A New Synthesis of Macrocyclic Lactones by Rearrangement of 2-Hydroxyalkyl-2-phenylsulphonylcycloalkanones

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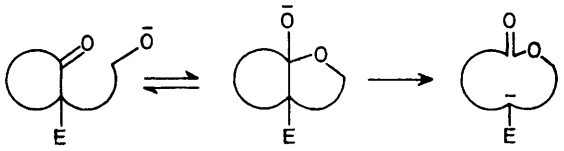
Summary 2-Hydroxyalkyl-2-phenylsulphonylcycloalkanones undergo base-catalysed isomerisation into phenylsulphonyl-lactones with incorporation of the side-chain into the ring.

THE macrocyclic lactones constitute a large and diverse group of natural products, many with strong biological activity. Present syntheses of such compounds usually close the large ring as the final step, and therefore require the use of very dilute solutions to avoid formation of oligomers or polymers. New methods of ring formation introduced over the last few years generally, but not always, involving formation of the acyl–oxygen bond, elegant though some of them are, still need very slow mixing of reactants with a syringe-pump, which merely transfers the limitation from space to time. Syntheses are required which proceed through ring expansions involving intermediates or transition states containing only the common ring sizes (3 to 7 atoms), and which thus allow the use of normal concentrations of reactants. One such sequence is shown in Scheme 1, where E is an electronegative group.†



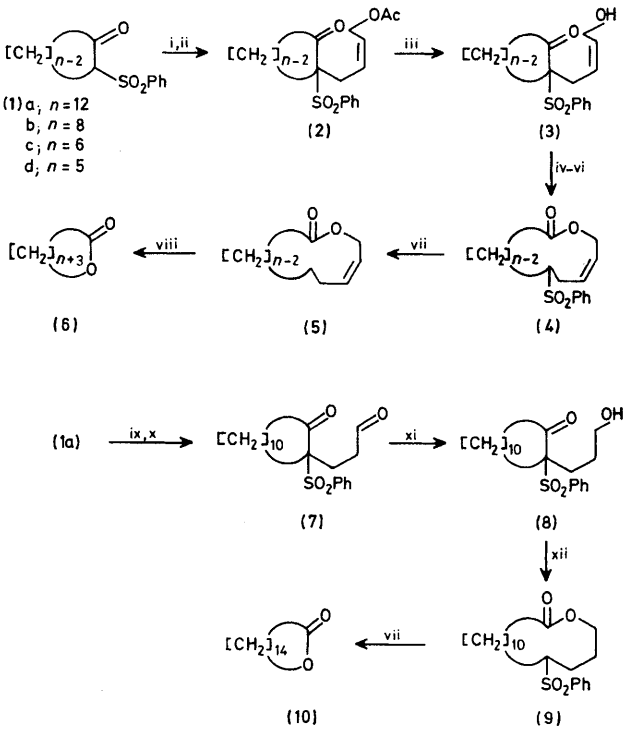
SCHEME 1

Alkylation of the sodium enolates of the 2-phenylsulphonylketones (**1a**—**d**) (easily made by reaction of the 2-bromo-ketones with sodium benzenesulphinate in dimethylformamide) with *cis*-4-acetoxy-1-chlorobut-2-ene[1] in 1,2-dimethoxyethane (DME), followed by acid hydrolysis of the acetates (**2**) gave the necessary 2-(*cis*-4-hydroxybut-2-enyl) derivatives (**3**) (Scheme 2) in good yield (Table). The 3-hydroxypropyl derivative (**8**) was made by Michael addition of the keto-sulphone (**1a**) to acrolein and reduction of the aldehyde group with $NaBH_4$.

TABLE. Percentage yields of isolated products.

	(2)	(3)	(4)	(5)	(6)
(a)	86	97	89	82	93
(b)	80	98	79	—	—
(c)	79	93	76	—	—
	(7)	(8)	(9)	(10)	
	61	98	90	90	

Treatment of the two cyclododecanone derivatives (**3a**) and (**8**) with sodium hydride in benzene led to the expected rearrangement to give the lactones (**4a**) and (**9**), respectively, in high yield. The cyclo-octanone (**3b**) required NaH in boiling diglyme (120 °C) and the cyclohexanone (**3c**) the even more drastic conditions of potassium t-butoxide in diglyme to induce rearrangement in good yield; the cyclopentanone (**3d**) resisted even those conditions. The role of the *cis* double bond in easing ring expansion of (**3**) through the seven-membered ring (Scheme 1) was made clear by the failure of the dihydro-derivative of (**3a**) or (**3c**) to react.



SCHEME 2. *Reagents and conditions:* i, NaH, DME, 65—80 °C, 3—4 h; ii, *cis*-4-acetoxybut-2-enyl chloride, 0·2—1·0 mol. equiv. NaI, 65—80 °C, 30—36 h; iii, 10% aqueous HCl in EtOH or tetrahydrofuran, heat, 8 h; iv, NaH, C_6H_6, heat, N_2, 8 h; v, NaH, diglyme, 120 °C, N_2, 16 h; vi, Me_3COK, diglyme, 120 °C, N_2, 24 h; vii, *large excess* of 6% Na–Hg + Na_2HPO_4, MeOH–DME, −25 °C, 3 h; viii, H_2, 5% Pd/C, MeOH, room temperature; ix, cat. amount Me_3COK, Me_3COH–dioxan, room temperature, 4 h; x, acrolein (1:1 mol. ratio), room temperature, 18 h; xi, $NaBH_4$, MeOH, 10—15 °C, 20 min; xii, NaH, C_6H_6, heat, N_2, 24 h.

† Related ring-enlargements are the base-catalysed rearrangement of 2-(hydroxyalkyl)-2-alkylcyclohexane-1,3-diones to keto-lactones (J. R. Mahajan, *Synthesis*, 1976, 110; J. R. Mahajan and J. S. Resck, *ibid.*, 1980, 998; P. W. Scott, I. T. Harrison, and S. Bittner, *J. Org. Chem.*, 1981, **46**, 1914) and the acid-catalysed *trans*-lactonisation of ω-hydroxyalkyl-lactones (E. J. Corey, D. J. Brunelle, and K. C. Nicolaou, *J. Am. Chem. Soc.*, 1977, **99**, 7359).

The sulphone group could be reductively cleaved in good yield by a large excess of sodium amalgam and disodium hydrogen phosphate in MeOH–DME.[2] The lactone (**9**) gave 15-pentadecanolide (exaltolide) (**10**), and (**4a**), after hydrogenation, gave 16-hexadecanolide (dihydroambrettolide) (**6a**) in overall yields from cyclododecanone of 36 and 42%, respectively.

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[1] W. Reppe, *Liebigs Ann. Chem.*, 1955, **596**, 123.
[2] B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.*, 1978, **100**, 3435. Lithium naphthalenide- and electrochemical-reductions were less satisfactory.