2.52 (s, 3, SCH_3), 3.73 (dd, 1, J = 8.6, 15.0 Hz, CHO), 4.01 (dt, 1, J = 5.6, 5.6 Hz, allylic CHO), 5.23 (dd, 1, J = 7.3, 15.5 Hz, vinyl), 5.39 (dd, 1, J = 5.4, 15.3 Hz, vinyl), 6.39 (d, 1, J = 2.3 Hz, CH(Si)O), 7.2-7.6 (m, 5, aromatic); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ -4.6, -4.4, -4.0, -3.7, -3.4, 14.1, 18.0, 18.3, 18.5, 18.7, 22.7, 25.1, 26.0, 32.0, 36.6, 38.7, 40.0, 45.5, 55.5, 69.0, 73.0, 78.0, 80.5, 83.4, 127.7, 127.9, 129.7, 130.2, 134.3, 136.1, 213.8; MS, m/z 732 (M^+); HRMS, m/z calcd for $C_{39}H_{68}O_3Si_3S_2$ 732.3917, found 732.3908.

[3a*R*-[3aα,4α(1*E*,3*R),5β,6aα]]-(1,1-Dimethylethyl)[[1-[2-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-(dimethylphenylsilyl)-2-methylene-4-octahydropentalenyl]ethenyl]hexyl]oxy]dimethylsilane (24).** The solution of **22** (20.0 mg, 2.45×10^{-2} mmol), $Mg(ClO_4)_2$ (5.5 mg, 2.46×10^{-2} mmol), and *N*-methylcarbazole (4.5 mg, 2.48×10^{-2} mmol) in a 10:1 mixture of THF and water (7.5 mL) was irradiated by using a 500-W high-pressure mercury lamp at 20 °C for 4 h. This solution was poured into a saturated $NaHCO_3$ aqueous solution (5 mL). The resulting mixture was extracted with ether (5 mL × 3). The combined organic extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (2 g) using a 100:1 mixture of hexane/ethyl acetate as eluant to give **24** (7.7 mg, 50%) as a colorless oil: TLC R_f 0.77 (5:1 hexane/ethyl acetate); $[\alpha]^{24}_D$ -27.5° (c 1.04, hexane); IR ($CHCl_3$) 1640, 1460, 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ -0.01, 0.02 (s each, 12, 4 $OSiCH_3$), 0.28, 0.29 (s each, 6, 2 $SiCH_3$), 0.85, 0.88 (s each, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.1-1.5 (m, 9, 4 CH_2 and CH), 1.8-2.4 (m, 7, 2 CH_2 and 3 CH), 3.67 (dd, 1, J = 9.2, 16.2 Hz, CHO), 3.9-4.1 (m, 1, allylic CHO), 4.55, 4.74 (br s each, 2, methylene), 5.3-5.6 (m, 2, vinyl), 7.2-7.6 (m, 5, aromatic); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ -4.6, -4.4, -4.2, -4.1, 14.0, 18.1, 18.3, 22.7, 25.1, 26.0, 31.9, 38.7, 39.3, 41.0, 43.9, 44.7, 46.1, 55.7, 73.3, 78.2, 104.8, 127.6, 128.9, 130.8, 134.0, 134.5, 138.2, 153.4; MS, m/z 626 (M^+); HRMS, m/z calcd for $C_{37}H_{66}O_2Si_3$ 626.4370, found 626.4387.

[3a*R*-[3aα,4aα(1*E*,3*R),5β,6aα]]-(1,1-Dimethylethyl)[[1-[2-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-(dimethylphenylsilyl)-2-methylene-4-octahydropentalenyl]ethenyl]hexyl]oxy]dimethylsilane (24).** In a 20-mL test tube was placed a solution of the xanthate **23** (17.5 mg, 2.4×10^{-2} mmol) in benzene (1.0 mL). Tributyltin hydride (0.01 mL, 3.7×10^{-2} mmol) and di-*tert*-butyl peroxide (2.5 mg, 1.71×10^{-2} mmol) were added at 75 °C, and the mixture was stirred for 36 h. The reaction mixture was evaporated, and the residual material was subjected to column chromatography on silica gel (3 g) using a 25:1 mixture of hexane/ethyl acetate as eluant to give **24** (11.9 mg, 79%) as a colorless oil. TLC R_f value and spectral data of this compound were identical with those of the product derived from the *m*-(trifluoromethyl)benzoate **22** by the photochemical method described above.

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A Stereoselective Synthesis of (+)-Prelog-Djerassi Lactone from Furanoid Intermediates

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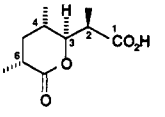
A facile and concise asymmetric synthesis of the methyl ester of Prelog-Djerassi lactonic acid **22** has been completed in nine chemical operations and 10% overall yield from furaldehyde (**4**) by employing a strategy that featured the use of homochiral furfuryl carbinols as latent hydropyranones. The stereocenters at C(2) and C(3) of **22** were established in an absolute sense by the diastereoselective aldol condensation of furaldehyde (**4**) with the boron enolate derived from the chiral imide **5** using the methodology developed by Evans. Removal of the chiral auxiliary followed by oxidation of the furan ring unmasked the hydropyranone ring system, and subsequent protection of the anomeric hydroxyl group led to the production of the glycoside derivative **13a** in good overall yield. Homologation of **13a** via conjugate addition of lithium dimethylcuprate followed by oxidation afforded the enone **17**, which was olefinated by a Wittig reaction to give the diene **18**. Sequential stereoselective, catalytic hydrogenation of **18** and Jones oxidation completed the asymmetric synthesis of the methyl ester of Prelog-Djerassi lactone **22**.

Introduction

The Prelog-Djerassi lactonic acid **1**, which was originally isolated as a degradation product of narbomycin, methymycin, picromycin, and neomethymycin,[2-4] has served as an important focal point for the design and application of new methods that allow the stereoselective elaboration of cyclic and acyclic carbon skeleta bearing a number of contiguous and/or alternating stereocenters. Since the stereochemical relationships present in **1** are found in other macrolide and ionophore antibiotics, the strategies and tactics that have been developed for its assemblage may be extended to the stereoselective syntheses of those more complex natural products. It is therefore not surprising that Prelog-Djerassi lactonic acid **1** has emerged as one of the standard benchmarks against which new methodology for effecting stereoselective carbon-carbon bond construction and functionalization of carbon frameworks is measured, and at this writing some 34 successes in this venture have been recorded.[5]



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(1) Recipient of a National Institutes of Health (National Cancer Institute) Research Career Development Award, 1980-1985.

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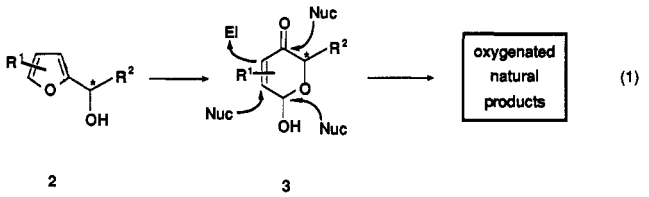
Several years ago we initiated a program directed toward the invention of general, concise strategies for the asymmetric syntheses of oxygenated natural products. Examination of such targets often reveals the presence of substituted hydropyrans or arrays derived therefrom as structural subunits, and it is therefore logical that these oxygen heterocycles have frequently been exploited as crucial synthetic intermediates. Consequently, it occurred to us that the furfuryl carbinols **2**, which may be conveniently transformed into the hydropyranones **3** by established oxidative techniques,[6] would be well suited as starting materials for the preparation of a variety of biologically important molecules.[7] An important feature inherent in the hydropyranones **3** is that they are admirably endowed with differentiated functionality suitable for further elaboration by reaction with selected nucleophiles and electrophiles (eq 1). Significantly, the stereochemical course of these operations should be directed in a highly predictable manner by the preexisting stereocenter at C* of the hydropyran which could be fixed at an early stage by the asymmetric synthesis of the furfuryl carbinol **2**. Since epimerization at a carbon α to the carbonyl group of the hydropyranones **3** and related intermediates would prove detrimental in a stereochemical sense, it would be necessary to execute all reactions under sufficiently mild conditions that such enolization did not ensue. The first successful reduction of this general strategy to practice resulted in an efficacious, asymmetric synthesis of (+)-tirandamycic acid,[8] and we now report the details of its further application to the preparation of the methyl ester of Prelog–Djerassi lactone in optically pure form.[9]



(1)

Results and Discussion

Although there are a number of tactics that could be employed to establish the stereocenter at C(2) of **1** with the correct absolute stereochemistry,[10] the aldol methodology developed by Evans[11] proved to be well suited to the task. In the event, condensation of furaldehyde (**4**) with the boron enolate derived from the chiral imide **5** provided the adduct **6** with >99% diastereoselectivity, and subsequent reaction of **6** with saturated methanolic K_2CO_3 delivered the enantiomerically pure β-hydroxy ester **7** in 72% overall yield from **4**. When **7** was treated with bromine in methanol followed by the treatment of the intermediate 2,5-dihydro-2,5-dimethoxyfurans thus generated in situ with aqueous acid, the hydropyranone **8** was produced in 88% yield as a mixture (2–2.5:1) of α- and β-anomers.

The synthetic plan ultimately required the stereoselective, catalytic hydrogenation of an unsaturated hydropyran possessing the general structure **9** or **10** from the β face to establish simultaneously the stereocenters at C(4) and C(6). Based upon ample literature precedent involving the reduction of similar substances,[12] it was apparent from the outset that a bulky protecting group for the anomeric hydroxyl function would play a critical role in maximizing the stereoselectivity of this process. In initial experiments directed toward this end, **8** was allowed to undergo reaction with isobutylene in the presence of various acid catalysts (e.g., H_2SO_4, BF_3/Et_2O, BF_3/H_3PO_4, *p*-TsOH, and polyphosphoric acid) to afford a mixture (9:1) of the separable,

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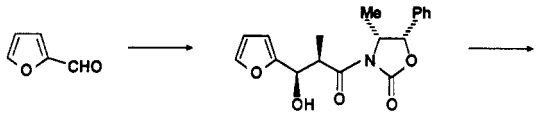

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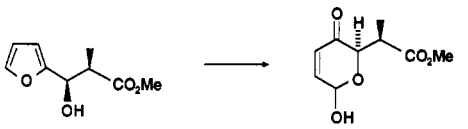

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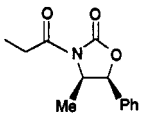
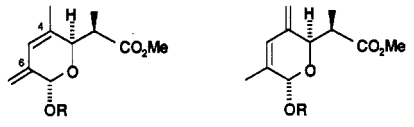


5

α- and β-*tert*-butyl glycosides **11a,b**. Unfortunately, the yield for this transformation was typically low, and the formation of considerable quantities of polymeric material rendered the isolation of the desired product difficult. Whereas the related dimethylmethoxy glycosides **12a,b** (2:1) were readily formed in high yield upon the reaction of **8** with excess 2-methoxypropene in the presence of pyridinium *p*-toluenesulfonate (PPTS), these mixed acetals proved too labile for use in subsequent operations. On the other hand, treatment of **8** with neat ethyl vinyl ether in the presence of a catalytic amount of PPTS provided a mixture (4:1) of the more stable α- and β-ethoxyethyl glycosides **13a,b**, and the requisite α-anomer could be isolated in 58% yield by conventional HPLC. In principle, the β-anomer **13b** could be recycled, but this labor-intensive operation was not performed in practice.



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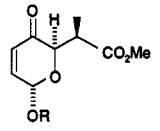
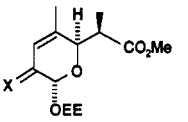


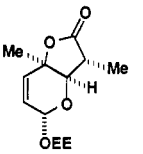
11a,b: R = Bu^t
12a,b: R = C(OMe)Me$_2$
13a,b: R = CH(OEt)Me = EE

Series a: α-OR
Series b: β-OR

At this juncture two options for the stereoselective installation of the two methyl groups at C(4) and C(6) via catalytic hydrogenation of either the diene **15** or **18** were envisioned. For example, 1,2-addition of methyllithium to the hydropyranone **13a** followed by oxidative rearrangement[13] of the intermediate tertiary allylic alcohol was expected to provide the transposed enone **14**. Wittig olefination of **14** to give **15** followed by selective catalytic hydrogenation from the less hindered β-face would then be anticipated[5f,i] to provide primarily the requisite α orientation for each of the methyl groups at C(4) and C(6). Unfortunately, access to **15** was precluded since the 1,2-addition of both methyllithium and methylmagnesium bromide to **13a** was unavoidably succeeded by lactonization to form **16** (ν 1770 cm^{-1}) as the major product.



14: X = O
15: X = CH$_2$



16

Alternatively, the conjugate addition of lithium dimethylcuprate to **13a** occurred smoothly from the β face as expected on the basis of examination of the available literature precedent.[14] In order to correct the stereochemistry at C(6), the intermediate enolate was trapped in situ with chlorotrimethylsilane, and the resulting crude silyl enol ether was oxidized with an excess (ca. 4–8 equiv) of palladium acetate in anhydrous acetonitrile according to the Ito–Saegusa protocol[15] to give **17**[16] in 60–65% overall yield from **13a**. In addition to the desired enone **17**, variable quantities (ca. 15–25%) of the saturated ketone **19** were also routinely isolated. The production of **19**, which appeared to be a consequence of the rather sluggish oxidation of the silyl enol ether, was minimized by conducting the reaction under rigorously anhydrous conditions. Use of lesser quantities of Pd(OAc)$_2$, even in the presence of added co-oxidants such as benzoquinone, gave increased quantities of the saturated ketone **19**. The application to the problem at hand of other standard methods for converting ketone enolates or their derivatives into the corresponding enones via the corresponding α-phenylselenenyl, α-phenylsulfenyl, or α-bromo derivatives was less satisfactory since all such tactics gave inferior results. Wittig olefination of **17** proceeded in a straightforward fashion to afford the diene **18** in 86% yield.

Although a variety of conditions and catalysts were examined for the transformation of **18** into **20**, the highest level of stereoselectivity was obtained by the catalytic hydrogenation of **18** in EtOAc at 1 atm over 10% Pd/C to give a mixture (9:1 by capillary GLC) of **20** together with a diastereomer that was tentatively assigned as the C(4) epimer **21**. These diastereomers could be separated on capillary GLC, but all attempts to effect the preparative chromatographic separation of **20** and **21** were unsuccessful. Nevertheless, the synthesis of the methyl ester of Prelog–Djerassi lactone **22** was conveniently completed in a single operation by treating the mixture of **20** and **21** with Jones reagent at room temperature to effect the sequential removal of the ethoxyethyl protecting group and the oxidation of the resultant lactol to give a mixture (9:1) of **22** contaminated with its C(4) epimer **23**, from which pure **22** could be readily isolated in 76% yield by recrys-

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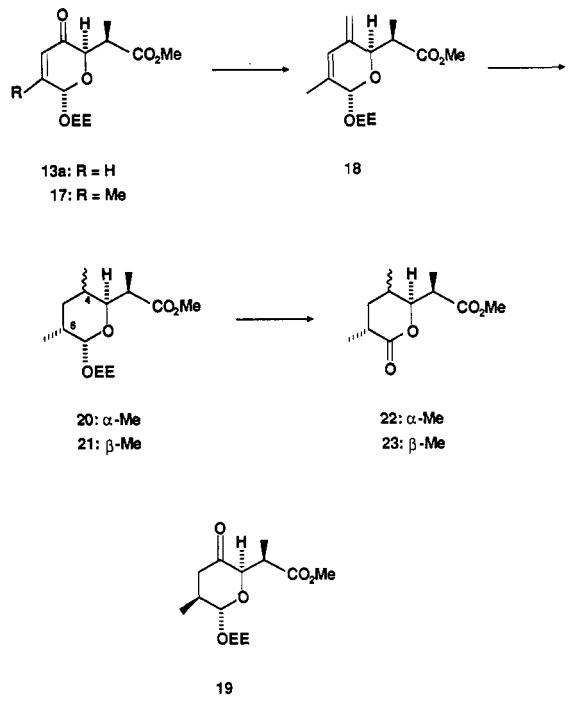
(16) The mixture of diastereoisomeric enones **17**, which are epimeric at the acetal carbon of the ethoxyethyl group, could be separated for full spectral characterization by normal-phase HPLC, but this laborious operation was unnecessary for preparative purposes since the ethoxyethyl group was ultimately removed in the last step of the synthesis. Nevertheless, in order to characterize completely intermediates **18** and **20**, each diastereoisomer of **17** was converted individually to **22** via **18** and **20**.



tallization. The synthetic methyl ester of Prelog–Djerassi lactone **22** thus obtained had spectroscopic properties identical with those previously reported.[5j,17]

Thus, this concise entry to **22** in homochiral form convincingly establishes the viability of the strategy depicted in eq 1 for the asymmetric synthesis of oxygenated natural products from optically active furfuryl carbinols via intermediate hydropyranones. Further applications of this strategy are the subjects of present investigations, the results of which will be described in due course.

Experimental Section

General Procedures. Unless otherwise indicated, all reagents were obtained from commercial suppliers and were used without further purification. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium or potassium/benzophenone ketyl immediately prior to use. Triethylamine, methylene chloride (CH_2Cl_2), and acetonitrile were distilled from calcium hydride and stored under nitrogen over 4A molecular sieves. Trimethylsilyl chloride was distilled from *N,N*-dimethylaniline. Methanol was distilled from magnesium methoxide and stored under nitrogen over 3A molecular sieves. Reactions involving air- and/or moisture-sensitive reagents were routinely conducted under an atmosphere of nitrogen, and the glassware was flame-dried under a stream of dry nitrogen prior to use. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Beckmann Acculab 8 spectrometer either neat or as solutions in the solvent indicated, and all spectra are reported in wavenumbers (cm^{-1}) and referenced to the 1601.8-cm^{-1} absorption of a polystyrene film. Nuclear magnetic resonance (NMR) spectra were recorded as solutions in $CDCl_3$ as indicated on Varian EM-390 and FT-80A and Bruker WH-90FT, NT-200, NT-360, or GN-500 instruments. Chemical shifts are reported in parts per million (δ units) relative to tetramethylsilane as an internal standard. Coupling constants are reported in hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentuplet; m, multiplet, comp, complex; and br, broad. Low resolution mass spectra were obtained with a DuPont (CEC) 21-491 instrument at an ionizing voltage of 70 eV, and exact mass measurements were made with a DuPont (CEC) 21-110 instrument. Optical rotations were determined on a Perkin-Elmer 141 digital polarimeter. Elemental analyses were performed by Dr. Franz Scheidl of Hoffmann-La Roche Inc., Nutley, NJ. Capillary GC analyses were determined on an HP 5890A gas chromatograph with an SGE 25 QC3/BP1 0.5 column or a Varian Aerograph series 2700 modified for capillary columns with an SGE 50 QC2/BP1 0.25 column, and the integration of peaks was performed on an HP 3390A reporting integrator. Preparative high performance chromatography (HPLC) was performed on Waters Prep LC 500 or 6000A/U6K instruments by using silica gel (PrepPak) or Porasil A columns. Flash chromatography was conducted by using Brinkmann silica gel G using mixtures of hexanes and EtOAc (ratio given).

[4*R*-[4α(2*R,3*R**),5α]]-3-[3-(2-Furanyl)-3-hydroxy-2-methyl-1-oxopropyl]-4-methyl-5-phenyl-2-oxazolidinone (6).** To a solution of **5** (17.23 g, 73.9 mmol) in CH_2Cl_2 (75 mL) cooled to −78 °C was added dropwise (10 min) di-*n*-butylboryl triflate[18] (24.31 g, 21.71 mL, 88.7 mmol). The cooling bath was removed, and the resulting mixture was stirred at room temperature until the solution was homogeneous. The orange solution was recooled to −78 °C, triethylamine (9.72 g, 13.4 mL, 96.1 mmol) was added dropwise (30 min), and the boron enolate was stirred at −78 °C for 0.5 h and then at 0 °C for 1 h. The solution was recooled to −78 °C, and freshly distilled **4** (7.82 g, 6.74 mL, 81.3 mmol) was added dropwise (15 min). Stirring was continued for 0.5 h at −78 °C and for 1 h at 0 °C, whereupon the reaction was quenched with external cooling (≤0 °C) by sequential and slow addition of a phosphate buffer (72 mL of 0.05 N; pH 7), MeOH (ca. 150 mL), and then a cold (0 °C) solution of 30% H_2O_2 in MeOH (145 mL, 1:1 v/v). The resulting mixture was stirred at 0 °C for 1 h at which time the milky white solution was allowed to warm to room temperature. The methanol was removed under reduced pressure while maintaining the bath temperature at <25 °C. The resulting aqueous solution was extracted with CH_2Cl_2 (3 × 150 mL), and the combined organic extracts were washed with 5% $NaHCO_3$ (100 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded a pale yellow oil, and flash chromatography (400 g silica gel; 9:1 hexanes/EtOAc) followed by recrystallization from hexanes/EtOAc yielded 22.45 g (92%) of **6** as a shiny white crystalline solid in >99% diastereomeric purity (capillary GC): mp 84–85 °C; $[\alpha]_D$ +15.32° (*c* 2.2, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$) δ 7.42 (comp, 4 H), 7.30 (m, 2 H), 6.35 (m, 2 H), 5.62 (d, 1 H, J = 7.0 Hz), 5.10 (t, 1 H, J = 4.3 Hz), 4.73 (p, 1 H, J = 7.0 Hz), 4.21 (qd, 1 H, J = 7.0, 4.8 Hz), 3.07 (d, 1 H, J = 4.3 Hz), 1.32 (d, 3 H, J = 7.0 Hz), 0.89 (d, 3 H, J = 7.0 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 176.0, 154.3, 152.3, 142.0, 133.2, 128.7, 125.7, 110.3, 106.8, 79.1, 68.9, 54.9, 42.7, 14.4, 12.0; IR ($CHCl_3$) ν 3500–3600, 1800, 1700 cm^{-1}; mass spectrum, *m/e* 329.1254 ($C_{18}H_{19}NO_5$ requires 329.12630), 311, 233, 177, 116, 107 (base), 96, 95, 77. Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.62; H, 5.89; N, 4.29. Found: C, 65.64; H, 5.81; N, 4.25.

Methyl [*R*-(*R,*R**)]-β-Hydroxy-α-methyl-2-furanpropanoate (7).** Compound **6** (5.00 g, 15.2 mmol) was dissolved in anhydrous MeOH (48 mL) at 0 °C, whereupon a saturated solution of K_2CO_3 in MeOH (100 mL, ca. 0.0056 M, 5.6 mmol) was gradually added (0.5 h). The reaction was stirred at 0 °C for 0.5 h and at 25 °C for 3 h, whereupon the reaction mixture was recooled to 0 °C and quenched by the dropwise addition of saturated NH_4Cl (50 mL). The methanol was removed under reduced pressure at room temperature; the majority of the chiral oxazolidinone precipitated and was removed by suction filtration. The aqueous solution was extracted with CH_2Cl_2 (4 × 75 mL), and the combined organic extracts were washed with saturated NaCl (50 mL), back-extracted with CH_2Cl_2 (40 mL), and dried ($MgSO_4$). Removal of the excess solvent under reduced pressure afforded a yellow oil, which was purified by flash chromatography (75 g silica gel, 7:1 hexanes/EtOAc) to provide 2.20 g (78%) of **7** as a viscous yellow oil. Subsequent elution of the column with 100% EtOAc provided an additional small quantity of oxazolidinone, and recrystallization of the combined portions of the oxazolidinone from hexanes/EtOAc resulted in a total recovery of 90% of the chiral auxiliary. For **7**: $[\alpha]_D$ +14.75° (*c* 1.8, $CHCl_3$); ^1H NMR (90 MHz, $CDCl_3$) δ 7.25 (br s, 1 H), 6.20 (comp, 2 H), 4.95 (t, 1 H, J = 6 Hz), 3.58 (s, 3 H), 2.89 (br d, 1 H, J = 6 Hz),

(17) We thank Professor S. Masamune (MIT) for a ^1H NMR spectrum of the sodium salt of **1** for the purpose of comparison.

(18) This reagent was prepared according to literature procedure[19] using commercially available (Callery Chemical Co.) tri-*n*-butylborane.

(19) Inoue, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174.

1.12 (d, 3 H, J = 6 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 175.0, 154.4, 141.6, 110.0, 106.4, 68.6, 51.6, 44.1, 11.5; IR ($CHCl_3$) ν 3400–3600, 1730 cm^{-1}; mass spectrum, m/e 184.0740 ($C_9H_{12}O_4$ requires 184.0736) 166, 97 (base).

Methyl [2*R*-[2α(*R),6α]- and [2*R*-[2α(*R**),6β]]-3,6-Dihydro-6-hydroxy-α-methyl-3-oxo-2*H*-pyran-2-acetate (8).** To a solution of the β-hydroxy ester **7** (1.06 g, 5.75 mmol) dissolved in anhydrous MeOH at −78 °C was added dropwise with stirring a solution of Br_2 in $CHCl_3$ (24.4 mL of 0.5 M, 12.1 mmol). After stirring for 1 h at −78 °C, the reaction was quenched with a saturated bisulfite solution (25 mL) and then allowed to warm to room temperature. The MeOH was removed under reduced pressure, and the resulting aqueous solution was extracted with CH_2Cl_2 (3 × 35 mL). The combined organic extracts were washed with saturated $NaHCO_3$ (25 mL), and the solvent was removed in vacuo to afford a yellow oil, which was dissolved in a mixture (1:1, v/v) of THF (15 mL) and 10% aqueous H_2SO_4 (15 mL). The resulting mixture was stirred vigorously at room temperature for 24 h, whereupon solid NaCl was added, and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 25 mL), and the combined organic extracts were washed with H_2O (50 mL), saturated $NaHCO_3$ (2 × 50 mL), and saturated NaCl (50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford 0.92 g (80%) of **8** as an inseparable mixture (ca. 2:1) of α- and β-anomers, which was used in the next step without further purification: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.98 (dd, 0.3 H, J = 10.2, 1.1 Hz), 6.95 (dd, 0.7 H, J = 10.2, 3.5 Hz), 6.20 (dd, 0.3 H, J = 10.2, 1.7 Hz), 6.10 (d, 0.7 H, J = 10.2 Hz), 5.72 (br s, 0.3 H), 5.65 (d, 0.7 H, J = 3.5 Hz), 5.06 (d, 0.7 H, J = 4.0 Hz), 4.55 (dd, 0.3 H, J = 4.5, 1.5 Hz), 3.72 (s, 2.1 H), 3.70 (s, 0.9 H), 3.21 (qd, 0.7 H, J = 7.1, 3.9 Hz), 3.05 (m, 0.3 H), 1.25 (d, 0.9 H, J = 7.1 Hz), 1.15 (d, 2.1 H, J = 7.2 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 195.1 + 194.6, 174.6 + 174.4, 149.2 + 145.2, 128.5 + 126.9, 91.2 + 87.4, 78.9 + 74.2, 51.9, 39.9 + 39.7, 11.2 + 10.8; IR ($CHCl_3$) ν 3300–3600, 1730, 1700 cm^{-1}; mass spectrum, m/e 200.06882 ($C_9H_{12}O_5$ requires 200.06846), 183, 169, 151, 123, 113, 84 (base).

Methyl [2*R*-[2α(*R),6β(*R**)]]- and [2*R*-[2α(*R**),6β-(*S**)]]-6-(1-Ethoxyethoxy)-3,6-dihydro-α-methyl-3-oxo-2*H*-pyran-2-acetate (13a).** A solution of the crude anomeric mixture of lactols **8** (2.75 g, 13.7 mmol) dissolved in neat ethyl vinyl ether (28 mL) containing pyridinium *p*-toluenesulfonate (PPTS) (21 mg) was stirred in a sealed flask at room temperature for 16 h. Most of the excess ethyl vinyl ether was removed under reduced pressure, whereupon Et_2O (25 mL) and saturated aqueous $NaHCO_3$ (25 mL) were added and the layers separated. The aqueous layer was extracted with Et_2O (3 × 25 mL), and the combined ethereal extracts were washed with saturated NaCl (25 mL) and dried ($MgSO_4$). The solvent was removed in vacuo to afford a yellow oil as a mixture (ca. 4:1) of α- and β-anomers. The mixture was separated by preparative HPLC (7:1 hexanes/EtOAc) to afford 2.15 g (58%) of the α-anomers **13a**, as an inseparable mixture (ca. 1:1) of diastereomers epimeric at the stereogenic center of the ethoxyethyl protecting group: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.90 (dd, 0.5 H, J = 10.2, 3.5 Hz), 6.83 (dd, 0.5 H, J = 10.2, 3.5 Hz), 6.13 (d, 0.5 H, J = 10.2 Hz), 6.09 (d, 0.5 H, J = 10.2 Hz), 5.57 (d, 0.5 H, J = 3.5 Hz), 5.55 (d, 0.5 H, J = 3.5 Hz), 5.02 (q, 0.5 H, J = 5.4 Hz), 5.01 (d, 0.5 H, J = 4.2 Hz), 4.96 (d, 0.5 H, J = 3.7 Hz), 4.95 (q, 0.5 H, J = 5.4 Hz, 3.50–3.85 (m, 2 H), 3.72 (s, 1.5 H), 3.71 (s, 1.5 H), 3.22 (m, 1 H), 1.39 (d, 3 H, J = 5.4 Hz), 1.23 (t, 3 H, J = 7.1 Hz), 1.16 (d, 1.5 H, J = 7.1), 1.15 (d, 1.5 H, J = 7.1 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 194.8 + 194.5, 173.7, 144.3 + 143.6, 127.4 + 127.0, 99.5 + 98.2, 89.4 + 87.3, 75.1 + 74.6, 63.2 + 61.2, 51.6, 39.8 + 39.4, 20.4 + 20.3, 15.1 + 14.9, 10.6 + 10.4; IR ($CHCl_3$) ν 1730, 1695 cm^{-1}; mass spectrum, m/e 183.06653 [$C_9H_{11}O_4$ ($M^+ - C_4H_9O_2$) requires 183.06573] 151, 123, 95, 83, 73 (base).

Methyl [2*R*-[2α(*R),6β(*R**)]]- and [2*R*-[2α(*R**),6β-(*S**)]]-6-(1-Ethoxyethoxy)-3,6-dihydro-α,5-dimethyl-3-oxo-2*H*-pyran-2-acetate (17).** To a suspension of purified CuI (0.49 g, 2.55 mmol) in anhydrous Et_2O (20 mL) at 0 °C was added MeLi (1.52 N in Et_2O, 5.1 mmol), and the solution of $LiCuMe_2$ thus formed was cooled to −78 °C. A solution of the epimeric enones **13a** (0.70 g, 2.5 mmol) in anhydrous Et_2O (10 mL) was added dropwise, and the resulting yellow slurry was stirred for 1 h at −20 °C. Trimethylsilyl chloride (0.5 mL, 4.0 mmol) was then added, and the reaction was stirred for 0.5 h while warming gradually to 0 °C. The reaction was quenched at 0 °C by the successive addition of saturated $NaHCO_3$ (25 mL) and NH_4OH/NH_4Cl (pH 8) (25 mL), and the mixture was exposed to air and stirred vigorously until all of the copper salts had dissolved. The resulting blue aqueous phase was extracted with ether (4 × 50 mL), and the combined ethereal layers were washed with saturated NaCl (50 mL) and dried ($MgSO_4$). The solvent was evaporated to afford 0.85 g (95%) of the crude silyl enol ether, which was immediately dissolved in anhydrous acetonitrile (100 mL) containing palladium(II) acetate (2.00 g, 9.65 mmol). The resulting mixture was stirred at room temperature until all of the starting material had been consumed as judged by TLC (72–92 h). The reaction was diluted with Et_2O (100 mL), and the mixture was filtered through a bed of Celite. The resulting red solution was washed with 10% sodium bisulfite (4 × 100 mL), and the combined organic layers were washed with saturated NaCl (100 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded the crude enones **17**, the two epimers of which could be separated by preparative HPLC (7:1 hexanes/EtOAc) with recycling to give 0.21 g (31%) of each of the pure enones **17** that were diastereomeric at the methine carbon of the ethoxyethyl group.

For isomer I: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.94 (q, 1 H, J = 1.5 Hz), 5.33 (s, 1 H), 5.04 (q, 1 H, J = 5.4 Hz), 4.85 (d, 1 H, J = 3.7 Hz), 3.71 (s, 3 H), 3.65 (dq, 1 H, J = 9.2, 7.1 Hz), 3.56 (dq, 1 H, J = 9.2, 7.1 Hz), 3.22 (dq, 1 H, J = 3.7, 7.1 Hz), 2.02 (d, 3 H, J = 1.5 Hz), 1.39 (d, 3 H, J = 5.4 Hz), 1.23 (t, 3 H, J = 7.1 Hz), 1.14 (d, 3 H, J = 7.1 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 195.0, 174.4, 157.0, 124.7, 100.9, 91.6, 74.4, 63.8, 52.0, 40.1, 20.7, 19.7, 15.1, 10.8.

For isomer II: ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.93 (q, 1 H, J = 1.5 Hz), 5.30 (s, 1 H), 4.95 (q, 1 H, J = 5.4 Hz), 4.91 (d, 1 H, J = 3.7 Hz), 3.85 (dq, 1 H, J = 9.5, 7.1 Hz), 3.70 (s, 3 H), 3.55 (dq, 1 H, J = 9.5, 7.1 Hz), 3.21 (dq, 1 H, J = 3.7, 7.1 Hz), 1.98 (d, 3 H, J = 1.5 Hz), 1.40 (d, 3 H, J = 5.4 Hz), 1.23 (t, 3 H, J = 7.1 Hz), 1.1 (d, 3 H, J = 7.1 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 194.8, 174.3, 156.5, 124.9, 98,4. 93.2, 73.9, 61.1, 51.9, 39.7, 20.5, 19.8, 15.4, 10.6; IR ($CHCl_3$) ν 1745, 1695, cm^{-1}; mass spectrum, m/e 197.08182 [$C_{10}H_{13}O_4$ ($M^+ - C_4H_9O_2$) requires 197.08138], 132, 117, 98 (base), 85.

Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.75. Found: C, 58.93; H, 7.86.

Methyl [2*R*-[2α(*R),6β(*R**)]]- and [2*R*-[2α(*R**),6β-(*S**)]]-6-(1-Ethoxyethoxy)-3,6-dihydro-α,5-dimethyl-3-methylene-2*H*-pyran-2-acetate (18).** To a suspension of methyltriphenylphosphonium bromide (0.96 g, 2.7 mmol) in THF (10 mL) at 0 °C was added dropwise a solution *n*-butyllithium (2.54 N in hexanes, 2.5 mmol), and the resulting yellow mixture was stirred for 0.5 h at 0 °C and then cooled to −78 °C. A solution of one of the diastereomeric enones **17** (178 mg, 0.62 mmol) in THF (5 mL) was added dropwise, and the reaction was stirred at −78 °C for 15 min and then gradually allowed to warm to room temperature over the course of 1.5 h. The reaction was then quenched by the addition of saturated $NaHCO_3$ (10 mL), and the layers were separated. The aqueous phase was washed with Et_2O (4 × 15 mL), and the combined ethereal extracts were washed with saturated NaCl (25 mL), back-extracted with Et_2O (2 × 15 mL), and dried ($MgSO_4$). Removal of the solvent under reduced pressure afforded a brown-yellow oil, which was purified by flash chromatography (5.0 g silica gel, 7:1 hexanes/EtOAc) to afford 132 mg (86%) of **18** as a waxy, white solid.

For isomer I: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.03 (br s, 1 H), 5.07 (br s, 1 H), 5.05 (br m, 1 H), 4.94 (br s, 1 H), 4.87 (q, 1 H, J = 5.4 Hz), 4.79 (br m, 1 H), 3.86 (dq, 1 H, J = 9.3, 7.1 Hz), 3.70 (s, 3 H), 3.48 (dq, 1 H, J = 9.3, 7.1 Hz), 3.02 (dq, 1 H, J = 3.5, 7.1 Hz), 1.79 (br s, 3 H), 1.35 (d, 3 H, J = 5.4 Hz), 1.22 (t, 3 H, J = 7.1 Hz), 1.19 (d, 3 H, J = 7.1 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 175.0, 140.2, 134.6, 125.8, 109.6, 99.4, 92.5, 69.7, 63.5, 51.8, 41.4, 20.7, 20.8, 18.9, 15.2, 10.1.

For isomer II: ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.04 (br s, 1 H), 5.13 (br s, 1 H), 4.92–5.08 (br m, 2 H), 4.77 (br m, 1 H), 3.71 (s, 3 H), 3.47–3.72 (m, 2 H), 3.02 (dq, 1 H, J = 3.1, 7.1 Hz), 1.83 (br s, 3 H), 1.35 (d, 3 H, J = 5.4 Hz), 1.21 (t, 3 H, J = 7.1 Hz), 1.20 (d, 3 H, J = 7.1 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 174.9, 140.1, 134.6, 126.0, 109.7, 97.2, 94.0, 69.1, 60.5, 51.8, 40.8, 20.7, 19.0, 15.5,

9.8; IR ($CHCl_3$) ν 1735 cm^{-1}; mass spectrum, m/e 195.10179 [$C_{11}H_{15}O_3$ ($M^+ - C_4H_9O_2$) requires 195.10211] 167, 153, 137, 123, 109 (base), 95.

Methyl [2*S*-[2α(*R),3β,5β,6β(*S**)]]- and [2*S*-[2α-(*S**),3β,5β,6β(*S**)]]-6-(1-Ethoxyethoxy)-3,4,5,6-tetrahydro-α,3,5-trimethyl-2*H*-pyran-2-acetate (20).** A solution of one of the diastereomerically pure enones **18** (18 mg, 0.063 mmol) in EtOAc (1 mL) containing 10% Pd/C (5 mg) was stirred overnight under H_2 (1 atm). The catalyst was removed by filtration through glass wool, and the solvent was evaporated under reduced pressure to afford 14 mg (77%) of a colorless oil that was a mixture (9:1, capillary GLC) of **20** together with a substance that was tentatively assigned to be the C(4) epimer **21**. All attempts to separate these products by HPLC (reverse phase, normal phase, μ-Porasil) failed.

For isomer I: ^1H NMR (200 MHz, $CDCl_3$) δ 4.79 (d, 1 H, J = 3.2 Hz), 4.76 (q, 1 H, J = 5.2 Hz), 3.96 (dd, 1 H, J = 3.0, 10.2 Hz), 3.86 (dq, 1 H, J = 9.5, 7.1 Hz), 3.66 (s, 3 H), 3.47 (dq, 1 H, J = 9.5, 7.1 Hz), 2.72 (dq, 1 H, J = 3.0, 7.1 Hz), 1.55–1.80 (m, 2 H), 1.45 (m, 2 H), 1.29 (d, 3 H, J = 5.2 Hz), 1.22 (t, 3 H, J = 7.1 Hz), 1.12 (d, 3 H, J = 7.1 Hz), 0.85 (d, 6 H, J = 6.4 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 174.4, 97.7, 94.7, 73.9, 62.2, 50.5, 39.9, 34.3, 33.9, 31.3, 19.3, 16.5, 15.7, 14.3, 7.9.

For isomer II: ^1H NMR (200 MHz, $CDCl_3$) δ 4.86 (d, 1 H, J = 3.6 Hz), 4.81 (q, 1 H, J = 5.4 Hz), 3.88 (dd, 1 H, J = 3.0, 10.2 Hz), 3.67 (s, 3 H), 3.30–3.70 (m, 2 H), 2.72 (qd, 1 H, J = 7.1, 3.0 Hz), 1.50–1.80 (m, 2 h), 1.40 (m, 2 H), 1.34 (d, 3 H, J = 5.4 Hz), 1.16 (t, 3 H, J = 7.1 Hz), 1.12 (d, 3 H, J = 7.1 Hz), 0.89 (d, 3 H, J = 6.4 Hz), 0.83 (d, 3 H, J = 6.4 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 174.7, 96.2, 95.7, 73.7, 59.6, 50.7, 39.8, 34.3, 31.3, 19.6, 16.5, 15.9, 14.7, 7.8; IR ($CHCl_3$) ν 1745 cm^{-1}; mass spectrum, m/e 288.19443 ($C_{15}H_{28}O_5$ requires 288.19366) 287, 199, 167, 139, 111, 73 (base), 69.

(+)-Prelog–Djerassi Lactonic Acid Methyl Ester (22). To a stirred solution of the mixture (9:1) of the tetrahydropyrans **20** and **21** (9.0 mg, 0.03 mmol) dissolved in acetone (1 mL) was added Jones reagent (0.7 N, 0.35 mmol). The resulting orange solution was stirred at room temperature for 2 h, whereupon the excess oxidant was quenched by the addition of 2-propanol (0.5 mL). The mixture was then partitioned between Et_2O (5 mL) and H_2O (5 mL), and the aqueous phase was extracted with Et_2O (3 × 5 mL). The combined ethereal extracts were washed with saturated $NaHCO_3$ (5 mL) and saturated NaCl (10 mL), backextracted with Et_2O (10 mL), and dried ($MgSO_4$). The excess solvent was removed under reduced pressure, and the crude product thus obtained was filtered through silica gel (0.2 g) (8:1 hexanes/EtOAc). Evaporation of the solvent followed by recrystallization of the residue from hot n-pentane yielded **22** (5.1 mg, 76%) in >99% diastereomeric purity (GC integration): mp 77.0–77.5 °C [lit.[5j] mp 75.5–76.5 °C]; $[\alpha]_D$ +39.0° (c 0.2, $CHCl_3$) [lit.[5j] $[\alpha]_D$ +38.0° (c 1.03, $CHCl_3$)]; ^1H NMR (200 MHz, $CDCl_3$) δ 4.54 (dd, 1 H, J = 2.6, 10.4 Hz), 3.73 (s, 3 H), 2.73 (dq, 1 H, J = 2.6, 7.1 Hz), 2.49 (ddq, 1 H, J = 12.0, 6.0, 7.1 Hz), 1.80–2.05 (br m, 2 H), 1.45 (dd, 1 H, J = 12.0, 12.0 Hz), 1.29 (d, 3 H), J = 7.1 Hz), 1.20 (d, 3 H, J = 7.1 Hz), 1.00 (d, 3 H, J = 6.4 Hz); ^{13}C NMR (360 MHz, $CDCl_3$) δ 173.6, 173.3, 86.2, 52.2, 41.4, 37.4, 36.3, 31.0, 17.3, 17.0, 8.8; IR ($CHCl_3$) ν 1730 cm^{-1}; mass spectrum, m/e 214.12109 ($C_{11}H_{18}O_4$ requires 214.12050) 183, 155, 144, 127, 99, 69, 56 (base).

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