

# MECHANISTIC VIEWS OF INTRAMOLECULAR HYDROXYCYCLOPROPANATION OF $\omega$ -VINYL CARBOXYLIC ESTERS

José A. Bravo,\* Patricia Mollinedo, J. Mauricio Peñarrieta, José L. Vila

Department of Chemistry, Universidad Mayor de San Andrés, P.O. Box 303, La Paz, Bolivia

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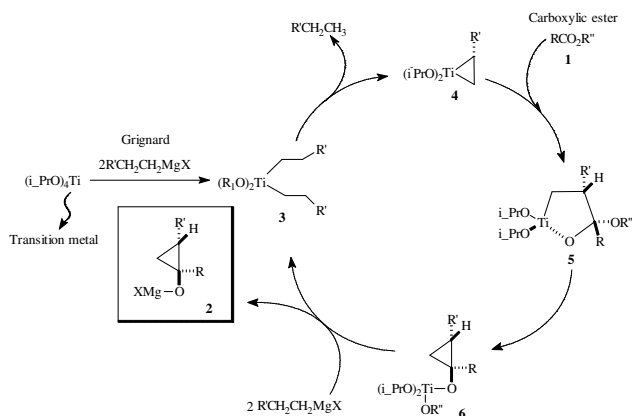
## ABSTRACT

The overwhelming presentation of plenty of synthetic steps in a verbally reduced or succinct form as appearing in any paper is here focused in an extensive and particularly graphical manner; just to extend the screen when the reader is boarding a published series of synthesis. The Intramolecular Hydroxycyclopropanation of  $\omega$ -Vinyl Carboxylic Esters appeared to us to be a fascinating synthesis thematic and served us as an example to propose didactical and mechanistic views.

\*Corresponding author: [jabravo@umsa.bo](mailto:jabravo@umsa.bo)

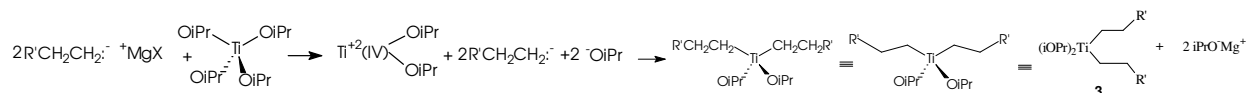
## ANALYSIS AND MECHANISTIC PROPOSALS

As academics we are highly concerned with the didactical importance of covering the needs of debutant students in organic synthesis. This article presents an analytical and didactical approach to synthetic works by Jin Kun Cha and col. by means of reactions' theoretical mechanisms. We are continuing the previously published: "A Theoretical Mechanistic Approach to Diastereoselective Synthesis of *cis*-1,2-dialkenylcyclopropanols and Subsequent Oxy-Cope Rearrangement" (1) presenting now another synthesis by Cha and coworkers concerning Grignard reagents in the presence of transition metals (2). Cha worked with organotitanium compounds to effect cyclopropane-mediated natural product synthesis. Prof. Cha group became interested in the Kulinkovich hydroxycyclopropanation (3). They published first the treatment of a carboxylic ester with an excess (3 equiv) of Grignard reagent in the presence of  $\text{Ti}(\text{O}i\text{-Pr})_4$  (1 equiv) affording *cis*-1,2-dialkylcyclopropan-1-ols (4). We already proposed a mechanistic approach (1) about such article. The second related article by Cha and col. (2) reports an intramolecular version of the Kulinkovich hydroxycyclopropanation (4) and imposes the treatment of  $\omega$ -vinyl carboxylates with *n*-BuMgCl in the presence of  $\text{Ti}(\text{O}i\text{-Pr})_4$  or  $\text{ClTi}(\text{O}i\text{-Pr})_3$ . The Kulinkovich hydroxycyclopropanation's scheme 1 (2) is reproduced here in Scheme 1 and it can be depicted through the next mechanistic proposal which has already been graphically and verbally described (1) and it is re-explained here.



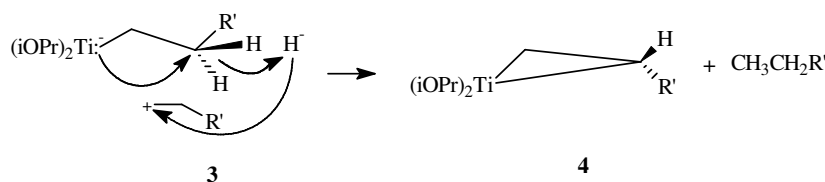
Scheme 1. Kulinkovich's Hydroxycyclopropanation virtual loop (2)

To depict this Kulinkovich hydroxycyclopropanation scheme we start with our 2 equiv of Grignard reagent or 2  $R'CH_2CH_2MgX$  or 2  $R'CH_2CH_2^+MgX$ . A first interaction occurs between Grignard reagent and the titanium tetraisopropoxy derivative. Titanium is linked to the four alkoxy substituents. The reaction provokes the expulsion of two alkoxy residues to leave a  $Ti^{2+(IV)}(OiPr)_2$  species. The metal di-cationic charge is used by two carbanions each from 1 equiv of the Grignard reagent, to obtain a dialkoxy-dialkyl titanium derivative **3**. (Figure 1).



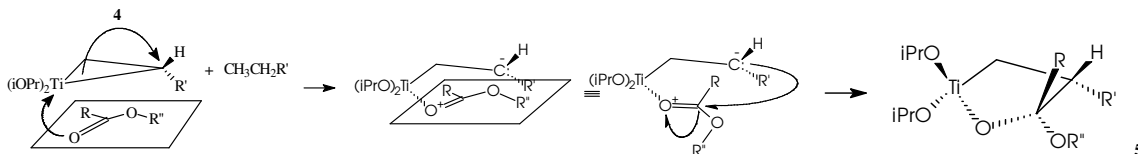
**Figure 1.** Obtaining of dialkoxy-dialkyl titanium derivative **3**

Titanium receives temporarily an extra electron from an alkyl methylene to afford the  $Ti^{-1(IV)}(iPrO)_2(CH_2CH_2R')$  species and the carbonium ion  $R'CH_2CH_2^+$ . A reductive nucleophilic attack by the anionic titanium leads to the apparition of the Ti 3-membered ring intermediate **4** (or a titanacyclopropanoid or titanacyclopropane (**2**)). (Figure 2).



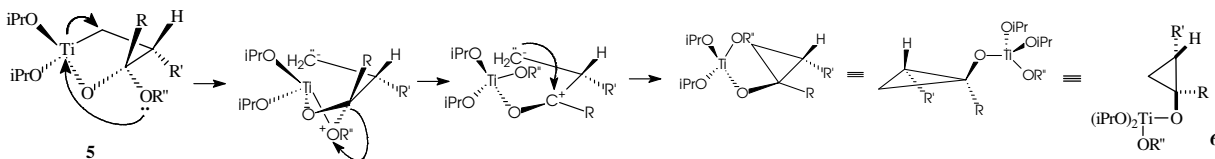
**Figure 2.** Formation of Titanacyclopropane, **4**

The next step in this pathway consists of the condensation of intermediate **4** with a carboxylic ester  $RCO_2R''$ . The carbonyl group of this ester drives the reaction by interacting with the Titanacyclopropane in a transition state that implies a co-planarity of both species. A nucleophilic attack by the nucleophile carbonyl oxygen over titanium dispatches the two electrons of the bond  $Ti-CH(R')(CH_2)$  over that carbon. Hence the Titanacyclopropane splits to afford a carbanion and a cationic oxygen over the same molecule. A nucleophilic attack over the carbonyl carbon (with an exacerbated electrophilic character) leads to the formation of a titanium furanoid ring (Figure 3)



**Figure 3.** Formation of a titanium furanoid ring, **5**

An intramolecular nucleophilic attack by the ethereal oxygen of the “ $\alpha$ -O-R” substituent group over the electrophilic titanium dispatches the two electrons of the  $Ti-CH_2-$  bond on intermediate **5** to afford the corresponding splat species bearing a carbanion and a cationic oxygen, which in turn recovers neutrality by splitting the four-membered, di-oxygenated (oxirane-type) ring. The result is the dipolar (a carbanion and carbonium ion) species that neutralizes the charged extremes into a substituted cyclopropane or intermediate **6** (Figure 4).



**Figure 4.** Formation of a substituted cyclopropane **6** from a titanium furanoid ring, **5**

It is now time for two more equiv of Grignard reagent and for intermediate **6** to interact to afford species **2**, closing thus our looping cycle. This meeting takes place by means of cationic interchange, or the cationic moiety of Grignard  $\text{MgX}^+$  that replaces cationic  $\text{Ti}^+(\text{OiPr})_2(\text{OR}')$  through the temporary apparition of an anionic oxygen. The remaining  $\text{Ti}^{2+}(\text{OiPr})_2$  species neutralizes the two anionic moieties liberated by the 2 equiv of Grignard reagent to form two new equiv of the species **3** to continue the cycle (Figure 5).

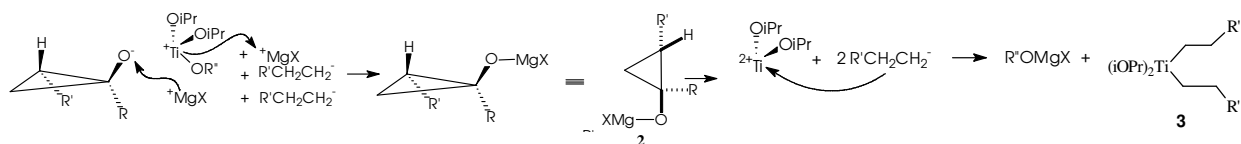
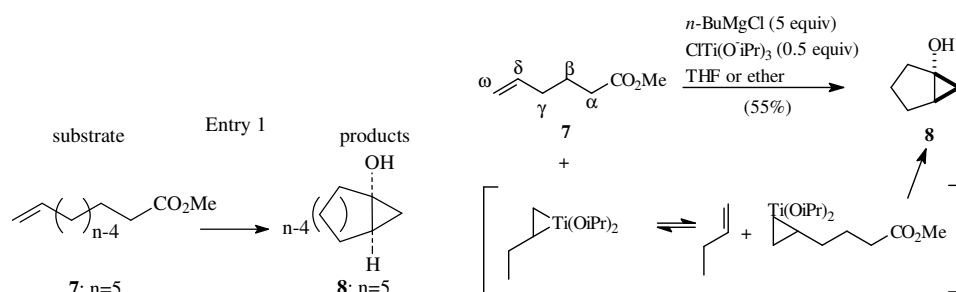


Figure 5. Generation of  $\text{Ti}^{(\text{IV})}(\text{iPrO})_2(\text{CH}_2\text{CH}_2\text{R}')$  **3**, in the virtual cycle

This synthetic pathway (Scheme 1) was largely applied by Cha and coworkers to produce a number of azulene sesquiterpene derivatives as published by these authors. Cyclisation (Scheme 1) goes on under stoichiometric or catalytic conditions involving the double alkylation of the titanacyclopropane intermediate **4**, itself formed by the reaction of  $\text{Ti}(\text{Oi-Pr})_4$  or  $\text{ClTi}(\text{Oi-Pr})_3$  and a Grignard reagent followed by elimination of the corresponding alkane ( $\text{R}'\text{CH}_2\text{CH}_3$ ). The thesis that the putative intermediate **4** or the Titanacyclopropane intermediate could undergo a reversible exchange with an alkene has been thought. If a carboxylic ester is chained to the alkene moiety, then an intramolecular hydroxycyclopropanation is feasible. And this is the method currently under discussion. The numerous results afforded by Cha and coworkers include, structurally, two-fused cycles compounds all of them showing the cyclopropane feature, characteristic of the Kulinkovich synthesis. The second fused cycle comprises many models depending on the alkene used to be condensed to the Kulinkovich's intermediate substrate. The following mechanisms correspond to entries 1 to 15 in table 1, page 292, (2).

#### Entry 1.

It regards the first intramolecular hydroxycyclopropanation achieved by the original paper authors. Methyl 5-hexenoate with 3 or 5 equiv of Grignard's  $n\text{-BuMgCl}$  in the presence of 0.5 equiv of  $\text{ClTi}(\text{OiPr})_3$  afforded the first intramolecular hydroxycyclopropanation product or cyclopropanol **8** (Scheme 2).



Scheme 2. Intramolecular hydroxycyclopropanation: cyclopropanol **8** (2)

To explicitly understand this reaction we must follow the mechanism exposed above as a model; however some different explanations must be given in order to achieve the reported results (4). This implies a modification of the section comporting the intermolecular interaction between the Titanacyclopropane derivative **4** and the carboxylic ester for now we must explain the apparition of the intramolecular process product. Thus, once generated intermediate **4** as shown mechanistically above what is provoked now contrasting with the intermolecular version is that before proceeding to a coplanar interaction between the Titanacyclopropane and the carboxylic ester, a splitting of **4** happens in order to generate the 1-butene residue (Figure 6).

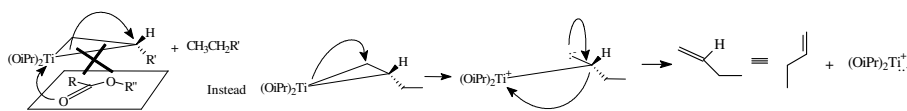


Figure 6. Splitting of **4** (Titanacyclopropane) into the 1-butene residue

Titanium liberates one electron splitting so the bonding with its neighboring methylene which in turn receives the two bonding electrons acquiring an anionic character. Indeed, titanium becomes a cationic nucleus. Neutrality returns to the Ti nucleus by means of receiving an electron coming from the splitting of its bonding to the protoalkene. The alkene appears due to the driving force derived from the re-accommodation of the electronic excess over the carbanion into a  $\pi$  bond. Titanium is now a neutralized nucleus; however there should be an electronic re-accommodation in different atomic orbitals generating so a dipolar situation giving titanium a nucleophilic character. This nucleophile will attack the terminal alkene of the  $\omega$ -vinyl carboxylic ester. This fact collapses finally in the tricycle titanium derivative, some kind of eptitanium (like epoxy) or a Titanacyclopropane appearing after addition over the double bond of the  $\omega$ -vinyl ester (Figure 7).

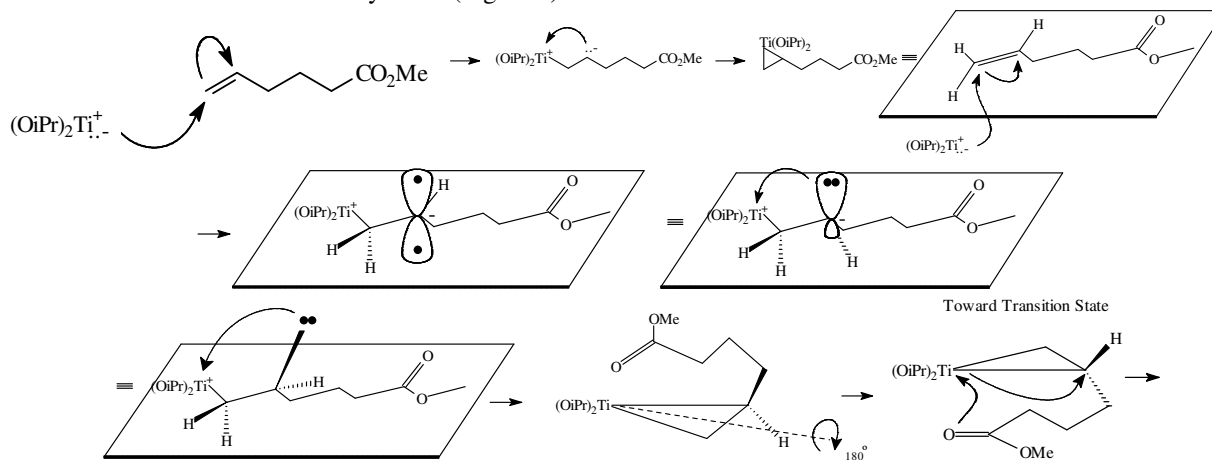


Figure 7. Apparition of eptitanium after addition of  $(\text{OiPr})_2\text{Ti}^+$  over the double bond of the  $\omega$ -vinyl ester

The intramolecular nucleophilic attack by the carbonyl oxygen in the methyl ester moiety occurs to produce a dipolar transition state. This nucleophilic attack excinds heterolytically the bond  $\text{Ti-C(H)(CH}_2\text{)}[(\text{CH}_2)_3\text{CO}_2\text{Me}]$  and establishes a new link between oxygen and titanium. Stereochemistry in these mechanisms has a speculative character. A supraplanar attack over carbonyl electrophilic center ( $\text{C}^{\delta+}=\text{O}^{\delta-}$ ) itself contained in a parallel plan to that containing the titanium derivative occurs placing the methoxy group upwards, adopting thus an axial position in the fusion bridge of the newest fused cycles compound. An isomerization towards a more comfortable conformer occurs changing all axial into equatorial bonds. The new conformer is particularly benefited by the absence of the previous through-space Van der Waals radii interaction of the axial methoxy and the axial isopropoxy substituents, all according to framework molecular models (Figure 8). All these steps conduct to the formation of the fused rings according to the reported reaction products (2). The polar attraction manifested by oxygen and titanium establishes a bridge for a much tensed four-side cycle including a highly stressing double oxy function. This tension incites the carbanion next to the stressed di-oxy ring to attack establishing a less tensed cycle *a` trois*. This enterprise generates the stable enough 3/5 fused rings compound, which is analog to intermediate 6 in the Scheme 1 of the present paper.

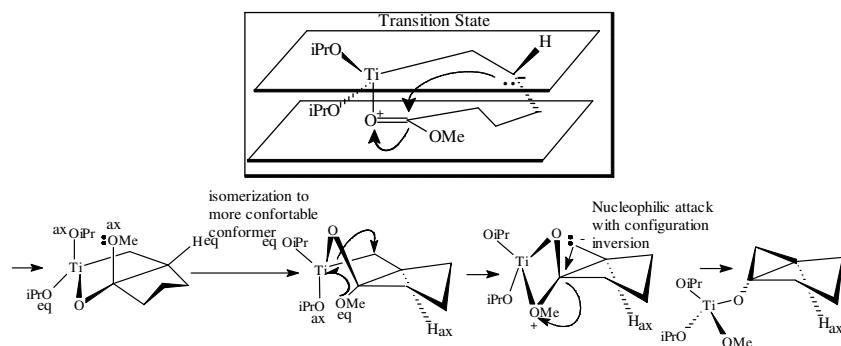


Figure 8. Formation of a 3/5 fused cycles compound

We return now to Scheme 1 to observe that intermediate **6** will interact with the Grignard reagent that for entry 1 corresponds to  $n\text{Bu}^+\text{MgCl}$ . This happens first by means of excising the **Ti-O-Cycles** bond to generate an alcoxy function which in turn is neutralized by the Lewis acid from Grignard r. namely  $^+\text{MgCl}$  giving rise to the intermediate to element **2** in the scheme. This Grignard adduct is finally destroyed in a protic medium to afford alcohol **8** (Figure 9).

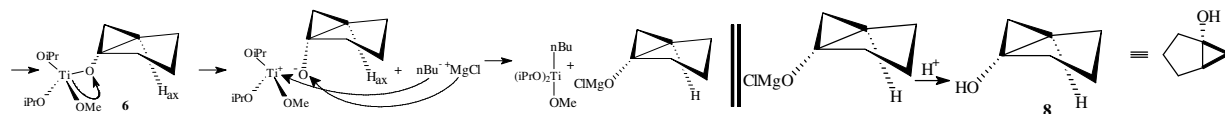


Figure 9. Generation of compound **8** (entry 1, (2))

What follows next is the different interactions for cation  $^+\text{Ti}(\text{OiPr})_2(\text{OMe})$ . This is first neutralized by the basic moiety of the Grignard reagent or the  $n\text{Bu}^-$  carbanion (Figure 9). Next the basic  $^- \text{OMe}$  is separated from titanium due to a better interaction with Lewis acid  $^+\text{MgCl}$  from a second equiv of Grignard r. The just formed Ti cation reacts with the basic moiety left by the second Grignard equiv to generate intermediate **3** (Figure 10) in Scheme 1 thus giving continuity to the virtual reacting loop.

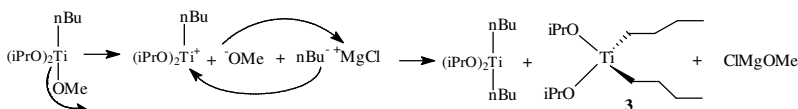


Figure 10. Interactions for cation  $^+\text{Ti}(\text{OiPr})_2(\text{OMe})$ .

### Entry 2.

Under the standard conditions (5 equiv of  $n\text{BuMgCl}$ , 0.5 equiv of  $\text{ClTi}(\text{OiPr})_3$ , ether, room temperature) the authors achieved the synthesis of bicyclic **10** out of the homologue **9**. The mechanism is the same as the previously presented. This demarche is graphically described as follows in Figure 11.

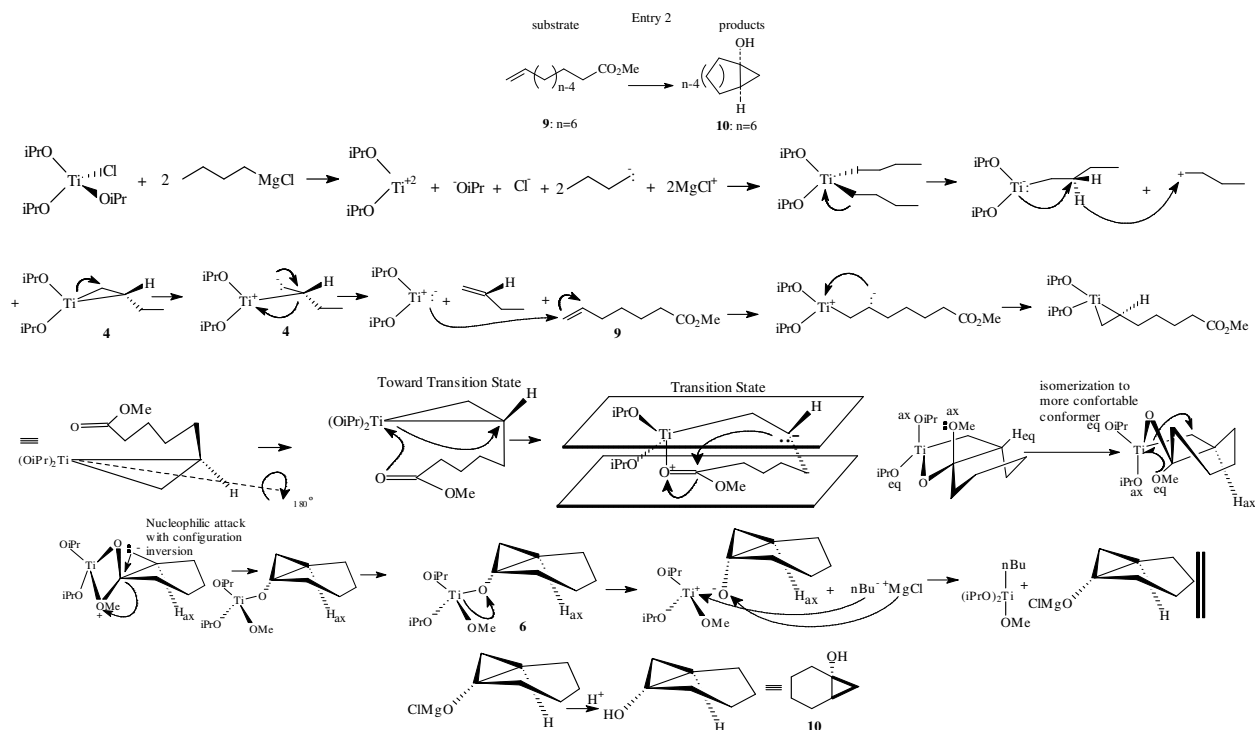


Figure 11. Generation of compound **10** (entry 2, (2))

### Entry 3.

According to Cha and coworkers (2) a precipitous decrease in yield was observed for the intramolecular hydroxycyclopropanation of **11** to afford bicyclo[5.1.0]octan-1-ol **12** in a 11% yield. Now we start our discussion from the apparition of the transition state (Figure 12).

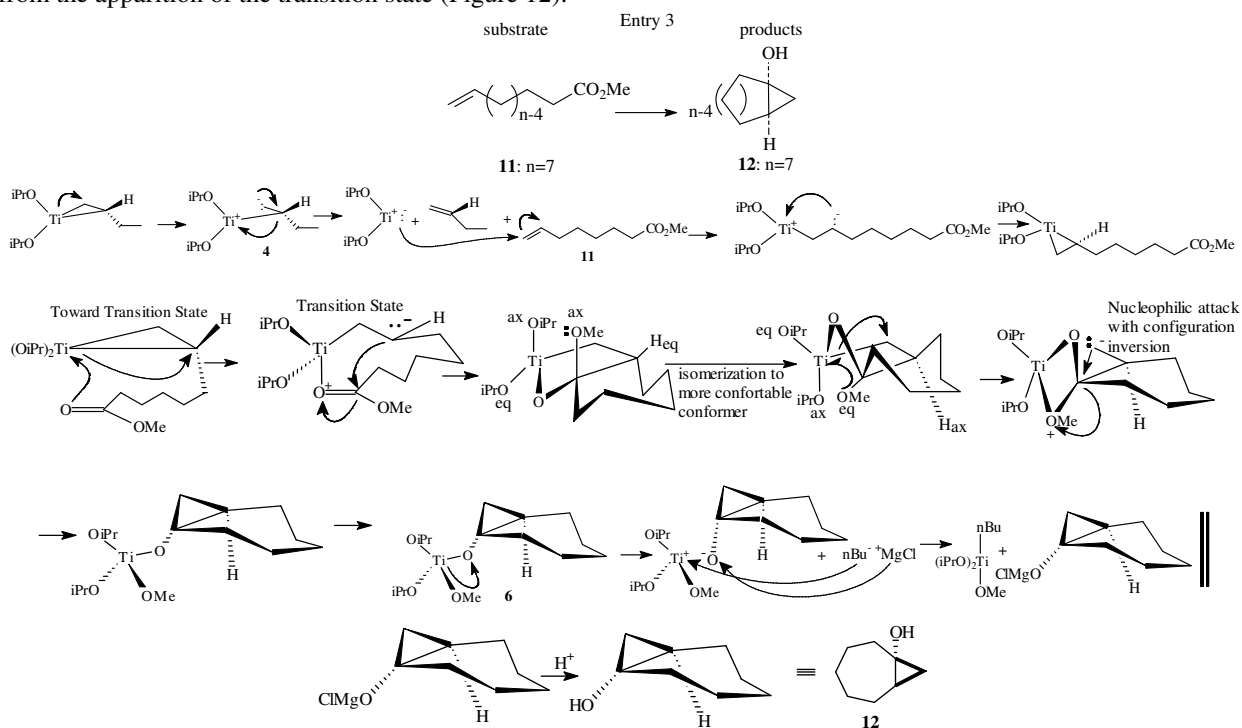


Figure 12. Generation of compound **12** (entry 3, (2))

As observed in the above graphics and after framework molecular models construction, the  $sp^3$  carbons of the fusion bridge become very deformed from the tetrahedral geometry. It means that the instability of compound **12** is increased regarding that of compound **10**. This could be a reason to explain the lower yield for compound **12** with respect to the yield of **10** and **8**.

### Entries 4 and 5

The original paper's authors (2) mentioned that further extension to methyl 8-nonenoate and methyl 4-pentenoate failed to produce the corresponding bicyclic cyclopropanols **14** and **16** (0% yield for both). See Figure 13.

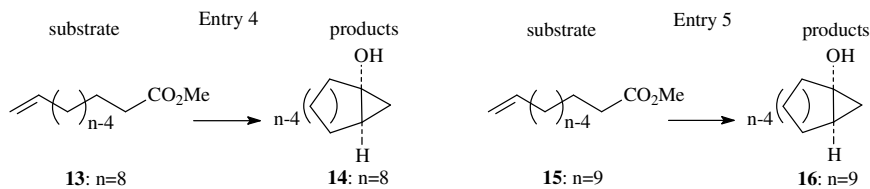


Figure 13. Entries 4 and 5 (2)

### Entries 6 and 7

According to Cha and coworkers, as a rule, the intramolecular hydroxycyclopropanations are not much influenced as a result of the presence of different substituents in the chain (entries 6-13, (2)). We start this reaction graphic description from the nucleophilic attack over the terminal vinyl of the methyl carboxylate **17**. This compound is actually being substituted at positions  $\alpha$  and  $\gamma$  from carbonyl (Figure 14).

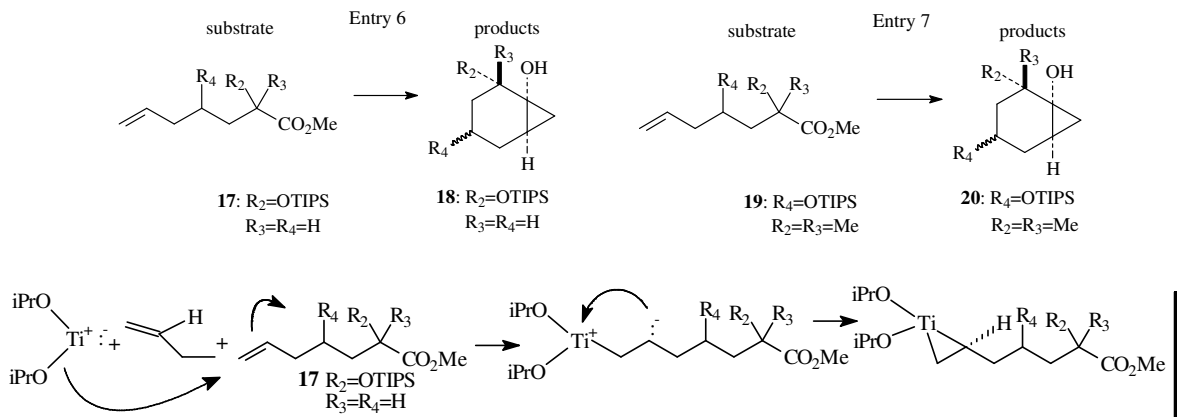


Figure 14. Nucleophilic attack over vinyl 17 toward the formation of 18 (entry 6, (2))

In order to better propose the corresponding theoretical mechanism, we will imagine stereochemistry for the two chiral centers under a speculative scope (Figure 15).

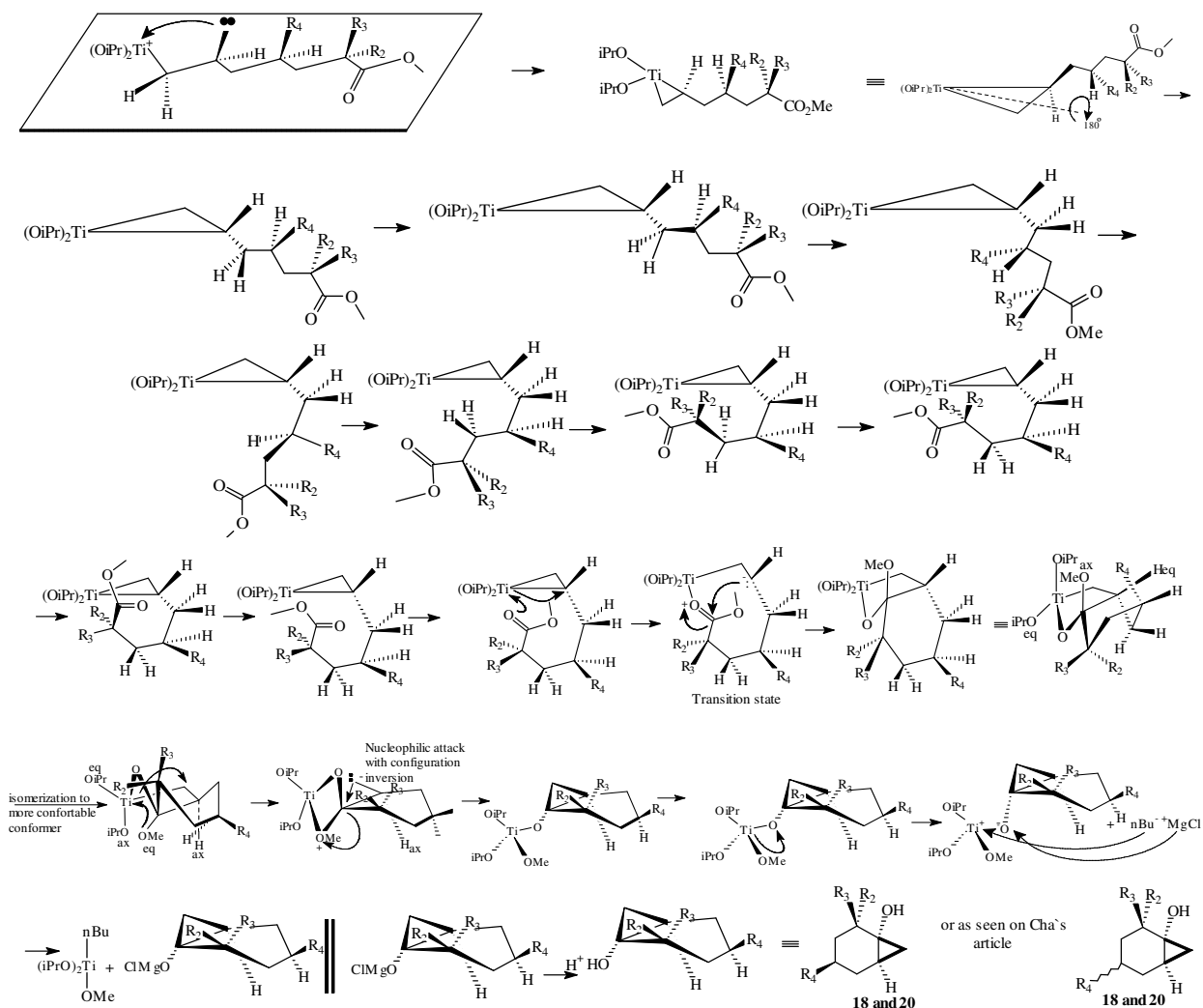
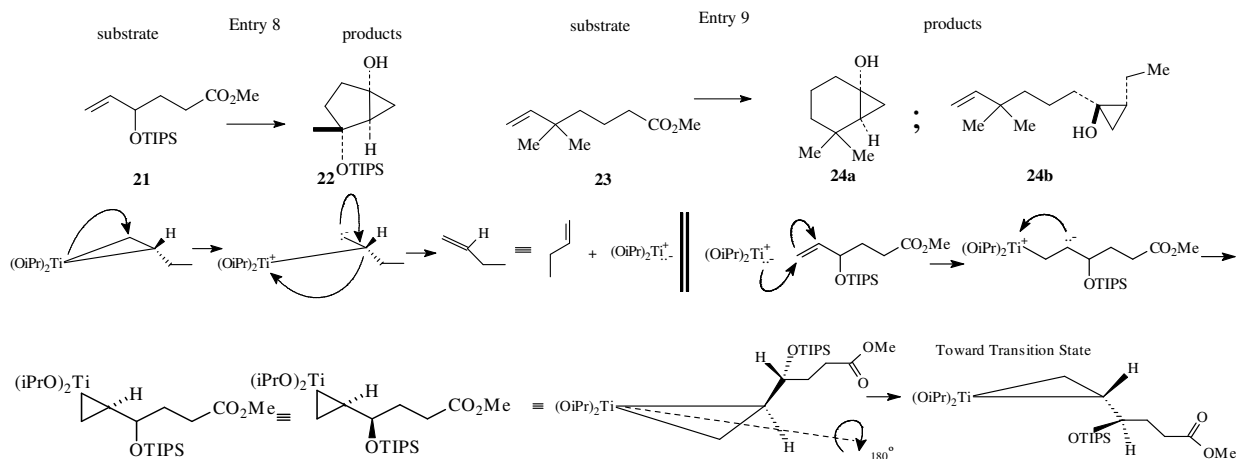


Figure 15. Generation of compounds 18 and 20 (entries 6 and 7, (2))



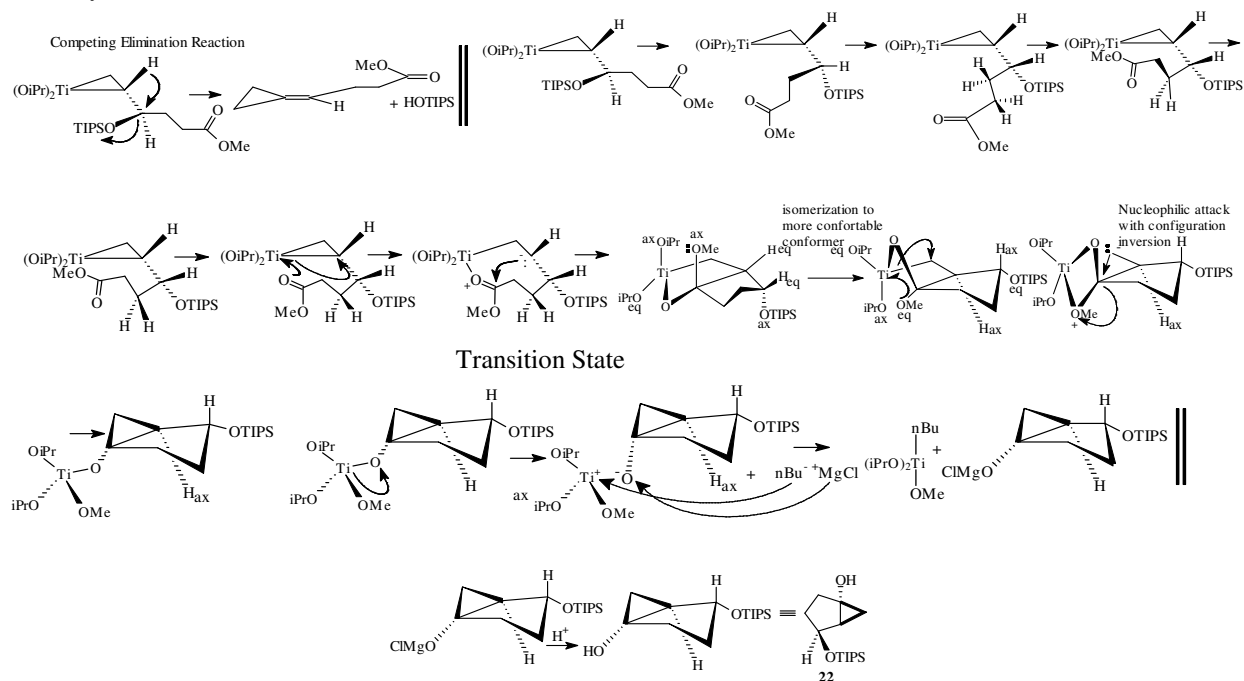
Entry 8 and entry 9

Contrasting to entries six and seven, the intramolecular hydroxycyclopropanation in entries 8 and 9 becomes influenced by the presence of substituents at the allylic position in the side chain. This can be translated as a dramatic diminution in yields (14% for product **22**, entry 8, and 0% for the expected **24a**, entry 9). This entry is graphically described as follow in Figures 16, 17 and 18.



**Figure 16.** Nucleophilic attack over vinyl **21** toward the formation of **22** (entry 8, (2))

At this point a competitive elimination of the HOTIPS group takes place to give the corresponding tricyclic alkene. This fact is responsible for the low yield in the intramolecular product **22** (Figure 17).  
For entry 8:



**Figure 17.** Generation of **22** (entry 8, (2))

For entry 9:

The expected intramolecular product **24a** did not appear giving no yield. Instead product **24b** (Figure 18) appeared as a result of a known intermolecular mechanism, it was yielded in a 61%. This result clearly shows that under the



given conditions, and with respect to eventual substituent groups present at the allyl position of the alkene, both mechanisms, have a competitive character.

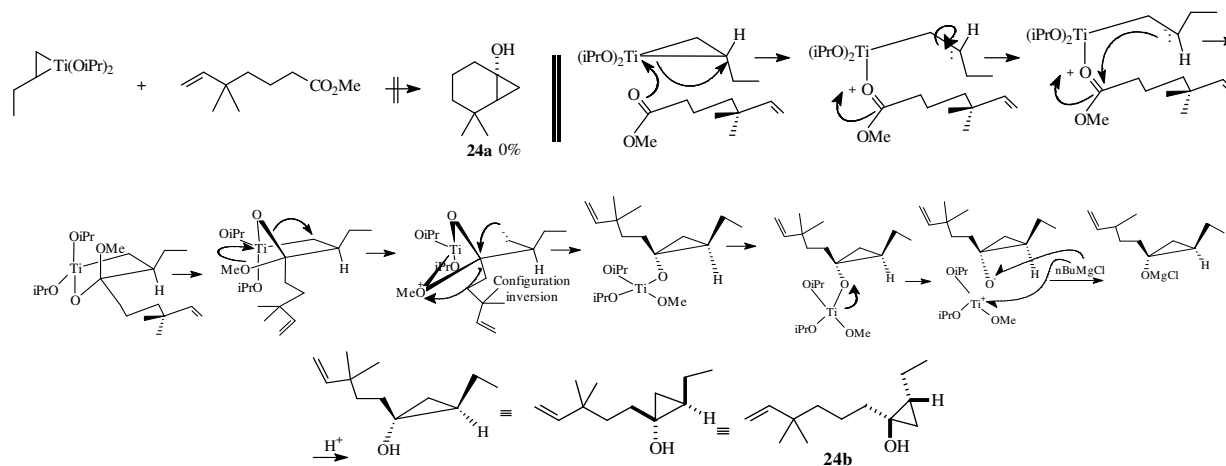


Figure 18. Generation of **24b** (entry 9, (2))

### Entry 10

Mechanism for entry 10 is the same as that proposed for entries 6, 7 and 8. As a practice for the novel, it should be done apart using entry 8 as a guide. However the apparition of a mixture of epimers as resulting products encourages us to develop graphically one of such reactions (Figure 19).

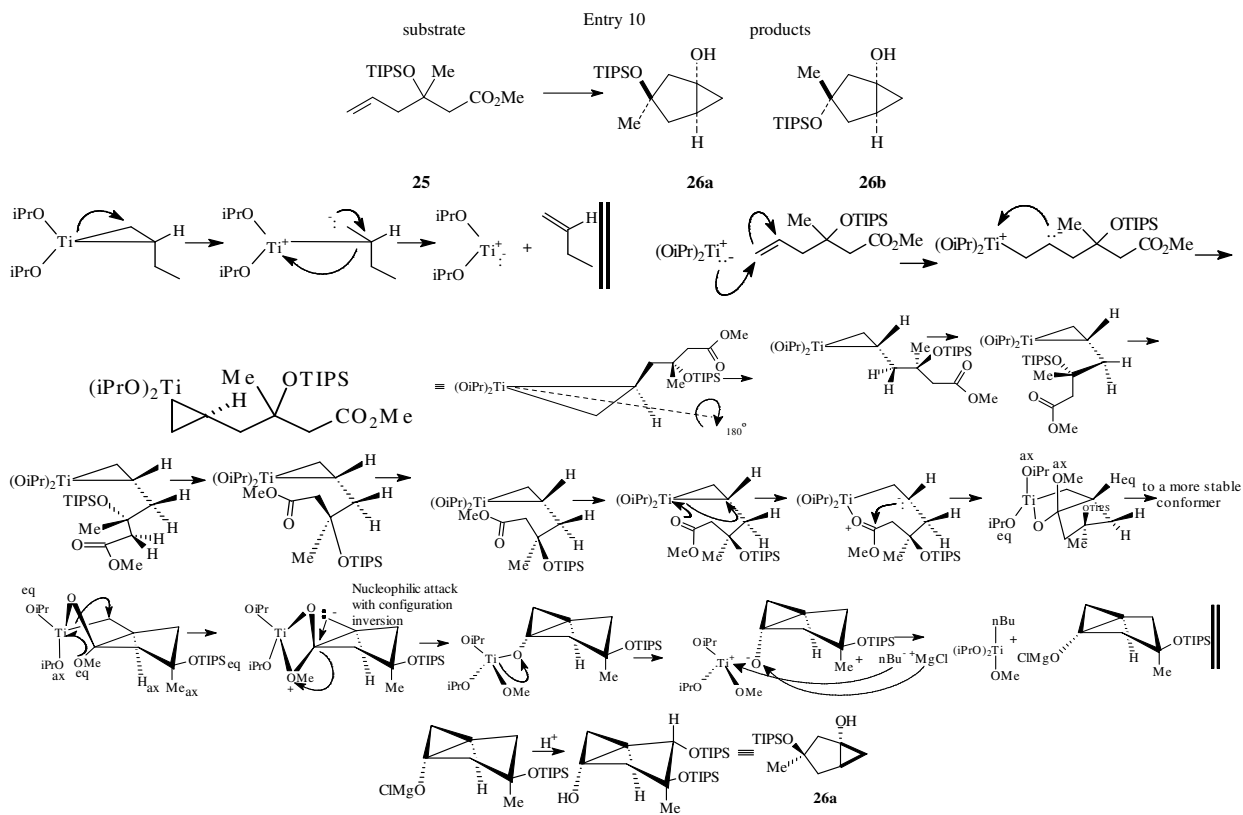


Figure 19. Generation of **26a** (entry 10, (2))

This same mechanistic demarche gives rise to epimer **26b** with the only fact of departing from at the  $\beta$ -of-carbonyl inverted configuration position in the methyl ester compound.

### Entry 11

Entry eleven presents new structural features and consequently new challenges in proposing a theoretical reaction mechanism. Now the side chain includes a substituted cyclohexane (Figure 20).

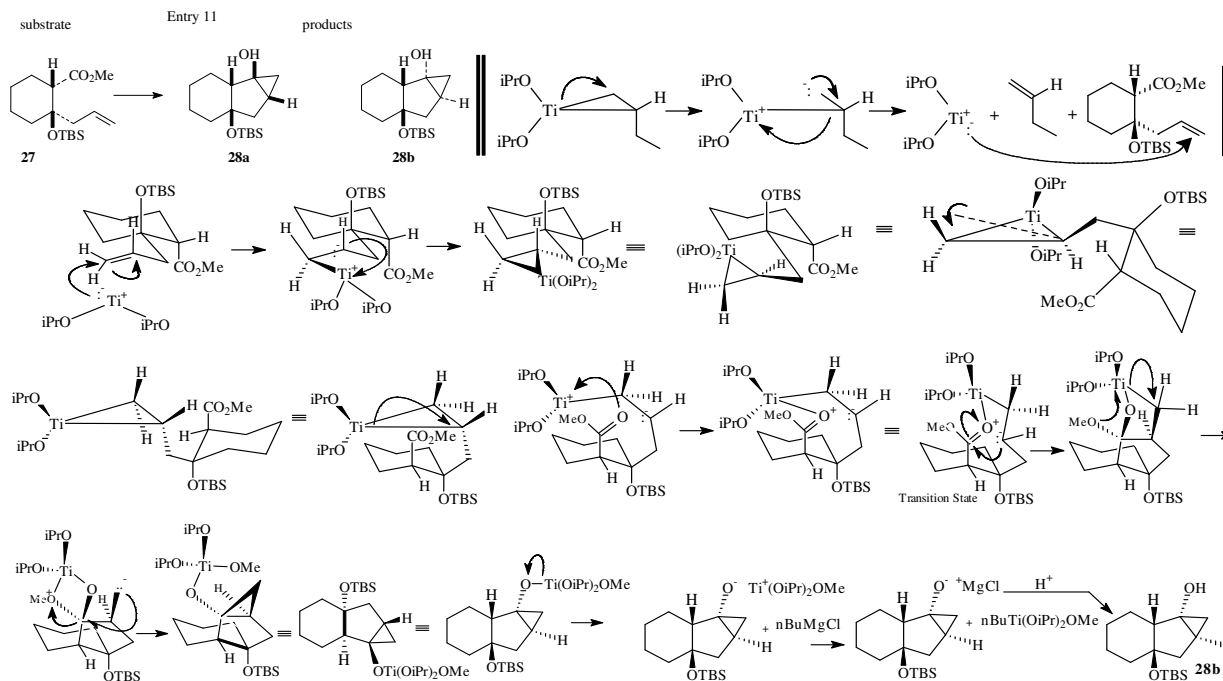


Figure 20. Obtention of **28b** (entry 11, (2))

In order to obtain the isomer **28a** (Figure 21), we must follow the mechanism below. We observe here that the stereochemical definition for one or the other isomer comes out just before establishing one or the other transition state. At that stage the free rotation about the sigma bond of the methyl ester group and the way for it to face the Lewis acid-base interaction between the carbonyl oxygen and the cationic titanium provokes a *beta* or *alpha* orientation for the tricycle. It is obvious that the most favored diastereoisomer in yielding was **28a** due to an easier nucleophilic attack from the carbonyl oxygen to titanium in comparison to **28b** (2:1).

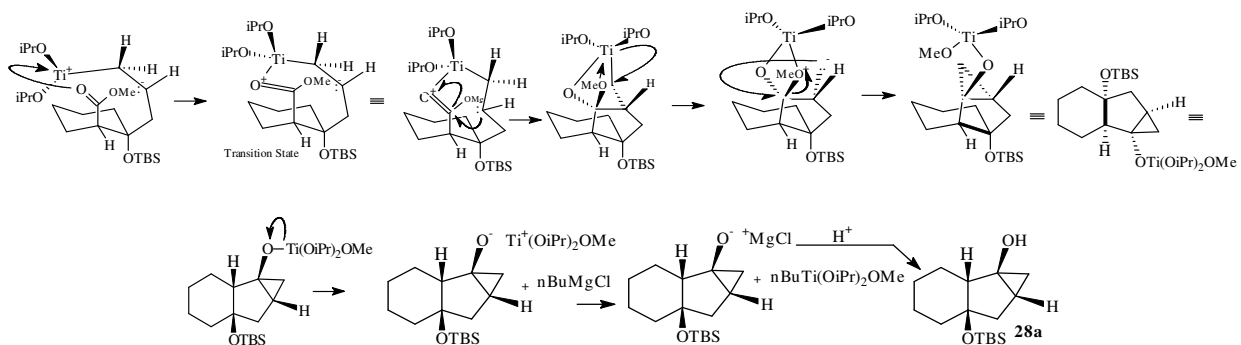


Figure 21. Obtention of **28a** (entry 11, (2))

### Entry 12

The prodigious synthetic work by Cha and coworkers also permitted these authors to afford the *trans*-ring junction diastereoisomers **30a** and **30b** besides the *cis*-ring junction diastereoisomers **28a** and **28b** exposed in entry 11. The *trans* isomers resulted less favored in yielding due to the additional associated strain, all according to the original paper authors (2). No immediate references are given regarding the experimental conditions applicable in order to obtain *cis* or *trans* diastereoisomers. As expected the mechanistic proposal regards a close similarity to the ones expressed in entry 11 (Figure 22).

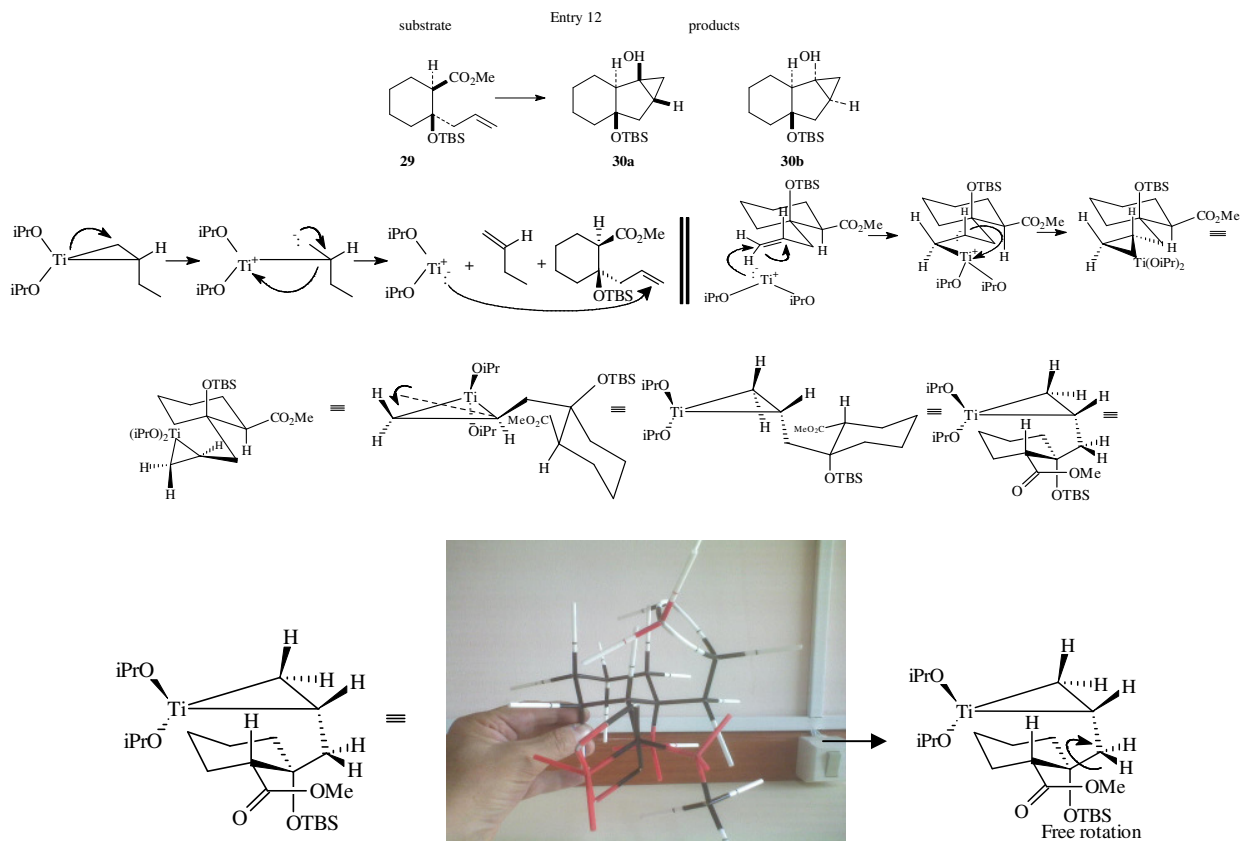


Figure 22. Toward the obtention of the *trans*-ring junction diastereoisomers **30a** and **30b**

At this point, the mechanism goes toward provoking an interaction between the ester moiety and titanium (Figure 23). To achieve such relationship an appropriate approaching of the ester function to titanium is necessary. Thus there must be a sigma bond free rotation of the tripod conformed by the cyclohexane and -OTBS as shown above in Figure 22.

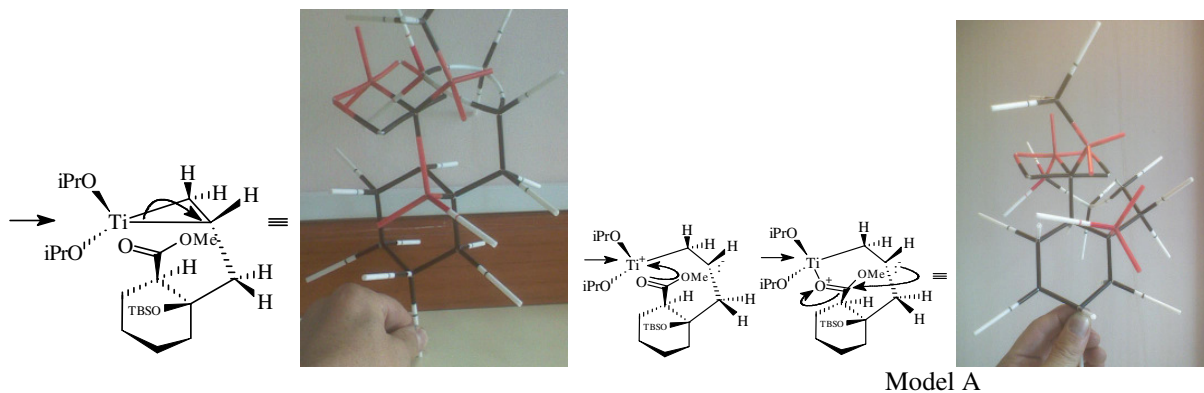


Figure 23. Interaction between the ester moiety and titanium (toward **30a**)

Once established the Ti-O link, the formation of a 5 membered cycle comes out from a nucleophilic attack from the carbanion faced to the carbonyl carbon avoid itself of electronic charge (Figure 22). The result is apparent in the three-fused-cycles non-ionic intermediate in Figure 24. The proximity of an oxygen atom from a methoxy group to the titanium nucleus in such intermediate makes possible the continuation of the reaction by means of a nucleophilic attack over Ti. This splits the furanoid ring to give a highly instable 4-membered dioxy-titanium cycle and a methylene carbanion (Figure 25).

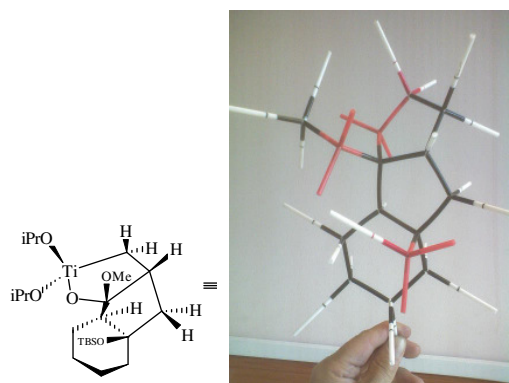


Figure 24. A three-fused-cycles non-ionic Intermediate (toward 30a)

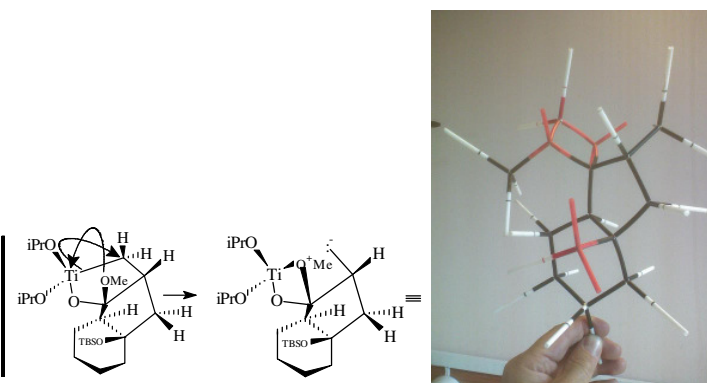


Figure 25. Splitting of the furanoid ring, apparition of the instable 4-membered dioxy-titanium cycle (toward 30a)

Being the 4-membered dioxy-titanium cycle besides an electronic deficient charged species, this reacts by splitting the 4-membered cycle by the attack of the nucleophile basic methylene. An important feature of the electronic movement at this stage of the intramolecular interactions is that the nucleophilic attack taking place between the already mentioned nucleophilic carbanion ( $\text{:CH}_2$ ) and the dioxygenated carbon at the just formed 4-membered dioxytitanio cycle, implies as a result the apparition of the fused tricycle in an  $\alpha$  orientation all through the inversion of the configuration of this chiral carbon  $[(i\text{PrO})_2\text{TiO}(\text{MeO}^+)\underline{\text{C}}]$  (Figure 26). The complementing mechanism to obtain the alcohol derivative form out fro the titanium intermediate is shown in Figure 27.

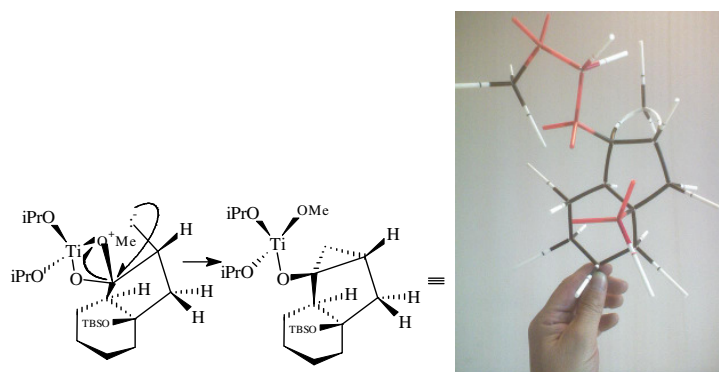


Figure 26. Apparition of the fused tricycle in an  $\alpha$  orientation all through configuration inversion of the chiral carbon  $[(i\text{PrO})_2\text{TiO}(\text{MeO}^+)\underline{\text{C}}]$ , (toward 30a)

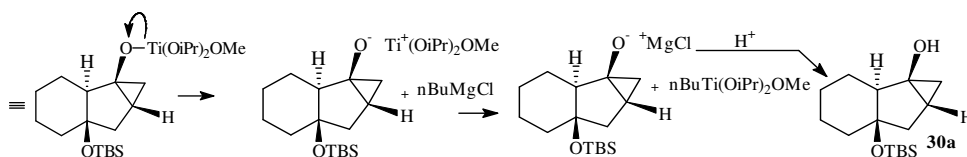


Figure 27. Obtaining of alcohol form derivative out from the titanium intermediate, or final product 30 a

In order to propose a mechanistic explanation for product **30b** we must observe at model A (Figures 23 and 28) that the two electrons are in the inner position, ready for a nucleophilic attack over the electrophilic carbon of carbonyl in the ester moiety actually linked to titanium through the carbonyl oxygen. To achieve the attended inverted (relative to the  $\alpha$  position of the tricycle in **30a**) stereochemistry for the 3-membered cycle as shown in **30b** (2), we locate temporarily the two electrons in the outer position just as shown in Model B (Figure 28). Afterwards there must be an accommodation of the two electrons on that carbanion, currently at a  $sp^2$  hybrid state, in order to be located (the  $2e^-$ ) again in the inner position. So, model B must be turned for the  $2e^-$  to regain the inner position being thus ready again for the nucleophilic attack over the carbonyl carbon. The result of turning atoms through bonds is shown below on model C (Figure 28).

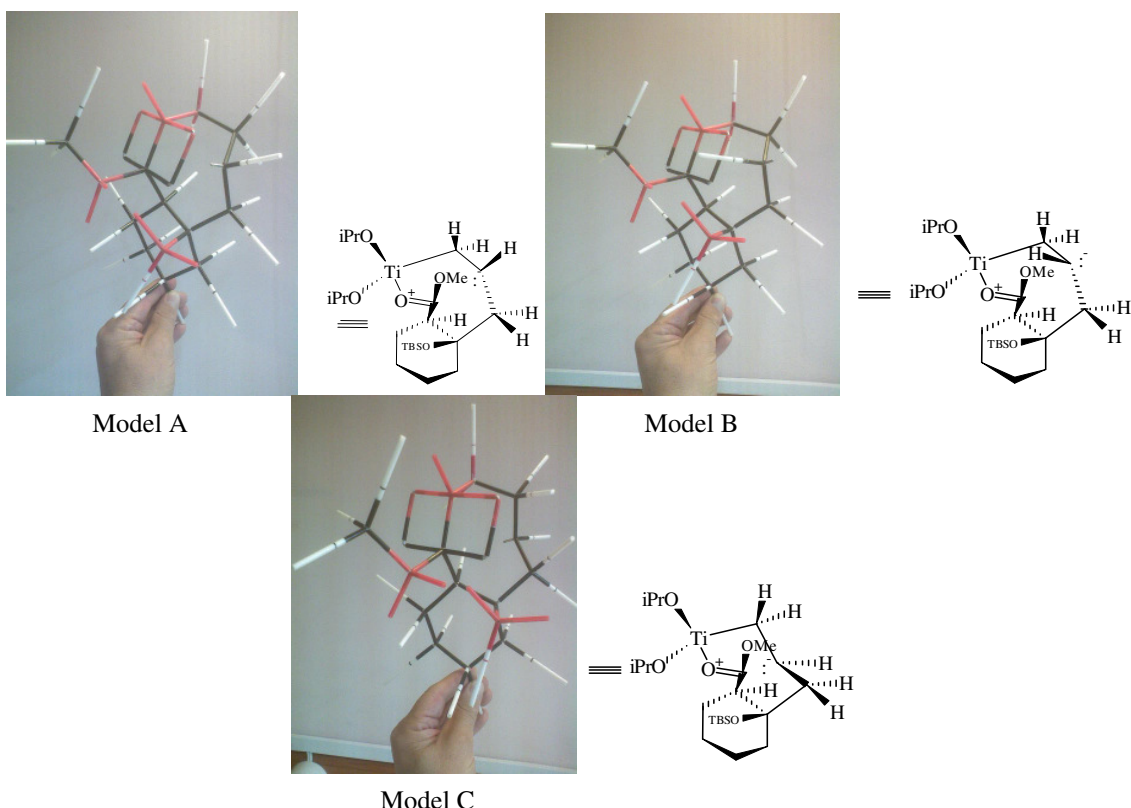


Figure 28. Positioning demarche of 2 electrons of one cyclic carbanion methyne to obtain product **30b**

This conformer (Model C, Figure 28) presents already the hydrogen of this carbanion ( $sp^2$ ) in an *alpha* position differing from the same cycle junction hydrogen in diastereomer **30a**, where it appears in the *beta* position.

Let us proceed now to the nucleophilic attack by the electrons from the inner position into the carbonyl carbon. This provokes indeed the displacement of the  $\pi$  electrons of carbonyl to compensate the cationic charge over oxygen

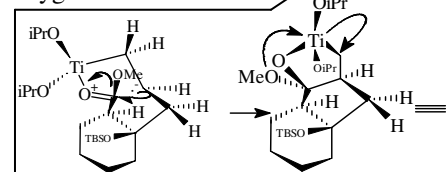
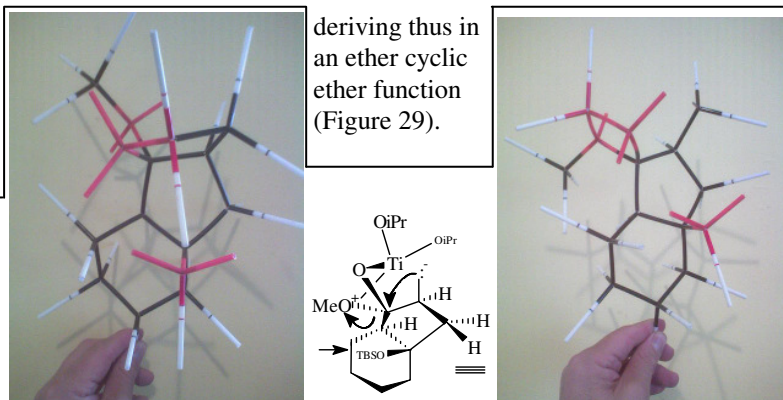
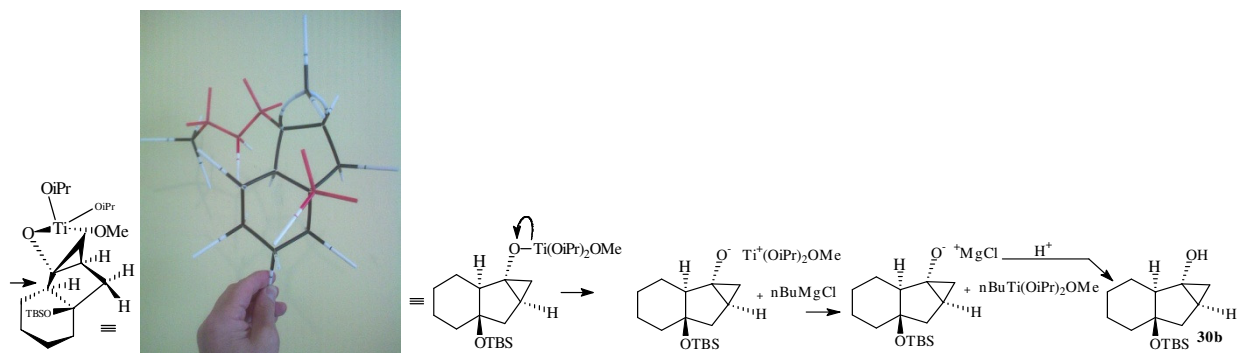


Figure 29. The nucleophilic attack by the electrons from the inner position in Model C to drive reaction to the obtention of compound **30b**





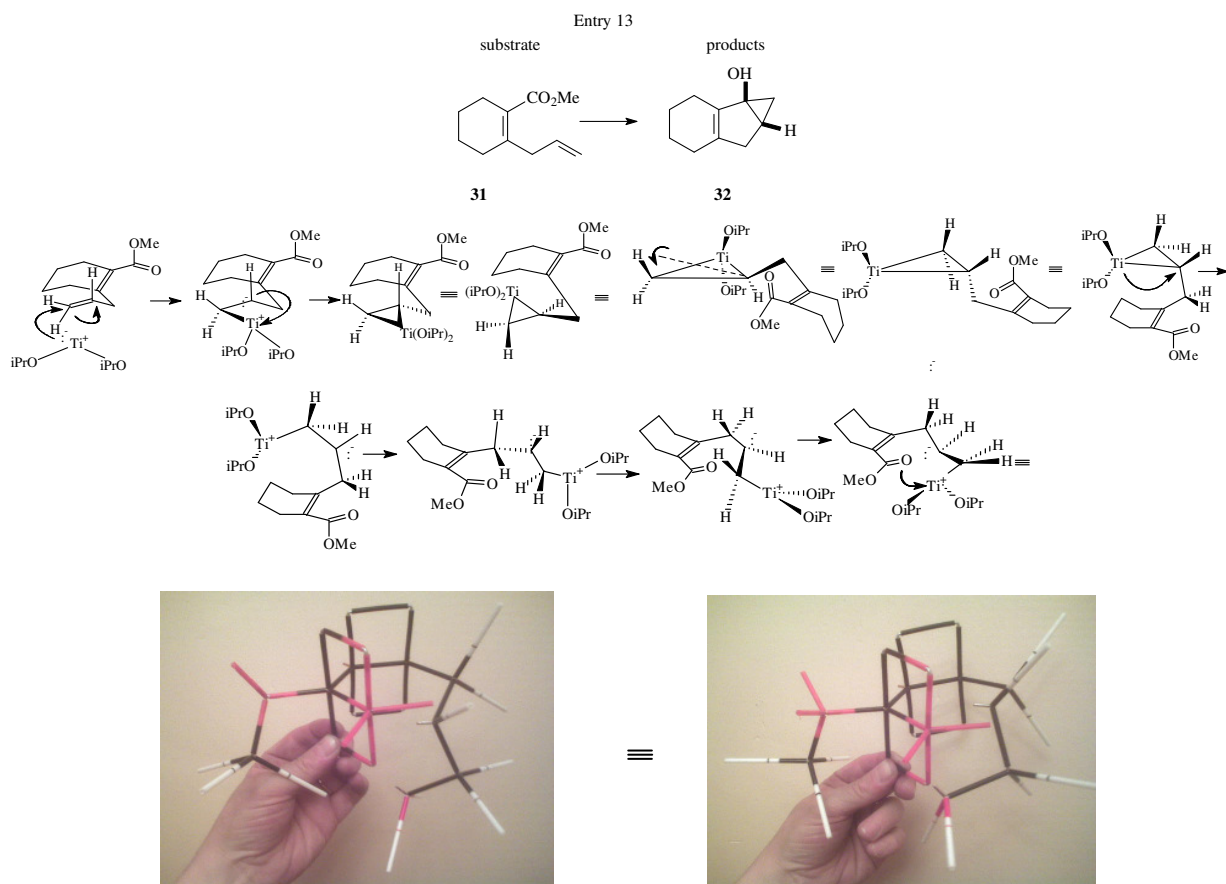
The remaining operations regards the replacement of the titanium moiety by the Grignard's cation and the final alcoholic water residue to afford **30b** (Figure 30). This intramolecular nucleophilic attack driving to the apparition of the  $\beta$ -oriented-three-membered cycle characterizing compound **30b**, happens with inversion of configuration at the chiral centre supporting the  $^+OMe$  and  $OTi$  residues.



**Figure 30.** Successive replacement of the titanium moiety by the Grignard's cation and of this by  $H^+$  to afford **30b**

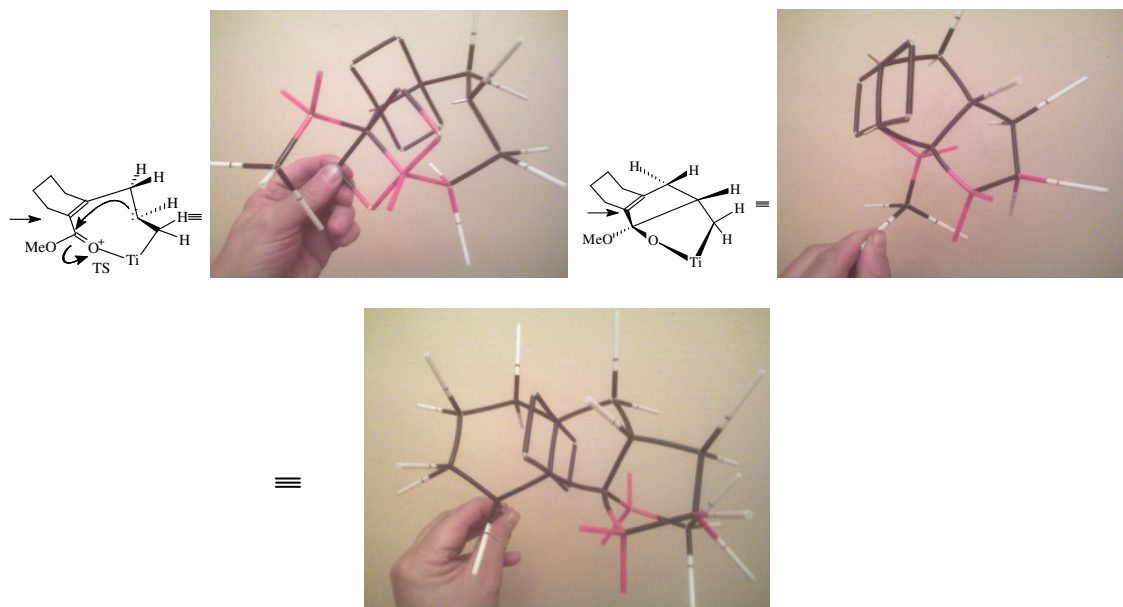
### Entry 13

Even though the failure to accomplish derivative **32** (0% yielding (2)) we propose with a didactical purpose how such reaction should happen from a strictly theoretical standpoint (Figure 31).



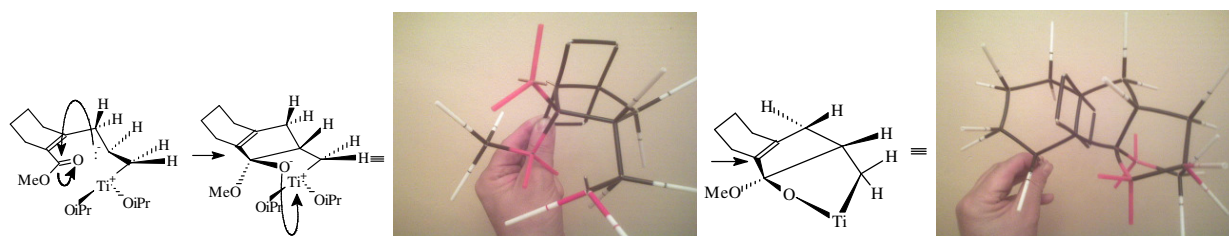
**Figure 31.** Speculative mechanism to obtain **32** (entry 13, (2))

The constructed model at this stage shows partially our molecule, particularly the conjugated C=C and C=O(OCH<sub>3</sub>) systems. We do also identify the methine carbanion as well as the Ti<sup>+</sup>(OiPr)<sub>2</sub> cation. The next electronic movement comports the nucleophilic attack C=O→Ti<sup>+</sup> (Figure 31). This gives rise to an eight-membered cycle which according to the constructed model exhibits annular tension because of failing to reach the previous and normally expected coplanarity of both π conjugated systems (Figure 32). Isn't this the cause for the reaction failure? However still theorizing we can suppose from there on another nucleophilic intramolecular attack from the methine carbanion to the electrophilic carbonyl carbon. As a result we've got a three fused cycles system 6-5-5 (Figure 31).



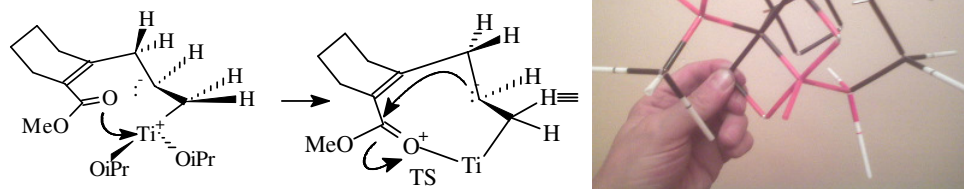
**Figure 32.** Speculative mechanism to obtain **32**: non-coplanarity of π conjugated systems. Formation of 6-5-5 fused tricycle (entry 13, (2))

We can describe these steps inverting the order of the nucleophilic attacks episodes (Figure 33): we first propose an CH<sup>-</sup> attack on C=O and then, once free from the contracting non-planarity of the π conjugated systems (now existing only the C=C system), the second nucleophilic attack of C=O<sup>-</sup> to the Ti<sup>+</sup>(OiPr)<sub>2</sub> cation. Anyway the first attack may never happen because of the currently absence of the Lewis acid catalytic action of Ti<sup>+</sup>(OiPr)<sub>2</sub>, once linked to C=O as it was our first option. The problem arising from these mechanistic proposals is the *trans* disposition reached by the 1,2-*trans*-H-OMe group at the ring junction after the methine attack on the carbonyl carbon of the ester moiety. This does not conduct to the expected stereochemistry at the ring junction of the final structure comporting the 5- and 3-membered fused rings. The good structure (2) **32** (Figure 31) presents a *cis* disposition for the just mentioned groups. It forces to another pre-disposition of the methine before attack on the C=O. For solving this we will only consider the case of a first nucleophilic attack on titanium by the carbonyl oxygen and then a second by the carbanion methine on the carbonyl carbon of the ester moiety. The transition state has already been described as we can see in Figure 34.



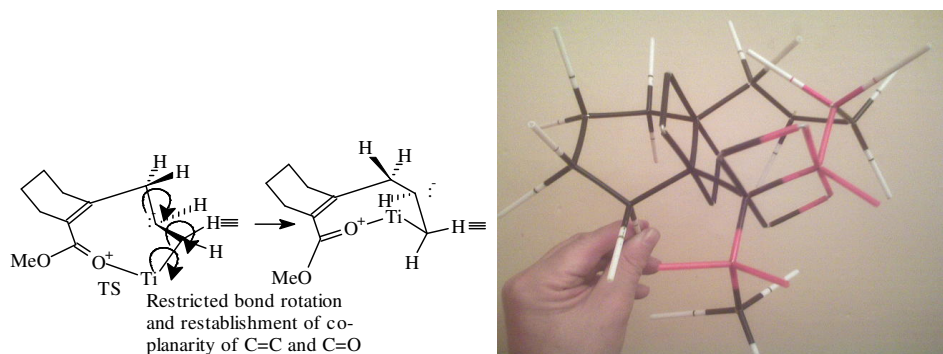
**Figure 33.** Speculative mechanism to obtain **32**: Inverting the order of the nucleophilic attacks episodes





**Figure 34.** Speculative mechanism to obtain 32: Transition state, the case of a first nucleophilic attack on titanium by the carbonyl oxygen and then a second by the carbanion methine on the carbonyl carbon of the ester moiety

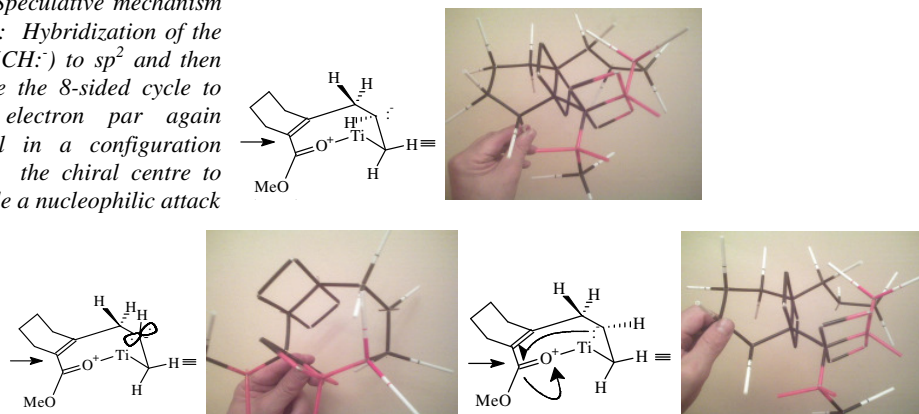
Nevertheless, the intramolecular carbanion attack on C=O as just described, proved to give rise to the 1,2-*trans*-H-OMe isomer. This TS shows the methine hydrogen in an outer position regarding the 8-membered ring. Thus it becomes necessary to employ the opposite position for that methine hydrogen before the carbanion attack, or the inner hydrogen position on the carbanion. For that purpose the 8-sided cycle must be re-accommodated throughout restricted sigma bonding rotation. The result can be drawn and constructed as follows (Figure 35):



**Figure 35.** Speculative mechanism to obtain 32: Re-accommodation of the 8-sided cycle throughout restricted sigma bonding rotation, recovery of co-planarity in the conjugated  $\pi$ -systems (cf. Figure 34)

This TS shows after rotation the inner hydrogen which means the electron pair placed in an outer position. It signifies that there is no spatial disposition for the nucleophilic intramolecular action of the Lewis base ( $\text{CH}^-$ ). This TS needs anyway the electron pair in an inner or well disposed situation. In order to place the electron pair inside the 8-sided cycle, the  $sp^3$  carbon ( $\text{CH}^-$ ) hybridize to  $sp^2$  and then to  $sp^3$  state again resulting all in a configuration inversion of the chiral centre and thus the electron pair placed inside the ring ready for a nucleophilic attack (Figure 36).

**Figure 36.** Speculative mechanism to obtain 32: Hybridization of the  $sp^3$  carbon ( $\text{CH}^-$ ) to  $sp^2$  and then to  $sp^3$  inside the 8-sided cycle to place the electron pair again resulting all in a configuration inversion of the chiral centre to make possible a nucleophilic attack



The next steps would involve the formation of the highly tensioned dioxotitano 4 membered ring and the formation of the three membered fused ring by the carbanion attack over the electrophilic carbon supporting the  $\text{MeO}^+$  function. All this is followed by the known steps leading to the final alcohol form of the hypothetical product **32** (Figure 37).

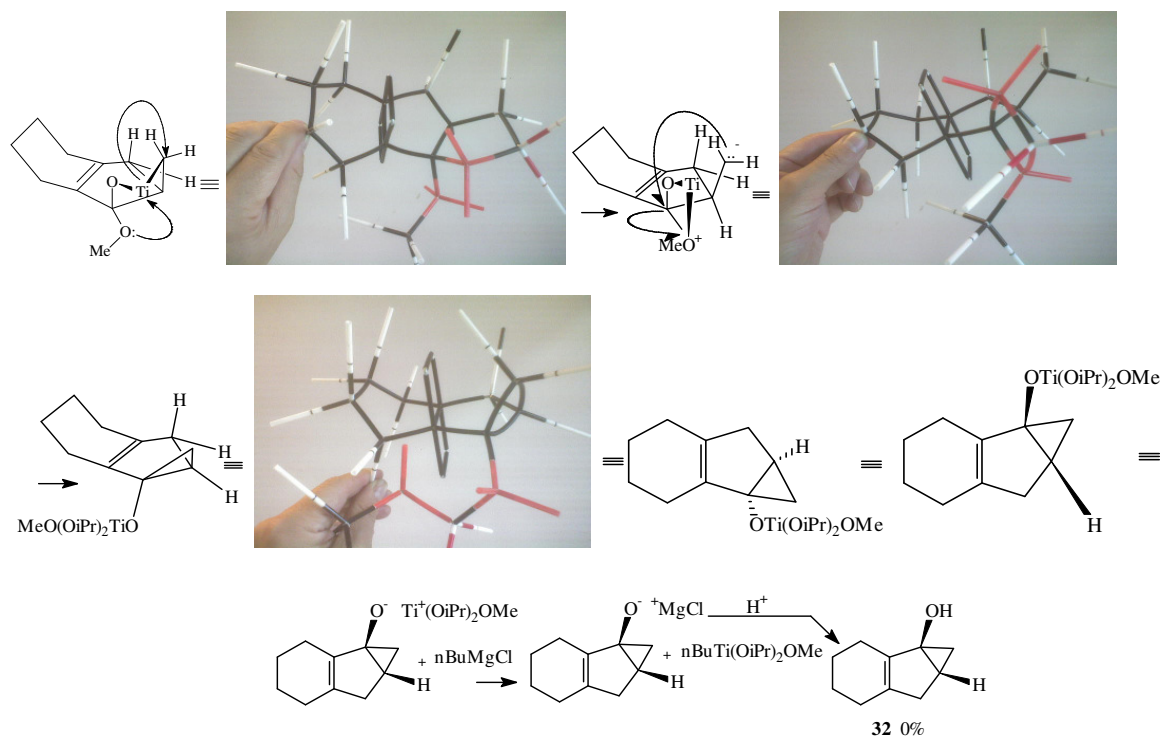
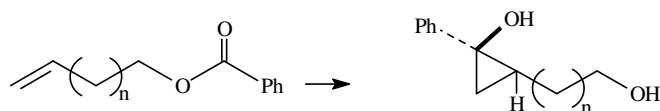


Figure 37. Speculative mechanism to obtain **32**: final steps

#### Entries 14 and 15

According to Cha and col. esters of  $\omega$ -alken-1-ols, particularly 3-buten-ols, seem to be amenable to intramolecular hydroxycyclopropanations. Thus, Cha and col. also effected the reaction of benzoate **33** to give a 7:1 mixture of the cyclopropanols **34a** and **34b**. A further extension to the homologue **35**, lacked of good yield. These reaction entries can be mechanistically envisaged as follow (Figure 38).



Entry 14: n=1 **33**  $\xrightarrow{\quad}$  **34a**:  $\alpha$ -H **34b**:  $\beta$ -H (7:1, 78%)  
 Entry 15: n=2 **35**  $\xrightarrow{\quad}$  **36a**:  $\alpha$ -H **36b**:  $\beta$ -H (15%)

For entry 14:

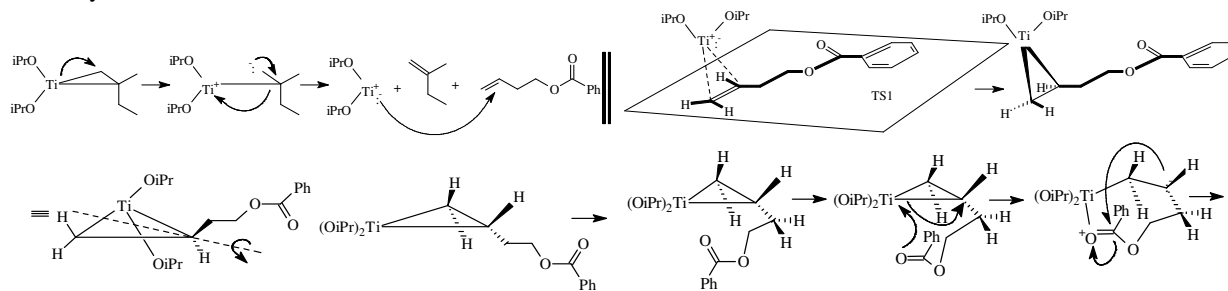


Figure 38. Views of the synthesis of **34a** and **34b** (entry 14 (2))

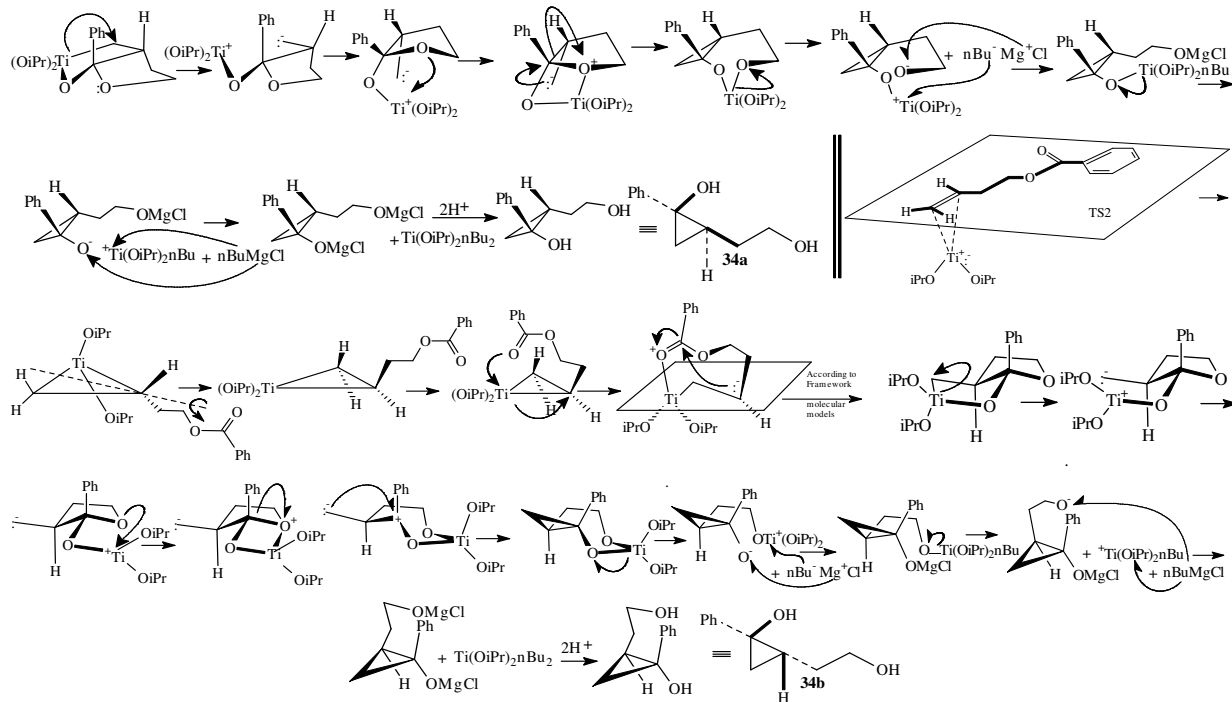


Figure 38(Cont.). Views of the synthesis of **34a** and **34b** (entry 14 (2))

For entry 15: The mechanistic approach for the **33**-homologue **35** is the same as for **33** (see entry 14 mechanistic approach for details).

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