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A Free Radical Route to Syn Lactones and other Prostanoid Intermediates in Isoprostaglandin Synthesis.

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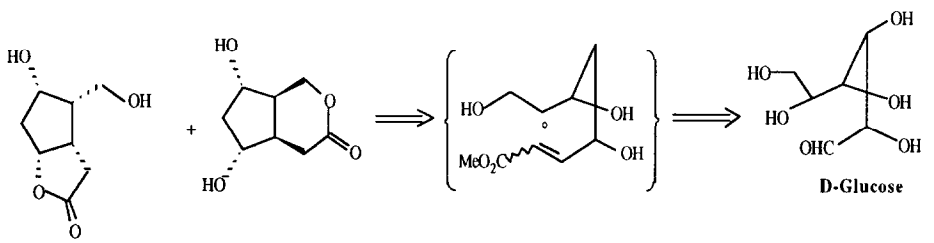
Abstract : *The hex-5-enyl radical cyclization methodology was applied to the formation of optical active prostanoid intermediates 7,8,9 with readily available diacetone-D-glucose as starting material.This result should lead to isoprostaglandins, a novel class of arachidonic acid metabolites obtained by a non-cyclooxygenase mechanism involving free radical-catalysed peroxidation of arachidonic acid.*

The involvement of prostaglandins in inflammatory diseases has provoked considerable interest in these metabolites of arachidonic acid[1]. The surprising finding that 8-epi-PGF2α, produced *in vivo* in humans by a non-cyclooxygenase free radical-catalyzed mechanism, was biologically active as a potent and selective renal vasoconstrictor [2] is for us an important point in assessing the role of prostanoids in the inflammatory field. The exact mode of the pharmacological action of 8-epi-PGF2α and related compounds (isoprostaglandins) is at present obscure because of their non-availability in larger quantities. Syntheses of 8-epi PGF2α have been published by Corey [3] (by biomimetic cyclization of endoperoxide) and Larock [4] (tandem organopalladium approaches).

We report herein an enantiospecific convergent synthesis of cyclic compounds, precursors of these isoprostaglandins, from D-glucose, a readily available chiral carbohydrate. The retrosynthetic analysis of isoprostaglandin precursors is outlined in Scheme 1. Our strategy relies on a radical cyclization [5,6,7] which should lead mainly to the isoprostaglandin precursors with the syn configuration for the side chains.

Scheme 1

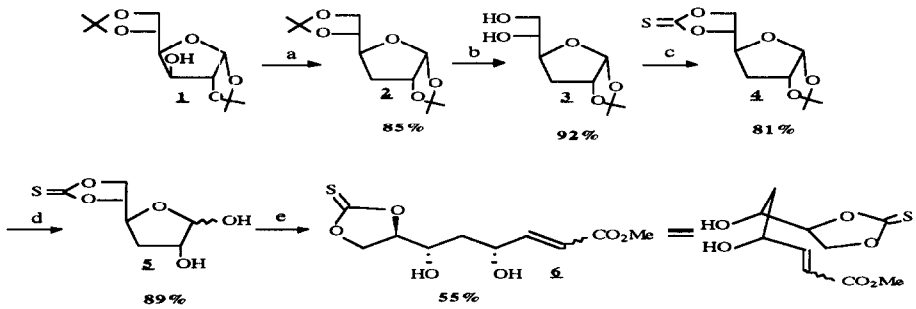


Isoprostaglandin precursors

The synthesis (Scheme 2) began with diacetone D-glucose 1, which was submitted to a deoxygenation of the 3-hydroxyl group by a Barton, McCombie's reaction [8], followed by a selective deprotection of the terminal acetonide under mild conditions by treatment with 70% aqueous solution of acetic acid (7 hrs at r.t.) to give rise to the diol 3.

The thionocarbonate 4 obtained with 1,1'-thiocarbonyldiimidazole in 1,2-dichloroethane was transformed into the diol 5 followed by deprotection of the 1,2-acetonide under sulfuric acid conditions. Subsequently 5 was converted by a Wittig reaction with carbomethoxymethylene triphenylphosphorane into the cyclization precursor compound 6 (31% overall; E / Z = 95:5 determined by 360 MHz ^{1}H-NMR and GPC).

Scheme 2



a) 1.5 equiv. NaH, $4x10^{-3}$ equiv. imidazole in dry THF, 3.05 equiv. CS_2 at r.t., 1.8 equiv. MeI and 1.6 equiv. Bu_3SnH in refluxing toluene, 3 hrs; b) AcOH 70%, 7 hrs, r.t.; c) 1.5 equiv. $(Im)_2C=S$ in refluxing $C_2H_4Cl_2$, 4 hrs.; d) H_2SO_4 4% in refluxing THF, 3 hrs.; e) 1.35 equiv. $Ph_3P=CHCO_2Me$ in dry THF, r.t., 22 hrs.

The last step was the radical cyclization of **6** under several conditions [8,9,10]. The percentage of the various products isolated and the yields are collected in Table 1.
The cyclization conditions were adjusted using the model compound **10** (entry 1) which was obtained from commercially available 1,2,6-hexanetriol in three steps (thionocarbonate formation followed by Collins oxydation of primary alcohol and Wittig reaction with carbomethoxymethylene triphenylphosphorane; 41% overall). The derivative **11** was identical to an authentic sample synthetized by an another route [11].The 5,6-O-isopropylidene compound **6a** (entry 2), does not react under several cyclization conditions, because of the acetonide function. Indeed this protective group prevent the radical attack to the Michael acceptor. Cyclization with the diol **6b** (entry 3), led to the major syn lactones **7** / **8** and trans lactone **9** [12]. When the same reaction was carried out with or without an automatic syringe, we obtained similar results (yields and percentages of products; entry 3 and 4). Finally to try to improve the yield of syn lactones **7** and **8**, and to avoid the unwanted reduction products we carried out the reaction in the presence of tris(trimethylsilyl)silane [10], a well known reductive agent for the radical cyclization from halides and thionocarbonates substrates, but only starting material was recovered (entry 5).

The structure determination and purity of lactones **7**,**8**,**9** were obtained by NMR ^1H, ^{13}C, ^1H / ^1H COSY [12]. The $[\alpha]_D$ of compounds **7** and **9** was respectively + 12.0° (c $1.5x10^{-2}$, $CDCl_3$) and + 45.0° (c $1.2x10^{-2}$, $CDCl_3$). The enantiomerically assignment of the lactone **9** (Scheme 3) was performed by comparison with an authentical sample **12**[12] prepared from Corey lactone, after hydrolysis of 4-phenylbenzoate ester (K_2CO_3 in THF/MeOH, r.t., 4 hrs; 83% yield). The diastereoisomeric relationship between lactones **7** and **9** was established by the ^1H and ^{13}C signals. Finally we compared compounds **8** with the lactone **11**[11] which showed many similarities for the lactonic cycle[12].

Scheme 3

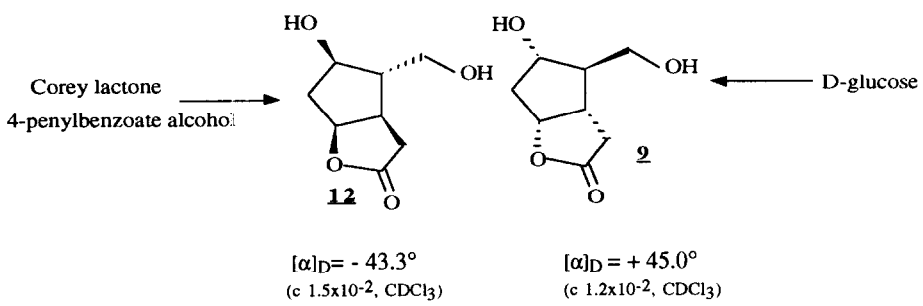
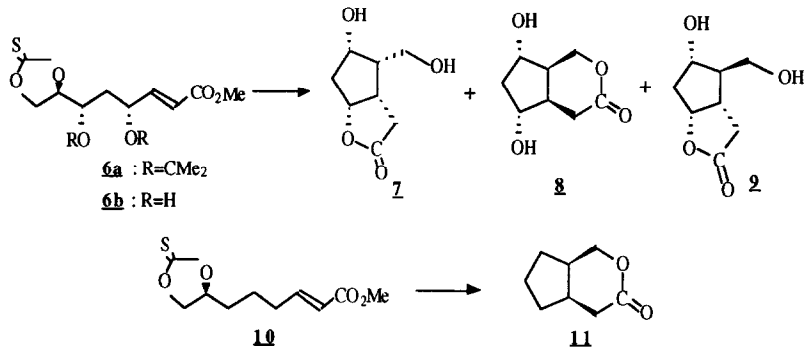


Table 1



Entry	Substrate	Experimental conditions	Products (%)
1	**10**	Bu_3SnH (1.3 equiv.) / AIBN (0.3 equiv.) Benzene 80°C / 2.30 hrs Addition with automatic syringe	11; 63% yield[b]
2	**6a**	Bu_3SnH (1.3 equiv.) / AIBN (0.3 equiv.) Benzene 80°C / 2.30 hrs Addition with automatic syringe	Starting material
3	**6b**	Bu_3SnH (1.3 equiv.) / AIBN (0.3 equiv.) Benzene 80°C / 2.30 hrs Addition with automatic syringe	7 (54), 8 (24), 9 (22); 45 % yield[a]
4	**6b**	Bu_3SnH (1.3 equiv.) / AIBN (0.3 equiv.) Benzene 80°C / 1 hr	7 (57), 8 (23), 9 (20); 47 % yield[a]
5	**6b**	$(TMS)_3SiH$ (1.3 equiv.) / AIBN (0.3 equiv.) Benzene 80°C / 1 hr	Starting material

a : performed by HPLC, Nucleosil $SiO_2$with CH_2Cl_2/MeOH 96/4 and refractometric detector.
b : performed by capillary GPG, OV 17 at 110-250°C, 3°Cmin.

In conclusion this synthetic route offers major advantages in terms of conciseness, simplicity of reactions and good yields. It would be better still if we could improve the radical cyclization yield. Experiments towards this goal and the total synthesis of 8-epi-PGF2α and isomers are in progress.

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12. compound **7** : ^{1}H NMR (360 MHz, DMSO) δ 5.01 (t, J = 7.16 Hz, 1H), 4.57 (d, J = 2.45 Hz,1H, OH) 4.38 (d, J = 5.15 Hz, 1H, OH) 4.07 (d, J = 2.84 Hz, 1H), 3.64-3.70 (m, J = 6.52 Hz and 13.03 Hz, 1H) 3.48-3.55 (m, J = 7.88 Hz, 1H) 2.94-3.03 (m,1H), 2.38-2.53 (m, J = 18.46 Hz, 2H) 1.90-1.95 (m, 2H), 1.75-1.85 (qd, J = 6.55 Hz and 14.9 Hz, 1H); ^{13}C NMR (63 MHz, DMSO) δ 84.71 (C4), 71.51 (C6), 57.94 (C8), 49.31 (C3), 41.61 (C7), 37.96 (C5), 30.21 (C2); 2D -NMR ^{1}H / ^{1}H COSY (360 MHz, DMSO) 2-2', 2-3, 2'-3, 3-7, 3-4, 4-5, 4-5', 4-6, 5-6, 5'-6, 6-OH, 6-7, 7-8, 7-8', 8-OH, 8'-OH; IR (neat) 3420 (υOH), 1750 (υCO) cm^{-1}; IE mass (70 eV, FAB>0) m/z 301 (M + 2TMS - 15), 173 (M + H$^+$); $[\alpha]_D$= + 12.0° (c 1.510^{-2}, $CDCl_3$).

compound **8**: ^{1}H NMR (360 MHz, DMSO) δ 4.98 (d, J = 5.18 Hz, 1H, OH), 4.94 (d, J = 5.44 Hz, 1H, OH) 4.21-4.26 (dd, J = 11.48 Hz and 4.18 Hz, 1H) 4.11-4.15 (dd, J = 11.45 Hz and 3.49 Hz, 1H), 3.69-3.74 (m, 1H) 3.34-3.42 (m, 1H) 2.58-2.65 (dd, J = 15.05 Hz and 6.84 Hz, 1H), 2.35-2.45 (dd, J = 15.08 Hz and 3.91 Hz, 1H) 2.28-2.33 (m, 1H), 2.17-2.21 (m, 1H), 1.96-2.03 (m, 1H), 1.40-1.50 (q, 1H); ^{13}C NMR (63 MHz, DMSO) δ 82.81, 80.05, 65.74, 43.91, 41.61, 37.66, 32.11; 2D-NMR ^{1}H / ^{1}H COSY (360 MHz, DMSO) 2-2', 2-3, 2'-3, 3-4, 4-OH, 4-5, 4-5', 5-6, 5'-6, 6-OH, 6-7, 7-8, 7-8'; IR (neat) 3420 (υOH), 1750 (υCO) cm^{-1}; IE mass (70 eV, FAB>0) m/z 301 (M + 2TMS - 15), 173 (M + H$^+$).

compound **9** : ^{1}H NMR (360 MHz, DMSO) δ 4.84-4.88 (td, J = 6.98 Hz and 2.20 Hz, 1H), 4.69 (d, J = 4.00 Hz, 1H, OH) 4.54-4.77 (t, J = 5.15 Hz, 1H, OH) 3.87-3.92 (m, 1H), 3.25-3.42 (dd, J = 10.62 Hz and 5.26 Hz, 2H) 2.73-2.82 (dd, J = 17.82 Hz and 10.37 Hz, 1H) 2.57-2.64 (m, J = 6.80 Hz, 1H), 2.34-2.40 (dd, J = 17.86 Hz and 2.63 Hz, 1H) 2.12-2.20 (td, 1H), 1.70-1.79 (m, 2H); ^{13}C NMR (63 MHz, DMSO) δ 83.77 (C4), 72.77 (C6), 61.18 (C8), 56.05 (C3), 39.90 (C7), 39.00 (C5), 35.40 (C2); 2D-NMR ^{1}H /^{1}H COSY (360 MHz, DMSO) 2-2', 2-3, 2'-3, 3-4, 3-7, 4-5, 4-5', 5-5', 5-6, 5'-6, 6-OH, 7-8, 7-8', 8-OH, 8'-OH; IR (neat) 3420 (υOH), 1750 (υCO) cm^{-1}; IE mass (70 eV, FAB>0) m/z 301 (M + 2TMS - 15), 173 (M + H$^+$); $[\alpha]_D$= + 45.0° (c 1.210^{-2}, $CDCl_3$).

compound **11** : ^{1}H NMR (360 MHz, DMSO) δ 4.17-4.21 (dd, J = 11.48 Hz and 4.93 Hz, 1H) 3.68-3.95 (dd, J = 11.41 Hz and 6.76 Hz, 1H) 2.49-2.55 (dd, J = 14.4 Hz and 6.52 Hz, 1H) 2.34-2.47 (m, 2H) 2.19-2.26 (dd, J = 14.33 hz and 6.26 hz, 1H) 1.83-1.93 (m, 1H) 1.73-1.82 (m, 1H) 1.59-1.65 (td, 1H) 1.30-1.46 (m, 2H) 1.18-1.24 (m, 1H); ^{13}C NMR (63 MHz, DMSO) δ 69.76 (C8), 36.21 (C7), 34.23 (C3), 34.20 (C2), 34.00 (C4), 29.34 (C6), 25.41 (C5); 2D-NMR^{1}H/^{1}H COSY (360 MHz, DMSO) 2-2', 2-3, 2'-3, 3-4, 3-4', 4-4', 4-5, 4-5', 4'-5, 4'-5', 4-6, 5-5', 5-6, 5'-6, 5'-6', 5-6', 6-6',6-7, 6'-7, 7-8, 7-8', 8-8'; IR (neat) 1750 (υCO) cm^{-1}.

compound **12** : ^{1}H NMR (360 MHz, DMSO) δ 4.84-4.90 (td, J = 6.97 Hz and 2.27 Hz, 1H), 4.73 (d, J = 3.94 Hz, 1H, OH) 4.58-4.62 (t, J = 4.90 Hz, 1H, OH) 3.86-3.92 (m, 1H), 3.24-3.43 (dd J = 10.59 Hz and 4.20 Hz, 2H) 2.74-2.85 (dd, J = 17.60 Hz and 10.36 Hz, 1H) 2.56-2.67 (m, J = 6.76 Hz, and 2.21 Hz 1H), 2.34-2.42 (dd, J = 17.63 Hz and 2.43 Hz, 1H) 2.11-2.22 (td, 1H), 1.69-1.79 (m, 2H); ^{13}C NMR (63 MHz, DMSO) δ 83 51 (C4), 72.48 (C6), 60.85 (C8), 55.77 (C3), 39.90 (C7), 39.05 (C5), 35.14 (C2); 2D-NMR ^{1}H / ^{1}H COSY (360 MHz, DMSO) 2-2', 2-3, 2'-3, 3-4, 3-7, 4-5, 4-5', 4-6, 5-5', 5-6, 5'-6, 6-OH, 6-7, 7-8, 7-8', 8-OH, 8'-OH; IR (neat) 3420 (υOH), 1750 (υCO) cm^{-1}; $[\alpha]_D$= - 43.3° (c 1.510^{-2}, $CDCl_3$).

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