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THE SPIROOXIRANE ROUTE TO *TRANS*-FUSED γ-LACTONES

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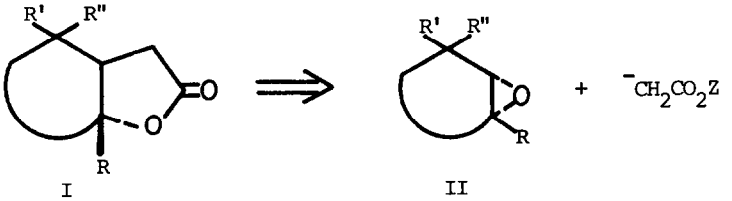
Summary: Convenient access to trans-fused γ-lactones is provided by sodium benzenethiolate promoted ring opening of appropriate γ,δ-spiroepoxyesters.

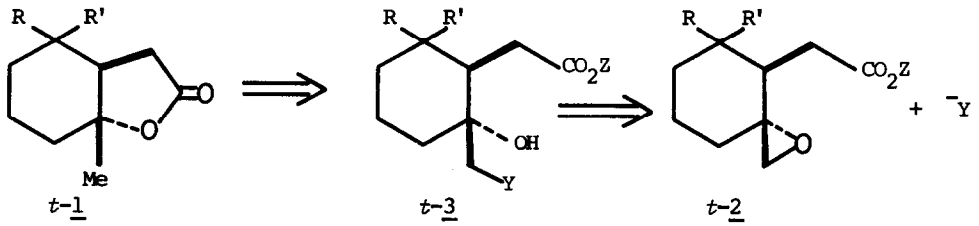
In contrast to the many and varied synthetic routes to *cis*-fused γ-lactones[2] stereoselective access to the analogous *trans*-lactones I appears to be largely limited to cyclizations of the corresponding *trans*-γ-hydroxyacids. The latter acids are in turn most directly generated by nucleophilic opening of a fused oxirane ring with a suitable equivalent of the acetate synthon.[3] Although this



strategy is effective when applied to sterically unencumbered oxiranes II (R = H or alkyl; R' = R'' = H) we have confirmed that it is virtually useless when sterically crowded epoxides of structure II (R, R', R'' = alkyl, aryl, and/or alkenyl) are employed. To circumvent this difficulty we have developed a strategic alternative to the classic oxirane approach which has proven useful for the synthesis of lactones of type I (R = CH_3; R', R'' = H, alkyl, and/or alkenyl).

The application of this new approach, the spirooxirane route, to the synthesis of the *trans*-7a-methyl-2(3H)-hexahydrobenzofuranone systems *t*-1 (R = R' = H; R = CH_3; R' = $CH{=}CH_2$) forms the basis of this report. In addition a study of the effect of benzenethiol concentration on γ-lactone formation from sodium benzenethiolate promoted ring opening of γ,δ-epoxyesters is described.

Retrosynthetic analysis of *t*-1 as indicated readily identified the *trans*-spirooxirane ester *t*-2 as a logical precursor for *trans*-lactonization. Nucleophilic opening of the oxirane ring in *t*-2 by a hydride equivalent (Y = SR, SeR, or halide) should afford the *trans*-hydroxy ester *t*-3 (or the analogous lactone). Cyclization of *t*-3 with dicyclohexylcarbodiimide followed by reductive replacement of Y completes the projected synthesis. Scheme I illustrates the application of this route to the synthesis of the model lactone *t*-1a[4].

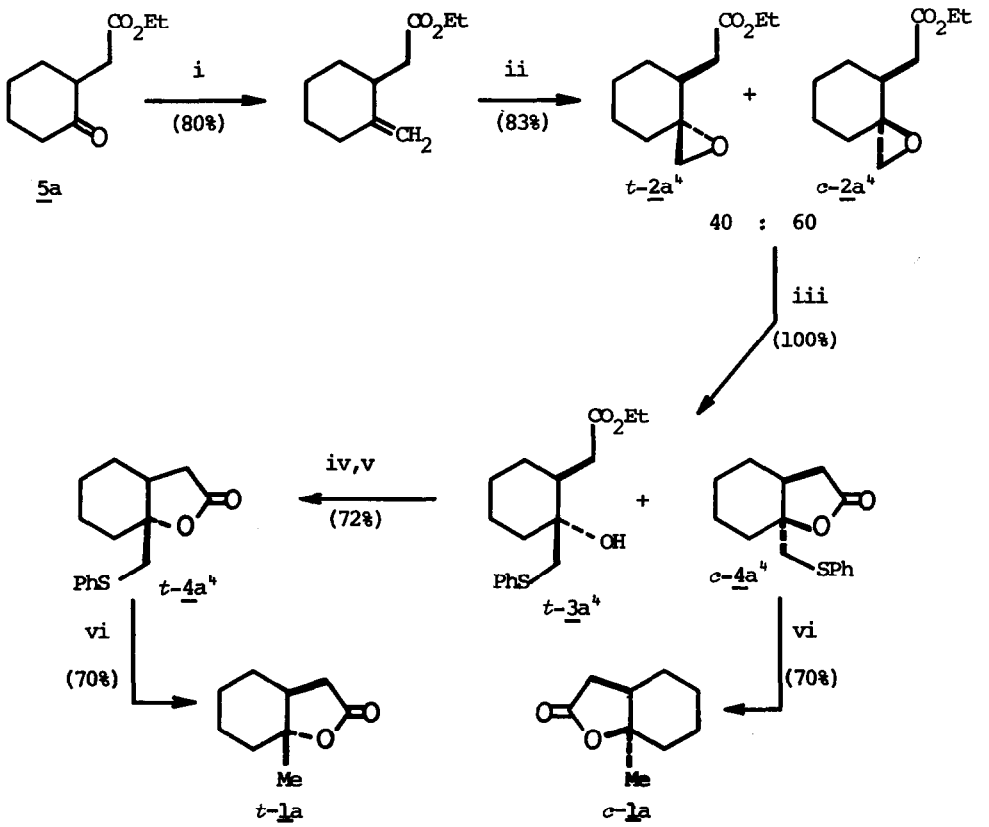


a, R=R'= H; b, R= Me, R'= CH=CH$_2$

A critical feature to the general procedure as outlined in Scheme I is the stereoselectivity of the olefin epoxidation step. If controlling steric and stereoelectronic factors favor the *trans*-spirooxirane *t*-2a with high stereoselectivity, then conditions are ideal for application of the procedure as given. If the reverse situation obtains, i.e. *cis*-epoxidation is greatly favored, then a reversal of the stereoselectivity for oxirane formation may be effected by employing the appropriate sulfur ylid reagent in reaction with the carboxylate salt of the γ-ketoacid. For the example given in Scheme I, little stereoselectivity is observed, as expected, the spirooxiranes *t*-2a and *c*-2a being formed in a ratio of 2:3, respectively. This lack of stereospecificity is not the liability it would appear as acceptable yields of the *trans*-lactone *t*-1a[5] are obtained *via* the spirooxirane route, whereas direct reaction of ketoester 5a or its corresponding acid with methyl Grignard reagents affords primarily the *cis*-lactone *c*-1a[5] with only small amounts (*ca.* 10%) of the *trans*-hydroxy acid being detected.[6] Of course *t*-1a is most readily obtained by the classic oxirane route and served only as a model lactone for our studies.

Despite the lack of stereoselectivity for epoxide formation, it is important to note that separation of the isomeric spirooxiranes. although possible, is not required. Under the proper conditions for oxirane ring opening with PhSH/PhSNa (see Table I) the two major, almost exclusive, products are *cis*-lactone *c*-1a and the *trans*-hydroxyester *t*-3a. Normal chromatographic procedures afforded clean separation of *t*-3a which was subsequently hydrolyzed, cyclized to *t*-4a, and the latter desulfurized with Raney-nickel in DMSO[7] to provide *t*-1a in good yield (*ca.* 12% overall yield from 5a). Application of the identical procedure in Scheme I to the 6,6-disubstituted ketoester 5b (mixture of isomers) afforded pure samples of the previously unknown diastereomeric pair of *trans*-lactones *t*-1b which were required for other purposes.[8] Although some problems were encountered in the desulfurization of *t*-4b due to the presence of the vinyl group acceptable yields were obtained. The spirooxirane approach is thus shown to be of general synthetic utility for *trans*-lactones of type I not readily available by previously documented methodology.

SCHEME I



i, $Ph_3P{=}CH_2$, DMSO ; ii, *m*-$ClC_6H_4CO_3H$, $CHCl_3$, 0°C ; iii, PhSH - PhSNa(0.65:1.0) , DMSO , 2h , r.t. ; iv, KOH , MeOH - H_2O , 70°C , 1h ; v, $C_6H_{11}N{=}C{=}NC_6H_{11}$, pyr. , 30h , r.t. ; vi, Ra-Ni(W2), DMSO , 2h , r.t.

TABLE I. Sodium Benzenethiolate Promoted Ring Opening of *c*-2a/*t*-2a (60:40) in Dimethyl Sulfoxide[a]

Entry	No of Equiv PhSH	Ratio PhSH/PhSNa	Product Ratio				% Total Yield[b]
			c-4a	*c*-3a	*t*-4a	*t*-3a	
1	-	0	+	-	+	+	<20
2	0.75	0.4	50	-	15	10	75
3	1.03	0.55	55	-	10	25	90
4	1.23	0.65	60	-	5	35	100
5	2.25	1.2	-	60	-	40	100
6	2.5	c	-	60	-	40	100

[a]Reactions were carried out at room temperature for 2 h using 1.85-1.90 equivalent of PhSNa. [b]Product analysis by nmr; reactions were judged to be quantitative by absence of starting material and any other product. [c]Only catalytic amounts (0.05 equiv) of PhSNa employed.

The interesting results in Table I deserve some comment although further work is required before the effect of increasing relative concentrations of the benzenethiol is completely understood. The total shutdown of lactone formation at relatively high thiol concentrations is best explained by rapid proton quenching of the reactive alkoxy anions generated by nucleophilic opening of the oxirane ring. At the intermediate concentrations (PhSH/PhSNa <1.0) the reaction mixture is still sufficiently basic to promote lactonization, particularly in the cis case. At even lower thiol concentrations the increased basicity of the medium apparently promotes serious competition from other base-catalyzed reactions.

References and Footnotes

1. On leave of absence from the Institute of Chemistry, Adam Mickewicz University, Poznam, Poland.
2. K. C. Nicolaou, S. P. Seitz, W. J. Sipio and J. F. Blount, *J. Am. Chem. Soc.*, 101, 3884 (1979) and references cited therein.
3. Sodiomalonate: M. S. Newman and C. A. VanderWerf, *J. Am. Chem. Soc.*, 67, 233 (1945); E. E. van Tamelen, G. Van Zyl and G. D. Zuidema, *ibid.*, 72, 488 (1950) and references cited therein; Dilithioacetate: P. L. Creger, *J. Org. Chem.*, 37, 1907 (1972); S. Danishefsky, P. F. Schuda, T. Kitahara and S. J. Etheredge, *J. Am. Chem. Soc.*, 99, 6066 (1977)
4. All new compounds reported in Scheme I gave elemental analysis and spectral data in accord with their assigned structures.
5. The physical and spectral characteristics of the methyl lactones *t*-1a and *c*-1a were identical to those previously reported by Ficini and Maujean.[6]
6. Cf. J. Ficini and A. Maujean, *Bull. Soc. Chim. France*, 219 (1971)
7. J. P. Demoute, D. Hainaut, E. Toromanoff, *C. R. Acad. Sci. Paris*, 277C, 49 (1973)
8. This work will be reported in detail elsewhere.

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