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Synthetic Study on Tautomycin. Stereocontrolled Synthesis of C(1)-C(18) Fragment using a Strategy of Selective Reduction of Spiroketal

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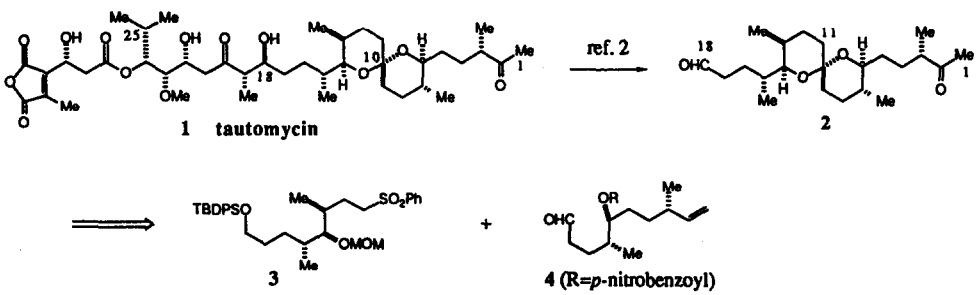
Key Words: tautomycin; protein phosphatases inhibitor; spiroketal; reduction

Abstract: A stereocontrolled synthesis of C(1)-C(18) fragment of tautomycin is accomplished employing asymmetric crotylboration, selective reduction of spiroketal, and addition of crotylstannane as the key steps.

In 1987, Isono and co-workers isolated an antifungal antibiotic named tautomycin **1** from the culture of *Streptmyces spiroverticillatus*[1] and later determined its structure.[2] It was found that tautomycin **1** specifically inhibits protein phosphatases type 1 (PP1) and type 2A (PP2A), and binds to the same site of PP2A as okadaic acid, the well-known tumor promoter.[3a] This antibiotic also causes morphological change (bleb formation) of human leukemia cells.[3b, 3c] These interesting biological activities as well as the unique structure attracted us to develop the synthetic pathway of this compound.

Tautomycin **1** is known to be degraded into the fragment **2** by two sequencial alkaline hydrolyses (Scheme 1).[2] Retrosynthetically this fragment or its synthetic equivalent seemed to suit well as the intermediate for the total synthesis of **1**. Further we divided the fragment **2** at the C(10)-C(11) bond into two segments, **3** and **4**. Now we describe the stereocontrolled synthesis of the fragment **2** corresponding to C(1)-C(18) of **1**.



1 tautomycin

2

3

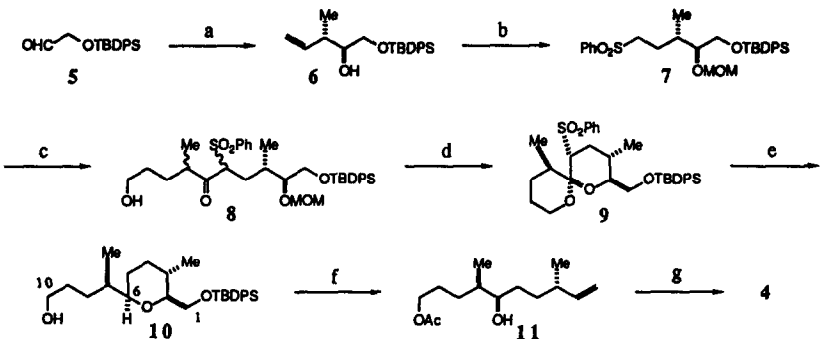
4 (R=*p*-nitrobenzoyl)

Scheme 1

For the synthesis of the segment **4**, we applied the selective reduction of spiroketals[4] as a key asymmetric transfer process, and the synthesis was achieved in the following way (Scheme 2). α-(*t*-Butyldiphenylsiloxy)acetaldehyde **5** was obtained in two steps (protection and ozone treatment, 98% yield) from cis-1,4-butenediol. The aldehyde **5** was subjected to Brown's asymmetric crotylboration protocol[5] using the reagent derived from (+)-α-pinene to yield the alcohol **6** in good selectivity (100%de, and 92%ee).[6] Then the alcohol **6** was converted to the sulfone **7** via the following sequence: (1) protection of the hydroxyl group as

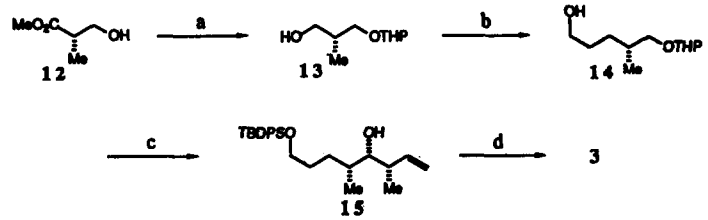
MOM (methoxymethyl) ether, (2) hydroboration, (3) substitution of the hydroxyl group by the phenylthio group, (4) oxidation of sulfide to sulfone. The α-lithiosulfonylcarbanion generated from **7** was coupled with 2-methyl-δ-valerolactone[8] to yield the ketosulfone **8** as a diastereomeric mixture. Deprotection of MOM ether, spiroketalization and equilibration were simultaneously achieved by bromotrimethylsilane in CH_2Cl_2[9] to give the crystalline **9** as a single isomer. The structure of **9** was unambiguously confirmed by X-ray diffraction.[10] Desulfurization followed by regio- and stereoselective reduction of the acetal moiety[4] with triethylsilane-$SnCl_4$ in CH_2Cl_2 and subsequent acid treatment of the resulting triethylsilylether afforded the alcohol **10**. The structure of **10** was confirmed by ^{1}H-NMR analysis, and the stereochemistry at C(7) (tautomycin numbering) was established after conversion to the spiroketal **17**. Since **10** has the requisite carbon chain and the correct stereochemistry for the C(1)-C(10) segment except the C(6) position, the cleavage of the tetrahydropyran moiety and the inversion of the stereochemistry at C(6) were examined next. After acetylation of **10**, the siloxy moiety was converted to bromide by the sequence of deprotection, mesylation, and bromination. Subsequent reduction with large excess of zinc dust in ethanol-water gave the acyclic alcohol **11**. The secondary hydroxyl group in **11** was inverted by the Mitsunobu reaction[11] and the product was further converted to the aldehyde **4** by selective deacylation and Swern oxidation.[12]

The synthesis of the C(11)-C(18) segment **3** started from commercially available methyl (S)-(+)-3-hydroxy-2-methylpropionate **12** (Scheme 3). This hydroxyester **12** was protected as THP (tetrahydropyranyl) ether, and then reduced with $LiAlH_4$ to afford the alcohol **13**.[13] Oxidation of this alcohol followed by Wittig-Horner reaction yielded the unsaturated ester as a mixture concerning its olefin portion (E:Z=85:15), which was subsequently hydrogenated and reduced. After protection of the alcohol **14** as TBDPS ether, the THP group was removed. The aldehyde obtained by oxidation of the resulting alcohol was submitted to erythroselective crotyladdition (tributylcrotylstannane-BF_3 system)[14] to give the adducts in 92% yield with moderate selectivity (66/22/12, Cram/anti-Cram/others).[15] The desired Cram adduct **15** was separated, and the enantiomeric purity was determined to be 94%ee by HPLC analysis of the corresponding Mosher's α-methoxy-α-(trifluoromethyl)phenylacetic acid ester. After **15** was protected as MOM ether, the olefin portion was converted to terminal phenylsulfone in three steps (hydroboration, substitution by phenylthio group and oxidation to sulfone) to yield the C(11)-C(18) segment **3**.



(a) (-)-*E*-crotyldiisopinocampheylborane/ THF, -78°C, then H_2O_2/ NaOH, 58%. (b) 1) MOMCl/ ^{i}Pr$_2$NEt/ CH_2Cl_2, 87%. 2) 9-BBN/ THF, 15°C, then H_2O_2/ NaOH, 94%. 3) PhSSPh/ pyridine/ ^{n}Bu$_3$P, 92%. 4) mCPBA/ CH_2Cl_2, 100%. (c) ^{n}BuLi/ ether-hexane (1:1)/ 2-methyl-δ-valerolactone, -78°C, 61%. (d) TMSBr/ CH_2Cl_2, -40→0°C, 88%. (e) 1) Raney Ni (W-2)/ EtOH, reflux, 88%. 2) Et_3SiH/ $SnCl_4$/ CH_2Cl_2, -94→-60°C, followed by AcOH-THF-H_2O (8:8:1), RT, 89%. (f) 1) Ac_2O/ pyridine/ DMAP/ CH_2Cl_2, 97%. 2) TBAF/ THF, 100%. 3) MsCl/ pyridine/ DMAP/ CH_2Cl_2. 4) LiBr/ DMF, 65°C. 5) Zn/ EtOH-H_2O (9:1), reflux, 61% in 3 steps. (g) 1) *p*-NO_2-C_6H_4COOH/ PPh_3/ DEAD/ benzene, RT, 67%. 2) NaH/ MeOH, 5°C, 80%. 3) DMSO/ $(COCl)_2$/ CH_2Cl_2, -78°C, then Et_3N, quant.

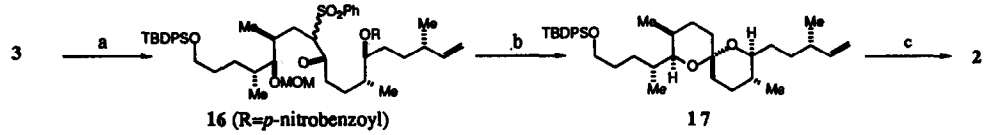
Scheme 2



(a) 1) DHP/ *p*-TsOH/ ether, 100%. 2) LAH/ ether, 3°C, 87%. (b) 1) DMSO/ $(COCl)_2$/ CH_2Cl_2, -78°C, then Et_3N. 2) $(EtO)_2P(O)CH_2CO_2Et$/ NaH/ THF, -78°C, 92% in 2 steps. 3) H_2/ Pd-C/ EtOH. 4) LAH/ ether, 3°C, 86% in 2 steps. (c) 1) TBDPSCl/ imidazole/ DMF, 99%. 2) *p*-TsOH/ MeOH, 80%. 3) DMSO/ $(COCl)_2$/ CH_2Cl_2, -78°C, then Et_3N. 4) tri-*n*-butylcrotylstannane/ $BF_3{\cdot}Et_2O$/ CH_2Cl_2, 61% in 2 steps. (d) 1) MOMCl/ $^iPr_2NEt$/ CH_2Cl_2, 99%. 2) 9-BBN/ THF, then H_2O_2/ NaOH, 94%. 3) PhSSPh/ pyridine/ $^nBu_3P$, 87%. 4) mCPBA/ $NaHCO_3$/ CH_2Cl_2, 100%.

Scheme 3

Since both segments **3** and **4** were available, our attention was turned to the connection of these segments and the synthesis of the C(1)-C(18) fragment **2** (Scheme 4). After the lithium salt of **3** was coupled efficiently with the aldehyde **4**, the stereoisomeric adducts were successively oxidized to give two ketosulfones **16** in good overall yield. Desulfurization from the β-ketosulfone **16** was accomplished best with SmI_2[16] compared with other reagents such as Al(Hg) or $^nBu_3SnH$, followed by removal of the ester and the acetal protective groups to yield the spiroketal **17** as a single product. Finally, TBDPS group was removed by tetrabutylammonium fluoride and the terminal olefin was selectively converted to the methylketone by the palladium(II)-assisted oxidation.[17] Then the remaining hydroxyl group was further oxidized to the aldehyde **2**. No epimerization at the base-sensitive C(3) chiral center[2d] was observed in this process, and the synthetic sample **2** proved to be identical with the degradation product of tautomycin in spectroscopic properties (^{1}H-NMR, IR, HR-MS) including optical rotation, $[\alpha]_D^{25}$ -42.2° (*c*0.45, $CHCl_3$) (lit.[2b] $[\alpha]_D^{25}$ -45.8°, *c*1.35,$CHCl_3$).



(a) 1) ^{n}BuLi/ ether-hexane (1:1), then **4**, -78°C→RT. 2) DMSO/ $(COCl)_2$/ CH_2Cl_2, -78°C, then Et_3N, 82% in 2 steps. (b) 1) SmI_2/ THF-MeOH (6:1), -78°C, 10min, 50%. 2) K_2CO_3/ MeOH, 60°C, quant. 3) TMSBr/ CH_2Cl_2, -30→5°C, quant. (c) 1) TBAF/ THF. 2) O_2/ $PdCl_2$/ CuCl/ DMF-H_2O (7:1), RT. 3) DMSO/ $(COCl)_2$/ CH_2Cl_2, -78°C, then Et_3N, 50% in 3 steps.

Scheme 4

In conclusion, we have completed a stereocontrolled synthesis of the right half of tautomycin. The synthesis includes the effective asymmetric transfer using the spiroketal template. Our stereodefined synthesis of the degradation product **2** unambiguously established the relative and absolute configuration of **2**. Further synthetic study on this compound toward total synthesis are now undertaken.

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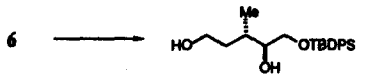
6. The diastereomeric ratio was determined on ^{1}H-NMR spectroscopy, and the enantioselectivity was also examined by ^{1}H-NMR spectrum of the corresponding Mosher's α-methoxy-α-(trifluoromethyl)-phenylacetic acid ester. The structure of **6** was confirmed by leading to the known compound **18**[7] (1. MOMCl, 2. 9-BBN, 3. TMSBr).



18 $[\alpha]_D^{25}$ +3.6° (*c*0.66, $CHCl_3$)
lit.[7] $[\alpha]_D$ +4.0° (*c*2.4, $CHCl_3$)

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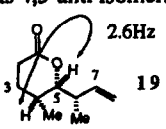
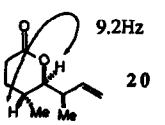
15. The diastereoselectivity was examined by HPLC analysis. The structures of **15** and the anti-Cram adduct were determined after conversion to lactones **19** and **20** respectively in two steps (TBAF, followed by Ag_2CO_3-celite). In the ^{1}H-NMR spectrum (270MHz, $CDCl_3$), the coupling constant ($J_{4,5}$=2.6Hz) in **19** derived from the Cram adduct **15** revealed the 4,5-syn relationship whereas **20** derived from the anti-Cram adduct was determined as 4,5-anti isomer.





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