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A GENERAL SYNTHESIS OF PRIMARY PROSTAGLANDINS[1]

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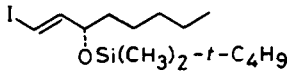
Summary: Combination of (R)-4-t-butyldimethylsiloxy-2-cyclopentenone, (S)-(E)-3-t-butyldimethylsiloxy-1-iodo-1-octene, and 6-methoxycarbonyl-2-hexynal via the tandem organocopper conjugate addition—aldol reaction procedure leads directly to a 5,6-dehydroprostaglandin E_2 derivative, which can be transformed to a variety of chiral primary prostaglandins in a stereoselective manner.

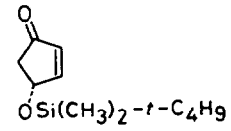
We here outline a straightforward, general entry to optically active primary prostaglandins (PGs), which depends on the highly enantioselective reduction of prochiral ketones with a binaphthol-modified lithium aluminum hydride reagent (BINAL-H)[3] and the organocopper-mediated vicinal carba-condensation with 4-hydroxy-2-cyclopentenone derivatives.[2] Combination of these two methodologies offers a satisfactory solution to stereochemical problems in PG synthesis. The asymmetric reduction determines the 11R and 15S absolute stereochemistries and the three-component coupling process via the tandem enone conjugate addition—aldol reaction allows stereoselective creation of the trans,trans relationship of the vicinal C-11, C-12, and C-8 functionalities of the five-membered ring.

First, a vinylcopper reagent was prepared by treatment of the chiral vinylic iodide (S)-1, $[\alpha]_D^{23}$ -37.5° (c 0.97, CH_3OH, 98% ee), with 2 equiv of t-butyllithium in ether at -78 °C for 2.5 h followed by addition of an ethereal solution of copper(I) iodide (1 equiv) and tributylphosphine (2.6 equiv). A stoichiometric amount of the optically active enone (R)-2, $[\alpha]_D^{22}$ +67.4° (c 0.4, CH_3OH, 100% ee), was then added to this solution at -78 °C. After 1-h stirring, 1 equiv of 6-methoxycarbonyl-2-hexynal was introduced, and the mixture was stirred at -78 °C for 30 min. After ordinary workup, the aldol 3[4] was obtained in 50% yield. Treatment of the adduct with thiobenzoyl chloride—4-dimethylaminopyridine (18 °C, 3 h) in dichloromethane afforded the thiobenzoate 4[5] (68% yield), which upon heating at 50 °C for 35 min in tributyltin hydride with added di-t-butyl peroxide[6] afforded the deoxygenated compound 5 in 98% yield, $[\alpha]_D^{21}$ -13.9° (c 1.59, CH_3OH).[7,8] This compound was homogeneous as assayed by TLC and ^{13}C NMR analysis.

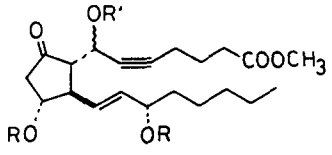
Obviously the 5,6-dehydro-PGE_2 derivative 5 thus obtained serves as a common intermediate for the synthesis of a variety of primary PGs. Partial catalytic hydrogenation of the



(S)-**1**

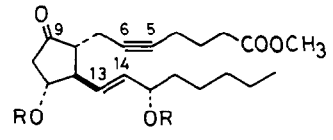


(*R*)-**2**

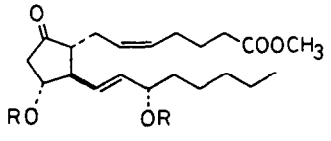


3, R = $Si(CH_3)_2$-*t*-C_4H_9; R' = H

4, R = $Si(CH_3)_2$-*t*-C_4H_9; R' = $C(=S)C_6H_5$

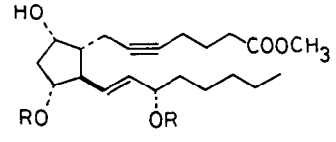


5, R = $Si(CH_3)_2$-*t*-C_4H_9

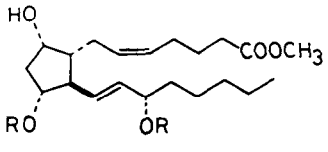


6, R = $Si(CH_3)_2$-*t*-C_4H_9

7, R = H

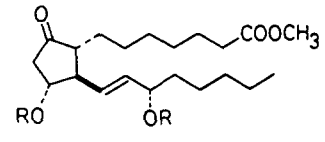


8, R = $Si(CH_3)_2$-*t*-C_4H_9



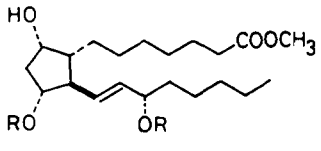
9, R = $Si(CH_3)_2$-*t*-C_4H_9

10, R = H



11, R = $Si(CH_3)_2$-*t*-C_4H_9

12, R = H



13, R = $Si(CH_3)_2$-*t*-C_4H_9

14, R = H

5,6-triple bond over 5% Pd/$BaSO_4$[9] in benzene—cyclohexane containing synthetic quinoline (1 atm H_2, 40 °C, 4.5 h) led to 6, $[\alpha]_D^{21}$ -52.7° (c 1.28, CH_3OH), in 87% yield. Removal of the silyl groups with hydrogen fluoride—pyridine (24 °C, 3 h) completed the preparation of PGE_2 methyl ester (7) (98% yield), $[\alpha]_D^{20}$ -71.7° (c 1.04, CH_3OH).[10] The optical and spectroscopic properties (IR, ^1H and ^{13}C NMR) as well as chromatographic behavior were identical with those of the authentic sample prepared from commercial PGE_2 and diazomethane, $[\alpha]_D^{20}$ -71.1° (c 1.56, CH_3OH). Exposure of the ketone 5 in toluene to a reducing agent formed from diisobutylaluminum hydride and 2,6-di-t-butyl-4-methylphenol (1:2 ratio)[11] at -78 °C for 0.5 h and then at -20 to -25 °C for 2 h resulted in the formation of the 9α alcohol 8[8], $[\alpha]_D^{21}$ +0.37° (c 0.71, CH_3OH), with high stereoselectivity (α:β = 92:8) in 92% yield. The same compound was also obtained stereoselectively from 4 by treatment with sodium borohydride in methanol (9α:9β = 9:1) and then with tributyltin hydride—di-t-butyl peroxide[6] (73% overall yield). Catalytic hydrogenation of 8 over Lindlar catalyst[9] in benzene—cyclohexane (1 atm H_2, 22—24 °C, 12 h) gave 9 (81%), $[\alpha]_D^{23}$ +12.3° (c 1.04, CH_3OH), identical with the compound formed in 87% yield by stereoselective reduction of 6 with diisobutylaluminum hydride—2,6-di-t-butyl-4-methylphenol[11] (9α:9β = 91:9). Finally, desilylation of 9 was effected in a 10:3.3:1 mixture of acetic acid, water, and THF (55 °C, 1.5 h) to give $PGF_{2\alpha}$ methyl ester (10) (85%), $[\alpha]_D^{20}$ +31.4° (c 0.42, CH_3OH), identical in all respects with the authentic specimen (IR, ^1H and ^{13}C NMR, and TLC; $[\alpha]_D^{20}$ +28.3° (c 1.2, CH_3OH)).

PGE_1 and $PGF_{1\alpha}$ methyl esters were also prepared from 5 and 8, respectively, by selective saturation of the 5,6-triple bond leaving the 13,14-double bond intact.[12] Exposure of 5 and 5% Pd/C[9] in methanol to atmospheric pressure of hydrogen at 0 °C[13] produced 11, $[\alpha]_D^{21}$ -41.0° (c 0.78, CH_3OH), in 71% yield, which was desilylated by hydrogen fluoride—pyridine (19 °C, 4 h) to give (-)-PGE_1 methyl ester (12) (95% yield).[2] Catalytic hydrogenation of 8 over 5% Pd/$BaSO_4$[9] in benzene—cyclohexane containing synthetic quinoline (1 atm H_2, 40 °C, 2.7 h)[13] afforded the $PGF_{1\alpha}$ derivative 13, $[\alpha]_D^{21}$ +7.7° (c 0.49, CH_3OH), in 60% yield. Stereoselective reduction of 11 with diisobutylaluminum hydride—2,6-di-t-butyl-4-methylphenol[11] (9α:9β = 91:9) also gave 13 in 76% yield. Heating of 13 at 60 °C for 1 h in a 10:3.3:1 acetic acid—water—THF mixture gave rise to $PGF_{1\alpha}$ methyl ester (14) (76%), $[\alpha]_D^{21}$ +29.3° (c 0.30, CH_3OH), identical with the authentic material (IR, ^1H and ^{13}C NMR, and TLC).

Thus this method marks realization of the first general synthesis of primary PGs via the three-component coupling process. Further application of this flexible procedure to the synthesis of other PG derivatives is in progress.

Acknowledgments: We are grateful to Ono Pharmaceutical Co. for providing authentic samples of PGs. We also thank Dr. C. H. Lin of Upjohn Company for sending us IR and ^1H NMR spectra of 5 and 8.

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2. M. Suzuki, T. Kawagishi, T. Suzuki, and R. Noyori, Tetrahedron Lett., in press.

3. R. Noyori, Pure Appl. Chem., 53, 2315 (1981).

4. A mixture of stereoisomers at C-7. Rigorously, some contamination of other epimers could not be excluded. $[\alpha]_D^{23}$ -16.6° (c 0.81, CH_3OH); IR (neat) 3640–3200, 1743 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03–0.1 (m, 12, $SiCH_3$ x 4), 0.8–1.0 (m, 21, CCH_3 x 7), 1.1–3.0 (m, 19, CH_2CO x 2, CH_2 x 5, $CH_2C\equiv$, CH x 2, and OH), 3.69 (s, 3, OCH_3), 4.09 (m, 3, CHO x 3), 5.6 (m, 2, vinyl); Anal. Calcd for $C_{33}H_{60}O_6Si_2$: C, 65.08; H, 9.93. Found: C, 65.26; H, 9.92.

5. A mixture of two stereoisomers, both of which gave natural PGE_2. $[\alpha]_D^{22}$ +2.64° (c 1.21, CH_3OH); IR (neat) 2230, 1743, 1596 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.1, 0.17 (s, 6 each, $SiCH_3$ x 4), 0.8–1.1 (m, 21, CCH_3 x 7), 1.2–1.6 (m, 8, CH_2 x 4), 1.8–3.3 (m, 10, CH_2, CH_2CO x 2, $CH_2C\equiv$, and CH x 2), 3.74 (s, 3, OCH_3), 3.9–4.4 (m, 2, CHOSi x 2), 5.6–5.8 (m, 2, vinyl), 6.37, 6.66 (br, 0.5 each, CHOCS), 7.3–7.6 (m, 3, aromatic), 8.1–8.4 (m, 2, aromatic); Anal. Calcd for $C_{40}H_{64}O_6SSi_2$: C, 65.88; H, 8.85. Found: C, 65.83; H, 8.78. Yet unidentified products were formed in ca. 20% yield. Attempted reduction by tributyltin hydride[6] failed to give the PG derivatives.

6. D. H. R. Barton and S. W. McCombie, J. Chem. Soc., Perkin I, 1574 (1975).

7. R_f 0.50 (ethyl acetate—hexane (1:5)); IR (neat) 1746 cm^{-1}; ^1H NMR ($CDCl_3$—CCl_4 (1:1)) δ 0.04, 0.06 (s, 6 each, $SiCH_3$ x 4), 0.89 (s, 18, $SiC(CH_3)_3$ x 2), 0.92 (t, 3, ^4J = 6.5 Hz, CH_3), 1.1–1.5 (m, 8, CH_2 x 4), 1.7–2.9 (m, 12, CH_2CO x 2, $CH_2C\equiv$ x 2, $\overline{C}H$ x 2, and CH_2), 3.65 (s, 3, OCH_3), 4.05 (m, 2, CHOSi x 2), 5.4–5.7 (m, 2, vinyl); ^{13}C NMR ($CDCl_3$) δ -4.7, -4.5 (2C), -4.2, 13.6, 14.0, 16.9, 18.0, 18.2, 22.6, 24.2, 25.0, 25.8 (3C), 25.9 (3C), 31.9, 32.7, 38.6, 47.7, 51.4, 51.9, 52.9, 72.7, 73.1, 77.3, 80.8, 128.2, 136.8, 173.4, 213.4.

8. This compound was previously obtained from $PGF_{2\alpha}$ via several steps: C. H. Lin, S. J. Stein, and J. E. Pike, Prostaglandins, 11, 377 (1976).

9. Supplied from Nippon Engelhard Co.

10. For enzymatic conversion of the methyl ester to PGE_2, see C. J. Sih, J. B. Heather, R. Sood, P. Price, G. Perzzotti, L. F. Hsu, and S. S. Lee, J. Am. Chem. Soc., 97, 865 (1975).

11. S. Iguchi, H. Nakai, M. Hayashi, H. Yamamoto, and K. Maruoka, Bull. Chem. Soc. Jpn., 54, 3033 (1981).

12. For previous methods for selective hydrogenation of the 5,6-double bond, see J. S. Bindra and R. Bindra, "Prostaglandin Synthesis", Academic Press: New York, 1977; Chapter 18, pp 340–341.

13. Progress of the reaction was monitored carefully by thin-layer chromatography on $AgNO_3$-impregnated silica gel plates.

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