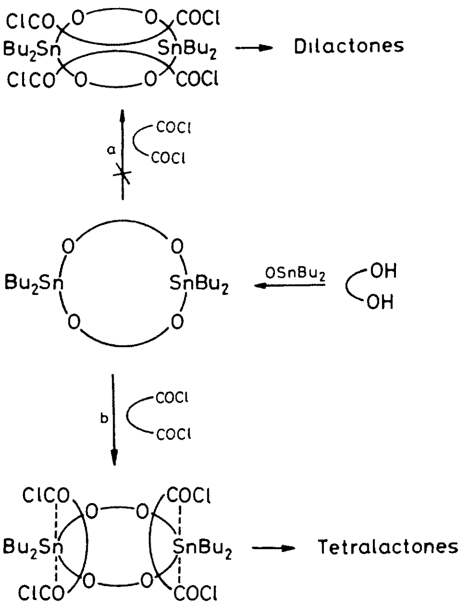
Tin Derivatives for Synthesis: the Preparation of Macrocyclic Lactones

By ABRAHAM SHANZER and NAVA MAYER-SHOCHET

(*Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot, Israel*)

Summary The specific synthesis of macrocyclic tetralactones *via* the use of tin derivatives as covalent templates is described.

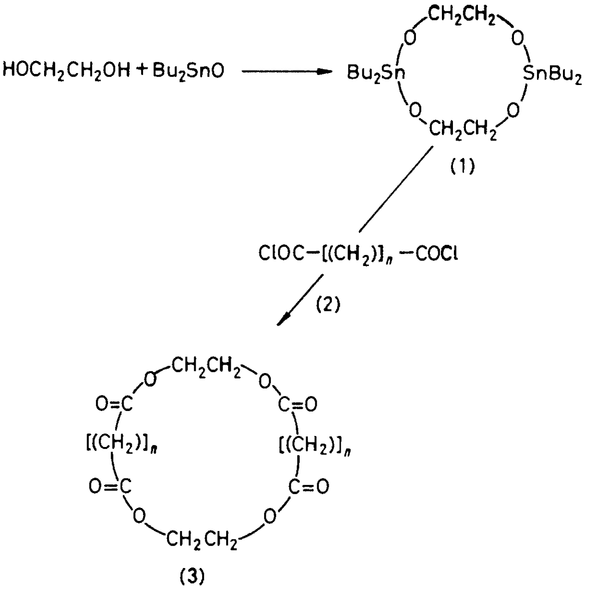
MACROCYCLIC COMPOUNDS, particularly ethers and esters, are attracting attention because of their ability to complex with a large range of metal cations.[1] The preparation of macrocyclic esters has hitherto been achieved by two main approaches, by condensation of dibasic acid derivatives with glycols[2] or dihalides[3] and by depolymerization of linear polyesters.[4] The major drawback of these methods is the lack of external tools to modify product distribution, which is controlled by intrinsic thermodynamic factors. We here introduce a new approach towards the preparation of macrocyclic tetralactones and discuss their structural features.



SCHEME 1

The method is based on the use of tin as a covalent template, which is capable of arranging the glycolic substrates in a cyclic intermediate, the stannoxane (**1**)[5] which subsequently reacts with diacyl chlorides to provide tetralactones exclusively, *via* concerted attack of two acyl chloride groups at each tin atom (Scheme 1 pathway b). The detailed reaction may be represented by Scheme 2.

The 24 membered tetralactone (**3a**) was prepared using sebacoyl chloride (**2a**) as an acylating agent as follows. The distannoxane (**1**) (3.0 mmol) was dissolved in refluxing carbon tetrachloride (70 ml) and was treated dropwise at the same temperature with sebacoyl chloride (**2a**) (6.0 mmol). The mixture was refluxed for 20 h and then concentrated to give a solid residue. Chromatography of this residue afforded 0.413 mg (9.06×10^{-4} mol, 30%) of the pure tetralactone (**3a**) which was recrystallized from methylene chloride–pentane: m.p. 79—81 °C,[4] mass spectrum, M^+, *m/e* 456.9.



SCHEME 2
a, $n = 8$
b $n = 7$
c $n = 5$
d, $n = 3$

The macrocyclic tetralactones (**3b**) (m.p. 147—148 °C, 53% yield), (**3c**) (m.p. 147—148 °C, 15% yield), and (**3d**) (m.p. 144—145 °C, 20% yield) were also prepared using this procedure by condensation of the stannoxane (**1**) with azelaoyl chloride (**2b**), pimeloyl chloride (**2c**), and glutaryl chloride (**2d**), respectively, without optimizing the reaction conditions. All products were characterized by their physical and spectroscopic properties which were in agreement with the assigned structures. Mass spectral analysis showed in each case a molecular ion peak and a strong fragment for $M/2 + 1$. The latter fragment has been reported to be characteristic for cyclic tetralactones as it is completely lacking in the corresponding dilactones.[3] The structures of compounds (**3b**) and (**3d**) have in addition been confirmed by *X*-ray diffraction studies.† These show a regularly alternating arrangement of the ester carbonyl groups: one pair of opposing carbonyl groups being oriented outside the plane of the ring, the other pair above and below the plane of the ring.

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The exclusive formation of macrocyclic 24-, 22-, 18-, and 14-membered tetralactones in preference to the corresponding dilactones demonstrates the unique role of the tin element as a covalent template. Conventional methods have so far been reported to provide various mixtures of tetralactones and dilactones,[3,4] depending on the respective ring size.

A priori, reaction of the diacyl dichlorides (**2**) with the stannoxane (**1**) could occur by one of two possible modes: (a) by attack of the acyl chloride across the stannoxane ring or (b) by attack of the acyl chlorides around each tin element (Scheme 1). The isolation of tetralactones is compatible with pathway b and implies simultaneous attack of two acyl chloride groups at each tin element. Since tin has a pronounced tendency to expand its co-ordination number from four to six,[6] concerted attack of two acyl chloride groups *via* formation of a six co-ordinated transition state seems a likely process, although direct evidence is still lacking.

The application of the method for the preparation of metal ion carriers is under current investigation, as is its expansion toward the synthesis of chiral cavities.

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