Tetrahedron Letters,Vol.26,No.52,pp 6423-6426,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

SYNTHESIS OF 7,8-ACETYLENIC ANALOGS OF HEXAHYDRO LEUKOTRIENE-E_4 WITH AGONIST AND ANTAGONIST ACTIVITIES: CONVENIENT STEREOSELECTIVE ROUTES TO E- AND Z-ENYNES

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Abstract: E- and Z-enynes available by stereoselective dehydrations of $Co_2(CO)_6$ complexed and uncomplexed propargyl alcohols 13 and 5 produced acetylenic LT-E_4 analogs with contractile activity similar to leukotrienes. Their 5-desoxy analogs were found to have antagonist activity against LT-C_4 induced contractions on isolated guinea pig lung parenchyma.

The discovery of lipoxygenase catalysed transformations of arachidonic acid and structure elucidation of the derived 'leukotrienes'[1] marked a breakthrough in revealing the chemical nature of slow reacting substance of anaphylaxis (SRS-A).[2] Studies have indicated that the cysteinyl containing leukotrienes (LT)C_4, D_4 and E_4 are the prime mediators of airway anaphylaxis.[3] Several elegant syntheses[4] of these scarce and unstable natural products have made them available for extensive biological evaluation. It is possible that rational design of leukotriene antagonists,[5a] or inhibitors of leukotriene biosynthesis[5b] may lead to new approaches in alleviating symptoms of bronchial asthma.

The structural features that are necessary for contractile activity of LT-C_4, D_4 and E_4 have been studied in detail. Thus it was shown that both E- and Z- 9,10,11,12,14,15-hexahydroleukotrienes retained substantial agonist activity[1b] while the fully saturated analogs[6] were inactive. It appeared therefore that replacement of the 7,8-ene with a relatively more stable triple bond may lead to analogs having interesting biological activities. Based on this premise we describe here a novel series of antagonists of LT-C_4.

Coupling of 1-tetradecynyl zinc chloride 1 with 3[7] followed by $NaBH_4$ reduction of the resulting ketone 4 provided the alcohol 5 (65% overall). Dehydration of 5 was expected to produce a mixture of the E- and Z-enynes 16 and 19 from which all the four isomers of hexahydro-7-yne LT-E_4 could be derived. However, when 5 was treated with P_2O_5 (2.5 equiv.; in CH_2Cl_2; temp. 0-5°; 20 min.), the Z-enyne 19 was obtained in a highly stereoselective manner (Z:E, 9:1; 65% yield). Treatment of the alcohol 6 under the same conditions led to the identical result giving 20 (60% yield).[8,9] Epoxidation of 19 (Z:E, 9:1) with m-chloroperbenzoic acid gave the pure cis-epoxide 22 after chromatography (n-hexane:$CHCl_3$, 1:1).[10] Opening of this epoxide with N-triflouroacetyl-L-cysteine methyl ester[16] gave 24 as a mixture of diastereoisomers(5S, 6S + 5R, 6R) which were not separated. Hydrolysis of 24 with 0.13M K_2CO_3 in MeOH/H_2O (3:1)[1b] for 36 hours followed by XAD-4 chromatography[6] provided 24a (X=R=H) as a di-potassium salt.

Stablized cations generated from vinyl[11a] and cyclopropyl[12] ethynyl carbinols complexed with $Co_2(CO)_6$ group are known to generate E-enynes with excellent stereoselectivity. We therefore felt that dehydrations of complexed ethynyl carbinols such as 13 were likely to pro-

duce the desired E-enyne 16. Indeed when 13 and 14 were treated with P_2O_5 as above, the E-enynes 16 and 17 were obtained after oxidative deprotection[11a] of the complexes (E:Z, 9:1; 60-66% yields). Epoxidation of 16 and reaction of the pure trans-epoxide 23 with protected cysteine as above provided the diastereomers 25a (5R,6S) and 25b (5S, 6R).[13] These were separated by chromatography[10] and hydrolysis of each (as with 24) provided 25c (X=R=H) and 25d (X=R=H) respectively as di-potassium salts.

Both 25c and 25d exhibited significant agonist activity on the isolated guinea pig lung strip and ileum at 1 X 10^{-6}M. The ileum contractions were completely prevented by prior addition of the specific SRS-A antagonist FPL 55712 (1 X 10^{-6}M).[14] In contrast 24a produced only a weak contraction of lung strip.

Since 5-desoxy LT-D_4 was devoid of agonist activity[15] we then proceeded to prepare such analogs of 25c/25d to see if antagonist activity could be produced. The alcohol 5 was converted to the mesylate 7a (X=OMs; R'=H) at -10°C which was then treated (without isolation) with N-triflouroacetyl-L-cysteine methyl ester (Et_3N, CH_2Cl_2, R.T., 24 hrs.)[15] to provide 26 (78% yield). Hydrolysis of 26 with 0.13M K_2CO_3 in aqueous methanol as above gave the expected 26a (X=R=H) as a di-potassium salt. Controlled hydrolysis of 26 (0.13M K_2CO_3, aq. MeOH, 5 hours) provided 26b (X=$COCF_3$; R=H) as a di-potassium salt following XAD-4 chromatography.[6] Interestingly both 26a and 26b were found to have antagonist activity against LT-C_4 induced contractions of isolated guinea pig lung strip (50% inhibition at 5 X 10^{-5}M).[22]

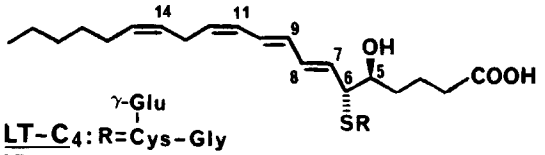
The activity shown by 26b suggested that perhaps the free amino group was not required for the antagonist activity. We therefore prepared the simple thioalkyl acid analogs such as 8a (R"=H) and 9a (R"=H) either by addition of the alcohol 5 and a thiol to a solution of $Ph_3P(OCH_2CF_3)_2$ in CH_2Cl_2-Et_2O[17a] (30-60% yields), or reaction of 7b (X=Br, R'=H)[18] with Cs-thiolates[17b] (60-80% yields).

Both 8a and 9a were more potent as LT-C_4 antagonists compared to the above 5-desoxy analogs 26a and 26b (70% inhibition at 5 X 10^{-5}M and 60% inhibition at 1 X 10^{-5} M respectively). Further, the (+) 6R and (-) 6S enriched forms of 9a prepared from 6R and 6S 5[19] were equally active suggesting that chirality at C-6 is not critical for antagonist activity. Furthermore the sulfur could be substituted with oxygen (e.g. 10) with retention of antagonist activity (90% inhibition at 5 X 10^{-5}M; 40% at 1 X 10^{-5}M).[22]

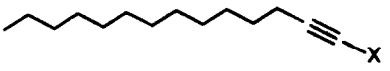
Syntheses of the all carbon analogs 18a (R"=H), 21a (R"=H), and 12 (R"=H) provided further examples of the stereoselective control in the elimination of propargyl alcohols by the uncomplexed (giving Z-enynes) and complexed acetylene (giving E-enynes). Thus dehydration of the tertiary alcohols 15 and 11 (R"=Me)[20a] with P_2O_5 as above formed the E- and Z-enynes 18 (R"=Me) and 21 (R"=Me) respectively (>90% stereoselective; >90% yields). The diacids 11a, 18a and 21a (R"=H) obtained by hydrolysis of the corresponding esters were weak antagonists of LT-C_4 at 5 X 10^{-5}M.

The complexed enyne derived from 15 upon selective reduction of the double bond with diimide (large excess)[11b,21] followed by oxidative deprotection[11a] and hydrolysis provided the diacid 12 (R"=H) which was also active as an antagonist.

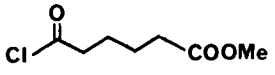
These acetylenic diacids represent one of the first classes of SRS-A antagonists, based upon the structure of the leukotrienes, to be reported to date. Extensive structure-activity



LT-C_4: R=Cys-Gly
LT-D_4: R=Cys-Gly
LT-E_4: R=Cys



1: X=ZnCl
2: X=Li



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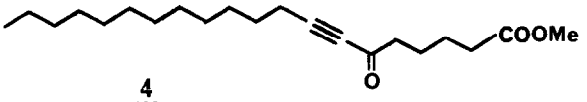

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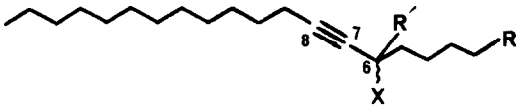
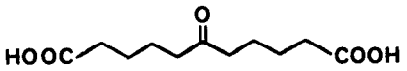


5: X=OH; R′=H; R=COOMe
6: X=OH; R′=H; R=Me
7: R′=H; R=COOMe
8: X=S$(CH_2)_2$COOR″; R=COOR″; R′=H
9: X=S$(CH_2)_5$COOR″; R=COOR″; R′=H
10: X=O$(CH_2)_5$COOH; R=COOH; R′=H
11: X=OH; R′=$(CH_2)_4$COOR″; R=COOR″
12: X=H; R′=$(CH_2)_4$COOR″; R=COOR″



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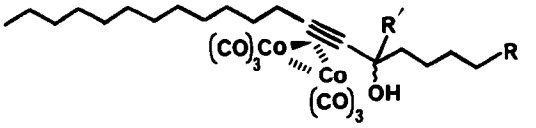
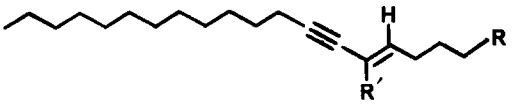
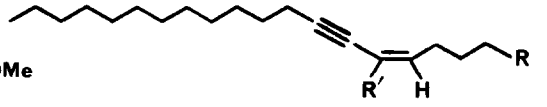


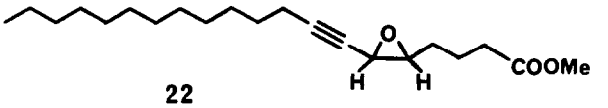
13: R′=H; R=COOMe
14: R′=H; R=Me
15: R′=$(CH_2)_4$COOMe; R=COOMe



16: R′=H; R=COOMe
17: R′=H; R=Me
18: R=COOR″; R′=$(CH_2)_4$COOR″



19: R′=H; R=COOMe
20: R′=H; R=Me
21: R=COOR″; R′=$(CH_2)_4$COOR″



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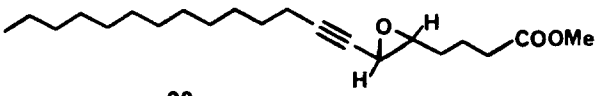

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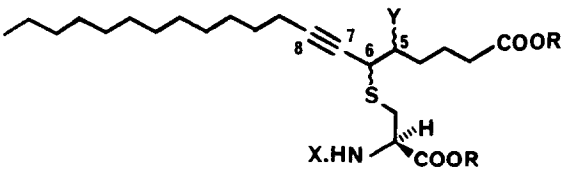

24: X=$COCF_3$; Y=OH; R=Me(5R*, 6R*)
25: X=$COCF_3$; Y=OH; R=Me(5R*, 6S*)
26: X=$COCF_3$; Y=H; R=Me

relationships and additional analogs will be presented elsewhere.[22]

The stereoselective formation of Z- and E-enynes (from a common precurser) reported here may provide in some cases (e.g. insect pheromone syntheses) a more convenient alternative to other elegant procedures.[23,24]

Acknowledgements: We cordially thank Drs. Leon Mendel[8] and 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:

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8. Hydrophobic binding of the hydrocarbon chains do not seem to explain this result since dehydrations in the presence of urea (in dioxane) did not alter the Z:E ratio in favor of E-enynes; cf. F.M. Menger and C.E. Portonoy, J.A.C.S., 90, 1875 (1968).
9. For a related reaction under somewhat drastic conditions ($KHSO_4$; temp. 140-160°C), see: A. Cugola, M. Orena, and S. Sandri, Gazz. Chim. Ital., 112, 232 (1982).
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13. 25a and 25b: Less Polar, $[\alpha]_D$ - 10.9° ($CHCl_3$); More Polar, $[\alpha]_D$ + 22.1° ($CHCl_3$).[22] cf. LT-E_4 methyl esters:[16] 5R, 6S (less polar), $[\alpha]_D$ - 19.6° (dioxane); 5S, 6R (more polar) $[\alpha]_D$ + 35.2° (dioxane).
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18. Prepared in over 90% yield by treatment of the alcohol 5 with Ph_3P/CBr_4 in CH_2Cl_2 according to, P.C. Crofts and I.M. Downie, J. Chem. Soc., 2559 (1963);[3] Unlike the mesylate 7a, the bromides of the type 7b were stable to manipulations at room temperature.
19. Prepared by Midland's procedure (J.A.C.S., 102, 867, 1980). The 6S, $[\alpha]_D$ -3.4 (neat) and 6R, $[\alpha]_D$ + 3.4° (neat) bromides 7b (ref. 18) were treated with Cs-thiolates[17b] to provide the 6R, $[\alpha]_D$ + 34.2° ($CHCL_3$) and 6S, $[\alpha]_D$ -23.3° ($CHCl_3$) 9a.
20. (a) Formed by reaction of 2 (3 equiv.) with 28 in THF followed by methylation (CH_2N_2; 30% overall yield). The 6-keto diacid 28 preparation: L.J. Durham, D.J. McLeod, and J. Cason, Org. Syn., Coll IV, 55 (1963).
21. Presumably due to steric factors, this diimide reduction was extremely sluggish. Even more than 20 equivalents of the reagent added in portions[11b] gave only a 10% yield of 12 (R"=H) besides unchanged 18 (R"=Me).
22. 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.
23. E. Negishi and A. Abramovitch, Tet. Lett., 411 (1977); H.C. Brown and G.A. Molander, J.O.C., 46, 647 (1981), and cited references.
24. Satisfactory IR, PMR, CMR, and MS (EI and FAB) were obtained for all new compounds.

(Received in USA 11 September 1985)