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A Selective Baeyer-Villiger Oxidation: A Total Synthesis of (-)-Acetomycin

Frederick E. Ziegler* and Hakwon Kim

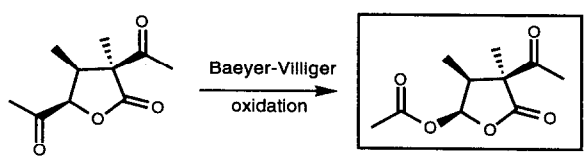
Sterling Chemistry Laboratory
Yale University, New Haven, CT 06511-8118 USA

Abstract: A short, stereoselective synthesis of (-)-acetomycin (**2**) from L-threonine is reported. The final step in the synthesis is a selective Baeyer-Villiger oxidation that discriminates between two methyl ketones.

(-)-Acetomycin (**2**), a small but richly functionalized antibiotic, has attracted renewed interest because of its *in vitro* activity against L1210 murine leukemia cells and HCT-8 human colon adenocarcinoma cells.[1] However, *in vitro* activity is destroyed by esterases, a process that presumably accounts for the the lack of activity *in vivo*.[2]

Acetomycin was first isolated from *Streptomyces ramulosus* by Prelog and his coworkers in 1958.[3] The Swiss group was able to demonstrate the gross structure of the antiobiotic[4] but the relative and absolute stereochemistry followed years later as a result of x-ray studies on a derivative[5] and, eventually, upon the natural product itself.[6]

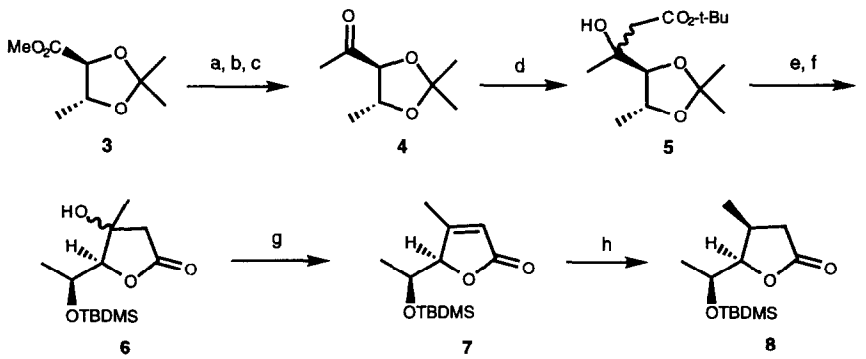
Tadano reported the first total synthesis of (-)-acetomycin and (+)-5-epi-acetomycin from D-glucose in 1990.[7] The acetoxy group was introduced in a displacement of the mesylate of an inseparable lactol mixture late in the synthesis. This process was improved in Uenishi's synthesis of (±)-acetomycin by a selective, crown ether-assisted displacement of a related lactol mesylate.[8] The two other diastereomers of acetomycin, 4-epi and 4, 5-di-epi, have been prepared.[7b,9] Because the introduction of the C_5 acetoxy group with control of stereochemistry proved to be problematic in the former study and dependent upon access to a lactol formed under thermodynamic control in the latter investigation, our synthetic approach to acetomycin (**2**) rested upon the premise that a selective Baeyer-Villiger oxidation (kinetic control) could be accomplished at C_5 of diketone **1** with retention of configuration rather than at C_3 owing to the reduced steric congestion at the C_3 locus. The presence of the lactone carbonyl and oxygen was expected to slow the rate of rearrangement at either site. In this Letter we present a synthesis of (-)-acetomycin that realizes this strategy.



1 **2**

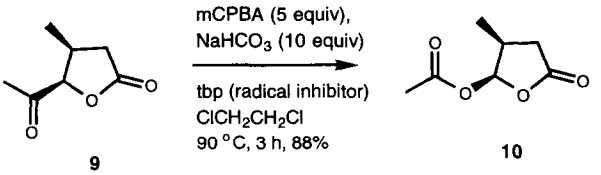
Methyl (4S)-trans-2,2,5-trimethyl-1,3-dioxolane-4-carboxylate (**3**), which is commercially available[10] or readily prepared from L-threonine,[11] was converted into the corresponding methyl ketone **4** in high yield by the method of Weinreb (Scheme 1).[12] Addition of t-butyl lithioacetate to ketone **4** followed by hydrolysis and selective

Scheme 1



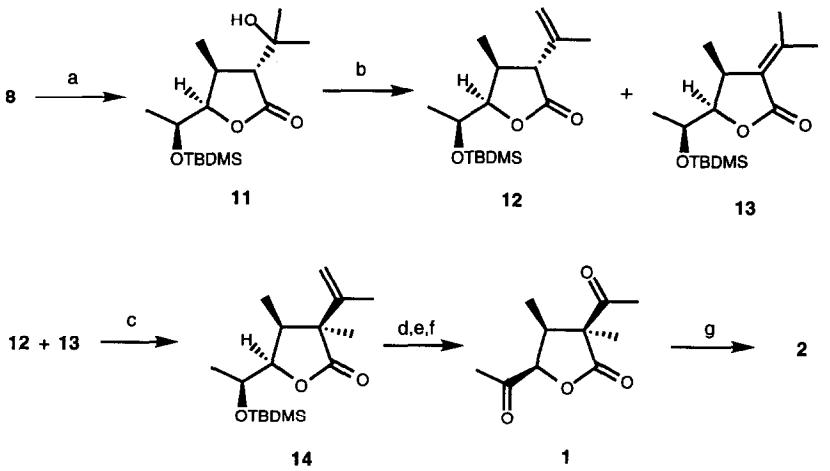
a) LiOH, aq. THF (92%). b) $ClCO_2$-i-Bu, N-methylmorpholine, THF, -15 °C; NH(OMe)Me·HCl, Et_3N, -15 °C--->0 °C (86%). c) MeMgBr, THF, -10 °C (75%). d) $LiCH_2CO_2$-t-Bu, THF, -78 °C (97%). e) aq. AcOH, 60 °C (74%). f) TBDMSOTf, pyr., CH_2Cl_2, 0 °C (100%). g) MsCl, Et_3N, CH_2Cl_2, -15 °C, 30 min.; Et_3N, -15 °C-->rt ; 2 h (97%). h) H_2, Rh/Al_2O_3, 50 psi, EtOAc (83%).

silylation gave the β-hydroxy γ-butyrolactone **6** as a mixture of diastereomers in 72% yield for the three steps. Dehydration of tertiary alcohol **6** to the butenolide **7** with methanesulfonyl chloride was not accompanied by epimerization.[13] Stereoselective hydrogenation as described by Hanessian[14] afforded the cis-substituted γ-butyrolactone **8** along with a minor amount of the desilylated alcohol of **8**.



With lactone **8** in hand, the opportunity arose to explore the principal tenet of the synthesis---the Baeyer-Villiger reaction. Desilylation of **8** (2% aq. HF/CH_3CN, rt, 72%) and oxidation (Dess-Martin periodinane, CH_2Cl_2, rt, 95%) provided keto lactone **9**. Baeyer-Villiger oxidation was effected under the Kishi-Goto conditions,[15] which employ 5-*tert*-butyl-4-hydroxy-2-methyl phenyl sulfide (tbp) as a radical inhibitor, to afford the cis-lactone **10** in 88% yield. The coupling constant of the C_5-H proton ($J_{4,5}$ = 5.2 Hz) of **10** was in accord with the coupling constant in acetomycin ($J_{4,5}$ = 5.0 Hz[5]; 5.1 Hz[8]; 5.5 Hz[7]; 5-epi-acetomycin, J = 6.2 Hz[7]).

Scheme 2



a) LDA, HMPA-THF, -78 °C; acetone, - 78 °C (93%). b) Et_3N, MsCl, -15 °C, 30 min; Et_3N, -15 °C ---> rt, 1 h. c) KH, THF, rt, 30 min; MeI, 18h, rt (74%). d) 2 % aq. HF/CH_3CN, rt, 30 min (92%). e) Dess-Martin periodinane, CH_2Cl_2, rt, 2 h (78%). f) O_3, CH_2Cl_2, -78 °C; Me_2S (77%). g) m-CPBA, $NaHCO_3$, tbp, $ClCH_2CH_2Cl$, 90 °C, 24 h (50%).

Condensation of the lithium enolate of lactone **8** with dry acetone provided a single tertiary alcohol that was assigned the stereochemistry of **11** owing to steric approach control considerations (Scheme 2). Dehydration of the β-hydroxylactone afforded approximately a 6:2:1 mixture (^1H NMR) of the β,γ-unsaturated lactone **12**, α,β-unsaturated lactone **13**, and a minor amount of an unidentified product, respectively. Although the two major components could be separated by chromatography and subsequently methylated, the direct methylation of the mixture with I_2-activated KH[16] proved to be advantageous. Only the single diastereomer **14** from alpha alkylation was detected and isolated. Desilylation and oxidation without epimerization afforded a ketolactone, which upon ozonolysis cleanly gave rise to the penultimate product of the synthesis, diketolactone **1**.

The Baeyer-Villiger oxidation of diketone **1** to (-)-acetomycin (**2**) under the Kishi-Goto conditions required more vigorous conditions for the consumption of **1** than were required in the formation of lactonic ester **10** from ketolactone **9**. Thus, oxidation at 90 °C for 24 hours afforded the labile (-)-acetomycin in 50% yield upon flash chromatography (1:2, EtOAc/hexane, 1% Et_3N). The IR, ^1H NMR, ^{13}C NMR, and optical rotation data were in accord with the reported data for (-)-acetomycin and they were distinctly different from the NMR values of the diastereomers.[5,7,8,9,17,18] No other products of oxidation were isolated.

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17 (-)-acetomycin (**2**): mp 100-101 °C, lit.[4b] 108-109 °C; lit.[5] 115-116 °C; $[\alpha]^{20}_D$ -139.3° (c 0.15, EtOH), $[\alpha]^{23}_D$ -148.5° (c 1.39, EtOH),[4b] $[\alpha]^{20}_D$ -157° (c 1.25, EtOH)[5]; IR (CHCl3) 1794, 1768, 1716 cm^{-1}; ^1H NMR (300 MHz) δ 6.59 (1H, d, J=5.3 Hz), 2.57 (dq, J=7.2, 5.4 Hz), 2.31, 2.13, 1.45 (3 x 3H), 1.07 (3H, d, J=7.3 Hz); ^{13}C NMR (75 MHz) 203.3, 176.9, 168.5, 94.0, 56.8, 45.5, 28.9, 21.0, 20.6, 9.4 ppm.

18 All new compounds gave satisfactory spectroscopic or combustion analysis data. ^1H NMRs were recorded at 300 MHz ($CDCl_3$). Partial data is provided: **4**: ^1H NMR (300 MHz) δ 2.30, 1.49, 1.47 (3 x 3H, s), 1.43 (3H, d, J=5.9 Hz); IR (film) 1718 cm^{-1}; $[\alpha]_D$ -81° (c 1.9, $CHCl_3$), lit[19] (ent-**4**) $[\alpha]_D$ +75° (c 1.6, $CHCl_3$). **7**: ^1H NMR (300 MHz) δ 5.84 (1H, m, vinyl), 4.73 (1H, d, J=3.0 Hz), 4.25 (1H, m), 2.12, 0.09, 0.08, (3 x 3H, s), 1.10 (3H, d, J=6.3 Hz), 0.87 (9H, s); IR (film)1765 cm^{-1}; $[\alpha]_D$ +88° (c 1.9, $CHCl_3$). **8**: ^1H NMR (300 MHz) δ 4.15 (dd, J=6.8, 3.7 Hz), 4.02 (1H, m), 1.23 (3H, d, J=6.3 Hz), 1.11 (3H, d, J=6.8 Hz); 1780 cm^{-1}; $[\alpha]_D$ -48.5° (c 2.91, $CHCl_3$). **11**: mp 67-68 °C; ^1H NMR (300 MHz) δ 1.31 (3H, d, J=6.5 Hz), 1.30 (3H, s), 1.28 (3H, d, J=7.5 Hz), 1.24 (3H, s); IR (CCl_4); 1761 cm^{-1}; $[\alpha]_D$ -86.5° (c 1.0, $CHCl_3$). **12**: mp 57-57.5 °C; ^1H NMR (300 MHz) δ 5.03 and 4.87 (1H each, brd. s, vinyl H), 4.21 (1H, dd, 8.0, 1.3 Hz), 4.13 (1H, dq, J=6.4, 1.3 Hz), 1.76 (3H, s, vinyl Me); IR (CCl_4); $[\alpha]_D$ -105° (c 1.0, $CHCl_3$). **13**: ^1H NMR (300 MHz) δ 2.21 and 1.88 (3H each, vinyl Me); IR (CCl_4) 1756 cm^{-1}. **14**: mp 56-57 °C; ^1H NMR (300 MHz) δ 5.28 (1H, s, vinyl H), 5.10 (1H, s, vinyl H), 1.45 (3H, s, C_4-Me); $[\alpha]_D$ -146° (c 1.0, $CHCl_3$). **1**: mp 74-75 °C; ^1H NMR (300 MHz) δ 4.77 (1H, d, J=7.8 Hz), 2.76 (1H, app. quint., J=7.5 Hz, coupled to δ 4.77 and 1.07), 2.33, 2.32, 1.57 (3 x 3H, s), 1.07 (3H, d, J=7.4 Hz); 1782, 1716, 1714 cm^{-1} ($CHCl_3$); $[\alpha]_D$ -84° (c 0.54, $CHCl_3$); ^{13}C NMR (75 MHz) 205.6, 205.5, 175.6, 82.4, 58.5, 44.3, 29.1, 28.4, 20.4, 10.8 ppm.

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