100% conversion to two photoproducts in a 6.7:1 ratio. The solvent was removed on a rotary evaporator to give 182 mg of the photoproduct mixture as a yellow oil. The mixture was mixture was purified by flash chromatography (20–70% ethyl acetate–hexane gradient) to yield 130 mg of the higher R_f photoproduct **11b**-β-OH and 23 mg of the lower R_f photoproduct **12b**-β-OH as colorless oils. The properties of **11b**-β-OH are as follows: IR ($CHCl_3$) 3450, 2960, 1740, 1665 cm^{-1}; ^1H NMR δ ($CDCl_3$) 5.04 (t, 1, J = 2.7 Hz), 4.92 (t, 1, J = 2.7 Hz), 4.23–4.24 (m, 1), 3.43–3.53 (m, 1), 3.39 (m, 1), 2.55–2.62 (m, 2), 2.32–2.53 (m, 1), 1.89–2.14 (m, 2), 1.66 (d, 2, J = 11.0 Hz); ^{13}C NMR δ ($CDCl_3$) 217.1, 149.8, 110.4, 76.6, 54.4, 44.8, 43.2, 41.3, 40.5, 39.9; mass spectrum, exact mass calcd for $C_{10}H_{12}O_2$ m/e 164.0837, found m/e 164.0841. The properties of **12b**-β-OH are as follows: IR (thin film) 3410, 2920, 1735 cm^{-1}; ^1H NMR δ ($CDCl_3$) 5.44 (dd, 1, J = 4.3, 2.0 Hz), 4.17 (m, 1), 3.47 (m, 1), 3.05–3.20 (m, 1), 2.56–2.73 (m, 4), 2.33 (d, 2, J = 8.0 Hz), 1.80–1.96 (m, 2); ^{13}C NMR δ ($CDCl_3$) 221.9, 134.3, 117.3, 67.4, 49.1, 43.5, 38.9, 37.4, 37.3, 30.4. Anal. Calcd for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 73.11; H, 7.40.

Preparative Irradiation of *syn*-4-[1-[(*tert*-Butyldimethylsilyl)oxy]-3,4-pentadienyl]cyclopent-2-en-1-one (10b). A solution of enone **10b** (441 mg, 1.58 mmol) in 330 mL of dry, distilled ether was irradiated for 18 h. GC analysis indicated 100% conversion to two photoproducts in a 6.6:1 ratio. The solvent was removed by rotary evaporation to give 431 mg of the photoproduct mixture. The mixture was purified by flash chromatography (0–10% ethyl acetate–hexane gradient) to give 315 mg of the higher R_f photoproduct **11c**-β-t-**BuMe$_2$Si** ether and 30 mg of the lower R_f photoproduct **12c**-β-t-**BuMe$_2$Si** ether as colorless oils. The properties of **11c**-β-t-$BuMe_2Si$ ether are as follows: IR (thin film) 2950, 1740, 1670, 1260, 1100 cm^{-1}; ^1H NMR δ ($CDCl_3$) 5.02 (t, 1, J = 2.2 Hz), 4.89–4.91 (m, 1), 4.12 (q, 1, J = 5.4 Hz), 3.37–3.48 (m, 1), 3.26–3.34 (m, 2), 2.61–2.69 (m, 1), 2.53 (dd, 1, J = 9.0, 1.0 Hz), 2.30 (dd, 1, J = 16.0, 1.0 Hz), 1.80–2.04 (m, 2), 0.86 (s, 9), 0.03 (s, 6); ^{13}C NMR δ ($CDCl_3$) 216.8, 147.9, 110.5, 81.6, 53.7, 46.8, 45.9, 44.6, 41.5, 41.4, 25.7, 17.9, −4.6, −4.7. Anal. Calcd for $C_{16}H_{26}O_2Si$: C, 69.01; H, 9.41. Found: C, 68.96; H, 9.54. The properties of **12c**-β-t-$BuMe_2Si$ ether are as follows: IR (thin film) 2950, 1740, 1260, 1090 cm^{-1}; ^1H NMR δ ($CDCl_3$) 5.44 (dd, 1, J = 4.6, 2.2 Hz), 4.12 (m, 1), 3.41–3.47 (m, 1), 3.07–3.16 (m, 1), 2.61–2.71 (m, 1), 2.52 (d, 2, J = 5.8 Hz), 2.43–2.47 (m, 1), 2.34 (d, 1, J = 3.8 Hz), 2.30 (d, 1, J = 5.7 Hz), 1.85–1.97 (m, 1), 0.87 (s, 9), 0.05 (s, 6); ^{13}C NMR δ ($CDCl_3$) 222.3, 134.0, 117.9, 67.8, 48.9, 43.7, 38.9, 37.9, 37.8, 31.3, 25.7, 18.0, −4.6, −4.8. Anal. Calcd for $C_{16}H_{26}O_2Si$: C, 69.01; H, 9.41. Found: C, 69.02; H, 9.52.

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Registry No. 1, 97253-59-3; 6, 97253-58-2; 7, 97253-60-6; 8, 97253-61-7; **9a**, 97253-62-8; **9b**, 97253-63-9; 8 (TBDMS), 97253-64-0; **10a**, 97253-66-2; **10b**, 97253-65-1; **11a**, 97253-67-3; **11b** (isomer 1), 97253-69-5; **11b** (isomer 2), 97334-51-5; **11c** (isomer 1), 97253-71-9; **11c** (isomer 2), 97335-05-2; **12a**, 97253-68-4; **12b** (isomer 1), 97253-70-8; **12b** (isomer 2), 97334-52-6; **12c** (isomer 1), 97253-72-0; **12c** (isomer 2), 97334-53-7; 1-iodo-3,4-pentadiene, 32442-48-1; 3,8-dihydroxy-5-methylenetricyclo[4.2.1.$0^{4,9}$]nonane, 97253-73-1; 3-ethoxycyclopent-2-en-1-one, 22627-70-9; 3,4-pentadienal, 4009-55-6.

Supplementary Material Available: Tables of atomic positional and crystal and data collection parameters (6 pages). Ordering information is given on any current masthead page.

Synthesis of Karahanaenone

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Karahanaenone (1) has been prepared from dehydrolinalyl acetate. Electrochemical epoxidation of dehydrolinalyl acetate provided the corresponding epoxide **6a** (75%) which was converted to keto acetate **7a** (82%) by an electrogenerated acid-catalyzed rearrangement. Hydrogenation followed by alkaline hydrolysis gave 6-hydroxy-2,6-dimethyl-7-octen-3-one (**7c**) (86%), which was subjected to thermal dehydration at 200 °C to give **1** (85%) via Claisen type rearrangement of the intermediate 2-methyl-2-ethenyl-5-propylidenetetrahydrofuran (**2**). An alternative route to **1** via thermolysis of the xanthate of 1-(5-ethenyl-5-methyl-2-tetrahydrofuranyl)-1-methylethanol (**10b**) is also described.

Karahanaenone (1) was isolated as a key flavor of a hop oil by Naya and Kotake[1] and has been synthesized by a number of investigators using cationic rearrangements[2,3] and cyclizations[4], a Diels–Alder approach,[5,6] and by a Cope [3, 3] sigmatropic rearrangement.[7,8] As far as a convenient precursor of **1** is concerned, tetrahydrofuran derivative **2** is promising because Claisen rearrangement of **2** would provide **1**. Demole demonstrated that the collidine-promoted dehydrobromination of **3b** leads to **1**,[9] most likely

Scheme I

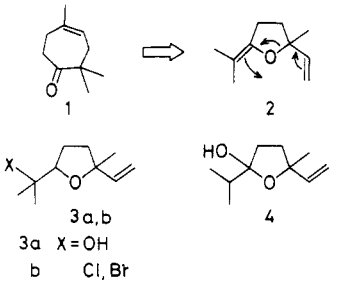

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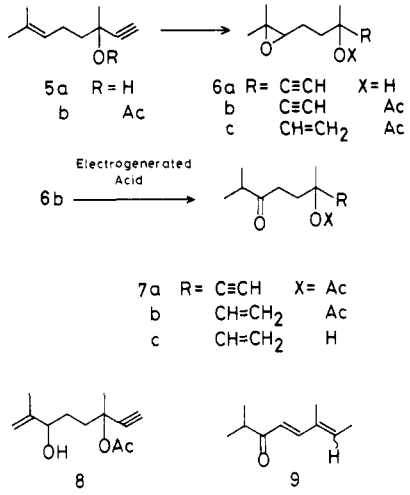
Table I. Acid-Catalyzed Ring Opening of Epoxide 6b[a]

entry	acid	solvent	temp, °C	reactn time	yield, % 7a	yield, % 8
1	EGA[b]	CH_2Cl_2–THF	rt[f]	5 min	82	10
2	BF_3–OEt_2	benzene	10	5 min	60	10
3	60% $HClO_4$[c]	CH_2Cl_2	rt	1 min	54	25
4	*p*-TsOH	CH_2Cl_2	rt	30 min	20	56
5	CF_3CO_2H	CH_2Cl_2	rt	2 h	3	15[d]
6	$MgBr_2$	benzene	reflux	20 h	35	19
7	HCO_2H	CH_2Cl_2	rt	10 h	0	0[e]

[a] Substrate (0.5 mmol) was employed in 5 mL of solvent in the presence of 0.5 mmol of acid. [b] EGA is electrogenerated acid. Substrate **6b** (2.42 mmol) in 8 mL of solvent was employed. [c] 60% aqueous perchloric acid. [d] 4-Acetoxy-1-(1-hydroxy-1-methylethyl)-4-methyl-5-hexynyl trifluoroacetate was produced as a major product in 57% yield. [e] Starting material (95%) was recovered. [f] rt = room temperature.

Scheme II



by way of **2**. However, the preparation of **3b** from linalool[9] by the action of NBS in methylene chloride is accompanied by the formation of 3-bromo-2,2,6-trimethyl-6-ethenyltetrahydropyran, which is difficult to separate from **3b**. On this basis, the question to be solved is how to get **2** by a simple and selective synthetic route. Herein we describe a selective preparation of alcohols **3a** and **4** and the efficient transformation of these alcohols to **1** via **2** (Scheme I).

Karahanaenone (1) via Hemiacetal 4. Dehydrolinalool (**5a**) and its acetate **5b** were chosen as starting materials. In order to avoid the acid-catalyzed rearrangement of **6a**, which leads partially to 6-ethynyl-3-epoxy-2,2,6-trimethyltetrahydropyran as a byproduct,[10] and to seek an economical process for a practical synthesis of **1**, an electrochemical epoxidation was examined instead of the conventional peracid oxidation (Scheme II). Bromide ion mediated electrooxidation[11] of **5a** in aqueous acetonitrile (H_2O:MeCN = 94:6) at room temperature with an undivided cell fitted with platinum electrodes afforded **6a** in 77% yield. Similarly, acetate **5b** was electroepoxidized in 75% yield in an MeCN–THF–H_2O–(Pt) system.

The conversion of the epoxide **6b** into ketone **7a** was next examined. A study of the action of a variety of acids on epoxide **6b** is shown in Table I. It can be seen that in most instances the yield of ketone **7a** is low and the ketone is accompanied by appreciable, sometimes predominant, quantities of the undesired allylic alcohol **8**.[12] Although the reaction of boron trifluoride etherate in benzene gave 60% of **7a** and only 10% of **8**, much better results were observed with an electrogenerated acid (EGA).[13] The electrolysis of **6b** in $ClCH_2CH_2Cl$–LiClO_4–Et_4NClO_4–(Pt) system under a constant current (0.03 F/mol) in a beaker-type undivided cell generates a very strong acid, presumably dry perchloric acid, which instantaneously converts the epoxide into the ketone **7a** via a perchlorate anion associated carbenium ion.[14] Likewise, **7b** was obtained in 75% yield by the EGA reaction of **6c**.

Hydrogenation with Pd/$BaSO_4$ provided **7b** in 97% yield, whose alkaline hydrolysis in methanol afforded **7c**[9] in 89% yield. The ^1H NMR spectrum reveals that the keto alcohol **7c** equilibriates with hemiacetal **4** in $CDCl_3$. The thermal dehydration of **7c** followed by [3, 3] sigmatropic rearrangement proceeds smoothly on simply heating at 200 °C for 1 h, affording **1** as a sole product in 85% yield. The IR and ^1H NMR spectra of **1** were consistent with those reported[1,5,9] earlier. On the other hand, thermolysis of **7b** gave **1** in only 44% yield, accompanied by 17% of **9**.[15] This fact suggests that hemiacetalization and the subsequent dehydration to **2** is essential for the selective formation of **1**.

Karahanaenone via Alcohol 3a. Regioselective tetrahydrofuran ring formation from **6a** proceeds smoothly by treatment with aqueous sodium hydroxide to give **10a** as a mixture of stereoisomers (57:43 by VPC) in 77% yield (Scheme III). Hydrogenation of **10a** with Pd/$BaSO_4$ gave **3a**[10] (93%), whose dehydration was examined in detail. The alcohol **3a** was found to be thermally stable under neutral conditions; **3a** was completely recovered on heating in a glass tube at 200 °C for 1.5 h. Upon treating **3a** with $KHSO_4$ at 200 °C, furan ring opening rather than the desired dehydration took place predominantly to give the dienone **9** (41%) along with a trace of **1** (0.7%). Acid-catalyzed dehydration of **3a** with *p*-toluenesulfonic acid in refluxing benzene also resulted in the preferential ring opening.[10a,15]

Conversion of the alcohol **3a** to the corresponding xanthate derivative **10b** (92%) and thermolysis of **10b** at 200 °C provided a mixture of **1** and **11** (**1**:**11** = 5:95) in 93% yield). The preferential formation of **11**[10b] over **1** is due to the lower acidity of methine proton of the tetrahydrofuran ring compared with that of the methyl proton and the statistically larger number of the abstractable protons

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Scheme III

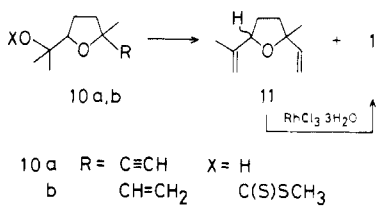

Table II. Thermolysis of the Xanthate 10b[a]

temp, °C	yield of 1 + 11, %	ratio 1:11
200	93	5:95
250	93	18:82
300	84	20:80
350	74	31:69
400	70	33:67

[a] 2 mmol of **10b** was dropped into a glass reaction tube settled in an air bath and products (1 and 11) distilled out were collected.

on methyl groups. Raising the thermolysis temperature led to the increase of the relative ratio of **1** and **11**, although the total yield of **1** and **11** decreased as shown in Table II. On heating **11** in a sealed tube at 300 °C for 1 h, **1** was only obtained in 17% yield. Therefore, the kinetically controlled product **11** isomerizes thermally, but slowly, to **2**, which undergoes spontaneously [3, 3] sigmatrophic rearrangement leading to **1**. Rhodium trichloride catalyzed isomerization[16] of the double bond of **11** to the tetrasubstituted double bond of **2** leads to **1** in 44% yield.

Experimental Section

Boiling points are uncorrected and shown as the air bath temperature. The ^1H NMR spectra were measured at 100 MHz in $CDCl_3$ with Me_4Si as an internal standard.

Electroepoxidation of 5b. 4,5-Epoxy-1-ethynyl-1,5-dimethylhexyl Acetate (6b). A mixture of **5b** (510 mg, 2.6 mmol) and NaBr (328 mg, 3.2 mmol) dissolved in MeCN (40 mL), THF (20 mL), and H_2O (16 mL) was electrolyzed by using two platinum foil electrodes (2 × 3 cm^2) in an undivided beaker-type cell (4 cm in diameter and 10 cm in height). A constant current (40 mA for 9 h, 5.1 F/mol) was passed at room temperature by using a DC power supply (Metronix Model 543B). After evaporation of MeCN and THF under a reduced pressure and addition of saturated NaCl, the organic substances were extracted with ether and the usual workup gave **6b** (413 mg, 75%): bp 108 °C (25 mm); IR (neat) 3260 (≡CH), 1740 (AcO), 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78 (t, J = 6 Hz, 1 H, CH), 2.60 (s, 1 H, ≡CH), 2.06 (s, 3 H, CH_3), 2.2–1.9 (m, 2 H, CH_2), 1.9–1.7 (m, 2 H, CH_2), 1.74 (s, 3H, CH_3), 1.35 (s, 3 H, CH_3), 1.32 (s, 3 H, CH_3). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.62. Found; C, 68.43; H, 8.61.

Electrolysis of 6b to 7a. 1-Ethynyl-1,5-dimethyl-4-oxohexyl Acetate (7a) and 1-Ethynyl-4-hydroxy-1,5-dimethyl-5-hexenyl Acetate (8). A mixture of **6b** (509 mg, 2.42 mmol), $LiClO_4$ (105 mg, 0.98 mmol), and Et_4NClO_4 (102 mg, 0.45 mmol) dissolved in $ClCH_2CH_2Cl$ (8 mL, distilled over P_2O_5) was electrolyzed by using platinum foil electrodes (2 × 1.5 cm^2) under a constant current (10 mA for 10 min, 0.03 F/mol) in an undivided beaker-type cell (3 cm in diameter and 10 cm in height). After addition of saturated $NaHCO_3$ and the usual workup, **7a** (417 mg, 82%) and **8** (51 mg, 10%) were obtained. **7a**: bp 80 °C (0.01 mm); IR (neat) 3250 (≡CH), 2090 (C≡C), 1740 (AcO), 1710 (C=O), 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (t, J = 7 Hz, 2H, CH_2), 2.60 (s, 1 H, CH), 2.4–1.9 (m, 3 H, CH, CH_2), 2.06 (s, 3 H, CH_3), 1.73 (s, 3 H, CH_3), 1.15 (d, J = 7 Hz, 6 H, CH_3). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.62. Found: C, 68.42; H, 8.54. **8**: bp 85 °C (0.01 mm); IR (neat) 3400 (OH), 3280 (≡CH), 2110 (C≡C), 1740 (AcO), 1640 (C≡C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.7–4.95 (m, 2 H, =CH_2), 3.98 (t, J = 6 Hz, 1 H, CH), 2.47 (s, 1 H, ≡CH), 1.97 (s, 3 H, AcO), 1.5–1.9 (m, 7 H, CH_2, CH_3), 1.63 (s, 3 H, CH_3). Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.62. Found: C, 68.64; H, 8.53.

Hydrogenation of 7a to 7b. 1-Ethenyl-1,5-dimethyl-4-oxohexyl Acetate (7b). A mixture of 5% Pd/$BaSO_4$ (12 mg) and quinoline (0.05 mL) was stirred for 30 min under H_2 and then **7a** (296 mg, 1.4 mmol) dissolved in distilled MeOH (3 mL) was added. The mixture was stirred under H_2 at room temperature until 31.5 mL of H_2 was absorbed. The usual workup gave **7b** (289 mg, 97%): bp 65 °C (0.01 mm); IR 3060 (=CH_2), 1730 (AcO), 1710 (C=O), 1635 (C=C), 1245 cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.97 (dd, J_1 = 18 Hz, J_2 = 11 Hz, 1 H, =CH), 6.30–6.08 (m, 2 H, =CH_2), 2.8–2.3 (m, 3 H, CH, CH_2), 2.2–1.9 (m, 2 H, CH_2), 2.03 (s, 3 H, CH_3), 1.57 (s, 3 H, CH_3), 1.11 (d, J = 7 Hz, 6 H, CH_3). Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.68; H, 9.57.

Hydrolysis of 7b to 7c. A mixture of **7b** (202 mg) and KOH (77 mg) dissolved in MeOH (5 mL) was stirred at room temperature for 5 h. The usual workup gave **7c**[9] (144 mg, 89%) as a colorless oil.

Karahanaenone (1) from 7c. The alcohol **7c** (228 mg, 1.34 mmol) was heated in a glass tube (0.7 cm in diameter and 20 cm in height) at 200 °C for 1 h. After chromatography (SiO_2, hexane/ether = 10/1) **1** was obtained as a colorless oil (173 mg, 85%), whose IR and ^1H NMR spectra were consistent with those reported.[1,5,9]

Thermolysis of 7b. In a glass tube settled in an air bath (200 °C) **7b** (116 mg) was heated for 30 min and the reaction mixture was chromatographed (SiO_2, hexane/ether = 5/1) to give a volatile compound (71 mg) which contained **1** (44%) and **9**[15] (17%).

1-(5-Ethynyl-5-methyl-2-tetrahydrofuranyl)-1-methylethanol (10a). A mixture of dehydrolinalool (**5a**) (456 mg, 3 mmol) and NaBr (510 mg, 5 mmol) dissolved in MeCN (4 mL)–H_2O (40 mL) was electrolyzed as described for **5b** (10 mA, 3.5 F/mol). After electrolysis, 10% NaOH (5 mL) was added to the mixture, which was stirred at room temperature for 1 h. Evaporation of MeCN under reduced pressure was followed by ether extraction, and chromatography (SiO_2, hexane/ether = 2/1) provided **10a** (388 mg, 77%) as a stereoisomeric mixture (57:43 by VPC NPGS, 3 mm i.d. × 3m, 120 °C): bp 57 °C (0.01 mm); IR (neat) 3420 (OH), 3280 (≡CH), 2090 (C≡C); ^1H NMR ($CDCl_3$) δ 4.1–3.7 (m, 1 H, CH), 2.50 and 2.43 (s, 1 H, ≡CH), 2.32 (OH), 2.5–1.7 (m, 4 H, CH_2), 1.56 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3), 1.13 (s, 3 H, CH_3). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.11; H, 9.31.

Hydrogenation of 10a. A mixture of 5% Pd/$BaSO_4$ (99 mg) and quinoline (0.1 mL) was stirred under H_2 for 30 min and then **10a** (3.7 g, 22 mmol) dissolved in distilled MeOH (5 mL) was added. The mixture was stirred at room temperature under H_2 until 470 mL of H_2 was absorbed and the usual workup gave **3a** (3.65 g, 92%).[10b]

***S*-Methyl-*O*-1-(5-ethenyl-5-methyl-2-tetrahydrofuranyl)-1-methylethyl Dithiocarbonate (10b).** Into a NaH (550 mg, 23 mmol) solution of dry THF (10 mL) was added dropwise **3a** (3.0 g, 17.6 mmol) dissolved in THF (10 mL) under N_2 on ice-cooling. After being stirred at room temperature for 1 h and cooled again in an ice bath, CS_2 (1.17 mL, 19.4 mmol) was added to the mixture which was further stirred for 20 min. Then MeI (1.21 mL, 19.4 mmol) was added on ice-cooling and the mixture was stirred for 20 min. After quenching with saturated NH_4Cl and evaporating the THF, the residue was extracted with ether. The usual workup and chromatography (SiO_2, hexane–ether = 20/1) gave **10b** as a yellow oil (4.2 g, 93%): bp 68 °C (0.005 mm); IR (neat) 3080 (=CH_2), 2980, 1240, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.2–5.6 (m, 1 H, =CH), 5.3–4.8 (m, 2 H, =CH_2), 4.3–3.9 (m, 1 H, CH), 2.45 (s, 3 H, CH_3), 2.1–1.7 (m, 4 H, CH_2), 1.73 (s, 6 H, CH_3), 1.31 and 1.27 (s, 3 H, CH_3). Anal. Calcd for $C_{12}H_{20}O_2S_2$: C, 55.34; H, 7.74. Found: C, 55.24; H, 7.92.

Thermolysis of 10b. A glass distilling tube (1 cm in diameter and 10 cm in height) fitted with a sidearm to distill out a distillate was heated at 200 °C in an air bath. Into the tube was added **10b** (1.04 g, 4.01 mmol) dropwise through a syringe. The collected distillate was chromatographed (SiO_2, hexane/ether = 10/1) to give a mixture of **1** and **11**[10b] (575 mg, 93%, 1:11 = 5:95 by VPC SE-30, 3 mm i.d. × 3 m).

Rhodium Chloride Catalyzed Isomerization of 11. A mixture of **11** (61 mg), $RhCl_3·3H_2O$ (7.7 mg), and Na_2CO_3 (6.8 mg) in a glass sealed tube was heated at 200 °C in an air bath for 10

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h, affording 1 (27 mg, 44%) after chromatography (SiO_2, hexane/ether = 10/1).

Thermolysis of 3a. A mixture of **3a** (200 mg, 1.2 mmol) and $KHSO_4$ (40 mg, 0.3 mmol) was heated at 200 °C in an air bath for 30 min and chromatographed (SiO_2, hexane/ether = 5/1) to give 103 mg of a volatile compound, which was found to contain **9** (41%) and **1** (trace) by VPC (NPGS, 3 mm i.d. × 3 m, 120 °C).

Registry No. **1**, 19822-67-4; **3a**, 60047-17-8; **5a**, 29171-20-8; **5b**, 29171-21-9; **6b**, 74026-67-8; **7a**, 87575-35-7; **7b**, 81893-37-0; **7c**, 81253-22-7; **8**, 94617-00-2; **9**, 91056-18-7; **10a**, 97277-67-3; **10b**, 97277-68-4; **11**, 13679-86-2.

L-*threo*- and L-*erythro*-3-Fluoroglutamic Acids. Synthesis by Fluorodehydroxylation and Enzymatic Resolution

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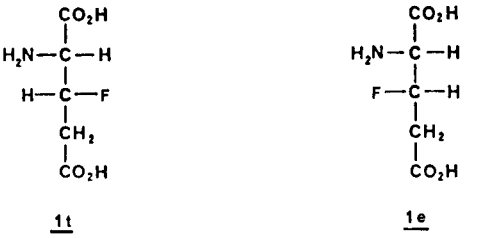
threo- and *erythro*-3-fluoroglutamic acids were prepared by fluorodehydroxylation of *N*-acetyl-3-hydroxyglutamic acids according to Kollonitsch. Following ion exchange column separation of the diastereoisomers, enzymatic deacylation by acylase I afforded optically pure L-isomers of the 3-fluoroglutamic acid. Assignment of structure was achieved by correlation with *cis*- and *trans*-3-fluoropyroglutamic acids. The results indicate predominant inversion of configuration during the fluorodehydroxylation reaction.

Threo and erythro isomers of L-3-fluoroglutamic acid are two potential k_{cat} inhibitors of pyridoxal phosphate dependent enzymes that use glutamic acid as substrate: transaminases, glutamate racemase, and glutamate decarboxylase.[1] However, these acids have not yet been described, even as racemates.

Among the various methods available for synthesis of 3-fluoro amino acids, such as photofluoration,[2] hydroxyl group substitution,[3,4] or aziridine ring opening,[5] we selected the substitution of the hydroxyl group by sulfur tetrafluoride in liquid hydrogen fluoride, a mild and specific method that has been developed by Kollonitsch and coworkers.[6,7]

We report here the synthesis of 3-fluoroglutamic acids (**1e** and **1t**) by fluorodehydroxylation of 3-hydroxyglutamic acid derivatives, the separation of the threo and erythro isomers, and their enzymatic resolution (Chart I).

Chart I. L-*threo*- and L-*erythro*-3-Fluoroglutamic Acids

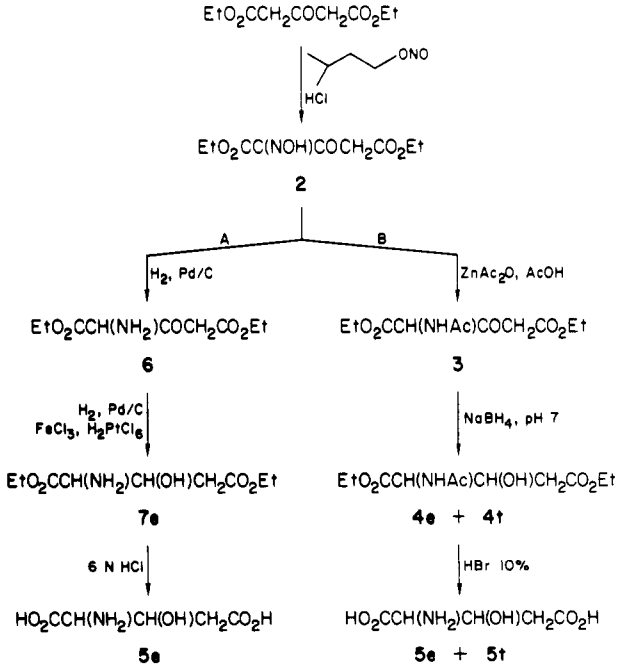


1t **1e**

Results and Discussion

D,L-*erythro*-3-Hydroxyglutamic acid (**5e**) was specifically prepared according to Harington and Randall[8] from diethyl acetonedicarboxylate by catalytic reduction of intermediate diethyl α-aminoacetonedicarboxylate (**6**) (Scheme I, pathway A) whereas a mixture of D,L-*threo*- and -*erythro*-3-hydroxyglutamic acid (**5t** + **5e**) was obtained by reducing diethyl α-acetamidoacetonedicarboxylate (**3**)[9] with sodium borohydride in medium buffered at pH 7 (Scheme I, pathway B) in order to avoid saponification, which we observed, even in ethanol. The high stereoselectivity observed (path A) can be interpreted easily on the basis of Cram's model,[10] if it is assumed that during the catalytic reduction, the reducing agent chelates the carbonyl and the free amino groups and delivers hydrogen to the less hindered face of the chelate (Scheme II).

Scheme I. Syntheses of D,L-*threo*- and -*erythro*-3-Hydroxyglutamic Acids



Hydrolysis of a mixture of diethyl *N*-acetyl-3-hydroxyglutamates (**4e** + **4t**) afforded *threo*- and *erythro*-3-

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