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\(^1\)\(^-\)\(^3\). Although many kinds of oleandomycin chemistry have been investigated\(^4\)\(^-\)\(^7\), 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\(_2\)O (2:2:1 :1) and recrystallization from EtOAc - hexane, needles of deoleandrosyl-oleandomycin (3) in 45% yield: MP 177°C; \([\alpha]_{D}^2 -63^\circ\) (c 1.0, CHCl\(_3\)); \(\mathrm{FD-MS\ m/z\ 544\ (M+H)}\). 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, \([\alpha]_{D}^2 -28^\circ\) (c 1.0, CHCl\(_3\)) in 85% yield by treatment with CrCl\(_2\)\(^5\)\(^-\)\(^6\) followed by NaBH\(_4\) reduction\(^5\)\(^-\)\(^6\). Hydrolysis of 4 with a 1.5%-methanolic hydrochloric acid solution at 25°C for 15 hours gave the deoleandrosyl compound. This was treated with 3% H\(_2\)O\(_2\) 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); \([\alpha]_{D}^2 +30^\circ\) (c 1.0, CHCl\(_3\)); \(\mathrm{FD-MS\ m/z\ 373\ (M+H)}\). The stereochemistry at the C-9 was determined to be the same as that of the previously reported (8R, 9S)-9-dihydro-8-methyl-oleandolide\(^5\) (6) by quantitative hydrogenation of 5 to 6. The presence of the C-9 \(\beta\)-hydroxyl group was anticipated, in the following epoxidation, to reasonably control the approach of perbenzoic acid to the \(\beta\)-face of the methylene group to generate the natural epoxide in view of the Henbest principle\(^5\). Then, the C-3 and 5 hydroxyl groups were selectively protected by benzylideneation with \(p\)-bromobenzaldehyde dimethyl acetal\(^5\) in the presence of \(p\)-camphorsulfonic acid in CH\(_2\)Cl\(_2\) at 25°C for 3 hours to afford 7 in 90% yield: MP 223°C (cubes from Me\(_2\)CO - hexane); \([\alpha]_{D}^2 +26^\circ\) (c 1.0, CHCl\(_3\)); \(\mathrm{FD-MS\ m/z\ 555\ and\ 557\ (M+H)}\). Epoxidation of 7 was done by using \(m\)-chloroperbenzoic acid in CCl\(_4\) at 25°C for 2 hours to provide exclusively the \(\beta\)-epoxide 8: MP 235°C (needles from EtOAc-hexane); \([\alpha]_{D}^2 +8^\circ\) (c 1.0, CHCl\(_3\)); \(\mathrm{FD-MS\ m/z\ 555\ and\ 557\ (M+H)}\). The epoxide ring is confirmed to have the right configuration required for the synthesis by the two standpoints: i) the aforesaid \(\beta\)-hydroxyl group assistance\(^5\), 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 20, in 91% yield: MP 122~126°C (crystals from EtOAc-hexane); \([\alpha]_{D}^2 -13^\circ\) (c 1.0, CHCl\(_3\)); \(\mathrm{FD-MS\ m/z\ 387\ (M+H)}\). The \(\mathrm{\textsuperscript{13}C\ NMR\ spectrum\ (125\ MHz\ in\ CD\textsubscript{2}OD\ showed\ the\ signals\ due\ to\ the\ 8-exo-methylene\ carbonyl\ carbon\ at\ \delta\ 178\ (for\ 2)\ and\ 179\ (for\ 20\ in\ a\ ratio\ of\ 2:1,\ and\ also\ those\ of\ the\ 9-carbonyl\ carbon\ at\ \delta\ 209.5\ (for\ 2)\ and\ the\ hemiacetal\ carbon\ at\ \delta\ 100.5\ (for\ 20\ in\ a\ 2:1\ ratio).\ The\ ^1H\ NMR\ spectrum\ (500\ MHz\ in\ CD\textsubscript{2}OD\ also\ showed\ the\ presence\ of\ two\ isomers\ 2\ and\ 2'\ in\ a\ 2:1\ ratio;\ 2: \delta\ 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': \delta\ 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 $R_1, R_2 = \text{CH-CH-Br}$

6

8 $X = \text{OH}$

9 $X = O$

11
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); [α]D 25 +43° (c 1.0, CHCl₃); 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 procedure9) using the S-pyrimidyl glycoside. The thioglycoside 11 (needles from EtOAc-hexane, mp 114°C, [α]D 25 +77° (c 1.0, CHCl₃)) was prepared in 79% yield from desosamine9) by treatment with 2-mercaptopurinylidine, tri-n-butylphosphine and diethyl azodicarboxylate in PhCH₃ 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 PhCH₃ and CH₂Cl₂ at 25°C for 5 hours gave, after silica gel column chromatographies with CHCl₃-MeOH (20:1 and 10:1), an amorphous solid of the desired β-glycoside 12 as the major product in 42% yield: [α]D 25 -48° (c 1.0, CHCl₃); FD-MS m/z 586 (M+H). Methanalysis of 12 with Et₃N 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 Ac₂O (1.2 equiv) and Et₃N (0.2 equiv) in CH₃CN at 30°C overnight.

The conversion of 3 into oleandomycin (1) will be reported and discussed elsewhere10).

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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References
