

One-Pot Synthesis of Metastable 2,5-Dihydrooxepines Through Retro-Claisen Rearrangements: Methods and Applications

Wei Zhang, Emmanuel Baudouin, Marie Cordier, Gilles Frison, Bastien Nay

▶ **To cite this version:**

Wei Zhang, Emmanuel Baudouin, Marie Cordier, Gilles Frison, Bastien Nay. One-Pot Synthesis of Metastable 2,5-Dihydrooxepines Through Retro-Claisen Rearrangements: Methods and Applications. Chemistry - A European Journal, 2019, 10.1002/chem.201901675 . hal-02135526

HAL Id: hal-02135526
https://hal.science/hal-02135526

Submitted on 21 May 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

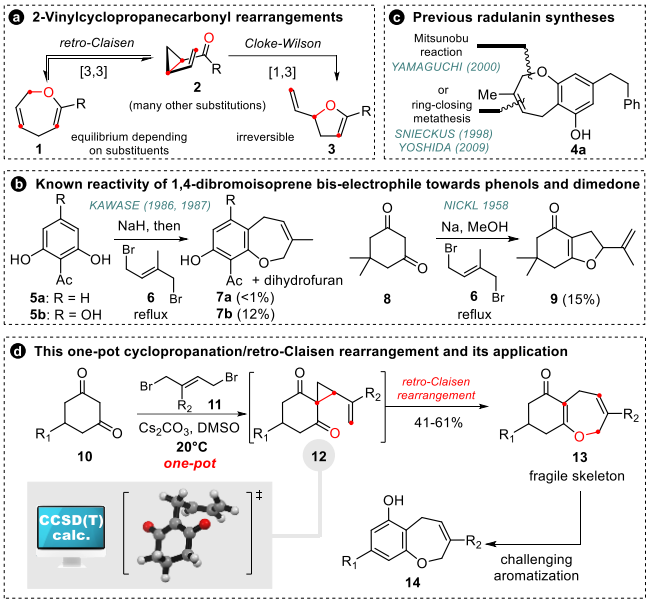
One-Pot Synthesis of Metastable 2,5-Dihydrooxepines Through Retro-Claisen Rearrangements: Methods and Applications

Wei Zhang,[a],[b] Emmanuel Baudouin,[c] Marie Cordier,[d] Gilles Frison*,[d] and Bastien Nay*,[a]

Abstract: A one-pot methodology to synthesize metastable bicyclic 2,5-dihydrooxepines from cyclic 1,3-diketones and 1,4-dibromo-2-butenes is reported, through the retro-Claisen rearrangement of syn-2-vinylcyclopropyl diketone intermediates. High-level quantum chemical calculations were performed to understand the reaction selectivity and mechanisms towards [1,3] or [3,3]-sigmatropic rearrangements, highlighting the crucial influence of temperature in close relation to experimental results. The reaction was successfully applied to a short protecting group-free total synthesis of radulanin A, a natural 2,5-dihydrobenzoxepine, featuring an unprecedented aromatization strategy of the transient bicyclic 2,5-dihydrooxepine. We demonstrate for the first time the strong herbicidal potential of this natural product.

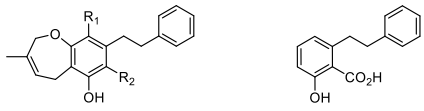
Introduction

Pioneering reports by Vogel,[1] Dreiding,[2] and Rhoads[3] on the valence tautomerism between unsubstituted 2,5-dihydrooxepines **1** and *syn*-2-vinylcyclopropane-1-carboxaldehydes **2** (Scheme 1a, R = H) highlighted an equilibrium in favor of **2**. In the 1990s, Reißig,[4] Boeckman,[5] and then Yamaguchi,[6] demonstrated that the retro-Claisen (also 1-oxa-Cope) seven-membered product can be strongly favored by the presence of donor-acceptor stabilizing groups on the vinylcyclopropane (VCP) moiety.[7] More recently, the use of stabilizing substituents allowed the development of catalytic enantioselective synthesis of 2,5-dihydrooxepines,[8] or their use as synthetic intermediates towards polysubstituted 5-membered rings.[9] However, these works only concern VCP-carboxaldehyde substrates (**2**, R = H), since for yet untargeted reasons, linear *syn*-VCP ketones (R ≠ H) are unreactive towards [3,3]-sigmatropic rearrangements. There are two exceptions with ketone substrates, when they are part of an oxalyl system,[10] or of a cyclic 1,3-diketone.[11] Furthermore, even though this retro-Claisen [3,3]-rearrangement often occurs at room temperature or below through a concerted mechanism, it rapidly enters in detrimental competition with the Cloke-Wilson rearrangement towards dihydrofurans (**3**, Scheme 1a),[12] which has been theoretically investigated by Fabian and Reißig.[13] Such a competition can have dramatic consequences when heating is needed to install the VCP system, leading to mixtures of products (case of **7a-b**) or full recovery of the Cloke-Wilson product (case of **9**) (Scheme 1b).[11,14] Overall, the reversibility of the retro-Claisen rearrangement and the competing Cloke-Wilson reaction result in metastable 2,5-dihydrooxepines, which have precluded further synthetic developments. As far as we know, this rearrangement has only been once and fortuitously reported in a total synthesis context, that of salvileucalin B by Reisman.[15]



Scheme 1. Synthetic strategies developed towards 2,5-dihydrooxepines.

The oxepane ring is present in a wide variety of natural products and we thought this retro-Claisen rearrangement could be further extended to the rapid construction of some of them.[16] In particular, radulanins (**4a-c**) are phenolic compounds containing a 2,5-dihydrooxepine, isolated from liverworts (Fig. 1).[17] They were previously prepared by Snieckus[18] and Yoshida[19] by ring-closing olefin metatheses, while Yamaguchi used a Mitsunobu reaction (Scheme 1c).[20] Interestingly, Kawase reported in 1986 the direct formation of a 2,5-dihydrobenzoxepin ring (**7a-b**) by the alkylation of phenolic substrates (**5a-b**) with bis-electrophile 1,4-dibromoisoprene **6**, but this work suffered from very limited yields (Scheme 1b).[14]



[a] Dr. W. Zhang, Dr. B. Nay
Laboratoire de Synthèse Organique, Ecole Polytechnique, CNRS, ENSTA, Institut Polytechnique de Paris, 91128 Palaiseau, France
E-mail: bastien.nay@polytechnique.edu
[b] Dr. W. Zhang
Unité Molécules de Communication et Adaptation des Micro-organismes, Muséum National d'Histoire Naturelle, CNRS, 57 rue Cuvier, 75005 Paris, France
[c] Dr. E. Baudouin
Laboratoire de Biologie du Développement, Institut de Biologie Paris Seine, Sorbonne Université, CNRS, Paris 75005, France
[d] Marie Cordier, Dr. G. Frison
Laboratoire de Chimie Moléculaire, Ecole polytechnique, CNRS, Institut Polytechnique de Paris, 91128 Palaiseau, France
E-mail: gilles.frison@polytechnique.edu

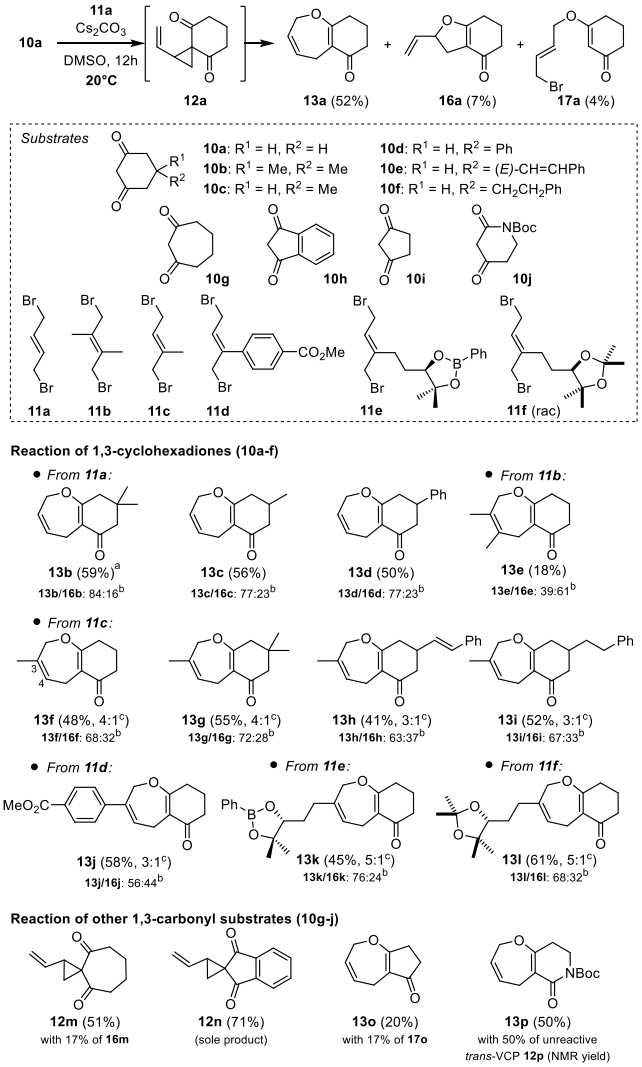
Supporting information for this article is given via a link at the end of the document.((Please delete this text if not appropriate))

Figure 1. Structure of radulanins and their structural analogy with lunularic acid.

Herein we describe the experimental and theoretical studies we performed on VCP-substituted ketones to tame this sensible retro-Claisen rearrangement prior synthetic application (Scheme 1d). Our rearrangement is part of a simple tandem sequence, starting with the annulation of a 1,3-cyclohexadione (**10**) by conjunctive 1,4-dibromo-2-butene reagents (**11**)[21] to form VCP intermediate **12**, which spontaneously cyclized into fused 2,5-dihydrooxepine **13**. Remarkably, a similar sequence was reported by Nickl in 1958, performed in methanol at reflux, but only resulted in isomeric 2-vinyl-2,3-dihydrofuran **9**.[22] Quantum chemical calculations will be described to understand the outcome of this rearrangement, comparatively with stable linear VCP-1,3-diketones, and competing with the thermodynamically favoured [1,3]-sigmatropic rearrangement (Scheme 1a).[12] This theoretical study closely follows the trend of our experiments, and rationalizes the required experimental strict control of the temperature to obtain the seven-membered ring in reasonable yields. As an application, radulanin A (**4a**) was successfully synthesized by this methodology, after a challenging aromatization of the cyclohexenone ring on **13**. Based on an allelopathic hypothesis, we supposed that radulanins would affect plant physiology due to their structural analogy with the bibenzyl natural product lunularic acid (**15**, Figure 1),[17d,23] and finally demonstrated the weedkiller property of natural product **4a**.

Results and Discussion

We first used 1,4-dibromo-2-butene **11a** as a suitable conjunctive reagent to generate VCP **12a**[21] from 1,3-cyclohexadione **10a** at 20 °C (Scheme 2). To our delight, by contrast with Nickl's result,[22] this reaction resulted in 2,5-dihydrooxepine **13a** in 52% isolated yield, through the retro-Claisen rearrangement of VCP intermediate **12a** (not isolated), when it was conducted in the presence of Cs_2CO_3 in DMSO (for structure confirmation, see the X-ray crystallography of diol **22**, Scheme 4).[24] Cloke-Wilson product **16a** (7%) and *O*-alkylated product **17a** (4%) were also observed as minor side products, while ^{1}H NMR spectra of **13a** occasionally showed the presence of non-isolatable traces of VCP intermediate **12a**. *Importantly, the reaction temperature had to be strictly maintained at 20°C at maximum, while purifications were performed over chilled chromatography columns (<10°C), in order to avoid the formation of substantial amounts of undesired dihydrofuran **16a***. Extensive optimization of the reaction was performed (bases, solvents, temperature), with yields being limited by the dihydrooxepine stability (see Charts S1-S3 in the SI). Interestingly, the use of tertiary amines as bases strongly favored the formation of dihydrofuran **16a**, while ether and alcohol solvents majored the *O*-alkylation. Among carbonates, Cs_2CO_3 was the most efficient, minimizing the formation of **16a**. Lowering the temperature at 0°C in DMF did not improve yields. In all cases, the temperature window of this transformation was narrow, impacting the reproducibility of the reaction under uncontrolled "room temperature" (>20 °C). Incidentally, heating **13a** at 80°C in DCM for 12 hours led to **16a** in 63% yield.



Scheme 2. Tandem vinylcyclopropanation/retro-Claisen rearrangements toward 2,5-dihydrooxepines (**13**) from various 1,3-cyclohexadiones (**10**) (isolated yields shown). — [a] The NMR yield of this reaction, before isolation, was estimated to 74%, showing some loss of material during purification over chilled (<10°C) silica gel column; [b] Ratio of products **13** (2,5-dihydrooxepine) and **16** (2,3-dihydrofuran) based on NMR of the crude product; [c] Regioisomeric 3-Me/4-Me ratio.

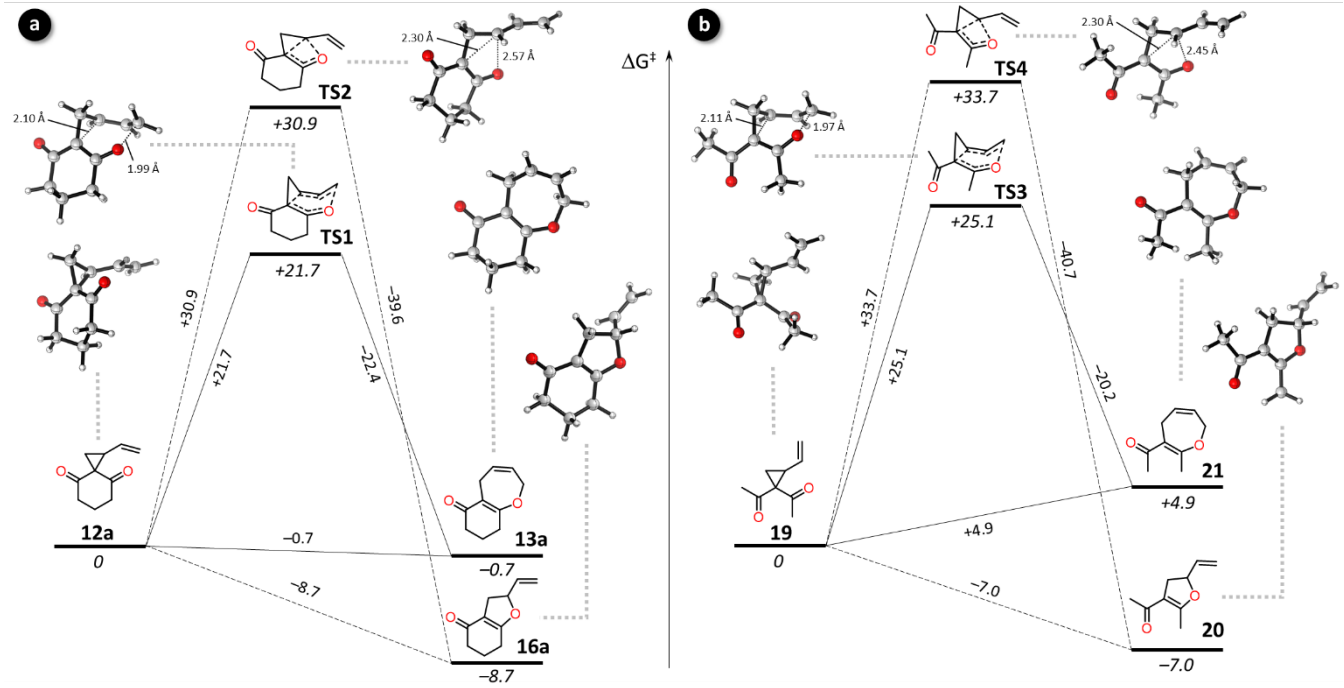
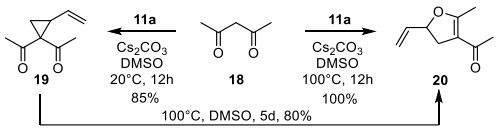


Figure 2. Energy profile of the rearrangement reactions of substrates **12a** (a) and **19** (b). Gibbs free energies relative to starting materials are given in kcal·mol^{-1}.

The reaction was applied to various cyclic 1,3-dicarbonyl substrates (**10a-j**) and 1,4-dibromo-2-butenes (**11a-f**), resulting in substituted 2,5-dihydrooxepine products (Scheme 2). Unsymmetrical dibromobutenes **11c-f** led to regioisomeric products in favor of the 3-substituted dihydrooxepine for obvious steric reasons (3:1 to 5:1 ratios), while **11b** afforded poor yields of the seven-membered ring product, clearly favouring Cloke-Wilson product **16e**. More importantly, an ester (**13j**), a phenylboronate (**13k**) or an acetal (**13l**) were well tolerated during the reaction, while products **13h** and **13i** prefigured the radulanin skeleton. We finally tested other types of 1,3-dicarbonyl substrates to expand the scope of this transformation. 1,3-Cycloheptanedione **10g** and 1,3-indanedione **10h** resulted in VCP adducts **12m** and **12n** in 51 and 71% yields, respectively, which were unable to furnish the corresponding dihydrooxepines, even at higher temperatures. However, 1,3-cyclopentadione **10i** afforded dihydrooxepine **13o** in 20% yield. Since this product was found stable at temperatures up to 80°C, the low yield was attributed to the many tars formed and to the formation of *O*-alkylation product (**17o**). Finally, β-ketolactam **10j** behaved fairly well in this tandem process if we consider that vinylcyclopropanation in that case furnishes an equimolar mixture of *syn*- and *anti*-VCP isomers (relatively to the ketone). Dihydrooxepine **13p** was obtained in 50% yield according to NMR, as an inseparable mixture with the *trans*-VCP isomer.

Comparatively, the reactivity of diketone **10a** upon cyclopropanation contrasts with that of acetylacetone **18**, which afforded VCP **19** with no retro-Claisen rearrangement at 20°C, while it quantitatively yielded dihydrofuran **20** at 100 °C (Scheme 3). Compound **20** could also be obtained in 80% yield by heating **19** in DMSO at 100°C, although needing longer reaction times (5 days). These observations motivated the following theoretical study not only to explain the different reactivity of ketones **10a** and **18**, but also to understand the metastability of dihydrooxepin **13a**.



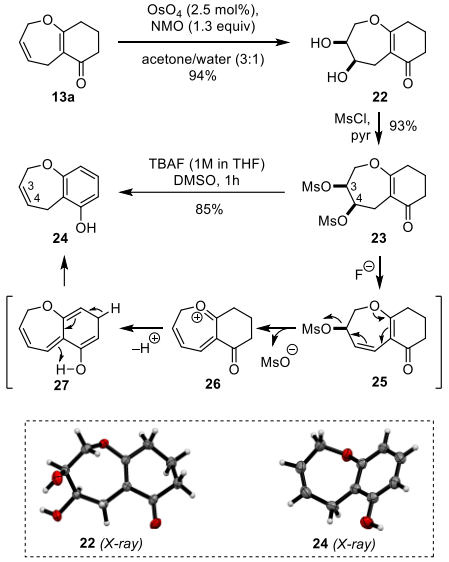
Scheme 3. Reaction outcome of acetylacetone under various conditions. No retro-Claisen product was observed, even at intermediate temperatures.

Compared to the retro-Claisen rearrangement of VCP-carboxaldehydes,[13] that of VCP-ketones has never been theoretically investigated. At our best computational level, CCSD(T)/6-311++G(2d,2p)//M06/6-311G(d,p) including solvent effect (Fig. 2a; see the SI for details), 2,5-dihydrooxepine **13a** was kinetically favoured, yet nearly isoenergetic with VCP **12a** (ΔG_r = –0.7 kcal·mol^{-1}, corresponding to a **13a:12a** ratio of *ca.* 3:1 according to Boltzmann distribution law if thermal equilibrium is assumed). This reaction operates through lower-energy boat-like transition state **TS1** ($\Delta G_0^{\ddagger}$ = +21.7 kcal·mol^{-1}), confirming it can proceed easily and reversibly. Alternatively, 2,3-dihydrofuran isomer **16a** showed better stability (ΔG_r = –8.7 kcal·mol^{-1}), with a higher activation energy of transition state **TS2** ($\Delta G_0^{\ddagger}$ = +30.9

kcal·mol^{-1}), suggesting a more energetic and irreversible reaction. These results indicate a possible competition between the [1,3] (thermodynamic process) and the [3,3]-rearrangements (kinetic process) depending on the reaction temperature, as experimentally observed. A transition structure for the direct isomerization of 2,5-dihydrooxepine **13a** to 2,3-dihydrofuran **16a** was sought, yet without success. Combined with the energetic profile, this fact strongly supports a thermal isomerization through VCP **12a** reversibly formed from **13a**. Furthermore, by contrast with Fabian's results on the [1,3]-rearrangement of VCP-carboxaldehydes,[13] we did not observe a biradicaloid character for **TS2**. It could be explained by the strong donor-acceptor character of **12a**. Additional comparisons of activation energies of both reactions in vacuo and in DMSO also support the polarized or zwitterionic character of **TS2** that may be stabilized by DMSO (see the SI for more discussion).

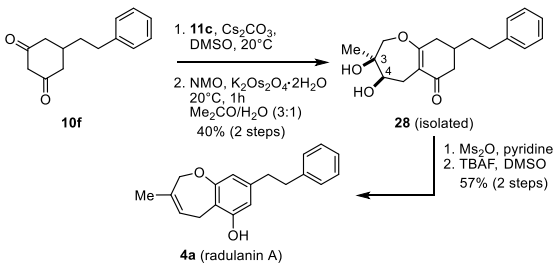
To explain the absence of formation of dihydrooxepine **21** from 1,1-diacetyl-2-vinylcyclopropane **19**, calculations at the same level were performed (Fig. 2b), showing higher thermodynamic stability of substrate **19** compared to **21** (ΔG_r = +4.9 kcal·mol^{-1}), thus disfavouring a retro-Claisen rearrangement through **TS3**. The higher relative Gibbs free energy of **21** compared to **13a** may indicate higher conformational constraints in the acyclic substrate, resulting in lower conjugation of the oxy enone system of **21** (see SI for more details). Finally, as previously, Cloke-Wilson product **20** is thermodynamically favoured (ΔG_r = –7.0 kcal·mol^{-1}), with a higher activation energy of **TS4** ($\Delta G_0^{\ddagger}$ = +33.7 kcal·mol^{-1}). These last results, which, as for the study of the reactivity of **12a**, do not take into account the possible influence of some experimental factors such as the presence of Cs_2CO_3, nevertheless allow to reproduce and explain the trend observed experimentally (Scheme 3).

The synthetic potentiality of bicyclic 2,5-dihydrooxepines was then challenged by targeting the 2,5-dihydrobenzoxepine system. Although common desaturation methods for cyclohexenone aromatization (*e.g.* using halogenation reagents, IBX, CAN, MnO_2, DDQ or Saegusa-Ito reaction) proved unsuccessful due to the thermal sensibility of **13a**, a useful transformation into 2,5-dihydrobenzoxepine **24** was serendipitously discovered after an Upjohn dihydroxylation of **13a** into diol **22** (Scheme 4) and mesylation. Indeed dimesylate **23**, in spite of poor reactivity toward elimination under basic conditions (*e.g.* Cs_2CO_3, t-BuOK, DBU), underwent rapid and clean conversion into aromatic compound **24** in 85% yield, in the presence of TBAF in DMSO.[25] The structure of this compound was confirmed by X-ray crystallography[24] and we were delighted to find a new entry to the synthesis of natural 2,5-dihydrobenzoxepines. This transformation could result from a TBAF-promoted elimination of the mesylate group in position 4, resulting in a conjugated system (**25**) and favoring the elimination of the second mesylate, positioning an olefin at position 3,4 in **26**. Final tautomerization and aromatization into **27** would release 2,5-dihydrobenzoxepine **24**.



Scheme 4. Transformation of 2,5-dihydrooxepine **13a** into 2,5-dihydrobenzoxepine **24**, and possible mechanism for this transformation. ORTEP structures are shown at a probability level of 60%.

With these new transformations in hand, the tandem cyclopropanation/retro-Claisen rearrangement strategy was applied to a short synthesis of radulanin A. Starting from 5-(2-phenylethyl)-1,3-cyclohexanedione **10f** (available from cinnamaldehyde),[26] and 1,4-dibromo-2-methyl-2-butene **11c** (available from isoprene),[22,27] the reaction proceeded as expected, providing 2,5-dihydrooxepine **13i** (Scheme 2) in 52% isolated yield, as a 3:1 regioisomeric mixture. In an optimization procedure, dihydroxylation was directly performed on the crude reaction mixture of **13i**, allowing the formation of diol **28** in 40% yield (2 steps) upon purification from its 4-methyl isomer (Scheme 5). Aromatization of the 6-membered ring was then undertaken from **28**, after mesylation of **28** in the presence of Ms_2O in pyridine and through TBAF-promoted elimination,[25] finally furnishing radulanin A (**4a**) in 57% yield over 2 steps. This challenging transformation was particularly efficient if we consider the trisubstituted nature of the double bond to be regioselectively installed. The NMR data of **4a** were fully consistent with those of the literature.[18]



Scheme 5. Total synthesis of radulanin A (**4a**).

Having identified structural similarities with lunularic acid (**15**), an allelopathic natural product interacting with the abscisic acid pathways and inhibiting seed germination and plant growth,[23] radulanin A (**4a**) was evaluated on *Arabidopsis thaliana* seedlings. It showed remarkable phytotoxic effects at 50 µg/mL after 24h, with a persistent effect after 120 h (Figure 3), to be compared to the similar effect of glyphosate at 25 µg/mL. Interestingly, the dihydrobenzoxepine core alone (**24**) was nearly inactive at the concentration of 100 µg/mL. Although the mechanism of action and toxicity profile of **4a** have to be evaluated, such a relatively simple compound may constitute a new phytopharmaceutical lead. Indeed, there is an urgent need for alternatives to current herbicides, some of which, being a subject of controversy, are threatened to be banned.[28]

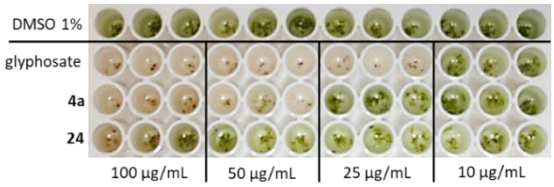


Figure 3. Herbicide activities of radulanin A (**4a**) and 2,5-benzoxepine (**24**) on *Arabidopsis thaliana* seedlings, comparatively to glyphosate (line 2) (DMSO 1% taken as a reference). The picture was taken after 96h (see Figure S3 for activities at 24 and 120 h).

Conclusions

We demonstrated that the tandem vinylcyclopropanation/retro-Claisen rearrangement of 1,3-cyclohexadione substrates can be synthetically useful for the preparation of 2,5-dihydrooxepines when properly controlling the reaction temperature. The reaction was theoretically studied, matching experimental results, and explaining the reactivity difference observed between substrates derived from cyclic or linear 1,3-diketones. This study thus complements the chapter on this powerful rearrangement discovered in the 1960s.[1-6] Importantly, this one-pot retro-Claisen rearrangement was applied to a short total synthesis of a natural product, radulanin A, especially using an ingenious final aromatization procedure. With this compound in hand, we demonstrated for the first time its phytotoxic property, validating our allelopathic hypothesis and paving the way to the development of natural herbicides, which may have better environmental profiles than those currently used synthetic derivatives.

Experimental Section

General procedure for tandem cyclopropanation/retro-Claisen sequence towards 2,5-dihydrooxepines: Cs_2CO_3 (1.1 equiv.) was added to a solution of cyclohexadione **10** (1 equiv.) in DMSO (0.1 M) and the solution was stirred at 20°C (thermostated) for 20 min. Then a solution of 1,4-dibromo-2-butene **11** (1.1 equiv.) in DMSO was added to the mixture at 20˚C (precisely). The reaction was stirred at 20˚C for another 12 h, before being diluted with Et_2O and quenched with chilled water (0˚C). The organic layer was washed 3 times with brine. The aqueous phases were further extracted 3 times with diethyl ether. The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure, avoiding heating above 20°C. The residue was then purified by flash chromatography on silica gel, using a chilled column (<10°C) to furnish dihydrooxepin **13**.

Acknowledgements

We thank Sorbonne Université and the Graduate School of Molecular Chemistry for providing a PhD grant to WZ. We thank Mr. Davy Lin for experimental support in the synthesis of compound **10f**. The CNRS, Sorbonne Université and Ecole Polytechnique are acknowledged for financial supports.

Keywords: 2,5-dihydrooxepines • sigmatropic rearrangement • density functional calculations • total synthesis • herbicide

[1] E. Vogel, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 1-11.
[2] M. Rey, A. S. Dreiding, *Helv. Chim. Acta* **1965**, *48*, 1985-1987.
[3] S. R. Rhoads, R. D. Cockroft, *J. Am. Chem. Soc.* **1969**, *91*, 2815-2816.
[4] a) B. Hofmann, H.-U. Reißig, *Synlett* **1993**, 27-29; b) B. Hofmann, H.-U. Reißig, *Chem. Ber.* **1994**, *127*, 2327-2335.
[5] R. K. Boeckman Jr., M. D. Shair, J. R. Vargas, L. A. Stolz, *J. Org. Chem.* **1993**, *58*, 1295-1297.
[6] S. Yamaguchi, A. Arisawa, N. Katoh, K. Hatanaka, H. Yokoyama, Y. Hirai, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2215-2219
[7] T. F. Schneider, J. Kaschel, D. B. Werz, *Angew. Chem. Int. Ed.* **2014**, *53*, 5504-5523.
[8] S. Y. Shim, S. M. Cho, A. Venkateswarlu, D. H. Ryu, *Angew. Chem. Int. Ed. Engl.* **2017**, *56*, 8663-8666.
[9] a) C. G. Nasveschuk, T. Rovis, *Angew. Chem. Int. Ed.* **2005**, *44*, 3264-3267; b) M. L. Piotrowski, M. A. Kerr, *Org. Lett.* **2018**, *20*, 7624-7627.
[10] a) M. E. Alonso, P. Jano, M. I. Hernandez, R. S. Greenberg, E. Wenkert, *J. Org. Chem.* **1983**, *48*, 3047-3050; b) E. Wenkert, R. S. Creenherg, H.-S. Kim, *Helv. Chim. Acta* **1987**, *70*, 2159-2165.
[11] Y. R. Lee, J. C. Hwang, *Eur. J. Org. Chem.* **2005**, *8*, 1568-1577.
[12] a) J. B. Cloke, *J. Am. Chem. Soc.* **1929**, *51*, 1174-1187; b) C. L.Wilson, *J. Am. Chem. Soc.* **1947**, *69*, 3002-3004.
[13] a) D. Sperling, H.-U. Reißig, J. Fabian, *Liebigs Ann./Recueil* **1997**, 2443-2449; b) D. Sperling, H.-U. Reißig, J. Fabian, *Eur. J. Org. Chem.* **1999**, 1107-1114.
[14] a) S. Yamaguchi, A. Saitoh, Y. Kawase, *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3983-3984; b) S. Yamaguchi, M. Takai, I. Hanazome, Y. Okada, Y. Kawase, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3603-3605. See also Nickl's anterior result instead showing the formation 2-isopropenyl-2,3-dihydrobenzofurans (ref. 22).
[15] S. Levin, R. R. Nani, S. E. Reisman, *J. Am. Chem. Soc.* **2011**, *133*, 774-776.
[16] General reviews on oxepane chemistry: a) D. R. Boyd, in D.R. Boyd, in *Comprehensive Heterocyclic Chemistry, Vol. 7* (Eds: A. R. Katritzky and C. W. Rees), Elsevier Ltd., **1984**, pp. 547-592; b) N. L. Snyder, H. M. Haines, M. W. Peczuh, *Tetrahedron* **2006**, *62*, 9301-9320.
[17] a) Y. Asakawa, M. Toyota, T. Takemoto, *Phytochemistry* **1978**, *17*, 2005-2010; b) Y. Asakawa, E. Kusube, T. Takemoto, C. Suire, *Phytochemistry* **1978**, *17*, 2115-2117; c) Y. Asakawa, R. Takeda, M. Toyota, T. Takemoto, *Phytochemistry* **1981**, *20*, 858-859; d) Y. Asakawa, K. Takikawa, M. Toyota, *Phytochemistry* **1982**, *21*, 2481-2490; e) Y. Asakawa, T. Hashimoto, K. Takikawa, M. Tori, S. Ogawa, *Phytochemistry* **1991**, *30*, 235-251.
[18] M. Stefinovic and V. Snieckus, *J. Org. Chem.* **1998**, *63*, 2808-2809.

[19] M. Yoshida, K. Nakatani, K. Shishido, *Tetrahedron* **2009**, 5702-5708.
[20] a) S. Yamaguchi, K. Furihata, M. Miyazawa, H. Yokoyama, Y. Hirai, *Tetrahedron Lett.* **2000**, *41*, 4787-4790; b) S. Yamaguchi, N. Tsuchida, M. Miyazawa, Y. Hirai, *J. Org. Chem.* **2005**, *70*, 7505-7511.
[21] a) R. W. Kierstead, R. P. Linstead, B. C. L. Weedon, *J. Chem. Soc.* **1952**, 3610-3616; b) R. W. Kierstead, R. P. Linstead, B. C. L. Weedon, *J. Chem. Soc.* **1953**, 1799-1803.
[22] J. Nickl, *Chem. Ber.* **1958**, 553-565.
[23] a) I. F. M. Valio, R. S. Burdon, W. W. Schwabe, *Nature* **1969**, *223*, 1176-1178; b) H. Yoshikawa, Y. Ichiki, K. D. Sakakibara, H. Tamura, M. Suiko, *Biosci. Biotechnol. Biochem.* **2002**, *66*, 840-846.
[24] Crystallographic data of compounds **22** and **24** are available free of charge at the Cambridge Crystallographic Data Centre under number CCDC 1890832 and 1890833, respectively.
[25] M. Bérubé, F. Kamal, J. Roy, D. Poirier, *Synthesis*, **2006**, *18*, 3085-3091.
[26] G. R. Ames, W. Davey, *J. Chem. Soc.* **1956**, 3001-3006.
[27] C. A. Falciola, K. Tissot-Crosset, H. Reyneri, A. Alexakis, *Adv. Synth. Catal.* **2008**, *350*, 1090-1100.
[28] a) K. Z Guyton, D. Loomis, Y. Grosse, F. El Ghissassi, L. Benbrahim-Tallaa, N. Guha, C. Scoccianti, H. Mattock, K. Straif, *Lancet Oncol.* **2015**, *16*, 490-491; b) S. Foucart and S. Horel, *Nature* **2018**, *555*, 443; c) G. Andreotti, S. Koutros, J. N. Hofmann, D. P. Sandler, J. H. Lubin, C. F. Lynch, C. C Lerro, A. J. De Roos, C. G. Parks, M. C. Alavanja, D. T. Silverman, L. E. B. Freeman, *J. Natl. Cancer Inst.* **2018**, *110*, 509-516.

Graphical abstract:

