Kurzmitteilungen

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Synthesis of Leukotriene Analogs

Synthese von Leukotrien-Analoga

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Oxidative metabolism of arachidonic acid and certain other polyunsaturated fatty acids results in the formation of biologically active compounds including the prostaglandins, thromboxane and prostacyclin[1–3]. The family of biologically active derivatives of polyunsaturated fatty acids was recently extended by the discovery of a new group of compounds, the leukotrienes[3]. These compounds have pronounced biological effects which are related to immediate hypersensitivity reactions and inflammation. It has been found that the natural leukotrienes and their geometrical isomers are biologically highly active, but little is known about leukotrienes derived from short unsaturated fatty acids via the 5-lipoxygenase pathway[4].

We describe in the following a simple chemical synthesis of C-15 and C-17 leukotriene analogs as partial agonists/antagonists of slow reacting substance of anaphylaxis (SRS-A). Starting from the epoxide **1**[5–7] and its reaction with two equivalents of formylmethylenetriphenylphosphorane in refluxing benzene for 24 h with subsequent flash chromatography in the presence of triethylamine, a 70 : 30 mixture of **2a** and **2b** (^{1}H-NMR: δ (ppm) = **2a** H/aldehyde = 9,579 ppm $^3J_{10,11}$ = 7,8 Hz; **2b** H/aldehyde = 9,563 ppm $^3J_{8,9}$ = 7,6 Hz) resulted which cannot be separated by column chromatography. We were able to show that this mixture of **2a/2b** can be used for the synthesis of the natural leukotrienes and their analogs[8,9]. Thus **2a/2b** was treated with hexyltriphenylphosphorane in THF/HMPT and worked up in the usual manner[10–12] providing the new C-17 LTA_3methyl ester **3** and C-15 LTA_2methyl ester **4** which were purified by semipreparative h.p.l.c.[13] (70 % yield: 70 % **3**: 30 % **4**).

^{1}H-NMR ($CDCl_3$) **3**: δ (ppm) = 2,38 (H-2), 1,50–2,0 (H-3,4), 2,86 (H-5,$J_{5,6}$ = 2,2Hz), 3,14 (H-6,$J_{6,7}$ = 8,0Hz), 5,37 (H-7,$J_{7,8}$ = 15,0Hz), 6,49 (H-8,$J_{8,9}$ = 10,2Hz), 6,15 (H-9,$J_{9,10}$ = 14Hz), 6,55

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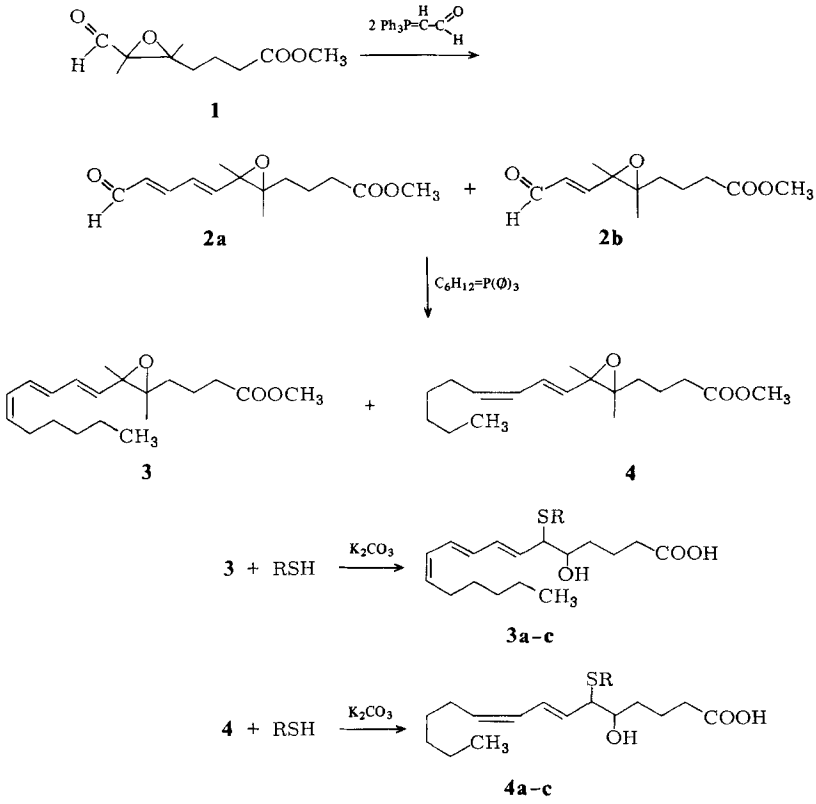
(H-10,$J_{10,11}$ = 11Hz), 6,01 (H-11,$J_{11,12}$ = 10Hz), 5,50 (H-12,$J_{12,13}$ = 7,5Hz), 2,20 (H-13), 1,26 (H-14-16), 0,88 (H-17), 3,68 (OCH_3). ^{1}H-NMR ($CDCl_3$) **4**: δ (ppm) = 2,39 (H-2), 1,50–2,01 (H-3,4), 2,86 (H-5,$J_{5,6}$ = 2,2Hz), 3,16 (H-6,$J_{6,7}$ = 8,0 Hz), 5,35 (H-7,$J_{7,8}$ = 15Hz), 6,71 (H-8,$J_{8,9}$ = 11,0Hz), 5,99 (H-9,$J_{9,10}$ = 10,7Hz), 5,48 (H-10,$J_{10,11}$ = 7,5Hz), 2,19 (H-11), 1,26 (H-12-14), 0,89 (H-15), 3,68 (OCH_3).



Reaction of **3** and **4** with glutathione, cycsteinylglycine and cysteine after recently published procedures[14–17] yield the peptide conjugates **3a–c** and **4a–c**, resp. which were purified by RP-h.p.l.c. (60 % yield). Hydrolysis (0,1M-K_2CO_3, 12h) gave the free leukotrienes in essentially quantitative yield which were tested on isolated guinea pig jejunum. The C-15 analogs compared with the C-17 analogs show a stronger contractile activity[18].

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Experimental Part

For experimental details see [14–17].

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

[KPh 303]

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Synthese des Calmodulinantagonisten N-(6-Aminohexyl)-5-chlor-1-naphthalinsulfonamid (W-7)

Synthesis of the Calmodulin Antagonist *N*-(6-Aminohexyl)-5-chloro-1-naphthalenesulfonamide (W-7)

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Auf der Suche nach calmodulinbindenden Pharmaka[1] mit gefäßrelaxierender Wirkung stießen *Hidaka* und Mitarb.[2] auf die in der Überschrift genannte und von ihnen als „W-7" bezeichnete Verbindung. Ihre Publikation enthält auch eine Synthesevorschrift von W-7, ausgehend vom Sulfonylchlorid **3**. Da wir beim Nacharbeiten zunächst Schwierigkeiten hatten, **3** darzustellen, möchten wir die schließlich erfolgreiche Synthese kurz beschreiben.

Im Prinzip kann in Anlehnung an *Beattie* und *Whitmore*[3] ausgehend von 1-Naphthylamin-5-sulfonsäure, „Laurent'sche Säure" **(1)**, über eine *Sandmeyer*-Reaktion 5-Chlor-1-naphthalinsulfonsäure **(2)** und daraus mit Phosphorpentachlorid 5-Chlor-1-naphthalinsulfonylchlorid **(3)** dargestellt werden.

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