Radical cyclization of highly functionalized precursors: stereocontrol of ring closure of acyclic 1-substituted-2,4-dihydroxylated hex-5-enyl radicals

Arlène Roland, Thierry Durand,* David Egron, Jean-Pierre Vidal and Jean-Claude Rossi

Laboratoire de Chimie Biomoléculaire et des Interactions Biologiques Associé au C.N.R.S. Université Montpellier I, Faculté de Pharmacie, 15 Avenue Charles Flahault, 34060 Montpellier, France. Tel: 33-4-67-54-86-23, Fax: 33-4-67-54-86-25. E-mail: Thierry.Durand@pharma.univ-montp1.fr

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Polysubstituted cyclopentane rings can be synthesized with good to high stereocontrol by radical cyclization using tributyltin hydride and a radical initiator, triethylborane–O_2 in anhydrous xylene at room temperature. We have demonstrated that the nature (protected or unprotected) of the hydroxy functions in position 2 and 4 is responsible for the stereochemical cyclization outcome of acyclic 1-substituted-2,4-dihydroxylated hex-5-enyl compounds. The presence of a 2,4-diol leads to the all-*syn* precursor of isoprostanes while the diprotected diol affords the diastereoisomer *syn-anti-syn* precursor.

Introduction

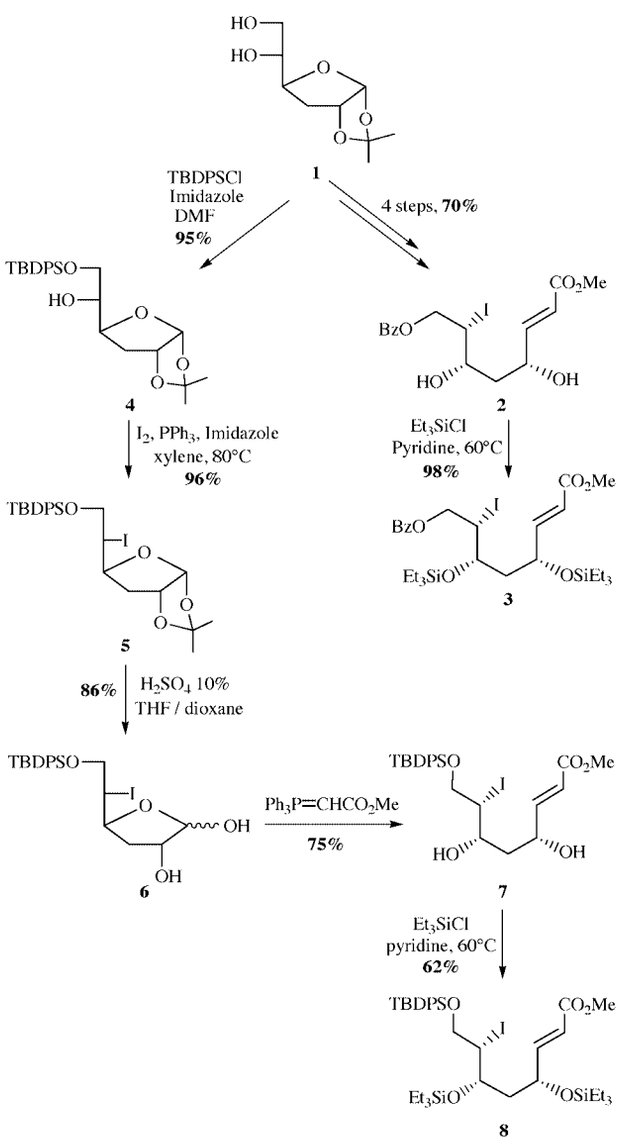
A new class of natural products called isoprostanes (isoPs) is formed in humans and possesses powerful biological activity.[1] Because of their non-enzymatic free-radical catalyzed biosynthesis from arachidonic acid, isoprostanes are all regiomers of well-known prostaglandins. Indeed, isoPs are mainly characterized by a polysubstituted cyclopentane ring bearing two hydroxy groups in a *cis* position and two side chains also in a *cis* position.

Carbocyclic annulations are extremely important reactions[2] and the stereocontrolled intramolecular free-radical cyclization has emerged as a powerful tool for carbon–carbon bond formation in synthetic chemistry.[3,4] Among all these reactions, the hex-5-enyl radical cyclization is the most well-known for the synthesis of cyclopentane rings. The conversion of carbohydrates to highly *O*-functionalized carbocyclic compounds through the intramolecular cyclization of hex-5-enyl radicals possesses considerable synthetic utility because of its application to the total synthesis of biologically active natural products.[5] Over the last six years, we have focused our interest on the synthesis of chiral cyclopentane rings[6] from glucose leading to new isoprostanes.[7] We have studied herein which factors could influence the stereochemical course of the radical key step in the case of our previous intramolecular cyclization of acyclic 1-substituted polyhydroxylated hex-5-enyl radical.[6b] This study allowed us to control the cyclization outcome to yield the all-*syn* precursors (**9** or **17**) or the *syn-anti-syn* precursors (**13** or **24**). To confirm the relative configuration of such polysubstituted cyclopentane precursors, we have performed steady-state difference NOE spectroscopy (DNOES) experiments.

Results and discussion

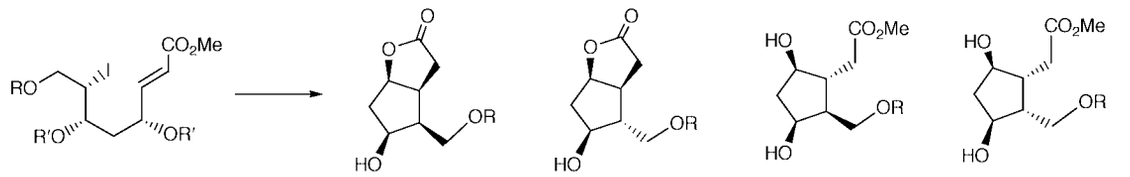
1) Synthesis of radical precursors 2, 3, 7 and 8

The synthesis of unprotected and protected radical generators **2**/**7** and **3**/**8**, respectively, depicted in Scheme 1, was achieved with the commercially available di-*O*-isopropylidene-α-D-glucofuranose as starting material. This aldofuranose, after radical Barton deoxygenation[8] and Wittig reaction, was converted to highly functionalized radical generators. The precursor **2** (56% overall yield after 6 steps[6]) is characterized by two free hydroxy

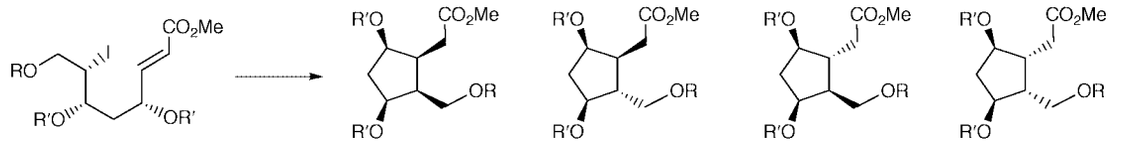


Scheme 1

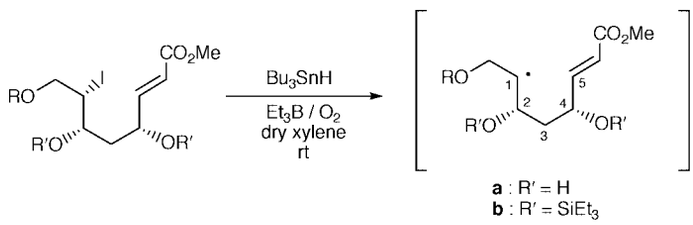
Table 1



Substrate	Total yield (%)	Products (yield)			
2 R = Bz, R′ = H	100	**9** (64%)	**10** (17%)	**11** (11%)	**12** (8%)
7 R = TBDPS, R′ = H	96	**17** (55%)	**18** (22%)	**19** (9%)	**20** (14%)



Substrate	Total yield (%)	Products (yield)			
3 R = Bz, R′ = $SiEt_3$	97		**14**, **15**, and **16** (30%)		**13** (70%)
8 R = TBDPS, R′ = $SiEt_3$	100	**21** (9%)	**22** (4%)	**23** (12%)	**24** (75%)



groups at C-4 and C-6 as well as a benzoyl protecting group on the primary hydroxy group at C-8. From the previous compound **2**, the two secondary hydroxy functions were protected in the presence of Et_3SiCl (8 equiv.) at 60 °C in pyridine leading to **3** in 98% yield.

For precursor analogues **7** and **8** bearing a TBDPS protecting group instead of a benzoyl group on the primary hydroxy function, the synthetic route is the same as those previously described.[7,9] We started from the diol **1** which was protected on its primary alcohol in the presence of TBDPSCl (1.1 equiv.) and imidazole (2.3 equiv.) in DMF to provide the compound **4** in 95% yield. The substitution of the hydroxy group in position 5 (compound **5**) by an iodine was achieved with Ph_3P (1.02 equiv.), imidazole (2 equiv.) and I_2 (1.1 equiv.) in xylene at 80 °C in 96% yield.[9] Deprotection of the 1,2-isopropylidene using aqueous H_2SO_4 10% in a mixture of THF and dioxane yielded 86% of the hemiacetal **6**. Finally a Wittig reaction in the presence of 2 equiv. of methoxycarbonylmethylene(triphenyl)phosphorane in dry THF permitted the introduction of the double bond in 75% yield.[10] The compound **7** represents a new cyclization precursor and the protection of its secondary hydroxy functions with Et_3SiCl provided the other precursor **8** with a non-optimized 62% yield (30% overall yield after 7 steps).

2) Radical cyclization reactions

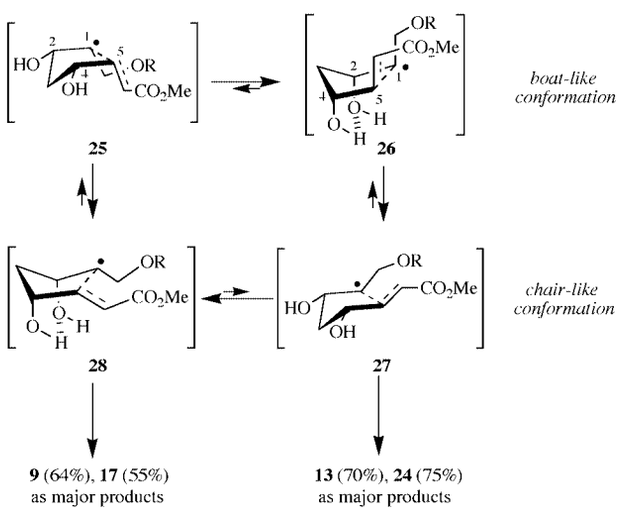
Intramolecular ring closure of radical species is one of the most powerful tools for the synthesis of a variety of cyclic compounds.[3] In particular, the 5-*exo*-*trig* closure reaction of the hex-5-enyl radical kinetically controlled according to Baldwin's rules[11] is well established and has been used to construct complex five-membered rings. The critical 1,5-*cis* selectivity is the one that has found the most use in the construction of cyclic or polycyclic natural products.[3] The radical generators **2**, **3**, **7** and **8** were converted to highly functionalized hex-5-enyl radicals then the intramolecular cyclization reaction was achieved[6b] at room temperature in xylene with *n*-Bu_3SnH (1.2 equiv.) and the Et_3B (0.2 equiv.)–O_2 (dry air) system[12] to yield quantitatively in each experiment a mixture of four cyclopentane compounds (**9**–**12**, **13**–**16**, **17**–**20** and **21**–**24**; Table 1). In all cases, the radicals **a** or **b** cyclize to give predominantly the 1,5-*cis* products (**9**, **13**, **17** and **24**) as expected, with observed 1,5-*cis* : 1,5-*trans* ratios between 2.2 and 2.6 from compounds **2**/**7** and between 4.0 and 5.2 from compounds **3**/**8**. But the main result (Table 1) was the reversal of the stereochemistry in the 1,5-*cis* major products between the unprotected and protected radical precursors **2**/**7** and **3**/**8** (64% and 55% of unprotected all-*syn* compounds **9** and **17**; 70% and 75% of protected *syn*-*anti*-*syn* compounds **13** and **24**).

3) Discussion

The stereoselectivity in the hex-5-enyl radical cyclization has been widely studied and rational guidelines have been provided to predict their stereochemical outcome.[13] Moreover, an advanced understanding of these details was provided by Beckwith,[13b] Spellmeyer,[14] and RajanBabu's works.[15] According to Beckwith, in the case of simple 1,*n*-disubstituted hex-5-enyl acyclic radicals ($n = 2$ to 5), the most favorable transition state adopts a "chair-like" or a folded envelope conformation where all the substituents are in a *pseudo*-equatorial orientation because of the steric constraints. Consequently, the 1,5-ring closure of 1- or 3-substituted hex-5-enyl radicals affords mainly *cis*-disubstituted cyclic products, whereas 2- or 4-substituted

species give *trans* compounds.[13b] It has also been shown that the stereoelectronic effects caused by the substituent in position 1 favors the 1,5-*cis* cyclization in relation to the 1,5-*trans* junction.[16] Unfortunately, in the case of polysubstituted acyclic hex-5-enyl compounds bearing a prostereogenic radical and a double bond, only a few articles provide an interesting discussion about the influence of the substituents on the stereochemical outcome of the radical cyclization.[5b,15] The previously described results follow exactly Beckwith's model since the major cyclic compound obtained in each case has a 1,5-*cis* junction. However, the 4,5- and 1,2-*cis* or *trans* configurations can only be explained by focusing our attention on the possible transition states of the radical cyclization step.

Now, we propose an explanation of these results to provide an in-depth understanding of the factors controlling the stereoselectivity of the radical cyclization in the case of polyhydroxylated acyclic hex-5-enyl radicals. These new data allowed us to understand how we were able to reverse the stereocontrol of the radical cyclization described in Scheme 2 and get mostly 4,5-



Scheme 2

trans and 1,2-*trans* junctions instead of 4,5-*cis* and 1,2-*cis* ones, without modifying our synthetic scheme profoundly. According to the accepted rules, the major transition state should adopt a "chair-like" conformation with all its substituents in a *pseudo*-equatorial position. However, in accordance with our first observed results from the radical precursor **2** (major compound **9** and minor compound **12**), the most stable transition state could only be **25** or **28** (Scheme 2).

As shown previously by Houk *et al.*,[14b] the energetic barrier between the "chair-like" and the "boat-like" conformations is very weak (less than 1 kcal mol^{-1}). In a first approach, the transition state **25** should be the most stable because the weakest steric strain is observed when the two substituents have a *pseudo*-equatorial orientation. But, among the different factors responsible for the stereochemical outcome of the radical cyclization, the effect of the weakest allylic strain, like the one observed in the transition state **28**, should be predominant. So between the transition states **25** and **28**, only the "chair-like" conformation **28** explains the major all-*syn* product formation **9** or **17** and this despite the presence of a drastic and destabilizing steric diaxial interaction between the two hydroxy groups. However, when we looked at the transition state **27**, we noticed a "chair-like" conformation bearing a weak allylic strain too and the two hydroxy groups in an apparently more favored *pseudo*-equatorial position. Consequently, according to us, the only probable reason why the transition state **27** is not the most favorable one for the radical cyclization of **2** and **7** comes from the fact that in the transition states **28**, such as occurs in cyclohexane-1,3-diol,[17] the 1,3-diaxial orientation is favored by

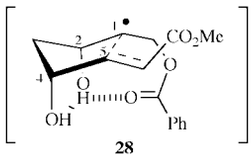


Fig. 1

an intramolecular hydrogen bond. So in order to force the radical transition state to assume the reverse "chair-like" conformation with two *pseudo*-equatorial hydroxy groups, leading to the *syn-anti-syn* compounds **13** and **24**, we have broken the hydrogen bonds by adding bulky silyl ethers as protecting groups which initiate very drastic steric interactions. When we carried out the cyclization reaction on the 2,4-silyl ether radical precursors **3** and **8**, the soundness of our opinion was confirmed by newly observed results: the major products were now the expected **13** (70%) and **24** (75%) compounds, *i.e.* those which were minor compounds (**12** 8% and **20** 14% respectively) from the unprotected radical generators **2** and **7** (Table 1).

Another point must be emphasized now: the reason why two different protecting groups have been used on the primary alcohol (R = Bz or TBDPS) comes from the fact that we had suspected the benzoyl protecting group also to have an influence on the stereochemical outcome of the radical cyclization. Indeed, it was not excluded that a stabilizing intramolecular H-bond between the carbonyl moiety of the benzoyl group and the hydroxy group at C-2 (Fig. 1) could exist, favoring a 1,2-*cis* junction.

The comparison of the 1,2-*cis*:1,2-*trans* ratios when R = Bz, R′ = H (1,2-*cis*:1,2-*trans* = 3.0) and R = TBDPS, R′ = H (1,2-*cis*:1,2-*trans* = 1.8) shows effectively that the protecting group on the primary hydroxy has an influence on the stereochemical outcome of the radical cyclization (Table 1). Moreover, since the 1,2-*cis*:1,2-*trans* ratios are equal when R = Bz, R′ = $SiEt_3$ and R = TBDPS, R′ = $SiEt_3$ (1,2-*cis*:1,2-*trans* = 0.25), we can confirm that the 1,2-*cis* orientation is due to an intramolecular interaction between the benzoyl group and the alcohol at C-2 when this hydroxy group is free. All these new cyclization products were separated by chromatography on silica gel and a structural analysis by one and two dimensional NMR, homo- and heteronuclear, together with a differential NOE study, allowed the determination of the configuration for each chiral centre (*vide infra*).

If the cyclizations of conformationally rigid cyclic radicals are critically influenced by the orientation of the side chains,[15] in the conformationally less rigid systems, a conformational equilibrium between several transition states can explain the outcome more satisfactorily.

4) Determination of relative configuration of compounds 21, 22, 23 and 24 by ^{1}H NMR NOE study

We have determined and confirmed the relative configurations of compounds **21, 22, 23** and **24** by steady-state difference NOE spectroscopy (DNOES) experiments, which have previously been employed by our group.[6b]

Irradiation of 5a-H in products **21**, **22**, **23** and **24** induces a significant NOE on the protons 4-H and 1-H, while irradiation of 5b-H induces little or no NOE. The 1,3-triethylsilyl ethers are therefore in a *cis* configuration with respect to each other, in agreement with the synthesis, and a *cis* configuration as compared to the 5b-H proton (Fig. 2, Tables 2 and 3, for NOE spectra for compounds **21**, **22**, **23** and **24**, see Fig. 3).

Concerning the relative configuration of chains situated in C-3 and C-2 positions: for compound **24** the irradiation of 5b-H (at 1.60–1.50 ppm) induces an NOE of 0.8% on 3-H (at 2.62–2.53 ppm) and 0.3% on 2-H (at 2.17–2.10 ppm), the irradiation of 7a-H (at 2.60–2.48 ppm) (7b-H being superposed on 7a-H) induces an NOE of 0.3% on 1-H (at 4.09 ppm) and 1.3% on

Table 2 ^{1}H NMR chemical shifts of compounds **21**, **22**, **23** and **24** (δ, 360 MHz, $CDCl_3$)

Compound	1-H	2-H	3-H	4-H	5a-H
24	4.09	2.17–2.10	2.62–2.53	3.92	2.31
22	4.24–4.20	1.95–1.80	2.45–2.36	4.37–4.34	2.34–2.25
23	4.19	1.87–1.78	2.38–2.23	3.93–3.83	2.22–2.15
21	4.08	2.09–2.01	2.53–2.49	4.14	2.31
Compound	5b-H	6a-H	6b-H	7a-H	7b-H
24	1.60–1.50	3.64–3.55	3.64–3.55	2.60–2.48	2.60–2.48
22	1.75–1.65	3.88–3.84	3.72–3.67	2.64	2.19
23	1.68–1.58	3.93–3.83	3.68	2.45	2.45
21	1.50–1.45	3.88	3.88	2.71	2.55

Table 3 ^{13}C NMR chemical shifts of compounds **21**, **22**, **23** and **24** (δ, 90 MHz, $CDCl_3$)

Compound	C-1	C-2	C-3	C-4	
24	72.8	50.0	44.7	75.6	
22	71.8	53.0	40.7	71.7	
23	70.8	48.9	45.9	75.3	
21	71.6	48.3	41.3	72.4	
Compound	C-5	C-6	C-7	C-8	OCH_3
24	45.0	62.8	32.9	173.8	51.3
22	44.6	61.9	32.2	173.7	50.9
23	44.5	63.7	35.5	173.2	51.1
21	44.7	61.3	30.4	174.6	51.1

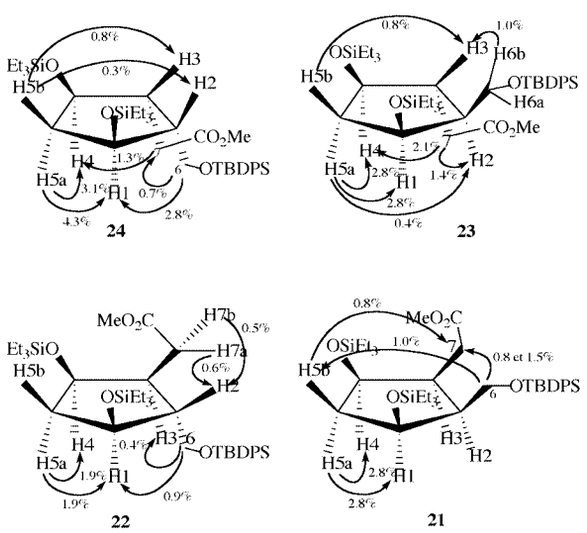


Fig. 2

4-H (at 3.92 ppm), and the irradiation of 6a-H (at 3.64–3.55 ppm) induces an NOE of 2.8% on 1-H (at 4.09 ppm), 0.9% on 4-H (at 3.92 ppm) and 0.7% on 7a-H (at 2.60–2.48 ppm). These observations allow one to check the relative *cis* configuration of the protons 3-H (at 2.62–2.53 ppm), 2-H (at 2.17–2.10 ppm) and 5b-H (at 1.60–1.50 ppm).

An identical reasoning is applied to compound **22**. Assignment of the relative *cis* configuration between the protons 7a-H (at 2.64 ppm) and 2-H (at 1.95–1.80 ppm), and between the protons 6a-H (at 3.88–3.84 ppm), 1-H (at 4.24–4.20 ppm) and 3-H (at 2.45–2.36 ppm) is made by successive irradiations of 7a-H (at 2.64 ppm) and 7b-H (at 2.19 ppm): NOE induced on 2-H (at 1.95–1.80 ppm; 0.6% and 0.5% respectively), and by irradiation of 6a-H (at 3.88–3.84 ppm): NOE induced on 1-H (at 4.24–4.20 ppm; 0.9%) and 3-H (at 2.45–2.36 ppm; 0.4%).

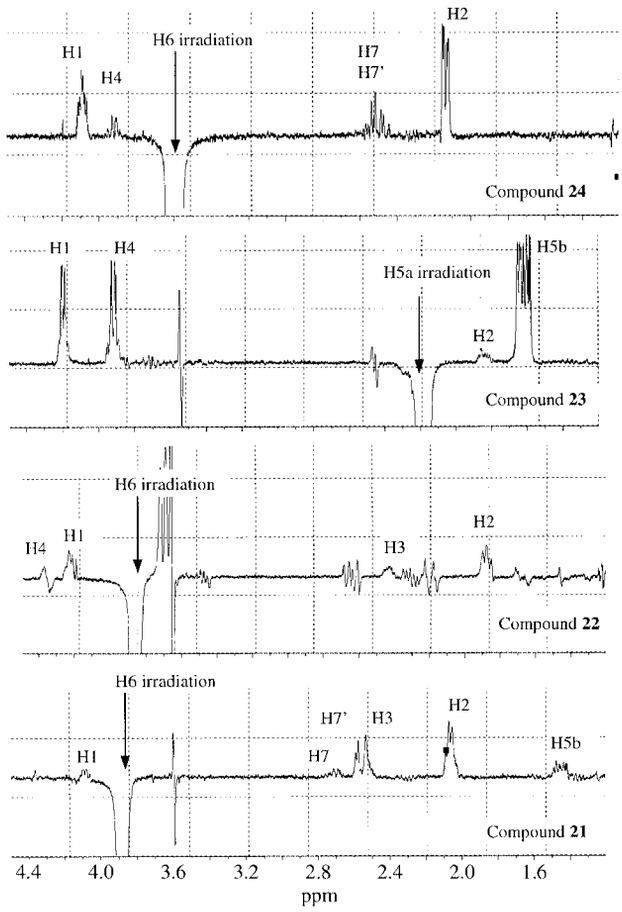


Fig. 3 NOE Spectra for compounds **21** to **24**.

The irradiation of 5a-H (at 2.22–2.15 ppm) in compound **23** induces an NOE of 0.4% on 2-H (at 1.87–1.78 ppm). Similarly, irradiation of 5b-H (at 1.68–1.58 ppm) induces an NOE of 0.8% on 3-H (at 2.38–2.23 ppm) and irradiation of 7a-H (at 2.45 ppm) induces an NOE of 2.1% on 4-H (at 3.93–3.83 ppm) and 1.4% on 2-H (at 1.87–1.78 ppm). The irradiation of 6a-H (at 3.93–3.83 ppm) is without effect on 7a-H (at 2.45 ppm). These results are in agreement with a relative *trans* configuration between the protons 2-H (at 1.87–1.78 ppm) and 3-H (at 2.38–2.23 ppm), and a relative *cis* configuration between 7a-H (at 2.45 ppm) and 5a-H (at 2.22–2.15 ppm), and between 6a-H (at 3.93–3.83 ppm) and 5b-H (at 1.68–1.58 ppm).

For compound **21** the relative *cis* configuration of the protons 2-H (at 2.09–2.01 ppm), 3-H (at 2.53–2.49 ppm) and 5a-H (at 2.31 ppm) is determined in the same manner. Indeed, the irradiation of the proton 5b-H (at 1.50–1.45 ppm) induces an NOE of 0.8% on 7a-H (at 2.71 ppm), the irradiation of 7b-H (at 2.55 ppm) induces an NOE of 0.4% on 6a-H (at 3.88 ppm) and the irradiation of 6a-H (at 3.88 ppm) induces an NOE of 1.0% on 5b-H (at 1.50–1.45 ppm), 0.8% on 7a-H (at 2.71 ppm) and 1.5% on 7b-H (at 2.55 ppm).

Conclusion

In conclusion, this study has highlighted the different parameters responsible for the stereochemical outcome of the radical cyclization of acyclic 1-substituted polyhydroxylated hex-5-enyl radicals and their relative importance. This can be helpful for the prediction of radical cyclization outcomes from other conformationally flexible systems. Our results have demonstrated, as Beckwith predicted before, that the most important parameter is the presence of a substituent at C-1 which is responsible for the 1,5-*cis* stereoselectivity. In addition to this observation, our results have pointed out the parameter of secondary importance which is the nature of the substituent at

C-2 and C-4. When they are hydroxy groups, as in our case, the stereocontrol of the radical cyclization depends also on an equilibrium between van der Waals' and steric interactions: if the hydroxy groups are protected, only the steric interactions control the transition states' equilibrium, leading in our case to *syn-anti-syn* cyclic compounds while, if the hydroxy groups are free, the van der Waals' forces overcome the steric interaction and control the 1,2- and 4,5- *cis*/*trans* stereoselectivities to yield all-*syn* compounds in our case. Moreover, as the last important factor, we have found that the nature of the protecting group on the primary alcohol at C-1 could also affect the 1,2-*cis*/*trans* stereoselectivities due to the appearance of another intramolecular hydrogen bond when R′ = Bz. Consequently, in order to predict the stereoselectivity of intramolecular cyclizations of acyclic 1-substituted polyhydroxylated hex-5-enyl radicals, all these parameters should be considered and comparison of the stability of each possible transition state should be made.

Finally these results allowed us to devise a very convergent strategy for the total synthesis of isoP. We can reach, using the cheaper D-glucose, all the different IsoPs diastereoisomers by choosing whether or not to protect the radical precursors. We have demonstrated the efficacy of our synthetic route by the achieved total synthesis of 8-*epi*- or 12-*epi*-$PGF_{2\alpha}$.[6b,7b,18]

Experimental

Materials

Xylene and methanol were distilled from sodium, tetrahydrofuran from sodium–benzophenone and dichloromethane from CaH_2. Triethylborane, tributyltin hydride and Corey lactone were purchased from Aldrich Chemical Company Inc. Reactions were monitored by thin layer chromatography on E. Merck aluminium sheet 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). ^{1}H 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 DNOES experiments, ^{1}H 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. Thirty-two scans (preceded by two dummy scans to establish equilibrium: $l1 = 2$) 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 neighboring multiplets. NOE Values were calculated by comparing summed peak heights in the vertically expanded difference spectra with the control irradiation spectra.

Methyl (2*E*,4*R*,6*S*,7*R*)-8-benzoyloxy-4,6-bis(triethylsilyloxy)-7-iodooct-2-enoate 3

To a solution of compound **2**[7b] (50 mg, 0.115 mmol) previously dissolved in anhydrous pyridine at 60 °C was added triethylsilyl chloride (360 µl, 0.922 mmol) under an inert atmosphere. The solution was stirred for 2 hours at 60 °C. The crude mixture was allowed to reach room temperature and was diluted with water and extracted three times with CH_2Cl_2. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (heptane–ethyl acetate 90 : 10) and a colorless oil was finally identified as the compound **3** (75 mg, 98% yield).

R_f 0.45 (heptane–ethyl acetate 80 : 20). IR: ν_{max}/cm^{-1} 1715 (C=O). ^{1}H NMR (100 MHz, $CDCl_3$): δ (ppm) = 0.4–1.0 (m, 30H, 2 Si(CH_2CH_3)$_3$), 1.57–2.14 (m, 2H, H-5), 3.38 (t, 1H, J = 6.3 Hz), 3.58 (s, 3H, OCH_3), 4.30–4.75 (m, 4H, H-4, H-7, H-8), 5.91 (d, 1H, H-2, J = 15.7 Hz), 6.87 (dd, 1H, H-3, J = 4.7, 15.7 Hz), 7.27–7.55 (m, 3H, Phenyl), 7.89–7.97 (m, 2H, Phenyl). ^{13}C NMR (25 MHz, $CDCl_3$): δ (ppm) = 4.5, 4.9, 5.6, 6.0, 6.3, 6.5 (2 Si(CH_2CH_3)$_3$), 38.1 (C-5), 44.3 (C-7), 51.2 (OCH_3), 66.3, 66.5, 68.8 (C-4, C-6, C-8), 119.9 (C-2), 128.1, 129.4, 132.8 (Phenyl), 149.8 (C-3), 165.3 (CO_2 methyl ester), 166.2 (CO_2 benzoyl group).

Methyl (2*E*,4*R*,6*S*,7*R*)-8-*tert*-butyldiphenylsilyloxy-4,6-bis(triethylsilyloxy)-7-iodooct-2-enoate 8

To a solution of compound **7**[10] (1.25 g, 2.2 mmol) previously dissolved in anhydrous pyridine (18 ml) at 60 °C was added triethylsilyl chloride (1.7 ml, 10.09 mmol) under an inert atmosphere. The solution was stirred for 4 hours at 60 °C. The crude mixture was allowed to reach room temperature and was diluted with water and extracted three times with CH_2Cl_2. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (cyclohexane–ethyl acetate 90 : 10) and a colorless oil was finally identified as the compound **8** (1.08 g, 62% yield).

R_f 0.53 (cyclohexane–ethyl acetate 90 : 10). IR: ν_{max}/cm^{-1} 1720 (C=O). ^{1}H NMR (360 MHz, $CDCl_3$): δ (ppm) = 0.54–0.69 (m, 12H, Si(CH_2CH_3)$_3$), 0.94–1.04 (m, 27H, Si(CH_3)$_3$, Si(CH_2CH_3)$_3$), 1.76–1.84 (m, 1H, H-5), 2.08–2.16 (m, 1H, H-5), 3.60 (m, 1H, H-6), 3.73 (s, 3H, OCH_3), 3.93 (dd, 2H, H-8, J = 1.8, 6.3 Hz), 4.43–4.48 (m, 2H, H-4 and H-7), 6.08 (dd, 1H, H-2, J = 1.4, 15.7 Hz), 7.02 (dd, 1H, H-3, J = 4.7, 15.7 Hz), 7.38–7.44 (m, 6H, Phenyl), 7.71–7.69 (m, 4H, Phenyl). ^{13}C NMR (90 MHz, $CDCl_3$): δ (ppm) = 4.9, 5.3, 6.4, 6.7, (2 Si(CH_2CH_3)$_3$), 19.1 ($C(CH_3)_3$), 26.8 ($C(CH_3)_3$), 44.3 (C-5 and C-7), 51.3 (OCH_3), 66.4 (C-8), 67.4 (C-4), 69 (C-6), 120.2 (C-2), 127.6, 129.7, 133.1, 133.5, 135.6 (Phenyl), 150.2 (C-3), 166.5 (CO). Elemental analysis (Found C, 55.78; H, 7.67. Calc. for $C_{37}H_{61}O_5SiI_3$: C, 55.76; H, 7.71%).

General procedure for the radical cyclization step

The cyclization precursor (1 equiv.) was dissolved in anhydrous xylene (4 ml for 0.3 mmol of starting material at room temperature). The oxygen was removed from the solvent by smoothly flushing nitrogen through the solution for 1 hour. Then, tributyltin hydride (1.2 equiv.) and triethylborane (0.2 equiv. of a 1 M solution in hexane) were added successively under nitrogen before smoothly flushing dry air through the solution for 10 minutes. The solvent was concentrated under reduced pressure and the crude product was purified by chromatography on silica gel. For compound **13**, a cyclohexane–ethyl acetate mixture (100 : 0 to 95 : 5) was used as eluent. Even after chromatographing several times, it was still difficult to isolate the compounds **14** to **16** since they have quite similar polarities. Cyclohexane–ethyl acetate (100 : 0 to 50 : 50) and cyclohexane–methylene dichloride (100 : 0 to 50 : 50) mixtures were used as eluents to isolate compounds **17** to **20** and compounds **21** to **24**, respectively. The yields are shown in Table 1.

(1*S*,2*S*,3*R*,4*R*)-2-Benzoyloxymethyl-1,4-bis(triethylsilyloxy)-3-(methoxycarbonylmethyl)cyclopentane 13. This product was also synthesized in another way from the compound **12**.

Triethylsilyl chloride (1.59 ml, 4.080 mmol) was added to a solution of **12** (157 mg, 0.510 mmol) previously dissolved in anhydrous pyridine (8.2 ml) at 60 °C under an inert atmosphere. The solution was stirred for 15 min at 60 °C before being cooled to room temperature. The crude mixture was washed with water and extracted three times with CH_2Cl_2. The organic layers were combined, washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by chromatography on silica gel (cyclohexane–ethyl acetate 90 : 10) which gave a pure colorless oil identified as the compound **13** (243 mg, 89% yield).

R_f 0.65 (heptane–ethyl acetate 80 : 20). IR (NaCl): ν_{max}/cm^{-1} 1715, 1725 (C=O). ^1H NMR (100 MHz, $CDCl_3$): δ (ppm) = 0.3–0.6 (m, 12H, 2 Si(CH_2CH_3)$_3$), 0.8–1.2 (m, 18H, 2 Si(CH_2CH_3)$_3$), 1.4–1.7 (m, 1H, H-5b), 2.2–2.7 (m, 4H, H-2, H-3, H-5a, H-7), 3.54 (s, 3H, OCH_3), 3.6–3.9 (m, 1H, H-1), 3.9–4.1 (m, 1H, H-4), 4.2–4.4 (m, 2H, H-6), 7.2–7.6 (m, 3H, Phenyl), 8.4–8.0 (m, 2H, Phenyl). ^{13}C NMR (25 MHz, $CDCl_3$): δ (ppm) = 4.6, 4.7, 5.7, 6.3, 6.4, 6.6 (2 Si(CH_2CH_3)$_3$), 33.7 (C-7), 44.3 (C-3, C-5), 47.1 (C-2), 51.4 (OCH_3), 63.8 (C-6), 72.5 (C-1), 75.2 (C-4), 128.3, 129.4, 129.8, 133.0 (Phenyl), 167.2 (CO_2 benzoyl group), 173.2 (CO_2 methyl ester).

(1*R*,5*S*,6*S*,7*S*)-7-Hydroxy-6-*tert*-butyldiphenylsilyloxymethyl-2-oxabicyclo[3.3.0]octan-3-one 17. R_f 0.60 (cyclohexane–ethyl acetate 50 : 50). ^1H NMR (100 MHz, $CDCl_3$): δ (ppm) = 1.05 (s, 9H, tBu), 1.8–2.3 (m, 3H, H-6, H-8), 2.6 (d, 1H, H-4b, J = 14.6 Hz), 2.65 (d, 1H, H-4a, J = 8.3), 2.9–3.3 (m, 1H, H-5), 3.7 (d, 1H, H-1′b, J = 11.1 Hz), 3.95 (d, 1H, H-1′a, J = 7.7 Hz), 4.3–4.4 (m, 1H, H-7), 5.1 (t, 1H, H-1, J = 6.9 Hz), 7.2–7.4 (m, 3H, Phenyl), 7.5–7.8 (m, 2H, Phenyl). ^{13}C NMR (25 MHz, $CDCl_3$): δ (ppm) = 19.0 (quat. C tBu), 26.6 (CH_3 tBu), 30.5 (C-4), 38.4 (C-5), 42.0 (C-8), 49.4 (C-6), 60.7 (C-1′), 73.0 (C-7), 84.6 (C-1), 127.6, 129.7, 135.3 (Phenyl), 177.5 (CO). Elemental analysis (Found C, 70.13; H, 7.41. Calc. for $C_{24}H_{30}O_4Si$: C, 70.21; H, 7.36%).

(1*R*,5*S*,6*R*,7*S*)-7-Hydroxy-6-*tert*-butyldiphenylsilyloxymethyl-2-oxabicyclo[3.3.0]octan-3-one 18. R_f 0.55 (cyclohexane–ethyl acetate 50 : 50). ^1H NMR (100 MHz, $CDCl_3$): δ (ppm) = 1.05 (s, 9H, tBu), 1.6 (s, 1H, OH), 2.2–2.7 (m, 3H, H-4, H-5), 3.6–3.8 (m, 1H, H-1′), 4.15 (q, 1H, H-7, J = 6.2 Hz), 4.8–4.9 (m, 1H, H-1), 7.2–7.4 (m, 3H, Phenyl), 7.6–7.7 (m, 2H, Phenyl). ^{13}C NMR (25 MHz, $CDCl_3$): δ (ppm) = 19.0 (quat. C tBu), 26.7 (CH_3 tBu), 35.0 (C-4), 39.2 (C-5), 40.5 (C-8), 55.0 (C-6), 64.1 (C-1′), 75.0 (C-7), 83.2 (C-1), 127.7, 129.8, 135.3 (Phenyl), 177.3 (CO). Elemental analysis (Found C, 70.11; H, 7.29. Calc. for $C_{24}H_{30}O_4Si$: C, 70.21; H, 7.36%).

(1*S*,2*S*,3*R*,4*R*)-3-(Methoxycarbonylmethyl)-2-*tert*-butyldiphenylsilyloxymethylcyclopentane-1,4-diol 19. R_f 0.35 (cyclohexane–ethyl acetate 50 : 50). ^1H NMR (100 MHz, $CDCl_3$): δ (ppm) = 1.03 (s, 9H, tBu), 1.8–2.2 (m, 4H, H-3, H-3, H-5), 2.4–2.6 (m, 2H, H-7), 3.63 (s, 3H, OCH_3), 3.5–3.8 (m, 2H, H-6), 4.0–4.3 (m, 2H, H-1, H-4), 7.2–7.4 (m, 3H, Phenyl), 7.6–7.7 (m, 2H, Phenyl). ^{13}C NMR (25 MHz, $CDCl_3$): δ (ppm) = 19.2 (quat. C tBu), 26.7 (CH_3 tBu), 33.6 (C-7), 42.2, 42.9 (C-3, C-5), 51.5 (OCH_3), 54.5 (C-2), 64.5 (C-6), 74.1 (C-1), 76.0 (C-4), 127.6, 129.6, 135.4 (Phenyl), 174.4 (CO). Elemental analysis (Found C, 67.72; H, 8.11. Calc. for $C_{25}H_{34}O_5Si$: C, 67.84; H, 8.04%).

(1*S*,2*R*,3*R*,4*R*)-3-(Methoxycarbonylmethyl)-2-*tert*-butyldiphenylsilyloxymethylcyclopentane-1,4-diol 20. R_f 0.2 (cyclohexane–ethyl acetate 50 : 50). ^1H NMR (100 MHz, $CDCl_3$): δ (ppm) = 1.03 (s, 9H, tBu), 1.5–1.8 (m, 1H, H-5a), 1.81 (s, 1H, OH), 2.2–2.6 (m, 5H, H-2, H-3, H-5a, H-7), 3.1 (d, 1H, OH, J = 3.5 Hz), 3.63 (s, 3H, OCH_3), 3.4–3.7 (m, 2H, H-6), 3.8–4.2 (m, 2H, H-1, H-4), 7.3–7.5 (m, 3H, Phenyl), 7.5–7.7 (m, 2H, Phenyl). ^{13}C NMR (25 MHz, $CDCl_3$): δ (ppm) = 18.9 (quat. C tBu), 26.7 (CH_3 tBu), 33.4 (C-7), 42.3 (C-3), 44.2 (C-5), 50.9 (C-2), 51.7 (OCH_3), 62.8 (C-6), 74.3 (C-1), 76.8 (C-4), 127.6, 129.7, 132.7, 135.4 (Phenyl), 174.5 (CO). Elemental analysis (Found C, 67.72; H, 7.94. Calc. for $C_{25}H_{34}O_5Si$: C, 67.84; H, 8.04%).

(1*S*,2*R*,3*S*,4*R*)-1,4-Bis(triethylsilyloxy)-3-(methoxycarbonylmethyl)-2-*tert*-butyldiphenylsilyloxymethylcyclopentane 21. R_f 0.5 (cyclohexane–CH_2Cl_2 50 : 50). COSY homonuclear ^1H–^1H ($CDCl_3$): (H-4–H-3), (H-4–H-5a), (H-4–H-5b), (H-1–H-5a), (H-1–H-5b), (H-1–H-2), (H-1–H-5a), (H-1–H-5b), (H-6–H-2), (H-7a–H-7b), (H-7a–H-3), (H-7b–H-3), (H-5a–H-5b). COSY heteronuclear ^1H–^{13}C ($CDCl_3$): HMQC: (H-1–C-1), (H-4–C-4), (H-6–C-6), (H-3–C-3), (H-2–C-2), (H-5a–C-5), (H-5b–C-5), (H-7a–C-7), (H-7b–C-7). HMBC: (OCH_3–C=O), (H-7a–C=O), (H-7b–C=O), (H-1–C-4), (H-7a–C-4), (H-7b–C-4), (H-2–C-4), (H-5b–C-4), (H-6–C-1), (H-5b–C-1), (H-2–C-6), (H-4–C-3), (H-1–C-3), (H-6–C-3), (H-7a–C-3), (H-7b–C-3), (H-5a–C-3), (H-3–C-7), (H-2–C-7). Elemental analysis (Found C, 66.25; H, 9.39; O, 11.91. Calc. for $C_{25}H_{34}O_5Si$: C, 66.21; H, 9.31; O, 11.91%).

(1*S*,2*S*,3*S*,4*R*)-1,4-Bis(triethylsilyloxy)-3-(methoxycarbonylmethyl)-2-*tert*-butyldiphenylsilyloxymethylcyclopentane 22. R_f 0.4 (cyclohexane–CH_2Cl_2 50 : 50). COSY homonuclear ^1H–^1H ($CDCl_3$): (H-4–H-3), (H-4–H-5a), (H-4–H-5b), (H-1–H-5a), (H-1–H-5b), (H-1–H-2), (H-6a–H-6b), (H-6a–H-2), (H-6b–H-2), (H-7a–H-3), (H-7a–H-7b), (H-3–H-7b), (H-5a–H-5b). COSY heteronuclear ^1H–^{13}C ($CDCl_3$): HMQC: (H-1–C-1), (H-4–C-4), (H-6a–C-6), (H-6b–C-6), (H-3–C-3), (H-2–C-2), (H-5a–C-5), (H-5b–C-5), (H-7a–C-7), (H-7b–C-7), (OCH_3–OCH_3). HMBC: (OCH_3–C=O), (H-7a–C=O), (H-7b–C=O), (H-1–C-6), (H-4–C-2), (H-5–C-2), (H-7a–C-3), (H-7b–C-3), (H-5a–C-3), (H-5b–C-3). Elemental analysis (Found C, 66.24; H, 9.24; O, 11.91. Calc. for $C_{25}H_{34}O_5Si$: C, 66.21; H, 9.31; O, 11.91%).

(1*S*,2*R*,3*R*,4*R*)-1,4-Bis(triethylsilyloxy)-3-(methoxycarbonylmethyl)-2-*tert*-butyldiphenylsilyloxymethylcyclopentane 23. R_f 0.35 (cyclohexane–CH_2Cl_2 50 : 50). COSY homonuclear ^1H–^1H ($CDCl_3$): (H-1–H-8), (H-1–H-5a), (H-1–H-5b), (H-4–H-5a), (H-4–H-5b), (H-4–H-3), (H-6a–H-2), (H-6b–H-2), (OCH_3–H-7), (H-7–H-3), (H-5a–H5b). COSY heteronuclear ^1H–^{13}C ($CDCl_3$): HMQC: (H-4–C-4), (H-2–C-2), (H-6a–C-6), (H-3–C-3), (H-2–C-2), (H-5a–C-5), (H-5b–C-5), (H-7–C-7), (OCH_3–OCH_3). HMBC: (H-1–C-4), (H-7–C-4), (H-3–C-4), (H-5a–C-4), (H-5b–C-4), (H-4–C-1), (H-6–C-1), (H-7–C-1), (H-5a–C-1), (H-5b–C-1), (H-2–C-6), (H-5a–C-2), (H-7–C-2), (H-6a–C-2), (H-6b–C-2), (H-5a–C-3), (H-7–C-3), (H-6–C-3), (H-1–C-3), (H-4–C-5), (H-7–C-5), (H-4–C-7). Elemental analysis (Found C, 66.24; H, 9.24; O, 12.01. Calc. for $C_{25}H_{34}O_5Si$: C, 66.21; H, 9.31; O, 11.91%).

(1*S*,2*S*,3*R*,4*R*)-1,4-Bis(triethylsilyloxy)-3-(methoxycarbonylmethyl)-2-*tert*-butyldiphenylsilyloxymethylcyclopentane 24. R_f 0.25 (cyclohexane–CH_2Cl_2 50 : 50). COSY homonuclear ^1H–^1H ($CDCl_3$): (H-1–H-2), (H-1–H-5a), (H-1–H-5b), (H-4–H-3), (H-4–H-5a), (H-4–H-5b), (H-6–H-2), (H-7–H-3), (H-3–H-2), (H-5a–H5b). COSY heteronuclear ^1H–^{13}C ($CDCl_3$): HMQC: (H-4–C-4), (H-1–C-1), (H-6–C-6), (H-2–C-2), (OCH_3–OCH_3), (H-5a–C-5), (H-5b–C-5), (H-3–C-3), (H-2–C-2), (H-7–C-7). Elemental analysis (Found C, 66.31; H, 9.39; O, 11.85. Calc. for $C_{25}H_{34}O_5Si$: C, 66.21; H, 9.31; O, 11.91%).

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