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Synthesis of Spiro γ-Lactones from Conjugated Dienes

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Summary: Stepwise reactions of conjugated dienemagnesium reagents with a ketone at −78 °C, followed by carbon dioxide at 0 °C to room temperature, provide a one-pot method for the synthesis of spiro γ-lactones containing a vinyl group at the β-position.

The difficulties associated with the synthesis of spiro γ-lactones are often the generation of a quaternary carbon center and the introduction of functionalities used for lactonization. Much work has been done in an effort to develop useful synthetic routes.[1-3] However, most methods require the use of complex reagents and multiple synthetic steps to accomplish the overall process. One of the efficient methods involves the treatment of bis(bromomagnesio)alkanes with dicarboxylic anhydrides.[3] In this paper, we would like to present a direct method for a one-pot synthesis of spiro γ-lactones by using conjugated dienemagnesium reagents.[4]

Previous reports[5] from our laboratory have shown that reactions of dienemagnesium reagents with bis-electrophiles provide a new approach for annulation, including the generation of complex carbocycles,[6] spiro compounds,[7] and fused rings.[8] Recently, we found that spiro γ-lactones containing a vinyl group at the β-position can also be synthesized in one pot based on stepwise reaction of dienemagnesium reagents with ketones followed by reaction with carbon dioxide.

Scheme I illustrates a route for spiro γ-lactone synthesis from the magnesium complex of 1,2-bis(methylene)cyclohexane (1). Initially, it was observed that treatment of 1,2-bis(methylene)cyclohexanemagnesium (2) reagent with 1 equiv of acetone at −78 °C resulted in the formation of a 1,2-addition adduct (3) derived from the incorporation of one molecule of acetone with the diene complex.[9] Protonation of the adduct 3 at −78 °C yielded a tertiary alcohol containing a quaternary center 4. It was considered that upon warming intermediate 3 should be able to undergo nucleophilic addition to another electrophile. Thus,

Scheme I

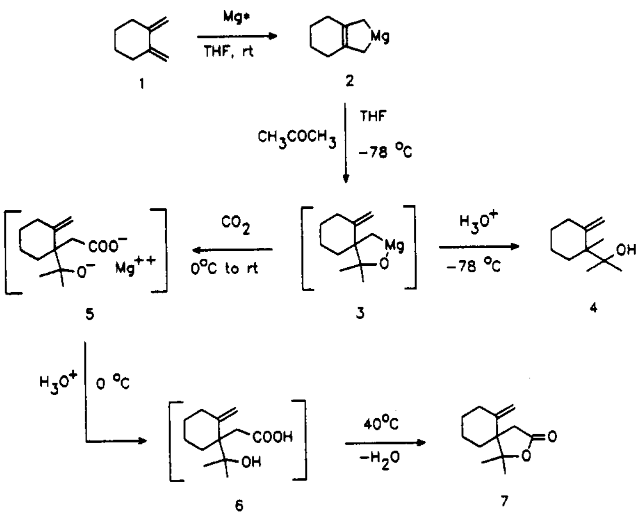
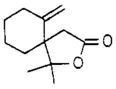
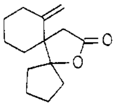
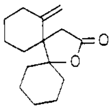
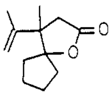
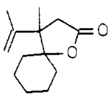
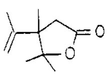


Table I. Reactions of Conjugated Dienemagnesium Reagents with Ketones Followed by CO$_2$

entry	diene[a]	ketone[b]	product[c]	% yield[d]
1	1	acetone	7 	68
2	1	cyclopentanone	8 	66
3	1	cyclohexanone	9 	60
4	10	cyclopentanone	14a 	68
5	10	cyclohexanone	14b 	61
6	10	acetone	15 	59

[a] 1: 1,2-bis(methylene)cyclohexane; 10: 2,3-dimethyl-1,3-butadiene. [b] Ketone was added to the dienemagnesium complex at −78 °C, and the mixture was stirred at −78 °C for 10 min and then gradually warmed to 0 °C followed by the bubbling of CO$_2$. [c] All products have been fully characterized spectroscopically, including ^{1}H NMR, ^{13}C NMR, FTIR, and mass spectra. [d] Isolated yields.

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(9) Grignard reagent 3 possibly exists as oligomeric form in THF. A similar species, 1-oxa-2-magnesiacyclopentane, has been shown to be trimeric in THF. (a) Blomberg, C.; Schat, G.; Grootveld, H. H.; Vreugdenhil, A. D.; Bickelhaupt, F. *Liebigs Ann. Chem.* **1972**, *763*, 148. (b) Freijee, F.; Schat, G.; Mierop, R.; Blomberg, C.; Bickelhaupt, F. *Heterocycles* **1977**, *7*, 237.

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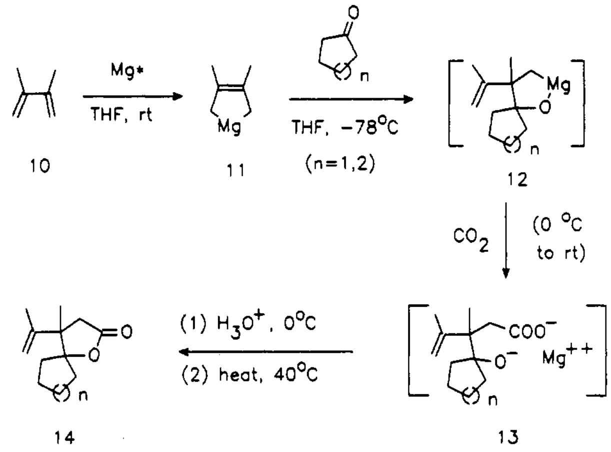
Scheme II



carbon dioxide was bubbled as the second electrophile through the reaction mixture at 0 °C to room temperature. As expected, the intermediate reacted quickly with carbon dioxide, yielding presumably a magnesium salt of a γ-hydroxy acid **5**. After acidic hydrolysis followed by slight warming, a spiro γ-lactone, 4,4-dimethyl-6-methylene-3-oxaspiro[4.5]decan-2-one (**7**) was obtained in 68% isolated yield.

It is necessary to point out that when **2** was treated with only 1 equiv of acetone, no product derived from the reaction of **2** with two molecules of acetone was observed, indicating that in the presence of **2**, the initially formed adduct **3** did not add competitively to the unreacted acetone. This feature allowed that both acetone and subsequently added CO_2 were delivered to the original diene at desired positions. However, if excess acetone was used, **3** was found to be able to undergo further nucleophilic addition to the ketone, yielding the corresponding diol.[10] Therefore, it is essential to use not more than 1 equiv of acetone for the synthesis of **7**.

Significantly, the approach described in Scheme I can also be used to prepare spiro γ-lactones containing two spiro centers. The representative examples of this dispiroannulation are listed in Table I (entries 2 and 3). For example, **2** was treated with cyclopentanone at −78 °C, and the reaction mixture was then bubbled with CO_2 at 0 °C to room temperature. Workup gave 7-methylene-14-oxadispiro[4.0.5.3]tetradecan-13-one (**8**) in 66% isolated yield (Table I, entry 2). Similar chemistry was observed when cyclohexanone was used as the first electrophile (Table I, entry 3).

When this approach is applied to the magnesium complexes of acyclic 1,3-dienes, it provides an easy route to both spiro γ-lactones and γ-lactones. Scheme II gives an outline for the synthesis of spiro γ-lactones from (2,3-dimethyl-2-butene-1,4-diyl)magnesium (**11**) reagent.[11] Generally, reaction of a cyclic ketone with **11** at −78 °C resulted in initial attack at the 2-position of the diene complex, giving an internal alkoxy Grignard (**12**).[12] After warming, the intermediate was allowed to react with carbon dioxide at 0 °C to room temperature. Upon hydrolysis and gentle heating, a spiro γ-lactone containing a quaternary center was obtained (**14**) (Table I, entries 4 and 5). The use of acyclic ketones as initial electrophiles will lead to the synthesis of substituted γ-lactones. For example, treatment of **11** with acetone followed by carbon dioxide afforded β,γ,γ-trimethyl-β-(1-methylethenyl)-γ-butyrolactone (**15**) in 59% isolated yield (Table I, entry 6).

The overall procedure of the spiro γ-lactone and γ-lactone synthesis can be regarded as a molecular assembling process in which three simple independent species, i.e., a conjugated diene, a ketone, and carbon dioxide, are used to build a complex organic molecule in a well-controlled fashion. In the process, the construction of a quaternary center and the introduction of both a hydroxyl and a carboxyl used for lactonization are accomplished in one synthetic operation. Further studies are underway to define the scope and limitations of the process and to extend the present approach for the synthesis of optically active spiro γ-lactones. It is believed that variations of initial and/or second electrophile(s) will lead to new types of chemical transformations of 1,3-dienes.

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Supplementary Material Available: Details of preparation of **7** and ^1H and ^{13}C NMR spectra of **4**, **7–9**, **14a,b**, and **15** (16 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(10) Treatment of **2** with 2 equiv of acetone at −78 °C followed by acidic hydrolysis at −78 °C gave **4** as well as a diol, 1-(1-hydroxy-1-methylethyl)-1-(2-hydroxy-2-methylpropyl)-2-methylenecyclohexane, in 50% and 29% isolated yields, respectively.

(11) (2,3-Dimethyl-2-butene-1,4-diyl)magnesium was prepared by using highly reactive magnesium (ref 6a,b). For an alternative method of its preparation, see: Yasuda, H.; Kajihara, Y.; Mashima, K.; Nagasuna, K.; Lee, K.; Nakamura, A. *Organometallics* **1982**, *1*, 388.

(12) Reaction of **11** with cyclopentanone at −78 °C followed by hydrolysis at −78 °C yielded a tertiary alcohol, 1-(1,1,2-trimethyl-2-propenyl)cyclopentanol, in 78% isolated yield.