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1,1-DISUBSTITUTED-2,5-CYCLOHEXADIENES: SELECTIVE INHIBITORS OF 5-LIPOXYGENASE

William J. Sipio*
E. I. du Pont de Nemours & Company, Inc.
Biomedical Products Department
Pharmaceuticals Research and Development Division
Wilmington, DE 19898

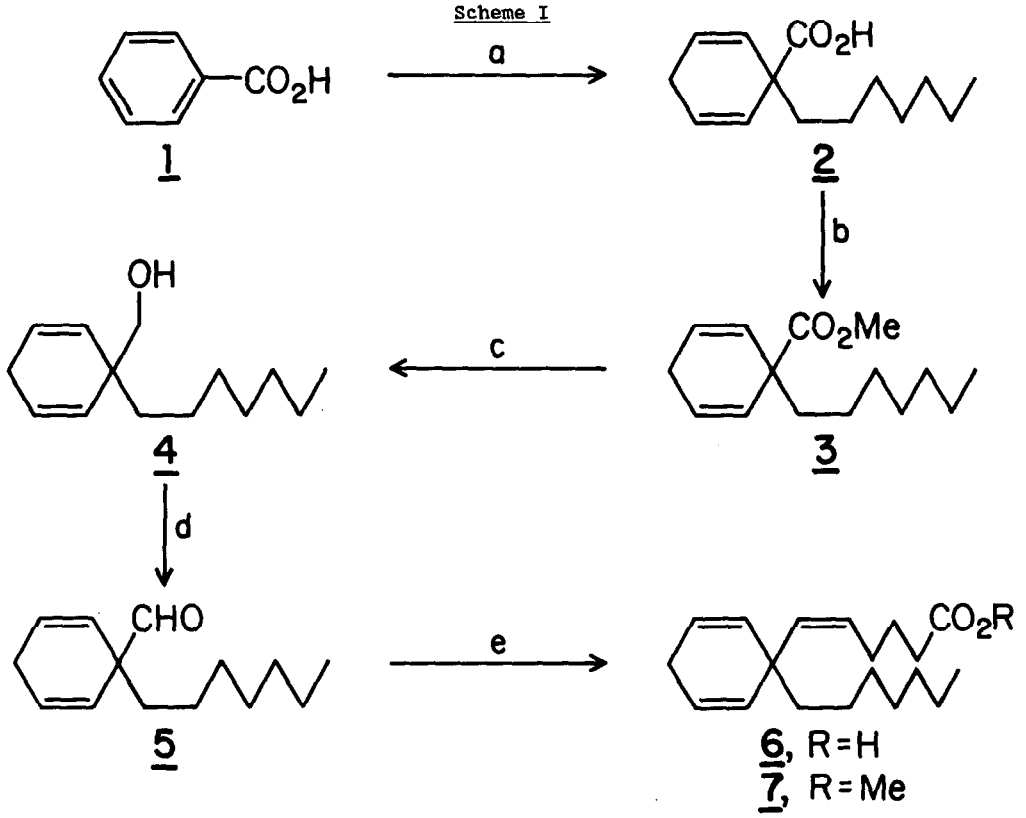
Abstract: 1,1-Disubstituted-2,5-Cyclohexadienes, modeled after arachidonic acid and 15-HETE, selectively inhibit 5-Lipoxygenase.

A variety of substituted arachidonic acids (AA) have been identified as selective inhibitors of the 5-lipoxygenase pathway of AA metabolism. Via this pathway, the biosynthesis of leukotrienes (LT) is initiated by stereospecific proton abstraction[1] from C-7 of AA. Inhibition of this process may be therapeutically useful in treating inflammatory disease. AA analogs have been designed to function as inhibitors by blockade of proton abstraction from C-7, C-10, and C-13 of AA either by insertion of a gem-dimethyl[2-5] or cyclopropane[3,6] moiety. Using similar reasoning, the spiro-triene 7 was designed as a potential inhibitor of LT biosynthesis. By creating a quaternary center at C-7, we envisioned potential inhibition of 5, 11, and 15-lipoxygenase.

Birch reductive alkylation (Scheme I) of benzoic acid (1) [Li/NH_3:THF (4:1)] with iodoheptane (-78° → -33°C, 2 hr) afforded 2. The crude acid 2 was esterified (3) with methyl iodide (K_2CO_3, Acetone, 0°C) and reduced to the alcohol 4 (LAH, Et_2O) in 85% yield. Careful oxidation of 4 (-20°C → r.t.) with pyridinium chlorochromate afforded crude aldehyde 5 with no evidence of dienone formation. Treatment of the crude aldehyde 5 with the ylid derived from 4-carboxybutyltriphenylphosphonium bromide (NaH, DMSO, 25°C) afforded acid 6[7] which was directly esterified (CH_2N_2, Et_2O, 0°C) producing the ester 7. The ester 7 selectively inhibited the 5-lipoxygenase from RBL-1 cells[8] (IC_{50} = 120 μM) while having a negligible effect on prostaglandin synthetase (IC_{50} >750 μM).

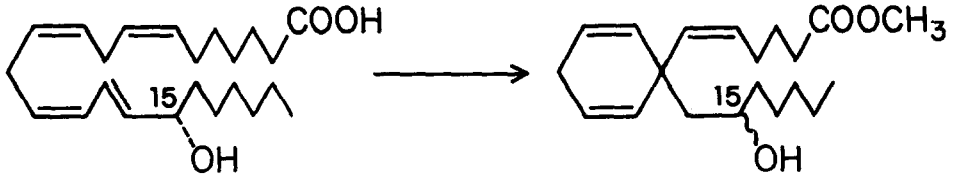
Having obtained moderate activity with 7, we decided to introduce a hydroxy group in the lower chain of 7 (Figure I) based on a report by Vanderhoek[9] that 15-(S)-HETE is a potent inhibitor of 5-lipoxygenase (IC_{50}=3.7 μM). Also, the presence of three olefins and an ester function appears to afford maximum inhibitory activity. Our target selection incorporates a hydroxyl function at C-15, ester at C-1, and three Z-olefins at C-5,8,11.

Scheme I



a: 1) Li/NH_3:THF (4:1), -50°C, 1 hr; 2) 1-iodoheptane, -78° → -33°C, 2 hr; b: CH_3I, K_2CO_3, Acetone, 0°C; c: $LiAlH_4$, Et_2O, 0°C; d: PCC, CH_2Cl_2, -20°C → r.t.; e: NaH, DMSO, $HO_2C(CH_2)_4P(C_6H_5)_3Br$, 25°C, 6; CH_2N_2, 0°C, Et_2O, 7.

Figure I

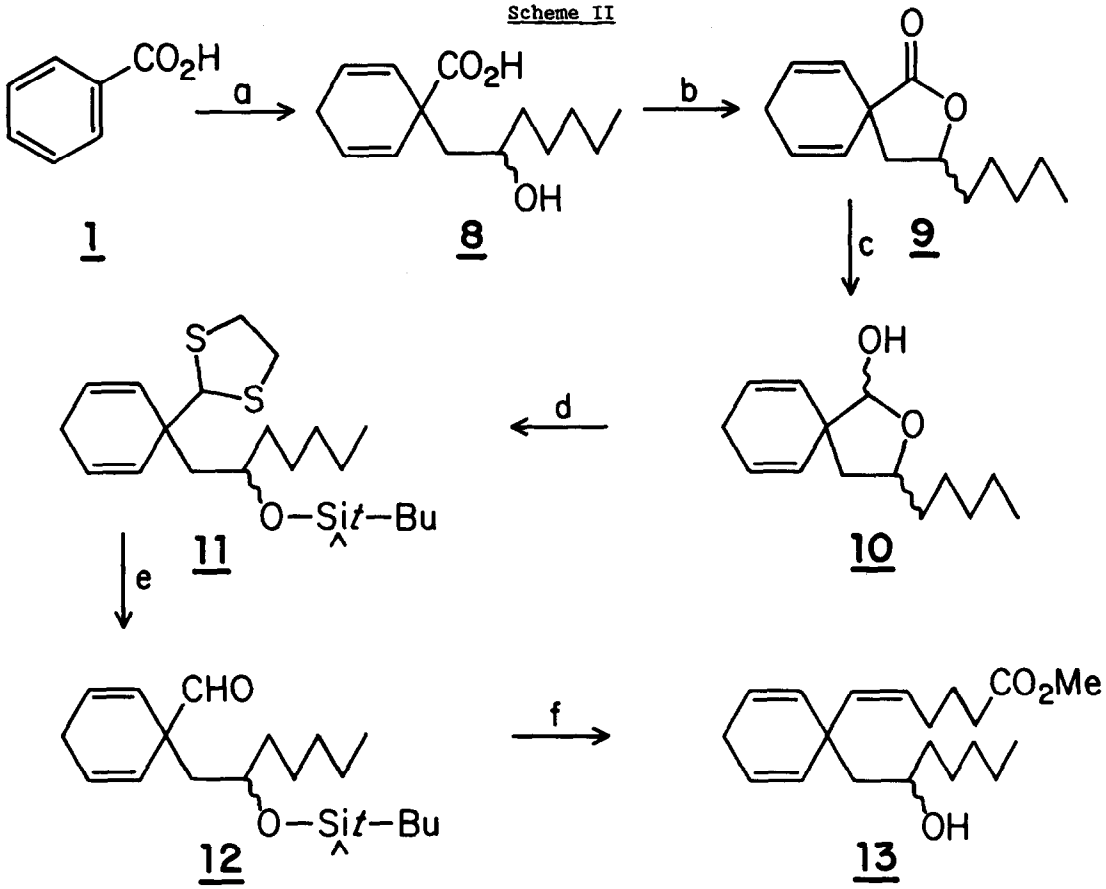


15-(S)-HETE

Birch reductive alkylation (Scheme II) of benzoic acid (1) (Li/NH_3:THF, 4:1) with epoxyheptane (-78°C → -33°C, 2 hr) afforded the diene 8, which was cyclized to the spirolactone 9 (p-TsOH, Benzene) in 85% yield. Reduction of 9 (DIBAL, -78°C, Toluene) produced the key intermediate lactol 10 in 86% yield. Attempts to convert 10 directly to the ester 13 under a variety of conditions gave low Z-stereoselectivity. Alternatively, we chose to use the free aldehyde 12 for conversion to 13. Treatment of the lactol 10 with

ethanedithiol under acid catalysis ($TiCl_4$, CH_2Cl_2, 0°C) yielded a hydroxy dithiolane (70%), which was silylated under standard conditions (imidazole, DMF, + Si-Cl) to give 11 (91%). The dithiolane moiety in 11 was removed (CH_3I, $CaCO_3$, THF) affording the key aldehyde 12 (90%). The aldehyde 12 was treated with the ylid derived from 4-carboxybutyl-triphenylphosphonium bromide (NaH, DMSO, 25°C) to give the crude acid, which was esterified (CH_2N_2, Et_2O, 0°C) and desilylated (n-Bu_4NF, THF, 25°C) to yield the ester 13[7] (>95% Z). Compound 13 also selectively inhibited 5-lipoxygenase (IC_{50}=6 μM) over prostaglandin synthetase (IC_{50} >750 μM).

Scheme II



a: 1) Li/NH_3:THF (4:1), -50°C, 1 hr; 2) 1-epoxyheptane, -78° → -33°C, 2 hr; b: p-TsOH, Benzene, r.t.; c: DIBAL, Toluene, -78°C; d: 1) $HS(CH_2)_2SH$, $TiCl_4$, CH_2Cl_2, 0°C, 1 hr; 2) Imidazole, DMF, $(CH_3)_3CSi(CH_3)_2Cl$; e: CH_3I, $CaCO_3$, THF; f: 1) $HO_2C(CH_2)_4P(C_6H_5)_3Br$, NaH, DMSO, 25°C, 3 hr; 2) CH_2N_2, Et_2O, 0°C; 3) n-Bu_4NF, THF, 25°C.

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References and Notes

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7. Compounds 6 & 13 gave satisfactory IR, ^{1}HNMR, and mass spectra. 6: ^{1}HNMR ($CDCl_3$, 360MHz)δ: 0.87 (t, J=8.0Hz, 3H, CH_3), 1.10-1.63 (m, 14H, CH_2) 2.14 (q, J=8.0Hz, 2H, allylic CH_2), 2.30 (t, J=7.0 Hz, 2H, CH_2CO_2H), 2.58 (m, 2H, diallylic CH_2), 5.32-5.67 (m, 6H, olefin). 13: ^{1}HNMR ($CDCl_3$, 200 MHz) δ: 0.95 (t, J=7.0 Hz, 3H, CH_3), 1.16-1.20 (m, 12H, CH_2), 2.08 (m, 2H, allylic CH_2), 2.26 (t, J=7.0 Hz, 2H, CH_2CO_2Me) 2.70 (m, 2H, diallylic CH_2), 3.68 (s, 3H, OCH_3), 3.75 (br m, 1H, CHOH), 5.30-5.82 (m, 6H, olefinic).
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