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Communications to the Editor

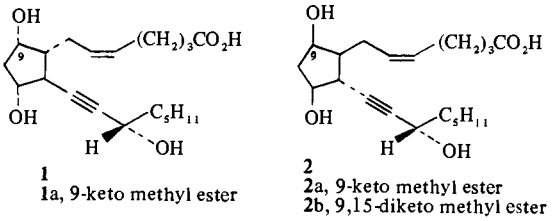
Synthesis and Biological Effects of 13-Dehydro Derivatives of Natural Prostaglandin $F_{2\alpha}$ and E_2 and Their 15-Epi Enantiomers¶

Sir:

In recent communications[1,2] we have described synthetic routes leading to all the primary prostaglandins *via* acetylenic intermediates of type **3** and **11**. The convertibility of these same intermediates into acetylenic prostaglandins, *e.g.*, **1** and **2**, appeared an attractive synthetic goal, in view of the possibility that such substances containing a propargyl in place of the allylic alcohol moiety might turn out to be nonsubstrates, or even antagonists, for the highly specific prostaglandin 15-dehydrogenase[3,4] and thus possess longevity of action not observed with the natural prostaglandins. Such blockage of dehydrogenation had previously been achieved by substituting a methyl group for the 15-hydrogen.[5] We wish to report here the synthesis and biological properties in five test systems of *nat*-13-dehydroprostaglandin $F_{2\alpha}$† (**1**) and *ent*-13-dehydro-15-epiprostaglandin $F_{2\alpha}$† (**2**) and their corresponding E_2 methyl esters **1a** and **2a**. The data presented show that substitution of an acetylenic for the trans-olefinic function does indeed render these substances antagonists of the 15-dehydrogenase and, moreover, gives rise to remarkable changes in their activity profiles.

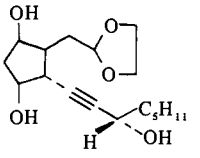
In planning the synthesis of **1** and **2** it was evident that one of the features of our synthetic route, namely, the resolution of the racemic cyclopentane moiety, *e.g.*, **9**, by introduction of the acetylenic 8-carbon side chain in optically active form[1,2] as in **10** or **11** appeared to be precluded since chromatographic separation of the acetylenic diastereomers of type **3** and **11** could not be achieved. Fortunately, one of the diastereomers, **3**,‡ could be obtained in crystalline form,§ mp 102°, $[\alpha]_D$ −2.0° (*c* 2.15),# and the synthesis of **2** completed by hydrolysis of the former with 0.1 *N* HCl in acetonitrile-water (2:1) at 25° for 24 hr to the hemiacetal **4**, $[\alpha]_D$ +1.4° (*c* 2.60), followed by a Wittig reaction as previously described.[1] The resulting *ent*-13-dehydro-15-epiprostaglandin $F_{2\alpha}$ (**2**) obtained in 67% yield from **3**, after purification by high-pressure chromatography, had mp 22–23° and $[\alpha]^{EtOH}_D$ −39.5° (*c* 0.85).** Conversion of the methyl ester of **2** into the corresponding PGE_2 derivative by selective 11,15-silylation with *N*-trimethylsilyldiethylamine in acetone at −40° followed by Collins oxidation[6] furnished **2a**,** $[\alpha]^{EtOH}_D$ −5.6° (*c* 0.45), in 40% yield, together with the recovered methyl ester of **2** (18%) and the 9,15-diketo methyl ester **2b** (20%), λ^{alc}_{max} 222 nm (ε 9600).

Since the other diastereomer corresponding to **3** could not be obtained in pure crystalline form, it was necessary to carry out the synthesis of **1** with resolved (+)-**5**, and, of course, (3*S*)-3*t*-butyloxy-1-octynyldimethylalane,[7] the resolution and determination of absolute configuration of



1
1a, 9-keto methyl ester

2
2a, 9-keto methyl ester
2b, 9,15-diketo methyl ester



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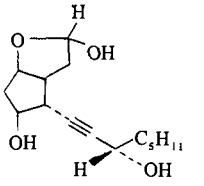

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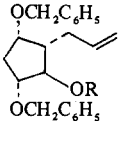
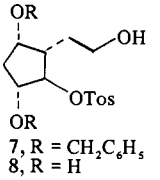
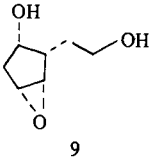


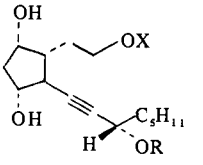
5, R = H
6, R = Tos



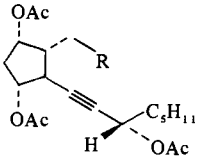
7, R = $CH_2C_6H_5$
8, R = H



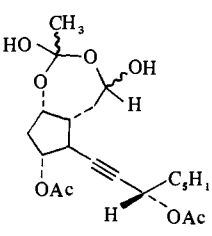
9



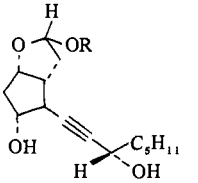
10, X = H; R = *tert*-Bu
11, X = H; R = H
12, X = Tr; R = H



13, R = CH_2OTr
14, R = CH_2OH
15, R = CHO



15a



16, R = CH_3
17, R = H

¶Presented in part at the International Conference of Prostaglandins, Vienna, Sept 25–28, 1972.

†The prefixes nat and ent are employed here to indicate that all the chiral centers present in these prostaglandin analogs correspond to those in the natural prostaglandins (nat) or in their enantiomers (ent).

‡All structural formulas represent the absolute configurations shown.

§*Cf.* footnote 13 in ref 1. The purity of this substance was verified by $LiAlH_4$ reduction to the allylic alcohol, which proved to be a single diastereomer by tlc, a technique which readily distinguishes between such allylic 15-epimers.

#Rotations in chloroform at 28–30° unless indicated otherwise.

**The ir and nmr spectra of this substance as well as the low-resolution mass spectrum of its trimethylsilyl ether methyl ester which showed the M^+ peak were in accord with the assigned structure. Mass spectra were taken on a Finnigan 1015 quadrupole instrument equipped with gc inlet and interfaced with a Systems Industries computer system.

Table I. Biological Activities of 13-Dehydroprostaglandins

Compd	Gerbil colon contraction,[a,b] $F_{2\alpha}$ = 1	cAMP synthesis, mouse ovary[c,d]	Rat lipocyte binding[e,f]	Antifertility hamster,[g,h] $F_{2\alpha}$ = 1	Placental 15-dehydrogenase inhibition,[k] I_{50},[l] μM
1	0.33 ± 0.15	1–2 × $F_{2\alpha}$	0.24 × $F_{2\alpha}$ ± 0.07	2[i] 5[j]	47
1a		0.1–0.3 × E_1	0.21 × E_1 ± 0.07		7
2	0.0052 ± 0.0014	1–2 × $F_{2\alpha}$	<0.04 × $F_{2\alpha}$	0.25[i]	50
2a		0.02–0.05 × E_1	0.08 × E_1 ± 0.03		20

[a]Reference 11. [b]Potencies and 95% CL calculated from dose-response curves for $PGF_{2\alpha}$ (six levels from 2 to 100 ng/ml) and test compounds. [c]Reference 9. [d]Potency ranges derived by comparing per cent stimulation of adenylyl cyclase over control of test compounds at three dose levels, with maximum stimulation obtained with $PGF_{2\alpha}$ (100 μg/ml) and PGE_1 (1 μg/ml), respectively. Data for 1 and 2 from two independent experiments; those for 1a and 2a from one experiment. [e]Reference 12. [f]Potencies and 95% CL obtained by comparing binding of test compounds at three dose levels with standard curves for PGE_1 and $PGF_{2\alpha}$. [g]Reference 10. [h]Derived by comparing "minimum effective doses" of test compounds with those for $PGF_{2\alpha}$. The "minimum effective dose" is the minimum dose/animal/day that will result in no pregnancies in a group of five animals. For $PGF_{2\alpha}$ this dose is 12.5 μg, sc, and 1.0 mg, po. [i]Subcutaneously. [j]Perorally. [k]Reference 8. [l]Concentration producing 50% inhibition as measured by the $\Delta OD_{340\ nm}$ after 15-min incubation at 25° of placental enzyme (0.01 ml), PGE_1 (20 μg), test substance (40, 60, 80 μg), and NAD (1 mg, added after 5 min) in 3 ml of phosphate buffer at pH 7.0.

which had already been achieved.[1] The synthetic sequence employed was identical up to (+)-**11** with that previously described for *rac*-**5**,[1,2] and the relevant structures are shown here for the purpose of presenting the specific rotation data: **6**, $[\alpha]_D$ +16.6° (*c* 2.31); **7**, +3.7° (*c* 2.14); **8**, +27.0° (*c* 1.98); **9**, +0.4° (*c* 1.0); **10**, −33.4° (*c* 2.08); **11**, +16.0° (*c* 2.85). Tritylation of **11** at 25° for 20 hr furnished in 80% yield the primary trityl ether **12**, $[\alpha]_D$ −17.5° (*c* 2.70), which was acetylated quantitatively to **13**, $[\alpha]_D$ −8.7° (*c* 2.50), and detritylated with 90% acetic acid at 25° for 24 hr to yield **14** (89%), $[\alpha]_D$ −43.5° (*c* 1.76). Collins oxidation of the latter for 10 min at 25° afforded the aldehyde **15**,†† $[\alpha]_D$ −25.6° (*c* 1.16), which on treatment with 2% potassium carbonate in methanol at 25° for 5 hr gave rise to the methyl glycoside **16**,‡‡ so characterized by nmr [broad singlets at δ 3.30 (OCH_3) and 5.10 (-$CH(OR)_2$)] and glc-ms of its bis(trimethylsilyl) ether, M^+ 426. Hydrolysis of **16** with 0.1 *N* HCl in acetonitrile-water (2:1) at 25° for 48 hr gave the free hemiacetal **17**, $[\alpha]_D$ −5.0° (*c* 0.42), in 63% yield from **14** after tlc. The synthesis was completed as described above for the enantiomeric **2** and **2a** resulting in *nat*-13-dehydroprostaglandin $F_{2\alpha}$ (**1**),** $[\alpha]^{EtOH}_D$ +34.0° (*c* 0.66), as well as *nat*-13-dehydroprostaglandin E_2 methyl ester (**1a**).**,[6]

Bioassay data for 1, 1a, 2, and 2a are summarized in Table I. All four 13-dehydro derivatives proved to be nonsubstrates for the human placental 15-dehydrogenase[8] as well as inhibitors of that highly specific prostaglandin-metabolizing enzyme. Furthermore, they all caused stimulation of cAMP synthesis in the mouse ovary.[9] Most remarkable in this respect was the unexpectedly high activity of the enantiomeric substances 2 and 2a, in which all the asymmetric centers with the exception of C-15 are of unnatural chirality. Moreover, both chiral types, 1 and 2, caused termination of pregnancy in hamsters.[10] Of prime interest is the highly significant dissociation in compound 2 of smooth muscle stimulating activity[11] and binding to a rat lipocyte "receptor" preparation specific for prostaglandins[12] from adenylcyclase stimulating and antifertility activity. It is this latter fact which gives cause for optimism that the activity profiles of prostaglandins can be drastically altered by chemical modification.

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††The triacetate aldehyde **15** exhibited aldehyde characteristics, methine proton at δ 9.78 (broad singlet), when the work-up excluded washing of the ether extract with bicarbonate. When a bicarbonate wash was performed the aldehyde methine proton was replaced by the hemiacetalic methine signal in the δ 5.3–5.7 region and the 9-proton was shifted upfield to form a multiplet centered at δ 3.75. We propose structure **15a** for this intermediate. It is this bicarbonate washed material that was used in the subsequent step.

‡‡This unusual reaction appears to involve the cyclic hemiacetal **15a**, since the desacetyl hemiacetal **17** on treatment with potassium carbonate in methanol led to intractable products, probably by aldolization.