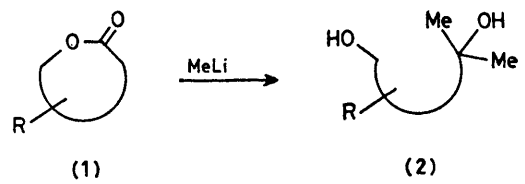
General Method for Determining Enantiomeric Purities of Chiral Lactones

By IGNAC J. JAKOVAC and J. BRYAN JONES*
(*Department of Chemistry, University of Toronto, Toronto, Ontario, Canada* M5S 1A1)

Summary An easy, convenient, and generally applicable method for determining enantiomeric purities of chiral lactones of all ring sizes is provided by treating small samples of the lactones with methyl-lithium, followed by n.m.r. examination of the resulting diols in the presence of chiral shift reagents such as Optishift I.

WE report a convenient and general procedure for establishing the enantiomeric purities of chiral lactones, regardless of their ring size. It involves reaction of lactones (**1**) with methyl-lithium followed by n.m.r. examination of the diols (**2**) produced in the presence of tris[trifluoromethylhydroxymethylene-(−)-camphorato]europium(III) (Optishift I).†



(1) (2)

The 5-, 6-, and 7-membered ring lactones (**3**)—(**7**) (5 mg) were treated with excess of MeLi in tetrahydrofuran at −78 °C. Neutralisation with 10% aqueous acetic acid followed by ether extraction afforded diols‡ of sufficient purity for direct n.m.r. examination. The results obtained are recorded in the Table.

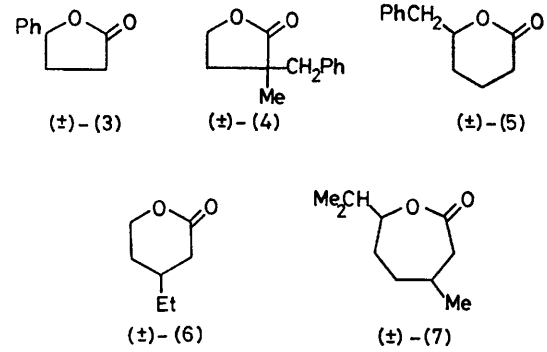
At the shift reagent concentrations indicated the peak separations are large enough for accurate integration of all the designated proton resonances, with the relative areas being 1 : 1 as expected for each racemic diol. The applicability of the method to optically active lactones was confirmed using (**6**) and (**7**) of known enantiomeric excess (e.e.). Samples of (−)-(**6**)[1] (65% e.e. by g.l.c.[2]) and (−)-(**7**)[1] (25 and 75% e.e., by weight) were measured as 67, 28, and 74% e.e., respectively, by this n.m.r. technique, with an accuracy of ±3%.

The most useful resonances for enantiomeric purity determinations will generally be those of the diastereotopic methyl groups of the $(CH_3)_2COH$ group. However, protons of the other spectroscopically non-equivalent groups present can also be used, as illustrated for (±)-(**4**), (**6**), and (**7**). The technique is a convenient and versatile one, and, in contrast to previous lactone e.e. determination methods,[2,3] it is not subject to any limitations with respect to ring size.

TABLE. Enantiomeric shift differences induced by Optishift I with diols derived from the lactones (**3**)—(**7**)[a]

Lactone	Diols	ΔΔδ/p.p.m.[b]	Equiv. of Optishift I
(±)-(**3**)[c]	$PhCH(OH)[CH_2]_2C(OH)(CH^A_3)_2$	0·160 (H^A)	0·27
(±)-(**4**)[d,e]	$HO[CH_2]_2C(CH^B_3)(CH_2Ph)C(OH)(CH^A_3)_2$	0·128 (H^A); 0·059 (H^B)	0·25
(±)-(**5**)[e]	$PhCH_2CH(OH)[CH_2]_3C(OH)(CH^A_3)_2$	0·200 (H^A)	0·32
(±)-(**6**)[e]	$HO[CH_2]_2CH(CH_2CH^B_3)CH_2C(OH)(CH_3)_2$	0·042 (H^B)	0·26
(±)-(**7**)[f]	$(CH^A_3)_2CHCH(OH)[CH_2]_2CH(CH^B_3)CH_2C(OH)(CH_3)_2$	0·440 (H^A); 0·020 (H^B)	0·25

[a] Spectra determined at 100 and 220 MHz on CCl_4 solutions. [b] The magnitudes of ΔΔδ are strongly dependent on [Optishift I]. [c] N. H. Cromwell, P. L. Creger, and K. E. Cook, *J. Amer. Chem. Soc.*, 1956, **78**, 4412. [d] J. L. Herrmann and R. H. Schlessinger, *J.C.S. Chem. Comm.*, 1973, 711. [e] Ref. 1. [f] A. Baeyer and V. Villiger, *Ber.*, 1899, **32**, 3729.



We thank the National Research Council of Canada and Hofmann-La Roche, Inc. for support.

(*Received, 28th December* 1978; *Com.* 1306.)

† We also examined the n.m.r. spectra of various chiral lactones themselves in the presence of the commonly available chiral shift reagents (D. H. Williams, *Pure Appl. Chem.*, 1974, **40**, 25; M. D. McCreary, D. W. Lewis, D. L. Wernick, and G. M. Whitesides, *J. Amer. Chem. Soc.*, 1974, **96**, 1038). This was not satisfactory as a routine method for enantiomeric purity determinations.

‡ Each new diol was fully characterized spectroscopically and by elemental analysis.

[1] I. J. Jakovac, K. P. Lok, and J. B. Jones, to be published.
[2] G. Saucy, R. Borer, D. P. Trullinger, J. B. Jones, and K. P. Lok, *J. Org. Chem.*, 1977, **42**, 3206.
[3] W. H. Pirkle, D. L. Sikkenga, and M. S. Pavlin, *J. Org. Chem.*, 1977, **42**, 384; W. H. Pirkle and D. L. Sikkenga, *ibid.*, 1370.