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SYNTHESIS OF NOVEL ANTAGONISTS OF LEUKOTRIENE B_4

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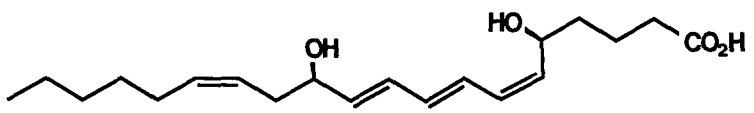
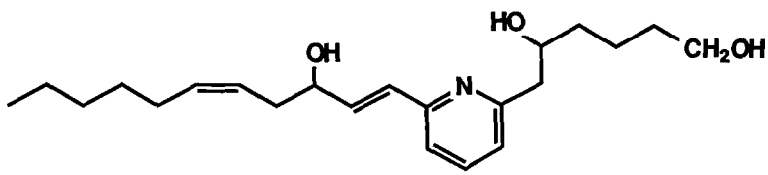
Abstract As part of a program to identify a stable LTB_4 antagonist, several novel compounds containing a 2,6-disubstituted pyridine ring in place of carbons 7-9 of the natural eicosanoid were synthesized utilizing a Pd-Cu cross coupling reaction

Leukotriene B_4, 5S,12R-6,14-cis-8,10-trans-eicosatetraenoic acid (LTB_4), is believed to be a potent mediator of immediate hypersensitivity reactions and inflammation [1] It stimulates aggregation and degranulation of human neutrophils, promotes chemotaxis and chemokinesis of leukocytes, and is a mediator of lysosomal enzyme release and superoxide generation [2] LTB_4 also constricts respiratory smooth muscle *via* an indirect mechanism involving stimulation of the release of cyclooxygenase products [3]

Receptors for leukotriene B_4 have been characterized in human neutrophils and HL-60 cells [4] Given its significant biological activity it is possible that a receptor level antagonist of leukotriene B_4 might be therapeutically useful in the treatment of inflammatory diseases Although many compounds are known which interfere with the biosynthesis of LTB_4,[5] relatively few agents have been prepared which directly block its pharmacological effects [6] We have begun a program with the goal of identifying a stable LTB_4 receptor level antagonist Our strategy is to design molecules in which the cis,trans,trans-triene unit of leukotriene B_4 has been modified so as to render it a more stable entity Herein we describe our initial efforts in this area with the synthesis of compounds (typified by U-75302) where a 2,6-disubstituted pyridine ring has replaced carbons 7-9 of LTB_4 The



LTB_4

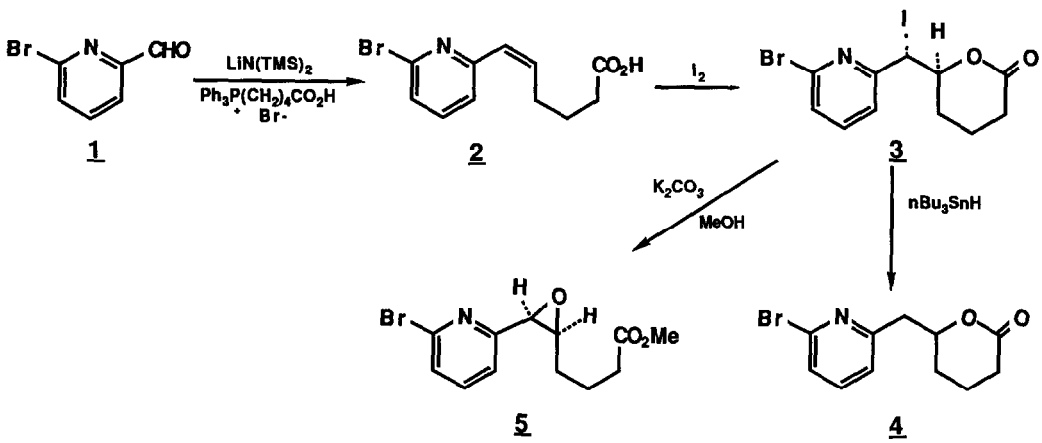


U-75302

pyridine ring was selected with the hope that the basic nitrogen would be a source of internal hydrogen bonding to the C-5 hydroxyl group, thereby enhancing the molecule's conformational similarity to LTB_4

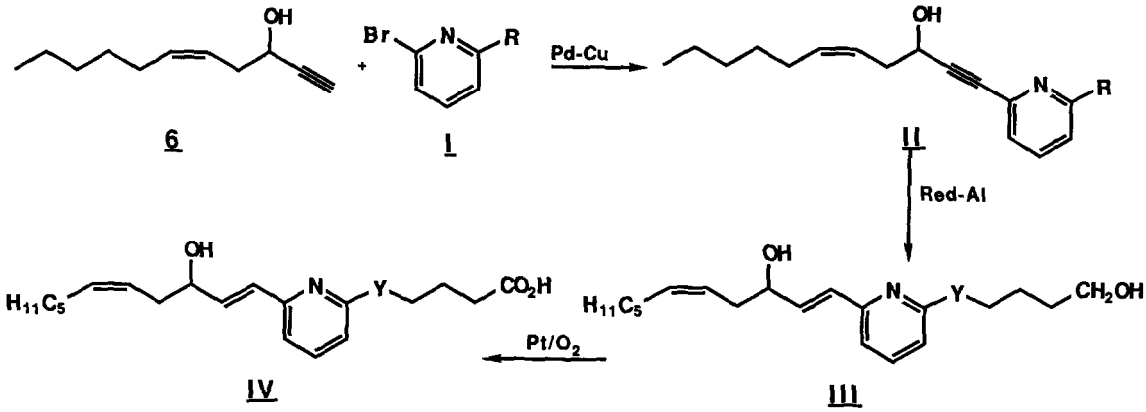
The carbon skeleton of the target compound and some closely related analogs were assembled by a series of palladium-copper catalyzed cross coupling reactions[7] between suitably functionalized pyridyl bromides and 3-hydroxy-undec-5Z-en-1-yne (6) [8] The required pyridyl bromides were prepared starting with 6-bromo-2-formyl pyridine (1)[9] (Scheme 1) Reaction of 1 with the ylid formed from 4-carboxybutyltriphenylphosphonium bromide and lithium (bis)trimethylsilylamide (THF, 23°C) afforded the corresponding olefin-acid as a 4 1 mixture of cis/trans isomers in 69% yield [10] Careful chromatography of the mixture allowed the isolation of the pure cis olefin 2 in 54% yield Iodolactonization of 2 (I_2, $KHCO_3$, KI, aq THF) provided iodolactone 3 in 94% yield Reductive removal of the iodine of 3 with tri-n-butyltin hydride (AIBN, toluene, 75°C) afforded lactone 4 (71%) Alternatively, base catalyzed methanolysis of 3 cleanly gave epoxy-ester 5 in 81% yield

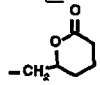
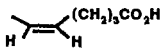
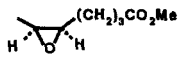
Scheme 1[16]



The palladium-copper catalyzed coupling reactions between the bromopyridine substrates I and acetylene 6 proceeded smoothly as shown in Scheme 2 In general, the reactions were carried out in triethlyamine at 50°C for 1 5-4 h using 1 2 equivalents of acetylene and 2 mol % of (bis)triphenylphosphinepalladium-dichloride The yields for this process ranged from good to excellent Treatment of the coupled products II with excess sodium (bis)-2-methoxyethoxy aluminum hydride (Red-Al) (0°C, toluene) served to reduce the acetylene to the desired trans allylic alcohol as well as effected reduction of the C-1 carbonyl [11] In the case of IIa it was necessary to run the reaction at 23°C to allow for complete reduction, producing IIIa [12] The corresponding carboxylic acids IV were obtained via selective oxidation of the primary alcohol of III with oxygen, catalyzed by platinum black (aq acetone, 50°C) [13]

Scheme 2[16]



	I	R	II (%)	Y	III (%)	IV (%)
a.	4		99		U-75302(92)	U-75305(32)
b.	2		65		U-75483(68)	U-75360(60)
c.	5		97		U-75485(65)	U-76015(52)

Compounds III and IV were tested for their ability to inhibit the binding of 1nM [^{3}H]LTB$_4$ to human neutrophil membranes [14] At a dose of 1 μM, all of the compounds were found to compete effectively for receptor sites with inhibitions ranging from 40-92% (% inhibition for 1 μM LTB$_4$ = 96) In addition, several of these compounds have been found to significantly inhibit LTB$_4$-induced neutrophil aggregation at concentrations at least 100 times less than their inherent agonist activity [14] The compounds were also tested for their effect on LTB$_4$-induced contraction of guinea pig lung parenchyma strips [15] At least one compound, U-75302 (IIIa), proved to be an effective antagonist in this assay at a dose (0 3 μM) where it was void of agonist activity

Several structural variants of these compounds are currently under investigation in order to probe the nature of the interaction of this class of compounds with the leukotriene B$_4$ receptor The results of these studies, as well as detailed biological evaluations, will be reported separately

References and Notes

1 (a) B Samuelsson, Science, 220, 568-575 (1983) (b) R A Lewis and K F Austen, J Clin Invest , 73, 889-897 (1984) (c) P Borgeat and B Samuelsson, J Biol Chem , 254, 7865-7869 (1979) (d) P Borgeat and B Samuelsson, J Biol Chem , 254, 2643-2646 (1979)

2 (a) A W Ford-Hutchinson, M A Bray, M V Doig, M E Shipley, and M J H Smith, Nature (London), 286, 264-265 (1980) (b) J Palmblad, C L Malmsten, A M Udén, O Rådmark, L Engstedt and B Samuelsson, Blood, 58, 658-661 (1981) (c) A W Ford-Hutchinson, M A Bray, M E Shipley, M V Doig, and M J H Smith, Int J Immunopharmacol, 2, 232 (1980) (d) J T O'Flaherty, M J Hammett, T B Shewmake, R L Wykle, S H Love, C E McCall, M J Thomas, Biochem Biophys Res Commun, 103, 552-558 (1981) (e) G M Bokoch and P W Reed, J Biol Chem, 256, 5317-5320 (1981) (f) E J Goetzl and W Pickett, J Immunol, 125, 1789-1791 (1980)

3 (a) P Sirois, S Roy, P Borgeat, S Picard and P Vallerand, Prostaglandins, Leukotrienes and Medicine, 8, 157-170 (1982) (b) K F Austen, E J Corey, J Drazen and A G Leitch, Brit J Pharmacol, 80, 47-53 (1983) (c) M Samhoun and P J Piper, Prostaglandins, 27, 711-724 (1984)

4 (a) A H Lin, P L Ruppel and R R Gorman, Prostaglandins, 28, 837-849 (1984) (b) A H Lin, P L Ruppel and R R Gorman, Biochem Biophys Res Commun, 128, 878-883 (1985) (c) C W Benjamin, P L Ruppel and R R Gorman, J Biol Chem, 260, 14208-14213 (1985) (d) D W Goldman and E J Goetzl, J Immunol 129, 1600-1604 (1982) (e) D W Goldman and E J Goetzl, J Exp Med, 159, 1027 (1984) (f) R A Kreisle and C W Parker, J Exp Med, 157, 628-641 (1983)

5 J R Cashman, Pharm Res, 253-261 (1985)

6 (a) E J Goetzl and W C Pickett, J Exp Med, 153, 482-487 (1981) (b) H J Showell, I G Otterness, A Marfat and E J Corey, Biochem Biophys Res Commun, 106, 741-747 (1982) (c) S J Feinmark, J Å Lindgren, H -E Claesson, C Malmsten and B Samuelsson, FEBS Lett, 136, 141-144 (1981) (d) M Namiki, Y Igarashi, K Sakamoto, T Nakamura and Y Koga, Biochem Biophys Res Commun, 138, 540-546 (1986)

7 (a) K Sonogashira, Y Tohda, and N Hagihara, Tetrahedron Lett 4467-4470 (1975) (b) S Takahashi, Y Kuroyama, K Sonogashira, N Hagihara, Synthesis, 627-630 (1980) (c) K C Nicolaou, R E Zipkin, R E Dolle, and B D Harris, J Am Chem Soc, 106, 3548 (1984)

8 Propargyl alcohol 6 was synthesized by a modification of the procedure reported by S Tsuboi, T Masuda, A Takeda, Chem Lett 1829-1832 (1983)

9 J E Parks, B E Wagner and R H Holm, Inorganic Chem, 10, 2472-2478 (1971)

10 The preferential formation of the cis isomer using pyridine aldehydes in this reaction is in contrast to studies reported by Maryanoff on the Wittig reaction of unstablized ylids and benzaldehydes in the presence of lithium (bis)hexamethyldisilylazide See B E Maryanoff, B A Duhl-Emswiler, Tetrahedron Lett, 4185-4188 (1981)

11 S E Denmark and T K Jones, J Org Chem, 47, 4595-4597 (1982)

12 Reaction of IIa with Red-Al in toluene at 0°C afforded a 62% yield of the corresponding lactol

13 J Fried and J C Sih, Tetrahedron Lett 3899-3902 (1973)

14 Neutrophil studies with these analogs, including competitive binding experiments and aggregation inhibition were performed by Dr Robert R Gorman and Alice H Lin, The Upjohn Company

15 Evaluations of these analogs for their effects on guinea pig lung parenchyma were accomplished by Dr Frank A Fitzpatrick and Norman J Crittenden, The Upjohn Company

16 All new compounds exhibited satisfactory ^{1}H NMR, IR and elemental analysis and/or high resolution mass spectral data Diastereomeric mixtures of compounds II, III and IV were not separated

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