Registry No. L-Tryptophan ethyl ester *p*-toluenesulfonate, 71260-63-4; L-tryptophan, 73-22-3; *p*-toluenesulfonyl chloride, 98-59-9; L-tryptophan benzyl ester hydrochloride, 35858-81-2; glycine ethyl ester hydrochloride, 623-33-6; L-leucine ethyl ester *p*-toluenesulfonate, 4783-17-9; L-methionine ethyl ester *p*-toluenesulfonate, 5074-32-8; L-tyrosine ethyl ester *p*-toluenesulfonate, 5002-67-5; glycine, 56-40-6; L-leucine, 61-90-5; L-methionine, 63-68-3; L-tyrosine, 60-18-4; glycine benzyl ester *p*-toluenesulfonate, 1738-76-7; L-leucine benzyl ester *p*-toluenesulfonate, 1738-77-8; L-tyrosine benzyl ester *p*-toluenesulfonate, 53587-11-4.

New Synthesis of *trans,trans*-2-[6-(Ethoxycarbonyl)hexyl]-3-(ethoxycarbonyl)-4-hydroxycyclopentanone, a Useful Intermediate for the Synthesis of Prostaglandins

Roberto Danieli, Giorgio Martelli, Giuseppe Spunta, and Sandra Rossini

Istituto dei Composti del Carbonio contenenti eteroatomi e loro applicazioni, Consiglio Nazionale delle Ricerche, 40064 Ozzano Emilia, Italy

Gianfranco Cainelli* and Mauro Panunzio

Istituto Chimico "G. Ciamician", Università di Bologna, 40126 Bologna, Italy

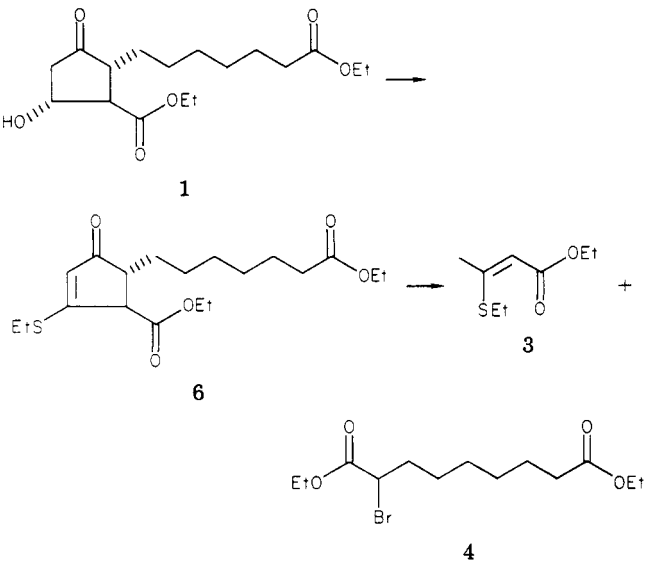
Received April 14, 1982

Several approaches to prostanoid synthesis involving formation of the cyclopentane ring from acyclic precursors have been reported.[1] In this paper we describe a new approach of this kind which involves the regiospecific base-induced formation of a monothioenol ether of a 1,3-cyclopentanedione derivative starting from easily available compounds. The retrosynthetic analysis depicted in Scheme I illustrates the key steps of our synthesis.

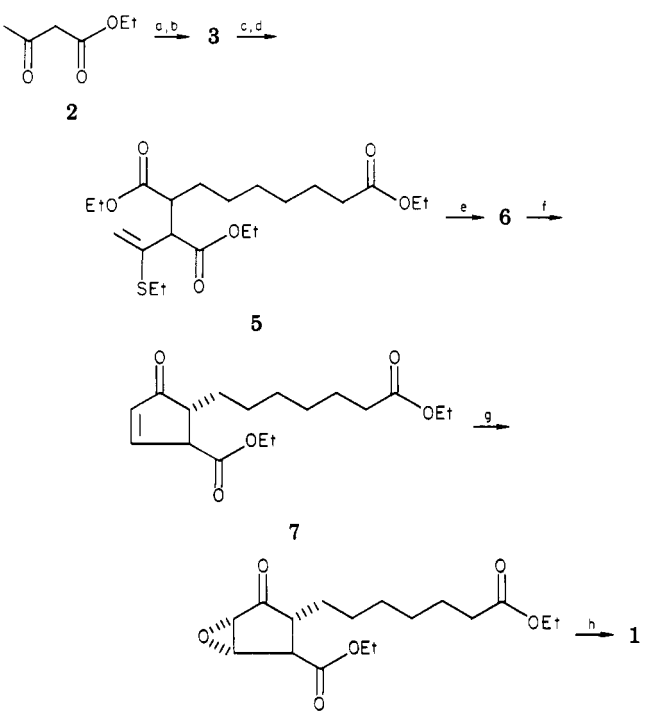
The introduction of the two oxygen functionalities with the natural configuration in the cyclopentane ring via a suitable 1,3-diketone derivative has already been explored.[2] The main drawback of this early synthesis lies, however, in its almost complete lack of regiospecificity in the crucial reductive step and in the consequent low overall yields. In our approach the thioenol ether **6**, which constitutes the only product of cyclization of the acyclic precursor **5** (Scheme II) can be easily desulfurated to the corresponding cyclopentenone. The target molecule (**1**), which may be obtained from the cyclopentenone **7** by standard methods, constitutes an interesting intermediate for the synthesis of PG_1 derivatives and has been used, for instance, in the Ciba-Geigy PGE_1 total synthesis.[3]

Ethyl acetoacetate when treated with 2 equiv of ethanethiol and 1 equiv of trimethylchlorsilane[4] at room temperature gives the corresponding thioketal in quantitative yield. Pyrolysis of this compound in the presence of potassium hydrogen sulfate as an acidic catalyst followed by distillation led to the thioenol ether **3** quantitatively[5] (Scheme II). Metalation of **3** with LDA in THF at −78 °C

Scheme I



Scheme II[a]



[a] a, $EtSH/(CH_3)_3SiCl/CHCl_3$; b, $KHSO_4$; c, LDA/HMPTA/THF; d, $EtOOC(CH_2)_6CH(Br)COOEt$; e, NaH/Me_2SO; f, Raney nickel/acetone; g, $H_2O_2/OH^-/MeOH$; h, $Al/Hg/THF/H_2O$.

in the presence of HMPA[6] followed by alkylation of the so-obtained anionic species with diethyl 2-bromononanedioate[7] affords in good yield the α-alkylation product **5**. Treatment of **5** with sodium hydride in Me_2SO gives the cyclic thioenol ether **6** in 62% yield. Finally, carefully controlled desulfurization of **4** with Raney nickel[8] in refluxing acetone led to the corresponding cyclopentenone **7** as a single isomer. Concerning the stereochemistry of the two side chains of **7**, the more stable trans configura-

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tion may be inferred from its formation which goes through a cyclization under equilibrating conditions. In fact, it is known that prostaglandin precursors bearing activating groups like formyl[9] or alkoxycarbonyl groups[3] directly linked to the cyclopentane ring easily undergo base- or acid-induced equilibration to the trans isomer. Moreover, the trans configuration of the two protons at C(8) and C(12) has been demonstrated by ^{1}H NMR analysis using double-irradiation technique. In fact, the value of the coupling constant for the C(8) and C(12) Hs is 2.7 Hz, consistent with a trans configuration of the two interacting protons on the five-membered ring.[10]

The cyclopentenone derivative **7** was then converted into the title compound **1** via epoxidation and reductive opening of the intermediate keto epoxide **8** by following the well-established Corey procedure (H_2O_2–OH^- and then Al/Hg).[11] It is known that the stereochemistry of the epoxidation of PGA derivatives under similar conditions depends upon the structure of the side chains and the reaction temperature. Best results (94% α, 6% β) have been obtained at −45 °C for compounds bearing a large protecting group (e.g., tri-*p*-xylyl group) attached at the 15-hydroxyl group.[11,12] In our case, where the C(8) side chain is substituted by an ester group, the epoxidation under the conditions reported above led to an α/β isomer ratio of about 85:15 as estimated by NMR spectroscopy and silica gel chromatography. The stereochemistry of the keto epoxide with the α configuration was established by ^{1}H NMR spectroscopy by using double-irradiation techniques. The C(11) proton appears as a doublet which, after irradiation of the C(8) proton, is converted to a singlet. The coupling constant value of the C(11) H and C(12) H is therefore near zero, according to a trans configuration of the two protons. In fact, the inspection of the Dreiding model of the α isomer shows an angle of about 90°, consistent with experimental data. Since the following reduction of **8** with aluminum amalgam in THF/H_2O at room temperature occurs with retention of the configuration of the hydroxyl group formed, the stereochemistry of the final product, **1**, is also established.

Owing to the great difficulty in separation of the epimeric mixture of keto epoxides, **1** may be more conveniently prepared by aluminum amalgam reduction of the epimeric mixture followed by chromatography of the keto alcohols obtained.

Work is now in progress to further develop this synthetic approach.

Experimental Section

General Methods. Infrared spectra (IR) were recorded as Nujol mulls on a Perkin-Elmer 710 B spectrometer and the frequencies are given in reciprocal centimeters. ^{1}H NMR spectra was determined in $CDCl_3$ or C_6D_6 solutions on a Varian FT 80 spectrometer, and the chemical shifts are expressed as δ values in parts per million from Me_4Si as an internal standard. Mass spectra were taken on a Varian Mat III instrument (70 eV). Thin-layer chromatography (TLC) was performed on silica gel sheets (1B2F Baker) and column chromatography on a Chromatospac Prep 10 (Jobin-Ivon instrument) with silica gel (H 60 Merk).

Materials. Tetrahydrofuran (THF) was obtained anhydrous and oxygen free by distillation over sodium benzophenone ketyl under argon. Hexamethylphosphoric triamide (HMPTA) was distilled over calcium hydride under reduced pressure. Diisopropylamine was refluxed over molecular sieves (Type 4A, Fluka) and distilled at atmospheric pressure. *n*-Butyllithium (15% solution in hexane) was purchased from Aldrich. Acetone (Baker analyzed reagent grade) was refluxed over potassium permanganate and distilled at atmospheric pressure. Nonanedioic acid and ethanethiol were purchased from Aldrich and used without further purification.

Ethyl 3-(Ethylthio)-2-butenoate (3). To a vigorously stirred solution of ethyl acetoacetate (13 g, 0.1 mol) in $CHCl_3$ (100 mL) were added ethanethiol (12.4 g, 0.2 mol) and trimethyl chlorosilane (12.6 g, 0.11 mol). The internal temperature was kept between 40 and 50 °C by occasional cooling. Stirring was continued overnight, and then the reaction mixture was poured into 100 mL of ice–water. The organic layer was washed with $NaHCO_3$ 5% solution and then dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude dithioketal was mixed with $KHSO_4$ (30 g) in a 250-mL flask connected to a 40-cm Vigreux column. Careful distillation afforded the product, bp 62 °C (0.5 mm). The product was obtained as a light yellow oil: 15 g (86%); IR (neat) 1720, 1600; NMR 5.4 (s, 1 H), 4.06 (q, 2 H), 2.8 (q, 2 H), 2.33 (s, 3 H), 1.33 (t, 3 H), 1.27 (t, 3 H); MS, *m/e* 174 (M). Anal. Calcd for $C_8H_{14}O_2S$: C, 55.14; H, 8.10; S, 18.14. Found: C, 55.36; H, 8.13; S, 18.19.

Diethyl 2-[1-(Ethylthio)vinyl]-3-(ethoxycarbonyl)decanedioate (5). *n*-Butyllithium (1.4 M, 24 mL, 33 mmol) was added at 0 °C with stirring under argon to a solution of diisopropylamine (4.6 mL, 33 mmol) in THF (20 mL). After 30 min, HMPTA (6 g, 33 mmol) was added at −78 °C, followed by ethyl 3-(ethylthio)-2-butenoate (5.8 g, 33 mmol). After 10 min, diethyl nonanedioate (10.8 g, 33 mmol) was added. The reaction mixture was stirred for 3 h at −78 °C, allowed to reach room temperature, and quenched with aqueous ammonium chloride. The organic phase was extracted with ether (200 mL), washed with brine, dried over Na_2SO_4, and evaporated under reduced pressure. The crude reaction product was distilled under vacuum to give the target compound: bp 202–205 °C (0.3 mm); 10 g (72%); IR (neat) 1740 (s), 1600 (s); NMR 5.26 (s, 1 H), 4.83 (s, 1 H), 4.13 (m, 6 H), 3.3 (d, 1, H, J = 10 Hz); 3.1–2.8 (m, 1 H), 2.66 (q, 2 H), 2.2 (t, 2 H), 1.86–1.1 (m, 22 H); MS, *m/e* 416 (M). Anal. Calcd for $C_{21}H_{36}O_6S$: C, 60.53; H, 8.54; S, 7.68. Found: C, 60.54; H, 8.57; S, 7.70.

***trans*-2-[6-(Ethoxycarbonyl)hexyl]-3-(ethoxycarbonyl)-4-(ethylthio)cyclopent-4-en-1-one (6).** To sodium hydride (50% mineral oil suspension, 3 g, 0.12 mol) in anhydrous Me_2SO was added the compound **5** (10 g, 0.024 mol) at 0 °C with stirring under argon at rate sufficient to promote gentle evolution of hydrogen. The resulting deep brown suspension was allowed to reach room temperature and was stirred until no more starting material was detectable in TLC. The crude material from the cyclization reaction was stirred at 0 °C with 2 N HCl (100 mL). The aqueous mixture was extracted with ether, and the organic extracts were washed with water and brine and dried over Na_2SO_4. The solution was filtered and the solvent removed. The crude product was separated by medium-pressure column chromatography (70/30 hexane/ether). The target compound (**6**) was isolated as a clear pale yellow oil: 5.5 g (62%); IR (neat) 1750 (s), 1700 (s), 1550 (s); NMR 5.9 (br s, 1 H), 4.13 (m, 4 H), 3.35 (d, 1 H, J = 3 Hz, C_{12} H), 2.95 (q, 4 H), 2.63 (m, 1 H, C_8 H), 2.2 (t, 2 H, C_2 H), 2–1.1 (m, 19 H); MS, *m/e* 370 (M). Anal. Calcd for $C_{19}H_{30}O_5S$: C, 62.27; H, 8.16. Found: C, 62.01; H, 8.16; S, 8.65.

***trans*-2-[6-(Ethoxycarbonyl)hexyl]-3-(ethoxycarbonyl)-cyclopent-4-en-1-one (7).** Raney nickel (W-2, 10 g) was washed with distilled, dry acetone (100 mL) under an inert atmosphere. Most of the acetone was removed via syringe. Acetone (100 mL) was added once more and the suspension refluxed for 3 h. A solution of **6** (0.9 g, 2.4 mmol) in acetone was added, and the mixture was heated at reflux overnight, cooled, and filtered on Celite. The solid phase was washed with acetone. Most of the solvent was removed in vacuo. The mixture was taken up in ether (200 mL) and washed with water and brine. The organic phase was dried over Na_2SO_4 and filtered, and the solvent was concentrated on a rotary evaporator. The title compound (0.377 g, 50%) was separated by medium-pressure chromatography (hexane/ethyl acetate, 1:1), the rest being starting material: IR (neat) 1750–1700 (s, br), 1600 (s); NMR ($CDCl_3$) 7.61 (dd, 1 H, $J_{10,11}$ = 6.0 Hz, $J_{11,12}$ = 2.3 Hz, C_{11} H), 6.25 (dd, 1 H, $J_{10,11}$ = 6.0 Hz, $J_{10,12}$

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= 2.3 Hz C_{10} H), 4.15 (dq, 4 H), 3.52 (m, 1 H, $J_{12,8}$ = 2.7 Hz, $J_{12,11}$ = 2.7 Hz, $J_{12,10}$ = 2.3 Hz C_{12} H), 2.68 (m, 1 H, C_8 H), 2.28 (t, 2 H, C_2 H), 2-1.1 (m 16 H); MS, *m/e* 310 (M), 265 (M - OCH_2CH_3). Anal. Calcd for $C_{17}H_{26}O_5$: C, 67.01; H, 8.40. Found: C, 66.74; H, 8.43.

2,3-*trans*:3,4-*trans*:4,5-*cis*-2-[6-(Ethoxycarbonyl)hexyl]-3-(ethoxycarbonyl)-4,5-epoxycyclopentanone (8). To a solution of **7** (1.55 g, 5 mmol) dissolved in 100 mL of methanol at -45 °C were added 30 mL of 2 N NaOH and 10 mL (40 mmol) of 30% H_2O_2. After the mixture was stirred for 12 h at -45 °C, 30 mL of 2 N NaOH and 10 mL of 30% H_2O_2 were added, and then the solution was stirred for 24 h at -45 °C. The solution was added to 100 mL of saturated ammonium chloride, and the methanol was evaporated under reduced pressure. The aqueous residue was extracted with methylene chloride. The organic layers were washed with saturated sodium chloride solution. After the organic layers were dried and the solvent evaporated, the epoxide (1.3 g, 79%) was obtained as a mixture of α and β epimeric isomers (85/15). A portion of the mixture (0.100 g) was purified by using preparative TLC with 1:3 ethyl acetate-hexane as the solvent to give pure α isomer (0.05 g). The spectral data were as follows: IR (neat) 1740; NMR 4.15 (m, 5 H, 2 CH_2, C_{10} H), 3.4 (m, 1 H, C_{11} H), 3.1 (d, 1 H, C_{12} H, $J_{8,12}$ = 3 Hz), 2.5 (m, 1 H, C_8 H), 2.2 (t, 2 H), 1.9-1 (m, 16 H); MS, *m/e* 326 (M), 281 (M - OCH_2CH_3). Anal. Calcd for $C_{17}H_{26}O_6$: C, 61.76; H, 8.09. Found: C, 62.00; H, 8.06.

***trans,trans*-2-[6-(Ethoxycarbonyl)hexyl]-3-(ethoxycarbonyl)-4-hydroxycyclopentanone (1).** Aluminum amalgam (12.5 g of Al) prepared according to Corey[11] was added to a solution of the epimeric mixture of the epoxides (0.7 g, 2.15 mmol) in THF-H_2O (2:1, 100 mL), and the mixture was stirred at room temperature for 1 h and then filtered. The solid phase was washed with THF. Most of the solvent was removed in vacuo, ethyl acetate (50 mL) was added, the aqueous phase was separated, and the organic phase was dried (Na_2SO_4) and concentrated in vacuo at room temperature to give **1** (0.510 g, 72%) with a good purity degree after chromatography on a short column on silica gel (ethyl acetate-methylene chloride, 1:4): IR (neat) 3500 (w), 1736 (s); NMR 4.15 (m, 5 H, 2 CH_2, C_{11} H), 3.75 (s, 1 H, OH), 2.8 (m, 1 H, C_8 H), 2.6-2.1 (m, 5 H), 1.8-1 (m, 16 H); MS, *m/e* 328 (M), 310 (M - H_2O), 283 (M - OCH_2CH_3). Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.27; H, 8.60. Found: C, 62.19; H, 8.63.

Registry No. **1**, 83693-21-4; **2**, 141-97-9; **3**, 83693-22-5; **4**, 760-95-2; **5**, 83693-23-6; **6**, 83693-24-7; **7**, 83693-25-8; **8** (isomer 1), 83693-26-9; **8** (isomer 2), 83730-10-3.

Canin from *Artemisia cana* Pursh ssp. *cana*. Crystal Structure and Identification of Chrysartemin A

Rick G. Kelsey and Fred Shafizadeh

Wood Chemistry Laboratory, Department of Chemistry, University of Montana, Missoula, Montana 59812

James A. Campbell and Arnold C. Craig

Department of Chemistry, Montana State University, Bozeman, Montana 59717

Charles F. Campana

Nicolet XRD Corporation, Cupertino, California 95014

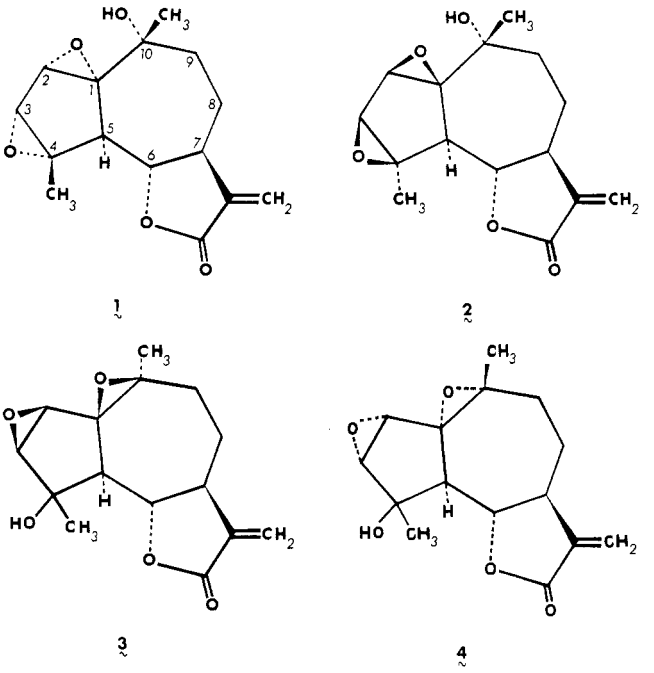
Rhoda E. R. Craig*

Department of Chemistry, Kalamazoo College, Kalamazoo, Michigan 49007

Received June 17, 1982

A number of stereoisomeric guaianolides having the molecular formula $C_{15}H_{18}O_5$ have been reported in the literature. Canin, originally isolated from *Artemisia cana* Pursh ssp. *cana* by Lee,[1a] is widely distributed in different species of this genus:[2] *Artemisia caucasica* Willd.,[3] *Artemisia rutifolia* Steph. et Spring.,[4] *Artemisia tripartita* Rydb. ssp. *tripartita*,[5] and *Artemisia frigida* Willd.[6] Artecanin, sometimes occurring with canin, has been isolated from *A. cana* ssp. *cana*[1] and *Artemisia ludoviciana* var. *ludoviciana* Nutt.[7] Chrysartemin A and B were both present in *Chrysanthemum parthenium* (L.) Sch. Bip.[8] whereas only the former occurred in *Artemisia klotzchiana* Bess.[8] and *Artemisia mexicana* Willd.[8] Chrysartemin B is a constituent of *Handelia trichophylla*[9] and *Chrysanthemum morifolium* Ram.[10]

The original structure of canin (1) was reported in 1969[1a] and was subsequently revised to **2**[1b] in 1975 on the basis



of chemical and spectral properties. At this later date artecanin was assigned structure **1**.[1b] In 1970 chrysartemin A and B were isolated and assigned structures **3** and **4**, respectively. As a consequence of a single X-ray crystallographic analysis in 1977, the structure of chrysartemin B was changed to **2**.[10] Subsequent spectral comparison confirmed the identity of chrysartemin B (**2**) as artecanin,[7] necessitating the revision of canin (recently equated with chrysartemin A[6]) back to the original structure of Lee (**1**).[1a]

Hence, a single X-ray crystallographic analysis of canin was undertaken for the following reasons: (1) to unambiguously establish the structure and stereochemistry of canin and verify its relationship to artecanin, chrysartemin A, and chrysartemin B (this information is part of a continuing effort to clarify duplication of literature compounds isolated from different natural sources)[11] and (2) to study

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