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SYNTHESIS OF OPTICALLY ACTIVE 15-THIAPROSTAGLANDINS

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The interest in novel prostaglandins exhibiting pharmacological specificity and increased metabolic stability has led to the synthesis of analogs possessing diverse structural modifications.[1] One approach which has recently received considerable attention has been the introduction of nitrogen, oxygen and sulfur heteroatoms into the prostanoic acid skeleton. Principal efforts in this area have focused on replacement of the 5-membered ring carbon atoms, especially the C-9 and C-11 functionalities, which are known to be intimately connected with biological activity. We now report the first synthesis of prostaglandin analogs in which the C-15 carbinol has been replaced by a sulfur heteroatom.[2]

The known[3] optically active Corey-intermediate **1** was homologated to **6** by the following sequence.[4] Mesylation of **1** with methanesulfonyl chloride/pyridine at room temperature for 10 hr gave **2** quantitatively [nmr ($CDCl_3$) δ 2.04 (3H, s, $C\underline{H}_3CO_2$), 3.01, (3H, s, $C\underline{H}_3SO_3$), 4.30 (2H, d, J = 6 Hz, $C\underline{H}_2OSO_2$), 5.06 (2H, m, C<u>H</u>OCO and C<u>H</u>OCOCH$_3$)]. This intermediate was allowed to react with 2.5 equivalents of sodium cyanide in dimethylformamide at 65° for 15 hr to give nitrile **3** (mp 109-111°) in 70% yield. Hydrolysis of **3** with 7.5 equivalents of sodium hydroxide in refluxing 70% aqueous ethanol for 20 hr led to the water soluble hydroxyacid **4**, which was isolated as the acetate **5** by treatment of crude **4** with acetic anhydride overnight [90% from **3**; nmr ($CDCl_3$) δ 2.03 (3H, s, $C\underline{H}_3CO_2$), 4.96 (2H, m, C<u>H</u>OCO and C<u>H</u>OCOCH$_3$)]. Selective reduction of the carboxyl in **5** with one equivalent of diborane in tetrahydrofuran at -20° afforded homolog **6** after chromatographic purification on silica gel [72%; nmr ($CDCl_3$) δ 2.01 (3H s, $C\underline{H}_3CO_2$), 3.71 (2H, t, J = 6 Hz, $C\underline{H}_2OH$), 5.00 (2H, m, C<u>H</u>OCO and C<u>H</u>OCOCH$_3$)].

For introduction of the prostaglandin ω-chain, alcohol **6** was quantitatively converted to mesylate **7** (mp 95-96°) with methanesulfonyl chloride/pyridine at 25° and thence to sulfide **8** by treatment of **7** with 1.02 equivalents of sodium n-pentylmercaptide in dimethylsulfoxide/tetrahydrofuran (50/50) at 0° [96%; nmr ($CDCl_3$) δ 0.88 (3H, t, J = 5 Hz, $CH_2C\underline{H}_3$), 2.03 (3H, s, $C\underline{H}_3CO_2$), 5.00 (2H, m, C<u>H</u>OCO a C<u>H</u>OCOCH$_3$)].

Elaboration of intermediate **8** to final products closely followed the procedures developed by Corey[5] in his synthesis of the natural prostaglandins. Thus, deacetylation of **8** with potassium carbonate in anhydrous methanol afforded carbinol **9** [nmr ($CDCl_3$) δ 0.90 (3H, t, J = 5 Hz, $CH_2C\underline{H}_3$), 4.0 (1H, q, C<u>H</u>OH), 4.93 (1H, m, C<u>H</u>OCO)] which gave tetrahydropyranyl ether **10** upon treatment with dihydropyran/p-toluenesulfonic acid in methylene chloride (98% from **8**). Reduction of the lactone moiety with diisobutylaluminum hydride in toluene at -78° afforded hemiacetal **11** whose reaction with the ylide derived from 5-triphenylphosphoniopentanoic acid in dimethylsulfoxide led to the $PGF_{2\alpha}$ derivative **12** [65% from **10**, nmr ($CDCl_3$) δ 5.43 (2H, m, C<u>H</u>=C<u>H</u>)]. Esterification of acid **12** with diazomethane in ether was followed by Pfitzner-Moffatt oxidation[6] and hydrolysis of the tetrahydropyranyl group with acetic acid/water (65/35, 25°, 16 hr) to give the 15-thia-13,14-dihydro PGE_2 analog **13** [74% from **12**, nmr ($CDCl_3$) δ 0.93 (3H, t, J = 5 Hz, $CH_2C\underline{H}_3$), 3.71 (3H, s, $OC\underline{H}_3$), 4.16 (1H, m, C<u>H</u>OH), 5.46 (2H, m, C<u>H</u>=C<u>H</u>)].

Preparation of the 15-sulfinyl and 15-sulfonyl analogs of **13** was achieved as follows. Oxidation of **13** with one equivalent of sodium periodate[7] in aqueous methanol at 0° afforded an R,S mixture of sulfoxides **14** [74%; nmr ($CDCl_3$) δ 0.93 (3H, t, J = 5 Hz, $CH_2C\underline{H}_3$), 3.68 (3H, s, $OC\underline{H}_3$), 4.10 (1H, m, C<u>H</u>OH), 5.41 (2H, m, C<u>H</u>=C<u>H</u>)]. Further oxidation of **14** with m-chloroperbenzoic acid at 0° in methylene chloride gave sulfone **15** [78%; nmr ($CDCl_3$) δ 0.93 (3H, t, J = 5 Hz, $CH_2C\underline{H}_3$), 3.73 (3H, s, $OC\underline{H}_3$), 4.23 (1H, m, C<u>H</u>OH), 5.46 (2H, m, C<u>H</u>=C<u>H</u>)].

Acknowledgement

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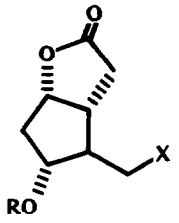
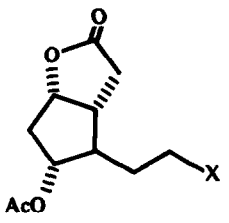
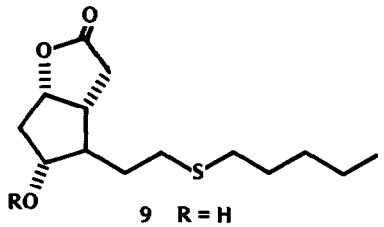


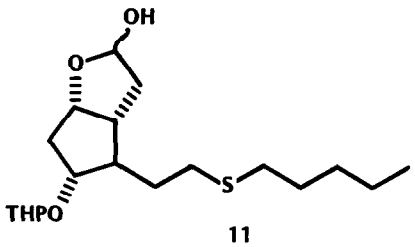
1 X = OH, R = Ac
2 X = OMes, R = Ac
3 X = CN, R = Ac
4 X = COOH, R = H
5 X = COOH, R = Ac



6 X = OH
7 X = OMes
8 X = $S(CH_2)_4CH_3$



9 R = H
10 R = THP



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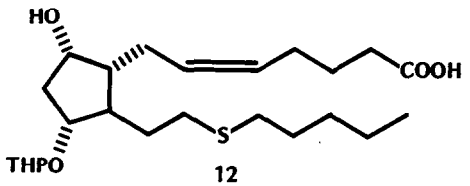

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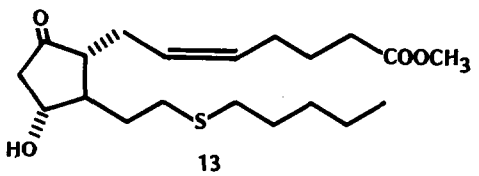

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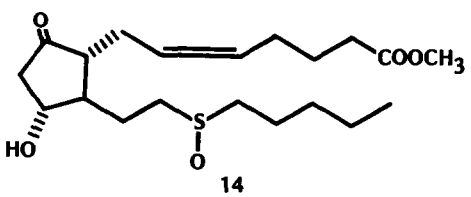

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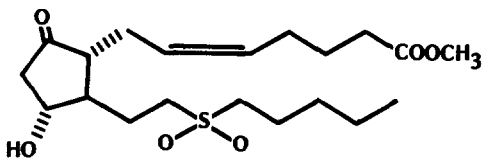

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   c) 11-Thia – I.T. Harrison, R.J.K. Taylor and J.H. Fried, Tetrahedron Letters, 1165 (1975).
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4. Final products were homogeneous on TLC and gave correct nuclear magnetic resonance and high resolution mass spectra. Key intermediates gave spectral data in agreement with the assigned structures.
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