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TOTAL SYNTHESIS OF PROSTAGLANDIN D_1 METHYL ESTER AND 9-EPI-PROSTAGLANDIN D_1 METHYL ESTER

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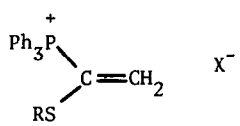
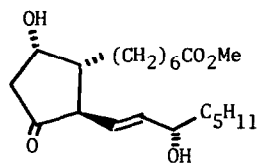
Summary: Syntheses of the title compounds are described via the dithiane enone (VIII); cuprate addition to (VIII) proceeds with asymmetric induction.

Although much effort has been devoted to prostaglandin synthesis there have been very few approaches[1] to the D series of compounds, which are of interest in view of their ability to inhibit platelet aggregation. We have previously described the synthesis of the vinyl phosphonium salt (I) and its use in the synthesis of cyclopentanones.[2] We now describe the use of the related salt (II)[3] in the synthesis of PGD_1 derivatives including PGD_1 methyl ester (III).



I, R = Ph, X = I
II, R = Me, X = Cl



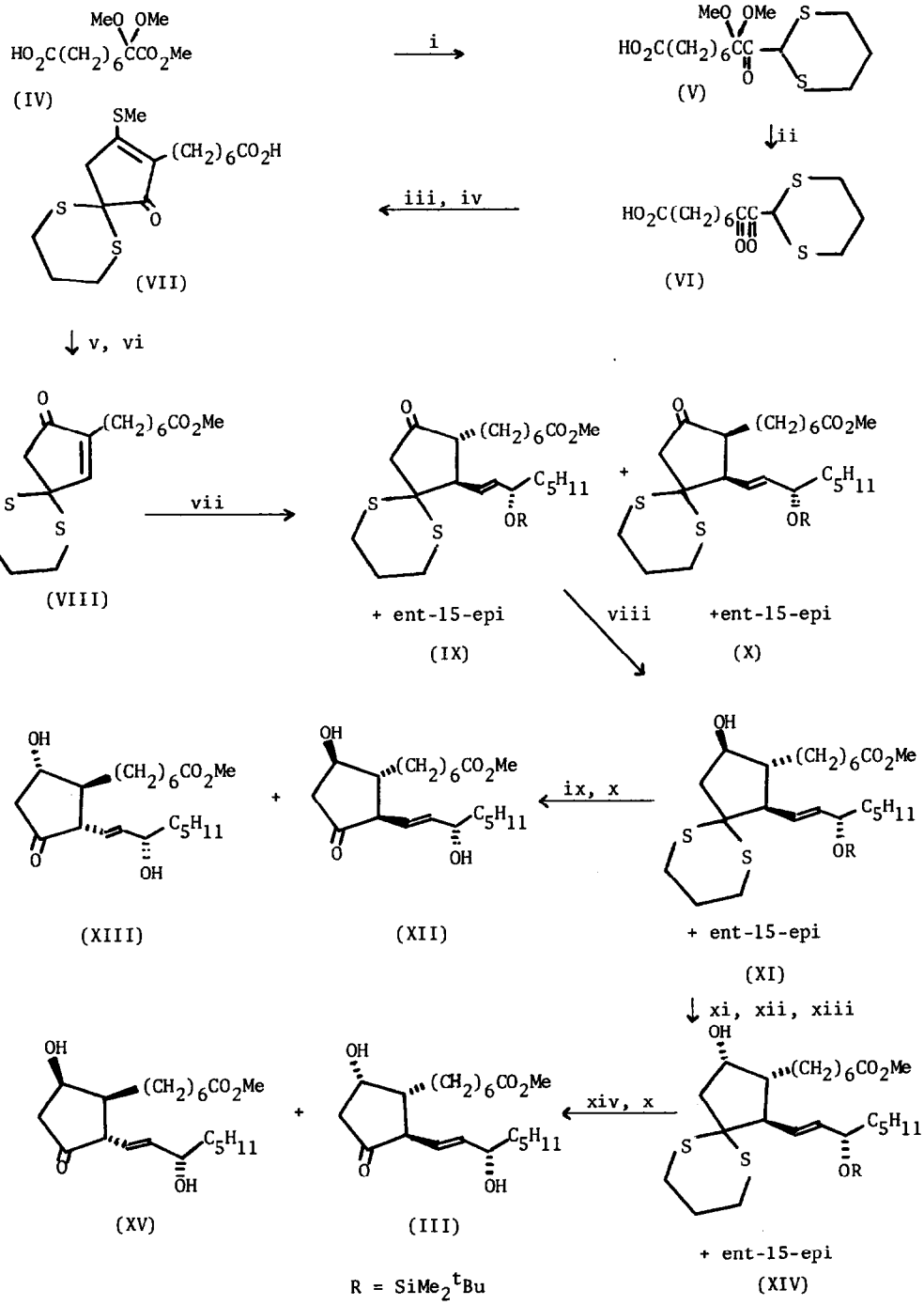
III

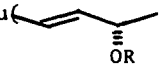
Alkylation of methyl dimethoxyacetate[4] with the lithium salt of 7-iodoheptanoic acid gave (IV) (73%) which was treated with the anion of dithiane to give (V)[5,6] (59%). Hydrolysis with aqueous TFA gave the diketodithiane (VI) (97%; m. 96-98°). Cyclisation was accomplished on treatment of (VI) with phosphonium salt (II) in the presence of sodium hydride, giving (VII) (79%; m. 88-90°). Reduction of the vinylogous thioester in (VII) followed by acid catalysed rearrangement and esterification gave (VIII) (59%; oil; IR (neat) 1745, 1708, 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.45, s, 1 H).

The enone (VIII) was unreactive towards heterocuprate reagents of the type often used in PG synthesis[1,7] but reacted with an excess of the homocuprate reagent to give a 2.2:1 mixture of (IX) (IR (neat) 1750 cm^{-1}) and (X) (IR (neat) 1750 cm^{-1}) (total 56%)[8].

If an excess of cuprate reagent was not used then considerable amounts of the enone (VIII) were recovered. The production of the *cis*-isomer (X) is unusual. It is presumed that the dithiane ring is affecting the conformation of the cyclopentane in such a way as to reduce the preference for protonation of the enolate from that side which leads to the *trans* arrangement of the C-8 and C-12 side chains. Attempts to isomerise (X) to (IX) using a mild base were unsuccessful.

Scheme


MeO OMe
HO2C(CH2)6CCO2Me
(IV)
i
(V)
ii
iii, iv
(VI)
SMe
(CH2)6CO2H
(VII)
v, vi
(CH2)6CO2Me
(VIII)
vii
C5H11
OR
+ ent-15-epi
(IX)
viii
+ent-15-epi
(X)
OH
ix, x
(XIII)
(XII)
+ ent-15-epi
(XI)
xi, xii, xiii
xiv, x
(XV)
(III)
+ ent-15-epi
(XIV)
R = SiMe2tBu

Reagents (see scheme opposite) i, LDA, dithiane; ii, TFA/H_2O; iii, NaH; iv, (II); v, $LiBH_4$, THF, MeOH; vi, HCl, MeOH; vii, $LiCu($  $C_5H_{11})_2$; viii, $NaBH_4$, MeOH; ix, trichloroisocyanuric acid, $AgNO_3$; x, HF, MeCN, H_2O; xi, $MeSO_2Cl$, pyridine; xii, $Bu_4N^+OAc^-$; xiii, NaOMe, MeOH; xiv, HgO, $BF_3.Et_2O$.

Reduction of (IX) with sodium borohydride proceeded stereospecifically to give, rather surprisingly, the 9β-alcohol (XI) (100%; IR (neat) 3460, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.88, br s, 1 H). Careful analysis of the 400 MHz ^1H NMR spectrum showed the absence of the 9α-alcohol. H-9 in 9β-hydroxy PG's is known to occur at approx. 0.3 ppm upfield from the corresponding signal in 9α-hydroxy PG's[9]. Hydrolysis of the dithiane group followed by desilylation gave a separable mixture of (XII) (IR (neat) 3450, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) similar to that of (III) except the signal at δ 4.55 in the latter for H-9 is replaced by a signal at δ 4.1) and (XIII) (total 43%).

Inversion of stereochemistry at C-9 in (XI) was accomplished via an S_N2 displacement on the mesylate leading to (XIV) (58%; IR (neat) 3500, 1740 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.2, m, 2 H). Hydrolysis of the dithiane in (XIV) proceeded only in poor yield using trichloroisocyanuric acid/$AgNO_3$[10] but was readily achieved (50%) using $HgO/BF_3.Et_2O$[11]. Desilylation then afforded a 3.7:1 separable mixture of PGD_1 methyl ester (III) (IR (neat 3560, 1745, 1730 (sh) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.61, dd, 1 H; 5.41, dd, 1 H; 4.55, m, 1 H; 4.09, m, 1 H; 3.68, s, 3 H; 2.78, dd, 1 H; 2.44, d, 1 H; 2.31, t, 2 H; 2.01-0.88, m, 22 H) and (XV) (total 68%).

Further confirmation of the stereochemical assignments was obtained by the synthesis of 11-deoxy PGF derivatives. Thus the mixture (XI) was desilylated and then separated. The major isomer was treated with Raney Ni followed by NaOH to give a product which co-chromatographed with authentic 11-deoxy $PGF_{1\alpha}$. Similar treatment of (XIV) gave a product chromatographically identical to 11-deoxy $PGF_{1\beta}$.

The ratios of (XII):(XIII) and (III):(XV) indicate that the cuprate reaction shows considerable selectivity in producing the configuration found in the natural PG's[12]. Such a pronounced selectivity is not usually observed in cuprate reactions which add the intact C-12 PG side chain to enones either unsubstituted or with a single oxygen functionality at C-11. Again it is presumed to be the spiro dithiane system which is causing subtle differences in the transition states leading to the two diastereoisomers.

Acknowledgement

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References and footnotes

1. T.W. Hart, D.A. Metcalfe and F. Scheinmann, Chem. Comm., 1979, 156 and refs. cited therein; D.P. Reynolds, R.F. Newton and S.M. Roberts, Chem. Comm., 1979, 1150.
2. A.T. Hewson, Tet. Let., 1978, 3267.
3. Prepared in an analogous manner to (I). The reasons for using (II) rather than (I) will be discussed in a full paper.
4. J.M. Conia, F. Huet and M. Pellet, Synthesis, 1979, 33.
5. This reaction is general and further applications will be reported.
6. I. Kawamoto and Y. Yura, Tet. Let., 1974, 4223.
7. C.J. Sih, J.B. Heather, R. Sood, P. Price, G. Peruzzotti, L.F. Hsu Lee and S.S. Lee, J. Am. Chem. Soc., 1975, 97, 865.
8. The two diastereomers in each of (IX) and (X) were not separable by TLC. The mixture (IX) was carried forward. Assignment of stereochemistry in (IX) and (X) was made on the basis of the ^{13}C NMR spectra. In the *cis*-isomer (X) the γ-gauche effect causes an upfield shift of the signals for C7 and C13 relative to those in the *trans*-isomer (IX).
9. F.H. Lincoln, W.P. Schneider and J.E. Pike, J. Org. Chem., 1973, 38, 951.
10. G.A. Olah, S.C. Narang and G.F. Salem, Synthesis, 1980, 659.
11. E. Vedejs and P.L. Fuchs, J. Org. Chem., 1971, 36, 366.
12. Desilylation of (X) showed it was also a 3.7:1 mixture of diastereomers.

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