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.

K. C. Nicolaou,*[2a-c] N. A. Petasis, W. S. Li
T. Ladduwahetty, J. L. Randall
S. E. Webber, P. E. Hernandez[2d]
Department of Chemistry
University of Pennsylvania
Philadelphia, Pennsylvania 19104
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

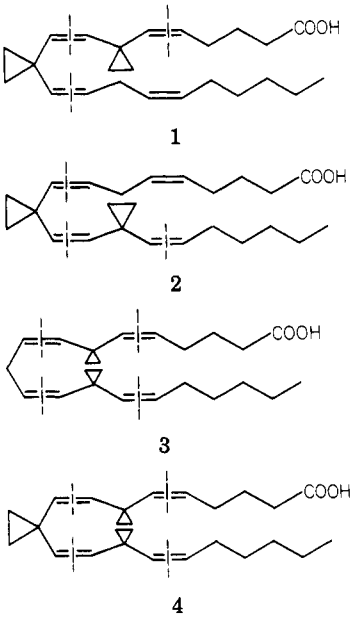
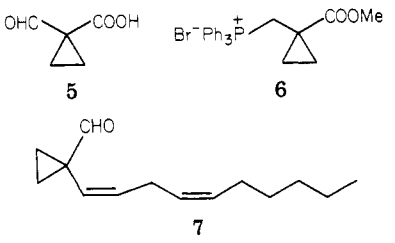
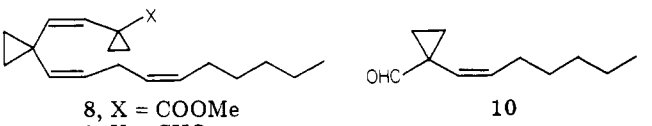
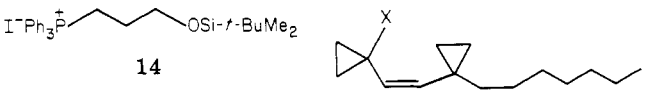
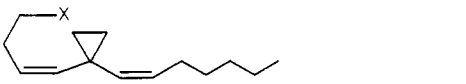


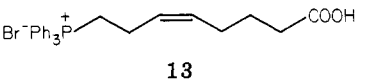
Chart II

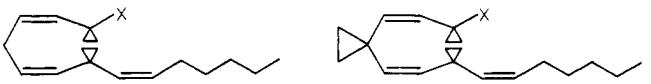












(1) (a) Fellow of the A. P. Sloan Foundation, 1979–1983. (b) Recipient of a Camille and Henry Dreyfus Teacher-Scholar Award, 1980–1984. (c) J. S. Guggenheim Fellow, 1984. (d) NSF Minority Graduate Fellow, 1982–1985.

(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.

(4) Bestmann, H. J.; Stransky, W.; Vostrowsky, O. *Chem. Ber.* **1976**, *109*, 1694.

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

0022-3263/83/1948-5403$01.50/0

$(SiMe_3)_2$, DME, 0 °C)[4] led to 7,7,10,10-diethanoarachidonic acid (1, 70%), in high stereochemical purity.[6]

10,10,13,13-Diethanoarachidonic acid (2) was constructed from methyl ester 11 by similar reactions and in comparable yields. Thus, sequence 11 → 12 was carried out as in 8 → 9 in ca. 80% overall yield. The final coupling of 12 with Wittig reagent 13[2] was performed under slightly different conditions ($NaN(SiMe_3)_2$, HMPA, 25 °C, 70%), leading to 2 in a high Z/E ratio.[6]

The synthesis of 7,7,13,13-diethanoarachidonic acid (3) was initiated again with aldehyde 10[2] which was now condensed with the ylide derived from 14[7] ($NaN(SiMe_3)_2$, DME, 0–25 °C) to form 15 (96%, ca. 20:1 Z/E). Transformation of 15 to phosphonium salt 18 (Ph_3P, MeCN, 70 °C) proceeded conventionally via the alcohol 16 (n-Bu_4NF, THF, 25 °C), chromatographic[5] removal of undesired E isomer, and removal of bromide 17 (1.3 equiv of CBr_4, 1.5 equiv of Ph_3P, CH_2Cl_2, 0 °C). Condensation of the phosphorane derived from 18 ($NaN(SiMe_3)_2$, DME, 0 °C) with the sodium salt of 5 led, after CH_2N_2 treatment, to methyl ester 19 (70%, ca. 20:1 Z/E ratio). Reduction (2.2 equiv of DIBAL, CH_2Cl_2, 0 °C) of 19 followed by isomer separation[5] (90% pure Z isomer) and oxidation as in 8 → 9 furnished 20 (90%) which was coupled with excess of the PG ylide [$Br^-Ph_3P^+(CH_2)_4COOH$, 2 equiv of $NaN(SiMe_3)_2$, DME–HMPA, 3:1, 0–25 °C], leading to the desired acid 3 in 82% yield.[6]

Finally, condensation of 12 with the ylide of 6 ($NaN(SiMe_3)_2$, THF–HMPA, 3:1, −30 to +25 °C) gave 21 (81% yield, ca. 1:1 Z/E ratio). Transformation of 21 to 22 as in 8 → 9 (chromatographic separation at the alcohol stage)[5] followed by coupling with the standard PG ylide under the above-mentioned conditions led to 7,7,10,10,13,13-trieth-anoarachidonic acid (4, 90% yield).[6]

The syntheses described in this set of papers demonstrate clearly the power and limitations of modern synthetic technology in building carbon frameworks by stereocontrolled double bond construction and by acetylene alkylation reactions and make available a number of rationally designed and important biological tools for investigating the arachidonic acid cascade.

Extensive biological investigations of these polyethanoarachidonic acids and their methyl esters are currently in progress,[8] and preliminary data suggest powerful modulatory properties within the AA cascade, including lipoxygenase inhibitory activities.[9]

Acknowledgment. We express our many thanks to Professors A. M. Lefer and J. B. Smith for helpful discussions and to Dr. G. T. Furst of the NMR facility, Chemistry Department, University of Pennsylvania, for valuable spectroscopic assistance. Gratefully acknowledged are also the A. P. Sloan Foundation, the Camille and Henry Dreyfus Foundation, Merck Sharp & Dohme, USA, Smith Kline & Boeckmann, USA, Grünenthal Gmbh, West Germany, and the University of Pennsylvania for their generous financial support and the National Science Foundation for a minority fellowship to P.E.H.

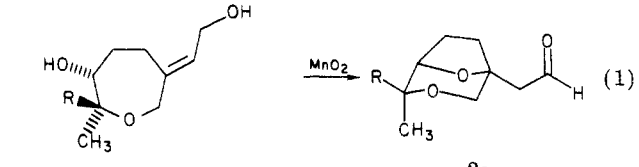
Supplementary Material Available: Listing of full spectroscopic (^1H NMR, IR, MS) data of the methyl esters of 1–4 and of aldehydes 9, 12, 20, and 22 (5 pages). Ordering information is given on any current masthead page.

K. C. Nicolaou,*[1a-c] P. E. Hernandez[1d]
T. Ladduwahetty, J. L. Randall, S. E. Webber
W. S. Li, N. A. Petasis
Department of Chemistry
University of Pennsylvania
Philadelphia, Pennsylvania 19104
Received August 23, 1983

New Route to Biologically Active 3,8-Dioxabicyclo[3.2.1]octane Derivatives Related to Zoapatanol

Summary: A new approach to the total synthesis of novel biologically active 3,8-dioxabicyclo[3.2.1]octane derivatives is described with the stereospecific oxidative cyclization of 1,5-dienes as the key step.

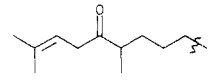
Sir: Two novel oxepane-containing diterpenes, zoapatanol (**1a**) and montanol (**1b**), possessing unique "uteroevacuant" activity, have recently been isolated from the leaves of the zoapatle plant (*Montanoa tomentosa*).[1-3] In connection with work done on the structure elucidation, a very facile transformation of zoapatanol (**1a**) to the novel 3,8-dioxabicyclo[3.2.1]octane derivative **2a** was reported by chemists at the Ortho Pharmaceutical Corp., as shown in eq 1.[1a] Recently, it has been shown that the bicyclic



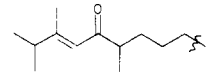
(1)

2a

1a, R =



b, R =



derivatives **3a** and **3b** (Scheme I, as mixtures of diastereomers) have pharmacological profiles similar to those of

(6) Trace amounts of isomeric materials were chromatographically removed at the methyl ester stage (CH_2N_2, 0 °C) from where the acid could easily be regenerated (LiOH, THF–H_2O, 25 °C).

(7) Prepared in 80–90% overall yield from 3-chloro-1-propanol by sequential displacement of chloride (NaI, acetone, Δ), silylation (t-$BuMe_2SiCl/Et_3N$/DMAP, CH_2Cl_2), and heating with Ph_3P (MeCN, 70 °C).

(8) These investigations are being conducted in the laboratories of Professors A. M. Lefer, Department of Physiology, Thomas Jefferson University, Philadelphia, PA, and J. B. Smith, Thrombosis Research Center, Temple University, Philadelphia, PA.

(9) For example, 10,10,13,13-diethanoarachidonic acid (3) at a 40 μM concentration induced a greater than a twofold increase in the arachidonic acid-induced production of malondialdehyde (MDA) in intact human platelets, strongly suggesting potent and specific inhibition of 12-lipoxygenase. We are indebted to Professor J. B. Smith of the Thrombosis Research Center, Temple Medical School, Temple University, Philadelphia, PA, for these tests. Further studies with these compounds are currently in progress and will be reported in detail in due course.

(1) (a) Levine, S. D.; Adams, R. E.; Chen, R.; Cotter, M. L.; Hirsch, A. F.; Kane, V. V.; Kanojia, R. M.; Shaw, C.; Wachter, M. P.; Chin, E.; Huettemann, R.; Ostrowski, P.; Mateos, J. L.; Noriega, L.; Guzman, A.; Mijarez, A.; Tovar, L. *J. Am. Chem. Soc.* **1979**, *101*, 3404-3405. (b) Kanojia, R. M.; Wachter, M. P.; Levine, S. D.; Adams, R. E.; Chen, R.; Chin, E.; Cotter, M. L.; Hirsch, A. F.; Huettemann, R.; Kane, V. V.; Ostrowski, P.; Shaw, C. J. *J. Org. Chem.* **1982**, *47*, 1310–1319.

(2) Levine, S. D.; Hahn, D. W.; Cotter, M. L.; Greenslade, R. C.; Kanojia, R. M.; Pasquale, S. A.; Wachter, M. P.; McGuire, J. L. *J. Reprod. Med.* **1981**, 524–528.

(3) To our knowledge, the relative configuration at the chiral center in the side-chain of the naturally occurring materials is unknown. All work accomplished to date on modification or synthesis of these compounds in our laboratories and elsewhere deals with mixtures diastereomeric at that center.

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