AN ALTERNATIVE AND FACILE SYNTHESIS OF PIKRONOLIDE ‡

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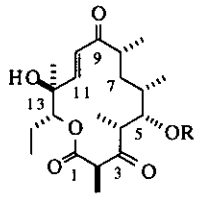
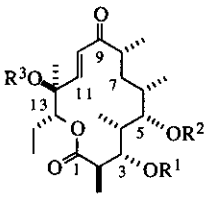
Abstract *- An alternative and facile synthesis of pikronolide (**2**), the aglycon of pikromycin (**1**), via coupling between the C_{11}- C_{15} fragment (**10**) and the C_1-C_{10} fragment (**12**), Horner-Emmons cyclization, regioselective protection of the C_5-hydroxy group, and oxidation of the C_3-hydroxy group, is described. In this synthesis, the conformational analysis by NMR played an important role.*

Pikromycin (**1**) was isolated from a strain of *Streptomyces* as the first macrolide antibiotic in 1950.[1] In 1986, we reported the first total synthesis of its aglycon, pikronolide (**2**)[2,3] *via* **3** by taking advantage of the benzyl-type protecting groups, 3,4-dimethyoxybenzyl (DMPM), 4-methoxybenzyl (MPM) and benzyl (Bn) groups, which are selectively deprotectable.[4] One of the points of issue in this synthesis was the construction of the aldol system at C_3-C_5 of **2**,[5] which was predicted to be unstable, because even under very mild conditions (pH 6.5, 60 ℃), **1** lost desosamine to give the 4,5-anhydro compound, kromycin (**7**).[6,7] In order to avoid such undesirable elimination into **7** and to complete the selective synthesis of **2**, we decided to form the C_3 ketone at the final synthetic stage and **3** was chosen as a promising intermediate. However, the synthesis of C_1-C_{10} fragment (**10**) required multi-step transformations (12 steps and less than 19 % overall yield from **12**) due to protection of MPM and DMPM. The MPM protection at C_5 position was quite difficult and poorly reproducible and the DMPM group was not sufficiently stable under Lemieux-Rudloff's oxidation conditions (*vide infra*).[8] In this paper we describe an alternative synthesis of **2** *via* the acetonide (**11**), which was more readily synthesized also from **12**.[3] Coupling of **11** with **9** gave **8**, which was cyclized to **4** and then converted to **5** and **6**. On the basis of conformational analysis, selective oxidation of the C_3-hydroxy group and protection of the C_5-hydroxy group were examined.

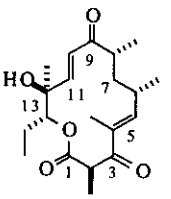
‡ This Paper is dedicated to the memory of Dr. Shun-ichi Yamada, Professor Emeritus Tokyo University.



1 : R = Desosaminyl
2 : R = H



3 : R^1= DMPM, R^2= MPM, R^3= Bn
4 : R^1R^2= CMe_2, R^3= Bn
5 : R^1=R^2= H, R^3= Bn
6 : R^1=R^2= R^3= H



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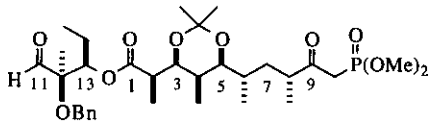

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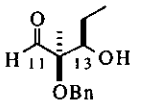

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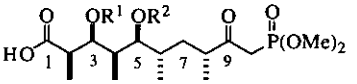
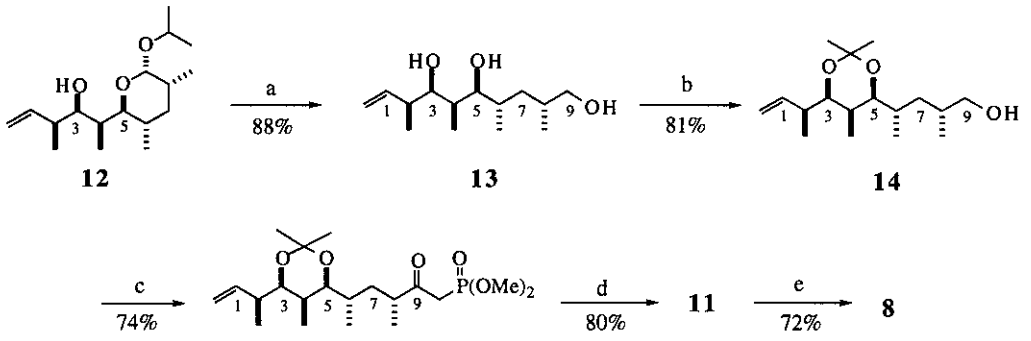


10 : R^1 =DMPM, R^2= MPM
11 : R^1R^2 = CMe_2

Figure 1

Transformation of **12** into **11** was readily achieved *via* a series of conventional reactions. The isopropyl protecting group of **12**, which was derived from D-glucose,[3] was removed with 1N HCl, and the resulting hemiacetal was reduced with $Ca(BH_4)_2$ to give the triol (**13**). Protection of the 1,3-diol of **13** as an acetonide gave **14**, and the remaining primary hydroxy group was oxidized under Swern's conditions to give the aldehyde, which was treated with the lithio derivative of dimethyl methylphosphonate at -88 ℃ and then oxidized with pyridinium dichromate (PDC) to give the β-ketophosphonate (**15**). The terminal

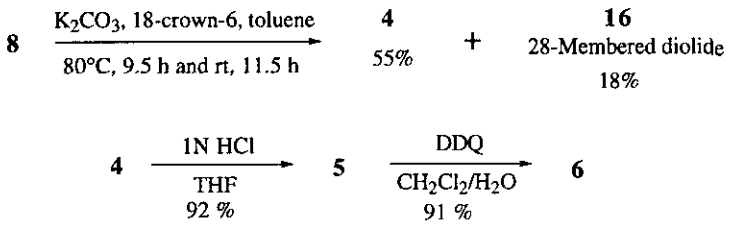


(a) 1) 1N HCl/THF(1:3), 50°C 2) $Ca(BH_4)_2$, EtOH (b) $Me_2C(OMe)_2$, CSA, CH_2Cl_2, rt (c) 1) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2, -78°C 2) $LiCH_2P(O)(OMe)_2$, THF, -88°C 3) PDC, DMF, rt (d) $KMnO_4$, $NaIO_4$, $NaHCO_3$, acetone-H_2O (1 : 1), rt (e) **9**, 2,4,6-C_6H_2COCl, NEt_3, DMAP, toluene, rt

Scheme 1

olefin of **15** was directly oxidized to a carboxylic acid under Lemieux-Rudloff's conditions. Thus, the synthesis of the C_1-C_{10} fragment (**11**), in which the C_3, C_5-diol was protected as an acetonide, was completed. All the reaction steps from **12** to **11** proceeded without difficulty, and the overall yield for the seven steps was 42 %. Coupling of **11** with **9** into the ester (**8**) was achieved by the Yamaguchi method[9] using 2,4,6-trichlorobenzoyl chloride and 4-dimethylaminopyridine (DMAP) in toluene (Scheme 1), and **8** was next subjected to macrocyclization.

The macrocyclization is usually the most crucial step in the synthesis of macrolides. In this synthesis of **2**, the macrocyclization of **8** into **4** was accomplished by an intramolecular Horner-Emmons reaction.[10] When a 1 mM solution of **8** in toluene was treated with K_2CO_3 (6 equiv.) and 18-crown-6 (12 equiv.) for rather prolonged times (80 ℃, 9.5 h and room temperature, 11.5 h), the cyclization proceeded slowly to give the expected 14-membered lactone (**4**) in 55% yield with the concomitant formation of 28-membered diolide (**16**) in 18% yield. The reaction of a 4 mM solution of **8** gave only a poor result, 29 % yield of **4** and 15 % yield of **16**. The structure of **16** was confirmed by FD mass spectroscopic measurements. Acid hydrolysis of the acetonide of **4** readily gave **5**, which was treated with a large excess of DDQ to give **6** in high yield (Scheme 2).

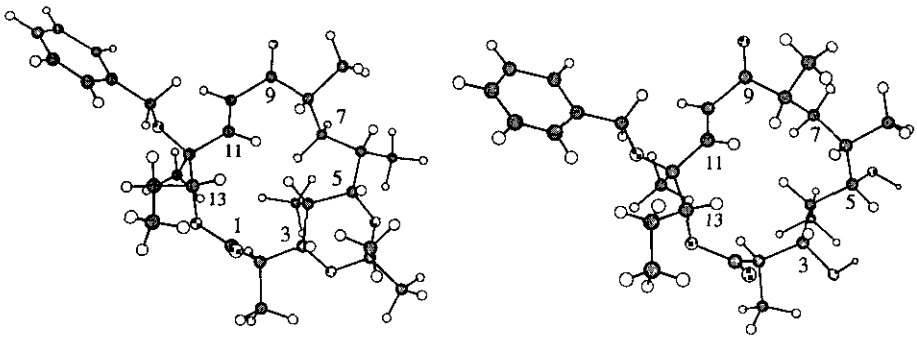


Scheme 2

In order to synthesize **2**, the regioselective oxidation of the C_3-hydroxy group of **5** and/or **6** was required. Functional group transformations on macrorings are usually controlled by their ring conformations. Since the conformational control is crucial for the regio- and/or stereoselective reactions, we first examined global conformations of **4**, **5** and **6** by NMR studies. All the proton signals were assigned with the aid of 2D NMR (H-H COSY, C-H COSY, HMBC) experiments, and then NOE, NOESY and ROESY were taken. On the basis of 1D and 2D data and *J* values (Table 1), the most probable conformations of **4** and **5** are depicted as shown in Figure 2 with reference to the conformational analysis of 16-membered lactones.[12] The differences of coupling constant at C_4-C_8 between **5** and **6**, and corresponding coupling constants of **6** are averaged over all conformation indicated that the conformation of **6** seemed to be more flexible than that of **5**. The enone part of **5** and **6** has a 9,10-*s*-trans conformation, and is placed nearly in the plane of the 14-membered ring. The protons at C_2, C_3, C_4 and C_6 are situated inside the ring, while only the C_5 proton is directed to the outside. Therefore, the C_5 hydroxy group was presumed to be oxidized more easily than the C_3 hydroxy group.

Table 1. Vicinal proton coupling constants (*J*: Hz) of **4**, **5** and **6**

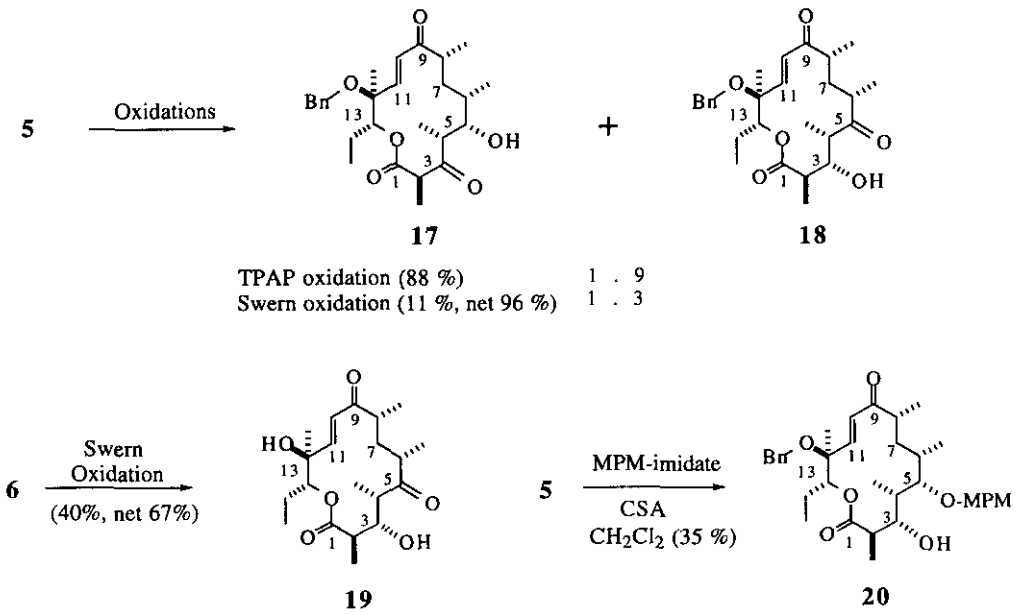
J H-H, Hz	**4**	**5**	**6**
2-3	10.3	8.5	7.5
3-4	1.5	2.2	2.2
4-5	1.5	7.6	5.9
5-6	5.9	2.5	3.0
6-7a	12.2	7.3	6.8
6-7b	2.9	6.0	6.3
7a-8	2.0	10.0	6.9
7b-8	10.7	3.9	6.3
10-11	17.0	16.6	16.5
13-14a	3.0	2.2	2.2
13-14b	9.7	10.8	11.0



4 **5**

Figure 2

When **5** was treated with tetra-*n*-propylammonium perruthenate (TPAP)[14] and 4-methylmorpholine *N*-oxide (NMO) in CH_2Cl_2 for 30 min, a 1 : 9 mixture of the desired C_3-ketone (**17**) and its C_5-isomer (**18**) was obtained in 88 % yield. Swern oxidation improved somewhat the selectivity to 1 : 3 although still this was practically useless.[15] Oxidation of **6** under Swern's conditions gave only the undesired C_5-ketone (**19**) and no trace of the desired C_3-ketone was detected. As we presumed, the oxidation occurred mainly at the C_5 position, and hence the selective protection of the C_5-hydroxy group was next examined. Protection of hydroxy groups with 4-methoxybenzyltrichloroacetimidate (MPM-imidate) under mild acidic conditions is quite useful,[16] and this method was now applied to the selective protection of **5**. When **5** was treated with MPM-imidate (3 equiv.) and camphorsulfonic acid (CSA) in CH_2Cl_2 at room temperature for 20 h, the expected C_5-MPM ether (**20**) was isolated as the sole product, although the yield (35 %) is still unsatisfactory. Compound (**20**) was readily converted to **2** in 81 % yield as described in the previous papers and all the spectral data [NMR, IR, mass] collected for **20** were identical with those of authentic sample.[3]



Scheme 3

In conclusion, we completed the alternative synthesis of **2** from **12**, in which all reactions are rather simple and easy to perform (11 steps, 5.4 % overall yield) compared with original synthesis (15 steps, 3.3 % overall yield), although improvements of some reactions, especially the Horner-Emmons cyclization of **8** and the selective protection of the C_5-hydroxy group of **5** with MPM-imidate, are still required. The conformational analyses of presented compounds by MM calculation and more synthetic details will be reported in due course.

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