Short Synthetic Routes to Sulphur-bridged Analogues of 6,7-Didehydroleukotriene B_3

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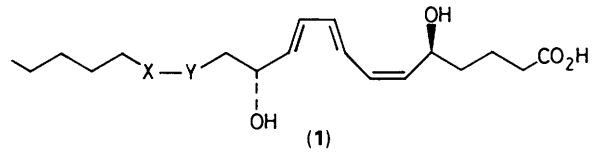
Two extremely short routes to the 8,11-sulphur bridged leukotriene B_3 analogue (**2**) are reported. Key steps involve (i) the introduction of the leukotriene C(1)–C(7) fragment by palladium-copper catalysed alkyne coupling reactions and, (ii) acylation of the thiophene tri-anion (**7**).

The potent biological activity of the dihydroxyleukotrienes, *e.g.* leukotriene B_4 (LTB_4; **1a**)[1] and leukotriene B_3 (LTB_3; **1b**)[2] has stimulated a number of research groups to design and prepare synthetic leukotriene analogues in order to define structure–activity parameters and, therefore, eventually to prepare leukotriene receptor antagonists.[1–5] As part of a programme to prepare conformationally-restricted leukotriene B analogues in which the 8*E*,10*E*-diene unit is constrained by incorporation into an aromatic ring,[3] we have now developed two extremely concise routes for the preparation of sulphur-bridged analogues, as illustrated in the Scheme for the synthesis of the thiophene (**2**), an 8,11-sulphur bridged analogue of leukotriene B_3 (**1b**). The palladium-copper catalysed coupling reaction[5,6] of 2-iodothiophene (**3**) and methyl 5-hydroxyhept-6-ynoate (**4**),[5] gave the monosubstituted thiophene (**5**) which was efficiently saponified to the acid (**6**).[7] Treatment of the latter with butyl-lithium (3.2 equiv.) followed by *N*-methoxy-*N*-methylnonanamide (**8**)[8] gave the disubstituted thiophene (**9**), as a crystalline solid, in 69% unoptimized yield after protonation. This transformation, which presumably proceeds by way of the trilithiated intermediate (**7**), is noteworthy[9] and of great potential for the preparation of related analogues. Borohydride reduction of the ketone (**9**) gave the sulphur-bridged 6,7-dehydro-LTB_3 (**2**) as an inseparable mixture of diastereoisomers. Confirmation that ring lithiation of thiophene (**6**) had occurred at the C-5 position (C-11 in leukotriene numbering) was obtained by preparing the LTB_3 analogue (**2**) by an alternative, regiodefined route (see Scheme). Thus, application of the coupling reaction to 5-bromothiophene-2-carbaldehyde (**10**) gave the adduct (**11**) in 63% yield. Saponification to the acid (**12**) followed by addition of an excess of octyl-lithium gave the same leukotriene analogue (**2**) in 61% yield.

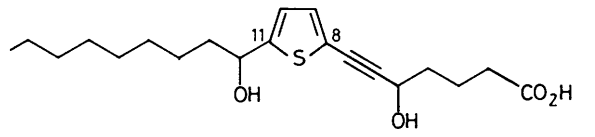
We are currently applying this route to the synthesis of the LTB_4 analogues in chiral form. In this regard, it is worth noting that the 5*S*-enantiomer of the alkyne (**4**) is readily available.[5]



(**1**)

a; X–Y = *Z*-CH=CH

b; X–Y = CH_2–CH_2

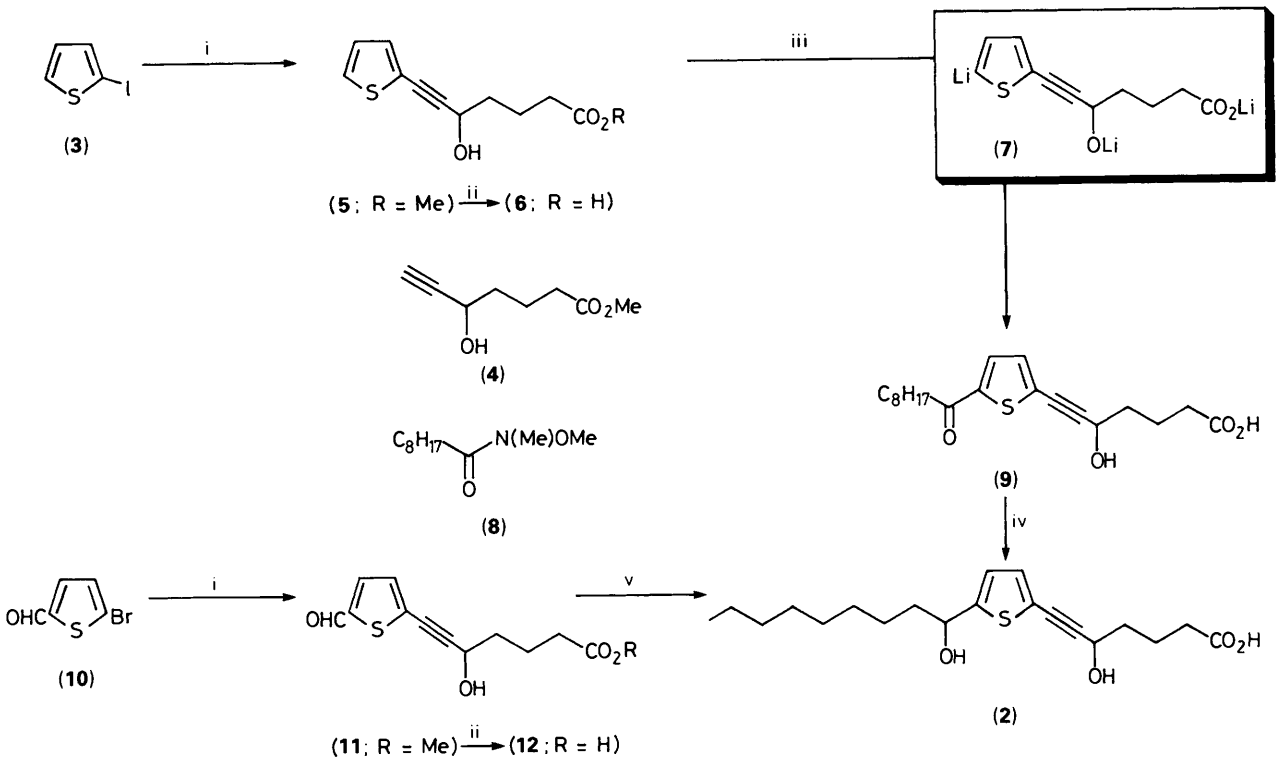


(**2**)

Experimental[10]

Methyl 5-Hydroxy-7-(2-thienyl)hept-6-ynoate (**5**).—To a mixture of 2-iodothiophene (**3**) (4.44 g, 21.14 mmol) and methyl 5-hydroxyhept-6-ynoate (**4**)[5] (1.65 g, 10.58 mmol) in dry triethylamine (165 ml) was added $Pd(Ph_3P)_4$ (0.24 g, 0.21 mmol) and CuI (0.02 g, 0.105 mmol). The reaction mixture was stirred at room temperature under nitrogen for 93 h. The palladium catalyst was filtered off and the solvent removed under reduced pressure. Column chromatography (May & Baker Sorbsil C60; light petroleum–ethyl acetate, 2:1) gave the *title compound* (**5**) (2.30 g, 91%) as a yellow oil, b.p. (Kugelrohr) 210 °C/0.5 mmHg; R_F 0.28 (light petroleum–ethyl acetate, 2:1); ν_{max}(film) 3 440, 2 965, 2 220, and 1 740 cm^{-1}; δ 1.70–1.98 (4 H, m), 2.24–2.52 (2 H, m), 2.60 (1 H, br s, exchangeable), 3.68 (3 H, s), 4.48–4.72 (1 H, m), 6.82–7.00 (1 H, m), and 7.10–7.28 (2 H, m); *m/z* (e.i.) 238 (M^+; 1%) (Found: C, 60.3; H, 6.0. $C_{12}H_{14}O_3S$ requires C, 60.48; H, 5.92%).

5-Hydroxy-7-{2-[5-(1-oxononyl)]thienyl}hept-6-ynoic Acid (**9**).—Butyl-lithium in hexane (0.92 ml, 2.39 mol, 2.20 mmol) was added dropwise to a stirred solution of the hydroxy acid (**5**) (150 mg, 0.68 mmol) in THF (15 ml) at −70 °C under nitrogen. The resulting pale yellow precipitate was stirred at −70 to −35 °C for 1 h and then recooled to −70 °C when *N*-methoxy-*N*-methylnonanamide (**8**) (0.18 g, 0.89 mmol) [prepared from nonanoyl chloride using a literature[8] procedure] was added. The reaction was left to warm to room temperature and then stirred for 18 h. Saturated aqueous NH_4Cl (3 ml) was then added and the mixture extracted with ethyl acetate (3 × 10 ml). The combined organic phases were then re-extracted with dilute aqueous NaOH and the alkaline aqueous extract was re-acidified to pH 1 with dilute hydrochloric acid and re-extracted with ethyl acetate (2 × 50 ml). The organic extracts were washed with brine, dried ($MgSO_4$), and the solvent removed under reduced pressure to give the *title compound* (**9**) (0.17 g, 69%) as a pale yellow, chromatographically pure solid. An analytical sample was obtained by column chromatography (May & Baker Sorbsil C60; ether–methanol, 49:1): m.p. 59.5–62 °C; ν_{max}(Nujol) 3 450, 1 702, and 1 665 cm^{-1}; δ 0.64–1.06 (3 H, m), 1.06–2.14 (14 H, m), 2.14–2.62 (4 H, m), 2.62–3.02 (2 H, m), 4.42–4.80 (1 H, m), 5.80–6.50 (2 H, br s, exchangeable), 7.08 (1 H, d, *J* 4 Hz), and 7.50 (1 H, d, *J* 4 Hz); *m/z* (e.i.) 206 ($M^+ - C_8H_{17}CO - H_2O$; 70%) [Found (NH_3 C.I.): $(M + H)^+$, 365.179 32. $C_{20}H_{29}O_4S$ requires $(M + H)^+$, 365.178 66].



Scheme. *Reagents:* i, (**4**), Et_3N, cat. CuI–$Pd(PPh_3)_4$ [(**5**), 91%; (**11**), 63%]; ii, K_2CO_3, aq. MeOH [(**6**), 90%; (**12**), 78%]; iii, 3.2 BuLi then (**8**) (69%); iv, $NaBH_4$, MeOH (95%); v, 3.3 $C_8H_{17}Li$ (61%).

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References

1 L. W. Chakrin and D. M. Bailey, 'The Leukotrienes: Chemistry and Biology,' Academic Press, New York, 1984.

2 B. Spur, A. Crea, W. Peters, and W. Konig, *Arch. Pharm.*, 1985, **318**, 225

3 S. C. Burford, M. Furber, and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1987, 1573.

4 J. Morris and D. G. Wishka, *Tetrahedron Lett.*, 1988, **29**, 143.

5 K. C. Nicolaou, R. E. Zipkin, R. E. Dolle, and B. D. Harris, *J. Am. Chem. Soc.*, 1984, **106**, 3548.

6 K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.*, 1975, 4467; S. Takahashi, Y. Kuroyama, K. Sonogashira, and N. Hagihara, *Synthesis*, 1980, 627.

7 All new compounds gave consistent spectral and analytical/mass spectrometric data. All synthetic compounds are racemic.

8 S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, 1981, **22**, 3815.

9 For reviews of lithiated thiophene derivatives see S. Rajappa, 'Comprehensive Heterocyclic Chemistry,' Pergamon Press, 1984, ch. 3.14; H. W. Gschwend and H. R. Rodriguez, *Org. React.*, 1979, **26**, 1.

10 For experimental directions see ref. 3.

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