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The Claisen rearrangement in the syntheses of bioactive natural products☆

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1. Introduction

Since its discovery in 1912 by Ludwig Claisen[1] the Claisen rearrangement has stimulated the interest of several generations of organic chemists and its importance is ever-increasing owing to its ability to form carbon–carbon and carbon–heteroatom bonds. This rearrangement was discovered with the aliphatic substrate viz., allyl ether of the enol form of acetic ester, but was almost forgotten for a long period till early sixties when the activities were mainly limited to its aromatic counter. Then suddenly the organic chemists found renewed interest in the aliphatic rearrangement for the stereocontrolled syntheses of complex natural products. From 1960 the aliphatic Claisen rearrangement gained momentum with the discovery of its several variations[2]. Some of the variations of the aliphatic Claisen rearrangement offer stereoselective C–C bond formation, which is extremely important in the synthesis of useful highly functionalized compounds and complex natural products. Some applications of the rearrangement in the syntheses of natural products have been appeared earlier in a book[3] and in review

☆ A tribute to L. Claisen on the occasion of 100 years of the Claisen rearrangement.

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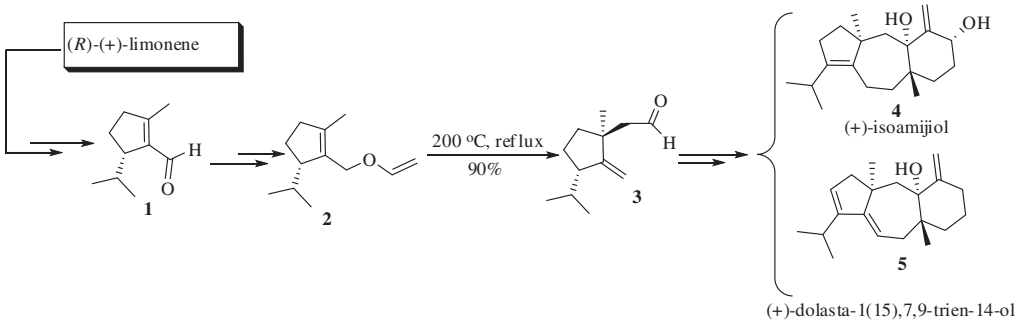
articles[4] on Claisen rearrangement in general, covering only a portion of the relevant literature published until 2004. However, to date there is no review in literature solely devoted to the application of the Claisen rearrangement in the syntheses of natural products. This brief comprehensive review summarizes discussions on the relevant literature published mostly between 2004 and 2012 and some papers, which were not included earlier in the book or in any of the general reviews. Emphasis has been given to the source and bioactivity of the natural products, and application of the Claisen rearrangement in their syntheses.

2. Aliphatic Claisen rearrangement

The aliphatic Claisen rearrangement has emerged as a very important tool for stereoselective C–C bond formation. Many natural products have been synthesized by applying variants of this rearrangement as a key step for achieving regio- and stereoselectivity. Dolastane-type diterpenes were first discovered in nature from a poisonous Indian Ocean sea-hare.[5] A couple of dolastane-type tricyclic marine natural products (+)-isoamijiol (**4**) and (+)-dolasta-1(15),7,9-trien-14-ol (**5**) were synthesized by Mehta et al[6] by utilizing the Claisen rearrangement as one of the steps from aldehyde **1** as starting material (readily available from (*R*)-(+)-limonene). The Claisen precursor **2**, obtained from **1**, was stereospecifically rearranged under thermal condition to **3** in 90% yield, which was then converted to the natural products **4** and **5** in several steps (Scheme 1).



Scheme 1. Synthesis of (+)-isoamijiol and (+)-dolasta-1(15),7,9-triesn-14-o1.

The natural products (±)-tochuinyl **11** acetate and (±)-dihydrotochuinyl acetate **12**, a pair of metabolites were first isolated[7] by Williamson and Andersen from the skin extracts of *Tochuina tetraquetra* commonly found in Kuril Islands (USSR) to the Santa Cruz Islands (USA). Both belong to the cuparane class of sesquiterpenes and these two acetates **11** and **12** were the first examples of cuparanes to be isolated from soft coral.

Srikrishna and Reddy reported[8] the first approach to the total synthesis of these natural products via a cyclopentenone derivative **10**, a known precursor of the sesquiterpene cuparenes, by utilizing aliphatic Claisen rearrangement as one of the steps. They obtained the rearranged product **9** through **8** by the treatment of the allyl alcohol **6** and ethyl vinyl ether **7** at 170–180 °C in a sealed tube. The cyclopentenone derivative **10**, accessed in few steps from **9**, gave the natural products **11** and **12** by two different routes in few steps (Scheme 2).

Tetrodotoxin (**16**), a marine natural product, was first isolated from puffer fish *Spheroides rubripes* belongs to the 'Tetraodontidae' family[9]. The broad spectrum of bioactivity due to its toxic principle and structural complexity attracted challenges to its total synthesis. Kishi et al. group first reported[10] the total synthesis of racemic tetrodotoxin. However, the first total asymmetric synthesis of this natural product was achieved by Isobe et al.[11] They made use of the Claisen rearrangement in a key step in their long synthetic route. The Claisen rearrangement of **14** was carried out under thermal condition in the presence of K_2CO_3 in *o*-DCB (*o*-dichlorobenzene) to afford **15** in 94% yield. The rearranged product **15** was successfully transformed to the natural product **16** in 31 steps starting from **13** (Scheme 3).

(+)-Xeniolide F, a bioactive cytotoxic diterpene natural product, was first isolated by Jiménez et al[12] from *Xenia* species collected from near Sulawesi Island of Indonesia. It contains a xenicane framework of a nine-membered carbocyclic ring. The synthetic efforts toward xenicane diterpene are rare[13]. Hiersemann and Pollex projected[14a] a building block for the synthesis of (−)-xeniolide F (**20**) and also synthesized the building block **19** by applying a catalytic asymmetric Claisen rearrangement (CAC) of **17**.

The thermal Claisen rearrangement of **17** (*E*/*Z*=9:1) in 1,2-dichloroethane, at 80 °C for 32 h afforded the rearrangement product (±)-*anti*-**19** in moderate yield (50%) along with unreacted (*Z*,*Z*)-**17**. The desired rearrangement product (±)-*anti*-(2*S*,10*R*)-**19** was also obtained in 64% yield by treating the 9:1 mixture of (*E*/*Z*)-**17** with chiral Cu^{II} Lewis acid [Cu{(*S*,*S*)-^{t}Bu-box}]$(H_2O)_2(SbF_6)_2$, i.e., (*S*,*S*)-**18** in the presence of activated 4 Å molecular sieves in CH_2Cl_2 at room temperature. Single diastereo- and enantiomer along with minor unreacted (*Z*,*Z*)-**17** were obtained. Their attempt to access the desired rearrangement product *anti*-(2*S*,10*R*)-**19** by the treatment of (*Z*,*Z*)-**17** under the same condition also failed. The CAC was carried out with pure (*E*,*Z*)-**17** isomers and pleasingly the desired building block *anti*-(2*S*,10*R*)-**19** was obtained in >80% yield in the presence of (*S*,*S*)-**18**. The different reactivity of (*Z*,*Z*)-**17** may be rationalized by the model **21**, where the steric repulsion of axial group increases the energy level of the chair-like transition state (TS), which is absent in **22** (Scheme 4).

Similar catalytic asymmetric Claisen rearrangement has been utilized by Hiersemann et al. in the total synthesis of fungicidal polyketide natural products curvicollides A–C (**26a**–**c**) and C10–C18 segment **27** of (−)-ecklonialactone B (**28**)[14]. In both the cases, the key C–C bond formations were achieved by CAC rearrangement of **24a**,**b** to give intermediates **25a**,**b**. The rearranged products gave the corresponding natural products **26a**–**c** and the segment **27** in few steps (Scheme 5).

(±)-Frondosin B (**32**), a sesquiterpene hydroquinone was isolated from the Micronesia marine sponge *Dysidea frondosa* along with other four structurally related isomers (frondosins A, C–E)[15a]. These natural products act as inhibitors of protein kinase C in low micromolar range[15b]. The frondosin family also plays an important role in tumor progression and metastasis in several human cancers[16].