

Chiral Homoenate Anion Equivalents: Synthesis of Optically Pure 5-Substituted Furan-2(5*H*)-ones

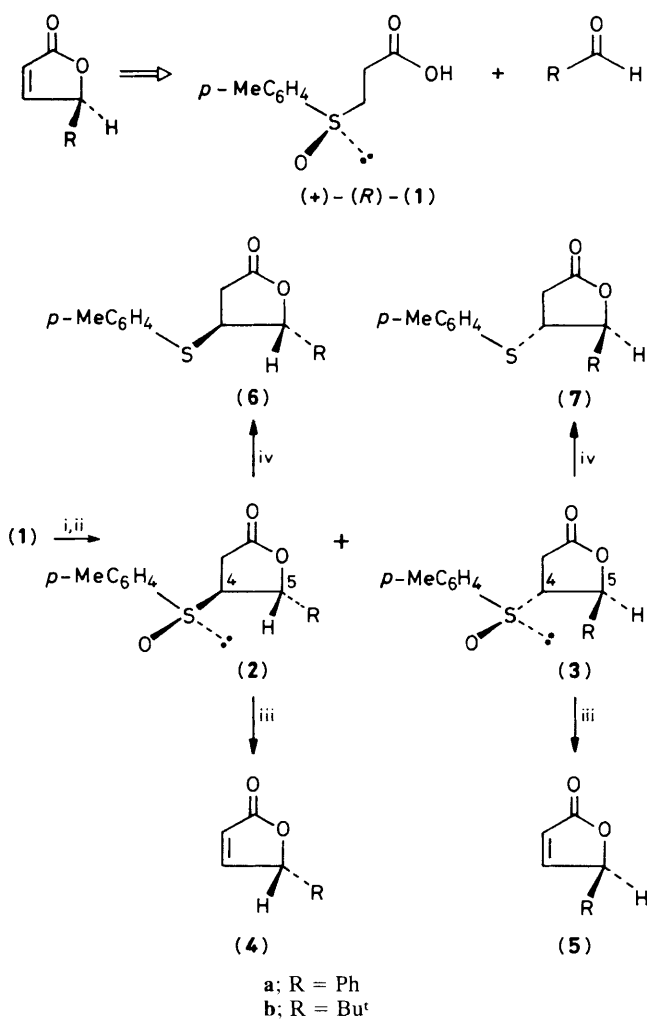
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Addition of the dianion of (+)-(*R*)-3-[(4-methylphenyl)sulphinyl]propionic acid (**1**) to aldehydes affords two main diastereoisomeric β -sulphinyl- γ -lactones, pyrolysis of which gives the two enantiomers of 5-substituted furan-2(5*H*)-ones in optically pure form.

As a part of a programme directed towards the synthesis of γ - and δ -lactone natural products we needed a versatile method for the construction of optically pure 5-substituted furan-2(5*H*)-ones. Synthetic approaches to this functional array involve use of natural optically active starting materials,¹

chiral resolution of intermediates,² and asymmetric synthesis of appropriate precursors.³ As the sulphinyl group has been successfully used to obtain chiral d¹, d², and a² synthons,⁴ we decided to study its utilization as a d³ key building block in the synthesis of furan-2(5*H*)-ones.



Scheme 1. i, Lithium di-isopropylamide, 30 min, tetrahydrofuran (THF), -75°C ; ii, RCHO, THF, 10 min, -75°C , 65–70% yield, (2):(3) = ca. 60:40; iii, toluene, heat, 80% yield; iv, $(\text{CF}_3\text{CO})_2\text{O}$, NaI, acetone, 90% yield.

Specifically, (+)-(R)-3-[(4-methylphenyl)sulphinyl]-propionic acid (1) $\{[\alpha]_D^{20} +180^{\circ}$, c 0.7, CHCl_3 , m.p. (AcOEt) $132\text{--}133^{\circ}\text{C}\}$ was obtained in 56% yield by addition of a suspension of lithium bromoacetate to a solution of the anion of (+)-(R)-methyl 4-methylphenyl sulphoxide. Dimetallation of (1) with lithium di-isopropylamide and addition of a solution of an aldehyde gave (Scheme 1) two main diastereoisomeric β -sulphinyl- γ -lactones[†] (+)-(S_{C4},R_{C5},R_S)-(2) and

(+)-(R_{C4},S_{C5},R_S)-(3) (ratio ca. 60:40).[‡] These compounds were separated by flash chromatography: their pyrolysis afforded optically pure 5-substituted furan-2(5H)-ones (–)-(S)-(4) and (+)-(R)-(5) respectively,[§] while their reduction with trifluoroacetic anhydride–sodium iodide gave enantiomeric β -sulphide- γ -lactones (–)-(S_{C4},R_{C5})-(6) and (+)-(R_{C4},S_{C5})-(7).[§]

The absolute stereochemistry at C(5) in (4) and (5) was determined by the sign of the $\pi \rightarrow \pi^*$ Cotton effect at 212 nm in circular dichroism spectra.⁷ The *trans* relative stereochemistry of ring substituents both in (2a,b) and in (3a,b) was deduced by the difference between ¹H n.m.r. spectroscopic data for reduced compounds (6) or (7) and reported values for similarly *cis*-substituted β -sulphide- γ -lactones.⁵ Compounds (2) and (3) probably arise from a six-membered ring transition state⁸ in which the *si* face of the aldehyde approaches the anion derived from abstraction of the *pro-S* and *pro-R* proton respectively.[¶]

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[‡] ¹H N.m.r. (CDCl_3) δ , J in Hz: (2a) 5.70 (d, 1H, CHO, ³ J 6.6), 3.47 (m, 1H, CHSO, ³ J = ³ J = 7.8); (3a) $\{[\alpha]_D^{20} +65^{\circ}$, c 1, CHCl_3 \} 5.78 (d, 1H, CHO, ³ J 3.6), 3.52 (m, 1H, CHSO, ³ J 7.0, ³ J 7.8); (2b) 4.46 (d, 1H, CHO, ³ J 5.0), 3.30 (m, 1H, CHSO, ³ J 8.5, ³ J 5.6); (3b) 4.43 (d, 1H, CHO, ³ J 2.1), 3.38 (m, 1H, CHSO, ³ J = ³ J = 6.3). Trace amounts of other diastereoisomers could be identified *via* t.l.c. The stereochemistry of these compounds has not been studied as yet.

[§] ¹H N.m.r. and mass spectra were in accord with literature data for racemic compounds (refs. 5 and 6): $[\alpha]_D^{20}$ CHCl_3 (4a) -304° , c 1; (5a) $+303^{\circ}$, c 1; (4b) -129° , c 3.7; (5b) $+129^{\circ}$, c 3.7; (6a) $+63^{\circ}$, c 2; ¹H n.m.r. (CDCl_3) δ , J in Hz: (6a) 5.30 (d, 1H, CHO, ³ J 5.5), 3.72 (m, 1H, CHS, ³ J 7.0, ³ J 7.5); (6b) 4.11 (d, 1H, CHO, ³ J 4.0), 3.63 (m, 1H, CHS, ³ J 4.5, ³ J 8.0), 0.89 (s, 9H, Me₃C). The optical purity for new compounds was assessed by ¹H n.m.r. with europium or ytterbium chiral shift reagents.

[¶] Preliminary experiments aimed at increasing stereoselectivity show that reaction conditions adopted in C–C bond formation play an important role in determining relative abundance of diastereoisomers.

[†] Racemic β -sulphinyl- γ -lactones have already been used in the synthesis of furan-2(5H)-ones, ref. 5.