traction, drying of the extract, and solvent evaporation. 5-Vinylindan (0.32 g, 18%) was obtained as a colorless oil after vacuum distillation, bp 116–121 °C (17 Torr) (lit.[26] 95–100 °C (10 Torr)).

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A Stereoselective Total Synthesis of the Prelog–Djerassi Lactone

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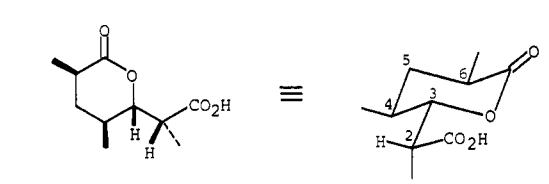
Abstract: A total synthesis of racemic Prelog–Djerassi lactone (**1**) has been achieved using the mercuric ion induced cyclization of aldehyde acid **12a** to control the stereochemistry at C-2 and C-3. Demercuration of the product (**14a**) is selectively accomplished with sodium trithiocarbonate in methanol at −60 °C, affording the Prelog–Djerassi lactone (**1**) and the 2-epi isomer **17** in a 3.5:1 ratio after hydrolysis and oxidation. Demercuration with sodium borohydride, hydrolysis, and oxidation result in the 2-epi compound **17** almost exclusively.

Introduction

The Prelog–Djerassi lactonic acid (**1**) occupies a prominent position in the chemistry of the macrolide antibiotics, having served both in their structure elucidation and in their synthesis. Isolated independently by Prelog[1] and Djerassi,[2] as a degradation product of narbomycin and methymycin, respectively, its full stereochemistry was not correctly assigned until 1970 by Rickards and Smith.[3] In 1963, Bergel'son and Batrakov reported a synthesis of this material, by a nonstereorational route involving the reduction of a keto diester precursor.[4] This synthesis has been repeated by Yamaguchi and co-workers, who noted its nonstereoselective nature.[6] In connection with the first synthesis of methymycin, Masamune prepared the Prelog–Djerassi lactone from bicyclo[4.2.1]nona-2,4,7-triene, using a carbocyclic framework to facilitate stereochemical control.[7] More recently, Masamune has reported a much shorter route employing an erythro-selective aldol condensation.[8] Three stereospecific syntheses were recently communicated by White, Stork, and Grieco, who also introduced the chiral centers on a carbocyclic framework.[9] Because of our interest in the synthesis of macrolides and in the control of stereochemistry using cyclization reactions,[10] we developed a synthesis of the Prelog–Djerassi lactone from acyclic precursors.



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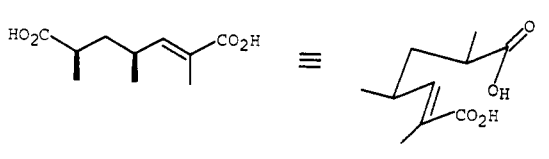

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Synthetic Plan

Our strategy was to attempt, in effect, the isomerization of the unsaturated diacid **2** to the Prelog–Djerassi lactone (**1**),

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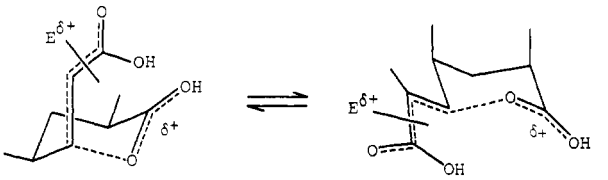
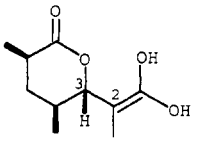
a transformation which formally involves the anti addition of one carboxyl O–H across the double bond. We were confident that any cyclization reaction would generate the correct stereochemistry at C-3, because transition states such as **3** or **4** leading to 3-epi isomers would be severely congested. However,



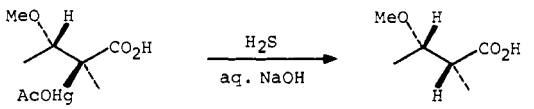
3 4



5

the likelihood that an acid-catalyzed cyclization would occur via a 1,4 addition to give the enol intermediate **5** argued against stereocontrol at the extracyclic C-2 position during such a process.

An alternative cyclization method was suggested by a study done by Maskens and Polgar on the stereochemistry of demercuration of α-mercuricarboxylic acids.[11] Of particular interest was their report that **6**, the methoxymercuration product of tiglic acid, is cleaved with retention of configuration



6 7a

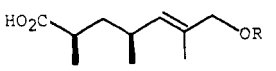
and high stereoselectivity using hydrogen sulfide in aqueous alkali to afford the erythro compound **7a.** In this system, the two steps of mercuration and demercuration accomplish the stereocontrolled anti addition process which we desired. Demercuration of **6** using sodium borohydride in alkaline methanol, on the other hand, gives a 50:50 mixture of **7a** and its diastereomer (**7b**).[11]

Cyclizations

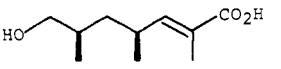
The synthetic routes to the various cyclization substrates are described at the end of the discussion section.

The olefinic diacid **2** is, unfortunately, inert to mercuric ion as well as acid under a variety of conditions.[12] Although lactonizations of both types are well precedented,[13] in this instance the deactivated double bond and the weakly nucleophilic carboxyl group apparently conspire to prevent cyclization from occurring.

To increase the reactivity of the double bond, the allylic ethers **8** were prepared. In the presence of mercuric acetate or trifluoroacetate, however, these materials undergo oxidation in preference to cyclization. The hydroxy acid **9a**, on the other hand, cyclizes smoothly with mercuric acetate in methanol to provide a single isomer of the cyclic ether **10** in 92% yield. This compound crystallizes from the reaction mixture as the acetate-free (presumably dimeric) inner salt, as confirmed by NMR and elemental analysis.[14] Acid- and base-catalyzed cyclizations of the methyl ester of **9a** are also successful, affording the methyl ester of **11** as a mixture of diastereomers. However, from these intermediates no method for selective introduction of the requisite lactone carbonyl was apparent.



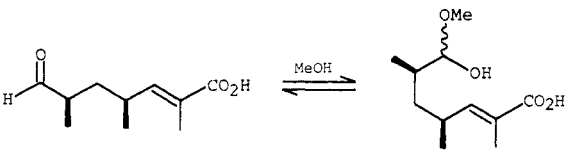
8 (R = t-BuMe$_2$Si, PhCH$_2$)



9a

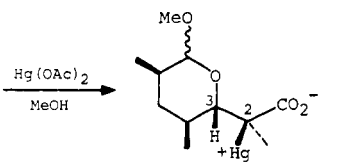
10 11

These problems can be circumvented by employing the aldehyde **12a** as the cyclization substrate. In methanol, this material exists in equilibrium with the hemiacetal **13a**, a species with a sufficiently nucleophilic hydroxyl that mercuric



12a 13a

(12b = Z-isomer)



14a

(14b = C-2 epimer)

acetate readily induces cyclization to a mixture of epimeric acetals **14a** (70% yield). After demercuration, the acetal can be converted into the lactone by hydrolysis (aqueous HCl/dioxane, 65 °C, 30 min) and oxidation (Ag_2CO_3/Celite or Jones reagent). With the problem of cyclization solved, we turned our attention to the stereochemistry of this step and of the subsequent cleavage of the carbon–mercury bond.

Stereochemical Studies

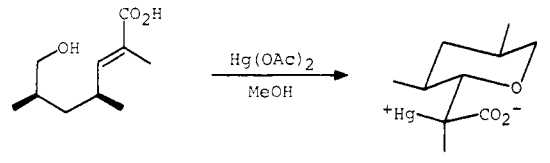
Cyclization. The presence of epimeric acetals in **14a** complicates the stereochemical analysis of the cyclization of **12a.** Moreover, the acid lability of the mercuri group precludes conversion of the acetal moiety to the lactone prior to demercuration. These complications are not present in the cyclic ethers **10** and **11**, however, and their formation provided excellent model systems.

The mercuricyclization of (*E*)-hydroxy acid **9a** results in a single product (>95% stereoselectivity), to which we assign structure **10a**. The isomeric (*Z*)-hydroxy acid **9b** cyclizes under identical conditions to a diastereomeric mercuri ether, **10b** (86% yield, >95% stereoselectivity). For each isomer, the ^{1}H NMR spectrum reveals a doublet of J = 9.5 Hz, corresponding to the axial proton at C-3. Confirmation of this stereochemical assignment was obtained from subsequent transformations of the analogous products derived from the aldehydes **12.** No specific determination of configuration at the C-2 position has been made, however, and the structures of **10a** and **10b** are

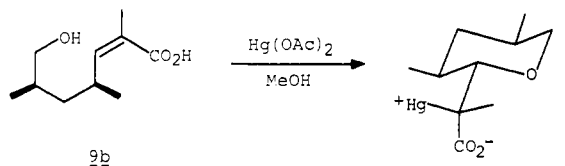
Table I. Stereochemistry of Demercuration: Ratio[a] of **a** Isomer (Erythro) to **b** Isomer (Threo)

cleavage conditions[b]	reaction				
	10a → 11	**10b → 11**	**14a → 15**[c]	**14b → 15**[c]	**6 → 7**
$NaBH_4$, aqueous NaOH	<5:95	<5:95	<5:95		50:50[d]
H_2S, pyridine	<5:95	<5:95	<5:95[e]	<10:90	55:45[e]
H_2S, aqueous NaOH	50:50	50:50	55:45		>95:5[d]
Na_2CS_3, alkaline MeOH, −60 °C	66:33	45:55	78:22	33:66	>95:5
H_2, $(Ph_3P)_3RhCl$, MeOH[f]	25:75	25:75			90:10
3% Na-Hg, MeOH, KH_2PO_4	50:50				90:10[g]
aqueous Na_2S, pH 9	50:50				
Na_2S, MeCN	10:90				

[a] Determined by VPC analysis of the methyl esters (diazomethane), unless otherwise indicated. [b] All reactions run at 0 °C with yields >90%, unless otherwise indicated. [c] Ratios determined after acetal hydrolysis and oxidation to lactone. [d] We have confirmed the previously reported results.[11] [e] Ratio determined by ^1H NMR. [f] Reaction run at 25 °C; cleavage products accompanied by ~40% of olefinic acid from reductive elimination. [g] Cleavage product accompanied by ~10% of tiglic acid.



9a 10a



9b 10b

assigned on the basis of the documented preference for anti attack in electrophilic substitution of unstrained olefins by mercuric species.[15]

As we had anticipated, the acid-catalyzed cyclization of the methyl ester of **9a** is nonstereoselective, affording a 4:6 mixture of the esters of **11a** and **11b.** Since these two isomers can be related to those produced on demercuration of **10a** and **10b** (see

X = H_2	11a	11b
X = H,OCH_3	15a	15b
X = H,OH	16a	16a
X = O	1	17

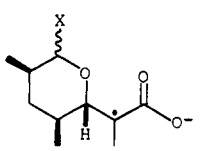
below), they are epimeric at the extracyclic C-2 position. The base-induced cyclization of the same hydroxy ester was similarly nonstereoselective with respect to the configuration at C-2.

Demercuration. When the alkaline hydrogen sulfide demercuration procedure of Maskens and Polgar[11] is applied to **14a**, and followed by hydrolysis and oxidation, a 55:45 mixture of the Prelog-Djerassi lactone (**1**) and an isomer is obtained. After chromatographic separation, the Prelog-Djerassi lactone, mp 116–117 °C, was identified by spectral and mixture melting point comparison with authentic racemic material.[16] On the other hand, when **14a** is reduced using alkaline sodium borohydride, which produces a 50:50 mixture of diastereomeric products with **6**,[11] the unwanted isomer is almost the exclusive product (>95% selectivity) after identical hydrolysis and oxidation steps. The demonstration that the isomerism arises in the demercuration step proves that the unwanted isomer is the C-2 epimer **17.**

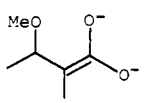
Assuming that the assignment of stereochemistry of the mercuri acetal **14a** is correct, the borohydride demercuration of this material proceeds formally with *inversion* of configuration, a highly unprecedented result. To clarify this point, we subjected the diastereomeric mercuri ether model compounds **10a** and **10b** to the same cleavage conditions. Regardless of the configuration of the mercury-bearing carbon atom in the starting material, the ratio of diastereomeric products is the same: alkaline hydrogen sulfide gives approximately a 50:50 mixture of the two isomers (**11**), and alkaline borohydride gives only one of them (**11b**). It is clear, therefore, that with both of these reagents the stereochemistry of the product is determined during a step subsequent to the cleavage of the carbon-mercury bond.

A number of demercuration conditions were explored, and the results are summarized in Table I. The stereoselectivity of the aqueous sulfide cleavage is unaffected by changes in pH or order of mixing of substrates and reagents. However, reversal of the mercuration reaction occurs under acidic conditions (pH <3), returning the starting olefinic acid. In the case of the acetal products, the ratios of the epimers **15a** and **15b** were determined after acetal hydrolysis and oxidation to the lactones **1** and **17**. It is interesting to note that the diastereomeric lactols **16a** and **16b** are oxidized by silver carbonate on Celite at different rates; the Prelog-Djerassi lactone (**1**) is produced significantly faster than its C-2 epimer (**17**). Unless completion of the oxidation reaction is ensured, therefore, a false stereoselectivity is projected for the demercuration reactions of **14a** and **14b**.

Two general classes of reagents, and presumably therefore mechanisms, are discernible on the basis of the stereochemical results. One class, which includes alkaline sodium borohydride and hydrogen sulfide in pyridine,[17] produces the threo (**b**) isomers very selectively from the cyclic ethers and a 50:50 mixture from the tiglic acid adduct. A radical-chain mechanism for borohydride demercuration reactions is well established[18]; it appears likely therefore that an intermediate such as **18** is involved in the hydrogen sulfide-pyridine cleavage as well.



18



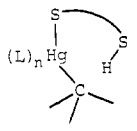
19

The other class of demercuration reagents, which includes alkaline aqueous sodium sulfide and sodium amalgam, exhibits

no stereoselectivity in the cleavage of the cyclic ethers, but provides the erythro product (**a**) in the acyclic case. The sodium amalgam cleavage of alkyl mercurials involves a carbanionic intermediate, as Jensen and co-workers have demonstrated.[19] In the present cases, intermediates having the carbanionic character of a carboxylate enolate such as **19** would appear to be involved.

Only two sets of cleavage conditions were found which demonstrate selectivities different from the two classes just discussed. Hydrogenolytic cleavage using the Wilkinson catalyst[20] favors the threo (**b**) products on cleavage of the cyclic ethers (although with less selectivity than borohydride or hydrogen sulfide–pyridine), but also shows high selectivity (for the erythro (**a**) isomer) with the tiglic acid adduct **6**. Nonetheless, as the results with the diastereomeric ethers **10a** and **10b** attest, the stereochemical course of this reaction is still independent of the configuration of the starting material. The significance of the results, moreover, is clouded by the fact that the hydrogenolysis is accompanied by comparable amounts of reductive elimination back to the olefinic starting materials.

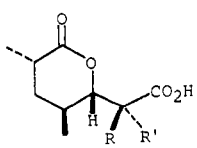
We were able to discover one reagent which exhibits a preference for retention of configuration with all of the substrates studied: sodium trithiocarbonate in methanol at low temperature. Although in most instances the selectivity is only moderate, with the crucial substrate for the synthesis of the Prelog–Djerassi lactone, **14a**, a 3.5:1 ratio in favor of the desired product can be obtained. We tried sodium trithiocarbonate because we sought a sulfur-containing reagent which was capable of intramolecular proton delivery, as illustrated schematically in **20**. However, the greatest selectivity is ob-

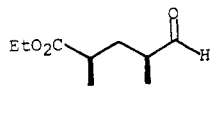


20

served with this reagent in alkaline alcoholic media, not under conditions in which a significant amount of the protonated species would be present. Nonetheless there are clearly factors other than solvent and temperature effects involved, since sodium sulfide in alkaline methanol at −60 °C produces only a 2:1 mixture (**15a–15b**) from **14a.**

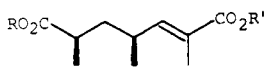
Epimerization at C-2 was ruled out as a factor influencing any of the reactions discussed above. Interconversion of **11a** and **11b** could not be accomplished under the alkaline conditions of the demercuration reaction; the stereoselectivities observed in the cleavage reactions arise therefore from kinetic control. Furthermore, the lactones (**1** and **17**) are unchanged when resubmitted to the acetal hydrolysis or oxidation conditions. Epimerization of these compounds requires prolonged heating with HCl in aqueous dioxane, but does not lead to their interconversion. The new isomers, therefore, are the 6-epi derivatives **21a** and **21b**. These assignments were corroborated by ^{13}C NMR, which revealed significant upfield shifts[21] for C-3, -4, -5, and -6 of the 6-epi isomers **21** in comparison with the all-equatorial isomers **1** and **17** (see Experimental Section, Table III).





22

21a: R = H, R' = Me
21b: R = Me, R' = H



2: R = R' = H
23: R = Me, R' = H
24: R = R' = Me

Synthesis of Cyclization Substrates

The aldehyde ester **22** is readily prepared in 75% yield from *meso*-2,4-dimethylglutaric anhydride[22] by a modification of the reported route[23] of alcoholysis, acid chloride formation, and Rosenmund reduction.[24] Condensation of this material with ethyl 2-(triphenylphosphoranylidene)propionate followed by alkaline hydrolysis furnishes the stereochemically pure erythro *E* diacid **2** in almost quantitative yield. The *E* geometry of the olefin is well precedented and was confirmed by ^{13}C NMR comparison of the dimethyl ester with its *Z* photoisomer (see Experimental Section).

The two carboxyl groups of **2** are easily distinguished by selective Fischer esterification of the nonconjugated one. This process is quite efficient, affording a 4:1 mixture of the monoester **23** and the diester **24** if interrupted as soon as the diacid **2** is consumed. These two compounds are separated by extraction, and the diester is recycled. With only one recycle of diesterified material, a 95% yield of **23** can be realized.

The allylic alcohol **8** is prepared by reduction of the monoester **23** with borane–tetrahydrofuran at 0 °C[25] and subsequent hydrolysis. Alternatively, reduction of the monoester **23** with diisobutylaluminum hydride in toluene at −78 °C[26] provides the aldehyde acid **12a** (77% yield); further reduction of **12a** with lithium borohydride gives the hydroxy acid **9a** (90% yield).

A mixture of the (*E*)-hydroxy acid **9a** and its *Z* isomer **9b** is produced on irradiation of **9a** in acetone with a medium-pressure mercury arc lamp through a Vycor filter. These isomers, as well as the isomeric aldehyde acids **12a** and **12b** prepared analogously, are easily separated by column chromatography on silica gel.

Summary

With the discovery of the trithiocarbonate cleavage reaction, a high-yield, stereoselective synthesis of the Prelog–Djerassi lactone was in hand. From *meso*-2,4-dimethylglutaric anhydride, the steps which lead to the aldehyde acid **12a** proceed in 55% overall yield. The mercuricyclization–demercuration steps and the subsequent acetal hydrolysis and lactol oxidation sequence can be accomplished in 32% combined yield, including the chromatographic separation of the Prelog–Djerassi lactone from its C-2 epimer.

Experimental Section[27]

(*E*)-(4*R,6*S**)-2,4,6-Trimethyl-2-heptenedioic Acid (2).** A solution of 3.0 g (17.4 mmol) of the aldehyde ester **22** and 8.0 g (22 mmol) of ethyl 2-(triphenylphosphoranylidene)propionate in 22 mL of CH_2Cl_2 was heated at reflux for 14 h. After removal of the solvent at reduced pressure, the mixture was triturated with several portions of 1:1 ether–hexane to leave the bulk of the triphenylphosphine oxide behind as a residue. After reevaporation of the supernatant, the crude diester was hydrolyzed in 20 mL of methanol and 20 mL of 2 N NaOH at 75 °C for 45 min. This mixture was partitioned between ether and water, and the aqueous layer was washed with ether. After back-extraction of the organic phase with water and acidification of the combined aqueous layer, ether extraction and subsequent workup furnished 3.4 g (97% yield) of the diacid **2**: mp 140–141.5 °C after crystallization from ether; ^1H NMR δ 1.03 and 1.20 (each d, 3, CH_3CH), 1.83 (d, 3, J = 1.5 Hz, $CH_3C\leqslant$), 6.6 (dq, 1, J = 11, 1.5 Hz, =CH–), 12.4 (br s, 2, CO_2H); IR ($CHCl_3$) 2500–2800, 1700 (CO_2H), 1650 (C=C) cm^{-1}. Anal. ($C_{10}H_{16}O_4$) C, H.

(*E*)-(4*R,6*S**)-2,4,6-Trimethyl-6-methoxy-6-oxo-2-heptenoic Acid**

Table II. Distinguishing ^{1}H NMR Resonances for Prelog-Djerassi Lactone Epimers

assignment[a]	isomer 1	2-epi (**17**)	6-epi (**21a**)	2,6-diepi (**21b**)
CH_3 C-4	1.02	1.02	1.03	1.06
CH_3 C-2	1.19	1.28	1.19	1.23
CH_3 C-6	1.28	1.33	1.23	1.31
H-3	4.59	4.17	4.54	4.22
$J_{2,3}$, Hz	2.3	3	3	4
$J_{3,4}$, Hz	10	10	10	9

[a] Note 28.

Table III. ^{13}C NMR Resonances of Prelog-Djerassi Lactone Epimers

assignment[a]	isomer 1	2-epi (**17**)	6-epi (**21a**)	2,6-diepi (**21b**)
CH_3 C-2	8.2	12.8	8.6	12.3
CH_3 C-4/CH_3 C-6	16.7 17.0	16.7 17.0	16.3 17.1	16.3 17.4
C-5	30.1	31.1	28.5	28.2
C-4/C-6	36.0 37.1	35.8 37.0	32.3 34.6	32.2 34.7
C-2	40.9	41.7	40.7	41.7
C-3	86.2	87.4	82.7	84.4
C=O	174.3 177.5	174.3 177.3	175.8 177.8	176.6 177

[a] Note 28.

(**23**). A solution of 8.74 g (44 mmol) of the diacid **2**, 0.1 mL of concentrated HCl, 20 mL of 2,2-dimethoxypropane, and 20 mL of methanol was kept at 0 °C for 3 days and at 25 °C for 7 h, at which point TLC analysis indicated that no diacid remained. The mixture was diluted with ether and extracted twice with aqueous $NaHCO_3$, and the combined aqueous layer was washed with ether. From these combined ether extracts was obtained 1.95 g (19% yield) of the dimethyl ester (**24**). The aqueous layer was acidified and extracted twice with ether, and the ether layer was worked up to give 7.40 g (79% yield) of the monoester **23**. Saponification of the diester followed by a repetition of the sequence above afforded an additional 1.44 g of the monoester, for a combined yield of 95%: ^{1}H NMR δ 1.05 and 1.17 (each d, 3, >CHCH_3), 1.85 (d, 3, J = 2 Hz, ≥CCH_3), 3.67 (s, 3, OCH_3), 6.58 (dq, 1, J = 2, 10 Hz, ≥CH); IR (film) 2500-2700, 1700 (CO_2H), 1740 (CO_2CH_3), 1660 (C=C) cm^{-1}. Dimethyl ester **24**: ^{13}C NMR δ 11.6, 16.6, 19.2 (CCH_3), 30.7 (CH_2), 37.0, 39.9 (CH), 50.5, 50.7 (OCH_3), 126.2 (=CH-), 145.9 (=C<), 167.5, 175.7 (C=O). The geometric isomer of **24**, obtained by preparative VPC (190 °C) after irradiation of an 18 mM solution of **24** in cyclohexane with a medium-pressure Hg lamp through a Vycor filter, showed resonances in the ^{1}H NMR spectrum at δ 5.65 (dq, 1, J = 10, 2 Hz, =CH-) and in the ^{13}C NMR spectrum at δ 16.9, 20.6, and 20.8 (CCH_3), characteristic of the Z stereochemistry. An analytical sample of **24** was purified by preparative VPC (190 °C). Anal. ($C_{12}H_{20}O_4$) C, H.

(***E*-(4*R**,6*S**)-2,4,6-Trimethyl-7-oxo-2-heptenoic Acid (12a).** A solution of 2.25 g (10.5 mmol) of the monoester **23** in 45 mL of hexane and 45 mL of glyme was stirred at −75 °C, and 17.5 mL of a 1.54 M solution of diisobutylaluminum hydride in toluene was added over a 10-min period. After a further 30 min, the reaction was quenched by the addition of 1 mL of methanol, and the mixture was partitioned between 50 mL of ether and 250 mL of 0.7 N HCl. The aqueous phase was extracted with another portion of ether, and the combined organic layer was worked up to give 2.1 g of an oily product. Chromatography furnished 1.48 g (77% yield) of the aldehyde acid **12a** and 310 mg (16% yield) of the hydroxy acid **9a**. Aldehyde acid **12a**: ^{1}H NMR δ 1.04 and 1.08 (each d, 3, >CHCH_3), 1.85 (d, 3, J = 2 Hz, ≥CCH_3), 6.64 (dq, 1, J = 10, 2 Hz, =CH-), 9.58 (d, 1, J = 2 Hz, CHO), 11.0 (s, 1, CO_2H); ^{13}C NMR δ 11.7, 13.1, 19.7 (CH_3), 30.7 (CH_2), 36.9, 44.2 (CH), 126.5 (=CH-), 148.6 (=C<), 173.0 (CO_2H), 204 (CHO); IR (film) 2500-2800, 1690 (CO_2H), 1720 (CHO) cm^{-1}. An analytical sample of the methyl ester of **12a** (diazomethane) was purified by preparative VPC (190 °C). Anal. ($C_{11}H_{18}O_3$) C, H.

(2*R,3*R**,5*S**,6*R***S***)-2-[(1*R**)-1-Carboxy-1-(hydroxymercuri)-ethyl]-3,4,5,6-tetrahydro-6-methoxy-3,5-dimethyl-2*H*-pyran Inner Salt (14a).** A solution of 514 mg (2.79 mmol) of the (*E*)-aldehyde acid **12a** and 980 mg (3.07 mmol) of mercuric acetate in 6 mL of dry methanol was stirred at 25 °C for 10 days. The mixture was centrifuged, the supernatant was decanted, and the precipitate was washed with 5 mL of methanol and two 5-mL portions of ether. After drying (24 h at 70 °C (1 Torr)), 815 mg (70% yield) of analytically pure mercuri acetal **14a** was obtained as a mixture of anomers: mp 190 °C dec; ^{1}H NMR[28] (NaOD, D_2O, referenced to TSP as δ 0), major isomer (β), δ 0.85 and 1.14 (each d, 3, CH_3 C-4 and CH_3 C-6), 1.5 (s, 3, CH_3CHg), 3.39 (s, 3, OCH_3), 3.95 (d, 1, J = 11 Hz, H-3) (H-7 obscured by HOD), and minor isomer (α), δ 0.88 and 1.14 (each d, 3, CH_3 C-4 and CH_3 C-6), 1.5 (s, 3, CH_3CHg), 3.45 (s, 3, OCH_3), 3.75 (d, 1, J = 11 Hz, H-3), 4.08 (d, 1, J = 8 Hz, H-7); IR (KBr) 1560 (CO_2^-) cm^{-1}. Anal. ($C_{11}H_{18}O_4Hg$) C, H.

(2*R,3*R**,5*S**,6*R***S***)-2-[(1R*)-1-Carboxyethyl]-3,4,5,6-tetrahydro-6-methoxy-3,5-dimethyl-2*H*-pyran (15b) by Sodium Borohydride Demercuration of 14a.** To a stirred suspension of 470 mg (1.13 mmol) of the mercuri acetal **14a** in 4 mL of methanol and 1 mL of 2 N NaOH at 0 °C was added 2 mL of a 0.5 M solution of sodium borohydride in 2 N NaOH, resulting in an immediate precipitation of mercury. After 25 min, the mercury was removed by centrifugation, and the supernatant was partitioned between ether and 2 N HCl. The organic layer was worked up to furnish 196 mg (80% yield) of the acetal mixture **15b**. ^{1}H NMR[28] analysis of this material indicated an α:β anomer ratio of 3:7: α anomer, δ 3.5 (s, OCH_3), 3.9 (d, J = 8 Hz, H-7); β anomer, δ 3.4 (s, OCH_3), 4.6 (d, J = 3.5 Hz, H-7); both anomers, δ 1.3 (d, CH_3 C-2). An analytical sample of the methyl ester of **15b** (diazomethane) was purified by preparative VPC (190 °C). Anal. ($C_{12}H_{22}O_4$) C, H.

(3*R,5*S**,6*S**)-6-[(1*S**)-Carboxyethyl]-3,4,5,6-tetrahydro-3,5-dimethyl-2-pyranone (2-Epi Prelog-Djerassi Lactone) (17).** The mixture of anomeric acetals of **15b** (196 mg, 0.9 mmol) was heated at 65 °C in 4 mL of dioxane and 4 mL of 0.4 N HCl for 35 min. The solution was partitioned between water and ether, and the organic layer was worked up to afford the crude lactol **f6b**. This material was oxidized in 7 mL of acetone at 15-20 °C with 1 mL of 0.7 M Jones reagent. The reaction was quenched after 35 min with 2-propanol, and the mixture was partitioned between water and ether. After workup of the organic layer and column chromatography, 100 mg (55% yield based on **15b**) of the 2-epi Prelog-Djerassi lactone (**17**) was obtained. Recrystallization from ether-hexane furnished material with mp 105-107.5 °C; ^{1}H and ^{13}C NMR (see Tables II and III); IR ($CHCl_3$) 2500-2800, 1705 (CO_2H), 1735 (CO_2R) cm^{-1}. An analytical sample of the methyl ester (diazomethane) was purified by preparative VPC (190°C). Anal. ($C_{11}H_{18}O_4$) C, H.

(2*R,3*R**,5*S**,6*R***S***)-2-[(1*R***S***)-1-Carboxyethyl]-3,4,5,6-tetrahydro-6-methoxy-3,5-dimethyl-2*H*-pyran (15a and 15b) by Sodium Trithiocarbonate Demercuration of 14a.** A sample of crude mercuri acetal **14a**, prepared from 6.2 mmol of the aldehyde acid **12a**, was suspended in 30 mL of methanol and stirred at 25 °C for 3 h and then cooled in an ice bath. In a separate flask a solution of 10.6 g (60 mmol) of Na_2CS_3·$2H_2O$[29] in 50 mL of methanol and 2 mL of 2 N NaOH was stirred at −70 °C. NaOH (2 N, 1 mL) was added to the suspension of mercuri acetal, which was then added over a 5-min period to the vigorously stirred Na_2CS_3 solution. The slushlike mixture was stirred at −50 °C for 1 h, warmed to 25 °C, concentrated at reduced pressure, and brought to pH 7-8 with 2 N HCl. The precipitated HgS was removed by centrifugation, and the supernatant was diluted with water, brought to pH 2 with 2 N HCl, and extracted with two portions of ether. Workup of the ether layer provided 1.0 g of the acetals **15** (75% yield from aldehyde acid **12a**). In comparison with isomer **15b**, the ^{1}H NMR[28] spectrum of this material showed additional resonances assignable to **15a**: α anomer, δ 3.4 (s, OCH_3), 3.9 (d, J = 8 Hz, H-7); β anomer, δ 3.3 (s, OCH_3), 4.5 (d, J = 3.5 Hz, H-7); both anomers, δ 1.1 (d, CH_3 C-2).

(3*R,5*S**,6*S**)-6-[(1*R**)-1-Carboxyethyl]-3,4,5,6-tetrahydro-3,5-dimethyl-2-pyranone (Prelog-Djerassi Lactone) (1).** The mixture of acetals from above was dissolved in 25 mL of dioxane and 25 mL of 0.4 N HCl and kept at 80 °C for 30 min. After extraction with ether and workup, the crude lactol mixture was dissolved in 50 mL of acetone and treated at 17 °C with two 5-mL portions of 0.7 M Jones re-

agent over 30 min. After the excess oxidant was quenched with 2-propanol, the mixture was partitioned between ether and water, and the organic layer was worked up to finish 0.75 g of isomeric lactones. Column chromatography of this mixture provided 107 mg (12% yield) of 2-epi Prelog–Djerassi lactone (**17**) and 395 mg (43% yield) of the Prelog–Djerassi lactone (**1**), mp 100–108 °C (>95% pure by NMR). Recrystallization from diisopropyl ether gave an analytical sample, mp 116–117 °C, identical with an authentic sample[16] by mixture melting point and spectral comparison: ^{1}H NMR and ^{13}C NMR (see Tables II and III); IR (KBr) 2500–2700 (CO_2H), 1710 br (C=O), 1460, 1380, 1240, 1210, 1190, 1165, 1100 cm^{-1}. Anal. ($C_{10}H_{16}O_4$) C, H.

Equilibration of the Prelog–Djerassi Lactone 1 with the 6-Epi Isomer 21a and of the 2-Epi Prelog–Djerassi Lactone 17 with the 2,6-Diepi Isomer 21b. A 105-mg sample of the Prelog–Djerassi lactone was heated in 5 mL of dioxane and 5 mL of 2 N HCl at 90 °C for 18 h. After workup of an ether solution of the reaction mixture, 102 mg of material was recovered and characterized by ^{1}H and ^{13}C NMR as a 60:40 mixture of the starting material and its 6 epimer **21a** (see Tables II and III).

Similarly, the 2-epi Prelog–Djerassi lactone was isomerized to afford a mixture containing the 2,6-diepi compound **21b** (see Tables II and III).

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Supplementary Material Available: Experimental procedures for the formation of compounds **8, 9a, 9b, 10a, 10b, 11a, 11b, 12b, 14b,** and **22** and for the acid- and base-catalyzed cyclizations of **9a** methyl ester (5 pages). Ordering information is given on any current masthead page.

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