Synthesis and determination of *cis* or *trans* isoprostane precursors by a ^{1}H NMR NOE study

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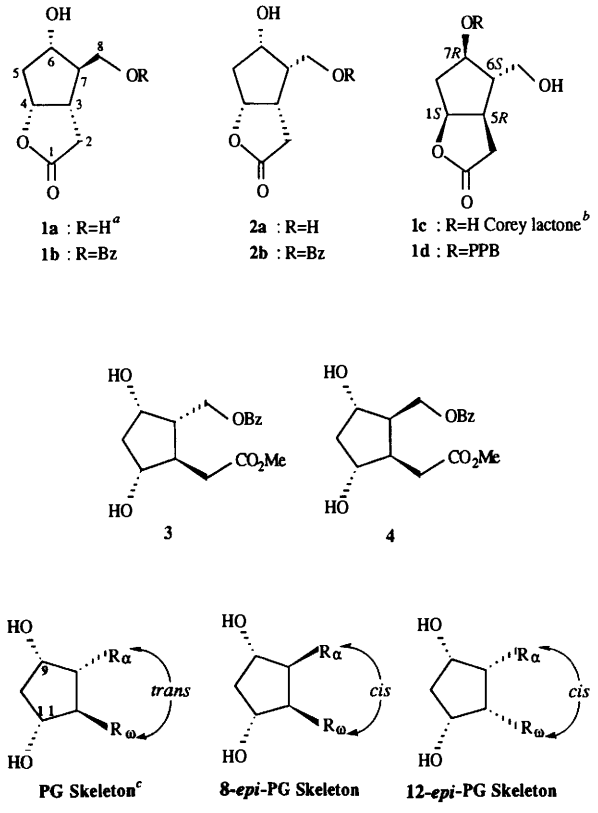
Different isoprostane precursors have been synthesized from a 5-iodo-sugar *via* a radical cyclization initiated by azoisobutyronitrile (AIBN)–Et_3B. The NOE ^{1}H NMR experiment is a simple and efficient method for the determination of the relative functional configuration of tetrasubstituted cyclopentane derivatives. Applied to chiral lactone structures or hydroxy esters, this method allows the determination *a priori* of their relative configuration.

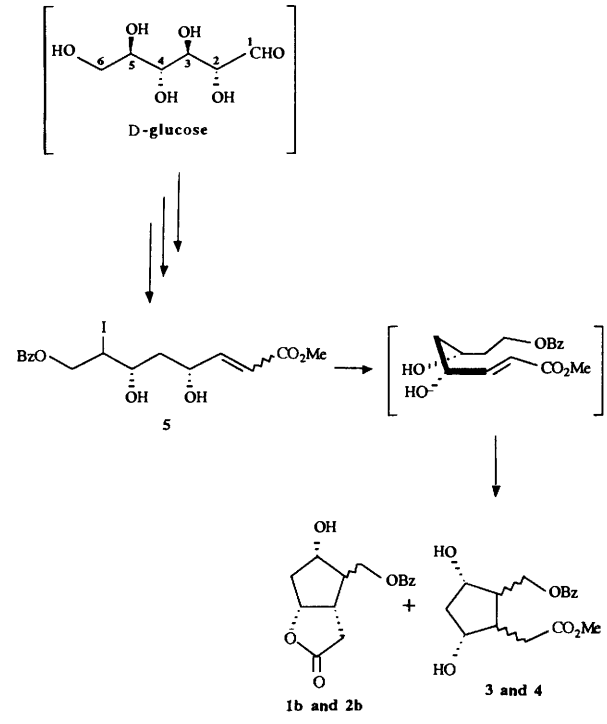
Diversely substituted cyclopentane compounds are intermediates in the total synthesis of various natural products.[1] Our interest has focused on the synthesis of chiral cyclopentane lactones **1** and **2**,[2] as well as hydroxy esters **3** and **4** (Scheme 1).



Scheme 1 (*a*) Numbering of compounds used in this paper; (*b*) IUPAC numbering; PPB = *para*-phenylbenzoyl; (*c*) numbering of prostanoid structures; Bz = benzoyl

These structures are the key synthons which allow us to access various isoprostane F_2-like compounds (8-*epi*- and 12-*epi*-$PGF_{2\alpha}$). These new natural products, synthesized *in vivo* by a free radical-catalysed mechanism[3] are, indeed endowed with powerful biological activites.[4] Their total synthesis has therefore become an actual target.[5]

Compounds **1**–**4** have been synthesized from commercial D-glucose (Schemes 2–4). Chiral centres 9 and 11 of the cyclopentane ring of the prostanoids correspond to hydroxy functions 2 and 4 of D-glucose.



Scheme 2

Results and discussion

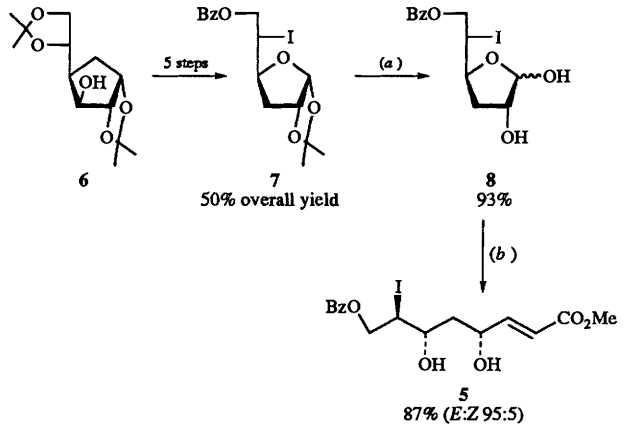
Synthesis of isoprostane precursors

The thionocarbonate approach had allowed us to synthesize chiral lactones, the precursors of isoprostanes.[2] This strategy was confirmed by the good results obtained in the generation of alkyl radicals during the reductive deoxygenation[6] and the few attempts concerning the carbon–carbon bond formation *via* thionocarbonyl esters.[7] Unfortunately, the choice of thionocarbonate as a cyclization precursor was not the optimum, because of major difficulties in the separation step of lactone components from several by-products (> 50–55%) which the carbocyclization irreproducibly yields. The carbocyclization from thionocarbonate allowed us to establish the biomimetic approach toward the chiral lactones, but was inadequate for isoprostane synthesis in large quantities.

In connection with our previous work, we report a new strategic pathway based on a novel alkyl radical precursor and a more convenient radical-initiated cyclization. We have chosen

iodinated precursors such as compound **5**, because of the low bond dissociation energy of the C–I linkage[8,9] and these are good as radical generators with a *cis* stereoselectivity using the hex-5-enyl radical.[10] However, it was important to obtain more precise data concerning the difference of the radical carbocyclization step between a thionocarbonate and an iodinated precursor. The chain reaction is expected to be fragmentation of the intermediate radical derived from the fast addition of the tributyltin radical to the thionocarbonate substrate with subsequent β-cleavage[10] *vs.* the fast α-cleavage introduced by $Bu_3Sn^{\bullet}$ on the iodinated derivative.

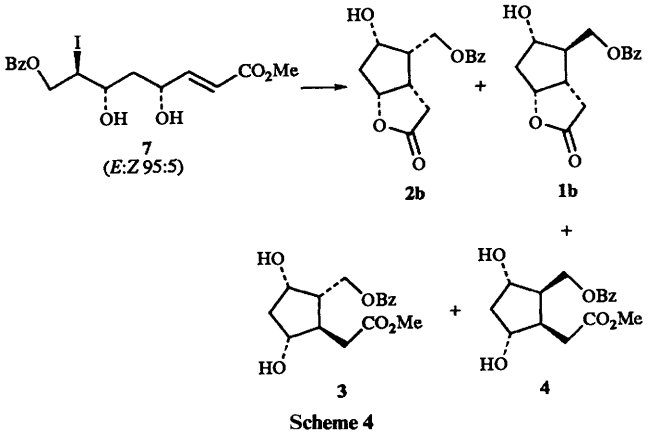
The synthesis of **5** (Scheme 3) began with 1,2-*O*-isopropyli-



Scheme 3 *Reagents and conditions:* (*a*) AcOH, 50% THF, 3 h; (*b*) 1.35 equiv. $Ph_3P{=}CHCO_2Me$ in dry THF, room temp., 22 h

dine-D-glucose **6**, which was transformed in five steps (50% overall yield) into an iodinated derivative 6-*O*-benzoyl-3,5-dideoxy-5-iodo-1,2-*O*-isopropylidene-β-L-*lyxo*-hexofuranose **7**; $[\alpha]_D$ −4.4 (*c* 2, $CHCl_3$). The key step was the S_N2 substitution, close to Garegg's procedure,[11] which worked well in the case of 3-hydroxy sugars, but which had to adjust for the 3-deoxy-series.[12] The deprotection of the acetal was carried out with acetic acid to give rise to the diol **8**. Subsequently, **8** was converted by a Wittig reaction with methoxycarbonylmethylidenetriphenylphosphorane into the cyclization precursor **5** (43% overall; E/Z = 95:5 determined by 360 MHz ^1H NMR and GPC).

The last step was the radical cyclization of **5** (Scheme 4).



Scheme 4

Because the organoboranes are known to be excellent sources of free radicals,[13] we used triethylborane as radical initiator. This method has been successfully applied to the radical cyclization[14] or the deoxygenation of alcohols.[15] The reaction proceeded easily at low temperatures, which are better for a kinetic control.[10] It is worth noting that the initiation step using AIBN had to be carried out above 60–65 °C which was the solubilization temperature of the thionocarbonate substrate in the solvent.[2]

The reaction was performed under an argon atmosphere, with Bu_3SnH–Et_3B in xylene and a controlled dry air source.[15,16] The all-*cis* lactone **2b** was obtained in 64% yield. The *cis–trans* ratio of 2.57 is in accord with literature values.[10,17] After deprotection of the benzoyl group, by hydrolysis (K_2CO_3 in THF–MeOH, room temp., 4 h; 83% yield), compounds **1b** and **2b** led to lactones **1a** and **2a**, as published in a previous paper from our group.[2] The change between the different precursors is shown by the quantitative yield from iodinated derivative **5** *vs.* 45–47% from the thionocarbonate precursor.[2]

Recently the same approach starting from a bromo-sugar from levoglucosane was published giving another isoprostane precursor as (1*S*,6*S*,7*R*,9*R*)-1,9-dihydroxy-3-oxabicyclo[4.3.0]-nonan-4-one.[18]

Determination of the relative configuration by difference NOE spectroscopy

The problem of determination *a priori* of the relative configurations of compounds **1–4** has been posed. Currently NMR spectroscopy is a method of choice for such a determination.[19] We have solved this problem of configuration determination directly by steady-state NOE difference spectroscopy (DNOES) without using structural data obtained from complementary or close compounds. A similar technique has been applied successfully for the determination of the stereochemical configuration of a variety of protected *C*-furanoside derivatives.[19] We have, however, verified our results by applying DNOES to the Corey lactone **1c** of well established configuration, the enantiomer of lactone **1a**.

The principle of the DNOE experiment relies on measurement of two spectra under identical conditions except for the irradiation position of the ratio frequency signal.[20] One collects therefore alternately NMR signals with selective irradiation of a proton and without irradiation of the resonance ^1H studied, that is to say by displacing the irradiation frequency in a spectral zone deprived of signals. Observations (with and without irradiations) are recorded in two separated memory blocks from the computer and one obtains the difference before Fourier transformation. From the observations of the two spectra one obtains from each proton a value expressed in percentage of NOE and the nuclear Overhauser amplification observed constitutes the DNOE spectrum. As it is well known that the magnitude of NOE diminishes rapidly as the interproton distance is increased, one will note a larger NOE in a vicinal proton with *cis* stereochemistry than when the two protons have *trans* stereochemistry. The value of NOE being thus directly connected to the distance between irradiated neighbouring protons, one can deduce the relative configuration and the molecular geometry.[19] Under this form DNOES is a simple and sensitive method that allows the clear observation of small differences, since signals are recorded under identical conditions. The ^1H and ^{13}C NMR of compounds **1–4** are collected in Tables 1 and 2.

Results of the DNOES are collected in Table 3 and are obtained after irradiation of each proton. All the protons have been irradiated and only the most significant results are collected in Table 3.

The systematic study of observed values leads to the determination of the relative configuration. To illustrate this method we will consider (Table 3) the two lactones **1c** and **2a**. The hydroxy function in the 6-position of compound **1c**, arbitrarily oriented in *endo* configuration with respect to the lactone ring is irradiated. The percentage NOE noted for the

Table 1 ^{1}H NMR chemical shifts of lactones and benzoate esters (δ, 360 MHz, $CDCl_3$,* [$^2H_6$]DMSO,** 32 °C)

Compound	2-H	2'-H	3-H	4-H	4-OH	5-H	5'-H	6-H	6-OH	7-H	8-H	8'-H	8-OH	OCH_3	Others
1a, 1c**	2.77	2.37	2.6	4.86	—	2.16	1.73	3.89	4.69	1.75	3.32	3.29	4.56	—	—
1b*	2.79	2.57	2.72	4.94	—	2.39	2.07	4.16	—	2.26	4.36	4.30	—	—	7.41–7.97
1b**	2.84	2.46	2.72	4.92	—	2.33	1.76	3.99	5.00	2.08	4.33	4.21	—	—	7.52–7.98
2a**	2.51	2.43	2.99	5.01	—	1.92	1.81	4.08	4.57	1.92	3.68	3.52	4.38	—	—
2b*	2.81	2.57	3.17	5.12	—	2.27	1.94	4.32	—	2.33	4.77	4.41	—	—	7.42–8.00
2b**	2.55	2.55	3.13	5.06	—	1.94	1.94	4.21	4.93	2.31	4.52	4.41	—	—	7.50–7.98
3*	2.63	2.40	2.25	4.05	—	2.03	1.92	4.23	—	1.93	4.69	4.33	—	3.68	7.41–7.99
3**	2.54	2.41	2.14	3.67	4.75	2.21	1.49	4.11	4.67	1.90	4.40	4.24	—	3.44	7.51–7.96
4*	2.60	2.41	2.70	4.04	—	2.47	1.74	4.17	—	2.63	4.38	4.22	—	3.65	7.43–7.97
4**	2.2–2.4	2.2–2.42	2.2–2.4	3.68	4.78	2.2–2.4	1.40	3.89	4.82	2.2–2.4	4.23	4.23	—	3.46	7.53–7.92

Table 2 ^{13}C NMR chemical shifts of lactones and benzoate esters (δ, 90 MHz, $CDCl_3$,* [$^2H_6$]DMSO,** 32 °C)

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11, -15	C-12, -14	C-13	OCH_3
1c, 1a**	177.2	35.4	39.3	83.7	40.2	72.7	56.0	61.1	—	—	—	—	—	—
1b*	177.1	35.4	40.1	83.4	40.4	74.1	53.0	64.5	166.6	129.5	129.5	128.5	133.3	—
2a**	177.7	30.2	37.9	84.6	41.6	71.5	49.3	57.9	—	—	—	—	—	—
2b*	177.5	30.5	38.7	84.6	41.8	72.5	46.8	61.8	166.9	129.6	129.6	128.3	133.3	—
3*	173.6	37.2	46.3	78.4	41.7	72.9	50.2	63.7	167.1	129.8	129.6	128.4	133.2	51.7
4*	174.2	33.7	44.5	76.8	42.5	73.8	48.8	63.4	166.5	129.7	129.5	128.5	133.2	51.9

Table 3 NOE values for compounds **1–4** ($CDCl_3$,* [$^2H_6$]DMSO**)[a]

Compound	Proton irradiated	2-H	2'-H	3-H	4-H	4-OH	5-H	5'-H	6-H	6-OH	7-H	8-H	8'-H
1c**	4-H	0.7	0	4.1	Irr.		2.3	0.6	0.5	−0.2	0	0	0
	6-OH	−0.2	0.3	0.3	−0.3		−0.4	2.0	7.1	Irr.	2.3		
	6-H	0	0	1.3	0.5		2.7	0.6	Irr.	2.9	1.2	1.1	0.9
	3-H			Irr.	4.9			0	1.0	0.1	0.7	0.5	1.2
2a**	4-H	0.1		5.2	Irr.		1.0	1.5	0	0		0	0
	6-OH	0.2		0	0		1.3	−0.3	8.4	Irr.	0	1.7	1.3
	3-H	1.1		Irr.	5.1		0	0	−0.1	0	3.6	0.2	0.4
	5'-H	0	0	0	3.3		6.4	Irr.	2.1	−0.2	0	0	0
1a**	4-H			3.0	Irr.		2.1	0.8	0.6				
	6-OH						0	2.7	4.9	Irr.	2.7		
	6-H			1.2					Irr.	7.5		1.0	0.8
	3-H			Irr.	3.3			1.0	0.7		−0.9	0.6	1.1
3**	4-OH	1.0	0.7	2.5	7.6	Irr.	0.8	1.9	0.8	−2.4	0.5	0	0
	6-OH			1.5	0.6	5.0	0	2.2		Irr.	0	1.4	0.7
	6-H	0	0	0.8	1.0	0	4.1	1.7	Irr.	5.4	5.9	0.8	−1.0
	4-H	1.8	1.5	1.0	Irr.	5.0	4.5	0	0.9		2.5	0	0
	8-H	0	0	2.3	0	0	0	0.5	1.3	1.2	4.1	Irr.	
	2'-H	10.9	Irr.	2.5	1.0	0.2		0	0	0	1.1	0	0.4
4**	4-OH				13.8	Irr.		3.8	1.8			0	0
	6-OH				2.1			3.5	12.3	Irr.		1.3[b]	1.3[b]
	6-H				0	0		0	Irr.	11.6		4.8[b]	4.8[b]
	8-H; 8'-H	0	0		10.0	0		0	25.8	0		Irr.	Irr.
4*	3-H			Irr.	0						0	0	0
	5'-H				0			Irr.	0			0	0
	8-H		0.7	0			0	0				Irr.	
1b**	6-OH				0.6			0.6	2.4	Irr.	0.8		
	6-H			1.0	0.5		2.0		Irr.	2.0	1.1	0.4	
	8'-H			2.2					1.2		3.6	13.5	Irr.
2b**	6-OH						1.0	0.4	4.3	Irr.	0		0.3
	3-H	3[b]	3[b]	Irr.	3.8		0.06	0.1			3.7	0.1	0.3
	8'-H	0.5[b]	0.5[b]	0.2					0	0.36	1.6	11.0	Irr.

[a] 0 = NOE not observed. [b] NOE with degenerated protons (see Table 1).

7-H (1.75 ppm; 2.3%), 5'-H (1.73 ppm; 2.0%) and 2'-H (2.37 ppm; 0.3%) leads us to attribute them to an *endo* configuration. The opposite *endo* configuration is given to 5-H (2.16 ppm; −0.4%) and 2-H (2.77 ppm; −0.2%). The irradiation of 6-H confirms the *exo* orientation of 5-H for the signal observed at 2.16 ppm with an NOE stronger (2.7%) than that for the *endo* signal of 5'-H situated to 1.73 ppm (0.6%). In this experiment the *exo* 3-H and *exo* 4-H configurations are also demonstrated with an increase of the NOEs, respectively, of 1.3% and 0.5%. All the irradiations carried out on all of the protons of compound **1c** confirm the relative configuration given for each of them. Furthermore, the coupling constant $J_{2',3} = 2.19$ Hz is in agreement of the *endo* configuration attributed to the 2'-H and a dihedral angle $H^{2'}$–C^2–C^3–H^3 close to 120° (a dihedral angle of 0°)[21] corresponds to a value of J close to 8.2 Hz. The *cis*-configuration of 3-H as compared to 4-H is confirmed by

results of their corresponding irradiations: 4.9% NOE on 4-H and 4.1% on 3-H. These experiments (irradiations of 3-H and 4-H) demonstrate *endo* configurations for 6-H (1.0% NOE effect) and *exo* for 4-H, with observed effects of 2.3% (5-H *exo*), 0.6% (5'-H *endo*) and 0.5% (6-H *exo*).

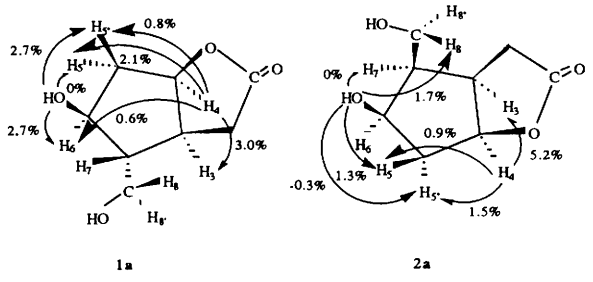
An identical reasoning is followed for observations (Table 3) concerning the lactone **2a**. The irradiation of the hydroxy function at the 6-position, arbitrarily oriented *endo*, allows one to attribute an identical *endo* configuration to 2-H (2.51 ppm; 0.2%), 5-H (1.92 ppm; 1.3%) and 8'-H (3.68 ppm; 1.3%) on the basis of increases of their respective NOEs. The opposite *exo* configuration is given to 5'-H (1.81 ppm; −0.3%) and 7-H (1.92 ppm; 0%). The irradiation of 4-H induces a NOE of 1.0% for 5-H *endo* (to 1.9 ppm), 1.5% for 5'-H *exo* (to 1.81 ppm) and 5.2% for 3-H *exo*, in agreement with the proximity of 5'-H *exo* and 3-H as compared to 4-H, as can be seen using molecular models. The other values noted after irradiation are in agreement with this assignment.

The irradiation of 3-H *exo* allows one to check the *cis* configuration of this proton as compared to 4- and 7-H, with, respectively, 5.1% and 3.6% NOE. Similarly, the *exo* configuration of 5'-H is deduced by NOE of 3.3% and 2.1% for signals of 4-H *exo* and 6-H *exo*, respectively, when the irradiation is at the 5'-H resonance.

The Corey lactone **1c** is obtained by basic hydrolysis of 4-phenylbenzoate ester **1d** (K_2CO_3; 83% yield). The resulting lactone **1c** presents the same ^1H and ^{13}C NMR spectra as its isomer **1a**. Only the sign of the optical rotation $[\alpha]_D$ of −43.3 (lit.,[22] −44; c = 1.4, CH_3OH) for lactone **1c** and +45 (c = 1.5 × 10^{-2}; $CDCl_3$)[2] for derivative **1a** allows the demonstration of the enantiomeric relationship.

A difference NOE experiment applied to lactone **1a** allows the verification of assignments of the previously obtained functional configuration. It is possible to deduce and attribute the configuration 1*R*,5*S*,6*R*,7*S* to lactone **1a** due to the existence of the enantiomeric relationship with Corey lactone **1c** of known absolute configuration 1*S*,5*R*,6*S*,7*R*.[22,23] In another way, the absolute configuration 1*R*,5*S*,6*S*,7*S* is given to the lactone **2a** in relation to the Corey lactone as (1*S*,5*R*,6*S*,7*R*)-7-hydroxy-6-hydroxymethyl-2-oxabicyclo[3.3.2]octan-3-one.

Scheme 5 illustrates effects of irradiations on 6-OH, as well



Scheme 5 Observed NOEs resulting from irradiation of 6-OH and 4-H are indicated with solid lines; 0% = NOE not observed

as on 4-H of lactones **1a** and **2a**. Their relationship with the interprotonic distance is indicated by arrows connecting the irradiated protons and assigned by a NOE.

One has to underline in derivatives **1c** and **2a**, the influence of the *exo* and *endo* configuration of the $HOCH_2$ group in the 7-position: the *endo* protons 2- and 5-H in lactone **2a** are shifted downfield when the CH_2OH function is *endo*. These same protons in **1c** with an *exo* configuration are also shifted downfield in the opposite *exo* configuration.

In the case of the benzoate esters **3** and **4**, it is necessary to employ $[^2H_6]$DMSO as solvent, to separate the spin system and also to observe the 4- and 6-OH exchangeable proton resonances. Irradiation of 4- and 6-OH of compound **3** allows the assignment of the *cis* configuration as compared to 5'-H (to 1.49 ppm with a NOE of 1.9% and 2.2%), as well as the *cis* configuration of 8-H (to 4.40 ppm, 1.4%) as compared to 6-OH. A *trans* configuration of 3- and 7-H is an agreement with the NOE observed by irradiation of 8-H (2.3% for 3-H to 2.14 ppm; 0% for 2'-H to 2.41 ppm) and 2'-H (1.1% for 7-H to 1.90 ppm; 0% for 8-H). Analysis of diester **4** is more difficult because of the superposition of several signals in the solvent used. However, the *cis* configuration of 4-OH and 6-OH is verified in the $[^2H_6]$DMSO solution after irradiation of 6-OH (to 4.82 ppm) and 4-OH (to 4.78 ppm) by the observation of a NOE with similar magnitude (3.5% and 3.8%) for 5'-H to 1.40 ppm. Irradiation of 6-H to 3.89 ppm confirms the *trans* configuration of 5'-H (0%), as well as the *cis* configuration of 8-H to 4.23 ppm (1.8%) as compared to 6-H. In $CDCl_3$, irradiation of the 3-H signal to 2.70 ppm being observed in the multiplet of other proton resonances, allows it to be assigned a *trans* configuration as compared to 8-H (0% NOE), assignment confirmed by irradiation of 8-H.

A similar study has been undertaken on derivatives **1b** and **2b** corresponding to lactones **1a** and **2a** with a benzoyloxy group in the 8-position. The results obtained confirm these assignments.

Irradiation of *endo* 6-OH in compound **1b** allow the assignment of the *cis* configuration for 5'-H (to 1.76 ppm, with 0.6% NOE) and 7-H (to 2.08 ppm; 0.8%) and *trans* configuration for 5-H (to 2.33 ppm; 0%) as compared to 6-OH. The *cis* configuration for 3-H and 4-H as compared to 6-H is confirmed by 6-H irradiation (1.0% for 3-H to 2.72 ppm and 0.5% for 4-H to 4.92 ppm). This assignment is also confirmed by irradiation of 8'-H (to 4.21 ppm) with an induced NOE of 1.2% for *exo* 6-H and 2.2% for *exo* 3-H.

An identical reasoning is applied on lactone **2b**. Assignment of the *endo* configuration for 5-H and 8'-H and *exo* for 5'-H and 7-H is made by successive irradiations of 6-OH (to 4.21 ppm): 5-H (to 1.94 ppm; 1.0%); 8'-H (to 4.41 ppm; 0.3%); 5'-H (to 1.94 ppm; 0.4%) and 7-H (to 2.31 ppm; 0%). Similarly the *exo* configuration for 3-H, 4-H, 7-H and 5'-H is confirmed by irradiation of 3-H (to 3.13 ppm), NOE induced on these protons are 3.8% for 4-H (to 5.06 ppm), 3.7% for 7-H (to 2.31 ppm) and 0.1% for 5'-H (to 1.94 ppm).

All the configuration assignments for protons of isoprostane precursors **1–4** are collected in Table 4.

Table 4 Configurations for protons of compounds **1–4**

	3-H	4-H	5-H	5'-H	6-H[a]	7-H
1a, 1c	*exo*	*exo*	*exo*	*endo*	*exo*	*endo*
2a	*exo*	*exo*	*endo*	*exo*	*exo*	*exo*
3	*endo*	*exo*	*exo*	*endo*	*exo*	*exo*
4	*endo*	*exo*	*exo*	*endo*	*exo*	*endo*
1b	*exo*	*exo*	*exo*	*endo*	*exo*	*endo*
2b	*exo*	*exo*	*endo*	*exo*	*exo*	*exo*

[a] 6-OH has *endo* configuration by convention.

Conclusions

This route using the iodinated derivative allowed improvement in the cyclization to give a quantitative yield in isoprostane precursors, with a good *cis*/*trans* ratio and an easier separation of reaction products. The homonuclear ^1H NOE experiment was a versatile and reliable method for the *a priori* determination of *cis* and *trans* configuration of isoprostane precursors. This technique allows us to determine and confirm all the relative configuration of chiral centres of derivatives **1–4**. Conversion of these lactones and benzoate esters to prosta-

glandins and *epi*-prostaglandins is currently being investigated in our laboratory.

Experimental

Materials

Xylene and methanol were distilled from sodium, tetrahydrofuran (THF) from sodium–benzophenone and dichloromethane from CaH_2. Triethylborane, tributyltin hydride and Corey lactone were purchased from Aldrich Chemical Co. Inc. Reactions were monitored by TLC on E. Merck aluminium sheets silica gel $60F_{254}$ (0.2 mm) and visualized using UV light (254 nm) and/or heating with *p*-anisaldehyde solution or phosphomolybdic acid (20 wt% in ethyl alcohol). All reactions were carried out under argon and crude products were purified by chromatography using 70–200 mesh silica gel (E. Merck). ^1H NMR (360 MHz) and ^{13}C NMR (90 MHz) spectra were recorded on a Bruker AMX-360 spectrometer at ambient temperature. IR spectra were obtained with a Beckmann Acculab-2 spectrophotometer. Elemental analyses were performed by the *Centre National de la Recherche Scientifique, Service Central d'Analyse*, Vernaison, France.

For DNOE experiments, ^1H NMR spectra were recorded on a Bruker AMX 360 spectrometer operating in the pulse mode. Compounds were dissolved in the indicated solvent (Table 1). The probehead temperature was 32 °C. Solutions were degassed by argon bubbling. The NOE procedure was as follows. The standard Bruker library microprogram was used to perform steady-state NOE difference spectroscopy. The experiments were performed with interleaving. 32 Scans (preceded by two dummy scans to establish equilibrium: $l_1 = 2$) were acquired for each irradiation frequency and the entire process was automatically repeated to afford the requisite signal-to-noise ratio. The irradiation time was typically 3 s. A 90° read pulse was employed in all cases. The decoupler power setting was chosen so as to minimize frequency spillover to neighbouring multiplets. NOE values were calculated by comparing summed peak heights in the vertically expanded difference spectra with the control irradiation spectra.

Diol 8. To a solution of iodinated compound **7** (4.92 g, 11.75 mmol) in dry THF (90 cm^3) was added acetic acid (72 cm^3, 50% vol). The reaction mixture was then heated at 65 °C and stirred for 3 h before being cooled to room temperature and diluted with ethyl acetate (50 cm^3). The mixture was washed with a saturated solution of NaCl (20 cm^3) and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure and purified by flash chromatography (silica gel, cyclohexane–ethyl acetate 70:30) to yield diol **8** (4.14 g, 93%); δ_H(360 MHz, $CDCl_3$, Me_4Si) 1.97–2.30 (3 H, m, CH_2 and OH), 3.42–3.62 (1 H, t, *J* 3.7, CHOH), 4.25–4.50 (3 H, m, CHO, CHI and OH), 4.62–4.77 (2 H, m, CH_2O), 5.65–5.72 (1 H, d, *J* 3.6, CHOH), 7.32–7.70 (3 H, m, Ar) and 7.90–8.12 (2 H, m, Ar); δ_C(90 MHz, $CDCl_3$, Me_4Si) 34.25, 37.53, 55.09, 67.07, 80.06, 109.12, 128.50, 129.70, 133.37 and 165.95; ν(film)/cm^{-1} 3360 and 1720 (Found: C, 41.1; H, 4.05. Calc. for $C_{13}H_{15}IO_5$: C, 41.29; H, 3.99%).

Iodinated precursor 5. To a solution of diol **8** (2.66 g, 7.03 mmol) in dry THF (65 cm^3) was added the methoxycarbonylmethylidenetriphenylphosphorane (3.3 g, 9.86 mmol). The reaction mixture was stirred for 22 h at ambient temperature. Concentration under reduced pressure and purification by flash chromatography (silica gel, CH_2Cl_2–CH_3OH 99:1) gave **5** (2.65 g, 87% of mixture *E*/*Z* 95:5); δ_H(360 MHz, $CDCl_3$, Me_4Si) for **5** (*E* isomer) 1.70–1.92 (2 H, m, CH_2), 3.38–3.48 (1 H, m, CHOH), 3.56–3.65 (2 H, br s, OH), 3.67 (3 H, s, OCH_3), 4.32–4.41 (1 H, m, CHOH), 4.50–4.56 (1 H, m, CHI), 4.59–4.63 (1 H, dd, *J* 6, 11.6, CH_2O), 4.68–4.75 (1 H, dd, *J* 8.7, CH_2O), 6.02–6.07 (1 H, dd, *J* 1.7, 15.7, vinylic H), 6.85–6.90 (1 H, dd, *J* 4.7, vinylic H), 7.40–7.57 (3 H, m, Ar) and 7.99–8.03 (2 H, m, Ar); δ_C(90 MHz, $CDCl_3$, Me_4Si) 38.2, 43.0, 51.6, 66.2, 69.4, 70.1, 120.1, 128.4, 129.7, 133.5, 148.7, 166.2 and 167.9; ν(film)/cm^{-1} 3440, 1720 and 1650 (Found: C, 44.0; H, 4.5. Calc. for $C_{16}H_{19}IO_6$: C, 44.26; H, 4.41%).

General cyclization procedure

To a solution of diol **5** (150 mg, 0.34 mmol) in anhydrous xylene (4 cm^3) at room temperature under dry air, were sequentially added tributyltin hydride (112 cm^3, 0.41 mmol) and triethylborane (70 cm^3, 0.069 mmol). The resulting solution was stirred for 15 min at room temperature. The crude mixture was flash chromatographed on silica gel. Elution with cyclohexane–ethyl acetate (90:10) gave pure **1b** (16 mg, 17%), pure **2b** (60 mg, 64%), pure **3** (8 mg, 8%) and pure **4** (11 mg, 11%).

(1*R*,5*S*,6*S*,7*S*)-6-Benzoyloxymethyl-7-hydroxy-2-oxabicyclo-[3.2.0]octan-3-one 1b. $[\alpha]_D$ +8.3 (*c* 4.8 × 10^{-2}, $CHCl_3$); ν(film)/cm^{-1} 3420 and 1720 (Found: C, 65.0; H, 5.9. Calc. for $C_{15}H_{16}O_5$: C, 65.21; H, 5.84%).

(1*R*,5*S*,6*R*,7*S*)-6-Benzoyloxymethyl-7-hydroxy-2-oxabicyclo-[3.3.0]octan-3-one 2b. $[\alpha]_D$ −13.9 (*c* 1.6 × 10^{-2}, $CHCl_3$); ν(film)/cm^{-1} 3420 and 1720 (Found: C, 65.0; H, 5.8%).

Methyl (1*S*,2*R*,3*R*,4*R*)-2-(2-benzoyloxymethyl-3,5-dihydroxycyclopentyl)ethanoate 3. $[\alpha]_D$ −2 (*c* 1.5 × 10^{-2}, $CHCl_3$); ν(film)/cm^{-1} 3390 and 1740 (Found: C, 62.1; H, 6.6. Calc. for $C_{16}H_{20}O_6$: C, 62.33; H, 6.54%).

(1*S*,2*S*,3*R*,4*R*)-2-(2-benzoyloxymethyl-3,5-dihydroxycyclopentyl)ethanoate 4. $[\alpha]_D$ +19 (*c* 2.6 × 10^{-2}, $CHCl_3$); ν(film)/cm^{-1} 3380 and 1740 (Found: C, 62.1; H, 6.6%).

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