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Secondary Compounds in the Catalytic Hydrogenation of Enone and Allylic Alcohol Prostaglandin Intermediates: Isolation, Characterization, X-Ray Crystallography.

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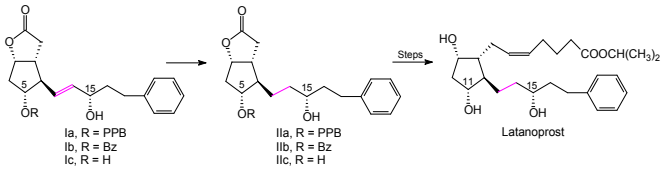
The discovery of the intraocular pressure reduction of 13,14-hydrogenated prostaglandins, from which Latanoprost is the most used drug in the glaucoma treatment, stimulated the researchers to improve its synthesis and that of structural analogues. We studied the hydrogenation of the 13,14-double bond of unsaturated allylic and ketone γ-lactone prostaglandin intermediates with a 17-phenyl or 16-(3-chloro- or 3-trifluoromethyl)phenoxy radical in ω-side chain); these intermediates, without α-side chain, are the last in the Corey prostaglandin sequence that could be chemo-selectively hydrogenated. The influence of the protection of the hydroxyl(s) on the yield and the formation of the secondary compounds in the hydrogenation was also studied. 33 Hydrogenation reactions were made. 13 Secondary compounds were also isolated and fully characterized, including by X-ray crystallography for two compounds, to understand the hydrogenation reactions. The reduction by a factor of ten of quantity of the noble palladium catalyst needed has been also obtained. The amount of catalyst, solvent, reaction time in hydrogenations were also described. The data for such compounds were not found in the literature and our results could be useful not only for researchers in the field, but also for organic chemists who encounter secondary products in this type of hydrogenations.

1. Introduction

Hydrogenation of a double bond has been known for a long time as a method in organic chemistry for building an aliphatic C (sp^3)-C(sp^3) single bond. The hydrogenation of the double bond of an allylic alcohol is usually accompanied by secondary reactions, like des-oxygenation of the hydroxyl. In the synthesis of prostaglandin analogues, this reaction was extensively used after the discovery of the intraocular pressure reduction effect of Latanoprost [1], a 17-phenyl-13,14 dihydro trinor $PGF_{2\alpha}$ isopropyl ester, and its large applications in the treatment of glaucoma. In the synthesis of Latanoprost, the hydrogenation of the double bond was realized on the key intermediate **Ia**, with the ω-side chain built (Scheme 1), protected as *p*-phenylbenzoate (PPB) at the 5-secondary alcohol. The hydrogenation was realized at atmospheric pressure of H_2 on 10% Pd/C (*catalyst*†) as catalyst (25% / substrate), in ethanol (in the presence of 1M NaOH, 100 % [2]) giving the 13,14-dihydro-intermediate **IIa**. Latanoprost was then obtained by the deprotection of the ester group, followed by the next steps for building the α-side chain of the $PGF_{2\alpha}$ analogue, and the final isopropyl esterification. The benzoate intermediate **Ib** was also hydrogenated in the presence of 1M NaOH, but at 4-5 atm of H_2 (5-8 h, 96%) [3], with Et_3N as base, in THF as solvent (2h, 100% on crude product (CP)) [4] or without base (methanol, 1.5 h, 85%) [5]. 5% Pt/C was also used as catalyst (THF as solvent, Et_3N as base, 0.34 atm H_2) [6] (Scheme 1):



Scheme 1. Hydrogenation of the key intermediate **I** to **II** as a step for synthesis of Latanoprost

The unprotected intermediate **Ic** was also hydrogenated as follows: at atm pressure H_2 (Pd/C in MeOH, 83%) [7], with NaOH as base on 5-10% Pd/C catalyst (10% based on substrate, AcOEt or EtOH, 72-78%) [3,8], or Raney Ni catalyst (EtOH, 68%) [8], in the presence of sodium nitrite (in EtOH-water, 33:1, (5% *catalyst*† / substrate), 1.5 atm H_2 for 5h, 94.8-98.4% yield given on CP) (Scheme 1) [9,10]. A hydrogenation **Ic** was also realized with potassium formate and 20% Pd/C as catalyst in ethanol-water (1 h), with a combined yield with the next DIBAL reduction of the γ-lactone to γ-lactol of 79.2-89.9 % [11]. Some patents mentioned that during the hydrogenation of **Ic**,

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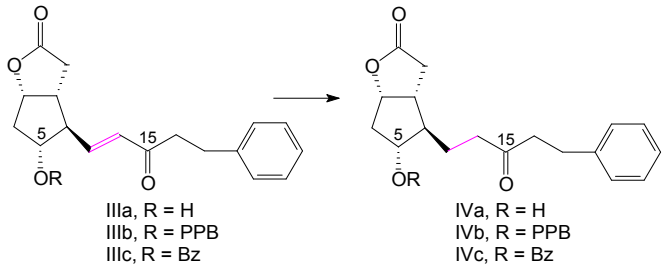
Electronic Supplementary Information (ESI) available: [^{1}H-NMR and ^{13}C-NMR copy spectra for compounds: **IIc** to **IIh**, **2a-2c**, **3a-3c**, **1b-1**, **2a-1**, **2b-1**, **5-7**, **9a- 9d**, **12a**, **12b**, **13a**, **15**, **15+16**, **11b-1**, **11a-1**, **10a-2**, **11a-2**, crystallography data in Table 1S for compounds **9** and **(-)-3c**. See DOI: 10.1039/x0xx00000x

secondary products were obtained in more than 30% yield, mainly 15 desoxy compound, without giving their full characterizations [12].

For diminish the secondary reactions in the hydrogenation of **Ia**-**Ic**, some patents used both hydroxyl groups protected, like 5-PPB-15-TBDMS [TBDMS = tertbutyldimethylsilyl] (5 % (w/w) *catalyst*[†] / substrate, toluene, 5.8 atm H_2, overnight, 87.4% on the 98.2% purity of the hydrogenated product) [13a], 5-PPB-15-THP in AcOEt (10.2 atm H_2, 3h, with 20 % (w/w) *catalyst*[†] / substrate), 89%) (15-*epi* isomer was also hydrogenated with 40 % (w/w) *catalyst*[†] / substrate)) [13b] or 5,15-bis-THP (38% *catalyst*[†] / substrate, THF, atm pressure, 4 h, 97%) [12].

A second strategy was to first hydrogenate the double bond of enones **III** to the keto derivative **IV** (Scheme 2), followed by the selective reduction of the ketone to 15α-OH intermediate at the next step, though this last reaction was generally less selective; for example, **IIIb** was hydrogenated at atm pressure H_2 (40.6 % *catalyst*[†] / **IIIb**) in THF (86% on CP) [14]. No data are presented in the literature for other compounds of type **III**, with R = H, Bz, THP, TBDMS, etc.



Scheme 2. Hydrogenation of enones **III** to ketones **IV**.

Other modified enones were also hydrogenated, as follows: 5-PPB enones with natural **IIIe** or 16-F substituted ω-side chain **IIIf** (Fig.1) [16], compound **Id** (a 16-cyclohexyl derivative of **Ic,** see Figure 1) with a catalytic amount of 5%Pd/C (0.77% / substrate, AcOEt, 2-2.7 atm H_2, 3h, 100%) [17], or even a more complex enone like 15-keto-16-difluoro $PGF_{2\alpha}$ benzyl ester used in the final stage of the synthesis of Lubiprostone (0.77% 5%Pd/C / substrate, AcOEt, 2-2.7 atm H_2, 3h, 100%) [17,18]. A promising enzymatic reduction of enone **IIIc** was also realized in a one-pot three reactions to **IIc** (82% yield) with *P. anomala* yeast, which acted as esterase, enoate-reductase and keto-reductase [19].

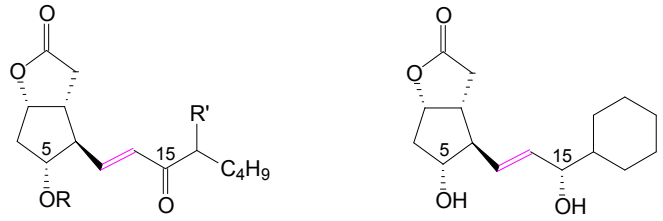
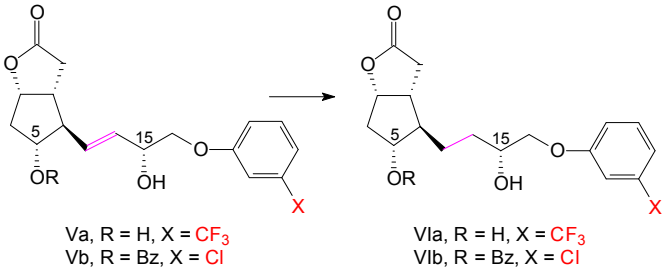


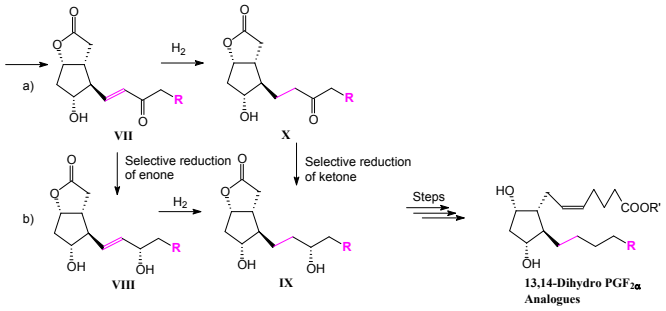
Figure 1. Other enone and allylic prostaglandin intermediates hydrogenated at the 13,14-double bond.

In the series of the corresponding 16-phenoxy (un)substituted intermediates, only a few hydrogenations were done in the search to achieve similar intraocular pressure reduction effect in the corresponding prostaglandin analogues as that of Latanoprost. For example, **Va** was reduced in methanol (2 atm H_2, 1.5 h, 100 %) with *catalyst*[†] (4.2% *catalyst*[†] / substrate) [15], and **Vb** was reduced in AcOEt ((10% *catalyst*[†] / substrate, 2.7 atm H_2, 1 h, 100 %) (Scheme 3) (See ref. [15], and also enzyme reduction, [19]).



Scheme 3. Hydrogenation of 3-trifluoromethylphenoxy or 3-chlorophenoxy allylic alcohols prostaglandin intermediates

From the data presented above, there are two steps in the sequences of prostaglandin synthesis at which hydrogenation can be selectively done and both ways were used to obtain diol **IX** from enone **VII** (see Scheme 4): *a)* at the key enone intermediate **VII** (hydrogenation to the ketone **X**, followed by the stereoselective reduction of the ketone to diol **IX**) or *b)* at the key allylic alcohol intermediate **VIII** (previously obtained from enone **VII** by stereoselective reduction) to obtain diol **IX**. As an observation, the stereoselective reduction of enone **VII** to the allylic alcohol **VIII** is easier than the similar reduction of the ketone **X** to the diol **IX**. The hydrogenation is introduced as a supplementary step in the usual sequence for synthesis of prostaglandins:



Scheme 4. The hydrogenation sequences to obtain the key allylic alcohol intermediate **IX** from enone **VII**.

The hydrogenations of prostaglandin enones with catalysts supported on different mesoporous supports [20] were studied mainly for the selective reduction of the ketone group to the allylic alcohol. None were applied to production level and are not discussed in the paper.

In the hydrogenations described above:

1) the yields are high and in those reactions with smaller yields there is no identification of the potential secondary compounds. Resul B. et al. mentioned in some patents [12] that the unprotected compound **Ic** gave nearly 30% deoxygenation of the 15-hydroxyl

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group, concomitant with the hydrogenation of the 13,14-double bond; the author mentioned that this secondary reaction was suppressed by the protection of both hydroxyl groups as THP and subsequent hydrogenation (97% yield on crude product) [12].

2) the hydrogenation of unprotected diol **Ic** in the presence of $NaNO_2$ [9.10] improved the yield to 94-98% with no mention of the formation of 15-desoxy secondary compound.

3) generally, the protection of the hydroxyl groups of diols **I** or enones **III** increased the yield, without formation of secondary compounds.

4) the amount of used *catalyst*$^+$ was usually 10% (wt./wt.) based on the substrate. In a lot of other examples, considerably larger amounts of catalyst were used, from 20% [13b]-25% [2] to 38% [12], 40% [13b] and 40.6% [14].

5) the influence of the solvent was not mentioned or clearly explained.

In the present paper, we first studied the hydrogenation of the (un)protected intermediate **Ic**, used in the synthesis of Latanoprost. Then we extended the experiments to *m*-phenoxy-substituted analogues of type **V** or to α,β-unsaturated ketone intermediates of type **III**. In these reactions we wanted to identify the secondary compounds encountered during the hydrogenation of the prostaglandin key intermediates of types **I**, **III** and **V**. The second goal of the paper was to study the hydrogenation of the double bond of the intermediates of types **I**, **III** and **V** with a reduced amount of *catalyst*$^+$ (near 1% / substrate).

2. Results and discussion

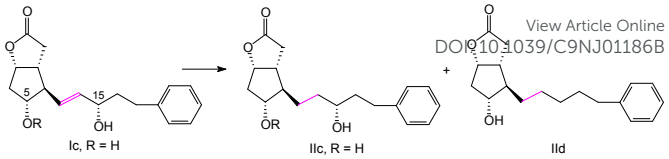
In this paper we tried to find some insight into the problems encountered in the hydrogenation of the prostaglandin intermediates of allylic diol or α,β-unsaturated ketone types. We organized section 2 in the following subsections:

1. *Hydrogenation of allylic alcohol or enone prostaglandin intermediates over catalyst*$^+$ *(in a ratio of 10% or greater / substrate):*
   - 1.1. *Hydrogenation of (un)protected diols used in the synthesis of Latanoprost,*
   - 1.2. *Hydrogenation of 16-(m-substituted)phenoxy intermediates,*
   - 1.3. *Hydrogenation of enone intermediates,*
2. *Hydrogenations with a reduced amount of catalyst*$^+$ *to 1-3% / substrate*
3. *Analysis of the compounds*
   - 3.1. *NMR and IR Spectroscopic analysis*
   - 3.2. *X-Ray crystallography of the secondary compounds* ***9b*** *and (-)-****3c****.*

1. Hydrogenation of allylic alcohol or enone prostaglandin intermediates over 10% Pd/C (in a ratio of 10% or greater / substrate),

1.1. Hydrogenation of (un)protected diols used in the synthesis of Latanoprost

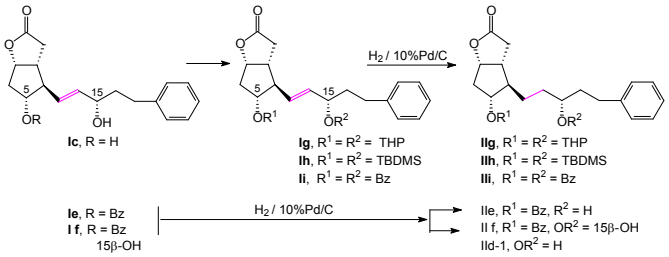
We began with the hydrogenation of the diol intermediate **Ic** used for obtaining Latanoprost. The allylic alcohol **Ic** (1 mmol) was hydrogenated with a 10% quantity of catalyst (30 mg *catalyst*$^+$) based on substrate, in methanol at 20 atm. H_2 for 2 h. The crude product was purified by low pressure chromatography (LPC) and we obtained the 13,14-hydrogenated compound **IIc** in 88.0% yield (Scheme 5), in a greater yield then the 70% mentioned by Resul B. in a different experiment [12], the yield being of course influenced by pressure, solvent used, and reaction time.



Scheme 5. Hydrogenation of compound **Ic** at 20 atm H_2 in methanol on *catalyst*$^+$ for 2h.

However, the 15-desoxy-13,14-hydrogenated by-product **IId** was obtained in a smaller yield of 9.0% then the 30% yield specified in the literature [12] and characterized; a fraction of ~ 3% contained another lower polar secondary compound, but it was not isolated in pure form to be analyzed. It is worth mentioning that the formation of **IId** was observed even in the hydrogenation with only a smaller quantity of 5.3 mg *catalyst*$^+$ (1.75 % / **Ic**) and at 3 atm H_2.

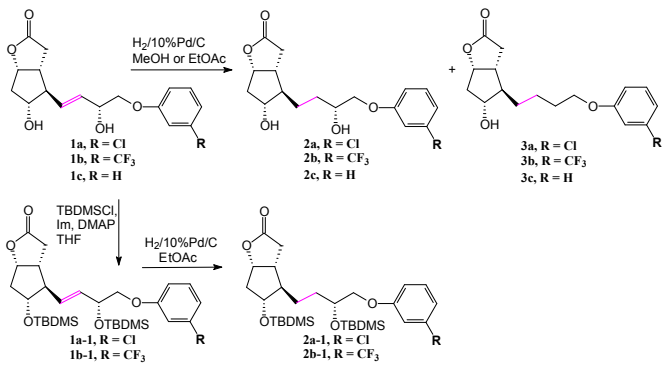
We then found that the 5,15-bis-THP protection of **Ic** prevented the formation of the secondary by-products in hydrogenation and **IIg** was obtained as the only compound (99 % on CP) on a batch of 0.4 mol **Ic** (Scheme 6), as it was mentioned by Resul [12]. We then protected the 5,15-hydroxyl groups of intermediate **Ic** as TBDMS ether and the hydrogenation was performed also in nearly 99 % yield (in ethyl acetate-methanol or toluene-methanol, and $NaHCO_3$ as base to neutralize the HCl present in the catalyst, at 20 atm H_2 for 2h) (Scheme 6). The advantage of this protecting group over THP or other ether groups obtained from ethyl-vinyl ether, *iso*-butyl-vinyl ether, is that the hydrogenated compound **IIg** is easily crystallized (hexane-ethyl acetate, as thin needles, mp 79.7-80.2 ˚C, >83 % crystalized), to obtain the purest compound; at this step, all other protected compounds **II** were obtained as an oil. In the literature, **IIg** was obtained by the hydrogenation of **Ig** (as a mixture with 15-*epi*- isomer) over Pt/C catalyst, and crystallized from methanol-water [21], from the hydrogenated **II** (R^1 = TBDMS, R^2 = H) [22] or from **IIc** [3] by silylation. We got the same results with the 5,15-bis-benzoate intermediate **Ii**, the hydrogenated compound **IIi** being obtained in 98.9% yield as oil. Hydrogenation of mono 5-benzoate protected compound **Ie** with 2 % *catalyst*$^+$ / substrate (MeOH, 3 atm H_2 for 3 h) gave 66.0 % **IIe**, 16.5 % 15-desoxy compound **IId-1** and another (lower polar) secondary compound not isolated in pure form, in a yield close to the one mentioned by Resul. By the hydrogenation in the presence of $NaHCO_3$ to neutralize the acid present in the catalyst and for half time (90 min), the yield of **IIe** increased to 91.5%. In these last conditions, the 15-epimer **IIf** was obtained in 91%. In conclusion, the protection of the 5,15-hydroxyl groups increased the chemo-selectivity of hydrogenation, and as a consequence, the yield of the reaction increased to ~99%; for monobenzoates **Ie** and **If**, the neutralization of the acid present in the catalyst and the reduction of the time for hydrogenation increased the yield to 91%; it is to be mentioned that the hydrogenation was done with ~2% *catalyst*$^+$ / substrate. The 15-desoxy secondary compound **IId-1** was isolated and characterized after hydrolyzation to **IId**.



Scheme 6. Hydrogenation of 5- or 5,15,-OH protected groups of compound **Ic**.

1.2. Hydrogenation of 16-(m-substituted)phenoxy intermediates

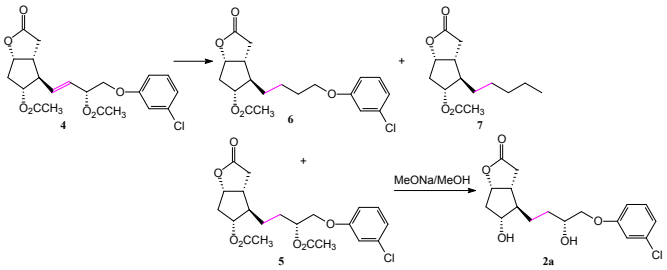
After these findings on 16-phenyl diol intermediates **I**, we studied the hydrogenation of 16-(3-substituted phenoxy) allylic alcohol intermediates **1**, in order to obtain the corresponding 13,14-hydrogenated intermediates **2** (Scheme 7) to be used in the synthesis of 16-aryloxy analogues of Latanoprost (The next steps to the final prostaglandin analogues are well established and we do not describe them here). In the literature, a few patents described the synthesis of 13,14-hydrogenated 3-trifluoromethyl- and 3-chloro-phenoxy analogues of type 2, the hydrogenation being done on the unprotected diol **1b** [15] or on the 5-benzoate protected diol **Vb** (100% yield), (Scheme 3) [15]. We started with the racemic diol **1a** (2 g) which contained also the 15-*epi*-isomer (Scheme 7), and hydrogenated it at 2 atm H_2 for 2h, in methanol (300 mg *catalyst*†, 15%w/w). We discovered two compounds, **2c** and **3c**, both formed by the dehydrohalogenation of the chlorine linked to the phenoxy group, instead of the **2a** desired compound:



Scheme 7. Hydrogenation of the allylic alcohols **1a** and **1b** to the key intermediates **2a**, **2b** and **2c**, or the corresponding TBDMS-protected compounds **1a-1** and **1b-1** to **2a-1** and **2b-1**.

The phenoxy compound **2c** was obtained in 44.3 % yield. From the 15-desoxy-hydrogenated compound **3c**, a pure fraction was isolated in 23.3% yield, as an oil. A better yield (76.6 %) of pure enantiomer (-)-**2c** was obtained with a 4.2 % Pd/C catalyst ((-)-**3c** was also isolated). In this case, both compounds were by-products of the hydrogenation reaction and their structure was easily proved in ^{1}H- and ^{13}C-NMR by the appearance of the five protons and four carbon types characteristic for the phenoxy group, instead of the signals for 3-chloro-phenoxy fragment; (-)-**3c** was also characterized by X-ray crystallography (See 3.2). It is worth mentioning that the phenoxy analogue **2c** could be obtained in this way in moderate yield from **1a**, especially in small quantities, an important aspect for its use in obtaining the corresponding 13,14-dihydro-phenoxy-prostaglandin analogues for their preliminary screening. Using a smaller quantity of catalyst, compounds **2a** and **3a** were obtained in 75.5% yield, respectively 16.9% yield. For **2a,** this was close to the reported 70% yield for the phenyl analogue **IIc** [15]. In the hydrogenation of **1b** with 3-(trifluoromethyl) phenoxy, **2b** was obtained in 78% yield together with only 9.5% **3b**. 15-Desoxy by-products **3a**, **3b** and **3c** were obtained pure, as an oil ((-)-**3c** also as white crystals), by low pressure chromatography (LPC) purification of the crude hydrogenation mixture of compounds **2** and **3**, and characterized, no physico-chemical data having been presented in the literature. From these experiments it resulted that in all cases, the 15-desoxy by-products **3a**, **3b** and **3c** were formed in the hydrogenations and the yields of the 13,14-hydrogenated compounds **2a**, **2b** and **2c** were high, but a little smaller than those mentioned in the literature (100% in refs [15]).

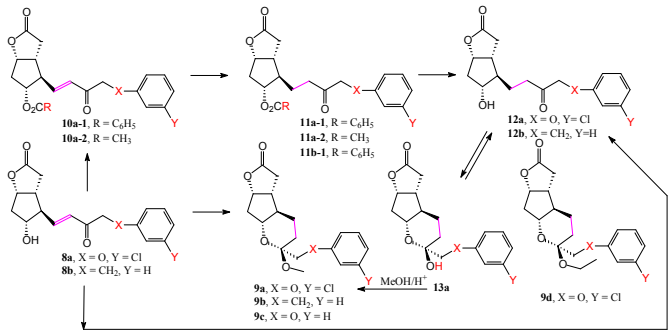
We then used the 5,15-bis acetate compound **4**, considering that this protected compound could give only the hydrogenated product **5** (Scheme 8). Its hydrogenation (3.38 g, 8 mmol) with 300 mg *catalyst*† (in 150 mL ethyl acetate at 3 atm H_2 for 1.5 h) did not finish (but in TLC only one hydrogenated compound was observed) and the compound remained in the autoclave overnight, without stirring. We changed the idea to obtain only one compound, **5**. Therefore, a supplementary quantity of *catalyst*† (120 mg) was added and the mixture was stirred for 2h at 3 atm H_2. We wanted to see to what extent the secondary byproducts were formed in the hydrogenation, and then to isolate and characterize them; in the literature, there is little or no data about these secondary compounds and their characterization. Indeed, the TLC showed the formation of two other secondary compounds, besides the major compound **5.** The crude product was purified by LPC; the major product and the two secondary compounds were obtained pure and their structure was established by ^{1}H-, ^{13}C- and 2D NMR spectroscopy. The major more polar 13,14-hydrogenated product **5** was isolated in 73.0% yield; the smaller polar compound, isolated in 15.7 % yield, was the 13,14-hydrogenated-15-desoxy compound **6**; the one with the smallest polarity was compound **7**, isolated in 11.4% yield, and formed by breaking the link between the aliphatic part of the side chain and the oxygen of the *m*-chloro-phenoxy group (Scheme 8). It is very interesting that the aromatic chlorine atoms of compounds **5** and **6** were not dehydrohalogenated, as it could be seen in the NMR by the presence of the four protons and 6 different carbon atoms of the aromatic fragment. By transesterification (MeONa/MeOH), the bis-acetate compound gave the hydrogenated diol **2a**, in 94.1% yield, with the same characteristics as those of the compound obtained by the hydrogenation of the allylic alcohol intermediate **1**.



Scheme 8. Hydrogenation of 5,15-bis-acetate protected diol compound **4**.

1.3. Hydrogenation of enone intermediates

The hydrogenation of the enone type intermediates was also studied. The hydrogenation of enone **8a** in the same conditions [16.7 % *catalyst*$^{+}$/ **8a**, methanol, 3 atm H_2 for 1.5 h] as for **1a** to **2c + 3c**, gave the intramolecular six-atom cyclized ketal compound **9c**, formed by the chemo-selective hydrogenation of the double bond, followed by the also chemo-selective reaction of the ketone with the 11-hydroxyl and methanol, catalyzed by the trace HCl present in the *catalyst*$^{+}$ (Scheme 9); in the reaction, the chlorine atom was also dehydrohalogenated as previously described. A similar cyclized compound **9a** is presented in the literature as obtainable by the treatment of **12** (X = O, Y = Cl) with methanol in the presence of H_2SO_4 as acid catalyst [23]. Compound **12** is postulated to be in equilibrium with the hydroxyl-ketal **13a**, which is shifted toward the methoxy-ketal **9a** by acid catalysis with methanol.

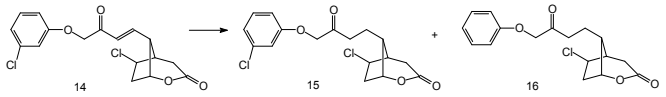


Scheme 9. Catalytic hydrogenation of the prostaglandin enone intermediates **8** and **9**.

With a reduced quantity of *catalyst*$^{+}$ (3.3% / **8a**) and reduced hydrogenation time to 15 min, **9a** was the only compound formed in the reaction, in 94.4% yield, with similar characteristics as presented in refs [23]. By changing the solvent, ethanol instead of methanol, the corresponding ethoxy-ketal **9d** was obtained in 90.4% yield. In the case of **8b**, with a benzyl fragment instead of the previous *m*-chlorophenoxy fragment, the same type of intramolecular ketal compound **9b** was obtained after 25 min, in 92.6% yield. All compounds **8** were chemo-selectively hydrogenated to the double bond, followed by an also chemo-selective reaction of the ketone with the secondary 5- hydroxyl and the solvent (MeOH or EtOH) with closing a six-atom alkoxy-ketal; **9a**-**9d** were obtained in yields greater than 90%, which is very interesting, since they are all byproducts instead of the awaited **12a**-**12b** hydrogenated compounds. Their structure was established by NMR and confirmed by X-ray crystallography for compound **9b** (see X-ray crystallography).

By changing the solvent from a primary alcohol (like methanol or ethanol) to a secondary alcohol, like *iso*-propanol, **12a** was obtained as the only compound from **8a**, the internal cyclization of ketone to the corresponding *iso*-propoxy-ketal being sterically hindered. In a non-alcohol solvent like ethyl acetate, **12a** and **12b** were also obtained in high yield (~94 %) as singular compounds from **8a** and respectively from **8b**. It is evidenced that for enones **8,** the solvent influenced the course of the hydrogenations towards either the internal ketals **9** or the ketone compounds **12**. It is to be mentioned that the crude compound **12a** was partially cyclized to **13a** in time at rt, and isolated in 16.2% after LPC purification. This is easy to put in evidence in ^{1}H-NMR and ^{13}C-NMR by the disappearance of the signals for ketone **12a** (OH, δ 3.38, C_{15}, δ 205.46 ppm) and the appearance of the signals for semiketal **13a** (OH, δ 6.00, δ C_{15}, 96.1 ppm). The pure (-)-**12a** was stable in the freezer (-15 °C) for over one month.

The hydrogenation of δ-lactone-enone intermediate **14** in the usual conditions (9.6% *catalyst*$^{+}$ / **14**, $NaHCO_3$, 3 atm H_2, 45 min), gave **15** as the only product observed in TLC (isolated pure in 88.1% yield) (Scheme 10). With an increased quantity of catalyst (13.3% / **14**, $NaHCO_3$, atm pressure of H_2, 4 h) an unseparable mixture of **15** and **16** was obtained in a ratio of 60: 40, as estimated by NMR, in a combined 78% yield. An increased quantity of catalyst favored the dehydrochlorination, and as a consequence, a decrease in the chemo-selectivity like in the similar previous examples.



Scheme 10. Hydrogenation of δ-lactone-enone intermediate **14**.

Hydrogenation of the 5-protected enones **10a-1**, **10b-1** and **10a-2** with a reduced quantity of *catalyst*$^{+}$ / substrate (1.13% **10a-1**, 2.5% **10b-1**, 5% and 1% **10a-2**) gave compounds **11** straightforward, in yields greater than 90% (Scheme 9) (>88% **11a-1**, quant% **11b-1**, 97.7 % and 94.7% **11a-2**) with the predicted chemo-selectivity.

Hence, the hydrogenation of enones **8** in methanol and ethanol lead to the crystallized alkoxy-ketals **9** in high yields, in isopropanol or in a non-alcoholic solvent like ethyl acetate to the awaited compounds **12** (the same is for enone **14**), and of 5-hydroxy protected enones **10** to the compounds **11**, all cases with remarkable chemo-selectivity. The hydrogenation of α,β-unsaturated ketones proceeded faster than that of the diol type intermediates. With an increased quantity of *catalyst*$^{+}$ (~16%) and reaction time, a dehydrochlorination of the *m*-substituted chlorine was also observed.

In the hydrogenation conditions of the diol and α,β-ketone prostaglandin intermediates, a great number of secondary compounds were obtained and each by-product was isolated and fully characterized, including by X-ray crystallography for two of them. The data for such compounds were not found in the literature and our results could be useful for researchers in the prostaglandin field and more generally for organic chemistry, where secondary compounds could result in the hydrogenation of allylic alcohols or enones.

The formation of the secondary compounds should be taken as a challenge, not as a tragedy. They must be isolated and characterized, the mechanism by which they appeared must be understood, and then the reaction conditions must be optimized in order to minimize or to prevent their formation.

2. *Hydrogenations of diol and enone-intermediates with a reduced amount of 10% Pd/C catalyst (1-3 % based on the substrate), in an environmentally friendly manner.*

The hydrogenations of the diol or enone type prostaglandin intermediates are usually performed with a *catalyst*$^{+}$ / substrate ratio of 10% or greater which was observed to be associated (among other things) with the formation of secondary compounds, and so with a decrease in the selectivity of the reaction. Only in a few patents a reduced amount of *catalyst*$^{+}$ was used [17,18].

We observed in our preliminary experiments that the amount of *catalyst*$^{+}$ / substrate could be reduced to nearly 1-2% and the

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hydrogenation of the compounds **Ie** and **If**, presented above, was realized with ~2% *catalyst*† /substrate in near 91% yield (Table 1, entries 11-12). Then we extended the hydrogenation with a reduced amount of catalyst to all types of diol and enone intermediates used above; the results are presented in Table 1:
One can observe from Table 1 that the yields of the hydrogenated prostaglandin intermediates, diols and enones, with a reduced amount of *catalyst*† were very close to those obtained with a 10% (w/w) *catalyst*† / substrate ratio (entries 1-6). Enones **10b-1**, **10a-1**, **10a-2** and **14** were also hydrogenated in high yields (entries 7-10) with a reduced amount of *catalyst*†.

Table 1. Hydrogenation of diol and enone prostaglandin intermediates with a reduced amount of *catalyst*†

Starting compd / *exp. no*	Substrate (g or mg)	Substrate mmol	*catalyst*† amount (mg)	*catalyst*†/ substrate ratio	Solvent (mL)	H_2 (atm)	Time h or min	Product	Conditions[1] with >10% *catalyst*†
1a ***3.1***	4.5 g	13.28	70	1.56 %	EtOAc (150)	3	45 min	**2a**, 3.58 g (79.2 %)	Press.atm. 75.5% **2a**, 16.9% **3a**
Ic ***3.2***	302 mg	1	5.3	1.75 %	MeOH (50)	3	2 h	**IIc**, 267 mg (88.5 %)	20 atm, 2 h 88.0% **IIc**, 9% **IId**
8a ***3.3***	2 g	5.94	20	1 %	EtOAc (150)	3	60 min	**12a**, 1.88 g, 93.5 %	3 atm[2], 50 min 94.8% (-)-**12a**
8a ***3.4***	2 g	5.94	40	2 %	*i*-PrOH (150)	3	75 min[4]	**12a**, 1.86 g, 92.4 %	3 atm, 20 min 94.5 % (±)-**12a**
8a ***3.5***	4 g	11.88	40	1 %	MeOH (150)	3	50 min	**9a**, 4.18 g, 95.5 %	3 atm, 15 min 94.4%
8b ***3.6***	1.6 g	6	40	2.2 %	*i*-PrOH (150)	3	75 min[4]	**12b**, 1.69 g (93.2 %)	3 atm[3], 50 min 94.8% **12b**
10b-1 ***3.7***	10 g	24.7	250	2.5 %	THF (150)	6	TLC monitoring	**(-)-10b-2**, quant.	-
10a-1 ***3.8***	1.33 g	3	15	1.13 %	EtOAc (150)	3	135 min	**11a-1**, 1.17g crist (88%)	-
10a-2 ***3.9***	2.59 g	6.8	27	1 %[3]	EtOAc (150)	3	135 min	**11a-2**, 2.53 g (94.7%)	3 atm[3], 30 min 97.7% **11a-2**
14 ***3.10***	3 g	8.4	30	1 %	EtOAc (150)	3	50 min	**15**, 2.84 g (94.7 %)	-
Ie ***1.1.5***	0.406	1	8.5	2.1%	MeOH (50)[5]	3	90 min	**IIe**, 372 mg (91.5%)	-
If ***1.1.6***	6.34 g	15.6	150	2.4%	MeOH (150)	3	90 min	**IIf**, 5.77 g (91%)	-

[1]Hydrogenation with 10% *catalyst*†/ substrate, where no other ratio is specified. [2]Hydrogenation with 5.3% *catalyst*†/ substrate; [3]Hydrogenation with 5% *catalyst*†/ substrate, [4]Not optimized; < 20% enone remains after 40 min reaction, [5]with 100 mg $NaHCO_3$ for **Ie** and 200 mg $NaHCO_3$ for **If**. In all cases, the NMR analysis of the crude product established the end of hydrogenation.

We observed a slight increase of the yield of **2a** (from 75.5% to 79.2%) in the case of diol **1a,** and a decrease in the quantity of the 15-desoxy byproduct **IId** (from 9% to 4.4%) in the case of diol **Ic**.
Generally, a little longer hydrogenation time is necessary to finish the reaction, but this is not a problem. These findings show that the reduction of the amount of *catalyst*[†] comes with beneficial effects, besides the reduction of the price of the noble catalyst used. The formation of the secondary compounds is suppressed in the case of the protected prostaglandin intermediates in the hydrogenation with a *catalyst*[†] / substrate ratio of 10% (w/w) or greater, but the use of a reduced amount of catalyst is still desirable and possible (see entry 7). In conclusion, the reduction of the amount of *catalyst*[†] could be applied to other allylic or α,β-unsaturated compounds, an aspect interesting for organic chemists, for the economical (aspect) and cleaner hydrogenation (with reduced byproducts).

3. *Analysis of the compounds*

3.1 *NMR and IR Spectroscopic analysis*

In the hydrogenation of all prostaglandin intermediates, the difference between the R_f's of the starting compounds and R_f's of the hydrogenated products in TLC are too small to precisely indicate the end of the reaction. The spots of the starting compounds developed shortly after spraying with 15% H_2SO_4 in methanol and heating at 110˚C, but the spots of the corresponding hydrogenated products (and of the byproducts also) appeared with difficulty after a prolonged time of heating the plate. Under these conditions, the end of the hydrogenation was determined with accuracy by the NMR analysis of the reaction mixture, which confirmed the disappearance of the alkene protons. For pure products, ^{1}H-, ^{13}C- and 2D-NMR analysis are indispensable for determining their correct chemical structure. The same is true for the byproducts resulted in those hydrogenations where they appear. The ^{13}C-NMR spectra of 15-desoxy byproducts show the disappearance of the C_{15}-OH atoms from δ (ppm): 71.25 (**IIc**), 77.53 (**2a**), 69.92 (**2b**), 68.47 (**2c**) and the appearance of the methylene C_{15} carbon atom at δ (ppm): 31.22 (**IId**), 29.06 (in DMSO) (**3a**), 32.83 (**3b**), 29.31 (**3c**). The same is observed in the ^{1}N-NMR spectra, namely the disappearance of H-C_{15}-OH at δ (ppm): 3.61 (**IIc**), 3.99 (**2a**), 4.06-3.96 (**2b**), 3.80-3.68 (**2c**), and appearance of δ (ppm): 1.65-1.57 (**IId**), 1.78-1.60 (**3a**), 1.81 (**3b**), 1.78 ((-)-**3c**), in the field of ppm for the methylene protons linked to C_{15} carbon atoms (See SI 1.2.). The hydrogenation of enones **8a** and **8b** in methanol and ethanol gave byproducts **9a**-**9b**, by a sequence of two chemo-selective reactions: hydrogenation of the double bond followed by acid catalyzed internal closing of a six-atom ring of a ketal structure through addition of the 5-OH and methanol or ethanol to the 15-ketone. The formation of the cyclic ketal is evidenced especially in the ^{13}C-NMR spectra were the signals for the ketone group at δ (ppm): 205.50 (**12a**) or 209.91 (**12b**) disappeared and the new signals appeared at δ (ppm): 99.09 (**9a**), 100.60 (**9b**), 98.88 (**9c**), 99.08 (**9d**) for a ketal C_{15} carbon atom, and of course, the appearance of the carbon for the methoxy or ethoxy group, δ (ppm): 48.15 (**9a**), 47.15 (**9b**), 45.57 (**9c**), 55.86 and 15.41 for ethyl group of **9d** (See SI 1.3.1-1.3.4.). All other signals confirmed the chemical structure of each product and byproduct.
Tetrahydropyranyl (THP) is a good chemically stable protecting group in base conditions, but the interpretation of the ^{1}H-, ^{13}C- and 2D-NMR spectra for the compounds protected in this way becomes very difficult. The THP group has a chiral C_1 atom which makes the protected compound to appear as a mixture of two compounds. For the two protecting groups, as for the chromatographically pure compound **IIg**, there is a mixture of 4 compounds. This is clearly observed in ^{13}C-NMR spectra (See SI 1.1.3.), where four signals appear for a specified carbon atom. This is more evident for the following carbon atoms: C_{3a} (43.02, 42.90, 42.51, 42.43), C_4 (53.32, 53.01, 52.13, 51.69), C_{15} (76.38, 76.33, 76.05, 75.98), for example. In the ^{1}H-NMR spectra of **IIg**, only multiplet signals appear for each proton. We also confirmed the chemical structures of two of the byproducts, **9b** and (-)-**3c**, by X-ray crystallography, in addition to the NMR data.
The IR Spectra in ATR present accurately the vibration bands of the functional groups of each molecule. The vibration band for the lactone group of **2a** appears at 1719 cm^{-1}, probably due to an intramolecular hydrogen bond with 15-OH in the crystal. In $CHCl_3$, the polarity of the solvent does not favour the hydrogen bond and this band moves to 1756 cm^{-1}, a correct value for the lactone group.

3.2 *X-Ray crystallography of the secondary compound 9b and (-)-3c*

According to X-ray crystallography the crystal belongs to a monoclinic system and crystallizes in the $P2_1$ space group, with one molecular species as the crystallographic asymmetrical entity in the unit cell, as shown in Figure 2. The values of the bond lengths and angles are summarized in Table1S.

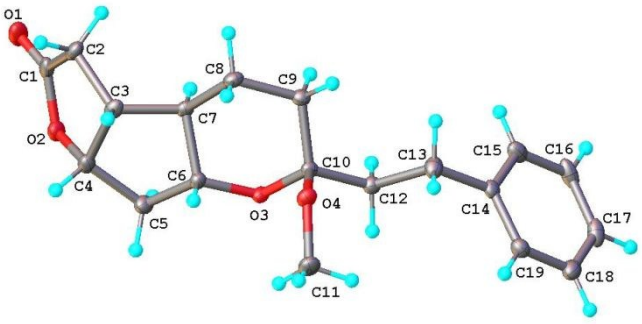

Figure 2. X-ray molecular structure of compound **9b**, with atom labeling and thermal ellipsoids at 50% probability. The angles and torsion angles around the ketal group (deg.): C_7-C_6-O_3 =113.1(2), C_6-O_3-C_{10} = 111.8(2), O_3-C_{10}-O_4 = 110.8(2), C_9-C_{10}-O_4 = 104.4(2), C_9-C_{10}-C_{12} = 113.0(3), O_4-C_{10}-C_{12} = 112.7(2), C_{11}-O_4-C_{10} = 115.9(2); C_{10}-O_3-C_6-C_7 = 59.6(3), C_6-O_3-C_{10}-O_4 =61.9(3), C_6-O_3-C_{10}-C_9 = -54.2(3), C_6-O_3-C_{10}-C_{12} = -176.7(2), C_{11}-O_4-C_{10}-O_3 = 55.2(3), O_3-C_{10}-C_{12}-C_{13} = -175.8(3), C_8-C_9-C_{10}-O_3 = 51.5(4), C_{11}-O_4-C_{10}-C_9 = 175.((2), C_9-C_{10}-C_{12}-C_{13} = 62.5(4), O_4-C_{10}-C_{12}-C_{13} = -55.6(4), C_9-C_{10}-C_{12}-C_{13} = 62.5(4), C_{11}-O_4-C_{10}-C_{12} = -61.1(3)

The neutral molecules in the crystal are associated due to the C-H---π interactions of 2.886 to form supramolecular chains, as shown in Figure 3. The further analysis of the crystal packing indicates the presence of a discrete parallel packed 1D architecture running along the *b*-axis.

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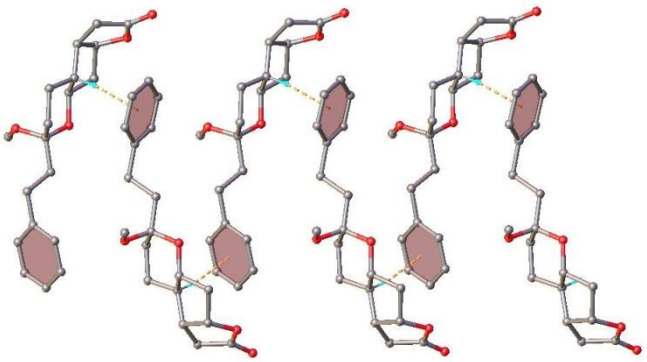

Figure 3. A view of the supramolecular chain in the crystal structure of **9b**.

The result of the X-ray diffraction study for **(-)-3c** is shown in figure 4. The compound crystallizes in the $P2_12_12$ space group of the orthorhombic system without co-crystallized solvent molecules. The values of the bond lengths and angles are summarized in Table1S. The crystal packing essentially results from the parallel packing of the supramolecular chains (Figure 5) formed by the hydrogen bonding between adjacent molecules where the hydroxyl group acts as donor while the oxygen atom of the heterocycle as acceptor of proton.

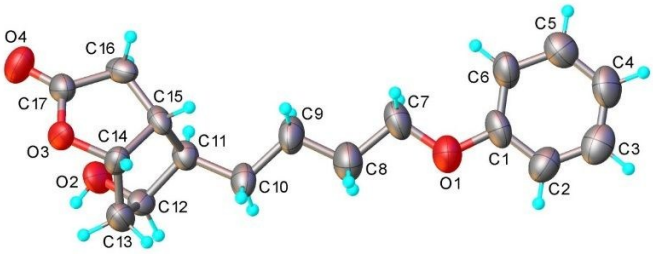

Figure 4. X-ray molecular structure of compound **(-)-3c**, with atom labeling and thermal ellipsoids at 50% probability. Selected bond angles and torsion angles around the cyclopentane fragment (deg.): C10-C11-C15 = 112.9(5), C16-C15-C11 = 115.3(5), C16-C15-C14 = 103.1(4), C13-C14-C15 = 106.7(4), O3-C14-C13 = 110.3(5), O3-C14-C15 = 106.5(4), C14-C13-C12 = 104.7(5), O2-C12-C13 = 112.0(5), C13-C12-C11 = 103.5(5), O2-C12-C11 = 106.2(5); C10-C11-C15-C16 = 148.6(5), C10-C11-C15-C14 = -98.4(5), C13-C14- C15-C11 = 1.5(6), C13-C14- C15-C16 = 122.8(5), O3-C14-C15-C11 = -116.4(5), O3-C14-C15-C16 = 4.9(6), C12-C13-C14-C15 = -24.9(6), C12-C13-C14-O3 = 90.5(5), O2-C12-C13-C14 = -75.1(5), C11-C12-C13-C14 = 38.9(6), C10-C11-C12-C13 = 84.1(6), C10-C11-C12-O2 = -157.8(5).

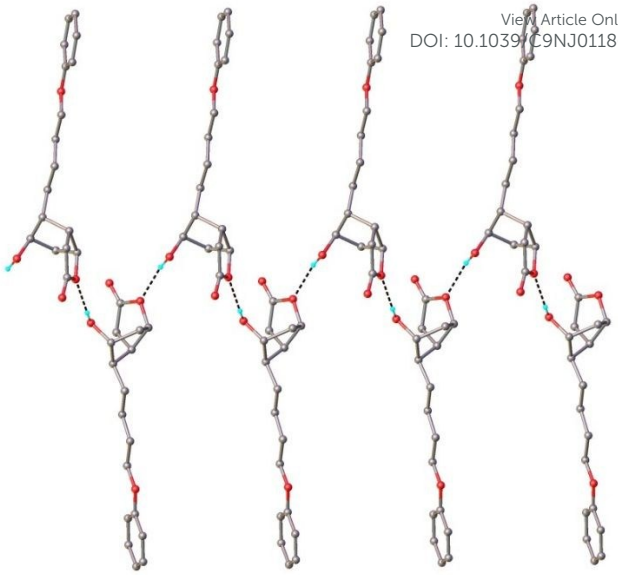

Figure 5. 1D H-bonded supramolecular architecture in the crystal structure of **(-)-3c**. H-bond parameters: O2-H---O3[O2-H 0.82 Å, H---O3 2.072 Å, O2---O3(-0.5 + *x*, 1.5 - *y*, 2 - *z*) 2.863(5) Å, ∠O2HO3 163.0].

4. Experimental

Melting points (uncorrected) were determined in open capillary on an OptiMelt melting point apparatus. The progress of the reaction was monitored by TLC on silica gel 60 or $60F_{254}$ plates (Merck) eluted with the solvent systems: I ethyl acetate-hexane-acetic acid (5:4:0.1), II (benzene-ethyl acetate-methanol-80% formic acid, 20:80:3:2), III (ethyl acetate-hexane-acetic acid, 5:1:0.1), IV (toluene-ethyl acetate, 1:1), V (ethyl acetate-methanol-acetic acid, 90:13:1), VI (benzene-acetone, 1:1), VII (heptane-ethyl acetate). Spots developed in UV, 2,4-dinitrophenylhydrazine reagent or with 15% H_2SO_4 in MeOH (heating at 110˚C, 10 min). IR spectra were recorded on FT-IR-100 Perkin Elmer spectrometer, in solid phase by ATR and frequencies were expressed in cm^{-1}, with the following abbreviations: w = weak, m = medium, s = strong, v = very, br = broad. MS were recorded on a 1200 L/MS/MS triple-quadrupole Varian with ESI interface, fragments, obtained by collision with Ar are given in parenthesis. ^{1}H-NMR and ^{13}C-NMR spectra are recorded on Varian Gemini 300 BB spectrometer (300 MHz for ^{1}H and 75 MHz for ^{13}C), or Bruker Avance III 500 MHz spectrometer (500 MHz for ^{1}H and 125 MHz for ^{13}C), spectrometer chemical shifts are given in ppm relative to TMS as internal standard. Complementary spectra: 2D-NMR and decoupling were done for the correct assignment of NMR signals. The numbering of the atoms in the compounds is presented in Schemes. 10% Pd / C has been bought from Merck, solvents were of pure grade.

X-Ray crystallographic measurements were carried out with an Oxford-Diffraction XCALIBUR E CCD diffractometer equipped with graphite-monochromated Mo-Kα radiation. Single crystals were positioned at 40 mm from the detector and 716 and 194 frames were measured each for 5 and 15 s over 1° scan width for **9b** and **(-)-3c**, respectively. The unit cell determination and data integration were carried out using the CrysAlis package of Oxford Diffraction [24]. The structure was solved by direct methods using Olex2 [25] and refined by full-matrix least-squares on F^2 with SHELXL-97 [26].

Atomic displacements for non-hydrogen atoms were refined using an anisotropic model. All H atoms attached to carbon were introduced in idealized positions (d_{CH} = 0.96 Å) using the riding model with their isotropic displacement parameters fixed at 120% of the riding atom. Hydrogen atoms for OH and NH groups have been placed by Fourier Difference and refined accounting for hydrogen bonds parameters. In the absence of significant anomalous scattering, the absolute configuration of the structure could not be reliably determined. As a result, Friedel pairs were merged and any references to the Flack parameter were removed. The molecular plots were obtained using the Olex2 program. The crystallographic data and refinement details are quoted in Tables 2, while bond lengths are summarised in Tables 1S. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as Supplementary Publication No. CCDC – 1561067 (for **9b**) and -. 1883073 (for (-)-**3c**). Copies of the data can be obtained free of charge from CCDC (12 Union Road, Cambridge CB2 1EZ, UK; Tel.: + 44 1223 336 408; fax: +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk; www:http://ccdc.cam.ac.uk).

Table 2. Crystallographic data, details of data collection and structure refinement parameters.

	9b	**(-)-3c**
Chemical formula	$C_{19}H_{24}O_4$	$C_{17}H_{22}O_4$
M/g mol^{-1}	316.38	290.34
Temp./K	160	293
Crystal system	monoclinic	orthorhombic
Space group	$P2_1$	$P2_12_12$
a/Å	7.4702(4)	7.6481(17)
b/Å	8.3687(4)	30.186(4)
c/Å	13.8595(7)	6.7702(6)
α/°	90	90
β/°	103.173(5)	90
γ/°	90	90
V/Å^3	843.64(7)	1563.0(4)
Z	2	4
D_c/g cm^{-3}	1.245	1.234
μ/mm^{-1}	0.086	0.087
Crystal size/mm^3	0.45 × 0.3 × 0.15	0.2 × 0.15 × 0.05
ϑ_{min}, ϑ_{max}/°	5.6 to 50.05	5.398 to 50.04
Reflections collected	6077	4747
Independent reflections	2976 [R_{int} = 0.0319]	2747 [R_{int} = 0.0348]
Data/restraints/parameters	2976/1/209	2747/0/191
R_1^a [($I > 2\sigma(I)$)]	0.0439	0.0804
wR_2^b (all data)	0.0950	0.1731
GOF^c	1.039	1.102
Largest diff. peak and hole/e·Å^{-3}	0.13/-0.19	0.20/-0.16

^{a} $R_1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$, ^{b} $wR_2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$. ^{c} GOF $= \{\Sigma[w(F_o^2 - F_c^2)^2]/(n-p)\}^{1/2}$, where n is the number of reflections and p is the total number of parameters refined.

1. Hydrogenation of allylic alcohol or enone prostaglandin intermediates over 10% Pd/C catalyst (in ratio equal or greater than 10% w/w based on substrate)

1.1. Hydrogenation of (un)protected diols used in the synthesis of Latanoprost

1.1.1. Hydrogenation of the diol Ic

Ic (1 mmol, 302 mg) with *catalyst*$^+$ (30 mg) in methanol (50 mL) was hydrogenated at 20 atm H_2 for 2 h, monitoring the end of reaction by TLC (I, $R_{f\ IIc}$ = 0.12, $R_{f\ IId}$ = 0.44). The catalyst was filtered, washed with methanol, the solvent distilled under reduced pressure and the crude product was purified by LPC (ethyl acetate-heptane, 1:1), resulting 27 mg (~9%) of secondary compound (3aR,4R,5R,6aS)-5-hydroxy-4-(5-phenylpentyl)hexahydro-2H-cyclopenta[b]furan-2-one, as an oil, **IId**, $[\alpha]_D$ = -19.0 ˚(0.685% in THF), IR: 3440brm, 2927s, 2855m, 1757vs, 1495w, 1453w, 1363w, 1307w, 1176m, 1073m, 1032m, 747m, 699m, IR: 3438brm, 2927s, 2855m, 1453w, 1362w, 1308w, 1175s, 1073m, 1032m, 971w, 747w, 699m, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, J Hz): 7.28 (tl, 2H, H-*m*, 7.9), 7.18 (brt, 1H, H-*p*, 7.9), 7.16 (dl, 2H, H-*o*, 7.9), 4.96 (dd, 1H, H-6a, 1.6, 7.0), 4.01 (dt, 1H, H-5, 4.4, 4.6), 2.80 (dd, 1H, H-3, 11.2, 18.8), 2.60 (t, 2H, H-17, 7.6), 2.54 (m, 1H, H-3a), 2.51 (dd, 1H, H-3, 2.8, 18.8), 2.22 (dt, 1H, H-6, 5.7, 14.9), 2.04 (brd, 1H, H-6, 14.9), 1.83 (m, 1H, H-4), 1.66-1.57 (m, 2H, H-15), 1.40-1.31 (m, 5H, 2H-13, 2H-14,1H-16), 1.14 (m, 1H, H-16), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 177.87 (C-2), 142.50 (C-1Ar), 128.32, 128.21 (4CH, C-*o*, C-*m*), 125.61 (C-*p*), 84.28 (C-6a), 77.56 (C-5), 54.28 (C-4), 42.96 (C-3a), 40.42 (C-6), 36.79 (C-3), 36.22 (C-17), 33.03 (C-16), 31.22 (C-15), 29.29 (C-14), 27.53 (C-13), (ESI 1.1.2),

and 268 mg (88.0%) of compound (3aR,4R,5R,6aS)-5-hydroxy-4-(5-phenylpentyl)hexahydro-2H-cyclopenta[b]furan-2-one, **IIc**, as an oil, $[\alpha]_D$ = -32.6 ˚(1 % in THF), IR: 3389brs, 2931s, 2859m, 1747vs, 1453m, 1415w, 1363w, 1179s, 1074m, 1030s, 969w, 748w, 700m, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, J Hz): 7.28 (t, 2H, H-*m*, 8.0), 7.30-7.17 (m, 3H, 2H-*o*, 1H-*p*), 4.93 (dt, 1H, H-6a, 2.0, 6.8), 3.98 (q, 1H, H-5, 5.1), 3.61 (m, 1H, H-15), 2.78 (dd, 1H, H-3, 11.0, 18.3), 2.71 (dt, 1H, H-17, 8.2, 14.8), 2.65 (m, 1H, H-17), 2.49 (m, 1H, H-3a), 2.49 (d, 1H, H-3, 18.3), 2.28 (dt, 1H, H-6, 6.1, 14.0), 2.02 (brd, 1H, H-6, 14.0), 1.82-1.72 (m, 3H, H-4, 2H-16), 1.57-1.47 (m, 3H, H-13, 2H-14), 1.25 (m, 1H, H-13), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 177.89 (C-2), 141.86 (C-1'), 128.43, 128.36 (2C-*o*, 2C-*m*), 125.89 (C-*p*), 84.02 (C-6a), 77.35 (C-5), 71.25 (C-15), 53.86 (C-4), 43.12 (C-3a), 40.34 (C-6), 39.06 (C-16), 35.99 (C-3), 35.17 (C-14), 32.00 (C-17), 28.91 (C-13), (See ref. 1, 5 and ESI 1.1.1.), MS 304.38 calcd. for $C_{18}H_{24}O_4$ $[M+1]^+$: th. 305.1747, found 305.17583 [287.16 ($C_{18}H_{23}O_3$), 269.15 ($C_{18}H_{21}O_2$), 91.05 (C_7H_7), 105.07 (C_8H_9)].

1.1.2. Hydrogenation of Ih

The crude **Ih** obtained from **Ic** (0.34 mol) was hydrogenated in toluene (810 mL) and methanol (250 mL), in the presence of $NaHCO_3$ (3 g) over *catalyst*$^+$ (10 g, 5.5% /th wt **Ih**) at 20 atm H_2 for 2 h. TLC and NMR showed the complete hydrogenation of the 13,14-double bond. The catalyst was filtered, the filtrate washed with sat. soln. $NaHCO_3$ (100 mL), water (500 mL), dried (Na_2SO_4) and concentrated under reduced pressure [Autoclave and aqueous

phases were washed with toluene (2 × 1L) and unified with the product), resulting 214 g (99% crude) of compound **IIh**, (3aR,4R,5R,6aS)-5-((tert-butyldimethylsilyl)oxy)-4-((R)-3-((tert-butyldimethylsilyl)oxy)-5-phenylpentyl)hexahydro-2H-cyclopenta[b]furan-2-one, as an oil which crystallized at rt (150.4 g, 83%) from hexane-ethyl acetate, mp 79.7-80.2 ˚C, $[\alpha]_D$ = -25.1 ˚(in THF), IR: 2953s, 2927vs, 2887m, 2856vs, 1752vs, 1472w, 1457w, 1386w, 1360w, 1246m, 1186m, 1127m, 1085w, 1062m, 1030m, 969m, 833vs, 771vs, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.28 (t, 2H, H-***m***, 8.1), 7.21-7.16 (m, 3H, 2H-*o*, H-*p*), 4.96 (t_l, 1H, H-6a, 5.7), 3.95 (q, 1H, H-5, 4.0), 3.70 (qv, 1H, H-15, 5.5), 2.80 (dd, 1H, H-3, 11.7, 18.8), 2.70-2.48 (m, 3H, H-3a, 2H-17), 2.51 (d, 1H, H-3, 18.8), 2.13 (dt, 1H, H-6, 5.7, 14.4), 2.00 (brd, 1H, H-6, 14.4), 1.82-1.65 (m, 3H, H-4, 2H-16), 1.55-1.48 (m, 2H, H-14), 1.39 (m, 1H, H-13), 1.15 (m, 1H, H-13), 0.91, 0.87 (2s, 18H, CH_3C), 0.07, 0.05, 0.04 (3s, 12H, CH_3Si), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 177.46 (C-2), 142.40 (C*q*-Ar), 128.38, 128.26 (4C, C-*o*, C-*m*), 125.78 (C-*p*), 84.05 (C-6a), 77.94 (C-5), 71.61 (C-15), 52.24 (C-4), 42.74 (C-3a), 40.60 (C-6), 38.88 (C-16), 36.25 (C-3), 35.08 (C-14), 31.70 (C-17), 28.64 (C-13), 25.87, 25.70 (CH_3C), 18.10, 17.91 (CH_3C), -4.34, -4.36, -4.69, -4.98 (CH_3Si), (See ESI 1.1.4.) MS 532.90, $C_{30}H_{52}O_4Si_2$, calcd for $[M+1]^+$: th 533.34769, found 533.34863 [131.09 ($C_6H_{15}OSi$), 91.05 (C_7H_7), 105.07 (C_8H_9), 117.07 (C_9H_9), 143.09 ($C_{11}H_{11}$)]. The mother liquors from crystallization contain a slightly impure **IIh**.

Hydrogenation of **Ih** in THF proceeded similarly.

1.1.3. Hydrogenation of Ig

The crude **Ig** obtained from **Ic** 0.40 mol) was hydrogenated as in the previous example: toluene (950 mL), methanol (300 mL), $NaHCO_3$ (3.5 g), *catalyst*$^+$ (11.8 g, 6.2 % /th wt **Ig**), 20 atm H_2 for 2 h at 45 ˚C, resulting 189.5 g (~ 99 % based on **Ic**) of crude compound **IIg**, (3aR,4R,5R,6aS)-4-((3R)-5-phenyl-3-((tetrahydro-2H-pyran-2-yl)oxy)pentyl)-5-((tetrahydro-2H-pyran-2-yl)oxy)hexahydro-2H-cyclopenta[b]furan-2-one as an oil, R_f = 0.13 (I), R_f = 0.58 (VII), $[\alpha]_D$ = -40.4 ˚(1% in THF), IR: 2938vs, 2865m, 1769vs, 1463w, 1351w, 1200m, 1174m,1131m, 1116m, 1074s, 1022m, 989w, 700w, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.27 (m, 2H, H-*m*), 7.21-7.16 (m, 3H, 2H-*o*, 1H-*p*), 4.98 (m, 1H, H-6a), 4.69-4.56 (m, 2H, H-1-THP), 4.08 (m, 0.5H-5), 3.96-3.78 (m, 2.5H, 0.5H-5, 2H-5-THP), 3.67 (m, 1H, H-15), 3.54-3.43 (m, 2H-5-THP), 2.83-2.48 (m, 5H, H-3a, 2H-3, 2H-17), 2.20 (m, 1H, H-6, 15.3), 2.01 (m, 1H, H-4, from HETCOR), 2.00-1.45 (m, 19H, H-6, 2H-14, 2H-16, 4H-2-THP, 4H-3THP, 4H-4-THP), 1.34-1.22 (m, 2H- H-13), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 177.69, 177.49, 177.39, 177.18 (C-2), 142.42, 142.11 (C-1'), 128.38, 128.35, 128.29, 128.22 (C-*o*, C-*m*), 125.82, 125.71 (C-*p*), 98.83, 98.65, 97.67, 95.68 (C-1-THP), 84.08, 84.03 (C-6a), 82.88, 82.70, 79.78, 79.64 (C-5), **76.38, 76.33, 76.05, 75.98** (C-15), 63.60, 63.49, 62.51, 62.42 (C-5-THP), **53.32, 53.01, 52.13, 51.69 (C-4), 43.02, 42.90, 42.51, 42.43 (C-3a),** 39.01, 38.94, 36.64, 36.58 (C-6), 36.11, 36.04 (C-16), 35.67, 35.62, 35.53, 35.49 (C-3), 33.03, 32.89, 31.75, 31.62 (C-2THP), 31.91, 31.62 (C-17), 31.42, 30.71 (C-14), 28.87, 28.68, 28.57, 28.36 (C-13), 25.41 (C-4THP), 20.47, 19.98, 19.37, 18.87 (-3THP) (See ESI 1.1.3.).

1.1.4. Hydrogenation of Ii

Ii (8.42 g, 16.5 mmol), ethyl acetate (120 mL), *catalyst*$^+$ (1 g), 20 atm. H_2 for 2h, followed by another 1 g catalyst, [total: 2 g, 2.38 % / **Ii**] 2 atm. H_2, 2h, TLC (silica gel, II, $R_{f\,Ii}$ = 0.72, $R_{f\,IIi}$ = 0.75); 8.33 g (98.9 %) (R)-1-((3aR,4R,5R,6aS)-5-(benzoyloxy)-2-oxohexahydro-2H-cyclopenta[b]furan-4-yl)-5-phenylpentan-3-yl benzoate **IIi** were obtained as an oil, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 8.05-7.97 (m, 4H, H-*o*), 7.47-7.14 (3m, 11H, 3H-*p*, 2H-*o*, 6H-*m*), 5.24-5.17 (m, 2H, H-6a, H-5), 5.04 (m, 1H, H-15), 2.87 (dd, 1H, H-3, 10.4, 18.1), 2.74-2.59 (m, 3H, 2H-17, H-3a), 2.47 (dd, 1H, H-3, 2.4, 18.1), 2.35-2.32 (m, 3H, 2H-6, H-14), 2.14-1.97 (m, 4H, H-4, H-14, 2H-16), 1.55-1.40 (m, 2H, H-13), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 177.78 (C-2), 166.27, 165.95 (2CO-Bz), 141.19 (C*q*-Ph), 133.57, 133.22 (2-C-*p*, Bz), 130.17, 130.09 (2C-*q*-Bz), 129.57, 129.43, 128.46, 128.31, 128.26, 128.20 (C-*o*, C-*m* Ph and Bz), 125.90 (C-*p* Ph), 84.30 (C-6a), 77.33 (C-5), 73.75 (C-15), 52.36 (C-4), 43.39 (C-3a), 37.70 (C-16), 36.14 (C-6), 35.90 (C-3), 32.25 (C-14), 31.68 (C-17), 29.03 (C-13) (See ESI 1.1.5.).

1.1.5. Hydrogenation of Ie

a) **Ie** (10.98 g, 27.0 mmol), *catalyst*$^+$ (220 mg, 2 % / **Ie**), methanol (150 mL), 3 atm H_2 for 3 h; TLC (I, $R_{f\,Ie}$ = 0.48, $R_{f\,IIe}$ = 0.38, $R_{f\,IId\text{-}1}$ = 0.62, $R_{f\,SP\ Rf\ superior}$ = 0.83); LPC (ethyl acetate-hexane, 1:1) gave 7.52 g (66.03%) **IIe**, (3aR,4R,5R,6aS)-4-((R)-3-hydroxy-5-phenylpentyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl benzoate as an oil, $[\alpha]_D$ = -80.6 ˚ (1% in THF), IR: 3486brm, 2934m, 2860w, 1766s, 1712vs, 1452w, 1315w, 1272vs, 1176m, 1109m, 1069m, 1045m, 1026m, 909w, 711s, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.99 (d, 2H, H-*o*, Bz, 7.6), 7.53 (t, 1H, H-*p*, Bz, 7.6), 7.42 (t, 2H, H-*m*, Bz, 7.6), 7.29-7.14 (m, 5H, H-*p*, 2H-*o*, 2H-*m*, Ph), 5.24 (m, 1H, H-5), 5.03 (t, H-6a, 5.9), 3.62 (m, 1H, H-15), 2.86 (dd, 1H, H-3, 10.6, 18.4), 2.79 (t , 1H, H-17, 7.0), 2.70-2.59 (m, 2H, H-17, H-3a), 2.47 (brd, 1H, H-3, 18.4), 2.34 (dt, 1H, H-6, 5.5, 15.7), 2.28 (brd, 1H, H-6, 15.7), 2.11 (m, 1H, H-4), 1.77 (brq, 2H, H-16, 7.0), 1.64-1.52 (m, 3H, 2H-14, H-13), 1.36 (m, 1H, H-13), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 176.98 (C-2), 165.75 (CO-Bz), 141.71 (C*q*-Ph, Bz), 133.02 (C-*p*, Bz), 128.30 (Cq-Ph), 129.38, 128.25, 128.11, (C-*o*, C-*m* Ph and Bz), 125.64 (C-*p* Ph), 84.36 (C-6a), 80.06 (C-5), 70.38 (C-15), 52.36 (C-4), 43.16 (C-3a), 38.81 (C-16), 37.43 (C-6), 36.01 (C-3), 34.82 (C-14), 31.71 (C-17), 29.08 (C-13) (See refs [6] and ESI 1.1.6.), MS 408.49, $C_{25}H_{28}O_5$, calcd for $[M+1]^+$: th 409.20095, found 409.20022 [299.1 ($C_{18}H_{19}O_4$), 91.05 (C_7H_7)].

1.75 g (16.5 %) of pure compound, (3aR,4R,5R,6aS)-2-oxo-4-(5-phenylpentyl)hexahydro-2H-cyclopenta[b]furan-5-yl benzoate **IId-1** and ~1.2 g of impure compound with lower polarity were obtained. A fraction of 15-desoxy compound **IId-1** (200 mg) was hydrolyzed to **IId** (10 mL anh. methanol, 10 mL 0.1% MeONa in MeOH for 3 h; LPC of crude compound gave a pure fraction of 120 mg **IIc** as an oil) with IR and NMR spectra similar with those of compound **IIc**.

The lower polarity secondary compound was not re-purified and characterized.

b) The hydrogenation of compound **Ie** (1 mmol, 406.5 mg) with 8.5 mg catalyst (2.1%) for only 90 min in the presence of $NaHCO_3$ (100 mg), gave 372 mg of **IIe** in 91.5% yield.

1.1.6. Hydrogenation of 15-*epi*-compound If

If (6.34 g, ~15.6 mmol) (with mp 89.4-90.5 ˚C, $[\alpha]_D$ = -87.7 ˚ (1% in THF)), *catalyst*$^+$ (150 mg, 2.4 % / **If**), methanol (150 mL), 3 atm H_2 for 90 min. TLC (II, $R_{f\,If}$ = 0.71, $R_{f\,IIf}$ = 0.63). *Observation: After only 90 min of hydrogenation, the secondary compounds were formed only in small amounts*. LPC (ethyl acetate-hexane, 1:1) gave 5.77 g (91.0%) of pure compound **IIf**, (3aR,4R,5R,6aS)-4-((S)-3-hydroxy-5-phenylpentyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl benzoate as an oil, $[\alpha]_D$ = -78.5 ˚ (1% in THF), IR: 3450brw, 2936m, 2860w, 17655, 1711vs, 1452w, 1272vs, 1176m, 1097m, 1070m, 1026m, 908m, 728m, 711s, ^{1}H-NMR-500 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.99 (d, 2H, H-*o*, Bz, 7.8), 7.53 (t, 1H, H-*p*, Bz, 7.8), 7.41 (t, 2H, H-*m*, Bz, 7.8), 7.29-7.15 (m, 5H, H-*p*, 2H-*o*, 2H-*m*, Ph), 5.22 (dt, 1H, H-5, 2.5, 5.0), 5.03 (t, H-6a, 5.7), 3.59 (m, 1H, H-15), 2.87 (dd, 1H, H-3, 10.7, 18.3), 2.77 (dt, 1H, H-17, 6.6, 13.8), 2.68-2.62 (m, 2H, H-17, H-3a), 2.45 (dd, 1H, H-3, 2.6, 18.3), 2.35 (dt, 1H, H-6, 5.6, 15.8), 2.29

(brd, 1H, H-6, 15.8), 2.09 (m, 1H, H-4), 1.76 (dt, 2H, H-16, 6.6, 8.0), 1.62-1.45 (m, 4H, 2H-14, 2H-13), ^{13}C-NMR-125 MHz ($CDCl_3$, *δ* ppm): 176.95 (C-2), 165.86 (CO-Bz), 141.69 (C*q*-Ph, Bz), 133.09 (C-*p*, Bz), 129.37, 128.30, 128.19, 128.14, (C-*o*, C-*m* Ph and Bz), 125.64 (C-*p* Ph), 84.43 (C-6a), 80.28 (C-5), 70.50 (C-15), 52.62 (C-4), 43.05 (C-3a), 38.93 (C-16), 37.46 (C-6), 36.09 (C-3), 34.97 (C-14), 31.75 (C-17), 29.27 (C-13) (See ESI 1.1.7.).

0.42 g (~6.9 %) of (3aR,4R,5R,6aS)-2-oxo-4-(5-phenylpentyl)hexahydro-2H-cyclopenta[b]furan-5-yl benzoate, **IId-1**, similar with the compound obtained above, and 0.47 g of impure lower polarity compound (not identified).

1.2. Hydrogenation of 16-(*m*-substituted)phenoxy diol intermediates

1.2.1. Hydrogenation of compound 1 (with 15-*epi* isomer) in *methanol*

a) with 10% Pd/C (catalyst†) in amount of 15% w/w based on substrate: **(±)**- Compound **1a** with 15-*epi*-**1a** (2.0 g, 5.9 mmol), methanol (100 mL), *catalyst†* catalyst (300 mg, 15 % / **1a**), 3 atm of H_2 for 2 h. TLC (III, $R_{f\ 2c}$ = 0.24, $R_{f\ 3c}$ = 0.64, $R_{f\ 3c}$ = 0.54). The catalyst was filtered, the filtrate was concentrated on a rotavapor and the crude product was purified by LPC (eluent: ethyl acetate-toluene, 1:1), resulting a pure fraction of 0.8 g (44.3%) of compound **2c** as an oil, which, after crystallization from anh. ethyl ether-anh. petroleum ether (bp 40-67 ˚C), gave 410 mg crystals, mp 104-110 ˚C, ^{1}H-NMR-300 MHz (DMSO-*d6*, *δ* ppm, *J* Hz): 7.28 (dd, 2H, H-*m*, 7.0, 8.0), 6.93 (d, 2H, H-*o*, 7.0), 6.91 (m, 1H, H-*p*), 4.89 (dt, 1H, H-6a, 2.6, 7.0), 3.82 (d, 2H, H-16, 5.5), 3.80-3.68 (m, 2H, H-5, H-15), 2.80 (ddd, 1H, H-3, 2.2, 10.5, 17.9), 2.46 (m, 1H, H-3a), 2.34 (ddd, 1H, H-3, 3.0, 4.5, 17.9), 2.17 (ddd, 1H, H-6, 5.8, 6.7, 14.4), 1.73 (ddd, 1H, H-6, 2.7, 5.1, 14.4), 1.66-1.17 (m, 5H, H-4, 2H-13, 2H-14), ^{13}C-NMR-75 MHz ($CDCl_3$, *δ* ppm): 177.33 (CO, C-2), 158.70 (C*q*-Ar), 129.46 (C-*m*), 120.44 (C-*p*), 114.47 (2C-*o*), 83.44 (C-6a), 76.04, 75.94 (C-5), 72.09, 72.04 (C-16), 68.47 (C-15), 53.42, 53.29 (C-4), 42.22, 42.07 (C-3a), 40.06 (C-6), 35.64, 35.58 (C-14), 31.71, 31.61 (C-3), 28.34 (C-13) (See ESI 1.2.1.1.),

By a similar re-purification of the impure fractions (eluent: ethyl acetate-toluene, 1:3), a pure fraction of **3c** (0.4 g, 23.3 %) was obtained as an oil, ^{1}H-NMR-300 MHz (DMSO-*d6*, *δ* ppm, *J* Hz): 7.30-7.25 (m, 2H, H-*m*), 6.93-6.89 (m, 3H, 2H-*o*, H-*p*), 4.88 (dt, 1H, H-6a, 2.9, 7.3), 4.78 (brs, OH), 3.94 (t, 2H, H-16, 6.6), 3.75 (q, 1H, H-5, 5.8), 2.80 (dd, 1H, H-3, 10.5, 18.0), 2.45 (m, 1H, H-3a), 2.34 (dd, 1H, H-3, 3.0, 18.0), 2.17 (ddd, 1H, H-6, 5.8, 6.8, 14.3), 1.76-1.60 (m, 4H, H-4, H-6, 2H-15), 1.50-1.22 (m, 4H, 2H-13, 2H-14), ^{13}C-NMR-75MHz (DMSO-*d6*, *δ* ppm): 177.30 (C-2), 158.63 (C*q*-Ar), 129.45 (2C-*m*), 120.34 (C-*p*), 114.37 (2C-*o*), 83.36 (C-6a), 75.91, 75.82 (C-5), 67.15 (C-16), 53.14 (C-4), 42.05 (C-3a), one C in DMSO = 40.05 (C-6), 35.55 (C-3), 32.03 (C-13), 28.95 (C-15), 23.69 (C-14) (See ESI 1.2.1.2.); the impure fractions of both compounds were no further purified.

b) By hydrogenation of (-)-**1** (7.74 g, 22.8 mmol) in 250 mL methanol with a fresh catalyst obtained from 3.6 g 7% $PdCl_2$/C (4.2% Pd/C, 30 atm, 1.5 h), after LPC (toluene-ethyl acetate, 2:1) purification of the crude product, a fraction of 5.93 g (76.3 %) of pure (3aR,4R,5R,6aS)-5-hydroxy-4-((R)-3-hydroxy-4-phenoxybutyl)hexahydro-2H-cyclopenta[b]furan-2-one (-)-**2c** was obtained as an oil (a fraction was crystallized from EtOH-Et_2O, mp 119-122 ˚C, $[\alpha]_D$ = -18.6 ˚ (1% in THF)) and pure fraction of 1.30 g (19.6 %) of secondary compound (3aR,4R,5R,6aS)-5-hydroxy-4-(4-phenoxybutyl)hexahydro-2H-cyclopenta[b]furan-2-one, **(-)-3c**, as an oil, which crystalized from ethyl acetate-hexane, mp 65.6-67.1 ˚C, $[\alpha]_D$ = - 31.2 ˚ (1% in THF), IR: 3526vs, a broad shoulder for water in the crystal, 3470-3200m, 2971w, 2935s, 2856m, 1771vs, 1598m, 1584m, 1492m, 1473w, 1248s, 1162vs, 1074m, 1048m, 1018m, 764m, ^{1}H-NMR-300 MHz ($CDCl_3$, *δ* ppm, *J* Hz): 7.28 (d, 2H, H-*m*, 7.5), 6.93 (t, 1H, H-*p*, 7.5), 6.89 (d, 2H, 2H-*o*, 7.5), 4.97 (dt, 1H, H-6a, 2.1, 6.9), 4.04 (q, 1H, H-5, 4.5), 3.96 (t, 2H, H-16, 6.2), 2.82 (dd, 1H, H-3, 11.1, 18.8), 2.56 (m, 1H, H-3a), 2.53 (dd, 1H, H-3, 2.9, 18.8), 2.26 (dt, 1H, H-6, 6.0, 15.0), 2.05 (brd, 1H, H-6, 15.0), 1.87 (m, 1H, H-4), 1.78 (dt, 2H, 2H-15, 6.3, 7.4), 1.60-1.50 (m, 2H, H-14), 1.44 (m, 1H, H-13), 1.26 (m, 1H, H-13), ^{13}C-NMR-75MHz ($CDCl_3$, *δ* ppm): 177.64 (C-2), 158.87 (C*q*-Ar), 129.43 (2C-*m*), 120.63 (C-*p*), 114.40 (2C-*o*), 84.10 (C-6a), 77.57 (C-5), 67.35 (C-16), 54.22 (C-4), 43.05 (C-3a), 40.55 (C-6), 36.17 (C-3), 32.83 (C-13), 29.31 (C-15), 24.27 (C-14) (See ESI 1.2.1.3.), MS 290.35, $C_{17}H_{22}O_4$, calcd for $[M+1]^+$ th. 533.34769, found 533.34863 [131.09 ($C_6H_{15}OSi$), 91.05 (C_7H_7), 105.07 (C_8H_9), 117.07 (C_9H_9), 143.09 ($C_{11}H_{11}$)], X ray crystallography for (-)-**3c**.

1.2.2. Hydrogenation of 1a with a smaller quantity of catalyst

(±)-1a (9.01 g, 26.6 mmol), *catalyst†* (0.9 g, 10 % / **1a**), ethyl acetate (200 mL), H_2 (atm. pressure); TLC (IV, $R_{f\ 2a}$ = 0.13, $R_{f\ 3a}$ = 0.26, $R_{f\ PS}$ = 0.46); LPC (toluene-ethyl acetate 2:1); 6.84 g (75.5%) (3aα,4β,5α,6aα)-4-((β)-4-(3-chlorophenoxy)-3-hydroxybutyl)-5-hydroxyhexahydro-2H-cyclopenta[b]furan-2-one, **2a** were obtained, mp 107.6-109.6 ˚C, IR-in *ATR*: 3439s, 2915w, 1719vs, 1595m, 1575w, 1485m, 1371m, 1250m, 1225s, 1065w, 1047s, 1020s, 910s, 762m, IR in *$CHCl_3$*: 3424brs, 2934s, 2867m, 1756vs, 1592s, 1480m, 1457w, 1428w, 1364w, 1288w, 1231m, 1187m, 1073w, 1037m, ^{1}H-NMR-300 MHz ($CDCl_3$, *δ* ppm, *J* Hz)[15]: 7.21 (t, 1H, H-5', 8.1), 6.96 (ddd, 1H, H-4', 1.0, 2.1, 8.1), 6.91 (t, 1H, H-2', 2.1), 6.79 (ddd, 1H, H-6', 1.0, 2.1, 8.1), 4.96 (dt, 1H, H-6a, 2.4, 6.8), 4.05 (dt, 1H, H-5, 4.8, 5.0), 3.99 (m, 1H, H-15), 3.93 (dd, 1H, H-16, 3.1, 9.2), 3.82 (dd, 1H, H-16, 7.3, 9.2), 2.83 (dd, 1H, H-3, 10.8, 18.5), 2.55 (dd, 1H, H-3, 2.6, 18.5), 2.54 (m, 1H, H-3a), 2.32 (m, 2H, OH) deuterable with TFA, 2.34 (m, dt with TFA, 1H, H-6, 6.8, 15.6), 2.05 (m, 1H, H-6), 1.94 (m, 1H, H-4), 1.69-1.62 (m, 3H, H-13, H-14), 1.40 (t, 1H, H-14, 6.6), ^{13}C-NMR-75MHz ($CDCl_3$, *δ* ppm): 177.46 (C-2), 159.15 (C*q*-Ar), 134.96 (C-3'), 130.35 (C-5'), 121.46 (C-4'), 114.97 (C-2'), 113.04 (C-6'), 83.81 (C-6a), 77.53 (C-15), 72.33 (C-16), 69.94 (C-5), 53.81 (C-4), 43.28 (C-3a), 40.62 (C-6), 35.94 (C-3), 30.84 (C-13), 28.86 (C-14) (See ESI 1.2.2.1.), MS 340.80 calcd. for $C_{17}H_{21}ClO_5$ $[M+1]^+$: th. 341.11503, found 341.11465 [141.00 (C_7H_6ClO), 303.08 ($C_{17}H_{16}O_3Cl$), 243.06 ($C_{15}H_{12}ClO$), 167.01 (C_9H_8OCl), 117.07 (C_9H_9)].

and 1.46 g (16.9%) (3aα,4β,5α,6aα)-4-(4-(3-chlorophenoxy)butyl)-5-hydroxyhexahydro-2H-cyclopenta[b]furan-2-one, **3a**, 91.7-92.0 ˚C, IR: 3430s, 2943m, 2854w, 1735vs, 1584s, 1483w, 1466m, 1366w, 1306s, 1258s, 1201brm, 1073w, 1048w, 1023m, 979w, 865w, 805w, ^{1}H-NMR-300 MHz (DMSO-*d6*, *δ* ppm, *J* Hz): 7.26 (t, 1H, H-5', 8.1), 6.97 (t, 1H, H-2', 2.1), 6.94 (ddd, 1H, H-4', 1.0, 2.1, 8.1), 6.87 (ddd, 1H, H-6',1.0, 2.1, 8.1), 4.87 (dt, 1H, H-6a, 2.6, 7.2), 3.96 (t, 2H, H-16, 6.5), 3.75 (dt, 1H, H-5, 5.4, 11.1) +THF, 2.80 (dd, 1H, H-3, 10.5, 18.0), 2.45 (m, 1H, H-3a), 2.32 (ddd, 1H, H-3, 3.0, 7.7, 18.0), 2.19 (dt, 1H, H-6, 4.5, 15.2), 1.78-1.60 (m, 4H, H-4, H-6, 2H-15), 1.45 (m, 2H, H-14), 1.29 (m, 2H, H-13), ^{13}C-NMR-75MHz (DMSO-*d6*, *δ* ppm): 177.02 (C-2), 159.36 (C-1'-Ar), 134.45 (C-3'), 130.55 (C-5'), 120.05 (C-4'), 114.11 (C-2'), 113.29 (C-6'), 83.09 (C-6a), 75.64 (C-5), 67.49 (C-16), 52.87 (C-4), 41.78 (C-3a), 40.05 (C-6) in DMSO, 35.27 (C-3), 31.71 (C-13), 29.06 (C-15), 23.32 (C-14) (See ESI 1.2.2.2.), elem. analysis, calctd for $C_{17}H_{21}ClO_4$, th Cl: 10.91 %, found: 10.85 %, MS 324.80 calcd. for $C_{17}H_{21}ClO_4$ $[M+1]^+$: th. 325.12011, found 325.11998 [307.11 ($C_{17}H_{20}ClO_3$), 197.12 ($C_{11}H_{17}O_3$), 179.11 ($C_{11}H_{15}O_2$), 161.10 ($C_{11}H_{13}O$), 141.01 (C_7H_6OCl)].

1.2.3. Hydrogenation of 1b

1b (1 mmol, 372 mg) with mp 115.4-117.0 ˚C, *catalyst*† (37.2 mg, 10 % / **1b**), methanol (50 mL), hydrogenated at 20 atm H_2 for 2 h. LPC (ethyl acetate-heptane, 1:1), gave 34.1 mg (9.5 %) of secondary 15-desoxy-compound (3aR,4R,5R,6aS)-5-hydroxy-4-(4-(3-(trifluoromethyl)phenoxy)butyl)hexahydro-2H-cyclopenta[b]furan-2-one **3b** as an oil, $[\alpha]_D$ = -28.1 ˚(1 % in THF), IR: 3443brw, 3075m, 2867w, 1761s, 1591w, 1493w, 1452m, 1326vs, 1295w, 1237w, 1162s, 1119vs, 1097m, 1064s, 1031s, 790w, 698w, 698w, ^{1}H-NMR-300 MHz ($CDCl_3$, *δ* ppm, *J* Hz): 7.38 (m, 1H, H-5', 8.1), 7.19 (d, 1H, H-4', 81), 7.10 (s, 1H, H-2'), 7.05 (d, 1H, H-6', 8.1), 4.97 (t, 1H, H-6a, 6.3), 4.05 (q, 1H, H-5, 4.6), 3.99 (t, 2H, H-16, 6.1), 2.83 (dd, 1H, H-3, 11.0, 18.5), 2.57 (m, 1H, H-3a), 2.53 (dd, 1H, H-3, 2.8, 18.5), 2.27 (dt, 1H, H-6, 6.0, 15.0), 2.07 (brd, 1H, H-6, 15.0), 1.88 (m, 1H, H-4), 1.81 (cv, 2H, H-15, 7.0), 1.61-1.51 (m, 2H, H-14), 1.46 (m, 1H, H-13), 1.30 (m, 1H, H-13), ^{13}C-NMR-75MHz ($CDCl_3$, *δ* ppm): 177.64 (C-2), 159.01, (C-1'), 131.24 (q, C-3', J_{C-F} = 32.3Hz), 129.94 (C-5'), 123.94 (q, CF_3, J_{C-F} = 270.75), 117.94 (C-6'), 117.28 (q, C-2', J_{C-F} =3Hz), 111.09 (q, C-4', J_{C-F} =3Hz), 84.11 (C-6a), 77.59 (C-5), 67.77 (C-16), 54.19 (C-4), 43.04 (C-3a), 40.56 (C-6), 36.17 (C-3), 32.83 (C-15), 29.19 (C-13), 24.25 (C-14) (See ESI 1.2.3.2.),

and 292 mg (78.0%) of pure (3aR,4R,5R,6aS)-5-hydroxy-4-((R)-3-hydroxy-4-(3-(trifluoromethyl)phenoxy)butyl)hexahydro-2H-cyclopenta[b]furan-2-one, **2b** (*+ 35 mg impure compound **2b***) as an oil, $[\alpha]_D$ = -23.1 ˚(1% in THF), IR: 3400brm, 2935m, 1750s, 1592w, 1493w, 1450m, 1327vs, 1295m, 1237m, 1162s, 1118vs, 1097m, 1065s, 1032s, 891w, 791w, 697w, ^{1}H-NMR-300 MHz ($CDCl_3$, *δ* ppm, *J* Hz)[15]: 7.40 (t, 1H, H-5', 8.1), 7.23 (d, 1H, H-4', 8.1), 7.13 (s, 1H, H-2'), 7.08 (d, 1H, H-6', 8.1), 4.96 (t, 1H, H-6a, 6.8), 4.06-3.96 (m, 3H, H-5, H-15, H-16), 3.90 (d, 1H, H-16, 8.5), 2.82 (dd, 1H, H-3, 10.8, 18.5), 2.57-2.51 (m, 2H, H-3, H-3a), 2.42 (brs, OH), 2.32 (dt, 1H, H-6, 6.1, 15.1), 2.05 (m, 1H, H-6), 1.88 (m, 1H, H-4), 1.71-1.58 (m, 3H, H-13, 2H-14), 1.41 (m, 1H, H-13), ^{13}C-NMR-125MHz ($CDCl_3$, *δ* ppm): 177.60 (C-2), 158.54 (C*q*-Ar), 131.69 (q, C-3', J_{C-F} = 32.3Hz), 130.11 (C-5'), 123.84 (q, CF_3, J_{C-F} = 270.8), 118.00 (C-6'), 117.96 (q, C-2', J_{C-F} =3Hz), 111.30 (q, C-4', J_{C-F} =3Hz), 83.88 (C-6a), 77.49 (CH, C-5), 72.25 (C-16), 69.92 (C-15), 53.76 (C-4), 43.25 (C-3a), 40.54 (C-6), 35.96 (C-3), 30.86 (C-13), 28.85 (C-14) (See ESI 1.2.3.1.), MS 374.35, $C_{18}H_{21}F_3O_5$, calcd. for $[M+1]^+$: th. 375.14139, found 375.14227 [357.1 ($C_{18}H_{20}F_3O_4$), 355.1 ($C_{18}H_{21}F_2O_5$), 337.1 ($C_{18}H_{19}F_2O_4$), 131.09 ($C_{10}H_{11}$), 117.1 (C_9H_9), 105.1 (C_8H_9), 91.1 (C_7H_7), 93.1 (C_7H_9), 107.1 (C_8H_{11}).

1.2.4. Hydrogenation of the bis-TBDMS-protected diol 1a-1.

Diol **1a** (1.5 mmol, 508 mg) was protected as 5,11-bis TBDMS-ether with TBDMSCl (6 mmol, 910 mg), imidazole (8 mmol, 545 mg), DMAP (50 mg) in THF (5 mL) overnight at rt, then for 2 h at 50 ˚C. TLC (I, $R_{f\ \mathbf{1a}}$ = 0.13, $R_{f\ \mathbf{1a\text{-}1}}$ = 0.80). The crude product was purified by LPC (Hexane-ethyl acetate, 9:1), obtaining 675 mg (92.0%) of pure **1a-1**, (3aα,4β,5α,6aα)-5-((tert-butyldimethylsilyl)oxy)-4-((R,E)-3-((tert-butyldimethylsilyl)oxy)-4-(3-chlorophenoxy)but-1-en-1-yl)hexahydro-2H-cyclopenta[b]furan-2-one, as a powder. A fraction was crystalized from hexane-ethyl acetate, mp 95-99.8 ˚C, IR: 2931vs, 2885m, 2858s, 1753vs, 1595m, , 1474m, 1250s, 1124s, 1090m, 1038sm, 972m, 833vs, 774vs, 671m, ^{1}H-NMR-300 MHz ($CDCl_3$, *δ* ppm, *J* Hz): 7.17 (t, 1H, H-5', 8.1), 6.92 (brd, 1H, H-4', 81), 6.84 (t, 1H, H-2', 2.1), 6.74 (dd, 1H, H-6', 2.1, 8.1), 5.64-5.55 (m, 2H, H-13, H-14), 4.94 (dt, 1H, H-6a, 2.1, 6.9), 4.475 (m, 1H, H-15), 3.99 (q, 1H, H-5, 5.6), 3.80 (d, 2H, H-16, 5.9), 2.74 (dd, 1H, H-3, 10.1, 17.6), 2.62 (m, 1H, H-3a), 2.45 (m, 1H, H-4), 2.47 (dd, 1H, H-3, 2.0, 17.6), 2.27 (dt, 1H, H-6, 6.9, 14.6), 1.96 (ddd, 1H, H-6, 2.1, 5.2, 14.6), ^{13}C-NMR-75MHz ($CDCl_3$, *δ* ppm): 177.00 (C-2), 159.39 (C-1'), 134.81 (C-3'), 131.62, 131.08 (C-13, C-14), 130.24 (C-5'), 120.95 (C-4'), 114.79 (C-2'), 112.89 (C-6'), 83.20 (C-6a), 77.79 (C-5), 71.31 (C-15), 63.70 (C-16), 56.68 (C-4), 42.25 (C-3a), 40.70 (C-6), 34.82 (C-3), 25.80, 25.71 ($\mathit{C}H_3C$), 18.30, 17.99 ($CH_3\mathit{C}$), -4.62, -4.65, -4.69, -4.87 ($\mathit{C}H_3Si$), MS 567.3, $C_{29}H_{47}ClO_5Si_2$, $[M+1]^+$: th. 567.27233, found 567.2773.

1a-1 (0.5 mmol, 266 mg) was hydrogenated in EtOAc (30 mL), *catalyst*† (27 mg), 20 atm H_2 for 40 min. TLC shows only one compound formed in the hydrogenation. LPC (hexane-ethyl acetate, 9:1) gave a pure fraction of 246.8 mg (92.8%) **2a-1**, (3aα,4β,5α,6aα)-5-((tert-butyldimethylsilyl)oxy)-4-((β)-3-((tert-butyldimethylsilyl)oxy)-4-(3-chlorophenoxy)butyl)hexahydro-2H-cyclopenta[b]furan-2-one, as an oil which crystallized in time, mp 67.5-71.5 ˚C, (68.5-72.0 ˚C, Hexane), IR: 2952s, 2929vs, 2857s, 1752s, 1597w, 1485w, 1468w, 1252s, 1180m, 1126m, 1101m, 1067w, 1019m, 973m, 832s, 774s, ^{1}H-NMR-300 MHz ($CDCl_3$, *δ* ppm, *J* Hz): 7.19 (t, 1H, H-5', 8.1), 6.93 (brd, 1H, H-4', 8.1), 6.86 (brt, 1H, H-2', 2.1), 6.76 (dd, 1H, H-6', 2.1, 8.1), 4.96 (dt, 1H, H-6a, 2.2, 7.0), 4.02-3.94 (m, 2H, H-15, H-5), 3.83 (dd, 1H, H-16, 6.0, 9.2), 3.77 (dd, 1H, H-16, 5.3, 9.2), 2.82 (dd, 1H, H-3, 11.8, 19.0), 2.55 (m, 1H, H-3a), 2.51 (dd, 1H, H-3, 3.1, 19.0), 2.15 (dt, 1H, H-6, 5.8, 14.4), 1.99 (brd, 1H, H-6, 14.4), 1.83 (m, 1H, H-4), 1.68-1.32 (m, 4H, 2H-13, 2H-14), 0.89, 0.87 (2s, 15H, $\mathit{C}H_3C$), 0.10, 0.08, 0.05 (3s, 12H, CH_3Si), ^{13}C-NMR-125MHz ($CDCl_3$, *δ* ppm): 177.33 (C-2), 159.38 (C*q*-Ar), 134.88 (C-3'), 130.25 (C-5'), 121.02 (C-4'), 114.68 (C-2'), 112.92 (C-6'), 83.90 (C-6a), 77.74 (C-5), 71.91 (C-16), 70.47 (C-15), 55.01 (C-4), 42.70 (C-3a), 40.62 (C-6), 36.17 (C-3), 32.65 (C-13), 28.36 (C-14), 25.82, 25.68 ($\mathit{C}H_3C$), 18.12, 17.89 ($CH_3\mathit{C}$), -4.22, -4.67, -4.71, -4.98 ($\mathit{C}H_3Si$) (See ESI 1.2.4.), MS 569.32, $C_{29}H_{49}ClO_5Si_2$, calcd for $[M+1]^+$: th 569.28798, found 569.2883 [226.07 ($C_{12}H_{15}O_2Cl$), 212.06 ($C_{11}H_{13}O_2Cl$), 244.09 ($C_{12}H_{17}O_3Cl$)].

1.2.5. Hydrogenation of bis-TBDMS-protected diol 1b-1.

Diol **1b** (30 mmol, 11.17 g) was protected as 5,11-bis TBDMS-ether with TBDMSCl (120 mmol, 18.1 g), imidazole (180 mmol, 12.3 g), DMAP (1.5 g) in THF (100 mL) overnight at rt, then for 2 h at 50 ˚C. TLC (I, $R_{f\ \mathbf{1a}}$ = 0.13, $R_{f\ \mathbf{1a\text{-}1}}$ = 0.80). The crude product was purified by LPC (Hexane-ethyl acetate, 9:1), obtaining 16.84 g (93.4.0%) of pure **1b-1**, (3aR,4R,5R,6aS)-5-((tert-butyldimethylsilyl)oxy)-4-((R,E)-3-((tert-butyldimethylsilyl)oxy)-4-(3-(trifluoromethyl)phenoxy)but-1-en-1-yl)hexahydro-2H-cyclopenta[b]furan-2-one, mp 91.3-92.1˚C, (lit[21] 91-93˚C) $[\alpha]_D$ = -32.4˚(1% in THF), IR: 2953m, 2930s, 2888w, 2857m, 1772vs, 1449m, 1329s, 1252m, 1166s, 1125vs, 1094m, 1065m, 1039m, 832vs, 774vs, ^{1}H-NMR-300 MHz ($CDCl_3$, *δ* ppm, *J* Hz)[21]: 7.38 (t, 1H, H-5', 8.1), 7.21 (d, 1H, H-4', 8.1), 7.07 (s, 1H, H-2'), 7.04 (d, 1H, H-6', 8.1), 5.63 (m, 2H, H-13, H-14), 4.94 (dt, 1H, H-6a, 2.4, 7.0), 4.51 (dt, 1H, H-15, 2.7, 5.7), 3.99 (q, 1H, H-5, 5.8), 3.86 (d, 2H, H-16, 5.9), 2.75 (dd, 1H, H-3, 10.0, 17.6), 2.63 (~ddt, 1H, H-3a, 2.1, 7.1, 10.0), 2.47 (dd, 1H, H-3, 2.1, 17.6), 2.46 (m, 1H, H-4), 2.30 (dt, 1H, H-6, 6.4, 14.8), 1.98 (ddd, 1H, H-6, 2.3, 5.6, 14.8), 0.90, 0.87 (2s, 15H, $\mathit{C}H_3C$), 0.08, 0.05, 0.04 (3s, 12H, CH_3Si), ^{13}C-NMR-75MHz ($CDCl_3$, *δ* ppm): 177.81 (C-2), 158.84 (C*q*-Ar), 132.28 (q, C-3', J_{C-F} = 32.3Hz), 131.64, 131.21 (C-13, C-14), 129.98 (C-5'), 123.92 (q, CF_3, J_{C-F} = 270.8), 118.08 (C-6'), 117.53 (q, C-2', J_{C-F} =3.7Hz), 111.05 (q, C-4', J_{C-F} =3.7Hz), 83.06 (C-6a), 77.73 (CH, C-5), 72.44 (C-16), 71.09 (C-15), 56.68 (C-4), 42.25 (C-3a), 40.66 (C-6), 34.72 (C-3), 25.77, 25.68 ($\mathit{C}H_3C$), 18.29, 17.97 ($CH_3\mathit{C}$), -4.65, -4.68, -4.91 ($\mathit{C}H_3Si$) (See ESI 1.2.5.1.), MS 600.86, $C_{30}H_{47}F_3O_5Si_2$, $[M+1]^+$: th. 601.29869, found 601.2999.

1b-1 (0.5 mmol, 300.4 mg) was hydrogenated in EtOAc (30 mL), *catalyst*† (27 mg), 20 atm H_2 for 40 min. TLC shows only one compound formed in the hydrogenation. LPC (hexane-ethyl acetate,

9:1) gave a pure fraction of 290 mg (96.5 %) **2b-1**, (3aR,4R,5R,6aS)-5-((tert-butyldimethylsilyl)oxy)-4-((R)-3-((tert-butyldimethylsilyl)oxy)-4-(3-(trifluoromethyl)phenoxy)butyl)hexahydro-2H-cyclopenta[b]furan-2-one, as an oil, $[\alpha]_D$ = -31.6 ˚(1% in THF), IR: 2951s, 2932s, 2892m, 2858m, 1772vs, 1494m, 1328s, 1250m, 1167s, 1124vs, 1094s, 1063m, 1039m, 833vs, 775s, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.39 (t, 1H, H-5', 8.1), 7.22 (d, 1H, H-4', 8.1), 7.09 (s, 1H, H-2'), 7.05 (d, 1H, H-6', 8.1), 4.97 (brt, 1H, H-6a, 6.5), 4.03-3.95 (m, 2H, H-15, H-5), 3.88 (dd, 1H, H-16, 5.3, 9.2), 3.83 (dd, 1H, H-16, 5.5, 9.2), 2.81 (dd, 1H, H-3, 11.6, 18.8), 2.56 (m, 1H, H-3a), 2.51 (dd, 1H, H-3, 3.3, 18.8), 2.17 (dt, 1H, H-6, 6.2, 14.7), 2.00 (brd, 1H, H-6, 14.7), 1.84 (m, 1H, H-4), 1.67-1.58 (m, 2H, H-14), 1.49 (m, 1H, H-13), 1.28 (m, 1H, H-13), 0.90, 0.87 (2s, 15H, CH_3C), 0.11, 0.09, 0.07, 0.05 (4s, 12H, CH_3Si), ^{13}C-NMR-75MHz ($CDCl_3$, δ ppm): 177.31 (C-2), 158.77 (C*q*-Ar), 131.87 (q, C-3', $J_{C\text{-}F}$ = *32.3Hz*), 130.02 (C-5'), 123.91 (q, CF_3, $J_{C\text{-}F}$ = 270.8), 117.64 (C-6'), 117.60 (q, C-2', $J_{C\text{-}F}$ =3.7Hz), 110.94 (q, C-4', $J_{C\text{-}F}$ =3.7Hz), 83.85 (C-6a), 77.73 (C-5), 71.95 (C-16), 70.45 (C-15), 54.98 (C-4), 42.69 (C-3a), 40.63 (C-6), 36.14 (C-3), 32.66 (C-14), 28.34 (C-13), 25.81, 25.67 (*C*H_3C), 18.12, 17.88 (CH_3*C*), -4.24, -4.66, -4.69, -5.00 (*C*H_3Si) (See ESI 1.2.5.2.), MS 602.87, $C_{30}H_{49}F_3O_5Si_2$, $[M+1]^+$: th. 603.31434, found 609.34434 [305.12 ($C_{18}H_{16}OF_3$), 327.16 ($C_{18}H_{22}O_2F_3$)].

1.2.6. Hydrogenation of compound 4.

(±)-(β,E)-4-((3aα,4β,5α,6aα)-5-acetoxy-2-oxohexahydro-2H-cyclopenta[b]furan-4-yl)-1-(3-chlorophenoxy)but-3-en-2-yl acetate **4** (3.38 g, 8 mmol) with *catalyst*† (300 mg) in 150 mL ethyl acetate was hydrogenated at 3 atm H_2 for 1.5 h. TLC showed only one product, but the reaction had not ended. During the next day, another 120 mg catalyst were added and hydrogenated for 2 h at 3 atm H_2. TLC showed that three compounds were formed in the reaction, and the crude product was purified by LPC (eluent, toluene-ethyl acetate, 2:1), resulting 220 mg (11.4%) (3aα,4β,5α,6aα)-4-butyl-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl acetate, **7** as an oil, 460 mg (15.7%) (3aα,4β,5α,6aα)-4-(4-(3-chlorophenoxy)butyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl acetate **6** as an oil and 2.48 g (5.84 mmol, 73.0%) **5** (±)-(β)-4-((3aα,4β,5α,6aα)-5-acetoxy-2-oxohexahydro-2H-cyclopenta[b]furan-4-yl)-1-(3-chlorophenoxy)butan-2-yl acetate, as an oil.

5: ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.21 (t, 1H, H-5', 8.1), 6.96 (dd, 1H, H-4', 2.2, 8.1), 6.90 (t, 1H, H-2', 2.2), 6.79 (dd, 1H, H-6', 2.2, 8.1), 5.14 (m, 1H, H-15), 5.03 (dt, 1H, H-6a, 2.1, 6.3), 4.95 (m, 1H, H-5), 4.02 (dd, 1H, H-16, 5.0, 10.9), 3.98 (dd, 1H, H-16, 4.8, 10.9), 2.89 (dd, 1H, H-3, 10.6, 18.1), 2.64 (m, 1H, H-3a), 2.46 (dd, 1H, H-3, 2.6, 18.1), 2.29 (dd, 1H, H-6, 5.4, 15.8), 2.21 (m, 1H, H-6), 2.09, 2.03 (2s, 6H, CH_3), 2.10 (m, 1H, H-4), 1.85-1.77 (m, 2H, H-14), 1.49-1.25 (m, 2H, H-13), ^{13}C-NMR ($CDCl_3$, δ ppm): 176.54 (C-2), 170.59, 170.42 (CH_3*C*O), 159.09 (C*q*-Ar), 134.96 (C-3'), 130.31 (C-5'), 121.47 (C-4'), 115.02 (C-2'), 113.00 (C-6'), 83.94 (C-6a), 79.43, 79.38 (C-5), 71.49, 71.40 (C-15), 68.72, 68.62 (C-16), 52.23, 52.07 (C-4), 43.28, 43.21 (C-3a), 37.59 (C-6), 36.18 (C-3), 28.91, 28.85, 28.81 (C-13, C-14), 21.13, 21.05 (*C*H_3CO) (See ESI 1.2.6.1.),

6: ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.22 (t, 1H, H-5', 8.1), 6.95 (ddd, 1H, H-4', 0.9, 2.1, 8.1), 6.90 (t, 1H, H-2', 2.1), 6.80 (dd, 1H, H-6', 2.2, 8.1), 5.06 (ddd, 1H, H-6a, 1.9, 5.8, 7.0), 4.99 (dt, 1H, H-5, 3.2, 5.2), 3.97 (t, 2H, H-16, 6.2), 2.91 (dd, 1H, H-3, 10.6, 18.1), 2.68 (m, 1H, H-3a), 2.49 (dd, 1H, H-3, 2.6, 18.1), 2.31 (dd, 1H, H-6, 5.6, 15.7), 2.24 (m, 1H, H-6), 2.05 (s, 3H, CH_3), 2.04 (m, 1H, H-4), 1.81 (dt, 2H, H-15, 6.2, 14.4), 1.62-1.28 (m, 4H, 2H-14, 2H-13), ^{13}C-NMR ($CDCl_3$, δ ppm): 176.85 (C-2), 170.54 (CH_3*C*O), 159.69 (C-1'), 134.89 (C-3'), 130.27 (C-5'), 120.88 (C-4'), 114.80 (C-2'), 113.05 (C-6'), 84.15 (C-6a), 79.71 (C-5), 67.70 (C-16), 52.28 (C-4), 43.22 (C-3a), 37.71 (C-6), 36.29 (C-3), 32.99 (C-15), 29.10 (C-13), 24.20 (C-14), 21.22 (*C*H_3CO) (See ESI 1.2.6.2.).

7: ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 4.96 (ddd, 1H, H-6a, 1.9, 5.9, 7.4), 4.88 (dt, 1H, H-5, 3.2, 5.1), 2.81 (dd, 1H, H-3, 10.7, 18.1), 2.59 (m, 1H, H-3a), 2.40 (dd, 1H, H-3, 2.8, 18.1), 2.31 (dd, 1H, H-6, 5.5, 15.7), 2.13 (m, 1H, H-6), 1.95 (s, 3H, CH_3), 1.90 (m, 1H, H-4), 1.30-1.15 (m, 6H, 2H-13, 2H-14, 2H-15), 0.83 (t, 3H, H-16, 6.8), ^{13}C-NMR ($CDCl_3$, δ ppm): 176.94 (C-2), 170.45 (CH_3*C*O), 84.16 (C-6a), 79.79 (C-5), 52.22 (C-4), 43.13 (C-3a), 37.61 (C-6), 36.22 (C-3), 32.90 (C-14), 29.63 (C-13), 22.58 (C-15), 21.12 (*C*H_3CO), 13.86 (C-16) (See ESI 1.2.6.3.).

1.2.7. Hydrolysis of the acetate groups of compound 5

5 (1.67 g, 3.93 mmol) was dissolved in methanol (50 mL), anh. K_2CO_3 (0.5 g) was added and the mixture was stirred overnight. TLC (III, $R_{f\ 5}$ = 0.77, $R_{f\ 2a}$ = 0.28) showed the end of the reaction. The solvent was distilled under reduced pressure, the residue was taken in water (15 mL) and ethyl acetate (30 mL), phases separated (aqueous phase was extracted with 30 mL ethyl acetate), unified phases were washed with brine (20 mL), dried ($MgSO_4$), concentrated and purified by LPC (ethyl acetate-hexane, 1:1), resulting 1.26 g (94.1%) of pure **2a** as an oil, with the same spectral data (IR, ^{1}H- and ^{13}C-NMR) as mentioned in 1.2.2.).

1.3. Hydrogenation of enone intermediates

1.3.1. Hydrogenation of 8a with greater amount of catalyst (16.7% catalyst / substrate)

Enone compound (±)-**8a** (1.22 g, 3.56 mmol), methanol (100 mL), *catalyst*† (200 mg, 16.67 % / **8a**), 3 atm H_2 for 1.5 h. TLC (IV, $R_{f\ 8a}$ = 0.39, $R_{f\ 9c}$ = 0.76). After filtration, concentration of the filtrate and crystallization of the crude product from ethyl acetate-hexane, 0.92 g (81.2 %) of crystallized compound (3aα,3bβ,6R,7aα,8aα)-6-methoxy-6-(phenoxymethyl)octahydrofuro[3',2':3,4]cyclopenta[1,2-b]pyran-2(3H)-one, **9c** were obtained as prisms, mp 165-168 ˚C, ^{1}H-NMR-300 MHz (DMSO-*d6*, δ ppm, *J* Hz): 7.28 (dd, 2H, H-*m*, 7.2, 8.8*)*, 6.82-6.92 (m, 3H, 2H-*o*, H-*p*), 4.87 (dt, 1H, H-6a, 4.1, 7.1), 4.06 (d, 1H, H-16, 10.3), 3.78 (d, 1H, H-16, 10.3), 3.53 (dt, 1H, H-11, 7.2, 11.1), 3.15 (s, 3H, CH_3), 2.74 (dd, 1H, H-3, 9.2, 18.1), 2.39 (dd, 1H, H-3, 1.5, 18.1), 2.46-2.26 (m, 2H, H-6, H-3a), 1.97 (m, 1H, H-14, 12.7), 1.82 (m, 1H, H-13), 1.62 (dd, 1H, H-14, 4.2, 12.7), 1.59-1.45 (m, 2H, H-6, H-13), 1.26 (dq, 1H, H-4, 3.5, 11.1), ^{13}C-NMR-75 MHz (DMSO-*d6*, δ ppm): 176.72 (C-2), 158.32 (C-1'), 129.49 (C-*m*), 120.84 (C-*p*), 114.59 (C-*o*), 98.88 (C-15), 80.84 (C-6a), 72.66 (C-5), 68.38 (C-16), 47.57 (CH_3O), 46.10 (C-4), 39.44 (C-3a) in DMSO, 36.16 (C-6), 32.03 (C-3 or C-14), 31.43 (C-14 or C-3), 22.40 (C-13) (See ESI 1.3.1.).

1.3.2. Hydrogenation of 8a with reduced amount of catalyst (3-4 % catalyst / substrate) and shorter reaction time

(±)-**8a** (3 g, 8.9 mmol), *catalyst*† (100 mg, 3.33 % / **8a**), methanol (140 mL), 3 atm H_2 for 15 min. TLC (I, $R_{f\ 8a}$ = 0.22, $R_{f\ 9a}$ = 0.62). The crude product crystalized from ethyl acetate-hexane, resulting 2.474 g (78.8%) (±)-(3aα,3bβ,6R,7aα,8aα)-6-((3-chlorophenoxy)methyl)-6-methoxyoctahydrofuro[3',2':3,4]cyclopenta[1,2-b]pyran-2(3H)-one, **9a**, mp 198.2-199.4 ˚C (benzene), mp 200.2-201.0 ˚C (ethyl acetate, then benzene) [another 0.49 g of pure compound were obtained by LPC purification of the product which had remained in mother liquors; total 94.4%], IR: 2946w, 2873w, 1757vs, 1596m, 1474s, 1436w, 1356w, 1287w, 1223m, 1168s, 1120s, 1093w, 1077m,

1062m, 1041m, 1023s, 986m, 941w, 880m, 762m, 678m, ^{1}H-NMR-500 MHz ($CDCl_3$, *δ* ppm, *J* Hz): 7.20 (t, 1H, H-5', 8.2), 6.96-6.93 (m, 2H, H-2', H-4'), 6.82 (dd, 1H, H-6', 1.8, 8.2), 4.90 (dt, 1H, H-6a, 4.3, 7.2), 4.06 (d, 1H, H-16, 9.9), 3.75 (d, 1H, H-16, 9.9), 3.60 (dt, 1H, H-5, 7.2, 11.2), 3.26 (s, 3H, CH_3), 2.71 (dd, 1H, H-3, 9.2, 18.2), 2.55 (dt, 1H, H-6, 7.2, 13.3), 2.42 (dd, H, H-3 1.0, 18.2), 2.33 (m, 1H, H-3a), 2.15 (m, 1H, H-14), 1.86 (m, 1H, H-13), 1.83 (dd, 1H, H-6, 4.3, 13.3), 1.69-1.56 (m, 2H, H-13, H-14), 1.39 (dq, 1H, H-4, 3.3, 11.2), ^{13}C-NMR-125 MHz ($CDCl_3$, *δ* ppm): 176.48 (C-2), 159.24 (C-1'), 134.91 (C-3'), 130.26 (C-5'), 121.40 (C-4'), 115.12 (C-2'), 113.06 (C-6'), **99.09 (C-15),** 81.16 (C-6a), 73.05 (C-5), 68.95 (C-16), 48.15 (CH_3O), 46.58 (C-4), 40.17 (C-3a), 36.47 (C-6), 32.57 (C-3), 32.02 (C-14), 22.82 (C-13) (See ESI 1.3.2.), MS 352.81 calcd. for $C_{18}H_{21}ClO_5$ $[M+1]^+$: th. 353.11503, found 353.1154 [105.07 (C_8H_9), 325.12 ($C_{17}H_{22}ClO_4$), 303.08 ($C_{17}H_{16}ClO_3$)].

1.3.3. Hydrogenation of 8b in methanol

8b (3.024 g, 10 mmol), *catalyst*† (120 mg, ~4 % / **8b**), methanol (140 mL), 3 atm H_2 for 25 min. TLC (I, $R_{f\ \mathbf{8b}}$ = 0.22, $R_{f\ \mathbf{9a}}$ = 0.54). The crude product was crystalized from ethyl acetate-hexane, resulting 2.316 g (73.2 %) [another 0.614 g of pure compound were obtained by LPC purification of the product which had remained in mother liquors; total 2.93 g, 92.6 %], (3aR,3bR,6R,7aR,8aS)-6-methoxy-6-phenethyloctahydrofuro[3',2':3,4]cyclopenta[1,2-b]pyran-2(3H)-one, **9b**, mp 163.2-166.7 ºC, $[\alpha]_D$ = 8.64 º (1% in THF), IR: 2939s, 2862w, 1757vs, 1709m, 1452m, 1201m, 1159s, 1114s, 1080m, 1043m, 1024s, 984m, 943m, 882m, 765m, 704m, ^{1}H-NMR-500 MHz ($CDCl_3$, *δ* ppm, *J* Hz): 7.26 (t, 2H, H-*m*, 7.5), 7.17 (d, 2H, H-*o*, 7.5), 7.16 (m, 1H, H-*p*), 4.85 (dt, 1H, H-6a, 4.4, 7.2), 3.50 (dt, 1H, H-5, 7.2, 11.1), 3.18 (s, 3H, CH_3), 2.68 (dd, 1H, H-3, 9.1, 18.1), 2.63 (m, 2H, H-17), 2.50 (dt, 1H, H-6, 7.2, 13.3), 2.37 (brd, 1H, H-3, 18.1), 2.26 (m, 1H, H-3a), 2.01 (dt, 1H, H-16, 5.3, 11.6), 1.93 (dt, 1H, H-14, 3.4, 12.4), 1.84 (m, 1H, H-16, 6.2, 11.6), 1.80 (m, 1H, H-13), 1.79 (m, 1H, H-16), 1.77 (dt, 1H, H-6, 4.4, 13.3), 1.58 (dq 1H, H-14, 3.5, 12.4), 1.50 (dt, 1H, H-13, 4.4, 13.0), 1.29 (dq, 1H, H-4, 3.3, 11.5), ^{13}C-NMR-125 MHz ($CDCl_3$, *δ* ppm): 176.50 (C2), 141.57 (Cq Ar), 128.21 (CH, C-*m*), 127.97 (C-*o*), 125.68 (C-*p*), 100.60 (C-15), 81.22 (C-6a), 79.90 (C-5), 47.15 (CH_3O), 46.32 (C-4), 39.99 (C-3a), 37.31 (C-16), 36.41 (C-6), 32.45, 32.40 (C-3, C-14), 29.73 (C-17), 22.92 (C-13) (See ESI 1.3.3.), MS 316.39 calcd. for $C_{19}H_{24}O_4$ $[M+1]^+$: th. 317.17474, found 317.17425 [239.14 ($C_{13}H_{19}O_4$), 267.14 ($C_{18}H_{19}O_2$), 105.07 (C_8H_9), 225.12 ($C_{16}H_{17}O$)].

1.3.4. Hydrogenation of 8a in ethanol

(±)-8a (3 g, 8.9 mmol), *catalyst*† (100 mg, 3.33 % / **8a**), ethanol (140 mL), 3 atm H_2 for 25 min. TLC (I, $R_{f\ \mathbf{8a}}$ = 0.22, $R_{f\ \mathbf{9a}}$ = 0.72) showed the presence of a single product. The crude product crystalized from ethyl acetate-hexane, resulting 1.85 g (56.6 %) (another 1.1 g of pure compound were obtained by LPC purification of the product present in mother liquors; total 90.4 %), **9d**, (3aα,3bβ,6R,7aα,8aα)-6-((3-chlorophenoxy)methyl)-6-ethoxyoctahydrofuro[3',2':3,4]cyclopenta[1,2-b]pyran-2(3H)-one**,** mp 123.5-126.9˚C (ethyl acetate-hexane)**,** IR: 2970m, 2928m, 2885w, 2863w, 1771vs, 1595m, 1576w, 1487w, 1465w, 1274w, 1256s, 1221w, 1205w, 1175s, 1119m, 1072w, 1043m, 1025s, 982s, 886m, 870m, 765w, ^{1}H-NMR-300 MHz ($CDCl_3$, *δ* ppm, *J* Hz): 7.20 (t, 1H, H-5', 8.1), 6.95 (brd, 1H, H-4', 8.1), 6.93 (brs, 1H, H-2'), 6.82 (brd, 1H, H-6', 8.2), 4.90 (dt, 1H, H-6a, 4.3, 7.1), 4.04 (d, 1H, H-16, 9.8), 3.77 (d, 1H, H-16, 9.8), 3.60 (dt, 1H, H-5, 7.3, 11.0), 3.54 (q, 2H, CH_2CH_3, 7.1), 2.72 (dd, 1H, H-3, 9.1, 18.2), 2.54 (dt, 1H, H-6, 7.2, 13.3), 2.42 (d, H, H-3 18.2), 2.34 (m, 1H, H-3a), 2.16 (m, 1H, H-14), 1.89-1.78 (m, 2H, H-6, H-13), 1.67 (m, 1H, H-14), 1.59 (dt, 1H, H-13, 4.2, 12.6), 1.38 (dq, 1H, H-4, 3.1, 11.1), 1.20 (t, 3H, CH_3, 7.1), ^{13}C-NMR-75 MHz ($CDCl_3$, *δ* ppm): 176.54 (C-2), 159.26 (C-1'), 134.86 (C-3'), 130.24 (C-5'), 121.31 (C-4'), 115.09 (C-2'), 113.04 (C-6'), **99.08 (C-15),** 81.21 (C-6a), 73.20 (C-5), 69.66 (C-16), 55.86 (CH_2CH_3), 46.66 (C-4), 40.15 (C-3a), 36.50 (C-6), 32.58 (C-3), 32.18 (C-14), 22.83 (C-13), 15.41 (CH_3) (See ESI 1.3.4.), MS 366.84 calcd. for $C_{19}H_{23}ClO_5$ $[M+1]^+$: th. 367.13068, found 367.13088 [303.08 ($C_{17}H_{16}ClO_3$), 275.08 ($C_{16}H_{16}ClO_2$), 105.07 (C_8H_9), 163.08 ($C_{10}H_{11}O_2$), 147.08 ($C_{10}H_{11}O$)].

1.3.5. Hydrogenation of 8a in ethyl acetate at atmosphere pressure of hydrogen

a) **(±)-8a** (14.15 g, 42 mmol), *catalyst*† (2 g, 14.2 % / **8a**), ethyl acetate (200 mL) H_2 (atm. pressure), TLC (IV, $R_{f\ in}$ = 0.27, $R_{f\ \mathbf{12a}}$ = 0.33, $R_{f\ \mathbf{13a}}$ = 0.74). The catalyst was filtered off, the filtrate was concentrated and the crude product was purified by LPC (benzene-ethyl acetate, 2:1), after a time at rt, resulting 2.3 g (16.2 %) cyclized semiketal (3aα,3bβ,6R,7aα,8aα)-6-((3-chlorophenoxy)methyl)-6-hydroxyoctahydrofuro[3',2':3,4]cyclopenta[1,2-b]pyran-2(3H)-one **13a**, ^{1}H-NMR-300 MHz (DMSO-*d6*, *δ* ppm, *J* Hz): 7.29 (t, 1H, H-5', 8.2), 7.02 (t, 1H, H-2', 2.2), 6.99 (ddd, 1H, H-4', 0.9, 2.2, 8.2), 6.92 (ddd, 1H, H-6', 0.9, 2.2, 8.2), 6.00 (s, 1H, OH), 4.87 (dt, 1H, H-6a, 4.4, 7.3), 3.84 (s, 2H, H-16), 3.81 (dt, 1H, H-5, 7.2, 11.3), 2.74 (dd, 1H, H-3, 10.2, 17.9), 2.49-2.20 (m, 4H, H-3a, H-3, 2H-14), 1.70-1.12 (m, 5H, H-4, 2H-6, 2H-13), ^{13}C-NMR-75 MHz (DMSO-*d6*, *δ* ppm): 176.79 (C-2), 159.58 (C-1'), 133.67 (C-3'), 130.83 (C-5'), 120.63 (C-4'), 114.78 (C-2'), 113.75 (C-6'), **96.12 (C-15),** 81.05 (C-6a), 73.99 (C-16), 72.39 (C-5), 46.48 (C-4), 40.21 (C-3a), 36.33 (C-6), 32.08 (C-3), 30.90 (C-14), 22.38 (C-13) (See ESI 1.3.5.2.),

and 11.78 g (82.8 %) (3aα,3bβ,6R,7aα,8aα)-4-(4-(3-chlorophenoxy)-3-oxobutyl)-5-hydroxyhexahydro-2H-cyclopenta[b]furan-2-one **12a**, mp 110-114 ˚C, ^{1}H-NMR-300 MHz (DMSO-*d6*, *δ* ppm, *J* Hz): 7.29 (t, 1H, H-5', 8.4), 7.02-6.98 (m, 2H, H-2', H-4'), 6.88 (ddd, 1H, H-6', 1.0, 2.4, 8.4), 4.88 (s, 2H, H-16), 4.86 (dt, 1H, H-6a, 3.0, 7.1), 3.74 (cv, 1H, H-5, 5.6), 3.38 (OH is in water) [4.88 for DMSO without water], 2.78 (dd, 1H, H-3, 10.2, 17.9), 2.60 (t, 2H, H-14, 7.3), 2.43 (m, 1H, H-3a), 2.33 (dd, 1H, H-3, 2.7, 17.9), 2.23 (dt, 1H, H-6, 6.8, 14.3), 1.69 (ddd, 1H, H-6, 3.0, 6.0, 14.3), 1.61-1.42 (m, 3H, H-4, 2H-13), ^{13}C-NMR-75 MHz (DMSO-*d6*, *δ* ppm): 205.46 (C-15), 177.05 (C-2), 158.78 (C-1'), 133.65 (C-3'), 130.76 (C-5'), 120.86 (C-4'), 114.56 (C-2'), 113.61 (C-6'), 82.91 (C-6a), 75.75 (C-5), 71.87 (C-16), 52.11 (C-4), 41.93 (C-3a), 40.18 (C-6) in DMSO, 36.11 (C-3), 35.10 (C-14), 25.30 (C-13).

b) **(-)-8a** (717 mg, 3 mmol), *catalyst*† (38 mg, 5.3 % / **8a**), ethyl acetate (50 mL), $NaHCO_3$ (50 mg), 3 atm H_2 for 50 min, TLC (I, $R_{f\ in}$ = 0.31, $R_{f\ \mathbf{12a}}$ = 0.31). LPC (ethyl acetate-hexane, 1:1) gave a pure fraction of 678 mg (94.0 %) of pure compound (3aR,3bR,6R,7aR,8aS)-6-((3-chlorophenoxy)methyl)-6-hydroxyoctahydrofuro[3',2':3,4]cyclopenta[1,2-b]pyran-2(3H)-one (-)-**12a** as an oil, $[\alpha]_D$ = -12.9 ˚ (1% in THF), IR: 3480m, 2962w, 2912m, 2884w, 1753vs, 1719s, 1589s, 1470m,1308w, 1290m, 1231m, 1180s, 1074m, 1027s, 951w, 892w, 849w, 758m, 678w, ^{1}H-NMR-300 MHz (DMSO-*d6*, *δ* ppm, *J* Hz): 7.29 (t, 1H, H-5', 8.4), 7.01-6.99 (m, 2H, H-2', H-4'), 6.88 (ddd, 1H, H-6', 0.9, 2.4, 8.4), 4.88 (s, 2H, H-16), 4.85 (t, 1H, H-6a, 6.7), 3.74 (cv, 1H, H-5, 5.9), 2.78 (dd, 1H, H-3, 10.2, 17.9), 2.60 (t, 2H, H-14, 7.2), 2.45 (m, 1H, H-3a), 2.34 (dd, 1H, H-3, 2.8, 17.9), 2.24 (dt, 1H, H-6, 6.7, 14.3), 1.69 (ddd, 1H, H-6, 2.9, 5.9, 14.3), 1.62-1.42 (m, 3H, H-4, 2H-13), ^{13}C-NMR-75 MHz (DMSO-*d6*, *δ* ppm): 205.50 (C-15), 177.16 (C-2), 158.79 (C-1'), 133.67 (C-3'), 130.81 (C-5'), 120.85 (C-4'), 114.52 (C-2'), 113.64 (C-6'), 82.97 (C-6a), 75.82 (C-5), 71.81 (C-16), 52.13 (C-4), 41.94 (C-3a), 40.20 (C-6),

36.12 (C-3), 35.15 (C-14), 25.30 (C-13) (See ESI 1.3.5.1.), MS 338.78, $C_{17}H_{19}ClO_5$, calcd for $[M+1]^+$: th 339.09938, found 339.09987 [137.06 ($C_8H_9O_2$), 107.05 (C_7H_7O), 321.09 ($C_{17}H_{18}O_4Cl$), 125.09 ($C_7H_9O_2$)].

1.3.6. Hydrogenation of 8a in isopropanol

(±)-**8a** (1.53 g, 4.52 mmol), *catalyst*[†] (153 mg, 10% / **8a**), isopropanol (150 mL), 3 atm H_2 for 20 min. TLC (I, $R_{f\ \mathbf{12a}}$ = 0.31) showed the presence of a single product. The solvent was distilled under reduced pressure, the product was crystallized from benzene, resulting 1.27 g (63.2%) (±)-**12a**, mp 110-114 ˚C. By LPC purification of the mother liquors, another 0.63 g of pure product were obtained (total yield 94.5 %).

1.3.7. Hydrogenation of 8b in ethyl acetate

The hydrogenation of (-)-**8b** (3 mmol, 907 mg) was performed as for (-)-**8a**, example 2.5, with 45 mg *catalyst*[†] (5% / (-)-**8b**)), resulting 866 mg (94.8%) (3aR,4R,5R,6aS)-5-hydroxy-4-(3-oxo-5-phenylpentyl)hexahydro-2H-cyclopenta[b]furan-2-one, **12b** as an oil, $[\alpha]_D$ = -30.7 ˚ (1% in THF), IR: 3456brm, 2933m, 1760vs, 1707vs, 1496w, 1453w, 1413w, 1369m, 1175s, 1074m, 1033m, 909m, 727s, 609m, ^{1}H-NMR- 500 MHz ($CDCl_3$, δ ppm, J Hz): 7.27 (m, 2H, 2H-*m*, 7.2), 7.18 (t, 1H, H-*p*, 7.2), 7.17 (d, 2H, H-*o*, 7.2), 4.89 (dt, 1H, H-6a, 2.4, 7.0), 3.89 (q, 1H, H-5, 5.5), 3.10 (brs, OH), 2.88 (t, 2H, H-17, 7.4), 2.74 (m, 1H, H-3, 18.0), 2.73 (m, 1H, H-3), 2.73 (dt, 2H, H-16, 10.7, 7.4), 2.48 (t, 2H, H-14, 7.2), 2.44-2.38 (m, 2H, H-3, H-3a), 2.28 (dt, 1H, H-6, 6.3, 15.0), 1.97 (ddd, 1H, H-6, 2.4, 5.5, 15.0), 1.69 (qv, 1H, H-4, 6.1), 1.55 (q, 2H, H-13, 7.2), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 209.77 (CO, C-15), 177.15 (C-2), 140.83 (C-1'), 128.51, 128.36 (2C-*o*, 2C-*m*), 126.20 (C-*p*), 83.27 (C-6a), 77.16 (C-5), 52.83 (C-4), 44.27 (C-16), 42.92 (C-3a), 40.64, 40.58 (C-6, C-14), 35.49 (C-3), 29.78 (C-17), 25.78 (C-13) (See ESI 1.3.6.), MS 302.37, $C_{18}H_{22}O_4$, calcd for $[M+1]^+$: th 303.15909, found 303.15947 [105.07 (C_8H_9), 285.1 ($C_{18}H_{21}O_3$), 133.06 (C_9H_9O), 141.0 ($C_7H_9O_3$)].

1.3.8. Hydrogenation of enone 14

a) 9.6 % catalyst / substrate, 3 atm H_2 for 45 min: ***ent*-14** (1.044 g, 2.94 mmol), *catalyst*[†] (100 mg, 9.6 % / ***ent*-14**), $NaHCO_3$ (200 mg), ethyl acetate (100 mL), 3 atm H_2 for 45 min, TLC [IV, $R_{f\ \mathbf{14}}$ = $R_{f\ \mathbf{15}}$ = 0.78, (**15** is yellow **14** orange) and turns black harder in oven]. By LPC (ethyl acetate-hexane, 1:1), a pure fraction of 920 mg (88.1 %) of (1R,5R,6R,8R)-6-chloro-8-(4-(3-chlorophenoxy)-3-oxobutyl)-2-oxabicyclo[3.2.1]octan-3-one **15** was obtained as an oil, $[\alpha]_D$ = 38.3 ˚(1% in THF), IR:2927w, 1728vs, 1593s, 1478s, 1430m, 1364m, 1285w, 1230m, 1184m, 1161s, 1073m, 1031s, 885w, 857w, 771w, 680w, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, J Hz): 7.24 (t, 1H, H-5'', 821), 7.00 (d, 1H, H-4'', 8.2), 6.91 (brs, 1H, H-2''), 6.78 (dd, 1H, H-6'',1.9, 8.2), 4.70 (s, 1H, H-1), 4.56 (s, 2H, H-16), 4.25 (dd, 1H, H-6, 4.4, 8.0), 2.96 (dd, 1H, H-7, 8.0, 16.5), 2.77-2.62 (m, 5H, H-5, 2H-4, 2H-14), 2.46 (dt, 1H, H-7, 4.3, 16.5), 2.23 (t, 1H, H-8, 7.7), 1.95 (q, 2H, H-13, 7.4), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 206.15 (C-15), 168.15 (C-3), 158.22 (C-1''), 135.25 (C-3''), 130.59 (C-5''), 122.21 (C-4''), 115.15 (C-2''), 112.73 (C-6''), 84.03 (C-1), 72.81 (C-16), 59.30 (C-6), 47.28 (C-8), 45.68 (C-5), 44.12 (C-7), 40.75 (C-14), 36.65 (C-4), 22.64 (C-13) (See ESI 1.3.7.1.), MS 357.23, $C_{17}H_{18}Cl_2O_4$, $[M+1]^+$: th. 357.06549, found 357.06592 [165.01 (C_9H_6OCl), 243.06 ($C_{15}H_{12}OCl$), 191.07 ($C_{11}H_{11}O_3$)].

b) 13.3 % catalyst / substrate, atm. pressure H_2, 4 h: **14** (391 mg, 1.22 mmol), *catalyst*[†] (52 mg, 13.3 % / **14**), ethyl acetate (20 mL), $NaHCO_3$ (90 mg), atm pressure H_2 for 4 h, TLC (I, $R_{f\ \mathbf{14}}$ = 0.53, $R_{f\ \mathbf{15}}$ = 0.55). LPC (eluent: ethyl acetate-hexane, 1:1). 325 mg of a product containing ~ 60% **15** and ~ 40% **16** (Y = H), according with NMR, were obtained as an oil: IR:2958w, 1729vs, 1593s, 1479s, 1432m, 1365m, 1286w, 1230m, 1188m, 1161s, 1075w, 1032s, 885w, 858w, 756m, 681m, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, J Hz) etalon $CHCl_3$: 7.31 (t, 2H, H-*m*, 7.6), 7.23 (t, 1H, H-5'', 8.1), 7.01 (7, 1H, H-*p*, 7.6), 7.00 (d, 1H, H-4'', 8.1), 6.90 (s, 1H, H-2''), 6.89 (d, 2H, H-*o*, 7.6), 6.78 (d, 1H, H-6'', 8.1), 4.69 (s, 1H, H-1), 4.56 (s, 2H, H-16), 4.23 (m, 1H, H-6), 2.94 (dd, 1H, H-7, 6.1, 15.5), 2.85-2.72 (m, 4H, 2H-2', 2H-4), 2.67 (d, 1H, H-5, 4.9), 2.47 (d, 1H, H-7, 15.5), 2.22 (m, 1H, H-8, 5.7), 1.98-1.80 (m, 2H, H-1'), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): *207.2 (C-15Ph),* 206.11 (C-15), 168.28, 168.22 (C-3), 158.18 (C-1''), *157.50 (C-1Ph),* 135.17 (C-3''), 130.55 (C-5''), *129.77 (C-m)*, 122.14 (C-4''), *121.90 (C-p),* 115.11 (C-2''), *114.38 (C-o)*, 112.73 (C-6''), 84.04 (C-1), 72.15 (C-16), 59.28 (C-6), 47.21 (C-8), 45.60 (C-5), 44.07 (C-7), 40.70 (C-14), 36.60 (C-4), 22.59 (C-13) (See ESI 1.3.7.2.); italic for signals of **15**, MS for **16**: 322.78, $C_{17}H_{19}ClO_4$, $[M+1]^+$: th. 323.10446, found 323.10444 [107.05 (C_7H_7O), 131.05 (C_9H_7O), 209.09 ($C_{15}H_{13}O$)].

2. Hydrogenations with a reduced amount of 10% Pd/C catalyst (1-3 % based on the substrate)

2.1. Hydrogenation of 1a:

1a (4.5 g, 13.28 mmol), ethyl acetate (150 mL), *catalyst*[†] (70 mg, 1.56 % / **1a**), 3 atm H_2 for 50 min. By crystallization of the crude product from benzene, 1.95 g (43.3 %) **2a** were obtained. From mother liquors, by LPC (eluent: toluene-methanol, 9:1), another 1.63 g of pure **2a** (total yield: 79.2 %) were obtained.

2.2. Hydrogenation of Ic

Ic (1 mmol, 302 mg), *catalyst*[†] (5.3 mg, 1.75 %/ **Ic**), methanol (50 mL), 3 atm H_2 for 2 h; LPC (ethyl acetate-heptane, 1:1), resulting 13.2 mg **IId** and 267 mg (88.5 %) of pure compound **IIc** as an oil, IR: 3396brs, 2934s, 2862m, 1749vs, 1456m, 1417w, 1365w, 1179s, 1076m, 1032s, 971w, 899w, 750w, 702m, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, J Hz): 7.28 (br t, 2H, H-*o*, 8.0), 7.22-7.17 (m, 3H, 2H-m, 1H-p), 4.93 (dt, 1H, H-6a, 1.9, 6.8), 3.98 (q, 1H, H-5, 5.1), 3.61 (m, 1H, H-15), 2.78 (dd, 1H, H-3, 11.0, 18.3), 2.73 (dt, 1H, H-17, 8.1, 14.4), 2.63 (m, 1H, H-17), 2.50 (m, 1H, H-3a), 2.50 (d, 1H, H-3, 18.3), 2.28 (dt, 1H, H-6, 6.2, 15.0), 2.01 (brd, 1H, H-6, 15.0), 1.83-1.73 (m, 3H, H-4, 2H-16), 1.57-1.45 (m, 3H, H-13, 2H-14), 1.27 (m, 1H, H-13), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 177.82 (C-2), 141.84 (C-1'), 128.43, 128.35 (2C-*o*, 2C-*m*), 125.89 (C-*p*), 83.99 (C-6a), 77.37 (C-5), 71.26 (C-15), 53.86 (C-4), 43.14 (C-3a), 40.37 (C-6), 39.05 (C-16), 35.98 (C-3), 35.16 (C-14), 32.00 (C-17), 28.90 (C-13).

2.3. Hydrogenation of 8a in ethyl acetate

8a (2.0 g, 5.94 mmol), ethyl acetate (150 mL), *catalyst*[†] (20 mg, 1 % / **8a**), 3 atm. H_2, 60 min; by crystallization from benzene, 1.26 g (62.6 %) **12a** were obtained, mp 110-114 ˚C. From mother liquors, a pure fraction of 0.62 g **12a** was also obtained (total yield 93.5 %).

2.4. Hydrogenation of 8a in isopropanol

(±)-8a (2.0 g, 5.94 mmol), isopropanol (150 mL), *catalyst*[†] (40 mg, 2 % /**8a**), 3 atm. H_2, 75 min; by crystallization from benzene, 1.27 g (63.1 %) (±)-**12a** were obtained. From mother liquors, a pure fraction of 0.59 g **12a** was also obtained (total yield 92.4%).

2.5. Hydrogenation of 8a in methanol

Intermediate (±)-**8a** (4.0 g, 11.88 mmol), methanol (150 mL), *catalyst*[†] (40 mg, 1 % / **8a**), 3 atm. H_2, 50 min; by crystallization from methanol, 3.0 g (71.6 %) (±)-**9a** were obtained, mp 192-196 ˚C. From mother liquors, by LPC (eluent, benzene-acetone, 9:1), 1.18 g (±)-**9a** were obtained (total yield 95.5 %).

2.6. Hydrogenation of 8b in isopropanol

8b (1.8 g, 6 mmol), isopropanol (150 mL), *catalyst*$^{+}$ (40 mg, 2.2 % / **8b**), 3 atm. H_2, 75 min; LPC (hexane-ethyl acetate, 2:1) gave 1.69 g (93.2 %) of pure (-)-**12b**, as an oil.

2.7. Hydrogenation of 10b-1

10b-1 (10 g, 24.7 mmol), THF (150 mL), 5% Pd/C (0.5 g, equivalent to 0.25 g *catalyst*$^{+}$, 2.5% catalyst / **10b-1**), 6 atm H_2 until the reaction ended in TLC (ethyl acetate-methanol, 90:13, $R_{f\ \mathbf{10b\text{-}1}}$ = 0.42, $R_{f\ \mathbf{11b\text{-}1}}$ = 0.36). The crude product was crystallized from ethyl acetate-hexane, as needle, giving in almost quantitative yield (3aR,4R,5R,6aS)-2-oxo-4-(3-oxo-5-phenylpentyl)hexahydro-2H-cyclopenta[b]furan-5-yl benzoate, **11b-1**, mp 77.2-77.8 ˚C, $[\alpha]_D$ = -87.1 ˚(1% in THF), IR: 3025w, 2992w, 2951w, 1750s, 1706vs, 1601w, 1495w1449w, 1359w, 1316w, 1276s, 1111m, 1064m, 1043m, 1027m, 999m, 710m: ^{1}H-NMR- 500 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.97 (d, 2H, H-*o*Bz, 7.7), 7.56 (t, 1H, H-*p*Bz, 7.7), 7.44 (t, 2H, H-*m*Bz, 7.7), 7.26 (t, 2H, 2H-*m*, 7.2), 7.17 (t, 1H, H-*p*, 7.2), 7.16 (t, 2H, H-*o*, 7.2), 5.16 (dt, 1H, H-5, 2.6, 5.4), 5.07 (t, 1H, H-6a, 6.5), 2.90-2.84 (m, 2H, H-17), 2.87 (dd, 1H, H-3, 10.7, 18.1), 2.75 (brt, 2H, H-16, 7.4), 2.63 (m, 1H, H-3a), 2.56 (t, 2H, H-14, 7.21), 2.45 (dd, 1H, H-3, 3.3, 18.1), 2.41 (dt, 1H, H-6, 6.5, 15.9), 2.32 (brd, 1H, H-3, 15.9), 2.06 (m, 1H, H-4), 1.70 (cv, 1H, H-13, 6.9), 1.61 (cv, 1H, H-13, 6.9), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 208.91 (CO, C-15), 176.63 (C-2), 165.97 (COO), 140.80 (C-1'), 133.31 (C-*o*Bz), 129.56 (C-*p*Bz), 128.52, 128.46, 128.28 (2C-*o*, 2C-*m*, 2C-*m*-Bz), 126.13 (C-*p*), 84.29 (C-6a), 79.736 (C-5), 52.27 (C-4), 44.30 (C-16), 43.72 (C-3a), 40.52, (C-14), 37.58 (C-6), 36.14 (C-3), 29.69 (C-17), 26.67 (C-13) (See ESI 2.7.), MS 406.47, $C_{25}H_{26}O_5$, calcd for $[M+1]^+$: th 407.1853, found 407.18628 [105.07 (C_8H_9), 299.13 ($C_{18}H_{19}O_4$), 161.1 ($C_{11}H_{13}O$), 159.08 ($C_{11}H_{11}O$), 145.06 ($C_{10}H_9O$)].

2.8. Hydrogenation of compound 10a-1.

*Synthesis of **10a-1***: (±)-**8a** (6.8 g, 20 mmol) was dissolved in pyridine (30 mL), the solution was cooled on an ice-bath, 96% benzoyl chloride (2.9 mL, 24 mmol) was added dropwise and stirred overnight. TLC (I, $R_{f\ \mathbf{in}}$ = 0.35, $R_{f\ \mathbf{fin}}$ = 0.51) showed the end of the reaction, the reaction mixture was poured under stirring on crashed-ice for 1 h, the product was extracted with ethyl acetate (2×100 mL) the unified organic phases were washed with sat son. $NaHCO_3$, (100 mL) brine (100 mL), dried (Na_2SO_4) and concentrated under reduced pressure. The crude product was purified by LPC (eluent: benzene) resulting a pure fraction of 8.3 g (94.1%) as an oil.

*Hydrogenation of the intermediate **10a-1** in ethyl acetate:* Intermediate **10a-1** (1.33 g, 3.01 mmol), ethyl acetate (150 mL), *catalyst*$^{+}$ (15 mg, 1.13 % / **10a-1**), 3 atm. H_2, 135 min, TLC (I, $R_{f\ \mathbf{10a\text{-}1}}$ = 0.51, $R_{f\ \mathbf{11a\text{-}1}}$ = 0.51). By crystallization from ethanol, 1.17 g (88.0 %) (3aα,4β,5α,6aα)-4-(4-(3-chlorophenoxy)-3-oxobutyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl benzoate (±)-**11a-1** were obtained, mp 92-94 ˚C (from ethyl acetate-hexane, mp 97.8-99.3 ˚C), IR: 2944w, 2927w, 2861w, 1764s, 1723vs, 1595m, 1483m, 1429m, 1313m, 1271s, 1251s, 1171s, 1109m, 1071m, 1045m, 1027m, 913m, 895m, 780m, 709s, 682m, ^{1}H-NMR-500 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.98 (d, 2H, H-*o*, 7.4), 7.55 (t, 1H, H-*p*, 7.4), 7.42 (t, 2H, H-*m*, 7.4), 7.18 (t, 1H, H-5', 8.1), 6.96 (brd, 1H, H-4', 8.1), 6.84 (brt, 1H, H-2', 1.8), 6.73 (dd, 1H, H-6', 1.8, 8.1), 5.19 (dt, 1H, H-5, 3.1, 5.7), 5.09 (t, 1H, H-6a, 6.1), 4.56 (s, 2H, H-16), 2.90 (dd, 1H, H-3, 10.4, 18.3), 2.83-2.78 (m, 2H, H-14), 2.67 (m, 1H, H-3a), 2.49 (d, 1H, H-3, 18.3), 2.45 (dt, 1H, H-6, 5.9, 14.7), 2.33 (brd, 1H, H-6, 14.7), 2.12 (m, 1H, H-4), 1.80 (m, 1H, H-13), 1.67 (m, 1H, H-13), ^{13}C-NMR-100 MHz ($CDCl_3$, δ ppm): 205.93 (CO, C-15), 176.51 (C-2), 166.02 (C_6H_5CO), 158.25 (C-1'), 135.06 (C-3'), 133.36 (C-*p*), 130.44 (C-5'), 129.57 (C-*o*), 129.41 (Cq, Bz), 128.52 (C-*m*), 121.99 (C-4'), 115.11 (C-2'), 112.78 (C-6'), 84.17 (C-6a), 79.62 (C-5), 72.71 (C-16), 52.02 (C-4), 43.83 (C-3a), 37.58 (C-6), 36.67 (C-3), 36.08 (C-14), 26.02 (C-13) (See ESI 2.8.), MS 442.89, $C_{24}H_{23}ClO_6$, calcd for $[M+1]^+$: th 443.12559, found 443.12622 [415.2 ($C_{23}H_{24}ClO_6$), 321.09 ($C_{17}H_{18}ClO_4$), 105.03 (C_7H_5O), 121.08 ($C_7H_5O_2$)].

2.9. Hydrogenation of the intermediate 10a-2 in ethyl acetate

*Synthesis of 31-Ac **10a-2** (R = CH_3):* (±)-**8a** (6.8 g, 20 mmol), pyridine (30 mL), acetic anhydride (3 mL), stirred overnight. TLC (I, $R_{f\ \mathbf{8a}}$ = 0.35, $R_{f\ \mathbf{10a\text{-}2}}$ = 0.61); the reaction mixture was processed as above, the crude product was purified by LPC (eluent: benzene) resulting a pure fraction of 7.3 g (96.5%) (3aα,4β,5α,6aα)-4-((E)-4-(3-chlorophenoxy)-3-oxobut-1-en-1-yl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl acetate, **10a-2**, as an oil, ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.23 (t, 1H, H-5', 8.1), 7.00 (ddd, 1H, H-4', 0.9, 2.0, 8.1), 6.90 (t, 1H, H-2', 2.0), 6.78 (ddd, 1H, H-6', 0.9, 2.0, 8.1), 6.84 (dd, 1H, H-13, 7.9, 15.7), 6.51 (dd, 1H, H-14, 1.1, 15.7), 5.05 (m, 1H, H-6a, 5.3), 5.01 (td, 1H, H-5, 2.1, 6.6), 4.68 (s, 2H, H-16), 2.90-2.70 (m, 3H, H-3, H-3a, H-4), 2.50 (dt, 1H, H-6, 6.6, 15.3), 2.40 (m, 1H, H-3), 2.15 (ddd, 1H, H-6, 2.1, 5.3, 15.3), 2.02 (s, 3H, CH_3), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 194.47 (C-15), 175.46 (C-2), 170.12 (CO-Ac), 158.37 (C-1'), 145.43 (C-13), 135.17 (C-3'), 130.48 (C-5'), 126.43 (C-14), 122.13 (C-4'), 115.25 (C-2'), 112.97 (C-6'), 82.66 (C-6a), 77.71 (C-5), 72.26 (C-16), 53.81 (C-4), 42.48 (C-3a), 37.70 (C-6), 34.65 (C-3), 20.79 (CH_3CO) (See ESI 2.9.1.).

*Hydrogenation of (±)-**10a-2** in ethyl acetate:* (±)**10a-2** (2.59 g, 6.8 mmol), *catalyst*$^{+}$ (130 mg, 5 % / **10a-2**), ethyl acetate (150 mL), 3 atm H_2 for 30 min; TLC (I, $R_{f\ \mathbf{10a\text{-}2}}$ = 0.61, $R_{f\ \mathbf{11a\text{-}2}}$ = 0.52; VI, $R_{f\ \mathbf{11a\text{-}2}}$ = 0.28) showed only one product; 2.53 g (97.7 %) (3aα,4β,5α,6aα)-4-(4-(3-chlorophenoxy)-3-oxobutyl)-2-oxohexahydro-2H-cyclopenta[b]furan-5-yl acetate (±)-**11a-2** were obtained as an oil, after work-up of the reaction mixture), ^{1}H-NMR-300 MHz ($CDCl_3$, δ ppm, *J* Hz): 7.22 (t, 1H, H-5', 8.2), 7.00 (dd, 1H, H-4', 1.9, 8.2), 6.90 (t, 1H, H-2', 1.9), 6.78 (dd, 1H, H-6', 2.2, 8.2), 5.03 (dt, 1H, H-6a, 1.6, 6.4), 4.90 (dt, 1H, H-5, 3.0, 5.4), 4.57 (s, 2H, H-16), 2.87 (dd, 1H, H-3, 10.6, 18.2), 2.80-2.69 (m, 2H, H-14), 2.63 (m, 1H, H-3a), 2.45 (d, 1H, H-3, 18.2), 2.01 (s, 3H, CH_3CO), 2.32 (dt, 1H, H-6, 5.7, 15.7), 2.20 (m, 1H, H-6), 2.01 (s, 3H, CH_3), 1.98 (m, 1H, H-4), 1.80-1.58 (m, 3H, H-14, 2H-13), ^{13}C-NMR-75 MHz ($CDCl_3$, δ ppm): 205.95 (C-15), 176.36 (C-2), 170.46 (CO-Ac), 158.37 (C-1'), 135.23 (C-3'), 130.54 (C-5'), 122.16 (C-4'), 115.17 (C-2'), 112.89 (C-6'), 83.85 (C-6a), 79.14 (C-5), 72.84 (C-16), 51.73 (C-4), 43.56 (C-3a), 37.65 (C-6), 37.49 (C-14), 36.60 (C-3), 36.06 (C-13), 21.06 (CH_3CO) (See ESI 2.9.2.).

In the same conditions, with only 27 mg *catalyst*$^{+}$ (1 % / **10a-2**), and 135 min hydrogenation time, the yield of 94.7% (2.45 g) of (±)-**11a-2**.

2.10. Hydrogenation of 14 in ethyl acetate

(±)-**14** (3.0 g, 8.4 mmole), ethyl acetate (150 mL), *catalyst*$^{+}$ (30 mg, 1 % / **14**), 3 atm. H_2, 50 min, TLC (IV, $R_{f\ \mathbf{14}}$ = 0.34, $R_{f\ \mathbf{15}}$ = 0.37). By crystallization from methanol, 2.72 g (90.7 %) (±)-**15** were obtained, mp 95-96 ˚C, with the same IR and NMR presented at 2.7. From mother liquors, 0.12 g (±)-**15** were obtained (total yield: 94.7 %).

Conclusions

The hydrogenation of the 13,14-double bond of allylic alcohol and enone intermediates from the synthesis of 17-phenyl- or

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16-(3-substituted-phenoxzy)-prostaglandins was studied. In the reaction, the *allylic alcohols* gave, besides the main 13,14 hydrogenated compounds, the 15-desoxy-13,14 hydrogenated byproducts in a large quantity which increases with the amount of catalyst, the hydrogen pressure, and the reaction time. The *m*-chloro-phenoxy intermediate **1a** was also dehydrohalogenated to the phenoxy-compound **2c** under these forced reaction conditions. The protection of the 5,15-hydroxyl groups as THP, TBDMS, benzoate, increased the yield of the 13,14-hydrogenated-17-phenyl compound **IIg-IIh** to nearly 100%. Hydrogenation of *enone intermediates* **8** in ethyl acetate, isopropanol, tetrahydrofuran gave the chemo-selectively desired 13,14-hydrogenated ketone compounds **12**. In the case of the *m*-chloro-phenoxy compound, **12a** is transformed in time into the cyclized semi-ketal **13a**. In methanol and ethanol, the hydrogenated ketone is transformed almost quantitatively in an acid catalyzed (by traces of HCl in the catalyst) reaction to the six-atom cyclized ketals with methoxy and ethoxy groups in two consecutive chemo-selective reactions (13,14-hydrogenation, followed by intramolecular addition of 5-OH, concomitant with the alcohol from the solvent, to the 15-ketone). A dehydrohalogenated cyclized ketal **9c** was also obtained from **8a**, when increased amount of the catalyst, pressure of hydrogen and reaction time were used. Generally, the hydrogenation of enones was easier than that of allylic alcohols intermediates. In the reactions described above, we also studied the effect of using a more economically amount of Pd/C catalyst smaller than 10% / substrate (1-2%), and we found that the hydrogenations were also realized near the high yields obtained with 10 % catalyst amount / substrate. A great number (13) of byproducts formed in the above hydrogenation reactions were isolated and fully characterized, in addition to the main 13,14-hydrogenated compounds; compounds **9b** and **(-)-3c** were also characterized by X-ray crystallography. We have not been able to find the data for such compounds anywhere in the literature therefore we believe our work could be useful not only for researchers in the prostaglandin field, but also for organic chemists, where hydrogenation of allylic alcohols or enones may be accompanied by secondary compounds.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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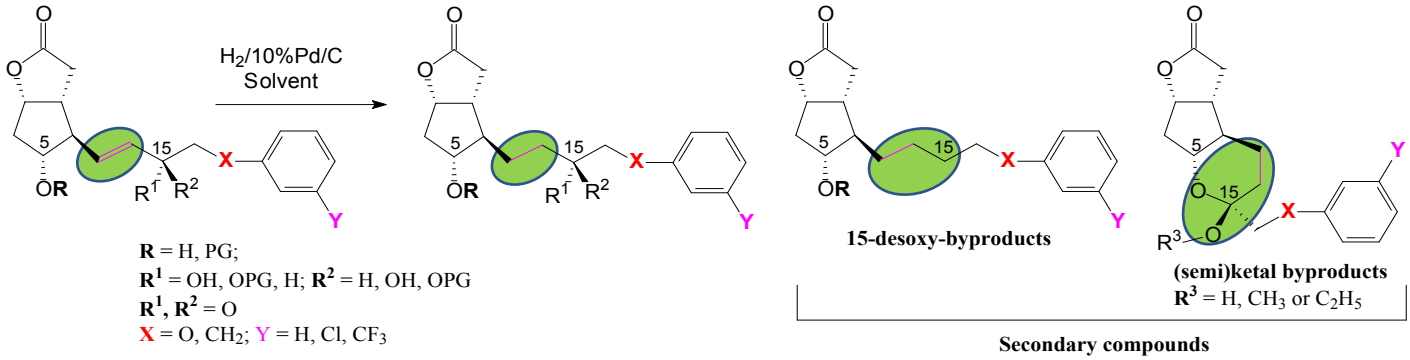
Hydrogenation of the double bond in ω-side chain of prostaglandin intermediates: conditions to increase the yield and minimize the formation of secondary compounds



R = H, PG;
R^1 = OH, OPG, H; **R^2** = H, OH, OPG
R^1, R^2 = O
X = O, CH_2; Y = H, Cl, CF_3
R^3 = H, CH_3 or C_2H_5

33 Hydrogenation examples
13 Hydrogenation byproducts