Communications to the Editor

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SYNTHESIS OF NEW ANTINEOPLASTIC PROSTAGLANDINS[1)]

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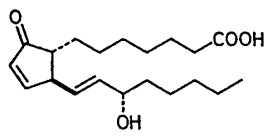
The three-component coupling process allows a single-pot entry to protected 7-hydroxy-PGE_1 derivatives, leading to a variety of new PGs functionalized or unsaturated at C-7. The enone and dienone derivatives exhibit potent inhibitory activity on L1210 tumor cell growth in vitro.

KEYWORDS —— 7-hydroxy-PGA_1; Δ^7-PGA_1; Δ^7-PGE_1; 12-epi-Δ^7-PGA_1; prostaglandin; antineoplastic

The relationship between tumor cell growth and prostaglandin (PG) formation is an attractive problem for scientists in a variety of areas.[2)] Recent in vitro and in vivo studies indicate that some naturally occurring PGs such as PGE_1,[3)] $PGF_{2\alpha}$,[4)] PGD_2,[5)] PGI_2,[6)] and related compounds[3a,7)] possess antineoplastic activities. Particularly potent are such compounds having a 2-cyclopentenone structure as PGA_1 (1),[8)] 9-deoxy-Δ^9-PGD_2 (or PGJ_2) (2),[9)] 9-deoxy-Δ^9,Δ^{12}-13,14-dihydro-PGD_2 (3),[10)] and clavulone (4)[11)] of a naturally occurring eicosanoid. These findings have opened a new approach to cancer chemotherapy. We here report a series of new synthetic PG analogs such as 7-hydroxy-PGA_1 (5), Δ^7-PGA_1 (6), Δ^7-PGE_1 (7), and their derivatives.



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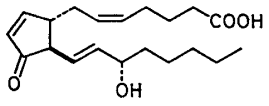

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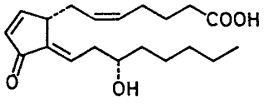

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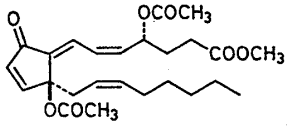

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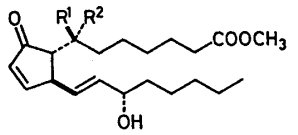
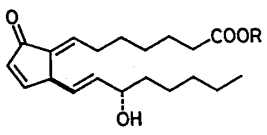
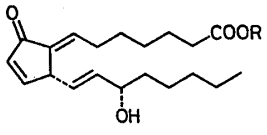
Synthesis of these analogs starts from the protected 7-hydroxy-PGE_1 derivatives (8), aldol products easily accessibly by the three-component coupling process mediated by organocopper chemistry.[12,13)] The absolute configurations of the hydroxylated carbons of 8a and 8b were substantiated by chemical correlation with the 5,6-unsaturated derivatives 9[14)] and 10, coupled with the exciton chirality method.[16)] The less polar 7S-isomer 9a and the more polar 7R-isomer 9b were



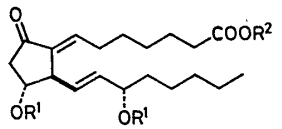
5a: R^1 = H, R^2 = OH
5b: R^1 = OH, R^2 = H



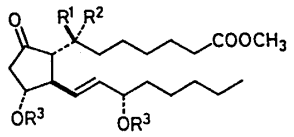
6a: R = CH_3
6b: R = H



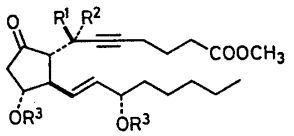
6c: R = CH_3
6d: R = H



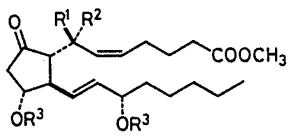
7a: R^1 = $Si(CH_3)_2$-t-C_4H_9, R^2 = CH_3
7b: R^1 = H, R^2 = CH_3
7c: R^1 = H, R^2 = H



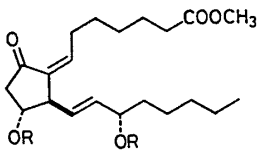
8a: R^1 = H, R^2 = OH, R^3 = $Si(CH_3)_2$-t-C_4H_9
8b: R^1 = OH, R^2 = H, R^3 = $Si(CH_3)_2$-t-C_4H_9
8c: R^1 = H, R^2 = OH, R^3 = H
8d: R^1 = OH, R^2 = H, R^3 = H



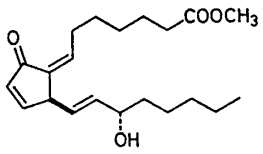
9a: R^1 = H, R^2 = OH, R^3 = $Si(CH_3)_2$-t-C_4H_9
9b: R^1 = OH, R^2 = H, R^3 = $Si(CH_3)_2$-t-C_4H_9



10a: R^1 = H, R^2 = $OCOC_6H_5$, R^3 = $Si(CH_3)_2$-t-C_4H_9
10b: R^1 = $OCOC_6H_5$, R^2 = H, R^3 = $Si(CH_3)_2$-t-C_4H_9



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



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converted to the corresponding allyl benzoates, 10a (44%)[15] and 10b (84%), respectively, by catalytic half hydrogenation of the triple bond over the Lindlar catalyst (CH_3OH, room temp, 20 h) followed by benzoylation (C_6H_5COCl, pyridine, room temp, 4 h). Measurements of the CD spectra of the benzoates indicated that 10a [$\Delta\varepsilon$ = +10.5 (226 nm, cyclohexane)] and 10b [$\Delta\varepsilon$ = -7.37 (226 nm, cyclohexane)] have 7S and 7R configuration, respectively, confirming the C-7 configuration of the precursors 9a and 9b. Catalytic hydrogenation of the triple bond of the 7S-isomer 9a and the 7R-isomer 9b over Pd-$CaCO_3$ catalyst (CH_3OH, room temp, 30 h) afforded the 5,6-saturated alcohols, 8a (50%)[15] and 8b (84%), having 7R and 7S configuration, respectively. Both stereoisomers serve as useful intermediates for the preparation of antineoplastic artificial PGs.

The first targets, 7R-hydroxy-PGA_1 methyl ester (5a) and the 7S-hydroxy isomer (5b), were obtained from 8a and 8b. The starting materials have two kinds of hydroxyl groups β to the 9-keto function. In a 2:1:1 CH_3COOH-THF-H_2O mixture (70°C, 16 h), dehydration of 8a and 8b occurred preferentially in such a way as to create the 2-cyclopentenone structure rather than the 2-alkylidenecyclopentanone moiety to give 5a (35%) and 5b (36%), respectively.[15] In order to compare the biological activities of the 2-cyclopentenones and ketones conjugated with an exocyclic double bond, Δ^7-PGE_1 derivatives of type 7 were then prepared by aldol dehydration using CH_3SO_2Cl (1 eq) and 4-dimethylaminopyridine (2 eq) (CH_2Cl_2, room temp, 6 h).[12] Dehydration of 8b gave the 7E-isomer 7a (80%) (^{1}H-NMR, H-7, δ 6.88) as a major

product accompanied by a small amount of the 7Z-isomer 11 (<5%) (^{1}H-NMR, H-7, δ 5.84). The reaction of 8a gave the stereoisomers (7a, 11) in a similar ratio (64%).[17] Deprotection of 7a was made by HF-pyridine (CH_3CN, room temp, 1 h) to afford Δ^7-PGE_1 methyl ester (7b) (81%), which was then hydrolyzed with porcine liver esterase.[19] Acid treatment (2:1:1 CH_3COOH-THF-H_2O mixture, 60°C, 15 h) of 7b gave Δ^7-PGA_1 methyl ester (6a) (72%) having a cross-conjugated dienone structure. As a by-product, the 7Z-isomer 12 was isolated (<5%). Enzymatic hydrolysis of 6a afforded Δ^7-PGA_1 (6b) (67%). The most stable products among the compounds (5), (6), (7) was the cross-conjugated dienone (6).

As expected, when the three-component coupling process was carried out using the ω-side chain unit of the "natural" C-15 S configuration and (±)-4-t-butyldimethylsilyloxy-2-cyclopentenone instead of the optically active 4R compound, a 1:1 mixture of 6a and 12-epi-Δ^7-PGA_1 methyl ester (6c) was obtained after dehydration. Enzymatic hydrolysis of the latter gave the free carboxylic acid 6d (63%).

The preliminary biological tests indicated that these newly synthesized PG analogs having a functionalized or unsaturated carbon at the 7-position exhibited significant inhibitory activity (IC_{50} 0.3 μg/ml) on L1210 tumor cell growth. Particularly, Δ^7-PGA_1 methyl ester (6a) and its C-12 epimer (6c) were the most active among the analogs synthesized. They were more potent than natural PGs such as PGA_1, PGE_1, and PGD_2, and were equipotent to clavulone in this evaluation.[20]

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13) Reaction of (R)-4-t-butyldimethylsilyloxy-2-cyclopentenone (1 eq) and the mixed cuprate formed from (E,S)-3-t-butyldimethylsilyloxy-1-octen-1-yllithium (1 eq), 1-pentynylcopper (1 eq), and hexamethylphosphorous triamide (2 eq) at -78°C followed by condensation of the resultant enolate with methyl 7-oxoheptanoate yielded 8a (12%) and 8b (42%).
14) S. Sugiura, T. Toru, T. Tanaka, N. Okamura, A. Hazato, K. Bannai, K. Manabe, and S. Kurozumi, Chem. Pharm. Bull., 32, 1248 (1984).
15) Yields are not optimized.
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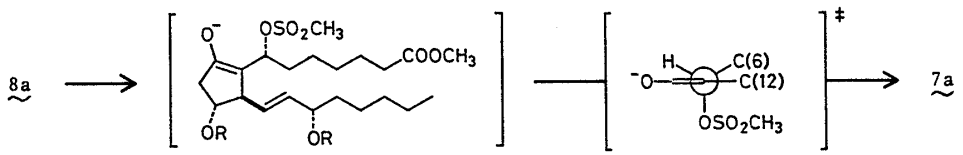
17) There was no equilibrium between 7a and 11 under the reaction condition. This stereoselectivity, leading to the same isomer 7a, is explainable by the consideration that the elimination of the methanesulfonate group occurred via the E1cB mechanism[18] involving the less hindered enolate conformations, A and B. The allylic type repulsion between the α-side chain and the oxygen at C-9 is avoided in such conformations.



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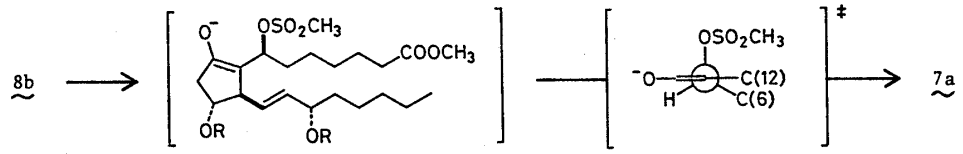

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