$\lambda = 0.7106_9$ Å). Of the 2600 independent reflections obtained for **1**, 1812 with $I > 3\sigma(I)$ were used in the full-matrix least-squares refinement without absorption correction, and after solution of the structure by direct methods. In the case of **5**, of 2628 independent reflections, 1999 with $I > 3\sigma(I)$ were similarly treated. Thermal parameter treatment was isotropic (constrained) for hydrogen atoms and anisotropic for the other atoms; $(x,y,z)_H$ were constrained at idealized values in **5** and refined for the non-metal hydrogens in **1**. Residuals at convergence were $R = 0.041$, $R' = 0.051$ for **1** and $R = 0.044$, $R' = 0.053$ for **5**, reflection weights being $[\sigma^2F_o) + 0.0003(F_o)^2]^{-1}$. Neutral complex scattering factors were used.[17] Computation was performed with the X-RAY 76 program system.[18]

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Registry No. 1, 96165-79-6; **2**, 96165-80-9; **3**, 96165-81-0; **4**, 96165-82-1; **5**, 96165-83-2; **6**, 96165-84-3; **7**, 96165-85-4; **8**, 96165-86-5; 1,10*b*-dihydro-**8**·HCl, 96165-97-8; **8** (ethyl bromoacetate derivative), 96165-98-9; **9**, 55302-27-7; 1,11*b*-dihydro-**9**·HCl, 4823-63-6; **10**, 96165-87-6; **11**, 96193-98-5; **12**, 96165-88-7; **12** (alcohol), 96165-95-6; **13**, 96165-89-8; **13** (alcohol), 96165-96-7; **14**, 96165-90-1; **15**, 96165-91-2; **16**, 96165-92-3; **17**, 96165-93-4; **18**, 96165-94-5; $EtOCOCH_2Br$, 105-36-2.

Supplementary Material Available: Listing of structure factor amplitudes for **1** and **5**, and Tables S1–S4 listing non-hydrogen atom thermal parameters and hydrogen atom parameters for **1** and **5** (18 pages). Ordering information is given on any current masthead page.

Application of [2,3] Sigmatropic (Wittig) Rearrangements in Synthesis. The Synthesis of (+)-Prelog–Djerassi Lactone

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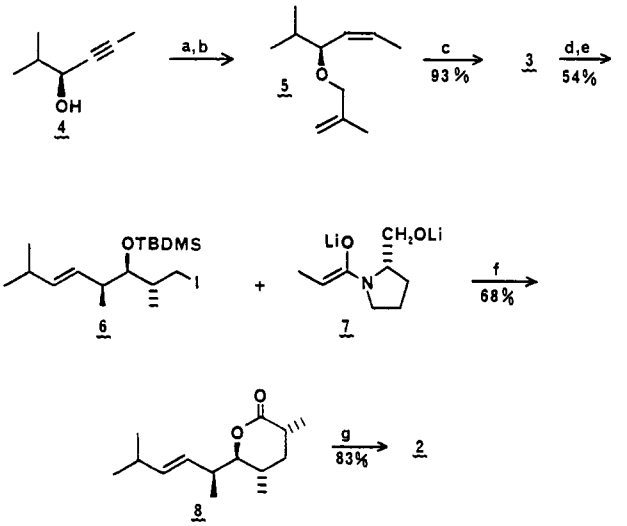
Abstract: The [2,3] sigmatropic (Wittig) rearrangement has been used as a key step in the synthesis of (+)-Prelog–Djerassi lactonic aldehyde. This reaction was used to control the relative and absolute configuration of two of the four chiral centers of the lactone. The remaining centers were introduced by a stereoselective hydroboration and an asymmetric alkylation of a prolinol amide enolate. The synthesis is short, efficient, and amendable to analogue synthesis. The final lactone is obtained in essentially 100% epimeric and optical purity.

Chirality transfer via [3,3] sigmatropic rearrangements of allylic alcohols is a powerful method for absolute control of chirality during carbon–carbon bond-forming reactions.[1] It has recently been demonstrated that [2,3] sigmatropic (Wittig) rearrangements also proceed with essentially complete chirality transfer and a high degree of diastereoselectivity.[2] Since the resulting products contain functionality which may be manipulated into more complex products, this reaction should also provide a powerful method for the construction of complex molecules.[3] Herein we demonstrate the use of the [2,3] sigmatropic rearrangement in the synthesis of the Prelog–Djerassi lactonic aldehyde.

The Prelog–Djerassi lactonic acid, **1**, a degradation product of narbormycin and methylmycin,[4] has been prepared by many groups.[5] The lactonic aldehyde, **2**, a key intermediate in the syntheses of the macrolide antibiotics, 6-deoxyerythronolide B and narbomycin, has been prepared from the acid in two steps.[6] Our strategy for the synthesis of these compounds was to use the high diastereoselectivity of the [2,3] Wittig rearrangement to control

Scheme I



a: H_2, Pd/$BaSO_4$. b: NaH, $CH_2{=}CH(CH_3)CH_2Cl$, THF reflux. c: *n*-BuLi/*t*-BuOK, −78 → 0 °C. d: TBDMSCl, imidazole, DMF. e: $(C_6H_{11})_2BH$ then I_2/NaOMe. f: HCl, THF, 25 °C, 24 h. g: O_3, $(CH_3)_2S$. (yields are of isolated product)

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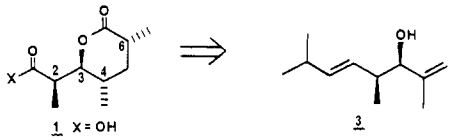
the chiral centers at carbons 2 and 3. The rearrangement product



1 X = OH
2 X = H

3

3 contains dissimilar double bonds which may then be functionalized into the remainder of the target. It was envisioned that the terminal double bond would undergo stereoselectivity and regioselective hydroboration. The organoborane could then be converted into an electrophilic species for alkylation with an appropriate enolate. The remaining double bond could then be cleaved to provide the final product.

Results and Discussion

Our synthesis is outlined in Scheme I. The required starting propargyl alcohol **4** was obtained in 92% ee (100% enantiomeric efficiency) by asymmetric reduction of the corresponding ketone with *S*-Alpine-Borane[7] (from (−)-α-pinene, 92% ee). Although 100% ee α-pinene is available[8] (in either (+) or (−) form) our synthesis does not require enantiomerically pure starting material. Further steps in the synthesis remove the minor enantiomer as a diastereomeric impurity and final recrystallization provides optically pure product.

The propargyl alcohol (**4**) was reduced to the (*Z*)-allylic alcohol with palladium on barium sulfate as a catalyst. The resulting alcohol was then converted to the ether **5** by alkylation of the alkoxides. Treatment of the ether with *n*-butyllithium at −78 °C followed by warming to 0 °C provided the rearrangement product **3** in high yield. The desired syn isomer (**3**) was obtained in a 93:7 ratio (analysis by HPLC). The ratio was modestly increased to 97:3 by using potassium *tert*-butoxide/*n*-butyllithium as a base. Pure syn product could be obtained by flash chromatography.[9] Examination of the enantiomeric purity with NMR shift reagent ($Eu(hfc)_3$) indicated that the product was 91% ee.

It was expected that chemoselective hydroboration of the terminal double bond of **3** could be achieved with use of a dialkylborane. Furthermore, Still has demonstrated that hydroboration of chiral olefins structurally related to **3** may be highly stereoselective.[10] He has obtained products with the correct relative configuration for carbons 3 and 4 in **1** in ratios of up to 15:1. We found that hydroboration of **3** with 9-BBN (9-borabicyclo[3.3.1]nonane) was highly stereoselective. The desired alcohol product was the only isomer detected by ^{13}C NMR or HPLC. The stereochemistry of the diol was confirmed by conversion to the acetonide which exhibited a trans coupling constant of 10.3 Hz for the axial hydrogens.[11] The alcohol could be converted into a leaving group by standard techniques. However, we found it more convenient to protect the alcohol of **3** (*tert*-butyldimethylsilyl ether, TBDMS) and convert the terminal olefin directly into a terminal iodide with use of dicyclohexylborane followed by iodine.[12] Although the diastereoselectivity of this process was lower (15:1) than that obtained in hydroboration with 9-BBN, the operational simplicity of making the iodide in one pot was attractive.

The final chiral center at C-6 was introduced by alkylation of Evans' (*l*)-prolinol enolate **7**[13] with iodide **6** to provide the desired isomer in a greater than 10:1 epimeric ratio at C-6. At this point the product was a mixture of the desired epimer (2*R*, 4*S*, 5*S*, 6*S*) along with small amounts of the diastereomeric isomers epimeric at each of the chiral centers. In addition the minor enantiomer of the starting propargyl alcohol **4** had been carried through the synthesis. This enantiomer would be transformed in each of the succeeding steps into the 4*R*,5*R*,6*R* isomer of **8** as the major product. If one assumes that alkylation of *epi*-6 with **7** proceeds with no secondary asymmetric induction (from the chiral centers in **6**), then the major isomer of the product would have the 2*R* configuration. The minor enantiomer of the starting material is thus largely transformed into a diastereomer of the desired final product and may in principle be removed.

Hydrolysis of the amide and lactonization to provide **8** under standard conditions (1 N HCl, 100 °C, 2 h) caused considerable epimerization. However, mild hydrolysis (1 N HCl, 25 °C, 24 h) provided lactone **8** as a >13:1 ratio of two isomers (the minor isomer was not identified). As observed by Hoye, kinetic lactonization favors the desired product.[5b] Ozonolytic cleavage of the double bond of **8** followed by recrystallization provided pure (+)-Prelog–Djerassi lactonic aldehyde **2**.

This process provides a short and versatile route to the Prelog–Djerassi lactone. The enantiomer could easily be prepared by starting with the *R* propargyl alcohol (from *R*-Alpine-Borane). A variety of analogues could be prepared by appropriate substitutions in the scheme. The double bond of **8** provides a convenient, common precursor to the C-1 alcohol, aldehyde, or acid. Finally, the overall sequence is highly stereoselective, only one epimer of **2** could be detected.

Experimental Methods

General. All operations involving air-sensitive reagents were performed under a dry nitrogen atmosphere with syringe techniques.[14] All glassware was dried at 135 °C for at least 4 h, assembled hot, and cooled while being purged with N_2. ^1H NMR spectra were obtained on a Varian EM-390 (90 MHz) instrument, JEOL FX-200 (200 MHz) FT instrument, or Nicolet NT-300WB (300 MHz) FT instrument. ^{13}C NMR spectra were obtained on the JEOL FX-200 (50.1 MHz) instrument. The solvent for both ^1H and ^{13}C spectra was $CDCl_3$. Areas of *R* and *S* proton signals in the presence of $Eu(hfc)_3$ were determined by cutting and weighing expanded spectra. Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter. High resolution mass spectra were obtained on a VG-ZAB-1HF instrument. HPLC analyses were performed on a Waters 6000A system with a Whatman M9 10/50 partisil column.

Tetrahydrofuran (THF) was distilled under N_2 from potassium benzophenone ketyl and stored under a positive N_2 pressure. (−)-β-Pinene and 0.5 M 9-BBN in THF were obtained from Aldrich Chemical Co. (−)-α-Pinene ($[\alpha]^{22}_D$ −46.6° (neat, d = 0.858, lit.[15] $[\alpha]^{20}_D$ +51.8°)) was prepared by isomerization of of (−)-β-pinene according to the method of Cocker.[16]

5-Methyl-2-hexyn-4-one. A graduated cylinder was flushed with nitrogen and cooled to −78 °C. Tetrahydrofuran (80 mL) was added to the cylinder and then propyne was condensed in the cylinder until the volume increased by 40 mL. A 1-L round-bottom flask was charged with 200 mL of THF and cooled to −78 °C. The propyne solution was transferred to the round-bottom flask with a double-ended needle. *n*-Butyllithium (312 mL, 1.6 M in hexane, 500 mmol) was placed in the graduated cylinder and cooled to −78 °C. The *n*-butyllithium was then transferred via double-ended needle to the propyne solution over a 40-min period. The mixture containing a white precipitate was stirred for 20 min. Isobutyraldehyde (600 mmol in 20 mL of THF) was cooled to −78 °C and then added to the reaction mixture via double-ended needle. The mixture was stirred at −78 °C for 1 h and then warmed to room temperature over a 3-h period. The reaction mixture was poured into saturated aqueous NH_4Cl (250 mL) and the aqueous layer extracted with ether. The organic extracts were dried ($MgSO_4$) and the solvent removed. Distillation provided 45.6 g (81%) of 5-methyl-2-hexyn-4-ol (bp 72–76 °C (25 mm)). The alcohol (10.9 g, 97 mmol) was placed in 100 mL of acetone and cooled to 0 °C. Jones reagent (70 g of CrO_3 in 500 mL of water and 61 mL of concentrated sulfuric acid[17]), 40 mL, was added dropwise over a period of 15 min. After 5 min the ice bath was

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removed and the reaction mixture stirred at room temperature for 1 h. Ethanol (95%, 20 mL) was added to destroy excess Jones reagent. After 10 min the solution was diluted with 100 mL of saturated aqueous sodium chloride and extracted with ether. The ether layer was dried ($MgSO_4$) and concentrated. The product was distilled (Kughelrohr, bath temperature 65 °C, 25 mm) to give 7.4 g of the ketone, 69% yield. Analysis by GC and ^{13}C NMR indicated less than 2% impurities.

(−)-(4*S*)-5-Methyl-2-hexyn-4-ol (4). *S*-Alpine-Borane was prepared by refluxing 150 mL of 0.5 M 9-BBN (75 mmol) with (−)-α-pinene (88 mmol) for 4 h. The THF was then removed by water aspirator and then by vacuum pump. Nitrogen was admitted to the flask and the organoborane cooled to 0 °C. 5-Methyl-2-hexyn-4-one (7.7 g, 66 mmol) was added. The mixture was slowly warmed to room temperature and stirred for 24 h. Propionaldehyde (5 mL) was added to destroy excess Alpine-Borane. After 30 min, the excess aldehyde and (−)-α-pinene were removed, first using a water aspirator and then a vacuum pump (0.05 mm, 50 °C, 2 h). Then 25 mL of THF and 25 mL of 3 M NaOH were added to the flask followed by the dropwise addition of 25 mL of 30% H_2O_2 (exothermic!). The mixture was stirred at 40–50 °C for 15 min and then diluted with 20 mL of saturated aqueous NaCl and extracted with ether. The organic extracts were dried ($MgSO_4$) and concentrated. Distillation provided 5.53 g (74% yield) of the product (bp 72 °C (25 mm)): $[\alpha]^{24}_D$ −14.27 (neat, d = 0.886); ^1H NMR (200 MHz) δ 4.07 (dd, J = 5.4 and 2.4 Hz, 1 H), 2.42 (br, 1 H), 1.60–2.00 (m, 1 H), 1.80 (d, J = 2.0 Hz, 3 H), 0.93 (d, J = 6.4 Hz, 3 H), 0.91 (d, J = 6.5 Hz, 3 H); ^{13}C NMR (50.1 MHz) δ 81.18, 78.99, 67.90, 34.48, 17.94, 17.31, 3.25. Examination of the ^1H NMR in the presence of Eu(hfc)$_3$ indicated a mixture of 95% *S* and 5% *R* enantiomers. The carbinol proton of the *R* isomer shifted downfield faster than that of the *S* isomer.

(+)-(2*Z*,4*S*)-5-Methyl-2-hexen-4-ol. The acetylene **4** was reduced according to the literature procedure[7] to give the pure *Z* isomer in 85% yield; $[\alpha]^{24}_D$ +31.56 (neat, d = 0.857). ^1H NMR in the presence of Eu(hfc)$_3$ indicated the product was 90% ee.

(−)-(2*Z*,4*S*)-5-Methyl-2-hexen-4-yl 2-Methyl-2-propen-1-yl Ether (5). A 100-mL reaction flask was charged with 7 g of 57% sodium hydride (about 160 mmol) in mineral oil and the mineral oil was removed by washing with hexane. Then 20 mL of dry THF was added followed by 2.97 g (26.0 mmol) of (+)-(2*Z*,4*S*)-5-methyl-2-hexen-4-ol. After 10 min, 5 mL (51.2 mmol) of 3-chloro-2-methylpropene was added and the reaction mixture refluxed overnight. After the mixture was cooled to room temperature, 3 mL of H_2O was added to quench the excess of sodium hydride. The mixture was poured into water and extracted with ether. The combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Distillation at 78 °C (25 mmHg) produced 4.13 g (94.4%) of bis-allylic ether **5** as a colorless oil: optical rotation $[\alpha]^{24}_D$ −6.28 (neat, d = 0.821); IR (film) 1663, 1467, 1457, 898 cm^{-1}; ^1H NMR (200 MHz) δ 5.73 (dqd, J = 10.3, 6.9, and 1.4 Hz, 1 H), 5.27 (ddq, J = 10.3, 9.4, and 1.7 Hz, 1 H), 4.94 (m, 1 H), 4.87 (m, 1 H), 3.71–3.91 (m, 3 H), 1.90–1.60 (m, 1 H), 1.75 (s, 3 H), 1.65 (dd, J = 6.9 and 2.0 Hz, 3 H), 0.98 (d, J = 6.6 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (50.1 MHz) δ 143.01, 130.32, 127.91, 111.90, 78.46, 71.79, 33.02, 19.67, 18.79, 18.14, 13.54.

(−)-(3*R*,4*S*,5*E*)-2,4,7-Trimethyl-1,5-octadien-3-ol (3). Potassium *tert*-butoxide, 6.17 g (55 mmol), was dissolved in 100 mL of THF. The solution was cooled to −78 °C and 8.51 g (50.6 mmol) of the bis-allylic ether **5** was added. *n*-Butyllithium (40 mL, 1.55 M, 62 mmol) was slowly added. The mixture was warmed to 0 °C over 4 h. The reaction was quenched with water and the product extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated. Kugelrohr distillation (90 °C, 25 mm) gave 7.41 g (87%) of the product. Analysis by HPLC (0.5 methanol, 5 ethyl acetate, 100 hexane, Partisil M9 column) indicated a 97:3 ratio of syn and anti product (the syn isomer eluted second). The ratio was confirmed by ^1H NMR (200 MHz): syn 3.87 (d, J = 5.9 Hz); anti 3.66 (d, J = 8.3 Hz). Diastereomerically pure material was obtained by flash chromatography (0.5 methanol, 5 ethyl acetate, 100 hexane): ^1H NMR (200 MHz) δ 5.46 (dd, J = 15.6 and 6.2 Hz, 1 H), 5.30 (dd, J = 15.6 and 6.8 Hz, 1 H), 4.93 (m, 1 H), 4.87 (m, 1 H), 3.87 (d, J = 5.9 Hz, 1 H), 2.20–2.40 (m, 2 H), 1.70 (s, 3 H), 1.64 (br, OH), 0.99 (d, J = 6.8 Hz, 3 H), 0.97 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (50.1 MHz), δ 145.4, 138.1, 129.3, 111.7, 79.0, 39.7, 31.1, 22.6, 18.5, 14.6; $[\alpha]^{24}_D$ +2.56 (*c* 3.36, THF). Examination by ^1H NMR with Eu(hfc)$_3$ indicated a 95:5 mixture of enantiomers. Exact mass calcd for $C_{11}H_{20}O$: m/e 168.1514. Found: m/e 168.1517.

***tert*-Butyldimethylsilyl Ether of 3.** A mixture of alcohol **3** (1.39 g, 8.26 mmol), imidazole (1.41 g, 20.65 mmol), and *t*-BuMe$_2$SiCl (1.46 g, 9.69 mmol) in 8.3 mL of DMF was stirred overnight.[18] The mixture was partitioned between ether (100 mL) and water (30 mL × 3). The water layer was extracted with ether (50 mL × 2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Bulb-to-bulb distillation (70 °C (0.05 mmHg)) gave 2.20 g (94.1%) of product as a colorless oil (98% pure by VPC): ^1H NMR ($CDCl_3$) (200 MHz) δ 5.39 (dd, 15.6 and 5.8 Hz, 1 H), 5.22 (dd, J = 15.6 and 7.1 Hz, 1 H), 4.81 (m, 1 H), 4.78 (m, 1 H), 3.75 (d, J = 6.8 Hz, 1 H), 2.10–2.30 (m, 2 H), 1.65 (s, 3 H), 0.88–0.98 (m, 9 H), 0.91 (s, 9 H), +0.04 (s, 3 H)8 +0.00 (s, 3 H); ^{13}C NMR (50.10 MHz) δ 146.63, 136.52, 130.18, 111.75, 81.22, 40.92, 31.04, 25.90, 22.60, 18.30, 17.90, 15.92, −4.59, −5.00; IR 1795, 1650, 1460, 1250 cm^{-1}; $[\alpha]^{24}_D$ 10.84 (*c* 3.23, THF).

(2*S*,3*R*,4*S*,5*E*)-2,4,7-Trimethyl-1-hydroxy-5-octen-3-yl 3-*tert*-Butyldimethylsilyl Ether. The TBDMS ether of **3** (0.210 g, 0.74 mmol) in 1 mL of THF was added to a stirred solution of 9-BBN (0.78 mmol in 1.55 mL of THF) at 0 °C (the 9-BBN was a precipitate). After 10 min the ice bath was removed and the reaction mixture stirred at room temperature for 3 h. Then 0.4 mL of 3 N NaOH was added followed by 0.4 mL of 30% H_2O_2. The mixture was maintained at 40–50 °C for 15 min and then poured into 20 mL of ether and 5 mL of saturated aqueous NaCl. The aqueous phase was extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated. ^1H NMR of the crude reaction mixture indicated less than 10% remaining starting material. ^{13}C NMR indicated only one isomer. The product was isolated by flash chromatography (0.5 methanol, 10 ethyl acetate, 100 hexane): 0.209 g, 94% yield; ^1H NMR (300 MHz) δ 5.34–5.37 (m, 2 H), 3.68 (dd, J = 10.8 and 4.5 Hz, 1 H), 3.53 (dd, J = 10.8 and 5.4 Hz, 1 H), 3.49 (dd, J = 5.7 and 4.3 Hz, 1 H), 2.60 (br, OH), 2.36–2.40 (m, 2 H), 1.80–1.95 (m, 1 H), 0.99–0.94 (m, 9 H), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H); ^{13}C NMR (50.1 MHz) δ 137.6, 129.7, 81.4, 65.5, 41.8, 37.4, 31.1, 26.1, 26.0, 22.5, 18.2, 16.7, 16.3, −3.9, −4.0. The protecting group was removed with *n*-Bu$_4$NF.[18] A mixture of the diol (64 mg), 3 crystals of TsOH, and 1 mL of 2,2-dimethoxypropane were stirred at room temperature for 30 min. The solution was concentrated and filtered through silica gel (1 methanol, 10 ethyl acetate, 100 hexane): ^1H NMR (200 MHz), 5.38–5.42 (m, 2 H), 3.68 (dd, J = 11.5 and 5.1 Hz, 1 H), 3.49 (dd, J = 10.3 and 11.2 Hz, 1 H), 3.38 (dd, J = 10.3 and 2.9 Hz, 1 H), 2.20–2.40 (m, 2 H), 1.65–1.90 (m, 1 H), 1.38 (s, 3 H), 1.36 (s, 3 H), 0.96 (d, J = 6.8 Hz, 9 H), 0.73 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (50.1 MHz) δ 136.6, 130.8, 98.1, 78.4, 66.2, 38.2, 31.5, 30.9, 29.4, 22.7, 19.3, 14.0, 13.0. See Thaisrivongs and Seebach for assignment of stereochemistry.[11]

(−)-(2*R*,3*R*,4*S*,5*E*)-1-Iodo-2,4,7-trimethyl-5-octen-3-yl *tert*-Butyldimethylsilyl Ether (6). A flask was charged with 10 mL of 1 M BH_3 in THF and cooled to 0 °C. Cyclohexene, 20.5 mmol, was added and the slurry stirred at 0 °C for 1 h. The TBDMS ether of **3**, 9.55 mmol, was added and the solution stirred for 1 h at 0 °C and then 2 h at room temperature. The white precipitate disappeared during this time. Iodine, 7.61 g, 30 mmol, was added followed by the slow addition of 10 mL of 3 N NaOMe in methanol. After 1 h the excess iodine was destroyed with sodium thiosulfate (10% aqueous solution). The product was extracted with ether and the organic phase dried ($MgSO_4$), concentrated, and then filtered through silica gel with hexane as an eluant. The crude yield was 70%. The product was Kugelrohr distilled (105 °C, 0.025 mm) to give 2.16 g, 55% yield: $[\alpha]^{26}_D$ −7.23 (*c* 8.24, THF); ^1H NMR (200 MHz), δ 5.30–5.40 (m, 2 H), 3.35–3.50 (m, 2 H), 3.04 (dd, J = 9.6 and 8.5 Hz, 1 H), 2.15–2.35 (m, 2 H), 1.70–1.90 (m, 1 H), 1.05 (d, J = 6.8 Hz, 3 H), 0.99 (d, J = 6.6, Hz, 6 H), 0.97 (d, J = 6.8 Hz, 3 H), 0.91 (s, 9 H), 0.09 (s, 3 H), 0.08 (s, 3 H); IR (film) 1465, 1385, 1365, 1260, 1200, 1170; ^{13}C NMR (50.1 MHz) δ 137.3, 130.0, 79.7, 40.9, 40.4, 31.1, 26.1, 22.6, 22.5, 18.3, 16.6, 14.0, −3.8. The minor isomer was less than 5% as indicated by 200-MHz ^1H NMR. The product was somewhat unstable and was used immediately for the next step.

(+)-Lactone 8. Lithium diisopropyl amide was prepared in THF (50 ml) from diisopropylamine (11.8 mmol) and *n*-BuLi (11.8 mmol). The propionamide of prolinol (5.86 mmol) in 2 mL of THF was slowly added and the mixture stirred at room temperature for 30 min to provide enolate **7**.[13] The solution was cooled to −78 °C, and the TBDMS ether iodide **6** (4.5 mmol) was added. The dry ice bath was removed after 5 min and the mixture stirred at room temperature for 4 h. The mixture was poured into concentrated NH_4Cl and extracted with ether. The organic phase was dried ($MgSO_4$), concentrated, and filtered through silica gel with hexane and then ethyl acetate as eluants. A small portion was analyzed and purified by HPLC (1:1 ethyl acetate/hexane, Partisil M9). HPLC indicated a 10:1 ratio of products. The crude product was placed in 10 mL of THF and 5.5 mL of 1 N HCl. The mixture was stirred at room temperature for 24 h. The product was extracted with ether and the ether layer dried and concentrated. The product was isolated by flash chromatography (20:100 ethyl acetate/hexane) to give a 68% yield of the lactone. The lactone was Kugelrohr distilled (80 °C, 0.025 mm) $[\alpha]^{23}_D$ +64.12 (*c* = 5.71, ethyl acetate) for material purified by HPLC (1:10 ethyl acetate/hexane, Partisil M-9). HPLC indicated a >13:1 mixture of isomers. ^1H NMR (200 MHz) δ 5.44 (m), 3.87 (dd,

(18) Greene, T. W. "Protecting Groups in Organic Synthesis"; Wiley: New York, 1981; p 44.

J = 2.6 and 9.7 Hz), 2.37 (m), 2.20 (m), 1.85 (m), 1.3 (m), 1.22 (d, J = 7.1 Hz), 0.95 (d, J = 6.1 Hz), 0.92 (d, J = 6.5 Hz); ^{13}C NMR (50.1 MHz) δ 174.5, 137.9, 129.2, 90.3, 39.4, 37.3, 36.0, 30.9, 30.7, 22.4, 22.3, 27.6, 17.1, 13.5. Exact mass calcd for $C_{14}H_{24}O_2$: m/e 224.1776. Found: m/e 224.1776.

(+)-Prelog-Djerassi Lactonic Aldehyde (2). Ozone was introduced into a solution of the lactone **8** (1.23 mmol) in 30 mL of ethyl acetate at -78 °C. After the solution became blue, the ozone flow was stopped and excess ozone swept from the reaction flask. After 10 min 2 mL of methyl sulfide was added to the solution and the mixture warmed to room temperature (2 h). The solution was concentrated and then dissolved in 20 mL of ethyl ether and treated with 10 mL of 1 M aqueous potassium iodide. The iodine was destroyed with sodium thiosulfate and the aqueous phase extracted with ether. The organic phase was dried ($MgSO_4$) and concentrated. The product was isolated as a white solid by flash chromatography (1:1 ethyl acetate/hexane) in 83% yield. Recrystallization from hexane-ether provided material of mp 62-64 °C; $[\alpha]^{26}_D$ +27.3° (c 3.11, $CHCl_3$) (lit.[6b] mp 57-62 °C, $[\alpha]^{26}_D$ + 27.0° (c 3.60, $CHCl_3$)); ^{1}H NMR (200 MHz) δ 9.75 (s, 1 H), 4.59 (dd, J = 10.2 and 2.1 Hz, 1 H), 1.65-2.90 (m, 5 H), 1.30 (d, J = 7.0 Hz, 3 H), 1.22 (d, J = 7.0 Hz, 3 H), 1.03 (d, J = 6.4 Hz, 3 H); ^{13}C NMR (50.1 MHz) δ 202.5, 173.4, 84.8, 47.4, 37.2, 36.2, 30.4, 17.0, 16.6, 6.3.

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Registry No. 2, 77405-46-0; **3**, 96346-17-7; **3** (*tert*-butyldimethylsilyl ether), 96258-97-8; **4**, 89998-89-0; **4** (ketone), 52066-33-8; **5**, 96391-34-3; **6**, 96258-95-6; **6** (alcohol), 96258-98-9; **6** (diol), 96258-99-0; **6** (isopropylidene derivative), 96259-00-6; **7**, 79563-15-8; **7** (alcohol amide), 74036-66-1; **8**, 96258-96-7; **8** (amide precursor)-Li, 96259-01-7; (+)-(2*Z*,4*S*)-5-methyl-2-hexen-4-ol, 96346-18-8; (*S*)-prolinol propionamide; $CH_3CH(CHO)CH_3$, 78-84-2; $ClCH_2C(CH_3)=CH_2$, 563-47-3; $CH\equiv C-CH_3$, 74-99-7.

Ionization of the PH Bond in Diethyl Phosphonate

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Abstract: Diethyl phosphonate is oxidized by halogens in a reaction subject to general base catalysis when the halogen concentration is sufficiently high. Under these conditions the reaction is zero order in iodine or bromine and the Brønsted exponent, β, is, contrary to earlier reports, about 0.7. When the halogen concentration is quite low, but still within the range of the spectrophotometric analysis used, a third-order rate law is obeyed and the product of the ionization constant of the phosphonate and the rate constant for the reaction of the anion with halogen (which is probably diffusion controlled) can be derived. This gives an acid dissociation constant of 2.5×10^{-15}. When the diethyl phosphonate is exchanged with D_2O, a substantial kinetic isotope effect is observed for the oxidation, again contrary to expectation from previous reports on a similar reaction. This reaction is thus closely analogous to the ionization of hydrogen α to a carbonyl group or a nitro group in all of which the proton transfer is slower than the diffusion-controlled rate in both directions.

In aqueous solution dialkyl phosphonates react with halogens according to eq 1. Using a titrimetric analysis, Nylen[1] found

$$(RO)_2PHO + I_2 + 3OH^- \rightarrow (RO)_2PO_2^- + 2I^- + 2H_2O \quad (1)$$

that the reaction was subject to general base catalysis and the rate was independent of iodine concentration as long as the concentration was not too small. There was also an acid catalysis with the simple oxidation complicated by some ester hydrolysis. A study of different bases appeared to show conformity with the Brønsted equation with a β value of unity. Although the difficulty of observing very high β values is well-known, as shown (for example) by Bell,[2] the inconsistency was apparently overlooked for a long time. Naturally, large β values can be measured if the point for OH^- lies far below the value expected from the Brønsted equation. This can easily happen if the diffusion limit is already reached with weaker bases, but Nylen's rates are far too slow for this to be the case. A further indication of the inconsistency is the natural assumption from the large β value that the reverse reaction (with α 0) is diffusion limited, yet iodine at modest concentrations could compete for the intermediate anion to the exclusion of the reverse protonation. An apparent inconsistency was found again in a study of the exchange rate in D_2O and of the deuterated ester into H_2O by Luz and Silver,[3] who confirmed the general base catalysis, but found that the isotope effect expected with the general base catalysis was very small with acetate ion as the base. They used an NMR analysis to measure the exchange. They concluded that the r.d.s. was not a simple proton transfer. In work on the acid catalysis[4] they did find an isotope effect. The general base catalysis also showed up less convincingly in a study of the reaction of the dimethyl ester with diazonium salts.[5]

In spite of the problems, the mechanism is plausibly given by eq 2-4.

$$(RO)_2PHO + B^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (RO)_2PO^- + BH \quad (2)$$

Table I. Rate Constants for Attack of Various Bases on Diethyl Phosphonate

base	k_1 (M^{-1} s^{-1})
CH_3COO^-	2.98×10^{-3}
HPO_4^{2-}	2.25×10^{-1}
CO_3^{2-}	3.4
NH_3	2.35×10^{-3}
OH^-	$\sim 10^4$ [a]

[a] The extrapolation to zero buffer concentration makes this value somewhat uncertain. Furthermore, the value is based only on phosphate buffer data.

(1) Nylen, P. *Z. Anorg. Allg. Chem.*, **1938**, *235*, 161.
(2) Bell, R. P. "Acid-Base Catalysis"; Clarendon Press: Oxford, 1941; Chapter 5.
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