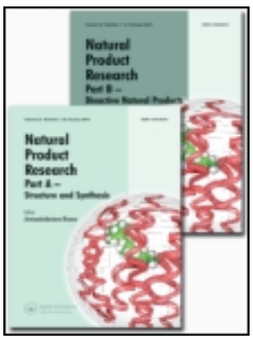

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A NEW SERIES OF NATURAL PROSTAGLANDINS
IDENTIFICATION OF 1a,1b-DIHOMO-2,3-DIDEHYDRO-PGE_2 IN RAM SEMINAL VESICLES

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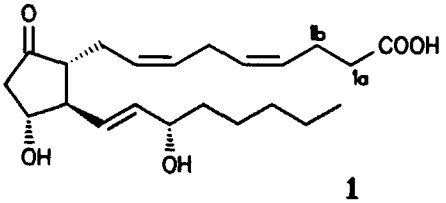
Abstract: A novel natural E-prostaglandin - 1a,1b-dihomo-2,3 didehydro-PGE_2 (**1**) was isolated from ram seminal vesicles and its structure was elucidated by MS and NMR analysis.

Key Words: Ram seminal vesicles, natural E-prostaglandin

Ram seminal vesicles (RSV) contain a large amount of the primary E-prostaglandins, viz. PGE_1, PGE_2 and PGE_3[1], derived from dihomo-γ-linolenic ($C_{20:3}\omega6$), arachidonic ($C_{20:4}\omega6$) and eicosapentaenoic ($C_{20:5}\omega3$) acids, respectively. In addition, a strong selective inhibitor of platelet aggregation, 5,6-dihydro-PGE_3[2], was recently described in the same tissue[3].The present work reports the identification of a new natural prostaglandin, 1a,1b-dihomo-2,3-didehydro-PGE_2 (**1**), in RSV. Its obvious precursor, all cis-4,7,10,13,16-docosapentaenoic acid ($C_{22:5}\omega6$), can be biosynthesized in mammals by the chain elongation of arachidonic acid and subsequent delta-4 desaturation of adrenic acid ($C_{22:4}\omega6$). Previously it was found that both the docosaenoic acids mentioned above are present in the phospholipids of seminal vesicles[4] and, therefore, they can serve as natural precursors of prostaglandins *in vitro*[5]. Furthermore, it was shown that RSV microsomes convert adrenic acid to 1a,1b-dihomo-prostaglandins E_2 and $F_{2\alpha}$ *in*

vitro[6]. Thus, it seemed plausible that $C_{22}\omega 6$ prostaglandins occur in RSV in detectable amounts.

The E-type prostaglandins were separated from the lipid fraction[7] of RSV (5 kg)on silica gel using a MeOH/$CHCl_3$ gradient. The PGE fraction (1.1g) eluted with 3.5% MeOH in $CHCl_3$ was fractionated by repeated normal and reversed phase preparative HPLC[8] to give, in addition to PGE_1, PGE_2, PGE_3, 1a,1b-dihomo-PGE_2, 5,6-dihydro-PGE_3, 8-iso-PGE_1, 8-iso-PGE_2, 8-iso-PGE_3, 11β-8-iso-PGE_1, 15β-PGE_2 and 15β-PGE_1, also 5.2 mg of pure compound **1** as colorless oil, $[\alpha]_D^{22}$ -31° (c 0.6, $CHCl_3$). **1** was converted with 0.4 N KOH/MeOH to the corresponding PGB compound with ϵ=27,000 at λmax=278.



1

The molecular formula $C_{22}H_{35}O_5$ was established by negative ion CI-MS (details of MS study are given below) and NMR study[9].

To elucidate the structure of **1** mass-spectrometrically, the PFB-$(TMS)_3$-9-enol derivatives of **1** and authentic 1a,1b-dihomo-PGE_2, PGE_2, PGE_1, PGE_3 and 5,6-dihydro-PGE_3 were prepared. The NICI spectrum of 9-enol-1-$(TMS)_3$-PFB showed a base peak at m/z 593[M-PFB] and two minor peaks 503[M-(PFB+90)] and 413[M-(PFB-2*90)], indicating the presence of one carboxylic and two hydroxyl groups. The EI-MS of the same derivative of **1** showed a molecular ion at m/z-774, as well as ions at m/z 703$[M-71]^+$, 684$[M-90]^+$, 613$[M-(71+90)]^+$, 594$[M-2*90]^+$, 523$[M-(71+2*90)]^+$, 504$[M-3*90]^+$, 483, 441[M-(C1-C7)]$^+$, 352, 313, 269, 217 (C9-C11), 181 (PFB), 173 (C15-C20), 73 (a base peak). The fragmentation pattern was similar to that of 1a,1b-dihomo-PGE_2 with the exception of the fact that all high-mass ions above m/z 441 were two mass units lower than the corresponding ones in the spectrum of the latter, indicating the presence of an additional double bond in the molecule of **1**. The presence of ions $[M-71]^+$, $[M-(71+90)]^+$ and 173 demonstrates that the ω-chain of **1** is identical to that of

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1a,1b-dihomo-PGE_2 and PGE_2. The fragment ions at m/z 441 (loss of C1-C7) observed in both the spectra indicate that an additional double bond of compound **1** is located in the α-chain. The fragment $[M-333]^+$ (loss of α-chain) was dominating in the spectrum of the TMS-PFB derivative of B type PG formed from **1** in alkali.

The location and configuration of the double bonds and substituents in the molecule of **1** were established by 2D ^1H-^1H and ^1H-^{13}C COSY correlations[9] on a Bruker AMX-500 instrument. Data on PGE_1, PGE_2 and other prostaglandins[8,10] confirm unambiguously the substitution pattern and relative configurations of substituents on a 5-membered ring, the 15-hydroxyl group and the C-13,14 E double bond ($^3J_{HH}$=15.1 Hz). The positions of the two remaining double bonds were elucidated from 2D correlation diagrams. The Z-configuration of the Δ2 bond follows from the carbon chemical shifts of model 4Z- and 4E-nonenoic acids (cf. C-1b at 22.7 ppm with 22.6 for Z- and 27.8 for the E-isomer of the corresponding acid)[11]. The Z-configuration of the Δ5 bond is confirmed by the carbon chemical shift of C-7 at 25.1 ppm (cf. C-7 of PGE_2 at 25.2 ppm[8,10]) and by the chemical shift of C-4 at 25.5 ppm (cf. C-10 of 8Z,11Z,14Z-hexadecatrienoic acid at 25.7 ppm[12]).

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