REVIEW

The vinylogous Mukaiyama aldol reaction (VMAR) in natural product synthesis

Markus Kalesse,*[ab] Martin Cordes,[a] Gerrit Symkenberg[a] and Hai-Hua Lu[a]

Covering: XXXX to YYYY / up to YYYY / up to the end of YYYY

The vinylogous Mukaiyama aldol reaction (VMAR) allows efficient access to larger segments for complex natural product synthesis, primarily polyketides, through the construction of vicinal hydroxyl and methyl groups as well as di and tri-substituted double bonds in one single operation. In this review, we will highlight stereoselective protocols that have been used in natural product synthesis and cluster them into the four groups that can be obtained from different silyl ketene acetals or enol ethers. At the beginning, an overview on different stereoselective VMARs is presented; disregarding their applications in total syntheses.

[a]Institute for Organic Chemistry and Centre of Biomolecular Drug Research (BMWZ), Leibniz Universität Hannover, Schneiderberg 1B, 30167 Hannover, Germany. E-mail: Markus.Kalesse@oci.uni-hannover.de; Fax: +49 511 7623011; Tel: +49 511 762 4688
[b]Helmholtz Centre for Infection Research (HZI), Inhoffenstr. 7, Braunschweig, Germany. E-mail: Markus.Kalesse@helmholtz-hzi.de; Tel: +49 531 6181 9400

1   Introduction

In 1973, Mukaiyama published a new protocol for an aldol type reaction using trimethylsilyl enol ethers with ketones or aldehydes in the presence of titanium tetrachloride.[1] It was immediately recognized that this protocol allows to perform cross aldol reactions and the authors concluded their paper with the statement that "further development is in progress". Now, 40 years later, we know that this was an understatement and the Mukaiyama aldol reaction belongs to one of the elemental transformations in organic chemistry. In an application of Fuson's principle of vinylogy,[2] Mukaiyama and Ishida published the first vinylogous Mukaiyama aldol reaction (VMAR) using crotonaldehyde derived silyl dienol ether (**1**) and cinnamaldehyde dimethyl acetal (**2**) with $TiCl_4$ as the Lewis acid in analogy to their pivotal 1973 paper (Fig. 1).[3]

The fact that vinylogous silyl ketene acetals unfold their nucleophilicity at the γ-position, in contrast to the corresponding metal dienolates, can be rationalized by different

Fig. 1   The first vinylogous Mukaiyama aldol reaction (VMAR).

Fig. 2   Comparison of orbital coefficients and electrophilic susceptibility of vinylogous silyl ketene acetals with metal dienolates.

orbital coefficients and/or electrophilic susceptibility. Analysis of both values shows that for metal dienolates, both the orbital coefficients and electrophilic susceptibility are larger at the α-position, whereas for vinylogous silyl ketene acetals the γ-position displays larger values (Fig. 2).[4b]

In this review, we will cover the applications of VMARs in the total syntheses of natural products and group them based on the different methyl substitution patterns of the target molecules. Considering the natural functional group distance in polyketides, four major methyl substitution patterns are feasible (Fig. 3). As we will discuss below, each substitution pattern requires unique strategies to generate high levels of stereoselectivity.[4] However, we will start this review with a brief overview of existing protocols and concepts used in VMARs, disregarding their applications in total syntheses.

Markus Kalesse obtained his Dr rer. nat. in 1991 at the Leibniz Universität Hannover from Prof. D. Schinzer. After two post-doctoral studies with Prof. S. D. Burke and Prof. L. L. Kiessling at the University of Wisconsin/ Madison he completed his habilitation at the Universität Hannover (1997) in the periphery of Prof. E. Winterfeldt. He became C3-Professor at Freie Universität Berlin and was appointed, in 2003, as C4-Professor at the Universität Hannover. In 2005 he became co-appointed director at the Helmholtz Centre for Infection Research (HZI) in Braunschweig. Prof. Kalesse was awarded the Novartis-Lectureship in 2004/2005. His research interests include natural products synthesis, asymmetric catalysis and medicinal chemistry.

Gerrit Symkenberg was born in 1985 in Oldenburg, Germany. He studied chemistry at the Leibniz Universität Hannover and received his diploma degree under the supervision of Prof. Dr Markus Kalesse in 2011. Currently he works on his Ph.D. thesis in the field of natural product synthesis and vinylogous Mukaiyama aldol reactions (VMAR).

Martin Cordes is a Private Lecturer in the Department of Chemistry at the Leibniz Universität Hannover. He received a diploma in Organic Chemistry at the Georg August Universität, Göttingen (1990), and a doctoral degree (Dr rer. nat.) from the Technische Universität Braunschweig (1994). During the year 1995, he was a post-doctoral fellow at The Scripps Research Institute, La Jolla, CA (USA) and from 1996 until 1997 he was a research fellow at the Technische Universität Braunschweig. Dr Cordes received his venia legendi for Organic Chemistry from the Otto von Guericke Universität, Magdeburg in 2004. Since 2008 he is a member of the Department of Chemistry at the Leibniz Universität Hannover.
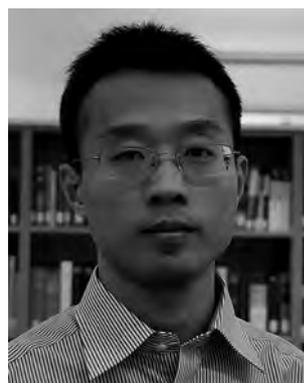
Hai-Hua Lu was born in Suzhou in 1981, studied chemistry at the Huazhong Agricultural University and received his diploma in 2003. After earning his Ph.D. in 2010 with Professor Wen-Jing Xiao at the Central China Normal University, investigating organocatalysis, he had an experience in pharmaceutical industry for one and a half years. Since 2010, he has been doing postdoctoral studies on natural product chemistry with Professor Markus Kalesse at the University of Hannover, supported by the Alexander von Humboldt (AvH) foundation. His research interest is method developments for the synthesis of natural products.
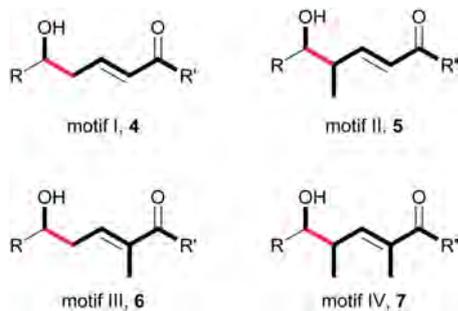
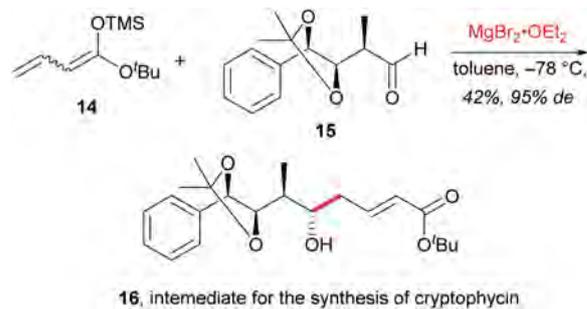Fig. 3 Substitution patterns observed in polyketide natural products.

Fig. 5 Chelation-controlled addition.

2 Diastereoselective VMARs

Simple diastereoselectivities can be obtained through Felkin control addition of silyl ketene acetals to α-chiral aldehydes. In the synthesis of ratjadone the all-*syn* stereotriade was established by a diastereoselective VMAR using tris(pentafuorophenyl) borane (TPPB) as the Lewis acid (Fig. 4).[5] It was realized that TPPB as a bulky substitute for BF$_3$ provided better selectivities. Later, it turned out that not TPPB itself but its hydrate was the efficient promoter. A similar transformation was employed during the synthesis of (+)-lepicidin A,[6] albeit with TiCl$_2$(O^{i}Pr)$_2$ as the Lewis acid (Fig. 4). It should be mentioned, that these transformations tolerate a 1,3-functional group distance between the aldehyde and a protected hydroxyl group and conversion can be achieved without elimination or protecting group cleavage. In this case, the use of TiCl$_2$(O^{i}Pr)$_2$ as a retarded Lewis acid compared to TiCl$_4$ was necessary for high conversion.

On the other hand, chelation-controlled transformations using MgBr$_2$ produced the *anti*-Felkin product as demonstrated in the synthesis of cryptophycin-1 (Fig. 5).[7]

Also, a 1,3-*anti*-relationship can be achieved by taking advantage of the polar-Evans-Cornforth transition state. A
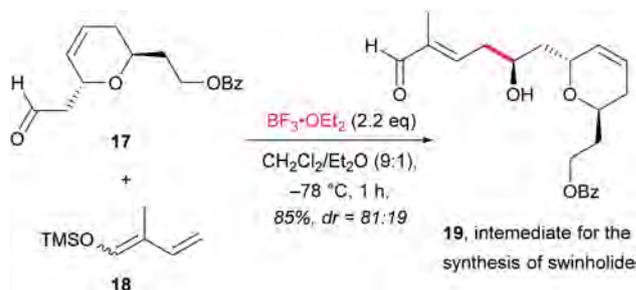

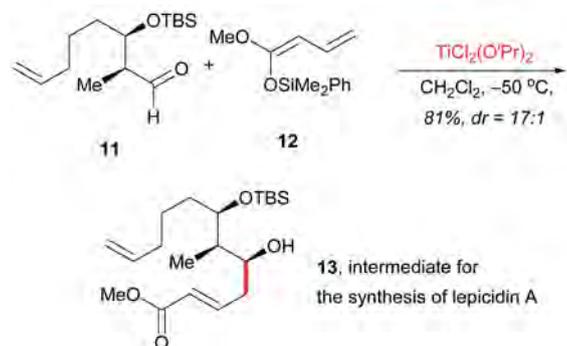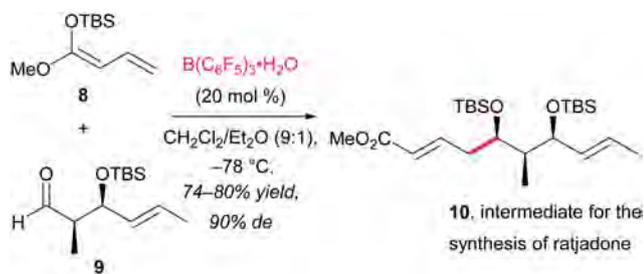Fig. 6 Addition controlled by the polar Evans-Cornforth transition state.
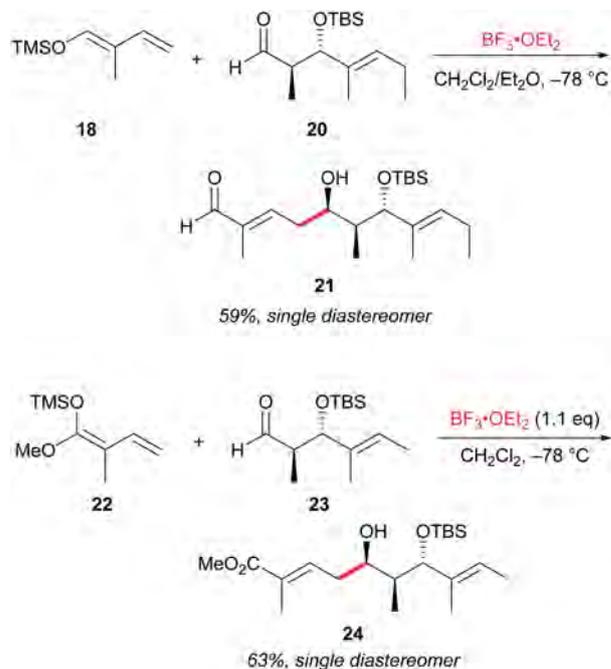

Fig. 4 Felkin-controlled addition to α-chiral aldehydes.

Fig. 7 Felkin-reinforced additions by double directing effects.

This journal is © The Royal Society of Chemistry 2014
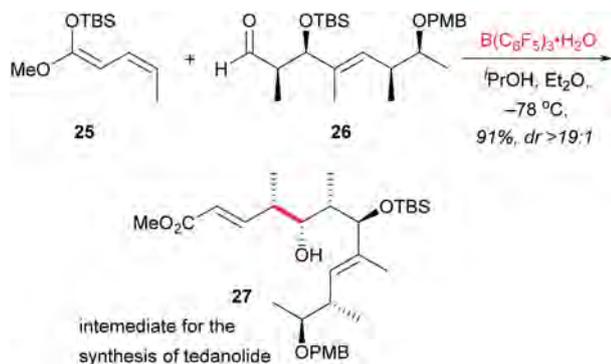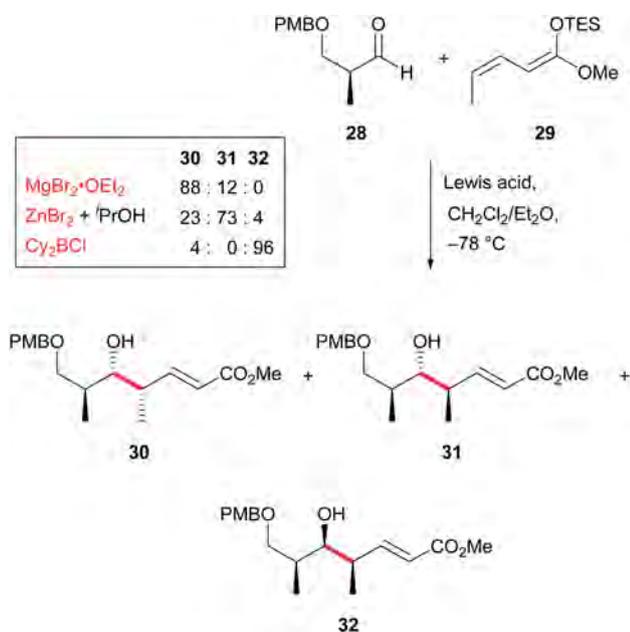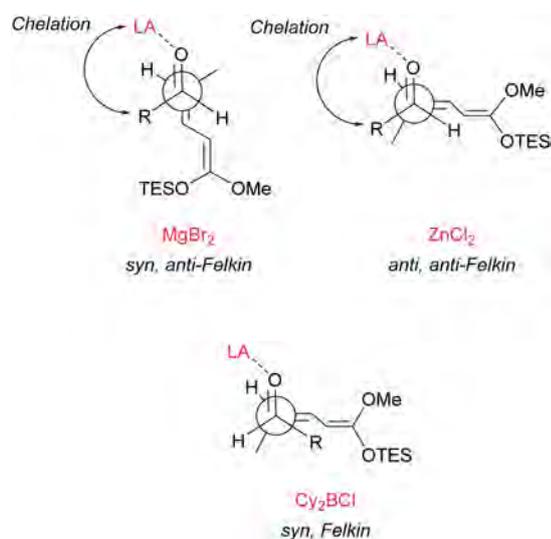
Nat. Prod. Rep., 2014, xx, 1–32 | 3

Fig. 8   *Syn*-selective addition of γ-substituted nucleophiles.

Fig. 9   Stereodivergent addition to α-chiral aldehyde **28**.

Fig. 10   Transition states controlled by different Lewis acids.

Fig. 11   Transition states for the Kobayashi VMAR.

diastereomeric ratio of 4 : 1 was achieved with BF_3 as the Lewis acid during the synthesis of swinholide A (Fig. 6).[8]

Finally, taking advantage of both directing effects at the α- and β-position, it was possible to obtain only one stereoisomer using silyl ketene acetals and the corresponding enol ethers (Fig. 7).[9]

An additional level of complexity adds to the vinylogous Mukaiyama aldol reaction if nucleophiles exhibiting a terminal methyl group were employed. Such an example was provided in the course of the synthesis of the marine natural product tedanolide.[10] As described above, the hydrated form of TPPB gave the best selectivities for the *syn*-Felkin product (Fig. 8).

The inherent directing effects of aldehydes were investigated using the aldehyde derived from the commercially available Roche ester. Depending on the nature of the Lewis acid employed, one could obtain the chelation-controlled *anti,syn*-product (**30**), the *anti,anti*-product (**31**) or the all *syn*-product (**32**), respectively. The highest selectivities were observed for the all-*syn* product when Cy_2BCl was used as the Lewis acid (Fig. 9).[11]

The selectivities were rationalized based on the recent transition state calculations published by the Wiest group.[12] Their conclusion was that both the *anti*-periplanar transition state and the *syn*-clinal transition state are electronically favoured. For non-chelating Lewis acids the Lewis acid adopts a conformation in close proximity of the aldehyde's formyl proton. For Lewis acids with bulky substituents the *syn*-clinal conformation
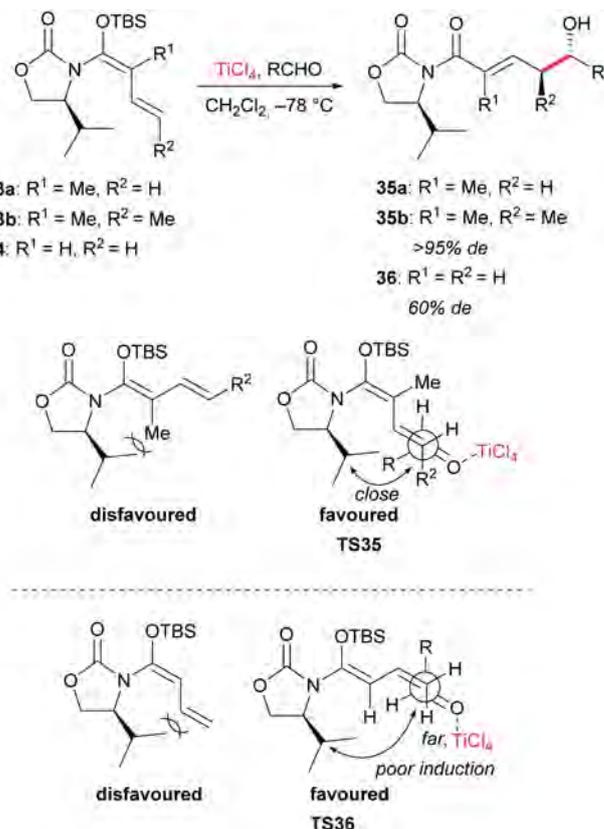
4 | *Nat. Prod. Rep.*, 2014, **xx**, 1–32
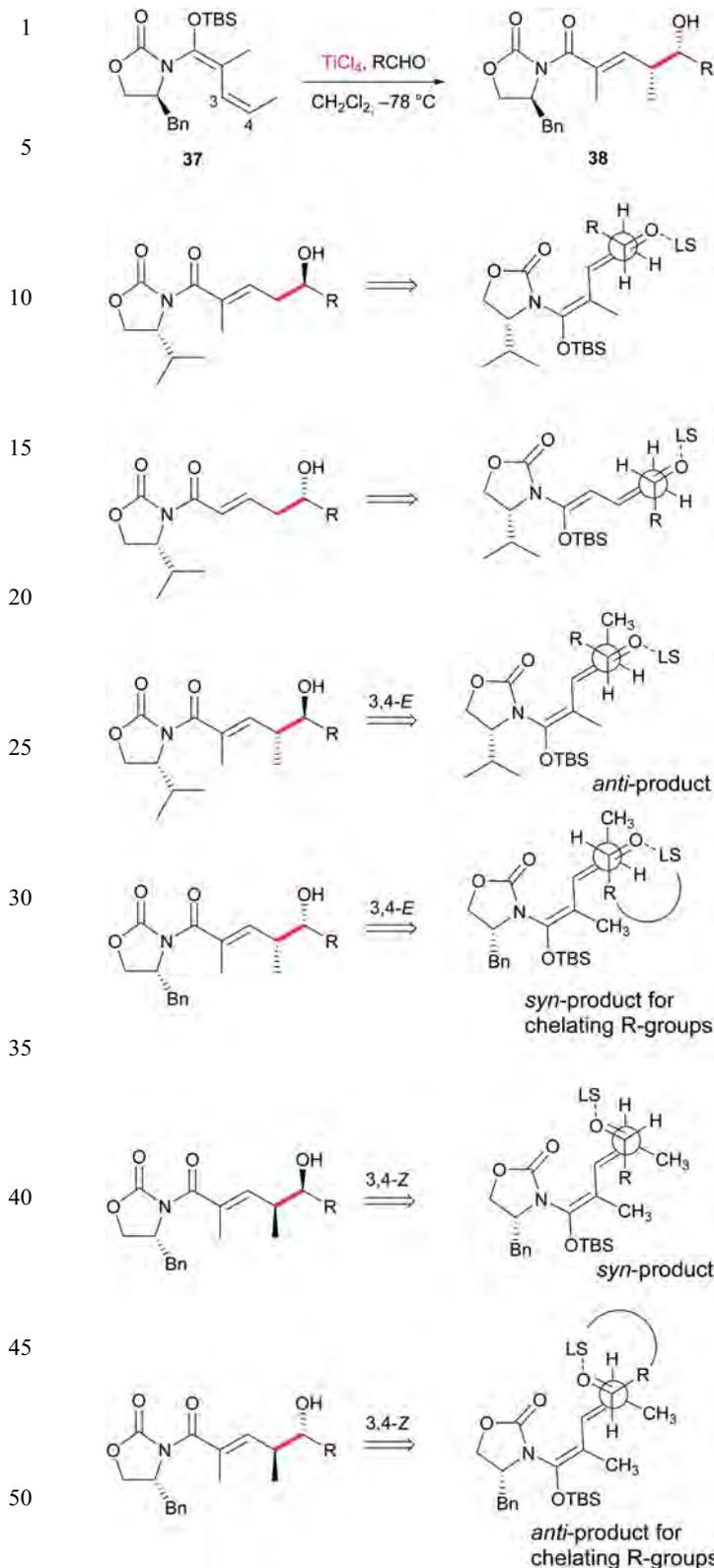
This journal is © The Royal Society of Chemistry 2014

Fig. 12 The *syn*-selective vinylogous Kobayashi aldol reaction and transition states for *E* and *Z*-configured silyl ketene N,O-acetals.

is favoured due to the larger distance with respect to the terminal methyl group. A different situation must be drawn for chelating Lewis acids and aldehydes exhibiting α-substituents

with donor atoms. In these cases, the Lewis acid is orientated towards the R-groups at the aldehyde. As in the previous case, the steric hindrance of residues at the Lewis acid determines whether the *anti-* or the *syn*-clinal orientation is adopted.

A major contribution to the stereoselective vinylogous Mukaiyama aldol reactions was put forward by the Kobayashi group. They used the Evans auxiliary for the induction of chirality. The methyl group at the α-position of the silyl ketene acetals is important to achieve high selectivities.[13] As it can be seen for starting materials **33** and **34**, the α-methyl group controls the C2–C3 double bond geometry as well as the orientation of the aldehyde's R-group in the proposed transition state (Fig. 11). As a consequence silyl ketene *N,O*-acetals without α-methyl groups transform only with 60% de, whereas the same transformation in the presence of α-methyl groups provides selectivities >95% de. By simple deprotonation for generating the terminal double bond, one obtains *E*-configuration leading to the *anti*-product as depicted by transition state **TS35**.

For quite some time, it was not possible to perform the Kobayashi protocol on non-chelating aldehydes to get *syn*-products. Recently, Symkenberg and Kalesse published a protocol for obtaining the 3,4-*Z*-configured silyl ketene *N,O*-acetal (**37**) and consequently the *syn*-product (**38**) in the course of the vinylogous Mukaiyama aldol reaction (Fig. 12).[14] Interestingly, when using aldehydes with heteroatoms that could be utilized for coordinating to the Lewis acid, the selectivities were reversed.[15] The silyl ketene *N,O*-acetal exhibiting an *E*-configured terminal double bond provided the *syn*-product and *vice versa*. Also, when neat TiCl$_4$ was used the *E*-configured silyl ketene *N,O*-acetals provided the *syn*-aldol products.[16] The selectivities can be rationalized by employing the transition state as depicted in Fig. 12. For the *anti*-selective Kobayashi aldol reaction an *anti*-periplanar transition state is adopted and the R-group at the aldehyde is pointing away from the α-methyl group. Additionally, the Lewis acid is opposite to the R and to the terminal methyl group. For aldol reactions with a terminal *Z*-configured double bond, a *syn*-clinal transitions state is proposed.

3 Enantioselective VMARs

Enantioselective VMARs with aldehyde-derived dienolates were performed with valine-based oxazaborolidinone (**40**). Using propionitrile at −78 °C selectivities up to 91% ee were obtained (Fig. 13).[17] When using the silyl ketene acetal **25** as the nucleophile, oxazaborolidine **43** was the optimum Lewis acid. In these cases not only enantioselectivities up to 90% ee but also diastereoselectivities of >95% were observed.[18]

A different approach, using silyl ketene acetals in asymmetric vinylogous aldol reactions takes advantage of [CuF$_2$(*S*)-Tol-BINAP] as the catalytic system and is considered to be an alternative to the established activation using [(*R*)-BINOL-Ti(O^{i}Pr)$_4$] (Fig. 14). Both types of activation use chiral titanium(IV)-based Lewis acids. It was proposed that the Tol-BINAP, Cu(OTf)$_2$, (^{n}Bu$_4$N)$^+$Ph$_3$SiF$_2^-$ system yields in enolate activation, generating a chiral bisphosphine copper(I) metallodienolate (Fig. 15).[19,20] Both catalysts provided comparable
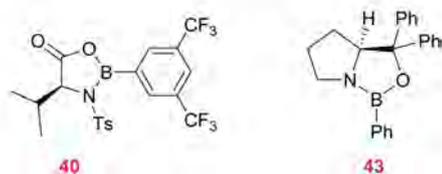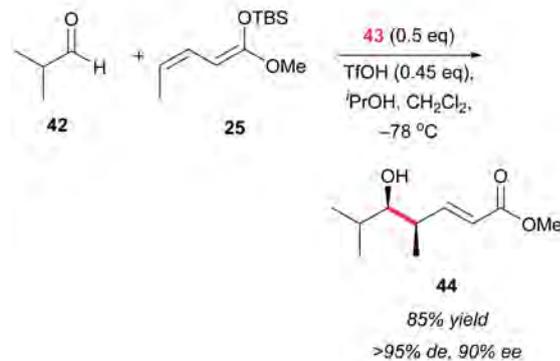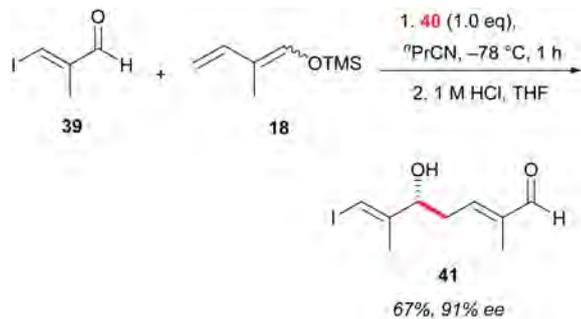
This journal is © The Royal Society of Chemistry 2014

Nat. Prod. Rep., 2014, **xx**, 1–32 | 5

Fig. 13 Enantioselective addition using oxazaborolidine catalysts.

enantioselectivities with respect to each other but do not reach the selectivities obtained with the above mentioned chiral boron-based Lewis acids. An application of this strategy was provided during the synthesis of the natural product octalactin.

In contrast to the above mentioned catalytic systems that used a copper enolate for activation, air-stable copper(II)
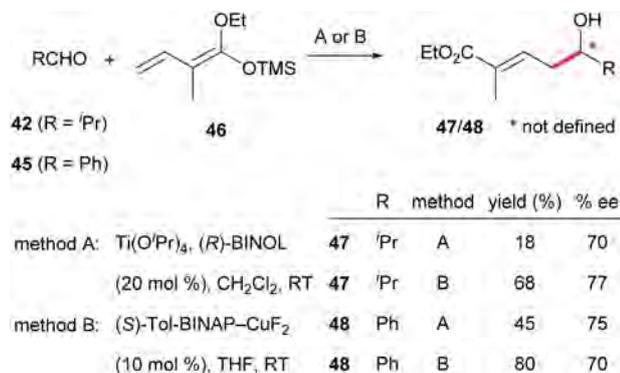

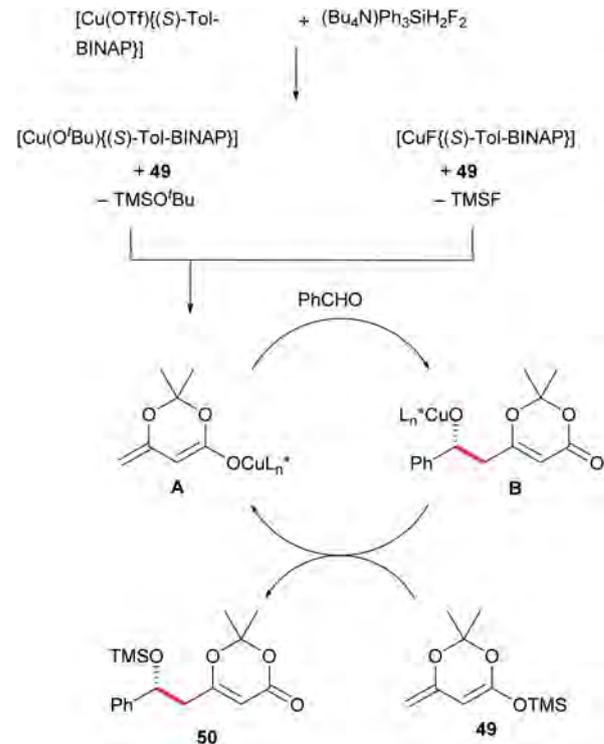Fig. 14 Enantioselective addition using the Ti(O^{i}Pr)$_4$/BINOL and the Tol-BINAP–CuF$_2$ catalytic systems.

Fig. 15 Catalytic cycle of the Tol-BINAP–CuF$_2$ catalytic system.

complexes were also employed as Lewis acids. However, this strategy requires aldehydes that have an additional substituent capable of chelating the chiral Lewis acid. Nevertheless, this approach was applied during the total synthesis of (−)-callipeltoside A (102) and provided the desired product with high yields and excellent enantioselectivity (97% ee) (Fig. 16).[21]

A similar concept that takes advantage of a chiral copper catalyst used in combination with a bidentate substrate was put forward by Bolm and co-workers (Fig. 17). They used their chiral sulfoximine ligands in vinylogous Mukaiyama aldol reactions with reactive ketones. After a thorough survey of different reaction conditions and sulfoximine substitution patterns they identified sulfoximine 57 as the ligand that provides the highest yields and selectivities (up to 99% ee).[22]
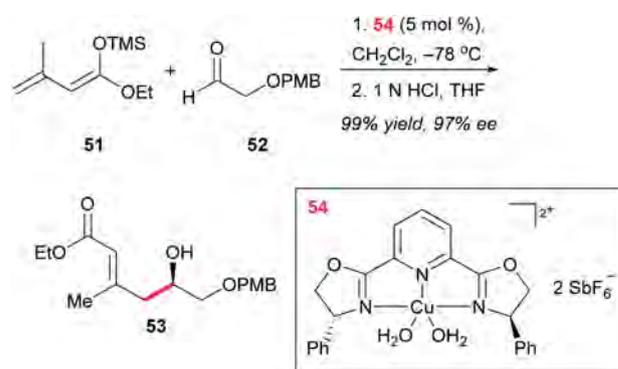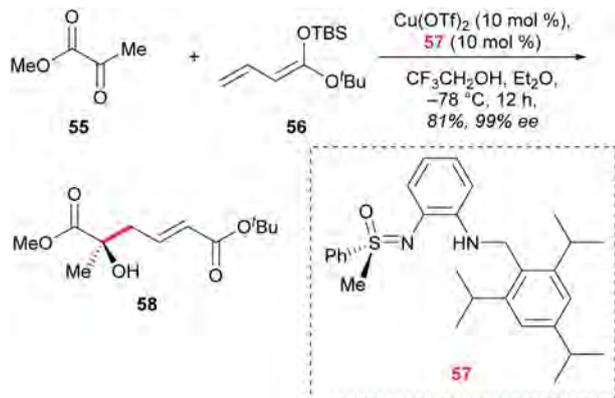

Fig. 16 Cu-pybox as active Lewis acid.

Fig. 17 Chiral sulfoximine catalyst in VMAR.

Denmark and co-workers employed their concept of Lewis base activation of Lewis acids for the vinyloguos Mukaiyama aldol reaction. Addition of the chiral Lewis base bisphosphoramide **59** to SiCl$_4$ extended its coordination sphere and the increased Lewis acidity leads to successful activation of aldehydes.[23] The transition state model (**60**) places the aldehyde *trans* to one of the phosphoramides, which is rationalized by the nature of hypervalent silicon (Fig. 18). This conformation places the aldehyde against one of the binaphthyl units and consequently allows exposure of the aldehyde's *re* face towards nucleophilic attack. Additionally, potential edge-to-face interactions between the aromatic aldehydes and the aromatic rings of the ligands can be used to rationalize the higher selectivity
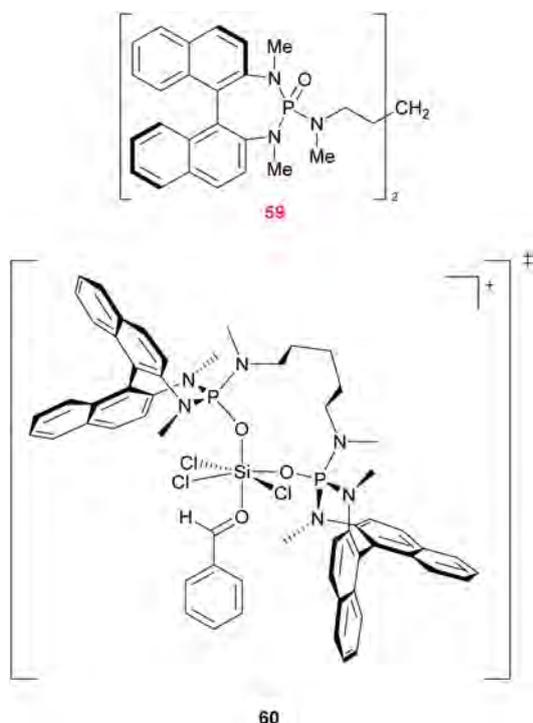

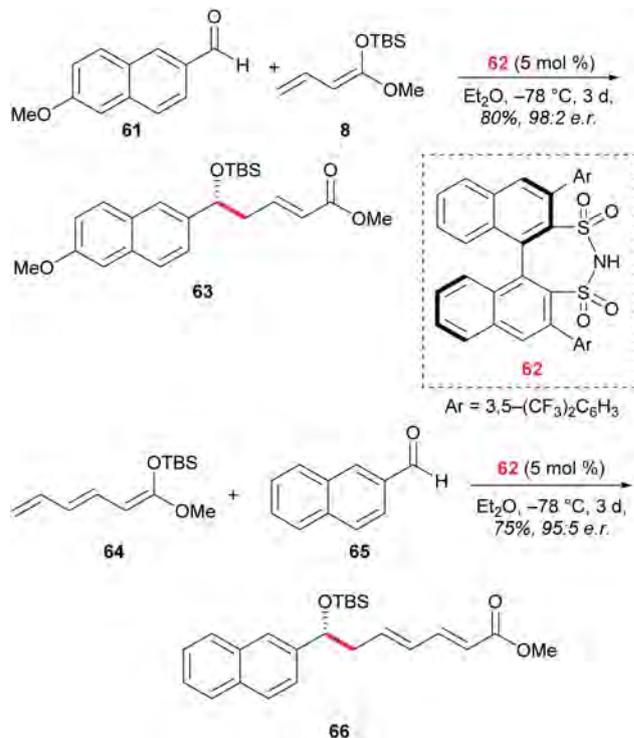**Fig. 18** Transition state model involving hypervalent silicon species.

Fig. 19 Organocatalytic VMAR.

observed for unsaturated aldehydes compared to aliphatic aldehydes.

Comparable to the Denmark catalyst is the organocatalytic approach put forward by the List group.[24] They used the chiral disulfonimide **62** as Brønsted acid to induce the stereoselective VMAR. By using aromatic aldehydes as substrates, selectivities up to 98 : 2 er (Fig. 19) could be achieved. Additionally, they were able to perform bisvinylogous Mukaiyama aldol reactions with triene **64**.

Even though a chiral Brønsted acid is used, they proposed a mechanism that includes an activated Lewis acid which
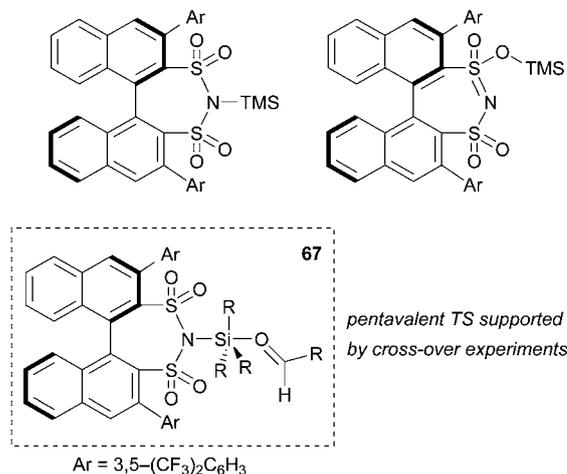
Fig. 20 Putative pentavalent transition state **67**.

comprised the counterion of the Brønsted acid and a silicon species (Fig. 20). There could be potentially a silatropic rearrangement involved. In any case, crossover experiments supported the proposal that a silicon species released from the nucleophile generating in combination with the Brønsted acid a new activated Lewis acid that is active in inducing the VMAR reaction and ultimately regenerating the active Lewis acid. This concept has its advantage in that the active species is not required to be prepared prior to the transformation but generates itself during the catalytic cycle.

4   Natural product syntheses generating motif I

motif I, 4   type I
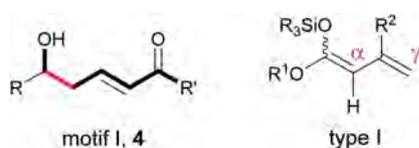
In the last few decades, either diastereoselective or enantioselective VMARs of γ-unsubstituted silyl ketene acetals have been successfully developed. Meanwhile, their applications in natural product syntheses have been demonstrated and we will discuss their role in syntheses below.

4.1   Substrate-controlled processes

The applications of type I silyl ketene acetals can be dated back to Evans' first total synthesis of (+)-A83543A (lepicidin A 68, Fig. 21),[6] a structurally unique macrolide natural product shown to have potent insecticidal activity, especially against Lepidoptera larvae.

Their initial approach is based on a VMAR between aldehyde 11 and silyl ketene acetal 12 (Fig. 22). Using $TiCl_2(O^iPr)_2$ as the catalytic Lewis acid the desired Felkin product (13) was obtained in 81% yield and excellent diastereoselectivity (dr = 17 : 1). Although this route had to be given up due to selectivity problems in the subsequent Michael addition (undesired
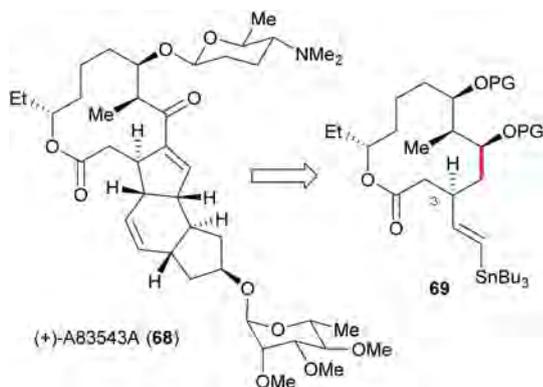
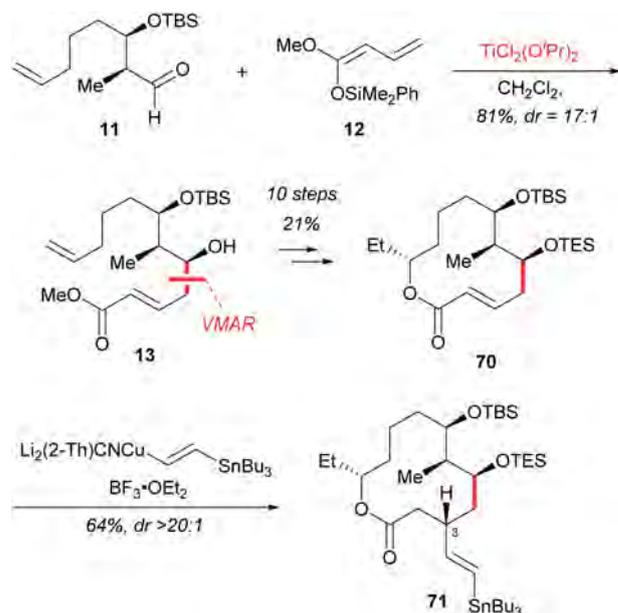Fig. 21   Evans' strategy to (+)-A83543A (lepicidin A, 68).

Fig. 22   Evans' initial VMAR approach to fragment 70.

configuration at C3), this example is still an important contribution to synthetic chemistry.

The polyketide ratjadone (72) was isolated from cultures of *Sorangium cellulosum* strain So ce360 by Höfle and co-workers in 1994.[25] Initial biological studies indicated that ratjadone displays a unique mode of action as one of the most active inhibitors of cellular export (L929, IC_{50} = 50 pg mL^{-1}). Accordingly, synthetic efforts arose from the chemical community towards its synthesis. The first report from the Kalesse group features a highly convergent approach involving three fragments, as depicted in Fig. 23.[5]

To access fragment 73, a key VMAR between aldehyde 9 and silyl ketene acetal 8 was undertaken (Fig. 20).[5] After a survey of different Lewis acids, $B(C_6F_5)_3$ emerged as the most superior one. In the presence of this bulky but still highly active Lewis
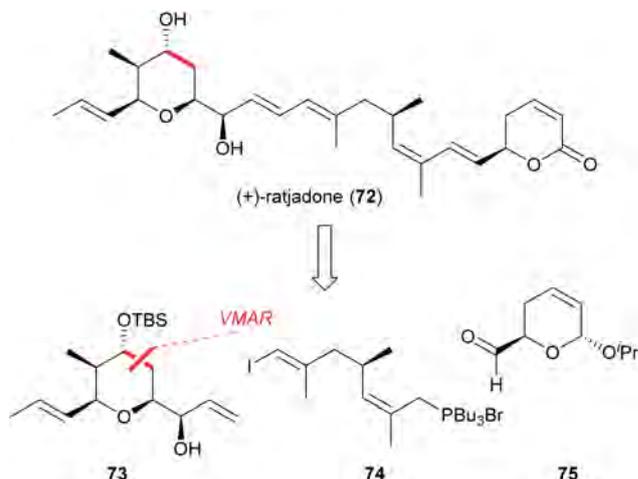
Fig. 23   Kalesse group's strategy towards (+)-ratjadone (72).

acid, the reaction proceeded smoothly, and transfer of the TBS group to the newly formed hydroxyl group occurred *in situ* to provide the desired Felkin adduct **10** in 80% yield and excellent diastereoselectivity (dr >19 : 1). As pointed out in the introduction, later it turned out that the mono-hydrate was the active Lewis acid. With the all *syn* stereo triad constructed, a subsequent four-step sequence, involving ester reduction with D^{i}BAlH, alkene epoxidation with *m*-CPBA, TBS deprotection and amberlyst-15 catalyzed intramolecular epoxide ring opening, successfully provided highly functionalized tetrahydropyran **77**, further manipulation produced fragment **73** in good overall yield after 5 steps (Fig. 23 and 24).

Constanolactones A (**78**) and B (**79**) isolated in 1990 from a red alga *Constantinea simplex* are eicosanoid natural products and belong to the family of oxylipins as well.[26] Due to their potential applications in medicine like other known eicosanoids but scarcity from natural sources, their syntheses have been actively explored.[27] In 2000, the Pale group devised a convergent approach based upon a latent chiral cyclopropane
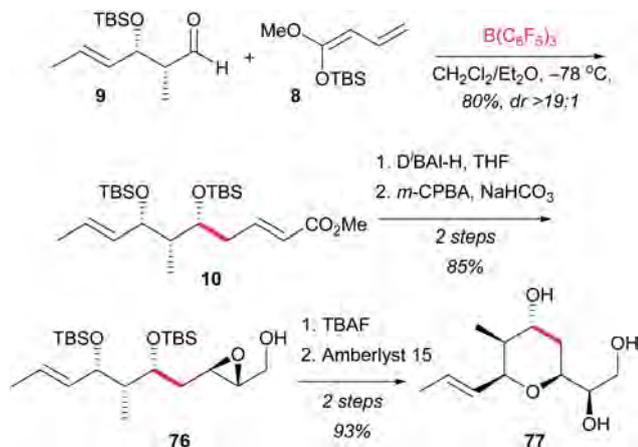

Fig. 24   Synthesis of fragment **77** with VMAR.

constanolactone A (**78**): R = OH, R' = H
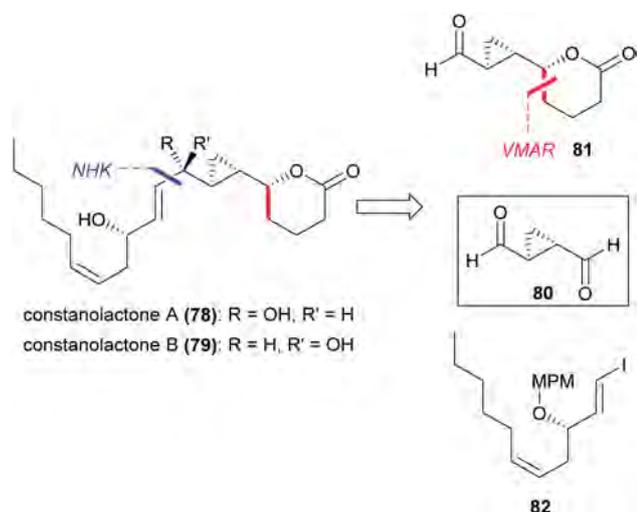constanolactone B (**79**): R = H, R' = OH

Fig. 25   Pale group's strategy to constanolactones A (**78**) and B (**79**).
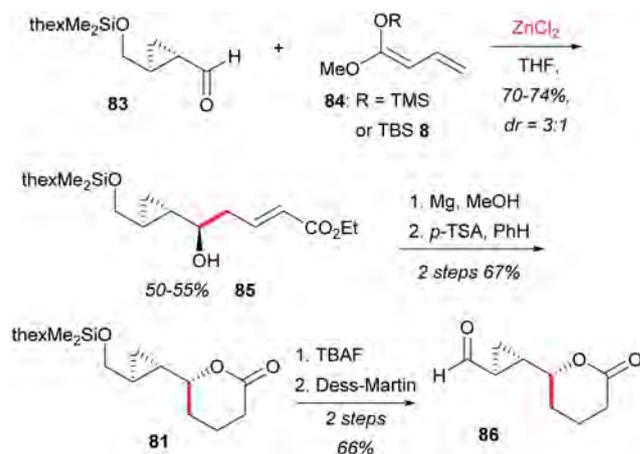

Fig. 26   Synthesis of fragment **81** with VMAR.

dialdehyde **80**. A key VMAR was employed for the first functionalization to access fragment **81** (Fig. 25).[28]

In this VMAR, ZnCl$_2$ was finally identified to be the best Lewis acid promoter (Fig. 26). Under the catalysis of ZnCl$_2$, the VMAR between aldehyde **83** and silyl ketene acetal **84** or **8** successfully provided the product in good yield albeit with moderate diastereoselectivity (dr = 3 : 1). Fortunately however, the two diastereoisomers could be separated and the desired *anti*-isomer **85** was obtained in 50–55% yield and could be conveniently elaborated to aldehyde fragment **81**.

Crytophycin belongs to 16-membered depsipeptides. The first reported crytophycin-1 (**87**) and related compounds have tumour-selective cytotoxicity even against multidrug-resistant cell lines.[29] Recently, the Sewald group reported an elegant synthesis of crytophycin-1 (**87**), in which a VMAR was used as the pivotal transformation (Fig. 27).[7] In this case, magnesium bromide diethyl etherate as the Lewis acid provided the key intermediate in moderate yields but with excellent diastereoselectivity (95% de). Furthermore, its relative configuration was confirmed by X-ray crystal structure analysis.
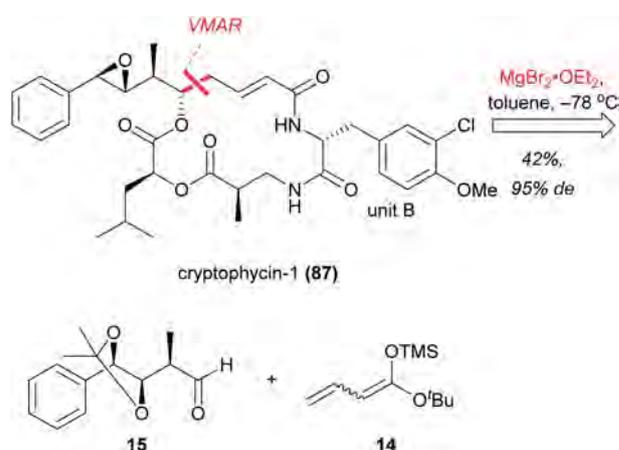

Fig. 27   Sewald group's VMAR-based strategy to crytophycin-1 (**87**).

(−)-Zampanolide (**88**) is a 20-membered highly cytotoxic macrolide, featuring a high degree of unsaturation.[30] Since its isolation in 1996, researchers failed to obtain this interesting molecule from natural sources any more. To date, considerable synthetic efforts towards this target have been reported.[31] The most recent one is described by the Porco group in 2008.[32] Their strategy is depicted in Fig. 28, in which aldehyde fragment **89** plays the central role.

To access this fragment, they designed a chelation-controlled VMAR process between aldehyde **91** and silyl ketene acetal **92** (Fig. 29). From L-serine methyl ester, aldehyde **91** could be obtained in two steps. Under the catalysis of Me$_2$AlCl, the desired VMAR product could be obtained. However, epimerization is a problematic issue during the separation of aldehyde **91**. Therefore, the authors evaluated both one-pot protocols developed independently by the groups of Polt (D^{i}BAl-H/Me$_2$AlCl)[33] and Kiyooka [D^{i}BAl-H/TiCl$_2$(O^{i}Pr)$_2$][34] to avoid the purification of **91**. Finally, a three-step, one-pot protocol was identified using the Kiyooka method, and the desired product **93** was obtained in good yield and excellent diastereoselectivity (dr = 16 : 1).

4.2 Enantioselective processes

The Campagne group was the first to report catalytic asymmetric versions of the vinylogous aldol reaction using either Ti(O^{i}Pr)$_4$/BINOL or the Carreira group's CuF$_2$(tol-BINAP) system.[35] Furthermore, a novel synthesis of α,β-unsaturated δ-lactones from asymmetric VMARs was also developed by this

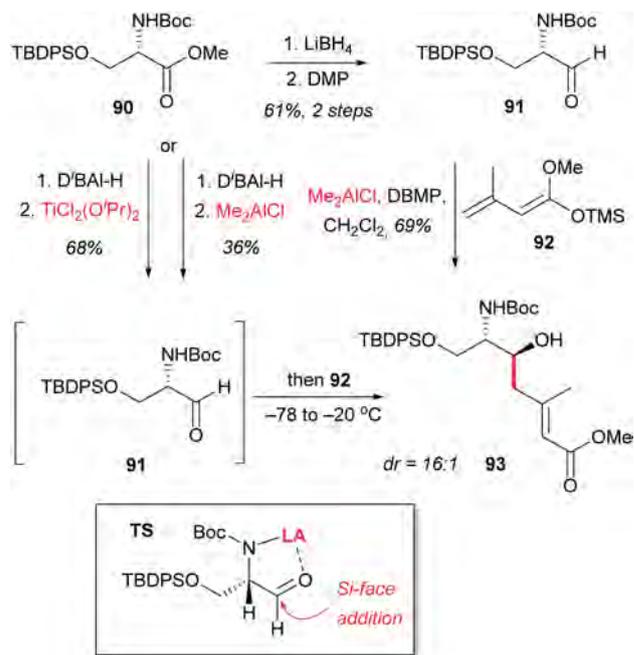**Fig. 28** Porco group's strategy to (−)-zampanolide (**88**).

Fig. 29 Synthesis of fragment **93** *via* chelation-controlled VMAR.

group and resulted in one-step synthesis of natural product goniothalamin (**95**) (Fig. 30)[36] though there was still room for enantioselective improvement.

More recently, this methodology was extended by the Kalesse group for the synthesis of simplified disoazole analogue **96** (Fig. 31),[37] which exhibits cytotoxic selectivity between mouse fibroblast cells and tumor cell lines in contrast to the natural product **97**. Their approach takes advantage of the C2-symmetry of disoazoles as illustrated in Fig. 31, and retrosynthetic analysis resulted in the key fragment **98**. Using the Campagne protocol, the desired VMAR adduct **100** was isolated in 30% yield, however along with linear isomer **101** in 25% yield both with moderate diastereoselectivities.

Besides the use of copper for chiral enolate formation this metal has been used as a chiral Lewis acid in asymmetric VMARs as well. In 1996, callipeltoside A (**102**) was isolated by Minale and coworkers.[38] Due to its interesting biological activities and unique structure considerable synthetic efforts have been reported,[21,39–41] including studies on asymmetric VMARs
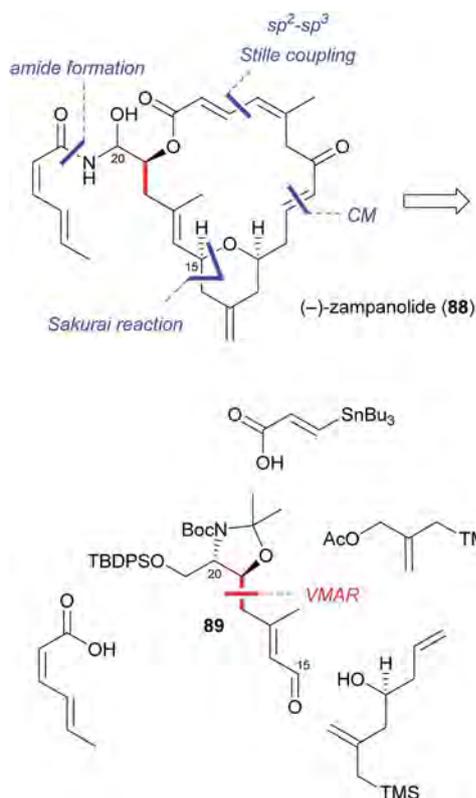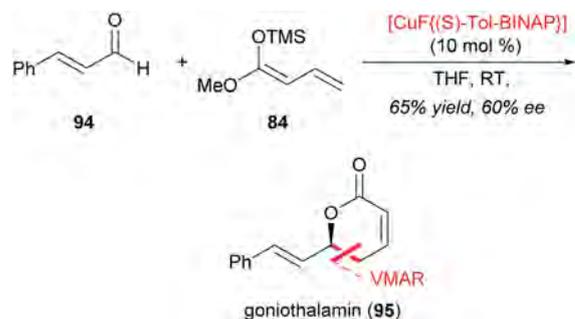
Fig. 30 Synthesis of goniothalamin (**95**).

10 | *Nat. Prod. Rep.*, 2014, **xx**, 1–32

This journal is © The Royal Society of Chemistry 2014

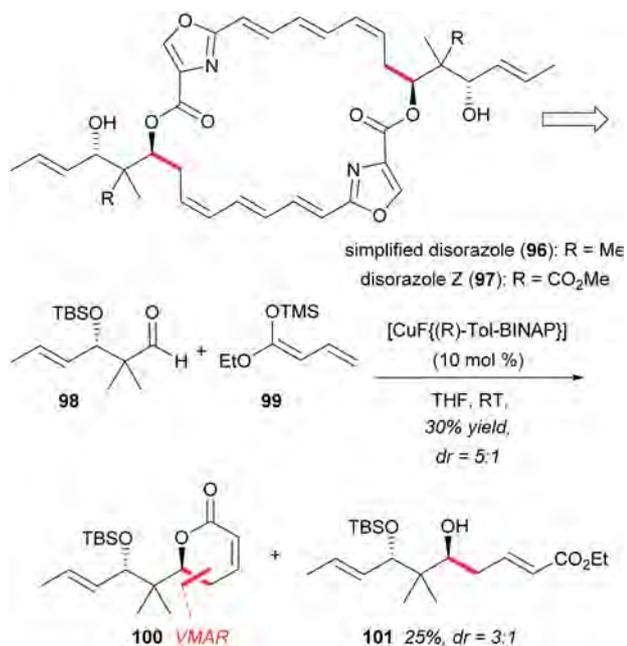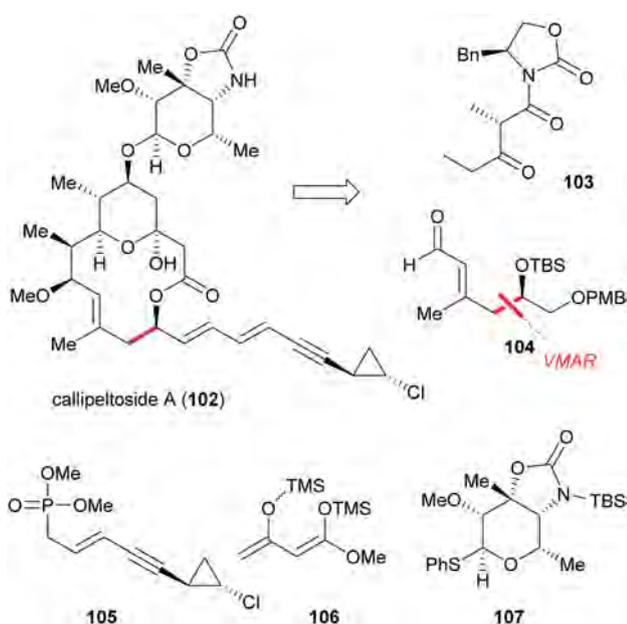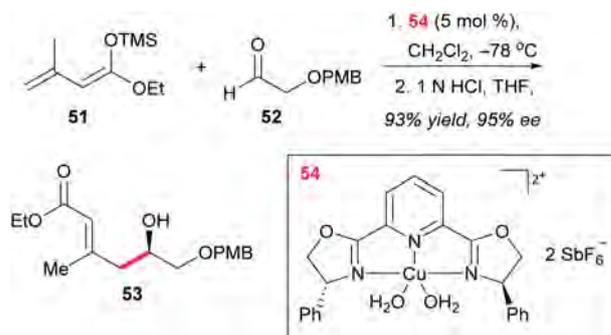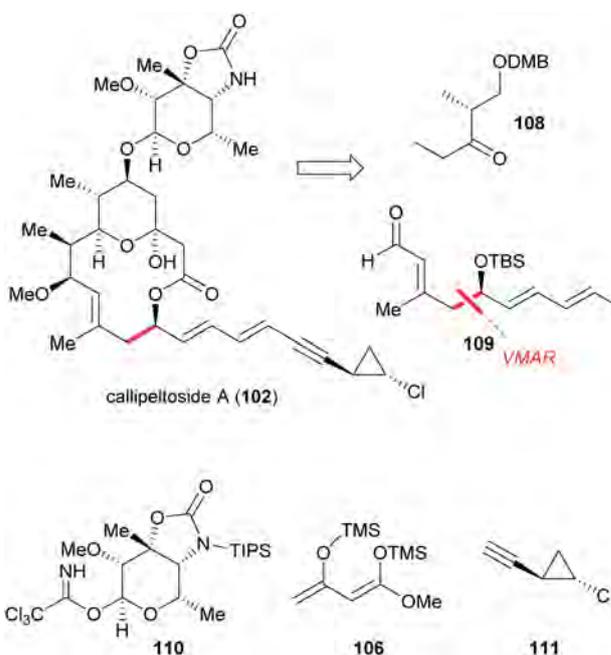Fig. 33   Synthesis of fragment 53 by py-box catalyst 54.

Fig. 31   Asymmetric synthesis of simplified disorazole (96).

by the Evans and Paterson groups. The key features of Evans group's synthesis of callipeltoside A (102) are depicted in Fig. 32, which involves five main fragments.[21,39]

Their synthesis starts with the preparation of aldehyde fragment 104, which can be accessed through an asymmetric VMAR by a chiral Lewis acid catalyst (Fig. 33). In the presence of bench-stable copper catalyst 54, the VMAR between silyl ketene acetal 51 and aldehyde 52 produced adduct 53 in excellent yield and selectivity (complete E-selectivity and 97% ee). A further 3-step elaboration of 53 provided fragment 104 in good overall

Fig. 34   Paterson group's strategy to callipeltoside A (102).

yield. At this point, we want to point out that this catalysis requires bicoordinative aldehydes such as 52. Recently, this excellent chemistry was applied by the Floreancig group in their synthesis of (+)-dactylolide,[42] which is a cytotoxic natural product structurally related to zampanolide (88).

The Paterson group's strategy (Fig. 34) to callipeltoside (102) parallels the Evans group's synthesis.[40]

This time, fragment 109 was constructed from enal 112a (X = I) and silyl ketene acetal 92 (Fig. 35). After systematic investigations, Paterson and co-workers established a new catalytic protocol. In the presence of 50 mol % $Ti(O^iPr)_4/(R)$-BINOL and CaH_2 as additive, the VMAR between 92 and 112 proceeded smoothly to produce 113 in excellent yields and enantioselectivities. It is worth mentioning that the addition of CaH_2 is crucial and prevents both competing hydrolysis of the silyl ketene acetal and isomerization of the double bonds.

From 113a, the Paterson group conveniently obtained aldehyde fragment 109. Meanwhile, VMAR adducts 113b and 113c

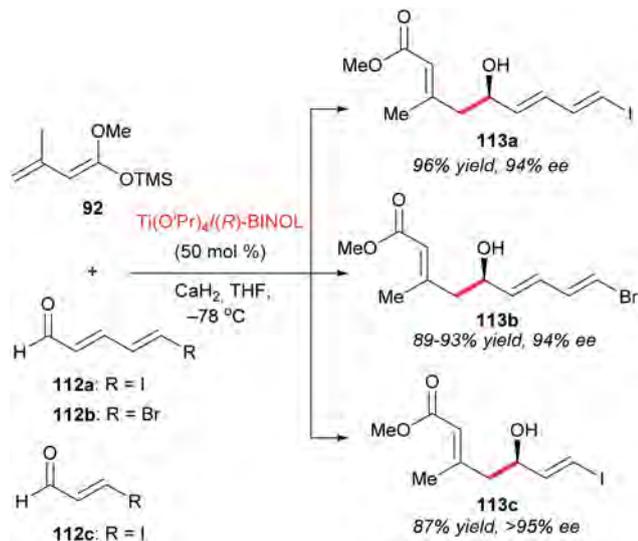Fig. 32   Evans group's strategy to calipeltoside A (102).

Fig. 35   Paterson group's chiral Ti-catalyzed VMARs.

were successfully used in the synthesis of dolastatin 19 (**114**),[43] aurisides A and B (**115, 116**)[44] and phorbaside A (**117**, Fig. 36),[45] which are all biologically active marine natural products related to callipeltoside A (**102**).

Besides chiral copper and titanium complex, chiral oxazaborolidinones are the third class of Lewis acid promoters for asymmetric VMARs. Chiral oxazaborolidinones were independently developed by the Yamamoto and Helmchen groups in 1990,[46] and
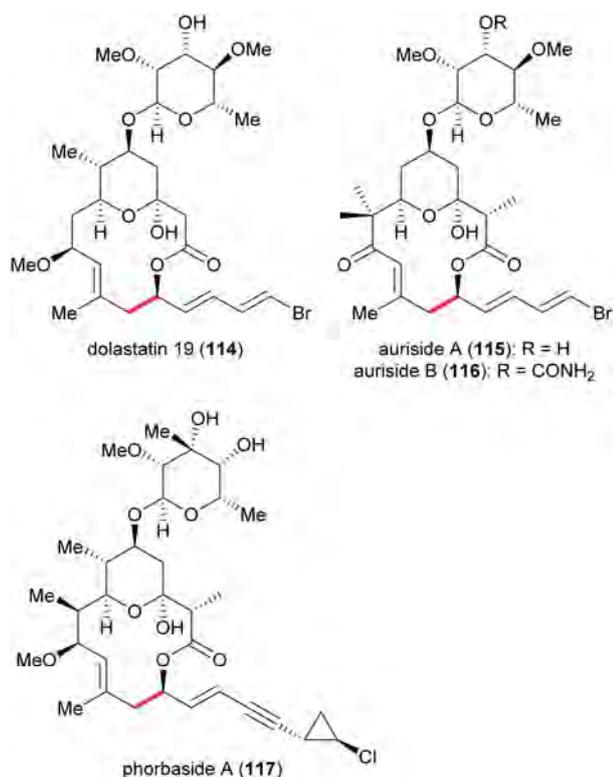

Fig. 36   Other marine natural products completed by the Paterson group.

applied in various asymmetric transformations including the Mukaiyama aldol reaction. However, only in 2007 its application in VMAR was reported (Fig. 37).[17b] Using tryptophane-derived B-phenyl-oxazaborolidinone **119**, various VMAR adducts were obtained in good yields and enantioselectivities. A plausible
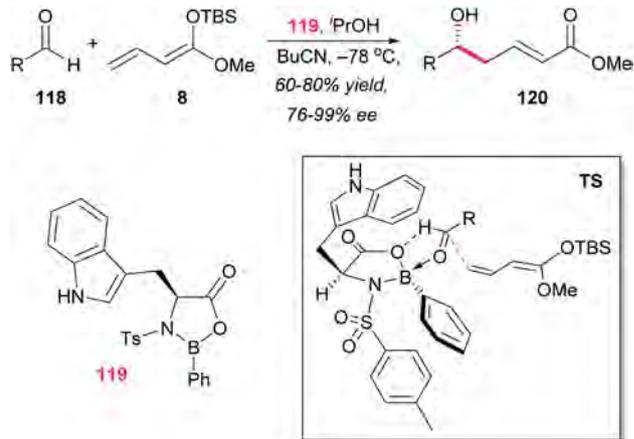

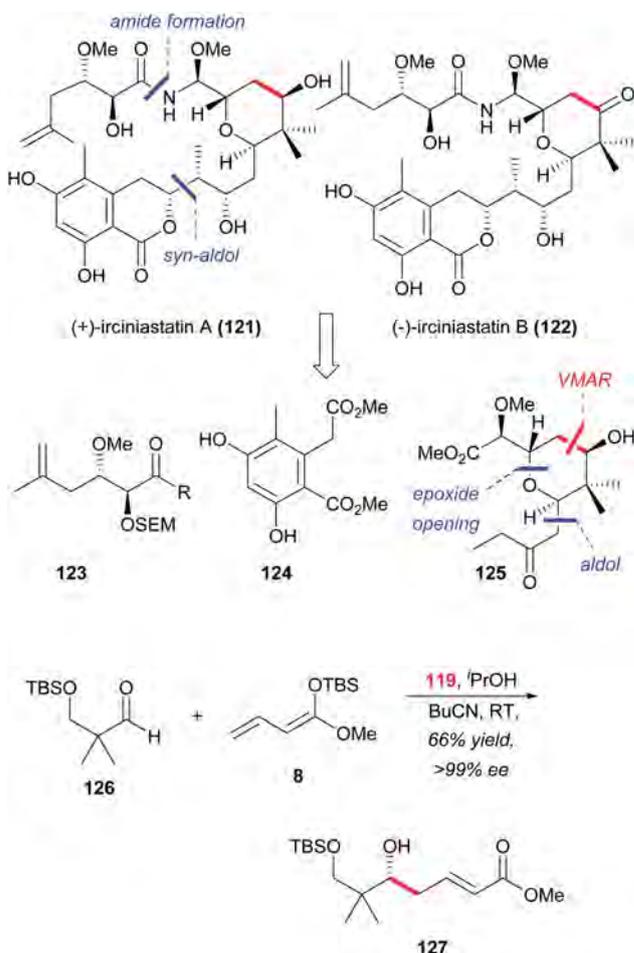Fig. 37   Kalesse's asymmetric VMAR by OXB.

Fig. 38   Smith group's strategy to irciniastatins.

transition state was proposed for the observed stereochemistry and provides an efficient access to polyketide motifs.

Recently, the usefulness of this VMAR transformation in natural product synthesis was demonstrated by the Smith group in their second generation syntheses of (+)-irciniastatin A (**121**) and (−)-irciniastatin B (**122**).[47] Their key features are illustrated in Fig. 38. The synthesis of fragment **125** starts from the VMAR between aldehyde **126** and silyl ketene acetal **8** catalyzed by oxazaborolidinone **119**. Under Kalesse's conditions, the VMAR adduct was obtained in good yield as a single enantiomer and additional steps provided fragment **125** in considerably improved overall yield, which led to the completion of the irciniastatin total synthesis.

In asymmetric vinylogous aldol reactions, the Denmark group's concept of Lewis base activation of Lewis acids has also found important applications.[48] The first was demonstrated by the Denmark group themselves in the highly convergent total synthesis of RK-397 (**128**), a polyene macrolide.[23a] Their elegant strategy is illustrated in Fig. 39, with the asymmetric VMAR playing a pivotal role.

The synthesis starts with the designed VMAR, as compound **129** is known in the literature, while **130** could be easily accessed by classic Evans' aldol chemistry. In the presence of
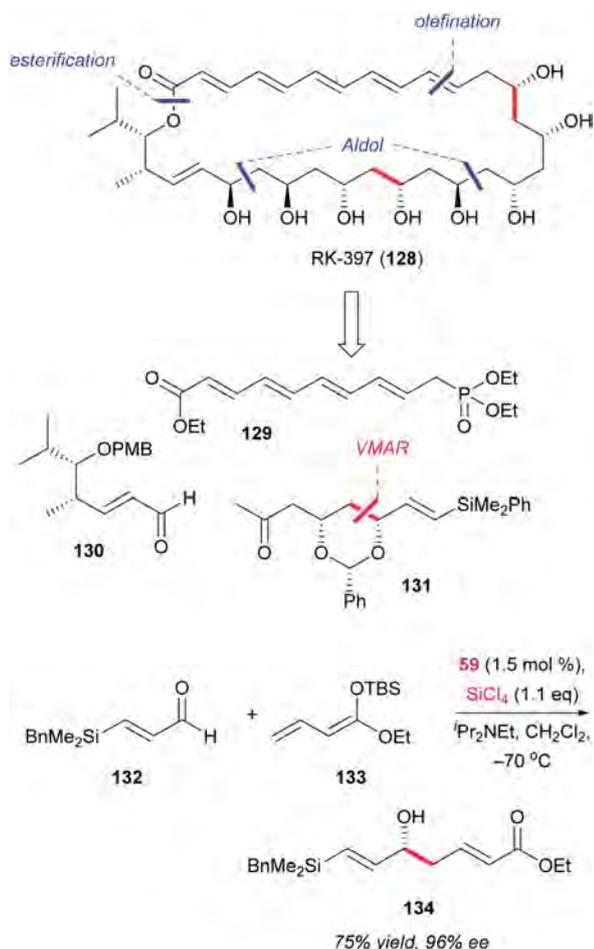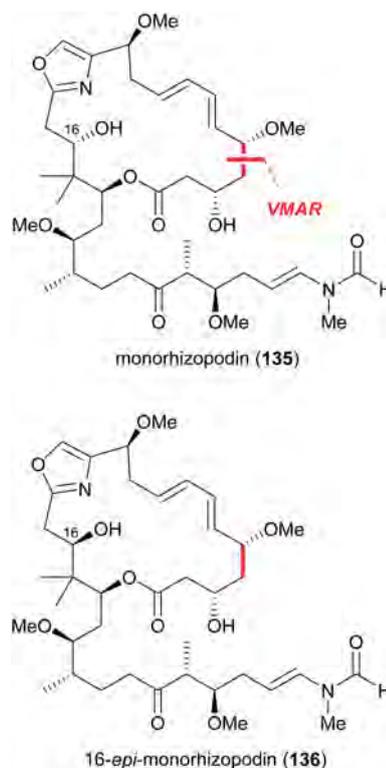

Fig. 40 Nicolaou group's strategy to monorhizopodin (**135**) and 16-epi-monorhizopodin (**136**) using the Denmark group's VMAR.

low concentrations of catalyst **59** (Fig. 18), the VMAR between aldehyde **132** and silyl ketene acetal **133** proceeded smoothly to afford the desired key intermediate **134** in good yield and
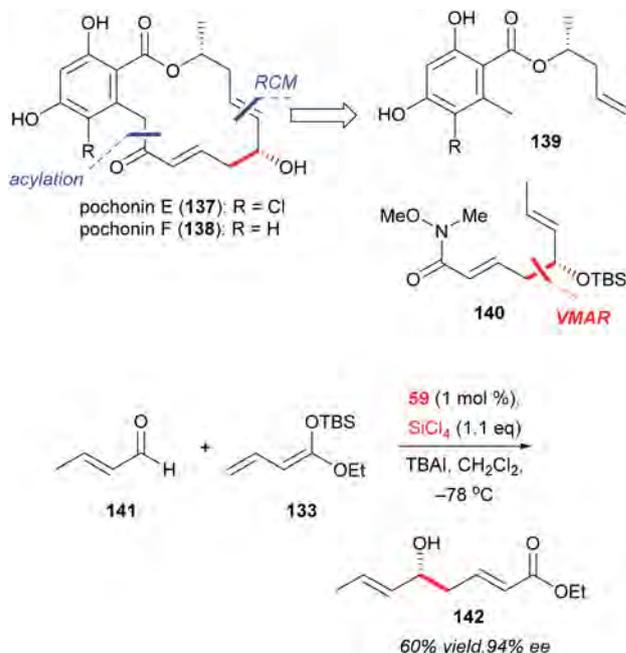

Fig. 39 Denmark group's strategy to RK-397 (**128**).

Fig. 41 Winssinger group's VMAR strategy to pochonins E (**137**) and F (**138**).

This journal is © The Royal Society of Chemistry 2014

Nat. Prod. Rep., 2014, xx, 1–32 | 13

excellent enantioselectivity, which paved the way towards the completion of RK-397 (**128**). Recently, this VMAR was successfully applied again by the Nicolaou group during their synthetic and biological studies on monorhizopodin (**135**) and 16-*epi*-monorhizopodin (**136**),[49] which shows actin-binding properties but no associated cytotoxicity compared to the natural product rhizopodin (Fig. 40).

Very recently, Winssinger and co-workers investigated the VMAR with crotonaldehyde (**141**), previously reported to be a challenging substrate,[50] using the Denmark group's catalyst during their syntheses of pochonins E (**137**) and F (**138**, Fig. 41).[51] The VMAR product **142** was obtained in 60% yield and excellent enantioselectivity. From **142**, fragment **140** was conveniently accessed in good yields after two further steps and consequently resulted in structure revision and concise syntheses of pochonins E and F.

Unfunctionalized aliphatic aldehydes are also compatible with Denmark's VMAR catalyst and have been applied towards natural product syntheses. In 2006, the Kirschning group described a VMAR employing highly functionalized aliphatic aldehyde **148** in the presence of Denmark's catalyst **59** (Fig. 18) during their synthetic efforts towards the RNA polymerase inhibitors ripostatins A (**143**) and B (**144**) (Fig. 42).[52] They successfully obtained the desired VMAR product **149** in moderate yield and good diastereoselectivity.
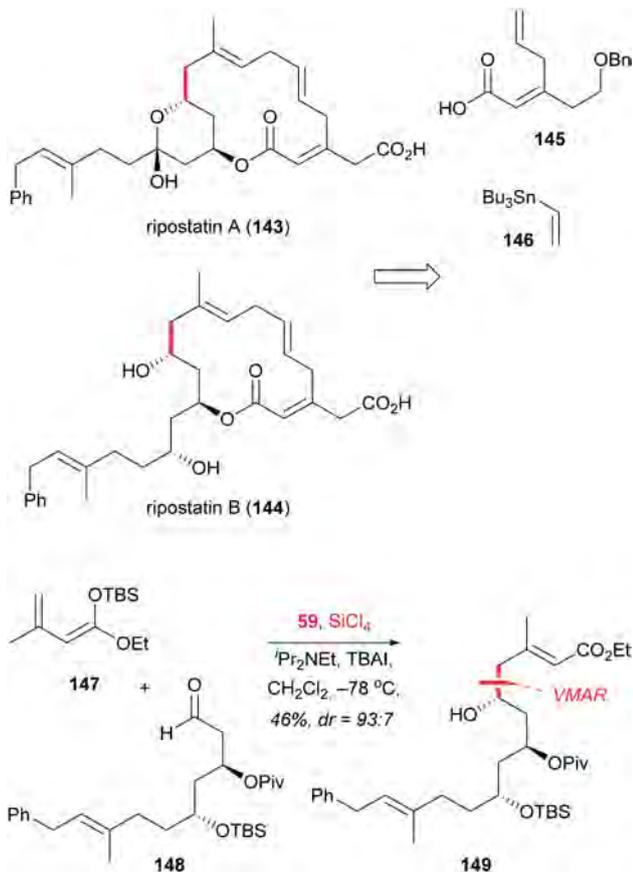

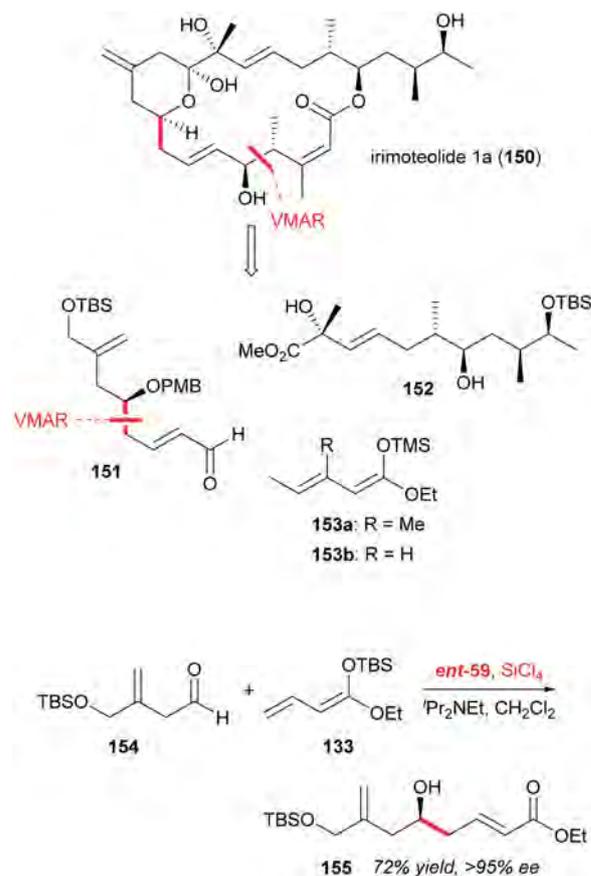Fig. 42 Kirschning group's strategy towards ripostatins A (**143**) and B (**144**).

Fig. 43 Yang group's strategy towards iriomoteolide 1a (**150**).

Meanwhile, the Yang group reported a VMAR of β,γ-unsaturated aldehyde **154** during their studies towards the synthesis of iriomoteolide 1a (**150**), which exhibits potent cytotoxicity even though the mode of action is not known (Fig. 43).[53] The β,γ-unsaturated aldehyde **154** was initially found to isomerise easily to its corresponding enal during preparation. Interestingly however, under the Denmark group's conditions using catalyst *ent*-**59** (Fig. 18), the desired VMAR adduct **155** could be isolated in 72% yield and excellent enantioselectivity (>95% ee). The desired fragment **151** was then completed in 70% yield after three simple operations, and set the stage for the second VMAR (to be discussed below, Fig. 48).

5   Natural product syntheses generating motif II
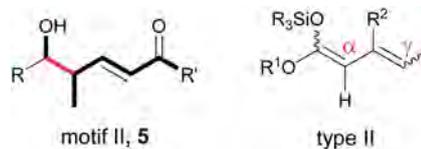
Compared to the type I silyl ketene acetals described in the previous section, transformations with type II silyl ketene
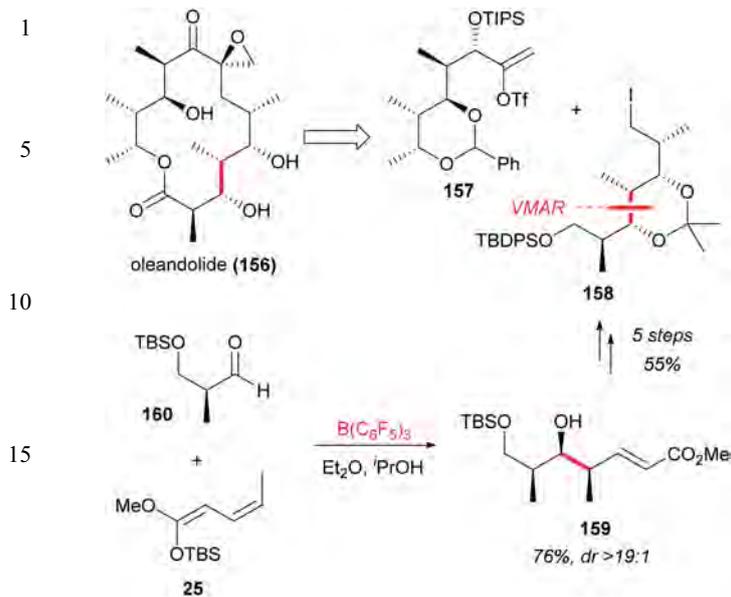
Fig. 44 Studies towards oleandolide (**156**).

acetals are more challenging since one additional stereocenter is generated during the VMAR. Consequently, examples using this motif are relatively rare.
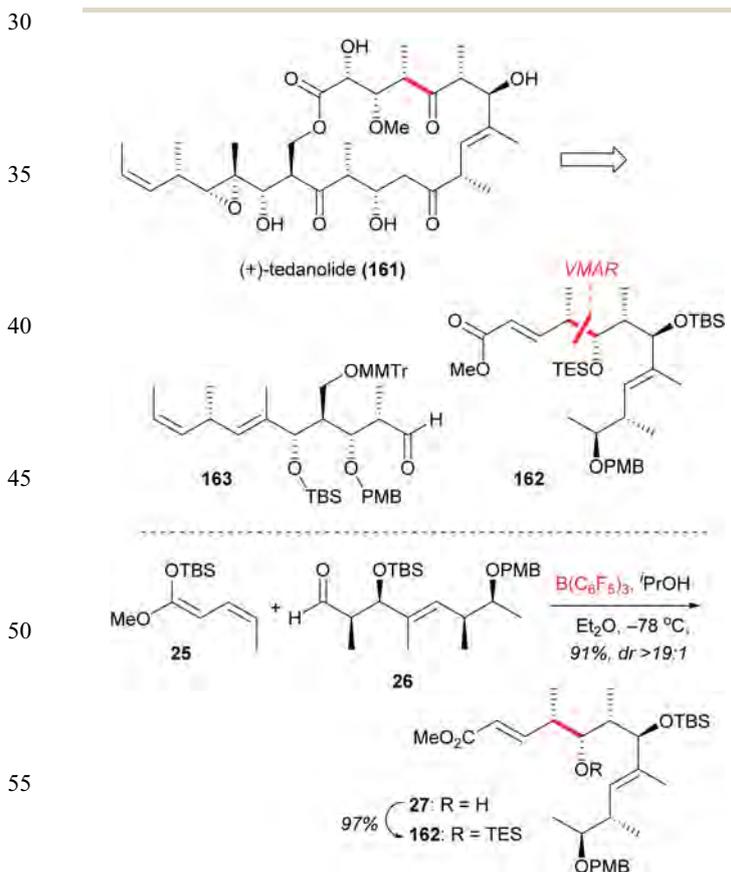
5.1 Substrate-controlled processes

The long and continuing interests of the Kalesse group in polyketides prompted them to develop efficient synthetic protocols. In 2001, they thoroughly investigated the VMAR reaction between type II silyl ketene acetals and various aldehydes and discovered that the bulky $B(C_6F_5)_3$ was also an excellent promoter for this type of VMARs.[54] Subsequently, this methodology was successfully employed in the preparation of a pivotal fragment of oleandolide (**156**), as illustrated in Fig. 44.[55] In the presence of $B(C_6F_5)_3$, the VMAR between Roche ester-derived aldehyde **160** and silyl ketene acetal **25** provide the desired Felkin product (**159**) in good yield and excellent selectivity.

(+)-Tedanolide (**161**), a 18-membered marine polyketide isolated in 1984, unfolds high cytotoxicity against P388 murine leukemia cells.[56] Its interesting biological profile combined with its complex structure has initiated a variety of synthetic studies.[57] In 2005, the Kalesse group reported the first total synthesis based on their VMAR approach.[10,58] The main features of their VMAR strategy are shown in Fig. 45. Starting from aldehyde **26**, the VMAR using silyl ketene acetal **25** and $B(C_6F_5)_3$ as the Lewis acid afford the desired product **27** in good yield and
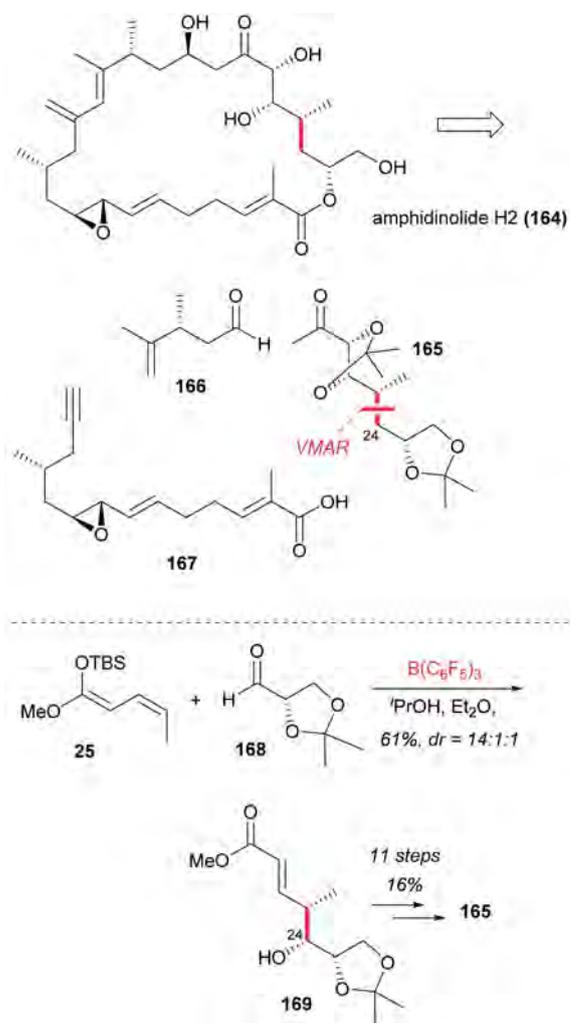

Fig. 45 Kalesse group's VMAR strategy to (+)-tedanolide (**161**).

Fig. 46 Studies towards amphidinolide H2 (**164**).
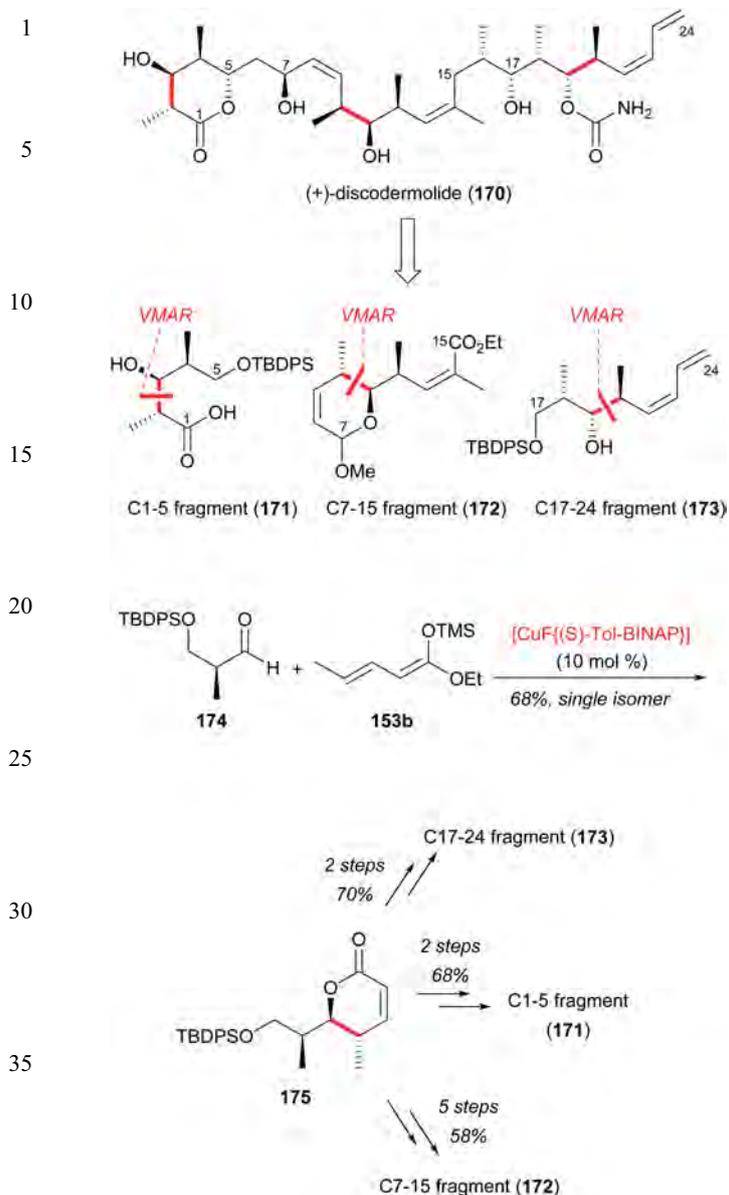
Fig. 47 Campagne group's VMAR for the synthesis of (+)-discodermolide (170).

Fig. 48 Yang group's second VMAR towards iriomoteolide 1a (154).

diastereoselectivity. Protection of the resulting hydroxyl group in 27 furnished fragment 162 used for the total synthesis of (+)-tedanolide (161).

The usefulness of substrate-controlled VMAR with this type of silyl ketene acetal was further demonstrated by the Kalesse group in their synthetic studies towards amphidinolide H2 (164),[59] a highly cytotoxic marine natural product isolated in 2002.[60] As shown in Fig. 46, the VMAR with the acetonide of L-glyceraldehyde 168 provided the desired Felkin adduct in good yield and excellent diastereoselectivity. It is noteworthy that in this case only a catalytic amount of $B(C_6F_5)_3$ is sufficient and the concentration could be reduced to 1 mol% $B(C_6F_5)_3$ without sacrificing yields or selectivities. Finally, fragment 165 was successfully synthesized from 169 in 11 steps and 16% overall yield.

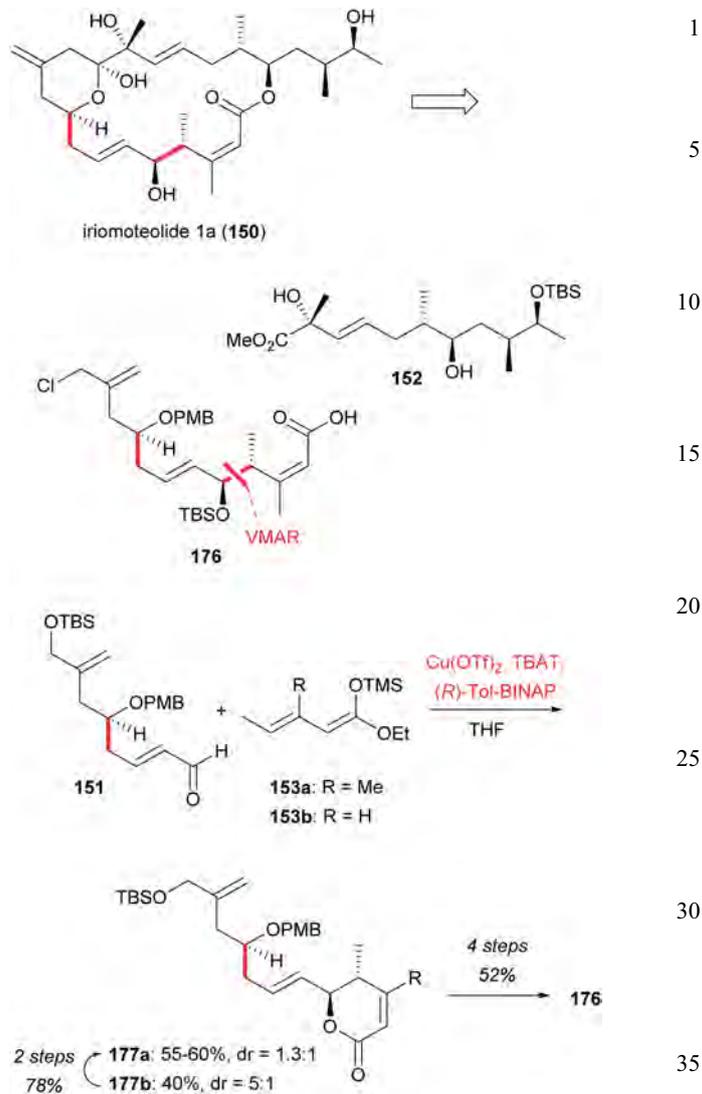## 5.2 Enantioselective processes

After identifying a novel approach to α,β-unsaturated δ-lactones by asymmetric VMAR using Carreira's CuF_2(tol-BINAP) catalyst, the Campagne group further investigated this chemistry for the collective synthesis of the C1–C5 (171), C7–C15 (172) and C17–C24 (173) fragments of (+)-discodermolide (170, Fig. 47),[61] a scarce but highly active anti-cancer marine natural product.[62] Under optimized conditions, the VMAR product 175 was obtained in good yields as a single stereoisomer. From this common building block, the three fragments 171, 172, 173 were synthesized efficiently in 2–5 steps and good yields (58–70%).

The Campagne group's VMAR strategy with type II silyl ketene acetal was also applied by the Yang group in their synthesis of iriomoteolide 1a (150, Fig. 48).[53] After performing the first VMAR with type I silyl ketene acetal 133 using the Denmark group's protocol (Fig. 43), they conveniently obtained enal 151 in 3 steps. Then, quite notably, the second VMAR

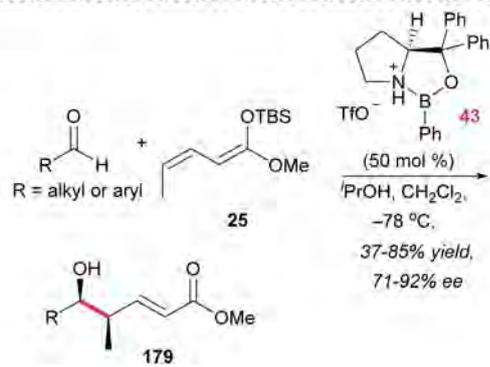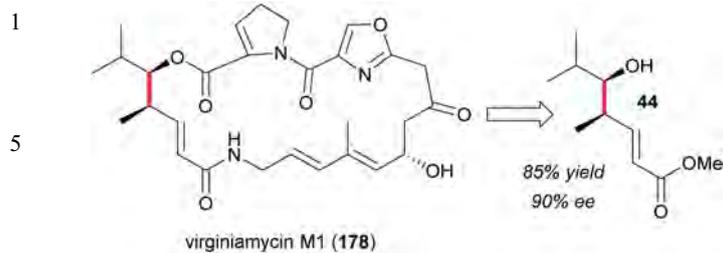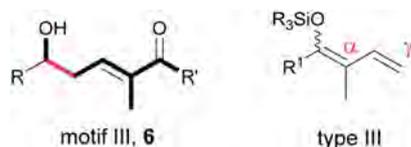Fig. 50   Synthesis of TMS–dienol **18**.

using aldehyde-derived dienols is that subsequent manipulations do not require additional oxidation state changes.

In the course of the total synthesis of swinholide A (**181**) (Fig. 51), Paterson and co-workers studied the addition of TMS-dienolether **18** to aldehyde **182**.[8] They expected the addition of **18** to occur through a chelation-controlled transition state generating the desired 1,3-*anti* product **183**. Initial experiments with $TiCl_4$ as the Lewis acid only led to decomposition. Also, using $TiCl_2(O^iPr)_2$ as a Lewis acid with reduced activity gave poor conversion. However, $BF_3 \cdot OEt_2$, which precludes chelation led to good yields and selectivities for the desired product **183**. In a series of different transformations they identified the mixed solvent system (10% Et_2O/CH_2Cl_2) to provide best yield (70%) and selectivity (dr = 9 : 1).

The observed selectivity can be rationalized by the polar Evans-Cornforth transition state **184** (Fig. 52),[64,65] that leads to a 1,3-*anti*-selectivity of the two functional groups.
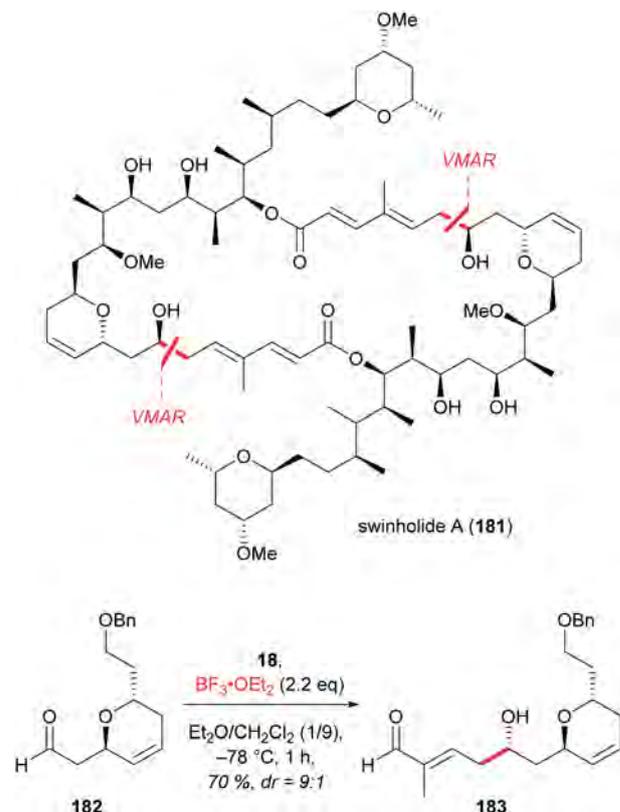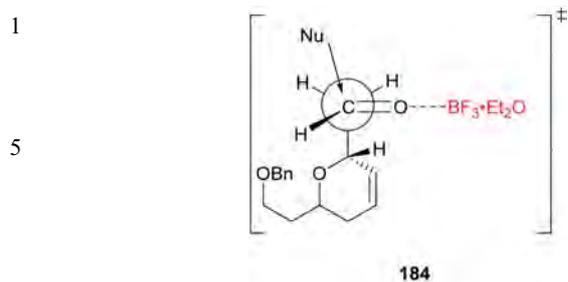

swinholide A (**181**)

Fig. 51   VMAR in the total synthesis of swinholide A (**181**) by Paterson *et al.*

---

between the highly functionalized enal **151** and silyl ketene acetal **153** under the Campagne group's conditions successfully provided the desired product **177** in moderate yield and diastereoselectivity. Four additional operations afforded the desired fragment **176** in 52% yield.

Recently, the Kalesse group systematically investigated the VMAR of type II silyl ketene acetals with borane-based Lewis acids, and found Corey's catalyst **43** to be the most efficient catalyst compared to the previous OXB catalysts for the VMAR which is excellent for type I silyl ketene acetals (Fig. 49).[18] It is worth to note that with this protocol, the western fragment **44** of virginiamycin M1 (**178**) could be obtained in good yield and high enantioselectivity after one single transformation.

6   Natural product syntheses generating motif III

In this section we will focus on different methods that can be used to build up motif III.

6.1   Diastereoselective processes of aldehyde-derived dienols

A widely used nucleophile for VMARs is TMS dienol ether **18** (Fig. 50), derived from tiglic aldehyde (**180**).[63] The advantage of

Fig. 49   Synthesis of the fragment of virginiamycin M1 (**178**) by catalytic asymmetric VMAR.

Fig. 52 Polar-Evans-Cornforth-model that leads to 1,3-*anti*-aldol adducts.

Due to the reliability of this vinylogous Mukaiyama aldol reaction several other groups used the Paterson group's procedure for their natural product syntheses. In the synthesis of preswinholide A methyl ester (**187**, Fig. 53), Nakata *et al.* utilized the Paterson group's protocol at a very late stage.[66] They added TMS-dienolether **18** to aldehyde **185** and stereoselectively obtained the 7-β-alcohol. Subsequent Horner–Emmons olefination and acetylation provided the pentaacetate of preswinholide A methyl ester (**187**) in 68% over three steps.

The cytotoxic natural product, scytophycin C (**188**) (Fig. 54), whose structure is close to swinholide A (**181**) stimulated the interest of various groups in its synthesis, that resulted in two
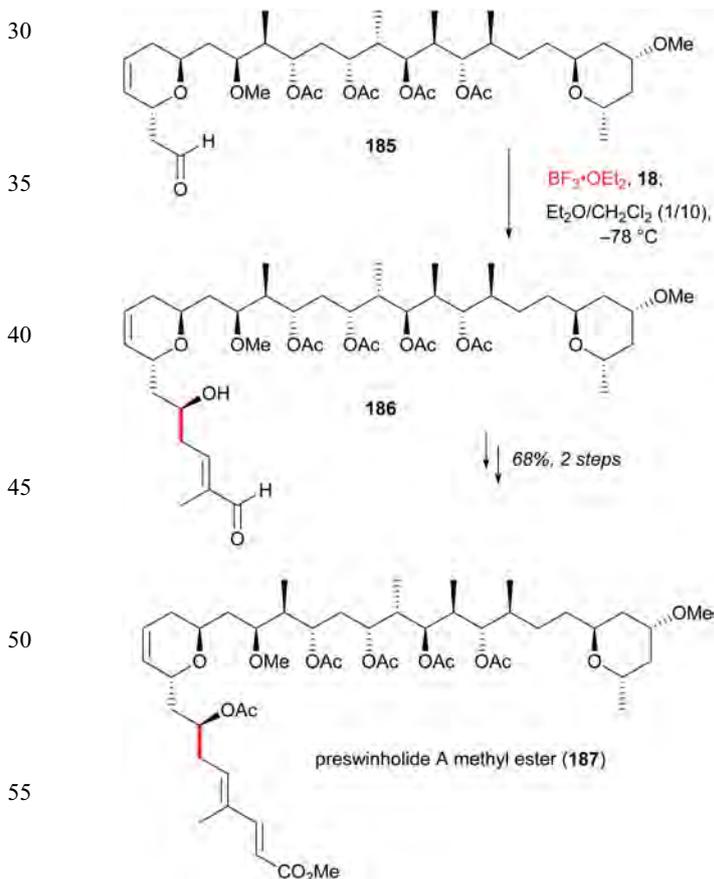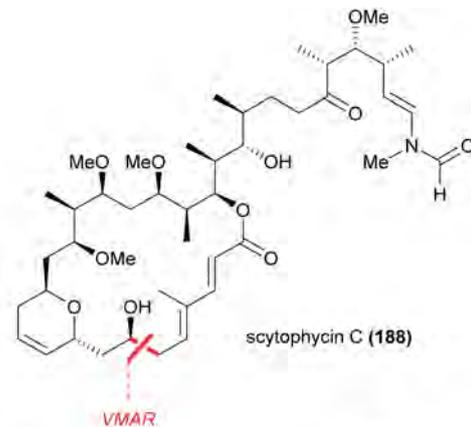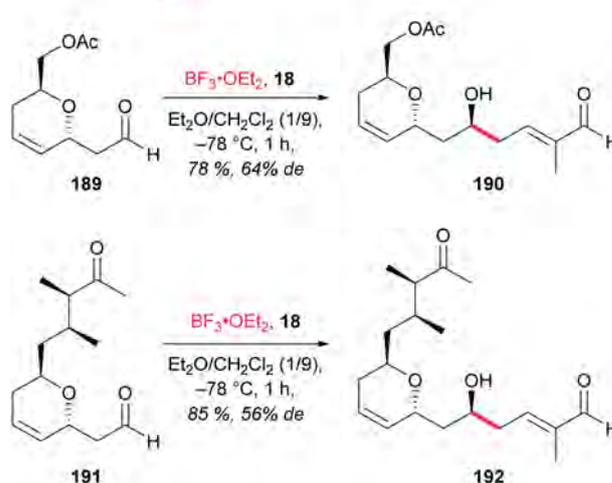

Fig. 54 VMARs in the total synthesis of scytophycin C (**188**).

very similar syntheses by Grieco and Speake[67] in 1997 and Miyashita *et al.*[68] in 2003. Both used the Paterson group's VMAR procedure and obtained comparable yields and selectivities for the transformations on their particular segments **190** and **192**.

The two cytotoxic depsipeptides palu'amide (**193**) (Fig. 55) and aurilide (**194**) were synthesized by the groups of Yamada[9a] and Ma,[69] respectively. Both used the Paterson group's protocol to build up the polyketide skeleton and obtained similar results. Notably, both obtained the 1,3-*anti* adduct and had to invert the newly generated stereocenter for the aim of their total synthesis.

The excellent selectivity of these two reactions can be explained by two directing effects. The α-substituent leads to Felkin-selectivity and the configuration in β-position to a Felkin reinforcing effect due to the polar Evans-Cornforth transition state **197** (Fig. 56).[64,65]

6.2 Enantioselective processes of aldehyde-derived dienols

Although a variety of diastereoselective VMARs have been used to construct fragments of natural products, the first enantioselective VMAR using aldehyde-derived dienols was reported in 2011 by the Kalesse group (Fig. 57).[17a,c] As catalyst for their enantioselective process, they utilized the Helmchen-Yamamoto[46] catalyst **40** for the total synthesis of angiolam A (**198**).
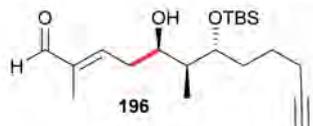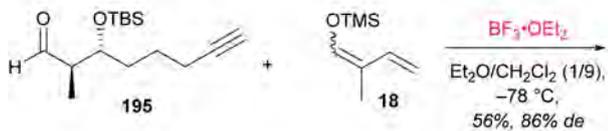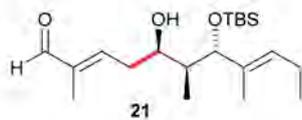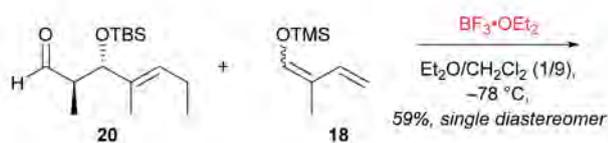

Fig. 53 VMAR in the synthesis of preswinholide A (**187**) by Nakata *et al.*

Fig. 56 Transition state for the VMARs in palu'amide (**193**) and aurilide (**194**).
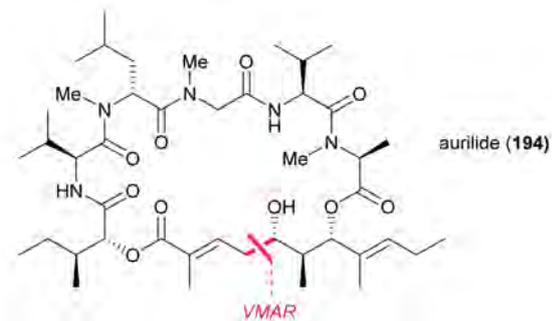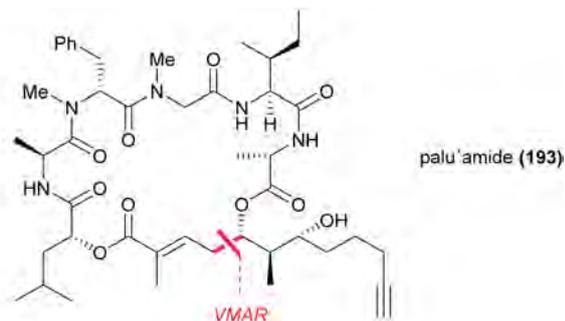
Fig. 55 VMARs in the total syntheses of palua'amide (**193**) and aurilide (**194**).
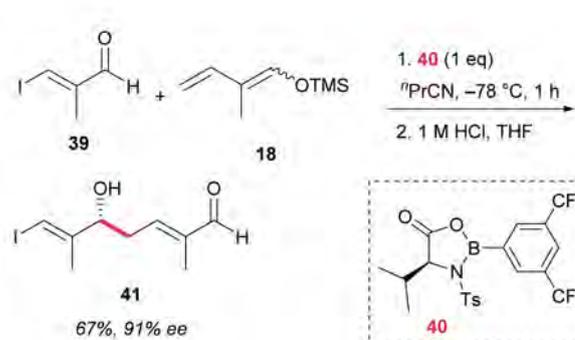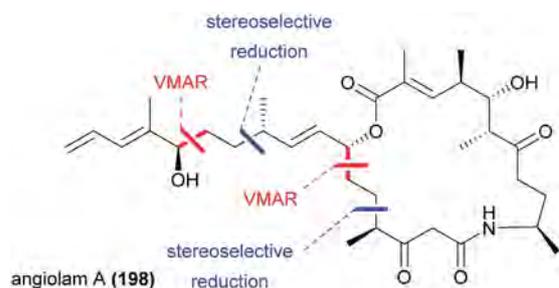
angiolam A (**198**)

Fig. 57 Enantioselective VMAR towards the synthesis of angiolam A (**198**).

In this reaction the L-valine based oxazaborolidinone coordinates to the aldehyde according to transition state **199** (Fig. 58). The favored *Re*-face attack of the nucleophile rationalizes the absolute configuration.[70]

6.3 Diastereoselective transformations using silyl ketene acetals

For their total synthesis of the depsipeptide kulokekahilide-2 (**200**) (Fig. 59), Nakao *et al.* used the ester-derived silyl ketene
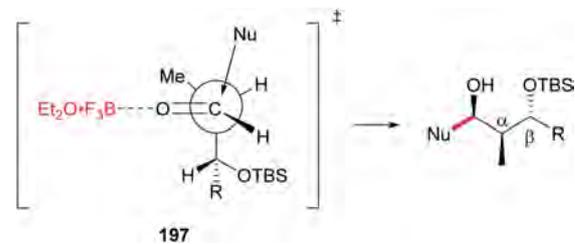

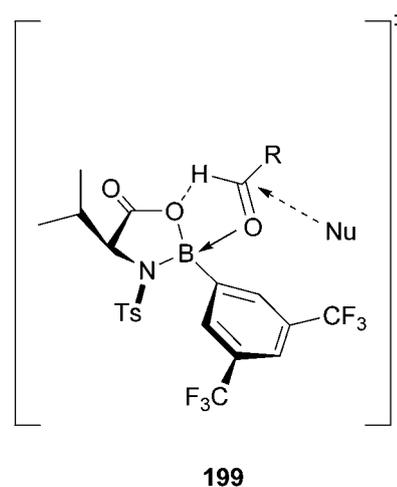**199**

Fig. 58 Proposed transition state for the VMAR using *N*-tosyl-L-valine-based oxazaborolidinone **40**.

This journal is © The Royal Society of Chemistry 2014

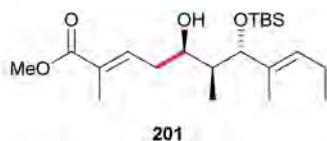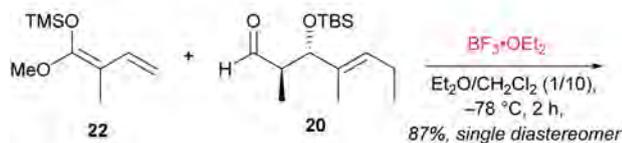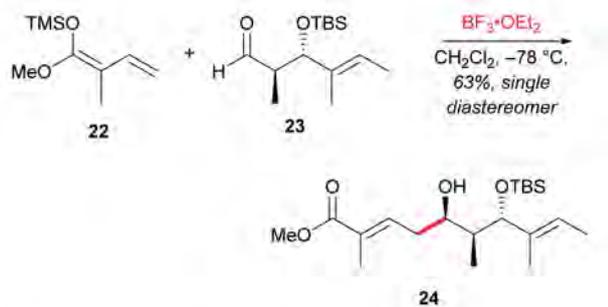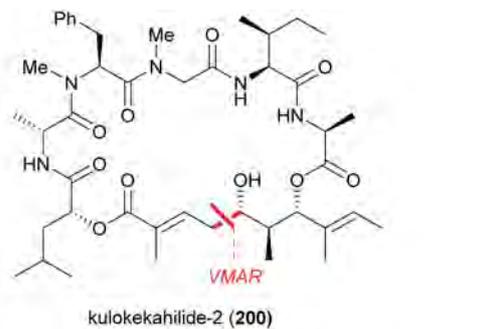*Nat. Prod. Rep.*, 2014, **xx**, 1–32 | **19**

Fig. 59 VMARs of ester-derived silyl ketene acetals in the total syntheses of kulokekahilide-2 (**200**) and aurilide (**194**).

acetal **22** in a substrate controlled vinylogous Mukaiyama aldol reaction.[9b] They obtained aldol adduct **24** in 63% as a single diastereomer. In a second generation synthesis of the similar depsipeptide aurilide (**194**), Yamada *et al.*[71] used silyl ketene acetal **22** instead of the aldehyde derived dienol **18**. They obtained the desired product **201** also as a single diastereomer in 87% yield. These transformations show perfect Felkin–Anh and 1,3-*anti* diastereoselectivity which can be explained by the transition state model **197** proposed by the Evans group (Fig. 56).[64,65]

6.4   Enantioselective transformations using silyl ketene acetals

An enantioselective process for VMARs was developed by the Campagne group in 1999.[19] They established a conceptually new enantioselective enol activation using the Carreira group's catalyst (Fig. 60).[20,36]
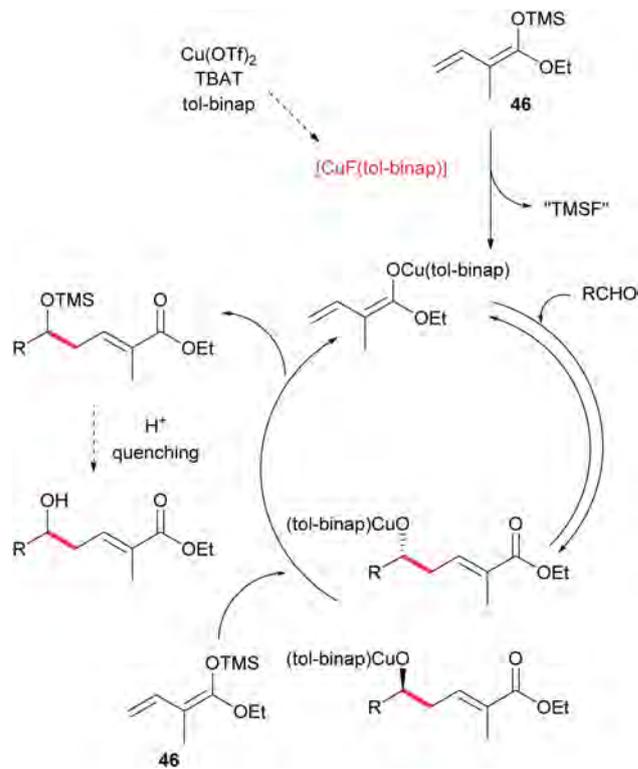
Fig. 60 A catalytic cycle involving the formation of a copper dienol for a catalytic asymmetric VMAR using the Carreira group's catalyst.

Nevertheless, this catalytic cycle does not explain the enantioselectivity of this process, since the chiral copper center seems to be too distant from the prochiral aldehyde (Fig. 61). To rationalize the enantioselectivity, the authors propose the formation of a α-copper enol **202** which leads to the six-membered transition state **203**.[36]

In the total synthesis of octalactin A (**204**) (Fig. 62),[72] a potent cytotoxic eight-membered lactone, Bluet and Campagne made

Fig. 61 Proposed mechanism involving α-copper species **202** and the corresponding six-membered transition state **203**.

Fig. 62 Campagne's synthesis of octalatin A (**204**) by catalytic asymmetric VMAR.

use of their enol activated catalytic asymmetric VMAR. The reaction of dienol **46** and isobutyraldehyde (**42**) proceeded in 90% yield with 80% ee.
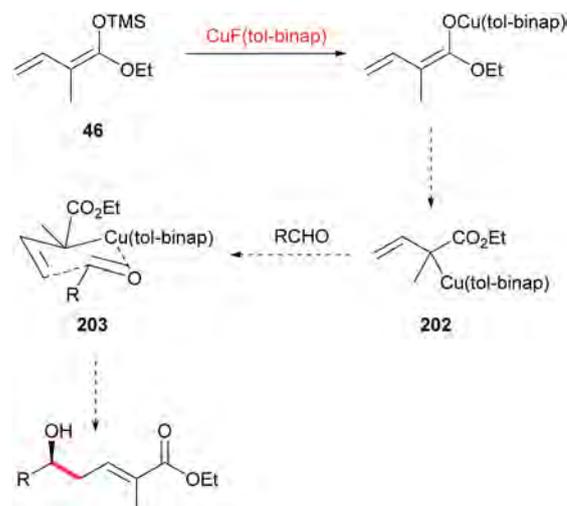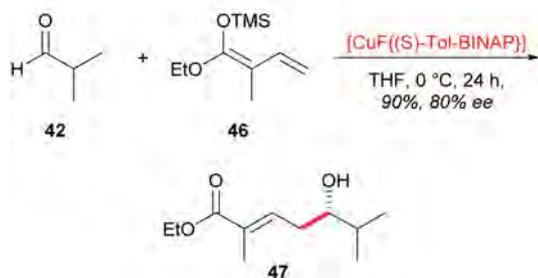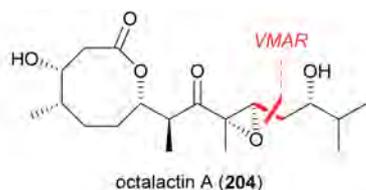
Keck and Heumann reported that a combination of (*S*)-BINOL species **208** and B(OMe)$_3$ is very effective in catalytic asymmetric VMARs (Fig. 63).[73] B(OMe)$_3$ reacts as a
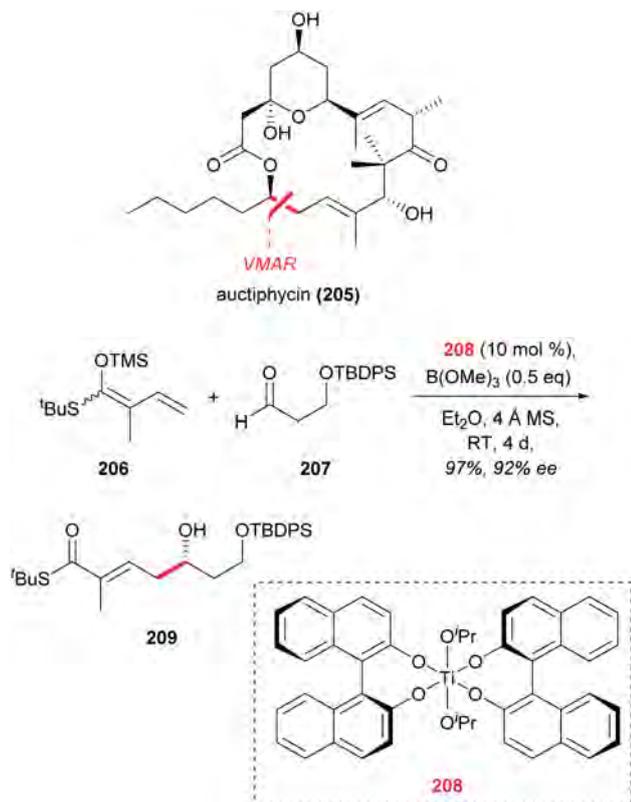

Fig. 63 Catalytic asymmetric VMAR using a combination of **208** and B(OMe)$_3$.

"turnover-reagent" which promotes the dissociation of the product from the Lewis acid.[74] The reaction of thioester-derived dienol **206** and aldehyde **207**, catalyzed by 10 mol % of **208**, afforded α,β-unsaturated thioester **209** in 97% yield and 92% ee, which is a potential intermediate for acutiphycin (**205**).

One further example of the catalytic enantioselective vinylogous Mukaiyama aldol reaction is the Denmark group's Lewis base activation protocol (Fig. 64).[4b,23] Their concept used chiral bisphosphoramide **59** and SiCl$_4$. It takes advantage of the fact that by extending the coordination sphere the hypervalent silicon becomes more Lewis acidic than the initial SiCl$_4$ and thus leads to catalysis of the chiral Lewis acid. In the following reaction VMAR adduct **211** was achieved, by catalysis with (*R*,*R*)-configured **59**, in 93% yield and 99% ee.

6.5 Stereoselective transformations using silyl ketene *N,O*-acetals

In an extension to the Evans group's aldol methodology, Kobayashi *et al.* utilized the Evans auxiliary for VMARs.[13] Amide-derived silyl ketene *N,O*-acetal **33a** (Fig. 65) provides an efficient and hitherto unprecedented high degree of remote 1,7-asymmetric induction.

To rationalize the stereochemical outcome of these reactions, the Kobayashi group proposed transition states **213** and **214** (Fig. 11 and 66).[13] The isopropyl group of the auxiliary shields the upper face of the dienol, and the aldehyde approaches from the least hindered side. The corresponding Newman projection **214** provides a rationale for the orientation of the R-group at the aldehyde.

Kobayashi *et al.* screened a variety of different aldehydes in vinylogous Mukaiyama aldol reaction of *N,O*-acetal **33a** (Fig. 67).[13] Under optimized conditions (1.0 eq of TiCl$_4$ and 2.0
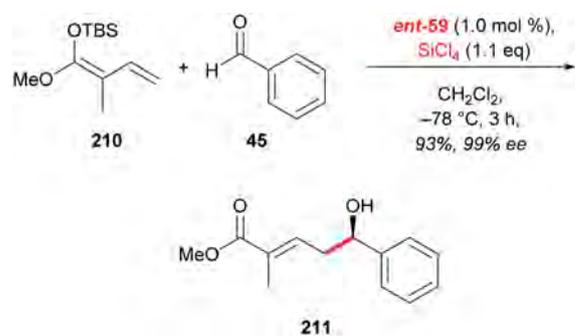

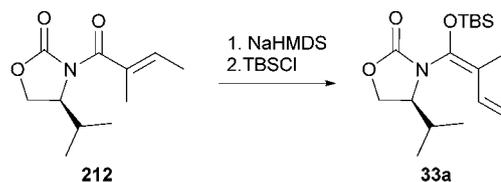Fig. 64 Denmark's concept of Lewis base activation of Lewis acids.

Fig. 65 Synthesis of amide-derived chiral silyl ketene *N,O*-acetal **33a**.
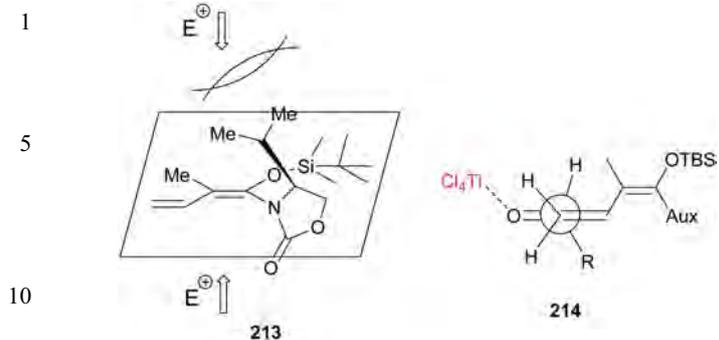
This journal is © The Royal Society of Chemistry 2014

Nat. Prod. Rep., 2014, **xx**, 1–32 | 21

Fig. 66 Proposed transition states for the nucleophilic attack of silyl ketene *N,O*-acetal **33a**.

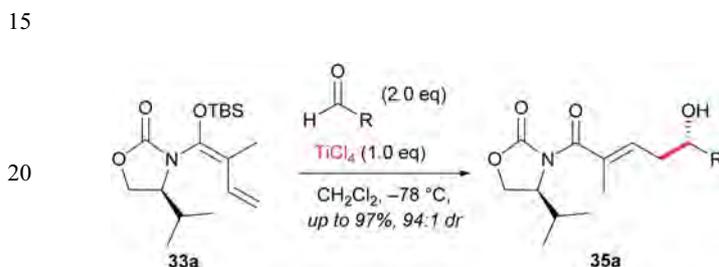**Fig. 67** Kobayashi group's VMAR of chiral vinyl silyl *N,O*-acetal **33a**.

eq of the corresponding aldehyde in CH_2Cl_2 at −78 °C), they could obtain VMAR adducts in up to 97% yield and excellent selectivities of at least 20 : 1 dr (up to 94 : 1).
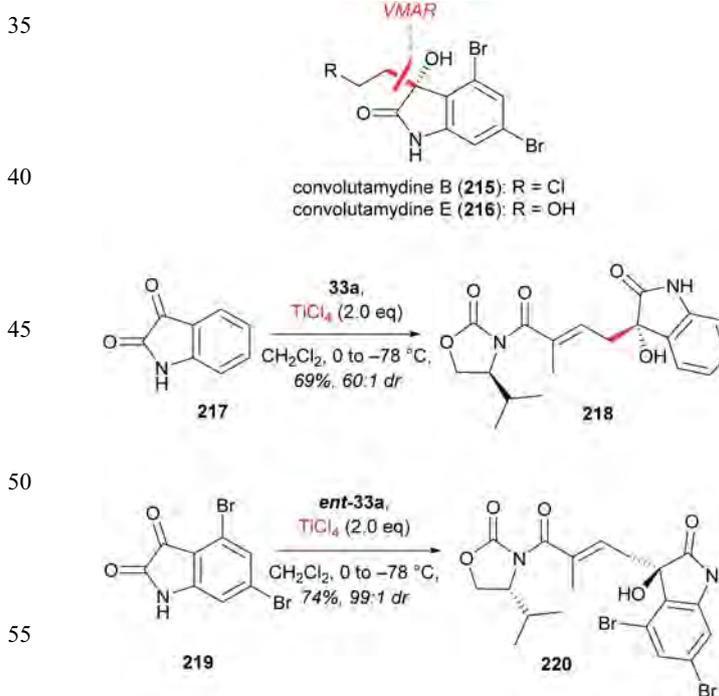

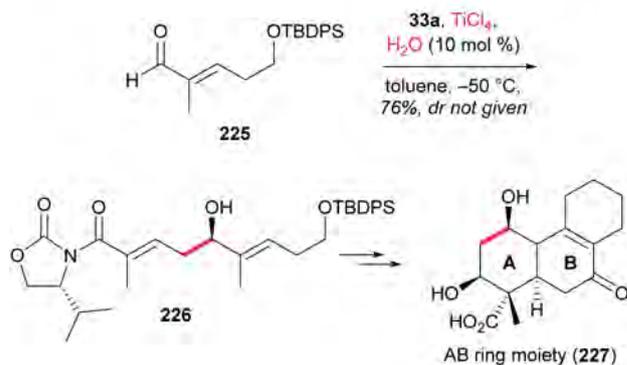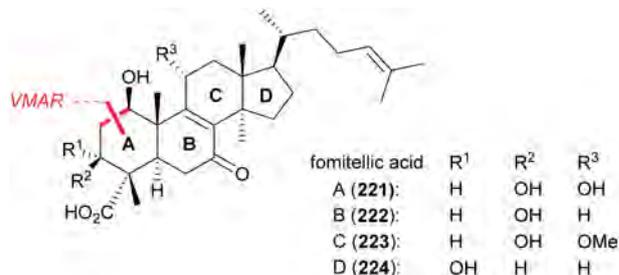**Fig. 68** VMAR of isatins in the total syntheses of convolutamydines E and B by Kobayashi *et al.*

Fig. 69 VMAR in the synthesis of the AB ring moiety (**227**) of fomitellic acids.

For their enantioselective total syntheses of con-volutamydines B (**215**) and E (**216**) (Fig. 68),[75] Kobayashi and co-workers envisioned the usage of their methodology to build up a quaternary stereocenter. In a first attempt they used isatin (**217**) as a model substrate to optimize the reaction conditions. As in the previous protocol, they added $TiCl_4$ (2.0 eq) to a CH_2Cl_2 solution of isatin (**230**) at −78 °C, followed by addition of *N,O*-acetal **33a**. The reaction then was stirred at −20 °C to afford aldol adduct **218** in only 32% yield and 9 : 1 dr. Kobayashi increased the yield and selectivity of this reaction due to the usage of an excess of isatin (**217**) (6.0 eq) and stirring the $TiCl_4$-isatin solution at 0 °C for 30 min prior to the addition of **33a** at −78 °C. This modified procedure afforded adduct **218** in 69% yield and 60 : 1 dr.

With this new established procedure, Kobayashi *et al.* accomplished the total syntheses of the convolutamydines B (**215**) and E (**216**) (Fig. 69). Both syntheses started with the VMAR of D-valine derived *N,O*-acetal ***ent*-33a** and 4,6-dibromoi-satin (**219**) which proceeded smoothly in 74% yield almost as a single isomer (>99 : 1 dr).[75]

In 2009, the Kobayashi group published the synthesis of the AB ring moiety **227** of fomitellic acids using a VMAR between enal **225** and *N,O*-acetal **33a** (Fig. 69).[76] Under their standard conditions ($TiCl_4$, 0.1 M in CH_2Cl_2, −50 °C), the VMAR adduct **226** was obtained in only 43% yield. However, changing the solvent to toluene in higher concentration (0.5 M) and adding a catalytic amount of water (10 mol %) significantly improved the yield of the VMAR adduct (76% yield).[77]

7   Natural product syntheses generating motif IV

motif IV, 7   type IV
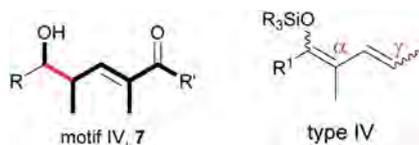
In this chapter we will focus on different methods that can be used to construct motif IV.

In 2004, the Kobayashi group reported on an extension of the vinylogous Mukaiyama aldol reaction. The use of Evans auxiliary based chiral silyl ketene *N,O*-acetal **228** or **33b** (Fig. 70) provided a hitherto unprecedented degree of 1,6,7-remote asymmetric induction.[13]

Kobayshi and co-workers proposed transition state **229** (Fig. 71) to explain the high regio- and diastereoselectivity of this transformation. Transition state **230** is disfavored due to steric interactions between the Lewis acid and the terminal methyl group as well as the R of the aldehyde and the α-methyl group of the silyl ketene *N,O*-acetal.[13]

7.1   *Anti*-Kobayashi VMARs

This chapter focuses on the Kobayashi group's VMARs of either phenylalanine or valine-derived silyl ketene *N,O*-acetals. For saturated, α-unbranched aldehydes, silyl ketene *N,O*-acetal **228** and **33b** generate the same selectivities and yields (Fig. 72).

Due to the power of Kobayashi group's protocol for the construction of polyketide natural products it was employed in a variety of total syntheses. One of those natural products is palmerolide A (**231**) (Fig. 72). In 2007 and 2008, the Nicolaou[78] and De Brabander[79] groups independently used this VMAR-protocol for their syntheses of palmerolide A (**231**). Both groups envisioned to build up a similar vinyl iodide as a
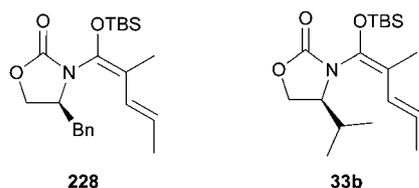

Fig. 70   *E*-Silyl ketene *N,O*-acetals **228** and **33b** used in Kobayashi group's VMAR.
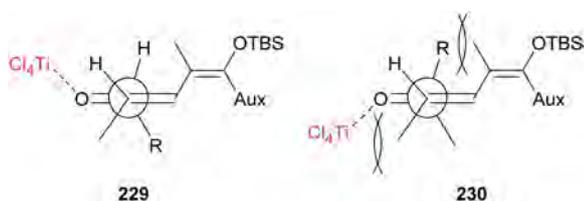

Fig. 71   Transition states for the Kobayashi group's VMAR.
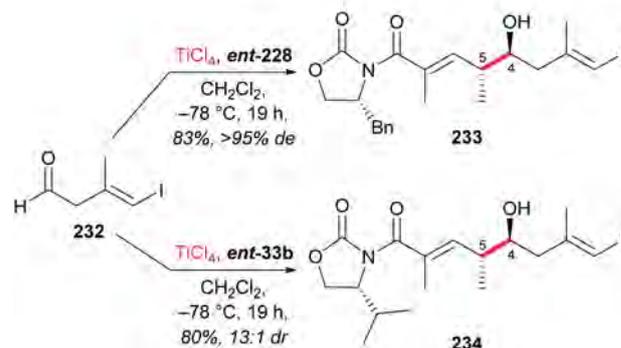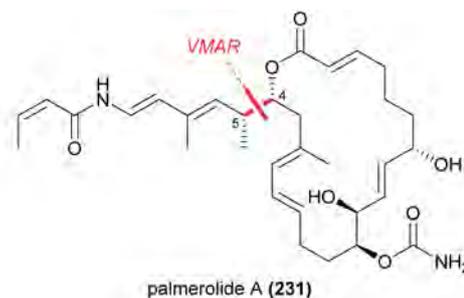

palmerolide A (**231**)

Fig. 72   Kobayashi group's VMAR in the total syntheses of palmerolide A (**231**).

building block. The Nicolaou group produced the desired vinyl iodide **233** with the use of phenylalanine derived silyl ketene *N,O*-acetal ***ent*-228** in 83% yield and >95% de. While the De Brabander group used the valine derived silyl ketene *N,O*-acetal ***ent*-33b** and obtained vinyl iodide **234** in 80% yield and 13 : 1 dr.

It should be pointed out that the Kobayashi group's VMAR leads to C4-C5-*anti*-products, but for palmerolide A (**231**) a C4-C5-*syn*-configuration was required. Therefore, both groups faced an inversion of the C4-stereocenter to complete their synthesis.

For the concise route to defined stereoisomers of the hydroxyl acid of the chondramides, the group of Maier faced the same situation. The *anti*-configuration established by the Kobayashi reaction was inverted through a Mitsunobu reaction (Fig. 73).[80] For the first total synthesis of salinipyrone A (**236**) (Fig. 73), Ramesh and Meshram started their synthesis with a VMAR of propionaldehyde (**240**) and acetal **228**, which proceeded in 91% yield and >20 : 1 dr.[81]

So far, there is no report of vinylogous Mukaiyama aldol reactions of phenylalanine derived silyl ketene *N,O*-acetal **228** to saturated α-branched aldehydes in literature. It seems that for these kind of aldehydes only the valine derived silyl ketene *N,O*-acetal **33b** would work.

In the first total synthesis of lagunamycin (**242**) (Fig. 74) Hosokawa *et al.* used the Kobayashi group's protocol with **33b** and isobutyraldehyde (**42**).[82] As expected, they obtained aldol adduct **243** in 99% yield as a single diastereoisomer. In order to obtain the desired building block deoxygenation of the secondary alcohol was achieved by reducing the phenylsulfonate with LiBEt$_3$H.
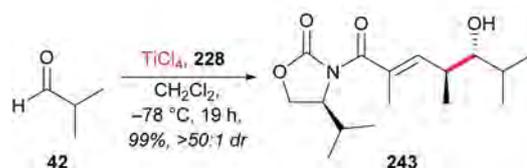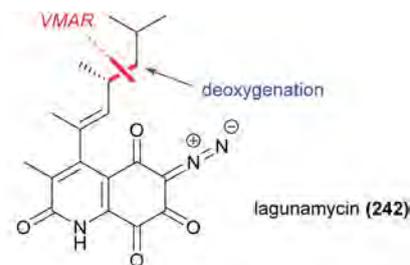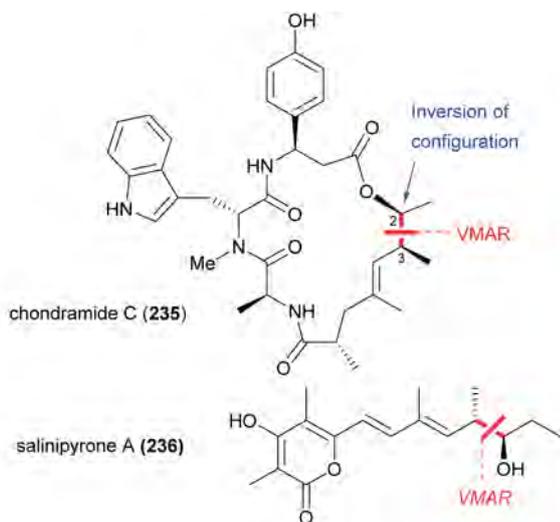
Fig. 74 The use of Kobayashi group's method in the total synthesis of lagunamycin (242).

product 252 in 89% yield and as a single diastereomer (Fig. 76).[84]

Pellasoren A (253), a natural product isolated from myxobacteria that exhibits potent cytotoxic activity against HCT-116
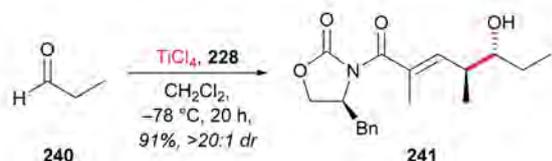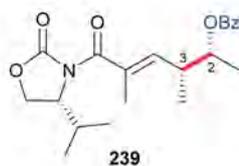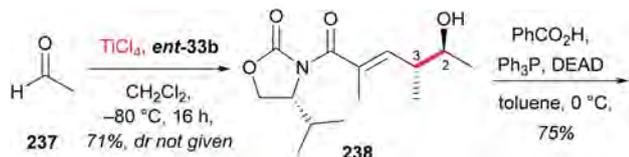
Fig. 73 The use of Kobayashi group's VMA reaction in the synthesis of chondramide C (235) and salinipyrone A (236).
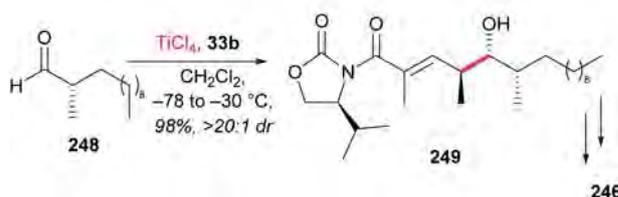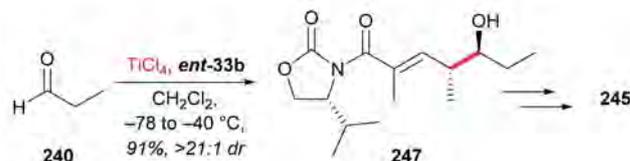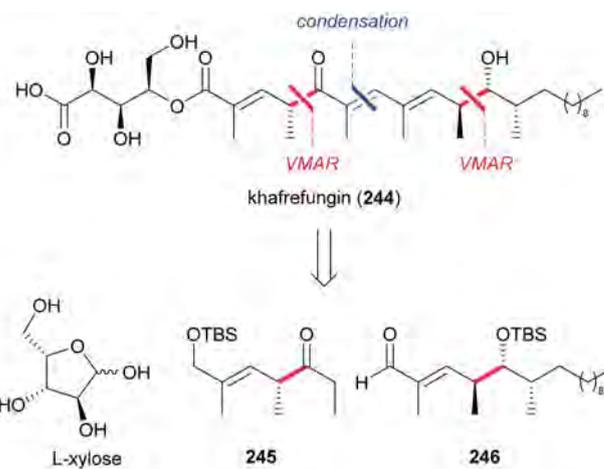
Fig. 75 VMARs in the total synthesis of khafrefungin (244).

For the total synthesis of khafrefungin (244) (Fig. 75) Kobayashi and co-workers envisioned to build up two fragments 245 and 246 according to their method.[83] Both fragments could be joined by an aldol condensation. Consequently one vinylogous aldol reaction established only the α-methyl branch of the ethyl ketone. The synthesis of this fragment started from propionaldehyde (240) and furnished the desired product in 91% yield (>21 : 1 dr). The second fragment took advantage of the α-chiral aldehyde 248. This matched case (Felkin product) afforded *anti*-aldol adduct 249 in 98% yield and >20 : 1 dr.

A further example for the effectiveness of the Kobayashi group's VMAR is the reaction of aldehyde 251 and valine derived acetal 233b in Hosokawa group's first total synthesis of *epi*-cochlioquinone A (250). They obtained the desired aldol

24 | *Nat. Prod. Rep.*, 2014, xx, 1–32

This journal is © The Royal Society of Chemistry 2014

Fig. 76 Kobayashi group's aldol with in the total synthesis of epi-cochlioquinone A (250).

human colon cancer cells, was synthesized by the Kalesse group in 2012.[85] For their synthesis of the hemiketal moiety 257 they used silyl ketene N,O-acetal 33b and α-chiral aldehyde 254. The

transformation proceeded with 61% yield and 17 : 1 dr. At a later stage they made use of Stryker's reagent ([(PPh$_3$)CuH]$_6$) for conjugate reduction of an α,β-unsaturated ester and subsequent stereoselective intramolecular protonation[86] that leads to hemiketal 257 in 61% yield and 20 : 1 dr. (Fig. 77).

A challenging problem by using the Kobayashi group's VMAR is the use of α-branched unsaturated aldehydes. Different conditions and protocols have been established to use these substrates in combination with valine derived silyl ketene N,O-acetals.

Hosokawa et al. addressed this problem when using p-dimethylaminobenzaldehyde (259) in their total synthesis of trichostatin D (258) (Fig. 78).[87] The only satisfying results were achieved with BF$_3$·OEt$_2$ as the Lewis acid after five days. They obtained the desired (6R,7R)-aldol product in 88% yield and dr of 89 : 8 : 1.5 : 1.5. It should be mentioned here, that as in the case of Kobayashi's khafrefungin synthesis the VMAR was used to construct one chiral centre, the secondary alcohol, also established stereoselectively, was oxidized later. For further examination they performed the VMAR with p-bromo-benzaldehyde (261), which could be transformed to the N,N-dimethylalanine derivative 260. They studied different Lewis acids in VMARs of aldehyde 261 and TBS-dienolether ent-33b and concluded that TiCl$_4$ provided the best yields and selectivities.

Fig. 77 Total synthesis of pellasoren A (253) using the Kobayashi group's VMAR and stereoselective intramolecular protonation–cyclization sequence.
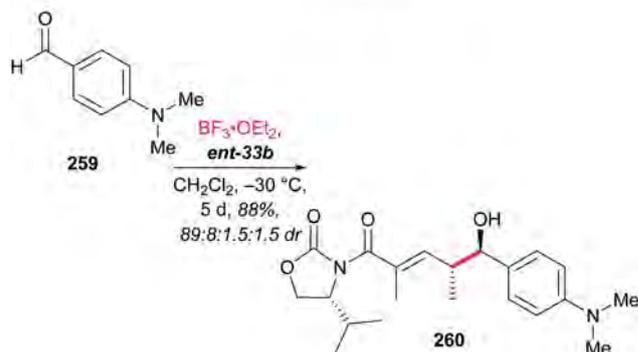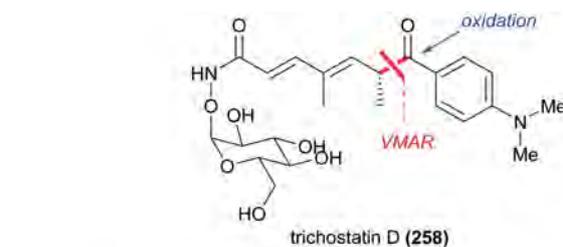
Fig. 78 Kobayashi group's VMA-reaction in the total synthesis of trichostatin D (258).

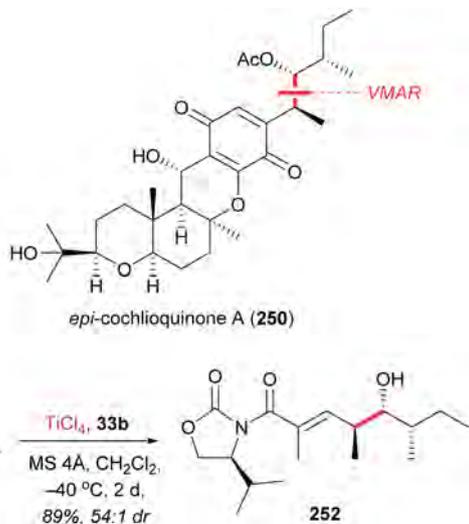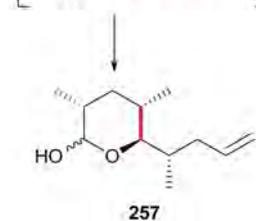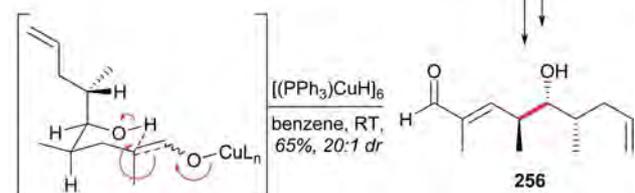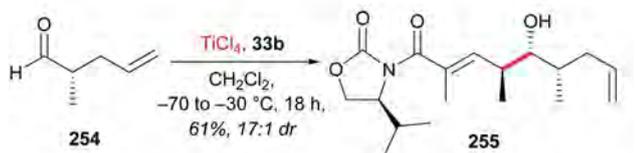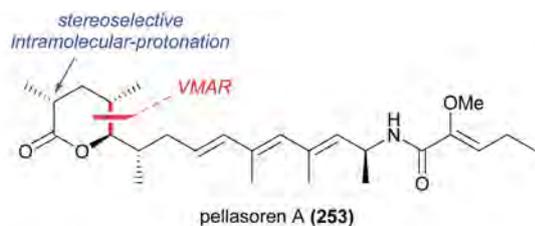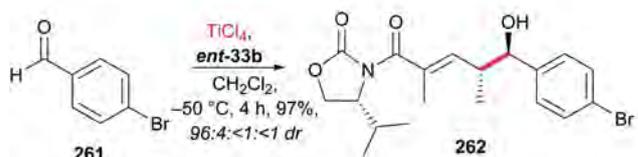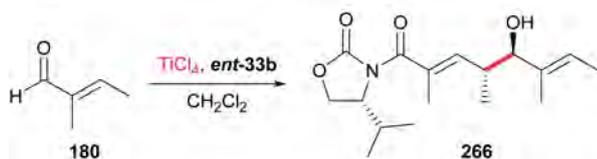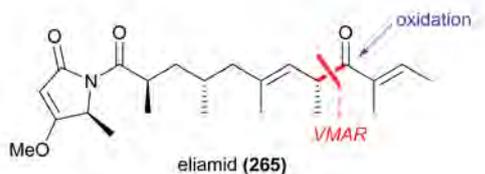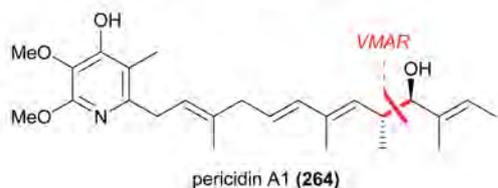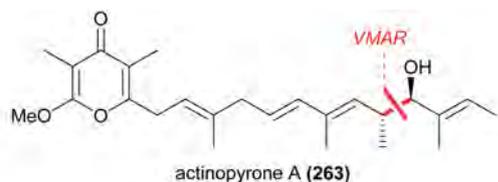Fig. 79 The use of the Kobayashi group's VMAR in the total syntheses of actinopyrone A (263), pericidin A1 (264) and eliamid (265).

Fig. 80 VMAR in the total syntheses of JBIR-02 (267) and Mer-A2026B (268).

In the total synthesis of actinopyrone A (263, Fig. 76), Hosokawa et al. started their synthesis with a VMAR of silyl ketene N,O-acetal ent-33b and tiglic aldehyde (180) in the presence of TiCl₄.[88] This gave the desired anti-aldol adduct 266 in 82% as a single isomer, however the reaction took four days.

Also, Lipshutz et al. made use of this Kobayashi vinylogous Mukaiyama aldol reaction with tiglic aldehyde (180) for their total synthesis of pericidin A1 (264).[89] They utilized different reaction conditions (–35 °C instead of –60 °C) and obtained product 266 in 68% yield after two days.

A third synthesis starting with VMAR of N,O-acetal ent-33b and tiglic aldehyde (180) was published by Prusov and co-workers in their total synthesis of eliamid (265). They obtained 63% yield after five days at –50 °C.[90] As already mentioned before, Kobayashi and co-workers realized that also for remote 1,6,7-asymmetric induction with silyl ketene N,O-acetal 33b, a small amount of water (10 mol%) accelerates the reaction with α,β-unsaturated aldehydes (Fig. 79).[77]

Compared to pericidin A1 (264) two similar natural products, JBIR-02 (267) and Mer-A2026B (268) (Fig. 80), were synthesized by the group of Gademann.[91] They envisioned to build up the

tail fragments of these molecules starting with Kobayashi's method. The first route for the synthesis of JBIR-02 (267) starting with aldehyde 269 failed and they were not able to obtain any product. This could be explained by the extended conjugation that makes the dienal 269 a rather unreactive substrate towards nucleophilic attack. An optimized route used bromoacrylate (270) as starting material and allowed construction of the diene through cross coupling at a later stage.
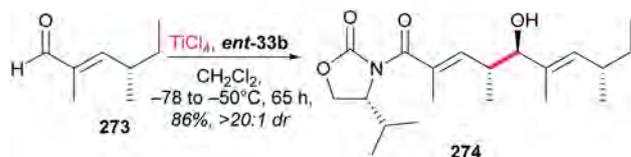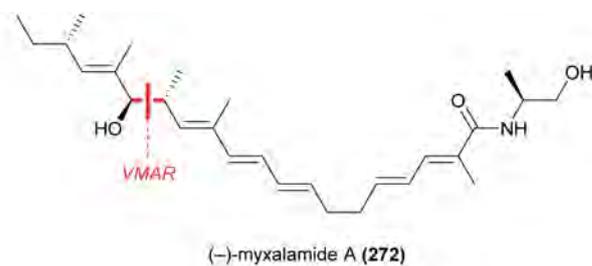
Fig. 81 VMAR reaction in the total synthesis of (–)-myxalamide A (272).

Kobayashi *et al.* took advantage of the remote stereo-induction of his reliable method in the synthesis of (−)-myxalamide A (272) (Fig. 81).[92] For the VMAR of acetal *ent*-33b and unsaturated aldehyde 273 they used their standard conditions which furnished adduct 274 in 86% yield and >20 : 1 dr.

The synthesis of (+)-TMC-151C (275) was chosen as a showcase by Kobayashi *et al.* to probe whether iterative VMARs could be used to construct complex natural products. (Fig. 82).[93] The first VMAR between aldehyde 276 and silyl ketene *N,O*-acetal 33b proceeded under standard conditions as expected well with 91% yield and >20 : 1 dr. Standard transformations established the aldehyde functionality for the second VMAR for which the reaction conditions had to be adjusted. They had to increase the concentration of the Lewis acid to an excess of TiCl$_4$ (4.0 eq) and the aldehyde 278 to 5.0 eq due to the low reactivity of the substrate. Nevertheless, the second VMAR provided the desired product in 51% yield and a diastereomeric ratio of 13 : 1. The third VMAR, however, performed on

aldehyde 280, did not produce any of the desired product even under optimized conditions and increased concentration of Lewis acid and aldehyde. This result is remarkable since the close proximity at each aldehyde functionality was always the same. In each case it was an α,β-unsaturated aldehyde with a methyl group in α-position.

Consequently, they had to change their synthetic strategy. The new route uses a more convergent approach that joins both segments through a silicon-tethered ring-closing metathesis. Consequently the VMAR was performed on methacrolein (281) and the double bond originally constructed through the second VMAR was generated by crotylation and ring-closing metathesis (Fig. 83).[93] Even this transformation had to be optimized since it produced under standard conditions (CH$_2$Cl$_2$, 2.0 eq of aldehyde) the desired aldol product 282 in only 23% yield. After extensive survey of reaction conditions they identified the combination of toluene as the solvent and 4.0 eq of the aldehyde to provide the highest yield and selectivity (65%, >20 : 1 dr).
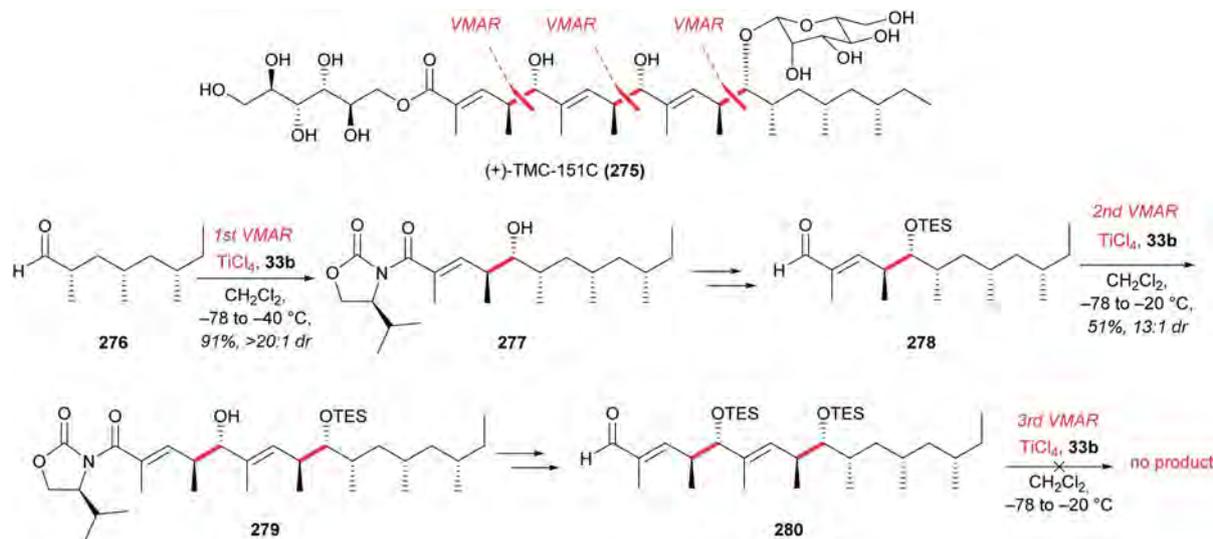
Fig. 82 The use of iterative VMARs in towards the synthesis of (+)-TMC-151C (275).
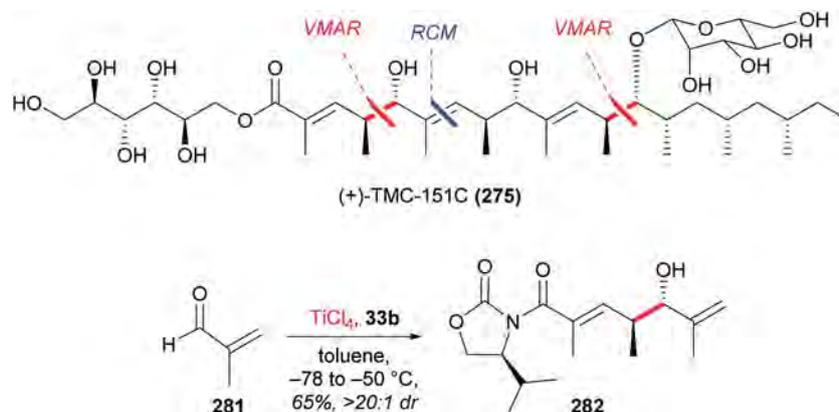
Fig. 83 Second convergent route to (+)-TMC-151C (275).

This journal is © The Royal Society of Chemistry 2014

Nat. Prod. Rep., 2014, xx, 1–32 | 27

In further studies to VMA-reactions, Kobayashi and co-workers found, that α-haloenals work perfect in their VMA reaction and are even more reactive than tiglic aldehyde (**180**) (Fig. 84).[94] Different α-haloenals require different reaction times and give yields up to 95% with >20 : 1 dr. It should be pointed out that those α-haloenals can be used as substrates for Pd-mediated cross coupling reactions in further transformations.

7.2 *Syn*-selective Kobayashi VMAR

All Kobayshi vinylogous Mukaiyama aldol reactions we have covered above are perfectly suited to build up *anti*-configured ketides. However, as mentioned in the total syntheses of palmerolide A (**231**) (Fig. 72), by the Nicolaou[78] and De Brabander[79] groups, they had to invert one of the two stereo centres in order to get *syn*-configured diastereomers which is certainly a drawback for the VMAR methodology.

In the following chapter we will cover *syn*-selective variations of the Kobayashi group's VMAR.

During their continuing studies on the Kobayashi group's VMAR, Hosokawa *et al.* found, that the reaction of 1-formylpyrene (**286**) gives predominantly the *syn*-configured aldol adduct **287** in 56% yield (Fig. 85).[95] So far there is no explanation to this phenomenon, but they envisioned to use this kind of reaction in their total synthesis of benzopyrenomycin (**285**).
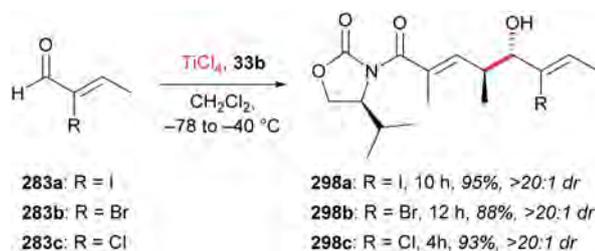
Fig. 84 Studies on α-haloenals as electrophiles in VMARs by Kobayshi *et al.*
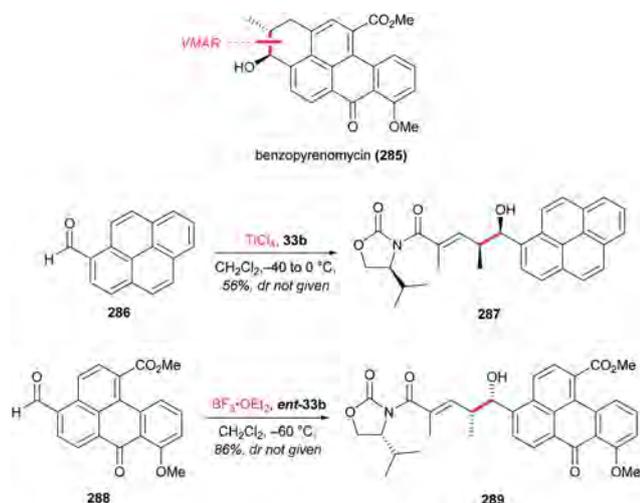
Fig. 85 *Syn*-selective VMARs with 1-formylpyrenes in the total synthesis of benzopyrenomycin (**285**).
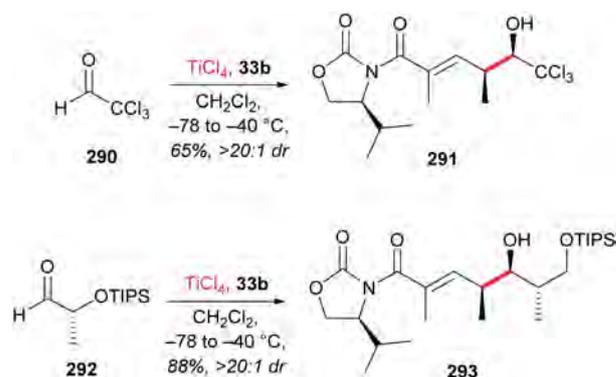
Fig. 86 *Syn*-selective Kobayashi VMARs with α-heteroatom substituted aldehydes.

They used chiral silyl ketene *N,O*-acetal **ent-33b** and aldehyde **288** in the presence of $BF_3 \cdot OEt_2$ to obtain product **289** in 86% yield.

Kobayashi *et al.* found, that the use of α-heteroatom substituted chiral and non-chiral aldehydes provides under their standard conditions *syn*-configured products with up to >20 : 1 dr (Fig. 86).[15a] Interestingly, there is no difference in selectivity whether *R*- or *S*-((triisopropylsilyl)oxy)propanal (**292**) was used.

For the synthesis of *N*-methylmaysenine precursor (**294**) (Fig. 87), Chen *et al.*[15b] envisioned that by using an aldehyde with a dithiane moiety at its β-position a $TiCl_4$-chelating transition state **297** should favour the *syn*-configured aldol product **296**. This transition state **297** would also explain the *syn*-selectivity for α-heteroatom substituted aldehydes.
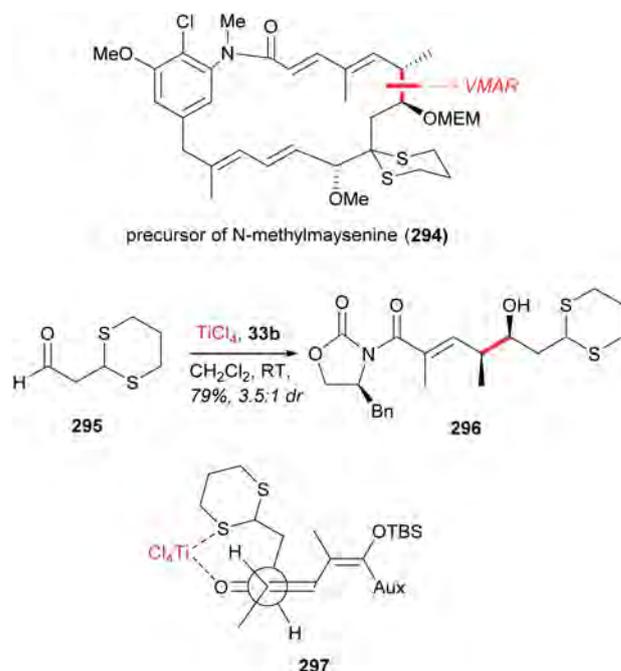
Fig. 87 *Syn*-selective VMAR in the synthesis of a precursor of *N*-methylmaysenine (**294**).

Using 1.0 eq of titanium tetrachloride at room temperature generates the expected *syn*-adduct **296** in 79% yield and moderate selectivity of 3.1 : 1 dr.[15b]

In an continuing effort towards the synthesis of the *N*-methylsmaysenine precursor (**294**) synthesis,[15b] Chen *et al.* found during their total synthesis of NFAT-68 (**298**)[15c] that *ortho*-substituted benzaldehydes such as aldehyde **299**, give *syn*-configured aldol products with selectivities up to >10 : 1 dr (Fig. 88).

Chen explains these results with transition state **301**[15c] where TiCl$_4$ is chelating to the aldehyde's *ortho*-methoxy group. Consequently, the Lewis acid is not pointing away from the rest of the aldehyde. To avoid repulsive interactions between the Lewis acid and the terminal methyl group of the silyl ketene *N,O*-ketene acetal the facial selectivity is changed.

In 2012, Hosokawa and co-workers published that the use of 4.0 eq of TiCl$_4$ switches the facial selectivity of the Kobayashi group's VMAR (Fig. 89).[16] They investigated different ratios of aldehyde, dienol ether and Lewis acid and identified a ratio of 1 : 1.5 : 4 to provide the highest yields and selectivities (up to 94% yield and *anti:syn* >1 : 50). They do not propose a transition state to explain the stereochemical outcome but report that the colour of the reaction solution turns blue instead of brown as under standard *anti*-selective Kobayashi conditions. This observation might be consistent with a different titanium complex to be active.[16]

In a subsequent publication the Hosokawa group focused on the reaction of acetals with silyl ketene *N,O*-acetal **33b** (Fig. 90).[96] During their studies of this type of reaction they screened a variety of different conditions by changing Lewis
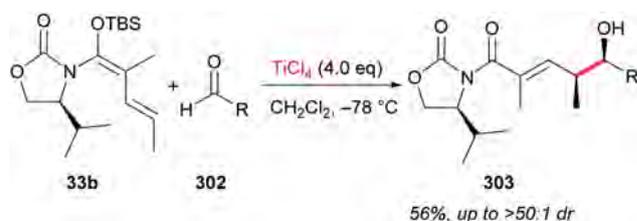
Fig. 89 *Syn*-selectivity with the use of 4 eq of TiCl$_4$.
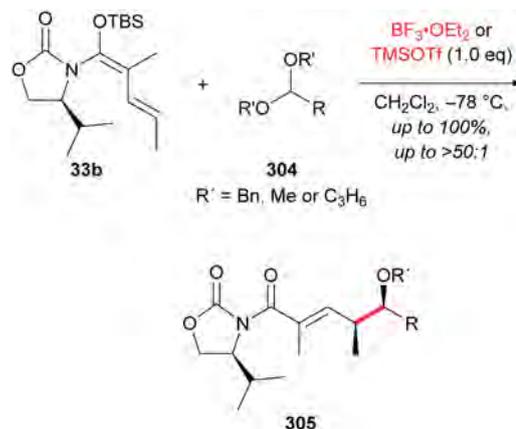
Fig. 90 *Syn*-selectivity using acetals.
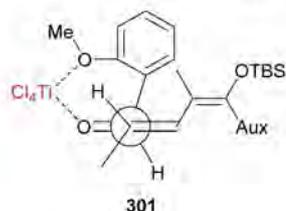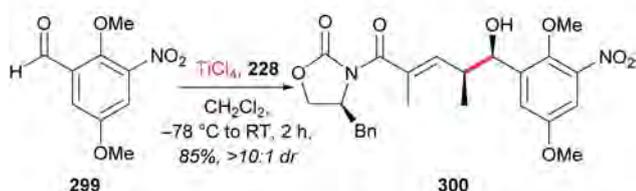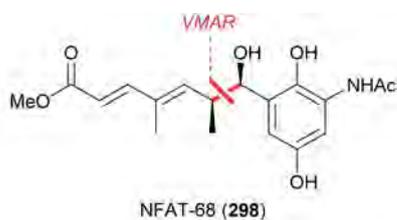
acids and using different acetals. Surprisingly, the reaction predominately gives *syn*-configured aldol adducts with up to >50 : 1 dr and quantitative yields.

However, it was proposed for quite some time that if one were able to generate the *Z*-configured silyl ketene *N,O*-acetal the *syn*-product should be obtained under the Kobayashi group's conditions. By simple deprotonation of the unsaturated precursor to the Kobayashi group's silyl ketene *N,O*-acetal the *E*-configuration is obtained to avoid 1,3-allylic strain. With that in mind, Symkenberg and Kalesse established a route that first forms the *Z*-configured double bond and then introduces the α-methyl group. Using this particular orchestration of transformations, they were capable of generating the *Z*-configured silyl ketene *N,O*-acetal.[14] The subsequent VMAR produced the expected *syn*-aldol product and in parallel to the chelation-controlled VMARs, aldehydes that are capable of chelating TiCl$_4$ generated the *anti*-aldol product (Fig. 91). The stereochemical outcome of this reaction can be explained with their proposed transition states in Fig. 12.

Dudley and co-workers used this *syn*-selective Kobayashi VMAR, in their formal total synthesis of palmerolid A (**231**) (Fig. 92).[97] They utilized the same aldehyde (**232**), that the De Brabander and Nicolaou groups used in their total syntheses of palmerolide A (**231**), as described above. However, Dudley *et al.* was able to obtain the desired 4,5-*syn*-configuration, needed for palmerolide A (**231**), directly in the vinylogous Mukaiyama aldol reaction with 69% yield without the need to invert the configuration at C4-hydroxy group.

Fig. 88 *Syn*-selective vinylogous Mukaiyama aldol reaction with *ortho*-substituted benzaldehyde.
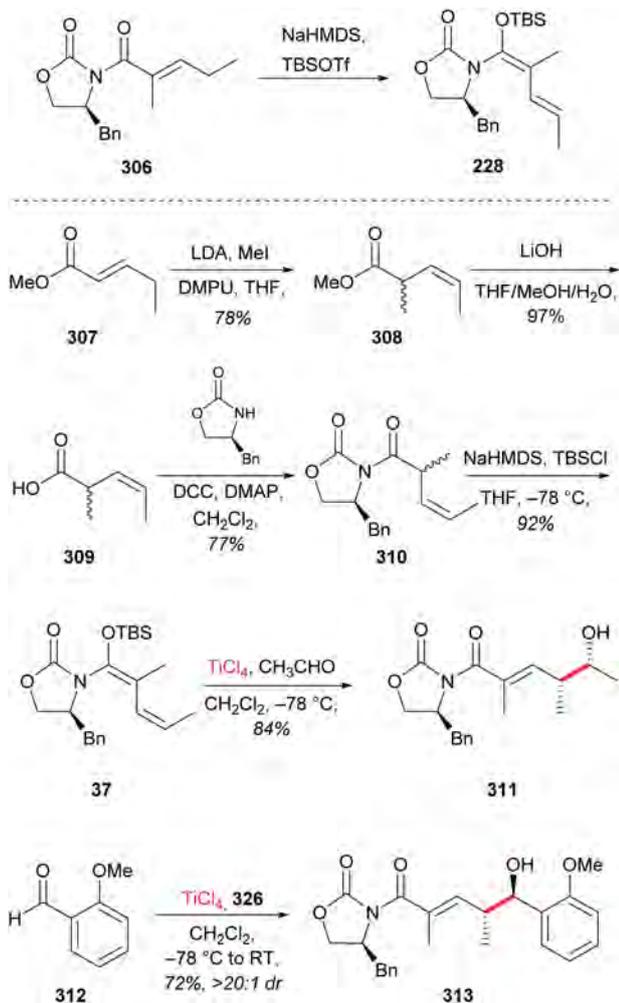
Fig. 91 *Syn*-selective Kobayashi VMAR with *Z*-configured *N,O*-acetal (**37**) by Kalesse and Symkenberg.
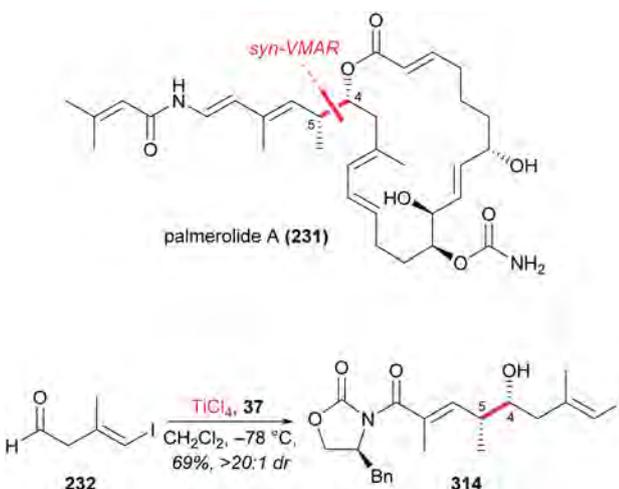
Fig. 92 Kalesse group's *syn*-selective Kobayashi aldol reaction in the Dudley group's total synthesis of palmerolide A (**231**).

8 Conclusions

The efficient synthesis of complex natural products is often one hurdle that has to be taken before issues of chemical biology can be addressed. On that background the vinylogous Mukaiyama aldol reaction has become one of the pivotal transformations to gain rapid access to natural products. Over the years, a variety of different enantioselective and diastereoselective transformations have been put forward that allow the synthesis of all structural motifs found in natural products and polyketides in particular. Besides improvement of existing methods one can expect the elaboration of subsequent transformation in order to further functionalize the structural motifs, generated by the vinylogous Mukaiyama aldol reaction.

9 Notes and references

1 T. Mukaiyama, K. Narasaka and K. Banno, *Chem. Lett.*, 1973, 1011–1014.
2 R. C. Fuson, *Chem. Rev.*, 1935, **16**, 1–27.
3 T. Mukaiyama and A. Ishida, *Chem. Lett.*, 1975, 319–322.
4 We will focus on vinylogous silyl ketene acetals and silyl dienolethers and not cover dienolates derived from β-keto esters and other 1,3-carbonyl compounds, as these have been thoroughly discussed before: (*a*) M. Kalesse, *Top. Curr. Chem.*, 2005, **244**, 43–76; (*b*) S. E. Denmark, J. R. Heemstra Jr. and G. L. Beutner, *Angew. Chem., Int. Ed.*, 2005, **44**, 4682–4698; (*c*) A. Soriente, R. M. De, R. Villano and A. Scettri, *Curr. Org. Chem.*, 2004, **8**, 993–1007; (*d*) G. Casiraghi, F. Zanardi, G. Appendino and G. Rassu, *Chem. Rev.*, 2000, **100**, 1929–1997; (*e*) G. Casiraghi, L. Battistini, C. Curti, G. Rassu and F. Zanardi, *Chem. Rev.*, 2011, **111**, 3076–3154; (*f*) M. Cordes and M. Kalesse, in *Modern Methods in Stereoselective Aldol Reactions*, ed. R. Mahrwald, Wiley-VCH, Weinheim, 2013.
5 (*a*) M. Christmann, U. Bhatt, M. Quitschalle, E. Claus and M. Kalesse, *Angew. Chem., Int. Ed.*, 2000, **39**, 4364–4366; (*b*) U. Bhatt, M. Christmann, M. Quitschalle, E. Claus and M. Kalesse, *J. Org. Chem.*, 2001, **66**, 1885–1893; (*c*) M. Christmann and M. Kalesse, *Tetrahedron Lett.*, 2001, **42**, 1269–1271.
6 D. A. Evans and W. C. Black, *J. Am. Chem. Soc.*, 1993, **115**, 4497–4513.
7 (*a*) S. Eissler, M. Nahrwold, B. Neumann, H.-G. Stammler and N. Sewald, *Org. Lett.*, 2007, **9**, 817–819; (*b*) S. Eissler, T. Bogner, M. Nahrwold and N. Sewald, *Chem.–Eur. J.*, 2009, **15**, 11273–11287; (*c*) C. Weiss, B. Sammet and N. Sewald, *Nat. Prod. Rep.*, 2013, **30**, 924–940.
8 (*a*) I. Paterson and J. D. Smith, *Tetrahedron Lett.*, 1993, **34**, 5351–5354; (*b*) I. Paterson, J. D. Smith and R. A. Ward, *Tetrahedron*, 1995, **51**, 9413–9436.
9 (*a*) T. Mutou, K. Suenaga, T. Fujita, T. Itoh, N. Takada, K. Hayamizu, H. Kigoshi and K. Yamada, *Synlett*, 1997, 199–201; (*b*) Y. Nakao, W. Y. Yoshida, Y. Takada, J. Kimura, L. Yang, S. L. Mooberry and P. J. Scheuer, *J. Nat. Prod.*, 2004, **67**, 1332–1340.

10 J. Hassfeld, U. Eggert and M. Kalesse, *Synthesis*, 2005, 1183–1199.

11 D. Landsberg, O. Hartmann, U. Eggert and M. Kalesse, *Synlett*, 2013, 1105–1108.

12 J. M. Lee, P. Helquist and O. Wiest, *J. Am. Chem. Soc.*, 2012, **134**, 14973–14981.

13 S.-i. Shirokawa, M. Kamiyama, T. Nakamura, M. Okada, A. Nakazaki, S. Hosokawa and S. Kobayashi, *J. Am. Chem. Soc.*, 2004, **126**, 13604–13605.

14 G. Symkenberg and M. Kalesse, *Org. Lett.*, 2012, **14**, 1608–1611.

15 (*a*) M. Shinoyama, S.-i. Shirokawa, A. Nakazaki and S. Kobayashi, *Org. Lett.*, 2009, **11**, 1277–1280; (*b*) L. Wang, J. Gong, L. Deng, Z. Xiang, Z. Chen, Y. Wang, J. Chen and Z. Yang, *Org. Lett.*, 2009, **11**, 1809–1812; (*c*) L. Wang, Y. Xi, S. Yang, R. Zhu, Y. Liang, J. Chen and Z. Yang, *Org. Lett.*, 2011, **13**, 74–77.

16 Y. Mukaeda, T. Kato and S. Hosokawa, *Org. Lett.*, 2012, **14**, 5298–5301.

17 (*a*) M. T. Gieseler and M. Kalesse, *Org. Lett.*, 2011, **13**, 2430–2432; (*b*) S. Simsek, M. Horzella and M. Kalesse, *Org. Lett.*, 2007, **9**, 5637–5639; (*c*) M. T. Gieseler and M. Kalesse, *Org. Lett.*, 2014, **16**, DOI: 10.1021/ol403423r.

18 S. Simsek and M. Kalesse, *Tetrahedron Lett.*, 2009, **50**, 3485–3488.

19 G. Bluet and J.-M. Campagne, *Tetrahedron Lett.*, 1999, **40**, 5507–5509.

20 (*a*) B. L. Pagenkopf, J. Krüger, A. Stojanovic and E. M. Carreira, *Angew. Chem., Int. Ed.*, 1998, **37**, 3124–3126; (*b*) J. Krüger and E. M. Carreira, *J. Am. Chem. Soc.*, 1998, **120**, 837–838.

21 D. A. Evans, J. D. Burch, E. Hu and G. Jaeschke, *Tetrahedron*, 2008, **64**, 4671–4699.

22 P. Rémy, M. Langner and C. Bolm, *Org. Lett.*, 2006, **8**, 1209–1211.

23 (*a*) S. E. Denmark and S. Fujimori, *J. Am. Chem. Soc.*, 2005, **127**, 8971–8973; (*b*) S. E. Denmark, G. L. Beutner, T. Wynn and M. D. Eastgate, *J. Am. Chem. Soc.*, 2005, **127**, 3774–3789.

24 (*a*) L. Ratjen, P. Garcia-Garcia, F. Lay, M. Edmund Beck and B. List, *Angew. Chem., Int. Ed.*, 2011, **50**, 754–758; (*b*) L. Ratjen, Dissertation, Universität Köln, 2012.

25 D. Schummer, K. Gerth, H. Reichenbach and G. Höfle, *Liebigs Ann.*, 1995, 685–688.

26 (*a*) D. G. Nagle and W. H. Gerwick, *Tetrahedron Lett.*, 1990, **31**, 2995–2999; (*b*) D. G. Nagle and W. H. Gerwick, *J. Org. Chem.*, 1994, **59**, 7227–7237.

27 (*a*) S. Varadarajan, D. K. Mohapatra and A. Datta, *Tetrahedron Lett.*, 1998, **39**, 5667–5670; (*b*) J. D. White and M. S. Jensen, *J. Am. Chem. Soc.*, 1995, **117**, 6224–6233.

28 C. Barloy-Da Silva, A. Benkouider and P. Pale, *Tetrahedron Lett.*, 2000, **41**, 3077–3081.

29 (*a*) R. E. Schwartz, C. F. Hirsch, D. F. Sesin, J. E. Flor, M. Chartrain, R. E. Fromtling, G. H. Harris, M. J. Salvatore, J. M. Liesch and K. Yudin, *J. Ind. Microbiol. Biotechnol.*, 1990, **5**, 113–123; (*b*) T. Golakoti, I. Ohtani, G. M. L. Patterson, R. E. Moore, T. H. Corbett, F. A. Valeriote and L. Demchik, *J. Am. Chem. Soc.*, 1994, **116**, 4729–4737.

30 (*a*) J. Tanaka and T. Higa, *Tetrahedron Lett.*, 1996, **37**, 5535–5538; (*b*) J.-i. Tanaka, T. Higa, G. Bernardinelli and C. W. Jefford, *Chem. Lett.*, 1996, 255–256; (*c*) T. Higa, J.-i. Tanaka and D. Garcia Gravalos, *PCT Int. Appl. WO 9710242A9710241*, 1997.

31 (*a*) A. B. Smith, I. G. Safonov and R. M. Corbett, *J. Am. Chem. Soc.*, 2001, **123**, 12426–12427; (*b*) A. B. Smith and I. G. Safonov, *Org. Lett.*, 2002, **4**, 635–637; (*c*) A. B. Smith, I. G. Safonov and R. M. Corbett, *J. Am. Chem. Soc.*, 2002, **124**, 11102–11113; (*d*) T. R. Hoye and M. Hu, *J. Am. Chem. Soc.*, 2003, **125**, 9576–9577; (*e*) T.-P. Loh, J.-Y. Yang, L.-C. Feng and Y. Zhou, *Tetrahedron Lett.*, 2002, **43**, 7193–7196.

32 D. M. Troast, J. Yuan and J. A. Porco Jr, *Adv. Synth. Catal.*, 2008, **350**, 1701–1711.

33 (*a*) R. Polt, M. A. Peterson and L. Deyoung, *J. Org. Chem.*, 1992, **57**, 5469–5480; (*b*) D. Sames, Y. Q. Liu, L. Deyoung and R. Polt, *J. Org. Chem.*, 1995, **60**, 2153–2159.

34 S.-i. Kiyooka, K. Suzuki, M. Shirouchi, Y. Kaneko and S. Tanimori, *Tetrahedron Lett.*, 1993, **34**, 5729–5732.

35 (*a*) J. Kruge and E. M. Carreira, *J. Am. Chem. Soc.*, 1998, **120**, 837–838; (*b*) B. L. Pagenkopf, J. Kruge, A. Stojanovic and E. M. Carreira, *Angew. Chem., Int. Ed.*, 1998, **37**, 3124–3126.

36 B. Bazán-Tajeda, G. Bluet, G. Broustal and J.-M. Campagne, *Chem.–Eur. J.*, 2006, **12**, 8358–8366.

37 R. Schäckel, B. Hinkelmann, F. Sasse and M. Kalesse, *Angew. Chem., Int. Ed.*, 2010, **49**, 1619–1622.

38 A. Zampella, M. V. D'Auria, L. Minale, C. Debitus and C. Roussakis, *J. Am. Chem. Soc.*, 1996, **118**, 11085–11088.

39 D. A. Evans, E. Hu, J. D. Burch and G. Jaeschke, *J. Am. Chem. Soc.*, 2002, **124**, 5654–5655.

40 (*a*) I. Paterson, R. D. M. Davies and R. Marquez, *Angew. Chem., Int. Ed.*, 2001, **40**, 603–607; (*b*) I. Paterson, R. D. M. Davies, A. C. Heimann and R. Marquez, *Org. Lett.*, 2003, **5**, 4477–4480.

41 B. M. Trost, O. Dirat and J. L. Gunzner, *Angew. Chem., Int. Ed.*, 2002, **41**, 841–843.

42 D. L. Aubele, S. Wan and P. E. Floreancig, *Angew. Chem., Int. Ed.*, 2005, **44**, 3485–3488.

43 (*a*) I. Paterson, A. D. Findlay and G. J. Florence, *Org. Lett.*, 2006, **8**, 2131–2134; (*b*) I. Paterson, A. D. Findlay and G. J. Florence, *Tetrahedron*, 2007, **63**, 5806–5819.

44 I. Paterson, G. J. Florence, A. C. Heimann and A. D. Findlay, *Angew. Chem., Int. Ed.*, 2005, **44**, 1130–1133.

45 I. Paterson and T. Paquet, *Org. Lett.*, 2010, **12**, 2158–2161.

46 (*a*) M. Takasu and H. Yamamoto, *Synlett*, 1990, 194–196; (*b*) D. Sartor, J. Saffrich and G. Helmchen, *Synlett*, 1990, 197–198; (*c*) K. Ishihara, S. Kondo and H. Yamamoto, *J. Org. Chem.*, 2000, **65**, 9125–9128.

47 (*a*) A. B. Smith III, J. A. Jurica and S. P. Walsh, *Org. Lett.*, 2008, **10**, 5625–5628; (*b*) C. An, J. A. Jurica, S. P. Walsh, A. R. Hoye and A. B. Smith III, *J. Org. Chem.*, 2008, **10**, 4278–4296.

48 (*a*) S. E. Denmark and G. L. Geutner, *J. Am. Chem. Soc.*, 2003, **125**, 7800–7801; (*b*) S. E. Denmark and G. L. Geutner, *J. Am. Chem. Soc.*, 2006, **128**, 1038–1039.

This journal is © The Royal Society of Chemistry 2014

Nat. Prod. Rep., 2014, **xx**, 1–32 | 31

49 K. C. Nicolaou, X. Jiang, P. J. Lindsay-Scott, A. Corbu, S. Yamashiro, A. Bacconi and V. M. Fowler, *Angew. Chem., Int. Ed.*, 2011, **50**, 1139–1144.

50 G. Karthikeyan, C. Zambaldo, S. Barluenga, V. Zoete, M. Karplus and N. Winssinger, *Chem.–Eur. J.*, 2012, **18**, 8978–8986.

51 S. E. Denmark and S. Fujimori, *J. Am. Chem. Soc.*, 2005, **127**, 3774–3789.

52 C. Kujat, M. Bock and A. Kirschning, *Synlett*, 2006, 419–422.

53 L. Fang, H. Xue and J. Yang, *Org. Lett.*, 2008, **10**, 4645–4648.

54 J. Hassfeld, M. Christmann and M. Kalesse, *Org. Lett.*, 2001, **3**, 3561–3564.

55 J. Hassfeld and M. Kalesse, *Tetrahedron Lett.*, 2002, **43**, 5093–5095.

56 F. J. Schmitz, S. P. Gunasekera, G. Yalamanchili, M. B. Hossain and D. van der Helm, *J. Am. Chem. Soc.*, 1984, **106**, 7251–7252.

57 (*a*) J. R. Dunetz, L. D. Julian, J. S. Newcom and W. R. Roush, *J. Am. Chem. Soc.*, 2008, **130**, 16407–16416; (*b*) J. R. Dunetz and W. R. Roush, *Org. Lett.*, 2008, **10**, 2059–2062; (*c*) A. B. Smith III and D. Lee, *J. Am. Chem. Soc.*, 2007, **129**, 10957–10962.

58 (*a*) G. Ehrlich, J. Hassfeld, U. Eggert and M. Kalesse, *J. Am. Chem. Soc.*, 2006, **128**, 14038–14039; (*b*) G. Ehrlich, J. Hassfeld, U. Eggert and M. Kalesse, *Chem.–Eur. J.*, 2008, **14**, 2232–2247; (*c*) N. Diaz, M. Zhu, G. Ehrlich, U. Eggert, Y. Muthukumar, F. Sasse and M. Kalesse, *Chem.–Eur. J.*, 2012, **18**, 4946–4952.

59 F. P. Liesener, U. Eggert and M. Kalesse, *Synthesis*, 2006, 2590–2602.

60 J. Kobayashi, K. Shimbo, M. Sato and M. Tsuda, *J. Org. Chem.*, 2002, **67**, 6585–6592.

61 B. Bazán-Tajeda, M. Georgy and J.-M. Campagne, *Synlett*, 2004, 720–722.

62 (*a*) S. P. Gunasereka, M. Gunasereka and G. K. Schulte, *J. Org. Chem.*, 1990, **55**, 4912–4915; corrigendum: *J. Org. Chem.*, 1991, **56**, pp. 1346–1346; (*b*) M. Kalesse, *ChemBioChem*, 2000, **1**, 171–175.

63 K. Krohn, K. Tolkiehn, V. Lehne, H. W. Schmalle and H.-F. Grützmacher, *Liebigs Ann. Chem.*, 1985, 1311–1328.

64 J. W. Cornforth, R. H. Cornforth and K. K. Mathew, *J. Chem. Soc.*, 1959, 112–127.

65 D. A. Evans, M. J. Dart, J. L. Duffy and M. G. Yang, *J. Am. Chem. Soc.*, 1996, **118**, 4322–4343.

66 K. Nagasawa, I. Shimizu and T. Nakata, *Tetrahedron Lett.*, 1996, **37**, 6885–6888.

67 P. A. Grieco and J. D. Speake, *Tetrahedron Lett.*, 1998, **39**, 1275–1278.

68 R. Nakamura, K. Tanino and M. Miyashita, *Org. Lett.*, 2003, **5**, 3579–3582.

69 B. Zou, K. Long and D. Ma, *Org. Lett.*, 2005, **7**, 4237.

70 E. J. Corey, C. L. Cywin and T. D. Roper, *Tetrahedron Lett.*, 1992, **33**, 6907–6910.

71 K. Suenaga, T. Mutou, T. Shibata, T. Itoh, T. Fujita, N. Takada, K. Hayamizu, M. Takagi, T. Irifune, H. Kigoshi and K. Yamada, *Tetrahedron*, 2004, **60**, 8509–8527.

72 G. Bluet and J.-M. Campagne, *Synlett*, 2000, 221–222.

73 L. V. Heumann and G. E. Keck, *Org. Lett.*, 2007, **9**, 4275–4278.

74 C.-M. Yu, H.-S. Choi, S.-K. Yoon and W.-H. Jung, *Synlett*, 1997, 889–890.

75 T. Nakamura, S.-i. Shirokawa, S. Hosokawa, A. Nakazaki and S. Kobayashi, *Org. Lett.*, 2006, **8**, 677–679.

76 M. Yamaoka, Y. Fukatsu, A. Nakazaki and S. Kobayashi, *Tetrahedron Lett.*, 2009, **50**, 3849–3852.

77 M. Yamaoka, A. Nakazaki and S. Kobayashi, *Tetrahedron Lett.*, 2010, **51**, 287–289.

78 (*a*) K. C. Nicolaou, R. Guduru, Y.-P. Sun, B. Banerji and D. K. Chen, *Angew. Chem., Int. Ed.*, 2007, **46**, 5896–5900; (*b*) K. C. Nicolaou, Y.-P. Sun, R. Guduru, B. Banerji and D. K. Chen, *J. Am. Chem. Soc.*, 2008, **130**, 3633–3644.

79 X. Jiang, B. Liu, S. Lebreton and J. K. De Brabander, *J. Am. Chem. Soc.*, 2007, **129**, 6386–6387.

80 A. Schmauder, S. Müller and M. E. Maier, *Tetrahedron*, 2008, **64**, 6263–6296.

81 P. Ramesh and H. M. Meshram, *Tetrahedron*, 2012, **68**, 9289–9292.

82 S. Hosokawa, S. Kuroda, K. Imamura and K. Tatsuta, *Tetrahedron Lett.*, 2006, **47**, 6183–6186.

83 S.-i. Shirokawa, M. Shinoyama, I. Ooi, S. Hosokawa, A. Nakazaki and S. Kobayashi, *Org. Lett.*, 2007, **9**, 849–852.

84 S. Hosokawa, K. Matsushita, S. Tokimatsu, T. Toriumi, Y. Suzuki and K. Tatsuta, *Tetrahedron Lett.*, 2010, **51**, 5532–5536.

85 C. Jahns, T. Hoffmann, S. Müller, K. Gerth, P. Washausen, G. Höfle, H. Reichenbach, M. Kalesse and R. Müller, *Angew. Chem., Int. Ed.*, 2012, **51**, 5239–5243.

86 A. Kena Diba, C. Noll, M. Richter, M. T. Gieseler and M. Kalesse, *Angew. Chem., Int. Ed.*, 2010, **49**, 8367–8369.

87 S. Hosokawa, T. Ogura, H. Togashi and K. Tatsuta, *Tetrahedron Lett.*, 2005, **46**, 333–337.

88 S. Hosokawa, K. Yokota, K. Imamura, Y. Suzuki, M. Kawarasaki and K. Tatsuta, *Chem.–Asian J.*, 2008, **3**, 1415–1421.

89 B. H. Lipshutz and B. Amorelli, *J. Am. Chem. Soc.*, 2009, **131**, 1396–1397.

90 G. Höfle, K. Gerth, H. Reichenbach, B. Kunze, F. Sasse, E. Forche and E. V. Prusov, *Chem.–Eur. J.*, 2012, **18**, 11362–11370.

91 J. Hoecker and K. Gademann, *Org. Lett.*, 2013, **15**, 670–673.

92 K. Fujita, R. Matsui, T. Suzuki and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2012, **51**, 7271–7274.

93 R. Matsui, K. Seto, Y. Sato, T. Suzuki, A. Nakazaki and S. Kobayashi, *Angew. Chem., Int. Ed.*, 2011, **50**, 680–683.

94 Y. Iwasaki, R. Matsui, T. Suzuki, A. Nakazaki and S. Kobayashi, *Chem. Pharm. Bull.*, 2011, **59**, 522–524.

95 S. Hosokawa, Y. Mukaeda, R. Kawahara and K. Tatsuta, *Tetrahedron Lett.*, 2009, **50**, 6701–6704.

96 H. Tsukada, Y. Mukaeda and S. Hosokawa, *Org. Lett.*, 2013, **15**, 678–681.

97 M. P. Lisboa, D. M. Jones and G. B. Dudley, *Org. Lett.*, 2013, **15**, 886–889.