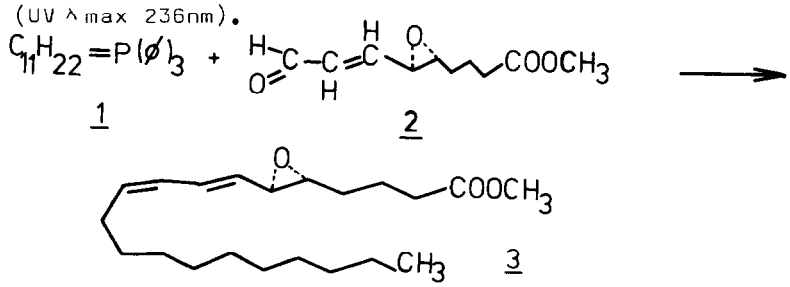
Tetrahedron Letters,Vol.24,No.21,pp 2135-2136,1983 0040-4039/83/212135-02$03.00/0
Printed in Great Britain

SYNTHESIS OF 11,12,14,15-TETRAHYDRO-LEUKOTRIENE C,D,E VIA A

Bernd Spur+, Attilio Crea, Wilfried Peters
Institut für OrganischeChemie I und Anorganische Chemie I der Universität Düsseldorf, Universitätsstr. 1, D-4000 Düsseldorf, West Germany
Wolfgang König
Lehrstuhl für Medizinische Mikrobiologie und Immunologie, Ruhr-Universität Bochum, Postfach, D-4630 Bochum, West Germany

Abstract: The synthesis of tetrahydro-7E,9Z-leukotriene A methyl ester and its reaction with glutathione, cysteinylglycine and cysteine providing the tetrahydro analogues of leukotriene C_4, D_4, E_4.

The pioneering work by Samuelsson et al [1] and others [2] established the structures of the "slow reacting substance of anaphylaxis" (SRS) as the polyolefinic fatty acid-peptide conjugates. It is notable that leukotrienes with five or three double bonds are biologically very active, if three double bonds are conjugated. Furthermore the stereochemistry of the 7,8-double bond should be trans for the biological activity [3-5].
We report the synthesis of the novel 11,12,14,15-tetrahydro analogues of the natural leukotrienes in order to evaluate the full effect of the polyene system on biological activity and its chemical and biochemical inactivation. Reaction of the phosphorane 1 (n-undecyltriphenylphosphonium bromide BuLi,THF -78°C, 15min) with the oily unsaturated epoxyaldehyde 2 [2] and standard work up furnished the tetrahydro-7E,9Z-leukotriene A methyl ester 3 as the only product in 57% yield (UV λmax 236nm).

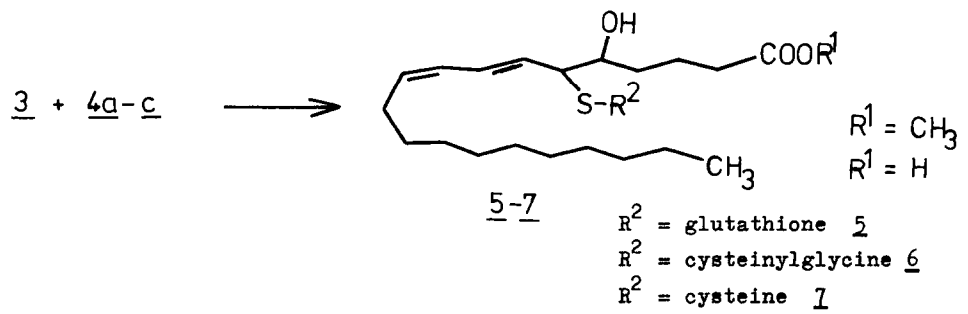


1 2 3

^{1}H-NMR (90MHz, $CDCl_3$,δppm): H-2, 2.38; 3, 1.52-1.98; 4, 1.52-1.98; 5, 2.84, $J_{5,6}$=2.1Hz; 6, 3.15, $J_{6,7}$=7.9Hz; 7, 5.34, $J_{7,8}$=15.1Hz; 8, 6.70, $J_{8,9}$=10.9Hz; 9, 5.98, $J_{9,10}$=10.7Hz, $J_{9,11}$=2.7Hz; 10, 5.46, $J_{10,11}$=7.5Hz; 11, 2.20; 12-19, 1.27; 20, 0.88; OCH_3, 3.66. - ^{13}C-NMR (22.63MHz, $CDCl_3$,δppm): C-1, 173.56; 2, 33.6; 3, 21.35; 4, 31.42; 5, 60.34; 6, 58.39; 7-10, 133.78;129.75;129.66;127.28; 11 27.85; 12, 29.64; 13, 29.38; 14-16, 29.64; 17, 29.38; 18, 31.94; 19, 22.71;

20, 14,10; OCH_3, 51.50. All NMR data are in full agreement with the proposed structure. The 7E,9Z stereochemistry of the double bond system unambiguously follows from the ^1H NMR coupling constants.

Reaction of 3 as previously described [5] with glutathione 4a, cysteinylglycine 4b and cysteine 4c in methanol/triethylamine (1:1) with subsequent RP-HPLC (methanol : water : acetic acid 65:35:0,1) provided the tetrahydroleukotriene C,D, E 5-7 in form of the monomethylester. Alkaline hydrolysis with K_2CO_3 liberates the free leukotrienes which were tested on isolated guinea pig jejunum. Only LTC exhibits a strong activity. The vasculare permeability in rat skin is enhanced stronger by LTC in comparison with LTD [6].



ACKNOWLEDGMENT:

The authors would like to extend their thanks to Prof. J. Mulzer for helpful discussions during the preparation of this manuscript.

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6)The results of the full biological activity as well as the chemical and biochemical inactivating will be reported separately when the ongoing investigations have been completed.

(Received in Germany 19 January 1983)