b) 0,2 g **7** in 6 ml CH_2Cl_2 werden mit 0,4 g Ag_2O und 0,5 ml CH_3I unter Rühren 1 h erwärmt. Danach werden erneut 0,4 g Ag_2O und 0,5 ml CH_3I zugesetzt. Nach einer weiteren Reaktionsdauer von 1 h wird über eine kurze mit SiO_2 gefüllte Säule filtriert und der Rückstand aus Ethanol kristallisiert, gelbe Nadeln, Schmp. 126–127°. Der Mischschmp. der Kristalle aus a) und b) zeigt keine Depression, die IR-Spektren sind identisch. $C_{12}H_{10}O_3$ (202,0630) Mol.-Masse: 202,0639 (ms).

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[KPh 288]

Arch. Pharm. (Weinheim) *317*, 280–282 (1984)

Syntheses of the Leukotrienes C_5, D_5, and E_5

Synthese der Leukotriene C_5, D_5 und E_5

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The leukotrienes recently discovered derivates of arachidonic acid have rapidly gained recognition as agents of remarkable biological potency in a number of tissues and organ systems. In particular, interest has been devoted to the cysteinyl-containing LTC_4 **(1a)**, LTD_4 **(1b)**, and LTE_4 **(1c)** apparently representing the biological active components of the "slow reacting substance of anaphylaxis" and, hence, presumed mediators of allergic bronchoconstriction[1,2].

Other leukotrienes are of considerable interest, too. Thus the leukotrienes LTC_5 **(2a)**, LTD_5 **(2b)**, and LTE_5 **(2c)** formed in vivo from eicosapentaenoic acid via the 5-lipoxygenase pathway are reported to possess biological activities comparable to that of the "natural" leukotrienes[3].

Up till now thorough medical studies of these important metabolites were hampered by lack of substance. Only few nanograms could be isolated from biological sources. In this

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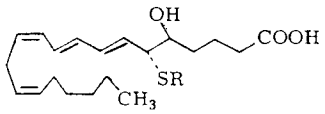
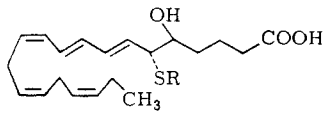


1a-c

LTC_4, LTD_4, LTE_4

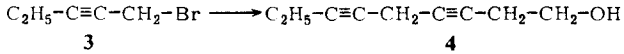


2a-c

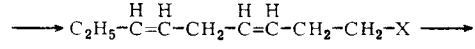
LTC_5, LTD_5, LTE_5

R = glutathione LTC; R = cysteinylglycine LTD; R = cysteine LTE;

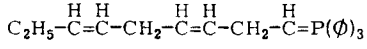
paper we wish to report the first chemical synthesis of LTC_5 **(2a)**, LTD_5 **(2b)** and LTE_5 **(2c)**. As a result of our synthetic work these rare substances are available for the first time in quantities sufficient for biological and medical studies[4].



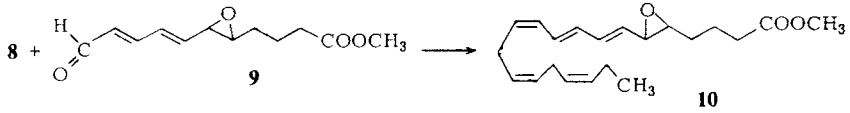
3 **4**



5 X = OH; **6** X = Br; **7** X = $P(\phi)_3^{\oplus}Br^{\ominus}$



8



9 **10**

1-Bromo-pent-2-yne **(3)**[5] was converted into 3,5-nonadiyn-1-ol **(4)**[6] by the method of *Eiter*[7] (DBU, CuJ, HMPT, THF, 3-butyne-1-ol). Selective hydrogenation of **4** (*Lindlar* catalyst, THF, $(C_2H_5)_3N$) to 3,5-nonadien-1-ol **(5)**[6] followed by treatment with $CBr_4/P(C_6H_5)_3$ (CH_2Cl_2, O°C, 10 min)[8] led to the corresponding bromide **6** which after further reaction with $P(C_6H_5)_3$ in acetonitrile under reflux afforded the phosphonium bromide **7** in an over all yield of 20 % **(3–7)**.

Generation of the phosphorane **8** (BuLi, THF, HMPT, −78 °C) and addition of the dienealdehyde **9**[9–11] (−78 °C, 5 min) gave after standard work up (chromatography over SiO_2 in the presence of triethylamine and subsequent HPLC separation) the highly unstable LTA_5 **10** in 30 % yield (UVλmax 270 sh, 280, 291 sh nm)[12]. LTA_5 **10** is readily converted into its isomers by light and air. Instant decomposition is effected by slight traces of acid. Reaction of **10** as previously described[13–15] with glutathione, cysteinylglycine and cysteine provided the novel LTC_5, LTD_5, LTE_5 monomethyl esters (60 % yield) which were purified by RP-HPLC ($CH_3OH/H_2O/CH_3COOH$ = 65 : 35 : 0,01; pH: 6.8). Hydrolysis (0,1 M · K_2CO_3; 12 h) gave the free LTC_5 **2a**, LTD_5 **2b**, LTE_5 **2c** in essentially quantitative yield.

The biological activity of the leukotrienes **2a–c** was determined in the terminal guinea pig ileum. While LTC_5 **(2a)** and LTD_5 **(2b)** exhibit high SRS-activity at concentrations of 1–10 ng LTE_5 **(2c)** is about 40–50 fold less active[4].

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[KPh 290]

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Darstellung von „Dithiophenolphthalein"

Synthesis of "Dithiophenolphthalein"

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Eingegangen am 24. November 1983

3,3-Bis-(4-mercaptophenyl)-phthalid, „Dithiophenolphthalein" **(4)** ist unseres Wissens bisher nicht beschrieben. Diese Verbindung interessierte als mögliches stark nucleophiles Chromophor im Zusammenhang mit Untersuchungen über die Reaktivität aktivierter Sulfone[1].

Zur Darstellung von **4** wird Phenolphthalein **(1)** mit Dimethylthiocarbamoylchlorid (DMTCC) zu Bis-(thiocarbamidsäure-O-arylester) **2** umgesetzt. Dieser isomerisiert in einer *Newman-Kwart*-Umlagerung[2] zu Bis-(thiocarbamidsäure-S-arylester) **3**, dessen anschließende alkalische Hydrolyse **4** liefert. Ein analoger Reaktionsweg zur Darstellung einfacher Thiophenole ist beschrieben worden[2,3].

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