Stereoselective Routes to Functionalised Hexa-2,4-dienals from Cyclobutenes

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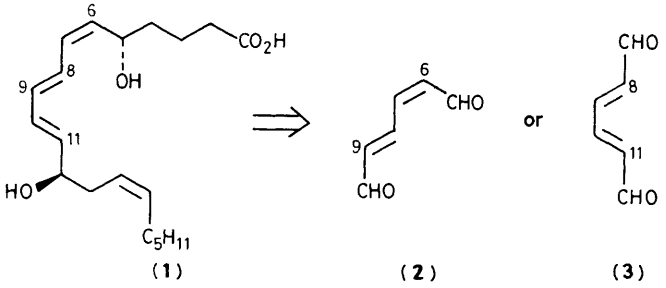
6-Substituted (2*Z*),(4*E*)- and (2*E*),(4*E*)-hexa-2,4-dienals have been prepared from a cyclobutene derivative *via* stereoselective electrocyclic ring-opening and isomerisation processes.

Our interest in the lipoxygenase-derived metabolites of arachidonic acid (leukotrienes[1] and lipoxins[2]) prompted us to seek intermediates capable of serving as central fragments in convergent syntheses of these biologically important compounds. Our strategy, outlined for leukotriene B_4 (**1**) in Scheme 1, required the preparation of equivalents of the isomeric dialdehydes (**2**) and (**3**), suitably masked for sequential elaboration of each carbonyl function using appropriate permutations of the Wittig and aldol reactions. Herein we describe short routes to both of these structural types, starting



Scheme 1

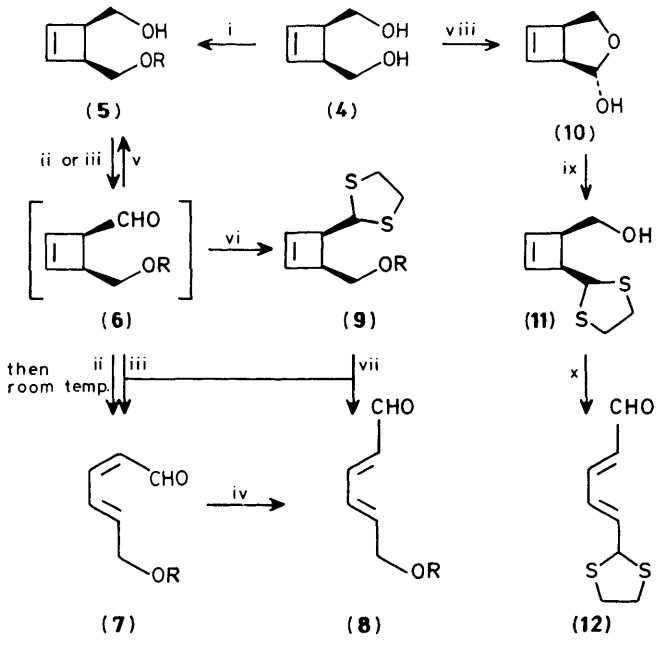
from a readily available cyclobutene system and proceeding *via* stereoselective electrocyclic ring-opening and isomerisation processes.

The diol (**4**),[3] prepared in 92% yield by reduction of *cis*-3,4-cyclobutenedicarboxylic acid anhydride,[4] was monoalkylated[5] using 4-methoxybenzyl bromide[6] to give the ether (**5**)† in 80% yield (Scheme 2). Oxidation of (**5**) under Swern conditions[8] at −78 °C was expected to produce the aldehyde (**6**), but gave on work-up the ring-opened dienal (**7**), 90%, as an oil [$\lambda_{max.}$(EtOH) 226 and 270 nm; δ_H ($CDCl_3$, 400 MHz) 10.15 (1 H, d, *J* 8 Hz, 1-H), 7.26 (2 H, d, *J* 9 Hz, 2'-H), 7.24 (1 H, ddd, *J* 2, 11, 15 Hz, 4-H), 6.94 (1 H, dd, *J* 11, 11 Hz, 3-H), 6.89 (2 H, d, *J* 9 Hz, 3'-H), 6.19 (1 H, ddd, *J* 5, 5, 15 Hz, 5-H), 5.85 (1 H, dd, *J* 8, 11 Hz, 2-H), 4.48 (2 H, s, CH_2Ar), 4.15 (2 H, dd, *J* 2, 5 Hz, 6-H), and 3.79 (3 H, s, OMe); semicarbazone, m.p. 147 °C (decomp.) (EtOAc)]. The high stereoselectivity of the process leading to (**7**) was apparent from the n.m.r. spectrum, the coupling constants $J_{2,3}$ and $J_{4,5}$ (11 and 15 Hz respectively) and integration indicating that the (2*Z*),(4*E*)-isomer constituted at least 95% of the isolated material. By contrast, oxidation of (**5**) with pyridinium chlorochromate (PCC)[9] at room temperature gave an inseparable mixture of the (2*Z*),(4*E*)- and (2*E*),(4*E*)-dienals (**7**) and (**8**) (1:4; 97%), which on standing at room temperature in deuteriochloroform for a few days was converted to pure (**8**) [oil; $\lambda_{max.}$ (EtOH) 226 and 269 nm; δ_H ($CDCl_3$, 60 MHz) 9.55 (1 H, d, *J* 8 Hz, 1-H); semicarbazone, m.p. 197 °C (acetone)]. The isomerisation, which confirms the greater thermodynamic stability of the (*E*),(*E*)-dienal, proceeds with variable ease in daylight or darkness and is considerably slower at −10 °C, but is rapid on addition of acid.

The formation of the cyclobutene aldehyde (**6**) *en route* to (**7**) was demonstrated by treating a triethylamine-quenched Swern oxidation mixture, in which the substrate (**5**) was not detectable, with sodium borohydride, whereupon the alcohol (**5**) was regenerated (t.l.c., n.m.r. confirmation). Moreover, treatment of the cold oxidation product with ethanedithiol and titanium(IV) chloride[10] gave the dithiolane (**9**) as an oil [δ_H ($CDCl_3$, 60 MHz) 6.3 (2 H, m, HC=C), 4.58 (1 H, s, SCHS), 3.87 (2 H, s, CH_2Ar), 3.27 (4 H, s, SCH_2), *etc.*]. Deprotection of (**9**) under standard conditions gave a mixture of (**7**) and (**8**) (ratio approx. 1:2).

Further transformations of the diol (**4**) yielded an alternative dialdehyde equivalent. Oxidation of (**4**) with pyridinium dichromate (PDC)[11] gave 3-oxabicyclo[3.2.0]hept-6-en-2-ol (**10**), m.p. 46—48 °C (sublimed), in yields which varied owing to its volatility at room temperature. The orientation of the

† All products were isolated by flash chromatography (ref. 7) and gave satisfactory spectroscopic, microanalytical, and/or high resolution mass spectral data.



R = 4-Methoxybenzyl

Scheme 2. *Reagents:* i, NaH, *N,N*-dimethylformamide, RBr, −10 °C to room temp. (80%); ii, oxalyl chloride, Me_2SO, CH_2Cl_2, −78 °C, 15 min, then Et_3N (90%); iii, PCC, CH_2Cl_2, room temp., 2 h (97%); iv, $CDCl_3$, room temp., 5 to 10 days, or $CDCl_3$, *p*-toluenesulphonic acid catalyst, room temp., 24 h (>97%); v, as ii, then $NaBH_4$, EtOH, MeOH, −78 °C to room temp., 3 h; vi, as ii, then $HS(CH_2)_2SH$, $TiCl_4$, −78 °C, 30 min (45%); vii, MeI, Na_2CO_3, H_2O, Me_2CO, room temp., 3 days; viii, PDC, trace oxalic acid, CH_2Cl_2, room temp., 4 h (50—75%); ix, $HS(CH_2)_2SH$, $TiCl_4$, CH_2Cl_2, −15 °C to room temp., 45 min (86%); x, PCC, Celite 521, CH_2Cl_2, room temp., 14 h (40%).

2-hydroxy group was established by n.m.r. spectroscopy [δ_H ($CDCl_3$, 200 MHz) 5.33 (1 H, s, 2-H), 3.8 (2 H, m, 4-H_2), 3.49 (1 H, dd, *J* 4, 4 Hz, 5-H), 3.34 (1 H, d, *J* 4 Hz, 1-H), *etc.*], the absence of coupling between H-1 and H-2 being consistent with the *exo*-arrangement depicted. Although in solution the lactol (**10**) tended to decompose, with the appearance in the ^1H n.m.r. spectrum of alkene and aldehyde signals, treatment with ethanedithiol and titanium(IV) chloride converted it cleanly into the protected form (**11**), m.p. 71 °C {3,5-dinitrobenzoate, m.p. 116 °C [chloroform:light petroleum (b.p. 40—60 °C) 1:2]}. Oxidation of (**11**) gave the monoprotected dienedial (**12**) as an oil [δ_H ($CDCl_3$, 200 MHz) 9.56 (1 H, d, *J* 8 Hz, 1-H), 7.08 (1 H, dd, *J* 10, 15 Hz, 4-H), 6.38 (1 H, dd, *J* 10, 15 Hz, 3-H), 6.20 (1 H, dd, *J* 8.5, 15 Hz, 5-H), 6.15 (1 H, dd, *J* 8, 15 Hz, 2-H), 5.10 (1 H, d, *J* 8.5 Hz, 6-H), and 3.32 (4 H, m, SCH_2)]. The coupling constants $J_{2,3}$ and $J_{4,5}$ (each 15 Hz) confirm the (*E*),(*E*)-geometry of (**12**).

In addition to its obvious synthetic value, the behaviour of the cyclobutene (**6**) is of considerable mechanistic significance, since the aldehyde (**7**) is one of two 'allowed' products of thermal conrotatory electrocyclic ring-opening.[12] The aldehyde group appears to exert a pronounced influence on the rate of the electrocyclic reaction, which occurs below 0 °C, compared to 60—70 °C for the diol (**4**).[13] This presumably reflects the additional stabilisation resulting from conjugation within (**7**). The origin of the stereoselectivity is not so obvious. It can be argued that the preferential outward conrotation of the alkoxyalkyl substituent has a steric basis. However, we subscribe to the view that electronic factors contribute to the

observed result, since other examples of this type of selectivity cannot be explained using steric arguments alone.[14] The selective formation of (**7**) from (**6**) is in fact consistent with the frontier orbital arguments recently advanced by Rondan and Houk in this context.[15]

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