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A NOVEL APPROACH TO THE TOTAL SYNTHESIS OF PROSTAGLANDINS. PREPARATION OF A STEREOISOMERIC MIXTURE CONTAINING (±)-13,14-DIHYDROPROSTAGLANDIN E_1 (1)

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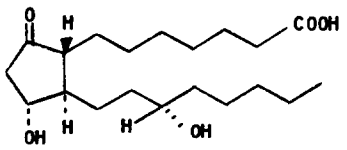
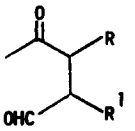
We wish to report a new total synthesis of the (±)-11,15-dihydroxy-9-oxoprostanoic acid structure which, we believe, has yielded a mixture containing racemic 13,14-dihydroprostaglandin E_1 (I) (2), the enantiomorph of which is a naturally occurring, physiologically active metabolite of prostaglandin E_1 (PGE_1) (3).

The synthesis was designed to involve an appropriately substituted levulic aldehyde (II) (4) which was expected to undergo thermodynamically controlled intramolecular aldolization to give predominantly the isomer of III corresponding stereochemically to the prostaglandins at the 8,11 and 12-positions (prostaglandin numbering). In model experiments 2,3-dimethyl levulic aldehyde (IIa) (5) was converted by base (e.g. 0.5N NaOH for 15 min at 25°) to IV (6), found by GLC to contain in the ratio of 9:1 two components which were identified by pmr analysis as the trans and cis-dimethyl isomers of IV, respectively (7). No conditions were found whereby the aldol precursor was obtained, but IV was transformed to the stereoisomeric mixture IIIa [M^+ at m/e 128.0843 (theory 128.0837)] by epoxidation with alkaline hydrogen peroxide followed by hydrogenolysis in methanol over palladium charcoal [cf. (8)]. Aqueous 0.5N NaOH at 25° for 15 min converted IIIa back to IV.



I



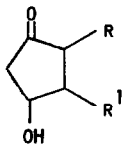
II

IIa: $R=R^1=CH_3$

IIb: $R=(CH_2)_6CO\ C_2H_5$

$R^1=(CH_2)_2CHOPy^*(CH_2)_4CH_3$

*Py=2′-tetrahydropyranyl

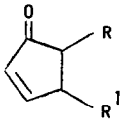


III

IIIa: $R=R^1=CH_3$

IIIb: $R=(CH_2)_6CO_2H$;
$R^1=(CH_2)_2CHOPy(CH_2)_4CH_3$

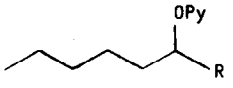
IIIc: $R=(CH_2)_6CO_2H$;
$R^1=(CH_2)_2CHOH(CH_2)_4CH_3$



IV: $R=R^1=CH_3$

IVa: $R=(CH_2)_6CO_2H$;
$R^1=(CH_2)_2CHOPy(CH_2)_4CH_3$

IVb: $R=(CH_2)_6CO_2H$;
$R^1=(CH_2)_2CHOH(CH_2)_4CH_3$

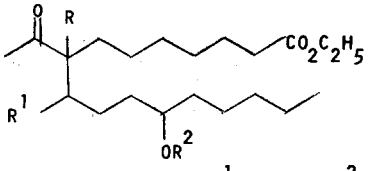


V: $R=C{:}CCH(OC_2H_5)_2$

Va: $R=(CH_2)_2CHO$

Vb: $R=(CH_2)_2CHOHC{:}CCH_3$

Vc: $R=(CH_2)_2CH(OSO_2CH_3)C{:}CCH_3$



VI: $R=CO_2t\text{-}Bu$; $R^1=CH_3C{:}C$; $R^2=Py$

VIa: $R=R^2=H$; $R^1=CH_3C{:}C$

VIb: $R=R^2=H$; $R^1=CH_3CH{:}CH$

VIc: $R=H$; $R^1=CH_3CH{:}CH$; $R^2=Py$

The above findings were used to synthesize a mixture of stereoisomers containing I as follows. Oct-1-yn-3-ol 2′-tetrahydropyranyl ether (9) with ethynylmagnesium bromide and ethyl orthoformate in ether gave V, bp 143°/0.15 mm which was transformed to Va, bp 100-102°/0.05 mm by acid hydrolysis, immediate tetrahydropyranylation of the resulting unstable hydroxyaldehyde, and catalytic hydrogenation over palladized charcoal in ethyl acetate. With propynylmagnesium bromide in THF, Va gave Vb, bp 134°/0.05 mm (27% from oct-1-yn-3-ol 2′-tetrahydropyranyl ether) [M^+ at m/e 282 (theory 282)] which was converted with methanesulfonyl chloride in pyridine at 0° to Vc. Ethyl 8-t-butyloxycarbonyl-9-oxodecanoate (from t-butylacetoacetate and ethyl 7-bromoheptanoate) on alkylation as the sodium enolate in benzene-DMF with Vc afforded VI containing all of the skeletal carbons required for I. The neat oily diester was heated with calcium iodide at 150° and the resulting crude VIa was hydrogenated over palladized charcoal in ethyl acetate to VIb (23% from Vb) [M^+ at m/e 396 (theory 396)]. Tetrahydropyranylation then gave VIc, which was ozonolyzed (methylene chloride-pyridine at -60°; Zn/CH_3CO_2H reduction of the ozonide)

to IIb. With 0.5N aqueous ethanolic NaOH IIb gave IVa [M^+ at m/e 422 (theory 422)], which, with acid, afforded IVb [M^+ at m/e 338 (theory 338)] displaying TLC, IR and pmr characteristics almost identical to those of authentic dihydro-PGA_1 prepared from biosynthetically derived (10) PGE_2 by catalytic hydrogenation in ethanol over platinum black and base-induced dehydration of the resulting 13,14-dihydro PGE_1 (I) (11). IVa (49% from VIb) was converted by epoxidation and catalytic hydrogenation as before to IIIb [$M^+ - H_2O$ at m/e 422 (theory 422)] which was readily dehydrated by base to IVa. With acid, IIIb was converted to the mixture of stereoisomers (IIIc) (25% from IVa) [M^+ -18 at m/e 338.2459 (theory 338.2456)] which displayed almost identical TLC, IR, and pmr characteristics to authentic I prepared as previously discribed. With diazomethane in ether IIIc gave a mixture of methyl esters [M^+ at m/e 370 (theory 370)] which showed the principal mass spectral fragmentations of 13,14-dihydro-PGE_1 methyl ester (12).

From the model experiments and the known ready isomerization of 8-iso-PGE_1 to PGE_1 (13), IIIb and c, IVa and b are expected to consist mainly of stereoisomers having trans-C_8 and C_{12}-protons. Since it is expected that the C_{11} and C_{15} asymmetric centers are generated non-stereoselectively, IIIc is predicted to contain predominantly the four stereoisomeric racemates having trans-C_8 and C_{12}-protons, necessarily including that corresponding to authentic I. In agreement, IIIc showed bronchodilatory effects of the same order of potency as authentic 13,14-dihydro-PGE_1 and 10% of the potency of PGE_2 in a standard test in guinea pigs (14) when administered intravenously in a dosage range of 2-10 γ/Kgr. Additionally, in a modification (15) of an in vitro test (16) IIIc exhibited the same order of potency as authentic 13,14-dihydro-PGE_1 in inhibiting the ADP induced aggregation of rat blood platelets in platelet rich plasma.

References and Footnotes

(1) Some of this work is described in Belgian Patent 727,755 (1969), priority from February 1, 1968.

(2) P.F. Beal, III, J.C. Babcock, and F.H. Lincoln, J. Am. Chem. Soc., 88, 3131 (1966).

(3) E. Anggard, and B. Samuelsson, J. Biol. Chem., 239, 4097 (1964).

(4) In this paper I is the only structural formula bearing stereochemical implications.

(5) E. Bosshard, N.A. Goeckner, and W. Keller-Schierlein, Helv. Chim. Acta, 42, 2746 (1959).

(6) All substances prepared had infrared, ultra-violet and proton nuclear magnetic resonance spectra consistent with their assigned structures, and acceptable elemental analyses and/or mass spectra.

(7) This identification will be discussed in a more detailed publication.

(8) Chem. Abs., 50, 6505 (1956); Swiss Patent 298,873 (1954).

(9) E. Crundwell, M.A. Pinnegar, and W. Templeton, J. Med. Chem., 8, 41 (1965).

(10) M. Lapidus, N.H. Grant, and H.E. Alburn in "Prostaglandin Symposium of the Worcester Foundation for Experimental Biology", P.W. Ramwell, and J.E. Shaw, Ed., Interscience Publishers, New York, New York, 1968.

(11) Preparation by Dr. D. Herbst (Wyeth Laboratories Inc.).

(12) E. Anggard, and B. Samuelsson, J. Biol. Chem., 239, 4097 (1964).

(13) E.G. Daniels, W.C. Krueger, F.P. Kupiecki, J.E. Pike, and W.P. Schneider, J. Am. Chem. Soc., 90, 5894 (1968).

(14) H. Konzett, and R. Rossler, Arch. exp. Path. Pharmak., 195, 71 (1940); M.E. Rosenthale, and A. Dervinis, Arch. int. Pharmacodyn., 172, 91 (1968); M.E. Rosenthale, A. Dervinis, A.J. Begany, M. Lapidus, and M.I. Gluckman, Pharmacologist, 10, 175 (1968).

(15) R. Fenichel, and H.E. Alburn, Wyeth Laboratories (unpublished work).

(16) A. Fantl, Australian J. Exp. Biol. Med. Sci., 45, 355 (1968).