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Preliminary communication

REARRANGEMENTS OF ORGANOMETALLIC COMPOUNDS

XVII*. SYNTHESIS OF LACTONES VIA THE TITANIUM-CATALYZED HYDROMAGNESIATION OF ALKENOLS

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Summary

An efficient, two-step synthesis is presented for preparing γ- and δ-lactones from aldehydes or ketones: (1) the addition of vinyl- or allyl-Grignard reagents to the appropriate carbonyl substrate; and (2) the titanium-catalyzed hydromagnesiation of the resulting alkenols with ethyl Grignard reagent and $(\eta^5\text{-}C_5H_5)_2TiCl_2$, followed by carbonation. The selectivity of hydrometallation observed with 3-butenyl(methyl)vinylcarbinol indicates the importance of alkoxytitanium hydrides in determining the course of reaction.

The titanium catalyzed hydrometallation of alkenes has proved valuable for the synthesis of organomagnesium [2—4] and organoaluminum derivatives [5—7]. Attempts to extend such hydrometallations to functionally-substituted alkenes, however, have been rather limited. In a study of the hydromagnesiation of allylic alcohols by a combination of propyl Grignard reagent and a nickel chloride catalyst [4] hydrolysis led to good yields of the saturated alcohol, but carbonation resulted in a poor yield of the lactone.

In the present investigation we have examined the feasibility of synthesizing lactones by the titanium-catalyzed hydromagnesiation of alkenols. The synthesis of a variety of lactones, especially those of the α-methylene type, has become of great importance in current natural product research. Interest in such lactones has been heightened by the finding that such a structural unit is often associated with antitumor activity: e.g., vernolepin, which contains both an α-methylene-γ-lactone and an α-methylene-δ-lactone [8,9]. In light of this, we wish to report the efficient hydromagnesiation of both allylic and homoallylic alcohols and the carbonation of the organomagnesium intermediates, to produce the γ- and δ-lactones (VI—XI) in good yields (Table 1). Ethylmagnesium

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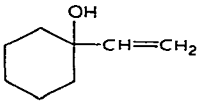
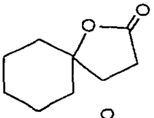
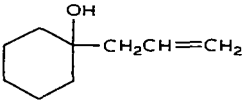
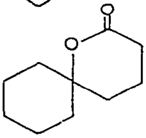
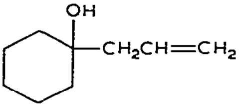
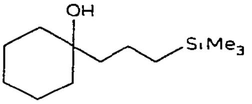
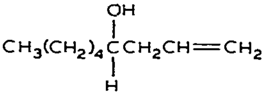
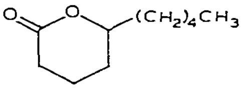
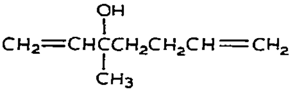
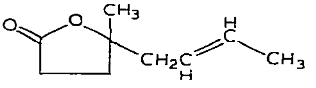
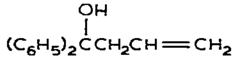
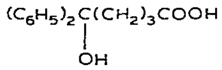
*For part XVI see ref. 1.

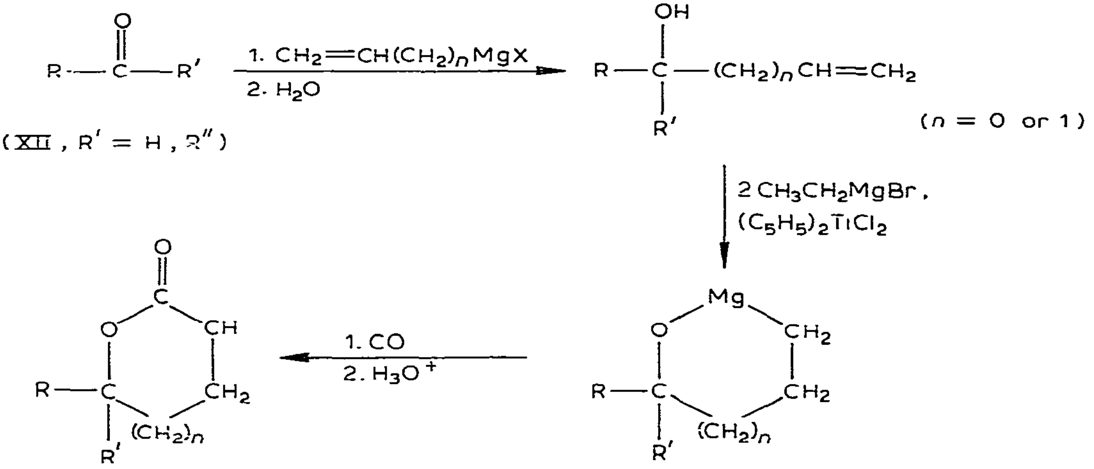
TABLE 1

HYDROMAGNESIATION OF ALKENOLS WITH ETHYLMAGNESIUM BROMIDE CATALYZED BY TITANOCENE DICHLORIDE[a]

Alkenol[b]		Catalyst (mol %)	Electrophile	Product[c]		Yield (%)[d]
	(I)	2.6	CO_2		(VI)	58
	(II)	2.0	CO_2		(VII)	55
	(II)	2.0	Me_3SiCl		(VIII)	59
 $CH_3(CH_2)_4C(OH)(H)CH_2CH{=}CH_2$	(III)	2.6	CO_2		(IX)	55
 $CH_2{=}CHC(OH)(CH_3)CH_2CH_2CH{=}CH_2$	(IV)	3.0	CO_2		(X)[e]	46
 $(C_6H_5)_2C(OH)CH_2CH{=}CH_2$	(V)	2.0	CO_2	 $(C_6H_5)_2C(OH)(CH_2)_3COOH$	(XI)	64

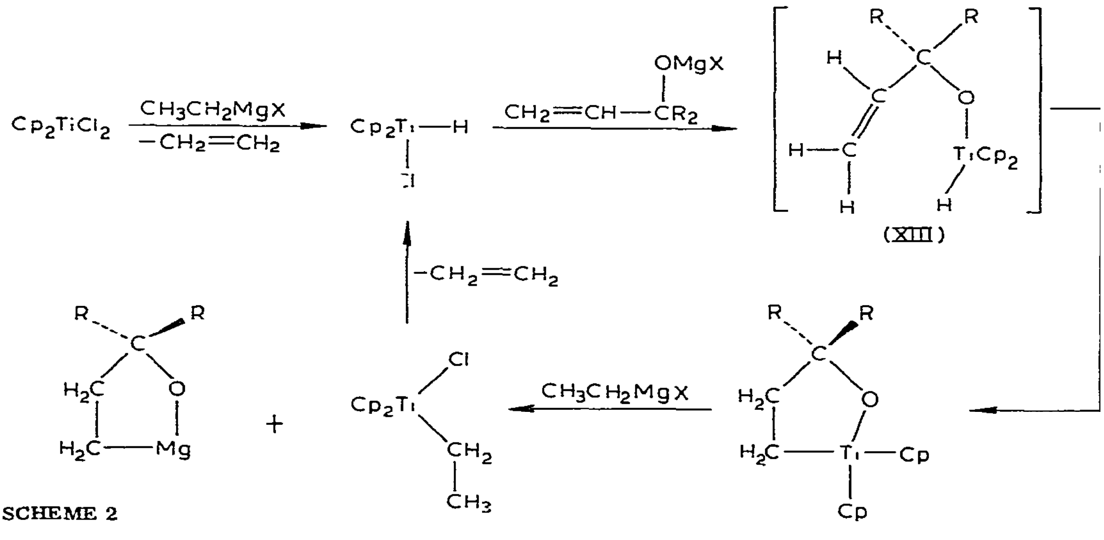
[a] In a typical procedure, an ice-cooled stirred solution of 0.100 g (4.0 mmol) of $(\pi\text{-}C_5H_5)_2TiCl_2$ and 18.9 g (0.150 mol) of 1-vinylcyclohexanol (I) dissolved in 300 ml of anhydrous tetrahydrofuran and maintained under a nitrogen atmosphere was treated over a period of 15 min with 137 ml of a 2.38 *M* solution of ethylmagnesium bromide in ether (0.375 mol). The ice bath was removed and the solution heated at reflux for 20 h, during which time the extent of hydromagnesiation could be monitored by the ethylene evolution. The warm solution was then added over a period of 30 min to a THF suspension of solid carbon dioxide. After another 60 min at 20—25°C 400 ml of 2 *N* sulfuric acid was cautiously added. The organic layer was separated, washed several times with concentrated aqueous NaCl solution and dried over anhydrous $MgSO_4$. Solvent evaporation and distillation gave 9.5 g of forerun (I and propionic acid) and 12.6 g (58%) of lactone VI, b.p. 135—140°C. The yield of VI, based upon unrecovered I, was 85%. [b] The alkenols I—V were obtained in 70—90% yields by the interaction of the appropriate carbonyl compound with vinyl- or allyl-magnesium halide. [c] The presence and size of the lactone ring were ascertained by noting the absence of the OH infrared stretch in the region of 3300—3500 cm^{-1} and the presence of the appropriate C=O stretch; γ-lactones at 1775 cm^{-1} and δ-lactone at 1735 cm^{-1}. The *trans*-1,2-disubstituted ethylenic linkage in X was deduced from the NMR spectrum and the IR bands at 1660 (C=C) and 955 (HC=CH) cm^{-1}. [d] The yields indicated apply to the isolated product and are not yet optimized. The yields determined by GLPC analysis of the crude lactonized products were ca. 15% higher. [e] The GLPC analysis of this compound revealed the presence of ca. 10% of what appeared to be the hydroxy acid (IR: 3500 cm^{-1}).

bromide in ether/THF proved to be a most suitable source of the magnesium hydride, since the ethylene evolved could serve as an indicator of reaction. As catalyst, dicyclopentadienyltitanium dichloride (titanocene dichloride) in 2—3 molar percent proved to be efficient and convenient. The requisite alkenols (I—V), in turn, were readily obtainable by the addition, in 70—90%, of vinyl or allyl Grignard reagents to the appropriate aldehyde or ketone (XII) (Scheme 1). Such readily accessible lactones should prove of interest per se or as substrates for preparing α-methylene-lactones by known methods [9].



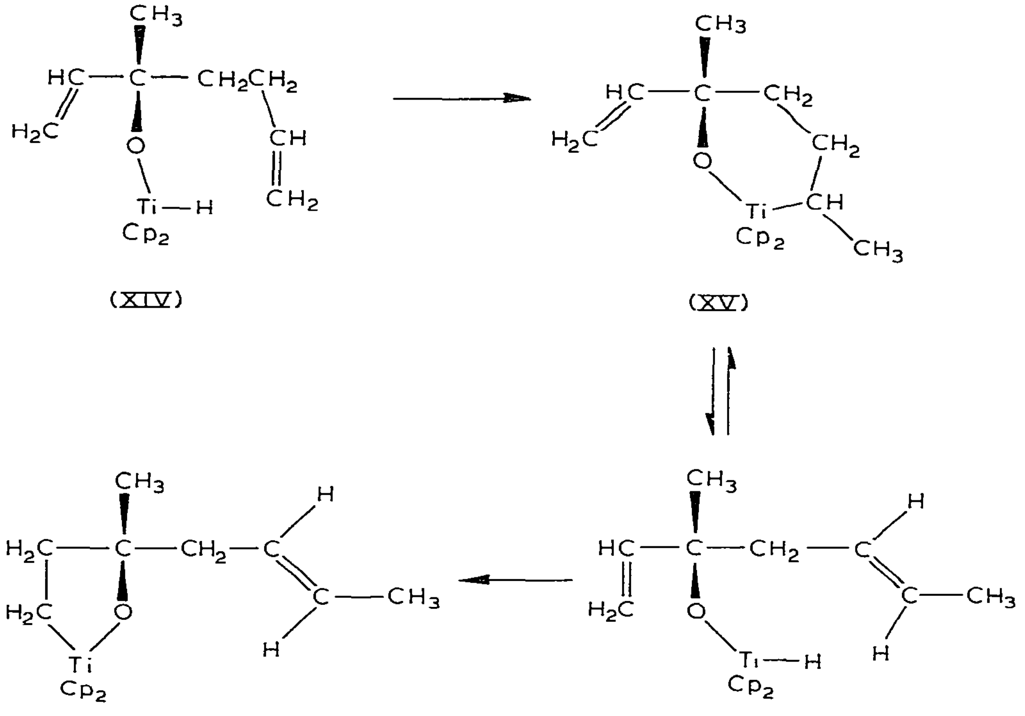
SCHEME 1

In formulating a reaction pathway it seems reasonable to propose the generation of a titanium(III) or titanium(IV) hydride as the active agent, followed by a transmetallation of the resulting alkyltitanium with the excess Grignard reagent [2—4] (Scheme 2). The suggestion that the intermediate titanium hydride brings about the hydrotitanation while coordinated at the alkenoxide



SCHEME 2

oxygen (XIII) is supported by the behavior of 3-butenyl(methyl)vinylcarbinol (IV). If such titanium hydride coordination at oxygen were not decisive for the course of reaction, one would expect both α-olefinic sites (the vinyl and the 3-butenyl groups) to be attacked at comparable rates. Instead the vinyl group underwent hydrometallation preponderantly and, significantly, the 3-butenyl group was isomerized to the *E*-2-butenyl group. Such reactions are best in accord with competitive hydrotitanations occurring via an alkadienoxytitanium complex XIV, the regiochemistry at the 3-butenyl group being determined by the kinetic favoring of a six-membered (XV) over a seven-membered ring. The facile reversibility of metal hydride elimination from such secondary alkylmetal compounds would then lead to isomerization; hydrometallation at the vinyl group would then yield the much more stable primary alkylmetal (Scheme 3).



SCHEME 3

Once formed, the disubstituted olefinic group (*E*-2-butenyl) would not be expected to undergo further hydrotitanation [4].

The extensions of these catalyzed hydromagnesiations to other functionalized unsaturated substrates and to other derivatizing reactions (e.g., silyl VIII in Table 1, alkyl and acyl) are being actively pursued.

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