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# A SIMPLE ROUTE TO METHYL 5S-(BENZOYLOXY)-6-OXOHEXANOATE, A KEY INTERMEDIATE IN LEUKOTRIENE SYNTHESIS

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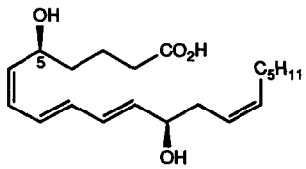
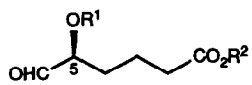
**Summary:** Methyl 5*S*-(benzoyloxy)-6-oxohexanoate **2**, an intermediate in synthetic routes to the lipoxygenase-derived arachidonic acid metabolite leukotriene $B_4$, is available in three steps from 2-cyclohexen-1-one, using Schreiber's unsymmetrical ozonolysis protocol.

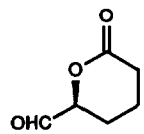
Various synthetic routes to the arachidonic acid metabolite leukotriene $B_4$ **1**[1] involve the Wittig olefination of a protected $C_1$-$C_6$ unit based on 5*S*-hydroxy-6-oxohexanoic acid. These include the methyl ester–benzoate **2** [prepared from 2-deoxy-D-ribose (6 steps),[2,3] D-glyceraldehyde acetonide (8 steps),[4] cinnamaldehyde (9 steps),[5] cyclopentadiene (9 steps),[6] or monomethyl glutarate (6 steps)[7]], the ethyl ester–benzoate **3** [from 2-deoxy-D-ribose (6 steps),[8] D-arabinose (10 steps),[9] D-mannitol (10 steps),[10] D-xylose (11 steps),[11] or (+)-diethyl tartrate (8 steps)[12]], the ethyl ester–silane **4** [from 2-deoxy-D-ribose (6 steps)[13] or D-arabinose (10 steps)[14]], and the lactone **5** [from tri-*O*-acetyl-D-glucal (6 steps)[15]]. We now report an alternative route to such compounds based on the unsymmetrical ozonolysis procedure described by Schreiber and coworkers.[16]




**1**

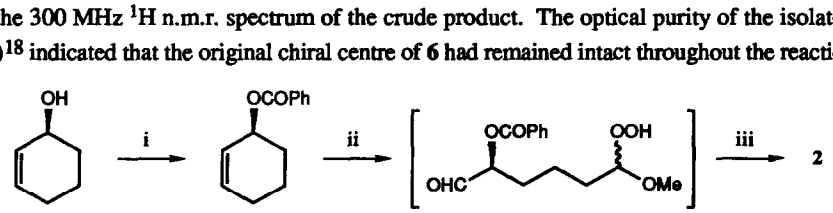



| | $R^1$ | $R^2$ |
|---|---|---|
| **2** | COPh | Me |
| **3** | COPh | Et |
| **4** | $SiPh_2Bu^t$ | Et |




**5**

The route is shown in Scheme 1. A sample of (*S*)-2-cyclohexen-1-ol **6** (e.e. 78±6%)[17] was benzoylated and the product **7** treated with ozone as described.[16] Dehydration of the intermediate methoxy hydroperoxide **8** with acetic anhydride–pyridine gave the ester-aldehyde **2**, with only a trace (<3%) of the alternative regioisomer being detected in the 300 MHz $^1H$ n.m.r. spectrum of the crude product. The optical purity of the isolated product **2** (e.e. 74±5%)[18] indicated that the original chiral centre of **6** had remained intact throughout the reaction sequence.




**6** **7** **8**

**Scheme 1** *Reagents*: i, PhCOCl, pyridine, $CH_2Cl_2$, 0 to 20 °C, 0.5 h (94%); ii, $O_3$, MeOH, $CH_2Cl_2$, $NaHCO_3$, –78 °C; iii, $C_6H_6$, $CH_2Cl_2$, pyridine, $Ac_2O$, 0 to 20 °C, 22 h (56%).

The origin of the observed selectivity has been discussed by Schreiber *et al.*[16] Since (*S*)-2-cyclohexen-1-ol **6** [or the (*R*)-antipode] is available in one step from 2-cyclohexen-1-one (98–100% e.e.)[19] or 1,3-cyclohexadiene (92% e.e.),[20] the sequence shown in Scheme 1 represents a convenient alternative to the existing routes to the ester-aldehyde **2** and analogues, and provides further confirmation of the synthetic potential of the unsymmetrical ozonolysis protocol.

Procedure for the preparation of methyl 5*S*-(benzoyloxy)-6-oxohexanoate **2**. – Ozone was bubbled through a stirred solution of (*S*)-1-(benzoyloxy)cyclohex-2-ene **7** (e.e. 78±6%;[17] 368 mg, 1.82 mmol) in methanol (1 ml) and dichloromethane (5 ml) containing sodium hydrogen carbonate (0.5 g, 6 mmol) at –78 °C.[16] When the solution acquired a pale blue colouration the addition of ozone was stopped and the excess removed by passing nitrogen through the solution until it became colourless. The mixture was allowed to reach room temperature, diluted with benzene (20 ml), filtered, and evaporated under reduced pressure to a volume of *ca.* 1 ml. Dichloromethane (3 ml) was added and, with stirring under nitrogen, the solution was cooled to 0 °C and treated with pyridine (310 mg, 3.92 mmol) and acetic anhydride (185 mg, 1.81 mmol). After 22 h at room temperature the reaction mixture was diluted with ether (30 ml), washed successively with 0.1 M hydrochloric acid, water, sodium carbonate solution, and water, dried, and evaporated under reduced pressure. The resulting pale yellow oil was purified by chromatography over Florisil®, eluting with hexane - ethyl acetate (4:1), giving the title compound (270 mg, 56%) as a colourless oil, $[\alpha]_D^{25} = -25.3°$ (*c* 3.16, $CHCl_3$) (e.e. 74±5%).[18]

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18 The quoted e.e. value is based on polarimetry {optically pure **2** has $[\alpha]_D^{23} = -34.4°$ (*c* 1.3, $CHCl_3$); *cf.* reference 3) and was confirmed *via* 300 MHz $^1H$ n.m.r. analysis of the product in the presence of (*R*)-(–)-2,2,2-trifluoro-1-(9-anthryl)ethanol.
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