# The hetero-Diels–Alder approach to spiroketals

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The hetero-Diels-Alder reaction can provide spiroketal systems with excellent stereoselectivity. This perspective article will briefly outline the scope and limitations of this approach for the production of naturally occurring spiroketals and derivatives.

## Introduction

Many secondary metabolites isolated from fungi, bacteria, plants and marine organisms, and a range of insect pheromones contain the spiroketal (or spiroacetal) structure.[1,2] These are cyclic ketals consisting of two rings linked by a single atom, a spiro carbon atom. The two ketal oxygens that are connected to the central spiro atom are each part of one of the two rings (Fig. 1). The examples shown are 1,7-dioxaspiro[5.5]undecane (**1**) or 6,6-spiroketal, 1,6-dioxaspiro[4.5]decane (**2**) (5,6-spiroketal) and 1,6-dioxaspiro[4.4]nonane (**3**) (5,5-spiroketal).

There are four distinctive conformations of the 6,6-spiroketal core. In most cases the double anomeric (diaxial) conformation **A** is preferred (Fig. 1), *i.e.* a conformation with each oxygen atom of the respective THF rings adopting an axial orientation.[3] This enables a stabilizing interaction between one of the lone pairs of the ring oxygens and the antibonding $\sigma^*$-orbital of the attached axial C–O-bond. Orbital overlapping reaches a maximum for an antiperiplanar arrangement of the two interacting orbitals.[4] The resulting anomeric stabilization has been estimated to contribute approximately 1.4–2.4 kcal/mol per interaction to the total energy.[5] Non-anomeric spiroketals (having less than the maximal number of anomeric relations) arise from the presence and steric demand of substituents and intramolecular interactions such as hydrogen bonding.

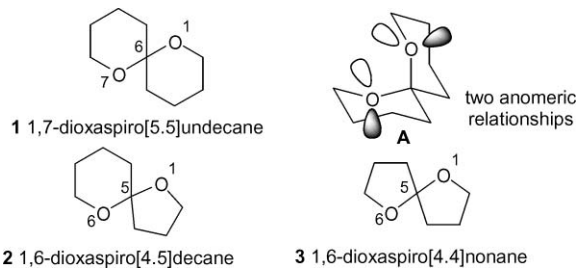


**Fig. 1** Common spiroketals: 6,6-spiroketal (**1**), 6,5-spiroketal (**2**) and 5,5-spiroketal (**3**).

As shown in Fig. 2, spiroketals are found in numerous natural product classes with varying complexities.[6] Many of them exhibit interesting biological activities, *e.g.* antiproliferative,[7] antifungal[8] and antibacterial properties.[9] Some examples shown in Fig. 2 include reveromycin A (**4**), an inhibitor of the mitogenic activity of EGF,[6b] the streptomyces metabolite β-rubromycin (**5**),[6c] the mycotoxin talaromycin B (**6**)[6a] and the steroid spiroketal hecogenin (**7**).[6d]

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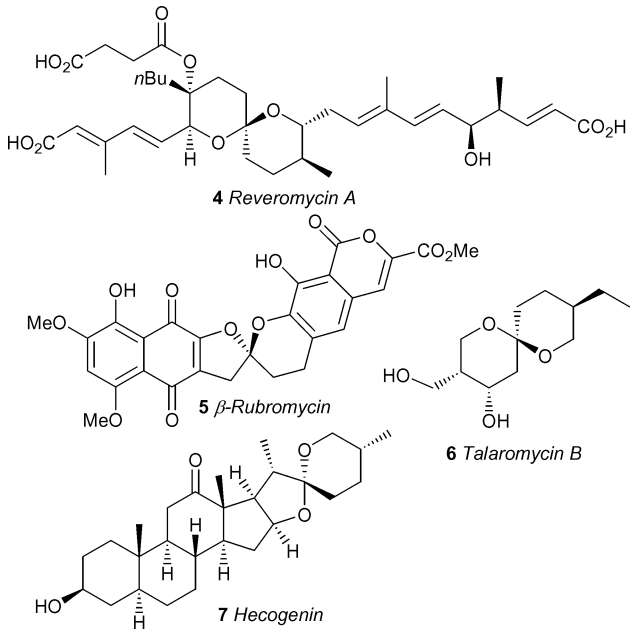
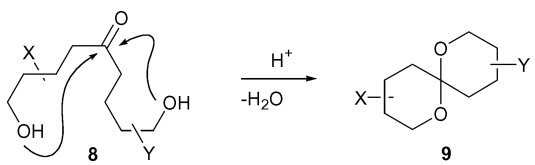



**Fig. 2** Selected spiroketal containing natural products.

## General synthesis of spiroketals

Acid-catalyzed spirocyclization of dihydroxyketones **8** (or a synthetic equivalent thereof) is by far the most common strategy for the generation of spiroketals (Scheme 1).[10] This method generally produces a thermodynamic mixture of the spiroketals, favouring the more stable configuration.[11] Hence, it is particularly useful for the synthesis of bisanomeric spiroketals. However, quite a number of natural products exist in non-anomeric conformations and a number of successful strategies for their synthesis have been reported recently.[3,12]

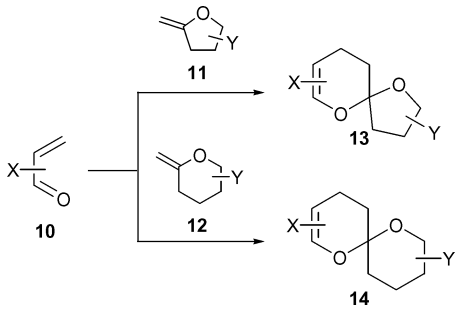


**Scheme 1** Generation of spiroketals by acid-catalyzed spirocyclization.

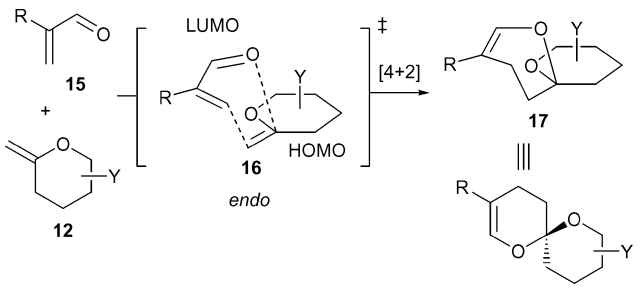
## Synthesis of spiroketals by hetero-Diels–Alder reaction

Alternatively, a spiroketal may be formed by an inverse electron demand hetero-Diels–Alder (HDA) reaction (Scheme 2).[13] The [4+2]-cycloaddition of an α-methylene pyran **12** (HOMO) with an acrolein derivative **10** (LUMO) would generate 6,6-spiroketals **14** in one step. Utilization of α-methylene furans **11** would provide the corresponding 5,6-spiroketals **13**.

In contrast to spirocyclizations, the HDA reaction usually provides the kinetic rather than the thermodynamic product. As illustrated in Scheme 3, the α-substituted heterodiene **15** approaches the dienophile **12** preferably in *endo*-fashion with an axial attack of the heterodiene-oxygen, as in the transition state **16**, resulting in the diaxial spiroketal system **17**. In addition, an enolic alkene is formed in the adduct **17** which can be further functionalised in a stereoselective manner.

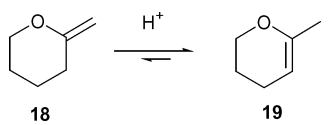


**Scheme 2** Hetero-Diels–Alder (HDA) reaction for spiroketal synthesis.



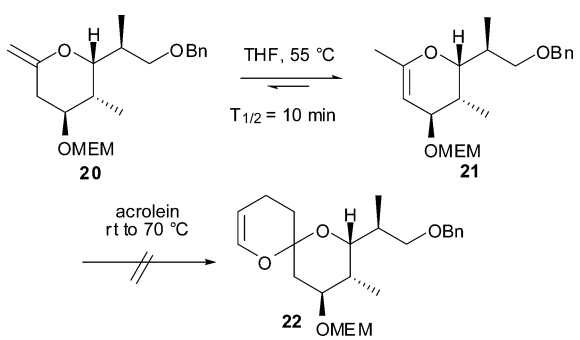
**Scheme 3** Axial oxygen approach during the HDA reaction.

This feature is particularly important if the anomeric and the non-anomeric spiroketal isomers are energetically similar and hence would be formed as a mixture under equilibrium conditions. One limitation of the HDA approach to spiroketals is the facile isomerization of the α-methylene furans and pyrans from the *exo* to the *endo* enol ether and thus some care is required especially when handling functionalized dienophiles.[14] Under mildly acidic conditions (*e.g.* $CDCl_3$ at room temperature overnight) methylene pyran **18** isomerizes to the more stable product **19** with an endocyclic double bond (Scheme 4).



**Scheme 4** Undesired isomerization of α-methylene pyrans.

An instructive example of this problem is depicted in Scheme 5.[14] The particularly facile isomerization of **20** to **21** (half-life around 10 min in base-washed glassware) rendered the intended hetero-Diels-Alder strategy for the total synthesis of monensin unfeasible. No product **22** was formed for a range of reaction conditions.



**Scheme 5** Facile isomerization of substituted dienophiles.[14]

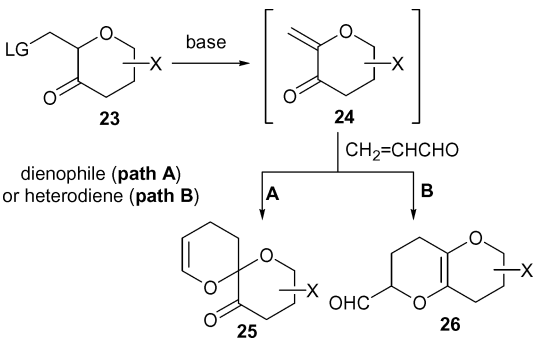
Though known for more than half a century,[15] successful applications of the HDA reaction for the synthesis of naturally occurring spiroketals are still limited. The next section will highlight some selected examples, illustrating the scope and limitations of this convergent route.

### HDA with non-isomerizable dienophiles

The problematic isomerization of methylene furans and pyrans has inspired a number of strategies utilizing non-isomerizable dienophiles. The following section illustrates several examples of this approach.

### 3-Oxo-2-methylene pyran dienophiles

The presence of a carbonyl group adjacent to the exocyclic double bond prevents double bond isomerization. Base induced elimination of the precursor **23** provides the enol ether dienophile **24**. A HDA reaction between **24** and acrolein then gives the spiroketal **25** (Path A: Scheme 6). However, **24** can also react as the heterodiene and acrolein as the dienophile in the cycloaddition reaction resulting in the formation of the undesired constitutional isomer **26** (Path B: Scheme 6). Initial studies utilising this so-called 'acrolein dimerization' approach were conducted by Ireland and Daub.[16] Indeed, depending on the heterodiene structure the formation of varying amounts of the regioisomer **26** (~15%) has been observed and the diastereoselectivity has been rather poor.

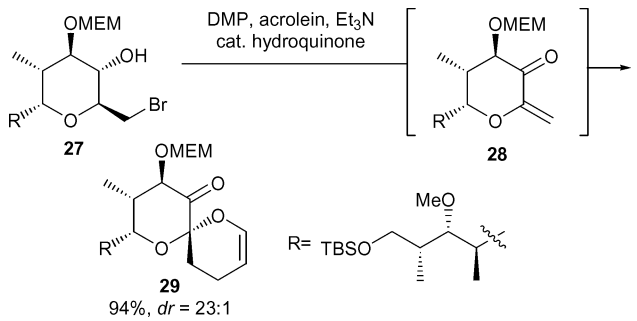



**Scheme 6** HDA reaction with 3-oxo-2-methylene pyran dienophiles. LG = leaving group.

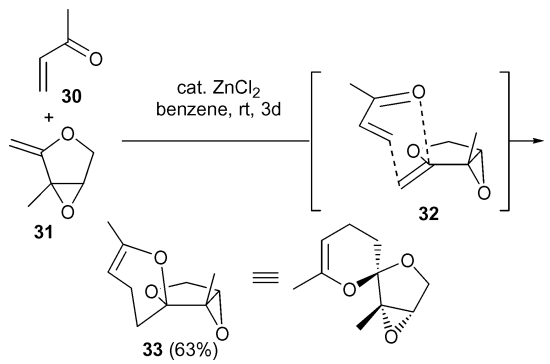
The acrolein dimerization approach was later successfully employed for the synthesis of an advanced spiroketal intermediate **29** for the total synthesis of the polyether ionophore monensin (Scheme 7).[17] The dienophile precursor **27** was subjected to base induced elimination to form the sensitive dienophile **28**. Immediate HDA reaction with acrolein gave the diaxial spiroketal **29** with excellent diasteroselectivity.

### 3,4-Epoxy-2-methylenetetrahydrofuran dienophiles

Pale has pioneered the use of 3,4-epoxy-2-methylenetetrahydrofurans (*e.g.* **31**) in the formation of 5,6-spiroketals (Scheme 8).[18] The 3,4-epoxy substitutent prevented isomerization of the exocyclic double bond. Different Lewis acid catalysts ($Yb(fod)_3$, $SnCl_2$, $ZnCl_2$) were tested, with $ZnCl_2$ giving the best yields.[18b] The HDA reaction between heterodiene **30** and dienophile **31** proceeds *via* the *endo* transition state **32** and on the




**Scheme 7** Application of the HDA reaction with a methylene pyran dienophile.[17] DMP = Dess-Martin periodinane.

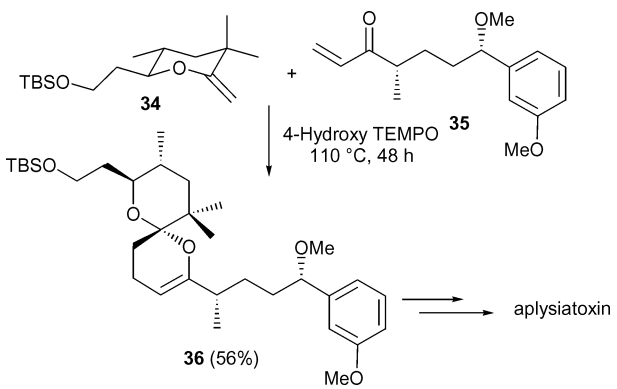



**Scheme 8** HDA reaction with 3,4-epoxy-2-methylenetetrahydrofuran dienophiles.[18b]

face of the enol opposite to the epoxide to give the 5,6-spiroketal **33** as the major product in good yield.

### 3,3-Dimethyl-2-methylene pyran dienophiles

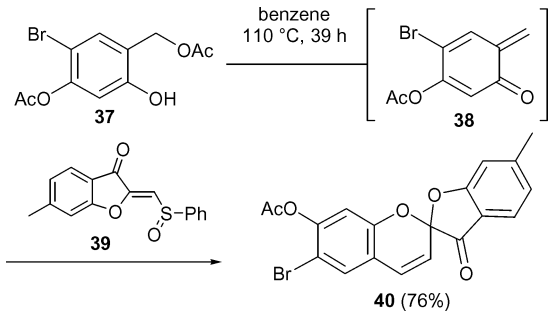
In Ireland's approach towards aplysiatoxin the 3,3-dimethyl-2-methylene pyran **34** has been employed for the HDA reaction (Scheme 9).[19] The quaternary carbon adjacent to the double bond prevented the undesired isomerization. The HDA reaction between **34** and **35** gave the adduct **36** as the only isomer isolated in good yield. The cycloaddition was conducted in the presence of TEMPO to prevent oligomerization of the diene **35**.




**Scheme 9** HDA reaction with 3,3-dimethyl-2-methylene pyran dienophiles.[19] 4-Hydroxy TEMPO = 4-hydroxy-2,2,6,6-tetramethylpiperidine 1-oxyl free radical.

### Vinyl sulfoxides as dienophiles

Very recently, the efficient synthesis of aromatic spiroketals utilizing vinyl sulfoxides (*e.g.* **39**) as dienophiles has been reported as shown in Scheme 10.[20] In this sequence, the phenol **37** undergoes elimination under thermal conditions to afford an intermediate *o*-quinone methide heterodiene **38**. Subsequent HDA reaction with the reactive dienophile **39** followed by concomitant elimination of the sulfoxide affords the spiroketal **40**. This provides a rapid and efficient approach to highly substituted aromatic 5,6-spiroketal natural products such as heliquinomycin which can be difficult to access *via* traditional syntheses of spiroketals under equilibrium conditions.

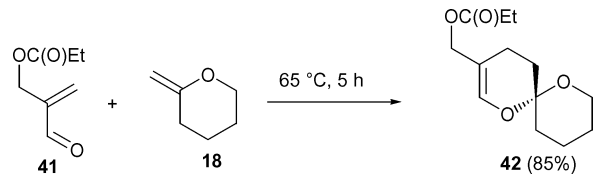



**Scheme 10** HDA reaction with vinyl sulfoxides as dienophiles.[20]

### HDA reactions with isomerizable dienophiles

The scope of the HDA strategy for the generation of spiroketals has been significantly increased by examples employing isomerizable dienophiles. The following examples illustrate these developments.

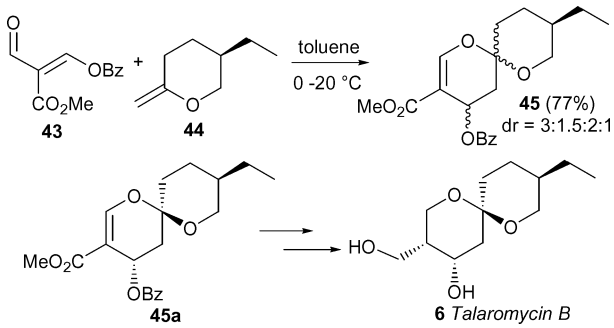
An early example was reported by Deslongchamps as shown in Scheme 11. A HDA reaction between methylene pyran **18** with acrolein derivative **41** provided spiroketal **42**, an advanced intermediate in the formal total synthesis of erythronolide A.[21] The rigid spiroketal conformation in adduct **42** enabled the diastereoselective side-chain functionalization. In this case, dienophile isomerization was not problematic in the HDA reaction.




**Scheme 11** Application of the hetero-Diels–Alder reaction for the formal total synthesis of erythronolide A.[21]

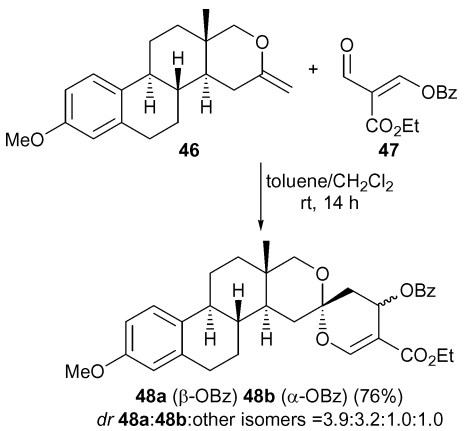
Tietze and Schneider reported the first HDA reaction of a chiral dienophile.[22] At ambient temperature the highly reactive methyl *O*-benzoyldiformylacetate **43** reacted with enantiopure dienophile **44**[23] to afford the cycloaddition products **45** in good yield (Scheme 12). However, all four possible diastereoisomers were formed with low diastereoselectivity. The major diastereoisomer **45a** arises by an *exo*-cycloaddition, *anti* to the ethyl group in dienophile **44**. Spiroketal **45a** was then transformed to the mycotoxin (–)-talaromycin B (**6**).[22]

Later, the synthesis of a talaromycin–estrone hybrid was successfully accomplished utilizing a HDA reaction between dienophile




**Scheme 12** HDA of chiral dienophiles.[22]

**46** and heterodiene **47** as key step (Scheme 13).[24] Four possible isomers were formed with the anomeric products **48a** and **48b** as the major isomers and diastereoisomer **48a** as the major product.




**Scheme 13** Application of the HDA reaction for the enantioselective synthesis of talaromycin–estrone hybrids.[24]

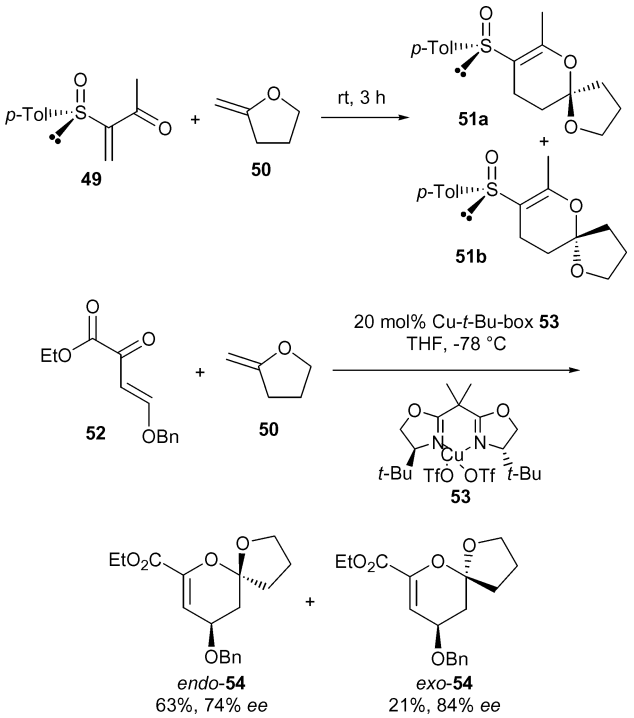
Reactive heterodienes containing a C3 chiral sulfinyl group have been successfully employed by Maignan and Hayes (Scheme 14).[25] Cycloaddition between methylene furan **50** and the chiral sulfoxide heterodiene **49** gave the diastereoisomers **51a** and **51b** which were easily separated by chromatography. Hence, starting from enantiopure sulfinyl heterodiene **49** enantiopure spiroketals could be obtained after sulfinyl cleavage.

Jørgensen has reported a catalytic enantioselective HDA employing a copper bisoxazoline complex for the synthesis of 5,6-spiroketals (Scheme 14).[26] The reactive diene **52** and dienophile **50** underwent a HDA reaction in the presence of the chiral Lewis acid Cu catalyst Cu-*t*-Bu-box (**53**)[26b] to afford the *endo* and *exo* products **54** in high yield but poor diastereoselectivity favouring *endo*-**54**. However, the enantioselectivity for each isomer was reasonably high.

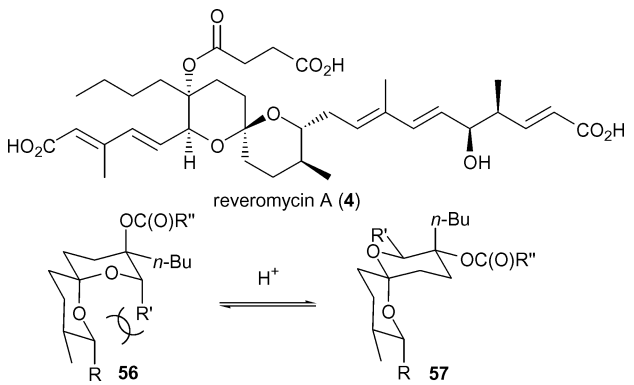
An interesting target for the HDA strategy is (–)-reveromycin A (**4**).[6b] Though the conformation of the spiroketal in the natural product is the one with the maximum number of anomeric effects (diaxial), this conformation is destabilized by an unfavorable steric interaction involving the axial C19 side chain. This steric interaction is reduced in conformer **57** with one less anomeric effect (Scheme 15).

Hence, the energy difference between **56** and **57** is expected to be quite small and thus, thermodynamic equilibration during the spirocyclization will furnish diastereomeric mixtures. Indeed,

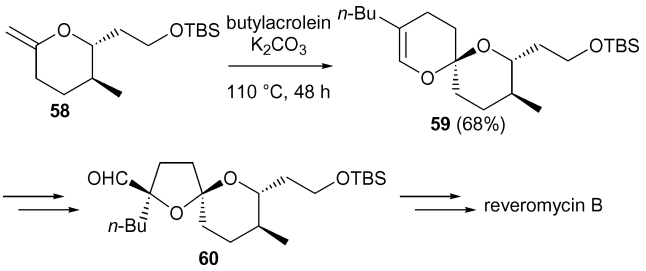



**Scheme 14** Examples of asymmetric HDA reactions for enantioselective spiroketal synthesis.[25,26]



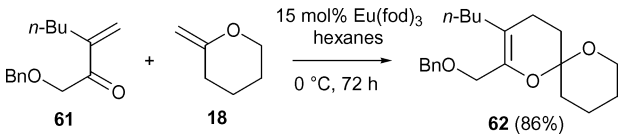

**Scheme 15** Facile isomerization of the reveromycin A type 6,6-spiroketal.

that has been the case for all the approaches to the spiroketal core under equilibrating conditions. For example, Theodorakis reported a 1:1.5 mixture of spiroketals using a thermodynamic approach to reveromycin A[27] while Shimizu and Nakata obtained 1:2 in their total synthesis of reveromycin A (**4**).[28] Rizzacasa reported a successful total synthesis of reveromycin A (**4**) utilizing a kinetically stereocontrolled HDA reaction for the construction of the spiroketal fragment.[29] Earlier studies for the total synthesis of the related reveromycin B showed that the cycloaddition of isomerizable methylene pyrans with simple heterodienes can be promoted thermally in the presence of $K_2CO_3$.[30] As well, the additive helped to suppress the undesired *exo* to *endo* isomerization of the dienophile. Despite unfavourable steric interactions, **59** was formed as a single diastereoisomer (Scheme 16). Epoxidation of **59** and rearrangement provided **60** that was further transformed to (−)-reveromycin B.[30]



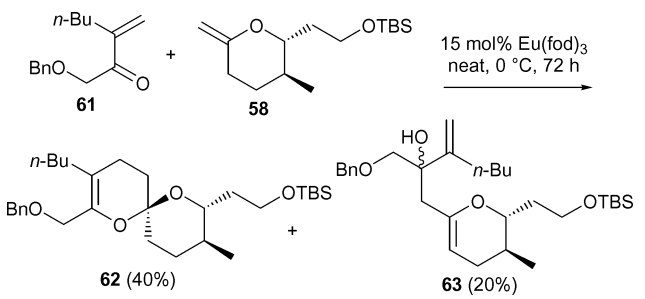

**Scheme 16** Thermal HDA for the total synthesis of (−)-reveromycin B.[30]

Due to the base lability of heterodiene **61** different conditions were required to promote the HDA reaction. Studies on a model system showed that the mild Lewis acid $Eu(fod)_3$ was an effective catalyst for the reaction (Scheme 17).[29] Treatment of a solution of **61** and dienophile **18** in hexanes with $Eu(fod)_3$ resulted in a smooth HDA reaction to afford the spiroketal adduct **62** in excellent yield.




**Scheme 17** Model HDA reaction for the synthesis of reveromycin A (**4**).[29]

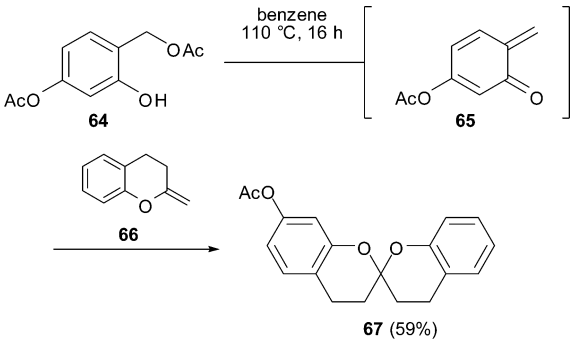
When applied to dienophile **58**, a neat mixture of the starting materials **61** and **58** had to be used since only slow isomerization of the methylene pyran **58** was observed in solution. The side product **63** was formed as a mixture of diastereoisomers *via* an ene reaction. Although the formation of **63** significantly reduced the yield of the desired product, compound **62** was formed as sole diastereomer in one step (Scheme 18). Spiroketal **62** was then converted into (−)-reveromycin A (**4**).



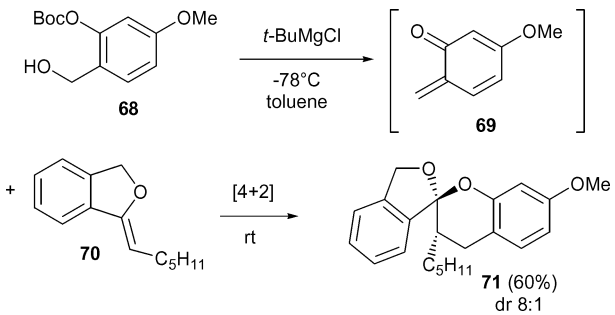

**Scheme 18** HDA approach to the spiroketal core of reveromycin A.[29]

Recently, the synthesis of aromatic 6,6-spiroketals such as **67** from a highly reactive *o*-quinone methide has been reported (Scheme 19).[31] Thermally induced elimination of precursor **64** affords the reactive heterodiene **65**. Subsequent cycloaddition with methylene chromane **66** then provides spiroketal **67**.

A similar approach to the challenging chromane type spiroketal natural products has been reported by Pettus however, in this case isomerization of the dienophile **70** is blocked by the aromatic ring (Scheme 20).[32] Treatment of the carbonate **68** with a Grignard reagent at low temperature results in migration of the Boc group to the benzylic alcohol followed by facile elimination to provide the *o*-quinone methide **69**.[33] A HDA reaction between **69** and dienophile **70** occurred at room temperature to give the spiroketal **71** with good stereoselectivity.




**Scheme 19** Generation of aromatic 6,6-spiroketals using a HDA reaction.[31]




**Scheme 20** HDA synthesis of chromane spiroketals *via* *o*-quinone methides.[32]

The HDA reaction detailed in Scheme 20 proceeds *via* an *endo* transition state **72** as shown in Fig. 3 and this strategy could be applied to the synthesis of the natural product paecilospirone **73**.

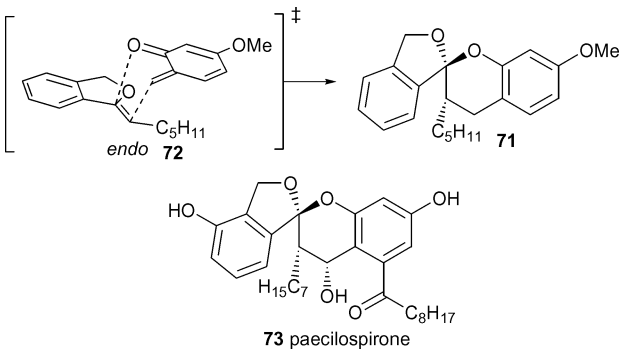



**Fig. 3** Transition state for HDA reaction between **69** and **70**.

## Conclusions

The hetero-Diels–Alder reaction is an excellent strategy for the convergent and stereoselective synthesis of diaxial spiroketal type natural products. This perspective article highlights the power of such an approach with only a few examples. It is envisaged that the scope of this method could be further developed for the production of a wide variety of naturally occurring spiroketals.

## Notes and references

1 This structural subunit is often named a spiroacetal but will be referred to as a spiroketal throughout this article.

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