5-(*Z*)-Oct-2-enyltetrahydrofuran-2-one as a Key Intermediate in the Synthesis of Leukotriene B_4

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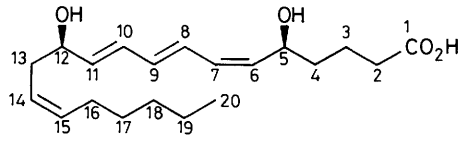
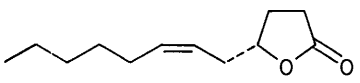
The synthesis of a compound, representing the C(9)–C(20) portion of leukotriene B_4, has been accomplished *via* 5-(*Z*)-oct-2-enyltetrahydrofuran-2-one.

Leukotriene B_4 (**1**) is a very important natural product. It has very high chemotactic potency for macrophage and neutrophils [1] and it has been implicated in many types of inflammation,[2] including psoriasis [3] and inflammatory bowel disease.[4]

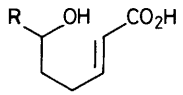
Pirillo *et al.*, demonstrated that the lactone (**2**) could in principle serve as the source of the C(9)–C(20) portion of the



(**1**)



(**2**)



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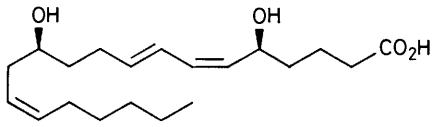
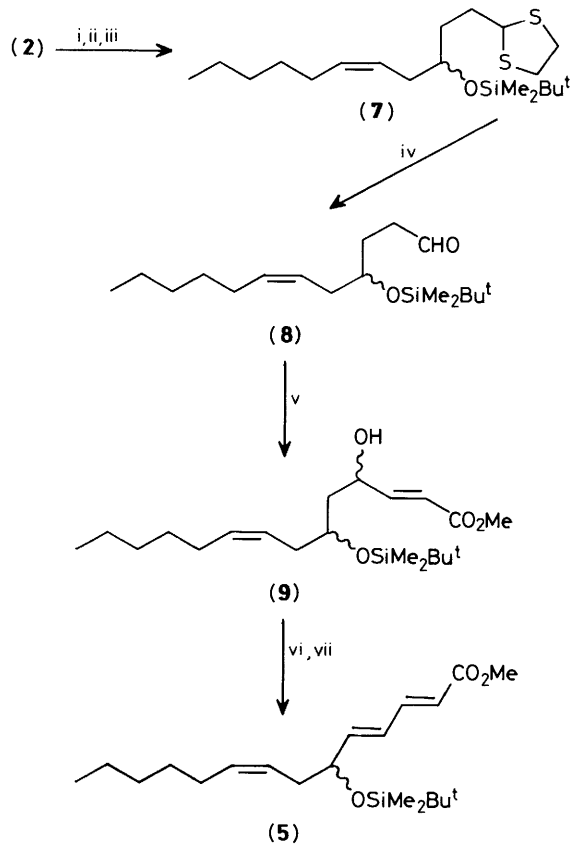


(**3**)

dihydroleukotriene B_4 (**3**),[5–7] and the complete synthesis of this LTB_3 (**3**) by this route was recently reported by Falck, Capdevila *et al.*[8] The lactone (**2**) appeared an attractive starting material for the synthesis of LTB_4 (**1**) itself, but several plausible routes for the incorporation of the *E*-C(10)–C(11) double bond have proved unsatisfactory. For example, the tendency of hydroxy esters such as (**4**) to cyclise by intramolecular Michael addition was a major problem.[9] Furthermore, selenation of α,β-unsaturated esters tends to occur at the α- rather than the γ-position.[10]

We now report a route for the synthesis of the known LTB_4 intermediate (**5**) [11] from the lactone (**2**) (see Scheme 1).

Reduction of the lactone to the lactol, followed by thioacetalisation of the masked aldehyde and silylation of the hydroxy group, gave the diprotected hydroxy aldehyde (**7**). Cleavage of the dithioacetal proved difficult but was achieved in good yield by a combination of mercury(II) chloride and iodomethane. The free aldehyde (**8**) was extended to the α,β-unsaturated ester (**9**) by reaction with methyl (4-chlorophenylsulphinyl)acetate.[12] Finally, benzoylation of the free hydroxy

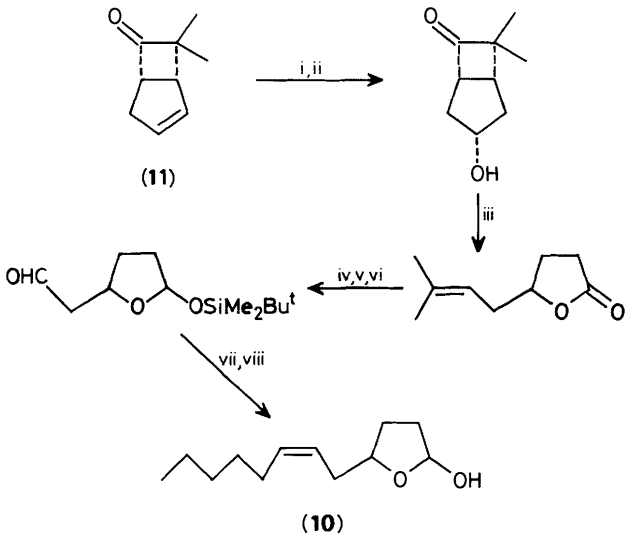


Scheme 1. *Reagents and Yields:* i, DIBAL-H, 73%; ii, $HSCH_2CH_2SH$, $TiCl_4$, 78%; iii, $Bu^tMe_2SiOCOCF_3$, 92%; iv, MeI, $HgCl_2$, $CdCO_3$, 80%; v, 4-$ClC_6H_4S(O)CH_2CO_2Me$, 78%; vi, PhCOCl, Et_3N, DMAP, 91%; vii, $(Ph_3P)_4Pd$, Et_3N, 80%.

group, followed by elimination induced by triethylamine with Pd^0 catalyst,[13] gave the (*E*,*E*)-dienoate (**5**).†

The American group obtained the lactone (**2**) in the required 5*R*-configuration by a multi-step synthesis from L-glutamic acid.[8,14] We have prepared the corresponding racemic lactol (**10**) from the readily available bicyclo[3.2.0]heptenone (**11**) [15] as shown in Scheme 2.

† Spectral data for (**5**): ^1H n.m.r. (300 MHz, $CDCl_3$), δ_H 0.002 and 0.03 (3 × 3 H, 2 × s, MeSi), 0.83—0.87 (10 H, m, Me_3C and CH_2Me_3), 1.20—1.32 (6 H, m, 17-, 18-, 19-H), 1.93—2.00 (2 H, m, 16-H), 2.25 (2 H, q, 13-H), 3.71 (3 H, s, CO_2Me), 4.17—4.22 (1 H, m, 12-H), 5.29—5.46 (2 H, m, 14-, 15-H), 5.83 (1 H, d, *J* 15.3 Hz, 8-H), 6.07 (1 H, dd, *J* 15.5 and 5.6 Hz, 11-H), 6.28 (1 H, ddd, *J* 15.5, 10.8 Hz, 10-H), and 7.24 (1 H, dd, *J* 15.3, 10.8 Hz, 9-H).



Scheme 2. *Reagents and Yields:* i, *N*-Bromoacetamide, H_2O, Me_2CO, 83%; ii, Bu_3SnH, AIBN, 63%; iii, *hν*, benzene, 42%; iv, DIBAL-H, 82%; v, Bu^tMe_2SiCl, imidazole, 84%; vi, O_3, then Me_2S, 80%; vii, $Me(CH_2)_5PPh_3Br$, BuLi, 72%; viii, AcOH, THF, H_2O, 80%.

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References

1 G. A. Higgs and S. Moncada, *Drugs*, 1985, **30**, 1; B. Samuelsson, S. E. Dahlen, J. A. Lindren, C. A. Rouzer, and C. N. Serhan, *Science*, 1987, **237**, 1171.
2 S. Thorsen, *Scand. J. Rheumatol.*, 1986, **15**, 225; M. A. Bray, *Agents Actions*, 1986, **19**, 87; R. M. McMillan and S. J. Foster, *ibid.*, 1988, **24**, 114.
3 A. M. Lammers and P. C. M. Van de Kerthof, *Br. J. Dermatol.*, 1987, **116**, 521.
4 E. A. Lobos, P. Sharon, and W. F. Stenson, *Digestive Diseases and Sciences*, 1987, **32**, 1380; J. L. Wallace, W. H. MacNaughton, G. P. Morris, and T. L. Beck, *Gastroenterology*, 1989, **96**, 29.
5 D. Pirillo, A. Malamidis, D. Vercesi, O. Azzolina, L. Portaluppi, and G. Traverso, *Farmaco, Ed. Sci.*, 1987, **42**, 101.
6 D. Pirillo, D. Vercesi, O. Azzolina, and G. Traverso, *Farmaco, Ed. Sci.*, 1987, **42**, 111.
7 D. Pirillo, L. Portaluppi, M. DiGiacomo, O. Azzolina, D. Vercesi, and G. Traverso, *Farmaco, Ed. Sci.*, 1987, **42**, 603.
8 P. Yadagiri, S. Lumin, J. R. Falck, A. Karava, and J. Capdevila, *Tetrahedron Lett.*, 1989, **30**, 429.
9 J. A. Winders, unpublished work.
10 T. A. Hase and P. Kukkola, *Synth Commun.*, 1980, **10**, 451.
11 Y. Guindon, D. Delorme, C. K. Lau, and R. Zamboni, *J. Org. Chem.*, 1988, **53**, 267.
12 R. Tanikaga, Y. Nozaki, T. Tamura, and A. Kaji, *Synthesis*, 1983, 134.
13 T. Sakai, K. Seka, A. Tsuji, M. Utaka, and A. Takeda, *J. Org. Chem.*, 1982, **47**, 1101; *cf.*, B. H. Trost, T. R. Verhoeven, and J. M. Fortunatle, *Tetrahedron Lett.*, 1979, **25**, 2301.
14 J. P. Vigneron, R. Meric, M. Larchevêque, A. Debal, G. Kunesch, P. Zagatti, and M. Gallois, *Tetrahedron Lett.*, 1982, **23**, 5051.
15 M. Rey, S. M. Roberts, A. Dieffenbacher, and A. S. Dreiding, *Helv. Chim. Acta*, 1970, **43**, 417.

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