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SYNTHESIS OF OLEANDOMYCIN THROUGH THE INTACT AGLYCONE, OLEANDOLIDE

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Summary: Oleandomycin has been reconstructed by an introduction of the two sugar units onto the intact aglycone, oleandolide, which was first synthesized through the stereoselective oxidation of the 8-exo-methylene derivative.

Oleandomycin (1) is a medically important macrolide antibiotic. Although synthetic efforts have been focused on the aglycone part,[1,2] neither the isolation nor the synthesis of the intact aglycone, oleandolide (8), has been reported to date. Herein we describe the synthesis of oleandolide (8) from oleandomycin (1) and the reconstruction of 1, the latter of which corresponds to the epilogue of the total synthesis, through effective removal and introduction of the sugar moieties.

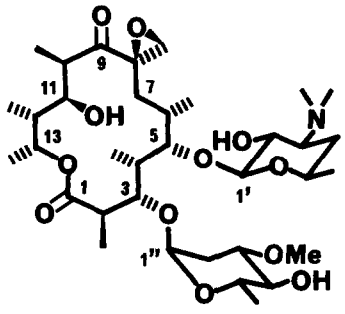
Oleandomycin (1) was converted into the 9-dihydro-8-exo-methylene 2[3] (85%; amorphous, $[\alpha]_D$ -28°, Rf 0.26 ($CHCl_3$-MeOH 3:1)) by treatment with $CrCl_2$[1] (1M HCl/Me_2CO/Ar, 12 h)[3] followed by reduction ($NaBH_4$/i-PrOH-EtOAc, 1 h). The product 2 was hydrolyzed with a 1.5% methanolic hydrogen chloride solution to give the deoleandrosyl compound, which was treated with 3% H_2O_2 (MeOH, 14 h) to give the N-oxide followed by hydrolysis with 2M HCl ($CHCl_2CH_2Cl$, 60°C, 5 h) to afford the 8-methylene aglycone 3[3] (62% from 2; cubes, mp 192°C, $[\alpha]_D$ +30°, Rf 0.86 ($CHCl_3$-MeOH 3:1)). The stereochemistry at the C-9 was confirmed to be the same as that of the previously reported (8R,9S)-9-dihydro-8-methyl-oleandolide[1] (4) by quantitative hydrogenation of 3. Consequently, in the following epoxidation, the presence of the C-9 β-hydroxyl group was expected to assist the approach of perbenzoic acid from the β face of the methylene to generate the natural epoxide in view of the Henbest principle.[4] The C-3 and 5 hydroxyl groups were selectively protected by benzylidenation[1] with p-bromobenzaldehyde dimethyl acetal (CSA/CH_2Cl_2, 3 h) to afford 5[3] (90%; cubes, mp 223°C, $[\alpha]_D$ +26°, Rf 0.52 (hexane-EtOAc 1:1)). Subsequent epoxidation of 5 with m-chloroperbenzoic acid (CCl_4, 2 h) provided exclusively the β-epoxide 6[3] (needles, mp 235°C, $[\alpha]_D$ +8°, Rf 0.45 (hexane-EtOAc 1:1)), which was oxidized with pyridinium dichromate (CH_2Cl_2, 8 h) to give the C-9 ketone 7[3] (64% from 5; amorphous, $[\alpha]_D$ -70°, Rf 0.50 (hexane-EtOAc 4:1)). The epoxide ring in question is confirmed to have the natural configuration by the aforesaid hydroxyl group assistance[4] and, finally, the completion of the synthesis presented below. Hydrogenolysis of 7 (H_2/20% Pd(OH)$_2$-C, dioxane, 1 h) afforded the aglycone, oleandolide[3] (8 and its 5,9-hemiacetal 8'), in 91% yield (crystals, mp 122-126°C, $[\alpha]_D$ -13°, Rf 0.31 (hexane-EtOAc 1:1), Rf 0.43 ($CHCl_3$-

MeOH 20:1)). Although the TLC showed a single spot with more than 20 solvent systems, the ^{13}C-NMR in $CDCl_3$ showed the signals due to the C-1 lactone carbonyl carbon at δ176 and 178 in a ratio of 1:3, and also those of the C-9 carbonyl carbon at δ207 and the hemiacetal carbon at δ99 in a 1:3 ratio.[3] In CD_3OD, the corresponding signals were similarly observed in 2:1 ratios.[3] The ^{1}H-NMR also showed the presence of two isomers 8 and 8' in the following ratios depending upon the solvent: approximately 1:3 in $CDCl_3$; 1:2 in C_6D_6; 3:2 in $(CD_3)_2CO$; 2:1 in CD_3OD.[3] However, acetylation (Ac_2O/Py, 2 days) of the aglycone gave exclusively the triacetate 9[3] (82%; plates, mp 231°C, $[\alpha]_D$ +43°, Rf 0.28 (PhH-EtOAc 3:1)). These results reveal that oleandolide exists in an interconvertible mixture of the C-9 ketone (8) and the 5,9-hemiacetal (8') structures in solutions.

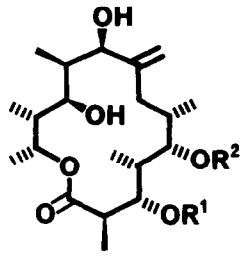
The introduction of the desosamine moiety onto 8 was accomplished by a modified Woodward procedure.[5] The thioglycoside 10[3] (needles, mp 114°C, $[\alpha]_D$ +77°) was prepared in 79% yield from desosamine by treatment with 2-mercaptopyrimidine (Bu_3P/DEAD/PhMe/Ar, −30°→20°C, 15 h) followed by acetylation (Ac_2O/Py, 15 h).[5] Reaction of 8 with 10 (5 equiv) in the presence of silver triflate (6 equiv) (MS 4A/PhMe-CH_2Cl_2/Ar, 5 h) gave, after silica gel column chromatography with $CHCl_3$-MeOH (20:1 and 10:1), the desired β-glycoside 11[3] (42%; amorphous, $[\alpha]_D$ −48°, Rf 0.55 (PhH-Me_2CO-MeOH 3:1:1; Rf 0.74 and 0.63 for 8 and 10)). Methanolysis (MeOH/Et_3N, 10 h) of 11 produced deoleandrosyloleandomycin[3] (12) in 90% yield (needles, mp 177°C, $[\alpha]_D$ −63°, Rf 0.27 ($CHCl_3$-MeOH 5:1)) identical in all respects with the authentic sample, which was derived in 45% yield from 1 by acid hydrolysis (7% $CHCl_2COOH$, 60°C, 18 h).

The second glycosidation of the acetate 11 was widely investigated by a variety of conditions including our method[6] (glycal and NBS), Thiem and Danishefsky method[7] (glycal and NIS) and others.[5] The best result was realized by using the glycal 13 and camphorsulfonic acid.[8] The glycal 13[3] (bp_1 165°C, $[\alpha]_D$ +11°) was prepared (TsCl/Et_3N/DMAP/MeCN, 8 h) from 4-O-benzyloxycarbonyloleandrose, which was in turn obtained from methyl L-oleandroside by acylation (CbzCl/DMAP/CH_2Cl_2, 2 days) and selective hydrolysis (0.8 M HCl/MeCN, 50°C, 24 h) in 70% yield. Thus, reaction of 11 with 13 (7 equiv) in the presence of CSA (6 equiv) in CH_2Cl_2 (MS 4A, 32°C, 2 days) afforded a mixture of condensed products having Rf 0.45, 0.38 and 0.27 on TLC ($CHCl_3$-Me_2CO 2:1; Rf 0.06 and 0.9 for 11 and 13), which was chromatographed on silica gel with $CHCl_3$-Me_2CO (2:1) to give the Rf 0.38-substance as the major product. Hydrogenolysis (H_2/Pd-black, EtOH, 0.5 h) of the major product followed by methanolysis (MeOH/Et_3N, 15 h) gave, after silica gel column chromatography (CH_2Cl_2-MeOH-PhH-DMF 28:7:7:1), oleandomycin[3] (1: 40% from 11; amorphous, mp 101°C, $[\alpha]_D$ −59° (MeOH)) identical in all respects with that obtained from natural sources.

Acknowledgment. We thank Pfizer Taito Co., Ltd. for a generous gift of oleandomycin. Financial support by the Ministry of Education, Science and Culture (Grant-in-Aid for Scientific Research) is gratefully acknowledged.

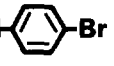


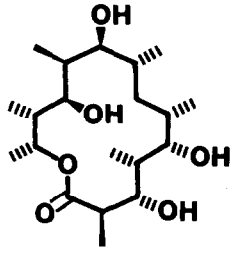
1: Oleandomycin



2 : R^1 = oleandrosyl
R^2 = desosaminyl

3 : $R^1 = R^2 = H$

5 : R^1, R^2 = >CH-  -Br



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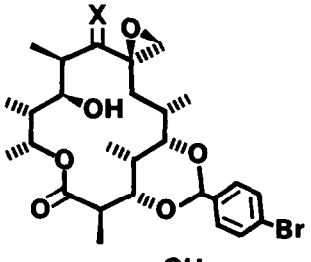
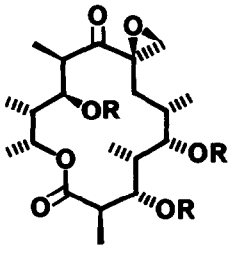


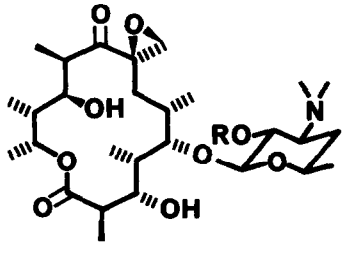
6 : X = 

7 : X = O



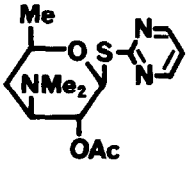
8 : Oleandolide
R = H

9 : R = Ac



11 : R = Ac

12 : R = H



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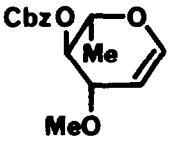

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References and Notes:

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2) I. Paterson & P. Arya, Tetrahedron, 44, 253 (1988), and references cited therein.

3) All reactions were done at room temperature, unless otherwise stated. All compounds except for 13 were recrystallized or reprecipitated from EtOAc-hexane, after silica gel column chromatography, and were fully characterized by spectroscopic means and elemental analyses. Melting points were uncorrected. Optical rotations were measured in $CHCl_3$ at *c* 1.0 (23°C) except for 1 in MeOH. Rf-values were measured on silica gel Merck TLC 60F-254. NMR (400 or 500 MHz: δ, ppm from TMS, and J in Hz) spectra were in $CDCl_3$ solution, unless otherwise stated. Significant ^{1}H-NMR spectral data are the following (with ^{13}C-NMR for 8 and 8'). 1: 2.37(s, NMe_2), 2.82 & 2.96(ABq, J=4.8, CH_2-8), 3.41(s, OMe), 4.24(d, J=8.1, H-1'), 4.97(d, J=3.7, H-1"), 5.61(q, J=6.6, H-13). 2: 4.22(d, J=7.4, H-1'), 4.97(d, J=3.0, H-1"), 5.06 & 5.38 (each s, CH_2-8). 3: 5.05 & 5.50(each s, CH_2-8), 5.33(q, J=6.6, H-13). 5: 5.48(q, J=5.9, H-13), 5.14 & 5.50(each s, CH_2-8), 5.58(s, benzylidene CH). 6: 2.69 & 3.10(ABq, J=4.8, CH_2-8), 3.74(dd, J=10.1 & 3.1, H-9), 5.58(q, J=6.2, H-13). 7: 3.00 & 3.12(ABq, J=3.6, CH_2-8), 3.05(dq, J=6.2 & 1.6, H-10), 5.77 (q, J=6.9, H-13). 8: 2.79 & 3.07(ABq, J=5.4, CH_2-8), 5.68(dq, J=7.2 & 1.2, H-13), and 8': 2.71 & 2.98(ABq, J=5.4, CH_2-8), 5.02(dq, J=7.2 & 2.2, H-13) in $CDCl_3$. In C_6D_6, 8: 5.82(dq, J=7.0 & 2.0, H-13), and 8': 5.31(dq, J=7.0 & 3.0, H-13). In $(CD_3)_2CO$, 8: 5.58(dq, J=6.6 & 1.4, H-13), and 8': 4.89(dq, J=6.4 & 2.4, H-13). In CD_3OD, 8: 5.68(dq, J=6.9 & 1.3, H-13), and 8': 4.96(dq, J=6.9 & 2.2, H-13). ^{13}C-NMR in $CDCl_3$; 8: 176(C-1), 207(C-9), and 8': 99(C-9), 178 (C-1). In CD_3OD; 8: 178(C-1), 209.5(C-9), and 8': 100.5(C-9), 179(C-1). 9: 4.75(d, J=6.8, H-5), 5.01(dd, J=6.8 & 1.8, H-11), 5.19(q, J=7.2, H-13), 5.22 (dd, J=10.4 & 2.1, H-3). 10: 1.28(d, J=6.4, Me-5), 5.06(t, J=9.3, H-2), 5.65 (d, J=9.3, H-1). 11: 2.85 & 3.04(ABq, J=4.8, CH_2-8), 4.44(d, J=8.2, H-1'), 5.66(q, J=6.2, H-13). 12: 2.89 & 3.09(ABq, J=5.0, CH_2-8), 4.32(d, J=6.1, H-1'), 5.67(q, J=7.1, H-13). 13: 1.32(d, J=6.8, Me-5), 4.85(dd, J=6.3 & 2.9, H-2), 6.38(dd, J=6.3 & 1.5, H-1).

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