Communications to the Editor

[Chem. Pharm. Bull. 30(1) 379—382 (1982)]

SYNTHESIS OF (±)-CARBA-ANALOGS OF 5-HPETE AND LEUKOTRIENE A_4, UNSTABLE INTERMEDIATES OF SLOW-REACTING SUBSTANCE (SRS)

Yoshinobu Arai, Mitoshi Konno, Katsuichi Shimoji, Yoshitaka konishi, Haruki Niwa, Masaaki Toda* and Masaki Hayashi

Research Institute, Ono Pharmaceutical Co., Ltd., Shimamoto, Mishima, Osaka 618, Japan

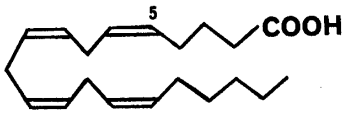
The carba-analogs of 5-HPETE and leukotriene A_4, unstable intermediates of slow-reacting substance (SRS), were synthesized. These carba-analogs inhibited the 5-lipoxygenase. The carba-analog of leukotriene A_4 was a particularly potent specific inhibitor of the 5-lipoxygenase.

KEYWORDS —— slow-reacting substance; 5-lipoxygenase inhibitor; 5-HPETE; leukotriene A_4; analog of 5-HPETE; analog of leukotriene A_4

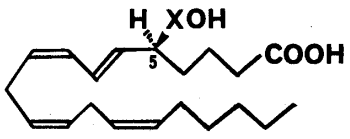
Slow-reacting substance (SRS) induces immediate hypersensitivity.[1] Its structure was recently elucidated.[2] Two major products, leukotriene C_4 (LTC_4) and leukotriene D_4 (LTD_4), are formed from arachidonic acid (1) *via* 5(S)-HPETE (2) and leukotriene A_4 (LTA_4, 3).[2] The synthesis of 2 and 3 has been reported.[2a,3] These intermediates are very unstable because they contains, respectively, hydroperoxy and allylic epoxide functions.

In this connection it seemed worthwhile to synthesize the carba-analogs (5) and (6) of 5-HPETE and LTA_4 respectively for biological study.[4] This is a report on the synthesis of 5 and 6 and their inhibitory activities against the 5-lipoxygenase of the polymorphonuclear leukocytes of guinea pig.

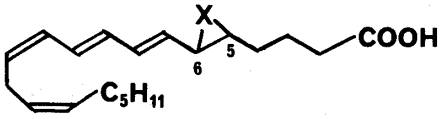
The carba-analog (5) of 5-HPETE was synthesized as follows. Diethyl malonate was converted to the alcohol (7) by the following sequence: (1) monoalkylation of diethyl malonate with 1-bromo-3-chloropropane in the presence of sodium ethoxide



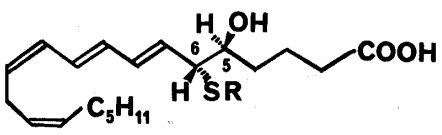
1



2 X= O(5-HPETE)
5 X= CH_2



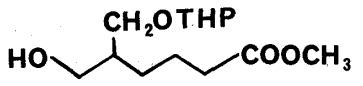
3 X= O(LTA_4)
6 X= CH_2



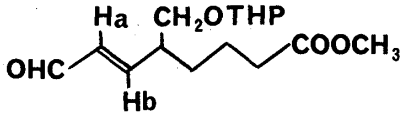
4 LTC_4: R=Glutathione
LTD_4: R=L-Cys-Gly

in ethanol at reflux temperature to afford diethyl 3-chloropropylmalonate (62% yield) ; (2) reduction of the diester with diisobutylaluminum hydride in toluene at -78°C to 0°C to afford the dialcohol (65% yield) ; (3) monotetrahydropyranylation of the dialcohol with dihydropyran (1 eq) in the presence of catalytic amount of p-TsOH in CH_2Cl_2 at 0°C (70% yield) ; (4) conversion of the chloride group to the cyanide group with sodium cyanide (2 eq) and lithium bromide (0.1 eq) in DMSO at 50°C (80% yield) ; (5) hydrolysis of the nitrile group with aqueous sodium hydroxide (5 eq) at reflux temperature followed by treatment with diazomethane to afford the alcohol-ester (7) [PMR δ ($CDCl_3$) 2.30 (2H,t,J=6.5Hz), 3.1-4.1 (6H,m), 3.60 (3H,s) and 4.50 (1H,br s). IR ν (film) 1735. MS m/e 259 (M^+-1)] in 85% yield. Oxidation of the alcohol-ester (7) with oxalyl chloride-DMSO[5] in CH_2Cl_2 at -70°C afforded the aldehyde-ester (90% yield), which was treated with 1-lithio-2-ethoxyethylene[6] in THF at -70°C followed by treatment with methanesulfonyl chloride (1.3 eq) and NEt_3 (1.8 eq) in CH_2Cl_2 at -45°C to afford the enal-ester (8) [PMR δ ($CDCl_3$) 3.67 (3H,s), 6.17 (1H,ddd,J=0.5,7.5,15.5Hz, Ha), 6.77 (1H,dd,J=8.0,15.5Hz, Hb) and 9.53 (1H,d,J=7.5Hz, -CHO). IR ν (film) 1735 and 1690. MS m/e 284(M^+)] in 35% yield. The Wittig reaction of the enal-ester (8) with the ylide (1.5 eq), generated from 1-triphenylphosphonium-cis,cis-3,6-dodecadiene bromide[7] with n-butyllithium, in THF-HMPA (1.2 eq) at -70°C to room temperature afforded 9 in 80% yield. Treatment of 9 with p-TsOH in methanol at room temperature followed by sodium hydroxide (3 eq) in water-THF gave (±)-carba-analog (5) of 5-HPETE [PMR δ ($CDCl_3$) 3.50 (1H,dd, J=7.0,10.5Hz), 3.60 (1H,dd,J=5.5,10.5Hz), 5.98 (1H,t,J=10.5Hz, H_8), 6.45 (1H,dd,J= 10.5,15Hz, H_7). IR ν (film) 1710. UV λ (EtOH) 236 (ε, 28000). MS Calcd for $C_{21}H_{34}O_3$: m/e 334.25078, found m/e 334.24918][8] in 80% yield.

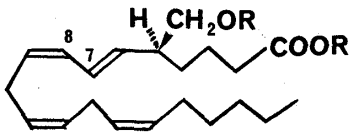
The synthesis of the carba-analog (6) of LTA_4 was readily effected by the following process. The Simmons-Smith reaction[9] of methyl 7-hydroxy-5-trans-heptanoate[10] with methylene iodide (3 eq) and zinc-copper couple (3 eq) in ether at reflux temperature for 2.5 hr afforded the alcohol (10) [PMR δ ($CDCl_3$) 2.36 (2H,t,



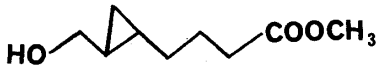
7



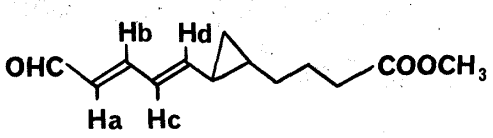
8



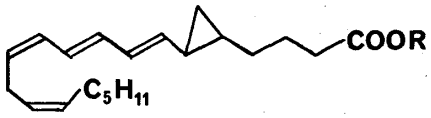
9 R= THP, R'= CH_3
5 R=R'= H



10



11



12 R= CH_3
6 R= H

J=7.5Hz, -CH_2COOCH_3), 3.44 (2H,d,J=7.0Hz, -CH_2OH) and 3.67 (3H,s). IR ν (film) 1740. MS m/e 174 (M^+)] in 40% yield. Oxidation of the alcohol (10) with the Collins reagent in CH_2Cl_2 at 0°C for 10 min afforded the corresponding aldehyde [PMR δ ($CDCl_3$) 9.50 (1H,d,J=5.0Hz, -CHO)], which was treated with 1-lithio-4-ethoxybutadiene[5] in THF at -78°C for 1 h followed by treatment with p-TsOH in water-THF (1:10) at room temperature for 15 min to afford the dienal (11) [PMR δ ($CDCl_3$) 2.35 (2H,t,J=7.5Hz, -CH_2COOCH_3), 3.67 (3H,s), 5.80 (1H,dd,J=9.5,15.0Hz, Hd), 6.04 (1H,dd,J=8.0,15.0Hz, Ha), 6.36 (1H,dd,J=10.5,15.0Hz, Hc), 7.04 (1H,dd,J=10.5,15.0Hz, Hb) and 9.50 (1H,d,J=8.0Hz, -CHO). IR ν (film) 1740, 1680 and 1630. MS m/e 222 (M^+)] in 70% yield. The Wittig reaction[2a] of the dienal (11) with the ylide (1.2 eq), generated from 1-triphenylphosphonium-3-cis-nonene iodide[2a] with n-butyllithium, in THF-HMPA (12 eq) at -78°C to room temperature for 30 min afforded 12 [UV λ (MeOH) 274 (ε, 42000), 283.5 (50000) and 294 (39000)] in 70% yield. Hydrolysis of 12 with 2N KOH (2 eq) in methanol-THF (2:1) at room temperature overnight gave (±)-carba-analog (6) of LTA_4 [PMR δ ($CDCl_3$) 2.38 (2H,t,J=7.5Hz) 2.70-3.05 (2H,m, =CH-CH_2-CH=), 5.00-5.60 (4H,m, olefinic protons) and 5.80-6.60 (4H,m, olefinic protons). IR ν (film) 1715 and 1640. UV λ (MeOH) 273 (ε, 42000), 283 (50000) and 294 (39000).[11] MS Calcd for $C_{21}H_{32}O$: m/e 316.24022, found: m/e 316.24227] in 97% yield.

The carba-analog (5) and (6) were more stable than 5-HPETE and LTA_4 respectively, and showed inhibitory activities against the 5-lipoxygenase from the polymorphonuclear leukocytes of guinea pig with IC_{50} values of 100 μM and 3 μM respectively. Especially 6 selectively inhibited the 5-lipoxygenase without inhibiting the cyclooxygenase and the 12-lipoxygenase.

REFERENCES AND NOTES

1) K.F. Austen, Harvey Lect., 73, 93 (1977).

2) a) E.J. Corey, D.A. Clark, G. Goto, A. Marfart, C. Mioskowski, B. Samuelsson and S. Hammarström, J. Amer. Chem. Soc., 102, 1436 (1980); b) R.C. Murphy, S. Hammarström and B. Sammuelsson, Proc. Natl. Acad. Sci. USA, 76, 4275 (1979); c) L. Örning, S. Hammarström and B. Samuelsson, ibid., 77, 2014 (1980); d) S. Hammarström, B. Samuelsson, D.A. Clark, G. Goto, A. Marfart, C. Mioskowski and E.J. Corey, Biochem. Biophys. Res. Commun., 92, 946 (1980).

3) E.J. Corey, J.O. Albright, A.E. Barton and S. Hashimoto, J. Amer. Chem. Soc., 102, 1435 (1980).

4) Recently the synthesis of 5,6-thialeukotriene A_4 and 5,6-methanoleukotriene A_4 were reported: E.J. Corey, H. Park, A.E. Barton and Y. Nii, Tetrahedron Lett., 1980, 4243; K.C. Nicolaou, N.A. Petasis and S.P. Seitz, J. C. S. Chem. Commun., 1981, 1195.

5) A.J. Mancao, S. Huang and D. Swern, J. Org. Chem., 43, 2480 (1978).

6) R.H. Wollenberg, Tetrahedron Lett., 19, 717 (1978).

7) The phosphonium salt was prepared from 1-bromo-3,6-cis,cis-dodecadiene and triphenylphosphine in acetonitrile. 3,6-Cis,cis-dodecadien-1-ol [PMR δ ($CDCl_3$) 3.66 (2H,t,J=6.5Hz) and 5.15-5.75 (4H,m, olefinic protons). MS m/e 182(M^+)] was prepared by the Lindlar reduction of corresponding diyne, which was prepared starting with 3-butyn-1-ol and 1-bromo-2-octyne according to Ann. Chem., 1978, 658, and converted to the bromide [PMR δ ($CDCl_3$) 3.37 (2H,t,J=7.0Hz) and 5.10-

5.75 (4H,m, olefinic protons). MS m/e 246 and 244 (M^+)] by the reaction with triphenylphosphite dibromide[12] and pyridine in ether at 0°C.

8) 6,8-Cis,trans-HC=CH_8-CH_7=CH- unit of 5-HPETE methyl ester had PMR δ ($CDCl_3$) 6.54 (1H,dd,J=10.5,15.0Hz) for H_7 and 5.98 (1H,t,J=10.5Hz) for H_8 and UV λ (MeOH) 235 nm (ε, 28600).[3]

9) H.E. Simmons, "Organic Reactions", Vol. 20, ed. by W.G. Dauben, John Willey & Sons, Inc., New York, 1973, P. 1.

10) E.J. Corey, H. Park, A.E. Barton and Y. Nii, Tetrahedron Lett., 21, 4243 (1980).

11) LTA_4 methyl ester had UV λ (MeOH) 269, 279 (ε, 40000) and 289 nm.

12) D.K. Balack, S.R. Landor, A.N. Patel and R.F. Whiter, Tetrahedron Lett., 1963, 483.

(Received December 2, 1981)