Total Synthesis of Prostaglandin $F_{2\alpha}$ via Nickel-Promoted Stereoselective Cyclization of 1,3-Diene and Aldehyde

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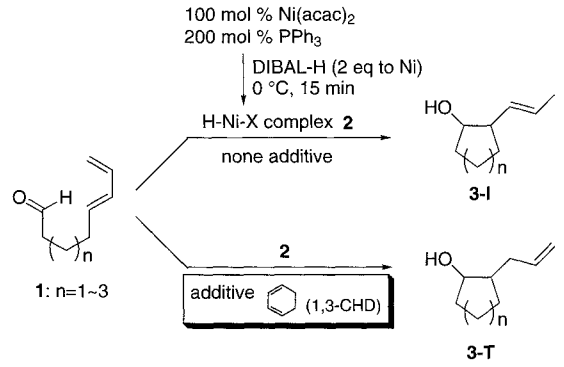
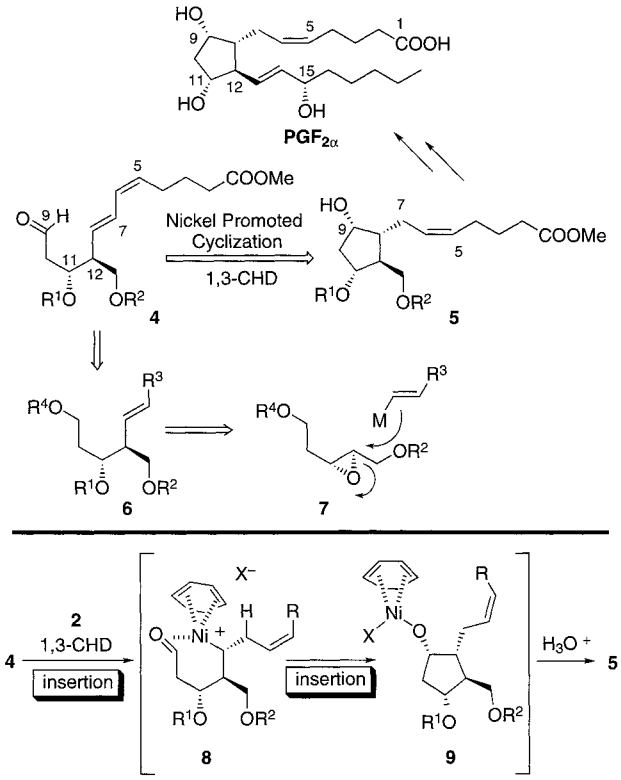
Abstract: The total synthesis of prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$) was accomplished *via* nickel-promoted cyclization of 1,3-diene and aldehyde in a chain in the presence of 1,3-cyclohexadiene (1,3-CHD). The cyclization of **16** prepared in an optically active form from chiral epoxy alcohol **10** stereoselectively gave the key intermediate **18**, which has both an α-chain and the four contiguous chiral carbon centers in $PGF_{2\alpha}$, in a one-pot reaction. Intermediate **18** was successfully transformed into $PGF_{2\alpha}$.

The nickel-promoted intramolecular oligomerization of a 1,3-diene and multiple bonds is a promising method for the regio- and stereospecific construction of cyclic compounds.[1,2] In a recent study, we found that the reaction of **1** with hydride nickel complex **2**, generated from $Ni(acac)_2$ and PPh_3 by treatment with DIBAL-H, gave the 5- to 7-membered cyclized products **3-I** stereoselectively *via* a π-allylnickel complex.[3a] We also found that the cyclized product **3-T**, which is a regio-isomer of **3-I** with respect to the olefin, is produced predominantly under similar reaction conditions, except for the addition of 1,3-cyclohexadiene (1,3-CHD) to the reaction mixture *via* a double-insertion process.[3b] These unique properties encouraged us to use this cyclization for the synthesis of natural products.



Scheme 1

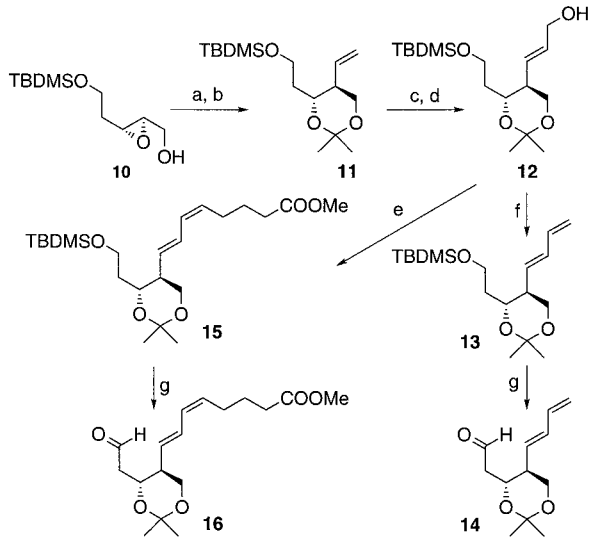
For decades, prostaglandins (PGs) have attracted the interest of synthetic organic chemists as targets for total synthesis, and various efficient methods for their syntheses have been reported.[4] In this study, we sought to apply nickel-promoted cyclization in the presence of 1,3-CHD to the synthesis of $PGF_{2\alpha}$, as shown in Scheme 2. If the nickel-promoted cyclization of 1,3-diene **4**, which has an aldehyde in a tether, in the presence of 1,3-CHD proceeds according to our reaction mechanism,[3b] stereoselective C-C bond formation is expected to occur between C-8 and C-9[5] in the cyclization of **4**. During this cyclization, the *Z*-olefin at C-5 in **4** would be intact and retain its geometry to give the cyclopentanoid **5**, since the added 1,3-CHD would prevent the coordination of the 1,3-diene moiety of **4** to the nickel metal, which would result in the insertion of the *E*-olefin at C-7 in **4** into the hydride-nickel bond of **2** to produce nickel complex **8**. The cyclized product **5** should be readily transformed into $PGF_{2\alpha}$. The substrate **4**, which has a side chain corresponding to the α-chain in $PGF_{2\alpha}$, should be easily prepared in an optically active form from a chiral epoxy alcohol **7**.



Scheme 2

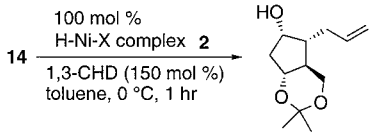
Initially, we investigated the cyclization of **14** using hydride nickel complex **2** in the presence of 1,3-CHD. The regiospecific ring-opening reaction of **10**[6] was accomplished by treatment with vinylmagnesium bromide (5 equiv.) in the presence of CuCN (0.5 equiv.)[7] to give the desired 1,3-diol in 70% yield,[8] which was converted into acetonide **11**. Ozonolysis of **11** and successive reaction of the resulting crude aldehyde with (carbomethoxymethylene)triphenylphosphorane gave α,β-unsaturated ester, which was treated with DIBAL-H to produce allyl alcohol **12**. After PCC oxidation of **12**, the resulting aldehyde was condensed with the Wittig reagent generated from methyl triphenylphosphonium bromide and BuLi to give 1,3-diene **13**, which was converted into **14** by deprotection of the TBDMS group followed by oxidation with Dess-Martin reagent. To a stirred toluene solution of hydride nickel complex **2**, generated *in situ* by treatment of $Ni(acac)_2$ (100 mol %) and PPh_3 (200 mol %) with DIBAL-H (200 mol %), was added 150 mol % of 1,3-CHD at 0 °C, and the solution was stirred for a few minutes. A toluene solution of substrate **14** was then added to the resulting mixture and the solution was stirred at room temperature for 1 hr. After hydrolysis of the reaction mixture, the cyclized product **17** was obtained in 93% yield as a single isomer. The stereochemistry of **17** was unambiguously determined by its NOESY spectrum, which indicated that the four contiguous chiral carbon centers in $PGF_{2\alpha}$ were present.

Next, the cyclization of **16**, which has a side chain corresponding to the α-chain in $PGF_{2\alpha}$, was examined. After oxidation of **12** with PCC reagent, the resulting aldehyde was reacted with the Wittig reagent



(a) CH_2=CHMgBr, CuCN, Et_2O-THF, -12 °C, 70%. (b) 2,2-dimethoxypropane, PPTS, rt, 88%. (c) (1) O_3, CH_2Cl_2, -78 °C; (2) Ph_3P=$CHCO_2Me$ benzene, 65 °C, 90% (2 steps). (d) DIBAL-H, toluene, -78 °C, 95%. (e) (1) PCC, MS 4A, NaOAc, CH_2Cl_2, 0 °C; (2) $BrPh_3PC_4H_8COOH$, NaH, DMSO, rt; (3) CH_2N_2, MeOH-Et_2O, 65% (3 steps). (f) (1) PCC, MS 4A, CH_2Cl_2, 0 °C; (2) Ph_3PMeBr, BuLi, THF, -78 °C~0 °C, 81% (2 steps). (g) (1) TBAF, THF, rt; (2) Dess-Martin reagent, CH_2Cl_2, 0 °C, **14** from **13**: 79%, **16** from **15**: 84% (2 steps).

Scheme 3



17: 93%

Scheme 4

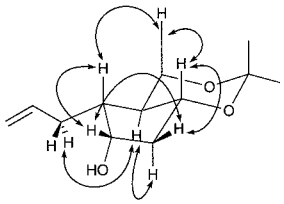
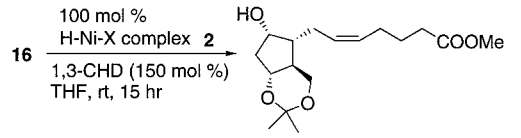


Fig. 1. NOESY correlation of **17**

generated from (4-carboxybutyl)triphenylphosphonium bromide and sodium methylsulfinylmethylide in DMSO,[9] and then treated with diazomethane to give the desired (5*Z*,7E)-dodecadienoic acid derivative **15** (65% from **12**) along with the (5*E*,7*E*)-isomer (14%), which were easily separated by silica gel column chromatography. The substrate **16** for nickel-promoted cyclization was obtained in good yield, using procedures similar to those for **14**. Compound **16** was reacted with hydride nickel complex **2** in toluene in the presence of 1,3-CHD, and we were very pleased to find that the cyclized product **18** was obtained in 28% yield as a single isomer. As expected, the α-side chain of **18** had a *Z*-geometry and the four contiguous chiral carbon centers in $PGF_{2\alpha}$ were constructed stereoselectively from the simple linear diene **16**.[10] When THF was used as a solvent, the yield of **18** was improved and we succeeded in obtaining **18** in 53% yield.

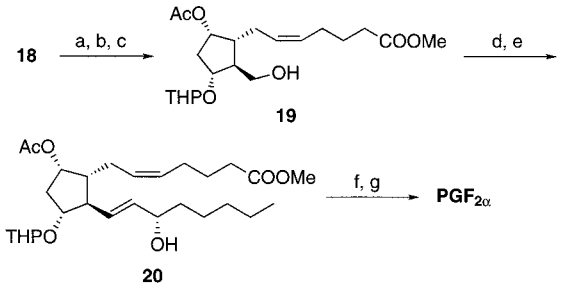
Compound **18** was transformed into $PGF_{2\alpha}$ according to a procedure similar to those in the literature,[11] as shown in Scheme 6. After manipulation of the protecting groups in **18**, introduction of a ω-chain



18: 53% (recovery of **16**: 15%)

Scheme 5

followed by stereoselective reduction with (*S*)-BINAL-H[12] provided **20** in good yield, which was successfully converted into $PGF_{2\alpha}$ in the naturally occurring form.[13]



(a) Ac_2O, Pyridine, CH_2Cl_2, rt, 95%. (b) (1) DOWEX 50WX8, MeOH, 50 °C; (2) $^tBuPh_2SiCl$, Et_3N, CH_2Cl_2, 90% (2 steps). (c) (1) DHP,PPTS, CH_2Cl_2, rt; (2) TBAF, THF, rt, 100% (2 steps). (d) (1) PCC, MS 4A, NaOAc, CH_2Cl_2, 0 °C; (2) $(MeO)_2POCH_2CO(CH_2)_4CH_3$, NaH, THF, rt, 76% (2 steps). (e) (*S*)-binaphthol, $LiAlH_4$, EtOH, THF, -100 °C~-78 °C, 92%. (f) AcOH-H_2O-THF, 40 °C, 93%. (g) 1*N* NaOH, MeOH-THF, rt, 95%.

Scheme 6

In conclusion, we have demonstrated that nickel-promoted cyclization can be used to construct cyclopentanoids, and have achieved the total synthesis of $PGF_{2\alpha}$. A unique characteristic of this synthesis is the stereoselective formation of the key intermediate **18** from the simple linear diene **16** in a one-pot reaction. The present results pave the way for the development of conceptually new methods for the synthesis of cyclopentanoids. Further studies along these lines are in progress.

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References and Notes

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2. (a) For [4+4] cycloadditions, see: Wender, P. A.; Tebbe, M. J. *Synthesis* **1991**, 1089 and references cited therein. (b) Tamao, K.; Kobayashi, K.; Ito, Y. *Synlett* **1992**, 539. Tamao, K.; Kobayashi, K.; Ito, Y. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 381. (c) For [4+2] cycloadditions, see: Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1996**, *61*, 824 and references cited therein. (d) For nickel-promoted intermolecular reactions of 1,3-diene and carbonyl compound, see: Baker, R.; Cook, A. H.; Crimmin, M. J. *J. Chem. Soc. Chem. Commun.* **1975**, 727. Baker, R.; Crimmin, M. J. *J. Chem. Soc. Perkin I* **1979**, 1264.

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5. All numbering used in Scheme 2 shows the position of the carbons in the eventual $PGF_{2\alpha}$.

6. The epoxy-alcohol **10** was obtained in 94% yield (91% ee) by Sharpless epoxidation of 6-(*tert*-butyldimethylsiloxy)-2-pentenol using $Ti(OPr^i)_4$ (6 mol %), (–)-diethyl tartrate (8 mol %), and ^tBuOOH (2.0 equiv.) in the presence of MS 4A in CH_2Cl_2 at -20 °C.

7. Tius, M. A.; Fauq, A. H. *J. Org. Chem.* **1983**, *48*, 4131.

8. In this reaction, the 1,2-diol formed by nucleophilic attack of vinyl cuprate at the C-3 position in **10** was also obtained in 17% yield, and this was easily separated from the desired 1,3-diol by silica gel column chromatography.

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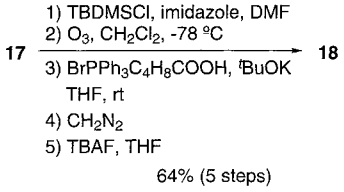
10. To confirm the stereochemistry of **18**, **17** was converted into **18** as described below. All of the spectral data of the product derived from **17** were completely identical to those of **18** obtained by nickel-promoted cyclization.



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13. The synthesized $PGF_{2\alpha}$ showed $[\alpha]_D^{29}$ +22.7 (*c* 1.59, THF), which agreed with the reported $[\alpha]_D^{25}$ +23.5 (*c* 1.00, THF),[14] and its ^{13}C-NMR spectrum was identical to those reported elsewhere.[15] The spectral data of $PGF_{2\alpha}$ methyl ester, obtained by treatment of synthetic $PGF_{2\alpha}$ with diazomethane, were also completely identical to those reported previously.[16]

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