The steering pathway: Ketene-Claisen rearrangement (KCR)-1978–2016

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1. Introduction

Ludwig Claisen\(^1\) reported in 1912, the Claisen rearrangement, which involved the [3,3]-sigmatropic rearrangement of an allylvinyl ether to give a \(\gamma,\delta\)-unsaturated carbonyl scaffold (Scheme 1). Simply the Claisen rearrangement to construct a C–C \(\sigma\)-bond can be considered as the intramolecular nucleophilic substitution addition of a carbonyl enol (Claisen rearrangement), thiocarbonyl enol (thia-Claisen rearrangement) or enamine (aza-Claisen rearrangement) to an allylic ether, sulfide or amine, respectively. The process involves \(\pi\)-bond migration and falls under the classification [3,3]-sigmatropic shift.\(^2\)

In addition, the esteemed growth of this reaction can be seen from different variants such as the Carroll (1940),\(^3\) Eschenmoser (1964),\(^4\) Saucy-Marbet (1967),\(^5\) Johnson (1970),\(^6\) Ireland (1972),\(^7\) Reformatsky-Claisen rearrangement (1973),\(^8\) Malherbe and Bellus (1978)\(^9\) and Denmark (1982).\(^10\)

The ketene-Claisen reaction (the Malherbe-Bellus rearrangement or ketene-[3,3]-sigmatropic rearrangement) was first described by Bellus and Malherbe in 1978.\(^1\) Treatment of allylic ethers with \textit{in situ} prepared dichloroketene (a solo subunit) afford...
The [3,3]-sigmatropic rearrangement adducts in good yield (Scheme 2). This protocol works as well with allylic sulfides and tertiary allylic amines. The ketene-Claisen reaction can be quite efficient and usually takings with high levels of stereocontrol. Accordingly, it has been used in making natural products and medicinal agents.

All the reports published in this area between 1978 (the year of its discovery) and 2016 have been summarized in this review article, in order to provide detailed information about this smart and useful reaction.

### 1.1. Stereochemical aspects for the ketene-Claisen reaction

The high level of stereocontrol of the [3,3]-sigmatropic rearrangements in the acyclic systems can be achieved through the chair-like transition states depending on the temperature (Scheme 3).

Consequently, a high stereo-control can be attained of usually well-ordered transition states. However such desired conversion frequently involves in elevated temperatures in order to the survival of different functional moieties. Accordingly this issue has been determined through the fixing of a π-donor substituent at position 2 or a negative charge at position 1 in the enolate coordination and a heteroatom with a positive charge at position 3 (Fig. 1).

A facile synthesis of compound Scheme 4 via [3,3]-sigmatropic rearrangement, can be depicted as a two-step reaction commenced by a nucleophilic addition reaction of the allylic heteroatom (O, S, N) at the ketene’s sp carbon atom to generate the 1,3-dipolar intermediate (preferred chair-like transition state with least 1,3 diaxial steric hindrances).

The structure-function relation study on the chemo- and stereoselectivity of the ketene-Claisen reaction was initially recognized by Bellus et al. that depicted the full chirality shift from C=S to C=C bond. For instance, chiral cyclic allyl thioethers as a precursor, gave almost a complete chirality transfer (99% ee) (Scheme 5), whilst, a chirality transfer of 96–98% was observed when chiral acyclic allyl thioethers were employed as starting precursors (Scheme 6). Here the more favoured nucleophilic sulphur showed the complete chemoselection due to compete for dichloroketene. Likewise, Aggarwal et al. depicted a stereospecifically complete chirality transfer of tertiary and quaternary stereocenters via the reaction of dichloroketene with camphor-derived 1,3-oxathianes of α,β-unsaturated aldehydes to give macrocyclic thiolactones.

A novel 1,2-asymmetric induction in the ketene-Claisen rearrangement was also described by Bellus and co-workers, where the optically active allyl thioethers (a moiety for the rearrangement) showed the excellent chemo-selectivity (syn-selectively ca 20:1). Only the sulphur migration was observed in the rearranged thio-esters that subsequently gives the cyclization products and (Scheme 7).

Two decades later, after the discovery of reversal of diastereoselectivity, Porter et al. has attempted to produce reversal of facial selectivity in a thia-Claisen rearrangement via the reaction of N-benzylpyrrolidine-2-thione and D-mannitol derived chiral allylic bromides. The presence of a bromine atom on the allylic bromide double bond turns around the logic of diastereoselectivity in the [3,3]-sigmatropic rearrangement. A research on the stereochemical reaction pathway demonstrates a quality for reaction through the facial selectivity: N,S-ketene acetal proceeds through Re-face selectivity (conformation I) whereas vinyl bromide reacts mostly through Si-face selectivity (conformation II) (Scheme 8).

In contrast to the Bellus’s study of high 1,2-stereoinduction, Gonda obtained, under the similar conditions, only 60% and 80% of...
1,2-stereo-induction originating from protected chiral (2S,3E)-5-(iso-propylsulfonyl)-3-penten-2-amines 26 with Boc and Tos respectively (Scheme 5). To support this fact, Gonda has performed theoretical calculations subsequently and has established the mechanism and stereoselectivity in the ketene-Claisen rearrangement relating to the models for the steric and electronic

Scheme 5. Chirality transfer in ketene-Claisen rearrangement.

Scheme 6. Chemo- and Stereoselective ketene-Claisen rearrangement of chiral allyloethers.

Scheme 7. A 1,2-asymmetric induction in the ketene-Claisen rearrangement.
course of [3,3]-sigmatropic reactions previously investigated by many research groups.\textsuperscript{19} Whilst the initial steps towards an enantioselective catalytic ketene-Claisen process were reported by MacMillan and co-workers.\textsuperscript{16}

Hence because of the development of the Claisen reaction, opposite stereochemistry in any reaction can be accounted through the suitable selection of olefinic double bond geometry in the substrate.

1.2. The scope of ketenes

Dihaloketene i.e. dichloroketene is the most reactive, high electrophilic and commonly used precursor in the ketene-Claisen rearrangement. The chlorines in the rearranged gem-dichloro substrates can be conveniently separated by metal (Zn, Fe) reduction, making this reagent very handy for further transformations.\textsuperscript{22}

Due to less stability and quick polymerization of dichloroketene, it is furnished \textit{in situ} in presence of the allylic olefin by (a) the dehydrohalogenation of a dichloroacetyl halide 33 with triethylamine or (b) the dehalogenation of a trichloroacetyl halide 34 with activated zinc (Scheme 10). Although, there are certain drawbacks like ammonium salts catalyse the decomposition of dichloroketene in (a) and certain olefins are polymerised by zinc salts in (b).\textsuperscript{23}

Furthermore, the ketenes for the acylation process of an allyl ether, allyl thio-ether or allyl amine involved in the ketene-Claisen rearrangement, have been generally formed via one of the two methods showed above (Scheme 10).\textsuperscript{15,24}

In addition, the reactions of ketenes with electrophilic and
nucleophilic reagents by concerning the dipole moment, make them more prominent (Scheme 11).25

Most interestingly, the cyclic four membered transition states having the polarized electron density at the olefin linkage in most of the ketene addition reactions were reported to give products 37 and 38 (Scheme 12). Likewise the ketene dimerizes via addition reactions to generate 39 and 40.25 Whereas the reaction of ketenes with alkenes go through concerted [2 + 2] cycloaddition process to give cyclobutanones 42.26,27 However, alkenes having heteroatoms at the allylic position can experience competitive reaction at the heteroatom to form zwitterionic intermediates 43 which instigate the Malherbe-Bellus variant of the Claisen rearrangement particularly in presence of Lewis acids.28

The selection of the ketene-Claisen reaction appears to be inadequate to highly electrophilic ketenes,9,11 while dichloroketene, chloroalkylketenes and diphenylketene15 have shown to be well-organized in providing the rearrangement. The application of Lewis acid-activated ketenes as alkylketenes and ketenes bearing oxygen, sulphur and nitrogen substituents have been described initially by MacMillan and co-workers.16

Many others haloketenes were employed by Malherbe and Bellus11 in order to substantiate the reactivity of dichloroketene. None of them were capable for the ketene-Claisen rearrangement. Accordingly, dibromoketene, prepared in situ from tribromoacetyl bromide and an amine, could not react with starting allyl ethers and thio-ethers (possibly due to less electrophilic affinity and the presence of bulky bromo-substituents near the reaction centers); difluoroketene (prepared by dehalogenation of bromodi-fluoroacetyl fluoride) was too unstable and readily decomposed into carbon monoxide and fluorocarbene; whilst monochloroketene (prepared from zinc wool and dichloroacetyl chloride) and chlorocyanoketene (prepared by thermolysis of 4-azido-3-chlor-5-methoxy-2-chloride-2-(5H)-furanone) afforded poor yields.

1.3. The Malherbe-Bellus rearrangement’s role in synthetic chemistry

1.3.1. Ketene-Claisen reactions

Conceptually, the initial novel ketene-Claisen rearrangement was investigated by Malherbe and Bellus in 1978.9,11 In attempt to achieve a [2 + 2]-cycloaddition, the authors demonstrated that

Scheme 11. Reactions of ketenes with electrophilic and nucleophilic reagents.25

Scheme 12. The reactivity of ketenes in ketene-Claisen rearrangement.25–28
treatment of an allyl ether 45 (Scheme 13) with dichloroketene resulted instead in the formation of a 1,3-dipolar allyl vinyl ether 46, which subsequently underwent [3,3]-bond reorganization to give 47 as a major product. This work initially shown the ability of zwitterionic 1,5-dienes to readily involve in charge accelerated sigmatropic isomerization. The very simple synthesis of the naturally occurring 10-membered ring macrolides (+)-phoracantholide I 51, and (+)-phoracantholide J 53.9

Scheme 13. The reaction of allyl ether 45 with dichloroketene.11

Scheme 14. The synthesis of (+)-phoracantholide I 51, and (+)-phoracantholide J 53.9

Scheme 15. The cycloaddition reaction of 2-vinyloxiranes 54 and dichloroketene.29
(±)-phoracantholide J 53 demonstrates the felicity of this versatile rearrangement to convert cyclic n-membered, α-vinylsubstituted ethers 50 into unsaturated (n+4)-membered lactones 52 (Scheme 14).

Another convenient and regioselective synthesis of 4,6-diaryl-2,3,4,7-tetrahydrooxepin-2-ones 55 from the cycloaddition reaction between easily available 2-vinyloxiranes 54 and dichloroketene (Scheme 15) have been demonstrated by Ishida et al. 29 Where the synthesis of lactone derivatives such as 57 is proved to be one of the most demanding targets in organic chemistry due to its occurrence in natural products and synthetic utilities as acylating reagents.

1.3.2. Thia ketene-Claisen reaction

Malherbe and Bellu 30,31 also reported the reaction of allyl sulfides (thia-ketene reaction) 58 (Scheme 16) with in situ prepared dichloroketene, two competing pathways were observed. Moreover instead of [2+2]-cycloaddition, a [3,3]-sigmatropic rearrangement took place predominantly.

Similarly when an allyl cyclothioether 61 was used as starting unit, a cycloenlargement of the cycle 62 by four carbon atoms was obtained due to [3,3]-rearrangement (Scheme 17). In addition, the merging of vinylic bromide substituent 63 has also been reported to establish high facial selectivity, where a thia-Claisen rearrangement of S-allylic ketene N.S-acetals were carried out using substrate with an external allylic stereogenic centre 30 (Scheme 17).

Rosini and Spinetti 32 adopted quite similar approach in order to synthesize multifunctional di-thia-macro cyclic systems. Starting from the reaction of dichloroketene with the cyclic thioketals (precursors of α,β-cycloalkenones 66) to give ring enlargement 1,7-dithiapentacyclopent-5-en-2-one derivatives 67 even at room temperature and in high yield (Scheme 18).

As mentioned above in Scheme 7, Bellus and co-workers 12,17 had described a route to optically active γ-butyrolactones through a reaction of appropriate substituted precursors 21 and dichloroketene. Furthermore the major advantage is that the less reactive dichloromethylketene also reacts with thioether 21. The significant thioester 68, which holds a further stereocenter in the α-position to the carbonyl group was acquired as an inseparable mixture of diastereomers (de ≈ 50%) 30 (Scheme 19). Subsequently, desilylation through the chromatography provided the separable lactones 69 and 70 in ratio 3:1. Reduction of ester 68 furnished the chlorine free lactones 71 and 72 (ratio 3:1). Moreover, the radical dechlorination of 69 and 70 directed the same ratio of dechlorinated lactones.

Aggarwal and co-workers 31 have investigated the in control reactivity of camphor-derived 1,3 oxothianes 73 (previously available from commercial (+)-(±)-(10)-camphorsulfonyl chloride) with dichloroketene. They have described that the nucleophilic sulphur atom of the oxathiane moiety 66 attacks stereoselectively to the haloketene to form a macrocyclic product 74 (Scheme 20). As an outcome of the high level of stereo-control of tertiary and quaternary chiral centers via the tightly ordered transition state ([3,3]-sigmatropic rearrangement), diastereomerically pure oxathianes 67 furnish the final diastereoisomerically pure products 74 in high yield and with complete transfer of chirality. They have noticed that the elimination conditions (Et3N and Cl2CHCOCl) for the formation of the dichloroketene were found to be superior to the reductive conditions (Zn-Cu and Cl3CCOCl) so far as yields and side products were concerned.

1.3.3. Aza-ketene Claisen reaction

Early studies on the aza-ketene Claisen reaction relied on the use of long-lived, electron poor ketenes (Scheme 21) that were either isolated before 12 or generated in situ. 13 Many researchers have introduced modifications to the aza-ketene-Claisen rearrangement with a view to removing the need for electron-poor ketenes. 34
Scheme 18. Rosini and Spineti’s synthetic approach of dichloroketene with the cyclic thioketals.18

Scheme 19. The Bellu’s route to optically active γ-butyrolactones via substituted thioether 21 and dichloroketene.30

Scheme 20. The Aggarwal’s stereocontrolled approach to form a macrocyclic product 74 from the camphor-derived 1,3 oxothianes 73 with dichloroketene.31

Scheme 21. The general aza-ketene-Claisen rearrangement.32–34
Nubbemeyer and co-workers further depicted the reaction of N-allyl pyrrolidines 78 with ketenes, generated in situ via dehalogenation of α-halogenated acyl chlorides or via dehydrohalogenation of acyl chlorides, with no success. Only ‘von Braun’ type side products 79 and 80 were recovered (Scheme 22). While a modified approach using two phase systems was successful — a sequential addition of K2CO3 of allyl-pyrrolidines, acetyl chloride and trimethyl aluminium furnished the desired rearranged product 81. In an attempt to eliminate the competing ‘von Braun’ process, acyl fluorides were brought in to contact with Lewis acid. The observed stereochemistry in this research was not as simple as in other Claisen rearrangements as the allylic amines were chiral nonracemic compounds and therefore the authors anticipated for a diastereoselective rearrangement by using allyl amines.

Moreover Craig and co-workers prescribed a ketene-Ireland-Claisen hybrid rearrangement utilising stoichiometric amount of trimethylsilyl trifluoromethane sulfonate (TMSOTf) as a Lewis acid to trap the enolate during rearrangement to an imine followed by dehydrohalogenation von Braun process, acyl ketenes, generated in situ via dehalogenation of acyl chlorides through an intermediate (vinylogous urethane formation of the very stable intermediate (vinylogous urethane 85). The Roberts’s extension of the aza-ketene-Claisen rearrangement. The lactam 93, was obtained from the direct reaction of (S)-phenylethylamine, optically pure (1R,4R,1’S)-2-(phenylethyl)-2-azabicyclo[2.2.1]hept-5-ene 91 with ketenes through an intermediate 92 (Scheme 26).

Accordingly, Edstrom had got idea to develop a new approach for the building of structural subunits; indolizidine 97a, 97b and quinolizidine 100a, 100b across many families of alkaloids possessing promising biological profiles (Scheme 27). Their strategy involves an aza-ketene-Claisen rearrangement starting from simple monocyclic precursors 95a, 95b. This approach affords a novel region-controlled mode for the synthesis of nine- and ten-membered unsaturated lactams 96a, 96b and 99a, 99b (Scheme 27).

The zwitterionic aza-Claisen ketene rearrangement, another synthetic common approach analogous to aza-Claisen ketene reaction to synthesize hydrosisoquinoline subunits has been initially depicted by Mariano in 1983. The zwitterionic intermediate 103, produced by reversible addition reaction of tertiary isoquinuclidines 101 to acetylenic esters 102, experiences [3,3] sigmatropic rearrangement to furnish corresponding cis-fused hydrosisoquinoline 104 (Scheme 28). The reaction involves the formation of the very stable intermediate (vinyllogous urethane 103, an attractive precursor of yohimbane derivatives. Similarly, Hegedus et al. has reported a versatile approach to form unsaturated lactams (as an intermediate 106 via a zwitterion aza-Cope rearrangement subsequently furnish indolizidine and quinolizidine ring structures 107 (Scheme 29). In the presence of a Lewis acid, the ketenes were formed by photolysis of chromium carbene complexes. The importance of chromium carbene...
complexes is to fit substituents α-to the carbonyl carbon despite the dichlorosubstituents resulting from the dichloroketene. As depicted earlier that McMillan and co-workers have provided an attractive platform for the development of an enantioselective catalytic ketene-Claisen method. The process involves an acid-catalyzed ketene [3,3]-sigmatropic rearrangement using allyl morpholines (Scheme 30). Moreover, this flourishing rearrangement has capability to form a reaction with a series of Lewis acids to furnish a high yield and good stereocontrol 1,2-disubstituted Claisen adduct (Table 1). Besides above, the proper geometry of olefinic double bond on the allyl component in the substrate also gives the respective stereocontrol. For instance, with trans allylic morpholines, the syn product with excellent levels of stereoselection were observed while the cis double bond isomer introduced the anti Claisen adduct (Scheme 31). The ability of this protocol was further
enhanced on cyclic and acyclic architectures in which the transition state-controlled π-facial bigotry to prefer quaternary carbon stereocenters on both.

Another major development in the ketene-Claisen rearrangement is a tandem ketene-Claisen reaction. This is based on the highly stereoselective three-component coupling reaction which facilitates the formation of versatile acyclic systems e.g. acyclic 2,3,6-trisubstituted-1,7-dioxoheptane structure (previously formed from allyl diamine and propionyl chloride (Scheme 32). Here the depicted tandem sequence was thriving with a range of Lewis acids furnishing the tandem adduct in excellent yield and stereoselectivity. This sort of reaction is quite simple with respect to the nature of the tertiary amine component, the structure of the acyl chloride and the olefin substituent (see Scheme 33).

Moreover, the tandem ketene-Claisen rearrangement proves itself a powerful significant tool in the natural product synthesis. Compound 119 is a stereochemical model commonly originated throughout the building blocks of macrolide antibiotics. This sort of protocol in acyclic stereochemical arrangement can be employed conveniently from allyl diamine 118 and propionyl chloride to furnish product in excellent yield (72%) and high stereoselectivity (91:9 syn-anti:anti-syn).

Correspondingly, MacMillan and Yoon have developed the first enantioselective ketene-Claisen reaction that involves the vital use of a Lewis acid. Specially, the optically active Lewis acid metal-chelating complex (Scheme 34), MgI2 derivative and bis(oxazolinyl)aryl (Arbox) ligand, provide a very effectual chiral space for a wide variety of ketene-Claisen rearrangements that utilize chelating substrates.

In addition, it was also observed that the structure of both the acid chloride and the tertiary allylic amine have an influence on enantioselectivity. Their ability to contribute in metal chelation is related to the enantiofacial favouritism of the [3,3] isomerization process. The appended Scheme 35 shows the importance of chelation as an organisational control element in asymmetric catalysis to afford enantioselective access to subtle acyclic systems.
structural precursors. The outcome of this asymmetric reaction is to align quaternary carbon centers on an allylic framework that is controlled by the Lewis acid.

Moreover, the high level of asymmetric induction and the good yields in the convergent stereoselective synthesis of the α-amino acids encouraged Nubbemeyer and co-workers to test the scope and limitation of the zwitterionic ketene aza-Claisen rearrangement. This has been reported as a persistent makeover for the synthesis of an optically active α, β-disubstituted and γ, δ-unsaturated amino acid derivatives of type 128 using chiral pyrrolidine precursors as auxiliaries 126 (Scheme 36). The activated ketenes 125 could form through the action of trimethylaluminium on acid fluorides which subsequently add to substituted pyrrolidines 126 to give intermediate 127 with preferred Z-enolate geometry. The anti-amides 128 could form through [3,3]-open chain Claisen rearrangement of syn adduct.

More recently, Shen and Xu has introduced the methodology for the stereoselective synthesis of α-allyl-α-cyano-lactams 131 from N-allyl amino ketene 130. In which an electron withdrawing group (-CN) at α-position favours the intramolecular zwitterionic ketene-aza-Claisen rearrangement (Scheme 37). The most
Scheme 34. MacMillan and Yoon's first enantioselective ketene-Claisen reaction.16c

Scheme 35. The effect of chelation on the enantioselective ketene-Claisen reaction.16c

Scheme 36. The Nubbemeyer's convergent stereoselective synthesis of the \( \alpha \)-amino acids.39

Scheme 37. Shen and Xu's stereoselective synthesis of \( \alpha \)-allyl-\( \alpha \)-cyano-lactams 131 from \( N \)-allyl amino ketene 130.40
importantly, an unsymmetrical bis-N-allyl moiety in the reactant displays significant chemoselectivity.

1.3.4. Diversity in ketene-Claisen reaction

The ketene-Claisen reaction is not only limited to allyl ethers, allyl thio-ethers and tertiary allyl amines but also involve allyl Se-esters. This study was carried out by Bellus and co-workers in which they described the combination of allyl Se-ethers with dichloroketene to form Se-esters of \( \gamma\delta \)-unsaturated acids smoothly at room temperature (Scheme 38).11

Recently a convenient method of the use of ketene-acetal variation or ester-enolate variation was demonstrated by Bravo et al.40b This protocol involves in the stereoselective synthesis of a natural monoterpen, \( \gamma\delta \)-unsaturated amino acids precursors and vinyl lactones (Scheme 39).

Another important type of Pummerer rearrangement to construct a variety of enantiopure substituted lactone precursors has been developed by Marino and co-workers.41 Here the \( [3,3] \)-sigmatropic rearrangement of intermediate vinylic oxosulfonium enolates, is represented by the reaction of cyclopentene sulfoxide with dichloroketene (Scheme 40).

An asymmetric, cationic 3-aza-Cope rearrangement has also been described by Vedejs and Gingras.42 As depicted in Scheme 41, the asymmetric tertiary allylic amine after Michael addition with dimethyl acetylenedicarboxylate (DMAD) gave the allylic enamine system, which subsequently undergo \( [3,3] \)-sigmatropic rearrangement that isomerised to enaminoester.44 Then ketoester after hydrolysis undergo cleavage and decarboxylation reaction to furnish the amide after amidation of mixed anhydride with \( (S) \)-phenylethylamine.

Nubbemeyer and Diedrich have illustrated the zwitterionicaza-Claisen rearrangement in chiral allylamines to produce optically active hexahydroazoninones via with complete 1,3-chirality transfer.43 This protocol permits the formation of optically active nine-membered ring lactams in high yields. Regarding the mechanism, it looks rational to suppose that the acyl ammonium salt forms first. This intermediary compound then undergo the addition reactions by a base (e.g. the chloride ion) and ultimately it forms the zwitterionic intermediate via lithiation on the \( \alpha \)-position of the activated carbonyl and subsequently undergoes the \( [3,3] \)-sigmatropic rearrangement to give azoninones. Which upon selective reduction furnishes.

An application of the ketene-acetal Claisen reaction was illustrated by Werchkun and Thiem that \( C\)--\( C \) bond formation in novel divalent saccharide structures can be achieved conveniently. In this protocol, \( C\)-allyl branched urinate could be achieved by the enolization of the allyl ester prepared from the analogous uronic acid (Scheme 43).

Ryan and co-workers described the in-situ formation of a potentially advanced precursor (hydroxylated vinyl-appended nine-membered lactones) for many natural products, from tartaric acid via the ketene acetal that undergoes spontaneous Claisen rearrangement (Scheme 44).

It was described that \( \gamma\delta \)-unsaturated functionalized \( \alpha\alpha \)-dibromo esters were synthesized through the Claisen rearrangements of dibromo-ketene acetals by allylic alcohols. Besides, the \( \alpha\alpha \)-dibromo esters have capability to undergo various important carbon–carbon bond-forming reactions, oxidations, and lactonizations (Scheme 45).

Barcan and co-workers have further showed a novel low-
temperature dibromo-ketene acetal Claisen rearrangement in exocyclic dienylbromide precursor which involved a palladium-catalyzed cross-coupling reaction (Scheme 46). Furthermore, the relative stereochemistry at positions C-3 and C-18 in the adduct 165, can be directed by an extremely torquoselective thermal triene 6π electrocyclization. The product 165 is an important framework of reserpine-type alkaloids.

Another novel discovery for the synthesis and Claisen rearrangement of bridged bicyclic enol ethers through ketene (S)-cisdiene cycloaddition has been investigated via a non-dissociative pathway for the rearrangement (Scheme 47). In which the bicyclic cyclobutanones 167 synthesis is described through the Claisen
Scheme 45. Dupper and Kwon’s strategy involving dibromo-ketene acetals 160.47

Scheme 46. The Barcan’s protocol of low-temperature dibromo-ketene acetal Claisen rearrangement.48

Scheme 47. The synthesis bridged bicyclic enol ethers through ketene (S)-cis-diene cycloaddition.49

Scheme 48. The reactions of allylic amines and ketenes in the presence of the silyl-reagent.50

Scheme 49. Ring enlargement through the ketene-Claisen rearrangement.51
rings give the product with e.g. potential starting material and ketenes (Scheme 48). 

Ring enlargement through ketene-Claisen rearrangement has been demonstrated with a range of allylic amines (Scheme 49). Unsaturated nine-member lactones 175, 176 have been formed by ketene-Claisen reaction for the total synthesis of different bioactive metabolites. Based on this versatile methodology, one can synthesize any ring core of selective conformation and its scope and stereochemistry in the Irland-Claisen rearrangement by a variety of 3-alkylidene-2-oxabicyclo[2.2.1]hept/ oct-5-ene precursors thermally or in the presence of a Lewis acid.

Also a silyl-modified alternative of the ketene-Claisen rearrangement has been demonstrated with a range of allylic amines and ketenes (Scheme 48). 

Ring enlargement through ketene-Claisen rearrangement is a very significant synthetic tool and could be carried out easily in a single step (Scheme 49). Unsaturated nine-member lactones 175, 176 have been formed by ketene-Claisen reaction for the total synthesis of different bioactive metabolites. Based on this versatile methodology, one can synthesize any ring core of selective configuration by the choice of starting heterocyclic precursors, for example, six-member tetrahydropyrans as a precursors give the ten member ring with E configured double bond, similarly the five-member tetrahydrofuran rings produce expected unsaturated nine-member rings with Z configuration. Whilst the use of the a potential starting material e.g. four-member oxygen containing rings give the product with E configuration due to the more ring strain and even three-member oxiranes has been reported of which a double bond with Z configuration 174.

An examination for the promoting boron-ketene acetal formation and its scope and stereochemistry in the Irland-Claisen rearrangement has been described by Ferreira and Seizert (Scheme 50). It was observed that the relative stereochemistry originates through a competing chair-like and boat-like transition states, where the major diastereomer is most reliable with (Z)-boron ketene acetal 180 proceeding through a favoured chair-like conformation 179 to furnish desired product 181. Alternatively, severe non-bonded interactions in the E-isomer 183 could lead to disfavoured path and it unlikely proceed via boat like transition state 182.

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