthoquinones (13) and (14) with cerium(IV) ammonium nitrate and comparison of the magnitudes of their long-range ^{1}H n.m.r. coupling constants ($J_{1,4}$). The naphthoquinone (14) derived from the main product (12), which had larger $J_{1,4}$ values (4.0 and 2.5 Hz), was assigned the *trans*-structure, and (13) derived from the minor product (11), which had smaller values (2.5 and <1 Hz), the *cis*-isomer as discussed in Part 1.[1] Both methoxynaphthoquinones (13) and (14) were then demethylated with aluminium chloride [6] giving the phenolic products (15) and (16) (=nanaomycin A methyl ester) in 62 and 64% yields respectively. The ester (16) was hydrolysed in concentrated hydrochloric acid to afford racemic nanaomycin A (1), the structure

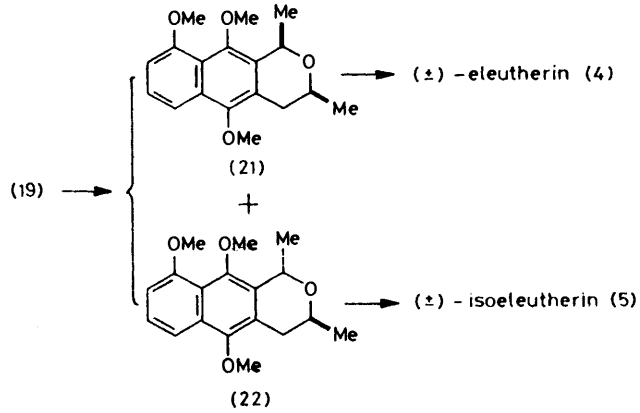
bromo-1,4,5-trimethoxynaphthalene (18) in 79% yield. Treatment of (18) with butyl-lithium [9] in tetrahydrofuran at −78 °C and subsequent addition of acetaldehyde



SCHEME 3

resulted in the formation of the naphthylcarbinol (19) in 61% yield. Cleavage of the olefinic bond in (19) with osmium tetraoxide–sodium metaperiodate gave the lactol (20) as a mixture of diastereoisomers. Wittig–Horner reaction of compound (20) employing trimethyl phosphonoacetate and sodium hydride produced the isomeric naphthopyrans (11) and (12) in a ratio of 2.1 : 1 (by g.l.c.), which were separated by silica gel chromatography giving the *cis*-isomer (11) in 39% yield and the *trans*-isomer (12) in 21% yield. Although the production of the *cis*-isomer is favoured by this method in contrast with the method in Scheme 2, this fact presents no serious problem for nanaomycin synthesis since the *cis*-isomer can be isomerised to the thermodynamically more stable *trans*-isomer [7] at a later stage of the synthesis.

Finally, a new route to eleutherin and isoeleutherin employing the key intermediate (19) of the nanaomycin synthesis is shown in Scheme 4. Acetoxymercuration–



SCHEME 4

demercuration of the naphthylcarbinol (19) afforded in nearly quantitative yield the cyclisation product as a *ca.* 1 : 0.9 mixture of stereoisomers (21) and (22) (by g.l.c.). Both isomers (21) and (22) were separated by silica gel chromatography and oxidised with cerium(IV) ammonium nitrate to afford (±)-eleutherin (4) and (±)-isoeleutherin (5) in 87 and 82% yields respectively. The structures of these compounds were confirmed by comparison of their m.p.[10] and n.m.r. data [11] with those reported.

EXPERIMENTAL

General experimental details are as reported in Part 1.[1]

3-Bromo-5-methoxy-2-(2-methoxycarbonylethyl)-1,4-naphthoquinone (6).—A solution of ammonium persulphate (12.8 g, 0.056 mol) in water (50 ml) was added dropwise, over 20 min, to a stirred solution of 2-bromo-8-methoxy-1,4-naphthoquinone [2] (2) (3.5 g, 0.013 mol), methyl hydrogen succinate [3] (5.0 g, 0.038 mol), and silver nitrate (1.6 g, 9.4 mmol) in acetonitrile (50 ml) at 60—65 °C and the mixture was stirred at the same temperature for 2 h, poured into water, and extracted with ethyl acetate. The extract was washed with dilute sodium hydrogencarbonate solution and water, dried ($MgSO_4$), and the solvent removed under reduced pressure. Column chromatography on silica gel, with benzene–ethyl acetate as eluant, gave *3-bromo-5-methoxy-2-(2-methoxycarbonylethyl)-1,4-naphthoquinone* (6) (2.5 g, 54%). Recrystallisation from benzene–ethyl acetate afforded an analytically pure sample, m.p. 125—127 °C; $\nu_{max.}$ (KBr) 1 725 and 1 660 cm^{-1}; $\delta(CDCl_3)$ 2.55 and 3.08 (each 2 H, t, *J* 7 Hz, CH_2CH_2), 3.64 and 3.96 (each 3 H, s, 5-OMe and CO_2Me), 7.15—7.30 (1 H, m, Ar-H), and 7.50—7.70 (2 H, m, Ar-H); *m/e* 354 and 352 (M^+), 322 and 320 (M^+ — MeOH), 273 (M^+ — Br, 100%), and 241 (M^+ — MeOH — Br) (Found: C, 50.7; H, 3.45. $C_{15}H_{13}BrO_5$ requires C, 51.0; H, 3.7%).

4,8,9-Trimethoxybenz[f]indanone (3).—A solution of the ester (6) (0.934 g, 2.65 mmol) in ethyl acetate (50 ml) was vigorously shaken twice with saturated sodium hydrosulphite solution (2 × 50 ml) and the organic layer was concentrated under reduced pressure. To a solution of the residual oil in 20% potassium hydroxide solution (15 ml) was added dimethyl sulphate (3.3 g, 0.026 mol) dropwise over 20 min under nitrogen, and the mixture stirred at room temperature for 30 min. To the mixture was further added 20% potassium hydroxide solution (10 ml) and the resultant mixture was stirred at 60—70 °C for 10 min, and washed with ethyl acetate. The aqueous solution was acidified (pH 1) with concentrated hydrochloric acid and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and the solvent evaporated off under reduced pressure to give crude 3-(3-bromo-1,4,5-trimethoxy-2-naphthyl)propanoic acid (7) (0.874 g, 87%); $\nu_{max.}$ (KBr) 3 600—2 300 and 1 700 cm^{-1}; $\delta(CDCl_3)$ 2.72 and 3.37 (each 2 H, t, *J* 7 Hz, CH_2CH_2), 3.88, 3.93, and 4.03 (each 3 H, s, 1-, 4-, and 5-OMe), 6.93 (1 H, d, *J* 8 Hz, Ar-H), 7.47 (1 H, t, *J* 8 Hz, Ar-H), and 7.70 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 370 and 368 (M^+, 100%), 355 and 353 (M^+ — Me), and 274 (M^+ — Me — Br). A solution of butyl-lithium in hexane (15%; 3 ml, 5 mmol) was added to a solution of the crude acid (7) (0.83 g, 2.25 mmol) in tetrahydrofuran (30 ml) over 10 min at −78 °C under nitrogen and the mixture was stirred at the same temperature for 1 h. Water was added and the mixture was extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and the solvent removed under reduced pressure to give a solid. Repeated crystallisation from ethyl acetate–ether afforded *4,8,9-trimethoxybenz[f]indanone* (3) (0.378 g, 62%), m.p. 154—155 °C; $\nu_{max.}$ (KBr) 1 705 cm^{-1}; $\delta(CDCl_3)$ 2.65—2.80 (2 H, m, CH_2), 3.15—3.30 (2 H, m, CH_2), 3.96 (3 H, s, OMe), 4.00 (6 H, s, two OMe), 6.81 (1 H, d, *J* 8 Hz, Ar-H), 7.45 (1 H, t, *J* 8 Hz, Ar-H), and 7.68 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 272 (M^+, 100%) and 257 (M^+ — Me) (Found: C, 70.4; H, 5.9. $C_{16}H_{16}O_4$ requires C, 70.6; H, 5.9%).

Methyl 4-(3-Acetyl-1,4,5-trimethoxy-2-naphthyl)but-2-enoate (10).—This compound was prepared from the benzindanone (3) *via* the benzindene (8) and the keto-aldehyde (9) employing essentially the same procedures described in the preceding paper.[1] Compounds (8), (9), and (10) had the following properties: 4,5,9-trimethoxy-3-methylbenz[*f*]indene (8) (82%); $\delta(CDCl_3)$ 2.24 (3 H, q, *J* 2 Hz, 3-Me), 3.44 (2 H, quintet, *J* 2 Hz, 1-H), 3.84, 3.97, and 4.01 (each 3 H, s, 4-, 5-, and 9-OMe), 6.12 (1 H, sextet, *J* 2 Hz, 2-H), 6.86 (1 H, d, *J* 8 Hz, Ar-H), 7.36 (1 H, t, *J* 8 Hz, Ar-H), and 7.80 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 270 (M^+, 100%) and 265 (M^+ — Me); 3-acetyl-2-formylmethyl-1,4,5-trimethoxynaphthalene (9) (81%); $\nu_{max.}$ (neat) 2 720, 1 720, and 1 680 cm^{-1}; $\delta(CDCl_3)$ 2.62 (3 H, s, Ac), 3.78, 3.80, and 4.02 (each 3 H, s, 1-, 4-, and 5-OMe), 3.87 (2 H, d, *J* 1 Hz, CH_2), 6.92 (1 H, d, *J* 8 Hz, Ar-H), 7.47 (1 H, t, *J* 8 Hz, Ar-H),

7.68 (1 H, d, *J* 8 Hz, Ar-H), and 9.75 (1 H, t, *J* 1 Hz, CHO); *m/e* 302 (M^+, 100%) and 274 (M^+ — CO); methyl 4-(3-*acetyl*-1,4,5-*trimethoxy*-2-*naphthyl*)*but*-2-*enoate* (10) (38%), b.p. 200—210 °C at 1 Torr; $\nu_{max.}$ (neat) 1 700 and 1 640 cm^{-1}; δ($CDCl_3$) 2.56 (3 H, s, Ac), 3.65—3.75 (2 H, m, CH_2), 3.67, 3.76, 3.84, and 4.01 (each 3 H, s, 1-, 4-, and 5-OMe and CO_2Me), 5.72 (1 H, dt, *J* 16 and 1.5 Hz, C:C*H*·CO_2-Me), 6.90 (1 H, d, *J* 8 Hz, Ar-H), 7.02 (1 H, dt, *J* 16 and 7 Hz, C*H*:CH·CO_2Me), 7.50 (1 H, t, *J* 8 Hz, Ar-H), and 7.69 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 358 (M^+, 100%), 343 (M^+ — Me), and 316 ($M^+ - C_2H_2O$) (Found: C, 66.8; H, 6.1. $C_{20}H_{22}O_6$ requires C, 67.0; H, 6.2%).

cis- (11) *and* trans- (12) *Methyl* 5,9,10-*Trimethoxy*-1-*methyl*-3,4-*dihydro*-1H-*naphtho*[2,3-c]*pyran*-3-*ylacetate*.—Reductive cyclisation of the conjugated ester (10) with sodium borohydride gave a mixture of naphthopyrans as a pale yellow oil showing two spots on t.l.c. due to the two diastereoisomers, R_F 0.40 and 0.35 (SiO_2; benzene–ethyl acetate, 10 : 1). The individual isomers were obtained by preparative t.l.c. (SiO_2; benzene-ethyl acetate, 9 : 1) as pale yellow oils. The less polar compound was *methyl* cis-5,9,10-*trimethoxy*-1-*methyl*-3,4-*dihydro*-1H-*naphtho*[2,3-c]*pyran*-3-*ylacetate* (11) (17%), b.p. 190—200 °C at 1 Torr; $\nu_{max.}$ (neat) 1 740 cm^{-1}; δ($CDCl_3$) 1.61 (3 H, d, *J* 7 Hz, 1-Me), 2.54 (1 H, dd, *J* 15 and 11 Hz, 4-H), 2.63 (2 H, m, CH_2CO_2Me), 3.04 (1 H, dd, *J* 15 and 2.5 Hz, 4-H), 3.63, 3.64, 3.74, and 3.88 (each 3 H, s, 5-, 9-, and 10-OMe and CO_2Me), 3.60—3.90 (1 H, m, 3-H), 5.13 (1 H, q, *J* 7 Hz, 1-H), 6.65 (1 H, d, *J* 8 Hz, Ar-H), 7.17 (1 H, t, *J* 8 Hz, Ar-H), and 7.49 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 360 (M^+, 100%) and 345 (M^+ — Me) (Found: C, 66.5; H, 6.7. $C_{20}H_{24}O_6$ requires C, 66.65; H, 6.7%). The more polar compound was the trans-*isomer* (12) (37%), b.p. 190—200 °C at 1 Torr, $\nu_{max.}$ (neat) 1 740 cm^{-1}; δ($CDCl_3$) 1.63 (3 H, d, *J* 7 Hz, 1-Me), 2.62 (1 H, dd, *J* 17 and 11 Hz, 4-H), 2.66 (2 H, d, *J* 7 Hz, CH_2CO_2Me), 3.09 (1 H, dd, *J* 17 and 3.5 Hz, 4-H), 3.71, 3.75, 3.80, and 3.95 (each 3 H, s, 5-, 9-, and 10-OMe and CO_2Me), 4.30—4.60 (1 H, m, 3-H), 5.28 (1 H, q, *J* 7 Hz, 1-H), 6.75 (1 H, d, *J* 8 Hz, Ar-H), 7.28 (1 H, t, *J* 8 Hz, Ar-H), and 7.59 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 360 (M^+, 100%) and 345 (M^+ — Me) (Found: C, 66.8; H, 6.7%). The *cis*- to *trans*-isomer ratio was determined by g.l.c. to be 1 : 1.9 (t_R 5 and 6 min; 1.5% silicone OV-17 on Shimalite W at 265 °C).

cis- (15) *and* trans- (16) *Methyl* 9-*Hydroxy*-1-*methyl*-5,10-*dioxo*-3,4,5,10-*tetrahydro*-1H-*naphtho*[2,3-c]*pyran*-3-*ylacetate*.—Methyl *cis*-9-methoxy-1-methyl-5,10-dioxo-3,4,-5,10-tetrahydro-1*H*-naphtho[2,3-*c*]pyran-3-ylacetate (13) was prepared in 89% yield by oxidation of the *cis*-naphthopyran (11) with cerium(IV) ammonium nitrate as reported in the preceding paper;[1] $\nu_{max.}$ (neat) 1 740 and 1 660 cm^{-1}; δ($CDCl_3$) 1.52 (3 H, d, *J* 7 Hz, 1-Me), 2.23 (1 H, ddd, *J* 18, 11, and 4 Hz, 4-H), 2.66 (2 H, dd, 6.5 and 3.0 Hz, CH_2CO_2Me), 2.84 (1 H, dt, *J* 18 and 2.5 Hz, 4-H), 3.73 and 3.99 (each 3 H, s, 9-OMe and CO_2Me), 3.60—3.90 (1 H, m, 3-H), 4.70—5.00 (1 H, m, 1-H), 7.20—7.35 (1 H, m, Ar-H), and 7.60—7.75 (2 H, m, Ar-H); *m/e* 330 (M^+, 100%) and 257 ($M^+ - CH_2CO_2Me$). To a solution of the crude product (13) (96 mg, 0.29 mmol) in dichloromethane (5 ml) was added aluminium chloride (1.0 g, 7.5 mmol) and the mixture was stirred at room temperature for 1 h. Water was added, the mixture extracted with chloroform, and the extract washed with dilute hydrochloric acid and water. Evaporation of the dried ($MgSO_4$) organic layer left a reddish solid. Repeated crystallisation from methanol afforded *methyl* cis-9-*hydroxy*-1-*methyl*-5,10-*dioxo*-3,4,5,10-*tetrahydro*-1H-*naphtho*[2,3-c]*pyran*-3-*ylacetate* (15) (57 mg, 62%), m.p. 130—132 °C; $\nu_{max.}$ (KBr) 1 735, 1 655, and 1 630 cm^{-1}; δ($CDCl_3$) 1.55 (3 H, d, *J* 7 Hz, 1-Me), 2.26 (1 H, ddd, *J* 18.5, 10, and 4 Hz, 4-H), 2.62 (2 H, dd, *J* 6.5 and 3.5 Hz, CH_2CO_2Me), 2.81 (1 H, dt, *J* 18.5 and 2.8 Hz, 4-H), 3.69 (3 H, s, CO_2Me), 3.70—4.00 (1 H, m, 3-H), 4.70—4.90 (1 H, m, 1-H), 7.10—7.30 (1 H, m, Ar-H), 7.50—7.60 (2 H, m, Ar-H), and 11.86 (1 H, s, OH); *m/e* 316 (M^+), 301 (M^+ — Me), 298 ($M^+ - H_2O$), and 284 (M^+ — MeOH, 100%) (Found: C, 64.3; H, 4.83. $C_{17}H_{16}O_6$ requires C, 64.55; H, 5.1%).

Similarly, the *trans*-naphthopyran (12) was converted into the *trans*-compound (14) (85%), $\nu_{max.}$ (Nujol) 1 740 and 1 660 cm^{-1}; δ($CDCl_3$) 1.55 (3 H, d, *J* 7 Hz, 1-Me), 2.23 (1 H, ddd, *J* 18, 11, and 2.5 Hz, 4-H), 2.58 (2 H, d, *J* 6 Hz, CH_2CO_2Me), 2.70 (1 H, dd, *J* 18 and 3.5 Hz, 4-H), 3.68 and 3.94 (each 3 H, s, 9-OMe and CO_2Me), 4.10—4.30 (1 H, m, 3-H), 4.95 (1 H, q, *J* 7 Hz, 1-H), 7.20—7.30 (1 H, m, Ar-H), and 7.50—7.70 (2 H, m, Ar-H); *m/e* 330 (M^+, 100%) and 257 ($M^+ - CH_2CO_2Me$). Treatment of this crude product (14) (47 mg, 0.14 mmol) with aluminium chloride yielded a yellow solid, which was recrystallised from methanol to afford the trans-*isomer* (16) (64%), m.p. 133—135 °C; $\nu_{max.}$ (KBr) 1 735 and 1 635 cm^{-1}; δ($CDCl_3$) 1.57 (3 H, d, *J* 7 Hz, 1-Me), 2.29 (1 H, ddd, *J* 19, 10.5, and 2.2 Hz, 4-H), 2.64 (2 H, d, *J* 7 Hz, CH_2CO_2Me), 2.81 (1 H, dd, *J* 19 and 3.5 Hz, 4-H), 3.73 (3 H, s, CO_2Me), 4.20—4.40 (1 H, m, 3-H), 4.97 (1 H, q, *J* 7 Hz, 1-H), 7.10—7.30 (1 H, m, Ar-H), 7.50—7.60 (2 H, m, Ar-H), and 11.92 (1 H, s, OH); *m/e* 316 (M^+), 302 (M^+ — Me), 298 ($M^+ - H_2O$), and 284 (M^+ — MeOH, 100%) (Found: C, 64.5; H, 4.8%).

(±)-*Nanaomycin A* (1).—A suspension of the *trans*-ester (16) (20 mg, 0.063 mmol) in concentrated hydrochloric acid (1 ml) was stirred at room temperature for 8 h. The mixture was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and the solvent removed under reduced pressure to give a solid, which was chromatographed on silica gel, with benzene–ethyl acetate as eluant, to afford (±)-nanaomycin A (1) (12 mg, 63%), m.p. 171—173 °C (lit.,[7] 171—174 °C); $\nu_{max.}$ (KBr) 3 600—2 400 cm^{-1}, the n.m.r. data for which were completely identical with those reported by Ōmura [8] (Found: M^+, 302.082 8. Calc. for $C_{16}H_{14}O_6$: *M*, 302.079 1).

2-*Allyl*-3-*bromo*-5-*methoxy*-1,4-*naphthoquinone* (17).—A solution of vinylacetic acid (0.145 g, 1.69 mmol) in acetonitrile (1 ml) was added to a suspension of 2-bromo-8-methoxy-1,4-naphthoquinone (2) (0.3 g, 1.11 mmol) and silver nitrate (24 mg, 0.14 mmol) in acetonitrile (5 ml) and water (2 ml) at 60—65 °C and then a solution of ammonium persulphate (0.45 g, 1.97 mmol) in water (2.5 ml) was added dropwise over 20 min. The mixture was stirred at 60—65 °C for 2.5 h, diluted with water, and extracted with ethyl acetate. The extract was washed with dilute sodium hydrogen carbonate solution and water, dried ($MgSO_4$), and the solvent evaporated off. Column chromatography on silica gel, with benzene as eluant, afforded 2-*allyl*-3-*bromo*-5-*methoxy*-1,4-*naphthoquinone* (17) (0.22 g, 65%), m.p. 130—132 °C (from benzene); $\nu_{max.}$ (KBr) 1 660 cm^{-1}; δ($CDCl_3$) 3.57 (2 H, d, *J* 6 Hz, CH_2), 4.00 (3 H, s, OMe), 5.05—5.40 (2 H, m, CH:CH_2), 5.60—6.20 (1 H, m, C*H*:CH_2), 7.20—7.35 (1 H, m, Ar-H), and 7.50—7.90 (2 H, m, Ar-H); *m/e* 308 and 306 (M^+), 293 and 291 (M^+ — Me), and 227 (M^+ — Br, 100%) (Found: C, 54.85; H, 3.5. $C_{14}H_{11}$-BrO_3 requires C, 54.75; H, 3.6%).

2-*Allyl*-3-*bromo*-1,4,5-*trimethoxynaphthalene* (18).—A solution of the quinone (17) (0.14 g, 0.46 mmol) in ether (100 ml) was vigorously shaken twice with saturated sodium hydrosulphite solution (2 × 50 ml) and the organic layer was concentrated under reduced pressure. To a solution of the residual oil in 10% potassium hydroxide solution (5 ml) was added dimethyl sulphate (0.575 g, 4.6 mmol) dropwise over 20 min under nitrogen and the mixture was stirred at room temperature for 20 min. To the mixture was further added 10% potassium hydroxide solution (5 ml) and the resultant mixture was stirred at 60—70 °C for 5 min, diluted with water, and extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and the solvent removed under reduced pressure. Column chromatography on silica gel, with benzene as eluant, afforded 2-*allyl*-3-*bromo*-1,4,5-*trimethoxynaphthalene* (18) (0.112 g, 79%) as an oil, b.p. 130—140 °C at 1 Torr; δ($CDCl_3$) 3.70—3.80 (2 H, m, CH_2), 3.83 (6 H, s, 2 × OMe), 3.95 (3 H, s, OMe), 4.95—5.20 (2 H, m, CH:CH_2), 5.80—6.30 (1 H, m, CH:CH_2), 6.88 (1 H, d, *J* 8 Hz, Ar-H), 7.42 (1 H, t, *J* 8 Hz, Ar-H), and 7.68 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 338 and 336 (M^+, 100%) and 323 and 321 (M^+ − Me) (Found: C, 56.7; H, 4.9. $C_{16}H_{17}BrO_3$ requires C, 57.0; H, 5.1%).

2-*Allyl*-3-(1-*hydroxyethyl*)-1,4,5-*trimethoxynaphthalene* (19).—A 15% solution of butyl-lithium in hexane (2.1 ml, 3.3 mmol) was added at −78 °C, over 10 min, to a solution of the bromonaphthalene (18) (1.11 g, 3.3 mmol) in tetrahydrofuran (30 ml) and the mixture was stirred for 50 min. A solution of acetaldehyde (0.29 g, 6.6 mmol) in tetrahydrofuran (2 ml) was then added and the resultant mixture was stirred at −78 °C for 15 min. Water was added and the mixture was extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$), and the solvent removed under reduced pressure. Column chromatography on silica gel, with benzene–ethyl acetate as eluant, afforded 2-*allyl*-3-(1-*hydroxyethyl*)-1,4,5-*trimethoxynaphthalene* (19) (0.609 g, 61%) as an oil, $\nu_{max.}$ (neat) 3 150 cm^{-1}; δ($CDCl_3$) 1.62 (3 H, d, *J* 6 Hz, CHOH*Me*), 3.60—3.80 (2 H, m, CH_2·CH:CH_2), 3.84, 3.88, and 3.98 (each 3 H, s, 1-, 4-, and 5-OMe), 4.80—5.30 (3 H, m, CH:CH_2 and CHOHMe), 5.90—6.30 (1 H, m, CH:CH_2), 6.88 (1 H, d, *J* 8 Hz, Ar-H), 7.40 (1 H, t, *J* 8 Hz, Ar-H), and 7.72 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 302 (M^+, 100%), 287 (M^+ − Me), and 284 (M^+ − H_2O) (Found: C, 71.75; H, 7.4. $C_{18}H_{22}O_4$ requires C, 71.5; H, 7.3%).

5,9,10-*Trimethoxy*-1-*methyl*-3,4-*dihydro*-1H-*naphtho*-[2,3-c]*pyran*-3-*ol* (20).—This compound was prepared in 68% yield by oxidation of the naphthylcarbinol (19) with osmium tetraoxide–sodium metaperiodate as reported in the preceding paper;[1] m.p. 142—145 °C (from MeOH), $\nu_{max.}$ (KBr) 3 400 cm^{-1}; *m/e* 304 (M^+, 100%) and 289 (M^+ − Me) (Found: C, 67.3; H, 6.6. $C_{17}H_{20}O_5$ requires C, 67.1; H, 6.6%).

Alternative Preparation of the cis- (11) *and* trans- (12) *Esters*.—Trimethyl phosphonoacetate (1.014 g, 5.6 mmol) was added dropwise, over 10 min, to a suspension of sodium hydride (50% in oil; 0.267 g, 5.6 mmol) in dimethoxyethane (40 ml) and the mixture was stirred at room temperature for 1 h. To the mixture was added a solution of the lactol (20) (0.339 g, 1.1 mmol) in dimethoxyethane (10 ml) over 10 min. The resultant mixture was stirred at room temperature for 3 h and then refluxed for 1 h, diluted with water, and extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$), and the solvent evaporated off under reduced pressure to afford an oil, which was fractionated by silica gel chromatography (benzene–ethyl acetate). The first-eluted material (0.156 g, 39%) was identical (t.l.c. and n.m.r. spectrum) with the *cis*-compound (11) and the second-eluted material was identical with the *trans*-isomer (12). The *cis*- to *trans*-isomer ratio was determined by g.l.c. to be 2.1 : 1 (t_R 5.0 and 6.0 min; 1.5% silicone OV-17 on Shimalite W at 165 °C).

cis- (21) *and* trans- (22) 5,9,10-*Trimethoxy*-1,3-*dimethyl*-3,4-*dihydro*-1H-*naphtho*[2,3-c]*pyran*.—A mixture of the naphthylcarbinol (19) (0.13 g, 0.43 mmol) and mercury(II) acetate (0.137 g, 0.43 mmol) in tetrahydrofuran (1 ml) and water (1 ml) was stirred for 1 h and then 3M-sodium hydroxide solution (0.43 ml) was added. The mixture was stirred for 1 h, and sodium borohydride (3M-solution in 3M-aqueous sodium hydroxide; 0.65 ml, 2.1 mmol) added. The mixture was stirred at room temperature for 40 min, diluted with water, and extracted with ethyl acetate. The extract was washed with brine, dried ($MgSO_4$), and the solvent evaporated off under reduced pressure to give a mixture of naphthopyrans as a pale yellow oil showing two spots on t.l.c. owing to the presence of two diastereoisomers, R_F 0.6 and 0.55 (SiO_2; benzene–ethyl acetate, 5 : 1). The individual isomers were obtained by preparative t.l.c. (SiO_2; benzene–ethyl acetate, 5 : 1) as pale yellow oils. The less polar compound was *cis*-5,9,10-trimethoxy-1,3-dimethyl-3,4-dihydro-1*H*-naphtho[2,3-*c*]pyran (21) (39 mg, 30%), δ($CDCl_3$) 1.40 (3 H, d, *J* 6.5 Hz, 3-Me), 1.67 (3 H, d, *J* 6.5 Hz, 1-Me), 2.51 (1 H, ddd, *J* 16, 11, and 1 Hz, 4-H), 3.01 (1 H, ddd, *J* 16, 2, and 1 Hz, 4-H), 3.50—3.80 (1 H, m, 3-H), 3.69, 3.80, and 3.92 (each 3 H, s, 5-, 9-, and 10-OMe), 5.18 (1 H, q, *J* 6.5 Hz, 1-H), 6.73 (1 H, d, *J* 8 Hz, Ar-H), 7.27 (1 H, t, *J* 8 Hz, Ar-H), and 7.61 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 302 (M^+) and 287 (M^+ − Me, 100%). The more polar compound was the *trans*-isomer (22) (29 mg, 22%), δ($CDCl_3$) 1.38 (3 H, d, *J* 6.5 Hz, 3-Me), 1.63 (3 H, d, *J* 6.5 Hz, 1-Me), 2.54 (1 H, dd, *J* 17 and 11 Hz, 4-H), 3.05 (1 H, dd, *J* 17 and 3.5 Hz, 4-H), 3.76, 3.80, and 3.94 (each 3 H, s, 5-, 9-, and 10-OMe), 3.90—4.30 (1 H, m, 3-H), 5.29 (1 H, q, *J* 6.5 Hz, 1-H), 6.75 (1 H, d, *J* 8 Hz, Ar-H), 7.28 (1 H, t, *J* 8 Hz, Ar-H), and 7.60 (1 H, d, *J* 8 Hz, Ar-H); *m/e* 302 (M^+) and 287 (M^+ − Me, 100%). The *cis*- to *trans*-isomer ratio was determined by g.l.c. to be 1 : 0.9 (t_R 4.0 and 4.8 min; 1.5% silicone OV-17 on Shimalite W at 230 °C).

(±)-*Eleutherin* (4) *and* (±)-*Isoeleutherin* (5).—These compounds were prepared by oxidation of the naphthopyrans (21) and (22) with cerium(IV) ammonium nitrate as described in the preceding paper.[1] (±)-*Eleutherin* (4) (87%), m.p. 155—156 °C (EtOH) (lit.,[10] 155.5—156.5 °C), $\nu_{max.}$ (KBr) 1 660 cm^{-1}, showed n.m.r. data which were completely identical with those reported by Todd,[11] *m/e* 272 (M^+) and 257 (M^+ − Me, 100%) (Found: C, 70.3; H, 5.9. Calc. for $C_{16}H_{16}O_4$ C, 70.6; H, 5.9%). (±)-*Isoeleutherin* (5) (82%), m.p. 154—155 °C (EtOH) (lit.,[10] 154.5—155.5 °C), $\nu_{max.}$ (KBr) 1 660 cm^{-1}, showed n.m.r. data which were identical with those reported by Todd,[11] *m/e* 272 (M^+) and 257 (M^+ − Me, 100%) (Found: C, 70.3; H, 6.2%).

[0/1117 *Received*, 15*th July*, 1980]

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