MeOH (30:1)) afforded **23**[8a] (5.3 mg, 70%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (s, 3 H), 1.28 (s, 3 H), 2.03–2.20 (m, 2 H), 2.08, 2.40 (ABq, J = 12.9 Hz, 2 H), 2.17, 2.26 (ABq, J = 15.4 Hz, 2 H), 2.61–2.68 (m, 1 H), 3.44–3.51 (m, 2 H), 4.02 (d, J = 16.6 Hz, 1 H), 4.10, 5.34 (ABq, J = 12.5 Hz, 2 H), 4.47 (br s, 1 H), 5.16 (br s, 1 H), 5.91 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 29.7, 29.9, 34.1, 34.9, 43.7, 44.2, 53.7, 59.8, 61.6, 74.5, 77.2, 130.1, 132.8, 170.9, 171.2; IR (CH_2Cl_2) 1733, 1675 cm^{-1}; MS m/z 279 (M^+), 234, 218; HRMS calcd for $C_{15}H_{21}O_4N$ 279.1471, found 279.1494; $[\alpha]^{24}_D$ +42.4° (c 0.17, $CHCl_3$) (lit.[8a] $[\alpha]^{22}_D$ +42.4° ($CHCl_3$)).

Supplementary Material Available: ^{1}H NMR spectra for compounds **2a–f, 3a–f, 4a–f, 6, 7, 10–16,** and **19–23** and ^{13}C NMR spectra for compounds **16, 19,** and **21–23** (50 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and may be ordered from the ACS; see any current masthead page for ordering information.

Total Syntheses of (−)-Acetomycin and Its Three Stereoisomers at C-4 and C-5

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The total synthesis of the antitumor and antimicrobial agent (−)-acetomycin (**1**) from the previously reported tetrahydrofuran **10**, a derivative of D-glucose is described. Reactions which altered only the side chains of **10** gave the substituted tetrahydrofuran **20**, which was then converted into the acyclic alcohol **38** and oxidized to the corresponding carboxylic acid **39**. Ozonolysis of the vinyl group of **39** gave an aldehyde, spontaneous cyclization of which afforded a 5:1 mixture of the diastereomeric γ-hydroxy γ-lactone **40**. Treatment of the mixture with acetic anhydride in pyridine gave predominantly (>45:1) the α-acetate **41**. On the other hand, treatment of compounds **40** with methanesulfonyl chloride/triethylamine in benzene, followed by treatment of the mixture of mesylates so formed with silver acetate and tetrabutylammonium acetate, resulted in the formation of a 1.3:1 mixture of **41** and the β-acetate **42**. Removal of the MOM protecting group of **41** and **42** and pyridinium chlorochromate (PCC) oxidation of the products gave (+)-5-*epi*-acetomycin (**2**) and **1**, respectively. In a similar manner, (−)-4-*epi*-acetomycin (**3**) and (+)-4,5-di-*epi*-acetomycin (**4**) were synthesized from the substituted tetrahydrofuran **11**. The results of preliminary studies of the in vitro inhibitory effects of compounds **2–4** on the growth of several tumor cells are also presented.

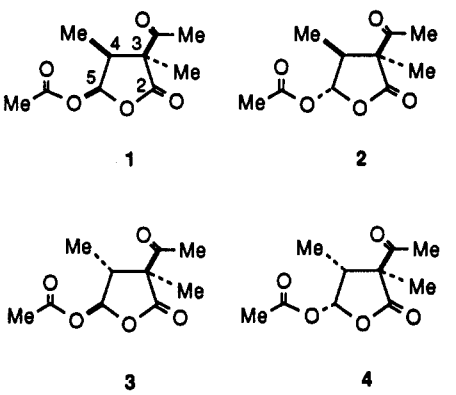
Introduction

In 1958, Prelog, Keller-Schierlein, and their co-workers isolated acetomycin from cultures of *Streptomyces ramulosus* (ETH 17653).[1] This antibiotic displayed broad but weak antimicrobial activity toward both Gram-positive and Gram-negative bacteria. Spectroscopic (UV, IR) analysis of acetomycin and its degradation products showed the structure to be 4-acetoxy-2-acetyl-4-hydroxy-2,3-dimethylbutanoic acid γ-lactone.[2,3] However, the configurations about its three asymmetric carbons were not established. Feeding experiments demonstrated that acetomycin is biosynthesized from acetate, L-methionine, and D-glucose.[4]

In 1985, Zeeck and co-workers[5] determined the absolute and relative configurations of the bromo acetate of one of the two diastereomeric alcohols formed by the $NaBH_3CN$ reduction of the keto carbonyl group of acetomycin. Recently, an X-ray crystallographic analysis of acetomycin itself confirmed the absolute configuration.[6]

Acetomycin also inhibits the growth, in vitro, of such tumor cells as those of HCT-human colon adenocarsinoma and L1210 murine leukemia.[7] However, no inhibitory activity is observed in vivo. It has been suggested[8] that, in the latter case, acetomycin is inactivated by enzymatic hydrolysis of the acetoxy group. Reduction of the keto carbonyl group of acetomycin and acetylation of the resulting diastereomeric alcohols yields products which display no antimicrobial activity.[5]

Chart I

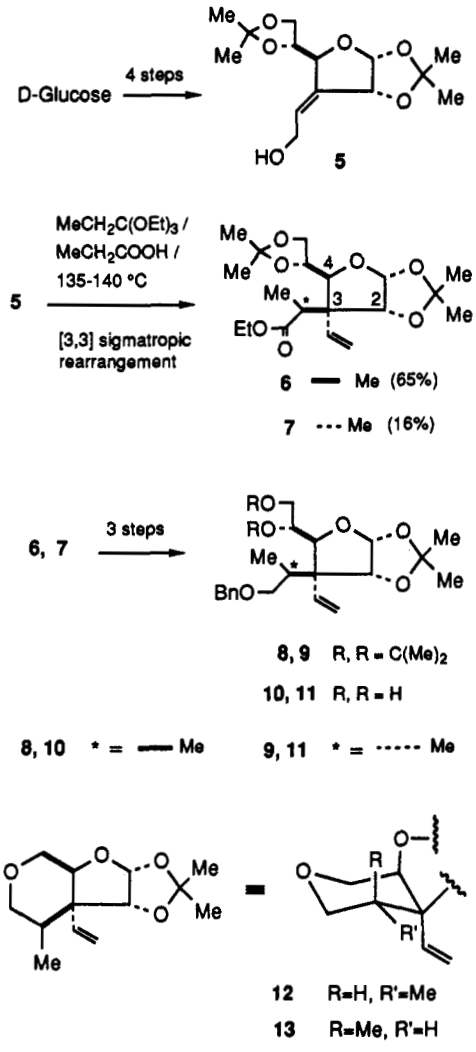


The novel structure and potential pharmacological importance of this antibiotic prompted us to carried out total syntheses of acetomycin and three of its stereoisomers. We describe here, in detail, the total syntheses of (−)-1; its (+)-5-epimer, (+)-5-*epi*-acetomycin (**2**);[9,10] and two other

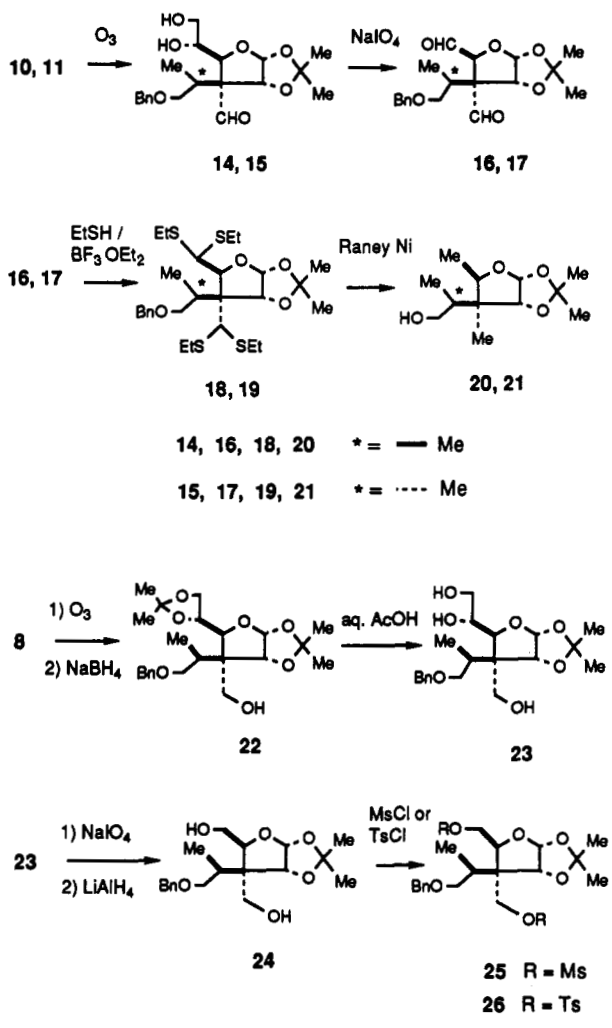
(1) Ettlinger, L.; Gäumann, E.; Hütter, R.; Keller-Schierlein, W.; Kradolfer, F.; Neipp, L.; Prelog, V.; Zähner, H. *Helv. Chim. Acta* **1958**, *41*, 216.
(2) Keller-Schierlein, W.; Mihailovic, M. Lj.; Prelog, V. *Helv. Chim. Acta* **1958**, *41*, 220.
(3) Bosshard, E.; Goeckner, N. A.; Keller-Schierlein, W. *Helv. Chim. Acta* **1959**, *42*, 2746.
(4) Bachmann, E.; Gerlach, H.; Prelog, V.; Zähner, H. *Helv. Chim. Acta* **1963**, *46*, 605.
(5) Uhr, H.; Zeeck, A.; Clegg, W.; Egert, E.; Fuhrer, H.; Peter, H. H. *J. Antibiot.* **1985**, *38*, 1684.
(6) Cano, F. H.; Foces-Foces, C.; Elguero, J. *Acta Crystallogr.* **1988**, *C44*, 919.
(7) Mamber, S. W.; Mutulski, J. D.; Hamelehle, K. L.; French, J. C.; Hokanson, G. C.; Shillis, J. L.; Leopold, W. R.; Von Hoff, D. D.; Tunac, J. B. *J. Antibiot.* **1987**, *40*, 73.
(8) Mamber, S. W.; Mitulski, J. D.; Borondy, P. E.; Tunac, J. B. *J. Antibiot.* **1987**, *40*, 77.
(9) A preliminary report of the total syntheses of **1** and **2** has appeared. See: Tadano, K.; Ishihara, J.; Ogawa, S. *Tetrahedron Lett.* **1990**, *31*, 2609.

0022-3263/92/1957-3789$03.00/0

Scheme I



Scheme II



stereoisomers of 1, namely (−)-4-*epi*- (3) and (+)-4,5-di-*epi*-acetomycin (4) (for the numbering of the atoms of the acetomycin framework, see Chart I). The results of preliminary assays of 1–4 as in vitro growth inhibitors of several tumor cells are also presented.

Results and Discussion

Several years ago, we described[11] a method for converting the C-3 skeletal carbon of certain hexofuranoses into a quaternary asymmetric carbon by the Johnson-variant[12] of the Claisen rearrangement. The [3,3]-sigmatropic rearrangement of the ketene acetal intermediate simultaneously, and stereoselectively, introduces (ethoxycarbonyl)methyl and vinyl groups at C-3 of the carbohydrate. The synthetic utility of these products derived has been demonstrated.[13] For example, the Claisen rearrangement of the ketene acetal from (*Z*)-allylic alcohol 5 (Scheme I) and triethyl orthoacetate yielded a key precursor for enantiospecific total synthesis of (+)-asteltoxin[14] and a homolog of (+)-pantolactone.[15] Other ortho esters can also be used. Thus, reaction of 5 with triethyl orthopropionate gave the diastereomeric esters 6 and 7, in yields of 65% and 16%, respectively.[16] The configuration about the skeletal 3-carbon was unambiguously established by ^{1}H NMR analysis of the cyclic ether acetal 12, formed from 6 via 8 and 10. Diastereomer 7 was similarly converted into 13 via 9 and 11. The preferential formation of 6 can be rationalized by means of a six-membered, chairlike transition state.

Retrosynthetic analysis indicated that 6 possesses the requisite elements for the carbon framework of (−)-acetomycin. Thus, C-3 of 6 (the quaternary asymmetric carbon) would become C-3 of 1, and C-2 of 6 would be converted into the lactone carbonyl carbon by oxidative one-carbon degradation. In addition, the ester group of 6 would be converted into an aldehydo group, which would temporarily serve as the equivalent of C-5. The C-4 side chain and the C-3 vinyl group would both be transformed into methyl groups.

Total Syntheses of (−)-Acetomycin (1) and (+)-5-*epi*-Acetomycin (2). Our first goal was to convert the C-4 side chain and the C-3 vinyl group of 10 into methyl groups efficiently, and simultaneously. Thus, ozonolysis of the vinyl group of 10 and reductive workup (Ph_3P)

(10) Very recently, total syntheses of racemic 1 and racemic 2 were achieved. See: Uenishi, J.; Okadai, T.; Wakabayashi, S. *Tetrahedron Lett.* **1991**, *32*, 3381.

(11) Tadano, K.; Idogaki, Y.; Yamada, H.; Suami, T. *Chem. Lett.* **1985**, 1925; *J. Org. Chem.* **1987**, *52*, 1201.

(12) Johnson, W. S.; Werthemann, L.; Bartlett, W. R.; Brochsom, T. J.; Li, T.-t.; Faulkner, D. J.; Petersen, M. R. *J. Am. Chem. Soc.* **1970**, *92*, 741.

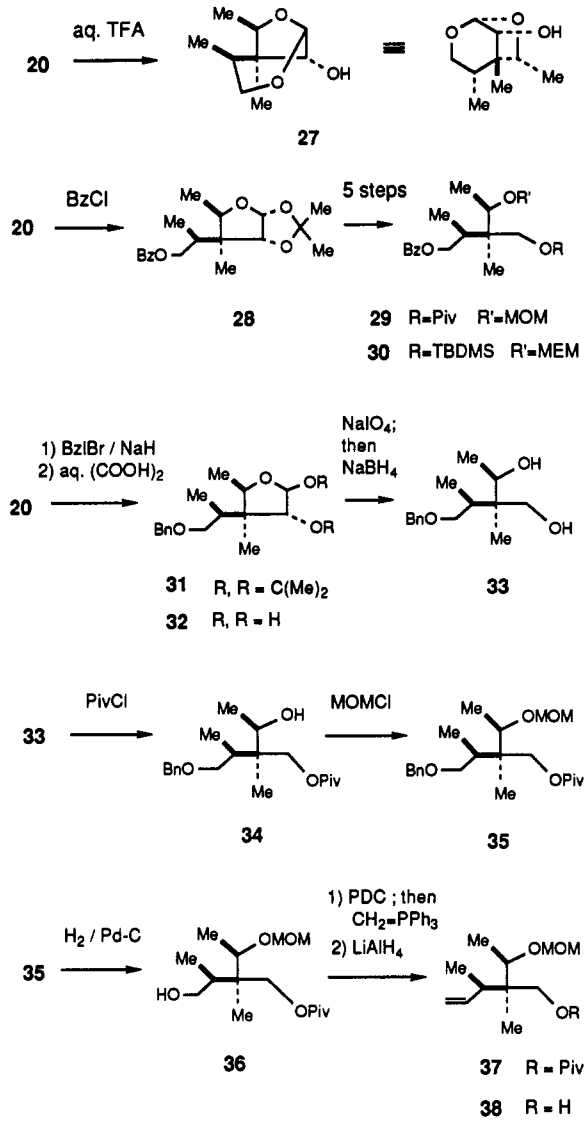
(13) Tadano, K. Natural Products Synthesis Starting with Carbohydrates Based on the Claisen Rearrangement Protocol. In *Studies in Natural Products Chemistry: Stereoselective Synthesis*; Atta-ur-Rahman, H. E. J., Ed.; Elsevier Science: Amsterdam, in press.

(14) Tadano, K.; Yamada, H.; Idogaki, Y.; Ogawa, S.; Suami, T. *Tetrahedron Lett.* **1988**, *29*, 655; *Tetrahedron* **1990**, *46*, 2353.

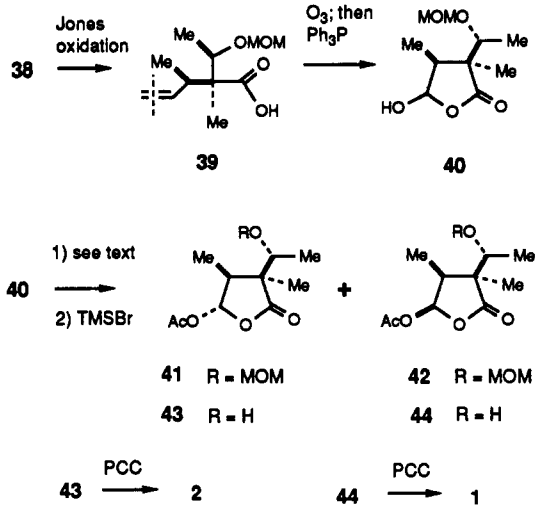
(15) Tadano, K.; Kanazawa, S.; Ogawa, S. *J. Org. Chem.* **1988**, *53*, 3868.

(16) Tadano, K.; Ishihara, J.; Yamada, H.; Ogawa, S. *J. Org. Chem.* **1989**, *54*, 1223.

Scheme III



Scheme IV



afforded the aldehyde **14** (Scheme II). Oxidative cleavage ($NaIO_4$) of the 1,2-glycol moiety of **14** and thiolacetalization ($EtSH/BF_3$-OEt_2) of the resulting dialdehyde **16**[17] provided the bis(ethylthio) acetal **18**. Desulfurization (Raney Ni/refluxing EtOH) of **18** furnished the trimethyl derivative **20**. Under the conditions of desulfurization, the benzyl group was also removed. The conversion of **10** to **20** was achieved in 40% yield overall.[18] Incidentally, attempts to prepare **20** by a different route, i.e., by the $LiAlH_4$ reduction of either the mesylate **25** or the tosylate **26** (each prepared from **8**[16] in six steps via **22**–**24**) failed. In both cases, no reduction occurred; the sulfonate was recovered quantitatively.

Our next task was to cleave oxidatively the C-1–C-2 bond of **20**. It was necessary to first remove the isopropylidene protecting group. Exposure of **20** to 60% aqueous trifluoroacetic acid (TFA) at 5 °C gave, to our surprise, the bicyclic acetal **27**, which possesses a 2,7-dioxabicyclo[3.2.1]octane structure, in 92% yield (Scheme III). The structure of **27** was inferred from its ^1H NMR spectrum and that of its acetate. This unexpected, and undesirable, result led us to conclude that it was also necessary to protect the hydroxyl group of **20**. Thus, the benzoate **28** was prepared in 96% yield by treating **20** with benzoyl chloride. Removal of the isopropylidene protecting group of **28** by acidic hydrolysis (60% aqueous TFA) proceeded uneventfully. The cyclic 1,2-glycol so produced was converted, in acceptable yield, into the O-protected species **29** (or **30**) by, successively, (1) oxidatively cleaving ($NaIO_4$) to its 1,2-glycol moiety, (2) reducing ($NaBH_4$) the product to a diol, and (3) protecting the hydroxyl group of the diol by pivaloylation (or *tert*-butyldimethylsilylation) of the primary hydroxy group and methoxymethylation (or (2-methoxyethoxy)methylation) of the secondary hydroxyl group. Unfortunately, neither **29** nor **30** could be efficiently debenzoylated under any of several conditions (methanolic NaOMe, Dibal-H or $LiAlH_4$ reduction). O-Benzylation seemed to be a logical alternative to O-benzoylation for protecting the hydroxyl group of **20**. Thus, the benzyl ether **31**[19] (obtained by treating **20** with benzyl bromide in the presence of sodium hydride) was subjected to acidic hydrolysis in order to remove the isopropylidene protecting group. After some experimentation,[20] we found that stirring **31** with 20% oxalic acid in aqueous THF at 50 °C for 3 days gave the best results. Compound **32** was obtained thereby in 79% yield. Compound **31** was recovered in 22% yield. Prolonging the reaction time led to a decrease in the yield of **32**.[21] Oxidative cleavage ($NaIO_4$) of the 1,2-glycol moiety of **32** and $NaBH_4$ reduction of the product provided the diol **33** in 78% yield. Selective protection of the primary hydroxyl group of **33** was achieved by pivaloylation, which gave ester **34** (80%). Methoxymethylation of the secondary hydroxyl group of **34** gave **35** in 96% yield. The benzyl group of **35** was then smoothly removed by hydrogenolysis (10% Pd/C, EtOH, 1 atm H_2) to give **36** in 98% yield. The hydroxy-

(17) An alternative route to the dialdehyde **16**, one which involved ozonolysis of the 5-aldehydo compound prepared by the $NaIO_4$ oxidation of **10**, was also explored. However, ozonolysis was accompanied by oxidation of the 5-aldehydo group to a carboxylic acid group.

(18) Compound **10** was also subjected to Lemieux–Johnson oxidation ($NaIO_4/OsO_4$, aqueous MeOH) in an attempt to gain one-step access to **16**. Compound **16** was then converted into **18** in 35% yield overall from **10**. However, the method was not practicable because the results of large-scale preparations were not reproducible.

(19) An attempt was made to prepare **31** directly from **18**, i.e., by desulfurization without concurrent debenzylation. Thus, Raney nickel T-4 was deactivated by heating it in refluxing acetone for 2 h prior to adding **18**. Refluxing the mixture for several hours did produce **31**, but in insufficient yield (40%). See: Spero, G. B.; McIntosh, A. B., Jr.; Levin, R. H. *J. Am. Chem. Soc.* **1948**, *70*, 1907.

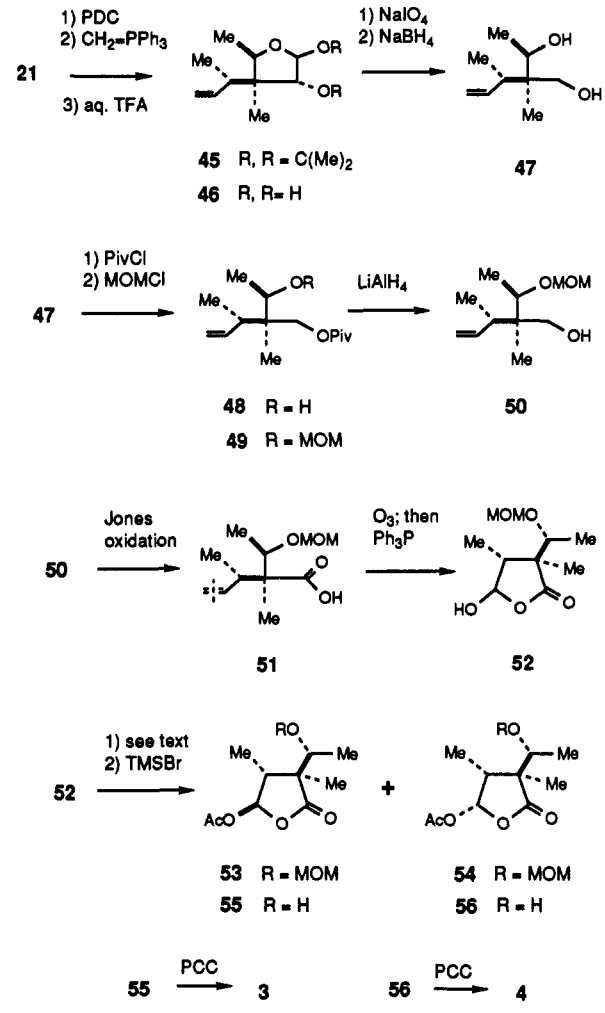
(20) The following acidic conditions were tested: (1) 60% aqueous TFA, 5 °C (yield of **32**, 34%); (2) 4 M aqueous HCl/THF, 5 °C (45%); (3) 8% oxalic acid in H_2O/THF, rt (0%); (4) 8% oxalic acid in refluxing H_2O/THF (49%).

(21) The bicyclic acetal **27** was also formed when the hydrolysis was continued until **31** was completely consumed.

methyl group of **36** was converted into a vinyl group by treating the aldehyde produced by PDC oxidation[22,23] with methylenetriphenylphosphorane.[24] Compound **37** was obtained in 63% yield. $LiAlH_4$ reduction of the pivalate **37** gave the alcohol **38** (82% yield), which is, in effect, a masked aldehydo alcohol. It was our intention to unmask the aldehydo group, without disturbing the MOM protecting group, by ozonolyzing the vinyl group during the last stages of the synthesis.

The stage was now set for the constructing the γ-hydroxy γ-lactone framework of **1** (Scheme IV). The pivotal transformations, of **38** to the carboxylic acid **39** by way of Jones oxidation and of **39** to an aldehydo carboxylic acid by way of ozonolysis, were accomplished uneventfully. As expected, the aldehydo acid underwent spontaneous cyclization to give, in 90% yield overall, what ^1H NMR analysis showed to be a ca. 5:1 mixture of two diastereomeric γ-hydroxy-γ-lactones, compounds **40**. Compounds **40** differed from each other only in the configuration about the hemiacetal carbon. The two could not be separated, and no attempt was made to establish the configuration of either compound. Treatment of the mixture with acetic anhydride in pyridine gave essentially a single product, acetate **41** (**41**:**42** > 45:1 by 270-MHz ^1H NMR analysis) in 91% yield. A doublet (J = 6.6 Hz) attributable to H-5 (*H*COAc), appears in the ^1H NMR spectrum of **41**. Because the magnitude of the coupling constant (J = 5.0 Hz) of the signal due to H-5 of **1** is similar to that of the signal due to H-5 of **41**, we believed that the orientation of H-5 of **41** must therefore also be β. The total synthesis of **1** was now two steps away from completion. The MOM group of **41** was efficiently removed, by applying Hanessian's conditions[25] [bromotrimethylsilane (TMSBr)/CH_2Cl_2, −30 °C], to provide crystalline epimerically pure **43** in 79% yield.[26] Then **43** was treated with PCC to oxidize the C-3 1-hydroxyethyl group to an acetyl group. To our surprise, the crystalline product that was obtained differed from natural acetomycin in all respects (mp, $[\alpha]_D$, TLC, ^1H and ^{13}C NMR). We eventually concluded that the acetylation of compound **40** under the conditions described gave the α-acetate instead of the β-acetate. We had prepared not (−)-acetomycin but (+)-5-*epi*-acetomycin (**2**)! Therefore, we tried to find a way whereby compound **40** could be converted into the β-acetate **42** in acceptable yield.[27] Eventually, we did find a method which provided the β-acetate **42** preferentially but not exclusively. Thus, exposing a mixture of compounds **40** to methanesulfonyl chloride in the presence of triethylamine and then refluxing the mixture of mesylates so formed together with silver acetate and tetrabutylammonium acetate gave an

Scheme V



inseparable mixture of **41** and **42** in 77% combined yield.[28] The ratio of **41** to **42** was estimated to be 1.3:1.0 by ^1H NMR analysis. The transformation **40** → **41**/**42** presumably involved mesylation of the hemiacetal hydroxyl group and subsequent nucleophilic displacement of the mesyloxy group by acetate ion. We could not isolate and characterize the intermediate mesylates because they were unstable on silica gel. We cannot explain why, in this case, the β-acetate was formed preferentially. Fortunately, the components of the diastereomeric mixture could be separated cleanly after removal of the MOM group. Thus, **43** and **44** were obtained in yields of 48% and 33%, respectively, after exposing the mixture of **41** and **42** to TMSBr. The physical properties (mp, ^1H and ^{13}C NMR spectral data) of β-acetate **44** coincided well with those of an authentic sample prepared by $NaBH_3CN$ reduction of natural acetomycin.[5] Oxidation (PCC) of **44** afforded (−)-acetomycin **1** in 90% yield. Synthetic **1** was identical to the natural product in all respects (mp, mixed mp, TLC, $[\alpha]_D$, IR, ^1H and ^{13}C NMR, LRMS). Synthetic **1** is levorotatory, which confirmed that the absolute configuration of natural **1** is that depicted.

Total Syntheses of (−)-4-*epi*- (3) and (+)-4,5-Di-*epi*-acetomycin (4). Encouraged by achieving total syntheses of **1** and **2**, we decided next to synthesize the

(22) Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, 399.

(23) The following oxidation methods were also tested: (1) Pfitzner–Moffatt or Swern oxidations (the corresponding (methylthio)methyl ether was formed exclusively); (2) PCC/NaOAc/CH_2Cl_2 (60% yield of the desired aldehyde); (3) PDC/DMF (34% yield of the desired aldehyde).

(24) The Wittig reagent was prepared by refluxing a mixture of $CH_3P^+Ph_3Br^-$ and $NaNH_2$ in THF for 3–4 h. After being cooled, the supernatant liquid was passed through a filter paper under Ar. When the aldehyde was treated with the filtrate, only one olefin (compound **37**) was produced. That this was so was established by ozonolyzing **37** and treating the product with $NaBH_4$. Compound **36** was obtained exclusively. On the other hand, when the Wittig reagent was not filtered before use, a mixture of **37** and its allylic epimer was produced.

(25) Hanessian, S.; Delorme, D.; Dufresne, Y. *Tetrahedron Lett.* **1984**, *25*, 2515.

(26) When deprotection was effected under acidic conditions (aqueous HCl/THF or 80% aqueous HOAc), it was accompanied by hydrolysis of the ester moiety.

(27) Acetylation by treatment with acetic anhydride in the presence of sodium acetate gave only **41**. Application of the Mitsunobu inversion procedure (diethyl azodicarboxylate/Ph_3P/HOAc/THF) gave no product of acetylation.

(28) In their total synthesis of racemic acetomycin, Uenishi's group[10] described another method for stereoselectively introducing an acetyl group. They used an intermediate structurally similar to **40**. However, it bore a [(*tert*-butyldimethylsilyl)oxy]methyl group at C-3 instead of a 1-[(methoxymethyl)oxy]ethyl group. For details, see ref 10.

stereocongeners 3 and 4, the C-4 epimers of 1 and 2, respectively. We planned to use the minor Claisen rearrangement product 7 as the starting material for both syntheses. We expected that both syntheses could be achieved in much the same manner as were those of 1 and 2. The routes to 3 and 4 from 7, which are somewhat shorter than those to 1 and 2, are outlined in Scheme V. Thus, the diol 11 (prepared from 7[16]) was converted into the trimethyl derivative 21 by methods very similar to those used to prepare 20 from 10 (see Experimental Section). The overall yield of 21 (via 15, 17, and 19) was 55% (Scheme II). We decided to minimize the number of protection–deprotection steps required by converting the hydroxymethyl group of 21 into a vinyl group prior to oxidative cleavage of the C-1–C-2 bond. Thus, the Wittig reaction of methylenetriphenylphosphorane and the aldehyde produced by the oxidation (PDC) of 21 yielded the olefin 45 in 66% yield. None of the allylic epimer of 45 was produced. Removal (60% aqueous TFA, 0 °C) of the isopropylidene group of 45 afforded 46 in 84% yield. Oxidative cleavage ($NaIO_4$) of the 1,2-glycol moiety of 46 and reduction ($NaBH_4$) of the product gave the diol 47 in 84% yield. Because the product of glycol cleavage is very volatile, the conversion of 46 into 47 should be carried out with great care (see Experimental Section). Pivaloylation of 47 gave the ester 48 (90% yield), methoxymethylation of which yielded 49 (93%). Reductive removal ($LiAlH_4$/THF) of the pivaloyl group of 49 gave the primary alcohol 50 in 95% yield. Jones oxidation of 50 gave the carboxylic acid 51, direct ozonolysis of which afforded an inseparable mixture of diastereomeric γ-hydroxy γ-lactones, compound 52, in 58% combined yield. The diastereomeric ratio was estimated to be ca. 5:1 by 270-MHz ^1H NMR analysis. Treatment of compounds 52 with acetic anhydride in pyridine gave the β-acetate 53 and the α-acetate 54. The ratio of 53 to 54 was estimated to be >20:1 by ^1H NMR analysis. Removal of the MOM groups under Hanessian's conditions[25] and column chromatography of the products gave the pure crystalline β-acetate 55 in 70% yield overall from 52. As was also the case for the acetylation of compounds 40, the acetylation of compounds 52 afforded predominantly the β-acetate, in which the C-4 methyl group and the C-5 acetoxy group are trans to each other. On the other hand, exposure of compounds 52 to methanesulfonyl chloride in the presence of triethylamine and treatment of the mixture of mesylates so formed with potassium acetate and a crown ether (dicyclohexyl-18-crown-6)[29] produced an inseparable mixture of 53 and 54 (ca. 1:3 by 270-MHz ^1H NMR analysis) in 78% combined yield.[30] Removal[25] of the MOM protecting group and column chromatography afforded 55 and 56 in yields of 14% and 57%, respectively. A 2% yield of a mixture of 55 and 56 was also obtained. Compounds 55 and 56 were individually oxidized (PCC) to give (−)-4-*epi*-acetomycin (3, 92%) and (+)-4,5-di-*epi*-acetomycin (4, 71%), respectively. The ^1H NMR spectra of 3 and 4 both show a doublet, at δ 6.15 (J = 2.9 Hz) in the case of 3 and at δ 6.59 (J = 5.9 Hz) in the case of 4, due to H-5 (*H*COAc). The chemical shift of the signal due to H-5 of 4 is close to that of the signal due to H-5 of 1. Thus, in both 1 and 4 the C-4 and C-5 substituents are cis to each other. Furthermore, the results of NOE experiments with 3 and 4 also suggested that the configuration about C-5 is indeed that depicted. When the signal due to the protons of the methyl group at C-4 of 3 was irradiated, both the signal due to H-5 and the signal due to the protons of the C-3 methyl group were enhanced by 6.6%. On the other hand, irradiation of the signal due to H-5 of 4 caused a remarkable enhancement (7.9%) of the H-4 signals, but no enhancement of the signal due to the protons of the C-4 methyl group. As to the optical activity of 1–4, it is interesting to note that the C-5 epimers which possess the *R*-configuration (1 and 3) are levorotatory whereas those which possess the *S*-configuration (2 and 4) are dextrorotatory, irrespective of the configuration about C-4.

Table I. Inhibition of the Growth, in Vitro, of Murine Tumor Cells by 1 and 2. Comparison with the Inhibition Exerted by Adriamycin

compd	dosage (μg/mL)	inhibition rate[a] (%) P388	colon 26	L1210	sarcoma 180
1	10	101	136	102	98
	1	78	47	92	99
	0.1	10	13	9	20
2	10	75	98	68	87
	1	5	14	−3	−4
	0.1	15	14	0	3
adriamycin	1	98	100	100	100
	0.1	92	75	95	86
	0.01	33	31	21	11
	0.001	6	7	3	−5

[a] In the cases of P388, L1210, and sarcoma 180, the inhibition rate (IR) (%) was calculated using the following equation

$$\mathrm{IR}\ (\%) = \left[1 - \left(\frac{CT^{48h} - C^{0h}}{CC^{48h} - C^{0h}}\right)\right]100$$

where C^{0h} = number of tumor cells present at initiation of incubation, CT^{48h} = number of tumor cells present after 48 h incubation in the presence of compound specified, and CC^{48h} = number of tumor cells present after 48 h incubation in the absence of compound specified. In the case of colon 26, the following equation was used

$$\mathrm{IR}\ (\%) = \left[1 - \left(\frac{CT^{48h} - C^{48hADR}}{CC^{48h} - C^{48hADR}}\right)\right]100$$

where C^{48hADR} = absorbance measured by the MTT method after 48 h incubation in the presence of 1 μg/mL of adriamycin, CT^{48h} = absorbance after 48 h incubation in the presence of the compound specified. In the case of adriamycin, absorbance measured after 48 h incubation in the presence of 1.0, 0.1, 0.01, or 0.001 μg/mL of adriamycin. In the presence of 1.0 μg/mL adriamycin, IR is 100% because $CT^{48h} = C^{48hADR}$, and CC^{48h} = absorbance after 48 h incubation in the absence of the compound specified.

The Inhibitory Effect of 1–4 on the Growth of Certain Tumor Cells. Preliminary Results.[31] The in vitro inhibitory effect of synthetic 1–4 on the growth of several tumor cells was compared with that of adriamycin (Doxorubicin), a clinically important anthracycline antitumor agent. Results are summarized in Tables I (for 1 and 2) and II (for 3 and 4). The potency of 1 in inhibiting the growth of murine L-1210, P388, sarcoma 180, and colon 26 tumor cells is approximately one-tenth that of adriamycin (compare IR (%) for tested tumor cells of 1 at a dosage of 10 μg/mL to those of adriamycin at a dosage of 1 μg/mL). On the other hand, the (+)-5-epimer (2) of 1 is approximately 100 times less potent (compare IR of 2 at a dosage of 10 μg/mL to that of adriamycin at a dosage of 0.1 μg/mL). At a dosage of 1 μg/mL, the inhibitory effect of 3 is almost the same as that of adriamycin (10

(29) This method was first employed by Uenishi's group.[10]

(30) The following methods were also tested: (1) MsCl/Et_3N in benzene at rt, then reflux with added n-$Bu_4N^+OAc^-$/HOAc/AgOAc (53:54 = ca. 1:1, 91% combined yield); (2) MsCl/Et_3N in benzene, then reflux with added KOAc/HOAc/18-crown-6 ether (53:54 = ca. 2:1, 94% yield).

(31) The pharmacological assays were performed at the Biological Research Laboratory of Sumitomo Pharmaceuticals Co. Ltd. in Osaka, Japan.

Table II. Inhibition of the Growth, in Vitro, of Murine Tumor Cells by 3 and 4. Comparison with the Inhibition Exerted by 1 and Adriamycin

compd	dosage (μg/mL)	inhibition rate[a] (%) P388	colon 26	L1210	sarcoma 180
3	10	108	145		
	1	102	104	NT	NT
	0.1	36	−13		
4	10	105	145	109	79
	1	34	6	17	65
	0.1	2	−13	−5	55
1	10	105	143	107	102
	1	101	31	104	106
	0.1	33	−6	10	59
adriamycin	1	105	100	107	100
	0.1	102	82	89	83
	0.01	67	7	11	5
	0.001	20	−20	2	18

[a] The inhibition rate was calculated using the same equations used in the case of 1 and 2 (Table I), but the assays for 3 and 4 were performed individually at a different time. NT = not tested.

μg/mL) for P388 and colon 26. Although more pharmacological data are needed to define more clearly the relationship between structure and antitumor activity, it is reasonable to conclude tentatively that the 5-*R* epimers (1 and 3) are more potent growth inhibitors than the 5-*S* epimers (2 and 4) and that the configuration about C-4 has little effect on inhibitory activity.

In conclusion, we have achieved the total synthesis of (−)-acetomycin (1), a pharmacologically interesting γ-hydroxy γ-lactone. Three stereoisomers of 1, compounds 2–4, were also synthesized. The relationship between structure and potency on inhibiting tumor cell growth was partly defined. The results of the work described here open a synthetic route to structurally related compounds.

Experimental Section[32]

(βS,2R,3S,4R,5R)-4,5-(Isopropylidenedioxy)-β,2,3-trimethyltetrahydrofuran-3-ethanol (20). Through a cold (−78 °C) stirred solution of 10 (9.76 g, 25.8 mmol) in CH_2Cl_2 (120 mL) was bubbled ozone (O_2 containing ca. 3% O_3) for 4 h. Then a solution of Ph_3P (8.79 g) in CH_2Cl_2 (20 mL) was added. The mixture was kept for 30 min at −78 °C, and then it was allowed to warm to rt over 1 h. The solvent was evaporated to give the crude aldehyde 14 [TLC R_f 0.25 (EtOAc/hexane (1:2))].

To a stirred solution of the crude 14 in MeOH (150 mL) was added $NaIO_4$ (16.7 g, 78.1 mmol, in 80 mL H_2O). The mixture was stirred for 30 min, and then the solid that precipitated was removed by filtration and was washed well with MeOH. The filtrate and washings were combined, and the whole was concentrated. The residue was partitioned between CH_2Cl_2 (200 mL) and H_2O (200 mL). The two liquid layers were separated. The aqueous layer was extracted with CH_2Cl_2 (200 mL × 2). The extracts and organic layer were combined, and the whole was dried and concentrated to give the crude dialdehyde 16 [TLC R_f 0.41 (EtOAc/hexane (1:3))].

To a cold (0 °C) stirred solution of the crude 16 in CH_2Cl_2 (150 mL) were added EtSH (38.3 mL, 513 mmol)) and BF_3·OEt_2 (6.35 mL, 24.3 mmol). The mixture was stirred at 0 °C for 11.5 h. Aqueous NH_3 (9 mL) was then added to neutralize the mixture. Then the whole was concentrated. The residue was partitioned between CH_2Cl_2 (150 mL) and H_2O (150 mL). The aqueous layer was drawn off and was extracted with CH_2Cl_2 (150 mL × 2). The extract and the organic layer were combined, and the whole was dried and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane (1:20)) to give 11.2 g of bis(ethylthio) acetal 18: TLC R_f 0.60 (EtOAc/hexane (1:5)); $[\alpha]^{24}_D$ +45.0° (*c* 1.10, $CHCl_3$); IR (neat) 2975, 2930, 2870, 1500, 1455, 1375, 1265, 1220 cm^{-1}; ^1H NMR (400 MHz) δ 1.24, 1.24–1.30 (t, *J* = 7.3 Hz, and m, 3 H and 15 H), 1.54 (s, 3 H), 1.56 (s, 1 H), 2.53–2.57 (m, 1 H), 2.65–2.90 (m, 8 H), 3.65–3.71 (m, 2 H), 4.22 (d, *J* = 1.0 Hz, 1 H), 4.49 and 4.54 (ABq, *J* = 12.0 Hz, 2 H), 4.70 (s, 2 H), 5.64 (d, *J* = 3.4 Hz, 1 H), 7.26–7.34 (m, 5 H); HRMS calcd for $C_{25}H_{38}O_4S_3$ (M − C_2H_5SH) *m/z* 498.1930, found 498.1914.

To a suspension of Raney nickel T-4 (ca. 100 g) in EtOH (300 mL) was added a solution of 18 (11.2 g) in EtOH (200 mL). The mixture was refluxed for 4 h, and then it was cooled to rt and was filtered through a pad of Celite. The catalyst that was collected was washed well with EtOH. The filtrate and washings were combined, and the whole was concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:3)) afforded 2.39 g (40% overall from 10) of 20: a colorless oil; TLC R_f 0.10 (EtOAc/hexane (1:4)); $[\alpha]^{22}_D$ +9.2° (*c* 1.08, $CHCl_3$); IR (neat) 3470, 2980, 2945, 2880, 1465, 1455, 1380, 1310, 1260, 1220 cm^{-1}; ^1H NMR (400 MHz) δ 1.04 (s, 3 H), 1.06 (d, *J* = 6.8 Hz, 3 H), 1.24 (d, *J* = 6.8 Hz, 3 H), 1.32, 1.51 (2 s, 3 H × 2), 1.60–1.68 (m, 1 H), 3.63 (dd, *J* = 6.3 and 10.5 Hz, 1 H), 3.78 (dd, *J* = 3.4 and 10.5 Hz, 1 H), 3.99 (q, *J* = 6.8 Hz, 1 H), 4.53 (d, *J* = 3.9 Hz, 1 H), 5.73 (d, *J* = 3.9 Hz, 1 H). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.22; H, 9.28.

(βR,2R,3S,4R,5R)-4,5-(Isopropylidenedioxy)-β,2,3-trimethyltetrahydrofuran-3-ethanol (21). Compound 21 was prepared from 11 in a manner similar to that used to prepare 20 from 10. Thus, 4.59 g (12.1 mmol) of 11 was converted into 1.54 g (55% from 11) of 21. Some changes were made in an attempt to improve the overall yield. Thus, (1) 6.0 equiv of $NaIO_4$ was used for the glycol cleavage (15 to 17); (2) 2.0 equiv of BF_3·OEt_2 was used to form to bis(ethylthio) acetal (17 to 19); and (3) EtOAc was used as the solvent in the desulfurization of 19, in place of EtOH. 15: TLC R_f 0.31 (EtOAc/hexane (1:3)). 17: TLC R_f 0.31 (EtOAc/hexane (1:4)). 19: TLC R_f 0.30 (EtOAc/hexane (1:15)). 21: a colorless oil; TLC R_f 0.10 (EtOAc/hexane (1:4)); $[\alpha]^{28}_D$ +5.8° (*c* 1.15, $CHCl_3$); IR (neat) 3450, 2980, 2940, 2880, 1460, 1380, 1255, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 1.00 (d, *J* = 7.0 Hz, 3 H), 1.00 (s, 3 H), 1.28 (d, *J* = 6.6 Hz, 3 H), 1.33, 1.51 (2 s, 3 H × 2), 1.79–1.87 (m, 1 H), 2.42 (br s, 1 H), 3.39 (dd, *J* = 5.5 and 11.8 Hz, 1 H), 3.62 (dd, *J* = 6.6 and 11.8 Hz, 1 H), 4.02 (q, *J* = 7.0 Hz, 1 H), 4.46 (d, *J* = 4.0 Hz, 1 H), 5.75 (d, *J* = 4.0 Hz, 1 H). Anal. Calcd for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.49; H, 9.39.

(2R,3S,4R,5R)-3-[(1S)-1-[(Benzyloxy)methyl]ethyl]-4,5-(isopropylidenedioxy)-2,3-dimethyltetrahydrofuran (31). To a stirred suspension of NaH (834 mg, 34.8 mmol) in DMF (25 mL) was added a solution of 20 (1.96 g, 8.51 mmol) in DMF (35 mL). After 30 min, benzyl bromide (3.0 mL, 25.0 mmol) was added. Then the mixture was stirred overnight and EtOH (5 mL) was added to quench the reaction. The mixture was diluted with CH_2Cl_2 (100 mL) and was washed (1 × 100 mL of saturated aqueous $NaHCO_3$, 2 × 100 mL of H_2O), dried, and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:20)) afforded 1.90 g (70%) of 31: a colorless oil; TLC R_f 0.40 (EtOAc/hexane (1:10)); $[\alpha]^{32}_D$ +14.4° (*c* 1.66, $CHCl_3$); IR (neat) 2980, 2940, 2880, 1500, 1455, 1380, 1370, 1310, 1255, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 1.02 (s, 3 H), 1.06 (d, *J* = 7.0 Hz, 3 H), 1.20 (d, *J* = 6.6 Hz, 3 H), 1.31, 1.51 (2 s, 3 H × 2), 1.72–1.83 (m, 1 H), 3.47 (dd, *J* = 6.4 and 9.2 Hz, 1 H), 3.55 (dd, *J* = 3.7 and 9.2 Hz, 1 H), 4.00 (q, *J* = 6.6 Hz, 1 H), 4.50 (s, 2 H), 4.63 (d, *J* = 3.8 Hz, 1 H), 5.70 (d, *J* = 3.8 Hz, 1 H), 7.33 (s, 5 H). Anal. Calcd for $C_{19}H_{28}O_4$: C, 71.22; H, 8.81. Found: C, 71.62; H, 9.11.

The Diastereomeric Mixture of (2RS,3R,4S,5R)-4-[(1S)-1-[(Benzyloxy)methyl]ethyl]-4,5-dimethyltetrahydrofuran-2,3-diols (32). To a stirred solution of 31 (1.90 g, 5.93 mmol) in THF (50 mL) was added aqueous oxalic acid (12.5 g of oxalic acid dihydrate in 50 mL of H_2O). The mixture was

(32) **General.** Melting points are uncorrected. ^1H NMR spectra (90, 270, and 400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded in $CDCl_3$ solution with tetramethylsilane as internal standard. Unless otherwise specified, reactions were carried out at room temperature. Organic extracts were dried over anhydrous Na_2SO_4. Solvents were removed by rotary evaporator below 40 °C. Silica gel column chromatography was performed by using silica gel 60 K070 (Katayama Chemicals) unless otherwise specified. Commercial NaH (60% emulsion in mineral oil) was washed with hexane, dried in vacuo, and weighed. The following reagents were used for drying solvents prior to distillation: CaH_2 (CH_2Cl_2, benzene, DMF, and DMSO); NaOH (pyridine); $LiAlH_4$ then Na/benzophenone (THF); $CaSO_4$ (acetone); P_2O_5 (HOAc).

kept at 50 °C for 3 days, and then it was neutralized by adding 5 N aqueous NaOH. The solid that precipitated was removed by filtration. The filtrate was diluted with H_2O (100 mL) and then was extracted with CH_2Cl_2 (100 mL × 3). The combined extracts were dried and concentrated. Purification of the residue by column chromatography on silica gel afforded 1.35 g (79%) of **32**, a colorless oil, and 0.422 g (22%) of **31**. **32**: TLC R_f 0.43 and 0.39 (EtOH/toluene (1:10)); IR (neat) 3410, 2970, 2940, 2880, 1490, 1450, 1380, 1300 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.98, 0.99 (2 s, total 3 H, ca. 1:1), 1.06, 1.08 (2 d, each J = 7.0 Hz, total 3 H, ca. 1:1), 1.16, 1.28 (2 d, each J = 6.6 Hz, total 3 H, ca. 1:1), 1.86–1.99, 2.02–2.10 (2 m, total 1 H), 2.62 (br s, 0.5 H), 2.76 (d, J = 7.0 Hz, 0.5 H), 3.26–3.36 (m, 2 H), 3.86 (br s, 0.5 H), 4.00–4.11 (m, total 2.5 H), 4.467, 4.471 (2 s, total 2 H, ca. 1:1), 5.18 (t, J = 2.9 Hz, 0.5 H), 5.34 (t, J = 4.6 Hz, 0.5 H), 7.28–7.37 (m, 5 H). Anal. Calcd for $C_{16}H_{24}O_4$: C, 68.54; H, 8.63. Found: C, 68.35; H, 8.48.

(2*R*,3*R*,4*S*)-5-(Benzyloxy)-3-(hydroxymethyl)-3,4-dimethylpentan-2-ol (33). To a solution of compounds **32** (1.19 g, 4.24 mmol) in MeOH (36 mL) was added aqueous $NaIO_4$ (2.27 g, 10.6 mmol, in 18 mL of H_2O). The mixture was stirred for 3 h. The solid that precipitated was removed by filtration. The filtrate was concentrated. The residue was partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL). The aqueous layer was then drawn off and was extracted with CH_2Cl_2 (20 mL × 2). The extracts and the organic layer were combined, and the whole was dried and concentrated. The residue was used in the next step.

To a stirred solution of the residue (1.25 g) in EtOH (25 mL) was added $NaBH_4$ (241 mg, 6.37 mmol). The mixture was stirred for 1 h, and then it was cooled to 0 °C and 35% aqueous H_2O_2 (3 mL) was added. The mixture was stirred for 1 h at 0 °C, and then saturated aqueous $NaHSO_3$ (10 mL) was added. The solid that precipitated was removed by filtration. The filtrate was diluted with 1 N aqueous NaOH (50 mL) and was extracted with CH_2Cl_2 (50 mL × 3). The combined extracts were dried and concentrated. Purification of the residue by column chromatography on silica gel (EtOH/toluene (1:20)) afforded 0.830 g (78%) of **33**: a colorless oil; TLC R_f 0.38 (EtOH/toluene (1:10)); $[\alpha]^{29}_D$ -9.4° (*c* 0.68, $CHCl_3$); IR (neat) 3370, 2970, 2870, 1490, 1450, 1380, 1300, 1200 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.87 (s, 3 H), 1.04 (d, J = 7.1 Hz, 3 H), 1.21 (d, J = 6.7 Hz, 3 H), 1.81–2.17 (m, 1 H), 3.06 (br s, 2 H), 3.48–3.65 (m, 4 H), 3.86 (q, J = 6.7 Hz, 1 H), 4.51 (s, 2 H), 7.31 (s, 5 H). Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.25; H, 9.56.

(2*R*,3*R*,4*S*)-5-(Benzyloxy)-3,4-dimethyl-3-[(trimethylacetoxy)methyl]pentan-2-ol (34). To a stirred solution of **33** (830 mg, 3.29 mmol) in 1:3 CH_2Cl_2/pyridine (16 mL) was added pivaloyl chloride (1.22 mL, 9.91 mmol). The mixture was stirred for 2 h, and then it was diluted with saturated aqueous $NaHCO_3$ (60 mL). The whole was extracted with CH_2Cl_2 (60 mL × 3). The combined extracts were dried and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:10)) afforded 880 mg (80%) of **34**: a colorless oil; TLC R_f 0.39 (EtOAc/hexane (1:3)); $[\alpha]^{30}_D$ +7.7° (*c* 1.06, $CHCl_3$); IR (neat) 3480, 2970, 2940, 2880, 1725, 1500, 1480, 1460, 1400, 1370, 1285 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.86 (s, 3 H), 1.03 (d, J = 6.8 Hz, 3 H), 1.18 (d, J = 6.4 Hz, 3 H), 1.20 (s, 9 H), 1.87–2.24 (m, 1 H), 2.93 (br s, 1 H), 3.41, 3.60 (2 dd, each J = 5.3 and 9.3 Hz, 1 H × 2), 3.89 (q, J = 6.4 Hz, 1 H), 3.95 (s, 2 H), 4.50 (s, 2 H), 7.32 (s, 5 H). Anal. Calcd for $C_{20}H_{32}O_4$: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.53.

(2*S*,3*R*,4*R*)-1-(Benzyloxy)-4-(methoxymethoxy)-2,3-dimethyl-3-[(trimethylacetoxy)methyl]pentane (35). To a stirred solution of **34** (863 mg, 2.57 mmol) in CH_2Cl_2 (18 mL) were added chloromethyl methyl ether (MOMCl) (1.0 mL, 13.2 mmol) and (*i*-Pr)$_2$EtN (2.3 mL). The mixture was stirred for 4 h, and then more MOMCl (0.2 mL) was added. The mixture was stirred for 4 h, and then it was diluted with CH_2Cl_2 (30 mL). The mixture was washed (1 × 30 mL of 0.1 N aqueous HCl, 1 × 30 mL of H_2O), dried, and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:20)) afforded 937 mg (96%) of **35**: a colorless oil; TLC R_f 0.53 (EtOAc/hexane (1:8)); $[\alpha]^{30}_D$ +9.4° (*c* 1.10, $CHCl_3$); IR (neat) 2970, 2930, 2880, 1730, 1480, 1460, 1400, 1370, 1280 cm^{-1}; ^{1}H NMR (90 MHz) δ 0.87 (s, 3 H), 1.03 (d, J = 6.9 Hz, 3 H), 1.18 (s, 9 H), 1.20 (d, J = 6.0 Hz, 3 H), 2.00–2.27 (m, 1 H), 3.19–3.78 (m, 3 H), 3.36 (s, 3 H), 3.91, 4.08 (ABq, J = 12.0 Hz, 2 H), 4.49 (s, 2 H), 4.55, 4.69 (ABq, J = 6.7 Hz, 2 H), 7.32 (s, 5 H). Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.29; H, 9.27.

(2*S*,3*R*,4*R*)-4-(Methoxymethoxy)-2,3-dimethyl-3-[(trimethylacetoxy)methyl]pentan-1-ol (36). A mixture of **35** (926 mg, 2.43 mmol), EtOH (20 mL), and 10% Pd/C (700 mg) was stirred under H_2 (1 atm) for 1 h. The catalyst was removed by filtration and was then washed well with EtOH. The washings and the filtrate were combined, and the whole was concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:4)) afforded 690 mg (98%) of **36**: a colorless oil; TLC R_f 0.39 (EtOAc/hexane (1:4)); $[\alpha]^{29}_D$ -5.2° (*c* 1.19, $CHCl_3$); IR (neat) 3440, 2975, 2935, 2885, 1715, 1480, 1460, 1400, 1365, 1280 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.91 (s, 3 H), 1.05 (d, J = 7.0 Hz, 3 H), 1.21 (s, 9 H), 1.24 (d, J = 6.6 Hz, 3 H), 1.84–1.97 (m, 1 H), 2.11 (br s, 1 H), 3.37 (s, 3 H), 3.49–3.57 (m, 1 H), 3.71–3.79 (m, 2 H), 3.96, 4.03 (ABq, J = 11.7 Hz, 2 H), 4.59, 4.72 (ABq, J = 6.8 Hz, 2 H). Anal. Calcd for $C_{15}H_{30}O_5$: C, 62.04; H, 10.41. Found: C, 62.03; H, 10.31.

(3*R*,4*R*,5*R*)-5-(Methoxymethoxy)-3,4-dimethyl-4-[(trimethylacetoxy)methyl]hex-1-ene (37). To a stirred solution of **36** (587 mg, 2.02 mmol) in CH_2Cl_2 (20 mL) were added PDC (2.07 g, 5.50 mmol) and powdered molecular sieve 4A (1.05 g). The mixture was stirred for 1 h. The whole was passed through a short column of silica gel which was then eluted with excess Et_2O. Concentration of the eluate gave an aldehyde (486 mg): TLC R_f 0.55 (EtOAc/hexane (1:4)); IR (neat) 2970, 1780, 1730, 1480, 1460, 1390, 1370, 1280 cm^{-1}; ^{1}H NMR (90 MHz) δ 1.21 (s, 3 H), 3.36 (s, 3 H), 3.68 (q, J = 6.3 Hz, 1 H), 4.51, 4.63 (ABq, J = 6.9 Hz, 1 H × 2), 9.71 (d, J = 4.0 Hz, 1 H).

To a solution of the aldehyde (486 mg) in THF (10 mL) under Ar was added methylenetriphenylphosphorane (5.0 mmol, 5.0 mL of a 1.0 M solution in THF). The mixture was stirred for 10 min, and then it was diluted with Et_2O (20 mL). The solution was washed (2 × 20 mL H_2O, 1 × 20 mL saturated brine), dried, and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:25)) afforded 368 mg (63%) of **37**: a colorless oil; TLC R_f 0.72 (EtOAc/hexane (1:5)); $[\alpha]^{24}_D$ +26.5° (*c* 0.58, $CHCl_3$); IR (neat) 2970, 1730, 1635, 1480, 1395, 1365, 1280 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.86 (s, 3 H), 1.00 (d, J = 7.0 Hz, 3 H), 1.20 (d, J = 6.2 Hz, 3 H), 1.21 (s, 9 H), 2.46–2.57 (m, 1 H), 3.37 (s, 3 H), 3.65 (q, J = 6.2 Hz, 1 H), 3.95, 4.03 (ABq, J = 11.5 Hz, 2 H), 4.57, 4.69 (ABq, J = 7.0 Hz, 2 H), 4.98–5.05 (m, 2 H), 5.80 (dt, J = 18.7 and 8.8 Hz, 1 H). Anal. Calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 66.85; H, 10.24.

(3*R*,4*R*,5*R*)-4-(Hydroxymethyl)-5-(methoxymethoxy)-3,4-dimethylhex-1-ene (38). To a stirred suspension of $LiAlH_4$ (62 mg, 1.63 mmol) in THF (2 mL) was added a solution of **37** (403 mg, 1.41 mmol) in THF (6 mL). The mixture was stirred for 30 min, and then the reaction was quenched by adding, successively, H_2O (0.1 mL), 15% aqueous NaOH (0.1 mL), and H_2O (0.3 mL). The gel that was produced was removed by filtration. The filtrate was diluted with H_2O (25 mL) and then was extracted with CH_2Cl_2 (25 mL × 3). The combined extracts were dried and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:5)) afforded 233 mg (82%) of **38**: a colorless oil; TLC R_f 0.38 (EtOAc/hexane (1:3)); $[\alpha]^{28}_D$ -5.9° (*c* 1.70, $CHCl_3$); IR (neat) 3460, 2970, 2940, 2890, 1635, 1450, 1380, 1200 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.98 (d, J = 7.0 Hz, 3 H), 1.01 (s, 3 H), 1.24 (d, J = 6.2 Hz, 3 H), 2.10–2.22 (m, 1 H), 3.39 (s, 3 H), 3.34–3.79 (m, 2 H), 3.67 (q, J = 6.2 Hz, 1 H), 4.57, 4.68 (ABq, J = 6.8 Hz, 2 H), 4.93–5.01 (m, 2 H), 5.77 (ddd, J = 9.2, 11.4 and 16.1 Hz, 1 H). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 64.99; H, 10.66.

The Diastereomeric (2*S*,3*S*,4*RS*)-4,4-Dihydroxy-2-[(1*R*)-1-(methoxymethoxy)ethyl]-2,3-dimethylbutanoic Acid γ-Lactones (40). To a cold (0 °C) stirred solution of **38** (270 mg, 1.33 mmol) in acetone (15 mL) was added Jones's reagent (4.0 mmol, 1.50 mL of a 2.67 M aqueous solution). The mixture was stirred at 0 °C for 4 h, and then the reaction was quenched by adding *i*-PrOH (0.5 mL). The solid that precipitated was removed by filtration through a pad of Celite. The filtrate was diluted with H_2O (20 mL) and then was extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried and concentrated to give the crude carboxylic acid **39** (480 mg): TLC R_f 0.36 (EtOAc/hexane (1:2)). ^{1}H NMR (270 MHz) δ 1.05 (d, J = 6.6 Hz, 3 H), 1.18 (s, 3 H), 1.28 (d, J = 6.2 Hz, 3 H), 2.65–2.75 (m, 1 H), 3.39

(s, 3 H), 3.82 (q, J = 6.6 Hz, 1 H), 4.61, 4.72 (ABq, J = 7.0 Hz, 2 H), 5.03–5.10 (m, 2 H), 5.72 (ddd, J = 9.0, 10.4 and 16.7 Hz, 1 H).

Through a cold (−78 °C) stirred solution of crude **39** (480 mg) in CH_2Cl_2 (10 mL) was bubbled ozone (O_2 containing ca. 3% O_3) for 20 min. Then a solution of Ph_3P (453 mg, 1.73 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was stirred for 30 min at −78 °C, and then it was allowed to warm to rt over 1 h. The solvent was evaporated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (2:5)) afforded 260 mg (90%) of compounds **40**: a colorless oil; TLC R_f 0.22 (EtOAc/hexane (1:2)); IR (neat) 3390, 2970, 2940, 2880, 1760, 1460, 1380, 1280, 1205 cm^{-1}; ^{1}H NMR (400 MHz) δ 1.21 (s, 3 H), 1.24 (d, J = 7.3 Hz, 3 H), 1.29 (d, J = 6.4 Hz, ca. $^1/_6$ × 3 H), 1.33 (d, J = 6.8 Hz, ca. $^5/_6$ × 3 H), 2.08–2.15 (m, ca. $^1/_6$ × 1 H), 2.52 (dq, J = 5.9 and 6.8 Hz, ca. $^5/_6$ × 1 H), 3.34 (s, ca. $^1/_6$ × 3 H), 3.37 (s, ca. $^5/_6$ × 3 H), 3.93 (q, J = 6.8 Hz, ca. $^1/_6$ × 1 H), 4.03 (q, J = 6.8 Hz, ca. $^5/_6$ × 1 H), 4.54, 4.67 (ABq, J = 6.8 Hz, ca. $^1/_6$ × 2 H), 4.62, 4.78 (ABq, J = 7.3 Hz, ca. $^5/_6$ × 2 H), 5.37 (d, J = 13.2 Hz, 1 H), 5.53 (dd, J = 5.9 and 13.7 Hz, ca. $^5/_6$ × 1 H), 5.58–5.59 (m, ca. $^1/_6$ × 1 H).

(2*S*,3*S*,4*S*)-4-Acetoxy-4-hydroxy-2-[(1*R*)-1-(methoxymethoxy)ethyl]-2,3-dimethylbutanoic Acid γ-Lactone (41). The mixture **40** (21.2 mg, 0.097 mmol) was acetylated by treatment with acetic anhydride (0.5 mL) in pyridine (0.5 mL) for 1 h. The mixture was then concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:3)) afforded 22.9 mg (91%) of **41**: a colorless oil; TLC R_f 0.33 (EtOAc/hexane (1:2)); $[\alpha]^{22}_D$ +43.1° (*c* 0.15, $CHCl_3$); IR (neat) 2975, 2935, 2890, 1780, 1750 (sh), 1455, 1380, 1360, 1290, 1200 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.25 (s, 3 H), 1.306 (d, J = 7.3 Hz, 3 H), 1.313 (d, J = 7.0 Hz, 3 H), 2.14 (s, 3 H), 2.31 (quint., J = 7.3 Hz, 1 H), 3.36 (s, 3 H), 3.95 (q, J = 7.0 Hz, 1 H), 4.56, 4.70 (ABq, J = 7.0 Hz, 2 H), 6.31 (d, J = 6.6 Hz, 1 H). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.75. Found: C, 55.15; H, 7.61.

(2*S*,3*S*,4*S*)-4-Acetoxy-4-hydroxy-2-[(1*R*)-1-hydroxyethyl]-2,3-dimethylbutanoic Acid γ-Lactone (43). To a cold (−30 °C) stirred solution of **41** (21.6 mg, 0.083 mmol) in CH_2Cl_2 (1.5 mL) under Ar were added bromotrimethylsilane (TMSBr, 0.033 mL, 0.25 mmol) and powdered molecular sieve 4A (20 mg). The mixture was stirred at −30 °C for 1.5 h, and then saturated aqueous $NaHCO_3$ (5 mL) was added. The mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined extracts were dried and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:4)) afforded 14.2 mg (79%) of **43**: white crystals; mp 88.0–89.0 °C; TLC R_f 0.26 (EtOAc/hexane (1:2)); $[\alpha]^{26}_D$ +77.1° (*c* 0.33, $CHCl_3$); $[\alpha]^{25}_D$ +76.8° (*c* 0.46, EtOH); IR (neat) 3500, 2980, 2925, 1760, 1455, 1390, 1380, 1370, 1300, 1260, 1220 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.28 (d, J = 7.3 Hz, 3 H), 1.33 (s, 3 H), 1.36 (d, J = 6.6 Hz, 3 H), 1.79 (d, J = 5.4 Hz, 1 H), 2.15 (s, 3 H), 2.36 (dq, J = 5.1 and 7.3 Hz, 1 H), 4.01 (quint., J = 6.2 Hz, 1 H), 6.26 (d, J = 5.1 Hz, 1 H); ^{13}C NMR (100 MHz) δ 11.7, 19.3, 19.9, 20.9, 45.8, 50.9, 70.2, 98.3, 169.4, 178.6. Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.81; H, 7.18.

(2*S*,3*S*,4*S*)-4-Acetoxy-2-acetyl-4-hydroxy-2,3-dimethylbutanoic Acid γ-Lactone, (+)-5-*epi*-Acetomycin (2). To a stirred solution of **43** (47.6 mg, 0.22 mmol) in CH_2Cl_2 (2.5 mL) were added PCC (200 mg, 0.92 mmol) and powdered molecular sieve 4A (92 mg). The mixture was stirred for 2.5 h, and then it was passed through a short column of silica gel. The column was eluted with excess Et_2O. The eluate was concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:3)) afforded 38.4 mg (81%) of **2**: white crystals; mp 69.0–69.5 °C; TLC R_f 0.23 (EtOAc/hexane (1:3)); $[\alpha]^{25}_D$ +79.5° (*c* 0.36, EtOH); IR ($CHCl_3$) 3020, 1785, 1710, 1510, 1420, 1380, 1360, 1330, 1225 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.13 (d, J = 7.3 Hz, 3 H), 1.60 (s, 3 H), 2.16 (s, 3 H), 2.27 (s, 3 H), 2.38 (dq, J = 6.2 and 7.3 Hz, 1 H), 6.36 (d, J = 6.2 Hz, 1 H); ^{13}C NMR (100 MHz) δ 11.2, 20.1, 20.8, 28.9, 46.7, 60.6, 97.8, 169.1, 173.8, 204.0. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.37; H, 6.47.

Mixture of 41 and Its (2*S*,3*S*,4*R*)-Diastereomer 42. To a stirred solution of compounds **40** (146 mg, 0.67 mmol) in benzene (5 mL) were added methanesulfonyl chloride (0.155 mL, 2.0 mmol) and Et_3N (0.05 mL). The mixture was stirred for 3.5 h, and then silver acetate (563 mg, 3.37 mmol) and tetrabutylammonium acetate (1.01 g, 3.35 mmol) were added. The mixture was refluxed for 2 h, and then it was cooled to rt and the solid that precipitated was removed by filtration through a pad of Celite. The filtrate was concentrated to ca. one-half its original volume, and then it was diluted with water (25 mL) and was extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:4)) afforded 134 mg (77% yield) of an inseparable mixture of **41** and **42**: a colorless oil; TLC R_f 0.34 (EtOAc/hexane (1:3)); IR (neat) 2980, 2940, 2890, 1780, 1760, 1465, 1455, 1380, 1370, 1210 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.164, 1.191, 1.246, 1.254, 1.287, 1.292, 1.301, 1.317, 1.319, 1.326, 1.340 (each s, total 9 H), 2.140, 2.145 (2 s, total 3 H), 3.36, 3.38 (2 s, ca. 1.3:1, total 3 H), 6.31, 6.53 (2 d, J = 6.6 Hz and 5.9 Hz, ca. 1.3:1, total 1 H).

43 and Its (2*S*,3*S*,4*R*)-Diastereomer 44. To a cold (−30 °C) stirred solution of compounds **41** and **42** (118 mg, 0.45 mmol) in CH_2Cl_2 (4 mL) under Ar were added TMSBr (0.24 mL, 1.82 mmol) and powdered molecular sieve 4A (73 mg). The mixture was stirred at −30 °C for 1 h, and then it was allowed to warm to rt, where it was kept for 30 min. Saturated aqueous $NaHCO_3$ (10 mL) was then added, and the whole was extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated. Purification of the residue by column chromatography on silica gel (Wako gel C-300, Wako Pure Chemicals; EtOAc/hexane (1:3)) afforded 47.6 mg (48%) of **43**, 32.8 mg (33%) of **44**, and 2.2 mg (2%) of a mixture of **43** and **44**. A small quantity (6.4 mg, 6%) of the mixture of **41** and **42** was recovered. **44**: white crystals; mp 68.0–69.5 °C (lit.[5] mp 63 °C); TLC R_f 0.17 (EtOAc/hexane (1:2)); $[\alpha]^{28}_D$ −118.2° (*c* 0.34, $CHCl_3$); $[\alpha]^{22}_D$ −131.1° (*c* 1.52, EtOH) (lit.[5] $[\alpha]^{20}_D$ −144° (*c* 0.71, EtOH)); IR (neat) 3510, 2980, 2945, 1780, 1760, 1455, 1380, 1325, 1260, 1220 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.19 (d, J = 7.3 Hz, 3 H), 1.31 (s, 3 H), 1.34 (d, J = 6.2 Hz, 3 H), 1.53 (d, J = 7.3 Hz, 1 H), 2.15 (s, 3 H), 2.55 (dq, J = 5.9 and 7.3 Hz, 1 H), 4.18 (quint, J = 6.5 Hz, 1 H), 6.55 (d, J = 5.9 Hz, 1 H); ^{13}C NMR (100 MHz) δ 9.1, 17.9, 20.0, 20.9, 44.4, 48.8, 68.0, 94.1, 169.0, 178.8.

(2*S*,3*S*,4*R*)-4-Acetoxy-2-acetyl-4-hydroxy-2,3-dimethylbutanoic Acid γ-Lactone, (−)-Acetomycin (1). To a stirred solution of **44** (31.2 mg, 0.144 mmol) in CH_2Cl_2 (2 mL) were added PCC (128 mg, 0.60 mmol) and powdered molecular sieve 4A (85 mg). The mixture was stirred for 30 min, and then it was passed through a short column of silica gel. The column was eluted with an excess Et_2O. The eluate was concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane (2:7)) to give 27.8 mg (90%) of **1**: white crystals; mp 108.0–109.0 °C (lit.[1] mp 115–116 °C); TLC R_f 0.30 (EtOAc/hexane (1:3)) and 0.30 (Et_2O/pentane (1:2)); $[\alpha]^{23}_D$ −148.5° (*c* 1.39, EtOH) (lit.[5] $[\alpha]^{20}_D$ −157° (*c* 1.25, EtOH)); IR ($CHCl_3$) 3040, 1790, 1765, 1710, 1455, 1420, 1375, 1355, 1320, 1220 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.07 (d, J = 7.3 Hz, 3 H), 1.45 (s, 3 H), 2.13 (s, 3 H), 2.31 (s, 3 H), 2.57 (dq, J = 5.5 and 7.3 Hz, 1 H), 6.59 (d, J = 5.5 Hz, 1 H). ^{13}C NMR (100 MHz) δ 9.4, 20.6, 21.1, 28.9, 45.6, 56.8, 94.0, 168.6, 177.0, 203.3.

(2*R*,3*R*,4*S*,5*R*)-2,3-(Isopropylidenedioxy)-4,5-dimethyl-4-[(1*S*)-1-methyl-2-propenyl]tetrahydrofuran (45). To a stirred solution of **21** (964 mg, 4.20 mmol) in CH_2Cl_2 (16 mL) were added PDC (4.73 g) and powdered molecular sieve 4A (2.36 g). The mixture was stirred for 40 min, and then it was passed through a short column of silica gel. The column was eluted with excess Et_2O. The eluate was concentrated to give a crude aldehyde (781 mg): TLC R_f 0.55 (EtOAc/hexane (1:3)).

To a stirred solution of the crude aldehyde (781 mg) in THF (10 mL) was added methylenetriphenylphosphorane (20.9 mmol, 21.0 mL of a 1.0 M solution in THF). The mixture was stirred for 15 min, and then the reaction was quenched by adding saturated aqueous NH_4Cl (15 mL). The mixture was extracted with Et_2O (15 mL × 3). The combined extracts were dried and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:40)) afforded 622 mg (66%) of **45**: a colorless oil; TLC R_f 0.65 (EtOAc/hexane (1:4)); $[\alpha]^{25}_D$ −23.3° (*c* 1.14, $CHCl_3$); IR (neat) 2990, 2940, 2880, 1635, 1455, 1380, 1370, 1310, 1250 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.00 (s, 3 H), 1.06 (d, J = 6.8 Hz, 3 H), 1.26 (d, J = 6.8 Hz, 3 H), 1.30, 1.50 (2 s, 3 H × 2), 2.28–2.34 (m, 1 H), 4.00 (q, J = 6.8 Hz, 1 H), 4.29 (d, J = 3.9 Hz, 1 H), 4.94–5.05 (m, 2 H), 5.60 (d, J = 3.9 Hz, 1 H), 5.92 (ddd,

J = 7.3, 10.7, and 17.1 Hz, 1 H); HRMS calcd for $C_{12}H_{19}O_3$ (M - CH_3) m/z 211.1334, found m/z 211.1334.

Mixture of (2*R*,3*R*,4*S*,5*R*)-4,5-Dimethyl-4-[(1*S*)-1-methyl-2-propenyl]tetrahydrofuran-2,3-diol and Its (2*S*)-Diastereomer 46. A solution of **45** (1.12 g, 4.97 mmol) in 60% aqueous TFA (20 mL) was stirred at 0 °C for 6 h. The solution was then neutralized by adding 7.5 N aqueous NaOH (20 mL) and was extracted with CH_2Cl_2 (40 mL × 3). The combined extracts were dried and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:3)) afforded 781 mg (84%) of a mixture of compounds **46**: a colorless oil; TLC R_f 0.19 (EtOH/toluene (1:20)); IR (neat) 3400, 3080, 2970, 2940, 1635, 1460, 1420, 1380, 1280, 1200 cm^{-1}; ^1H NMR (270 MHz) δ 0.94 (d, J = 7.0 Hz, 0.5 × 3 H), 1.00 (d, J = 7.0 Hz, 0.5 × 3 H), 1.01 (s, 0.5 × 3 H), 1.04 (s, 0.5 × 3 H), 1.20 (d, J = 6.6 Hz, 0.5 × 3 H), 1.30 (d, J = 6.6 Hz, 0.5 × 3 H), 1.75 (d, J = 8.1 Hz, 0.5 × 1 H), 2.29–2.42 (m, 1 H), 2.95 (d, J = 4.8 Hz, 0.5 × 1 H), 3.93–4.09 (m, 2 H), 4.50 (br s, 0.5 × 1 H), 4.65 (d, J = 3.7 Hz, 0.5 × 1 H), 4.99–5.14 (m, 2 H), 5.20–5.33 (m, 1 H), 5.87–6.01 (m, 1 H).

(2*R*,3*R*,4*S*)-3-(Hydroxymethyl)-3,4-dimethylhex-5-en-2-ol (47). To a stirred solution of **46** (781 mg, 4.20 mmol) in MeOH (3 mL) was added aqueous $NaIO_4$ (2.70 g, 12.6 mmol in 15 mL of H_2O). After 1 h, more aqueous $NaIO_4$ (0.90 g in 5 mL H_2O) was added. The mixture was stirred for 20 min, and then saturated aqueous $NaHCO_3$ (15 mL) was added. The mixture was extracted with Et_2O (15 mL × 3). The combined extracts were dried, and the drying reagent was removed by filtration. To the stirred filtrate were then added EtOH (10 mL) and $NaBH_4$ (476 mg, 12.6 mmol). After 40 min, 35% aqueous H_2O_2 (5 mL) was added. The mixture was stirred for 15 min, and then 2 N aqueous NaOH (30 mL) was added. After 15 min, the organic layer was drawn off. The aqueous layer was extracted with EtOAc (30 mL × 3). The extracts and the organic layer were combined, and the whole was dried and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (2:9)) afforded 561 mg (84%) of **47**: a colorless oil; TLC R_f 0.17 (EtOAc/hexane (1:3)); $[\alpha]^{23}_D$ -26.1° (c 1.05, $CHCl_3$); IR (neat) 3400, 3080, 2980, 2930, 2890, 1635, 1460, 1375, 1290, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 0.95 (s, 3 H), 0.98 (d, J = 6.9 Hz, 3 H), 1.28 (d, J = 6.6 Hz, 3 H), 2.23–2.37 (m, 1 H), 3.50, 3.77 (ABq, J = 11.4 Hz, 2 H), 3.88 (q, 1 H, J = 6.6 Hz, 1 H), 4.97–5.06 (m, 2 H), 5.96 (ddd, J = 9.2, 10.3 and 17.2 Hz, 1 H). Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.47. Found: C, 67.95; H, 11.17.

(2*R*,3*R*,4*S*)-3,4-Dimethyl-3-[(trimethylacetoxy)methyl]-hex-5-en-2-ol (48). To a stirred solution of **47** (534 mg, 3.38 mmol) in pyridine (8 mL) and CH_2Cl_2 (3 mL) was added pivaloyl chloride (0.50 mL, 4.06 mmol). The mixture was stirred for 2 h, and then it was diluted with saturated aqueous $NaHCO_3$ (10 mL). The mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:10)) afforded 741 mg (90%) of **48**: a colorless oil; TLC R_f 0.44 (EtOAc/hexane (1:3)); $[\alpha]^{24}_D$ -14.4° (c 0.97, $CHCl_3$); IR (neat) 3500, 3075, 2975, 2930, 2900, 2880, 1725, 1710, 1630, 1480, 1390, 1370, 1280 cm^{-1}; ^1H NMR (270 MHz) δ 0.89 (s, 3 H), 1.02 (d, J = 7.3 Hz, 3 H), 1.20 (d, J = 6.6 Hz, 3 H), 1.21 (s, 9 H), 2.44–2.50 (m, 1 H), 3.89 (q, J = 6.6 Hz, 1 H), 3.94, 4.00 (ABq, J = 11.7 Hz, 2 H), 5.00–5.09 (m, 2 H), 5.92 (ddd, J = 9.2, 10.3, and 17.2 Hz, 1 H).

(3*S*,4*R*,5*R*)-5-(Methoxymethoxy)-3,4-dimethyl-3-[(trimethylacetoxy)methyl]hex-1-ene (49). To a stirred solution of **48** (728 mg, 3.0 mmol) in CH_2Cl_2 (15 mL) were added MOMCl (1.14 mL, 15.0 mmol) and (i-Pr)$_2$EtN (5.2 mL, 30.0 mmol). The mixture was stirred for 8 h, and then it was diluted with CH_2Cl_2 (15 mL) and was washed with 0.1 N aqueous HCl (40 mL). The washing was extracted with CH_2Cl_2 (30 mL × 2). The combined organic layers were dried and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:30)) afforded 800 mg (93%) of **49**: a colorless oil; TLC R_f 0.68 (EtOAc/hexane (1:4)); $[\alpha]^{24}_D$ -6.2° (c 0.97, $CHCl_3$); IR (neat) 2970, 2930, 2880, 2820, 1725, 1630, 1480, 1460, 1395, 1370, 1280, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 0.86 (s, 3 H), 0.99 (d, J = 7.0 Hz, 3 H), 1.20 (s, 9 H), 1.22 (d, J = 6.6 Hz, 3 H), 2.53–2.58 (m, 1 H), 3.38 (s, 3 H), 3.69 (q, J = 6.6 Hz, 1 H), 3.87, 4.00 (ABq, J = 11.4 Hz, 2 H), 4.60, 4.70 (ABq, J = 7.0 Hz, 2 H), 4.95–5.01 (m, 2 H), 5.77–5.90 (m, 1 H). Anal. Calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56. Found: C, 67.34; H, 10.50.

(3*S*,4*R*,5*R*)-4-(Hydroxymethyl)-5-(methoxymethoxy)-3,4-dimethylhex-1-ene (50). To a stirred suspension of $LiAlH_4$ (303 mg, 7.98 mmol) in THF (3 mL) was added a solution of **49** (763 mg, 2.66 mmol) in THF (3 mL). The mixture was stirred for 30 min, and then H_2O (0.8 mL), 15% aqueous NaOH (0.8 mL), and H_2O (2.4 mL) were added successively. The gel that was produced was removed by filtration and was washed with excess CH_2Cl_2. The washings were added to the filtrate, and the whole was concentrated. The residue was partitioned between CH_2Cl_2 (15 mL) and H_2O (15 mL). The aqueous layer was drawn off and was extracted with CH_2Cl_2 (15 mL × 2). The extracts and the organic layer were combined, and the whole was concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:8)) afforded 511 mg (95%) of **50**: a colorless oil; TLC R_f 0.42 (EtOAc/hexane (1:4)); $[\alpha]^{25}_D$ -37.9° (c 0.95, $CHCl_3$); IR (neat) 3475, 3080, 2975, 2940, 2880, 2825, 1630, 1450, 1370, 1200 cm^{-1}; ^1H NMR (270 MHz) δ 0.94 (d, J = 7.0 Hz, 3 H), 1.00 (s, 3 H), 1.25 (d, J = 6.6 Hz, 3 H), 2.12–2.18 (m, 1 H), 3.00 (dd, J = 2.4 and 9.0 Hz, 1 H), 3.38–3.45 (m, 1 H), 3.40 (s, 3 H), 3.70–3.80 (m, 2 H), 4.59, 4.71 (ABq, J = 7.0 Hz, 2 H), 4.94–5.01 (m, 2 H), 5.77–5.90 (m, 1 H). Anal. Calcd for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.38; H, 10.55.

Mixture of (2*S*,3*R*,4*R*)-4,4-Dihydroxy-2-[(1*R*)-1-(methoxymethoxy)ethyl]-2,3-dimethylbutanoic Acid γ-Lactone and Its (4*S*)-Diastereomer 52. To a cold (0 °C) stirred solution of **50** (467 mg, 2.32 mmol) in acetone (9 mL) was added Jones's reagent (6.94 mmol, 2.6 mL of a 2.67 M aqueous solution). The mixture was stirred at 0 °C for 100 min, and then i-PrOH (5 mL) was added. The mixture was diluted with H_2O (30 mL) and was extracted with CH_2Cl_2 (30 mL × 3). The combined extracts were dried and concentrated to give the crude carboxylic acid **51**: TLC R_f 0.25 (EtOAc/hexane (1:4)); ^1H NMR (270 MHz) δ 1.00 (d, J = 7.3 Hz, 3 H), 1.17 (s, 3 H), 1.27 (d, J = 6.6 Hz, 3 H), 2.58–2.69 (m, 1 H), 3.37 (s, 3 H), 3.86 (q, J = 6.6 Hz, 1 H), 4.55–4.73 (m, 3 H), 4.99–5.05 (m, 2 H), 5.80–5.94 (m, 1 H).

Through a cold (-78 °C) stirred solution of crude **51** in CH_2Cl_2 (10 mL) was bubbled ozone (O_2 containing ca. 3% O_3) for 35 min. Then a solution of Ph_3P (913 mg) in CH_2Cl_2 (5 mL) was added. The mixture was stirred for 40 min at -78 °C, and then a solution of Ph_3P (540 mg) in CH_2Cl_2 (3 mL) was again added. The mixture was stirred for 30 min at -78 °C, and then it was allowed to warm to rt over 1 h. The mixture was concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:5)) afforded 294 mg (58%) of an inseparable mixture of compounds **52**: a colorless oil; TLC R_f 0.23 (EtOAc/hexane (1:2)); IR (neat) 3400, 2980, 2950, 2900, 2830, 1750, 1440, 1370, 1320, 1280, 1205 cm^{-1}; ^1H NMR (270 MHz) δ 1.09 (s, 3 H), 1.13 (d, J = 7.7 Hz, 3 H), 1.21 (d, J = 6.6 Hz, 3 H), 2.45 (dq, J = 1.5 and 7.7 Hz, $^5/_6$ × 1 H), 2.83–2.93 (m, $^1/_6$ × 1 H), 3.34 (s, $^1/_6$ × 3 H), 3.37 (s, $^5/_6$ × 3 H), 3.89 (q, J = 6.6 Hz, $^1/_6$ × 1 H), 3.98 (q, J = 6.6 Hz, $^5/_6$ × 1 H), 4.63, 4.73 (ABq, J = 6.9 Hz, 2 H), 5.25 (br s, $^5/_6$ × 1 H), 5.72 (d, J = 5.9 Hz, $^1/_6$ × 1 H).

(2*S*,3*R*,4*R*)-4-Acetoxy-4-hydroxy-2-[(1*R*)-1-hydroxyethyl]-2,3-dimethylbutanoic Acid γ-Lactone (55). The mixture of compounds **52** (41.6 mg, 0.19 mmol) was treated with acetic anhydride (1 mL) in pyridine (1 mL) for 2 h. The mixture was then concentrated. The residue was purified by column chromatography on silica gel (EtOAc/hexane (1:6)) to give an inseparable mixture (40.3 mg) of **53** and **54** (**53**:**54** > 20:1 by ^1H NMR analysis): TLC R_f 0.28 (EtOAc/hexane (1:4)); IR (neat) 2980, 2950, 2900, 2850, 2830, 1780–1760, 1465, 1450, 1390, 1370, 1320, 1300, 1240–1205 cm^{-1}. **53**: ^1H NMR (270 MHz) δ 1.12 (s, 3 H), 1.14 (d, J = 7.3 Hz, 3 H), 1.21 (d, J = 6.6 Hz, 3 H), 2.16 (s, 3 H), 2.84 (dq, J = 6.2 and 7.3 Hz, 1 H), 3.36 (s, 3 H), 3.96 (q, J = 6.6 Hz, 1 H), 4.66 (s, 2 H), 6.11 (d, J = 6.2 Hz, 1 H). Anal. Calcd for $C_{12}H_{20}O_6$: C, 55.37; H, 7.74. Found: C, 55.43; H, 7.38.

To a cold (-30 °C) stirred solution of the mixture of **53** and **54** (40.3 mg) in CH_2Cl_2 (2 mL) under Ar were added TMSBr (0.081 mL, 0.62 mmol) and powdered molecular sieve 4A (28 mg). The mixture was stirred at -30 °C for 5 h, and then saturated aqueous $NaHCO_3$ (12 mL) was added. The mixture was extracted with CH_2Cl_2 (10 mL × 3). The combined extracts were dried and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:5)) afforded 28.8 mg (70%

overall from **52**) of **55**: white crystals; mp 130.0–131.0 °C; TLC R_f 0.13 (EtOAc/hexane (1:3)); $[\alpha]^{26}_D$ −114.6° (*c* 0.66, $CHCl_3$); IR ($CHCl_3$) 3600, 3025, 2985, 1775, 1450, 1390, 1370, 1225 cm^{-1}; ^1H NMR (270 MHz) δ 1.14 (d, *J* = 6.6 Hz, 3 H), 1.15 (s, 3 H), 1.22 (d, *J* = 6.6 Hz, 3 H), 2.16 (s, 3 H), 2.79 (dq, *J* = 6.6 and 6.6 Hz, 1 H), 4.07 (q, *J* = 6.6 Hz, 1 H), 6.15 (d, *J* = 6.6 Hz, 1 H). Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.38; H, 7.24.

(2*S*,3*R*,4*R*)-4-Acetoxy-2-acetyl-4-hydroxy-2,3-dimethylbutanoic Acid γ-Lactone, (−)-4-*epi*-Acetomycin (3). To a stirred solution of **55** (21.6 mg, 0.10 mmol)) in CH_2Cl_2 (1.5 mL) were added PCC (109.4 mg, 0.51 mmol) and powdered molecular sieve 4A (23 mg). After 5 h, the mixture was passed through a short column of silica gel, which was then eluted with excess Et_2O. The eluate was concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:5)) afforded 19.6 mg (92%) of **3**: a colorless oil; TLC R_f 0.37 (EtOAc/hexane (1:3)); $[\alpha]^{21}_D$ −140.6° (*c* 0.98, $CHCl_3$); $[\alpha]^{21}_D$ −126.4° (*c* 0.98, EtOH); IR (neat) 2990, 2950, 2890, 1770, 1715, 1450, 1365, 1300, 1200 cm^{-1}; ^1H NMR (270 MHz) δ 1.11 (d, *J* = 7.3 Hz, 3 H), 1.37 (s, 3 H), 2.09 (s, 3 H), 2.36 (s, 3 H), 3.05 (dq, *J* = 2.9 and 7.3 Hz, 1 H), 6.15 (d, *J* = 2.9 Hz, 1 H); ^{13}C NMR (100 MHz) δ 12.0, 16.2, 20.7, 26.0, 40.7, 59.3, 98.1, 168.9, 175.0, 202.9. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.04; H, 6.37.

Mixture of (2*S*,3*S*,4*R*)-4-Acetoxy-4-hydroxy-2-[(1*R*)-(methoxymethoxy)ethyl]-2,3-dimethylbutanoic Acid γ-Lactone (53) and Its (2*S*,3*S*,4*S*)-Diastereomer 54. To a stirred solution of compounds **52** (130.6 mg, 0.60 mmol) in toluene (4 mL) were added methanesulfonyl chloride (0.09 mL, 1.16 mmol) and Et_3N (0.83 mL, 5.95 mmol). The mixture was stirred for 30 min, and then KOAc (293.5 mg, 2.99 mmol) and dicyclohexyl-18-crown-6 (111.4 mg, 0.29 mmol) were added. The mixture was refluxed for 15 min. The mixture was then cooled to rt and was concentrated. The residue was partitioned between CH_2Cl_2 (10 mL) and H_2O (10 mL). The aqueous layer was drawn off and was extracted with CH_2Cl_2 (10 mL × 2). The extracts were added to the organic layer, and the whole was dried and concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:6)) afforded 121.4 mg (78%) of an inseparable mixture of **53** and **54**: a colorless oil; TLC R_f 0.48 (EtOAc/hexane (1:2)); IR (neat) 2970, 2930, 2890, 2850, 2820, 1790–1750, 1460, 1445, 1365, 1320, 1300, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 1.07 (d, *J* = 7.3 Hz, $^3/_4$ × 3 H), 1.12 (s, $^1/_4$ × 3 H), 1.14 (d, *J* = 7.3 Hz, $^1/_4$ × 3 H), 1.19 (s, $^3/_4$ × 3 H), 1.21 (d, *J* = 6.6 Hz, $^1/_4$ × 3 H), 1.22 (d, *J* = 6.6 Hz, $^3/_4$ × 3 H), 2.12 (s, $^3/_4$ × 3 H), 2.17 (s, $^1/_4$ × 3 H), 2.84 (dq, *J* = 6.6 and 7.3 Hz, $^1/_4$ × 1 H), 3.07 (dq, *J* = 5.9 and 7.3 Hz, $^3/_4$ × 1 H), 3.34 (s, $^3/_4$ × 3 H), 3.37 (s, $^1/_4$ × 3 H), 3.88–3.95 (m, 1 H), 4.58–4.67 (m, 2 H), 6.11 (d, *J* = 6.6 Hz, $^1/_4$ × 1 H), 6.55 (d, *J* = 5.9 Hz, $^3/_4$ × 1 H).

55 and (2*S*,3*R*,4*S*)-4-Acetoxy-4-hydroxy-2-[(1*R*)-1-hydroxyethyl]-2,3-dimethylbutanoic Acid γ-Lactone (56). To a cooled (−30 °C) stirred solution of the mixture of **53** and **54** (119 mg, 0.46 mmol) in CH_2Cl_2 (4 mL) under Ar were added TMSBr (0.18 mL, 1.36 mmol) and powdered molecular sieve 4A (95 mg). After 1.5 h, more TMSBr (0.12 mL) was added. The mixture was stirred for 30 min, and then it was diluted with saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with CH_2Cl_2 (20 mL × 3). The combined extracts were dried and concentrated. Repeated purification of the residue by column chromatography on silica gel (Wako gel C-300, EtOAc/hexane, 1:3) afforded 14.3 mg (14%) of **55**, 56.1 mg (57%) of **56**, and 1.5 mg (2%) of a mixture of **55** and **56**. **56**: a colorless oil; TLC R_f 0.12 (EtOAc/hexane (1:3)); $[\alpha]^{21}_D$ +92.8° (*c* 0.48, $CHCl_3$); IR (neat) 3500, 2980, 2940, 2890, 1790–1750, 1460, 1450, 1390, 1370, 1310, 1210 cm^{-1}; ^1H NMR (270 MHz) δ 1.07 (d, *J* = 7.0 Hz, 3 H), 1.21 (s, 3 H), 1.22 (d, *J* = 6.6 Hz, 3 H), 2.13 (s, 3 H), 3.02 (dq, *J* = 5.9 and 7.0 Hz, 1 H), 4.05 (q, *J* = 6.6 Hz, 1 H), 6.55 (d, *J* = 5.9 Hz, 1 H). Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.55; H, 7.46. Found: C, 55.55; H, 7.30.

(2*S*,3*R*,4*S*)-4-Acetoxy-2-acetyl-4-hydroxy-2,3-dimethylbutanoic Acid γ-Lactone, (+)-4,5-Di-*epi*-acetomycin (4). To a stirred solution of **56** (47.1 mg, 0.22 mmol) in CH_2Cl_2 (2.5 mL) were added PCC (244 mg, 1.13 mmol) and powdered molecular sieve 4A (43 mg). After 5 h, the mixture was passed through a short column of silica gel. The column was eluted with excess Et_2O. The eluate was concentrated. Purification of the residue by column chromatography on silica gel (EtOAc/hexane (1:5)) afforded 32.9 mg (71%) of **4**: white crystals; mp 42.0–43.0 °C; TLC R_f 0.34 (EtOAc/hexane (1:3)); $[\alpha]^{21}_D$ +85.1° (*c* 1.65, $CHCl_3$); $[\alpha]^{21}_D$ +91.5° (*c* 1.65, EtOH); IR ($CHCl_3$) 3025, 1790, 1765, 1715, 1450, 1360, 1325, 1230 cm^{-1}; ^1H NMR (270 MHz) δ 1.03 (d, *J* = 7.3 Hz, 3 H), 1.54 (s, 3 H), 2.15 (s, 3 H), 2.38 (s, 3 H), 3.24 (dq, *J* = 5.9 and 7.3 Hz, 1 H), 6.59 (d, *J* = 5.9 Hz, 1 H); ^{13}C NMR (100 MHz) δ 8.3, 17.1, 20.8, 25.8, 38.0, 57.1, 94.4, 168.8, 175.5, 202.9. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.30; H, 6.36.

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Supplementary Material Available: Spectroscopic data (^1H NMR and IR) for **23**, **24**, and **27**–**30** and the experimental procedure for the pharmacological assays (3 pages). Ordering information is given on any current masthead page.