Unexpected Contrasteric Alkylation Leading to a Model for Five-Membered Ring Enolate Alkylation: Short Stereoselective Synthesis of (±)-Acetomycin†

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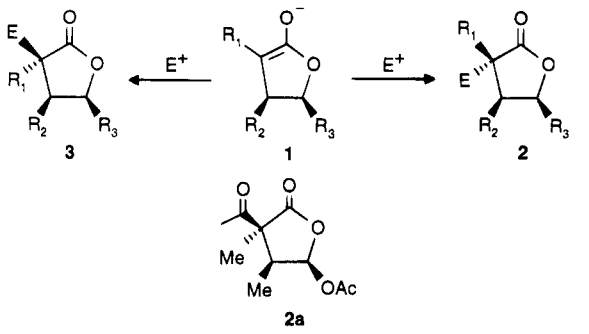
It is well established that the alkylation of cyclic enolates **1** bearing an asymmetric center at the β-position should provide mainly lactones **2** where the electrophile (E^+) ends up trans to the β-substituent (R_2). Our interest in such processes lies in the fact that according to this principle, alkylation of **1a** with methyl iodide should provide direct access to (±)-acetomycin (**2a**). However, this reaction unexpectedly afforded the contrasteric alkylation product **3a** ((±)-3-*epi*-acetomycin) with high diastereoselectivity. To elucidate this observation, alkylation studies have been carried out on various enolates **1**. As normally expected, when R_2 and R_3 are alkyl groups, only product **2** is obtained. On the other hand, when R_3 is an acetoxy or an alkoxy group and methyl iodide is used as electrophile, the contrasteric products **3** are predominant. With sterically more demanding electrophiles, the "normal" alkylation products **2** are obtained in moderate to extremely high selectivity. Thus, the use of 1,3-dithienium tetrafluoroborate, a bulky methyl equivalent, allowed us to complete a stereoselective synthesis of (±)-acetomycin. These results led to the elaboration of a model for five-membered ring enolate alkylation based on steric and stereoelectronic effects, as well as ring conformations.

The understanding of diastereoselectivity in cyclic enolate alkylations has been the subject of intense research efforts over the last few decades. The diastereofacial differentiation generated by an asymmetric center at the -position of these enolates allowed many stereoselective syntheses of natural products. Based on this principle, reaction of **1** (Scheme 1) with an alkylating agent should provide lactones **2** arising from alkylation by the less hindered face of the enolate. In the same way, methylation reaction on the appropriate enolate **1** should provide direct access to (±)-acetomycin (**2a**). This compound is a small highly functionalized antibiotic, isolated from *Streptomyces ramulosus* sp. by Prelog *et al.* in 1958.[1] The relative and absolute stereochemistry were determined many years later by X-ray analysis.[2] In 1987, (−)-acetomycin was found to be an antitumor agent (*in vitro*) against HCT-8 human colon adenocarcinoma cells, L1210 murine leukemia cells, and human tumor stem cells.[3] However, the product showed no *in vivo* activity due to rapid degradation caused by esterase-mediated hydrolysis.[4] We became interested in the preparation of stable analogs of acetomycin and thus a short and versatile synthetic approach was needed.

The first total synthesis of acetomycin was reported in 1990 by Tadano *et al.*[5] Very recently, Ziegler and Kim reported an elegant synthesis of (−)-acetomycin using a selective Baeyer–Villiger oxidation as their key step.[6] Our synthetic approach is based on a regioselective acetylation of lactone **5** (Scheme 2) and on stereoselective

Scheme 1



methylation reaction of **1a**. Inspired by Ziegler's synthesis, the starting material **4**[7] is acetylated in standard conditions and stereoselectively hydrogenated[8] over palladium in methanol at 0 °C affording the cis-substituted γ-butyrolactone **5**[6] in 95% overall yield from **4** and with 95% diasteroselectivity. The key step was realized by regioselectively generating the lactone enolate using 1.5 equiv of LiHMDS at −78C and quenching after 1 min by rapidly adding 2 equiv of acetyl chloride, affording β-keto ester **1a** in 40% yield after flash chromatography. This reaction was successfully carried out on several runs on a gram scale. Interestingly, when the acetoxy on C-5 was replaced by a benzoyloxy or a pivaloyloxy group (results not shown), the yield was increased to 80%. The enolate of this bis-acylated acetal function seems to be relatively

† Dedicated to the memory of Mr. L. P. Dubeau, 1901–1995.

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(7) Easily obtained on multigram scale by a one-step procedure from glyoxylic acid. See: Bourguignon, J. J.; Wermuth, C. G. *J. Org. Chem.* **1981**, *46*, 4889.

(8) Feringa, B. L.; de Lange, B.; de Jong, J. C. *J. Org. Chem.* **1989**, *54*, 2471.

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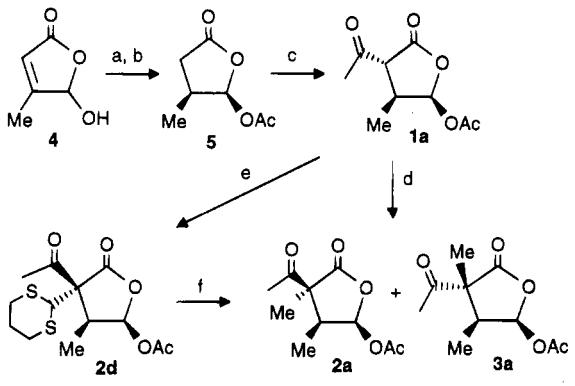
Scheme 2[a]

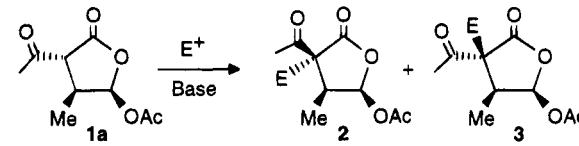


[a] (a) Ac_2O, pyridine, CH_2Cl_2, 0 °C; (b) H_2, 10% Pd/C, MeOH, 0 °C (95% from **4**); (c) LiHMDS (1.5 equiv), THF, −78 °C; then AcCl (2 equiv) (40%); (d) MeI, K_2CO_3, acetone, reflux (83%); (e) LiHMDS (1.0 equiv), THF, −78 °C; then 1,3-dithienium tetrafluoroborate (1.1 equiv) (86%); (f) Raney nickel, acetone, rt (50%).

stable at −78 °C. Methylation of **1a** using iodomethane and K_2CO_3 in acetone[9] or Cs_2CO_3 in acetonitrile gave 83−85% yield of (±)-acetomycin (**2a**) and (±)-3-epi-acetomycin (**3a**) in a 1:6 mixture, respectively. The products were separated by flash chromatography, and their spectroscopic data are in perfect agreement with reported values.[6,10] Using different bases, solvents or temperatures did not change the **2a**:**3a** ratio. This rather unusual stereoselective contrasteric alkylation can be rationalized in terms of stereoelectronic effects and ring conformations (*vide infra*). In order to reverse the facial selectivity of the reaction, we turned our attention to 1,3-dithienium tetrafluoroborate, an electrophile known to give trans adducts in its reaction with β-substituted silyl enol ethers.[11] Indeed, direct reaction on lithium enolate of **1a** in THF at −78 °C afforded a single isomer in 86% yield. Reductive desulfurization of **2d** gave (±)-acetomycin (**2a**) in 50% yield.

Results for Alkylation of β-keto Ester enolates. There are only very few reported cases of contrasteric alkylation[12] and for most of them, the reasons for the observed diastereoselectivity are uncertain.[13,14] On the other hand, it is well established that enolate−alkyl halide transition states are largely reactantlike in character.[13] Consequently, the contrasteric alkylation, as pointed out by Seebach[12b] and Ladner,[12c] may arise from a special conformation of the starting enolate. In order to investigate this hypothesis, we first studied the reaction of β-keto ester **1a** with various electrophiles (Table 1). Relative to methyl iodide (entry 1), the use of methyl bromide as electrophile (entry 2) did not change the ratio between **2a** and **3a**. When benzyl bromide was used (entry 3), the anti product became predominant. The Michael addition on methyl vinyl ketone gave a 4:1 mixture of anti and syn products **2c** and **3c** (entry 4). As stated before, 1,3-dithienium tetrafluoroborate (entry 5) led exclusively to the anti product **2d**.

Table 1. Reaction of β-Keto Ester 1a with Various Electrophiles



entry	electrophile	products	ratio[a] 2:3	yield[b] %
1	MeI	**2a/3a** (E= Me)	14:86	83
2	MeBr	**2a/3a** (E= Me)	14:86	80
3	BnBr	**2b/3b** (E= Bn)	66:34	69
4	$CH_3COCHCH_2$	**2c/3c** (E= $(CH_2)_2COCH_3$)	80:20	90
5	1,3-dithienium tetrafluoroborate	**2d/3d** (E=$CHS(CH_2)_3S$)	>99:1	86

[a] Ratios determined by ^1H NMR.

[b] Isolated yields.

The steric requirements imposed by the electrophile determine the stereochemical outcome of the reaction. For a S_N2 reaction (entries 1−3), the ratio between the products can be inverted. A sterically less demanding electrophile (entries 1, 2) led mainly to the syn product, while a bulkier one (entry 3) led mainly to the anti product. For addition on sp^2 electrophilic carbon (entries 4, 5) the anti product was obtained, in both cases, as the major product. Using the synthetic route developed for acetomycin (Scheme 2) or others,[15] we prepared different β-keto esters (Table 2) and studied the diastereoselectivity of their methylation reaction. The stereochemistry of the products was easily determined by ^1H NMR. Because of the anisotropic effect created by the carbonyl of the methyl ketone side chain on C-3, the C-4 proton appears at 3.20 ppm for the syn products **3** and at 2.60 ppm for the anti products **2**. NOE experiments on compounds **2j,l,m** were carried out and confirmed this general observation. Moreover, treatment of β-keto esters **1** (except **i,k,l**) with 1,3-dithienium tetrafluoroborate followed by Raney nickel, gave in all cases, a single isomer to which was assigned structure **2**. Benzoate **1f** and pivaloate **1g** (entries 3, 4) gave, in both cases, a 91:9 mixture favoring the syn products **3f** and **3g**. The introduction of a *n*-propyl side chain on C-5 (entry 6) reversed the stereospecificity of the reaction and led exclusively to the anti product **2i** in high yield. Removing the methyl group on C-4 (entry 8) did not affect the ratio of the products when C-5 bears an ethoxy group (entry 2): the syn products **3e** and **3k** prevailed with the same ratio (72:28). On the other hand, when these two groups have a trans relationship (entry 7), the syn:anti ratio is reversed to 13:87. Similarly, when two alkyl groups are changed from a cis to a trans relationship (entries 6, 9), the ratio is reversed from >3:97 to 80:20.[16] The presence of only one alkyl group on C-4 or C-5 of the lactone ring (entries 5, 10) slightly favored the anti products **2h** and **2m** with the same magnitude (27:73). Finally, the

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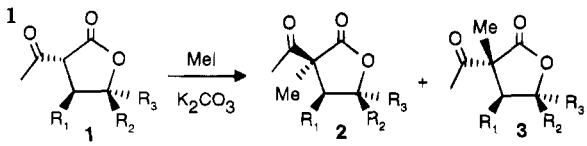
(16) Interestingly, the rigid trans system gave a syn/anti ratio 97:3. See Marshall, J. A.; Wuts, P. G. M. *J. Org. Chem.* **1978**, *43*, 1086.

Table 2. Methylation Reaction of Various β-Keto Esters



entry	β-keto ester	ratio[a] 2:3	yield[b] %
1	**1a** R_1 = Me, R_2 = OAc, R_3 = H	14:86	83
2	**1e** R_1 = Me, R_2 = OEt, R_3 = H	27:73	86
3	**1f** R_1 = Me, R_2 = OBz, R_3 = H	9:91	86
4	**1g** R_1 = Me, R_2 = OPv, R_3 = H	9:91	88
5	**1h** R_1 = Me, R_2 = H, R_3 = H	71:29	70
6	**1i** R_1 = Me, R_2 = n-Propyl, R_3 = H	>97:3	95
7	**1j** R_1 = Me, R_2 = H, R_3 = OEt	87:13	88
8	**1k** R_1 = H, R_2 = OEt, R_3 = H	29:71	79
9	**1l** R_1 = Me, R_2 = H, R_3 = n-Propyl	20:80	92
10	**1m** R_1 = H, R_2 = Ethyl, R_3 = H	75:25	85
11	**1n** R_1 = iso-Propyl, R_2 = OAc, R_3 = H	50:50	40

[a] Ratios determined by ^{1}H NMR. [b] Isolated yields.

introduction of an isopropyl group on C-4 resulted in a total loss of stereochemical control.

Model for Alkylation of Five-Membered Ring Enolates. The classic studies associated with the alkylation of enolates derived from 4-*tert*-butylcyclohexanone led, 25 years ago, to a model based on two different transition states (TS): the chairlike TS for "axial alkylation" and the boatlike TS for "equatorial alkylation".[17] Although this model is useful to rationalize the diastereoselectivity in the reaction of 4- and 5-substituted six-membered ring enolates, it cannot be used for the 3-substituted case nor for five-membered ring enolates. In these latter cases, the results are rationalized on the basis of intuitive steric factors.[13,14]

It is well known that γ-butyrolactone exists in two envelope forms which interconvert rapidly at room temperature. Adding substituents to the ring will shift the equilibrium depending on the energy differences between pseudoaxial and pseudoequatorial positions.[18] Enolates of β-keto esters derived from γ-butyrolactone also have two possible envelope forms, A and B, in Newman projections (Figure 1). Both conformers can react by their α or β faces. With respect to stereoelectronic principles,[19] the electrophile must have a perpendicular approach to the enolate, thereby leading to four possible transition states for the alkylation of five-membered ring enolates. Two of them can be called "staggered transition states" (Aβ, Bα) and the two others "eclipsed transition states" (Aα, Bβ). On the basis of relative energy of butane conformations, the former set should be at least 3.4 kcal/mol lower in energy than the latter set.[20a] Because each staggered TS leads to a different stereoisomer, and according to the Curtin–Hammett principle, the ratio of the products should reflect the $G^{\ddagger}_{A\beta} - G^{\ddagger}_{B\alpha}$.

For β-keto esters without OR group on C-5 (entries 5, 6, 9, 10), the $G^{\ddagger}_{A\beta} - G^{\ddagger}_{B\alpha}$ can be easily estimated. In most cases, using standard values for steric interactions, a relatively good estimation of the ratios of products is obtained. The estimated $G^{\ddagger}_{A\beta} - G^{\ddagger}_{B\alpha}$ for methylation reaction of **1h,i,l,m** are 0.8, 2.7, −1.2, and −2.0 kcal/mol, respectively, which correspond to 78:22, 99:1, 13:87, and 4:96 ratios (at 56 °C).[20b] The experimental results are 71:29, >97:3, 20:80, 25:75. In all cases, except **1i**, the expected ratios of products are higher than the experimental values. This observation suggests that the reaction may also occur *via* essentially planar intermediate conformations laying between the two possible envelope forms. These conformations provide access to distorted TS Aα and TS Bβ, which may have a lower $\Delta G^{\ddagger}$ than the fully eclipsed TS, and consequently, increase the amount of the minor products. For β-keto ester **1i**, it seems that these intermediate conformations are too high in energy to be significantly present in solution due to severe steric interaction between the C-4 and C-5 alkyl side chains. An alternative explanation to the difference between the estimated and experimental values would come from the fact that the steric interaction values used in the calculations of $G^{\ddagger}_{A\beta} - G^{\ddagger}_{B\alpha}$ do not exactly reflect the steric interaction energies at the TS level.

The conformational studies and ^{1}H NMR coupling constant analysis reported by Jaime and co-workers suggest that for γ-butyrolactones, a C-5 OR substituent will prefer a pseudoaxial orientation.[18b] For β-keto esters like **1a,e,f,g** at equilibrium, this conformation should be almost exclusive.[21] Assuming that enolates derived from these β-keto esters retain the favored conformation with the same magnitude, A should be 3 kcal/mol more stable than B.[22] Adding steric interactions for Aβ and Bα, the $G^{\ddagger}_{A\beta} - G^{\ddagger}_{B\alpha}$ is estimated to be −1.3 kcal/mol,[23] which corresponds to a 88:12 ratio favoring the contrasteric products **3**. For β-keto ester **1j** (entry 7), both staggered transition states have about the same steric interactions generated by the incoming methyl group. The experimental ratio of 87:13 corresponds perfectly to the equilibrium value of envelope forms reported for γ-butyrolactones related to **1j** (86:14).[18b] When sterically more demanding electrophiles are used (Table 1, entries 3–5), the G_A and G_B are unequally increased because of the

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(20) (a) In the present case, both carbon atoms of the Newman projections bear more than one methyl group. Consequently, the eclipsed conformations should be higher than 3.4 kcal/mol, which is the value for methyl–hydrogen eclipsed conformation of butane. The methyl–methyl eclipsed conformation is 6 kcal/mol higher in energy then the anti-staggered conformation. (b) 0.8 kcal/mol for a gauche interaction, 0.9 kcal/mol for a methyl-hydrogen 1,3 diaxial interaction, 2.8 kcal/mol for methyl–alkyl 1,3 diaxial interaction. As example, the estimated $G^{\ddagger}_{A\beta} - G^{\ddagger}_{B\alpha}$ for **1i** is: (2.8 kcal + 0.8 kcal) for Aβ − (0.9 kcal) for Bα = 2.7 kcal/mol. For relative energies of butane conformations and energies values for 1,3 diaxial steric interactions see: Carey, F. A.; Sundberg, R. J. *Advanced in Organic Chemistry*; Plenum Press: New York, 1993.

(21) The proton coupling constants observed for all starting β-keto esters are in perfect agreement with the reported values[18] and allowed us to asign A or B as the favored conformation.

(22) The allylic strain generated by this type of exocyclic enolate should favor B over A. But because of β-keto ester **1h** (entry 5) did not show a very good stereoselectivity for the anti compound **2h**, we assumed that the $A^{1,3}$ does not have a significant contribution to ΔG_c (ΔG between A and B). On the other hand, replacing the C-3 acetyl group on **1a** by a pivaloyl group led to a 1:1 diastereomeric mixture of **2** and **3** (result not shown). In this case, the allylic strain is probably responsible for the absence of stereoselectivity. This explanation is also applicable to β-keto ester **1n** (entry 11).

(23) The 1,3 Me–OR diaxial interaction has been estimated to 1.8 kcal/mol. See: Eliel, E. L.; Allinger, N. L.; Angyal, S. J.; Morrison, G. A. *Conformational Analysis*; John Wiley & Sons, Inc.: New York, 1967; $G^{\ddagger}_{A\beta} - G^{\ddagger}_{B\alpha} = \Delta G^{\ddagger}_{A\beta} - \Delta G^{\ddagger}_{B\alpha} + \Delta G_c$: $\Delta G^{\ddagger}_{A\beta}$ = C +0.8 kcal/mol + 1.8 kcal/mol; $\Delta G^{\ddagger}_{B\alpha}$ = C + 0.9 kcal/mol (in which C is the $\Delta G^{\ddagger}$ of 2-acetylbutyrolactone); ΔG_c = −3.0 kcal/mol; $G^{\ddagger}_{A\beta} - G^{\ddagger}_{B\alpha}$ = −1.3 kcal/mol.

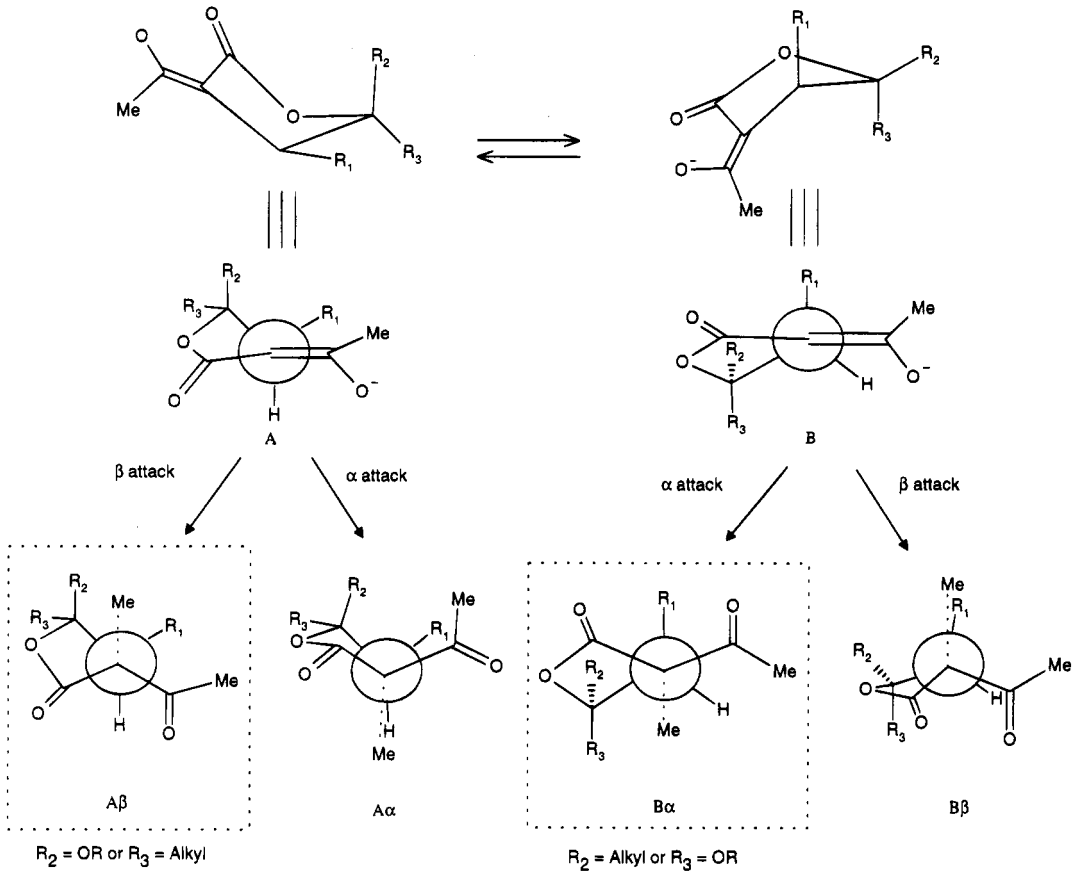

Figure 1. Transition states for methylation of five-membered ring β-keto ester enolates.

steric interactions created by the substituents on the face. Consequently, the energy difference between the starting enolate conformers A and B becomes less important in $G^{\ddagger}_{A\beta} - G^{\ddagger}_{B\alpha}$, and the major product **2** corresponds to the expected anti alkylation pathway. In others words, the early TS of the methylation reaction becomes a late TS for these electrophiles.

There is a similarity between the presented model and the one proposed by McGarvey and Williams for acyclic enolate alkylation.[24] Both support a perpendicular approach of the electrophile leading to a staggered conformation, and neither can be rationalized using a purely steric model. In fact, our model shows clearly that even a hydrogen atom at the perpendicular position can shield the enolate and prevent an electrophilic attack on this face of the molecule.

Conclusion

In summary, a five-step synthesis of (±)-acetomycin was developed. The sequence requires no protecting groups and only one chromatographic step. Based on recent promising results,[25] the enantioselective version of this approach would be applicable in a near future. For structure–activity relationship purposes, the side chains of the basic skeleton can be easily modified.[26] Moreover, we have clearly shown that the formation of the contrasteric alkylation products is due to a special conformation of the starting enolates. A model for five-membered ring enolate alkylation based on steric and stereoelectronic effects has also been proposed. We believe that the staggered and eclipsed TS concept is an alternative model to the chairlike and boatlike TS model used to rationalize the results for reactions such as enolate alkylation, 1, 4 addition, epoxide opening, in the six-membered ring series.

Experimental Section

General Methods. Unless otherwise noted, all common reagents and solvents were used as obtained from commercial suppliers without further purification. Elemental analysis were carried out by Canadian Microanalytical Service Ltd., Delta, BC. Melting points were determined on a Digital Melting Point Apparatus and are uncorrected. Merck precoated silica gel 60 F254 plates were used for thin-layer chromatography (TLC). All reactions requiring anhydrous conditions were conducted under a positive pressure of argon.

5-Acetoxy-4-methyltetrahydrofuran-2-one (5). To a stirred solution of 5-hydroxy-4-methyl furan-2-one (**4**) (17.4 g, 152 mmol) in CH_2Cl_2 (160 mL) at 0 °C were added acetic anhydride (28.8 mL, 305 mmol) and pyridine (37 mL, 457 mmol). The solution was stirred at 0 °C for 15 min and then at room temperature for 45 min. The reaction mixture was worked up in CH_2Cl_2 and 0.1 N HCl. The organic layer was washed with 0.1 N HCl, followed by H_2O and brine, and then dried over $MgSO_4$. The solvents were evaporated, and the product was placed under vacuum to give 4-methyl-5-acetoxy-2-furanone (23.4 g, 98%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) 6.80 (s, 1H), 5.97 (s, 1H), 2.19 (s, 3H), 2.09 (s, 3H); ^{13}C NMR: (75 MHz, $CDCl_3$) 169.9, 169.2, 163.0, 119.3, 94.4, 20.6, 13.1; IR (neat film) 1800, 1760, 1656 cm^{-1}; MS ($M^+ + H$) calcd for $C_7H_9O_4$ 157.0501, found 157.0498. The crude product (23.4

(24) McGarvey, G. J.; Williams, J. M. *J. Am. Chem. Soc.* **1985**, *107*, 1435.

(25) The precursor of **5** has been partially resolved by the use of a lipase; See: van der Deen, H.; Hof, R. P.; van Oeveren, A.; Feringa, B. L.; Kellogg, R. M. *Tetrahedron Lett.* **1994**, *35*, 8441.

(26) Many analogs of acetomycin have been prepared using this approach. For synthesis and biological evaluation of these compounds see: Chen, D.; Sprules, T. J.; Lavallée, J.-F. *BioMed. Chem. Lett.* **1995**, *5*, 759.

g, 150 mmol) was dissolved in methanol (150 mL), and 10% Pd/C (2.45 g) was added. The solution was stirred under a hydrogen atmosphere at 0 °C for 7.5 h and was then filtered through Celite. The solvent was evaporated to give **5** (22.9 g, 97%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) 6.56 (d, J = 5.3 Hz, 1H), 2.75 (m, 1H), 2.60 (dd, J = 8.5, 17.4, 1H), 2.34 (dd, J = 12.9, 17.4 Hz, 1H), 2.14 (s, 3H), 1.15 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 175.2, 169.2, 96.0, 34.1, 33.2, 20.7, 12.7; IR (neat film) 1800, 1761, cm^{-1}; MS calcd for $C_7H_{10}O_4$ 158.0579, found 158.0582. Anal. Calcd for $C_7H_{10}O_4$: C, 53.16; H, 6.37. Found: C, 52.82; H, 6.35.

5-Acetoxy-3-acetyl-4-methyltetrahydrofuran-2-one (1a). To a stirred solution of **5** (2.22 g, 14 mmol) in THF (200 mL) at −78 °C was rapidly added a solution of LiHMDS in THF (19 mL, 1.1 M in THF, 21 mmol). The solution was stirred for 1 min and then a solution of acetyl chloride (1.99 mL, 28 mmol) in THF (2 mL) was rapidly added. After 1 min the solution was quenched with 0.1 N HCl and warmed to room temperature. The organic layer was extracted into ether, washed with water and brine, and then dried over $MgSO_4$. After evaporation of the solvents, the crude product was purified by flash chromatography (hexane−EtOAc−triethylamine 75:20:5) on a short column of silica gel to give **1a** (1.12 g, 40%) as a colorless oil: ^{1}H NMR (300 MHz, $CDCl_3$) 6.57 (d, J = 5.5 Hz, 1H), 3.50 (d, J = 11.0 Hz, 1H), 3.19 (m, 1H), 2.48 (s, 3H), 2.14 (s, 3H), 1.11 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 199.2, 170.8, 168.8, 94.4, 56.9, 35.6, 30.1, 20.6, 12.0; IR (neat film) 1795, 1766, 1723 cm^{-1}; MS (M$^+$ + H) calcd for $C_9H_{13}O_5$ 201.0763, found 201.0756. Anal. Calcd for $C_9H_{12}O_5$: C, 54.00; H, 6.04. Found: C, 53.77; H, 6.00.

(±)-Acetomycin and (±)-3-*epi*-Acetomycin (2a/3a). To a stirred solution of **1a** (31 mg, 0.15 mmol) in dry acetone (0.5 mL) was added potassium carbonate followed by iodomethane (48 μL, 0.77 mmol). The resulting solution was stirred at 50 °C for 45 min. After cooling to room temperature, the reaction mixture was diluted with CH_2Cl_2 and filtered. The solvents were evaporated to give **2a** and **3a** (27.5 mg, 83%) in a 1:6 ratio. The products were separated by flash chromatography (CH_2Cl_2−hexane−EtOAc 5:5:1). **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) 6.59 (d, J = 6.0 Hz, 1H), 3.24 (dq, J = 6.0 Hz, 7.3 Hz, 1H), 2.39 (s, 3H), 2.16 (s, 3H), 1.54 (s, 3H), 1.03 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.5, 176.1, 169.4, 94.9, 57.7, 38.6, 26.4, 21.3, 17.6, 8.8; IR (neat film) 1795, 1766, 1723 cm^{-1}; MS (M$^+$ + H) calcd for $C_{10}H_{15}O_5$ 215.0919, found 215.0926. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.62; H, 6.54. **2a**: mp 108−110 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.59 (d, J = 5.4 Hz, 1H), 2.57 (dq, J = 5.4 Hz, 7.2 Hz, 1H), 2.32 (s, 3H), 2.13 (s, 3H), 1.45 (s, 3H), 1.07 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.3, 176.9, 168.6, 94.0, 56.8, 45.5, 28.9, 21.0, 20.6, 9.4; IR (neat film) 1795, 1766, 1723 cm^{-1}; MS (M$^+$ + H) calcd for $C_{10}H_{15}O_5$ 215.0919, found 215.0924. Anal. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59. Found: C, 56.06; H, 6.30.

5-Acetoxy-3-acetyl-3-(1,3-dithianyl)-4-methyltetrahydrofuran-2-one (2d). To a stirred solution of **1a** (107 mg, 0.53 mmol) in THF (7 mL) at −78 °C was added LiHMDS (530 μL, 1.0 M in THF, 0.53 mmol), followed 5 min later by 1,3-dithienium tetrafluoroborate (120 mg, 0.58 mmol). After 20 min, the reaction mixture was worked up in dichloromethane and water. The organic layer was washed with water and brine and dried over $MgSO_4$. The solvents were evaporated, and the crude product was triturated in ether to give **2d** (145 mg, 86%) as a white solid: mp: 145−147 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.60 (d, J = 5.6 Hz, 1H), 4.45 (s, 1H), 3.38 (m, 1H), 3.18 (m, 1H), 2.95 (m, 1H), 2.81 (m, 2H), 2.42 (s, 3H), 2.11 (s, 3H), 2.05 (m, 2H), 1.14 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 200.3, 173.3, 168.5, 94.2, 65.5, 48.6, 40.6, 30.1, 29.9, 29.6, 24.9, 20.5, 9.7; IR (neat film) 1793, 1765, 1717 cm^{-1}; MS calcd for $C_{13}H_{18}O_5S_2$ 318.0596, found 318.0601. Anal. Calcd for $C_{13}H_{18}O_5S_2$: C, 49.04; H, 5.70. Found: C, 48.50; H, 5.59.

(±)-Acetomycin from 2d. To a stirred solution of Raney nickel in acetone was added **2d** (104 mg, 0.33 mmol). After 3 h the solution was filtered through Celite, the solvent was evaporated, and the crude product was purified by crystallization in hexane−ether to give (±)-acetomycin (35 mg, 50%).

5-Acetoxy-3-acetyl-3-benzyl-4-methyltetrahydrofuran-2-one (2b and 3b). To a solution of **1a** (100 mg, 0.50 mmol) in acetonitrile (5 mL) were added cesium carbonate (138 mg, 1.0 mmol) and benzyl bromide (178 μl, 1.5 mmol). The reaction mixture was stirred at room temperature for 50 min, diluted in CH_2Cl_2, and filtered through a short plug of silica gel. After evaporation of the solvents, the products were separated by flash chromatography (EtOAc−hexane 20:80) to give **2b** (58mg, 40%), a mixed fraction (14 mg, 10%), and **3b**, slightly impure (39 mg, 26%), which was purified by crystallization in hexane−ether. **2b**: ^{1}H NMR (300 MHz, $CDCl_3$) 7.30 (m, 3H), 7.16 (m, 2H), 6.34 (d, J = 5.4 Hz, 1H), 3.36 (d, J = 14.0 Hz, 1H), 3.09 (d, J = 14.0 Hz, 1H), 2.56 (dq, J = 5.4, 7.3 Hz, 1H), 2.39 (s, 3H), 2.10 (s, 3H), 1.05 (d, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.7, 176.7, 169.0, 135.2, 131.2, 129.4, 128.2, 94.8, 63.2, 40.0, 38.4, 30.0, 21.1, 9.7; MS calcd for $C_{16}H_{18}O_5$ 290.1154, found 290.1146. Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 66.72; H, 6.18. **3b**: mp 83−85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.34 (m, 3H), 7.12 (bd, 2H), 6.60 (d, J = 5.6 Hz, 1H), 3.50 (d, J = 14.3 Hz, 1H), 3.20 (d, J = 14.4 Hz, 1H), 3.08 (dq, J = 5.6, 7.5 Hz, 1H), 2.17 (s, 3H), 2.13 (s, 3H), 1.18 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.5, 174.1, 169.4, 135.7, 130.5, 128.9, 127.8, 94.7, 62.8, 40.7, 36.6, 28.1, 21.3, 9.0; MS calcd for $C_{16}H_{18}O_5$ 290.1154, found 290.1149. Anal. Calcd for $C_{16}H_{18}O_5$: C, 66.19; H, 6.25. Found: C, 65.74; H, 6.14.

5-Acetoxy-3-acetyl-3-(3-oxobutyl)-4-methyltetrahydrofuran-2-one (2c and 3c). To a solution of **1a** (82 mg, 0.41 mmol) in acetonitrile (2 mL) were added cesium carbonate (25 mg, 0.08 mmol) and methyl vinyl ketone (166 μL, 2.0 mmol). After 50 min the reaction mixture was diluted with dichloromethane and filtered through silica gel. After evaporation of the solvent, the crude product was purified by flash chromatography (EtOAc−hexane 1:2) to give an inseparable mixture of **2c** and **3c** (4:1) (100 mg, 90%); **2c** was obtained in pure form by crystallization in hexane−ether: mp: 84−86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.58 (d, J = 5.4 Hz, 1H), 2.90 (ddd, J = 4.9, 10.4, 17.8 Hz, 1H), 2.62 (dq, J = 5.4, 7.5 Hz, 1H), 2.39 (m, 1H), 2.33 (s, 3H), 2.24 (m, 1H), 2.14 (s, 3H), 2.12 (s, 3H), 1.92 (m, 1H), 1.03 (d, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 205.8, 201.9, 175.3, 167.5, 93.1, 58.4, 42.8, 36.8, 29.0, 28.9, 27.6, 19.6, 8.5; MS (M$^+$ + H) calcd for $C_{13}H_{19}O_6$ 271.1182, found 271.1176. Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.76; H, 6.71. Found: C, 57.79; H, 6.85. **3c**: ^{13}C NMR (75 MHz, $CDCl_3$) 205.9, 201.3, 174.1, 168.0, 93.4, 58.6, 39.3, 37.2, 25.7, 21.8, 19.6, 6.9.

NMR Data for Starting β-keto Esters. 3-Acetyl-5-ethoxy-4-methyltetrahydrofuran-2-one (1e): ^{1}H NMR (300 MHz, $CDCl_3$) 7.35 (m, 5H), 6.50 (d, J = 5.4 Hz, 1H), 5.47 (d, J = 2.6 Hz, 1H), 2.87 (m, 1H), 2.78 (dd, J = 10.8, 2.3 Hz, 1H), 2.60 (bs, 1H), 2.09 (s, 3H), 0.56 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 200.4, 171.9, 103.8, 65.2, 57.9, 36.6, 30.2, 14.7, 12.01; MS calcd for $C_9H_{14}O_4$ 186.0892, found 186.0896.

3-Acetyl-5-(benzoyloxy)-4-methyltetrahydrofuran-2-one (1f): mp 83−85 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 8.04 (d, J = 7.6 Hz, 2H), 7.64 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.5 Hz, 2H), 6.82 (d, J = 5.4 Hz, 1H), 3.62 (d, J = 11.1 Hz, 1H), 3.33 (m, 1H), 2.53 (s, 3H), 1.23 (d, J = 6.8 Hz, 3H); MS calcd for $C_{14}H_{14}O_5$ 262.0841, found 262.0838. Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.11; H, 5.38. Found: C, 63.37; H, 4.90.

3-Acetyl-4-methyl-5-(trimethylacetoxy)tetrahydrofuran-2-one (1g): mp 46−48 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.56 (d, J = 5.4 Hz, 1H), 3.49 (d, J = 11.2 Hz, 1H), 3.21 (m, 1H), 2.49 (s, 3H), 1.24 (s, 9H), 1.12 (d, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 199.3, 176.2, 170.8, 94.4, 57.1, 39.1, 35.8, 30.1, 26.8, 12.2; MS (M$^+$ + H) calcd for $C_{12}H_{19}O_5$ 243.1232, found 243.1236. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.49; H, 7.49. Found: C, 59.71; H, 7.43.

3-Acetyl-4-methyltetrahydrofuran-2-one (1h): ^{1}H NMR (300 MHz, $CDCl_3$) 4.45 (dd, J = 8.2, 8.4 Hz, 1H), 3.85 (dd, J = 8.3, 8.5 Hz, 1H), 3.29 (d, J = 8.5 Hz, 1H), 3.09 (m, 1H), 2.44 (s, 3H), 1.16 (d, J = 6.6 Hz, 3H); MS calcd for $C_7H_{10}O_3$ 142.0630, found 142.0629.

3-Acetyl-4-methyl-5-propyltetrahydrofuran-2-one (1i): ^{1}H NMR (300 MHz, $CDCl_3$) 4.54 (m, 1H), 3.35 (d, J =

6.0 Hz, 1H), 3.03 (m, 1H), 2.40 (s, 3H), 1.75–1.30 (m, 4H), 1.03 (d, J = 7.1 Hz, 3H), 0.96 (t, J = 6.8 Hz, 3H).

3-Acetyl-5-ethoxy-4-methyltetrahydrofuran-2-one (1j): ^{1}H MNR (300 MHz, $CDCl_3$) 5.11 (d, J = 5.1 Hz, 1H), 3.88 (m, 1H), 3.63 (m, 1H), 3.24 (d, J = 7.9 Hz, 1H), 2.87 (m, 1H), 2.43 (s, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.18 (d, J = 6.6 Hz, 3H).

3-Acetyl-5-ethoxytetrahydrofuran-2-one (1k). As a mixture of isomers: ^{1}H NMR (300 MHz, $CDCl_3$) 5.55 (m, 1H), 3.88 (m, 2H), 3.64 (m, 1H), 2.90 and 2.70 (2m, 1H), 2.48 and 2.45 (2s, 3H), 2.50 and 2.15 (2m, 1H), 1.24 (t, J = 7.1 Hz, 3H); MS calcd for $C_8H_{12}O_4$ 172.0736, found 172.0734.

3-Acetyl-4-methyl-5-propyltetrahydrofuran-2-one (1l): ^{1}H NMR (300 MHz, $CDCl_3$) 4.00 (dt, J = 3.7, 9.1 Hz, 1H), 3.33 (d, J = 10.7 Hz, 1H), 2.65 (m, 1H), 2.45 (s, 3H), 1.80–1.35 (m, 4H), 1.11 (d, J = 6.7 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H).

3-Acetyl-5-ethyltetrahydrofuran-2-one (1m): As a mixture of isomers: ^{1}H NMR (300 MHz, $CDCl_3$) 4.55–4.30 (m, 1H), 3.76 (m, 1H), 3.00–2.70 (m, 1H), 2.47 and 2.43 (2s, 3H), 2.40–2.25 (m, 1H), 1.80–1.55 (m, 2H), 1.01 (t, J = 7.4 Hz, 3H); MS calcd for $C_8H_{12}O_3$ 156.0786, found 156.0789.

5-Acetoxy-3-acetyl-4-isopropyltetrahydrofuran-2-one (1n): ^{1}H NMR (300 MHz, $CDCl_3$) 6.65 (d, J = 5.4 Hz, 1H), 3.67 (d, J = 11.1 Hz, 1H), 2.98 (m, 1H), 2.49 (s, 3H), 2.14 (s, 3H), 1.85 (m, 1H), 0.95 (d, J = 6.5 Hz, 3H), 0.82 (d, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 199.7, 171.3, 168.8, 93.7, 55.2, 47.7, 30.9, 25.7, 27.7, 21.6, 20.8, 20.3; MS (M^+ + H) calcd for $C_{11}H_{17}O_5$ 229.1076, found 229.1073.

Typical Experimental Procedure for Alkylation of β-keto Esters. 3-Acetyl-3,4-dimethyl-5-ethoxytetrahydrofuran-2-ones (2e/3e). A solution of **1e** (100 mg, 0.54 mmol), potassium carbonate (150 mg, 1.08 mmol), and iodomethane (170 μL, 2.7 mmol) in acetone (1.5 mL) was heated to reflux for 1 h. The reaction mixture was diluted with dichloromethane and filtered through a short pad of silica gel. The solvent was evaporated to give a 27:73 mixture of **2e** and **3e** (93 mg, 86%) as a colorless oil: Major isomer **3e**: ^{1}H NMR (300 MHz, $CDCl_3$) 5.40 (d, J = 5.5 Hz, 1H), 3.89 (m, 1H), 3.59 (m, 1H), 3.04 (dq, J = 5.5, 6.8 Hz, 1H), 2.36 (s, 3H), 1.51 (s, 3H), 1.24 (t, J = 7.0 Hz, 3H), 1.01 (d, J = 6.8 Hz, 3H); MS (M^+ + H) calcd for $C_{10}H_{17}O_4$ 201.1127, found 201.1130. Minor isomer **2e** was obtained in pure form using 1,3-dithienium tetrafluoroborate as electrophile, followed by the desulfurization step with Raney nickel: mp 51.0–52.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 5.38 (d, J = 5.3 Hz, 1H), 3.95 (m, 1H), 3.65 (m, 1H), 2.38 (dq, J = 5.3, 7.2 Hz, 1H), 2.29 (s, 3H), 1.39 (s, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.03 (d, J = 6.8 Hz, 3H); MS (M^+ + H) calcd for $C_{10}H_{17}O_4$ 201.1127, found 201.1130.

3-Acetyl-5-(benzoyloxy)-3,4-dimethyltetrahydrofuran-2-ones (2f/3f) were obtained in 86% yield as a 9:91 mixture, respectively. Major isomer **3f** was obtained in pure form by recrystallization from ether–hexane: mp 98.0–99.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 8.03 (d, J = 7.7 Hz, 2H), 7.65 (m, 1H), 7.50 (t, J = 7.2 Hz, 2H), 6.82 (d, J = 5.7 Hz, 1H), 3.33 (dq, J = 5.7, 7.0 Hz 1H), 2.39 (s, 3H), 1.63 (s, 3H), 1.10 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.5, 176.2, 165.2, 134.6, 130.5, 130.4, 129.3, 95.6, 57.7, 39.1, 26.4, 17.7, 9.1; MS (M^+ + H) calcd for $C_{15}H_{17}O_5$ 277.1076, found 277.1078. Anal. Calcd for $C_{15}H_{16}O_5$: C, 65.20; H, 5.84. Found: C, 64.87; H, 5.70. Minor isomer **2f** was obtained in pure form using 1,3-dithienium tetrafluoroborate as electrophile, followed by desulfurization with Raney nickel and recrystallization from ether/hexane: mp 106.5–108.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 7.97 (d, J = 7.1 Hz, 2H), 7.63 (m, 1H), 7.50 (m, 2H), 6.83 (d, J = 5.2 Hz, 1H), 2.70 (dq, J = 5.2, 7.3 Hz, 1H), 2.37 (s, 3H), 1.53 (s, 3H), 1.21 (d, J = 7.3 Hz, 3H); MS (M^+ + H) calcd for $C_{15}H_{17}O_5$ 277.1076, found 277.1070.

3-Acetyl-3,4-dimethyl-5-(trimethylacetoxy)tetrahydrofuran-2-ones (2g/3g) were obtained in 88% yield as a 9:91 mixture, respectively. Major isomer **3g** was obtained in pure form by recrystallization from ether–hexane: mp 85.0–86.5 °C;^{1}H NMR (300 MHz, $CDCl_3$) 6.56 (d, J = 5.7 Hz, 1H), 3.25 (dq, J = 5.7, 7.1 Hz, 1H), 2.36 (s, 3H), 1.53 (s, 3H), 1.22 (s, 9H), 1.01 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.5, 176.8, 176.2, 94.9, 57.6, 38.9, 27.4, 17.4, 8.8; MS (M^+ + H) calcd for $C_{13}H_{21}O_5$ 257.1389, found 257.1396. Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.91; H, 7.86. Found: C, 60.82; H, 7.36. Minor isomer **2g** was obtained in pure form using 1,3-dithienium tetrafluoroborate as electrophile, followed by desulfurization with Raney nickel and recrystallization from ether/hexane: mp 126.1–128.0 °C); ^{1}H NMR, (300 MHz, $CDCl_3$) 6.57 (d, J = 5.4 Hz, 1H), 2.58 (dq, J = 5.4, 7.3 Hz, 1H), 2.34 (s, 3H), 1.47 (s, 3H), 1.22 (s, 9H), 1.09 (d, J = 7.3 Hz, 3H); MS (M^+ + H) calcd for $C_{13}H_{21}O_5$ 257.1389, found 257.1393.

3-Acetyl-3,4-dimethyltetrahydrofuran-2-ones (2h/3h) were obtained in 70% yield as a 71:29 mixture, respectively. The products were separated by flash chromatography (EtOAc–hexane 30:70) and obtained as oils. Major isomer **2h**: ^{1}H NMR (300 MHz, $CDCl_3$) 4.39 (dd, J = 7.1, 8.7 Hz, 1H), 3.86 (t, J = 7.8 Hz, 1H), 3.06 (ddq, J = 6.8, 7.3, 8.2 Hz, 1H), 2.35 (s, 3H), 1.37 (s, 3H), 1.04 (d, J = 7.3 Hz, 3H); MS calcd for $C_8H_{12}O_3$ 156.0789, found 156.0792. Minor isomer **3h**: ^{1}H NMR (300 MHz, $CDCl_3$) 4.40 (dd, J = 8.1, 8.4 Hz, 1H), 3.97 (dd, J = 9.2, 9.5 Hz, 1H), 2.50 (m, 1H), 2.25 (s, 3H), 1.52 (s, 3H), 1.08 (d, J = 7.3 Hz, 3H); MS calcd for $C_8H_{12}O_3$ 156.0789, found 156.0789.

3-Acetyl-3,4-dimethyl-5-propyltetrahydrofuran-2-one (2i) was obtained as an oil in 95% yield: ^{1}H NMR (300 MHz, $CDCl_3$) 4.52 (m, 1H), 2.46 (dq, J = 6.8, 7.0 Hz, 1H), 2.34 (s, 3H), 1.68–1.42 (m, 4H), 1.53 (s, 3H), 0.99 (d, J = 7.0 Hz, 3H), 0.98 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 206.3, 177.0, 80.6, 59.8, 43.8, 32.1, 29.6, 20.8, 19.3, 13.8, 10.7; MS calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1260.

3-Acetyl-3,4-dimethyl-5-ethoxytetrahydrofuran-2-ones (2j/3j) were obtained in 88% yield as a 87:13 mixture, respectively. Major isomer **2j**: ^{1}H NMR (300 MHz, $CDCl_3$) 5.31 (d, J = 6.6 Hz, 1H), 3.94 (m, 1H), 3.73 (m, 1H), 2.24 (s, 3H), 2.20 (dq, J = 6.6, 7.0 Hz, 1H), 1.56 (s, 3H), 1.27 (t, J = 7.0 Hz, 3H), 1.10 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 205.5, 174.5, 107.9, 66.9, 61.4, 48.0, 28.9, 19.7, 15.0, 10.8; MS Calcd for $C_{10}H_{16}O_3$ 200.1049, found 200.1051. Minor isomer **3j**: ^{1}H NMR (300 MHz, $CDCl_3$) 5.08 (d, J = 5.4 Hz, 1H) 2.32 (s, 3H), 1.59 (s, 3H), 1.30 (t, J = 7.0 Hz, 3H), 1.06 (d, J = 7.3 Hz, 3H).

3-Acetyl-5-ethoxy-3-methyltetrahydrofuran-2-ones (2k/3k) were obtained in 79% yield as a 29:71 mixture, respectively. The products were separated by flash chromatography (EtOAc–hexane 20:80) and obtained as oils. Major isomer **3k**: ^{1}H NMR (300 MHz, $CDCl_3$) 5.50 (dd, J = 3.9, 6.2 Hz, 1H), 3.89 (m, 1H), 3.64 (m, 1H), 3.09 (dd, J = 6.2, 13.8 Hz, 1H), 2.35 (s, 3H), 1.86 (dd, J = 3.8, 13.8 Hz, 1H), 1.63 (s, 3H), 1.25 (t, J =7.1 Hz, 3H); MS (M^+ + H) calcd for $C_9H_{15}O_4$ 187.0970, found 187.0974. Minor isomer **2k**: ^{1}H NMR (300 MHz, $CDCl_3$) 5.48 (br d, J = 5.8 Hz, 1H), 3.84 (m, 1H), 3.61 (m, 1H), 2.80 (br d, J = 14.7 Hz, 1H), 2.34 (s, 3H), 2.18 (dd, J = 5.8, 13.5 Hz, 1H), 1.46 (s, 3H), 1.21 (t, J = 7.0 Hz, 3H); MS (M^+ + H) calcd for $C_9H_{15}O_4$ 187.0970, found 187.0974.

3-Acetyl-3,4-dimethyl-5-propyltetrahydrofuran-2-ones (2l/3l) were obtained in 92% yield as a 20:80 mixture, respectively. The products were separated by flash chromatography (EtOAc–hexane 10:90) and obtained as oils. Major isomer **3l**: ^{1}H NMR (300 MHz, $CDCl_3$) 4.01 (dt, J = 3.0, 9.7 Hz, 1H), 2.61 (dq, J = 6.9, 9.7 Hz, 1H), 2.35 (s, 3H), 1.76–1.45 (m, 4H), 1.36 (s, 3H), 0.97 (d, J = 6.9 Hz, 3H), 0.97 (t, J = 7.1 Hz, 3H); MS (M^+ + H) calcd for $C_{11}H_{19}O_3$ 199.1334, found 199.1338. Minor isomer **2l**: ^{1}H NMR (300 MHz, $CDCl_3$) 4.19 (dt, J = 2.7, 10.0 Hz, 1H), 2.22 (s, 3H), 2.00 (dq, J = 7.1, 10.0 Hz, 1H), 1.75–1.45 (m, 4H), 1.48 (s, 3H), 1.04 (d, J = 7.1 Hz, 3H), 0.98 (m, 3H); MS Calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1264.

3-Acetyl-5-ethyl-3-methyltetrahydrofuran-2-ones (2m/3m) were obtained in 85% yield as a 75:25 mixture, respectively. The products were separated by flash chromatography (ether–hexane 40:60) and obtained as oils. Major isomer **2m**: ^{1}H NMR (300 MHz, $CDCl_3$) 4.43 (m, 1H), 2.56 (dd, J = 8.1, 13.2 Hz, 1H), 2.39 (s, 3H), 2.05 (dd, J = 6.7, 13.2 Hz, 1H), 1.75 (m, 1H), 1.66 (m, 1H), 1.54 (s, 3H), 1.02 (t, J = 7.6 Hz, 3H); MS (M^+ + H) calcd for $C_9H_{15}O_3$ 171.1021, found 171.1018. Minor isomer **3m**: ^{1}H NMR (300 MHz, $CDCl_3$) 4.28 (m, 1H), 2.99 (dd, J = 5.7, 12.9 Hz, 1H), 2.32 (s, 3H), 1.74 (m, 1H), 1.61 (m, 2H), 1.54 (s, 3H), 1.01 (t, J = 7.5 Hz, 3H); MS ($M^+ - C_2H_5$) calcd for $C_7H_9O_3$ 141.0552, found 141.0545.

5-Acetoxy-3-acetyl-4-isopropyl-3-methyltetrahydrofuran-2-ones (2n/3n) were obtained in 40% yield as a 50:50 mixture. The products were separated by flash chromatography (EtOAc–hexane 17:83) and obtained as white solids and purified by recrystallization from ether/hexane. **2n**: mp 86.0–87.0 °C; ^{1}H NMR (300 MHz, $CDCl_3$) 6.62 (d, J = 5.1 Hz, 1H), 2.35 (s, 3H), 2.14 (s, 3H), 2.10 (dd, J = 5.2, 11.5 Hz, 1H), 1.97 (m, 1H), 1.57 (s, 3H), 1.11 (d, J = 6.4 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H); MS (M^+ + H) calcd for $C_{12}H_{19}O_5$ 243.1232, found 243.1239. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.48; H, 7.49. Found: C, 59.76; H, 7.01; **3n**: mp 93.0–94.0 °C); ^{1}H NMR (300 MHz, $CDCl_3$) 6.68 (d, J = 5.4 Hz, 1H), 2.97 (dd, J = 5.4, 11.4 Hz, 1H), 2.36 (s, 3H), 2.16 (s, 3H) 1.90 (m, 1H), 1.65 (s, 3H), 0.94 (d, J = 6.5 Hz), 0.79 (d, J = 6.6 Hz, 3H); MS (M^+ + H) calcd for $C_{12}H_{19}O_5$ 243.1232, found 243.1239. Anal. Calcd for $C_{12}H_{18}O_5$: C, 59.48; H, 7.49. Found: C, 59.63; H, 7.13.

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Supporting Information Available: Copies of ^{1}H and/or ^{13}C NMR spectra for all compounds (46 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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