

Direct Synthesis of Spiro δ -Lactones from Conjugated Dienes and Epoxides

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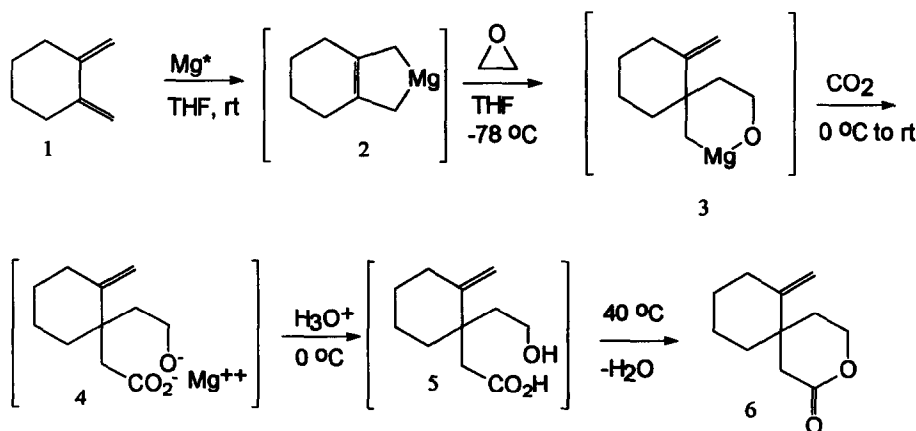
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Abstract: Stepwise reactions of conjugated diene-magnesium reagents with an epoxide followed by carbon dioxide provide a direct method for a one-pot synthesis of spiro δ -lactones accommodating a vinyl moiety at the β -position.

The obstacles associated with the synthesis of spiro δ -lactones include the introduction of functionalities required for lactonization and the generation of a quaternary carbon center. Much work has been done to elucidate novel synthetic routes for these types of molecules.¹ In particular, δ -substituted δ -lactones have recently attracted considerable attention, mainly because molecules of this class include many natural products that exhibit significant biological activity.^{2,3} However, most methods require the use of complex reagents and multiple synthetic steps to accomplish the overall process. One of the more adept methods involves the treatment of bis(bromomagnesium)alkanes with dicarboxylic anhydrides.⁴ We would like to present a direct method for a one-pot synthesis of spiro δ -lactones utilizing conjugated diene-magnesium complexes.⁵



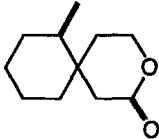


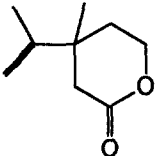


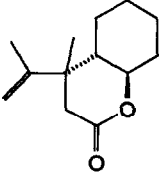
Previous reports⁶ from these laboratories have demonstrated that reactions of diene-magnesium reagents with bis-electrophiles provide a novel approach for annulation, including the generation of complex carbocycles,⁷ spiro compounds,⁸ and fused ring systems.⁹ We have also reported a direct one-step synthesis of spiro γ -lactones.¹⁰ Recently, we found that spiro δ -lactones can also be synthesized utilizing this methodology.

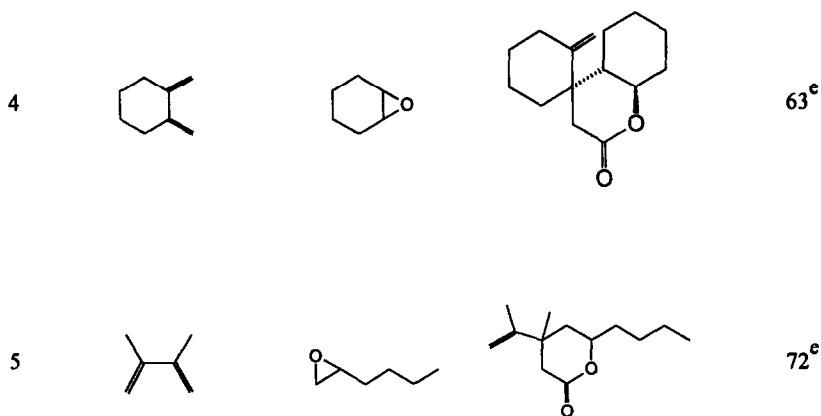
Scheme I



Scheme 1 illustrates a route for the spiro δ -lactone synthesis from the magnesium complex of 1,2-bis(methylene)cyclohexane **1**.¹¹ Initially, treatment of 1,2-bis(methylene)-cyclohexane-magnesium reagent **2** with an excess of ethylene oxide at $-78\text{ }^{\circ}\text{C}$, resulted in the formation of the 1,2-addition adduct **3** derived from the incorporation of one equivalent of epoxide with the diene complex. Significantly, the bis-organomagnesium reagent **2** reacted with only one mole of epoxide and reacted with 100% regioselectivity in the 2-position to give intermediate **3**. Upon warming to $0\text{ }^{\circ}\text{C}$, **3** reacted with CO_2 to yield the magnesium salt of a δ -hydroxy acid **4**. Acidic hydrolysis, followed by warming to $40\text{ }^{\circ}\text{C}$ generated the spiro δ -lactone, 7-methylene-3-Oxaspiro [5.5] undecan-2-one **6** in 69% yield (Table I, entry 1).

Table I. Reactions of Conjugated Diene-Magnesium Reagents with Epoxides followed by Carbon Dioxide.

Entry	Diene	Epoxide ^a	Product ^b	% Yield ^c
1				69
2				39 ^d
3				69 ^e



- a) The epoxide was added to the diene-magnesium complex at $-78\text{ }^{\circ}\text{C}$ and the reaction mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min, then gradually warmed to $0\text{ }^{\circ}\text{C}$ followed by the bubbling of CO_2 . b) Elemental analysis, mass spectra, ^1H NMR, ^{13}C NMR, and FTIR were all consistent with the indicated formulation. c) Isolated yields. d) Yield was based on amount of active magnesium. e) A 1:1 mixture of diastereomers as determined by ^1H NMR.

Importantly, the approach described in Scheme I can be used to prepare both bicyclic and tricyclic spiro δ -lactones, and representative examples are listed in Table I (entries 3 and 4, respectively). For example, 1,2-bis(methylene)cyclohexane-magnesium reagent was treated with cyclohexene oxide at $-78\text{ }^{\circ}\text{C}$ followed by the introduction of CO_2 at $0\text{ }^{\circ}\text{C}$ and acidic hydrolysis with subsequent warming to $40\text{ }^{\circ}\text{C}$. Workup afforded the tricyclic spiro δ -lactone, hexahydro-2'-methylene-Spiro [4*H*-1-benzopyran-4,1'-cyclohexan] -2 (3*H*)-one, in 63% isolated yield as a 1:1 mixture of diastereomers (Table 1, entry 4).

This methodology also exhibited good regioselectivity when unsymmetric epoxides were utilized as the primary electrophile. The formation of 6-butyltetrahydro-4-methyl-4-(1-methylethenyl)-2*H*-Pyran-2-one (Table I, entry 5), demonstrates that the attack of the unsymmetric epoxide occurs at the less sterically hindered carbon.

The overall procedure of the spiro δ -lactone synthesis can be thought of as a molecular assembling process in which three simple independent species, *i.e.* a conjugated diene, an epoxide, and carbon dioxide, mediated by active magnesium are transformed into a complex organic molecule in a well-controlled fashion in good isolated yields. In the process, the construction of a quaternary carbon center and the introduction of both the hydroxyl and carboxyl groups required for lactonization are achieved in one synthetic step. Further studies are currently underway to define the scope and limitations of the process.

Representative Procedure

Spiro δ -lactone: Lithium (8.96 mmol), naphthalene (1.39 mmol), and MgCl_2 (4.41 mmol) were

dissolved in THF (15 mL) under argon and stirred for 3 h which afforded active magnesium.⁶⁻¹⁰ 1,2-Bis(methylene)cyclohexane (3.70 mmol) was added to active magnesium and stirred 4 h. The solution was allowed to stand until it became transparent and was then transferred to another flask. Ethylene oxide (1 mL) was added to the reaction mixture at -78 °C and stirred for 30 min and then warmed to 0 °C. The flask was then charged with carbon dioxide for 10 min at 0 °C, and continued for 10 min at room temperature. A solution of 3N HCL (10 mL) was added and the mixture was heated at 40 °C for 1 h. After cooling to ambient temperature the reaction mixture was extracted with diethyl ether (3 X 20 mL) and the combined organic layers were washed with saturated aqueous NaHCO₃ (2 X 20 mL), water (1 X 20 mL) and dried over anhydrous MgSO₄. Removal of solvents in vacuo followed by flash chromatography afforded 7-methylene-3-Oxaspiro [5.5] undecan-2-one (Table I, entry 1) (0.378 g) in 69% isolated yield.

Acknowledgments. The financial support by the National Institutes of Health (Grant GM35153) is gratefully acknowledged. The authors would also like to thank Walter R. Klein for helpful discussions.

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(Received in USA 15 June 1993; accepted 22 July 1993)