Stereospecific Synthesis of Dienes and Trienes from Pyrylium Perchlorate: a Convergent Approach to Leukotrienes

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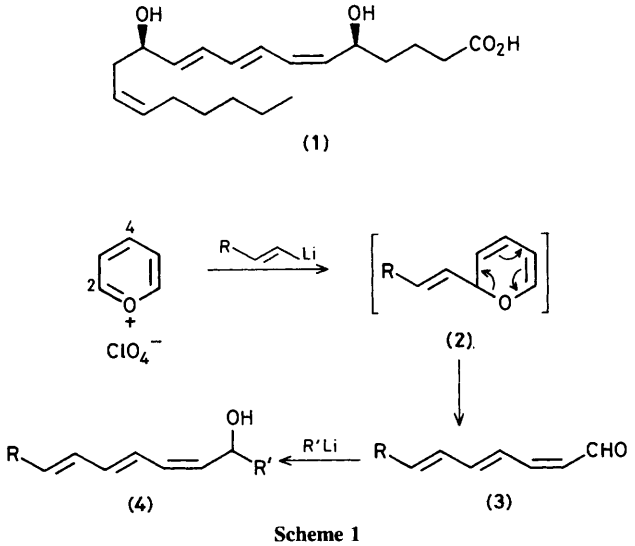
A range of conjugated dienes and trienes have been prepared in a stereospecific manner by the treatment of pyrylium perchlorate with organolithium reagents; model studies have been carried out which demonstrate the suitability of this methodology for the synthesis of leukotriene B_4.

There is considerable current interest in the development of new stereospecific routes to conjugated dienes and trienes. We became interested in this area when designing a synthetic approach to leukotriene B_4 (LTB_4) (**1**) and its analogues.[1] We hoped to construct the hydroxy-triene unit of LTB_4 in a single step using the novel, highly convergent sequence shown in Scheme 1.

The addition of vinyl organometallic reagents to pyrylium perchlorate[2]† at C-2 should give the 2-vinyl-2*H*-pyran (**2**) which would be expected[3,4] to rearrange to the *Z,E,E*,-trienal (**3**) at room temperature. The addition of a second organometallic reagent should then give the trienol (**4**). There have been scattered reports of organometallic additions to substituted pyrylium salts,[4] and addition to both C-2 and C-4 has been observed, but to our knowledge no-one has looked at the corresponding reactions of the parent system. We therefore investigated simple addition reactions between pyrylium perchlorate and organometallic reagents.

Trial reactions using Grignard reagents were not encouraging but with organolithium reagents the required C-2-addition–electrocyclic rearrangement proceeded smoothly (Table 1, entries i—iii). Products derived from C-4 addition were not observed. The resulting 5-substituted penta-2*Z*,4*E*-dienals (**5**)—(**7**) were obtained as single isomers according to ^1H and ^{13}C n.m.r. spectroscopy. The stereospecificity of the ring-opening reaction was confirmed in the case of compounds (**5**) and (**11**) using high-field ^1H n.m.r. spectroscopy. Decoupling experiments revealed coupling constants which were consistent with the assigned 2*Z*,4*E*-stereochemistry [(**5**): $J_{2,3}$ 10.7, $J_{4,5}$ 14.4 Hz; (**11**): $J_{2,3}$ 10.0, $J_{4,5}$ 15.1 Hz].

Having established the viability of the first part of the overall strategy, we next looked at *in situ* aldehyde trapping (Table 1, entries iv—vi). After the initial alkyl-lithium addition (a) at −70 °C the reaction mixture was warmed to room temperature and then recooled before addition of the second alkyl-lithium reagent (b). This protocol gave fair to good yields of dienols (**8**)—(**10**) in a stereospecific manner.



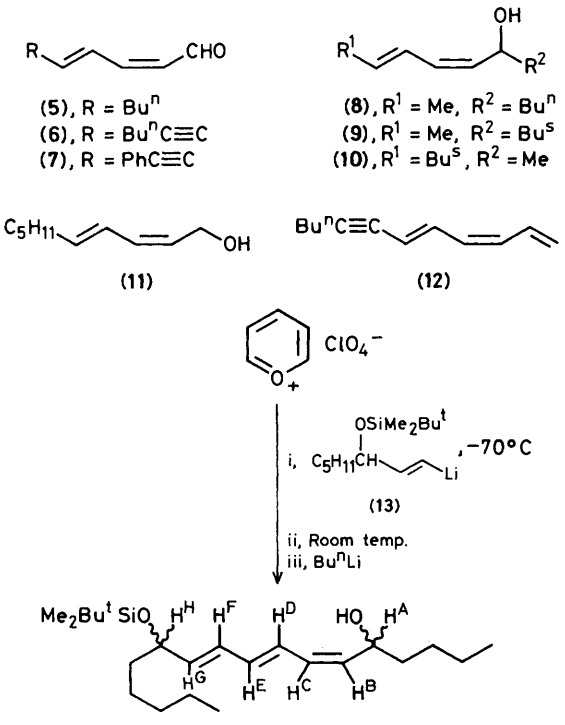
Scheme 1

† This compound is potentially explosive and should be handled with care. To date we have experienced no problems of this kind.

Table 1. Products obtained from pyrylium perchlorate by organolithium addition–rearrangement followed by isolation or *in situ* elaboration.

Entry	Organolithium reagents (a)	(b)	Product	% Yield[a]
i	Bu^nLi	—	(**5**)	63
ii	$BuC{\equiv}CLi$	—	(**6**)	59
iii	$PhC{\equiv}CLi$	—	(**7**)	65
iv	MeLi	Bu^nLi	(**8**)	57
v	MeLi	Bu^sLi	(**9**)	60
vi	Bu^sLi	MeLi	(**10**)	48
vii	$C_5H_{11}Li$	(Bu^i_2AlH)	(**11**)	60[b]
viii	$BuC{\equiv}CLi$	$(Ph_3{=}CH_2)$	(**12**)	32

[a] Yields are of isolated materials after chromatography and are unoptimized. All new compounds are fully characterized. [b] Spectral parameters are consistent with published data.[5]



(**14**), 51%

Scheme 2

The intermediate aldehydes could also be reduced (Table 1, entry vii) or subjected to the Wittig reaction (entry viii). Finally, the original sequence was tested using the readily available[6] silyloxy-vinyl-lithium (**13**) followed by butyl-lithium (Scheme 2). The vinyl-lithium compound (**13**) closely resembles the reagent needed for LTB_4 synthesis. An acceptable yield of the desired *Z,E,E*-trienol (**14**) was obtained uncontaminated by stereoisomers according to n.m.r. spectroscopy and g.l.c.‡ We are now using this methodology in a chiral approach to LTB_4 and analogues.

‡ G.l.c. OV101, 100 °C then 8 °C min^{-1}; R_t 13.88 min (maximum amount of isomeric impurity 2.5%). ^{13}C n.m.r. ($CHCl_3$) δ 143.25 (d), 138.79 (d, 2C), 134.50 (d), 133.36 (d), 131.63 (d), 78.02 (d), 72.57 (d) + higher field aliphatic carbons. (Diastereoisomeric splittings and isomeric impurities could not be seen.) 360 MHz ^1H n.m.r. ($CHCl_3$) δ 4.16 (dt, H^H), 4.615 (br. dt, H^A), 5.43 (dd, H^B), 5.74 (dd, H^G), 6.105 (dd, H^C), (m, H^E and H^F), and 6.48 (dd, H^D). These chemical shifts and coupling constants correlate well with those for natural LTB_4 (M. Sugiura, H. Beierbeck, P. C. Belanger, and G. Kotovych, *J. Am. Chem. Soc.*, 1984, **106**, 4021).

We are grateful to the S.E.R.C. and Fisons Pharmaceutical Division for a C.A.S.E. award (M. F.) and to Dr. S. C. Burford for his interest and advice. We also thank the S.E.R.C. WH-400 n.m.r. Service at Warwick University and Fisons Pharmaceutical Division for high-field n.m.r. spectra.

Received, 25th February 1985; Com. 258

References

1 K. C. Nicolaou, R. E. Zipkin, R. E. Dolle, and B. D. Harris, *J. Am. Chem. Soc.*, 1984, **106**, 3548, and references therein.
2 F. Klages and H. Trager, *Chem. Ber.*, 1953, **86**, 1327.
3 E. N. Marvell and T. Gosink, *J. Org. Chem.*, 1972, **37**, 3036.
4 J. Kuthan, *Adv. Heterocycl. Chem.*, 1983, **34**, 145; J. Royer and J. Dreux, *Bull. Soc. Chim. Fr.*, 1972, 707.
5 H. Bosshardt and M. Schlosser, *Helv. Chim. Acta*, 1980, **63**, 2393.
6 E. J. Corey and D. J. Beames, *J. Am. Chem. Soc.*, 1972, **94**, 7210.