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Synthetic Studies on Tautomycin. Stereoselective Construction of the C_1-C_{26} Region

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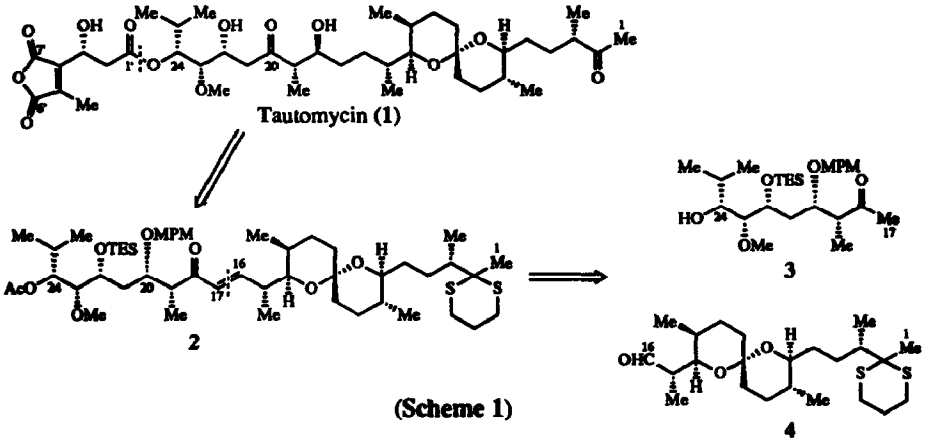
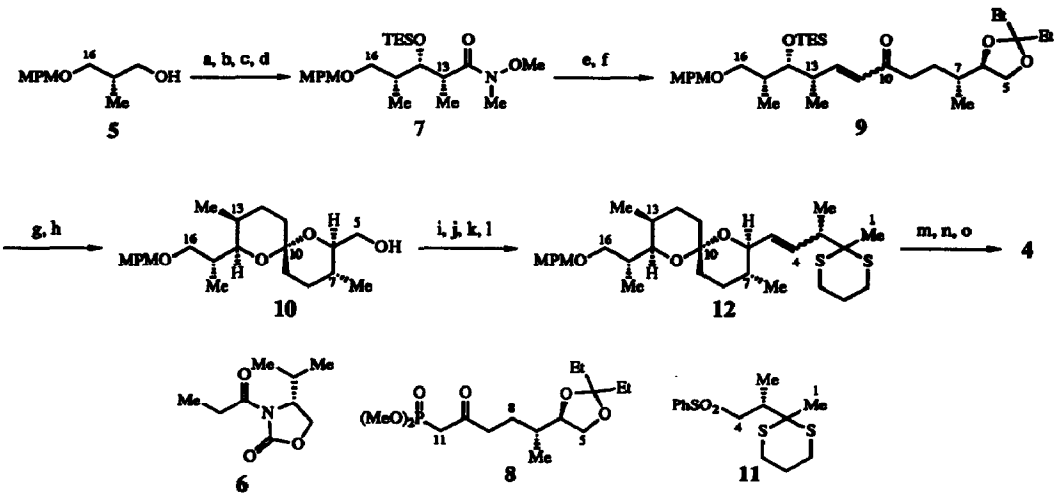
Abstract: A convergent, stereocontrolled synthesis of the C_1-C_{26} portion of tautomycin has been achieved through the coupling of the fragments **3** and **4** by an aldol condensation.

Isono and co-workers reported the isolation of the novel antifungal antibiotic tautomycin (**1**) from a culture of *Streptomyces spiroverticillatus*[1] and more recently determined its structure.[2] It also exhibits a specific inhibition of protein phosphatases 1 and 2A.[3] This interesting biological activity and its unique structure has tempted chemists to effect its total synthesis.[4] To date, however, no such completed synthesis has been reported. Herein we describe our studies directed toward the synthesis of the polyketide portion of this molecule.



Retrosynthetic disconnection of the C_{16}-C_{17} bond generated two fragments of comparable complexity, namely the methyl ketone **3** and the aldehyde **4** (Scheme 1). Due to the potential ease of dehydration and retroaldol reaction about the C_{20} carbonyl moiety, we decided to incorporate it as a reduced form.

The synthesis of the C_1-C_{16} fragment began with Swern oxidation[5] of the known alcohol **5**[6] (Scheme 2). Auxiliary-based aldol reaction,[7] subsequent transamination[8] and protection with TESCl afforded **7** as an 8:1 mixture of two diastereomers. Reduction of **7**, followed by Masamune-modified Horner-Emmons reaction[9] with **8**[10] furnished the α,β-unsaturated ketone **9**, which was hydrogenated with Raney Ni (W2). Treatment with a catalytic amount of CSA in MeOH at room temperature then resulted in removal of the TES group and pentylidene acetal, spiroketalization in one-pot, to give thermodynamically favored product **10** as a single isomer. Swern oxidation and Julia olefination[11] with the sulfone **11**[12] provided **12** as a mixture of olefin isomers. Hydrogenation of **12**, deprotection of the MPM group with DDQ[13] and Parikh-Doering oxidation[14]



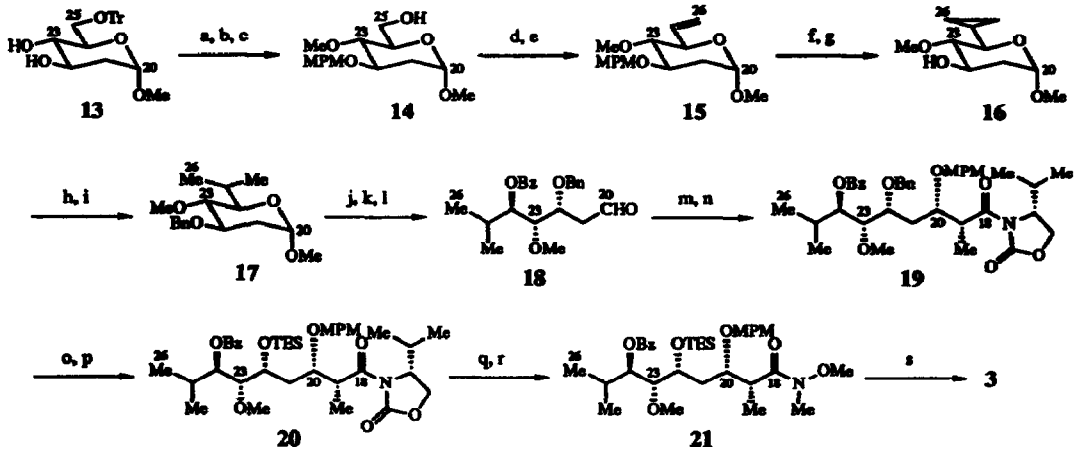
(a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 0 °C, 97%; (b) **6**, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, -78 to 0 °C, 94% (*diastereoselection* 89:11); (c) $AlMe_3$, MeONHMe-HCl, THF, -30 °C to r.t.; (d) TESCl, imidazole, DMF, r.t., 84% (2 steps); (e) DIBALH, THF, -78 °C, 99%; (f) **8**, LiCl, *i*-Pr_2NEt, CH_3CN, r.t., 97%; (g) H_2, Raney Ni (W2), AcOEt, quant.; (h) CSA, MeOH, r.t., 98%; (i) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 to 0 °C, 97%; (j) **11**, *n*-BuLi (2 equiv.), THF, -78 to 0 °C; (k) Ac_2O, Py, DMAP, CH_2Cl_2; (l) 5% Na-Hg, Na_2HPO_4, THF-MeOH (3:1), -20 to 0 °C, 42% (3 steps); (m) H_2, $(Ph_3P)_3RhCl$, PhH, 79%; (n) DDQ, CH_2Cl_2-H_2O (18:1), 97%; (o) SO_3•Py, DMSO, Et_3N, quant.

(Scheme 2)

completed the synthesis of the C_1-C_{16} fragment **4**.[15]

The C_{17}-C_{26} fragment was synthesized by the route outlined in Scheme 3. Monoprotection of the diol **13**[16] via formation of a stannylene acetal, followed by *O*-methylation and removal of the trityl ether, gave **14**. Introduction of the isopropyl group was successfully achieved through a cyclopropanation-ring fission process. Hence the aldehyde, generated by Swern oxidation of **14**, was subjected to the olefination reaction developed by Nozaki[17] to afford **15**. Cyclopropanation of **15** was carried out almost quantitatively using the conditions of Suda.[18] Removal of the MPM group with DDQ then gave **16**. Regioselective opening of the cyclopropane ring was achieved by hydrogenolysis with a catalytic amount of PtO_2 and the C_{22}-alcohol was protected with a Bn group; the only protecting group which would be resistant to the conditions utilized later. Transformation to the acyclic compound **18** was accomplished by transacetalization with $HS(CH_2)_3SH$, protection of the liberated alcohol with BzCl and removal of the thioacetal group. Subsequent diastereoselective aldol reaction and MPM protection under acidic conditions[19] gave **19**. At this juncture, in order to make it easy to carry out the deprotection at the last stage, exchange of the C_{22} protecting group was accomplished through the selective deprotection of Bn group with Raney Ni (W2) followed by reprotection with TESOTf. Hydrolytic removal of the chiral auxiliary with basic hydrogen peroxide[20] and direct conversion to the Weinreb's amide with DEPC[21] afforded **21**. Finally, treatment with MeLi provided the C_{17}-C_{26} fragment **3**.[22]

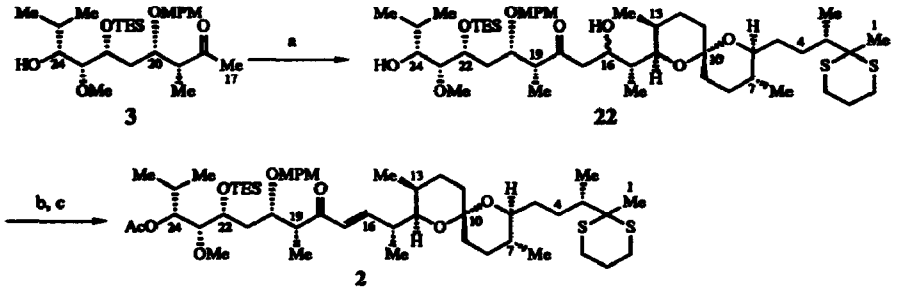
With the two fragments **3** and **4** in hand, their coupling reaction was then investigated (Scheme 4).[23] Methylketone **3** was metalated with two equiv of LDA and the aldehyde **4** was added to the resulting enolate to give the aldol adduct **22** as a mixture of diastereomers with almost no selectivity (55:45). The aldol **22** was



(a) *n*-Bu_2SnO, PhMe, reflux; CsF, MPMBr, DMF, r.t., 85%; (b) NaH, MeI, THF, 0 °C to r.t., 97%; (c) HCO_2H-Et_2O-THF (4:3:1), r.t., 84%; (d) $(COCl)_2$, DMSO, *i*-Pr_2NEt, CH_2Cl_2, -78 to 0 °C, 97%; (e) Zn, CH_2I_2, $AlMe_3$, THF, 0 °C, 68%; (f) CH_2N_2, $Pd(OAc)_2$, Et_2O, 0 °C; 99%; (g) DDQ, CH_2Cl_2-H_2O (18:1), 93%; (h) H_2, PtO_2, AcOH, 91%; (i) NaH, BnBr, THF-DMF, 0 °C to r.t., 98%; (j) $HS(CH_2)_3SH$, BF_3•OEt_2, CH_2Cl_2, 0 °C to r.t., 81%; (k) BzCl, Py, DMAP, CH_2Cl_2; (l) NBS, Me_2CO-H_2O (19:1), 86% (2 steps); (m) **6**, *n*-Bu_2BOTf, Et_3N, CH_2Cl_2, -78 to 0 °C, 90%; (n) $Cl_3CC(NH)OMPM$, TfOH, Et_2O, r.t., 86%; (o) H_2, Raney Ni (W2), EtOH, 84%; (p) TESOTf, Et_3N, CH_2Cl_2, 0 °C, 92%; (q) LiOH, 30% H_2O_2, THF-H_2O (3:1), 0 °C to r.t.; (r) MeONHMe-HCl, DEPC, Et_3N, DMF, 0 °C to r.t., 79% (2 steps); (s) MeLi, THF, -78 °C, 92%.

(Scheme 3)

diacetylated and treated with DBU to afford **2**[24] possessing all the functionalities required for the total synthesis. Further studies to achieve the completion of the total synthesis of tautomycin are currently in progress.



(a) **3** (1.3 equiv.), LDA (2.6 equiv.), THF, -78 °C then **4**, 65%; (b) Ac_2O, DMAP, CH_2Cl_2, 0 °C to r.t.; (c) DBU, CH_2Cl_2, 0 °C to r.t., 87% (2 steps).

(Scheme 4)

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10. The β-ketophosphonate **8** was prepared from (2*R*, 3*R*)-3-methylbutane-1,2,4-triol[25] in 5 steps. (1) $Et_2C(OMe)_2$, CSA, CH_2Cl_2, r.t., 83%; (2) Swern oxidation; (3) $(i\text{-PrO})_2P(O)CH_2CO_2Et$, *t*-BuOK, THF, -78 °C to r.t., 93% (2 steps); (4) H_2, 10%-Pd/C, EtOH, 94%; (5) $(MeO)_2P(O)CH_3$, *n*-BuLi, THF, -78 °C, quant.
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12. The sulfone **11** was prepared from (*S*)-methyl 3-hydroxy-2-methylpropionate in 6 steps. (1) PhSSPh, $n\text{-}Bu_3P$, THF, 0 °C to r.t., 98%; (2) $AlMe_3$, MeONHMe·HCl, CH_2Cl_2, reflux, 95%; (3) MeLi, THF, -78 °C, 99%; (4) $HO(CH_2)_2OH$, PPTS, PhH, reflux, 99%; (5) *m*-CPBA, $NaHCO_3$, CH_2Cl_2, 0 °C, quant.; (6) $HS(CH_2)_3SH$, $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to r.t., 87%.
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15. ^{1}H-NMR data of **4** ($CDCl_3$, 400MHz): δ 9.69 (d, 1H, *J* = 3.5 Hz, C_{16}-*H*), 3.99 (dd, 1H, *J* = 2.3 and 10.0 Hz, C_{14}-*H*), 3.21 (m, 1H, C_6-*H*), 2.74-2.97 (m, 4H, $SCH_2CH_2CH_2S$), 2.55 (ddq, 1H, *J* = 3.5, 6.8, and 10.0 Hz, C_{15}-*H*), 1.97-2.18 (m, 4H), 1.86 (m, 1H, one of SCH_2CH_2), 1.63 (s, 3H, C_1-H_3), 1.25-1.76 (m, 12H), 1.21 (d, 3H, *J* = 6.8 Hz, C_{15}-CH_3), 1.11 (d, 3H, *J* = 6.8 Hz, C_3-CH_3), 0.95 (d, 3H, *J* = 7.0 Hz, C_{13}-CH_3), 0.85 (d, 3H, *J* = 6.6 Hz, C_7-CH_3).
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22. ^{1}H-NMR data of **3** ($CDCl_3$, 400MHz): δ 7.23 (m, 2H), 6.87 (m, 2H), 4.45 (s, 2H, $ArCH_2$), 4.18 (ddd, 1H, *J* = 3.3, 6.2, and 6.6 Hz, C_{22}-*H*), 3.89 (ddd, 1H, *J* = 4.5, 5.8, and 7.0 Hz, C_{20}-*H*), 3.80 (s, 3H, $ArOCH_3$), 3.62 (ddd, 1H, *J* = 2.5, 2.8, and 8.6 Hz, C_{24}-*H*), 3.59 (d, 1H, *J* = 2.5 Hz, C_{24}-O*H*), 3.36 (s, 3H, C_{23}-OCH_3), 3.11 (dd, 1H, *J* = 3.3 and 8.6 Hz, C_{23}-*H*), 2.78 (dq, 1H, *J* = 4.5 and 7.0 Hz, C_{19}-*H*), 2.17 (s, 3H, C_{17}-H_3), 2.04 (ddd, 1H, *J* = 5.8, 6.2, and 14.4 Hz, one of C_{21}-*H*), 1.89 (dqq, 1H, *J* = 2.8, 6.8, and 6.8 Hz, C_{25}-*H*), 1.79 (ddd, 1H, *J* = 6.6, 7.0, and 14.4 Hz, one of C_{21}-*H*), 1.14 (d, 3H, *J* = 7.0 Hz, C_{19}-CH_3), 0.983 (d, 3H, *J* = 6.8 Hz, C_{26}-H_3), 0.978 (t, 9H, *J* = 7.9 Hz, $Si(CH_2CH_3)_3$), 0.92 (d, 3H, *J* = 6.8 Hz, C_{25}-CH_3), 0.66 (q, 6H, *J* = 7.9 Hz, $Si(CH_2CH_3)_3$).
23. At first we synthesized the C_{17}-C_{26} fragment as a β-ketophosphonate, but all attempts to couple with **4** by a Horner-Emmons reaction were unsuccessful.
24. ^{1}H-NMR data of **2** ($CDCl_3$, 400MHz): δ 7.23 (m, 2H), 6.85 (m, 2H), 6.80 (dd, 1H, *J* = 9.5 and 15.7 Hz, C_{16}-*H*), 6.31 (d, 1H, *J* = 15.7 Hz, C_{17}-*H*), 5.03 (dd, 1H, *J* = 3.7 and 7.2 Hz, C_{24}-*H*), 4.45 (d, 1H, *J* = 11.3 Hz, one of $ArCH_2$), 4.43 (d, 1H, *J* = 11.3 Hz, one of $ArCH_2$), 3.96 (ddd, 1H, *J* = 3.3, 6.0, and 7.4 Hz, C_{22}-*H*), 3.82 (m, 1H, C_{20}-*H*), 3.80 (s, 3H, $ArOCH_3$), 3.59 (dd, 1H, *J* = 2.0 and 10.3 Hz, C_{14}-*H*), 3.41 (s, 3H, C_{23}-OCH_3), 3.27 (dd, 1H, *J* = 3.3 and 7.2 Hz, C_{23}-*H*), 3.22 (m, 1H, C_6-*H*), 2.87-3.00 (m, 3H, C_{19}-*H*, two of $SCH_2CH_2CH_2S$), 2.73-2.83 (m, 2H, two of $SCH_2CH_2CH_2S$), 2.42 (ddq, 1H, *J* = 6.5, 9.5, and 10.3 Hz, C_{15}-*H*), 1.99 (s, 3H, C_{24}-$OCOCH_3$), 1.65 (s, 3H, C_1-H_3), 1.24-2.16 (m, 20H), 1.17 (d, 3H, *J* = 6.8 Hz, C_{19}-CH_3), 1.16 (d, 3H, *J* = 6.5 Hz, C_{15}-CH_3), 1.10 (d, 3H, *J* = 6.8 Hz, C_3-CH_3), 0.95 (t, 9H, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$), 0.89-0.94 (m, 6H, C_{26}-H_3, C_{25}-CH_3), 0.82-0.88 (m, 6H, C_7-CH_3, C_{13}-CH_3), 0.61 (q, 6H, *J* = 8.0 Hz, $Si(CH_2CH_3)_3$).
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