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A HIGHLY EFFICIENT SYNTHESIS OF NATURAL PGE_3 AND 5,6-DIHYDRO PGE_3 VIA TWO-COMPONENT COUPLING PROCESS

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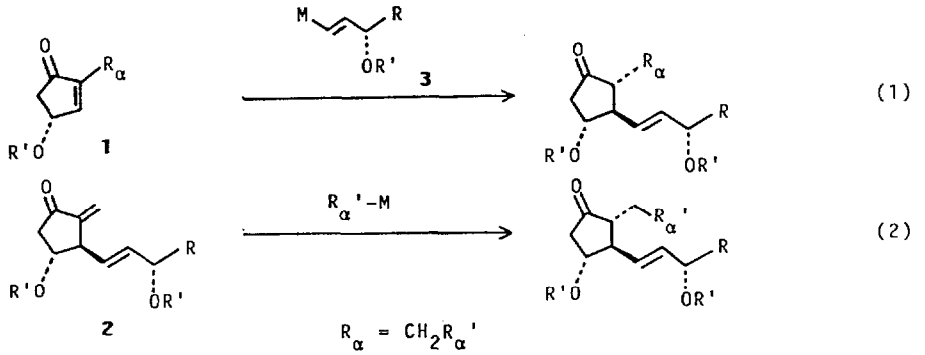
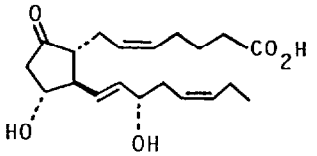
Summary: A highly practical synthesis of natural PGE_3 and 5,6-dihydro PGE_3 via two-component coupling process is described.

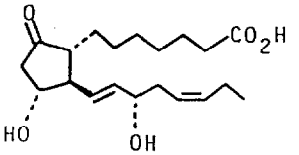
One of the most reliable and attractive methods for synthesis of natural prostaglandins (PGs) and their analogues is the two component coupling process via conjugate addition, which is classified into two possible routes shown in eq 1 and 2.[2] Recently we have developed highly



practical methods to prepare all chiral key intermediates used in eq 1 and 2, i. e. enones **1** and **2**,[3] and the ω side-chain unit **3**.[4] Thus, the two component coupling process has now become industrially viable.[5] Continued from our recent synthesis of PGE_1 and PGE_2 by using eq 1 and/or eq 2,[3] we have selected PGE_3 and 5,6-dihydro PGE_3 as next targets. PGE_3 is distinguished from PGE_2 by an additional cis-double bond between C-17 and C-18. The presence of this double bond seems to make its synthesis more difficult.[6]



PGE_3

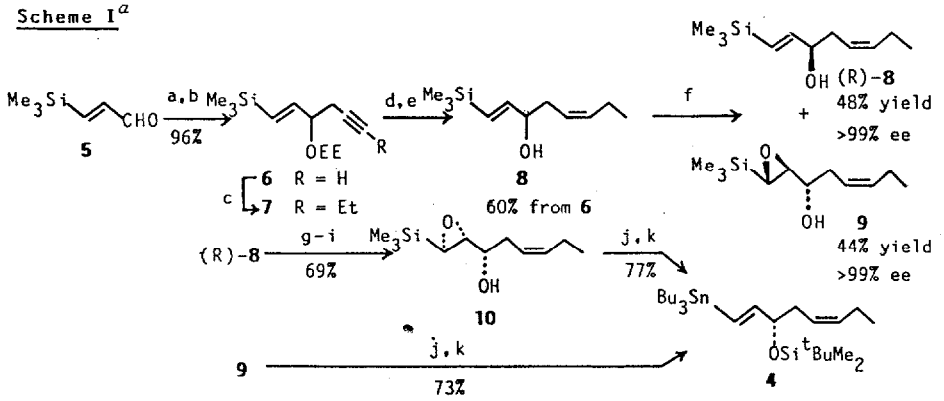


5,6-Dihydro PGE_3

5,6-Dihdro PGE_3 was isolated from ram seminal vesicles recently and was shown to be 14 times less active uterine stimulant than PGE_1, while it retains a similar potency in inhibition of platelet aggregation to that of PGE_1.[7] Because of this unique physiological activity, an efficient supply of 5,6-dihydro PGE_3 by chemical synthesis is desirable for its clinical investigations.

We herein report synthesis of PGE_3 and 5,6-dihydro PGE_3 according to eq 2. The preparation of the common ω side-chain unit **4** was carried out according to the procedure shown in Scheme I. Starting with (E)-3-trimethylsilyl-2-propenal (**5**), the compound **6** was prepared in 96% yield by propargylation followed by protection of the hydroxyl group as the ethoxyethyl ether.[8] Reaction of lithium anion of **6** with EtBr afforded **7** in 70% yield. Hydrolysis of **7** with 3N HCl in MeOH-H_2O and cis-reduction using Lindlar catalyst furnished **8** in 86% yield. The kinetic resolution of **8** by the Sharpless procedure using TBHP, Ti(O-i-Pr)$_4$, and L-(+)-DIPT gave (R)-**8** (>99% ee) in 48% yield and **9** (>99% ee) in 44% yield.[9,10] After separation of (R)-**8** and **9** by chromatography on silica gel, **9** was converted into **4** in 73% yield by silylation followed by the reaction with Bu_3SnLi. Similarly, (R)-**8** was converted into **4** in 53% overall yield via the epoxy alcohol **10** by epoxidation followed by inversion of the hydroxyl group using the Mitsunobu procedure.[4a]

Scheme I[a]

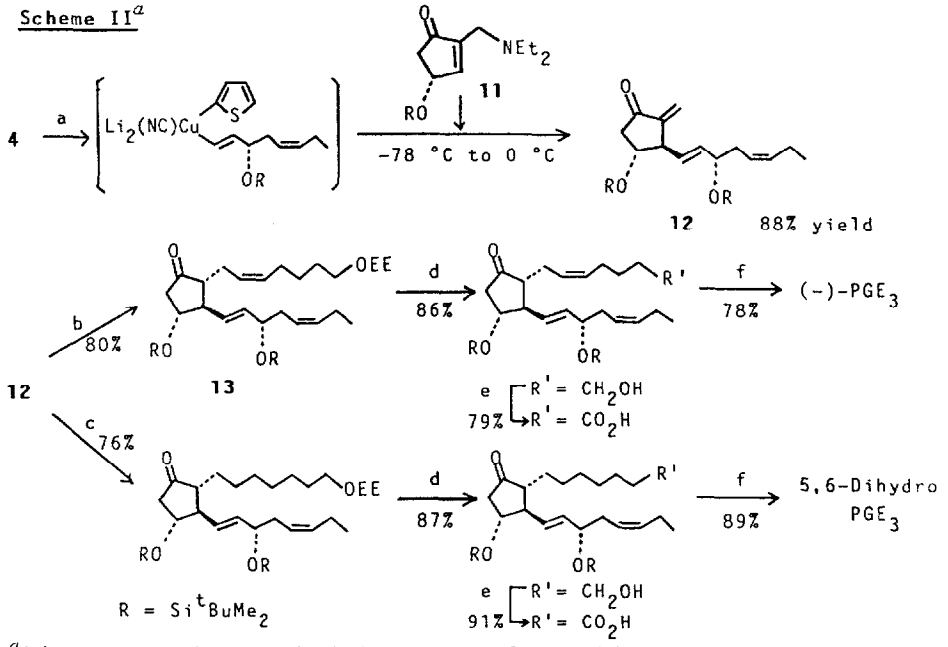


[a](a) $BrCH_2C{\equiv}CH$, Zn powder, $TiCl_4$ (cat.), THF; (b) $H_2C{=}CHOEt$, PPTS (cat.), CH_2Cl_2; (c) n-BuLi, EtBr, THF; (d) PPTS (cat.), MeOH; (e) H_2 (1 atm), Lindlar catalyst, MeOH; (f) L-(+)-DIPT, Ti(O-i-Pr)$_4$, TBHP, CH_2Cl_2; (g) D-(-)-DIPT, Ti(O-i-Pr)$_4$, TBHP, CH_2Cl_2; (h) $EtO_2CN{=}NCO_2Et$, p-O_2N-$PhCO_2H$, PPh_3, THF; (i) 1N NaOH, THF-H_2O; (j) t-$BuMe_2SiCl$, imidazole, DMF; (k) n-Bu_3SnH, LDA, THF.

With the ω side-chain unit **4** in hand we carried out the synthesis of (-)-PGE_3 and 5,6-dihydro PGE_3 (Scheme II). The enone **12**[11] ($[\alpha]_D^{25}$ -46.8° (c 1.03, $CHCl_3$)) was prepared in 88% yield by the reaction of the enone **11**[3,12] (1.1 equiv) with the higher ordered cyano mixed cuprate prepared from

the vinyllithium derived from **4** and (2-thienyl)Cu(CN)Li[13] (1.2 equiv) (THF, -78 °C to 0 °C, 1 h). The enone **12** reacted with the higher ordered cuprate derived from (Z)-LiCH=CH$(CH_2)_4$OEE (1.3 equiv, EE = ethoxy ethyl) and (2-thienyl)Cu(CN)Li (1.5 equiv) in THF-Et_2O-pentane at -78 °C to 0 °C for 1h to give the 1,4-addition product **13** in 80% yield. The compound **13** was converted into (-)-PGE_3 (mp 84.5-85.5 °C (recrystallized from hexane-Et_2O), $[\alpha]_D^{24}$ -50.0° (c 1.08, THF), lit.[6a] $[\alpha]_D^{24}$ -48.9° (c 1.2, THF)) by the following sequence: (1) PPTS (cat.), i-PrOH-Et_2O, room temp., 5 h, 86% yield; (2) Jones reagent (2.6 equiv), acetone-Et_2O, 0 °C, 30 min, 79% yield;(3) aq. HF, CH_3CN, room temp., 40 min, 78% yield. The spectroscopic data of (-)-PGE_3 thus obtained were in good agreement with the reported one.[14] In a similar way, 5,6-dihydro PGE_3 ($[\alpha]_D^{25}$ -50.6° (c 0.83, THF), mp 60.0-61.0 (recrystallized from hexane-Et_2O)) was obtained in 54% overall yield from **12** and the higher ordered cuprate derived from $ClMg(CH_2)_6OEE$ and (2-thienyl)Cu(CN)Li. The spectral data of 5,6-dihydro PGE_3 thus synthesized supported the structure.[15]

Scheme II[a]



[a](a) n-BuLi then (2-Thienyl)Cu(CN)Li, THF, -78 °C; (b) (Z)-ICH=CH$(CH_2)_4$OEE, t-BuLi, Et_2O then (2-Thienyl)Cu(CN)Li, THF, -78 °C to 0 °C; (c) $ClMg(CH_2)_6OEE$, (2-Thienyl)Cu-(CN)Li, THF, -78 °C to 0 °C; (d) PPTS (cat.), i-PrOH-Et_2O, room temp., 4-5 h; (e) Jones reagent, acetone-Et_2O, 0 °C, 20-30 min; (f) aq. HF, CH_3CN, room temp., 40 min.

References and Footnotes

(1) Fellow of the Japan Society for the Promotion of Science for Japanese Junior Scientists, 1988-1990. (2) R. Noyori, M. Suzuki, Angew. Chem., Int.

Ed. Engl., 23, 847(1984) and references cited therein. (3) S. Okamoto, Y. Kobayashi, H. Kato, K. Hori, T. Takahashi, J. Tsuji, F. Sato, J. Org. Chem., 53, 5590(1988). (4) (a) S. Okamoto, T. Shimazaki, Y. Kobayashi, F. Sato, Tetrahedron Lett., 28, 2033(1987). (b) Y. Kitano, T. Matsumoto, S. Okamoto, T. Shimazaki, Y. Kobayashi, F. Sato, Chem. Lett., 1523(1987). (c) Y. Kitano, T. Matsumoto, T. Wakasa, S. Okamoto, T. Shimazaki, Y. Kobayashi, F. Sato, K. Miyaji, K. Arai, Tetrahedron Lett., 28, 6351(1987). (5) The intermediates **1**, **2**, and **3** are now commercially available from Nissan Chemical Industries, Ltd. (Japan). (6) Total synthesis of (-)-PGE_3: (a) E. J. Corey, H. Shirahama, H. Yamamoto, S. Terashima, A. Venkateswarlu, T. K. Schaaf, J. Am. Chem. Soc., 93, 1490(1971). See also: (b) J. Fried, C. H. Lin, C. J. Sih, P. Dalven, G. F. Cooper, J. Am. Chem. Soc., 94, 4342(1972). Synthesis of dl-PGE_3 methyl ester: (c) U. Axen, J. L. Thompson, J. E. Pike, J. Chem. Soc., Chem. Commun., 602(1970). (7) (a) N. Samel, I. Järving, M. Lõhmus, A. Lopp, G. Kobzar, V. Sadovskaya, T. Välimäe, Ü. Lille, PROSTAGLANDINS, 33, 137(1987). (b) E. H. Oliw, H. Sprecher, M. Hamberg, J. Biol. Chem., 261, 2675(1986), in this paper this PG was named as 17,18-dehydro PGE_1. (8) T. Shimazaki, Y. Kobayashi, F. Sato, Chem. Lett., 1785(1988). (9) Optical purities of (R)-**8** and **9** were determined by ^1H NMR analysis of the corresponding MTPA esters. (10) Y. Kitano, T. Matsumoto, F. Sato, J. Chem. Soc., Chem. Commun., 1323(1986). Y. Kitano, T. Matsumoto, F. Sato, Tetrahedron, 44, 4073(1988). (11) **12**: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.01 and 0.04 (2s, 12H), 0.86 and 0.88 (2s, 18H), 0.93 (t, J = 7.6 Hz, 3H), 1.92-2.10 (m, 2H), 2.11-2.35 (m, 2H), 2.32 (dd, J = 7.0, 17.8 Hz, 1H), 2.62 (dd, J = 17.8, 6.4 Hz, 1H), 3.21-3.33 (m, 1H), 4.01-4.21 (m, 2H), 5.20 (dd, J = 1.7, 2.8 Hz, 1H), 5.21-5.56 (m, 2H), 5.49 (dd, J = 7.4, 15.2 Hz, 1H), 5.63 (dd, J = 15.2, 4.6 Hz, 1H), 6.08 (dd, J = 2.8, 1.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ -4.9, -4.7, 14.0, 17.8, 18.0, 20.5, 25.6, 25.7, 36.2, 46.8, 54.4, 72.5, 72.9, 119.3, 124.8, 127.7, 133.7, 137.4, 147.0, 203.6. (12) The enone **11** is also commercially available from Nissan Chemical Industries, Ltd., see note 5. (13) B. H. Lipshutz, M. Koerner, D. A. Parker, Tetrahedron Lett., 28, 945(1987). B. H. Lipshutz, Synthesis, 325(1987). (14) B. Samuelson, J. Am. Chem. Soc., 85, 1878(1963). (15) 5,6-Dihydro PGE_3: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.96 (t, J = 7.5 Hz, 3H), 1.13-1.75 (m, 10H), 1.90-2.49 (m, 7H), 2.31 (t, J = 7.3 Hz, 2H), 2.72 (dd, J = 17.8, 7.1 Hz, 1H), 4.04 (q, J = 8.7 Hz, 1H), 4.17 (q, J = 6.4 Hz, 1H), 4.20-5.40 (br s, 3H), 5.30 (dt, J = 10.8, 7.5 Hz, 1H), 5.53 (m, 1H), 5.58 (dd, J = 8.1, 15.2 Hz, 1H), 5.69 (dd, J = 15.2, 6.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.0, 20.5, 24.3, 26.2, 27.3, 28.5, 29.0, 33.8, 34.7, 45.6, 54.2, 54.6, 71.7, 72.5, 123.5, 132.6, 135.0, 135.9, 179.1, 215.6.

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