Synthesis of Some Semi-synthetic Nemadectins

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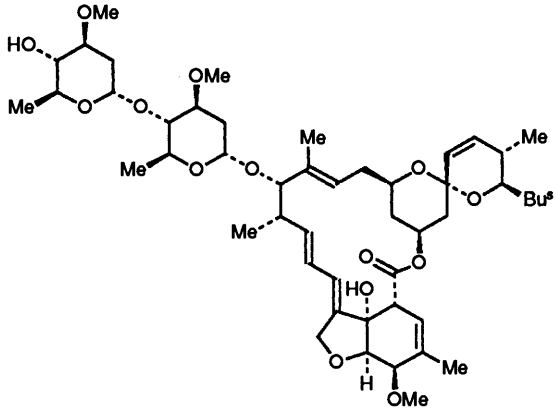
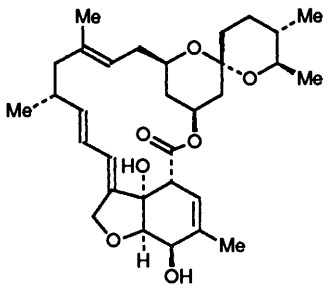
The natural product (**3**) has been modified to provide the semi-synthetic nemadectins (**15**), (**17**), and (**18**).

There has been a considerable amount of interest focussed on the naturally occurring macrocyclic lactones called the avermectins and the milbemycins [*e.g.* avermectin-A_{1a} (**1**) and milbemycin-1a (**2**)].[1] Both the milbemycins and avermectins display potent anthelmintic activity and modification of peripheral functional groups on the molecule has been undertaken to optimize desirable biological activity.[2]

Recently a series of 16-membered ring lactones, referred to as the nemadectins [*e.g.* nemadectin B and C, compounds (**3**) and (**4**)], was discovered independently by scientists in the Cyanamid[3] and Glaxo[4] laboratories; the biological activity of these nemadectins and their derivatives surpasses that observed for most members of the avermectin family and indeed rivals the most potent members of that family. Therefore, transformation of the functional groups on the periphery of these molecules also has been undertaken.[5]



(1)



(2)

The biologically active avermectins and nemadectins have two bicyclic ring systems connected by an ester linkage and a C_8-triene 'tether'. Undoubtedly both the spiroacetal moiety and the oxabicyclononene unit are crucial for the observation of the exquisite anthelmintic activity while the connecting octatriene unit may well be less important. With this in mind, we have explored methods for the radical modification of the nemadectin backbone whilst leaving the bicyclic units intact.

Results

Ozonolysis of nemadectin B (**3**) gave the ketone (**5**) (17%), the keto-aldehyde (**6**) (20%) and the keto–dial (**7**) (25%). (The yields are based on consumed starting material.) Obviously the C_{26}-alkene unit and the backbone triene systems are attacked non-specifically by the oxidizing agent.[6]

Protection of the exocyclic double bond was achieved by initial conversion of the natural product (**3**) into the chloro-compound (**8**) (62%) using calcium hypochlorite and solid carbon dioxide in dichloromethane–water.[7] The mono-halogeno compound (**8**) was separated from a small quantity of the dichloro compound (**9**) by chromatography over silica. Ozonolysis of the Δ^{26}-27-chloro-27-hydronemadectin B (**8**) proceeded relatively cleanly to provide the dial (**10**) (59%) as a yellow foam. In a separate experiment, nemadectin Factor B (**3**) was chlorinated and ozonized, without purification at either step, and the crude product was reduced using sodium borohydride and cerium(III) chloride. Chromatography provided the tetraol (**11**) in 28% overall yield.

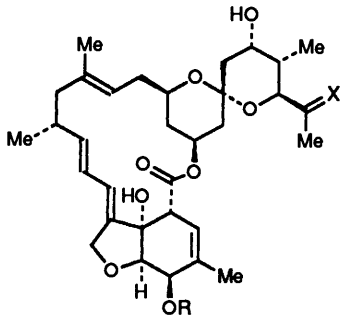
Reduction of the chloro compound (**11**) with tributyltin hydride in dry toluene furnished the *E*-alkene (**12**) contaminated with a small amount (*ca.* 20%) of the isomeric alkene (**13**).

The halogeno tetraol (**11**) was treated with oxalyl chloride, malonyl chloride, succinyl chloride, and glutaryl chloride to give a series of tris-lactones (**14**; n = 0, 1, 2, and 3). The yield of the unstable oxalate (**14**; n = 0) was very low (4%), but the malonate, succinate and glutarate derivatives were isolated in yields of 24, 26, and 41%, respectively (these yields are based on recovered starting material). Similarly the mixture of alkenes (**12**) and (**13**) reacted with malonyl chloride to afford the compounds (**15**) and (**16**) (n = 1) (23%) in the ratio 82:18, whilst the same mixture of alkenes gave the lactones (**15**; n = 3) and (**16**; n = 3) (28%) (ratio 81:19) on reaction with glutaryl chloride.

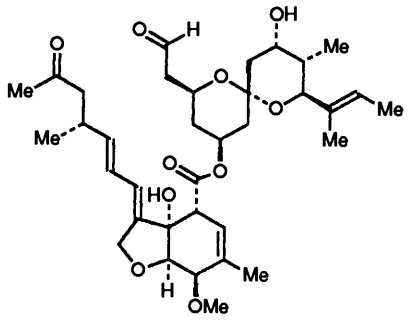
The malonate diester (**15**; n = 1) was converted into the 5-hydroxy compound (**17**; n = 1) by sequential treatment with mercuric acetate, acetic acid and sodium borohydride.[8] The triol (**17**; n = 1) was obtained free from isomeric alkenes after chromatography over silica; the compound is a close analogue of nemadectin Factor C (**4**). Treatment of the halogeno tetraol (**11**) with toluene-*p*-sulphonyl chloride and pyridine in dichloromethane produced the ether (**18**) and two tosylates (**19**) and (**20**) in yields of 18, 18, and 8% based on recovered starting material.

Conclusions

Nemadectin B (**3**) gave a mixture of the mono-, di-, and tri-carbonyl compounds (**5**)–(**7**) when oxidized by ozone: in



(3) R = Me; X = CHMe (*E*)
(4) R = H; X = CHMe (*E*)
(5) R = Me; X = O



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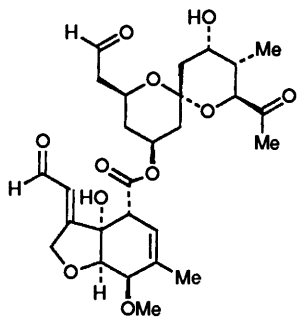

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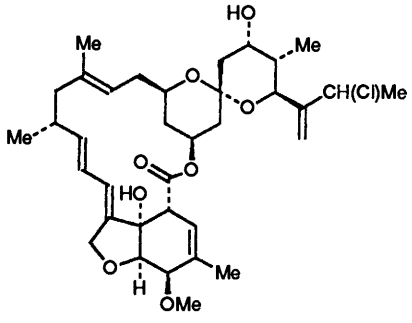

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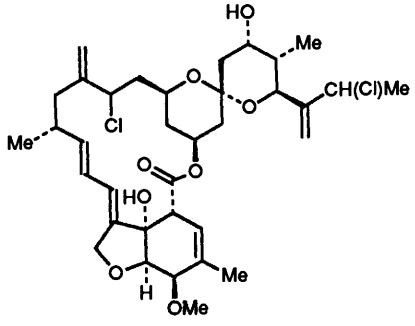

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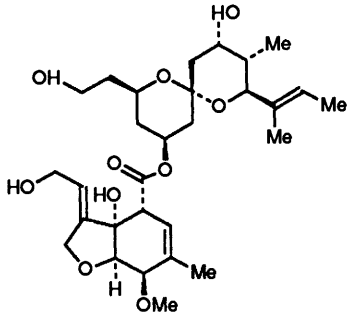

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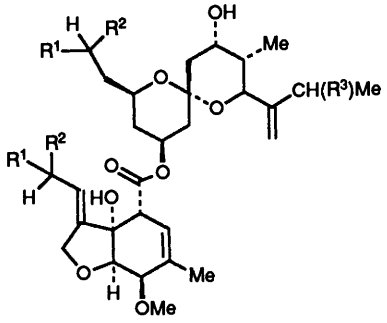
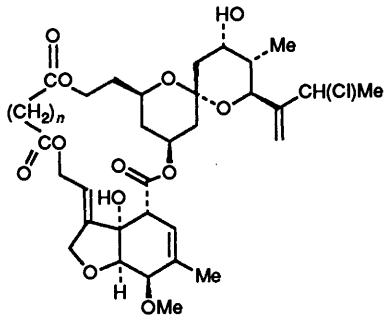


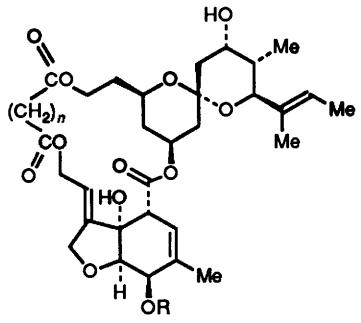
(10) R^1R^2 = O; R^3 = Cl
(11) R^1 = H; R^2 = OH; R^3 = Cl
(13) R^1 = R^3 = H; R^2 = OH



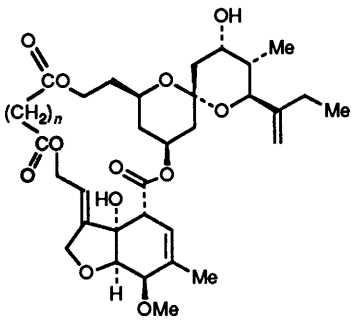
(14)

contrast halogenation with calcium hypochlorite is a very selective process and this affords the allylic chloride (**8**) in good yield. The 26-methylene unit in compound (**8**) is not readily oxidized such that ozonolysis of (**8**) gives, as required, the dial (**10**) or the tetraol (**11**) in reasonable yield. The chlorine atom in compound (**11**) can be replaced by a hydrogen atom by a radical reduction process such that the C(26)-*E*-alkene unit, a feature of nemadectin B, is largely regenerated, though the triene (**12**) that is produced is contaminated with a small amount of the isomeric triene (**13**). On reaction of the seco-compound (**11**) with dicarboxylic acid chlorides the lactones (**14**) are formed with re-establishment of the macrocyclic ring. Similarly the tetraols (**12**) and (**13**) provide the tris-lactones (**15**) and (**16**) and the former compound was converted into the 5-hydroxy compound (**17**). The halogeno tetraol (**11**) was converted into the allylic ether (**18**) in low yield.

In all the work described above care was taken to avoid the



(15) R = Me
(17) R = H



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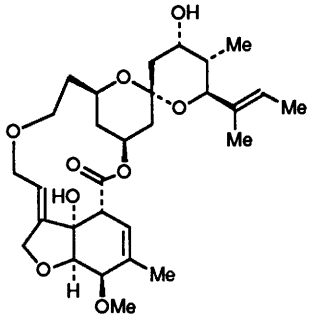

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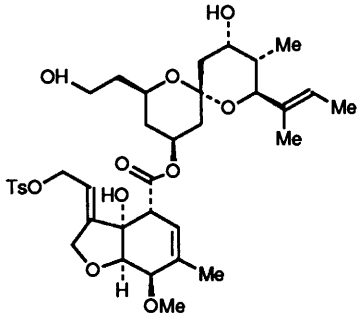

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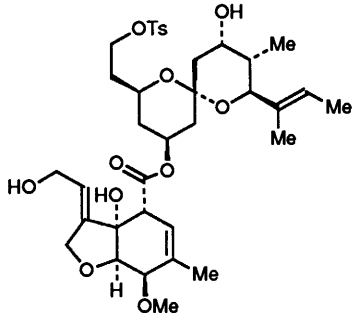

(20)

migration of the Δ^3-double bond into conjugation with the carbonyl group. The nemadectins are highly functionalized molecules and therefore it should not be surprising that yields of products are often modest. Nevertheless many of the reactions described above were highly selective allowing access to the semi-synthetic nemadectins (**15**), (**17**), and (**18**) having, as a sole change, a substantially modified backbone unit. The biological activity of these semi-synthetic nemadectins will be reported elsewhere.

Experimental

Unless stated otherwise, all reagents were obtained from commercial suppliers and used without further purification. Toluene was dried over, and distilled from, sodium wire. Methanol and ethanol were distilled from the corresponding magnesium alkoxides. Dichloromethane was dried over, and distilled from, calcium hydride. Pyridine was dried over, and distilled from, potassium hydroxide. Hexane and ethyl acetate were redistilled prior to use. Brine refers to a saturated aqueous solution of sodium chloride. Ozone was generated with a BOC ozonizer MK II.

Reactions were monitored by TLC on Merck Kieselgel 60 F_{254}, 0.25 mm plates. Preparative column chromatography was performed under low pressure on Camlab silica gel (0.04–0.063 mm/230–400 mesh). Solvent mixtures are expressed as volume:volume ratios.

250 MHz ^{1}H and 63 MHz ^{13}C NMR spectra were recorded on a Bruker AM250 spectrometer except for experiments conducted by the SERC High Field NMR Service, Warwick, as indicated. Spectra were measured in deuteriochloroform and chemical shifts are quoted in ppm downfield from tetramethylsilane used as internal reference. The multiplicity of ^{13}C signals was determined by separate DEPT experiments and all assignments are consistent with this information. IR spectra of solutions in chloroform were recorded on a Perkin-Elmer 881 IR spectrophotometer. Mass spectra were obtained on a VG Micromass MM16F mass spectrometer and from the SERC Mass Spectrometry Centre, Swansea. Elemental analyses were conducted by Butterworth Laboratories Ltd., Teddington.

Ozonolysis of Nemadectin B (**3**).—Nemadectin B (**3**) (2.15 g; 3.59 mmol) was dissolved in dichloromethane (215 ml) and stirred at −48 °C. A stream of oxygen-containing ozone was bubbled through the solution until TLC indicated the consumption of most of the starting material and the appearance of several more polar products. The solution was purged with oxygen and then nitrogen and dimethyl sulphide (2.28 g, 36.6 mmol; 2.69 ml) was added. The solution was allowed to warm to room temperature and was then stirred for 17 h to give a negative starch–iodide test for peroxidic material. Concentration of the solution under reduced pressure followed by chromatography on silica gel (250 g), eluting with a gradient of 83:16:1–0:95:5 hexane–ethyl acetate–ethanol, gave recovered starting material (**3**) (0.893 g) and the ketone (**5**) (0.185 g); δ_H 5.81–5.67 (2 H, m, 9-H, 10-H), 5.41–5.19 (3 H, m, 3-H, 11-H, 19-H), 4.99–4.89 (1 H, m, 15-H), 4.72–4.57 (2 H, AB, 8a-H_2), 4.01 (1 H, d, *J* 6 Hz, 6-H), 3.98–3.92 (1 H, m, 5-H), 3.87 (1 H, d, 11 Hz, 25-H), 3.84–3.76 (1 H, m, 23-H), 3.72 (1 H, s, 7-OH), 3.69–3.56 (1 H, m, 17-H), 3.49 (3 H, s, 5-OMe), 3.44 (1 H, d, *J* 10 Hz, 23-OH), 3.33–3.28 (1 H, m, 2-H), 2.51–2.31 (1 H, m, 12-H), 2.24 (3 H, s, 26-Me), 1.80 (3 H, s, 4-Me), 1.52 (3 H, s, 14-Me), 2.31–1.41 (10 H, m, 13-H_2, 16-H_2, 18-H_{eq}, 20-H_2, 22-H_2, 24-H), 0.99 (3 H, d, *J* 7 Hz, 12-Me), 0.93 (3 H, d, *J* 7 Hz, 24-Me), and 1.03–0.83 (1 H, m, 18-H_{ax}); δ_C 207.1 (26), 173.5 (1), 142.5 (11), 139.8 (8), 137.8 (14), 136.1 (4), 123.5 (10), 119.9 (15), 119.6 (9), 118.4 (3), 99.5 (21), 80.5 (7), 77.7 (6), 76.9 (5), 76.6 (25), 69.4 (23), 68.4 (17), 68.2 (8a), 67.2 (19), 57.7 (5-OMe), 48.5 (13), 45.7 (2), 40.7 (22), 40.6 (20), 35.9 (12 and 24), 35.8 (18), 34.6 (16), 25.6 (26a), 22.3 (12a), 19.8 (4a), 15.5 (14a), and 12.9 (24a); ν_{max} 3 512, 2 969, 2 922, 1 712, 1 450, 1 372, 1 165, 1 142, 1 118, 1 093, 992, and 965 cm^{-1} (Found: M^+, 586.3156. $C_{33}H_{46}O_9$ requires *M*, 586.3142]. Also isolated were the keto–aldehyde (**5**) (0.239 g); δ_H 5.95 (1 H, dt, *J* 2, 11 Hz, 9-H), 5.83 (1 H, ddd, *J* 1, 11, 15 Hz, 10-H), 5.67–5.53 (2 H, m, 11-H, 27-H), 5.36–5.21 (2 H, m, 3-H, 19-H), 4.70–4.55 (2 H, AB, 8a-H_2), 4.35–3.73 (6 H, m, 5-H, 6-H,

7-OH, 23-H, 23-OH, 25-H), 3.48 (3 H, s, 5-OMe), 3.53–3.42 (1 H, m, 17-H), 3.37–3.31 (1 H, m, 2-H), 2.83–2.56 (3 H, m, 12-H, 16-H_2), 2.52–2.34 (2 H, AB, 13-H_2), 2.12 (3 H, s, 14-Me), 1.80 (3 H, s, 4-Me), 1.64 (3 H, dd, *J* 1, 7 Hz, 27-Me), 1.59 (3 H, s, 26-Me), 2.17–1.24 (6 H, m, 18-H_{eq}, 20-H_2, 22-H_2, 24-H), 1.02 (3 H, d, *J* 7 Hz, 12-Me), 0.81 (3 H, d, *J* 7 Hz, 24-Me), 1.08–0.75 (1 H, m, 18-H_{ax}); δ_C 207.3 (14), 199.0 (15), 172.8 (1), 143.1 (8), 140.4 (11), 137.0 (4), 133.7 (26), 124.4 (27), 124.2 (10), 119.6 (9), 117.8 (3), 99.8 (21), 80.4 (7), 78.6 (6), 77.2 (5), 76.7 (25), 69.1 (23), 68.8 (8a), 68.1 (19), 63.1 (17), 57.9 (5-OMe), 50.5 (13), 49.0 (16), 47.0 (2), 41.1 (22), 40.2 (20), 36.1 (18), 35.9 (24), 32.6 (12), 30.4 (14a), 20.0 (12a), 19.6 (4a), 13.7 (24a), 13.1 (27a), and 10.7 (26a); ν_{max} 3 444, 2 969, 2 935, 1 711, 1 602, 1 451, 1 378, 1 199, 1 121, 1 089, 995, and 909 cm^{-1}; *m/z*: 612 ($[M - H_2O]^+$), 596 ($[M - H_2O - O]^+$), 580 ($[M - H_2O - MeOH]^+$), and the keto–dialdehyde (**7**) (0.261 g); δ_H 9.77 (1 H, s, 15-H), 9.73 (1 H, d, *J* 5 Hz, 10-H), 6.18 (1 H, dt, *J* 2.5, 5 Hz, 9-H), 5.38–5.20 (2 H, m, 3-H, 19-H), 4.97 (2 H, d, *J* 2.5 Hz, 8a-H_2), 4.24 (1 H, d, *J* 11.3 Hz, 25-H), 4.14 (1 H, d, *J* 6.0 Hz, 6-H), 4.36–3.97 (3 H, m, 5-H, 7-OH, 23-H), 3.83–3.75 (1 H, br s, 23-OH), 3.50 (3 H, s, 5-OMe), 3.53–3.45 (1 H, m, 17-H), 3.37–3.31 (1 H, m, 2-H), 2.84–2.60 (2 H, AB, 16-H_2), 2.27 (3 H, s, 26-Me), 1.83 (3 H, s, 4-Me), 0.99 (3 H, d, *J* 7.2 Hz, 24-Me), and 2.28–0.78 (7 H, m, 18-H_2, 20-H_2, 22-H_2, 24-H); δ_C 206.5 (26), 198.7 (15), 190.0 (10), 172.5 (1), 166.4 (8), 137.0 (4), 118.5 (3), 117.1 (9), 99.6 (21), 79.4 (7), 78.4 (6), 76.4, 76.1 (25 and 5), 69.8 (8a), 68.4 (23), 68.3 (19), 63.6 (17), 58.0 (5-OMe), 48.8 (16), 45.2 (2), 40.7 (22), 39.9 (20), 35.80 (18), 35.76 (24), 26.6 (26a), 19.6 (4a), and 13.1 (24a); ν_{max} 3 460, 2 971, 2 937, 1 722, 1 358, 1 199, 1 144, 1 087, and 1 014 cm^{-1} (Found: M^+, 554.2590. $C_{27}H_{40}NO_{11}$ requires $M + NH_4$, 554.2601).

Δ^{26}-27-*Chloro*-27-*hydronemadectin B* (**8**).—Nemadectin B (**3**) (10.00 g, 16.7 mmol) was dissolved in dichloromethane (200 ml) and stirred at 0 °C. A slurry of calcium hypochlorite (3.34 g, 23.4 mmol) in water (144 ml) was added to the rapidly-stirred solution. Solid carbon dioxide (6 × *ca.* 1.5 g portions) was added and stirring was continued for 20 min. Further calcium hypochlorite (1.43 g, 10.0 mmol) and solid carbon dioxide (4 × *ca.* 1.5 g portions) were added to the mixture and after a further 2 h the cooling bath was removed. After being stirred at room temperature for 1 h, further calcium hypochlorite (2.39 g, 16.7 mmol) and solid carbon dioxide (12 × *ca.* 0.75 g portions) were added. After being stirred at room temperature for 30 min the mixture was diluted with brine (125 ml), water (125 ml), and dichloromethane (50 ml), filtered, and the organic layer was separated. The aqueous phase was extracted with dichloromethane (3 × 120 ml) and the combined organic layers were washed with water (100 ml), dried ($MgSO_4$), filtered and the solvent was evaporated under reduced pressure to give a white foam. Flash chromatography on silica gel (400 g) eluting with 3:1 then 1:1 hexane–ethyl acetate gave the title compound (**8**) (6.24 g), the dihalogeno-compound (**9**) (1.49 g) and a mixture of these two compounds (1.55 g). Further chromatography of the mixed compounds on silica gel (150 g) eluting with 3:1 then 1:1 hexane–ethyl acetate gave the allylic chloride (**8**) (0.34 g; total 6.57 g, 10.4 mmol, 62%); δ_H 5.79–5.65 (2 H, m, 9-H, 10-H), 5.50 (1 H, s, 26a-H), 5.37 (1 H, s, 3-H), 5.32 (1 H, s, 26a-H), 5.40-5.09 (2 H, m, 11-H, 19-H), 4.99–4.88 (1 H, m, 15-H), 4.72–4.54 (3 H, m, 8a-H_2, 27-H), 4.06 (1 H, d, *J* 10.8 Hz, 25-H), 3.99 (1 H, d, *J* 5 Hz, 6-H), 3.96–3.90 (1 H, m, 5-H), 3.48 (3 H, s, 5-OMe), 3.85–3.45 (4 H, m, 7-OH, 17-H, 23-H, 23-OH), 3.31–3.25 (1 H, m, 2-H), 2.50–2.31 (1 H, m, 12-H), 1.78 (3 H, s, 4-Me), 1.72 (3 H, d, *J* 6.5 Hz, 27-Me), 1.51 (3 H, s, 14-Me), 2.31–1.35 (10 H, m, 13-H_2, 16-H_2, 18-H_{eq}, 20-H_2, 22-H_2, 24-H), 0.98 (3 H, d, *J* 7 Hz, 12-Me), 0.90 (3 H, d, *J* 7 Hz, 24-Me), and 1.02–0.82 (1 H, m, 18-H_{ax}); δ_C 173.4 (1), 148.7 (26), 142.5 (11), 139.7 (8), 137.5 (14), 136.0 (4), 123.5 (10), 120.2 (15), 119.6 (9), 118.5 (3), 116.3 (26a), 100.0 (21), 80.4 (7), 77.8 (6), 76.9 (5), 73.5 (25), 69.11 (23), 69.06 (17), 68.2 (8a), 67.5 (19), 57.7 (5-OMe), 54.7 (27), 48.5 (13), 45.7 (2), 41.0 (22), 40.7 (20), 38.1 (24), 35.93 (18), 35.90 (12), 34.6 (16), 25.2 (27a), 22.3 (12a), 19.8 (4a), 15.5 (14a), and 13.9 (24a); ν_{max} 3 506, 2 972, 2 933, 1 710, 1 451, 1 372, 1 339, 1 166, 1 119, 1 092, and 1 000 cm^{-1} (Found: C, 65.45; H, 7.8; Cl, 5.4. $C_{35}H_{49}ClO_8 0.5\ CH_3OH$ requires C, 65.7; H, 7.9; Cl, 5.5%). The bis-chloride (**9**) (0.16 g; total 1.65 g, 15%); δ_H 5.92–5.72 (2 H, m, 9-H, 10-H), 5.67–5.54 (1 H, m, 11-H), 5.49 (1 H, s, 26a-H), 5.35 (1 H, br s, 3-H), 5.29 (1 H, s, 26a-H), 5.43–5.23 (1 H, m, 19-H), 5.10 (1 H, s, 14a-H), 5.02 (1 H, s, 14a-H), 4.74–4.52 (4 H, m, 8a-H_2, 15-H, 27-H), 4.30 (1 H, d, *J* 10 Hz, 25-H), 4.13–3.89 (4 H, m, 5-H, 6-H, 7-OH, 23-H), 3.88–3.77 (1 H, br s, 23-OH), 3.48 (3 H, s, 5-OMe), 3.53–3.27 (2 H, m, 2-H, 17-H), 1.78 (3 H, s, 4-Me), 1.68 (3 H, d, *J* 7 Hz, 27-Me), 2.37–1.48 (11 H, m, 12-H, 13-H_2, 16-H_2, 18-H_{eq}, 20-H_2, 22-H_2, 24-H), 1.03 (3 H, d, *J* 6 Hz, 12-Me), 0.92 (3 H, d, *J* 7 Hz, 24-Me), and 0.87–0.71 (1 H, m, 18-H_{ax}); δ_C 174.4 (1), 148.2 (26), 148.0 (14), 142.8 (11), 141.2 (8), 136.3 (4), 124.1 (10), 119.4 (9), 117.5 (3), 116.9 (26a), 114.7 (14a), 99.9 (21), 80.7 (7), 77.0 (6), 76.9 (5), 73.6 (25), 69.0 (23), 68.0 (8a), 67.3 (19), 66.3 (17), 57.8 (5-OMe), 57.4 (15), 54.3 (27), 45.1 (2), 42.8, 42.4 (16 and 13), 40.9 (22), 40.5 (12), 39.6 (20), 37.6 (24), 36.8 (18), 25.2 (27a), 22.8 (12a), 19.8 (4a), and 13.9 (24a); ν_{max} 3 511, 2 969, 2 936, 1 708, 1 449, 1 370, 1 340, 1 169, 1 116, 1 090, 1 000, and 974 cm^{-1}; *m/z* 666.2 (M^+ for 2 × ^{35}Cl).

Ozonolysis of Δ^{26}-27-*Chloro*-27-*hydronemadectin B* (**8**).—*Method A*. The allylic chloride (**8**) (412 mg, 0.65 mmol) was ozonized by the method described for the lactone (**3**) and chromatographed on silica gel (80 g), eluting with 3% then 5% methanol–dichloromethane, to give a pale yellow foam (262 mg). The foam was dissolved in ethyl acetate (20 ml), washed with brine (3 × 5 ml), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield the dialdehyde (**10**) as a pale yellow foam (225 mg, 0.39 mmol, 59%); δ_H 9.77 (1 H, s, 15-H), 9.70 (1 H, d, *J* 4.5 Hz, 10-H), 6.16 (1 H, dt, *J* 4.5, 2.5 Hz, 9-H), 5.52 (1 H, s, 26a-H), 5.40 (1 H, s, 26a-H), 5.37–5.32 (1 H, m, 3-H), 5.29–5.12 (1 H, m, 19-H), 4.95 (2 H, d, *J* 2.5 Hz, 8a-H_2), 4.61 (1 H, q, *J* 6.5 Hz, 27-H), 4.35 (1 H, d, *J* 11 Hz, 25-H), 4.39–4.22 (1 H, m, 23-H), 4.12 (1 H, d, *J* 4.5 Hz, 6-H), 4.02–3.95 (1 H, m, 5-H), 3.80 (1 H, br s, 7-OH), 3.48 (3 H, s, 5-OMe), 3.51–3.42 (1 H, m, 23-OH), 3.34–3.28 (1 H, m, 2-H), 3.42–3.25 (1 H, m, 17-H), 2.75 (1 H, ddd, *J* 1.5, 9, 18 Hz, 16-H), 2.61 (1 H, dd, *J* 3.5, 18 Hz, 16-H), 1.81 (3 H, s, 4-Me), 1.69 (3 H, d, *J* 6.5 Hz, 27-Me), 2.22–0.82 (7 H, m, 18-H_2, 20-H_2, 22-H_2), 24-H), and 0.91 (3 H, d, *J* 7 Hz, 24-Me); δ_C 199.0 (15), 189.9 (10), 172.3 (1), 166.4 (8), 148.4 (26), 136.7 (4), 118.5 (3), 117.2 (9), 116.7 (26a), 99.8 (21), 79.3 (7), 78.3 (6), 76.4 (5), 73.6 (25), 69.7 (8a), 68.9 (23), 68.5 (19), 63.3 (17), 57.9 (5-OMe), 54.6 (27), 48.9 (16), 45.5 (2), 40.9, 40.0 (20 and 22), 37.7 (24), 35.9 (18), 25.1 (27a), 19.6 (4a), and 13.9 (24a); ν_{max} 3 520, 2 978, 2 935, 1 721, 1 622, 1 449, 1 376, 1 255, 1 088, and 1 002 cm^{-1}.

Method B. Nemadectin B (**3**), was treated with calcium hypochlorite as described for the preparation of allylic chloride (**8**), but the crude product was not chromatographed. A portion of this crude product (4.00 g) was dissolved in dichloromethane (200 ml) and stirred at −48 °C. A stream of oxygen-containing ozone was bubbled through the clear solution until TLC indicated complete consumption of all starting material. The resulting pale yellow solution was purged with nitrogen, and methanol (50 ml) was added. The stirred solution was maintained at −48 °C and cerium(III) chloride heptahydrate (10.69 g, 28.7 mmol) was added. Sodium borohydride (2.17 g, 75.4 mmol) was cautiously added to the mixture in small portions over 8 min, causing vigorous evolution of gas. The mixture was stirred at −48 °C for 10 min, then at room temperature for 2 h, and was then cooled to 0 °C. Ice cold dilute hydrochloric acid (2M; 100 ml) was carefully added to the cooled solution over 5 min and stirred for a further 5 min. The mixture gave a negative

starch–iodide test. The organic phase was separated and the aqueous layer was extracted with dichloromethane (3 × 100 ml). The combined organic phases were dried ($MgSO_4$), filtered, concentrated under reduced pressure and chromatographed on silica gel (200 g), eluting with 5% methanol–dichloromethane to yield some mixed fractions (161 mg) and the tetraol (**11**) (860 mg). The mixed fractions were rechromatographed on silica gel (16 g) with the same solvent system to give more of the tetraol (**11**) (124 mg; total 984 mg, 1.68 mmol, 28% for three steps); δ_H(400 MHz) 5.61 (1 H, tt, *J* 3.2, 6.0 Hz, 9-H), 5.49 (1 H, s, 26a-H), 5.35 (1 H, dq, *J* 0.9, 0.9 Hz, 3-H), 5.31 (1 H, s, 26a-H), 5.23–5.14 (1 H, m, 19-H), 4.64–4.43 (3 H, m, 8a-H_2, 27-H), 4.16 (1 H, d, *J* 11.0 Hz, 25-H), 4.18–4.06 (3 H, m, 6-H, 10-H_2), 4.03–3.91 (2 H, m, 5-H, 17-H), 3.87 (1 H, ddd, *J* 3.0, 3.0, 3.0 Hz, 23-H), 3.85–3.75 (2 H, m, 15-H_2), 3.48 (3 H, s, 5-OMe), 3.35–3.31 (1 H, m, 2-H), 2.57–1.91 (4 H, very br., 4 × OH), 2.10–1.97 (3 H, m, 18-H_{eq}, 20-H_{eq}, 22-H), 1.81 (3 H, m, 4-Me), 1.70 (3 H, d, *J* 6.8 Hz, 27-Me), 1.88–1.69 (4 H, m, 16-H_2, 22-H, 24-H), 1.51 (1 H, dd, *J* 10.8, 10.8 Hz, 20-H_{ax}), 1.36 (1 H, ddd, *J* 10.6, 10.6, 10.6 Hz, 18-H_{ax}), 0.90 (3 H, d, *J* 6.8 Hz, 24-Me); δ_C 172.5 (1), 148.7 (26), 144.9 (8), 136.7 (4), 119.7 (9), 118.0 (3), 116.4 (26a), 99.0 (21), 80.1 (6), 78.3 (7), 77.2 (5), 73.1 (25), 68.8 (23), 68.5 (19), 68.4 (17), 68.3 (8a), 60.8 (15), 59.8 (10), 58.0 (5-OMe), 54.9 (27), 46.9 (2), 41.1, 40.2 (20 and 22), 37.9 (24), 37.7, 36.8 (16 and 18), 25.1 (27a), 19.6 (4a), and 13.9 (24a); ν_{max} 3 470, 3 003, 2 938, 1 709, 1 425, 1 379, 1 335, 1 200, 1 085, and 1 001 cm^{-1}; *m/z* 586.5 (M^+).

Dehalogenation of the Chlorotetraol (**11**).—A solution of tetraol (**11**) (50 mg, 0.09 mmol) in dry toluene (5 ml) was heated to reflux under nitrogen. Tributyltin hydride (229 μl, 248 mg, 0.85 mmol) and a catalytic quantity of AIBN in dry toluene (2 ml) was added dropwise to the refluxing mixture over 3.5 min. After 1.5 h the solution was allowed to cool to room temperature and was concentrated under reduced pressure to yield an oily residue. Partition of this mixture between hexane (20 ml) and acetonitrile (20 ml) was followed by extraction of the hexane layer with acetonitrile (10 ml). The combined acetonitrile phases were washed with hexane (10 ml) and the solvent was removed under reduced pressure to leave an oily residue. This was purified by chromatography on silica gel (7 g) eluting with 95:5 dichloromethane–methanol to give an inseparable 3.8:1 mixture (by ^1H NMR spectroscopy) of isomers (**12**) and (**13**) (30 mg, 0.05 mmol, 64%); δ_H 5.62 (1 H, tt, *J* 2.5, 6.0 Hz, 9-H), 5.45 (0.8 H, dq, *J* 0.9, 6.7 Hz, major isomer 27-H), 5.38–5.32 (1 H, m, 3-H), 5.31–5.16 (1 H, m, 19-H), 4.98 (0.2 H, s, minor isomer 26a-H), 4.92 (0.2 H, q, *J* 1.5 Hz, minor isomer 26a-H), 4.66–4.49 (2 H, AB, 8a-H_2), 4.49–4.45 (1 H, m, OH), 4.13 (1 H, d, *J* 5 Hz, 6-H), 4.08 (2 H, d, 6 Hz, 10-H_2), 3.86 (1 H, d, *J* 10.5 Hz, 25-H), 3.76 (2 H, t, *J* 5.5 Hz, 15-H_2), 4.15–3.72 (3 H, m, 17-H, 23-H, OH), 3.56 (1 H, br s, OH), 3.48 (3 H, s, 5-OMe), 3.37–3.31 (1 H, m, 2-H), 3.11 (1 H, br s, OH), 1.80 (3 H, s, 4-Me), 1.62 (2.4 H, dd, *J* 0.9, 6.7 Hz, major isomer 27-Me), 1.58 (2.4 H, s, major isomer 26-Me), 2.26–1.21 (9.4 H, m, 16-H_2, 18-H_2, 20-H_2, 22-H_2, 24-H, minor isomer 27-H_2), 1.08 (0.6 H, t, *J* 7.2 Hz, minor isomer 27-Me), 0.81 (0.6 H, d, *J* 7 Hz, minor isomer 24-Me), and 0.77 (2.4 H, d, *J* Hz, major isomer 24-Me); ν_{max} 3 450, 2 934, 1 709, 1 450, 1 378, 1 332, 1 260, 1 166, 1 089, and 997 cm^{-1}.

Condensation of the Tetraol (**11**) *with Succinyl Chloride*.—The tetraol (**11**) (50 mg) and pyridine (0.25 ml) were stirred in dry dichloromethane (10 ml) at rt under argon. Succinyl chloride (13 mg, 0.09 mmol, 9.4 μl) was dissolved in dry dichloromethane (5 ml) and added dropwise to the solution over 45 min. The purple then red and finally red-brown solution was stirred for 4 days and then the solvent was evaporated under reduced pressure. The residue was dissolved in ethyl acetate (10 ml) and washed with dilute hydrochloric acid (2 ml), water (2 ml) and brine (2 ml) and was then dried ($MgSO_4$), filtered and concentrated under reduced pressure. The residue was chromatographed on silica gel (6 g) eluting with 2–5% methanol–dichloromethane to yield recovered starting material (20 mg, 40%) and compound (**14**; *n* = 2) (9 mg, 0.01 mmol, 16%); δ_H(400 MHz): 5.61–5.56 (1 H, m, 9-H), 5.49 (1 H, s, 26a-H), 5.35–5.32 (1 H, m, 3 H), 5.31 (1 H, s, 26a-H), 5.24–5.14 (1 H, m, 19-H), 4.69–4.53 (5 H, m, 8a-H_2, 10-H_2, 27-H), 4.44 (1 H, dd, *J* 8.2, 12.8 Hz, 15-H), 4.29–4.17 (2 H, m, 15-H, OH), 4.04 (1 H, d, *J* 10.9 Hz, 25-H), 4.01 (1 H, d, *J* 4.8 Hz, 6-H), 3.99–3.92 (2 H, m, 5-H, 17-H), 3.86–3.81 (1 H, m, 23-H), 3.49 (3 H, s, 5-OMe), 3.42 (1 H, d, *J* 9.6 Hz, OH), 3.31–3.27 (1 H, m, 2-H), 2.68–2.51 (4 H, m, succinyl –CH_2CH_2–), 2.14–1.93 (5 H, m, 16-H_2, 18-H_{eq}, 20-H_{eq}, 22-H), 1.82 (3 H, s, 4-Me), 1.70 (3 H, d, *J* 7.0 Hz, 27-Me), 1.87–1.67 (2 H, m, 22-H, 24-H), 1.62 (1 H, dd, *J* 12.1, 12.1 Hz, 20-Ha_{ax}), 1.41 (1 H, ddd, *J* 12.1, 12.1, 12.1 Hz, 18-H_{ax}), and 0.91 (3 H, d, *J* 7.0 Hz, 24-Me); δ_C(100 MHz) 175.1 (succinyl CO), 173.2 (1), 171.6 (succinyl CO), 148.4 (26), 147.7 (8), 135.5 (4), 118.1 (3), 116.1 (26a), 147.7 (9), 99.9 (21), 78.6 (6), 78.5 (7), 77.6 (5), 73.0 (25), 69.0 (23), 68.5 (19 or 17), 67.9 (8a), 67.8 (17 or 19), 61.2, 60.8 (15 and 10), 57.6 (5-OMe), 55.0 (27), 45.4 (2), 40.8 (22), 39.9 (20), 38.3 (24), 35.0, 33.6 (18 and 16), 29.5, 29.0 (succinyl –CH_2CH_2–), 24.6 (27a), 19.6 (4a), and 13.8 (24a); ν_{max} 3 523, 2 932, 1 733, 1 601, 1 450, 1 363, 1 260, 1 167, 1 090, and 1 001 cm^{-1}.

Condensation of the Tetraol (**11**) *with Malonyl Chloride*.—This condensation was carried out as for succinyl chloride by adding a pale yellow solution of malonyl chloride (18.0 mg, 0.128 mmol; 12.4 μl) in dry dichloromethane (5 ml) to the tetraol (**11**) over 17 min to give a pink, then red and finally purple solution which was stirred for 3 h. Chromatography on silica gel (6 g), eluting with 2% then 10% methanol–dichloromethane, yielded recovered starting material (6 mg, 12%) and lactone (**14**; *n* = 1) (11.6 mg, 0.02 mmol, 21%); δ_H 5.67–5.57 (1 H, m, 9-H), 5.50 (1 H, s, 26a-H), 5.37–5.32 (1 H, m, 3-H), 5.30 (1 H, s, 26a-H), 5.29–5.13 (1 H, m, 19-H), 4.76–4.53 (5 H, m, 8a-H_2, 10-H_2, 27-H), 4.49–4.34 (2 H, m, 15-H, OH), 4.17 (1 H, ddd, *J* 2.5, 7.3, 11.7 Hz, 15-H), 4.05 (1 H, d, *J* 11 Hz, 25-H), 4.03 (1 H, d, *J* 4.8 Hz, 6-H), 4.00–3.79 (3 H, m, 5-H, 17-H, 23-H), 3.49 (3 H, s, 5-OMe), 3.38 (2 H, s, malonyl –CH_2–), 3.36–3.28 (2 H, m, 2-H, OH), 1.80 (3 H, s, 4-Me), 1.70 (3 H, d, *J* 6.8 Hz, 27-Me), 1.59 (1 H, dd, *J* 12.2, 12.2 Hz, 20-H_{ax}), 1.43 (1 H, ddd, *J* 12.2, 12.2, 12.2 Hz, 18-H_{ax}), 2.14–1.58 (7 H, m, 16-H_2, 18-H_{eq}, 20-H_{eq}, 22-H_2, 24-H), and 0.92 (3 H, d, *J* 6.9 Hz, 24-Me); δ_C 173.5 (1), 166.2 (malonyl CO), 165.6 (malonyl CO), 148.6 (26), 148.5 (8), 135.8 (4), 118.1 (3), 116.3 (26a), 114.3 (9), 100.0 (21), 78.8 (6), 78.7 (7), 76.7 (5), 73.1 (25), 69.1 (23), 68.6 (19 or 17), 68.0 (8a), 67.9 (17 or 19), 62.3, 61.7 (10 and 15), 57.7 (5-OMe), 55.0 (27), 45.4 (2), 41.6 (malonyl CH_2), 41.0, 40.1 (20 and 22), 38.3 (24), 35.7, 33.6 (16 and 18), 24.8 (27a), 19.7 (4a), and 13.9 (24a); ν_{max} 3 510, 3 012, 2 936, 1 736, 1 601, 1 456, 1 338, 1 275, 1 167, 1 146, and 995 cm^{-1}.

Condensation of the Tetraol (**11**) *with Glutaryl Chloride*.—This condensation was carried out as for succinyl chloride by adding a colourless solution of glutaryl chloride (14.4 mg, 0.09 mmol; 10.9 μl) in dry dichloromethane (5 ml) to the tetraol (**11**) over 8 min to give a colourless solution which was stirred for 20 h. Another equal aliquot of glutaryl chloride in dichloromethane was added to the solution over 10 min giving a yellow solution which was stirred for 24 h. Chromatography on silica gel (6.5 g), eluting with 2% methanol–dichloromethane, yielded recovered starting material (14.7 mg, 29%) and the lactone (**14**; *n* = 3) (17.0 mg, 0.02 mmol, 29%); δ_H 5.60–5.51 (1 H, m, 9-H), 5.49 (1 H, s, 26a-H), 5.31 (1 H, s, 26a-H), 5.25–5.10 (1 H, m, 19-H), 5.12 (1 H, s, 3-H), 4.78–4.44 (5 H, m, 8a-H_2, 10-H_2, 27-H), 4.38–4.28 (1 H, m, 15-H), 4.06 (1 H, d, *J* 10.5 Hz, 25-H), 4.03 (1 H, d, *J* 4.7 Hz, 6-H), 4.15–3.80 (5 H, m, 5-H, 15-H, 17-H, 23-H, OH), 3.48 (3 H, s, 5-OMe), 3.37–3.26 (2 H, m, 2-H, OH), 2.40–2.30

(4 H, m, 2 × glutaryl $-CH_2CO-$), 1.82 (3 H, s, 4-Me), 1.70 (3 H, d, *J* 6.9 Hz, 27-Me), 1.59 (1 H, dd, *J* 12.0, 12.0 Hz, 20-H_{ax}), 1.42 (1 H, ddd, *J* 12.0, 12.0, 12.0 Hz, 18-H_{ax}), 2.18–1.60 (9 H, m, 16-H_2, 18-H_{eq}, 20-H_{eq}, 22-H_2, 24-H, glutaryl $-CH_2CH_2CH_2-$), and 0.92 (3 H, d, *J* 7.0 Hz, 27-Me); δ_C 173.6 (1), 172.3 (glutaryl CO), 172.2 (glutaryl CO), 148.7 (26), 148.6 (8), 135.8 (4), 118.0 (3), 116.2 (26a), 114.2 (9), 100.0 (21), 78.7 (6), 78.3 (7), 76.7 (5), 72.9 (25), 69.1 (23), 68.7, 68.3 (17 and 19), 68.2 (8a), 61.1 (10 and 15), 57.7 (5-OMe), 55.3 (27), 45.5 (2), 41.0 (22), 40.2 (20), 38.5 (24), 36.3 (16 or 18), 34.2 (glutaryl $-CH_2CO-$), 33.6 (18 or 16), 33.5 (glutaryl $-CH_2CO$), 24.6 (27a), 20.3 (glutaryl $-CH_2CH_2CH_2-$), 19.6 (4a), and 13.9 (24a); ν_{max} 3 520, 2 969, 2 938, 1 726, 1 450, 1 368, 1 335, 1 241, 1 167, 1 090, 1 001, and 908 cm^{-1} (Found: M^+, 683.2834. $C_{34}H_{47}{}^{35}ClO_{12}$ requires *M*, 683.2384).

Condensation of the Tetraol (**11**) *with Oxalyl Chloride*.—This reaction was carried out as for succinyl chloride by adding a solution of oxalyl chloride (32.4 mg, 0.26 mmol, 22.3 μl) in dry dichloromethane (12.5 ml) to the tetraol (**11**) over 5.5 h and stirring the solution for 17 h. Chromatography on silica gel (6 g) eluting with 2% methanol–dichloromethane gave a mixture (by TLC) of two components (19 mg). Further chromatography of the mixture on silica gel (5 g), eluting with 1% then 2% methanol–dichloromethane, gave the very unstable lactone (**14**; *n* = 0) (2 mg, 0.003 mmol, 4%); δ_H 5.50 (1 H, s, 26a-H), 5.54–5.44 (1 H, m, 9-H), 5.32 (1 H, s, 26a-H), 5.32–5.28 (1 H, m, 3-H), 5.32–5.13 (1 H, m, 19-H), 5.09 (1 H, br s, OH), 4.88–4.70 (2 H, m, 10-H_2), 4.65–4.44 (4 H, m, 8a-H_2, 15-H, 27-H), 4.36–4.19 (1 H, m, 15-H), 4.07 (1 H, d, *J* 5.5 Hz, 6-H), 4.06 (1 H, d, *J* 10.5 Hz, 25-H), 4.03–3.78 (3 H, m, 5-H, 17-H, 23-H), 3.51 (3 H, s, 5-OMe), 3.32–3.24 (2 H, m, 2-H, OH), 1.82 (3 H, s, 4-Me), 1.71 (3 H, d, *J* 6.7 Hz, 27-Me), 1.62 (1 H, dd, *J* 12.0, 12.0 Hz, 20-H_{ax}), 1.46 (1 H, ddd, *J* 12.0, 12.0, 12.0 Hz, 18-H_{ax}), 2.40–1.56 (7 H, m, 16-H_2, 18-H_{eq}, 20-H_{eq}, 22-H_2, 24-H), and 0.93 (3 H, d, *J* 6.8 Hz, 24-Me); ν_{max} 3 467, 3 011, 2 930, 2 859, 1 774, 1 739, 1 709, 1 602, 1 452, 1 370, 1 335, 1 298, 1 172, 1 113, 1 090, 1 018, 999, and 927 cm^{-1} (Found: M^+, 658.2379. $C_{31}H_{45}{}^{35}ClNO_{12}$ requires $M + NH_4$, 658.2630).

Reaction of the Tetraols (**12**) *and* (**13**) *with Malonyl Chloride*.—This condensation was carried out as for succinyl chloride by adding a pale yellow solution of malonyl chloride (50.5 mg, 0.36 mmol; 34.9 μl) in dry dichloromethane (21.1 ml) to the tetraols (**12**) and (**13**) (66 mg, 0.12 mmol) in dry dichloromethane (14 ml) over 6 h and stirring for 15 h to give a pink then blue green and finally a green colour. Chromatography on silica gel (10 g) eluting with 2% methanol–dichloromethane yielded an inseparable 4.3:1 mixture of isomeric lactones (**15**; *n* = 1) and (**16**; *n* = 1) (17 mg, 0.03 mmol, 23%); δ_H 5.67–5.57 (1 H, m, 9-H), 5.42 (0.8 H, dq, *J* 1.0, 6.6 Hz, 27-H), 5.32 (1 H, s, 3-H), 5.35–5.20 (1 H, m, 19-H), 4.99–4.89 (1.4 H, m, OH, minor isomer 26-H_2), 4.75–4.53 (3 H, m, 8a-H_2, 10-H), 4.48–4.33 (2 H, m, 10-H, 15-H), 4.25–4.12 (1 H, m, 15-H), 4.03 (1 H, d, *J* 5 Hz, 6-H), 4.00–3.93 (1 H, m, 5-H), 3.93–3.76 (2 H, m, 17-H, 23-H), 3.72 (1 H, d, *J* 10.7 Hz, 25-H), 3.48 (3 H, s, 5-OMe), 3.38 (2 H, s, malonyl $-CH_2-$), 3.47–3.28 (2 H, m, 2-H, OH), 1.82 (3 H, s, 4-Me), 1.64 (2.4 H, d, *J* 6.6 Hz, 27-Me), 1.57 (2.4 H, s, 26-Me), 2.30–1.31 (9.4 H, m, 16-H_2, 18-H_2, 20-H_2, 22-H_2, 24-H, minor isomer 27-H_2), 1.08 (0.6 H, t, *J* 7 Hz, minor isomer 27-Me), 0.83 (0.6 H, d, *J* 7 Hz, minor isomer 24-Me), 0.78 (2.4 H, d, *J* 7 Hz, 24-Me); ν_{max} 3 503, 3 039, 2 971, 2 935, 1 752, 1 735, 1 709, 1 599, 1 429, 1 337, 1 264, 1 186, 1 147, 1 090, 1 057, 994, and 908 cm^{-1} (Found: M^+, 620.2833. $C_{32}H_{14}O_{12}$ requires *M*, 620.2833).

Condensation of the Tetraols (**12**) *and* (**13**) *with Glutaryl Chloride*.—This reaction was performed as for succinyl chloride by adding a solution of glutaryl chloride (170 mg, 1.00 mmol; 128 μl) in dry dichloromethane (55 ml) to the tetraols (**12**) and (**13**) (198 mg, 0.36 mmol) in dry dichloromethane (40 ml) over 17 h and stirring for an additional 19 h to give a yellow-green solution. Chromatography on silica gel (30 g), eluting with 2% methanol–dichloromethane yielded an inseparable 4.1:1 mixture of isomeric lactones (**15**; *n* = 3) and (**16**; *n* = 3) (64 mg, 0.10 mmol, 28%); δ_H 5.61–5.51 (1 H, m, 9-H), 5.43 (0.8 H, dq, *J* 1.0, 6.7 Hz, 27-H), 5.31 (1 H, s, 3-H), 5.34–5.11 (1 H, m, 19-H), 4.96 (0.2 H, s, minor isomer 26a-H), 4.95–4.93 (0.2 H, m, minor isomer 26a-H), 4.73 (1 H, dd, *J* 2.0, 14.2 Hz, 10-H), 4.64–4.41 (4 H, m, 8a-H_2, 10-H, OH), 4.39–4.28 (1 H, m, 15-H), 4.17–4.05 (1 H, m, 15-H), 4.03 (1 H, d, *J* 4.8 Hz, 6-H), 4.00–3.93 (1 H, m, 5-H), 3.93–3.78 (2 H, m, 17-H, 23-H), 3.74 (1 H, d, *J* 10.9 Hz, 25-H), 3.48 (3 H, s, 5-OMe), 3.35 (1 H, d, *J* 9.8 Hz, OH), 3.27–3.32 (1 H, m, 2-H), 2.40–2.30 (4.4 H, m, 2 × glutaryl $-CH_2CO-$, minor isomer 27-H_2), 1.82 (3 H, s, 4-Me), 1.64 (2.4 H, dd, *J* 0.8, 6.7 Hz, 27-Me), 1.59 (2.4 H, s, 26-Me), 2.19–1.24 (11 H, m, 16-H_2, 18-H_2, 20-H_2, 22-H_2, 24-H, glutaryl $-CH_2CH_2CH_2-$), 1.09 (0.6 H, t, *J* 7 Hz, minor isomer 27-Me), 0.84 (0.6 H, d, *J* 7 Hz, minor isomer 24-Me), and 0.79 (2.4 H, d, *J* 7 Hz, 24-Me); δ_C 173.8 (1), 172.3 (glutaryl CO), 172.2 (glutaryl CO), 148.7 (8), 135.8 (4), 133.8 (26), 124.2 (27), 118.0 (3), 114.1 (9), 99.7 (21), 78.7 (6), 78.3 (7), 76.9 (25), 69.2 (23), 69.0 (19 or 17), 68.2 (8a), 67.9 (17 or 19), 61.2, 61.1 (10 and 15), 57.7 (5-OMe), 45.5 (2), 41.0 (22), 40.2 (20), 36.4 (16 or 18), 36.0 (24), 34.3 (glutaryl $-COCH_2-$), 33.7 (18 or 16), 33.5 (glutaryl $-COCH_2-$), 20.3 (glutaryl $-CH_2CH_2CH_2-$) 19.6 (4a), 13.7 (24a), 13.1 (27a), and 10.8 (26a); ν_{max} 3 518, 2 968, 2 935, 1 728, 1 451, 1 377, 1 335, 1 169, 1 091, 997, and 908 cm^{-1} (Found: M^+, 648.3146. $C_{34}H_{48}O_{12}$ requires *M*, 648.3146).

Conversion of the Lactone (**15**) *into the Lactone* (**17**).—Lactones (**15**) and (**16**) (15 mg, 0.02 mmol) were dissolved in dry dichloromethane (1 ml) and stirred under nitrogen. Mercuric acetate (23.1 mg, 0.07 mmol) was added to the solution and the resulting heterogeneous mixture was heated at reflux for 23 h. Further dichloromethane (1 ml) was added to the mixture and reflux continued for 3 h. The mixture was cooled to room temperature, diluted with dichloromethane (7 ml), filtered through Celite, washed with brine (1.5 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a white glass. This glass was dissolved in glacial acetic acid (0.5 ml) and stirred at room temperature for 19 h. The glacial acetic acid was evaporated under reduced pressure and the residue was dissolved in dry ethanol (0.5 ml) and stirred at −23 °C under argon. Sodium borohydride (1.4 mg, 0.04 mmol) was added in one portion and the colourless solution turned grey and a precipitate formed. After 1 h the mixture was diluted with aqueous acetic acid (0.1M, 2 ml), and was extracted with ether (3 × 2 ml). The combined extracts were washed with brine (2 ml), dried ($MgSO_4$), filtered and concentrated under reduced pressure. Chromatography of the residue on silica gel (2 g) eluting with 2% methanol–dichloromethane yielded unchanged starting material (**15**) and (**16**) (3.0 mg, 20%) and 5-hydroxy lactone (**17**) (4.4 mg, 0.007 mmol, 30%); δ_H 5.65–5.55 (1 H, m, 9-H), 5.43 (1 H, dq, *J* 1.0, 6.8 Hz, 27-H), 5.33 (1 H, s, 3-H), 5.38–5.21 (1 H, m, 19-H), 4.92 (1 H, s, OH), 4.76–4.13 (8 H, m, 5-H, 8a-H_2, 10-H_2, 15-H_2, OH), 3.95 (1 H, d, *J* 5.5 Hz, 6-H), 3.74 (1 H, d, *J* 10.9 Hz, 25-H), 3.97–3.78 (2 H, m, 17-H, 23-H), 3.38 (2 H, s, malonyl $-CH_2-$), 3.30–3.24 (1 H, m, 2-H), 1.87 (3 H, m, 4-Me), 1.65 (3 H, dd, *J* 0.9, 6.8 Hz, 27-Me), 1.59 (3 H, s, 26-Me), 2.19–1.17 (9 H, m, 16-H_2, 18-H_2, 20-H_2, 22-H_2, 24-H), and 0.80 (3 H, d, *J* 7 Hz, 24-Me); ν_{max} 3 530, 2 932, 2 859, 1 751, 1 734, 1 713, 1 603, 1 456, 1 378, 1 335, 1 268, 1 171, 1 145, 1 125, and 993 cm^{-1}.

Cyclization of Tetraol (**11**) *to the* 10,15-*Ether* (**18**).—Tetraol (**11**) (50 mg, 0.09 mmol) and dry pyridine (13.5 mg, 0.17 mmol; 13.8 μl) in dry dichloromethane (1 ml) were stirred at 0 °C under argon. Toluene-*p*-sulphonyl chloride (16.2 mg, 0.09 mmol) was added to the solution in small portions over 1 min and the

solution was stirred at 0 °C for 1.5 h then at room temperature for 21 h. More toluene-*p*-sulphonyl chloride (16.2 mg, 0.09 mmol) was added to the solution and stirring was continued for a further 22 h. The pale yellow solution was diluted with ethyl acetate (10 ml) and washed with dilute hydrochloric acid (2M; 2 ml), and then sodium hydrogen carbonate solution (2M; 2 ml) which formed an emulsion. Brine (2 ml) was added to the emulsion and the mixture was filtered. The organic layer was successfully separated, washed with brine (2 ml), dried ($MgSO_4$), concentrated under reduced pressure and chromatographed on silica gel (6 g), eluting with 1–10% methanol–dichloromethane, to yield a tosylate (**19**) (4 mg, 0.005 mmol, 6%), the 10,15-ether (**18**) (7 mg, 0.01 mmol, 14%), and another tosylate (**20**) (9 mg, 0.01 mmol, 14%) and recovered starting material (**11**) (10 mg, 20%). Data for compound (**19**): δ_H 7.81 (2 H, d, *J* 8.2 Hz, 2 × ArH), 7.36 (2 H, d, *J* 8.2 Hz, 2 × ArH), 5.67 (1 H, tt, *J* 2.5, 7.8 Hz, 9-H), 5.53 (1 H, s, 26a-H), 5.40 (1 H, s, 26a-H), 5.38–5.32 (1 H, m, 3-H), 5.26–5.11 (1 H, m, 19-H), 4.67–4.56 (3 H, m, 8a-H_2, 27-H), 4.44 (1 H, s, OH), 4.22–3.80 (9 H, m, 5-H, 6-H, 10-H_2, 15-H_2, 17-H, 23-H, 25-H), 3.66 (1 H, s, OH), 3.50 (3 H, s, 5-OMe), 3.36–3.29 (1 H, m, 2-H), 3.07 (1 H, d, *J* 9.5 Hz, OH), 2.45 (3 H, s, ArMe), 1.82 (3 H, s, 4-Me), 1.71 (3 H, d, *J* 6.8 Hz, 27-Me), 2.12–1.18 (9 H, m, 16-H_2, 18-H_2, 20-H_2, 22-H_2, 24-H), and 0.94 (3 H, d, *J* 7 Hz, 24-Me); ν_{max} 3 528, 2 933, 1 709, 1 600, 1 451, 1 364, 1 174, 1 144, 1 119, 1 094, and 998 cm^{-1}. Data for compound (**18**): δ_H(400 MHz) 5.66 (1 H, tt, *J* 2.4, 7.8 Hz, 9-H), 5.49 (1 H, s, 26a-H), 5.34 (1 H, dq, *J* 1.2, 1.2 Hz, 3-H), 5.31 (1 H, s, 26a-H), 5.24–5.15 (1 H, m, 19-H), 4.64–4.57 (3 H, m, 8a-H_2, 27-H), 4.56 (1 H, s, OH), 4.17 (1 H, d, *J* 10.6 Hz, 25-H), 4.12 (1 H, d, *J* 4.8 Hz, 6-H), 4.02–3.89 (4 H, m, 5-H, 10-H_2, 17-H), 3.88 (1 H, ddd, *J* 3.0, 3.0, 3.0 Hz, 23-H), 3.81 (2 H, t, *J* 5.2 Hz, 15-H_2), 3.49 (3 H, s, 5-OMe), 3.33–3.29 (1 H, m, 2-H), 2.09–1.99 (3 H, m, 18-H_{eq}, 20-H_{eq}, 22-H), 1.82 (3 H, s, 4-Me), 1.71 (3 H, d, *J* 6.8 Hz, 27-Me), 1.89–1.64 (4 H, m, 16-H_2, 22-H, 24-H), 1.53 (1 H, dd, *J* 10.8, 10.8 Hz, 20-H_{ax}), 1.38 (1 H, ddd, *J* 10.8, 10.8, 10.8 Hz, 18-H_{ax}), and 0.91 (3 H, d, *J* 6.8 Hz, 24-Me); ν_{max} 3 478, 2 935, 1 709, 1 450, 1 337, 1 169, 1 145, 1 119, 1 089, and 1 001 cm^{-1}; *m/z* (EI) 570 [M^+ (^{37}C)], 568 [M^+ (^{35}Cl)], 552 {[$M - H_2O$]$^+$ (^{37}Cl)}, and 550 {[$M - H_2O$]$^+$ (^{35}Cl)}. Data for compound (**20**): 7.81 (2 H, d, *J* 8.2 Hz, 2 × ArH), 7.36 (2 H, d, *J* 8.2 Hz, 2 × ArH), 5.63–5.59 (1 H, m, 9-H), 5.52 (1 H, s, 26a-H), 5.38 (1 H, s, 26a-H), 5.35 (1 H, s, 3-H), 5.26–5.10 (1 H, m, 19-H), 4.70–4.48 (3 H, m, 8a-H_2, 27-H), 4.32 (1 H, s, OH), 4.22–3.75 (9 H, m, 5-H, 6-H, 10-H_2, 15-H_2, 17-H, 23-H, 25-H), 3.50 (4 H, s, 5-OMe, OH), 3.40–3.33 (1 H, m, 2-H), 3.09 (1 H, d, *J* 9.5 Hz, OH), 2.45 (3 H, s, ArMe), 1.82 (3 H, s, 4-Me), 1.72 (3 H, d, *J* 7 Hz, 27-Me), 2.15–1.18 (9 H, m, 16-H_2, 18-H_2, 20-H_2, 22-H_2, 24-H), and 0.94 (3 H, d, *J* 7 Hz, 24-Me); ν_{max} 3 499, 2 934, 1 710, 1 602, 1 450, 1 364, 1 173, 1 087, and 997 cm^{-1}.

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