Enantiocomplementary Total Asymmetric Syntheses of Prostaglandin A_2

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Both enantiomers of the racemic ketone (4) have been converted into (+)-PGA_2 by utilizing two different synthetic pathways. In one route the reaction of the strained tricyclic ketone (8) with the cuprate reagent (9) was the critical step, while in the 'enantiocomplementary' process the S_N' reaction of the same cuprate reagent with the epoxide (16) was the crucial transformation.

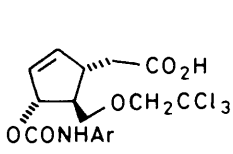
Prostaglandin A_2 (PGA_2) is an important natural product. Not only does it display biological activity itself [1] but it can be converted into other biologically active prostaglandins [2] and interesting analogues.[3]

Previously, optically active PGA_2 possessing the natural configuration has been obtained by (i) dehydration of prostaglandin E_2,[4] (ii) modification of simple PGA_2 derivatives obtained from the Caribbean coral *Plexaura homomalla*,[5] and (iii) total synthesis. Corey's syntheses of PGA_2 [6,7] required the resolution of the acid (1) or the acid (2) and in both cases the unwanted enantiomer was discarded. Stork's elegant but lengthy synthesis of (+)-PGA_2 commenced from the readily available sugar derivative (3).[8]

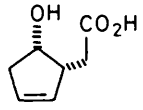
We have previously reported that the ketone (4) can be resolved by microbiological reduction to the diastereoisomeric alcohols (5) and (6) in excellent chemical and optical yields [9] and we describe herein the conversion of *both* alcohols into optically active PGA_2. This is the second example of enantiocomplementary asymmetric syntheses of a prostaglandin from the racemate (4): our earlier work concerning the preparation of (−)-PGE_2 and (+)-$PGF_{2\alpha}$ from (±)-(4) has been discussed elsewhere.[10]

The bicycloheptenol (5) was brominated and the product was oxidized with *N*-bromosuccinimide (NBS) in acetic acid to give the ketone (7) (Scheme). Treatment of compound (7) with base gave the tricycloheptanone (8)† which reacted with the cuprate reagent (9) [10] to give the norbornanone (10) in good yield. Baeyer–Villiger oxidation and then dehydrobromination gave the lactone (11). Rearrangement of compound (11) in warm dimethylformamide solution followed by treatment of the crude reaction product with HF in aqueous acetonitrile gave the γ-lactone (12), $[\alpha]_D^{23}$ +294° (*c*, 1.00 in chloroform) {lit.,[6] $[\alpha]_D^{20}$ +275° (*c*, 1.36 in chloroform); lit.,[7] $[\alpha]_D^{18}$ +252° (*c*, 0.2 in chloroform)}, the conversion of which into (+)-PGA_2 has been described previously.[6]

Alternatively, the alcohol (6) was oxidized to the γ-lactone, (13) allylic bromination of which gave a mixture of the 8-bromo- (14) and the 6-bromo-oxabicyclo-octenone (15). The required 8-bromo-isomer (14) was separated by column chromatography: a further quantity of this compound was obtained by refluxing a mixture of the bromo-lactones (14) and (15) in toluene, followed by removal of the solvent and chromatography.‡ The yield of the bromo-lactone (14) from the γ-lactone (13) was 44%.



(1)



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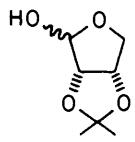


(3)

The lactone (14) was treated with methoxide ion to furnish the epoxide (16). Reaction of this epoxide with the cuprate reagent (9) gave the required γ-lactone (17) (34%) and the isomer (18) (21%). The lactone (17), which was purified by flash chromatography over silica gel, was treated with HF in aqueous acetonitrile to give the PGA_2 precursor (12), $[\alpha]_D^{23}$ +291° (*c*, 1.71 in chloroform).

The overall yield of the lactone (12) from the alcohol (5) was 10.3%, while from the alcohol (6) the overall yield of compound (12) was 6.4%.

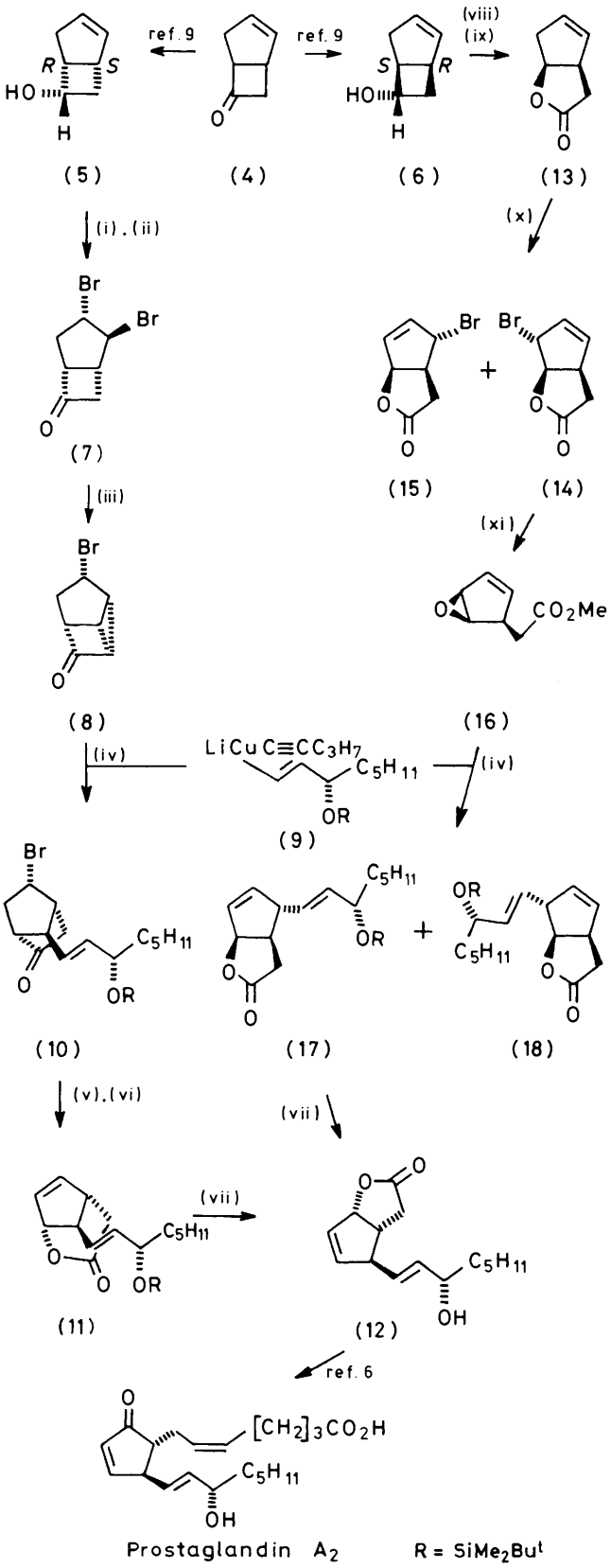
Experimental

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 $MgSO_4$ was used for drying solutions in organic solvents. Unless otherwise stated, experiments were conducted on a scale in the range 0.5 mmol—6.5 mmol.

(+)-2,3-*Dibromobicyclo*[3.2.0]*heptan*-6-*one* (7).—To a solution of the alcohol (5) (1.1 g) in carbon tetrachloride (20 ml) containing sodium hydrogen carbonate (2.0 g) at 0 °C was added, dropwise, a solution of bromine (1.6 g) in carbon tetrachloride (10 ml). The mixture was stirred for 2 h at 0 °C. After filtration of the mixture and evaporation of the filtrate under reduced pressure, acetone (40 ml), water (4 ml), acetic acid (0.5 ml) and NBS (2.1 g) were added to the residue. The mixture was stirred for 24 h and a second batch of NBS (2.1 g) was then added. After filtration of the mixture the acetone was removed from the filtrate under reduced pressure. Diethyl ether (50 ml) was added to the residue and this solution was washed in turn, with 2M hydrochloric acid (2 × 50 ml), water (1 × 50 ml), dilute aqueous sodium hydrogen carbonate (2 × 50 ml), and water (1 × 50 ml). The organic phase was dried

† The corresponding reactions on racemic materials have been described previously: J. C. Gilbert, T. Luo, and R. E. Davies, *Tetrahedron Lett.*, 1975, 2545; J. C. Gilbert, T. Luo, and U. Patel, *J. Org. Chem.*, 1981, **46**, 4042; M. A. W. Finch, S. M. Roberts, G. T. Woolley, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1981, 1725.

‡ The corresponding reactions using racemic materials have been described previously: C. B. Chapleo, M. A. W. Finch, T. V. Lee, S. M. Roberts, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2084.



Scheme. *Reagents*: (i) Br_2, $NaHCO_3$, CCl_4; (ii) NBS, H_2O, Me_2CO, $MeCO_2H$; (iii) $NaN(SiMe_3)_2$; (iv) reagent (9), −78 °C, CH_2Cl_2 or Et_2O; (v) *m*-$ClC_6H_4CO_3H$; (vi) diazabicycloundecene; (vii) heat, Me_2NCHO; then HF, H_2O, MeCN; (viii) Collins oxidation; (ix) $MeCO_3H$; (x) NBS, CCl_4, *hν*; (xi) K_2CO_3, MeOH, Et_2O; (xii) HF, H_2O, MeCN

and evaporated to dryness, and the residue was chromatographed over silica with light petroleum (b.p. 40—60 °C)–diethyl ether (95 : 5) as eluant to give the ketone (7), $[\alpha]_D^{23}$ +16.2° (*c*, 1.0 in chloroform).*

(−)-8-*Bromo*-2-*oxabicyclo*[3.3.0]*oct*-6-*en*-3-*one* (14).—The alcohol (6) was oxidized under Collins conditions to give (1*R*,5*S*)-bicyclo[3.2.0]hept-2-en-6-one (1*R*,5*S*)-(4) (90%), $[\alpha]_D^{22}$ −60° (*c*, 1.0 in chloroform).* Baeyer–Villiger oxidation of this ketone with peracetic acid under the usual conditions [11] gave the γ-lactone (13), $[\alpha]_D^{23}$ −104° (*c*, 2.85 in methanol) {lit.,[12] $[\alpha]_D^{20}$ −104° (*c*, 1.1 in methanol)}. To a solution of this lactone (5.0 g) in dry carbon tetrachloride (50 ml) was added NBS (7.5 g). The mixture was irradiated (150-W light bulb) and refluxed for 0.75 h. The mixture was filtered and the filtrate was washed in turn with 2M hydrochloric acid (50 ml) and saturated aqueous sodium chloride (100 ml). The organic phase was dried and evaporated to dryness under reduced pressure and the residue was chromatographed over silica gel with 40% methylene dichloride–hexane as eluant to give the bromo-lactone (14) (37.5%), $[\alpha]_D^{22}$ −427° (*c*, 2.2 in chloroform). Later fractions from the column chromatography gave mixtures of the lactones (14) and (15). These mixtures were refluxed in toluene for 48 h, the toluene was removed under reduced pressure, and the residue was chromatographed to give a further quantity of the 8-bromo-lactone (14) (6.5%).

Preparation of the γ-*Lactone* (12).—The conversion of the ketone (+)-(7) into the tricyclic ketone (8), the reaction of this ketone with the cuprate reagent (9), and the conversion of the resulting norbornanone (10) into the γ-lactone (12) utilized experimental conditions that have been described previously † 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 bromo-ketone (+)-(7) was treated with base to furnish the tricycloheptanone (8) (90%) which was immediately treated with the cuprate reagent (9) to give the bicycloheptanone (10) (60%), $[\alpha]_D^{20}$ +31.4° (*c*, 1.0 in chloroform). Oxidation of the ketone (10) gave the bromo-δ-lactone (83%), $[\alpha]_D^{23}$ −6.3° (*c*, 1.0 in chloroform) which was dehydrobrominated to give the unsaturated lactone (11) (61%), $[\alpha]_D^{23}$ −90° (*c*, 1.0 in chloroform). Rearrangement of compound (11) and desilylation of the product gave the desired lactone (12) (62%), $[\alpha]_D^{21}$ +294° (*c*, 1.0 in chloroform).

Alternative preparation of the Lactone (12) via *Compounds* (17) *and* (18).—The conversion of the bromo-lactone (−)-(14) into the epoxide (16) and subsequent reaction of this epoxide with the cuprate reagent (9) followed experimental procedures that have been documented previously for the corresponding reactions of racemic substrates.‡ The data below include the yields of the reactions involving optically active compound and the optical rotations of key intermediates.

The bromo-lactone (−)-(14) gave the epoxide (16) (76%), $[\alpha]_D^{22}$ +133° (*c*, 4.6 in chloroform). This epoxide reacted with the cuprate reagent (9) to give the 6-substituted lactone (17)

* Other physical characteristics were as described previously: Z. Grudzinski and S. M. Roberts, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1767.

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‡ C. B. Chapleo, M. A. W. Finch, T. V. Lee, S. M. Roberts, and R. F. Newton, *J. Chem. Soc., Perkin Trans. 1*, 1980, 2084.

(34%), $[\alpha]_D^{22}$ +161.5° (*c*, 2.8 in chloroform) and its 8-substituted isomer (18) (21%), $[\alpha]_D^{22}$ −139° (*c*, 2.16 in chloroform) which were separated by flash chromatography [13] over silica gel with 20% diethyl ether–light petroleum (b.p. 60—80 °C) as eluant. Treatment of the lactone (17) with a mixture of aqueous hydrofluoric acid and acetonitrile gave the lactone (12) (86%), $[\alpha]_D^{23}$ +291° (*c*, 1.7 in chloroform).

The other physical and spectroscopic properties of compounds (8) and (10)—(18) were identical with those reported for the racemic compounds.

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