



## The Meyer–Schuster rearrangement: a new synthetic strategy leading to prostaglandins and their drug analogs, Bimatoprost and Latanoprost

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### ABSTRACT

Gold(I) mediated Meyer–Schuster rearrangement for the installation of the ‘lower’ side chain of prostaglandins and their analogs has been developed. This Au-mediated rearrangement, featuring a low catalyst loading and mild reaction conditions, has been demonstrated to be an efficient alternative to the standard Horner–Wadsworth–Emmons reaction in prostaglandin chemistry. Moreover, the present results provide a new synthetic process leading to pharmacologically active prostanoids: Latanoprost and Bimatoprost, that continue to hold key positions in the anti-glaucoma drug market.

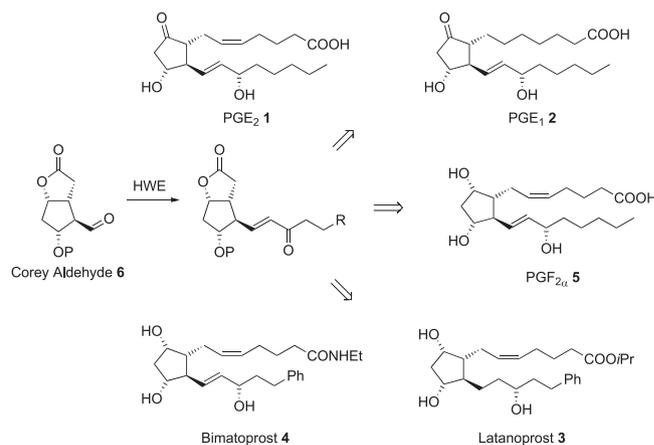
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### 1. Introduction

Recently, following the groundbreaking work of Hutchings,<sup>1</sup> there has been a dramatic increase in the number of published papers focusing on gold catalysis, a 21st Century ‘Gold Rush’. The numerous examples published describing transformations that were previously only possible with other reagents/catalysts or only in multi-step syntheses, have highlighted the benefits of gold catalysis that most often displays high activity and improved selectivity, can be carried out under mild reaction conditions, and remarkably presents a high degree of atom economy.<sup>2</sup> Concomitant with rapid developments in the flourishing golden catalysis arena, prostaglandins and their derivatives have encountered renewed interest due to their clinical utility.<sup>3</sup>

Indeed, prostaglandin E<sub>1</sub> **2** has been used in both impotence (Alprostadil) and maintenance of a patent ductus in newborns with congenital heart disease (Prostin VR), whilst PGE<sub>2</sub> **1** (Cervidil™, Prostin E<sub>2</sub>™) is currently used for cervical dilation during parturition or as an adjunct for cervical ripening and to induce uterine contractions in other obstetrical situations (Fig. 1).<sup>4</sup>

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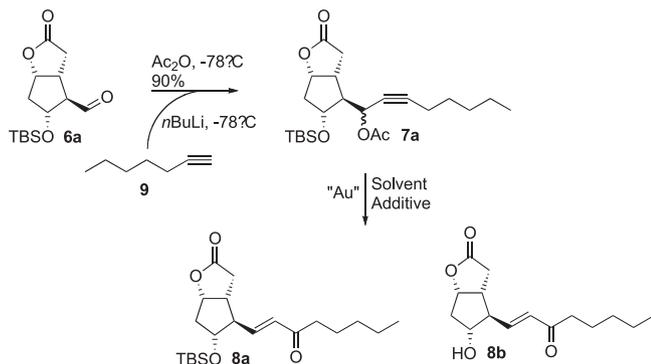
**Figure 1.** Schematic representation of Corey's method for the construction of the prostaglandin lower chain, involving the Horner–Wadsworth–Emmons (HWE) condensation.

On the other hand, Latanoprost **3** and Bimatoprost **4**, structurally related to PGF<sub>2α</sub> (**5**) are two prostaglandins analogs that continue to hold key positions in the anti-glaucoma drug market with a global annual sales of over \$1.5 billion (>€1 billion) (Fig. 1). Therefore, we considered it worthy to reconsider the venerable

prostaglandin chemistry in the light of some recent organic synthesis developments.

## 2. Results and discussion

Most synthetic procedures used to attain compounds **1–4**, including those patented, employ one of the known variants of the Corey method, in which the lower and upper side chains are sequentially attached to a derivative of the commercially available (–)-Corey-aldehyde/lactone **6** (Fig. 1). Thus, the Corey strategy involves, first, the installation of the lower side chain ( $\omega$ -chain) via a non atom-economical reaction, namely, a Horner–Wadsworth–Emmons (HWE) condensation of the Corey-aldehyde with a suitable keto-phosphonate.<sup>5a</sup> In addition, the HWE reaction is generally affected by other drawbacks, such as easy epimerization of labile stereogenic centers<sup>5b</sup> and, depending on the base used for deprotonation, formation of additional byproducts.<sup>5c</sup> Moreover, formation of one phosphate equivalent in the products to be disposed, makes the entire procedure scarcely ecofriendly. We envisioned that gold catalyzed Meyer–Schuster (M–S) rearrangement<sup>6</sup> of propargylic acetate **7** to the key enone **8**, could significantly improve the procedure of the  $\omega$ -chain installation, by overcoming most disadvantages of the classic HWE reaction (Scheme 1).<sup>7</sup>



Scheme 1. Meyer–Schuster approach to prostaglandin synthesis.

### 2.1. Prostaglandin synthesis

According to our gold mediated M–S strategy, syntheses of PGF<sub>2 $\alpha$</sub> , PGE<sub>2</sub>, and PGE<sub>1</sub>, which display the same  $\omega$ -side chain, being from

propargylic acetate **7a** as the common intermediate. Acetate **7a** was readily obtained in 90% overall yield by reaction of enantiopure (–)-O-TBS-protected Corey-aldehyde **6a** with the lithium salt of 1-heptyne **9** in THF at  $-78^\circ\text{C}$  for 30 min, followed by treatment with neat acetic anhydride and DMAP. In accordance with our initial synthetic plan, acetate **7a** was then exposed to a catalytic amount of [Au(PPh<sub>3</sub>)NTf<sub>2</sub>] (2 mol%), using the M–S protocol developed by Zhang and co-workers.<sup>6b</sup> However, carrying out the reaction in anhydrous 2-butanone, the expected enone **8a** was obtained in very low yield (10%), accompanied by extensive decomposition (Table 1, entry 1). With acetone as solvent, **8a** was obtained in 50% isolated yield, accompanied by some decomposition (entry 2).<sup>8</sup>

Table 1  
Optimization of Meyer–Schuster condition on propargyl acetate **7a**<sup>a</sup>

| Entry | Solvent                           | Au(I) (mol%) | Time (h) | Yield <sup>b</sup> <b>8a</b> (%) | Yield <sup>b</sup> <b>8b</b> (%) |
|-------|-----------------------------------|--------------|----------|----------------------------------|----------------------------------|
| 1     | Butanone (dry)                    | 2            | 12       | —                                | —                                |
| 2     | Acetone                           | 1            | 0.5      | 50                               | —                                |
| 3     | Butanone/H <sub>2</sub> O (150:1) | 2            | 7        | 50 (70) <sup>c</sup>             | 25                               |
| 4     | Butanone/H <sub>2</sub> O (100:1) | 1.5          | 16       | 68 (75) <sup>c</sup>             | 20                               |
| 5     | Butanone/H <sub>2</sub> O (100:1) | 1            | 19       | 70 (80) <sup>c</sup>             | 15                               |
| 6     | Butanone/H <sub>2</sub> O (80:1)  | 1            | 22       | 72 (80) <sup>c</sup>             | 10                               |
| 7     | Butanone/H <sub>2</sub> O (90:1)  | 0.7          | 24       | 75 (80) <sup>c</sup>             | 10                               |
| 8     | Butanone/H <sub>2</sub> O (90:1)  | 0.6          | 36       | 95 <sup>d</sup>                  | —                                |

<sup>a</sup> The reaction was carried out at 0.1 mmol scale.

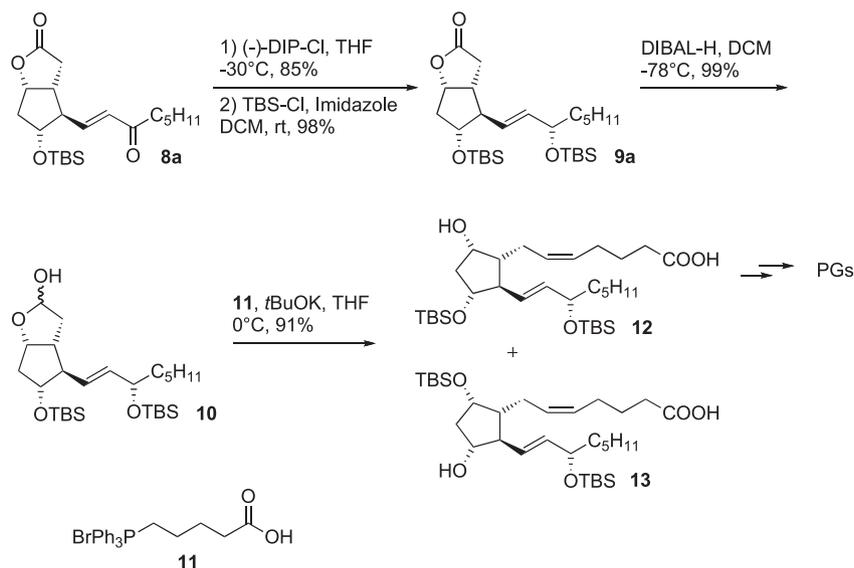
<sup>b</sup> Isolated yield.

<sup>c</sup> Yield of **8a** after silylation of **8b**.

<sup>d</sup> *t*-BuOH (5 equiv) was added.

When using wet butanone (butanone/H<sub>2</sub>O=150:1), we were delighted to obtain enone **8a** in 50% yield accompanied by the corresponding free alcohol **8b** in 25% yield (entry 3). After silylation of **8b** (TBS/Cl, CH<sub>2</sub>Cl<sub>2</sub>, 95% yield), the overall yield of enone **8a** increased to 70%. After further optimization (entries 4–7), we discovered that addition of *t*-BuOH (5 equiv) completely suppressed the desilylation side-reaction, affording the desired enone **8a**, [ $\alpha$ ]<sub>D</sub><sup>20</sup> –24.7 (c 1, CH<sub>2</sub>Cl<sub>2</sub>), in 95% yield. Furthermore, only 0.6% catalyst loading was necessary (entry 8) and, remarkably, the enone formed exhibited only the (*E*)-stereochemistry.

Enone **8a** was then elaborated to the *O*-TBS-protected allylic alcohol **9a** in two steps involving enantioselective diisopinocampheyl chloroborane (DIP-Cl) mediated enone reduction, followed by silylation of the corresponding alcohol (Scheme 2). In this conversion, DIP-Cl in THF at  $-30^\circ\text{C}$  afforded the corresponding allyl



Scheme 2. The 1,5-TBS shift issue.

alcohol in 82% isolated yield as a single (*S*)-stereoisomer,  $[\alpha]_D^{20} -19.4$  (*c* 0.71, CH<sub>2</sub>Cl<sub>2</sub>), which after silylation, afforded the key intermediate **9a** in 98% yield. With lactone **9a** in hand, each synthesis to the target prostanoids PGF<sub>2α</sub>, PGE<sub>2</sub>, and PGE<sub>1</sub> was expected to proceed readily via the classical prostanoid chemistry.<sup>9</sup>

In the follow-up, DIBAL-H reduction of **9a** provided lactol **10**, which upon Wittig condensation with (4-carboxybutyl)-triphenylphosphonium bromide **11** and *t*-BuOK in THF, delivered the expected product **12**, as a single *Z* stereoisomer (<sup>13</sup>C NMR), which, however, was accompanied by the corresponding 1,5-TBS migrated isomer **13** (**12/13**, 7:3).<sup>10</sup>

It must be pointed out that while formation of the free 11-OH **13** was of no consequence in the synthesis of PGF<sub>2α</sub>, synthesis of PGE<sub>2</sub> and PGE<sub>1</sub> required to suppress such 1,5-migration, since only compound **12** would readily deliver both prostanoids (cf. structures **1** and **2** with compounds **12** and **13**).

Indeed, fine tuning of the reaction conditions, involving the choice of the solvent, base, temperature, and ylide/lactol equivalents ratio, was necessary to prepare olefin **12** efficiently while avoiding the deleterious 1,5-TBS shift.<sup>11</sup>

In the event, under optimal conditions, lactol **10** was treated with the ylide generated from the phosphonium salt **11** and KHMDS (4.8 equiv) in THF/toluene (1:9), from -20 °C to -10 °C for 4 h, to deliver only the desired cyclopentanol **12** in 90% isolated yield, as a single (*5Z*)-stereoisomer (<sup>13</sup>C NMR). With a TBS-like protection securing the free C(11)-OH (prostanoid numbering) function,

syntheses of PGE<sub>2</sub>, PGF<sub>2α</sub> and PGE<sub>1</sub> proceeded straightforwardly in a few additional steps (Scheme 3).

PGE<sub>2</sub> (**1**),  $[\alpha]_D^{20} -71.4$  (*c* 0.7, EtOH<sub>abs</sub>), was readily obtained by Dess–Martin periodinane oxidation (DMP, CH<sub>2</sub>Cl<sub>2</sub>, 3 h, rt, 92%) of alcohol **12**, followed by aqueous HF mediated TBS deprotection (48% HF, MeCN, 5 h, rt, 90%).

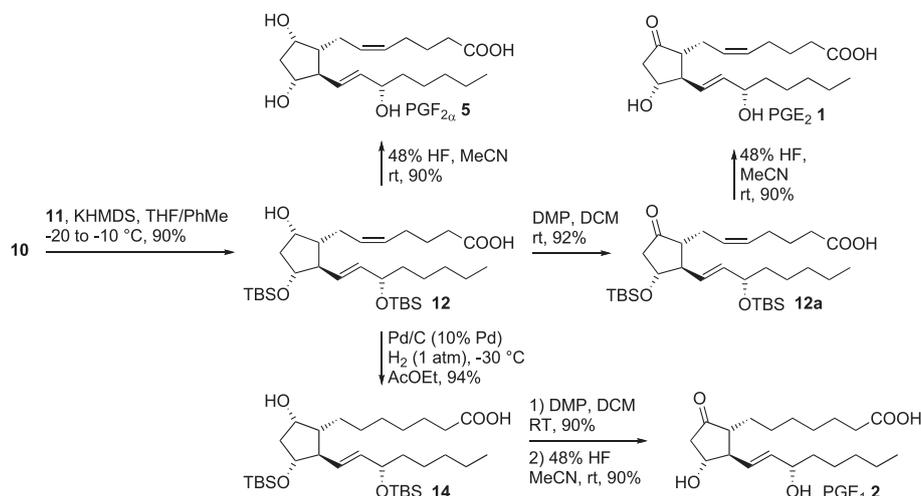
Exposure of cyclopentanol **12** to 48% HF in MeCN afforded directly PGF<sub>2α</sub> (**5**),  $[\alpha]_D^{20} 24.0$  (*c* 1, THF), in 90% isolated yield.

Finally, PGE<sub>1</sub> (**2**), was prepared by regioselective hydrogenation of the C(12)–C(13) double bond of **12** using Pd/C under H<sub>2</sub> (101.325 kPa) at -30 °C in EtOAc (94% yield). DMP oxidation of mono-saturated derivative **14**, followed by HFAq-promoted TBS deprotection, afforded expected PGE<sub>1</sub> in 81% overall yield  $[\alpha]_D^{20} -52$  (*c* 0.25, EtOH<sub>abs</sub>).

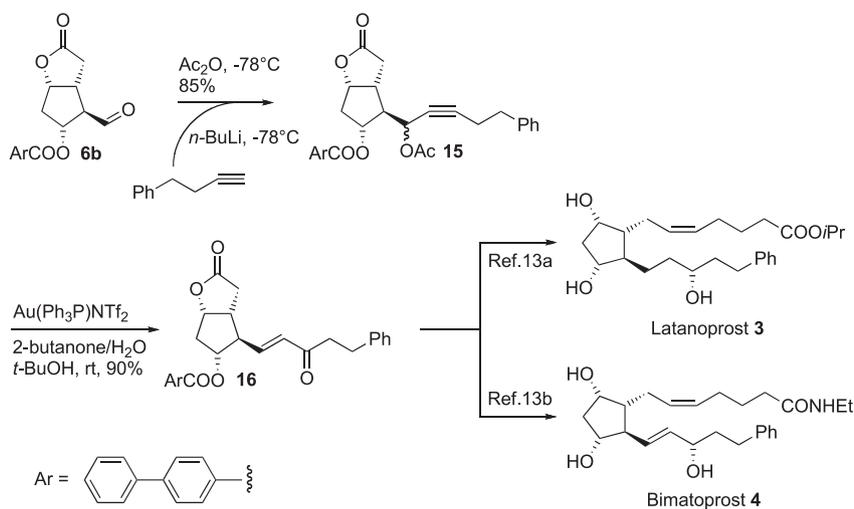
The <sup>1</sup>H and <sup>13</sup>C NMR spectra of compounds **1**, **2**, and **5** were in excellent agreement with literature values.<sup>12</sup>

## 2.2. Latanoprost and Bimatoprost synthesis

Having secured the classic prostanoids **1**, **2**, and **5** in a highly efficient and stereoselective manner, we envisaged an easy access to the important and widely used anti-glaucoma PGF<sub>2α</sub>-like drugs, Bimatoprost and Latanoprost, through Au-mediated propargylic ester rearrangement of intermediate **15**, readily prepared from commercially available Corey-aldehyde **6b** and 4-phenyl butyne (Scheme 4).



Scheme 3. Total syntheses of prostaglandins PGF<sub>2α</sub>, PGE<sub>1</sub>, and PGE<sub>2</sub>.



Scheme 4. New approach to the anti-glaucoma drugs Bimatoprost and Latanoprost.

Thus, M–S reaction of acetate **15** smoothly afforded the expected (*E*)-enone **16** in 90% isolated yield (0.7 mol% Au(PPh<sub>3</sub>)NTf<sub>2</sub>, 2-butanone/H<sub>2</sub>O=90:1, *t*-BuOH 5 equiv, 23 h, rt). With the key enone **16** in hand, synthesis of Latanoprost **3** and Bimatoprost **4** proceeded according to the literature.<sup>13</sup>

### 3. Conclusion

An innovative and expeditious route was established to synthesize the natural prostaglandins PGE<sub>1</sub>, PGE<sub>2</sub>, and PGF<sub>2α</sub>, and the potent anti-glaucoma drugs Latanoprost and Bimatoprost.

We anticipate that this straightforward Au-mediated rearrangement, featuring a low catalyst loading, mild reaction conditions, and complete stereoselectivity, is not only an efficient alternative to the standard Horner–Wadsworth–Emmons reaction in prostaglandin chemistry, but will likely find numerous applications in the synthesis of multi-functionalized compounds containing the enone group or moieties derived thereof.

## 4. Experimental section

### 4.1. General procedures

All solvents were of commercial quality and were purified by distillation over the drying agents indicated: THF (Na/benzophenone), CH<sub>2</sub>Cl<sub>2</sub>, hexane, Et<sub>3</sub>N (CaH<sub>2</sub>), toluene (Na/K). All other reagents were used as supplied. All moisture-sensitive reactions were carried out under a positive static atmosphere of Ar in flame-dried glassware. Syringes and needles for the transfer of reagents were dried at 140 °C and allowed to cool in a desiccator over P<sub>2</sub>O<sub>5</sub> before use. Routine monitoring of reactions was performed using silica gel 60 (0.25 mm), aluminum-supported TLC plates. Compounds were visualized by UV irradiation at a wavelength of 254 nm, or stained by exposure to a 0.5% soln of vanillin in H<sub>2</sub>SO<sub>4</sub>/EtOH, followed by charring. Flash column chromatography was performed on silica gel (40–63 μm). Yields are reported for isolated compounds with >96% purity established by NMR unless otherwise indicated. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker AVX-300 instrument at 300 MHz and 75 MHz, respectively, in the solvents indicated; chemical shifts (δ) are given in parts per million relative to TMS, coupling constants (*J*) in hertz. The solvent signals were used as references and the chemical shifts converted to the TMS scale (CDCl<sub>3</sub>: δ<sub>C</sub> 77.16; residual CHCl<sub>3</sub> in CDCl<sub>3</sub>: δ<sub>H</sub> 7.26; CD<sub>2</sub>Cl<sub>2</sub>: δ<sub>C</sub> 53.8; residual <sup>1</sup>H: δ<sub>H</sub> 5.32 ppm). The number of H-atoms attached to each C-atom (s=0H, d=1H, t=2H, q=3H) was determined by DEPT experiments. High resolution mass spectra were recorded on a Xevo Waters Q-TOF. Optical rotations were recorded on a digital Perkin–Elmer 241 polarimeter at 589 nm, concentration (*c*) in g/100 mL.

### 4.2. Synthesis of propargylic acetate **7a**

*n*-BuLi (1.6 M in hexane, 0.38 mL, 1.15 equiv) was added to a solution of 1-heptyne (0.063 mL, 0.66 mmol, 1.25 equiv) in dry THF (3 mL) at –78 °C. After stirring at –78 °C for 30 min aldehyde **6a** (97 mg, 0.53 mmol, 1 equiv) in dry THF (2 mL) was added via cannula, followed, after 30 min, by excess Ac<sub>2</sub>O (0.088 mL, 0.95 mmol, 1.8 equiv) and a catalytic amount of DMAP (4 mg). The resulting mixture was allowed to reach rt and stirred for 15 min, followed by the addition of a saturated solution of NH<sub>4</sub>Cl (5 mL). The layers were separated and the aqueous phase was extracted with Et<sub>2</sub>O (3×10 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (8:2) gave the desired diastereomeric mixture **7a** (218 mg, 90%) as a colorless oil, *R*<sub>f</sub>(hexane/

AcOEt, 9:1) 0.2; ν<sub>max</sub> (film) 2363, 1769, 1730 cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 5.46–5.42\* (m, 0.2H), 5.30 (m, 1H), 5.01–4.92 (m, 1H), 4.25 (q, *J*=4.9 Hz, 1H), 4.14\* (q, *J*=5.7 Hz, 0.2H), 2.92–2.81 (m, 2H), 2.73–2.56 (m, 1H), 2.30–2.18 (m, 4H), 2.11–2.01 (m, 4H), 1.58–1.47 (m, 2H), 1.35 (m, 4H), 0.90 (m, 12H), 0.10\* (s, 0.6H), 0.08\* (s, 0.6H), 0.07 (s, 3H), 0.06 (s, 3H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 176.8 (s), 169.7 (s), 169.4\* (s), 87.8 (s), 83.8 (d), 83.4\* (d), 75.8 (s), 75.0\* (d), 74.4 (d), 65.0\* (d), 63.3 (d), 59.2 (d), 58.0\* (d), 41.4 (t), 41.1\* (t), 38.8\* (d), 38.6 (d), 36.0 (t), 35.7\* (t), 31.1 (t), 28.0 (t), 25.6 (3×q), 22.1 (t), 21.0 (q), 18.6 (t), 17.8 (s), 13.9 (d), –4.7\* (q), –4.8 (q), –5.0\* (q), –5.1 (q), (\*) minor diastereoisomer peaks; HRMS-ESI, *m/z* for C<sub>23</sub>H<sub>38</sub>O<sub>5</sub>Si [M+H]<sup>+</sup> calcd 423.2567, found 423.2578.

### 4.3. Synthesis of enone **8a**

Propargylic acetate **7a** (43 mg, 0.101 mmol) was dissolved in butanone (2.2 mL) and water (0.022 mL) followed by *t*-BuOH (0.047 mL, 0.505 mmol) and Au(PPh<sub>3</sub>)NTf<sub>2</sub> (0.5 mg, 0.00067 mmol) (see Table 1, entry 8). The solution was stirred at rt for 36 h, Et<sub>3</sub>N (three drops) was then added and the volatiles was removed under reduced pressure, the residue was purified by flash chromatography on silica gel. Elution with hexanes/AcOEt (8:2) gave the enone **8a** (36 mg, 95%) as pale yellow oil, *R*<sub>f</sub>(hexane/AcOEt, 9:1) 0.25; [α]<sub>D</sub><sup>20</sup> –24.7 (c 1.0, CH<sub>2</sub>Cl<sub>2</sub>); ν<sub>max</sub> (film) 2929, 2857, 1777, 1769, 1698, 1673, 1632, 1471, 1251, 1165, 1126, 980, 837, 777 cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 6.61 (dd, *J*=15.8, 8.3 Hz, 1H), 6.19 (dd, *J*=15.8, 1.1 Hz, 1H), 4.98 (td, *J*=6.9, 2.8 Hz, 1H), 4.06 (q, *J*=6.2 Hz, 1H), 2.85–2.70 (m, 2H), 2.61–2.49 (m, 3H), 2.44–2.34 (m, 2H), 2.03 (ddd, *J*=14.7, 6.2, 2.8 Hz, 1H), 1.68–1.58 (m, 2H), 1.36–1.28 (m, 4H), 0.94–0.87 (m, 12H), 0.06 (s, 3H), 0.04 (s, 3H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 199.8 (s), 176.2 (s), 144.0 (d), 131.1 (d), 82.6 (d), 77.2 (d), 56.7 (d), 41.7 (d), 41.0 (t), 40.9 (t), 34.5 (t), 31.4 (t), 25.6 (3×q), 23.7 (t), 22.3 (t), 17.9 (s), 13.9 (d), –4.7 (q), –4.9 (q); HRMS-ESI, *m/z* for C<sub>21</sub>H<sub>36</sub>O<sub>4</sub>Si [M+H]<sup>+</sup> calcd 381.2461, found 381.2485.

### 4.4. Diastereoselective reduction of enone **8a**

(–)-DIP-Cl (2.3 M in heptane, 0.97 mL, 2.23 mmol) was added dropwise to a stirred solution of enone **8a** (170 mg, 0.447 mmol) at –30 °C in dry THF (3 mL). After 4 h NaHCO<sub>3</sub> (700 mg) and methanol (2 mL) were added and the reaction mixture was warmed at rt. The resulting suspension was stirred at the same temperature for 12 h, the solid was removed by filtration with a paper filter and the volatiles was removed under reduced pressure; the crude colorless oil was dissolved in DCM (5 mL) and 2% aqueous solution of NaHCO<sub>3</sub> (5 mL) was added, the organic layer was collected and the water phase was extracted with DCM (4×10 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. Elution with hexanes/AcOEt (6:4) gave the allylic alcohol **8c** (141 mg, 82%) as a colorless oil, *R*<sub>f</sub>(hexane/AcOEt, 9:1) 0.25; [α]<sub>D</sub><sup>20</sup> –19.43 (c 0.71, CH<sub>2</sub>Cl<sub>2</sub>); ν<sub>max</sub> (CHCl<sub>3</sub>) 3602, 1772 cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz, CDCl<sub>3</sub>) 5.56 (dd, *J*=15.5, 5.7 Hz, 1H), 5.45 (dd, *J*=15.5, 7.5 Hz, 1H), 4.93 (td, *J*=6.9, 2.3 Hz, 1H), 4.07 (q, *J*=6.1 Hz, 1H), 3.97 (q, *J*=5.8 Hz, 1H), 2.84–2.54 (m, 2H), 2.52–2.21 (m, 3H), 1.96 (ddd, *J*=14.7, 5.4, 2.2 Hz, 1H), 1.67–1.20 (m, 8H), 0.88 (m, 12H), 0.04 (s, 6H); δ<sub>C</sub> (75 MHz, CDCl<sub>3</sub>) 176.9 (s), 135.4 (d), 129.6 (d), 83.1 (d), 77.7 (d), 72.4 (d), 56.6 (d), 42.0 (d), 40.5 (t), 37.3 (t), 34.7 (t), 31.5 (t), 25.6 (3×q), 25.1 (t), 22.5 (t), 17.9 (s), 13.9 (q), –4.7 (q), –4.9 (q); HRMS-ESI, *m/z* for C<sub>21</sub>H<sub>38</sub>O<sub>4</sub>Si [M+H]<sup>+</sup> calcd 383.2617, found 383.2619.

### 4.5. Synthesis of silyl ether **9a**

Allylic alcohol **8c** (207 mg, 0.541 mmol) was dissolved in dry DCM (6 mL) and imidazole (110 mg, 1.62 mmol) was added

followed by TBS-Cl (86 mg, 0.57 mmol). The mixture was stirred at rt for 12 h then water (6 mL) was added followed by DCM (15 mL), the water phase was extracted with DCM (3 × 10 mL). The combined organic layers were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel. Elution with hexane/AcOEt (9:1) gave the allylic silyl ether **9a** (263 mg, 98 %) as a colorless oil, *R<sub>f</sub>* (hexane/AcOEt, 9:1) 0.2;  $[\alpha]_D^{20}$  –25.3 (c 1.5, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}$  (film) 1772, 1092 cm<sup>-1</sup>;  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 5.52 (dd, *J*=15.5, 5.5 Hz, 1H), 5.38 (dd, *J*=15.5, 7.5 Hz, 1H), 4.97 (td, *J*=7.0, 2.1 Hz, 1H), 4.13–3.92 (m, 2H), 2.85–2.58 (m, 2H), 2.56–2.36 (m, 2H), 2.34–2.17 (m, 1H), 2.06–1.92 (m, 1H), 1.58–1.13 (m, 8H), 0.89 (m, 21H), 0.14–0.11 (m, 12H);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>) 177.0 (s), 135.8 (d), 128.3 (d), 83.4 (d), 78.1 (d), 72.9 (d), 56.7 (d), 42.3 (d), 40.6 (t), 38.3 (t), 35.0 (t), 31.7 (t), 25.8 (3 × q), 25.7 (3 × q), 25.0 (t), 22.6 (t), 18.2 (s), 18.0 (s), 14.0 (q), –4.5 (q), –4.7 (q), –4.8 (q), –4.9 (q); HRMS-ESI, *m/z* for C<sub>27</sub>H<sub>52</sub>O<sub>4</sub>Si<sub>2</sub> [M+H]<sup>+</sup> calcd 497.3482, found 497.3476.

#### 4.6. Synthesis of lactol **10**

DIBAL-H (1 M in hexane, 175 μL, 0.175 mmol) was added dropwise to a stirred solution of lactone **9a** (83 mg, 0.167 mmol) at –78 °C in dry DCM (2 mL). After 30 min Rochelle's salt (8 mL, satd aq) was added and resulting two layers was vigorously stirred at rt for 4 h. The organic layer was then collected and the water phase was extracted with DCM (3 × 10 mL), the combined organic phases were dried over Na<sub>2</sub>SO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude lactol **10** was obtained in quantitative yield and used for the next step.

**4.6.1. Wittig olefination on lactol **10**: classical procedure.** Solid 4-carboxybutyl-triphenyl phosphonium bromide **11** (467 mg, 1.03 mmol, 4 equiv) was suspended in dry THF (5 mL) in a two-neck round-bottom flask under an argon atmosphere. To the suspension was added freshly sublimed potassium *tert*-butoxide (236 mg, 2.051 mmol, 8 equiv) portionwise at rt. After being stirred for 20 min, the solution became deeply orange, the ylide solution was cooled at 0 °C and a THF solution (1.5 mL) of crude lactol **10** (128 mg, 0.256 mmol) was added dropwise via cannula. Stirring was continued for an additional 4 h at 0 °C, and the reaction was quenched by adding a saturated aqueous solution of NH<sub>4</sub>Cl (15 mL) and acetic acid (0.127 mL, 1.05 equiv); Et<sub>2</sub>O (20 mL) was added to the mixture and the organic layer was separated, whereas the aqueous phase was extracted with Et<sub>2</sub>O (3 × 20 mL). The combined organic phases were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was then purified by flash chromatography on silica gel. Elution gradient (85:15) to (80:20) and finally (70:30) hexanes/AcOEt was used in order to obtain two compounds **12** (107 mg, 72%) and **13** (27 mg, 18%). Compound (**12**), *R<sub>f</sub>* (hexane/AcOEt, 7:3) 0.3;  $[\alpha]_D^{20}$  +21.36 (c 0.88, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}$  (film) 3518, 3457, 1710 cm<sup>-1</sup>;  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 5.61–5.23 (m, 4H), 4.13 (br s, 1H), 4.05 (m, 2H), 2.42–2.05 (m, 6H), 1.93–1.81 (m, 2H), 1.72 (p, *J*=7.5 Hz, 2H), 1.55–1.36 (m, 3H), 1.36–1.17 (m, 7H), 0.90 (m, 21H), 0.14–0.02 (m, 12H);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>) 178.8 (s), 134.4 (d), 130.7 (d), 129.7 (d), 129.0 (d), 80.0 (d), 74.7 (d), 73.2 (d), 56.4 (d), 51.8 (d), 42.8 (t), 38.4 (t), 33.4 (t), 31.8 (t), 26.6 (t), 26.5 (t), 25.9 (3 × q), 25.8 (3 × q), 25.0 (t), 24.6 (t), 22.6 (t), 18.3 (s), 17.8 (s), 14.0 (q), –4.3 (q), –4.6 (q), –4.7 (q), –4.9 (q); HRMS-ESI, *m/z* for C<sub>32</sub>H<sub>62</sub>O<sub>5</sub>Si<sub>2</sub> [M+H]<sup>+</sup> calcd 583.4214, found 583.4223. (**13**), *R<sub>f</sub>* (hexane/AcOEt, 7:3) 0.33;  $[\alpha]_D^{20}$  +21.65 (c 0.55, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}$  (film) 3520, 3466, 1719 cm<sup>-1</sup>;  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 5.56–5.32 (m, 4H), 4.26 (t, *J*=3.4 Hz, 1H), 4.08 (q, *J*=5.9 Hz, 1H), 3.90 (quintet, *J*=3.3 Hz, 1H), 2.39–2.31 (m, 3H), 2.20 (q, *J*=6.4 Hz, 2H), 2.10 (q, *J*=7.3 Hz, 2H), 1.99 (ddd, *J*=14.2, 6.8, 3.9 Hz, 1H), 1.75 (m, 3H), 1.51 (d, *J*=18.1 Hz, 3H), 1.35–1.24 (m, 8H), 0.93–0.85 (m, 21H), 0.12 (s, 3H), 0.09 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>) 178.0 (s), 134.4 (d),

131.3 (d), 129.6 (d), 128.9 (d), 78.9 (d), 74.6 (d), 73.6 (d), 56.6 (d), 51.4 (d), 43.2 (t), 38.2 (t), 33.2 (t), 31.8 (t), 26.5 (t), 26.1 (t), 25.9 (3 × q), 25.8 (3 × q), 25.1 (t), 24.5 (t), 22.6 (t), 18.3 (s), 18.0 (s), 14.0 (q), –4.2 (q), –4.4 (q), –4.7 (q), –5.1 (q); HRMS-ESI, *m/z* for C<sub>32</sub>H<sub>62</sub>O<sub>5</sub>Si<sub>2</sub> [M+H]<sup>+</sup> calcd 583.4214, found 583.4199.

**4.6.2. Wittig olefination on lactol **10**: optimized procedure, no scrambling.** KHMDS (8.9 equiv, 2.9 mL, 0.5 M in toluene) was added under an Ar atmosphere to a stirred suspension of 4-carboxybutyl-triphenyl phosphonium bromide **11** (4.5 equiv, 0.247 g) in dry THF (1.5 mL). After 45 min the orange solution of the resulting ylide was cooled at –20 °C and dry toluene (4 mL) was added followed by toluene solution (1.5 mL) of crude lactol **10** (83 mg, 0.166 mmol). The resulting reaction mixture was warmed at –10 °C and stirred at this temperature for 4 h. The reaction was quenched by adding a saturated aqueous solution of NH<sub>4</sub>Cl (15 mL) and acetic acid (0.127 mL, 1.05 equiv); Et<sub>2</sub>O (20 mL) was added to the mixture and the organic layer was separated, whereas the aqueous phase was extracted with Et<sub>2</sub>O (3 × 20 mL). Combined organic phases were dried over MgSO<sub>4</sub>, filtered, and concentrated under reduced pressure. The crude was then purified by flash chromatography on silica gel. Elution with hexanes/AcOEt (8:2) gave the hydroxyacid **12** (89 mg, 90 %) as pale yellow oil, *R<sub>f</sub>*=0.25 (hexane/AcOEt, 8:2). <sup>13</sup>C NMR show the presence of the single compound **12**. Characterization data of **12** described in the previous reaction.

#### 4.7. Oxidation of hydroxyacid **12**

Dess–Martin periodinane (24 mg, 0.055 mmol) was added in one portion to a solution of the hydroxyacid **12** (28 mg, 0.048 mmol) in dry DCM (4 mL) at rt. The solution was stirred for 2 h and then quenched with dry Et<sub>2</sub>O (8 mL). The resulting suspension was filtered over short pad of silica washed with 25 mL 1:1 (dry)-hexane/(dry)-Et<sub>2</sub>O. The solvents were removed under reduced pressure *without heating over 30 °C*. The crude ketone was purified by flash chromatography on silica gel. Elution with hexane/AcOEt (8:2) gave pure ketone **12a** as pale yellow oil (27 mg, 95%), *R<sub>f</sub>* (hexane/AcOEt) 0.24;  $[\alpha]_D^{20}$  –49.1 (c 0.82, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}$  (film) 2955, 2929, 2857, 1745, 1709, 1458, 1362, 1255, 1070, 1006, 968, 836, 776 cm<sup>-1</sup>;  $\delta_H$  (300 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 5.69–5.50 (m, 2H), 5.49–5.32 (m, 2H), 4.25–3.90 (m, 2H), 2.66 (ddd, *J*=18.1, 6.9, 0.8 Hz, 1H), 2.55–2.23 (m, 5H), 2.21–2.00 (m, 5H), 1.71 (quintet, *J*=7.4 Hz, 2H), 1.57–1.42 (m, 2H), 1.38–1.21 (m, 5H), 1.01–0.80 (m, 21H), 0.32–0.25 (m, 12H);  $\delta_C$  (75 MHz, CD<sub>2</sub>Cl<sub>2</sub>) 214.8 (s), 178.6 (s), 136.1 (d), 130.1 (d), 128.4 (d), 126.6 (d), 72.8 (d), 72.3 (d), 53.5 (d), 52.4 (d), 47.3 (t), 38.2 (t), 32.9 (t), 31.5 (t), 26.2 (t), 25.3 (3 × q), 25.2 (3 × q), 24.7 (2 × t), 24.1 (t), 22.3 (t), 17.7 (s), 17.5 (s), 13.5 (q), –4.9 (q), –5.2 (q), –5.2 (q), –5.3 (q); HRMS-ESI, *m/z* for C<sub>32</sub>H<sub>60</sub>O<sub>5</sub>Si<sub>2</sub> [M+H]<sup>+</sup> calcd 581.4057, found 581.4076.

#### 4.8. Synthesis of compound **14**

The hydroxyacid **12** (51 mg, 0.088 mmol) was dissolved in AcOEt (5 mL) and Pd/C (10% w/w; 7 mg) was added. The suspension was cooled at –30 °C under hydrogen atmosphere and vigorous stirring. After 2 h the catalyst was removed by filtration and the solution was concentrated under vacuo. The crude product was purified by flash chromatography on silica gel. Elution with hexane/AcOEt (8:2) gave pure **14** (48 mg, 94%), *R<sub>f</sub>* (hexane/AcOEt, 7:3) 0.33;  $[\alpha]_D^{20}$  +5 (c 0.36, CH<sub>2</sub>Cl<sub>2</sub>);  $\nu_{\max}$  (film) 3521, 3462, 1712 cm<sup>-1</sup>;  $\delta_H$  (300 MHz, CDCl<sub>3</sub>) 5.56 (dd, *J*=15.3, 5.7 Hz, 1H), 5.46 (dd, *J*=15.3, 8.4 Hz, 1H), 4.24 (br s, 1H), 4.18–4.12 (m, 2H), 2.45 (t, *J*=7.5 Hz, 2H), 2.34 (td, *J*=8.1, 1.3 Hz, 1H), 1.97 (br s, 2H), 1.77–1.70 (m, 3H), 1.62–1.39 (m, 16H), 1.03 (m, 21H), 0.19–0.14 (m, 12H);  $\delta_C$  (75 MHz, CDCl<sub>3</sub>) 178.8 (s), 134.0 (d), 131.1 (d), 81.2 (d), 74.9 (d), 73.2 (d), 57.0 (d), 51.8 (d), 42.9 (t), 38.5 (t), 33.9 (t), 31.8 (t), 29.5 (t), 29.0 (t), 28.9 (t), 28.2 (t),

25.9 (3×q), 25.8 (3×q), 25.0 (t), 24.7 (t), 22.6 (t), 18.3 (s), 17.8 (s), 14.0 (d), −4.3 (q), −4.6 (q), −4.7 (q), −4.9 (q); HRMS-ESI,  $m/z$  for  $C_{32}H_{64}O_5Si_2$   $[M+H]^+$  calcd 585.4370, found 585.4388.

#### 4.9. Oxidation of hydroxyacid **14**

Dess–Martin periodinane (28 mg, 0.066 mmol) was added in one portion to a solution of the hydroxyacid **14** (33 mg, 0.057 mmol) in dry DCM (2 mL) at rt. The solution was stirred for 2 h and then quenched with dry  $Et_2O$  (4 mL). The resulting suspension was filtered over short pad of silica washed with 15 mL of 1:1 (dry)-hexane/(dry)- $Et_2O$ . The solvents were removed under reduced pressure without heating over 30 °C. The crude ketone was purified by flash chromatography on silica gel. Elution with hexane/AcOEt (8:2) gave pure ketone **14a** as pale yellow oil (30 mg, 90%),  $R_f$  (hexane/AcOEt) 0.25;  $[\alpha]_D^{20}$  −45.2 (c 0.5,  $CH_2Cl_2$ );  $\nu_{max}$  (film) 2950, 2931, 2853, 1746, 1707, 1462, 1361, 1253, 1075, 1002, 966, 833, 780  $cm^{-1}$ ;  $\delta_H$  (300 MHz,  $CD_2Cl_2$ ) 5.67–5.50 (m, 2H), 4.18–4.05 (m, 2H), 2.64 (ddd,  $J=18.2, 7.0, 1.2$  Hz, 1H), 2.46 (dt,  $J=11.1, 7.5$  Hz, 1H), 2.36 (td,  $J=7.5, 2.2$  Hz, 2H), 2.18 (ddd,  $J=18.2, 8.3, 2.4$  Hz, 1H), 1.96 (dt,  $J=11.1, 5.6$  Hz, 1H), 1.68–1.23 (m, 18H), 0.94–0.90 (m, 21H), 0.10–0.06 (m, 12H);  $\delta_C$  (75 MHz,  $CD_2Cl_2$ ) 215.4 (s), 178.9 (s), 135.8 (d), 128.7 (d), 72.9 (d), 72.4 (d), 53.4 (d), 53.2 (d), 47.2 (t), 38.2 (t), 33.5 (t), 31.5 (t), 29.1 (t), 28.5 (t), 27.4 (t), 26.4 (t), 25.3 (3×q), 25.2 (3×q), 24.7 (t), 24.3 (t), 22.3 (t), 17.7 (s), 17.5 (s), 13.5 (d), −4.9 (q), −5.2 (q), −5.3 (q), −5.3 (q); HRMS-ESI,  $m/z$  for  $C_{32}H_{62}O_5Si_2$   $[M+H]^+$  calcd 583.4214, found 583.4210.

#### 4.10. Synthesis of PGE<sub>2</sub> **1**

Aqueous HF (48%, 0.111 mL) was added to a stirred solution of ketone **12a** (45 mg, 0.077 mmol) in MeCN (4.5 mL) in a PE test tube. After 6 h phosphate buffer (pH 6.8, 8 mL) was added. The layers were separated and the aqueous phase was extracted with EtOAc (6×6 mL). The combined organic phases were washed with brine, dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with EtOAc/MeOH (90:10) gave pure PGE<sub>2</sub> **1** (23 mg, 86%) as a colorless oil,  $R_f$  (3% MeOH in AcOEt) 0.2;  $[\alpha]_D^{20}$  −71.4 (c 0.7, EtOH);  $\nu_{max}$  (film) 3379, 2931, 2856, 1732, 1709, 1398, 1204, 1158, 1120, 1084, 1033, 973  $cm^{-1}$ ;  $\delta_H$  (300 MHz,  $CD_3CN$ ) 5.59 (dd,  $J=3.7, 2.6$  Hz, 2H), 5.48–5.04 (m, 2H), 4.04 (q,  $J=9.0$  Hz, 2H), 2.63 (dd,  $J=18.3, 7.4$  Hz, 1H), 2.41–2.19 (m, 5H), 2.18–1.87 (m, 5H), 1.70–1.56 (m, 2H), 1.54–1.19 (m, 7H), 1.04–0.77 (m, 3H);  $\delta_C$  (75 MHz,  $CD_3CN$ ) 215.7 (s), 175.0 (s), 137.5 (d), 131.4 (d), 131.0 (d), 128.0 (d), 72.9 (d), 72.6 (d), 55.0 (d), 53.9 (d), 47.3 (t), 38.3 (t), 33.6 (t), 32.5 (t), 27.2 (t), 26.0 (t), 25.6 (t), 25.5 (t), 23.4 (t), 14.3 (q); HRMS-ESI,  $m/z$  for  $C_{20}H_{32}O_5$   $[M+H]^+$  calcd 353.2327, found 353.2353.

#### 4.11. Synthesis of Alprostil PGE<sub>1</sub> **2**

Aqueous HF (48%, 0.111 mL) was added to a stirred solution of ketone bis-silyl ether **14** (45 mg, 0.077 mmol) in MeCN (4.5 mL) in a PE test tube. After 6 h phosphate buffer (pH 6.8, 8 mL) was added. The layers were separated and the aqueous phase was extracted with EtOAc (6×6 mL). The combined organic phases were washed with brine, dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with EtOAc/MeOH (90:10) gave pure PGE<sub>1</sub> **2** (24.5 mg, 90%) as a colorless oil,  $R_f$  (3% MeOH in AcOEt) 0.2;  $[\alpha]_D^{20}$  −52 (c 0.25, EtOH);  $\nu_{max}$  (film) 3369, 2937, 2860, 1733, 1710, 1391, 1206, 115, 1120, 1084, 1033, 973  $cm^{-1}$ ;  $\delta_H$  (300 MHz,  $CD_3CN$ ) 5.65–5.51 (m, 2H), 4.06–3.98 (m, 2H), 2.61 (dd,  $J=17.1, 6.3$  Hz, 1H), 2.39–1.82 (m, 7H), 1.63–1.20 (m, 19H), 0.91 (br s, 3H);  $\delta_C$  (75 MHz,  $CD_3CN$ ) 216.2 (s), 175.1 (s), 137.5 (d), 131.5 (d), 72.9

(d), 72.5 (d), 54.9 (d), 54.9 (d), 47.1 (t), 38.3 (t), 34.1 (t), 32.5 (t), 30.0 (t), 29.5 (t), 28.3 (t), 27.3 (t), 25.9 (t), 25.5 (t), 23.4 (t), 14.3 (q); HRMS-ESI,  $m/z$  for  $C_{20}H_{34}O_5$   $[M+H]^+$  calcd 355.2484, found 355.2467.

#### 4.12. Synthesis of PGF<sub>2 $\alpha$</sub> **5**

Aqueous HF (48%, 0.096 mL) was added to a stirred solution of bis-silyl ether **12** (30 mg, 0.051 mmol) in MeCN (2 mL) in a PE test tube. After 7 h phosphate buffer (pH 6.8, 6 mL) was added. The layers were separated and the aqueous phase was extracted with EtOAc (6×5 mL). The combined organic phases were washed with brine, dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with EtOAc/MeOH (90:10) gave pure PGF<sub>2 $\alpha$</sub>  **5** (16.3 mg, 90%) as a colorless oil,  $R_f$  (3% MeOH in AcOEt) 0.2;  $[\alpha]_D^{20}$  +25.3 (c 0.7, THF);  $\nu_{max}$  (film) 3383, 3004, 1742  $cm^{-1}$ ;  $\delta_H$  (300 MHz,  $CD_3COCD_3$ ) 5.60–5.46 (m, 3H), 5.41–5.28 (m, 1H), 4.12 (td,  $J=5.2, 1.6$  Hz, 1H), 4.04 (dd,  $J=12.0, 5.7$  Hz, 1H), 3.87 (ddd,  $J=7.8, 6.0, 4.5$  Hz, 1H), 2.42–1.99 (m, 8H), 1.74–1.58 (m, 3H), 1.57–1.18 (m, 9H), 0.90 (t,  $J=6.8$  Hz, 3H);  $\delta_C$  (75 MHz,  $CD_3COCD_3$ ) 174.6 (s), 136.1 (d), 132.9 (d), 130.5 (d), 129.7 (d), 78.1 (d), 72.9 (d), 72.2 (d), 56.2 (d), 51.2 (d), 44.4 (t), 38.5 (t), 33.6 (t), 32.6 (t), 27.2 (t), 26.1 (t), 26.0 (t), 25.6 (t), 23.3 (t), 14.3 (q); HRMS-ESI,  $m/z$  for  $C_{20}H_{34}O_5$   $[M+H]^+$  calcd 355.2484, found 355.2501.

#### 4.13. Synthesis of propargylic acetate **15**

$n$ -BuLi (1.6 M in hexane, 0.153 mL, 1.15 equiv) was added to a solution of 4-phenyl-1-butyne (0.038 mL, 0.26 mmol, 1.25 equiv) in dry THF (3 mL) at −78 °C. After stirring at −78 °C for 30 min aldehyde **6b** (75 mg, 0.21 mmol, 1 equiv) in dry THF (2 mL) was added via cannula, followed, after 30 min, by excess  $Ac_2O$  (0.036 mL, 0.38 mmol, 1.8 equiv) and a catalytic amount of DMAP (2 mg). The resulting mixture was allowed to reach rt and stirred for 15 min, followed by the addition of a saturated solution of  $NH_4Cl$  (5 mL). The layers were separated and the aqueous phase was extracted with  $Et_2O$  (3×10 mL). The combined organic phases were dried over  $MgSO_4$ , filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography on silica gel. Elution with hexane/EtOAc (8:2) gave the desired diastereomeric mixture **15** (93 mg, 85%) as a colorless oil,  $R_f$  (1:1 hexane/AcOEt) 0.4;  $\nu_{max}$  (film) 2360, 1770, 1731, 1715  $cm^{-1}$ ;  $\delta_H$  (300 MHz,  $CDCl_3$ ) 8.07 (dd,  $J=8.3, 2.3$  Hz, 2H), 7.70–7.62 (m, 4H), 7.51–7.41 (m, 3H), 7.35–7.21 (m, 5H), 5.53 (t,  $J=5.6$  Hz, 1H), 5.48–5.44 (m), 5.32–5.26 (m, 1H), 4.88 (dt,  $J=13.0, 6.4$  Hz, 1H), 2.86–2.79 (m, 4H), 2.61–2.42 (m, 5H), 2.26 (m, 1H), 2.11 (s, 3H);  $\delta_C$  (75 MHz,  $CDCl_3$ ) 176.3 (s), 176.2 (s), 169.6 (s), 169.5 (s), 165.6 (s), 165.5 (s), 146.0 (s), 146.0 (s), 140.0 (s), 139.9 (s), 130.2 (d), 128.9 (d), 128.4 (d), 128.2 (d), 128.2 (d), 127.3 (d), 127.1 (d), 126.5 (d), 87.7 (s), 87.4 (s), 84.4 (d), 84.1 (d), 76.8 (d), 76.6 (d), 75.9 (s), 75.6 (s), 64.5 (d), 63.8 (d), 56.2 (d), 55.6 (d), 40.0 (d), 39.9 (d), 38.9 (t), 38.2 (t), 36.1 (t), 36.0 (t), 34.3 (t), 34.2 (t), 20.9 (d), 20.9 (d), 20.5 (t), 20.4 (q); HRMS-ESI,  $m/z$  for  $C_{33}H_{30}O_6$   $[M+H]^+$  calcd 523.2120, found 523.2111.

#### 4.14. Synthesis of enone **16**

Propargylic acetate **15** (72 mg, 0.138 mmol) was dissolved in butanone (3 mL) and water (0.03 mL) followed by  $t$ -BuOH (0.047 mL, 0.505 mmol), than was added  $Au(PPh_3)NTf_2$  (0.7 mol %, 0.7 mg, 0.00096 mmol). The solution was stirred at rt for 23 h, than  $Et_3N$  (three drops) was added and the volatiles were removed under reduced pressure, the residue was purified by flash chromatography on silica gel. Elution with hexanes/AcOEt (8:2) gave the enone **16** (60 mg, 90%) as a white solid, mp 130–131 °C,  $R_f$  (hexane/AcOEt, 7:3) 0.17;  $[\alpha]_D^{20}$  −120.8 (c 1.0,  $CH_3CN$ );  $\nu_{max}$  (Nujol) 1771,

1713, 1269, 1178, 1102, 1070, 858, 748  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 8.17 (d,  $J=8.6$  Hz, 2H), 7.79 (d,  $J=8.6$  Hz, 2H), 7.77–7.72 (m, 2H), 7.62–7.52 (m, 3H), 7.42–7.29 (m, 5H), 6.78 (dd,  $J=15.9$ , 7.6 Hz, 1H), 6.34 (dd,  $J=15.8$ , 0.8 Hz, 1H), 5.43 (q,  $J=5.7$  Hz, 1H), 5.21 (t,  $J=6.2$  Hz, 1H), 3.08–2.94 (m, 7H), 2.78–2.59 (m, 2H), 2.48–2.40 (m, 1H);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 198.6 (s), 175.8 (s), 165.7 (s), 146.2 (s), 143.0 (d), 140.8 (s), 139.8 (s), 131.4 (d), 130.2 (d), 128.9 (d), 128.5 (d), 128.4 (d), 128.2 (d), 127.9 (s), 127.3 (d), 127.2 (d), 126.2 (d), 83.1 (d), 78.5 (d), 54.1 (d), 42.5 (d), 42.5 (t), 37.8 (t), 34.9 (t), 29.9 (t); HRMS-ESI,  $m/z$  for  $\text{C}_{31}\text{H}_{28}\text{O}_5$   $[\text{M}+\text{H}]^+$  calcd 481.2015, found 481.2020.

#### 4.15. Synthesis of Latanoprost 3

To a solution of (9S,11R,15R)-9,11,15-trihydroxy-17-phenyl-18,19,20-trinor-5Z-prostenoic acid<sup>13b</sup> (200 mg, 0.52 mmol) in DMF (5 mL) is added  $\text{Me}_2\text{CHI}$  (178 mg, 1.04 mmol) and  $\text{Cs}_2\text{CO}_3$  (256 mg, 0.77 mmol), the solution is stirred for 14 h at rt, than poured into stirred of 3% aqueous citric acid (2 g) at 5 °C. The mixture is extracted with MTBE (3×5 mL). The combined organic layers were washed with 8% aqueous  $\text{NaHCO}_3$  (10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (heptane/IPA 97:3 then 8:2) giving Latanoprost 3 (161 mg, 72%) as a colorless oil,  $R_f$  (AcOEt) 0.3;  $[\alpha]_{\text{D}}^{20} +32.7$  (c 1.03,  $\text{CH}_3\text{CN}$ ), [lit.<sup>13a</sup>  $[\alpha]_{\text{D}}^{20} +31.6$  (c 0.91,  $\text{CH}_3\text{CN}$ )];  $\nu_{\text{max}}$  (film) 3378, 2979, 2933, 1729, 1496, 1454, 1374, 1312, 1248, 1180, 1108, 1041, 966, 822  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.32–7.17 (m, 5H), 5.52–5.36 (m, 2H), 5.01 (septet,  $J=6.3$  Hz, 1H), 4.18 (d,  $J=2.6$  Hz, 1H), 3.96 (d,  $J=2.5$  Hz, 1H), 3.68 (quintet,  $J=6.1$  Hz, 1H), 2.75 (m, 2H), 2.39–2.12 (m, 7H), 1.88–1.32 (m, 13H), 1.24 (d,  $J=6.3$  Hz, 6H);  $\delta_{\text{C}}$  (75 MHz,  $\text{CDCl}_3$ ) 173.5 (s), 142.1 (s), 129.5 (d), 129.3 (d), 128.4 (4xd), 125.8 (d), 78.7 (d), 74.6 (d), 71.3 (d), 67.6 (d), 52.8 (d), 51.8 (d), 42.5 (t), 39.0 (t), 35.7 (t), 34.0 (t), 32.1 (t), 29.6 (t), 26.9 (t), 26.6 (t), 24.9 (t), 21.8 (2xq); HRMS-ESI,  $m/z$  for  $\text{C}_{26}\text{H}_{40}\text{O}_5$   $[\text{M}+\text{H}]^+$  calcd 433.2954, found 433.2978.

#### 4.16. Synthesis of Bimatoprost 4

A solution of (9S,11R,15S)-9,11,15-trihydroxy-17-phenyl-18,19,20-trinor-5Z,13E prostadienoate<sup>13b</sup> (150 mg, 0.37 mmol) and 70 % aqueous  $\text{EtNH}_2$  (10 mL) was stirred for 60 h at rt. When the reaction was completed the solution was concentrated in vacuo to half of the starting volume, neutralized with 2 M aqueous  $\text{NaHSO}_4$  and extracted with AcOEt (5×20 mL). The combined organic layers were washed with brine (2×10 mL), dried over  $\text{Na}_2\text{SO}_4$ , filtered, and concentrated in vacuo. The residue was treated with  $\text{Et}_2\text{O}$  (5 mL) and the precipitate was filtered off and dried under reduced pressure to give Bimatoprost 4 (122 mg, 80%) as a white solid, mp 67–68 °C;  $R_f$  (AcOEt) 0.1;  $[\alpha]_{\text{D}}^{20} +32.7$  (c 0.33,  $\text{CH}_2\text{Cl}_2$ );  $\nu_{\text{max}}$  (Nujol) 3412, 3325, 2918, 1619, 1545, 1496, 1455, 1376, 1054, 1026, 975, 920, 722, 697  $\text{cm}^{-1}$ ;  $\delta_{\text{H}}$  (300 MHz,  $\text{CDCl}_3$ ) 7.30–7.18 (m, 5H), 5.95 (t,  $J=5.3$  Hz, 1H), 5.64–5.31 (m, 4H), 4.17–4.05 (m, 2H), 3.92 (t,  $J=8.5$  Hz, 1H), 3.27–3.18 (m, 2H), 2.76–2.60 (m, 2H), 2.39–1.57 (m, 13H), 1.46 (tt,  $J=10.2$ , 4.8 Hz, 1H), 1.10 (t,  $J=7.3$  Hz, 3H);  $\delta_{\text{C}}$  (75 MHz,

$\text{CDCl}_3$ ) 173.3 (s), 142.0 (s), 135.1 (d), 133.2 (d), 129.6 (d), 129.1 (d), 128.4 (2×d), 128.3 (2×d), 125.7 (d), 77.6 (d), 72.2 (d), 72.2 (d), 55.4 (d), 50.1 (d), 42.9 (t), 38.7 (t), 35.8 (t), 34.3 (t), 31.8 (t), 26.6 (t), 25.6 (t), 25.3 (t), 14.7 (q); HRMS-ESI,  $m/z$  for  $\text{C}_{25}\text{H}_{37}\text{NO}_4$   $[\text{M}+\text{H}]^+$  calcd 416.2801, found 416.2793.

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#### Supplementary data

Supplementary data associated with this article, includes copy of  $^1\text{H}$  and  $^{13}\text{C}$  NMR. Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.07.069. These data include MOL files and InChIKeys of the most important compounds described in this article.

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