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SUBSTITUTED CYCLOHEXANE AS CONFORMATIONALLY-RESTRICTED ANALOGUES OF THE PEPTIDO-LEUKOTRIENES

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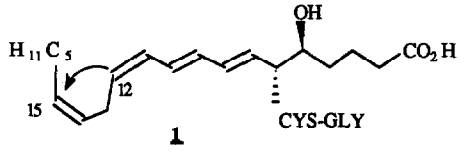
Abstract : A new class of potential leukotriene analogues is synthesized which atttempts to restrict the conformationally mobile lipophilic chain. Biological evaluation shows weak agonist activity, giving key information on LTD_4 geometry to the receptor.

The peptido-leukotrienes LTC_4, LTD_4 and LTE_4 are potent contractile agents on airway smooth muscle and may contribute to the pathophysiology of asthma and other immediate hypersensitivity diseases [1-4]. Thus, the discovery of selective leukotriene receptor antagonists may provide a new therapeutic approach to the treatment of allergic asthma. Numerous stereochemical and structural analogues of leukotrienes LTC_4 and LTD_4 have been synthesized previously and evaluated for agonist-antagonist potency [5-7]. Structure-activity studies on the natural agonists suggested that the hydrophobic region C-7/C-20 of the molecules was less critical for activity on the smooth muscle.

A large degree of flexibility for the lipophilic chain seemed to be tolerated [8]. However, in opposition to previous studies, we have shown, guided by the structure of the natural leukotrienes, that the 11,12 portion in the triene structure was critical for a leukotriene-like activity [9]. To define the structural requirements in this region on agonist and antagonist activity, we decided to prepare a model which restricts the conformationally mobile lipophilic chain.

In this Letter, we report the synthesis of the new cyclohexane analogue **2** of the natural LTD_4 **1** in order to evaluate the full effects of this new triene system on biological activity. Our analogue contains the normal peptide portion LTD_4 and also has the natural (5S, 6R) stereochemistry.



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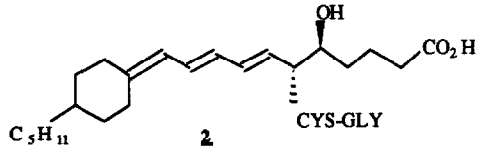
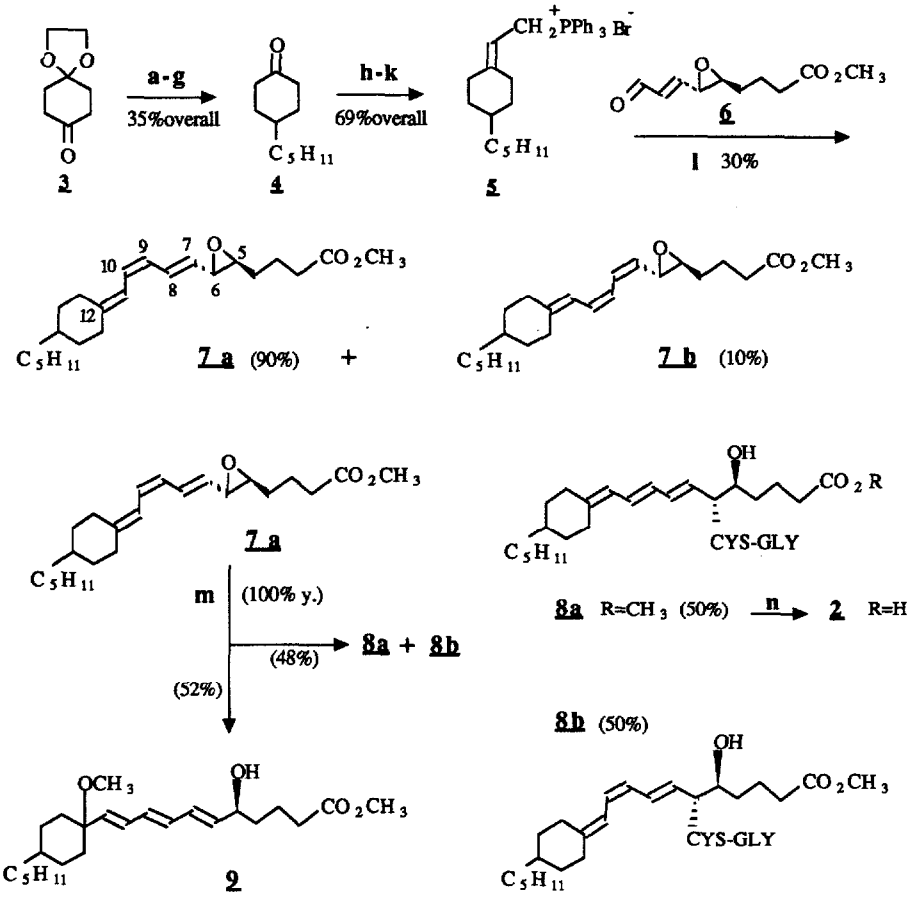


2

Our synthesis of the required precursor **5** corresponding to C-10/C-20 (Scheme 1) starts with 4-pentyl cyclohexanone[10] **4**, conveniently obtained from 1,4 cyclohexadione monoethyleneketal **3** The ketone **4** is transformed into 4-pentyl-cyclohexylidenylmethyl-triphenyl-phosphonium bromide **5** in 69 % overall yield by Wittig-Horner reaction [11], diisobutyl-aluminium hydride (DIBAH) reduction [12] and treatment by CBr_4 / PPh_3 [13].



Scheme 1 - **a** : LAH (100%y.) ; **b** : PTSCl, Py. (88%y.) ; **c** : NaI, Acetone ; **d** : AcOH, H_2O (68%y). **c** and **d**) ; **e** : Ethylene glycol, Toluene, PTS acid monohydrate (85%y.) ; **f** : $(C_5H_{11})_2$ Cu (CN) Li_2, THF, -78°, (79%y.); **g** : AcOH, H_2O (88%y.) ; **h** : 1 eq. $(C_2H_5O)_2P(O)CH_2CO_2Et$, 1eq. NaH (95%y.) ; **i** : 2 eq. Dibal-H, Toluene, 25°c (93%y.) ; **j** : 1.3 eq. CBr_4, 1.3eq PPh_3, 0°C ; **k** : 1.5 eq. PPh_3, CH_3CN, 82°, 48h (78%y. **j** and **k**); **l** : 1.05 eq. nBuLi, 15 eq. HMPA, anh. THF, -78° (30%y.) ; **m** : 3 eq. L-Cysteinylglycine, MeOH-H_2O-Et_3N 7-1-1, 4h ; **n** : 10eq. KOH, MeOH-H_2O 1-6.

Z-Selective Wittig condensation of the ylide **5** with the readily available pure 7E-(5S,6S)-epoxyenal **6** (^{1}H-NMR, 360 MHz, $J_{7,8}$ = 14.5), a key intermediate in the original stereocontrolled synthesis[14] of leukotriene LTA_4, affords **7a** (90 %) and its 7, 8 cis isomer **7b** (10 %), 30 % yield after HPLC purification[15]. The geometry of the characteristic triene is confirmed by 360 MHz ^{1}H NMR [15]. The isomer **7b** could be obtained as a result of isomerization

of the 7,8-double bound during the Wittig reaction and non-selective reaction with epoxyenal **6**. Several key factors[16] could affect the final stereochemistry of the reaction between the unsaturated aldehyde **6** and the semistabilized allylic ylide **5**. To our knowledge, this is the first example observed in leukotriene synthesis. We checked, on the one hand, that the Δ 7,8 isomerization of epoxyenal **6** was unsuccessful in the Wittig conditions (nBuLi, THF) and that, on the other hand, the 7E, 9Z isomer **7a** did not undergo partial isomerization to 7Z, 9Z isomer **7b** during isolation .

Quantitative S_N2 ring-opening of **7a** by L-cysteinylglycine (3 equi.) in methanol, water, triethylamine (7.1.1) yields a 1:1 mixture of the sulfido esters **8a** and **8b** (48% yield) . Noteworthy is the fact that S_N1 addition of the solvent to C-12 of **7a** competes with epoxide ring-opening and affords the new (5S)-hydroxy -12-methoxy LTB_4 analogue **9** in 52% yield; this possesses an all trans-geometry in the conjugated triene unit [17] as insured by its mode of formation [18]; the products were purified by HPLC and the stereochemistry was assigned by ^1H NMR [17]. Hydrolysis of **8a** with potassium hydroxide in methanol / water provides the new analogue **2** as its di-K salt in essentially quantitative yield . In binding studies using radiolabeled LTD_4 and a guinea pig lung membrane preparation [19], compound **2** has an affinity two orders of magnitude lower than LTD_4 for the LTD_4 receptor (7×10^{-7} M compared to 2×10^{-9} M).

This result agrees with the contractile agonist activity ($EC_{50} = 2 \times 10^{-7}$M). Unfortunately, this analogue fails to antagonize the effects of LTD_4 in the guinea pig ileum smooth muscle contraction assay [20]. Introduction of the 12,15- annelation in the lipophilic region of **1** does not reverse its activity from leukotriene agonism to antagonism but causes an important reduction in intrinsic activity. Clearly, these results, in a model which restricts the conformationally mobile hydrophobic moiety, suggest that the stereochemical requirements of the ω portion of the leukotriene for the interactions with the LTD_4 binding site are strictly defined. Additional results concerning the pharmacological profile for these analogues will be reported elsewhere.

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15. Physical data for **7a** and **7b** : HPLC: Waters μPorasil (8 mm x 300mm)Hexane-AcOEt-Et_3N 99-1-1, 2 ml / min flow rate, Rt = 17 min **7a** and 20 min **7b**, monitored at 280 nm. ^{1}H-NMR (360 MHz, $CDCl_3$) **7a** : δ 0.87 (t, 3H), 1.26 (m,8H), 1.81 (m, 2H, H_3), 2.13 (m), 2.27 (m), 2.37 (t, 2H, H_2), 2.85 (m, H_5), 3.16 (q, H_6, $J_{6,7}$ = 7.81 Hz), 3.66 (s, 3H), 5.37 (q, H_7 , $J_{7,8}$= 15.13Hz), 5.88 (t, H_9, $J_{9,10}$ = 11 Hz), 6.05 to 6.42 (m, 2H, H_{10} and H_{11}), 6.89 (q, H_8, $J_{8,9}$ = 11.24 Hz). MS (EI) m/z : 360, 342, 329, 231, 147, 129 (100%), 101. **7b** : δ 0.87 (t,3H), 1.26 (m,8H), 1.81 (m, 2H, H_3), 2.13 (m), 2.27 (m), 2.37 (t, 2H, H_2), 2.85 (m, H_5), 3.50 (d, H_6 , $J_{6,7}$ = 8.3 Hz), 3.66 (s, 3H), 5.06 (t, H_7 $J_{7,8}$ = 11.23 Hz), 6.05 to 6.42 (m, 2H, H_{10} and H_{11}), 6.72 (t, H_8, $J_{8,9}$ = 11.23Hz, 6.06 (q, H9 , $J_{9,10}$ = 11 Hz) ; MS (EI) m/z : 360, 342, 329, 231, 147, 129 (100%), 101.
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17. Physical data for **8a** and **8b** : RP-HPLC : Merck Lichrosorb RP18 (4mm x 250mm), MeOH-H_2O 85-15, pH 5.6, 0.450 ml / min flow rate, Rt = 18.5 min **8a** and 20 min **8b** , monitored at 270 nm. UV (MeOH-H_2O 85-15) : λ max = 276 nm . ^{1}H-NMR (360 MHz, CD_3OD): **8a** δ 0.92 (t, 3H), 1.20 to 1.40 (m, 8H), 1.53 (m, 2H, H_4), 1.83 (m, 2H, H_3), 1.90 (m), 2.37 (t, 2H, H_2), 2.79 (m, 1H), 2.84 (m), 2.94 (m, 1H), 3.44 (m, H_6), 3.69 (s, 3H), 3.73 (m, H_5), 3.78 (m, 1H), 3.92 (m, 2H), 5.61 (q, H_7 $J_{7,8}$ = 15.0 Hz), 5.85 (d, H_{11}), 6.17 (q, H_9 $J_{9,10}$ =14,7 Hz), 6.57(q, H_{10}), 6.30 (q, H_8).MS (FAB positif, NBA) m/z 539, 361, 343; **8b** δ 0.92 (t, 3H), 1.20 to 1.40 (m, 8H), 1.53 (m, 2H, H_4), 1.83 (m, 2H,H_3), 1.90 (m), 2.37 (t, 2H, H_2), 2.79 (m, 1H), 2.84 (m), 2.94 (m, 1H), 3.46 (m, H_6), 3.69 (s, 3H), 3.73 (m, H_5), 3.78 (m, 1H), 3.92 (m, 2H), 5.66 (q, H_7, $J_{7,8}$ = 16.0), 5.96 (t, H_9, $J_{9,10}$ = 11.0), 6.26 (m, H_{10}), 6.34 (q, H_{11}), 6.73(q,H_8). MS (FAB positif, NBA) m/z 539, 361, 343.
    9 : RP-HPLC : Macherey-Nagel Nucleosil C18 (10 μ - 8mm x 300mm), MeOH-H_2O 85-15, pH 5.6, 1.6 ml / min flow rate, Rt = 36.5 min, monitored at 270 nm. UV (MeOH-H_2O 85-15) : λ max = 258, 268, 278 nm. ^{1}H-NMR (360 MHz, CD_3OD) δ 0.95 (t,3H),1.56 (m,2H, H_4), 1.70 (m, 2H, H_3), 2.40 (t, 2 H, H_2), 3.13 (s,3H), 3.69 (s, 3H), 4.14 (q, H_5 $J_{5,6}$ = 8.3 Hz), 5.74 (q, H_6, $J_{6,7}$ = 13.68 Hz), 5.63 (d, H_{11}, $J_{10,11}$ =15.14 Hz), 6.22 to 6.35 (m, H_7, H_8, H_9 , H_{10}, $J_{9,10}$= 9.76 Hz).MS (EI, 30 ev) m/z 125,191, 234, 263, 333 (100%).
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