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SYNTHESIS OF PROSTAGLANDIN D_1 AND D_2 VIA THE THREE-COMPONENT COUPLING PROCESS[1]

M. Suzuki, A. Yanagisawa, and R. Noyori*
Department of Chemistry, Nagoya University, Chikusa, Nagoya 464, Japan

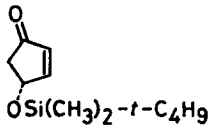
Summary: Facile, convergent entries to prostaglandin D_1 and D_2 are outlined.

Prostaglandins (PGs) of D series, whose biological significance was little appreciated earlier, have recently received revaluation in view of the potent ability to inhibit blood platelet aggregation,[2a] antitumor activity,[2b] and other unique physiological properties.[2c] Described herein are convergent syntheses of PGDs[3] via the three-component coupling process. The organocopper conjugate addition to protected 4-hydroxy-2-cyclopentenones followed by aldehyde trapping of the enolate intermediates leads to the single-step construction of PG skeletons.[4] Appropriate selection of protective groups in the five-membered ring and ω side-chain units allows easy synthesis of PGDs.

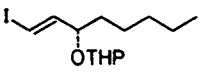
A phosphine-complexed organocopper reagent was prepared as previously[5] by mixing an organolithium compound formed from the optically active vinylic iodide (S)-2 ($[\alpha]_D^{22}$ -65.9° (c 1.05, CH_3OH), 98% ee), CuI, and $P(n\text{-}C_4H_9)_3$ in 1:1:2.6 mol ratio in ether at -78 °C. When this reagent was condensed with equimolar amounts of the optically pure cyclopentenone derivative (R)-1 ($[\alpha]_D^{22}$ +67.4° (c 0.4, CH_3OH)) (-78 °C, 50 min) and 6-methoxycarbonylhexanal (-78 °C, 10 min), the aldol 3[6] was obtained in 70% yield. Treatment of 3 with methanesulfonyl chloride–4-dimethylaminopyridine in dichloromethane gave the dehydration product 4 (75%, $[\alpha]_D^{20}$ +16.0° (c 0.796, CH_3OH)), which upon exposure to excess tributyltin hydride–di-tert-butyl peroxide (110 °C, 15 min) afforded 5 (88%, $[\alpha]_D^{23}$ -66.2° (c 0.599, CH_3OH)). The stereoselective reduction of the ketone 5 with diisobutylaluminum hydride modified by 2,6-di-tert-butyl-4-methylphenol[7] (12 equiv, toluene, -78 to -20 °C for 3 h and -20 °C for 2.5 h) produced the 9α alcohol 6 ($[\alpha]_D^{20}$ -13.8° (c 0.620, CH_3OH)) in 86% yield together with the 9β isomer (12%). Tetrahydropyranyl protection of the alcohol under the standard conditions to give 7 (94%, $[\alpha]_D^{25}$ +15.9° (c 0.365, CH_3OH)) and removal of the silyl group with $(n\text{-}C_4H_9)_4NF$ in THF (10 equiv, 23 °C, 5 h) produced 8 (84%, $[\alpha]_D^{25}$ +0.65° (c 0.588, CH_3OH)). Alkaline hydrolysis of the methyl ester (20%, NaOH–H_2O, 25 °C, 3.7 h), Jones oxidation of the 11-hydroxyl function (-30 °C, 40 min), and deblocking of the THP groups (3:1:1 CH_3COOH–H_2O–THF, 25 °C, 23 h) completed the synthesis of dextrorotatory PGD_1(9), $[\alpha]_D^{26}$ +9.8° (c 0.165, THF), mp 64.5–65 °C,[8] in 61% overall yield from 8.

A general procedure for the preparation of PGDs is accessible, when 6-methoxycarbonyl-2-hexynal is employed as the α side-chain component.[4b] Thus the vicinal carba-condensation using (R)-1, (S)-2, and the acetylenic aldehyde (1:1:1 mol ratio) afforded the aldol 10[10] (a mixture of the diastereomers) in 65% yield. Conversion of the aldol 10 to the thiobenzoate 11 (56%) by treatment with thiobenzoyl chloride–4-dimethylaminopyridine (dichloromethane, 0 to 4

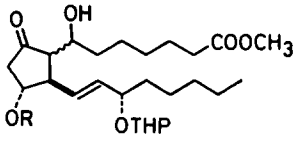
°C, 21 h) was followed by reduction with excess tributyltin hydride—di-tert-butyl peroxide (50 °C, 7.5 h)[11] to give the deoxygenated, acetylenic ketone 12 (85%, $[\alpha]_D^{26}$ -46.1° (c 0.375, CH_3OH)). Subsequent stereoselective reduction with diisobutylaluminum hydride modified by 2,6-di-tert-butyl-4-methylphenol[7] (12 equiv, toluene, -78 to -20 °C for 2 h and then -20 °C for 1.7 h) gave the 9α alcohol 13[12] (86%, $[\alpha]_D^{26}$ -28.8° (c 1.30, CH_3OH)). The undesired 9β isomer was formed in only 8% yield. Partial hydrogenation of the acetylenic bond over Lindlar catalyst in a benzene—cyclohexane—cyclohexene mixture (1 atm, 26 °C, 13 h) gave the suitably protected $PGF_{2\alpha}$ derivative 14, $[\alpha]_D^{27}$ -20.6° (c 1.02, CH_3OH), in 96% yield. Tetrahydropyranyl protection of the 9-hydroxyl group to give 15 (100%, $[\alpha]_D^{27}$ -8.3 (c 0.92, CH_3OH)), desilylation with $(n\text{-}C_4H_9)_4NF$ in THF (15 equiv, 26 °C, 3 h) giving 16 (95%, $[\alpha]_D^{28}$ -6.76° (c 0.72 CH_3OH)), and saponification (20% NaOH—H_2O, 16 °C, 18.3 h) followed by Jones oxidation of the resulting hydroxy carboxylic acid (-30 °C, 20 min) and removal of the THP group (3:1:1 CH_3COOH—H_2O—THF, 16 °C for 1 h and 27 °C for 29 h) gave (+)-PGD_2 (17), $[\alpha]_D^{18}$ +8.8° (c 0.169, THF)[13], mp 58—58.5 °C,[14] in 75% yield. Catalytic hydrogenation of 12 over 5% Pd/C in a 1:1 benzene—cyclohexane mixture containing 3 equiv of cyclododecene (1 atm, 27 °C, 3 h) produced selectively 5, a precursor of PGD_1, leaving the 13,14-double bond intact (68% yield).



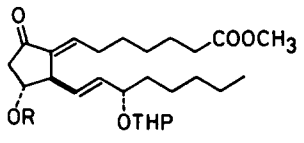
(*R*)-1



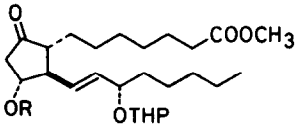
(*S*)-2



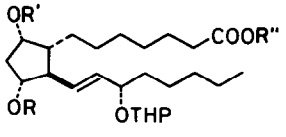
3, R = $Si(CH_3)_2$-*t*-C_4H_9



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



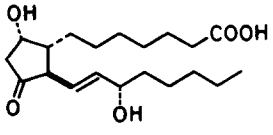
5, R = $Si(CH_3)_2$-*t*-C_4H_9



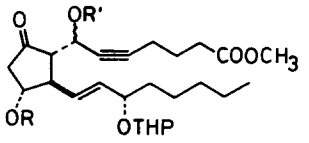
6, R = $Si(CH_3)_2$-*t*-C_4H_9; R' = H; R" = CH_3

7, R = $Si(CH_3)_2$-*t*-C_4H_9; R' = THP; R" = CH_3

8, R = H; R' = THP; R" = CH_3

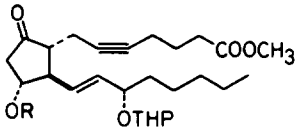


9, PGD_1

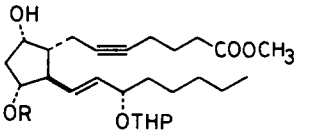


10, R = $Si(CH_3)_2$-*t*-C_4H_9; R' = H

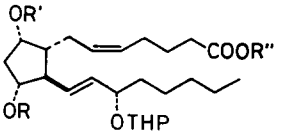
11, R = $Si(CH_3)_2$-*t*-C_4H_9; R' = CSC_6H_5



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



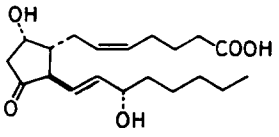
13, R = $Si(CH_3)_2$-*t*-C_4H_9



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

15, R = $Si(CH_3)_2$-*t*-C_4H_9; R' = THP; R'' = CH_3

16, R = H; R' = THP; R'' = CH_3



17, PGD_2

Acknowledgment: We are grateful to Ono Pharmaceutical Co. for the identification of PGD_1 and PGD_2 by comparison of the TLC behavior and 200-MHz ^{1}H-NMR spectra with those of authentic samples. Supply of precious sample of PGD_2 is also deeply appreciated.

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6. A mixture of diastereomers, which was submitted to the dehydration procedure. $[\alpha]_D^{20}$ +14.3° (c 1.74, CH_3OH); R_f 0.44 (1:2 ethyl acetate—hexane); IR ($CHCl_3$) 3600—3300, 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.06 (s, 6, 2 $SiCH_3$), 0.7—1.1 (m, 12, $SiC(CH_3)_3$ and CH_3), 1.1—2.9 (m, 29, 13 CH_2, 2 CH, and OH), 3.1—4.2 (m, 8, OCH_3, 3 CHO, and CH_2O), 4.63 (m, 1, OCHO), 5.4—5.7 (m, 2, vinyl).

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8. Reported mp: 62—65 °C,[9] 71.3—72.1 °C.[2a]

9. P. S. Foss, C. J. Sih, C. Takeguchi, and H. Schnoes, Biochemistry, 11, 2271 (1972).

10. More polar isomer: $[\alpha]_D^{25.5}$ -26.2° (c 0.185, CH_3OH); R_f 0.41 (1:2 ethyl acetate—hexane); IR ($CHCl_3$) 3700—3000, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.0—0.1 (m, 6, 2 $SiCH_3$), 0.7—1.1 (m, 12, $SiC(CH_3)_3$ and CH_3), 1.1—3.1 (m, 25, 2 CH_2CO, 9 CH_2, 2 CH, and OH), 3.4—4.2 (m, 8, OCH_3, 3 CHO, and CH_2O), 4.68 (m, 1, OCHO), 5.57 (m, 2, vinyl). Less polar isomer: $[\alpha]_D^{25.5}$ -80.2° (c 0.5, CH_3OH); R_f 0.45 (1:2 ethyl acetate—hexane); IR ($CHCl_3$) 3720—3000, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.0—0.1 (m, 6, 2 $SiCH_3$), 0.7—1.1 (m, 12, $SiC(CH_3)_3$ and CH_3), 1.1—3.2 (m, 25, 2 CH_2CO, 9 CH_2, 2 CH, and OH), 3.3—4.8 (m, 9, OCH_3, 3 CHO, CH_2O, and OCHO), 5.51 (m, 2, vinyl).

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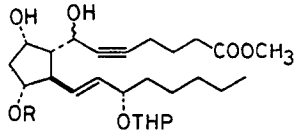
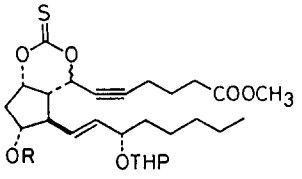
12. This compound was also synthesized via a cyclic thiocarbonate intermediate: When the more polar isomer of 10 was reduced by $NaBH_4$ in CH_3OH (0 °C, 5 min), the corresponding diol i, $[\alpha]_D^{26}$ -38.4° (c 0.498, CH_3OH), was obtained in a stereoselective manner (77% yield, α:β = 97.5:2.5). Formation of the cyclic thiocarbonate ii, $[\alpha]_D^{27}$ -7.66° (c 0.319, CH_3OH), was effected in 92% yield by treating i with thiocarbonyl diimidazolide—4-dimethylaminopyridine in acetonitrile (25 °C, 12 h). Then exposure of ii to tributyltin hydride—di-tert-butyl peroxide (50 °C, 50 min)[11] followed by treatment with 1N CH_3ONa—CH_3OH—THF (26 °C, 13 h) afforded the 7-deoxy compound 13 in 77% yield. The same compound was also derived in 35% overall yield from the less polar isomer of 10 via the corresponding thiocarbonate ($[\alpha]_D^{28}$ +13.2° (c 1.52, CH_3OH)). It should be added that reduction of the less polar isomer of 10 by $NaBH_4$ in CH_3OH (0 °C, 15 min) gave a mixture of the 9α ($[\alpha]_D^{26}$ -20.7° (c 0.663, CH_3OH)) and 9β alcohols in 54 and 14% yields, respectively.



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



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

13. Optical rotation value informed from Ono Pharmaceutical Co. is $[\alpha]_D^{21}$ +7.5° (c 1, THF) for its pure sample. Reported value was +28° (C_2H_5OH).[3c]

14. Authentic sample melted at 60—60.5 °C. Mp on admixture with authentic sample was 59.5 °C Reported mp: 62.8—63.3 °C,[3b] 68 °C.[3a]

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