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Syntheses of 7*Z*, 9*E*, 11*E*, 14*Z*-Leukotrienes

Synthese von 7*Z*, 9*E*, 11*E*, 14*Z*-Leukotrienen

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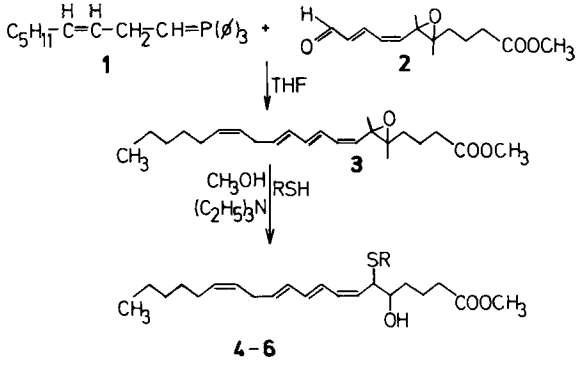
The discovery of the leukotrienes and the further elucidation of the biosynthesis of these important mediators of inflammatory and allergic disorders has initiated syntheses of a large number of leukotriene analogues in order to find the biological active sites and antagonists[1–3]

Until now there have been only 2 descriptions of the synthesis of a 7-*cis* isomer of the naturally occurring leukotrienes. This isomer displayed contractile activity on isolated guinea pig ileum and induced bronchoconstriction in guinea pig, its activity is about 1/10 of the natural leukotrienes[4,5].

In this paper we wish to describe the first synthesis of the 7*Z*,9*E*,11*E*,14*Z*-LTA_4, C_4,D_4, and E_4 possessing the same stereochemistry as the highly chemotactic LTB_4 in order to evaluate the full biological effect of the polyene system on the contractile and chemotactic activity of these peptide conjugates.



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The synthesis is based on the *Wittig* coupling of the phosphorane of (*Z*)-3-nonen-1-yl triphenylphosphonium bromide **(1)**[6] with the dienealdehyde **2** which was synthesized according to *Ernest* et al.[4]. This strategy seems to be superior to a *Wittig* reaction using an appropriately modified C-13 *Wittig* reagent and the well known C-7 epoxyaldehyde, because the final reaction step is not stereospecific[3,5].

The crude dienealdehyde **2** was purified by column chromatography over SiO_2 using 2 : 1 hexane, ethyl acetate. ^{1}H-NMR indicates a 4 : 1 mixture of the 7-*cis*-aldehyde **2** and its 7-*trans* isomer which was further purified by low temperature crystallization. Thus the 7-*cis* aldehyde **2** was obtained as a yellow to green oil and subjected to the final *Wittig* coupling with **1** in THF for 15 min (–78°C). Standard work up furnished the 7*Z*,9*E*,11*E*,14*Z*-LTA_4 methyl ester **3** in 65 % yield with a geometrical purity of 85 % (^{1}H-NMR). This product could be purified by h.p.l.c. using 100 : 0,7 : 0,7 hexane/ethyl acetate/triethylamine on μ-Porasil.

It was fully characterized by UV (271sh, 280, 290sh nm) and ^{1}H-NMR spectroscopy. ^{1}H-NMR ($CDCl_3$) of **3** : δ (ppm) = 2,38 (H-2), 1,90–1,50 (H-3,4), 2,86 (H-5, $J_{5,6}$ = 2,0 Hz), 3,48 (H-6, $J_{6,7}$ = 9,0 Hz), 5,05 (H-7, $J_{7,8}$ = 11 Hz), 6,0–6,7 (H-8 – 11), 5,47 (H-12, $J_{11,12}$ = 15 Hz, $J_{12,13}$ = 7,5 Hz), 2,92 (H-13), 5,40 (H-14), 5,45 (H-15), 2,05 (H-16), 1,28 (H-17 – 19), 0,88 (H-20), 3,67 (OCH_3).

Reaction of **3** as previously described[7–11] with glutathione, cysteinylglycine, and cysteine in methanol/triethylamine (1 : 1) with subsequent RP-h.p.l.c. provided the 7*Z*,9*E*,11*E*,14*Z*-LTC_4 **4**, LTD_4 **5**, and LTE_4 **6** in the form of the monomethyl esters. Alkaline hydrolysis with K_2CO_3 liberates the free leukotrienes which were homogenous on RP-h.p.l.c.. They were tested on isolated guinea pig jejunum. Only LTC_4 **4** showed a weak activity whereas LTD_4 **5** and LTE_4 **6** were nearly inactive indicating that the stereochemistry is an important factor for the contractile activity[11]. We are hopeful that related analogs can be found that will exhibit SRS-A antagonism. The possible mode of action and potential utility of these and related compounds will be the subject of further communications.

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