Total synthesis of leukotriene B_4 analogues: 3-thia-LTB_4 and 3-thia-20,20,20-trifluoro-LTB_4

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Using *C*-furanosides as chiral precursors of (*Z*,*E*) 1,3-dienes has permitted the synthesis of two leukotriene B_4 analogues: 3-thia-LTB_4 and 3-thia-20,20,20-trifluoro-LTB_4.

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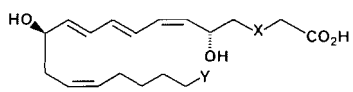
L'utilisation de *C*-furanosides comme précurseurs chiraux de diènes-1,3 de stéréochimie (*Z*,*E*) a permis de synthétiser divers analogues du leucotriène B_4, en particulier le thia-3 LTB_4 et le thia-3 trifluoro-20,20,20 LTB_4.

LTB_4 1 (Scheme 1) is an oxygenated metabolite of arachidonic acid that has been recently isolated (1), characterized, and synthesized by us and others (2, 3). Putative important roles in allergic, inflammatory (4), and immunological reactions (5) have been attributed to LTB_4. This local hormone is rapidly and extensively metabolized in vivo first by hydroxylation at C-20 to give **2** (ω-oxidation), followed by oxidation to the diacid **3** and subsequent β-oxidation of the two acidic chains (6). Metabolically stable analogues (7) of LTB_4 would lead to a better comprehension of the biological effects of this important mediator. This would also permit the elaboration of in vivo assays suitable for the evaluation of chemical entities as potential therapeutic agents. We would like to report herein on the total synthesis of two such analogues, 3-thia-LTB_4 **4** and 3-thia-20,20,20-trifluoro-LTB_4 **5**.

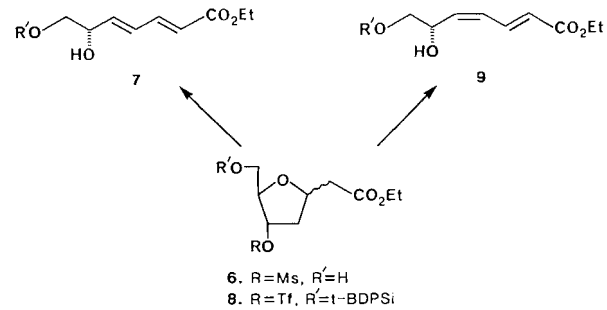


1. X = CH_2, Y = CH_3 : LTB_4
2. X = CH_2, Y = CH_2OH : 20-OH-LTB_4
3. X = CH_2, Y = CO_2H : 20-CO_2H-LTB_4
4. X = S, Y = CH_3 : 3-thia-LTB_4
5. X = S, Y = CF_3 : 3-thia-20-CF_3-LTB_4

SCHEME 1

Our approach to the synthesis of LTB_4 analogues is based on the utilization of properly substituted tetrahydrofurans as masked dienic functionalities. Recently, we described the transformation of *C*-furanosides (e.g. **6**) (Scheme 2) to chiral (*E*,*E*)-dienic precursors (e.g. **7**) in the synthesis of LTB_4 (2*a*). Our initial success was based on consecutive retro-Michael reaction followed by elimination of an activated oxygen in one chemical step. In this paper we present another alternative, which consists of using structurally similar tetrahydrofuran derivatives (e.g. **8**) as precursors of the (*Z*,*E*)-dienic functionality **9**. In this case the elimination of the leaving group is accomplished first, using the tetrahydrofuran ring as a template for the formation of the *cis* double bond (e.g. **13**). Our synthesis is summarized in Scheme 3.

The *C*-furanosides **12** were prepared from a known synthetic sequence using 2-deoxy-D-ribose **10** (8). The intracyclic olefin **13** was obtained, in 78% yield, through the formation of a secondary triflate ester **8** (9) followed by treatment, in the same



6. R=Ms, R′=H
8. R=Tf, R′=t-BDPSi

SCHEME 2

reaction mixture, with DBU. We were pleased to note that the efficient opening of **13** by LDA in THF (for LDA induced retro-Michael reactions see refs. 8, 10) led cleanly and exclusively to the optically active (*Z*,*E*)-diene ester **14**, $[\alpha]_D$ + 73.9° (*c* 1.33, $CHCl_3$), in very high yield.[2] It should be noted that the same *C*-furanosides may be expediently transformed to the optically active (*E*,*E*)-diene **7** by simply adding sodium ethoxide directly to the triflate ester reaction mixture. This latter transformation underscores the versatility of this approach and confirms the synthetic utility of tetrahydrofurans as masked 1,3-dienes.[3]

The allylic alcohol in **14** was to become the hydroxyl group at C-5 of our LTB_4 analogues, so that an inversion of configuration at this centre was necessary. This was achieved using a well-known procedure (DEAD, triphenylphosphine, benzoic acid, ref. 12) to give the benzoate **16**[4] in 89% yield,

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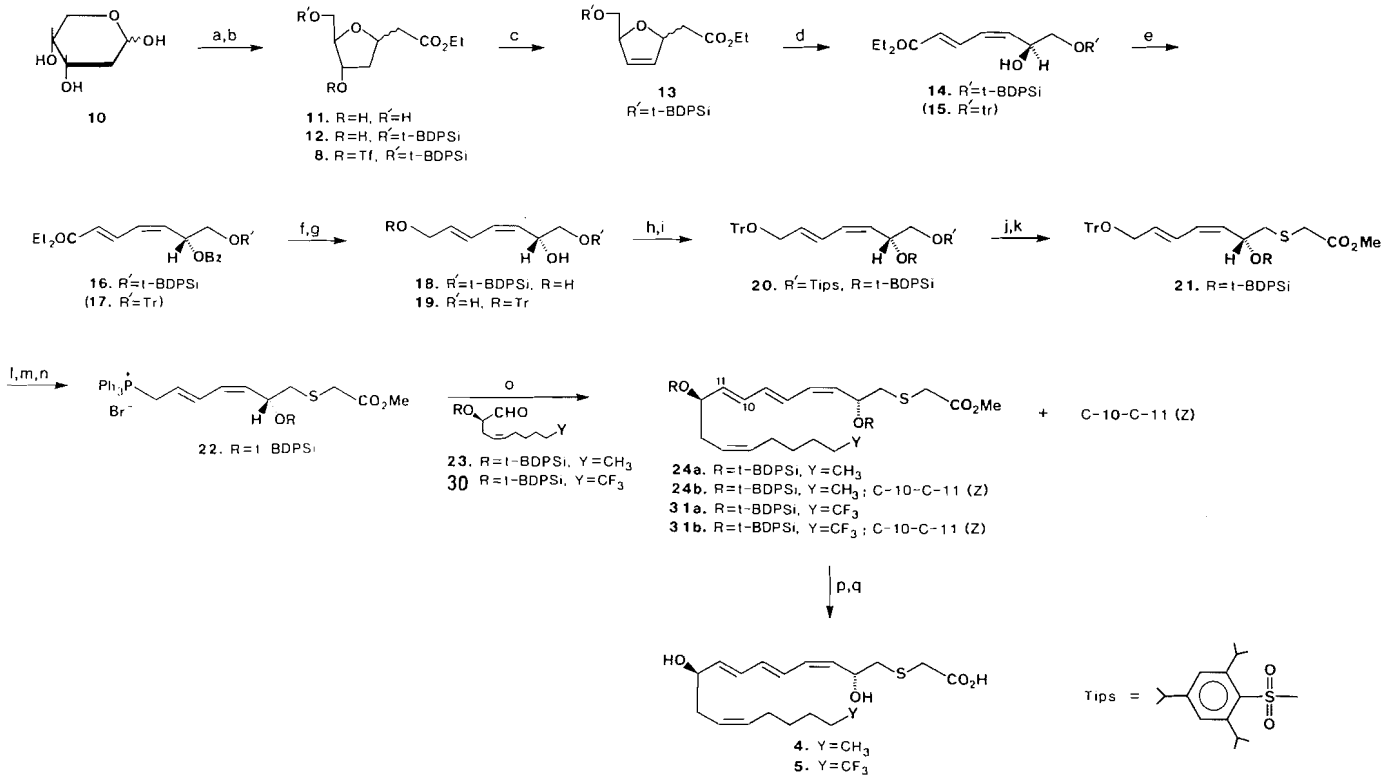
[2]^{1}H nuclear magnetic resonance (250 MHz, $CDCl_3$) δ 1.09 (s, 9H, $(CH_3)_3$), 1.34 (t, 3H, *J* = 7.5 Hz, CH_2CH_3), 2.68 (m, 1H, OH), 3.63 (ddd, 2H, *J* = 11 Hz, *J* = 8.0 Hz, *J* = 4.2 Hz, $SiOCH_2$), 4.22 (q, 2H, *J* = 7.5 Hz, CH_2CH_3), 4.78* (m, 1H, C*H*—OH), 5.73 (dd, 1H, *J* = 11 Hz, *J* = 8 Hz, H-5), 5.90 (d, 1H, *J* = 15 Hz, H-2), 6.20 (t, 1H, *J* = 11 Hz, H-4), 7.55 (dd, 1H, *J* = 12 Hz, *J* = 15 Hz, H-3), 7.35–7.71 (m, 10H, 2Ph).

*Decoupling experiment: 5.73 (d, 1H, *J* = 11 Hz, H-5); *Z* olefin; ir (neat); 3440, 2930, 2860, 1700, 1640, 1610 cm^{-1}. High resolution mass spectrum, *m*/*z* calcd. for $C_{25}H_{30}O_3Si$ (M^+ H_2O) 406.1964; found: 406.1986.

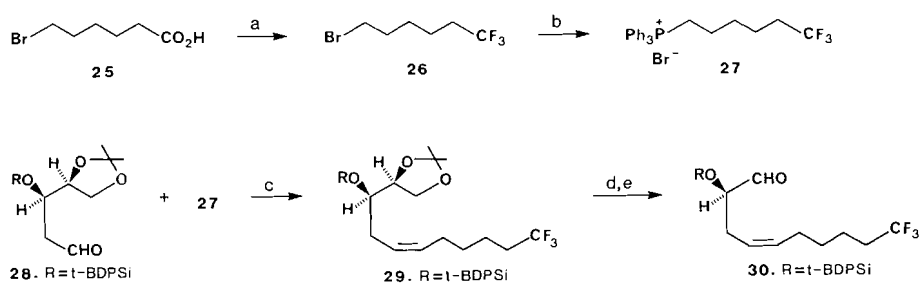
[3]A procedure for obtaining chiral (*Z*,*E*)-diene using a Wittig reaction on pseudoglucal was recently reported (11).

[4]The extent of the inversion of the allylic alcohol has been verified in the following way. In trityl series the benzoate **17** was treated sequentially with sodium ethoxide and LDA to give the corresponding alcohol with $[\alpha]_D$ −77.2° (*c* 1.55, $CHCl_3$) as opposed to $[\alpha]_D$ +79.4° (*c* 1.11, $CHCl_3$) for **15** (Scheme 3). Mosher esters (13) of both alcohols were, as well, made and ^{1}H nmr indicated that **17** was obtained with >97% inversion.



(a) See ref. 8; (b) *t*-BDPSiCl, iPr_2NEt, DMAP, CH_2Cl_2; (c) trifluoromethanesulfonic anhydride, (2 equiv.) pyridine, CH_2Cl_2; then DBU (6 equiv.), 78% (isolated yield); (d) LDA (1.2 equiv.), THF, 0°C, 92% (isolated yield)[2]; (e) Ph_3P, benzoic acid, DEAD, THF, r.t., 89% (isolated yield); (f) DIBAH, toluene, −10°C → r.t., 79% (isolated yield); (g) TrCl, pyr., DMAP, 50°C; then $nBu_4N^+F^-$, THF, r.t., 61% (isolated yield); (h) 2,4,6-triisopropylbenzenesulfonyl chloride, Et_3N, CH_2Cl_2, r.t., 63% (i) *t*-BDPSiCl, CH_2Cl_2, iPr_2NEt, r.t., 87%; (j) NaI, MEK, 70°C, 83%; (k) methylthioglycolate, NaH, THF, 50°C, 96%; (l) 20% aq. TFA, CH_2Cl_2, 63%; (m) CBr_4, DIPHOS, CH_2Cl_2, 0°C → r.t., 82%; (n) Ph_3P, CH_3CN, r.t.; (o) LiHMDS, THF, −78°C; then 23 → 0°C, 56%; (p) Bu_4NF, AcOH, THF, −10°C → r.t.; then CH_2N_2, then K_2CO_3, MeOH, r.t.; (q) NaOH, MeOH, 0°C → r.t.

SCHEME 3



(a) SF_4, 130°C; (b) Ph_3P, CH_3CN, reflux; (c) BuLi, THF, −78°C → r.t.; (d) TFA, THF, H_2O, 0.4:4:1, 60°C, 91%; (e) $Pb(OAc)_4$, CH_2Cl_2, K_2CO_3, −78°C, 87%.

SCHEME 4

$[\alpha]_D$ +74.8° (*c* 1.01, $CHCl_3$). DIBAH reduction (14) of both esters led to the dienediol **18**, $[\alpha]_D$ −42.0° (*c* 1.24, $CHCl_3$). The resulting primary alcohol was then tritylated, followed by desilylation using nBu_4 N^+F^- in THF, affording **19** in 61% yield from **16**. Selective primary sulfonylation of **19** with triisopropylbenzenesulfonyl chloride (15) in the presence of triethylamine was then followed by protection of the secondary alcohol as *tert*-butyldiphenylsilyl ether (16) to give **20**. Successive displacement of the sulfonate **20** with sodium iodide in hot 2-butanone, followed by sodium thiolate of methylthioglycolate in THF at 50°C for 4 h, led to C-1—C-10 unit **21** in 79% yield.

Completion of the synthesis of 3-thia-LTB_4 was then performed in the following way. Regeneration of the primary hydroxyl group from **21** was achieved with 20% aqueous trifluoroacetic acid (17) in CH_2Cl_2. The resulting primary alcohol was converted to the corresponding bromide and treated with triphenylphosphine in acetonitrile to give the phosphonium salt **22**. The Wittig coupling between **22** and the aldehyde **23** (2*b*) was then achieved through ylide formation at −78°C (THF) using LiHMDS, followed by the addition of aldehyde **23** and warming of the reaction mixture to 0°C. Trienes **24***a* and **24***b* were thus obtained in a 1:1 ratio. Removal of both silyl ethers using nBu_4 N^+F^- in the presence of acetic acid, followed by

separation of the isomers using hplc,[5] led to the 3-thia-LTB_4 methyl ester. Subsequent saponification gave the 3-thia-LTB_4, **4**.

The introduction of a metabolically stable group such as trifluoromethyl (CF_3) at C-20 of 3-thia-LTB_4 **4** was then achieved as follows. Treatment of 6-bromohexanoic acid **25** with sulfur tetrafluoride (18) gave the trifluoro derivative **26** (Scheme 4). The corresponding phosphonium salt **27** was treated with butyllithium in dry THF followed by addition of aldehyde **28** (19) to afford the *Z*-olefin **29**. Selective removal of the acetonide and cleavage of the resulting diol in the presence of potassium carbonate gave the aldehyde **30**, $[\alpha]_D$ −14.7° (*c* 1.02, $CHCl_3$), in 79% isolated yield from **29**.

The aldehyde **30** was then coupled with the phosphonium bromide **22** (the C-1—C-10 unit) as described previously (Scheme 3). Removal of silyl ethers followed by separation of the resulting trienes and saponification gave 3-thia-20,20,20-trifluoro-LTB_4 **5**.[6] Both analogs **4** and **5** were shown to be biologically active in a PMN aggregation assay (20), with similar potency to LTB_4 itself. Functional effects and in vivo activities will be reported elsewhere.

In conclusion, the potential usefulness of optically active tetrahydrofurans as masked stable precursors of stereochemically well-defined 1,3-dienes has been illustrated in the synthesis of 3-thia-LTB_4 and 3-thia-20,20,20-trifluoro-LTB_4.

Acknowledgements

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[5]The hplc condition: Waters μ-Porasil column, 30% ethyl acetate in hexanes. In this system the 3-thia-LTB_4 methyl ester is more polar as the C-10—C-11 (*Z*) isomer.

[6]For the corresponding methyl ester: $[\alpha]_D$ +11.3° (*c* 0.23, $CHCl_3$); uv (MeOH); λ_{max}: 271.2 nm; ^1H nmr (250 MHz, acetone-d_6) δ: 2.20 (m, H-13, H-16, H-19), 2.83 (m, 2H, CH_2S), 3.43 (s, 2H, SCH_2CO), 3.70 (s, 3H, CO_2Me), 4.20 (m, 1H, H-12), 4.80 (m, 1H, H-5), 5.48 (m, 3H, H-6, H-14, H-15), 5.83 (dd, 1H, $J_{10,11}$ = 14.6 Hz, $J_{11,12}$ = 6.3 Hz, H-11), 6.12 (t, 1H, $J_{6,7} = J_{7,8}$ = 11 Hz, H-7), 6.32 (m, 2H, H-9, H-10), 6.65 (t, 1H, $J_{8,9}$ = 12.5 Hz, H-8).