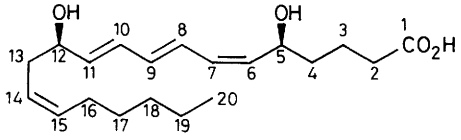
5-(*Z*)-Oct-2-enyltetrahydrofuran-2-one as a Key Intermediate in the Synthesis of Leukotriene B_4

György Dormán,[a] Stanley M. Roberts,[b,c] Basil J. Wakefield,[a,*] and John A. Winders[a,b]
[a] *Department of Chemistry and Applied Chemistry, University of Salford, Salford, M5 4WT*
[b] *Glaxo Group Research Ltd., Greenford, Middlesex, UB6 0HE*
[c] *Department of Chemistry, University of Exeter, Stocker Road, Exeter, EX4 4QD*

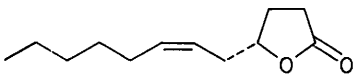
The synthesis of a compound, representing the C(9)–C(20) portion of leukotriene B_4, has been accomplished *via* 5-(*Z*)-oct-2-enyltetrahydrofuran-2-one.

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]

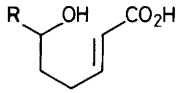
Pirillo *et al.*, demonstrated that the lactone (**2**) could in principle serve as the source of the C(9)–C(20) portion of the



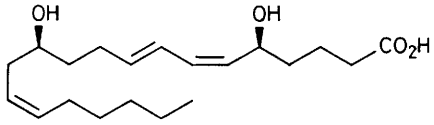
(**1**)



(**2**)



(**4**)

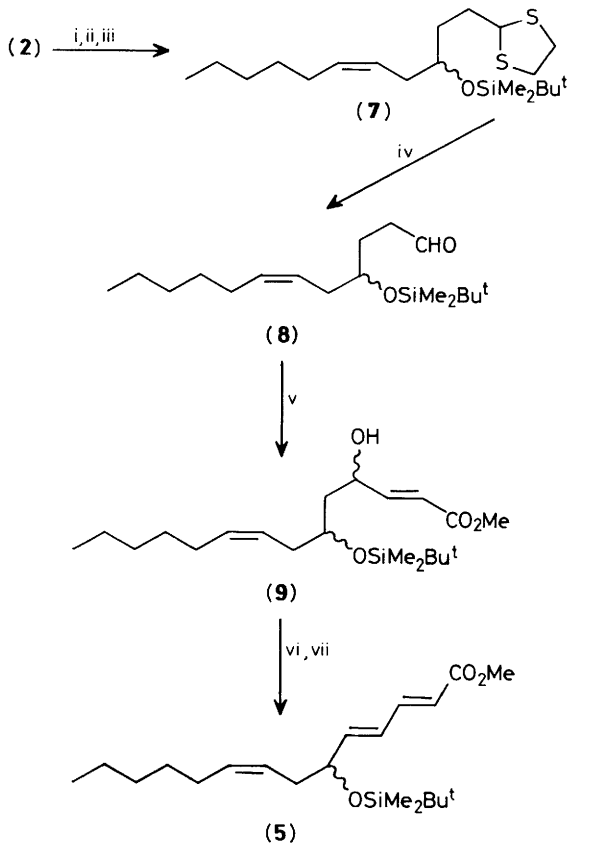


(**3**)

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

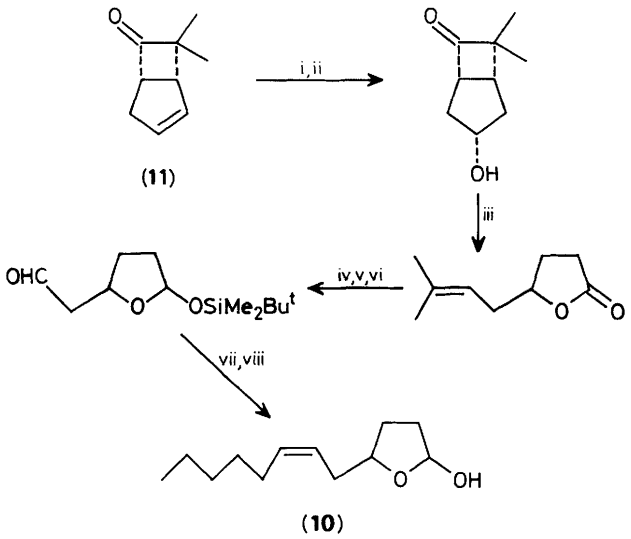


Scheme 1. *Reagents and Yields:* i, DIBAL-H, 73%; ii, $HSCH_2CH_2SH$, $TiCl_4$, 78%; iii, $Bu^tMe_2SiOCOCF_3$, 92%; iv, MeI, $HgCl_2$, $CdCO_3$, 80%; v, 4-$ClC_6H_4S(O)CH_2CO_2Me$, 78%; vi, PhCOCl, Et_3N, DMAP, 91%; vii, $(Ph_3P)_4Pd$, Et_3N, 80%.

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%.

Acknowledgements

We thank the British Council and Salford Ultrafine Chemicals and Research Ltd. for financial assistance and CHINOIN, Budapest, for leave of absence (to G. D.) and Glaxo Group Research Ltd. for a grant (to J. W.).

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.

Received 7*th April* 1989; *Paper* 9/01438A