but we have found that our reactions are not affected.

Examination of Table I reveals that the reaction proceeds with complete regio- and stereochemical control with a variety of vinyllithiums. The Z/E ratios were determined by examination of the 360-MHz NMR spectra and reflect those of the precursor vinyl halides. The ortho ester (entry 7) is of interest in that it provides ready access to α-methylene lactones. Of greater interest is the δ-alkoxyallylboronates (entries 8–11) in that these provide the first operational equivalent to α-alkoxy carbanions **6** and **7**.[14]

6 7

In conclusion we have developed a regio- and stereospecific synthesis of allylboronates which is operationally simple and may be used to prepare reagents with diverse substitution patterns. The attractiveness of this approach is further augmented by the large number of methods available for the preparation of stereochemically pure vinyllithium reagents[11] and precursor vinyl halides[13] with a variety of functionality. We are currently exploring the application of this methodology in natural product synthesis.[15]

Registry No. (*E*)-**1** ($R_1 = R_3 = H$, $R_2 = Me$), 6386-72-7; (*Z*)-**1** ($R_1 = R_3 = H$, $R_2 = Me$), 6524-17-0; **1** ($R_1 = R_2 = H$, $R_3 = Me$), 6386-71-6; **1** ($R_1 = R_3 = Me$, $R_2 = H$), 57012-95-0; **1** ($R_1 = R_2 = H$, $R_3 = C(OEt)_3$), 87938-75-8; **1** ($R_1 = R_3 = H$, $R_2 = THPOCH_2$), 87938-76-9; **2**, 83622-42-8; (*E*)-**4** ($R_1 = R_3 = H$, $R_2 = Me$), 69611-02-5; (*Z*)-**4** ($R_1 = R_3 = H$, $R_2 = Me$), 69611-01-4; (*E*)-**4** ($R_1 = R_3 = Me$, $R_2 = H$), 87938-71-4; (*Z*)-**4** ($R_1 = R_3 = Me$, $R^2 = H$), 87938-72-5; (*E*)-**4** ($R_1 = R_3 = H$, $R_2 = THPOCH_2$), 87938-73-6; (*Z*)-**4** ($R_1 = R_3 = H$, $R_2 = THPOCH_2$), 87938-74-7; **5** (R = Ph, $R_1 = R_2 = R_3 = H$) (isomer 1), 52922-10-8; **5** (R = Ph, $R_1 = R_2 = R_3 = H$) (isomer 2), 52922-19-7; **5** (R = 3-(benzyloxymethyl)-oxiran-2-yl)$R_1 = R_3 = H$, R_2 Me), 87938-62-3; **5** (R = Ph, $R_1 = R_3 = Me$, $R_2 = H$) (isomer 1), 87938-63-4; **5** (R = Ph, $R_1 = R_3 = Me$, $R_2 = H$) (isomer 2), 87938-64-5; **5** (R = $AcOCH_2CH_2$, $R_1 = R_3 = H$, $R_2 = THPOCH_2$) (isomer 1), 87938-67-8; **5** (R = $AcOCH_2CH_2$, $R_1 = R_3 = H$, $R_2 = THPOCH_2$) (isomer 2), 87984-11-0; **5** (R = $PhSCH_2CH_2$, $R_1 = R_3 = H$, $R_2 = THPOCH_2$) (isomer 1), 87938-68-9; **5** (R = $PhSCH_2CH_2$, $R_1 = R_3 = H$, $R_2 = THPOCH_2$) (isomer 2), 87984-12-1; **5** (R = C_5H_{11}, $R_1 = R_3 = H$, $R_2 = THPOCH_2$) (isomer 1), 87938-69-0; **5** (R = C_5H_{11}, $R_1 = R_3 = H$, $R_2 = THPOCH_2$) (isomer 2), 87984-13-2; **5** (R = (*E*)-PhCH=CH, $R_1 = R_3 = H$, $R_2 = THPOCH_2$) (isomer 1), 87938-70-3; **5** (R = (*E*)-PhCH=CH, $R_1 = R_3 = H$, $R_2 = THPOCH_2$) (isomer 2), 87984-14-3; PhCHO, 100-52-7; $AcOCH_2CH_2CHO$, 18545-28-3; $PhSCH_2CH_2CHO$, 27098-65-3; $C_5H_{11}CHO$, 66-25-1; (*E*)-PhCH=CHCHO, 14371-10-9; α-(2-cyclohexen-1-yl)benzenemethanol (isomer 1), 87938-65-6; α-(2-cyclohexen-1-yl)benzenemethanol (isomer 2), 87938-66-7; 1-cyclohexenyllithium, 37609-34-0; 3-[(benzyloxy)methyl]oxirane-2-carboxaldehyde, 87938-77-0; 2-(2-cyclohexen-1-yl)tetramethyl-2-bora-1,3-dioxacycloheptane, 87938-78-1.

Supplementary Material Available: Experimental details for entries 2 and 11 of Table I (2 pages). Ordering information is given on any current masthead page.

(14) Schlessinger has prepared the anion of a β-alkoxy carboxylate, but this is not an anion equivalent. See: Herrmann, J. L.; Schlessinger, R. H. *Tetrahedron Lett.* **1977**, 4575. Seebach later exploited this chemistry. See: Seebach, D. In "Modern Synthetic Methods 1980"; Scheffold, R., Ed.; Verlag Chemie: Weinheim/Bergstr., Germany, 1980; pp 91–171.

(15) We acknowledge support of this work by NIH and NSF.

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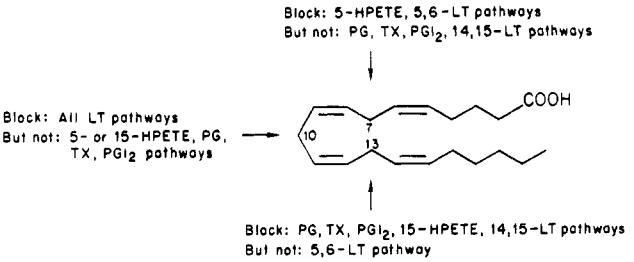
Ethanoarachidonic Acids. A New Class of Arachidonic Acid Cascade Modulators. 1. Monoethano Compounds[1]

Summary: The rational design, total synthesis, and preliminary biological data of ethanoarachidonic acids **1–3** are described.

Sir: Biosynthetic considerations of the various biologically active metabolites of arachidonic acid (AA) suggest that the major peroxidation pathways, including the cyclooxygenase pathway leading to prostaglandins and thromboxanes[3] and the lipoxygenase pathways leading to mono- and polyhydroxyarachidonic acids and leukotrienes,[4] begin with an enzymatic abstraction of a hydrogen radical from the bis-allylic position 7, 10, or 13. Therefore, by blocking one or more of these positions of arachidonic acid, it might be possible to "shut off" one or more peroxidation pathways at will.[5] Such analogues of arachidonic acid should only undergo the "allowed" transformations and, furthermore, may prove to be selective inhibitors of certain enzymes of the AA cascade by successfully competing for receptors with the parent arachidonic acid or some of its early metabolites. This strategy for modulation of the AA cascade is summarized below.



As one of the most promising and convenient ways to block these active positions we considered the introduction of an ethano group in the form of a cyclopropane ring.[6]

(1) This work was partially disclosed at the 16th ACS-MARM meeting, Newark, DE, April 21–23, 1982.

(2) (a) Fellow of the A. P. Sloan Foundation, 1979–1983. (b) Recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980–1984. (c) J. S. Guggenheim Fellow, 1984. (d) NSF Minority Graduate Fellow, 1982–1985.

(3) Reviews: (a) Samuelsson, B.; Goldyne, M.; Granström, E.; Hamberg, M.; Hammarstrom, S.; Malmsten, C. *Annu. Rev. Biochem.* **1978**, *47*, 997. (b) Nicolaou, K. C.; Smith, J. B. *Annu. Rep. Med. Chem.* **1979**, *14*, 178. (c) Schaaf, T. K. *Ibid.* **1977**, *12*, 182.

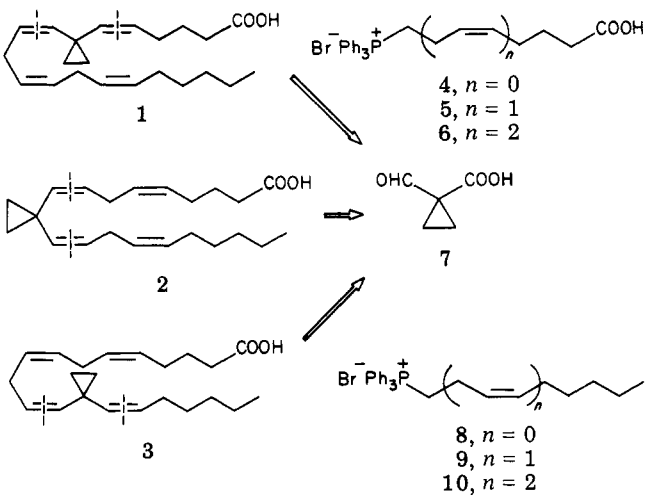
(4) Reviews: (a) Corey, E. J. *Experientia* **1982**, *38*, 1259. (b) Samuelsson, B. *Pure Appl. Chem.* **1981**, *53*, 1203; *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 902. (c) Bailey, D. M.; Casey, f. B. *Annu. Rep. Med. Chem.* **1982**, *17*, 203. (d) Bailey, D. M.; Chakrin, L. W. *Ibid.* **1981**, *16*, 213. (e) Borgeat, P.; Sirois, P. *J. Med. Chem.* **1981**, *24*, 121.

(5) An alternative approach to the selective modulation of the AA cascade, utilizing dehydroarachidonic acids, was recently developed by E. J. Corey: (a) Corey, E. J.; Park, H. *J. Am. Chem. Soc.* **1982**, *104*, 1750. (b) Corey, E. J.; Munroe, J. E. *Ibid.* **1982**, *104*, 1752. (c) Corey, E. J.; Kang, J. *Tetrahedron Lett.* **1982**, *23*, 1651. (d) Corey, E. J.; Kantner, S. S.; Lansbury, P. T., Jr. *Tetrahedron Lett.* **1983**, *24*, 265. For other acetylenic arachidonic acids see: (e) Wilhem, T. E.; Sankarappa, S. K.; VanRollins, M.; Sprecher, H. *Prostaglandins* **1981**, *21*, 323. (f) Sun, F. F.; McGuire, J. C.; Morton. D. R.; Pike, J. E.; Sprecher, H.; Kunan, W. H. *Ibid.* **1981**, *21*, 333. (g) Eiter, K.; Lieb, F.; Disselnkötter, H.; Oediger, H. *Liebigs Ann. Chem.* **1978**, 658.

(6) After our initial disclosure of this strategy and our preliminary report on the synthesis of compound **1**[1] we became aware of similar work: (a) Cohen, N.; Rosenberger, M.; Lovey, A. J.; Aig, E.; Banner, B. L.; Lopresti, R. J.; Weber, G. "Abstracts of Papers", 186th National Meeting of the American Chemical Society, Washington, DC, Aug 28–Sept 2, 1983; American Chemical Society: Washington, DC, 1983; MEDI 15. (b) Perchonock, C. D.; Finkelstein, J. A.; Uzinskas, I.; Gleason, J. G.; Sarau, H. M.; Cieslinski, L. B., *Tetrahedron Lett.* **1983**, *24*, 2457. (c) Pfister, J. R.; Krishna Murthy, D. V. *J. Med. Chem.* **1983**, *26*, 1099. (d) Reference 7a. (e) The synthesis of an eicosanoid cyclooxygenase inhibitor possessing a 13,13-dimethyl blocking arrangement to prevent H abstraction at that position has been reported: Yeh, C.-L.; Dawson, M.; Hemler, M. E.; Lands, W. E. M. *Tetrahedron Lett.* **1977**, 4257.

0022-3263/83/1948-5400$01.50/0

Scheme I

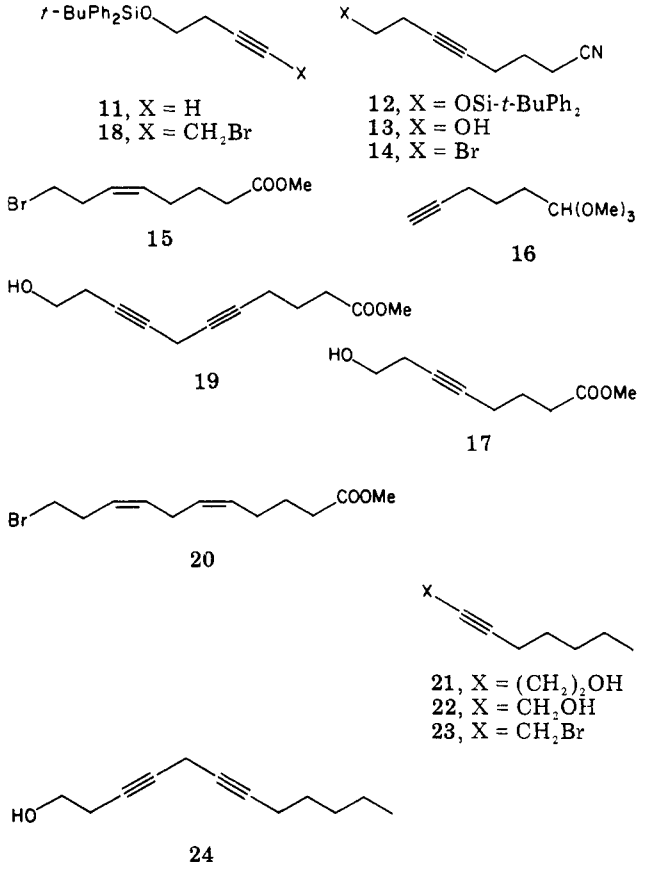


This approach not only would potentially reach the above-mentioned goals but also would be expected to induce higher rigidity and stability to the arachidonic acid skeleton and thus enhance its biological potential. In this and the following paper[23] we report the efficient syntheses of the complete set of these designed ethanoarachidonic acids and preliminary biological data. These syntheses are characterized by (a) high geometrical stereocontrol by utilizing Lindlar hydrogenations and Wittig reactions under specific experimental conditions and (b) minimization of protection–deprotection operations by using suitably substituted building blocks that allow selectivity and further direct elaboration.

A common strategy for constructing the arachidonic acid skeleton of the monoethano compounds **1–3** was devised as depicted in Scheme I. This retrosynthetic analysis disconnects each compound at the double bonds adjacent to the cyclopropane ring by retro-Wittig-type operations leading to the common central fragment **7**, the α fragments **4–6** and the ω fragments **8–10**. As described below, this strategy was successfully executed after securing these fragments in stereochemically pure form by acetylene alkylation and selective hydrogenation techniques.

Alkylation of the lithio derivative (1.1 equiv of *n*-BuLi, THF, −78 to +25 °C) of acetylene **11** (Chart I) with Br-$(CH_2)_3$Cl (1.5 equiv, 0–25 °C) followed by cyanation (5 equiv of NaCN, HMPA, 25 °C)[8] led to **12**[9] (90%) which was desilylated (1.1 equiv of *n*-Bu_4NF, THF, 25 °C) to **13**, brominated (1.3 equiv of CBr_4, 1.3 equiv of Ph_3P, CH_2Cl_2, 0 °C)[10] to **14**, hydrogenated (H_2, Lindlar catalyst, MeOH, 25 °C), and finally transformed to methyl ester **15** (1.2 equiv of MeCOCl, MeOH, 0 °C) in 80% overall yield from **12**. An alternative and shorter route to this fragment involved ortho ester **16**,[11] which was first converted to **17** in 80% yield by (a) metalation (1.3 equiv of *n*-BuLi, THF, 1.0 equiv of TMEDA, −30 °C) (b) quenching with excess ethylene oxide, and (c) hydrolysis (MeOH, 0.05 equiv of PPTS, 25 °C) and then to **15** (95% overall) by Lindlar

Chart I



hydrogenation (CH_2Cl_2, 25 °C) and bromination as above (**13** → **14**). Conversion of **15** to the desired phosphonium salt **5** proceeded smoothly after hydrolysis of the ester (LiOH, THF–H_2O, 25 °C, 95%) and heating (70 °C) with Ph_3P in MeCN (87%).

For the synthesis of **6**, compound **11** was converted to bromide **18** [1.1 equiv of *n*-BuLi, THF, 0 °C followed by excess $(CH_2O)_n$, 25 °C (84%), and then bromination as in **13** → **14**, 95%] which was then used to alkylate ortho ester **16** (1.1 equiv of *n*-BuLi, 0.5 equiv of CuI, THF, −78 to +25 °C),[11] leading, after hydrolysis (MeOH, 0.05 equiv of CSA, 25 °C) and desilylation (as in **12** → **13**), to intermediate **19** (68% overall from **18**). The transformation of **19** to **6** proceeded cleanly as in **17** → **5**.

As starting materials for the synthesis of **9**[12a,b] and **10**,[12c] we used the commercially available[13] acetylenic alcohols **21** and **22** which were subjected to similar methodology and with similar results. Noteworthy here is the elongation of **22** to **24** via bromide **23** and direct reaction with 3-butyn-1-ol (1.5 equiv) pretreated with EtMgBr (2.8 equiv) and CuCl (2.0 equiv) in THF (0 °C) in over 80% yield despite the absence of any OH protection.[12d]

The crystalline cyclopropane derivative **7** was synthesized in large quantities by selective reduction (2.2 equiv of DIBAL, CH_2Cl_2, −78 °C followed by acid workup, 85%) of the corresponding nitrile carboxylic acid (readily available) according to Singh and Danishefsky.[14] This

(7) (a) Arai, Y.; Shimoji, K.; Konno, M.; Konishi, Y.; Okuyama, S.; Iguchi, S.; Hayashi, M.; Miyamoto, T.; Toda, M. *J. Med. Chem.* **1983**, *26*, 72. (b) Arai, Y.; Konno, M.; Shjimoji, K.; Konishi, Y.; Niwa, H.; Toda, M.; Hayashi, M. *Chem. Pharm. Bull.* **1982**, *30*, 379.

(8) Shaw, J. E.; Hsia, D. Y.; Parries, G. S.; Sawyer, T. K. *J. Org. Chem.* **1978**, *43*, 1017.

(9) All new compounds were fully characterized by spectroscopic means (^1H, NMR, IR, MS) and exhibited satisfactory analytical and/or high-resolution mass spectra data. Yields refer to isolated, chromatographically and spectroscopically homogeneous materials.

(10) Kocienski, P. J.; Cernigliaro, G.; Feldstein, G. *J. Org. Chem.* **1977**, *42*, 353.

(11) Just, G.; Luthe, C. *Tetrahedron Lett.* **1982**, *23*, 1331.

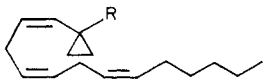
(12) (a) Rokach, J.; Girard, Y.; Guindon, Y.; Atkinson, J. G.; Larue, M.; Young, R. N.; Masson, P.; Holme, G. *Tetrahedron Lett.* **1980**, *21*, 1485. (b) For an alternative synthesis of the iodide salt corresponding to **9** see: Corey, E. J.; Arai, Y.; Mioskowski, C. *J. Am. Chem. Soc.* **1979**, *101*, 6748. (c) Compound **10** has recently been synthesized in a similar fashion.[7] (d) For similar couplings see: (i) Gleason, J. G.; Bryan, D. B.; Kinzig, C. M. *Tetrahedron Lett.* **1980**, *21*, 1129. (ii) Kigoshi, H.; Shizuri, Y.; Niwa, H.; Yamada, K. *Tetrahedron Lett.* **1981**, *22*, 4729.

(13) Farchan Laboratories, Willoughby, OH.

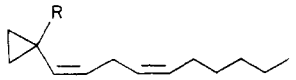
(14) Singh, R. K.; Danishefsky, S. *J. Org. Chem.* **1975**, *40*, 2969.

compound was chosen as an ideal source of the requisite building block with self-protecting functionality, thus avoiding extra protection–deprotection steps.

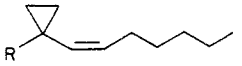
In coupling the three fragments toward the desired targets, molecules **1–3**, we relied on the Wittig reaction and specific modifications of it which led predominantly to the required *Z* geometry at the newly generated double bonds. In these circumstances this task became highly demanding due to the presence of the bulky cyclopropane ring. Indeed, condensation of the ylide derived from **10** (3.0 equiv of **10**, 3.0 equiv of *n*-BuLi, THF–HMPA (5:1), −78 °C) with the sodium salt of **7** (1.1 equiv of NaH, THF–HMPA (5:1), 0 °C) at −78 → to +25 °C led, after CH_2N_2 treatment, to **25a** as a mixture with a ca. 8:1 *Z*/*E* ratio at the newly



25



26



27

a, R = COOMe; b, R = CH_2OH; c, R = CHO

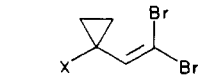
generated double bond (70%). Reduction of **25a** (2.2 equiv of DIBAL, CH_2Cl_2, −78 °C, 90%) followed by chromatographic removal[15] of the undesired isomer and mild oxidation (1.2 equiv of CrO_3·pyr·HCl, CH_2Cl_2, 25 °C[16] or 6.0 equiv of SO_3·pyr, 10.0 equiv of Et_3N, Me_2SO, 25 °C[17]) led to aldehyde **25c** (90%). Finally, coupling of **25c** with the standard PG ylide derived from **4** according to Bestmann's conditions[18] (1.5 equiv of **4**, 3.0 equiv of $NaN(SiMe_3)_2$, DME, 0–25 °C) furnished 7,7-ethanoarachidonic acid (**1**) in 70% yield.[19]

Similarly, 10,10-ethanoarachidonic acid (**2**) was constructed by (a) condensing the ylide derived from the phosphonium salt **9** (3.0 equiv of **9**, 3.0 equiv of *n*-BuLi, THF–HMPA (5:1), −78 °C) with the sodium salt of **7** (−78 to +25 °C) to afford, after CH_2N_2 treatment, the methyl ester **26a** (70% yield, ca. 8:1 *Z*/*E*) which was converted to aldehyde **26c** as in **25a** → **25c**. Attachment of the α fragment **5** proceeded smoothly under basic conditions (2.0 equiv of **5**, 4.0 equiv of $NaN(SiMe_3)_2$, HMPA, 25 °C) and led to 10,10-ethanoarachidonic acid (**2**, 70%).[19]

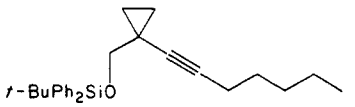
Finally, condensation of aldehyde **7** with the ylide generated from **8** (1.5 equiv of **8**, 2.5 equiv of *t*-BuOK, THF–HMPA (7:1), 25 °C, and then add **7** at −78 to +25 °C) gave, after esterification (CH_2N_2), **27a** in 85% yield and with a *Z*/*E* ratio of ca. 91:9. After reduction, separation of the *Z* and *E* isomers,[15] and oxidation as in **25a** → **25c** above, the aldehyde **27c** was obtained and reacted with the ylide corresponding to **6** (2.0 equiv of **6**, 4.0 equiv of $NaN(SiMe_3)_2$, HMPA, 25 °C), leading to 13,13-ethanoarachidonic acid (**3**) in 80% yield.[19]

An alternative and completely stereocontrolled total synthesis of 13,13-ethanoarachidonic acid (**3**) based on the acetylene unit as a stereoselective precursor for each of the four *Z* double bonds was also developed. Thus, starting with the methyl ester of **7** (CH_2N_2, 0 °C, 100%), we prepared the dibromo olefin **28** (2.0 equiv of CBr_4, 2.0 equiv of Ph_3P, CH_2Cl_2, 0 °c, 70%)[20] (Chart II) and subjected it to the following transformations: (a) reduction to **29** (2.2 equiv of DIBAL, CH_2Cl_2, −78 °C, 80%); (b) silylation to **30** (1.2 equiv of *t*-$BuMe_2SiCl$, 1.3 equiv of Et_3N, 0.04 equiv of DMAP, CH_2Cl_2, 90%); (c) metalation (2.2 equiv of *n*-BuLi, THF, −78 °C) followed by quenching with excess $I(CH_2)_4CH_3$ (−78 °C to reflux) to give **31** (60%); (d) mild hydrogenation (H_2, $Pd/BaSO_4$ catalyst, pyridine, 25 °C)[21] to **32** (100%); (e) desilylation and oxidation as described above to afford **27e**. Similar chemistry was then applied to convert **27c** to **35**: **27c** → **33** (as in the synthesis of **28**), **33** → **34** (2.2 equiv of *n*-BuLi, THF, −78 °C then excess ClCOOEt, 99%), **34** → **35** (as in **28** → **29**, 92%).

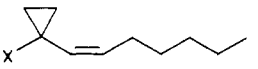
Chart II



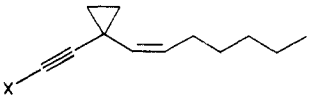
28, X = COOMe
29, X = CH_2OH
30, X = CH_2OSi-*t*-$BuPh_2$



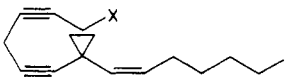
31



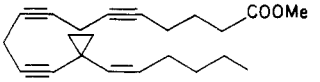
32, X = CH_2OSi-*t*-$BuPh_2$
33, X = CH=CBr_2



34, X = COOEt
35, X = CH_2OH
36, X = CH_2Br



37, X = OSi-*t*-$BuPh_2$
38, X = OH
39, X = Br



40

Conversion of **35** to the bromide **36** (as in **13** → **14**, 100%), followed by coupling with the *tert*-butyldiphenylsilyl ether of 2-propyn-1-ol (1.1 equiv of *n*-BuLi, 0.5 equiv of CuI, THF, −78 to +25 °C, 91%) led to **37**, which was transformed to the bromide **39** by deprotection (75%) and bromination (as in **13** → **14**, 92%). Finally, coupling of this bromide with **16** as above (**16** → **19**) led to **40** (88% yield) which was hydrogenated (H_2, Lindlar catalyst, ethyl acetate, 25 °C, 75%), affording the methyl ester of **3**.

Biological studies to define the profiles of these stable and now readily available molecules are in progress, and preliminary results reveal interesting and selective properties including, in vitro inhibition of SRS-A biosynthesis, 5-lipoxygenase inhibition, phospholipase A_2 inhibition, and antithrombotic activity.[22] In the following paper[23] we describe the total synthesis of the remaining members of this intriguing family of arachidonic acids.[24]

(15) Flash column, silica, ether–petroleum ether mixtures.
(16) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.
(17) Parikh, J. R.; Doering, W. von E. *J. Am. Chem. Soc.* **1967**, *89*, 5505.
(18) Bestmann, H. J.; Stransky, W.; Vostrowsky, O. *Chem. Ber.* **1976**, *109*, 1694. See also: Hanessian, S.; Lavellee, P. *Can. J. Chem.* **1981**, *59*, 870.
(19) Minor undesired isomers were removed by flash column chromatography (silica, ether–petroleum ether mixtures) of the esterification product (CH_2N_2, ether, 0 °C), followed by recovery of the desired acid by hydrolysis (LiOH, THF, H_2O, 25 °C).
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(22) For example, 7,7-ethanoarachidonic acid (**1**) exhibited the following activities: (a) at 10 μM, 82 ± 6% inhibition of ionophore A23187-induced SRS-A biosynthesis in rat peritoneal cells; (b) at 100 μM, 86% inhibition of conversion of ^{14}C-AA to ^{14}C-5-HETE in supernatant from RBL-1 cells; (c) at 100 μM, 100% inhibition (IC_{50} = 18) of phospholipase A_2 (from Naja Naja snake venom, liposomes of dipalmitoylphosphatidylcholine as substrate); (d) at 80 μM, 50% inhibition of AA-induced platelet aggregation (human gel-filtered platelet suspension containing 0.2% albumin). We are indebted to Drs. N. Cohen and A. Welton of Roche Research Center, Hoffmann-La Roche, Nutley, NJ, for tests a–c and to Professor J. B. Smith of the Thrombosis Research Center, Temple Medical School, Temple University, Philadelphia, PA, for test d. Full biological data will be reported elsewhere in due course.
(23) Nicolaou, K. C.; Hernandez, P. E.; Ladduwahetty, T.; Randall, J. L.; Webber, S. E.; Li, W. S.; Petasis, N. A. *J. Org. Chem.*, following paper in this issue.

Supplementary Material Available: Listing of selected physical properties of the methyl esters of 1–3 and of aldehydes **25c–27c** (4 pages). Ordering information is given on any current masthead page.

(24) This work was financially supported by the A. P. Sloan Foundation, the Camille and Henry Dreyfus Foundation, Merck Sharp and Dohme, USA, Smith Kline & Boeckmann, USA, Grünenthal Gmbh, West Germany, the University of Pennsylvania, and the National Science Foundation through a minority fellowship to P.E.H.

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Received August 23, 1983

Ethanoarachidonic Acids. A New Class of Arachidonic Acid Cascade Modulators. 2. Polyethano Compounds

Summary: The total synthesis and preliminary biological data of di- and triethanoarachidonic acids 1–4 are described.

Sir: In the preceding paper[2] we discussed the rational design of certain ethanoarachidonic acids and the total synthesis of the 7,7, 10,10, and 13,13, members of this series of compounds. In this paper we detail the total synthesis of the polyethano members of this series, namely, compounds 1–4 (Chart I).

The synthesis of these modified arachidonic acids proceeded along lines indicated by the disconnections at all double bonds adjacent to cyclopropanes as shown in Chart I. The chemistry utilized for the synthesis of these members of the series is similar to that outlined in the preceding paper with the important introduction of the new cyclopropyl reagent **6**[3] (Chart II). This phosphonium salt was prepared from **5**[2] as follows: (a) CH_2N_2 Et_2O, 0 °C, 100%; (b) 0.6 equiv of $NaBH_4$, MeOH, −35 °C, 75%; (c) 1.3 equiv of CBr_4, 1.5 equiv of Ph_3P, CH_2Cl_2 0 °C, 90%; (d) 1.3 equiv of Ph_3P, MeCN, 65 °C, 90%. As shown below, **6** is a convenient means for attachment of the cyclopropyl unit and should prove to be of general use for this purpose.

Condensation of the ylide derived from **6** [1.2 equiv of **6**, 1.1 equiv of $NaN(SiMe_3)_2$,[4] DME-HMPA (4:1), −30 to +25 °C] with aldehydes **7**[2] and **10**[2] proceeded in 65–85% yields and *Z*/*E* ratios ranging from 55:45 to 85:15, furnishing methyl esters **8** and **11**, respectively. These rather poor *Z*/*E* ratios can be attributed to the bulky cyclopropane substituents on both sites of the newly formed double bond. Reduction of methyl ester **8** (2.2 equiv of DIBAL, CH_2Cl_2, −78 °C, 94%) to the corresponding alcohol, followed by chromatographic removal[5] of the undesired *E* isomer and oxidation (6 equiv of SO_3·pyr, 10 equiv of Et_3N, Me_2SO, 25 °C, 90%) gave aldehyde **9**. Condensation of **9** with the standard prostaglandin ylide (5.0 equiv of $Br^-Ph_3P^+(CH_2)_4COOH$, 9.0 equiv of NaN-

Chart I

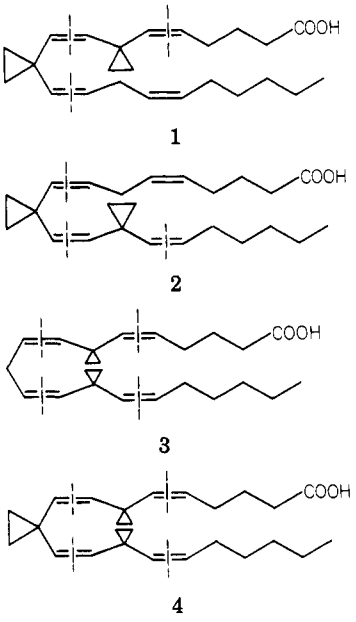
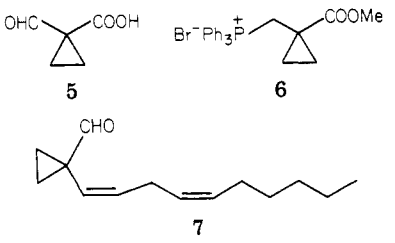
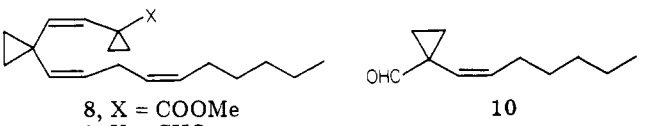
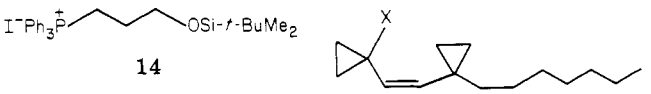
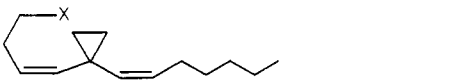


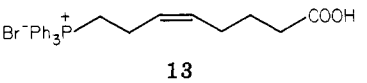
Chart II

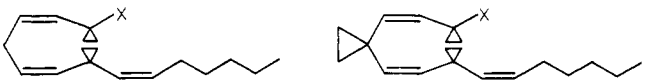












(1) (a) Fellow of the A. P. Sloan Foundation, 1979–1983. (b) Recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980–1984. (c) J. S. Guggenheim Fellow, 1984. (d) NSF Minority Graduate Fellow, 1982–1985.

(2) Nicolaou, K. C.; Petasis, N. A.; Li, W. S.; Ladduwahetty, T.; Randall, J. L.; Webber, S. E.; Hernandez, P. E. *J. Org. Chem.*, preceding paper in this issue.

(3) All new compounds were fully characterized by spectroscopic means (^1H NMR, IR, MS) and exhibited satisfactory analytical and/or high-resolution mass spectral data. Yields refer to isolated, chromatographically and spectroscopically homogenerous materials.

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(5) Flash column, silica gel, ether–petroleum ether mixtures.

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