International Journal of Chemical Research
ISSN: 0975-3699 & E-ISSN: 0975-9131, Volume 8, Issue 2, 2016, pp.-173-194.
Available online at http://www.bioinfopublication.org/jouarchive.php?opt=&jouid=BPJ0000219

Review Article

RECENT DEVELOPMENT IN THE ORTHOESTER JOHNSON-CLAISEN REARRANGEMENT AND APPLICATION

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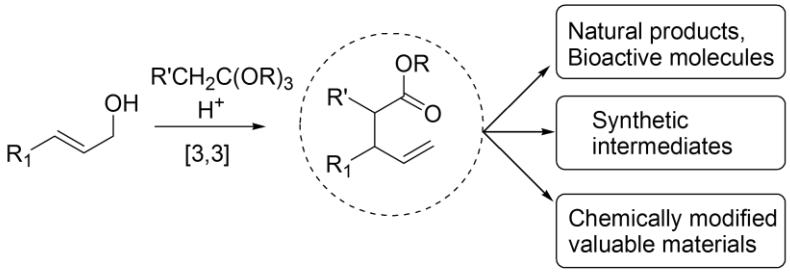
Received: April 07, 2016; Revised: May 10, 2016; Accepted: May 11, 2016; Published: May 21, 2016

Abstract-Orthoester Johnson-Claisen rearrangement is a very powerful C-C bond forming reaction. Its precise region-selectivity, high level of stereo-selectivity and opportunity of stereo-control makes this reaction as a very useful tool in organic synthesis. Over last few years this reaction has been widely explored towards the synthesis of a varied range of natural products, bioactive molecules, synthetic intermediates and chemically modified valuable materials. Recent development in this rearrangement and applications since 2010 is presented in this review article.



Orthoester Johnson-Claisen rearrangement and application

Keywords- Oxy-Claisen rearrangement, Regioselectivity, Stereoselective synthesis, Catalysis, Sequential Claisen rearrangement, Exo-pericyclic stereocontrol, Bioactive molecules, Natural products.

Citation: Safiul Alam, (2016) Recent Development in the Orthoester Johnson-Claisen Rearrangement and Application. International Journal of Chemical Research, ISSN: 0975-3699 & E-ISSN: 0975-9131, Volume 8, Issue 2, pp.-173-194.

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Academic Editor / Reviewer: Dr Santosh Balasaheb Kamble

Introduction

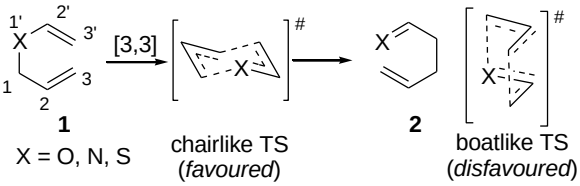
The Claisen rearrangement enjoys widespread use as a key strategy-level transformation in organic synthesis [1]. In 1912, Ludwig Claisen discovered this rearrangement with aliphatic substrate *viz.*, allyl vinyl ether of the enol form of acetic ester to give the corresponding *γ,δ*-unsaturated carbonyl compound via new carbon-carbon (C-C) bond formation. Since then its application in C-C bond formation reactions is increasing rapidly on both aliphatic and aromatic substrates. The power of the Claisen rearrangement stems from its (i) ability to deliver new C-C bonds, specially quaternary carbon centers with regiospecific allylic transposition from simple derivatives of alcohol precursors; (ii) high levels of stereoslectivity and (iii) compatibility with a wide range of functionality. Enormous synthetic utility of this rearrangement has prompted the scientific community for its development and modifications [2-3]. In 1970, Johnson et al. [3] developed a simple method for the *in situ* generation of starting allyl vinyl ether from suitable allyl alcohol followed by a [3,3]-sigmatropic rearrangement to give the corresponding *γ,δ*-unsaturated carbonyl compound via new C-C bond formation, known as Johnson Claisen rearrangement, which opened a broad scope in organic synthesis, as different types of chiral as well as achiral allyl alcohols are readily available or easily synthesizable. Among the different variants of *oxy*-Claisen rearrangement have been discovered, the Johnson-Claisen rearrangement reaction has been widely used due to its potential to form new C-C bond with precise regio- and stereoselectivity from simple allyl alcohols itself. This review aims to highlight the recent development in orthoester Johnson-Claisen rearrangement emphasizing the stereocontrol, catalysis, sequential rearrangement, regioselectivity and applications toward the synthesis of natural products, bioactive molecules, building blocks, synthetic intermediates and chemically modified valuable materials, based on the relevant literature published since 2010, excluding the works which were shown in the previous reviews, [2] however some earlier works have been included to discuss the particular aspect.

Orthoester Johnson-Claisen rearrangement

Definition

Claisen rearrangement can be defined as symmetry allowed [3,3]-sigmatropic rearrangement of allyl vinyl ether (**1,** X = O) to γ,δ-unsaturated carbonyl compound **(2)** by a concerted pericyclic intramolecular process involving a superficial pathway, proceeds through a high preference of chair like six member transition state **(Scheme 1)** [1]. Based on the key hetero atom involve, it is

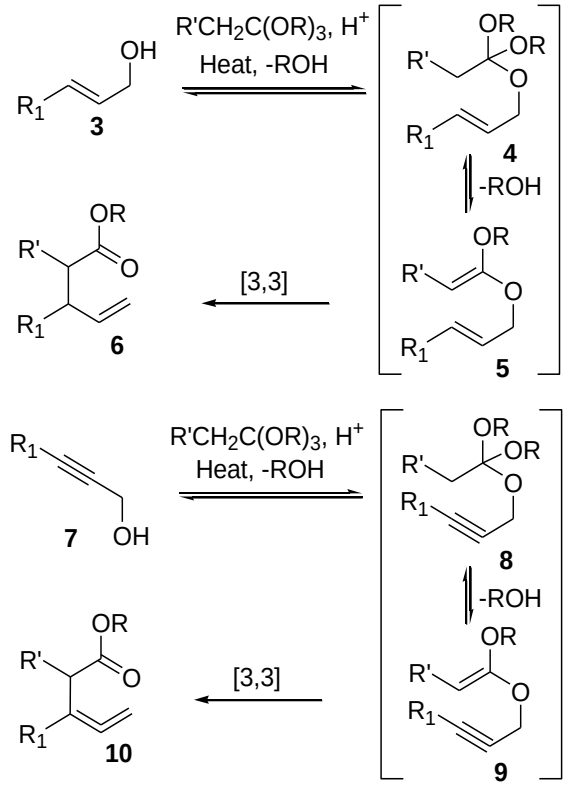
classified as oxy- Claisen rearrangement [1-3] (X = O), *amino*- or *aza*-Claisen [4] (X = N) and *thio*-Claisen rearrangement [5] (X = S), the other positions of **1** may also be occupied by hetero atoms. It is also classified as aliphatic Claisen rearrangement when both the allyl and vinyl groups are the part of aliphatic groups (e.g. alkene, alkyne groups) and aromatic Claisen rearrangement when either or both of the allyl and vinyl groups are the part of aromatic ring.



Scheme 1 Aliphatic Claisen rearrangement.

The method of allyl vinyl ether generation and subsequent [3,3] rearrangement develops further subtypes of aliphatic oxy-Claisen rearrangement as orthoester Johnson-Claisen, [3] Reformatskii-Claisen, [6,2l] Ireland-Claisen, [7,2k] Carroll rearrangement, [8] Meerwein-Eschenmoser-Claisen, [9] Overman rearrangement, [10] Bellus-Claisen, [11] Gosteli-Claisen, [12] Arnold-Claisen, [13] Olefin isomerization-Claisen, [14] Propargyl Claisen rearrangement [15, 2m] etc.

Conversion of an allylic alcohol in presence of orthoester and catalytic amount of a weak protic acid into γ, δ-unsaturated ester via a [3,3]-sigmatropic rearrangement is known as Johnson-Claisen rearrangement, it is also called orthoester Johnson-Claisen rearrangement [3]. Treatment of allylic alcohol **3** or, propargylic alcohol **7** with more than stoichiometric amount of orthoester [$MeC(OEt)_3$, $EtC(OEt)_3$ etc] and substiochiometric amount of weak acid [$EtCO_2H$, nitrophenol etc] in refluxing toluene or xylene solvent produces γ,δ-unsurated ester **6** or allenic ester **10**. Step for the formation of mixed orthoester **4** or **8** is reversible and the equilibrium can be shifted at the forward direction by distilling off the low boiling alcohol by-product (ROH). Further acid-catalyzed elimination of alcohol from the in situ generated **4** gives ketene acetal intermediate **5**, which subsequently undergoes a [3,3] sigmatropic rearrangement to give the rearranged product **6**. Similarly, rearranged product **10** is obtained from the in situ generated **8 (Scheme 2)**.



Scheme 2 Orthoester Johnson-Claisen rearrangement

Regioselectivity and stereoselectvity

Precise regioselectivity and opportunity of stereocontrol make this rearrangement as a powerful tool to access γ, δ-unsaturated carbonyl compounds, which are then elaborated to functionalized organic molecules. The involvement of six-member cyclic transition state in the pericyclic process is the origin of the precise regioselectivity [1]. Stereocontroled chirality transfer reactions of enantioenriched allylic alcohols are promising synthetic tools to access chiral compounds [16, 2h]. Stereocontrol has been achieved by different means and the development on its stereoselective version has drawn intense attention. However, an extension to asymmetric version is a challenging task. The asymmetric Claisen rearrangement [16b] can be classified into two types- diastereoselective and enantionselective Claisen rearrangement [Fig-1].

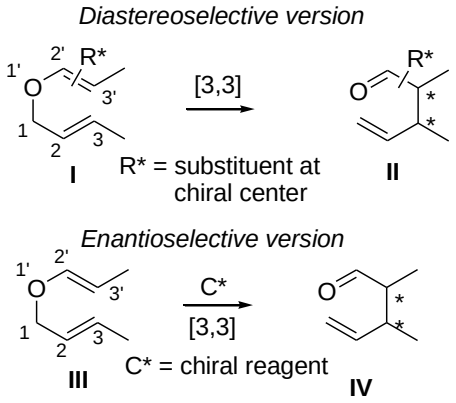


Fig-1 Asymmetric *oxy*-Claisen rearrangement

In diastereoselective Claisen rearrangement, usually a chiral centre at 1-pisition is quite efficient for 1,3-chirality transfer and substituent at different positions display different effects involving the reactivity and the stereochemical outcome of the rearrangement. For, substrate, having substituent at 3- and/or 3'-positions, the relative stereochemistry (*syn/anti*) at the newly formed adjacent chiral carbons is highly controlled by the geometry of the alkene (E/Z) [17]. Another version involving chiral reagent to give diastereomeric transition states, is known as enantioselective Claisen rearrangement, which usually involve a chiral Lewis acid as mediator. However, the higher Lewis basicity of the carbonyl group in the rearranged product than that of the ethereal oxygen in the substrate is the major barrier towards the enantioselective Claisen rearrangement employing a catalytic amount of chiral Lewis acid.

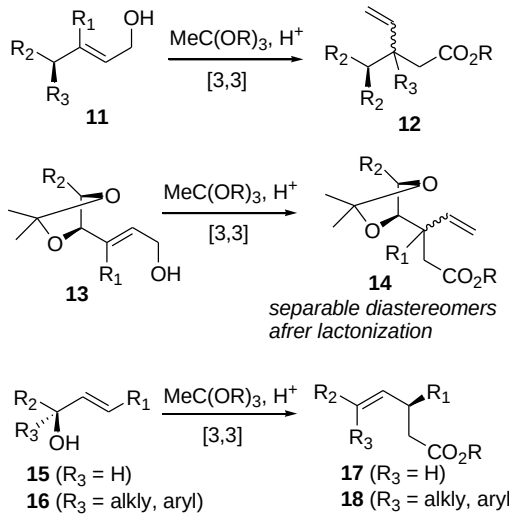
In brief, the stereochemical outcome can be described as follows. The Johnson-Claisen rearrangement of primary allyl alcohol **11**, produces diastereomeric mixture of rearranged products **12** and similarly allyl alcohol **13** gives diastereomeric mixture of rearranged products **14,** where the exopericyclic substituents and the geometry of olefin controls the stereoselectivity. Whereas chiral secondary allyl alcohol **15** is known for 1,3-chirality transfer to give rearranged γ,δ-unsaturated ester **17** [18] and rearrangement of tertiary allyl alcohol **16** produces chiral rearranged ester **18 (Scheme 3)**. Thus, Johnson-Claisen rearrangement of primary allyl alcohols offer the scope for further elaboration of the rearranged γ,δ-unsaturated ester to chiral target molecules through diastereomeric separation, rearrangement of secondary and tertiary allyl alcohols provide the opportunity for chiral induction.

Recent development in the orthoester Johnson-Claisen rearrangement and applications

Rearrangement of primary allyl alcohols

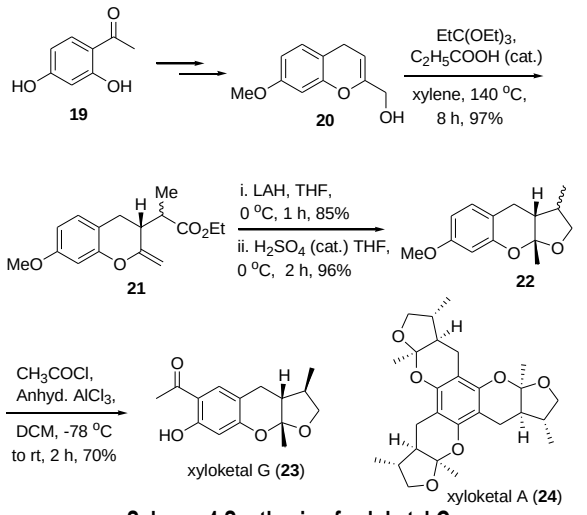
Venkateswaran et al. [19] have achieved the stereocontrolled synthesis of xyloketal G **(23)** employing orthoester Johnson-Claisen rearrangement of chrominol and intramolecular cataionic cyclization reaction strategy. Xyloketals were isolated from mangrove fungus belongs to the xylaria species and have unique structural feature of *cis* disposition of three contiguous stereogenic centers in the linear tetrahydropyran component. They exhibits various bioactivities,

xyloketal A **(24)** is a potent inhibitor of acetyl choline esterase and used to treat Alzheimer's disease [20]. In their synthesis, the primary allyl alcohol **20**, prepared from **19,** was subjected to Johnson-Claisen rearrangement in triethyl orthopropionate with catalytic amount of propanoic acid at 140 °C to give γ,δ-unsaturated ester **21** having required chirality at the β-carbon. Reduction of ester **21** followed by acid catalyzed cyclization gave *cis* fused liner tetrahydropyran **22**. In the last step, acetylation, isomerizaion and demethylation of **22** occurred in a single pot to give xyloketal G **(23)** in stereoselective manner (Scheme4).



R = alkyl; R_1, R_2 , R_3 = hydrogen, alkyl, aryl group

Scheme 3 Chirality transfer in Johnson-Claisen rearrangement



Scheme 4 Synthesis of xyloketal G

The alkaloid manzamine A (**25**) [Fig-2] was first reported in 1986, and which has a complex pentacyclic ABCDE ring structure [21] and posses important biological activities [22].

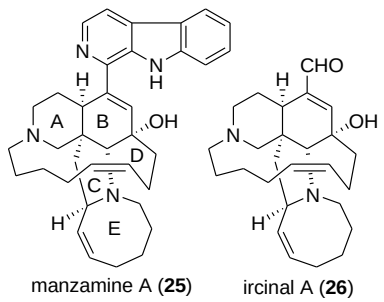
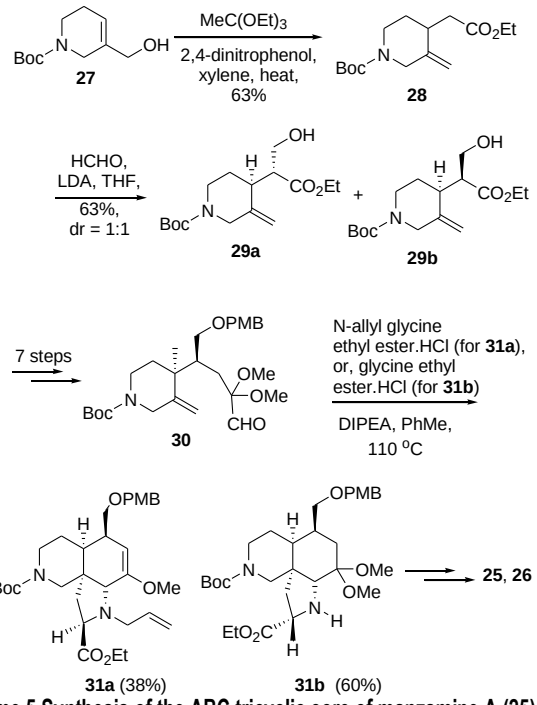


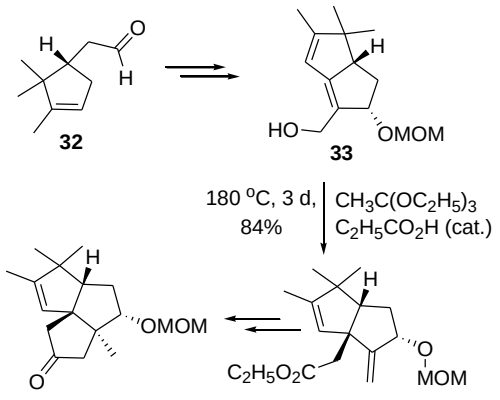
Fig-2 Structures of manzamine A and ircinal A.

Recently, Coldham et al.[23] have developed a short and stereoselective route utilizing the Johnson-Claisen rearrangement to incorporate one carbone unit in ring B to generate the aldehyde functional group found in ircinal A (**26**) [Fig-2] and hence the beta-carboline unit in **25**. In their synthesis, the reaction of allylic alcohol **27** with triethyl orthoacetate and 2,4-dinitrophenol resulted in the rearranged ester **28**. Then enolate alkylation of the rearrange ester **28** produced a diastereomeric mixture of **29a** and **29b** (*dr* 1:1). After separation, the desired isomer **29b** was transformed into the key aldehyde **30** in 7 steps. Then stereoselective intramolecular dipolar cycloaddition of an azomethine ylide, obtained from the reaction of aldehyde **30** with glycine ester provided the desired tricyclic ABC core structure with protected hydroxymethyl group to access the beta-carboline unit in manzamine (**25**) and the required aldehyde group in ircinal A (**26**) (**Scheme 5**).



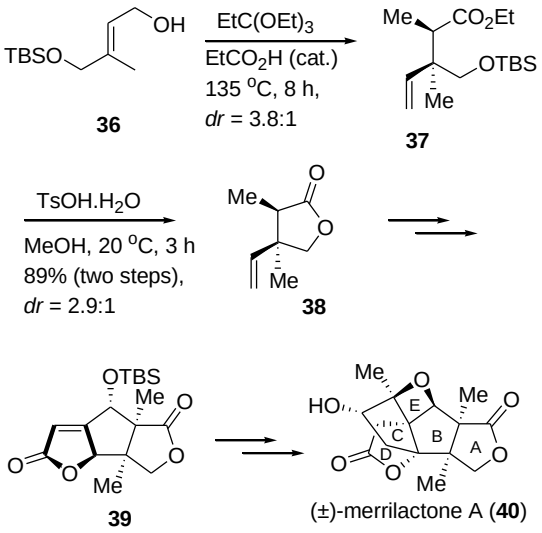
Scheme 5 Synthesis of the ABC tricyclic core of manzamine A (25) and ircinal A (26).

Johnson-Claisen rearrangement has the potential to construct quaternary carbon centres with regiospecific allylic transposition from allylic alcohol precursors. Srikrishna et al. [24] have utilized the Johnson-Claisen rearrangement strategy for the enantiospecific synthesis of a sesquiterpene triquinane **35** [25]. In the reaction sequence the chiral allyl alcohol **33** was prepared from campholenaldehyde **32** through rhodium carbenoid CH insertion [26] reaction. Then **33** was heated in presence of triethyl orthoacetate and propaonic acid ($C_2H_5CO_2H$) to give the rearranged ester **34**, having quaternary carbon atom with required chirality in 84% yield. Ester **34** was further transformed into angular triquinane **35** (**Scheme 6**).



Scheme 6 Enantiospecific synthesis of triquinane (35).

Zhai et al.[27] have applied the Johnson-Claisen rearrangement reaction in the total synthesis of (±)-merrilactone A (**40**), [28] a complex cage-shaped pentacyclic sesquiterpene. Their synthesis began with the Johnson-Claisen rearrangement of primary allylic alcohol **36** in triethyl orthopropionate and propaonic acid at 135 °C to afford the ester **37** (*dr* = 3.8:1) having quaternary chiral carbon centre, which after desilylation followed by lactonization afforded the lactone **38** having required chiral centre at A ring. The lactone **38** was then elaborated to the tricyclic compound **39** and finally transformed into (±)-merrilactone A (**40**), by the application of intramolecular Pauson-Khand reaction, [29] Mukaiyama-Michael[30] and SmI_2-induced reductive carbonyl-alkene coupling reaction [31] (**Scheme 7**).



Scheme 7 Total synthesis of merrilactone A (40)

Tong et al. [32] have utilized Johnson-Claisen rearrangement to stereoselectively install of all-carbon quaternary stereocentre in (+)-*ent*-psoracorylifol C (*ent*-**43**). Psoracorylifol A-C **41-43** [Fig-3] were isolated from the seeds of *Psoralea corylifolia* L, they have shown significant antimicrobial activity *in vitro* as potent inhibitors against two strains of *Helicobacter pylori* (ATCC 43504 and SSI) [33].

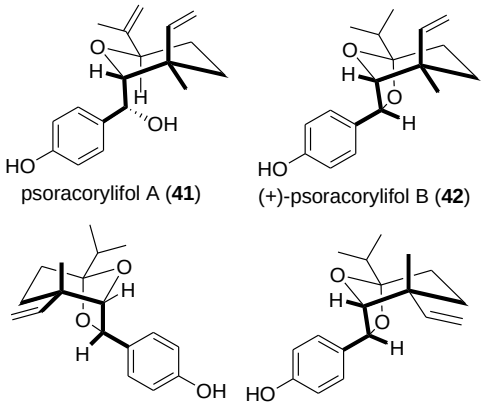
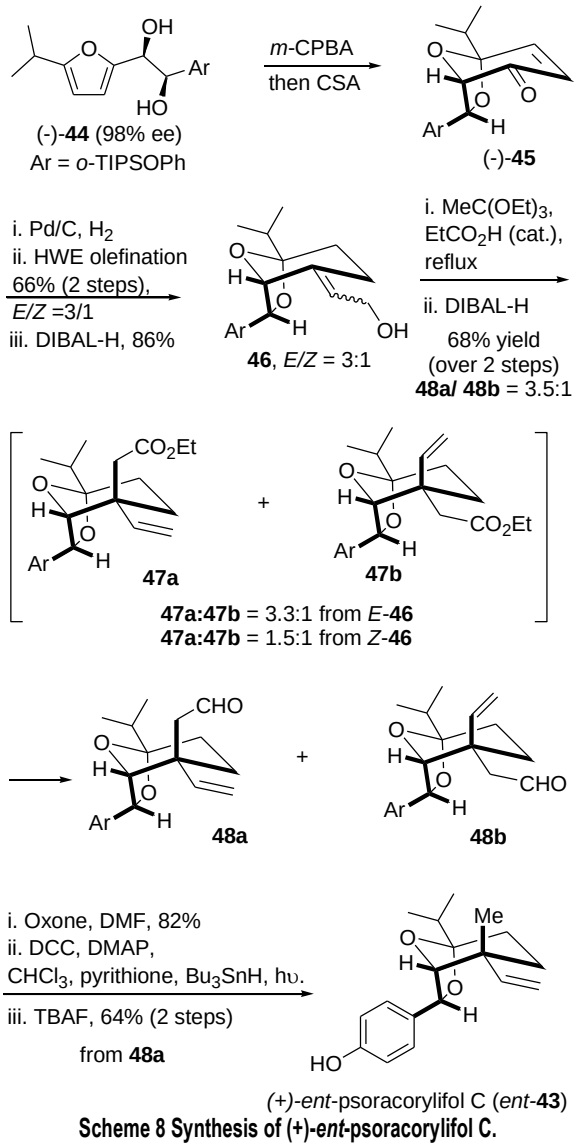


Fig-3 Structures of psoracorylifol A-C.

In their reaction sequence the 6,8-dioxobicyclo [3.2.1] octane part **45** was constructed by Achmatowich rearrangement/ bicycloketalization of **44**, which was in turn prepared from 5-bromo-2-furaldehyde. Then **45** was converted in 3 steps into primary allylic alcohol **46** as separable *E*/*Z* (3/1) mixture. The primary allylic alcohol *E*/*Z*-**46** was employed to Johnson-Claisen rearrangement condition using catalytic amount of propionic acid in triethyl orthoacetate under reflux and subsequent DIBAL-H-mediated reduction of the rearranged γ,δ-unsaturated ester **47** produced a diastereomeric mixture of aldehyde **48a** and **48b** (3.5:1). In this study, the Johnson-Claisen rearrangement was found non-stereospecific and for this reason, the *E*/*Z* mixture of **46** was used for the subsequent transformation. The Claisen rearrangement of pure *E*-**46** gave 3.3:1 diastereomeric mixture of **47a** and **47b**; whereas the pure *Z*-**46** gave that in 1.5:1 ratio. Then oxidation of **48a**, followed by Barton's reductive decarboxylation [34] and finally desilylation furnished (+)-psoracorylifol C (*ent*-**43**) as a single diastereomer in 4.3% overall yield in 16 steps (**Scheme 8**).

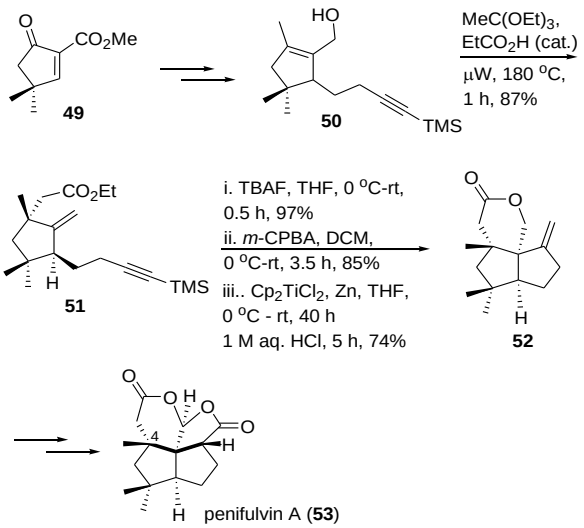


Scheme 8 Synthesis of (+)-*ent*-psoracorylifol C.

Chakraborty et al. [35] have applied the ortoester Johnson-Claisen rearrangement for the installation of the C-4 quaternary carbon centre of penifulvin A (**53**), an architecturally challenging sesquiterpenoid. It was isolated from *Penicillium griseofulvum* and found to have insecticidal activity.[36] In their synthesis, the enone **49** was transformed into the primary allyl alcohol **50**, which was subjected to microwave assisted Johnson-Claisen rearrangement protocol to furnish γ,δ-unsaturated ester **51**. The relative stereochemistry observed in **51** was due to the steric crowding offered by the alkynyl chain, which directed the [3,3]-sigmatropic rearrangement from the less sterically hindered face of the double bond. The rearranged γ,δ-unsaturated ester **51** was converted into **52**, in 3 steps involving TMS deprotection, epoxidation and Ti(III)-mediated reductive epoxide opening [37] -cyclization [38]. Then **52** was elaborated to penifulvin A (**53**) by Lewis acid catalyzed epoxy-aldehyde rearrangement followed by substrate controlled oxidative cascade lactonization process to complete the total synthesis in 12 steps with 16% overall yield (**Scheme 9**).

Xie et al.[39] have utilized the Johnson-Claisen rearrangement to accomplish the total synthesis of (±)-przewalskin B (**62**), having a tetracyclic skeleton with a spirocyclic enone system containing α-hydroxy-β-ketone lactone part. Przewalskin B was isolated from *S. przewalskii Maxim*,[40a] a medicinal plant used for treating cardiovascular diseases [40b]. The key steps in their synthetic sequence involves

Diels–Alder reaction to make the A ring, Johnson-Claisen rearrangement to construct the spiro-quaternary carbon center and RCM of a sterically crowded diene to generate the cyclic enone part. Their synthesis began with the Diels-Alder reaction of **54** derived in 3 steps from 2-cyclohexenone, to get the aldehyde **55**.

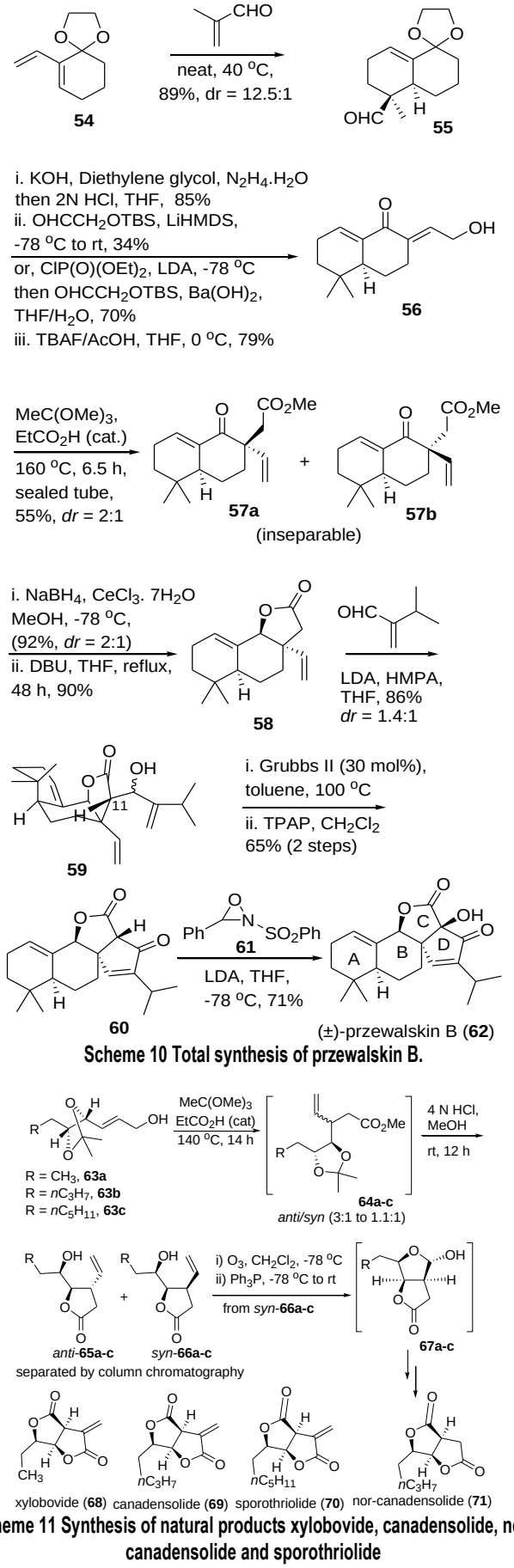


Scheme 9 Synthesis of penifulvin A (53).

The aldehyde **55** was converted into the key allylic alcohol **56**, which under Johnson-Claisen rearrangement condition in trimethyl orthoacetate and catalytic amount of propanoic acid gave esters **57a** and **57b** (*dr* = 2:1) as an inseparable mixture. However, here diastereoselectivity could not be improved due to the slight steric difference between the α- and β-faces of **56**. Then the reduction of ketone part in **57** under Luche condition afforded the desired γ-hydroxy ester in 92% yield (*dr* = 2:1, from 61%:31% yield), which upon treatment with 1,8-diazabicyclo-[5.4.0] undec-7-ene (DBU), the major *syn*-isomer was only transformed into lactone **58**. Aldol reaction of **58** with an unsaturated aldehyde produced diastereomeric mixture of *syn*-diene **59** (*dr* = 1.4:1), which under RCM reaction followed by tetrapropyl ammonium perruthenate (TPAP)-mediated oxidation afforded the β-ketoester **60** and the success of RCM reaction here confirmed the stereochemistry at C-11. Finally, the α-hydroxy group was installed with required chirality using Davis oxaziridine [41] **61** to give (±)-przewalskin B (**62**) (**Scheme 10**).

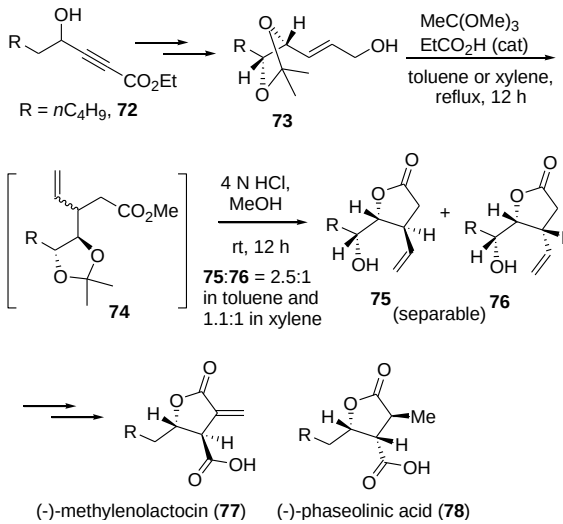
Fernandes et al. [42] have done study on the orthoester Johnson-Claisen rearrangement of allylic alcohols having acetonide protected diols, which provide an excellent platform for the generation of separable diastereomers (*syn/anti*) through lactonization. The required primary allyl alcohol **63a**, prepared from corresponding the alkene by Sharpless asymmetric dihydroxylation, [43] was treated under orthoester Johnson-Claisen rearrangement condition with excess trimethyl orthoacetate and catalytic amount of propaonic acid in refluxing xylene to give a diastereomeric mixture of γ,δ-unsaturated esters **64a** (*anti:syn* = 1.1:1). The acetonide group deprotection followed by lactonization afforded two separable diastereomeric lactones *anti*-**65a** and *syn*-**66a** in 46% and 42% yields, respectively. Similarly, allylic alcohol **63b** resulted in the separable lactones **65b** and **66b**; and **63c** also gave separable lactones **65c** and **66c** respectively. Oxidative cleavage of the β-vinyl group and subsequent lactonization of the *syn*-lactones **66a-c** were employed in the synthesis of natural products **68-71**. Lactones **66a** and **66c** were utilized to prepare xylobovide (**68**) and (-)-sporothriolide (**70**) respectively. Lactone **66b** afforded both (-)-nor-canadensolide (**69**) and (-)-canadensolide (**71**) (**Scheme 11**).

Fernandes et al. [44] have disclosed the synthesis of natural products (–)-methylenolactocin [45a] and (–)-phaseolinic acid, [45b] exploring a stereodivergent approach utilizing both diastereomeric lactones (**75** and **76**) obtained from Johnson-Claisen rearrangement of an acetonide protected diol containing primary allylic alcohol **73**. The hydroxy alkynoate **72**, was transformed into allylic alcohol **73**, which under Johnson-Claisen rearrangement condition (to give **74**) followed by deprotection of the acetonide functionality and subsequent lactonization resulted in a diastereomeric mixture of lactones **75** and **76** (*dr* 2.5:1 in toluene and 1.1:1 in xylene). After separation, the *trans*-lactone **75** was elaborated to (–)-methylenolactocin (**77**), whereas the *cis*-lactone **76** was transformed into (–)-phaseolinic acid (**78**) (**Scheme 12**).

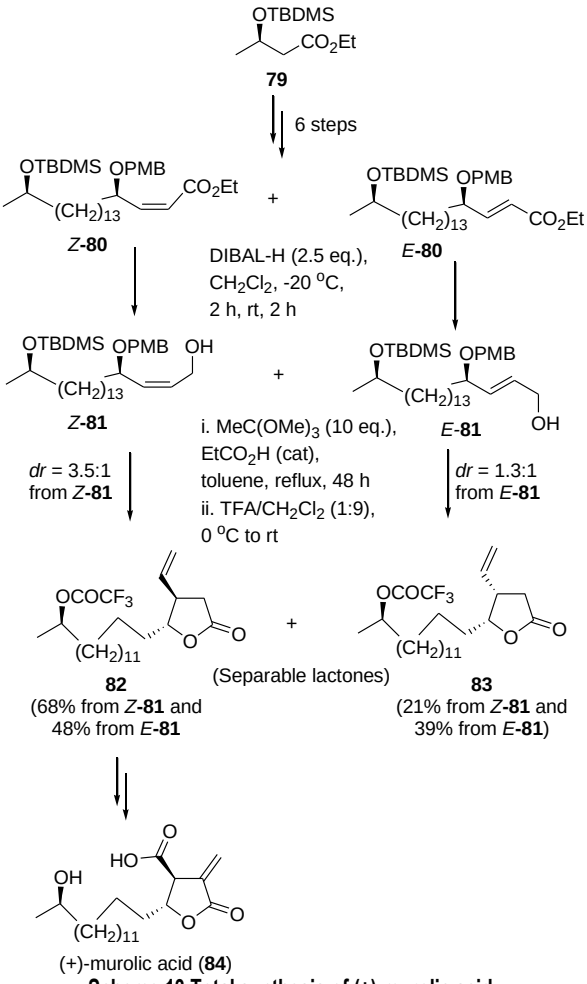


Scheme 10 Total synthesis of przewalskin B.

Scheme 11 Synthesis of natural products xylobovide, canadensolide, nor-canadensolide and sporothriolide



Scheme 12 Synthesis of (-)-methylenolactocin and (-)-phaseolinic acid.

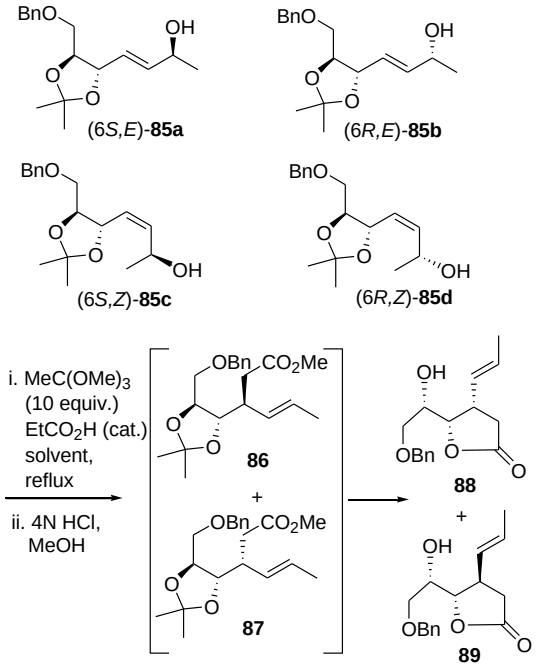


Scheme 13 Total synthesis of (+)-murolic acid.

Murolic acid (**84**) belongs to the paraconic acids family,[46] and constitute a small class of variously functionalized chiral γ-lactones. They were isolated from different species of *moss*, *lichens*, *fungi* and cultures of *Penicillium* sp. [47] and show various pharmacological proprerties including antibacterial, antifungal, antitumor and growth-regulating effects [48]. Fernandes et al. successfully utilized the Johnson-Claisen rearrangement in first total synthesis of **84** [49]. In their synthesis, the ester **79** was converted in 6 steps into the α,β-unsaturated esters **80**, which were reduced to get the key primary allyl alcohols *E*-**81** and *Z*-**81**. Johnson-Claisen rearrangement of allyl alcohol *Z*-**81** with $MeC(OMe)_3$ and catalytic propionic acid in refluxing toluene and subsequent acid mediated one-pot debenzylation-lactonization cascade using trifluoroacetic acid gave separable lactones *anti*-**82** and *syn*-**83** as a diastereomeric mixture in 3.5:1 ratio, however lower diastereoselectivity (*anti*:*syn* = 1.3:1) was observed from *E*-**81**. Then oxidative cleavage of β-vinyl group into $-CO_2H$ group (via ozonolysis) followed by α-methylenation of major lactone **82** furnished the synthesis of (+)-murolic acid (**84**). Interestingly, the late stage β-epimerization of **83** also produced (+)-murolic acid **84** (**Scheme 13**).

Rearrangement of secondary allyl alcohols

Chiral secondary allyl alcohol is a potential substrate for 1,3-chirality transfer in Johnson-Claisen rearrangement. Fernandes et al. explored the strategy containing acetonide protected diol in orthoester Johnson-Claisen rearrangement also for the secondary allyl alcohols.



Scheme 14 Diastereoselective orthoester Claisen rearrangement of allylic alcohols 85a-d.

It was found that the chiral allyl alcohols ***85a-d*** offered good to excellent diastereoselectivity, and there the chirality at protected diol part, olefin geometry (*E*/*Z*), and reaction temperature together were found to control the diastereoselectivity (Scheme 14), [Table-1] [50,42f]. However, the racemic secondary allyl alcohol **85** was found to produce a 1:1 mixture of **86** and **87** [42g]. Orthoester Claisen rearrangement of chiral allyl alcohol (6*S*,*E*)-**85a** in benzene and subsequent acid catalyzed lactonization afforded **88** and **89** as a 4:1 diastereomeric mixture and diastereoselectivity gradually increased with rising reaction temperature [Table-1], and maximum selectivity was achieved in decalin (**88**/**89** = 9:1, [Table-1], entry 6). Similar trends in diastereoselectivity was also observed for (6*R*,*Z*)-**85d** and gave mixture of **88**/**89** in 5:1 ratio in benzene, and increased up to 10:1 in decalin. Whereas, allyl alcohol (6*R*,*E*)-**85b** and (6*S*,*Z*)-**85c** offered opposite trends in diastereoselectivity. (6*R*,*E*)-**85b** gave a diastereomeric mixture of **88**/**89** in 1:8 ratio in benzene and ratio gradually decreased till 1:4 decalin, on rising temperature. For, (6*S*,*Z*)-**85c** mixture of **88**/**89** was obtained in a 1:16 ratio in benzene, and that gradually decreased up to 1:5 in decalin [Table-1].

Table-1 *Claisen rearrangement of allyl alcohols 85a-d.*

Entry	Time (h)	Yield (%)	88:99 from 85a	88:99 from 85d	88:99 from 85b	88:99 from 85c
1[a]	60	81	4:1	5:1	1:8	1:16
2[b]	24	82	5:1	6:1	1:6	1:8
3[c]	12	85	6:1	7:1	1:6	1:7.5
4[d]	4	90	7:1	9:1	1:5	1:6
5[e]	2	80	7:1	9:1	1:4	1:5
6[f]	1	80	9:1	10:1	1:4	1:5

[a]Reaction in benzene, [b]in $MeC(OMe)_3$, [c]in toluene, [d]inxylene, [e]in mesitylene, [f]in decalin.

Here the observed diastereoselectivity could be rationalized by considering the non-bonded interaction to give chair like lowest-energy transition states. Transition states **A** [from **85a**] and **B** [from **85d**] should be favored due to the presence of smallest number of nonbonding interactions, and both of them produce the product **88** as major diastereomer through lactonization of the intermediate ester **86**. Similarly, **85b** and **85c** yield **89** as the major diastereomer [Fig-4]. Thus, along with alkene geometry (*E*/*Z*), the acetonide part present outside the pericyclic chair like transition state influences the stereoselectivity. The increase in diastereoselectivity for **85a** with rising reaction temperature might be due to the formation of the thermodynamically favored product (**88**) at higher temperature, whereas the decrease in diastereoselectivity for **85b** might be due to the formation of the kinetically favored product (**89**) at lower temperature.

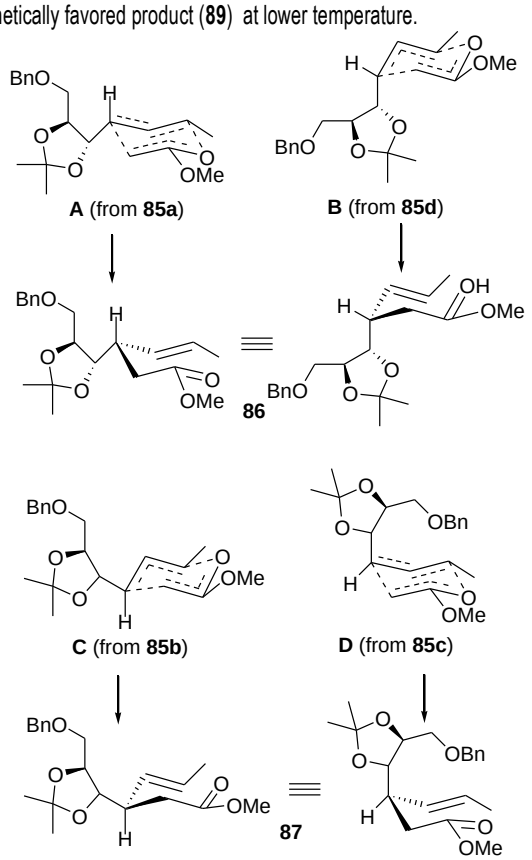
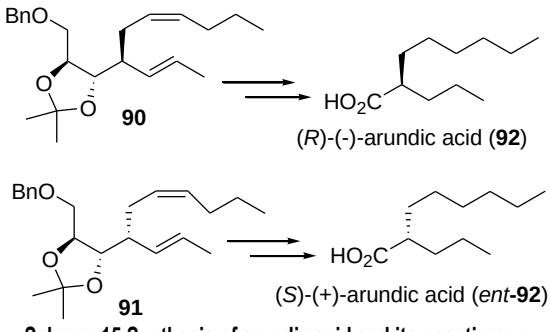


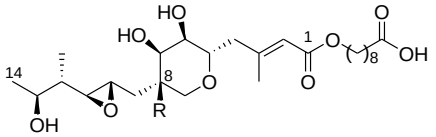
Fig-4 Rationale of diastereoselectivity for the rearrangement of 85a-d.

This development in Johnson-Claisen rearrangement has been applied in the stereoselective synthesis of the two enantiomers of arundic acid **92**, [50] potential therapeutic agent for Alzheimer's and Perkinson's disease. [51] The diastereomeric mixture of γ,δ-unsaturated ester **86**/**87** obtained from **85a** [Table-1], entry-6) or from **85b** [Table-1], entry-1) were elaborated to two separable diastereomeric dienes **90** and **91**, through DIBAL-H reduction followed by Wittig olefination. Compound **90** was isolated from the reaction mixture of **85a** (via **86**/**87** = 9:1) and compound **91** was collected from the reaction mixture of **85b** (via **86**/**87** = 1:8). Diene **90** and **91** were separately transformed into (*R*)-(-)- arundic acid (**92**) and (*S*)-(+)- arundic acid (*ent*-**92**) (**Scheme 15**).

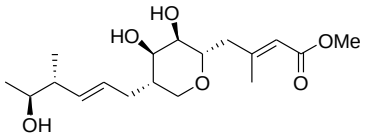


Scheme 15 Synthesis of arundic acid and its enantiomer.

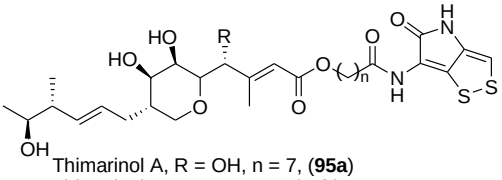
Srihari et al. [52] have disclosed a stereoselective route to access the common C1–C14 skeleton present in natural products of the pseudomonic acid family [Fig-5]. Pseudomonic acids are isolated from the bacterium *Pseudomonas fluorescens* NCIB 10586 species, [53] and are found to act as inhibitors of Gram-positive bacteria and mycoplasmal pathogens.



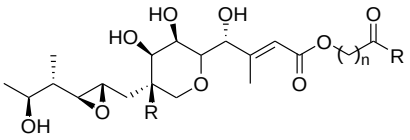
Pseudomonic acid A, R = H, (**93a**)
Pseudomonic acid B, R = OH, (**93b**)
Pseudomonic acid C, R = H, C10/C11 *E*-alkene (**93c**)



Pseudomonic acid methyl monate C (**94**)



Thimarinol A, R = OH, n = 7, (**95a**)
Thimarinol C, R = H, n = 7, (**95b**)
Thimarinol D, R = H, n = 7, Me at C-14 (**95c**)
Thimarinol E, R = OH, n = 9, (**95d**)
Thimarinol F, R = OH, n = 7, keto on C-13 (**95e**)

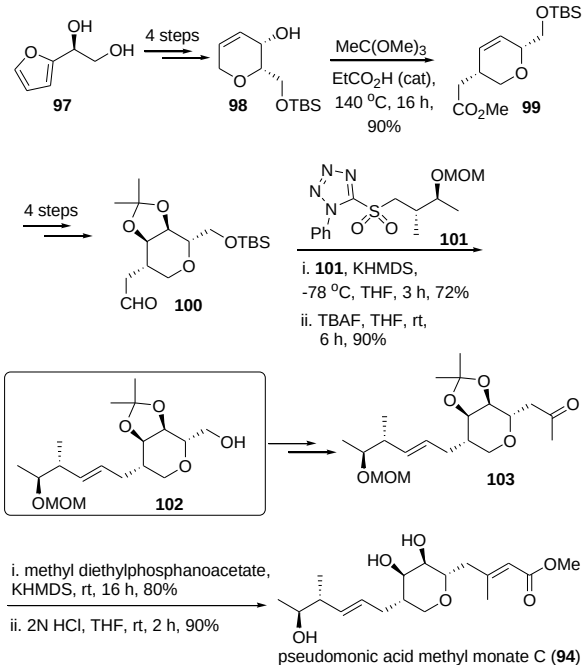


Marinolic acid A, R = OH, n = 7 (**96a**)
Marinolic amide, R = NH_2, n = 7 (**96b**)
Marinolic acid A_6, R = OH, n = 5 (**96c**)
Marinolic acid A_4, R = OH, n = 3 (**96d**)

Fig-5 Structures of pseudomonic acids, thimarinols and marinolic acids.

Their synthetic sequence involved Achmatowicz rearrangement, Johnson–Claisen rearrangement, Julia–Kocienski olefination, and Horner–Wadsworth–Emmons olefination as the key reactions. The chiral furyl alcohol **97** was converted into the chiral allylic alcohol **98** in four steps utilizing Achmatowicz reaction [54a]. The chiral secondary allyl alcohol **98** was treated under standard Johnson–Claisen rearrangement condition to give the ester **99** with 1,3-chirality transfer. Then, substrate controlled dihydroxylation [54b] and subsequent acetonide protection of resulting diol followed by reduction of ester and subsequent oxidation of the alcohol afforded the aldehyde **100** in good yield. *E*-Selective Julia-Kocienski oleination[54c] of **100** with sulfone **101** and subsequent TBS deprotection gave the key alkene **102**, containing the central tetrahydropyran ring attached with the side chain having required stereochemistry, and **102** is potential precursor of psedomonic acids **A**-**C** and thimarinols **A**, **C**, **E**-**F** and marinolic acids [Fig-5]. Compound **102** was elaborated to ketone **103**, which upon HWE olefination followed by acid catalyzed deprotection of acetonide and methoxy methyl (MOM) group furnished the total synthesis of pseudomonic acid methyl monate C (**94**) (**Scheme 16**).

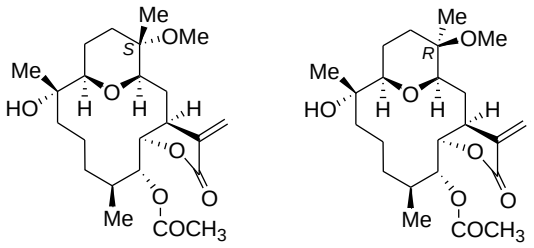
Recently, Tong et al. [55] have utilized the Johnson-Claisen rearrangement in the first asymmetric total synthesis of the proposed structure [56d] of (+)-uprolide G acetate (UGA) **112a** and structural revision of (+)-UGA. UGA belongs to the marine natural products isolated from marine soft corals and gorgonians, and display a wide array of biological activities. [56] The synthesis began with the preparation of enantiomerically pure furfuryl alcohol (+)-**105**, derived from the aldehyde **104** in 5 -



Scheme 16 Total synthesis of pseudomonic acid methyl monate C.

steps. Achmatowicz rearrangement of (+)-**105** produced the dihydropyranone acetal (+)-**106**, which was subsequently reduced under Kishi reduction [57] (BF_3-Et_2O/Et_3SiH) condition and palladium-catalyzed chemoselective hydrogenation to provide the 2,6-*cis*-dihydropyranone (+)-**107**. Then in 20 steps (+)-**107** was converted to the chiral secondary allyl alcohol (+)-**108**. The diastereoselective Johnson-Claisen rearrangement of (+)-**108** in ethyl orthoacetate with a catalytic amount of propionic acid provided the key γ,δ-unsaturated ester (+)-**110** with exclusive diastereoselectivity, which might arise from a putative chair like six membered cyclic transition state **109**. Then Sharpless asymmetric dihydroxylation [43] of (+)-**110** accompanied by concomitant lactonization, followed by and another 7 steps sequence resulted in the diene (+)-**111**. Diene **111** under ring-closing metathesis and subsequent double bond reduction produced the desired 14-member cembrane skeleton, then α-methylenation and subsequent acid catalyzed deprotection of both the TES and MOM groups and regioselective acetylation furnished the total synthesis of (+)-UGA (**112a**) (**Scheme 17**). However, mismatching of NMR data of this synthetic (+)-UGA (**112a**) with the reported natural UGA suggested that the proposed structure was incorrect.

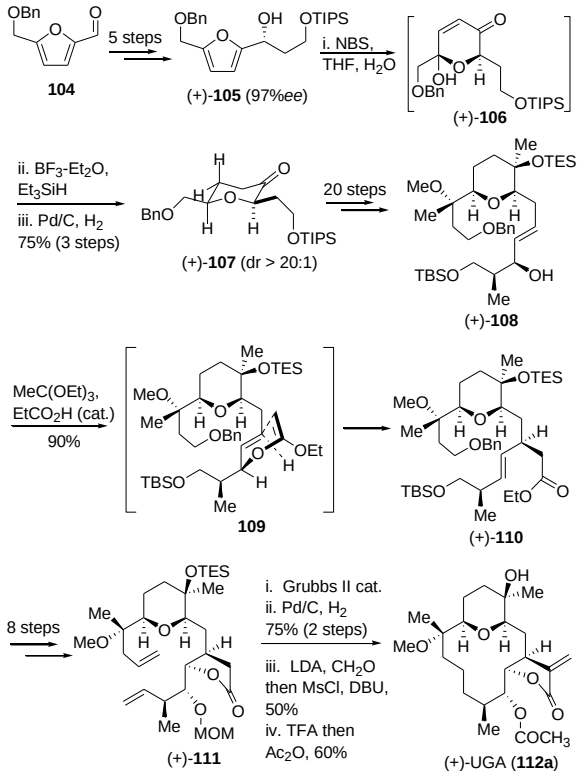
The author then done the total synthesis of both the other two possible structures of UGA, **112b** and **112c** using similar synthetic strategy. Then comparison of analytical data and optical rotation confirmed the absolute configuration of the natural UGA as **112b** [Fig-6].



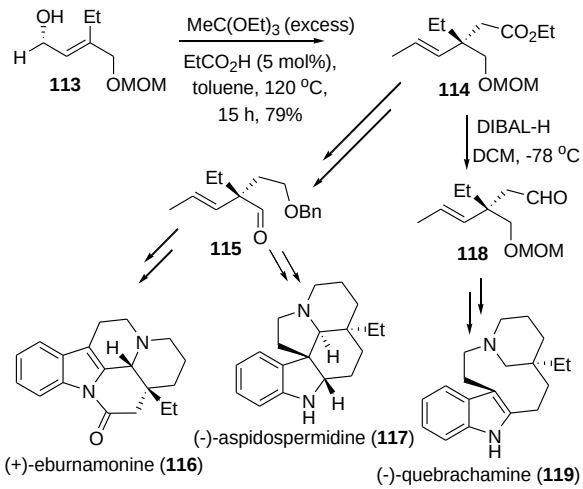
112b **112c**

Fig-6 Possible structures of UGA.

Construction of all carbon quaternary centres in stereoselective manner from allylic alcohols is a challenging task. Prasad et al. [58] have reported an enantiospecific total syntheses of the indole alkaloids (+)-eburnamonine (**116**), (–)-aspidospermidine (**117**) and (–)-quebrachamine (**119**) having all carbon quaternary center, based on Johnson–Claisen rearrangement. The secondary chiral allyl alcohol **113**, synthesized from ethyl (*S*)-lactate in four steps, was subjected to [3,3]-rearrangement under heating with triethyl orthoacetate and propanoic acid to give the desire chiral ester **114**, having chiral quaternary carbon atom via 1,3-chirality transfer. Ester **114** was then converted into aldehyde **115**, which was employed in Pictet–Spengler reaction [59] with tryptamine to prepare **116** and **117**. In another route, the ester **114** was reduced to aldehyde **118**, which was elaborated to **119** (**Scheme 18**).



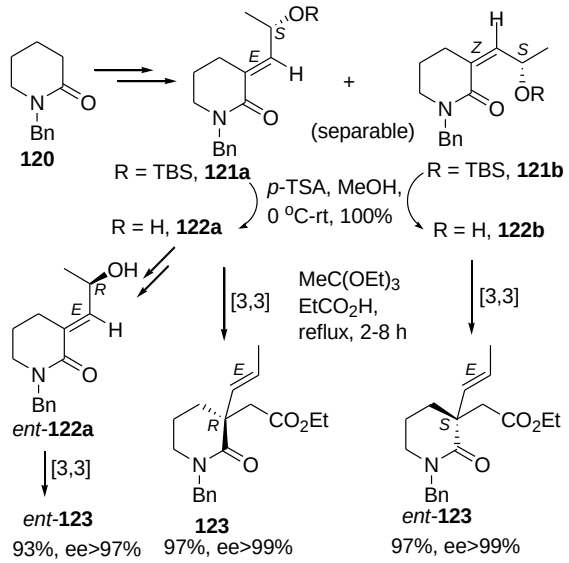
Scheme 17 First asymmetric total synthesis of the proposed structure of (+)-uprolide G acetate (UGA).



Scheme 18 Synthesis of (+)-eburnamonine, (-)-aspidospermidine and (-)-quebrachamine.

Recently, Pandey et al.[60] have developed a new route for the construction of diastereomerically enriched all carbon quaternary stereocenters at the C-3 position of cyclic lactams by Johnson-Claisen rearrangement of corresponding γ-hydroxy-α,β-unsaturated lactams. They observed that the stereochemical outcome in the rearrangement product depends on both the olefin geometry and –C-OH

configuration of the chiral secondary allyl alcohols. In their study, the TBS protected allyl alcohols **121a** and **121b** were prepared as a separable diastereomeric mixture from 1-benzylpiperidine-2-one (**120**), through Wittig-Horner olefination reaction of the corresponding phosphonate of **120** with –OTBS protected L-lactaldehyde. Then **121a** and **121b** under TBS deprotection gave the chiral allylic alcohols **122a** and **122b** respectively. The chiral allyl alcohols **122a** and **122b** were subjected to standard Johnson-Claisen rearrangement condition to afford quaternary carbon containing chiral ester **123** and opposite isomer *ent*-**123**, respectively with excellent yield and enantiomeric excess (*ee*). Also, the rearrangement of the inverted alcohol *ent*-**122a**, derived from **122a** by Mitsunobu's reaction gave the opposite isomer *ent*-**123** in >97% *ee* with 93% yield (**Scheme 19**).



Scheme 19 Diastereoselective Johnson-Claisen rearrangement of 122a-b.

The excellent diastereoselectivity could be explained with the help of proposed transition states **A2**-**C2** [Fig-7]. In **A2**, the suprafacial approach of the incoming –CH_2CO_2Et group makes the C3-C2 bond above the plane leading to the formation of **123**, whereas *ent*-**123** is formed by involving **B2**, where owing to Z-geometry of the olefinic bond, the C3-C4 bond is pushed above the plane by the –CH_2CO_2Et group. Furthermore, through **C2** it may be clearly visualized that suprafacial attack of the incoming group forces the C3-C2 bond below the plane for the formation of **123**.

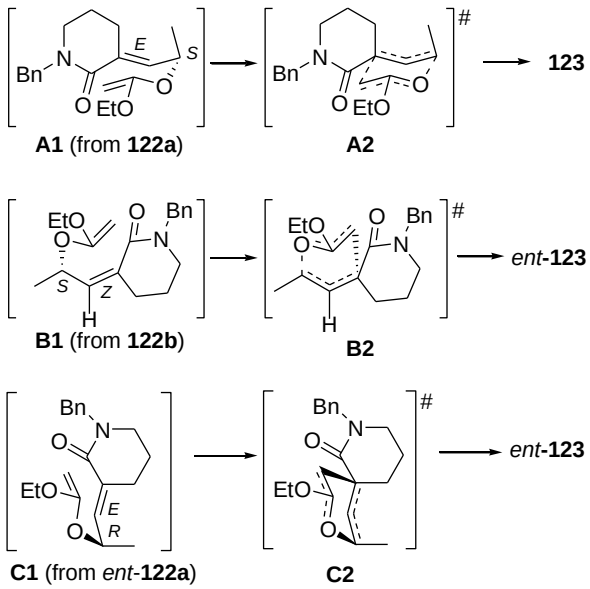
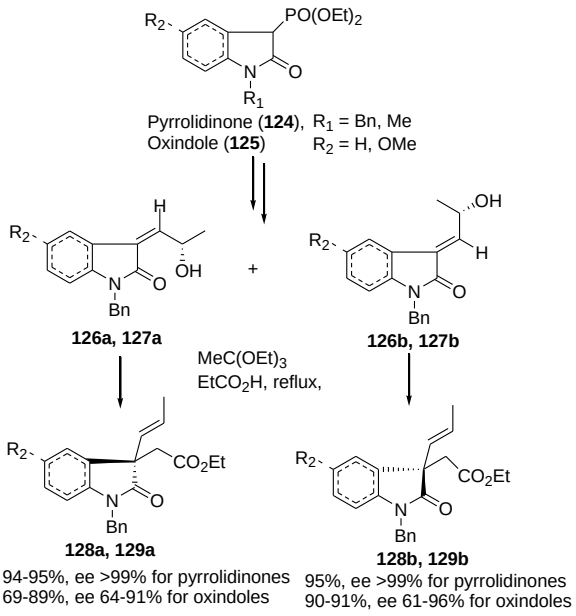


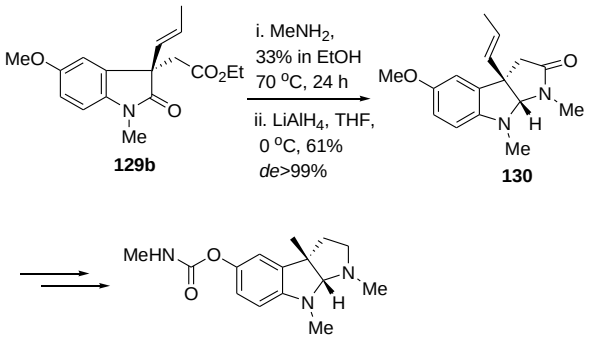
Fig-7 Transition states for [3,3]-sigmatropic rearrangements.

Similar results were also found for pyrrolidinone (**124**) and oxindole (**125**) (**Scheme 20**).



Scheme 20 Diastereoselective Johnson-Claisen rearrangement.

They explored this development in the total synthesis of (−)-physostigmine (**131**). Physostigmine was isolated from the *Physostigma venenosum*, [61a] and clinically used for the treatment of glaucoma, myasthenia gravis and Alzheimer's disease [61]. The rearranged ester **129b** was subjected to enamine formation reaction followed by reduction to give **130** and finally was transformed into (−)-physostigmine (**131**) in 11 linear steps and 4.5% overall yield (**Scheme 21**).

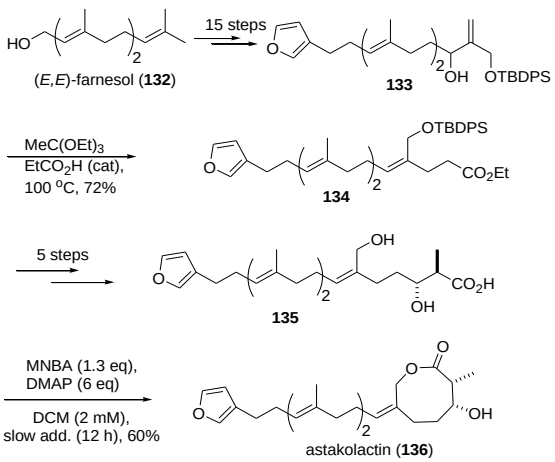


Scheme 21 Total synthesis of (-)-physostigmine.

Astakolactin (**136**), a novel sesterterpene metabolite was isolated from *Cacospongia scalaris,* the marine sponge collected from the gulf of Astakos in the Ionian Sea near Greece.[62] The first total synthesis of the proposed structure of astakolactin (**136**), has been performed utilizing the Johnson-Claisen rearrangement, asymmetric Mukaiyama aldol reaction and MNBA-mediated lactonization [63]. The required secondary allyl alcohol **133** was prepared from (*E*,*E*)-farnesol (**132**) in 15 steps. The alcohol **133** was then subjected to the standard Johnson orthoester-Claisen rearrangement condition to afford only the ester (*Z*)-**134** in 72% yield. The ester **134** was transformed into the desired seco-acid **135**, using the sequence of reactions involving DIBAL-H mediated reduction of ester group to give aldehyde and subsequent aldol reaction with ethyl acetate followed by diastereoselective methylation of the ester enolate as the key steps. Finally, MNBA (2-methyl-6-nitrobenzoic anhydride)-mediated lactonization of **135** afforded the targeted 8-member lactone to complete the total synthesis of **136** (**Scheme 22**).

Miuraenamides were isolated from myxobacteria, [64] belongs to a class of cyclodepsipeptides of the jaspalkinolide type and are found to display high

antitumor activity [65]. Recently, Kazmaier et al.[66] have disclosed the total synthesis of miuraenamide A (**137**), D (**138**) and E (**139**) [Fig-8].



Scheme 22 First total synthesis of the proposed structure of astakolatin.

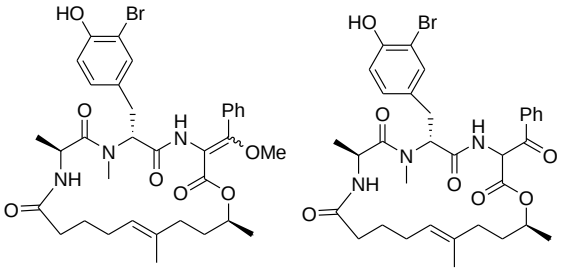
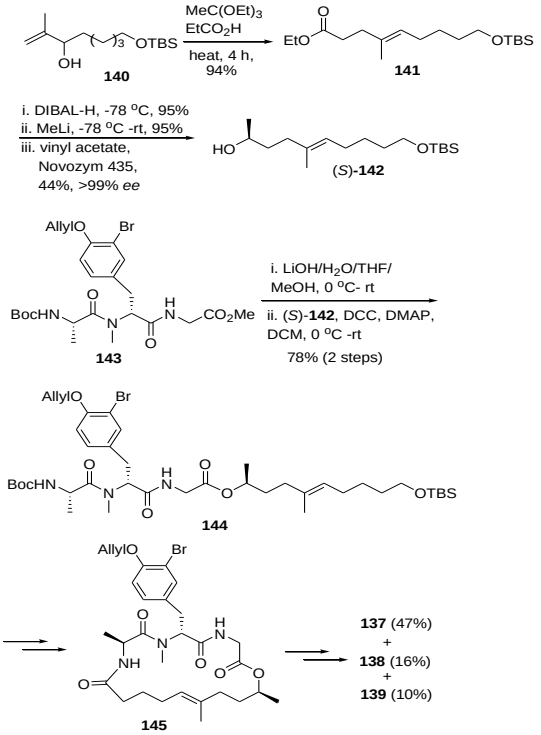


Fig-8 Structures of miuraenamide A, D and E.

The Johnson-Claisen rearrangement was chosen as the key reaction to prepare the required unsaturated ester **141**. In their synthesis, the allyl alcohol **140**, derived from the TBS protected 5-hydroxypentanal through addition of the Grignard reagent from 2-bromopropene. Allyl alcohol **140** under Johnson-Claisen rearrangement condition afforded the *E*-configured γ,δ-unsaturated ester **141** stereoselectively in excellent yield. Ester **141** was converted to the chiral alcohol (*S*)-**142** through reduction of ester to aldehyde using DIBAL-H and subsequent MeLi addition followed by enzymatic kinetic resolution of the resulting racemic alcohol using Novozym 435. Saponification of tripeptide containing ester **143** followed by esterification using (*S*)-**142** provided linear precursor **144**. After TBS deprotection of **144** and subsequent Jones oxidation resulted in the formation of an acid, which under macrolactamization afforded the desired macrocycle **145**. Macrolactam **145** was finally elaborated to miuraenamide A (**137**,47%), D (**138**, 16%) and E (**139**, 10%) which were separated by flash column chromatography (**Scheme 23**).

Naturally occurring and synthetic isoprenoid lactones are known for their broad variety of biological activities such as antifungal, [67a-b] antibacterial, [67c] antitumor [67d] and antifeedant behaviour [67e-f] activity. The Johnson-Claisen rearrangement has been utilized in the short and rapid access of racemic and enantiomeric pairs of halolactones having *p*-menthane system in two or three steps from *cis*- and *trans*-piperitols. The Johnson-Claisen rearrangement of *cis*-piperitols (-)-(3*S*, 4*R*)-**146a**, (+)-(3*R*, 4*S*)-**146b** and *rac*-**146c** produced the γ,δ-unsaturated esters (-)-(1'*S*, 4'*R*)-**148a**, (+)-(1'*R*, 4'*S*)-**148b** and *rac*-**148c**, respectively with the *cis*-oriented carboethoxymethylene group in the relation to the isopropyl group. Then their hydrolysis to acid (-)-(1'*S*, 4'*R*)-**149a**, (+)-(1'*R*, 4'*S*)-**149b**, *rac*-**149c**, followed by lactonization under two different conditions using I_2/KI/$NaHCO_3$ condition and Br_2/$NaHCO_3$ afforded the iodolactones (-)-(1*S*, 4*R*, 5*R*, 6*R*)-**150a** (*ee* 97%), (+)-(1*R*, 4*S*, 5*S*, 6*S*)-**150b** (*ee* 96%), *rac*-**150c** and bromolactone (-)-(1*S*, 4*R*, 5*R*, 6*R*)-**151a** (*ee* 97%), (+)-(1*R*, 4*S*, 5*S*, 6*S*)-**151b** (*ee* 91%), *rac*-**151c**, respectively with high enantiomeric excess for chiral lactones. Similarly, *trans*-piperitols (-)-(3*S*, 4*R*)-**152a**, (+)-(3*R*, 4*R*)-**152b** and *rac*-**152c** were rearranged to **154a-c** and the hydrolysis followed by halolactonization afforded iodolactones (+)-(1*S*, 4*S*, 5*R*, 6*R*)-**156a** (*ee* 96%), (-)-(1*R*, 4*R*, 5*S*, 6*S*)-**156b** (*ee* 94%), *rac*-**156c** and bromolactones (+)-(1*S*, 4*S*, 5*R*, 6*R*)-**157a** (*ee* 94%), (-)-(1*R*, 4*R*, 5*S*, 6*S*)-**157b** (*ee* 96%), *rac*-**157c**, respectively with high enantiomeric excess for chiral lactones. The esters **154a-c** were also transformed into chlorolactones (-)-(1*S*, 4*S*, 5*R*, 6*R*)-**158a** (*ee* 91%), (+)-(1*R*, 4*R*, 5*S*, 6*S*)-**158b** (*ee* 96%), *rac*-**157c**, using NCS/THF/H_2O. However, the NBS, NIS treatment on ester **148a-c**, **154a-c** and NCS treatment on **148a-c** produced inseparable mixture of compounds (**Scheme 24**) [68].



Scheme 23 Synthesis of miuraenamide A, D and E.

Lactones bearing aromatic ring are found to show diverse biological activities, like analgesic and anti-inflammatory, anticancer, antiparasitic, antimicrobial, insecticidal, antibacterial, antifungal, anti-HIV, antiplatelet, antiestrogenic activity and anticonvulsant activity connected with stimulation of GABAA receptors [69]. Recently, Gladkowski et al. [70] have utilized the Johnson-Claisen rearrangement in the stereoselective preparation of chiral δ-iodo-γ-lactones **159-160** and γ-iodo-δ-lactones **161** [Fig-9] in both enentiomeric forms from enantiomerically enriched allyl alcohols (-)-**162** and (+)-**162** with efficient 1,3-chirality transfer.

The starting enantiomerically enriched allyl alcohols (-)-**162** and (+)-**162** (*ee* 88-99%) were obtained through lipase-catalyzed transesterification of racemic allyl alcohol **162**. Chiral allyl alcohols (-)-**162** and (+)-**162** were separately heated with triethylorthoacetate and propionic acid to afford chiral ester (+)-**164** and (-)-**164** respectively. The high stereoselectivity of this rearrangement led to retention of (*E*)-configuration of the double bond as well as with complete 1,3-chirality transfer. Their hydrolysis followed by iodolactonization of acids afforded six new enantiomeric pairs of iodolactones **159**, **160** and **161** with excellent stereoselectivity (*ee* 97-99%) (**Scheme 25**).

Here the stereochemical outcome in the Johnson-Claisen rearrangement relies on the configuration of the olefin part and the chirality of allyl alcohol **162** as well as the conformation of the six-membered ring formed in the transition states, [17] such as conformations **A** and **B**. The [3,3] rearrangement through **A** retains the configuration of the double bond as well as configuration of the stereogenic centre, whereas **B** gives esters with the opposite configurations of both the double bond and stereogenic centre. However, here the rearrangement passes through the involvement of energetically favored conformer **A**, because of the lack of 1,3-diaxial interaction between the ethoxy group and the methyl substituent, which occur in conformer **B** [Fig-10].

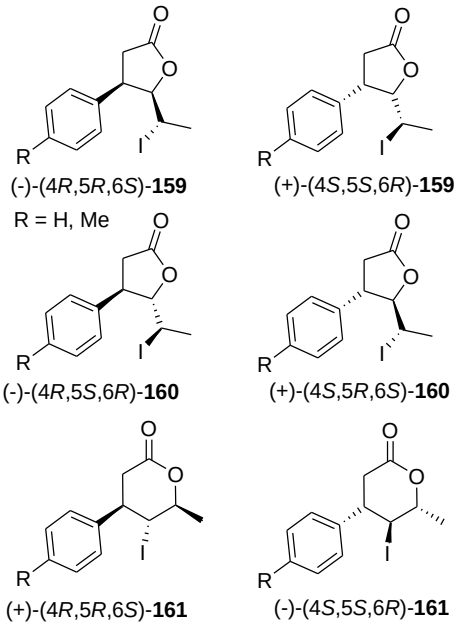
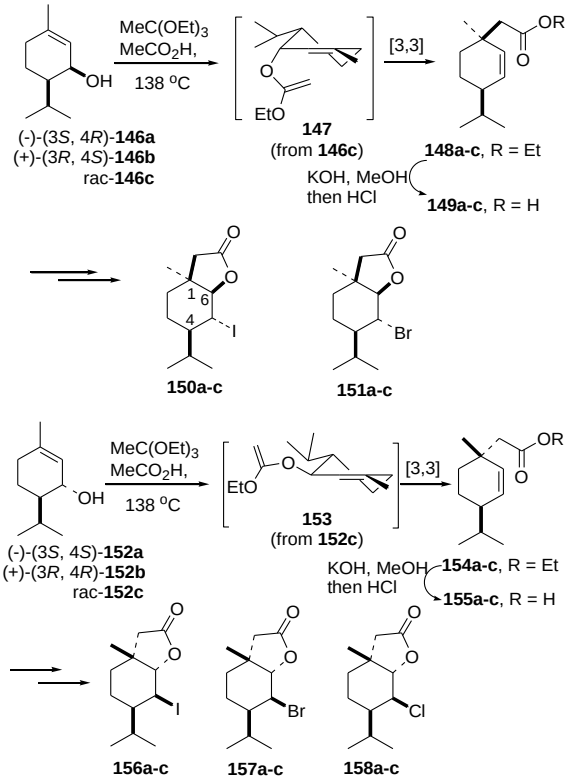


Fig-9 Structures of δ-iodo-γ-lactones and γ-iodo-δ-lactones.



Scheme 24 Application of diastereoselective Johnson-Claisen rearrangement in the synthesis of halolactones.

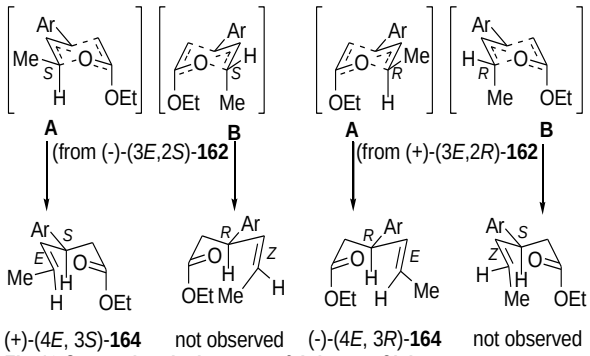
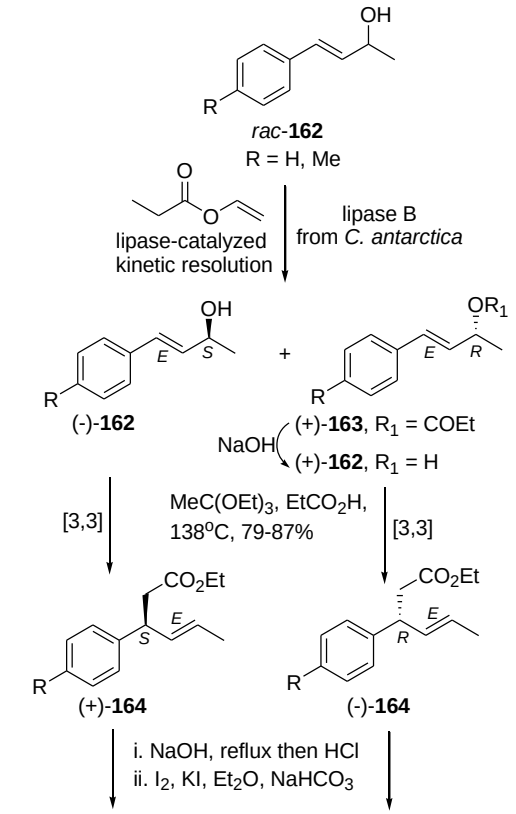


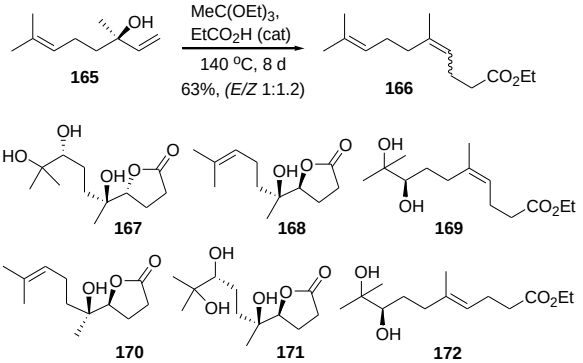
Fig-10 Stereochemical course of Johnson-Claisen rearrangement.



Scheme 25 Synthesis of enantiomeric pairs of iodolactones 162-164.

Rearrangement of tertiary allyl alcohols

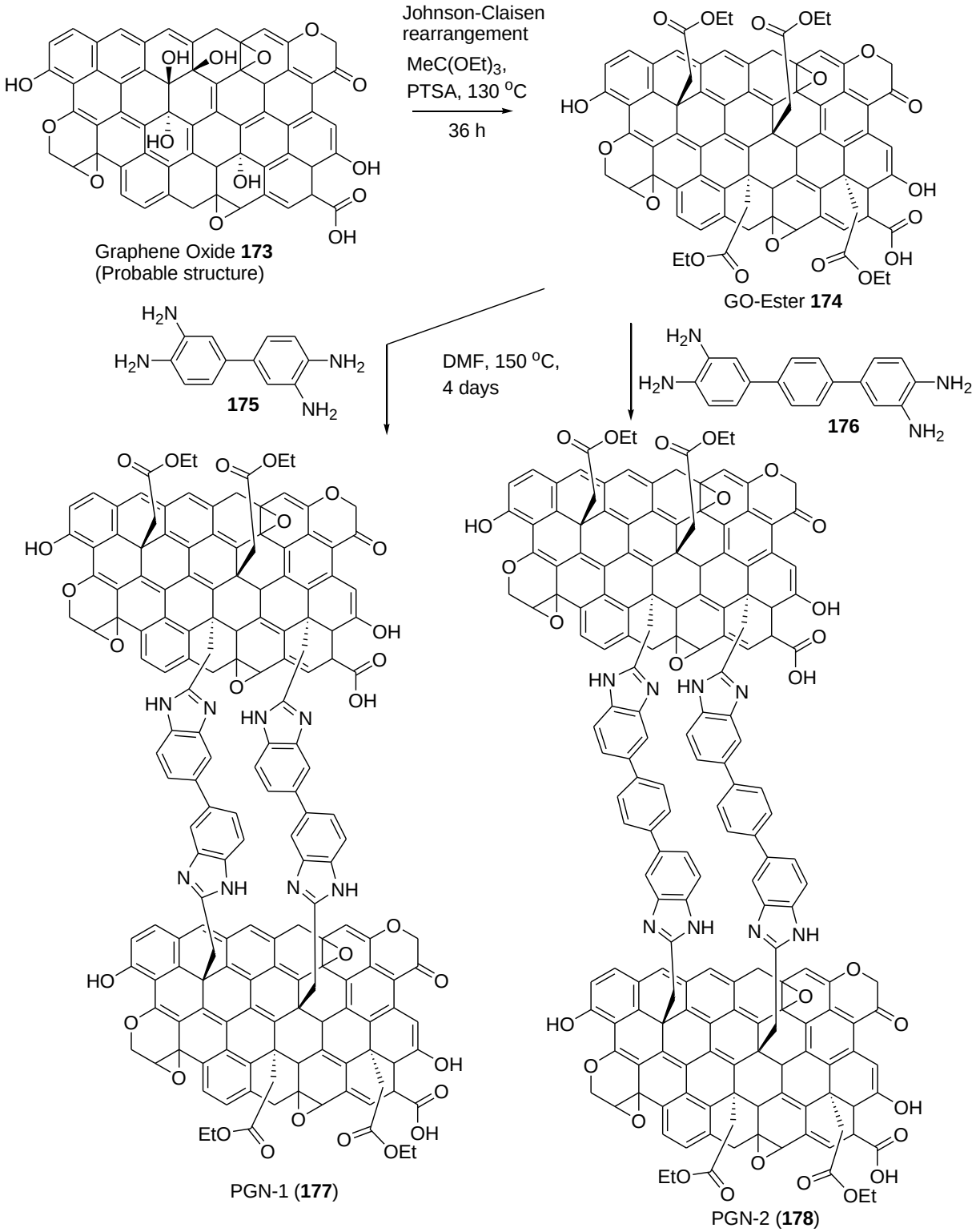
Tertiary allyl alcohols are also used in Johnson-Claisen rearrangement to access the γ,δ-unsaturated esters toward the synthesis of valuable compounds having important biological activities [71]. δ-Hydroxy-γ-lactones are structural unit of different natural products and they are also valuable synthetic precursors to access important building blocks. Many of them are familiar for their fragrance properties. Bombarda et al. [72] have utilized the Johnson-Claisen rearrangement for the preparation of δ-hydroxy-γ-lactones **167-168** and **170-171**. The chiral tertiary allyl alcohol (–)-linalool (**165**), under Johnson-Claisen rearrangement gave a mixture of separable γ,δ-unsaturated ester *Z*-**166** and *E*-**166** in 1:1.2 ratio. The Sharpless asymmetric dihydroxylation [48] on *Z*-**166** gave polydroxylated lactone **167** (15%) and γ-lactone **168** (2%) along with predominant formation of 8,9-dihydroxy compound **169** (65%). Similarly, ester *E*-**166** was converted to **170** (10%) and **171** (31%) and **172** (44%) (**Scheme 26**).



Scheme 26 Preparation of δ-hydroxyl- γ-lactones.

Application of Johnson-Claisen rearrangement has also been extended in the field of material science to access chemically modified valuable materials. Recently, research on chemically modified graphenes are growing day by day due to their

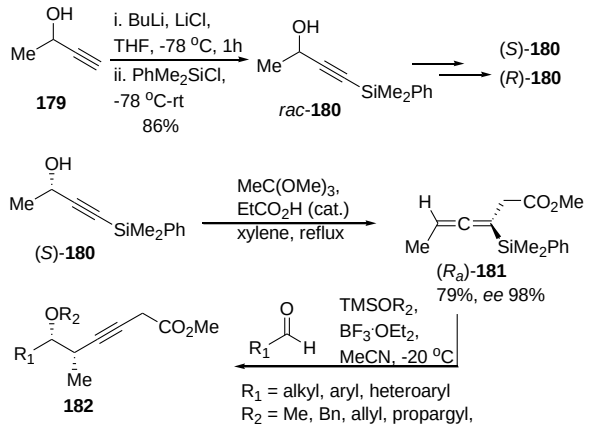
diverse applications in materials science [73]. The chemical modifications of graphene oxide (GO) **173** using its carboxylic acid, alcohol, and epoxide functional groups have been extensively studied. Swager and Sydlik [74] noticed that most of the hydroxyl groups in graphene oxide are allylic alcohols, which might be employed in the Johnson-Claisen rearrangement. Upon heating the graphene oxide **173** with triethyl orthoacetate and catalytic amount of *p*-toluenesulfonic acid (PTSA), it was converted into the rearranged GO-ester **174**, also known as Claisen graphene. The ester functional groups in **174** offer easy transformations to carboxylic acids, acid derivatives, and various heterocyclic compounds, which have been successfully utilized to build layer-by-layer films [75]. Recently, Sond and Coskun [76] have explored the Johnson-Claisen rearrangement on GO **173** in the synthesis of porous graphene network (PGNs). After the successful synthesis of GO-Ester **174** through Johnson-Claisen rearrangement [74] of **173**, it was subjected in the condensation reaction with 3,3',4,4'-tetraaminobiphenyl (**175**) and 3,3',4,4'-tetraaminoterphenyl (**176**) to form PGN-1 (**177**) and PGN-2) (**178**) respectively, through the formation of benzimidazole moieties (**Scheme 27**). These PGNs exhibited high surface areas up to 732 m^2g^{-1} and showed the highest CO_2 uptake capacity (3.75 $mmolg^{-1}$ at 273 K, 1 bar) along with a remarkable CO_2/N_2 selectivity (130 at 273 K, 1 bar) of all the **GO** and graphene frameworks reported to date. These applications emphasize the importance of the Johnson-Claisen rearrangement for the covalent functionalization of graphene layers through C-C bond formation.



Scheme 27 Synthesis of porous graphene networks (PGNs) by Johnson-Claisen rearrangement

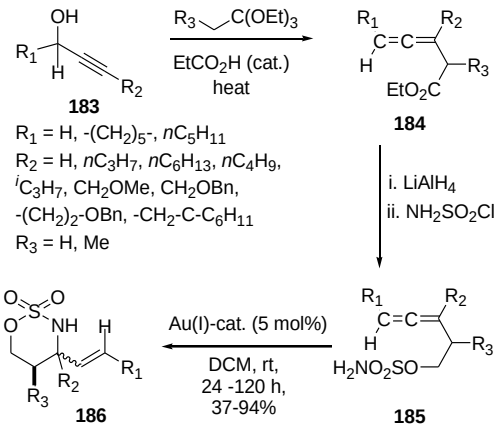
Rearrangement of propargyl alcohols

The Johnson-Claisen rearrangement has also been explored on propargyl alcohols to access synthetically important allene intermediates, which can serve as carbon nucleophiles [77] and have significant applications in synthesis involving cycloaddition, [78] cyclization, [79] addition and cross coupling[80] reactions. Panek et al. [77] have disclosed a convenient method for the preparation of enantio-enriched allenylsilanes **181** utilizing the Johnson-Claisen rearrangement of chiral 1-silylpropargylic alcohols **180**. The racemic propargyl alcohol-**180** was prepared through C-silylation of 3-butyn-2-ol (**179**) and then enentioenriched (*S*)-**180** and (*R*)-**180** were obtained by kinetic enzymetic resolution of *rac*-**180** with Amano lipase AK [81]. The individual (*R*)-**180** and (*S*)-**180** were separately treated with a catalytic amount of propionic acid in triethyl orthoacetate under refluxing xylene to afford the enantio-enriched allenylsilanes (S_a)-**181** (81% yield, *ee* 98%) and (R_a)-**181** (79% yield, *ee* 98%) respectively with excellent yield and enantioselectivity, while the use of toluene or other lower boiling hydrocarbon solvents resulted in lower conversion. The allenylsilane (R_a)-**181** was then used as carbon nucleophile in three-competent, Lewis acid-mediated addition to the *in situ* generated oxonium ions, resulting in enantio-enriched homopropargylic esters **182** (**Scheme 28**).



Scheme 28 Stereoselective Johnson-Claisen rearrangement of chiral 1-silylpropargyl alcohol to access chiral allene intermediate

Recently, Bebbington et al. [82] have utilized the Johnson-Claisen rearrangement towards the synthesis of cyclic sulfamidates, a versatile intermediate, used in the synthesis of substituted amines and its derivatives [83]. In their synthesis, the propargyl alcohols **183** were subjected to Johnson-Claisen rearrangement condition to get key allenic esters **184**, which were converted to allenic sulfamates **185**, through reduction of ester group to alcohol and subsequent sulfamoylation. Allenes **185** were then transformed into six-membere cyclic sulfamidates **186** in high yields by gold (I)-catalyzed ($Ph_3PAuNTf_2$) reaction (Scheme 29). This gold (I)-catalyzed cyclic sulfamidates formation cycloisomerisation reaction enables the construction of *N*-substituted quaternary centres.



Scheme 29 Stereoselective Johnson-Claisen rearrangement of propargylic alcohols toward the synthesis of cyclic sulfamidates.

Catalysis

Substituent effects on the rate of Claisen rearrangement have been studied, and the most impressive substituent-induced rate enhancement is observed for the 4-cyano-substituted allyl vinyl ether, which leads to a 270-fold rate enhancement, with respect to an un-substituted allyl vinyl ether [Fig-11] [84].

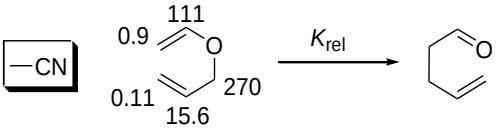
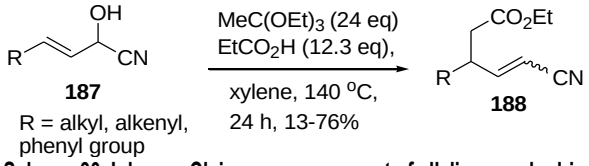


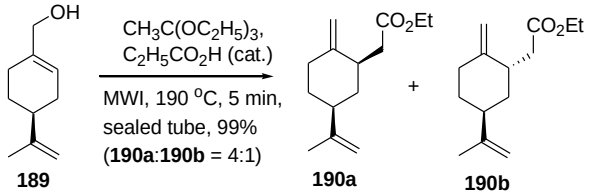
Fig-11 Effect of substituent on the rate in oxy-Claisen rearrangement

However, Johnson-Claisen rearrangement fails for allylic cyanohydrin **187** under conventional condition due to the thermal decomposition. Later, Cosgrove and McGeary have developed a modified condition to perform the rearrangement of allylic alcohols **187**, which were prepared by the TMSCN addition to the corresponding α,β-unsaturated aldehydes followed by treatment with 5% HCl at room temperature. Rearrangement of allylic cyanohydrin **187** at 140 °C with triethyl orthoacetate and excess propanoic acid afforded δ-ethoxycarbonyl-α,β-unsaturated nitriles **188** in good yields with moderate *E/Z* selectivity. Here this modified condition using excess propanoic acid drastically slowed the rate of cyanohydrin decomposition (**Scheme 30**) [85].



Scheme 30 Johnson-Claisen rearrangement of allylic cyanohydrin

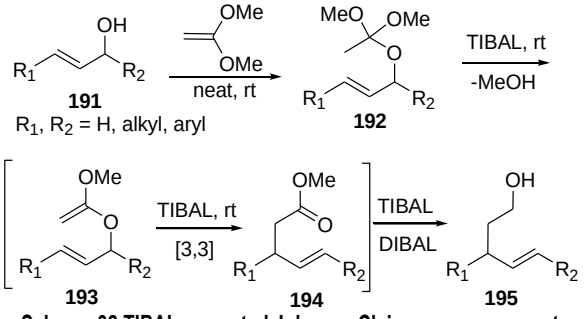
The effectiveness of Johnson-Claisen rearrangement can be attributed to the execution of multiple steps in a one-pot procedure and is catalyzed by weak acids (like $MeCO_2H$, $EtCO_2H$ etc). However, the major limitations associated with the standard condition of this rearrangement is the requirement of high reaction temperatures (140-200 °C), excess acid catalyst and long reaction times (12-120 h), which may not always be compatible with sensitive substrates. Hence, the development of methodologies for milder reaction conditions has been investigated. Microwave irradiation is found to assist the Johnson-Claisen rearrangement, [35] and excellent rate acceleration associated with yield improvements have been achieved for the rearrangements of cyclohexenol and propargyl alcohol under microwave conditions in ortho-acetate with prpanoic acid catalyst[86a] where the rearrangements were completed within 15 min, in good to excellent yields (78-100%), whereas, the conventional heating method required longer times (12 h) and gave lower yields (53-68%). Microwave assisted Johnson-Claisen rearrangement condition was further modified by using catalytic amount of propionic acid in absence of solvent [86b] to rearrange the monoterpenols - perillyl alcohol (**189**). Allylic alcohol **189** was rearranged to their corresponding *γ,δ*-unsaturated esters **190a** and **190b** (*dr* 4:1) with excellent yield within 5 min however at elevated temperature (**Scheme 31**).



Scheme 31 Microwave assisted Johnson-Claisen rearrangement

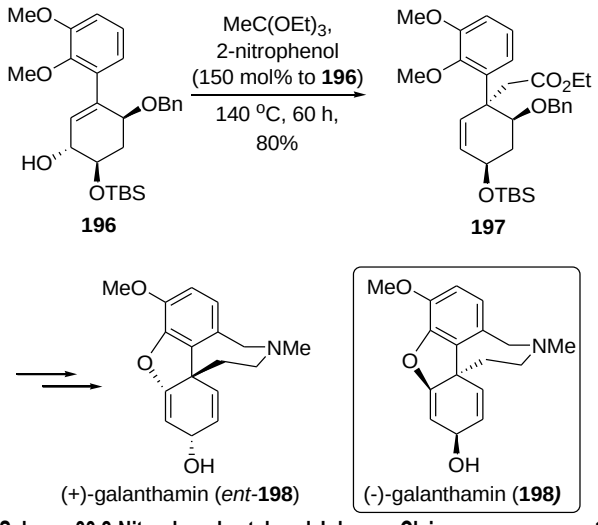
Cosgrove and McGeary have identified the Lewis acidic reagent, triisobutylaluminium (TIBAL) to promote Johnson-Claisen rearrangement at room temperature. The mixed orthoesters **192**, derived from allyl alcohols **191** and 1,1-dimehoxyethene were subjected to TIBAL catalyzed [3,3]-rearrangement to give *γ,δ*-unsaturated esters **194**, which were subsequently reduced (*in situ*) to

unsaturated alcohols **195** with good *E/Z* selectivity, in a one-pot fashion at room temperature (**Scheme 32**). Although the substrates containing reducible functional group like aldehyde was incompatible under this condition, however an additional double bond, aromatic methyl ether, vinyl bromide, benzyl ether were compatible [87].



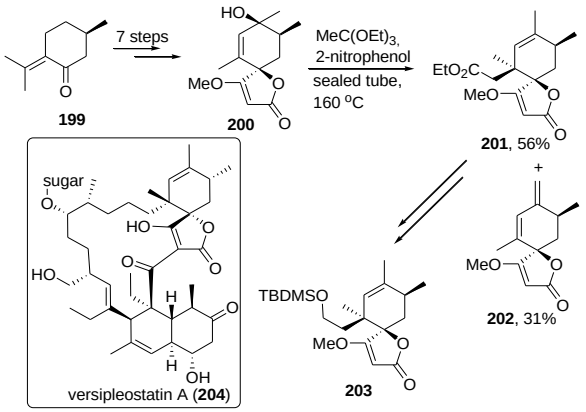
Scheme 32 TIBAL promoted Johnson-Claisen rearrangement

Commonly, propanoic acid or propionic acid ($C_2H_5CO_2H$) is used to catalyze the orthoester Johnson-Claisen rearrangement. However, for acid sensitive substrate nitrophenols are found as good alternative. [23,88-89a] Compare to propanoic acid (P_{Ka} 4.62), 2-nitrophenol (P_{Ka} 7.04) is weaker acidic reagent and the later is supposed to suppress the substrate's decomposition, but can catalyze the formation of the ketene acetal in Johnson-Claisen rearrangement. Chida et al.[89a] have explored the 2-nitrophenol catalyzed Johnson-Claisen rearrangement in the stereoselective total synthesis (+)-galanthamin (*ent*-**198**), enantiomer of the natural product (-)-galanthamin (**198**). (-)-Galanthamin (**198**) was isolated from some species of the *Amaryllidacea family*, [90] and found to be a centerally acting acetylcholinesterase inhibitor[91a-b] and an allosteric modulator of the neuronal nicotinic receptor for acetylcholine [91c]. In their synthesis the chiral secondary allyl alcohol **196**, derive from D-glucose, [89b] was subjected to the Johnson-Claisen rearrangement under heating in triethyl orthoacetate in presence of 2-nitrophenol to afford the chiral ester **197** with 1,3-chirality transfer in 80% yield. Whereas, the use of propionic acid resulted in very poor yield (less than 25%) associated with unidentified by-products formation. The poor yield was due to the acid sensitivity and the steric congestion at the reaction centre caused by the presence of the *o*-methoxy substituent of **196**. Then ester **197** was elaborated to (+)-galanthamin (*ent*-**198**) (**Scheme 33**). Here, the chiral quaternary carbon was created via 1,3-chirality transfer in Johnson-Claisen rearrangement.



Scheme 33 2-Nitrophenol catalyzed Johnson-Claisen rearrangement

Katsuta et al. [92] have disclosed the preparation of the spirotetronoate unit **203** of versipelostatin A (**204**), employing 2-nitrophenol catalyzed Johnson-Claisen rearrangement of chiral allylic alcohol **200**. Versipelostatin A was isolated from *Streptomyces versipellis* and has been identified as a specific down regulator of GRP78 gene expression [93]. In their synthesis, the allylic alcohol **200**, obtained from pulegone (**199**), was heated with triethyl orthoacetate and catalytic 2-nitrophenol to get the rearrangement product **201**, along with the formation of undesired dehydration product **202**. However, the application other conditions employing propionic acid catalyst or microwave irradiation produced **201** only in poor yields. Ester **201** was elaborated to **203**, as the opposite enantiomer in **204** (**Scheme 34**).



Scheme 34 2-Nitrophenol catalyzed Johnson-Claisen rearrangement in the preparation of the spirotetronate unit 203

To address and overcome the acid sensitivity of different substrates, alternative methods for the generation of allyl vinyl ether via DBU-mediated [94a-b] elimination of benzene seleninic acid from the mixed acetal and triethyl amine-mediated hydrobromic acid elimination from bromoacetals were developed [94c]. Recently, Tokuyama et al. [95] have disclosed the asymmetric total synthesis of (-)-isoschizogamine (**205**), featuring the installation of the quaternary carbon center by the modified Johnson-Claisen rearrangement in basic media. Isoschizogamine (**205**), isoschizogaline (**206**), and their congeners (**207**, **208a-c**) are belong to schizozygane alkaloids, isolated from *Schizozygia caffaeoides* [Fig-12] and exhibit antimicrobial activity [96].

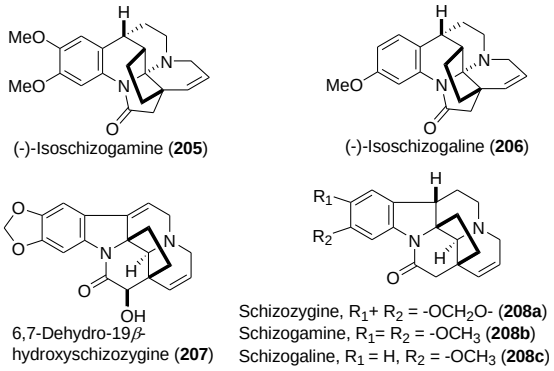
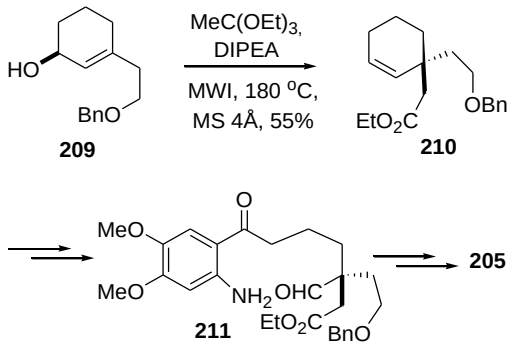


Fig-12 Structures of schizozygane alkaloids.

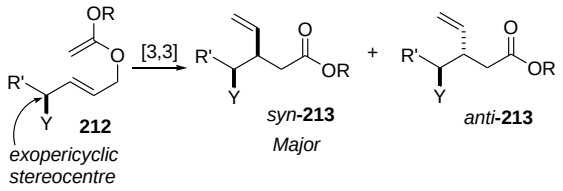
Their synthesis commenced with the enantioselective construction of the quaternary carbon center in **210** by the Johnson-Claisen rearrangement of **209**. After extensive investigation, they performed the rearrangement in presence of organic base diisopropylethylamine (DIPEA) and MS 4Å, where basic media suppressed the loss of optical purity. Whereas, conventional Johnson-Claisen rearrangement condition in the presence of weak acids resulted in a complex mixture of compounds and the use of MS 4Å in absence of base resulted lowering in optical purity. Thus, heating a Hunig's base solution of the reaction mixture in the presence of MS 4Å under microwave irradiation promoted the Johnson-Claisen rearrangement to produce the desired ester **210** in 55% yield without the loss of optical purity. The rearranged chiral ester **210** having the required quaternary carbon atom was elaborated to **211**, which was transformed into isoschizogamine (**205**) having that quaternary carbon atom (**Scheme 35**).



Scheme 35 DIPEA mediated Johnson-Claisen rearrangement

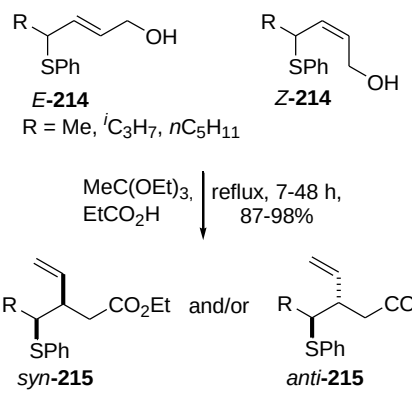
Exopericyclic stereocontrol

In Claisen rearrangement, high and predictable stereoselectivity is observed due to the involvement of six-membered cyclic transition state, and effect of the substituents within the pericyclic array has been studied comprehensively [1]. However, the effect of the configuration of exopericyclic substituents and stereocentres, [42f, 50] towards the stereochemistry of C–C bond formation during the [3,3]-sigmatropic rearrangement is comparatively less investigated. Scattered reports [97] in this rearrangement, indicate that high exopericyclic stereoselectivities can be achievable and stereoelectronic effects play a vital role in controlling the stereoselectivity. The Claisen rearrangement of ketene acetal **212**, having exo-pericyclic stereocentre bearing a heteroatom Y, is generally found to give the *syn*-213 as major product (**Scheme 36**). The formation of *syn*-213 has been explained by considering the favourable antiperiplanar alignment of the C–Y and incipient C–C bonds in the reactive conformation, with the allylic, exo-pericyclic C–H bond eclipsing the adjacent C=C bond [97-99].



Scheme 36 Exopericyclic stereoselectivity in *oxy*-Claisen rearrangement

Craig et al. [100] have studied on the exopericyclic stereocontroling effects on the stereoselectivity in the Johnson-Claisen rearrangements of thio-ether containing allylic alcohols **214**. The individual allyl alcohols *E*-**214** and *Z*-**214**, were separately treated under standard Johnson-Claisen rearrangement condition to give the γ,δ-unsaturated esters **215** as a diastereomeric mixture in good yields. It was observed that while the Johnson-Claisen rearrangement of *E*-**214** were completely unselective (*syn:anti* = 1:1 for R = -CH_3-$^nC_5H_{11}$, and 3:2 for R = -$^iC_3H_7$), the rearrangement of *Z*-**214** offered moderate to good diastereoselectivity favouring the product *syn*-**215** (*syn:anti* = 3:1 to 5:1) (**Scheme 37**).



dr 3:1 (*syn:anti*), from *Z*-**214**, R = Me, iC_3H_7
dr 5:1 (*syn:anti*), from *Z*-**214**, R = nC_5H_{11}

Scheme 37 Stereoselectivity in Johnson-Claisen rearrangement

Here the observed stereoselectivity has been rationalized by considering the diastereomeric transition states **A–D**, having the antiperiplanar alignment of the C6'–SPh and incipient C1–C6 bonds in all cases. For *Z*-**214**, the major product *syn*-**215** forms from an orientation in which the C6'–H bond (transition state **A**) rather than the C6'–R bond (transition state **B**) eclipses the allylic C4–C5 double bond. For *E*-**214**, the corresponding allylic 1,3-interactions are between the bonds C5–H and C6'–H (transition state **C**) leading to *syn*-**215** or C5-H and C6'–R (transition state **D**) leading to *anti*-**215** products; moreover the lesser steric bulk associated with C5–H compared to C4–C5 leads to lower selectivity for *E*-substrates [Fig-13].

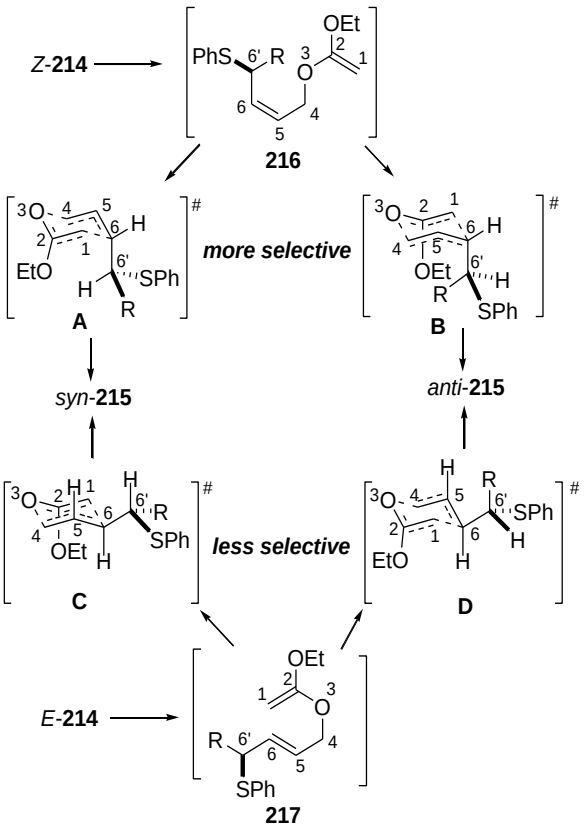


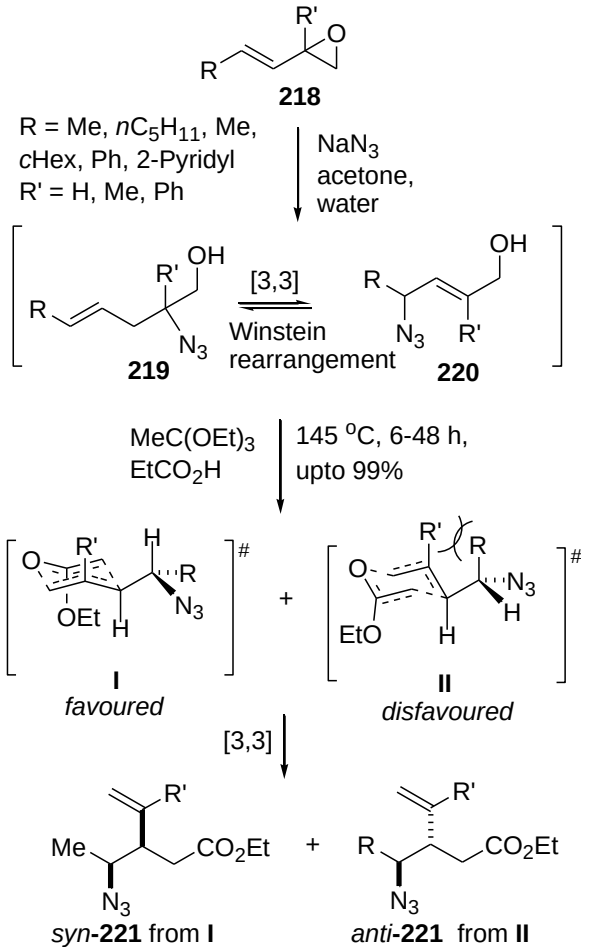
Fig-13 Rationale for stereoselectivity in Johnson-Claisen rearrangement of *E*-214 and *Z*-214

Later, they have studied [101] the Johnson-Claisen rearrangement on equilibrating mixture (due to Winstein rearrangement [102]) of allylic azide-containing allylic alcohols **220** to give unsaturated γ-azidoesters **221**. Allylic azido alcohol mixture of **219** and **220**, derived from vinylic oxiranes **218**, was treated with triethyl orthoacetate and sub-stiochiometric amount of propanoic acid at 145 °C to give unsaturated γ-azidoesters **221** with moderate *syn* stereosecectivity (**Scheme 38**). Selectivity for the 3,4-*syn* products **221** (where R'=Me), may result from unfavourable 1,3-diaxial interaction in the transition states leading to the 3,4-*anti* isomer. However, *Z*-allylic azides could isomerise to the more reactive *E*-isomer by [3,3]-sigmatropic rearrangement, and therefore it was considered that changing olefin geometry would not result in an increase stereoselectivity. However, it was anticipated that increased steric bulk at the terminal position of the ketene acetal would increase the diastereofacial selectivity of attack on the allylic moiety.

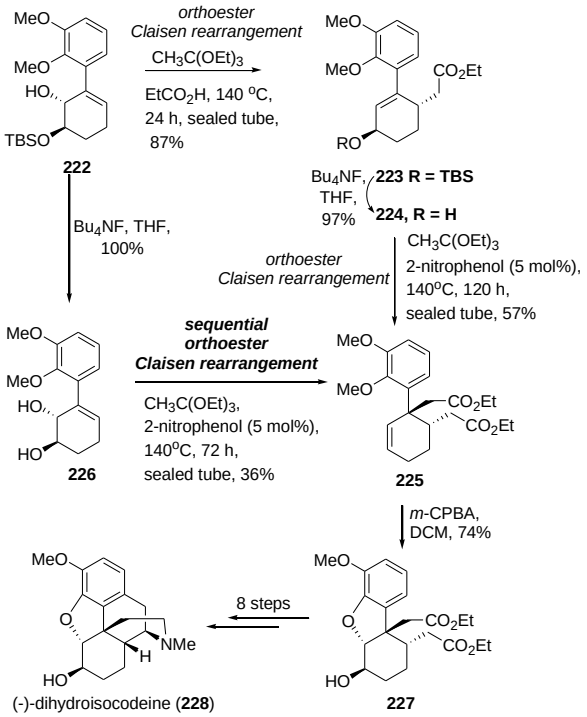
Sequential orthoester Johnson-Claisen rearrangement

Allylic vicinal diols having two hydroxyl groups at allylic and homoallylic positions are potential substrate for sequential Johnson-Claisen rearrangements, which may offer successive 1,3-chirality transfer [103]. Stereoselective synthesis of (-)-dihydroisocodeine **228**, the key intermediate in the synthesis of (-)-morphine, an analgesic, was done by the sequential orthoester Johnson-Claisen rearrangement of an allylic vicinal diol derivative **222**. First orthoester Claisen rearrangement of **222** furnished chiral ester **223**. Its TBS deprotection gave another allyl alcohol

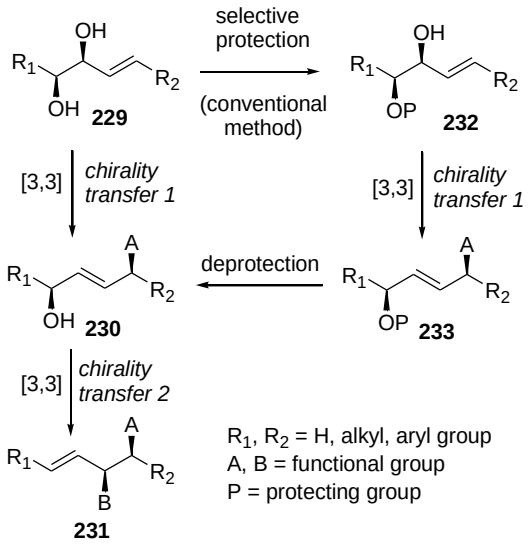
224, which underwent second orthoester Johnson-Claisen rearrangement to produce the chiral ester **225**. Alternatively, TBS deprotection of **222** gave the allylic vicinal diol **226** having two free hydroxyl group at allylic and homo-allylic position, which underwent sequential orthoster Johnson-Claisen rearrangement in presence of catalytic amount 2-nitrophenol in triethyl orthoacetate to give chiral ester **225** with successive 1,3-chirality transfer, which was then transformed into **227** and finally elaborated to **228**. Here, the vicinal tertiary and quaternary chiral carbon centres in **225** were stereoselectively generated in a one-step reaction by the cascade orthoester Claisen rearrangement (**Scheme 39**) [104].



Scheme 38 Origin of stereoselectivity in Johnson-Claisen rearrangement of 220.



Scheme 39 Application of sequential orthoester Claisen rearrangement towards the synthesis of (-)-dihydroisocodeine

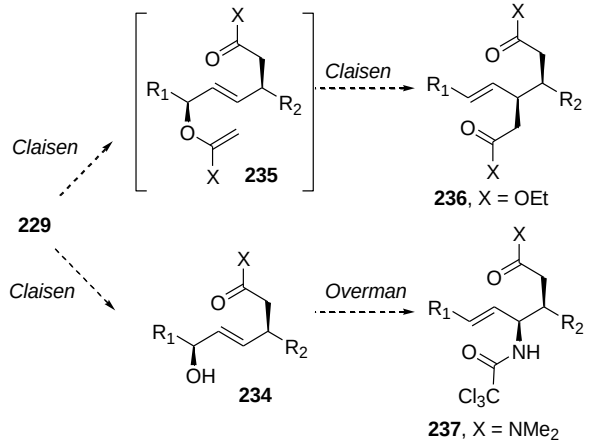


Scheme 40 Opportunity for successive 1,3-chirality transfer in sequential Johnson-Claisen rearrangement

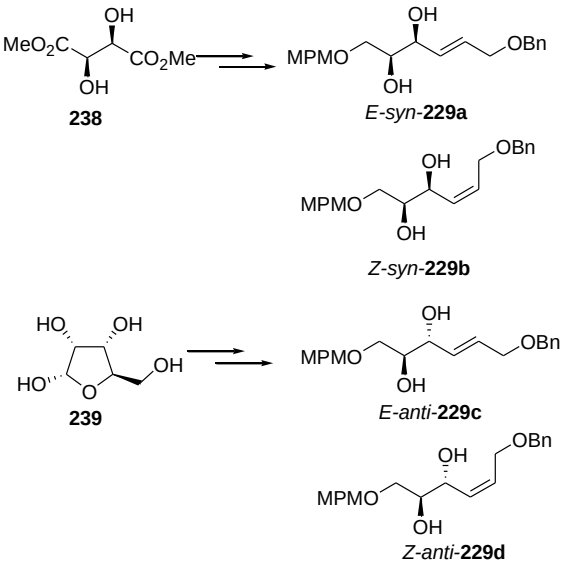
Similar to cyclic allylic vicinal diols, acyclic allylic vicinal diols **229** are also potential substrates for sequential orthoester Johnson-Claisen rearrangement and hence potentially enable for two successive 1,3-chirality transfer reactions. The transformation may be done in two ways: one is the execution of two successive chirality transfer through sequential [3,3]-rearrangements [105, 2g] from free diol **229** (**229→230→231**). Where the first chirality transfer in **229** offers the stereoselective installation of functional group **A**, associated with the transposition of the double bond to generate new allylic alcohol **230**, and **230** then undergo a second chirality transfer to install functional group **B**. And the another is the conventional way involving selective protection of the homoallylic alcohol **229** for performing first chirality transfer through [3,3]-rearrangement followed by deprotection of the rearrangement compound **233** to generate new allylic alcohol **230** for second chirality transfer through another [3,3]-rearrangement reaction (**229→232→233→230→231**), However, the more reactivity of the allylic hydroxyl group than the homoallylic hydroxyl group creates difficulty in its selective protection and also after the first chirality transfer reaction, an extra deprotection step is required (**Scheme 40**). Hence, the path without protecting group manipulations involving stereocontrolled chirality transfer using sequential [3,3]-rearrangements of **229** should be preferred.

Sato and Chida [106] have explored the scope of this path, involving stereocontrolled chirality transfer reactions using sequential Johnson-Claisen rearrangement of acyclic free allylic vicinal diols **229** without protecting group manipulation. The treatment of chiral allylic diol **229** under orthoester Claisen rearrangement condition would initiate the first [3,3] rearrangement to afford **235**, which could then instantly undergo the second orthoester Claisen rearrangement to give **236**. They have also studied the scope of competitive Claisen/Claisen rearrangement [107a] of **229** to install two identical functional groups (in **236**) and Claisen/Overman rearrangement to install two different functional groups (in **237**). The latter one (**229→234→237**) was inherently more challenging, because it requires the suppression of the second competitive Claisen rearrangement (**234→235→236**) (**Scheme 41**) [107].

They have studied the sequential [3,3]-rearrangements of many allylic diols including **229a-d**. Allylic diols **229a-b** were prepared from L-tartaric acid dimethyl ester (**238**) and allylic diols **229c-d** were derived from D-ribose (**239**) (**Scheme 42**).



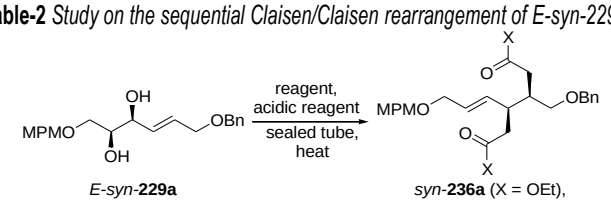
Scheme 41 Competitive sequential rearrangement and chirality transfer



Scheme 42 Preparation of allylic diols 229a-d.

The sequential Claisen/Claisen rearrangement of *E-syn*-**229a** under Johnson's condition with triethyl orthoacetate and catalytic propanoic acid at 140 °C produced the bis(ester) **236a** in 14% yield [Table-2], (entry 1). The nature of the acidic reagents [88] showed insignificant effect on the yield of **236a** [Table-2], (entries 2-3). Whereas sequential Claisen/Claisen rearrangement under Eschenmoser's condition employing an excess amount of $MeC(OMe)_2NMe_2$ at 180 °C [Table-2], (entry 4), proceed in stereoselective manner and gave the *syn*-bis (amide) **240a** in 87% yield, as a single diastereomer. Hence, execution of sequential orthoester Johnson-Claisen rearrangement to afford the final rearrangement product in good yield is still a challenging task and demands further study.

Table-2 *Study on the sequential Claisen/Claisen rearrangement of E-syn-229a.*[a]

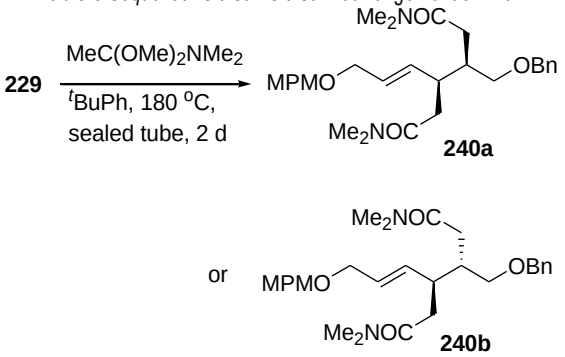


Entry	Reagent	Acidic reagent	Temp	Product, Yield (%)
1	$MeC(OEt)_3$	$EtCO_2H$	140 °C	**236a**, 14
2	$MeC(OEt)_3$	4-nitro phenol	140 °C	**236a**, 14
3	$MeC(OEt)_3$	2-nitro phenol	140 °C	**236a**, 22
4[b]	$MeC(OMe)_2NMe_2$	None	180 °C	**240a**, 87

[a] *E-syn*-**229a** (50µmol), $MeC(OEt)_3$ (0.03 M solution) or $MeC(OMe)_2NMe_2$ (20 equiv.), acidic reagent (0.1 equiv.) in sealed tube, 2 days, [b] ^{t}BuPh (0.03 M solution) was used as solvent

The study on the substrate scope of the sequential Claisen/Claisen rearrangement with **229a-d** revealed the remarkable stereoselectivity [Table-3]. The reaction proceed in a completely diastereoselective manner producing **240a** from **229a** and **229d** [Table-3], (entries 1 and 4) whereas **240b** from **229b-c** [Table-3], (entries 2-3). They have also developed the sequential Claisen/Overman rearrangement for different allylic diols including **229a-d** and that also showed excellent stereoselectivity [Table-4].

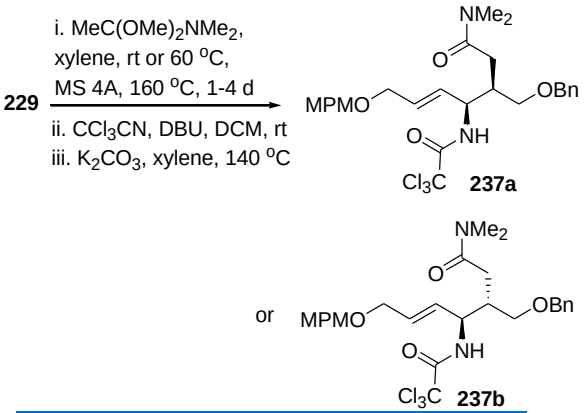
Table-3 *Sequential Claisen/Claisen rearrangement of* **229**.[a]



Entry	Diol 229	Bisamide, Yield (%)
1	*E-syn*-**229a**	**240a**, 87
2	*Z-syn*-**229b**	**240b**, 81
3	*E-anti*-**229c**	**240b**, 66
4	*Z-anti*-**229d**	**240a**, 88

[a] **229** (50µmol), $MeC(OMe)_2NMe_2$ (20 equiv.), ^{t}BuPh (0.03 M solution).

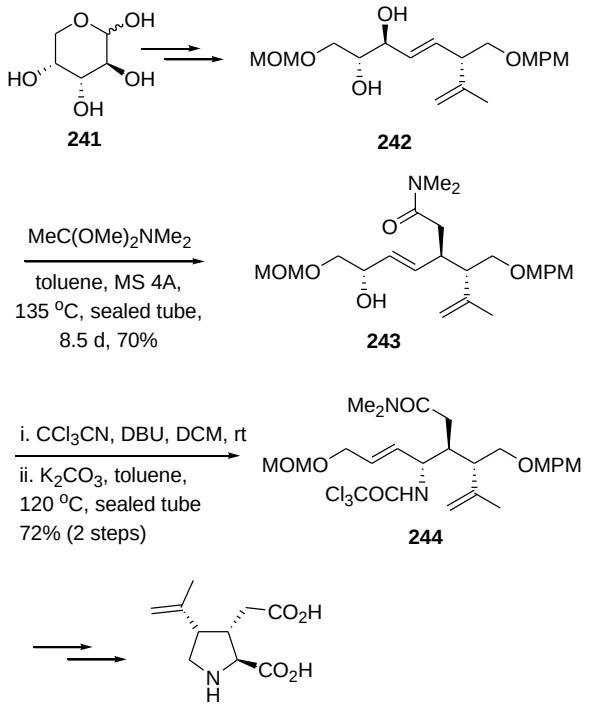
Table-4 *Study on the sequential Claisen/Overman rearrangement of* **229**.[a]



Entry	Diol 229	Bisamide, Yield (%)
1	*E-syn*-**229a**	**237a**, 80
2	*Z-syn*-**229b**	**237b**, 81
3	*E-anti*-**229c**	**237b**, 73
4	*Z-anti*-**229d**	**237a**, 81

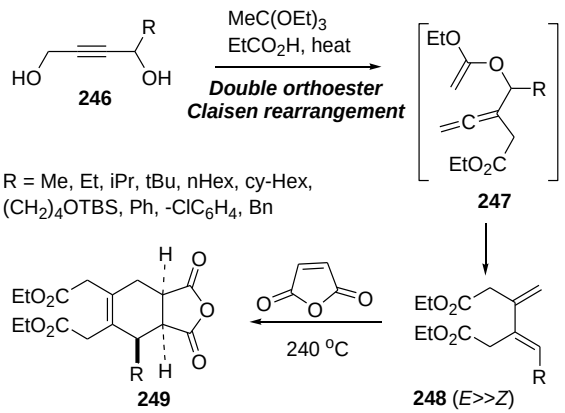
[a] **229** (50µmol), $MeC(OMe)_2NMe_2$ (2 equiv.), *o*-xylene (0.03M), rt, 3 h for syn-**229** or 60 °C for *anti*-**229** then MS 4A, 160 °C, sealed tube, 4 days for *syn*-**229** or 1.5 days for *anti*-**229**, (ii) CCl_3CN (2 equiv.), DBU (1 equiv.), CH_2Cl_2, 0.05 M, 0 °C–rt, 3 h, (iii) K_2CO_3 (25 mol%), *o*-xylene (0.1 M), 140 °C, sealed tube, 2h.

This development was applied in the total synthesis of (–)-kainic acid (**245**), [108] isolated from *Digenea simplex*, [108a] a Japanese marine alga, shows anthelmintic and insecticide proterties and also used in neuropharmacology [109]. In their synthesis the key allylic diol **242**, derived from D-arabinose (**241**) was rearranged diastereoselectively to **243** in 70% yield. Here the Claisen rearrangement of **242** through the cyclic orthoamide was performed at lower temperature (135 °C) to avoid the competing Cope rearrangement of the generated **243** at higher temperature (180 °C). The resulting allylic alcohol was converted into the imidate, which was heated with K_2CO_3 in toluene at 120 °C to give trichloroacetoamide **244** through second rearrangement, and then **244** was transformed into (–)-kainic acid (**245**) (**Scheme 43**), involving three chirality transfers in the reaction sequence.



Scheme 43 Synthesis of (-)-kainic acid

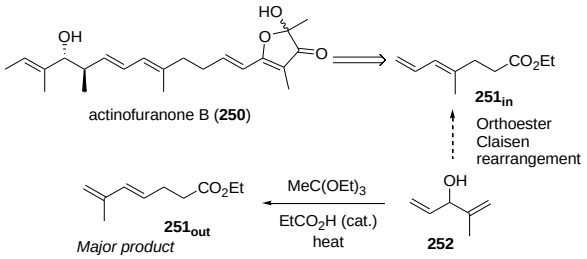
Propargylic diols **246** were subjected to sequential orthoester Claisen rearrangement, where the first orthoester Claisen rearrangement afforded the reactive allenic ester intermediate **247**, which subsequently underwent second orthoester Johnson-Claisen rearrangement to afford dienes **248** with high *E*-selectivity. The substituted dienes **248** were used in the Diels-Alder reaction to synthesize bi-cyclic diester **249** in good yields with excellent stereoselectivity (*endo:exo* = 99:1) (**Scheme 44**) [110].



Scheme 44 Double orthoester Claisen rearrangement of propargylic diols.

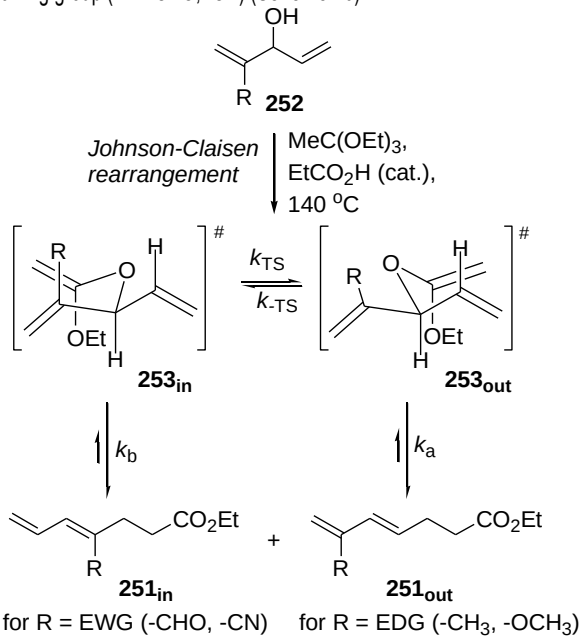
Regio-selectivity in the orthoester Johnson-Claisen rearrangement of bis-allyl alcohols

The Johnson-Claisen rearrangement of allyl alcohols is regiospecific as it passes through highly ordered six member cyclic transition state [3]. However, for bisallyl alcohols the question of regioselectivity arises. Recently, Lawrence et al. have planned the total synthesis of actinofuranone B (**250**) [111] from the γ,δ-unsaturated ester **251**$_{in}$, and initially they planned its synthesis through Johnson-Claisen rearrangement of the corresponding bisallyl alcohol **252** (**Scheme 45**). However, previously Parker et al. [112] reported that the orthoester Claisen rearrangement of such bis-allylic alcohols **252** having electronically similar olefins afforded the rearrangement product **251** with modest to good selectivity in favor of **251**$_{out}$ (**251**$_{out}$: **251**$_{in}$ = 2:1 to 19:1), the undesired rearrangement product. There the near exclusive formation of **251**$_{out}$ was explained solely from steric crowding in the transition state, where the competing hindered transition state leading to minor product **251**$_{in}$.



Scheme 45 Retro-synthesis of actinofuranone B.

Lawrence et al. have studied the orthoester Johnson-Claisen rearrangement of bisallyl alcohols **252** to find out the electronic origin of regioselectivity and observed that the nature of substituent controls the regioselectivity [113]. In their computational study, a scenario was assumed in which rapid equilibrium between the ketene acetals **253** would occur (i.e., under thermal control), also the energy barrier corresponding to rotation around the C4-O3 bond of ketene acetal **253** would expected to be relatively small (fast k_{TS}, k_{-TS}) and more significantly, smaller than the corresponding energy barrier for orthoester Claisen rearrangement at either olefin of transition states **253**$_{in}$ and **253**$_{out}$ (i.e., k_{TS}, $k_{-TS} \gg k_a$, k_b). From computational study (calculations using semiemperical methods) they observed that the formation of the transition state **253**$_{in}$ or **253**$_{out}$ depends on the directing group R. The transition state **253**$_{out}$ is found to favor when R is electron donating group (R = -CH_3, -OCH_3), whereas **253**$_{in}$ is preferred when R is electron withdrawing group (R = -CHO, -CN) (**Scheme 46**).



Scheme 46 Regioselectivity in Johnson-Claisen rearrangement through desymmetrization of pseudo-symmetric bisallylic alcohols.

Conclusion

Since its discovery in 1970, orthoester Johnson-Claisen rearrangement has been developed enormously over last few decades and becomes a reliable tool to access γ,δ-unsaturated ester units from allylic alcohols through a new C-C bond formation. This reaction provides an opportunity to access various functional groups, intermediates and building blocks in the synthesis of natural products and bioactive molecules. Beyond its application in organic synthesis, its application has also been extended in the field of material science to prepare chemically modified materials having diverse applications. Author has described the recent developments in this rearrangement and discussed them according to the type of starting allyl alcohols, including the sequential orthoester Johnson-Claisen

rearrangement to introduce two functional groups stereoselectively and the controlling effects in regioselectivity. Microwave promoted rate acceleration, catalysis using acidic reagent and organic bases in case of sensitive substrates and the stereoselectivity involving pericyclic and exopericyclic stereocontrolling features are also discussed. Hope this article will be helpful for researchers to design their synthesis and do further development in orthoester Johnson-Claisen rearrangement.

Acknowledgment

SA is thankful to the Department of Science and Technology (DST), New Delhi, India for providing research funding (SB/FT/CS-066/2013) and Aliah University, Kolkata, for providing research facilities.

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