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SYNTHESIS OF METHYLENE CYCLOPROPANE ANALOGS OF ARACHIDONIC ACID. POTENTIAL MECHANISM-BASED INHIBITORS OF LEUKOTRIENE BIOSYNTHESIS

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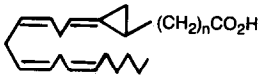
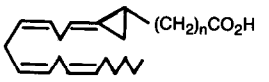
Abstract: The synthesis of methylene cyclopropane arachidonic acid analogs 1 and 2 is described.

Since the unambiguous structural identification of the leukotrienes[1,2], lipoxygenase-derived products of arachidonic acid metabolism have emerged as potential mediators of increasing significance in a number of disease states. In particular leukotrienes (e.g. LTB_4, LTC_4, LTD_4) derived by initial oxidation of arachidonic acid by $^5\Delta$-lipoxygenase (5-LO) have been implicated as important contributors to inflammatory and hypersensitivity related ailments.[3]

We have been interested in developing substrate-modeled inhibitors of leukotriene biosynthesis and have prepared methylene cyclopropanes 1 and 2 as potential mechanism-



1 a: n=1
b: n=2

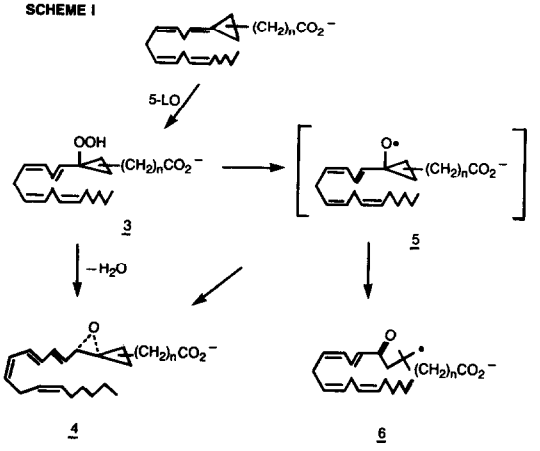


2 a: n=1
b: n=2

based inhibitors of 5-LO derived leukotrienes.[4] We envisaged 1b and/or 2a would be converted by 5-LO to the intermediate HPETE-like hydroperoxide 3 which could subsequently cause enzyme inactivation via several pathways. Enzymatic dehydration would generate reactive oxaspiropentane LTA_4 analog 4 (Scheme I). The additional strain energy provided by the cyclopropyl ring and cyclopropylcarbinyl stabilization of the carbonium ion resulting from epoxide opening of 4 should produce a species of sufficient reactivity within the active site of the enzyme to undergo irreversible binding to an available enzyme nucleophile. Alternatively conversion of hydroperoxide 3 to 5 via a homolytic cleavage mechanism may result in formation of enone 6 by cyclopropyl ring fragmentation. Enone 6 would also be expected to inactivate the enzyme by binding to an enzyme nucleophile.

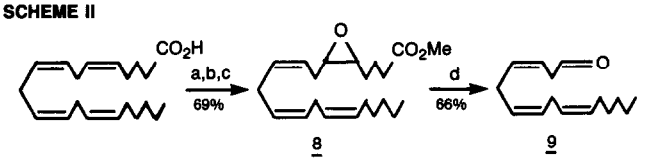
Correlating the relative abilities of 1 and 2 to inhibit leukotriene biosynthesis with structure would also allow determination of substrate conformational preferences. In this respect 1 and 2 can be considered conformationally-restricted analogs of arachidonic acid which specify the orientation about the 5,6-double bond of the C1-C4 carboxyl side chain relative to the aliphatic portion of the molecule. We anticipated the methylene cyclopropane analog best able to mimic the reactive conformation of the natural substrate would be the most effective inhibitor.

SCHEME I



The synthetic route leading to 1 and 2 is depicted in Schemes II and III. Thus, iodolactonization of arachidonic acid followed by aqueous base treatment of the iodolactone and subsequent esterification with diazomethane gave epoxy ester 8[5a].

SCHEME II

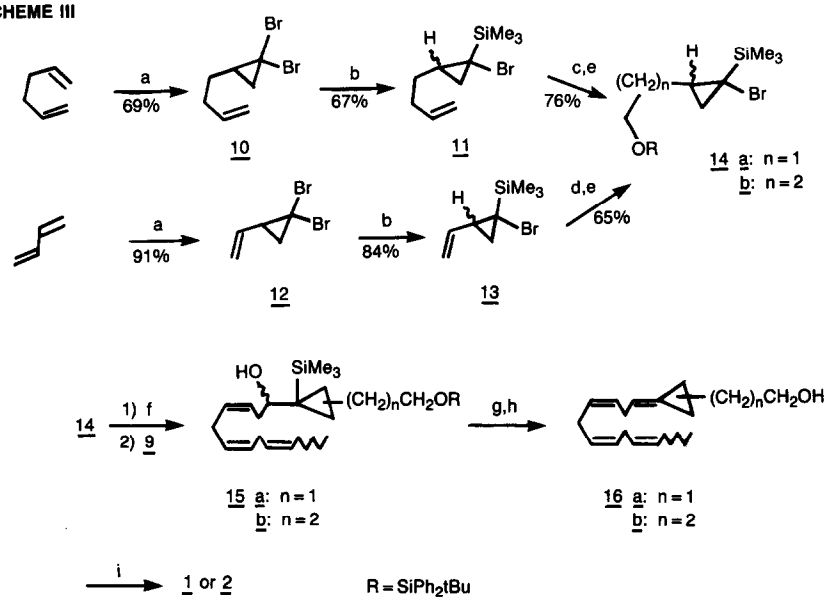


a. $KI_3/KHCO_3$, aq THF, 0°; b. LiOH, aq THF, 25°; c. CH_2N_2, ether; d. H_5IO_6, ether, 25°.

Periodic acid cleavage of epoxy ester 8 (H_5IO_6/1 eq./ether, 25°, 45 minutes)[6] followed by rapid flash chromatography afforded labile aldehyde 9[5b,7]. Introduction of the methylene cyclopropane to aldehyde 9 was accomplished by addition of an α-lithiotrimethylsilylcyclopropane followed by Petersen olefination. The required α-lithiotrimethylsilylcyclopropanes were obtained by metalation of the corresponding 1,1-bromotrimethylsilylcyclopropanes 14a,b.[7] Cyclopropyl bromides 14a,b were synthesized in good yields, in four steps, from readily available 1,5-hexadiene and 1,3-butadiene using literature methods as shown in Scheme III.[8,9] Metalation of 14b (n-BuLi/THF, -78°, 1 hour) and addition of aldehyde 9 to the anion afforded a mixture of four diastereomeric β-hydroxysilanes 15b; A (14%), B(11%), C and D (9%, C and D), R_f (silica gel, 1:9 ether/pet. ether) = 0.60, 0.35, 0.28, 0.25, respectively.

Chromatographic separation and conversion of diastereomer A or B independently to the β-chlorosilane ($SOCl_2/Et_3N/CH_2Cl_2$, 0°, 1 hour) followed by fluoride-induced elimination (n-Bu_4NF/DMSO, 25°, 24 hours)[10] of the crude β-chlorosilane afforded Z-16b (41%). By an

SCHEME III



a. $tBuOK/HCBr_3$, 30eq neat diene, −20 to 0°; b. nBuLi, ether, THF, −95° then TMSCl, −95° to −78°;
c. O_3, MeOH, −78°, then $NaBH_4$, −78° to 25°; d. BH_3, THF then H_2O_2, aq NaOH;
e. $ClSiPh_2tBu$, Et_3N, DMAP, CH_2Cl_2; f. nBuLi, THF, ether, −78°; g. $SOCl_2$, Et_3N, CH_2Cl_2, 0°;
h. nBu_4NF (3eq), THF, DMSO, 25°; i. Jones.

identical sequence the mixture of diastereomers C and D were converted to E-16b (24%). Jones oxidation[11] of the alcohols 16b afforded desired acids 1b and 2b (80-90%).[12,14] By a similar sequence, 1a and 2a were also prepared, from 14a and 9. These compounds are currently being evaluated as inhibitors of leukotriene biosynthesis.

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b. Physical data for 9: IR (film) 2907, 2695, 1727, 1462, 1397 cm^{-1}; 60 MHz ^1H NMR ($CDCl_3$) δ0.90 (crude t, 3H), 1.33 (m, 6H), 2.07 (m, 2H), 2.82(m, 4H), 3.23 (dd, J = 2,6,2H), 5.40 (m, 4H), 5.67 (m, 2H), 9.73 (m, 1H); MS (CI): 221 $(M+H)^+$; TLC:R_f(silica gel, 1:5 EtOAc/pet ether) = 0.52, phosphomolybdic acid.

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12. The stereochemistry of the 5,6-double bond was based on comparison of the 400 MHz ^1H NMR spectrum of 1b and 2b, which showed the olefinic methylene cyclopropane protons at δ5.71(m) and δ5.79(m) respectively, with literature compounds Z and E-17 in which the reported values for the olefinic methylene cyclopropane protons were δ5.68(m) and δ5.77(m), respectively.[13]

Z-17

E-17

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14. Physical data for 1b: IR (film) 3.41 (broad), 5.85, 6.96, 7.82, 8.25, 10.70, 14.06 μ; 400 MHz ^1H NMR ($CDCl_3$) δ 0.76 (m, 1H), 0.89 (t, J = 7, 3H), 1.15-1.43 (m, 7H), 1.50 (m, 2H), 1.95 (m, 1H), 2.05 (dt, J = 6, 7, 2H), 2.47 (t, J = 7, 2H), 2.80-2.90 (m, 4H), 2.94 (t, J=6, 2H), 5.30-5.53 (m, 6H), 5.71 (m, 1H); MS (CI): 317 $(M+H)^+$; TLC: R_f (silica gel, 1:3 EtOAc/pet. ether) = 0.23, phosphomolybdic acid. Physical data for 2b: IR (film) 3.41 (broad), 5.85, 6.90, 7.84, 8.24, 10.69, 13.89 u; 400 MHz ^1H NMR ($CDCl_3$) δ 0.75-0.82 (m, 1H), 0.90 (t, 3H), 1.20-1.50 (m), 1.57-1.82 (m, 3H), 2.05 (dt, J=7, 7, 2H), 2.45 (t, J=7, 2H), 2.81 (dd, J=6, 6, 2H), 2.85 (dd, J=6, 6, 2H), 2.94 (dd, J=7, 7, 2H), 5.28-5.45 (m, 5H), 5.46-5.53 (m, 1H), 5.79 (m, 1H); MS (CI): 317 $(M+H)^+$; TLC: R_f (silica gel, 1:3 EtOAc/pet. ether) = 0.18, phosphomolybdic acid.

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