Alkylation of quinones. Formation of cyclopropyl-1,4-naphthoquinones and related compounds

Robin G.F. Giles, Peter R.K. Mitchell, and Gregory H.P. Roos

Alkylation of 1,4-naphthoquinone with cyclopropyl carboxylic acid in the presence of ammonium peroxodisulphonate and silver nitrate afforded a mixture of 2-cyclopropyl- and 2,3-dicyclopropyl-1,4-naphthoquinones. In reactions directed at the synthesis of 5-deoxyjuglomycins A and B, a substituted cyclopropyl-1,4-naphthoquinone was also obtained.
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Alkilering van 1,4-naftokinoon met siklopropielkarboksielsuur in teenwoordigheid van ammoniumperoksodisulfonaat en silwernitraat lewer 'n mengsel van 2-siklopropiel- en 2,3-disiklopropiel-1,4-naftokinoon. In reaksies wat gerig is op die sintese van 5-deoksijuglomisien A en B is ook 'n gesubstitueerde siklopropiel-1,4-naftokinoon verkry.
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This article is dedicated to the University of Cape Town on the occasion of its 150th Anniversary.

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The thermal[1] and photochemical[2] isomerizations of vinylcyclopropanes to cyclopentenes are well-established processes. We have synthesized 2-cyclopropyl-1,4-naphthoquinone (1) to determine whether rearrangement would take place to benz[*f*]indane-4,9-quinone (2), which we had earlier hoped would lead to the elusive benz[*f*]indene-4,9-quinone.[3] We have also described elsewhere[4] attempts to effect the related conversion of 2-aziridin-1-yl-1,4-naphthoquinone (3) into benz[*f*]indoline-4,9-quinone (4) using iodide ion.

Jacobsen and Torssell[5,6] had reported the alkylation of quinones with radicals from the decarboxylation of carboxylic acids with silver ions and peroxodisulphonate. More recently they described[7] the alkylation of 2-methyl-1,4-naphthoquinone with a series of cycloalkyl carboxylic acids, including cyclopropyl carboxylic acid; the latter reaction afforded 2-cyclopropyl-3-methyl-1.4-naphthoquinone (5) in moderate yield.

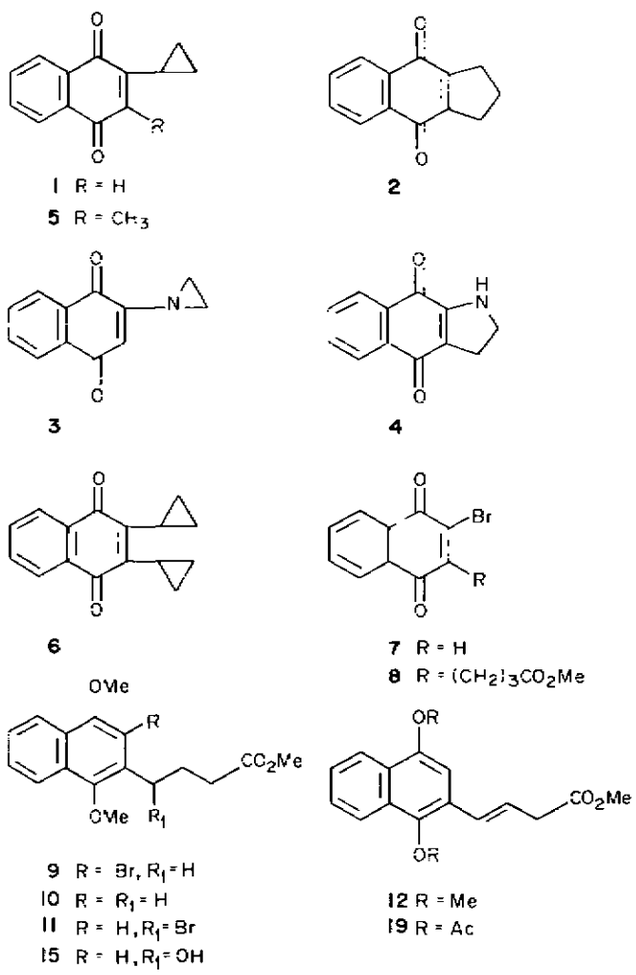
We therefore treated 1,4-naphthoquinone with cyclopropyl carboxylic acid under similar conditions and isolated two products, 2-cyclopropyl-1,4-naphthoquinone (1) (48%) and 2,3-dicyclopropyl-1,4-naphthoquinone (6) (26%). In the ^{1}H n.m.r. spectrum of the former, the quinonoid proton, resonating at δ 6,38, was somewhat shielded by the adjacent cyclopropyl group, the cyclopropyl methine proton signal appeared as a multiplet at δ 2,28, the signal for the methylene protons *cis* to the methine proton as a multiplet at δ 1,0 − 1,3, and that for the methylenes *trans* to the methine proton as a multiplet at δ 0,7 − 0,9. The last two assignments could be made since $J_{cis} > J_{trans}$ in cyclopropyl systems.[8] The minor product (6) by comparison exhibited a highly symmetrical spectrum, which included the signal for the methine protons as a quintet at δ 2,00 which split that of the magnetically equivalent methylene protons into a doublet at δ 1,08 (J 8 Hz).

Structural and conformational information derived from the disubstituted quinone (6) in the solid state is presented elsewhere.[9]

Subjection of 2-cyclopropyl-1,4-naphthoquinone (1) to heating, and to ultraviolet irradiation in cyclohexane (450 W high-pressure Hanovia photoreactor and a Pyrex filter) led to decomposition of starting material without the isolation of any new products. Unlike its heterocyclic

analogue, 2-aziridin-1-yl-1,4-naphthoquinone (3), quinone (1) was recovered unchanged on exposure to sodium iodide either in acetone or in 1,2-dimethoxyethane.

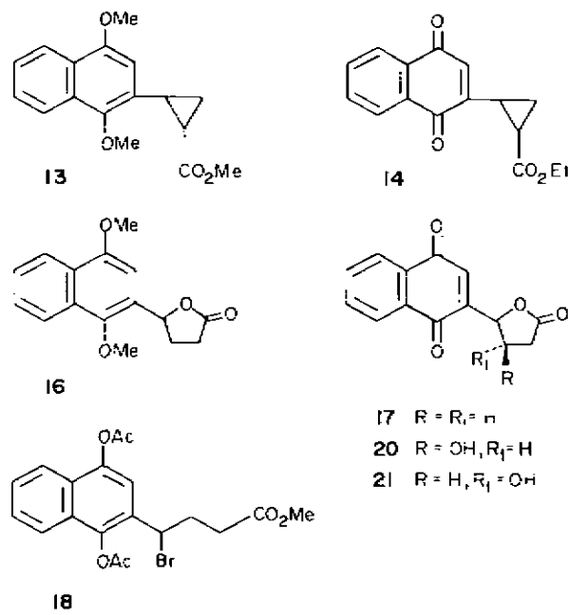
Access to 2-cyclopropyl-1,4-naphthoquinone substituted in the three-membered ring was gained during studies related to the synthesis of the juglomycins A and B.[10] 2-Bromo-1,4-naphthoquinone (7),[11] on alkylation with monomethyl (or monoethyl) glutarate by the Jacobsen–Torssell method, afforded the quinonoid ester (8) (in the case of the methyl ester), which gave the corresponding naphthalene dimethyl ether (9) on reductive methylation. Removal of bromine by hydrogenolysis yielded the naphthalene (10). This was converted into the bromo-ester (11), with *N*-bromosuccinimide; the formation of the product (11) was established by its ^{1}H n.m.r. spectrum, which included a one-proton multiplet at δ 5,76. Boiling the crude product (11) in lutidine furnished the *trans*-olefinic ester (12) as evidenced by the olefinic proton coupling constant of 16 Hz. This compound was a key intermediate from which the 5-deoxy-juglomycins A and B (20) and (21) could be synthesized by divergent routes.[10] Alternatively, treatment of the crude bromo-ester (11) under reflux with potassium t-butoxide in tetrahydrofuran yielded the naphthalenic cyclopropyl ester (13) (73%).



The ethyl ester analogue (which was used in this instance, as all material available in the methyl series was required for the synthesis of the 5-deoxyjuglomycins) of 13, which was prepared by the same route from monoethyl glutarate, was converted to the corresponding quinone (14) by oxidative demethylation with silver(II) oxide.[12] The stereochemistry about the cyclopropane rings of 13 and 14 has not been determined.

The bromo-ester (11) was used without purification since its formation proceeded virtually quantitatively. Attempted chromatography on silica to remove trace impurities resulted in its partial conversion to the hydroxy-ester (15), presumably by means of adventitious moisture. Hydroxy-ester (15) was in turn partly cyclized on the silica to the lactone (16). This lactone gave a high yield of the quinonoid lactone (17) upon oxidative demethylation with silver(II) oxide.

No doubt the ease of displacement of bromide ion from the dimethyl ether (11) was associated with the *ortho*-methoxyl group, since the corresponding diacetate (18), prepared by a related route, *viz.* reductive acetylation of the quinone (8), hydrogenolysis, and subsequent bromination of the product, was readily purified by chromatography without loss of bromide. On heating in lutidine, this gave the corresponding *trans*-olefin (19).



2-Bromo-1,4-naphthoquinone (7) was chosen as starting material for the juglomycin models since, in the natural products themselves, selective alkylation of juglone at the 2-position relative to the 5-hydroxyl group was necessary. Therefore bromine in 3-bromojuglone[13] was used to direct alkylations at C(2).[14] In the synthesis of the cyclopropyl quinone (14), it might well be possible to mono-alkylate naphthoquinone directly, thereby obviating the use of bromine, although complications with bisalkylation might arise. This avenue was not investigated.

Experimental

Unless otherwise stated, i.r. spectra were measured for solutions in $CHCl_3$. N.m.r. spectra were measured in [^{2}H]-chloroform with tetramethylsilane as internal reference. Dry-column chromatography was performed using Merck Kieselgel 60 (70 – 230 mesh), and light petroleum refers to the fraction, b.p. 60 – 80 °C.

2-Cyclopropyl-1,4-naphthoquinone (1) *and 2,3-dicyclopropyl-1,4-naphthoquinone* (6)

Ammonium peroxodisulphonate (6,2 g) in water (50 ml) was added at a bath temperature of 80 – 85 °C to a stirred mixture of cyclopropyl

carboxylic acid (0,95 g), silver nitrate (1 g) and naphthoquinone (1,58 g) in water (25 ml) and cyclohexane (25 ml) over 45 min. The reaction mixture was stirred for 10 min after addition was completed, and then worked up by cooling and extracting with ether. The ether extract was washed with 10% sodium bicarbonate solution until excess acid had been removed, and then once with water. The ethereal solution was dried with sodium sulphate and evaporated under reduced pressure. The resulting brown oil (1,87 g) was chromatographed on a silica column using ethyl acetate-light petroleum (5:195 – 1:9) as eluent. An early fraction afforded 2,3 *dicyclopropyl*-1,4-*naphthoquinone* (**6**) as yellow needles (0,62 g, 26%), m.p. 73 – 75 °C, δ 1,08 (8H, d, J 8 Hz, cyclopropyl CH_2), 2,00 (2H, quintet, J 8 Hz, cyclopropyl CH), 7,65 (2H, m, 6- and 7 H), and 7,96 (2H, m, 5- and 8 H) (Found: M^+, 238,09983. Calc. for $C_{16}H_{14}O_2$: M, 238,09935). A later fraction afforded 2-*cyclopropyl*-1,4-*naphthoquinone* (**1**) as yellow needles (0,96 g, 48,5%) m.p. 110 – 112 °C, δ 0,85 (2H, m, cyclopropyl CH_2), 1,16 (2H, m, cyclopropyl CH_2), 2,28 (1H, m, cyclopropyl CH), 6,38 (1H, s, 3-H), 7,75 (2H, m, 6- and 7-H), and 8,08 (2H, m, 5- and 8-H) (Found: C, 78,5; H, 5,15. Calc. for $C_{13}H_{10}O_2$: C, 78,75; H, 5,1%).

3-*Bromo*-2-(3-*carbomethoxypropyl*)-1,4-*naphthoquinone* (**8**)

2-Bromo-1,4-naphthoquinone (1,0 g) was alkylated directly with glutaric acid monomethyl ester (1,3 g) and silver nitrate (1,0 g) in a mixture of acetonitrile (12 ml) and water (12 ml) to which was added a solution of ammonium peroxodisulphonate (2,6 g) in water (10 ml) at 60 – 65 °C with vigorous stirring over 1 h. The mixture was stirred for a further 10 min and then worked up as for **1**. Chromatography (ethyl acetate-light petroleum, 1:9) as above afforded the *quinone* (**8**) as yellow needles (1,0 g, 70%), m.p. 104 – 105 °C, ν_{max} (CCl_4) 1742, 1681, 1668, and 1596 cm^{-1}, δ 1,92 (2H, quintet, J 7Hz, 2′-CH_2), 2,46 (2H, t, J 7Hz, 3′-CH_2), 2,91 (2H, t, J 7Hz, 1′-CH_2), 3,67 (3H, s, CO_2CH_3), 7,62 – 7,80 (2H, m, 6- and 7-H), and 8,00 – 8,20 (2H, m, 5- and 8-H) (Found: C, 53,45; H, 3,9. Calc. for $C_{15}H_{13}BrO_4$: C, 53,45; H, 3,9%).

3 *Bromo* 2-(3 *carbomethoxypropyl*)-1,4 *dimethoxynaphthalene* (**9**)

The quinone (**8**) (1,5 g) in diethyl ether (30 ml) was shaken with a solution of sodium dithionite (2,4 g) in water (30 ml) until the organic layer had lost its yellow colour. The ether layer was then dried with magnesium sulphate and evaporated to give the hydroquinone as an off-white solid which was immediately dissolved in dry acetone (50 ml) and treated with anhydrous potassium carbonate (3 g) and dimethyl sulphate (3 g) under nitrogen. The mixture was stirred vigorously and heated under gentle reflux for 5 h. The mixture was cooled and filtered, and the filtrate was evaporated to give an oily residue. This oily residue was taken up in diethyl ether and washed successively with concentrated aqueous ammonia solution (10 ml), water, 2M-hydrochloric acid (20 ml), and finally with water. The organic layer was dried with magnesium sulphate and evaporated to yield the *dimethyl ether* (**9**), (1,57 g, 96%), m.p. 80 – 81 °C (from dichloromethane-light petroleum), ν_{max} 1727, 1581, and 1456 cm^{-1}, δ 2,00 (2H, quintet, J 7 Hz, 2′-CH_2), 2,45 (2H, t, J 7Hz, 3′-CH_2), 3,04 (2H, t, J 7 Hz, 1′-CH_2), 3,66 (3H, s, CO_2CH_3), 3,90 (3H, s, OCH_3), 3,96 (3H, s, OCH_3), 7,40 – 7,62 (2H, m, 6- and 7-H), and 7,94 – 8,18 (2H, m, 5- and 8-H) (Found: C, 55,4; H, 5,2. Calc. for $C_{17}H_{19}BrO_4$: C, 55,6; H, 5,2%).

2-(3-*Carbomethoxypropyl*)-1,4-*dimethoxynaphthalene* (**10**)

The dimethyl ether (**9**) (500 mg), in glacial acetic acid (5 ml) containing palladium-carbon catalyst (10% Pd; 100 mg) and anhydrous sodium acetate (100 mg) was hydrogenolysed at 35 °C. The mixture was then cooled and filtered, and the solvent was removed to give the *product* (**10**) as a clear oil (390 mg, 100%), ν_{max} (neat) 1740, 1630, and 1600 cm^{-1}, δ 2,04 (2H, quintet, J 7 Hz, 2′-CH_2), 2,42 (2H, t, J 7 Hz, 3′-CH_2), 2,84 (2H, t, J 7 Hz, 1′-CH_2), 3,66 (3H, s, CO_2CH_3), 3,86 (3H, s, OCH_3), 3,96 (3H, s, OCH_3), 6,59 (1H, s, 3-H), 7,35 – 7,60 (2H, m, 6- and 7-H), and 7,82 – 8,09 and 8,10 – 8,18 (1H each, 2×m, 5- and 8-H) (Found: C, 70,5; H, 6,9. Calc. for $C_{17}H_{20}O_4$: C, 70,8; H, 6,9%).

Trans-2-(3-*carbomethoxyprop*-1-*enyl*)-1,4-*dimethoxynaphthalene* (**12**)

The compound (**10**) (300 mg) was heated under gentle reflux in dry carbon tetrachloride (15 ml) containing *N*-bromosuccinimide (225 mg) and a catalytic amount of benzoyl peroxide. The reaction was halted when t.l.c. indicated that all the starting material had reacted. The solution was cooled and filtered, and the solvent was removed to give crude 2-(1-*bromo*-3-*carbomethoxypropyl*)-1,4-*dimethoxynaphthalene* (**11**), δ 2,34 – 2,84 (4H, m, CH_2CH_2), 3,64 (3H, s, CO_2CH_3), 3,93 (3H, s, OCH_3), 3,98 (3H, s, OCH_3), 5,76 (1H, m, 1′-H), 6,81 (1H, s, 3-H), 7,38 – 7,64 (2H, m, 6- and 7 H), and 7,94 – 8,30 (2H, m, 5- and 8 H).

The crude bromide (**11**) (150 mg) was heated under reflux in dry lutidine for 1,5 h. The solution was cooled and the lutidine hydrobromide was filtered off. Removal of the solvent gave a dark solid residue which yielded the *olefin* (**12**) on recrystallization from dichloromethane light petroleum (130 mg, 90%), m.p. 61,5 – 62 °C, ν_{max} 1739 and 1600 cm^{-1}, δ 3,34 (2H, d, J 7 Hz, CH_2), 3,70 (3H, s, CO_2CH_3), 3,84 (3H, s, OCH_3), 3,94 (3H, s, OCH_3), 6,34 (1H, d×t, J 16 Hz and 7 Hz, 2′ H), 6,84 (1H, s, 3-H), 7,00 (1H, d, J 16 Hz, 1′-H), 7,30 – 7,58 (2H, m, 6- and 7-H), and 7,94 – 8,09 and 8,10 – 8,28 (1H each, 2×m, 5- and 8-H) (Found: C, 71,35; H, 6,5. Calc. for: $C_{17}H_{18}O_4$: C, 71,3; H, 6,35%).

2-(2-*Carbomethoxycyclopropyl*)-1,4-*dimethoxynaphthalene* (**13**)

The bromo-compound (**11**) (100 mg) and potassium t-butoxide (60 mg) were heated under reflux in dry tetrahydrofuran for 1 h. The mixture was cooled, poured into water, and extracted with ether. The organic layer was dried with magnesium sulphate and evaporated to give a residue which was purified on p.l.c. (ethyl acetate-light petroleum, 1:99). After three developments, the major band afforded the *cyclopropyl product* (**13**) as a clear oil (55 mg, 73%), ν_{max} 1720, 1632, and 1598 cm^{-1}, δ 1,35 – 2,17 (3H, m, $CH_2CHCO_2CH_3$), 2,89 – 3,13 (1H, m, Ar-$CHCH_2$), 3,75 (3H, s, CO_2CH_3), 3,91 (3H, s, OCH_3), 3,93 (3H, s, OCH_3), 7,21 (1H, s, 3-H), 7,37 – 7,80 (2H, m, 6- and 7-H), and 7,95 – 8,25 (2H, m, 5- and 8-H) (Found: C, 71,2; H, 6,5. Calc. for $C_{17}H_{18}O_4$: C, 71,3; H, 6,35%).

2-(2-*Carbethoxycyclopropyl*)-1,4-*naphthoquinone* (**14**)

2-(2-Carbethoxycyclopropyl)-1,4-dimethoxynaphthalene (51 mg) was treated with silver(II) oxide (84 mg) and 6M-nitric acid (0,5 ml, dropwise) in dry dioxane (10 ml). The reaction was stopped, when the silver(II) oxide had been consumed, by the addition of chloroform (8 ml) and water (4 ml). The chloroform layer was washed with water, dried, and evaporated. The residue was purified by p.l.c. (ethyl acetate-light petroleum, 1:9) which afforded the *quinone* (**14**) as yellow needles (32 mg, 71%), m.p. 120 – 121 °C, ν_{max} 1746, 1678, 1605, 1378, and 1338 cm^{-1}, δ 1,27 (3H, t, J 7Hz, -OCH_2CH_3), 1,60 – 1,79 (2H, m, 3′-CH_2), 1,95 – 2,14 (1H, m, 2′-CH), 2,66 – 2,86 (1H, m, 1′-CH), 4,18 (2H, q, J 7Hz, -OCH_2CH_3), 6,42 (1H, s, 3H), 7,59 – 7,73 (2H, m, 6- and 7-H), 7,92 – 8,07 (2H, m, 5- and 8-H) (Found: C, 70,8; H, 5,0. Calc. for $C_{16}H_{14}O_4$: C, 71,1; H, 5,2%).

2-(γ *Butyrolacton*-5-*yl*)-1,4-*dimethoxynaphthalene* (**16**)

Attempted purification of the bromo-compound (**11**) (100 mg) by p.l.c. gave two products which could be isolated separately from the plate. The front band proved to be the *lactone* (**16**) (35 mg, 47%), m.p. 128 – 129 °C, ν_{max} 1765, 1630, and 1600 cm^{-1}, δ 2,10 – 2,89 (4H, m, lactone CH_2CH_2), 3,92 (3H, s, OCH_3), 3,99 (3H, s, OCH_3), 5,97 (1H, dd, J 3 and 5 Hz, Ar-$CHCH_2$), 6,69 (1H, s, 3-H), 7,40 – 7,65 (2H, m, 6- and 7 H), and 7,92 – 8,10 and 8,14 – 8,35 (1H each, 2×m, 5- and 8-H) (Found: C, 70,35; H, 5,85. Calc. for $C_{16}H_{16}O_4$: C, 70,55; H, 5,90%). A second band gave the *hydroxy-ester* (**15**) (40 mg, 48%) as an oil, ν_{max} 3450br, 1720br, 1633, and 1599 cm^{-1}, δ 2,00 – 2,78 (4H, m, CH_2CH_2), 3,66 (3H, s, CO_2CH_3), 3,89 (3H, s, OCH_3), 3,98 (3H, s, OCH_3), 5,28 (1H, t, J 6Hz, 1′-H), 6,83 (1H, s, 3-H), 7,38 – 7,62 (2H, m, 6- and 7-H), and 7,92 – 8,09 and 8,10 – 8,30 (1H each, 2×m, 5- and 8-H).

2-(γ *Butyrolacton*-5-*yl*)-1,4-*naphthoquinone* (**17**)

The lactone (**16**) (50 mg) in dry dioxane (5 ml) was oxidized with silver (II) oxide (100 mg) and 6M-nitric acid (0,3 ml) as described for preparing compound (**14**). Work-up afforded a yellow solid which was purified by p.l.c. (ethyl acetate-light petroleum, 1:4). This treatment gave the pale yellow *quinone* (**17**) (32 mg, 72%), m.p. 152 – 154 °C (decomp.) (from dichloromethane-light petroleum), ν_{max} 1787, 1670, and 1600 cm^{-1}, δ 1,94 – 3,06 (4H, m, lactone CH_2CH_2), 5,60 (1H, t, J 7 Hz, lactone $CHCH_2CH_2$), 7,02 (1H, d, J 2 Hz, 3-H), 7,68 – 7,90 (2H, m, 6- and 7-H), and 8,00 – 8,20 (2H, m, 5- and 8-H) (Found: C, 69,3; H, 4,1. Calc. for $C_{14}H_{10}O_4$: C, 69,4; H, 4,1%).

3-*Bromo*-1,4-*diacetoxy*-2-(3-*carbomethoxypropyl*)*naphthalene*

3-Bromo-2-(3-carbomethoxypropyl)-1,4-naphthoquinone (500 mg) in pyridine (1 ml) and acetic anhydride (6 ml) was treated with zinc dust

(280 mg), and the solution was heated on a steam bath. Further additions of zinc dust were made after 7 and 16 min (2×280 mg). The mixture was then heated under gentle reflux for a further 10 min, poured into ice water, and extracted with chloroform. The organic layer was dried with magnesium sulphate and the solvent was removed to give an oily residue, which was chromatographed on silica (ethyl acetate–light petroleum, 1:9) to afford the *bromo-diacetate* as a colourless solid (570 mg, 90%), m.p. 113 – 114 °C, ν_{max} 1764, 1724, and 1600 cm^{-1}, δ 1,94 (2H, quintet, J 7Hz, 2'-CH_2), 2,43 (2H, t, J 7Hz, 3'-CH_2), 2,50 (3H, s, $COCH_3$), 2,52 (3H, s, $COCH_3$), 2,92 (2H, t, J 7Hz, 1'-CH_2), 3,68 (3H, s, CO_2CH_3), and 7,42 – 7,82 (4H, m, 5-, 6-, 7-, and 8-H) (Found: C, 54,4; H, 4,6. Calc. for $C_{19}H_{19}BrO_6$: C, 53,9; H, 4,5%).

1,4-*Diacetoxy*-2-(3-*carbomethoxypropyl*)*naphthalene*

3-Bromo-1,4-diacetoxy-2-(3-carbomethoxypropyl)naphthalene (300 mg), in glacial acetic acid (5 ml) containing palladium–carbon catalyst (10% Pd, 100 mg) and anhydrous sodium acetate (100 mg), was hydrogenolysed for 4 h at 65 – 70 °C and atmospheric pressure. The mixture was cooled and filtered, and the solvent was removed. The colourless oily residue was taken up in chloroform (25 ml) and washed with water (2×10 ml). The organic layer was dried and evaporated to afford the *product* as a clear oil (230 mg, 95%). An analytical sample was prepared by p.l.c. (ethyl acetate–light petroleum, 1:4) ν_{max} (CCl_4) 1788, 1770, 1740, and 1605 cm^{-1}, δ 1,97 (2H, quintet, J 7 Hz, 2'-CH_2), 2,37 (2H, t, J 7 Hz, 3'-CH_2), 2,46 (3H, s, $COCH_3$), 2,48 (3H, s, $COCH_3$), 2,71 (2H, t, J 7 Hz, 1'-CH_2), 3,67 (3H, s, CO_2CH_3), 7,15 (1H, s, 3-H), 7,40 – 7,60 (2H, m, 6- and 7-H), and 7,61 – 7,87 (2H, m, 5- and 8-H) (Found: C, 66,05; H, 5,9. Calc. for $C_{19}H_{20}O_6$: C, 66,25; H, 5,85%).

1,4-*Diacetoxy*-2-(1-*bromo*-3-*carbomethoxypropyl*)*naphthalene* (18)

1,4-Diacetoxy-2-(3-carbomethoxypropyl)naphthalene (130 mg) was heated under gentle reflux in dry carbon tetrachloride (15 ml) containing *N*-bromosuccinimide (81 mg) and a catalytic amount of benzoyl peroxide. The reaction was halted when t.l.c. indicated the total consumption of the starting material. The solution was cooled and filtered, and the solvent was removed. The oily residue was chromatographed on silica (ethyl acetate–light petroleum, 1:4) to afford the *bromo-product* (18) (130 mg, 81%), m.p. 94 – 95 °C, ν_{max} 1764, 1735, and 1608 cm^{-1}, δ 2,44 (3H, s, $COCH_3$), 2,52 (3H, s, $COCH_3$), 2,30 – 2,80 (4H, m, 2×CH_2), 3,64 (3H, s, CO_2CH_3), 5,46 (1H, m, 1'-H), 7,42 (1H, s, 3-H), and 7,38 – 7,92 (4H, m, 5-, 6-, 7-, and 8-H) (Found: C, 54,1; H, 4,6. Calc. for $C_{19}H_{19}BrO_6$: C, 53,9; H, 4,5%).

Acknowledgements

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14 The synthesis of the juglomycins A and B will be recorded elsewhere.