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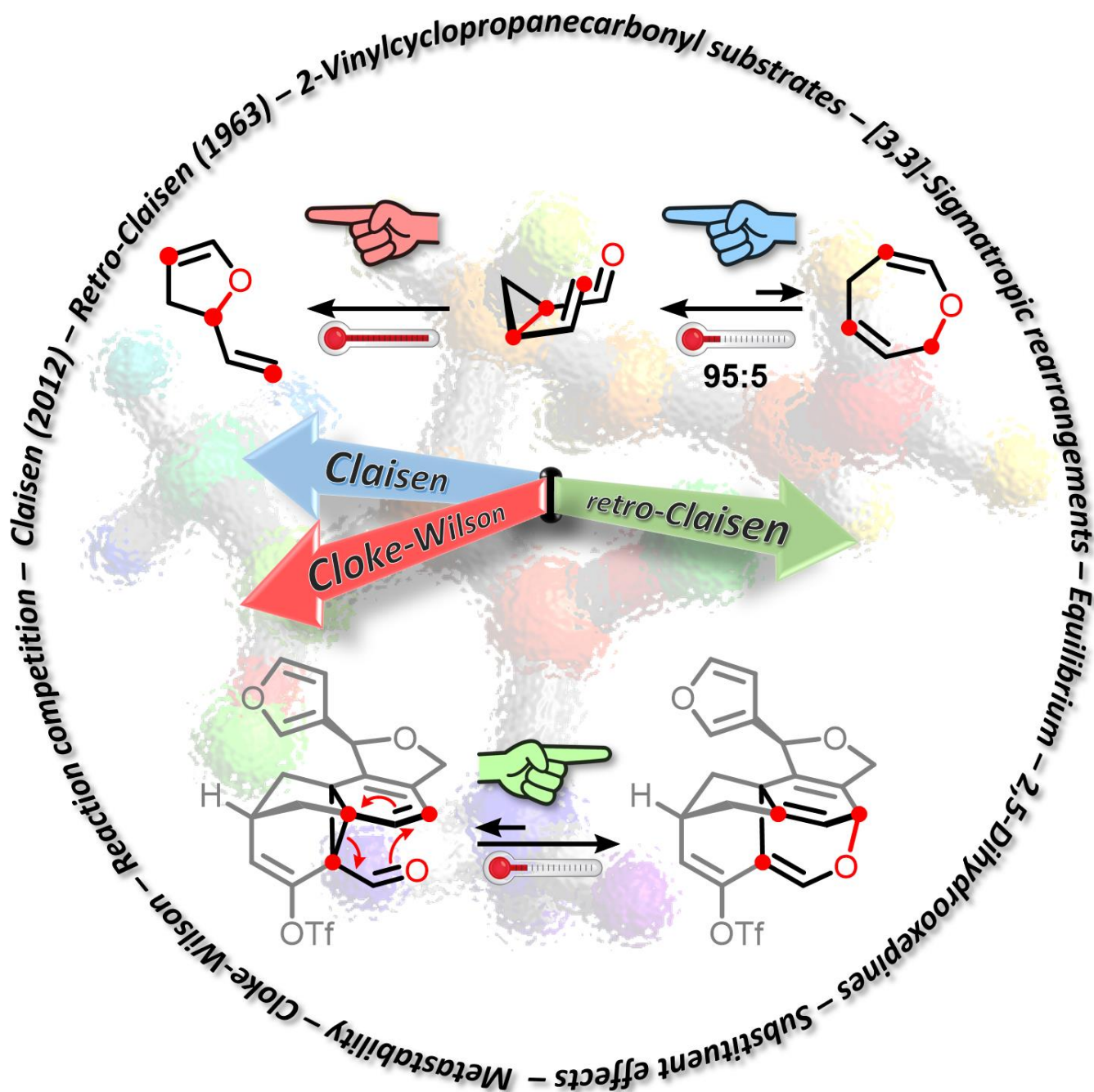
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The retro-Claisen rearrangement of 2-vinylcyclopropylcarbonyl substrates and the question of its synthetic potential

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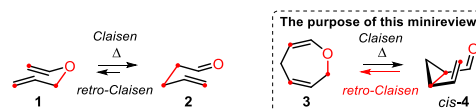
Abstract: The retro-Claisen [3,3]-sigmatropic rearrangement of γ,δ -enyl compounds allows to form a C-O bond while breaking a C-C bond in a concerted process. It is rarely observed with acyclic substrates. However, when the alkene and carbonyl groups are tethered by a cyclopropane, this rearrangement results in ring expansion, to form a 2,5-dihydrooxepine whose stability entirely depends on the substitution pattern. After its discovery in the 1960's, applications have resulted in the development of original methodologies and total synthesis, mainly spread over the last 20 years. This minireview aims at describing the historical discovery, the study of substrate reactivity, and the recent applications of this reaction, discussing the formation of stable, metastable or elusive 2,5-dihydrooxepines.

1. Introduction

Since its discovery in 1912,¹ the Claisen [3,3]-sigmatropic rearrangement has grown as a powerful synthetic tool in organic synthesis. It involves the valence isomerization of allyl enol ether substrates, forming a C-C bond and breaking a C-O bond in a concerted process, with a high degree of regiochemical and stereochemical control.² This rearrangement and its *retro-Claisen* (or oxa-Cope) counterpart (Scheme 1) are strongly dependent on factors such as strain, conjugation, electronic effects, or the presence of additional heteroatom substituents. The equilibrium, which is under thermodynamic control, most commonly favors the Claisen rearrangement, yet with several exceptions.³

On a synthetic point of view, these rearrangements offer big opportunities for C-C bond formation or cleavage, and stereoselective chain branching. Thus δ,γ -unsaturated carbonyl compounds (**2**) have been considered as "hidden retrons" to be identified during retrosynthetic planning, while allyl enol ethers (**1**) have mostly been used as the corresponding reactive

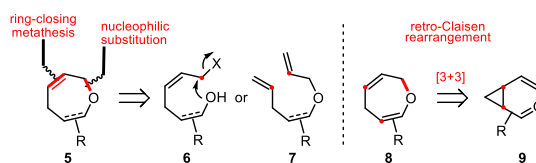
intermediates (synthon).⁴ Nevertheless, the occurrence of the allyl enol ether motif in valuable compounds also makes the retro-Claisen rearrangement of particular utility. Indeed, when the broken σ^{C-C} bond in this rearrangement is engaged in a cyclopropane ring (**4**),⁵ it results in ring expansion to form 2,5-dihydrooxepine heterocycles (**3**, Scheme 1). This rearrangement can only occur when the substituents on the cyclopropane ring are in a *cis* relative configuration.



Scheme 1. Classical (left) and homologated version (right) of the Claisen rearrangement (red bonds are those broken and formed).

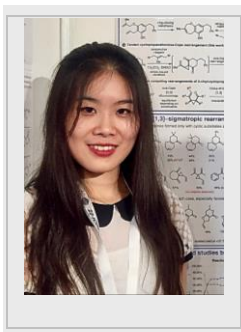
2-Vinylcyclopropane-1-carboxaldehyde *cis*-**4** provides a stunning example to illustrate the equilibrium issue of this reaction, with its retro-Claisen rearrangement furnishing 2,5-dihydrooxepine **3**. In fact, as we shall see later, both compounds are engaged in a 95:5 equilibrium at room temperature, in favor of cyclopropane *cis*-**4**.⁶ An additional difficulty of this reaction is the possible competition with other types of valence isomerization, like the Cloke-Wilson rearrangements into 2-vinyl-2,3-dihydrofuran (**20**)⁷ or 3-cyclopentenecarboxaldehyde (**17**),⁸ or with the *cis/trans* cyclopropane isomerization (*trans*-**4**). In that context, it is clear that the synthetic utility of the retro-Claisen rearrangement toward 2,5-dihydrooxepine rings may have limitations, unless key parameters can be controlled, like the temperature and the use of stabilizing substituents.

Ring-closure methods towards unsaturated oxepane cycles either involve C-O or C-C bond connections,⁹ but as medium-sized rings, unfavorable entropic factors could affect their formation.¹⁰ Concerning 3,4-dehydrooxepanes (**5**), C-O bond forming reactions have most often involved intramolecular nucleophilic substitutions at terminal allylic positions by hydroxyl groups (**6**), while C-C bond forming strategies have been dominated by the ring-closing metathesis of dienes (**7**) (Scheme 2).



Scheme 2. Examples of disconnection in the 3,4-dehydrooxepane ring.

Wei Zhang graduated with a Master degree in Chemistry from Sorbonne University in Paris, conducting projects with Dr. C. N. Boddy in Ottawa University (2014), and with B. Nay in the National Museum of Natural History, Paris (2015). Then she performed her doctoral studies under the guidance of B. Nay on the total synthesis of oxepine-containing natural products. After her PhD graduation from Sorbonne University in 2018, she joined Ecole Polytechnique as a postdoctoral researcher, to work on the C-H functionalization of biologically relevant compounds.



Bastien Nay was born in Bordeaux in 1974. After pharmaceutical studies, he got a PhD in organic chemistry from the University of Toulouse (2000), and then undertook two postdoctoral stays in the UK and in France. He was appointed as a CNRS researcher at the National Museum of Natural History in Paris in 2004, and joined Ecole Polytechnique in 2017. His research concerns synthetic methodologies and total synthesis at the edge of biology. He joined the board of *Natural Product Reports* in 2012, and of the *Beilstein Journal of Organic Chemistry* in 2020.



However, more than 50 years after its discovery,^{11,12} it is clear that the retro-Claisen rearrangement still offers a paradigmatic retrosynthetic opportunity to oxepane formation (Scheme 2), especially increased by the number of mild cyclopropanation methods.¹³ With this review, we want to promote the transfer of the current knowledge on this fundamental reaction towards synthetic purposes. Indeed, the occurrence of oxepine rings in a large variety of biologically and structurally appealing natural products, like some of those shown in Figure 1 (**10-16**), makes the retro-Claisen rearrangement particularly attractive.

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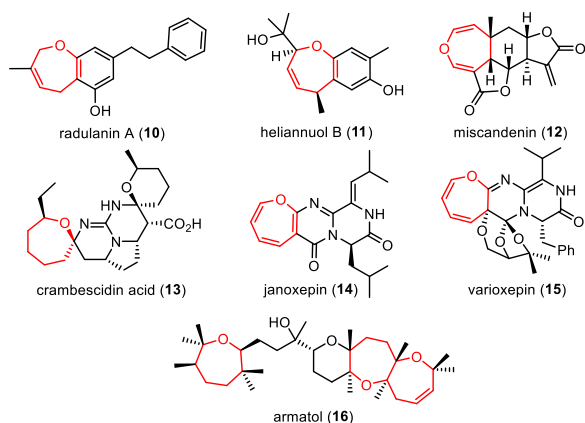
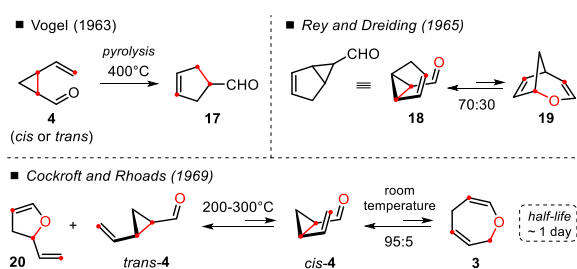


Figure 1. Examples of complex oxepane-containing natural products.

2. Pioneer works on the retro-Claisen reaction

The retro-Claisen rearrangement of 2-vinylcyclopropanecarboxaldehyde **4** into 2,5-dihydrooxepine **3** was first hypothesized by Vogel in 1963.¹¹ Both *cis* and *trans* isomers of **4** were reported to have a high thermal stability, only resulting in 3-cyclopentenecarboxaldehyde **17** upon pyrolysis in the gas phase at 400°C (Scheme 3). However, two years later, Rey and Dreiding observed this reversible retro-Claisen rearrangement during the preparation of aldehyde **18**, which after chromatography was in equilibrium with its valence bridged isomer 2-oxabicyclo[3.2.1]octa-3,6-diene **19** as a 7:3 mixture (assigned by NMR).¹² This equilibrium could be displaced toward retro-Claisen product **19** when this compound was engaged in a [2+2] cycloaddition of its enol ether double bond with tetracyanoethylene (60% yield). A similar rearrangement was observed a few years later with substituted analogues of aldehyde **18**,¹⁴ while the presence of a chloro substituent α to the aldehyde remarkably shifted the equilibrium towards the dihydrooxepine (95%), presumably by destabilizing the aldehyde.^{3d,15}

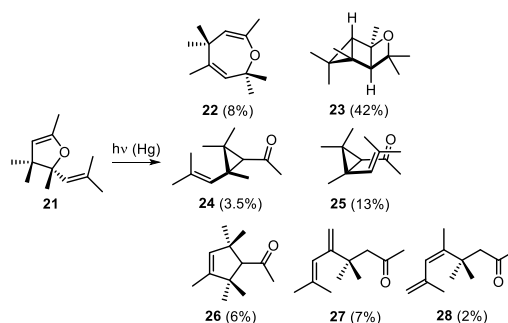


Scheme 3. Pioneer works on the retro-Claisen reaction (1963-1969).

In 1969, Cockroft and Rhoads finally succeeded in synthesizing 2,5-dihydrooxepine **3**, showing that *cis*-**4** is in fact "quite thermolabile and may be diverted quantitatively to **3** under mild conditions",⁶ de facto rebutting Vogel's preliminary observation on its "surprisingly high thermal stability" up to 400°C (Scheme 3).¹¹ Compound **3** could be isolated in a >95% purity level, by slow distillation of aldehyde *cis*-**4** (which allowed enrichment in the more volatile component **3**) and then gas chromatography at 50°C. Compound **3** slowly reverted to *cis*-**4** at room temperature with a half-life of 1 day, to finally reconstitute the equilibrium mixture of *cis*-**4**/**3** in a 95:5 ratio. During the same study, Cockroft and

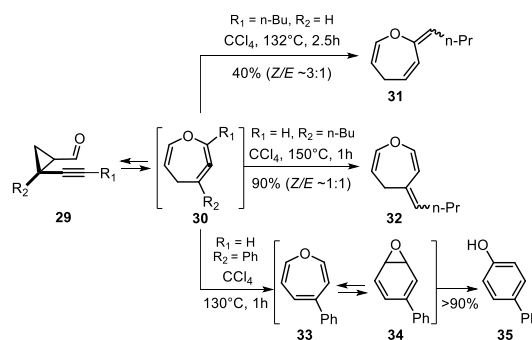
Rhoads showed that *cis*-**4** interconverted with its *trans* isomer and with its valence isomer 2-vinyl-2,3-dihydrofuran **20** under more energetic conditions at ~200-300°C (Scheme 3). Together with Vogel's results, these studies illustrated the stability and the reactivity landscape of 2-vinylcyclopropanecarbonyl derivatives like *cis*-**4**, and prefigured possible synthetic challenges when working with these compounds.

A marginal study was reported by Wiemann and co-workers in 1970, concerning the photoisomerization of 2-vinyl-2,3-dihydrofuran **21**, leading to a mixture of valence isomerization (**22-26**) or rearranged linear (Norrish-type) compounds **27-28** (Scheme 4). The major product of this reaction (**23**, 42% yield) resulted from the transannular [2+2] cyclization of 2,5-dihydrooxepine **22**, which was isolated in 8% yield.¹⁶ In fact, it is remarkable that intermediate compound **22** could be formed, if we consider that the retro-Claisen rearrangement involving 2-vinylcyclopropyl ketones (like **25**) are exceptional and strongly depend on structural characters (see later discussion). Here, the steric hindrance induced by the high density of methyl groups on intermediate **25** may be responsible for this observation, by destabilizing it.



Scheme 4. Photoisomerization of 2-vinyl-2,3-dihydrofuran **21**.

Later on, the retro-Claisen rearrangement of 2-alkynylcyclopropane carboxaldehydes (**29**) was first reported by Chuche in 1979. It may be synthetically useful for the synthesis of oxepine rings, but it has never been exploited.¹⁷ In solution at temperatures between 130 and 150°C, aldehydes **29** afforded alkylidenedihydrooxepines **31** and **32**, or transient oxepine **33**, depending on substituents (Scheme 5). This rearrangement would involve highly strained oxacycloheptatrienes **30** and a [1,3] hydrogen shift. Oxepine **33** was not isolated, being in equilibrium with arene oxide **34**, and finally leading to phenol **35**.



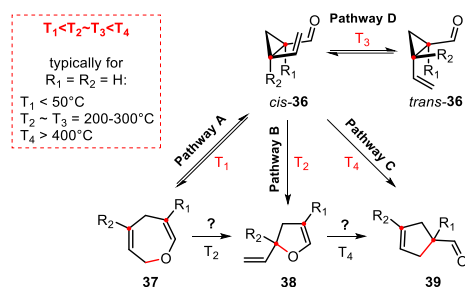
Scheme 5. Rearrangement of 2-alkynylcyclopropyl-1-carboxaldehydes **29**.

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In the 1990's, the scope of this reaction was more thoroughly investigated by Reißig¹⁸ and Boeckman,¹⁹ who independently showed that the equilibrium of the retro-Claisen rearrangement can be displaced towards the 2,5-dihydrooxepine thanks to the presence of substituents. These findings paved the way towards new synthetic studies. Methodological developments rely on the reactivity of the 2-vinylcyclopropane carbonyl partner. Before describing the recent progress on synthetic developments, a theoretical and practical overview of the reactivity and stability of these two reactive species shall be given.

3. Reactivity landscape of 2-vinylcyclopropane-1-carbonyl compounds

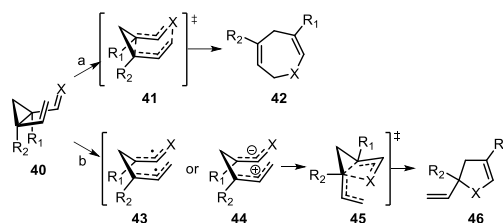
Cis-2-vinylcyclopropane-1-carbonyl compounds (**36**) are donor-acceptor cyclopropanes, bearing a labile C-C bond at the 1,2-position.²⁰ Their high functional group density and reactivity make them prompt to rearrangements. However, several questions arise on the selectivity with regard to the reaction conditions. The 2,5-dihydrooxepine products (**37**) are indeed in competition with other rearrangement products such as 2-vinyl-2,3-dihydrofurans (**38**) or cyclopentene-4-carbonyl derivatives (**39**), both arising from Cloke-Wilson-type rearrangements (Scheme 6).^{7,8} Being in equilibrium with their cyclopropane precursors (*cis*-**36**), 2,5-dihydrooxepines may thus be metastable, depending on the thermodynamic parameters of this transformation. Their easy conversion to dihydrofuran products (**38**) has been observed^{18b,21} and it is questionable if this transformation (**37**→**38**) is direct, or if a cyclopropane intermediate from cycloreversion is a prerequisite to this rearrangement (**37**→*cis*-**36**→**38**). Finally, the literature has rarely mentioned the retro-Claisen rearrangement of 2-vinylcyclopropyl ketones,^{22,23} unlike that of carboxaldehyde. During our recent work on such ketones, we observed that this transformation satisfyingly works with cyclic 1,3-diketones, but not with linear 1,3-diketones.²¹ These various aspects and mechanistic considerations will be discussed in the following lines.



Scheme 6. Overview of the reactivity landscape of 2-vinylcyclopropane-1-carbonyl compound *cis*-**36** (the rearrangement of *trans* isomer *trans*-**36** into **38** and **39** is not discussed).

The relationship between the three possible pathways A-C and the *cis-trans* isomerization (pathway D), depicted in Scheme 6, has first been theoretically studied by Fabian and co-workers.²⁴ They used a spin-unrestricted (U)DFT method²⁵ for the [1,3]-sigmatropic rearrangement, and DFT and *ab initio* calculations for the [3,3]-sigmatropic rearrangement. From vinylcyclopropane **40**, both Cope and retro-Claisen transition states adopt a boat-like conformation (**41**) towards **42**, the breaking and the forming bonds being of approximately equal length during a concerted

mechanism (Scheme 7, route a). This [3,3] sigmatropic rearrangement mechanism strikingly contrasts with that of the [1,3] sigmatropic rearrangement, which would involve a biradicaloid (**43**) or zwitterionic (**44**) transition structure towards **46** (Scheme 7, route b). In fact, this last mechanism has been ambiguous for a long time, exhibiting characteristics of both stepwise and concerted pathways.²⁵⁻²⁷



Scheme 7. Mechanism of Cope ($X = \text{CH}_2$) and hetero-Cope ($X = \text{O}, \text{S}, \text{NH}$) (route a), and of the Cloke-Wilson (route b) rearrangements.

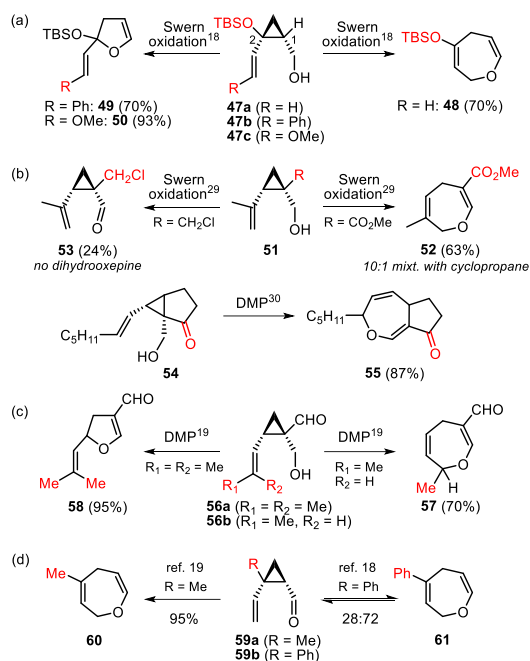
Fabian's study showed that the trends in thermodynamic stability and in activation energies for the three pathways A-C shown in Scheme 6 run in opposite directions.^{24b} Hence, the retro-Claisen rearrangement of cyclopropane *cis*-**36** into 2,5-dihydrooxepine **37** is kinetically favored compared to the Cloke-Wilson rearrangement into 2-vinyl-2,3-dihydrofuran **38**, which is itself kinetically favored over the most thermodynamically stable cyclopentene **39**. Cyclopropane *cis*-**36** and dihydrooxepine **37** were found to be nearly isoenergetic, with an activation energy of 23.4 kcal/mol ($R_1 = R_2 = H$),^{24a} comforting experimental data⁶ and prefiguring the metastability of **37**. Activation energies towards dihydrofuran **38** and cyclopentene **39** were calculated as 32.7 and 36.7 kcal, respectively.^{24b} Overall, these findings are in agreement with experimental results found in the literature, with the formation of dihydrooxepine **37** being kinetically favored, possibly in equilibrium with cyclopropane *cis*-**36** at room temperature (pathway A),⁶ while thermodynamically controlled reactions lead to cyclopentene **39** at high temperatures $>400^\circ\text{C}$.¹¹ In between, at $200\text{-}300^\circ\text{C}$, a *cis-trans* stereoisomerization of the disubstituted cyclopropane (**36**) occurs (pathway D).⁶ At intermediate temperatures ($50\text{-}300^\circ\text{C}$, see Scheme 3), pathway B towards dihydrofurans (**38**) is often observed, especially with substituted substrates whose transition states **43** or **44** can be stabilized (Scheme 7).²⁸

4. Effect of substituents on the retro-Claisen rearrangement

The effect of substituents on the retro-Claisen equilibrium was also theoretically tested by Fabian, showing that substitution of the cyclopropane ring at positions 1 or 2 by CHO and OH lowers the barrier and increases the exothermicity of the reaction towards dihydrooxepine **37**.^{24a} Substituents were theoretically shown to stabilize both reactants and products, with a general preference to the seven-membered ring, except when $R^1 = \text{OH}$, due to hydrogen bonding with the geminal aldehyde. These results were in close agreement with the experiments of Hofmann and Reißig,¹⁸ Boeckman,¹⁹ and later on of Yamaguchi,²⁹ and are particularly relevant to be considered in future synthetic prospects. For example, an OTBS in position 2 of 2-vinylcyclopropane-2-carboxaldehyde (**47a**) allows the retro-Claisen rearrangement

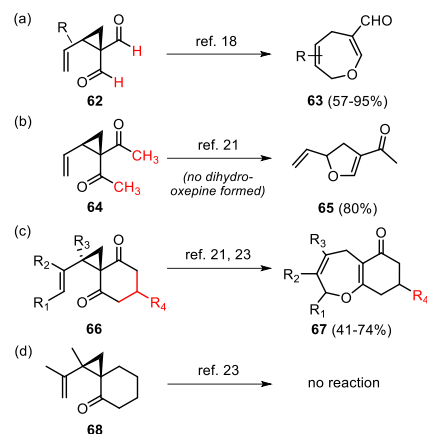
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into **48**, unless a disfavoring substituent on the vinyl group is present (Scheme 8a).¹⁸ This substituent may stabilize the transient cationic charge present on the transition state (see **44**, Scheme 7) towards dihydrofurans **49** and **50**. Furthermore, marked differences can be observed depending on the nature of substituents on position 1 (Scheme 8b and c).^{19,29,30} Carbonyl substituents would destabilize the cyclopropanecarboxaldehyde form, through dipole repulsion, favoring the retro-Claisen rearrangements towards **52**, **55** or **57**. The rearrangement was not observed in the case of a chloromethyl substituent in **53**.²⁹ Substituents on the vinyl group have also a dramatic effect on the reaction equilibrium. In particular, substituents stabilizing zwitterionic transition state **44** would favor the Cloke-Wilson rearrangements instead of the concerted retro-Claisen process. A typical example is found with 2-styrylcyclopropane **47b** studied by Hofmann and Reißig (Scheme 8a).^{18a} The presence of an additional phenyl group induces the formation of a more stabilized cinnamyl cation, compared to the allyl cation, favoring the formation of five-membered product **49**. Similar stabilizing effects have been observed with *gem*-dimethyl substituted vinyl groups (**56a**), compared to the monomethylated analogue **56b** (Scheme 8c). Additional factors influencing the rearrangement may be steric repulsion between substituents (**59a**→**60**) or the gain of resonance between an aryl group and a resulting double bond (**59b**→**61**) (Scheme 8c).



Scheme 8. Effect of substituents on the retro-Claisen rearrangement (DMP: Dess-Martin periodinane). Compound **48** was described as too unstable to be purified, due to moisture and oxygen sensitivity.

With dialdehyde substrates like **62**, the retro-Claisen rearrangement is driven by the increased stability of the donor-acceptor alkene in the enlarged product **63** (Scheme 9a).^{18,19} However, this rearrangement does not work with diketone **64**, which only affords Cloke-Wilson product **65** upon heating (Scheme 9b). By contrast, cyclic diketones **66** afford bicyclic dihydrooxepines **67** in moderate to good yields, as demonstrated by Lee and Hwang,²³ and by us²¹ (Scheme 9c). Remarkably, monoketone **68** is a stable, isolatable compound (Scheme 9d).²³



Scheme 9. Effect of carbonyl substituents on the retro-Claisen rearrangement.

The contrasting behavior of dialdehydes and diketones was recently computationally investigated.²¹ It was found that the presence of a methyl substituent in position 2 of the dihydrooxepine (**69**) was sterically detrimental to the stability ($\Delta G_r = 4.9$ kcal/mol), by comparison with **70**, and thus disfavored the retro-Claisen rearrangement of 2-vinylcyclopropylketones (see Figures 2a and 2b). However, bicyclic dihydrooxepine **71** (Figure 2c) had a better stability and was experimentally attainable, although it was found metastable and nearly isoenergetic with the vinylcyclopropane reactant ($\Delta G_r = -0.7$ kcal/mol).

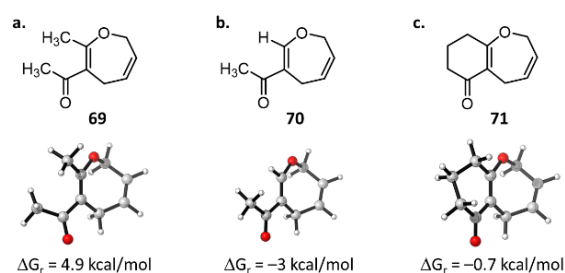
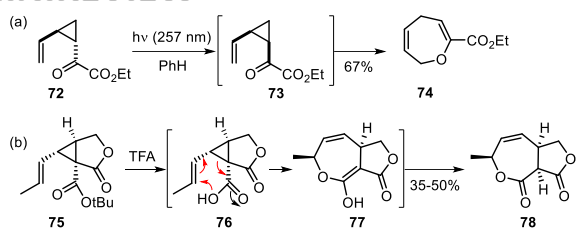


Figure 2. Effect of carbonyl substituents on the stability of retro-Claisen rearrangement products: computed Gibbs free energies (ΔG_r , lowest-energy conformers are shown), relatively to cyclopropane reactants.²¹

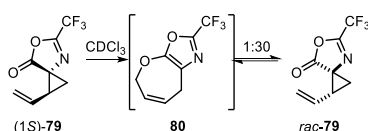
Nevertheless, α -ketoesters like **72-73** seem to be good substrates for dihydrooxepine (**74**) formation as reported by Wenkert, presumably due to the existence of coulombic repulsion between the two carbonyl groups (Scheme 10a).^{22a} Notably, this transformation was performed under UV light irradiation in order to promote the isomerization of **72** into **73**. Furthermore, a peculiar rearrangement of cyclopropylcarboxylic acid **76** into dihydrooxepine **77** was reported by Koskinen during the deprotection of its *t*-butyl ester **75** (Scheme 10b), leading to bislactone **78**.³¹ However, this transformation would not involve a [3,3]-rearrangement, as proposed by the author.

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Scheme 10. Effect of carbonyl substituents on the retro-Claisen rearrangement.

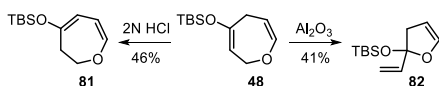
2-Vinylcyclopropyl-1-carboxylates, carboxythiolates and carboxamides are not usually known to be reactive towards the retro-Claisen rearrangement. One example however indicates that this rearrangement may occur with azlactone (1*S*)-**79**, leading to the racemization of this compound through dihydrooxepine **80** (Scheme 11).³² This unstable intermediate was observed as a minor component by ¹H NMR (*rac*-**79**:**80** in a 30:1 ratio).



Scheme 11. Mechanism of the racemization of azlactone **79**.

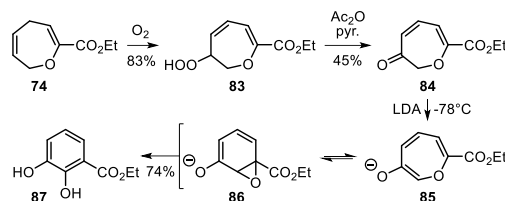
5. Experimental stability of 2,5-dihydrooxepines

In addition to the substitution pattern already discussed,²¹ acidic conditions may also affect the stability of dihydrooxepines by promoting the ring opening, releasing an allylic cation and a nucleophilic enol or enolate. Reißig and co-workers studied the stability of dihydrooxepines under several acidic conditions.¹⁸ Remarkably, 2,5-dihydrooxepine **48** was isomerized to conjugated 2,3-dihydrooxepine **81** in 46% yield by treatment with 2*N* HCl, while basic alumina provoked its isomerization into dihydrofuran **82** in 41% (Scheme 12). It was also observed that storage of other dihydrooxepines in CDCl₃ at room temperature or contact with Florisil or silica gel resulted in the dihydrofuran formation.^{18,22}



Scheme 12. Stability of dihydrooxepine **48** under Brønsted or Lewis acidic conditions.

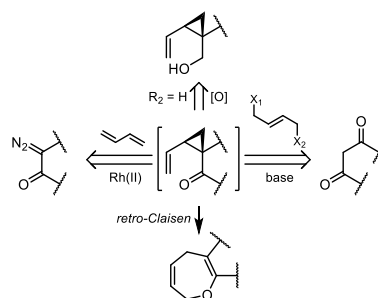
2,5-Dihydrooxepines, as electron-rich compounds, were suspected to be oxygen sensitive. Dehydrogenation conditions to form oxepine heterocycles were attempted by Wenkert with no success.^{22a} However, the oxygenation of dihydrooxepine **74**, under a stream of oxygen, yielded hydroperoxide **83** in 83% b.r.s.m. yield, whose Kornblum-DelaMare reaction furnished 2,5-dihydrooxepin-3-one **84** in 45% yield (Scheme 13). This compound, upon LDA deprotonation, gave *o*-pyrocatechuate **87**, indicative of the transient formation of oxepine **85**.



Scheme 13. Transformation of dihydrooxepine **74** through hydroperoxide **83**.

6. Synthetic applications towards and from 2,5-dihydrooxepines

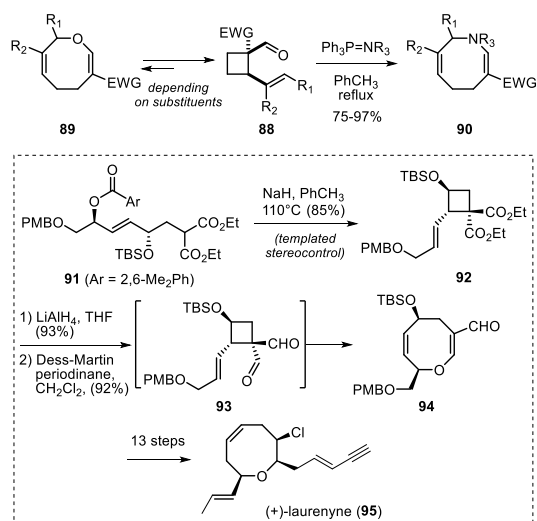
The retro-Claisen strategy towards 2,5-dihydrooxepines necessitates the construction of reactive 2-vinylcyclopropyl-1-carbonyl intermediates. Two major routes have been exploited to install the vinylcyclopropane ring, either through metal carbene-mediated cyclopropanation³³ or through the dialkylation of a 1,3-dicarbonyl anions by 2-butene conjunctive bis-electrophiles,³⁴ (Scheme 14). In many cases, the aldehyde involved in retro-Claisen rearrangements was also installed by the oxidation of a primary alcohol. Examples will be given in the following lines.



Scheme 14. Strategies for the construction of 2-vinylcyclopropyl-1-carbonyl intermediates.

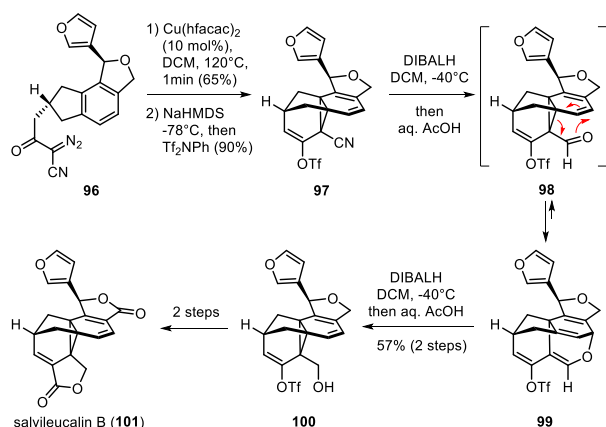
Boeckman's preliminary studies of the retro-Claisen rearrangement showed that dihydrooxepines can be favored, over their cyclopropane precursors, by π -conjugated stabilizing groups.¹⁹ These results inspired further works on functionalized, chiral 2-vinylcyclobutane homologues (**88**) as key intermediates to construct oxygenated (**89**) and nitrogenated (**90**) eight-membered rings (Scheme 15).³⁵ It culminated with the asymmetric total synthesis of (+)-laurenyne **95**³⁶ from linear intermediate **91**.^{35b} Compound **91** was first cyclized into cyclobutane **92** with a high stereoselectivity thanks to chelation control, before generating dialdehyde **93**, substrate of the retro-Claisen rearrangement. This rearrangement completely favored oxocine **94**, which afforded natural product **95** after 13 additional steps.

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Scheme 15. Boeckman's applications of the retro-Claisen rearrangement and its total synthesis of (+)-laurenyne (**95**). Substituents: EWG = CHO, SO₂Ph; R₁ = H, CH₃, CH₂OPMB; R₂ = H, CH₃, OTBS; R₁, R₂ = (CH₂)₃; R₃ = Bn, *n*-Bu, (CH₂)₂CO₂Et, TMS, Ph.

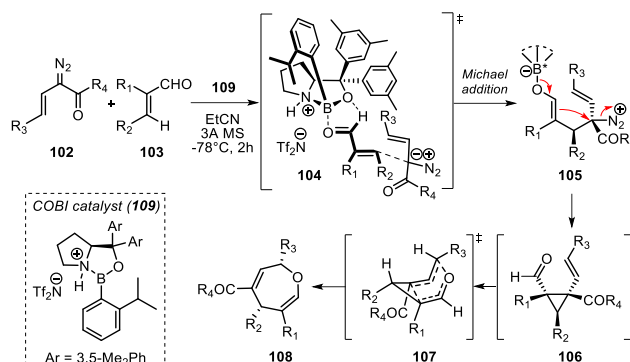
In 2011, the total synthesis of salvileucalin B (**101**) by Reisman and co-workers highlighted the fortuitous formation of [3.2.2] bridged 2,5-dihydrooxepine **99** (Scheme 16).³⁷ A copper(II) catalyzed intramolecular cyclopropanation followed by enol triflation was used to set up cyanocyclopropane intermediate **97** from **96**. The nitrile group was then reduced in the presence of diisobutylaluminum hydride (DIBALH) and after an acidic treatment (aq. AcOH), instead of expected aldehyde **98**, retro-Claisen product **99** was obtained as a light and oxygen sensitive material. Further reduction afforded alcohol **100** which was transformed into salvileucalin B (**101**) after two additional steps.



Scheme 16. Reisman's total synthesis of salvileucalin B (**101**).

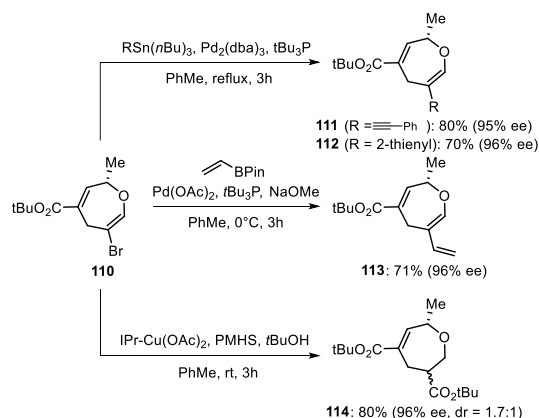
2,5-Dihydrooxepine synthesis until 2017 was characterized by the lack of enantioselective methods. This gap was filled by Ryu and co-workers who developed a remarkable catalytic enantioselective synthesis of highly substituted 2,5-dihydrooxepines (Scheme 17).³⁸ A Michael addition of vinyl diazoesters **102** onto substituted acroleins **103** was enantiospecifically catalyzed by chiral, Lewis acidic, oxazaborolidinium salt **109** (COBI), initiating the cyclopropanation through putative transition state **104**. *Cis*-1-, 2,5-dihydrooxepines

108 were directly obtained in moderate to good yields (52-82%) and good to excellent enantioselectivities ($ee = 76$ -99%), with formyl-2-vinylcyclopropanes **106** as the intermediate undergoing the retro-Claisen rearrangement.



Scheme 17. Ryu's catalytic enantioselective synthesis of highly substituted 2,5-dihydrooxepines (**108**). Substituents: R₁ = Br, Cl, I, Me, Bn, *n*-Pent, Ph; R₂ = H, Me, Et; R₃ = Me, Et, Bn, *n*-Hex, *i*-Pr, *t*-Bu, Ph, 3-ClPh, 3-MePh, 4-FPh, 4-BrPh; R₄ = Ot-Bu, N(Me)OMe.

During this work, bromo derivative **110** could easily be engaged in palladium-catalyzed cross coupling reactions, or the α,β -unsaturated ester part in a copper-catalyzed conjugate reduction, showing the amenability of such 2,5-dihydrooxepines to the synthesis of more complex compounds (Scheme 18). In particular, the Stille coupling of **110** into **111** or **112**, being performed in refluxing toluene, is a stunning result if we consider the temperature sensibility of 2,5-dihydrooxepines. Above all, there was no loss of optical purity during this reaction.

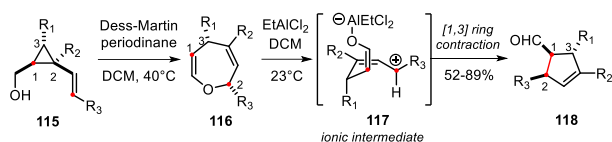


Scheme 18. Functionalization of 6-bromo-2,5-dihydrooxepine **110**.

Nasveschuk and Rovis took advantage of the instability of some 2,5-dihydrooxepines (**116**) to stereoselectively synthesize polysubstituted cyclopentenes (**118**) by Lewis acid-mediated [1,3]-ring contraction.³⁹ The requisite 2,5-dihydrooxepines **116** were prepared at 40°C by the Dess-Martin periodinane oxidation of cyclopropylmethanols **115** (obtained from Simmons-Smith reactions), followed in the same pot by the retro-Claisen rearrangement into **116** (Scheme 19). The stereoselective [1,3]-ring contraction was then performed in diluted DCM solutions (to prevent the formation of oligomeric products) in the presence of EtAlCl_2 at ambient temperature. With R₁ ≠ H, the stereocenter at

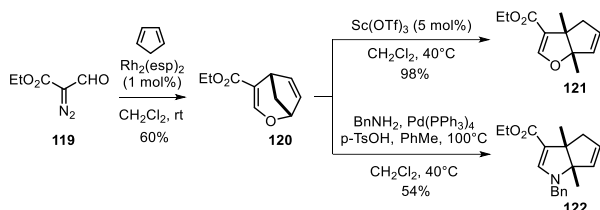
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C-3 allowed controlling the diastereoselectivity of the reaction, through ionic intermediate **117**, which minimized $A_{1,2}$ strain between R_1 and R_2 , and $A_{1,3}$ strains between R_1 and the alkoxide. In fact, the rearrangement was also achieved by using stable 2-vinylcyclopropylcarboxaldehydes, indicating that the formation of the dihydrooxepin is not necessary to the formation of cyclopentene products.



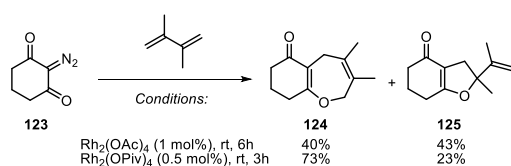
Scheme 19. Rovis' Lewis acid mediated [1,3]-ring contraction of 2,5-dihydrooxepines **116**. Substituents: $R_1 = \text{H, Me}$; $R_2 = \text{Ph, p-Tol, p-CF}_3\text{Ph, CH}_2\text{CH}_2\text{Ph}$; $R_3 = \text{Me, CH}_2\text{CH}_2\text{Ph, CH}_2\text{CH}_2\text{OTBS}$.

Recently, the 2,5-dihydrooxepine products (**120**) of a tandem $\text{Rh}_2(\text{esp})_2$ -catalyzed cyclopropanation/retro-Claisen rearrangement (so-called vinylogous Cloke-Wilson rearrangement by the authors) were used by Piotrowski and Kerr to synthesize heterocyclic scaffolds (**121**, **122**) through ring contraction (Scheme 20).⁴⁰ Monocyclic and bridged dihydrooxepines were submitted to scandium triflate catalysis in dichloromethane at 40°C, leading to 2,3-dihydrofurans (**121**). In the presence of an amine, dihydropyrrole **122** was formed.



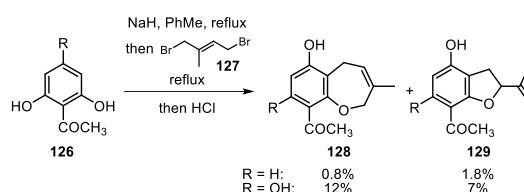
Scheme 20. Kerr's synthesis of heterocyclic scaffolds by the ring contraction of 2,5-dihydrooxepines.

All previous examples focused on the reactivity of cyclopropanecarboxaldehyde substrates. Cases dealing with cyclopropylketones are rarer, as previously discussed (Scheme 9 and Figure 2). Wenkert and co-workers demonstrated that α -(2-vinylcyclopropyl-1-keto)esters (**73**) are good substrates for retro-Claisen rearrangement (Scheme 10a).²² Later, Lee and Hwang used 2-diazocyclohexadiones (**123**) for the cyclopropanation of various 1,3-dienes, and observed the formation of bicyclic 2,5-dihydrooxepine products (e.g. **124**), as separable mixtures with 2,3-dihydrofurans (**125**) (Scheme 21). The yields could be optimized by the use of $\text{Rh}_2(\text{OPiv})_4$ as a cyclopropanation catalyst, allowing shortening reaction times to 3 hours at room temperature. Comparatively, $\text{Rh}_2(\text{OAc})_4$ led to lower product selectivity.



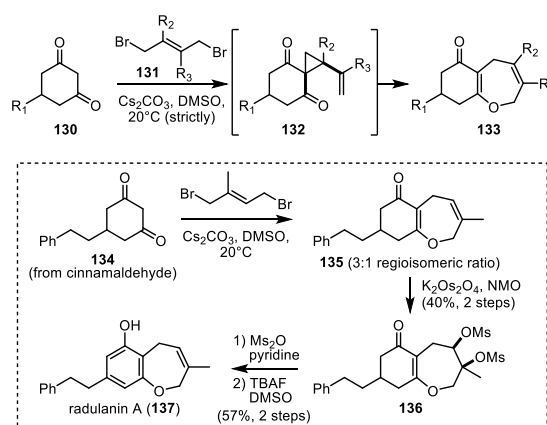
Scheme 21. Lee and Hwang's synthesis of bicyclic dihydrooxepines.

In 1986, Kawase and co-workers reported the use of acetophenones **126** as nucleophiles reacting with conjunctive bis-electrophile **127**,³⁴ giving dihydrobenzoxepines **128** in poor yields, presumably through cyclopropane intermediates, along with 2,3-dihydrobenzofurans **129** (Scheme 22).⁴¹ With phloroglucinol dimethyl ether, a 2,3-dihydrobenzofuran product was only observed. The poor yields of these transformations showed the limitation of this method when using phenolic nucleophiles to generate the vinylcyclopropane intermediates.



Scheme 22. Kawase's synthesis of 2,5-dihydrobenzoxepines from phenolic nucleophiles.

Indeed, using similar retrosynthetic disconnections, we investigated the application of the retro-Claisen rearrangement to the synthesis of natural products with a 2,5-dihydrobenzoxepine core. We found that simple cyclohexadiones (**130**) were annulated with 1,4-dibromobutene electrophiles (**131**) at 20°C in the presence of Cs_2CO_3 in DMSO, giving bicyclic dihydrooxepines **133** (Scheme 23).²¹ On this occasion, we highlighted the temperature sensitivity of this reaction, which was also explained by a theoretical study of the retro-Claisen rearrangement of 2-vinylcyclopropyl diketones (**132**, $R_1, R_2, R_3 = \text{H}$). Critical to the success of the method was the strict control of the temperature (20°C) and the purification over chilled column chromatography. The reaction was applied to the short total synthesis of radulanin A (**137**) from diketone **134**. During this work, bicyclic 2,5-dihydrooxepine **135** was efficiently converted to 2,5-dihydrobenzoxepine **137** thanks to a peculiar sequence of dihydroxylation-mesylation-elimination.



Scheme 23. Nay's approach to bicyclic 2,5-dihydrooxepines and the total synthesis of radulanin A (**137**). Substituents: $R_1 = \text{H, Me, (CH}_2)_2\text{Ph, CH=CHPh}$; $R_2 = \text{H, Me}$; $R_3 = \text{H, Me, Ar, Alk}$.

7. Conclusion

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As demonstrated in this article, the retro-Claisen rearrangement of 2-vinylcyclopropylcarbonyl substrates into 2,5-dihydroxepines can be a useful tool in organic synthesis, provided that several conditions are met regarding substrate and product reactivity. Although the applications may be limited by the temperature-sensitivity of products, this rearrangement is generally performed under mild reaction conditions, especially at room temperature. In fact, this limitation may be directly dependent on the strategy used to generate the 2-vinylcyclopropylcarbonyl substrate. As an intramolecular process, it also tolerates a wide variety of functional groups, which may often stabilize the 2,5-dihydroxepine products. Considering the number of biologically active natural products sharing an oxepane ring, we believe that this report will be helpful to synthetic chemists seeking to develop short and efficient total synthesis, and new synthetic methodologies towards biologically relevant compounds.

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Keywords: [3,3] sigmatropic rearrangements • retro-Claisen rearrangements • vinylcyclopropanes • oxepanes • synthetic methodologies

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