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A DIRECT, HIGHLY CONVERGENT ROUTE TO α-METHYLENE-γ-LACTONES FUSED TO MEDIUM AND LARGE RINGS

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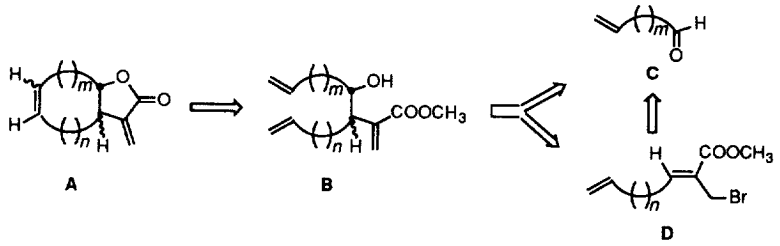
Abstract: A general procedure for the synthesis of α-methylene lactones cis- or trans-fused to larger rings is described. The convenient approach originates with two ω-unsaturated aldehydes of the same or different chain length.

Keywords: indium, metathesis, lactones, Baylis-Hillman reactions, Barbier reactions

The presence of the α-methylene-γ-lactone structural unit in many biologically significant natural products has stimulated considerable synthetic effort directed toward the synthesis of these systems.[1] Often this physiologically pivotal building block[2] is found fused to carbocyclic rings ranging in size from six- to fourteen-membered. Included among these complex structures are vernolepin,[3] elephantopin,[4] and kericembranolide A.[5] Although many methods are available for proper grafting of an exo-methylene group onto a γ-lactone ring,[1] and more direct approaches have been devised,[6-14] a simpler tactic would clearly be desirable. The useful and expedient building block approach described herein presents the opportunity to merge the rapidly expanding fields of aqueous organoindium chemistry[15] and ring-closing olefin metathesis (RCM).[16]

The new strategy is based on recognition of the fact that the key structural elements embedded in **A** can be assembled by twofold cyclization of **B** and that the interconnective C-C bond between the upper and lower sectors of this hydroxy ester can be readily generated (Scheme 1). A striking aspect of this particular construction is its convergency, particularly when one considers the prospect that both halves may be crafted from the same aldehyde **C**. Baylis-Hillman coupling[17] of **C** to methyl acrylate followed by formation of the bromide[18] leads to **D** whose coupling to **C** ($m = n$ or $m \neq n$) in the presence of wet indium powder generates **B**. Acidification of **B** and exposure to an appropriate RCM catalyst quickly produces **A**. Although the retrosynthetic scheme has been drawn without consideration of stereochemistry, salient features of this important consideration are summarized below.

Scheme 1



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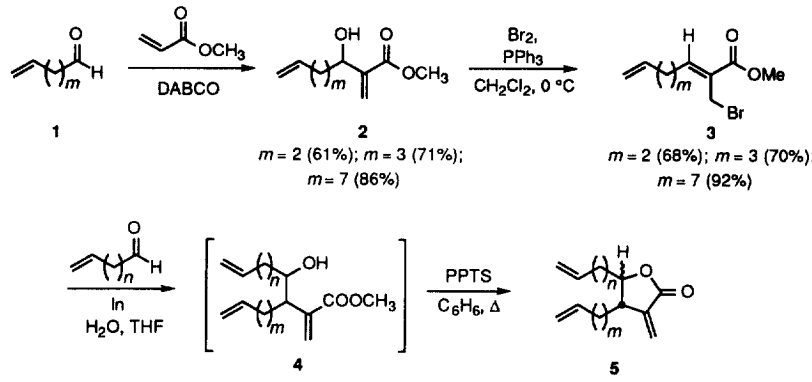
The conversion of **2** to **3** proceeds with very predominant formation of the thermodynamically favored *Z* isomer[19] as determined by NOE analysis. The addition of **3** to a second aldehyde of type **1**, as mediated with indium in THF-H_2O (1:1) at high bromide concentration (1 M), proved to be entirely γ-regioselective but not diastereoselective.[20] Therefore, the mixtures of hydroxy esters **4** so formed were directly cyclized with pyridinium *p*-toluenesulfonate in refluxing benzene to furnish the chromatographically separable cis and trans lactones **5**. These isomers were readily distinguished on the basis of the strong NOE interactions between the methine protons of the cis lactones.

Scheme 2

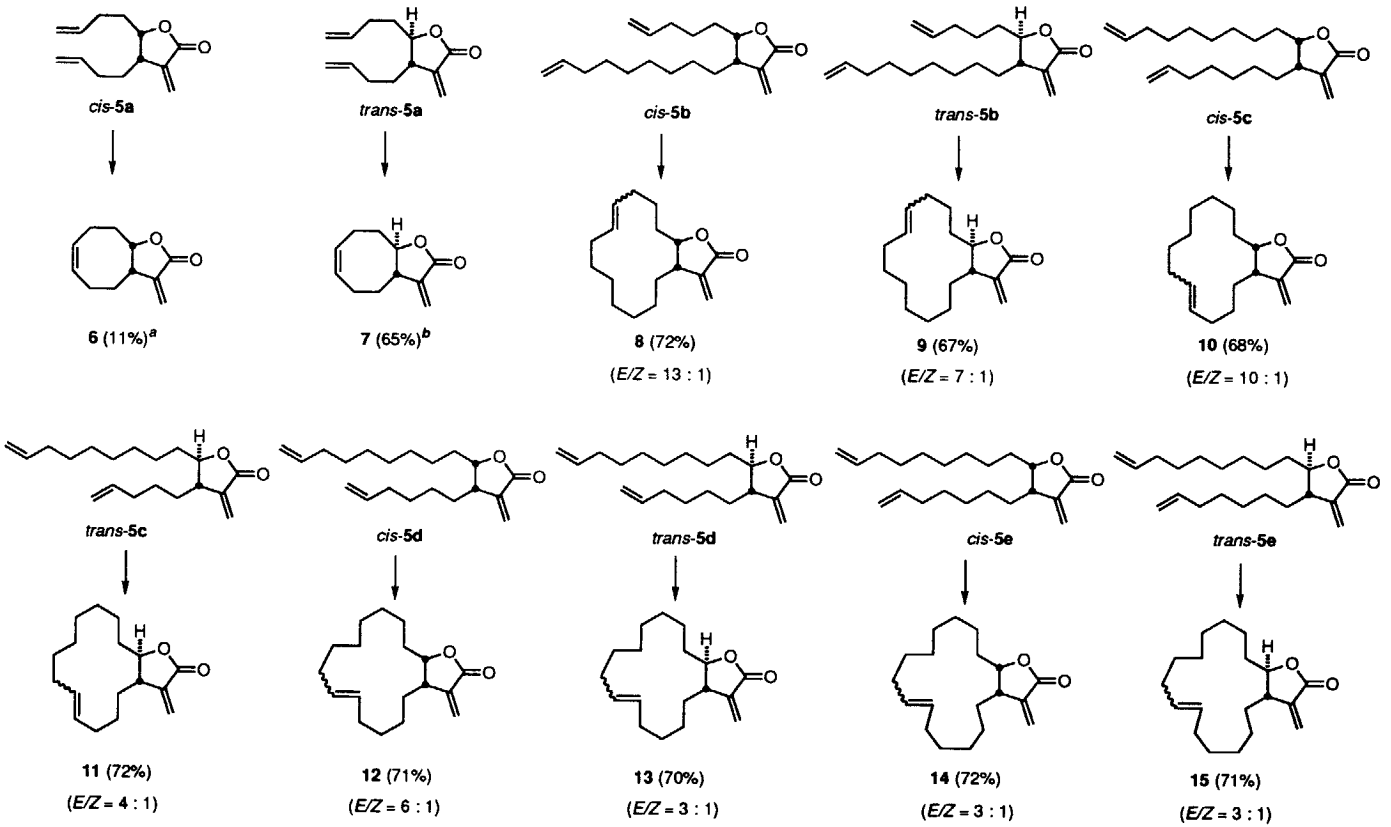


compd	*m*	*n*	cis/trans ratio	combined yield, %
a	2	2	3 : 2	74
b	3	7	3 : 2	72
c	7	3	3 : 2	70
d	7	4	3 : 2	69
e	7	5	3 : 2	64

The RCM step was performed at the 6 mM concentration level in CH_2Cl_2 at 50 °C in the presence of 30 mol % phenylmethylenebis(tricyclohexylphosphine)ruthenium dichloride. Under these conditions, cyclization occurs smoothly during the course of 24 hours to give a mixture of *E* and *Z* isomers, except for the *cis*-cyclooctene example **6**. The *E* isomers were readily distinguished on the basis of the narrow chemical shift difference exhibited by their two olefinic protons, usually a narrow multiplet near δ 5.5 in $CDCl_3$. In contrast, the *Z* isomers are characterized by two widely spaced multiplets ($\Delta\delta \approx 0.2$ ppm).[22] Grubbs has previously noted that conformational predisposition for RCM is low in this instance.[21] A main strength of the protocol is that it allows for fully regiocontrolled introduction of an internal double bond (compare **8/9** versus **10/11**). This relative positioning is dictated uniquely by timing the use of the ω-unsaturated aldehyde **1** ($m \neq n$). In no case did the conjugated double bond provide indication of its involvement in the metathesis process despite its favorable positioning in several of the examples.

A notable feature of the cyclizations that provide 14-membered rings is the more elevated *E*/*Z* ratio observed when a cis lactone is involved. This heightened stereoselectivity is construed to be a reflection of the more elevated barrier to ring closure in the cis series due to ring strain. At the 15-membered ring level, more

Catalytic Ring Closing Metathesis Reactions



[a] Under the reaction conditions employed, unreacted *cis*-**5a** was uncovered to the extend of 39%. [b] Bensel, N.; Marschall, H.; Weyerstahl, P. *Chem. Ber.* **1975**, *108*, 2697.

comparable *E/Z* distributions approaching 3:1 are the norm, indicating that the stereochemistry of the lactone precursor is no longer sterically discriminating.

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