Tetrahedron Letters No. 13, pp 1165 - 1168, 1975. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF 11-THIAPROSTAGLANDINS[1]

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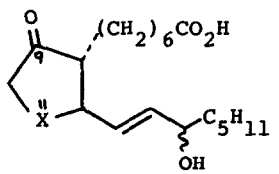
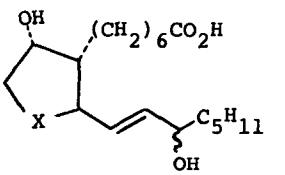
(Received in USA 22 January 1975; received in UK for publication 25 February 1975)

We have described[2] the preparation of (1a), the 11-oxa analog of the natural prostaglandin (1b). The 11-thia analogs (1c), (1d) and (2c) have now been prepared.[3]



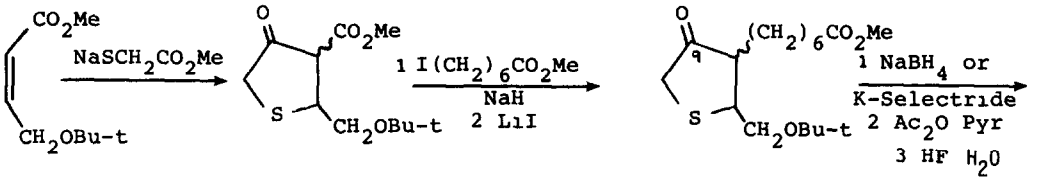
(1)

a, X=O
b, X=CHOH
c, X=S
d, X=S+ O-

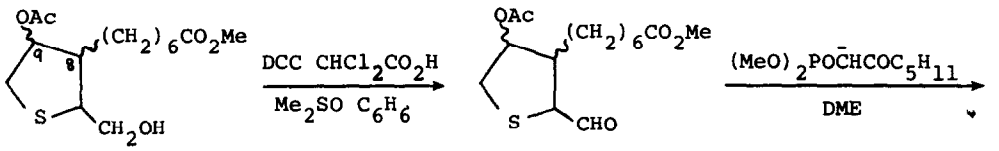


(2)

Methyl 4-t-butoxybut-2-enoate[2,4] (3) was prepared in 68% yield by carbomethoxylation (EtMgBr, $(MeO)_2CO$ in THF) of 3-t-butoxyprop-1-yne[5] followed by partial hydrogenation with palladium-on-charcoal catalyst in methanol. Addition[6] of methyl thioglycolate gave the tetrahydrothiophenone (4) [52%; b.p. 115-118°/1 mm; ν_{max} (film) 1760, 1740 cm^{-1}; m/e (%) 190 (22), 246 (M, 3)], which was alkylated with methyl 7-iodoheptanoate (NaH in DMF-HMPA, 1:1) and decarbomethoxylated with LiI in DMF under reflux, forming the ketoester (5) [24%; ν_{max} ($CHCl_3$) 1730 cm^{-1}; m/e (%) 211 (31), 242 (32), 274 (26), 330 (M, 9)]. Reduction with sodium borohydride in methanol, acetylation with acetic anhydride pyridine, and cleavage of the t-butyl protecting group with 48% aqueous HF in

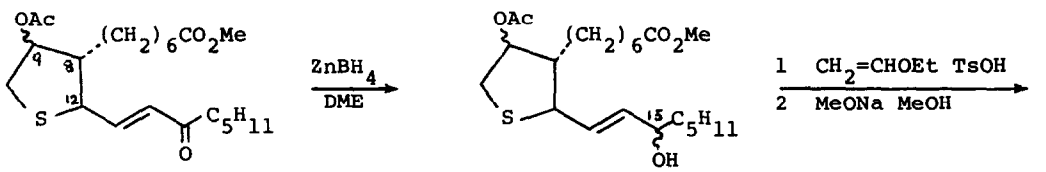


(3) (4) (5)



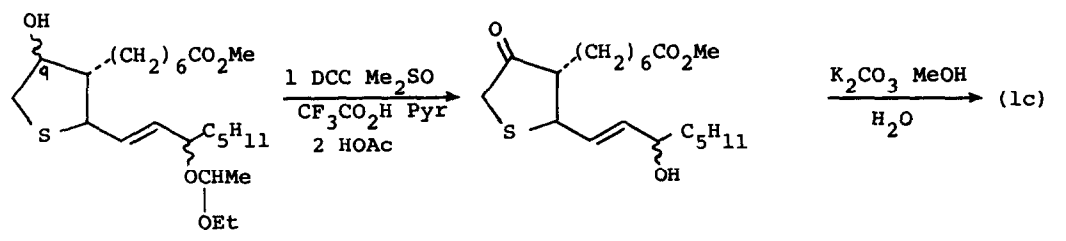
(6) 8,9-cis + trans
(7) 8,9-cis

(8) 8,9-cis + trans
(9) 8,9-cis



(10) 9(α + β)
(11) 9α

(12) 9(α + b)
(13) 9α



(14) (15)

THF (100:15, v/v) gave the alcohol (6) [59%; m/e (%) 228 (21), 240 (8), 258 (M-HOAc, 3)]. The t-butyl group was not cleaved in satisfactory yield by the more usual reagents HBr in HOAc, HSO_3F in CH_2Cl_2, $HClO_4$ in Et_2O, or CF_3CO_2H.

The remaining steps in the synthesis were completed by methods described previously[2], via the aldehyde (8), enone (10) [ν_{max} ($CHCl_3$) 1725, 1665, 1630 cm^{-1}; m/e (%) 352 (3), 412 (M, 3)] (which is assumed to have the more stable trans disposition of the side chains at positions 8 and 12), the 15(α + β) alcohols (12) [m/e (%) 336 (1), 396 (M-H_2O, 4)], the 9(α + β) alcohols (14) [ν_{max} ($CHCl_3$) 1730 cm^{-1}; m/e (%) 354 (4), 426 (M-H_2O, 0.4)] and the ketone (15) [ν_{max} (film) 3300, 1730 cm^{-1}; m/e (%) 352 (43), 370 (M, 19)]. Hydrolysis of the methyl ester group of (15) gave 15(α + β)-hydroxy-9-oxo-11-thiaprost-13-enoic acid (1c) [14% from (6); gum; m/e 338 (M-H_2O)]. Oxidation of (15) with one equivalent of m-chloroperbenzoic acid in CH_2Cl_2 gave the sulfoxide isomer mixture (1d) methyl ester [ν_{max} ($CHCl_3$) 1735 cm^{-1}; m/e (%) 352 (1), 370 (1), 386 (M, 1)]. Hydrolysis of the methyl ester group of this substance was attended by decomposition.

For the synthesis of the prostaglandin $F_{2\alpha}$ analog (2c), the ketone (5) was reduced with K-Selectride (potassium tri-sec-butylborohydride)[7] to the 8,9-cis alcohol [m/e (%) 259 (1), 314 (0.3), 332 (M, 0.3)]. Using the methods described above, this was converted into acetoxyalcohol (7), aldehyde (9), enone (11) [m/e (%) 352 (1), 380 (M-MeOH, 1), 412 (M, 33)], and the 15(α + β) epimer mixture (13) [ν_{max} ($CHCl_3$) 3500-3300, 1735 cm^{-1}]. Hydrolysis gave the required 9α,15(α + β)-dihydroxy-11-thiaprost-13-enoic acid (2c) [6% from (5); ν_{max} ($CHCl_3$) 3350-3150, 1700 cm^{-1}; m/e (%) 129 (M-$(CH_2)_6CO_2H$, 66), 281 (59), 340 (M-H_2O, 58)].

The prostaglandin analogs (1c) and (2c) were active (ca. 0.005 x PGE_2) in the gerbil colon assay.[8]

REFERENCES AND FOOTNOTES

1. Contribution No. 449 from the Syntex Institute of Organic Chemistry and No. 42 in the series Studies in Prostaglandins.

2. I. T. Harrison, V. R. Fletcher and J. H. Fried, Tetrahedron Letters, 2733 (1974).

3. I. Vlattas and L. Della Vecchia, Tetrahedron Letters, 4267 (1974), have

prepared the 9-thia analogs.

4. Satisfactory elemental analyses were obtained for (3), (4) and (5). H^1 nmr spectra of compounds (3)-(15), (1c), (1d) methyl ester, and C^{13} spectra of (10), (11), (12), (13), (15), (1c), (1d) methyl ester and (2c) were consistent with the assigned structures. We thank M. Maddox, L. Tökés, J. Nelson and B. Amos for the nmr and mass spectra and for their interpretation. All synthetic products are racemic.

5. R. Mantione, Bull. Soc. Chim. Fr., 4523 (1969).

6. M. A. Gianturco, P. Friedel and A. S. Giammarino, Tetrahedron, 20, 1763 (1964).

7. C. A. Brown, J. Amer. Chem. Soc., 95, 4100 (1973). H. C. Brown and S. Krishnamurthy, ibid., 94, 7159 (1972). E. J. Corey and R. K. Varma, ibid., 93, 7319 (1971).

8. We wish to thank W. Rooks and S. Jubb for these assays.