Communications

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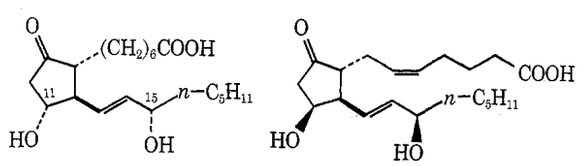
11,15-Epiprostaglandin E_2 and Its Enantiomer. Biological Activity and Synthesis

Summary: *ent*-11,15-Epiprostaglandin E_2 (**3**) has been synthesized starting from the hydroxy acid **4** *via* the lactone **6** (X = H; Y = OH). The bioactivity of **3** as measured by the stimulation of smooth muscle contraction was found to exceed by far that of its optical antipode 11,15-epiprostaglandin E_2 and to approach the activity of prostaglandin E_2 itself.

Sir: Prostaglandin E_1 (PGE_1) (**1**) stimulates contraction of a variety of smooth muscle tissues[1] at concentrations in the range 10^{-9} g/ml. The response of the same tissues to 15-epi-PGE_1 or 11-epi-PGE_1 is lower by one or two orders of magnitude.[2] It was of considerable interest therefore that racemic 11,15-epi-PGE_1 was found to exhibit approximately the same activity as PGE_1.[2] This observation brought into question the relative contributions of the two mirror image forms in the racemate to the measured biological activity. Preliminary tests with partially resolved material indicated that the *ent*-11,15-epi-PGE_1 component of the racemate might be more active than the antipode 11,15-epi-PGE_1.[2] These results prompted the synthetic and biological studies reported here for the PGE_2 series which have allowed an unambiguous conclusion. Both 11,15-epi-PGE_2 (**2**) and *ent*-11,15-epi-PGE_2 (**3**) have been synthesized, and the latter compound (**3**) has now been found to be far more active in smooth muscle stimulation than the former substance (**2**). Indeed, the activity of the *ent* form **3** approaches that of PGE_2 itself.



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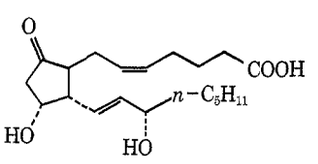

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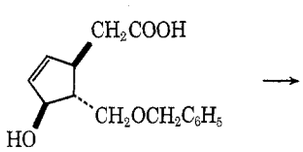
The synthesis of *ent*-11,15-epi-PGE_2 was carried out starting from the readily available salt of the levo acid **4** with (−)-amphetamine[3] by a modification of the scheme which has been employed for the synthesis of the various primary prostaglandins.[4] Iodolactonization[4] of **4** produced **5** [Z = I, R = H, X = $CH_2OCH_2C_6H_5$;[5] mp 120–121°; $[\alpha]^{28}D$ +36.1° (*c* 1.2, $CHCl_3$) (97%)], which was converted[4] to the *p*-phenylbenzoate ester **5** [Z = I, R = *p*-$C_6H_5C_6H_4CO$, X = $CH_2OCH_2C_6H_5$;[5] mp 164–166°; $[\alpha]^{28}D$ −1.43° (*c* 1.05, $CHCl_3$) (98% yield)], and further *sequentially* by deiodination using tributyltin hydride to **5** [Z = H, R = *p*-$C_6H_5C_6H_4CO$, X = $CH_2OCH_2C_6H_5$;[5] mp 98–100°; $[\alpha]^{25}D$ +88.2° (*c* 1.2, $CHCl_3$) (95%)], hydrogenation[4] (Pd/C catalyst) to the primary alcohol **5** [Z = H, R = *p*-$C_6H_5C_6H_4CO$, X = CH_2OH;[5] mp 130–131°; $[\alpha]^{24}D$ +88.3° (*c* 1.1, $CHCl_3$) (92%)], and oxidation[4] (Collins reagent) to the aldehyde **5** (Z = H, R = *p*-$C_6H_5C_6H_4CO$, X = CHO).[5a] This last intermediate was directly condensed with the sodio derivative of dimethyl 2-oxoheptylphosphonate[4] to yield (67% over two steps) the oily enone **5** [Z = H, R = *p*-$C_6H_5C_6H_4CO$, X = $CH{=}CHCO\text{-}n\text{-}C_5H_{11}$; $[\alpha]^{25}D$ +146.4° (*c* 1.2, $CHCl_3$)],[5a] reduction of which by sodium borohydride in ethanol at −20° afforded the 15*S* alcohol **6** (X = $OCOC_6H_4C_6H_5$, Y = H, R = H),[5] along with the 15*R* epimer.[6] The configuration at C-11 in this 15*S* derivative was inverted in ~50% overall yield by the sequence (1) tetrahydropyranylation of the 15-hydroxyl; (2) cleavage of the *p*-phenylbenzoate ester (1 equiv of potassium carbonate in methanol at 25° for 1 hr) to form **6** (X = HO, Y = H, R = THP);[5a] (3) tosylation (2.0 equiv of tosyl chloride in pyridine at 25° for 19 hr) to form **6** (X = TsO, Y = H, R = THP);[5a] (4) reaction with 6.7 equiv of tetrabutylammonium formate in acetone at 25° for 16 hr[7] to form **6** (X = H, Y = HCO_2, R = THP);[5a] and (5) formate cleavage (potassium carbonate in methanol) and tetrahydropyranylation to



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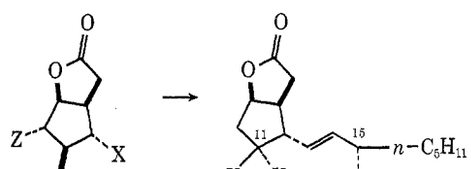

5 **6**

(1) For example, rat uterus, guinea pig ileum, gerbil colon.

(2) P. W. Ramwell, J. E. Shaw, E. J. Corey, and N. Andersen, *Nature*, **221**, 1251 (1969).

(3) This salt had mp 111–112.5°, $[\alpha]^{28}D$ −17.25° (*c* 1.0, $CHCl_3$). For the preparation of the enantiomeric salt, see E. J. Corey, S. M. Albonico, U. Koelliker, T. K. Schaaf, and R. K. Varma, *J. Amer. Chem. Soc.*, **93**, 1491 (1971).

(4) See (a) E. J. Corey, T. K. Schaaf, W. Huber, U. Koelliker, and N. M. Weinshenker, *ibid.*, **92**, 397 (1970); (b) E. J. Corey, N. M. Weinshenker, T. K. Schaaf, and W. Huber, *ibid.*, **91**, 5675 (1969).

(5) Satisfactory (a) ir and nmr spectra and (b) analytical data have been obtained for this substance.

(6) The 15*S*- and 15*R*-epimeric alcohols (which exhibited, respectively, R_f 0.23 and 0.44 upon thin layer chromatography using silica gel plates with benzene–ethyl acetate, 3:1) were separated chromatographically. The 15*S* alcohol **6** (X = OH, Y = H, R = H) was obtained as an oil, $[\alpha]^{28}D$ +99.3° (*c* 1.1, $CHCl_3$).

(7) E. J. Corey and S. Terashima, *Tetrahedron Lett.*, 111 (1972).

form 6 [X = H, Y = THPO, R = THP;[5a] $[\alpha]^{25}D$ $-103°$ (*c* 0.54, $CHCl_3$)] as a colorless oil. The synthesis of *ent*-11,15-epi-PGE_2 (**3**) from this last intermediate was accomplished by the standard[4] sequence (1) lactone → lactol reduction[4] (97% yield) using 2.0 equiv of diisobutylaluminum hydride in hexane at $-70°$ for 25 min; (2) Wittig reaction of the lactol with the ylide derived from 5-triphenylphosphoniopentanoic acid[4] (51% yield); (3) Jones oxidation of the resulting 11,15-bistetrahydropyranyl derivative of *ent*-11,15-epi-$PGF_{2\alpha}$ to form the 11,15-bistetrahydropyranyl derivative of **3** (90%); and finally (4) THP cleavage using 2:1 acetic acid–water to form *ent*-11,15-epi-PGE_2 (**3**) (80% yield), obtained as a colorless oil by thin layer chromatographic purification,[8] $[\alpha]^{22}D$ $+25.5°$ (*c* 1.04, tetrahydrofuran). The nmr and ir spectra of a purified sample of **3** synthesized in this way were identical with those obtained for its enantiomer **2**.[9]

The preparation of 11,15-epi-PGE_2 (**2**) was carried out from 15-epi-PGA_2[10] by a previously reported[11] sequence. The material so obtained was a colorless oil, $[\alpha]^{25}D$ $-26.7°$ (*c* 0.49, tetrahydrofuran), chromatographically and spectroscopically identical with a reference sample provided by Dr. John E. Pike of the Upjohn Co.

Tissue contraction in response to PGE_2 and the two test substances **2** and **3** were measured *in vitro* as previously[2] outlined for (a) isolated rat uterus and (b) isolated gerbil colon preparations.[12] For a given tissue preparation a log dose–response curve was obtained first for the standard PGE_2 and immediately thereafter for the test substance **2** or **3**, and in this way relative potencies were ascertained. These results are summarized in Table I. From these data it is apparent that *ent*-11,15-epi-PGE_2 (**3**) is considerably more active than 11,15-epi-PGE_2 (**2**) in agreement with the results of the preliminary studies reported earlier[2] for the corresponding PGE_1 isomers.

TABLE I
RELATIVE POTENCIES OF PROSTAGLANDINS IN SMOOTH MUSCLE CONTRACTION

Prostaglandin	Rat uterus	Gerbil colon
PGE_2 (standard)	1.0	1.0
11,15-Epi-PGE_2[a]	0.011–0.012[b]	0.01–0.02[b]
ent-11,15-Epi-PGE_2[c]	0.50–0.55[b]	0.18–0.20[b]

[a] Concentration range 50–100 ng/ml. [b] Range of potencies covers results from different muscle specimens. [c] Concentration range 1–4 ng/ml.

An interesting inhibitory behavior was also observed for substances **2** and **3**. These were found to inhibit strongly the action of PGE_2 on rat uterus and gerbil colon preparations. That is, after exposure of the tissue to either **2** or **3** at concentrations in the test range, replacement of the tissue bath and addition of PGE_2, little if any response could be measured. For example, addition of 1 ng/ml of PGE_2 to the treated tissue produced <5% of the normal response. Although pretreatment with **2** and **3** in effect desensitized the tissue to PGE_2, such tissue responded normally to addition of more of the original substrate **2** or **3**.

The high biological activity of *ent*-11,15-epi-PGE_2 is most intriguing. The many possibilities for rotation about the carbon–carbon bonds in the α and ω side chains lead to a substantial number of reasonable conformations which can in principle interact with a receptor site. This flexibility in fact allows the generation of conformers from PGE_2 and *ent*-11,15-epi-PGE_2 which have quite similar geometry, especially with regard to overall molecular shape and the relative disposition of polar groups.

It seems reasonable to conclude from the above results that the *ent*-11,15-epi series of prostaglandins deserves further study at least with regard to (1) biological activity in different tissues, (2) mode of interaction with receptor sites, and (3) inhibition of other prostaglandins.[13]

(8) Two successive chromatographic separations were used, one with silica gel using 10% methanol in chloroform for development and the second with silver nitrate impregnated silica gel using *n*-hexane–methylene chloride–tetrahydrofuran–acetic acid (6:2:2:1) for development. Because both **3** and **2** undergo slow dehydration to PGA_2-type products even upon storage at $-20°$, the samples employed for the biological tests were additionally purified by high pressure liquid chromatography on silica gel (Chromatronix instrument) shortly before use.

(9) *ent*-11,15-Epi-PGE_2 was prepared both in Cambridge and Palo Alto by essentially identical procedures and, after similar purification procedures, exhibited identical bioassay, tlc, high pressure chromatography, and nmr results. However, the Palo Alto sample had $[\alpha]D$ $+39.8°$ (*c* 0.67, tetrahydrofuran) which is as yet unexplained. The corresponding (−)-ephedrine salt of the levo methoxy ether,[4] $[\alpha]D$ $-36.0°$ (*c* 1.4, methanol), was used as starting material for this preparation.

(10) A. J. Weinheimer and R. L. Spraggins, *Tetrahedron Lett.*, 5185 (1969).

(11) G. L. Bundy, F. H. Lincoln, N. A. Nelson, J. E. Pike, and W. P. Schneider, *Ann. N. Y. Acad. Sci.*, **180**, 76 (1971).

(12) The general method was that of J. R. Weeks, J. R. Schultz, and W. E. Brown, *J. Appl. Physiol.*, **25**, 783 (1968), with the following modifications. Mature *Meriones unguiculatus* (80–120 g) were sacrificed and the ascending colon was suspended in 2 ml of aerated De Jalon's solution maintained at 28–30° under a resting tension of 0.5 g.

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