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# A CONCISE ROUTE TO A KEY INTERMEDIATE IN THE TOTAL SYNTHESES OF (+)-TIRANDAMYCIC ACID AND (-)-TIRANDAMYCIN A†

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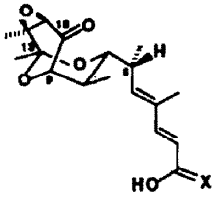
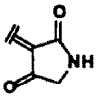
**Abstract.** An efficacious, asymmetric synthesis of the 2,9-dioxabicyclo[3.3.1]nonane **4** has been completed in nine chemical steps from 4,5-dimethylfuraldehyde (**8**). Since enantiomerically pure **4** has been previously converted in five steps by Ireland into (+)-tirandamycic acid (**3**) and more recently by Schlessinger into (-)-tirandamycin A (**1**), this achievement constitutes in a strictly formal sense the total syntheses of these substances. The key step in the synthesis of **4** features the transformation of the enantiomerically pure furfuryl diol **25** into **29** by initial selective oxidation of the furan ring and subsequent acid-catalyzed bicycloketalization.

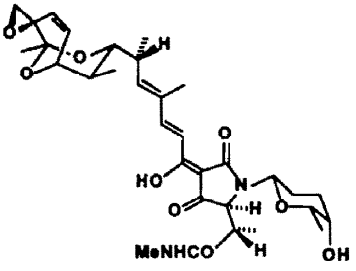
## INTRODUCTION

Tirandamycin A (**1**)[2] and streptolydigin (**2**)[3] are representative members of a novel class of natural antibiotics which are characterized by the presence of an enolized 3-dienoyl tetramic acid moiety linked with a densely functionalized, bridged bicyclic ketal subunit, and they have engendered significant biological and chemical interest over the past few years. For example, **1** exhibits antimicrobial activity, it inhibits bacterial DNA-directed RNA polymerase, and it interferes with oxidative phosphorylation. The unique structural features of these substances coupled with their aforementioned biological properties have served as the inspiration for a number of ingenious synthetic endeavors.[4-14]



**1**: X = 

**3**: X = O



**2**

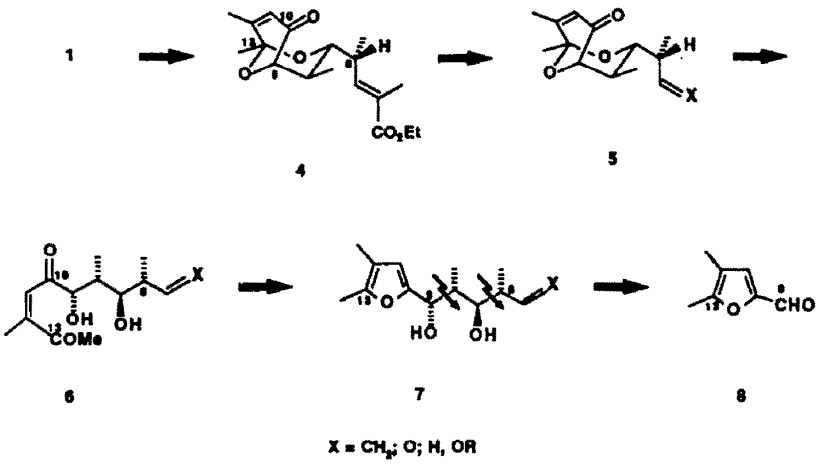
The early synthetic work directed toward these targets focused upon the preparation of (+)-tirandamycic acid (**3**),[5-8] a degradation product of tirandamycin A (**1**), and one of the major achievements was the synthesis of **3** from D-glucose by Ireland.[5] More recently, **1** itself succumbed to total synthesis owing to the efforts in the laboratories of DeShong,[11] Schlessinger,[12] Boeckman,[13] and Bartlett.[14] We now wish to disclose the complete details of our own investigations in this area that culminated in the facile preparation of **4** in enantiomerically pure form,[8] a key intermediate in Ireland's[5] synthesis of **3** and Schlessinger's[12] total synthesis of **1**.

## RESULTS AND DISCUSSION

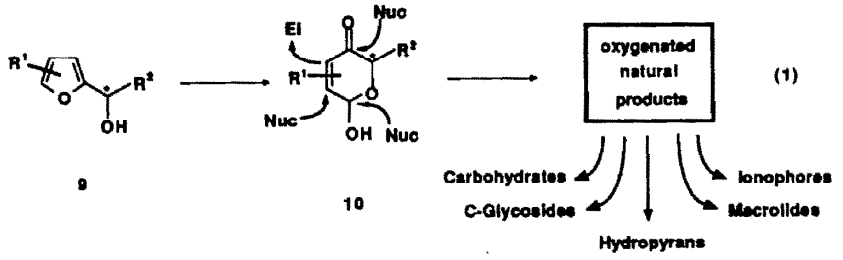
**Synthetic Plan.** The essential features of the strategy and the perceived logical disconnections that originally evolved in our own plan for the synthesis of **1** are summarized in the antithetic sequence depicted in Scheme 1, wherein **4** was envisaged as a key intermediate and the primary subgoal of the project. Further simplification leads to the bicyclic ketal **5**, which may be unraveled by deketalization to the dihydroxy ene-1,4-dione **6**. Since the synthetic equivalencies of the 1,4-dione and ene-1,4-dione moieties with a furan ring have been well established,[15] it occurred to us as well as others[6,7] that a furan might serve admirably as the crucial C(10)-C(13) core of substances of the general type **4** - **6**. Consequently, the substituted furan **7** became the initial target of our investigation, and a variety of entries

to this intermediate from 4,5-dimethylfuraldehyde (**8**) may be formulated that involve stereoselective aldol or related constructions for the formation of the C(6)-C(7) and the C(8)-C(9) bonds.

**Scheme 1**



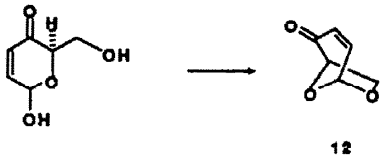

It is noteworthy that the retrosynthetic analysis adumbrated above nicely serves as the basis for the design of a more global strategy for the development of concise approaches to cyclic and acyclic oxygenated natural products in enantiomerically pure form according to eq. 1. Namely, oxidation of the chiral furfuryl carbinols **9** would lead to the production of the hydro-3-pyranones **10**. These key intermediates are admirably endowed with differentiated functionality to allow the facile introduction of other functional groups and/or alkyl residues by reaction with the appropriate nucleophiles and electrophiles as shown. Moreover, the stereochemical course of each of these operations should be directed in a predictable fashion by the stereogenic center at C* of the hydropyran ring. One might reasonably argue that compounds related to **10** should be useful precursors for the preparation of a wide variety of synthetic targets, and numerous testimonials to support this assertion may be found in the literature.[16]




(1)

**9** **10**

**Model Studies.** At the commencement of our investigations in this area, a critical concern was whether a transient and unstable intermediate hydroxy ene-1,4-dione such as **6** would indeed undergo efficient bicycloketalization to deliver **5**. Although anhydro sugars are well documented in the carbohydrate literature, there was only a solitary account of a related, though not identical, cyclization of the unsaturated hydropyranone **11** to provide the bicyclic acetal **12** (eq. 2), but this reaction proceeded in low yield.[15b] Consequently, in order to test the feasbility of the crucial cyclization, we embarked upon the initial model study that is summarized in Scheme 2.

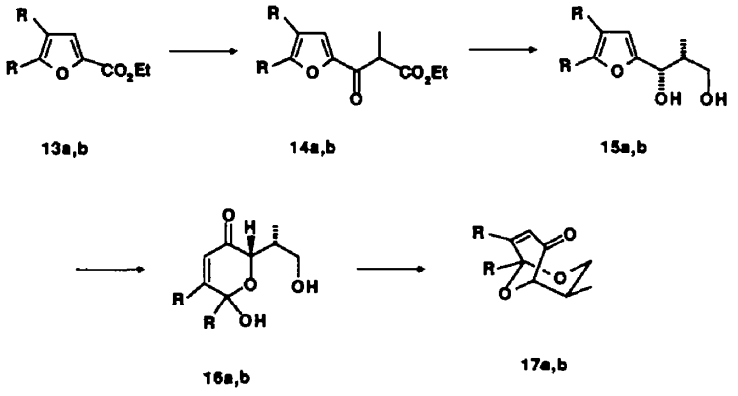


(2)

**11** **12**

The known[17] ß-keto ester **14a** was converted into the *syn*-diol **15a** by the highly stereoselective, chelation-controlled reduction of the ketone function with zinc borohydride[18] followed by reduction of the remaining ester group with lithium aluminum hydride. Sequential oxidation of **15a** with bromine in methanol and hydrolysis of the intermediate 2,5-dimethoxy-2,5-dihydrofurans with aqueous acid according to standard protocols[15] afforded the expected hydropyranone **16a**, but all attempts to induce its cyclization failed to give detectable quantities of **17a**. However, we speculated that the bicycloketalization of the more closely related model **16b** would be more favorable, since this latter process would entail the cyclization of a more stable and, hence more readily formed, tertiary oxygen-stabilized carbocation,[19] and moreover the ß-methyl group on the conjugated olefin would be anticipated to protect the enone array from untoward 1,4-addition. Consequently, the ß-keto ester **14b**, which was conveniently prepared from **13b** by a crossed Claisen condensation with ethyl propionate, was converted into the *syn*-diol **15b** by sequential reduction with zinc borohydride and lithium aluminum hydride in strict analogy with the procedure previously described for the synthesis of **15a**. When **15b** was treated with bromine in methanol followed by hydrolysis of the intermediate ketals in aqueous acid, the bicyclic ketal **17b** was obtained as the sole product in 85% yield. Interestingly, there was no evidence of the intermediate formation of the hydropyranone **16b**. Encouraged by these results, we set to the more demanding task of applying these tactics to the asymmetric synthesis of **1** and precursors thereof.

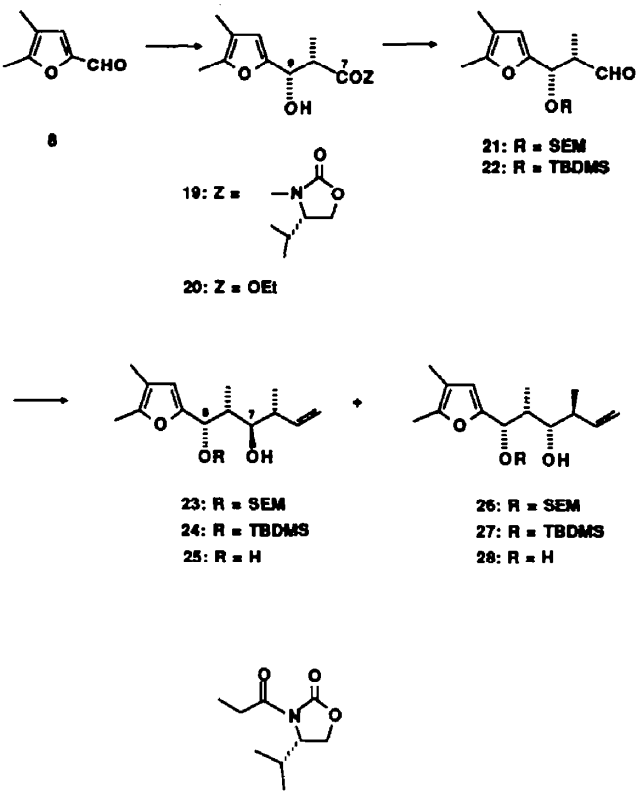
**Scheme 2**




**Formal Syntheses of (+)-Tirandamycic Acid (3) and (-)-Tirandamycin A (1).** Based upon our preliminary findings outlined above, the target that was defined as the initial objective was a substituted furan related to **7** (X = $CH_2$) since it possessed the four contiguous stereocenters at C(6) - C(9) of **1**. A variety of possibilities existed for the establishment of the two stereocenters at C(8) and C(9) with the correct absolute configuration via a diastereoselective *syn*-aldol or related process.[20,21] The remaining stereocenters at C(6) and C(7) having the pendant methyl and hydroxyl groups in an *anti* orientation together with a terminal vinyl group at C(5) could be installed by the addition of a crotyl organometallic reagent[21] to a protected aldehyde. The major challenge would arise during the construction of the second carbon-carbon bond, since an effective means would be required for controlling the relative stereochemistry between C(7) and C(8) via the nucleophilic addition to the aldehyde function in an *anti*-Cram sense. The terminal vinyl group at C(5) would serve expeditiously as a latent aldehyde function that could subsequently be exploited in a Wittig reaction for the further elaboration of the dienoyl side chain in the targeted antibiotics.

The synthesis commenced with the reaction of 4,5-dimethylfuraldehyde (**8**),[22] which was conveniently prepared in 96% yield from 2,3-dimethylfuran[23] by Vilsmeier-Haack formylation, with the di-*n*-butylboron enolate derived from the chiral imide **18** according to the elegant methodology developed by Evans[24] to provide the *syn*-adduct **19** (89% yield) with a high degree of diastereoselectivity (>99%). In the early attempts to cleave the chiral auxiliary from **19**, some difficulties arose involving the competing rupture of the oxazolidinone ring as well as epimerization at C(8). However, when **19** was allowed to react with lithium ethoxide in tetrahydrofuran/ethanol under carefully controlled conditions, the smooth conversion of **19** into the desired ethyl ester **20** could be effected.

**Scheme 3**



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Protection of the hydroxyl group at C(9) was now mandated, and owing to the extreme lability of the furfuryl alcohol function toward acid, it was necessary to select a protecting group that could not only be removed under mild, neutral conditions but which would also be stable to the action of organometallic and hydride reducing reagents. In recognition of these constraints, the ß-trimethylsilylethoxymethyl (SEM)[25] and the *tert*-butyldimethylsilyl (TBDMS)[26] protecting groups, each of which may be readily cleaved by the action of fluoride ion, were selected for further scrutiny. Thus, the free hydroxyl group of **20** was protected as the ß-trimethylsilylethoxymethyl and the *tert*-butyldimethylsilyl ethers according to standard procedures, and the resulting protected ß-hydroxy esters were selectively reduced with diisobutylaluminum hydride (DIBAL) (-95 °C, $CH_2Cl_2$) under carefully controlled conditions to provide the corresponding aldehydes **21** and **22** in 80 - 85% overall yield from **20**.

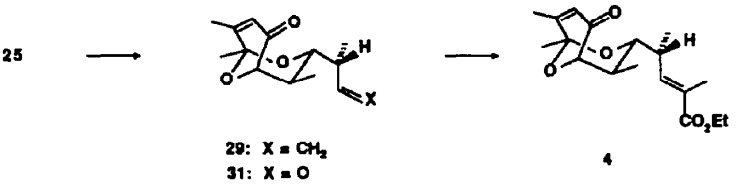
At this juncture, the potential options for effecting the stereoselective installation of the stereocenters at C(6) and C(7) via an aldol reaction or related process were considered. As mentioned previously, this construction requires the *anti*-selective addition of the carbon nucleophile to either of the protected aldehydes **21** or **22** via a chelation-controlled, or an *anti*-Cram, transition state.[27,28] After examining the various possibilities, we selected for further scrutiny the chromium (II) mediated additions of crotyl bromide[29,30] to **21** and **22**, since such processes were known to occur with a high degree of *anti*-selectivity. Owing to the paucity of examples involving such reactions with ß-alkoxy aldehydes, it was not easy to evaluate *a priori* the prospects for attaining a high level of diastereofacial selectivity. Nevertheless, there was one encouraging report from Kishi's laboratory detailing a related addition that proceeded with a high level of stereoselectivity, and this observation was then *tentatively* rationalized on the basis of a transition state model in which the carbonyl group was incorporated in a six-membered chelate with a ß-alkoxy substituent.[30b] Although this early result suggested that the adducts **23** and **24** might be the dominant products from the chromium (II) mediated addition of crotyl bromide to **21** and **22**, respectively, more recent and extensive investigations in his laboratory, which were reported after our own experiments had been completed, led to the more firmly based conclusion that steric effects, not chelation, were the principal stereochemical control elements in these processes.[30c]

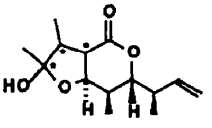
In the event, the reaction of **21** with crotyl bromide in the presence of chromous chloride afforded the adducts **23** and **26** in which the Cram product **26** dominated by an approximately 1:1.7 ratio, whereas subjection of **22** to the same protocol gave a similar mixture (1:1.5) of **24** and **27**.[31] All efforts to achieve a higher level of diastereofacial

selectivity in the desired *anti*-Cram sense by altering the conditions were unsuccessful, and it presently appears that the chromium (II) mediated addition of crotyl bromide to neither **21** nor **22** proceeds via a metal-chelated transition state.

The adduct **24** was selected as the intermediate of choice for completing the synthesis of **4**, since the diastereoselectivity in the addition reaction was slightly more favorable, and furthermore the experimental requirements for protection and deprotection using the TBDMS-ether moiety were known to be more expedient than for the SEM-ether. Thus, fluoride-induced removal of the hydroxyl protecting group from **24** afforded the diol **25**. Although preliminary experiments to effect the conversion of **25** into **29** by oxidation with bromine in methanol followed by treatment with aqueous acid according to our model studies were unavailing, we eventually discovered that oxidation of the furan ring of **25** with *m*-chloroperbenzoic acid (MCPBA) followed by direct treatment of the intermediate hydropyranones with a mixture of HI and KI in aqueous acetonitrile afforded **29** in 75 - 80% overall yield. Careful control over the experimental conditions proved to be essential, since the prolonged exposure of **29** to aqueous acid led to the production of a mixture of substances, several of which have been tentatively identified as stereoisomers of the rearranged, fused lactone **30**.[33]

Selective ozonolysis of the terminal vinyl group present in **29** proceeded smoothly to afford the unstable aldehyde **31**, which was then subjected without further purification to a Wittig olefination with purified (α-carbethoxyethylidene)triphenylphosphorane to deliver the unsaturated ester **4** in 41% overall yield from **29**. The **4** thus obtained gave spectral data that were completely identical to those obtained independently by Ireland for a sample of **4** that had been prepared from D-glucose.[32] Since enantiomerically pure **4** was converted in five steps by Ireland[5] into (+)-tirandamycic acid (**3**) and more recently by Schlessinger[11] into (-)-tirandamycin A (**1**), the extraordinarily concise (nine steps from the known aldehyde **8**) preparation of **4** outlined herein constitutes in a strictly formal sense the total syntheses of these substances.



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Further applications of the general strategy outlined in eq 1 for the asymmetric synthesis of natural products are the subjects of current investigations, and those results will be communicated in due course.

## EXPERIMENTAL SECTION

**General.** Ether ($Et_2O$) and tetrahydrofuran (THF) were distilled from either sodium or potassium-benzophenone ketyl immediately prior to use, and triethylamine and diisopropylethylamine were distilled from calcium hydride. All reactions involving organometallic reagents or other moisture sensitive reactants were executed under an atmosphere of dry nitrogen or argon using oven-dried glassware. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were determined as solutions in $CHCl_3$ unless otherwise specified using a Beckman Acculab 8 spectrometer. The $^1H$ and $^{13}C$ NMR spectra were determined as solutions in $CDCl_3$, unless otherwise indicated, on a Varian EM-390 (90 MHz), a Varian FT-80 H (80 MHz), a Nicolet NT-200, NT-360, or a GN-500 spectrometer as indicated. Chemical shifts are expressed in parts per million (δ units) downfield from internal tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, complex multiplet; br, broad. Coupling constants are given in hertz (Hz). Low-resolution mass spectra were obtained on a DuPont (CEC) 21-491 instrument at an ionization voltage of 70 eV, and the exact mass determinations were obtained on a DuPont (CEC) 21-110 instrument. The bulb to bulb distillations were executed on a Kugelrohr apparatus.

**Ethyl 4,5-dimethylfuroate (13b).** To a stirred solution of 2,3-dimethylfuran (23) (10.00 g, 104.2 mmol) in THF (200 mL) at -78 °C was added dropwise *n*-butyllithium (42.5 mL of a 2.94 M solution in hexane, 125 mmol), and the solution was then stirred at 0 °C for 4 h. The resulting 4,5-dimethyl-2-lithiofuran was then slowly transferred via cannula to a solution of freshly distilled (from $CaH_2$) ethyl chloroformate (24.86 g, 230.0 mmol) in THF (100 mL) at -78 °C, and the reaction mixture was allowed to warm slowly (ca. 1 h) to room temperature and stirred for 1 h. Saturated $NH_4Cl$ (250 mL) was added, and the layers were separated. The aqueous phase was extracted with $Et_2O$ (3 x 150 mL), and the extracts were combined and washed with saturated $NaHCO_3$ (2 x 100 mL), saturated NaCl (2 x 150 mL) and dried ($MgSO_4$). Removal of the excess solvent under reduced pressure and distillation of the residue (63-65 °C, 0.025 mm Hg) yielded 14.06 g (80%) of **13b**. $^1H$ NMR (90 MHz) δ 6.95 (s, 1 H), 4.30 (q, J = 7 Hz, 2 H), 2.27 (s, 3 H), 1.98 (s, 3 H), 1.35 (t, J = 7 Hz, 3 H); $^{13}C$ NMR (20 MHz) δ 158.1, 152.1, 141.3, 120.4, 116.3, 59.8, 13.7, 11.0, 8.8; IR (film) 1730 $cm^{-1}$; Mass spectrum, *m/e* 168.0789 ($C_9H_{12}O_3$ requires 168.0786), 140, 123 (base), 96, 95, 67.

**(2*S*/*R*)-Ethyl 2-[2'-(4,5-dimethyl)furoyl]propionate (14b).** To a suspension of NaH (7.99 g, 333.0 mmol) in toluene (125 mL) at reflux was added *tert*-butyl alcohol (24.70 g, 333.0 mmol). After the initial reaction had subsided, a neat mixture of **13b** (14.00 g, 83.3 mmol) and ethyl propionate (34.00 g, 333 mmol) was slowly added, whereupon the reaction was heated at a gentle reflux for 2 h. The mixture was cooled to 0 °C, glacial acetic acid (25 mL) was added slowly, and the mixture was diluted with $H_2O$ (100 mL). The phases were separated, and the aqueous layer was extracted with $Et_2O$ (3 x 75 mL). The combined extracts were washed with $H_2O$ (3 x 100 mL), saturated $NaHCO_3$ (2 x 100 mL), saturated NaCl (2 x 100 mL) and then dried ($MgSO_4$). Evaporation of solvent under reduced pressure followed by purification of the crude product by preparative HPLC [hexanes/EtOAc (11:1)] afforded 12.50 g (67%) of **14b** as a pale yellow oil. An analytical sample was prepared by bulb to bulb distillation, [120-122 °C (oven temperature), 0.20 mm Hg]. $^1H$ NMR (90 MHz) δ 6.93 (s, 1 H), 4.06 (q, J = 7 Hz, 2 H), 3.92 (q, J = 6 Hz, 1 H), 2.27 (s, 3 H), 1.98 (s, 3 H), 1.30 (d, J = 6 Hz, 3 H), 1.16 (t, J = 7 Hz, 3 H); $^{13}C$ NMR (20 MHz) δ 183.0, 169.9, 153.8, 148.4, 121.6, 117.5, 60.4, 47.3, 13.3, 12.7, 11.2, 8.9; IR (film) 1750, 1685 $cm^{-1}$; Mass spectrum, *m/e* 224.1044 ($C_{12}H_{16}O_4$ requires 224.1048), 179, 123 (base), 67, 43.

**(2*S**, 3*S**)-Ethyl 3-[2-(4,5-dimethyl)furyl]-3-hydroxy-2-methylpropionate.** To a solution of **14b** (12.5 g, 56.0 mmol) in $Et_2O$ (100 mL) at 0 °C was slowly added a solution of $Zn(BH_4)_2$ (115 mL of a ca. 0.15 M solution in ether), and the resulting solution was stirred at 0 °C for 1 h. The excess hydride was destroyed by the sequential addition at 0 °C of $H_2O$ (15 mL) and 33% aqueous acetic acid (50 mL). The layers were separated, and the aqueous phase was extracted with $Et_2O$ (3 x 50 mL). The combined extracts were then washed with $H_2O$ (2 x 75 mL), saturated $NaHCO_3$ (2 x 100 mL), saturated NaCl (2 x 100 mL) and dried ($MgSO_4$). The excess solvent was evaporated under reduced pressure, and the residual oil was purified by column chromatography on $SiO_2$ [75 g, hexanes/EtOAc (4:1)] to afford 10.32 g (82%) of pure β-hydroxyester. An analytical sample was prepared by bulb to bulb distillation,[130-132 °C (oven temperature), 0.20 mm Hg]. $^1H$ NMR (90 MHz) δ 5.92 (s, 1 H), 4.85 (d, J = 6 Hz, 1 H), 4.03 (q, J = 7 Hz, 3 H), 2.77 (p, J = 7 Hz, 1 H), 2.11 (s, 3 H), 1.87 (s, 3 H), 1.17 (t, J = 7 Hz, 6 H); $^{13}C$ NMR (20 MHz) δ 174.6, 151.2, 146.3, 114.0, 109.6, 68.6, 60.3, 44.2, 13.7, 11.9, 10.9, 9.4; IR (film) 3455, 1775 $cm^{-1}$; Mass spectrum, *m/e* 226.1200 ($C_{12}H_{18}O_4$ requires 226.1205), 208, 181, 135, 126, 125 (base), 123, 43, 41.

**(2*S**, 3*S**)-3-[2'-(4,5-dimethyl)furyl]-3-hydroxy-2-methylpropan-1-ol (15b).** To a stirred suspension of $LiAlH_4$ (1.34 g, 35.2 mmol) in $Et_2O$ (50 mL) at 0 °C was slowly added a solution of the β-hydroxyester prepared in the preceding experiment (5.31 g, 23.5 mmol) in $Et_2O$ (5 mL). The reaction was then stirred at room temperature for 5 h at which time it was recooled to 0 °C, and the reaction was quenched by the sequential addition of $H_2O$ (1.3 mL), 15% NaOH (1.3 mL) and $H_2O$ (3.9 mL). The ethereal solution was decanted from the aluminate salts, which were then washed thoroughly with $Et_2O$ (3 x 25 mL). The washes were combined with the original $Et_2O$ layer and then dried ($Na_2SO_4$). Removal of solvent under reduced pressure followed by purification of the residue by chromatography on $SiO_2$ [25 g, hexanes/EtOAc (3:2)] gave 3.97 g (92%) of pure **15b** as a viscous, colorless oil that decomposed upon attempted bulb to bulb distillation. $^1H$ NMR (90 MHz) δ 5.97 (s, 1 H), 4.73 (d, J = 5 Hz, 1 H), 3.60 (m, 2 H), 2.93 (br s, 2 H), 2.16 (s, 3 H), 1.88 (s, 3 H), 0.89 (d, J = 7 Hz, 3 H); $^{13}C$ NMR (20 MHz) δ 151.3, 146.2, 114.1, 109.5, 68.0, 65.4, 39.6, 12.13, 10.8, 9.6; IR (film) 3345, 1640, 1575 $cm^{-1}$; Mass spectrum, *m/e* 184.1096 ($C_{10}H_{16}O_3$ requires 184.1099), 166, 136, 125 (base), 109, 43.

**(1*S**, 4*S**, 5*S**)-1, 4, 8-Trimethyl-2,9-dioxabicyclo[3.3.1]non-7-ene-6-one (17b).** To a solution of **15b** (54 mg, 0.27 mmol) in MeOH (0.5 mL) at -78 °C was added a freshly prepared solution of bromine in MeOH (0.56 mL of a 0.5 M solution, 0.278 mmol), and the resulting dark red solution was stirred at -78 °C for 15 min. The excess bromine was destroyed by the addition of saturated aqueous $NaHSO_3$ (3 drops), and the mixture was allowed to warm to room temperature. The MeOH was evaporated under reduced pressure, and 2 N HCl (1 mL) and THF (1 mL) were added. The mixture was stirred vigorously at room temperature for 1.5 h, solid NaCl (100 mg) was added, and the mixture was extracted with $CH_2Cl_2$ (3 x 10 mL). The extracts were combined, washed with saturated aqueous $NaHCO_3$ (10 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to yield 43 mg (87%) of **17b** as a clear pale yellow oil, which was purified by bulb to bulb distillation, 170 °C (oven temperature), 0.05 mm Hg. $^1H$ NMR (90 MHz) δ 6.13 (s, 1 H), 4.06 (d, J = 5 Hz, 1 H), 3.76 (dd, J = 6, 12 Hz, 1 H), 3.40 (t, J = 12 Hz, 1 H), 2.37 (m, 1 H), 1.91 (d, J = 1 Hz, 3 H), 1.50 (s, 3 H), 0.80 (d, J = 8 Hz, 3 H); Mass spectrum, *m/e* 182.0948 ($C_{10}H_{14}O_3$ requires 182.0943), 112, 111 (base), 69, 43.

**4,5-Dimethylfuraldehyde (8).** 2,3-Dimethylfuran[23] (5.00 g, 52.0 mmol) was added dropwise (5 min) at 0-5 °C to the iminium salt that had been prepared by the reaction of DMF (4.6 mL, 4.38 g, 60.0 mmol) with $POCl_3$ (5.1 mL, 8.43 g, 55.0 mmol), and the resulting viscous solution was stirred at room temperature for 2.5 h. The reaction was quenched at 0 °C by the addition of cold $H_2O$ (50 mL), and the resulting mixture was slowly poured with stirring into a cold solution of $Na_2CO_3$ (20 g) in $H_2O$ (100 mL). The mixture was stirred at room temperature for 15 h during which time the pH was maintained at ca. 8 by the addition of solid $Na_2CO_3$. The resulting brown suspension was diluted with $H_2O$ (100 mL) and extracted with hexane/$Et_2O$ (1:1, 3 x 75 mL). The organic layers were combined and dried ($MgSO_4$), and the excess solvent was removed under reduced pressure. The residue was distilled to yield 6.20 g (96%) of **8** as a colorless oil, (bp 31-33 °C, 0.04 mm), which solidified upon storage in the freezer. $^1H$ NMR (90 MHz) δ 9.44 (s, 1 H), 7.01 (s, 1 H), 2.32 (s, 3 H), 2.04 (s, 3 H); IR (film) 1685 $cm^{-1}$; Mass spectrum, *m/e* 124.05288 ($C_7H_8O_2$ requires 124.05242) (base), 95, 67, 43, 41.

**3-[(4,5-Dimethylfuryl)-3'*S*-hydroxy-2'*S*-methylpropionyl]-4*S*-(isopropyl)-2-oxazolidin-2-one (19).** To a solution of **18**[24] (2.78 g, 15 mmol) in $CH_2Cl_2$ (15 mL) at -78 °C was sequentially added dropwise *n*-$Bu_2BOTf$[34] ( 4.52 g, 16.5 mmol) and diisopropylethylamine (2.33 g, 18.0 mmol), and the resulting mixture was stirred at -78 °C for 20 min and at 0 °C for 1 h. After recooling the solution to -78 °C, **8** (2.05 g, 16.5 mmol) was added dropwise, and the resulting yellow suspension was stirred at -78 °C for 10 min and then at 0 °C for 30 min. The reaction was quenched at 0 °C by the dropwise addition of aqueous phosphate buffer (15 mL of pH 7) and MeOH (25 mL) followed by MeOH/30% $H_2O_2$ (1:1 v/v, 16 mL). The mixture was stirred at 0 °C for 1 h, whereupon $H_2O$ (25 mL) was added. The organic solvents were removed under reduced pressure (bath temperature <25 °C), and the resulting mixture was extracted with $Et_2O$ (3 x 50 mL). The combined extracts were washed with 5% $NaHCO_3$ (1 x 10 mL), saturated NaCl (1 x 10 mL), dried ($MgSO_4$) and concentrated under reduced pressure, and the crude product **19** was then recrystallized [hexanes/EtOAc (5:1)] to yield 4.11 g (89%) of **19** as fine white needles, mp 93-94 °C. $[\alpha]_D$ = +64.1° (*c* =0.70, $CHCl_3$); $^1H$ NMR (200 MHz) δ 6.05 (s, 1 H), 4.95 (d, J = 5.3 Hz, 1 H), 4.40 (m, 1 H), 4.10-4.32 (comp, 3 H), 2.91 (br s, 1 H), 2.32 (m, 1 H), 2.18 (s, 3 H), 1.90 (s, 3 H), 1.35 (d, J = 7.4 Hz, 3 H), 0.94 (d, J = 7 Hz, 3 H), 0.91 (d, J = 7 Hz, 3 H); $^{13}C$ NMR δ 176.4, 153.3, 151.1, 146.7, 114.4, 109.8, 68.4, 63.4, 58.3, 42.4, 28.4, 17.8, 14.7, 12.5, 11.2, 9.7; IR ($CH_2Cl_2$) 1790, 1710, 1700 $cm^{-1}$; Mass spectrum, *m/e* 309, 185, 142, 85 (base). Anal. Calcd. for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.21; H, 7.39; N, 4.45.

**(2*S*, 3*S*)-Ethyl 3-(4,5-dimethylfuryl)-3-hydroxy-2-methylpropionate (20).** To a solution of **19** (5.25 g, 17.0 mmol) in THF (275 mL) at -78 °C was added dropwise (20 min) with rapid stirring 0.2 M EtOLi (82 mL) in EtOH/THF (1:1 v/v). The mixture was then allowed to warm to room temperature while monitoring the disappearance of **19** (usually within 20-30 min) by TLC, whereupon the reaction mixture was immediately recooled to 0 °C and quenched by the sequential addition of saturated $NH_4Cl$ (30 mL) and $H_2O$ (30 mL). The aqueous layer was extracted with $Et_2O$ (3 x 100 mL), and the combined organic extracts were washed with saturated NaCl (2 x 30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on $SiO_2$ [25 g, hexanes/EtOAc (19:1)] to yield 2.87 g (75%) of **20** as a pale yellow oil: $[\alpha]_D$ = -10.8° (*c*= 5.8, $CCl_4$); $^1H$ NMR (90 MHz) δ 6.02 (s, 1 H), 4.91 (d, J = 6 Hz, 1 H), 4.14 (q, J = 7 Hz, 2 H), 2.61-3.03 (comp, 2 H), 2.11 (s, 3 H), 1.83 (s, 3 H), 1.12-1.31 (comp, 6 H); $^{13}C$ NMR δ 174.6, 151.2, 146.3, 114.1, 109.6, 68.6, 60.3, 44.1, 13.7, 11.9, 10.9, 9.5; IR (neat) 3200-3700, 1735 $cm^{-1}$; Mass spectrum, *m/e* 226.12020 ($C_{12}H_{18}O_4$ requires 226.12050), 208, 181, 153, 135, 125 (base), 95, 67, 43.

**(2*S*, 3*S*)-Ethyl-3-*tert*-butyldimethylsilyloxy-3-(4,5-dimethylfuryl)-2-methyl propionate.** A solution of **20** (2.85 g, 12.6 mmol), imidazole (1.71 g, 25.2 mmol), and *tert*-butyldimethylsilylchloride (2.26 g, 15.0 mmol) in DMF (12 mL) was stirred at room temperature for 7.5 h, whereupon $H_2O$ (20 mL) was added. The mixture was extracted with hexane/$Et_2O$ (1:1) (3 x 25 mL), and the combined organic extracts were washed with 5% $NaHCO_3$ (5 mL), saturated NaCl (5 mL), dried ($MgSO_4$). The excess solvents were removed under reduced pressure, and the residue was chromatographed on $SiO_2$ [14 g, hexanes/EtOAc (25:1)] to yield 3.95 g (92%) of protected ß-hydroxy ester as a colorless oil: $[\alpha]_D$ = -26.3° (*c* = 4.5, $CCl_4$); $^1H$ NMR (90 MHz) δ 5.95 (s, 1 H), 4.91 (d, J = 6 Hz, 1 H), 4.10 (q, J = 7 Hz, 2 H), 2.90 (m, 1 H), 2.18 (s, 3 H), 1.90 (s, 3 H), 1.15-1.30 (comp, 6 H), 0.89 (s, 9 H), 0.07 (s, 3 H), -0.06 (s, 3 H); $^{13}C$ NMR δ 174.1, 152.2, 146.1, 114.1, 109.9, 70.0, 60.2, 46.1, 18.1, 14.0, 12.1, 11.2, 9.8, -4.8, -5.4; IR 1730, 1255 $cm^{-1}$; Mass spectrum, *m/e* 340.20606 ($C_{18}H_{32}O_4Si$ requires 340.2069), 284 (base), 240, 159, 136, 115, 103, 73.

**(2*S*, 3*S*)-3-*tert*-Butyldimethylsilyloxy-3-(4,5-dimethylfuryl)-2-methylpropionaldehyde (22).** To a rapidly stirred solution of the protected ß-hydroxy ester obtained according to the preceding procedure (5.00 g, 14.7 mmol) in $CH_2Cl_2$ (200 mL) at -95 °C was slowly added (40 min) a solution of DIBAL (1 M in toluene) (26.4 mL, 26.4 mmol). The solution was then stirred at -95 °C for 1 h, and then the reaction was quenched by the dropwise addition of 2 M isopropanol in $CH_2Cl_2$ (50 mL). The mixture was then warmed to 0 °C, and $H_2O$ (7 mL), Celite (13 g), and anhydrous $Na_2SO_4$ (12 g) were added. After stirring for 5 min, hexane (100 mL) was added, and the mixture was filtered through a Celite pad by suction filtration. The salts were washed thoroughly with hexane (3 x 50 mL), and the combined filtrates and washings were dried ($Na_2SO_4$) and concentrated under reduced pressure to yield 4.25 g (98% mass balance) of crude **22**, which contained approximately 5% of the corresponding primary alcohol. The unstable aldehyde **22** thus obtained was used immediately in the next experiment without further purification. $^1H$ NMR (90 MHz) δ 9.81 (s, 1 H), 6.03 (s, 1 H), 4.93 (d, J = 5.Hz, 1 H), 2.74 (m, 1 H), 2.11 (s, 3 H), 1.82 (s, 3 H), 1.10 (d, J = 7 Hz, 3 H), 0.80 (s, 9 H), 0.12 (s, 3 H), -0.14 (s, 3 H).

**Chromium (II) Mediated Addition of Crotyl Bromide to 22.** To a stirred mixture of crude **22** from the preceding experiment (4.05 g, 13.6 mmol) in degassed THF (100 mL) containing $CrCl_2$ (5.98 g, 48.6 mmol) at 0 °C was cannulated a degassed solution of freshly distilled (from $CaH_2$) crotyl bromide (3.67 g, 27.2 mmol) in THF (20 mL). The resulting mixture was then stirred at room temperature for 2 h at which time it was cooled to 0 °C, diluted with $Et_2O$ (50 mL) and quenched by the addition of 5% $NaHCO_3$ (50 mL). The layers were separated, and the aqueous phase was extracted with $Et_2O$ (3 x 50 mL). The combined organic extracts were washed with 5% $NaHCO_3$ (20 mL), $H_2O$ (20 mL), saturated NaCl (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The mixture of products was then separated by preparative HPLC [hexanes/EtOAc (60:1)] to afford **24** (1.10 g, 26%) and **27** (1.65 g, 39%) as colorless oils.

**(1*S*, 2*R*, 3*R*, 4*R*)-1-*tert*-Butyldimethylsilyloxy-1-(4,5-dimethylfuryl)-2,4-dimethyl-5-hexen-3-ol (24):** $[\alpha]_D$ = -34.1° (*c* = 2.9, $CCl_4$); $^1H$ NMR (200 MHz) δ 5.75-6.10 (comp, 2 H), 5.12 (m, 2 H), 4.85 (d, J = 4 Hz, 1 H), 3.71 (br d, J = 2.5 Hz, 1 H), 3.50 (dt, J = 2.5, 9.0 Hz, 1 H), 2.10-2.41 (comp, 5 H), 1.91 (s, 3 H), 1.13 (d, J = 7.3 Hz, 3 H), 0.90 (s, 9 H), 0.79 (d, J = 7.3 Hz, 3 H), 0.08 (s, 3 H), -0.09 (s, 3 H); $^{13}C$ NMR δ 151.9, 146.0, 139.4, 115.0, 114.3, 110.5, 76.7, 73.0, 42.0, 40.6, 25.8, 18.1, 17.9, 17.8, 12.1, 11.3, -5.0, -5.5; IR 3300-3600 $cm^{-1}$; Mass spectrum, *m/e* 352.24402 ($C_{20}H_{36}O_3Si$ requires 352.24336), 239 (base), 203, 199, 165, 137, 109, 75, 43.

**(1*S*, 2*R*, 3*S*, 4*S*)-1-*tert*-Butyldimethylsilyloxy-1-(4,5-dimethylfuryl)-2,4-dimethyl-5-hexen-3-ol (27):** $[\alpha]_D$ = -16.5° (*c* = 2.7, $CCl_4$); $^1H$ NMR (200 MHz) δ 5.95 (s, 1 H), 5.71 (m, 1 H), 4.95-5.14 (comp, 3 H), 4.62 (d, J = 7.2 Hz, 1 H), 3.17 (dd, J = 1.8, 8.5 Hz, 1 H), 2.30 (m, 1 H), 2.17 (s, 3 H), 2.03 (m, 1 H), 1.90 (s, 3 H), 1.02 (d, J = 6.9 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H), 0.87 (s, 9 H), 0.04(s, 3 H), -0.16 (s, 3 H); $^{13}C$ NMR δ 152.6, 146.1, 142.0, 115.6, 114.1, 110.6, 75.0, 72.3, 42.4, 40.6, 25.9, 18.2, 16.5, 11.3, 9.9, 8.3, -4.9, -5.1; IR ($CH_2Cl_2$) 3300-3650 $cm^{-1}$; Mass spectrum, *m/e* 352.24480 ($C_{20}H_{36}O_3Si$ requires 352.24336), 295, 239, 185 (base), 165, 135, 115, 95, 75, 43.

**(1*S*, 2*R*, 3*R*, 4*R*)-1-(4,5-Dimethylfuryl)-2,4-dimethyl-5-hexen-1,3-diol (25).** To a solution of **24** (140 mg, 0.40 mmol) in THF (1 mL) was added a solution of *n*-$Bu_4NF$ (2 M in THF) (1 mL, 2.0 mmol), and the reaction was stirred at room temperature for 15 min at which time $Et_2O$ (5 mL) and $H_2O$ (5 mL) were added. The layers were separated, and the aqueous layer was extracted with $Et_2O$ (3 x 5 mL). The combined organic extracts were washed with saturated NaCl (5 mL), dried (anhydrous $K_2CO_3$) and concentrated under reduced pressure. The residue was purified by chromatography on $SiO_2$ [0.5 g; hexanes/EtOAc (9:1)] to yield 90 mg (95%) of **25** as a colorless oil: $[\alpha]_D$ = -9.3° (*c* = 1.6, $CCl_4$); $^1H$ NMR (200 MHz) δ 5.98 (s, 1 H), 5.78 (m, 1 H), 5.09 (m, 2 H), 4.91 (br s, 1 H), 3.94 (br s, 1 H), 3.38 (br s, 1 H), 2.35 (m, 1 H), 2.12 (s, 3 H), 2.06 (m, 1 H), 1.87 (s, 3 H), 1.03 (d, J = 6.9 Hz, 3 H), 0.91 (d, J = 6.9 Hz, 3 H); $^{13}C$ NMR δ 152.7, 146.0, 139.5, 116.2, 114.2, 109.4, 78.0, 69.7, 41.1, 39.3, 17.1, 11.8, 11.2, 9.7; IR 3300-3600 $cm^{-1}$; Mass spectrum, *m/e* 238.15752 ($C_{14}H_{22}O_3$ requires 238.15688), 220, 125 (base), 109, 96, 81, 55, 43.

**(1*S*, 3*R*, 4*R*, 5*S*)-3-[(3'*R*)-1'-Buten-3'-yl]-1,4,8-trimethyl-2,9-dioxabicyclo[3.3.1]non-7-en-6-one (29).** To a solution of **25** (45 mg, 0.19 mmol) in $CH_2Cl_2$ (1 mL) at -23 °C containing anhydrous NaOAc (31 mg, 0.38 mmol) was added in one portion purified MCPBA (95%) (34 mg, 0.20 mmol), and the reaction was stirred at -23 °C for 1 h. Saturated $NaHCO_3$ (2 mL) was then added, and the layers were separated. The aqueous phase was extracted with $CH_2Cl_2$ (3 x 10 mL), and the organic extracts were combined and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure afforded 46 mg (96%) of a mixture of crude epimeric hydropyranones [$^1H$ NMR (90 MHz) δ 4.92 - 6.14 (comp, 3 H), 3.73 (m 2 H), 2.82 (br s, 2 H), 2.21 (br s, 1 H), 1.83 (m, 3 H), 1.52 (m, 3 H), 1.10 (m, 6 H)], which were dissolved without further purification in $CH_3CN$ (1.5 mL). An aqueous solution of HI/KI (3.8 mL) (generated by combining 35% HI and saturated KI, 4:1) was then added slowly to the above solution at -23 °C, and the resulting pale yellow solution was stirred at 0 °C for 50 min. The reaction was quenched with saturated sodium thiosulfate (5 drops), and the mixture was added slowly with stirring to saturated $NaHCO_3$ (20 mL) at 0 °C and then extracted with $Et_2O$ (3 x 30 mL). The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure to provide an oil, which contained small amounts of **30** as a suspended solid. Cold hexane (25 mL) was added, the **30** was removed by filtration, and the filtrate was evaporated to provide 35 mg (78%) of **29** as a clear pale yellow oil. An analytical sample was prepared by preparative HPLC [hexanes/EtOAc (10:1)].

For **29**: $[\alpha]_D$ = -112.7° (*c* = 0.76, $CCl_4$); $^1H$ NMR (200 MHz) δ 6.13 (br s, 1 H), 5.86 (m, 1 H), 5.08 (dd, J = 5.6, 1.9 Hz, 1 H), 5.01 (dd, J = 12.3, 2 Hz, 1H), 4.03 (d, J = 6 Hz, 1 H), 3.33 (dd, J = 11.1, 2.1 Hz, 1 H), 2.28 (comp, 2 H), 1.91 (d, J = 1.5 Hz, 3 H), 1.52 (s, 3 H), 1.05 (d, J = 7 Hz, 3 H), 0.72 (d, J = 8.0 Hz, 3 H); $^{13}C$ NMR δ 194.9, 155.2, 138.3, 126.5, 115, 95, 78.6, 76.5, 38.7, 32.4, 23.7, 18.5, 16.9, 10.5; IR 1670 $cm^{-1}$; Mass spectrum, *m/e* 236.14055 ($C_{14}H_{20}O_3$ requires 236.14123), 181, 111, 69, 55, 43 (base).

**For 30:** mp 152-153.5 °C; $^1H$ NMR (500 MHz, $d_6$-DMSO) δ 5.71-5.63 (m, 1 H), 5.11-5.05 (m, 2 H), 3.93 (dd, J = 2.0, 10.5 Hz, 1 H), 3.86 (t, J = 10.0 Hz, 1 H), 2.85 (t, J = 10.0 Hz, 1 H), 2.48-2.42 (m, 1 H), 1.88-1,82 (m, 1 H), 1.31-1.25 (m, 1 H), 1.20 (s, 3 H), 1.02 (d, J = 7.0 Hz, 3 H), 1.01 (d, J = 7.0 Hz, 3 H), 0.88 (d, J = 7.0 Hz, 3 H); $^{13}C$ NMR (125 MHz, $d_6$-DMSO) δ 173.1, 137.1, 116.6, 103.4, 81.8, 76.8, 47.8, 45.9, 37.7, 37.4, 24.4, 17.4, 13.8, 13.1; Mass spectrum, *m/e* 236.14172 ($M^+$-18) ($C_{14}H_{20}O_3$ requires 236.14123), 199, 181,153, 123, 113 (base), 95, 43.

**(2*E*, 4*R*)-Ethyl 2-methyl-4-[(1'*S*, 3'*R*, 4'*R*, 5'*S*)-1',4',8'-trimethyl-2',9'-dioxabicyclo[3.3.1]non-7'-en-6'-one-3'-yl]-2-pentenoate (4).** Ozone was gently passed through a solution of **29** (23 mg, 0.1 mmol) in $CH_2Cl_2$ (0.5 mL) containing MeOH (0.05 mL) at -78 °C while the progress of the reaction was monitored by TLC. When all of the starting material had been consumed, the solution was warmed to -50 °C, and triphenylphosphine (51 mg, 0.2 mmol) was added. The mixture was warmed to room temperature with stirring, the solvent was removed under reduced pressure, and the residue was dissolved in benzene (0.5 mL). Base-free (α-carbethoxyethylidene)triphenylphosphorane (106 mg, 0.3 mmol), which had been recrystallized five times from benzene, was added, and the reaction mixture was sealed and heated at 80 °C for 18 h. The benzene was evaporated under reduced pressure, and the residue was triturated with cold hexane (3 x 10 mL). The combined triturates were concentrated under reduced pressure, and the residue was chromatographed on $SiO_2$ (0.5 g, 5% EtOAc/hexane) to provide 13 mg (41%) of **4** as a clear, colorless oil. $[\alpha]_D$ = -185.2° (*c*= 1.10, $CHCl_3$), lit.[5] $[\alpha]_D$ = -186.3° (*c* = 1.085, $CHCl_3$); $^1H$ NMR (200 MHz) δ 6.92 (dd, J = 10.3, 1.3 Hz, 1 H), 6.11 (br s, 1 H), 4.22 (q, J = 7.0 Hz, 2 H), 4.02 (d, J = 6.1 Hz, 1 H), 3.41 (dd, J = 11.3, 2.1 Hz, 1 H), 2.75 (m, 1 H), 2.00 (m, 1 H), 1.93 (d, J = 1.4 Hz, 3 H), 1.85 (d, J = 1.4 Hz, 3 H), 1.56 (s, 3 H), 1.32 (t, J = 7.0 Hz, 3 H), 1.05 (d, J = 7.0 Hz, 3 H), 0.71 (d, J = 7.0 Hz, 3 H); $^{13}C$ NMR δ 194.2, 167.1, 155, 140.7, 127.8, 126.4, 95.4, 78.3, 76.3, 59.7, 33.4, 32.8, 23.5, 18.3, 15.7, 13.5, 11.6, 10.8; IR 2985, 1695, 1725 $cm^{-1}$; Mass spectrum, *m/e* 322.17706 ($C_{18}H_{26}O_5$ requires 322.17801), 277, 181 (base), 111, 69, 55, 43.

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