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Nitro-Olefin Trapping Reaction of Enolates In Situ Generated by Conjugate Addition Reaction: Short Syntheses of PGE_1, 6-Oxo-PGE_1, 6-Oxo-$PGF_{1\alpha}$, and PGI_2[1]

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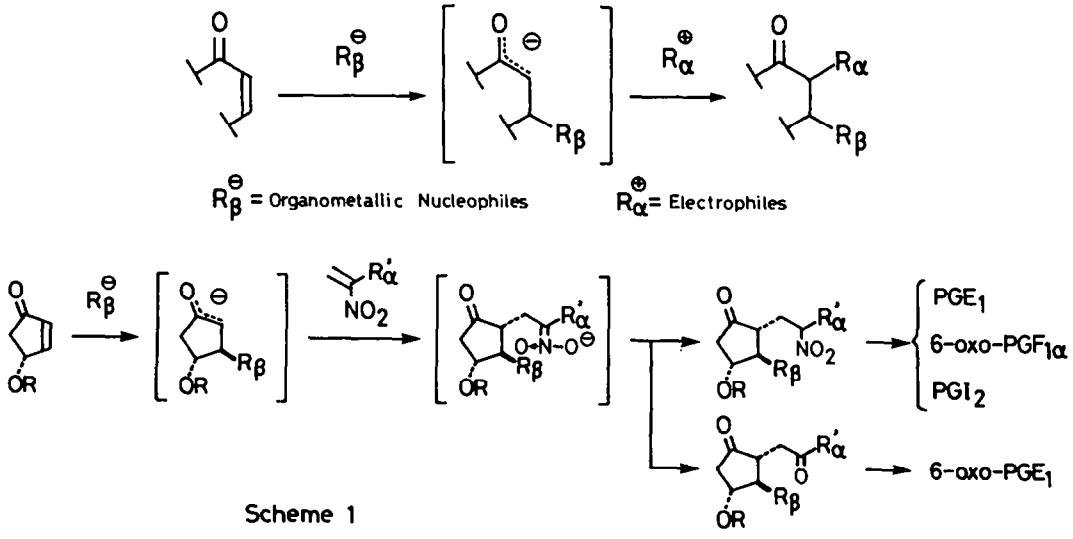
Abstract--The nitro-olefin trapping of the enolates in situ generated by conjugate addition of organocopper reagents to the chiral oxygenated cyclopentenone synthon, **R-4**, gives the three-component coupling products in a regiospecific manner. The intermediary nitronate anion **17** is further transformed into the nitro compound or 6-oxo-PGE_1 (**19**) in a single pot. This coupling reaction is applicable to syntheses of naturally occurring prostaglandins such as PGE_1, 6-oxo-$PGF_{1\alpha}$, and PGI_2.

Directed vicinal carbacondensation of α,β-unsaturated ketones constitutes an important and useful class of synthetic operations.[2] In this connection, intensive efforts have been made on the electrophilic trapping of the regio-defined enolates generated by conjugate addition of organometallic reagents to α,β-unsaturated ketones. Consequently, a variety of α, β-disubstituted ketones become available by combining the conjugated enones, organometallic nucleophiles, and electrophiles such as α-silylated vinyl ketones,[3] alkyl halides,[4,5] aldehydes,[5,6] formates,[7] diphenyl disulfide or benzenesulfenyl chloride,[8] and 1,1-bis(methylthio)ethene S-oxide[9] (Scheme 1). Organocopper reagents among other organometallics find particularly a wide utility in this context.

A practical applicability of this methodology has been shown by prostaglandin (PG) syntheses. Preliminarily, 2-cyclopentenone was condensed with organocopper reagents and allylic or propagylic



Scheme 1

halides, leading to 11-deoxy-PG skeletons.[10] The convergent, three-component coupling process[11] using chiral 4-oxygenated 2-cyclopentenone[12] was firstly realized by using a carboxylic acid chloride as the enolate trap, allowing the synthesis of a 7-oxo-PGE_1 derivative.[13] A more elaborated three-component coupling process was accomplished by using saturated[14] or acetylenic aldehydes[15] as trapping agents to furnish after removal of the resulting 7-hydroxy function all the naturally occurring prostaglandins including PGI_2[16] and PGD series.[17] Recently, the trapping of the enolate intermediates with allylic and acetylenic halides has been achieved by the aid of the lithium (or copper) to tin transmetalation in the enolate stage to result in the direct synthesis of E-type of prostaglandins.[18] At the same time, the synthesis of a (5E)-PGE_2 derivative has been realized by an indirect way, which involves the intramolecular palladium-catalyzed decarboxylative allylic alkylation of the allylic ester of β-keto carboxylic acid obtained by an enolate trapping with a formate ester derivative.[19]

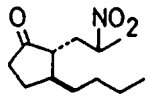
In the three-component coupling process, our attention has been focused on further finding a new type of enolate-trapping agents, that is, nitro olefins[20] as a Michael acceptor. In this paper, we wish to describe the details of the nitro-olefin Michael trapping[21] of the enolates and the related reactions,[22] which enabled us to synthesize a series of 6-oxygenated PG derivatives such as 6-oxo-PGE_1, 6-oxo-$PGF_{1\alpha}$, and PGI_2 as well as PGE_1 (Scheme 1).

Nitro-olefin trapping of the enolate and the synthesis of (-)-PGE_1

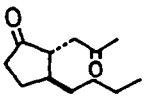
The first successful result was obtained by the reaction between a 3-alkylated cyclopentanone enolate and 2-nitropropene. When the conjugate adduct of an organocopper reagent, n-C_4H_9Cu--$2P(n\text{-}C_4H_9)_3$,[23] to 2-cyclopentenone was reacted with 2-nitropropene, there was obtained a three-component coupling product **1** in 66% yield. Treatment of the above reaction mixture with 1N HCl gave the diketone **2** in 57% yield accompanied with **1** (9%). This product, **2**, appeared homogeneous by its ^{13}C-NMR spectrum proving the regiospecificity of the trapping reaction. Similar reaction using the copper reagent prepared from (±)-(E)-3-t-butyldimethylsilyloxy-1-iodo-1-octene[24] [(±)-**3**], (±)-4-t-butyldimethylsilyloxy-2-cyclopentenone [(±)-**4**], and nitroethylene afforded the coupling product **5** in 27% yield.

These results suggested the possibility that the use of methyl 6-nitro-6-heptenoate[25] (**6**) as a Michael acceptor would construct a PGE_1 skeleton in one pot. Indeed, the enolate generated by conjugate addition of the organocopper reagent[29] prepared from (S,E)-3-t-butyldimethylsilyloxy-1-iodo-1-octene[12c,24] (**S-3**) to the chiral enone **R-4**, was trapped with the nitro olefin **6** to afford the three-component coupling product **9** in 71% yield. The newly formed C-12 stereochemistry of the product **9** was defined in a C-11/C-12 trans relationship by steric interactions between the C-11 functionality and the entering organometallic reagent (PG numbering).[11] The stereochemically favorable[30] C-8/C-12 trans isomer of **9** was obtained predominantly accompanied with a small amount (ca. 10%) of the C-8 epimer[30] detectable by HPLC analysis. The main stereoisomer **9** was found to be an approximately equal portion mixture of the 6R and 6S epimers, because the ^{13}C-NMR spectrum showed eight pairs of signals due to C(5)-C(9) and C(12)-C(14). Desilylation of the product **9** with aqueous hydrogen fluoride in acetonitrile yielded 6-nitro-PGE_1 methyl ester[31] (**10**) (86%). Reduction of the nitro compound **9** with tributyltin hydride in refluxing toluene in the presence of a catalytic amount of azobisisobutyronitrile gave the denitrated product (**11**) in 44% isolated yield. Desilylation of **11** with hydrogen fluoride-pyridine in acetonitrile produced PGE_1 methyl ester (**12**) (86%). Hydrolysis of the methyl ester **12** with porcine liver esterase[32] completed the synthesis of (-)-PGE_1 (**13**) (86%), which was identical with an authentic sample[14,33].

This synthetic method provides a short, four-step process to construct the PGE_1 skeleton from the chiral enone **R-4**. By application of this three-component coupling process, Misoprostol[34] (**16**), a well-known anti-ulcer agent, was obtained from racemic enone (±)-**4**. Combination of (±)-(E)-1-iodo-4-methyl-4-trimethylsilyloxy-1-octene,[34] (±)-**4**, and nitro olefin **6** gave **14** as a diastereometric mixture (57%), which afforded the Misoprostol **16** via the denitrated **15** (37% from **14**).



1



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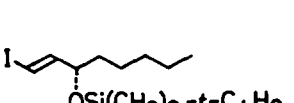
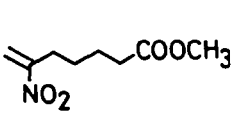
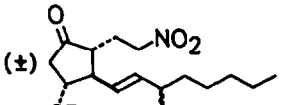


S-3

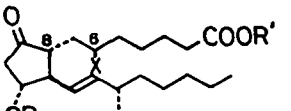
R-4



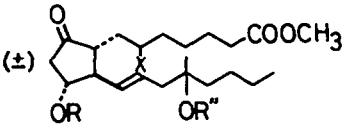
6



5, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$



9, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$, R'=CH$_3$, X=NO$_2$
10, R=H, R'=CH$_3$, X=NO$_2$
11, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$, R'=CH$_3$, X=H
12, R=X=H, R'=CH$_3$
13, R=R'=X=H

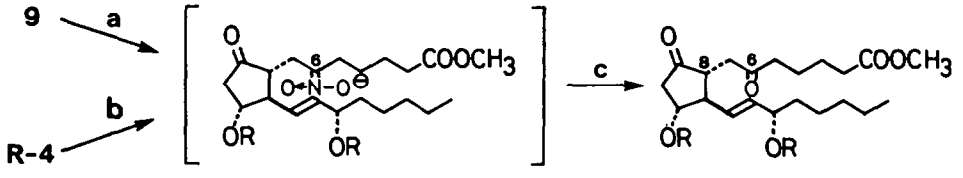


14, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$, R"=Si(CH$_3$)$_3$, X=NO$_2$
15, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$, R"=Si(CH$_3$)$_3$, X=H
16, R=R"=X=H

In situ conversion of the nitro-olefin trapping adduct to the 1,4-dicarbonyl compound

As mentioned above, treatment of the nitro-olefin-trapped intermediate with aqueous hydrogen chloride was found to give a 1,4-diketone product. A possible application of this methodology would be a single-pot construction of the 6-oxo-PGE$_1$ skeleton possessing a 1,4-diketone functionality. Preliminarily attempted conversion of the nitro derivative **9** into an oxo compound **19** under the original or modified Nef reaction conditions[35] was unsuccessful probably because of the instability of the β-hydroxy ketone system on the cyclopentanone ring of **9** under the conditions. Treatment of **9** only with the combination of triphenylphosphine[36] and aqueous buffered titanium(III) trichloride[35b] afforded the desired 6-oxo compound **19** in 16% yield.

It was conceivable that the nitro-olefin trapping should generate a nitronate intermediate, which corresponded to the intermediate in Nef reaction to convert a nitro group into an oxo function (Scheme 2). Thus, when conjugate-addition enolates was trapped with nitro olefin **6**, followed by the exposure of the reaction mixture to aqueous tetrahydrofuran solution of titanium(III) trichloride (12 equiv) and ammonium acetate[35b] (r.t., 18 h), there was successfully obtained the 6-oxo-PGE$_1$ derivative **19** (66%) accompanied with the C-8 epimer of **19** (10%) (Scheme 2). The C-8 epimer might be formed either in the trapping of the enolate with the nitro olefin **6** or during the reaction treating with the buffered titanium(III) trichloride solution. The isolated C-8 epimer was epimerized easily to the more stable isomer **19** under alkaline conditions using potassium acetate or with silica gel on TLC plate. It was considered that the reduction of the nitronate anion species **17** with a buffered titanium(III) trichloride solution



17 **19**

a) Ph$_3$P / aq. TiCl$_3$ / NH$_4$OAc; b) (i) **S-3**-*t*-BuLi / CuI-*n*-Bu$_3$P, (ii) **6**;
c) aq. TiCl$_3$ / NH$_4$OAc

Scheme 2 R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$

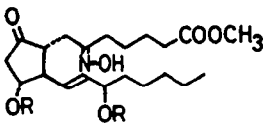
would proceed *via* 6-hydroxyimino derivatives[35b] **18** to result in the final 6-oxo product **19**. In fact, exposure of the reaction mixture to 3 equiv of the above reducing reagent at 0°C for 1.5 h gave the hydroxyimino compound **18** (21%) together with recovered **9** (28%), while treatment with 6 equiv of the reducing reagent at room temperature for 1.5 h gave **19** (17%) in addition to **18** (44%) and **9** (6%). Desilylation of separated more polar **19** with hydrogen fluoride-pyridine in acetonitrile produced 6-oxo-PGE_1 methyl ester (**20**) (92%), and hydrolysis of **20** with porcine liver esterase completed the synthesis of naturally occurring 6-oxo-PGE_1[37] (**21**) (89%). Thus conversion of the *in situ* generated nitronate intermediate **17** into the oxo compound **19** worked quite smoothly. According to this methodology, the known cytoprotective anti-ulcer agent[41] **24** (OU-1308) was obtained in two steps starting from **R-4**. The organocopper-mediated coupling reaction of (3*S*,5*S*,*E*)-3-*t*-butyldimethylsilyloxy-1-iodo-5-methyl-1-nonene[42] with the chiral enone **R-4**, and then with nitro olefin **6** resulted in the formation of the corresponding nitronate anion **22**. This intermediate **22** was treated *in situ* with a buffered titanium(III) trichloride solution to give the 6-oxo-PGE_1 derivative **23** (52%) which provided **24** after desilylation.

Application of the nitro-olefin trapping to the syntheses of 6-oxo-$PGF_{1\alpha}$ and PGI_2

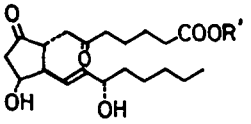
The three-component coupling reaction using the nitro-olefin trap resulted in the one-pot formation of 6-nitro- or 6-oxo-PGE_1 derivatives. Further chemical transformations of their C-6 functionalities open alternative ways to useful PGs such as PGI_2 or 6-oxo-$PGF_{1\alpha}$ (**28**). The latter compound is an inactive metabolite which is derived only from PGI_2[43] by hydration under chemical or physiological conditions and, consequently, is a useful compound as a diagnostic parameter[44] representing the concentration of PGI_2 under physiological conditions. An efficient synthesis of **28** has been achieved starting from the protected 6-nitro-PGE_1 (**9**) by the following four-step procedure. Reduction of **9** with diisobutylaluminum 2,6-di-*t*-butyl-4-methylphenoxide[45] in toluene gave 9α-alcohol **25a** (70%) accompanied with 9β-isomer **25b** (10%). Sodium borohydride reduction of **9** gave a mixture of **25a** (59%) and **25b** (31%). The nitronate intermediate formed by exposure of the nitro alcohol **25a** to 1 equiv of sodium methoxide in methanol was treated with a buffered titanium(III) trichloride[35b] in aqueous tetrahydrofuran to give the corresponding 6-oxo alcohol **26a** (70%). Removal of the silyl groups from **26a** with hydrogen fluoride-pyridine provided 6-oxo-$PGF_{1\alpha}$ methyl ester (**27a**) (96%). Hydrolysis of **27a** with 5N sodium hydroxide in methanol afforded 6-oxo-$PGF_{1\alpha}$ (**28**) (84%). This procedure opens a direct way to prepare 6-oxo-$PGF_{1\alpha}$ (**28**) from the chiral enone **R-4** not *via* PGI_2 derivatives.

Attempted generation of the PGI_2 skeleton from either 6-oxo-$PGF_{1\alpha}$ or its methoxy lactol resulted in the formation of a Δ^6-PGI_1 product.[46] An attempt[47] to reconstruct PGI_2 structure from 11,15-di-*O*-acetyl-6-oxo-$PGF_{1\alpha}$ methyl ester gave a mixture of PGI_2, (5*E*)-PGI_2, and Δ^6-PGI_1 derivatives in the ratio of 3.6:1.0:5.6 under the dehydration conditions. Under similar dehydrating conditions using anhydrous magnesium sulfate, bis-silylated 6-oxo-$PGF_{1\alpha}$ methyl ester **26a** gave a mixture of PGI_2 (**29**), (5*E*)-PGI_2 (**30**), and Δ^6-PGI_1 (**31**) in a ratio of 4.0:1.0:8.5 in 89% conversion yield. In order to improve the selectivity of the PGI_2 formation, **26a** was allowed to react at 0°C in the presence of zinc iodide and molecular sieves 4 Å, and the products, **29** and **31**, were obtained in a ratio of 1.0:2.3 in 16% conversion yield without the formation of **30**. Thus synthesis of PGI_2, as one of the ultimate goals, was feasible from the chiral enone **R-4** by a retro-biogenetic way *via* 6-oxo-$PGF_{1\alpha}$ easily available by the three-component coupling process.

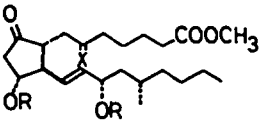
In conclusion, the present nitro-olefin trapping of the enolates *in situ* generated by conjugate addition of organocopper reagent to α,β-unsaturated ketones proceeded successfully to afford in a regiospecific manner the vicinally functionalized products such as 6-nitro-PGE_1 and 6-oxo-PGE_1 skeletons. The latter oxo products were obtained by *in situ* transformation of the nitronate species formed by the second Michael trapping of the initial conjugate adduct with nitro olefins in the same pot. Furthermore the three-component coupling product, 6-nitro-PGE_1, was converted into PGE_1, 6-oxo-$PGF_{1\alpha}$, and PGI_2.



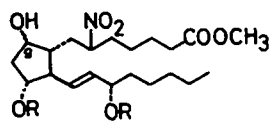
18, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$



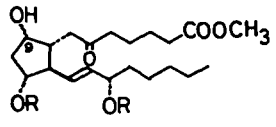
20, R'=CH$_3$
21, R'=H



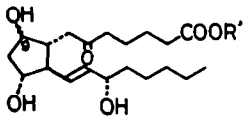
22, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$, X=N$^{\oplus}$O$^{\ominus}$O
23, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$, X=O
24, R=H, X=O



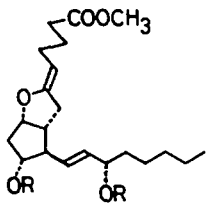
25a, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$, 9α-OH
25b, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$, 9β-OH



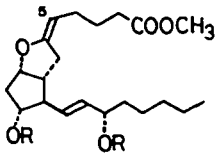
26a, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$, 9α-OH
26b, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$, 9β-OH



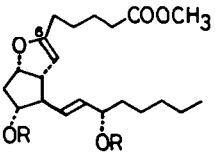
27a, R'=CH$_3$, 9α-OH
27b, R'=CH$_3$, 9β-OH
28, R'=H, 9α-OH



29, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$



30, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$



31, R=Si(CH$_3$)$_2$-*t*-C$_4$H$_9$

Experimental

IR spectra were recorded on a JASCO A102 spectrometer. ^{1}H- and ^{13}C-NMR spectra were obtained on a JEOL JNM-GX400 (400 MHz), a JEOL JNM-PS-100 (100 MHz), or a Varian EM 360A (60 MHz) spectrometer. Chemical shifts and coupling constants (J) are given in δ (ppm) relative to internal tetramethylsilane and Hz, respectively. The following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), b (broad). Mass spectra (MS) were taken at 70 or 20 eV on a HITACHI M-80B (FD-MS and high-resolution MS), a JEOL JMS D300 (high-resolution MS), or a LKB-9000 (EI-MS) mass spectrometer. Optical rotations were measured on a Union Giken PM-101 automatic polarimeter. For high-performance liquid chromatography (HPLC) analysis, a Shimadzu Model LC-6A equipped with a Shimadzu SPD-6A UV detector and a Shimadzu C-R3A chromatopac was employed. Thin-layer chromatography (TLC) was performed using Merck silica gel (Kiesel gel 60 F_{254}) analytical or preparative plates. Column chromatography was carried out on Wako gel C-300 or Daiso gel IR-60 silica gel. All reactions were carried out under argon or nitrogen. Solvents for reactions were purified if necessary before use by distillation from suitable drying agents. Solvents for extraction and chromatography were GR grades.

Nitro-olefin trapping of the enolates

3-Butyl-2-(2-nitropropyl)cyclopentanone (1)

Tributylphosphine (933 mg, 4.62 mmol) was added at room temperature (r.t.) to a suspension of copper(I) iodide (400 mg, 2.10 mmol) in dry ether (20 ml), and the resulting mixture was stirred at r.t. for 15 min. A 1.60 M hexane solution of n-butyllithium (1.31 ml, 2.10 mmol) was added at -78°C to the mixture. The whole mixture was stirred at -78°C for 5 min, then 2-cyclopentenone (164 mg, 2.00 mmol) in dry ether (6 ml) was added at -78°C during 2 min. After stirring at -78°C for 15 min, 2-nitropropene (183 mg, 2.10 mmol) in dry ether (6 ml) was added at -78°C , and the resulting mixture was stirred at -78°C for 20 min, at -30°C for 10 min, then at 0°C for 5 min. The reaction mixture was poured into saturated aq. NH_4Cl. The organic layer was taken up in hexane (100 ml), and the separated organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo to leave an oily residue. The residue was chromatographed on silica gel (40 g) with hexane-ethyl acetate (5:1) to give the three-component coupling product **1** (300 mg, 1.32 mmol, 66%) as a diastereomeric mixture: IR (neat), 1743 and 1552 cm^{-1}; NMR ($CDCl_3$) , δ 0.92 (3H, t), 1.1-2.7 (17H, m), 4.7-5.4 (1H, m); MS (m/z), 227 (M^+), 197, 181, 179, 170, 163, 155, 137, 123, 109, 95, 83, 81, 69, 67, 55 (100), 41; High-resolution MS for $C_{12}H_{21}NO_3$(M^+): Calcd m/z: 227.1521; Found: 227.1534.

3-Butyl-2-(2-oxopropyl)cyclopentanone (2)

After similar trapping reaction of the above cyclopentanone enolate with 2-nitropropene to the preparation of **1**, a 1.0 N solution of hydrochloric acid (20 ml) was added at 0°C to the reaction mixture, and the resulting mixture was stirred at 0°C for 5 min. Then, THF (10 ml) was added and the mixture was stirred at 40°C for 2 h. The resulting mixture was neutralized with $NaHCO_3$, extracted with ethyl acetate (2 × 15 ml). The organic extracts were combined, dried over

$MgSO_4$, and evaporated. The product mixture was separated by silica gel column chromatography using hexane-ethyl acetate (5:1) as eluant, to give the oxo product **2** (224 mg, 1.14 mmol, 7%) together with **1** (39 mg, 0.17 mmol, 9%). **2**: IR (neat), 1745 and 1723 cm^{-1}; NMR ($CDCl_3$), δ 0.90 (3H, t), 2.17 (3H, s), 1.1-2.4 (12H, m), 2.70 (2H, m); ^{13}C-NMR (multiplicity), δ 219.1 (s), 206.2 (s), 51.3 (d), 41.8 (t), 41.7 (t), 37.2 (t), 34.3 (t), 30.0 (d), 29.3 (t), 27.4 (q), 22.9 (t), 14.0 (q); MS (m/z), 196 (M^+), 153, 140, 139 (100), 135, 125, 97, 83, 79, 70, 55; High-resolution MS for $C_{12}H_{20}O_2$ (M^+): Calcd m/z: 196.1461: Found: 196.1332.

(±)-(2R*,3R*,4R*)-4-t-Butyldimethylsilyloxy-3-[(RS)-(E)-3-t-butyldimethylsilyloxy-1-octenyl]-2-(2-nitroethyl)cyclopentanone (5)

A 2.2 M pentane solution of t-butyllithium (0.9 ml, 2.0 mmol) was added at -78°C to a stirred solution of (±)-(E)-3-t-butyldimethylsilyloxy-1-iodo-1-octene [(±)-**3**; 405 mg, 1.1 mmol] in dry ether (10 ml), and the mixture was stirred at -78°C for 2 h. A solution of copper(I) iodide (200 mg, 1.05 mmol) and tributylphosphine (444 mg, 2.2 mmol) in dry ether (3 ml) was then added at -78°C, and the resulting mixture was stirred at -78°C for 1 h. Then, a solution of (±)-4-t-butyldimethylsilyloxy-2-cyclopentenone [(±)-**4**; 212 mg, 1.0 mmol] in dry ether (6 ml) was added at -78°C, and the resulting mixture was stirred at -78°C for 15 min, then at -40°C for 30 min. An ether solution (6 ml) of nitroethylene (73 mg, 1.0 mmol) was added at -78°C and the whole mixture was stirred at -78°C for 30 min, then at -40°C for 30 min. The reaction mixture was poured into saturated aq. NH_4Cl. The organic layer was taken up in hexane (2 × 100 ml), and the separated organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to afford 1.174 g of an oily product. Separation of the product by preparative TLC (hexane : ethyl acetate = 6:1) provided the enolate-trapping product **5** (142 mg, 0.27 mmol, 27%) as a racemic mixture of diastereoisomers: IR (neat), 1745, 1555, 1255, 1155, 1120, 1100, 970, 910, 840, 775, and 735 cm^{-1}; NMR ($CDCl_3$), δ 0.06 (12H, s), 0.86 (21H), 1.1-1.6 (8H, m), 1.8-3.0 (6H, m), 3.9-4.3 (2H, m), 4.63 (2H, t, J=7 Hz), 5.5-5.7 (2H, m); MS (m/z), 527 (M^+, 0.1), 512, 470 (100), 456, 338, 324, 313, 296, 271, 265, 240, 212, 185, 175, 155, 153, 99, 75, 73.

Application of nitro-olefin trapping to the synthesis of (-)-PGE_1

Preparation of 6-methoxycarbonyl-2-nitro-2-hexene (6)

Methyl 6-bromohexanoate (36.8 g, 176 mmol) was added at r.t. to a solution of sodium nitrite (20.7 g, 300 mmol) and phloroglucinol (25 g, 154 mmol) in DMSO (100 ml), and the mixture was stirred at r.t. for 20 h. The resulting mixture was poured into ice-water (200 ml) and ether (200 ml) with stirring. The organic layer was separated and the aqueous layer was extracted with ether (2 × 100 ml). The combined organic layers were washed with water, dried ($MgSO_4$), and evaporated under vacuum to give 26.9 g of a crude product, which was distillated to provide methyl 6-nitrohexanoate (**7**; 15.7 g, 89.7 mmol, 51%): bp 94-104°C/0.8 mmHg; IR (neat), 1740, 1550, 1435, 1380, 1255, 1200, 1175, 1100, 1010, and 875 cm^{-1}; NMR ($CDCl_3$), δ 1.2-1.8 (4H, m), 1.8-2.2 (2H, m), 2.36 (2H, t, J=6.5 Hz), 3.67 (3H, s), 4.44 (2H, t, J=7 Hz).

The nitro ester **7** (15.7 g, 89.7 mmol) was added at 0°C to a 3.0 N sodium hydroxide solution (90 ml). After stirring at 0°C for 3 h, a 35% aqueous formaldehyde solution (7.46 g, 91.5 mmol) was added, and the resulting mixture was continued to stir at 0°C for 5 h. To the mixture was added acetic acid (19.2 g, 320 mmol), and the resulting mixture was stirred at r.t. for 20 h. The mixture was treated with water, and the product was extracted with ethyl acetate (3 × 150 ml). The separated organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give a crude hydroxymethylated acid, which was treated with MeOH (200 ml) containing a catalytic amount of H_2SO_4 under reflux for 5 h. Removal of the solvent left a crude ester, which was taken up in ethyl acetate. The organic layer was washed with aq. $NaHCO_3$ and then brine, dried ($MgSO_4$), and concentrated in vacuo to give an almost pure hydroxymethylated nitro ester **8** (16.2 g, 78.9 mmol, 88%): IR (neat), 3480, 1735, 1555, 1460, 1440, 1365, 1330, 1210, 1180, 1075, 1020, 860, and 735 cm^{-1}; NMR ($CDCl_3$), δ 1.3-1.9 (6H, m), 2.32 (2H, t, J=6.5 Hz), 2.73 (1H, bs), 3.76 (3H, s), 3.90 (2H, d, J=5 Hz), 4.3-4.8 (1H, m).

A mixture of the above **8** (8.2 g, 40 mmol) and phthalic anhydride (8.88 g, 60 mmol) was heated at 180°C for 30 min, then at 150°C for 3 h. Ethyl acetate (200 ml) was added to the mixture, and the organic layer was washed with aq. $NaHCO_3$ and brine, dried ($MgSO_4$), and evaporated to give an oily residue (6.18 g), which was purified by silica gel column chromatography with hexane-ethyl acetate (4:1) to produce the nitro olefin **6** (2.68 g, 14.3 mmol, 36%). The product **6** (21.6 g, 115 mmol) was also obtained from **8** (30 g, 146 mmol) by treatment with mesyl chloride (16.7 g, 146 mmol) and triethylamine (38.6 g, 383 mmol) in methylene chloride (200 ml) at 0°C for 1 h in 79% yield after a similar work-up and purification. **6**: IR (neat), 3150, 3010, 1740, 1530, 1240, 1200, 1175, 1065, 1010, 945, 860, 810, and 750 cm^{-1}; NMR ($CDCl_3$), δ 1.4-1.8 (4H, m), 2.33 (2H, t, J=6 Hz), 2.60 (2H, dt, J=1 & 7 Hz), 3.64 (3H, s), 5.60 (1H, m), 6.41 (1H, d, J=2 Hz).

6-Nitro-PGE_1 methyl ester (10)

Treatment of (S,E)-3-t-butyldimethylsilyloxy-1-iodo-1-octene (**S-3**; 3.83 g, 10.4 mmol), $[\alpha]_D^{21}$ - 30.6°(c 1.57, CCl_4), with a 2.0 M pentane solution of t-butyllithium (10.4 ml, 20.8 mmol) in dry ether (100 ml) followed by mixing of the resulting vinyllithium solution with a solution of copper(I) iodide (1.98 g, 10.4 mmol) and tributylphosphine (4.20 g, 20.8 mmol) in dry ether (30 ml) gave the chiral organocopper reagent. To this reagent was added an ethereal solution (20 ml) of (R)-4-t-butyldimethylsilyloxy-2-cyclopentenone (**R-4**; 1.91 g, 9.0 mmol), $[\alpha]_D^{22}$ + 66.0° (c 1.00, MeOH, 98.5%ee), and then an ethereal solution (10 ml) of the nitro olefin **6** (1.94 g, 10.4 mmol). After sequential reaction under similar conditions, the resulting mixture was poured into saturated aq. NH_4Cl (500 ml), and taken up in hexane (500 ml). The extracted organic layer was separated, and the aqueous layer was extracted twice with hexane (500 ml). The combined extracts were washed with brine (500 ml), dried ($MgSO_4$), and concentrated under reduced pressure to leave 12 g of an oily residue, which was chromatographed on silica gel (150 g) with hexane-ethyl acetate (19:1 up to 4:1) to yield **9** (4.10 g, 6.4 mmol, 71%) as a diastereomeric mixture of the 6R and 6S epimers: $[\alpha]_D^{22}$ - 23.5° (c 1.07, MeOH); IR (neat), 1740, 1555, 1255, 1160, 1100,

1005, 970, 875, 860, 840, 810, and 775 cm^{-1}; NMR ($CDCl_3$), δ 0.06 (12H, s), 0.85 (21H), 1.1-2.6 (22H, m), 3.61 (3H, s), 3.8-4.3 (2H, m), 4.5-5.2 (1H, m), 5.35-5.55 (2H, m); MS (m/z), 626 (M-15), 610, 584, 570, 553, 498, 493, 464, 438, 421, 405, 330, 299, 277 (100), 245, 215, 175, 75; High-resolution MS for $C_{32}H_{60}NO_7Si_2$ (M-Me), Calcd m/z: 626.3908; Found 626.3913. ^{13}C-NMR spectral data for diastereomeric **9** are listed in Table 1.

A stirred solution of the bis-silyl ether **9** (630 mg, 0.98 mmol) in acetonitrile (10 ml) was treated with 47% aq. hydrogen fluoride (1.0 ml) at r.t. The mixture was stirred at r.t. for 1.5 h, neutralized with saturated aq. $NaHCO_3$, and the product was extracted twice with ethyl acetate (100 ml). The combined extracts were washed with brine, and dried over $MgSO_4$. Removal of the solvents in vacuo left a crude product, which contained the C-8 epimers of **10** as minor components (ca. 10%) estimated by HPLC (Zorbax SIL 4.6 mm × 25 cm, 7.5% isopropyl alcohol in hexane, 1.0 ml/min, t_R=43.5, 47.2 min for diastereomeric **10**, and t_R=31.3, 37.5 min for the C-8 epimers of **10**. The crude product was purified by silica gel (50 g) column chromatography using hexane-ethyl acetate (1:3) for elution to give an epimeric mixture (347 mg, 0.84 mmol, 86%) of the desilylated product **10**: $[\alpha]_D^{22}$ - 24.5° (c 0.20, MeOH); IR (neat), 3400, 1740, 1550, 1245, 1200, 1160, 1075, 1015, and 975 cm^{-1}; NMR ($CDCl_3$), δ 0.87 (3H, m), 1.0-3.1 (24H, m), 3.57 (3H, s), 3.8-4.2 (2H, m), 4.5-5.1 (1H, m), 5.3-5.6 (2H, m); MS (m/z), 395 (M-18), 377, 364, 347, 342, 324, 315, 299, 298, 277, 245, 227, 217, 199, 99 (100), 71; High-resolution MS for $C_{21}H_{33}NO_6$ (dehydration peak from molecular ion): Calcd m/z: 395.2306; Found: 395.2241.

(-)-PGE_1 (**13**)

To a refluxing solution of tributyltin hydride (2.18 g, 75 mmol) and azobisisobutyronitrile (41 mg, 0.25 mmol) in toluene (10 ml) was added dropwise during 15 min a solution of the nitro compound **9** (320 mg, 0.50 mmol) in toluene (5 ml), and the resulting mixture was heated to reflux at 110°C for 15 min. After cooling, the solution was chromatographed on silica gel (40 g) with hexane and then hexane-ethyl acetate (19:1) to give the denitrohydrogenated product **11** (130 mg, 0.22 mmol, 44%): $[\alpha]_D^{21}$ - 34° (c 0.62, MeOH); IR (neat), 1740, 1250, 1195, 1155, 1110, 1095, 1000, 965, 935, 865, 830, 805, and 770 cm^{-1}; NMR ($CDCl_3$), δ 0.05 (12H, s), 0.87 (21H), 1.1-1.9 (18H, m), 1.9-2.7 (6H, m), 3.70 (3H, s), 4.0-4.3 (2H, m), 5.55-5.70 (2H, m); MS (m/z), 581 (M-15), 565, 539, 536, 504, 464, 408, 407, 393, 376, 375, 301, 215, 75 (100); ^{13}C-NMR spectral data are listed in Table 1.

Pyridine (0.25 ml) and then hydrogen fluoride-pyridine (0.5 ml) were added to a stirred solution of the bis-silyl ether **11** (30 mg, 0.050 mmol) in acetonitrile (10 ml) at r.t., and the resulting mixture was stirred at r.t. for 2.5 h. The mixture was neutralized with saturated aq. $NaHCO_3$, and taken up in ethyl acetate (50 ml). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 50 ml). The combined organic layers were washed with aq. $KHSO_4$, then brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford an oily residue, which was separated by preparative TLC (ethyl acetate) to yield the desilylated **12** (16 mg, 0.043 mmol, 86%): $[\alpha]_D^{21}$ - 52° (c 0.03, MeOH), (lit.[24] $[\alpha]_D^{23}$ - 53.8° (c 1.04, MeOH); IR (neat), 3400, 1740, 1250, 1200, 1165, 1105, 1075, 1020, 965, and 720 cm^{-1}; NMR ($CDCl_3$), δ 0.89 (3H, m), 1.16-1.72 (18H, m), 1.96-3.0 (8H, m), 3.68 (3H, s), 3.96-4.24 (2H, m), 5.56-5.72 (2H, m); MS (m/z), 350 (M-18), 332, 306, 297, 281, 279 (100), 274, 265, 247, 229, 221, 219, 193, 169, 151, 137, 123, 122, 109, 109, 99, 95, 81, 71. ^{13}C-NMR spectrum of **12** was identical with that of the authentic sample.[14]

A solution of the methyl ester **12** (55 mg, 0.150 mmol) in acetone (1.0 ml), and then porcine liver esterase (0.1 ml) were added at r.t. to a phosphate buffer solution (10 ml, pH 8). After stirring at r.t. for 4 h, the mixture was acidified to pH 5 with 0.1 N HCl, saturated with $(NH_4)_2SO_4$, and the product was extracted with ethyl acetate (4 × 50 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to give an almost pure PGE_1 **13** (46 mg, 0.129 mmol, 86%), which was recrystallized from ethyl acetate to furnish a crystalline product: mp 115-116°C, $[\alpha]_D^{21}$ - 55° (c 0.73, THF) (lit.[33] mp 115-116°C, $[\alpha]_D^{20}$ - 54.3° (c 1.0, THF). The product **13** was identical (TLC, IR, MS, ^1H-NMR and ^{13}C-NMR) with an authentic sample[14] of PGE_1.

(±)-(16RS)-15-Deoxy-16-hydroxy-16-methyl-PGE_1 methyl ester (**16**)

A similar three-component coupling procedure using (±)-(E)-1-iodo-4-methyl-4-trimethylsilyloxy-1-octene (1.87 g, 5.5 mmol), (±)-**4** (1.27 g, 6.0 mmol), and nitro olefin **6** (1.03 g, 5.5 mmol) gave **14** (2.06 g, 3.14 mmol, 57%) after usual work-up and purificaton: IR (neat), 1740, 1555, 1250, 1100, 970, 860, 835, and 775 cm^{-1}; NMR ($CDCl_3$), δ 0.04 (6H, s), 0.12 (9H, s), 0.85 (12H), 1.14 (3H, s), 1.1-2.7 (22H, m), 3.63 (3H, s), 3.9-4.4 (1H, m), 4.5-5.2 (1H, m), 5.3-5.7 (2H, m); High-resolution MS for $C_{30}H_{56}NO_7Si_2$ (M-Me): Calcd m/z: 598.3595; Found: 598.3583.

Reductive denitration of **14** (1.66 g, 2.70 mmol) with tributyltin hydride (3.68 g, 12.7 mmol) and azobisisobutyronitrile (100 mg) in toluene (10 ml) at 110°C for 10 min yielded the denitrohydrogenated **15** (644 mg, 1.13 mmol, 42%) after purification of the crude product by column chromatography: IR (neat), 1740, 1250, 1170, 1100, 1060, 970, 860, 835, 775, and 750 cm^{-1}; NMR ($CDCl_3$), δ 0.05 (6H, s), 0.10 (9H, s), 0.86 (12H), 1.15 (3H, s), 1.1-1.9 (16H, m), 2.1-2.6 (8H, m), 3.64 (3H, s), 4.2-4.5 (1H, m), 5.2-5.8 (2H, m); FD-MS (m/z), 512 (M-56), 395, 173 (100), 58 (6); High-resolution MS for $C_{27}H_{51}O_5Si_2$ (M-^{t}Bu): Calcd m/z: 511.3275; Found 511.3269.

Deprotection of **15** (568 mg, 1.0 mmol) with hydrogen fluoride-pyridine (0.4 ml) in acetonitrile (10 ml) at r.t. for 2 h produced the desilylated **16** (336 mg, 0.88 mmol, 88%) after similar work-up and purification by column chromatography: IR (neat), 3410, 1740, 1160, 970, and 730 cm^{-1}; NMR ($CDCl_3$), δ 0.87 (3H, t), 1.13 (3H, s), 1.1-1.8 (16H, m), 2.0-3.0 (10H, m), 3.63 (3H, s), 3.7-4.3 (1H, m), 5.1-5.9 (2H, m); High-resolution MS for $C_{22}H_{36}O_4$ (dehydration peak from molecular ion): Calcd m/z: 364.2613; Found 364.2621.

In situ conversion of the nitro-olefin trapping adduct to the 1,4-dicarbonyl compound 6-Oxo-PGE_1 (**21**)

Treatment of the chiral vinyl iodide **S-3** (883 mg, 2.4 mmol) with a 2.0 M pentane solution of t-butyllithium (2.4 ml, 4.8 mmol) in ether (20 ml) followed by mixing of the resulting vinyllithium

solution with a solution of copper(I) iodide (457 mg, 2.4 mmol) and tributylphosphine (970 mg, 4.8 mmol) in ether (6 ml) formed the chiral organocopper reagent. To the solution was added an ethereal solution (5 ml) of the chiral enone **R-4** (424 mg, 2.0 mmol) and then an ethereal solution (5 ml) of the nitro olefin **6** (449 mg, 2.4 mmol) in a similar procedure. The resulting reaction mixture was poured into a solution of 25% aq. titanium(III) trichloride solution (15 ml, 24 mmol) and ammonium acetate (11 g, 144 mmol) in water (50 ml) and THF (100 ml). After stirring at r.t. for 18 h, the mixture was neutralized with aq. $NaHCO_3$, and taken up in hexane (300 ml). The extracted organic layer was separated and the aqueous layer was extracted twice with hexane (500 ml). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo to provide 3.09 g of a crude oily product, which was separated by silica gel column chromatography (100 g, hexane : ethyl acetate = 19:1 up to 1:1) to give a more polar oxo product **19** (806 mg, 1.32 mmol, 66%) and a less polar C-8 epimer of **19** (118 mg, 0.193 mmol, 10%). The less polar C-8 epimer of **19** was found to be epimerized to the thermodynamically more stable **19** under an alkaline condition using potassium acetate or with silica gel on TLC plate. **19**: $[\alpha]_D^{22}$ - 39.3° (c 1.04, MeOH); IR (neat), 1745, 1720, 1250, 1155, 1100, 1000, 965, 935, 865, 835, 805, 775, and 640 cm^{-1}; NMR ($CDCl_3$), δ 0.03 (12H, s), 0.86 (21H), 1.1-1.7 (12H, m), 2.15-2.70 (10H, m), 3.60 (3H, s), 3.85-4.20 (2H, m), 5.35-5.60 (2H, m); MS (m/z), 553 (M-57), 478, 422, 421, 407, 403, 389, 371, 321, 297, 289, 269, 215, 203, 143, 132, 111, 76, 75 (100); High-resolution MS for $C_{29}H_{53}O_6Si_2$ ($M-^tBu$): Calcd m/z: 553.3380; Found 553.3367. C-8 epimer of **19**: IR (neat), 1740, 1720, 1250, 1155, 1100, 830, and 770 cm^{-1}; NMR ($CDCl_3$), δ 0.04 (12H, s), 0.83 (21H), 1.1-2.0 (12H, m), 2.0-3.3 (10H, m), 3.57 (3H, s), 3.8-4.3 (2H, m), 4.65-5.65 (2H, m); MS (m/z), a similar pattern to **19**; High-resolution MS for $C_{29}H_{53}O_6Si_2$ ($M-^tBu$): Calcd m/z: 553.3380; Found 553.3393.

Desilylation of the bis-silyl ether **19** (305 mg, 0.5 mmol) by treatment with pyridine (0.5 ml) and hydrogen fluoride-pyridine (1.0 ml) in acetonitrile (20 ml) at r.t. for 1.5 h followed by usual work-up gave a crude product (213 mg). Purification of the product by silica gel (10 g) column chromatography (hexane : ethyl acetate = 1:4) to provide **20** (176 mg, 0.46 mmol, 92%): $[\alpha]_D^{21}$ - 48.5° (c 0.71, MeOH); mp 44-44.5°C (recrystallized from hexane-ether) (lit.[40] mp 39-40°C); IR (neat), 3400, 1740, 1720, 1250, 1200, 1160, 1075, 1020, 970, and 730 cm^{-1}; NMR ($CDCl_3$), δ 0.87 (3H, m), 1.1-1.7 (12H, m), 2.0-3.0 (12H, m), 3.63 (3H, s), 3.7-4.3 (2H, m), 5.45-5.65 (2H, m); MS (m/z), 382 (M^+), 378, 368, 365, 364, 347, 346, 315, 293, 269, 265, 261, 243, 233, 215, 204, 203, 187, 151, 143 (100), 133, 121, 115, 111 (100), 107, 99, 83, 71, 55; High-resolution MS for $C_{21}H_{34}O_6$ (M^+): Calcd m/z: 382.2354; Found 382.2372.

A similar desilylation of the C-8 epimer of **19** (115 mg, 0.189 mmol), usual work-up, and purification gave the C-8 epimer of **20** (59 mg, 0.154 mmol, 82%): $[\alpha]_D^{20}$ + 80° (c 2.25, MeOH); IR (neat), 3450, 1740, 1710, 1245, 1160, 1075, and 965 cm^{-1}; NMR ($CDCl_3$), δ 0.86 (3H, t), 1.0-1.7 (12H, m), 2.1-3.3 (12H, s), 3.60 (3H, s), 3.70-4.40 (2H, m), 4.75-5.75 (2H, m); MS (m/z), a similar pattern to **20**: High-resolution MS for $C_{21}H_{34}O_6$ (M^+): Calcd m/z: 382.2354; Found 382.2366. ^{13}C-NMR spectral data for **20** and its C-8 epimer are listed in Table 1.

A similar hydrolysis of the methyl ester **20** (88 mg, 0.23 mmol) with porcine liver esterase (0.2 ml) in acetone (2 ml) and pH 8 phosphate buffer solution (20 ml) at r.t. for 20 h gave the acid **21** (75 mg, 0.20 mmol, 89%), after usual work-up and purification: $[\alpha]_D^{20}$ - 50° (c 1.55, MeOH); mp 65°C (recrystallized from hexane-ether) (lit.[40] 67-69°C); IR (KBr), 3400, 1740, 1720, 1710, 1245, 1160, 1075, and 970 cm^{-1}; NMR ($CDCl_3$), δ 0.83 (3H, t), 1.1-1.7 (12H, m), 2.1-2.7 (10H, m), 3.75-4.15 (2H, m), 5.27 (3H, bs), 5.43 (2H, m).

11,15-Bis-O-(t-butyldimethylsilyl)-6-hydroxyimino-PGE$_1$ methyl ester (18)

Treatment of a nitronate intermediate **17**, formed from **R-4** (1.12 g, 5.3 mmol) by a similar three-component coupling process, with a solution of 25% aq. titanium(III) trichloride (12 ml, 19 mmol) and ammonium acetate (8.7 g, 114 mmol) in water (100 ml) and THF (80 ml) at 0°C for 1.5 h yielded **9** (948 mg, 1.48 mmol, 28%), **18** (688 mg, 1.10 mmol, 21%), and **19** (128 mg, 0.22 mmol, 4%). Another reaction (r.t., 1.5 h) of **17** from **R-4** (424 mg, 2.0 mmol) with a solution of 25% aq. titanium(III) trichloride (8 ml, 13 mmol) and ammonium acetate (6 g, 78 mmol) in water (20 ml) and MeOH (70 ml) also afforded **9** (69 mg, 0.108 mmol, 6%), **18** (547 mg, 0.875 mmol, 44%), and **19** (211 mg, 0.346 mmol, 17%). **18** as a mixture of syn and anti isomers: IR (neat), 3370, 1740, 1720, 1250, 1080, 965, 870, 835, and 775 cm^{-1}; NMR ($CDCl_3$), δ 0.03 (12H, s), 0.87 (21H, s), 1.1-1.8 (12H, m), 2.0-2.7 (10H, m), 3.64 (3H, s), 3.8-4.3 (2H, m), 5.4-5.7 (2H, m); FD-MS (m/z), 625 (M^+), 568, 436, 384, 57; High-resolution MS for $C_{33}H_{63}NO_6Si_2$ (M^+): Calcd m/z: 625.4193; Found 625.4168. ^{13}C-NMR spectral data are listed in Table 1.

The 6-hydroxyimino **18** (100 mg, 0.16 mmol) was treated with a solution of 25% aq. titanium(III) trichloride (1.14 ml, 1.84 mmol) and ammonium acetate (848 mg, 11.0 mmol) in water (1.4 ml) and THF (7 ml) at r.t. for 24 h. A similar work-up and purification gave the oxo compound **19** (89 mg, 0.15 mmol, 94%).

Preparation of 19 from 9

Triphenylphosphine (173 mg, 0.66 mmol) was added at r.t. to a solution of **9** (144 mg, 0.22 mmol) in THF (5 ml), and the resulting mixture was stirred at r.t. for 15 min. Then, a solution of 25% aq. titanium(III) trichloride (1.64 ml, 2.64 mmol) and ammonium acetate (1.22 g, 15.8 mmol) in water (2 ml) and MeOH (5 ml) was added to the reaction mixture, and the whole mixture was stirred at r.t. for 5 h. A usual work-up and purification gave the oxo product **19** (21 mg, 0.034 mmol, 16%), which was identical (IR, NMR, MS, and TLC) with the foregoing authentic one.

(17S)-17,20-Dimethyl-6-oxo-PGE$_1$ methyl ester (24)

A similar three-component coupling process using (3S,5S,E)-3-t-butyldimethylsilyloxy-1-iodo-5-methyl-1-nonene, $[\alpha]_D^{21}$ -35.4° (c 0.55, MeOH), (5.16 g, 13.0 mmol), **R-4** (2.12 g, 10 mmol), and **6** (2.25 g, 12.0 mmol) followed by treatment with a solution of 25% aq. titanium(III) trichloride (74.4 ml, 120 mmol) and ammonium acetate (55.5 g, 720 mmol) in water (184 ml) and THF (500 ml) at r.t. for 18 h gave the 6-oxo product **23** (3.32 g, 5.2 mmol, 52%) after usual work-up and purification: $[\alpha]_D^{25}$ - 35.5° (c 1.02, MeOH); IR (neat), 1740, 1720, 1250, 1100, 967, 835, and

pyridine (0.15 ml) at r.t. for 1 h also gave **27a** (42 mg, 0.106 mmol, 96%) after isolation.

The epimeric **26b** (47 mg, 0.077 mmol) was desilylated with hydrogen fluoride-pyridine (0.25 ml) in acetonitrile (5 ml) at r.t. for 2 h yielded the corresponding **27b** (25 mg, 0.064 mmol, 83%), after isolation: IR (neat), 3300, 1735, 1710, 1260, 1170, 1040, and 960 cm^{-1}; NMR ($CDCl_3$), δ 0.87 (3H, t), 1.1-2.7 (22H, m), 3.62 (3H, s), 3.0-4.2 (6H, m), 5.30-5.55 (2H, m); MS (m/z), a similar pattern to **27a**; High-resolution MS for $C_{21}H_{34}O_5$ (dehydration peak from molecular ion): Calcd m/z: 366.2404; Found: 366.2399. ^{13}C-NMR spectral data for **27b** are listed in Table 1.

Hydrolysis of the ester **27a** (26 mg, 0.068 mmol) with a 5.0 N NaOH solution (0.14 ml, 0.68 mmol) in MeOH (1 ml) was carried out at r.t. for 3 h, then at 40°C for 3 h. Aq. NH_4Cl was added to the reaction mixture, and the whole mixture was acidified with dilute HCl. The organic layer was taken up in ethyl acetate (50 ml), and the separated aqueous layer was extracted with ethyl acetate (4 × 50 ml). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated to provide a crude product (25 mg), which was chromatographed on silica gel (5 g) with ethyl acetate-acetone-acetic acid (90:10:1) to give 6-oxo-$PGF_{1\alpha}$ **28** (21 mg, 0.057 mmol, 84%): $[\alpha]_D^{21}$ - 9.6° (c 1.04, MeOH); IR (neat), 3400, 1715, 1245, 1045, 975, 915, 875, 845, 800, and 730 cm^{-1}; NMR ($(CD_3)_2CO$: $CDCl_3$ = 2:3), δ 0.86 (3H, t), 1.1-2.5 (22H, m), 3.5-4.7 (3H, m), 5.2-5.5 (2H, m), 5.6-6.1 (4H, bs).

Dehydration of **26a**

A solution of **26a** (180 mg, 0.29 mmol) in benzene (10 ml) was refluxed for 10 h over anhydrous $MgSO_4$ (400 mg). A few drops of triethylamine was added to the cooling reaction mixture, and the precipitated $MgSO_4$ was filtered off. Evaporation of the resulting filtrate left an oily residue, which was chromatographed on Florisil treated with hexane containing 5% triethylamine with hexane-ethyl acetate (200:1) containing 0.1% triethylamine as an eluant to give a mixture (44 mg, 25%) of three cyclized products together with the recovered **26a** (130 mg, 72%): ^1H-NMR (400 MHz) spectrum of the dehydrative cyclization products separated from the reaction mixture showed the characteristic signals of PGI_2 skeleton **29** (δ 4.07-4.13 and 4.54-4.59), (5E)-PGI_2 isomer **30** (δ 4.49-4.54 and 4.64-4.68), and Δ^6-PGI_1 isomer **31** (δ 3.70-3.77, 4.60-4.64, and 4.74-4.80). The product ratio was estimated by the integration of these peak area to be **29:30:31** = 8.5:4.0:1.0.

Molecular sieves 4 Å (500 mg), and then ZnI_2 (22 mg, 0.07 mmol) were added at 0°C to a solution of **26a** (86 mg, 0.14 mmol) in methylene chloride (2 ml), and the resulting mixture was stirred at 0 °C for 2 h. Triethylamine was added to the reaction mixture, and the organic layer was taken up in ether. The resulting organic layer was washed with aq. $NaHCO_3$, and then brine. The separated organic layer was dried ($MgSO_4$) and evaporated to afford a crude product, which was chromatographed on Florisil treated with 5% triethylamine-hexane using the same elution solvent to give a mixture (8 mg, 10%) of dehydrated products **29** and **31** accompanied with the recovered **26a** (31 mg, 36%). The ratio of **29** and **31** was established to be 1.0:2.3 by ^1H-NMR (400 MHz) in a similar manner.

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