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Research Paper

Metathesis Approach to the Formal Synthesis of Aliskiren

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Abstract: Formal synthesis of aliskiren by employing Grubbs second generation catalyst in cross olefin metathesis, iron (III) catalyzed vinylation and biocatalysis by using PLE is disclosed.

There are myriad of approaches disclosed for the synthesis of aliskiren hemifumarate **1**.[1-16]Aliskiren is found to restrain rennin activity or angiotensin-converting enzyme (ACE) activity, consequently resulting in antihypertensive effects. Novartis Pharma AG discovered aliskiren hemifumarate (Figure 1) as a non-peptide orally active rennin inhibitor.[17-20]

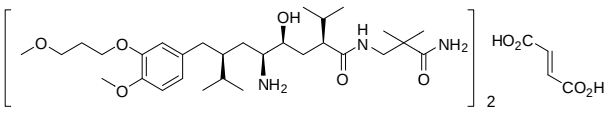

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Figure 1. Structure of Aliskiren **1**

Herein, we disclose the synthesis of aliskiren hemifumarate **1** featuring vinylation and cross olefin metathesis.

Cross olefin metathesis has been viewed as one of the most prolific tools in organic synthesis. This strategy relies on the use of different version of catalysts discovered by Grubbs. In our endeavor we employed Grubbs second generation catalyst. Vinylation strategy for homologation is well developed concept that has gained importance in metal catalyzed coupling reactions. In our campaign we utilized the catalytic potential of iron (III). In order to synthesize amide component essential to the synthesis of aliskiren, we utilized enzyme PLE (Pig Liver Esterase) for resolution.

One of the possible disconnection approaches as shown in Figure 2 for the synthesis of aliskiren indicated that the coupling of **3** and **4** is the key step which can give ene intermediate **2** that can further be utilized in the downstream chemistry without stereochemical loss with high yields.[21]

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This disclosure is mainly about the intermediates **3** & **4.** Intermediate **3** have been synthesized by employing vinylation. Whereas intermediate **4** that has been synthesized by employing the chiral auxiliary based allylation or biocatalysis starting from **6**. In order to synthesize **5**, we adopted the precedented literature.[22] Thereafter, the intermediate **5** was subjected to homologation by employing vinyl Grignard reagent that afforded olefin **3**. To address the challenges in this transformation several groups have made unsuccessful attempts.[23] As expected, in our endeavor, without modification of standard procedure for vinyl Grignard reaction, we were able to achieve the product **3** in 73% yields as shown in Scheme 1. Thereafter, key metathesis reaction has been performed to couple **3** and **4** to afford advanced and known intermediate **2** which is used in the synthesis of aliskiren by several groups.[1-16]

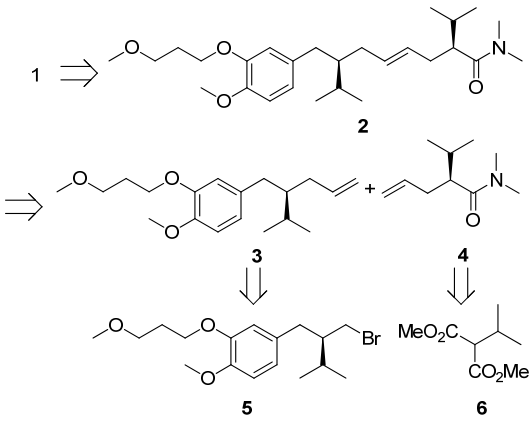
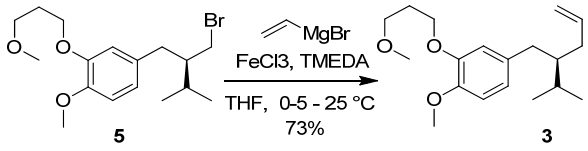
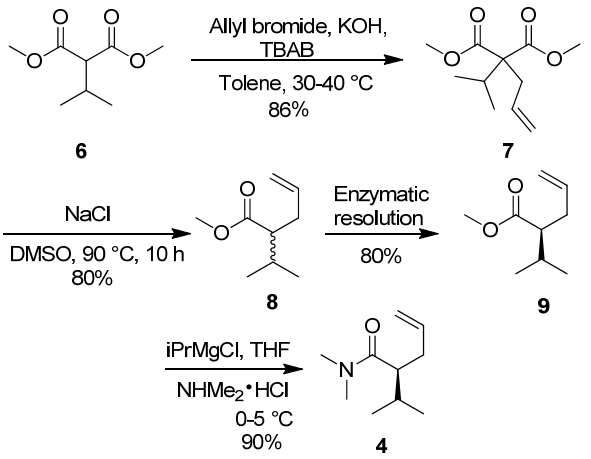


Figure 2. Disconnection approach for Aliskiren **1**



Scheme 1. Synthesis of intermediate **3**

There are many approaches reported for the synthesis of **4**.[1-16] In order to devise novel approach, we successfully attempted base mediated allylation followed by decarboxylation on substrate **6** that afforded advanced intermediate **8** via **7** in 80% yields.[24] Thereafter, we employed enzymatic resolution on **8**. In this transformation, we used PLE that afforded the desired enantiomer **9** in 40% yield and 89.1% ee. Thereafter, **9** was subjected to amidation to afford intermediate **4** as shown in Scheme 2.



Scheme 2. Synthesis of intermediate **4**

After preparation of these two intermediates (**3** and **4**) we focused on the key step which is olefin cross metathesis using Grubbs second generation catalyst. The intermediates **3** and **4** derivatives were dissolved in CH_2Cl_2 and catalytic amount (10 mol%) of Grubbs II generation catalyst and heated the reaction mixture to reflux temperature (40 °C) for 8 h that afforded the ene derivative **2**.

In order to obtain *E* selective metathesis product we attempted this with olefin esters and amides. We also studied the impact of solvent and additive (CuI)[25] and it was observed that the conversion and *E*/*Z* ratio

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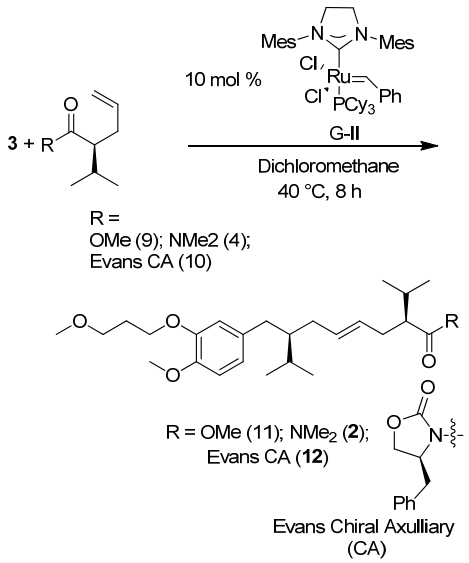
were nearly same in all the experiments as shown in Table 1.

Table 1. Metathesis reactions



Entry	Olefin	Sol./M	G-II/CuI (mol %)	T(°C)/t(h)	Conv.(%)	*E/Z* ratio
1	**10**	CH_2Cl_2/1	10/ -	40/8	50	2/1
2	**9**	CH_2Cl_2/1	10/ -	40/8	51	6.6/1
3	**4**	CH_2Cl_2/1	10/ -	40/8	50.5	5.2/1
4	**10**	CH_2Cl_2/0.5	10/ -	40/8	48.5	2.3/1
5	**10**	Et_2O/0.5	10/3	40/8	52	3.1/1
6	**10**	Et_2O/0.5	1/ 3	40/8	52.5	1.9/1

During metathesis reaction, we were able to isolate olefin metathesis by-products (**13** and **14**). These by-products can potentially be used in the synthesis of aliskiren **1** by following the reported procedures.[26]

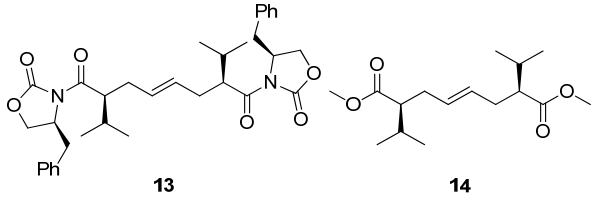
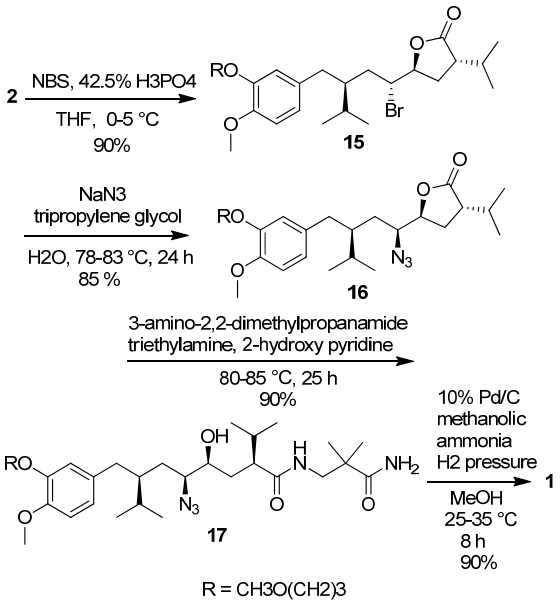


Figure 2. Byproducts formed in the metathesis reaction

Considering the reported literature with slight modification in the process we could able to synthesize aliskiren **1**.[3a] End game strategy starts with compound **2** which on reaction with NBS and H_3PO_4 in THF afforded corresponding bromo lactone derivative **15**. Compound **15** was allowed to react with sodium azide in tripropylene glycol that gave rise azide derivative **16**. Intermediate **16** on lactone aminolysis with 3-amino-2,2-dimethylpropanamide yielded azide intermediate **17** which on reduction afforded aliskiren **1** as shown in Scheme 3.



Scheme 3. End game strategy for the synthesis of aliskiren **1**

Conclusion

We demonstrated here a formal synthesis of aliskiren **1** by employing vinylation, biocatalysis by using PLE and olefin cross metathesis strategy which is straight forward and unprecedented. This work was carried out around one and half year back and we have collected all the data at that point of time. Meanwhile, a very competitive work that has been published by Hanessian et al. in *Organic Letters* recently.[27]

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Supplementary Material

Experimental procedures and compound characterization data are described in supplementary material.

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