Pergamon

Tetrahedron, Vol. 53, No. 14, pp. 5123-5142, 1997

0040-4020/97 $17.00 + 0.00

PII: S0040-4020(97)00230-5

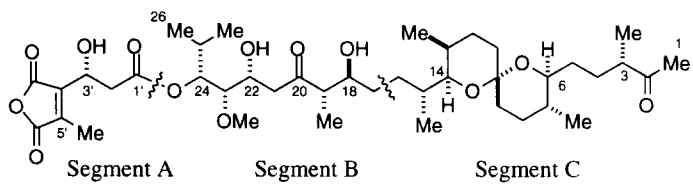
Total Synthesis of (+)-Tautomycin

Katsunori Tsuboi, Yoshiyasu Ichikawa, Yimin Jiang, Atsushi Naganawa and Minoru Isobe*

Laboratory of Organic Chemistry, School of Agricultural Sciences
Nagoya University, Chikusa, Nagoya 464-01, Japan

Abstract: The synthesis of Segment B/C corresponding to the C26 through to the C1 positions of tautomycin was achieved by coupling between Segment B (an epoxide) and Segment C (a sulfone carbanion) in the presence of boron trifluoride etherate ($BF_3{\cdot}OEt_2$). Two routes have been developed in esterification of Segment A with Segment B/C. The first route employed Segment A with furan moiety as masked maleic anhydride. In the second route, maleic anhydride as Segment A was directly used to accomplish the improved synthesis. Removal of the silyl protecting group with pyridinium poly(hydrogen fluoride) (HF-Py) at the final step completed the total synthesis of tautomycin.

In the two preceding papers, we reported the synthetic plan and synthesis of Segment B and C of tautomycin.[1,2] Since we previously reported the synthesis of Segment A, we have obtained all the three segments for the total synthesis in hand.[3] Here, we describe the final stage of the synthesis of **1**, involving i) coupling between Segment B and Segment C, ii) esterification of Segment B/C with Segment A by two different strategies and iii) effective deprotection to complete the total synthesis of tautomycin **1**.

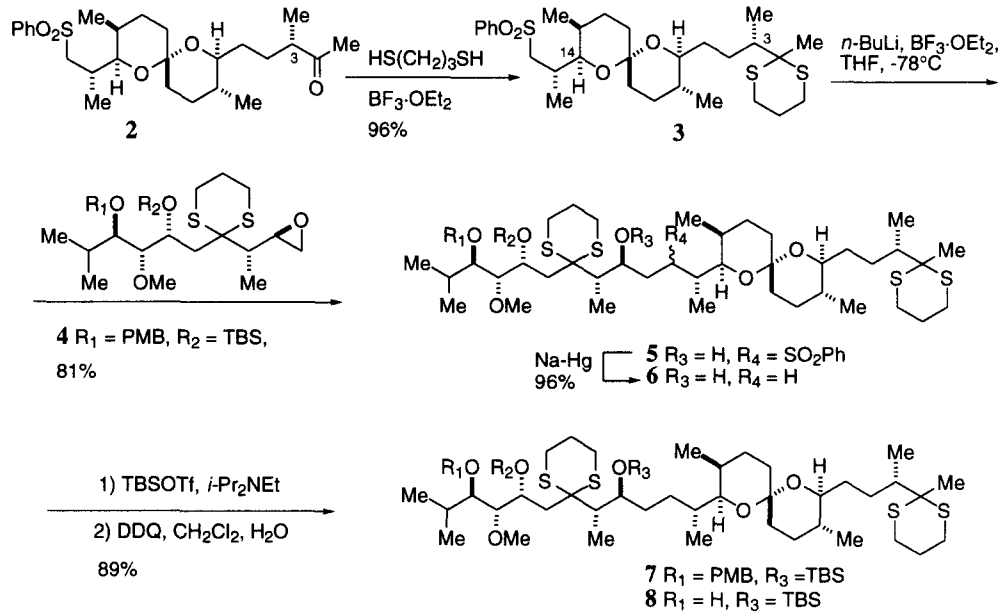


Tautomycin **1**

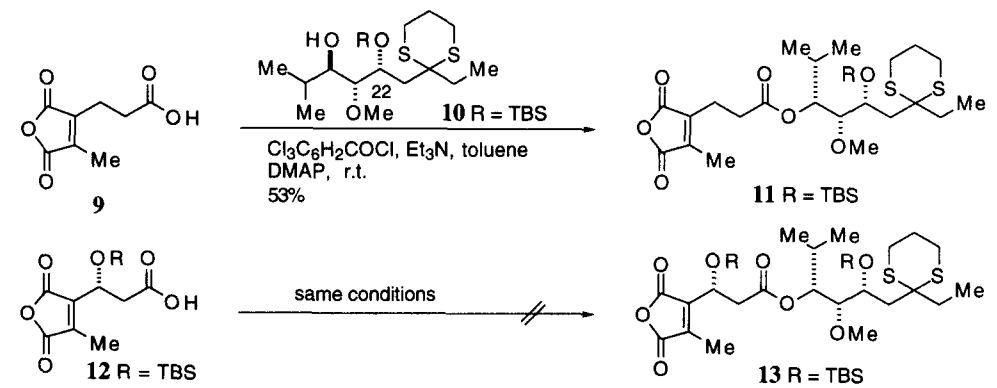
Coupling between Segment B and Segment C 1,3-Dithiane was selected as a protecting group at the C2 ketone of Segment C **2** because of Segment B **4** possessing 1,3-dithiane at the C20 ketone, so that these two protections could be removed in a single operation. Epimerization problem at the C3 stereogenic center of **2** during thioketalization could be avoided by employing diluted (12 mM) borontrifluoride etherate ($BF_3{\cdot}OEt_2$) catalyst and propanedithiol (3 equiv.) at room temperature overnight to furnish the protected Segment C **3** in 96% yield without detectable amount of epimerization (>20 :1).[4]

A series of the coupling between **3** and **4** under a variety of conditions eventually led us to find that use of both $BF_3{\cdot}OEt_2$[5] and five equiv. of **3** guaranteed the yield of this coupling. Thus, treatment of **3** with *n*-butyllithium at -78 °C for 30 min gave the sulfone carbanion which was successively treated with $BF_3{\cdot}OEt_2$ for 30 min at -78 °C. This reaction sequence provided the reactive yellow solution of the sulfone carbanion. To this

solution was added Segment B **4**, and the temperature was maintained at -78 °C for 2 h and then at -50 °C for 1 h. After work-up, the coupling product **5** was isolated as a diastereomeric mixture in 81% yield along with excess Segment C. The resultant diastereomeric mixture of sulfones **5** was treated with a large excess of 5% sodium amalgam powder to effect reductive desulfurization in 96% yield of **6**. Further manipulation of protection (TBSOTf, *i*-Pr_2NEt, CH_2Cl_2) and deprotection (DDQ, CH_2Cl_2/ H_2O)[6] furnished Segment B/C **8** in 89% overall yield from **6**.



Scheme 1

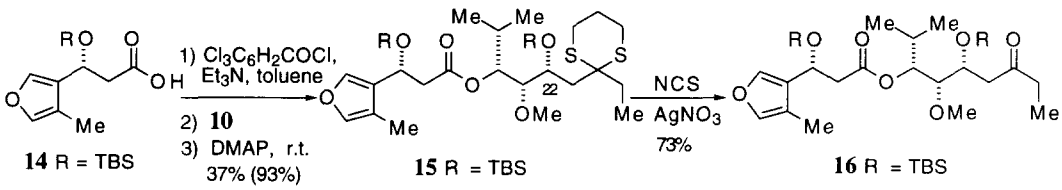


Scheme 2

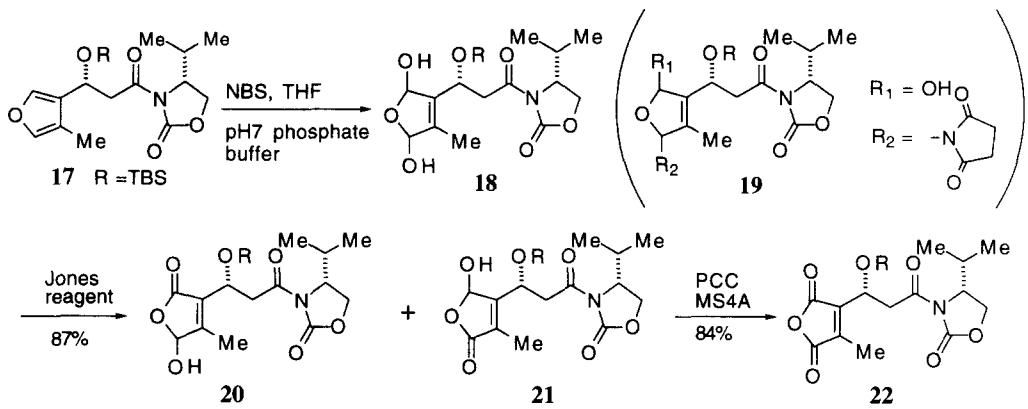
Strategy of the coupling between Segment B (the epoxide) and Segment C (the sulfone carbanion) led us to construct the carbon backbone of Segment B/C. Further esterification of the resulting Segment B/C with Segment A is the next problem.

Model Studies of Esterification of Segment B/C with Segment A Esterification of Segment B/C with Segment A was initially examined by model compounds in Scheme 2. An acid chloride prepared from deoxy-Segment A **9** by a reported method [$(COCl)_2$, HMPA][7] did not react with a model Segment B/C **10**. The acid **9**, however, reacted with **10** under Yamaguchi esterification method[8] to provide **11** in 53% yield. The low yield in this esterification may be due to the steric congestion arising from the *t*-butyldimethylsilyl group at the C22 (R = TBS). In spite of the success of deoxy-Segment A **9**, all attempts to esterify Segment A **12** with **10** under a variety of esterification conditions failed with no detectable coupling product suggesting undesirable reaction of the maleic anhydride portion seemed to occur. Under these circumstances, we decided to protect the 2,3-disubstituted maleic anhydride functionality of Segment A **12** as furan ring.

Scheme 3 illustrates that Segment A with furan ring **14** did give the ester **15** in 37% yield by employing Yamaguchi esterification method (93% yield based on the consumed **10**). In this case, it should be noted that enforcing reaction conditions, for example, by heating the reaction mixture resulted in the elimination of *t*-butyldimethylsiloxy moiety of **14**. Although this model study suffered from low conversion of the coupling reaction, Segment B/C could easily be recovered and recycled for next lot of esterification; thus, no practical problem would arise to finish the total synthesis.



Scheme 3

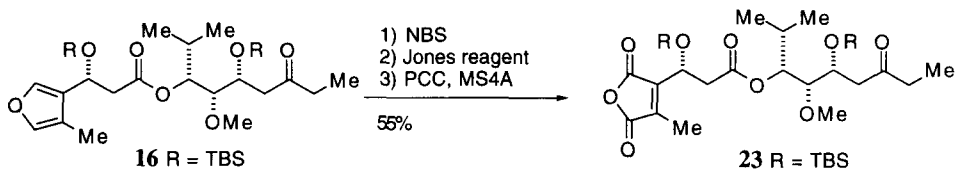


Scheme 4

The strategy using Segment A with furan ring caused another problem. Previous studies employed photosensitized oxidation for the transformation of the furan ring into the maleic anhydride moiety which proceeded well in the synthesis of Segment A.[3(a)] After deprotection of the dithioketal of **15** with *N*-chlorosuccinimide in the presence of silver nitrate,[9] **16** was subjected to photosensitized oxidation, which gave the corresponding 2,3-disubstituted-4-hydroxy-butenolides in low yield (less than 10%). This unexpected results led us to reinvestigate the oxidation condition of furan moiety as illustrated in Scheme 4.

N-Bromosuccinimide (NBS) oxidation of furan **17** in a mixture of THF and phosphate buffer (pH7) cleanly gave the 2,5-dihydroxy-2,5-dihydrofuran **18**.[10] In this oxidation, succinimide should be removed under basic work-up condition, because succinimide reacted with **18** under acidic conditions to form the stable adduct such as **19**.[11] Since the resulting 2,5-dihydroxy-2,5-dihydrofuran **18** was unstable, it should be immediately subjected to the Jones oxidation[12] to afford a regioisomeric mixture of the 2,3-disubstituted-4-hydroxybutenolides **20** and **21** in 87% combined yield. A mixture of the 4-hydroxybutenolides **20** and **21** resisted further oxidation, and no maleic anhydride formation was observed even by use of excess Jones reagent. Hence, a mixture of **20** and **21** was treated with pyridinium chlorochromate in the presence of molecular sieves 4A to furnish the maleic anhydride **22** in 84% yield.

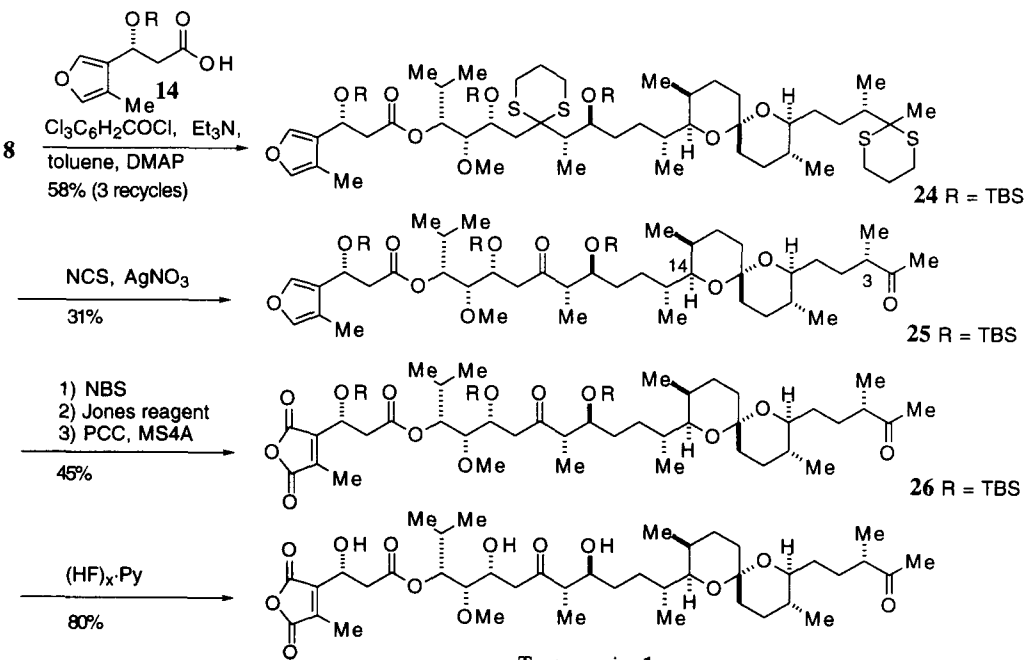
Scheme 5 illustrates an successful application of the three-step oxidation procedure to another model compound **16** providing the maleic anhydride **23** in 55% overall yield. With these results in mind, we have undertaken the final stage of the synthesis.



16 R = TBS **23** R = TBS

Scheme 5

Total Synthesis of Tautomycin by three step oxidation procedure Esterification of Segment B/C **8** with Segment A **14** under Yamaguchi conditions provided **24** in 39% yield (corresponding to 88% yield



24 R = TBS **25** R = TBS **26** R = TBS

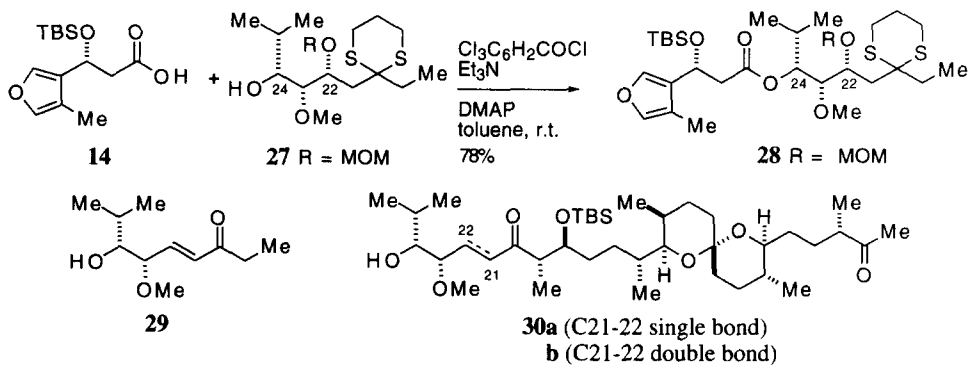
Tautomycin **1**

Scheme 6

based on the consumed Segment B/C). The recovered Segment B/C **8** was recycled, and after three recycles, we obtained **24** in 58% yield. Removal of the two dithioketal rings in **24** with *N*-chlorosuccinimide in the presence of silver ion gave **25** in 31% yield without epimerization at the C3 stereogenic center which was monitored through chemical shift of H-14 in its 400 MHz ^{1}H NMR spectroscopy.[4] The moderate yield of this reaction might be partially due to the undesirable oxidation of the furan ring. Conversion of the furan ring of **25** into the maleic anhydride structure proceeded in a similar fashion described in Scheme 5. Thus, transformation of **25** was achieved by the three-step oxidation procedure involving i) *N*-bromosuccinimide oxidation, ii) Jones oxidation into a mixture of 2,3-disubstituted-4-hydroxy butenolides and iii) pyridinium chlorochromate oxidation to afford the maleic anhydride **26** in 45% overall yield. This synthetic material **26** proved to be identical in all respects ($[\alpha]_D$, ^{1}H and ^{13}C NMR, IR, TLC, HRMS) with tris(*t*-butyldimethylsilyl)tautomycin[13] derived from natural tautomycin. Finally *t*-butyldimethylsilyl groups of **26** were removed with pyridinium poly(hydrogen fluoride)pyridine complex to furnish synthetic tautomycin **1**. The spectrum of 400 MHz ^{1}H NMR and the behavior of TLC were identical to those of natural tautomycin.[1]

Although the total synthesis of (+)-tautomycin was completed, we felt it seemed to be difficult to synthesize a variety of analogs of tautomycin for further studies because of low yields at the final stage from **8** to **1**. In order to improve this final stage, an alternative route was investigated.

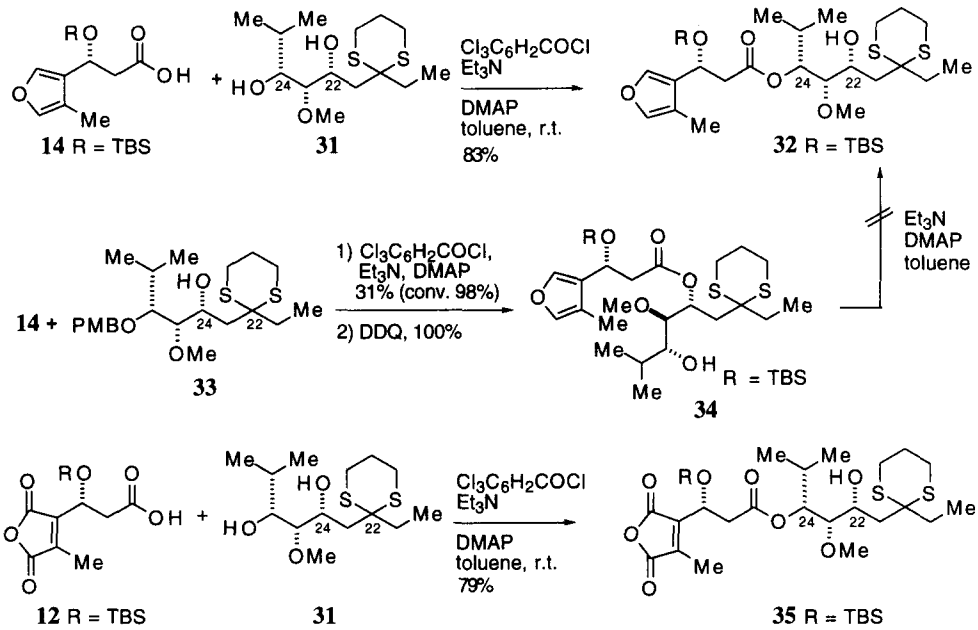
Improved Total Synthesis of Tautomycin In the esterification of Segment B/C with Segment A using model compounds (in Scheme 2), we observed a serious steric effect of the protecting group at C22. Model Segment B/C **27** with methoxymethyl ether as the C22 protection reacted with Segment A **14** to provide **28** in 78% yield (Scheme 7). Furthermore, **29**, **30a** and **30b** having no hydroxy group at C22 were easily esterified under Yamaguchi conditions[8] not only with furan **14** but also with maleic anhydride **12** in higher than 90% yield.[14]



Scheme 7

These results suggested that a small size of protecting group at the C22 hydroxy group would facilitate the esterification. We envisioned that the free hydroxy group at C22 might bear the least steric environment around the C24 hydroxy group. Indeed, esterification of model compound **31** with Segment A **14** under Yamaguchi conditions gave the C24 acylated product **32** in good yield (Scheme 8). Notably, this coupling reaction proceeded regioselectively and the formation of the C22 acylated isomer **34** has never been observed. This regioselective esterification appeared to be kinetic in origin, because treatment of the isomer **34**, prepared from

33, with triethylamine and *N, N*-dimethylaminopyridine in toluene gave no detectable formation of **32**. Moreover, it was gratifying that even **12** with maleic anhydride moiety furnished **35** in 79% yield. Further studies were necessary to understand its precise origins, and we could imagine that biosynthesis of tautomycin in the esterification step of the maleic acid portion precursor could involve such an intermediate with the free C24 and C22 hydroxy groups.

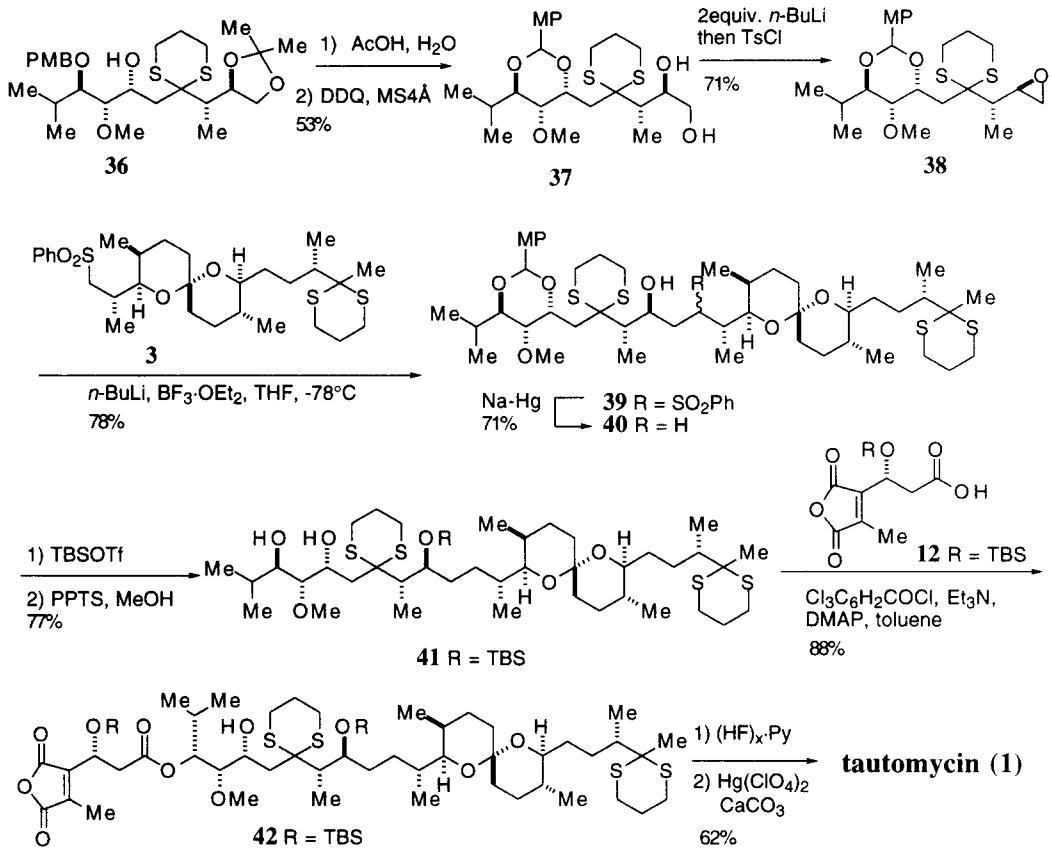


Scheme 8

Encouraged by these model experimental results, an improved synthetic approach to tautomycin has been established as shown in Scheme 9. Hydrolysis of the acetonide **36** with aqueous acetic acid followed by DDQ promoted intramolecular benzylidene formation[15] gave **37** in 53% overall yield. The diol **37** was further transformed into new Segment B **38** in 71% yield by employing the similar method as described before.[3b] It should be noted that protection of the two hydroxy groups at the C24 and the C22 positions as *p*-methoxybenzylidene group increased the stability of Segment B **38** which was stockable at -20 °C for a few months.

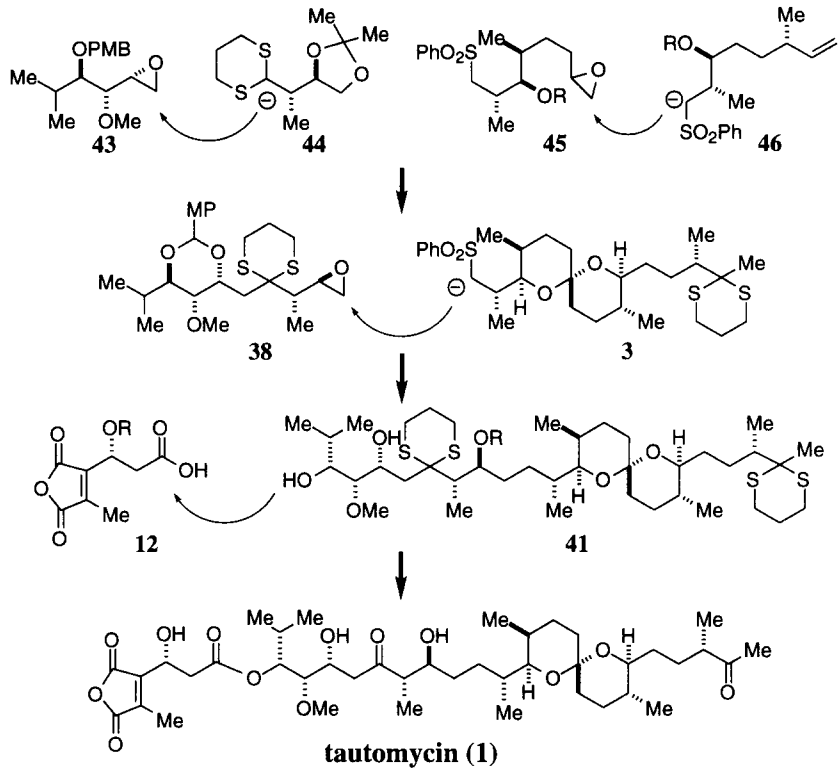
Smooth coupling between the new Segment B **38** and Segment C **3** proceeded to give **39** in 78% yield. Desulfonylation was followed by protecting group manipulation involving i) silylation at C18 hydroxy group with *t*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) , and ii) hydrolysis of the *p*-methoxybenzylidene group with pyridinium *p*-toluenesulfonate (PPTS) in methanol to give the diol **41** in 77% yield. Selective esterification of **41** with Segment A **12** under Yamaguchi conditions[8] proceeded expectedly to afford the desired product **42** in 88% yield. Two-step deprotection of **42** involving removal of *t*-butyldimethylsilyl groups with poly(hydrogen fluoride)pyridine complex and cleavage of the two dithioketals using mercury perchlorate in aqueous acetonitrile[16] furnished the synthetic tautomycin **1** in 62% overall yield. This synthetic

material proved to be identical in all respects ($[\alpha]_D$, ^1H and ^{13}C NMR, IR, TLC, HRMS, biological activity[17]) with natural tautomycin.[1]



Scheme 9

Conclusions An improved total synthesis of tautomycin was summarized in Scheme 10. The C1-C26 carbon backbone was constructed by the epoxide opening reaction with carbanions (**43+44**, **45+46**, **38+3**). Esterification of Segment B/C **41** with Segment A **12** having maleic anhydride moiety was achieved in high yield. This improved total synthesis provided the three-step synthesis of tautomycin **1** from Segment B/C **41** in 54% overall yield (the previous route involved six steps from Segment B/C **8** in 6.8% overall yield). Segments A **12**, B **38** and C **3** were prepared in 8, 21 and 43 steps, and tautomycin was synthesized in 8 steps from Segment C. Based on this route, the preparation of structural analogs of tautomycin and studies on molecular shape and activity relationship in the protein phosphatase inhibition are currently in progress.[14,17,18]



Scheme 10

Experimental Section

For the general experimental details, see the preceding paper of this article.

[2*S*,2(3*S*),3*R*,6*R*,8*R*,8(1*S*),9*S*]-3,9-Dimethyl-2-[3-(2-methyl-1,3-dithian-2-yl)butyl]-8-[1-methyl-2-(phenylsulfonyl)ethyl]-1,7-dioxaspiro[5,5]undecane (3).

A solution of boron trifluoride etherate (9.5 μl, 0.077 mmol) in dichloromethane (2 ml) was added to a solution of **2** (119 mg, 0.26 mmol) and 1,3-propanedithiol (0.08 ml, 0.77 mmol) in dichloromethane (4 ml) at 0 °C and the mixture was stirred for 1 h. The cooling bath was removed and stirring was continued overnight. The mixture was poured into saturated aqueous sodium hydrogencarbonate and extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated to give a residue which was purified by silica gel chromatography (ether/hexane, 1:1) to afford protected Segment C **3** (137 mg, 96%). IR (KBr) ν_{max} 2933, 1448, 1380, 1306, 1231, 1147, 1086, 989, 745, 690 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.67 (3H, d, *J* = 7 Hz, C_{13}-CH_3), 0.79 (3H, d, *J* = 6 Hz, C_7-CH_3), 1.06 (3H, d, *J* = 7 Hz, C_3-CH_3), 1.22 (3H, d, *J* = 7 Hz, C_{15}-CH_3), 1.20-2.13 (18H, m, H-3, H-4, H-5, H-7, H-8, H-9, H-11, H-12, H-13,

H-15, $SCH_2CH_2CH_2S$), 1.61 (3H, s, H-1), 2.69-2.97 (4H, m, $SCH_2CH_2CH_2S$), 3.08 (1H, dd, J = 14, 10 Hz, one of H-16), 3.10 (1H, td, J = 10, 2 Hz), 3.18 (1H, dd, J = 14, 2 Hz, one of H-16), 3.49 (1H, dd, J = 10, 2 Hz, H-14), 7.53-7.64 (3H, m, ArH), 7.90-7.94 (2H, m, ArH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 10.6, 13.7, 16.8, 17.9, 23.2, 25.6, 26.3, 26.4, 26.6, 26.8, 27.3, 28.0, 30.0, 31.0, 31.2, 34.8, 35.8, 41.6, 54.9, 59.0, 72.9, 73.9, 95.9, 128.0, 129.2, 133.5, 140.0. $[\alpha]_D^{27}$ -27.8° (*c* 0.30, $CHCl_3$). Anal. Calcd for $C_{29}H_{46}O_4S_3$: C, 62.79; H, 8.36. Found: C, 62.79; H, 8.50.

[2*R*,2[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*],5*S*,6*S*,9*R*,10*S*,11*R*]-9-(*tert*-Butyldimethylsilyl)oxy-2-[3,9-dimethyl-8-[3-(2-methyl-1,3-dithian-2-yl)butyl]-1,7-dioxaspiro[5,5]undecan-2-yl]-10-methoxy-11-(4-methoxybenzyl)oxy-6,12-dimethyl-7-(1,3-dithian-2-yl)-5-tridecanol (6).

n-Butyllithium (1.64 M solution in hexane, 0.066 ml, 0.108 mmol) was added to a solution of **3** (54 mg, 0.098 mmol) in tetrahydrofuran (2.5 ml) at -78 °C. After stirring for 30 min, boron trifluoride etherate (0.018 mmol, 0.147 mmol) was added to the reaction mixture, and stirring was continued for 30 min. A solution of Segment B **4** (12 mg, 0.021 mmol) in tetrahydrofuran (0.4 ml) was added, and the reaction mixture was stirred at -78 °C for 2 h and then at -50 °C for 1 h. The reaction mixture was quenched with pH 7 phosphate buffer and then extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated under reduced pressure to give a residue which was purified by preparative thin layer chromatography (ether/hexane 1:2) to afford **5** (19 mg, 81%) and recovered **3** (37 mg).

Sodium amalgam (5%) was added to a solution of **5** (18 mg, 0.017 mmol) dissolved in methanol (2 ml) until TLC analysis showed the absence of the starting material. The reaction mixture was diluted with ether and water, and the separated aqueous phase was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated to give a residue which was purified by preparative thin layer chromatography (ether/hexane 1:1) to afford **6** (15 mg, 96%). IR (KBr) ν_{max} 2933, 1615, 1515, 1458, 1377, 1249, 1095, 987, 836, 775 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.14 (3H, s, $SiCH_3$), 0.18 (3H, s, $SiCH_3$), 0.83 (3H, d, J = 7 Hz, $CHCH_3$), 0.89 (9H, s, Si*t-Bu*), 0.90 (3H, d, J = 7 Hz, $CHCH_3$), 1.00 (3H, d, J = 7 Hz, $CHCH_3$), 1.04 (3H, d, J = 7 Hz, $CHCH_3$), 1.06 (3H, d, J = 7 Hz, $CHCH_3$), 1.10 (3H, d, J = 7 Hz, $CHCH_3$), 1.14 (3H, d, J = 7 Hz, $CHCH_3$), 1.25-2.12 (25H, m), 1.59 (3H, s, H-1), 2.28-2.48 (3H, m, H-19, H-21), 2.74-2.91 (8H, m, $SCH_2CH_2CH_2S$), 3.24 (1H, td, J = 9, 3 Hz, H-6), 3.36-3.40 (2H, m, H-14, H-23), 3.45 (1H, dd, J = 7, 3 Hz, H-24), 3.45 (3H, s, OCH_3), 3.79 (3H, s, Ar-OCH_3), 3.81 (1H, m, H-18), 4.08 (1H, br, OH), 4.50 (1H, d, J = 11 Hz, one of CH_2Ar), 4.60 (1H, m, H-22), 4.70 (1H, d, J = 11 Hz, one of CH_2Ar), 6.84 (2H, d, J = 9 Hz, ArH), 7.35 (2H, d, J = 9 Hz, ArH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -3.1, -2.5, 11.0, 13.6, 14.3, 16.9, 16.9, 18.0, 18.5, 21.1, 23.4, 24.6, 25.6, 26.0, 26.3, 26.4, 26.8, 27.4, 27.5, 27.6, 28.3, 29.7, 30.3, 32.0, 32.6, 34.9, 35.0, 36.2, 38.4, 41.7, 43.9, 54.8, 55.3, 58.1, 59.2, 70.9, 72.6, 73.7, 74.5, 75.0, 83.1, 84.3, 95.7, 113.5, 129.2, 131.5, 158.9. HRMS (FAB, *m*-nitrobenzyl alcohol) calcd for $C_{53}H_{94}O_7S_4Si$ $(M+H)^+$ 999.5730, found 999.5724. $[\alpha]_D^{26}$ -21.5° (*c* 0.19, $CHCl_3$).

[3*R*,4*R*,5*R*,8*S*,9*S*,12*R*,12[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-5,9-Bis(*tert*-butyldimethylsilyl)oxy-12-[3,9-dimethyl-8-[3-(2-methyl-1,3-dithian-2-yl)butyl]-1,7-dioxaspiro[5,5]undecan-2-yl]-4-methoxy-2,8-dimethyl-7-(1,3-dithian-2-yl)-3-tridecanol (8).

t-Butyldimethylsilyl trifluoromethanesulfonate (0.028 ml, 0.12 mmol) was added to a solution of **6** (35 mg, 0.035 mmol) and *N,N*-diisopropylethylamine (0.027 ml, 0.16 mmol) in dichloromethane (1.5 ml) at 0 °C.

After being stirred for 15 min, the mixture was poured into saturated aqueous sodium hydrogencarbonate and the separated aqueous phase was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated to afford crude *t*-butyldimethylsilyl ether **7** (40 mg).

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (15 mg, 0.067 mmol) was added to a solution of **7** (40 mg) in a mixture of dichloromethane and water (2.2 ml, 10:1). After stirring at room temperature for 30 min, saturated sodium hydrogencarbonate was added. The separated aqueous phase was extracted with dichloromethane and the combined organic phase was dried and then concentrated under reduced pressure to give a residue which was purified by thin layer chromatography (ether/hexane 1:5) to provide **8** (31 mg, 89%, 2 steps). IR (KBr) ν_{max} 3508, 2931, 1464, 1383, 1256, 1056, 1006, 983, 834, 775 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.08 (3H, s, SiC*H*$_3$), 0.11 (3H, s, SiC*H*$_3$), 0.24 (6H, s, SiC*H*$_3$), 0.83 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.88 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.90 (9H, s, Si*t-Bu*), 0.91 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.92 (9H, s, Si*t-Bu*), 1.02 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.04 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.08 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.10 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.19-2.27 (26H, m), 1.59 (3H, s, H-1), 2.39 (1H, dd, *J* = 16, 1 Hz, one of H-21), 2.51 (1H, dd, *J* = 16, 7 Hz, one of H-21), 2.57-2.99 (8H, SC*H*$_2$CH$_2$C*H*$_2$S), 3.19 (1H, dd, *J* = 9, 4 Hz, H-23), 3.27 (1H, td, *J* = 9, 3 Hz, H-6), 3.36 (1H, dd, *J* = 10, 2 Hz, H-14), 3.38 (3H, s, OC*H*$_3$), 3.66 (1H, dt, *J* = 9, 2 Hz, H-24), 3.70 (1H, br, OH), 4.22 (1H, m, H-18), 4.32 (1H, m, H-22). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -4.1, -3.7, -3.5, -3.1, 7.3, 10.9, 14.3, 15.0, 17.0, 18.0, 18.0, 18.1, 19.8, 23.6, 25.4, 25.6, 25.9, 26.2, 26.3, 26.3, 26.4, 26.8, 27.1, 27.4, 27.6, 28.3, 29.3, 29.5, 30.4, 30.8, 31.8, 34.8, 35.3, 36.2, 38.6, 41.4, 46.1, 54.8, 55.8, 58.1, 70.1, 74.0, 74.3, 75.4, 75.4, 80.5, 95.6. HRMS (FAB, *m*-nitrobenzyl alcohol) calcd for $C_{51}H_{100}O_6S_4Si_2$ $(M+H)^+$ 993.6019, found 993.5992. $[\alpha]_D^{25}$ -34.8° (*c* 0.31, $CHCl_3$).

(3*R*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyl)oxy-4-methoxy-2-methyl-7-(1,3-dithian-2-yl)nonan-3-yl 3-(2,5-dihydro-4-methyl-2,5-dioxofuran-3-yl)-propionate (11).

2,4,6-Trichlorobenzoyl chloride (0.051 ml, 0.33 mmol) was added to a solution of **9** (50 mg, 0.27 mmol) and triethylamine (0.047 ml, 0.35 mmol) in toluene (1 ml) at room temperature. After stirring for 1.5 h, a solution of **10** (23 mg, 0.054 mmol) and 4-dimethylaminopyridine (40 mg, 0.33 mmol) in toluene (1 ml) was added at room temperature. After stirring for 2 h, saturated aqueous ammonium chloride was added and the solution was acidified with 1N HCl. The mixture was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated to give a residue which was purified by silica gel chromatography (ether/hexane, 1:3) to afford **11** (17 mg, 53%, 76% yield based on the consumed **10**) and the recovered **10** (7 mg). IR (KBr) ν_{max} 2931, 1770, 1735, 1462, 1372, 1260, 1180, 1112, 911, 836, 775, 735 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.14 (6H, s, Si(C*H*$_3$)$_2$), 0.85 (3H, d, *J* = 7 Hz, H-26), 0.90 (3H, d, *J* = 7 Hz, H-26), 0.90 (9H, s, Si*t-Bu*), 0.97 (3H, t, *J* = 7 Hz, C$_{19}$-C*H*$_3$), 1.79-2.04 (5H, m, SCH$_2$C*H*$_2$CH$_2$S, H-19, one of H-21), 2.12 (1H, m, H-25), 2.14 (3H, s, Ar-C*H*$_3$), 2.34 (1H, dd, *J* = 16, 2 Hz, one of H-21), 2.61-2.93 (8H, SC*H*$_2$CH$_2$C*H*$_2$S, H-2', H-3'), 3.39 (1H, dd, *J* = 9, 3 Hz, H-23), 3.44 (3H, s, OC*H*$_3$), 4.28 (1H, m, H-22), 5.04 (1H, dd, *J* = 9, 3 Hz, H-24). HRMS (FAB, *m*-nitrobenzyl alcohol) calcd for $C_{28}H_{49}O_7S_2Si$ $(M+H)^+$ 589.2689, found 589.2676. $[\alpha]_D^{25}$ +17.6° (*c* 0.25, $CHCl_3$).

(3*R*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyl)oxy-4-methoxy-2-methyl-7-(1,3-dithian-2-yl)nonan-3-yl (3*R*)-3-(*tert*-butyldimethylsilyl)oxy-3-(4-methylfuran-3-yl)-propionate (15).

2,4,6-Trichlorobenzoyl chloride (0.010 ml, 0.063 mmol) was added to a solution of **14** (12 mg, 0.042 mmol) and triethylamine (0.010 ml, 0.072 mmol) in toluene (0.3 ml) at room temperature. After stirring for 2 h, a solution of **10** (10 mg, 0.023 mmol) and 4-dimethylaminopyridine (5 mg, 0.042 mmol) in toluene (0.3 ml) was added to the reaction mixture at room temperature. After being stirred for 4 h, the mixture was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated to give a residue which was purified by preparative thin layer chromatography (ether/hexane, 1:5) to afford **15** (6.0 mg, 37%, 93% yield based on the consumed **22**) and the recovered **10** (6.0 mg, 60%). IR (KBr) ν_{max} 2930, 2858, 1736, 1464, 1388, 1257, 1174, 1100, 1006, 836, 778 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ -0.09 (3H, s, SiC*H*$_3$), 0.03 (3H, s, SiC*H*$_3$), 0.12 (3H, s, SiC*H*$_3$), 0.13 (3H, s, SiC*H*$_3$), 0.84 (9H, s, Si*t-Bu*), 0.87 (9H, s, Si*t-Bu*), 0.89-1.01 (9H, m), 1.82-2.00 (5H, m, $SCH_2CH_2CH_2S$, H-19, one of H-21), 2.03 (3H, d, J = 1 Hz, Ar-C*H*$_3$), 2.12 (1H, m, H-25), 2.40 (1H, dd, J = 15, 2 Hz, one of H-21), 2.57 (1H, dd, J = 16, 4 Hz, one of H-2'), 2.53-2.97 (4H, m, $SCH_2CH_2CH_2S$), 2.83 (1H, dd, J = 16, 9 Hz, one of H-2'), 3.38 (1H, dd, J = 9, 3 Hz, H-23), 3.42 (3H, s, OC*H*$_3$), 4.27 (1H, m, H-22), 5.05 (1H, dd, J = 9, 3 Hz, H-24), 5.17 (1H, dd, J = 9, 4 Hz, H-3'), 7.11 (1H, m, ArH), 7.26 (1H, d, J = 2 Hz, ArH). EI-MS m/z 688 (M^+). HRMS (EI) calcd for $C_{34}H_{64}O_6S_2Si_2$ (M^+) 688.3683, found 688.3661. $[\alpha]_D^{23}$ +48.1° (*c* 0.97, $CHCl_3$).

(3*R*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyl)oxy-4-methoxy-2-methyl-7-oxononan-3-yl (3*R*)-3-(*tert*-butyldimethylsilyl)oxy-3-(4-methylfuran-3-yl)-propionate (16).

To a solution of **15** (33 mg, 0.048 mmol) in a mixture of acetonitrile (1.2 ml) and water (0.3 ml) were added silver nitrate (41 mg, 0.24 mmol) and *N*-chlorosuccinimide (32 mg, 0.24 mmol) at room temperature. The mixture was stirred for 10 min and then diluted with ether and phosphate buffer (pH7). Sodium bisulfite (36 mg, 0.29 mmol) was added at 0 °C, and stirring was continued for 10 min. The reaction mixture was filtered through a pad of Celite and the filtrate was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated under reduced pressure to give a residue which was purified by preparative thin layer chromatography (ether/hexane 1:5) to afford **16** (21 mg, 73%). IR (KBr) ν_{max} 2932, 2859, 1738, 1723, 1546, 1473, 1390, 1292, 1257, 1222, 1171, 1094, 1048, 1006, 955, 835, 778 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ -0.09 (3H, s, SiC*H*$_3$), 0.00 (3H, s, SiC*H*$_3$), 0.04 (3H, s, SiC*H*$_3$), 0.07 (3H, s, SiC*H*$_3$), 0.82 (9H, s, Si*t-Bu*), 0.83 (9H, s, Si*t-Bu*), 0.91 (3H, d, J = 7 Hz, H-26), 0.92 (3H, d, J = 7 Hz, H-26), 1.02 (3H, t, J = 7 Hz, C_{19}-C*H*$_3$), 2.05 (3H, d, J = 1 Hz, Ar-C*H*$_3$), 2.08 (1H, m, H-25), 2.40 (1H, q, J = 7 Hz, H-19), 2.44 (1H, q, J = 7 Hz, H-19), 2.58 (1H, dd, J = 16, 4 Hz, one of H-2'), 2.59 (2H, d, J = 5 Hz, H-21), 2.83 (1H, dd, J = 16, 9 Hz, one of H-2'), 3.21 (1H, dd, J = 6, 5 Hz, H-23), 3.35 (3H, s, OC*H*$_3$), 4.38 (1H, q, J = 5 Hz, H-22), 4.88 (1H, dd, J = 6, 4 Hz, H-24), 5.17 (1H, dd, J = 9, 4 Hz, H-3'), 7.11 (1H, m, ArH), 7.26 (1H, d, J = 2 Hz, ArH). EI-MS m/z 598 (M^+). HRMS (EI) calcd for $C_{31}H_{58}O_7Si_2$ (M^+) 598.3721, found 598.3718. $[\alpha]_D^{21}$ +50.1° (*c* 0.21, $CHCl_3$).

(3*R*,4*R*,5*R*)-5-(*tert*-Butyldimethylsilyl)oxy-4-methoxy-2-methyl-7-oxononan-3-yl (3*R*)-3-(*tert*-butyldimethylsilyl)oxy-3-(2,5-dihydro-4-methyl-2,5-dioxofuran-3-yl)-propionate (23).

A solution of **16** (19 mg, 0.032 mmol) in a mixture of tetrahydrofuran (0.8 ml) and phosphate buffer (pH 7) (0.2 ml) cooled to 0 °C was treated with *N*-bromosuccinimide (8.5 mg, 0.048 mmol). After stirring for 15 min, saturated aqueous sodium hydrogencarbonate was added and the separated aqueous phase was extracted with a mixture of ether and hexane (1:1). The combined organic phase was washed with saturated

aqueous sodium hydrogencarbonate, water and brine, dried and then concentrated. The resulting residue was dissolved in acetone (1 ml) and then cooled to -20 °C. Jones reagent (1.9 M; 0.025 ml, 0.048 mmol) was added with stirring. After 15 min, 2-propanol was added. The mixture was extracted with ether and the combined organic phase was dried and then concentrated. Purification by preparative thin layer chromatography (ether/hexane 1:1) afforded a mixture of 4-hydroxybutenolides (11 mg, 55%, 2 steps).

Pyridinium chlorochromate (15 mg, 0.070 mmol) was added to a suspension of powdered molecular sieves 4A (150 mg) and a mixture of 4-hydroxybutenolides (11 mg, 0.017 mmol) in dichloromethane (0.7 ml) at room temperature. After being stirred for 1.5 h, the mixture was diluted with ether, filtered through a pad of Celite and then concentrated under reduced pressure to afford **23** (11 mg, 100%). IR (KBr) ν_{max} 2930, 2858, 1826, 1773, 1732, 1463, 1379, 1257, 1181, 1099, 913, 838, 779, 731 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.01 (3H, s, SiCH_3), 0.02 (3H, s, SiCH_3), 0.06 (3H, s, SiCH_3), 0.12 (3H, s, SiCH_3), 0.82 (9H, s, Si*t-Bu*), 0.86 (9H, s, Si*t-Bu*), 0.91 (6H, d, *J* = 7 Hz, H-26), 1.03 (3H, t, *J* = 7 Hz, C_{19}-CH_3), 2.10 (1H, m, H-25), 2.23 (3H, d, *J* = 1 Hz, Ar-CH_3), 2.42 (1H, q, *J* = 7 Hz, one of H-19), 2.45 (1H, q, *J* = 7 Hz, one of H-19), 2.59 (2H, d, *J* = 6 Hz, H-21), 2.73 (1H, dd, *J* = 16, 6 Hz, one of H-2'), 2.88 (1H, dd, *J* = 16, 7 Hz, one of H-2'), 3.23 (1H, dd, *J* = 6, 4 Hz, H-23), 3.36 (3H, s, OCH_3), 4.38 (1H, m, H-22), 4.90 (1H, dd, *J* = 6, 4 Hz, H-24), 5.15 (1H, dd, *J* = 7, 6 Hz, H-3'). HRMS (FAB, *m*-nitrobenzyl alcohol) calcd for $C_{31}H_{57}O_9Si_2$ $(M+H)^+$ 629.3541, found 629.3520. $[\alpha]_D^{24}$ +39.7° (*c* 0.20, $CHCl_3$)

[3*R*,4*R*,5*R*,8*S*,9*S*,12*R*,12[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-5,9-Bis(*tert*-butyldimethylsilyl)oxy-12-[3,9-dimethyl-8-[3-(2-methyl-1,3-dithian-2-yl)butyl]-1,7-dioxaspiro[5,5]undecan-2-yl]-4-methoxy-2,8-dimethyl-7-(1,3-dithian-2-yl)tridecan-3-yl (3*R*)-3-(*tert*-butyldimethylsilyl)oxy-3-(4-methylfuran-3-yl)-propionate (24).

2,4,6-Trichlorobenzoyl chloride (0.018 ml, 0.11 mmol) was added to a solution of Segment A **14** (16 mg, 0.056 mmol) and triethylamine (0.016 ml, 0.12 mmol) in toluene (0.4 ml) at room temperature. After stirring for 2 h, a solution of Segment B/C **8** (20 mg, 0.020 mmol) and 4-dimethylaminopyridine (14 mg, 0.11 mmol) in toluene (0.8 ml) was added to the reaction mixture. After being stirred overnight, the mixture was diluted with ether. The organic layer was washed with water and brine, dried and then concentrated to give a residue which was purified by preparative thin layer chromatography (ether/hexane 1:5) to afford **24** (10 mg, 39%, 88% yield based on the consumed **8**) and recovered **8** (11 mg). IR (KBr) ν_{max} 2930, 1735, 1473, 1374, 1254, 1171, 1082, 1005, 834, 775 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ -0.09 (3H, s, SiCH_3), 0.04 (3H, s, SiCH_3), 0.07 (3H, s, SiCH_3), 0.10 (3H, s, SiCH_3), 0.12 (3H, s, SiCH_3), 0.14 (3H, s, SiCH_3), 0.82-0.96 (12H, m), 0.83 (9H, s, Si*t-Bu*), 0.88 (9H, s, Si*t-Bu*), 0.89 (9H, s, Si*t-Bu*), 0.94 (3H, d, *J* = 7 Hz, CHCH_3), 1.02 (3H, d, *J* = 7 Hz, CHCH_3), 1.07 (3H, d, *J* = 7 Hz, CHCH_3), 1.10 (3H, d, *J* = 7 Hz, CHCH_3), 1.20-2.34 (27H, m), 1.58 (3H, s, H-1), 2.05 (3H, d, *J* = 1 Hz, Ar-CH_3), 2.60 (1H, dd, *J* = 16, 4 Hz, one of H-2'), 2.50-2.91 (8H, m, SCH_2CH_2CH_2S), 2.85 (1H, dd, *J* = 16, 9 Hz, one of H-2'), 3.27 (1H, td, *J* = 10, 2 Hz, H-6), 3.34-3.40 (2H, m, H-14, H-23), 3.40 (3H, s, OCH_3), 4.12-4.20 (2H, m, H-18, H-22), 5.08 (1H, dd, *J* = 8, 2 Hz, H-24), 5.17 (1H, dd, *J* = 9, 4 Hz, H-3'), 7.11 (1H, m, ArH), 7.28 (1H, d, *J* = 2 Hz, ArH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.0, -4.8, -4.2, -3.7, -3.6, -3.1, 7.4, 8.7, 10.9, 14.3, 16.2, 17.0, 18.0, 18.0, 18.4, 20.1, 23.6, 25.6, 25.6, 25.8, 25.9, 26.3, 26.3 ,26.3, 26.4, 26.9, 27.1, 27.3, 27.6, 28.3, 28.8, 29.6, 30.4, 30.6, 31.8, 34.8, 35.2, 36.2, 39.4, 41.4, 44.3, 46.1, 54.8, 56.1, 58.6, 64.1, 69.0, 74.1, 74.4,

75.2, 75.4, 81.9, 95.6, 118.6, 128.0, 139.9, 140.3, 170.0. FAB-MS (*m*-nitrobenzyl alcohol, NaI) m/z 1281 $(M+Na)^+$. $[\alpha]_D^{26}$ -14.1° (*c* 0.18, $CHCl_3$).

[3*R*,4*R*,5*R*,8*S*,9*S*,12*R*,12[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-5,9-Bis(*tert*-butyldimethylsilyl)oxy-12-[3,9-dimethyl-8-[3-methyl-4-oxopentyl]-1,7-dioxaspiro[5,5]undecan-2-yl]-4-methoxy-2,8-dimethyl-7-oxotridecan-3-yl (3*R*)-3-(*tert*-butyldimethylsilyl)oxy-3-(4-methylfuran-3-yl)-propionate (25).

To a solution of **24** (15 mg, 0.012 mmol) in a mixture of acetone (1 ml) and phosphate buffer (pH7) (50 µl) were added silver nitrate (20 mg, 0.12 mmol) and *N*-chlorosuccinimide (13 mg, 0.096 mmol) at room temperature. The mixture was stirred for 10 min and then diluted with ether and phosphate buffer (pH7). Sodium bisulfite (12 mg, 0.12 mmol) was added at 0 °C, and stirring was continued for 10 min. The reaction mixture was filtered through a pad of Celite and the filtrate was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated under reduced pressure to give a residue which was purified by preparative thin layer chromatography (ether/hexane 1:4) to afford **25** (4.0 mg, 31%). IR (KBr) ν_{max} 2929, 1734, 1718, 1464, 1387, 1257, 1098, 837, 778 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ -0.09 (3H, s, SiCH_3), -0.01 (3H, s, SiCH_3), 0.02 (3H, s, SiCH_3), 0.04 (3H, s, SiCH_3), 0.05 (3H, s, SiCH_3), 0.09 (3H, s, SiCH_3), 0.80 (3H, d, *J* = 5 Hz, CHCH_3), 0.81 (9H, s, Si*t*-*Bu*), 0.84 (9H, s, Si*t*-*Bu*), 0.86 (9H, s, Si*t*-*Bu*), 0.88 (3H, d, *J* = 7 Hz, CHCH_3), 0.89 (3H, d, *J* = 7 Hz, CHCH_3), 0.92 (3H, d, *J* = 7 Hz, CHCH_3), 0.94 (3H, d, *J* = 7 Hz, CHCH_3), 0.98 (3H, d, *J* = 7 Hz, CHCH_3), 1.10 (3H, d, *J* = 7 Hz, CHCH_3), 1.20-2.14 (19H, m), 2.04 (3H, d, *J* = 1 Hz, Ar-CH_3), 2.15 (3H, s, H-1), 2.56 (1H, m, H-3), 2.57 (1H, dd, *J* = 16, 4 Hz, one of H-2'), 2.63 (1H, dd, *J* = 17, 4 Hz, one of H-21), 2.70 (1H, m, H-19), 2.71 (1H, dd, *J* = 17, 8 Hz, one of H-21), 2.82 (1H, dd, *J* = 16, 9 Hz, one of H-2'), 3.17 (1H, td, *J* = 10, 2 Hz, H-6), 3.22 (1H, dd, *J* = 7, 4 Hz, H-23), 3.26 (1H, dd, *J* = 10, 2 Hz, H-14), 3.35 (3H, s, OCH_3), 3.98 (1H, m, H-18), 4.46 (1H, dt, *J* = 8, 4 Hz, H-22), 4.92 (1H, dd, *J* = 7, 4 Hz, H-24), 5.17 (1H, dd, *J* = 9, 4 Hz, H-3'), 7.11 (1H, m, ArH), 7.26 (1H, m, ArH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.0, -4.9, -4.8, -4.7, -4.5, -4.3, 8.7, 10.9, 11.4, 16.1, 16.6, 16.8, 18.0, 18.1, 20.0, 25.8, 25.9, 25.9, 26.7, 27.6, 28.0, 28.1, 28.7, 29.1, 30.3, 30.5, 34.8, 35.0, 36.1, 44.2, 46.7, 47.3, 52.1, 58.8, 64.2, 67.1, 73.0, 74.3, 75.1, 76.0, 81.9, 95.6, 118.5, 128.0, 139.9, 140.3, 170.4, 211.1, 212.8. FAB-MS (*m*-nitrobenzyl alcohol, NaI) m/z 1101 $(M+Na)^+$. $[\alpha]_D^{26}$ +15.1° (*c* 0.24, $CHCl_3$).

[3*R*,4*R*,5*R*,8*S*,9*S*,12*R*,12[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-5,9-Bis(*tert*-butyldimethylsilyl)oxy-12-[3,9-dimethyl-8-[3-methyl-4-oxopentyl]-1,7-dioxaspiro[5,5]undecan-2-yl]-4-methoxy-2,8-dimethyl-7-oxotridecan-3-yl (3*R*)-3-(*tert*-butyldimethylsilyl)oxy-3-(2,5-dihydro-4-methyl-2,5-dioxofuran-3-yl)-propionate (tris(*t*-butyldimethylsilyl)tautomycin) (26).

N-Bromosuccinimide (1.8 mg, 10 µmol) was added to a solution of **25** (5.4 mg, 5.0 µmol) in a mixture of tetrahydrofuran (0.4 ml) and phosphate buffer (pH 7) (0.1 ml) at 0 °C. After stirring for 15 min, saturated aqueous sodium hydrogencarbonate was added, and the aqueous phase was extracted with a mixture of ether and hexane (1:1). The combined organic phase was washed with saturated aqueous sodium hydrogencarbonate, water and brine, dried and then concentrated. The resulting residue was diluted with acetone (0.5 ml) and then cooled to 0 °C. Jones reagent (1.9 M; 4 µl, 7.5 µmol) was added. After stirring at 0 °C for 15 min, 2-propanol was added. The mixture was extracted with ether, and the combined organic phase

was dried and then concentrated to give a residue which was purified by preparative thin layer chromatography (ether/hexane 1:1) to afford a mixture of the 4-hydroxybutenolides (3.2 mg, 58% , 2 steps).

Pyridinium chlorochromate (2.5 mg, 12 μmol) was added to a suspension of the 4-hydroxybutenolides (3.2 mg, 2.9 μmol) and powdered molecular sieves 4Å (40 mg) in dichloromethane (0.4 ml) at room temperature. After being stirred for 3 h, the mixture was diluted with ether, filtered through a pad of Celite and then concentrated to afford tris(*t*-butyldimethylsilyl)tautomycin **26** (2.5 mg, 78%). IR (KBr) ν_{max} 2932, 1772, 1739, 1715, 1464, 1388, 1255, 1231, 1180, 1098, 987, 939, 915, 837, 813, 777, 731 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ -0.01 (3H, s, SiC*H*$_3$), 0.03 (6H, s, SiC*H*$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.08 (3H, s, SiC*H*$_3$), 0.12 (3H, s, SiC*H*$_3$), 0.80 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$), 0.82 (9H, s, Si*t-Bu*), 0.86 (9H, s, Si*t-Bu*), 0.86 (9H, s, Si*t-Bu*), 0.88 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.90 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.92 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.96 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.98 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.09 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.20-2.14 (20H, m), 2.15 (3H, s, H-1), 2.22 (3H, d, *J* = 1 Hz, Ar-C*H*$_3$), 2.56 (1H, sext, *J* = 7 Hz, H-3), 2.66-2.72 (3H, m, H-21, H-19), 2.72 (1H, dd, *J* = 16, 6 Hz, one of H-2'), 2.86 (1H, dd, *J* = 16, 7 Hz, one of H-2'), 3.17 (1H, td, *J* = 10, 2 Hz, H-6), 3.24 (1H, dd, *J* = 7, 4 Hz, H-23), 3.26 (1H, dd, *J* = 10, 2 Hz, H-14), 3.36 (3H, s, OC*H*$_3$), 3.96 (1H, m, H-18), 4.46 (1H, dt, *J* = 8, 4 Hz, H-22), 4.93 (1H, dd, *J* = 7, 4 Hz, H-24), 5.16 (1H, dd, *J* = 7, 6 Hz, H-3'). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.2, -4.9, -4.9, -4.7, -4.5, -4.3, 10.1, 10.9, 11.5, 16.0, 16.6, 16.8, 18.0, 18.1, 20.0, 25.6, 25.9, 25.9, 26.7, 27.6, 28.0, 28.1, 28.6, 29.1, 30.2, 30.4, 30.5, 34.8, 35.0, 36.1, 41.2, 46.8, 47.3, 52.1, 58.9, 63.0, 67.0, 73.1, 74.3, 75.1, 81.8, 95.6, 142.2, 143.6, 164.0, 165.9, 169.0, 210.9, 212.7. HRMS (FAB, *m*-nitrobenzyl alcohol, NaI) calcd for $C_{59}H_{108}O_{13}Si_3Na$ $(M+Na)^+$ 1131.6995, found 1131.6960. $[\alpha]_D^{25}$ +18.2° (*c* 0.22, $CHCl_3$).

Total Synthesis of Tautomycin (1).

A solution of tris(*t*-butyldimethylsilyl)tautomycin **26** (2.5 mg, 2.3 μmol) dissolved in tetrahydrofuran (0.5ml) was transferred into a teflon vial. Pyridinium poly(hydrogen fluoride) (three drops) was added at 0 °C and the reaction mixture was stirred overnight. After careful addition of saturated aqueous sodium hydrogencarbonate, the aqueous layer was extracted at pH 4 with ethyl acetate. The combined organic phase was dried and then concentrated to afford a residue which was purified by preparative thin layer chromatography (ethyl acetate/hexane 1:1) to afford tautomycin **1** (1.4 mg, 80%).

(3*R*,4*S*,5*R*)-5-Hydroxy-4-methoxy-2-methyl-7-(1,3-dithian-2-yl)nonan-3-yl (3*R*)-3-(*tert*-butyldimethylsilyl)oxy-3-(2,5-dihydro-4-methyl-2,5-dioxofuran-3-yl)-propionate (35).

2,4,6-Trichlorobenzoyl chloride (0.012 ml, 0.076 mmol) was added to a solution of **12** (20 mg, 0.064 mmol) and triethylamine (0.013 ml, 0.096 mmol) in toluene (1 ml) at room temperature. After stirring for 2 h, **31** (17 mg, 0.055 mmol) in toluene (1 ml) and 4-dimethylaminopyridine (12 mg, 0.096 mmol) in toluene (0.3 ml) were added to the reaction mixture. After stirring for 2 h, saturated aqueous ammonium chloride was added. The reaction mixture was acidified with 1N HCl and the separated aqueous phase was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated to yield a residue which was purified by silica gel chromatography (ether/hexane, 2:1) to provide **35** (26 mg, 79%) and the corresponding diester (5.6 mg, 11%). IR (KBr) ν_{max} 2931, 1770, 1735, 1462, 1372, 1260, 1180, 1112, 911, 836, 775, 735 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.14 (6H, s, Si(C*H*$_3$)$_2$), 0.85 (3H, d, *J* = 7 Hz, H-26), 0.90 (3H, d, *J* = 7 Hz, H-26), 0.90 (9H, s, Si*t-Bu*), 0.97 (3H, t, *J* = 7 Hz, C_{19}-C*H*$_3$), 1.79-2.04 (5H,

m, $SCH_2CH_2CH_2S$, H-19, one of H-21), 2.12 (1H, m, H-25), 2.14 (3H, s, Ar-CH_3), 2.34 (1H, dd, J = 16, 2 Hz, one of H-21), 2.61-2.93 (8H, m, $SCH_2CH_2CH_2S$, H-2', H-3'), 3.39 (1H, dd, J = 9, 3 Hz, H-23), 3.44 (3H, s, OCH_3), 4.28 (1H, m, H-22), 5.04 (1H, dd, J = 9, 3 Hz, H-24). HRMS (FAB, *m*-nitrobenzyl alcohol) calcd for $C_{28}H_{49}O_8S_2Si$ $(M+H)^+$ 605.2672, found 605.2620. $[\alpha]_D^{25}$ +17.6° (*c* 0.25, $CHCl_3$).

(2*R*,3*S*,6*R*,7*S*,8*R*)-7-Methoxy-6,8-(4-methoxybenzylidenedioxy)-3,9-dimethyl-4-(1,3-dithian-2-yl)-decan-1,2-diol (37).

A solution of the alcohol **36** (583 mg, 1.10 mmol) dissolved in a mixture of acetic acid (16 ml) and water (4 ml) was stirred overnight and heated at 50 °C for 2 h. The solvent was removed by evaporation, and the residue was diluted with ethyl acetate and saturated aqueous sodium hydrogencarbonate. The aqueous solution was extracted with ethyl acetate. The combined organic phase was dried and concentrated under educed pressure to afford the crude triol (574 mg).

A solution of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (375 mg, 1.65 mmol) in dichloromethane (20 ml) was added to a solution of the triol (574 mg) in dichloromethane (30 ml) at room temperature. After stirring for 1.5 h, saturated sodium hydrogencarbonate was added and the mixture was extracted with dichloromethane (3 times). The combined organic phase was dried and then concentrated under reduced pressure to give a residue which was purified by silica gel chromatography (ethyl acetate/hexane, 1:1) to afford the diol **37** (287 mg, 53%, 2steps). IR (KBr) ν_{max} 3421, 2934, 1616, 1517, 1464, 1395, 1302, 1249, 1173, 1092, 1035, 910, 830, 736 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.99 (3H, d, J = 7 Hz, H-26), 1.04 (3H, d, J = 7 Hz, H-26), 1.15 (3H, d, J = 7 Hz, C_{19}-CH_3), 1.92-1.99 (2H, m, $SCH_2CH_2CH_2S$), 2.08 (1H, m, H-25), 2.25 (1H, br, OH), 2.38 (1H, dd, J = 16, 1 Hz, one of H-21), 2.50 (1H, qn, J = 7 Hz, H-19), 2.68 (1H, dd, J = 16, 8 Hz, one of H-21), 2.82-3.00 (4H, m, $SCH_2CH_2CH_2S$), 3.46 (3H, s, OCH_3), 3.50-3.55 (3H, m, H-23, H-24, OH), 3.76 (1H, m, one of H-17), 3.79 (3H, s, Ar-OCH_3), 3.86-4.00 (2H, m, one of H-17, H-18), 4.83 (1H, m, H-22), 5.79 (1H, s, OC*H*O), 6.87 (2H, d, J = 9 Hz, ArH), 7.42 (2H, d, J = 9 Hz, ArH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.6, 15.7, 19.4, 24.3, 25.8, 26.0, 28.3, 30.0, 41.2, 55.2, 57.5, 57.9, 65.3, 71.1, 73.0, 75.6, 79.4, 94.5, 113.6, 127.6, 130.9, 159.9. $[\alpha]_D^{22}$ +51.5° (*c* 0.49, $CHCl_3$). Anal. Calcd for $C_{24}H_{38}O_6S_2$: C, 59.23; H, 7.88. Found: C, 59.25; H, 7.91.

(2*R*,3*S*,6*R*,7*S*,8*R*)-1,2-Epoxy-7-methoxy-6,8-(4-methoxybenzylidenedioxy)-3,9-dimethyl-4-(1,3-dithian-2-yl)-decane (38).

n-Butyllithium (1.68 M in hexane, 0.53 ml, 0.90 mmol) was added to a solution of **37** (170 mg, 0.36 mmol) in tetrahydrofuran (6 ml) at 0 °C. After stirring for 10 min, a solution of *p*-toluenesulfonyl chloride (171 mg, 0.90 mmol) in tetrahydrofuran (3 ml) was added. After being stirred at 0 °C for 20 min, the reaction mixture was quenched by the addition of pH 7 phosphate buffer. The separated aqueous layer was extracted with ether, and the combined organic phase was washed with water and brine, dried and then concentrated. Purification by silica gel chromatography (ether/hexane, 1:3) afforded Segment B **38** (116 mg, 71%). IR (KBr) ν_{max} 2962, 1616, 1589, 1517, 1464, 1368, 1302, 1249, 1173, 1089, 1036, 911, 829 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.99 (3H, d, J = 7 Hz, H-26), 1.05 (3H, d, J = 7 Hz, H-26), 1.12 (3H, d, J = 7 Hz, C_{19}-CH_3), 1.85-2.13 (3H, m, $SCH_2CH_2CH_2S$, H-25), 2.26 (1H, qn, J = 7 Hz, H-19), 2.42 (1H, dd, J = 5, 3 Hz, one of H-17), 2.56 (1H, dd, J = 16, 2 Hz, one of H-21), 2.68 (1H, dd, J = 5, 4 Hz, one of H-17), 2.69 (1H, dd, J = 16, 8 Hz, one of H-21), 2.73-3.04 (4H, m, $SCH_2CH_2CH_2S$), 3.28 (1H, ddd, J = 7, 4, 3 Hz, H-

18), 3.47 (3H, s, OC*H*$_3$), 3.51-3.58 (2H, m, H-23, H-24), 3.79 (3H, s, Ar-OC*H*$_3$), 4.82 (1H, ddd, *J* = 8, 5, 2 Hz, H-22), 5.84 (1H, s, OC*H*O), 6.87 (2H, d, *J* = 9 Hz, ArH), 7.42 (2H, d, *J* = 9 Hz, ArH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.6, 15.7, 19.5, 24.9, 25.4, 26.1, 28.3, 30.6, 41.8, 45.1, 52.8, 55.2, 57.6, 58.1, 71.5, 76.0, 79.3, 94.3, 113.4, 127.5, 131.3, 159.7. HRMS (FAB, *m*-nitrobenzyl alcohol) calcd for $C_{24}H_{37}O_5S_2$ $(M+H)^+$ 469.2116, found 469.2102. $[\alpha]_D^{22}$ +47.8° (*c* 0.40, $CHCl_3$).

[2*R*,2[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*],5*S*,6*S*,9*R*,10*S*,11*R*]-2-[3,9-dimethyl-8-[3-(2-methyl-1,3-dithian-2-yl)butyl]-1,7-dioxaspiro[5,5]undecan-2-yl]-10-methoxy-9,11-(4-methoxybenzylidenedioxy)-6,12-dimethyl-7-(1,3-dithian-2-yl)-5-tridecanol (40).

Starting from Segment C **3** (58 mg, 0.11 mmol), *n*-butyllithium (1.68 M solution in hexane, 0.09 ml, 0.16 mmol), boron trifluoride etherate (0.02 ml, 0.16 mmol), Segment B **38** (10 mg. 0.021 mmol) and tetrahydrofuran (3.5 ml), the coupling product **39** (17 mg, 78%) was obtained by the same procedure described before.

Starting from **39** (23 mg, 0.023 mmol), sodium amalgam (5%) and methanol (1.5 ml), **40** (14 mg, 71%) was isolated by the same procedure described before. IR (KBr) ν_{max} 3467, 2931, 1615, 1518, 1459, 1380, 1302, 1251, 1173, 1091, 1036, 986, 829 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.83 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.88 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.99 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.00 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.04 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.10 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.16 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.24-2.15 (25H, m), 1.56 (3H, s, H-1), 2.24 (1H, m, H-19), 2.56 (1H, brd, J = 16 Hz, one of H-21), 2.72-3.00 (9H, m, SC*H*$_2$CH$_2$C*H*$_2$S, one of H-21), 3.24 (1H, td, J = 10, 3 Hz, H-6), 3.36 (1H, dd, *J* = 10, 2 Hz, H-14), 3.46 (3H, s, OC*H*$_3$), 3.54-3.57 (2H, m, H-23, H-24), 3.72 (1H, m, H-22), 3.78 (3H, s, Ar-OC*H*$_3$), 4.77 (1H, m, H-18), 5.80 (1H, s, OC*H*O), 6.85 (2H, d, *J* = 9 Hz, ArH), 7.41 (2H, d, *J* = 9 Hz, ArH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 11.0, 12.3, 14.3, 15.6, 16.7, 18.0, 19.4, 23.4, 24.6, 25.6, 25.7, 25.9, 26.25, 26.33, 26.8, 27.5, 27.6, 28.2, 28.3, 28.6, 30.1, 30.3, 31.7, 32.0, 34.8, 34.9, 36.1, 41.4, 45.0, 54.8, 55.2, 57.8, 58.0, 71.5, 72.8, 74.5, 75.1, 75.6, 79.3, 94.8, 95.7, 113.6, 127.7, 130.7, 160.0. HRMS (FAB, *m*-nitrobenzyl alcohol) calcd for $C_{47}H_{79}O_7S_4$ $(M+H)^+$ 883.4708, found 883.4687. $[\alpha]_D^{26}$ -9.6° (*c* 0.20, $CHCl_3$).

[3*R*,4*S*,5*R*,8*S*,9*S*,12*R*,12[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-9-(*tert*-Butyldimethylsilyl)oxy-12-[3,9-dimethyl-8-[3-(2-methyl-1,3-dithian-2-yl)butyl]-1,7-dioxaspiro[5,5]undecan-2-yl]-4-methoxy-2,8-dimethyl-7-(1,3-dithian-2-yl)-tridecan-3,5-diol (41).

To a solution of **40** (21 mg, 0.025 mmol) in dichloromethane (1.5 ml) cooled to 0 °C were added *N,N*-diisopropylethylamine (0.017 ml, 0.096 mmol) and *t*-butyldimethylsilyl trifluoromethanesulfonate (0.017 ml, 0.072 mmol). After being stirred for 30 min, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and the separated aqueous layer was extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated under reduced pressure to afford crude *t*-butyldimethylsilyl ether (30 mg).

Pyridinium *p*-toluenesulfonate (10 mg, 0.032 mmol) was added to a solution of the crude *t*-butyldimethylsilyl ether (30 mg) in methanol (1 ml). After being stirred at room temperature overnight and then heated at 50 °C for 1 h, the reaction mixture was poured into saturated aqueous sodium hydrogencarbonate and then extracted with ether. The combined organic phase was washed with water and brine, dried and then

concentrated to give a residue which was purified by preparative thin layer chromatography (ether/hexane, 1:1) to afford **41** (16 mg, 77%, 2 steps). IR (KBr) ν_{max} 3433, 2929, 1463, 1379, 1255, 1099, 1006, 834, 775 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.07 (3H, s, SiC*H*$_3$), 0.10 (3H, s, SiC*H*$_3$), 0.82 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.88 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.89 (9H, s, Si*tBu*), 0.96 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.01 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.04 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.06 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.10 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.13-2.13 (25H, m), 1.58 (3H, s, H-1), 2.22 (1H, dd, J = 16, 1 Hz, one of H-21), 2.22 (1H, m, H-19), 2.66-3.17 (8H, m, SC*H*$_2$CH$_2$C*H*$_2$S), 2.79 (1H, dd, *J* = 16, 9 Hz, one of H-21), 3.16 (1H, dd, *J* = 7, 3 Hz, H-23), 3.26 (1H, td, *J* = 9, 3 Hz, H-6), 3.37 (1H, dd, *J* = 10, 2 Hz, H-14), 3.45 (3H, s, OC*H*$_3$), 3.47 (1H, brd, *J* = 5 Hz, OH), 3.63 (1H, m, H-24), 4.22-4.34 (3H, m, H-18, H-22, OH). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -4.3, -3.8, 7.9, 10.8, 14.2, 16.9, 17.1, 18.0, 19.6, 23.5, 25.0, 25.6, 25.9, 26.3, 26.3, 26.7, 26.8, 27.5, 27.6, 28.3, 29.4, 30.4, 31.5, 31.8, 34.9, 35.2, 36.1, 41.3, 46.8, 54.8, 55.5, 58.1, 68.5, 73.8, 74.4, 75.3, 75.4, 81.5, 95.7. HRMS (FAB, *m*-nitrobenzyl alcohol) calcd for $C_{45}H_{87}O_6S_4Si$ $(M+H)^+$ 879.5154, found 879.5142. $[\alpha]_D^{23}$ -37.8° (*c* 0.15, $CHCl_3$).

[3*R*,4*S*,5*R*,8*S*,9*S*,12*R*,12[2*S*,3*S*,6*R*,8*S*,8(3*S*),9*R*]]-9-(*tert*-Butyldimethylsilyl)oxy-12-[3,9-dimethyl-8-[3-(2-methyl-1,3-dithian-2-yl)butyl]-1,7-dioxaspiro[5,5]undecan-2-yl]-5-hydroxy-4-methoxy-2,8-dimethyl-7-(1,3-dithian-2-yl)tridecan-3-yl (3*R*)-3-(*tert*-butyldimethylsilyl) oxy-3-(2,5-dihydro-4-methyl-2,5-dioxofuran-3-yl)-propionate (42).

2,4,6-Trichlorobenzoyl chloride (9.0 μl, 0.053 mmol) was added to a solution of Segment A **12** (11 mg, 0.035 mmol) and triethylamine (9.0 μl, 0.063 mmol) dissolved in toluene (1 ml) at room temperature. After stirring for 2 h, a solution of **41** (23 mg, 0.026 mmol) in toluene (1 ml) and 4-dimethylaminopyridine (7 mg, 0.053 mmol) in toluene (0.5 ml) were added. After being stirred for 30 min at room temperature, the mixture was diluted with water, adjusted to pH 3 by 1N HCl and then extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated to give a residue which was purified by silica gel chromatography (ether/hexane, 2:3) to provide **42** (27 mg, 88' IR (KBr) ν_{max} 2931, 1771, 1734, 1464, 1378, 1255, 1182, 1100, 912, 836, 776, 730 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.02 (3H, s, SiC*H*$_3$), 0.06 (3H, s, SiC*H*$_3$), 0.07 (3H, s, SiC*H*$_3$), 0.12 (3H, s, SiC*H*$_3$), 0.82 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.85 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.85 (9H, s, Si*t-Bu*), 0.87 (9H, s, Si*t-Bu*), 0.92 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 0.93 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.03 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.04 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.10 (3H, d, *J* = 7 Hz, CHC*H*$_3$), 1.09-2.22 (26H, m), 1.59 (3H, s, H-1), 2.22 (3H, s, Ar-C*H*$_3$), 2.60-3.13 (12H, m, H-2', H-21, SC*H*$_2$CH$_2$C*H*$_2$S), 3.20 (1H, dd, *J* = 7, 3 Hz, H-23), 3.26 (1H, td, *J* = 9, 3 Hz, H-6), 3.37 (1H, dd, *J* = 10, 2 Hz, H-14), 3.44 (3H, s, OC*H*$_3$), 4.04 (1H, m, H-22), 4.22 (1H, m, H-18), 5.09 (1H, dd, *J* = 7, 5 Hz, H-24), 5.16 (1H, dd, *J* = 7, 6 Hz, H-3'). ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -5.2, -4.9, -4.3, -3.8, 7.7, 10.2, 10.8, 14.2, 16.8, 16.9, 17.9, 17.9, 18.0, 19.7, 23.6, 25.1, 25.6, 25.6, 25.8, 26.0, 26.3, 26.3, 26.6, 26.8, 27.4, 27.6, 28.3, 28.3, 29.4, 30.4, 31.3, 31.7, 34.8, 35.2, 36.1, 39.0, 41.2, 41.4, 46.7, 54.8, 55.6, 59.4, 62.9, 67.5, 73.7, 74.4, 75.3, 75.9, 81.9, 95.7, 142.4, 143.5, 164.1, 165.9, 169.3. FAB-MS (*m*-nitrobenzyl alcohol, NaI) m/z 1197 $(M+Na)^+$. $[\alpha]_D^{24}$ -17.3° (*c* 0.17, $CHCl_3$).

Total Synthesis of Tautomycin (1).

A solution of **42** (15 mg, 0.012 mmol) dissolved in tetrahydrofuran (1 ml) was transferred into a teflon vial. Pyridinium poly(hydrogen fluoride) (8 drops) was added to this solution at room temperature. After being

stirred overnight, the reaction mixture was neutralized by saturated aqueous sodium hydrogencarbonate to pH 3 and then extracted with ether. The combined organic phase was washed with water and brine, dried and then concentrated. The residue was immediately dissolved in a mixture of acetonitrile (0.7 ml) and water (0.07 ml). Mercury (II) perchlorate trihydrate (17 mg, 0.037 mmol) and calcium carbonate (6.0 mg, 0.060 mmol) were added at room temperature. After being stirred for 5 min, the mixture was diluted with ether and then filtered through Celite. The filtrate was concentrated, and the resulting residue was purified by silica gel chromatography (0.8 g, ethyl acetate/hexane, 1:1) to afford tautomycin **1** (6.0 mg, 62%, 2 steps). IR (KBr) ν_{max} 3470, 2932, 1830, 1768, 1739, 1710, 1458, 1381, 1256, 1231, 1179, 1099, 1022, 987, 908, 732 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 0.80 (3H, d, *J* = 6.6 Hz, CHC*H*$_3$), 0.89 (3H, d, *J* = 7.0 Hz, CHC*H*$_3$), 0.97 (3H, d, *J* = 7.2 Hz, CHC*H*$_3$), 0.98 (3H, d, *J* = 7.0 Hz, CHC*H*$_3$), 0.99 (1H, m, one of H-16), 1.00 (3H, d, *J* = 6.5 Hz, CHC*H*$_3$), 1.10 (3H, d, *J* = 6.9 Hz, CHC*H*$_3$), 1.11 (3H, d, *J* = 7.0 Hz, CHC*H*$_3$), 1.20-2.12 (20H, m), 2.11 (1H, m, H-25), 2.15 (3H, s, H-1), 2.27 (3H, d, *J* = 1.3 Hz, 5'-C*H*$_3$), 2.53 (1H, sext, *J* = 6.8 Hz, H-3), 2.67 (1H, m, H-19), 2.67 (1H, dd, *J* = 17.5, 4.2 Hz, one of H-21), 2.78 (1H, dd, *J* = 16.3, 9.8 Hz, one of H-2'), 2.92 (1H, dd, *J* = 16.3, 3.4 Hz, one of H-2'), 2.99 (1H, dd, *J* = 17.5, 8.4 Hz, one of H-21), 3.16 (1H, td, *J* = 9.7, 2.4 Hz, H-6), 3.28 (1H, dd, *J* = 6.0, 2.0 Hz, H-23), 3.28 (1H, dd, *J* = 9.9, 2.2 Hz, H-14), 3.44 (3H, s, OC*H*$_3$), 3.70 (1H, td, *J* = 8.0, 2.9 Hz, H-18), 4.35 (1H, ddd, *J* = 8.4, 4.2, 2.0 Hz, H-22), 5.10 (1H, t, *J* = 6.0 Hz, H-24), 5.21 (1H, m, H-3').[19] ^{13}C NMR ($CDCl_3$, 150.9 MHz) δ 10.13, 10.99, 13.71, 16.20, 16.69, 17.87, 17.95, 19.42, 26.80, 27.45, 27.67, 28.11, 28.14, 28.75, 29.06, 30.22, 30.69, 31.48, 34.81, 34.85, 36.07, 40.95, 45.84, 47.33, 52.41, 59.07, 63.95, 66.47, 74.30, 74.33, 74.77, 76.56, 80.69, 95.69, 142.09, 142.96, 164.82, 165.77, 169.57, 213.05, 215.25. FAB-MS (*m*-nitrobenzyl alcohol, NaI) m/z 789 (M+Na). HRMS (FAB, *m*-nitrobenzyl alcohol+glycerine) calcd for $C_{41}H_{65}O_{12}$ $(M+H-H_2O)^+$ 749.4476, found 749.4457. $[\alpha]_D^{27}$ +3.5° (*c* 0.315, $CHCl_3$). *lit* .$[\alpha]_D^{25}$ +3.4° (*c* 1, $CHCl_3$).[1]

ACKNOWLEDGMENTS

We are grateful to Prof. K. Isono at Tokai University and Prof. M. Ubukata at Toyama Prefecture University for supplying a sample of tautomycin and spectroscopic data. We also thank to Dr. Sugiyama and Dr. Ohtani for their spectroscopic analysis and chromatographic purification of tautomycin and its related compounds. We appreciate the supports from JSPS-RFTF ("Research for the Future" program) 96L00504 and Grant-In-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan and Iyaku-Shigen-Shinkoh-Zaidan. Research Fellowships of Japan Society for the Promotion of Science for Young Scientists to K. T. are gratefully acknowledged. Y. J. expresses his gratitude to scholarship from the Ministry E.S.C.J. and Iyaku-Shigen-Shinkoh-Zaidan.

REFERENCES AND NOTES

1. (a) Ubukata, M.; Cheng, X.-C.; Isono, K. *J. Chem. Soc., Chem. Commun.* **1990**, 244. (b) Cheng, X.-C.; Ubukata, M.; Isono, K. *J. Antibiot.* **1990**, *43*, 809. (c) Ubukata, M.; Cheng, X.-C.; Isobe, M.;

Isono, K. *J. Chem. Soc., Perkin Trans. 1* **1993**, 617. (d) Ichikawa, Y.; Isobe, M.; Ubukata, M.; Isono, K. *Biosci. Biotech. Biochem.* **1993**, *57*, 1382.

2. Total synthesis, see: (a) Oikawa, H.; Oikawa, M.; Ueno, T.; Ichihara, A. *Tetrahedron Lett.* **1994**, *35*, 4809. (b) Oikawa, M.; Ueno, T.; Oikawa, H.; Ichihara, A. *J. Org. Chem.* **1995**, *60*, 5048. (c) Ichikawa, Y.; Tsuboi, K.; Jiang, Y.; Naganawa, A.; Isobe, M. *Tetrahedron Lett.* **1995**, *36*, 7101. (d) Shimizu, S.; Nakamura, S.; Nakada, M.; Shibasaki, M. *Tetrahedron* **1996**, *52*, 13363. Synthetic studies, see: (e) Oikawa, M.; Oikawa, H.; Ichihara, A. *Tetrahedron Lett.* **1993**, *34*, 4797. (f) Ueno, T.; Oikawa, M.; Oikawa, H.; Ichihara, A. *Biosci. Biotech. Biochem.* **1995**, *59*, 2104. (g) Nakamura, S.; hibasaki, M. *Tetrahedron Lett.* **1994**, *35*, 4145. (h) Maurer, K. W.; Armstrong, R. W. *J. Org. Chem.* **1996**, *61*, 3106.
3. Segment A; (a) Ichikawa, Y.; Naganawa, A.; Isobe, M. *Synlett* **1993**, 737. (b) Ichikawa, Y.; Tsuboi, K.; Naganawa, A.; Isobe, M. *Synlett* **1993**, 907. (c) Naganawa, A.; Ichikawa, Y.; Isobe, M. *Tetrahedron* **1994**, *50*, 8969. Segment C; (d) Jiang, Y.; Ichikawa, Y.; Isobe, M. *Synlett* **1995**, 285. (e) Jiang , Y.; Isobe, M. *Tetrahedron* **1996**, *52*, 2877.
4. This epimerization was confirmed from the ^{1}H NMR analysis that H-14 of **3** appeared at 3.49 ppm and that of 3-epimer at 3.40 ppm, respectively.
5. (a) Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391. (b) Eis, M. J.; Wrobel, J. E.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3693.
6. Oikawa, Y; Yoshioka, T.; Yonemitsu, O. *Tetrahedron Lett.* **1982**, *23*, 885.
7. (a) Normant, J. F.; Foullon, J. P.; Deshayes, H. *Compt. Rend., C* **1969**, *269*, 1325. (b) See the reference 3(a).
8. (a) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989. (b) Hikota, M.; Tone, H.; Horita, K.; Yonemitsu, O. *J. Org. Chem.* **1990**, *55*, 7. (c) Hikota, M; Sakurai, Y.; Horita, K.; Yonemitsu, O. *Tetrahedron Lett.* **1990**, *31*, 6367.
9. Corey, E, J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
10. Georgiadis, M. P.; Couladouros, E. A. *J. Org. Chem.* **1986**, *51*, 2725.
11. The structure of **19** was tentatively assigned, and we can not exclude another possibility (R_1 = succinimide and R_2 = OH).
12. Froborg, J.; Magnusson, G.; Thoren, S. *J. Org. Chem.* **1975**, *40*, 122.
13. See the preceding paper.
14. Sugiyama, Y.; Ohtani, I. I.; Isobe, M.; Takai, A.; Ubukata, M.; Isono, K. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 3.
15. Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O.*Tetrahedron* **1986**, *42*, 3021.
16. (a) Lipshutz, B. H.; Moretti, R.; Crow, R. *Tetrahedron Lett.* **1989**, *30*, 15. (b) Bernardi, R.; Ghiringhelli, D. *J. Org. Chem.* **1987**, *52*, 5021.
17. (a) Isobe, M.; Sugiyama, Y.; Ito, T.; Ohtani, I. I.; Toya, Y.; Nishigohri, Y.; Takai, A. *Biosci. Biotech. Biochem.* **1995**, *59*, 2235. (b) Sugiyama, Y.; Fujimoto, K.; Ohtani, I. I.; Takai, A.; Isobe, M. *Biosci. Biotech. Biochem.* **1996**, *60*, 1260.
18. (a) Takai, A.; Murata, M.; Torigoe, K.; Isobe, M.; Mieskes, G.; Yasumoto, T. *Biochem. J.* **1992**, *284*, 539. (b) Takai, A.; Sasaki, K.; Nagai, H.; Mieskes, G.; Isobe, M.; Isono, K.; Yasumoto, T. *Biochem. J.* **1995**, *306*, 657.

19. The spectra were identical with those of natural tautomycin; and the assignments were referred to following paper. (1) Cheng, X.-C.; Ubukata, M.; Isono, K. *J. Antibiot.* **1990**, *43*, 809. (2) Ohtani, I. I.; Isobe, M. unpublished result.

(*Received in Japan* 20 *December* 1996; *accepted* 26 *February* 1997)