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SYNTHESIS OF ALKENES: CLAISEN REARRANGEMENT OF ALLYL VINYL ETHERS, PART III; MECHANISTIC VIEWS; THE ORGANIC CHEMISTRY NOTEBOOK SERIES, A DIDACTICAL APPROACH, Nº 11

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ABSTRACT

This is the eleventh theoretical assay in the series: "The Organic Chemistry Notebook Series, a Didactical Approach".

The aim of this series of studies is to help students to have a graphical view of organic synthesis reactions of diverse nature. We have taken a series of reactions compiled by W. Carruthers in 'Some modern methods of organic synthesis', and we have proposed didactical and mechanistic views for them. This theme is included in the chapter "Formation of carbon-carbon double bonds" in the mentioned text.

In chapter 11, we expose a complementing of Claisen rearrangements of ally-vinyl ethers started two papers ago. Now it's turn for the use of a variation of the Claisen rearrangement: the ester-enolate variation (also known as the ketene acetal variation). In this sense, the synthesis of the natural product: methyl santolinate is briefly exposed in a mechanistic manner. Also, the mechanism of the synthesis of ¥¢-unsaturated amino acid derivative and ulterior lactone hydrochloride from the *Z*-crotyl glicine ester is proposed on the basis of theoretical approaches. The condensation between allylic alcohols and cyclic orthoesters to produce (*via* Claisen rearrangement) lactones with the inverted allyl group as a ~ substituent is mechanistically exposed. Vinyl lactones can be converted into cycloalkenes (*via* Claisen rearrangement of cyclic enol ethers); we've analyzed the mechanism.

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RESUMEN

***Spanish title**: Síntesis de alquenos mediante transposición de Claisen de éteres alil-vinílicos, parte III; vistas mecanicísticas; de la serie: El cuaderno de notas de química orgánica, un enfoque didáctico, Nº11.*
Este es el décimo ensayo teórico en la serie: "El cuaderno de química orgánica, un enfoque didáctico".

El objetivo de esta serie de estudios es ayudar a los estudiantes a disponer de una visión gráfica de reacciones de síntesis orgánicas de diversa naturaleza. Hemos tomado una serie de reacciones compiladas por W. Carruthers en: 'Some modern methods of organic synthesis', para las cuales hemos propuesto vistas mecanicísticas y didácticas. Este tema esta incluido en el capítulo "Formation of carbon-carbon double bonds" del mencionado texto.

En el capítulo 11 exponemos un complemento de la transposición de Claisen de éteres alil-vinílicos comenzado hace dos artículos. Ahora es turno del uso de una variación de la Transposición de Claisen: la variación ester-enolato (conocida también como variación ceteno acetal). En este sentido, la síntesis del producto natural santolinato de metilo es expuesta brevemente en una manera mecanicística. También el mecanismo de la síntesis de derivados de amino acido ¥¢-insaturados y producción del ulterior clorhidrato de lactona a partir de ester de *Z*-crotyl glicina es propuesto sobre la base de enfoques teóricos. La condensación entre alcoholes alílicos y ortoésteres cíclicos para dar lactonas con un grupo alilo invertido como sustituyente en ~, se expone mecanicísticamente. Vinil lactonas pueden convertirse en cicloalquenos vía transposición de Claisen de enol éteres; hemos propuesto el mecanismo.

INTRODUCTION

During master classes of organic chemistry, we noticed that students are confronted with a lack of knowledge with regard to mechanisms. A mechanistic approach about any kind of reaction enhances the capacity of facing new reactions with respect to an understanding of all processes involved in them, and also develops synthetic creativity. As academics we feel concerned with the didactical importance of covering these needs in debutant students in organic synthesis. This, the synthesis of alkenes by Claisen rearrangement of allyl vinyl ethers, part III; mechanistic views; is the eleventh study in the series: "The Organic Chemistry Notebook Series, a Didactical Approach" [1-10].

REACTIONS AND THEIR MECHANISTIC PROPOSALS, DISCUSSION

The variation of the Claisen rearrangement: the ester enolate (known also as the ketene acetal variation) is useful in stereocontrolled synthesis of natural products. Methyl santolinate **25**, an irregular monterpene can be synthesized from propionate ester **23**, which gives mainly the *Z*-ketene acetal **24** and this gives **25**. The reaction is carried on lithium isopropylcyclohexylamide in THF and after on *t*-butyldimethylsilyl chloride [11]. The reaction path is: C.R. (Claisen Rearrangement) at 65^0C followed by hydrolysis and esterification by using diazomethane to give santolinate with high stereoselectivity [11,12]. See Figure 1 for the schematic reaction and its proposed mechanism.

Comments

The propionate ester (**23**) forms a six membered cycle in the chair form with lithium and nitrogen. The nitrogen extracts a proton from the ~ carbon of the ester. The formed carbanion establishes an alkene by dispatching the "*pi*" electrons of the carbonyl over the oxygen atom which after establishes a covalence with Li^+ (or at least neutralizes it ionically). The *tert*-butyldimethylsilyl chloride interchanges its anion (Cl^-) with RO^-. Thus, with this alkoxy protected (**24**), the Claisen rearrangement (C.R.) becomes effective to form the ¥¢-alkene. There follows the separation of the protecting group, the *tert*-butyldimethylsilyl group from the substrate, and generates a hydroxyl group of an acid function. Final methylation converts the hydroxy group into a methoxy by the action due to diazomethane to afford methyl santolinate (**25**).

Another synthetic pathway employing a C.R. uses the *Z*-crotyl glycine ester **26** which is converted in the ¥¢-unsaturated amino acid derivative **27a** which at its turn converts into the lactone chloride **28**. This is a natural product isolated from *Amanita phalloides* (Green Death Cap Toadstool), after hydrolysis of ~- and -amanitin (toxic cyclic peptides) [13,14]. When the transition state is assumed to be a chair-like conformer (**29**), the stereochemical pathway of the rearrangement implies that the intermediate ketene acetal presents mostly the stereochemistry *E* (**26'**) instead of the *Z*-configuration [13,15]. This is the general case for esters of acids with a heterosubstituent on the ~-carbon like ~-amino and ~-hydroxy acids [15,16]. See Figure 2 for the reaction scheme and Figure 3 for the corresponding mechanistic proposal.

Comments

The ester **26** is submitted to the alkali action of $LiN(iso\text{-}pr)_2$ to afford the anion N^-. A charge transfer occurs from nitrogen to oxygen. Every negative charge is neutralized at any moment by Li^+. In this condition, the interaction of the lithiated substrate and another equivalent of $LiN(iso\text{-}pr)_2$ takes place under the form of the six membered cycle in the chair form conformed by the adduct of **26**-Li + $LiN(iso\text{-}pr)_2$. The nitrogen of $LiN(iso\text{-}pr)_2$ takes a hydrogen from the substrate currently under the form of a chair six membered cycle, generating thus a carbanion in the substrate. The tetravalent nitrogen positively charged [$LiN^+H(iso\text{-}pr)_2$] recovers neutrality and its tri-valence by excision of its covalence to Li. The Li cation thus formed makes ionic pair with the negative charge now situated on the oxygen of carbonyl after charge transfer from the carbanion; a new carbon-carbon double bond has formed. Lithium stabilizer is replaced by silicon of trimethylsilyl chloride through a nucleophilic attack of the enol oxygen of substrate to silicon of TMS chloride to expel Cl^-. The same happens to the other Li^+O^- couple in the substrate. This substrate with two protected enol groups (**26'**) suffers the Claisen rearrangement to afford the ¥¢-alkene. Acid hydrolysis withdraws the protecting group trimethylsilyl at the carbonyl adjacent position. The second protecting group ($OSiMe_3$) is withdrawn by methanolysis after protonation. Follows a deprotonation of the methoxy group and protonation of the nitrogen. This protic catalysis promotes the elimination of the methyl of the methoxy group and formation of a carbonyl group. The carbocation Me^+ establishes a bond with the anion $^-OSiMe_3$ to give $MeOSiMe_3$, we´ve reached the intermediate **27a** (Fig. 3).

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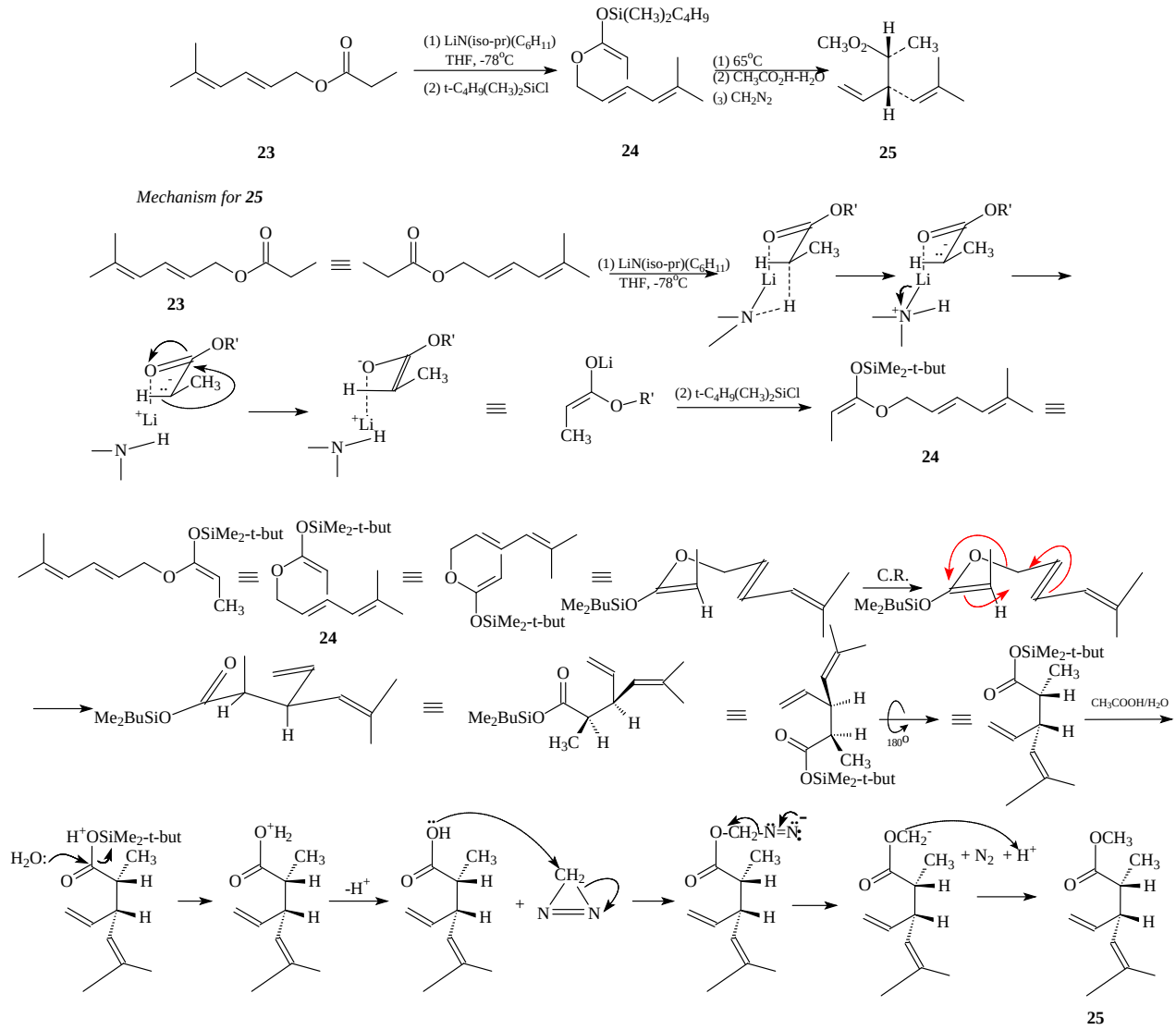

Figure 1. *Claisen rearrangement; synthesis of methyl santolinate (**25**) from propionate ester (**23**); reviewed by W. Carruthers [11]. Mechanistic views by the authors*

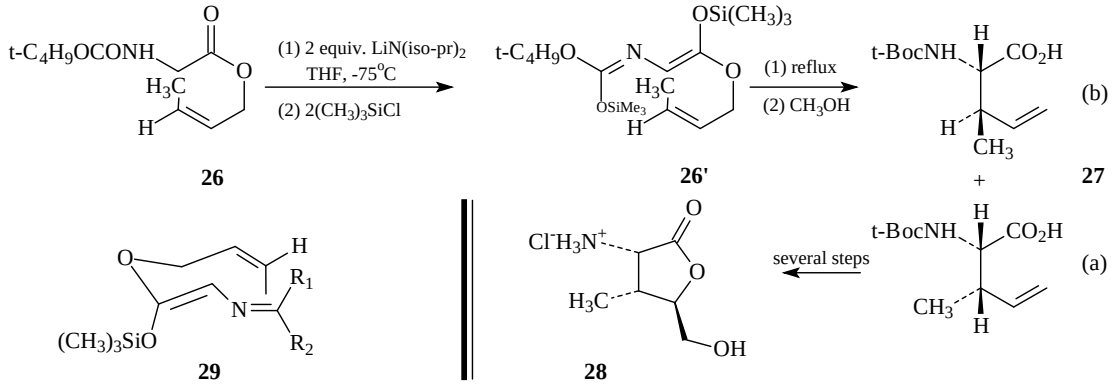

Figure 2. *Claisen rearrangement; synthesis of lactone hydrochloride (**28**) from Z-crotyl glycine ester (**26**); reaction passes by ketene acetal intermediate with the E-configuration (**26'**); reviewed by W. Carruthers [13].*

*Mechanism for **27a***

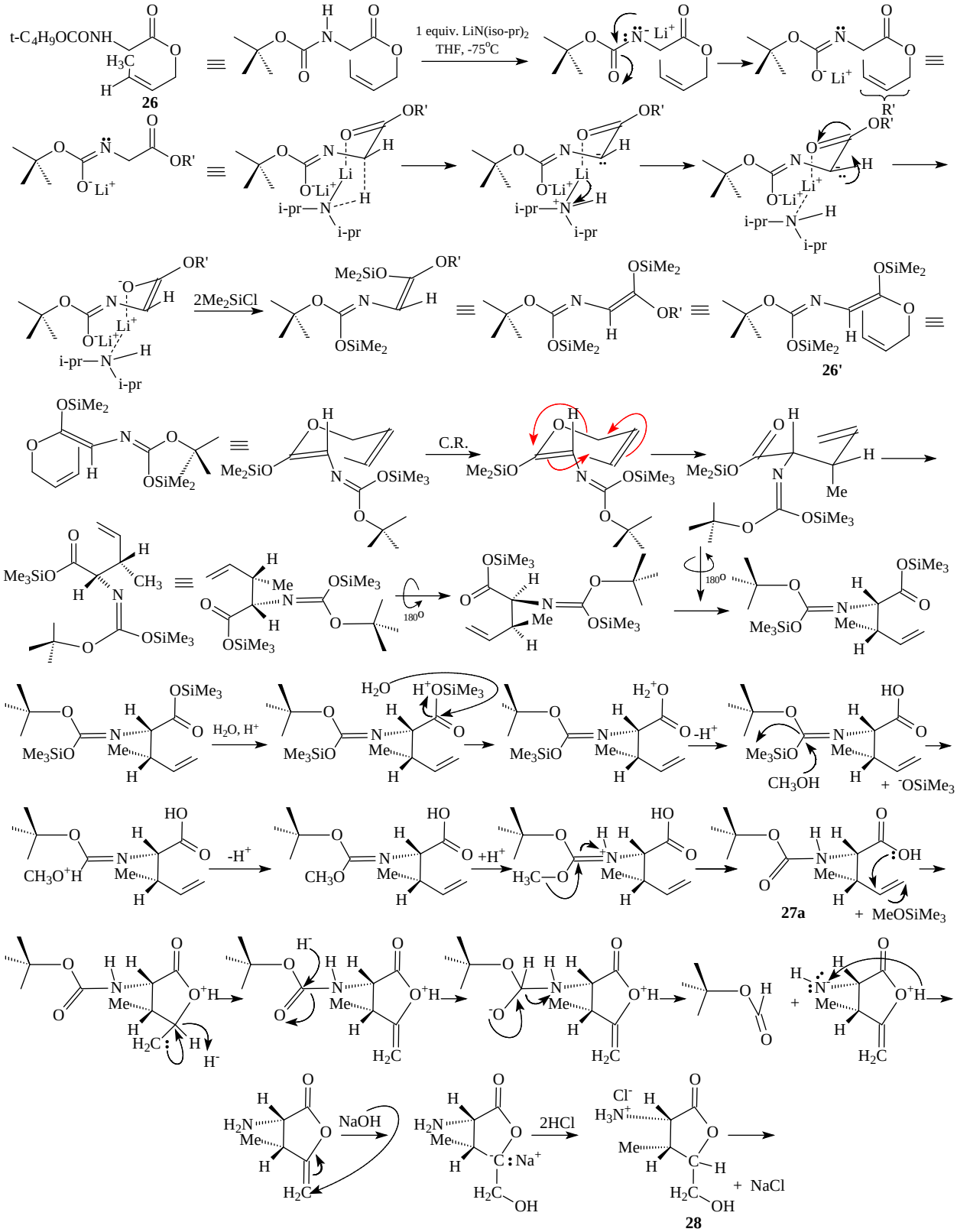

Figure 3. *Claisen rearrangement; synthesis of lactone hydrochloride (**28**) from Z-crotyl glycine ester (**26**); reaction passes by ketene acetal intermediate with the E-configuration (**26'**); reviewed by W. Carruthers [13]. Mechanistic views by the authors*

The ¥¢-unsaturated carboxylic acid **27a** suffers lactonization by means of an intracyclic nucleophilic attack over the alkenic double bond. The γ-lactone formed incorporates a terminal vinyl group by means of elimination of hydride which attacks the carbonyl group becoming thus a temporary alkoxy group. The alkoxy group regenerates the carbonyl and provokes the excision of the molecule by means of breaking the bond C-N. The γ-vinyllactone is now protonated. A proton transfer betweenthe positively charged oxygen and the anionic nitrogen gives the substrate electronic stability again. The hydroxyl addition over the vinyl terminal methylene occurs to afford a terminal primary alcohol. The lactone cycle resists against ring rupture and the electronic excess settles now over the quaternary carbon of the terminal vinyl group. This anion forms ionic pair with cation sodium. One of two equivalents of HCl serves to withdraw cationic sodium which makes couples with one Cl^- and installs a proton over the carbanion . The other HCl equivalent protonates the nitrogen which makes ionic pair with Cl^-. We´ve reached the product **28** (Fig. 3).

It's been established that the C.R. of vinyl ethers of acyclic allylic alcohols happens through T.S. of the chair type [15]. There are other examples where the substrates own a double bond of vinyl ether or of allylic alcohol as part of a cycle [15]. In such case, the T.S. is a well-defined boat conformer [15]. The T.S. in the chair form in these cases implies much strain [15]. For example, let's see the reaction between allylic alcohols and cyclic orthoesters that through Claisen rearrangement give lactones with the allyl group inverted as an ~-substituent [15]. The cyclic orthoester **29** reacts with the cyclic allyl alcohol **30**; the product is lactone **31**. The yield was 80 % and the stereoselectivity complete. The configuration of the chiral center at the cyclohexene is controlled by the configuration in the allylic hydroxyl group which is a leaving group. Regarding the configuration of the chiral center in the lactone, this is determined by the conformation of the chair type or the boat type of the transition state. Thus, the stereochemistry of **31** indicates that the reaction was carried on through a transition state of the boat type [15,16]. See Figure 4.

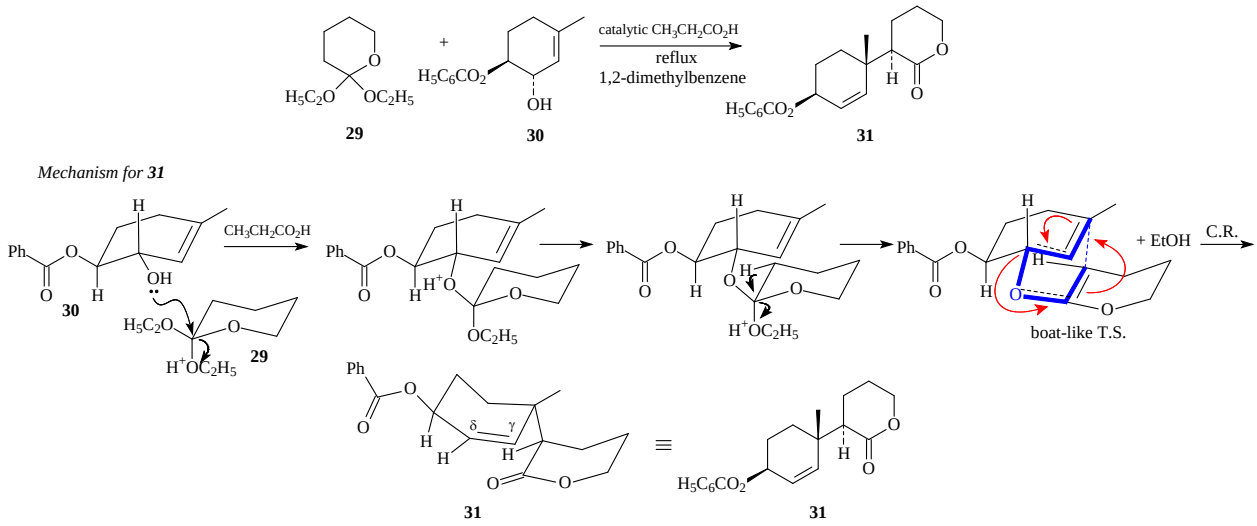

Figure 4. *Claisen rearrangement; reaction of cyclic orthoester **29** with allylic alcohol **30** to form lactone **31** (¥¢-unsaturated lactone); reviewed by W. Carruthers [15]. Mechanistic views by the authors*

Comments

Although the orthoester tri-oxygenated carbon (**29**) manifests a lower electrophilicity than the carbonyl carbon of the benzoyl substituent in **30**, proved by the fact of the lower chemical shift value of the $O_3\underline{C}$ from orthoester with respect of carbonyl carbon ($\delta o_3\underline{c}$ 114.2 *vs.* $\delta\underline{c}$=o 166.8 of methyl benzoate [17,18 respectively]), the nucleophilic attack occurs over the $H^+O_3\underline{C}$ from orthoester instead of the benzoyl carbonyl. The reason is attributable to the protic catalysis from propionic acid, experimented firstly by one of the oxygen atoms of the $O_3\underline{C}$ from orthoester instead of the carbonyl oxygen. By statistic reasons the catalyst interacts firstly with one of the oxygen atoms of the $O_3\underline{C}$ instead of the carbonyl's oxygen. In this three-oxygen group, the oxygen atoms are closer each other. In contrast, the benzoate presents only two oxygen atoms. This fact makes of this carbon ($H^+O_3\underline{C}$) a preferred nucleophile attack site in the mixture instead of the carbonyl of benzoate (O=$\underline{C}$-O with no H^+ catalyst, **30**). We mean by this that the

electrophile is the H^+O_3C of the orthoester (**29**) and the nucleophile, the hydroxyl oxygen of the allylic alcohol (**30**). On the contrary, due to the protic catalysis, a nucleophilic attack of the nucleophile oxygen from any of the ethoxy protonated groups of the orthoester (**29**) over the electrophile carbonyl carbon of the unprotonated benzoate of the allylic alcohol, is not feasible. The nucleophilic attack over carbonyl or H^+O_3C from ester depends on polar and steric factors. In spite of the fact that H^+O_3C from ester is tetrahedral and the carbonyl carbon is planar (steric factor), the polar factor (generated by the H^+ catalyst) drives the nucleophile (ROH) towards the H^+O_3C from ester. The benzoate-orthoester adduct transfers the catalyst from the recently formed (so far protonated) ether bridge to one of the ethoxy groups of the ester moiety of the adduct. This good leaving group leaves the adduct forming a carbocation (not graphically described in Fig. 4). The presence of the carbocation charge promotes a proton elimination from the vicinal CH_2 group to form an alkene. Both moieties are now situated in a transition state in the boat form. This mutual position makes the Claisen rearrangement possible to afford the final product **31**.

In a series of reactions related to those exposed above, vinyl lactones **32** are converted into cycloalkenes through Claisen rearrangements using cyclic enol ethers **33**. Un such reactions, the stereochemistry of the products implies a transition state employing a boat conformation [15,19]. See Figure 5.

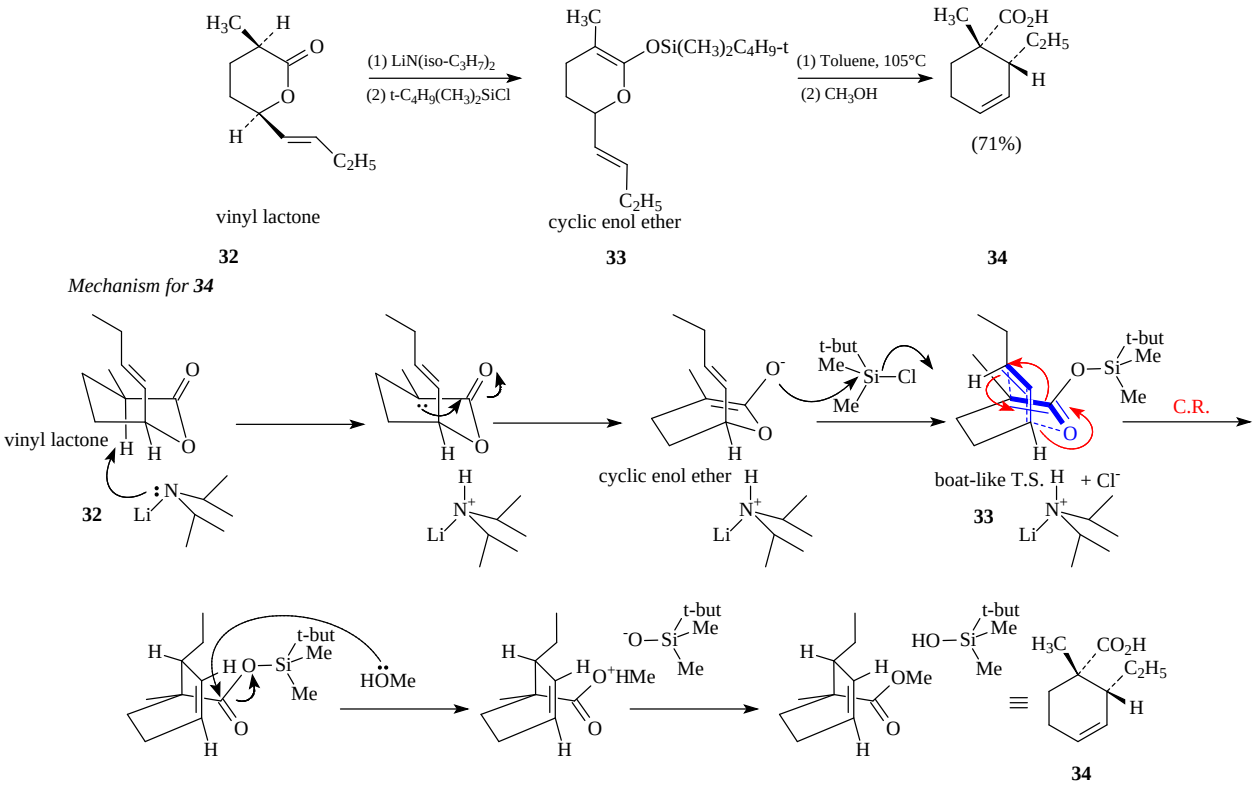

Figure 5. *Claisen rearrangement; transformation of vinyl lactone **32** via cyclic enol ether **33** to afford **34** (¥¢-unsaturated carboxylic acid); reviewed by W. Carruthers [15]. Mechanistic views by the authors*

Comments

In step one of the mechanism for **34**, the strong base $NLi(i\text{-}pr)_2$ extracts the acidic hydrogen in ~ of carbonyl of the substrate **32**. Thus, the just formed carbanion derives into a C-C double bond by *p*-orbital overlapping, sending thus the "pi" bond of carbonyl over the carbonyl oxygen. The oxygen atom (nucleophile) attacks silicon (electrophile) and expels chloride (leaving group) which makes ionic pair with the quaternary ammonium: $N^+LiH(i\text{-}pr)_2$. The oxydimethylterbutyl cyclic enol ether suffers the Claisen rearrangement employing a transition state in the boat type. This operation affords the ¥¢-unsaturated carboxylic acid silylated. Methanolysis gives rise to final product **34**.

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