Tetrahedron Letters Vol. 21, pp 4163 - 4166 0040-4039/80/1022-4163$02.00/0

SYNTHESIS OF OPTICALLY ACTIVE LEUKOTRIENE (SRS-A) INTERMEDIATES

Noal Cohen*, Bruce L Banner, and Rocco J. Lopresti

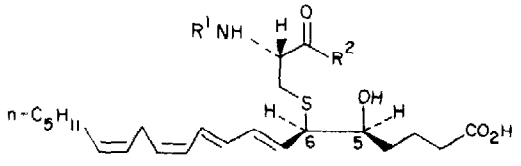
Chemical Research Department, Hoffmann-La Roche Inc ,
Nutley, New Jersey 07110

Summary. In an approach to SRS-A and analogues thereof, the key (5S,6S)-epoxy alcohol 9 and its 6-epimer 18 were prepared starting from D-araboascorbic acid and L-diethyl tartrate, respectively

Intensive recent investigations have led to the characterization of a family of "slow reacting substances" (SRS's) implicated in asthma and related anaphylactic conditions.[1] These unstable, spasmogenic compounds (1 a-c), named leukotrienes,[2] arise via antigen-triggered enzymatic transformations of arachidonic acid and possess intriguing and synthetically challenging structural features such as the attachment of amino acid residues via a sulfur atom at C-6 as well as the characteristic conjugated triene chromophore from which their names derive. Synthetic efforts in this area have already been forthcoming[3] and instrumental in providing structural confirmation [3b] These approaches all involve regioselective nucleophilic attack of sulfur nucleophiles upon the allylic epoxide moiety in LTA_4 methyl ester (2), whose parent acid is also the presumed biogenetic precursor to the SRS's [1]

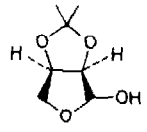
We, as others,[3b] envisioned a convergent, chiral approach in which an optically pure seven- or nine-carbon epoxy ester synthon would be united with an eleven- or thirteen-carbon olefinic fragment to form 2 Herein, we describe our approach to construction of the (-)-(5S,6S)- hydroxy epoxy ester 9 which has already been converted into LTC_4 by Corey and co-workers.[3b] In addition, a synthesis of the C-6 epimer (cis-epoxide) 18 is presented.

2,3-O-Isopropylidene-D-erythrose (3)[4] was prepared from inexpensive and readily available D-araboascorbic acid (erythorbic acid) by straightforward modifications of known procedures [5] Wittig condensation of 3 with the phosphorane derived from [2-(1,3-dioxan-2-yl)ethyl]triphenylphosphonium bromide[9] (n-BuLi,THF,-30°C-R.T.) followed by benzoylation (benzoyl chloride, pyridine, R.T.) gave the unsaturated ester acetal 4[10] (oil, $[\alpha]^{25}D$ +48.7°

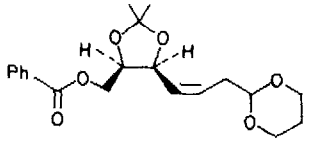


1a , R^1=γ-Glu, R^2 = Gly (LTC_4)
b , R^1 = H , R^2 = Gly (LTD_4)
c , R^1 = H , R^2 = OH (LTE_4)

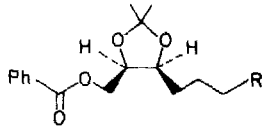
2 (LTA_4 methyl ester)

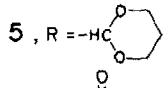


3

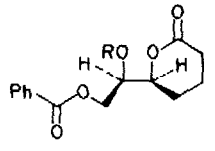


4



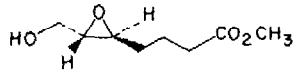
5 , R = 

6 , R = $-CO(CH_2)_3OH$

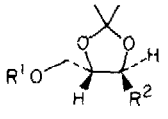


7 , R = H

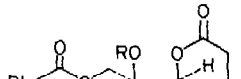
8 , R = SO_2CH_3



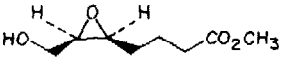
9



10 , R^1 = H, R^2 = CH_2OH
11 , R^1 =  , R^2 = CH_2OH
12 , R^1 =  , R^2 = CHO
13 , R^1 =  , R^2 =
14 , R^1 =  , R^2 =
15 , R^1 =  , R^2 = $(CH_2)_3$  $(CH_2)_3OH$



16 , R = H
17 , R = SO_2CH_3



18

(c 1,$CHCl_3$)) in 60% yield Catalytic hydrogenation of 4 over platinum, in ethyl acetate, quantitatively afforded 5[10] (oil,$[\alpha]^{25}D$ +15.2°(c 1,$CHCl_3$)) which smoothly provided the diester 6[10] (oil;$[\alpha]^{25}D$ +11.5°(c 1,$CHCl_3$)) when exposed to excess ozone, in ethyl acetate, at -78°C [11,12] In a crucial transformation, diester acetonide 6, upon treatment with 9 1 trifluoroacetic acid-water, (0°C,$NaHCO_3$quench), gave the beautifully crystalline erythro-hydroxy ester lactone 7[10] (mp 90 5-91 5°C from ether, $[\alpha]^{25}D$ +34 8°(c 1,$CHCl_3$)) in 70% yield In this process, the hydroxyl functions at C-5 and C-6 are differentiated by lactone formation selectively liberating the C-6 OH for conversion into a leaving group. Whereas, tosylation of 7 was sluggish, the corresponding oily mesylate 8 was formed quantitatively under standard conditions.[13] Treatment of 8 with sodium methoxide or, preferably, anhydrous potassium carbonate in methanol (1 1 equiv K_2CO_3,0-5°C,70% yield) led to the trans-(5S,6S)-epoxide 9[3b] (oil,$[\alpha]^{25}D$ -35°(c 0 2,$CHCl_3$)).[14]

A similar sequence was employed for synthesis of the cis-(5S,6R)-epoxide 18 Treatment of the trans-diol 10[15] with one equiv of benzoyl chloride in pyridine gave the monoester 11[10] (oil,$[\alpha]^{25}D$ -7.5°(c 1,$CHCl_3$)) in 45-50% yield along with diester and starting diol both of which could be removed by chromatography and recycled Oxidation[16] of 11 gave aldehyde 12[10] (oil,$[\alpha]^{25}D$ +17.1°(c 2,$CHCl_3$)) which, via the Wittig procedure described above for preparing 4, gave the epimer 13[10] (oil,$[\alpha]^{25}D$ -32 8°(c 1,$CHCl_3$)) in 45% overall yield from 11 Catalytic hydrogenation furnished 14[10] (oil;$[\alpha]^{25}D$ -16 2°(c 2,$CHCl_3$)) and ozone oxidation[11] then provided diester 15[10] (oil,$[\alpha]^{25}D$ -13 9°(c 2,$CHCl_3$)) Aqueous trifluoroacetic acid transformed 15 into the crystalline threo-hydroxy ester lactone 16[10] (mp 104 5-106°C from ethyl acetate-ether, $[\alpha]^{25}D$ +30 7° (c 1,$CHCl_3$)), the mesylate (17) of which yielded (70%) epoxide 18[10,17] (oil,$[\alpha]^{25}D$ +2 1°(c 0.5,$CHCl_3$)) when exposed to potassium carbonate in methanol.

Having the optically active synthons 9 and 18 available via the above schemes, we are currently preparing a variety of SRS analogs for pharmacological evaluation The results of these studies will be published in due course.

Acknowledgements We are grateful for the support and encouragement provided by Dr Gabriel Saucy during the course of this work The assistance provided by Dr. John W. Scott and Mr Gary Siwruk regarding the large scale preparation of certain intermediates must also be mentioned

References

1a. R C Murphy, S. Hammarstrom, and B Samuelsson, Proc Natl Acad Sci U.S.A , 76, 4275 (1979), (b) S. Hammarstrom, R C Murphy, B Samuelsson, D.A Clark, C. Mioskowski, and E.J. Corey, Biochem Biophys. Res. Commun , 91, 1266 (1979), (c) S Hammarstrom, B Samuelsson, D.A Clark, G Goto, A. Marfat, C Mioskowski, and E.J. Corey, ibid., 92, 946 (1980), (d) O Radmark, C. Malmsten, B. Samuelsson, D.A Clark, G Goto, A. Marfat, and E.J. Corey, ibid , 92, 954 (1980), (e) M.K. Bach, J R Brashler, S. Hammarstrom, and B. Samuelsson, ibid , 93, 1121 (1980), (f) H R Morris, G W Taylor, P.J Piper, M N. Samhoun, and J R Tippins, Prostaglandins, 19, 185 (1980), (g) L Örning, S Hammarstrom, and B Samuelsson, Proc Natl. Acad Sci U S A , 77,

2014 (1980), (h) W Dawson, Nature, 285, 68 (1980), (i) H R. Morris, G.W Taylor, P.J Piper, and J.R. Tippins, ibid., 285, 104 (1980)

2a. B. Samuelsson, P Borgeat, S Hammarstrom, and R C Murphy, Prostaglandins, 17, 785 (1979), (b) B. Samuelsson and S Hammarstrom, ibid , 19, 645 (1980).

3a. E.J Corey, Y. Arai, and C. Mioskowski, J. Am. Chem Soc , 101,6748 (1979), (b) E.J. Corey, D A. Clark, G. Goto, A Marfat, C. Mioskowski, B. Samuelsson, and S. Hammarstrom, ibid , 102, 1436 (1980), (c) E J Corey, A.E. Barton, and D.A Clark, ibid , 102, 4278 (1980), (d) M. Rosenberger and C Neukom, ibid , in press, (e) J.G. Gleason, D.B Bryan, and C.M. Kinzig, Tetrahedron Lett., 21, 1129 (1980), (f) J Rokach, Y Girard, Y Guindon, J.G Atkinson, M Larue, R N Young, P. Masson, and G Holme, ibid., 21, 1485 (1980)

4. C.E Ballou, J Am Chem Soc , 79, 165 (1957)

5. D-Araboascorbic acid was treated with diazotized p-toluidine ($NaNO_2$/aqueous H_2SO_4) at 0°C giving (-)-(3R-cis)-mono(tetrahydro-4-hydroxy-2-oxo-3-furanyl)ester 2-(4-methylphenyl)hydrazide of ethanedioic acid[6] (55%, mp 187-9°C d ,$[\alpha]^{25}D$ -59.3°(c 0.5,EtOH)), which,when hydrolyzed in boiling water,afforded D-erythronolactone[6] (74%, mp 97.5-99°C,$[\alpha]^{25}D$ -71 4°(c 0 5,H_2O)) The acetonide[7,8] was then prepared (2,2-dimethoxypropane-acetone-p-TsOH, 77%, mp 66-68°,$[\alpha]^{25}D$ -122.0°(c 1,H_2O)) which was reduced with DIBAH in CH_2Cl_2, at -78°C,[8] giving 3, $[\alpha]^{25}D$ -76°(c 1,$CHCl_3$), in 90% yield This sequence was easily carried out on 100-200 g scale

6. R. Weidenhagen and H. Wegner, Chem. Ber 72, 2010 (1939).

7. D.L Mitchell, Can. J Chem , 41, 214 (1963)

8. R.E Ireland, C S Wilcox, and S Thaisrivongs, J Org Chem , 43, 786 (1978).

9 J.C Stowell and D R. Keith, Synthesis, 132 (1979)

10 This compound provided compatible IR, NMR, and mass spectral data and a satisfactory (±0.3%) C,H microanalysis.

11. P. Deslongchamps, P. Atlani, D. Frêhel, A Malaval, and C Moreau, Can J. Chem , 52, 3651 (1974).

12. Attempted direct introduction of the carboxyethyl moiety by a Wittig reaction of 3 with the phosphorane from (2-carboxyethyl)triphenylphosphonium chloride (H S Corey, Jr., J R D. McCormick, and W E. Swensen, J Am Chem Soc , 86, 1884 (1964)) was unsuccessful.

13. R.K Crossland and K.L. Servis, J. Org. Chem , 35, 3195 (1970)

14. ^1H NMR ($CDCl_3$,100MHz) δ 3 66(s,3, CO_2CH_3), 3 59, 3 86 (2m,2, $-CH_2OH$), 2.91 (m,2, epoxide CH), 2 37 (t,2, J=6 5Hz, $CH_2CO_2CH_3$), 2.19 (t,1, J=6Hz,OH-exchanged with D_2O), 1.69 ppm (m,4,$(CH_2)_2$)

15. Readily available from L-(+)-diethyl tartrate- B A. Murrer, J.M. Brown, P A Chaloner, P.N Nicholson, and D. Parker, Synthesis, 350 (1979)

16 A.J Mancuso, S.-L Huang, and D. Swern, J Org Chem., 43, 2480 (1978)

17. ^1H NMR ($CDCl_3$, 100 MHz) δ 3 74 (m,2,CH_2OH), 3 67(s,3,CO_2CH_3), 3.14, 3 00 (2 d of t, 2, Jvic=4Hz, epoxide CH), 2 54(m,1,OH), 2 39 (t,2, J=6 5Hz, $CH_2CO_2CH_3$), 1 70ppm (m, 4,$(CH_2)_2$)

(Received in USA 11 July 1980)