4-[1-(4-Chlorphenyl)-propyl]-1,2-diphenylpyrazolidin-3,5-dion (**2c**)

Die Darstellung erfolgte analog *Rohkopf*[8] aus 31.2 g 4-Chlorphenylpropylmalonester und 18.4 g Diphenylhydrazin in 100 ml 0.1 M-Natriumethylat. Farblose Kristalle (Dioxan), Schmp. 213°, Ausb. 55 % d. Th. – $C_{24}H_{21}ClN_2O_2$ (404.4) Ber. c 71.2 H 5.23 N 6.9 Gef. C 70.9 H 5.17 N 7.0. – IR (KBr): 3440 (br), 3050, 2940, 2860, 1750, 1710, 1590, 1480, 1450, 1430, 1295, 1190, 1150, 1095, 1070, 1020, 900, 800, 750, 690, 640, 600 cm^{-1}. – ^{1}H-NMR ($CDCl_3$, 270 MHz): δ (ppm) = 7.30–7.06 (m, 10H, aromat.), 6.94 ("d", J = 8/2 Hz, 2H, aromat.), 6.80 ("d", J = 8/2 Hz, 2H, aromat.), 3.56 (d, 1H, H-4), 3.40 (m, 1H, aliph., C*-H), 2.22 (m, 2H, aliph., C-2'), 0.94 (t, J = 7 Hz, 3H, aliph., CH_3). – MS (80 eV): m/z = 404/406 (58/18 %, M^+), 301 (4), 284 (4), 252 (87), 212 (56), 183 (82), 153 (91), 131 (100), 125 (91), 103 (27), 91 (11), 77 (78), 51 (16).

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Syntheses of Leukotriene Analogs

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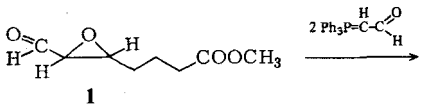
The synthesis of the C_{20} and C_{22} analogs of the leukotrienes from the unsaturated aldehydes **2a, b** with undecyl(triphenyl)phosphorane and reactions with thiopeptides providing the conjugates LTC, LTD, and LTE is described.

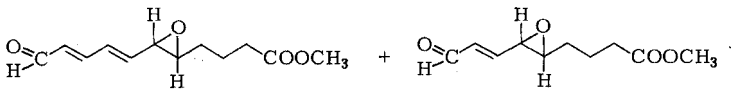
Synthese von Leukotrien-Analogen

Die Synthese von C_{20}- und C_{22}-Analogen der Leukotriene aus den ungesättigten Aldehyden **2a, b** mit Undecyltriphenylphosphoran und Reaktionen mit Thiopeptiden zu den Konjugaten LTC, LTD und LTE wird beschrieben.

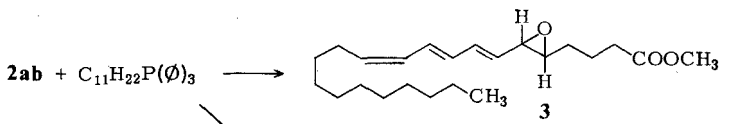
Recently the lipoxygenase metabolism of polyunsaturated fatty acids is increasingly demanding the attention of researchers in the chemical, biological and medical areas. Metabolites of interest are especially the leukotrienes. This class of superactive mediators of inflammation and allergy is 1000 to 10 000 times more effective than histamine[1-4]. Numerous biochemical investigations have shown that



1



2a **2b**



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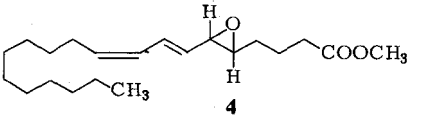

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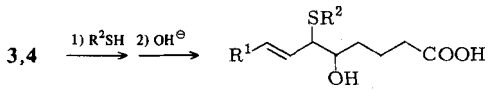

5a-c 6a-c

3: $R^1 = CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-\overset{H}{C}=\overset{H}{C}-\underset{H}{C}=\overset{H}{C}-$

4: $R^1 = CH_3-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-CH_2-\underset{H}{C}=\underset{H}{C}-$

5a,6a: R^2 = Glutathion, **5b,6b**: R^2 = Cysteinylglycin, **5c,6c**: R^2 = Cystein

also unsaturated fatty acids other than arachidonic acid can be metabolized to leukotrienes[5]. For example the docosahexaenoic acid can be transformed to only weakly active leukotriene analogs by the 5-lipoxygenase enzyme. On the other hand the C_{22} unsaturated fatty acid is reported to be a competitive inhibitor of the cyclooxygenase enzyme which produces prostaglandins. Thus, this C_{22} fatty acid may have cardiovascularic protecting properties[6]. This paper describes the synthesis of C_{22} leukotriene analogs as well as C_{20} analogs to make these compounds accessible for biological screening.

The epoxyaldehyde **1**[7-9] reacted with two equivalents of formylmethylene – triphenylphosphorane in refluxing benzene to give a mixture of the dienealdehyde **2a** and the α, β-unsaturated aldehyde **2b** in the ratio of 70 : 30 (^{1}H-nmr). The mixture was coupled with undecyltriphenylphosphorane to give the C_{22} leukotriene-A-analog **3** (70 %) and the C_{20} tetrahydro-analog **4**[10] (30 %). **3** and **4** were separated with hplc on μ-porasil. Structure and purity of **3** and **4** were corroborated by UV and ^{1}H-nmr. The triene system in **3** exhibits the characteristic absorptions at 270, 280 and 290 nm, whereas the diene **4** absorbs at 237 nm. Triene **3** and diene **4** are conveniently distinguished by silicagel-tlc (ether:pentane/triethylamine = 50 : 50 :1). When sprayed with 50 % sulfuric acid, **3** is stained deep-blue while **4** is stained red.

The reaction of **3** and **4** with glutathione, cysteinylglycine, and cysteine according to our earlier described procedure leads to the peptide – conjugates **5a–c** and **6a–c**, respectively, in 60 % isolated yield. This technique is superior to all variants working with protected peptides, because no isomerization is observed, which is an obstacle in protecting group removal[11-13].

The biological activity of the leukotriene analogs was tested on isolated guinea pig ileum. The C_{22} analogs of the natural leukotrienes had an activity comparable with the leukotrienes of the 3-series[14].

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Experimental Part

^{1}H-nmr ($CDCl_3$, int. stand. TMS): Bruker HX–90R; *UV:* Zeiss DMR–21; *HPLC:* Waters M–45, μ-Porasil, 30 cm × 7.9 mm and RP-C_{18} 30 cm × 7.9 mm, respectively.

Methyl 10-formyl-5(S),6(S)-epoxy-7E,9E-decadienoate **(2a)**

Methyl 8-formyl-5(S),6(S).epoxy-7E-octenoate **(2b)**

610 mg (20 mmol) of formylmethylenetriphenylphosphorane is added under argon to a solution of 172 mg (10 mmol) **1** in 10 ml benzene and the reaction mixture is heated 24 h under reflux. Subsequent to flash chromatography (ether) the 70 : 30 mixture of **2a, b** is used immediately. Yield: 125 mg (82 %).

C_{22}-Leukotriene-A-methylester **(3)** *and C_{20}-Tetrahydroleukotriene-A-methylester* **(4)**

At −78 °C 175 mg (8 mmol) **2a, b** is added to the solution of 8 mmol of undecyltriphenylphosphorane in 5 ml THF/1 ml HMPA. The mixture is stirred for 5 min. 30 ml Ether and 1 ml phosphate buffer (pH 7) are added. The ether phase is separated and dried (Na_2SO_4). After flash chromatography over

silicagel (ether/1 % triethylamine) the eluate is purified by hplc (μ-Porasil; hexane/ethylacetate/triethylamine = 100:1:1). Yield **3**: 120 mg (65 %), **4**: 36 mg (29 %). ^{1}H-nmr of **3**: δ (ppm) = 2.39 (H-2), 1.52–2.06 (H-3,4), 2.87 (H-5, $J_{5.6}$ = 2.2 Hz), 3.14 (H-6, $J_{6.7}$ = 8.0 Hz), 5.38 (H-7, $J_{7.8}$ = 14.9 Hz), 6.50 (H-8, $J_{8.9}$ = 10.3 Hz), 6.15 (H-9, $J_{9.10}$ = 14 Hz), 6.56 (H-10, $J_{10.11}$ = 11 Hz), 6.01 (H-11, $J_{11.12}$ = 10.1 Hz), 5.51 (H-12, $J_{12.13}$ = 7.5 Hz), 2.16 (H-13), 1.27 (H-14 – 21), 0.89 (H-22), 3.68 (OCH_3). UV (hexane) λmax = 270 sh, 280, 290 sh nm. Spectral data of **4** see lit. [10].

Synthesis of the peptide conjugates **5a–c** and **6a–c** according to lit. [11–13].

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14 The results of the full biological studies will be reported separately.

[Ph 29]

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Charge-Transfer Complexes of Sulfonamide Drugs with Tetracyanoethylene

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Formation of 1:1 complexes occurs between the sulfonamide drugs and tetracyanoethylene. Values of the formation constant (K_{ct}), the molar absorptivity (ε), the transition energy (E) and of the product ($K_{ct} \times \varepsilon$) have been obtained from optical data of the complexes. From the energies of charge-transfer transitions, the ionization potentials of the donors have been obtained. The spectroscopic data indicate that the complexes are weak in nature.

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