$(SiMe_3)_2$, 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-triethanoarachidonic 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]

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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.

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(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).

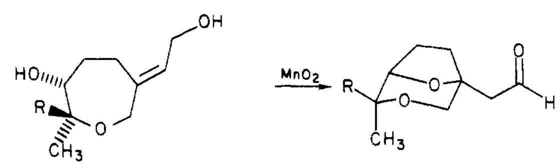
(8) These investigations are being conducted in the laboratories of Professors A. M. Lefer, Department of Physiology, Thomas Jefferson University, Philadelphia, PA, and J. B. Smith, Thrombosis Research Center, Temple University, Philadelphia, PA.

(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.

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

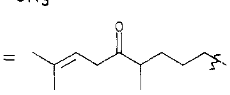
Summary: A new approach to the total synthesis of novel biologically active 3,8-dioxabicyclo[3.2.1]octane derivatives is described with the stereospecific oxidative cyclization of 1,5-dienes as the key step.

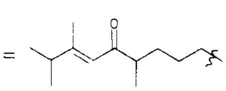
Sir: Two novel oxepane-containing diterpenes, zoapatanol (**1a**) and montanol (**1b**), possessing unique "utero-evacuant" activity, have recently been isolated from the leaves of the zoapatle plant (*Montanoa tomentosa*).[1–3] In connection with work done on the structure elucidation, a very facile 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 = 

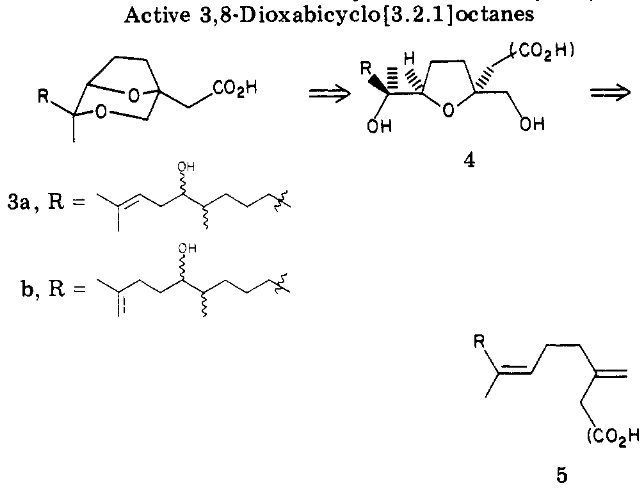
derivatives **3a** and **3b** (Scheme I, as mixtures of diastereomers) have pharmacological profiles similar to those of

(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.

Scheme I. Plan for Total Synthesis of Biologically Active 3,8-Dioxabicyclo[3.2.1]octanes

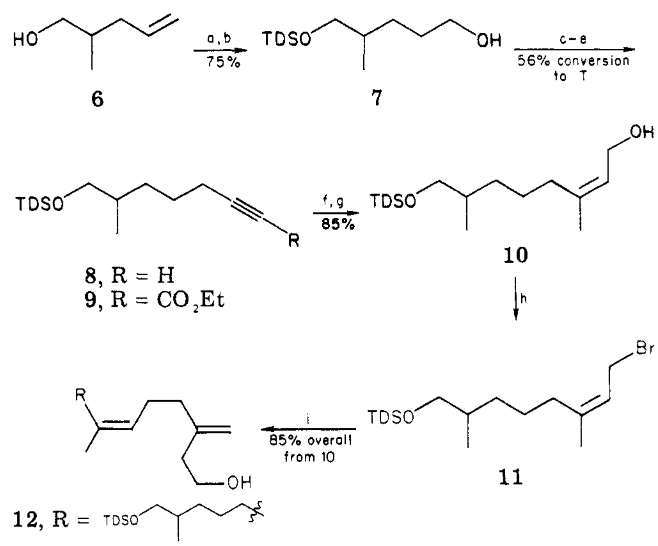


the natural products.[1,2,4-6] The novel structure of zoapatanol has captured the interest of many synthetic chemists, and several total syntheses of zoapatanol have been published in the chemical literature in the last 3 years.[7] In addition, the potentially important biological activity of compounds of type **3** has resulted in studies on the synthesis of structurally simplified monocyclic analogues.[5] An interesting directed total synthesis of compounds **3a**,**b** has been reported in the patent literature.[6]

In this paper we report a new general route to compounds of type **3** based upon utilization of the oxidative cyclization technology under investigation in our laboratories for the past several years.[8] As shown in Scheme I, retrosynthetic disconnection of the C2–O3 bond of a 3,8-dioxabicyclo[3.2.1]octane of type **3** suggests the 2,6-bis(hydroxymethyl)tetrahydrofuran (2,6-$(HOCH_2)_2$THF) **4** as a key intermediate. This is exactly the functional array which may be conveniently constructed in a stereospecific manner by the oxidative cyclization process. Thus, formation of THF **4** would result from oxidative cyclization of a 1,5-diene of type **5**. This approach is novel and quite attractive in its simplicity. Use of the oxidative cyclization process is particularly advantageous since a large positive change in molecular complexity, as defined by Bertz,[9] accrues in the transformation of diene **5** to THF diol **4**.

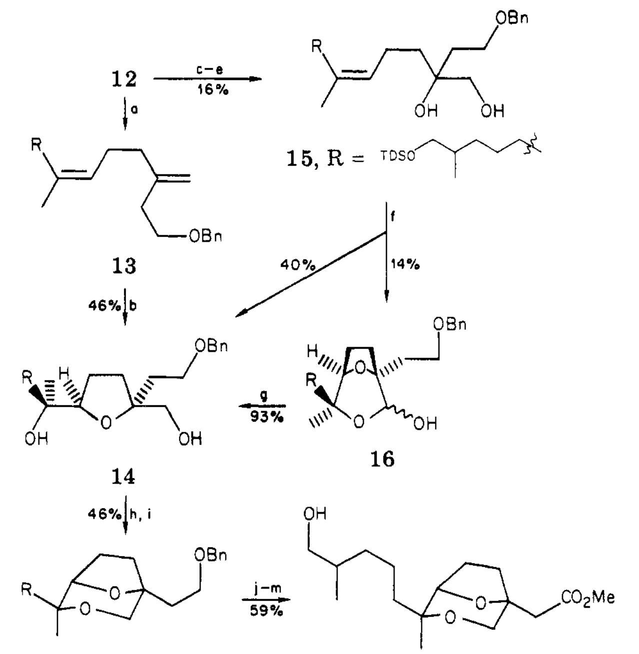
Realization of this strategy is outlined in Schemes II and III.[3,10] A synthesis of the required 1,5-diene substrate **12** is given in Scheme II. Thus, protection of the known alcohol **6**[11] as the *tert*-butyldiphenylsilyl (TDS) ether, followed by hydroboration–oxidation, gives the primary alcohol **7** in good yield. Alkylation of lithium acetylide in Me_2SO with the bromide derived from alcohol **7** gives acetylene **8**,[12] which is readily converted to the acetylenic

Scheme II. Synthesis of Key 1,5-Diene Intermediate **12**[a]



[a] (a) *t*-$BuPh_2SiCl$, imidazole, DMF, room temperature, 8 h; (b) (i) $BH_3 \cdot Me_2S$, THF, room temperature, 1 h, (ii) H_2O_2, NaOH, THF; (c) Ph_3P/CBr_4, CH_2Cl_2, room temperature, 1 h; (d) $HC{\equiv}CLi \cdot (NH_2CH_2)_2$, Me_2SO, 8 °C, (e) (i) *n*-BuLi/THF, (ii) $ClCO_2Et$; (f) Me_2CuLi, Et_2O, −70 °C; (g) $LiAlH_4$, Et_2O, 0 °C, 3 h; (h) PBr_3, solid K_2CO_3, pentane, 0 °C; (i) $LiOCH_2CH_2C(CH_2)_2^-Li^+$, THF/hexane/TMEDA, −78 °C, 4 h.

Scheme III. Synthesis of 3,8-Dioxabicyclo[3.2.1]octanes[a]



[a] (a) $PhCH_2Cl$, NaH/DMF, 0 °C to room temperature, 5 h; (b) $KMnO_4$, 10% aqueous acetone, CO_2 ebullition, 0 °C, 12 h; (c) $VO(acac)_2$/*t*-BuO_2H, CH_2Cl_2, room temperature, 12 h; (d) $PhCH_2Br$, NaH/DMF, 0 °C to room temperature, 5 h; (e) $HClO_4$, THF/H_2O, 24 h; (f) $CrO_3 \cdot 2pyr$, CH_2Cl_2, room temperature, 5 min; (g) room temperature, $NaBH_4$, EtOH; (h) TsCl, pyr, room temperature, 10 h; (i) NaH/DMF, room temperature, 13 h; (j) 10% Pd/C, H_2, EtOAc, 12 h; (k) $RuCl_3 \cdot 3H_2O/NaIO_4$, $CCl_4/CH_3CN/H_2O$ (2:2:3), room temperature, 4 h; (l) CH_2N_2, Et_2O; (m) 10 equiv of *n*-Bu_4NF, THF, 24 h.

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(10) All compounds prepared in this work are racemic. All new compounds gave consistent ^1H and ^{13}C NMR, IR, and mass spectra and were homogeneous by TLC. Yields are of isolated material of >95% purity. Satisfactory combustion analyses were obtained for all new compounds except allylic bromide **11** and hemiacetal **16**.

(11) Fanta, W. I.; Erman, W. F. *J. Org. Chem.* **1972**, *37*, 1624–1630.

ester **9**. Stereoselective carbometalation of acetylenic ester **9** with lithium dimethylcuprate followed by $LiAlH_4$ reduction of the resulting *Z* trisubstituted ester affords the allylic alcohol **10** in good yield. Conversion of alcohol **10** to unstable bromide **11**[10] is straightforward. Alkylation of the dianion derived from 3-methyl-3-buten-1-ol with bromide **11** by a modification of the procedure of Cardillo et al.[13] then provides the desired diene **12** in 30% overall yield from alcohol **6**.

The oxidative cyclization of diene **12** to a THF derivative of type **4** was accomplished in two ways. Thus, as shown in Scheme III, protection of the primary hydroxyl grouping of diene **12** gives the benzyl ether **13**. Oxidation with potassium permanganate in buffered aqueous acetone gives stereospecifically the THF diol **14** in 46% yield at 70% conversion (33% isolated yield of pure **14** and 30% recovered starting material after flash chromatography). An alternative route to THF diol **14** utilizing the Cr(VI) promoted oxidative cyclization of 5,6-dihydroxyalkenes[8c] was also explored. Thus, VO(acac)-promoted oxidation of the homoallylic alcohol moiety of diene **12**,[14] followed by protection of the hydroxyl grouping as the benzyl ether and then acid-catalyzed epoxide ring opening, gives the diol **15** (yields in this sequence are unoptimized). Chromium trioxide promoted oxidative cyclization of this substrate proceeded to give 40% of THF diol **14**, along with a 14% isolated yield of the aldehyde **16** resulting from over oxidation of diol **14**. This aldehyde, which exists primarily as the expected hemiacetal, affords a 93% yield of THF **14** upon reduction with sodium borohydride. Thus, the total yield of THF **14** from diol **15** by this approach was 53%. While the Cr(VI)-promoted oxidative cyclization process proceeds in higher yield than the permanganate-promoted process in this system, the extra steps involved in proceeding by this pathway makes it a somewhat less attractive option in this application. Of course, demonstration of the efficacy of the Cr(VI)-promoted process in this system is interesting since it suggests a possible approach to preparation of the target molecules in enantiomerically enriched form.

Completion of the synthesis is straightforward from THF diol **14**. Thus, treatment of THF **14** with TsCl gives the primary tosylate, which cyclizes to the bicyclic ether **17** upon treatment with NaH in DMF. Debenzylation by catalytic hydrogenation, followed by RuO_4 oxidation,[15] esterification, and then desilylation gives the known hydroxy ester **18**.[16] This ester is identical with material prepared at Ortho and converted by the Ortho group to the zoapatanol bicyclic acid **3a** by a straightforward route.[16,17]

Studies directed toward accomplishing the conversion of bicyclic ether **17** to zoapatanol itself are under way.

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Supplementary Material Available: Spectral and analytical data for all new compounds (10 pages). Ordering information is given on any current masthead page.

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(18) Alfred P. Sloan Foundation Fellow, 1982–1986; Dreyfus Teacher-Scholar, 1983–1985.

Preparation and Rearrangement of *trans*-3-(Allyloxy)acrylic Acids: A Claisen Sequence That Avoids Mercury Catalysis

Summary: Reaction of sodium or lithium salts of primary and secondary allylic alcohols with (*E*)-(carboxyvinyl)trimethylammonium betaine affords (*E*)-3-(allyloxy)acrylic acids, which on heating are transformed to γ,δ-unsaturated aldehydes.

Sir: The Claisen rearrangement of allyl vinyl ethers,[1] although a potentially very useful synthetic transformation, has severe limitations due to the lack of efficient general methods for the preparation of allyl vinyl ethers. These intermediates are normally prepared by vinyl ether exchange with simple alkyl vinyl ethers and an allylic alcohol in the presence of a Lewis acid (usually mercuric acetate) or mineral acid.[2] Yields in these reactions are often low, and the use of mercury is becoming unacceptable due to environmental problems.

Modifications of the Claisen rearrangement (e.g., those of Johnson,[3] Ireland,[4] and Eschenmoser[5]) are more widely applicable; however, all of these give products at the carboxylic acid oxidation level, and additional steps are required if an aldehyde is the desired product.

We have developed a modification of the Claisen rearrangement for primary and secondary allylic alcohols that does not require catalysis by mercury salts or mineral acids and gives aldehydes directly. Furthermore, sealed tubes or other high-pressure vessels are not necessary. The betaine **1**[6,7] prepared from ethyl propiolate and trimethylamine was shown to combine with alkoxide to give the corresonding *trans*-3-alkoxyacrylic acids (Scheme I).[7]

Heating the sodium alkoxides of allylic alcohols with the betaine **1** affords moderate to good yields of the corresponding *trans*-3-(allyloxy)acrylic acids **2**. Aqueous solutions of the adducts **2**, as their sodium salts, are first washed with ether and then acidified to give the adducts **2**. These crude products are heated with a trace of hydroquinone at temperatures of 150–200 °C to give the

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