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1,4-THIAZANES AS CONFORMATIONALLY-RESTRICTED ANALOGS OF THE PEPTIDO-LEUKOTRIENES

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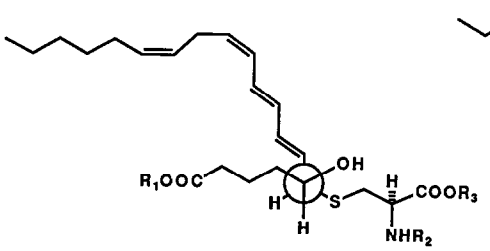
Abstract: A new class of leukotriene antagonists is proposed which represent rigidified approximations of the solution conformation of the peptido-leukotrienes. A representative member of this class has been synthesized and shown to elicit response in the guinea pig ileum assay.

The peptido-leukotrienes LTC_4, LTD_4, and LTE_4, known collectively as the "slow-reacting substance of anaphylaxis", or SRS-A, are arachidonic acid metabolites which elicit profound *in vivo* effects at minute concentrations.[1] Because these compounds are important mediators of asthma and immediate hypersensitivity responses, the modulation of their bioactivity is of tremendous therapeutic value. Attenuation of leukotriene synthesis by the inhibition of enzymes such as phospholipase A_2 or 5-lipoxygenase could lead to an unwanted diminution of other physiologically-important metabolites (e.g., LTB_4, prostaglandins, etc.). Receptor-level antagonism provides a selective approach to the regulation of *in vivo* leukotriene response. The search for leukotriene antagonists is an extremely active field of research in both the academic and industrial arenas. In this Letter, we describe a new class of potential antagonists for the peptido-leukotrienes which is based upon the known solution conformation of LTD_4.

In 1983, Loftus et al. reported the results of an NMR study on the solution conformations of several protected analogs of leukotriene D_4.[2] Their experiments identified a highest-populated conformation in which the aliphatic ester group at C-5 was oriented predominantly trans to the amino acid side chain at C-6 (**1**, Figure 1). We reasoned that this trans-relationship could be established ex-



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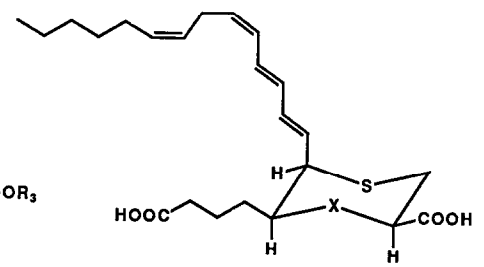


2a (X = O)
b (X = NH)

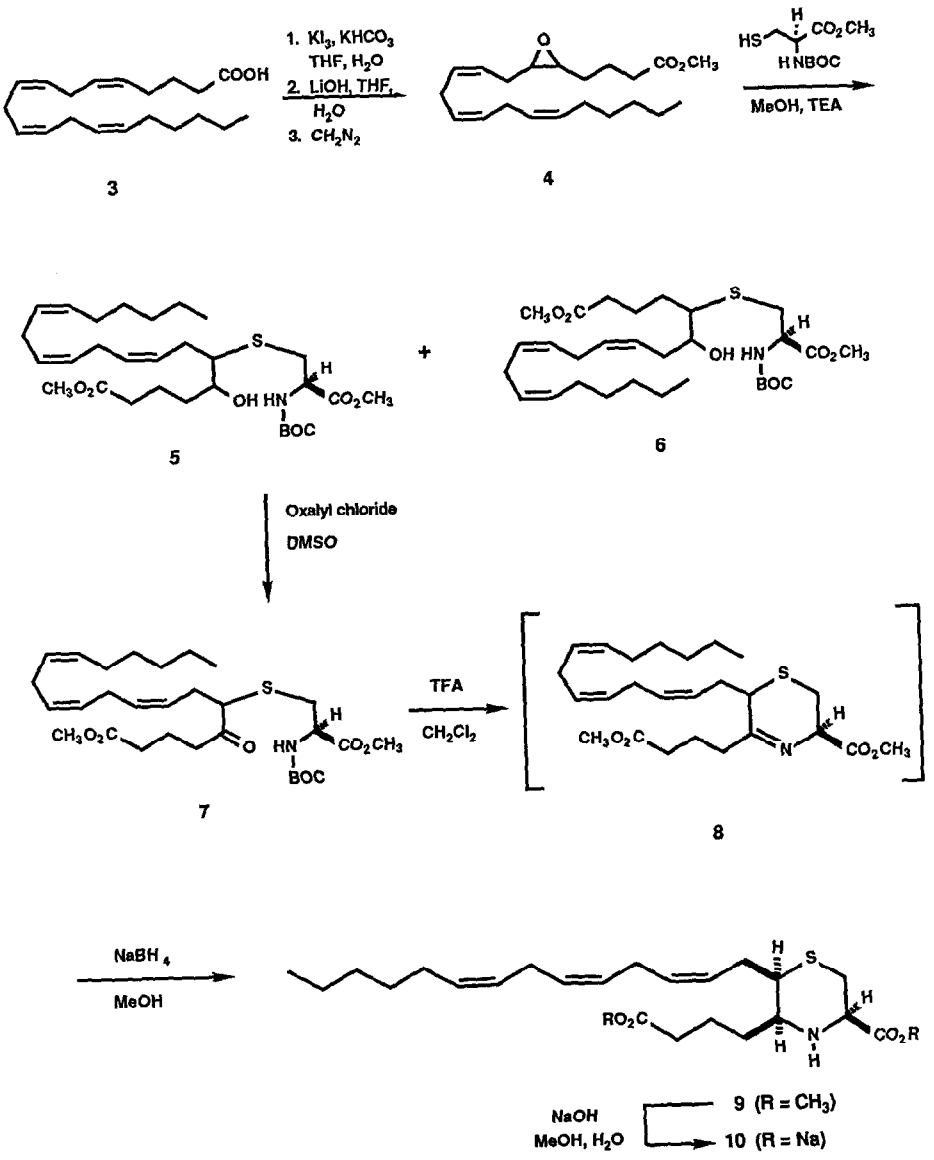
Figure 1: Newman projection down the C-5,6 bond of LTD_4 (**1**); conformationally-constrained analog (**2**)

clusively by joining the C-5 hydroxyl with the amino-acid side chain to form a six-membered ring (**2**, Figure 1). Furthermore, by incorporating a nitrogen atom into the ring, one maintains a hydrogen-bond donor at "C-5" as well as retaining the α-amino acid nature of the molecule. Thus, we were led to propose that 5-carboxy-2,3-disubstituted-1,4-thiazanes such as **2b** represent rigidified approximations of the lowest-energy solution conformation of LTD_4, and as such are intriguing candidates for a new class of peptido-leukotriene antagonists.[3]

In the Scheme is illustrated the synthesis of a "first-generation" 1,4-thiazane in which the conjugated leukotriene side chain has been replaced by the simpler skipped-triene system shown.[4] Arachidonic acid **3** is conveniently transformed into the 5,6-epoxide methyl ester **4** in 89% overall yield by the method of Corey, et al.[5] Nucleophilic ring-opening of **4** by methyl N-BOC-L-cysteinate in methanol afforded an 80% yield of a 1:1 mixture of regioadducts **5** and **6**.[6] Although inseparable by conventional chromatographic methods, we found that treatment of the mixture of isomers with p-toluenesulfonic acid in dichloromethane resulted in rapid lactonization of only isomer **5**, while **6** remained unchanged under these conditions. Following routine chromatographic separation, the desired adduct **5** was regenerated from the derived lactone in 81% yield by brief treatment with methanol and triethylamine. Oxidation of **5** with oxalyl chloride and DMSO provided the ketone **7** in 92% yield. Treatment of this ketone with trifluoroacetic acid results in sequential nitrogen deprotection and intramolecular dehydration to give the unstable cyclic imine **8**, which was not isolated but rather directly reduced with sodium borohydride.[7] As expected, this reduction afforded two major and two minor stereoisomeric products in 77% yield. The all-cis compound **9** has been assigned to one of the major products based on NOE-difference NMR experiments.[8] Hydrolysis of **9** with sodium hydroxide in methanol/water provided the disodium salt **10**.

In binding studies using radiolabeled LTD_4 and guinea pig lung membrane preparation, thiazane **10** exhibited an affinity for the LTD_4 receptor of about 1/1000 that of the natural ligand.[9] Unfortunately, this compound failed to antagonize the effects of LTD_4 in the guinea pig ileum smooth muscle contraction assay. However, **10** did display modest contractile agonist properties, a phenomenon unobserved with other 5-carboxy-1,4-thiazanes containing simple alkyl groups at C-2 and C-3. These results encourage us to speculate that **10** may owe its agonist activity to its similarity with the solution conformation of LTE_4. In order to further test this hypothesis, we are currently focusing our efforts on synthesizing 1,4-thiazanes such as **10** which possess conjugated, polyolefinic C-2 side chains which more closely resemble those found in the natural leukotrienes.

SCHEME


1. KI3, KHCO3
THF, H2O
2. LiOH, THF,
H2O
3. CH2N2
MeOH, TEA
Oxalyl chloride
DMSO
TFA
CH2Cl2
NaBH4
MeOH
NaOH
MeOH, H2O
9 (R = CH3)
10 (R = Na)

References

1. Charkin, L.W.; Bailey, D.M. "The Leukotrienes: Chemistry and Biology" Academic Press, 1984, New York.

2. Loftus, P.; Bernstein, P.R. J. Org. Chem. **1983**, 48, 40-44.

3. To the best of our knowledge, no 1,4-thiazanes with this substitution pattern have ever been described. Some simpler 1,4-thiazanes, including the natural product cycloalliin, are known to possess interesting biological properties (see ref. 7).

4. For all new and stable compounds, satisfactory infrared, proton magnetic resonance, combustion analysis and/or mass spectral data were obtained.

5. Corey, E.J.; Niwa, H.; Falck, J.R. J. Am. Chem. Soc. **1979**, 101, 1586-1587.

6. The regioadducts **5** and **6** are each necessarily 1:1 mixtures of stereoisomers, since the racemic epoxide **4** is being attacked by a homochiral reagent.

7. This strategy follows from previously-described syntheses of 1,4-thiazanes: Sakai, K.; Yoneda, N. Chem. Pharm. Bull. **1981**, 29, 1554-1560.

8. These experiments clearly established the cis-relationship between H_2, H_3, and H_5. We thank T. Scahill and D. Kloosterman (The Upjohn Company) for performing these experiments.

9. IC_{50} for **10** = 10^{-6}M. We thank F. Sun (The Upjohn Company) for measuring this activity.

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