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New Chiral Synthetic Intermediate for Prostaglandins

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Summary : Preparation of an optically active synthetic intermediate **3** starting from D-mannitol and its conversion to PGF2α (**1**) by using [3+2] cycloaddition of the nitrile oxide derivative of **3** followed by conjugate addition of the vinylzincate to exocyclic enone **2** are described.

Although a number of efficient routes to prostaglandins and prostacyclins have been explored,[1] little has been known about a common synthetic intermediate[2] for both prostaglandins and prostacyclins. We describe here synthesis of a new chiral synthetic intermediate **3** for these medicinally important compounds and its conversion to $PGF_{2\alpha}$ (**1**) via the Stork's intermediate **2**.[4a]

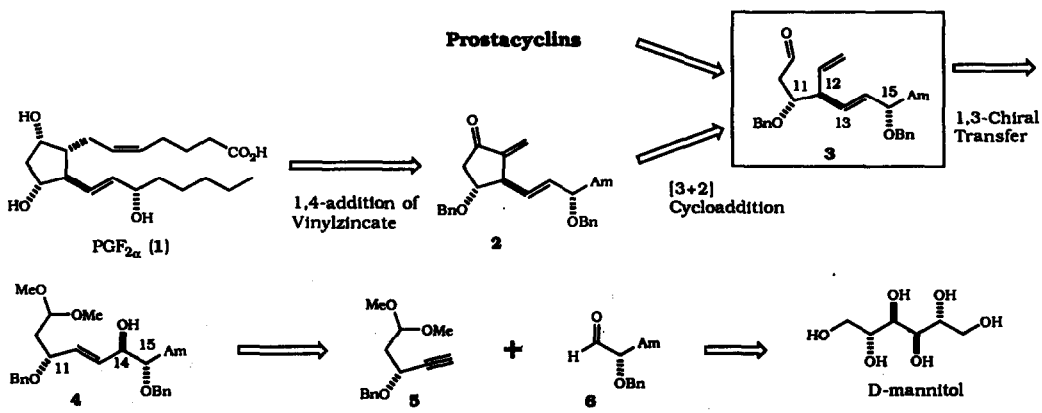
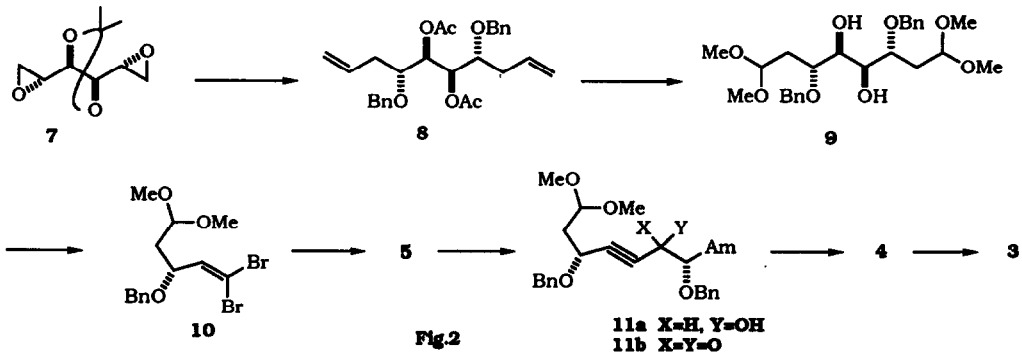


Fig.1

Our synthetic strategy (Fig.1) involves [3+2] cycloaddition[3] of the nitrile oxide derivative of aldehyde **3** to construct the 5 membered exocyclic enone **2**[4] and conjugate addition of the (*Z*)-vinylzincate[5] to **2**, leading to PGF2α(**1**). The C-C chirality at C-12 and the *E*-Δ^{13} double bond in **3** are introduced from the C-O chirality at C(14) in the allylic alcohol **4** by Claisen rearrangement.[6,7] The C-O chiralities of acetylene **5**

and aldehyde **6** are directly used as those of the hydroxy groups at C-11, 15 in **4**. Both **5** and **6** are prepared from D-mannitol.

The key intermediate **3** was synthesized as follows (Fig.2). The diepoxide **7** was prepared from D-mannitol in four steps.[8] Epoxide opening of **7** with vinylmagnesium chloride in the presence of CuCN[9] followed by protection of the secondary alcohol as the benzylether (BnBr, NaH in THF), hydrolysis of the isopropylidene group (p-TsOH/MeOH) and acetylation of the resulting diol gave the diacetate **8** in 70% overall yield from **7**. Transformation of the terminal double bonds to the dialdehydes (O_3 in MeOH at -78 °C, Me_2S) and those protections as the dimethylacetal ($CH(OMe)_3$/p-TsOH) and hydrolysis of the diacetates (K_2CO_3/MeOH) provided the diol **9** in 73% overall yield from **8**. Oxidative cleavage of the adjacent hydroxyl groups in **9** ($Pb(OAc)_4$, K_2CO_3 in benzene, 96% yield) and Wittig olefination[10] of the resulting aldehyde with CBr_4 and PPh_4 gave the dibromide **10** in 58% yield. Generation of the lithium acetylide of **5** from **10** using Corey-Fuchs protocol,[10] followed by addition of the aldehyde **6**[11] gave, in 62% yield, the alcohol **11a**, which was oxidized to the α-benzyloxyketone **11b** in 49% yield by using Swern oxidation. Stereoselective reduction[12] of the ketone in **11b** with $Zn(BH_4)_2$ in Et_2O (*anti* : *syn* = 92 : 8) and *E*-selective reduction[13] of the triple bond with $LiAlH_4$ gave the allylic alcohol **4** in 69% overall yield from **11a**. Johnson-Claisen rearrangement of **4** with $CH_3C(OEt)_3$ at 120 °C induced the required C-12(R) chirality with the formation of the *E*-Δ^{13} double bond. Reduction of the resulting ethyl ester with $LiAlH_4$ gave the primary alcohol in 98% overall yield from **4**. Selenation of the primary alcohol (o-$NO_2C_6H_4SeCN$, Bu_3P in THF)[14] followed by oxidative elimination of the o-nitrophenyl selenide (H_2O_2/THF) and acid hydrolysis of the acetal group gave the aldehyde **3**[15] in 80% overall yield.



7 **8** **9** **10** **5** **4** **3**

Fig.2

Then we examined the intramolecular [3+2] cycloaddition of the nitrile oxide derivative of **3** to construct the exocyclic enone **2** by using the Kozikowski's method.[3f] Treatment of the aldehyde **3** with NH_2OH·HCl in pyridine and reaction of the resulting oxime with 5% sodium hypochlorite in the presence of Et_3N gave the desired isoxazoline **12** in 68% yield. In this cycloaddition, attack of the nitrile oxide occurred

only toward the terminal olefin. Thus chemoselectivity and stereoselectivity of the [3+2]cycloaddition based on MM2 transition state modeling are discussed in subsequent publication. The isoxazoline **12** was converted to exocyclic enone **2**[16] in 86% yield by hydrogenation of **12** over W-2 Raney nickel in the presence of boric acid and subsequent treatment of the β-hydroxy ketone with MsCl and DMAP.

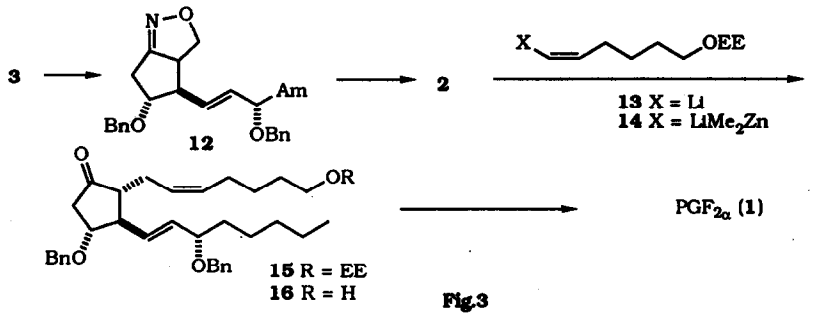


Fig.3

Introduction of the α-side chain to exocyclic enone **2** was carried out as follows. The (*Z*)-vinylzincate **14** was prepared by addition of the lithiated **13**[17] to a solution of $ZnMe_2$, which was generated[18] separately from $ZnCl_2$·TMEDA complex and two equiv. of MeLi in THF at -20 °C. The exocyclic enone **2** was added to the zincate **14** at -78 °C to give the ketone **15** in 95% yield. Deprotection of the ethoxyethyl group with PPTS in MeOH provided the alcohol **16**[19] in 97% yield. Oxidation of the primary alcohol in **16** to the carboxylic acid (CrO_3/H_2SO_4) followed by stereoselective reduction of the C-9 ketone with L-selectride gave the 9(S)-alcohol in 74% overall yield. Removal of the benzyl group with Na metal in liquid NH_3 afforded $PGF_{2\alpha}$(**1**) in 75% yield. Physical properties (NMR, IR) of the synthetic $PGF_{2\alpha}$ methyl ester were identical with those of authentic ester.[20] Further study on the synthesis of prostacyclins from the key intermediate **3** is currently under investigation.

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11) Optically active α-benzyloxyaldehyde **6** was synthesized in the following way. Treatment of the 2S,5S derivative of diepoxide **7**, which was prepared from D-mannitiol,[8a] with n-butylmagnesium bromide in the presence of CuCN gave the diol which was protected as a benzylether. Acid hydrolysis of the acetonide group followed by oxidative cleavage of the resulting diol with $Pb(OAc)_4$ gave aldehyde **6** in 44% overall yield. $[\alpha]^{25}_D$ = +33.08° (c 1.30, $CHCl_3$).
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15) ^{1}H NMR($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.1 Hz, 3 H), 1.2-1.7 (m, 8 H), 2.58 (ddd, J = 1.5, 4.0, 16.9 Hz, 1 H), 2.71 (ddd, J = 2.2, 7.7, 16.9 Hz, 1 H), 3.15 (m, 1 H), 3.73 (m, 1H), 4.04 (dt, J = 7.7, 4.0 Hz, 1H), 4.35 (d, J = 12.1 Hz, 1 H), 4.55 (d, J = 12.1 Hz, 1 H), 4.56 (d, J = 11.4 Hz, 1 H), 4.62 (d, J = 11.4 Hz, 1 H), 5.12 (dt, J = 17.2, 1.5 Hz, 1 H), 5.17 (dt, J = 10.3, 1.5 Hz, 1 H), 5.46 (ddd, J = 1.0, 7.7, 15.4 Hz, 1 H), 5.65 (dd, J = 7.7, 15.4 Hz, 1 H), 5.87 (ddd, J = 7.3, 10.3, 17.2 Hz, 1 H), 7.23-7.35 (m, 10 H), 9.77 (m, 1 H). IR (neat) 1725, 1456, 1355, 1089, 1030 cm^{-1}. $[\alpha]^{25}_D$ = +3.81° (c 0.892, $CHCl_3$).
16) ^{1}H NMR($CDCl_3$, 400 MHz) δ 0.87 (t, J = 7.1 Hz, 3 H), 1.18-1.73 (m, 8 H), 2.46 (dd, J = 7.3, 18.1 Hz, 1 H), 2.74 (ddd, J = 0.6, 6.7, 18.1 Hz, 1 H), 3.52-3.58 (m, 1H), 3.78 (q, J = 6.9 Hz, 1H), 3.95 (dt, J = 7.3, 6.7 Hz, 1 H), 4.38 (d, J = 11.8 Hz, 1 H), 4.60 (d, J = 11.8 Hz, 1 H), 4.62 (s, 2H), 5.26 (dd, J = 0.8, 3.0 Hz, 1 H), 5.58 (dd, J = 6.9, 15.2 Hz, 1 H), 5.61 (dd, J = 6.9, 15.2 Hz, 1 H), 6.14 (dd, J = 0.8, 3.0 Hz, 1 H), 7.27-7.34 (m, 10 H). IR (neat) 1731, 1640, 1495, 1454, 1350, 1250 cm^{-1}. HRMS Calcd for $C_{28}H_{34}O_3$: 418.2509 Found: 418.2540. mp. 42.0-43.0 °C (white needle, hexane). $[\alpha]^{25}_D$ = -90.38° (c 0.511, $CHCl_3$).
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19) ^{1}H NMR($CDCl_3$, 400 MHz) δ 0.88 (t, J = 7.1 Hz, 3 H), 1.20-1.75 (m, 12 H), 2.00-2.13 (m, 3 H), 2.23 (dd, J = 8.8, 18.9 Hz, 1 H), 2.28-2.48 (m, 2 H), 2.69-2.79 (m, 2 H), 3.61 (t, J = 6.4 Hz, 2H), 3.76 (m, 1 H), 3.91 (dt, J = 7.3, 8.8 Hz, 1 H), 4.37 (d, J = 11.7 Hz, 1 H), 4.61 (d, J = 11.7 Hz, 1 H), 4.55-4.62 (m, 2 H), 5.31 (m, 1 H), 5.44 (m, 1 H), 5.57 (dd, J = 7.3, 15.4 Hz, 1H), 5.62 (dd, J = 7.3, 15.4 Hz, 1H), 7.24-7.35 (m, 10 H). IR (neat) 3310, 1730, 1455, 1355, 1155, 1059, 968 cm^{-1}. mp. 49.5-50.5 °C (white needle, hexane). $[\alpha]^{25}_D$ = -38.51° (c 0.322, $CHCl_3$).
20) We thank Dr. Hamanaka (Ono pharmaceutical Co.) for providing us authentic sample of $PGF_{2\alpha}$.

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