CHEMISTRY LETTERS, pp. 2095-2098, 1992.

Synthesis of Allyl Ester of Prostaglandin E and the Conversion of the Allyl Ester Moiety into Carboxylic Acid by Chemical Method. A Highly Practical Synthesis of Natural PGE_1 and Limaprost

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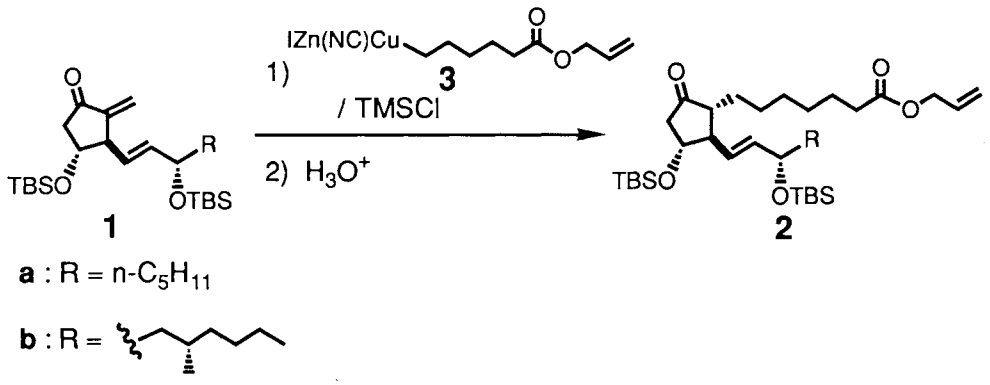
Synthesis of prostaglandin E allyl ester via two-component coupling process and the conversion of the allyl ester moiety into free carboxylic acid by the reaction with HCO_2H-Et_3N in the presence of a palladium catalyst has been described.

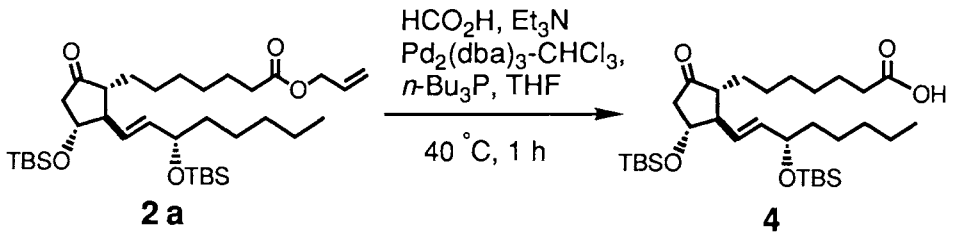
The hydrolysis of methyl ester of prostaglandin E (PGE) is unavoidable step for synthesis of PGE through two- and three-component coupling processes. This step is usually carried out by using enzymes or microorganisms, because the β-hydroxy (or alkoxy) ketone moiety embeded in PGE is intolerable under the conditions of chemical hydrolysis.[1] Enzymes or microorganisms, however, are sensitive in terms of structures of the substrate and it causes sometimes trouble for synthesis of PGE analogues, thus the development of an efficient chemical method for conversion of the ester moiety of PGE into free carboxylic acid has been anticipated.

Recently we have devoted our efforts to make the two-component coupling synthesis of prostaglandins as industrially viable process.[2] We have succeeded in developing highly practical method for synthesis of Stork's intermediate (**1**)[2a] and also have succeeded in introducing α-side chains having ester group directly onto **1** by using zinc-copper reagents.[2b] With these results in hand we were interested in the recent report from Tsuji's research group which described that allyl esters were converted to the 1-olefins and carboxylic acids by the reaction of ammonium formate using a palladium catalyst, and thus the allyl group could be used as a carboxy-protecting group.[3,4] Herein we report the synthesis of allyl ester of PGE (**2**) by the reaction of **1** with the corresponding zinc-copper reagent of α-side chain, and its conversion into PGE under the Tsuji's conditions.

The reaction of the enone **1a** with the copper regent **3** prepared from I-$(CH_2)_5$-COO-$CH_2CH{=}CH_2$ via zinc compound in the presence of Me_3SiCl[5] provided the corresponding silyl enol ether in essentially quantitative yield, which was hydrolyzed in aqueous *i*-PrOH-Et_2O in the presence of a catalytic amount of pyridium *p*-toluenesulfonate to afford the disilyl ether of PGE_1 allyl ester (**2a**)[6] in 76% yield.



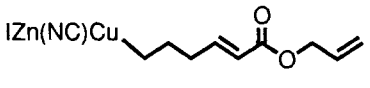
The conversion of the allyl ester moiety of **2a** into free carboxylic acid was carried out as follows: to a solution of aqueous HCO_2H (88%, 5.6 μL, 1.13 mmol), Et_3N (0.13 mL, 0.96 mmol) and $Pd_2(dba)_3$-$CHCl_3$ (33.1 mg, 0.032 mmol, dba = dibenzylideneacetone) in THF (3.2 mL) was added *n*-Bu_3P (31.9 μL, 0.128 mmol) and the mixture was stirred for 15 min at room temperature. To this mixture was added a solution of **2a** (200 mg, 0.32 mmol) in THF (0.7 mL), and then the mixture was heated at 40 °C for 1 h. To the reaction



mixture were added brine (10 mL) and hexane (10 mL). The organic layer was separated and the aqueous layer was extracted with hexane (5 mL). The combined organic layers were dried over $MgSO_4$, concentrated and chromatographed on silica gel to afford the disilyl ether of PGE_1 (**4**) (172.6 mg) in 93% yield, the spectroscopic data of which were identical with that of authentic sample.[2a]

Next, we applied this chemical conversion method for the synthesis of a powerful antithrombotic prostaglandin analogue Limaprost (Ono-Dainihon),[7] since we had found that the emzymatic hydrolysis of the methyl ester of Limaprost using porcine liver esterase was very slow and did not complete even after 5 days

reaction. The reaction of **1b** with the organocopper compound **5** afforded **6**[8] ($[\alpha]_D^{21}$ -32.9° (*c* 1.63, $CHCl_3$)) in 77% yield. The reaction of **6** with HCO_2H-Et_3N in the presence of $Pd_2(dba)_3$-$CHCl_3$ for 2 h at 40 °C



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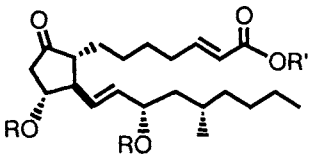

6 : R = TBS, R' = $CH_2CH{=}CH_2$

Limaprost : R = R' = H

afforded the disilyl ether of Limaprost[9] ($[\alpha]_D^{20}$ -35.1° (*c* 1.53, $CHCl_3$)) in 94% yield, which was in turn converted into Limaprost in 73% yield by treatment with aqueous HF (50%) in acetonitrile. The spectroscopic data, mp, and *Rf* value on thin layer chromatography of Limaprost thus obtained were in good agreement with the literature ones.[10]

In conclusion, we have succeeded for the first time in conversion of the ester moiety of PGE into free carboxylic acid by chemical method, which undoubtedly simplifies the two-component coupling synthesis of PGs.

References

1) A. F. Kluge, K. G. Untch, and J. H. Fried, *J. Am. Chem. Soc.*, **94**, 7827 (1972); C. J. Sih, R. G. Salomon, P. Price, and R. Sood, G. Peruzzotti, *ibid.*, **97**, 857 (1975); C. J. Sih, J. B. Heather, R. Sood, P. Price, G. Peruzzotti, L. F. H. Lee, S. S. Lee, *ibid.*, **97**, 865 (1975); A. Hazato, T. Tanaka, T. Toru, N. Okamura, K. Bannai, S. Sugiura, K. Manabe, and S. Kurozumi, *Nippon Kagaku Kaishi,* **1983**, 1390.

2) a) S. Okamoto, Y. Kobayashi, H. Kato, K. Hori, T. Takahashi, J. Tsuji, and F. Sato, *J. Org. Chem.*, **53**, 5590 (1988); b) H. Tsujiyama, N. Ono, T. Yoshino, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, **31**, 4481 (1990); c) T. Yoshino, S. Okamoto, and F. Sato, *J. Org. Chem.*, **56**, 3205 (1991) and references cited therein.

3) J. Tsuji, I. Minami, and I. Shimizu, *Synthesis*, **1986**, 623; J. Tsuji and T. Yamakawa, *Tetrahedron Lett.*, **1979**, 613.

4) H. Kunz and H. Waldmann, *Angew. Chem., Int. Ed. Engl.*, **23**, 71 (1984); R. Deziel, *Tetrahedron Lett.*, **28**, 4371 (1987); P. D. Jeffrey and S. W. McCombie, *J. Org. Chem.*, **47**, 587 (1982); Y. Shimoji, K. Tomita, T. Hashimoto, F. Saito, Y. Morisawa, H. Mizuno, R. Yorikane, and H. Koike, *J. Med. Chem.*, **35**, 816 (1992).

5) P. Knochel, M. C. P. Yeh, S. C. Berk, and J. Talbert, *J. Org. Chem.*, **53**, 2390 (1988).

6) ^{1}H NMR ($CDCl_3$, 300MHz) δ=0.01, 0.04 and 0.05 (12H, 3s), 0.87 and 0.89 (18H, 2s), 0.81-0.93 (3H, m), 1.16-1.75 (18H, m), 1.87-1.98 (1H, m), 2.17 (1H, dd, *J* = 8.3, 18.3 Hz), 2.31 (2H, t, *J* = 7.5 Hz), 2.44 (1H, dt, *J* = 10.9, 7.7 Hz), 2.62 (1H, dd, *J* = 18.3, 6.9 Hz), 3.98-4.15 (2H, m), 4.57 (2H, d, *J* = 5.7 Hz), 5.18-5.36 (2H, m), 5.49 (1H, dd, *J* = 7.2, 15.9 Hz), 5.59 (1H, dd, *J* = 15.9, 4.8 Hz), 5.91 (1H, ddt, *J* = 10.4, 17.2, 5.7 Hz). ^{13}C NMR ($CDCl_3$, 75MHz) δ=-4.8, -4.7, -4.4, 14.0, 17.9, 18.1, 22.6, 24.8, 25.0, 25.7, 25.8, 26.6, 27.6, 28.9, 29.4, 31.8, 34.1, 38.4, 47.5, 53.2, 53.8, 64.8, 72.6, 73.1, 117.9, 128.7, 132.2, 136.2, 173.2, 216.0.

7) M. Hayashi, S. Kori, I. Ohyama, S. Iguchi, and T. Okada, Br. Pat. 1 545 213. T. Tsuboi, N. Hatano, K. Nakatsuji, B. Fujitani, K. Yoshida, M. Shimizu, A. Kawasaki, M. Sakata, and M. Tsuboshima, *Arch. Int. Pharmacodyn.*, **247**, 89 (1980); *Adv. Prostaglandin Thromboxane Res.*, **6**, 347 (1980); P. G. Adaikan, S. M. M. Karim, *Prostaglandin Med.*, **6**, 449 (1981).

8) ^{1}H NMR ($CDCl_3$, 300MHz) δ=0.02 and 0.05 (12H, 2s), 0.87 and 0.89 (18H, 2s), 0.70-1.00 (6H, m), 1.02-1.81 (15H, m), 1.85-2.03 (1H, m), 2.08-2.25 (3H, m), 2.44 (1H, dt, *J* = 10.7, 6.9 Hz), 2.63 (1H, dd, *J* = 18.2, 6.9 Hz), 3.98-4.09 (1H, m), 4.11-4.25 (1H, m), 4.63 (2H, d, *J* = 5.0 Hz), 5.15-5.40 (2H, m), 5.45-5.64 (2H, m), 5.82 (1H, d, *J* = 15.4 Hz), 5.87-6.03 (1H, m), 6.97 (1H, dt, *J* = 15.4, 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75MHz) δ=-4.7, -4.6, -4.2, 14.2, 18.0, 18.2, 20.0, 23.1, 25.8, 25.9, 26.4, 27.5, 28.2, 29.2, 32.0, 36.9, 46.3, 47.5, 53.2, 53.5, 64.8, 71.1, 73.2, 117.9, 121.0, 128.9, 132.4, 136.3, 149.4, 166.1, 215.7.

9) ^{1}H NMR ($CDCl_3$, 300MHz) δ=0.02 and 0.05 (12H, 2s), 0.87 and 0.89 (18H, 2s), 0.75-0.99 (6H, m), 1.00-1.88 (15H, m), 1.90-1.99 (1H, m), 2.10-2.28 (3H, m), 2.44 (1H, dt, *J* = 10.7, 7.1 Hz), 2.63 (1H, dd, *J* = 18.1, 6.8 Hz), 3.98-4.09 (1H, m), 4.11-4.22 (1H, m), 5.45-5.62 (2H, m), 5.81 (1H, d, *J* = 15.7 Hz), 7.04 (1H, dt, *J* = 15.7, 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75MHz) δ= -4.6, -4.5, -4.1, 14.3, 18.1, 18.3, 20.1, 23.2, 25.9, 26.0, 26.5, 27.6, 28.2, 29.3, 32.2, 37.0, 46.3, 47.6, 53.3, 53.7, 71.2, 73.3, 120.8, 128.9, 136.4, 151.9, 172.0, 216.2.

10) M. Hayashi, S. Iguchi, T. Okada, and A. Kawasaki, Ger. Offen. DE 30 02 677 (1980).

(Received July 28, 1992)