J = 10.5 and 1.5 Hz, C-21 H), 5.32 (1 H, dd, J = 17 and 1.5 Hz, C-21 H), 6.11 (1 H, dd, J = 17 and 10.5 Hz, C-20 H), 6.67–7.30 (3 H, m, aromatic protons).

Anal. Calcd for $C_{21}H_{28}O_2$ (312.4): C, 80.73; H, 9.03. Found: C, 80.80; H, 9.06.

Further elution with benzene-ethyl acetate (99:1) gave the alcohol **1a** (73 mg, 23%).

Treatment of **4a** under the same conditions for 5 h afforded by elution with benzene–ethyl acetate (99:1) **1b** and **1a** (90 mg, relative yields 21 and 8%). Elution with benzene–ethyl acetate (9:1) gave the starting sulfoxide **4a** (286 mg, 68%).

Repetition of the procedure at room temperature for 3 weeks gave **1b** and **1a** in 11 and 3% yields, respectively, and unchanged **4a** (86%).

The preparation and rearrangement–cleavage of **4a** were repeated as described above, except that the second step was carried out directly on the residue of the THF evaporation to give **1b** and **1a** in 64 and 24% yields, respectively.

(*E*)-3-Methoxy-(*R*)-21-(phenylsulfinyl)-19-norpregna-1,3,5(10),17(20)-tetraene (4b) was prepared in the same manner as **4a** from **1b** in 55% yield after column chromatography: mp 100–101.5 °C (from acetone–hexane); $[\alpha]_D$ +10°; ^{1}H NMR δ 0.70 (3 H, s, 13-Me), 3.54 (2 H, d, J = 8 Hz, C-21 H_2), 3.76 (3 H, s,3-OMe), 5.00 (1 H, tt, J = 8 and 2 Hz, C-20 H), 6.63–7.73 (3 H, m, aromatic protons); ^{1} H NMR (C_6D_6) δ 0.57 (13-Me), 3.18 and 3.37 (AB of a ABX, 8 lines, J = 12 and 8 Hz, C-21 H_2), 3.44 (3-OMe), 4.98 (tt, J = 8 and 2 Hz, C-20 H), 6.67–7.63 (aromatic protons).

Anal. Calcd for $C_{27}H_{32}O_2S$ (420.7): C, 77.10; H, 7.67; S, 7.62. Found: C, 77.02; H, 7.82; S, 7.57.

Rearrangement–cleavage of 4b in methanol–trimethyl phosphite under the same conditions as for **4a** resulted in the formation of **1b** in 63% yield after 5 h at reflux. Only trace amounts (~1%) of **1a** were observed. The recovered sulfoxide (27%) consisted of a mixture of **4b** and **4a** in a 63:36 ratio.

Repetition of the procedure at room temperature for 3 weeks again afforded almost exclusively **1b** (47%), together with a 82:18 mixture of **4b** and **4a** (47%).

Equilibration of the sulfoxides 4a and 4b in C_6D_6 at 65 °C in an NMR tube was followed by measuring the relative intensities of the signals due to 13-Me protons at intervals. Equilibration to a 1:1 mixture was complete after 4 h with a first-order rate constant (k) of 1.64×10^{-4} s^{-1}.[14] At 80 °C, the equilibration was complete within 1 h. Equilibration in refluxing methanol was monitored by withdrawing samples at intervals and substituting C_6D_6 for methanol. A mixture containing 74% of the starting sulfoxide was obtained after 5 h.

(*E*)-3-Methoxy-21-(phenylsulfonyl)-19-norpregna-1,3,5-(10),17(20)-tetraene (4c). A solution of a 1:1 mixture of **4a** and **4b** (0.42 g, 1 mmol) and *m*-chloroperbenzoic acid (90%, 0.21 g, 1.1 mmol) in ether (20 mL) was stirred at room temperature for 1 h. The ether was evaporated, and the residue was chromatographed on a column of deactivated (grade IV) Woelm basic alumina (13 g). Elution with CH_2Cl_2 gave **4c** (380 mg, 87%): mp 130.5–132 °C (from methanol); $[\alpha]_D$ +30°; ^{1}H NMR δ 0.67 (3 H, s, 13-Me), 3.77 (3 H, s, 3-OMe), 3.78 (2 H, d, J = 8 Hz, C-21 H_2), 5.10 (1 H, tt, J = 8 and 2 Hz, C-20 H), 6.62–7.99 (3 H, m, aromatic protons).

Anal. Calcd for $C_{27}H_{32}O_3S$ (436.6): C, 74.27; H, 7.39; S, 7.34. Found: C, 74.27; H, 7.40; S, 7.30.

6β-Methoxy-3α,5-cyclo-5,17α-pregn-20-en-17-ol (2a). Treatment of a solution of 6β-methoxy-3α,5-cyclo-5α-androstan-17-one[15] (2.06 g, 6.82 mmol) in 20 mL of THF with 2 M vinyllithium in THF (11 mL, 22 mmol) at room temperature for 0.5 h using experimental conditions similar to those described by Olsen and Babler[12] afforded crude **2a**, which was freed from hydrocarbon impurities by chromatography on silica gel (150 g). Elution with benzene–ethyl acetate (97:3) and crystallization from hexane afforded 0.97 g (43%) of pure **2a**: mp 126–127 °C; $[\alpha]_D$ +35°; ^{1}H NMR δ 0.95 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 2.75 (1 H, m, 6α-H), 3.33 (3 H, s, 6β-OMe), 5.12 (1 H, dd, J = 10.5 and 1.5 Hz, C-21 H), 5.16 (1 H, dd, J = 17 and 1.5 Hz, C-21 H), 6.08 (1 H, dd, J = 17 and 10.5 Hz, C-20 H).

Anal. Calcd for $C_{22}H_{34}O_2$ (330.5): C, 79.95; H, 10.37. Found: C, 79.79; H, 10.50.

3,3-(Ethylenedioxy)-17α-pregna-5,20-dien-17-ol (3a) was prepared in the same manner as **2a** from 3,3-(ethylenedioxy)-androst-5-en-17-one[16] and crystallized from acetone–hexane: mp 184.5–186 °C; $[\alpha]_D$ –55°; ^{1}H NMR δ 0.91 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 3.94 (4 H, s, 3-ketal), 5.11 (1 H, dd, J = 10.5 and 1.5 Hz, C-21 H), 5.15 (1 H, dd, J = 17 and 1.5 Hz, C-21 H), 5.35 (1 H, m, C-6 H), 6.07 (1 H, dd, 17 and 10.5 Hz, C-20 H).

Anal. Calcd for $C_{23}H_{34}O_3$ (358.5): C, 77.05; H, 9.56. Found: C, 77.07; H, 9.50.

Typical "One-Pot" Epimerization Procedure of Alcohols 1a, 2a, and 3a. Compound **1a** (0.31 g, 1 mmol) was sequentially treated with *n*-butyllithium and phenylsulfenyl chloride as previously described. THF was evaporated, and the residue was refluxed in benzene (5 mL) for 1 h. The solvent was removed *in vacuo* and the residue was refluxed in methanol (4 mL) containing 1.2 mL (10 mmol) of trimethyl phosphite for 40 h. The mixture was diluted with water and extracted with ether. The extract was washed with water and dried (Na_2SO_4). The residue (0.35 g) was chromatographed on silica gel (10 g). Elution with benzene–ethyl acetate (99:1) afforded 237 mg (76%) of **1b**, followed by 37 mg (12%) of **1a**.

Repetition of this procedure on **2a** (0.33 g, 1 mmol) gave by elution with benzene–ethyl acetate (98:2) 241 mg (73%) of **6β-methoxy-3α,5-cyclo-5α,17β-pregn-20-en-17-ol (2b)**: mp 143–144 °C (from hexane); $[\alpha]_D$ +6°; ^{1}H NMR δ 0.74 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 2.77 (1 H, m, 6α-H), 3.34 (3 H, s, 6β-OMe), 5.13 (1 H, dd, J = 10.5 and 1.5 Hz, C-21 H), 5.29 (1 H, dd, J = 17 and 1.5 Hz, C-21 H), 6.08 (1 H, dd, J = 17 and 10.5 Hz, C-20 H).

Anal. Cald for $C_{22}H_{34}O_2$ (330.5): C, 79.95; H, 10.37. Found: C, 79.90; H, 10.39.

Further elution with the same eluant afforded 40 mg (12%) of **2a**.

In a similar fashion, **3a** (0.54 g, 1.5 mmol) afforded a residue of 0.64 g, which was rapidly chromatographed on silica gel (16 g). Elution with benzene–ethyl acetate (97:3) gave **3a** (91 mg, 17%), followed by **3,3-(ethylenedioxy)-17β-pregna-5,20-dien-17-ol (3b**; 377 mg, 70%): mp 170.5–172 °C (from methanol); $[\alpha]_D$ –85°; ^{1}H NMR δ 0.70 (3 H, s, 13-Me), 1.02 (3 H, s, 10-Me), 3.93 (4 H, s, 3-ketal), 5.12 (1 H, dd, J = 10.5 and 1.5 Hz, C-21 H), 5.27 (1 H, dd, J = 17 and 1.5 Hz, C-21 H), 5.36 (1 H, m, C-6 H), 6.07 (1 H, dd, J = 17 and 10.5 Hz, C-20 H).

Anal. Calcd for $C_{23}H_{34}O_3$ (358.5): C, 77.05; H, 9.56. Found: C, 77.12; H, 9.54.

Registry No. **1a**, 6885-48-9; **1b**, 83915-64-4; **2a**, 83845-62-9; **2b**, 83915-65-5; **3a**, 83845-63-0; **3b**, 83915-66-6; **4a**, 83845-64-1; **4b**, 83845-65-2; **4c**, 83845-66-3; 6β-methoxy-3α,5-cyclo-5α-androst-17-one, 14425-92-4; 3,3-(ethylenedioxy)androst-5-en-17-one, 3754-63-0; phenylsulfenyl chloride, 931-59-9; vinyllithium, 917-57-7.

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A Simple and Convenient Method for Esterification of Tryptophan and Other Amino Acids

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Esterification of amino acids is very important in peptide synthesis.[1,2] In most cases, the esters can be prepared by acid-catalyzed esterification.[1-8] However, acid-sensitive

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Table I. Amino Acid Ethyl Ester *p*-Toluenesulfonates

amino acid	yield, %	mp, °C obsd	mp, °C lit.[a]	$[\alpha]_D$, deg (*c*, DMF, t, °C) obsd	$[\alpha]_D$, deg (*c*, DMF, t, °C) lit.[a]
Gly	93[b]				
L-Leu	97	155	153-154	+7.5 (2, 22)	+6.0 (4, 18)
L-Met	97	127	128-129	+8.5 (2, 22)	+6.9 (4, 22)
L-Tyr	95	195	190-191	+12.4 (2, 22)	+12.3 (4, 21)
L-Trp	90	143	139-140	+16.6 (2, 22)[c]	+15.4 (4, 30)[c]

[a] Reference 12. [b] Isolated and identified as the hydrochloride, mp 143 °C (lit.[16] 145-148 °C). [c] Measured in EtOH.

Table II. Amino Acid Benzyl Ester *p*-Toluenesulfonates

amino acid	yield, %	mp, °C obsd	mp, °C lit.[a]	$[\alpha]_D$, deg (*c*, MeOH, t, °C) obsd	$[\alpha]_D$, deg (*c*, MeOH, t, °C) lit.[a,c]
Gly	97	131	132-134		
L-Leu	97	159	158.5-160	−1.8 (2, 22)	−1.7 (25)
L-Tyr	91	180	179-180.5	−12.4 (2, 22)	−12.2 (25)
L-Trp	85[b]				

[a] Reference 4. [b] Isolated and identified as the hydrochloride (see Experimental Section). [c] Measured in 1-2% solutions.

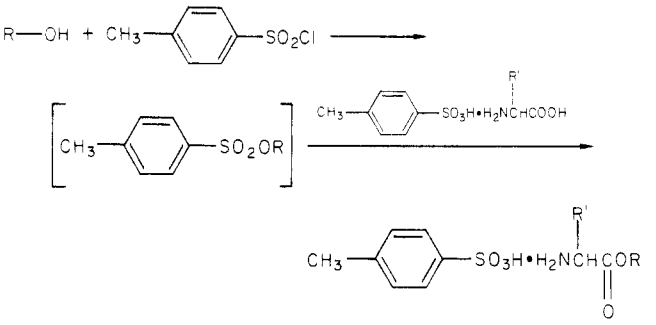
amino acids, such as tryptophan, are hardly esterified in a strongly acidic medium and at high temperature.

In 1963, Wilchek et al.[9] synthesized tryptophan benzyl ester via *N*-carboxy anhydride with phosgene, followed by treatment of the intermediate with benzyl alcohol.

Recently, Williams et al.[10] reported the preparation of tryptophan benzyl ester by the thermal decomposition of a benzyldimethylanilinium salt of N-protected tryptophan. However, application of this procedure directly to amino acids was not successful. Furthermore, since the esterification was carried out with a strong base, racemization occurred to some extent.[10] Later, Maclaren[11] improved on this method and synthesized benzyl and substituted-benzyl esters of amino acids.

More recently, a convenient method of preparing ethyl esters of amino acids was reported.[12] In this procedure, the esterification was achieved by transesterification between ethyl *p*-toluenesulfonate and an amino acid. This method is useful for the preparation of ethyl[12] and *p*-nitrobenzyl[13] esters, but it is not successful in the case of benzyl ester because benzyl *p*-toluenesulfonate is relatively unstable and decomposes at high temperature.[14] The use

Scheme I



of *p*-toluenesulfonyl chloride in benzyl alcohol solved this problem. We report here a mild, simple, and convenient method for effective esterification of tryptophan and other amino acids.

A mixture of amino acid *p*-toluenesulfonate and *p*-toluenesulfonyl chloride in an alcohol was stirred at 80 °C or, in the case of ethanol, was refluxed for 1–2 h. Then, treated in the usual way, the ester of the amino acid was easily isolated as the *p*-toluenesulfonate. Considering the fact that the *p*-toluenesulfonate is a very good leaving group and is easily displaced by carboxylate,[12,15] the esterification may be explained as shown in Scheme I.

The esterification proceeded rapidly, compared with the azeotropic method,[4,5] and was completed in 1–2 h. The addition of *p*-toluenesulfonic acid was necessary to increase the solubility of amino acid and also to prevent reaction of the amino group with *p*-toluenesulfonyl chloride. This method was applied not only to tryptophan but also to other amino acids to give excellent yields without byproduct.

Experimental Section

Melting points were determined with a hot-stage microscope and are uncorrected. Optical rotation were measured with a Shimazu polarimeter Type LP-2 equipped with a PEC-101 photometer.

Typical Procedure of Esterification. L-Tryptophan Ethyl Ester *p*-Toluenesulfonate. To a solution of 2.0 g (10 mmol) of L-tryptophan and 1.7 g (10 mmol) of anhydrous *p*-toluenesulfonic acid in 20 mL of ethanol was added 2.3 g (12 mmol) of *p*-toluenesulfonyl chloride at room temperature. The mixture was refluxed for 1.5 h and then concentrated in vacuo. A white precipitate formed by addition of ether to the residue, which was recrystallized from ethanol–ether to give 3.6 g (90%) of L-tryptophan ethyl ester *p*-toluenesulfonate: mp 143 °C; $[\alpha]^{22}_D$ +16.6° (*c* 2, EtOH).

L-Tryptophan Benzyl Ester Hydrochloride. L-Tryptophan benzyl ester *p*-toluenesulfonate was not crystallized from the reaction mixture and, therefore, was transformed to a hydrochloride. L-Tryptophan, *p*-toluenesulfonic acid, and its chloride in the same quantities as those in the above procedure were added to 20 mL of benzyl alcohol, and the mixture was heated at 80 °C for 1.5 h. The reaction mixture was diluted with 200 mL of chloroform and washed with 1 M sodium bicarbonate. The chloroform solution was concentrated to about 100 mL, and 2 mL of 7.5 M hydrochloric acid in dioxane was added to the solution. A white precipitate formed, which was recrystallized from methanol–ether to give 2.8 g (85%) of L-tryptophan benzyl ester hydrochloride: mp 215 °C (lit.[9] mp 222 °C); $[\alpha]^{20}_D$ +5.4° (*c* 2, MeOH) [lit.[9] $[\alpha]^{25}_D$ +4° (*c* 2, MeOH)].

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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

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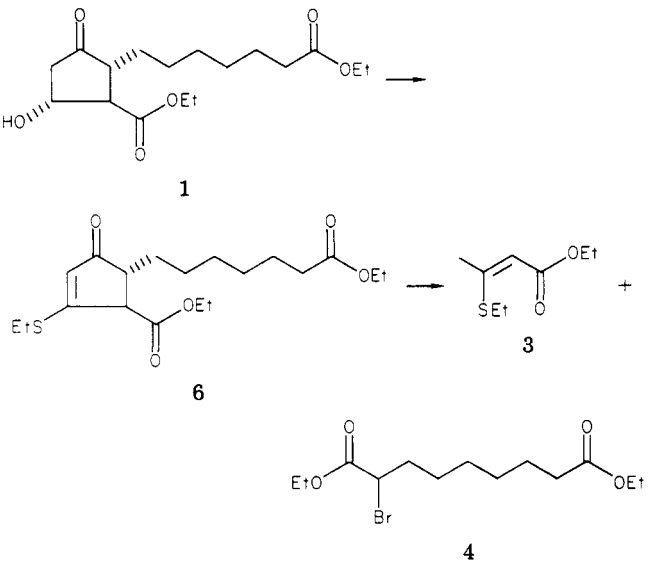
Several approaches to prostanoid synthesis involving formation of the cyclopentane ring from acyclic precursors have been reported.[1] In this paper we describe a new approach of this kind which involves the regiospecific base-induced formation of a monothioenol ether of a 1,3-cyclopentanedione derivative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

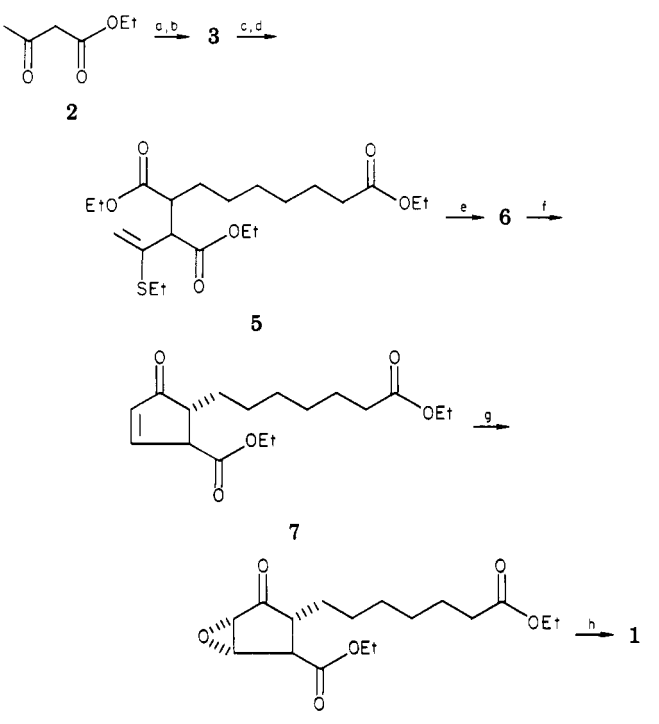
The introduction of the two oxygen functionalities with the natural configuration in the cyclopentane ring via a suitable 1,3-diketone derivative has already been explored.[2] The main drawback of this early synthesis lies, however, in its almost complete lack of regiospecificity in the crucial reductive 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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