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REVIEW

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Cite this: *Nat. Prod. Rep.*, 2024, **41**, 813

The Kornblum DeLaMare rearrangement in natural product synthesis: 25 years of innovation

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Received 30th October 2023

DOI: 10.1039/d3np00058c

rsc.li/npr

Covering: 1998 up to the end of 2023

Since its initial disclosure in 1951, the Kornblum DeLaMare rearrangement has proved an important synthetic transformation and has been widely adopted as a biomimetic step in natural product synthesis. Utilising the base catalysed decomposition of alkyl peroxides to yield a ketone and alcohol has found use in many syntheses as well as a key strategic step, including the unmasking of furans, as a biomimetic synthetic tool, and the use of the rearrangement to install oxygen enantioselectively. Since *ca.* 1998, its impact as a synthetic transformation has grown significantly, especially given the frequency of use in natural product syntheses, therefore this 25 year time period will be the focus of the review.

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1 Introduction

The base catalysed decomposition of an alkyl-peroxide to give a ketone and alcohol was first reported by Nathan Kornblum and Harold DeLaMare in 1952.[1] Unlike previous work by Milas and Surgenor,[2] who had demonstrated the stability of *t*-butyl hydroperoxide to base, Kornblum and DeLaMare exposed 1-phenylethyl-*t*-butyl peroxide **1** to piperidine giving acetophenone (**3**) and *t*-butyl alcohol (**5**) in 79% and 25%, respectively (Scheme 1a). This reaction was also found to be consistent with potassium hydroxide and sodium ethoxide as the base. Significantly, the authors identified the importance of an α-hydrogen relative to the peroxide, and accordingly they proposed an elimination mechanism as outlined in Scheme 1a. This mechanism was found to have similarities with the base mediated decomposition of nitrate esters[3] and has subsequently become the bedrock of what is now known as the Kornblum DeLaMare rearrangement of peroxides, which we will now refer to as the KDM rearrangement within this review.

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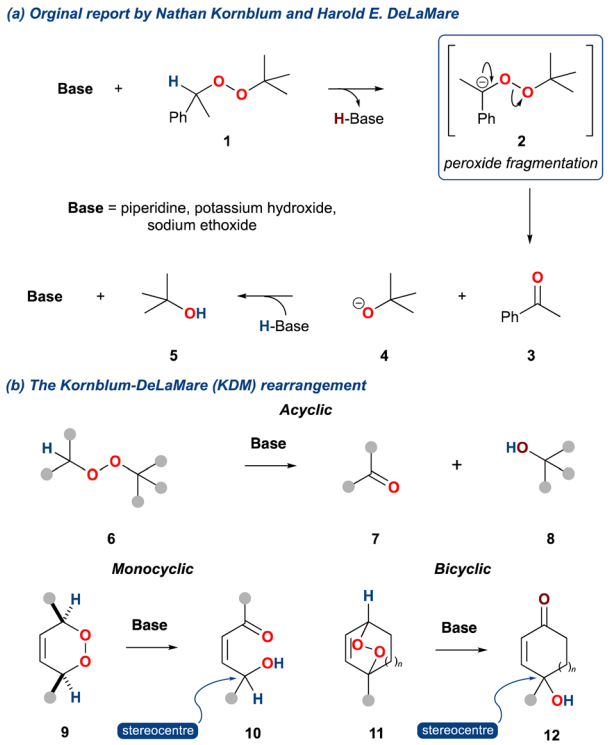

Scheme 1 (a) The original report of Nathan Kornblum and Harold DeLaMare; (b) product outcome of the Kornblum DeLaMare rearrangement for acyclic (**6**), monocyclic (**7**), and bicyclic peroxides (**10**).

In the KDM rearrangement, acyclic alkyl peroxides (**6**) upon treatment with base give rise to a ketone and an alcohol (Scheme 1b, **7** and **8**, respectively), while cyclic peroxides such as **9** give rise to γ-hydroxyenone **10**, and bicyclic peroxides (**11**) give rise γ-hydroxyenone such as **12**. The former variant can be used to access carbonyl products, while the later variant provides a very useful functional group possessing a stereocentre.[4] Since the disclosure of the KDM rearrangement considerable focus has been on this later variant, as the functional group, a γ-hydroxyenone, is present in several natural product classes. Furthermore, this functionality is a valuable synthon which can be harnessed in subsequent synthetic transformations. Notable examples of the use of the KDM rearrangement over the past 70 years are its application in tropone and cycloheptatriene chemistry,[5–11] its appearance in prostaglandin biosynthesis,[12,13] and more recently, its employment as a tool in biomimetic natural product synthesis.

The scope of this review is to show-case the increasing use of the KDM rearrangement in natural product synthesis over the past 25 years. A recent general review on peroxide rearrangements,[14,15] of which the KDM rearrangement sits, and the use of singlet oxygen in target synthesis[16] provides some excellent context, but the aim of this treatise is to equip the reader with the necessary tools to successfully incorporate the KDM rearrangement in their own natural product syntheses.

2 Mechanism

We will begin with a discussion of the underpinning mechanism of the KDM rearrangement. This is essential when considering the selectivity of the initial base catalysed deprotonation event and is informative when designing and implementing enantioselective variants of the KDM rearrangement.

The mechanism is centred on the bond dissociation energy of the oxygen–oxygen σ-bond in the peroxide; the bond energy of organic peroxides is *ca.* 45 kcal mol^{-1}.[17] The KDM rearrangement is initiated by treatment of an endoperoxide with a base. Non-nucleophilic bases promote an initial deprotonation of an α-hydrogen, leading to breakage of the weak oxygen–oxygen σ-bond; an example is shown for the bicyclic endoperoxide **13** (Scheme 2a).[18,19] Conversely, when an endoperoxide is treated with a nucleophilic base a competing process can occur. For example, treatment of the bicyclic endoperoxide **13** with an organolithium leads to direct reaction onto one of the oxygen

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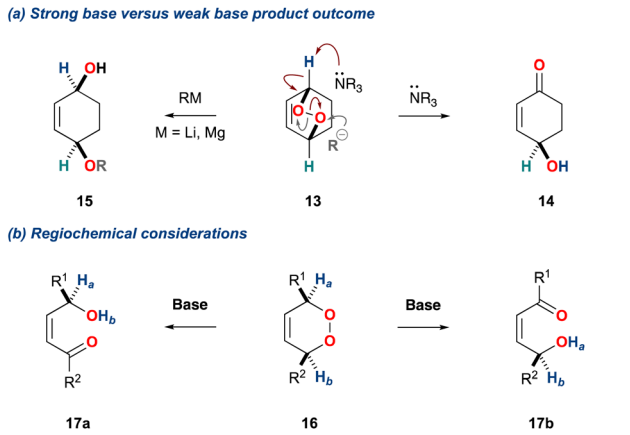


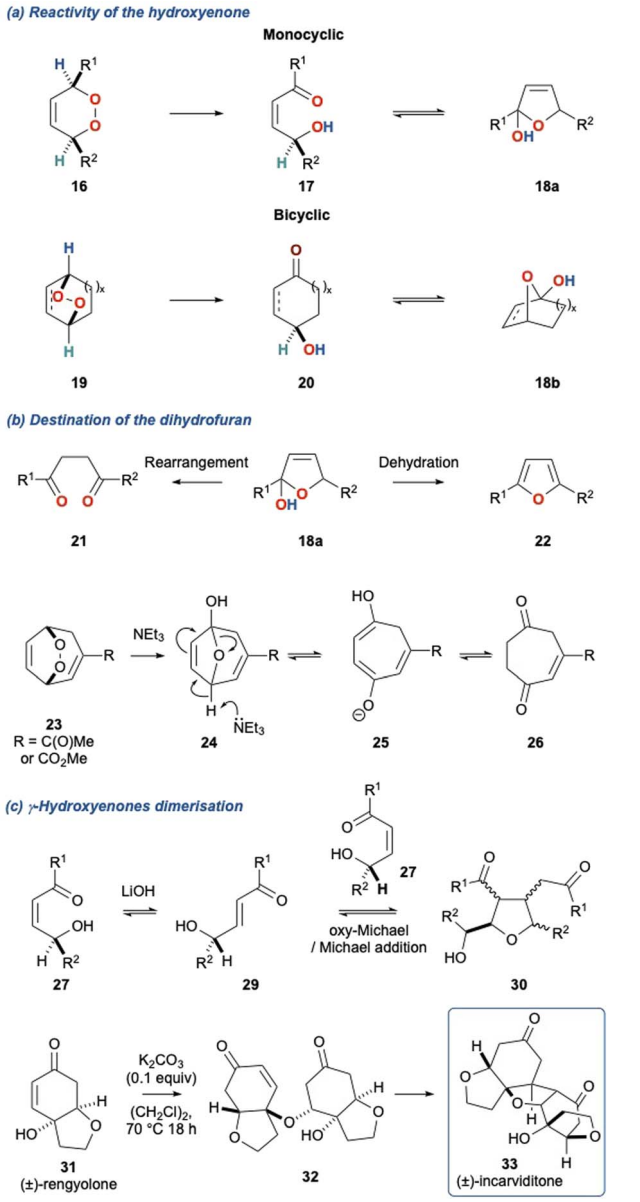
Scheme 2 (a) Product outcome of bicyclic peroxides with MgR/LiR *versus* tertiary amines; (b) regiochemical considerations with monocyclic peroxides.

centres and subsequent peroxide cleavage providing the diol **15** (Scheme 2a).

Additionally, the initial α-hydrogen deprotonation becomes crucial when considering the regiochemical outcome. For example, monocyclic peroxides of the type **16**, provide two potential α-hydrogens (Scheme 2b, **16** H_a and H_b) which can then deliver to isomeric γ-hydroxyenones **17a** and **17b**, respectively. This regiochemical complexity in the KDM rearrangement was observed by Taylor and co-workers in their first total synthesis of grenadamide **43**, a cyclopropyl amide from the marine cyanobacterium, *Lyngbya majuscula*;[20] this will be discussed later within this review.

Tertiary amines have been the predominant bases employed in the KDM rearrangement, and include Et_3N,[19,21,22] DIPEA,[23] DABCO,[24,25] DBU[26–28] and piperidine.[29] Other bases to be used in the KDM rearrangement include, LiOH,[30,31] phosphorus ylides,[30] stabilised phosphates,[32] malonates,[33] SiO_2,[34] and more recently bases derived from haloforms.[35] Each of these bases gives the key product of the KDM rearrangement for cyclic peroxides, the γ-hydroxyenone, whose fate is often defined by the base used in the initial rearrangement. Tertiary amines commonly provide the γ-hydroxyenone which then cyclises to give the dihydrofuran **20** (Scheme 3a).

This also occurs with monocyclic peroxides (**16** to **17** to **18a**) and bicyclic peroxides (**19** to **20** to **18b**); note that in each case the γ-hydroxyenone and dihydrofuran are in equilibrium. In the case of dihydrofuran **18** derived from monocyclic peroxides, this can be readily aromatised *via* dehydration to provide the furan **22**; alternatively, depending on the nature of the substituents, this dihydrofuran can rearrange to give a 1,4-diketone **21**. Bicyclic peroxides can also undergo this alternate rearrangement, for example peroxide **23** can undergo a NEt_3 mediated KDM rearrangement to provide dihydrofuran **24** which then undergoes a subsequent fragmentation to ultimately provide diketone **26**. Under basic conditions monocyclic and bicyclic γ-hydroxyenones can also undergo conjugate addition. This is particularly pertinent for γ-hydroxyenones such as **27** which can readily dimerise in the presence of LiOH to provide



Scheme 3 (a) Equilibrium between the γ-hydroxyenone and dihydrofuran for KDM rearranged mono- and bicyclic peroxide; (b) dihydrofuran dehydration to give furans, and the base catalysed rearrangement to 1,4-diketones; (c) the base catalysed dimerisation of γ-hydroxyenones and basis for the biomimetic synthesis of natural products.

tetrasubstituted tetrahydrofurans such as **30**.[31] This transformation is reminiscent of the proposed biomimetic synthesis of (±)-incarviditone (**33**) through the oxa-Michael/Michael dimerization of (±)-rengyolone (**31**) described by Sherburn and co-workers (Scheme 3c).[23,36] There are sparce examples of alternate bases such as acetates[37,38] as well as weak acids such as thiourea.[6,39] Bach and co-workers[40] described an acid mediated KDM rearrangement *via* protonation of the peroxide bridge and this report highlights an alternate mechanistic pathway for the KDM rearrangement.

The use of tertiary amine bases in the KDM rearrangement has led to it becoming an increasingly important tool in probing

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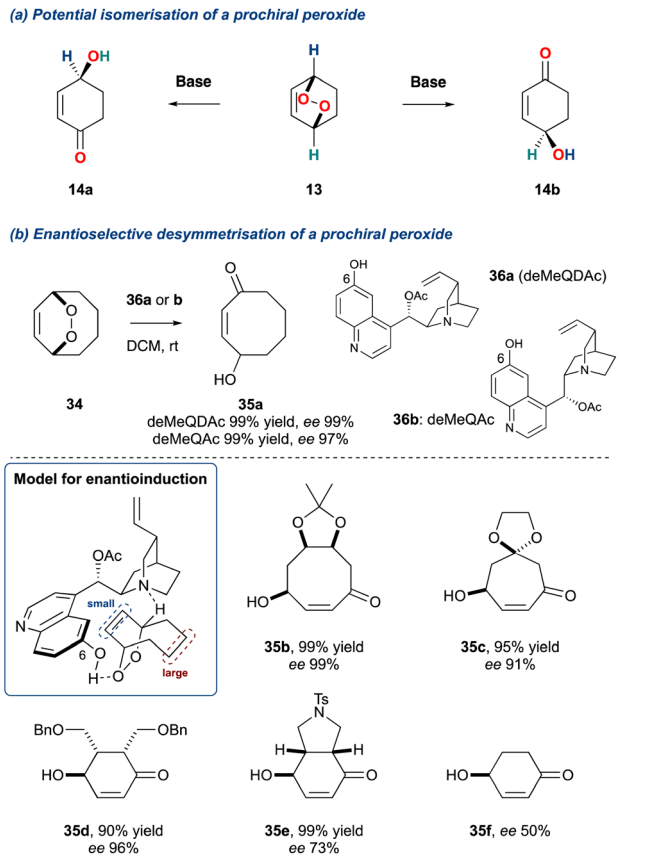
plausible biomimetic pathways in natural product synthesis. This stems from the work of Brame, Morrow and co-workers[41,42] who investigated the KDM reaction in the isoprostane pathway, followed by work by Kelly and co-workers[19] who identified the potential of an enantioselective isomerisation of a prochiral endoperoxide, and was subsequently realised in 2006 by Staben and Toste (Scheme 4).[43] This was achieved by desymmetrisation of *meso*-endoperoxides using cinchona-alkaloid catalysed enantio-determining deprotonation (Scheme 4b). The model proposed for achieving enantioselective induction is shown in Scheme 4b, where the cinchona alkaloid acts as a bifunctional catalyst providing the γ-hydroxyenone through an E2-elimination. The arrangement of the tertiary amine and the hydroxyl at the 6-position of the quinoline were key for this reaction, facilitating the heterolytic oxygen–oxygen σ-bond cleavage as well as providing a chiral pocket for enantio-discrimination. To achieve high enantio-induction, the pro-chiral endoperoxide must possess a size differential between the two bridges flanking the oxygen–oxygen bond; this was evidenced by the poor enantio-induction when forming 4-hydroxycyclohex-2-ene-1-one **35f**. Additionally, this protocol was shown to give poor enantio-induction for monocyclic endoperoxides.[44] It must be noted that the desymmetrisation of pro-chiral endoperoxides can also be achieved through a homolytic cleavage of the weak oxygen–oxygen σ-bond.[45] This also provides a route to enantioenriched γ-hydroxyenones, however, this is not technically a KDM rearrangement and will not be covered within this review.

This important disclosure by Stanben and Toste provides a general approach to the synthesis γ-hydroxyenones, crucial chiral building blocks, and significantly, this method has been harnessed by several groups to synthesise natural products, examples of which are discussed further within this review.

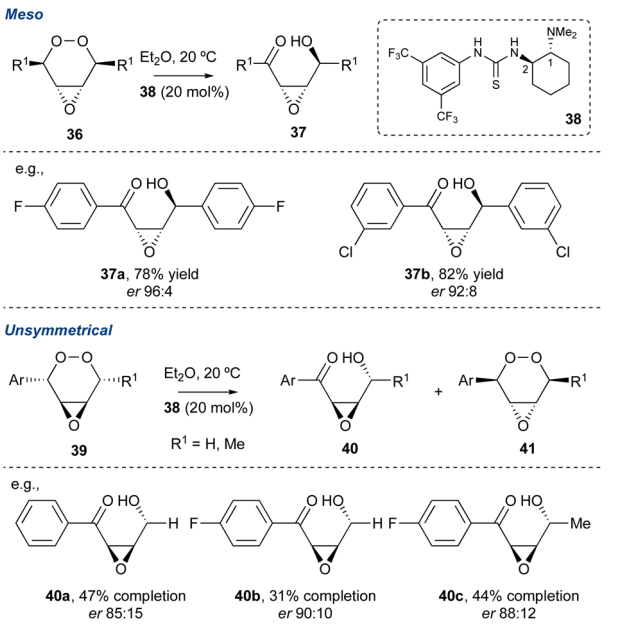
Recently, Greatrex and co-workers divulged an innovative thiourea/amine organocatalytic system to desymmetrise *meso*-endoperoxide of the type shown in Scheme 5.[46] Key to the success of this transformation is the steric requirement of the catalyst, particularly size of the dialkylamine at C1 (cat. **38**). The authors observed that if the steric bulk of the amine at C1 increased this was detrimental to the *er* of the product γ-hydroxyenones. Additionally, for unsymmetrical peroxides such as **39**, a kinetic resolution could be realised. The regiochemistry of the KDM rearrangement in this kinetic resolution is confined due to the benzylic proton, which are far more acidic. Therefore, to achieve a satisfactory *er* in the product γ-hydroxyenones (**40a–c**) the progress of each reaction required monitoring, and this is highlighted in the percentage completions. However, while this methodology is very recent, it should find applicability within future natural product syntheses.

3 Endoperoxides: the KDM rearrangement precursors

The precursors for a KDM rearrangement are endoperoxides, and their synthesis is achieved by treatment of a 1,3-diene with singlet oxygen, with the latter being generated from oxygen in the presence of a photosensitiser and a visible light source (there are examples of generating singlet oxygen through 'dark'



Scheme 4 (a) Potential desymmetrisation of a prochiral bicyclic peroxides; (b) Toste and co-workers desymmetrisation protocol.



Scheme 5 Greatrex and co-workers use of an organocatalysis in the desymmetrisation of endoperoxides.

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processes this has yet to be employed in the synthesis of natural products).[47–52] This transformation is well established and there are several reviews that describe the underlining mechanism, reaction scope and limitations.[15,16] Over recent decades there have been significant improvements in the practicality of this transformation, which has led to improved yields and more importantly improved safety, given the reputation of endoperoxides for their instability, and the challenges of using molecular oxygen at scale.[53,54] This includes the use of continuous flow methodology[16,53–55] and reactor design.[56–64] Often in natural product syntheses, the formation of the endoperoxide is undertaken in batch conditions. However, improvements in yield should be possible given the increasing availability of commercial continuous flow equipment and accessibility of simple homemade flow reactors.

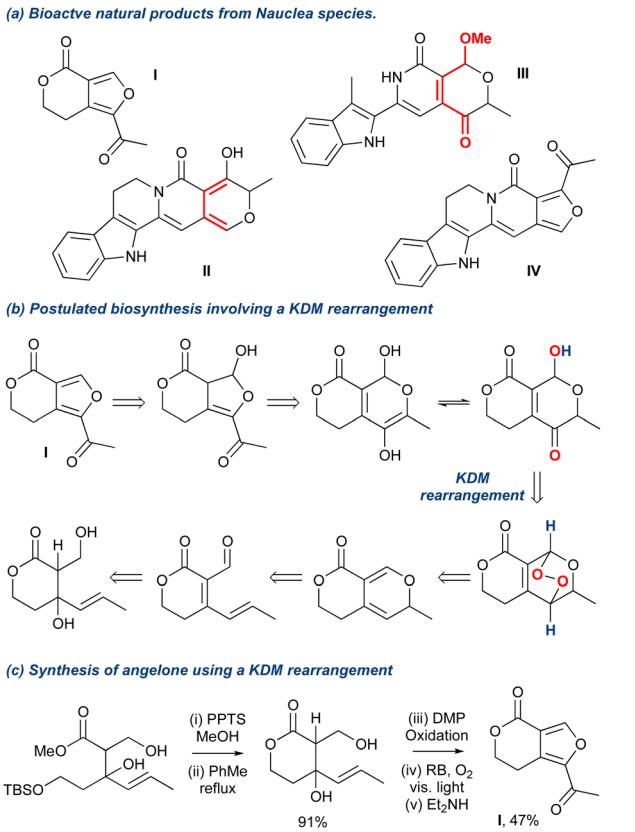
4 The KDM rearrangement and biomimetic relationship

The KDM rearrangement is often described as a biomimetic reaction and as such features in several bioinspired routes to different natural products. The incorporation of the KDM in such a route undoubtedly *must* proceed through an endoperoxide intermediate and have an accessible, acidic hydrogen atom that can be removed, see Section 2 for more details on the mechanism. For example, in the synthesis of angelone **I**, Tan *et al.* identified that several natural products isolated from *Nauclea* feature an "*oxygenation–deoxygenation relationship*" that could be attributed to the reaction of singlet oxygen with diene **II** and its subsequent KDM rearrangement and *O*-methylation into **III** (Scheme 6a).[65] The presence of **IV** was postulated as a ring contraction step going through a 6π-electrocyclic ring opening. With these key steps identified, they targeted **I** as their synthetic goal and designed their biomimetic retrosynthetic route based around the installation of a peroxide bridge, its subsequent KDM rearrangement and then the ring contraction step (Scheme 6b). They also hypothesised that should the forward route indeed mimic the postulated biomimetic conditions, then the reaction steps could be truncated into a facile process. Indeed, they completed the synthesis of **I** in a 3-pot procedure with 6 overall steps (Scheme 6c), and a full discussion of this natural product synthesis can be found in Section 5 of this review. Crucially, this example nicely highlights the relevance of the KDM rearrangement as a biomimetic tool and showcases the importance of recognising where it could occur in a biosynthetic pathway, exemplified in the above case between the isolated diene **II** and the γ-hydroxyenone derivative **III**.

5 Natural products

A summary of all natural product targets that have employed a KDM rearrangement over the past 25 years is shown in Fig. 1.

We have divided the analysis into two parts. The first section will describe the use of the KDM rearrangement as a key step. We have examined each natural product that uses a KDM rearrangement in chronological order. Where necessary we have provided clarification on the regiochemistry of the products that result from the KDM rearrangement, whether the key KDM rearrangement was enantioselective, and if the KDM rearrangement was employed as a biomimetic tool. The second section of this review describes natural products that specifically contain a butenolide. This structural motif, common to diterpene natural products, can be installed using a late stage KDM rearrangement when performed on a 3-substituted furan.



Scheme 6 An example of a KDM rearrangement used as a key biomimetic step in the total synthesis of angelone.

5.1 KDM rearrangement as a key step

5.1.1 (−)-Isocelorbicol, 2001. The KDM rearrangement was applied to a short, enantioselective synthesis of (−)-isocelorbicol (**41**), a sesquiterpene polyol of the agarofuran family of natural products (Scheme 7).

In their initial report, Zhou *et al.* prepared peroxide **76** in 8-steps from (−)-carvone and upon treatment with K_2CO_3 in THF produced diol **77** in high yield, which was subsequently transformed to enone **78** which they suggested was an enantioenriched precursor for polyhydroxylated agarofurans.[66] The regiochemistry of the KDM rearrangement is uncomplicated in this example given there is only one available hydrogen. Additionally, the stereochemistry of the OH at C-5 is defined by the initial endoperoxide formation which occurs *anti* to the methyl group at C-10. In a follow-up report, the group took enone **78** forward and completed the synthesis of **41**, which was realised in 5 linear steps.[67]

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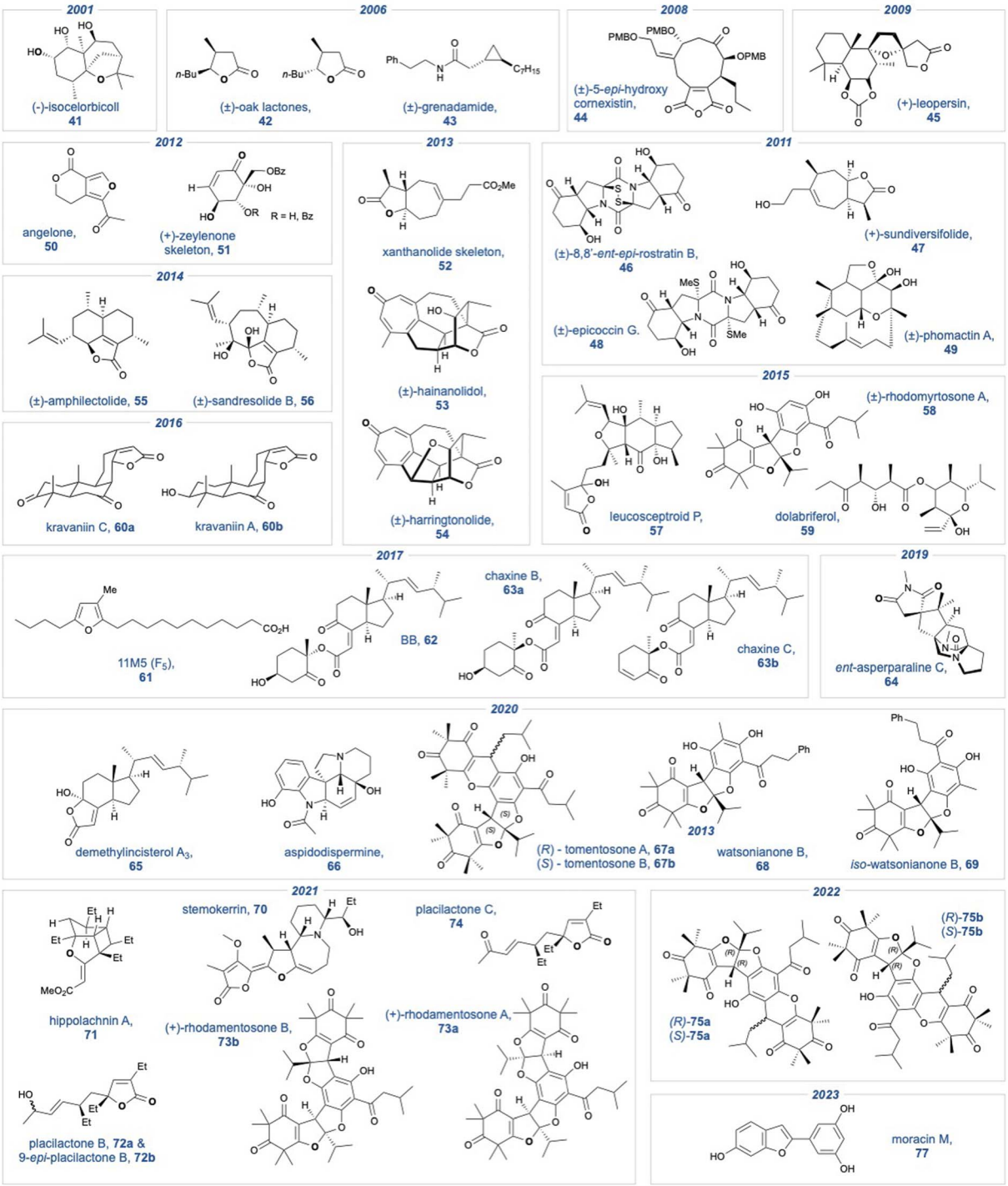

Fig. 1 Natural product targets that have used the KDM rearrangement as a key intermediate step.

5.1.2 Oak lactones, 2006. The isomers of oak lactone (Scheme 8; **42a,b**), an important flavour and fragrance compound often found in alcoholic beverages that have been fermented or matured in wooden vessels, were synthesised by Brown *et al.* using a KDM rearrangement to construct the enantioenriched lactone.[68] Endoperoxide **79** was treated with NaH in the presence of a chiral malonate diester (**80**) which, after scission of the peroxide, underwent a Michael addition and subsequent lactonisation yielding **81** as a mixture of diastereoisomers This approach to γ-lactones had been developed by the same group.[33] In this example the regiochemistry of the KDM is defined by the acidity of the hydrogen adjacent to the phenyl group. The relative stereochemistry observed in the γ-lactone results from an initial conjugate addition to *cis*-enone **V** to give **VI**, with subsequent lactonisation onto the malonate to give **VII**. Since a chiral malonate is used, this provides a mixture

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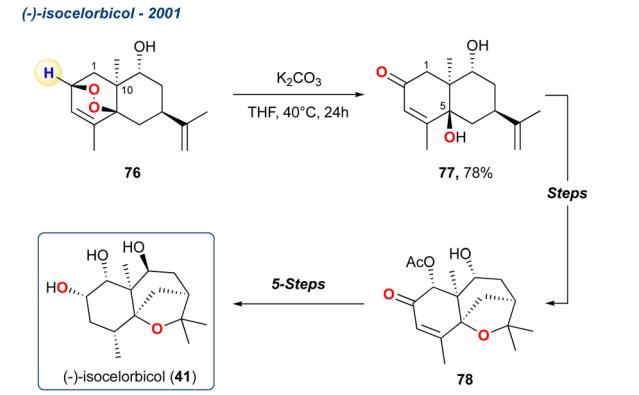
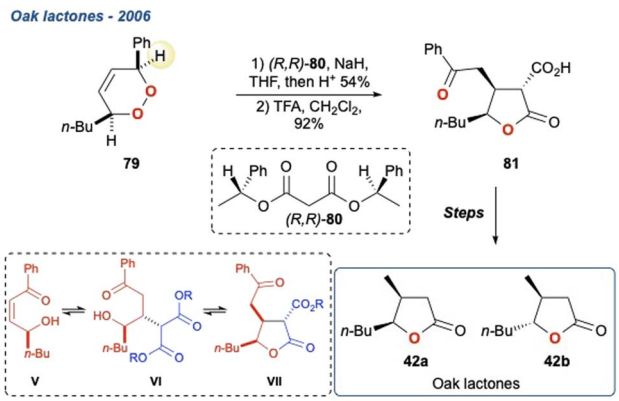


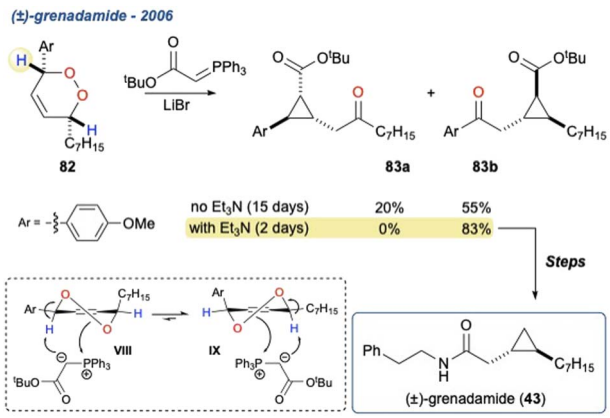
Scheme 7 Zhou *et al.* use of the KDM rearrangement to initially give precursor **77** which was subsequently used to give (−)-isocelorbicol **41**.



Scheme 8 The enantioselective total synthesis of oak lactones **42a** and **42b**, using a KDM rearrangement mediated by a chiral malonate with γ-lactonisation as a key step.

of diastereoisomers which are separated by chromatography, with the 3*R*,4*S*,5*S*-isomer being subsequently treated with TFA to yield the enantiopure acid **81**. This was taken forward to give the natural isomers of oak lactone **42a** and **42b**, respectively.

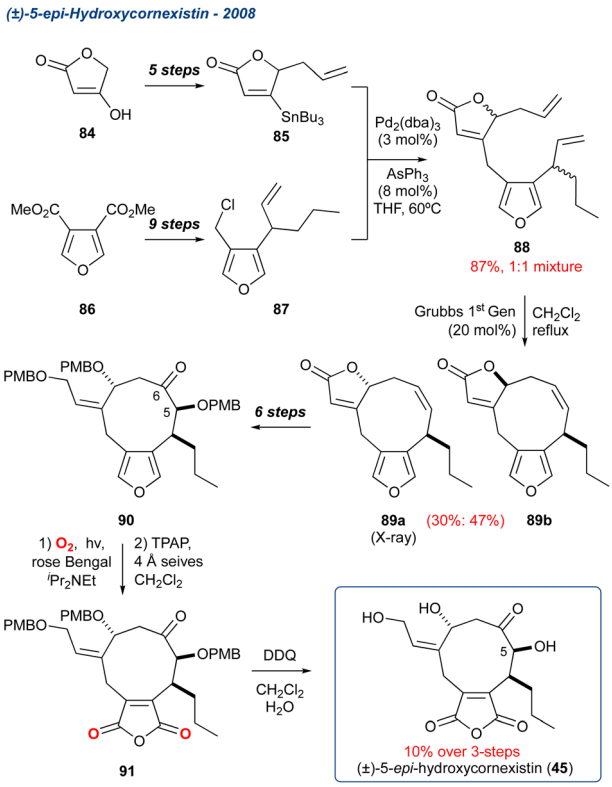
5.1.3 (±)-Grenadamide, 2006. Avery *et al.* reported the first synthesis of (±)-grenadamide (Scheme 9; **43**),[20] a cyclopropyl amide, which was isolated from a marine cyanobacterium *Lyngbya majuscula*.[69] The KDM rearrangement was employed as a key step in the formation of the cyclopropane ring as part of a diastereoselective cascade reaction.[30,70,71] Using the stabilised *tert*-butyl ester ylide as the base to facilitate the KDM cleavage yielded the desired cyclopropane **83b** in 55% yield after 15 day reaction time. The group also observed an unexpected isomer (**83a**) which arose from deprotonation of the less acidic proton adjacent to the O–O linkage of **82**. Upon further investigation they discovered that endoperoxide **82** remained present in solution and was reacting slowly, suggesting that deprotonation was the limiting step. They attributed the slow deprotonation and unexpected isomer to the conformation of **82** being fixed such that the alkyl chain is in a *pseudo* equatorial position (**VIII** to **IX**), limiting the ylides access to the more acidic proton.



Scheme 9 The first synthesis of (±)-grenadamide using a phosphorus ylide mediated KDM cascade, with initial conditions providing two isomeric cyclopropanes **83a** and **83b**.

When they performed the reaction in the presence of Et_3N, to access the more acidic proton, then the desired isomer **83b** was obtained in 83% yield with a much shorter reaction time. The racemic cyclopropane was then carried through a further 8-steps providing (±)-grenadamide (**43**).

5.1.4 (±)-5-*Epi*-hydroxycornexistin, 2008. In 2008, Clark *et al.*[72] divulged the synthesis of the 5-*epi* isomer of hydroxycornexistin, a nonadride natural product isolated from the fungus *Paecilomyces variotii*,[73] that displays (along with



Scheme 10 Unveiling of the anhydride of the cornexistin's using a KDM/oxidation protocol.

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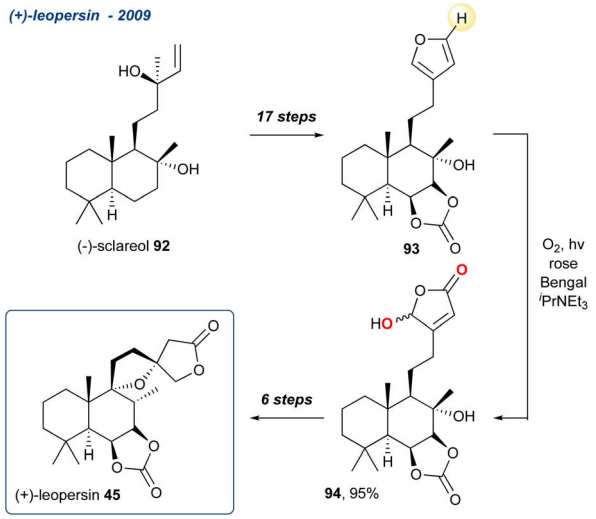
cornexistin) potent herbicidal activity (Scheme 10).[74] The unusual anhydride unit with hydroxycornexistin presents a significant synthetic challenge due to its reactivity. To overcome this challenge, Clark and co-workers sought to mask the anhydride as a furan. The furan would stay intact until the penultimate steps within the total synthesis, where it would then undergo a KDM rearrangement and subsequent oxidation. The core cyclononane was assembled through a Stille coupling of **85** with racemic chloride **87**, providing **88** as a 1 : 1 mixture of isomers, which subsequently underwent an RCM to provide diastereoisomers **89a** and **89b** in 30% and 47% yield, respectively. Diastereoisomer **89a** was then taken forward in 6-steps, introducing oxidation at C5 and C6, as well as opening of the butenolide. The PMB protected precursor **90** was then exposed to KDM rearrangement conditions followed by TPAP oxidation, and PMB global deprotection with DDQ, to give 5-*epi*-hydroxycornexistin **45** in 10% over these final three steps. While the sequence was low yielding, this synthesis proves the validity of masking the anhydride as its furan.

5.1.5 (+)-Leopersin, 2009. Marcos *et al.* reported the synthesis of (+)-leopersin D (Scheme 11; **45**), a naturally occurring spirolabdanolide first isolated in 1996 from the aerial parts of *Leonurus persicus*.[75]

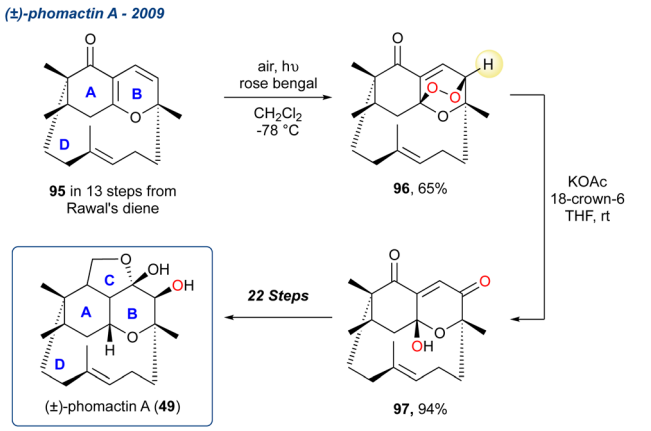
Starting their synthesis from (−)-sclareol (**92**) they accessed furan intermediate **93** in 17-steps and treated it with singlet oxygen in the presence of DIPEA yielding the γ-hydroxybutenolide **94** in 95% yield. The unmasking of a butenolide using a KDM rearrangement is discussed in more detail in Section 5.2. The synthesis was completed in a further 6-steps with **45** isolated with its C-13 epimer in a 1 : 1 ratio.

5.1.6 (±)-Phomactin A, 2009–2011. Tang *et al.* completed the total synthesis of (±)-phomactin A in 2009,[38,76] a complex structure consisting of 4-rings (Scheme 12; **49**). It was originally isolated by Sugano *et al.* from a culture of parasitic marine fungus *Phoma* sp. (SANK 11486) that was collected from the shell of a crab *Chionoecetes opilio* off the Japanese coast in the Fukui prefecture.[77] Following their earlier work into the synthesis of the ABD-tricycle,[78] the group utilised the KDM rearrangement after construction of the ABD-tricycle.[79] During several attempts to cleave the remarkably stable endoperoxide bridge of **96** they attempted to install an acetate using a Michael addition with KOAc/18-crown-6; however, instead they found peroxide **96** was converted cleanly to the KDM product **97** with no hydrolysis to the corresponding ene-trione. As with the synthesis of (−)-isocelorbicol (**41**) (Scheme 6), the configuration of the resultant hydroxy group within **97** is controlled by the initial endoperoxide formation, which occurs on the top face of **96** due to ring-D. However, this stereocentre is inconsequential, and **97** was carried forward to give (±)-phomactin A **49** in a further 22-steps.

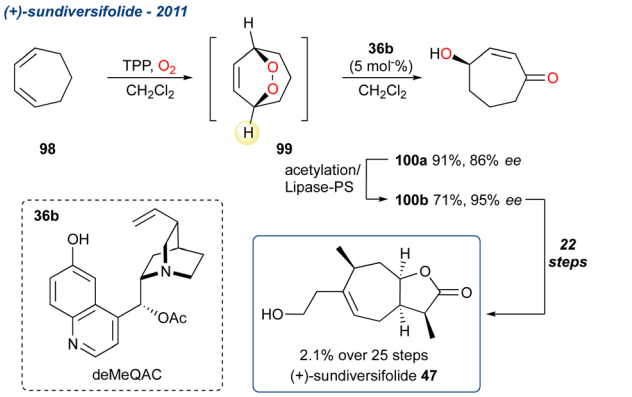
5.1.7 (+)-Sundiversifolide, 2011, enantioselective. Kawasumi *et al.* reported the formal synthesis of (+)-sundiversifolide **47**, a 7,5-bicyclic lactone containing 4-stereocenters (Scheme 13).[80] It was originally isolated from exudates of germinating sunflower seeds (*Helianthus annuus* L.) and demonstrated allelopathic activity.[81] Following on the work of Shishido and co-



Scheme 11 Semi-synthesis of (+)-leopersin (**45**) from (−)-sclareol (**92**).



Scheme 12 Tang and co-workers' racemic total synthesis of (±)-phomactin A (**49**) using the unexpected KDM rearrangement using KOAc and 18-crown-6.



Scheme 13 Kawasumi *et al.* approach to (−)-sundiversifolide (**47**) using an enantio-enriched γ-hydroxyenone synthesised using Toste's organocatalytic symmetrisation of a centro-symmetric endoperoxide.

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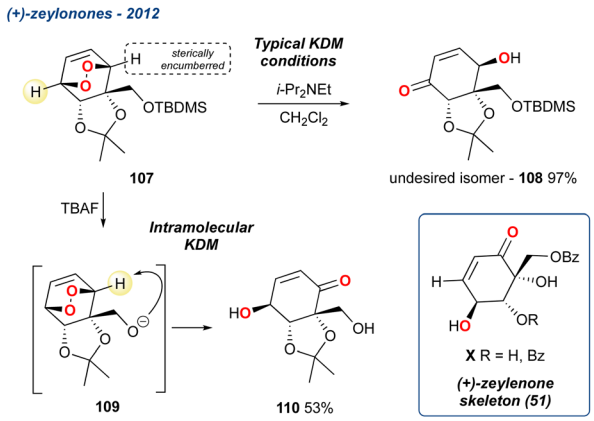
workers, who used ring-closing metathesis to construct the 7-membered ring,[82] the group opted for an oxidative approach, using cycloheptadiene (**98**) as the starting point. Oxidation with singlet oxygen yielded the symmetrical endoperoxide **99** which was then treated with catalytic deMeQAc to at ambient temperature, yielding the (*R*)-γ-hydroxyenone **100a** in 91% yield and 86% *ee*. This represents the first use of Toste and co-workers organocatalytic desymmetrisation described in Scheme 4. The *ee* of **100a** could be improved to 95% through a 2-step acetylation/lipase-PS protocol. Enantioenriched γ-hydroxyenone **100b** was then taken forward to (+)-sundiversifolide **47** in an additional 22-steps and an overall yield of 2.1%.

5.1.8 Epicoccin G and 8,8′-*epi-ent*-rostratin B, 2011. Two structurally similar diketopiperazines, epicoccin G (**48**) and 8,8′-*epi-ent*-rostratin B (**46**), were synthesised by Nicolaou *et al.* from a common intermediate **100** that was accessed from *N*-Boc tyrosine in 11-steps (Scheme 14).[83,84] Using different sulfenylation strategies **100** was transformed into either epidithiodiketopiperazine **104** or the *bis*-methylthio compound **101** that were reacted with singlet oxygen, generating the endoperoxide intermediates, which were used in the subsequent KDM step without purification. The KDM rearrangement was regioselective, initiated using DBU or Et_3N, and this gave **106** and **103** in 52 and 55% yields, respectively. The completion of each synthesis was *via* reduction of **103** to give epicoccin G (**48**), while a reduction/oxidation strategy was used to access 8,8′-*epi-ent*-rostratin B (**48**). Uniquely, the authors recognised that the γ-hydroxyenone present in **48** and **46** could be accessed efficiently by the rarely used, at the time of disclosure, KDM rearrangement.

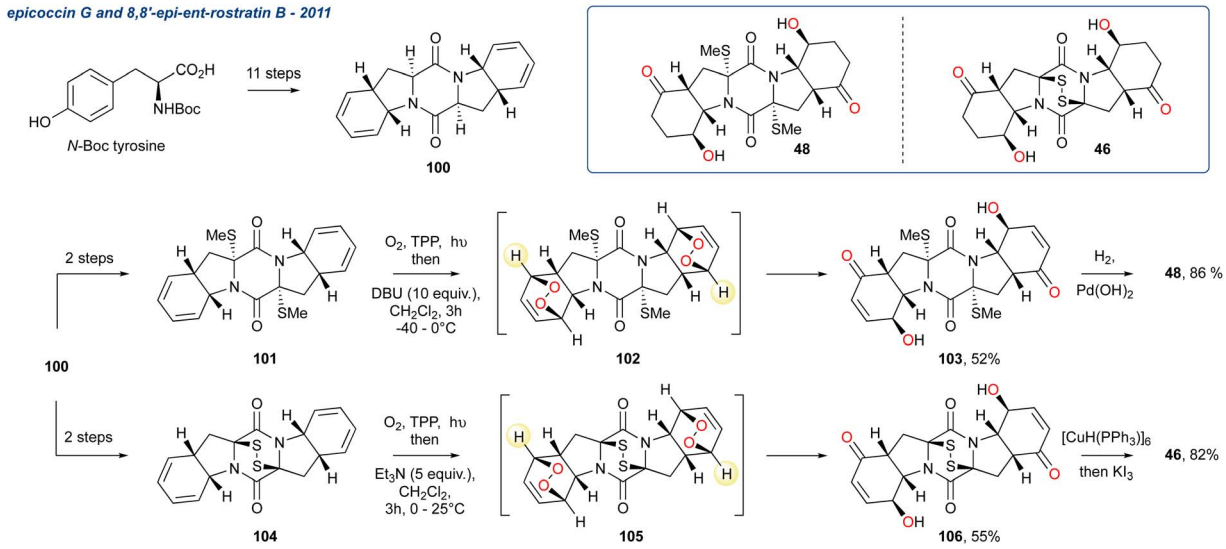
5.1.9 Toward (+)-zeylenones, 2012. In 2012, Palframan *et al.* reported the synthesis of a range of zeylenols[85,86] and zelenones[87,88] (Scheme 15, skeleton **51**) using a common endoperoxide intermediate **107**, by either reduction or KDM rearrangement, respectively.[39] The KDM rearrangement, initiated by Hünigs's base, was used to access the zeylenone family,



Scheme 15 An intramolecular KDM rearrangement, through TBAF deprotection, reported by Palframan *et al.* in their synthesis of the zeylenone skeleton (**51**).

however the intrinsic regioselectivity, attributed to the steric approach of the base, prevented formation of the desired isomer providing, instead, the enone **108**. To address the undesired regioselectivity, the group developed a neighbouring-group participation/directed approach to trigger an intramolecular KDM rearrangement using the neighbouring silyl protected alcohol.

When treated with tetrabutylammonium fluoride (TBAF), the resultant alkoxide triggered an intramolecular KDM rearrangement giving the desired isomer in 53% yield, with oxyanion **109** serving as the base; notably none of the undesired regioisomer **108** was observed. However, the KDM rearrangement product **110** was not taken forward in the synthesis due to its instability and instead the group used additional steps from the diol obtained from the reduced endoperoxide. Nevertheless, this methodology is a useful addition, demonstrating that the



Scheme 14 Use of a singlet oxygen formation/KDM rearrangement protocol to install the γ-hydroxyenones within epicoccin G and 8′8′-*epi*-entrostratin B.

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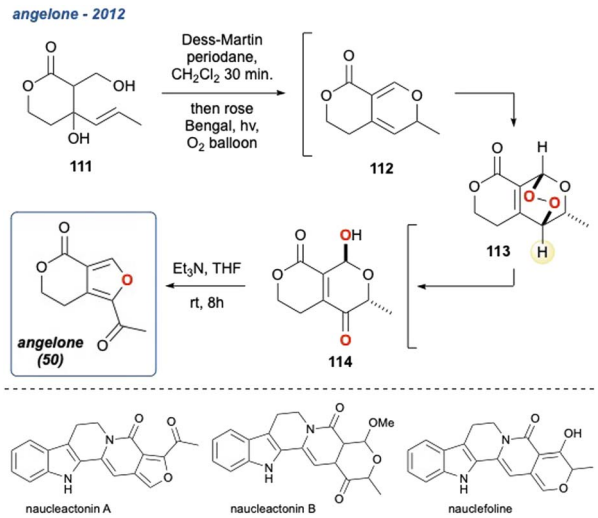
regioselectivity of the reaction can be tuned in some circumstances.

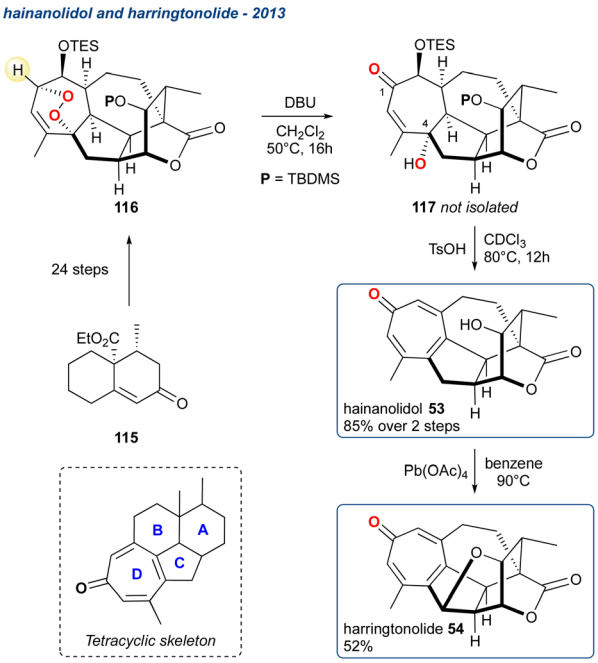
5.1.10 Angelone, 2012. A small bicyclic natural product angelone (Scheme 16; **50**)[89] was synthesised by Tan *et al.* using a biomimetic approach, where the team drew similarities between the biosynthesis of other indole alkaloids and devised a "three-pot" strategy that consisted of 6-steps.[65] Lactone **114**, was formed in 3-steps and the final one-pot reaction started with the treatment of **111** with Dess–Martin periodinane forming cyclic diene **112**, followed by endoperoxide formation from singlet oxygen. The KDM rearrangement occurred spontaneously with excellent regioselectivity to the desired γ-hydroxyenone (**114**) and it was noted that no deprotonation at the α-position of cyclic oxygen was observed. It was speculated that the source of base for the KDM rearrangement arose from residual acetate as the Dess–Martin periodinane reaction and the one-pot nature of the reaction. To complete the synthesis, **114** was treated with Et_2NH to initiate a 6π-disrotatory electrocyclic ring-opening cascade that yielded angelone **50** in 47% over the 3-steps and 35% overall. This synthesis was inspired by the biomimetic sequence postulated in the synthesis of structurally similar indole analogues such as naucleactonin A and B[90] as well as nauclefoline,[91] although the total synthesis of any these three intriguing natural products has yet to be divulged.

5.1.11 Hainanolidol and harringtonolide, 2013. The complex natural product harringtonolide (Scheme 17; **54**) was isolated from *C. harringtonia* in 1978 where its structure was assigned by X-ray crystallography.[92]

A year later, **54** was isolated again but from *C. hainanensis* and this alongside the related compound **53** (hainanolidol, formerly named hainanolide) which was later proposed as the precursor to harringtonolide. Whilst **54** shows antineoplastic and antiviral activity the proposed precursor **53** is inactive, suggesting the tetrahydrofuran ring is important for their bioactivity. These two related natural products were synthesised



Scheme 16 Tan and co-workers' biomimetic synthesis of angelone (**50**), inspired by the proposed biosynthesis of indole alkaloids, naucleactonin A, B, and nauclefoline.



Scheme 17 Zhang *et al.* synthesis of hainanolidol and harringtonolide.

in the laboratory by Zhang *et al.* starting from enone **115** producing peroxide **116** in 24-steps, which was then subjected to KDM conditions using DBU as the base furnishing the γ-hydroxyenone **117**.[93] The stereochemistry of the hydroxy group at C4 is a consequence of the [4 + 2]-cycloaddition in the preceding endoperoxide forming reaction, although this is inconsequential given it is subsequently eliminated. Additionally, **117** is used without further purification, being treated immediately with TsOH that gave deprotection and elimination forming the key tropone D-ring (see tetracyclic skeleton) and completing the synthesis of hainanolidol **53**, which was isolated in 85% over the 2-steps. Treatment of **53** with $Pb(OAc)_4$ produced the tetrahydrofuran ring, thereby forming harringtonolide **54** in 52%.

5.1.12 *trans*-Xanthanolide analogues, 2013. Priest *et al.* made use of the Toste organocatalysed asymmetric KDM[43] rearrangement as an intermediatory step in the formation of *trans*-fused butyrolactones (Scheme 18; **119**) from readily accessible symmetrical endoperoxides (**118**).[44]

Catalysts **36a** or **36b** (see Scheme 4) were used to promote the asymmetric reaction leading to the desired γ-hydroxyenones, that were then treated *in situ* with various nucleophiles followed by spontaneous lactonization to yield the desired butyrolactones (**119**) in high yields and ee's of up to 94%. The chemistry was then applied to the synthesis of a *trans*-xanthanolide analogue **52** with the installation of the methyl group with MeI followed by decarboxylation in AcOH to yield the desired butyrolactones **123** in 79% yield and good diastereoselectivity. An alternative strategy using α-methyl-diethylsodiomalonate yielded a similar overall yield (69%). The *trans*-xanthanolide analogue **52** was realised in 51% yield over an additional 3-steps.

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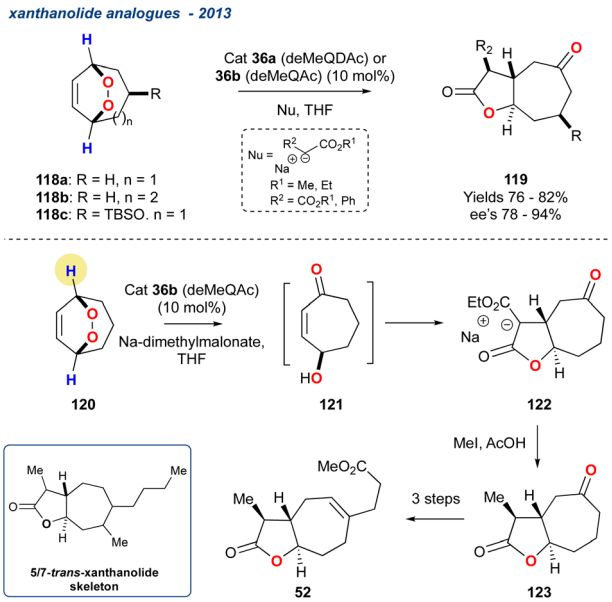


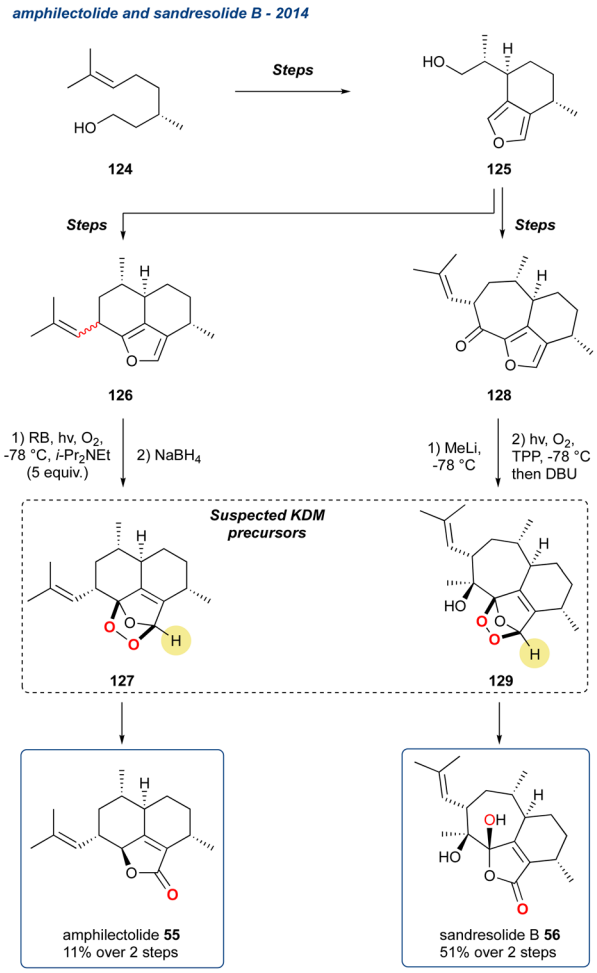
Scheme 18 Priest and co-workers use of the desymmetrisation of a prochiral endoperoxides to provide a rapid synthesis of the *trans*-xanthanolide skeleton.

5.1.13 Amphilectolide and sandresolide B, 2014. Two related natural products, amphilectolide (**55**) and sandresolide B (**56**) were synthesised by Chen *et al.* from a common intermediate where a regioselective KDM rearrangement was employed in the final step of the synthesis (Scheme 19).[94]

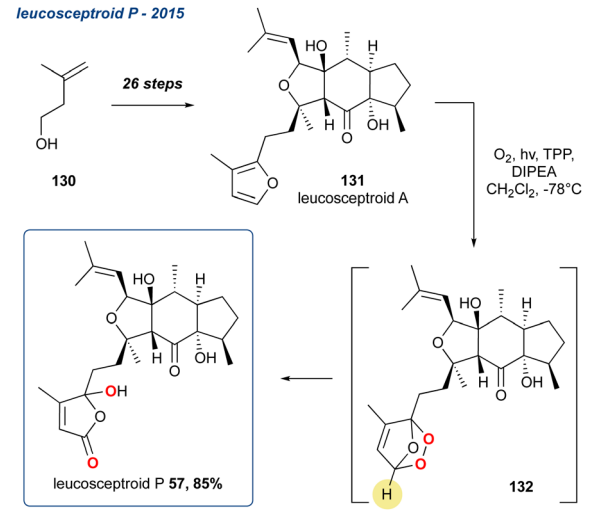
Belonging to a large family of marine metabolites, originally isolated from *Pseudopterogorgia elisabethae*, a Caribbean coral, natural products of this type demonstrate a broad range of biological activity, *i.e.*, inflammation, tuberculosis, anti-cancer, and antiplasmodial.[95] To complete their synthesis of amphilectolide (**55**) the researchers treated the diastereomeric mixture of **126** with singlet oxygen in the presence of Hünigs base (i-Pr_2NEt), and then immediately reduced with $NaBH_4$ yielding **55** in 11%, from a complex mixture of products, over the 2-steps (Scheme 19). It is unclear from the report whether the reaction proceeded by a KDM rearrangement, but given the conditions, the presence of a carbonyl at the 5-membered ring, it is highly likely the KDM precursors was **127**. The other target, sandresolide B (**56**), was obtained in 51% yield over 2-steps, where methylated **128** was subjected to, after some optimization, photo-oxidation with tetraphenylporphyrin (TPP) followed by treatment with DBU to trigger the regioselective KDM rearrangement. During optimisation, the authors found that DBU was the only base to give efficient transformation of the peroxide intermediate.

5.1.14 Leucosceptroid P, 2015. Hugelshofer *et al.* reported the synthesis of a range of leucosceptroids, including a leucosceptroid P (**57**) which was proposed *via* oxidation and KDM rearrangement of leucosceptroid A (**131**) (Scheme 20).[96,97]

They are a family of terpenes isolated from *Leucosceptrum canum* that exhibit antifeedant activities. Building upon their related synthesis of norleucosceptroids A–H, the researchers synthesised leucosceptroid A (**131**) in 26-steps from alcohol



Scheme 19 The synthesis of amphilectolide (**55**) and sandresolide B (**56**) *via* a suspected KDM rearrangement from endoperoxide precursors **127** and **129**, respectively.



Scheme 20 Hugelshofer *et al.* use of the KDM rearrangement in the synthesis of leucosceptroid P. Singlet oxidation of the furan is unselective, therefore leucosceptroid is obtained as a 1 : 1 mixture.

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130.[98] Oxidation with singlet oxygen yielded the corresponding endoperoxide (**132**) which was then converted *in situ* by Hünigs base forming the γ-hydroxyenone regioselectively in 85% yield. Due to a lack of substrate control, the oxidation of the furan ring by singlet oxygen provides a mixture of endoperoxides. This was predicted by the authors given their previous disclosure on the biomimetic studies on this family of natural products.[97] The KDM rearrangement therefore gives a 1 : 1 mixture of diastereoisomers in the furan ring, endoperoxide was formed racemically, therefore leading to leucosceptroid P (**57**) to be obtained as a 1 : 1 mixture of diastereoisomers at the carbon containing the newly formed hydroxyl group. This is inconsequential as the natural product is originally obtained as a 1 : 1 mixture.

5.1.15 Rhodomyrtosone A and related, 2015. Gervais *et al.* reported the total synthesis of rhodomyrtosone A (**58**), a bis-furan β-triketone natural product that was isolated from *Rhodomyrtus tomentosa*.[99] In their approach they synthesised endoperoxide **133** in 4-steps and then heated it in acetic acid at 100 °C in the presence of acylphloroglucinol **134** to give **58** in 60% yield (Scheme 21). Although no mechanistic studies were performed, it is proposed that the KDM rearrangement is part of a cascading sequence of steps starting with protonation of the peroxy acetal **135**. Subsequent elimination of water forms peroxycarbenium intermediate **136** which then undergoes Michael-type addition by **134**. Removal of the acidic proton adjacent to the peroxide of addition product **137** in KDM fashion yields diketone **138** which then cyclises twice under the acidic conditions with elimination of water yielding the desired natural product **58**.

Following the initial report of this synthesis by Gervais *et al.* there have been several reports utilizing the same approach, occasionally with minor modification to the conditions, to realise a variety of related natural products isolated from *Rhodomyrtus tomentosa* or other related plants in the same genus. Watsonianone B (**68**) and its isomer (**69**) were synthesised by Zhang *et al.* in a 2 : 1 ratio and 27% isolated yield for the desired **68** (Fig. 2).[100] Tomentosones A (**67a**) and B (**67b**) were also reported by the same group and synthesised in a similar manner, only this time using pyridinium *p*-toluenesulfonate (PPTS) in toluene which yielded a 1 : 10 mixture of **67a** and **67b** in 73% yield.[101] They also reported that the two isomers could be interconverted in the presence of *p*-toluenesulfonic acid. The following year Deng *et al.* reported the asymmetric synthesis of

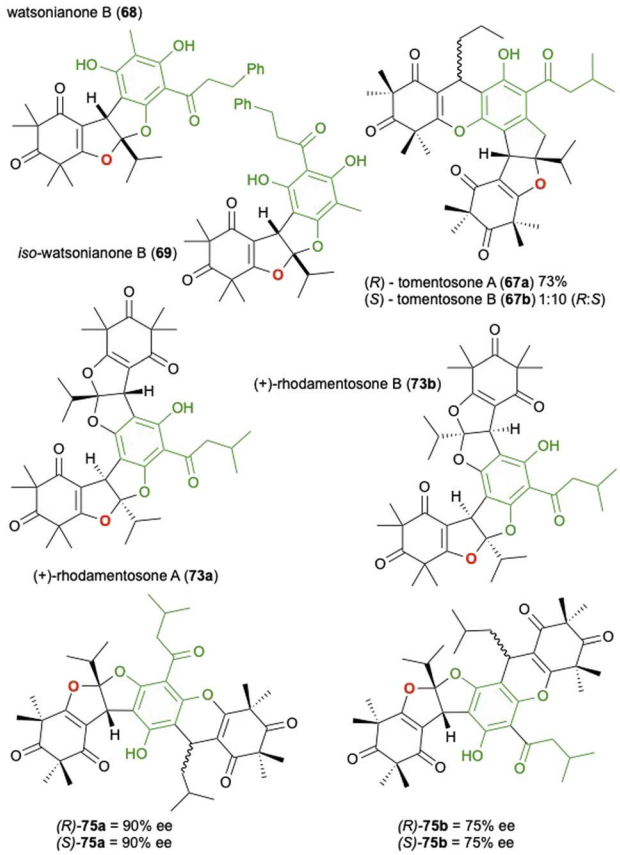
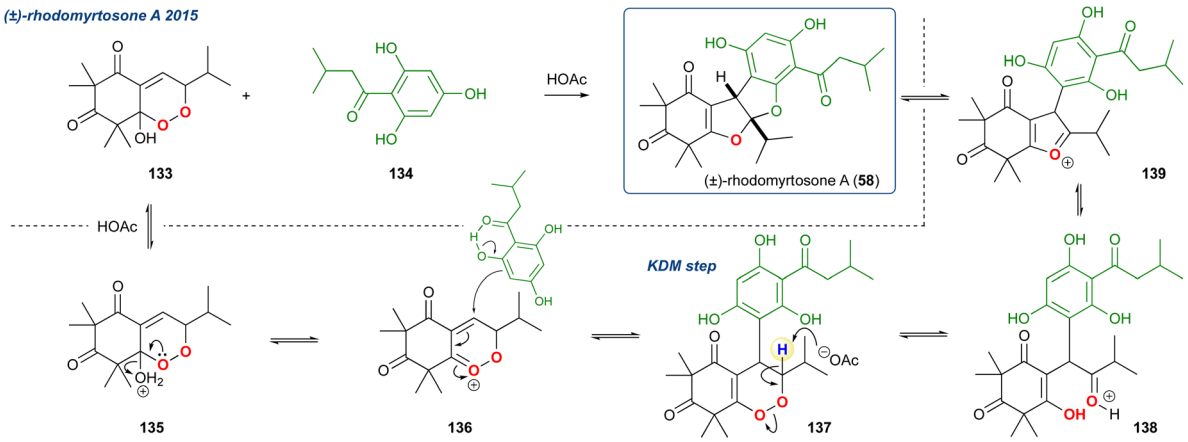


Fig. 2 The synthesis of related natural products from *Rhodomyrtus tomentosa* or related plants in the same genus using the cascade approach described in Scheme 20.



Scheme 21 Gervias *et al.* approach to (±)-rhodomyrtosone A. A unique KDM rearrangement occurs due to an initial conjugate addition to the peroxide oxycation **136**.

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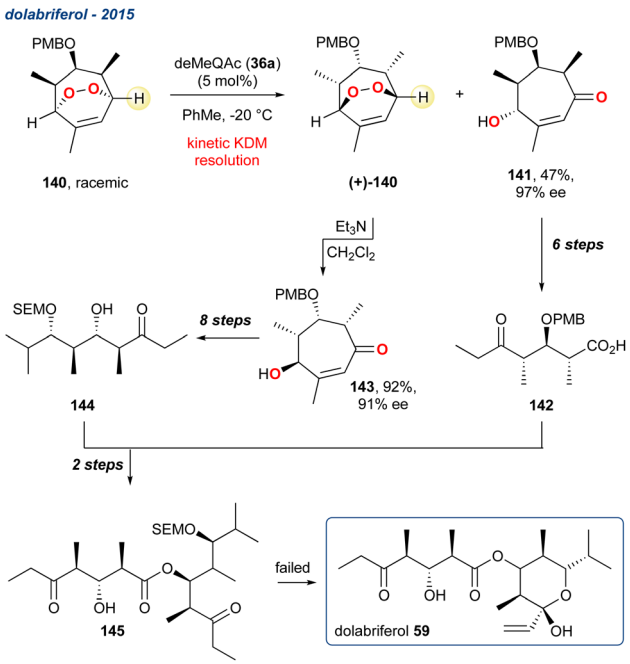
rhodomentosones A (**73a**) and B (**73b**), a pair of phloroglucinol trimers that contain an unusual 6/5/5/6/5/5/6 fused ring system.[102] In this report the group described an asymmetric approach to the domino reaction first reported by Gervais *et al.* by employing a catalytic amount of a chiral phosphoric acid in the presence of AlF_3 as a Lewis acid they could access the desired *bis*-furan in high *ee*. After separation of the isomers, the second *bis*-furan unit was installed giving rhodomentosone A (**73a**) and B (**73b**) in a ratio of 1 : 2 with 90% *ee* and a combined yield of 45%. This asymmetric approach was applied again by Deng *et al.* in the synthesis of four unnamed phloroglucinol trimers (**75a** and **75b**) isolated again from *Rhodomyrtus tomentosa*.[103]

5.1.16 Dolabriferol, 2015, enantioselective. Dolabriferol (**58**) belonging to the family of noncontiguous polypropionates, is a marine natural product isolated from *Dolabrifera dolabrifera* and was isolated from the acetone extracts of sea hare (*Anaspidean mollusk*) that was collected off the Cuban coast.[104] Gesinski *et al.* reported the attempted total synthesis of **58** in 2015, which centred around a divergent/convergent strategy that utilised a KDM kinetic resolution as the key step (Scheme 22).[105]

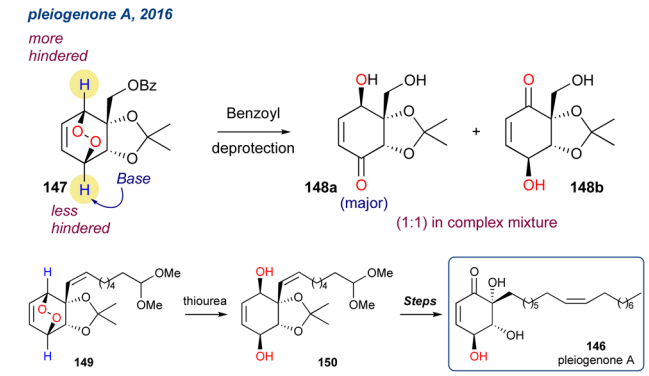
The two enantioenriched fragments of the target were constructed from a common racemic peroxide **140**. The authors used the established organocatalysts deMeQAc (**36a**), but unlike the centrosymmetric desymmetrisation described by Stanben *et al.*,[43] the authors used a racemic endoperoxide to achieve a kinetic resolution. The regioselectivity of the KDM rearrangement is central to this approach, given the highlighted proton in **140** is less sterically encumbered, and therefore more likely to be deprotonated in the key KDM rearrangement step. After some optimisation, they found that in toluene and when **140** was treated with deMeQAc (**36a**) a selective deprotonation occurred providing enone **141** as a single enantiomer in 47% yield and 97% *ee*. The remaining enantioenriched peroxide (+)-**140** could then be cleanly converted using a subsequent KDM rearrangement but using Et_3N, providing enantioenriched enone **143** in 92% yield and 91% *ee*. Each fragment was then taken forward in several steps and recombined, but unfortunately the synthesis of **59** failed on the last step.

5.1.17 Pleiogenone A, 2016. Froese *et al.* reported the first total synthesis of pleiogenone A (**146**),[106] a hydroxylated cyclohexenone that was isolated from the bark of *Pleiogynium timorense* with demonstrated potent biological activity (Scheme 23). In their approach they used acetal protected *ipso*-diol, synthesised with an enzymatic dihydroxylation, as the starting point. The subsequent endoperoxide **146** was then subjected to base catalysed KDM rearrangement conditions but suffered from undesired regioselectivity from abstraction of the least hindered proton as reported by Lewis and co-workers.[107] The group attempted to direct the proton abstraction with benzoyl deprotection (conditions not given in the original report) to yield an oxo-anion to serve as the base for the KDM rearrangement step, however this approach yielded equal amounts of **147a** and **147b** as part of a complex mixture and their isolation proved too laborious to be viable moving forward. Ultimately, they completed the synthesis using an alternative approach and installed the γ-hydroxyenone core by reduction of a peroxide with thiourea to yield a diol and then a selective TIPS protection and IBX oxidation (**148** to **149** to **150**).

5.1.18 Kravanhins C and A, 2016. Zhong and co-workers reported an innovative 'bioinspired' synthesis of kravanhins A and C (Scheme 24; **60a** and **60b**).[108] These natural products were isolated from the fruits of the *Amomum kravanh*; which are used in traditional Chinese medicine to treat digestive disorders.[109] The synthesis began with **151**, obtained in 4-steps from (−)-carvone, which was then carried forward in a further 6-steps to the furan **152**. The authors then unmasked the furan using the Faulkner method (see Section 5.2)[110] to reveal the γ-hydroxy butenolide **153** in 75%. The authors postulated that the ring opened form **153** would undergo an aldol cyclisation to form ring C; this was ultimately realised using PPTS in refluxing toluene, to give kravanhin C (**60b**) in 65%. Subsequent



Scheme 22 The use of an organocatalyst in a KDM rearrangement and kinetic resolution in the attempted total synthesis of dolabriferol **59**.



Scheme 23 Attempted synthesis of a key precursor (**147**) of pleiogenone A *via* a KDM rearrangement.

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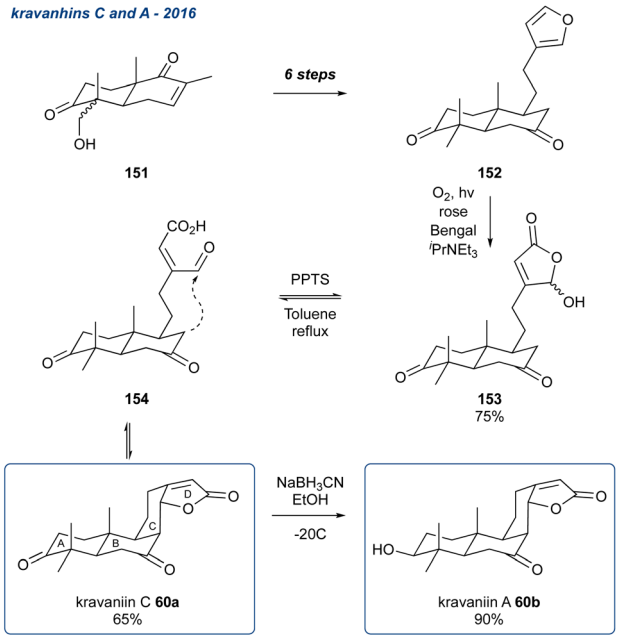


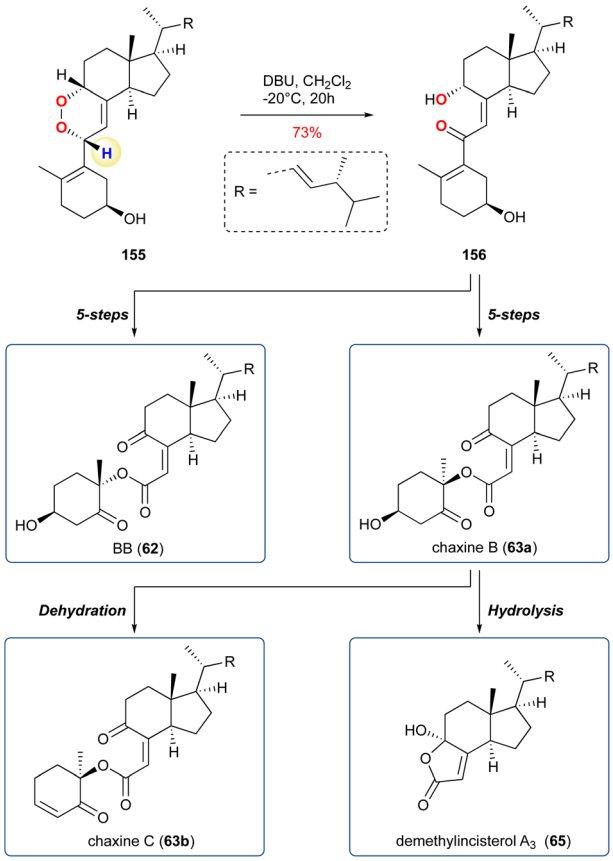
Scheme 24 Synthesis of kravanhins A (**60b**) and C (**60a**) using an oxidative ring opening of a 3-substituted furan and subsequent aldol condensation.

stereoselective reduction of the carbonyl in ring A then gave kravanhin A (**60a**) in 90% yield.

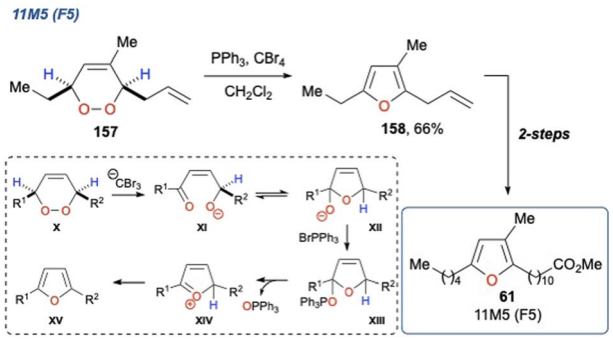
5.1.19 Chaxine B, C and related analogues, 2017, 2020. Hirata *et al.* reported the synthesis and structural revision of chaxine B and related natural products, which have been isolated from fungi and marine animals, with ergosterol as the starting point (Scheme 25).[111] Following their proposed biosynthetic route they planned a KDM rearrangement, which would lay the path for the synthesis of a key 1,4-diketone intermediate for a Baeyer–Villiger oxidation. From the endoperoxide **155** they used DBU as the base and obtained **156** in 73% yield and as a single product, with regioselectivity likely arising from the increased acidity of the proton in the bis-allyl position (Scheme 24 – in blue/yellow). Following the synthesis chaxine B (**63a**) and its epimer **62** (so called BB) which were achieved in 5-steps each and chaxine C (**63b**) could be obtained through dehydration. In a subsequent report, the group applied the chemistry to a range of unnatural analogues and in addition demonstrated that demethylincisterol A_3 (**65**) could be obtained through hydrolysis of **63a**.[112]

5.1.20 11M5 (F5), 2017. Lee *et al.* reported the total synthesis of the furan fatty acid 11M5 (F_5) (**61**), a class of natural products and metabolites that have demonstrated activity toward a range of inflammatory diseases (Scheme 26).[35]

In their synthesis, they employed Appel reaction conditions (PPh_3, CBr_4) on endoperoxide **157** (which was synthesised in 4-steps) to perform a dehydrative cyclisation to yield furan **158** in 66% yield. In this case the *in situ* generated CBr_3^- was used as a base to initiate the KDM rearrangement step yielding enone **XI**, and upon cyclisation to **XII** and subsequent dehydration with PPh_3Br^+ the desired furan **XV** could be realised. It is not



Scheme 25 The KDM rearrangement was employed by Hirata and co-workers to deliver a key *cis* γ-hydroxyenone.



Scheme 26 Lee *et al.* use of the Appel reagent in a KDM rearrangement, and its application to the synthesis of 11M5.

known which proton is deprotonated in the initial KDM step (**X** to **XI**); however, this is immaterial given that final product destination is the fully dehydrated furan. The synthesis of **61** was completed with a cross metathesis and hydrogenation to install the ester functionality. The researchers also demonstrated the scope and versatility of the reaction on a range of substrates, yielding a variety of multi-substituted furans in 50–98% yield. The authors framed this as a biosynthetically inspired route to these important natural products, given the biosynthesis of furan fatty acids in marine bacteria.[113]

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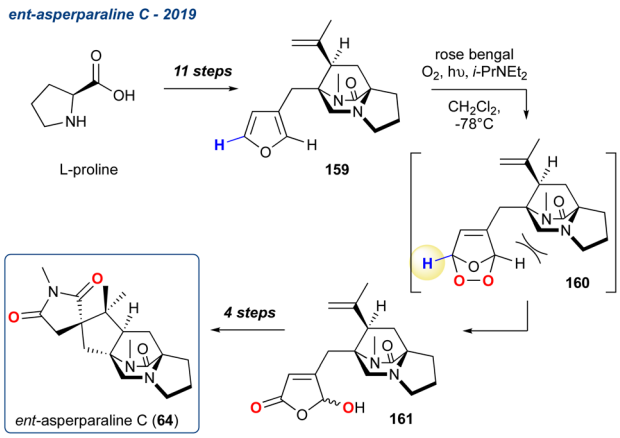
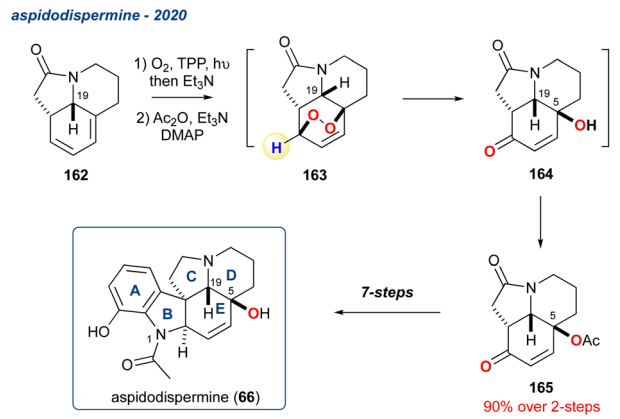
5.1.21 *Ent*-asperparaline C, 2019. Recently, Dokli, *et al.* reported the total synthesis of *ent*-asperparaline C (**64**), a natural product from a wider family of alkaloids containing a diketopiperazine unit, and a smaller subfamily that contains a bridged diazabicyclo-[2.2.2]-octanone core (Scheme 27).[114] Asperparalines A–C were isolated from *Aspergillus japonicus* and have shown strong paralytic effects on silkworms.[115] In their reported synthesis of **64**, the authors accessed furan **159** in 11-steps from L-proline, which was then converted to the γ-hydroxyenone **161** in 85% yield using singlet oxygen and Hünigs base in one-pot. This reaction showed high regioselectivity for the desired product, likely due to the bulky group on one side of the furan ring, in addition, the authors noted that **161** was isolated as an inseparable mixture of diastereoisomers in which the ratio could not be determined. It was also noted that no oxidation or ring fragmentation occurred under the conditions of oxidation-KDM rearrangement. Another 4-steps took **161** to the completed synthesis of **64**.



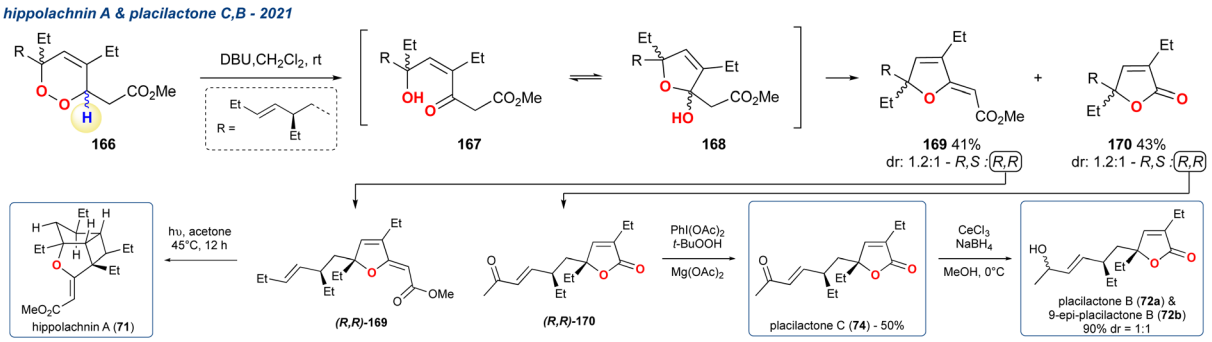
Scheme 27 The use of a regioselective KDM rearrangement by Dokli *et al.* in their synthesis of *ent*-asperparaline C (**64**).

5.1.22 Aspidodispermine, 2020. Reuß and Heretsch reported the use of a KDM rearrangement in a route to aspidodispermine (**66**), a member of the pyrroloquinoline alkaloids (Scheme 28).[116] Diene **162** was accessed in 10-steps and then subjected to photo-oxidation conditions to yield the endoperoxide which was reacted *in situ* with Et_3N with regioselectivity coming from the presence of the quaternary carbon in the diene. The KDM rearrangement product was then acetyl protected without isolation, yielding **165** in 90% over the 2-steps. The stereochemistry of the hydroxyl group at C5 on **165** is installed *via* the initial photooxidation, which occurs on the convex face (*syn* to the H at C19). The subsequent regioselective KDM then provides the desired stereochemistry at C5. The synthesis of the target **66** was completed in an additional 7-steps.



Scheme 28 A regioselective KDM rearrangement in the synthesis of aspidodispermine (**66**).

5.1.23 (+)-Hippolachnin A and plakilactone C, B, 2021. Several *Plakortin* polyketides were synthesised by Li *et al.* and among them was (+)-hippolachnin A (**71**), a tricyclic marine natural product isolated from a marine sponge *Plakinastrella mamillaris* (Scheme 29).[117–119] In this report the group employed the KDM rearrangement as a key strategic step in their synthesis. After accessing racemic peroxide **166** in 14-steps it was treated it with DBU as the base, forming the KDM rearrangement product (**167**) which upon cyclisation formed hemiketal **168**. Hemiketal **168** was found to undergo elimination yielding two major products **169** and **170** as a 1.2 : 1 mixture of diastereoisomers, of which the *R*,*R*-isomer (*R*,*R*-**169**) underwent UV-induced [2 + 2]-cyclisation to complete the formal synthesis of (+)-hippolachnin A (**71**). The group also demonstrated that the *R*,*R*-isomer of the undesired product (*R*,*R*-**170**) obtained from the KDM rearrangement step could be taken forward to



Scheme 29 Synthesis of hippolachnin A and placilactone C and B.

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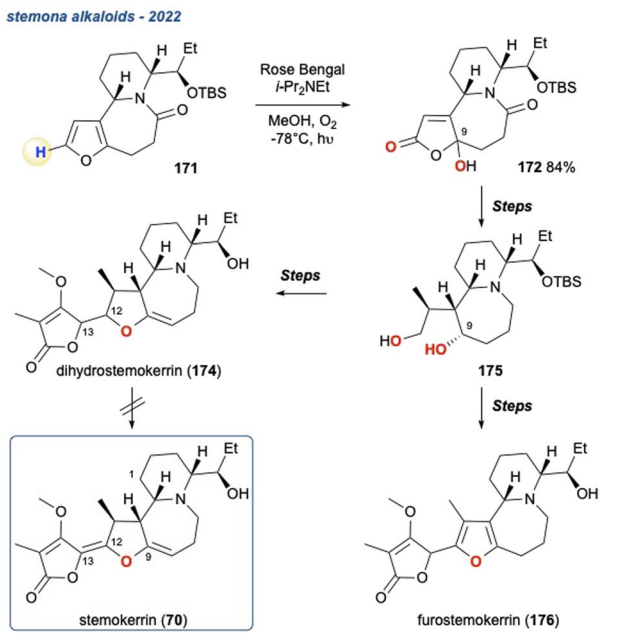
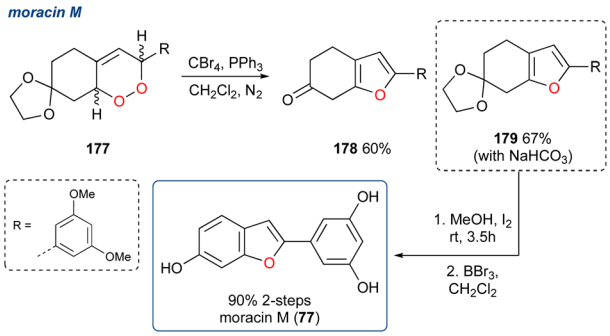
access another series of natural products plakilactone **C** (**74**) and **B** (**72**) in 1- and 2-steps, respectively.

5.1.24 Toward stemokerrin – pyrido[1,2-*a*]azepine stemona alkaloid skeleton, 2022. In an attempt to synthesise stemokerrin, a natural product of the pyrido[1,2-*a*]azepine subset of Stemona alkaloids, Morgenstern *et al.* employed a KDM rearrangement in the latter half of their synthesis (Scheme 30).[120] The peroxide intermediate was generated from furan **171** and quenched *in situ* by i-Pr_2NEt, in this case the regioselectively of the KDM rearrangement was due to the availability of a single H-atom. The γ-hydroxybutenolide **172** was then taken forward in their attempts to synthesise **70** and ultimately resulted in 2 non-natural products; dihydrostemokerrin **175** and furostemokerrin **176**, when attempts to construct the C12–C13 double bond of **174** proved unsuccessful.



Scheme 30 Morgenstern *et al.* use of the KDM rearrangement to install a γ-hydroxybutenolide in their unsuccessful synthesis of stemokerrin. However, two non-natural products dihydrostemokerren and furostemokerrin could be accessed.



Scheme 31 Synthesis of the benzofuran, moracin M (**77**) using an Appel reagent mediated KDM rearrangement.

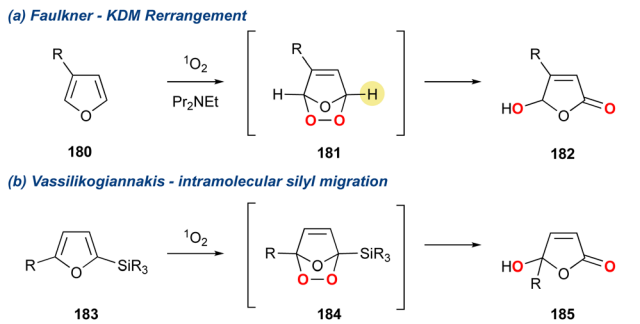
5.1.25 Moracin M, 2023. Using the same Appel approach to synthesise functionalized furans (Scheme 31), Al-Jawaheri *et al.* completed the synthesis of the benzofuran natural product moracin M (**77**).[121]

Using their reported route to 1,3-dienes[122,123] they synthesised endoperoxide **177** and subjected it to Appel conditions, which unexpectedly yielded ketone **178** in 60% yield. Here the furan was successfully constructed but due to the build-up of HBr during the reaction the acetal deprotection occurred and attempts to aromatise **178** failed. A minor modification to the procedure saw the inclusion of $NaHCO_3$ to quench the HBr *in situ* and prevent deprotection and under these conditions acetal **179** was obtained in 67% yield. The synthesis of moracin M (**77**) was completed in 90% yield over two deprotection steps.

5.2 Unmasking 3-substituted furans to reveal 4-hydroxybutenolides using the KDM rearrangement

The butenolide motif is found over several natural product families whose synthesis has been recently reviewed.[124,125] In 1988 Faulkner and co-workers[110] reported a convenient method for the direct conversion of 3-alkyl furans to 4-hydroxybutenolides through the action of singlet oxygen and a hindered base (Scheme 32a).[126] This method makes use of a hindered base to direct the deprotonation, thereby proving **182**. This methodology was further modified by Vassilikogiannakis and co-workers[127] who utilised 2-trialkylsilylfurans which could be directly converted to the corresponding butanolide using singlet oxygen, but in the absence of base (Scheme 32b). This latter method goes *via* an intramolecular silyl migration as described by Adam and Rodriguez.[128] Both methods have found application in the total synthesis of natural products over the past 25 years. However, this section will only centre on those syntheses that convert 3-alkylfurans instead of 2-trialkylsilylfurans, as the former proceeds solely by a base mediated KDM rearrangement.

We have summarised all the natural products that have been synthesised using this approach in Fig. 3. Fig. 3A demonstrates natural products giving a γ-hydroxybutenolide in the last step, while Fig. 3B, gives natural products that possess a butenolide, which is installed through a subsequent reduction. Given the uniform approach across all these natural products in unmasking of the 3-substituted furan in the last step using the



Scheme 32 Conversion of furans into butenolides *via* the KDM rearrangement.

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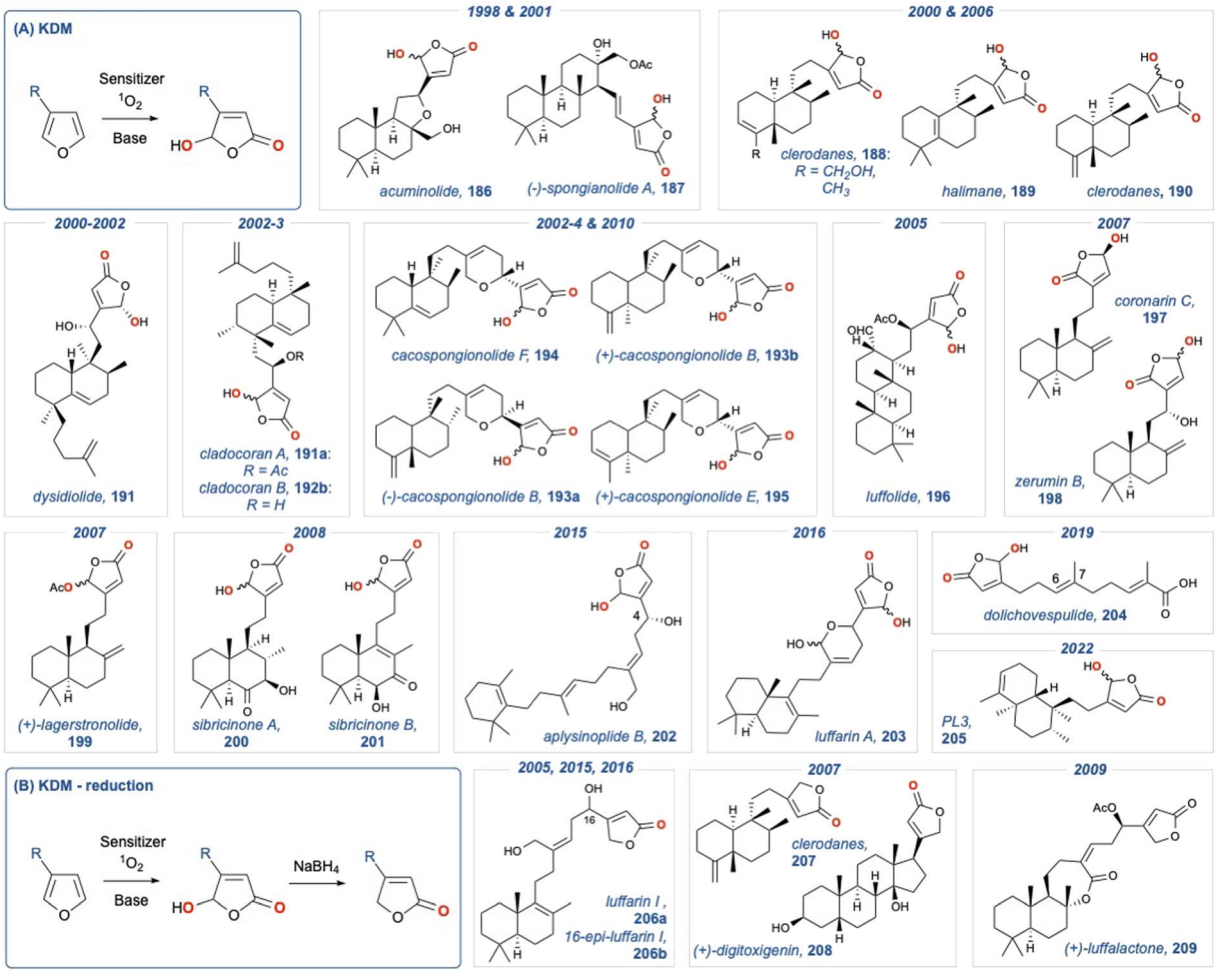

Fig. 3 Natural products that have been synthesised using (A) unmasking of a 3-substituted furan in the final step; (b) unmasking of a 3-substituted furan in the final step and then reduction.

Faulkner method, detailed analysis has not been undertaken; however, a summary is given below.

Dubay and co-workers synthesised acuminolide (**186**) in 1998 (and its 17-*O*-acetyl analogue, **187**) using a semisynthetic approach.[129] Acuminolide (**186**) is a labdane diterpene with cytotoxic activity, and their syntheses was achieved from commercially available (+)-sclareolide, with the key butenolide being revealed using a KDM rearrangement. Soetjipto and co-workers disclosed a synthesis of acuminolide (**186**) in 2001,[130] and again, the key butenolide was revealed using a last step KDM rearrangement. The clerodanes and halimanes (**188–190**) were synthesised by Costa and co-workers. The authors were able to assign the absolute configuration through a successful semi-synthesis from methyl (+)-hardwickiate; again, they utilised the KDM rearrangement to reveal the key butenolide.[131,132] Dysiodiolide (**191**) is a natural product isolated form the marine sponge *Dysidera etheris* and is a potent inhibitor of the human cdc25A protein phosphatase.[133] This natural product has received considerable attention since is identification in 1996. Consequently, several total syntheses[134–139] have been reported, with the key butenolide being revealed in the final step. Cladocoran A and B (**191a,b**), isolated form the coral *Cladocora cespitosa*[140] show structural homology with dysidiolide (**191**), consequently several groups use a final KDM rearrangement to reveal the butenolide. Marcos *et al.*[141,142] used a semisynthetic approach from *ent*-halimic acid to give a synthesis of their purported structures. Miyaoka *et al.*[143] then used a *de novo* synthesis and established clardocoran B (**192b**) to be an olefinic isomer of dysodiolide (**191**), with clardocoran A (**191a**) being its acetate. The cacospongionolides (**193–195**) are sesterterpenes isolated from sponges of the Thorectidae family and are inhibitors of phospholipase A_2 (PLA_2) and therefore show potential in treating inflammation. First to be synthesised was (−)- and (+)-cacospongionolides B (**193a,b**) by Chueng and Snapper,[144] who used a KDM rearrangement in the final step to reveal the butenolide, this was followed by a synthesis of (−)-cacospongionolides F (**194**) by Demeke and Forsyth,[145] and a follow up synthesis of cacospongionolides E (**195**) again by Snapper,[146] as well as latter synthesis of (−)-cacospongionolides B (**193a**) by Oshida *et al.*[147] Luffoilide (**196**) is a metabolite from the sponge *Luffariella*, and its semi-synthesis[148] was completed using a KDM rearrangement in the final step from methyl

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isoanticopalate, itself obtained from sclareol. The same group then reported a synthesis of (+)-laffalactone (**209**);[149] however, the key γ-hydroxybutenolide from the final KDM rearrangement was subsequently reduced to provide the desired natural product. Laffarin I (**206a**) was first synthesised by Urosa and co-workers from commercially available sclareol.[150] Luffarin A (**203**), a related metabolite, was synthesised using a similar last step KDM rearrangement approach, along with luffarin I (**206a**) and 16-*epi*-luffarin I (**206b**); the last two natural products were obtained by a subsequent reduction of the γ-hydroxybutenolide.[151] The labdane diterpenes, coronarin C (**197**) and zerumin B (**198**) underwent oxidation using rose Bengal or TPP as the photosensitiser. Oxidation using rose Bengal was undertaken in the absence of base, giving the required regioisomer of the butenolide; whereas, in the presence of base the undesired product was isolated.[152] Basabe and co-workers completed a semi-synthesis of the diterpene (+)-lagerstronolide (**199**) from (+)-sclareol.[153] (+)-Lagerstronolide (**199**) is a metabolite isolated from the *Lagerstreomia lancasteria* shrub in south-eastern Australia.[154] The key butenolide was introduced *via* a KDM rearrangement in the penultimate step, with the resultant γ-hydroxybutenolide being acetylated to give the desired natural product. A *de novo* synthesis of (+)-digitoxigenin (**208**) was reported by Homma and Nakata in 2007.[155] (+)-Digitoxigenin (**208**) has clinical value as a treatment for congestive heart failure and as well as displaying anticancer activity. The butenoilide was introduced by a two-step sequence involving a KDM rearrangement with subsequent reduction of the γ-hydroxybutenolide. Marcos and co-workers completed syntheses of both sibiricinone A and B (**200** and **201**), again from (+)-sclareol.[156] Kutsumura and co-workers completed a total synthesis of aplysinoplide B (**202**),[157] a cytotoxic sesterterpeniod isolated from the marine sponge *Aplysinopsis digitata*.[158] The purpose of the synthesis was the promising activity of these natural products against P388 mouse leukemia cells, as well as confirming the C4 hydroxyl group. Again, the butenolide was introduced in the last step *via* a KDM rearrangement. Dolichovespulide (**204**) is a sesquiterpene isolated from the body surface extracts of hornet queens (*Dolichovespula maculata*). This pheromone is a new member of relatively small class of terpenoids isolated from the Vespidae insect family. The key butenolide was unveiled using a KDM rearrangement, and the total synthesis confirmed the C6–C7 double bond geometry.[159] Technically, revealing of butenolide was the penultimate step in the synthesis, as the free acid needed to be revealed in the last step. In 2022, Zhu and co-workers provided a modular synthetic approach, using a metal mediated tail-to-head cyclisation strategy, to synthesise the central diterpene ring system of several *trans*-clerodane analogues. In their report they provided an effective synthesis of annonene, which was oxidised using a KDM rearrangement condition to provide the butenolide PL3 (**205**).[160]

6 Conclusions

This review provides valuable insight into the versatility of the KDM rearrangement in natural product synthesis. It is clear from the number of reports that this transformation is increasingly recognised as a key biomimetic step. There are several reports that utilise the enantioselective KDM, but here the methodology is limited to larger rings (≥6-membered) that contain some pre-existing steric bias. New developments in this area would open-up a raft of possibilities for installing chiral alcohols on a wider variety of substrates. Presently, there are limited reports of the reaction taking place under acidic conditions, apart from the report by Bach and co-workers.[40] This may provide scope to improve on the existing enantioselective desymmetrisation of prochiral endoperoxides described by Toste.[43] This method uses a chiral base to affect the KDM, has substrate limitations. The successful development of an enantioselective acid catalysed process could have significant impact and improve upon the already impressive range of natural products that can be synthesised using the KDM rearrangement.

7 Author contributions

MCK and DSL contributed equally to the conceptualisation and investigation of this research. They both contributed equally to the writing and preparation of the manuscript.

8 Conflicts of interest

There are no conflicts to declare.

9 Acknowledgements

MCK would like to thank Loughborough University. DSL would like to thank the Center for Green Chemistry and Green Engineering for their support and the JA team for their advice and fruitful discussions.

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