Communications to the Editor

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SYNTHESIS OF NEW ANTINEOPLASTIC ALKYLIDENECYCLOPENTENONES[1)]

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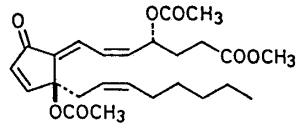
Novel conjugated cyclopentenones, 5-alkylidene-4-hydroxy-2-cyclopentenones (**3**) and 5-alkylidene-2-chloro-4-hydroxy-2-cyclopentenones (**4**) were synthesized from 4-tert-butyldimethylsilyloxy-2-cyclopentenone (**5**) by two different pathways. These new compounds and their synthetic intermediates strongly inhibited L1210 tumor cell growth in vitro.

KEYWORDS——5-alkylidene-2-cyclopentenone; 2-chloro-2-cyclopentenone; 2-chloro-4-hydroxy-2-cyclopentenone; 5-alkylidene-2-chloro-4-hydroxy-2-cyclopentenone; antineoplastic activity; cell growth inhibition

Suppression of tumor cell growth by prostaglandins (PGs) is an attractive subject.[2)] Naturally occurring PGE_1,[3)] $PGF_{2\alpha}$,[4)] PGD_2,[5)] PGI_2,[6)] and PGs with a cyclopentenone skeleton such as PGA_1,[7)] PGA_2,[7)] 9-deoxy-Δ^9-PGD_2,[8)] 9-deoxy-Δ^9,Δ^{12}-13,14-dihydro-PGD_2,[9)] Δ^7-PGA_1[10)] were shown to have antineoplastic activities in vitro and in vivo. Recently, it has been reported that clavulone (claviridenone) (**1**)[11)] and punaglandin (**2**),[12)] naturally occurring marine eicosanoids, have more potent antineoplastic activities[13)] than ordinary PGs. In this communication, we report synthetic analogs of these antineoplastic marine eicosanoids, **3** and **4**.

The syntheses of **3** and **4** were carried out in two ways starting from 4-tert-butyldimethylsilyloxy-2-cyclopentenone (**5**). The first route involves introduction of a hydroxyl group to the C-4 position of 5-alkylidene-2-cyclopentenones (**6**)[10)] or their 2-chloro derivatives (**7**). Intermediate **7a** was obtained by selective ring-epoxidation of **6a** with H_2O_2 (0.03 eq NaOH; CH_3OH, 0°C, 20 min, 78%),[14)] followed by treatment with hydrochloric acid (1:5 conc. HCl/acetone, room temp, 1.5 h) in 60% yield, accompanied by Z-isomers (**7c**). Alternatively, the intermediates **7b** (61%) and **7d** (12%) were obtained by the reaction of **6b** and C_6H_5SeCl (2 eq) in the presence of pyridine (CH_2Cl_2, reflux, 26 h).[15)] Treatment of **6a** or **7a** with tert-C_4H_9OOH in the presence of a catalytic amount of $Pd(OCOCH_3)_2$ (0.1 eq) ($(C_2H_5)_3N$; C_6H_6, 60°C, 30 h - 50 h) afforded the desired **3a** or **4a** though in low yield (10 and 7%, respectively).



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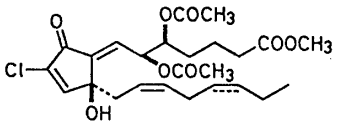

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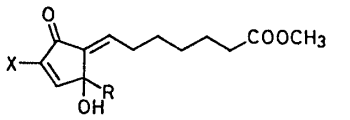
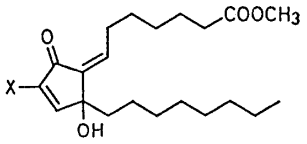
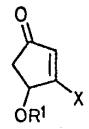


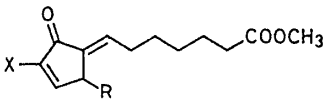
3a: X=H, R=
3b: X=H, R=
4a: X=Cl, R=
4b: X=Cl, R=



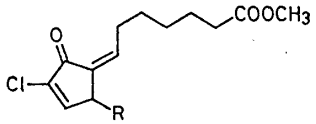
3c: X=H
4c: X=Cl



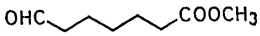
5: X=H, R^1=Si(CH$_3$)$_2$-tert-C$_4$H$_9$
8: X=Cl, R^1=Si(CH$_3$)$_2$-tert-C$_4$H$_9$



6a: X=H, R=
6b: X=H, R=
7a: X=Cl, R=
7b: X=Cl, R=



7c: R=
7d: R=



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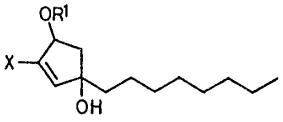
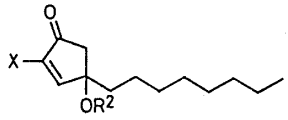
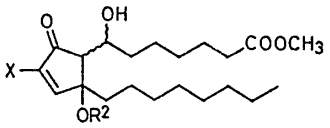


9a: X=H, R^1=Si(CH$_3$)$_2$-tert-C$_4$H$_9$
9b: X=Cl, R^1=Si(CH$_3$)$_2$-tert-C$_4$H$_9$



10a: X=H, R^2=Si(CH$_3$)$_3$
10b: X=Cl, R^2=Si(CH$_3$)$_3$



12a: X=H, R^2=Si(CH$_3$)$_3$
12b: X=Cl, R^2=Si(CH$_3$)$_3$

The second route uses **5** or protected 3-chloro-4-hydroxy-2-cyclopentenone (**8**)[16,17] as starting material. Reaction of the cyclopentenones (**5** and **8**) with n-C$_8$H$_{17}$MgBr (ether, room temp or -78°C) gave the corresponding 1,2-adducts (**9**). These products were converted to 4-hydroxy-4-octyl-2-cyclopentenones (**10**) (**10a**, 56% from **5**; **10b**, 61% from **8**) by desilylation ((C$_4$H$_9$)$_4$NF; THF, room temp), oxidation (pyridinium dichromate; CH_2Cl_2 or DMF, room temp), and silyl-protection ((CH$_3$)$_3$SiOSO$_2$CF$_3$, (iso-C$_3$H$_7$)$_2$NC$_2$H$_5$; CH_2Cl_2, 0°C, 15 min). Reaction of the lithium enolate formed from **10a** and LiN(iso-C$_3$H$_7$)$_2$ (THF, -78°C, 1 h) with aldehyde **11** (-78°C, 2 h)[18] gave the cross-aldol product **12a**[19] in 71%. The boron enolate of **10b** ((C$_4$H$_9$)$_2$BOSO$_2$CF$_3$, (iso-C$_3$H$_7$)$_2$NC$_2$H$_5$; ether, -78°C, 30 min) also reacted with **11** (-78°C, 80 min) to

give the condensation product **12b**[19] (32%). The product **12** was dehydrated by methanesulfonylation (CH_3SO_2Cl ; pyridine, 4°C, 10 h) followed by treatment with DBU (C_6H_6, 0°C, 1 h) to afford the expected products **3b** (21%),[20] **3c** (12%), and **4b** + **4c** (42%), after deprotection and chromatographic separation.

These new analogs (**3**, **4**, **7**), possessing a chlorine atom at the C-2 position and/or a hydroxy group at the C-4 position of 5-alkylidene-2-cyclopentenones, had potent inhibitory effects on L1210 tumor cell growth: IC_{50}; **3a**, 0.2 μg/ml; **3b**, 0.1 μg/ml; **4a**, 0.1 μg/ml; **4b**, 0.05 μg/ml; **7a**, 0.75 μg/ml; **7b**, 0.1 μg/ml. Particularly **4b** was even equipotent to the most potent punaglandins (**2**) (IC_{50}; 0.03 - 0.06 μg/ml).[13] These findings indicate that the 2-chloro and 4-hydroxy functionalities in the molecules are important in exerting the potent *in vitro* anti-neoplastic activity.

SPECTRAL DATA

3a: ^{1}H-NMR ($CDCl_3$) δ 5.50(d, 1H, J=16 Hz), 5.80(dt, 1H, J=16, 6.2 Hz), 6.22(d, 1H, J=6 Hz), 6.47(dt, 1H, J=7.5, 0.5 Hz). 7.10(dd, 1H, J=6, 0.5 Hz). **3b:** ^{1}H-NMR ($CDCl_3$) δ 6.15(d, 1H, J=6 Hz), 6.35(t, 1H, J=8 Hz), 7.20(d, 1H, J=6 Hz); IR (neat) 3450, 1740, 1710, 1640, 1360 cm^{-1}. **3c:** ^{1}H-NMR ($CDCl_3$) δ 6.1(t, 1H, J=6 Hz), 6.1(d, 1H, J=6 Hz), 7.1(d, 1H, J=6 Hz); IR (neat) 3450, 1740, 1700, 1650, 1360 cm^{-1}. **4a:** ^{1}H-NMR ($CDCl_3$) δ 5.50(d, 1H, J=15 Hz), 5.85(dt, 1H, J=15, 6.2 Hz), 6.68(dt, 1H, J=7.5, 0.5 Hz), 7.14(d, 1H, J=0.5 Hz). **4b:** ^{1}H-NMR ($CDCl_3$) δ 6.66(dd, 1H, J=7.5, 8.3 Hz), 7.24(s, 1H). **4c:** ^{1}H-NMR ($CDCl_3$) δ 6.35(t, 1H, J=7.9 Hz), 7.17(S, 1H). **7a:** ^{1}H-NMR ($CDCl_3$) δ 3.7-4.1(m, 1H), 5.11(dd, 1H, J=15.2, 8.0 Hz), 5.56(dt, 1H, J=15.2, 6.2 Hz), 6.62(brt, 1H, J=7.0 Hz), 7.11(d, 1H, J=2.8 Hz); IR (neat) 1738, 1710, 1657, 1568 cm^{-1}. **7b:** ^{1}H-NMR ($CDCl_3$) δ 3.3-3.8(m, 1H), 6.64(brt, 1H, J=7.7 Hz), 7.41(d, 1H, J=2.6 Hz); IR (neat) 1738, 1710, 1658, 1588 cm^{-1}. **7c:** ^{1}H-NMR ($CDCl_3$) δ 3.5-3.9(m, 1H), 5.08(dd, 1H, J=14.8, 7.8 Hz), 5.52(dt, 1H, J=14.8, 6.1 Hz), 5.89(brt, 1H, J=7.6 Hz), 7.07(d, 1H, J=2.4 Hz). **7d:** ^{1}H-NMR ($CDCl_3$) δ 3.1-3.5(m, 1H), 6.13(brt, 1H, J=7.8 Hz), 7.33(d, 1H, J=3.5 Hz); IR (neat) 1738, 1698, 1645, 1588 cm^{-1}. **10a:** ^{1}H-NMR ($CDCl_3$) δ 2.4(s, 2H), 5.95(d, 1H, J=6 Hz), 7.3(d, 1H, J=6 Hz); IR (neat) 1730, 1340, 1250 cm^{-1}. **10b:** ^{1}H-NMR ($CDCl_3$) δ 2.63(s, 2H), 7.34(s, 1H). **12a:** ^{1}H-NMR ($CDCl_3$) δ 3.2-4.0(m, 2H), 6.05(d, 1H, J=6 Hz), 7.25(d, 1H, J=6 Hz); IR (neat) 3500, 1740, 1710, 1350, 1255 cm^{-1}. **12b:** ^{1}H-NMR ($CDCl_3$) δ 3.8-4.1(m, 1H), 7.32 and 7.47(s, 1H).

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14) Under the reaction conditions, the exocyclic olefin epoxidation products were not obtained.
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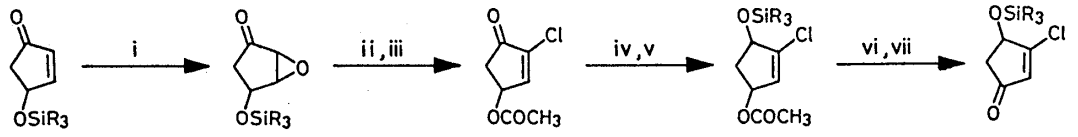
17) Alternatively we synthesized **8** from **5** by the following sequences.



SiR_3=$Si(CH_3)_2$-tert-C_4H_9

i) H_2O_2, NaOH (cat.) ii) HCl iii) CH_3COCl, pyridine iv) $NaBH_4$, $CeCl_3$
v) tert-C_4H_9-$(CH_3)_2SiCl$, 4-dimethylaminopyridine vi) $LiAlH_4$ vii) MnO_2

18) a) E. J. Corey and M. M. Mehrotra, J. Am. Chem. Soc., **106**, 3384 (1984); b) H. Nagaoka, T. Miyakoshi, and Y. Yamada, Tetrahedron Lett., **25**, 3621 (1984).
19) Mixture of stereoisomers.
20) Yield was not optimized.

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