

Communications to the Editor

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

SYNTHESIS OF (±)-CARBA-ANALOGS OF 5-HPETE AND LEUKOTRIENE A₄,
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

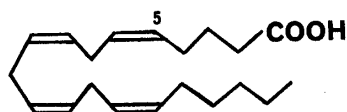
The carba-analogs of 5-HPETE and leukotriene A₄, unstable intermediates of slow-reacting substance (SRS), were synthesized. These carba-analogs inhibited the 5-lipoxygenase. The carba-analog of leukotriene A₄ was a particularly potent specific inhibitor of the 5-lipoxygenase.

KEYWORDS — slow-reacting substance; 5-lipoxygenase inhibitor; 5-HPETE; leukotriene A₄; analog of 5-HPETE; analog of leukotriene A₄

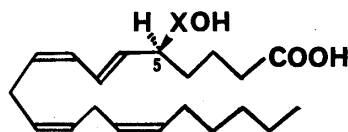
Slow-reacting substance (SRS) induces immediate hypersensitivity.¹⁾ Its structure was recently elucidated.²⁾ Two major products, leukotriene C₄ (LTC₄) and leukotriene D₄ (LTD₄), are formed from arachidonic acid (1) via 5(S)-HPETE (2) and leukotriene A₄ (LTA₄, 3).²⁾ The synthesis of 2 and 3 has been reported.^{2a,3)} These intermediates are very unstable because they contain, respectively, hydroperoxy and allylic epoxide functions.

In this connection it seemed worthwhile to synthesize the carba-analogs (5) and (6) of 5-HPETE and LTA₄ 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

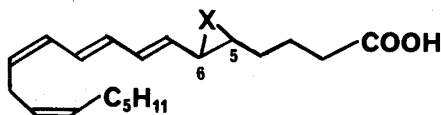


1



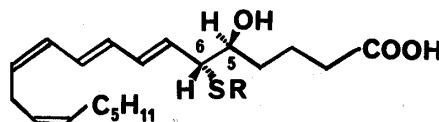
2 X= O (5-HPETE)

5 X= CH₂



3 X= O (LTA₄)

6 X= CH₂

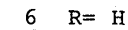
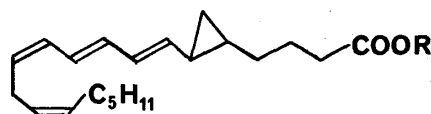
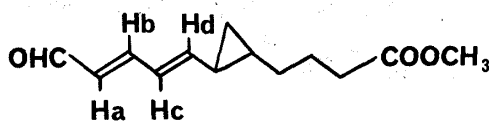
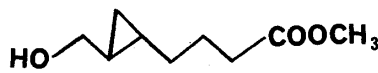
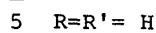
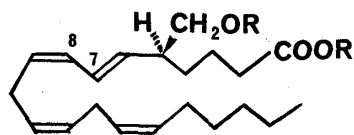
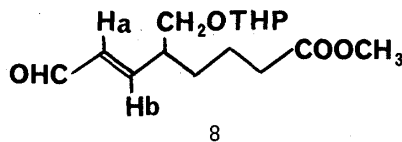
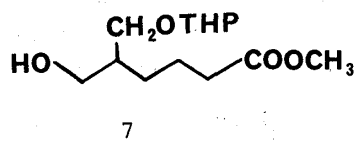


4 LTC₄: R=Glutathione

LTD₄: 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, $J=6.5\text{Hz}$), 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-DMSO⁵⁾ in CH_2Cl_2 at -70°C afforded the aldehyde-ester (90% yield), which was treated with 1-lithio-2-ethoxyethylene⁶⁾ 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, $J=0.5,7.5,15.5\text{Hz}$, H_a), 6.77 (1H,dd, $J=8.0,15.5\text{Hz}$, H_b) and 9.53 (1H,d, $J=7.5\text{Hz}$, $-\text{CHO}$). 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 bromide⁷⁾ 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 (\pm)-carba-analog (5) of 5-HPETE [PMR δ (CDCl_3) 3.50 (1H,dd, $J=7.0,10.5\text{Hz}$), 3.60 (1H,dd, $J=5.5,10.5\text{Hz}$), 5.98 (1H,t, $J=10.5\text{Hz}$, H_8), 6.45 (1H,dd, $J=10.5,15\text{Hz}$, H_7). IR ν (film) 1710. UV λ (EtOH) 236 (ϵ , 28000). MS Calcd for $\text{C}_{21}\text{H}_{34}\text{O}_3$: 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 reaction⁹⁾ of methyl 7-hydroxy-5-trans-heptanoate¹⁰⁾ 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,



J=7.5Hz, $-\text{CH}_2\text{COOCH}_3$), 3.44 (2H,d,J=7.0Hz, $-\text{CH}_2\text{OH}$) 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, $-\text{CHO}$)], which was treated with 1-lithio-4-ethoxybutadiene⁵ 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, $-\text{CH}_2\text{COOCH}_3$), 3.67 (3H,s), 5.80 (1H,dd,J=9.5,15.0Hz, H_d), 6.04 (1H,dd,J=8.0,15.0Hz, H_a), 6.36 (1H,dd,J=10.5,15.0Hz, H_c), 7.04 (1H,dd,J=10.5,15.0Hz, H_b) and 9.50 (1H,d,J=8.0Hz, $-\text{CHO}$). 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 (\pm)-carba-analog (6) of LTA_4 [PMR δ (CDCl_3) 2.38 (2H,t,J=7.5Hz) 2.70-3.05 (2H,m, $=\text{CH}-\text{CH}_2-\text{CH}=\text{CH}$), 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 $\text{C}_{21}\text{H}_{32}\text{O}$: 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. Samuelsson, 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-butyne-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 dibromide¹²⁾ and pyridine in ether at 0°C.
- 8) 6,8-Cis,trans-HC=CH₈-CH₇=CH- unit of 5-HPETE methyl ester had PMR δ (CDCl₃) 6.54 (1H,dd,J=10.5,15.0Hz) for H₇ and 5.98 (1H,t,J=10.5Hz) for H₈ 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) LTA₄ 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)