Enantio-complementary Total Asymmetric Syntheses of Prostaglandin E_2 and Prostaglandin $F_{2\alpha}$

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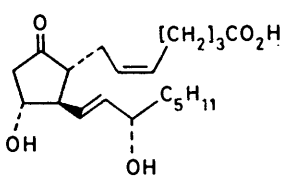
The racemic ketone (6) was converted into the diastereoisomeric alcohols (7) and (8) using actively fermenting yeast. These alcohols were separated and converted into the bromohydrins (−)-(9) and (+)-(9). The bromohydrin (−)-(9) was converted into prostaglandin E_2 (1) and prostaglandin $F_{2\alpha}$ (2) by reaction of the chiral cuprate reagent (15) with the tricyclic ketone (10), while the bromohydrin (+)-(9) was converted into the prostaglandins by reaction of the epoxyacetal (11) with the same cuprate reagent (15).

PROSTAGLANDINS-E_2 (1) and -$F_{2\alpha}$ (2) occur naturally and display potent and wide-ranging biological activities. The enantiomers of (1) and (2) are biologically inactive. It is therefore of interest to prepare prostaglandins in an optically active form by methods which are of general use for the asymmetric synthesis of chiral prostaglandin analogues.

Four methods have been used previously to prepare optically active prostaglandins of the natural configuration. (i) Classical resolution of a prostaglandin intermediate [*e.g.* (3) [1] or (4) [2]] which possesses a carboxylic



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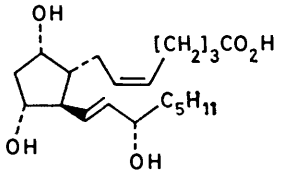

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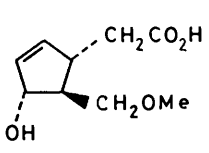

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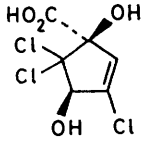

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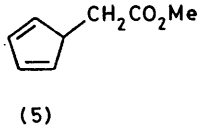

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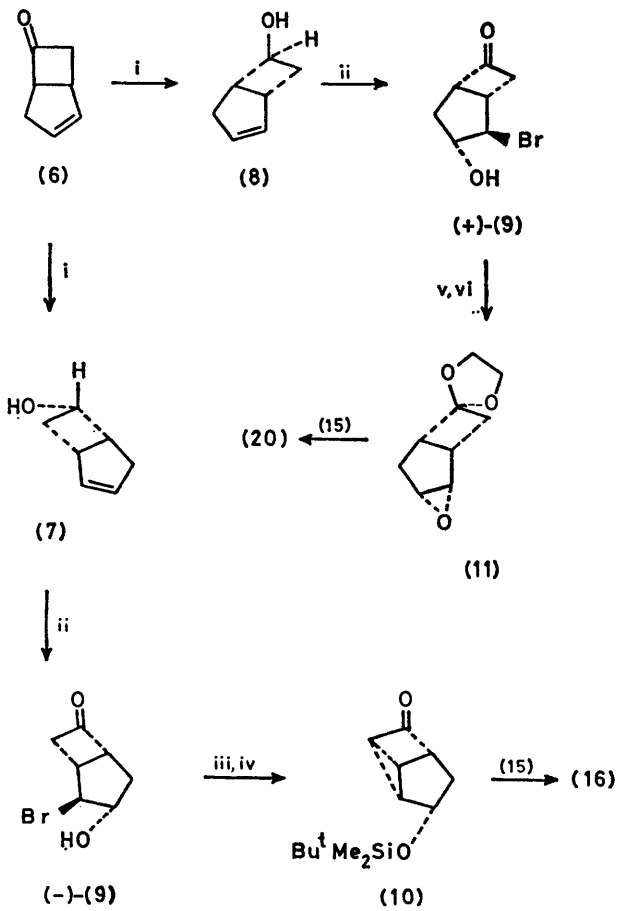
acid, oxime, or alcohol group. Usually half of the racemic material must be discarded at this stage.[3] (ii) Modification of an optically pure, readily available material (*e.g.* glucose,[4] glyceraldehyde,[5] aucubin,[6] or malic acid [7]). These ingenious routes are invariably protracted and quite unsuitable for large-scale production of prostaglandin analogues. (iii) Substrate-enantioselective, microbiological processes including reduction,[8] hydroxylation,[9] and hydrolysis [10] which provide simple, chiral synthons for prostaglandin synthesis. (iv) Reaction of a prostaglandin precursor with a chiral reagent [*e.g.*, hydroboration of the ester (5) using (−)-dipinan-3-ylborane [11]].

We now report a new approach, namely two total, asymmetric syntheses of (−)-prostaglandin E_2 (1) and (+)-prostaglandin $F_{2\alpha}$ (2) that effectively use both enantiomers of the readily available ketone (6).

RESULTS AND DISCUSSION

The racemic ketone (6) [12] was converted into the diastereoisomeric alcohols (7) and (8) in good chemical and optical yields using actively fermenting bakers yeast. The alcohols (7) and (8) were separated and con-

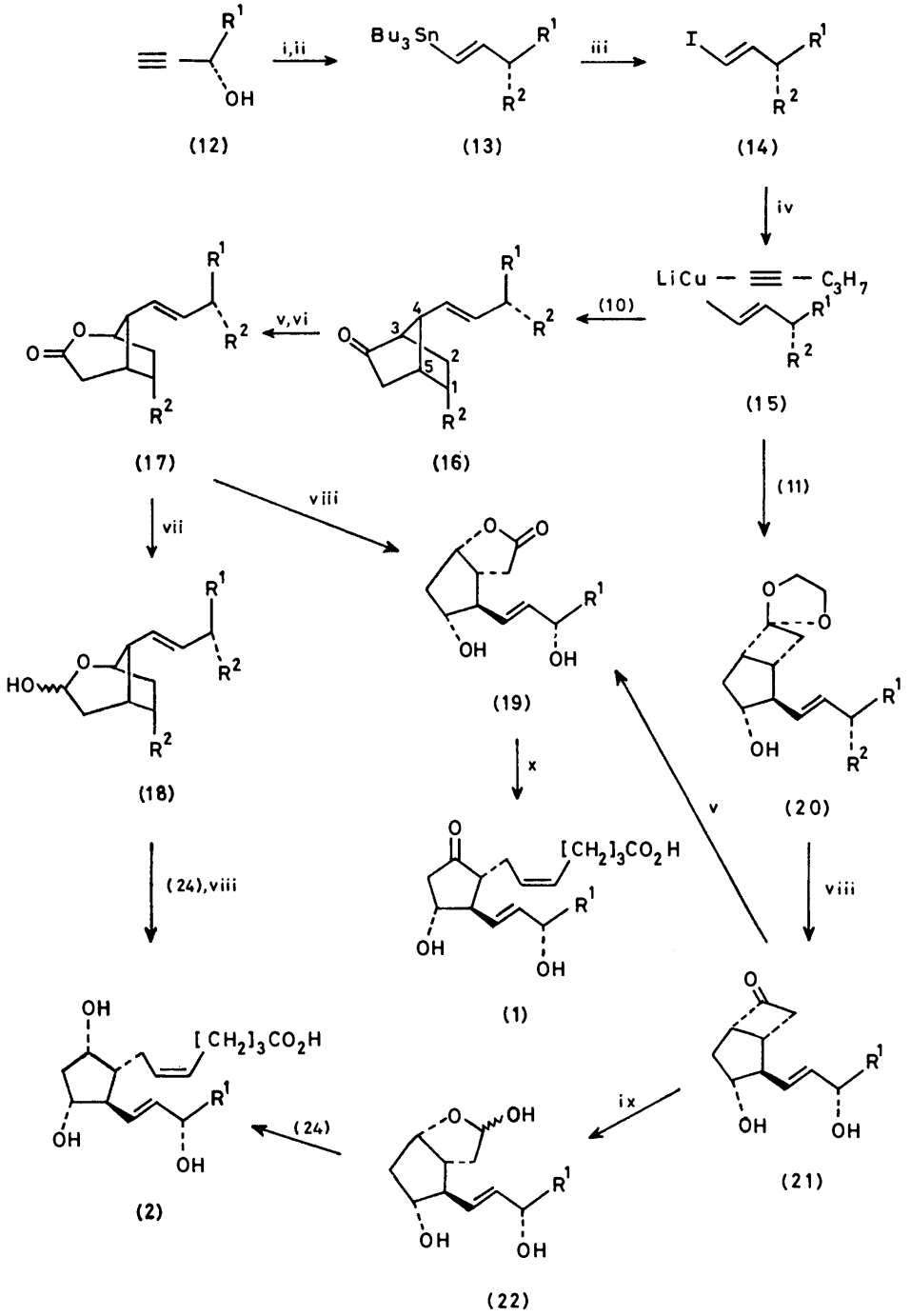


SCHEME 1 *Reagents:* i, Yeast, H_2O, glucose; ii, *N*-bromosuccinimide; iii, $ClSiMe_2Bu^t$, imidazole, dimethylformamide (DMF); iv, $KOBu^t$, $HOBu^t$; v, $(CH_2OH)_2$, H^+; vi, K_2CO_3, MeOH.

verted into the crystalline bromohydrins (−)-(9) and (+)-(9), respectively, using *N*-bromosuccinimide in aqueous acetone containing a small amount of acetic acid. One recrystallization of the bromohydrins furnished optically pure materials.[12]

The bromohydrin (−)-(9) was silylated and dehydrobrominated to give the tricycloalkanone (10),[13] while the bromohydrin (+)-(9) was converted into the epoxyacetal (11) [14] (Scheme 1).

(3*S*)-Oct-1-yn-3-ol (12) was obtained as described previously [15] and was converted into the vinylstannane (13) using the procedure outlined by Pappo *et al.* and Grudzinskas *et al.*[16] While it was possible to exchange the tin moiety for a lithium atom directly, we elected to prepare



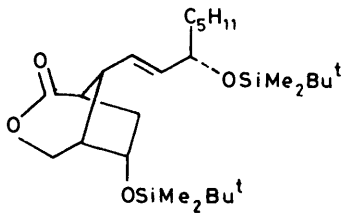
$R^1 = C_5H_{11}$, $R^2 = OSiMe_2Bu^t$

SCHEME 2 *Reagents:* i, $ClSiMe_2Bu^t$, imidazole, DMF; ii, $(Bu^n)_3SnH$; iii, I_2; iv, BuLi, CuC_5H_7; v, $MeCO_3H$, $MeCO_2H$; vi, NaOH; vii, $HAl(Bu^i)_2$; viii, H^+, H_2O; ix, $h\nu$, H_2O, MeCN; x, ref. 1

the iodoalkene (14) to assist in the final purification of this side-chain, prior to the lithiation and formation of the required cuprate reagent (15) using the standard methodology.

The cuprate reagent (15) reacted with the tricyclic ketone (10) to give the norbornanone (16) in very good yield. Baeyer–Villiger oxidation of the ketone (16) using peracetic acid gave the δ-lactone (17). The work-up of this oxidation reaction involved washing the crude product with a dilute, aqueous solution of sodium hydroxide to remove the small quantity of the isomeric δ-lactone (23) that was present (Scheme 2).[17]

The δ-lactone (17) was reduced to the lactol (18), treated with the ylide (24), and desilylated to give prostaglandin $F_{2\alpha}$ (2), $[\alpha]_D^{23}$ +23.0° [*c* 1.00, tetrahydrofuran (THF)] [lit.,[1] $[\alpha]_D^{25}$ +23.5° (*c* 1.00, THF)]. The δ-lactone (17) was converted also into the γ-lactone (19), $[\alpha]_D^{23}$ −7.8° (*c* 1.00, chloroform) [lit.,[1] $[\alpha]_D^{27}$ −7.0° (*c* 1.43, chloroform)] on treatment with acid,[18] and this lactone was converted into prostaglandin E_2 (1) (Scheme 2).[1]



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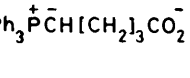

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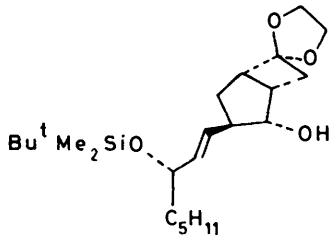

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The cuprate reagent (15) reacted with the epoxy-acetal (11) in a highly regioselective manner to give the hydroxy-acetal (20) in good yield, after chromatography to remove the small amount of the isomeric material (25) that was formed concurrently. Acid-catalysed deprotection of (20) gave the dihydroxy-ketone (21). This ketone was oxidized at low temperature, using peracetic acid, to give the γ-lactone (19), $[\alpha]_D^{23}$ −6.8° (*c* 1.00, chloroform). Photolysis of the ketone (21) in aqueous acetonitrile gave the lactol (22); this was allowed to react with the ylide (24) and the product chromatographed to give prostaglandin $F_{2\alpha}$ (2) $[\alpha]_D^{23}$ +22.6° (*c* 1.00, THF) (Scheme 2).

The yields obtained in the above asymmetric syntheses were very similar to those reported by us previously for the analogous reactions of racemic materials.[12,13,17,18] The overall yields are highly satisfactory. For example, the yield of prostaglandin $F_{2\alpha}$ from the bromohydrin (−)-(9) was 15% and from the bromohydrin (+)-(9), the overall yield of prostaglandin $F_{2\alpha}$ was 18%.

Other enantio-complementary syntheses of naturally occurring prostaglandins are currently under investigation.

EXPERIMENTAL

I.r. spectra were recorded on a Perkin-Elmer 297 spectrophotometer for neat films unless otherwise stated. N.m.r. spectra were recorded on a Varian EM-360 or Perkin-Elmer R-32 spectrometer ($CDCl_3$ solvent). Optical rotations were measured on a PBL-NPL/143D instrument. Camlab silica plates were used for t.l.c., Merck silica 60H was used for column chromatography, and anhydrous magnesium sulphate was used for drying solutions in organic solvents.

(3*S*)-3-*Dimethyl-t-butylsilyloxy*-1-*iodo-oct*-1-*ene* (14).—(3*S*)-Oct-1-yn-3-ol (12) [15] was silylated in the usual manner [19] to give (3*S*)-3-dimethyl-t-butylsilyloxyoct-1-yne (96%), b.p. 64 °C/2 × 10^{-1} mmHg; $[\alpha]_D^{23}$ −46.8° (*c* 1.00, diethyl ether). The protected octyne (43.0 g), tri-n-butyltin hydride (77.9 g), and azobisisobutyronitrile (0.25 g) were stirred under an atmosphere of nitrogen at 130 °C for 3 h. Excess of tri-n-butyltin hydride was removed by vacuum distillation and the residue was dissolved in dry ether (500 ml) and cooled to 0 °C. Iodine (45.5 g) was added, in portions, and the mixture was stirred for 1 h. The solvent was evaporated *in vacuo*. The residue was dissolved in ethanol (200 ml) and shaken with a slurry of potassium fluoride (50 g) in ethanol (200 ml) for 30 min. The mixture was filtered and the filtrate was evaporated. The residue was chromatographed over silica using light petroleum (b.p. 60—80 °C) as eluant to give (3*S*)-3-dimethyl-t-butylsilyloxy-1-iodo-oct-1-ene (14) (41.7 g), b.p. 106 °C/2.5 × 10^{-1} mmHg; $[\alpha]_D^{23}$ −28.9° (*c* 1.00, chloroform).

The bromohydrins (−)-(9) and (+)-(9) were prepared in optically pure form by the method described previously.[12]

The conversion of the bromohydrin (−)-(9) into the tricyclic ketone (10), the reaction of this ketone with the cuprate reagent (15) derived from the iodoalkene (14), and the conversion of the resulting norbornanone (16) into prostaglandin E_2(1) and prostaglandin $F_{2\alpha}$(2) utilized experimental conditions that have been described previously [13,16,18] for the corresponding reactions involving racemic materials. The yields obtained for the reactions involving the chiral substrates and the optical rotations of key intermediate compounds are described below. The bromohydrin (−)-(9) was silylated and treated with base to furnish the unstable tricyclic ketone (10) (76%) which was immediately treated with the cuprate reagent (15) to give the bicycloheptanone (16) (61%), $[\alpha]_D^{23}$ +37.2° (*c* 1.00, in $CHCl_3$). Baeyer–Villiger oxidation of the ketone (16) gave the lactone (17) (62%), $[\alpha]_D^{23}$ −13.5° (*c* 1.00, in $CHCl_3$). Reaction of the lactone (17) with di-isobutylaluminium hydride gave the unstable lactol (18) which was allowed to react directly with the ylide (24) and desilylated to give prostaglandin $F_{2\alpha}$ (2) (52%), $[\alpha]_D^{23}$ +23.0° [*c* 1.00, in tetrahydrofuran (THF)]. Treatment of the δ-lactone (17) with aqueous HF in acetonitrile gave the γ-lactone (19) (81%), $[\alpha]_D^{23}$ −7.8° (*c* 1.00, in $CHCl_3$). This lactone was converted into prostaglandin E_2 in the prescribed manner.[1]

The conversion of the bromohydrin (+)-(9) into the

epoxy-acetal (11), the reaction of this epoxide with the cuprate reagent (15), and the conversion of the resultant alcohol (20) into prostaglandin E_2 (1) and prostaglandin $F_{2\alpha}$ (2) used conditions that we had optimized earlier when working with the corresponding racemic compounds.[14] The yields obtained in this work and optical rotations of key intermediates are given below. The bromohydrin (+)-(9) was treated with ethylene glycol and dehydrobrominated to give the epoxy-acetal (11) (94%), $[\alpha]_D^{23}$ +3.7° (*c* 1.00, in $CHCl_3$). Reaction of the epoxy-acetal (11) with the cuprate reagent (15) gave the hydroxy-acetal (20) (58%), $[\alpha]_D^{23}$ +13.0 (*c* 1.00, in $CHCl_3$), which was deprotected using dilute sulphuric acid to give the dihydroxy-ketone (21) (95%), $[\alpha]_D^{23}$ +81.6° (*c* 1.00, in $CHCl_3$). Photolysis of the ketone (21) in aqueous acetonitrile followed by reaction of the crude product with the ylide (24) gave prostaglandin $F_{2\alpha}$ (40%), $[\alpha]_D^{23}$ +22.6° (*c* 1.00 in THF). Reaction of the ketone (21) with peracetic acid at −78 °C gave the dihydroxy-ketone (19) (98%), $[\alpha]_D^{23}$ −6.7° (*c* 1.00, in $CHCl_3$).

The other physical properties of the intermediates were identical with those reported for the racemic compounds.

We gratefully acknowledge Glaxo Group Research for the provision of a Research Fellowship (to J. D.).

[0/1416 *Received*, 15*th September*, 1980]

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