Macrolide Synthesis by the Polystyrene-Mediated Lactonization of ω-Hydroxycarboxylic Acids

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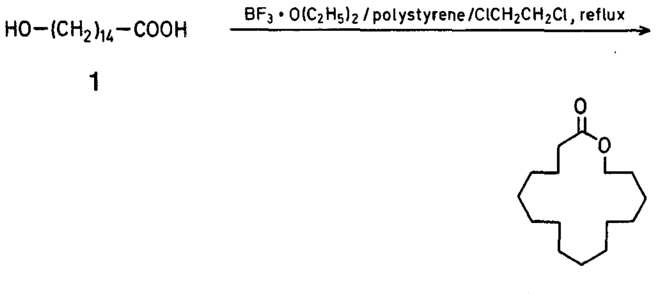
The discovery of numerous macrocyclic natural products exhibiting biological activity[1], particularly the macrolides[2], has generated a recent surge of interest in new solutions to the classic problem of large ring synthesis[3]. We wish to report a convenient method we have found for the direct cyclization of long chain ω-hydroxycarboxylic acids to macrocyclic lactones in good yield using boron trifluoride etherate in the presence of unfunctionalized polystyrene beads as catalyst. Thus the naturally occurring musk lactone Exaltolide (**2**) was prepared in 75% isolated yield by heating equal quantities of 15-hydroxypentadecanoic acid (**1**) and polystyrene[4] in 0.1 *M* boron trifluoride etherate/1,2-dichloroethane. Omission of the polystyrene reduces the yield to 58%, whereas polystyrene alone has no effect on the hydroxy acid. The mechanistic basis for yield enhancement by polystyrene remains unclear at this time.



2 Exaltolide

Other large ring lactones prepared by this method are listed in the Table. Medium ring lactones of 9 to 11 carbons are also produced under these cyclization conditions; however, the yields are lower and not significantly dependent on the presence of polystyrene.

Table. Cyclization of ω-Hydroxycarboxylic Acids $HO{-}(CH_2)_n{-}COOH$ to Large Ring Lactones

n	Yield[a] [%]	
17	78 (84)	products identified spectroscopically
16	78 (82)	
15	77 (83)	
14	77 (79)	
13	46 (51)	
11	41 (43)	

[a] These yields were determined by G.L.C. with an internal standard, making appropriate corrections for detector response factors; numbers in parentheses refer to the yield of lactone corrected for unconsumed starting material.

Preparation of Exaltolide (2):

A solution of 15-hydroxypentadecanoic acid (0.5 g, 1.94 mmol) in 1,2-dichloroethane (250 ml) containing insoluble polystyrene beads[4] (0.5 g) was brought to reflux in a 300-ml round-bottom flask fitted with a reflux condenser and calcium sulfate drying tube. Through the condenser, boron trifluoride etherate (3.0 ml) was then added. After 7 days at reflux, the mixture was cooled and filtered to remove the polystyrene beads. The beads were washed with chloroform which was combined with the filtrate, dried over $MgSO_4$, and evaporated under reduced pressure to give a white solid. Analysis at this point revealed 76.6% Exaltolide (G.L.C.) and 3.3% starting material (titration); the remaining 20.1% presumably represents higher molecular weight polyesters. The crude product was eluted through a 2 × 35 cm column of weakly basic anion exchange resin (Rohm and Haas Amberlyst A-21) with absolute ethanol (200 ml) to give Exaltolide, identified by comparison with an authentic sample (I.R., N.M.R.); yield: 0.35 g (75%); purity determined by superimposability of spectra (fingerprint).

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[4] Rohm and Haas XE 305 macroreticular polystyrene beads, crosslinked with 3–5% divinylbenzene; we thank the Rohm and Haas Company, Philadelphia for a generous gift of XE 305.