Synthesis of Okadaic Acid-Tautomycin Hybrid

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Abstract: One of the three spiro-segments in the synthesis of okadaic acid was synthesized under a new heteroconjugate addition strategy. Successive coupling of this spiro-segment with two tautomycin-synthetic segments afforded a hybrid molecule between okadaic acid and tautomycin.

Reversible phosphorylation and dephosphorylation of protein is a very interesting process for signal transduction in living cells. There have been two known classes of enzymes to catalyze the opposite activity for protein phosphates; thus, protein kinases mediating phosphorylation and protein phosphatases hydrolyzing the phosphorylated proteins.[1] Okadaic acid[2a] (**1**, OKA), microcystin LR,[2b] calyculin A[2c] and tautomycin[3] (**2**, TTM) are representatives of non-proteinous potent inhibitors[4] toward protein phosphatases,[5] and these inhibitors have invigorated recent research on dephosphorylation process of protein phosphates. Recent success in the X-ray crystal structure analysis provided a protein phosphatase and microcystin LR complex to have hydrophobic groove as a potential binding side.[6] On the other hand, biochemical analyses of inhibitors also provided information of the binding side.[7] Our syntheses of OKA[8] and TTM[9] also provided various opportunities for collaborating with biochemists,[4,10,11] and these collaborations have given birth to our expanding interests toward structural recognition between molecules such as OKA or TTM and protein phosphatases. As a result, we became interested in synthesizing a hybrid molecule **3** between OKA and TTM (Fig. 1), namely right-hand segment of OKA and left-hand segment of TTM as the target compound in this paper.

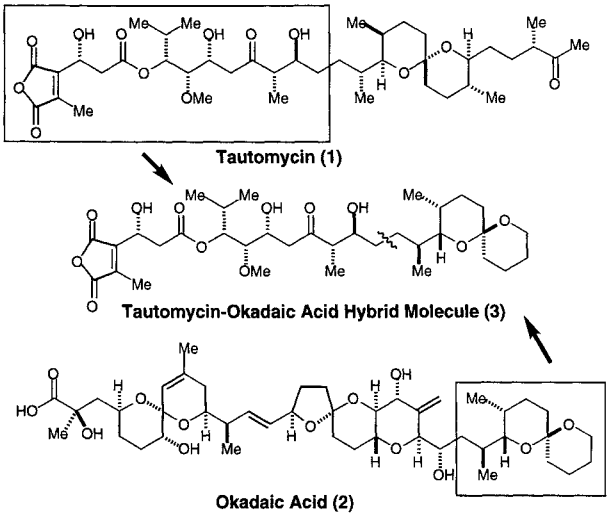


Figure 1

Figure 2 illustrates synthetic plan toward the hybrid **3**, which is based on the similar retrosynthetic analysis common for OKA and TTM. In our previous synthesis of Segment C of OKA,[12] a heteroconjugate addition[13] was employed on a precursor spiro-heteroolefin. We have decided to improve an alternative and effective route to Segment C of OKA for the current purpose; thus, enantio-switching methodology by the heteroconjugate addition to alpha/axial heteroolefin on a tetrahydropyrane nucleus as developed for TTM synthesis.[14] Two intermediates are enantiomeric, namely **4** for the current purpose being mirror image of **6** for one of the intermediates for TTM. For this purpose, we can start from a D-sugar derivative to receive C-glycosidation of thiophenyl(trimethylsilyl)acetylene[15] and subsequent hydrosilylation and oxidation to obtain the heteroolefin as a precursor of the intermediate **4**. The rest of the synthesis to **3** would follow the route for our total synthesis of TTM as reported from this laboratory.[9]

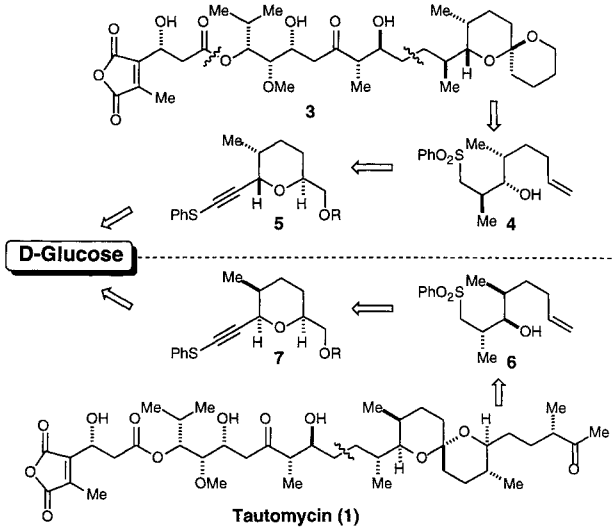
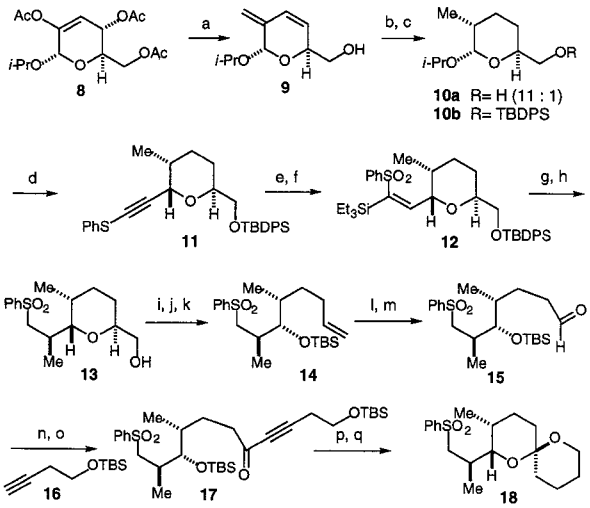


Figure 2. Retrosynthesis of **3**.

Scheme 1 is the new sequence of synthesis for Segment C of OKA. An isopropyl glycoside **8** was the starting material, and it reacted with a Wittig reagent to provide the diene alcohol **9**.[16] Reduction of this diene was stereoselective under hydrogen atmosphere in the presence of palladium catalyst to give **10a** as a major isomer with its 2-epimer (11 : 1 ratio).[17,18] Protection of the free hydroxyl group of **10a** as *t*-butyldiphenylsilyl ether **10b** was followed by C-glycosidation with phenylthio(trimethylsilyl)acetylene to give exclusively the alpha product **11**. Further 2 step transformation with hydrosilylation[19] and oxidation provided the heteroolefin **12** as only the product. Heteroconjugate addition to **12** with methyllithium (LiBr complex) in THF at -78 °C and removal of the silyl groups yielded **13** as exclusively single stereoisomer. Stereochemistry of the newly introduced methyl group was determined by the following three step transformation; involving 1) iodination of the primary alcohol **13**, 2) reductive ring opening reaction with zinc[20], 3) protection of the hydroxy group with *t*-butyldimethylsilyl triflate to afford **14**[21] in 83% overall yield. The compound **14** proved to be identical in all respects (^{1}H and ^{13}C NMR, IR and TLC behavior) to the intermediate **6**[14b] of tautomycin synthesis except its optical rotation, which was equal in magnitude with opposite sign. The terminal olefin of **14** was treated with catalytic amount of osmium tetroxide and sodium periodate to give the aldehyde **15** in 85% overall yield. Coupling between **15** and lithiated acetylene **16** was followed by oxidation to afford the ynone **17**. The completion of Segment C of OKA was achieved by successive hydrogenation and acid-catalyzed cyclization to provide the spiroketal **18** in 88% overall yield from **17**. The

spectroscopic data of **18** in this scheme was identical to those reported as Segment C of OKA previously.[12]



Reagents, condition and yields: (a) $Ph_3P{=}CH_2$, THF, 79%; (b) H_2, 10%Pd-C; (c) TBDPSCl, imidazole, DMF, 89% (2steps); (d) Me_3Si-C≡C-SPh, $BF_3{\cdot}OEt_2$, CH_3CN, 61%; (e) Et_3SiH, Na_2PtCl_6, 88%; (f) MCPBA, Na_2HPO_4, 96%; (g) MeLi·LiBr, THF, -78 °C; (h) TBAF, THF, 86% (2steps); (i) $(PhO)_3PMeI$, benzene, 95%; (j) Zn, Py, EtOH, 94%; (k) TBSOTf, *i*-Pr_2NEt, 93%; (l) OsO_4, NMO; (m) $NaIO_4$, THF-H_2O, 85% (2steps); (n) **16**, *n*-BuLi, THF; (o) PCC, MS4A, 65% (2steps); (p) H_2, 10%Pd-C; (q) TsOH, MeOH, reflux, 88% (2steps).

Scheme 1

Scheme 2 illustrates the synthesis of okadaic acid-tautomycin molecule **3**. In this synthesis, we employed the procedure recently established in the total synthesis of tautomycin[9]. Thus, epoxide opening reaction with lithiated sulfone **18** using $BF_3{\cdot}OEt_2$[22] gave a diastereomeric mixture of **20**, which was subsequently treated with sodium amalgam to give **21** in 62% yield. Further manipulation of protection (TBSOTf, *i*-Pr_2NEt) and deprotection (PPTS, MeOH) gave diol **22** in 75% overall yield. Esterification of **22** with maleic anhydride **23** under Yamaguchi conditions[23] regioselectively afforded **24** in 85% yield. Final deprotection of *tert*-butyldimethylsilyl group with poly(hydrogen fluoride)pyridine complex[24] and removal of the dithioketal with mercury perchlorate[25] furnished okadaic acid-tautomycin hybrid-molecule **3** in 77% overall yield.

In summary, we succeeded to establish more a preparative and efficient synthetic route of the Segment C of OKA than previous ones. Furthermore, we achieved the synthesis of a hybrid molecule and now investigate the inhibitory activity of this compound, which will give us much information to understand the different activity between tautomycin and okadaic acid towards protein phosphatases.[26]

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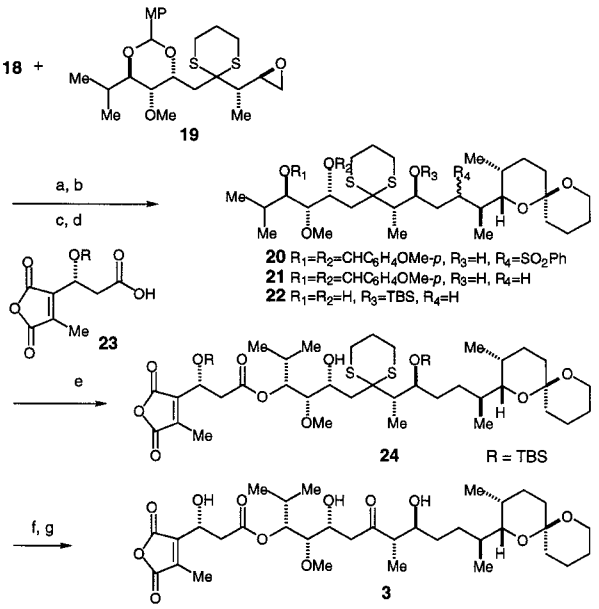

Reagents, condition and yields: (a) **18**, *n*-BuLi, $BF_3{\cdot}OEt_2$, -78 °C; then **19**; (b) Na-Hg, 62% (2steps); (c) TBSOTf, *i*-Pr_2NEt; (d) PPTS, MeOH, 75% (2steps); (e) $Cl_3C_6H_2COCl$, Et_3N; then **24**, DMAP, toluene, 85%; (f) $(HF)_x{\cdot}Py$; (g) $Hg(ClO)_4$, $CaCO_3$, 77% (2steps).

Scheme 2

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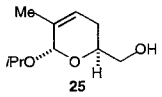
18. As the reaction intermediate, the formation of tri-substituted olefin **25** was observed by ^{1}H-NMR. The stereoselective hydrogenation seemed to occur through this intermediate.



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21. **14** ^{1}H-NMR ($CDCl_3$, 300 MHz), δ -0.07 (3H, s), 0.02 (3H, s), 0.77 (3H, d, J = 7 Hz), 0.86 (9H, s), 1.05 (3H, d, J = 7 Hz), 1.20 (1H, m), 1.42 (1H, m), 1.56 (1H, m), 1.87-2.14 (2H, m), 2.31 (1H, m), 2.90 (1H, dd, J = 14, 9 Hz), 3.35 (1H, dd, J = 14, 3.5 Hz), 3.55 (1H, t, J = 4 Hz), 4.93 (1H, brd, J = 10.5 Hz), 4.98 (1H, brd, J = 17 Hz), 5.75 (1H, ddt, J = 17, 10.5, 6.5 Hz), 7.52-7.68 (3H, m), 7.87-7.93 (2H, m). ^{13}C-NMR ($CDCl_3$, 75.4 MHz), δ -4.29, -4.21, 15.09, 15.69, 18.14, 25.90, 31.55, 33.27, 33.84, 35.11, 59.90, 77.56, 114.60, 127.92, 129.35, 133.59, 138.66, 140.25. $[\alpha]_D^{24}$ -12.3 (c 0.65, $CHCl_3$). Authentic sample $[\alpha]_D^{25}$ +9.8 (c 2.94, $CHCl_3$).[14b]
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