A Short Route to 8,11-Thioleukotriene B_4 Lithium Salt

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O sal de lítio do 8,11- tioleucotrieno B_4 (**2**) foi preparado, como uma mistura diastereomérica inseparável, através de uma rota sintética curta consistindo em quatro etapas e tendo como reações-chave: (a) a metalação de 2-iodotiofeno que então reage com um aldeído apropriado [(**5**) ou (**6**)] para produzir os derivados 2-iodo-5-substituído tiofeno [(**7**) ou (**8**)] e (b) a reação de acoplamento cruzado, catalisada por Pd-Cu, entre os derivados 2-iodo-5-substituído tiofeno [(**7**) ou (**8**)] e o alcino (**9**), levando aos derivados 2,5-disubstituído tiofeno [(**10**) ou (**11**)], que são os precursores imediatos de (**2**). O sal de lítio (**2**) foi submetido a ensaios biológicos tendo-se mostrado como agonista do produto natural LTB_4(**1**).

The title compound (**2**) was prepared, as an inseparable diastereomeric mixture, by a short four step route based on two key reactions: (a) the metallation of 2-iodothiophene followed by reaction with the appropriate aldehyde [(**5**) or (**6**)] affording a 2-iodo-5-substituted thiophene [(**7**) or (**8**)], and (b) the Pd-Cu catalyzed cross coupling reaction of 2-iodo-5-substituted thiophene {(**7**) or (**8**)] with the alkyne (**9**), leading to 2,5-disubstituted thiophene derivatives [(**10**) or (**11**)] which are immediate precursors of the title compound. The lithium salt (**2**) was submitted for biological screening and shown to be an agonist of natural LTB_4(**1**).

Key words: *leukotriene synthesis; 2-iodo-5-lithiothiophene; 8,11-thioleukotriene B_4.*

Introduction

Leukotriene B_4 (LTB_4, **1**), a potent chemotactic agent isolated from human polymorphonuclear leukocytes, is believed to play an important role in inflammatory and allergic processes[1].

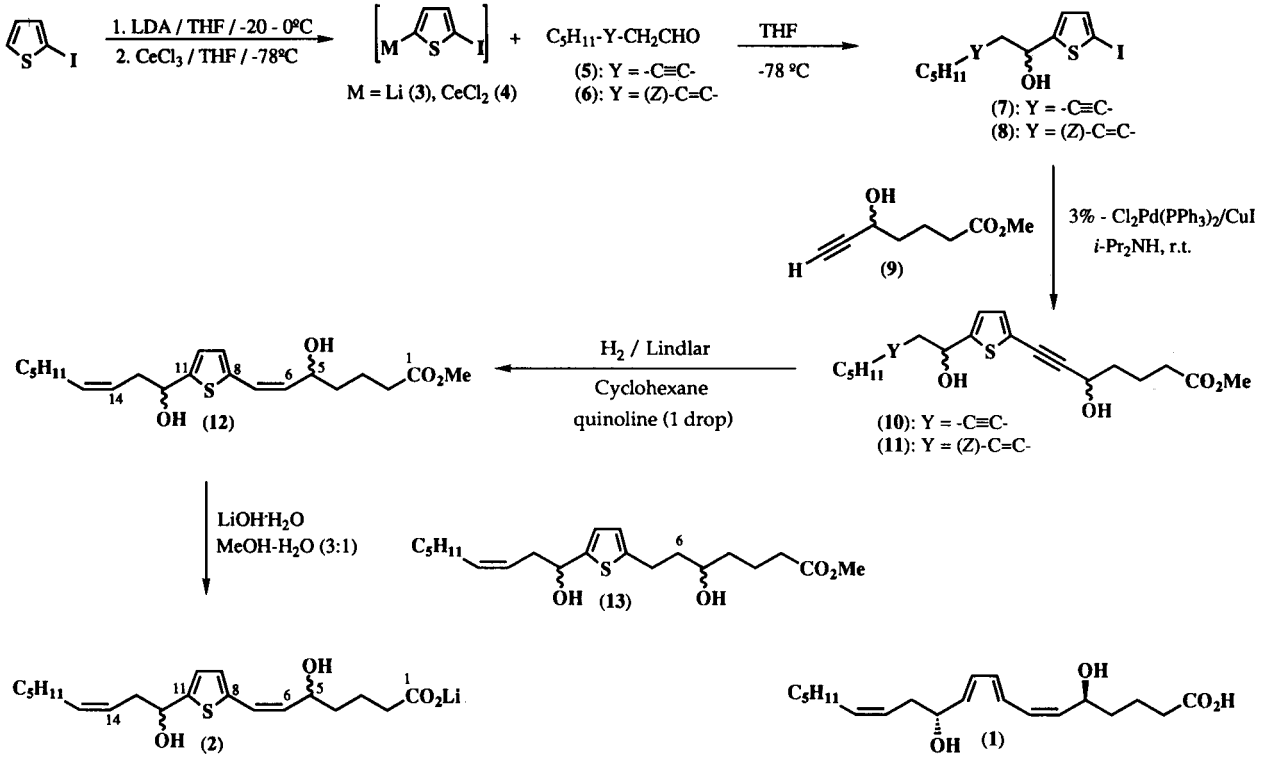
As part of a programme[2] to synthesise conformationally restricted analogues of leukotrienes for structure-activity studies, we recently[3] introduced the use of 2-iodo-5-lithiothiophene for the preparation of novel sulphur bridged LTB_3 analogues. In this paper we further illustrate the scope of this procedure by describing a very short route to 8,11-thio-LTB_4 lithium salt (2), an aromatic[4] LTB_4 analogue, in which the 8*E*, 10*E*-diene unit is constrained by incorporation into an aromatic ring (Scheme).

Method

The preparation of 2-iodo-5-lithiothiophene (**3**) from 2-iodothiphene and LDA has been described in one of our previous publications[3]. Addition of 3-nonynal[5] (**5**), at -78°C, to a THF solution of (**3**) led to (**7**), contaminated by a trace impurity, in yields varying from 34 to 41% after chromatography. On the assumption that the by-product resulted from deprotonation of (**5**), the less basic, more nucleophilic organocerium[6] derivative (**4**) was utilized. Thus, a THF solution of (**4**), prepared by addition of organolithium reagent (**3**) to anhydrous $CeCl_3$, was slowly added to a cold (-78°C) solution of aldehyde (**5**) giving the required product (**7**) in yields up to 78%, after chromatography, containing little or none of the earlier by-product.

Although good results could be obtained employing the organocerium derivative (**4**), the procedure for drying $CeCl_3$

SCHEME



was somewhat tedious, and so an alternative procedure was sought. Thus, we decided to investigate the use of the alkenyl aldehyde[7] (**6**), in which α-carbonyl deprotonation would be expected to occur less readily than in the corresponding alkyne (**5**). Thus, when the aldehyde (**6**) was added to a cold (-78°C) solution of the lithium salt (**3**) adduct (**8**) was obtained in 58% yield, after chromatography.

Compounds (**7**) and (**8**) were then submitted to the Pd-Cu cross-coupling reaction[8] with terminal alkyne[2b,3] (**9**) in diisopropylamine, at room temperature, affording the products (**10**) and (**11**) in 49-60% and 54% yields respectively, after chromatography.

Based on studies described in the accompanying paper[9], the reduction of (**10**) and (**11**) was effected with molecular hydrogen in the presence of Lindlar catalyst poisoned with quinoline, in cyclohexane as solvent. Thus reduction of diyne (**10**) led to the methyl ester (**12**) in 98% yield after chromatography. Reduction of enyne (**11**) was carried out in the same manner, affording (**12**) in 61% yield together with 11% of the 6,7-saturated by-product (**13**). Compound (**12**), which was fully characterised, was saponified with LiOH in MeOH-H_2O (3:1), affording (**2**) in quantitative yields after removal of the solvent *in vacuo*[10]. This procedure gave a diastereomeric mixture of the lithium salts (**2**), which could not be separated chromatographically, and which was characterized by 400 MHz ^{1}H NMR spectroscopy. The acid corresponding to (**2**) was unstable and biological screening was therefore carried on lithium salts (**2**)[11]. When rested *in vitro*, the mixture (**2**) promoted the adherence of human PMN cells to the cells of living blood vessel walls. Injected intradermally into rabbits, (**2**) caused leakage of plasma protein showing that it is undoubtedly an LTB_4 agonist.

In summary, two short synthetic routes to title compound (**2**) were developed. The preferred route has as its key step addiction of the organocerium reagent (**4**) to the alkynyl aldehyde (**5**) in view of the greater accessibility of (**5**) *vs.* (**6**) and the fact that the stereoselective reduction of diyne (**10**) proceeds more efficiently than the reduction of enyne (**11**).

Representative Procedures. ^{1}H NMR spectra were recorded on a Jeol JNM GX-400 (400 MHz) spectrometer. ^{13}C NMR spectra were recorded using a Jeol EX 90 (22.4 MHz) or Jeol JNM GX-400 (100 MHz) spectrometer. Infrared spectra (IR) were recorded using a Perkin-Elmer FT-IR 1720-X spectrometer. The liquid samples were deposited as thin films on sodium chloride plates. Low resolution mass spectra (MS) were recorded on a Kratos MS25 and high resolution mass spectra were recorded on a V. G. Analytical ZAB-IF spectrometer.

(a) 2-(1-Hydroxynon-3-ynyl)-5-iodothiophene (**7**). Cerium chloride heptahydrate (1.86 g, 5 mmol) was pounded in a mortar until finely divided and placed in a 50 ml round bottom flask. The flask was fitted with a gas outlet, connected to a vacuum pump and evacuated to 0.5 mm Hg with constant stirring. The system was heated initially to 190°C (1 h) and

then cooled to 150°C remaining at this temperature and pressure for an additional period of 9 h. The cerium salt was then allowed to cool to r.t., N_2 was introduced and THF (10 ml, freshly distilled) was slowly added at 0 °C with vigorous stirring. This THF suspension was stirred overnight in order to obtain a white uniformly dispersed suspension[6]. This was cooled to -78 °C and a solution of 2-iodo-5-lihiothiophene (**3**) [4.10 mmol, prepared from BuLi (2.6 M solution in hexane, 1.73 ml, 4.5 mmol) diisopropylamine (435 mg, 4.3 mmol) and 2-iodothiophene (861 mg, 4.1 mmol), according to reference 1c] in THF (10 ml), at -78°C, was slowly added *via* a cannula. The mixture was allowed to stir for 2 h, at -78°C, before 3-nonynal (**5**)[5] (622 mg, 4.5 mmol) was added and stirring was continued for 1 h. The reaction temperature was allowed to warm naturally to 0 °C, before aqueous HOAc solution (10 ml, 10%) was added and the product was isolated by extraction with Et_2O (3 × 10 ml). The organic fractions were combined, washed with brine (25 ml), $NaHCO_3$ (25 ml), brine (25 ml), dried ($MgSO_4$) and the solvent was removed *in vacuo*. The crude product was purified by centrifugal chromatography (petrol-EtOAc, 9:1) to afford *2-(1-hydroxynon-3-ynyl)-5-iodothiophene* (**7**) (1.11g, 78%) as a yellow oil; R_f 0.30 (petrol-EtOAc, 6:1); [Found M^+ 348.0045. $C_{13}H_{17}IOS$ requires 348.0045]; υ_{max} 3386 (OH), 2930 and 2858 (CH_2) cm^{-1}; δ_H (400 MHz, $CDCl_3$, TMS) 0.93 (3H, br t, H-9'), 1.36 - 1.39 (4 H, m, H-7' and H-8'), 1.47 - 1.55 (2 H, m, H-6'), 2.20 - 2.24 (2 H, m, H-5'), 2.71 - 2.75 (3 H, m, H-2' and exchangeable OH), 5.03 - 5.06 (1 H, m, H-1'), 6.74 (1 H, d, *J* 3.7 Hz, 3- or 4-Th.-H), 7.15 (1 H, d, *J* 3.7 Hz, 3- or 4-Th.-H); δ_C (22.4 MHz, $CDCl_3$) 14.00 (C-9'), 18.69, 22.17, 28.46, 29.82 (C-5' to C-8'), 30.99 (C-2'), 68.76 (C-1'), 72.68 (Th.-C-5), 74.91, 84.58 (C-3' and C-4'), 125.48, 136.35 (Th.-C-3 and Th.-C-4), 152.82 (Th.-C-2); m/z 348 (M^+, 5%), 239 (100, M^+ - C_8H_{13}).

(b) 6,7,14,15-Tetradehydro-8,11-thio-LTB4 methil ester (**10**). Cooper (I) Iodide (6 mg, 3 mol%) was added to a mixture of bis-(triphenylphosphine)palladium(II) chloride (23 mg, 3 mol%), 2-(1-hydroxynon-3-ynyl)-5-iodothiophene (**7**) (384 mg, 1.09 mmol) and methyl 5-hydroxyhept-6-ynoate (**10**) (172 mg, 1.1 mmol) in freshly distilled, dry, diisopropulamine (3 ml) under a nitrogen atmosphere and at room temperature. The mixture was allowed to stir until TLC showed all starting material disappeared (*ca.* 4 h). The precipitate was then removed by filtration, washed with ether (3 × 5 ml) and the solvent was removed from the combined filtrates *in vacuo*. After centrifugal chromatography (petrol-EtOAc, 5:1), *6,7,14,15-tetradehydro-8,11-thio-LTB4 methyl ester* (**10**) (249 mg, 60%) was obtained as an yellow oil; R_f 0.20 (petrol - EtOAc, 3:1); [Found M^+ 376.1708. $C_{21}H_{28}O4S$ requires 37c.1708]; υ_{max} 3435 (OH), 2930 (CH_2), 2228 (C≡C), 1735 (CO ester) cm^{-1}; δ_H(400 MHz, $CDCl_3$) 0.89 (3 H, t, $J_{20,19}$ 7.0 Hz, H-20), 1.25 - 1.34 (4 H, m, H-18 and H-19), 1.45 - 1.49 (2 H, m, H-17), 1.80 - 1.85 (4 H, m, H-3 and H-4), 2.15 (2H, tt, $J_{16,17}$ 7.0 Hz, H-16), 2.39 (3 H, t, $H_{2,3}$ 7.0 Hz, H-2 and exchangeable OH), 2.66 - 2.70 (2 H, m, H-13), 3.01 (1 H, br s, exchangeable OH), 3.67 (3 H, s, OMe), 4.59 (1 H, br t, H-5), 4.97 (1 H, br t, H-12), 6.85 (1 H, dd, $J_{10,12}$ 0.9 Hz and $J_{10,9}$ 3.7 Hz, H-10), 7.04 (1 H, d, $J_{9,10}$ 3.7 Hz, H-9); δ_C (100 MHz, $CDCl_3$) 13.89 (C-20), 18.63, 20.56, 22.12 (C-17 to C-19), 28.45, 29.85 (C-3 and C-4), 30.95 (C-16), 33.51 (C-2), 36.82 (C-13) 51.16 (OMe), 62.42 (C-12), 68.79 (C-5), 74.92, 78.35, 84.43, 93.64 (C-6, C-7, C-14 and C-15), 121.60, 123.60 (C-8 and C-11), 131.88 (C-10), 148.69 (C-9), 173.93 (C-1); m/z 376 (M^+, 3%), 345 (2, M^+ - OMe), 235 (100, M^+ - 141), 74 (45, M^+ - $C_{18}H_{22}O_2S$)

(c) 8,11-Thio-LTB4methyl ester (**12**). By hydrogenation of 6,7,14,15-tetradehydro-8,11-thio-LTB4 methyl ester (**10**). A 50 ml two neck flask was fitted with a gas inlet and a rubber septum. A mixture of Lindlar catalyst (15 mg), cyclohexane (25 ml) and one drop of quinoline were added to the flask. The system was connected to a hydrogenator, purged with hydrogen and stirring was maintained for 20 min. under H_2 atmosphere in order to saturate the catalyst. The stirring was interrupted and a solution of (**10**) 38 mg, 0.1 mmol) in Et_2O (2 ml) was added. The magnetic stirring was resumed and maintained until H_2 was no longer being consumed Extra catalyst (15 mg) was then added to ensure that the theoretical amount of H_2 (4.5 ml) was consumed. Celite was then added to the mixture, the catalyst was filtered off, quinoline removed by extraction with $CuSO_4$ (1%, 15 ml), and removal of the solvent *in vacuo*. Gave 8,11-thio-LTB4 methyl ester (**12**) (37 mg, 98% yield) as a chromatographically and spectroscopically pure oil; R_f 0.18 (petrol - EtOAc, 2:1) [Found M^+ 380.2021. $C_{21}H_{32}O_4S$ requires 380.2021]; ν_{max} (CCl_4) 3462 (OH), 2930 (CH_2), 2859 (CH_2), 1741 (CO ester) cm^{-1}; δ_H(400 MHz, $CDCl_3$) 0.84 (3H, t, $J_{20,19}$ 6.9 Hz, H-20), 1.28 - 1.34 (6 H, m, H-17 to H-19), 1.57 - 1.84 (4 H, m, H-3 and H-4), 2.02 - 2.05 (3 H, m, H-16 and exchangeable OH), 2.31 - 2.39 (3 H, br t, H-2 and exchangeable OH), 2.54 - 2.65 (2 H, m, H-13), 3.66 (3H, s, OMe), 4.87 - 4.91 (2 H, m, H-5 and H-12), 5.38 - 5.42 (1 H, m, H-15), 5.50 - 5.61 (2H, m, H-6 and H-14), 6.50 (1 H, d, $J_{7,6}$ 11.9 Hz, H-7), 6.84 - 6.87 (2 H, m, H-9 and H-10); δ_C (100 MHz, $CDCl_3$) 14.02 (C-20), 20.69, 22.50, 27.42, 29.20, 31.45, 33.79, 36.85 (C-2 to C-4, and C-16 to C-19), 37.06/37.13 (diastereomeric C-13), 51.54 (OMe), 67.95, 69.92/69.96 (diastereomeric C-5 and C-12), 123.14, 123.62, 123.80, 128.21, 132.14, 134.26 (C-6, C-7, C-9, C-10, C-14 and C-15), 138.10, 148.95 (C-8 and C-11), 174.07 (C-1); m/z 363 (M^+ - OH, 8%), 177 (100, M^+ - 203).

(d) 8,11-Thio-LTB4 lithium salt (**2**). An aqueous solution of $LiOH.H_2O$ (1.9 x 10^{-2} M, 1 ml, 0.018 mmol) in MeOH-H_2O (3:1. 20 ml). The mixture was allowed to stirr overnight at r.t. bevore TLC showed no more starting material. The product (**2**) (7 mg, 100%) was isolated as a white solid after removal of the solvent *in vacuo*; δ_H(400 MHz, D_2O) 0.86 (3 H, br t, H-20), 1.23 (6 H, br s, H-17 to H-19), 1.64 - 1.72 (4 H, m, H-3 and H-4), 1.90 - 2.04 (2 H, m, H-16), 2.15 - 2.33 (2 H, m, H-2), 2.45 - 2.68 (2 H, m, H-13), 5.44 - 5.59 (2 H, m, H-6 and H-15), 5.62 - 5.64 (1 H, m, H-14), 6.58 (1 H, d, $J_{7,6}$ 11.7 Hz, H-7), 6.89 - 6.92 (2 H, m, H-9 and H-10).

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11. The screens were carried out by the Pharmaceutical Division of Fisons plc. Loughborough, U.K. We would like to thank Dr. J. R. Bantick for coordinating these studies.