Pergamon

Tetrahedron Letters, Vol. 38, No. 45, pp. 7897-7900, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)10100-9

Synthetic Study of Tautomycetin: Synthesis of Two Large Subunits

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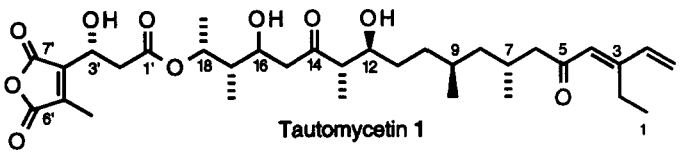
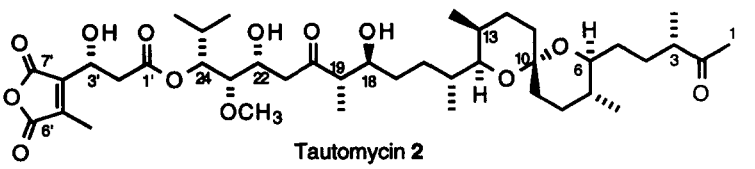
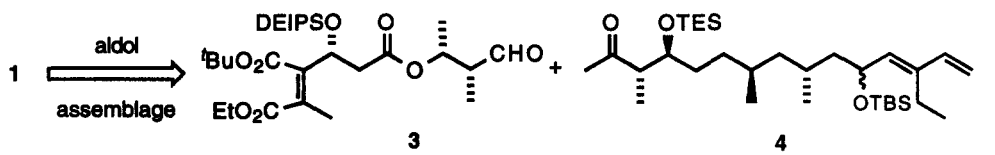
Key Words: tautomycetin; tautomycin; protein phosphatase inhibitor

Abstract: Two large subunits for synthesis of tautomycetin have been synthesized. Efficient construction of the dienone moiety has been achieved by regioselective hydrostannylation of an internal alkyne and subsequent Stille coupling. © 1997 Elsevier Science Ltd.

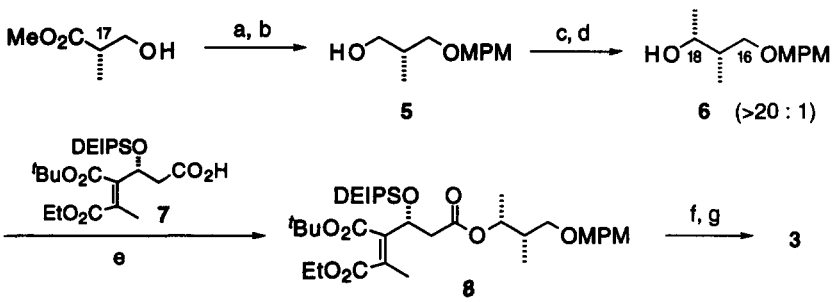
Tautomycetin **1** was isolated from *Streptomyces griseochromogenes* as an antifungal agent.[1,2] Recently, Shibasaki *et al.* determined the absolute stereochemistry of **1** except that of C16 by comparison of spectral data between the dehydration product of **1** and the synthetic diastereomers.[3] Tautomycetin **1** induces the morphological change (bleb formation) of human leukemia cells K562[1] as tautomycin **2**,[4] which is known as a potent inhibitor of protein phosphatases (PP) type 1 and 2A.[5] Although PP inhibitory activity of **1** has not been reported, the striking biological and the structural similarity between **1** and **2** strongly suggests that **1** is also an inhibitor of PP1 and PP2A and that the structural differences between **1** and **2** are exchangeable. In order to obtain pertinent data for this hypothesis and to develop a specific inhibitor for PP1, we started a synthetic study of **1**. Herein, we describe the synthesis of two large subunits **3** and **4**.







Since tautomycin **2** was efficiently constructed by aldol assemblage of two large subunits,[6] we adopted the same strategy in the total synthesis of **1**. Thus, tautomycetin **1** is retrosynthetically disconnected into two

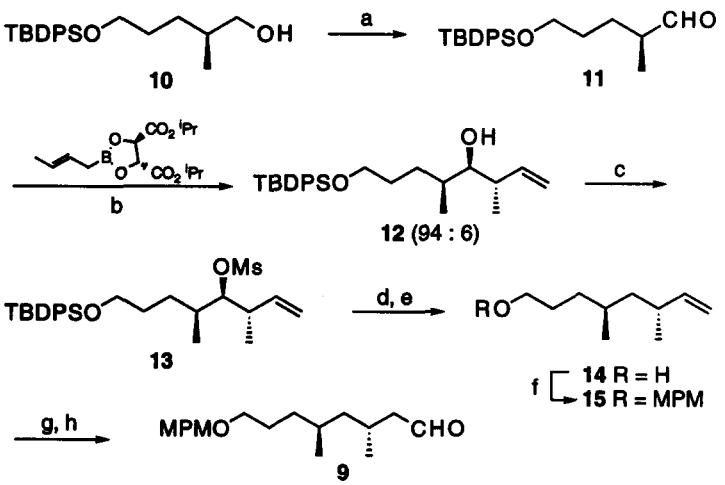


Scheme 1. (a) $MPMOC(=NH)CCl_3$, PPTS, CH_2Cl_2; (b) $LiAlH_4$, Et_2O (2 steps, 61 %); (c) DMSO, $(COCl)_2$, CH_2Cl_2, –78°C; Et_3N; (d) Me_2CuLi, Et_2O, -78°C (2 steps, 85 %); (e) 2,4,6-trichlorobenzoyl chloride, Et_3N, toluene, DMAP, 60°C (quant.); (f) DDQ, CH_2Cl_2-H_2O (10:1); (g) DMSO, $(COCl)_2$, CH_2Cl_2, –78°C; Et_3N (2 steps, 95 %)

segments named as the Left-wing **3** and the Right-wing **4**. The key issue for the synthesis of **4** is an efficient construction of the dienone moiety using regioselective hydrostannylation and subsequent Stille coupling.

The synthesis of the Left-wing **3** was started from methyl (*R*)-3-hydroxy-2-methylpropionate (Scheme 1). To set up the required stereochemistry of C17 and C18, a chelation-controlled nucleophilic attack of Gilman reagent to β-alkoxyaldehyde was selected.[7] Protection of the alcohol with MPMCl followed by reduction with $LiAlH_4$ afforded alcohol **5** in 61 % yield. After Swern oxidation,[8] the resultant aldehyde was treated with Me_2CuLi to afford adduct **6**[9] with high diastereoselectivity (>20:1). Using Yamaguchi method,[10] **6** was condensed with the anhydride segment **7**[6] to afford ester **8** in quantitative yield. Deprotection with DDQ[11] followed by Swern oxidation furnished the Left-wing **3**.[12]

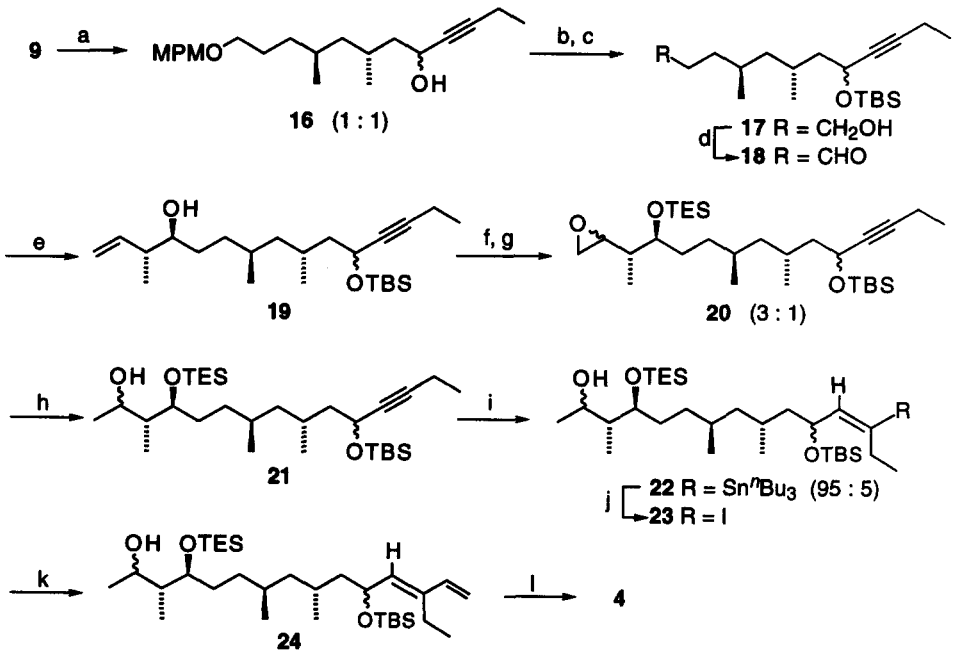
The synthesis of C5-C12 segment **9** began with a known alcohol **10**[6b,13] (Scheme 2). Oxidation and followed by crotylboration with (*R,R*)-(*E*)-crotylboronate[14] gave a 94: 6[15] ratio of the two diastereomers in favor of the desired adduct **12** which was purified by medium pressure SiO_2 chromatography. After mesylation of **12**, removal of C8 oxygen atom[16] was achieved by dissolving metal reduction followed by treatment with



Scheme 2. (a) DMSO, $(COCl)_2$, CH_2Cl_2, -78°C; Et_3N; (b) (*R,R*)-(*E*)-crotylboronate, MS4A, toluene, -78 °C (2 steps, 87 %); (c) MsCl, DMAP, Py, CH_2Cl_2 (94 %); (d) liq. NH_3, Li; (e) TBAF, THF (2 steps, 84 %); (f) MPMCl, NaH, THF (89 %); (g) BH_3, THF; H_2O_2, 3M NaOH (78 %); (h) TPAP, NMO, MS4A, CH_2Cl_2 (75 %).

TBAF to furnish **14** in 79 % yield. Since we later found that a silyl protective group was required at C5 hydroxyl group, replacement of the protective group was made at this stage. Protection of **14** with MPMCl gave **15** which was then connverted to aldehyde **9** by hydroboration and oxidation in 52 % yield.

Finally, the C5-C12 segment **9** was converted to the Right-wing **4** (Scheme 3). Lithium acetylide derived from 1-butyne was coupled with aldehyde **9** to afford alcohol **16** in 89 % yield. Protection of the resultant alcohol **16** with TBSCl followed by treatment with DDQ furnished alcohol **17** which was oxidized to give aldehyde **18**. Crotylboration of **18** with Roush's (*S,S*)-(*E*)-crotylboronate[14] gave adducts in a 5: 1 ratio but the mixture was unseparable. On the other hand, treatment of **18** with Brown's reagent[17] afforded **19** as a single product. Transformation of **19** using the same protocol reported previously[6b] via epoxide **20** gave alkyne **21** in 57 % yield. In preliminary study for palladium catalyzed hydrostannylation,[18] TBS protected substrate gave better regioselectivity than non-protected or MPM protected alkyne. Treatment of TBS ether **21** with a large excess *n*-Bu_3SnH in the presence of palladium catalyst proceeded smoothly to give desired adduct **22** with 95:5 regioselectivity in excellent yield. Stille coupling[19] between iodide **23** derived from **22** and vinylstannane furnished **24** in 50 % yield. Finally, oxidation of **24** with Dess-Martion periodinane[20] afforded the Right wing **4**.[12]



Scheme 3. (a) 1-butyne, *n*-BuLi, THF, –78 °C (89 %); (b) TBSOTf, 2,6-lutidine, CH_2Cl_2 (98 %); (c) DDQ, CH_2Cl_2-H_2O (10:1); (d) Dess-Martin periodinane, Py, CH_2Cl_2 (2 steps, 88 %); (e) (-)-(*E*)-crotyldiisopinocampheylborane, Et_2O-THF, -78°C; 3 M NaOH, H_2O_2 (61 %); (f) *t*-BuOOH, $VO(acac)_2$, CH_2Cl_2 (73 %); (g) TESCl, Et_3N, DMAP, CH_2Cl_2 (93 %); (h) $LiEt_3BH$, THF (quant.); (i) *n*-Bu_3SnH, $Pd(PPh_3)_4$, benzene (98 %); (j) I_2, $NaHCO_3$, CH_2Cl_2; (k) *n*-$Bu_3Sn(CH_2{=}CH)$, $Pd(PPh_3)_4$, DMF (2 steps, 64 %); (l) Dess-Martin periodinane, Py, CH_2Cl_2 (65 %).

This efficient synthetic pathway of the Right-wing **4** allowed us to investigate a solution conformation of the C1-C12 moiety in **1**. This will be reported near future.

Acknowledgment. We are grateful to Mr. K. Watanabe and Mrs. E. Fukushi in our department for their measurements of MS spectra. This work was supported by a Grant-in-Aids from the Ministry of Education, Science, and Culture of Japan.

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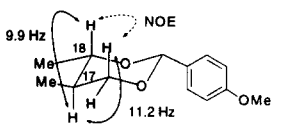

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(*Received in Japan* 25 *July* 1997; *revised* 8 *September* 1997; *accepted* 9 *September* 1997)