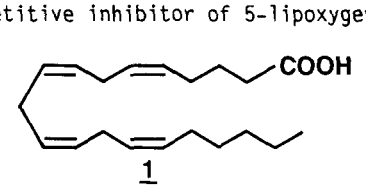
Tetrahedron Letters,Vol.26,No.18,pp 2143-2146,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain 

# EICOSATETRAENEHYDROXAMATES: INHIBITORS OF 5-LIPOXYGENASE

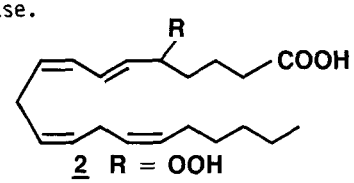
F.A.J. Kerdesky*, J.H. Holms, S.P. Schmidt, R.D. Dyer, and G.W. Carter
Abbott Laboratories, Department 47K, Abbott Park, Illinois 60064

ABSTRACT: The syntheses of 5-hydroxamyl and 5-hydroxamylmethyl-6,8,11,14,-eicosatetraenoic acids (3 and 4), which possess potent 5-lipoxygenase inhibitory activity, are described.

The oxidation of arachidonic acid 1 catalyzed by 5-lipoxygenase produces 5-hydroperoxy-6,8,11,14-eicosatetraenoic acid 2 (5-HPETE) which undergoes further bioconversions to the leukotrienes ($LTB_4$, $LTC_4$, $LTD_4$, and $LTE_4$) which have been implicated as important mediators of inflammation and allergic reactions.[1] Based on current knowledge of related lipoxygenase enzymatic mechanisms,[2] it is reasonable to assume that reaction of oxygen with 1 to form 5-HPETE 2 requires prior binding of oxygen to a metal, putatively iron, in the enzyme. Considering this premise, 5-hydroxamyl and 5-hydroxamylmethyl-6,8,11,14-eicosatetraenoic acids (3 and 4) were synthesized to interact with the iron moiety (hydroxamic acids being known iron chelators[3]) and provide additional binding compared to that of the substrate, arachidonic acid. Corey and co-workers[4] have recently prepared the hydroxamic acid of arachidonic acid and have shown it to be a potent, competitive inhibitor of 5-lipoxygenase.

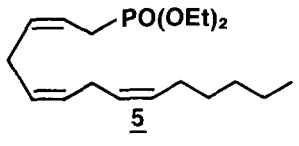



1




2 R = OOH
3 R = CONHOH
4 R = $CH_2CONHOH$

The synthetic strategy to 3 and 4 involved a Wittig-Horner-Emmons reaction of phosphonate 5 with aldehydes 6 or 7.




5

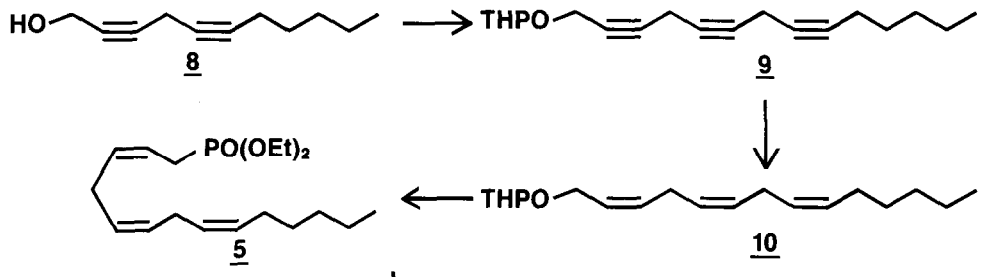

6 R = $CH_2OtBu$
7 R = $CH_2CH_2OSi$+

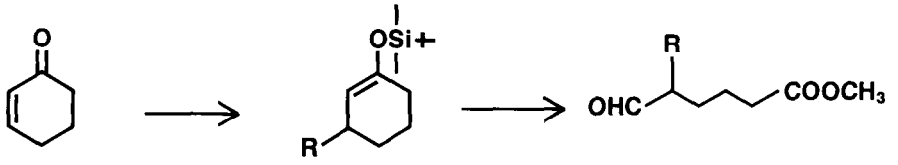
Diethyl 2Z,5Z,8Z-tetradecatrienylphosphonate 5 was synthesized by the following reaction sequence. Commercially available 2-octyn-1-ol was treated with phosphorous tribromide (pyridine, ether, 23°C, 3 hr, 94%) and the resulting bromide coupled with propargyl alcohol (EtMgBr, CuCl, THF, 66°C, 12 hr, 91%) to afford 2,4-undecadiyne-1-ol 8.[5,6] Alcohol 8 was subsequently treated with $Ph_2PCH_2CH_2PPh_2 \cdot 2Br_2$ ($CH_2Cl_2$, 23°C, 15 min, 99%) and the resulting bromide coupled with the THP ether of propargyl alcohol (EtMgBr, CuI, 23°C, 2 hr, 95%) to yield the triyne 9. The THP protection increased the stability of the triyne toward purification, storage, and further manipulation. Triyne 9 was then subjected to controlled hydrogenation employing Lindlar catalyst (quinoline, EtOAc, 23°C, 1 hr, 94%). Traces of overreduced or underreduced products were readily removed by argentation chromatography (20% $AgNO_3$ on silica gel). The resulting geometrically pure cis triene 10 was deprotected and converted to a bromide in one operation utilizing $Ph_2PCH_2CH_2PPh_2 \cdot 2Br_2$ ($CH_2Cl_2$, 23°C, 15 min, 95%). Reaction of this bromide with triethylphosphite ($CH_3CN$, 70°C, 6 hr, 96%) afforded 5[7] as a colorless oil.

Aldehyde 6 was prepared in an expeditious manner from commercially available 2-cyclohexenone. Conjugate addition of t-butoxymethyllithium[8] ($CuBr \cdot Me_2S$, TBME/THF, -30°C, 1 hr) to the α,β-unsaturated ketone followed by trapping of the enolate with t-butyldimethylsilyltriflate (HMPA, -20 to 23°C, 5 hr, 74%) gave the silyloxyalkene 11. The silyloxyalkene 11 was treated with ozone[9] (MeOH, -78°C, 1 hr, 94%) followed by reduction with dimethylsulfide, exposure to dilute acetic acid, and esterification with diazomethane (ether, 0°C, 5 min, 99%) to afford aldehyde 6.[10] Aldehyde 7 was synthesized in an analogous fashion. Conjugate addition of vinyl magnesium bromide[11] (CuI, THF, -78°C, 1 hr) to 2-cyclohexenone and subsequent trapping of the resulting enolate with t-butyldimethylsilyltriflate (HMPA, 0° to 23°C, 4 hr, 70%) yielded the silyloxyalkene 12. Hydroboration of 12 with 9-BBN[12] (THF, 23°C, 2 hr, 66%) gave, after alkaline hydrogen peroxide workup, the alcohol 13 which was silylated by treatment with t-butyldimethylsilylchloride (DMAP, imidazole, $CH_2Cl_2$, 23°C, 1 hr, 98%) to produce compound 14. Subjection of 14 to ozone[9] (MeOH, -78°C, 1 hr, 92%) followed by dimethylsulfide reduction, exposure to dilute acetic acid, and esterification with diazomethane (ether, 0°C, 5 min, 99%) provided 7.[13]

Horner-Emmons-Wittig coupling of the anion derived from phosphonate 5 (LDA, THF, -78°C, 1 min) with aldehyde 6 (THF, -78°C to 23°C, 20 hr) afforded, after flash chromatography,[14] a 66% yield of adduct 15. No trace of cis isomer was found as evidenced by 300 MHz NMR. The t-butyl protecting group of 15 was removed by treatment with acetic anhydride and anhydrous ferric chloride (THF, 0°C, 15 min, 96%) and the resulting acetate 16 was selectively hydrolyzed with potassium carbonate (MeOH, 0°C, 1 hr, 92%) to yield the alcohol 17.[15] The alcohol 17 was smoothly oxidized to the acid 18 with pyridinium dichromate (DMF, 23°C, 20 hr, 82%). Treatment of 18 with two equivalents of oxalyl chloride in the presence of one equivalent of dimethylformamide in THF gave the chloride which was not isolated but immediately reacted with hydroxylamine at 0°C to afford the hydroxamate ester 19 in 68% yield. Hydrolysis of 19 with lithium hydroxide ($iPrOH/H_2O$:2/1, 23°C, 1 hr, 94%) provided 3.[16]

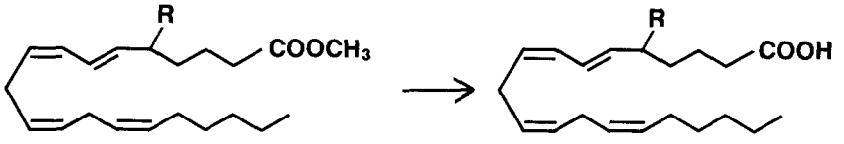
Hydroxamic acid 4 was prepared in similar fashion. Generation of the lithium salt of the phosphonate 5 (LDA, THF, -78°C, 1 min) and addition of the aldehyde 7 (-78°C) followed by gradual warming to 23°C resulted in a highly efficient and stereocontrolled coupling to form adduct 20 (65%, exclusively trans). Adduct 20 was deprotected with $nBu_4NF$ (THF, 23°C, 1 hr, 96%) and the resulting alcohol 21 oxidized with pyridinium dichromate (DMF, 23°C, 20 hr, 81%) to afford acid 22. Acid 22 was transformed into hydroxamic acid 4[17] by successive treatment with oxalyl chloride (DMF, THF, 0°C, 1 hr), hydroxylamine (THF/$H_2O$:2/1, 0°C, 2 hr) and lithium hydroxide (iPrOH/$H_2O$:2/1, 23°C, 1 hr) in an overall yield of 67%.




11 R = $CH_2OtBu$
12 R = $CH{=}CH_2$
13 R = $CH_2CH_2OH$
14 R = $CH_2CH_2O\overset{|}{Si}+$

6 R = $CH_2OtBu$
7 R = $CH_2CH_2O\overset{|}{Si}+$




15 R = $CH_2OtBu$
16 R = $CH_2OAc$
17 R = $CH_2OH$
18 R = COOH
19 R = CONHOH
20 R = $CH_2CH_2O\overset{|}{Si}+$
21 R = $CH_2CH_2OH$
22 R = $CH_2COOH$

3 R = CONHOH
4 R = $CH_2CONHOH$

Compounds 3 and 4 produced potent inhibition of 5-lipoxygenase activity in the 10,000 x g supernatant from homogenized rat basophilic leukemia cells[18] with $IC_{50}$'s of 1.4 and 0.19 μM, respectively. In our assay, compound 4 was 10 times more active than the recently described hydroxamic acid of arachidonic acid[4] ($IC_{50}$'s 0.19 vs 2.2 μM, respectively).

In conclusion, a synthetic scheme for preparing a variety of 5-substituted 5-HPETE analogs has been presented. Positioning a hydroxamic acid containing group at carbon-5 produced compounds with potent 5-lipoxygenase inhibitory activity. These results support the hypothesis that a metal atom is located in the active site of the enzyme.

ACKNOWLEDGEMENT

We are grateful to Mr. D. Bornemeier for excellent technical assistance and to Drs. R. Walters and D. Brooks for helpful discussions related to this work.

REFERENCES

1. D.M. Bailey and F.B. Casey, Ann. Rep. Med. Chem., 17, 203(1982) and references therein.
2. E.K. Pistorius and B. Axelrod, J. Biol. Chem., 249, 3183(1974).
3. B. Chatterjee, Coord. Chem. Rev., 26, 281(1978).
4. E.J. Corey, J.R. Cashman, S.S. Kantner, and S.W. Wright, J. Amer. Chem. Soc., 106, 1503(1984).
5. J.G. Gleason, D.B. Bryan, and C.M. Kinzig, Tett. Lett., 21, 1129(1980).
6. Satisfactory spectroscopic data were obtained for all compounds.
7. $^1$H NMR (60 MHz, $CDCl_3$) δ5.2-5.6 (m, 6H), 3.8-4.4 (q, 4H), 2.4-3.0 (m, 6H), 1.9-2.3(m, 2H), 1.3-1.6 (t, 6H), 1.1-1.6 (m, 6H), 0.9 (t, 3H).
8. E.J. Corey and T.M. Eckrich, Tett. Lett., 24, 3165(1983).
9. R.D. Clark and C.H. Heathcock, Tett. Lett., 23, 2027(1974).
10. $^1$H NMR (60MHz, $CDCl_3$) δ9.6 (d, 1H), 3.6 (s, 3H), 3.2 (d, 2H), 2.3 (m, 3H), 1.3-1.9 (m, 6H), 1.0 (s, 9H).
11. E. Erdik, Tetrahedron, 641(1984).
12. H.C. Brown, J. Chandrasekharan, and D.J. Nelson, J. Amer. Chem. Soc., 106, 3768(1984).
13. $^1$H NMR (60MHz, $CDCl_3$) δ9.6 (d, 1H), 3.6 (s, 3H), 3.6 (d, 2H), 2.3 (m, 3H), 1.3-1.9 (m, 6H), 1.0 (s, 9H), 0.02 (s, 6H).
14. W.C. Still, M. Kahn, and A. Mitra, J. Org. Chem., 43, 2923(1978).
15. M. Toda et al., J. Med. Chem., 26, 72(1983).
16. $^1$H NMR (300MHz, $CDCl_3$) δ8.30 (br s, 1H), 6.41 (dd, 1H, J=11 and 15Hz), 5.95 (t, 1H, J=11Hz), 5.30-5.65 (m, 6H), 2.96 (t, 2H, J=7Hz), 2.83 (t, 2H, J=7Hz), 2.35 (t, 2H, J=7Hz), 2.06 (q, 2H, J=7Hz), 1.50-1.80 (m, 5H), 1.20-1.45 (m, 6H), 0.90 (t, 3H, J=7Hz).
17. $^1$H NMR (300MHz, $CDCl_3$) δ8.30 (br s, 1H), 6.42 (dd, 1H, J=11 and 15Hz), 5.95 (t, 1H, J=11Hz), 5.30-5.55 (m, 6H), 2.96 (t, 2H, J=7Hz), 2.83 (t, 2H, J=7Hz), 2.35 (t, 2H, J=7Hz), 1.95-2.25 (m, 3H), 2.06 (q, 2H, J=7Hz), 1.50-1.80 (m, 5H), 1.20-1.45 (m, 6H), 0.90 (t, 3H, J=7Hz).
18. R.D. Dyer, F. Haviv, A.M. Hanel, D.A. Bornemeier, and G.W. Carter, Fed. Proc., 43, 1462A(1984).

(Received in USA 8 January 1985)