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SYNTHESIS OF NEW LIPOXYGENASE INHIBITORS 13-THIA- AND 10-THIAARACHIDONIC ACIDS

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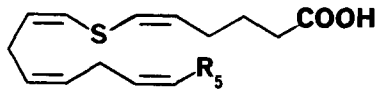
Summary: Short, efficient and stereocontrolled syntheses are reported for 13-thiaarachidonic acid (11) and 10-thiaarachidonic acid (17), valuable substrates for the study of the mechanisms of enzymatic lipoxygenation of polyunsaturated fatty acids.

The discovery of effective and specific inhibitors of leukotriene biosynthesis, preferably at the 5-lipoxygenation stage, is currently under investigation in many laboratories. A number of different types of inhibitors have been developed by our group, the most recent being 7-thiaarachidonate (1) which was shown to be an oxygen- and time-dependent irreversible inhibitor of the 5-lipoxygenase of rat basophilic leukemic cells.[1] The logical extension of this work to the study of the 15-lipoxygenation of arachidonate by soybean lipoxygenase, of special interest in connection with understanding the mechanism of enzymatic lipoxygenation, required the synthesis of 13-thia- and 10-thiaarachidonic acids (11 and 17 resp.). This paper reports the realization of this objective.



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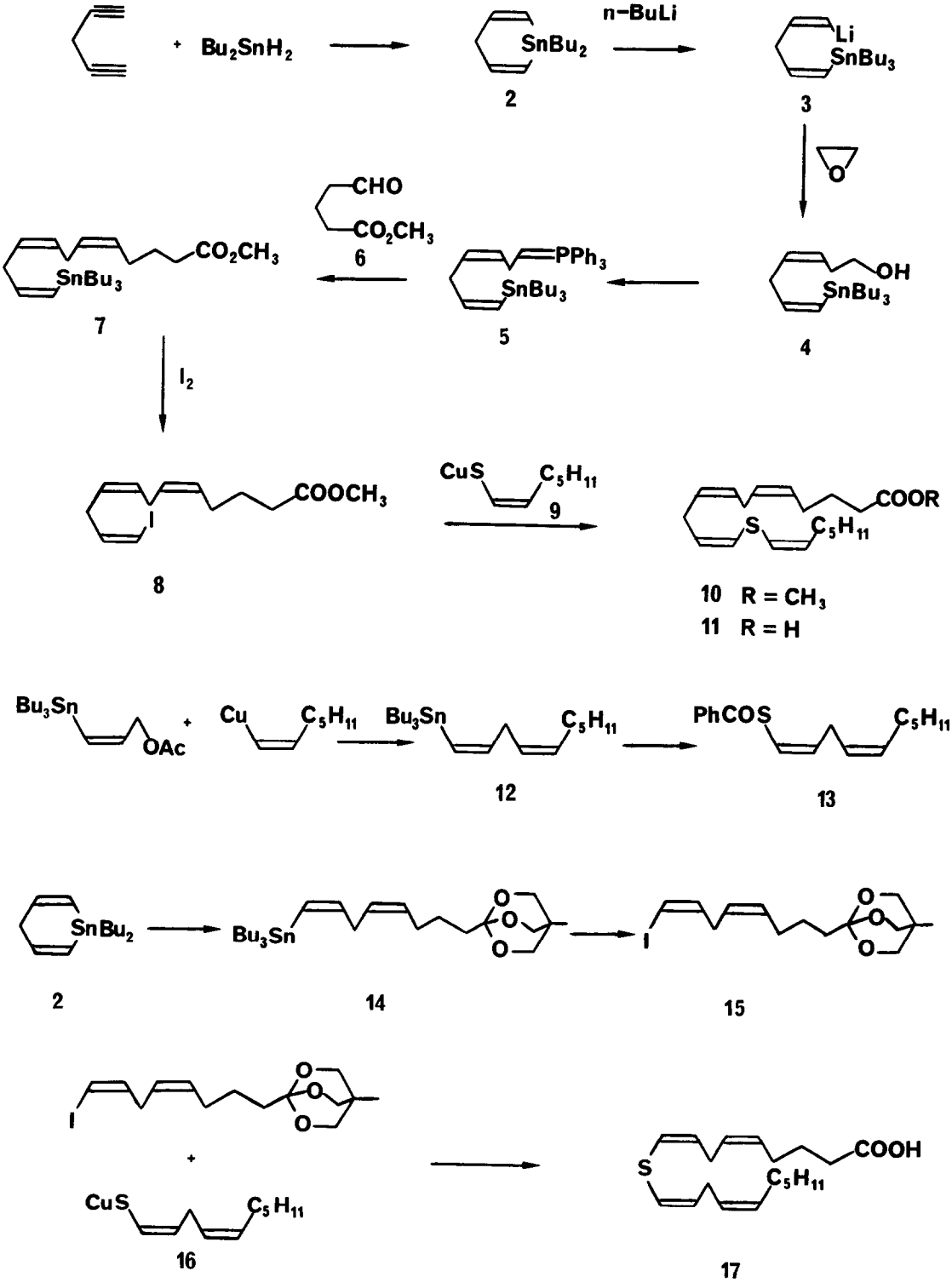
The synthesis of 13-thiaarachidonate was accomplished as follows. 1,1-Di-n-butyl-1-stanna-2,5-cyclohexadiene (2), readily available from 1,4-pentadiyne and di-n-butylstannane,[2,3] was treated with 1 equiv of n-butyllithium at -40° for 1.5 hr in ether to form 1Z,4Z-1-lithio-5-tributylstannyl-1,4-pentadiene (3) which was allowed to react with excess ethylene oxide and 1 equiv of boron trifluoride etherate at -40° for 2 hr and then 23° for 1 hr to give after extractive isolation and chromatography on silica gel (sg) the Z,Z-alcohol 4 in 71% yield.[4] The alcohol 4 was transformed into the corresponding triphenylphosphonium iodide (colorless, hygroscopic solid) in 69% yield by the sequence: (1) tosylation (1.2 equiv of tosyl chloride in pyridine at 0° for 3 hr and 23° for 2 hr), (2) displacement of tosylate by 5 equiv of sodium iodide in acetone at reflux for 4 hr to afford the iodide corresponding to 4 (86% overall from 4), and (3) displacement of iodide by triphenylphosphine (10 equiv, 10% by weight in acetonitrile at

reflux for 14 hr). The ylide 5 was generated from the phosphonium salt in tetrahydrofuran (THF) with 1 equiv of lithium diisopropylamide (1 hr at -78°) and then treated at -78° with 4 equiv of hexamethylphosphoramide and methyl 4-formylbutyrate (6)[5] (40 min, -78°) to give the all Z triene 7 contaminated with ca. 10% of the 5,6-E isomer (95% total yield; the mixture was used as such in the next step). Reaction of 7 with 1.3 equiv of iodine in methylene chloride containing 10 equiv of pyridine at -45° for 1.5 hr afforded after quenching at -45°, extractive isolation and sg chromatography (20 : 1 hexane - ether for elution) pure Z,Z,Z-iodotriene 8 in 78% yield. Reaction of 8 with Z-cuprous thiolate 9[6] (as described for the synthesis of 1[1]) in dimethylformamide at 105° for 6 hr gave after extractive isolation and sg chromatography (40 : 1 hexane-ether) methyl 13-thiaarachidonate (10, 75% yield) as a colorless oil; tlc R_f 0.81 (5 : 1 hexane-ether); IR: 1740 $cm.^{-1}$; ^1H NMR ($CDCl_3$): δ 6.05 (d, J = 10.5 Hz, 1H), 6.02 (d, J = 10.5 Hz, 1H), 5.60 (m, 2H), 5.40 (m, 4H), 3.67 (s, 3H), 2.89 (t, J = 6.0 Hz, 2H), 2.82 (t, J = 6.0 Hz, 2H), 2.32 (t, J = 7.3 Hz, 2H), 2.12 (q, J = 7.3 Hz, 4H), 1.71 (tt, 2H), 1.25 - 1.48 (m, 6H), 0.89 (t, J = 6.6 Hz, 3H). Saponification of 10 using 1 : 1 1N aqueous lithium hydroxide - dimethoxyethane at 23° for 4 hr afforded after extractive isolation 13-thiaarachidonic acid (11, > 90% yield).

10-Thiaarachidonic acid (17) was synthesized from 1-tri-n-butylstannyl-1,4-Z,Z-decadiene (12), which was prepared from 3-tri-n-butylstannyl-2-Z-propen-1-ol and Z-1-cuprioheptene as previously described.[7] Reaction of 12 in THF with 1 equiv of n-butyllithium at -4° for 5 min, followed by successive treatment with styrene episulfide (3.5 equiv, -78°, 1 hr) and benzoyl chloride (1.2 equiv, -78°, 0.5 hr) gave the thiol benzoate 13 (74%) as a colorless liquid after extractive isolation and sg chromatography (elution with carbon tetrachloride). The other component for the synthesis of 10-thiaarachidonate was the OBO ester 14[8] which was obtained by coupling of 1Z,4Z-1-lithio-5-tributylstannyl-1,4-pentadiene (3, obtained as described above from 2) with the OBO ester of 4-iodobutyric acid.[8] Iodination of 14 as described above for 8 gave the vinyl iodide 15 (88%). The thiolbenzoate 13 was treated successively with 2 equiv of n-butyllithium (THF, -78°, 1 hr) and 2 equiv of cuprous iodide (-10°, 20 min) to form 16. Addition of dimethylformamide, and the vinyl iodide 15, heating to 100° with distillation of THF and maintenance of the reaction mixture at 100° for 5 hr gave the OBO ester of 10-thiaarachidonic acid (58%) after extractive isolation and sg chromatography (90 : 9 : 1 hexane-ethyl acetate-triethylamine for elution). The OBO ester was cleaved by exposure to sodium bisulfate in 4 : 1 dimethoxyethane-water (20°, 15 min) and subsequent basification with lithium hydroxide and reaction at 23° for 2 hr to afford after acidification to pH 3 and extractive isolation 10-thiaarachidonic acid (17, 98% yield); IR: 1706 $cm.^{-1}$; ^1H NMR ($CDCl_3$): δ 6.01 - 6.06 (two d, J = 9.2, 8.9 Hz, 2H), 5.48 - 5.70 (m, 2H), 5.25 - 5.48 (m, 4H), 2.89 (m, 4H), 2.37 (t, J = 7.6 Hz, 2H), 1.90 - 2.25 (m, 4H), 1.72 (tt, 2H), 1.16 - 1.53 (m, 6H), 0.89 (t, J = 6.6 Hz, 3H); UV (ethanol - water, 1 : 1): 236 nm.

Biochemical studies with 13-thiaarachidonate (11) and 10-thiaarachidonate (17) will be reported in detail elsewhere. Briefly, 11 was found to be a time- and O_2-dependent irreversible inhibitor of soybean lipoxygenase (type I) whereas the 10-thia acid 17 was found to serve as a good substrate, in accord with predictions made on the basis of earlier studies.[1,9]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10 R = CH3
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Bu3Sn
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C5H11
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S
C5H11
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17

References and Notes

1. E. J. Corey, J. R. Cashman, T. M. Eckrich, and D. R. Corey, J. Am. Chem. Soc., 107, 713 (1985).
2. P. Jutzi and J. Baumgärtner, J. Organomet. Chem., 148, 257 (1978).
3. E. J. Corey and J. Kang, Tetrahedron Letters, 23, 1651 (1982).
4. Structural assignments were supported by 270 MHz proton magnetic resonance, infrared and mass spectral measurements using chromatographically purified and homogeneous samples. All reactions involving air sensitive reactants or products were conducted under an inert atmosphere.
5. Prepared from methyl 3-chloroformylbutyrate by modified Rosenmund reduction (H_2, 1 atm, 5% Pd-C, THF, 2,6-lutidine, 23°).
6. Cuprous thiolate 9 was generated from Z-1-heptenylthiolbenzoate (T. M. Eckrich Ph. D. dissertation, Harvard University, 1984) by reaction with 2 equiv of n-butyllithium in THF at -78° for 45 min followed by treatment with 1 equiv of cuprous iodide.[1] Pure Z-1-heptenylthiolbenzoate was synthesized from Z-1-lithioheptene[7] and styrene episulfide with subsequent reaction with benzoyl chloride and sg chromatography.
7. E. J. Corey and T. M. Eckrich, Tetrahedron Letters, 25, 2419 (1984).
8. E. J. Corey, K. Kyler and N. Raju, Tetrahedron Letters, 25, 5115 (1984).

9. This research was assisted financially by a grant from the National Institutes of Health.

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