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Synthesis of 15R-PGD_2: a potential DP_2 receptor agonist

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Abstract—The first total synthesis of 15R-PGD_2 **3** was accomplished. The approach used in this report is also an efficient method to produce 15R-PGE_2. 15R-PGD_2, a potential DP_2 receptor agonist, could be an important novel tool for defining the role of this receptor in inflammatory diseases.

Prostaglandin D_2 (PGD_2) **1**,[1–6] an arachidonic acid metabolite, is produced in mast cells,[7] dendritic cells,[8] Th_2 cells,[9] and in the central nervous system.[10]

A large amount of this natural product is released in the lung during asthma and mastocytosis,[11,12] suggesting that PGD_2 may play a role in these two diseases. We have also proposed that 5-oxo-ETE, a potent chemoattractant for neutrophils[13] and eosinophils,[14] can be a causative factor in asthma.[15,16] Until recently, PGD_2 was known to act by raising intracellular cAMP levels through its action on a single G_s–protein-coupled receptor termed the DP_1 receptor.[17] This increase in cAMP levels results in a strong inhibitory effect on platelet aggregation[18] as well as bronchodilator[19] and vasodilator[20] effects in humans. However, our group[21] and other researchers[22] independently discovered a second G_i–protein-coupled receptor for PGD_2, which we termed the DP_2 receptor, and which is responsible for the chemoattractant effect of PGD_2 on eosinophils and other white blood cells.[21,22] We have shown[21] that these cells possess both inhibitory DP_1 receptors and stimulatory DP_2 receptors. The balance between these two receptors is likely to regulate the response of eosinophils and basophils to PGD_2. We recently found that 15R-Me-PGD_2 **2** is a potent and selective agonist for the DP_2 receptor, being about 5 times more potent than PGD_2 and 75 times more potent than 15S-Me-PGD_2 in stimulating actin polymerization, chemotaxis, and expression of the adhesion molecule CD11b[23] (Table 1). Of particular interest is the fact that the stereochemistry of the 15-hydroxy group in **2** is opposite to that in PGD_2 (15S-OH). In contrast to PGD_2, **2** shows no activity on the DP_1 receptor.[23] It could therefore be an important novel tool for defining the physiological role of the DP_2 receptor in asthma, mastocytosis, etc.

The high potency of the 15R-Me-PGD_2 analog **2** raises the possibility that inversion of the configuration at

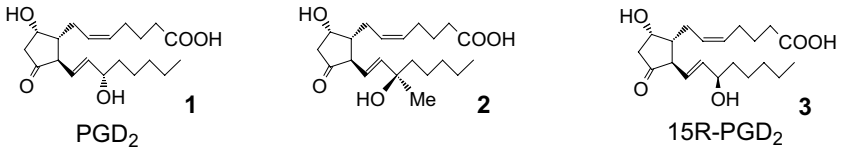

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Table 1. Effects of 15-methyl analogs of PGD_2 on DP_2 mediated responses (EC_{50}, nM) in eosinophils and DP_1, mediated cAMP formation (EC_{10}, nM) in platelets

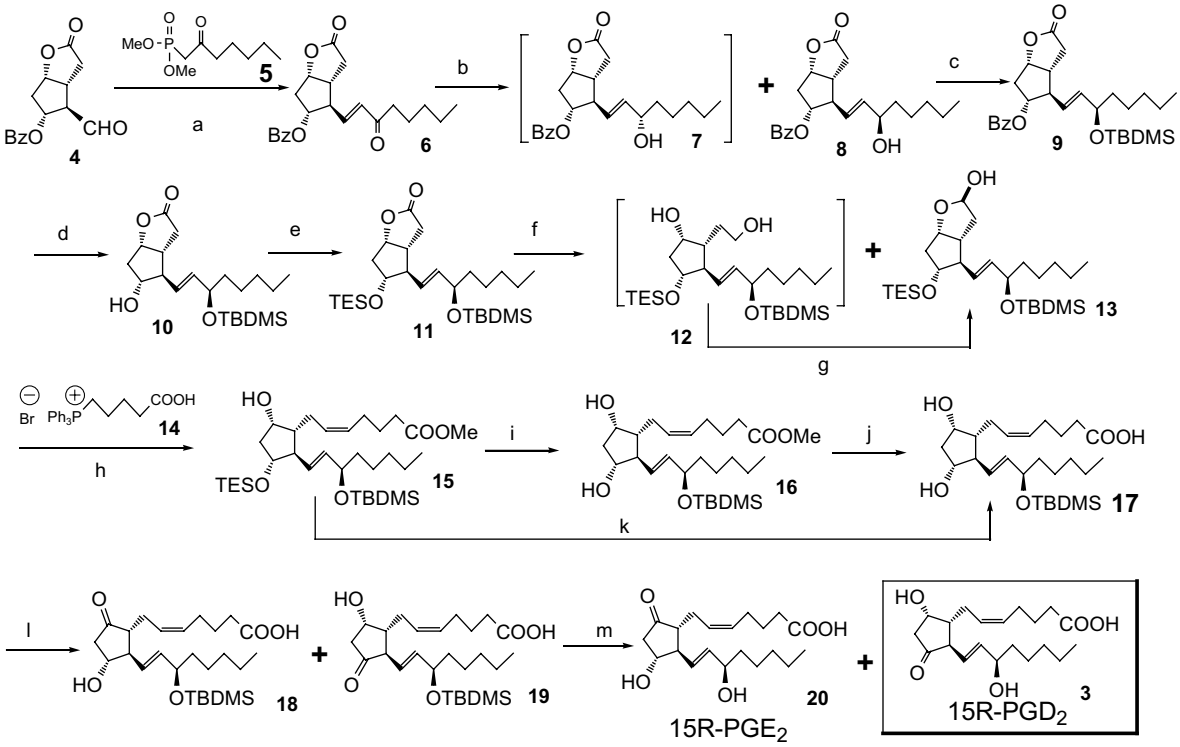
Compound	DP_2			DP_1
	CD11b	Actin	Chemotaxis	cAMP
PGD_2	7	13	10	11
15R-Me-PGD_2	1.4	3.8	1.7	>10,000
15S-Me-PGD_2	99	333	128	2100

carbon 15 of PGD_2 itself may result in enhanced DP_2 receptor activity. To this end we decided to undertake the total synthesis of 15R-PGD_2 (**3**). The synthesis of **3** was performed in 11 steps as described in Scheme 1. This approach to 15R-PGD_2 is also an efficient method to synthesize 15R-PGE_2 **20**.

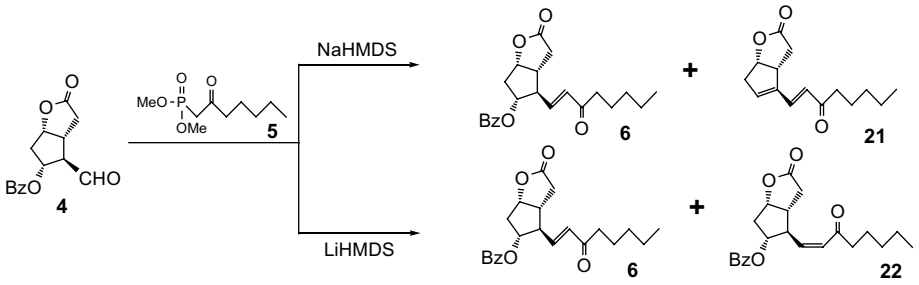
One general comment on the synthetic design is warranted. From the outset we decided that the generation of the 11-oxo group of 15R-PGD_2 would be performed at the last step of the synthesis. The facile elimination of the β-hydroxy group in PGE_2 and PGD_2 and related derivatives and analogs is well known.[24,25] In addition, we also elected not to use a protected carbonyl group, as the deprotection step could be too harsh. We did not want to find this out at the end of the synthesis.

The commercially available lactone benzoate aldehyde **4**[26] was our starting point. The Horner–Emmons reaction of **4** with the phosphonate **5**, using lithium hexamethyldisilyl amide (LiHMDS) or sodium hexamethyldisilyl amide (NaHMDS) as a base, produced **6** in 80% and 96% yield, respectively. Depending on the base used, different byproducts are formed as shown in Scheme 2.

In the case of NaHMDS, the eliminated compound **21** is obtained in variable amounts (1–10%), whereas with LiHMDS, the *Z*-isomer **22** is obtained in 20% yield. Given the difficulty to separate the *Z*-isomer **22** from the *E*-isomer **6**, the use of the NaHMDS base was preferred. The yield of these byproducts can be reduced from 20% to 5% in the case of **22** and to 1% in the case of **21** by maintaining the reaction at −78 °C for 3 h. Reduction of enone **6** with (*S*)-BINAL-H gave the expected *S*-isomer in >95% ee. Unfortunately the reduction of **6** with (*R*)-BINAL-H was not stereoselective and afforded a mixture of 15-*S* and 15-*R*. This was surprising considering that we have performed (*R*)-BINAL-H reduction in the isoprostane series with excellent stereocontrol.[27] A check of the literature reveals that similar compounds to **6** on reaction with (*R*)-BINAL-H also did not show much selectivity for the *R*-isomer.[28] Other reducing agents and other C11–OH protecting groups have also been reported.[29] We elected to carry the reduction of enone **6** with sodium borohydride, which gave a mixture of the *S*- and *R*-isomers, **7** and **8**. Flash column chromatography afforded the *S*- and *R*-isomer in 45% and 40%, respectively. The structural assignment of **7** and **8** was accomplished as shown in Scheme 3.



Scheme 1. Reagents and conditions: (a) NaHMDS, THF, −78 °C to rt, 96%; (b) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, EtOH, 0 °C to rt, 45% **7**, 40% **8**; (c)TBDMSCl, imidazole, THF, 60 °C, 83%; (d) K_2CO_3, MeOH, rt, 96%; (e) TESCl, pyridine, 60 °C, 98%; (f) DIBAL-H, CH_2Cl_2, −78 °C, 99%; (g) Dess Martin, CH_2CI_2, rt; (h) (i) *t*-BuOK, HMPA, THF, 0 °C to rt, (ii) CH_2N_2, 62%; (i) DDQ, H_2O, and THF, 0 °C to rt, 82%; (j) 5% KOH, THF, rt, 75%; (k) K_2CO_3, MeOH, rt, 48 h, 79%; (l) Dess Martin, CH_2Cl_2, rt, 94%; (m) formic acid/THF/H_2O (6:3:1), 29% 15R-PGD_2, 58% 15R-PGE_2.



Scheme 2. Side products of the Horner–Emmons reaction depending on the base used.

The identity of isomer **7** was derived from the well established relationship between (*S*)-BINAL-H and *S*-stereochemistry of the OH product. To confirm the identity of the isomer **8**, we oxidized each pure isomer separately with the Dess Martin reagent giving the identical enone **6**. Only the *R*-isomer **8** was used for the following steps of the synthesis.

Protection of **8** with the TBDMS group gave the compound **9** in 83% yield. The benzoate protection, too labile in basic conditions, was replaced in two steps by the more stable TES group to give the product **11**. Then reduction of the lactone **11** using DIBAL-H provided the lactol **13** in 99% yield. Some diol **12** was obtained (1–10%), which can be reoxidized into the lactol **13** with the Dess Martin reagent as shown in Scheme 1.

Wittig reaction of **13** with the phosphonium salt **14**, using potassium *tert*-butoxide as a base, produced selectively the *Z*-isomer **15** in 62% yield. Compound **15** was treated with dichlorodicyanobenzoquinone (DDQ), to deprotect the TES group to afford **16**, followed by 5% aqueous potassium hydroxide to hydrolyze the methyl ester and give **17**. Alternatively, compound **15** can be treated with potassium bicarbonate in methanol for 48 h to simultaneously deprotect the 11-hydroxy and the methyl ester to give **17** in 79% yield. This shortcut is the preferred modification we now use.

Oxidation of **17** with the Dess Martin periodinane reagent produced the compounds **18** and **19** in a 65:35 ratio. Although **18** and **19** separate on TLC (methanol/ethylacetate/hexane, 3:65:32), we found the separation by flash column chromatography to be quite tedious and the isolation of the desired 15R-PGD_2 was realized at the final step of the synthesis after deprotecting the mixture **18** and **19** with formic acid. We obtained not only 15R-PGD_2 **3**[30] in 29% yield, but also 15R-PGE_2 **20**[31] in 58% yield. The identity of **20** was confirmed by comparison with an authentic sample.

Table 2. Effect of 15R-PGD_2 on actin polymerization and cAMP

Treatment	Actin polymerization (eosinophils) (% above control)	cAMP (platelets) (pmol)
Vehicle	—	0.05 ± 0.02
15R-PGD_2 (1 μM)	83.8 ± 7.5	0.83 ± 0.21
PGD_2 (1 μM)	86.2 ± 4.2	15.48 ± 1.97

15R-PGD_2 is currently being analyzed for its potential activity on PGD_2 receptors. Preliminary results suggest that its activity at the DP_2 receptor is similar to that of PGD_2, but it has very little activity at the DP_1 receptor. As shown in Table 2, 15R-PGD_2 and PGD_2, using methodology we described recently,[23] induce virtually identical increases in actin polymerization in human eosinophils, which is a DP_2 receptor-mediated response. In contrast, 15R-PGD_2 induces only a very modest increase in cAMP levels in platelets, which is mediated by the DP_1 receptor. The cAMP response elicited by PGD_2 is about 20 times greater than 15R-PGD_2. Thus it would appear that 15R-PGD_2 is highly selective for the DP_2 receptor. Further studies are underway on the biological effects of this compound.

Acknowledgments

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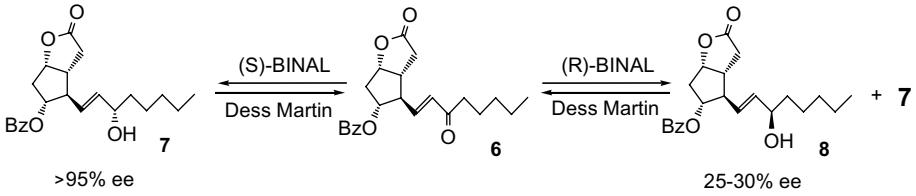

Scheme 3. Identification of the *S*- and *R*-isomers.

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30. *The NMR data of the compound* **3**: ^{1}H NMR (360 MHz, $CDCl_3$), δ 5.6 (m, 2H), 5.45 (m, 2H), 4.55 (m, 1H), 4.18 (q, J = 13 and 6.3 Hz, 1H), 2.8 (dd, J = 12.1 and 8.5 Hz, 1H), 2.45 (m, 3H), 2.35 (t, J = 6 Hz, 2H), 2.15 (m, 3H), 1.95 (m, 1H), 1.65 (m, 4H), 1.3 (m, 6H), 0.9 (t, J = 6 Hz, 3H); ^{13}C NMR (360 MHz, $CDCl_3$), δ 217, 175, 138.5, 131.5, 128, 127.5, 74, 68, 55, 54, 50, 48, 38, 33, 32, 26, 25.5, 25, 23, 14.
31. *The NMR data of the compound* **20**: ^{1}H NMR (360 MHz, $CDCl_3$), δ 5.72 (dd, J = 15.4 and 6.4 Hz, 1H), 5.6 (dd, J = 15.4 and 8.3 Hz, 1H), 5.45 (m, 2H), 4.15 (q, J = 15.3 and 9 Hz, 2H), 2.75 (dd, J = 18.5 and 7.5 Hz, 1H), 2.35 (m, 4H), 2.25 (m, 2H), 2.1 (m, 3H), 1.6 (m, 4H), 1.3 (m, 6H), 0.9 (t, J = 6 Hz, 3H).