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9-THIAPROSTAGLANDINS. THE SYNTHESIS OF OPTICALLY ACTIVE 9,9-DIOXIDE ANALOGS

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We have recently described the synthesis of 9-desoxy-9-thiaprostaglandin-E_1.[1] In this paper we wish to report an alternative synthetic method[2] leading to the preparation of racemic as well as optically active forms of the corresponding 9,9-dioxide analog 11.

Reaction[3] of ethyl 9-cyano-2-nonenoate[2] (1) with ethyl sodium thioglycolate produced the tetrahydrothiophenone 2[4] (70%; evaporative dist., b.p. 185°, 0.3 mm; ν_{max}^{film} 2250, 1755, 1725 cm^{-1}) which on reduction ($NaBH_4$/ethanol/-5°) gave a mixture of the two epimeric alcohols which were separated by preparative tlc (silica gel, EtOAc/CH_2Cl_2, 95:5, two developments). The polar isomer 3 (60%; Rf=0.37; ν_{max}^{film} 3460, 2240, 1720 cm^{-1}) was converted (dihydropyran/picric acid/CH_2Cl_2) to the tetrahydropyranyl ether 4 which in turn was reduced ($LiAlH_4$/THF/-20°) to the alcohol 5 (80%, $\nu_{max}^{CHCl_3}$ 3530, 2250 cm^{-1}). Hydrolysis of the nitrile group in 5 (KOH/CH_3OH/110°/48 hrs), followed by diazomethane esterification of the resulting carboxylic acid gave the methyl ester 6 (90%, ν_{max}^{film} 3460, 1730 cm^{-1}). The sulfide 6 was oxidized (m-$ClC_6H_4CO_3H$/CH_2Cl_2) to the sulfone 7, which in turn was converted (CrO_3/pyridine)[5] to the crystalline aldehyde 8 (m.p. 90-92°; ν_{max}^{KBr} 2730, 1735, 1730 cm^{-1}). Wittig reaction of 8 with 1-tributylphosphoranylidene-2-heptanone[6] produced the enone 9 (m.p. 100-101°; ν_{max}^{KBr} 1728, 1685, 1625 cm^{-1}).

Reduction ($NaBH_4$/ethanol) of the C_{15}-carbonyl in 9, followed by hydrolysis (CH_3OH/p-TsOH) of the tetrahydropyranyl group, produced a mixture of the C_{15}-epimeric alcohols which were

separated by preparative tlc (silica gel, EtOAc/CH_2Cl_2, 3:2) and gave the polar isomer 10 (Rf=0.18; m.p. 88-90°; ν_{max}^{KBr} 3460, 3300, 1730 cm^{-1}). The ester 10 was hydrolyzed (K_2CO_3/CH_3OH) to the desired di-9-desoxo-9-thiaprostaglandin-E_1 9,9-dioxide 11 (m.p. 87-89°; ν_{max}^{KBr} 3460, 1700 cm^{-1}).

The relative stereochemical identity of 11 with the previously described 9-thiaprostaglandin 12[1] was established by oxidation (m-$ClC_6H_4CO_3H/CH_2Cl_2$/0°) of 12 methyl ester to produce 10.

The enantiomeric forms of 11 were obtained by resolution of the intermediate enone 13, produced from 9 by hydrolysis (CH_3OH/p-TsOH) of the tetrahydropyranyl group. Esterification of 13 with R(-)α-methoxybenzeneacetyl chloride in pyridine, produced a mixture of two diastereomers[7] 14, which were separated by preparative tlc (silica gel, EtOAc/CH_2Cl_2, 4:96, two developments, Rf=0.213; m.p. 80-81°; $[\alpha]D^{25}$=+45.7° and Rf=0.32; m.p. 63-65°; $[\alpha]D^{25}$=0°.

Each diastereomer 14 was converted to the enantiomeric alcohols 10 by reduction with zinc borohydride followed by brief treatment with aq. K_2CO_3 in methanol and chromatography of the C_{15}-epimeric mixtures. The alcohols 10 were in turn hydrolyzed (K_2CO_3/CH_3OH) to the enantiomeric acids 11 (m.p. 101-103°; $[\alpha]D^{25}$= -8.15° and +7.3° respectively).

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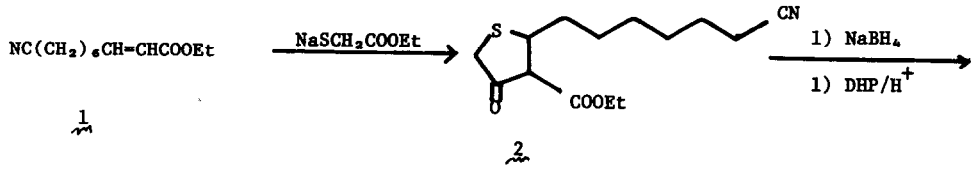

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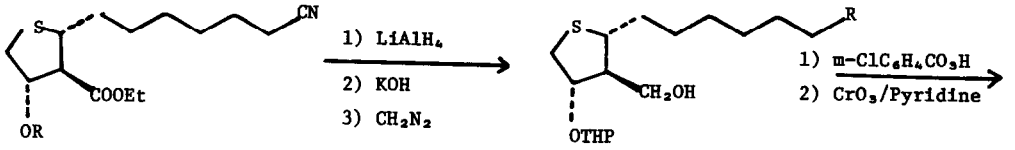
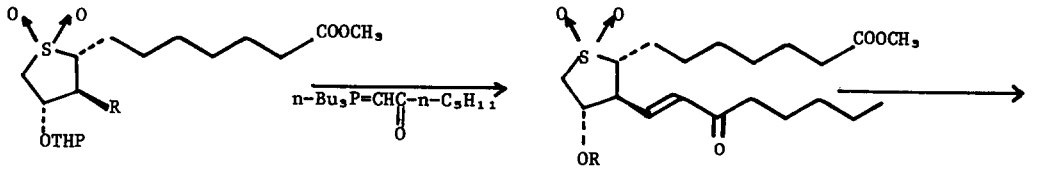


3 R= H

4 R= THP

5 R= CN

6 R= $COOCH_3$



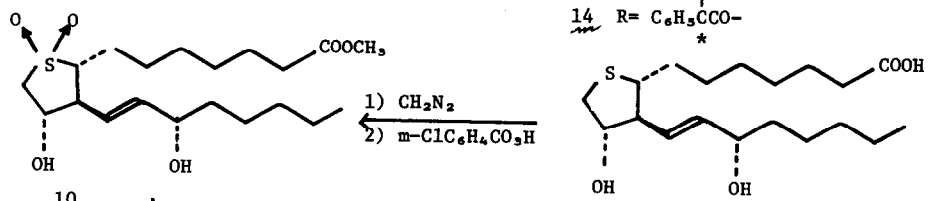
7 R= CH_2OH

8 R= CHO

9 R= THP

13 R= H

14 R= $C_6H_5\overset{*}{C}(OCH_3)CO-$



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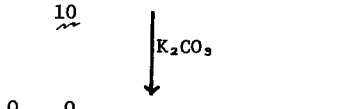

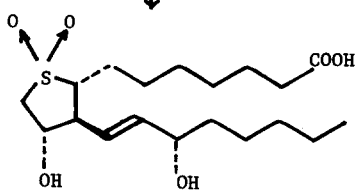

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