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SYNTHESIS AND REARRANGEMENT OF 13-THIAPROSTANOIDS

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Abstract—Thiaprostanoids **13** were prepared by conjugate addition of mercaptane **6** to cyclopentenones **12** and **20**. Novel rearrangements of these compounds to **14** and **15** were interpreted as enolate induced [1,5]-sigmatropic shift on the corresponding dehydration products **16**. Preparation of the various substrates and structural elucidation of new products are described.

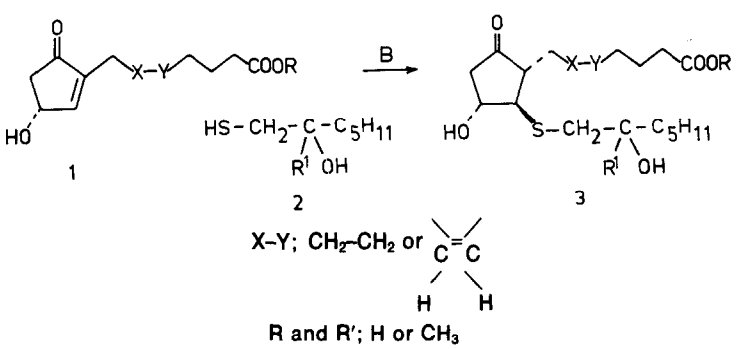
During the last years, the synthesis of novel heteroprostanoids have been receiving considerable attention, since some of these compounds exhibited interesting biological activity and increased metabolic stability.[1-11] Recently, Orth and Radunz reported the synthesis of 13-thiaprostanoids and the remarkable blood pressure lowering activity of its E-type analogs.[2,12]

For the preparation of the E-series of 13-thiaprostanoids, the above authors, used the conjugate addition of appropriately functionalized mercaptan to 4-hydroxy-2-cyclopentenone (Scheme 1). In connection with a program directed to prostaglandin analogues we required these compounds. Therefore, we repeated and thoroughly investigated this reaction. In this paper we now report a modified procedure for the preparation of 13-thiaprostanoids and novel molecular rearrangements of these compounds.

The precursor mercaptan **6a** was prepared from 1,2-heptanediol. The racemic diol[13] was converted by heating with phthalic anhydride into its hydrogen phthalate, which was resolved with brucine. Treatment of the hydrogen phthalate of 2(*S*)-hydroxy-1-heptanol with LAH afforded optically pure **4a**, which was reacted with p-toluenesulfonyl chloride in the presence of pyridine. Reaction of the resultant monotosylate **4b** with potassium thioacetate gave thioacetate **5a**. This compound was reduced with LAH to afford optically pure mercaptan **6a** (Scheme 2).

For the preparation of mercaptan **6b**, compound **7** was treated with lithium diisopropylamide under conditions of kinetic control, and the resultant enolate was quenched in excess trimethylsilyl chloride (Scheme 3). The oxidation of trimethylsilyl enol ether **8** with MCPBA, followed by the hydrolysis of the crude reaction mixture, afforded α-hydroxy ketone **9**. This compound was also synthesized with selective oxidation of 1,2-heptanediol. Standard ketalization of the hydroxy ketone **9** with ethylene glycol gave the ketal **10a**, which was transformed into the corresponding tosylate **10b** by treatment with p-toluenesulfonyl chloride. Reaction of the latter with potassium thioacetate gave thioacetate **11**, which was transformed into the desired mercaptan **6b** with LAH.

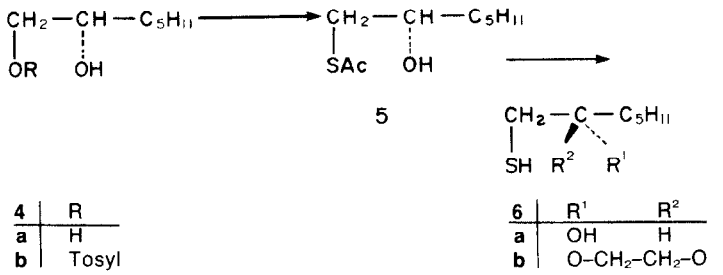
The reaction between mercaptan **6** and cyclopentenones **12** was carried out at room temperature in methanol, using an excess of triethylamine base. At given intervals aliquots were withdrawn, worked up, and analysed by tlc. Surprisingly, the reaction was rather slow under these conditions and in addition to the thiaprostaglandin **13** two less polar products were also detected. After the starting material had been consumed,



Scheme 1.

the reaction mixture was worked up, and besides a small amount of thiaprostaglandin **13**, compounds **14** and **15** were isolated (Scheme 4).

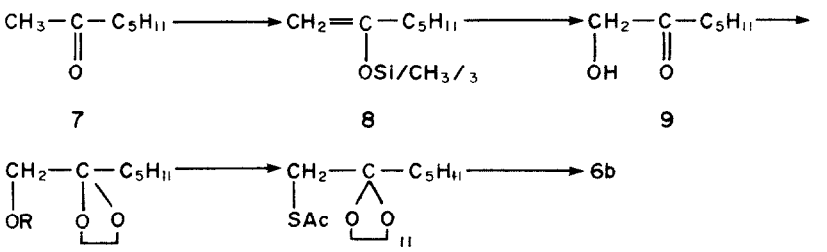
The structures of these new compounds **14** and **15** followed principally from spectral data. For instance, the mass spectrum of **14c** with a molecular ion M^+ 410 ($C_{22}H_{34}O_5S$) showed that it was a dehydration product of **13c**. The IR spectrum of **14c** showed absorption attributable to unsaturated ketone group, and the absence of absorption in the OH regions. The ^1H NMR spectrum of **14c** indicated the signals attributable to three olefinic protons, a methylene bounded to sulfur and a methine attached to sulfur, which was similar to that of **13c** except for downfield shift by 0.8 ppm. Furthermore, the



4	R
a	H
b	Tosyl

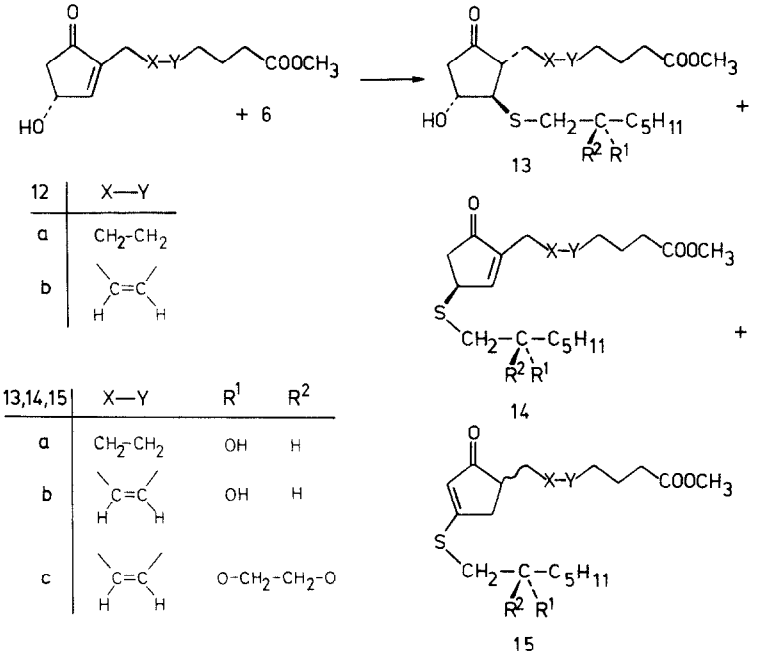
6	R¹	R²
a	OH	H
b	O–CH₂–CH₂–O	

Scheme 2.



10	R
a	H
b	Tosyl

Scheme 3.



12	X—Y
a	CH_2-CH_2
b	C=C (H, H)

13,14,15	X—Y	R¹	R²
a	CH_2-CH_2	OH	H
b	C=C (H, H)	OH	H
c	C=C (H, H)	O-CH_2-CH_2-O	

Scheme 4.

^{13}C NMR spectrum of **14c** showed 21 signals corresponding to 22 carbon atoms in the molecule. The spectrum also indicated the presence of two double bonds.

The mass spectrum of **15c** showed a molecular ion M^+ 410 ($C_{22}H_{34}O_5S$), indicated that **15c** was also a dehydration product of **13c**. The IR spectrum of **15c** showed also the presence of unsaturated ketone groups (1680 and 1540 cm^{-1}). This low value for the double bond stretching frequency is characteristic for the enol thioether moiety. This functionality was confirmed by the ^1H NMR spectrum, with signals at δ5.96 (H-2).

Furthermore, the absence of signals arising from a β-hydrogen on enone system and an allylic methine attached to sulfur, and the presence of singlet at δ 5.96, characteristic for β,β-disubstituted enon system, clearly indicated the position of double bond in the cyclopentenone moiety of the molecule.

Scheme 5 shows the reaction pathway we propose for the formation of these compounds **14** and **15**. The reaction between the mercaptan **6** and cyclopentenone **12** gives rise to thiaprostaglandin **13**, which then undergoes a base-catalysed dehydration to produce an A-type prostaglandin analogue **16**. Base-catalysed enolization of the latter, followed by simultaneous migration of the lower side chain and rearrangement of double bonds yield the intermediate anion **18**, which can give rise to two different products.

Protonation of anion **18** results in thioether **14**. Double bonds migration in **18**, followed by the protonation of the resultant anion **19**, eventuates in the formation of the thermodynamically more stable enol thioether **15**.

For the mechanism of the rearrangement we suggest a concerted suprafacial [1,5]-sigmatropic shift (**17**→**18**), followed by [1,5]-hydrogen shift (**18**→**19**) to the more stable isomer.

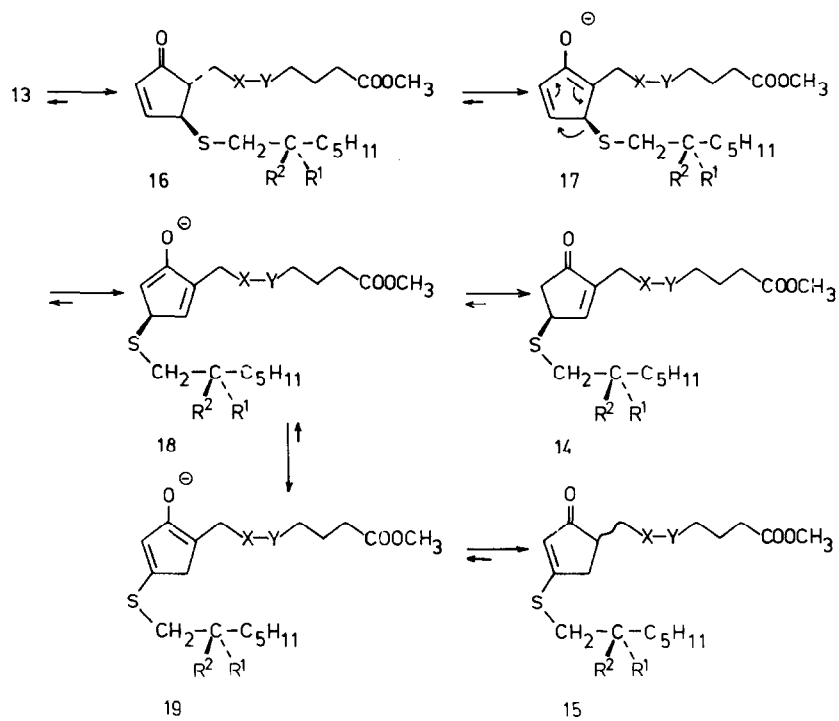
The proposed mechanism was supported by the following facts:

By analogy to the prostaglandin-E series, where the dehydration of 9,11-ketol to prostaglandin—As is well-known[14] the compound **13** would also be expected to generate **16**, under basic condition. Furthermore, the product ration was dependent on the reaction time. After a shorter time (12 hr at room temperature), the major isolation product from the reaction mixture was thioether **14**, since it was formed more rapidly from the intermediate enolate **18**. Using a longer reaction time (6 days, room temperature) or elevated temperature, the only product isolated was **15**, since it was thermodynamically more stable.

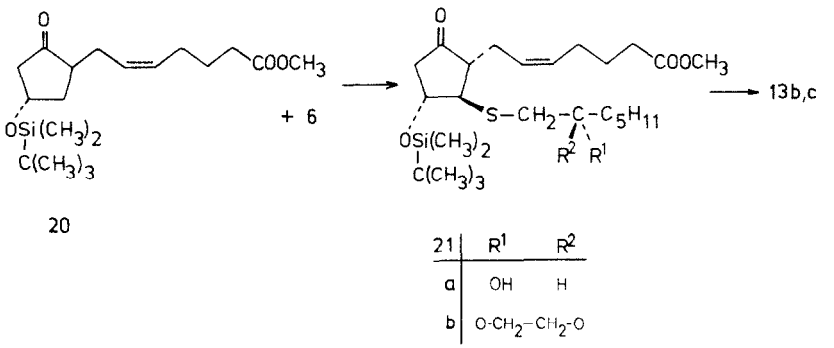
On the other hand, we were able to transform the isolated thiaprostanoid **13** into a mixture of **14** and **15**, or with a longer reaction time into enol thioether **15**. These reactions were catalysed by either base (triethylamine) or alumina. As expected, treatment of the other isomer **14** with base or alumina also afforded enol thioether **15**, probably via the corresponding enolate ion **18**.

The strongest evidence for the correctness of the proposed mechanism came from the chiroptical properties of compound **14c** and **15c**. Such [1,5]-sigmatropic shift is expected to occur with high stereospecificity in the suprafacial-inversion mode.[15] Actually, the CD spectra of **14c** confirmed the predicted configuration at C-4.

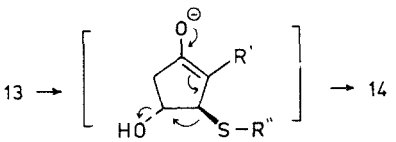
In the CD spectrum of **14c** obtained in acetonitrile, a weak negative (around 330 nm; $\Delta\epsilon + 0.17$) and two stronger positive (at 271 nm; $\Delta\epsilon + 0.96$ and at 224 nm; $\Delta\epsilon + 1.2$) maxima can be found. Supposing the thioether moiety to be present in quasiequatorial position, a 4(*S*) configuration can be assigned to **14c** on the basis of known rules relating to the chiroptical properties of noncoplanar cyclopentenones.[16] The low intensities of



Scheme 5.



Scheme 6.



the CD bands (see, e.g. **17**), however, indicate that the deviation from coplanarity of the enone chromophore and/or the difference in energy between the two enantiomeric conformation of the ring having the alkylthio substituent in quasiequatorial and quasiaxial position may be quite small. Similar $\Delta\epsilon$ values have also been found by other multisubstituted cyclopentenone derivatives.[18] The CD spectra of **13c** and its O-silyl derivative **21b** are in agreement with the proposed configurations of the substituents supposed to adopt quasiequatorial positions on the cyclopentanone ring of halfchair conformation. The stronger Cotton effect found in the CD spectrum of **21b** in comparison to **13c** is indicative to the higher population of the more preferred conformer having the large silyloxy group in quasiequatorial position.

However, the [1,5]-hydrogen shift in the rearrangement of enolate **18** generates an achiral intermediate **19**, which would lead through reprotonization to racemic compound. In accordance with this expectation, compound **15c** was a racemic mixture.

On the assumption that dehydration of thiaprostaglandin **13** was responsible for the rearrangement, we decided to protect the hydroxyl in question. Thus mercaptane **6** was reacted with the sylil ether of hydroxycyclopentanone **20** (Scheme 6). The reaction was quite rapid at room temperature and a single product **21** was isolated as determined by ^{1}H NMR, MS and tlc. Finally, deprotection of **21** using an excess of $BF_3 \cdot Et_2O$ afforded 13-thiaprostaglandin **13** in good yield.

An alternative mechanism for the rearrangement would involve enolization of thiaprostaglandin **13** and subsequent migration of the alkylthio moiety and elimination of hydroxy group. We disfavour this mechanism because of the basic reaction condition employed.

Although acid-catalyzed rearrangement of 2-phenylthioalcohols, probably by [1,3]-sigmatropic shift, had been reported,[19] this is the first example, to our knowledge, for a concerted [1,5]-sigmatropic rearrangement of thioethers.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. IR spectra were obtained with a Spectromom 2000 spectrometer. NMR spectra measurements were carried out using a JEOL FX-100 NMR Spectrometer. All signals are expressed by the ppm downfield from TMS used as an internal standard. Following abbreviations are used: singlet (s), doublet (d), triplet (t), quartet (q), multiplet center (mc), broad (br), intensive (int). MS measurements were taken on a JEOL-20K and JMS-0156-2 combined GC/MS system. (Ionizing energy 74 eV, accelerating voltage 10 KV, ionizing current 200A). Circular dichroism spectra were determined by means of a Roussel-Jouan Dichrographe III (Jobin-Yvon) in 1 mm quartz cells at room temperature.

Resolution of d,l-1,2-*heptanediol*

To a stirred mixture of dl-1,2-heptanediol (6.61 g, 50 mmol) and phthalic anhydride (14.8 g, 100 mmol) was added dropwise dry pyridine (7.76 ml, 97 mmol), and the resulting solution was heated for 2 hr at 100°. The reaction mixture was cooled, diluted with 100 ml of water and acidified with 10% HCl and then extracted twice with ether (50 ml each). The combined organic layers were washed with brine and dried. Evaporation of the solvent afforded crude 1,2-bis(0-carboxy-benzoyloxy) heptane (19.25 g, 90%), which was purified through its dicyclohexylamine salt.

To a stirred cooled solution of the above crude ester (19.25 g, 45 mmol) in dry ether (200 ml) was added freshly distilled dicyclohexylamine (18.0 g, 99 mmol) and the mixture was stirred at room temperature for 3 hr and then kept in the refrigerator for overnight. After filtration the dicyclohexylamine salt was washed with ether and recrystallized from a mixture of $CDCl_3$–ether to give crystalline dicyclohexylamine salt of 1,2-bis(0-carboxy-benzoyloxy)heptane (31.8 g, 89%), m.p. 162–163°. Found: C, 71.42; H, 9.06; N, 3.43. $C_{47}H_{70}N_2O_8$ requires: C, 71.29; H, 8.87; N, 3.54%. A stirred cooled suspension of the above salt (30 g, 37.9 mmol) in water (150 ml) was acidified with 10% HCl, and the resulting solution was extracted three times with ether (100 ml each). The combined organic layers were washed with brine and dried. Evaporation of the solvent afforded d,l-1,2-bis(0-carboxy-benzoyloxy)heptane (13.5 g, 83.2%) as a semi-solid. Found: C, 64.22; H, 5.87, $C_{23}H_{24}O_8$ requires: C, 64.48; H, 5.65%. To a solution of d,l-1,2-bis(0-carboxy-benzoyloxy)heptane (36.5 g, 85.5 mmol) in dry acetone (900 ml) was added brucine (67.7 g, 171 mmol) and the resulting clear solution was stirred at room temperature for 5 hr. A white crystalline precipitate started to separate almost immediately. The precipitate was filtered off, washed with a small amount of cold acetone, and then recrystallized from acetone to give the brucine salt of (−)-1,2(*S*)-heptanediol (41.5 g, 79.8%) as colorless needles, m.p. 151–152°, $[\alpha]_D^{25}$ −35 (C = 1, $CHCl_3$). Found: C, 67.31; H, 6.46; N, 4.63. $C_{69}H_{76}O_{16}N_4$ requires: C, 68.07; H, 6.29; N, 4.60%. To a well stirred solution of the above salt (54.3 g, 44.6 mmol) in water (280 ml) and $CHCl_3$ (280 ml) was added a 10% aqueous solution of NaOH (40 ml) at 5°. The organic layer was separated, the aqueous layer was extracted three times with $CHCl_3$, acidified with 10% HCl and then extracted three times with ether. The combined ethereal extracts were washed with brine and dried. Evaporation of the solvent afforded (−)-1,2-*S*)-bis(0-carboxy-benzoyloxy)heptane (17.6 g, 91.6%) as a semisolid. $[\alpha]_D^{25}$ −9.7 (C = 4, MeOH).

To a stirred suspension of LAH(5.7 g, 149 mmol) in dry ether (100 ml) was added a solution of (−)-1,2(*S*)-bis-(0-carboxy-benzoyloxy)heptane (16.1 g, 37.6 mmol) in dry ether (100 ml), under argon. After refluxing for 1 hr, the mixture was cooled and EtOAc was added dropwise. The reaction mixture was poured onto ice/water and the resulting mixture was acidified with 10% HCl, and then extracted with ether. The ethereal solution was washed with brine and dried. The solvent was evaporated and the residue was distilled to give (−)-1,2(*S*)-heptanediol (3.69 g, 73.5%), b.p. 128–132° (15 mm Hg), $[\alpha]_D^{25}$ − 12.5 (C = 4, EtOH). ^{1}H NMR (in $CDCl_3$): 0.9 (3H, t, J = 6 Hz, CH_3), 1.35 (8H, mc, $4CH_2$), 3.5 (2H, d, J = 3 Hz, CH_2–O), 3.65 (1H, mc, CH–O).

(−)-1-*Tosyloxy*-2(S)-*heptanol* **4b**

To a stirred cooled (−15°) solution of (−)-1,2(*S*)-heptanediol (5.04 g, 38 mmol) in dry pyridine (20 ml) was added p-toluenesulfonyl chloride (8.0 g, 42 mmol) over 30 min. The resulting solution was stirred at −20 to −15° for further 30 min and then allowed to warm to room temperature. The reaction mixture was poured onto ice/water and extracted three times with ether. The combined organic extracts were successively washed with dil HCl, water, sat $NaHCO_3$, brine and dried. The solvent was evaporated under reduced pressure and the residue was chromatographed with hexane-EtOAc (7:3) to give 7.3 g (66.0%) of **4b** as a yellowish oil. $[\alpha]_D^{25}$ − 1.1° (C = 4, EtOH). IR (film): 3400 (OH), 1595, 1480, 1460, 1380, 1350, 1160, 1090, 960, 800 cm^{-1}. ^{1}H NMR (in $CDCl_3$): 0.88 (3H, t, J = 6 Hz, CH_3), 1.3 (8H, mc, $4CH_4$), 2.4 (3H, s, CH_3), 2.95 (2H, br s, OCH_2), 3.92 (2H, mc, O–CH and OH), 7.3 (2H, d, J = 9 Hz, aromatic protons), 7.8 (2H, d, J = 9 Hz, aromatic protons). Ms: M^+ 286 (3), *m/e* 257 (9), 256 (59), 255 (8), 215 (8), 172 (5), 157 (29), 156 (71), 155 (65), 101 (94), 92 (81), 91 (100), 83 (74), 71 (8), 65 (28).

(−)-1-*Thioacetoxy*-2(S)-*heptanol* **5**

To a stirred solution of **4b** (6.0 g, 22 mmol) in dry acetone (100 ml) was added potassium thioacetate (2.64 g, 23 mmol), and the mixture was boiled gently for 1 hr. The solvent was removed in vacuo below 25°. The residue was taken up with water and the solution was extracted twice with ether. The combined organic extracts were washed with brine and dried. Removal of the solvent under reduced pressure gave 3.9 g (96%) of crude **5**. $[\alpha]_D^{25}$ − 3(C = 4, EtOH). IR (film): 3450 (OH), 1700 (CO), 1460, 1380, 1360, 1260, 1160, 1120, 1020, 940 cm^{-1}. ^{1}H NMR (in $CDCl_3$): 0.9 (3H, t, J = 7 Hz, CH_3), 1.35 (8H, mc, $4CH_2$), 2.3 (3H, s, CH_3), 2.9 (2H, br s, S–CH_2), 3.65 (2H, mc, O–CH and OH).

(−)-1-*Mercapto*-2(S)-*heptanol* **6a**

To a stirred suspension of LAH (0.79 g, 20 mmol) in dry ether was added dropwise at −15°, under argon, a solution of **5** (3.2 g, 16 mmol) in dry ether (20 ml). After stirring at −15° for 1 hr, EtOAc (*ca* 3 ml) was added dropwise and the mixture was poured onto ice/water. The resulting mixture was acidified with 10% HCl and extracted three times with ether. The combined organic extracts were washed with water and dried. Removal of solvent under reduced pressure and distillation under argon gave 2.1 g (84.3%) of **6a**. $[\alpha]_D^{25}$ − 10.8° (C = 4, EtOH). IR (film): 3380 (OH), 2520 (SH), 1460, 1410, 1380, 1280, 1230, 1100, 1060, 1020 cm^{-1}. ^{1}H NMR (in $CDCl_3$): 0.9 (3H, t, J = 6 Hz, CH_3), 1.4 (8H, mc, $4CH_2$), 2.65 (2H, d, J = 3 Hz, S–CH_2), 3.6 (2H, mc, O–CH and OH). MS: M^+ 148 (4), *m/e* 130 (10), 101 (38), 100(4), 84 (6), 83 (100), 82 (9), 77 (6), 59 (12), 66 (97).

1-*Hydroxy*-2-*heptanone* **9**

(*a*) *Hydroxylation of* 2-*heptanone* **7** *via silyl enol ether*

To a solution of 12.1 g (16.8 ml, 120 mmol) of diisopropylamine in 250 ml of dry THF under argon was added, at −78°, 133 ml (106 mmol) of n-butyllithium (0.8 M in hexane).

Then, 11.4 g (100 mmol) of 2-heptanone (**7**) in 10 ml of dry THF was added dropwise over 10 min. After 1 hr of stirring at −78°, 21.5 ml (170 mmol) of trimethylsilyl chloride was added rapidly. After stirring for 1 hr at room temperature, the reaction mixture was filtered and then THF removed *in vacuo*. The residue was dissolved in 100 ml of pentane and the salt precipitated was removed by filtration. The yellow oil obtained after removal of the solvent was distilled under vacuum to give 17.0 g (91%) of 2-trimethyl-silyloxy-1-heptane **8**, b.p. 62° (18 mm Hg). IR (film): 1620, 1460, 1380, 1240, 1180, 1090, 100 cm^{-1}. ^{1}H NMR (in CCl_4): 0.18 (9H, s, $3CH_3$), 0.9 (3H, t, J = 7 Hz, CH_3), 1.25 (6H, mc, $3CH_2$) 1.9 (2H, t, J = 7 Hz, CH_2), 3.87 (2H, s, $=CH_2$).

To a stirred solution of 10.0 g (54 mmol) of 2-trimethylsilyloxy-1-heptane (**8**) in 150 ml of dry CH_2Cl_2 at 0° was added 13.97 g (65 mmol, tech, 80%) of MCPBA. After stirring for 3 hr at room temperature, the reaction mixture was diluted with 100 ml of pentane and filtered. After evaporation of the filtrate the residue was purified by column chromatography (benzene-MeOH 9:1) to give 8.24 g (76%) of 1-hydroxy-2-heptanone **9** as colorless oil. IR (film): 3400 (OH), 1720 (CO), 1460, 1395, 1370, 1260, 1080, 1030 cm^{-1}. ^{1}H NMR (in $CDCl_3$): 0.9 (3H, t, J = 7 Hz, CH_3), 1.35 (6H, mc, $3CH_2$, 2.4 (2H, t, J = 6 Hz, CH_2), 3.5 (1H, br s, exchangeable with D_2O, OH) 4.2 (2H, br s, CH_2).

(*b*) *Selective oxidation of* 1,2-*heptanediol*

To a stirred suspension of 160 g of Fetizon reagent (silver carbonate on Celite) in 1 l of dry benzene was added dropwise 5.6 g (42.4 mmol) of dl-heptanediol. After refluxing for 2 hr, the mixture was cooled and filtered from the precipitate, which was washed with benzene. The combined filtrates were concentrated *in vacuo* to afford 3.85 g of a crude product, which was chromatographed with benzene-MeOH (9:1) to give 2.3 g (41%) of 1-hydroxy-2-heptanone **9**.

2,2-*Ethylenedioxy*-1-*heptanol* **10a**

A mixture of **9** (3.85 g, 29.6 mmol), 2.02 g (32.4 mmol) of ethylene glycol, and 0.2 of p-toluenesulfonic acid hydrate in 120 ml of benzene were heated for 3 hr in a Dean–Stark apparatus. After cooling, the solution was washed with water, dried and evaporated *in vacuo* to afford 4.4 g of an oily crude product, which was column chromatographed with $CHCl_3$–MeOH (10:0.5) to give 4.15 g (73%) of **10a** as an oil. IR (film): 3400 (OH), 1460, 1380, 1250, 1200, 1150, 1050 cm^{-1}. ^{1}H NMR (in CCl_4): 0.9 (3H, t, J = 6 Hz, CH_3), 1.4 (8H, mc, $4CH_2$) 3.3 (2H, br s, CH_2), 3.9 (4H, br s, O–CH_2–CH_2–O).

2,2-*Ethylenedioxy*-1-*tosyloxy*-*heptane* **10b**

To a stirred solution of 1.3 g (7.4 mmol) of **10a** in 3 ml of dry pyridine was added 2.4 g (10.8 mmol) of p-toluenesulfonyl chloride at −10°. The resulting solution was stirred at −5° for 1 hr. The reaction mixture was poured onto ice/water and extracted with ether. The organic layer was successively washed with N HCl, water, $NaHCO_3$ soln, brine and dried. The solvent was evaporated under reduced pressure and the residue was chromatographed with hexane-ether (7:3) to give 2.26 g (92%) of **10b** as an oil. IR (film): 1600, 1480, 1460, 1380, 1350, 1300, 1280, 1160, 1080, 1010, 960 cm^{-1}. ^{1}H NMR (in $CDCl_3$): 0.89 (3H, t, J = 7 Hz, CH_3), 1.3 (6H, mc, $3CH_2$), 1.6 (2H, t, J = 6 Hz, CH_2), 2.48 (3H, s, CH_3), 3.9 (6H, br s, CH_2 and O–CH_2–CH_2–O), 7.3 (2H, d, J = 10 Hz, aromatic protons), 7.7 (2H, d, J = 10 Hz, aromatic protons).

2,2-*Ethylenedioxy*-1-*thioacetoxy*-*heptane* **11**

A mixture of **10b** (1.63 g, 5 mmol), potassium thioacetate (1.42 g, 12.4 mmol) and 10 ml of DMF was heated at 110° for 6 hr. The reaction mixture was cooled to room temperature, poured onto water and extracted with ether. The ethereal solution was washed with brine and dried. Evaporation of the solvent afforded an oil, which was chromatographed with hexane–ether (7:3) to give 1.04 g (90%) of **11**. IR (film): 1700 (CO), 1460, 1430, 1380, 1360, 1320, 1280, 1200, 1130, 1100, 1080, 1030, 950 cm^{-1}. ^{1}H NMR (in $CDCl_3$): 0.9 (3H, t, J = 6 Hz, CH_3), 1.3 (6H, mc, $3CH_2$), 1.55 (2H, t, J = 6 Hz, CH_2), 2.3 (3H, s, CH_3), 3.2 (2H, s, CH_2), 4 (4Hm, mc, O–CH_2–CH_2–O).

2,2-*Ethylenedioxy*-1-*heptanethiol* **6b**

To a stirred suspension of LAH (0.13 g, 3.4 mmol) in 10 ml of dry ether was added dropwise a solution of **11** (0.74 g, 3.18 mmol) in dry ether (3 ml) at −15°, under argon. After stirring at −15° for 1 hr, EtOAc (*ca.* 2 ml) was added dropwise and the mixture was poured onto water. The organic layer was separated, the

aqueous layer was extracted with ether and the combined organic layers were washed with brine and dried. Removal of the solvent *in vacuo* afforded 0.58 g (95%) of crude **6b**. IR (film): 1460, 1420, 1380, 1180, 1120, 1100, 1070, 1020, 930, 880 cm^{-1}. ^1H NMR (in $CDCl_3$): 0.9 (3H, t, J = 6 Hz, CH_3), 1.3 (6H, mc, $3CH_2$), 1.5 (2H, t, J = 6 Hz, CH_2), 2.7 (2H, d, J = 8 Hz, S–CH_2), 4 (4H, br s, O–CH_2–CH_2–O). MS: M^+ 190 (3), *m/e* 189 (2), 145 (16), 144 (100), 143 (100), 142 (11), 120 (13), 119 (90), 118 (13).

13,14 - *Dihydro* - 13 - *thia* - *prostaglandin* - E_1 *Methyl Ester* **13a**, 4(R) - 2 - (6 - *methoxycarbonylhexyl*) - 4 - [2(S) - *hydroxyheptylthio*] - *cyclopentenone* **14a** *and* **5** - (6 - *methoxycarbonylhexyl*) - 3 - [2(S) - *hydroxyheptylthio*] - 2 - *cyclopentenone* **15a**

Triethylamine (1.7 g, 17 mmol) was added to a stirred solution of **12a**[17] (0.4 g, 1.7 mmol) and **6a** (0.37 g, 2.5 mmol) in dry MeOH (10 ml) at room temperature, under argon atmosphere. The reaction mixture was stirred for 48 hr at room temperature. The solvent and most of the triethylamine were removed *in vacuo*, and the residue was separated by column chromatography (benzene–EtOAc 3:2) to give **13a** as an oil (0.08 g, 12.3%), **14a** as an oil (0.15 g, 30.4%), and **15a** as an oil (0.05 g, 7.9%). The above three products showed the following properties. Compound **13a**,[12] tlc (benzene–EtOAc 3:2). $R_f = 0.42$. Compound **14a**, tlc (benzene–EtOAc, 3:2). $R_f = 0.65$. Found: C, 64.66; H, 8.76; S, 8.27. $C_{20}H_{34}O_4S$ requires: C, 64.82; H, 9.24; S, 8.65%. IR (film): 3400 (OH)l 1730, 1700 (CO), 1620 (C=C), 1460, 1440, 1360, 1250, 1190, 1160, 1080, 1030, 930 cm^{-1}. ^1H NMR (in $CDCl_3$): 0.9 (3H, t, J = 6 Hz, CH_3), 1.4 (14H, mc, $7CH_2$), 2.7 (2H, mc, S–CH_2), 2.85 (1H, mc, S–CH), 3.65 (3H, s, OCH_3), 4.0 (1H, mc, CH–O), 7.2 (1H, mc, CH=C–C=O). MS: M^+ 370 (19), *m/e* 294 (23), 224 (40), 192 (41), 155 (15), 147 (19), 142 (7), 129 (14), 127 (12), 115 (19), 97 (50), 83 (24), 75 (29), 55 (100).

Compound **15a**, tlc (benzene–EtOAc, 3:2). $R_f = 0.48$. Found: C, 64.59; H, 8.96; S, 8.32. $C_{20}H_{34}O_4$ requires: C, 64.82; H, 9.24; S, 8.65%. IR (film): 3300 (OH), 1730, 1680 (CO), 1470, 1450, 1360, 1320, 1260, 1200, 1170, 1100, 1060 cm^{-1}. ^1H NMR (in $CDCl_3$): 0.9 (3H, t, J = 6 Hz, CH_3), 1.4 (14H, mc, $7CH_2$), 3.1 (2H, mc, S–CH_2), 4.0 (1H, mc, CH–O), 5.95 (1H, br s, C=CH–C=O). MS: M^+ 370 (7), *m/e* 339 (8), 241 (12), 229 (17), 228 (100), 143 (23), 128 (9), 127 (10), 117 (16), 115 (20, 114 (54), 98 (13), 71 (10), 55 (17).

13,14 - *Dihydro* - 13 - *thia* - *prostaglandin* - E_2 *methyl ester* **13b**, 4(R) - 2 - [6 - *methoxycarbonyl* - (Z) - *hexenyl*] - 4 - [2(S) - *hydroxyheptylthio*] - 2 - *cyclopentenone* **14b**, *and* 5 - [6 - *methoxycarbonyl* - 2(Z) - *hexenyl*] - 3 - [2(S) - *hydroxyheptylthio*] - 2 - *cyclopentenone* **15b**

To a solution of **12b**[17] (0.98 g, 4.1 mmol) and **6a** (0.9 g, 6 mmol) in dry MeOH was added triethylamine (0.4 g, 4.1 mmol), and the mixture was stirred at room temperature for 48 hr, under argon atmosphere. The solvent and most of the triethylamine were removed *in vacuo*, and the residue was separated by preparative tlc (benzene–EtOAc, 3:2), to give **13b** as an oil (0.12 g, 7.5%), **14b** as an oil (0.5 g, 33.3%) and **15b** as an oil (0.28 g, 18.6%). Compound **13b**,[12] tlc (benzene–EtOAc, 3:2). $R_f = 0.40$. Compound **14b** tlc (benzene–EtOAc, 3:2). $R_f = 0.63$. Found: C, 64.82; H, 8.49, S, 8.42. $C_{20}H_{32}O_4S$ requires: C, 65.18; H 8.76; S, 8.70%. IR (film): 3350 (OH), 1730, 1705, (CO), 1620 (C=C), 1460, 1430, 1400, 1360, 1350, 1300, 1240, 1190, 1150, 1035, 940 cm^{-1}. ^1H NMR (in $CDCl_3$): 0.9 (3H, t, J = 6 Hz, CH_3), 1.45 (6H, mc, $3CH_2$), 2.75 (2H, mc, S–CH_2), 2.9 (3H, mc, =C–CH_2–C= and S–CH), 3.7 (3H, s, OCH_3), 4.05 (1H, mc, CH–O), 5.55 (2H, mc, CH=CH), 7.25 (1H, mc, CH=C–C=O). MS: M^+ 368 (38), *m/e* 294 (18), 240 (7), 223 (16), 222 (100), 190 (57), 189 (24), 147 (15), 129 (12), 119 (20), 105 (11), 97 (27), 67 (18), 55 (89). Compound **15b**, tlc (benzene–EtOAc, 3:2). $R_f = 0.45$. Found: C, 64.84; H, 8.53; S, 8.47. $C_{20}H_{32}O_4S$ requires: C, 65.18; H 8.76; S, 8.70%. IR (film): 3350 (OH), 1730, 1680 (CO), 1540 (S–C=C), 1460, 1430, 1360, 1260, 1170, 1030, 830 cm^{-1}. ^1H NMR (in $CDCl_3$): 0.9 (3H, t, J = 6 Hz, CH_3), 1.4 (6H, mc, $3CH_2$), 3.1 (2H, mc, S–CH_2), 3.7 (3H, s, OCH_3), 3.95 (1H, mc, CH–O), 5.45 (2H, mc, CH=CH), 6.0 (1H, br s, C=CH–C=O). MS: M^+ 368 (16), *m/e* 229 (21), 228 (100), 127 (10), 115 (21), 114 (61), 97 (18), 73 (100), 55 (60).

13,14 - *Dihydro* - 15 - *deoxy* - 15,15 - *ethylenedioxyprostaglandin* - E_2 - *methyl ester* **13c**, 4(S) - 2[6 - *methoxycarbonyl* - (2Z) - *hexenyl*] - 4 - (2,2 - *ethylenedioxyheptylthio*) - 2 - *cyclopentenone* **14c**, *and d,l* - 5 - [6 - *methoxycarbonyl* - 2(Z) - *hexenyl*] - 3 - (2,2 - *ethylenedioxyheptylthio*) - 2 - *cyclopentenone* **15c**

Triethylamine (0.78 g, 7.8 mmol) was added to a well stirred solution of **12b**[17] (1.56 g, 6.7 mmol) and **6b** (1.48 g, 7.8 mmol) in dry MeOH (30 ml) at room temperature, under argon atmosphere. The reaction mixture was stirred for 50 hr at room temperature. After evaporation *in vacuo*, the oily residue was separated by column chromatography (hexane–EtOAc 7:3) to give **13c** as an oil (0.18 g, 6.3%), **14c** as an oil (0.2 g, 7.4%) and **15c** as an oil (1.0 g, 37.0%). Three reaction products showed the following properties. Compound **13c**, tlc (benzene–EtOAc, 3:2) $R_f = 0.52$, CD (acetonitrile): λ, nm ($\Delta\epsilon$) 355 sh (−0.13), 338 (−0.35), 324 (−0.36), 312 (−0.18), 304 (+0.07), 294 (+0.18), 276 sh (−0.15), 226 (+2.20). IR (film): 3400 (OH), 1735 (CO), 1460, 1440, 1380, 1360, 1250, 1140, 1070, 1020 cm^{-1}. ^1H NMR (in $CDCl_3$): 0.9 (3H, t, J = 7 Hz, CH_3), 1.3 (6H, mc, 3 CH_2), 2.9 (2H, mc, S–CH_2), 3.05 (1H, mc, S–CH), 3.65 (3H, s, OCH_3), 4.05 (4H, mc, O–CH_2–CH_2–O), 4.3 (1H, m, 11–H), 5.45 (2H, mc, CH=CH). MS: M^+ 428 (5), *m/e* 396 (9), 357 (10), 220 (14), 207 (14), 189 (17), 188 (8), 160 (11), 143 (100), 121 (13), 99 (28), 91 (17), 71 (53). Compound **14c**, tlc (benzene–EtOAc, 3:2) $R_f = 0.77$. CD (acetonitril); λ, nm ($\Delta\epsilon$) 340 (−0.17), 326 (0.16), 271 (+0.96), 224 (+1.20). IR (film): 1730, 1700 (CO), 1620 (C=C), 1460, 1430, 1380, 1360, 1340, 1300, 1250, 1230, 1190, 1020 cm^{-1}. ^1H NMR (in $CDCl_3$): 0.89 (3H, t, J = 6 Hz, CH_3), 1.30 (6H, mc, $3CH_2$, $C_{5'}$–$C_{7'}$), 1.72 (4H, mc, $2CH_2$, $C_{3'}$ and $C_{4'}$), 2.07 (2H, m, CH_2, $C_{4'}$), 2.32 (2H, t, J = 6 Hz, CH_2–COO), 2.45 (1H, mc, H–C–H, C_5), 2.73 (2H, s, CH_2–S), 2.89 (1H, mc, H–C–H, C_5), 2.92 (2H, mc, =C–CH_2–C=, $C_{1'}$), 3.66 (3H, s, OCH_3), 3.99 (4H, s, –$O(CH_2)_2$O), 4.05 (1H, mc, CH–S, C_4), 5.50 (2H, mc, CH=CH), 7.18 (1H, mc, c=CH, C_3). ^{13}C NMR (25 MHz, in $CDCl_3$): 13.94 (CH_3), 22.52, 22.72, 23.19, 24.60, 26.45, 31.85, 33.32, 36.90, 37.28, 42.06 (CH–S, C_4), 43.39, 51.40 (OCH_3), 65.43 (int., O–CH_2–CH_2–O), 110.96 (O–C–O), 125.49 and 131.01 (CH=CH), 145.54 (C_2), 156.64 (C_3), 173.75 (–CO_2–) 206.48 (C=O). MS: M^+ 410 (17), *m/e* 378 (2), 364 (3), 339 (3), 221 (2), 189 (6), 143 (100), 132 (2), 129 (2), 119 (5), 91 (11), 71 (14), 55 (16), 44 (34).

Compound **15c**, tlc (benzene–EtOAc, 3:2). $R_f = 0.69$. IR (film): 1730, 1680, (CO), 1540 (S–C=C), 1460, 1430, 1380, 1360, 1250, 1155, 1070, 1020 cm^{-1}. ^1H NMR (in $CDCl_3$): 0.89 (3H, t, J = 6 Hz, CH_3), 1.29 (6H, mc, $3CH_2$, $C_{5'}$–$C_{7'}$), 1.72 (4H, mc, CH_2, $C_{3'}$ and $C_{4'}$), 2.13 (2H, m, CH_2, $C_{4'}$), 2.32 (2H, t, J = 6 Hz, CH_2–COO), 2.2–3.1 (5H, m, $2CH_2$ and CH, C_4, C_5 and $C_{1'}$), 3.16 (2H, s, CH_2–S), 3.76 (3H, s, OCH_3) 4.0 (4H, br s, O–CH_2–CH_2–O), 5.38 (2H, mc, CH=CH), 5.96 (1H, mc, C=CH–CO, C_2). ^{13}C NMR (25 MHz, in $CDCl_3$): 13.92, (CH_3) 22.54, 23.28, 24.75, 26.65, 28.71, 31.85, 33.41, 37.60 (int.) 39.98, 46.03, 51.46, (OCH_3), 65.78 (int., O–CH_2–CH_2–O) 109.87 (O–C–O), 123.64 (C_2), 126.66 and 131.10 (CH=CH), 173.90 (–CO_2–), 178.49 (C_3), 206.54 (C=O). MS: M^+ 410 (2), *m/e* 378 (4), 339 (2), 307 (2), 257 (6), 183 (3), 143 (100), 139 (9), 129 (14), 91 (21), 44 (36).

13,14 - *Dihydro* - 13 - *thia* - *prostaglandin* - E_2 11 - *tert* - *butyldimethylsilyl ether methyl ester* **21a**

Diisopropylamine (1.2 g, 12 mmol) was added to a stirred solution of **20** (2.76 g, 7.8 mmol) and **6a** (1.74 g, 12 mmol) in dry $CHCl_3$ (40 ml) at room temperature, under argon. After standing at room temperature for 48 hr, the solvent was removed by evaporation *in vacuo* and the residue was chromatographed with hexane–ether (7:3) to give **21a** as an oil (2.35 g, 59%). Tlc (hexane–ether–acetone 7:3:1). $R_f = 0.33$. IR (film): 3400 (OH), 1735 (CO), 1460, 1430, 1360, 1230, 1200, 1130, 1080, 1030, 810 cm^{-1}. ^1H NMR (in $CDCl_3$): 0.08 (3H, s, CH_3–Si), 0.1 (3H, s, CH_3–Si), 0.9 (12H, t + s, J = 6 Hz, CH_3 and $C(CH_3)_3$), 1.26 (6H, mc, $3CH_2$), 2.85 (2H, mc, CH_2–S), 3.1 (1H, mc, CH–O), 3.62 (3H, s, OCH_3), 4.2 (1H, mc, CH–O), 5.4 (2H, mc, CH–CH). MS: M^+ 500 (1), *m/e* 443 (7), 351 (1), 322 (4), 295 (56), 265 (7), 221 (4), 189 (25), 162 (8), 101 (19), 83 (52), 75 (100), 41 (38).

13,14 - *Dihydro* - 15 - *deoxy* - 15,15 - *ethylenedioxyprostaglandin* - E_2 11 - *tert* - *butyldimethylsilyl ether methyl ester* **21b**

Triethylamine (0.21 g, 2.1 mmol) was added to a stirred mixture of **20** (0.49 g, 1.4 mmol) and **6b** (0.4 g, 2.1 mmol) at room temperature, under argon atmosphere. After stirring at room tem-

perature for 1 hr, the oily crude product was chromatographed with hexane–ether (4:1) to give **21b** as an oil (0.49 g, 65%), tlc (hexane–ether, 7:3), $R_f = 0.36$. CD (acetonitrile); λ, nm ($\Delta\epsilon$) 320 sh (−0.71), 308.5 (−1.26), 300 (−1.24), 290 sh (−0.91), 231 (+0.51), 214 (−0.22). IR (film): 1735 (CO), 1460, 1430, 1350, 1300, 1230, 1100, 1050, 815 cm^{-1}. ^1H NMR (in $CDCl_3$): 0.08 (3H, s, CH_3–Si), 0.1 (3H, s, CH_3–Si), 0.9 {12H, t + s, J = 6 Hz, CH_3 and $C(CH_3)$}, 1.26 (6H, mc, $3CH_2$), 2.85 (2H, d, J = 2 Hz, CH_2–S), 3.1 (1H, mc, CH–S), 3.63 (3H, s, OCH_3), 3.98 (4H, br s, O–CH_2–CH_2–O), 4.25 (1H, mc, CH–O), 5.42 (2H, mc, CH=CH). MS: M^+ 542 (2), *m/e* 511 (3), 485 (3), 228 (8), 297 (20), 264 (18), 189 (60), 143 (100).

Conversion of silyl ether **21** *to thiaprostaglandin* **13**

To a stirred cooled solution of **21** (1 mmol) in dry $CHCl_3$ was added BF_3. Et_2O (6 mmol) and the resulting mixture was stirred at 0° for 15 min. The reaction mixture was poured onto cold sat $NaHCO_3$ and extracted twice with $CHCl_3$. The organic extracts were washed with brine and dried. Evaporation of the solvent and purification of the residue by chromatography (hexane–EtOAc 7:3) afforded pure **13** (63–65% yield).

Isomerization of **13c**

(a) To a solution of **13c** (0.1 g, 0.23 mmol) in dry MeOH (2 ml) was added triethylamine (0.15 g, 1.5 mmol), and the resulting solution was stirred at room temperature for 24 hr. The solvent was removed *in vacuo* and the residue was separated by preparative tlc (benzene–EtOAc) to give **14c** (0.058 g, 62%) and **15c** (0.012 g, 12.7%).

(b) **13c** (0.2 g) was dissolved in dry ether and then absorbed on alumina (3 g, Brockmann grade II neutral). After standing for 24 hr at room temperature, the resultant products were eluted with benzene–EtOAc (3:2). The solvents were evaporated and the residue was separated by preparative tlc (benzene–EtOAc) to give **14c** (1.25 g, 62.5%) and **15c** (0.52 g, 26.0%).

Isomerization of **14c**

(a) 0.10 g of **14c** was dissolved in dry ether and then absorbed on alumina (1.0 g, Brockmann grade II neutral). After the mixture had remained at room temperature for 4 days, the absorbed product was eluted with benzene–EtOAc (3:2), the solution was then concentrated to yield pure **15c** (0.086 g, 86.0%).

(b) To a solution of **14c** (0.2 g, 0.5 mmol) in dry MeOH (2 ml) was added triethylamine (0.05 g, 0.05 mmol) and the resulting solution was allowed to stand two weeks at room temperature. Evaporation of the solvent and purification of the residue by preparative tlc (benzene–EtOAc, 3:2) vave pure **15c** (0.14 g, 70.0%).

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REFERENCES

[1]Cs. Szántay and L. Novák, *Synthesis of Prostaglandins*, Akadémiai Kiadó, Budapest (1978).
[2]D. Orth and H.-E. Radunz, *Top. Current Chem.* **72**, 80 (1977).
[3]Kurozumi, T. Toru, M. Kobayashi and Y. Hashimoto, *Synth. Comm.* **7**, 169 (1977).
[4]J. J. Plattner and A. H. Gager, *Tetrahedron Letters* 1625 (1977).
[5]P. A. Zoretic, P. Soja and Th. Shiah, *J. Med. Chem.* **21**, 1330 (1978).
[6]D. L. Venton, S. E. Enke and G. C. Le Breton, *J. Med. Chem.* **22**, 824 (1979).
[7]H. Hayashi, Y. Arai, H. Wakatsuka, M. Kawamura, Y. Konishi, T. Tsuda and K. Matsumoto, *J. Med. Chem.* **23**, 525 (1980).
[8]A. Wissner, J. E. Birnbaum and D. E. Wilson, *J. Med. Chem.* **23**, 715 (1980).
[9]S. Saigo, M. Wada J-I-Himizu and A. Ishida, *Chem. Pharm, Bull.* **28**, 1449 (1980).
[10]H. Iwamoto, N. Inukai, I. Yanagisawa, Y. Ishii, T. Tamura, T. Shiozaki, T. Takagi, K-T. Tomioka and M. Murakami, *Chem. Pharm. Bull.* **28**, 1422 (1980).
[11]H. Miyake, T. Tanouchi, M. Hayashi, *Chem. Letters* 145 (1978).
[12]Merc and Co, *Belgian Pat.* 828925 (1975).
[13]D. Swern, G. N. Billen and J. T. Scaulon, *J. Am. Chem. Soc.* **68**, 1504 (1946).
[14]S. K. Perera and L. R. Fedor, *J. Am. Chem. Soc.* **101**, 7390 (1979), and Refs. cited therein.
[15]J. J. Gajewski, *Acc. Chem. Res.* **13**, 142 (1980), and Refs. cited therein.
[16]G. Snatzke, *Tetrahedron* **21**, 421 (1965).
[17]L. Novák, J. Rohály, M. Kajtár and Cs. Szántay, *Acta Chim. Hung.* **102**, 91 (1979).
[18]D. De Keukeleire and G. Snatzke, *Tetrahedron* **28**, 2011 (1972).
[19]P. Brownbridge, U. Fleming, A. Pearce and S. Warren, *J. Chem. Soc. Chem. Comm.* 751 (1976); P. Brownbridge and S. Warren, *J. Chem. Soc. Perkin I* 2125 (1976); P. Brownbridge and S. Warren, *J. Chem. Soc. Perkin I* 1131 *and* 2272 (1977); S. Warren, *Acc. Chem. Res.* **11**, 401 (1978).