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A Practical Synthesis of the ω Side-chain Unit Present in Mexiprostil and Its Use for Synthesis of Mexiprostil via Two-component Coupling Process.

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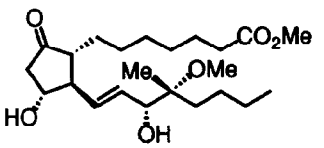
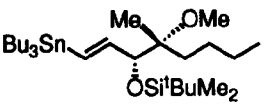
Abstract: A practical synthesis of the optically active ω side-chain unit present in mexiprostil, a PGE_1 analogue, by starting from readily available optically pure **4** has been developed. Synthesis of mexiprostil via two-component coupling process by using the ω side-chain thus prepared has been carried out.

In connection with a study directed toward an enantioselective synthesis of the prostaglandin derivative mexiprostil (**1**), a Merrell-Dow compound, which has been shown to inhibit gastric acid secretion and to protect the gastric mucosa,[1] the synthesis of the compound **2** which can be used as ω side-chain unit for synthesis of **1** via two- or three- component coupling process, has been attracted much interest.[2] The reported synthetic method, however, suffers from some disadvantages such as low optical purity (>70% ee).



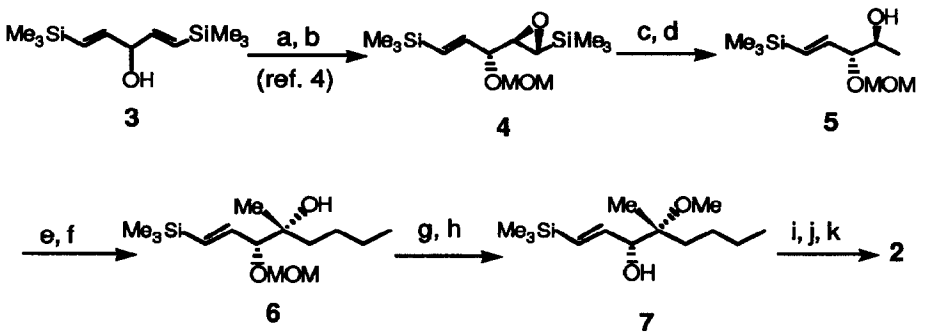
1



2

In relation to our recent project to make the two-component coupling synthesis of prostaglandins as industrially viable process by developing highly practical methods to prepare chiral intermediates required for this process including ω side-chain unit,[3] we have now succeeded in developing an efficient method for synthesis of **2** by starting from the epoxy ether **4** which can be readily prepared in an optically pure form by the Sharpless asymmetric epoxidation of the allylic alcohol **3**.[4] We also report the synthesis of the disilyl ether of **1** by using **2** via two-component coupling process.

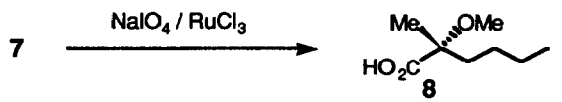
The synthesis of **2** from **4** is outlined in Scheme 1 in which the construction of the adjacent two chiral centers was carried out by applying the highly diastereoselective addition



Scheme 1[a]

[a] a) TBHP, $Ti(O^iPr)_4$, D-(-)-DIPT, CH_2Cl_2, -20°C, 3.5h ; b) MOMCl, NaH, THF, room temp., 10min. ; c) $^nBu_4NF$, THF, room temp., 3h ; d) $LiAlH_4$, THF, 0 °C, 10 min ; e) PCC, CH_2Cl_2, room temp., 6h, or $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -60 °C, 1h ; f) ^nBuMgBr, THF, -78 °C, 2h ; g) MeI, NaH, THF, room temp., 2h ; h) p-TsOH, MeOH, room temp., 8h ; i) cat. $VO(acac)_2$, TBHP, CH_2Cl_2 room temp., 5h ; j) $^nBu_3SnH$, LDA, THF, room temp., 3h ; k) TBDMSCl, imidazole, DMF, room temp., 5h.

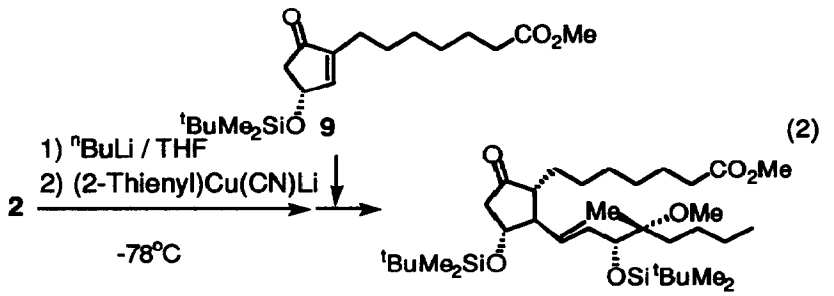
reaction of Grignard reagents to α-alkoxy ketones.[5] Thus, selective protodesilylation of epoxy ether **4**[4] followed by epoxide ring opening with $LiAlH_4$ gave the diol derivative **5** ($[\alpha]_D^{25}$ -130.5 (c 1.43, $CHCl_3$))[6] in 80% yield. Oxidation of **5** with PCC or $(COCl)_2$-DMSO-Et_3N and the reaction of the resulting ketone with ^nBuMgBr in tetrahydrofuran at -78 °C afforded the tertiary alcohol **6** ($[\alpha]_D^{25}$ -98.0 (c 1.09, $CHCl_3$))[7] with syn-configuration exclusively.[5] The overall yield of **6** from **5** was 71% (via PCC oxidation) or 78% (via Swern oxidation). Treatment of **6** with CH3I in the presence of NaH and deprotection of the secondery ether portion provided **7** ($[\alpha]_D^{25}$ +33.8 (c 1.11, $CHCl_3$))[8] in 77% yield. The optical purity of **7** thus obtained was confirmed to be >99% ee by ^1H nmr analysis after converting into its MTPA ester, while the absolute configuration of the newly created chiral center was found to be *R* by converting into the known compound **8**[1a] according to the procedure shown in eq 1. The compound **7** was converted into **2** ($[\alpha]_D^{25}$ -13.9 (c 1.52, $CHCl_3$)) [9] in 66% overall yield by the following sequences : 1) epoxidation, 2) regiospecific epoxide ring opening with $^nBu_3SnLi$ which was succeeded by *in situ* Peterson olefination, and 3) protection of the alcohol. Thus, **2** was prepared from **4** in 32% overall yield through 9 steps.



(1)

$[\alpha]_D^{25}$ +13.0° (c 1.03, $CHCl_3$)
lit.,[1a] $[\alpha]_D^{25}$ +12.9° (c 1.07, $CHCl_3$)

With optically pure **2** in hand we carried out the synthesis of disilyl ether of **1** via two-component coupling process (eq 2). The compound **2** was converted into higher ordered cyano mixed cuprate by successive treatment with nBuLi and (2-thienyl)Cu(CN)Li[10] in THF. To this solution was added optically pure enone **9**[3e,f] at -78°C and the reaction mixture was stirred for 1h at -78°C ~ 0°C to give the disilyl ether of **1** ($[\alpha]_D^{25}$ -22.6 (c 0.62, $CHCl_3$))[11,12] in 81% yield.



(2)

References and Notes.

1. a) U. Guzzi, R. Ciabatti, G. Padova, F. Battaglia, M. Cellentani, A. Depaoli, G. Galliani, P. Schiatti, and G. Spina, *J. Med. Chem.*, **29**, 1826 (1986). b) G. Pelizzi, R. Ciabatti, G. Padova, and G. Tarzia, *Prostaglandins*, **35**, 639 (1988). c) M. Petrillo, M. Lazzaroni, L. Fuccella, D. Sassella, and G. B. Porro, *Hepato-gastroenterol.*, **34**, 117 (1987).
2. a)M. Kolb, L. V. Hijfte, and R. E. Ireland, *Tetrahedron Lett.*, **29**, 6769 (1988). b) L. V. Hijfte, M. Kolb, and P. Witz, *ibid*, **30**, 3655 (1989).
3. Preparation of PGs ω side-chain units : a) S. Okamoto, T. Shimazaki, Y. Kobayashi, and F. Sato, *Tetrahedron Lett.*, **28**, 2033 (1987). b) Y. Kitano, T. Matsumoto, T. Wakasa, S. Okamoto, T. Shimazaki, Y. Kobayashi, and F. Sato, *ibid*, **28**, 6351 (1987). c) Y. Kitano, T. Matsumoto, S. Okamoto, T. Shimazaki, Y. Kobayashi, and F. Sato, *Chem. Lett.*, 1523 (1987). d) Y. Kitano, T. Matsumoto, and F. Sato, *Tetrahedron*, **44**, 4073 (1988).
   Preparation of cyclopentenone intermediates and synthesis of natural PGs : e) S. Okamoto, Y. Kobayashi, H. Kato, K. Hori, T. Takahashi, J. Tsuji, and F. Sato, *J. Org. Chem.*, **53**, 5590 (1988). f) H. Tsujiyama, N. Ono, T. Yoshino, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, **31**, 4481 (1990). g) S. Okamoto, Y. Kobayashi, and F. Sato, *ibid*, **30**, 4379 (1989).
4. Y. Kobayashi, N. Kato, T. Shimazaki, and F. Sato, *Tetrahedron Lett.*, **29**, 6297 (1988).
5. W. C. Still and J. H. McDonald, *Tetrahedron Lett.*, **21**, 1031 (1980).
6. Data of **5** : ^1H NMR (CCl_4, PhH, 90MHz) δ 0.21 (s, 9H), 1.17 (d, J = 6.7 Hz, 3H), 2.58 (br s, 1H), 3.34 (s, 3H), 3.57-3.98 (m, 2H), 4.47-4.71 (m, 2H), 5.61-6.21 (m, 2H).
   ^{13}C NMR ($CDCl_3$, 50MHz) δ 141.3, 136.3, 94.4, 83.7, 69.1, 55.4, 17.5, -1.7.
   IR (neat) 3445, 2955, 2895, 1640, 1250, 1030, 840 cm^{-1}.

7. Data of **6** : ^{1}H NMR (CCl_4, PhH, 90MHz) δ 0.13 (s, 9H), 0.84-1.21 (m, 3H), 1.09 (s, 3H), 1.21-1.63 (m, 6H), 2.10 (br s, 1H), 3.33 (s, 3H), 3.77 (dd, J = 2.9, 4.1 Hz, 1H), 4.42-4.71 (m, 2H), 5.76-6.04 (m, 2H).
   ^{13}C NMR ($CDCl_3$, 50MHz) δ 141.8, 136.9, 94.2, 85.2, 73.6, 55.6, 38.5, 25.2, 23.1, 22.0, 13.8, -1.7.
   IR (neat) 3470, 2950, 1615, 1245, 1155, 1030, 835 cm^{-1}.
8. Data of **7** : ^{1}H NMR (CCl_4, PhH, 90MHz) δ 0.13 (s, 9H), 0.99 (t, J = 6.6 Hz, 3H), 1.03 (s, 3H), 1.15-1.74 (m, 6H), 2.35 (br s, 1H), 3.17 (s, 3H), 3.96 (t, J = 1.8 Hz, 1H), 5.62-6.22 (m, 2H).
   ^{13}C NMR ($CDCl_3$, 22.5MHz) δ 143.7, 132.3, 78.9, 77.2, 48.9, 33.3, 24.8, 23.1, 17.6, 13.8, -1.5.
   IR (neat) 3450, 2950, 1620, 1250, 840 cm^{-1}.
9. Data of **2** : ^{1}H NMR (CCl_4, PhH, 90MHz) δ 0.10 and 0.14 (2s, 6H), 0.57-2.15 (m, 39H), 0.97 (s, 9H), 3.18 (s, 3H), 3.98 (d, J = 4.5 Hz, 1H), 5.97 (dd, J = 4.5, 19.1 Hz, 1H), 6.07 (d, J = 19.1 Hz, 1H).
   ^{13}C NMR ($CDCl_3$, 22.5MHz) δ 148.5, 129.9, 81.6, 78.9, 50.1, 34.1, 29.3, 27.4, 26.0, 25.4, 23.6, 19.4, 18.3, 14.1, 13.8, 9.6, -4.0, -4.8.
   IR (neat) 2930, 1605, 1470, 1255, 1090, 840 cm^{-1}.
10. B. H. Lipshutz, *Synthesis*, 325 (1987).
11. Data of disilyl ether of **1** : ^{1}H NMR ($CDCl_3$, 200MHz) δ -0.01, 0.04 and 0.05 (3s, 12H), 0.70-1.12 (m, 3H), 0.87 (s, 9H), 0.89 (s, 9H), 1.04 (s, 3H), 1.12-1.80 (m, 16H), 1.86-2.05 (m, 1H), 2.17 (dd, J = 7.5, 18.2 Hz, 1H), 2.28 (t, J = 7.5 Hz, 2H), 2.43-2.62 (m, 1H), 2.61 (dd, J = 18.2, 5.8 Hz, 1H), 3.22 (s, 3H), 3.65 (s, 3H), 3.96-4.18 (m, 2H), 5.47-5.73 (m, 2H).
    ^{13}C NMR ($CDCl_3$, 50MHz) δ 216.9, 174.4, 132.2, 131.5, 79.0, 77.6, 73.3, 53.3, 52.7, 51.3, 49.9, 47.5, 33.9, 33.7, 29.3, 28.8, 27.8, 26.5, 25.7, 25.6, 25.1, 24.7, 23.2, 19.0, 18.0, 17.7, 14.0, -4.3, -4.8, -5.0, -5.1.
    IR (neat) 2940, 2860, 1740, 1465, 1365, 1250, 1120, 840, 775 cm^{-1}.
12. Deprotection under the reported conditions[1a] afforded mexiprostil (**1**), the spectroscopic data of which was in good agreement with the reported one.[1a]