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The Manufacture of a Homochiral 4-Silyloxycyclopentenone Intermediate for the Synthesis of Prostaglandin Analogues

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Supporting Information

ABSTRACT: A process is described for the synthesis of kilogram quantities of homochiral 4-silyloxycyclopentenone (*R*)-**1**, a key intermediate useful for the synthesis of a plurality of prostaglandin analogue drugs. Cyclopentenone (*R*)-**1** was synthesized in 14 isolated steps from furfural. Key steps in the synthesis include a Wittig reaction, Piancatelli rearrangement, and an enzymatic resolution featuring in situ recycling of the undesired enantiomer furnishing the desired homochiral alcohol in ≥99.5% ee. As a retort to the unsatisfactory coformation of about 8% at best of the *trans*-olefin in the Wittig reaction, a change to the order of several steps and the identification of a recrystallisable, amine salt derivative, **2**, allowed the unwanted isomer to be controlled to as low as 0.2%.

INTRODUCTION

Prostaglandins (PGs) are naturally occurring, bioactive, polyunsaturated, fatty acid derivatives composed of 20 carbon atoms. Despite being highly potent and playing important roles in animal and human physiology, therapeutic applications of prostaglandins and their synthetic analogues as active pharmaceutical ingredients (APIs) have been surprisingly limited, in spite of extensive research efforts in both academia and industry beginning in the 1960s.[1] In contrast to typical small-molecule drugs, prostaglandins and their synthetic analogues are stereochemically complex, their syntheses are long, their intermediates are typically oils (rather than crystallisable solids), and they can be chemically unstable. Notwithstanding this, there are a variety of synthetic prostaglandin analogues on the market available for the treatment of a range of conditions including peptic ulcer, hypertension, and fertility control in humans, and veterinary uses.[1] $PGF_{2\alpha}$ analogues, such as latanoprost[2] (Xalatan), bimatoprost[3a] (Lumigan), and travoprost[4] (Travatan) have achieved success as first-line topical treatments of glaucoma. More recently tafluprost[5] (Zioptan) was also introduced into the glaucoma market, whilst bimatoprost (Latisse) was additionally approved for cosmetic use.[3b] Lubiprostone,[6] a bicyclic PGE_1 derivative, is the active drug substance in Amitiza, a gastrointestinal drug used for the treatment of chronic idiopathic constipation in adults.

It was envisioned that all of these APIs could be accessed from the single, common intermediate, 4-silyloxycyclopentenone (*R*)-**1**[7] (Figure 1). As part of the original platform technology design, the isopropyl ester functionality of this intermediate would act not only as part of the final molecular structure of APIs, such as travoprost and tafluprost, but also as a carboxyl protecting group that could be deprotected at a late stage in the synthesis of APIs, such as bimatoprost and lubiprostone. The advantages of the use of a single feedstock for a plurality of products is obvious and includes significant time and cost savings during the research and development stage as well as a lowering of manufacturing costs.[8]

Although the production volumes of these prostaglandin analogues would be small due to their extreme potency (a single dose of each of these drugs is in the order of micrograms), the upstream steps used to make the key diverging (*R*)-**1** intermediate needed to be robust. Because of working on kilograms to tens of kilograms, it was preferable to avoid particularly low or high temperatures, the use of air- and moisture-sensitive reagents, or specialised equipment. Further, the common intermediate had to be of high chemical and stereochemical purity as to be able to provide the downstream APIs with high stereochemical purity to meet the demands of regulatory authorities. This was particularly important given that the single chiral centre of 4-silyloxycyclopentenone (*R*)-**1** was responsible, through chiral induction, for the stereochemistry of up to three chiral centres formed in the subsequent synthetic steps.

Of the three main approaches (Corey's[9] lactone approach, the two-component approach,[10] and the three-component[11] approach) used for prostaglandin and analogue synthesis,[12] we favored the two-component approach, as this strategy would provide the degree of divergence that we required. The two-component approach comprises installation of the ω-side chain via a 1,4-addition of a vinyl cuprate to a cyclopentenone system already possessing the α-side chain (Figure 1). In this contribution we report our first-generation process for this

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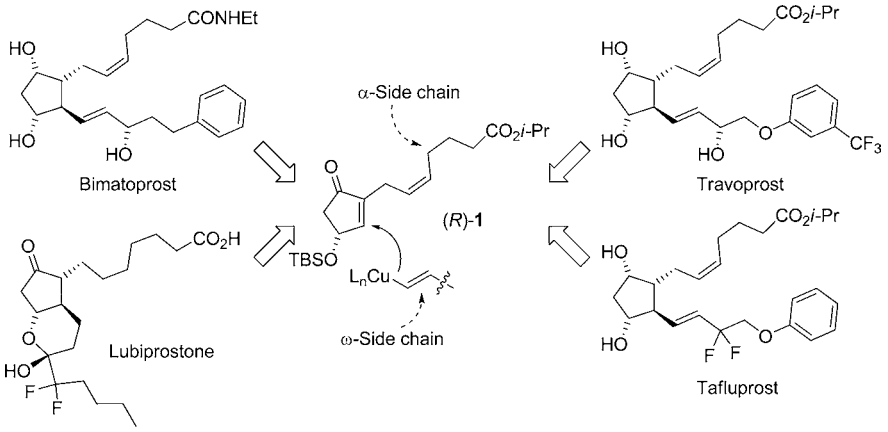
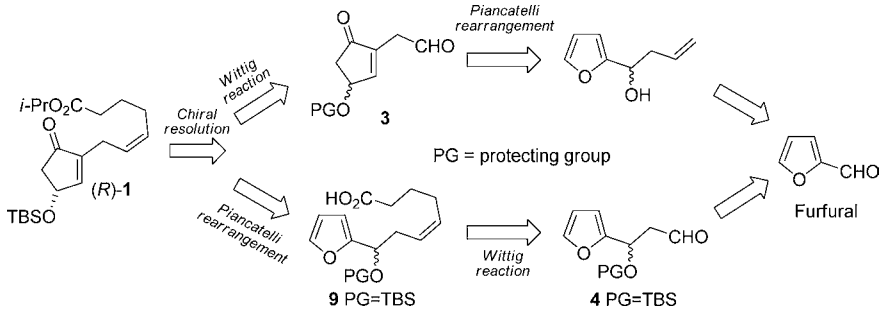


Figure 1. Use of cyclopentenone (*R*)-**1** as a common intermediate in prostaglandin analogue synthesis.

Scheme 1. Retrosynthetic analysis of cyclopentenone (*R*)-1



key intermediate, with a focus on the Wittig reaction and how the required levels of geometric and stereochemical purity were achieved.

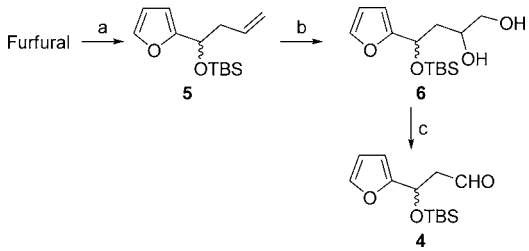
RESULTS AND DISCUSSION

Attempted Synthesis of Cyclopentenone (*R*)-1, via Aldehyde 3. Although a significant number of syntheses of 4-hydroxy-2-cyclopenten-1-ones with α-side chains useful for prostaglandin synthesis have been published,[7,13] the first approach to the requisite cyclopentenone intermediate (*R*)-**1** that we investigated was based on our retrosynthetic analysis shown in Scheme 1 (top pathway). This approach would rely upon the Piancatelli rearrangement[14] of 2-furylcarbinols to 2-substituted 4-hydroxy-2-cyclopenten-1-ones, a *cis*-selective Wittig reaction using the potentially labile aldehyde **3**,[15] and the enzymatic resolution of 2-substituted 4-hydroxy-2-cyclopenten-1-ones.[16]

Despite examining different solvents, temperatures, and concentrations and testing normal and reverse addition modes of the ylide and aldehyde, we were unable to convert aldehyde **3** into the desired olefin using the Wittig reaction. Multiple, unidentifiable products were formed due to the instability of aldehyde **3** under basic conditions.[17]

Synthesis of Aldehyde 4. We envisioned that this problem could be circumvented by exploiting the base-stable nature of the furan ring of aldehyde **4**, using it as a latent form of the sensitive 4-silyloxycyclopent-2-enone ring system. This would delay the Piancatelli rearrangement until after the α-side chain had been installed by Wittig reaction (Scheme 1, bottom pathway). To this end silyl ether **5** was prepared from furfural in one pot by reaction with in situ formed allyl zinc bromide followed by trapping of the resultant zinc alkoxide with TBSCl

Scheme 2. Synthesis of aldehyde 4[a]



[a]Reagents and conditions: (a) (i) Allylbromide, Zn, THF, 60−68 °C; (ii) TBSCl, imidazole, 1:1 DMF/THF, r.t., 70−77%; (b) NMO, $K_2OsO_2(OH)_4$, $(DHQ)_2PHAL$, acetone, H_2O, 87%; (c) $NaIO_4$, acetone, H_2O, r.t., 92−95%.

(Scheme 2). Dihydroxylation of olefin **5** using NMO in the presence of catalytic $K_2OsO_2(OH)_4$ and $(DHQ)_2PHAL$,[18] affording diol **6**, was followed by oxidative cleavage with $NaIO_4$ in aqueous acetone at ambient temperature to give desired aldehyde **4** in about 80% yield over two steps. Preliminary tests suggest that more expedient routes to aldehyde **4** exist.[19]

On a 3-kg scale, furfural was converted to silyl ether **5** in one reactor in 70−77% yield with 93−96% GC purity after fractional distillation. Nineteen kilograms of olefin **5** was dihydroxylated in a single batch, providing diol **6** (20.1 kg) in 87% yield that was then used without purification. Oxidative cleavage of diol **6** proceeded smoothly on a 0.2−0.6 kg scale, supplying oily aldehyde **4** in 92−95% yield (91−95% GC purity), following rapid flushing through a plug of silica gel. Aldehyde **4** was dissolved in THF under an inert atmosphere and used directly to avoid oxidation.[20] A 20.1-kg-scale run

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provided about 18 kg of crude aldehyde **4** with 93% purity by GC.

Wittig Reaction of Aldehyde 4. Owing to the failure of the Wittig reaction of aldehyde **4** and putative ester ylide **7** (Figure 2; instead yielding 3-(furan-2-yl)prop-2-enal and

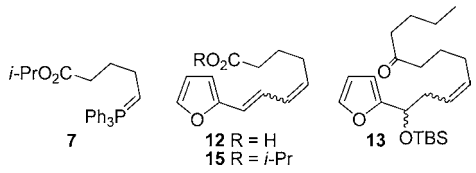
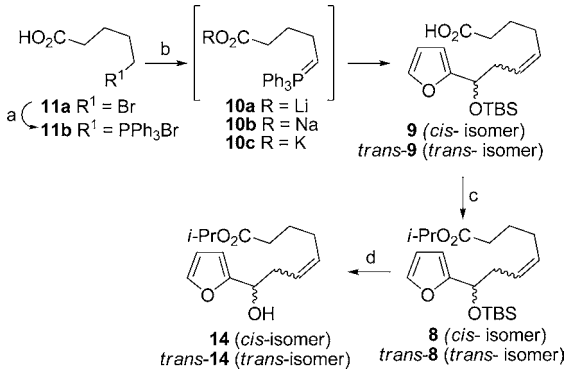


Figure 2. Miscellaneous compounds and Wittig reaction side products.

cyclopentenone) a two-step approach for the synthesis of ester **8** involving the Wittig reaction followed by esterification of the resulting carboxylic acid **9** was required (Scheme 3). A study of the Wittig reaction was initiated with a base screen.

Scheme 3. Synthesis of ester 8[a]



[a]Reagents and conditions: (a) PPh_3, PhMe, 87%; (b) (i) LiHMDS, NaH, NaHMDS, *t*-BuOK, or KHMDS/THF, THF, 0−10 °C; (ii) **4**, THF, <0 °C; (c) (i) *i*-PrI, K_2CO_3, acetone, reflux; (ii) chromatography; (d) TBAF, THF, 35−40 °C.

Ylides **10a**−**10c** were generated in situ from the phosphonium salt **11b** (prepared from 5-bromopentanoic acid (**11a**)) in THF using lithium, sodium, and potassium bases, respectively, followed by the addition of a THF solution of aldehyde **4**. In a Wittig reaction of a hemiacetal and ylide **10c** (synthesized from **11b** and *t*-BuOK) reported[21] for the synthesis of an advanced precursor of travoprost, good *cis*-/*trans*-selectivity was observed with only 3% of the corresponding *trans*-isomer being produced at 0 °C, and 5% at r.t. When we reacted aldehyde **4** and ylide **10c**, however, the main product was a geometric mixture of dienes **12** (Figure 2) accompanied by only a small amount of the desired olefin **9**. Surprisingly, treatment of ylide **10a**, generated using *n*-BuLi in THF at 0 °C, with aldehyde **4** provided ketone **13** (Figure 2) instead of the desired olefin **9**.[22] Although ylides generated using NaH in DMSO or KHMDS in THF did not provide any olefin **9**, the use of LiHMDS in THF led to the desired *cis*-alkene **9**, albeit contaminated with a relatively high 20 mol% (w.r.t. *cis*-isomer) of the undesired *trans*-isomer *trans*-**9**. Consistent with the "Lithium-Salt Effect"[23] the undesired *trans*-isomer was reduced to 13 mol% upon the use of sodium ylide **10b**, prepared with NaHMDS, in THF at −15 °C.

This isomer proved extremely troublesome; it could not be purged by any means applicable to scale up due to the complete absence of crystalline intermediates in our original process. Although the *trans*-isomer eluted slightly faster than *cis*-isomer, **9**, column chromatography did not present a viable method for enrichment of the *cis*-isomer.[24]

With an immediate need to demonstrate the platform technology depicted in Figure 1 and to allow development of the GMP steps (i.e., (*R*)-**1** through to the APIs) to begin, the process was moved to scale-up, albeit with the intention to return for a more thorough investigation of the Wittig reaction to reduce the levels of *trans*-isomer (see below). The first lot of ester **8** (10.1 kg; 14 batches of Wittig reaction and 3 batches of esterification) was prepared by a contractor. The Wittig reaction was conducted at −25 to −30 °C in THF using NaHMDS as the base, followed by esterification (*i*-PrI, K_2CO_3 at 55 °C in acetone[25]) and column chromatography, providing purified product **8** (91−95% GC purity). Desilylation (TBAF in THF) of a sample of silyl ether **8** gave alcohol **14** that upon HPLC analysis revealed that this lot of Wittig reaction product contained 12.2 mol% (relative to the mixture of *cis*- and *trans*-isomers) of the undesired *trans*-isomer.[26]

Investigations were resumed with a cosolvent study of the Wittig reaction step in THF at −15 °C, generating ylide **10b** using NaHMDS as the base (Table 1, entry 1).[27] The best improvement in *cis*-/*trans*-selectivity was observed when phosphoramide cosolvents HMPA and tripyrrolidinophosphoric acid triamide (TPPA) were used (entries 4−9).[28] Due to its toxicity, HMPA was replaced with the pyrrolidine analogue, TPPA.[30] When the amount of TPPA in THF was increased from 5 to 50% (entries 5 to 9) the *trans*-isomer steadily decreased from 10.2 to 7.7 mol%, albeit with a large drop in both the yield (from 75% down to 14%) and purity of olefin **8** along with a significant increase of diene side product **15**. The use of other polar additives in THF (entries 10−15) provided no overall improvement and were inferior to the two phosphoramide solvents tested. Using 10% TPPA in THF and NaHMDS, a study of the influence of temperature (−20 to −78 °C) on the yield and *cis*-/*trans*-selectivity (entries 16−19) suggested that the best temperature was around −20 to −35 °C.

Demonstration of these conditions (0.4 kg scale of **4** based on entry 17) in our kilo laboratory, followed by conversion of analytical test samples to ester **14** (entries 20 and 21), showed that about 8.0−8.3 mol% *trans*-isomer had formed (70−74% yield of **8** over two steps from **4**), consistent with laboratory-scale runs.[29]

As a result of this study, the original conditions (LiHMDS in THF) were improved such that the level of undesired *trans*-isomer could be reduced from ∼20 mol% down to ∼8 mol%, whilst maintaining the purity of the product, without necessitating the use of dedicated cryogenic equipment.[26] Although ostensibly small and falling short of our goal of ≤3%, the improvement in selectivity had a significant impact on the downstream API syntheses through reduced burden placed on the API and API precursor purification operations. As will be discussed below, this improvement was later operated together with a process modification that ultimately allowed levels of less than 1% of the *trans*-isomer to be achieved.

Deprotection of Silyl Ether 8 and Piancatelli Rearrangement. Silyl ether **8** was treated with 1 equiv of TBAF in THF at 35−40 °C to furnish alcohol **14** (Scheme 3) in a quantitative yield on a 6.5 kg scale (77% GC purity). This material was used as is in the next step without further purification.

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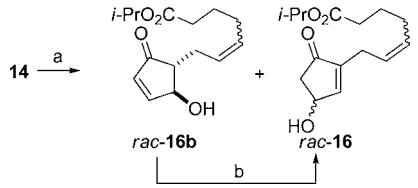
Table 1. Influence of solvent and temperature on the Wittig reaction

entry[a]	solvent	temp (°C)	**8** purity (area%)	**15** purity (area%)	yield (%) **8**	**14** *cis*-/*trans*-ratio
1	THF	−15	88	1.3	82	87.0/13.0
2[b]	THF	−15	88	4.6	79	87.5/12.5
3	50% PhMe in THF	−15	87	0.8	69	83.3/16.7
4	10% HMPA in THF	−15	81	5.4	43	90.9/9.1
5	5% TPPA in THF	−15	92	3.5	75	89.8/10.2
6	10% TPPA in THF	−15	88	5.7	71	91.1/8.9
7	20% TPPA in THF	−15	85	5.8	72	91.2/8.8
8	30% TPPA in THF	−15	64	23	44	92.2/7.8
9	50% TPPA in THF	−15	25	51	14	92.3/7.7
10	10% DMPU in THF	−15	93	3.4	49	87.9/12.1
11	10% NMP in THF	−15	91	4.1	58	89.5/11.5
12	10% DMAC in THF	−15	88	5.8	70	89.6/11.4
13	10% DME in THF	−15	92	5.5	57	86.7/13.3
14	10% TMEDA in THF	−15	89	4.0	68	86.1/13.9
15	10% DMSO in THF	−15	61	23	43	91.3/8.7
16	10% TPPA in THF	−20	94.3	3.0	79	91.9/8.1
17	10% TPPA in THF	−35	96.1	1.7	81	91.8/8.2
18	10% TPPA in THF	−55	88	5.2	61	91.4/8.6
19	10% TPPA in THF	−78	96	0.4	11	not analysed
20	10% TPPA in THF	−36	89	5.9	74	91.7/8.3
21	10% TPPA in THF	−36	92	5.6	70	92.0/8.0

[a]Whereas the yield and purity (**8** and **15**) were determined following esterification of **9**, the *cis*-/*trans*-ratio (Wittig reaction selectivity) was measured by analysis of **14**. [b]Double the normal volume of THF.

A key part of the overall strategy for the synthesis of cyclopentenone (*R*)-**1** relied upon the Piancatelli rearrangement,[14] which has been demonstrated in prostaglandin analogue synthesis (enisoprost) by Dygos et al.[31] When Piancatelli's $ZnCl_2$ modification[32] in aqueous dioxane[31,33a,c] was applied to crude 2-furylcarbinol **14**, a ∼1:1 to 2:1 mixture of cyclopentenone *rac*-**16** and its undesired isomer *rac*-**16b** was obtained within 6−12 h (Scheme 4). Heating beyond reaction completion encouraged further, secondary rearrangement of *rac*-**16b** to *rac*-**16**; however, after 2.75 days about 10% *rac*-**16b** still remained. With time and yield considerations in mind, instead of converting 2-furylcarbinol **14** completely through to cyclopentenone *rac*-**16**, it was preferred that upon complete consumption of furylcarbinol **14** the Piancatelli rearrangement was terminated, and the mixture of isomers (*rac*-**16b** and *rac*-**16**) was then processed through the second rearrangement step. Unlike that reported[31] for the methyl ester analogue, methyl 7-(2-hydroxy-5-oxo-3-cyclopenten-1-yl)-(4*Z*)-heptenoate, that underwent in situ hydrolysis back to its carboxylic acid derivative (as the major product therefore requiring a subsequent re-esterification step), the isopropyl ester functionality of **16** was left intact in the Piancatelli reaction.

Scheme 4. Piancatelli rearrangement of 14[a]



[a]Reagents and conditions: (a) $ZnCl_2$, hydroquinone (cat.), dioxane, H_2O, reflux; (b) chloral, Et_3N, PhMe, r.t., 55% over two steps

Following aqueous work-up, a PhMe solution of the crude Piancatelli rearrangement products *rac*-**16** and *rac*-**16b** was transformed in a second rearrangement reaction under known[31] conditions (catalytic chloral in the presence of Et_3N) into 4-hydroxycyclopentenone *rac*-**16**, devoid of the thermodynamically less stable isomer *rac*-**16b**, in about 55% yield calculated over the two rearrangement steps from 2-furylcarbinol **14**. Attempts to improve the disappointing yield of the furylcarbinol **14** to cyclopentenone *rac*-**16** conversion, which we attribute the first rearrangement step, will be addressed in future process development.[34]

In a scale-up run the Piancatelli rearrangement was complete within 6 h using 2-furylcarbinol **14** (manufactured from 15.8 kg of purified **8**), providing a 1.0:1.1 mixture of cyclopentenone isomers *rac*-**16** and *rac*-**16b**. This mixture converted smoothly in the second rearrangement step into racemic 4-hydroxycyclopentenone *rac*-**16** with 98−100% GC purity following purification.

Enzymatic Resolution of 4-Hydroxcyclopentenone *rac*-16. A critical part of the overall strategy[35] for the synthesis of homochiral cyclopentenone (*R*)-**1** relied upon the enzymatic resolution of the racemic alcohol precursor *rac*-**16**. Given the only modest efficiency already endured in the Piancatelli rearrangement, however, it was essential that both enantiomers of the racemate could be fully utilized without unnecessary wastage. Furthermore, given that the chiral centre at C4 of the cyclopentenone was crucial for inducing the relative and absolute configuration of other chiral centres in the prostaglandin analogues, it was critical that we were able to resolve the racemic 4-hydroxy-2-alkyl-cyclopentenone *rac*-**16** to a high degree of stereochemical purity.

To address these requirements, a 4-hydroxycyclopentenone enzymatic resolution protocol reported by Babiak and Wong,[16] and subsequently modified by Spur et al.,[33a] was chosen (this has not been reported previously for cyclopentenone *rac*-**16**). The original protocol involved stereoselective acetylation of the (*R*)-enantiomer of 4-hydroxy-2-alkyl-cyclopentenone substrates with neat vinyl acetate in the presence of porcine pancreatic lipase (PPL),[36] chromatographic separation of ester/alcohol enantiomorphic mixtures, and a Mitsunobu inversion. Spur et al.'s subsequent modification, as demonstrated on methyl 7-(3-hydroxy-5-oxo-1-cyclopenten-1-yl)-heptanoate, bypassed chromatographic separation of the first resolved pair (i.e., (*S*)-alcohol and (*R*)-acetate) by instead directly employing in situ Mitsunobu inversion of the (*S*)-alcohol of the (*R*)-acetate, providing the product in 96% ee in 76% yield following deacylation with guanidine.

Upon applying[37] Babiak and Wong's protocol[16] to the resolution of racemic alcohol *rac*-**16** (Scheme 5) it was found

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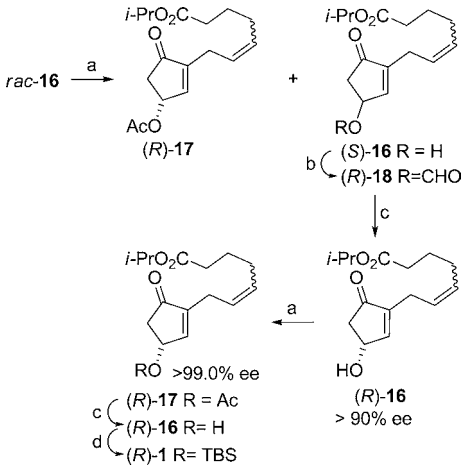
Scheme 5. Resolution of *rac*-16[a]



[a]Reagents and conditions: (a) Lipase PS (IM or SD), vinyl acetate, neat, or *n*-heptane or MTBE, 30−50 °C; (b) HCO_2H, Ph_3P, DEAD, THF, 0 °C−r.t.; (c) 0.5 M guanidine/MeOH, MeOH, 0−10 °C; (d) TBSCl, imidazole, DMF, r.t.

that the resolution was slow, and we therefore examined other lipases. Immobilized and free-form lipases derived from *Burkholderia cepacia*, namely Lipase PS "Amano" SD and Lipase PS "Amano" IM, provided much more rapid conversion than when using PPL, however. Use of either neat vinyl acetate or a mixture of vinyl acetate and MTBE as the solvent was most preferred. In contrast to that reported[16,33a] for analogues of racemic alcohol *rac*-**16** that required 4−9 days for the enzymatic resolution at r.t. to reach the desired end-point, alcohol *rac*-**16** was resolved in a matter of several hours providing a high ee of the (*R*)-acetate (*R*)-**17**.[38]

The resolution was scaled-up to 4.4 kg of racemic alcohol *rac*-**16** (>98% GC purity) using neat vinyl acetate at 38−42 °C and the free enzyme, Lipase PS "Amano" SD.[39] The reaction was terminated at 33 h when 2.7% of (*R*)-alcohol (*R*)-**16** remained. Once filtration and concentration were complete, a mixture of (*R*)-acetate (*R*)-**17** with 96.7% ee and unreacted (*S*)-alcohol (*S*)-**16** with 89.6% ee were obtained. As per Spur et al.'s adapted protocol,[33a] a Mitsunobu inversion of the (*R*)-acetate (*R*)-**17**/(*S*)-alcohol (*S*)-**16** mixture with formic acid was conducted directly, without prior chromatographic separation, and the resulting 1:1 mixture of the (*R*)-acetate and (*R*)-formate (**18**) was purified and then treated with guanidine in MeOH at 0−10 °C to provide 94% GC pure (*R*)-alcohol (*R*)-**16** with 91% ee in 92% yield (based on racemic alcohol *rac*-**16**). An enantiopurity upgrade was then accomplished by enzymatic reprocessing, but this time the resolution step was followed by column chromatography to remove the undesired (*S*)-alcohol, providing 4.34 kg of 98% GC pure (*R*)-acetate (*R*)-**17** with 99.9% ee.[40] Finally, guanidinolysis supplied 3.38 kg (87% yield) of 94% GC pure (*R*)-alcohol (*R*)-**16** in which its (*S*)-enantiomer was not detected. Thus, over the double enzymatic resolution, Mitsunobu inversion and guanidinolysis steps a 72% yield of high stereochemical purity (*R*)-alcohol (*R*)-**16** was obtained calculated on the basis of both enantiomorphs of the racemic alcohol input.

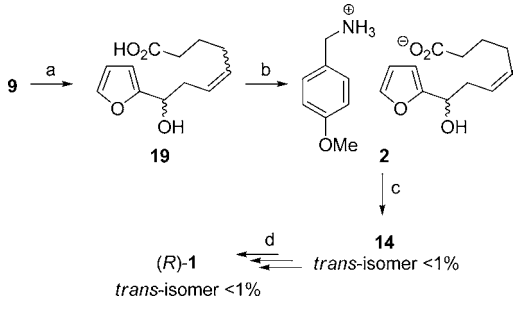
Finally, protection[41] of about 3.4 kg of (*R*)-**16** with TBSCl in DMF in the presence of imidazole at 20−25 °C furnished key intermediate (*R*)-**1** with 99.5% ee, 98% GC purity in 82% yield following column chromatography (Scheme 5). HPLC analysis of the silyl ether confirmed that it was composed of a 91:9 ratio of the *cis*- and *trans*-isomers of (*R*)-**1**.[42] This was consistent with the mixture of geometric isomers observed in the Wittig reaction feedstock that this material had originated from (see above), showing that no enrichment of either isomer occurred throughout the process. As will be described below, a recent batch of (*R*)-**1** comprising a 99.4:0.6 ratio of *cis*-/*trans*-isomers was prepared using an improved process.

Improved Process for (*R*)-1 with Reduced *trans*-Isomer. As described above, the synthesis of diverging intermediate (*R*)-**1** proceeded on multikilogram scales; however, significant improvements remained to be made to the original process to improve overall efficiency. In addition to resorting to a series of chromatographic purifications owing to the nonsolid nature of all intermediates, the *cis*-/*trans*-selectivity of the Wittig reaction was unsatisfactory. Apart from at least 8% w/w of material (i.e., the *trans*-isomer) processed through this route being useless, a costly burden was placed on the downstream purification operations to remove the unwanted isomers, which possessed very similar chromatographic behaviours, from the APIs themselves. Having now supplied sufficient homochiral (*R*)-**1** for preparation of hundreds of grams of prostaglandin analogue APIs, attention was focused back to the earlier synthetic steps to resolve the *trans*-isomer issue.

Attention was turned to the identification of a solid intermediate derivative that would be amenable to crystallization. Of the various intermediates that might form crystalline derivatives, it was thought that carboxylic acid **9** from the Wittig reaction would provide the best choice following its conversion to an amine salt. Unfortunately, of the nitrogen bases tested[43a] only the ammonium salt of **9** appeared to be a solid, and only so at low temperatures (< −20 °C), with analysis revealing that no enrichment of the *cis*-isomer had occurred.

Various salts of the desilylated analogue, hydroxycarboxylic acid **19**, were examined next with the expectation that removal of the lipophilic TBS group would impart better physical properties and provide a robust crystalline solid (Scheme 6). A screen of nitrogen bases in MTBE, EtOAc, or aqueous MeOH (for the amino acids) was conducted. Of all bases screened[43b] only the benzylamine series provided solids. Apart from the 4-methoxybenzylamine salt **2**,[43c] which possessed good physical properties[44] and being formed in good yield using 1 equiv of 4-

Scheme 6. Improved process for the synthesis of 14 and (*R*)-1[a]



[a]Reagents and conditions: (a) (i) TBAF, MTBE, reflux; (ii) 0.5 M HCl, 80−90%; (b) (i) $MeOC_6H_4CH_2NH_2$, MeCN, r.t., then 50 °C to recrystallise, 92%; (ii) Optionally recrystallize, 93%; (c) *i*-PrI, Cs_2CO_3, acetone, reflux, quantitative; (d) As per original process.

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methoxybenzylamine in EtOAc, the three others were initially obtained as sticky solids. Due to the significant rate of background aminolysis of EtOAc,[45] further solvent screening (MTBE, MIBK, MeCN) was required. MeCN was identified as the most preferred solvent for recrystallisation of 4-methoxybenzylamine salt **2**, supplying a high yield (94%) and high enrichment of the *cis*-isomer.

With these results in hand, a scalable process to convert crude, *trans*-isomer-contaminated Wittig reaction carboxylic acid **9** into pure ester *cis*-**14** was now in sight. On laboratory-to-kilogram scales, desilylation of crude Wittig reaction product **9**[46] with >70% potency assay and 80% HPLC purity with TBAF in MTBE followed by a 0.5 M HCl quench provided hydroxycarboxylic acid **19** with 62−65% potency assay in 80−93% assay yield. Recrystallisation of the crude acid as its 4-methoxybenzylamine salt from hot MeCN with seeding gave 83−92% assay yields of 4-methoxybenzylamine salt **2** with 98.0−98.5% HPLC purity. This salt was contaminated with less than 1 mol% of the *trans*-isomer, demonstrating the utility of the new process. Although this was low enough for our requirements, if necessary the *trans*-isomer could be reduced down to 0.2 mol% by a second recrystallisation of the salt from MeCN, as was demonstrated on about half-kilogram scales (92−97% yield).

Direct esterification of recrystallised salt **2**, without a salt-breaking step, was demonstrated on a 0.7-kg scale by treatment with isopropyl iodide in the presence of Cs_2CO_3[47] under reflux in acetone. Isopropyl ester **14**, which was an intermediate in the original process, was acquired as an oil in an almost quantitative yield with ≥98% HPLC purity without purification. The unalkylated amine was recovered from the aqueous phase of the acid wash step for recycling.

Using the redesigned process described above, one chromatography step was eliminated from the original process, and with a single recrystallization of the salt intermediate **2** on a 1.0-kg scale, an overall yield of about 70% based on crude **9** was achieved with the *trans*-isomer lowered to 0.7% by HPLC. Conversion of this through the remaining steps of the synthetic route provided the cyclopentenone (*R*)-**1** with 99.8% ee and only 0.62% of the *trans*-isomer, demonstrating good control of chiral purity and adequate control of the geometric isomer.

CONCLUSION

In summary, a robust and scalable process for the manufacture of the homochiral key intermediate cyclopentenone (*R*)-**1**, which is useful as an intermediate for the synthesis of prostaglandin analogues, has been developed. Cyclopentenone (*R*)-**1** was produced on multikilogram scales with a high chemical and chiral purity in 14 steps, starting with furfural. Controlling the level of the undesired *trans*-isomer formed in the Wittig reaction that tracked through to the APIs was later addressed by development of improved Wittig reaction conditions followed by recrystallisation of an amine salt derivative of hydroxycarboxylic acid intermediate **19**. The high enantiopurity of cyclopentenone (*R*)-**1** was achieved through a double enzymatic resolution protocol adapted from reported procedures, making use of both enantiomers of the original racemate, in good yield.

Improvements in process efficiency are still required, and these, with a particular focus on the Piancatelli rearrangement, will be addressed in future process development. A more expedient synthesis of aldehyde **4** is sought, and telescoping of reaction steps would provide much benefit. Further, additional chromatography steps might be eliminated by identification of new crystalline derivatives of intermediates.

Finally, it is worth commenting on the choice of the isopropyl ester of cyclopentenone (*R*)-**1** that was integral to our original strategy depicted in Figure 1. As we have disclosed elsewhere,[7b,48] this ester is not end-product or structure limiting in that it serves as both a carboxyl protecting group and as part of the final drug structure for some products (i.e., for travoprost[7b]) or as a protecting group that can be converted downstream to an amide by aminolysis (i.e., for bimatoprost[7b]) or to the parent carboxylic acid (i.e., for lubiprostone[48]) by enzymatic hydrolysis. Further, this ester proved to be resistant to hydrolysis in the Piancatelli rearrangement and trans-esterification in the enzymatic resolution steps.

EXPERIMENTAL SECTION

General. HPLC analyses were conducted using Agilent 1100 and 1200 HPLC systems. GC analyses were conducted using Agilent 6890 and 7890 GC systems. HPLC and GC purity is reported by area%. ^{1}H and ^{13}C NMR spectra were acquired using a Varian, Mercury Plus 300 MHz spectrometer. EIMS data were acquired using an Agilent 7890 GC system with a 5975C MSD. ESI data was acquired using an Agilent 1200 HPLC system coupled with a 6120 MSD. HRMS data was acquired using a Bruker APEX III 7.0 FTMS system. IR data was acquired using a Nicolet Avatar 360 FT-IR system. The specific rotation was calculated from data obtained using a Rudolph Autopol III polarimeter. Melting points were measured using Shanghai Jingke Scientific Instrument Co., Ltd.'s WRR melting point apparatus. The enzymatic resolution of *rac*-**16** was monitored throughout (both enantiomorphs and *cis*- and *trans*-geometric isomers of both the alcohol ((*R*)-**16**, (*S*)-**16**, *trans*-(*R*)-**16**, *trans*-(*S*)-**16** elute at about 49.0, 52.5, 55.3, 67.0 min, respectively) and the acetate esters ((*R*)-**17**, (*S*)-**17**, *trans*-(*R*)-**17**, *trans*-(*S*)-**17** elute at about 25.0, 29.6, 31.7, 35.0 min, respectively) are separated) using an Agilent HPLC system (as above) monitoring at 216 nm equipped with a Chiralcel OJ-H column (250 mm × 4.6 mm, 5 μm) maintained at 25 °C using a 100:2 *n*-hexane/isopropanol mobile phase (isocratic) with a flow rate of 1.2 mL/min. The ee of (*R*)-**1** ((*R*)-**1** and (*S*)-**1** elute at about 20.4 and 24.8 min, respectively) was determined using an Agilent HPLC system (as above) monitoring at 220 nm equipped with a Chiralcel OD-3 column (150 mm × 4.6 mm, 3 μm) maintained at 20 °C using a 99:1 *n*-hexane/isopropanol mobile phase (isocratic) with a flow rate of 0.2 mL/min. The *cis*- and *trans*-geometric isomer ratio of (*R*)-**1** and *trans*-(*R*)-**1** was determined using the same HPLC system ((*R*)-**1** and *trans*-(*R*)-**1** elute at about 20.4 and 21.6 min, respectively). The *cis*- and *trans*-geometric isomer ratio of **2** (*cis*-**2** and *trans*-**2** elute at 10.1 and 11.6 min, respectively) was determined using an Agilent HPLC system (as above) monitoring at 215 nm equipped with a Zorbax SB-C18 column (150 mm × 4.6 mm, 5 μm) maintained at 30 °C using a 90:10 10 mM K_2HPO_4 (pH = 6.0)/MeCN for 0−11 min (isocratic), then 90 to 50:10 to 50 10 mM K_2HPO_4 (pH = 6.0)/MeCN (linear gradient) from 11 to 15 min, then 50 to 20:50 to 80 10 mM K_2HPO_4 (pH = 6.0)/MeCN (linear gradient) for 15−20 min, then 20:80 10 mM K_2HPO_4 (pH = 6.0)/MeCN (isocratic) for 20−28 min as the mobile phase with a flow rate of 1.5 mL/min. The *cis*- and *trans*-geometric isomer ratio of **14** (*cis*-**14** and *trans*-**14** elute at 14.6 and 15.3 min, respectively) was determined using an Agilent HPLC system (as above) monitoring at 215 nm equipped with a

Zorbax SB-C18 column (150 mm × 4.6 mm, 5 μm) maintained at 30 °C using a 80 to 60:20 to 40 10 mM KH_2PO_4 (pH = 3.0)/MeCN for 0−5 min (linear gradient), then 60:40 10 mM KH_2PO_4 (pH = 3.0)/MeCN (isocratic) from 5 to 18 min, then 60 to 20:40 to 80 10 mM KH_2PO_4 (pH = 3.0)/MeCN (linear gradient) for 18−20 min, then 20:80 10 mM KH_2PO_4 (pH = 3.0)/MeCN (isocratic) for 20−28 min as the mobile phase with a flow rate of 1.5 mL/min.

Synthesis of 4-(*tert*-Butyldimethylsilyloxy)-4-(furan-2-yl)-butene (5). To a stirred mixture of zinc (2.475 kg, 38.08 mol) and anhydrous THF (5.874 kg) at 60−65 °C in a 20-L reactor was added a 4% portion of allyl bromide (4.587 kg, 38 mol) and furfural (3.3 kg, 34.38 mol) in anhydrous THF (2.937 kg). The mixture was stirred at 60−65 °C until the reaction had initiated (as indicated by reflux); then the remaining 96% of the mixture was added dropwise without any heating. After the addition was complete (3 h), the mixture was heated again until the reaction was complete (GC analysis). The mixture was cooled to <10 °C, transferred to a 50-L reactor, and a solution of TBSCl (8.283 kg, 55.2 mol), imidazole (5.61 kg, 82.5 mol), and THF (5.874 kg) in DMF (6.237 kg) was added over a 2.5 h period at 10−20 °C. The mixture was then warmed to 20−35 °C and stirred until alcohol **3** was consumed (2 h; GC analysis). The reaction solution was cooled to 10−15 °C; water (3.3 kg) and *n*-heptane (2.244 kg) were added and then separated, and the aqueous layer was extracted twice with *n*-heptane (4.488 kg each). The combined organic layers were washed twice with saturated aqueous NaCl (8.6 kg each), washed with saturated aqueous $NaHCO_3$ (3.3 kg), and then concentrated at 55−60 °C under reduced pressure (<0.1 MPa) to a volume of 4−5 L. The remaining residue was then fractionally distilled under reduced pressure (7−8 mmHg) with the fraction boiling at 95−101 °C being collected, giving 6.4 kg (24.2 mol, 70%) of olefin **5** with 95.5% GC purity. ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.06 (s, 3H, H9), 0.05 (s, 3H, H9), 0.87 (s, 9H, H11), 2.56 (t, J = 6.6 Hz, 2H, H3), 4.71 (t, J = 6.6 Hz, 1H, H4), 5.04 (m, 1H, H1), 5.05 (dm, J = 24.0 Hz, 1H, H1), 5.77 (m, 1H, H2), 6.17 (d, J = 3.3 Hz, 1H, H6), 6.30 (dd, J = 3.3 Hz, 1.8 Hz, 1H, H7), 7.34 (dd, J = 1.8 Hz, 0.9 Hz, 1H, H8). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 157.1, 141.5, 134.8, 117.4, 110.1, 105.1, 68.6, 41.8, 26.0, 18.4, −4.7, −4.8. EIMS m/z 73 (63%, $C_3H_9Si^+$), 75 (100, $C_2H_7SiO^+$), 77 (21), 91 (19), 103 (16), 111 (8), 121 (7), 129 (8), 195 (49, $M^{\cdot+} - C_4H_9$), 211, (32, $M^{\cdot+} - C_3H_5$), 237 (1, $M^{\cdot+} - CH_3$). IR 2929, 2956, 2887, 2858, 1472, 1463, 1344, 1257, 1089, 1005, 915, 847, 777, 735, 598 cm^{-1}.

Synthesis of 4-(*tert*-Butyldimethylsilyloxy)-4-(furan-2-yl)-butane-1,2-diol (6). A mixture of **5** (19.09 kg, 96% purity, 72.2 mol), $K_2OsO_2(OH)_4$ (0.1 kg, 0.271 mol), and $(DHQ)_2PHAL$ (0.2 kg, 0.257 mol) in acetone (86.5 kg) in a 200-L reactor was cooled to 10−15 °C. A solution of NMO (11.14 kg, 97% purity, 92.4 mol) in water (36.46 kg) was added at such a rate that the temperature stayed within a range of 10−25 °C. The reaction mixture was stirred at r.t. for 6.5 h; then more $K_2OsO_2(OH)_4$ (9 g, 0.024 mol), $(DHQ)_2PHAL$ (18 g, 0.023 mol), and NMO (0.984 kg, 8.4 mol) were added, and the mixture was stirred for a further 2 h. A solution of Na_2SO_3 (15.68 kg, 125.4 mol) in water (47.34 kg) was added, and the mixture was then heated to 40−43 °C for 1.5 h, filtered at 30−40 °C, and washed with acetone (27.3 kg). The combined filtrate was concentrated at <45 °C under reduced pressure. The concentrated residue was extracted twice with EtOAc (32.8 kg each), and the combined organic solutions were washed with saturated aqueous NaCl (41.1 kg), and then concentrated at <55 °C under reduced pressure, providing 20.1 kg (63.1 mol, 87.4%) of crude product **6** as a mixture of two diastereomers* with 90% GC purity. ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.15 (s, 1.5H, H9), −0.04 (s, 1.5H, H9), 0.08 (s, 1.5H, H9), 0.10 (s, 1.5H, H9), 0.88 (s, 4.5H, H11), 0.90 (s, 4.5H, H11), 1.83 (ddd, J = 14.4 Hz, 4.5 Hz, 2.7 Hz, 0.5H, H3), 1.91−2.05 (m, 2H, H3 and OH), 2.13 (dt, J = 14.4 Hz, 9.0 Hz, 0.5H, H3), 3.23 (d, J = 2.7 Hz, 0.5H, OH), 3.34 (d, J = 2.4 Hz, 0.5H, OH), 3.48 (m, 1H, H2), 3.62 (m, 1H, H1), 3.92 (m, 1H, H1), 4.98 (dd, J = 9.0 Hz, 4.5 Hz, 0.5H, H4), 5.09 (t, J = 5.1 Hz, 0.5H, H4), 6.22 (t, J = 3.0 Hz, 1H, H6), 6.32 (m, 1H, H7), 7.35 (m, 1H, H8). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 156.2, 156.0*, 141.9, 141.8*, 110.4, 110.3*, 106.8, 106.5*, 71.1, 69.3*, 68.5, 67.4*, 67.1, 67.0*, 39.8, 39.1*, 26.0, 18.3, 18.2*, −4.86, −5.08*, −5.13. EIMS m/z 73 (24%, $C_3H_9Si^+$ and/or $C_3H_7O_2^+$), 75 (100, $C_2H_7SiO^+$), 95 (23), 117 (77), 171 (18, $M^{\cdot+} - C_6H_{15}Si$), 211 (7, $M^{\cdot+} - C_3H_7O_2$). ESI (Negative) m/z 331 (100%, M[AcO]$^-$), 345 (30, M[AcO]$^-$). IR 3384, 2930, 2954, 2886, 2858, 1472, 1463, 1361, 1255, 1150, 1078, 1009, 837, 779, 736 cm^{-1}.

Synthesis of 3-(*tert*-Butyldimethylsilyloxy)-3-(furan-2-yl)propanal (4). To a stirred solution of $NaIO_4$ (20.54 kg, 95.98 mol) in water (61.8 kg) in a 200-L reactor under N_2 was added a solution of **6** (20.1 kg, 79.13 mol) in acetone (57.64 kg) at 10−30 °C over a 2.5 h period. The resulting mixture was stirred at 10−30 °C for 6 h; then over 24.5 h were added more $NaIO_4$ in four portions (1.3 kg, 6.08 mol, then 1.8 kg, 8.42 mol, then 0.9 kg, 4.21 mol, 0.9 kg, 4.21 mol), water (1.5 kg), and acetone (10 kg). Once complete (GC analysis), the mixture was filtered to remove the solids and washed with MTBE (14.9 kg). The combined filtrate was separated, and the aqueous layer was extracted with MTBE (14.9 kg); the combined organic layer was washed with saturated aqueous NaCl (26.73 kg) and then dried over anhydrous $MgSO_4$ for 2 h under an atmosphere of argon. The mixture was filtered through silica gel (6.63 kg), and the filter cake was washed with MTBE (50 kg). The filtrate was concentrated at <40 °C under reduced pressure to furnish **4** as a brown oil (17.8 kg; typical GC purity >90%) that was used directly without purification in the next step. ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.06 (s, 3H, H8), 0.08 (s, 3H, H8), 0.85 (s, 9H, H10), 2.75 (ddd, J = 16.2 Hz, 4.8 Hz, 2.1 Hz, 1H, H2), 2.96 (ddd, J = 16.2 Hz, 7.5 Hz, 2.7 Hz, 1H, H2), 5.24 (dd, J = 7.5 Hz, 4.8 Hz, 1H, H3), 6.22 (d, J = 3.3 Hz, 1H, H5), 6.32 (dd, J = 3.3 Hz, 1.8 Hz, 1H, H6), 7.37 (dd, J = 1.8 Hz, 0.9 Hz, 1H, H7), 9.82 (dd, J = 2.7 Hz, 2.1 Hz, 1H, H1).^{13}C NMR (75.45 MHz, $CDCl_3$): δ 201.0, 155.5, 142.2, 110.4, 106.8, 64.3, 50.2, 25.9, 18.3, −4.8, −5.0. IR 2956, 2930, 2888, 2858, 1728, 1472, 1464, 1362, 1343, 1256, 1149, 1097, 1007, 848, 779, 738 cm^{-1}.

Synthesis of Isopropyl (*Z*)-8-(*tert*-Butyldimethylsilyloxy)-8-(furan-2-yl)-oct-5-enoate (8) Using TPPA in Wittig Reaction. A mixture of 5-bromopentanoic acid (**11a**; 3.50 kg, 19.33 mol), triphenylphosphine (7.60 kg, 28.98 mol), and toluene (10.5 L) was heated under reflux for 6 h. The resulting slurry was cooled to 25−30 °C, and the solids were isolated by centrifuge and were washed with toluene (1.7 L) and dried at 90−100 °C for 12 h providing (4-carboxybutyl)-triphenylphosphonium bromide (**11b**; 7.42 kg, 16.74 mol). To a solution of (4-carboxybutyl)triphenylphosphonium bromide (0.90 kg, 2.03 mol) in a mixture of THF (3.36 kg) and TPPA (0.96 kg) in a 20 L glass-lined reactor under an atmosphere of nitrogen at 6−8 °C was added a solution of NaHMDS (2 M

solution in THF, 1.85 kg, 4.01 mol) over a 0.92-h period to maintain a temperature within 0−10 °C, furnishing a dark-orange mixture that was further stirred for 0.5 h. The solution was cooled to between −32 and −38 °C. A solution of aldehyde **4** (0.405 kg, 1.43 mol based on GC purity of 90%) in THF (1.80 kg) was then added over a 1-h period to maintain a temperature of between −32 and −38 °C and was further stirred at this temperature until the reaction was complete (GC analysis; about 1 h). Acetone (0.115 kg) was added and stirred for 30 min. EtOAc (3.79 kg) and saturated aqueous NH_4Cl (6.79 kg; adjusted to pH 1 with conc. HCl) were added at <5 °C, and the mixture was warmed to between ∼20 °C. Water (2.43 kg) and solid NaCl (0.324 kg) were added, and after the mixture stirred for 20 min, the aqueous phase was separated, and water was added and stirred for 20 min. The aqueous layer was separated and extracted with EtOAc (1.05 kg), and the combined organic layer was concentrated at <55 °C under reduced pressure (0.08−0.1 MPa) to provide crude **9** ((*Z*)-8-(*tert*-butyldimethylsilyloxy)-8-(furan-2-yl)-oct-5-enoic acid; 1.9 kg). ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.05 (s, 3H, H1′), 0.05 (s, 3H, H1′), 0.87 (s, 9H, H2′), 1.66 (p, J = 7.5 Hz, 2H, H3), 2.07 (q, J = 6.9 Hz, 2H, H4), 2.32 (t, J = 7.5 Hz, 2H, H2), 2.54 (t, J = 6.3 Hz, 2H, H7), 4.69 (t, J = 6.3 Hz, 1H, H8), 5.41 (m, 2H, H5 and H6), 6.16 (d, J = 3.0 Hz, 1H, H10), 6.28 (dd, J = 3.0 Hz, 1.8 Hz, 1H, H11), 7.33 (dd, J = 1.8 Hz, 0.9 Hz, 1H, H12). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 180.2, 157.1, 141.5, 130.7, 126.5, 110.2, 106.1, 68.7, 35.2, 33.7, 32.4, 26.8, 26.0, 24.7, 22.9, 18.4, −4.7, −4.8. EIMS m/z 73 (70%, $C_3H_9Si^+$), 75 (76, $C_2H_7SiO^+$), 81 (27), 211 (100, $M^{\cdot+} - C_7H_{11}O_2$), 212 (18), 263 (8, $M^{\cdot+} - C_3H_9Si$), 281 (4, $M^{\cdot+} - C_4H_9$). ESI (Negative) m/z 337 ($[M - H]^-$). IR 3016, 2955, 2930, 2857, 1710, 1472, 1463, 1412, 1255, 1151, 1087, 1006, 939, 837, 777, 735 cm^{-1}.

In a 20-L glass-lined reactor, an acetone (3.0 kg) solution of the crude product and K_2CO_3 (0.64 kg, 4.63 mol) and 2-iodopropane (0.785 kg, 4.62 mol) was heated under reflux for 4 h. After the mixture was cooled to <30 °C, water (2.55 kg) and MTBE (1.89 kg) were added, and the mixture was stirred for 20 min. Solid NaCl (0.219 kg, 0.5 P) was added, and the mixture was stirred for 20 min; the aqueous layer was separated and extracted with MTBE (0.6 kg), and the MTBE portions were combined, washed once with saturated aqueous NaCl (1.07 kg), and concentrated under reduced pressure (0.09−0.1 MPa) at <55 °C; the resulting oil was purified by column chromatography (eluting with a 1:20 mixture of EtOAc and *n*-heptane), and the fractions containing the title product were combined and concentrated under reduced pressure to provide **8** (0.412 kg, 1.00 mol, 70% based on aldehyde **4**) with 92.4% GC purity (contaminated with 5.6% **12**). A small sample was converted to ester **14** and analysed by HPLC, showing a 8.0:92.0 *trans*-/*cis*- ratio. ^{1}H NMR (300 MHz, $CDCl_3$): δ −0.06 (s, 3H, H13), 0.05 (s, 3H, H13), 0.87 (s, 9H, H9), 1.22 (d, J = 6.3 Hz, 6H, H2′), 1.65 (m, 2H, H3), 2.04 (m, 2H, H4), 2.24 (t, J = 7.5 Hz, 2H, H2), 2.54 (t, J = 6.0 Hz, 2H, H7), 4.68 (t, J = 6.6 Hz, 1H, H8), 5.00 (septet, J = 6.3 Hz, 1H, H1′), 5.40 (m, 2H, H5 and H6), 6.16 (d, J = 3.3 Hz, 1H, H10), 6.29 (dd, J = 3.3 Hz, 1.8 Hz, 1H, H11), 7.3 (dd, J = 1.8 Hz, 0.9 Hz, 1H, H12). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 173.4, 157.1, 141.5, 131.0, 126.3, 110.2, 106.1, 68.7, 67.6, 35.2, 34.3, 32.1, 26.9, 26.0, 25.1, 22.9, 22.1, 18.4, −4.7, −4.8. EIMS m/z 73 (53%, $C_3H_9Si^+$), 75 (27, $C_2H_7SiO^+$), 189 (11), 211 (100, $M^{\cdot+} - C_{10}H_{17}O_2$), 263 (6), 281 (2), 305 (1), 323 (3), 380 (0.2, $M^{\cdot+}$). ESI (Positive) m/z 403 (41%, MNa^+), 398 (80, MNH_4^+), 249 (100, $MH^+ - C_6H_{15}SiO$). IR 2956, 2930, 2895, 2858, 1732, 1471, 1374, 1361, 1348, 1252, 1151, 1110, 1006, 968, 940, 836, 778, 735 cm^{-1}.

Synthesis of Isopropyl (*Z*)-7-(3-Hydroxy-5-oxo-cyclopent-1-en-1-yl)-hept-5-enoate (*rac*-16). A mixture of **8** (15.83 kg, 41.66 mol) and TBAF·$3H_2O$ (13.12 kg, 42.05 mol) in THF (70.44 kg) in a 200-L reactor was stirred at 35−45 °C until the starting material **8** was consumed (GC analysis). Saturated aqueous NH_4Cl (23.11 kg) and solid NaCl (0.158 kg) were added, and the mixture was vigorously stirred for 30 min. The aqueous phase was separated, extracted with EtOAc (110.5 kg), and then combined with the organic phase and concentrated at <55 °C under reduced pressure. The residue was dissolved in EtOAc (110.5 kg) and was washed twice with water (45.91 kg each); following evaporation under reduced pressure isopropyl (*Z*)-8-(furan-2-yl)-8-hydroxy-oct-5-enoate was furnished (**14**; analytical data for this compound can be found below for its synthesis from **2**) as a brown oil. To a mixture of $ZnCl_2$ (64.75 kg, 476 mol) and water (72.8 kg) in a 500-L reactor was added a solution of the crude **14** and hydroquinone (4.6 g) in dioxane (86 kg). The mixture was heated at reflux under an atmosphere of nitrogen until **14** was consumed (6 h; GC analysis). The product mixture was cooled to 50−60 °C, and the dioxane was evaporated under reduced pressure until 72 kg of solvent had distilled. EtOAc (75.5 kg) and saturated aqueous NH_4Cl (44.16 kg) were added into the vigorously stirred mixture. The aqueous phase was separated and extracted with EtOAc (35.62 kg), and the combined organic layer was washed with saturated aqueous NaCl (44.17 kg) and concentrated at <55 °C under reduced pressure (0.1 MPa) to give a black oil (a mixture of *rac*-**16** and *rac*-**16b**). The oil was dissolved in toluene (81.2 kg) in a 200-L reactor and stirred in the presence of Et_3N (5.52 kg, 54.65 mol) and chloral (1.266 kg, 5.83 mol) at r.t. for 12 h. Extra portions of Et_3N (2.77 kg, 27.4 mol) and chloral (0.427 kg, 3.1 mol) were added, and the mixture was stirred at r.t. for a further 3 h. The product mixture was washed with a saturated aqueous solution of NH_4Cl (44.16 kg), and the aqueous phase was back-extracted with PhMe (28.96 kg). The organic portions were combined and washed with saturated aqueous NaCl (23.1 kg) and concentrated under reduced pressure at <55 °C to give a brown oil that was purified by chromatography (eluting with 1:2 EtOAc/*n*-heptane followed by an almost equal volume of 2:3 EtOAc/*n*-heptane) to furnish the title product *rac*-**16** (4.43 kg, 16.6 mol) with 100% GC purity plus another fraction consisting of 97% GC pure *rac*-**16** (452 g, 1.6 mol); total 44% over three steps based on **8**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (d, J = 6.3 Hz, 6H, H2′), 1.68 (m, 2H, H3), 2.06 (m, 2H, H4), 2.27 (t, J = 7.5 Hz, 2H, H2), 2.34 (dd, J = 18.6 Hz, 1.8 Hz, 1H, H10), 2.85 (dd, J = 18.6 Hz, 6.3 Hz, 1H, H10), 2.91 (m, 2H, H7), 4.98 (m, 2H, H11 and H1′), 5.53 (m, 2H, H5 and H6), 7.16 (dd, J = 1.8 Hz, 0.9 Hz, 1H, H12). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 206.0, 173.5, 156.3, 146.9, 132.0, 125.4, 68.0, 68.0, 45.2, 34.2, 26.7, 24.8, 22.9, 22.0. EIMS m/z 41 (59%), 43 (100, $C_3H_7^+$), 55 (43), 67 (31), 77 (33), 79 (40), 91 (44), 94 (56), 107 (30), 119 (51, $C_8H_7O^+$), 133 (54, $C_9H_9O^+$), 146 (49, $C_{10}H_{10}O^+$), 160 (49, $C_{11}H_{12}O^+$), 188 (37, $M^{\cdot+} - H_2O - C_3H_7O - H$), 189 (46, $M^{\cdot+} - H_2O - C_3H_7O$), 206 (62, $M^{\cdot+} - C_3H_7O - H$), 207 (26, $M^{\cdot+} - C_3H_7O$), 248 (11, $M^{\cdot+} - H_2O$). ESI (Positive) m/z 267 (100%, MH^+), 284 (57, MNH_4^+). IR 3446, 2980, 2936, 1713, 1456, 1419, 1375, 1316, 1260, 1199, 1147, 1109, 1037 cm^{-1}.

Synthesis of Isopropyl (3*R*,*Z*)-7-(3-Hydroxy-5-oxo-cyclopent-1-en-1-yl)-hept-5-enoate ((*R*)-16). A mixture of

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rac-**16** (4.43 kg, 16.64 mol), vinyl acetate (33 kg), and Lipase PS "Amano" SD (2.22 kg) was stirred in a 50-L reactor at 38−42 °C until chiral HPLC analysis showed that (*R*)-**16** was not more than 3.0% (the reaction was terminated at 33 h when (*R*)-**16** was 2.7%). The reaction mixture was filtered through a plug of Celite; the filter cake was washed three times with EtOAc (4 kg each) and then concentrated to give a yellow-brown oil comprising a mixture of isopropyl (3*R*,*Z*)-7-(3-acetoxy-5-oxo-cyclopent-1-en-1-yl)-hept-5-enoate ((*R*)-**17**; 96.7% ee) and isopropyl (3*S*,*Z*)-7-(3-hydroxy-5-oxo-cyclopent-1-en-1-yl)-hept-5-enoate ((*S*)-**16**; 89.6% ee). The mixture was dissolved in THF (22.26 kg) in a 50-L reactor and cooled to 0−10 °C, and triphenylphosphine (3.615 kg, 13.8 mol) and formic acid (0.655 kg, 13.8 mol) were added, followed by addition of a solution of diethyl azodicarboxylate (2.38 kg, 13.8 mol) in THF (4.53 kg) over 5.5 h, maintaining a temperature of 0−10 °C. The reaction mixture was allowed to warm to 20−25 °C and stirred until (*S*)-**16** was fully consumed (GC analysis; 1 h). The product mixture was partially concentrated under reduced pressure, and EtOAc (5.67 kg) was added to the concentrate followed by *n*-heptane (12.85 kg) causing precipitation. The mixture was filtered, and the filter cake was washed three times with 1:5 EtOAc/*n*-heptane (3.1 kg each), concentrated under reduced pressure, and purified by column chromatography (eluting with 1:3 EtOAc/heptane) providing a mixture of (*R*)-**17** and isopropyl (3*R*,*Z*)-7-(3-formyloxy-5-oxo-cyclopent-1-en-1-yl)-hept-5-enoate ((*R*)-**18**) with a combined GC purity of 96%. To a cold (−10 to 0 °C) MeOH (19.86 kg) solution of the mixture in a 50-L reactor was added a solution of guanidine in MeOH (0.5 M, 14.41 kg, 9.0 mol), and the mixture was stirred at 0−10 °C until the esters were consumed (TLC analysis; <30 min). AcOH (0.545 kg, 9.08 mol) was added, the mixture was stirred for 5 min, and the mixture was then allowed to warm to r.t. The product mixture was concentrated under reduced pressure at <55 °C. The residue was diluted with EtOAc (21.7 kg) and was washed with water (48.2 kg). The aqueous layer was separated and was extracted with EtOAc (21.7 kg); the combined organic layers were washed with water (24.1 kg) and with saturated aqueous NaCl (24.1 kg) and then were dried over $MgSO_4$ for 2 h and filtered, and the filter cake was washed three times with EtOAc (5 kg each) and concentrated under reduced pressure to give (*R*)-**16** (4.48 kg, 15.8 mol, 92% GC yield based on *rac*-**16**) with 94% GC purity and 91% ee. A mixture of the above prepared enantioenriched (*R*)-**16**, vinyl acetate (33.4 kg), and Lipase PS "Amano" SD (2.24 kg) in a 50-L reactor was stirred at 38−42 °C until chiral HPLC analysis showed that (*R*)-**16** was not more than 2.0% (observed: 1.7% at 34 h). The reaction mixture was filtered through a plug of Celite; the filter cake was washed three times with EtOAc (4.1 kg each) and then concentrated to give a yellow-brown oil (5.0 kg) that was purified by column chromatography (eluting with 1:3 EtOAc/heptane, followed by EtOAc), providing the intermediate (*R*)-**17** (4.34 kg, 13.8 mol, 83%) with 98.3% GC purity and 99.9% ee. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (d, J = 6.3 Hz, 6H, H2′), 1.69 (p, J = 7.5 Hz, H3), 2.09 (s, 3H, H14), 2.11 (m, 2H, H4), 2.27 (t, J = 7.5 Hz, 2H, H12), 2.38 (dd, J = 18.9 Hz, 2.1 Hz, 1H, H10), 2.88 (dd, J = 18.9 Hz, 6.3 Hz, 1H, H10), 2.95 (d, J = 6.3 Hz, 2H, H7), 5.00 (septet, J = 6.3 Hz, 1H, H1′), 5.51 (m, 2H, H5 and H6), 5.75 (ddd, J = 6.3 Hz, 4.2 Hz, 2.1 Hz, 1H, H11), 7.15 (dd, J = 4.2 Hz, 1.5 Hz,, 1H, H12). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 204.5, 173.3, 170.8, 152.2, 148.8, 131.9, 125.1, 70.6, 67.7, 41.8, 34.3, 26.8, 24.9, 23.0, 22.1, 21.2. EIMS m/z 41 (27%), 43 (100, $C_3H_7^+$), 55 (29), 91 (33), 94 (50), 105 (18), 119 (53, $C_8H_7O^+$), 133 (29, $C_9H_9O^+$), 146 (55, $C_{10}H_{10}O^+$), 160 (32, $C_{11}H_{12}O^+$), 188 (35, M^{+} − AcOH − C_3H_7O − H), 189 (53, M^{+} − AcOH − C_3H_7O), 206 (57, M^{+} − $C_5H_{10}O_2$), 248 (16, M^{+} − AcOH). ESI (Positive) m/z 309 (85%, MH^+), 326 (100, MNH_4^+).

Some unreacted (*R*)-**16** (0.46 kg, 34% ee, 65.9% GC purity) was isolated for recycling.

To a cold (−10 to 0 °C) MeOH (16.85 kg) solution of the enantiopure ester (*R*)-**17** in a 50-L reactor was added a solution of guanidine in MeOH (0.5 M, 11.09 kg, 6.9 mol), and the mixture was stirred at 0−10 °C until the ester was consumed (<30 min; TLC analysis). AcOH (0.426 kg, 7.0 mol) was added, and the mixture was stirred for 5 min and was then allowed to warm to r.t. The product mixture was concentrated under reduced pressure at <55 °C, and the residue was diluted with EtOAc (19.2 kg) and was washed with water (42.66 kg). The aqueous layer was separated and extracted with EtOAc (19.2 kg), and the combined organic layers were washed with water (21.33 kg) and with saturated aqueous NaCl (21.33 kg) and then were dried over $MgSO_4$ for 2 h and then filtered. The filter cake was washed three times with EtOAc (3.8 kg each) and concentrated under reduced pressure to give (*R*)-**16** (3.38 kg, 11.9 mol, 72% total yield based on *rac*-**16**) with 94% GC purity and for which none of the enantiomer was detected by chiral HPLC analysis. The NMR spectroscopic and mass spectrometric data of this compound were the same as those of the racemic precursor *rac*-**16**, which are reported above.

Synthesis of Isopropyl (3*R*,*Z*)-7-(3-(*tert*-Butyldimethylsilyloxy)-5-oxo-cyclopent-1-en-1-yl)-hept-5-enoate ((*R*)-1). To a chilled (0−10 °C) solution of (*R*)-**16** (3.38 kg, 11.9 mol) and imidazole (1.6 kg, 23.5 mol) in dry DMF (8.97 kg) in a 30-L reactor was added a solution of TBSCl (2.7 kg, 18 mol) in dry DMF (11.96 kg). The mixture was then stirred at 20−25 °C until the reaction was complete (TLC analysis; 2 h). The product mixture was diluted with water (22.23 kg) and extracted twice with MTBE (17 kg each). The combined organic portions were washed with water (22.23 kg) and twice with saturated aqueous NaCl (22.23 kg), concentrated under reduced pressure, and then chromatographed (eluting first with *n*-heptane (213 kg) and then 1:5 EtOAc/*n*-heptane (533 kg)) to furnish the title product (*R*)-**1** (3.752 kg, 9.7 mol, 82% yield based on (*R*)-**16**) with 99.5% ee and 98% GC purity, as a 90.8:9.2 ratio of *cis*-/*trans*-isomers as determined by HPLC analysis. Another batch of (*R*)-**1** that contained a 99.38:0.62 ratio of *cis*-/*trans*-isomers, as determined by HPLC analysis, was prepared using purified salt **2**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.12 (s, 3H, H13), 0.13 (s, 3H, H13), 0.91 (s, 9H, H15), 1.23 (d, J = 6.3 Hz, 6H, H2′), 1.69 (p, J = 7.5 Hz, 2H, H3), 2.09 (q, J = 6.9 Hz, 2H, H4), 2.27 (t, J = 7.5 Hz, 2H, H2), 2.29 (dd, J = 18.3 Hz, 2.1 Hz, 1H, H10), 2.77 (dd, J = 18.3 Hz, 6.0 Hz, 1H, H10), 2.91 (m, 2H, H7), 4.89 (m, 1H, H11), 5.00 (septet, J = 6.3 Hz, 1H, H1′), 5.51 (m, 2H, H5 and H6), 7.04 (m, 1H, H12). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 206.0, 173.3, 157.1, 146.0, 131.5, 125.6, 69.2, 67.7, 45.7, 34.3, 26.8, 26.0, 25.0, 22.8, 22.1, 18.4, −4.5. EIMS m/z 41 (24%), 43 (100, $C_3H_7^+$), 73 (59, $C_3H_9Si^+$), 75 (27, $C_2H_7SiO^+$), 91 (28), 107 (20), 119 (31, $C_8H_7O^+$), 129 (21), 133 (13, $C_9H_9O^+$), 143 (17), 161 (23, $C_{11}H_{13}O^+$), 171 (16), 189 (90, M^{+}- $C_6H_{16}SiO$ − C_3H_7O), 206 (13), 221 (6), 248 (7, M^{+}-$C_6H_{16}SiO$), 263 (83), 281 (4), 321 (18, M^{+} − C_3H_7O), 323 (6, M^{+} − C_4H_9). ESI (Positive) m/z 381 (9%, MH^+), 403 (100, MNa^+), 419 (12, MK^+). HRMS (ESI, positive) found 381.2432 (calc. 380.2383 for

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$C_{21}H_{36}O_4Si$), found 403.2260 (calc. 403.2281 for $C_{21}H_{36}NaO_4Si$), found 419.2040 (calc. 419.2020 for $C_{21}H_{36}KO_4Si$); $[\alpha]^{20}_D$ = +10.4 (c = 0.01, $CHCl_3$). IR 2955, 2931, 2886, 2858, 1716, 1471, 1374, 1352, 1257, 1162, 1109, 1084, 967, 900, 836, 778, 669 cm^{-1}.

Synthesis of (*Z*)-8-(furan-2-yl)-8-hydroxy-oct-5-enoic acid (19). To a stirred solution of a partial concentrate of crude **9** (7.210 kg, 3.13 mol, 14.7% HPLC assay) and EtOAc (6.47 kg) in a 50 L reactor at r.t. was added *n*-heptane (19.6 kg). The mixture was stirred at r.t. for 1 h, then separated and the upper layer was extracted twice with 1:4 EtOAc/*n*-heptane (5.21 kg). The combined organic layers was concentrated under reduced pressure (<0.1 MPa) at 50 °C providing a thick, red-coloured oil that was diluted with *n*-heptane (19.6 kg) causing precipitation (Ph_3PO). After stirring for 0.5 h, the mixture was filtered through Celite (1.44 kg), and the filter cake was washed twice with *n*-heptane (3.92 kg each). The combined organic phases were washed three times with water (14.4 kg each) and then concentrated at 50−55 °C under reduced pressure (<0.1 MPa) to furnish semipurified **9** as a brown oil (1.262 kg, 77.1% HPLC assay, yield 91.8%). To a MTBE (3.60 kg) solution in the oil in a 20-L reactor was added TBAF·$3H_2O$ (1.63 kg, 5.15 mol), and the mixture was heated under reflux for 7 h. After cooling to 30−35 °C, MTBE (4.32 kg) was added, and the mixture was quenched with 0.5 M HCl (11.5 kg). The aqueous phase was extracted twice with MTBE (3.96 kg each). The combined organic phases were heated to 40 °C, washed three times with water (5.35 kg each) at 40 °C, dried over $MgSO_4$ (0.66 kg) for 2 h, and filtered, and the filter cake was washed three times with MTBE (1.0 kg each). The solution was concentrated at 40−45 °C under reduced pressure (<0.1 MPa) providing crude **19** (0.836 kg, 68.6% HPLC purity, 61.5% HPLC assay, 80% based on semipurified **9**) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.69 (p, J = 7.5 Hz, 2H), 2.12 (q, J = 7.2 Hz, 2H), 2.34 (t, J = 7.5 Hz, 2H), 2.61 (t, J = 6.6 Hz, 2H), 4.71 (t, J = 6.6 Hz, 1H), 5.46 (m, 2H), 6.24 (dd, J = 3.3 Hz, 0.6 Hz, 1H), 6.32 (dd, J = 3.3 Hz, 1.8 Hz, 1H), 7.37 (dd, J = 1.9 Hz, 0.6 Hz, 1H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 179.6, 156.4, 142.2, 132.1, 125.6, 110.4, 106.4, 67.7, 33.8, 33.5, 26.8, 24.6. ESI (Negative) m/z 223 (100%, $[M - H]^-$), 224 (12, $[M + 1 - H]^-$), 447 (9, $[2M - H]^-$). ESI (Positive) m/z 207 (100%, $MH^+ - H_2O$), 247 (20, MNa^+), 413 (48, $2[M - H_2O]H^+$), 414 (15, $2[MH^+ - H_2O]$).

Synthesis and Recrystallization of (4-Methoxyphenyl)-methanaminium (*Z*)-8-(Furan-2-yl)-8-hydroxy-oct-5-enoate (2). To a MeCN solution (2.9 kg) of crude **19** (0.836 kg, 61.5% HPLC assay) under a nitrogen atmosphere in a 10-L reactor was added a MeCN (1.24 kg) solution of 4-methoxybenzylamine (0.32 kg, 2.33 mol) over a period of 20 min at 10−30 °C. An off-white solid precipitated from the solution, and the mixture was stirred for 2 h at 16−24 °C. The temperature was raised to 49 °C causing the solids to dissolve. The temperature was slowly cooled to 45 °C, and seed crystals of **2** (2.66 g, 7.4 mmol, HPLC ratio of **19**/*trans*-**19** was 99.3:0.03) were added to the solution at 45 °C and stirred slowly for 2 h at 45 °C for crystallization. The mixture was slowly cooled to 0−5 °C (at a rate of 10 °C/h) and stirred for 1 h at 0−5 °C. The cold mixture was filtered, and the filter cake was washed three times with chilled (0−5 °C) MeCN (0.83 kg each). The solids were dried at 50 °C under reduced pressure (<0.1 MPa) for 4 h to furnish **2** (0.778 kg, 2.15 mol, 92.3% yield based on HPLC assay) with 98.1% HPLC purity of the *cis*-isomer and a 99.3%/0.7% HPLC ratio of **19**/*trans*-**19** of an off-white solid. If required, the salt could be recrystallised in >92% yield from MeCN providing 0.22% by HPLC of the *trans*-isomer. Mp 90.6−91.1 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.55 (m, 2H), 2.91−2.18 (m, 4H), 2.55 (m, 2H), 3.76 (s, 3H), 3.81 (s, 2H), 4.65 (t, J = 6.6 Hz, 1H), 5.27−5.52 (m, 2H), 5.82 (bs, 4H), 6.20 (d, J = 3.3 Hz, 1H), 6.29 (dd, J = 3.3 Hz, 1.8 Hz, 1H), 6.84 (d, J = 8.7 Hz, 2H), 67.24 (d, J = 8.7 Hz, 2H), 7.32 (dd, J = 1.8 Hz, 0.6 Hz, 1H). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 180.8, 159.6, 156.9, 142.0, 132.6, 130.0, 125.7, 114.3, 110.4, 106.1, 67.4, 55.5, 43.6, 36.1, 34.0, 26.9, 25.8. LC−MS analysis of **2** provides ESI mass spectrometry data the same as for **19** reported above. IR 3357, 3009, 2956, 2915, 2839, 2644, 1616, 1586, 1519, 1460, 1422, 1406, 1302, 1253, 1225, 1180, 1028, 1010, 819, 749 cm^{-1}.

Synthesis of Isopropyl (*Z*)-8-(Furan-2-yl)-8-hydroxy-oct-5-enoate (14). Isopropyl iodide (1.026 kg, 6.04 mol) and Cs_2CO_3 (1.31 kg, 4.02 mol) were added to an acetone (5.75 kg) solution of **2** (0.728 kg, 2.01 mol, containing 0.74% of the *trans*-isomer by HPLC) at 20−30 °C in a 20-L reactor. The mixture was stirred under reflux for 6 h. The product mixture was cooled to ≤35 °C, and MTBE (5.39 kg) and H_2O (7.28 kg) were added; the mixture was stirred for 30 min. The aqueous layer was separated and extracted with MTBE (2.70 kg). The combined organic layers were washed with 0.5 M HCl (4.15 kg) and saturated aq NaCl (4.95 kg). The organic phase was concentrated at 40 °C under reduced pressure (<0.1 MPa) to furnish **14** (0.546 kg, quantitative yield based on **2**) with 98.3% HPLC purity with 0.72% of the *trans*-isomer (this material was used to provide (*R*)-**1** with 0.62% *trans*-isomer) by HPLC as an orange oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.23 (d, J = 6.3 Hz, 6H, H2′), 1.68 (p, J = 7.5 Hz, 2H, H3′), 2.10 (q, J = 7.3 Hz, 2H, H4), 2.27 (t, J = 7.5 Hz, 2H, H2), 2.62 (t, J = 6.9 Hz, 2H, H7), 4.72 (t, J = 6.6 Hz, 1H, H8), 5.00 (septet, J = 6.3 Hz, 1H, H1′), 5.48 (m, 2H, H5 and H6), 6.25 (d, J = 3.3 Hz, 1H, H10), 6.33 (dd, J = 3.3 Hz, 1.8 Hz, 1H, H11), 7.38 (dd, J = 1.8 Hz, 0.6 Hz, 1H, H12). ^{13}C NMR (75.45 MHz, $CDCl_3$): δ 173.5, 156.4, 141.1, 132.5, 125.5, 110.4, 106.3, 67.8, 67.6, 34.3, 33.9, 26.9, 25.9, 25.0, 22.1. ESI (Positive) m/z 208 (10%), 249 (100, $MH^+ - H_2O$), 266 (<5, MH^+), 305.2 (<5, MK^+). EIMS m/z 41 (23%), 43 (14, $C_3H_7^+$), 68 (20), 82 (13), 97 (100, $C_5H_5O_2^+$), 110 (34, $C_6H_6O_2^{+\cdot}$), 128 (23), 133 (5, $C_9H_9O^+$), 145 (6), 146 (5), 170 (20), 189 (5, $M^{+\cdot} - C_3H_7O - H_2O$), 207 (5, $M^{+\cdot} - C_3H_7O$), 248 (4, $M^{+\cdot} - H_2O$), 266 (1, $M^{+\cdot}$). IR 3446, 2980, 2936, 1729, 1375, 1224, 1181, 1146, 1109, 1010, 739, 597.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra of **5**, **6**, **4**, **8**, *rac*-**16**, (*R*)-**17**, (*R*)-**1**, **19**, **2**, **14**; HPLC chromatograms of (*R*)-**17**, (*R*)-**16**, (*R*)-**1**, **2**; a GC chromatogram of (*R*)-**1** and a high-resolution mass spectrum of (*R*)-**1**. Additional details on the synthesis of aldehyde **3** from furfural, a low-temperature Wittig reaction, and research of the first resolution step of *rac*-**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) A reviewer questioned how the use of (*R*)-**1** competes with the use of the Corey lactone, a compound commonly used in prostaglandin analogue synthesis on industrial scales. Through design, both the two-component route (that we use (*R*)-**1** for) and the Corey lactone route allow divergence and can be used to provide a plurality of products; both approaches have found use in industry for the synthesis of prostaglandin analogues. From a cost-wise point of view, a comparison between (*R*)-**1** and the Corey lactone is not valid. Whilst the Corey lactone comprises the cyclopentane moiety without either side chain, (*R*)-**1** already has the α-side chain installed and is a more advanced prostaglandin intermediate. Moreover, whereas we have shown,[7b] for example, that (*R*)-**1** can be converted into travoprost (as per the two-component approach) in three linear steps (1,4-conjugate addition, reduction, and desilylation), the Corey lactone approach requires another eight linear steps from the Corey lactone itself.[4] Further, we reasoned that for the targets shown in Figure 1, the two-component approach would allow divergence later in the synthesis. Note that whilst travoprost and tafluprost possess identical α-side chains and bimatoprost and lubiprostone require[7b,48] only single additional specific manipulations to the α-side chain late in the synthesis, the greater structural variance of the ω-side chains between targets means that it is best installed as late as possible.

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(15) For further details of the synthesis of aldehyde **3** see the Supporting Information.

(16) (a) Babiak, K. A.; Ng, J. S.; Dygos, J. H.; Weyker, C. L.; Wang, Y.-F.; Wong, C.-H. *J. Org. Chem.* **1990**, *55*, 3377. (b) Wong, C.-H.; Wang, Y.-F.; Hennen, W. J.; Babiak, K. A.; Dygos, J. H.; Ng, J. S. U.S. Patent 5,106,750, 1992.

(17) Facile, autocatalytic decomposition (contact with only 0.2 equiv of ylide caused full decomposition) of the 4-silyloxy substituent via deprotonation α- to the aldehyde was proposed to be responsible for its base sensitivity. By contrast, when the 4-silyloxy substituent is absent, successful Wittig reaction with the identical ylide is possible (see Armstead, D. A.; Mann, J. *Synth. Commun.* **1985**, *15*, 1147).

(18) (a) See Ahrgren, L.; Sutin, L. *Org. Process Res. Dev.* **1997**, *1*, 425 for a description of a Sharpless asymmetric dihydroxylation on an industrial scale. (b) To minimise risk to staff associated with the toxic, reactive, and volatile nature of OsO_4: (i) the non-volatile Os(VI) salt, $K_2OsO_2(OH)_4$ was used instead of OsO_4, and (ii) this salt was used at a level of 0.4 mol%. The Os(VI) precatalyst is oxidised in situ of the enclosed reactor to OsO_4 during the reaction. The reaction was conducted at ambient temperature to minimise volatilisation. (c) Upon work-up, the OsO_4 was reduced to a more water-soluble form using aqueous Na_2SO_3, and waste streams were handled as per local environmental regulations. (d) Although the chiral centre generated at C6 was destroyed in the next step, $(DHQ)_2PHAL$ provided a significant and useful rate acceleration; see Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. *J. Am, Chem. Soc.* **1988**, *110*, 1968. (e) Although we had ready access to this ligand and with it only being used at 0.4 mol%, cheaper ligands and modified reaction conditions may provide similar results (see Eames, J.; Mitchell, H. J.; Nelson, A.; O'Brien, P.; Warren, S.; Wyatt, P. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1095 and references therein). (f) One-pot dihydroxylation and oxidative cleavage of olefin **5** using $NaIO_4$ and catalytic $K_2OsO_2(OH)_4$ furnished aldehyde **4** in less than 20% yield.

(19) The addition of metalated derivatives of 1-bromo-2,2-dimethoxyethane to furfural, in an analogous fashion to that report Collins, P. W.; Kramer, S. W.; Gullikson, G. W. *J. Med. Chem.* **1987**, *30*, 1952 for a homologue of aldehyde **4** has shown promise..

(20) It is probable that the oily rather than solid nature of **4** meant that it was susceptible to aerobic oxidation. Therefore, on manufacturing scales where it was not appropriate to store **4** under argon and/or at low temperatures we preferred to use it soon after its preparation to avoid aerobic degradation.

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(22) This implies that the *n*-BuLi carbonyl 1,2-addition product in solution was a *gem*-dioxy species rather than a ketone and therefore resisted conversion to a tertiary alcohol or other products.

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(24) During chromatography (5% EtOAc/*n*-heptane/AcOH) of **9** contaminated with 12 mol% *trans*-**9**, the first eight fractions were more enriched with *trans*-**9** (18 mol% to 14 mol%) than the crude input. When the *cis*-isomer started to elute enriched (~9 mol% *trans*-isomer *trans*-**9**; factions 10−14) relative to the crude input, the HPLC purity fell to ~60% due to coelution of impurities.

(25) It was later found that it was better to replace K_2CO_3 with Cs_2CO_3, resulting in fewer equivalents of this base and of isopropyl iodide being required. DBU[21] can also be used.

(26) Laboratory experiments showed improvements in selectivity at lower temperatures. A scale-up run was conducted in-house (see Supporting Information for experimental details) in a liquid nitrogen-cooled reactor using 92% GC pure, precooled (−50 °C in a separate reservoir) aldehyde **4**. The Wittig reaction was conducted at −60 to −68 °C. Following esterification and column chromatography, olefin **8** was desilylated and analysed by HPLC showing that the desired *cis*-isomer had formed along with 9.5 mol% of the undesired *trans*-isomer. Although this confirmed that lower temperatures improved selectivity,

the improvement was too small to justify the use of specialised cryogenic equipment.

(27) *cis*-/*trans*-Selectivity was determined by HPLC analysis following conversion of analytical samples of **9** to **14**. No enrichment of either isomer occurred during the analytical sample preparation.

(28) The use of 5-chloropentanoic acid in place of 5-bromopentanoic acid (**11a**) in THF provided no improvement. When LiHMDS in THF was retested with 8% of the phosphoramide cosolvent, a very similar result in terms of *cis*-/*trans*-selectivity (9.5% *trans*-isomer), purity (96%), and yield (74%) was seen as when NaHMDS was used (entry 6). This indicated that the highly polar and Lewis basic solvent countered the negative impact of lithium ions.

(29) The best *cis*-/*trans*-selectivities (6.6 and 7.7 mol% *trans*-isomer, respectively) were obtained when KHMDS or *t*-BuOK was used in 10% HMPA in THF, but yields of less than 30% of olefin **8** were observed with low purities (38−53%) and large amounts (22−36%) of diene side-product **15**.

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(34) In related prostaglandin analogue syntheses using similar conditions, yields of 40−72% for the sequential rearrangement and isomerisation have been reported; see Clissold, D. W.; Craig, S. W.; Gadikota, R. R.; He, M.; Jurayj, J. F.; Kazerani, S.; Rannala, E.; Sharma, P. K. U.S. Patent 7,109,371, 2006 (and refs 31 and 33 herein). Addition of 0.1−110 mol% hydroquinone, conducting the reaction in the dark or under an inert atmosphere have so far proven unhelpful. A future solvent screen to eliminate the use of dioxane altogether, or to minimise its volume further, should focus on water-miscible ethers or alcohols (transesterification needs to be taken into account), and a reinvestigation of the use of acetone is required.

(35) The strategic combination of the Piancatelli rearrangement and an enzymatic resolution in the synthesis of nonracemic prostaglandin E_1- and E-type phytoprostanes has been reported previously.[33a,b] Those syntheses were demonstrated on scales of ≤30 g, unlike the multikilogram scale reported herein, and different furylcarbinols, 4-hydroxycyclopentenones, enzymes, and resolution conditions were used.

(36) A shortcoming of this protocol was that very long reaction times (4−9 days) were required.

(37) For further details see the Supporting Information.

(38) (a) Almost complete conversion of (*R*)-**16** occurred in 6 h providing a 97.4% ee of (*R*)-**17** leaving unreacted (*S*)-**16** with 87.6% ee when using 1.4 vol vinyl acetate and 5 vol MTBE and 5% w/w Lipase PS "Amano" IM at 50 °C. (*R*)-**16** was consumed within 3 h, providing 94.6% ee of (*R*)-**17** leaving (*S*)-**16** with 100% ee when using 25 w/w% of (w.r.t. *rac*-**16**) Lipase PS "Amano" IM in 8 vol vinyl acetate at 40 °C. (b) The experimental procedure reported herein is an adaptation of both Babiak and Wong's[16] method and Spur's[33a] modification. Whereas Babiak and Wong focused on producing highly enantioenriched (*S*)-alcohols, the approach reported in this contribution (demonstrated on a multikilogram scale) was directed towards obtaining more enriched (*R*)-acetate ((*R*)-**17**; 96.7% ee) at the expense of less enriched (*S*)-alcohol ((*S*)-**16**; 89.6% ee). The in-process control method that we used specified that the ee of (*R*)-**17** should not fall below 96.0%. Following the first resolution step, Spur's modification was adapted by utilisation of a purification step prior to guanidinolysis followed by subjecting the enantioenriched (*R*)-**16** to a second enzymatic resolution (Spur did not report a direct second resolution of their hydroxycyclopentenone without other manipulations being used). By contrast Babiak and Wong's second enzymatic resolution was conducted on the chromatographically separated (*R*)-hydroxycyclopentenone process stream.

(39) Although these were not the most expedient conditions identified in laboratory tests, they allowed adequate control on production scales where the several-hour turnaround time for sampling, analysis, and response to the analytical result could potentially lead to ee erosion due to over-reaction.

(40) A quantity of 0.46 kg unreacted (*R*)-**16** with 34% ee was recovered during chromatography. This was recycled by addition to feedstock *rac*-**16** of a subsequent campaign.

(41) A reviewer noted that the syntheses[7b,48] of prostaglandin analogues using (*R*)-**1** required protection of C11-O on two separate occasions. This was a necessity given the oxidative and anionic reaction conditions used in the total synthesis. It was also a necessity to free C11-OH for the enzymatic resolution stage. Despite this, some return in efficiency was achieved through (i) the first TBS protection step being combined with the allylation reaction and (ii) the final desilylations of C11-OTBS in travoprost and bimatoprost syntheses being conducted concurrently with deprotection of the ω-side chain.[7b] Corey reported[9] the use of two separate C11-O protecting groups (Ac and then THP) in his prototypical total synthesis of $PGF_{2\alpha}$.

(42) Although (*R*)-**1** was produced in the original process as a mixture of geometric isomers, this did not preclude its use in the synthesis of subkilogram quantities of prostaglandin analogues meeting the desired specification. The unwanted *trans*-isomer could be removed during chromatography (which is viable[21] given the small volume of these products) and/or crystallisation of the prostaglandin analogues.

(43) (a) $MeNH_2$, $BnNH_2$, DBU, piperidine, α-methyl-benzylamine, pyridine, and ammonia. (b) DMAP, DABCO, DBU, *N*-methylbenzylamine, *N*-methylmorpholine, Ph_2CHNH_2, Bn_2NH, benzylamine, 4-chlorobenzylamine, 4-bromobenzylamine, 4-methoxybenzylamine, L-arginine, L-lysine, and L-histidine. (c) Although the benzylamine salt was the first useful salt identified and reported by us,[7b] its 4-methoxy derivative was later found to possess superior properties. The benzylamine salt was obtained in disappointing yield with only a moderate enrichment of the *cis*-isomer (96.4/3.6 *cis*-/*trans*- ratio) being achieved after recrystallisation.

(44) Good solubility, stability (stable at 50 °C in vacuo and no exothermic events observed during DSC analysis) and melting point (mp 90.6−91.1 °C).

(45) At 55 °C HPLC purity of *N*-acetyl-4-methoxybenzylamine was detected at 6% at 1 h and 31% after 4 h.

(46) To obtain **9** of sufficient quality for desilylation and subsequent, direct crystallisation as its salt **2**, it was mixed with EtOAc/*n*-heptane, the insoluble oil layer was separated, and triphenylphosphine oxide was precipitated and filtered off upon dilution with *n*-heptane. Following extraction with water, 80−90% HPLC purity/70−80% HPLC potency assay **9** in almost quantitative recovery on a 0.5 kg scale was obtained.

(47) Cs_2CO_3 was preferred to K_2CO_3 (used in the synthesis of **8**) and required less isopropyl iodide and less base, and the esterification was more rapid.

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