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SYNTHESES OF PGJ_2 TYPE ANALOGUES: 16-HYDROXY-11-OXO-$\Delta^{5,9,12,14}$-PROSTATETRAENOIC ACID t-BUTYL ESTER AND ITS RELATED DERIVATIVES[1)]

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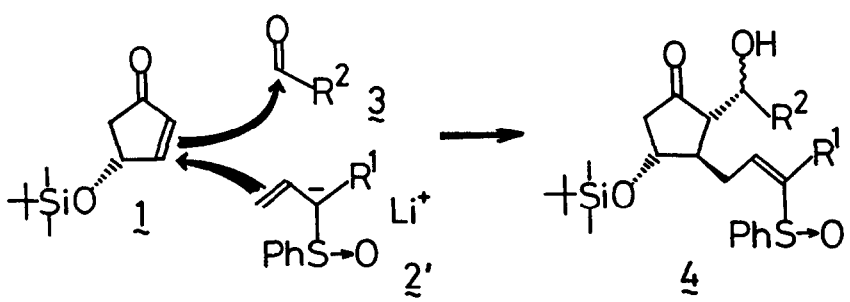
Summary: PGJ_2 analogues, the title compound (8c) and its related derivatives (8a, 8b), were synthesized via the three-component coupling process involving 1,4-addition reaction of phenylsulfinylallylic carbanion (2') to cyclopentenone derivative (1) followed by trapping the generated enolate with aldehyde (3).

Recently, it has been reported that PGJ_2, clavulone (claviridenone), and their analogues exhibit a notable antineoplastic activity.[2)] Therefore, our attention is focused on the synthesis of those new type prostaglandins. Here, we describe new syntheses of novel PGJ_2 type analogues (8).

We have previously reported[3)] that a phenylsulfinylallylic carbanion (2') derived from allylic sulfoxide (2) and lithiumdiisopropyl amide reacts with wide variety of cycloalkenones to give the 1,4-adducts selectively at the γ position of the sulfinyl group in good yield. Combination of this 1,4-addition of the sulfinyl carbanion (2') to the enone (1) and aldol reaction of aldehyde (3) with the resulting lithium enolate lead to the single-pot construction of a prostanoic acid skeleton such as 4. This process corresponds to the three-component coupling process[4)] as an alternative one.



Using this three-component coupling process, prostanoic acid derivatives (4) were obtained as shown in Table 1. These compounds (4) were further transformed into novel PGJ_2-type derivatives (8).

Table 1

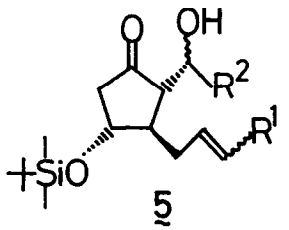
Formation of Prostanoic Acid Derivatives 4 via Three-component Coupling

Sulfoxide 2 R^1=		Aldehyde 3 R^2=		Reaction Temp. °C	Product 4	Yield/%
2a	$-(CH_2)_4CH_3$	3a	$-(CH_2)_5COOMe$	-76	4a	68
2b	$-(CH_2)_3CH_2OSiMe_2Bu^t$	3b	$-CH=CHCH(OSiMe_2Bu^t)(CH_2)_3CH_3$	-76	4b	70
2c	$-(CH_2)_3COOBu^t$	3b		-90	4c	62

For typical example, 4c was prepared as follows. To a stirring THF (3 ml) solution of 2c (200 mg, 0.65 mmol) was added a THF solution of lithiumdiisopropyl amide (prepared from 0.07 ml, 0.52 mmol, of diisopropylamine and 0.30 ml, 0.47 mmol, of butyllithium (1.56 M in hexane solution) in 1 ml of THF) at -90°C (on a dry ice-ether bath), and the mixture was stirred for additional 5 min. To the reaction mixture was quickly added a solution of 4-t-butyldimethylsilyloxycyclopent-2-en-1-one (1) (92 mg, 0.43 mmol) in THF (0.6 ml). After 10 min, a solution of the aldehyde 3b (111 mg, 0.43 mmol) in THF (0.5 ml) was added to the reaction mixture, and the reaction mixture was stirred for 30 min at -90°C and then was poured into saturated aqueous ammonium chloride (2 ml). After usual work up, the crude product was purified by column chromatography on silica gel (ether/hexane=1/2) to give 4c[5] in 62% yield.

Conversion of 4c to the title compound 8c was carried out as follows. To a solution of 4c (210 mg, 0.27 mmol) in ethanol (2 ml) was added an ethanol suspension of Raney nickel (W-1 type, ca. 100 mg), and the mixture was refluxed for 1 h and then was filtrated through a silica gel (ca. 2 g) column (15 φ) with ethyl acetate (EtOAc) as an eluent. After concentration of the eluate, the crude product was purified by column chromatography on silica gel (EtOAc/hexane=1/10) to give 5c[6] in 70% yield. Treatment of 5c (208 mg, 0.32 mmol) with diazabicyclo[5.4.0]undecene (0.1 ml, 0.64 mmol) in ether at 0°C gave 6c[7] after column chromatography on silica gel (EtOAc/hexane=1/8) in 81% yield. Dehydration of 6c to 7c was carried out by treatment of 6c (114 mg, 0.22 mmol) with CuCl(48 mg, 0.44 mmol) and dicyclohexylcarbodiimide (228 mg, 1.09 mmol) in 1 ml of dry benzene at r.t. for 10 h to afford the crude product which gave 7c (55 mg; Rf=0.69, EtOAc/hexane=1/5) and its 12Z[8] isomer (18 mg; Rf=0.83 and 0.78) after chromatographic separation (silica gel; EtOAc/hexane=

1/20). Treatment of 7c (49 mg, 0.1 mmol) with 0.5 ml of hydrofluoric acid (5%) in 2.5 ml of acetonitrile at r.t. for 1.5 h afforded the final product (8c) (30 mg, 79% yield) as a diastereoisomeric mixture concerning to the 16-hydroxyl group with Rf value of 0.60 and 0.50 (EtOAc/hexane=2/3).[9] The other related compounds (8a) and (8b) were also synthesized in a similar manner, by using the carbanions prepared from the corresponding allylic sulfoxides (2a) and (2b) followed by desulfurization, silanol elimination, and dehydration. The product (8a)[10] can be considered to be an analogue of antineoplastic Δ^7-PGA type compound,[11] and diol 8b was obtained as an inseparable diastereoisomeric mixture.[12] Moreover, we have succeeded to prepare an optically active 8b (8S, 16R, 5E and 5Z mixture (E/Z=ca. 6/4-4/6), $[\alpha]_D^{20}$+155±25° ($CHCl_3$)) from (4R)-4-t-butyldimethylsilyloxycyclopent-2-en-1-one ($[\alpha]_D$+62.2°) and (4R)-4-t-butyldimethylsilyloxyoct-2-enal (ca. 75% e.e., $[\alpha]_D$-12°). The bioactivities of recemic and optically active 8b will be described elsewhere as soon as possible.



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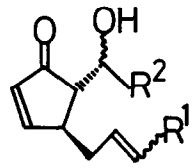

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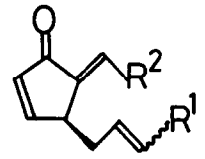

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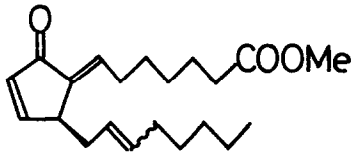
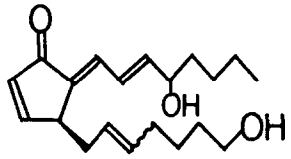
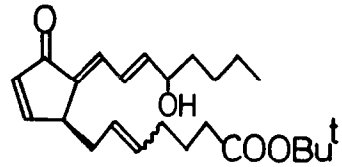


8a



8b



8c

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4) Direct formation of PG skeleton by "three-component coupling process" by combination of (i) organocopper reagent, (ii) cyclopentenone, and (iii) aldehyde or nitroolefin has been reported, M. Suzuki, T. Kawagishi, T. Suzuki, and R. Noyori, Tetrahedron Lett., 23, 4057 (1982); M. Suzuki, T. Kawagishi, and R. Noyori, ibid., 23, 5563 (1982); T. Tanaka, T. Toru, N. Okamura, A. Hazato, S. Sugiura, K. Manabe, S. Kurozumi, M. Suzuki, T. Kawagishi, and R. Noyori, ibid., 24, 4103 (1983).

5) Rf=0.37 (ether/hexane=3/2); ^{1}H NMR δ 3.48 (1H, m, 9-H), 4.14 (1H, m, 16-H), 4.44 (1H, m, 13-H), 5.67 (2H, m, 14,15-H), 6.52 (1H, t, J=7 Hz, 6-H); IR (neat) 3420, 1730, 1040 cm^{-1}.

6) 5E and 5Z mixture in the ratio of ca. 3/1 (E/Z) (determined by ^{13}C NMR); Rf=0.61 (EtOAc/hexane=1/1); ^{1}H NMR δ 3.76 (1H, m, 9-H), 4.15 (1H, m, 16-H), 4.32 (1H, m, 13-H), 5.45 (2H, m, 5,6-H), 5.65 (2H, m, 14,15-H); IR (neat) 3520, 1730 cm^{-1}.

7) Rf=0.52 (EtOAc/hexane=1/4); ^{1}H NMR δ 2.70 (1H, m, 8-H), 4.10 (1H, m, 16-H), 4.30 (1H, m, 13-H), 5.44 (2H, m, 5,6-H), 5.65 (2H, m, 14,15-H), 6.13 (1H, dd, J=2 and 6 Hz, 10-H), 7.65 (1H, dd, J=3 and 6 Hz, 9-H); IR (neat) 3500, 1730, 1705 cm^{-1}.

8) Prostanoic acid numbering.

9) These two isomers were separated by column chromatography on silica gel (EtOAc/hexane=1/4) though there was no difference in NMR (100 MHz) and IR spectra between two isomers; less polar isomer: ^{1}H NMR δ 3.60 (1H, m, 8-H), 4.30 (1H, m, 16-H), 5.41 (1H, m, 5,6-H), 6.19 (1H, dd, J=6 and 15 Hz, 15-H), 6.36 (1H, m, 10-H), 6.52 (1H, dd, J=11 and 15 Hz, 14-H), 6.97 (1H, d, J=11 Hz, 13-H), 7.51 (1H, m, 9-H); IR (neat) 3450, 1730, 1685, 1630 cm^{-1}, and polar isomer: ^{1}H NMR δ 3.60 (1H, m), 4.31 (1H, m), 5.40 (1H, m), 6.19 (1H, dd, J=5 and 15 Hz), 6.36 (1H, m), 6.53 (1H, dd, J=11 and 15 Hz), 6.98 (1H, d, J=11 Hz), 7.51 (1H, m).

10) Rf=0.40 (EtOAc/hexane=1/4); ^{1}H NMR δ 0.88 (3H, t, J=7 Hz), 1.00-2.70 (20H), 3.49 (1H, m), 3.67 (3H, s), 5.41 (2H, m), 6.31 (1H, dd, J=2 and 6 Hz), 6.55 (1H, t, J=7 Hz), 7.53 (1H, m); IR (neat) 1735, 1700, 1655 cm^{-1}.

11) Ref. 1) Prostaglandin Chemistry. Part XXVI.

12) 5E and 5Z mixture in the ratio of ca. 1/1; Rf=0.56 (EtOAc/hexane=4/1); ^{1}H NMR δ 3.59 (2H, t, J=6 Hz, 1-H), 3.60 (1H, m, 8-H), 4.28 (1H, m, 16-H), 5.37 (2H, m, 5,6-H), 6.20 (1H, dd, J=6 and 16 Hz, 15-H), 6.34 (1H, d, J=6 Hz, 10-H), 6.53 (1H, dd, J=11 and 16 Hz, 14-H), 6.96 (1H, d, J=11 Hz, 13-H), 7.53 (1H, dd, J=3 and 6 Hz, 9-H); IR (neat) 3430, 1735, 1685, 1625 cm^{-1}.

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