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An Enantioselective Synthesis of a Macrolide from the Polyketide Lactone Derived from Oleandomycin[#]

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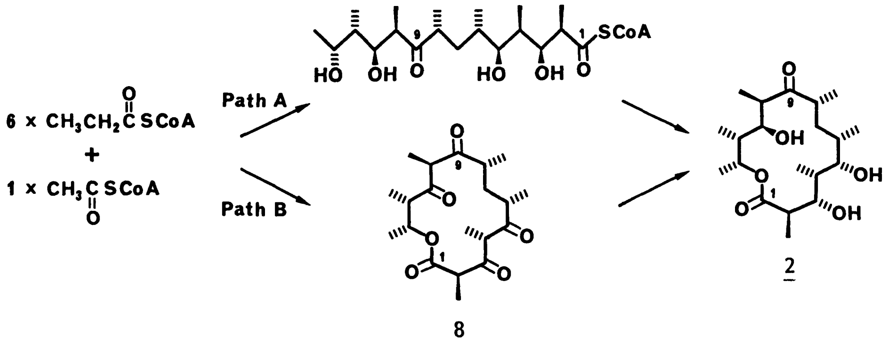
The polyketide lactone, 8-methyl-3,5,11-trioxo-oleandolide, which is obtained from a new aglycone of oleandomycin by ruthenium tetraoxide oxidation, is stereoselectively reduced by zinc borohydride in the presence of magnesium bromide to give a macrolide, (5*R*,8*R*,9*R*)-9-dihydro-8-methyl-*epi*-oleandolide in a good yield.

The discovery of naturally occurring macrolide antibiotics has raised many questions concerning various aspects of their interesting biochemical properties, their complex chemistry, and their intricate mechanism of biosynthesis.[1)] The biosynthetic hypothesis has been formulated by Cane[2)] and others, based mainly on empirical observations. However, the problem of when and how the secondary hydroxyl group stereochemistry is controlled remains one of the most challenging aspects of the macrolide biosynthesis. For example, although a biosynthetic precursor of oleandomycin[3)] (1) is known to be 8,8a-deoxyoleandolide (2: 8-methyl-oleandolide),[4)] no intermediates preceding the lactone 2 have ever been observed.

The retrobiogenetic analysis suggested that the macrolide 2 could be derived by path A or B from the one acetate and six propionate units. Path A involves stereospecific reduction of the carbonyl groups before the proper lactonization. In another pathway B, the lactonization takes place between the stereospecifically produced C-13 hydroxyl group and the C-1 carboxyl group leading to a polyketide lactone, followed by reduction of other carbonyl groups.

In a sense of organic synthesis, path A was successfully illustrated by stereospecific aldol reaction and lactonization by Mukaiyama[5)] and others.[6)]



[#] Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.

In this paper we wish to chemically simulate path B by stereoselectively synthesizing a macrolide from a polyketide lactone 8 derived from oleandomycin (1), which is an antibiotic of considerable commercial importance.

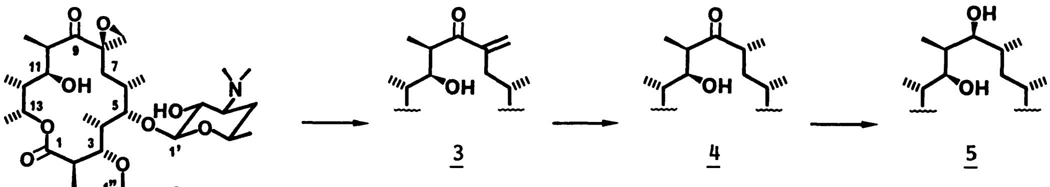
Oleandomycin (1) was treated with $CrCl_2$ (1 M $HCl/Me_2CO/Ar$, 25 °C, 12 h) to give the methylene ketone 3[7,8] (92%; $[\alpha]_D$ -69°). Hydrogenation of 3 (H_2/Raney Ni/EtOH) stereoselectively gave (8*R*)-8-methyloleandomycin[8,9] (4: 96%; $[\alpha]_D$ -75°), followed by hydride reduction ($NaBH_4$/i-PrOH/EtOAc, 25 °C, 3 h) to yield the (9*S*)-alcohol 5[8] [85%, mp 122 °C; $[\alpha]_D$ -35°; R_f 0.39($CHCl_3$-MeOH 3:1)]. The stereo-alignment was assigned by the ^{1}H-NMR spectrum of the aglycone 7 as follows.

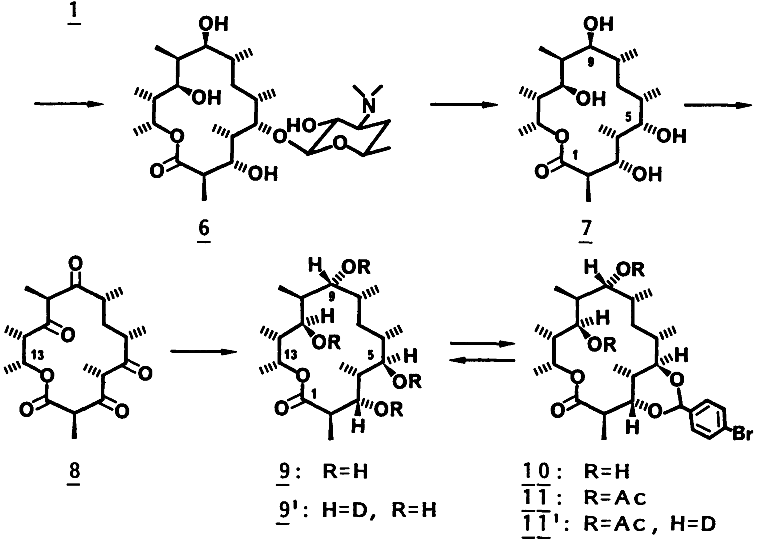
The aglycone, (8*R*,9*S*)-9-dihydro-8-methyloleandolide (7) was obtained in a 75% yield from 5 in 3 steps: (i) mild hydrolysis of 5 with methanolic hydrogen chloride (25 °C, 11 h) to give the deoleandorosyl compound 6;[8] (ii) oxidation with *m*-chloroperbenzoic acid ($CHCl_3$, 25 °C, 4 h) to give the N-oxide; (iii) treatment with trimethylsilyl iodide (PhMe/Ar, 25 °C, 1 h) to give 7[8] [cubes from Et_2O-hexane: mp 99 °C; $[\alpha]_D$ +22°; R_f 0.33(hexane-EtOAc 1:1)]. The latter two steps proved to be the effective procedure for removal of the amino sugar moiety. The ^{1}H-NMR spectrum[8] of 7 showed the similar signal patterns due to H-8(δ=1.4, $J_{8,9}$=10.0), H-9(δ=2.99, $J_{9,10}$=4.0) and H-10(δ=1.95, $J_{10,11}$=2.0) to those of (9*S*)-9-dihydroerythronolide A.[10]

Exhaustive oxidation of the four hydroxyl groups in 7 was attempted in a large number of variables to intercept the elusive polyketide lactone 8, since the C-11 hydroxyl group was reported to be resistant to chromic acid oxidation.[11] The best result was realized by exposure of 7 to RuO_4 (CCl_4, 25 °C, 1 h). After the reaction mixture was treated with isopropyl alcohol to decompose excess RuO_4, the precipitates were filtered and washed with CCl_4. The filtrates and washings were combined and the solvent was removed in vacuo below 30 °C to give the labile polyketide lactone, 8-methyl-3,5,11-trioxo-oleandolide (8) as a syrup [approximately 85%; R_f 0.63(hexane-EtOAc 1:1)].[12] Without further purification, the product was used for the next step. It should be noted that the configurations at all the methine carbons other than C-13 are changeable through the keto-enol tautomerism. The 3,5,9,11-tetraoxo structure was established by the spectral studies of the deuterated derivatives (9' and 11') as belows.

The reduction of 8 was achieved by $Zn(BH_4)_2$ in the presence of $MgBr_2$ (Et_2O - THF, 25 °C, 3 h) to provide, after silica-gel column chromatography (PhH-EtOAc 1:1), the tetraol 9 in a good yield [∿80%; R_f 0.17(hexane-EtOAc 1:1), with a very small amount of the isomer] as a major product, which was treated with *p*-bromobenzaldehyde dimethyl acetal (CH_2Cl_2, TsOH, 5 °C, 13 h) to give the benzylidene 10 (69% from 8).[8] The purity was confirmed by acetylation (Ac_2O/Py/DMAP, 25 °C, 1 h) to give quantitatively the corresponding diacetate 11[8] (cubes from Et_2O-hexane; mp 199 °C; $[\alpha]_D$ +26°]. The hydride reduction without $MgBr_2$ gave 10 in a lower yield (35% from 8). This fact suggested that the conformation and/or configuration in the lactone 8 could be considerably fixed by the metal chelation.

By hydrogenolysis (H_2/Pd-black, 25 °C, 12 h), 10 was converted back into a pure macrolide 9, which was recrystallized from acetone-hexane to give cubes[8] [83%; mp 235 °C; R_f 0.22(hexane-EtOAc 1:1)].





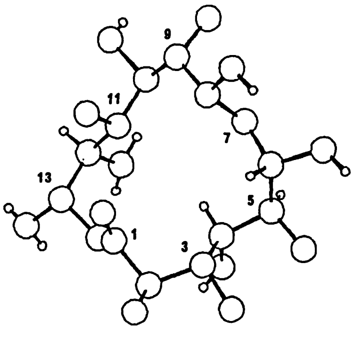


Fig. 1. A structural view of 9 as seen by X-ray analysis.

Deuteration of 8 with $Zn(BD_4)_2$ followed by the aforesaid transformations provided the corresponding deuterated compounds[8] of 9 [9' : FDMS(M$^+$+1) : 379; cf. 9: 375] and 11 [11' : FDMS(M$^+$+1) : 629 & 631; cf. 11: 625 & 627]. Their spectral analyses[8] gave unambiguous evidence for the production of the polyketide lactone 8.

The absolute structure of the macrolide 9 was defined as 2*R*,3*S*,4*R*,5*R*,6*S*,8*R*,9*R*, 10*S*,11*R*,12*R*,13*R* by the X-ray crystallographic analysis[13] as depicted in Fig. 1.

Thus, the enantioselective synthesis of (5*R*,8*R*,9*R*)-9-dihydro-8-methyl-*epi*-oleandolide (9) indicated that the hydride reduction of the polyketide 8 in question was stereochemically controlled and, in comparison with the original macrolide 7, was accomplished with complete retention of configurations at all the methine carbons except for the C-5 and C-9.

The stereochemistry of the macrolide 9 was incompatible with that of the natural macrolide 2 only at the C-5 position.

In the macrolide biosynthesis, it seems likely that such a polyketide lactone as 8 is much more stereospecifically reduced to give the macrolide 2 by at least the conformational bias in the skeleton.

Further extensions of this strategy for the enantioselective synthesis of natural macrolides are in progress.

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8) All compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means and elemental analyses. R_f-values were measured on silica gel Merck TLC 60F-254. Optical rotations (*c* 0.5, $CHCl_3$) were done using a 0.5 dm tube at 25 °C. Significant ^1H-NMR spectral data [δ ($CDCl_3$, TMS), J (Hz)] are the following. 3: 4.26(1H, d, H-1', J=7), 4.96(1H, d, H-1", J=3), 5.41(1H, dq, H-13), 5.55 and 5.62(each 1H, broad s, CH_2-8). 4: 2.47(6H, s, N-Me_2), 5.40(1H, dq, H-13). 5: 4.25(1H, d, H-1', J=7), 5.00(1H, dull d, H-1", J=3), 5.29(1H, dq, H-13, J=6.2 & 0.5). 6: 4.40(1H, d, H-1', J=7), 5.37(1H, dq, H-13). 7: ≈1.4(1H, m, H-8), ≈1.95(1H, m, H-10), 2.72(1H, dq, H-2, J=10.5 & 7.0), 2.99(1H, dt, H-9, J=10.0, 10.0 & 4.0), 3.37(1H, ddd, H-11, J=10.0, 5.0 & 2.0), 3.85(1H, dd, H-3, J=10.5 & 2.0), 3.99(1H, broad s, H-5), 5.39(1H, dq, H-13, J=7.0 & 1.0). 9: 2.74(1H, dq, H-2, J=10.5 & 7), 3.98(1H, dull d, H-3, J=10.5), 5.41(1H, dq, H-13, J=6.5 & 1.5); in 9', signals corresponding to H-3,5,9, and 11 were not observed. 10 (a diastereomeric mixture because of the benzylidene proton): 2.78 & 2.89(1H, dq, H-2, J=10.0 & 7.0), 3.94 & 3.98(1H, dd, H-3, J=10.0 & 2.0), 5.66 & 5.72(1H, s, benzylidene proton). 11: 3.14(1H, dd, H-5, J=8.0 & 4.0), 4.16(1H, dd, H-3, J=10.5 & 3.0), 4.78(1H, dd, H-9, J=8.0 & 3.0), 4.93(1H, dd, H-11, J=10.0 & 1.0); in 11', these signals were not observed.

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12) The satisfactory mass spectrum of 8 is not yet obtained.

13) The X-ray crystallographic analysis was kindly carried out by Prof. Yoichi Iitaka and Ms. Hikaru Nakamura, Faculty of Pharmaceutical Sciences, University of Tokyo. The crystal data are: $C_{20}H_{38}O_6$, MW=374.5, space group $P2_1$, *a*=9.961, *b*=12.491, *c*=9.560 Å, β=116.3°, *U*=1066.2 $Å^3$, z=2, D_{calc}=1.166 g cm^{-3}, R=0.11 and 1781 reflections.

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