Tetrahedron 69 (2013) 1634–1648

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

A novel convergent synthesis of the potent antiglaucoma agent travoprost

Iwona Dams [a,*], Michał Chodyński [a], Małgorzata Krupa [a], Anita Pietraszek [a], Marta Zezula [a], Piotr Cmoch [a,b], Monika Kosińska [a], Andrzej Kutner [a]

[a] R&D Chemistry Department, Pharmaceutical Research Institute, Rydygiera 8, 01-793 Warsaw, Poland
[b] Institute of Organic Chemistry, Polish Academy of Sciences, Kasprzaka 44/52, 01-224 Warsaw, Poland

ARTICLE INFO

Article history:
Received 20 June 2012
Received in revised form 11 November 2012
Accepted 26 November 2012
Available online 1 December 2012

Keywords:
Travoprost
Prostaglandins
Corey lactone
Nucleophilic addition

ABSTRACT

The 16-(3-trifluoromethyl)phenoxy $PGF_{2\alpha}$ analogue travoprost (**8a**) has potent topical ocular activity. A novel convergent synthesis of 13,14-en-15-ol $PGF_{2\alpha}$ analogues was developed employing Julia–Lythgoe olefination of the structurally advanced prostaglandin phenylsulfone (5*Z*)-(+)-**15** with a new enantiomerically pure aldehyde ω-chain synthon (*S*)-(−)-**16a**. Subsequent hydrolysis of protecting groups and final esterification of fluprostenol (**7a**) yielded travoprost (**8a**). The main advantages are the preparation of high purity travoprost (**8a**) and the application of comparatively cheap reagents. The novel convergent strategy allows the synthesis of a whole series of 13,14-en-15-ol $PGF_{2\alpha}$ analogues from a common and structurally advanced prostaglandin intermediate **15**. The preparation and identification of two synthetic impurities, 15-*epi* isomer (**8b**) of travoprost and a new prostaglandin related ester (5*Z*)-(+)-**18**, are also described.

1. Introduction

Glaucoma is a slowly progressive disease leading to optic nerve damage and irreversible loss of vision. It is the second most common cause of world blindness with estimated cases reaching 79.6 million by the year 2020.[1] Although the aetiology of glaucoma is multi-factorial, elevated intraocular pressure (IOP) is the only modifiable factor proven to alter the natural course of the disease. Numerous studies have shown that pharmacological IOP reduction prevents glaucoma or delays progression of glaucomatous damage.[2] Among various topical IOP-lowering medications currently available, prostaglandin analogues (Fig. 1) are the newest and the most potent class of first-line hypotensive drugs with a proven safety and efficacy.[3]

Endogenous prostaglandin $F_{2\alpha}$ (**1**) and its synthetic pro-drugs, such as $PGF_{2\alpha}$ isopropyl ester **2**, reduce IOP in animals and humans, but also cause conjunctival hyperaemia and foreign-body sensation.[4] Intense drug discovery efforts over decades, designed to improve the therapeutic index of the naturally occurring $PGF_{2\alpha}$, have yielded five FP-class prostaglandin drugs with extraordinary efficacy and relatively acceptable side effects. Unoprostone isopropyl ester (**4**, Rescula®, Ciba Vision, Duluth, GA), latanoprost (**6**, Xalatan®, Pfizer, New York, NY), travoprost (**8a**, Travatan®, Alcon, Fort Worth, TX), bimatoprost (**10**, Lumigan®, Allergan, Irvine, CA) and tafluprost (**12**, Taflotan®, Santen Oy, Finland) are the active ingredients of topical hypotensive medications approved by US FDA and EMEA for use as first-line agents for reducing IOP in patients with glaucoma or ocular hypertension.

The individual response to hypotensive pharmacotherapy in glaucomatous patients is different, which creates a continuous demand for a whole range of active $PGF_{2\alpha}$ analogues. Synthesis of diverse prostaglandin analogues over the past decades has attracted attention of many organic chemists as attested by the number of papers dealing with this subject. So far, however, there is no convergent methodology that would allow effective and highly diastereoselective preparation of a whole series of $PGF_{2\alpha}$ analogues from a common and structurally advanced prostaglandin intermediate. Most synthetic procedures used to attain $PGF_{2\alpha}$ (**1**) and its analogues **2**–**12** employ one of the known variants of the Corey method, in which lower and upper side chains are sequentially attached in a specific order to a derivative of the commercially available (−)-Corey aldehyde/lactone.[5–14] The Corey strategy involves first the installation of the lower side chain (ω-chain) via a Horner–Wadsworth–Emmons (HWE) condensation of the Corey aldehyde with a suitable ketophosphonate. The HWE reaction is generally affected by some drawbacks, such as easy epimerization of labile stereogenic centres[15] and, depending on the base used for deprotonation, formation of additional side products.[16] Subsequent reduction of the ω-chain 13,14-en-15-one to a 13,14-en-16-ol (prostaglandin

* Corresponding author. Tel.: +48 22 456 39 29; fax: +48 22 456 38 38; e-mail address: i.dams@ifarm.eu (I. Dams).

0040-4020/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2012.11.087

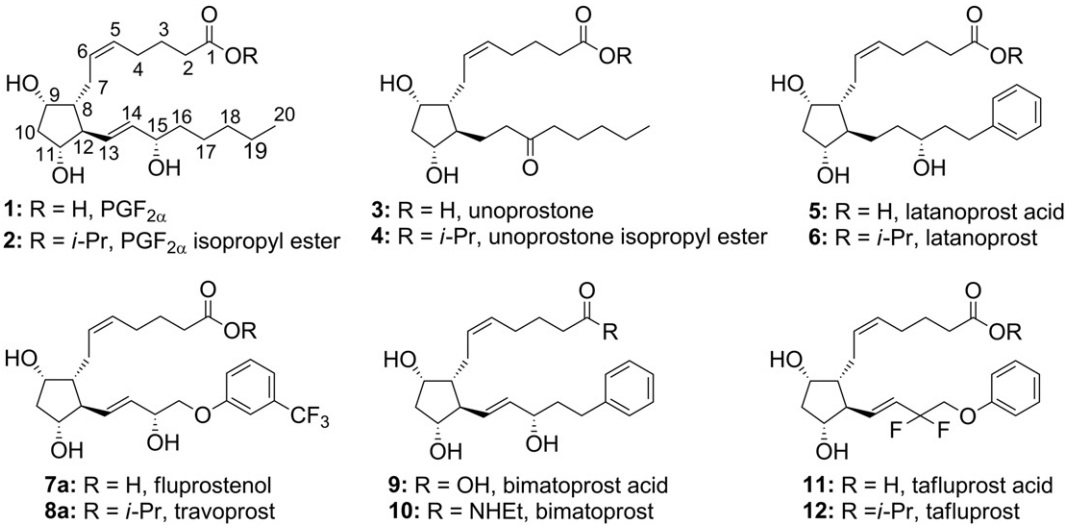


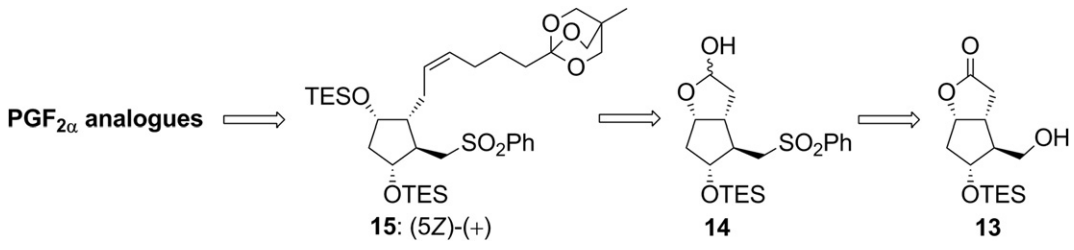
Fig. 1. Chemical structure of $PGF_{2\alpha}$ (**1**) and synthetic prostanoids **2**–**12** used in the therapy of glaucoma.

numbering, Fig. 1), addition of the α-chain by Wittig olefination leading to a *cis*-5,6-alkene and some further simple transformations comprise a sequence of reactions needed for the Corey synthesis of *trans*-13,14-en-15-ol $PGF_{2\alpha}$ analogues, such as travoprost (**8a**) and bimatoprost (**10**). Other methods for the preparation of $PGF_{2\alpha}$ analogues from the (−)-Corey lactone were reported, in which the introduction of the ω-chain already in the correct stereochemical arrangement preceded the attachment of the α-chain.[8,18–20] The problematic reduction of a 13-en-15-one to the corresponding 13-en-15-ol was avoided; however, the efficiency of these approaches was poor.

The tedious nature of prostaglandin purification and separation of diastereoisomers necessitates a highly diastereoselective industrial preparation of $PGF_{2\alpha}$ analogues used as active pharmaceutical ingredients. The multiple chiral centres present in prostaglandin molecules continue to create practical challenges and existing synthetic routes to $PGF_{2\alpha}$ analogues by the Corey strategy, in spite of considerable progress made in this field, are not completely free of contaminating diastereoisomers. Besides the α-chain 5,6-*trans* diastereoisomer typically formed from the Wittig reaction, particular difficulty has been associated with maintaining the purity at the ω-chain C-15 carbinol asymmetric centre, which typically is formed by a diastereoselective reduction. The known methods for such reduction require expensive reagents, often low-temperature conditions and, in practice, do not lead to a completely stereoselective formation of the desired prostaglandin diastereoisomer.[5–13,17] The 15-*epi* isomers of diverse $PGF_{2\alpha}$ analogues, including (15*S*)-latanoprost, (15*S*)-travoprost (**8b**) and (15*R*)-bimatoprost, have been reported to form even in diastereoselective reduction of the ω-chain 15-keto function in amounts exceeding at least several percent.[5–13,17] The physicochemical properties of 15*R*/15*S* $PGF_{2\alpha}$ diastereoisomers are usually very similar, so it is not a straightforward task to discern between them by NMR spectroscopy, optical rotation or even by analytical reverse-phase HPLC. Furthermore, the application of preparative scale HPLC to remove even small amounts of undesired 15-*epi* isomer is usually very costly and far from trivial, while 5,6-*trans* diastereoisomer is much easier to separate.

A growing demand for hypotensive $PGF_{2\alpha}$ analogues stimulates the need for the development of a novel convergent strategy for prostaglandin synthesis that would also overcome disadvantages of existing synthetic methods. The Corey lactone still provides the most facile and practical access to $PGF_{2\alpha}$ analogues, yet the difficulties with 15-*epi* isomers need to be overcome. In 2007, we reported the preparation of the structurally advanced prostaglandin phenylsulfone (5*Z*)-(+)-**15** (Scheme 1) with the attached α-chain possessing a carboxyl group protected by 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (methyl-OBO).[21]

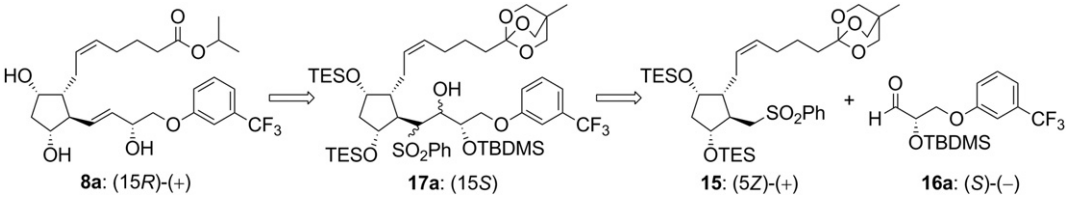
The ω-chain elongation of the phenylsulfone **15** by S_N2 alkylation with enantiomerically pure alkyl halides allowed the synthesis of 13,14-dihydro-15-ol $PGF_{2\alpha}$ analogues with the desired C-15 asymmetric centre configuration, such as latanoprost (**6**). Importantly, we envisaged that the new prostaglandin key intermediate **15** could find applications in the convergent syntheses of diverse active prostaglandins and related compounds, depending on the structure of the ω-chain and the sequence of chemical reactions needed for the ω-chain elongation. Since three other commercially available 13,14-en-15-ol $PGF_{2\alpha}$ drugs, precisely travoprost (**8**), bimatoprost (**10**) and tafluprost (**12**), contain the *trans*-13,14-double bond in the ω-chain, a new approach for the highly diastereoselective construction of the ω-chain allylic alcohol



Scheme 1. Strategy for convergent synthesis of $PGF_{2\alpha}$ analogues via prostaglandin phenylsulfone **15**, based on the reverse order of side chain attachment to the derivative of Corey lactone (**13**).

moiety with the desired C-15 asymmetric centre configuration needed to be developed.

Travoprost (**8a**) is a commonly prescribed synthetic prostaglandin analogue that continues to hold a key position in the antiglaucoma drug market with a global sale of over US $940 million in 2011. Travoprost has been shown to lower intraocular pressure more efficiently than latanoprost over a 24-h period.[22] As a result of growing demand for prostaglandins antiglaucoma drugs in the pharmaceutical market, we have developed a novel convergent synthesis of travoprost (**8a**) from the structurally advanced prostaglandin phenylsulfone **15** and a new, enantiomerically pure α-hydroxy protected aldehyde (*S*)-(−)-**16a** (Scheme 2). The paper describes the first application of the potent prostaglandin intermediate **15** to the highly diastereoselective synthesis of *trans*-13,14-en-15-ol $PGF_{2\alpha}$ analogues with the desired C-15 asymmetric centre configuration, based on the reverse order of side chain attachment to the Corey lactone via Wittig and Julia–Lythgoe olefinations. The preparation and identification of two synthetic impurities, 15-*epi* isomer ((15*S*)-(+)-**8b**) of travoprost and a new prostaglandin related ester (5*Z*)-(+)-**18** (Fig. 2), are also described.



Scheme 2. A novel strategy for convergent synthesis of travoprost (**8a**) from phenylsulfone **15** and aldehyde **16a**.

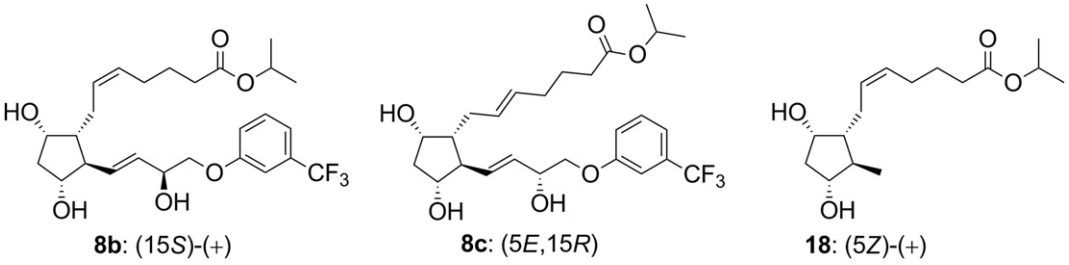


Fig. 2. Structures of the key impurities **8b**, **8c** and **18** of travoprost.

2. Results and discussion

The accessibility of the stable prostaglandin phenylsulfone **15** (Scheme 1) drew our attention to Julia–Lythgoe olefination,[23] which via reductive elimination of β-hydroxy sulfones could enable construction of the allylic alcohol moiety of various prostaglandins. The unique stereochemical features of the Julia–Lythgoe olefination should allow to preserve the relative cis/trans stereochemistry of side chains in the phenylsulfone **15** and give rise to the stereodefined *trans*-13,14-double bond (prostaglandin numbering, Fig. 1) required in the ω-chain. It is well documented that sodium amalgam reduction of aliphatic α-hydroxy sulfones furnishes olefins having the trans configuration of the ω-chain 13,14-double bond.[23b] Additionally, the appropriately functionalized aldehydes with steric encumbrance should afford trans alkenes as the only products of the Julia reaction.[24]

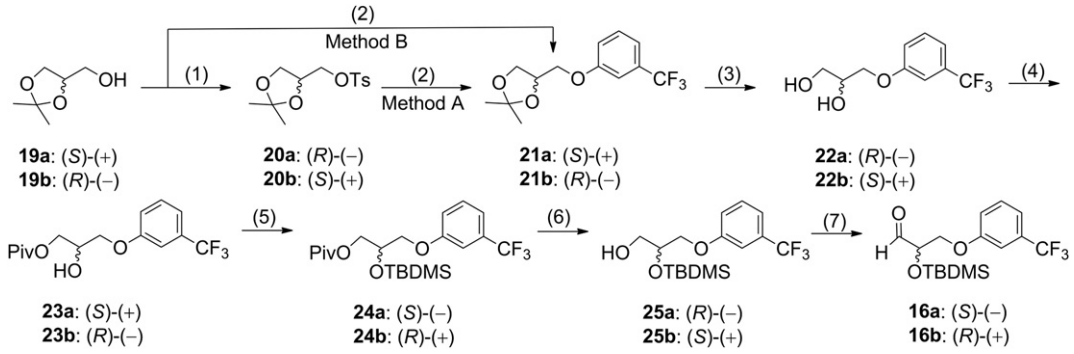
In the chemical structure of travoprost (**8a**) carbon 17 position in the ω-chain is substituted by a phenoxy group with a trifluoromethyl constituent. We envisaged that combining of the sulfone **15** (Scheme 2) with the α-hydroxy protected aldehyde **16a** should give a mixture of hydroxy sulfones **17a**, which in a few simple steps could be transformed to travoprost **8a**. Since the first step of the Julia–Lythgoe protocol is the nucleophilic addition of an α-sulfonyl carbanion to an aldehyde, the aldehyde synthon should possess the stereochemical arrangement corresponding to the '15*R*' stereochemistry in the final prostaglandin analogue. Critical to this disconnection, the enantiomeric purity of the aldehyde ω-chain synthon **16a** should be very high, thus a priori establishing a very high diastereoisomeric excess of the final product **8a**. Importantly, the aldehyde ω-chain synthon **16a** with a well-chosen protecting group should not be capable of epimerization under basic reaction conditions.

Our synthetic approaches to travoprost (**8a**) and its epimeric impurity **8b** are convergent. The structurally advanced prostaglandin phenylsulfone **15** and the appropriately functionalized novel ω-chain synthons **16a** and **16b** were prepared separately with well-defined stereochemistry and then united by an efficient Julia–Lythgoe olefination.

2.1. Synthesis of the aldehyde ω-chain synthon (*S*)-(−)-16a and its enantiomeric impurity (*R*)-(+)-16b

To the best of our knowledge, the enantiomerically pure aldehydes (*S*)-(−)-**16a** and (*R*)-(+)-**16b** (Scheme 3) are new chemical compounds that have never been obtained in optically active form. The novel aldehyde synthon **16a** used for the construction of the ω-chain of travoprost (**8a**) contains a stereogenic centre at the carbon C-2 corresponding to C-15 in the target molecule, with chirality corresponding to the '15*R*' configuration in the final product **8a**. In all areas of pharmaceutical research it is most essential to investigate pure and well-characterized compounds. Thus, the aldehyde **16a** should possess a very high enantiomeric excess, preferably above 99.8% ee, as individual impurity content below 0.1% facilitates the registration process of active pharmaceutical ingredients.

We envisaged, that the aldehyde ω-chain synthon **16a** could be prepared in a seven-step synthesis from optically active solketal (*S*)-(+)-**19a** (Scheme 3). The desired enantiomeric purity of the aldehyde **16a** was achieved by employing the known acetonide (*S*)-(+)-**21a** as a source of chirality. The acetonide **21a** was synthesized in high enantiomeric purity from solketal **19a**, which is commercially available or can be easily prepared from an important chiral template 1,2:5,6-di-*O*-isopropylidene-D-mannitol.[25,26] The solketal **19a** was first converted into the known tosylate (*R*)-(−)-**20a** with *p*-toluenesulfonyl chloride in pyridine according to the standard procedures. O-Alkylation of 3-trifluoromethylphenol with tosylate



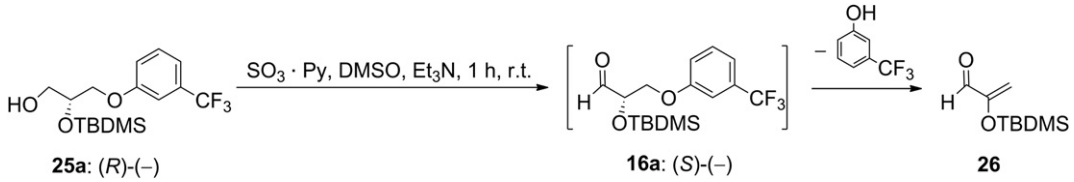
Scheme 3. Synthesis of the aldehyde ω-chain synthon (*S*)-(−)-**16a** and its enantiomer (*R*)-(+)-**16b**. Reagents and conditions: (1) TsCl, Py, 0 °C for 30 min, then rt overnight, 99% yield of (*R*)-(−)-**20a** (99.9% ee); (2) method A: 3-trifluoromethylphenol, NaOH, EtOH, H_2O, reflux, 20 h, 89% yield of (*S*)-(+)-**21a** (99.9% ee). Method B: 3-trifluoromethylphenol, PPh_3, DIAD, toluene, 90–100 °C, 1 h, 97% yield of **21a** (89.5% ee); (3) 1.0 M aq HCl, acetone, 70 °C, 1 h, 98% yield of (*R*)-(−)-**22a** (99.9% ee); (4) PivCl, Py, CH_2Cl_2, 0 °C for 1 h, then 1 h at rt, 95% yield of (*S*)-(+)-**23a** (99.9% ee); (5) TBDMSCl, ImH, DMF, 0 °C for 15 min, then rt for 18 h, 93% yield of (*S*)-(−)-**24a** (99.9% ee); (6) DIBAL-H, CH_2Cl_2, −78 °C for 20 min, rt for 2 h, 92% yield of (*R*)-(−)-**25a** (99.9% ee); (7) DMP, $NaHCO_3$, CH_2Cl_2, 0 °C, then 1 h at rt, 97% yield of (*S*)-(−)-**16a**.

20a gave the acetonide **21a** in 89% yield and with high enantiomeric purity (99.9% ee). The enantiomeric acetonide (*R*)-(−)-**21b** (99.2% ee) was synthesized by the same synthetic route as illustrated in Scheme 3, but using the solketal (*R*)-(−)-**19b** as the starting material. The course of all reactions and the enantiomeric purity of products were controlled by thin-layer (TLC) and high-performance liquid chromatography (HPLC). The stereochemical assignment of the acetonides **21a** and **21b** was confirmed by the values of optical rotation.[26] Their structures were also proved by NMR and IR spectra.

Although the route described above is expedient and amenable to a large supply of the acetonide **21a**, we envisaged that an alternative one-step approach could be etherification of solketal **19a** with 3-trifluoromethylphenol under Mitsunobu reaction conditions.[27] Encouraged by this perspective, we determined experimentally the optimal conditions for convenient etherification of solketal **19a** with 3-trifluoromethylphenol. However, the Mitsunobu reaction of solketal **19a** with acidic 3-trifluoromethylphenol resulted in partial racemization of the starting alcohol **19a** (5.3% of the opposite enantiomer), presumably due to the acetonide ring opening and closing by phenol/phenolate. A reasonable mechanism by which acidic reagents could cause the racemization of solketals was proposed earlier by Baldwin.[28]

The acetonide group in aryl ether **21a** was then removed using aqueous hydrochloric acid in acetone to afford the diol (*R*)-(−)-**22a** in 98% yield (99.9% ee). Selecting a protecting group strategy for hydroxyl groups in the diol **22a**, that would minimize side reactions, was critical in the design of the synthetic approach to the new aldehyde **16a**. Initially, we thought that selective monotosylation[29] of the primary hydroxyl group of **22a** followed by silylation of the secondary hydroxyl group and Kornblum oxidation[30] of tosylate would be the best way to synthesize the aldehyde **16a**. However, monotosylation of the diol **22a** was not selective enough, yielding 15% of the unwanted secondary monotosylate. The Kornblum oxidation of the α-silyloxy protected monotosylate also failed, probably due to the fast decomposition of the final product **16a**. After exploring various possibilities, trimethyl acetyl chloride was found to be the best protecting reagent of choice. Selective esterification of the primary hydroxyl group of **22a** with pivaloyl chloride afforded the pivaloate α-hydroxy ester (*S*)-(+)-**23a** as the main product of this reaction (95% yield, 99.9% ee). A silicon-based protecting group strategy at C-2 was envisaged to be sufficiently stable to the reaction sequence yet easily removed under mild basic conditions in the final steps of the synthesis. Our later attempts to olefinate the phenylsulfone **15** with various α-silyloxy protected aldehydes **16a** using the Julia–Lythgoe protocol showed that a *tert*-butyldimethylsilyl protecting group provided better 15*R*/15*S* stereoselectivity for ω-chain elongation than triethylsilyl protection. Thus, the secondary hydroxyl group of **23a** was protected by silylation with *tert*-butyldimethylsilyl chloride to give the silyl ether (*S*)-(−)-**24a** in 93% yield (99.9% ee). Subsequent deprotection of the C-1 pivaloate ester with DIBAL-H provided the desired alcohol (*R*)-(−)-**25a** in 70% yield over six steps from the solketal **19a**. The optical purity of the alcohol **25a** was determined as 99.9% ee on the basis of HPLC using a chiral stationary phase. The enantiomeric impurity (*S*)-(+)-**25b** (99.2% ee) was synthesized by the same strategy as illustrated in Scheme 3, but starting from the chiral acetonide (*R*)-(−)-**21b**.

The main problem accompanying the synthesis of the new aldehyde **16a** was facile, probably mild base-catalyzed, elimination of 3-trifluoromethylphenol leading to the corresponding α,β-unsaturated aldehyde. The Parikh–Doering oxidation[31] (SO_3·Py, DMSO, Et_3N) of the alcohol **25a** resulted in the formation of aldehyde **16a** immediately followed by 3-trifluoromethylphenol elimination to the more stable 2-(*tert*-butyldimethylsilyloxy)propenal (**26**) (Scheme 4). Importantly, the ω-chain synthon **16a** should not be contaminated with the aldehyde **26** as it easily reacts with phenylsulfone **15**. The attempts to synthesize the aldehyde **16a** by pyridinium chlorochromate oxidation also failed, mainly due to the low reactivity of the alcohol **25a**, accompanied by decomposition of the product **16a** under long-term oxidation conditions. After exploring various possibilities, we have found that oxidation of the alcohol **25a** with Dess–Martin periodinane[32] affords the crude aldehyde **16a** in good yield and chemical purity (ca. 90%). The use of Dess–Martin periodinane avoided some difficulties encountered with other methods, such as adverse products, long reaction times,

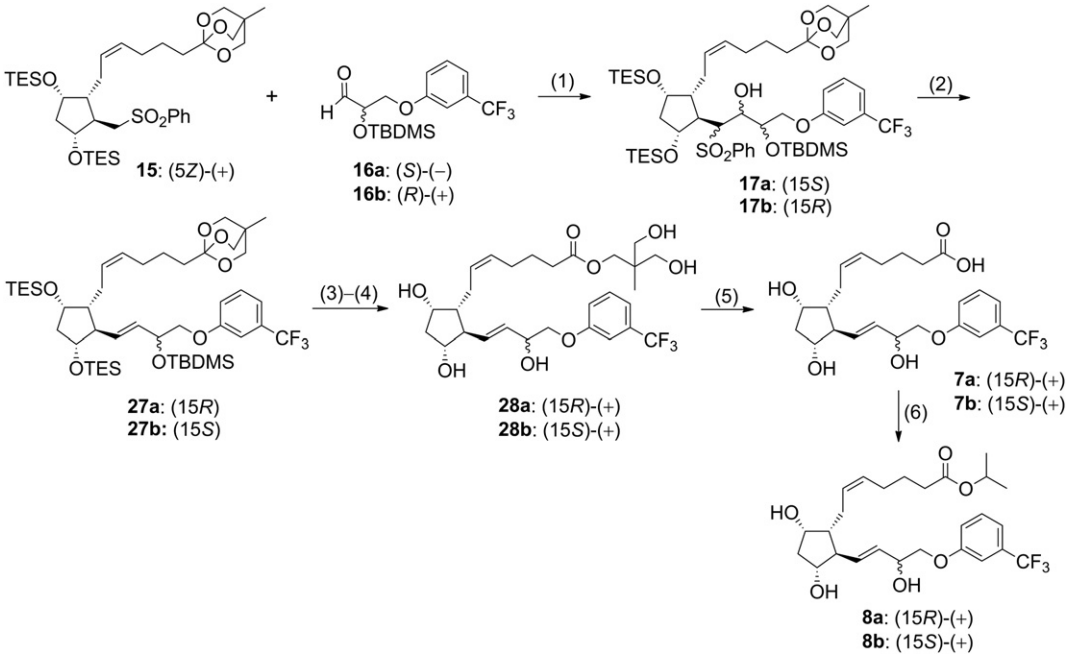


Scheme 4. The Parikh–Doering oxidation of the alcohol (*R*)-(−)-**25a** to the conjugated aldehyde **26**.

difficult workup procedures or the need to apply a large excess of the oxidizing agent. Most importantly, Dess–Martin periodinane is well-known not to racemize chiral centres of optically active compounds. Thus, the enantiomeric purity of the aldehyde ω-chain synthon **16a** should be the same as the starting alcohol **25a**. α-Hydroxy protected aldehydes are usually readily available and stable compounds. However, their stability is often insufficient for purification and identification purposes. It was not surprising then, that we observed a slight decomposition of the aldehyde **16a** during column chromatography and, in addition, we were unable to evaluate its enantiomeric and chemical purity by HPLC on various stationary phases. These problems were surmounted by applying the crude ω-chain synthon **16a** and experimental determination of the best conditions for the Julia–Lythgoe olefination of phenylsulfone **15**. The enantiomeric aldehyde (*R*)-(+)-**16b** was synthesized by the same strategy as illustrated in Scheme 3, but using the chiral alcohol (*S*)-(+)-**25b** as the starting material. The presence of the aldehyde and 3-(3-trifluoromethyl)phenoxy groups in compounds **16a** and **16b** was confirmed by NMR and IR spectra.

2.2. Synthesis of travoprost (15*R*)-(+)-8a and its (15*S*)-(+)-8b-*epi* isomeric impurity

With the novel aldehyde ω-chain synthon (*S*)-(−)-**16a** and the prostaglandin phenylsulfone (5*Z*)-(+)-**15**[21] (a mixture of 5*Z*/5*E* isomers in the ratio of 91.6%:8.4%, 83.2% de) in hand, we continued the synthesis of the target compound (15*R*)-(+)-**8a** according to the convergent strategy illustrated in Scheme 5. The main problems accompanying the ω-chain elongation of phenylsulfone **15** to the prostaglandin pentahydroxy ester (15*R*)-(+)-**28a** were moderate reactivity of the aldehyde **16a** and the lability of triethylsilyl protecting groups in phenylsulfone **15**. Considering the chemical structure of the ω-chain synthon **16a**, 3-trifluoromethylphenoxy- and *tert*-butyldimethylsilyloxy substituents with electron-withdrawing properties should activate the aldehyde **16a** in nucleophilic addition reactions. On the other hand, the bulky α-situated *tert*-butyldimethylsilyl group creates steric hindrance reducing the ability of phenylsulfone **15** addition to the aldehyde **16a**. The influence of steric encumbrance caused by the α-silyloxy substituent was clearly seen in our later attempts to olefinate the sulfone **15** with a bulky, α-*tert*-butyldiphenylsilyl protected aldehyde **16a** (ca. 45% conversion). Thus, the main problem accompanying the synthesis of the prostaglandin precursor **17a** was the choice of an optimal base capable of efficient and highly diastereoselective ω-chain elongation of phenylsulfone **15** with sterically hindered aldehyde **16a**. Based on the known behaviour of alkyl and aryl sulfones,[23,33] we studied the effects of various bases (LHMDS, KHMDS, *n*-BuLi, *t*-BuOK, LDA) to determine the optimal conditions for high-yield and highly diastereoselective synthesis of pentahydroxy ester **28a**. Of all the bases screened, freshly prepared LDA provided almost complete conversion (ca. 95%) of phenylsulfone **15** to the mixture of diastereoisomeric hydroxy sulfones **17a**. The choice of a 4-methyl-2,6,7-trioxabicyclo[2.2.2]octane (methyl-OBO) carboxyl masking group in phenylsulfone **15** was predicted by its high stability under basic Julia–Lythgoe reaction conditions. However, the limited stability of the methyl-OBO protecting group on silica gel accompanied by the effect of lithium salts present in the crude reaction product resulted in significant losses of **17a** during column chromatography. Thus, the crude mixture of β-hydroxy sulfones **17a** was subjected to reductive elimination with a fresh 20% sodium amalgam to afford the methyl-OBO protected prostaglandin precursor **27a**. The phosphate-buffered conditions of Trost[34] were used to ensure the optimal pH conditions and prevent deprotection of the cyclopentane hydroxyl groups. Similarly to the methyl-OBO protected β-hydroxy sulfones **17a**, the prostaglandin intermediate **27a** was not purified by means of silica gel column chromatography. Significantly, there was no need for purification of the prostaglandin intermediates **17a** and **27a**, which was a major advantage for any future scale-up. The triethylsilyl and *tert*-butyldimethylsilyl protecting groups in prostaglandin precursor **27a** were all removed under the action of tetrabutylammonium fluoride (TBAF) solution, immediately followed by hydrolytic opening of the methyl-OBO masking group with citric acid solution to the stable 2,2-bis(hydroxymethyl)propyl ester **28a**. The epimeric ester **28b**



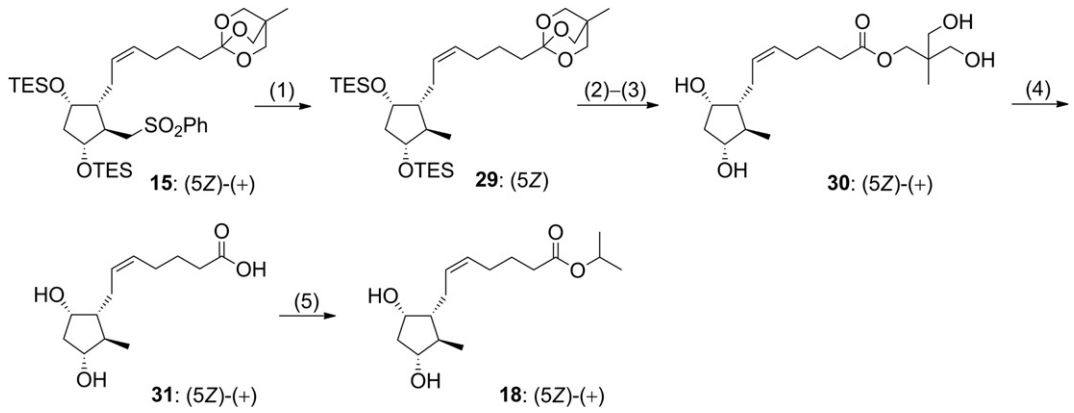
Scheme 5. Synthesis of travoprost (**8a**) and its (15*S*)-(+)-*epi* isomer **8b** from phenylsulfone **15** and aldehyde **16a** or **16b**. Reagents and conditions used: (1) LDA, THF, −78 °C, 1 h; (2) Na/Hg, Na_2HPO_4, MeOH, 0 °C for 30 min, then 5 h at rt; (3) *n*-Bu_4NF, 65–70 °C, 1 h; (4) $HOOCC(OH)(CH_2COOH)_2$, H_2O, 15 min, 89% yield of **28a** from **15**; (5) $LiOH·H_2O$, MeOH, overnight, 98% of **7a**; (6) *i*-PrI, DBU, acetone, 20 h, 95% yield of **8a**.

was synthesized by the same synthetic strategy as illustrated in Scheme 5, but using the chiral aldehyde **16b** and phenylsulfone **15** as the starting materials. The 15*R*/15*S* stereoselectivity of ω-chain elongation was first evaluated at this step. Thus, both compounds **28a** and **28b** were purified by silica gel flash chromatography and identified by spectroscopic and chromatographic methods. The HPLC and LC–MS recorded for the ester **28a** confirmed the presence of the (5*E*,15*R*)-isomer at the level of 8.5%, which was comparable with the content of (5*E*)-isomer in the starting phenylsulfone (5*Z*)-**15**. Fortunately, this kind of contamination leads to the (5*E*,15*R*)-**8c** diastereoisomer of travoprost in the final steps of the synthesis, which is easily removable from the final product **8a** by preparative HPLC. More importantly, the content of the epimeric impurity (15*S*)-**28b** in the prostaglandin precursor **28a** was scarcely more than a trace (0.2%). Considering the high enantiomeric purity of the alcohol **25a** (**25a**/**25b** 99.95%:0.05%), the chromatographic data for the ester **28a** (**28a**/**28b** 99.81%:0.19%) confirmed that the bulky *tert*-butyldimethylsilyl group made a very good protecting group for the aldehyde α-proton preventing the ω-chain synthon **16a** from racemization. Following the final steps of the synthesis illustrated in Scheme 5, the ester contaminant **28b** leads to the (15*S*)-**8b** epimer of travoprost, only a small amount of which is present in the final product **8a** and is readily separable by preparative HPLC. Since the olefinic diastereoisomers **28** proved to be hardly separable at this juncture, we found the better results could be obtained when separation was performed on the final and less polar product **8a**.

The pentahydroxy ester **28a** was subsequently cleaved with lithium hydroxide monohydrate and, after acidification with citric acid, fluprostenol (15*R*)-(+)-**7a** was isolated in almost quantitative yield (98%). In the final step of the synthesis, acid **7a** was successfully converted into travoprost (**8a**), with *i*-Pr/DBU/acetone, conditions commonly used in the prostaglandin field.[6,7,10,11,19] The diastereoisomeric impurity (15*S*)-(+)-**8b** of travoprost was synthesized by the same synthetic strategy as illustrated on Scheme 5, but using the 2,2-bis(hydroxymethyl)propyl ester **28b** as the starting material. The crude travoprost (**8a**) and its (15*S*)-*epi* isomer (**8b**) were purified by silica gel flash chromatography and identified by spectroscopic and chromatographic methods. The HPLC and LC–MS recorded for the travoprost (**8a**) confirmed the presence of the (5*E*,15*R*)-isomer (**8c**) (7.9%) formed from the (5*E*)-isomer present in the starting phenylsulfone (5*Z*)-**15**. The NMR spectra of travoprost **8a** and its 5,6-*trans* diastereoisomer **8c** are hardly discerned; however, the α-chain allylic carbons C-4 and C-7 of **8c** are seen in the ^{13}C NMR spectrum as two singlets at a lower field (32.2 and 31.4 ppm) compared with the same carbons of **8a** (26.9 and 25.7 ppm), therefore the C-4 and C-7 carbons of **8c** are more effectively deshielded by the trans-double bond of the ω-chain. Fortunately, this kind of contamination is easily detectable by reverse-phase analytical HPLC and can be easily removed by preparative HPLC on silica gel stationary phases. More importantly, the amount of the far more difficult to remove epimeric impurity (15*S*)-**8b** in the final product **8a** was scarcely more than a trace (0.2%). The physicochemical properties of **8a** and **8b** are very similar, so it is not a straightforward task to discern between these two compounds by NMR spectroscopy, optical rotation or even by analytical reverse-phase HPLC. The ^{1}H and ^{13}C NMR spectroscopic chemical shifts determined for epimers **8a** and **8b** are almost identical; however, slight differences can be noticed in peak multiplicity given by some ω-chain protons. The two protons of the ω-chain CH_2-4 group in travoprost (**8a**) are seen as two doublets of doublets at 3.80 and 3.84 ppm, whereas in the 15-*epi* isomer they give a doublet at 3.79 ppm. The H-1 and H-2 protons of the trans-double bond in travoprost (**8a**) are also seen as two doublets of doublets at 5.66 and 5.80 ppm, whereas in 15-*epi* isomer **8b** they give one broad multiplet. The ^{1}H and ^{13}C NMR spectroscopic chemical shifts and peak multiplicity determined for the ω-chain H-3 proton and C-3 carbon in travoprost **8a** (4.5 and 71.5 ppm) are highly comparable with those of the 15-*epi* isomer **8b** (4.5 and 70.6 ppm). Considering very similar physicochemical properties of epimers **8a** and **8b**, preparative HPLC can only be applied to remove trace amounts of (15*S*)-**8b** diastereoisomer.

2.3. Synthesis of the novel prostaglandin related ester (5*Z*)-(+)-18, the new synthetic impurity of travoprost (15*R*)-(+)-8a

The Julia–Lythgoe olefination entails one main drawback in the step of formation of the carbon–carbon bond with an α-sulfonyl carbanion and carbonyl compounds. Since the hydrogen on the carbon bearing the sulfonyl group is highly acidic, in some cases the addition reaction of an α-sulfonyl carbanion to carbonyl compounds is reversible.[35] The Julia–Lythgoe olefination of the phenylsulfone **15** with the aldehyde **16a** occurred under mild conditions and gave good yields of stereodefined *trans*-13,14 alkene **28a** (Scheme 5). The reaction stopped at ca. 95% conversion of phenylsulfone **15** to β-hydroxy sulfones **17a** despite using the aldehyde **16a** in excess under highly anhydrous and air-free conditions. The equilibrium was strongly shifted towards the products **17a**; however, up to 5% of phenylsulfone **15** was left unreacted and subsequently underwent reduction with Na/Hg to provide the novel prostaglandin related ester (5*Z*)-(+)-**18** (Scheme 6). Finally, the crude travoprost (**8a**) was contaminated with the new impurity **18**, which was readily separable by silica gel flash chromatography.



Scheme 6. Synthesis of the new impurity **18** of travoprost. Reagents and conditions used: (1) Na/Hg, Na_2HPO_4, MeOH, 0 °C, 30 min, then 5 h at rt; (2) *n*-Bu_4NF, 1 h; (3) HOOC-C(OH)(CH_2COOH)$_2$, H_2O, 15 min, 91% yield of **30** from phenylsulfone **15**; (4) LiOH·H_2O, MeOH, overnight, 97% yield of **31**; (5) *i*-PrI, DBU, acetone, 22 h, 93% yield of **18**.

The ester **18** was synthesized and identified to establish the full profile of impurities accompanying our novel synthesis of the active pharmaceutical ingredient **8a**. Thus, phenylsulfone **15** (83.2% de) was subjected to the reductive desulfonylation followed by deprotection of the triethylsilyl groups with TBAF solution and subsequent hydrolytic opening of the methyl-OBO protecting group with citric acid solution to afford the stable 2,2-bis(hydroxymethyl) propyl ester (5*Z*)-(+)-**30** (91% yield from **15**). Hydrolysis of the ester **30** with lithium hydroxide monohydrate followed by esterification of the acid **31** with *i*-Pr/DBU gave the new prostaglandin related ester **18**. The LC–MS confirmed the presence of (5*E*)-**18** isomer in the amount comparable with that of (5*E*)-**15** isomer in the starting phenylsulfone **15**. Similarly to travoprost (**8a**) and its α-chain 5,6-*trans* diastereoisomer **8c**, the allylic carbons C-4 and C-7 of (5*E*)-**18** isomer are seen in the ^{13}C NMR spectrum as two singlets at a lower field (31.8 and 31.9 ppm) compared with the same carbons of (5*Z*)-**18** isomer (26.4 and 26.6 ppm), therefore the C-4 and C-7 carbons of (5*E*)-**18** are more effectively deshielded by the trans-double bond. The (5*Z*)-**18** diastereoisomer can be easily separated from its (5*E*)-**18** isomer by preparative HPLC.

3. Conclusions

The 16-(3-trifluoromethyl)phenoxy $PGF_{2\alpha}$ analogue travoprost (**8a**) has potent topical ocular activity. A novel convergent synthesis of 13,14-en-15-ol $PGF_{2\alpha}$ analogues with the desired C-15 asymmetric centre configuration was developed employing Julia–Lythgoe olefination of the structurally advanced phenylsulfone (5*Z*)-(+)-**15** with a new enantiomerically pure aldehyde ω-chain synthon (*S*)-(−)-**16a**. Subsequent hydrolysis of protecting groups and final esterification of fluprostenol (**7a**) yielded travoprost (**8a**). The new strategy is based on the reverse order of side chain attachment to the Corey lactone by Wittig and Julia–Lythgoe olefinations. The occurrence of the (15*S*)-(+)-**8b** diastereoisomer has been an 'Achilles heel' of most existing syntheses of travoprost. Therefore, the new method for the synthesis of travoprost targeted a very high enantiomeric purity at the C-15 carbionol centre of the product. The novel aldehyde ω-chain synthon (*S*)-(−)-**16a** used for the construction of the ω-chain of travoprost (**8a**) was envisaged to contain a stereogenic centre at the carbon C-2 corresponding to C-15 in the target molecule, with chirality corresponding to the '15*R*' configuration in the final product **8a**. This ensured the absence of an appreciable quantity of the undesired (15*S*)-(+)-**8b** diastereoisomer in the final prostaglandin analogue **8a**. The main advantages of the new method are the preparation of high purity travoprost (**8a**) and the application of comparatively cheap reagents. The novel convergent strategy allows the synthesis of a whole series of *trans*-13,14-en-15-ol PGF_2 analogues from a common and structurally advanced prostaglandin intermediate (5*Z*)-(+)-**15**.

4. Experimental section

4.1. Reagents

(*S*)-(+)-2,2-Dimethyl-4-(hydroxymethyl)-1,3-diox-olane (99.9%, 99.7% ee), (*R*)-(−)-2,2-dimethyl-4-(hydroxymethyl)-1,3-dioxolane (98.6%, 99.4% ee), 3-trifluoromethylphenol (99%), Dess–Martin periodinane (97%), trimethyl acetyl chloride (99%), *tert*-butyldimethylsilyl chloride (97%), imidazole (99%), diisobutylaluminum hydride solution (1.0 M in toluene), diisopropylamine (99.5%), butyllithium solution (1.6 M in hexanes), sodium mercury amalgam (99.9% trace metal basis, Na 20% beads) and tetrabutylammonium fluoride solution (1.0 M in THF) were purchased from Sigma–Aldrich, Tokyo Chemical Industries and Iris Biotech Gmbh chemical companies. 1-⟨(*Z*)-6-{(1*R*,2*R*,3*R*,5*S*)-2-[(Phenylsulfonyl)-methyl]-3,5-bis(triethylsilyloxy)cyclopentyl}hex-4-en-yl⟩-4-methyl-2,6,7-trioxabicyclo[2.2.2]-octane[21] ((5*Z*)-(+)-**15**, a mixture of 5*Z*/5*E* isomers in the ratio of 91.6%:8.4%, 83.2% de) was manufactured by Pharmaceutical Research Institute (Warsaw, Poland). The HPLC standards, travoprost (**8a**) and its diastereoisomers **8b**–**8c**, were purchased from Cayman Chemicals.

4.2. General procedures

Reactions requiring anhydrous conditions were carried out using flame-dried glassware, which was cooled to 20 °C in a desiccator under an argon atmosphere. All moisture- or air-sensitive reactions were run under an argon atmosphere. Air-sensitive reagents were transferred via syringe or cannula and were introduced to the apparatus through rubber septa. Solids were introduced under a positive pressure of argon. Reactions were cooled via external cooling baths: ice water (0 °C) or dry-acetone (−78 °C). Heating was accomplished by either a heating mantle or silicone oil bath. Deionized water was used for all aqueous extractions and for obtaining all aqueous solutions. Solvents were removed under reduced pressure using standard rotary evaporators. The course of all reactions and the purity of products were checked by thin-layer chromatography (TLC). Analytical TLC was performed on silica gel DC-Alufolien Kieselgel 60 F_{254} (Merck) with mixtures of hexanes, ethyl acetate, dichloromethane, methanol, 2-propanol in various ratios as developing systems. Compounds were detected by spraying the plates with 1% $Ce(SO_4)_2$/2%$H_3[P(Mo_3O_{10})_4]$ in 10% H_2SO_4 followed by heating to 120 °C. Preparative column chromatography was carried out on silica gel (Kieselgel 60, 40–63 μm, 230–400 mesh, Merck) with mixtures of ethyl acetate, dichloromethane, methanol, 2-propanol in varying ratios as eluents. Flash chromatography was run with a positive air pressure generated by handheld, pear-shaped rubber pumps. The NMR spectra of all the compounds were measured in $CDCl_3$ or C_6D_6 solutions with a Varian-NMR-vnmrs600 (at temperature 298 K) equipped with a 600 MHz PFG Auto XID ($^1H/^{15}N–^{31}P$ 5 mm) indirect probehead. Standard experimental conditions and standard Varian programs were used. To assign the structures under consideration, the following 1D and 2D experiments were employed: the 1D selective NOESY and 2D gradient selected COSY, $^1H–^{13}C$ HSQC and $^1H–^{13}C$ HMBC. The ^1H and ^{13}C NMR chemical shifts were given relative to the TMS signal at 0.0 ppm. Concentration of all solutions used for measurements was about 20–30 mg of compounds in 0.6 mL of solvent. IR spectra were taken for liquid films or KBr pellets on a Nicolet Imapct 410 FT-IR spectrophotometer. HRMS spectra were recorded on an AMD 604 Inectra Gmbh spectrometer or a Mariner PE Biosystem ESI-TOF spectrometer. Melting points were determined from DSC termograms performed on a Mettler Toledo DSC822E differential scanning calorimeter. Optical rotations were measured with a Perkin Elmer 341 automatic polarimeter in EtOH, CH_2Cl_2 or $CHCl_3$ solutions as the solvents with percent concentrations. Analytical HPLC was performed on a Waters Alliance 2695 system equipped with 2998 PDA detector, using the following columns: Chiralpak IA (5 μm, 250×4.6 mm), Chiracel OJ (10 μm, 250×4.6 mm), Chiracel OD OD00CE-EL068 (10 μm, 250×4.6 mm), Chiracel OD-H (5 μm, 250×4.6 mm), Gemini C18 (3 μm, 250×4.6 mm) and AS-3R (3 μm, 150×4.6 mm). The LC–MS was recorded on a Shimadzu LC-2010A HT high-performance liquid chromatograph coupled with an Applied Biosystems Qtrap 3200 mass spectrometer equipped with a Gemini C18, AS-3R or Poroshell 120 EC-C8 column.

4.3. (*R*)-(−)-2,2-Dimethyl-4-(toluenesulfonyloxymethyl)-1,3-dioxolane (20a)

p-Toluenesulfonyl chloride (6.18 g, 31.7 mmol) was added portionwise over a period of 10 min to a solution of (*S*)-(+)-2,2-

dimethyl-4-(hydroxymethyl)-1,3-dioxolane (**19a**) (4.0 g, 30.2 mmol) in anhydrous pyridine (50 mL) in an ice bath. The resulting solution was slowly brought to room temperature and stirred overnight. During that time, a white precipitate formed. The pyridine was removed under reduced pressure and the residue was diluted with ethyl acetate (50 mL), washed subsequently with cold aqueous 1 M HCl (2×150 mL), saturated $NaHCO_3$ (100 mL) and brine (200 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated to give a light yellow oil. The crude product was purified by column chromatography over silica gel with gradient elution 10–30% AcOEt/hexanes to afford (*R*)-(−)-3-tosyloxy-1,2-propanediol acetonide **20a** (8.54 g, 99% yield, 99.9% ee) as a colourless viscous oil. R_f=0.37 (20% AcOEt/hexanes). $[\alpha]_D^{20}$ −4.8 (*c* 1.0, EtOH) (lit. $[\alpha]_D^{24}$ −4.6 (*c* 13.0, EtOH)).[25] FTIR (thin film) ν 3073, 2987, 2937, 2891, 1598, 1495, 1455, 1368, 1257, 1213, 1190, 1177, 1096, 1055, 979, 829, 788, 665, 555 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 1.31 (s, 3H, CH_3-2), 1.34 (s, 3H, CH_3-2), 2.45 (s, 3H, ArCH_3), 3.76 (dd, *J*=5.1 and 8.8 Hz, 1H, one of the CH_2-5 group), 3.98 (dd, *J*=6.0 and 10.2 Hz, 1H, one of the CH_2-1′ group), 3.99–4.05 (m, 2H, one of the CH_2-1′ group and one of the CH_2-5 group), 4.28 (m, 1H, CH-4), 7.35 (m, 2H, aromatic H-3 and H-5), 7.79 (m, 2H, aromatic H-2 and H-6) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 21.5 (Ar−CH_3), 25.1 (CH_3-2), 26.5 (CH_3-2), 66.1 (C-5), 69.4 (C-1′), 72.8 (C-4), 109.9 (C-2), 127.9 (2C, aromatic C-2 and C-6), 129.8 (2C, aromatic C-3 and C-5), 132.6 (aromatic C-1), 145.0 (aromatic C-4) ppm. HRMS (ESI): calcd for $C_{13}H_{18}NaO_5S$ $[M+Na]^+$ 309.07672; found 309.0762. Chiral HPLC: Chiralpak IA, 5 μm, 250×4.6 mm column, hexanes/2-propanol/methanol 97:2:1 (v/v/v), 1.0 mL/min, t_R=21.71 min (0.06% yield of **20b**), t_R=24.20 min (99.94% yield of **20a**), 99.88% ee. All physical and spectroscopic data match those reported in the literature.

*4.3.1. (S)-(+)-2,2-Dimethyl-4-(toluenesulfonyloxymethyl)-1,3-dioxolane (**20b**).* According to the procedure described for the preparation of (*R*)-(−)-**20a**, (*R*)-(−)-2,2-dimethyl-4-(hydroxymethyl)-1,3-dioxolane (**19b**) (2.50 g, 18.7 mmol) afforded the right-hand (*S*)-(+)-3-tosyloxy-1,2-propanediol acetonide **20b** (5.23 g, 98% yield, 99.2% ee). $[\alpha]_D^{20}$ +4.5 (*c* 1.0, EtOH) (lit. $[\alpha]_D^{25}$ +4.7 (*c* 1.0, EtOH)).[26] The characterization data from IR, NMR and HRMS spectra were identical in all aspects with those of (*R*)-(−)-**20a** enantiomer.

4.4. (*S*)-(+)-2,2-Dimethyl-4-(3-trifluoromethylphenoxy) methyl-1,3-dioxolane (21a)

Method A. Sodium hydroxide (1.73 g, 43.2 mmol) was added portionwise to a stirred solution of 3-trifluoromethylphenol (7.08 g, 43.2 mmol) in a mixture of EtOH and H_2O (4:1, 125 mL). After being stirred for 10 min, a solution of tosylate (*R*)-(−)-**20a** (8.25 g, 28.8 mmol) in EtOH (25 mL) was added dropwise and the reaction mixture was heated at reflux for 20 h with disappearance of the starting tosylate (*R*)-(−)-**20a** (TLC, AcOEt/hexanes 1:4). The EtOH was then evaporated, the residue was treated with 10% aq NaOH (25 mL) and extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with H_2O (3×100 mL), dried over Na_2SO_4, filtered and evaporated to give a light yellow oil (7.80 g, 98% yield). The crude product was distilled to afford the acetonide (*S*)-(+)-**21a** (7.06 g, 89% yield, 99.9% ee) as a colourless oil. Bp 80–94 °C (0.2 mmHg). $[\alpha]_D^{20}$ +7.5 (*c* 0.5, EtOH) (lit. $[\alpha]_D^{25}$ +11 (*c* 0.5, EtOH)).[26] FTIR (thin film) ν 3074, 2988, 2938, 2883, 1608, 1593, 1493, 1450, 1372, 1330, 1233, 1168, 1127, 1096, 1066, 976, 904, 843, 793, 698, 657, 520 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 1.41 (s, 3H, CH_3-2), 1.46 (s, 3H, CH_3-2), 3.91 (dd, *J*=5.8 and 8.5 Hz, 1H, one of the CH_2-5 group), 3.98 (dd, *J*=5.8 and 9.5 Hz, 1H, one of the CH_2-1′ group), 4.08 (dd, *J*=5.5 and 9.5, 1H, one of the CH_2-1′ group), 4.18 (dd, *J*=6.4 and 8.5 Hz, 1H, one of the CH_2-5 group), 4.49 (m, 1H, CH-4), 7.09 (dd, *J*=2.4 and 8.2 Hz, 1H, aromatic H-6), 7.15 (m, 1H, aromatic H-2), 7.22 (dm, *J*=7.6 Hz, 1H, aromatic H-4), 7.38 (m, 1H, aromatic H-5) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 25.3 (CH_3-2), 26.7 (CH_3-2), 66.6 (C-5), 69.0 (C-1′), 73.8 (C-4), 109.9 (C-2), 111.4 (d, *J*=3.7 Hz, aromatic C-2), 117.8 (d, *J*=3.4 Hz, aromatic C-4), 118.0 (d, *J*=1.2 Hz, aromatic C-6), 123.9 (q, *J*=272.1 Hz, $-CF_3$), 130.0 (aromatic C-5), 131.9 (q, *J*=32.4 Hz, aromatic C-3), 158.7 (aromatic C-1) ppm. HRMS (EI): calcd for $C_{13}H_{15}F_3O_3$ 276.09733; found 276.09712. Chiral HPLC: Chiracel OJ, 10 μm, 250×4.6 mm column, hexanes/ethanol 100:0.5 (v/v), 1.0 mL/min, t_R=8.27 min (0.06% yield of **21b**), t_R=14.24 min (99.94% yield of **21a**), 99.88% ee.

Method B. A solution of (*S*)-(+)-2,2-dimethyl-4-(hydroxymethyl)-1,3-dioxolane (**19a**) (3.56 g, 27.0 mmol) and DIAD (6.98 mL, 33.7 mmol) in toluene (10 mL) was slowly added to a mixture of 3-trifluoromethylphenol (2.75 mL, 22.5 mmol) and PPh_3 (8.93 g, 33.7 mmol) in toluene (50 mL) at 90 °C over 30 min. After heating at 100 °C for another 1 h, TLC analysis (CH_2Cl_2/MeOH, 20:1) indicated disappearance of the starting solketal **19a**. The excess of toluene (30 mL) was evaporated and the residue was put into refrigerator for several hours. Triphenylphosphine oxide was removed by filtration on a Büchner funnel and washed with cold toluene (3×15 mL). The filtrate and washings were combined and concentrated under reduced pressure to give the crude product **21a** (9.6 g) as an orange-yellow oil. The crude product was distilled to afford the acetonide (*S*)-(+)-**21a** (5.98 g, 97% yield, 89.5% ee) as a colourless oil. Bp 80–94 °C (0.2 mmHg). The characterization data from IR and NMR spectra were identical in all aspects with those of (*S*)-(+)-**21a** obtained according to the Method A.

*4.4.1. (R)-(−)-2,2-Dimethyl-4-(3-trifluoromethylphenoxy)methyl-1,3-dioxolane (**21b**).* In the same manner as described for the preparation of (*S*)-(+)-**21a** (Method A), the tosylate (*S*)-(+)-**20b** (5.0 g, 17.5 mmol) afforded the acetonide (*R*)-(−)-**21b** (4.13 g, 86% yield, 99.2% ee). $[\alpha]_D^{20}$ −7.4 (*c* 0.5, EtOH). The characterization data from IR, NMR and HRMS spectra were identical in all aspects with those of (*S*)-(+)-**21a** enantiomer.

4.5. (*R*)-(−)-3-(3-Trifluoromethylphenoxy)propane-1,2-diol (22a)

1.0 M aq HCl (40.0 mL) was added in one portion to a solution of acetonide (*S*)-(+)-**21a** (6.90 g, 25.0 mmol) in acetone (50 mL). After heating at 70 °C for 1 h, TLC analysis (CH_2Cl_2/MeOH, 20:1) indicated the reaction was complete. The solution was cooled, acetone was then evaporated and the aqueous acidic residue was slowly neutralized with slightly more than the equivalent amount of solid $NaHCO_3$. The resulting solution was extracted with CH_2Cl_2 (3×25 mL). The combined extracts were washed with water (3×150 mL), dried over Na_2SO_4, filtered and concentrated to give a light yellow oil (5.88 g). Purification by silica gel flash chromatography with CH_2Cl_2/MeOH (20:1) elution afforded the diol (*R*)-(−)-**22a** (5.79 g, 98% yield, 99.9% ee) as a white solid. R_f=0.30 (20% MeOH/CH_2Cl_2), mp 71–78 °C, peak 74 °C, heating rate 10.0 °C/min (lit. mp 68–69 °C).[26] $[\alpha]_D^{20}$ −12.6 (*c* 1.0, EtOH). FTIR (KBr) ν 3318, 3224, 2954, 2927, 1607, 1495, 1451, 1341, 1244, 1178, 1123, 1054, 996, 902, 862, 793, 698, 659 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 2.90 (br s, 2H, two −OH groups), 3.74 (dd, *J*=5.9 and 11.4 Hz, 1H, one of the CH_2-1 group), 3.84 (dd, *J*=3.6 and 11.4 Hz, 1H, one of the CH_2-1 group), 4.04 (m, 2H, CH_2-3), 4.13 (m, 1H, CH-2), 7.07 (dd, *J*=2.4 and 8.2 Hz, 1H, aromatic H-6), 7.14 (m, 1H, aromatic H-2), 7.22 (dm, *J*=7.6 Hz, 1H, aromatic H-4), 7.36 (m, 1H, aromatic H-5) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 63.5 (C-1), 69.3 (C-3), 70.4 (C-2), 111.4 (d, *J*=3.9 Hz, aromatic C-2), 117.9 (d, *J*=1.0 Hz, aromatic C-6), 118.0 (d, *J*=3.8 Hz, aromatic C-4), 123.8 (q, *J*=272.1 Hz, $-CF_3$), 130.1 (aromatic C-5), 131.9 (q, *J*=32.0 Hz, aromatic C-3), 158.5 (aromatic C-1) ppm. HRMS (EI): calcd for $C_{10}H_{11}F_3O_3$ 236.06603; found 236.06637. Chiral HPLC: Chiracel OD OD00CE-EL068, 10 μm, 250×4.6 mm column, hexanes/2-propanol 96:4 (v/v), 1.0 mL/min, t_R=25.21 min (99.97% yield of **22a**), t_R=31.14 min (0.03% yield of **22b**), 99.94% ee.

*4.5.1. (S)-(+)-3-(3-Trifluoromethylphenoxy)propane-1,2-diol (**22b**).* Treatment of the acetonide (*R*)-(−)-**21b** (4.0 g, 14.5 mmol) similar to the hydrolysis of (*S*)-(+)-**21a** afforded the diol (*S*)-(+)-**22b** (3.32 g, 97% yield, 99.2% ee). $[\alpha]_D^{20}$ +12.5 (*c* 1.0, EtOH). The characterization data from IR, NMR and HRMS spectra were identical in all aspects with those of (*R*)-(−)-**22a** enantiomer.

4.6. (*S*)-(+)-2-Hydroxy-3-(3-trifluoromethylphenoxy)propyl pivalate (23a)

Trimethylacetyl chloride (3.04 mL, 24.5 mmol) was added to a stirred solution of diol (*R*)-(−)-**22a** (5.50 g, 23.3 mmol) in a mixture of CH_2Cl_2 and pyridine (1:1, 50 mL) at 0 °C under an argon atmosphere. After stirring at 0 °C for 1 h and at room temperature for 1 h, the reaction was quenched with crushed ice (25 g) and the solution was partitioned between AcOEt (50 mL) and 10% aqueous HCl (50 mL). The resulting layers were separated and the aqueous phase was extracted with AcOEt (3×25 mL). The combined organic extracts were washed successively with H_2O (150 mL), saturated aqueous $NaHCO_3$ (150 mL), brine (200 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude ester (8.45 g), which was purified by flash column chromatography over silica gel (AcOEt/hexanes 1:4) to afford the pivalate (*S*)-(+)-**23a** (7.09 g, 95% yield, 99.9% ee) as a colourless oil. R_f=0.32 (20% AcOEt/hexanes), $[\alpha]_D^{20}$ +1.90 (*c* 1.0, EtOH). FTIR (thin film) ν 3467, 3075, 2975, 2938, 2876, 1731, 1593, 1493, 1481, 1451, 1330, 1285, 1240, 1167, 1128, 1066, 1047, 999, 940, 884, 793, 698, 659 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 1.22 (s, 9H, $-C(CH_3)_3$), 4.05 (dd, *J*=5.5 and 9.4 Hz, 1H, one of the CH_2-3 group), 4.08 (dd, *J*=4.6 and 9.4 Hz, 1H, one of the CH_2-3 group), 4.26 (m, 1H, CH-2), 4.30 (m, 2H, CH_2-1), 7.07 (dd, *J*=2.4 and 8.2 Hz, 1H, aromatic H-6), 7.15 (m, 1H, aromatic H-2), 7.24 (dm, *J*=7.9 Hz, 1H, aromatic H-4), 7.36 (m, 1H, aromatic H-5) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 27.1 (3C, $(CH_3)_3C-$), 38.9 ($(CH_3)_3C-$), 65.2 (C-1), 68.6 (C-2), 69.0 (C-3), 111.4 (d, *J*=3.8 Hz, aromatic C-2), 118.0 (d, *J*=1.0 Hz, aromatic C-6), 118.0 (d, *J*=3.8 Hz, aromatic C-4), 123.8 (q, *J*=271.6 Hz, $-CF_3$), 130.1 (aromatic C-5), 132.0 (q, *J*=32.3 Hz, aromatic C-3), 158.4 (aromatic C-1), 178.8 (C=O) ppm. HRMS (ESI): calcd for $C_{15}H_{19}F_3NaO_4$ $[M+Na]^+$ 343.11277; found 343.1134. Chiral HPLC: Chiracel OD-H, 5 μm, 250×4.6 mm column, hexanes/ethanol/methanol 98:1.5:1 (v/v/v), 1.0 mL/min, t_R=11.09 min (99.93% yield of **23a**), t_R=12.60 min (0.07% yield of **23b**), 99.86% ee.

*4.6.1. (R)-(−)-2-Hydroxy-3-(3-trifluoromethylphenoxy)propyl pivalate (**23b**).* According to the procedure described for the preparation of (*S*)-(+)-**23a**, the diol (*S*)-(+)-**22b** (3.0 g, 12.7 mmol) yielded the pivalate (*R*)-(−)-**23b** (3.83 g, 94% yield, 99.2% ee). $[\alpha]_D^{20}$ −1.5 (*c* 1.0, EtOH). The characterization data from IR, NMR and HRMS spectra were identical in all aspects with those of (*S*)-(+)-**23a** enantiomer.

4.7. (*S*)-(−)-2-(*tert*-Butyldimethylsilyloxy)-3-(3-trifluoromethylphenoxy)propyl pivalate (24a)

tert-Butyldimethylsilyl chloride (4.02 g, 25.9 mmol) was added in one portion to a stirred solution of alcohol (*S*)-(+)-**23a** (6.90 g, 21.5 mmol) and imidazole (3.70 g, 53.9 mmol) in anhydrous DMF (50 mL) at 0 °C under an argon atmosphere. The reaction was allowed to proceed for 18 h at room temperature and then quenched with crushed ice (25 g). The resulting mixture was partitioned between hexanes (50 mL) and H_2O (100 mL). The aqueous layer was extracted with hexanes (3×25 mL). The combined organic extracts were washed successively with H_2O (100 mL), brine (150 mL) and dried over Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (9.61 g) as a light yellow oil, which was purified by flash column chromatography (silica gel, 6–10% AcOEt/hexanes) to give TBDMS ether (*S*)-(−)-**24a** (8.66 g, 93% yield, 99.9% ee) as a colourless oil. R_f=0.49 (5% AcOEt/hexanes), $[\alpha]_D^{20}$ −6.7 (*c* 1.0, EtOH). FTIR (thin film) ν 3077, 2957, 2932, 2885, 2858, 1732, 1609, 1593, 1449, 1399, 1330, 1283, 1252, 1167, 1131, 1066, 1051, 1003, 880, 837, 780, 698 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 0.12 (s, 3H, CH_3-Si), 0.14 (s, 3H, CH_3-Si), 0.89 (s, 9H, $(CH_3)_3C-Si$), 1.21 (s, 9H, $(CH_3)_3C-C$), 3.96 (dd, *J*=5.9 and 9.5 Hz, 1H, one of the CH_2-3 group), 4.02 (dd, *J*=4.6 and 9.5 Hz, 1H, one of the CH_2-3 group), 4.12 (dd, *J*=6.7 and 13.0 Hz, 1H, one of the CH_2-1 group), 4.21–4.25 (m, 2H, one of the CH_2-1 group and CH-2), 7.07 (dd, *J*=2.4 and 8.3 Hz, 1H, aromatic H-6), 7.12 (m, 1H, aromatic H-2), 7.22 (dm, *J*=7.7 Hz, 1H, aromatic H-4), 7.39 (m, 1H, aromatic H-5) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.9 (CH_3-Si), −4.7 (CH_3-Si), 18.0 ($(CH_3)_3C-Si$), 25.7 (3C, $(CH_3)_3C-Si$), 27.2 (3C, $(CH_3)_3C-C$), 38.8 ($(CH_3)_3C-C$), 65.4 (C-1), 69.1 (C-2), 69.8 (C-3), 111.2 (d, *J*=4.1 Hz, aromatic C-2), 117.7 (d, *J*=4.1 Hz, aromatic C-4), 118.0 (d, *J*=1.2 Hz, aromatic C-6), 123.9 (q, *J*=272.2 Hz, $-CF_3$), 130.0 (aromatic C-5), 131.9 (q, *J*=32.4 Hz, aromatic C-3), 158.8 (aromatic C-1), 178.3 (C=O) ppm. HRMS (ESI): calcd for $C_{21}H_{33}F_3NaO_4Si$ $[M+Na]^+$ 457.19924; found 457.1973. Chiral HPLC: Chiracel OD-H, 5 μm, 250×4.6 mm column, hexanes/2-propanol 100:1 (v/v), 1.0 mL/min, t_R=7.08 min (0.06% yield of **24b**), t_R=7.49 min (99.94% yield of **24a**), 99.88% ee.

*4.7.1. (R)-(+)-2-(tert-Butyldimethylsilyloxy)-3-(3-trifluoromethylphenoxy)propyl pivalate (**24b**).* In the same manner as described for the preparation of (*S*)-(−)-**24a**, the alcohol (*R*)-(−)-**23b** (3.60 g, 11.2 mmol) afforded the ether (*R*)-(+)-**24b** (4.46 g, 91% yield, 99.2% ee). $[\alpha]_D^{20}$ +6.4 (*c* 1.0, EtOH). The characterization data from IR, NMR and HRMS spectra were identical in all aspects with those of (*S*)-(−)-**24a** enantiomer.

4.8. (*R*)-(−)-2-(*tert*-Butyldimethylsilyloxy)-3-(3-trifluoromethylphenoxy)propan-1-ol (25a)

Diisobutylaluminum hydride (1.0 M in toluene, 49.0 mL, 49.0 mmol) was added dropwise over 20 min to a stirred solution of pivalate (*S*)-(−)-**24a** (8.45 g, 19.4 mmol) in anhydrous CH_2Cl_2 (100 mL) at −78 °C under an argon atmosphere. The resulting mixture was allowed to warm to −20 °C for a 30 min period and stirred at this temperature for another 2 h. TLC analysis (hexanes/AcOEt, 8:1) indicated disappearance of the starting pivalate (*S*)-(−)-**24a**. The clear colourless solution was re-cooled to −78 °C and the excess of DIBAL was quenched by addition of MeOH (25 mL) dropwise. On warming to 0 °C, 10% aqueous potassium sodium tartrate (150 mL) was added and the mixture was stirred vigorously at room temperature for 2 h. The resulting layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×75 mL). The combined extracts were washed with water (150 mL), brine (200 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product (7.29 g), which was purified by flash column chromatography (silica gel, 3–11% AcOEt/hexanes) to afford the primary alcohol (*R*)-(−)-**25a** (6.28 g, 92% yield, 99.9% ee) as a colourless oil. R_f=0.41 (20% AcOEt/hexanes). $[\alpha]_D^{20}$ −29.4 (*c* 1.0, EtOH). FTIR (thin film) ν 3434, 3074, 2954, 2931, 2886, 2858, 1608, 1592, 1493, 1449, 1330, 1254, 1169, 1130, 1066, 1048, 999, 881, 837, 781, 697, 659 cm^{-1}. ^1H NMR (600 MHz, $CDCl_3$) δ 0.13 (s, 3H, CH_3-Si), 0.15 (s, 3H, CH_3-Si), 0.92 (s, 9H, $(CH_3)_3C-Si$), 2.02 (br s,1H, −OH), 3.69 (dd, *J*=4.2 and 11.3 Hz, 1H, one of the CH_2-1 group), 3.74 (dd, *J*=4.2 and 11.3 Hz, 1H, one of the CH_2-1 group), 3.96 (dd, *J*=6.3 and 9.3, 1H, one of the CH_2-3 group), 4.04 (dd, *J*=5.4 and 9.3 Hz, 1H, one of the CH_2-3 group), 4.13 (m, 1H, CH-2), 7.07 (dd, *J*=2.4 and 8.3 Hz, 1H, aromatic H-6), 7.12 (m, 1H, aromatic H-2), 7.21 (dm, *J*=7.7 Hz, 1H, aromatic H-4), 7.38 (m, 1H, aromatic H-5) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.9 (CH_3-Si), −4.6 (CH_3-Si), 18.1 ($(CH_3)_3C-Si$), 25.8 (3C, $(CH_3)_3C-Si$), 64.1 (C-1), 69.3 (C-3), 71.1 (C-2), 111.1 (d, *J*=3.7 Hz, aromatic C-2), 117.6 (d, *J*=4.0 Hz, aromatic C-

4), 118.0 (d, J=1.2 Hz, aromatic C-6), 123.9 (q, J=272.1 Hz, $-CF_3$), 130.0 (aromatic C-5), 131.9 (q, J=32.3 Hz, aromatic C-3), 158.8 (aromatic C-1) ppm. HRMS (ESI): calcd for $C_{16}H_{25}F_3NaO_3Si$ $[M+Na]^+$ 373.14173; found 373.1420. Chiral HPLC: Chiracel OD-H, 5 μm, 250×4.6 mm column, hexanes/2-propanol 100:0.5 (v/v), 1.0 mL/min, t_R=15.96 min (0.05% yield of **25b**), t_R=21.88 min (99.95% yield of **25a**), 99.90% ee.

*4.8.1. (S)-(+)-2-(tert-Butyldimethylsilyloxy)-3-(3-trifluoromethylphenoxy)propan-1-ol (**25b**).* Treatment of the pivalate (*R*)-(+)-**24b** (4.2 g, 9.67 mmol) similar to the reduction of (*S*)-(−)-**24a** afforded the primary alcohol (*S*)-(+)-**25b** (3.07 g, 91% yield, 99.2% ee). $[\alpha]_D^{20}$ +28.5 (*c* 1.0, EtOH). The characterization data from IR, NMR and HRMS spectra were identical in all aspects with those of (*R*)-(−)-**25a** enantiomer.

4.9. (*S*)-(−)-2-(*tert*-Butyldimethylsilyloxy)-3-(3-trifluoromethylphenoxy)propanal (16a)

Dess–Martin periodinane (9.06 g, 20.7 mmol) was added portionwise to a cold (0 °C) suspension of alcohol (*R*)-(−)-**25a** (6.05 g, 17.3 mmol) and dry $NaHCO_3$ (4.35 g, 51.8 mmol) in anhydrous CH_2Cl_2 (100 mL). After being stirred for 1 h at room temperature, TLC analysis (hexanes/AcOEt, 9:1) indicated disappearance of the starting alcohol (*R*)-(−)-**25a**. Saturated aqueous $NaHCO_3$ (100 mL) and Na_2SO_3 (15.2 g, 121 mmol) were then added simultaneously and the mixture was stirred at room temperature for 30 min. The resulting layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3×50 mL). The combined extracts were washed with water (3×150 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was co-evaporated with anhydrous tetrahydrofuran (3×50 mL) and carefully dried under reduced pressure to afford the crude aldehyde (*S*)-(−)-**16a** (5.82 g, 97%) as a light yellow oil. The aldehyde (*S*)-(−)-**16a** was directly used for the next step without further purification. $[\alpha]_D^{20}$ −26.4 (*c* 1.0, $CHCl_3$). FTIR (thin film) ν 3077, 2954, 2932, 2886, 2859, 1740, 1593, 1493, 1450, 1330, 1254, 1169, 1130, 976, 881, 838, 782, 697, 658 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 0.13 (s, 3H, CH_3–Si), 0.17 (s, 3H, CH_3–Si), 0.94 (s, 9H, $(CH_3)_3C$–Si), 4.13 (dd, J=6.6 and 9.9 Hz, 1H, one of the CH_2-3 group), 4.26 (dd, J=3.6 and 9.9 Hz, 1H, one of the CH_2-3 group), 4.40 (ddd, J=0.8, 3.6 and 6.6 Hz, 1H, CH-2), 7.07 (dd, J=2.4 and 8.3 Hz, 1H, aromatic H-6), 7.12 (m, 1H, aromatic H-2), 7.23 (dm, J=7.7 Hz, 1H, aromatic H-4), 7.39 (m, 1H, aromatic H-5), 9.75 (d, J=0.8 Hz, 1H, –CHO) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.9 (CH_3–Si), −4.7 (CH_3–Si), 18.2 ($(CH_3)_3C$–Si), 25.7 (3C, $(CH_3)_3C$–Si), 69.2 (C-3), 76.7 (C-2), 111.3 (d, J=3.5 Hz, aromatic C-2), 117.7 (d, J=4.0 Hz, aromatic C-4), 118.0 (d, J=1.2 Hz, aromatic C-6), 123.9 (q, J=272.1 Hz, $-CF_3$), 130.1 (aromatic C-5), 132.0 (q, J=32.2 Hz, aromatic C-3), 158.5 (aromatic C-1), 202.0 (–CHO) ppm.

*4.9.1. (R)-(+)-2-(tert-Butyldimethylsilyloxy)-3-(3-trifluoromethylphenoxy)propanal (**16b**).* According to the procedure described for the preparation of (*S*)-(−)-**16a**, the alcohol (*S*)-(+)-**25b** (3.80 g, 10.8 mmol) yielded the crude aldehyde (*R*)-(+)-**16b** (3.60 g, 95% yield). $[\alpha]_D^{20}$ +26.2 (*c* 1.0, $CHCl_3$). The characterization data from IR and NMR spectra were identical in all aspects with those of (*S*)-(−)-**16a** enantiomer.

4.10. 1-{(*Z*)-6-[(1*R*,2*R*,3*R*,5*S*)-2-[(1*R*/1*S*,2*R*/2*S*,3*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-(3-trifluoromethylphenoxy)-1-(phenylsulfonyl)-butyl]-3,5-bis(triethylsilyloxy)cyclopentyl]hex-4-enyl}-4-methyl-2,6,7-trioxabicyclo[2.2.2] octane (17a)

n-BuLi (8.25 mL, 13.2 mmol, 1.6 M in hexanes) was added dropwise to a solution of diisopropylamine (2.03 mL, 14.3 mmol) in anhydrous THF (15 mL) at −78 °C under an argon atmosphere. After 15 min at −78 °C, the phenylsulfone **15** (3.67 g, 5.28 mmol, 83.2% de) in anhydrous THF (5.0 mL) was added dropwise with vigorous stirring. The reaction mixture was allowed to warm to −40 °C and the crude aldehyde (*S*)-(−)-**16a** (4.60 g, 13.2 mmol) in anhydrous THF (5 mL) was added dropwise. After being stirred at −40 °C for another 1 h, TLC analysis (toluene/AcOEt 12:1) indicated disappearance of the starting phenylsulfone **15**. The cold reaction was quenched with saturated aqueous NaCl solution (50 mL). The resulting layers were separated and the aqueous phase was extracted with AcOEt (3×25 mL). The combined organic extracts were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was carefully dried in vacuo to yield a mixture of epimeric hydroxy sulfones **17a** (7.82 g) as a light yellow oil. The hydroxy sulfones **17a** were directly used for the next step without further purification.

*4.10.1. 1-{(Z)-6-[(1R,2R,3R,5S)-2-[(1R/1S,2R/2S,3S)-3-(tert-But-yldimethylsilyloxy)-4-(3-trifluoromethylphenoxy)-1-(phenylsulfonyl)butyl]-3,5-bis(triethylsilyloxy)cyclopentyl]-hex-4-enyl}-4-methyl-2,6,7-trioxabicyclo[2.2.2] octane (**17b**).* In the same manner as described for the preparation of hydroxy sulfones **17a**, the phenylsulfone **15** (2.16 g, 3.11 mmol, 83.2% de) and aldehyde (*R*)-(+)-**16b** (2.71 g, 7.77 mmol) afforded the crude mixture of hydroxy sulfones **17b** (4.78 g).

4.11. 1-{(*Z*)-6-[(1*R*,2*R*,3*R*,5*S*)-2-[(*R*)-3-(*tert*-Butyldimethylsilyloxy)-4-(3-trifluoromethylphenoxy)but-1-enyl]-3,5-bis(triethylsilyloxy)-cyclopentyl]hex-4-enyl}-4-methyl-2,6,7-trioxabicyclo[2.2.2] octane (27a)

The crude mixture of diastereoisomeric hydroxy sulfones **17a** (7.82 g) was dissolved in anhydrous MeOH (100 mL) and Na_2HPO_4 (6.0 g, 42.2 mmol) was added in one portion. On cooling to 0 °C under an argon atmosphere, sodium amalgam (20%, 7.28 g, 63.4 mmol Na) was added portionwise over 30 min with vigorous stirring. The cooling bath was removed and the resulting suspension was stirred at room temperature for 5 h to disappearance of the starting hydroxy sulfones **17a** (TLC, toluene/AcOEt 12:1). The solution was decanted from the remaining amalgam and concentrated under reduced pressure. The residue was diluted with water (100 mL) and AcOEt (50 mL). The resulting layers were separated and the aqueous phase was extracted with AcOEt (3×25 mL). The combined organic extracts were washed with brine (150 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product **27a** (6.14 g) as a light yellow oil. The crude olefin **27a** was directly used for the next step without further purification.

*4.11.1. 1-{(Z)-6-[(1R,2R,3R,5S)-2-[(S)-3-(tert-Butyldimethylsilyloxy)-4-(3-trifluoromethylphenoxy)but-1-enyl]-3,5-bis(triethylsilyloxy)cyclopentyl]hex-4-enyl}-4-methyl-2,6,7-trioxabicyclo[2.2.2] octane (**27b**).* Treatment of the mixture of epimeric hydroxy sulfones **17b** (4.78 g) similar to the reductive desulfonylation of **17a** afforded the crude olefine **27b** (4.19 g).

4.12. 2,2-Bis(hydroxymethyl)propyl (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(*R*,*E*)-3-hydroxy-4-(3-trifluoromethylphenoxy) but-1-enyl]cyclopentyl}hept-5-enoate (28a)

TBAF (15.8 mL, 15.8 mmol, 1.0 M in THF) was added dropwise to a solution of the crude silyl protected prostaglandin analogue **27a** (6.14 g) in anhydrous THF (15 mL). The resulting brown solution was stirred at 65–70 °C under an argon atmosphere for 1 h, whereupon the THF was evaporated under reduced pressure. The viscous residue was then diluted with 10% aqueous solution of citric acid (25 mL) to hydrolyze the 4-methyl-OBO carboxyl masking group. After being stirred for 15 min, the product was salted out with sodium chloride, separated and dried in vacuo to give the

crude pentaol **28a** (5.56 g). Purification by silica gel flash chromatography with gradient elution 1–6% methanol/ethyl acetate afforded the prostaglandin analogue (15*R*)-(+)-**28a** (2.63 g, 89% yield from phenylsulfone **15**, **28a**/**28b**/(5*E*,15*R*)-isomer=91.36%:0.18%:8.46%) as a light yellow viscous oil. R_f=0.45 (MeOH/CH_2Cl_2) $[\alpha]_D^{20}$ +18.7 (*c* 1.0, $CHCl_3$). FTIR (thin film) ν 3369, 2934, 1716, 1592, 1493, 1451, 1330, 1240, 1167, 1125, 1040, 972, 792, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 0.82 (s, 3H, $-CH_3$), 1.50 (m, 1H, cyclopentane CH-1), 1.66–1.70 (m, 3H, α-chain CH_2-3 and one of the cyclopentane CH_2-4 group), 2.04 (m, 2H, one of the α-chain CH_2-4 group and one of the α-chain CH_2-7 group), 2.11 (m, 1H, one of the α-chain CH_2-4 group), 2.24–2.34 (m, 5H, one of the α-chain CH_2-7 group, α-chain CH_2-2, one of the cyclopentane CH_2-4 group and cyclopentane CH-2), 3.51 (s, 4H, two $-CH_2OH$), 3.92 (m, 1H, cyclopentane CH-3), 3.97 (m, 2H, ω-chain CH_2-4), 4.07 (s, 2H, α-chain CH_2-1), 4.11 (m, 1H, cyclopentane CH-5), 4.49 (m, 1H, ω-chain CH-3), 5.32 (m, 1H, α-chain CH-5), 5.40 (m, 1H, α-chain CH-6), 5.66 (m, 2H, ω-chain CH-1 and ω-chain CH-2), 7.08 (dd, *J*=2.4 and 8.3 Hz, 1H, aromatic CH-6), 7.14 (m, 1H, aromatic CH-2), 7.20 (dm, *J*=7.7 Hz, 1H, aromatic CH-4), 7.37 (m, 1H, aromatic CH-5) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.7 ($-CH_3$), 24.6 (α-chain C-3), 25.5 (α-chain C-7), 26.4 (α-chain C-4), 33.3 (α-chain C-2), 40.5 ($-C(CH_3)(CH_2OH)_2$), 42.8 (cyclopentane C-4), 49.7 (cyclopentane C-1), 55.4 (cyclopentane C-2), 66.4 (2C, $-C(CH_3)(CH_2OH)_2$), 66.5 (α-chain CH_2-1), 71.0 (ω-chain C-3), 71.9 (ω-chain C-4), 72.4 (cyclopentane C-5), 77.4 (cyclopentane C-3), 111.4 (q, *J*=4.0 Hz, aromatic C-2), 117.8 (q, *J*=4.0 Hz, aromatic C-4), 118.0 (aromatic C-6), 124.4 (q, *J*=273.0 Hz, $-CF_3$), 129.2 (α-chain C-6), 129.4 (α-chain C-5), 130.0 (aromatic C-5), 130.3 (ω-chain C-2), 131.8 (q, *J*=32.0 Hz, aromatic C-3), 135.5 (ω-chain C-1), 158.7 (aromatic C-1), 174.6 (C=O) ppm. HRMS (ESI): calcd for $C_{28}H_{39}F_3NaO_8$ $[M+Na]^+$ 583.24892; found 583.2495. HPLC: Gemini C18, 3 μm, 250×4.6 mm column, KH_2PO_4 (4 g/L)/CH_3CN/MeOH (90:5:5) (phase A)/CH_3CN (phase B) with gradient elution 67–10%, 1.0 mL/min, t_R=36.13 min (8.46% yield of (5*E*,15*R*)-isomer) t_R=37.96 min (0.18% yield of (15*S*)-(+)-**28b**), t_R=39.62 min (91.36% yield of (15*R*)-(+)-**28a**). LC–MS (ESI): Gemini C18, 3 μm, 250×4.6 mm column, CH_3COONH_4 (1.44 g/L)/CH_3CN/MeOH (90:5:5) (phase A)/CH_3CN (phase B) with gradient elution 67–10%, 1.0 mL/min, t_R=37.33 min (*m*/*z*=561.2 $[M+H]^+$ for (5*E*,15*R*)-isomer), t_R=37.90 min (*m*/*z*=561.2 $[M+H]^+$ for (15*S*)-(+)-**28b**), t_R=40.56 min (*m*/*z*=561.2 $[M+H]^+$ for (15*R*)-(+)-**28a**).

*4.12.1. 2,2-Bis(hydroxymethyl)propyl (Z)-7-{(1R,2R,3R,5S)-3,5-dihydroxy-2-[(S,E)-3-hydroxy-4-(3-trifluoromethylphenoxy)but-1-enyl]cyclopentyl}hept-5-enoate (**28b**).* According to the procedure described for the preparation of the pentaol (15*R*)-(+)-**28a**, the crude silyl protected derivative **27b** (4.19 g) yielded the pure prostaglandin analogue (15*S*)-(+)-**28b** (1.49 g, 86% yield from phenylsulfone **15**, **28a**/**28b**/(5*E*,15*S*)-isomer=0.53%:91.1%:8.37%). $[\alpha]_D^{20}$ +23.8 (*c* 1.0, $CHCl_3$). FTIR (thin film) ν 3368, 2962, 2935, 2879, 1726, 1592, 1493, 1450, 1330, 1241, 1167, 1125, 1039, 972, 916, 882, 792, 699 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 0.84 (s, 3H, $-CH_3$), 1.55 (m, 1H, cyclopentane CH-1), 1.60–1.73 (m, 2H, α-chain CH_2-3), 1.80 (m, 1H, one of the cyclopentane CH_2-4 group), 2.12–2.24 (m, 4H, α-chain CH_2-4, one of the α-chain CH_2-7 group, one of the cyclopentane CH_2-4), 2.24–2.38 (m, 3H, α-chain CH_2-2 and one of the α-chain CH_2-7 group), 2.42 (m, 1H, cyclopentane CH-2), 3.53 (s, 4H, two $-CH_2OH$), 3.95 (dd, *J*=7.7 and 9.4 Hz, 1H, one of the ω-chain CH_2-4 group), 3.97 (m, 1H, cyclopentane CH-3), 4.02 (dd, *J*=3.8 and 9.4 Hz, 1H, one of the ω-chain CH_2-4 group), 4.10 (m, 2H, α-chain CH_2-1 group), 4.15 (m, 1H, cyclopentane CH-5), 4.53 (m, 1H, ω-chain CH-3), 5.35 (m, 1H, α-chain CH-5), 5.44 (m, 1H, α-chain CH-6), 5.70 (dd, *J*=5.4 and 15.5 Hz, 1H, ω-chain CH-2), 5.75 (dd, *J*=8.0 and 15.5 Hz, 1H, ω-chain CH-1), 7.09 (dd, *J*=2.4 and 8.3 Hz, 1H, aromatic CH-6), 7.15 (m, 1H, aromatic CH-2), 7.21 (dm, *J*=7.7 Hz, 1H, aromatic CH-4), 7.38 (m, 1H, aromatic CH-5) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.8 ($-CH_3$), 24.6 (α-chain C-3), 25.7 (α-chain C-7), 26.4 (α-chain C-4), 33.4 (α-chain C-2), 40.6 ($-C(CH_3)(CH_2OH)_2$), 42.9 (cyclopentane C-4), 50.3 (cyclopentane C-1), 55.7 (cyclopentane C-2), 66.6 (2C, $-C(CH_3)(CH_2OH)_2$), 66.7 (α-chain CH_2-1), 70.5 (ω-chain C-3), 72.1 (ω-chain C-4), 72.9 (cyclopentane C-5), 77.9 (cyclopentane C-3), 111.5 (q, *J*=3.8 Hz, aromatic C-2), 117.7 (q, *J*=3.8 Hz, aromatic C-4), 118.1 (s, aromatic C-6), 123.9 (q, *J*=271.0 Hz, $-CF_3$), 129.3 (α-chain C-6), 129.4 (α-chain C-5), 129.6 (ω-chain C-2), 130.0 (aromatic C-5), 131.8 (q, *J*=32.2 Hz, aromatic C-3), 134.7 (ω-chain C-1), 158.7 (aromatic C-1), 174.6 (C=O) ppm. HRMS (ESI): calcd for $C_{28}H_{39}F_3NaO_8$ $[M+Na]^+$ 583.24892; found 583.2507. HPLC: Gemini C18, 3 μm, 250×4.6 mm column, KH_2PO_4 (4 g/L)/CH_3CN/MeOH (90:5:5) (phase A)/CH_3CN (phase B) with gradient elution 67–10%, 1.0 mL/min, t_R=35.43 min (8.37% yield of (5*E*,15*S*)-isomer), t_R=37.96 min (91.1% yield of (15*S*)-(+)-**28b**), t_R=39.62 min (0.53% yield of (15*R*)-(+)-**28a**). LC–MS (ESI): Gemini C18, 3 μm, 250×4.6 mm column, CH_3COONH_4 (1.44 g/L)/CH_3CN/MeOH (90:5:5) (phase A)/CH_3CN (phase B) with gradient elution 67–10%, 1.0 mL/min, t_R=35.68 min (*m*/*z*=561.2 $[M+H]^+$ for (5*E*,15*S*)-isomer), t_R=37.90 min (*m*/*z*=561.2 $[M+H]^+$ for (15*S*)-(+)-**28b**), t_R=40.50 min (*m*/*z*=561.2 $[M+H]^+$ for (15*R*)-(+)-**28a**).

4.13. (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-[(*R*,*E*)-3-hydroxy-4-(3-trifluoromethylphenoxy)but-1-enyl]cyclopentyl}hept-5-enoic acid (7a)

$LiOH \cdot H_2O$ (0.67 g, 16.1 mmol) was added in one portion to a solution of ester (15*R*)-(+)-**28a** (1.80 g, 3.21 mmol) in MeOH (10 mL). The resulting suspension was stirred overnight resulting in disappearance of the starting material **28a** (TLC, CH_3CN/toluene 6:1). After cooling and evaporating the solvent, the residual solid was dissolved in water (100 mL) and washed with Et_2O (25 mL) to remove organic impurities. The water layer was acidified with citric acid to pH 4–5 and the product was extracted with ethyl acetate (3×25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo to afford the crude acid **7a** (1.67 g). Purification by silica gel flash chromatography (AcOEt/MeOH 10:1) afforded the pure fluprostenol (15*R*)-(+)-**7a** (1.43 g, 98%, **7a**/**7b**/(5*E*,15*R*)-isomer=91.84%:0.18%:7.98%) as a thick pale yellow oil. R_f=0.27 (AcOEt/MeOH 5:1). $[\alpha]_D^{20}$ +21.1 (*c* 1.0, $CHCl_3$). FTIR (thin film) ν 3363, 3009, 1710, 1593, 1493, 1451, 1330, 1239, 1168, 1125, 1066, 1035, 972, 913, 882, 792, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 1.49 (m, 1H, cyclopentane CH-1), 1.64 (m, 2H, α-chain CH_2-3), 1.70 (m, 1H, one of the cyclopentane CH_2-4 group), 2.08–2.14 (m, 3H, α-chain CH_2-4 and one of the α-chain CH_2-7 group), 2.18–2.40 (m, 5H, α-chain CH_2-2, one of the α-chain CH_2-7 group, one of the cyclopentane CH_2-4 group and cyclopentane CH-2), 3.93 (m, 1H, cyclopentane CH-3), 3.98 (m, 2H, ω-chain CH_2-4), 4.14 (m, 1H, cyclopentane CH-5), 4.52 (m, 1H, ω-chain CH-3), 5.35 (m, 1H, α-chain CH-5), 5.44 (m, 1H, α-chain CH-6), 5.64–5.72 (m, 2H, ω-chain CH-1 and ω-chain CH-2), 7.09 (dd, *J*=2.4 and 8.3 Hz, 1H, aromatic CH-6), 7.15 (m, 1H, aromatic CH-2), 7.21 (dm, *J*=7.7 Hz, 1H, aromatic CH-4), 7.38 (m, 1H, aromatic CH-5) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 24.5 (α-chain C-3), 25.1 (α-chain C-7), 26.3 (α-chain C-4), 33.0 (α-chain C-2), 42.6 (cyclopentane C-4), 50.0 (cyclopentane C-1), 55.3 (cyclopentane C-2), 70.7 (ω-chain C-3), 71.8 (ω-chain C-4), 72.1 (cyclopentane C-5), 77.2 (cyclopentane C-3), 111.4 (q, *J*=3.8 Hz, aromatic C-2), 117.7 (q, *J*=4.0 Hz, aromatic C-4), 118.0 (aromatic C-6), 123.9 (q, *J*=271.2 Hz, $-CF_3$), 128.9 (α-chain C-6), 129.6 (α-chain C-5), 129.9 (ω-chain C-2), 130.0 (aromatic C-5), 131.8 (q, *J*=32.2 Hz, aromatic C-3), 135.2 (ω-chain C-1), 158.7 (aromatic C-1), 176.8 (C=O) ppm. HRMS (ESI): calcd for $C_{23}H_{29}F_3NaO_6$ $[M+Na]^+$ 481.18084; found 481.1802. HPLC: Gemini C18, 3 μm, 250×4.6 mm column, with gradient elution 67–10% KH_2PO_4 (4 g/L)/CH_3CN/MeOH (90:5:5) (phase A)/CH_3CN (phase B),

1.0 mL/min, t_R=30.43 min (7.98% yield of (5*E*,15*R*)-isomer), t_R=33.18 min (0.18% yield of (15*S*)-(+)-**7b**), t_R=34.23 min (91.84% yield of (15*R*)-(+)-**7a**). LC–MS (ESI): Gemini C18, 3 μm, 250×4.6 mm column, with gradient elution 67–10% CH_3COONH_4 (4 g/L)/CH_3CN/MeOH (90:5:5) (phase A)/CH_3CN (phase B), 1.0 mL/min, t_R=36.06 min (*m*/*z*=497.4 $[M+H]^+$ for (5*E*,15*R*)-isomer), t_R=37.87 min (*m*/*z*=497.4 $[M+H]^+$ for (15*S*)-(+)-**7b**), t_R=38.62 min (*m*/*z*=497.4 $[M+H]^+$ for (15*R*)-(+)-**7a**).

*4.13.1. (Z)-7-{(1R,2R,3R,5S)-3,5-Dihydroxy-2-[(S,E)-3-hydroxy-4-(3-trifluoromethylphenoxy)but-1-enyl]cyclopentyl}hept-5-enoic acid (**7b**).* In the same manner as described for the preparation of fluprostenol (15*R*)-(+)-**7a**, hydrolysis of the ester (15*S*)-(+)-**28b** (1.0 g, 1.78 mmol) afforded the pure acid (15*S*)-(+)-**7b** (0.79 g, 96% yield, **7a**/**7b**/(5*E*,15*S*)-isomer=0.53%:91.37%:8.10%). $[\alpha]_D^{20}$ +24.0 (*c* 1.0, $CHCl_3$). FTIR (thin film) *ν* 3370, 3009, 2935, 1709, 1593, 1450, 1330, 1239, 1168, 1126, 1066, 1036, 972, 913, 882, 792, 698 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz, 25 °C) *δ* 1.48 (m, 1H, cyclopentane CH-1), 1.63 (m, 2H, α-chain CH_2-3), 1.77 (m, 1H, one of the cyclopentane CH_2-4 group), 2.10 (m, 2H, α-chain CH_2-4), 2.13–2.24 (m, 2H, α-chain CH_2-7), 2.25–2.32 (m, 3H, one of the cyclopentane CH_2-4 group and α-chain CH_2-2), 2.37 (m, 1H, cyclopentane CH-2), 3.95 (dd, *J*=7.4 and 9.4 Hz, one of the ω-chain CH_2-4 group), 3.98 (m, 1H, cyclopentane CH-3), 4.02 (dd, *J*=3.5 and 9.4 Hz, one of ω-chain CH_2-4 group), 4.18 (m, 1H, cyclopentane CH-5), 4.56 (m, 1H, ω-chain CH-3), 5.35 (m, 1H, α-chain CH-5), 5.47 (m, 1H, α-chain CH-6), 5.68 (dd, *J*=5.6 and 15.4 Hz, 1H, ω-chain CH-2), 5.72 (dd, *J*=8.2 and 15.4 Hz, 1H, ω-chain CH-1), 7.07 (dd, *J*=2.4 and 8.3 Hz, 1H, aromatic CH-6), 7.13 (m, 1H, aromatic CH-2), 7.20 (dm, *J*=7.7 Hz, 1H, aromatic CH-4), 7.36 (m, 1H, aromatic CH-5) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) *δ* 24.4 (α-chain C-3), 25.1 (α-chain C-7), 26.2 (α-chain C-4), 32.8 (α-chain C-2), 42.9 (cyclopentane C-4), 50.6 (cyclopentane C-1), 55.6 (cyclopentane C-2), 70.8 (ω-chain C-3), 71.9 (ω-chain C-4), 72.6 (cyclopentane C-5), 77.7 (cyclopentane C-3), 111.6 (q, *J*=4.1 Hz, aromatic C-2), 117.8 (q, *J*=3.6 Hz, aromatic C-4), 118.1 (aromatic C-6), 123.9 (q, *J*=272.4 Hz, $-CF_3$), 129.0 (α-chain C-6), 129.5 (ω-chain C-2), 129.7 (α-chain C-5), 130.1 (aromatic C-5), 131.9 (q, *J*=32.3 Hz, aromatic C-3), 135.1 (ω-chain C-1), 158.6 (aromatic C-1), 177.3 (C=O) ppm. HRMS (ESI): calcd for $C_{23}H_{29}F_3NaO_6$ $[M+Na]^+$ 481.18084; found 481.1809. HPLC: Gemini C18, 3 μm, 250×4.6 mm column, KH_2PO_4 (4 g/L)/CH_3CN/MeOH (90:5:5) (phase A)/CH_3CN (phase B) with gradient elution 67–10%, 1.0 mL/min, t_R=29.52 min (8.10% yield of (5*E*,15*S*)-isomer), t_R=33.18 min (91.37% yield of (15*S*)-(+)-**7b**), t_R=34.23 min (0.53% yield of (15*R*)-(+)-**7a**). LC–MS (ESI): Gemini C18, 3 μm, 250×4.6 mm column, with gradient elution 67–10% CH_3COONH_4 (4 g/L)/CH_3CN/MeOH (90:5:5) (phase A)/CH_3CN (phase B), 1.0 mL/min, t_R=33.82 min (*m*/*z*=497.4 $[M+H]^+$ for (5*E*,15*S*)-isomer), t_R=37.87 min (*m*/*z*=497.4 $[M+H]^+$ for (15*S*)-(+)-**7b**), t_R=38.62 min (*m*/*z*=497.4 $[M+H]^+$ for (15*R*)-(+)-**7a**).

4.14. Isopropyl (*Z*)-7-{(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-[(*R*,*E*)-3-hydroxy-4-(3-trifluoromethylphenoxy)but-1-enyl]cyclopentyl}hept-5-enoate (8a)

DBU (2.65 mL, 17.56 mmol) was added dropwise to a stirred solution of fluprostenol (15*R*)-(+)-**7a** (1.15 g, 2.51 mmol) in anhydrous acetone (10 mL) at 0 °C under an argon atmosphere. The mixture was allowed to warm to room temperature, whereupon 2-iodopropane (1.77 mL, 17.56 mmol) was added dropwise. The resulting solution was stirred for 20 h resulting in disappearance of the starting acid **7a** (TLC, CH_3CN/toluene 1:1). The reaction was quenched with ethyl acetate (100 mL). The resulting white solid was filtered off and washed with ethyl acetate (3×25 mL). The filtrate and washings were combined and acidified with 3% citric acid solution to pH 5–6. The resulting layers were separated and the aqueous phase was extracted with AcOEt (3×25 mL). The combined extracts were washed with saturated $NaHCO_3$ (100 mL), water (150 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product **8a** (1.42 g), which was purified by silica gel flash chromatography with gradient elution 5–10% 2-propanol/CH_2Cl_2 to afford the title compound (15*R*)-(+)-**8a** (1.19 g, 95% yield, **8a**/**8b**/**8c**=91.95%:0.18%:7.87%) as a pale yellow oil. This sample was further purified by preparative HPLC on silica gel to give travoprost (**8a**, 0.79 g, 64% yield) as a thick colourless oil. R_f=0.3 (2-propanol/CH_2Cl_2 8:1). $[\alpha]_D^{20}$ +16.3 (*c* 1.0, CH_2Cl_2). (lit. $[\alpha]_D^{20}$ +14.6 (*c* 1.0, CH_2Cl_2)).[19] FTIR (thin film) *ν* 3376, 2975, 2934, 1727, 1592, 1493, 1450, 1375, 1241, 1168, 1127, 1066, 1035, 970, 951, 915, 882, 792, 698 cm^{-1}. ^1H NMR (C_6D_6, 600 MHz) *δ* 1.05 (s, 3H, $-CH_3$), 1.06 (s, 3H, $-CH_3$), 1.36 (m, cyclopentane CH-1), 1.63 (m, 2H, α-chain CH_2-3), 1.88 (dd, *J*=4.2 and 15.0 Hz, one of the cyclopentane CH_2-4 group), 2.00–2.08 (m, 1H, one of the α-chain CH_2-4 group), 2.10–2.17 (m, 3H, α-chain CH_2-2 and one of the α-chain CH_2-4 group), 2.20–2.26 (m, 2H, one of the α-chain CH_2-7 group and one of the cyclopentane CH_2-4 group), 2.47 (m, 1H, one of the α-chain CH_2-7 group), 2.62 (m, 1H, cyclopentane CH-2), 3.80 (dd, *J*=4.2 and 9.6 Hz, one of the ω-chain CH_2-4 group), 3.86 (dd, *J*=6.9 and 9.6 Hz, one of the ω-chain CH_2-4 group), 3.96 (m, 1H, cyclopentane CH-3), 4.08 (br s, 1H, cyclopentane CH-5), 4.30 (s, 1H, −OH), 4.53 (m, 1H, ω-chain CH-3), 4.98 (septet, J=6.3 Hz, 1H, $-CH(CH_3)_2$), 5.37 (m, 1H, α-chain CH-5), 5.54 (m, 1H, α-chain CH-6), 5.66 (dd, *J*=9.2 and 15.4 Hz, ω-chain CH-1), 5.81 (dd, *J*=7.2 and 15.4 Hz, ω-chain CH-2), 6.90 (dd, *J*=2.2 and 8.5 Hz, 1H, aromatic CH-6), 6.98 (m, 1H, aromatic CH-5), 7.05 (dm, *J*=7.7 Hz, 1H, aromatic CH-4), 7.25 (m, 1H, aromatic CH-2) ppm. ^{13}C NMR (150 MHz, C_6D_6) *δ* 21.7 ($-CH_3$), 21.8 ($-CH_3$), 25.2 (α-chain C-3), 25.7 (α-chain C-7), 26.9 (α-chain C-4), 34.1 (α-chain C-2), 43.5 (cyclopentane C-4), 50.2 (cyclopentane C-1), 55.8 (cyclopentane C-2), 67.6 ($-CH(CH_3)_2$), 71.5 (ω-chain C-3), 72.2 (cyclopentane C-5), 72.3 (ω-chain C-4), 77.6 (cyclopentane C-3), 111.9 (q, *J*=3.8 Hz, aromatic C-2), 117.7 (q, *J*=3.8 Hz, aromatic C-4), 118.4 (aromatic C-6), 124.8 (q, *J*=274.2 Hz, $-CF_3$), 129.6 (α-chain C-6), 129.8 (α-chain C-5), 130.3 (aromatic C-5), 131.4 (ω-chain C2), 132.0 (q, *J*=32.2 Hz, aromatic C-3), 136.0 (ω-chain C-1), 159.4 (aromatic C-1), 173.3 (C=O) ppm. HRMS (ESI): calcd for $C_{26}H_{35}F_3NaO_6$ $[M+Na]^+$ 523.2278; found 523.2272. Chiral HPLC: AS-3R, 3 μm, 150×4.6 mm column, H_2O/CH_3CN with gradient elution from 80% to 10%, 1.0 mL/min, t_R=32.67 min (91.95% yield of (15*R*)-(+)-**8a**), t_R=35.97 min (0.18% yield of (15*S*)-(+)-**8b**), t_R=36.70 min (7.87% yield of (5*E*,15*R*)-**8c**). LC–MS (ESI): AS-3R, 3 μm, 150×4.6 mm column, H_2O/CH_3CN with gradient elution from 80% to 10%, 1.0 mL/min, t_R=34.60 min (*m*/*z*=501.3 $[M+H]^+$ for (15*R*)-(+)-**8a**), t_R=38.67 min (*m*/*z*=501.3 $[M+H]^+$ for (15*S*)-(+)-**8b**), t_R=39.40 min (*m*/*z*=501.3 $[M+H]^+$ for (5*E*,15*R*)-**8c**).

*4.14.1. Isopropyl (Z)-7-{(1R,2R,3R,5S)-3,5-dihydroxy-2-[(S,E)-3-hydroxy-4-(3-trifluoromethylphenoxy)but-1-enyl]cyclopentyl}hept-5-enoate (**8b**).* Treatment of the acid (15*S*)-(+)-**7b** (0.65 g, 1.42 mmol) similar to the esterification of (15*R*)-(+)-**7a** afforded the pure epimer (15*S*)-(+)-**8b** of travoprost (0.66 g, 92% yield, **8a**/**8b**/(5*E*,15*S*)-isomer=0.53%:91.84%:7.63%). $[\alpha]_D^{20}$ +27.15 (*c* 1.0, CH_2Cl_2). FTIR (thin film) *ν* 3394, 2981, 2936, 1726, 1593, 1493, 1450, 1330, 1241, 1168, 1127, 1109, 1066, 1036, 971, 917, 881, 792, 698 cm^{-1}. ^1H NMR (C_6D_6, 600 MHz) *δ* 1.05 (s, 3H, $-CH_3$), 1.05 (two d, *J*=6.6 Hz, 6H, two $-CH_3$), 1.40 (m, 1H, cyclopentane CH-1), 1.63 (m, 2H, α-chain CH_2-3), 1.85 (m, 1H, one of the cyclopentane CH_2-4 group), 2.05–2.13 (m, 2H, one of the cyclopentane CH_2-4 group and one of the α-chain CH_2-4 group), 2.13–2.20 (m, 3H, one of the α-chain CH_2-4 group and α-chain CH_2-2), 2.30 (m, 1H, one of the α-chain CH_2-7 group), 2.45 (m, 1H, one of the α-chain CH_2-7 group), 2.59 (m, 1H, cyclopentane CH-2), 2.96 (br s, 1H, −OH), 3.37 (br s, 1H, −OH), 3.49 (br s, 1H, −OH), 3.79 (d, *J*=5.5 Hz, 2H, ω-chain CH_2-

4), 3.97 (s, 1H, cyclopentane CH-3), 4.08 (m, 1H, cyclopentane CH-5), 4.51 (m, 1H, ω-chain CH-3), 4.99 (septet, J=6.3 Hz, 1H, $-CH(CH_3)_2$), 5.38 (m, 1H, α-chain CH-5), 5.57 (m, 1H, α-chain CH-6), 5.73–5.80 (m, 2H, ω-chain CH-1 and ω-chain CH-2), 6.87 (dd, J=2.4 and 8.3 Hz, 1H, aromatic CH-6), 6.97 (m, 1H, aromatic CH-5), 7.04 (dm, J=7.7 Hz, 1H, aromatic CH-4) and 7.23 (s, 1H, aromatic CH-2) ppm. ^{13}C NMR (150 MHz, C_6D_6) δ 21.7 ($-CH_3$), 21.8 ($-CH_3$), 25.2 (α-chain C-3), 25.8 (α-chain C-7), 26.9 (α-chain C-4), 34.0 (α-chain C-2), 43.6 (cyclopentane C-4), 50.9 (cyclopentane C-1), 55.8 (cyclopentane C-2), 67.7 ($-CH(CH_3)_2$), 70.6 (ω-chain C-3), 72.5 (ω-chain C-4), 72.6 (cyclopentane C-5), 78.1 (cyclopentane C-3), 111.9 (q, J=4.0 Hz, aromatic C-2), 117.7 (q, J=3.6 Hz, aromatic C-4), 118.5 (aromatic C-6), 124.8 (q, J=272.3 Hz, $-CF_3$), 129.7 (α-chain C-6), 129.8 (α-chain C-5), 130.3 (aromatic C-5), 130.6 (ω-chain C-2), 132.0 (q, J=32.2 Hz, aromatic C-3), 134.5 (ω-chain C-1), 159.4 (aromatic C-1), 173.4 (C=O) ppm. HRMS (ESI): calcd for $C_{26}H_{35}F_3NaO_6$ $[M+Na]^+$ 523.2278; found 523.2287. Chiral HPLC: AS-3R, 3 μm, 150×4.6 mm column, H_2O/CH_3CN with gradient elution 80–10%, 1.0 mL/min, t_R=32.67 min (0.53 yield of (15*R*)-(+)-**8a**), t_R=35.97 min (91.84% yield of (15*S*)-(+)-**8b**), t_R=39.43 min (7.63% yield of (5*E*,15*S*)-isomer). LC–MS (ESI): AS-3R, 3 μm, 150×4.6 mm column, H_2O/CH_3CN with gradient elution 80–10%, 1.0 mL/min, t_R=34.60 min (m/z=501.3 $[M+H]^+$ for (15*R*)-(+)-**8a**), t_R=38.67 min (m/z=501.3 $[M+H]^+$ for (15*S*)-(+)-**8b**), t_R=41.86 min (m/z=501.3 $[M+H]^+$ for (5*E*,15*S*)-isomer).

4.15. 1-{(*Z*)-6-[(1*R*,2*R*,3*R*,5*S*)-2-methyl-3,5-bis(triethylsilyloxy)cyclopentyl]hex-4-enyl}-4-methyl-2,6,7-trioxabicyclo[2.2.2] octane (29)

Sulfone **15** (5.0 g, 7.14 mmol, 83.2% de) was dissolved in anhydrous MeOH (70 mL) and Na_2HPO_4 (4.05 g, 28.56 mmol) was added in one portion. On cooling to 0 °C under an argon atmosphere, sodium amalgam (20%, 3.21 g, 27.948 mmol Na) was added portionwise with vigorous stirring. The cooling bath was removed and the resulting suspension was stirred for 3 h at room temperature with disappearance of the starting phenylsulfone **15** (TLC toluene/AcOEt 12:1). The solution was decanted from the remaining amalgam and concentrated under reduced pressure. The residue was diluted with water (100 mL) and AcOEt (50 mL). The resulting layers were separated and the aqueous phase was extracted with AcOEt (3×25 mL). The combined organic extracts were washed with brine (150 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product **29** (4.78 g) as a thick pale yellow oil. The crude olefin **29** was directly used for the next step without further purification.

4.16. 2,2-Bis(hydroxymethyl)propyl (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-methylcyclopentyl]hept-5-enoate (30)

TBAF (14.9 mL, 14.9 mmol, 1.0 M in THF) was added dropwise to a solution of the crude silyl protected alcohol **29** (4.78 g) in anhydrous THF (15 mL). The resulting solution was stirred at room temperature under an argon atmosphere for 1 h, whereupon THF was evaporated under reduced pressure. The viscous residue was then diluted with 10% aqueous solution of citric acid (20 mL) to hydrolyze 4-methyl-OBO carboxyl masking group. After being stirred for 15 min, the product was salted out with sodium chloride, separated and dried in vacuo to give the crude tetraol **30** (4.23 g). Purification by silica gel flash chromatography with gradient elution 6–10% methanol/ethyl acetate afforded the prostaglandin analogue **30** (2.25 g, 91% yield from phenylsulfone **15**, 83.3% de) as a thick pale yellow oil. R_f=0.32 (AcOEt/CH_3OH 10:1). $[\alpha]_D^{20}$ +31.8 (*c* 1.0, EtOH). FTIR (thin film) ν 3370, 2954, 1715, 1459, 1378, 1315, 1247, 1174, 1089, 1046, 974, 912, 736, 702, 597 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 0.85 (s, 3H, α-chain $-CH_3$), 1.06 (d, J=7.0 Hz, 3H, cyclopentane 2-CH_3), 1.35 (m, 1H, cyclopentane CH-1), 1.70–1.78 (m, 3H, α-chain CH_2-3 and cyclopentane CH-2), 1.80 (dm, J=14.5 Hz, 1H, one of the cyclopentane CH_2-4 group), 2.02 (ddd, J=4.4, 6.5 and 14.5 Hz, 1H, one of the cyclopentane CH_2-4 group), 2.10–2.26 (m, 3H, α-chain CH_2-4 and one of the α-chain CH_2-7 group), 2.31 (m, 1H, one of the α-chain CH_2-7 group), 2.39 (m, 2H, α-chain CH_2-2), 3.54 (d, J=11.1 Hz, 2H, $-CH_2OH$), 3.58 (d, J=11.1 Hz, 2H, $-CH_2OH$), 3.82 (m, 1H, cyclopentane CH-3), 4.16 (m, 1H, cyclopentane CH-5), 4.19 (s, 2H, α-chain CH_2-1), 5.39 (m, 1H, α-chain CH-5), 5.48 (m, 1H, α-chain CH-6) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 16.9 (α-chain $-CH_3$), 18.6 (cyclopentane 2-CH_3), 24.8 (α-chain C-3), 26.2 (α-chain C-4), 26.8 (α-chain C-7), 33.6 (α-chain C-2), 40.7 ($-C(CH_3)(CH_2OH)_2$), 42.3 (cyclopentane C-4), 47.4 (cyclopentane C-2), 52.7 (cyclopentane C-1), 66.5 ($-CH_2C(CH_3)(CH_2OH)_2$), 67.6 (2C, $-C(CH_3)(CH_2OH)_2$), 74.8 (cyclopentane C-5), 80.7 (cyclopentane C-3), 129.4 (α-chain C-5), 129.7 (α-chain C-6), 174.7 (C=O) ppm. HRMS (ESI): calcd for $C_{18}H_{32}NaO_6$ $[M+Na]^+$ 367.20911; found 367.2107. HPLC: Poroshell 120 EC-C8, 2.7 μm, 150×4.6 mm column, H_2O/CH_3CN (8:2, phase A)/H_2O/CH_3CN (1:1, phase B)/with gradient elution 100–10%, 1.0 mL/min, t_R=7.529 min (8.37% yield of (5*E*)-**30**), t_R=7.822 min (91.63% yield of (5*Z*)-**30**). LC–MS (ESI): Poroshell 120 EC-C8, 2.7 μm, 150×4.6 mm column, 0.1% CH_3COOH (phase A)/CH_3CN (phase B)/8:2, 1.0 mL/min, t_R=14.95 min (m/z=345.4 $[M+H]^+$ for (5*E*)-**30**), t_R=15.50 min (m/z=345.4 $[M+H]^+$ for (5*Z*)-**30**).

4.17. (*Z*)-(+)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-Dihydroxy-2-methylcyclopentyl]hept-5-enoic acid (31)

$LiOH\cdot H_2O$ (1.0 g, 24.0 mmol) was added in one portion to a solution of ester **30** (1.65 g, 4.79 mmol) in MeOH (15 mL). The resulting suspension was stirred overnight resulting in disappearance of the starting material **30** (TLC, AcOEt/MeOH 10:1). After cooling and evaporating the solvent, the residual solid was dissolved in water (100 mL) and washed with Et_2O (25 mL) to remove organic impurities. The water layer was acidified with citric acid to pH 4–5 and the product was extracted with ethyl acetate (3×25 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered and evaporated in vacuo to afford the crude product **31** (1.59 g). Purification by silica gel flash chromatography (AcOEt/MeOH 10:1) afforded the pure acid **31** (1.12 g, 97% yield, 83.5% de) as a thick pale yellow oil. R_f=0.35 (AcOEt/CH_3OH 10:1). $[\alpha]_D^{20}$ +48.1 (*c* 1.0, EtOH). FTIR (thin film) ν 3368, 3006, 2953, 2930, 2870, 1708, 1457, 1411, 1377, 1243, 1097, 1039, 973, 912, 780, 735, 626 cm^{-1}. ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.05 (d, J=7.0 Hz, 3H, $-CH_3$), 1.31 (m, 1H, cyclopentane CH-1), 1.70 (m, 2H, α-chain CH_2-3), 1.77 (m, 1H, cyclopentane CH-2), 1.79 (dm, J=15.0 Hz, 1H, one of the cyclopentane CH_2-4 group), 2.06 (m, 1H, one of the cyclopentane CH_2-4 group), 2.09–2.23 (m, 3H, α-chain CH_2-4 and one of the α-chain CH_2-7 group), 2.24–2.30 (m, 1H, one of the α-chain CH_2-7 group), 2.34 (m, 2H, α-chain CH_2-2), 3.81 (m, 1H, cyclopentane CH-3), 4.15 (m, 1H, cyclopentane CH-5), 5.38 (m, 1H, α-chain CH-5), 5.45 (m, 1H, α-chain CH-6), 5.69 (br s, 2H, two −OH) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.1 (CH_3), 24.5 (α-chain C-3), 26.3 (α-chain C-7), 26.4 (α-chain C4), 33.2 (α-chain C-2), 42.1 (cyclopentane C-4), 46.7 (cyclopentane C-2), 52.5 (cyclopentane C-1), 74.3 (cyclopentane C-5), 80.3 (cyclopentane C-3), 129.4 (α-chain C-5), 129.5 (α-chain C6), 178.3 (C=O) ppm. HRMS (ESI): calcd for $C_{13}H_{22}NaO_4$ $[M+Na]^+$ 265.14103; found 265.1420. Chiral HPLC: AS-3R, 3 μm, 150×4.6 mm column, H_2O/CH_3CN with gradient elution 90–10%, 1.0 mL/min, t_R=7.03 min (91.77% yield of (5*Z*)-**31**), t_R=7.56 min (8.23% yield of (5*E*)-**31**). LC–MS (ESI): Kinetex XB-18, 2.7 μm, 150×4.6 mm column, H_2O/CH_3CN (8:2, phase A)/CH_3CN (phase B) 8:2, 1.0 mL/min, t_R=8.99 min (m/z=243.3 $[M+H]^+$ for (5*Z*)-**31**), t_R=9.25 min (m/z=243.3 $[M+H]^+$ for (5*E*)-**31**).

4.18. Isopropyl (*Z*)-7-[(1*R*,2*R*,3*R*,5*S*)-3,5-dihydroxy-2-methylcyclopentyl]hept-5-enoate (18)

DBU (2.43 mL, 16.1 mmol) was added dropwise to a stirred solution of acid **31** (0.78 g, 3.22 mmol) in anhydrous acetone (10 mL) at 0 °C under an argon atmosphere. The mixture was allowed to warm to room temperature, whereupon 2-iodopropane (1.62 mL, 16.1 mmol) was added dropwise. The resulting solution was stirred for 22 h resulting in disappearance of the starting acid **31** (TLC, CH_3CN/toluene 1:1). The reaction was quenched with ethyl acetate (100 mL). The resulting white solid was filtered off and washed with AcOEt (3×25 mL). The filtrate and washings were combined and acidified with 3% citric acid solution to pH 5–6. The resulting layers were separated and the aqueous phase was extracted with AcOEt (3×25 mL). The combined extracts were washed with saturated aqueous $NaHCO_3$ (100 mL), water (150 mL) and dried over anhydrous Na_2SO_4. Filtration and evaporation in vacuo furnished the crude product **18** (1.14 g), which was purified by silica gel flash chromatography with gradient elution 5–10% 2-propanol/CH_2Cl_2 to afford the ester **18** (0.85 g, 93% yield, 84.4% de) as a pale yellow oil. This sample was further purified by preparative HPLC on silica gel to give the isopropyl ester **18** (0.62 g, 68.1% yield) as a thick colourless oil. R_f=0.47 (CH_2Cl_2/*i*-PrOH 8:1). $[\alpha]_D^{20}$ +31.4 (*c* 1.0, CH_2Cl_2). FTIR (thin film) ν 3395, 2979, 2953, 2933, 2870, 1731, 1456, 1375, 1312, 1247, 1180, 1109, 1040, 969, 822, 723 cm^{-1}. ^1H NMR ($CDCl_3$, 600 MHz) δ 1.06 (d, *J*=7.0 Hz, 3H, $-CH_3$), 1.23 and 1.24 (two s, 6H, $-CH(CH_3)$), 1.31 (m, 1H, cyclopentane CH-1), 1.69 (m, 2H, α-chain CH_2-3), 1.76 (m, 1H, cyclopentane CH-2), 1.80 (dm, *J*=15.0 Hz, 1H, one of the cyclopentane CH_2-4 group), 2.02 (ddd, *J*=4.4, 6.5 and 14.5 Hz, 1H, one of the cyclopentane CH_2-4 group), 2.07–2.24 (m, 3H, α-chain CH_2-4 and one of the α-chain CH_2-7 group), 2.29 (m, 2H, α-chain CH_2-2), 2.87 (br s, 2H, two −OH), 2.94 (m, 1H, one of the α-chain CH_2-7), 3.80 (m, 1H, cyclopentane CH-3), 4.15 (m, 1H, cyclopentane CH-5), 5.00 (septet, *J*=6.3 Hz, 1H, $-CH(CH_3)_2$), 5.39 (m, 1H, α-chain CH-5), 5.47 (m, 1H, α-chain CH-6) ppm. ^{13}C NMR (150 MHz, $CDCl_3$) δ 18.3 (CH_3), 21.8 (2C, $-CH(CH_3)_2$), 24.9 (α-chain C-3), 26.4 (α-chain C-7), 26.6 (α-chain C-4), 34.1 (α-chain C-2), 42.3 (cyclopentane C-4), 47.0 (cyclopentane C-2), 52.8 (cyclopentane C-1), 67.6 ($-CH(CH_3)_2$), 74.3 (cyclopentane C-5), 80.4 (cyclopentane C-3), 129.4 (α-chain C-6), 129.5 (α-chain C-5), 173.4 (C=O) ppm. HRMS (ESI): calcd for $C_{16}H_{28}NaO_4$ $[M+Na]^+$ 307.18798; found 307.1890. Chiral HPLC: AS-3R, 3 μm, 150×4.6 mm column, H_2O/CH_3CN with gradient elution 80–10%, 1.0 mL/min, t_R=15.65 min (91.88% yield of (5*Z*)-(+)-**18**), t_R=17.09 min (8.12% yield of (5*E*)-**18**). LC–MS (ESI): AS-3R, 3 μm, 150×4.6 mm column, H_2O/CH_3CN with gradient elution 80–10%, 1.0 mL/min, t_R=15.39 min (*m*/*z*=285.2 $[M+H]^+$ for (5*Z*)-(+)-**18**), t_R=16.95 min (*m*/*z*=285.2 $[M+H]^+$ for (5*E*)-**18**).

Acknowledgements

Financial support was provided by the European Union from the European Regional Development Fund (ERDF) under the Innovative Economy Operational Programme (UDA-POIG.01.03.01-14-068/08-00).

References and notes

1. Quigley, A. H.; Broman, A. T. *Br. J. Ophthalmol.* **2006**, *90*, 262–267.
2. (a) Hoyng, P. F. J.; Kitazawa, Y. *Surv. Ophthalmol.* **2002**, *47*, S116–S124; (b) McKinnon, S. J.; Goldberg, L. D.; Peeples, P.; Walt, J. G.; Bramley, T. J. *Am. J. Manage. Care* **2008**, *14*, S20–S27; (c) Soltau, J. B.; Zimmerman, T. J. *Surv. Ophthalmol.* **2002**, *47*, S2–S5; (d) Stamper, R. L.; Wigginton, S. A.; Higginbotham, E. J. *Surv. Ophthalmol.* **2002**, *47*, 63–73; (e) Sugrue, M. F. *J. Med. Chem.* **1997**, *40*, 2793–2809; (f) Costagliola, C.; dell'Omo, R.; Romano, M. R.; Rinaldi, M.; Zeppa, L.; Parmeggiani, F. *Expert. Opin. Pharmacother.* **2009**, *10*, 2663–2677; (g) Lee, D. A.; Higginbotham, E. J. *Am. J. Health Syst. Pharm.* **2005**, *62*, 691–699; (h) Collaborative Normal-Tension Glaucoma Study Group *Am. J. Ophthalmol.* **1998**, *126*, 487–497.
3. (a) Ishida, N.; Odani-Kawabata, N.; Shimazaki, A.; Hara, H. *Cardiovasc. Drug Rev.* **2006**, *24*, 1–10; (b) Bean, G. W.; Camras, C. B. *Surv. Ophthalmol.* **2008**, *53*, S69–S84; (c) Eisenberg, D. L.; Toris, C. B.; Camras, C. B. *Surv. Ophthalmol.* **2002**, *47*, S105–S115; (d) Alm, A. *Prog. Retin. Eye Res.* **1998**, *17*, 291–312; (e) Toris, C. B.; Gabelt, B. T.; Kaufman, P. L. *Surv. Ophthalmol.* **2008**, *53*, S107–S120; (f) Stjernschantz, J. W. *Invest. Ophthalmol. Vis. Sci.* **2001**, *42*, 1134–1145; (g) Brooks, T. C.; Burlingame, M.; Burk, M.; Tortorice, K.; Dong, D.; Glassman, P. A.; Lynch, J. A.; Good, C. B.; Rickman, H. S.; Claborn, M.; Appleman, D.; Jones, W.; Shaverd, L. *Formulary* **2009**, *44*, 322–328; (h) Waugh, J.; Jarvis, B. *Drugs Aging* **2002**, *19*, 465–471; (i) Burk, R. M.; Woodward, D. F. *Drug Dev. Res.* **2007**, *68*, 147–155; (j) Sharif, N. A.; Klimko, P. *Expert Rev. Ophthalmol.* **2009**, *4*, 477–489; (k) Easthope, S. E.; Perry, C. M. *Drugs Aging* **2002**, *19*, 231–248; (l) Woodward, D. F.; Phelps, R. L.; Krauss, A. H.-P.; Weber, A.; Short, B.; Chen, J.; Liang, Y.; Wheeler, L. A. *Cardiovasc. Drug Rev.* **2004**, *22*, 103–120; (m) Sit, A. J.; Asrani, S. *Surv. Ophthalmol.* **2008**, *53*, S45–S55; (n) Cantor, L. B. *Exp. Opin. Invest. Drugs* **2001**, *10*, 721–731; (o) Perry, C. M.; McGavin, J. K.; Culy, C. R.; Ibbotson, T. *Drugs Aging* **2003**, *20*, 597–630.
4. (a) Bito, L. Z.; Draga, A.; Blanco, J.; Camras, C. B. *Invest. Ophthalmol. Vis. Sci.* **1983**, *24*, 312–319; (b) Giufreé, G. *Graefe's Arch. Clin. Exp. Ophthalmol.* **1985**, *222*, 139–141; (c) Camras, C. B.; Bito, L. Z.; Eakins, K. E. *Invest. Ophthalmol. Vis. Sci.* **1977**, *16*, 1125–1134; (d) Bito, L. Z. *Surv. Ophthalmol.* **1997**, *41*, S1–S14.
5. For a review on Corey synthesis of $PGF_{2\alpha}$ see: (a) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675–5677; (b) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, U.; Weinshenker, N. M. *J. Am. Chem. Soc.* **1970**, *92*, 397–398; (c) Corey, E. J.; Noyori, R.; Schaaf, T. K. *J. Am. Chem. Soc.* **1970**, *92*, 2586–2587; (d) Corey, E. J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 455–465; (e) Corey, E. J.; Cheng, X.-M. *The Logic of Chemical Synthesis*; Wiley: New York, NY, 1989, pp 255–256.
6. Resul, B.; Stjernschantz, J.; No, K.; Liljebris, C.; Selén, G.; Astin, M.; Karlsson, M.; Bito, L. Z. *J. Med. Chem.* **1993**, *36*, 243–248.
7. Selliah, R.; Dantanarayana, A.; Haggard, K.; Egan, J.; Do, E. U.; May, J. A. *J. Labelled Cpd. Radiopharm.* **2001**, *44*, 173–183.
8. Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533–1564.
9. Liljebris, C.; Selén, G.; Resul, B.; Stjernschantz, J.; Hacksell, U. *J. Med. Chem.* **1995**, *38*, 289–304.
10. Klimko, P.; Hellberg, M.; McLaughlin, M.; Sharif, N.; Severns, B.; Williams, G.; Haggard, K.; Liao, J. *Bioorg. Med. Chem.* **2004**, *12*, 3451–3469.
11. Matsumura, Y.; Mori, N.; Nakano, T.; Sasakura, H.; Matsugi, T.; Hara, H.; Morizawa, Y. *Tetrahedron Lett.* **2004**, *45*, 1527–1529.
12. Bowler, J.; Crossley, N. S. GB Patent 1,350,971, 1974.
13. Gutman, A.; Nisnevich, G.; Etinger, M.; Zaltzman, I.; Yudovich, L.; Pertsikov, B.; Tishin, B. U.S. Patent 7,166,730, 2007.
14. Henegar, K. E. US Patent Application 2003/0187071 A1, 2003.
15. Hwang, S.-W.; Adiyaman, M.; Khanapure, S. P.; Rokach, J. *Tetrahedron Lett.* **1996**, *37*, 779–782.
16. Kim, S.; Bellone, S.; Maxey, K. M.; Powell, W. S.; Lee, G.-J.; Rokach, J. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1873–1876.
17. (a) Corey, E. J.; Albonico, S. M.; Koelliker, U.; Schaaf, T. K.; Varma, R. K. *J. Am. Chem. Soc.* **1971**, *93*, 1491–1493; (b) Corey, E. J.; Becker, K. B.; Varma, R. K. *J. Am. Chem. Soc.* **1972**, *94*, 8616–8618; (c) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926; (d) Aswathanarayanappa, C.; Bheemappa, E.; Bodke, Y. D. *Org. Process Res. Dev.* **2011**, *15*, 1085–1087; (e) Zanoni, G.; D'Alfonso, A.; Porta, A.; Feliciani, L.; Nolan, S. P.; Vidari, G. *Tetrahedron* **2010**, *66*, 7472–7478; (f) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209–1216; (g) Obadalová, I.; Pilarčík, T.; Slavíková, M.; Hájíček, J. *Chirality* **2005**, *17*, S109–S113; (h) Hutton, J.; Senior, M.; Wright, N. C. A. *Synth. Commun.* **1979**, *9*, 799–808; (i) Hutton, J. *Synth. Commun.* **1979**, *6*, 483–486; (j) Node, M.; Nishide, K.; Shigeta, Y.; Shiraki, H.; Obata, K. *J. Am. Chem. Soc.* **2000**, *122*, 1927–1936; (k) Noyori, R.; Tomino, I.; Yamada, M.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6717–6725.
18. Achmatowicz, B.; Baranowska, E.; Daniewski, A. R.; Pankowski, J.; Wicha, J. *Tetrahedron* **1988**, *44*, 4989–4998.
19. Boulton, L. T.; Brick, D.; Fox, M. E.; Jackson, M.; Lennon, I. C.; McCague, R.; Parkin, N.; Rhodes, D.; Ruecroft, G. *Org. Process Res. Dev.* **2002**, *6*, 138–145.
20. Das, S.; Chandrasekhar, S.; Yadav, J. S.; Grée, R. *Chem. Rev.* **2007**, *107*, 3286–3337.
21. (a) Martynow, J. G.; Jóźwik, J.; Szelejewski, W.; Achmatowicz, O.; Kutner, A.; Wiśniewski, K.; Winiarski, J.; Zegrocka-Stendel, O.; Gołębiewski, P. *Eur. J. Org. Chem.* **2007**, 689–703; (b) Martynow, J. G.; Szyc, J.; Szelejewski, W.; Achmatowicz, O.; Kutner, A.; Wiśniewski, K.; Winiarski, J.; Zegrocka-Stendel, O.; Gołębiewski, P. U.S. Patent 7,897,793 B2, March 1, 2011.
22. (a) Dubiner, H. B.; Sircy, M. D.; Landry, T.; Bergamini, M. V. W.; Silver, L. H.; Turner, F. D.; Robertson, S.; Andrew, R. M.; Weiner, A.; Przydryga, J. *Clin. Ther.* **2004**, *26*, 84–91; (b) Van der Valk, R.; Webers, C. A. B.; Schouten, J. S. A. G.; Zeegers, M. P.; Hendrikse, F.; Prins, M. H. *Ophthalmology* **2005**, *112*, 1177–1185.
23. (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833–4836; (b) Kocieński, P. J.; Lythgoe, B.; Ruston, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 829–834; (c) Kocieński, P. J.; Lythgoe, B.; Waterhouse, I. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1045–1050; (d) Kocieński, P. J. *Phosphorus Sulphur* **1985**, *24*, 97–127; (e) Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. *Synlett* **1998**, 26–28.
24. Blakemore, P. R.; Ho, D. K. H.; Nap, W. M. *Org. Biomol. Chem.* **2005**, *3*, 1365–1368.
25. Baer, E.; Fischer, H. O. L. *J. Am. Chem. Soc.* **1948**, *70*, 609–610.
26. Nelson, W. L.; Wennerstrom, J. E.; Sankar, S. R. *J. Org. Chem.* **1977**, *42*, 1006–1012.
27. Mitsunobu, O. *Synthesis* **1981**, 1–28.

28. Baldwin, J. J.; Raab, A. W.; Mensler, K.; Arison, B. H.; McClure, D. E. *J. Org. Chem.* **1978**, *43*, 4876–4878.
29. Martinelli, M. J.; Nayyar, N. K.; Moher, E. D.; Dhokte, U. P.; Pawlak, J. M.; Vaidyanathan, R. *Org. Lett.* **1999**, *1*, 447–450.
30. (a) Kornblum, N.; Jones, W. J.; Anderson, G. J. *J. Am. Chem. Soc.* **1959**, *81*, 4113–4114; (b) Kornblum, N.; Powers, J. W.; Anderson, G. J.; Jones, W. J.; Larson, H. O.; Levand, O.; Weaver, W. M. *J. Am. Chem. Soc.* **1957**, *79*, 6562.
31. Parikh, J. R.; Doering, W. E. *J. Am. Chem. Soc.* **1967**, *89*, 5505–5507.
32. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
33. (a) Trost, B. M. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 107–124; (b) Simpkins, N. S. *Tetrahedron* **1990**, *46*, 6951–6984; (c) Baldwin, I. R.; Whitby, R. J. *Chem. Commun.* **2003**, 2786–2787.
34. Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *17*, 3477–3478.
35. (a) Markó, I. E.; Murphy, F.; Dolan, S. *Tetrahedron Lett.* **1996**, *37*, 2089–2092; (b) Hart, D. J.; Wu, W.-L. *Tetrahedron Lett.* **1996**, *37*, 5283–5286.