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Synthesis and Pharmacological Activities of 13-Dehydro Derivatives of Primary Prostaglandins

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Abstract

13-Dehydro derivatives of prostaglandin E_1, E_2, E_3, $F_{1\alpha}$ and $F_{2\alpha}$ were synthesized. Compared with natural prostaglandins, 13-dehydro analogues were found to exhibit more potent inhibitory activity against human platelet aggregation and relaxation of guinea-pig isolated trachea, while they showed less potent activity of contraction of guinea-pig isolated ileum.

Keywords: prostaglandins; agonists

The synthesis and biological effects of 13-dehydro derivatives of natural prostaglandins(PGs) have attracted much interest. Fried *et al.*[1,2] reported the synthesis of 13-dehydro derivatives of natural PGE_2 and $F_{2\alpha}$. These derivatives caused stimulation of cAMP synthesis in mouse ovary, and also caused termination of pregnancy in hamsters. Furthermore, they have proved to be nonsubstrates for 15-dehydrogenase[1,3]. PG analogues in which the double bond at C-13 has been replaced by a triple bond have been developed, and some of these have deserved particular attention as promising therapeutic agents[4-13].

13-Dehydro derivatives of natural PGE_1, $F_{1\alpha}$ and E_3, however, have not been synthesized yet, in spite of the great interest in their biological effects. Herein we report a highly efficient synthesis and biological evaluation of 13-dehydro PGs including 13-dehydro PGE_1, $F_{1\alpha}$ and E_3.

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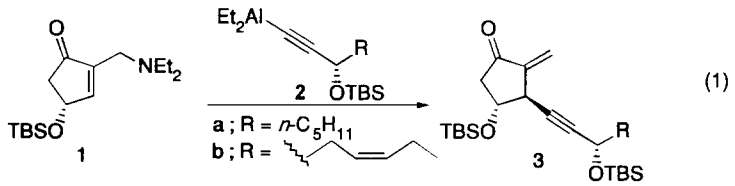
1. Synthesis

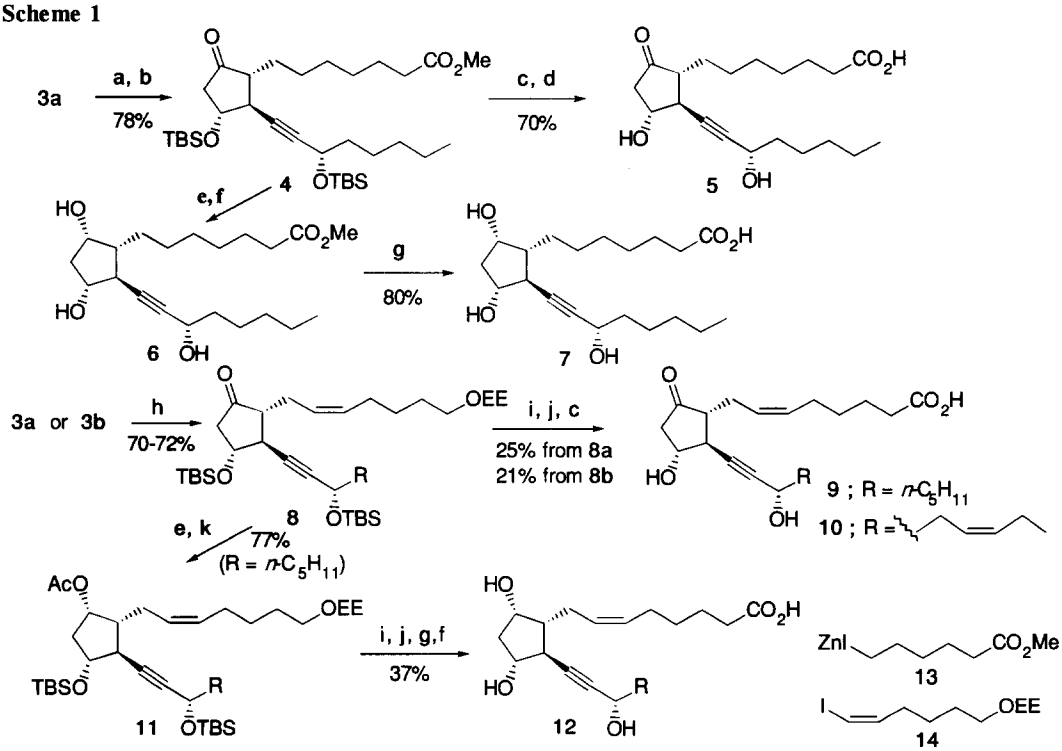
In a recent paper, we have reported the synthesis of α-methylenecyclopentanone **3**[14], which is a potential intermediate of the synthesis of 13-dehydro PGs *via* 1,4-addition reaction of α side-chain units, by the reaction of commercially available cyclopentenone **1** with alkynylaluminium compounds **2**(eq 1).



(1)

By starting from **3**, a variety of 13-dehydro PGs have been synthesized according to the procedure shown in Scheme 1. Thus, the compound **3a** reacted with an organocopper reagent derived from **13**(2.0 eq.) and CuCN-2LiCl(2.5 eq.) in the presence of trimethylsilyl chloride (1.8 eq.) to afford **4** in 78% yield[15,16].

Scheme 1



(a) **13**, CuCN-2LiCl, Me_3SiCl, THF, -78°C; (b) 1N-HCl, MeOH, THF, 0°C; (c)$(HF)_n$-pyridine, CH_3CN, 0°C; (d) porcine liver esterase, phosphate buffer(pH=8.0), room temperature; (e) L-selectride, THF, -78°C; (f) aqueous HF, THF, 0°C; (g) LiOH, MeOH or EtOH, H_2O then 1N-HCl, room temperature; (h) **14**, *t*-BuLi, Et_2O then (2-thienyl)Cu(CN)Li, THF, -78°C to 0°C (i) pyridinium *p*-toluenesulfonate, Et_2O, *i*-PrOH, room temperature; (j) Jones' reagent, acetone, Et_2O, 0°C; (k) Ac_2O, pyridine, cat. N,N-dimethylaminopyridine, room temperature

Protodesilylation of **4** with $(HF)_n$-pyridine followed by hydrolysis using porcine liver esterase provided 13-dehydro PGE_1 (**5**)[1] in 70% yield. Meanwhile, 13-dehydro PGF_1(**7**)[2] was prepared by the stereospecific reduction of a carbonyl group in **4** followed by protodesilylation and saponification. Similarly, 13-dehydro PGE_2 (**9**) ($[\alpha]_D^{23}$ -15.4 °(c 0.052, EtOH);lit.[17]$[\alpha]_D^{20}$ -15.1°(c 0.10, EtOH)) and -$PGF_{2\alpha}$ (**12**) ($[\alpha]_D^{23}$ +36.4°(c 0.188, EtOH); lit.[1]$[\alpha]_D$ +34.0°(c 0.66, EtOH)) were synthesized from **3a** and an organocopper reagent derived from **14**[18] *via* the compound **8a** in 18% and 21% overall yields, respectively. Similar synthetic reactions starting from **3b** and **14** provided 13-dehydro PGE_3 (**10**)[3] *via* the compound **8b** in 15% overall yield.

2. Biological activity

The results of pharmacological evaluation of these analogues are summarized in Table 1. The biological activities of all five 13-dehydro derivatives were compared with those of the corresponding natural compounds. 13-Dehydro PGE_1(**5**) showed 3.0 times more potent inhibitory effect on adenosine diphosphate(ADP)-induced human platelet aggregation *in vitro* [19] in comparison with natural PGE_1 and it was 8.9 times more potent against histamine-induced relaxation of guinea-pig isolated trachea precontracted with histamine[20]. On the other hand, it proved to be less potent on contraction of guinea-pig isolated ileum[21]. 13-Dehydro PGE_2(**9**) and PGE_3(**10**) also showed the same tendency of more potent activities of anti-aggregation and relaxation of trachea, and less potent activity on contraction of ileum. 13-Dehydro $PGF_{1\alpha}$(**7**) and $PGF_{2\alpha}$(**12**) proved to be 0.02 to 0.12-fold less potent than the corresponding natural compounds on contraction of guinea-pig ileum, and they showed almost the same potency on contraction of rat isolated uterus[22]. It is a noteworthy fact that the activity profiles of prostaglandins can be greatly altered by the structural modification of the 13,14-double bond to a triple bond. Of prime interest is the highly significant dissociation in 13-dehydro PGE_1(**5**) of the inhibitory activity against human platelet aggregation from the contraction activity of guinea-pig ileum which is an *in vitro* system that often predicts "diarrhea" potential, thus 13-dehydro PGE_1(**5**) may be a more selective anti-aggregating agent than natural PGE_1.

1. ^{1}H NMR ($CDCl_3$, 300MHz) δ ppm;0.89(t, J=6.3Hz, 3H), 1.14-1.91(m, 18H), 2.10-2.46(m, 1H), 2.24(dd, J=18.2, 9.6Hz, 1H), 2.33(t, J=7.1Hz, 2H), 2.52-2.86(m, 1H), 2.75(dd, J=18.2, 7.1Hz, 1H), 4.18-4.49(m, 1H), 4.39(t, J=6.3Hz, 1H); IR(KBr):3839, 2933, 2860, 2237, 2217, 1741, 1731, 1713, 1462, 1409, 1234, 1078, 727cm^{-1}; MS(FAB)(+KI) m/z:391(MK^+); HRMS(FAB) m/z; Calcd for $C_{20}H_{32}O_5$: 353.2328(MH^+). Found:353.2317.; mp 48.8-50.4°C(colorless needles, recrystallized from AcOEt-hexane); Anal Calcd for $C_{20}H_{32}O_5 \cdot 1/2H_2O$: C, 66.45: H, 9.20. Found: C, 66.35: H, 9.24.; $[\alpha]_D^{27}$ -35.05° (c 0.884, MeOH)
2. ^{1}H NMR ($CDCl_3$, 300MHz) δ ppm;0.89(t, J=6.9Hz, 3H), 1.24-1.87(m, 20H), 2.13-2.24(m, 1H), 2.35(t, J=7.1Hz, 2H), 2.54-2.61(m, 1H), 4.17-4.27(m, 2H), 4.37(dt, J=6.6, 1.9Hz, 1H) ; IR(KBr):3460, 3339, 2955, 2929, 2858, 2232, 1720, 1672, 1620, 1469, 1404, 1330, 1283, 1230, 1186, 1155, 1134, 1060, 1040, 1026, 978, 937, 888, 802, 727, 653, 522cm^{-1}; MS(FAB)(+KI) m/z:393(MK^+); HRMS(FAB) m/z; Calcd for $C_{20}H_{34}O_5K$: 393.2043(MK^+). Found:393.2030.
3. ^{1}H NMR ($CDCl_3$, 300MHz) δ ppm;0.98(t, J=7.5Hz, 3H), 1.64-1.78(m, 2H), 2.00-2.25(m, 5H), 2.29-2.53(m, 7H), 2.61-2.82(m, 2H), 4.28-4.49(m, 2H), 5.30-5.67(m, 4H); ^{13}C NMR ($CDCl_3$, 75MHz) δ ppm;14.2, 20.8, 24.6, 25.2, 26.3, 33.2, 35.6, 41.1, 46.0, 55.3, 62.2, 72.8, 84.0, 84.4, 122.8, 125.9, 132.0, 135.6, 178.0, 213.2; IR(neat):3417, 2929, 2220, 1730, 1407, 1247, 1047, 866, 756cm^{-1}; MS(FAB)(+KI) m/z:387(MK^+); HRMS(FAB) m/z; Calcd for $C_{20}H_{28}O_5K$: 387.1574(MK^+). Found:387.1581.

Table 1
Relative potency of 13-dehydro prostaglandins(*in vitro* assay)

Compound	Platelet [a,b,c]	Trachea [b,d,e]	Ileum [g,h,i]	Uterine [h,l,m]
5	$3.0\times PGE_1$	$8.9\times PGE_1$	$0.23\times PGE_1$	not tested
9	$3.4\times PGE_2$	$2.6\times PGE_2$ [f]	$0.18\times PGE_2$ [j]	not tested
10	$2.6\times PGE_3$	$5.4\times PGE_3$	$0.26\times PGE_3$	not tested
7	not tested	not tested	$0.02\times PGF_{1\alpha}$	$1.00\times PGF_{1\alpha}$
12	not tested	not tested	$0.12\times PGF_{2\alpha}$ [k]	$0.60\times PGF_{2\alpha}$ [k]

[a]Inhibition of ADP-induced human platelet aggregation.
[b]The activities relative to those of corresponding natural PGs were calculated based on IC_{50} values(N=4).
[c]IC_{50} values of natural PGE_1=77.6nM, PGE_2=0.23μM, PGE_3=10.0μM.
[d]Relaxation of guinea-pig trachea precontracted with histamine.
[e]IC_{50} values of natural PGE_1=0.16μM, PGE_2=18.2nM, PGE_3=0.48μM.
[f]13-Dehydro PGE_2-induced relaxation of guinea-pig trachea precontracted with carbachol was reported[23].
[g]Contraction of guinea-pig ileum.
[h]The activities relative to those of corresponding natural PGs were calculated based on ED_{50} values(N=4).
[i]ED_{50} values of natural PGE_1=47.9nM, PGE_2=22.9nM, PGE_3=0.12μM, $PGF_{1\alpha}$=0.12μM, $PGF_{2\alpha}$=47.9nM.
[j]Similar result was reported[21].
[k]Similar result was reported[24].
[l]Contraction of rat isolated uterine.
[m]ED_{50} values of natural $PGF_{1\alpha}$=0.17μM, $PGF_{2\alpha}$=44.7nM.

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