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Total Synthesis of Tautomycin: Efficient Aldol Coupling of Two Large Subunits

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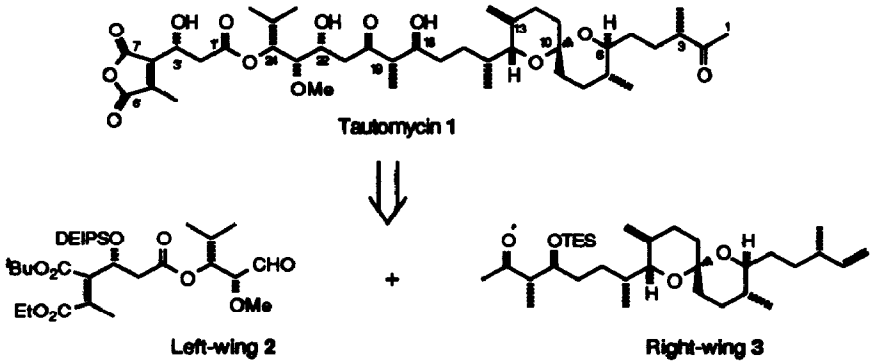
Abstract: **The total synthesis of tautomycin 1 has been achieved via key aldol condensation of the Left-wing 2 and the Right-wing 3.**

Recently, the reversible phosphorylation of proteins has been recognized to be a major mechanism for the intracellular signal transductions in eukaryotic cells.[1] The specific inhibitors of protein phosphatases (PP) become an useful tool for studying such the intracellular events. Tautomycin **1** was isolated from *Streptomyces spiroverticillatus* as an antifungal agent[2] and later was found to be a potent inhibitor of PP1 and PP2A.[3] Although molecular size and partial structure of **1** are similar to those of well-known phosphatase inhibitor okadaic acid (OA),[4] OA and **1** showed a different affinity for PP1 and PP2A.[3,4] Thus, systematic study of structure-activity relationship of **1** would elucidate the structural requirement for the inhibitory activity to design the new specific inhibitors for PP1 and PP2A. Our interest shown above led us to develop an efficient synthesis of **1**.

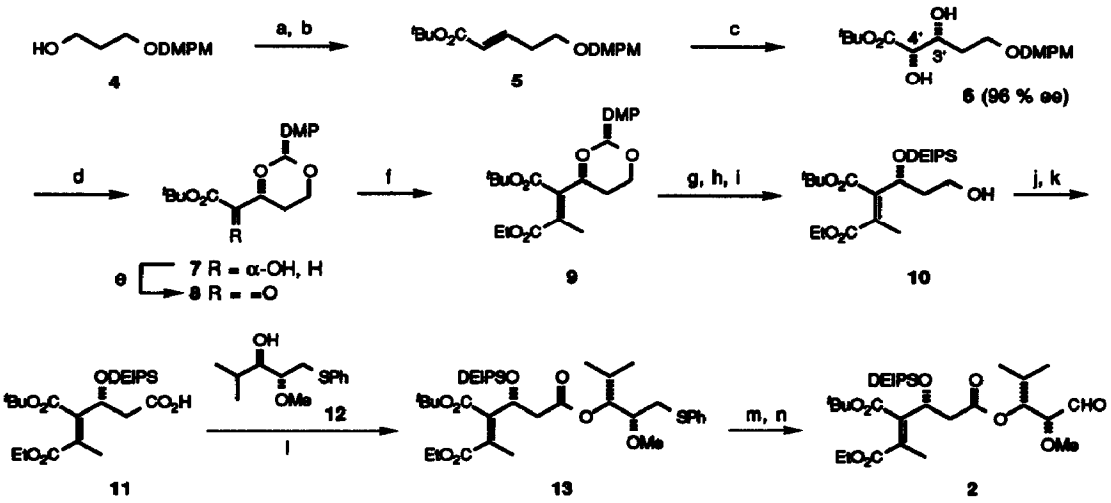
Retrosynthetic disconnection of the carbon backbone at the C_{21}-C_{22} bond divides the target into two subunits, named as the Left-wing **2** and the Right-wing **3** (Scheme 1). The key issue of our synthesis is a stereocontrolled aldol coupling of two key subunits. In the previous study, we have already established the efficient route to synthesize C_1-C_{18} fragment.[5] Herein, we describe the synthesis of the heavily functionalized Left-wing and the total synthesis of tautomycin.[6]



Scheme 1

The synthesis of the Left-wing **2** began with alcohol **4** (Scheme 2). Oxidation to aldehyde followed by Wittig reaction gave α, β-unsaturated ester **5** in 90 % yield. To set up the required chirality at $C_{3'}$, we selected the Sharpless asymmetric dihydroxylation protocol (tautomycin numbering).[7] Treatment of **5** with AD-mix-β

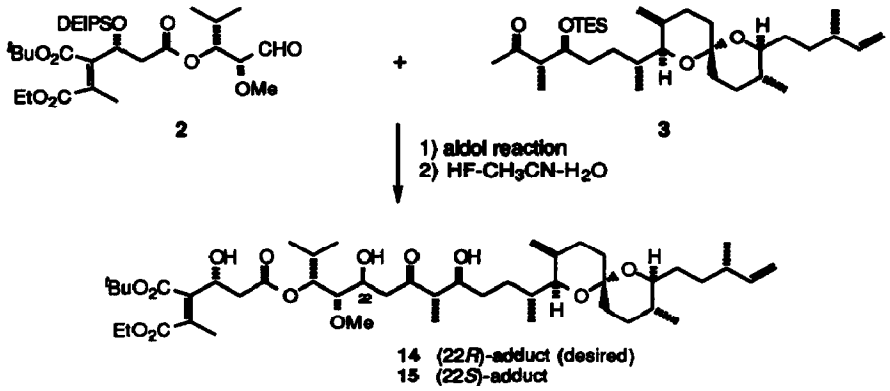
afforded (3'*R*, 4'*S*)-diol **6** in 99 % yield. Then, β-hydroxy group was selectively protected by DDQ oxidation[8] to afford benzylidene acetal **7**. Subsequent oxidation with Dess-Martin periodinane (DMP)[9] gave unstable α-keto ester **8**, which was directly subjected to Horner-Emmons olefination.[10] In this reaction, maleate **9** was preferentially provided in 67 % yield accompanying geometric isomer (28 %). Cleavage of acetal in **9** followed by protection with DEIPSCl[11] and selective deprotection of primary silyl ether gave **10** in 83 % overall yield. Sequential oxidation with DMP and then with $NaClO_2$ provided acid **11**, which was esterified with alcohol **12** by Yamaguchi method[12] to yield **13** in good overall yield. Finally, oxidation to sulfoxide followed by Pummerer reaction and methanolysis furnished **2** in 81 % yield. Thus, the synthesis of the Left-wing **2** has been attained in 20 % overall yield for the thirteen-step sequence.



Scheme 2 (a) SO_3-Py, DMSO, Et_3N, CH_2Cl_2; (b) $^tBuO_2CCH{=}PPh_3$, CH_2Cl_2, 90 % (2 steps); (c) AD-mix-β, $MeSO_2NH_2$, ^tBuOH-H_2O, 0°C, 99 %; (d) DDQ, MS3A, CH_2Cl_2, 5°C, 66 %; (e) Dess-Martin periodinane, Py, CH_2Cl_2; (f) $EtO_2CCH(CH_3)PO(OEt)_2$, ^tBuOK, THF, -60 →-20°C (67 %, 2 steps); (g) PPTS, MeOH, 98 %; (h) DEIPSCl, Im, CH_2Cl_2, 89 %; (i) AcOH-H_2O-THF (4:1:4), 95 %; (j) Dess-Martin periodinane, Py, CH_2Cl_2, 87 %; (k) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^tBuOH-H_2O, 91 %; (l) 2, 4, 6-trichlorobenzoylchloride, Et_3N, toluene; **12**, DMAP, 60°C, 94 %; (m) $NaIO_4$, MeOH-H_2O, 97 %; (n) TFAA, Py; $NaHCO_3$, MeOH, 84 %.

Next, our attention moved to the crucial coupling of the Left-wing **2** and the Right-wing **3**[13] (Scheme 3). The aldol reactions dealing with π-facial selectivity have been extensively studied in natural products synthesis.[14] We initially examined aldol reaction of metal enolates (Scheme 3). The lithium enolate derived from **3** was treated with aldehyde **2**, followed by desilylation to give a 1 : 4 ratio of the two epimers in favour of the undesired (22*S*)-aldol product **15** (Felkin adduct considering C_{23}-methoxy group as a large group). Using the titanium enolate under the condition described by Evans,[15] an increased amount of (22*R*)-adduct **14** was obtained in improved yield (combined yield 63 %) with essentially same selectivity. Unfortunately, all attempts to reverse the selectivity using metal enolate were unsuccessful.

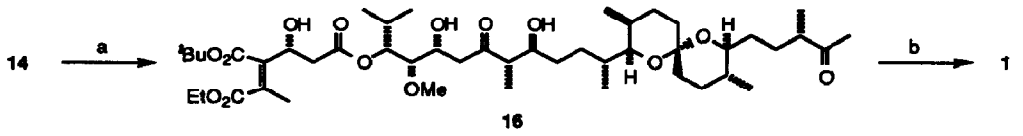
In order to reverse the diastereoselectivity in aldol reaction, Lewis acid-catalyzed silyl enol ether addition[16] (Mukaiyama aldol reaction) was examined. In the presence of $TiCl_4$, the silyl enol ether derived from **3** was reacted with aldehyde **2**, followed by desilylation to afford the desired anti-Felkin product **14** as a single adduct (Scheme 3). Based on precedents for chelation-controlled Mukaiyama aldol reaction,[17] the exceptional high selectivity in this reaction would be accounted for chelation of $TiCl_4$ with C_{23}-methoxy group of aldehyde **2**.



conditions	Yield	
	14 (22*R*)	15 (22*S*)
LiHMDS	7.5 %	30 %
$TiCl_4$, $^iPr_2NEt$	15 %	48 %
TMSOTf, Et_3N then $TiCl_4$	54 %	0 %

Scheme 3

Finally, the coupling product **14** was converted to **1** as shown in Scheme 4. Pd-assisted selective oxidation of terminal olefin of **14** afforded methyl ketone **16**.[5] Deprotection of *t*-butyl group with trifluoroacetic acid or aqueous HF was unsuccessful but was effected by the action of TESOTf.[14a] Thus, deprotection of *t*-butyl group with TESOTf and 2, 6-lutidine and concomitant ring closure[18] gave **1**. Our synthetic sample was identical in all respects with the natural tautomycin.



Scheme 4 (a) O_2, $PdCl_2$, CuCl, DMF-H_2O, 72 %; (b) TESOTf, 2, 6-lutidine, CH_2Cl_2, 41 %.

In conclusion, the first total synthesis of tautomycin has been achieved via efficient aldol coupling of two large subunits. Our synthetic route would provide efficient way to prepare various analogues of **1** for biological evaluation.

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