Synthesis of Optically Active Prostaglandin-J_2 and 15-Deoxy-$\Delta^{12,14}$-prostaglandin-J_2

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Abstract: An efficient route to optically pure prostaglandin-J_2 compounds has been discovered: *ent*-PGJ_2 is shown to display anti-viral activity against Sendai virus with a similar potency to the natural enantiomer.

Key words: prostaglandin-J_2, 15-deoxy- ^{12,14}-prostaglandin-J_2, lipase-catalysed resolutions

There is considerable current interest in the biological activity of the cyclopentenone prostaglandins.[1] In particular, prostaglandin-J_2 (PGJ_2) **1** and $\Delta^{12,14}$-15-deoxyprostaglandin-J_2 (15-d-PGJ_2) **2** (Figure 1) have been shown to be potent anti-viral agents.[2] The latter molecule has also attracted interest because of its action as an agonist on the PPAR-gamma receptor,[3] its anti-inflammatory activity[4] and its cytoprotective potential.[5]

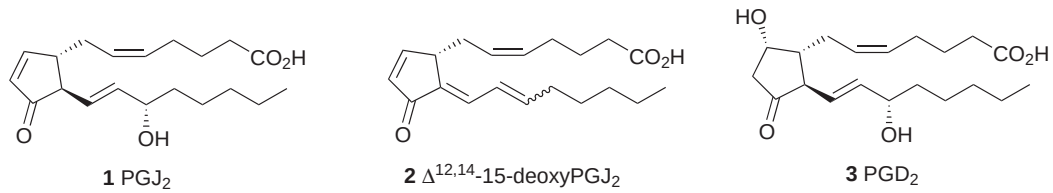
Both prostaglandins occur naturally, being derived from prostaglandin-D_2 **3** by dehydration.[6] The same process can be mimicked in the laboratory, ultimately generating 15d-PGJ_2 **2** as a mixture of isomers.[7]

Some years ago, we developed a synthesis of (±)-PGJ_2,[8] starting from 7-chloronorbornadiene **4**, which featured a Meinwald rearrangement of a norbornadiene mono-epoxide (Scheme 1 steps a–d, g–k). The synthesis suffered from the protracted conversion of the alkyne **5** into the triene **8**. In the first part of this paper, we report a more convenient method for the production of the PGJ_2 intermediate **8** as well as a new method for the preparation of 15-d-PGJ2. In later paragraphs new methods for the preparation of optically active materials are described.

Thus, 7-chloronorbornadiene **4** was converted into the 7-lithio compound and reacted with *trans*-oct-2-enal to give the alcohol **7**.[9] Rearrangement of this alcohol with methyltrioxorhenium[10] (MTO) and silylation under standard conditions gave the triene **8**. After the prescribed oxidation and Meinwald rearrangement, the hydroxyaldehyde **10** was obtained as a mixture of diastereoisomers.

The efficient preparation of the alcohol **7** is especially valuable inasmuch as the (*E*) stereochemistry is established for the C_{14}–C_{15} double bond early in the synthesis ensuring that the prostaglandin **2** is obtained as a single geometric isomer. Thus, the alcohol **7** was converted into the silyl ether and subjected to the oxidative rearrangement and hydrolysis procedure to provide a 2:1 mixture of hydroxyaldehydes **9**.[11] Interestingly the pre-existing stereogenic centre seems to influence the sense of the electron flow on rearrangement of the (protonated) epoxynorbornene. Wittig reaction, Dess–Martin oxidation and concommitant desilylation/dehydration furnished 15d-PGJ_2 **2** (Scheme 1).

Acetylation of the mixture of diastereomers **10** using *Pseudomonas cepacia* lipase efficiently produced a separable mixture of two pairs of diastereoisomers (–)-**10** (42%) and (+)-**11** (41%); hydrolysis of the acetates (+)-(**11**) gave the hydroxyaldehydes (+) **10** (Scheme 2).[12] The diastereomeric pairs were converted into PGJ_2 **1** and 15-*epi*-PGJ_2 [from (+)-**10**], *ent*-PGJ_2 and *ent*-15-*epi*-PGJ_2 [from (–)-**10**] which were required for biological evaluation.[13]



1 PGJ_2 **2** $\Delta^{12,14}$-15-deoxyPGJ_2 **3** PGD_2

Figure 1

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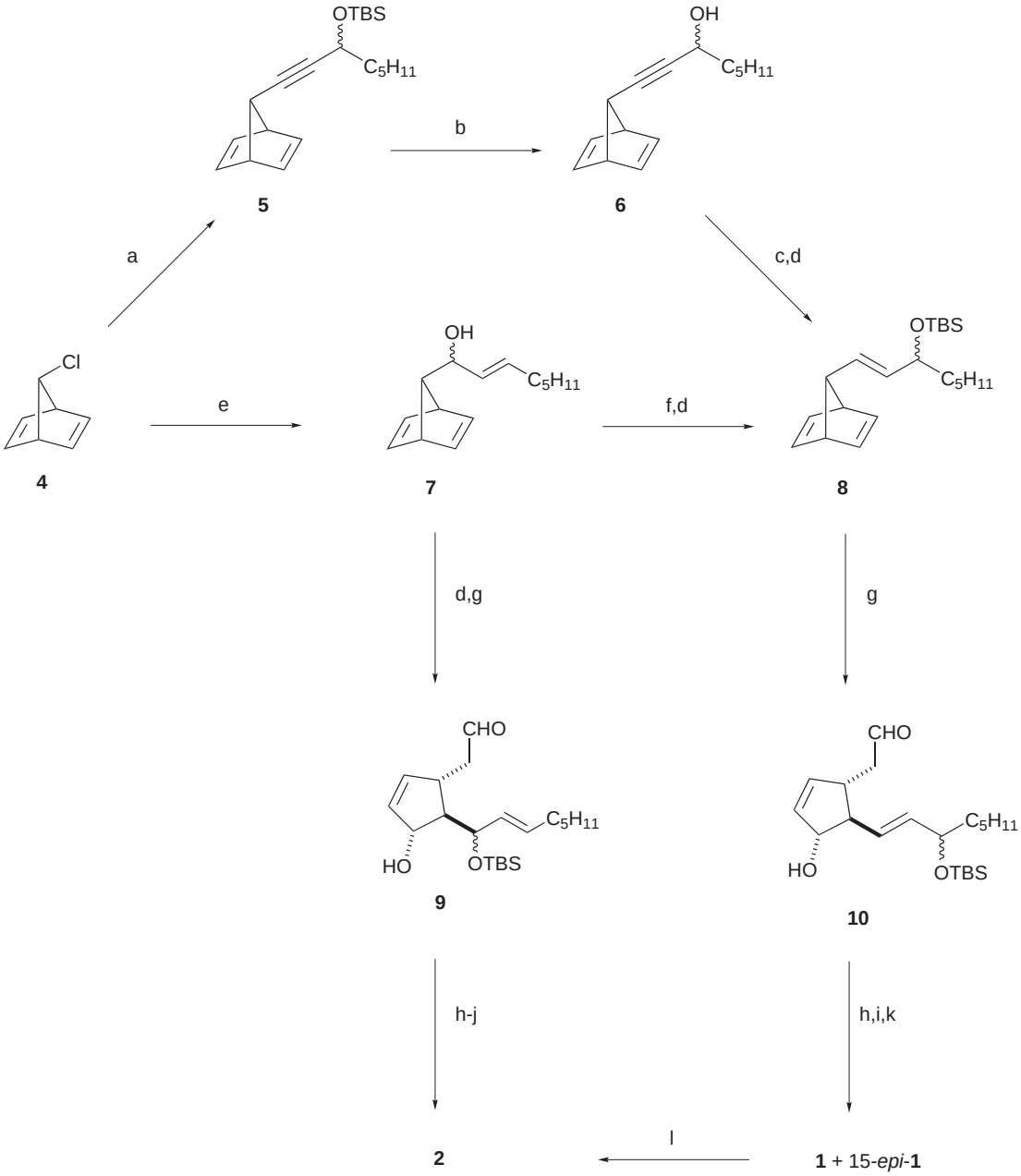
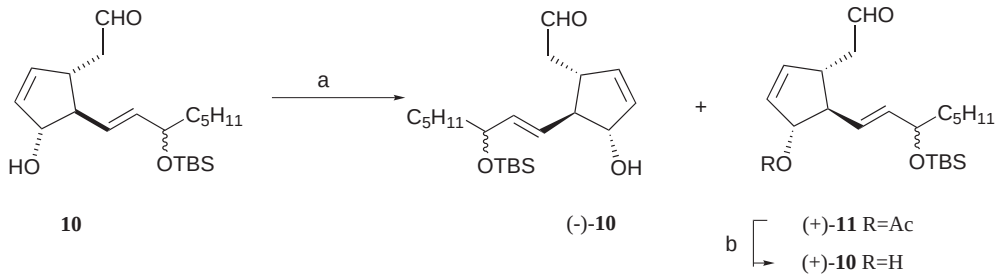


Scheme 1 *Reagents and conditions:* a) 3-silyloxyoct-1-yne, EtMgBr, CuI, THF, reflux, 3 h, 66%; b) TBAF, THF, 14 h, 75%; c) $LiAlH_4$, THF, reflux, 1 h, 64%; d) TBSCl, imidazole, CH_2Cl_2, 20 h, 90%; e) i. Li, DTBB, THF, 1 h; ii. *trans*-oct-2-enal, –78 °C–r.t., 1 h, 90%; f) MTO, CH_2Cl_2, 2 d, 58%; g) i. Oxone, $NaHCO_3$, acetone, H_2O, 0 °C 1.5 h; ii. 2 M HCl, CH_2Cl_2, 5 d, 48%; h) $Br^-Ph_3P^+(CH_2)_4CO_2H$, NaHMDS, THF, 1.5 h, 79%; i) Dess–Martin periodinane, CH_2Cl_2, 1 h, 90%; j) TFA, CH_2Cl_2, 3 h, 48%; k) HF (aq), MeCN, 1 h, **1** (21%) and 15-*epi*-**1** (25%); l) 1 M HCl, THF, reflux, 20 min, 14%.



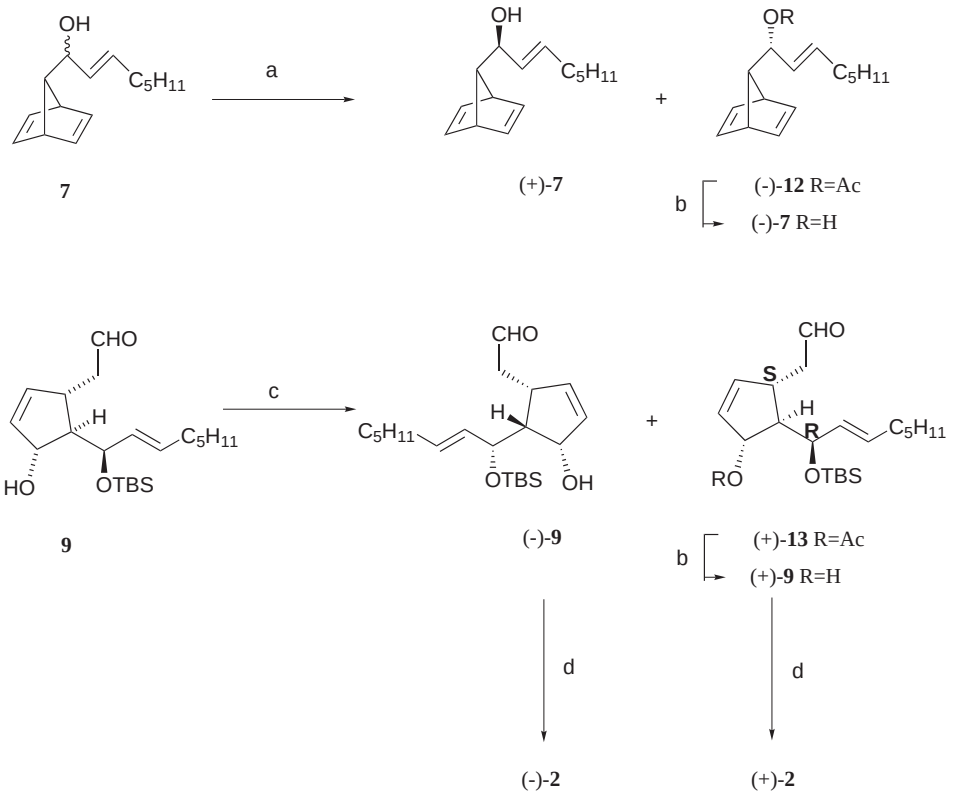
Scheme 2 *Reagents and conditions:* a) *Ps. cepacia* lipase, vinyl acetate, PhMe, 20 h, **10** (42%) and **11** (41%); b). K_2CO_3, H_2O, MeOH, 3 h, 79%.

Interestingly, the mirror image of the natural prostaglandin *ent*-**1** was almost equi-active to PGJ_2 **1** as an anti-viral agent, exhibiting an IC_{50} of 4 μM against Sendai virus. The compound was also an effective inhibitor of NF-κB. The *epi*-prostaglandins exhibited slightly less activity. To our knowledge this is the first time that enantiomerically enriched samples of these non-natural cyclopentenone prostaglandins have been made available for biological testing.

Two strategies were evaluated to access optically active 15-d-PGJ_2. First, treatment of the aldehydes **9** with Novozym 435™ (CaB) and vinyl acetate in toluene led to the acetylation of only one of the four stereoisomers to afford acetate (+)-**13**.[12] Hydrolysis furnished hydroxyaldehyde (+)-**9** which was converted into naturally occurring (+)-15-d-PGJ_2, (+)-(**2**) as prescribed in Scheme 1 therefore establishing the (*S*)-stereochemistry at C-8 (PG numbering).[14]

Secondly, in order to provide access to non-natural (–)-15-d-PGJ_2, (–)-(**2**), alcohol (**7**) was acetylated using *Candida antarctica* A lipase (Scheme 3) as the catalyst, to furnish (+)-**7** and acetate (–)-**12**. Simple hydrolysis of the latter compound gave (–)-**7**.[15] Oxidative rearrangement of (–)-**7** gave hydroxyaldehyde **9** as two diastereomers in a 2:1 ratio. CaB-catalysed acetylation removed (+)-**9** as the acetate (+)-**13** leaving (–)-**9** in an optically pure state.[12] Conversion of (–)-**9** into (–)-**2** followed the established routine. The remaining stereochemical assignments of (+)-**9**, in relation to the known stereochemistry at C-8, were found to be 11*R*, 12*S*, 13*R* (PG numbering) by X-ray analysis of the di-*p*-bromobenzoate ester **14** (Figure 2).[16]

Obviously, this new route to cyclopentenone prostaglandins can be modified to provide a range of prostanoids. For example, reaction of lithionorbornadiene with octanal gave the alcohol **15**, which was converted smoothly and efficiently into 15-deoxy-PGJ_2 **16** (Figure 2).



Scheme 3 *Reagents and conditions:* a) *Candida antarctica* A lipase, vinyl acetate, toluene, 2 d, **7** (41%) and **12** (41%); b) K_2CO_3, H_2O, MeOH, 3 h, 83%; c) *Candida antarctica* B lipase, vinyl acetate, PhMe, 24 h, **9** (24%) and **13** (57%); d) 3 steps (See Scheme 1).

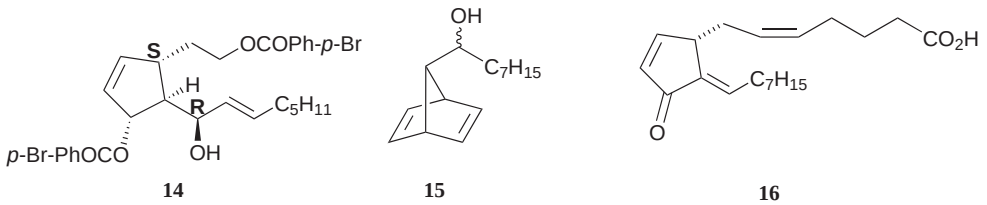


Figure 2

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(9) *Preparation of 7-(1′-Hydroxyoct-2′-enyl)bicyclo[2.2.1]hepta-2,5-diene* ***7***. 4,4′-Di-*tert*-butyl-biphenyl (DTBB) (8.40 g, 31.6 mmol) was added to a stirred suspension of lithium granules (11.25 g, 1.61 mol) in dry THF (300 mL) under an atmosphere of dry argon gas. After 30 min the resultant dark green solution was cooled to –78 °C and 7-chloronorbornadiene **4** (26.70 g, 0.21 mol) added followed by *trans*-2-octenal (31.40 mL, 0.21 mol) after a further 30 min. After 1 h, the excess lithium was removed by filtration and the solvent removed by distillation under reduced pressure. The residue was purified by chromatography over silica using ethyl acetate in hexane (1:10) as eluent to afford the title compound **7** (44.91 g, 90%) as a straw yellow oil; R_f = 0.15 (ethyl acetate/hexane, 1:6); IR (film/cm^{-1}) 3332, 2926, 2856, 1466, 1309; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.85 (2 H, m, H-2 and H-3), 6.62 (2 H, m, H-5 and H-6), 5.56 (1 H, dt, *J* = 15.4 Hz, 6.8 Hz, H-3′), 5.36 (1 H, ddt, *J* = 15.4 Hz, 7.4 Hz, 1.3 Hz, H-2′), 3.93 (1 H, dd, *J* = 9.3 Hz, 7.4 Hz, H-1′), 3.64 (1 H, m, H-1), 3.25 (1 H, m, H-4), 2.41 (1 H, d, *J* = 9.3 Hz, H-7), 2.00 (2 H, m, 2 × H-4′), 1.32 (6 H, m, 2 × H-5′, 2 × H-6′ and 2 × H-7′), 0.89 (3 H, t, *J* = 6.8 Hz, 3 × H-8′); ^{13}C NMR ($CDCl_3$; 75.4 MHz) δ 145.07, 144.64, 140.58, 140.55, 133.08, 132.16, 91.49, 73.39, 52.16, 52.05, 32.59, 31.75, 29.26, 22.85, 14.38; HRMS (CI, NH_3): calcd for $[M + H]^+$ $C_{15}H_{22}O$: 219.1749; found: 219.1751.

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(11) *Preparation of {5-[1′-(Dimethyl-t-butylsilyloxy)oct-2′-enyl]-4-hydroxycyclopent-2-enyl}acetaldehyde* ***9***. Oxone (2.32 g, 3.77 mmol) was added in one portion to a suspension of $NaHCO_3$ (0.63 g, 7.50 mmol) in acetone (30 mL) and water (30 mL) stirred at 0 °C. After 10 min, a solution of 7-[1′-(dimethyl-t-butylsilyloxy)oct-2′-enyl]bicyclo[2.2.1]hepta-2,5-diene (0.25 g) in acetone (30 mL) was added and the solution stirred for a further 1.5 h. The resultant solution was diluted with ethyl acetate (100 mL) and washed with water (2 × 100 mL) and brine (100 mL), dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. The residue was diluted with CH_2Cl_2 (10 mL) and a 2 M aqueous solution of HCl (10 mL) and stirred slowly for 5 d and the organic portion separated, dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. The residue was purified by chromatography over silica using ethyl acetate in hexane (1:3) as eluent to afford the title compound **9** (0.13 g, 48%) as a straw yellow oil; R_f = 0.25 (ethyl acetate/hexane); NMR ($CDCl_3$, 400 MHz, 1:2 mixture of diastereoisomers) δ 9.75 (2 H, t, *J* = 1.3 Hz, CHO), 9.72 (1 H, t, *J* = 1.3 Hz, CHO), 5.73 (6 H, s, H-2 and H-3), 5.60 (3 H, m, H-3′), 5.38 (3 H, m, H-2′), 4.70 (1 H, dd, *J* = 4.8 Hz, 1.0 Hz, H-4), 4.61 (2 H, d, *J* = 4.6 Hz, H-4), 4.15 (3 H, m, H-1′), 2.89 (2 H, m, H-1), 2.79 (1 H, m, H-1), 2.75 (2 H, ddd, *J* = 17.7 Hz, 5.3 Hz,1.3 Hz, CHCHO), 2.66 (1 H, ddd, *J* = 18.0 Hz, 5.8 Hz, 1.3 Hz, CHCHO), 2.53 (2 H, ddd, *J* = 17.7 Hz, 8.1 Hz, 1.3 Hz, CHCHO), 2.47 (1 H, ddd, *J* = 18.0 Hz, 8.0 Hz, 1.3 Hz, CHCHO), 2.00 (6 H, m, H-4′), 1.82 (3 H, m, H-5), 1.36–1.23 (18 H, m, H-5′, H-6′ and H7′), 0.85 [36 H, m, CH_3 and $(CH_3)_3$], 0.02 [18 H, m, $Si(CH_3)_2$]; ^{13}C NMR ($CDCl_3$; 75.4 MHz, 1:2 mixture of diastereoisomers) δ 201.88 and 201.73, 135.71 and 135.35, 133.01and 132.97, 132.96 and 132.90, 131.58 and 131.18, 79.82 and 79.19, 76.23 and 75.66, 60.71 and 60.53, 50.02 and 49.57, 40.94 and 40.66, 32.12 and 32.08, 31.39 and 31.38, 28.82 and 28.73, 25.83 and 25.82, 22.43, 18.01, 14.01 and 14.00, –3.75 and –3.92, –4.81 and –4.86; HRMS (CI, NH_3): calcd for $[M + H]^+$ $C_{21}H_{39}O_3Si$: 367.2669; found: 367.2675.

(12) Enantiomeric excesses were determined to be >99% by synthesis and analysis of the Mosher ester derivatives.

(13) Compounds gave satisfactory NMR (^{1}H and ^{13}C) and mass spectral data in accord with the literature. Specific rotations were (+)-PGJ_2 **1**, $[\alpha]_D$ +175.9 (*c* 1.1, $CHCl_3$); (+)-15-*epi*-PGJ_2, $[\alpha]_D$ +168.0 (*c* 1.2, $CHCl_3$); (–)-PGJ_2, $[\alpha]_D$ –171.7 (*c* 1.4, $CHCl_3$); (–)-15-*epi*-PGJ_2, $[\alpha]_D$ –171.7 (*c* 1.1, $CHCl_3$).

(14) Compound (+)-**2** gave satisfactory NMR (^{1}H) and mass spectral data in accord with the literature; $[\alpha]_D$ +194.3 (*c* 0.7, $CHCl_3$); ^{13}C NMR ($CDCl_3$; 75.4 MHz) δ 197.45, 178.86, 160.75, 146.98, 135.15, 134.85, 131.83, 131.23, 125.89, 125.50, 43.43, 33.44, 33.34, 31.37, 30.63, 28.42, 26.55, 24.42, 22.45, 13.99.

(15) *Lipase Resolution of 7-(1′-Hydroxyoct-2′-enyl)bicyclo[2.2.1]hepta-2,5-diene* ***7***. Lipase A from *Candida antarctica* (0.77 g) was added to a slowly stirred solution of the alcohol **7** (1.99 g, 9.14 mmol) in vinyl acetate (1.6 mL, 173.76 mmol) and toluene (25 mL). After 20 h the mixture was filtered through a glass sinter and the solvent removed by distillation under reduced pressure. The residue was purified by chromatography over silica using ethyl acetate in hexane (1:50) as eluent to afford the acetate **12** (0.97 g, 41%) as a clear colourless oil. Further elution using ethyl acetate in hexane (1:10) as eluent afforded the alcohol (+)-**7** (0.817 g, 41%) as a clear colourless oil; $[\alpha]_D$+22.5 (*c* 1.5, $CHCl_3$). Potassium carbonate (5.04 g, 36.49 mmol) was added to a stirred solution of the acetate **12** (0.968 g, 3.72 mmol) in methanol (20 mL) and water (10 mL). After 20 h the mixture was diluted with CH_2Cl_2 (50 mL) and washed with a 10% aqueous solution of citric acid (2 × 25 mL) and brine (25 mL), dried ($MgSO_4$) and the solvent removed by distillation under reduced pressure. The residue was purified by chromatography over silica using ethyl acetate in hexane

(1:10) as eluent to afford the alcohol (–)-**7** (0.67 g, 83%) as a clear colourless oil; $[\alpha]_D$ –21.2 (*c* 1.5, $CHCl_3$). Enantiomeric excesses were determined to be >99% by synthesis and analysis of the Mosher ester derivatives of aldehydes **9**.

(16) Crystal data (Figure 3). $C_{29}H_{32}Br_2O_5$, *M* = 620.37, *T* = 100(2)K, crystal dimensions = 0.25 × 0.05 × 0.02 mm, *Spacegroup* P21, *a* = 5.0940(11), *b* = 16.480(3), *c* = 16.695(3) Å, β = 98.689(4)°, *U* = 1385.4(5) $Å^3$, μ(Mo-K*α*) = 1.487 $mm^{-1,}$ 5565 reflections measured, 3004 unique (R_{int} = 0.0413). R1 = 0.1634, *w*R2 = 0.4116 (all data); Crystals consisted of fine hairy needles of low scattering power and high mosaicity, which contributed to the high R-value. However, the model refined well and allowed the determination of the molecular connectivity. The absolute configuration could not be determined.

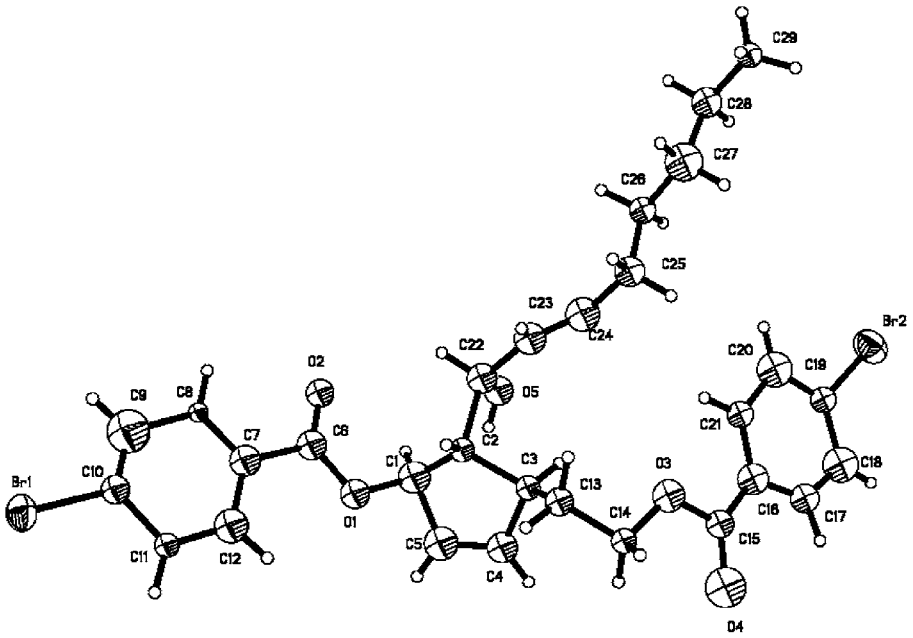

Figure 3