Total Synthesis of (±)-Acetomycin and Design of Esterase-Resistant Analogs

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Received November 18, 1998; accepted December 28, 1998

The synthesis of acetomycin and related analogs was investigated. Acetomycin was synthesized from diethyl allyl(methyl)malonate in 6.5% yield over 18 steps. The total number of steps was improved compared to our previous synthesis; *i.e.*, four steps shorter, and the total yield was 4.5% greater than the previous synthesis. Acetomycin analogs with benzoyloxy and pivaloyloxy groups, instead of an acetoxy group at the 5-position of the γ-butyrolactone ring were designed as esterase-resistant models and prepared similarly. Although they showed a similar level of cytotoxicity as acetomycin *in vitro*, they were not resistant to porcine liver esterase, and lost cytotoxicity *in vivo*.

Key words acetomycin; stereoselective synthesis; antibiotic; cytotoxicity; esterase

Natural products have been a good source of biologically interesting compounds.[1)] Many natural organic compounds have been used as lead structures to explore clinically useful medicines for human health, as well as being important reagents for biological chemistry. Acetomycin (**1**) was isolated from *Streptomyces ramulosus* sp. in 1958 by Prelog *et al.*[2)] Its two-dimensional structure[3)] and biological synthesis[4)] were studied by the same group. The three-dimensional structure of the brominated derivative,[5)] and later of acetomycin itself,[6)] was determined by X-ray crystallographic analysis. Before Mamber *et al.* showed that acetomycin possesses unique *anti*-cancer activity against L-1210 murine leukemia cells and HCT-8 human colon adenocarcinoma cells in 1987,[7)] it was only thought to have weak antibacterial activity.[8)] Since then, **1** has become a good synthetic target for organic chemists.

Acetomycin is a rather small molecule (M.W. 214) which has four substituent groups located consecutively on the small γ-lactone ring. Its highly oxygenated structure with three chiral centers, including a quaternary carbon, is particularly attractive for synthetic chemists. Four total syntheses, including ours, have been reported thus far.[9)] Unfortunately, acetomycin, which has been shown to have potent *anti*-cancer activity, is inactivated *in vivo* due to rapid hydrolysis by esterase present in tissues.[10)] Indeed, the synthesis of esterase-resistant analogs is desired. Therefore, an efficient synthesis of acetomycin and its derivatives is still required in order to produce a new acetomycin analog. Tadano *et al.* studied structure–activity relationships of all four possible stereoisomers **2**, **3** and **4** based on the 4,5-substituents of acetomycin.[11)] However, little effort has been made to develop esterase-resistant analogs.[12)] It was thought that an acetoxy group could be replaced by a carbon functional group to make it resistant to esterase. However, while the resulting molecules were esterase-resistant, they unfortunately had lost the potent cytotoxicity.[13)] The alternative idea presented here is to design acetomycin derivatives bearing a more bulky acyloxy group at C-5 instead of an acetoxy group, in the hope that the bulky acyloxy group may confer resistance to esterase. Although we have previously reported a total synthesis of acetomycin, we report here an improved total synthesis of (±)-acetomycin (**1**) and its bulky acyloxy derivatives **5** and **6**, and biological evaluation including cytotoxicity and esterase-resistance.

The retrosynthetic analysis is described in Chart 1. A challenging problem in this synthesis is the stereocontrol of the three consecutive chiral centers located on the same α-side of the lactone ring. The acetyl group at the quaternary carbon center can be obtained from the corresponding α-hydroxymethyl ether **22**. An α-acyloxy group at the 5-position can be introduced by S_N2-type reaction of **22** *via* methanesulfonate ester, with acyloxyl anion. Compound **22** can be derived from **18** by oxidation of the hydroxymethyl to carboxylic acid, and alternative oxidation of the alkene to an aldehyde. Compound **18** can be derived from α,β-dimethyl-β-silyloxymethyl-γ-butyrolactone **13***cis*, the methyl group of which may be introduced by stereoselective alkylation of lactone **12**. During this sequence, the two hydroxymethyl groups at the quaternary center can be discriminated, which leads to the desired stereochemistry for the consecutive carbon centers in the acetomycin skeleton. Lactone **12** can be obtained by standard procedures starting from diethyl allyl(methyl)malonate.

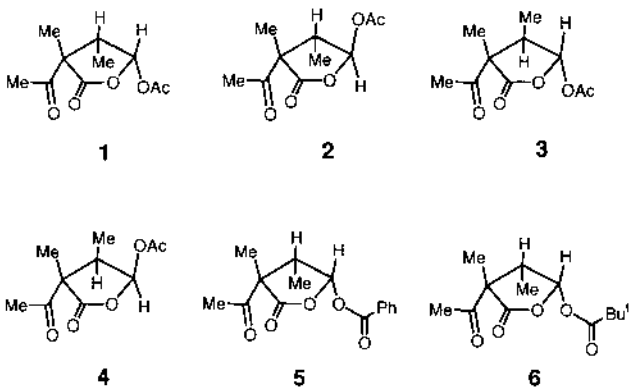

Fig. 1

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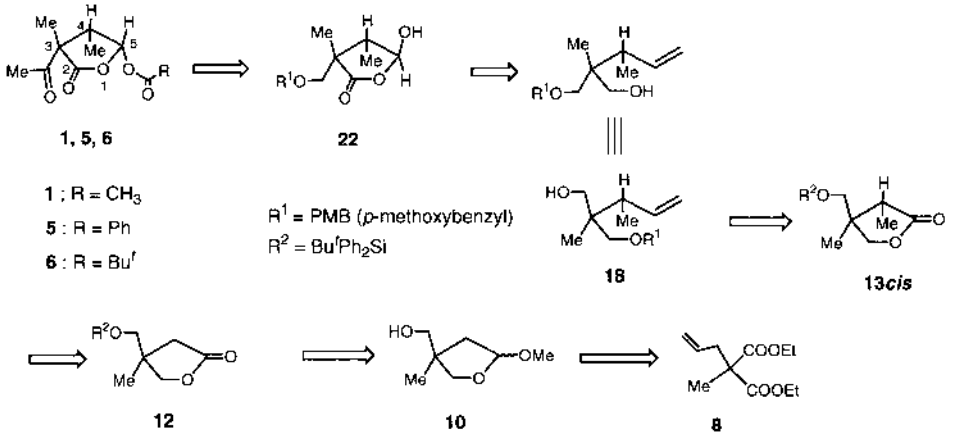


Chart 1. Retro-synthesis of Acetomycins, **1**, **5**, and **6**

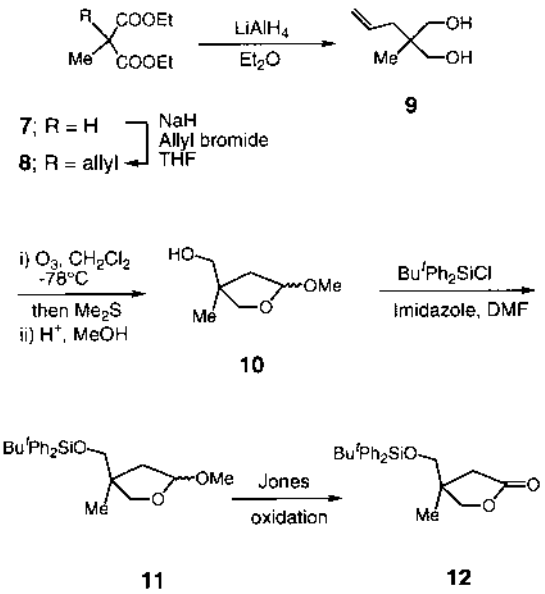


Chart 2. Preparation of γ-Butyrolactone **12**

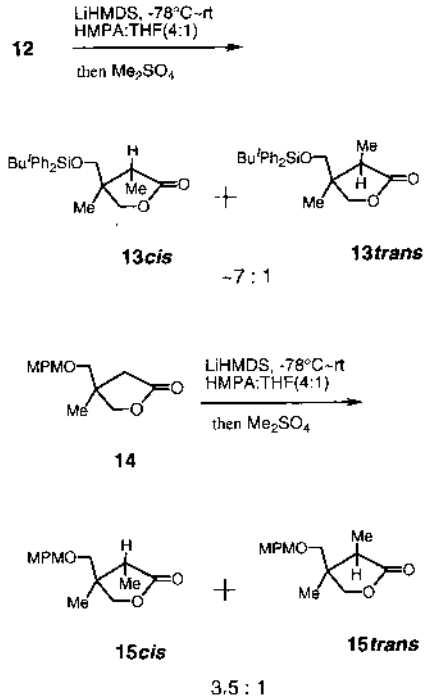


Chart 3. Stereoselective Methylation of 3,3-Disubstituted γ-Butyrolactone

Allylation of diethyl methylmalonate (**7**) gave diethyl allyl(methyl)malonate (**8**) in 98% yield, which was reduced by $LiAlH_4$ to give diol (**9**) in 89% yield. Ozonolysis of the double bond followed by treatment with a catalytic amount of sulfuric acid in methanol gave methyl glycoside (**10**) in 72% yield. The primary hydroxy group was protected as a silyl ether with *tert*-$BuPh_2SiCl$ (TBDPSCl) to give **11** in 81% yield. Finally, Jones oxidation of **11** completed the synthesis of lactone **12** in 51% yield from **8**. The Li enolate of **12** was generated with an excess of lithium hexamethyldisilazane (LiHMDS). Exposure of this enolate to dimethyl sulfate gave two mono methylated isomers (**13***cis* in 79% yield and **13***trans* in 11% yield) in a ratio of ~7 : 1. The reaction with iodomethane instead of dimethyl sulfate gave a mixture of **13***cis*, **13***trans*, and dimethylated product in a ratio of 5.3 : 1 : 3.5 and a combined yield of 67%. In the preliminary report,[9b] *p*-methoxybenzyl (PMB) was used as a protecting group for the hydroxymethyl group, instead of TBDPS, for the stereoselective methylation of lactone **14**. However, the diastereoselectivity remained at 3.5 : 1, although the *cis*-dimethyl product **15***cis* was formed in preference to **15***trans*.

Reduction of **13***cis* with diisobutylaluminum hydride (DIBAL-H) gave lactol **16** in 99% yield. Fortunately, Wittig methylenylation was successful for **16** bearing a TBDPS group as protection for the primary hydroxy group, in contrast to the failure using a PMB group. Compound **16** was treated with a 5-fold excess of methylenetriphenylphosphorane in tetrahydrofuran (THF) at −10 °C, and the mixture was then refluxed for 6 h. The desired alkene **17** was obtained in 79% yield without 1,5-migration of the TBDPS group, which would provide the alternative diastereomeric isomer. Protection of the resulting primary hydroxyl group with 4-methoxybenzyl trichloroacetimidate in the presence of CSA (10-camphorsulfonic acid) catalyst gave PMB ether **18** in 93% yield. Protection under anionic conditions with KH and PMBCl gave a mixture of diastereomers due to 1,5-silyl group migration. These three steps from 4β-methyl lactone **13***cis* provided **18** in 73% yield. Desilylation of the TBDPS group with Bu_4NF regenerated a hydroxymethyl group and gave **19** in 98% yield. This alcohol was subjected to oxida-

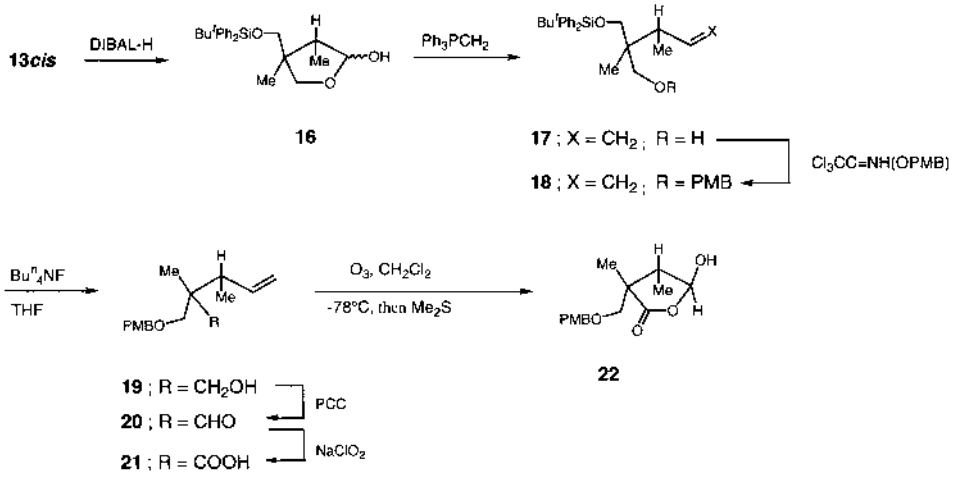


Chart 4.

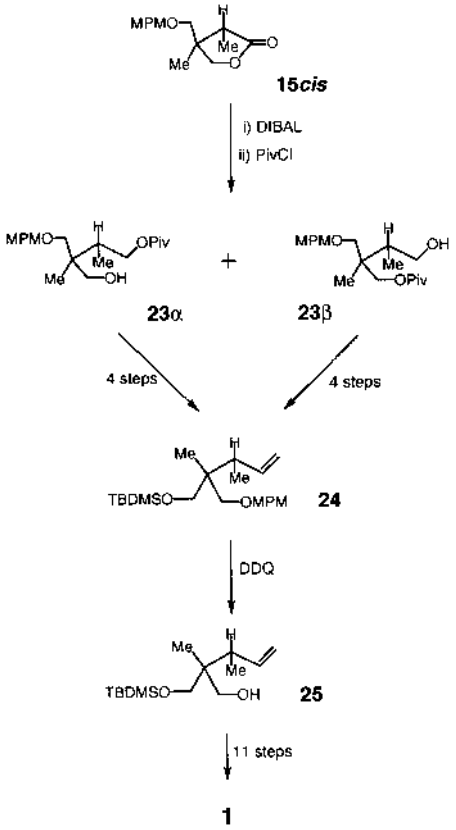


Chart 5. Previous Synthetic Route to Acetomycin

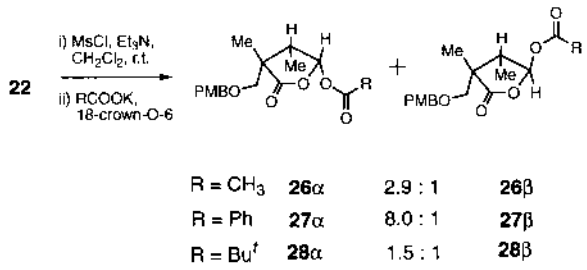
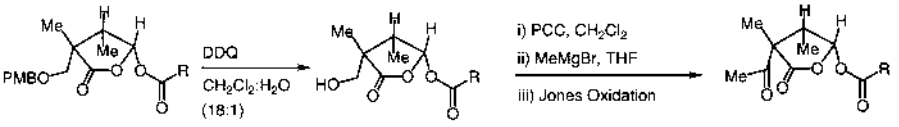


Chart 6. Introduction of Acyloxyl Groups to the Anomeric Position of **22**

tion to carboxylic acid *via* aldehyde **20** with pyridinium chlorochromate (PCC) followed by $NaClO_2$ to give **21** in 88% yield. Ozonolysis of the alkene gave an aldehyde, which immediately cyclized with the carboxylic acid to give 5-hydroxylactone **22** in 77% yield. In our previous synthesis,[9b] shown in Chart 5, after the lactone of **15***cis* was reduced, selective mono-protection of the two primary alcohols with a pivaloyl group was unsuccessful. Therefore, the synthesis was divided into two routes, but merges four steps later at **24**. Compound **24** eventually afforded acetomycin *via* **25**, which corresponded to the intermediate structure of **19** to **1**. The present key methylenylation from **16** to **17** shortened the previous synthetic route, and avoided the unnecessary synthesis of **24** from **15***cis via* **23**α and **23**β.

Compound **22** exists in a single anomeric form, the anomeric 5-hydroxyl group of which is presumably located at the β-side in a *trans* relation to the 4-methyl group. In fact, acetylation of **22** exclusively afforded **26**β in quantitative yield. When the ozonolysis of **21** was conducted in CH_2Cl_2 at $-78\,^{\circ}C$, and the resulting mixture was immediately acetylated in one-pot with acetyl chloride in the presence of Et_3N at the same temperature, the desired diastereomeric isomer **26**α was obtained as a minor product in a 3 : 1 ratio. The β-isomer could be transformed to 5-*epi*-acetomycin (**2**) in four steps using the method described for acetomycin.

Stereospecific Substitution Next, the problem is how to introduce an acetoxy group at the anomeric position, where the hydroxyl group of **22** stands favorably on the α-side. Steric 1,2- and 1,3-interactions against methyl and PMBoxymethyl groups were anticipated on the α-side of the ring. Displacement of the 5-hydroxyl group with a halide was totally unsuccessful. Direct introduction of an acetoxy group by Mitsunobu conditions using acetic acid, Bu_3P, and diethyl azodicarboxylate (DEAD) gave **26**β exclusively in 71% yield, where the reaction might proceed under an S_N1-like ion-pair mechanism, rather than by typical Mitsunobu displacement. Finally, **22** was transformed to the corresponding mesylate and treated with potassium acetate in the presence of crown ether in one-pot. After mesylation was complete in dry toluene at $0\,^{\circ}C$, a large excess of potassium acetate and crown ether (4 eq to **22**) were added and refluxed for 40 min in toluene. When 18-crown-*O*-6 was used, **26**α and **26**β were obtained as an inseparable mixture in a ratio of 2.9 : 1, as determined by ^{1}H-NMR. The use of dicyclohexyl-



26α ; R= CH_3 **29** ; R= CH_3 **1** ; R= CH_3
27α ; R= Ph **30** ; R= Ph **5** ; R= Ph
28α ; R= Bu^t **31** ; R= Bu^t **6** ; R= Bu^t

Chart 7

Table 1. Cytotoxicity and Half-Life Time to PLE[a)]

Substrate	IC_{50} (μg/ml)		Half-life time (h)
	KB Cell	L-1210	
1	0.28	0.045	1.0
5	0.22	0.052	1.2
6	0.32	0.050	1.0
AraC	0.50	0.030	—

a) Porcine liver esterase.

crown-*O*-6 gave a better ratio (4 : 1) in 82% yield. Somehow this selectivity was lower than in the previous case, where a *tert*-butyldimethylsilyl group was used instead of a PMB group. Selectivity was enhanced in the case of potassium benzoate, which gave **27**α and **27**β in an 8 : 1 ratio in 89% yield. When potassium pivaloate was used as a larger nucleophile for the substitution reaction, the selectivity for **28** decreased to 1.5 : 1 (**28**α : **28**β) with a combined yield of 77%.

The remaining step to reach **1** is manipulation of the PMBoxymethyl group to give an acetyl group. Deprotection of the PMB ether of **26**α and **26**β gave alcohols **29**α in 63% yield and **29**β in 16% yield. After the oxidation of **29**α under Swern conditions, the resulting aldehyde was reacted with methylmagnesium bromide to give diastereomeric alcohols, which upon oxidation with Jones reagent furnished **1** in 54% yield in 3 steps. The isomeric purity was confirmed by NMR and all spectroscopic data were consistent with those reported in the literature. For the benzoyloxy series, the major crystalline isomer **27**α was subjected to the same four steps as described for **1** to give benzoyl acetomycin **5** in 21% yield from **27**α *via* alcohol **30**. Pivaloyl acetomycin was also obtained in 38% yield from **28**α by the same reaction sequence.

Evaluation of Cytotoxicity and Resistance to Esterase The synthetic acetomycins **1**, **5**, and **6** were examined with regard to their cytotoxicity in cell culture of KB cells and L1210 murine leukemia cells, and for their resistance to porcine liver esterase. As shown in Table 1, synthetic **1** inhibited the growth of KB and L1210 cells at concentrations (IC_{50}) of 0.28 and 0.045 μg/ml, respectively. Benzoyl derivative **5** and pivaloyl derivative **6** were both as potent as **1** (0.22 and 0.052 μg/ml for **5** and 0.32 and 0.050 μg/ml for **6**). The anti-tumor activity of **6** was tested *in vivo* using colon 26 on mouse skin. However, compound **6** did not significantly reduce tumor weight compared to that in control mice. To examine the lack of activity *in vivo*, a hydrolysis experiment against porcine liver esterase was performed for **1**, **5**, and **6**. They were incubated in a phosphate buffer solution at pH 8.0 in the presence of porcine liver esterase and half-lives are shown in Table 1. Unexpectedly, compounds **5** and **6** were hydrolyzed as fast as **1**. This result confirms that they are inactivated by esterase *in vivo*. Consequently, the introduction of a bulky acyloxy group instead of an acetoxy group at the 5-position did not give new acetomycins that are effective *in vivo*. Further studies toward the design of esterase-resistant and anti-tumor acetomycin analogues are under way in our laboratory.

Experimental

Melting points were taken on a Yanako MP-3 melting point apparatus and are not corrected. ^{1}H-NMR were recorded on JEOL GXS(400 MHz) and Varian Gemini-300 (300 MHz) spectrometers in $CDCl_3$ with tetramethylsilane as an internal standard. Mass spectra were obtained on a JMS-MS700 instrument. IR spectra were recorded on a JASCO FT/IR-230 instrument. All air- or moisture-sensitive reactions were carried out in flame-dried glassware under an Ar atmosphere. THF and ether were distilled freshly over sodium/benzophenone ketyl under a nitrogen atmosphere. CH_2Cl_2 was dried over P_2O_5, and *N*,*N*-dimethylformamide (DMF), hexamethylphosphoramide (HMPA) and toluene were dried over CaH_2, and were distilled before use. Thin layer chromatography (TLC) was performed with Merck $60F_{254}$ precoated silica gel plates. Column chromatography was carried out using Merck Silica gel 60 (70—230 mesh) for gravity column, or Wako neutral aluminum oxide (200 mesh).

Diethyl Allylmethylmalonate (8) To an ice cooled suspension of NaH (2.75 g, 68.9 mmol) in anhydrous THF (70 ml) was added dropwise diethyl methylmalonate (10 g, 57.4 mmol) during 15 min, and the mixture was stirred for 15 min at the same temperature. Allyl bromide (8.32 g, 68.9 mmol) was added dropwise into the reaction mixture, and the mixture was stirred for 15 min. After the ice bath was removed, excess NaH was decomposed with ethanol. The mixture was diluted with ether (200 ml) and washed with sat. NH_4Cl, water and brine. The organic layer was dried over $MgSO_4$. After the solvent was removed, the residual liquid was distilled under reduced pressure to give **8** (12.1 g) in 98% yield, bp 103—105 °C/11 mmHg, *Rf*=0.46 (10% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 5.70 (1H, ddt, *J*= 16.5, 10.5, 7.4 Hz), 5.10 (1H, dd, *J*=16.5, 1.9 Hz), 5.09 (1H, dd, *J*=10.3, 1.9 Hz), 4.18 (4H, q, *J*=7.1 Hz), 2.61 (2H, d, *J*=7.4 Hz), 1.39 (3H, s), 1.25 (6H, t, *J*=7.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 171.6, 132.5, 118.7, 60.9, 53.2, 39.8, 19.5, 13.8. IR (film): 1730 cm^{-1}. MS *m/z* (rel. int. %): 214 (M^+, 22), 169 (20), 141 (45), 140 (59), 44 (base). HR-MS *m/z*: 214.1193 (Calcd for $C_{11}H_{18}O_4$: 214.1205).

2-Hydroxymethyl-2-methyl-4-penten-1-ol (9) To an ice cooled suspension of $LiAlH_4$ in anhydrous ether (100 ml) was added dropwise **8** (10.8 g, 50.4 mmol) dissolved in ether (50 ml) during 20 min. The mixture was stirred for 10 min and quenched with dil. HCl (15 ml). After stirring for an additional 10 min at room temperature, the precipitate was filtered off by suction and the filtrate was diluted with EtOAc (500 ml). The organic extract was washed with water, and brine and dried over $MgSO_4$. The solvent was removed and the residual liquid was distilled to give diol **9** (5.81 g) in 89% yield, bp 95—100 °C/2 mmHg, *Rf*=0.26 (50% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 5.81 (1H, ddt, *J*=17.6, 9.3, 7.6 Hz), 5.07 (1H, dm, *J*=17.3 Hz), 5.06 (1H, dm, *J*=9.3 Hz), 3.52 (2H, d, *J*=10.7 Hz), 3.48 (2H, d, *J*=10.7 Hz), 2.93 (2H, br), 2.08 (2H, d, *J*=7.6 Hz), 0.81 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 134.1, 117.8, 69.7, 39.2, 38.6, 18.4. IR (film): 3380 cm^{-1}. LR-MS (FAB): *m/z*: 131 (M^++1). HR-MS (FAB) *m/z*: 131.1065 (Calcd for $C_7H_{15}O_2$: 131.1072).

4-Hydroxymethyl-2-methoxy-4-methyltetrahydrofuran (10) To a solution of **9** (8.7 g, 66.8 mmol) in a mixture of CH_2Cl_2 and MeOH (1 : 3, *ca.* 240 ml), ozone gas was bubbled at −78 °C until a blue color appeared. After excess of ozone was removed by bubbling with nitrogen, the reaction was

quenched with tributylphosphine (13.5 g, 66.8 mmol). The mixture was stirred for 3 h at room temperature, and then for an additional 4 h in the presence of sulfuric acid (3 ml). The mixture was neutralized with saturated sodium carbonate. The organic phase was condensed under reduced pressure to *ca.* 20—30 ml and diluted with EtOAc (300 ml). This layer was washed with water, brine, dried over $MgSO_4$, and the solvent removed. The residual oil was purified by column chromatography on silica gel eluting with 50% EtOAc in hexane to give **10** (7.0 g) in 72% yield. Oil, a 3 : 2 diastereomeric mixture, *Rf*=0.41 (70% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 5.02 (1H, m), 3.94 (2/5H, d, *J*=8.6 Hz), 3.79 (3/5H, d, *J*=8.7 Hz), 3.58 (2/5H, d, *J*=8.6 Hz), 3.58 (3/5H, d, *J*=8.7 Hz), 3.56 (2/5H, d, *J*=10.7 Hz), 3.47 (2/5H, d, *J*=10.7 Hz), 3.43 (6/5H, s), 3.34 (3H, s), 2.07 (3/5H, dd, *J*=13.6, 5.8 Hz), 1.89 (4/5H, d, *J*=3.4 Hz), 1.61 (3/5H, dd, *J*=13.6, 2.3 Hz), 1.15 (9/5H, s), 1.12 (6/5, s). ^{13}C-NMR ($CDCl_3$) δ: 105.8 (3/5C), 105.5 (2/5C), 75.1 (2/5C), 73.9 (3/5C), 68.8 (3/5C), 68.7 (2/5C), 54.6 (3/5C), 54.4 (2/5C), 43.8 (3/5C), 43.6 (2/5C), 43.2 (2/5C), 42.5 (3/5C), 23.4 (2/5C), 21.0 (3/5C). IR (film): 3440 cm^{-1}. LR-MS *m/z* (rel. int. %): 115 (M^+-31, base), 97 (24), 85 (32), 84 (31), 83 (35). HR-MS (FAB) *m/z*: 147.1051 (Calcd for $C_7H_{15}O_3$: 147.1021).

4-(*tert*-Butyldiphenylsilyl)oxymethyl-2-methoxyl-4-methyltetrahydrofuran (11) A mixture of **10** (1.02 g, 6.96 mmol), imidazole (1.66 g, 24.4 mmol), and *tert*-butyldiphenylsilyl chloride (2.1 g, 7.66 mmol) was stirred in DMF (8 ml) at room temperature overnight. The mixture was diluted with 50% EtOAc in hexane (300 ml) and washed with water and brine. The organic layer was dried over $MgSO_4$ and condensed. The residual oil was chromatographed on silica gel eluting with 5—7.5% EtOAc in hexane to give **11** (2.18 g) as a 3 : 2 diastereomeric mixture in 81% yield. Oil, *Rf*=0.44 (10% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.66—7.63 (4H, m), 7.46—7.35 (6H, m), 5.04 (2/5H, dd, *J*=4.6, 3.5 Hz), 4.93 (3/5H, dd, *J*=5.7, 2.3 Hz), 3.88 (3/5H, d, *J*=8.5 Hz), 3.84 (2/5H, d, *J*=8.4 Hz), 3.61 (2/5H, d, *J*=9.6 Hz), 3.57 (2/5H, d, *J*=9.6 Hz), 3.55 (1H, d, *J*=8.4 Hz), 3.45 (3/5H, d, *J*=9.6 Hz), 3.34 (3/5H, d, *J*=9.6 Hz), 3.33 (9/5H, s), 3.30 (6/5H, s), 1.98 (3/5H, dd, *J*=13.6, 5.7 Hz), 1.80 (2/5H, d, *J*=3.5 Hz),1.80 (2/5H, d, *J*=4.6 Hz), 1.55 (3/5H, dd, *J*=13.6, 2.3 Hz), 1.20 (9/5H, s), 1.17 (6/5H, s), 1.06 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 135.6 (4C), 133.6 (6/5C), 133.5 (4/5C), 129.6 (6/5C), 129.6 (4/5C), 127.6 (12/5C), 127.6 (8/5C), 105.9 (3/5C), 105.8 (2/5C), 75.5 (2/5C), 74.1 (3/5C), 69.7 (2/5C), 69.5 (3/5C), 54.8 (3/5), 54.7 (2/5C), 44.7 (2/5C), 44.5 (3/5C), 42.9 (2/5C), 42.6 (3/5C), 26.8 (3C), 23.5 (2/5C), 21.7 (1C), 19.3 (3/5C). LR-MS *m/z* (rel. int. %): 384 (M^+, 31), 353 (25), 326 (55), 309 (21), 295 (81), 97 (base). HR-MS (FAB) *m/z*: 385.2058 (Calcd for $C_{23}H_{33}O_3Si$: 385.2199).

Dihydro-4-(*tert*-butyldiphenylsilyl)oxymethyl-4-methyl-2(3*H*)-furanone (12) To a solution of **11** (540 mg, 1.4 mmol) in acetone (5 ml) was added Jones reagent (1.85 M, 1.89 ml) at room temperature, and the mixture was stirred for 2 h. After excess reagent was decomposed by addition of isopropanol (1 ml), the mixture was diluted with EtOAc (70 ml) and washed with sat. $NaHCO_3$, water, and brine. The organic layer was dried over $MgSO_4$ and condensed. The residual oil was purified by column chromatography on silica gel eluted with 10—20% EtOAc in hexane to give **12** (513 mg) in 99% yield. Oil, *Rf*=0.40 (20% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.64—7.60 (4H, m), 7.48—7.36 (6H, m), 4.29 (1H, d, *J*=8.9 Hz), 3.94 (1H, d, *J*=8.9 Hz), 3.51 (1H, d, *J*=10.3 Hz), 3.46 (1H, d, *J*=10.3 Hz), 2.61 (1H, d, *J*=17.3 Hz), 2.23 (1H, d, *J*=17.3 Hz), 1.15 (3H, s), 1.07 (9H, s). ^{13}C-NMR ($CDCl_3$) δ: 176.8, 135.6, 132.7, 130.0, 127.8, 75.8, 68.4, 41.8, 38.3, 26.8, 21.6, 19.3. IR (film): 1780 cm^{-1}. LR-MS *m/z* (rel. int. %): 368 (M^+, 12), 336 (18), 311 (base). HR-MS *m/z*: 311.1088 (Calcd for $C_{18}H_{19}O_3Si$: 311.1104, M^+–*tert*-Bu).

Methylation of 12 LiHMDS was prepared from hexamethyldisilazane (1.13 g, 7.01 mmol), and BuLi (1.56 M in hexane, 4.35 ml, 6.78 mmol) in THF (9.5 ml) and HMPA (4 ml) by the standard procedure at −78 °C. A solution of **12** (418 mg, 1.13 mmol) in THF (2.5 ml) was dropped into the solution of LiHMDS at −78 °C, and the mixture was stirred for 2 h at the same temperature. Dimethyl sulfate (1.42 g, 11.3 mmol) was then added. After the addition, the bath was removed and the mixture stirred for an additional 1 h at room temperature and quenched with sat. NH_4Cl (8 ml) and extracted with ether (300 ml). The organic layer was washed with water, brine, and dried over $MgSO_4$. After solvent was removed, the residue was chromatographed on silica gel. Elution with 5—7.5% EtOAc in hexane gave **13***cis* (341 mg) in 79% yield, and elution with 15—20% EtOAc in hexane gave a mixture of **13***trans* and **12** (85 mg, 1.2 : 1), which were separated by HPLC. **13***cis*: mp 77—78 °C recrystallized from EtOH, *Rf*=0.50 (20% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.63—7.60 (4H, m), 7.46—7.38 (6H, m), 4.26 (1H, d, *J*=8.6 Hz), 3.89 (1H, d, *J*=8.6 Hz), 3.50 (1H, d, *J*=10.3 Hz), 3.47 (1H, d, *J*=10.3 Hz), 3.48 (1H, s), 2.75 (1H, q, *J*=7.3 Hz), 1.01 (3H, d, *J*=7.3 Hz), 0.94 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 179.6, 135.1, 132.7, 130.0, 127.9, 74.2, 66.4, 45.0, 39.5, 26.8, 19.3, 16.8, 8.7. IR (KBr): 1770 cm^{-1}. LR-MS *m/z* (rel. int. %): 325 (M^+-57, base), 267 (9) 238 (16), 199 (58). *Anal.* Calcd for $C_{23}H_{30}O_3Si$: C, 72.21; H, 7.90. Found: C, 72.25; H, 8.16. **13***trans*; Oil, *Rf*=0.38 (20% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.66—7.61 (4H, m), 7.45—7.38 (6H, m), 4.30 (1H, d, *J*=9.0 Hz), 3.85 (1H, d, *J*=9.0 Hz), 3.53, (1H, d, *J*=10.3 Hz), 3.37 (1H, d, *J*=10.3 Hz), 2.34 (1H, q, *J*=7.3 Hz), 1.16 (3H, d, *J*=7.3 Hz), 1.06 (9H, s), 1.03 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 179.1, 135.7, 132.7, 129.9, 127.7, 74.9, 66.7, 43.9, 43.1, 26.6, 19.9, 19.1, 8.0. IR (film): 1780 cm^{-1}. LR-MS *m/z* (rel. int. %) 325 (M^+-57, base), 297 (3), 267 (9), 199 (43). HR-MS (FAB) *m/z*: 383.2043 (Calcd for $C_{23}H_{31}O_3Si$: 383.2043). Some dimethylated product was obtained when iodomethane was used instead of dimethylsulfate. Dihydro-4-(*tert*-butyldiphenylsilyl)oxymethyl-3,3,4-trimethyl-2(3*H*)-furanone: Oil, *Rf*=0.50 (20%, EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.66—7.60 (4H, m), 7.47—7.36 (6H, m), 4.22 (1H, d, *J*=9.2 Hz), 3.89 (1H, d, *J*=9.0 Hz), 3.51 (1H, d, *J*=10.2 Hz), 3.42 (1H, d, *J*=10.2 Hz), 1.15 (3H, s), 1.08 (3H, s), 1.06 (9H, s), 0.97 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 182.2, 135.6, 132.7, 129.8, 127.7, 73.2, 67.4, 45.7, 43.3, 26.6, 21.2, 19.1, 17.8, 15.8. IR (film): 1780 cm^{-1}. LR-MS *m/z* (rel. int. %): 339 (M^+-57, base), 325 (7), 312 (20), 311 (75); HR-MS (FAB) *m/z*: 397.2174 (Calcd for $C_{24}H_{33}O_3Si$: 397.2199).

(3*S,4*S**)-4-(*tert*-Butyldiphenylsilyl)oxymethyl-3,4-dimethyl-2-hydroxytetrahydrofuran (16)** To a solution of **13***cis* (4.49 g, 11.7 mmol) in anhydrous CH_2Cl_2 (70 ml) was dropped DIBAL-H (0.93 M in hexane, 13.8 ml, 12.8 mmol) at −78 °C. After stirring for 20 min at the same temperature, the reaction was quenched with sat. NH_4Cl (15 ml). The solid was filtered off by suction and washed with EtOAc (300 ml). The combined filtrate was washed with water, brine, and dried over $MgSO_4$. The solvent was evaporated and the residual oil was purified by column chromatography on silica gel eluting with 20% EtOAc in hexane to give **16** (4.47 g) in 99% yield. Oil, a 1 : 2 diastereomeric mixture, *Rf*=0.43 (30% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.69—7.67 (4H, m), 7.48—7.39 (6H, m), 5.40 (1/3H, d, *J*=5.1 Hz), 5.12 (2/3H, d, *J*=5.1 Hz), 4.09 (2/3H, d, *J*=8.3 Hz), 3.97 (1/3H, d, *J*=8.4 Hz), 3.80 (1/3H, d, *J*=8.3 Hz), 3.63 (2/3H, d, *J*=8.3 Hz), 3.52 (4/3H, s), 3.44 (2/3H, s), 2.15 (1/3H, qd, *J*=7.2, 5.1 Hz), 2.02 (2/3H, qd, *J*=7.2, 5.1 Hz), 1.13 (1H, s), 1.10 (9H, s), 1.00 (2H, s), 0.99 (2H, d, *J*=7.2 Hz), 0.96 (1H, d, *J*=7.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 135.6 (4C), 133.3 (2/3C), 133.1 (4/3C), 129.7 (4/3C), 129.6 (2/3C), 127.7 (8/3C), 127.6 (4/3C), 105.4 (2/3C), 101.0 (1/3C), 76.3 (1/3C), 75.9 (2/3C), 69.6 (1/3C), 68.8 (2/3C), 46.7 (2/3C), 46.2 (2/3C), 44.8 (1/3C), 42.4 (1/3C), 26.8 (3C), 19.3 (2/3C), 18.7 (1/3C), 17.2 (1C), 11.2 (2/3C), 8.6 (1/3C). IR (film): 3380 cm^{-1}. LR-MS *m/z* (rel. int. %): 366 (M^+-18, 5), 327 (18), 309 (base). HR-MS (FAB) *m/z*: 367.2120 (Calcd for $C_{23}H_{31}O_2Si$: 367.2093, M^+-OH).

(2*S,3*R**)-2-(*tert*-Butyldiphenylsilyl)oxymethyl-2,3-dimethyl-4-penten-1-ol (17)** To a cooled suspension of methyltriphenylphosphonium bromide (1.12 g, 3.13 mmol) in anhydrous THF (20 ml) at −10 °C was dropped BuLi (1.56 M in hexane, 1.89 ml, 2.95 mmol) during 10 min, and the mixture was stirred for an additional 40 min at the same temperature. A solution of **16** (227 mg, 0.59 mmol) in THF (10 ml) was then added dropwise at −10 °C. After the addition, the bath was removed and the mixture was stirred for 10 min at room temperature and refluxed for 6 h. After cooling, the mixture was quenched with methanol (2 ml) and diluted with ether (300 ml). The organic mixture was washed with sat. NH_4Cl, water, and brine, and dried over $MgSO_4$. The solvent was removed and the residual oil was purified by column chromatography on silica gel eluting with 10% EtOAc in hexane to give **17** (179 mg) in 79% yield. Oil, *Rf*=0.36 (10% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.73—7.68 (4H, m), 7.49—7.38 (6H, m), 5.83 (1H, ddd, *J*=17.1, 10.2, 8.6 Hz), 5.06 (1H, dd, *J*=17.1, 1.9 Hz), 5.02 (1H, dd, *J*=10.2, 1.9 Hz), 3.62 (1H, d, *J*=9.4 Hz), 3.61 (2H, s), 3.55 (1H, d, *J*=9.4 Hz), 2.55 (1H, dq, *J*=8.6, 6.8 Hz), 2.34 (1H, br), 1.10 (9H, s), 0.87 (3H, d, *J*=6.8 Hz), 0.70 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 140.6, 135.7, 135.6, 132.9, 132.8, 129.9, 129.8, 127.8, 114.9, 69.4, 69.1, 41.5, 38.8, 26.9, 19.2, 14.4, 14.1. IR (film): 3460 cm^{-1}. LR-MS *m/z* (rel. int. %): 325 (M^+-57, 95), 295 (6), 269 (6), 247 (25), 229 (16), 199 (base). HR-MS (FAB) *m/z* 383.2432: (Calcd for $C_{24}H_{35}O_2Si$: 383.2406).

(2*S,3*R**)-[2-(*tert*-Butyldiphenylsilyl)oxymethyl-2,3-dimethyl-4-pentenyl] (4-methoxy-phenylmethyl)methyl Ether (18)** A mixture of **17** (338 mg, 0.883 mmol), 4-methoxyphenyl trichloroacetoimidate (674 mg, 2.38 mmol), and CSA (103 mg, 0.44 mmol) in anhydrous CH_2Cl_2 (10 ml) was stirred for 15 h at room temperature. The mixture was diluted with ether (300 ml), washed with sat. $NaHCO_3$, water, and brine, and dried over $MgSO_4$. The solvent was removed and the residual oil was purified by silica gel chromatography eluting with 2.5% EtOAc in hexane to give **18** (414 mg) in 93% yield. Oil, *Rf*=0.52 (10% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ:

7.67—7.63 (4H, m), 7.42—7.28 (6H, m), 7.22 (2H, d, J=8.6 Hz), 6.86 (2H, d, J=8.6 Hz), 5.77 (1H, ddd, J=17.1, 10.1, 8.9 Hz), 4.97 (1H, dd, J=17.1, 2.4 Hz), 4.93 (1H, dd, J=10.1, 2.4 Hz), 4.41 (2H, s), 3.81 (3H, s), 3.58 (1H, d, J=9.6 Hz), 3.52 (1H, d, J=9.6 Hz), 3.38 (2H, s), 2.43 (1H, dq, J=8.9, 7.0 Hz), 1.05 (9H, s), 0.87 (3H, d, J=7.0 Hz), 0.79 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 158.8, 141.2, 135.7, 133.8, 131.2, 129.4, 128.8, 127.5, 114.4, 113.6, 73.3, 72.8, 66.0, 55.3, 41.7, 40.3, 26.9, 19.4, 15.4, 14.5. LR-MS *m/z* (rel. int. %): 445 (M^+-57, 21), 395 (5), 325 (16), 247 (20), 199 (40), 122 (base), 121 (89). HR-MS (FAB) *m/z*: 503.2965 (Calcd for $C_{32}H_{43}O_3Si$: 503.2982).

(2*R,3*R**)-2,3-Dimethyl-2-(4-methoxyphenylmethyl)oxymethyl-4-penten-1-ol (19)** To a solution of **18** (2.34 g, 4.65 mmol) in THF (20 ml) was added Bu_4NF (1 M THF solution, 7 ml), and the mixture refluxed for 7 h. After cooling, the mixture was diluted with 20% EtOAc in hexane (150 ml), and washed with water, and brine. The organic layer was dried over $MgSO_4$, and evaporated. The residual oil was purified by column chromatography on silica gel eluting with 10% EtOAc in hexane to give **19** (1.2 g) in 98% yield. Oil, *Rf*=0.30 (30% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.25 (2H, d, J=8.6 Hz), 6.89 (2H, d, J=8.6 Hz), 5.75 (1H, ddd, J=17.0, 10.3, 8.9 Hz), 5.01 (1H, dd, J=17.0, 2.1 Hz), 5.00 (1H, dd, J=10.3, 2.1 Hz), 4.41 (2H, s), 3.81 (3H, s), 3.58 (1H, dd, J=9.9, 1.5 Hz), 3.54 (1H, d, J=9.9 Hz), 3.47 (1H, d, J=8.8 Hz), 3.29 (1H, d, J=8.8 Hz), 3.02 (1H, br), 2.64 (1H, dq, J=8.9, 7.0 Hz), 1.00 (3H, d, J=7.0 Hz), 0.69 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 159.1, 140.5, 129.9, 129.1, 115.0, 113.7, 77.7, 73.1, 69.5, 55.1, 40.5, 38.5, 14.5, 14.2. IR (film): 3430 cm^{-1}. LR-MS *m/z* (rel. int. %): 264 (M^+, 48), 242 (14), 199 (21), 156 (22), 121 (base). HR-MS *m/z*: 264.1701 (Calcd for $C_{16}H_{24}O_3$: 264.1726).

(2*R,3*R**)-2,3-Dimethyl-2-(4-methoxyphenylmethyl)oxymethy-4-pentenoic Acid (21)** To a solution of **19** (404 mg, 1.53 mmol) in CH_2Cl_2 (24 ml) was added PCC (495 mg, 2.29 mmol) and the mixture was stirred for 10 h at room temperature. The mixture was passed through a Florisil column to give aldehyde **20**, which was used for the next oxidation. When this aldehyde was re-purified by column chromatography on silica gel eluting with 10% EtOAc in hexane, the following physical and spectroscopic data for the pure aldehyde were obtained. Oil, *Rf*=0.40 (15% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 9.58 (1H, s), 7.20 (2H, d, J=8.6 Hz), 6.87 (2H, d, J=8.6 Hz), 5.68 (1H, ddd, J=17.0, 10.2, 8.6 Hz), 5.07 (1H, dd, J=17.0, 2.1 Hz), 5.06 (1H, dd, J=10.2 and 2.1 Hz), 4.39 (2H, s), 3.81 (3H, s), 3.54 (1H, d, J=9.2 Hz), 3.33 (1H, d, J=9.2 Hz), 2.68 (1H, dq, J=8.6, 6.9 Hz), 1.00 (3H, s), 0.91 (3H, d, J=6.9 Hz). The oxidant to give carboxylic acid was prepared from sodium chlorite (1.05 g, 11.6 mmol) and sodium phosphate monobasic monohydrate (1.31 g, 9.49 mmol) in distilled water (6.3 ml) at 0 °C. This mixture was added to a mixture of the above aldehyde, and 2-methyl-2-butene (1.7 ml) in a mixture of THF and *tert*-butanol (5 : 8, 13 ml) at 0 °C. The mixture was stirred for 30 min at the same temperature and diluted with ether (300 ml). The separated organic layer was washed with water and brine, dried over $MgSO_4$, and condensed. The residue was purified by column chromatography on silica gel eluting with EtOAc to give **21** (380 mg) in 88% yield. Oil, *Rf*=0.35 (40% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.22 (2H, d, J=8.7 Hz), 6.86 (2H, d, J=8.7 Hz), 5.65 (1H, ddd, J=17.0, 10.3, 8.8 Hz), 5.05 (1H, dd, J=17.0, 1.8 Hz), 5.03 (1H, dd, J=10.3, 1.8 Hz), 4.48 (1H, d, J=13.2 Hz), 4.44 (1H, d, J=13.2 Hz), 3.80 (3H, s), 3.58 (1H, d, J=8.9 Hz), 3.36 (1H, d, J=8.9 Hz), 2.64 (1H, dq, J=8.8, 6.9 Hz), 1.19 (3H, s), 0.99 (3H, d, J=6.9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 181.5, 159.0, 138.6, 130.0, 129.0, 116.2, 113.6, 75.1, 72.9, 55.1, 50.1, 41.9, 15.6, 14.4. IR (film): 2940, 1700 cm^{-1}. LR-MS *m/z* (rel. int. %): 278 (M^+, 26), 222 (3), 199 (4), 174 (8), 136 (24), 121 (base). HR-MS *m/z*: 278.1535. (Calcd for $C_{16}H_{22}O_4$: 278.1518).

Ozonization of 21, Synthesis of (3*S,4*S**,5*S**)-Dihydro-3,4-dimethyl-5-hydroxy-3-(4-methoxyphenylmethyl)oxymethyl-2(3*H*)furanone (22)** To a solution of **21** (380 mg, 1.37 mmol) in CH_2Cl_2 (50 ml), ozone gas was introduced through a glass tube bubbler at −78 °C. The reaction was monitored by TLC. When the starting carboxylic acid was consumed, ozone gas was stopped and nitrogen gas was bubbled for a few min in order to remove the remaining ozone. The mixture was then quenched with tributylphosphine (276 mg, 1.37 mmol), and stirred for 1.5 h at room temperature. After the solvent was removed, the residue was chromatographed on silica gel eluting with 30% EtOAc in hexane to give **22** (297 mg) in 77% yield, mp 52—54 °C recrystallized from ether, *Rf*=0.38 (40% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.22 (2H, d, J=8.7 Hz), 6.88 (2H, d, J=8.7 Hz), 5.52 (1H, dd, J=13.6, 6.0 Hz), 5.28 (1H, d, J=13.6 Hz), 4.56 (1H, d, J=11.2 Hz), 4.43 (1H, d, J=11.2 Hz), 3.80 (3H, s), 3.50 (1H, d, J=9.2 Hz), 3.33 (1H, d, J=9.2 Hz), 2.41 (1H, qd, J=7.4, 6.0 Hz), 1.13 (3H, s), 1.02 (3H, d, J=7.4 Hz). ^{13}C-NMR ($CDCl_3$) δ: 180.0, 159.8, 129.9, 127.4, 114.1, 98.9, 73.8, 71.0, 55.2, 45.6, 43.9, 19.9, 7.9. IR (KBr): 3360, 1740 cm^{-1}: LR-MS *m/z* (rel. int. %): 280 (M^+, 25), 262 (12), 138 (23), 137 (48), 136 (63), 121 (base). HR-MS *m/z*: 280.1286 (Calcd for $C_{15}H_{20}O_5$: 280.1311). *Anal.* Calcd for $C_{15}H_{20}O_5$: C, 64.27; H, 7.19. Found: C, 64.34; H, 7.43.

General Procedure for Introduction of Acyloxy Group to 22 To an ice cooled solution of **22** (46 mg, 0.164 mmol) in anhydrous toluene (2.4 ml) were added methanesulfonyl chloride (1 M toluene solution, 0.475 ml) and triethylamine (50 mg, 0.492 mmol), and the mixture was stirred for 20 min at the same temperature. After the ice bath was removed, the mixture was diluted with anhydrous toluene (1.3 ml). Anhydrous potassium carboxylate (3.28 mmol) and dicyclohexyl-18-crown-*O*-6 (244 mg, 0.656 mmol) were added, and the mixture was refluxed for 40 min for potassium acetate, 30 min for potassium benzoate, and 10 min for potassium pivaloate. After cooling the reaction mixture, it was directly passed through a silica gel column eluting with 15% EtOAc.

Reaction with AcOK; **26**α and **26**β were obtained in 82% yield as an inseparable mixture. Oil, a 4 : 1 mixture of α and β isomers. *Rf*=0.35 (30% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.24 (2/5H, d, J=8.9 Hz), 7.24 (8/5H, d, J=8.7 Hz), 6.87 (2/5H, d, J=8.9 Hz), 6.86 (8/5H, d, J=8.7 Hz), 6.51 (4/5H, d, J=6.1 Hz), 6.30 (1/5H, d, J=6.8 Hz), 4.48 (1/5H, d, J=11.8 Hz), 4.43 (8/5H, s), 4.37 (1/5H, d, J=11.8 Hz), 3.80 (3H, s), 3.56 (4/5H, d, J=9.3 Hz), 3.46 (4/5H, d, J=9.3 Hz), 3.42 (1/5H, d, J=9.2 Hz), 3.36 (1/5H, d, J=9.2 Hz), 2.49 (4/5H, qd, J=7.2, 6.1 Hz), 2.24 (1/5H, dq, J=7.1, 6.8 Hz), 2.13 (3/5H, s), 1.93 (12/5H, s), 1.28 (12/5H, s), 1.17 (3/5H, s), 1.10 (3/5H, d, J=7.1 Hz), 1.07 (12/5H, d, J=7.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 178.9 (4/5C), 170.8 (1/5C), 169.5 (1/5C), 169.3 (4/5C), 159.4 (1/5C), 159.2 (4/5C), 129.9 (4/5C), 129.3 (2C), 129.2 (1/5C), 113.8 (2/5C), 113.7 (8/5C), 98.4 (1/5C), 93.9 (4/5C), 73.1 (1C), 71.9 (1/5C), 71.3 (4/5C), 55.2 (1C), 48.4 (1/5C), 45.4 (4/5C), 45.0 (1/5C), 42.9 (4/5C), 20.8 (1/5C), 20.7 (4/5C), 20.6 (4/5C), 19.1 (1/5C), 9.2 (1/5C), 8.2 (4/5C). IR (film): 1790, 1760 cm^{-1}. LR-MS *m/z* (rel. int. %): 322 (M^+, 37), 262 (67), 176 (57), 137 (84), 136 (72), 121 (base). HR-MS *m/z*: 322.1397 (Calcd for $C_{17}H_{22}O_6$: 322.1417).

Reaction with PhCOOK: **27**α was obtained in 74% yield after crystallization of a diastereomeric mixture, mp 56—59 °C recrystallized from EtOAc : hexane (3 : 17), *Rf*=0.43 (30% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.87 (2H, dd, J=8.3, 1.5 Hz), 7.55 (1H, tt, J=7.6, 1.5 Hz), 7.36 (1H, d, J=8.3 Hz), 7.33 (1H, d, J=7.6 Hz), 7.23 (2H, d, J=8.6 Hz), 6.80 (2H, d, J=8.6 Hz), 6.79 (1H, d, J=6.1 Hz), 4.52 (1H, d, J=11.9 Hz), 4.48 (1H, d, J=11.9 Hz), 3.75 (3H, s), 3.60 (1H, d, J=9.4 Hz), 3.54 (1H, d, J=9.4 Hz), 2.62 (1H, qd, J=7.3, 6.1 Hz), 1.32 (3H, s), 1.16 (3H, d, J=7.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 179.0, 164.9, 159.2, 133.5, 129.8, 129.6, 129.2, 128.4, 128.3, 113.8, 94.4, 73.4, 71.5, 55.1, 45.4, 43.2, 21.0, 8.4. IR (KBr): 1780, 1730 cm^{-1}. LR-MS *m/z* (rel. int. %): 384 (M^+, 14), 279 (14), 262 (78), 176 (27), 137 (89), 121 (base). HR-MS *m/z*: 384.1552 (Calcd for $C_{22}H_{24}O_6$: 384.1573). *Anal.* Calcd for $C_{22}H_{24}O_6$: C, 68.96; H, 6.40. Found: C, 68.74; H, 6.29.

Reaction with *tert*-BuCOOK; After purification by HPLC, **28**α and **28**β were obtained in 46 and 31% yields, respectively. **28**α: mp 52—53 °C recrystallized from EtOAc : hexane (1 : 4), *Rf*=0.54 (30% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.23 (2H, d, J=8.6 Hz), 6.86 (2H, d, J=8.6 Hz), 6.52 (1H, d, J=6.0 Hz), 4.45 (2H, s), 3.81 (3H, s), 3.52 (1H, d, J=9.2 Hz), 3.45 (1H, d, J=9.2 Hz), 2.51 (1H, qd, J=7.3, 6.0 Hz), 1.30 (3H, s), 1.12 (9H, s), 1.07 (3H, d, J=7.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 178.9, 176.7, 159.3, 129.7, 129.4, 113.8, 93.8, 73.3, 71.1, 55.2, 45.3, 43.3, 38.8, 26.7, 20.7, 8.3. IR (KBr): 1790, 1740 cm^{-1}. LR-MS *m/z* (rel. int. %): 364 (M^+, 14), 262 (55), 176 (29), 137 (70), 121 (base). *Anal.* Calcd for $C_{20}H_{28}O_6$: C, 65.92; H, 7.74. Found: C, 65.90; H, 7.91. **28**β: Oil, *Rf*=0.54 (30% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.21 (2H, d, J=8.6 Hz), 6.87 (1H, d, J=8.6 Hz), 6.30 (1H, d, J=6.9 Hz), 4.48 (1H, d, J=11.8 Hz), 4.37 (1H, d, J=11.8 Hz), 3.81 (3H, s), 3.43 (1H, d, J=9.3 Hz), 3.37 (1H, d, J=9.3 Hz), 2.25 (1H, qd, J=7.2, 6.9 Hz), 1.23 (9H, s), 1.18 (3H, s), 1.09 (3H, d, J=7.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 178.3, 176.9, 159.2, 129.8, 129.2, 113.8, 98.5, 73.1, 71.8, 55.2, 48.3, 45.1, 38.7, 26.8, 19.2, 9.4. IR (film): 1790, 1750 cm^{-1}.

Deprotection of PMB Group, General Procedure for the Synthesis of 29, 30 and 31 A mixture of PMB ether (0.39 mmol) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (97 mg, 0.429 mmol) in CH_2Cl_2 (3.6 ml) and water (0.2 ml) was stirred for 3—4 h at room temperature. The mixture was diluted with CH_2Cl_2 (70 ml) and dried over $MgSO_4$. CH_2Cl_2 was removed and the residue was chromatographed on silica gel.

Reaction of **26**: Elution with 30% EtOAc in hexane gave the β-isomer **29**β in 22% yield, and elution with 40% EtOAc in hexane gave the α-isomer **29**α in 63% yield. **29**α: Oil, *Rf*=0.20 (40% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$)

δ: 6.58 (1H, d, J=5.9 Hz), 3.85 (1H, dd, J=11.3, 3.5 Hz), 3.64 (1H, dd, J=11.3, 9.3 Hz), 2.58 (1H, qd, J=7.4, 5.9 Hz), 2.15 (3H, s), 1.93 (1H, dd, J=9.3, 3.5 Hz), 1.33 (3H, s), 1.08 (3H, d, J=7.4 Hz). ^{13}C-NMR ($CDCl_3$) δ: 179.4, 168.9, 94.0, 64.6, 45.6, 42.8, 20.8, 19.6, 7.5. IR (film): 3520, 1780, 1750 cm^{-1}. LR-MS *m/z* (rel. int. %): 159 (M^+-43, 4), 143 (47), 112 (base), 98 (24), 97 (30). *Anal.* Calcd for $C_{19}H_{14}O_5$: C, 53.71; H, 6.84. Found: C, 53.46; H, 6.98. **29**β: Oil, *Rf*=0.32 (40% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 6.32 (1H, d, J=6.4 Hz), 3.75 (1H, dd, J=10.8, 5.0 Hz), 3.67 (1H, dd, J=10.8, 3.8 Hz), 2.31 (1H, qd, J=7.4, 5.9 Hz), 2.15 (3H, s), 1.91 (1H, dd, J=5.0, 3.8 Hz), 1.22 (3H, d, J=7.4 Hz), 1.20 (3H, s). ^{13}C-NMR ($CDCl_3$) δ: 178.9, 169.7, 98.6, 65.2, 49.4, 44.8, 20.9, 18.8, 9.4. IR (film): 3520, 1780, 1750 cm^{-1}. LR-MS *m/z* (rel. int. %): 159 (M^+-43, 4), 143 (47), 112 (55), 43 (base). *Anal.* Calcd for $C_{19}H_{14}O_5$: C, 53.71; H, 6.84. Found: C, 53.66; H, 6.68.

Reaction of **27**α: Elution with 40% EtOAc in hexane gave the β-isomer **30**β in 83% yield, mp 100—101 °C recrystallized from EtOAc : hexane (2 : 3), *Rf*=0.35 (40% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 8.03 (2H, dd, J=8.3, 1.4 Hz), 7.62 (1H, tt, J=7.3, 1.4 Hz), 7.49 (1H, d, J=8.3 Hz), 7.46 (1H, d, J=7.3 Hz), 6.84 (1H, d, J=5.9 Hz), 3.97 (1H, d, J=11.2 Hz), 3.77 (1H, d, J=11.2 Hz), 2.70 (1H, qd, J=7.3, 5.9 Hz), 1.98 (1H, br), 1.36 (3H, s), 1.19 (3H, d, J=7.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 179.7, 164.7, 133.9, 129.8, 128.6, 128.2, 94.6, 64.7, 45.8, 43.1, 19.8, 7.7. IR (KBr): 3520, 1760, 1730 cm^{-1}. LR-MS *m/z* (rel. int. %): 264 (M^+, 4), 234 (6), 159 (7), 143 (14), 123 (18), 112 (55), 105 (base). *Anal.* Calcd for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.48; H, 6.03.

Reaction of **28**α: Elution with 30% EtOAc in hexane gave **31**α in 89% yield, mp 29—30 °C recrystallized from EtOAc : hexane (3 : 7), *Rf*=0.32 (30% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 6.58 (1H, d, J=5.9 Hz), 3.86 (1H, d, J=11.3 Hz), 3.67 (1H, d, J=11.3 Hz), 2.61 (1H, qd, J=7.3, 5.9 Hz), 1.99 (1H, brs), 1.33 (3H, s), 1.24 (9H, s), 1.09 (3H, d, J=7.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 179.6, 176.4, 93.9, 64.5, 45.6, 42.9, 38.9, 26.7, 19.5, 7.5. IR (film): 3500, 1780, 1750 cm^{-1}. LR-MS *m/z* (rel. int. %): 143 (M^+-101, 84), 131 (5), 113 (19), 97 (43), 57 (base). HR-MS (FAB) *m/z*: 245.1399 (Calcd for $C_{12}H_{21}O_5$: 245.1389).

Transformation of Hydroxymethyl Group to Acetyl Group *via* Aldehyde Intermediate; Oxidation of Alcohol 29—31 A mixture of alcohol (0.5 mmol) and PCC (1.0 mmol) was stirred in anhydrous CH_2Cl_2 (5 ml) for 3—4 h at room temperature. The mixture was directly purified by Florisil column eluting with CH_2Cl_2 to give almost pure aldehyde, which was further purified by silica gel column chromatography to give the desired aldehyde. Eluted with 30% EtOAc in the oxidation of **29**, 63% yield. Oil, *Rf*=0.47 (40% EtOAc in Hexane). ^{1}H-NMR ($CDCl_3$) δ: 9.70 (1H, s), 6.66 (1H, d, J=5.1 Hz), 2.68 (1H, qd, J=7.3, 5.1 Hz), 2.16 (3H, s), 1.43 (3H, s), 1.14 (3H, d, J=7.3 Hz). Eluted with 30% EtOAc in the oxidation of **30**, 78% yield. Oil, *Rf*=0.50 (40% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 9.82 (1H, s), 7.98 (2H, dd, J=8.2, 1.5 Hz), 7.64 (1H, tt, J=7.2, 1.5 Hz), 7.50 (1H, d, J=8.2 Hz), 7.48 (1H, d, J=7.2 Hz), 6.92 (1H, d, J=5.1 Hz), 2.81 (1H, qd, J=7.3, 5.1 Hz), 1.25 (3H, d, J=7.3 Hz). Eluted with 10% EtOAc in the oxidation of **31**, 80% yield. Oil, *Rf*=0.41 (30% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 9.67 (1H, s), 6.63 (1H, d, J=5.2 Hz), 2.70 (1H, qd, J=7.2, 5.2 Hz), 1.43 (3H, s), 1.20 (9H, s), 1.13 (3H, d, J=7.2 Hz).

Addition of MeMgBr and Oxidation to Ketone: To a solution of aldehyde (0.25 mmol) in anhydrous THF (8 ml) was added dropwise MeMgBr (0.9 M THF solution, 0.75 mmol) carefully during 10 min at 0 °C, and the mixture was stirred for 5 min. It was quenched with ice water (3 ml) and extracted with EtOAc (100 ml). The extract was washed with water and brine, and dried over $MgSO_4$. After the solvent was removed, the crude product was dissolved in acetone (5 ml) and cooled on an ice bath. Jones reagent (1.85 M in water, 0.35 ml) was added, and the mixture was stirred for 30 min at the same temperature. Excess Jones reagent was decomposed by addition of isopropanol (0.5 ml), and the mixture was diluted with ether (100 ml). The organic mixture was washed with water and brine, and dried over $MgSO_4$. The solvent was removed and the residue was purified by column chromatography on silica gel eluting with 30% EtOAc in hexane to give the desired acetomycins, **1**, **5**, and **6** in 54, 21 and 38% yields, respectively. **1**: mp 108—110 °C recrystallized from ether, *Rf*=0.58 (50% EtOAC in hexane). ^{1}H-NMR ($CDCl_3$) δ: 6.59 (1H, d, J=5.3 Hz), 2.56 (1H, qd, J=7.3, 5.3 Hz), 2.31 (3H, s), 2.13 (3H, s), 1.45 (3H, s), 1.07 (3H, d, J=7.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 203.3, 177.0, 168.6, 94.0, 56.8, 45.5, 28.9, 21.0, 20.6, 9.4. LR-MS (FAB): *m/z* 215 (M^++1). **5**: mp 90—91 °C recrystallized from EtOAc–hexane, *Rf*=0.45 (30% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 7.96 (2H, dm, J=8.3 Hz), 7.63 (1H, tt, J=7.3, 1.2 Hz), 7.50 (1H, d, J=8.3 Hz), 7.47 (1H, d, J=7.3 Hz), 6.82 (1H, d, J=5.3 Hz), 2.69 (1H, qd, J=7.3, 5.3 Hz), 2.36 (3H, s), 1.52 (3H, s), 1.20 (3H, d, J=7.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 203.6, 176.8, 164.4, 134.1, 129.8, 128.8, 128.4, 94.5, 57.0, 45.9, 29.1, 20.9, 9.7. IR (KBr): 1795, 1745, 1700 cm^{-1}. LR-MS (FAB): *m/z* 277 (M^++1). *Anal*. Calcd for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84. Found: C, 65.14; H, 5.97. **6**: mp 108—110 °C recrystallized from ether, *Rf*=0.32 (20% EtOAc in hexane). ^{1}H-NMR ($CDCl_3$) δ: 6.60 (1H, d, J=5.4 Hz), 2.60 (1H, qd, J=7.3, 5.4Hz), 2.33 (3H, s), 1.46 (3H, s), 1.21 (9H, s), 1.08 (3H, d, J=7.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 203.2, 177.0, 176.3, 94.0, 56.9, 45.8, 39.1, 29.0, 26.9, 21.0, 9.5. IR (KBr): 1800, 1750, 1700 cm^{-1}. LR-MS (FAB) *m/z*: 257 (M^++1). HR-MS (FAB) *m/z*: 257.1420 (Calcd for $C_{13}H_{21}O_5$: 257.1389). *Anal*. Calcd for $C_{13}H_{20}O_5$: C, 60.41; H, 7.95. Found: C, 60.82; H, 7.87.

Acknowledgments This work was supported by a Special Grant for Cooperative Research administered by the Japan Private School Promotion Foundation

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