

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 C₁₁-C₁₅ fragment (10) and the C₁-C₁₀ fragment (12), Horner-Emmons cyclization, regioselective protection of the C₅-hydroxy group, and oxidation of the C₃-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-dimethoxybenzyl (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 C₃-C₅ of 2,⁵ which was predicted to be unstable, because even under very mild conditions (pH 6.5, 60 °C), 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 C₃ ketone at the final synthetic stage and 3 was chosen as a promising intermediate. However, the synthesis of C₁-C₁₀ 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 C₅ 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 acetone (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 C₃-hydroxy group and protection of the C₅-hydroxy group were examined.

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

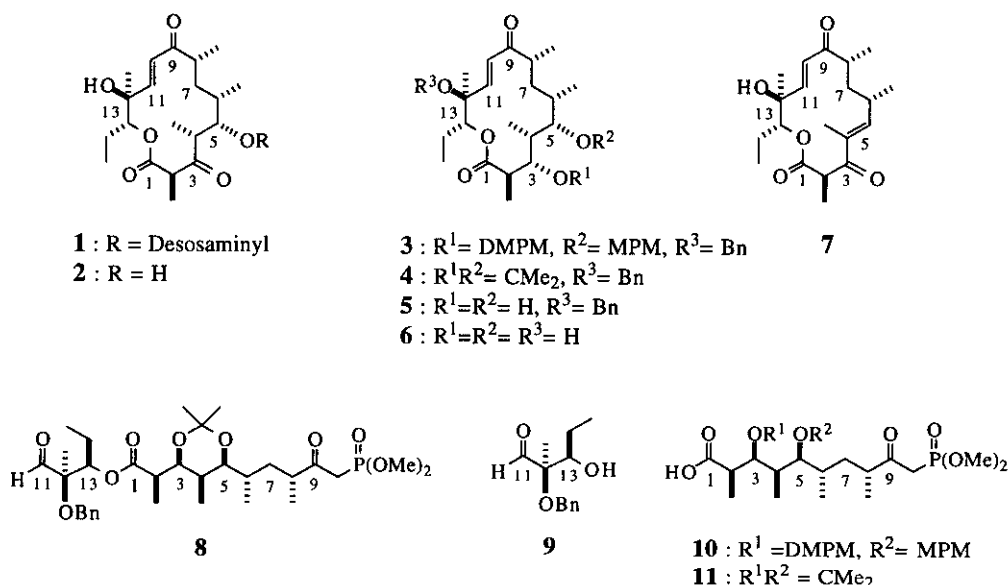
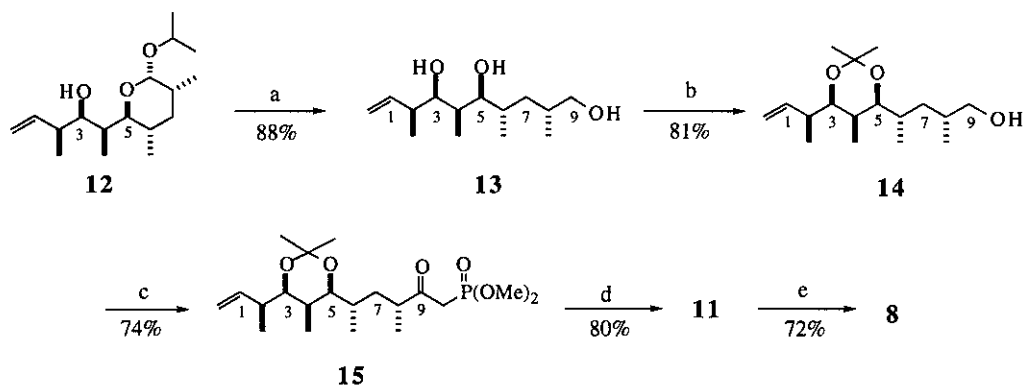


Figure 1

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(BH₄)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 °C and then oxidized with pyridinium dichromate (PDC) to give the β-ketophosphonate (**15**). The terminal

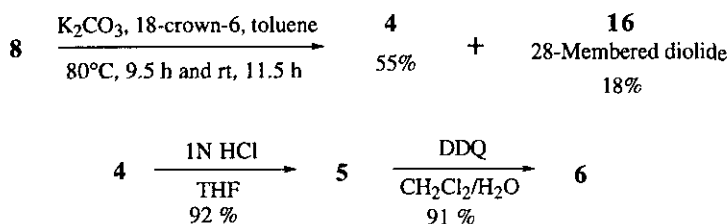


(a) 1) 1N HCl/THF(1:3), 50°C 2) Ca(BH₄)₂, EtOH (b) Me₂C(OMe)₂, CSA, CH₂Cl₂, rt (c) 1) (COCl)₂, DMSO, NEt₃, CH₂Cl₂, -78°C 2) LiCH₂P(O)(OMe)₂, THF, -88°C 3) PDC, DMF, rt (d) KMnO₄, NaIO₄, NaHCO₃, acetone-H₂O (1 : 1), rt (e) **9**, 2,4,6-C₆H₂COCl, NEt₃, DMAP, toluene, rt

Scheme 1

olefin of **15** was directly oxidized to a carboxylic acid under Lemieux-Rudloff's conditions. Thus, the synthesis of the C₁-C₁₀ fragment (**11**), in which the C₃, C₅-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 method⁹ 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 K₂CO₃ (6 equiv.) and 18-crown-6 (12 equiv.) for rather prolonged times (80 °C, 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 C₃-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 C₄-C₈ 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 C₂, C₃, C₄ and C₆ are situated inside the ring, while only the C₅ proton is directed to the outside. Therefore, the C₅ hydroxy group was presumed to be oxidized more easily than the C₃ 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

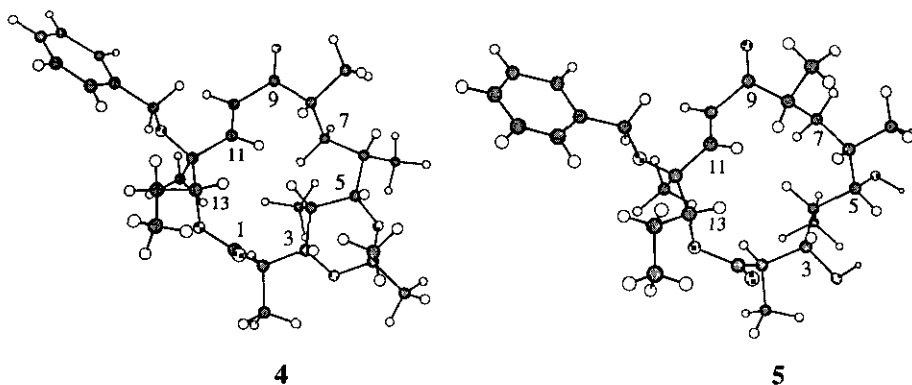
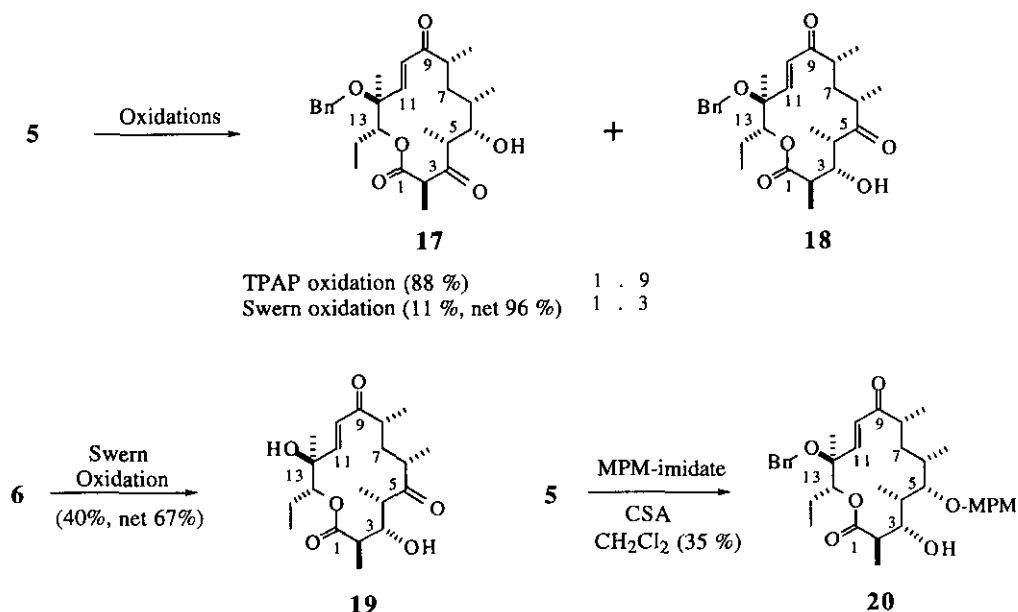


Figure 2

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 C₅-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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