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SYNTHESIS OF (±)-7-OXAPROSTAGLANDIN E_1

Josef Fried, M. M. Mehra
W. L. Kao and C. H. Lin

Ben May Laboratory for Cancer Research and
Departments of Chemistry and Biochemistry
University of Chicago, Chicago, Ill. 60637

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Previous reports have described the synthesis[1] and biological properties[2] of 7-oxa-prostaglandin $F_{1\alpha}$ and related substances. We now wish to describe the synthesis of 7-oxa-PGE_1. Several variants were devised, all of which depend on some unusual selective reactivity of polyhydroxylated cyclopentanes.

Trimethylsilylation of all-cis-1,2-epoxycyclopentane-3,5-diol in THF at 25° gave the disilyl derivative I (95% yield), which was treated without further purification with diethyl octynyl alane[3] in toluene at 65° for 40 hours to afford after work-up with dilute hydrochloric acid the triol II[4] (80%), which was converted to the acetonide, (91%), m/e 267 (M+1), 251 ($M-CH_3$) and thence into the benzyl ether III (80%), m/e 356 (M^+), 341 ($M-CH_3$), 250 ($M-CH_3-C_7H_7$). The latter was hydrolyzed with 50% aqueous trifluoroacetic acid at 0° for 24 hours to the diol benzyl ether IV, (75%), m/e 316 (M^+), 298 ($M-H_2O$), 207 ($M-H_2O-C_7H_7$). An alternative route to IV proceeds via the monotrityl epoxide V, prepared in pyridine at 45-50° for 24 hours,[5] m.p. 58-60°, which on benzylation furnished the trityl benzyl ether VI m.p. 114-115° (72%). The latter with diethyl octynyl alane in refluxing toluene for 3 days furnished IV (40%) and the isomeric 1,3-diol (15%).

Alkylation of the diol IV with 2 equiv. of t-butyl ω-iodohexanoate and 2.5 equiv. of NaH in DMF yielded the desired ether VII (55%) and in 20% yield the isomeric ether, readily separated by t.l.c.[6] The structure of VII followed from its conversion with 10% Pd/C in acetic acid into the known t-butyl 9,11-dihydroxy-7-oxaprostanoate.[7] Debutylation of VII was achieved with anhydrous trifluoroacetic acid at 0° to form the acid VIIa, (90%), m/e 430 (M^+), 412 ($M-H_2O$), 321 ($M-H_2O-C_7H_7$), 299 ($M-O(CH_2)_5CO_2H$). This acid was also obtained in 50% yield by selective debenzylation of the known dibenzyl ether VIII[1] with BF_3 etherate in benzene,[8] which links this synthesis with that of 7-oxa-$PGF_{1\alpha}$. Oxidation of the acid VIIa with Jones reagent at 25° afforded in 95% yield the keto acid IX, m/e 411 (M-OH), 337 ($M-C_7H_7$) which on ketalization with ethylene glycol and BF_3 etherate in benzene furnished the ketal ester X (52%), m/e 516 (M^+), 455 ($M-O(CH_2)_2OH$), 425 ($M-C_7H_7$), 347 ($M-(CH_2)_5CO_2(CH_2)_2OH$). Hydrolysis of the ester X with K_2CO_3 in

methanol gave quantitatively the acid Xa, which was debenzylated and reduced with lithium in methylamine to the olefinic acid XI (85%), m/e 384 (M^+), 366 ($M-H_2O$), 269 ($M-(CH_2)_5CO_2H$), 253 ($M-O(CH_2)_5-CO_2H$). Oxidation of XI with SeO_2 in dioxane at 90° for 18 hours produced a mixture of secondary alcohols XII, m/e 400 (M^+), 285 ($M-(CH_2)_5CO_2H$), 269 ($M-O(CH_2)_5CO_2H$), and ketone XIII which were separated on a silica gel column. The ketone could be reduced to XII with lithium tri-t-butoxy aluminum hydride, but it was more efficient to reduce the total reaction mixture to form XII in 40% yield. Removal of the ketal group with trifluoroacetic acid at 0° for 3 hours gave after column chromatography on silica gel and elution with ethyl acetate-methanol 4:1(±)-7-oxa-PGE_1 (XIV) and its 15-epimer (50%) IR 5.70μ (strong), m/e 338 ($M-H_2O$), 320 ($M-2H_2O$).[9] The above mixture was tested by Drs. J. Flack and P. Ramwell of the Worcester Foundation for Experimental Biology for its smooth muscle stimulating activity on the gerbil colon and found to produce a full response at 20 μg/ml, corresponding to $4x10^{-4}$ the activity of PGE_1.[10]

In order to ascertain that no isomerization at C8 takes place during the acid catalyzed reactions involving the 9-keto group the ketal acid XI was converted with trifluoroacetic acid to the crystalline keto acid XV, m.p. 62-64°. IR 5.70μ (strong), m/e 322 ($M-H_2O$), 207 ($M-H_2O-(CH_2)_5CO_2H$), 191 ($M-H_2O-O(CH_2)_5CO_2H$). Reduction of the latter with lithium tri-t-butoxy aluminum hydride followed by t.l.c. gave 40% of the crystalline 9α-hydroxy acid XVI, m.p. 55-58°, identical with an authentic sample. The remainder of the material consists mainly of the faster moving 9β-hydroxy acid.

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REFERENCES

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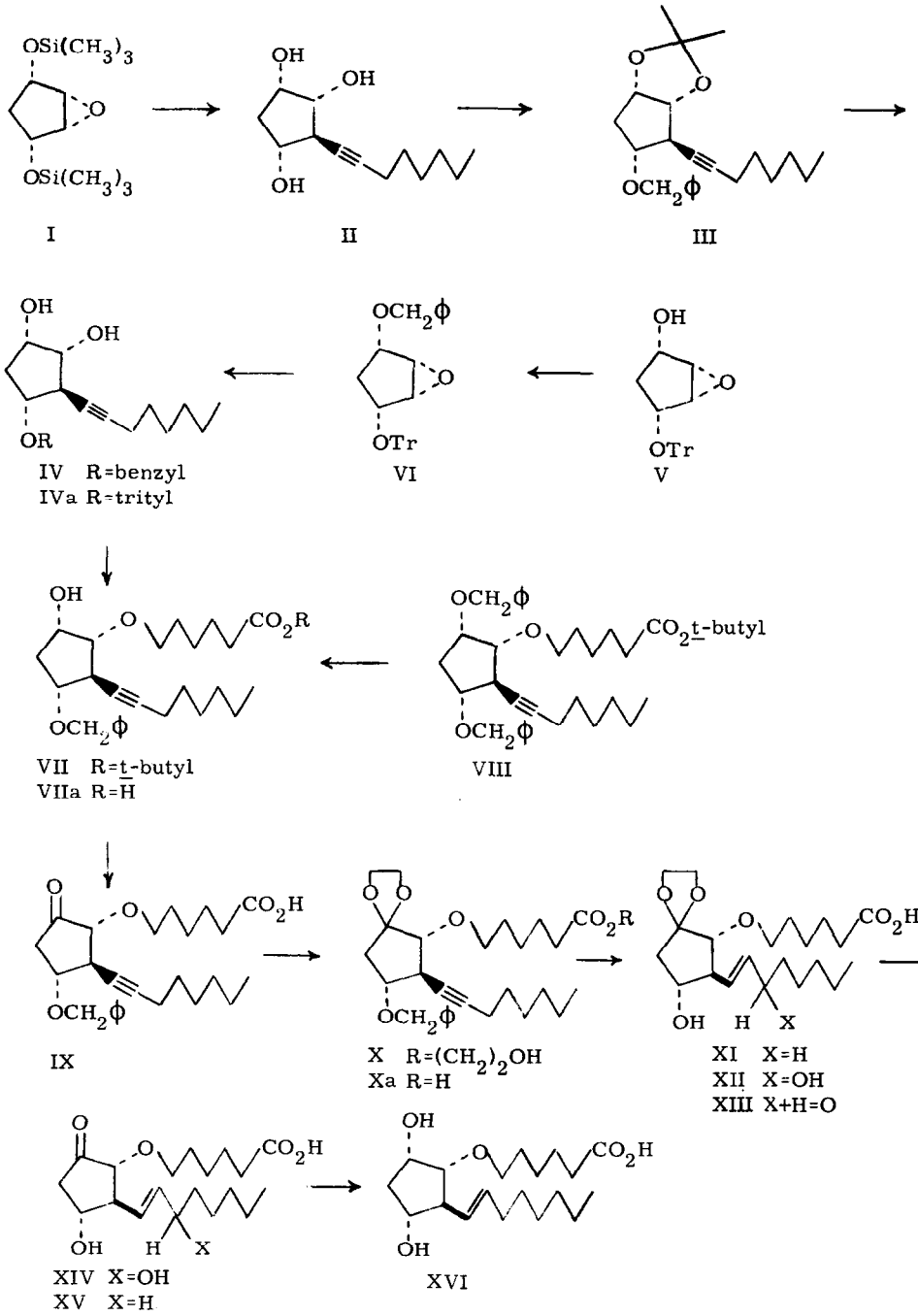
2. S. H. Ford and J. Fried, Life Sciences, 8, Part 1, 983 (1969).
3. J. Fried, C. H. Lin and S. H. Ford, Tetrahedron Letters, 1379 (1969).
4. All products were characterized by elemental analysis, n.m.r. (Varian A-60) and low resolution mass spectra (Finnigan 1015). G.l.c. was performed on 1.5% OV-1 on Diatoport S (carboxylic acids as methyl esters or TMS derivatives).
5. Under the reaction conditions the product of ring opening by HCl, 1-trityloxy-2-chloro-cyclopentane-3,4-diol is also formed. Treatment of the mixture with 2% KOH in MeOH furnishes 55% of the desired monotrityl epoxide. Tritylation of II in refluxing pyridine gave rise only to the monotrityl ether IVa.
6. The preference for alkylation in α-position to the octynyl group also holds for acylation.



I

II

III

IV R=benzyl
IVa R=trityl

VI

V

VII R=t-butyl
VIIa R=H

VIII

IX

X R=$(CH_2)_2OH$
Xa R=H

XI X=H
XII X=OH
XIII X+H=O

XIV X=OH
XV X=H

XVI

Thus, reaction of IV with 2 equiv. of tosyl chloride gave as the major product (37%) the analogous monotosylate.

7. J. Fried, S. Heim, P. Sunder-Plassmann, S. J. Etheredge, T. S. Santhanakrishnan and J. Himizu, Prostaglandin Symposium of the Worcester Foundation for Experimental Biology, Interscience, New York, 1968, p. 351.
8. The best conditions were: 2 mmoles of VIII, 8 mmoles BF_3 etherate in 20 ml benzene at 25° for 24 hours. Starting material (30%) and diol acid (15%) were also recovered. A 5 fold increase in the concentration of BF_3 etherate led to complete debenzylation (70%).
9. The final product contained ca. 10% of 7-oxa-PGA_1 the product of β-elimination of the 11-hydroxyl group as evidenced by IR-bands at 5.95 and 6.10μ, the UV maximum at 218 nm and vinyl signals at τ2.55 and 3.80. Handling and storage of this and related 9-keto-11-hydroxy derivatives in neutral solvents resulted in β-elimination demonstrating the great proclivity for this reaction in the 7-oxa series.
10. Re-assay of this solution after storage in the refrigerator for 5 weeks showed a negligible and uncharacteristic response at 25 μg/ml indicating far-reaching inactivation. 7-Oxa-$PGF_{1\alpha}$ and PGE_1 are stable under these conditions, re-emphasizing the facility with which elimination takes place in the case of 7-oxa-PGE_1.