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A Highly Efficient Approach to Prostaglandins via Radical Addition of α Side-Chains to Methylenecyclopentanones. Total Synthesis of Natural PGE_1, Limaprost and New Prostaglandin Derivatives.

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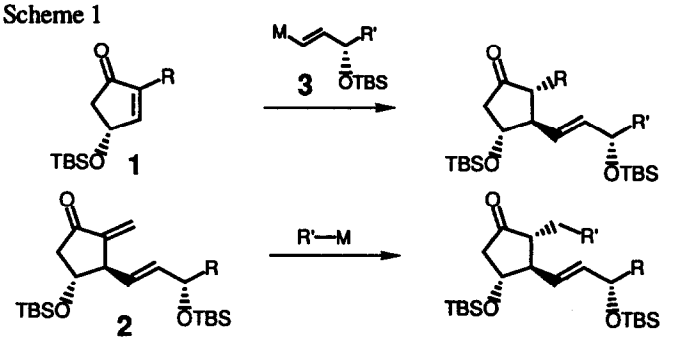
Abstract: Reaction of methylenecyclopentanones 2 with alkyl iodides via radical 1,4-addition pathway proceeds in good yields, thus providing an easy method for synthesis of not only known prostaglandins such as PGE_1 and Limaprost but also new prostaglandin derivatives.

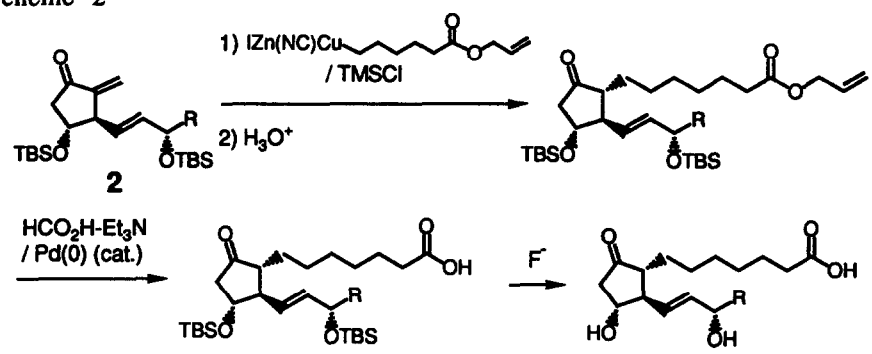
Chemical synthesis of natural and synthetic prostaglandins (PGs) has attracted much interest in laboratory and in industry. Although numerous synthetic methods have been developed,[1] only a few methods are efficient, general and flexible.[2] Recently we have directed our efforts to make the two-component coupling synthesis of PGs shown in Scheme 1 as general and industrially applicable process.[3] We have succeeded in developing highly practical methods to prepare all chiral key intermediates used in Scheme 1 as enantiomerically pure forms, i.e. enones 1[3b] and 2[3b] as well as the ω side-chain unit 3[3a), 4]. We

Scheme 1



have also succeeded in introducing the α side-chain unit having ester group directly into the enone 2 via zinc-copper reagent[3c] and in successive conversion of the C-1 (PG numbering) ester group into free carboxylic acid by a chemical method[3f] as shown in Scheme 2.

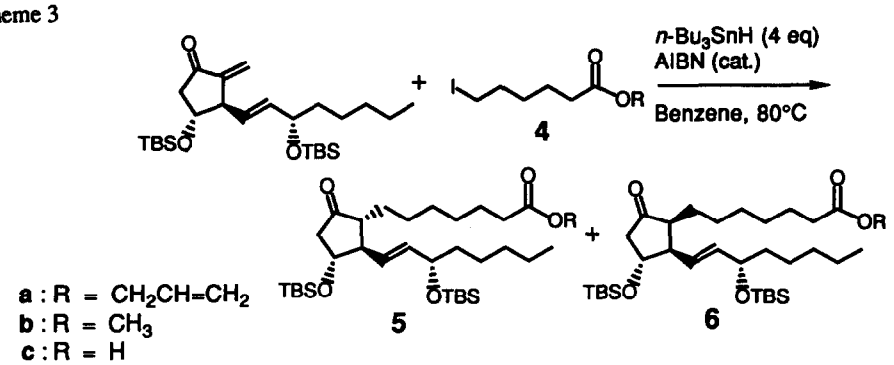
Scheme 2



Herein we report an alternative introduction of α side-chain into **2** via radical pathway, which not only simplifies the synthesis of natural PGs and PG analogues presently undergoing clinical trials but also enables the synthesis of new PGs.

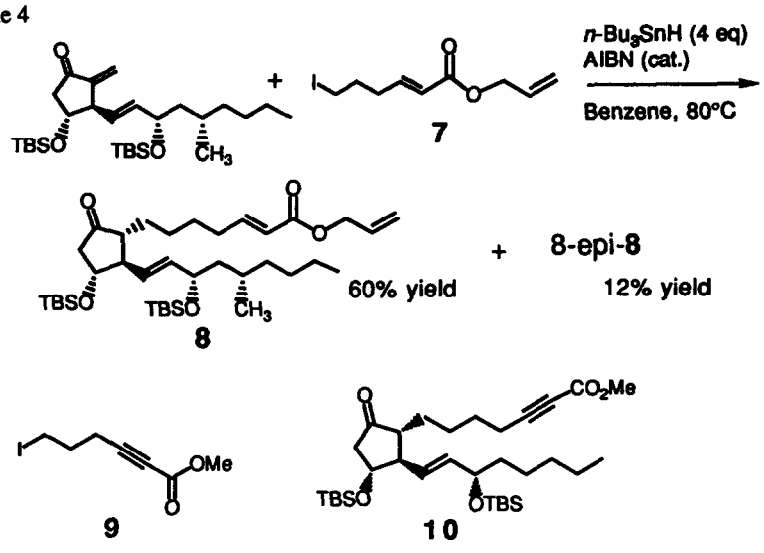
When **2** (R = *n*-C_5H_{11}) was reacted with allyl ester of 6-iodohexanoic acid (**4a**) (4 eq.) in the presence of $^nBu_3SnH$ (4 eq.) and AIBN (cat.) in benzene at 80°C, radical 1,4-addition took place to afford a mixture of two diastereoisomers. These were readily separated by column chromatography (SiO_2) to give **5a**[3f] having desired 8α configuration and 8β isomer **6a** in 61% and 12% yields, respectively (Scheme 3). Similarly, the reaction with methyl 6-iodohexanoate (**4b**) afforded **5b**[3c] in 55% isolated yield with 10% yield of **6b**. 6-Iodohexanoic acid (**4c**) also reacted with **2** to afford a 5:1 mixture of **5c** and **6c** in 50% total yield which, however, were not separable each other by column chromatography.

Scheme 3

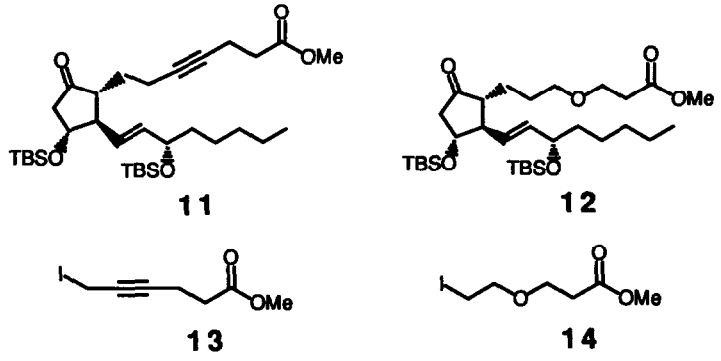


Application of this method to the synthesis of Limaprost (Ono-Dainihon),[5] a powerful antithrombotic PG analogue, was also carried out. As shown in Scheme 4, in spite of the presence of an additional double bond, the iodide **7** reacted cleanly with the corresponding enone to afford 60% isolated yield of allyl ester of Limaprost as bissilyl ether derivative (**8**)[3f] and 12% yield of its 8-epimer. Similarly 2,2,3,3-tetradehydro PGE_1 derivative **10**[3c] was obtained in 61% yield (with 12% yield of 8-epi-**10**) by the reaction of **2** (R = *n*-C_5H_{11}) with ω-iodoalkynyl ester **9**.[6]

Scheme 4



To demonstrate a further applicability of this radical method we have synthesized PG derivatives **11** and **12**. Thus the reaction of **2** (R = *n*-C_5H_{11}) with the iodides **13** and **14** provided **11**[7] in 33%



yield and **12**[8] in 65% yield, respectively.[9] Noteworthy is the fact that the reaction of **2** with the organometallic compound derived from **13** usually afforded a mixture of acetylenic and allenic compounds, while it is difficult to synthesize organometallic derivative from **14**.

The introduction of α side-chain into **2** was previously carried out by using organometallic derivatives. Since radicals are compatible with various functional groups which usually cannot coexist with organometallic derivatives, the present finding opens up an easy access to new PGs which has been difficult to synthesize so far. In all reactions, however, a considerable amount of 8-epi-PGs are coproduced. Thus we are now investigating the possibility of the epimerization of them to natural PGs under basic conditions.[10]

References

1) See, for example ; Roberts, S. M.; Scheinmann, F. *New Synthetic Routes to Prostaglandins and Thromboxanes*. Academic Press, New York, 1982 ; Bindra, J. S.; Bindra, R. *Prostaglandin Synthesis*, Academic Press, New York, 1977 ; See also 2d.

2) (a) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.*, **1969**, *91*, 5675. (b) Just, G.; Simonovitch, C.; Lincoln, F. H.; Schneider, W. P.; Axen, U.; Spero, G. B.; Pike, J. E. *J. Am. Chem. Soc.*, **1969**, *91*, 5364. (c) Kelly, R.; VanRheenen, V. *Tetrahedron Lett.*, **1973**, 1709. (d) Noyori, R.; Suzuki, M. *Angew. Chem. Int. Ed. Engl.*, **1984**, *23*, 847.

3) (a) Kitano, Y.; Matsumoto, T.; Wakasa, T.; Okamoto, S.; Shimazaki, T.; Kobayashi, Y.; Sato, F.; Miyaji, K.; Arai, K. *Tetrahedron Lett.*, **1987**, *28*, 6351. (b) Okamoto, S.; Kobayashi, Y.; Kato, H.; Hori, K.; Takahashi, T.; Tsuji, J.; Sato, F. *J. Org. Chem.*, **1988**, *53*, 5590. (c) Tsujiyama, H.; Ono, N.; Yoshino, T.; Okamoto, S.; Sato, F. *Tetrahedron Lett.*, **1990**, *31*, 4481. (d) Yoshino, T.; Okamoto, S.; Sato, F. *J. Org. Chem.*, **1991**, *56*, 3205. (e) Okamoto, S.; Yoshino, T.; Tsujiyama, H.; Sato, F. *Tetrahedron Lett.*, **1991**, *32*, 5793. (f) Ono, N.; Tsuboi, M.; Okamoto, S.; Tanami, T.; Sato, F. *Chem. Lett.*, **1992**, 2095. (g) Okamoto, S.; Yoshino, T.; Sato, F. *Tetrahedron:Asymmetry*, **1991**, *2*, 35.

4) The compounds **1**, **2** and **3** are now commercially available from Nissan Chemical Industries, Ltd (Japan).

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

6) The radical cyclization reaction of ω-iodoalkynyl esters has been reported ; Lowinger, T. B.; Weiler, L. *J. Org. Chem.*, **1992**, *57*, 6099.

7) Data of **11**: ^{1}H nmr ($CDCl_3$, 300 MHz) δ 0.03 and 0.05 (2s, 12H), 0.87 and 0.90 (2s, 18H), 0.80-0.94 (m, 3H), 1.20-1.80 (m, 10H), 2.04-2.12 (m, 1H), 2.19 (dd, J = 8.2, 18.2 Hz, 1H), 2.24-2.31 (m, 1H), 2.38-2.53 (m, 6H), 2.63 (ddd, J = 18.2, 1.1, 7.0 Hz, 1H), 3.68 (s, 3H), 4.01- 4.14 (m, 2H), 5.51 (dd, J = 7.6, 15.5 Hz, 1H), 5.63 (dd, J = 5.0, 15.5 Hz, 1H). ^{13}C nmr ($CDCl_3$, 75 MHz) δ -4.7, -4.6, -4.3, 14.0, 14.7, 16.5, 18.0, 18.2, 22.6, 25.0, 25.8, 25.9, 27.5, 31.9, 33.8, 38.5, 47.4, 51.7, 52.3, 53.6, 72.6, 73.2, 78.9, 80.2, 128.5, 136.6, 172.5, 215.7.

8) Data of **12**: ^{1}H nmr ($CDCl_3$, 300 MHz) δ 0.00 and 0.04 (2s, 12H), 0.86 and 0.88 (2s, 18H), 0.82-0.95 (m, 3H), 1.20-1.75 (m, 12H), 1.90-1.99 (m, 1H), 2.16 (dd, J = 8.1, 18.2 Hz, 1H), 2.44 (dt, J = 7.6, 11.0 Hz, 1H), 2.55 (t, J = 6.6 Hz, 2H), 2.61 (dd, J = 18.2, 7.1 Hz, 1H), 3.38 (t, J = 6.0 Hz, 2H), 3.65 (t, J = 6.6 Hz, 2H), 3.67 (s, 3H), 4.00-4.12 (m, 2H), 5.49 (dd, J = 7.7, 15.5 Hz, 1H), 5.59 (dd, J = 4.9, 15.5 Hz, 1H). ^{13}C nmr ($CDCl_3$, 75 MHz) δ -4.7, -4.6, -4.3, 14.0, 18.0, 18.2, 22.6, 24.5, 25.0, 25.8, 25.9, 26.8, 31.8, 34.9, 38.5, 47.5, 51.6, 53.4, 53.5, 65.9, 71.0, 72.6, 73.2, 128.6, 136.4, 172.0, 215.9.

9) 8-Epi-**11** and 8-epi-**12** were also isolated in 9% and 10% yields, respectively.

10) Tanaka, T.; Hazato, A.; Bannai, K.; Okamura, N.; Sugiura, S.; Manabe, K.; Toru, T.; Kurozumi, S.; Noyori, R. *Tetrahedron*, **1987**, *43*, 813.

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