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Enantio- and Stereospecific Syntheses of 15(*R*)-Me-PGD$_2$, A Potent and Selective DP$_2$−Receptor Agonist

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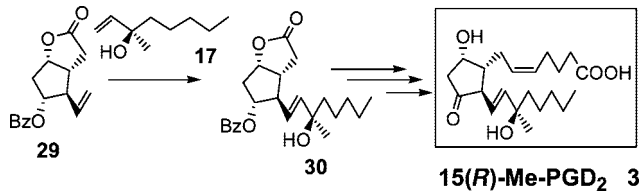

The first total synthesis of 15(*R*)-Me-PGD$_2$ **3** is reported. The synthesis is based on the enantioselective and stereospecific syntheses of synthon **17** and its attachment to the five-membered ring by a olefin cross metathesis reaction. This approach permits the introduction of a side chain with a predetermined stereogenic center into the prostanoid ring, resulting in the synthesis of 15*R*-methyl prostaglandin D$_2$ and allows rapid access to other prostanoids.

Introduction

PGD$_2$ **1** (Figure 1) is a member of the prostaglandin family. It was initially thought to exert its biological activity through a single dedicated G-protein-coupled receptor (the DP receptor) that is coupled to G$_s$, resulting in elevation of intracellular c-AMP levels, which through activation of protein kinase A promotes smooth muscle relaxation and inhibits platelet aggregation.

Recently, we[1] and others[2] have simultaneously and independently discovered a new PGD$_2$ receptor that we termed the DP$_2$ receptor (also known as CRTH2, chemoattractant receptor-homologous molecule expressed on Th2 cells). We now refer to the original DP receptor as the DP$_1$ receptor. Infiltration of eosinophils into the lungs during an asthma attack is the hallmark of the disease and most likely the cause of the inflammatory component of the late-phase asthmatic response. The DP$_2$ receptor mediates the chemotactic effect of PGD$_2$ on eosinophils, basophils, and the Th2 cells.

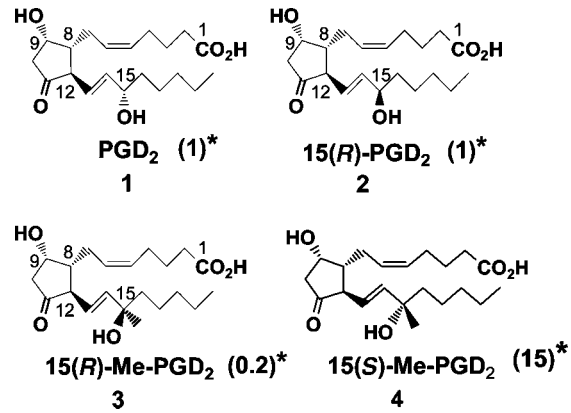

FIGURE 1. PGD$_2$ derivatives. Values in parentheses are the relative potencies in the CD11b assay PGD$_2$ being 1.

Since PGD$_2$ activates both DP$_1$ and DP$_2$ receptors, the availability of selective DP$_2$ receptor agonists is critical to clearly define the biological effects mediated by this receptor and its pathophysiological role. In a structure−activity study,[3] we previously identified 15(*R*)-Me-PGD$_2$ **3** as a selective DP$_2$ receptor agonist with a potency about five times greater than that of PGD$_2$ (Figure 1). In contrast, 15(*S*)-Me-PGD$_2$ **4**, which

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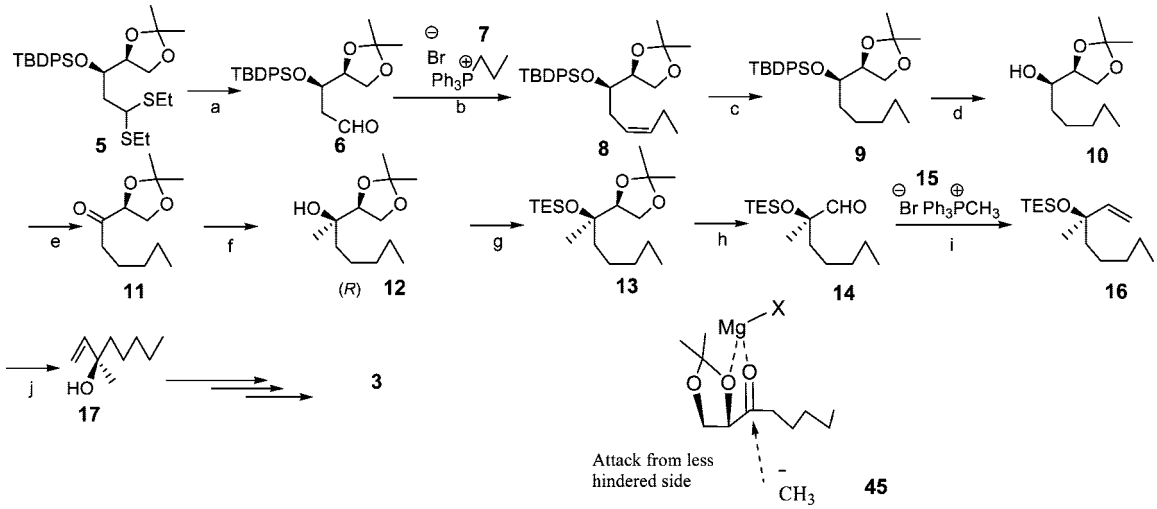
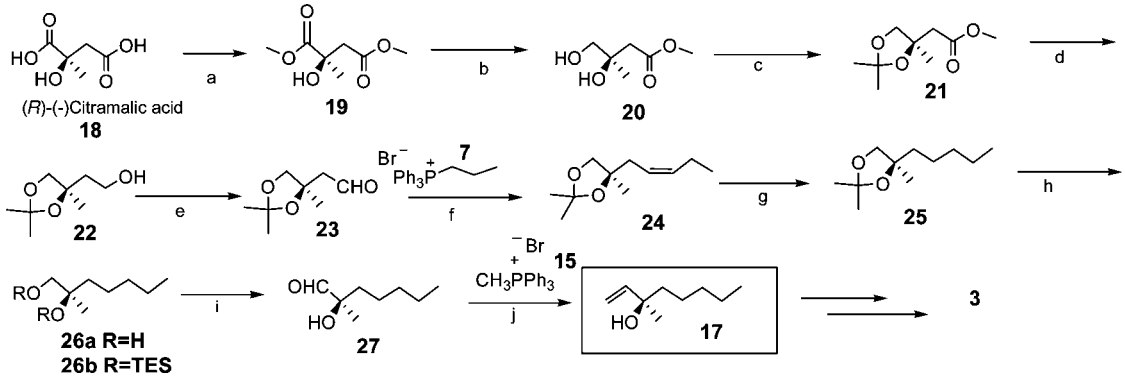
SCHEME 1. Enantioselective synthesis of synthon 17[a]



[a] Reagents and conditions: (a) H_5IO_6, THF:ether (1:2), 0 °C, 65%; (b) (**7**), LiHMDS, THF (5% HMPA), rt to −78 °C to rt, 93%; (c) Pd/C, H_2, EtOH, rt, 99%; (d) TBAF, THF, rt, 91%; (e) Dess−Martin periodinane, CH_2Cl_2, rt, 93%; (f) CH_3MgBr, THF, −100 °C, 80−85% (5−10% of the *S* isomer is also formed and separated by flash chromatography); (g) TESCl, imidazole, DMAP, THF, 60 °C, quantitive yield; (h) H_5IO_6, ether, rt, 99%; (i) (**15**), NaHMDS, THF, −20 to −78 °C to rt, 76%; (j) formic acid:THF:water (6:3:1), 99%.

SCHEME 2. Stereospecific synthesis of synthon 17 with predefined stereochemistry at C-15[a]



[a] Reagents and conditions: (a) $SOCl_2$, MeOH, rt, 16 h, 97.3%; (b) borane-methyl sulfide, $NaBH_4$, dry THF, rt, 20 min, 44%; (c) camphor sulfonic acid, CH_3CN, rt, 2,2-dimethoxy propane, 1 h, 74%; (d) $LiAlH_4$, dry THF, −78 °C, 2 h, 99%; (e) PCC, Al_2O_3, CH_2Cl_2, 0 °C to rt, 3 h, 90%; (f) (**7**), LiHMDS, dry THF, −78 °C, rt, 3 h, 57%; (g) Pd/C, EtOH, rt, 3 h, 99%; (h) TFA, THF/water (4:1), 0 °C to rt, 40 h, 99%; (i) (**26a**) sulfur trioxide−pyridine complex, Et_3N, DMSO/CH_2Cl_2 (1:5), 0 °C for 2 h, 55%; (j) (**15**), NaHMDS, THF, −20 to −78 °C, then rt, 12 h, 56%.

has the same chirality as PGD_2 at C-15, is 15−20 times less potent than PGD_2. We have recently also described the synthesis and bioprofile of 15(*R*)-PGD_2 **2**[4,5] and found it to be approximately equipotent to PGD_2, which has a 15(*S*)-hydroxyl group. Therefore, it would appear that, although the DP_2 receptor does not discriminate between the 15(*R*) and 15(*S*) isomers of PGD_2, it strongly favors the 15(*R*) isomer of 15-Me-PGD_2.

We are now reporting the first total synthesis of this 15(*R*)-Me-PGD_2 **3**, a potent and selective DP_2 receptor agonist.

The synthetic design for the synthesis of **3** relies on the enantioselective (Scheme 1) and stereospecific (Scheme 2) syntheses of synthon **17** and its attachment to the five-membered ring by an intermolecular olefin cross metathesis reaction (Scheme 3), which is a new approach to PGD_2 chemistry.

Results and Discussion

As shown in Scheme 3, the synthesis is based on the introduction of the lower side chain using synthon **17** in which the OH group is of a defined (*R*)-stereochemistry. We selected the olefin cross metathesis reaction to attach the bottom side chain to the five-membered ring.

The synthetic route we envisioned for the total synthesis of 15(*R*)-Me-PGD_2, as described in Scheme 3, relies on the preparation of synthon **17**, as shown in Scheme 1.

Compounds **6**−**10** were prepared as described previously by us for the diastereoisomer of **10**.[6] The key step for the transformation of **11** to **12** follows Cram's model with the approach of the nucleophile, in this case MeMgBr, to the carbonyl from the opposite and less hindered side of the adjacent groups.[7−10] Drawing **45** (Scheme 1) illustrates the process. As can be seen, the transformation of **11** to **12** proceeded with high diastereoselectivity with only minor amounts (5−10%) of the (*S*)-product being formed and separated by flash chromatogra-

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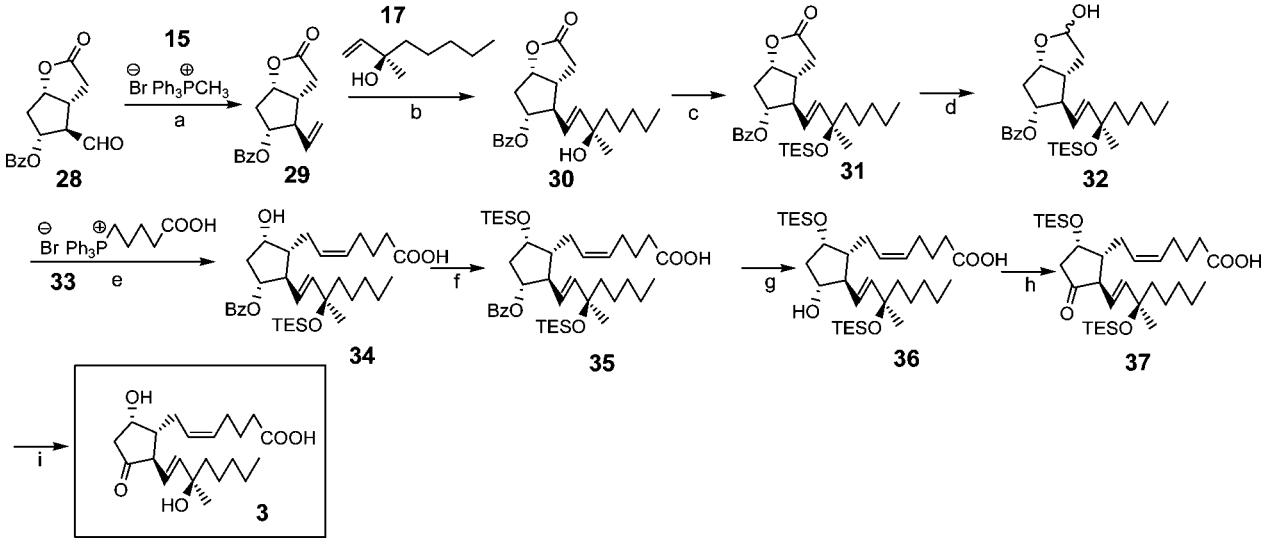
SCHEME 3. Synthesis of 15(*R*)-Me-PGD$_2$ 3 with predefined stereochemistry[a]



[a] Reagents and conditions: (a) (**15**) NaHMDS, THF, −78 °C to rt, 3 h, 51%; (b) Grubbs' catalyst (2nd generation), CH_2Cl_2, rt, 16 h, 60%; (c) TESCl, imidazole, DMAP, THF, 60 °C, 4 h, 90%; (d) DIBAL-H, CH_2Cl_2, −100 °C to rt, 2 h, 76%; (e) (**33**) *t*-BuOK, THF, rt, −78 °C to rt, 2 h, 88%; (f) TESCl, pyridine, 60 °C, 2 h, 85%; (g) ethylmagnesium bromide, THF, rt, 1.5 h, 81%; (h) Dess−Martin periodinane, CH_2Cl_2, rt, 0.5 h, 71%; (i) acetone:H_2O (9:1), PPTS, 4 h, 90%.

phy. This strategy will allow us not only to prepare the 15(*R*)-Me-PGD$_2$ but also to access derivatives of PGD$_2$ with different (*R*)-nucleophiles at C-15 in order to examine their biological profiles. Step b in Scheme 1 is another point of intervention, which will give us further substitution flexibility at C-15 by using variants of the phosphonium salt **7**. Furthermore, by using the enantiomer of synthon **12**,[11] we can have access to PGD$_2$ derivatives with 15(*S*)-stereochemistry at C-15.

In order to confirm the (*R*)-stereochemistry of the OH group in **3**, we devised another approach to the synthon **17**, which is shown in Scheme 2. This approach uses synthon **20**, which contains a stereogenic center, with established stereochemistry derived from (*R*)-(−)-citramalic acid **18**.[12]

The oxidation of **26a** with sulfur trioxide pyridine afforded a modest yield of **27** (55%). Dess−Martin periodinane and PCC oxidation of **26a** led to a mixture of products. Attempts to oxidize the bis-TES derivative **26b** with Swern's oxidation[13] were unsuccessful, and the starting material was recovered. On longer reaction time, the starting material decomposed. This was surprising since this method has worked well for us previously.[14]

Scheme 3 describes the synthesis of 15(*R*)-Me-PGD$_2$ **3**. This has been accomplished by the introduction of the bottom side chain first by a coupling of **17** with olefin **29** made from commercial **28**. This was followed by the introduction of the upper side chain.

The use of the olefin cross metathesis reaction for the synthesis of **3** merits some comment. Two general methods are known for introducing the hydroxyl group at position C-15 in prostaglandins and isoprostanes, that is, the Noyori *S*- and *R*-Binal-H reduction[15] of a ketone, and Julia's olefination reaction.[16] These are very different reactions, as shown in Scheme 4.

The Noyori reduction (Scheme 4a) relies on the generation of α,β-unsaturated (*trans*) carbonyl at C-15, which is then reduced stereoselectively with *S*- or *R*-Binal-H to afford the *S* and *R* hydroxy function in high enantiomeric excess, respectively. This is an excellent method which we have used on numerous occasions to establish the OH stereochemistry. However, depending on the substitution pattern at C-11, this method is not always stereoselective,[4,17] which sometimes makes the assignment of stereochemistry at C-15 unreliable. In addition, the separation of diastereoisomers is very difficult.

The second method is Julia's olefination reaction (Scheme 4 b), which proceeds in moderate yields and gives a mixture of *cis* and *trans* isomers. Although this is a very useful method, it is limited by the requirement to chromatographically separate the resulting *cis* and *trans* isomers, which is often quite difficult and results in overall low yields of the desired compound. This method is similar to the cross metathesis reaction in one important aspect: the stereochemistry of the OH group is predetermined and guaranteed.[18]

The use of the cross metathesis reaction in the prostanoid field was first reported for the synthesis of group III isoprostanes.[19] The olefin cross metathesis we[14] and others[20] used recently in prostaglandin and isoprostane syntheses is illustrated

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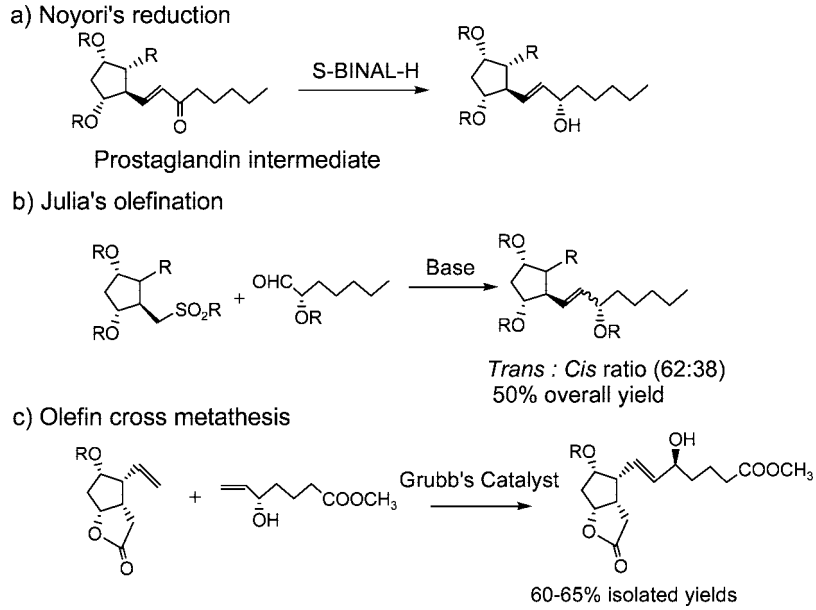
SCHEME 4



in Scheme 4c for the introduction of the top side chain in group V all-*syn* isoprostanes. This approach may provide an important third venue for the introduction of the side chains in prostanoids as it guarantees both a *trans* double bond and the desired OH stereochemistry. The present case extends the original contributions in that the carbon adjacent to the olefin is quaternary (Scheme 3). Before we attempted the reaction, we were concerned that the bulky substitution on the olefin and the silyl group at C-11 might hinder the reaction. To determine whether the olefin cross metathesis would be successful for this reaction, it was initially performed using a racemic version of synthon **17**. We were gratified to see that the reaction proceeded smoothly to afford 60% isolated yield of **30**, following an uncomplicated chromatographic purification.[21]

The selection of TES as a protecting group was done in order to facilitate the final deprotection of **37** with mild acid. This also has caused the yields of the various steps to drop somewhat because of the increased lability of the TES groups. We have focused on mild acid to effect the deprotection of the silyl groups in **37**. Our previous experience mitigates against the use of TBAF or TBAF/acetic acid as it causes substantial β-elimination of the *O*-silyl group to afford a cyclopentenone derivative when dealing with an oxo derivative at C-11. PPTS in acetone/water worked very well and in high yields to afford **3**. As can be noticed in the deprotection of the benzoate **35**, we used ethyl magnesium bromide which afforded **36** in 81% yields. We have tried this transformation first using hydrolytic condition K_2CO_3/MeOH/H_2O. This condition, however, resulted also in the deprotection of one of the two silyl groups. The slightly lower than expected yield of **32** is due to the competing formation of the over reduction product, the diol (not shown). If the reaction is carried out at −78 °C, a substantially higher yield of the diol is formed.

As mentioned earlier, because the synthesis of **17** is not trivial, we initially investigated the feasibility of the approach shown in Scheme 3 by using the racemic version of compound **17** which is readily prepared by the reaction of methyl pentyl ketone with vinyl magnesium bromide (not shown). The final two diastereoisomers obtained, **3** and **4**, were separated by reverse-phase HPLC (Figure 2). The isomer with the shorter retention time (t_R, 46 min) was identified as 15(*R*)-Me-PGD_2 by using 15(*R*)-Me-PGD_2 **3** prepared as per Scheme 3. The *S* isomer has been previously prepared by Bundy.[22]

Before we embarked on the synthesis of **3**, as shown in Schemes 1−3, we successfully completed a trial run of a different approach described in Scheme 5. However, the

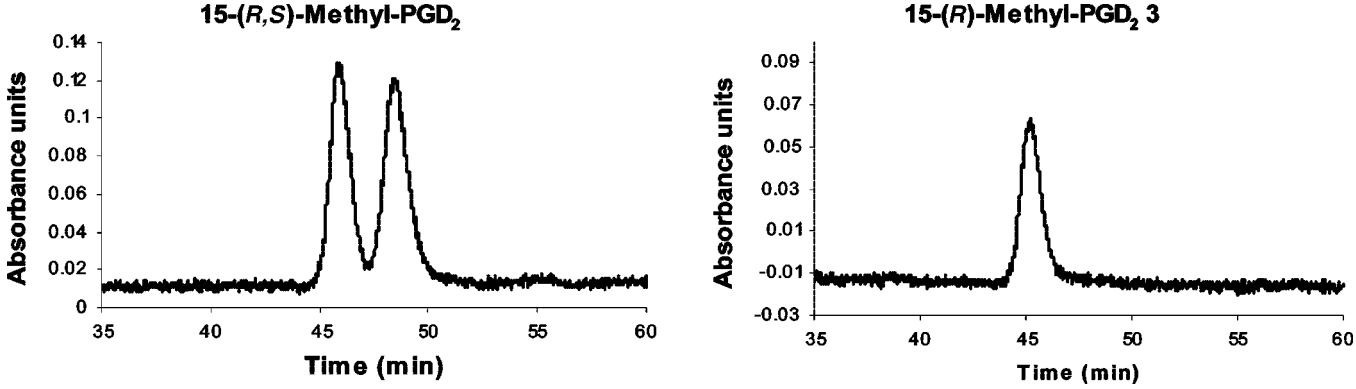
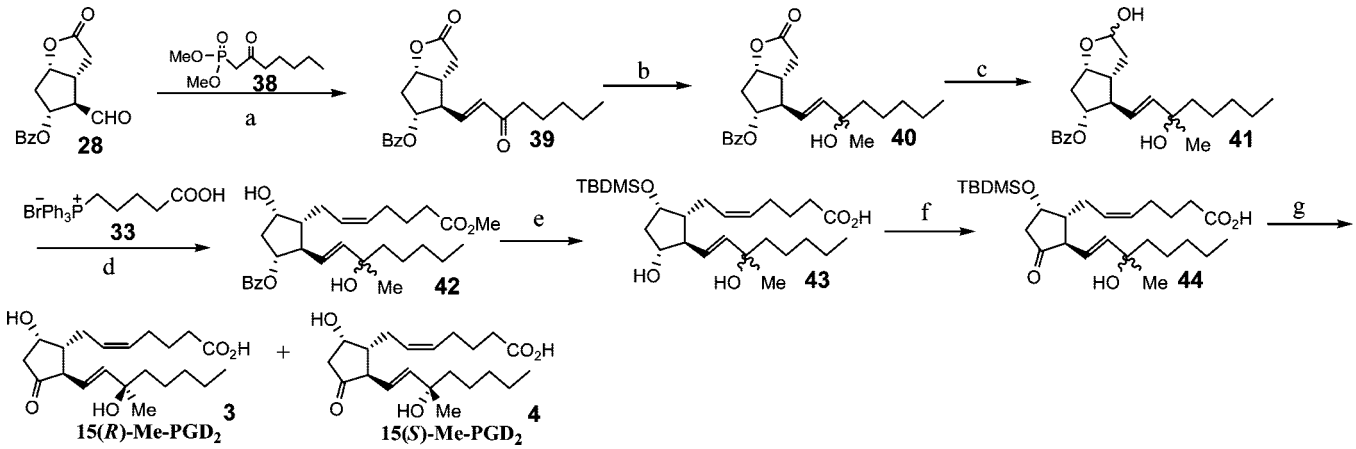


FIGURE 2. HPLC of 15(*R*,*S*)-Me-PGD_2 and 15(*R*)-Me-PGD_2 **3**. Reagents and conditions: The reversed-phase HPLC column was (250 × 4.6 mm) of Spherisorb ODS-2 (5 μm particle size; Phenomenex) maintained at a temperature of 35 °C, whereas the mobile phase was 49% MeOH in water containing 0.02% AcOH at a flow rate of 1.3 mL/min. The products were detected on the basis of UV absorbance at 200 nm.

SCHEME 5. Synthesis of 15(*R,S*)-Me-PGD$_2$[a]



[a] Reagents and conditions: (a) (**38**) NaHMDS, THF, −78 °C to rt, 96%; (b) CH_3MgBr, THF, 96%; (c) DIBAL-H, CH_2Cl_2, 73%; (d) (**33**) *t*-BuOK, HMPA, THF, 0 °C to rt; (2) CH_2N_2, 61% in 2 steps; (e) (1) TBDMSCl, py, 60 °C, 97%; (2) K_2CO_3, MeOH, rt, 90%; (f) Dess−Martin periodinane, CH_2Cl_2, rt, 94%; (g) (1) formic acid; (2) HPLC.

synthesis described in Schemes 1−3 has advantages over that shown in Scheme 5. The final compound (Scheme 5) is a mixture of diastereoisomers that needs HPLC for separation and still requires assignment of the stereochemistry at C-15. We were also disappointed at the lack of separation of the two isomers in **40**−**44** by flash chromatography. At the final stage, we separated **3** and **4** by HPLC. Also, the approach in Scheme 5 provides less flexibility in the synthesis of other PGD_2 derivatives.

The importance and relevance of 15(*R*)-Me-PGD_2 **3** goes beyond its enhanced agonist properties. It is highly selective for the DP_2 receptor,[3] and as such, it can be used to define the DP_2 receptor-mediated effects of PGD_2, which is not possible with PGD_2 itself. For example, we have used 15(*R*)-Me-PGD_2 along with a selective DP_1 receptor agonist (BW245C) to demonstrate that PGD_2-induced pulmonary eosinophilia in rats is mediated by the DP_2 receptor.[23] The high potency of 15(*R*)-Me-PGD_2, which has the unnatural *R* configuration at C-15, is interesting and suggests that the addition of a methyl group in this position may orient the C-15 OH and pentyl group in such a way as to maximize the interaction of this compound with the DP_2 receptor. Studies on the conformation of these compounds may be very useful in future molecular modeling of DP_2 agonists and in the design of selective antagonists of this receptor.

Experimental Section

2-(2,2-Dimethyl-[1,3]dioxolan-4-yl)-heptan-2-ol (12). To a stirred solution of **11** (0.197 g, 2.45 mmol) in dry THF as solvent was added methyl magnesium bromide at −100 °C under argon. The reaction mixture was slowly warmed to room temperature. The solvent was evaporated under reduced pressure, and the crude residue was purified by silica gel chromatography using 15% ether/hexane solvent as eluent to afford **12** as colorless oil (0.180 g, 84.9%) separated from the *S*-isomer approx (0.016 g, 7%): TLC R_f 0.38 (15% EtOAc/hexanes, developed two times); ^{1}H NMR ($CDCl_3$) δ (*R* isomer) 3.81−3.95 (3H, m), 1.47 (3H, s), 1.37 (3H, s), 1.23−1.36 (8H, m), 1.22 (3H, s), 0.83−0.95 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 109.2, 81.9, 71.9, 65.0, 37.9, 32.7, 26.6, 25.6, 24.3, 23.2, 22.8, 14.2; HRMS *m*/*z* calcd for $C_{12}H_{23}O_2^+$ ($M^+ - H_2O$) 199.1693, found 199.1679.

3-Methyl-oct-1-en-3-ol (17). To a stirred suspension of phosphonium salt **15** (3.53 g, 9.9 mmol) in 60 mL of dry THF was added dropwise NaHMDS (1 M solution in THF, 7.9 mL, 7.9 mmol) at −20 °C under argon. The mixture was stirred for 20 min and cooled to −78 °C, and a solution of aldehyde **27** (0.57 g, 4 mmol) in 5 mL of dry THF was added. The reaction mixture was warmed to room temperature, stirred for 8 h, quenched with saturated NH_4Cl solution, and extracted with ethyl acetate. The organic layers were combined, washed with brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude residue was purified by silica gel chromatography using 30% ethyl acetate/hexane as eluent to afford **17** as colorless oil (0.281 g, 56%): TLC R_f 0.55 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 5.81−5.88 (1H, dd, J = 17.4, 10.7 Hz), 5.10−5.15 (1H, d, J = 17.4 Hz), 4.96−4.99 (1H, d, J = 10.7 Hz), 1.49 (3H, s), 1.43−1.47 (2H, m), 1.18−1.28 (6H, m), 0.80−0.83 (3H, t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$) δ 145.3, 111.5, 73.3, 42.4, 32.3, 27.7, 23.6, 22.6, 14.0; HRMS *m*/*z* calcd for C_9H_{17} ($M^+ - H_2O$) 125.1330, found 125.1305.

Benzoic Acid 2-Oxo-4-vinylhexahydrocyclopenta[*b*]furan-5-yl ester (29). To a stirred suspension of phosphonium salt **15** (8.23 g, 23.05 mmol) in 80 mL of dry THF was added 19.2 mL of NaHMDS (1 M solution in THF) at −30 °C under argon. The reaction mixture was stirred for 30 min and cooled to −78 °C, and a solution of **28** (2.0 g, 7.68 mmol) in 20 mL of dry THF was added. The reaction was continued at −78 °C for 30 min, warmed to room temperature, quenched with saturated NH_4Cl, and extracted with ethyl acetate (three times). The organic layers were combined, washed with brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude residue was purified by silica gel chromatography using 35% ethyl acetate/hexane as eluent to afford **29** as a white solid (1.055 g, 51%): TLC R_f 0.30 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.00−8.05 (2H, d, J = 7.5 Hz), 7.55−7.60 (1H, t, J = 7.4 Hz), 7.44−7.48 (2H, t, J = 7.6 Hz), 5.71−5.82 (1H, ddd, J = 17.5, 10.1, 7.1 Hz), 5.25−5.31 (1H, m), 5.13−5.24 (2H, m), 5.03−5.11 (1H, td, J = 5.1, 1.8 Hz), 2.75−2.90 (2H, m), 2.72−2.75 (1H, m), 2.60 (1H, m), 2.49−2.56 (1H, m), 2.20−2.25 (1H, ddd, J = 15.6, 4.7, 1.7 Hz); ^{13}C NMR ($CDCl_3$) δ 172.3, 161.8, 132.0, 129.1, 125.4, 124.3, 113.3, 113.0, 79.1, 74.7, 50.9, 38.0, 33.3, 30.7; mp 65−66 °C; HRMS *m*/*z* calcd for $C_{16}H_{17}O_4^+$ 273.1127, found 273.1109; IR (cm^{-1}) 1709.6 (C=O benzoate), 1764.8 (C=O lactone).

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Benzoic Acid 4-(3-Hydroxy-3-methyloct-1-enyl)-2-oxohexahydrocyclopenta[*b*]furan-5-yl ester (30). To a stirred solution of **29** (0.191 g, 0.7 mmol) and **17** (0.05 g, 3.5 mmol) in 5 mL of CH_2Cl_2 was added Grubbs second generation catalyst (0.06 g, 0.07 mmol) at room temperature under argon. The reaction was stopped after 16 h. The solvent was evaporated under reduced pressure, and the crude residue was purified by silica gel chromatography using 55% ethyl acetate/hexane solvent as eluent. The starting material was recovered and recycled again to afford **30** as a yellow oil (0.165 g, 60%): TLC R_f 0.30 (50% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 8.00−8.05 (2H, d, J = 8.2 Hz), 7.57−7.61 (1H, t, J = 7.4 Hz), 7.44−7.48 (2H, t, J = 7.6 Hz), 5.68−5.76 (1H, d, J = 15.6 Hz), 5.53−5.59 (1H, dd, J = 15.6, 7.7 Hz), 5.21−5.28 (1H, m), 5.07−5.10 (1H, m), 2.71−2.94 (3H, m), 2.62−2.69 (1H, m), 2.53−2.56 (1H, d), 2.22−2.27 (1H, dd), 1.47−1.50 (2H, m), 1.23−1.30 (9H, m), 0.85−0.88 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 176.2, 166.1, 140.5, 129.7, 129.6, 129.5, 129.1, 125.3, 83.2, 79.1, 72.8, 54.0, 42.8, 42.7, 37.5, 34.8, 28.7, 28.1, 22.64, 22.55, 16.4; HRMS *m*/*z* calcd for $C_{16}H_{23}O_2$ (M^+ − OBz − H_2O) 247.1698, found 247.1725.

7-[3-Hydroxy-2-(3-methyl-3-triethylsilanyloxyoct-1-enyl)-5-triethylsilanyloxycyclopentyl]hept-5-enoic acid (36). To a stirred solution of **35** (0.1 g, 0.14 mmol) in 10 mL of dry THF was added ethyl magnesium bromide (3 M solution in ether, 1.4 mL, 4.2 mmol) at room temperature, and the mixture was stirred for 1.5 h. The reaction was quenched by adding saturated aqueous NH_4Cl solution and then extracted with ethyl acetate (three times). The organic layers were combined, washed with brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude residue was purified by silica gel chromatography using 30% ethyl acetate/hexane solvent as eluent to afford **36** (0.069 g, 81%): TLC R_f 0.45 (30% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$) δ 5.43−5.48 (1H, d, J = 15.4 Hz), 5.37−5.41 (1H, m), 5.29−5.35 (1H, dd, J = 15.4, 8.2 Hz), 5.22−5.27 (1H, m), 4.15−4.19 (1H, m), 3.76−3.79 (1H, m), 2.23−2.29 (3H, m), 2.10−2.16 (2H, m), 1.97−2.10 (2H, m), 1.88−1.94 (1H, m) 1.71−1.74 (1H, m), 1.57−1.69 (2H, m), 1.37−1.46 (3H, m), 1.15−1.24 (9H, m), 0.84−0.95 (18H, m), 0.78−0.82 (3H, t), 0.47−0.59 (12H, m); ^{13}C NMR ($CDCl_3$) δ 177.1, 138.6, 129.8, 128.4, 126.0, 79.1, 75.3, 74.6, 56.7, 51.6, 44.2, 43.5, 33.0, 32.3, 27.9, 26.5, 26.1, 24.6, 23.9, 22.7, 14.1, 7.1, 6.9, 6.8, 4.9; HRMS *m*/*z* calcd for $C_{27}H_{49}O_4Si$ (M^+ − OTES) 465.3395, found 465.3376.

7-[5-Hydroxy-2-(3-hydroxy-3-methyloct-1-enyl)-3-oxocyclopentyl]hept-5-enoic acid: 15(*R*)-Me-PGD$_2$ (3). To a stirred solution of **37** (0.009 g, 0.015 mmol) in acetone/water (total volume = 5 mL; 9:1) was added 4.52 mg of PPTS (0.018 mmol) at 0 °C, and the reaction mixture was stirred for 4 h under argon. The solvent was evaporated under reduced pressure. Ethyl acetate was added to the crude residue, and the solvent was washed with water, brine, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude residue was purified by silica gel chromatography (short column) using 10% MeOH/CH_2Cl_2 as eluent to afford **3** (0.0051 g, 90%): TLC R_f 0.40 (10% MeOH/CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 5.57−5.63 (1H, dd, J = 15.6, 7.4 Hz), 5.49−5.55 (1H, m), 5.34−5.44 (2H, m), 4.45−4.45 (1H, m), 2.70−2.75 (1H, m), 2.26−2.42 (4H, m), 2.03−2.19 (3H, m), 1.81−1.90 (1H, m), 1.56−1.72 (2H, m), 1.46−1.52 (2H, m), 1.18−1.30 (10H, m), 0.80−0.83 (3H, t, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 216.2, 177.7, 141.7, 130.8, 127.43, 123.0, 73.9, 67.9, 54.2, 49.0, 47.8, 42.7, 42.4, 32.2, 29.7, 27.4, 26.2, 25.2, 23.6, 22.6, 14.0; HRMS *m*/*z* calcd for $C_{21}H_{33}O_4$ (M^+ − H_2O) 349.2379, found 349.2370.

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Supporting Information Available: Experimental procedures, HRMS (compound **17** and **3**), ^{1}H and ^{13}C NMR spectra of all the compounds, and HPLC tracing of compound **3** are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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