



## Indium Mediated Intramolecular Carbocyclization in Aqueous Media. A Facile and Stereoselective Synthesis of Fused $\alpha$ -Methylene- $\gamma$ -butyrolactones

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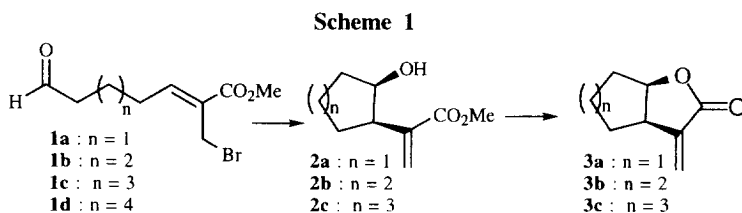
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**Abstract:** Indium mediated intramolecular carbocyclization in aqueous media gave *cis*-fused  $\alpha$ -methylene- $\gamma$ -butyrolactones selectively in good yields. Copyright © 1996 Elsevier Science Ltd

Recently, organometallic type reactions in aqueous media have found considerable use for the formation of carbon-carbon bonds in various organic synthesis.<sup>1,2</sup> Particularly useful is the allylation of carbonyl compounds mediated by indium in aqueous media.<sup>3</sup>

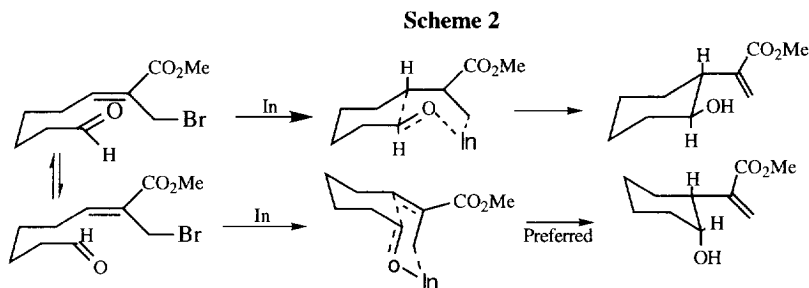
The reaction has been used for the construction of various structural types<sup>4</sup> and most conveniently for the synthesis of carbohydrates.<sup>5</sup> The synthetic usefulness is considerably enhanced by the fact that the reaction is quite stereoselective. For example, starting with a chiral  $\alpha$ -hydroxyaldehyde, the relative stereochemistry of the newly generated hydroxy bearing carbon is *syn* with respect to the adjacent chiral centre.<sup>6</sup> On the other hand, starting with prochiral aldehydes and coupling with  $\gamma$ -substituted allylic halides, the stereochemistry of the two newly generated stereogenic centres is *anti*-selective.<sup>7</sup> The *anti*-selectivity is rationalised on the basis of a cyclic transition state in which the allylic indium species is coordinated with the carbonyl oxygen.

Most of the coupling reactions studied thus far have involved intermolecular coupling. We report here examples of intramolecular coupling of compounds **1a-c** ( $n=1-3$ ) mediated by indium in aqueous media. The reaction proceeded readily to produce carbocyclic systems containing  $\gamma$ -hydroxy- $\alpha$ -methylene esters **2** which either spontaneously or readily cyclized to give fused  $\alpha$ -methylene- $\gamma$ -butyrolactones **3** (scheme 1). The following conditions were used for the cyclization step: to compound **1a** (1 mmol) in water (2 ml) was added indium powder (3 mmol). The mixture was stirred for 12h at room temperature, filtered and extracted with ether. The ether extract was dried, evaporated and the product purified by flash chromatography over silica gel to give lactone **3a**. In the cyclization of **1b** under identical conditions, the hydroxy ester **2b** was obtained in quantitative yield instead. Compound **2b** could be readily converted to the lactone **3b** under acidic conditions.



In the cyclization of **1c**, the reaction proceeded less readily and required stirring for 24hrs for completion. Even so, the product was the lactone **3c** in 60% isolated yield. When the same cyclization was attempted for **1d** (n=4) the closure was apparently too slow to compete with the side reactions in which the bromine was substituted by an hydroxy group.

The ring junction stereochemistry of the fused lactones **3** was found to be *cis* in all cases.<sup>8</sup> Knowing the geometry of compound **1** to be *trans*, the stereochemical results can be rationalised according to scheme 2, using the cyclization of **1b** as illustration. Of the two possible transition states, the one leading to the *cis* fused compound is preferred because the *chair-chair* conformation is favoured over the *chair-boat* conformation.



The  $\alpha$ -methylene- $\gamma$ -butyrolactone unit appears in many natural products and biologically active compounds.<sup>9</sup> Numerous methods have been developed for the synthesis of this substructure.<sup>10</sup> The present indium mediated intramolecular carbocyclization in aqueous media offers a facile and stereoselective route to these fused systems.

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