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Synthetic Study of Tautomycin. I Synthesis and Regioselective Enzymatic Acetylation of a Spiroketal Diol Related to the C_5-C_{16} Fragment

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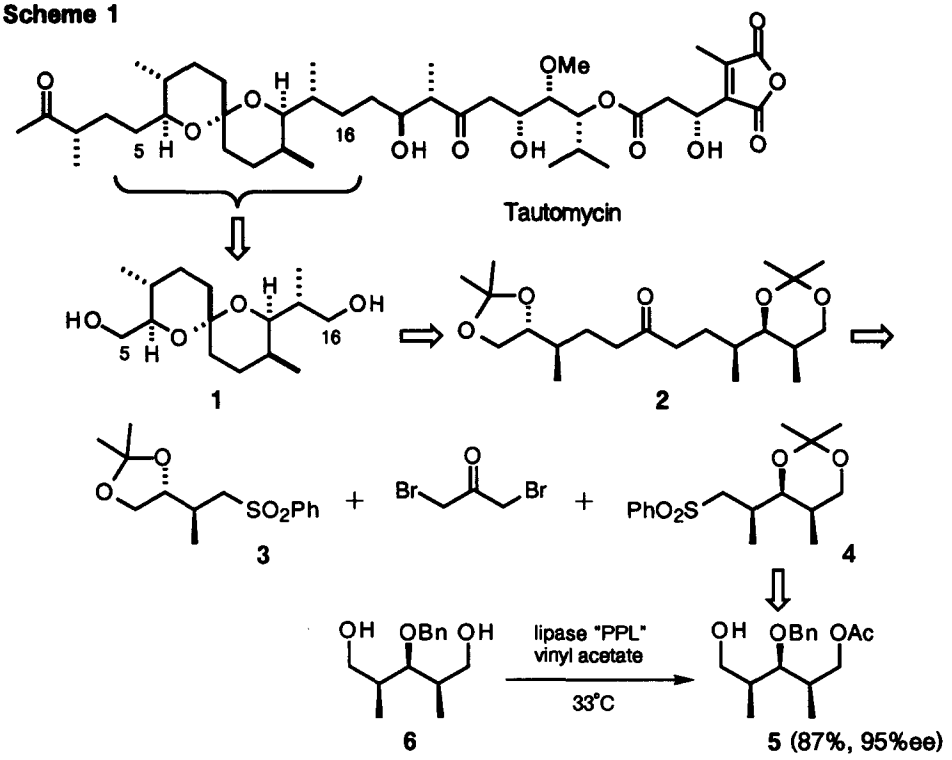
Abstract: Spiroketal diol **1** was prepared from **5**, which can be obtained by enantio-selective enzymatic acetylation of meso diol **6**, in 12 steps in 16.5% total yield and its regioselective protection was achieved by an enzymatic method to give **1 6** in high yield.

Enzymatic esterification or hydrolysis was successfully applied to the syntheses of a broad range of chiral synthons, which were converted into many biologically active compounds.[1] As a further step in research in this field, the enzymatic regioselective acetylation of compounds possessing a complex structure arouses our interest. Several pioneer works have been reported, but most of them are examples for limited types of substrates.[2] Furthermore, selective functionalization between different primary alcohol groups or acetyl groups has scarcely been studied.[3] We wish to report here the first enzymatic regioselective acetylation of a spiroketal compound with two primary alcohol groups.[4]

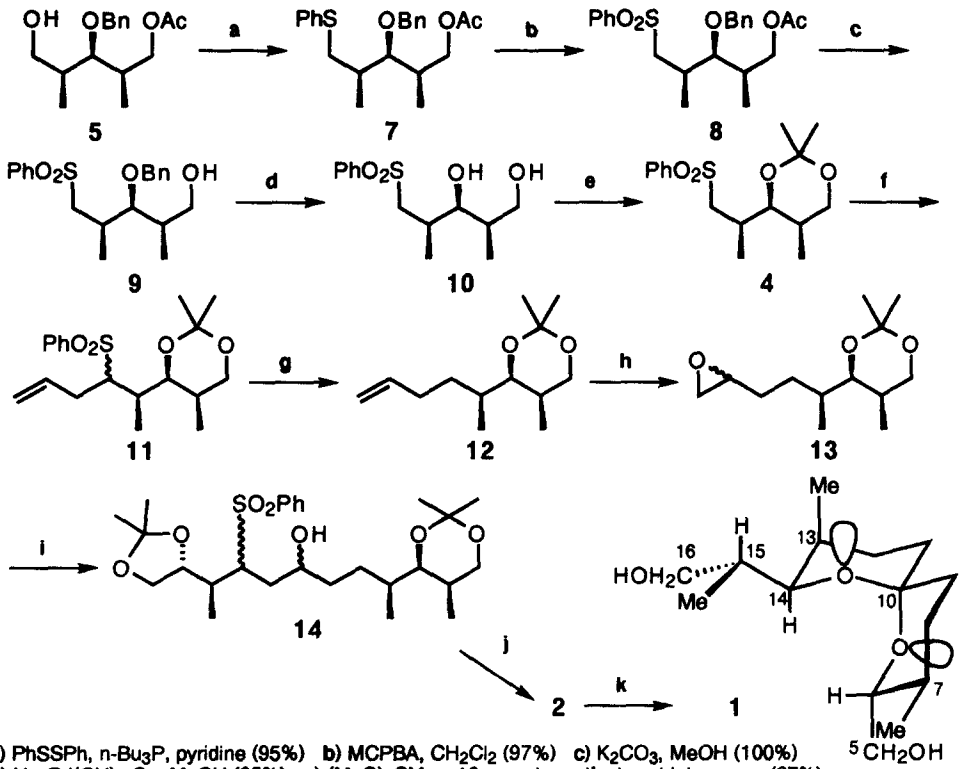
Tautomycin was isolated by Isono *et al.* from a culture of *Streptomyces spiroverticillatus*.[5] The compound exhibits antifungal activity against *Sclerotinia sclerotiorum* and inhibits type 1 and 2A protein phosphatases specifically.[6] The absolute configuration of the compound was determined by spectroscopic analysis of chemical degradation products[7] and the total syntheses were achieved by three groups.[8] The structural complexity and the biological activity provided the stimulus for elaborating the study of tautomycin on the basis of the original strategy. Spiroketal diol (**1**) is regarded as an essential chiral synthon corresponding to the C_5-C_{16} segment of tautomycin, if enzymatic regioselective acetylation is applicable to the differentiation between functions in the C_5 and C_{16} positions. We planned a synthetic route of **1** as shown in Scheme 1. The strategy identifies the ketone (**2**) with five stereocenters as equivalent to **1**. Thus, it was anticipated that the desired acetalization of **2** would proceed stereoselectively. Compound **2** can be retrosynthetically divided into a dibromoacetone equivalent and two chiral sulfones (**3** and **4**). Sulfone **3** can be easily prepared from (+)-malic acid.[9] The optically active alcohol (**5**) was chosen as a precursor to **4** because we had already achieved a highly enantioselective conversion of the *meso*-diol (**6**) into **5** using the lipase from *Porcine pancreas* "PPL".[10]

Scheme 1



Treatment of (-)-5 (95%ee) with PhSSPh and Bu_3P[11] followed by oxidation using MCPBA resulted in highly efficient formation of the sulfone (8). Deacetylation of 8 with K_2CO_3 in MeOH proceeded quantitatively to give 9. Reductive debenzylation of 9 followed by acetalization provided 4 efficiently. Alkylation of 4 with allylbromide in the presence of *tert*-BuLi proceeded to give the alkylation product (11) in 82% yield. Desulfurization[12] of 11 with Na(Hg) followed by epoxidation with MCPBA resulted in formation of the epoxide (13) as an inseparable epimeric mixture. The reaction of 13 and an anion generated from 3 in the presence of BF_3•Et_2O afforded efficiently the hydroxysulfone (14) in 68% yield.[13] Subsequent desulfurization of 14 followed by Swern oxidation provided the ketone (2). When 2 was treated with camphorsulfonic acid in MeOH, entirely stereoselective acetalization was realized to give 1 in 99% yield. The structure of 1 was assigned on the basis of spectroscopic data. The ^{1}H-NMR spectrum exhibited the signals for C_6-H at δ 3.35 (1 H, *ddd*, *J* = 9.8, 6.8, 2.9 Hz), C_{14}-H at δ 3.54 (1 H, *dd*, *J* = 9.6, 2.3 Hz), and C_{15}-Me proton at δ 1.09 (1 H, *d*, *J* = 6.8 Hz) The identification was supported by ^{13}C-^{1}H COSY and COLOC spectrum. The stereochemistry of acetal carbon was determined by observed NOEs between C_6-H and C_{14}-H or C_{15}-Me proton. The observation of NOEs described above suggests also that 1 exists in conformation stabilized by two anomeric effects[14] as shown in Scheme 2 because the distance between C_6-H and C_{14}-H is very far in any other conformation. The conformation is also sterically stable as substituents except for the methyl group at the C_{13} position are all equatorial. The high thermodynamical stability of the conformation contributed to the stereoselective formation of 1 in transacetalization of 2.

Scheme 2



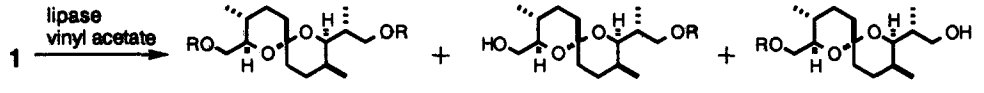
a) PhSSPh, n-Bu_3P, pyridine (95%) b) MCPBA, CH_2Cl_2 (97%) c) K_2CO_3, MeOH (100%)
d) H_2, $Pd(OH)_2$-C, MeOH (95%) e) $(MeO)_2CMe_2$, 10-camphorsulfonic acid, benzene (87%)
f) allyl bromide, *tert*-BuLi, THF (82%) g) 5% Na(Hg), MeOH, reflux (79%) h) MCPBA, CH_2Cl_2 (70%)
i) **3**, *tert*-BuLi, BF_3•Et_2O, THF (68%) j) i)5% Na(Hg), MeOH, reflux; ii) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2 (71%)
k) 10-camphorsulfonic acid, MeOH (99%)

The next problem to advance our synthetic study of tautomycin is how to distinguish between two alcohol groups in **1**. Highly selective protection of **1** was considered to be difficult on the basis of pure chemical methods. In fact, acetylation of **1** with an equivalent acetic anhydride in pyridine gave a mixture of diacetate (**15**), monoacetate (**16**), (**17**) and recovered **1**. The selectivity was not observed in spite of using bulky pivaloyl chloride instead of acetic anhydride. Under such circumstances, enzymatic acetylation was carried out by using three kinds of lipases, namely, Amano P from *Pseudomonas* sp., OF-360 from *Candida rugosa* and PPL. In the cases of using OF-360 and PPL, the selectivity was not observed. On the other hand, Amano P catalyzed selectively the acetylation of alcohol at the C_{16} position. To a solution of **1** (96.4 mg) in vinyl acetate (20 ml) was added commercially available Amano P (100 mg). After being stirred at 33°C for 40 h, the mixture was filtered, concentrated and purified by column chromatography on silica gel to afford **16** in 90% yield. The structure of **16** was assigned on the basis of spectroscopic data. Especially, the decoupling experiment of ^{1}H-NMR spectrum showed the correlation between two protons at the C_{16} position (δ 4.06, *dd*, *J* = 11.0, 4.2 Hz: δ 3.86, *dd*, *J* = 11.0, 6.4 Hz) and C_{15}-H.

In conclusion, optical pure diol **1** was prepared from **5**, which can be obtained by enantio-selective enzymatic acetylation of meso diol **6**, at 12 steps in 16.5% total yield and its selective protection was achieved by an enzymatic method to give **16** in high yield. The further conversion of **16** into tautomycin is under

investigation. The enzymatic regioselective protection aroused our interest because of its potential extension to the widespread complex polyol compounds. If the selectivities are predictable at the step of planning the synthesis of natural products, the methodology will be regarded to be more useful. Thus, we will explore systematically the enzymatic regioselective acetylation or hydrolysis of complex compounds having plural primary alcohols or acetates.

Table



15 (R = Ac) **16** (R = Ac) **17** (R = Ac)
18 (R = Piv) **19** (R = Piv) **20** (R = Piv)

	conditions	time	products			
			15	**16**	**17**	**1**
	Amano P, vinyl acetate, 33°C	40 h	5%	90%	2%	3%
enzymatic	OF 360, vinyl acetate, 33°C	5 d	30%	35%	30%	0%
	PPL, vinyl acetate, 33°C	5 d	0%	33%	12%	45%
	Ac_2O, pyridine	24 h	11%	36%	16%	31%
chemical			**18**	**19**	**20**	**1**
	PivCl, pyridine	18 h	5%	13%	13%	65%

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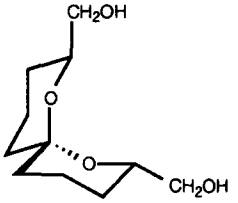

(+)-(2S,6S,8S)-**21**

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