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DEGRADATION OF OLEANDOMYCIN: CONTROLLED REMOVAL OF SUGARS TO GIVE OLEANDONOLIDE C_3,C_5-ACETONIDE

Ian Paterson and Prabhat Arya*

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, England.

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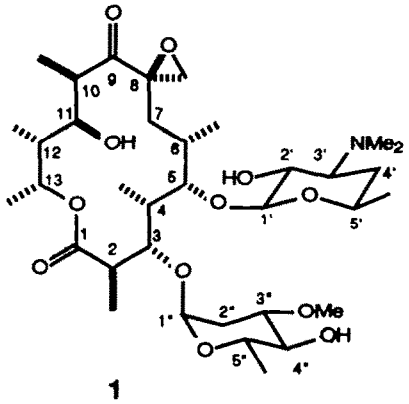
Abstract—A 7-step sequence is described for the controlled removal of *D*-desosamine and *L*-oleandrose from oleandomycin to give the C_3,C_5-acetonide **2**. A Cope elimination was first used to remove the NMe_2 group of desosamine, **3** → **4**. Treatment of **4** with hydroiodic acid gave the iodohydrin **12** with loss of oleandrose, which was followed by removal of the olefinic sugar by hydrolysis with dilute hydrochloric acid to give **14**. Acetonide formation and regeneration of the C_8 epoxide by mild base then gave **2**. The conversion of the C_8 epoxide of **4** to the glycols **5** and **6**, the enone **7**, and the phenylsulphide **8** is also described.

Oleandomycin **1**, produced by *Streptomyces antibioticus*, is a potent broad spectrum antibiotic in widespread clinical use.[1] Its 14-membered ring polyoxo macrolide structure was determined in 1960,[2a] while the absolute configuration was established in 1965 by Celmer[2b] and later confirmed[2c] by X-ray analysis. The exocyclic epoxide at C_8 is a unique structural feature, which does not appear in any of the other known polyoxo macrolides. In connection with our synthetic efforts[3-5] towards the aglycone of oleandomycin, we required access to oleandonolide C_3,C_5-acetonide **2**, together with some other aglycone derivatives, to investigate the late stages of our synthetic plan. Hydrolytic removal of the deoxysugars of



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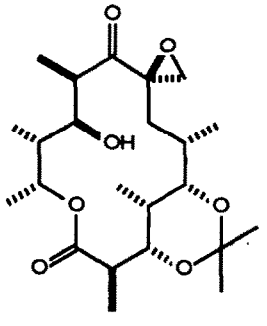

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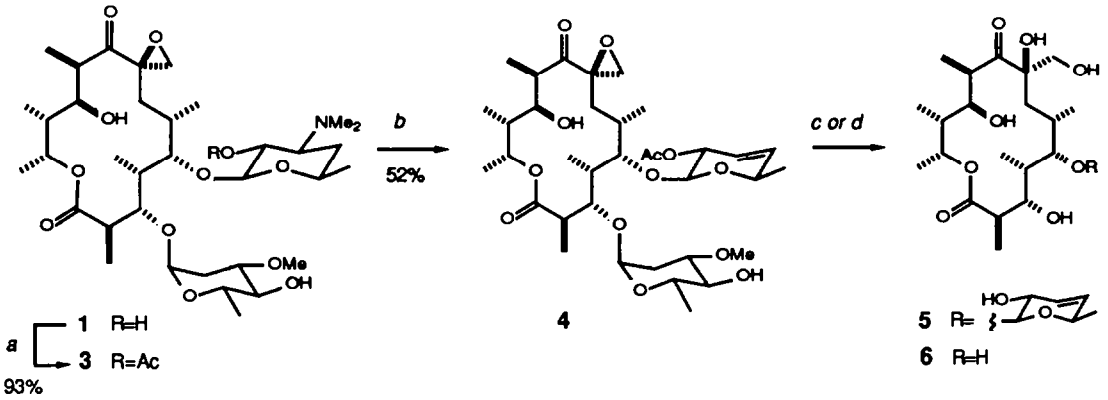
macrolide antibiotics is not trivial—extensive destruction of the macrolide skeleton often occurs under the acidic conditions required.[6] In the case of oleandomycin, acid treatment leads to opening of the C_8 epoxide[2a] as well as some remarkable macrolide ring contractions,[7] while mild base treatment induces dehydration across C_{10}-C_{11} to give anhydrooleandomycin.[2a] In our degradation studies, we were particularly concerned in identifying a reaction sequence that would provide us with the aglycone with the main structural features left intact. Thus we planned to degrade commercially available oleandomycin phosphate by removing both sugars in a controlled fashion to give the 3,5-*O*-protected oleandonolide **2**. In the original structural characterisation work,[2a] cleavage of the basic β-*D*-desosamine and neutral α-*L*-oleandrose sugars was described for anhydrooleandomycin, but not for the parent macrolide. Very recently Tatsuta[8] has described

a new method for cleavage of desosamine in 9-dihydro-8,8a-deoxyoleandomycin using trimethylsilyl-iodide, but this would not be compatible with the presence of the C_8 epoxide. We first decided to remove the basic NMe_2 group, which would make chromatographic purification easier, and then investigate ways of removing the sugars and handling the epoxide issue.

RESULTS AND DISCUSSION

A Cope elimination has been used successfully for removal of the dimethylamino group of *D*-desosamine in erythromycin A,[9] although it required a high temperature. We decided to first look at the corresponding transformation in oleandomycin (see **Scheme 1**). Oleandomycin was first selectively acetylated at the 2'-OH of *D*-desosamine in the absence of added base (Ac_2O, EtOAc, 20°C, 4 h; 93%) to give 2'-acetyloleandomycin **3**.[10,11] Treatment of **3** with mCPBA (CH_2Cl_2, -23°C, 3 h) gave the *N*-oxide,

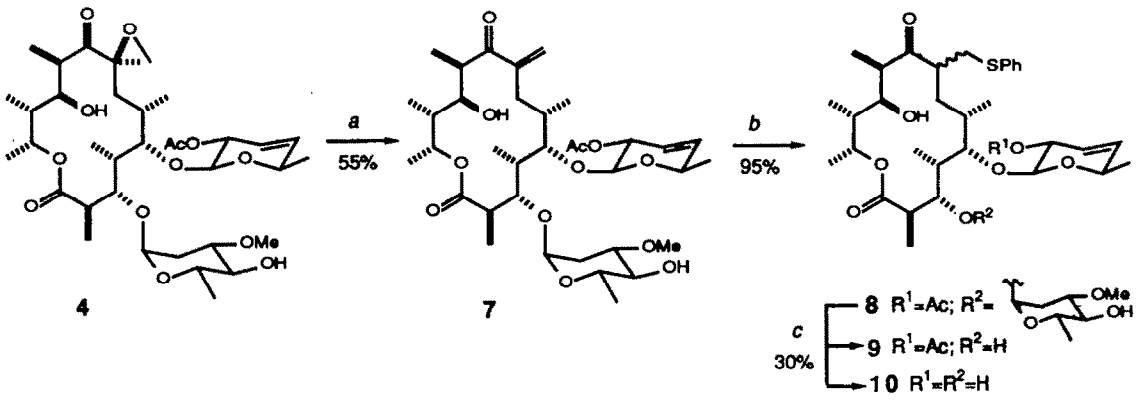


Scheme 1. (*a*) Ac_2O, 1.1 eq., EtOAc, 20°C, 4 h; (*b*) mCPBA, 1.1 eq., CH_2Cl_2, -23°C, 3 h; THF, 57°C, 18 h; (*c*) K_2CO_3, MeOH-H_2O, 3:2, 20°C, 1 h; 10% HCl, THF-H_2O, 1:1, 20°C, 24 h; (*d*) 10% HCl, THF-H_2O, 1:1, 35°C, 3 d.

which was unstable to chromatography and so was directly thermolysed. We were pleased to find that it underwent Cope elimination under mild conditions[2b,12] simply by warming in dry THF (57°C, 18 h). This gave 2'-acetyl-3'-de(dimethylamino)-3',4'-dehydrooleandomycin **4**, CI-MS *m/z* 702 ($M+NH_4$), in 52% yield after flash chromatography with the C_8 epoxide intact. The ^{1}H-NMR spectrum showed loss of the dimethylamino group and the appearance of two new olefinic signals at δ5.72 (dt, J=1.4, 10 Hz) and 5.51 (dt, J=2.1, 10 Hz) as well as retention of the epoxide protons at δ3.0 and 2.70 (ABq, J=4.5 Hz). The protection of the 2'-OH is advantageous as it avoids the possibility of hydrogen bonding with the *N*-oxide, which retards[9] the elimination step. We next focussed our efforts on sugar hydrolysis in **4**. After deacetylation, mild acid treatment (10% HCl, THF-H_2O, 1:1, 24 h) at room temperature selectively cleaved the more acid-labile α-sugar, *L*-oleandrose, and opened the epoxide to give the vicinal diol **5** in 43% yield. Epoxide opening under acidic conditions in oleandomycin is well documented.[2a] Extended acid treatment of **4** at 35°C for 3 days gave, together with **5**, the aglycone derivative **6** in low yield (19%), which equilibrates on standing to a *ca* 1:1 mixture of free ketone and 5-OH/C-9 hemiacetal tautomers. Attempts were made to convert the C_8 vicinal diol system in **6** to the corresponding epoxide *via* the primary tosylate, but these were

frustrated by the instability of **6** to mildly basic conditions. In view of this difficulty and the low yield obtained on sugar cleavage, we did not pursue this route further.

At this stage, we decided to convert the epoxide in **4** to a protected enone system, as in **8**, which could be used to regenerate the epoxide after sugar cleavage. Deoxgenation of the exocyclic epoxide of oleandomycin and various derivatives has been carried out previously using chromous chloride.[13] Thus **4** was first converted (**Scheme 2**) to the enone **7** with $CrCl_2$ (Me_2CO-H_2O, 2:1, 20°C, 45 min) in 55% yield. Since the enone was not expected to survive the sugar hydrolysis step, it was first protected by 1,4-addition

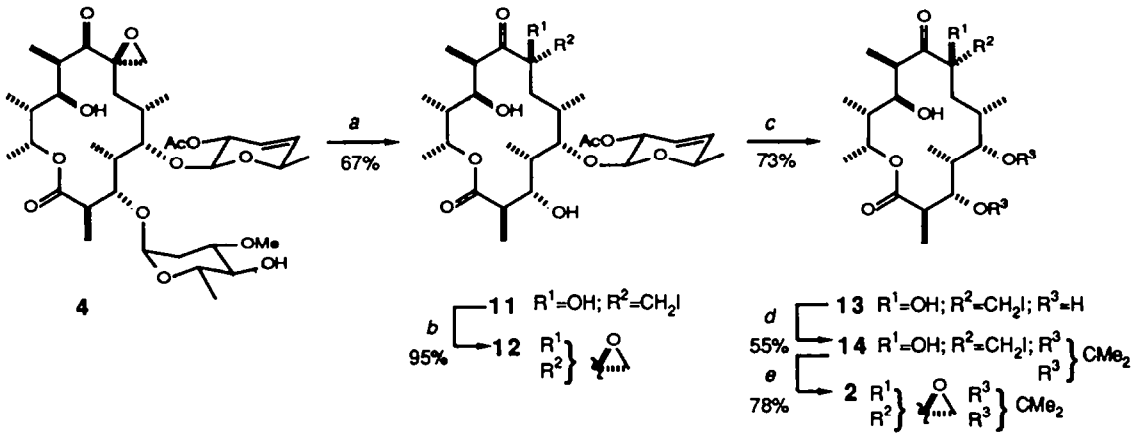


Scheme 2. (*a*) $CrCl_2$, 3 eq., Me_2CO-H_2O, 2:1, 20°C, 45 min; (*b*) PhSH, 1.1 eq., cat. piperidine, CH_2Cl_2, 20°C, 3.5 h; (*c*) 5% HCl, THF-H_2O, 1:1, 20°C, 48 h.

of thiophenol (cat. piperidine, CH_2Cl_2, 20°C, 3.5 h; 92%) to give the phenylsulphide **8** as a single isomer (C_8 stereochemistry not determined) by ^{1}H- and ^{13}C-NMR. Various attempts were made to remove both the sugars at this stage, but we could only succeed in cleaving *L*-oleandrose to give **9** together with the deacetylated derivative **10**; prolonged acid treatment led to extensive destruction of the compound.

Another possibility for protection of the epoxide through the acidic conditions of sugar hydrolysis is conversion to the halohydrin. In our final successful scheme, we were able to remove *L*-oleandrose and convert the epoxide to the iodohydrin in a single step, **4** → **11**, by brief exposure to hydroiodic acid ($CHCl_3$, 20°C, 15 min) in 67% yield (**Scheme 3**). As a test case, the epoxide was obtained from the iodohydrin using aqueous $NaHCO_3$, **11** → **12** (THF-H_2O, 1:1, 20°C, 2.5 h; 95%). Hence it was possible to regenerate[11] the epoxide in high yield without any competing dehydration across C_{10} and C_{11}. Treatment of **11** under the conditions already established for hydrolysis of the modified β-sugar (10% HCl, THF-H_2O, 1:1, 35°C, 60 h) then gave the aglycone **13**, CI-MS *m/z* 532 ($M+NH_4$), in a respectable 73% yield (again as a mixture of hydroxyketone and hemiacetal forms). Formation of the C_3,C_5-acetonide, **13** → **14**, was then directly carried out using 2,2-dimethoxypropane/PPTS (CH_2Cl_2, 20°C, 50 min; 55%). Finally, exposure of **14** to 10% aqueous $NaHCO_3$ (THF, 0°C, 45 min) smoothly gave the C_3,C_5-*O*-protected oleandonolide **2**, CI-MS *m/z* 444 ($M+NH_4$) and $[\alpha]^{20}_D$=-48.0 (c 2.0, $CHCl_3$), in 78% yield. The ^{1}H-NMR spectrum of **2** was well dispersed and readily assignable with the epoxide protons appearing at δ3.09 and 2.94 (ABq, *J*=4.2 Hz). The overall yield for the sugar cleavage/protection sequence, **4** → **2**, was 21% (*i.e.* 11% from oleandomycin).

This, therefore, provides a simple and reasonably direct route to the aglycone derivative **2**, which will be important in the closing stages of our synthetic studies towards oleandonolide.



Scheme 3. (*a*) 55% HI, $CHCl_3$, 20°C, 15 min; (*b*) $NaHCO_3$, THF-H_2O, 1:1, 20°C, 2.5 h; (*c*) 10% HCl, THF-H_2O, 1:1, 35°C, 60 h; (*d*) $(MeO)_2CMe_2$, PPTS, CH_2Cl_2, 20°C, 50 min; (*e*) $NaHCO_3$, THF-H_2O, 1:1, 0°C, 45 min.

EXPERIMENTAL

Dichloromethane was distilled from calcium hydride. THF was freshly distilled from sodium/benzophenone ketyl prior to use. Oleandomycin was obtained by dissolving oleandomycin phosphate (Sigma, *ca* 95%) in dichloromethane and washing with saturated $NaHCO_3$ solution, and then evaporating the organic layer *in vacuo*. 2'-Acetyloleandomycin was prepared from oleandomycin using acetic anhydride in ethyl acetate without added base (20°C, 4 h; 93%).[10,11] ^{1}H-NMR spectra were recorded on a Bruker WM250 (250 MHz); selected chemical shift data and assignments[7] from the spectra are reported. ^{13}C-NMR spectra were recorded on a Bruker AM400 (100.6 MHz).[14] Mass spectra were obtained by chemical ionization using NH_3, by electron impact at 70 eV, or by fast atom bombardment. IR spectra were recorded on a Perkin-Elmer 1310 machine. Flash chromatography was performed as described by Still.[15]

Preparation of 2'-acetyl-3'-de(dimethylamino)-3',4'-dehydrooleandomycin **4**—mCPBA (85%, 80 mg, 1.1eq.) was added to a stirred solution of 2'-acetyloleandomycin (365 mg, 0.5 mmol) in dry CH_2Cl_2 (20 ml) at -23°C under argon. After 3 h, the reaction mixture was diluted with CH_2Cl_2 and washed in turn with satd. $NaHCO_3$ solution (3x) and water. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give the *N*-oxide (370 mg), which was unstable on silica gel and so was used without purification in the next step. A solution of the crude *N*-oxide in dry THF (25 ml) was stirred at 57°C under argon. After 18 h, the solvent was evaporated *in vacuo* and the residue dissolved in CH_2Cl_2, which was then washed with pH7 buffer solution, dried ($MgSO_4$), and evaporated *in vacuo*. The crude product mixture (330 mg) was flash chromatographed (elution with 1:1 ethylacetate/hexane) to give *2'-acetyl-3'-de(dimethylamino)-3',4'-dehydrooleandomycin* **4** as an amorphous white solid (179 mg, 52%): R_f = 0.29 (2:1 EtOAc/hexane); m.p. 82-83°C; $[\alpha]^{20}_D$ = -61.4 (c 5.6, $CHCl_3$); IR($CHCl_3$) 3510 (br), 2980, 1740, 1720, 1700, 1235 cm^{-1}; ^{1}H-NMR δ(250 MHz, $CDCl_3$) 5.72 (1H, dt, J= 1.4, 10.0 Hz, H-3' or 4'), 5.60 (1H, dq, J= 0.8, 6.7 Hz, H-13), 5.51 (1H, dt, J= 2.1, 10.0 Hz, H-3' or 4'), 5.21 (1H, m, H-2'), 4.92 (1H, d, J= 2.8 Hz, H-1"), 4.53 (1H, d, J= 7.0 Hz, H-1'), 4.04 (1H, t, J= 6.6 Hz, H-4"), 3.88 (3H, s, OMe), 3.0, 2.7 (2H, ABq, J= 4.5 Hz, H-8a, 8b), 2.83 (1H, m, H-2), 2.06 (3H, s, Ac), 1.30, 1.27, 1.22, 1.21, 1.15, 1.07, 1.0, 0.89 (24H, 8xd, J= 6.4, 6.7, 5.7, 6.8, 6.1, 6.9, 6.6, 7.1 Hz, 8x Me); ^{13}C-NMR δ(100.6 MHz, $CDCl_3$) 207.6, 175.8, 170.0, 133.9, 123.5, 100.3, 100.2, 83.6, 82.7, 77.8, 75.9, 70.6, 70.3, 70.1, 69.1, 68.7, 61.8, 56.3, 53.3, 48.4, 44.9, 44.7, 42.3, 41.7, 33.8, 30.1, 29.2, 21.0, 20.7, 18.5, 17.8, 14.9, 9.3, 8.6, 6.5; EI-MS: *m/z* 684 (M); CI-MS (NH_3) *m/z* 702 (M+NH_4, 100), 558 (13), 532 (14), 386 (12), 372 (13), 190 (18), 170 (74), 162 (52), 155 (40), 130 (73), 113 (13), 102 (14); HRMS 684.3729, $C_{35}H_{56}O_{13}$ requires

684.3721.

Acid hydrolysis of 4 after deacetylation—An aqueous solution of K_2CO_3 (5%, 2 ml) was added to a stirred solution of **4** (100 mg) in MeOH (3 ml) at room temperature. After 1 h, the reaction mixture was diluted with pH7 buffer solution and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to give 83 mg of deacetylated product, which was added, as a solution in THF (1 ml), to a stirred solution of hydrochloric acid in aqueous THF (10 ml of *c* HCl/THF/H_2O, 1:4.5:4.5) at room temperature. After 24 h, the reaction mixture was poured into satd. $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$), evaporated *in vacuo* and the residue flash chromatographed (elution with 3:2 EtOAc/hexane) to give *(8R)-3'-de(dimethylamino)-8,8a-deepoxy-3',4'-dehydro-3-deoleandrosyl-8,8a-dihydroxyoleandomycin* **6** (29 mg, 44%): R*f* = 0.4 (2:1 EtOAc/hexane); $[\alpha]^{20}_D$ = -35.5 (c 1.7, $CHCl_3$); Found C 60.19, H 8.30, $C_{26}H_{44}O_{10}$ requires C 60.44, H 8.58; IR($CHCl_3$) 3460 (br), 2960, 1715 (br) cm^{-1}; ^{1}H-NMR δ(250 MHz, $CDCl_3$) 5.50-5.67 (3H, m, H-3', 4', 13), 4.39 (1H, d, J= 6.9 Hz, H-1'), 4.29 (1H, m, H-2'), 3.75 (2H, bs, H-8a, 8b), 3.08 (1H, dq, J= 1.1, 6.7 Hz, H-10), 2.62 (1H, dq, J= 6.8, 10.0 Hz, H-2), 1.25, 1.23, 1.22, 1.19, 1.12, 1.04, 0.91 (21H, 7xd, J= 6.5, 6.7, 7.2, 7.0, 6.8, 7.1, 7.1 Hz, 7x Me); EI-MS: *m/z* 516 (M); FAB-MS (thioglycerol) *m/z* 517 (M+H), 387 (8), 369 (8), 285 (10), 245 (10), 221 (14), 203 (15), 189 (12), 171 (17), 155 (13), 125 (18), 113 (100), 95 (30), 85 (75), 69 (64), 57 (83).

Extended acid hydrolysis of 4—A solution of **4** (550 mg, 0.8 mmol) in THF (2 ml) was added to a stirred solution of hydrochloric acid in aqueous THF (40 ml of *c* HCl/THF/H_2O, 1:4.5:4.5). After 3 days at 35°C, the reaction mixture was poured into satd. $NaHCO_3$ solution and extacted with CH_2Cl_2. The organic layer was washed with water, dried ($MgSO_4$) and evaporated *in vacuo*. The residue (300 mg) was flash chromatographed (elution with 1:1 EtOAc/hexane) to give **5** (30 mg, 7%), see above for data, and *(8R)-8,8a-deepoxy-8,8a-dihydroxyoleandonolide* **6** (60 mg, 19%) as a colourless oil, which was an interconvertible mixture of hydroxyketone and hemiacetal tautomers: R*f* = 0.38, 0.55 (2:1 EtOAc/hexane); $[\alpha]^{20}_D$ = -31.2 (c 3.9, $CHCl_3$); IR($CHCl_3$) 3490 (br), 2980, 1715(br) cm^{-1}; ^{1}H-NMR δ(250 MHz, $CDCl_3$) 5.64 (1H, dq, J= 1.1, 6.6 Hz, H-13), 3.77, 3.65 (2H, ABq, J= 11.6 Hz, H-8a, 8b), 3.48-3.60 (3H, m, H-3, 5, 11), 3.10 (1H, dq, J= 0.9, 6.9 Hz, H-10), 2.60 (1H, dq, J= 6.7, 9.9 Hz, H-2), 1.26, 1.22, 1.15, 1.14, 1.03, 0.94 (18H, 6xd, J= 6.6, 6.7, 6.6, 6.8, 6.9, 7.1 Hz, 6x Me); ^{13}C-NMR δ(100.6 MHz, $CDCl_3$) for ketone 214.3, 176.0, 82.3, 79.2, 69.9, 69.7, 49.6, 44.0, 41.7, 43.0, 40.9, 40.1, 35.9, 35.6, 19.9, 18.5, 14.3, 8.8, 8.7, 7.8; CI-MS (NH_3) *m/z* 404 ($M+NH_4-H_2O$, 100), 386 (77), 370 (100), 351 (38), 271 (58), 257 (61), 204 (43), 178 (49), 157 (41), 58 (83).

Preparation of 2'-acetyl-3'-de(dimethylamino)-8,8a-deepoxy-3',4'-dehydro-8,8a-methyleneoleandomycin **7**—Aqueous $CrCl_2$ (*ca*· 0.5 M) was prepared[16] from $CrCl_3.6H_2O$ (2.4 g), Zn dust (4.8 g), and $HgCl_2$ (0.48 g) and 1 M HCl (15 ml). The freshly prepared blue $CrCl_2$ solution (5 ml, *ca* 3 eq.) was added by syringe to a stirred solution of **4** (500 mg, 0.73 mmol) in acetone/water (5 ml, 2:1) at 20°C under argon. After 45 min, the reaction mixture was partitioned between ethylacetate and water. The separated aqueous layer was saturated with NaCl and further extracted with EtOAc (2x). The combined organic layers were washed with satd. $NaHCO_3$ solution, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was flash chromatographed (elution with 1:1 ethyl acetate-hexane) to give the enone **7** (268 mg, 55%) as an amorphous white solid: R*f* = 0.32 (2:1 EtOAc/hexane); m.p. 87-88°C; $[\alpha]^{20}_D$ = -99.4 (c 3.3, $CHCl_3$); IR($CHCl_3$) 3600, 3510 (br), 2980, 2940, 1720 (br), 1240 cm^{-1}; ^{1}H-NMR δ(250 MHz, $CDCl_3$) 5.74 (1H, dt, J= 1.6, 10.0 Hz, H-3' or 4'), 5.60, 5.49 (2H, 2xbs, H-8a, 8b), 5.52 (1H, dt, J= 2.0, 10.0 Hz, H-3' or 4'), 5.39 (1H, dq, J= 1.1, 6.5 Hz, H-13), 5.30 (1H, m, H-2'), 4.95 (1H, d, J= 3.4 Hz, H-1"), 4.54 (1H, d, J= 7.1 Hz, H-1'), 3.40 (3H, s, OMe), 2.07 (3H, s, Ac), 1.32, 1.27, 1.25, 1.20, 1.18, 1.01, 1.00, 0.87 (24H, 8xd, J= 6.1, 6.9, 6.7, 6.7, 7.0, 6.8, 6.9, 7.0 Hz, 8x Me); ^{13}C-NMR δ(100.6 MHz, $CDCl_3$) 206.8, 177.0, 170.1, 149.6, 134.6, 123.6, 120.5, 100.6, 100.0, 84.0, 81.5, 77.8, 76.0, 70.8, 70.5, 70.2, 68.7, 56.3, 45.0, 43.5, 43.0, 42.0, 34.8, 33.8, 32.8, 21.0, 20.7, 20.6, 18.4, 17.9, 14.9, 14.1, 9.4, 8.7, 6.1; EI-MS: *m/z* 668 (M); CI-MS (NH_3) *m/z* 686 ($M+NH_4$, 13), 544 (8), 516 (8), 372 (14), 356 (17), 190 (23), 170 (100), 162 (60), 130 (90), 113 (28), 99 (11), 77 (10), 58 (16), 52 (66); HRMS 668.3786, $C_{35}H_{56}O_{12}$ requires 668.3771.

Preparation of 2'-acetyl-3'-de(dimethylamino)-8,8a-deepoxy-3',4'-dehydro-8a-phenylthiooleandomycin **8**—Thiophenol (0.112 ml, 0.11 mmol) and a catalytic amount of piperidine (10 µl) were added to a stirred solution of the enone **7** (67 mg, 0.1 mmol) in dry CH_2Cl_2 (5 ml) at 20°C under argon. After 3.5 h, the reaction mixture was diluted with CH_2Cl_2 and washed in turn with satd. $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was flash chromatographed (elution with 1:2 ethyl acetate/hexane) to give the phenylsulphide **8** (72 mg, 92%) as a white solid: R*f* = 0.29 (2:1 EtOAc/hexane); m.p. 84-85°C; $[\alpha]^{20}_D$ = -78.8 (c 4.0, $CHCl_3$); Found C 62.86, H 8.16, $C_{41}H_{62}O_{12}S$ requires C 63.20, H 8.03; IR($CHCl_3$) 3610, 3520 (br), 2980, 1720 (br), 1240 cm^{-1}; ^{1}H-NMR δ(250 MHz, $CDCl_3$) 7.15-7.38 (5H, m, Ph), 5.72 (1H, dt, J= 1.5, 10.0 Hz, H-3' or 4'), 5.52 (1H, dt, J= 2.1, 10.0 Hz, H-3' or 4'), 5.40 (1H, dq, J= 1.2, 6.5 Hz, H-13), 5.21 (1H, m, H-2'), 4.91 (1H, d, J= 3.0 Hz, H-1"), 4.50 (1H, d, J= 7.0 Hz, H-1'), 4.27 (1H, m, H-5'), 3.39 (3H, s, OMe), 2.06 (3H, s, Ac), 1.30, 1.27, 1.23, 1.18, 1.08, 1.01, 0.85 (24H, 7xd, J= 6.5, 6.9, 6.7, 6.9, 6.8, 6.9, 7.0 Hz, 8x

Me); ^{13}C-NMR δ(100.6 MHz, $CDCl_3$) 214.3, 176.7, 170.0, 136.2, 133.8, 130.0, 128.8, 126.2, 123.5, 100.3, 99.6, 84.0, 80.9, 77.8, 75.8, 70.4, 70.3, 70.1, 68.7, 56.2, 50.8, 44.6, 43.0, 41.7, 41.6, 35.3, 35.2, 33.7, 32.0, 21.0, 20.7, 19.6, 18.1, 17.8, 14.3, 9.2, 8.5, 7.8; EI-MS: *m/z* 778 (M); CI-MS (NH_3) *m/z* 796 ($M+NH_4$, 2), 668 (7), 652 (9), 544 (7), 372 (8), 190 (13), 170 (32), 162 (33), 155 (45), 130 (100), 113 (37), 102 (7), 95 (12), 52 (35); HRMS 778.3961, $C_{41}H_{62}O_{12}S$ requires 778.3962.

Acid hydrolysis of **8**—A solution of the sulphide **8** (100 mg, 0.12 mmol) in THF (1 ml) was added to a stirred solution of HCl in aqueous THF (10 ml of *c* HCl/THF/H_2O, 0.5:4.75:4.75) at 20°C. After 48 h, the reaction mixture was diluted with CH_2Cl_2 and washed in turn with satd. $NaHCO_3$ solution and water, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was flash chromatographed (elution with 1:2 ethylacetate/hexane) to give *2'-acetyl-3'-de(dimethylamino)-8,8a-deepoxy-3',4'-dehydro-3-deoleandrosyl-8-phenylthiooleandomycin* **9** (7 mg, 8.5%) as a colourless oil: R_f = 0.53 (1:1 EtOAc/hexane); ^{1}H-NMR δ(250 MHz, $CDCl_3$) 7.24-7.45 (5H, m, Ph), 5.70 (1H, dt, J= 1.4, 10.0 Hz, H-3' or 4'), 5.50 (1H, dt, J= 1.9, 10.0 Hz, H-3' or 4'), 5.45 (1H, dq, J= 1.1, 6.6 Hz, H-13), 5.13 (1H, m, H-2'), 4.53 (1H, d, J= 7.2 Hz, H-1'), 2.04 (3H, s, Ac), 1.30, 1.23, 1.15, 1.06, 1.01, 0.98, 0.85 (21H, 7xd, J= 6.6, 7.1, 6.8, 6.8, 6.9, 6.9, 7.0 Hz, 7x Me); EI-MS: *m/z* 634 (M); CI-MS (NH_3) *m/z* 652 ($M+NH_4$, 0.3), 635 (M+1, 0.6), 371 (6), 353 (10), 272 (8), 225 (8), 177 (10), 155 (100), 128 (35), 111 (40), 97 (22), 84 (17), 72 (14), 58 (37), 44 (51); HRMS 634.3175, $C_{34}H_{50}O_9S$ requires 634. 3175; and *3'-de(dimethylamino)-8,8a-deepoxy-3',4'-dehydro-3-deoleandrosyl-8-phenylthiooleandomycin* **10** (17 mg, 22%). as a colourless oil: R_f = 0.42 (1:1 EtOAc/hexane); ^{1}H-NMR δ(250 MHz, $CDCl_3$) 7.20-7.45 (5H, m, Ph), 5.56-5.66 (2H, m, H-3', 4'), 5.44 (1H, dq, J= 1.1, 6.6 Hz, H-13), 4.23 (1H, d, J= 6.8 Hz, H-1'), 1.30, 1.26, 1.15, 1.09, 1.07, 1.01, 0.86 (21H, 7xd, J= 6.6, 6.9, 6.6, 7.3, 6.6, 7.0, 6.9 Hz, 7x Me); EI-MS: *m/z* 592 (M); FAB-MS (thioglycerol) *m/z* 593 (M+1, 14), 575 (8), 497 (17), 483 (13), 463 (12), 445 (8), 371 (40), 335 (21), 251 (13), 221 (21), 155 (62), 123 (100), 113 (56), 91 (45), 85 (63), 69 (46), 57 (64).

Preparation of (8S)-2'-acetyl-3'-de(dimethylamino)-8,8a-deepoxy-3',4'-dehydro-3-deoleandrosyl-8-hydroxy-8a-iodo-oleandomycin **11**—A solution of **4** (500 mg, 0.73 mmol) in $CHCl_3$ (5 ml) was added to a stirred solution of hydroiodic acid (5 ml, 55%) in $CHCl_3$ (45 ml) at 20°C. After 15 min, the reaction mixture was diluted with water and extracted with $CHCl_3$. The organic layer was washed in turn with $Na_2S_2O_3$ solution and pH7 buffer solution, then dried ($MgSO_4$) and evaporated *in vacuo*. The residue was flash chromatographed (elution with 1:1 ethylacetate/hexane) to give **11** (325 mg, 67%) as a white solid: R_f = 0.58 (1:1 EtOAc/hexane); m.p. 81-82°C; $[\alpha]^{20}_D$ = -67.6 (c 4.2, $CHCl_3$); IR($CHCl_3$) 3510 (br), 2980, 2940, 1730-1700 cm^{-1}; ^{1}H-NMR δ(250 MHz, $CDCl_3$) 5.72 (1H, dt, J= 1.4, 10.0 Hz, H-3' or 4'), 5.61 (1H, dq, J= 0.7, 6.6 Hz, H-13), 5.52 (1H, dt, J= 2.1, 10.0 Hz, H-3' or 4'), 5.20 (1H, m, H-2'), 4.65 (1H, d, J= 7.0 Hz, H-1'), 4.26 (1H, m, H-5'), 4.05 (1H, s, OH), 3.56-3.37 (3H, m, H-3, 5, 11), 3.46 (2H, bs, H-8a, 8b), 3.04 (1H, bq, J= 6.9 hz, H-10), 2.60 (1H, dq, J= 6.7, 9.8 Hz, H-2), 2.18 (1H, d, J= 5.5 Hz, OH), 2.04 (3H, s, Ac), 1.25, 1.22, 1.19, 1.16, 0.94, 0.88 (21H, 6xd, J= 6.9, 7.0, 6.6, 6.7, 7.2, 7.0 Hz, 7x Me); ^{13}C-NMR δ(100.6 MHz, $CDCl_3$) 214.1, 175.9, 170.3, 134.1, 123.5, 99.3, 85.7, 81.2, 76.1, 70.6, 69.8, 69.5, 44.0, 41.7, 41.3, 39.6, 36.7, 21.1, 20.8, 20.3, 18.6, 14.2, 13.4, 9.7, 8.8, 8.0; CI-MS (NH_3) *m/z* 686 ($M+NH_4$, 9), 600 (7), 558 (77), 542 (13), 404 (18), 386 (53), 369 (28), 353 (12), 190 (14), 155 (100), 128 (34), 95 (7), 52 (68); HRMS 668.2064, $C_{28}H_{45}O_{10}I$ requires 668.2056.

Preparation of 2'-acetyl-3'-de(dimethylamino)-3',4'-dehydro-3-deoleandrosyloleandomycin **12**—A saturated solution of $NaHCO_3$ (5 ml) was added to a stirred solution of **11** (300 mg, 0.45 mmol) in THF (9 ml) at room temperature. After 2.5 h, the reaction mixture was poured into CH_2Cl_2 and the separated organic layer was washed with water, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was flash chromatographed (elution with 2:1 ethyl acetate/hexane) to give the epoxide **12** (231 mg, 95%): R_f = 0.47 (2:1 EtOAc/hexane); m.p. 90-91°C; $[\alpha]^{20}_D$ = -71.2 (c 2.9, $CHCl_3$); IR($CHCl_3$) 3560 (br), 2980, 1725 (br), 1240 cm^{-1}; ^{1}H-NMR δ(250 MHz, $CDCl_3$) 5.72 (1H, dt, J= 1.5, 10.1 Hz, H-3' or 4'), 5.65 (1H, dq, J= 0.9, 6.7 Hz, H-13), 5.56 (1H, dt, J= 2.0, 10.1 Hz, H-3' or 4'), 5.17 (1H, m, H-2'), 4.65 (1H, d, J= 7.0 Hz, H-1'), 4.30 (1H, m, H-5'), 3.74-3.89 (3H, m, H-3, 5, 11), 3.15 (1H, d, J= 5.1 Hz), 3.00-3.15 (1H, m, H-10), 3.03, 2.83 (2H, ABq, J= 4.6 Hz, H-8a, 8b), 2.67 (1H, dq, J= 6.7, 10.0 Hz, H-2), 2.08 (3H, s, Ac), 1.27, 1.25, 1.22, 1.08, 1.01, 1.00, 0.93 (21H, 7xd, J= 6.6, 6.6, 6.8, 6.9, 6.6, 6.9, 7.1, 7.0 Hz, 7x Me); ^{13}C-NMR δ(100.6 MHz, $CDCl_3$) 206.8, 176.2, 170.3, 133.8, 100.7, 85.4, 69.8, 69.5, 69.3, 62.8, 47.2, 44.9, 44.0, 41.6, 39.1, 33.9, 31.5, 20.9, 20.8, 18.6, 14.4, 8.8, 7.9, 6.5; EI-MS: *m/z* 539 (M-1); CI-MS (NH_3) *m/z* 558 ($M+NH_4$, 8), 387 (14), 386 (13), 369 (22), 351 (24), 267 (5), 155 (100); HRMS 540. 2931, $C_{28}H_{44}O_{10}$ requires 540.2934.

Acid hydrolysis of **11**—A solution of the iodohydrin **11** (455 mg, 0.68 mmol) in THF (4 ml) was added to a stirred solution of HCl in aqueous THF (70 ml of *c* HCl/THF/H_2O, 1:4.5:4.5) at 35°C. After 60 h, the reaction mixture was extracted with CH_2Cl_2 (3x) and the combined organic layers washed in turn with pH7 buffer solution and water, dried ($MgSO_4$), and evaporated *in vacuo*. The residue was flash chromatographed (elution with 1:1 EtOAc/hexane) to give *(8S)-8,8a-deepoxy-8-*

hydroxy-8a-iodooleandonolide **13** (256 mg, 73%) as a white solid, which was an interconvertible mixture of hydroxyketone and hemiacetal tautomers (this material was submitted to the next step with the minimum of delay): R_f = 0.40, 0.56 (2:1 EtOAc/hexane); $[\alpha]^{20}_D$ = -17.4 (c 3.9, $CHCl_3$); IR($CHCl_3$) 3470 (br), 2970, 1730-1700 cm^{-1}; ^{1}H-NMR δ(250 MHz, $CDCl_3$) 5.62 (1H, dq, J= 1.1, 6.8 Hz, H-13), 4.09 (1H, s, OH), 3.47-3.63 (3H, m, H-3, 5, 11), 3.45 (2H, bs, H-8a, 8b), 3.20 (1H, d, J= 2.8 Hz), 3.10 (1H, bq, J= 6.9 Hz, H-10), 2.59 (1H, dq, J= 6.7, 9.9 Hz, H-2), 1.26, 1.22, 1.21, 1.14, 1.02, 0.93 (18H, 6xd, J= 6.6, 6.8, 6.8, 6.8, 7.0, 7.1 Hz, 6x Me); EI-MS 515 (M+1); CI-MS (NH_3) *m/z* 532 ($M+NH_4$, 13) , 497 (4), 479 (6), 404 (47), 386 (53), 371 (25), 369 (100), 351 (20), 338 (28), 321 (6); HRMS 514.1432, $C_{20}H_{35}O_7$ I requires 514.1426.

Preparation of (8S)-8,8a-deepoxy-8-hydroxy-8a-iodooleandonolide 3,5-acetonide **14**—A catalytic amount of PPTS (1 mg) was added to a stirred solution of **13** (75 mg, 0.14 mmol) in dry CH_2Cl_2/2,2-dimethoxypropane (8 ml, 5:3) at 20°C under argon. After 50 min, the reaction mixture was poured into pH7 buffer solution and extracted with CH_2Cl_2. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo*. The residue was flash chromatographed (elution with 1:3 ethyl acetate/hexane) to give the acetonide **14** (45 mg, 55%) as a colourless oil: R_f = 0.29 (2:1 EtOAc/hexane): R_f = 0.65 (1:1 EtOAc/hexane) $[\alpha]^{20}_D$ = -20.4 (c 2.8, $CHCl_3$); ^{1}H-NMR δ(250 MHz, $CDCl_3$) 5.60 (1H, dq, J=1.1, 6.8 Hz, H-13), 3.88-3.94 (2H, m, H-3,5), 3.78 (1H, s, OH), 3.61 (1H, dd, J= 1.1, 10.2 Hz, H-11), 3.52, 3.39 (2H, ABq, J= 10.1 Hz, H-8a, 8b), 3.05-3.17 (1H, m), 2.68 (1H, dq, J= 6.7, 10.0 Hz, H-2), 1.40, 1.37 (6H, 2xs, CMe_2), 1.29, 1.15, 1.10, 1.04, 0.99, 0.95 (18H, 6xd, J= 6.6, 6.9, 7.3, 6.6, 6.6, 7.1 Hz, 6x Me); ^{13}C-NMR δ(100.6 MHz, $CDCl_3$) 212.5, 175.6, 100.3, 79.4, 76.5, 73.5, 70.6, 70.1, 42.1, 41.6, 41.2, 37.9, 33.2, 32.9, 29.6, 19.8, 18.4, 17.0, 12.8, 12.6, 9.1, 8.7, 7.6; CI-MS (NH_3) *m/z* 572 ($M+NH_4$, 8), 555 (M+1, 22), 514 (50), 497 (28), 446 (7), 445 (28), 444 (100), 428 (57), 387 (50), 369 (90), 352 (34); HRMS 554.1742, $C_{23}H_{39}O_7I$ requires 554.1739.

Preparation of oleandonolide 3,5-acetonide **2**—An aqueous solution of $NaHCO_3$ (10%, 6 ml) at 0°C was added to a stirred solution of **14** (30 mg, 0.054 mmol) in THF (6 ml) at 0°C. After 45 min, the reaction mixture was poured into pH7 buffer solution and extracted with CH_2Cl_2. The combined organic extracts were dried ($MgSO_4$), evaporated *in vacuo*, and the residue flash chromatographed (elution with 1:3 ethyl acetate/hexane) to give the epoxide **2** (18 mg, 78%) as a colourless oil: R_f = 0.67 (1:1 EtOAc/hexane); $[\alpha]^{20}_D$ = -48.0 (c 2.0, $CHCl_3$); IR($CHCl_3$) 3560 (br), 2985, 1710 (br) cm^{-1}; ^{1}H-NMR δ(250 MHz, $CDCl_3$) 5.74 (1H, dq, J= 1.1, 6.6 Hz, H-13), 4.35 (1H, ddd, J=1.8, 5.6, 10.0, H-11), 4.01 (1H, dd, J= 1.4, 6.8 Hz, H-5), 3.73 (1H, dd, J= 1.3, 10.8 Hz, H-3), 3.09, 2.94 (2H, ABq, J= 4.2 Hz, H-8a, 8b), 3.02 (1H, dq, J= 2.0, 6.7 Hz, H-10), 2.73 (1H, dq, J= 6.6, 10.8 Hz, H-2), 2.40 (1H, d, J= 5.6 Hz, OH), 2.23 (1H, dd, J= 12.2, 15.5 Hz, H-7), 1.96-2.05 (3H, m), 1.41, 1.39 (6H, 2xs, CMe_2), 1.27, 1.14, 1.05, 1.03, 1.02, 0.99 (18H, 6xd, J= 6.6, 6.5, 6.5, 6.5, 7.1, 7.1 Hz, 6x Me); ^{13}C-NMR δ(100.6 MHz, $CDCl_3$) 205.8, 174.8, 100.3, 72.6, 69.7, 69.6, 63.1, 46.6, 46.5, 41.2, 32.8, 32.2, 31.3, 29.6, 18.4, 15.8, 12.9, 9.0, 7.6, 5.9; CI-MS (NH_3) *m/z* 444 ($M+NH_4$, 65), 427 (M+H, 72), 386 (42), 369 (100), 352 (14), 351 (60), 334 (6), 254 (7), 226 (8), 157 (5); HRMS 426.2623, $C_{23}H_{38}O_7$ requires 426.2617.

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