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PREPARATION OF THE LEUKOTRIENE B_4 ANALOG; 13,13-DIFLUORO-LEUKOTRIENE B_4

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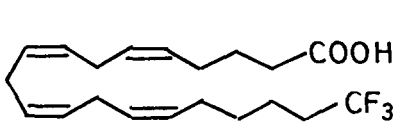
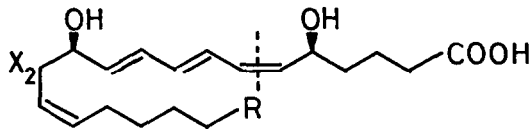
Summary: The procedure for the synthesis of 13,13-difluoro-leukotriene B_4 [(5S,12S)-5,12-Dihydroxy-6,14-cis-8,10-trans-Eicosatetraenoic Acid] is discribed.

The incorporation of a fluorine atom(s) into a molecule of biological interest is attracting much attention in the fields of medicinal and organofluorine chemistry.[1] Fluoro analogs may possibly elicit biological behavior different from that of a parent molecule due to the peculiar characteristics of fluorine. Recently, we prepared 20,20,20-trifluoro-arachidonic acid ($20F_3$-AA)(1) and 20,20,20-trifluoro-leukotriene B_4 ($20F_3$-LTB_4)(2) and found the latter to possess the same degree of chemotactic activity toward human neutrophils as natural LTB_4.[2] The metabolical stability of $20F_3$-LTB_4 when incubated with human neutrophils probably blocking *omega-oxidation was also demonstrated.*



$20F_3$-AA

1

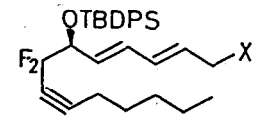


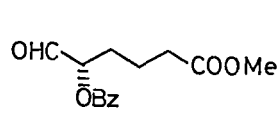
X	R		
H	CF_3	$20F_3$-LTB_4	2
F	CH_3	$13F_2$-LTB_4	3

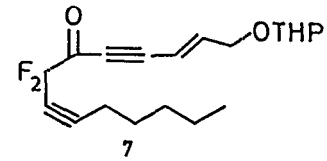
In connection with the chemistry of $20F_3$-LTB_4 and $20F_3$-AA, the synthesis of 13,13-difluoro-leukotriene B_4 ($13F_2$-LTB_4)(3) was carried out. The analog 3 , having C-12 hydroxyl group whose polarity is enhanced by virtue of the strong electron withdrawal effect of fluorine, may show enhanced biological activity or give some significant informations as to the nature of the binding site of the enzyme or receptor site of target tissues. Disconnection of $13F_2$-LTB_4 (3) at C_6-C_7 double bond (dotted line) led to the fluorine-containing fragment (4). Since 6 as a coupling partner with 4 has already been prepared in optically pure form,[3] it is of great importance to prepare fluorinated fragment (4) in optically active form.

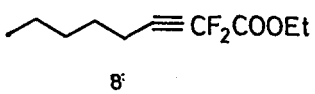
Having a knowledge[4] that asymmetric reduction of fluoroalkyl alkynyl ketone with Alpine-Borane[5] gave higher optical yield of the product than with BINAL-H[6] reagent, the asymmetric reduction of ketone (7), obtained in 79% yield by reaction of difluoro-ester (8)[7] with acetylene derivative (9)[8] (n-BuLi/THF, -78°C), was carried out with R-Alpine Borane to afford the (s)-alcohol (10)(72% yield).[9] The reduction of the C_4-C_5 triple bond (Red-Al/THF, 75%) to the trans double bond, following protection of secondary alcohol ($tBuPh_2SiCl$, imidazole/DMF, 74%) and deprotection of THP group (AcOH-THF-H_2O=3:2:2, 84%) gave the alcohol (4)([α]$_D$+80.9, c=0.69, $CHCl_3$) which was converted to the phosphonium salt (5)(CBr_4, DIPHOS, 91% then Ph_3P/CH_3CN, 80%). The Wittig reaction of 5 with 6 (nBuLi/THF-HMPA) gave a 3 : 1 mixture of 6Z and 6E stereoisomers (11a,11b) (63% yield), which could be separated by flash column chromatography. After desilylation (nBu_4NF/THF, 51%) and partial reduction of the triple bond

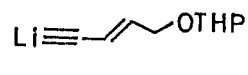
(H_2/Pd-$BaSO_4$-quinoline, 44%), the ester groups were cleaved (K_2CO_3/MeOH) to give the $13F_2$-LTB_4 (3), which was purified by RP-HPLC (C_{18}-column, MeOH-H_2O-AcOH=3:1:trace).[10] The results of biological experiments on $13F_2$-LTB_4 (3) will be presented in a future paper.

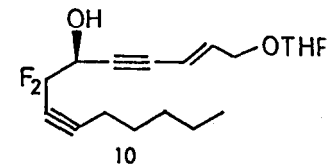


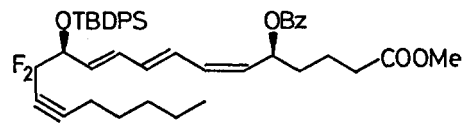












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References and Notes

1) Biomedical Aspects of Fluorine Chemistry, ed. by R. Filler and Y. Kobayashi, Elsevier Biomedical Press and Kodansha Ltd., 1982. 2) Y. Tanaka, T. M. Klauck, W. Jubiz, T. Taguchi, Y. Hanzawa, A. Igarashi, K. Inazawa, Y. Kobayashi and R. G. Briggs, Arch. Biochem. Biophys., 263, 178 (1988). 3) E. J. Corey, A. Marfat, G. Goto, F. Brion, J. Am. Chem. Soc., 102, 7984 (1980). 4) Y. Hanzawa, k. Kawaqoe and Y. Kobayashi, Chem. Pharm. Bull., 35, 2609 (1987). 5) B-3-Pinanyl-9-borabicyclo[3.3.1]-nonane; M. M. Midland, A. Tramontano, A. Kazubski, R. S. Graham, D. J. S. Tai and D. B. Cardin, Tetrahedron, 40, 1317 (1984). 6) Binaphthol modified aluminum hydride reagent; R. Noyori, I. Tomino, Y. Tanimoto and M. Nishizawa, J. Am. Chem. Soc., 106, 6709 (1984). R. Noyori, I. Tomino, N. Yamada and M. Nishizawa, ibid., 106, 6717 (1984). 7) Compound (8) was prepared by reaction of the corresponding ketoester with diethylaminosulfur trifluoride (DAST) in 75% yield. 8) K. C. Nicolaou and S. E. Webber, J. Chem. Soc., Chem. Commun., 1986, 1816. 9) The absolute configuration and enantiomeric excess (96%) of 10 were confirmed by converting it to 4 and comparison of its rotational value with that derived from the alternate synthesis which will be published in a full paper. 10) $13F_2$-LTB_4(3) was characterized by converting it to its methyl ester under normal conditions (CH_2N_2/Et_2O, 0°C). Yield by saponification and esterification was 85%. ^{1}H-NMR spectrum ($CDCl_3$) δ;0.9 (t, 3H, J=7Hz, 20-H), 1.3-1.8 (m, 12H), 2.15-2.37 (m, 4H, 12-H, 16-H), 3.67 (s, 3H, OMe), 4.37 (bs, 1H, 12-H), 4.6(m, 1H, 5-H), 5.45 (m, 2H, 6-H, 15-H), 5.74 (dd, 1H, J=14.7 and 10.7Hz, 11-H), 5.86 (m, 1H, 14-H), 6.09 (t, 1H, J=11.1Hz, 7-H), 6.25 (dd, 1H, J=14.7 and 10.7Hz, 9-H), 6.47 (dd, 1H, J=15.4 amd 10.7Hz, 10-H), 6.56 (dd, 1H, J=14.7 and 11.5Hz, 8-H). ^{19}F-NMR ($CDCl_3$); 39.6ppm (m) (at a higher field from the external benzotrifluoride signal). $[\alpha]_D$-17.3 (c=0.31, $CHCl_3$). UV λ_{max}^{EtOH}nm ; 260, 270, 281. MS; m/z 386 (M^+). IR (CCl_4)νcm^{-1}; 3500, 1700.

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