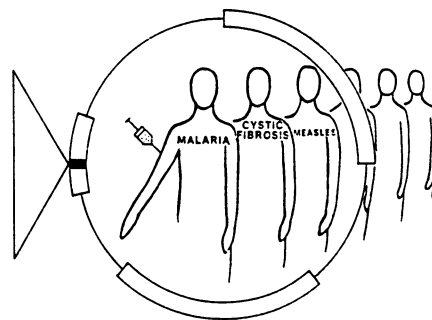


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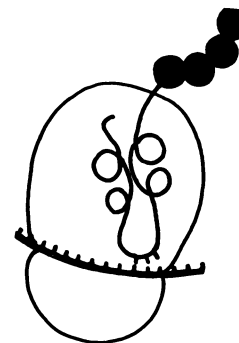
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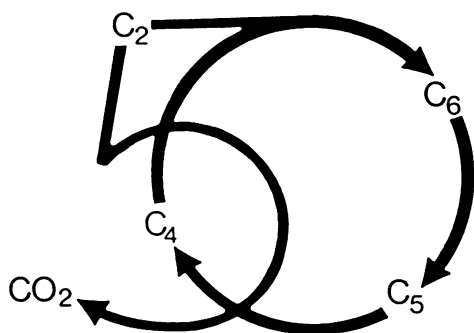
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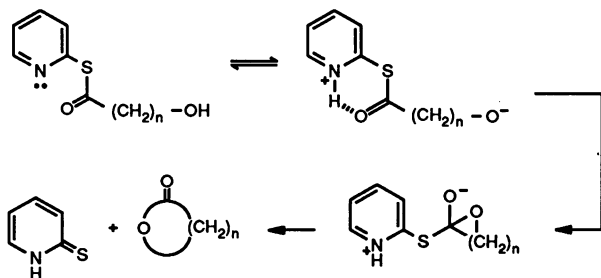
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# Macrolactonization Reagents

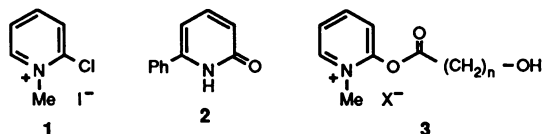
Synthesis of polyfunctional macrocyclic lactones (e.g. macrolides) is one of the masterpieces of the art of natural product synthesis. The therapeutic importance of these lactones has spurred a great deal of interest towards development of new strategies and reagents for their synthesis. The macrolactonization process must rely upon innovative carboxyl and/or hydroxyl activation techniques due to the unfavorable entropic factors and concomitant polymerization processes. The most frequently utilized methods are presented below.<sup>1</sup>

The Corey-Nicolaou method<sup>2</sup> employs 2-pyridylthiol generated *in-situ* from Aldrithiol™-2 and relies upon a "double activation" sequence, as shown below.



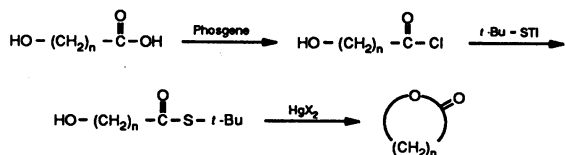
When silver ion activation is utilized in the above process, a much lower reaction temperature can be employed to achieve lactonization (Gerlach modification).<sup>3</sup> Other "thiol" type reagents have also been used successfully.<sup>4,5</sup>

Mukaiyama's method<sup>6</sup> resembles the "double activation" method in that it involves a similar "2-pyridonium" ester 3 derived from 1.



Mukaiyama has further modified this method by converting the initial intermediate 3 to a more reactive 6-phenyl-2-pyridyl ester derived from 2.<sup>7</sup>

The electrophilicity of Hg(II) towards bivalent sulfur serves as the basis of a thiolate ester-Hg(II)-mediated lactonization method, developed by Masamune, as shown below.<sup>8</sup> Masamune later refined this

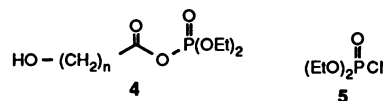


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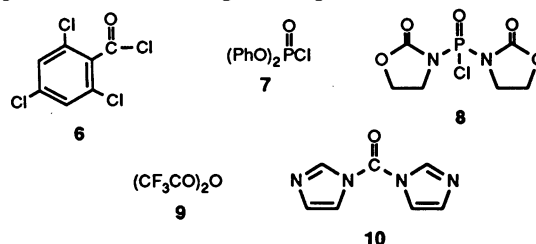
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method by using the mixed phosphoric anhydride, 4, instead of the acid chloride, thus providing a milder and more general method.<sup>9</sup> Diethyl phosphoryl chloride, 5, was found to exhibit optimum selectivity for the carboxylate activation.



Notable among the more traditional methods is Yamaguchi's mixed trichlorobenzoic anhydride method.<sup>10</sup> Other phosphoric and carboxylic anhydrides have also been utilized with varying degrees of success. Reagents 7 - 10 appear to be the most frequently employed reagents in addition to Yamaguchi's reagent, 6.<sup>11-14</sup>



The well-known Mitsunobu reaction<sup>15</sup> is the method of choice for hydroxyl activation, particularly for  $\gamma$ -keto- $\alpha,\beta$ -enoic acids and for diolide and triolide syntheses.

Examples of macrolide synthesis employing simple esterification conditions have also been reported.<sup>16,17</sup>

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