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SYNTHESIS OF BUTANOIC ACID 4,4'-[(4E, 6Z, 9Z-PENTADECATRIEN-2-YNYLIDENE)]-BIS WITH LEUKOTRIENE-LIKE ACTIVITY: NOVEL ACETYLENIC ACETALS AND DITHIOACETALS AS ANTAGONISTS OF LEUKOTRIENE-C_4

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Abstract: A selective exchange reaction of the symmetrical acetal 5a with protected cysteine readily provided the hemi-thioacetals 9a and 11a related to leukotriene-E_4. Use of acetylene-bis-(diethyl acetal) 12 led to a facile synthesis of the title compound 17a. Its corresponding hexahydro analogs displayed marked antagonist activity against LT-C_4 induced contractions on isolated guinea pig lung parenchyma.

Leukotrienes C_4, D_4 and E_4, now considered to be the main constituents of SRS-A, may be prime mediators of allergic diseases such as asthma and allergic rhinitis etc.[1] In the preceding communication we have described the synthesis and contractile activity of 7,8-acetylenic analogs of 9,10,11,12,14,15-hexahydro LT-E_4 and showed that their 5-desoxy analogs 8a/10a (R=Y=H) were antagonists of LT-C_4. Encouraged by this finding we sought to synthesize 9a/11a (R=Y=H) in the hope that such mixed O,S-acetals may be antagonists with enhanced potency. Analogs 9a and 11a are unique in having a 5-oxa function in the chain (which may allow affinity for the receptor) while lacking the 5-hydroxyl function necessary for intrinsic contractile activity.[2]

A rational synthesis of 9a/11a appeared to be exchange of one of the γ-oxa butyric acid chains in the symmetrical acetal 5a (R"=Me), with protected L-cysteine under controlled conditions. Although thioglycosides are well known, examples of this type of selective exchange reaction in acyclic systems are rare.[3] To our knowledge such an exchange reaction has not been carried out on acetylenic acetals.

The key starting material 1 was prepared in over 90% yield by reaction of 1-tetradecyne with triethyl orthoformate in the presence of ZnI_2.[4] Exchange reaction of the acetal 1 (1 equiv.) with butane 1,4-diol monobenzoate 2 (2 equiv.) in refluxing benzene (cat. TsOH) provided the dibenzoate 4.[5] Hydrolysis of 4 (1.0 N KOH, aq. ethanol) followed by oxidation of the resulting diol 4a ($R=CH_2OH$) with pyridinium dichromate[6] (8 equiv.) in DMF provided the crude diacid 5 (R"=H). Methylation of 5 (CH_2N_2) and chromatography[7] (5% acetone in n-hexane) gave the pure diester 5a (R"=Me) as a thick oil in overall 65% yield from 1.

A solution of the diester 5a in dry CH_2Cl_2 was treated with L-cysteine N-triflouro-acetamido methyl ester (1.1 equiv.) at -45°. With stirring (under argon), $BF_3.Et_2O$ (cat.) was syringed in. After 1 hour the reaction mixture was briefly allowed (~3 min.) to stir outside the cooling bath and promptly quenched with dilute (~7%) NH_4OH solution. The two diastereomers 9 and 11 (R=Me; $Y=COCF_3$) were readily obtained[8] by extractive isolation with CH_2Cl_2 followed by short-column chromatography[7] (>80% combined yield). Hydrolysis of the two dia-

stereomers (0.13M K_2CO_3 aq. MeOH)[1b] and chromatography on XAD-4 resin[9] provided 9a and 11a as di-potassium salts.

Contrary to our expectations both 9a and 11a failed to block the contractile activity of LT-C_4 up to 5 X 10^{-5}M on isolated guinea pig lung strip. However, the diacid 5 obtained by hydrolysis (1.0N NaOH, aq. EtOH) of the pure diester 5a exhibited good antagonist activity, blocking the contractile response to LT-C_4 by 84% at 5 X 10^{-5}M.

In view of the above result syntheses of the hemi- and dithioacetals 6 (R"=H)[17] and 7 (R"=H) were undertaken. A direct route to the dithioacetal-diacid 7 consisted of treating 2-pentadecynal[10] with γ-mercapto-butyric acid 3a (R"=H) in the presence of Me_3SiCl,[11] followed by chromatography (70% yield). Interestingly, the diacid 7 exhibited potent antagonist activity, blocking the response to LT-C_4 by 80% at 5 X 10^{-5}M and by 69% at 1 X 10^{-5}M (IC_{50} 2.8 X 10^{-6}M).

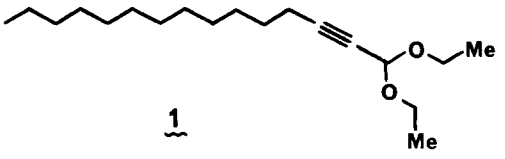
It has been shown that at least some of the double bonds in the leukotrienes play an important role in eliciting the high potency of these compounds.[1b,9] Thus it seemed possible that introduction of the 8,9,10,11,14,15-triene system (present in natural LT's)[2] in analogs such as 6 and 7 may enhance their antagonist potency. A successful synthesis of such an analog e.g. 17a (R=H) using the acetylene-bis-(diethyl acetal)[12] 12 as a key synthon is now described.

Partial hydrolysis of 12 with formic acid (2 equiv.)[13] provided the mono-diethyl acetal 13 (80% yield). The Wittig reaction of freshly prepared 13 with Ph_3P=CH.CHO (CH_2Cl_2; R.T., 15 hrs) gave the (E)-enyne-al 14 in 75% yield. The 11,12,14,15-(Z,Z,)-homo diene system was then generated by reaction of 14 with the ylid 15 (cf. Corey et. al.)[14] to provide 16 as a yellow oil (45% yield). An exchange reaction of 16 with 3 (R"=Me; 2 equiv.; -20°; CH_2Cl_2; $BF_3.Et_2O$ cat.) readily gave the diester 17 (R=Me). However, attempted hydrolysis of 17 (1.0N NaOH; Aq. EtOH) to 17a (R=H) led to a complex mixture lacking the acetal proton in the PMR spectrum. Since the hydrolysis of 7a to 7 was uneventful we attribute this failure (viz. 17→17a) to increased acidity of the acetal carbon in 17 due to extended conjugation.[15] This problem was circumvented by exchange of 16 with the acid 3a (R"=H) under the same conditions to provide the diacid 17a (58% yield) after rapid chromatography over coarse silica gel ($CHCl_3$:MeOH:AcOH; 10:1:0.1). Treatment of 17a with CH_2N_2 gave the same dimethyl ester 17 (R"=Me) confirming that no unexpected reaction took place during 16→17a transformation.[16]

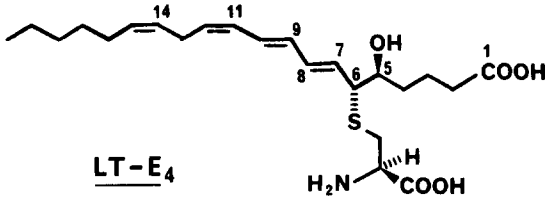
This compound, however, showed marked spasmogenic activity and no measurements of antagonist activity were possible. A concentration of 17a at 3X10^{-7}M gave a contraction on isolated guinea pig ileum (approx. equiv. to that produced by 5X10^{-9}M LT-C_4) which was blocked by over 90% by 1X10^{-6}M FPL 55712.[18]

Introduction of the 9,10,11,12,14,15-triene system[2] into the alkyl chain of 7 reversed its activity from leukotriene antagonism to agonism. It seems therefore that the double bonds in the terminal C_9-C_{20} portion of 17a are important for the nature of the activity in contrast to the leukotrienes themselves where they only appear to affect the potency of the compounds.

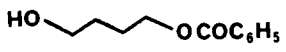
Application of the above methodology has led to a variety of additional antagonists and the detailed structure-activity relationships of this structural class will be discussed elsewhere.[17] As we noted in the preceding communication these are some of the first examples to



1



LT-E_4



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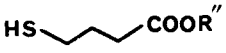

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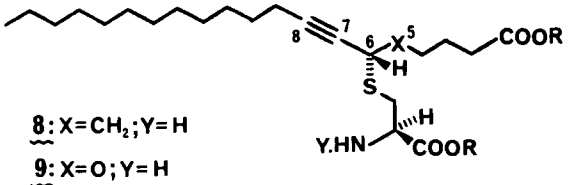
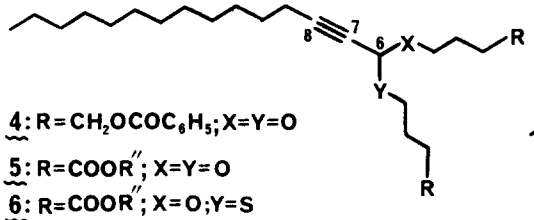


8: X=CH_2; Y=H

9: X=O; Y=H



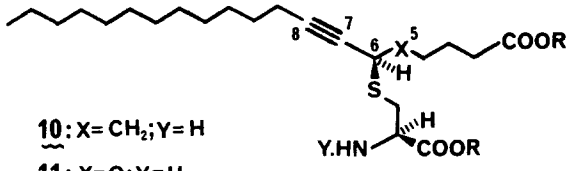
4: R=$CH_2OCOC_6H_5$; X=Y=O

5: R=COOR″; X=Y=O

6: R=COOR″; X=O; Y=S

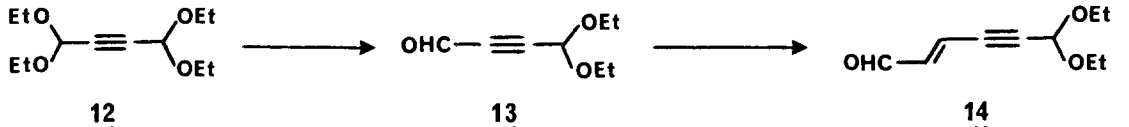
7: R=COOR″; X=Y=S

7a: R=COOMe; X=Y=S



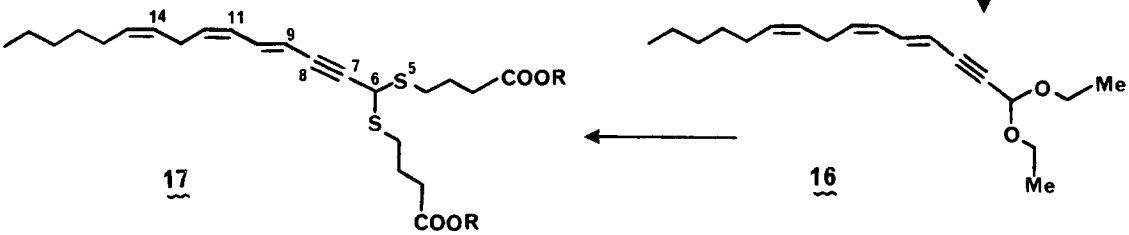
10: X=CH_2; Y=H

11: X=O; Y=H



12 13 14

15



16 17

be reported of SRS-A antagonists based upon the structure of leukotrienes. We hope that these studies may eventually contribute towards a better understanding of leukotriene receptors.[19,20]

Acknowledgements: We cordially thank Dr. Robert A. Lewis for many stimulating discussions. We also thank Drs. B. Pramanik, M.S. Puar and Mrs. Aileen Tseng for spectral and analytical support.

References and Notes:

1. Reviews: (a) B. Samuelsson, Angew. Chem. Int. Ed. Engl., 21, 902 (1982); (b) E.J. Corey, Experientia, 38, 1259 (1982); (c) P. Borgeat and P. Sirois, J. Med. Chem., 24, 121 (1981).
2. For comparision purpose, leukotriene numbering system has been used throughout the text (except for the title) as well as in the figures.
3. For an elegant example of dimethyl ketal → hemi-thioketal, see: F. Nakatsubo, A.J., Cocuzza, D.E. Keeley, Y. Kishi, J.A.C.S., 99, 4835 (1977).
4. B.W. Howk and J.C. Saver, J.A.C.S., 80, 4607 (1958).
5. We used this three-step sequence since direct exchange with γ-hydroxy butyric ester was expected to give polymeric products besides lactonization. Indeed in one such attempt a mixture of at least 20 products was obtained.
6. E.J. Corey and G. Schmidt, Tet. Lett., 399 (1979).
7. B.J. Hunt and W. Rigby, Chem. and Ind. 1868 (1969); Unless otherwise indicated E. Merck, Silica Gel 60G was used throughout.
8. 9 and 11: In the absence of suitable model systems, we have not assigned absolute configuration to these diastereomers. However they do display distinctly different PMR spectra (as do other similar isomers) indicating that they adopt different conformations in $CDCl_3$ solution.
   (i) Less Polar diastereomer: $[\alpha]_D^{26}$ -28° ($CHCl_3$) PMR ($CDCl_3$): δ3.75 (3H, s), 3.85 (3H, s), 5.1 (1H, m, -HN.CH -), 5.35 (1H, s, split, -O-CH-S-), 8.35 (1H, d, broad, $F_3C.CO.NH.CH$-).
   (ii) More Polar diastereomer: $[\alpha]_D^{26}$ + 50.4° ($CHCl_3$) PMR ($CDCl_3$): δ3.7 (3H, s), 3.82 (3H, s) 4.9 (1H, m, -HN.CH-), 5.4 (1H, s, split, -O-CH-S), 7.85 (1H, d, broad, $F_3C.CO.NH.CH$-).
9. R.N. Young, W. Coombs, Y. Guindon, J. Rokach, D. Ethier, and R. Hall, Tet. Lett., 4933 (1981).
10. Obtained by hydrolysis of 5a with formic acid under reflux (>80% yield).
11. B.S. Ong and T.H. Chan, Synthetic Comm. 7, 283 (1977).
12. A. Moureu, Ann. Chim, 8, (7), 550 (1906); A. Wohl and B. Mylo, Chem Ber., 45, 340 (1912).
13. A. Gorgues and Andre Le Coq, Tet. Lett., 4825 (1979); In a slight modification of this procedure, we found CH_2Cl_2 at reflux temperature more convenient.
14. E.J. Corey, Y. Arai, C. Miokowski, J.A.C.S., 101, 6748 (1979).
15. A similar observation was first made by Drs. R.J. Friary and V. Seidl in a related aromatic system; we thank them both for communicating their results prior to publication.
16. PMR of 17 ($CDCl_3$): δ0.9 (3H, t, broad), 1.25 (6H, m), 1.95 (6H, m), 2.45 (4H, t), 2.8 (6H, t), 3.65 (6H, s), 4.75 (1H, s, split), 5.2-7.05 (6H, m).
17. Complete details will be given in the full paper, manuscript in preparation; in-vitro data refer to 10^{-8}M LT-C_4 induced contractions on the isolated guinea pig lung parenchyma
18. P. Sheard, M.C. Holroyd, A.M. Ghelani, J.R. Bantik, and T.B. Lee, Leukotrienes and other Lipoxygenase Products, 229, Raven Press (1982).
19. Satisfactory IR, PMR, CMR, and MS (EI and FAB) were obtained for all new compounds.
20. After this manuscript was completed, two aromatic dithioacetals as selective antagonists of LT-D_4 were reported, see: C.D. Perchonock et. al., 189th ACS National Meeting (Abstract No. 85, Div. Med. Chem.), Miami Beach, Florida (1985).

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