Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2019, **17**, 9489

Synthesis of treprostinil: key Claisen rearrangement and catalytic Pauson–Khand reactions in continuous flow†

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Received 1st October 2019,
Accepted 15th October 2019

DOI: 10.1039/c9ob02124h

rsc.li/obc

A new synthesis of treprostinil is described using a plug flow reactor in two of the key steps. First, a Claisen rearrangement reaction is described in scaled flow at multigram amounts. Yields and selectivity of this step are sharply improved compared to those from previous syntheses. Second, the key Pauson–Khand reaction in flow is described under catalytic conditions with 5 mol% of cobalt carbonyl and only 3 equiv. of CO. Scaling up of this reaction safely ensures a good yield of an advanced intermediate which is transformed into treprostinil in three steps. Other improvements are the introduction of the carboxymethyl chain into the phenol from the beginning to reduce the protection–deprotection steps. The synthesis is completed in 14% global yield after 12 linear steps from (*S*)-epichlorhydrin.

Introduction

Treprostinil (**1**) is a tricyclic benzoindene analogous to prostacyclin PGI_2.[1] Its main effects are the inhibition of platelet aggregation and vasodilation, including acute pulmonary vasodilation.[2] These biological activities are relevant for the treatment of cardiovascular diseases such as pulmonary arterial hypertension, a disease with a very poor prognosis until approximately 2010.[3] Since then, up to 13 prostanoid therapies have been implemented. Mostly, continuous perfusion of a solution of the drug is used as an administration route. This treatment has numerous disadvantages[4] and makes therapeutic compliance difficult on the part of the patient. In pursuit of active and stable analogues that can be administered in a less invasive way, analogues have been synthesized in which the C5–C6 double bond has been eliminated or bioisosteres have been made by replacing the cyclic oxygen with a methylene group (iloprost), a sulfur atom (5Z-6,9-thiaprostacycline) or nitrogen (9-deoxy-9α,6-nitrile-PGF1). In the case of treprostinil the vinyl ether is embedded in a phenoxide system, making it resistant to acid hydrolysis (Fig. 1).

Treprostinil can be administered by inhalation and since 2013 it has been approved by the FDA as an oral drug. The cost of the annual treatment with this drug is in the range between 140 000 and 180 000$. One of the reasons for the high cost of the drug is its complex and expensive chemical synthesis and the high cost of its development. It is important to find new scalable synthesis processes that lower the production costs of the drug and result in less use of contaminating and harmful reagents for the environment.

The first synthetic strategies by Aristoff's group used either an intramolecular Wadworth–Emmons–Wittig reaction without stereochemical control to build cyclopentane A[5] or an intramolecular alkylation of the phenolic ring for the formation of the B ring.[6] A similar approach appeared later in the patents of Shin *et al.* and Gao *et al.*[7]

In 2004 Moriarty *et al.* published the first total synthesis of treprostinil based on an intramolecular stoichiometric Pauson–Khand reaction (PKR).[8] Enyne intermediate **4** is pre-

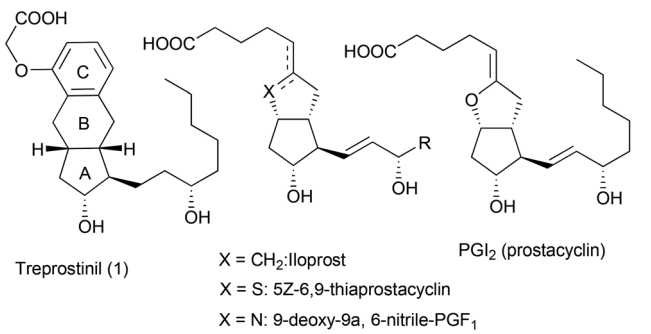

Fig. 1 Prostacyclin PGI_2 and analogues used as drugs for the treatment of pulmonary arterial hypertension.

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†Electronic supplementary information (ESI) available: Spectra collection and description of the flow systems. See DOI: 10.1039/c9ob02124h

pared by lithiation and alkylation of **2**, which is transformed into **4** in three steps. The synthetic route overcomes the problems of stereoselectivity by means of oxidation and subsequent stereoselective reduction of the enynic intermediate **4**. The resulting benzyl alcohol is protected with the bulky OTBDMS group (**5**), which serves as a temporary inducer group, achieving a totally stereoselective PKR. The PKR provides an 89% yield and 6 additional steps are required to obtain treprostinil. The route, with 15 linear steps, is known to afford an overall yield of 9% (Scheme 1).

Some small variants have been disclosed based on this synthesis such as the introduction of different esters into the carboxyl group of the treprostinil[9] or the use of an allyl group as a protecting group of the phenol.[10] Different protecting groups at the hydroxyl of the side chain[11] and variations in the synthesis of the alkyne that introduces the side chain were described.[12]

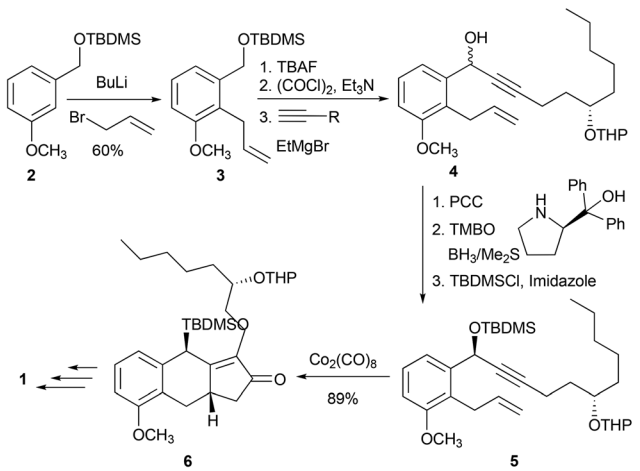
Flow reactors have important processing advantages including the improvement of energy and mass transfer, thermal management and the application of intense reaction conditions in a safe and controlled way. Over the past two decades, significant advances in the field of flow chemistry have permitted chemistries unachievable *via* conventional batch methods and helped to improve the manufacturing of Active Pharmaceutical Ingredients (APIs) *via* continuous processing.[13] Reactions with negative activation volumes, such as cycloadditions, condensations, and some rearrangements, including the Pauson–Khand reaction and the Claisen rearrangement, are particularly attractive for acceleration using flow technology. Application of high temperature and pressure on a reaction may lead to chemical intensification due to the finding of novel process windows.[14] The use of gases in flow chemistry has been one of the main challenges in the development of this tool in organic synthesis. With flow systems, the amount of hazardous and toxic gas reagents, such as hydrogen or carbon monoxide, can be significantly reduced.[15] Typical examples are hydrogenation,[16] oxidation[17] and carbonylations.[18] We have published favourable preliminary results from PKRs in a plug flow reactor (PFR).[19] Limiting the use of carbon monoxide and finding intensive condition windows was an important achievement.

A recent, very active area of research is the integration of individual process steps in the synthesis of a critical intermediate or final product into a single, fully continuous production line. Even though current pharmaceutical and fine-chemical production is by far dominated by batch processing, it has been demonstrated how the tendency towards continuous processes in the pharma industry, which in addition are considered greener,[20] is increasing.[21] In this work, we highlight the benefits of the production in a continuous flow system *via* two important steps in treprostinil synthesis. On the one hand we apply our methodology to the key PKR. On the other hand, we use for the first time a continuous system for the other key steps of the synthesis of treprostinil, the Claisen rearrangement showing the excellent performance and scalability of the flow methodology. Our method improves efficiency and selectivity while reducing risks and facilitates the isolation of the product saving time and reducing the use of solvents and energy.

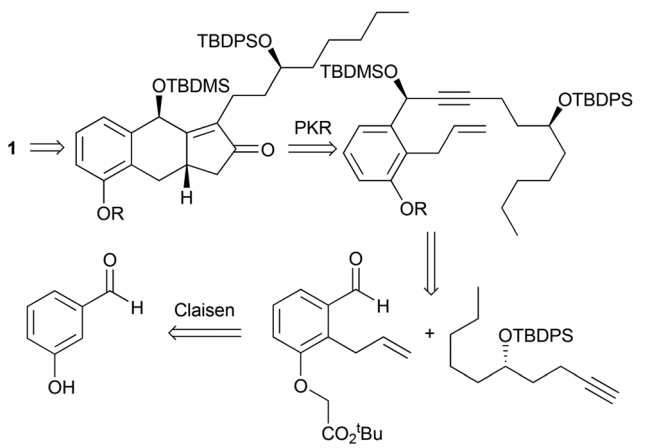
Results and discussion

Scheme 2 shows the retrosynthesis of treprostinil based on the convergent synthesis of an enyne as the precursor of the PKR that yields an advanced intermediate *en route* to the final product **1**.

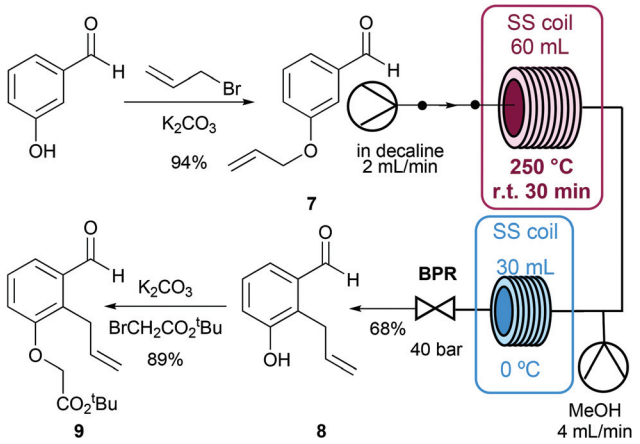
The first step in the synthesis is the protection of the hydroxyl group of 3-hydroxybenzaldehyde with allyl bromide in the presence of a base to give 3-allyloxybenzaldehyde **7** in a yield of 94% (Scheme 3). Then a Claisen rearrangement in the flow reactor gave **8**. The Claisen rearrangement in flow has been previously studied by several groups, including mechanistic studies but not for the synthesis of this substrate which involves two possible drawbacks: the lability of the aldehyde group and the possible formation of regioisomers.[22]



Scheme 1 Summary of Moriarty's synthesis of treprostinil.



Scheme 2 Retrosynthetic analysis of treprostinil.



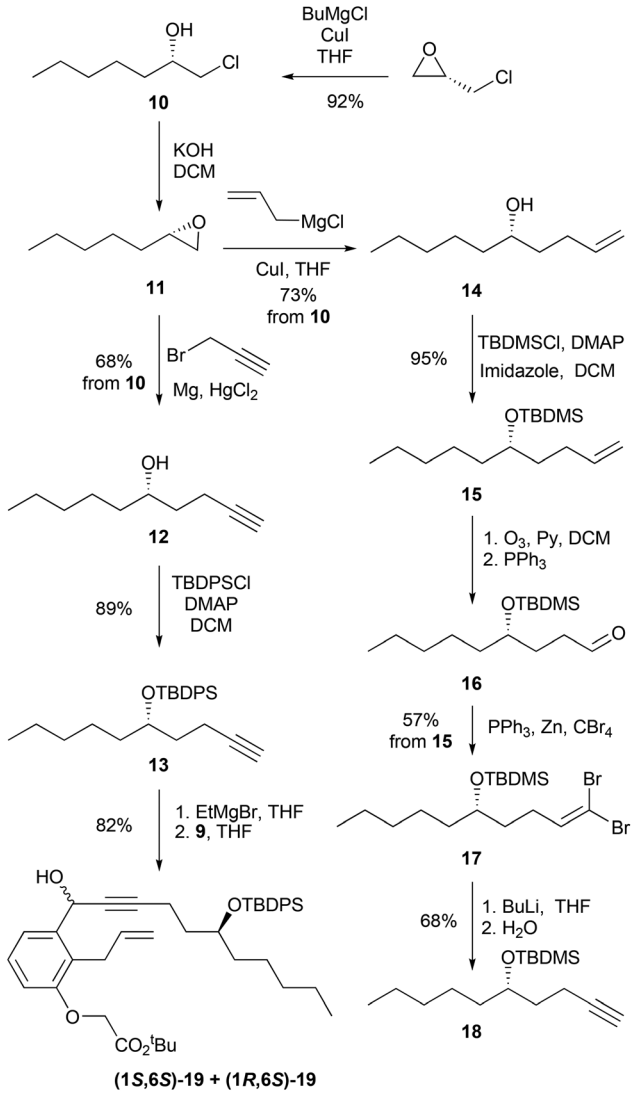
Scheme 3 Synthesis of the aldehyde block **9** using a Claisen rearrangement in flow.

The use of the Claisen rearrangement in batch to obtain aldehyde **8** has been described in several patents. However, the yields are generally low and the reaction times and isolation process are long. Moriarty *et al.* described this reaction for the first time, using a temperature of 150 °C, 41 h of reaction time and numerous extractions, separations by column chromatography and a recrystallization to obtain **8** with a 25% yield.[23] Other authors described higher reaction temperatures (180–217 °C) and shorter reaction times (7 h), but after the long workup, yields continued to be poor (33%,[10] 42%[24] and around 50%[25]). In another contribution, a bromine atom was introduced at the *ortho* position of the allyoxide group to avoid regioselectivity problems but the isolated yield was 27% after 2 days of reaction and two days of isolation.[26] Heating with MW led to a slight increase in the yield to 45% in a shorter time (800 W, 240 °C, 10 minutes) to transform just 1.5 g of the starting material.[27] All these previous studies indicate the formation of variable amounts of the other three possible regioisomers of the desired product **8**. Due to these poor results another group described the reaction using the methyl ester instead of the aldehyde as the starting substrate to obtain 80% of the product which had to be reduced.[28]

The intensification of conditions in the flow reactor allowed the use of high temperatures and pressures that improved dramatically the yields of the desired product. Screening of the conditions revealed the best conversions when using a solution of **7** in 10 volumes of decalin at 250 °C with a residence time of 30 min. Decalin was selected among various solvents as it gives the best solubility of the starting material. The equipment had the configuration shown in Scheme 3. It was necessary to introduce methanol to the system to solubilize the final product, in addition to a cooling bath. The crude reaction product is collected in an Erlenmeyer flask where decalin and methanol are separated in two layers. Interestingly, the final product is mainly found in the methanol phase. With these optimized conditions, 100 g of **7** were introduced in the system and transformed into **8**. The total time of this operation was 9.5 h.[29] Partial evaporation of the methanol layer produced a precipitate, which was washed with hexane to give 74.7 g of **8**. Remarkably, the solid contained the desired regioisomer of **8**, sufficiently pure to continue the synthesis (91% purity by ^{1}H NMR contaminated with other regioisomers). From the decalin layer, by addition of toluene and cooling, another precipitate of 19 g was obtained. This solid contained 28% of **8** measured by ^{1}H NMR and a mixture of other isomers. The result of this reaction is important not only because of the total yield of the final product but for the isolation process with methanol that gives high amounts of the product in an operationally easy and rapid method. The next step was the formation of product **9** by the reaction of **8** with *tert*-butyl bromoacetate using potassium carbonate as the base (89% yield). Our approach introduces the final chain of treprostinil very early in the synthesis avoiding the need to deprotect and introduce the carboxymethyl chain in the last steps of the synthesis, as, for instance, in Moriarty's synthesis where the phenol group is protected as methoxy. The cleavage of this group proved to be problematic and could only be achieved with lithium diphenylphosphine prepared *in situ* from diphenylphosphine and butyllithium.

The synthesis of the long alkyne fragment has been carried out by two different routes. The reaction of epichlorhydrin with butylmagnesium chloride gave chloroheptanol **10** which upon treatment with potassium hydroxide gave epoxide **11** which was not purified. In the first approach the opening of this epoxide with a Grignard reagent formed *in situ* and catalyzed by mercury chloride gave **12** which is protected to yield **13**. The fragment is built in 4 steps with an overall yield of 56%. The second route is based on using the more reactive allylmagnesium chloride that avoids the need for mercury catalysis and gives **14** which is protected as silylderivative **16**. The triple bond is generated through an ozonolysis of intermediate **16** (catalytic osmylation with NMO and oxidative cleavage with $NaIO_4$ in basic media were used alternatively, see the Experimental section) and the Corey–Fuchs reaction. Intermediate **18** is obtained after 7 steps from epichlorihydrin with a global yield of 25%. The overall yield of this approach is lower, but it has the advantage of avoiding the use of contaminating and highly toxic reagents such as mercury and uses a commercial Grignard reagent avoiding the *in situ* formation of the propargyl derivative. The synthesis was continued with **13** which was reacted with **9** in the presence of ethylmagnesium bromide to give **19** in 82% yield as a diastereomeric mixture.

The precursor of RPK is prepared from the diastereomeric mixture (**1*S*,6*S*-19** + **1*R*,6*S*-19**) following the methodology of Moriarty.[8] Thus, oxidation with MnO_2 and stereoselective reduction gave enantiomerically pure (**1*S*,6*S*-19**) which was protected as TBDMS derivative (**21**). This bulky group was introduced to direct the stereochemical outcome of the subsequent PKR. Thus, **21** was prepared in three steps with a global yield of 70% from **19**, a diasteromeric mixture (Scheme 4).



Scheme 4 Preparation of the alkyne containing fragment.

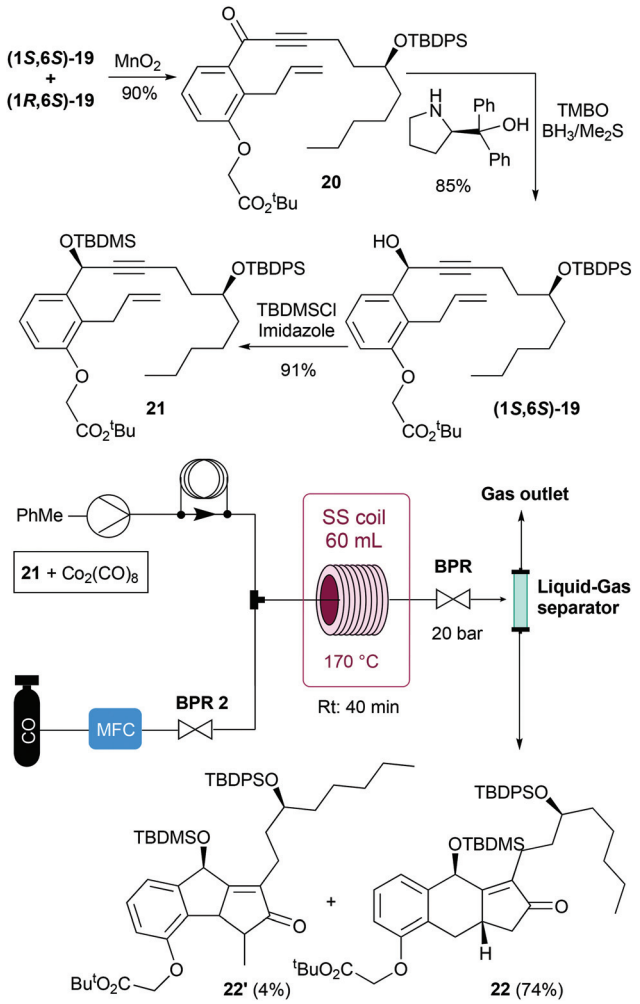
Table 1 Optimization of the PKR conditions for the synthesis of **22** (entries 1–3, batch conditions; 3–12, flow conditions)

Entry[a]	CO equiv.	Temp. (°C)	Res./ Reac. time (min h^{-1})	Cat. (mol %)	Conv.[b]	Yield[c] (%)
1[d]	6[d]	150	18 h	5	65	52
2[d]	6[d]	150	18 h	10	75	65
3[d]	6[d]	170	18 h	5	>99	70
4	3.0	170	21	5	50	28
5	6.2	170	23	5	52	34
6	3.0	170	31	5	63	42
7[e]	3.0	170	31	5	40	28
8[f]	3.0	170	31	5	70	41
9	3.0	170	40	5	>99	72
10	3.0	170	40	2	70	49
11	1.5	170	40	5	92	65
12[g]	3.0	170	40	5	>99	74[h]

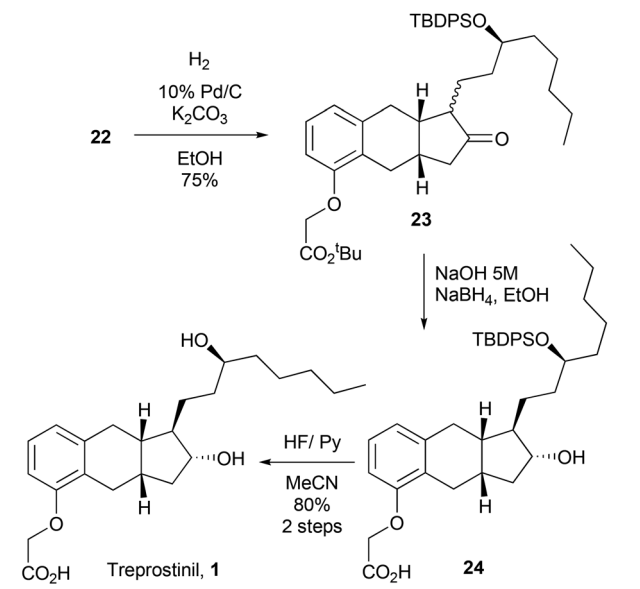
[a] All reactions in PFR (entries 4–11) at 20 bar of system pressure, 0.3 M concentration of **21** (0.35 mmol) except otherwise indicated. [b] Measured by HPLC. [c] In pure product. [d] Reactions in batch, in a stainless reactor at 6 bar of CO. [e] Concentration of **21**: 015 M. [f] System pressure: 25 bar. [g] Scaled up reaction using 7.5 g of starting material **21**. Total time: 1 h 45 min. [h] Plus 4% of **22′**.

The Pauson–Khand reaction (PKR) was optimized in the PFR system with the aim of minimizing the use of CO and the residence time whilst achieving a good yield. Two patents had mentioned the possibility of carrying out the PKR with catalytic amounts of cobalt and under carbon monoxide pressure.[26,30] However herein we present the first catalytic and scalable PKR in a flow reactor. Compound **21**, being an internal alkyne and forming a 6 membered ring in the PKR, is not a very favorable substrate. Thus, we performed 3 reactions in batches to determine the starting conditions for the optimization in flow (Table 1, entries 1–3). Total conversion was achieved at 170 °C with 5 mol% of $Co_2(CO)_8$. In the PFR, using this temperature, a 0.3 M concentration of **21** and the same catalyst loading the residence time was fixed to 40 min to achieve the total conversion of the substrate into **22** (entry 9). Some degradation products were observed but not isolated. Only 3 equiv. of CO were used in each reaction. Lowering this amount of CO or the catalyst loading or decreasing the concentration of **21** precluded the total conversion of this reaction (entries 7, 10 and 11). The system pressure was fixed at 20 bar as no improvement was observed on increasing the pressure to 25 bar (entry 8). With the optimized conditions in hand (entry 9), 7.5 g of **21** were transformed into **22** with a 74% yield in a total time of 1 h 45 min (entry 12). It is noteworthy that no precipitation/decomposition of the catalyst was observed. The crude reaction mixture was very clean. However it was purified by column chromatography to eliminate cobalt impurities. When the scale up reaction mixture was purified we isolated 410 mg (4% yield) of a side product which was characterized as **22′** where the emerging double bond had shifted. This was the only isolable side product. As the presence of traces of metal is a great concern in the synthesis of APIs, we performed a cobalt analysis by ICP (Scheme 5). The crude mixture contained 3050 ppm of cobalt which was reduced to 1855 ppm after washing with HCl. Finally after purification by column chromatography, the purified product **22** contained less than 0.2 ppm of cobalt.

Subsequently the benzylic alcohol group is eliminated by hydrogenolysis while reducing the double bond formed in the PKR giving **23**. The reduction of this double bond also takes place in a completely stereoselective manner with regard to the stereogenic center located at the fusion, although it gives a mixture of diastereomers in the center adjacent to the ketone. However, both isomers **23** are in equilibrium in ethanolic basic solution and, due to the different rates of the reduction of the ketone with $NaBH_4$, they are balanced and finally lead to a single isomer of product **24** with the correct stereochemistry in the 5 stereogenic centers.[8] This intermediate was treated without purification with the HF/pyridine complex to give treprostinil **1**, with a yield of 80% from **23** (Scheme 6).



Scheme 5 Preparation of PKR substrate 21 and its reaction in a PFR system to give intermediate 22.



Scheme 6 Completion of the synthesis of treprostinil.

Conclusion

A new synthesis of treprostinil through its intermediates is described, showing improvements in yields, in protecting groups and, above all, in the use of flow systems in two of the key steps. The carboxymethyl chain is introduced at the beginning of the reaction into the phenol to reduce the protection–deprotection steps. The Claisen rearrangement is described in scaled flow at multigram amounts. Two alternative syntheses of the side chain are described. The Pauson–Khand reaction in flow is described under catalytic conditions with 5 mol% of cobalt and only 3 equiv. of CO. The synthesis is completed in only three steps after the PKR. The overall yields are: 57% for aldehyde **9**, 56% for side chain **13**, 57% for the coupling of fragments **9** and **13** and preparation of the precursor of PK **21**. Then the PK reaction and the final stages afforded a yield of 44%. The overall yield of treprostinil is 14% from (*S*)-epichlorohydrin in 12 linear steps. Table 2 shows the main advantages of our synthesis compared with those described up to now using batch procedures.

Experimental

All starting materials and reactants were purchased from commercial sources and used without further purification. $Co_2(CO)_8$ is a stable solid, but it decomposes partially after some weeks reducing its activity. It is advisable to use freshly opened bottles. NMR data were measured using a Bruker AM-400. Chemical shifts (δ) are expressed in ppm downfield from TMS (0.00 ppm) as an internal standard for ^{1}H and the central signal of $CDCl_3$ (77.0 ppm) for ^{13}C. The letters s, d, t, q, m, dd, and bs are used to indicate singlet, doublet, triplet, quadruplet, multiplet, double doublet and broad singlet, respectively. The reaction progress was monitored by TLC or HPLC. IR spectra are recorded using a PerkinElmer Spectrum 100 FT-IR Spectrometer. Representative signals of functional groups are given in cm^{-1}. Optical rotation is measured using an Anton Parr polarimeter MCP100. ICP analysis was performed on an ICP_AES Varian Vista-MPX. Purification otherwise noted was performed by silica gel column chromatography using Merck silica gel 60 (0.040–0.063 mm) and eluents are indicated in each case. The melting point is measured using Stuart™ melting point apparatus SMP3.

The flow system is a PFR (plug flow reactor, tubular reactor, composed of a 316 stainless steel tube with an internal diameter of 17 mm and an external diameter of 25 mm, volume = 60.6 mL) in a forced air oven, with one feeding line with a Semipreparative HPLC pump ASI Model 501. In the case of the Claisen rearrangement, MeOH is introduced by using another pump of the same type. The system pressure is automatically controlled by a high precision needle backpressure valve and a WIKA pressure sensor. In the case of the Pauson–Khand reaction, CO is introduced by using a Bronkhorst mass flow controller calibrated for this gas, and it is mixed with the solution in a T-shaped stainless steel piece. The system has a gas liquid separator after the reactor (see the ESI† for pictures).

Table 2 Summary of improvements reported herein due to flow technology

Reaction	Reported protocols in batch	Continuous protocol described in this paper
Claisen rearr.	Long reaction times	30 min of res time
	Difficult isolation	Easy work-up
	Difficulties in achieving high *T* (200–250)	Easy and safe way to achieve high *T*. Energy saving. Ecofriendly
	22–50% yield	68% yield
Pauson–Khand reaction	Stoichiometric amounts of catalyst or	Only 5 mol% of catalyst
	Substoichometric catalyst + CO	Using CO in a safer a controlled way
	Complex formed in DCM and reaction in AcN	Direct reaction in toluene
	Reaction time: 4–15 h	40 min of res. time
	55–89% yield	74% yield

3-(Allyloxy)benzaldehyde (7)

To a solution of 3-hydroxybenzaldehyde (100 g, 0.82 mol) in ethanol (600 mL), NaI (12.3 g, 0.08 mol, 0.1 equiv.) and K_2CO_3 (147.3 g, 1.07 mol, 1.3 equiv.) were added. Then, allyl bromide (119.1 g, 0.98 mol, 1.2 equiv.) was added. The mixture was stirred at 60 °C for 3 hours. Afterwards, the mixture was filtered, and the solvent was evaporated *in vacuo*. After purification in silica gel column chromatography in hexane : ethyl acetate (4 : 1), the product was obtained as a yellow oil (125.0 g, 94%). R_f: 0.63 (hexane/AcOEt 9 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1H, CHO), 7.48–7.38 (m, 3H, Ar), 7.22–7.15 (m, 1H, Ar), 6.11–6.02 (m, 1H, C*H*═CH_2), 5.43 (dt, J_1 = 17.3 Hz, J_2 = 1.7 Hz, 1H, CH═CH_2 *trans*), 5.32 (dt, J_1 = 10.5 Hz, J_2 = 1.6 Hz, 1H, CH═CH_2 *cis*), 4.63–4.56 (m, 2H, OCH_2) ppm. The spectroscopic data obtained are consistent with those reported in the literature.[27]

2-Allyl-3-hydroxybenzaldehyde (8)

In an Erlenmeyer flask, 100 g (0.62 mol) of 3-(allyloxy)benzaldehyde were dissolved in decalin until a final volume of 1 L was reached. Once the solution became perfectly clear it was placed in the inlet of the pump (pump 1). A flask with MeOH was placed in the inlet of the second pump (pump 2). MeOH was pumped into the reactor at the point where the reaction mixture went out of the oven to avoid the precipitation of the final product. Furthermore, a cooling bath inside an ice–water bath was placed after mixing both solvents. The configuration of the system is shown in Scheme 3. The conditions of the system for this reaction were: temperature: 250 °C; pressure: 40 bar; residence time: 30 min; pump flow 1: 2 mL min^{-1}; pump flow 2: 4 mL min^{-1}; reactor volume: 60.6 mL; and total time: 9.5 hours. The mixture of MeOH and decalin was collected in a flask. The solution was allowed to cool to room temperature, and both layers were separated. The decalin layer was stirred with MeOH (1000 mL) and both phases separated again. Both methanolic phases were joined and partially evaporated *in vacuo* until a brownish solid precipitated. The solid was washed with hexane (3 × 100 mL), to obtain 74.3 g of a pale-yellow solid with 91% of the desired regioisomer (determined by ^{1}H NMR). The decalin phase was placed in an ice bath with toluene (400 mL), and the solid that precipitated was filtered and washed with hexane (3 × 50 mL). NMR analysis of the 19 g obtained in this way indicated the presence of a 28% of the desired regioisomer. Calculated yield of **8**: 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H, CHO), 7.45 (dd, J_1 = 7.7 Hz, J_2 = 1.3 Hz, 1H, Ar), 7.31 (t, J = 7.8 Hz, 1H, Ar), 7.09 (dd, J_1 = 8.0 Hz, J_2 = 1.3 Hz, 1H, Ar), 6.09–6.00 (m, 1H, C*H*═CH_2), 5.24 (s, 1H, OH), 5.13 (dd, J_1 = 10.1 Hz, J_2 = 1.6 Hz, 1H, CH═CH_2 *cis*), 5.05 (dd, J_1 = 17.2 Hz, J_2 = 1.6 Hz, 1H, CH═CH_2 *trans*), 3.91 (d, J = 5.8 Hz, 2H, CH_2CH═CH_2). The spectroscopic data obtained are consistent with those reported in the literature.[27]

tert-Butyl 2-(2-allyl-3-formylphenoxy)acetate (9)

To a solution of **8** (68 g, 0.42 mol, 91% purity) in 700 mL of acetone, powdered K_2CO_3 (230 g, 1.67 mol, 4 equiv.) was added. Then, *tert*-butyl bromoacetate (81.9 g, 0.42 mol, 1 equiv.) was slowly added. The mixture was stirred for 6 hours at 40 °C and all the starting products were consumed (TLC). The mixture was cooled to room temperature and it was filtered to remove the salts. The remaining salts were washed with acetone and all the solvents were evaporated *in vacuo*. Silica gel column chromatography in hexane : ethyl acetate (12 : 1) gave 94 g of a light yellow oil (89% yield). R_f: 0.51 (hexane/AcOEt 9 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.28 (s, 1H, CHO), 7.52 (dd, J_1 = 7.8 Hz, J_2 = 1.2 Hz, 1H, Ar), 7.32 (t, J = 8.0 Hz, 1H, Ar), 6.98 (dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz, 1H, Ar), 6.11–5.99 (m, 1H, C*H*═CH_2), 5.02 (dq, J_1 = 10.2 Hz, J_2 = 1.6 Hz, 1H, CH═CH_2 *cis*), 4.97 (dq, J_1 = 17.1 Hz, J_2 = 1.8 Hz, 1H, CH═CH_2 *trans*), 4.57 (s, 2H, CH_2O), 3.92 (dt, J_1 = 6.0 Hz, J_2 = 1.7 Hz, 2H, CH_2CH═CH_2) 1.47 (s, 9H, $(CH_3)_3C$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.1 (CO), 167.6 (CO), 156.2 (C), 136.5 (CH), 135.2 (C), 131.5 (C), 127.3 (CH), 123.3 (CH), 116.7 (CH), 115.6 (CH_2), 82.5 (C), 66.4 (CH_2), 28.2 (CH_2), 28.0 ($3CH_3$) ppm. IR (NaCl) ν = 2975, 2 932 1750, 1735, 1601 cm^{-1}. Elemental analysis calcd for $C_{16}H_{20}O_4$: C, 69.55; H, 7.30; found: C, 69.41; H, 7.29.

(*S*)-1-Chloro-2-heptanol (10)

To a solution of (*S*)-(−)-epichlorohydrin (50 g, 0.54 mol) in 420 mL of tetrahydrofuran was added 7.6 g (54.05 mmol, 0.1 equiv.) of CuI under argon. The reaction mixture was cooled to 0 °C, and a solution of 378 mL (0.65 mol, 1.2 equiv.) of butylmagnesium chloride (20wt% in THF-toluene) was added slowly with stirring. The temperature of the reaction was controlled to be between 5 and 15 °C inside the flask. When the addition was completed, the reaction mixture was allowed to warm to room temperature. The solution was stirred for 10 h and all the starting products were consumed (TLC). The reaction was quenched by adding saturated NH_4Cl solution (150 mL) and 1 M HCl to reach acidic pH. The obtained solid

was removed by filtration through Celite and washed with ethyl acetate (100 mL). The aqueous phase was extracted with ethyl acetate (3 × 200 mL). All the organic phases were combined, washed with a saturated solution of NH_4Cl (100 mL) and brine (100 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography in hexane : ethyl acetate (33 : 1) afforded 74.3 g (92% yield) of **10** as a pale yellow oil. R_f: 0.39 (hexane/AcOEt 9 : 1) ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.80 (bs, 1H, C*H*OH), 3.64 (dd, J_1 = 11.1 Hz, J_2 = 3.2 Hz, 1H, C*H*HCl), 3.47 (dd, J_1 = 11.1 Hz, J_2 = 7.1 Hz, 1H, CH*H*Cl), 2.19 (d, J = 4.1 Hz, 1H, OH), 1.56–1.30 (m, 8H, $4CH_2$), 0.89 (t, J = 6.8 Hz, 3H, CH_3) ppm. The spectroscopic data obtained are consistent with those reported in the literature.[8]

(*S*)-2-Pentyloxirane (11)

To a solution of **10** (72 g, 0.48 mol) in DCM (280 mL) placed in an ice bath, powdered KOH (53.9 g, 0.96 mol) was slowly added. When the addition was completed, the reaction mixture was allowed to slowly warm to room temperature, and it was stirred for 3 hours. The crude reaction product was filtered through a pad of Celite. The remaining salts and the pad of Celite were washed with DCM (2 × 50 mL). The organic extracts were washed with water (200 mL) and brine (200 mL), and dried with Na_2SO_4. The solvent was evaporated *in vacuo* in a 20 °C bath. 59 g of crude reaction product **11** were obtained as a clear orange oil containing DCM. The compound was subjected to the next step without further purification to avoid volatilization. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.90 (m, 1H, C*H*OH), 2.75 (t, J = 4.5 Hz, 1H, C*H*HO), 2.47 (dd, J_1 = 5.1 Hz, J_2 = 2.7 Hz, 1H, C*H*HO), 1.53–1.50 (m, 2H, CH_2), 1.48–1.41 (m, 2H, CH_2), 1.33–1.31 (m, 4H, $2CH_2$), 0.90 (t, J = 7.1 Hz, 3H, CH_3) ppm. The spectroscopic data obtained are consistent with those reported in the literature.[31]

(*S*)-Dec-1-yn-5-ol (12)

To a 2-neck flask previously dried and equipped with a condenser, Mg turnings (15 equiv.) were added. The metal was activated by 3 cycles of heating using a heating gun under vacuum and cooling down under argon. Then, dry Et_2O (200 mL) was added. A I_2 crystal was added to the suspension. After 20 min of stirring at room temperature, $HgCl_2$ (1.59 g, 5.9 mmol, 0.06 equiv.) was added and the flask was placed in an ice bath. 7.9 mL of propargyl bromide (80% propargyl bromide in toluene, 0.75 equiv.) were added dropwise. The flask was transferred to a 40 °C bath and once reflux began, it was placed in the ice bath again and the dropwise addition of propargyl bromide (44.7 mL, 4.25 equiv. total 491.6 mmol) was continued. The stirring was continued for a further 90 minutes at room temperature after completion of the addition. The Grignard reagent was added (*via* cannula) to a solution of the epoxide (12 g of crude **11**, *ca.* 97.6 mmol) in dry Et_2O (300 mL) and placed in an ice bath. After the addition the solution was stirred for 2 hours at room temperature and TLC showed no remaining epoxide. The reaction was quenched by adding a saturated solution of NH_4Cl until acidic pH is achieved. The crude reaction mixture was filtered through a pad of Celite and both phases were separated. The aqueous phase was extracted with Et_2O (3 × 200 mL). The organic extracts were washed with water (400 mL) and brine (400 mL), dried with $NaSO_4$ and concentrated *in vacuo*. Silica gel column chromatography in hexane : ethyl acetate (19 : 1) gave **12** as a colorless oil (10.2 g, 68% yield from **10**). R_f: 0.29 (hexane/AcOEt 9 : 1). $[\alpha]_D^{25}$ +2.4° (c 0.25, $HCHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78–3.70 (m, 1H, C*H*OH), 2.33 (td, J_1 = 7.1 Hz, J_2 = 2.7 Hz, 2H, $CH_2C{\equiv}$), 1.97 (t, J = 2.7 Hz, 1H, HC$\equiv$), 1.68–1.26 (m, 10H, $5CH_2$), 0.92–0.86 (t, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.3 (C), 70.8 (CH), 68.7 (CH), 37.4 (CH_2), 35.6 (CH_2), 31.8 (CH_2), 25.2 (CH_2), 22.6 (CH_2), 15.0 (CH_2), 14.0 (CH_3) ppm. IR (NaCl) ν = 3313, 2960, 2928, 2858 and 2119 cm^{-1}. Elemental analysis calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76; found: C, 77.99; H, 11.66.

(*S*)-*tert*-Butyl(dec-1-yn-5-yloxy)diphenylsilane (13)

25 g of **12** (0.16 mol) were dissolved in a mixture of DCM/DMF (360/36 mL) and placed in an ice bath, and dimethylaminopyridine (DMAP) (29.3 g, 0.24 mol, 1.5 equiv.) was added. After stirring for 20 minutes at room temperature, *tert*-butyl(chloro)diphenylsilane (TBDPSCl) (46.5 mL, 0.18 mol, 1.1 equiv.) was added. The resulting mixture was stirred for 12 h at room temperature until total consumption of the starting product (TLC). The reaction was quenched by adding saturated solution of NH_4Cl (150 mL). Both phases were separated, and the aqueous phase was extracted with DCM (3 × 200 mL), the organic phases were washed with water (600 mL) and brine (600 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography in hexanes afforded 55.9 g of **13** as a light-yellow oil (89% yield). R_f: 0.31 (hexane), $[\alpha]_D^{25}$ +6.50° (c 0.20, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72–7.64 (m, 4H, Ar), 7.44–7.34 (m, 6H, Ar), 3.80 (p, J = 5.7 Hz, 1H, C*H*O), 2.21 (td, J_1 = 7.7 Hz, J_2 = 2.7 Hz, 2H, $CH_2C{\equiv}$), 1.86 (t, J = 2.6 Hz, 1H, HC$\equiv$), 1.69 (td, J_1 = 7.7 Hz, J_2 = 5.6 Hz, 2H, CH_2), 1.39–1.35 (m, 2H, CH_2), 1.21–1.12 (m, 4H, $2CH_2$), 1.07–1.01 (m, 11H, $(H_3C)_3C$ and CH_2), 0.79 (t, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.9 (4CH), 134.5 (C), 134.2 (C), 129.5 (CH), 129.4 (CH), 127.5 (2CH), 127.4 (2CH), 84.7 (C), 72.2 (CH), 68.0 (CH), 36.2 (CH_2), 35.1 (CH_2), 31.7 (CH_2), 27.1 ($3CH_3$), 24.5 (CH_2), 22.5 (CH_2), 19.4 (C), 14.3 (CH_3), 14.0 (CH_2) ppm. IR (NaCl) ν = 3309, 3073, 3050, 2963, 2928, 2857, 2119, and 1589 cm^{-1}. Elemental analysis calcd for $C_{26}H_{36}OSi$: C, 79.53; H, 9.24; Si, 7.15; found: C, 79.68; H, 9.11.

(*S*)-Dec-1-en-5-ol (14)

To a solution of **11** (7.5 g of crude compound, *ca.* 61.0 mmol) and CuI (0.86 g, 6.1 mmol, 0.1 equiv.) in 40 mL of anhydrous THF, a solution of allylmagnesium chloride (1.7 M) was slowly added in an ice bath (53.8 mL, 91.5 mmol, 1.5 equiv.). The temperature inside the flask was controlled to be below 15 °C. When the addition was completed, the reaction mixture was stirred for 10 h and all the starting products were consumed (TLC). The reaction was quenched by adding a solution of saturated NH_4Cl to reach acidic pH. The aqueous phase was extracted with ethyl acetate (3 × 70 mL). All the organic phases

were combined and washed successively with a saturated solution of NH_4Cl (100 mL), H_2O (100 mL), and brine (100 mL). The organic extracts were finally dried with Na_2SO_4, filtered, and concentrated *in vacuo*. The crude reaction product was purified by silica gel column chromatography in hexane : ethyl acetate (9 : 1) to afford 6.96 g of **14** as a colorless oil (73% yield from **10**). R_f: 0.25 (hexane/AcOEt 9 : 1). $[\alpha]_D^{25}$ +1.3° (c 0.40, $CHCl_3$, lit + 1.7).[30] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89–5.79 (m, 1H, C*H*=CH_2), 5.05 (dq, J_1 = 17.1 Hz, J_2 = 1.6 Hz, 1H, CH=CH_2 *trans*), 4.97 (dq, J_1 = 10.2 Hz, J_2 = 1.6 Hz 1H, CH=CH_2 *cis*), 3.64–3.60 (m, 1H, C*H*OH), 2.28–2.09 (m, 2H, CH_2CH=), 1.53–1.29 (m, 10H, 5CH_2), 0.89 (t, J = 6.8 Hz, 3H, CH_3) ppm. The spectroscopic data obtained are consistent with those reported in the literature.[32]

(*S*)-*tert*-Butyl(dec-1-en-5-yloxy)dimethylsilane (15)

6 g of **14** (38.2 mol) were dissolved in a mixture of DCM/DMF (90/9 mL). Dimethylaminopyridine (DMAP) (2.3 g, 19.1 mol, 0.5 equiv.) and imidazole (3.9 g, 57.3 mmol, 0.5 equiv.) were added in an ice bath. After stirring for 20 min at room temperature, *tert*-butyldimethylsilyl chloride (TBDMSCl) (6.9 g, 45.8 mmol, 1.2 equiv.) was added. The resulting mixture was stirred for 12 h at room temperature until total consumption of the starting product. The reaction was quenched by adding a saturated solution of NH_4Cl (60 mL). The mixture was extracted with DCM (3 × 60 mL); the organic phases were washed with water (100 mL) and brine (100 mL), dried with Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel column chromatography in hexanes afforded 9.80 g of **15** (36.6 mmol) as a colourless liquid (95% yield). R_f: 0.48 (hexane). $[\alpha]_D^{25}$ +2.43° (c 0.06, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89–5.74 (m, 1H, C*H*=CH_2), 5.00 (dq, J = 17.1 Hz, J_2 = 1.6 Hz, 1H, CH=CH_2 *trans*), 4.94 (dd, J_1 = 10.1 Hz, J_2 = 1.8 Hz, 1H, CH=CH_2 *cis*), 3.70–3.59 (m, 1H, C*H*OTBS), 2.18–1.97 (m, 2H, CH_2CH=), 1.54–1.48 (m, 2H, CH_2), 1.45–1.40 (m, 2H, CH_2), 1.33–1.25 (m, 6H, 3CH_2), 0.90–0.87 (m, 12H, C$(CH_3)_3$ and CH_3), 0.04 (s, 6H, $(CH_3)_2$Si) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.1 (CH), 114.1 (CH_2), 71.8 (CH), 37.0 (CH_2), 36.2 (CH_2), 32.1 (CH_2), 29.7 (CH_2), 26.0 (3CH_3), 24.9 (CH_2), 22.7 (CH_2), 18.1 (C), 14.1 (CH_3), −4.38 (CH_3), −4.44 (CH_3) ppm. IR (NaCl) ν = 2955, 2930, 2856, 1643 cm^{-1}. Elemental analysis calcd for $C_{16}H_{34}OSi$: C, 71.04; H, 12.67; found: C, 71.17; H, 12.55.

(*S*)-4-((*tert*-Butyldimethylsilyl)oxy)nonanal (16)

To a cooled (−78 °C) and stirred solution of **15** (8 g, 29.6 mmol) in DCM (40 mL) and pyridine (2 equiv. 59.2 mmol, 4.77 mL) O_3 was continuously bubbled (provided by an ozoniser and an O_2 cylinder). After 90 min of bubbling TLC showed no starting product remaining. N_2 was passed though the solution for 15 minutes, and then, 11.6 g of PPh_3 (1.5 equiv. 44.4 mmol) were added in portions at −78 °C. The solution was slowly warmed to room temperature until the next day (16 hours) with vigorous stirring. The solvent is evaporated *in vacuo* and the residue is redissolved in hexane (50 mL). PPh_3 by-products are filtered and the solvent is evaporated *in vacuo*. The compound was subjected to the next step without further purification. For small scale synthesis, osmylation and oxidative cleavage were explored. To a cooled (0 °C) and stirred solution of the alkene (500 mg, 270.2 mmol) and NMO (867 mg, 7.4 mmol, 4 equiv.) in H_2O/acetone (7/7 mL), OsO_4 (4% H_2O, 0.94 mL, 0.05 equiv.) was slowly added. After overnight stirring (14 h) at room temperature TLC showed the total consumption of the starting material. 5 mL of a saturated solution of Na_2SO_3 were added to the crude reaction mixture in an ice bath and acetone was evaporated *in vacuo*. The aqueous residue was extracted with MTB ether (3 × 10 mL), the organic phases were washed with water (15 mL) and brine (15 mL) and dried with Na_2SO_4 and the solvent was evaporated *in vacuo*. Then, $NaHCO_3$ (170 mg, 2.03 mmol, 1.1 equiv.) and $NaIO_4$ (2.3 g, 11.1 mmol, 6 equiv.) were added to the residue previously redissolved in a mixture of MeOH/H_2O (7/5 mL). After 30 min stirring at room temperature, the reaction mixture was diluted with 10 mL of water and MeOH was evaporated *in vacuo.* The aqueous residue was extracted with MTB ether (3 × 10 mL). The organic extracts were washed with brine (20 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The residue was purified by a short column chromatography in hexane : ethyl acetate (33 : 1) to afford 259 mg (95% yield) of **16** as a colorless liquid. R_f: 0.52 (hexane/AcOEt 12 : 1). $[\alpha]_D^{25}$ +8.5° (c 0.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.79 (t, J = 1.7 Hz, 1H, CHO), 3.74–3.67 (m, 1H, CHOTBS), 2.48 (td, J_1 = 7.5 Hz, J_2 = 1.8 Hz, 2H, CH_2CHO), 1.88–1.65 (m, 2H, CH_2), 1.47–1.23 (m, 8H, 4CH_2), 0.92–0.84 (m, 12H, C$(CH_3)_3$ and CH_3), 0.04 (s, 3H, CH_3Si), 0.03 (s, 3H, CH_3Si) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 203.0 (CO), 71.1 (CH), 39.7 (CH_2), 36.9 (CH_2), 32.0 (CH_2), 28.8 (CH_2), 25.9 (3CH_3), 24.9 (CH_2), 22.6 (CH_2), 18.1 (C), 14.0 (CH_3), −4.4 (CH_3), −4.6 (CH_3) ppm. IR (NaCl) ν = 1713 cm^{-1}. Elemental analysis calcd for $C_{15}H_{32}O_2Si$: C, 66.11; H, 11.84; found: C, 66.02; H, 11.95.

(*S*)-*tert*-Butyl((1,1-dibromodec-1-en-5-yl)oxy)dimethylsilane (17)

To a suspension of PPh_3 (15.5 g, 59.2 mmol, 2 equiv.) and Zn (dust) (3.9 g, 59.2 mmol, 2 equiv.) in dry DCM (220 mL), CBr_4 (19.6 g, 59.2 mmol, 2 equiv.) was slowly added at 0 °C. After 10 minutes of stirring at 0 °C and 15 at room temperature, a solution of **16** (8.05 g, 29.6 mmol) in 70 mL of dry DCM was added at 0 °C and the resulting mixture was stirred for 12 hours at room temperature. All the salts were filtered over Celite, and the remaining salts were washed with hexane (80 mL). Then, the filtrate was concentrated *in vacuo*. Silica gel column chromatography in hexanes afforded 7.2 g of **17** (16.9 mmol) as a yellow oil (57% yield from **15**). R_f: 0.41 (hexane). $[\alpha]_D^{25}$ +1.5° (c 0.3, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.41 (t, J = 7.3 Hz, 1H, CH=), 3.69–3.62 (m, 1H, CHOTBS), 2.22–2.03 (m, 2H, CH_2CH=), 1.57–1.50 (m, 2H, CH_2), 1.44–1.40 (m, 2H, CH_2), 1.33–1.23 (m, 6H, 3CH_2), 0.90–0.88 (m, 12H, C$(CH_3)_3$ and CH_3), 0.049 (s, 3H, CH_3Si), 0.047 (s, 3H, CH_3Si) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.9 (CH), 88.6 (C), 71.5 (CH), 36.9 (CH_2), 34.7 (CH_2), 32.0 (CH_2), 29.1 (CH_2), 25.9 (3CH_3), 24.9 (CH_2), 22.7 (CH_2), 18.1 (C), 14.1 (CH_3), −4.4 (CH_3), −4.5 (CH_3) ppm. IR (NaCl) ν = 2952, 2933, 2861 and

1737 cm^{-1} Elemental analysis calcd for $C_{16}H_{32}Br_2OSi$: C, 44.87; H, 7.53; Br, 37.31; Si, 6.56; found: C, 44.99; H, 7.65.

(*S*)-*tert*-Butyl(dec-1-yn-5-yloxy)dimethylsilane (18)

To a stirred solution of **17** (5.0 g, 11.68 mmol) in anhydrous THF (55 mL) was added dropwise *n*-BuLi solution (1.6 M in hexane, 15.95 mL, 25.52 mmol) at −40 °C under an argon atmosphere. The solution was stirred for 15 min at −40 °C and then for 15 min at 0 °C. After the completion of the reaction as indicated by TLC, the reaction was quenched by dropwise addition of aqueous saturated solution of NH_4Cl (25 mL) at 0 °C and extracted with AcOEt (3 × 60 mL). The combined organic layers were washed with brine (60 mL) and dried with Na_2SO_4, and the product was concentrated *in vacuo*. Silica gel column chromatography in hexanes afforded 2.2 g of **18** (7.94 mmol) as a colourless oil (68% yield). R_f: 0.50 (Hexane). $[\alpha]_D^{25}$ +18.78° (c 0.13, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79–3.71 (m, 1H, CHO), 2.23 (t, J = 6.7 Hz, 2H, $CH_2C{\equiv}$), 1.93 (s, 1H, HC≡), 1.66–1.61 (m, 2H, CH2), 1.46–1.40 (m, 2H, CH_2), 1.33–1.25 (m, 6H, $3CH_2$), 0.89 (s, 12H, $(H_3C)_3C$ and CH_3), 0.06 (s, 3H, $SiCH_3$), 0.05 (s, 3H, $SiCH_3$) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 84.8 (C), 70.8 (CH), 68.1 (CH), 37.0 (CH_2), 35.6 (CH_2) 32.0 (CH_2), 25.9 ($3CH_3$), 24.7 (CH_2), 22.6 (CH_2), 18.1 (C), 14.6 (CH_2), 14.0 (CH_3), −4.4 (CH_3), −4.6 (CH_3) ppm. IR (NaCl) ν = 3317, 2959, 2926, 2856, 2120, and 1470 cm^{-1}. Elemental analysis calcd for $C_{16}H_{32}OSi$: C, 71.57; H, 12.01; Si, 10.46; found: C, 72.69; H, 11.13.

tert-Butyl 2-(2-allyl-3-((6*S*)-6-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxyundec-2-yn-1-yl)phenoxy)acetate (1*S*,6*S* + 1*R*,6*S*-19)

To a stirred and refluxing solution of **13** (20 g, 50.9 mmol, 1.1 equiv.) in anhydrous THF (370 mL) was slowly added a solution of EtMgBr (3 M in Et_2O) (16.9 mL, 50.9 mmol) under argon. As the reaction is exothermic heating was stopped during this addition. After complete addition, the reaction mixture was further refluxed for 90 min and cooled to 0 °C and then solution **9** (12.8 g, 46.3 mmol) in anhydrous THF (40 mL) was added slowly with stirring. After complete addition, the reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was cooled again to 0 °C, and a saturated aqueous solution of NH_4Cl was added with stirring (200 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (3 × 250 mL). The combined organic layers were washed with brine (600 mL) and dried with Na_2SO_4, and the solvents were removed *in vacuo*. Silica gel column chromatography in hexane : ethyl acetate (12 : 1) gave 41.7 g (82% yield) of **19** as a mixture of diastereomers.

tert-Butyl (*S*)-2-(2-allyl-3-(6-((*tert*-butyldiphenylsilyl)oxy)undec-2-ynoyl)phenoxy)acetate (20)

To a cooled (0 °C) and stirred solution of **(1*S*,6*S*)-19 + (1*R*,6*S*)-19** (20 g, 29.89 mmol) in acetone (700 mL) was added active MnO_2 (31.2 g, 0.36 mol). The reaction mixture was slowly allowed to warm to room temperature and stirred for 24 h. Then it was filtered through Celite and the solid was washed with acetone. The solvents were removed *in vacuo* and 17.9 g (26.9 mmol) of **20** were obtained as a yellow oil (90% yield) sufficiently pure to continue the synthesis. A small sample was purified for characterization by silica gel column chromatography in hexane : ethyl acetate (9 : 1). R_f: 0.36 (hexane/AcOEt 9 : 1). $[\alpha]_D^{25}$ −11.4 (c 0.34, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69–7.66 (m, 5H, Ar), 7.43–7.32 (m, 6H, Ar), 7.23 (t, J = 8.0 Hz, 1H, Ar), 6.93 (dd, J_1 = 8.3 Hz, J_2 = 1.2 Hz, 1H, Ar), 6.08–5.98 (m, 1H, C*H*═CH_2), 5.07 (dq, J_1 = 17.1 Hz, J_2 = 1.8 Hz, 1H, CH═CH_2 *trans*), 4.97 (dq, J_1 = 10.1 Hz, J_2 = 1.6 Hz, 1H, CH═CH_2 *cis*), 4.56 (s, 2H, CH_2O), 3.90–3.82 (m, 3H, C*H*OSi and CH_2CH═), 2.49 (td, J = 7.2, 1.3 Hz, 2H, $CH_2{\equiv}$), 1.83–1.74 (m, 2H, CH_2), 1.49 (s, 9H, $(H_3C)_3CO$), 1.46–1.40 (m, 2H, CH_2), 1.28–1.13 (m, 6H, $3CH_2$), 1.07 (s, 9H, $(H_3C)_3CSi$), 0.80 (t, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 179.8 (CO), 167.7 (CO), 156.5 (C), 137.6 (C), 136.6 (CH), 135.84 (2CH), 135.80 (2CH), 134.3 (C), 134.0 (C) 130.5 (C), 129.6 (CH), 129.5 (CH), 127.6 (2CH), 127.5 (2CH), 126.5 (CH), 125.5 (CH), 115.7 (CH), 115.0 (CH_2), 95.7 (C), 82.4 (C), 81.5 (C) 72.0 (CH), 66.6 (CH_2), 36.2 (CH_2), 34.2 (CH_2), 31.6 (CH_2), 29.9 (CH_2), 28.0 ($3CH_3$), 27.0 ($3CH_3$), 24.5 (CH_2), 22.4 (CH_2), 19.4(C), 15.0 (CH_2), 13.9 (CH_3) ppm. IR (NaCl) ν = 3069, 2956, 2932, 2858, 2210, 1754, 1731, 1648, 1574 and 1460 cm^{-1}. Elemental analysis calcd for $C_{42}H_{54}O_5Si$: C, 75.63; H, 8.16; Si, 4.21; found: C, 75.77; H, 8.10.

tert-Butyl 2-(2-allyl-3-((1*S*,6*S*)-6-((*tert*-butyldiphenylsilyl)oxy)-1-hydroxyundec-2-yn-1-yl)phenoxy)acetate ((1*S*,6*S*)-19)

To a solution of (*R*)-methyl oxazaborolidine (26.3 mL, 1 M in toluene) was added a solution of **20** (14.6 g, 21.9 mmol) (4.845 g, 11.74 mmol) in anhydrous THF (43 mL) under argon. Then the reaction mixture was cooled to −30 °C under argon and borane–methyl sulfide complex (3.32 g, 43.8 mmol) was added slowly with stirring. After complete addition, the reaction mixture was stirred at −30 °C for 1 h, and then methanol (13 mL) was added carefully with stirring to quench the reaction at −10 to −15 °C. The reaction mixture was allowed to warm to room temperature and left with stirring overnight. Then it was cooled to 0 °C and 5% aqueous solution of ammonium chloride was added with stirring (20 mL). The organic layer was separated and washed with 5% aqueous ammonium chloride solution (20 mL) and brine (20 mL). The combined aqueous layers were extracted with ethyl acetate (30 mL) and washed with brine (20 mL). The combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to yield a viscous oil which was purified by silica gel column chromatography in hexane : ethyl acetate (12 : 1) to give 12.45 g (85%) of **(1*S*,6*S*)-19** as a pale yellow oil. R_f: 0.30 (hexane/AcOEt 9 : 1). $[\alpha]_D^{25}$ −4.89 (c 0.42, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.63 (m, 4H, Ar), 7.41–7.31 (m, 7H, Ar), 7.19 (t, J = 8.0 Hz, 1H, Ar), 6.73 (dd, J_1 = 8.3 Hz, J_2 = 1.1 Hz, 1H), 6.09–5.99 (m, 1H, C*H*═CH_2), 5.58–5.56 (m, 1H, C*H*OH), 5.01–4.96 (m, 2H, CH═CH_2), 4.53 (s, 2H, CH_2O), 3.82 (p, J = 5.7 Hz, 1H, C*H*OSi), 3.72–3.57 (m, 2H, CH_2CH═), 2.29–2.28 (m, 2H, $CH_2{\equiv}$), 2.01 (d, J = 5.6 Hz, 1H, OH), 1.72–1.67 (m, 2H, CH_2), 1.48 (s, 9H, $(H_3C)_3CO$), 1.43–1.37 (m, 2H, CH_2), 1.25–1.11 (m, 6H, $3CH_2$), 1.05 (s, 9H, $(H_3C)_3CSi$), 0.80 (t, J = 7.2 Hz, 3H,

CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.0 (CO), 156.0 (C), 140.8 (C), 136.9 (CH) 135.90 (2CH), 135.88 (2CH), 134.5 (C), 134.3 (C) 129.5 (CH), 129.4 (CH), 127.5 (2CH), 127.4 (2CH), 127.2 (CH), 126.5 (C), 120.1 (CH), 114.9 (CH_2), 111.5 (CH), 87.3 (C), 82.2 (C), 79.7 (C), 72.2 (CH), 66.4 (CH_2), 62.1 (CH), 36.2 (CH_2), 35.1 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 28.0 ($3CH_3$), 27.0 ($3CH_3$), 24.5 (CH_2), 22.5 (CH_2), 19.4 (C), 14.8 (CH_2), 14.0 (CH_3) ppm. IR (NaCl) ν = 3517, 3072, 2953, 2930, 2857, 2332, 1753, 1734, 1588, and 1469 cm^{-1}. Elemental analysis calcd for $C_{42}H_{56}O_5Si$: C, 75.41; H, 8.44; Si, 4.21; found: C, 75.59; H, 8.29.

tert-Butyl 2-(2-allyl-3-((1*S*,6*S*)-6-*tert*-butyldiphenylsilyloxy-1-*tert*-butyldimethylsilyloxyundec-2-yn-1-yl)phenoxy)acetate (21)

12.45 g (18.6 mmol) of TBDMSCl (3.36 g, 22.32 mol) was added to a stirred and cooled (0 °C) solution of (1*S*,6*S*)-**19** (12.45 g, 18.6 mmol), imidazole (1.5 g, 22.32 mol), 4-(dimethylamino)pyridine (283 mg, 2.32 mmol), and DMF (1.5 mL) in dichloromethane (15 mL) under argon. The reaction mixture was slowly warmed to room temperature and stirring was continued for 15 h. The reaction mixture was washed with water (20 mL) and brine (20 mL) and concentrated *in vacuo*. The resulting viscous liquid was purified by silica gel column chromatography in hexane : ethyl acetate (12 : 1) to give 13.3 g (16.9 mmol) of **21** (91% yield). R_f: 0.53 (hexane/AcOEt 9 : 1). $[\alpha]_D^{25}$ −7.14 (c 0.40, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66–7.63 (m, 4H, Ar), 7.42–7.32 (m, 6H, Ar), 7.29 (dd, J_1 = 7.8 Hz, J_2 = 1.1 Hz, 1H, Ar), 7.16 (t, J = 8.0 Hz, 1H, Ar), 6.67 (dd, J_1 = 8.2 Hz, J_2 = 1.2 Hz, 1H, Ar), 6.04–5.93 (m, 1H, C*H*═CH_2), 5.56–5.54 (m, 1H, C*H*OTBS), 4.99–4.94 (m, 2H, CH═CH_2), 4.51 (s, 2H, CH_2O), 3.75 (p, J = 5.6 Hz, 1H, CHOSi), 3.68–3.51 (m, 2H, CH_2CH═), 2.25–2.14 (m, 2H, CH_2≡), 1.70–1.61 (m, 2H, CH_2), 1.47 (s, 9H, $(H_3C)_3CO$), 1.38–1.32 (m, 2H, CH_2), 1.16–1.11 (m, 4H, $2CH_2$), 1.03 (s, 9H, $(H_3C)_3CSi$), 0.90 (s, 9H, $(H_3C)_3CSi$), 0.92–0.87 (m, 2H, CH_2), 0.78 (t, J = 7.2 Hz, 3H, CH_3), 0.09 (s, 3H, H_3CSi) 0.08 (s, 3H, H_3CSi) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.2 (CO), 155.9 (C) 142.4 (C), 136.5 (CH), 135.86 (2CH), 135.84 (2CH), 134.6 (C), 134.3 (C), 129.5 (CH), 129.4 (CH), 127.5 (2CH), 127.4 (2CH), 126.9 (CH), 125.4 (C), 119.4 (CH), 114.6 (CH_2), 110.7 (CH), 85.8 (C), 82.1 (C), 80.7 (C), 72.4 (CH), 66.5 (CH_2), 62.3 (CH), 36.1 (CH_2), 35.1 (CH_2), 31.7 (CH_2), 29.6 (CH_2), 28.0 ($3CH_3$), 27.1 ($3CH_3$), 25.9 ($3CH_3$), 24.5 (CH_2), 22.5 (CH_2), 19.4 (C), 18.3 (C), 14.7 (CH_2), 13.9 (CH_3), −4.5 (CH_3), −4.8 (CH_3) ppm. IR (NaCl) ν = 2953, 2932, 2859, 2330, 1753, 1659, 1583 and 1466 cm^{-1}. Elemental analysis calcd for $C_{48}H_{70}O_5Si_2$: C, 73.61; H, 9.01; Si, 7.17; found: C, 73.74; H, 8.88.

tert-Butyl 2-(((4*R*,9a*S*)-4-((*tert*-butyldimethylsilyl)oxy)-3-((*S*)-3-((*tert*-butyldiphenylsilyl)oxy)octyl)-2-oxo-2,4,9,9a-tetrahydro-1*H*-cyclopenta[*b*]naphthalen-8-yl)oxy)acetate (22)

PKR optimization: $Co_2(CO)_8$ was dissolved in 0.5 mL of toluene. Then, 769 mg (1 mmol) of **21** was added and the solution is diluted with toluene until a final volume of 2 mL was reached (measured in a volumetric flask). The solution was degassed with Ar for 10 min and filtered through a 0.45 μm nylon filter. 0.8 mL were injected each time through a Rheodyne valve. The system was configured as shown in Scheme 5. Reaction conditions for the long run with 7.5 g of **21** (9.58 mmol) were dissolved in toluene until a final volume of 32 mL (0.3 M) and 164 mg of $Co_2(CO)_8$ (0.48 mmol, 5 mol%) was achieved. The solution is degassed with Ar for 15 min and filtered through a 0.45 μm nylon filter. The solution is placed in the pump inlet and the conditions were: temperature: 170 °C; pressure: 20 bar; 3 equivalents of CO; pump flow 1: 0.66 mL min^{-1}; CO flow: 15 mLN min^{-1}; reactor volume: 60.6 mL; residence time: 40 min; total time: 1 h 45 min. The solution was collected in a flask and it was washed with 1N HCl solution (25 mL). Then, it was washed with water (25 mL) and brine (25 mL), dried with Na_2SO_4, and concentrated *in vacuo*. 7.8 g of crude viscous brown oil were purified by silica gel column chromatography in a solvent gradient from hexane to hexane : ethyl acetate (12 : 1) to yield 5.75 g (74%). Samples of the crude reaction mixture were collected for Co determination (by ICP), after washing with HCl (1N) and samples of the pure compound were collected (after column chromatography) and they were digested with nitric acid. R_f: 0.43 (hexane/AcOEt 9 : 1). $[\alpha]_D^{25}$ −87.4 (c 0.42, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.59 (m, 4H, Ar), 7.42–7.25 (m, 6H), 7.19 (t, J = 7.9 Hz, 1H, Ar), 6.87 (d, J = 7.6 Hz, 1H, Ar), 6.66 (d, J = 7.7 Hz, 1H, Ar), 5.47 (s, 1H, C*H*OTBS), 4.54 (s, 2H, CH_2O), 3.75–3.71 (m, 1H, CHOSi), 3.62 (dd, J_1 = 17.2 Hz, J_2 = 7.5 Hz, 1H, C*H*HAr), 3.37–3.30 (m, 1H, C*H*), 2.67 (dd, J_1 = 18.8 Hz, J_2 = 6.4 Hz, 1H, C*H*HCO), 2.44–2.34 (m, 1H, C*H*HAr), 2.29–2.19 (m, 2H, C*H*HCO and C*H*HC═), 1.68–1.59 (m, 2H, C*H*HC = and C*H*H), 1.48 (s, 9H, $(H_3C)_3CO$), 1.44–1.36 (m, 3H, CH_2 and C*H*H), 1.18–1.11 (m, 6H, $3CH_2$), 1.06 (s, 9H, $(H_3C)_3CSi$), 0.81 (s, 9H, $(H_3C)_3CSi$), 0.78 (t, J = 7.2 Hz, 3H, CH_3), 0.10 (s, 3H, H_3CSi), 0.05 (s, 3H, H_3CSi) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5 (CO), 171.9 (CO), 167.9 (C), 155.2 (C), 138.7 (C), 137.6 (C), 135.87 (2CH), 135.85 (2CH), 134.7 (C), 134.2 (C), 129.42 (CH), 129.38 (CH), 127.4 (2CH), 127.3 (2CH), 127.2 (CH), 125.6 (C), 122.9 (CH), 110.2 (CH), 82.3 (C), 72.9 (CH), 65.8 (CH_2), 65.3 (CH), 42.1 (CH_2), 35.9 (CH_2), 34.5 (CH_2), 33.3 (CH_2), 32.0 (CH_2), 31.7 (CH_2), 28.0 ($3CH_3$), 27.1 ($3CH_3$), 25.6 ($3CH_3$), 24.5 (CH_2), 22.5 (CH_2), 19.4 (C), 18.6 (C), 18.0 (CH_2), 14.0 (CH_3), −4.1 (CH_3), −4.2 (CH_3) ppm. IR (NaCl) ν = 2956, 2936, 2958, 2754, 1754, 1707, 1664, 1589, and 1475 cm^{-1}. Elemental analysis calcd for $C_{49}H_{70}O_6Si_2$: C, 72.55; H, 8.70; Si, 6.92; found: C, 72.67; H, 8.91. ICP (Co, measured at λ = 230.786, 238.892 and 240.725 nm): <0.2 ppm for the pure compound, 1885 for the crude reaction product, and 3300 in the sample just coming out the reactor.

tert-Butyl 2-(((8*R*)-8-((*tert*-butyldimethylsilyl)oxy)-1-((*S*)-3-((*tert*-butyldiphenylsilyl)oxy)octyl)-3-methyl-2-oxo-2,3,3a,8-tetrahydrocyclopenta[*a*]inden-4-yl)oxy)acetate (**22′**). The scaled up reaction with 7.5 g of **21** was purified by column chromatography providing, in addition to **22**, 310 mg (4% yield) of **22′** as the only detectable side product. This product is formed by isomerization of the double bond in the substrate followed by the PK reaction. Pale yellow oil. R_f: 0.46 (hexane/AcOEt 9 : 1) ^1H NMR (400 MHz, $CDCl_3$) δ 7.69–7.63 (m, 4H, Ar), 7.41–7.32 (m, 6H, Ar), 7.22 (t, J = 7.9 Hz, 1H, Ar), 7.03 (d, J = 7.5 Hz, 1H, Ar),

6.71 (d, J = 8.2 Hz, 1H, Ar), 5.56 (s, 1H, CHOTBDMS), 4.57 (s, 2H, CH_2O), 3.97 (d, J = 4.0 Hz, 1H, C*H*CHCH$_3$), 3.75 (p, J = 5.6 Hz, 1H, CHOSi), 2.43 (m, 2H, C*H*CH$_3$ and C*H*HC═), 2.32–2.24 (m, 1H, C*H*HC═), 1.67–1.60 (m, 2H, CH_2), 1.55 (d, J = 7.2 Hz, 3H, CH_3CH), 1.48 (s, 9H, $(H_3C)_3CO$), 1.44–1.35 (m, 2H, CH_2), 1.18–0.99 (m, 6H, 3CH_2), 1.07 (s, 9H, $(H_3C)_3CSi$), 0.83 (s, 9H, $(H_3C)_3CSi$), 0.78 (t, J = 7.2 Hz, 3H, CH_3CH_2), 0.12 (s, 3H, CH_3Si), 0.10 (s, 3H, CH_3Si) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.9 (CO), 172.7 (CO), 167.6 (C), 154.4 (C), 147.1 (C), 137.2 (C), 135.91 (2CH), 135.89 (2CH), 134.7 (C), 134.2 (C), 131.8 (C), 129.5 (CH), 129.4 (CH), 128.8 (CH), 127.5 (2CH), 127.3 (2CH), 118.4 (CH), 111.4 (CH), 82.4 (C), 73.2 (CH), 69.7 (CH), 65.7 (CH_2), 51.9 (CH), 48.9 (CH), 36.2 (CH_2), 34.3 (CH_2), 31.7 (CH_2), 28.0 (3CH_3), 27.1 (3CH_3), 25.6 (3CH_3), 24.4 (CH_2), 22.5 (CH_2), 20.0 (CH_2), 19.4 (C), 18.0 (C), 14.1 (CH_3), 14.0 (CH_3), −4.1 (CH_3), −4.2 (CH_3) ppm. IR (NaCl) ν = 2956, 2932, 2860, 1749, 1725, 1590 cm^{-1}. Elemental analysis calcd for $C_{49}H_{70}O_6Si_2$: C, 72.55; H, 8.70; Si, 6.92; found: C, 72.72; H, 8.84.

tert-Butyl 2-(((3a*S*,9a*S*)-1-((*S*)-3-((*tert*-butyldiphenylsilyl)oxy) octyl)-2-oxo-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[b] naphthalen-5-yl)oxy)acetate (23)

To a solution of **22** (5.6 g, 7.02 mmol) in absolute ethanol (60 mL) were added anhydrous K_2CO_3 (280 mg, 5% w/w) and 10% Pd/C (1.4 g, 50% wet, 25% w/w) and the mixture was hydrogenated at 3 bar of pressure. After 15 h stirring at room temperature, the pressure was carefully released, and the reaction mixture was filtered through Celite and washed with DCM (100 mL). Silica gel column chromatography in hexane : ethyl acetate (15 : 1) gave **23** as mixture of 2 stereoisomers in a 3 : 1 ratio measured by ^{1}H NMR. 3.60 g (75% yield). A small sample of each isomer was isolated for characterization. Major isomer: R_f: 0.51 (hexane/AcOEt 6 : 1). ^{1}H NMR (400 MHz $CDCl_3$) δ 7.67–7.64 (m, 4H, Ar), 7.40–7.31 (m, 6H, Ar), 7.08 (t, J = 7.8 Hz, 1H, Ar), 6.71 (d, J = 7.6 Hz, 1H, Ar), 6.57 (d, J = 8.1 Hz, 1H, Ar), 4.51 (s, 2H, CH_2O), 3.73 (p, J = 5.1 Hz, 1H), 3.07 (dd, J_1 = 16.9 Hz, J_2 = 6.7 Hz, 1H, C*H*H), 2.87 (dd, J_1 = 16.4 Hz, J_2 = 6.6 Hz, 1H, C*H*H), 2.54–2.44 (m, 2H, CH and C*H*H), 2.40–2.33 (m, 2H, CH_2), 2.18–2.08 (m, 2H, C*H*H and CH), 1.77–1.73 (m, 1H, CH), 1.48 (s, 9H, $(H_3C)_3CO$), 1.51–1.40 (m, 6H, 3CH_2), 1.26–1.08 (m, 6H, 3CH_2), 1.05 (s, 9H, $(H_3C)_3CSi$), 0.82 (t, J = 7.1 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz $CDCl_3$) δ 220.4 (CO), 168.1 (CO), 155.1 (C) 137.2 (C), 135.9 (4CH), 134.7 (C), 134.5 (C) 129.4 (2CH), 127.41 (2CH), 127.38 (2CH), 126.2 (CH), 125.1 (C), 121.8 (CH), 108.4 (CH), 82.2 (C), 73.2 (CH), 65.8 (CH_2), 51.8 (CH), 45.1 (CH_2), 38.6 (CH), 36.0 (CH_2), 33.3 (CH_2), 31.82 (CH_2), 31.79 (CH_2), 30.5 (CH), 28.0 (3CH_3), 27.1 (3CH_3), 25.5 (CH_2), 24.6 (CH_2), 23.8 (CH_2), 22.5 (CH_2), 19.4 (C), 14.0 (CH_3) ppm. IR (NaCl) ν = 2955, 2930, 2856, 1737 and 1590 cm^{-1}. Elemental analysis calcd for $C_{43}H_{58}O_5Si$: C, 75.62; H, 8.56; Si, 7.17; found: C, 74.90; H, 8.39. Minor isomer: R_f: 0.48 (hexane/AcOEt 6 : 1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73–7.64 (m, 4H, Ar), 7.41–7.33 (m, 6H, Ar), 7.07 (t, J = 7.9 Hz, 1H, Ar), 6.68 (d, J = 7.7 Hz, 1H, Ar), 6.55 (d, J = 8.1 Hz, 1H, Ar), 4.53 (s, 2H, CH_2O), 3.75 (p, J = 5.8 Hz, 1H, CHOSi), 3.04–2.84 (m, 2H, CH_2), 2.63–2.53 (m, 1H, CH), 2.51–2.29 (m, 3H, CH and CH_2), 2.20–2.03 (m, 2H, CH_2), 1.87 (dd, J_1 = 18.8 Hz, J_2 = 12.1 Hz, 1H, C*H*H), 1.81–1.72 (m, 1H, CH), 1.50 (s, 9H, $(H_3C)_3CO$), 1.50–1.44 (m, 3H, C*H*H and CH_2), 1.30–1.18 (m, 8H, 4CH_2), 1.07 (s, 9H, $(H_3C)_3CSi$), 0.84 (t, J = 7.2 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, $CDCl_3$) δ 219.2 (CO), 168.1 (CO), 155.9 (C), 136.2 (C) 135.9 (4CH), 135.9 (C), 134.6 (C), 134.5 (C) 129.5 (CH), 129.4 (CH), 127.45 (2CH), 127.39 (2CH), 125.9 (CH), 122.0 (CH), 108.1 (CH), 82.2 (C), 73.3 (CH), 65.6 (CH_2), 57.0 (CH), 41.4 (CH_2), 36.3 (CH_2), 34.9 (CH_2), 34.7 (CH_2), 31.8 (CH_2), 31.4 (CH), 28.0 (3CH_3), 27.1 (3CH_3), 26.4 (CH_2), 24.5 (CH_2), 24.3 (CH_2), 22.6 (CH_2), 20.1(CH_2), 19.4 (C), 14.0 (CH_3) ppm. IR (NaCl) ν = 2952, 2927, 2858, 1740 and 1588 cm^{-1}. Elemental analysis calcd for $C_{43}H_{58}O_5Si$: C, 75.62; H, 8.56; Si, 7.17; found: C, 75.00; H, 8.41.

2-(((1*R*,2*R*,3a*S*,9a*S*)-1-((*S*)-3-((*tert*-Butyldiphenylsilyl)oxy)octyl)-2-hydroxy-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[b] naphthalen-5-yl)oxy)acetic acid (24)

To a cooled (−10 °C) and stirred solution of **23** (3.5 g, 5.12 mmol) in ethanol (20 mL) was added a 5 M aqueous sodium hydroxide solution (10.2 mL, 51.2 mmol). The reaction mixture was stirred for 30 min and then $NaBH_4$ (203 mg, 5.38 mmol, 1.05 equiv.) was added and stirring was continued at −10 °C for 1 h. An additional equiv. of $NaBH_4$ (203 mg) was added and stirring was continued for another 12 h at 0 °C. Upon completion (TLC), the reaction mixture was quenched with glacial acetic acid until pH 2–3 was achieved and the solvent was removed *in vacuo*. The crude reaction mixture was dissolved in ethyl acetate (25 mL), washed with 1N HCl (20 mL), water (20 mL), and brine (20 mL), dried with Na_2SO_4 and concentrated *in vacuo* to obtain 3.1 g of crude tricyclic alcohol **24** as a white solid. This was used for the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.67 (m, 4H, Ar), 7.41–7.34 (m, 6H, Ar), 7.08 (t, J = 7.8 Hz, 1H, Ar), 6.75 (d, J = 7.5 Hz, 1H, Ar), 6.67 (d, J = 8.3 Hz, 1H, Ar), 4.66 (s, 2H, CH_2O), 3.76–3.70 (m, 1H, C*H*OH), 3.61–3.55 (d, J = 7.4 Hz, 1H, C*H*OSi), 2.79 (dd, J_1 = 14.8 Hz, J_2 = 6.0 Hz, 1H, C*H*H), 2.62 (dd, J_1 = 14.3 Hz, J_2 = 6.1, 1H, C*H*H), 2.52 (dd, J_1 = 14.7 Hz, J_2 = 6.4 Hz, 1H, C*H*H), 2.33 (dd, J_1 = 14.2 Hz, J_2 = 6.4 Hz, 1H, C*H*H), 2.23–2.01 (m, 2H, C*H*H, and CH), 1.78–1.70 (m, 1H, CH), 1.54–1.42 (m, 6H, 3CH_2), 1.29–1.01 (m, 8H, 3CH_2, CH and C*H*H), 1.06 (s, 9H, $(H_3C)_3CSi$), 0.83 (t, J = 7.2 Hz, 3H, CH_3) ppm.^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6 (CO), 153.6 (C), 140.0 (C), 134.9 (4CH), 133.8 (C), 133.6 (C), 128.4 (2CH), 126.6 (C), 126.4 (4CH), 125.1 (CH), 120.9 (CH), 108.7 (CH), 76.1 (CH), 72.6 (CH), 64.5 (CH_2), 51.2 (CH), 40.0 (CH_2), 39.8 (CH), 35.1 (CH_2), 33.0 (CH_2), 32.7 (CH_2), 31.7 (CH), 30.9 (CH_2), 26.5 (CH_2), 26.1 (3CH_3), 24.8 (CH_2), 23.7 (CH_2), 21.6 (CH_2), 18.4 (C), 13.0 (CH_3) ppm. IR (NaCl) ν = 3417, 2952, 2934, 2857, 1734 and 1585 cm^{-1}.

2-(((1*R*,2*R*,3a*S*,9a*S*)-2-Hydroxy-1-((*S*)-3-hydroxyoctyl)-2,3,3a,4,9,9a-hexahydro-1*H*-cyclopenta[*b*]naphthalen-5-yl)oxy) acetic acid, treprostinil (1)

To a stirred and cooled solution of the 3.1 g of the crude acid in THF (31 mL) and pyridine (1.8 mL, 3.5 equiv.) in a falcon

tube, HF/pyridine (1.8 mL) was carefully added dropwise. The reaction mixture was allowed to warm to room temperature and stirred overnight (15 h). The reaction was quenched by adding $NaHCO_3$ until basic pH was achieved. Hexane (35 mL) was added to the mixture, and it was stirred at room temperature for 15 minutes. The organic and aqueous phases were separated, and the aqueous phase was extracted with hexane (2 × 30 mL). Then, 1N HCl was carefully added to the aqueous phase until pH 2–3 was achieved, and it was extracted with ethyl acetate (3 × 40 mL). These latter organic layers were washed with water (50 mL) and brine (50 mL), dried with Na_2SO_4, and concentrated *in vacuo* to give crude treprostinil which was recrystallized in EtOH : H_2O (1 : 1) to afford 1.6 g (80% yield from **23**) as a white solid. M.p.: 123–125 °C (lit 125–126 °C). Spectroscopic and physical data were identical to those obtained from a sample of treprostinil provided by Aldrich (see the ESI† for comparison). $[\alpha]_D^{25}$ +28.0 (c 0.05, EtOH, lit + 34.0, c 0.45, EtOH). ^{1}H NMR (400 MHz, D_3COD) δ 7.04 (t, J = 7.8 Hz, 1H, Ar), 6.79 (d, J = 7.5 Hz, 1H, Ar), 6.69 (d, J = 8.3 Hz, 1H, Ar), 4.62 (s, 2H, CH_2O), 3.62 (td, J_1 = 9.9 Hz, J_2 = 6.2 Hz, 1H, H2), 3.54–3.51 (m, 1H, H3′), 2.75 (td, J_1 = 14.8 Hz, J_2 = 6.1 Hz, 2H, H4 and H9), 2.64 (dd, J_1 = 14.7 Hz, J_2 = 5.9 Hz, 1H, H4), 2.49 (dd, J_1 = 14.2 Hz, J_2 = 5.9 Hz, 1H, H9), 2.30–2.21 (m, 1H, H4a), 2.08 (dt, J_1 = 13.4 Hz, J_2 = 6.8 Hz, 1H, H3), 1.91 (tt, J_1 = 10.6 Hz, J_2 = 6.0 Hz, 1H, H9a), 1.96–1.84 (m, 1H, H1′), 1.65–1.27 (m, 11H, H1′, 2H2′, 2H4′, 2H5′, 2H6′, 2H7′), 1.24–1.16 (m, 1H, 1H, H1), 1.14–1.06 (m, 1H, H3), 0.92 (t, J = 6.8 Hz, 3H, CH_3) ppm. ^{13}C NMR (101 MHz, D_3COD) δ 172.9 (CO), 156.5 (C), 142.2 (C), 128.7 (C), 127.2 (CH), 122.4 (CH), 110.8 (CH), 77.6 (CH), 72.9 (CH), 66.5 (CH_2), 52.7 (CH), 42.3 (CH), 42.0 (CH_2), 38.3 (CH_2), 36.0 (CH_2), 34.6 (CH_2), 34.1 (CH), 33.2 (CH_2), 29.6 (CH_2), 26.6 (CH_2), 26.5 (CH_2), 23.8 (CH_2), 14.5 (CH_3) ppm. IR (NaCl) ν = 3438, 3337, 3049, 2930, 2848 and 1737 cm^{-1}. Elemental analysis calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78. Found: C, 70.51; H, 8.89.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

Funding of this project by the Spanish MINECO, grant No. RTI2018-095588-B-I00 (Co-funded by the European Regional Development Fund/European Social Fund, "Investing in your future") and FUSP-CEU (PC17/17) is acknowledged. J. G. thanks the Fundación San Pablo-CEU for a pre-doctoral fellowship.

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