SYNTHESIS OF THE INTACT AGLYCONE OF OLEANDOMYCIN, OLEANDOLIDE, AND DEOLEANDROSYL-OLEANDOMYCIN

Sir:

Oleandomycin (**1**) is a clinically important 14-membered-ring macrolide antibiotic, whose structure contains a unique epoxide ring at the C-8 position[1,2]. Although many kinds of oleandomycin chemistry have been investigated[3~7], neither the isolation nor the synthesis of the intact aglycone, oleandolide (**2**), has been reported to date.

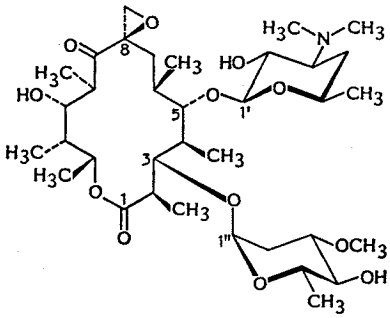
Herein we describe the synthesis of oleandolide (**2**) and deoleandrosyl-oleandomycin (**3**) from oleandomycin (**1**), and the antibacterial activities of the derivatives.

Oleandomycin (**1**) was selectively hydrolyzed with 7% aqueous dichloroacetic acid in THF at 60°C for 18 hours to afford, after silica gel column chromatography with BuOH - EtOH - $CHCl_3$ - H_2O (2:2:1:1) and recrystallization from EtOAc - hexane, needles of deoleandrosyl-oleandomycin (**3**) in 45% yield: MP 177°C; $[\alpha]_D^{23}$ −63° (*c* 1.0, $CHCl_3$); ^1H NMR spectrum (500 MHz) δ 2.89 and 3.09 (2H, ABq, J=5.0 Hz, 8-H_2), 4.32 (1H, d, J=6.1 Hz, 1′-H) and 5.67 (1H, q, J=7.1 Hz, 13-H); field desorption mass spectrum (FD-MS) *m/z* 544 (M+H). In the further hydrolysis of **3**, a large number of variables including acid, solvent and temperature were assayed in attempts to produce oleandolide (**2**). The desired aglycone **2**, however, was not produced even in a low yield. Consequently, the aglycone **2** was synthesized through the stereoselective oxidation of the 9-dihydro-8-exo-methylene compound **7** as follows.

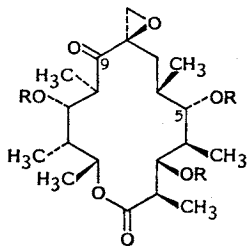
Oleandomycin (**1**) was converted to the 9-dihydro-8-exo-methylene analogue **4** (amorphous, $[\alpha]_D^{23}$ −28° (*c* 1.0, $CHCl_3$)) in 85% yield by treatment with $CrCl_2$[3,5] followed by $NaBH_4$ reduction[5,6].

Hydrolysis of **4** with a 1.5%-methanolic hydrogen chloride solution at 25°C for 15 hours gave the deoleandrosyl compound. This was treated with 3% H_2O_2 in MeOH at 25°C for 14 hours to give the *N*-oxide which was hydrolyzed with 2 M HCl in 1,1,2-trichloroethane at 60°C for 5 hours to afford the 8-exo-methylene aglycone **5** in 62% overall yield: MP 192°C (cubes after recrystallization from EtOAc - hexane); $[\alpha]_D^{23}$ +30° (*c* 1.0, $CHCl_3$); FD-MS *m/z* 373 (M+H). The stereochemistry at the C-9 was determined to be the same as that of the previously reported (8*R*, 9*S*)-9-dihydro-8-methyl-oleandolide[5] (**6**) by quantitative hydrogenation of **5** to **6**. The presence of the C-9 β-hydroxyl group was anticipated, in the following epoxidation, to reasonably control the approach of perbenzoic acid to the β-face of the methylene group to generate the natural epoxide in view of the HENBEST principle[8]. Then, the C-3 and 5 hydroxyl groups were selectively protected by benzylidenation with *p*-bromobenzaldehyde dimethyl acetal[5] in the presence of DL-camphorsulfonic acid in CH_2Cl_2 at 25°C for 3 hours to afford **7** in 90% yield: MP 223°C (cubes from Me_2CO - hexane); $[\alpha]_D^{23}$ +26° (*c* 1.0, $CHCl_3$); FD-MS *m/z* 539 and 541 (M+H). Epoxidation of **7** was done by using *m*-chloroperbenzoic acid in CCl_4 at 25°C for 2 hours to provide exclusively the β-epoxide **8**: MP 235°C (needles from EtOAc - hexane); $[\alpha]_D^{23}$ +8° (*c* 1.0, $CHCl_3$); FD-MS *m/z* 555 and 557 (M+H), followed by oxidation with pyridinium dichromate in CH_2Cl_2 at 25°C for 8 hours to give an amorphous solid of the C-9 ketone **9** in 64% overall yield: $[\alpha]_D^{23}$ −70° (*c* 1.0, $CHCl_3$); FD-MS *m/z* 552 and 554 (M^+). The epoxide ring is confirmed to have the right configuration required for the synthesis by the two standpoints: i) the aforesaid β-hydroxyl group assistance[8], and ii) the completion of the synthesis of **3** presented below.

Hydrogenolysis of **9** in dioxane in the presence of $Pd(OH)_2$ for 1 hour afforded the aglycone, oleandolide (**2** and its 5,9-hemiacetal **2′**), in 91% yield: MP 122~126°C (crystals from EtOAc - hexane); $[\alpha]_D^{23}$ −13° (*c* 1.0, $CHCl_3$); FD-MS *m/z* 387 (M+H). The ^{13}C NMR spectrum (125 MHz) in CD_3OD showed the signals due to the C-1 lactone carbonyl carbon at δ 178 (for **2**) and 179 (for **2′**) in a ratio of 2:1, and also those of the C-9 carbonyl carbon at δ 209.5 (for **2**) and the hemiacetal carbon at δ 100.5 (for **2′**) in a 2:1 ratio. The ^1H NMR spectrum (500 MHz) in CD_3OD also showed the presence of two isomers **2** and **2′** in a 2:1 ratio; **2**: δ 2.71 and 2.84 (2H, ABq, J=4.7 Hz, exocyclic 8-H_2), 5.68 (1H, dq, J=6.9 and 1.3 Hz, 13-H); **2′**: δ 2.67 and 2.93 (2H, ABq, J=5.7 Hz, exocyclic 8-H_2), 4.96 (1H, dq, J=6.9 and 2.2 Hz, 13-H). In $CDCl_3$, the corresponding signals were similarly observed in 1:3 ratios. However,

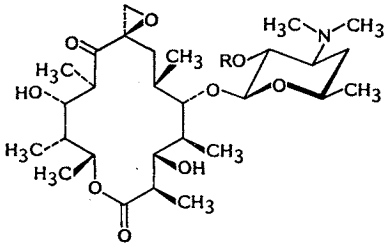


Oleandomycin (**1**)



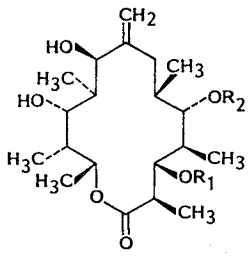
Oleandolide (**2**) R = H

10 R = Ac



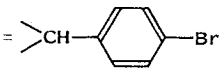
3 R = H

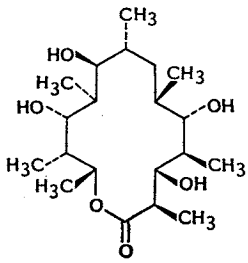
12 R = Ac



4 R_1 = Oleandrosyl R_2 = Desosaminyl

5 $R_1 = R_2 = H$

7 R_1, R_2 = 



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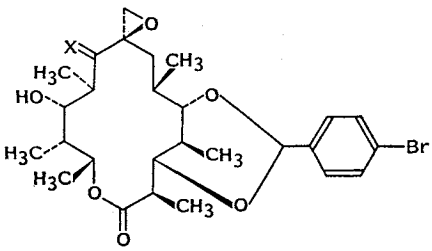
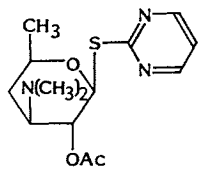


8 X = 

9 X = O



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acetylation of oleandolide with acetic anhydride in pyridine at 25°C for 2 days gave exclusively the triacetate **10** in 82% yield: MP 231°C (plates from EtOAc - hexane); $[\alpha]_D^{23}$ +43° (*c* 1.0, $CHCl_3$); FD-MS *m/z* 513 (M+H). These results indicate that oleandolide exists in an interconvertible mixture of the C-9 ketone (**2**) and the 5,9-hemiacetal (**2'**) structures in solutions, and the equilibrium lies closer to the structure **2** as the appropriate reaction proceeds.

Finally, the desosamine moiety was introduced onto the aglycone **2** by a modified WOODWARD procedure[9] using the *S*-pyrimidyl glycoside. The thioglycoside **11** (needles from EtOAc - hexane, mp 114°C, $[\alpha]_D^{23}$ +77° (*c* 1.0, $CHCl_3$)) was prepared in 79% yield from desosamine[9] by treatment with 2-mercaptopyrimidine, tri-*n*-butylphosphine and diethyl azodicarboxylate in $PhCH_3$ followed by acetylation. Reaction of **2** with **11** (5 equiv) in the presence of silver triflate (6 equiv) and Molecular Sieves 4A powder in a mixture of $PhCH_3$ and CH_2Cl_2 at 25°C for 5 hours gave, after silica gel column chromatographies with $CHCl_3$ - MeOH (20:1 and 10:1), an amorphous solid of the desired β-glycoside **12** as the major product in 42% yield: $[\alpha]_D^{23}$ −48° (*c* 1.0, $CHCl_3$); FD-MS *m/z* 586 (M+H). Methanolysis of **12** with Et_3N afforded a 90%-yield of deoleandrosyl-oleandomycin (**3**) identical in all respects with the aforesaid sample. The compound **3** could be quantitatively returned to the 2'-*O*-acetate **12** by selective acetylation with Ac_2O (1.2 equiv) and Et_3N (0.2 equiv) in CH_3CN at 30°C overnight.

The conversion of **3** into oleandomycin (**1**) will be reported and discussed elsewhere[10].

Derivatives **2**, **3** and **4** showed no antibacterial activities in the concentrations of 100 μg/ml, except that **3** showed activities against *Klebsiella pneumoniae* PCI 602 and *Shigella dysenteriae* JS11910 in 12.5 μg/ml.

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