SYNTHESIS OF A BIOSYNTHETIC PRECURSOR OF OLEANDOMYCIN, 8,8a-DEOXYOLEANDOLIDE (8-METHYLOLEANDOLIDE), FROM OLEANDOMYCIN†

Sir:

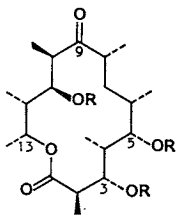
A 14-membered macrolide aglycone, 8,8a-deoxyoleandolide[1] (8-methyloleandolide[2]) (**1**) has been known as a precursor in the biosynthesis of oleandomycin (**2**), which is a clinically important macrolide antibiotic. The isolation and determination of structure of this interesting substance **1** by Abbott group[1] are among the most notable of developments in the field of the macrolide biosynthesis. Because of the biosynthetic significance and the extreme scarcity of the macrolide **1**, there has been considerable interest in the practical synthesis.

Very recently, we reported a novel enantioselective synthesis of the analogous aglycone, (5*R*,8*R*,9*R*)-9-dihydro-8-methyl-*epi*-oleandolide (**3**), which was incompatible with **1** only in the stereochemistry at the C-5 position, from the polyketide lactone **4** in order to chemically simulate a probable biosynthetic pathway of the macrolide[3]. The key intermediate **4** was effectively derived from a new aglycone of oleandomycin, (8*R*,9*S*)-9-dihydro-8-methyloleandolide (**5**)[3].

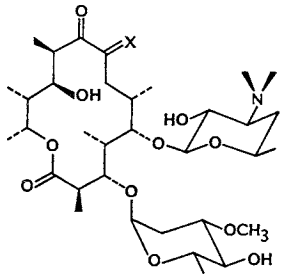
Herein, we describe an efficient synthesis of 8-methyloleandolide (**1**) by using the aglycone **5**.

The intermediary aglycone **5** [mp 99°C; $[\alpha]_D^{25}$ +22° (*c* 0.5, $CHCl_3$)] was prepared in six steps by our method[3] beginning with the formation of the exocyclic methylene **6** from oleandomycin **2** as follows: i) Treatment of **2** with $CrCl_2$ to give **6**; ii) successive stereospecific reductions with hydrogen and Raney Ni to give the (8*R*)-8-methyl compound, followed by $NaBH_4$ to give (8*R*,9*S*)-9-dihydro-8-methyloleandomycin (**7**); iii) removal of the sugar moieties by acid hydrolysis to give the deoleandrosyl compound, followed by reaction of the corresponding *N*-oxide with trimethylsilyl iodide. The overall yield from **2** was 56%.

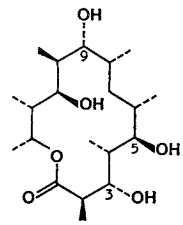
Regioselective benzylidenation of **5** with *p*-bromobenzaldehyde dimethyl acetal (bp_4 84°C) and a catalytic amount of *p*-toluenesulfonic acid in CH_2Cl_2 at 5°C for 5 hours afforded the corresponding 3,5-*O*-protected product **8** in 92%



1 R = H
11 R = Ac



2 X = O
6 X = CH_2



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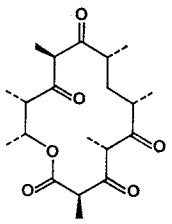

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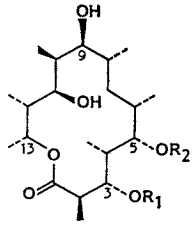
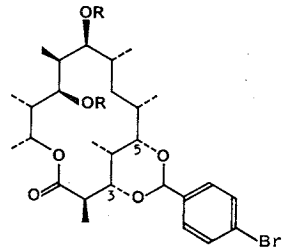
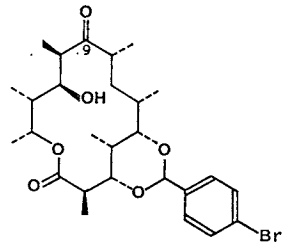


5 R_1 = R_2 = H
7 R_1 = Oleandrosyl
R_2 = Desosaminyl



8 R = H
9 R = Ac



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† Dedicated to the memory of Professor HAMAO UMEZAWA.

Table 1. Selected ^{1}H NMR parameters (500 MHz, $CDCl_3$) of **1** and **8**~**11**.

	Chemical shifts (δ)				
	1	**8**	**9**	**10**	**11**
H-2	2.74	2.86	2.82	2.90	2.78
H-3	3.89	3.74	3.85	3.81	5.22
H-4	1.86	1.91	~2.38	2.11	2.29
H-5	3.99	3.86	3.99	3.93	4.79
H-6	2.01	2.37	~2.38	2.36	~2.1
H-8	2.62	1.52	~2.2	2.67	~2.75
H-9	—	3.12	4.76	—	—
H-10	~2.77	2.00	~2.2	~2.85	3.08
H-11	3.66	3.68	5.25	3.98	4.94
H-12	~1.72	1.65	1.68	1.66	1.81
H-13	5.49	5.58	4.93	5.64	5.19

	Coupling constants (Hz)				
	1	**8**	**9**	**10**	**11**
$J_{2,3}$	10.5	10.5	10.5	10.5	10.5
$J_{3,4}$	<1	<1	1.0	<1	1.5
$J_{4,5}$	2.5	1.0	1.0	1.0	6.0
$J_{5,6}$	4.5	6.0	6.0	6.0	2.0
$J_{8,9}$	—	9.0	11.0	—	—
$J_{9,10}$	—	3.0	3.0	—	—
$J_{10,11}$	2.0	2.0	0.5	2.5	2.0
$J_{11,12}$	10.5	10.5	10.5	10.5	10.5
$J_{12,13}$	1.5	1.0	1.0	1.5	1.5

yield, after silica gel column chromatography with hexane - EtOAc (2:1). Recrystallization from acetone - hexane gave cubics of **8**: MP 240°C; $[\alpha]_D^{25}$ +15° (*c* 0.58, $CHCl_3$); field desorption mass spectrum (FD-MS) *m/z* (M+H) 542 and 544; ^{1}H NMR (see Table 1). The structure was confirmed by the ^{1}H NMR spectrum (Table 1) of the corresponding diacetate **9**: MP 200°C (needles after recrystallization from ether - hexane); $[\alpha]_D^{30}$ −1.5° (*c* 0.5, $CHCl_3$); FD-MS *m/z* (M+H) 625 and 627.

Selective oxidation of **8** with pyridinium dichromate in CH_2Cl_2 at 25°C for 3 hours gave exclusively the C-9 ketone **10** in 82% yield as a syrup, which was kept in hexane at 0°C to afford the amorphous solid: MP 117~125°C; $[\alpha]_D^{30}$ −48° (*c* 0.5, $CHCl_3$); Rf 0.45 on TLC (hexane - EtOAc, 2:1); FD-MS *m/z* (M+H) 540 and 542; ^{1}H NMR (see Table 1).

Removal of the benzylidene group without acetal formation between the C-5 hydroxyl and the C-9 carbonyl groups was best realized by hydrogenolysis[4] with 3-atm hydrogen and Pd-black in EtOH to give 8-methyloleandolide (**1**) as a syrup in 86% yield, after silica gel column chromatography with hexane - EtOAc (1:1). The syrup changed to needles of **1** by gradual evaporation of the $CHCl_3$ solution around 0°C: MP 68~70°C; $[\alpha]_D^{29}$ −47° (*c* 0.5, $CHCl_3$); Rf 0.43 on TLC (hexane - EtOAc 1:1); FD-MS *m/z* (M+H) 373; IR $\nu_{max}^{CHCl_3}$ cm^{-1} 2980, 2940, 2880, 1700, 1457, 1374 and 1332; ^{1}H NMR (see Table 1).

The compound **1** was further characterized by acetylation with Ac_2O and pyridine at 25°C for 24 hours to give, after silica gel column chromatography (benzene - EtOAc, 3:1), the crystalline triacetate **11** in 87% yield: MP 152~169°C (plates after recrystallization from MeOH - H_2O)[1]; mp 174~176°C (needles after recrystallization from ether - hexane); $[\alpha]_D^{28}$ −11° (*c* 0.5, $CHCl_3$); Rf 0.73 on TLC (benzene - EtOAc, 1:1); FD-MS *m/z* (M+H) 499; IR ν_{max}^{KBr} cm^{-1} 1733 and 1700; ^{1}H NMR (see Table 1).

These physico-chemical data of **1** and **11** were identical with those of naturally derived macrolides[1]. Thus, pure synthetic macrolide **1** is now available in multigram amounts. Further

the detailed structure has been established unambiguously.

Acknowledgments

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