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CONFORMATIONALLY RESTRICTED LEUKOTRIENE ANTAGONISTS. STEREOSELECTIVE SYNTHESIS OF SOME LEUKOTRIENE D_4 ANALOGS

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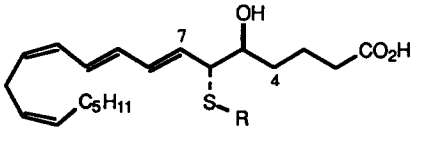
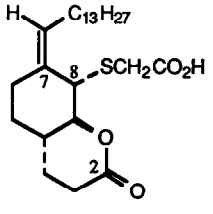
Abstract - *The stereocontrolled synthesis of conformationally restricted LTD_4 analogs* ***2a, b*** *is described. Epoxidation of enone* ***4*** *affords a 2.4:1 mixture of trans-epoxide* ***5*** *and cis-epoxide* ***9****. Stereocontrolled elaboration of each epoxide to final product involves stereoselective Wittig olefination to Z-olefins* ***6*** *and* ***10****, regiospecific epoxide ring opening with methyl mercaptoacetate to diesters* ***8*** *and* ***12****, and saponification to* ***2a, b****.*

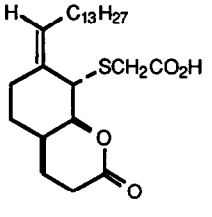
The peptidoleukotrienes LTC_4, LTD_4 and LTE_4 (1) the arachidonic acid metabolites collectively known as slow-reacting substance of anaphylaxis, are important mediators of asthma and other immediate hypersensitivity responses.[1] An attractive therapeutic approach to the treatment of asthma would be the use of drugs capable of either inhibiting the biosynthesis and/or release of the leukotrienes, or blocking their effects at the target tissues. We now report a successful approach to the design and synthesis of the LTD_4 receptor antagonists **2a, b**, which are conformationally restricted analogs[2] of the endogenous agonist.



1 SR = glutathionyl (LTC_4)
= cysteinylglycyl (LTD_4)
= cysteinyl (LTE_4)



2a



2b

We opted for conformationally-restricted analogs with the purpose of defining the conformation requirements for binding at the active site. Our objective was to prepare analogs of known relative stereochemistry to possibly "freeze-out" the conformer necessary for maximal binding at the active site, by modifying the basic LTD_4 structure with the aim of preparing a potent antagonist free of intrinsic agonist

properties. The proposed target molecules incorporate a six-membered ring between the C-4 and C-7 positions of the peptidoleukotriene skeleton in order to provide conformational stability in the polar region of the molecule. The choice of a six-membered ring allows for stereo- and regiocontrol. A single olefin corresponding to the Δ^7-double bond of LTD_4 simplified the labile triene system and the long aliphatic tail was considered necessary to approximate the lipophilicity of the leukotrienes.[3] Mercaptoacetic acid was incorporated in order to mimic the sulfido peptide moiety of the natural substrate. We chose as prime targets **8** (R = H) and **12** (R = H), but fortuitous lactone formation precluded their use. The results of our efforts are outlined in Scheme 1.

Epoxidation of the enone-ester **4**, *prepared*[4] *by fragmentation of methyl 1-methoxybicyclo*[2.2.2]*oct*-5-ene-2-carboxylate **3**, with 30% aqueous *t*-butyl hydroperoxide (2.5 equivalents) afforded a chromatographically separable mixture of *trans*-epoxide **5** (46%) and *cis*-epoxide **9** (19%). Stereo-selective Wittig olefination of **5** using a lithium-base procedure[5] for 2,3-epoxycyclohexanone afforded olefins **6** (53%) and **7** (8%) after chromatography. The double bond geometry of **6** was determined using Nuclear Overhauser Enhancement (NOE) difference spectroscopy[6]. Irradiation of the allylic epoxy-methine doublet at 3.68 ppm resulted in enhancement (4.4%) of the side-chain allylic methylene resonance at 2.19 ppm. A large NOE (13.3%) was also observed to the other epoxy-methine proton at 3.10 ppm as expected. There was no observed NOE to the olefinic proton at 5.58 ppm or the ring allylic methylene triplet at 2.42 ppm. In addition, a single crystal X-ray structural determination[7] confirmed these assignments and also established the relative stereochemistry of the ring substituents (Figure 1).

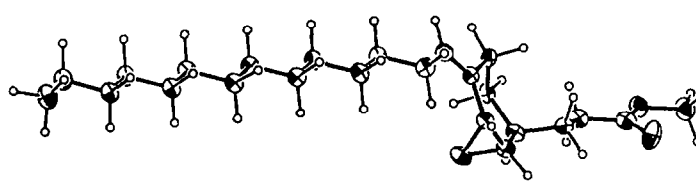
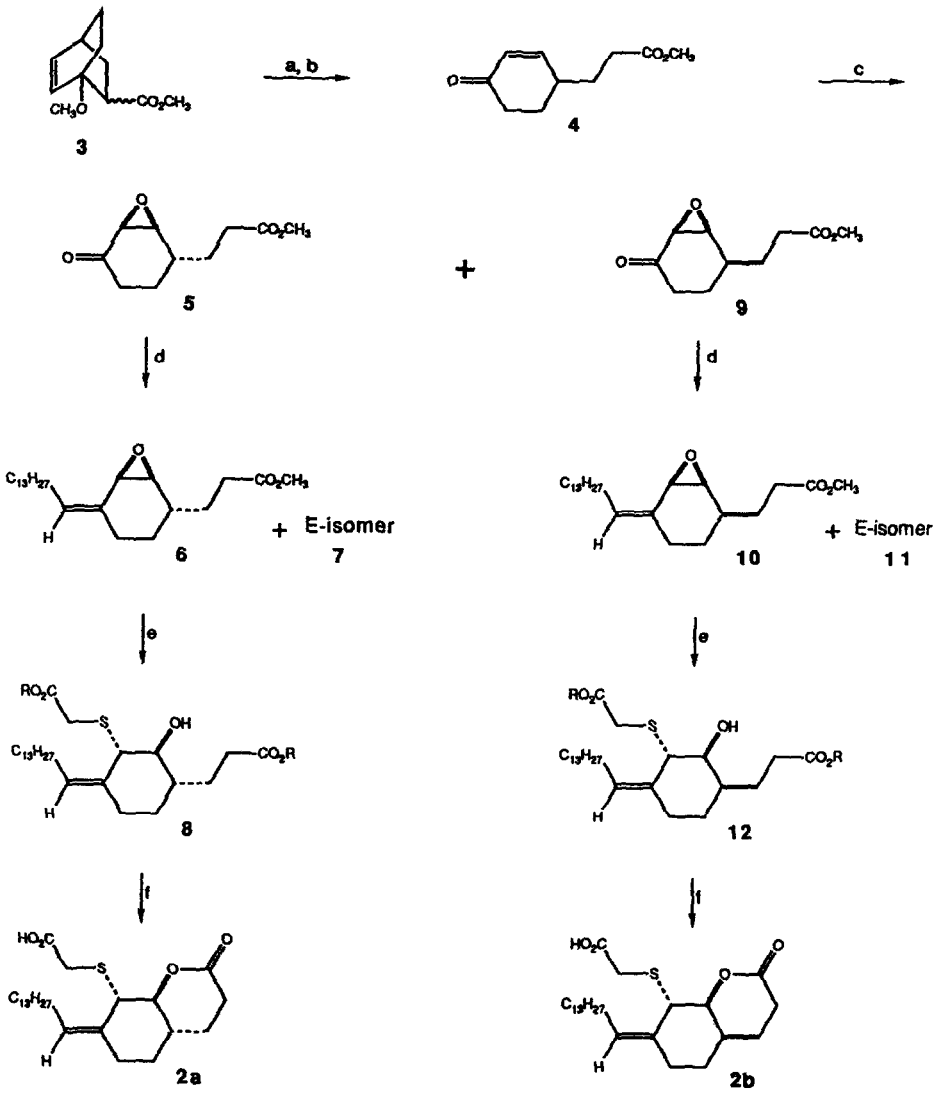


FIGURE 1. ORTEP Drawing of Compound **6**

Regiospecific opening of epoxy-olefin **6** with methyl mercaptoacetate gave diester **8** (R = CH_3) in 65% yield. The regiochemistry of the substitution was evident from the ^{1}H-NMR of **8** which displayed a triplet for the olefinic proton at δ 5.43, thus confirming that the reaction proceeded through an S_N2 rather than an S_N2' mechanism. Saponification gave a 66% yield of an acidic material which was shown by ^{1}H-NMR, elemental analyses and mass spectroscopy to be a mono-acid lactone. With the possibility for the formation of either of two δ-lactones, it was not obvious *a priori* which would form. MNDO[8] and MM2[9] calculations were performed to predict which lactone had formed.[10] Based on the assumption that the thermodynamically more stable lactone was isolated, these calculations indicated that lactone **2a** would be the more likely. This assignment was eventually confirmed by single crystal X-ray analysis.[11] The preparation of isomer **2b** followed a similar route. Wittig olefination of **9** gave olefins **10** (54%) and **11** (9%), then regiospecific epoxide opening of **10** with methyl mercaptoacetate followed by saponification of the diester **12** (R=CH_3) afforded mono-acid lactone **2b** in 45%

SCHEME 1



Conditions: a) BBr_3, CH_2Cl_2, 0°C; b) $(CH_3)_3COK$, $(CH_3)_3COH$, rt; c) 30% aq $(CH_3)_3COOH$, THF, rt; d) n-$C_{14}H_{29}{}^+PPh_3Br^-$, n-BuLi, THF, -40°C to rt; e) $HSCH_2CO_2CH_3$, MeOH, Et_3N, rt; f) KOH, EtOH, H_2O, rt.

overall yield. Lactone formation does not occur when the propionic acid chain is either shortened or lengthened by one carbon.

When evaluated *in vitro*, **2a** is a competitive antagonist of LTD_4 (pA_2 = 6.7) and LTE_4 (pA_2 = 6.7) and an apparent non-competitive inhibitor of LTC_4. The isomeric **2b** has a similar *in vitro* profile but is somewhat less potent. *In vivo*, 10-30 mg/kg of **2a** given intravenously effectively inhibits increases in insufflation pressure induced by 100 ng/kg LTD_4 intravenously.[12]

In summary, a facile approach to rigid, conformationally restricted LTD_4 antagonists has been developed with stereo- and regiochemical control of the three contiguous stereocenters. Also, the key intermediates **6** and **10** should serve as versatile intermediates for the regiospecific introduction of other sulfido-peptide mimics.

EXPERIMENTAL SECTION

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 1800 spectrometer. Proton and carbon NMR were obtained on Varian EM360L-90 or Varian VXR-300 spectrometers. The chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. Mass spectra were obtained on a Finnigan MAT 6400 mass spectrometer. Preparative high pressure liquid chromatography (HPLC) was performed on a Waters 500A instrument.

7-Oxabicyclo[4.1.0]heptane-2-propanoic acid, 5-oxo-, methyl ester, (1.beta, 2.alpha, 6.beta)-(5), and 7-Oxabicyclo[4.1.0]-heptane-2-propanoic acid, 5-oxo-, methyl ester, (1.beta, 2.beta, 6.beta)-(9). A solution of methyl-3-(4-oxocyclohex-2-enyl) propionate **4** (35.0 g, 0.192 mol) and 1,8-diazobicyclo[5.4.0]undecene (73.1 g, 0.479 mol) in THF (525 mL) was cooled in an ice-water bath and treated dropwise with 30% aqueous *tert*-butyl hydroperoxide (74 mL, 0.462 mol). The bath was then removed and the solution stirred at room temperature for 18 h. The reaction mixture was filtered through a pad of silica gel, washing it well with ether. The combined filtrate and wash was extracted with cold sodium sulfite (5 x 400 mL), dried ($MgSO_4$), filtered and evaporated. The residue was purified by preparative HPLC (silica gel, 20% ethyl acetate/hexane); *trans*-**5** (17.6 g, 0.089 mol, 46.2%) eluted first followed by *cis*-**9** (7.1 g, 0.036 mol, 18.6%).

For *trans*-**5**, oil; IR (neat): 1740, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 1.46-1.74 (m, 2H), 1.80-1.94 (m, 1H), 2.04-2.23 (m, 2H), 2.29-2.40 (m, 1H), 2.42-2.56 (m, 2H), 3.22 (d, 1H, J = 3.9 Hz), 3.44 (dd, 1H, J = 3.9, 2.0 Hz), 3.70 (s, 3H). *Anal.* Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.89; H, 7.19.

For *cis*-**9**, oil; IR (neat): 1735, 1715, 1630 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.46-1.74 (m, 2H), 3.24 (d, 1H), 3.47 (d, 1H), 3.72 (s, 3H). *Anal.* Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12. Found: C, 60.33; H, 7.27.

7-Oxabicyclo[4.1.0]heptane-2-propanoic acid, 5-tetra-decylidene-, methyl ester, (1.beta, 2.alpha, 5Z, 6.beta)-(6), and (1.beta, 2.alpha, 5E, 6.beta)-(7). A solution of n-tetradecyl-triphenylphosphonium bromide (7.07 g, 13.1 mmol) in dry THF (100 mL) under an atmosphere of argon was cooled to -41°C and treated with 2.5M n-butyllithium (5.0 mL, 12.5 mmol). The orange solution was stirred at -41°C for 15 min and then treated with a solution of epoxy-ketone **5** (2.36 g, 11.9 mmol) in dry THF (25 mL). The reaction was stirred for 1 h at -41°C and then slowly allowed to warm to room temperature over a 1-2 h period. The mixture was filtered through a pad of silica gel, washing with 10% ethyl acetate-hexane. The combined filtrate and wash was concentrated to a white solid, slurried with 7% ethyl acetate-hexane, filtered, and the filtrate concentrated to an oil. Preparative HPLC (silica gel, 7% ethyl acetate-hexane) afforded first Z-**6** (2.4 g, 6.3 mmol, 53.2%) followed by E-**7** (0.36 g, 0.95 mmol, 7.8%).

For Z-**6**, m.p. 41-43°C; IR (neat): 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H), 2.19 (q, 2H), 2.42 (t, 2H), 3.09 (d, 1H), 3.65-3.70 (m, 4H), 5.58 (t, 1H); cmr: d 173.35, 132.35, 131.74; MS (EI), m/z 378 (M^+, 30%), 346 (10%), 291 (30%), 177 (70%), 55 (90%), 43 (100%). *Anal.* Calcd for $C_{24}H_{42}O_3$: C, 76.14; H, 11.18. Found: C, 76.23; H, 11.14.

For E-**7**, oil; IR (neat): 1740, 1720, 1670 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, 3H), 3.02 (q, 2H), 3.68 (s, 3H), 5.16 (t, 1H); MS (EI), m/z 378 (M^+, 45%), 346 (25%), 177 (100%). *Anal.* Calcd for $C_{24}H_{42}O_3$: C, 76.14; H, 11.18. Found: C, 75.81; H, 11.10.

Cyclohexanepropanoic acid, 2-hydroxy-3-[(2-methoxy-2-oxoethyl)thiol]-4-tetra-decylidene-, methyl ester, (1.alpha, 2.beta, 3.alpha, 4Z)-(**8**, R = CH_3). To a slightly warmed solution of

Z-6 (6.9 g, 18.2 mmol) in methanol (185 mL) was added methyl mercaptoacetate (4.27 mL, 47.8 mmol) and triethylamine (7.22 mL, 51.9 mmol) sequentially. The solution was stirred for 18 h at room temperature under an argon atmosphere. The solvent and excess thiol were evaporated and the oil was purified by preparative HPLC (silica gel, 20% ethyl acetate-hexane) to afford **8** (5.8 g, 23.0 mmol, 65.7%) as an oil: IR (neat): 3490, 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H), 3.26 (d, 1H), 3.66 (s, 3H), 3.73 (s, 3H), 3.78 (m, 1H), 3.90 (d, 1H), 5.43 (t, 1H); MS (CI-CH_4), m/z 485 (M^+ + 1, 21%), 467 (100%), 379 (40%), 347 (20%). *Anal.* Calcd for $C_{27}H_{48}O_5S$: C, 66.90; H, 9.98; S, 6.61. Found: C, 66.67; H, 10.09; S, 6.57.

Acetic acid, [(octahydro-2-oxo-7-tetradecylidene-2H-l-benzo-pyran-8-yl)thio]-,(4a.alpha, 7Z,8.alpha, 8a.beta)-(2a). A solution of diester **8** (12.3 g, 25.4 mmol) in 95% ethanol (75 mL) was cooled in an ice-water bath and treated dropwise with a solution of potassium hydroxide (13.45 g, 240 mmol) in water (50 mL). The mixture was stirred for 18 h at room temperature and then partitioned between water (300 mL) and ether (150 mL). The aqueous layer was separated, cooled in an ice-water bath, acidified with 3N hydrochloric acid (100 mL) and thoroughly extracted with ethyl acetate (2 x 250 mL). The combined organic washes were dried ($MgSO_4$), filtered and evaporated to an oil which was crystallized from hexane to give **2a** (3.53 g, 8.05 mmol, 30.5%): m.p. 85-85.5°C; IR (KBr): 3200-2510, 1735, 1695 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (t, 3H, J = 6.7 Hz), 3.44 + 3.61 (pr d, 2H, J = 16 Hz), 4.05 (d, 1H, J = 6.6 Hz), 4.36 (dd, 1H, J = 6.6 Hz, 11 Hz), 5.41 (t, 1H, J = 7.1 Hz), 9.11 (br s, 1H); MS (EI): m/z 439 (M^+ + 1, 25%), 421 (20%), 349 (60%), 347 (70%), 93 (60%), 75 (100%). *Anal.* Calcd for $C_{25}H_{42}O_4S$: C, 68.45; H, 9.65; S, 7.31. Found: C, 68.21; H, 9.64; S, 7.33.

7-Oxabicyclo[4.1.0]heptane-2-propanoic acid, 5-tetradecylidene-, methyl ester, (1.beta, 2.alpha, 5Z, 6.beta)-(**10**), and (1.beta, 2.alpha, 5E, 6.beta)-(**11**). A solution of n-tetradecyl triphenylphosphonium bromide (4.19 g, 7.77 mmol) in dry THF (60 mL) under argon was cooled to -41°C and treated with 2.5 M n-butyllithium (2.9 mL, 7.4 mmol). After 15 min, a solution of epoxy-ketone **9** (1.4 g, 7.06 mmol) in THF (25 mL) was added. The reaction mixture was kept at -41°C for 1 h, then warmed slowly to room temperature over 1 h and worked up as described for **6** to afford crude product. Preparative HPLC (silica gel, 5% ethyl acetate-hexane) afforded first Z-**10** (1.2 g, 3.15 mmol, 44.9%) followed by E-**11** (0.2 g, 0.53 mmol, 7.5%).

For Z-**10**; oil; IR (neat): 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (t, 3H), 2.21 (m, 3H), 2.46 (t, 2H), 3.26 (d, 1H), 3.66 (br s, 4H), 5.59 (t, 1H); MS (CI-CH_4): m/z 379 (M^+ + 1, 100%), 361 (8%) 347 (70%); MS (EI), m/z 378 (M^+, 35%), 291 (45%), 286 (45%) 43 (100%). *Anal.* Calcd for $C_{24}H_{42}O_3$: C, 76.14; H, 11.18. Found: C, 76.24; H, 11.38.

For E-**11**; oil; IR (neat) 1740 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (t, 3H), 2.37 (d of t, 2H), 2.47 (t, 2H), 3.29 (d, 1H), 3.38 (d, 1H), 3.69 (s, 3H), 5.67 (t, 1H); MS (CI-CH_4): m/z 379 (M^+ + 1, 100%), 361 (4%), 347 (40%). *Anal.* Calcd $C_{24}H_{42}O_3$: C, 76.14; H, 11.18; Found: C, 76.07; H, 11.39.

Cyclohexanepropanoic acid, 2-hydroxy-3-[(2-methoxy-2-oxoethyl)thio]-4-tetradecylidine-, methyl ester, (1.beta, 2.beta, 3.alpha, 4Z)-(**12**, R=CH_3). A solution of epoxy-olefin **10** (11.4 g, 30.1 mmol) in methanol (275 mL) was treated sequentially with methyl mercaptoacetate (7.06 mL, 79.0 mmol) and triethylamine (11.9 mL, 85.8 mmol) and worked up as described for **8** to afford **12** (R=CH_3) (8.6 g, 34.1 mmol, 58.9%) as an oil: IR (neat): 3520, 1750 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (s, 3H), 3.06 (s, 2H), 3.71 (s, 3H), 3.86 (d, 1H), 4.14 (br s, 1H), 5.53 (t, 1H); MS (CI-CH_4), m/z 485 (M^+ + 1) 467 (100%). *Anal.* Calcd for $C_{27}H_{48}O_5S$: C, 66.90; H, 9.98; S, 6.61. Found: C, 66.88; H, 9.99; S, 6.54.

Acetic acid, [(octahydro-2-oxo-7-tetradecylidine-2H-1-benzopyran-8-yl)thio]-,(4a.beta, 7Z,8.alpha, 8a.beta)-(2b). A solution of diester **12** (8.2 g, 16.9 mmol) in 95% ethanol (75 mL) was cooled in an ice-water bath and treated with a solution of potassium hydroxide (8.96 g, 160 mmol) in water (35 mL) similar to the preparation of **2a** to give lactone **2b** as an oil (3.7 g, 8.45 mmol, 50%); IR (neat): 3200-2560, 1740, 1715 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 6.7 Hz), 3.26 (s, 2H), 4.32 (s, 1H), 4.57 (t, 1H, J = 2.5 Hz), 5.51 (dt, 1H, J = 7.3 Hz, 1.0 Hz), 8.92 (br s, 1H); MS (EI) m/z 438 (M^+, 2%), 379 (20%), 346 (90%), 177 (100%), 55 (95%). *Anal.* Calcd for $C_{25}H_{42}O_4S$: C, 68.45; H, 9.65; S, 7.31. Found: C, 67.97; H, 9.60; S, 6.63.

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7 Crystal data: Formula $C_{24}H_{42}O_3$, Crystal system triclinic, Space group Pibar, a = 39.345Å (25), b = 6.363Å (2), c = 4.829Å (1), α = 73.65° (2), β =79.21° (2), γ = 90.37° (3), V = 1137.45Å^3, Z = 2, d_{calc} = 1.105, Crystal dimensions = 0.25 x 0.25 x 0.25 mm. The analysis was carried out by Dr. J. Huffman, Indiana University. Bond distances and crystallographic details are available in microfiche form from the Chemistry, Indiana Universtiy, Bloomington, Indiana 47405. Request MSC Report 87714.

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