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Synthesis and evaluation of 2,3-dinorprostaglandins: Dinor-PGD_1 and 13-*epi*-dinor-PGD_1 are peroxisome proliferator-activated receptor α/γ dual agonists

Ayato Sato [a,b], Kosuke Dodo [a,b], Makoto Makishima [c], Yuichi Hashimoto [d], Mikiko Sodeoka [a,b,*]

[a] Sodeoka Live Cell Chemistry Project, ERATO, JST, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan
[b] RIKEN Advanced Science Institute, 2-1 Hirosawa, Wako-shi, Saitama 351-0198, Japan
[c] Division of Biochemistry, Department of Biomedical Sciences, Nihon University School of Medicine, 30-1 Oyaguchi-kamicho, Itabashi-ku, Tokyo 173-8610, Japan
[d] Institute of Molecular and Cellular Biosciences, The University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo 113-0032, Japan

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ABSTRACT

2,3-Dinorprostaglandins (dinor-PGs) have been regarded as β-oxidation products of arachidonic-acid-derived prostaglandins, but their biological activities in mammalian cells remain unclear. On the other hand, C18 polyunsaturated fatty acids (PUFAs), such as γ-linolenic acid (GLA), have various biological activities, and dinor-PGs are speculated to be biosynthesized from GLA. Here, we synthesized dinor-PGs that may possibly be derived from GLA and examined their activities towards peroxisome proliferator-activated receptors (PPARs). Dinor-PGD_1 (**1**) and its epimer 13-*epi*-dinor-PGD_1 (*epi*-**1**) were found to be dual agonists for PPARα/γ, whereas PGD_2 derived from arachidonic acid is selective for PPARγ. Thus, GLA-derived dinor-PGs may have unique biological roles.

Polyunsaturated fatty acids (PUFAs) and their derivatives are involved in a variety of biological signaling pathways. Among these compounds, C20 PUFAs, arachidonic acid (AA), dihomo-γ-linolenic acid (DGLA), and eicosapentaenoic acid (EPA), are converted to a variety of lipid mediators, such as prostaglandins and leukotrienes,[1] that play critical roles in smooth muscle contraction,[2] sleep,[3] platelet aggregation,[4] tumor suppression[5] and inflammation[6] in mammals.

γ-Linolenic acid (GLA), a representative C18 PUFA, has antitumor activity[7] and transcriptional activation activity.[8–11] GLA is generally recognized as a precursor in the biosynthesis of AA, but its biological activities are not always the same as those of AA, suggesting that GLA itself and/or its metabolites also act as physiological modulators. Interestingly, C18 PG-like molecules have been identified in plasma and urine.[12–14] Although they had been assumed to be formed by auto-oxidation of C18 PUFAs or β-oxidation of C20 PGs, they may themselves have significant biological activity. Indeed, biological activities of some dinor–isoprostanes have been reported.[15] Furthermore, GLA serves as a substrate of human prostaglandin-endoperoxide H synthases, raising the possibility that dinor-PGs having 18 carbon atoms may be enzymatically produced from GLA, at least in part.[16] It is noteworthy that C18 prostanoids derived from α-linolenic acid act as injury signaling factors in the plant kingdom.[17,18] But, as far as we know, no detailed biological studies on GLA-derived dinor-PGs have yet been reported. Therefore, we started a project to examine the chemistry and biology of dinor-PGs. Here, we report the syntheses of 2,3-dinorprostaglandin D_1 (dinor-PGD_1) and 13-deoxy-$\Delta^{10,12}$-2,3-dinorprostaglandin J_1 (13-deoxy-dinor-PGJ_1), and the evaluation studies of their activities towards peroxisome proliferator-activated receptor (PPAR) subtypes.

Peroxisome proliferator-activated receptors (PPARα, δ, and γ), which belong to the nuclear receptor superfamily of transcription factors, are key regulators of lipid metabolism and are considered to be important drug targets.[19] Various fatty acids, such as AA and GLA, are known to bind and activate PPARs.[20,21] Furthermore, the relationship between the chain length of fatty acids and their PPAR agonistic activities has been discussed.[8,21] In 1995, prostaglandin D_2 (PGD_2) and its dehydrated metabolites (Fig. 1) were found to be potent activators of PPARs, and among them, 15-deoxy-$\Delta^{12,14}$-PGJ_2 was significantly more potent than its precursors, AA and PGD_2.[22,23] Therefore, we speculated that GLA may also be directly transformed into dinor-PGs and that some of these molecules may activate PPARs. To test this hypothesis, we planned to synthesize and evaluate dinor-PGs corresponding to PGD_2, PGJ_2 and 15-deoxy-$\Delta^{12,14}$-PGJ_2, namely 2,3-dinorprostaglandin D_1 (dinor-PGD_1) (**1**), 2,3-dinor-prostaglandin

* Corresponding author. Tel.: +81 48 467 9373; fax: +81 48 462 4666.
E-mail address: sodeoka@riken.jp (M. Sodeoka).

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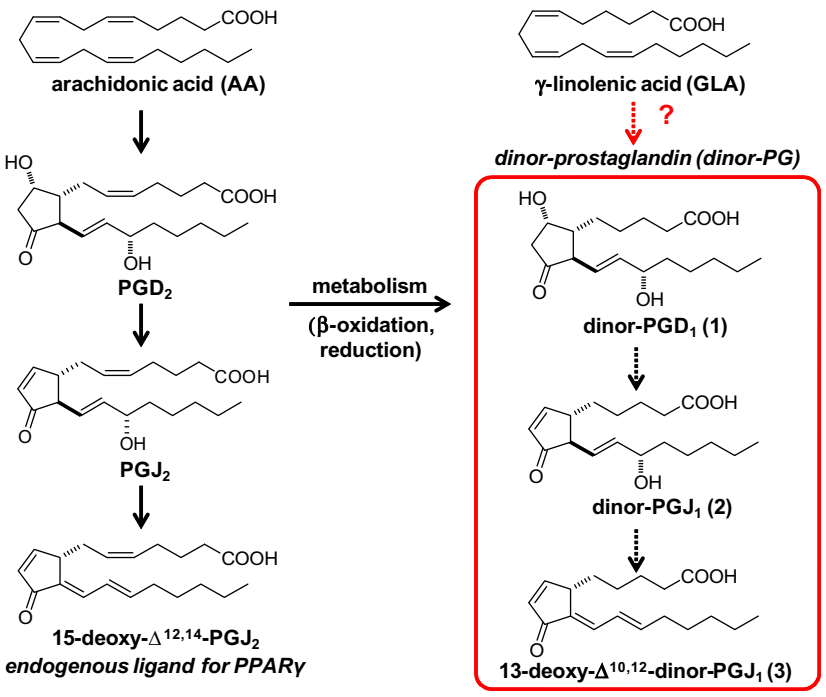
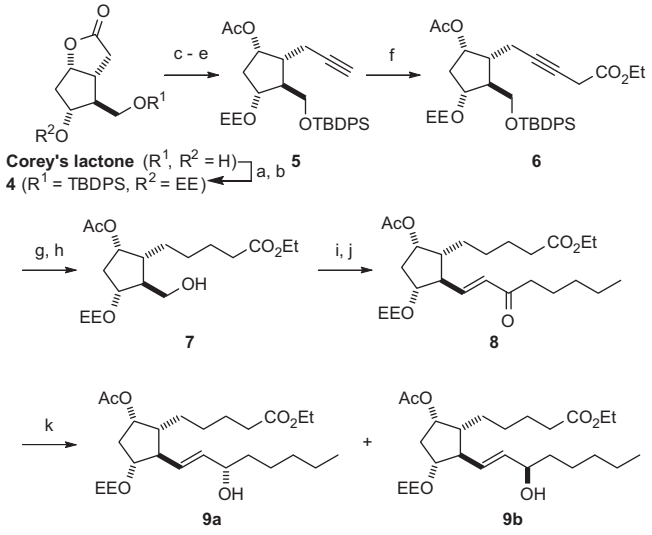


Figure 1. Hypothetical metabolic pathway of GLA in parallel to the AA cascade.

J_1 (dinor-PGJ_1) (**2**), and 13-deoxy-$\Delta^{10,12}$-2,3-dinor-prostaglandin J_1 (13-deoxy-dinor-PGJ_1) (**3**) (Fig. 1).

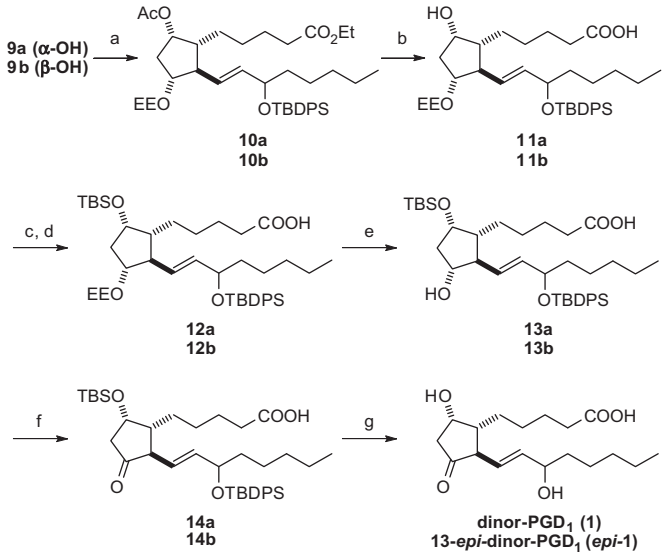
For the synthesis of these molecules, we used Corey's lactone as the starting material.[24] As shown in Scheme 1, after sequential protection of its alcohols with *t*-butyldiphenylsilyl (TBDPS) and ethoxyethyl (EE) groups, **4** was converted to the lactol by reduction with diisobutyl-aluminum hydride (DIBAL). To construct the α-chain, we first attempted to introduce the C-3 unit directly into the lactol by means of a Wittig reaction,[25,26] but this was unsuccessful. Therefore, we next tried to construct the α-chain in a stepwise manner. A C1 unit was successfully introduced by using Ohira–Bestmann homologation[27] in 69% yield over two steps, then acetylation of the resulting secondary alcohol gave alkyne **5** in 86% yield. Next, introduction of a C2 unit was achieved by a Cu-mediated coupling reaction with ethyl iodoacetate to give ester **6** in 89% yield.[28] Hydrogenation of **6** followed by removal of the TBDPS group afforded primary alcohol **7** in 94% yield over two steps. Swern oxidation of **7** and Horner–Wadsworth–Emmons reaction of the resulting aldehyde gave enone **8** in 69% yield over two steps. The diastereoselective reduction of **8** with (*S*)-BINAL-H[29] was examined, but the stereoselectivity was low (37% *de*). Other stereoselective reductions of **8** employed previously in prostaglandin synthesis[30,31] also gave unsatisfactory results. Therefore, we decided to employ Luche conditions for large-scale preparation. The reaction proceeded smoothly to give **9a** and **9b** in 49% and 47% yields, respectively.[32] The diastereomers were separated for use in subsequent reactions.

With compounds **9a** and **9b** in hand, we moved to the synthesis of **1**–**3** (Fig. 1). As shown in Scheme 2, protection of **9a** with TBDPS gave **10a** in 93% yield, then hydrolysis of the acetyl group and ethyl ester gave hydroxyacid **11a** in 96% yield. Protection of the secondary alcohol and carboxylic acid with *t*-butyldimethylsilyl triflate (TBSOTf) afforded stable bis-TBS ether ester, and consecutive treatment with acetic acid afforded carboxylic acid **12a** in quantitative yield over two steps. It was unexpected that the ethoxyethyl group was tolerated under these conditions, and selective removal of this group from **12a** in the presence of the TBS group was troublesome.



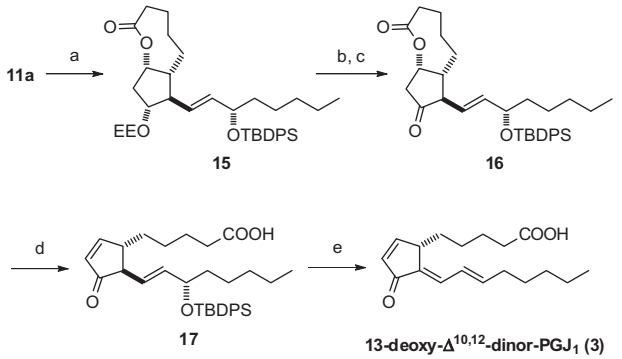
Scheme 1. Preparations of **9a** and **9b**. Reagents and conditions: (a) TBDPSCl, imidazole, DMF, −40 °C, 2 h, 84%; (b) ethyl vinyl ether, PPTS, CH_2Cl_2, 0 °C, 1.5 h then rt, 1 h, 84%; (c) DIBAL, toluene, −78 °C, 30 min; (d) $MeCOCN_2PO(OMe)_2$, K_2CO_3, MeOH, rt, 14 h then 45 °C, 5 h, 69% over two steps; (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1.5 h, 86%; (f) ICH_2CO_2Et, CuI, MeCN, rt, 24 h, 89%; (g) PtO_2, H_2, AcOEt, rt, 3 h; (h) TBAF, THF, 0 °C to rt, 22.5 h, 94% over two steps; (i) $(COCl)_2$, DMSO, −78 °C, 15 min; Et_3N, 0 °C, 45 min; (j) dimethyl-2-oxoheptyl phosphonate, NaH, THF, 0 °C to rt, 69% over two steps; (k) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −20 °C, 10 min, 49% for **9a**, 47% for **9b**.

After investigation of several reaction conditions, selective removal of the ethoxyethyl group was accomplished by treatment of **12a** with $CeCl_3{\cdot}7H_2O$ in MeOH at 10 °C for 2 d, affording the desired secondary alcohol **13a** in 84% yield. Oxidation of **13a** using Dess–Martin periodinane (DMP) gave protected dinor-PGD_1 **14a** (67%), and subsequent removal of TBS and TBDPS groups employing aqueous HF solution afforded **1** in 37% yield. By using the same conditions, 13-*epi*-dinor-PGD_1 (*epi*-**1**) was similarly synthesized from **9b**.[33]



Scheme 2. Syntheses of dinor-PGD_1 (**1**) and 13-*epi*-dinor-PGD_1 (*epi*-**1**). Reagents and conditions: (a) TBDPSCl, imidazole, DMAP, DMF/Et_3N (5:1), 93% for **10a** and 86% for **10b**; (b) NaOH, MeOH/H_2O (10:1), 96% for **11a** and 78% for **11b**; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, −60 °C, 15 min; (d) THF/AcOH/H_2O (4:1:1), quant. over two steps for both **12a** and **12b**; (e) $CeCl_3{\cdot}7H_2O$, MeOH/H_2O (20:1), 10 °C, 2 d, 84% for **13a** and 86% for **13b**; (f) DMP, CH_2Cl_2, 0 °C, 6 h, 67% for **14a** and 98% for **14b**; (g) HF, MeCN/H_2O (20:1), −10 °C, 6 d, 37% for **1** and 57% for *epi*-**1**.

Next we examined the synthesis of dinor-PGJ_1 (**2**) and 13-deoxy-$\Delta^{10,12}$-dinor-PGJ_1 (**3**). Unfortunately, attempts to synthesize **2** and **3** directly from **14a** or **1** by elimination of either silanol or water were unsuccessful. Therefore we decided to try the macrolactone method reported by Bundy et al. (Scheme 3).[34] Lactonization of **11a** gave eight-membered lactone **15** in 72% yield. Removal of the ethoxyethyl group gave the secondary alcohol (80%), and subsequent Dess–Martin oxidation afforded dinor-PGD_1 lactone **16** in quantitative yield. Treatment of **16** with silica gel resulted in β-elimination to give the desired carboxylic acid **17** in 67% yield. However, deprotection of the TBDPS group using HF did not give the desired dinor-PGJ_1 **2**, and further dehydration proceeded to afford 13-deoxy-$\Delta^{10,12}$-dinor-PGJ_1 (**3**) in 68% yield. All attempts to synthesize **2** were unsuccessful due to rapid elimination of the hydroxyl group at C13. Interestingly, when the same reactions were performed starting from the epimer **11b**, 13-*epi*-dinor-PGJ_1 was obtained as a minor product (34%), though again **3** was formed as the major product (62%).[35]



Scheme 3. Synthesis of 13-deoxy-$\Delta^{10,12}$-dinor-PGJ_1 (**3**). Reagents and conditions: (a) PySSPy, PPh_3, benzene; benzene (4 mM), reflux, 72%; (b) THF/H_2O/AcOH (2:1:6), 80%; (c) DMP, CH_2Cl_2, quant.; (d) silica gel (5000 wt %), *n*-hexane/AcOEt (7:3), 67%; (e) HF, MeCN/H_2O (20:1), 0 °C, 1 week, 68%.

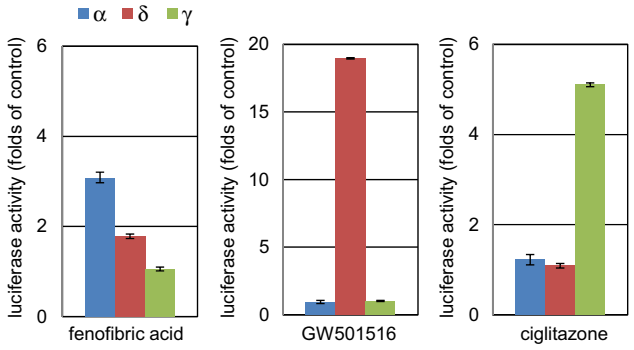


Figure 2. PPAR-agonistic activities of fenofibric acid (10 μM, PPARα agonist), GW50516 (100 nM, PPARδ agonist) and ciglitazone (10 μM, PPARγ agonist).

To evaluate the activities of these synthetic dinor-PGs towards PPARs, PPAR reporter assay using HEK293 cells was conducted according to a previous report.[36] As controls, we first evaluated the known subtype-selective PPAR ligands, fenofibric acid, GW501516, and ciglitazone. These synthetic PPAR ligands showed the expected subtype-selective activations (Fig. 2). Then, we examined the effects of the synthesized C18 dinor-PGs, compared with those of the parent C20 prostaglandins (Fig. 3). Dinor-PGD_1 (**1**) and its epimer 13-*epi*-dinor-PGD_1 (*epi*-**1**) both showed PPARα agonistic activity, whereas PGD_2 activated PPARγ more strongly than PPARα or δ. According to previous reports,[22,23] PGD_2 is transformed to PGJ_2 and 15-deoxy-PGJ_2 in cells, and 15-deoxy-PGJ_2 shows the most potent PPARγ activation among them. In contrast, 13-deoxy-dinor-PGJ_1 (**3**), which is the dinor-PG corresponding to 15-deoxy-PGJ_2, showed only weak activity towards PPARγ, as well as towards PPARα/δ.

We next examined the dose-dependent activations of PGD_2, **1**, and *epi*-**1** (Fig. 4). Both **1** and *epi*-**1** showed stronger PPARα and weaker PPARγ agonistic activities relative to PGD_2. These results indicate the change of subtype selectivity from γ to α in **1** and *epi*-**1**.

Based on the reported crystal structures of PPARα-LBD complex with synthetic ligand AZ 242[37] and PPARγ-LBD complex with 15-deoxy-PGJ_2[38] (Fig. 5a), we speculated that the reason for the PPARα-selectivity of dinor-PGD_1 is as follows. During PPAR activation, the hydrophobic ω-chain of PGs and dinor-PGs is thought to enter the cavity of PPARs, where it is surrounded by hydrophobic amino acid residues. The carboxylic acid moiety of the α-chain interacts with hydrophilic amino acids (His and Tyr in Fig. 5a) and changes the position of helix-12. The movement of helix-12 induces conformational change and recruitment of coactivators, leading to gene expression. Therefore, the position of the carboxylate should be critical for the activation. Distances between the

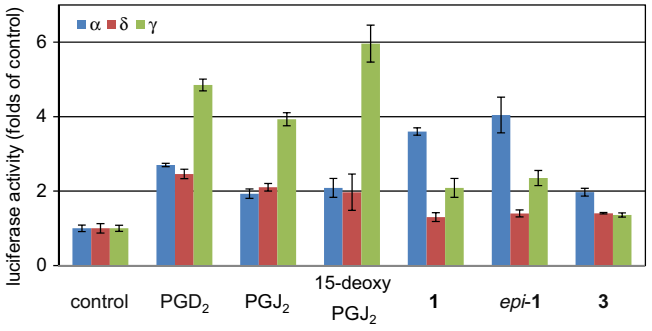


Figure 3. PPAR-agonistic activities of PGD_2 (10 μM), PGJ_2 (3 μM), 15-deoxy-PGJ_2 (3 μM), and dinor-PG compounds **1**, *epi*-**1**, and **3** (10 μM).

hydrophobic pocket and the hydrophilic amino acid residues are different between the two crystal structures, presumably reflecting the conformation required for activation. Dinor-PGD_1 (**1**) having a shorter α-chain, fits comfortably into the pocket of PPARα in comparison to AZ 242. On the other hand, the shorter α-chain appears to be too short to interact with the hydrophilic amino acid residues of helix-12 in PPARγ. As a result, dinor-PGD_1 clearly showed stronger agonistic activity for PPARα while at the same time weaker activity for PPARγ, compared to PGD_2.

Finally, to confirm the binding model, we conducted a docking study of PPARα (PDB ID 1I7G) and **1** with AutoDock 4.2 software[39] (Fig. 6). As predicted above, the results indicate that the carboxylic acid moiety of **1** can access the hydrophilic pocket of PPARα through hydrogen bonding (Tyr464, Tyr314 and Ser280), supporting our binding model of **1**.

In this study, we have succeeded in synthesizing dinor-PGD_1 (**1**), 13-*epi*-dinor-PGD_1 (*epi*-**1**) and 13-deoxy-dinor-PGJ_1 (**3**), and we examined their effects on the activity of PPARs. Dinor-PGD_1 (**1**) and its epimer, 13-*epi*-dinor-PGD_1 (*epi*-**1**), were found to be PPARα/γ dual agonists. Synthetic methods previously used to obtain PGs were not applicable to dinor-PGs, even though there is only a two-carbon difference in the α-chain. Our new synthetic routes should be applicable for the synthesis of other dinor-PGs. Further synthetic and biological studies are under way.

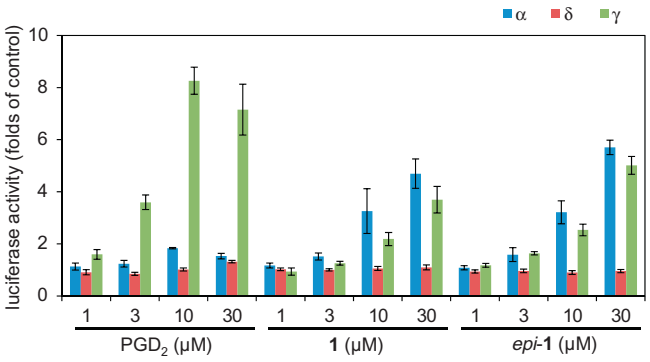


Figure 4. Dose-dependent PPAR-agonistic activities of PGD_2, **1**, and *epi*-**1**.

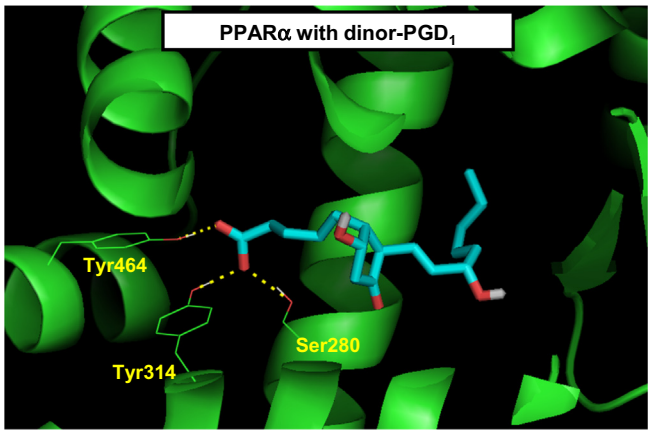


Figure 6. Docking study of dinor-PGD_1 (**1**) with PPARα. Calculated model of PPARα with **1** constructed by AutoDock 4.2. The image was drawn with PyMOL.

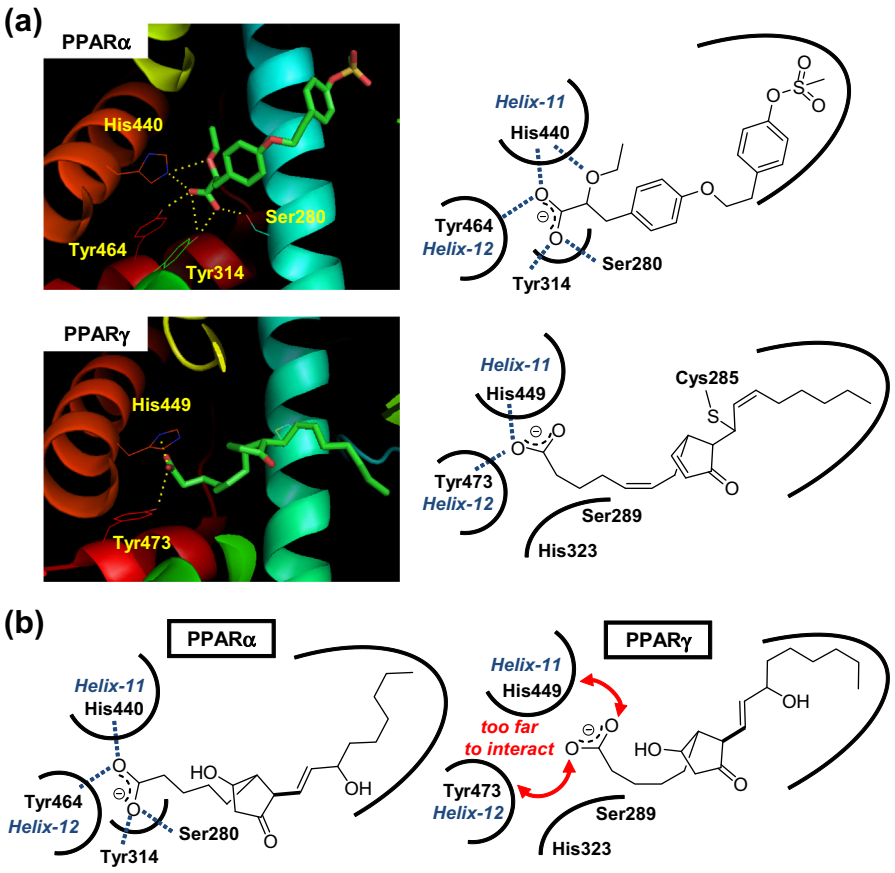


Figure 5. (a) Reported X-ray crystal structures of PPARα (PDB ID 1I7G) and PPARγ (PDB ID 2ZK1) complexed with agonists. The images were drawn by PyMOL; (b) binding model of dinor-PGD_1 (**1**) with PPARα and PPARγ.

Acknowledgment

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33. Dinor-PGD_1 (**1**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.54 (dd, J = 15.4, 7.1 Hz, 1H), 5.41 (dd, J = 15.4, 8.1 Hz, 1H), 4.41 (m, 1H), 4.01 (ddd, J = 13.0, 6.4, 6.4 Hz, 1H), 2.68 (dd, J = 11.7, 8.1 Hz, 1H), 2.49 (dd, J = 18.6, 6.4 Hz, 1H), 2.27–2.30 (m, 3H), 1.98 (m, 1H), 1.32–1.68 (m, 16H), 0.90 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.4, 179.0, 135.9, 125.9, 74.4, 68.5, 54.3, 48.5, 37.8, 33.9, 31.7, 27.5, 27.0, 26.7, 24.9, 24.3, 22.5, 14.0; HRMS (ESI) (m/z) calcd for $C_{18}H_{29}O_5$ $[M-H]^-$: 325.2020, found: 325.2010; 13-*epi*-dinor-PGD_1 (*epi*-**1**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (dd, J = 15.4, 6.6 Hz, 1H), 5.20 (dd, J = 15.4, 8.2 Hz, 1H), 4.35 (m, 1H), 4.10 (ddd, J = 13.9, 6.4, 6.4 Hz, 1H), 2.60 (dd, J = 11.8, 8.2 Hz, 1H), 2.33 (dd, J = 18.6, 6.4 Hz, 1H), 2.28–2.32 (m, 3H), 1.98–1.94 (m, 2H), 1.34–1.72 (m, 15H), 0.80 (t, J = 9.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.2, 172.0, 136.1, 125.8, 74.0, 68.6, 54.1, 48.6, 37.7, 31.7, 27.7, 27.0, 26.7, 25.7, 24.9, 24.3, 19.3, 14.0; HRMS (ESI) (m/z) calcd for $C_{18}H_{29}O_5$ $[M-H]^-$: 325.2020, found: 325.2024.
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35. 13-Deoxy-$\Delta^{10,12}$-dinor-PGJ_1 (**3**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (dd, J = 6.0, 0.5 Hz, 1H), 6.92 (d, J = 10.5 Hz, 1H), 6.34 (dd, J = 6.0, 2.0 Hz, 1H), 6.22 (m, 2H), 3.55 (dddd, J = 5.9, 3.9, 2.0, 0.5 Hz, 1H), 2.32 (dt, J = 7.1, 3.9 Hz, 2H), 2.20 (dt, J = 7.4, 6.9 Hz, 2H), 1.88 (m, 1H), 1.27–1.69 (m, 11H), 0.87 (t, J = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 178.5, 160.8, 147.1, 135.4, 135.2, 131.7, 125.5, 43.3, 33.6, 33.4, 32.5, 31.8, 28.4, 25.3, 24.8, 22.4, 14.0; HRMS (ESI) (m/z) calcd for $C_{18}H_{25}O_3$ $[M-H]^-$: 289.1809, found: 289.1811.
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