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THE PREPARATION OF OCTAHYDRO LEUKOTRIENES C, D, AND E VIA A STEREOSELECTIVE SULFENYLLACTONIZATION REACTION

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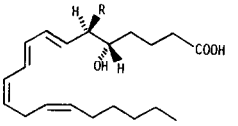
Summary: Sulfenyl halides derived from the N-trifluoroacetamido methyl ester derivatives of cysteine, cysteinylglycine and glutathione react stereoselectively with (5E)- and (5Z)-eicosenoic acids to provide, after separation of diastereomers and hydrolysis of the protecting groups, the fully saturated analogues of leukotrienes LTC_4, LTD_4 and LTE_4.

Since the pioneering work of Samuelsson *et al*[1] and others[2] establishing the structures of the "slow reacting substances of anaphylaxis" (SRS's) as the novel polyolefinic fatty acid-peptide conjugates now known as the leukotrienes, LTC_4, LTD_4 and LTE_4 (1a,b,c), more recent studies have suggested that other leukotrienes with three or even five double bonds (i.e. LTC_5) may exist in nature[3]. It is notable that LTC_5[3] and olefin isomers of the leukotrienes (such as 11-*trans*-LTC_4)[4] as well as analogues of LTC_4 and LTD_4 lacking up to three of the double bonds have been reported to be biologically very active[5], while positional isomers (e.g. having the S-peptide at C-12)[6] or the 6-*epi*-isomers,[7] are found to be considerably less active than the natural products.



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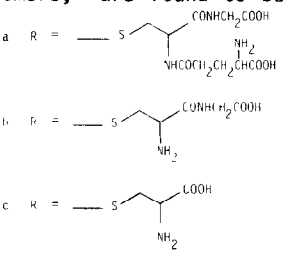


These data can be taken to indicate that the exact nature of the polyenic chain in these molecules is of relatively minor importance in defining biological activity.

As part of our studies on the relative importance of the various stereochemical and structural components of the leukotrienes as they relate to biological activity, we have undertaken to prepare the 7,8,9,10,11,12,14,15-octahydro analogues of LTC_4, D_4 and E_4 in order to evaluate the full effect of the polyene system on biological activity.

From the outset, it was apparent that the synthetic strategies used to prepare the leukotrienes C_4, D_4 and E_4, i.e. reaction of the highly activated epoxide LTA_4 as intermediate, with thiols or derivatives of thiols,[1,2] could not be expected to provide the same degree of regiocontrol if applied to the corresponding fully saturated epoxide.

One method which could be expected to provide the desired regioselectivity and stereoselectivity for the synthesis of saturated analogues of the leukotrienes and which would make use of readily available starting materials, is the sulfenyllactonization reaction[8]. Thus, reaction of a suitable fatty acid [i.e. (5Z)- or (5E)-eicosenoic acid] with an appropriate electrophilic thiol derivative would be expected to proceed to introduce the sulfur bearing moiety at C-6 and the lactone oxygen at C-5 via the known preference for the formation of δ- versus ε-lactones in these reactions[8]. Also, one expects that *trans*-addition would occur thus fixing the relative stereochemistry at C-5 and C-6 as *erythro* from a (E)-olefin or *threo* from a (Z)-olefin[8]. Simple hydrolysis would then provide the desired leukotriene analogues.

As there is no literature precedent for the viability of the sulfenyllactonization procedure using complex multifunctional amino acid or peptide thiols we set out to test this approach. In a series of model reactions the sulfenyl chloride derived from 3,3'-dithiopropionic acid bis methyl ester (one equivalent Cl_2, CH_2Cl_2, -35°, 0.5h) was reacted with the triethylammonium salt of (5Z)-eicosenoic acid (2) (-35°, 1h) to give the desired threo-δ-lactone (3a), and by hydrolysis (0.2N LiOH), 5,6-threo-5-hydroxy-6[(2'-carboxyethyl)thio]eicosanoic acid (4a) in excellent yield (65% overall). Similar reaction of (5E)-eicosenoic acid (5) (prepared by photolysis of (5Z)-eicosenoic acid (2) in the presence of diphenyldisulfide[9]) gave the 5,6-erythro-δ-lactone (6a) and subsequent hydrolysis provided 5,6-erythro-5-hydroxy-6[(2'-carboxyethyl)thio]eicosanoic acid (7a) (60% overall) (Scheme 1). As there remained some doubt as to the total overall stereochemical integrity of these reactions, it was decided that the best proof would be to regenerate the olefins from the β-hydroxysulfides. Thus, the two diacids (4a, 7a) were converted to the diesters (CH_2N_2) and treated sequentially with TMSCl, to form the 5-trimethysilyl ether derivatives, and then with TMSI in the presence of a catalytic amount of ZnI_2[10] to provide, in the case of the threo analogue exclusively methyl-(5Z)-eicosenoate and in the case of the erythro analogue, exclusively methyl (5E)-eicosenoate (Scheme 1). Thus it was shown that the sulfenyllactonization reaction was not only regioselective but also stereoselective as first proposed. The saturated analogues of leukotrienes C_4, D_4 and E_4 were similarly prepared by reactions of (5E)-eicosenoic acid and the sulfenyl chlorides derived from suitably protected disulfides (bis-N-trifluoroacetylcystine dimethyl ester, bis-N-trifluoroacetylcysteinyl-bis-glycine dimethyl ester and bis-N-trifluoroacetylglutathione tetramethyl ester). In the case of the cystine derivative a reaction was also carried out with (5Z)-eicosenoic acid (reaction 3, Table I). These reactions generally proceeded well but with reduced yields relative to the simple systems (30-40%). The derived lactones were obtained as mixtures of diastereoisomers which could be separated by chromatography[11].

Hydrolysis of the lactone products (1N NaOH) provided in each case the desired leukotriene analogues which could be obtained as pure di- or trisodium salts[12] (Table 1). The absolute stereochemistry of these diastereomers was determined by desulfurization of the lactones (or equally the final products) (Raney Ni, n-propanol, reflux, 5h, with subsequent treatment of the products with trifluoroacetic acid to effect lactonization) to provide either (5R)-5-hydroxyeicosanoic acid δ-lactone, m.p. 52-54°C, $[\alpha]_D^{RT}$ = +22.6° (c = 0.65, dioxane), indicating that the original substrate had the 5S configuration, or to provide the (5S)-lactone, $[\alpha]_D^{RT}$ = -22.2° indicating the original substrate had the 5R configuration.[13]

Despite our demonstrations of stereoselectivity in model reactions 1 and 2, and despite the reported stereoselectivity of sulfenyllactonization reaction[8], a small amount of 5,6-threo products was observed in the cases of reaction 6 (5-10%) and reaction 5 (20-30% of isolated lactones). That there was no prior isomerization of the double bond was evident from the fact that eicosenoic acid recovered unreacted from the reaction mixture was exclusively 5E. The amide functionalities would appear to play some role in this side reaction as, when (5E)-eicosenoic acid was reacted with the sulfenyl chloride derived from bis-N-carbobenzyloxycysteinyl-bis-glycine diethyl ester[14], a much improved yield of the erythro lactones (80%) was obtained with much less of the 5,6-threo by-products (ca. 5%) being observed. A possible explanation for the formation of these by-products could be that a competing, non-specific radical mechanism is operating in these cases[15]. Experiments to better elucidate the mechanism of this unusual side reaction are currently being pursued. It is evident however that by manipulation of protecting groups and reaction conditions, both the yields and stereoselectivity can be enhanced in these cases.

SCHEME 1:

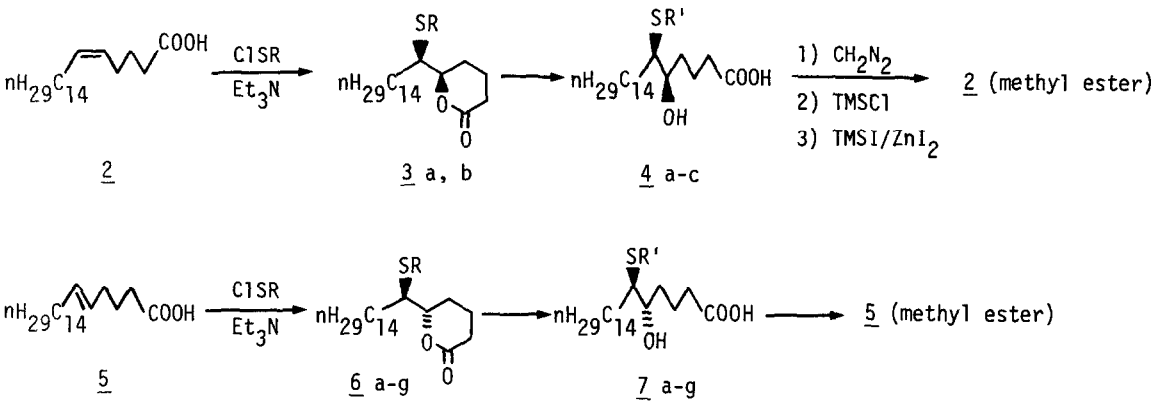
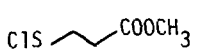
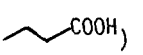
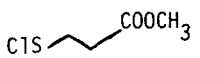
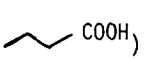
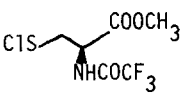
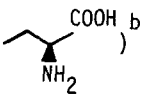
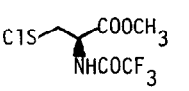
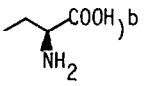
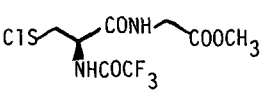
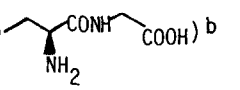
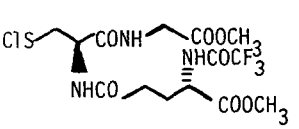
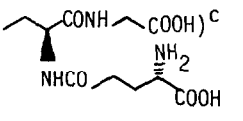


TABLE I: OCTAHYDRO-ANALOGUES OF LEUKOTRIENES

Reaction	Sulfenyl Halide	Olefin	Product(s) (SR')[a]
1		2	4a ()
2		5	7a ()
3		2	4b: 5S,6S()[b] 4c: 5R,6R
4		5	7b: 5S,6R()[b] 7c: 5R,6S
5		5	7d: 5S,6R()[b] 7e: 5R,6S
6		5	7f: 5S,6R()[c] 7g: 5R,6S

a. Satisfactory spectroscopic and analytical data were obtained for all new compounds.

b. Isolated as disodium salt.

c. Isolated as trisodium salt.

These leukotriene analogues have been tested in comparison with synthetic LTC_4 on guinea pig tracheal tissue. Results have indicated that the erythro compounds are contractile agonists about three orders of magnitude less potent than LTC_4 (pD_2 values ranged from 5.5-5.9)[16]. The threo analogues (4b,c) were essentially inactive. Differences between activities of the pairs of diastereomers (5S,6R versus 5R,6S) were not significant.

It is thus evident that at least some of the double bonds in the leukotrienes (and probably most importantly the 7,8-double bond) play an important role in determining the potent activity of the natural SRS's.

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11. In the case of the glutathione adducts the diastereomeric lactones were virtually inseparable. However, when treated with anh. MeOH in the presence of BIO-RAD AG50-WX8 acid resin, the lactones were smoothly converted to the corresponding 5-hydroxy methyl esters which could then be separated by preparative HPLC.
12. The pure salts were isolated by chromatography on XAD-8 resin, first washing with water to remove excess base and salts, then eluting with EtOH to provide the pure compounds.
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15. The sulfenyllactonization reaction is reported to occur via an essentially ionic mechanism, proceeding through an intermediate episulfonium ion[8]. If thiol radicals were present in the reaction one might expect that addition to the double bond would be followed by non-specific chlorination of the resultant carbon radicals. The resulting β-chlorosulfides could then proceed to mixtures of erythro and threo lactones via the episulfonium ion.
16. The pD_2 value of LTC_4 on isolated guinea pig trachea is 8.7; G. Holme, G. Brunet, H. Piechuta, P. Masson, Y. Girard and J. Rokach, Prostaglandins 20, 717 (1980).

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