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# Rapid Formation of Molecular Complexity in Organic Synthesis issue

Reviewing the latest advances in reaction development and complex, target-directed synthesis

Guest Editors Professors Erik J. Sorensen and Huw M. L. Davies

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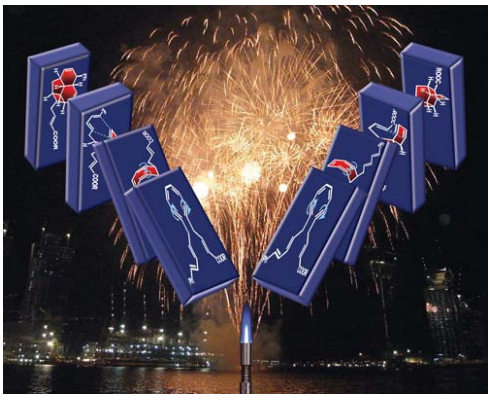

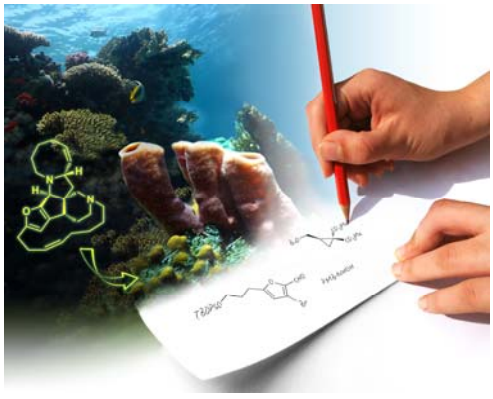

# Recent applications of intramolecular Diels–Alder reactions to natural product synthesis†

**Martin Juhl*[a] and David Tanner*[b]**

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This *tutorial review* presents some recent examples of intramolecular Diels–Alder (IMDA) reactions as key complexity-generating steps in the total synthesis of structurally intricate natural products. The opportunities afforded by transannular (TADA) versions of the IMDA reaction in complex molecule assembly are also highlighted. The review is aimed at a wide audience, ranging from advanced undergraduates to seasoned practitioners of total synthesis; since this is an educational overview, only selected highlights from the period 2000–2009 are presented, along with chosen references to other, more comprehensive, reviews.

## Introduction

The Diels–Alder (DA) [4 + 2] cycloaddition reaction was first described in 1928,[1a] and is a pericyclic process (*cf.* Fig. 1) involving a conjugated diene (4π-electron component, usually electron-rich) and a dienophile (2π-electron component, usually electron-deficient). The DA reaction is stereospecific, as well as diastereo- and regioselective, and can be used to generate a six-membered ring, a substituted π-bond, two new σ-bonds and up to four contiguous stereogenic centres in a single operation. Nothing goes to waste, since all of the atoms constituting the starting materials appear in the product. These exquisite features are the result of a highly-ordered transition state dictated by the nature of the frontier molecular orbitals (FMO) of the two reacting components. It was immediately recognised[1b] that the DA reaction opened up entirely new vistas in the field of synthetic organic chemistry, and it duly established itself as an indispensable synthetic tool; Diels and Alder shared the 1950 Nobel Prize in Chemistry for their discovery. Furthermore, the DA reaction[2] is amenable to catalysis, including the enantioselective variety, and can be conducted in the intramolecular mode[3] (IMDA, see Fig. 1). In this review, the IMDA reaction is subdivided into Type 1 and Type 2, where Type 1 refers to the connecting tether being attached to the diene moiety in the 1-position, while for the Type 2 IMDA the tether is connected to the 2-position. Few reactions lend themselves more readily to the rapid generation of molecular complexity than the DA cycloaddition. It is the IMDA reaction and the transannular version (TADA)[4] of this process which are the subjects of this review, highlighting some recent applications of IMDA and TADA in the total synthesis of complex natural products.[5] Since the aim of this educational overview is to provide an update, and to be selective rather

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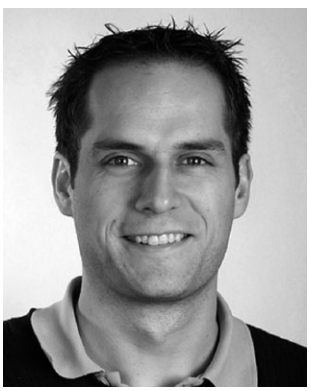
† Part of the rapid formation of molecular complexity in organic synthesis themed issue.



**Martin Juhl**

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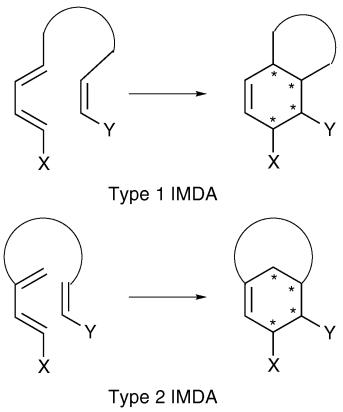


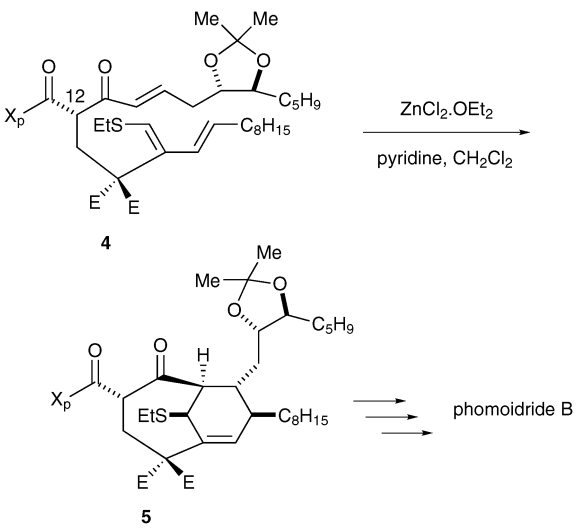

**Fig. 1** Classification of intramolecular Diels–Alder (IMDA) reactions, depending on the position of the tether between the diene and dienophile.

than comprehensive, it contains only recent examples taken from each of the years 2000 to 2009. The reader is referred to the literature[2–5] for more exhaustive discussions of the DA and IMDA reactions.

## Recent intramolecular Diels–Alder reactions

### Enantioselective total synthesis of phomoidride B

In 2000, the group of Fukuyama[6] reported an enantioselective total synthesis of the densely functionalised natural product phomoidride B (**1**, a.k.a. CP-263 114) by means of an IMDA reaction to set up the strained bicyclic system characteristic of this natural product class. The precursor **4** (Scheme 1) was assembled *via* an aldol reaction from two readily available chiral building blocks **2** and **3** (Fig. 2), and the IMDA reaction was mediated by a zinc chloride–diethyl ether complex in the presence of pyridine (which prevented untoward acid-catalysed double bond isomerisation). As a testimony to the power of IMDA reactions to rapidly generate molecular complexity, this process delivered the desired bicyclic system with concomitant




**Scheme 1** Type 2 IMDA in Fukuyama's total synthesis of phomoidride B.

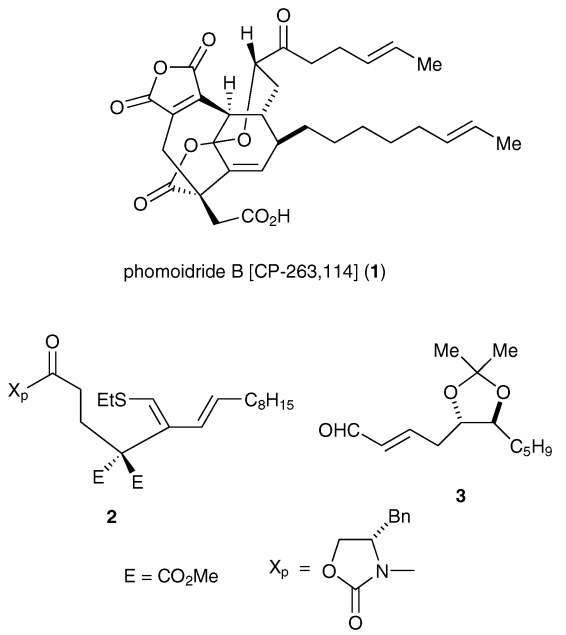


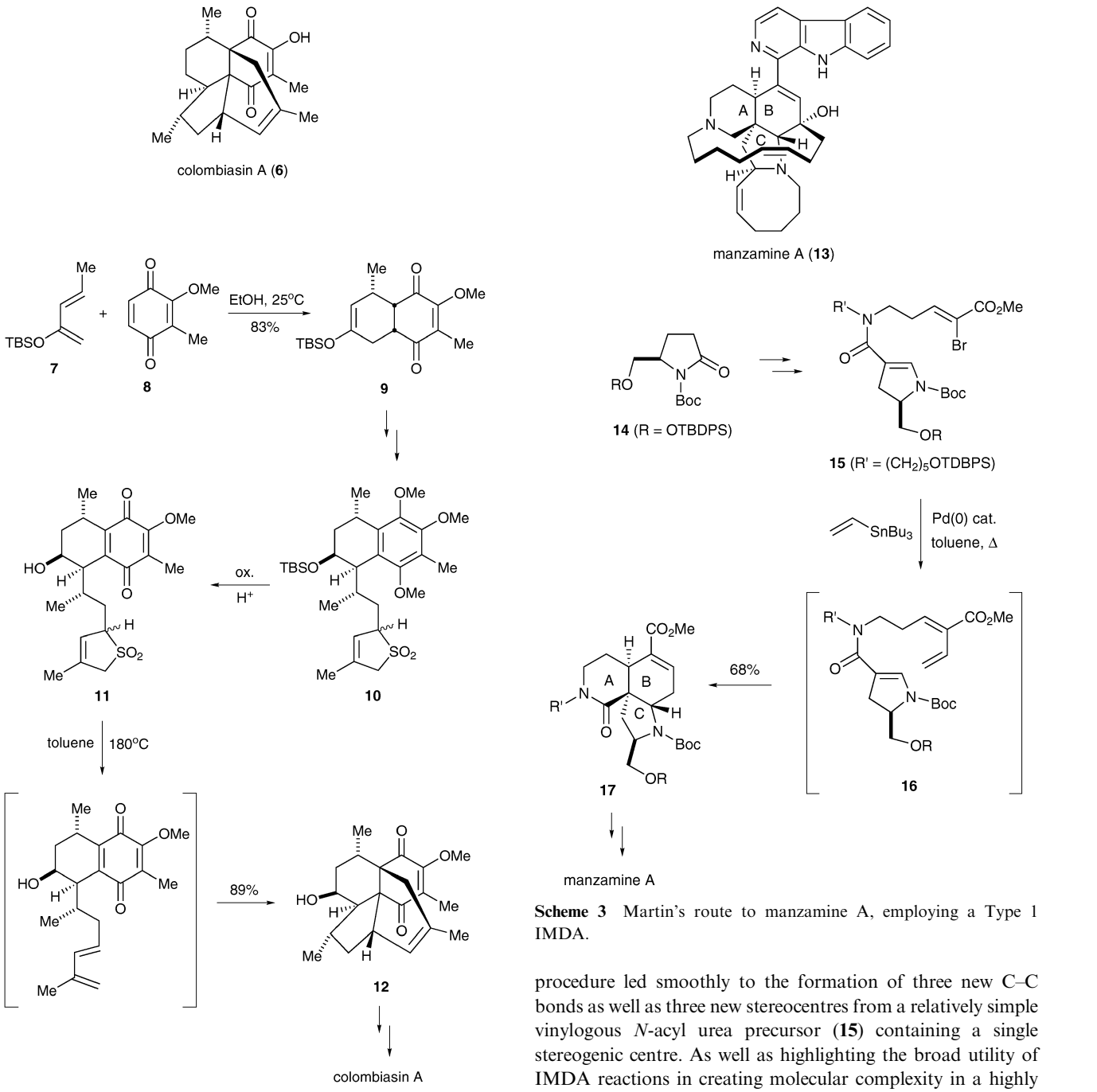

**Fig. 2** Key building blocks for the total synthesis of phomoidride B.

formation of four new contiguous stereogenic centres, the controlling element being the stereochemistry at C-12, itself the result of the use of an Evans chiral auxiliary. A further 15 operations were required to access the natural product, and this total synthesis enabled the assignment of the absolute configuration of phomoidride B.

### Total synthesis of colombiasin A

Colombiasin A (**6**) is a structurally intriguing diterpenoid natural product possessing a compact tetracyclic framework incorporating six stereogenic centres, two of which are adjacent quaternary carbons; this particular stereochemical feature presents a major challenge to modern synthetic methodology, and the Nicolaou group designed a route which relied on an IMDA to solve the problem (Scheme 2).[7] In fact, the Diels–Alder cycloaddition reaction was employed twice in the synthesis, first in its *intermolecular* form (**7** + **8** giving **9**) and then the IMDA *via* **11** to furnish **12**. This synthesis is also noteworthy for the use of a cyclic unsaturated sulfone (**11**) as a surrogate for the conjugated diene system, since the required oxidation of the aromatic unit of **10** could not be achieved without interference from the diene moiety. Upon heating, **11** ejected a molecule of $SO_2$ to unmask the conjugated diene which underwent the desired IMDA process, producing **12** in an impressive 89% yield. It should be noted that the IMDA reaction had to be run in the dark, to avoid competing photochemical [2 + 2] cycloaddition modes. With the final two (all-carbon quaternary) stereocentres in place, **12** was converted to the racemic form of colombiasin A in three more steps. Finally, repetition of the first (intermolecular) Diels–Alder reaction in the presence of a chiral catalyst yielded enantiomerically enriched material which could be used for the determination of the absolute configuration of the natural product.




**Scheme 2** Type 1 IMDA used by Nicolaou for the synthesis of colombiasin A.




**Scheme 3** Martin's route to manzamine A, employing a Type 1 IMDA.

### Enantioselective total synthesis of manzamine alkaloids

The highly unusual and complex structures of the manzamine alkaloids (*e.g.* manzamine A, **13**) coupled with their exciting biological profiles make these natural products irresistible targets for chemical synthesis (Scheme 3). In one route to manzamine A, Martin and co-workers developed a tandem sequence involving an intermolecular Stille cross-coupling in harness with an IMDA reaction to access the tricyclic ABC ring subunit (**17**) of the target molecule.[8] Once again, the IMDA rose admirably to the task, and the substrate-controlled tandem procedure led smoothly to the formation of three new C–C bonds as well as three new stereocentres from a relatively simple vinylogous *N*-acyl urea precursor (**15**) containing a single stereogenic centre. As well as highlighting the broad utility of IMDA reactions in creating molecular complexity in a highly stereoselective manner, this synthesis also underscores the advantages associated with tandem sequences, *i.e.* those in which the product of one reaction is the substrate for a subsequent one: the concentration of intermediate **16** never builds up, as it reacts as soon as it is formed, thus allowing the tricyclic product **17** to be generated in a single operation (68% overall yield) from a monocyclic precursor.

### Total synthesis of norzoanthamine

The total synthesis of the heptacyclic alkaloid norzoanthamine (**18**) by Miyashita and co-workers (Scheme 4) ranks as one of the landmarks in the field of chemical synthesis since the turn of the century.[9] At the heart of the strategy lies an IMDA reaction to set up the ABC ring system (**24**) of the target

molecule, with simultaneous formation of three contiguous stereogenic centres, two of which are quaternary. The IMDA precursor was assembled from **19** *via* a three-component coupling sequence, the dienophile being masked as a furan moiety, with an unsaturated methyl ketone as the latent diene. The dienophile was unmasked *via* a photochemical oxidation, and the diene moiety was generated by enolate formation and trapping. Heating **22** in trichlorobenzene at 240 °C led predominantly (72 : 28 ratio) to cycloadduct **23** which was formed *via* the *exo* transition state shown in Scheme 4. Cleavage of the silyl enol ether gave the crystalline intermediate **24** in 51% isolated yield. This material was taken on to the natural product, the entire synthesis requiring a total of 41 steps, with an average yield of 92% per step (3.5% overall yield).

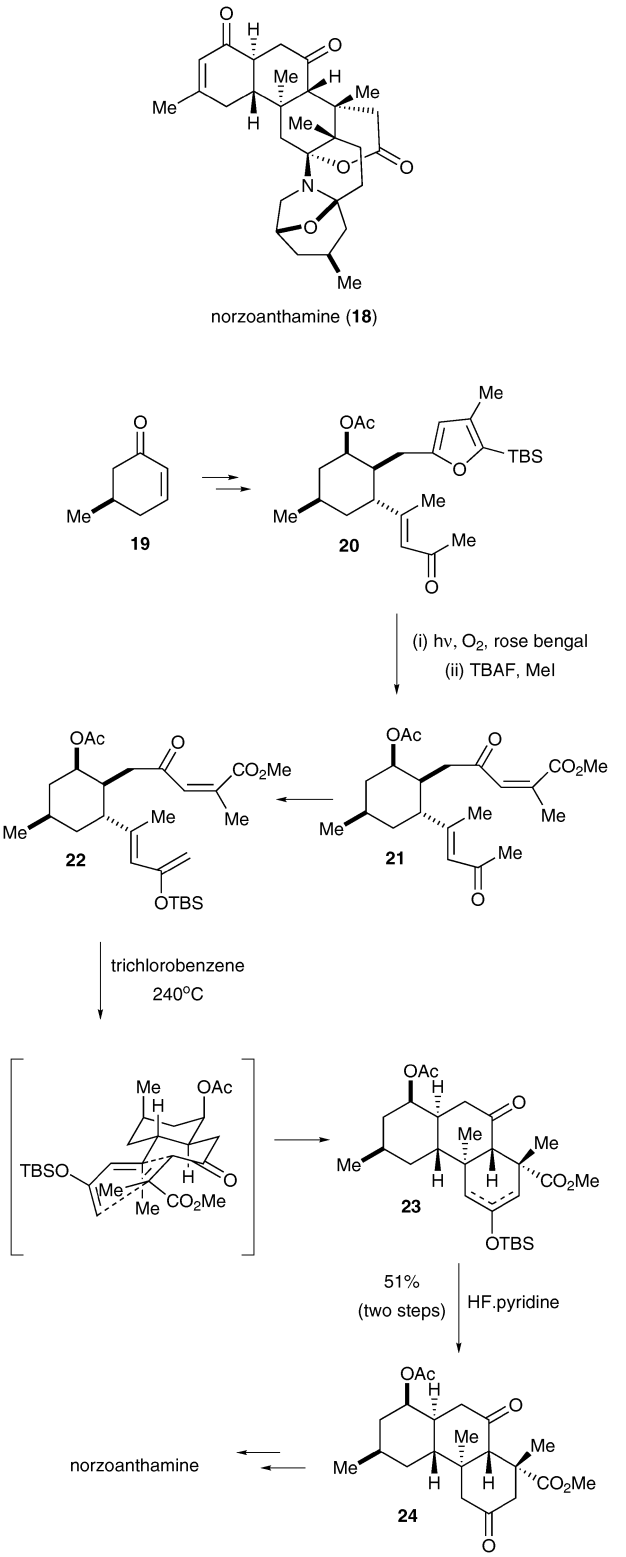
### Enantioselective macrocyclisation *via* IMDA reaction

Despite significant advances both within asymmetric catalysis and the scope and utility of the DA reaction, only limited examples of a catalytic enantioselective IMDA reaction have been reported.[10] A significant contribution to the advancement of the enantioselective DA reaction is the cationic oxazaborolidine catalysts (**24** + **25**) first introduced by Corey and co-workers in 2002 (Fig. 3).[11] The functional group tolerance and substrate scope are remarkable, the reaction mostly affording good yields and high stereoselectivity, while proceeding with predictable stereochemical outcomes in almost all cases.

In 2006 Corey and Snyder[12] pushed the boundaries of the IMDA reaction by reporting the first example of an enantioselective DA-based macrobicyclisation. The key step was embedded in the latest contribution to the long term research programme of the Corey laboratories to find efficient synthetic pathways to the dolabellane family of natural products, *e.g.* dolabellatrienone **27**, β-araneosene **28**, palominol **29**, and isoedunol **30** (Fig. 4). The retrosynthetic plan was designed such that the four congeners would arise from the same common intermediate, α,β-unsaturated ester **31**, as seen in Fig. 4. The disguised IMDA disconnection reveals itself after a retrosynthetic ring-expansion and aldehyde installation providing cyclohexene **32**. Disconnection according to the key IMDA bicyclisation affords the achiral pentaenal **33**, which arises from three readily accessible fragments, **34**, **35**, and, **36**.

The IMDA precursor **33** (Scheme 5) was accessed in ten steps from *trans–trans*-farnesol. The complexity-generating IMDA macrobicyclisation not only provides the absolute stereochemistry induced by oxazaborolidine **25**, but also sets the relative *trans* stereochemistry as well as constructing the challenging 11-membered carbocycle in [9.4.0]-bicyclopentadecatrienal **32**. There has been some debate regarding Corey's proposed transition state complexes, in which the catalyst binds to the substrate *via* a two point binding motif: the substrate's carbonyl oxygen complexing to boron and a B–O···H–C hydrogen bond as seen in Scheme 5.

Recently, Paddon-Row *et al.* provided support for Corey's proposed TS-model using density functional theory (B3LYP/6-31G(d)).[13] They found in each case examined that




**Scheme 4** Miyashita's total synthesis of norzoanthamine *via* a Type 1 IMDA.

the computational results successfully correlated with the experimental findings, both with regard to the sense of stereoinduction as well as the observed enantiomeric ratio. The IMDA reaction proceeded smoothly in 71–74% yield with

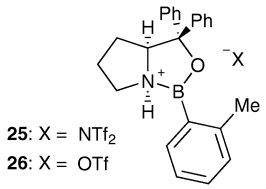



**Fig. 3** Corey's cationic oxazaborolidine catalysts for enantioselective IMDA reactions.

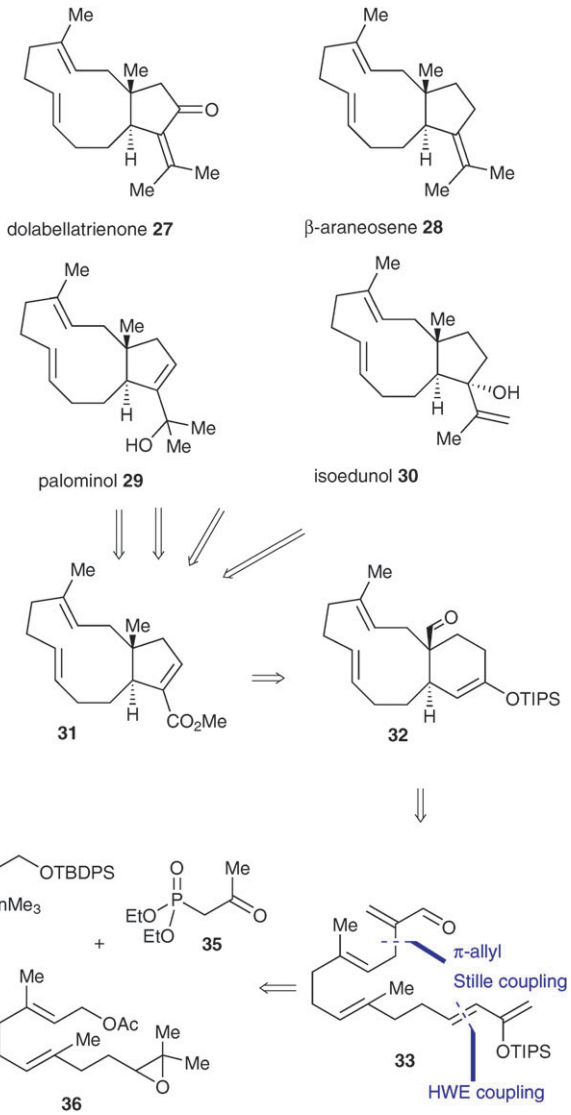
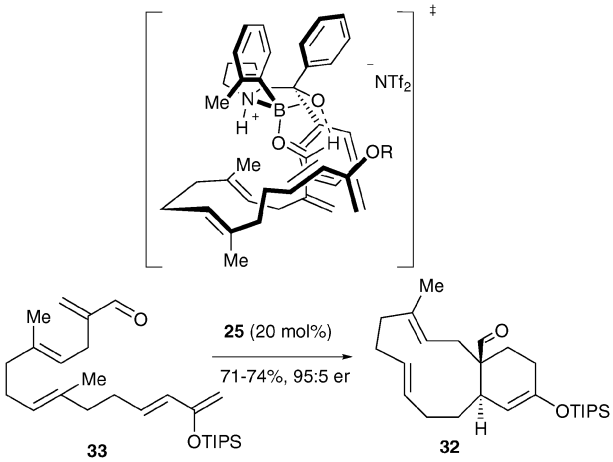



**Fig. 4** Corey's general retrosynthetic scheme for the synthesis of dolabellane natural products (HWE = Horner–Wadsworth–Emmons).

an enantiomeric ratio of 95 : 5. Interestingly, the use of simple achiral Lewis acids such as $Me_2AlCl$, $MeAlCl_2$, or $EtAlCl_2$ did *not* promote the reaction to give the racemic product, but led only to removal of the silyl protecting group and/or polymerisation. An additional five steps provided the common intermediate **31** which allowed access to four of the dolabellane family of natural products.




**Scheme 5** Enantioselective catalysis of a Type 1 IMDA in the total synthesis of dolabellanes by Corey.

## Enantioselective organocatalytic IMDA reaction

The first reports of the use of a small chiral organic molecule to mediate or catalyse an enantioselective reaction came in 1971 from two industrial research groups, using proline as the promoter.[14] The field lay essentially dormant[15] for almost 30 years, but in the last decade there has been a remarkable increase in the number of reports concerning what is now known as organocatalysis. The field of organocatalysis has had a substantial impact on organic chemistry in general, and especially within complexity-generating reactions and cascade reactions.[16] MacMillan and co-workers disclosed an elegant solution to the problem of converting an achiral triene to an enantiomerically enriched bicycle *via* an IMDA reaction.[17a] The solution consisted of using the LUMO-lowering capabilities of organocatalyst **37** or **38** depending on the starting triene used (Fig. 5) (er in the range of 88.5 : 11.5 to 97 : 3 and dr between 4 : 1 and >20 : 1).

To showcase the utility of the newly developed enantioselective organocatalytic IMDA reaction, MacMillan and co-workers used the reaction as the key step in a very short total synthesis of solanapyrone D (Scheme 6). Trienal **39** was subjected to 20 mol% of MacMillan's second generation imidazolidinone catalyst **38** along with an equimolar amount of trifluoromethane sulfonic acid as a cocatalyst. This impressive organocatalytic reaction sets all four contiguous stereocentres with respect to both relative and absolute configuration.

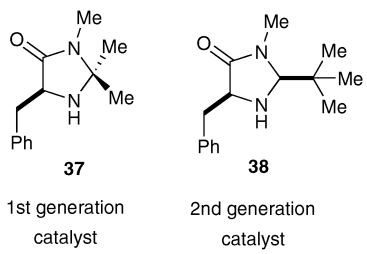
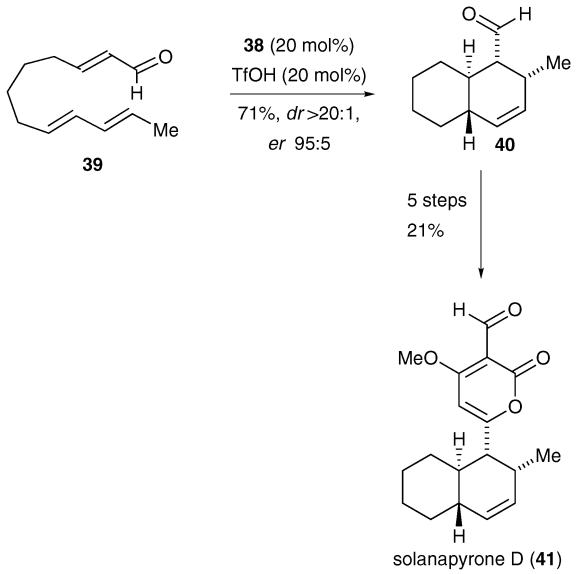


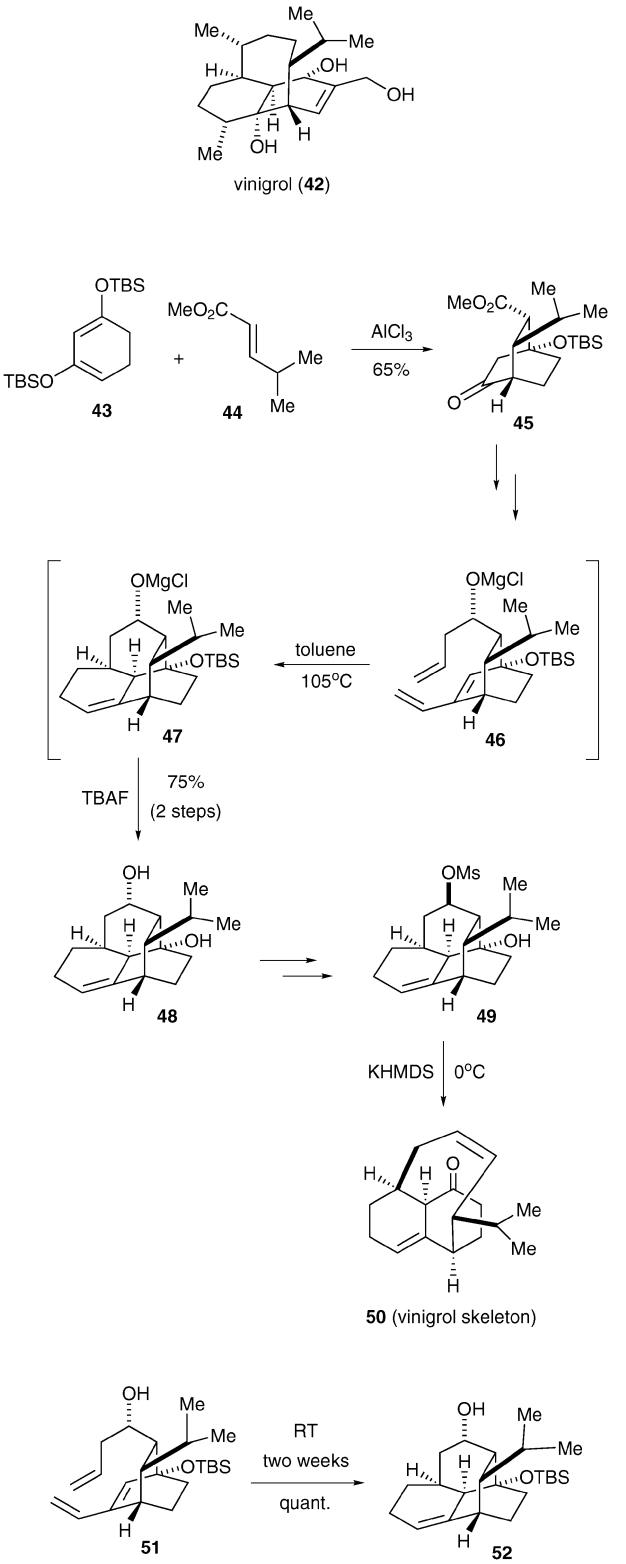

**Fig. 5** Examples of MacMillan's organocatalysts for enantioselective IMDA reactions.




**Scheme 6** Type 1 IMDA in the MacMillan organocatalytic route to solanapyrone D.

### A synthetic approach to vinigrol

Vinigrol (**42**), which contains eight stereogenic centres, is an unusual diterpene which can be viewed (*inter alia*) as a *cis*-decalin skeleton bridged by an eight-membered ring. This unique octahydro-1,5-butanonaphthalene stereochemical array has attracted much synthetic attention since the 1990s, but the molecule has yet to succumb to total synthesis. In a recent report, Baran and co-workers describe a remarkably succinct route to molecules of this type, taking advantage of an IMDA followed by a Grob fragmentation.[17b] The synthesis starts with an *intermolecular endo*-selective Diel–Alder reaction between **43** and **44** to give **45** which was elaborated to alkoxide **46**, the substrate for the IMDA process (toluene, 105 °C). This furnished, after removal of the protecting group, tetracycle **48** which was converted to **49** having the correct antiperiplanar bond arrangement for the Grob fragmentation which yielded the vinigrol-type skeleton **50** in excellent overall yield. The IMDA in this sequence is noteworthy in that neither the 4π nor the 2π component is electronically activated, but the reaction still takes place under relatively mild conditions. Indeed, the alcohol **51** corresponding to **46** undergoes the reaction *at room temperature* over two weeks (Scheme 7). This remarkable result is due to a powerful proximity effect which is highly conducive to bond formation, and the Baran synthesis provides an excellent example of the classical Woodwardian dictum: "enforced propinquity often leads on to greater intimacy".[18]




**Scheme 7** Baran's route to vinigrol, employing a Type 2 IMDA reaction.

## Recent transannular Diels–Alder reactions

Transannular Diels–Alder (TADA) reactions are an intriguing subgroup of IMDA reactions. Transannular reactions in general are often very chemo-, regio-, and stereoselective processes.[4] The same can be said about the DA reaction and combining a transannular process with the DA cycloaddition can be a powerful way of generating complexity from relatively simple starting materials (Fig. 6). The transformation can in theory generate three rings, two carbon–carbon bonds, and four stereocentres in both a relative and absolute sense, from a macrocycle. The following section will provide an overview of

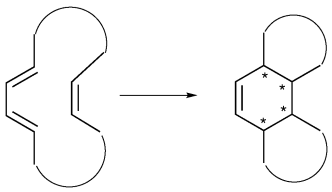


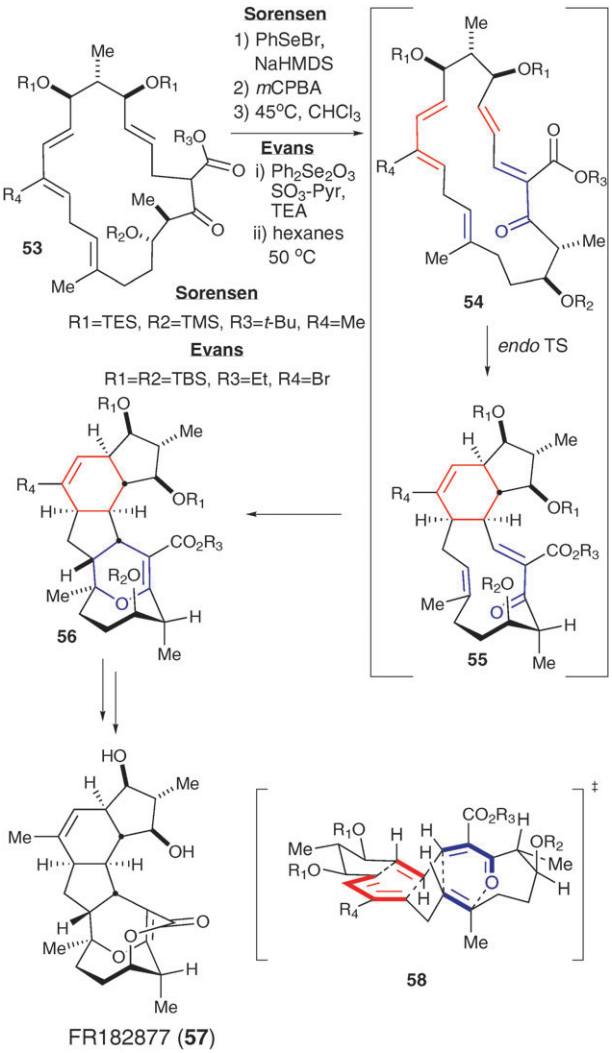
**Fig. 6** Schematic depiction of a transannular Diels–Alder (TADA) reaction.

selected examples of recent contributions to the field of TADA reactions.

### Diastereoselective transannular Diels–Alder reaction

One of the most elegant uses of the DA reaction in complex total synthesis is the cascade *double* transannular Diels–Alder (TADA) reaction used as the key step in the total synthesis of FR182877 (**57**), independently and concomitantly published by the research groups of Sorensen and Evans in 2002.[19] The two syntheses are remarkably alike, differing only in the four protecting groups and one substrate containing a methyl group *vs.* the other having a bromide at that position (Scheme 8). Both research groups utilised the same strategy to construct the hexacyclic ring system, first synthesising macrocyclic polyene **53**, then dehydrogenation using selenium chemistry. The dehydrogenation sequence afforded α,β,γ,δ-unsaturated β-ketoester **54**, which activated the normal electron demand dienophile by removal of electron density through conjugation to the β-ketoester moiety. Both Sorensen and Evans found that warming the activated macrocycle **54** resulted in the formation of pentacycle **56** in reasonable overall yields from **53**, considering the complexity of the cascade reaction sequence (Sorensen: 59%, three steps; Evans: 63%, two steps). The two total syntheses of the cytotoxic natural product FR182877 were accomplished *via* three additional manipulations in the case of the Sorensen synthesis, while the Evans group used an additional step, due to the late-stage installation of the $C_9$ methyl group *via* a Stille coupling.

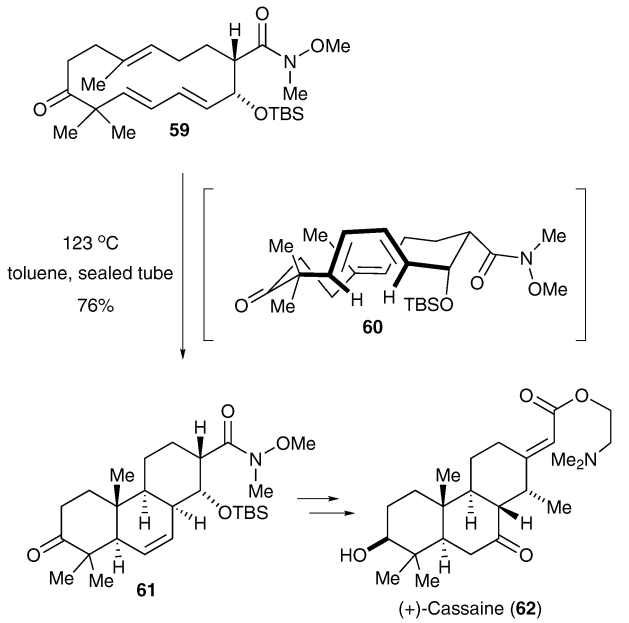
One of the pioneers within TADA chemistry is Deslongchamps, who early on recognised the potential of the TADA reaction: "The complexity and power of the TADA strategy arises from the judicious choice of substituents that will govern the conformation adopted by the macrocycle at the transition state level, *via* transannular steric repulsion and electronic interactions."[4] The Deslongchamps laboratories recently reported the completion of the total synthesis of (+)-cassaine (**62**), a non-steroidal inhibitor of the $Na^+$, $K^+$-ATPase, *via* a transannular strategy.[20] After an efficient synthesis of macrocycle **59**, the crucial TADA reaction was at hand. The two stereocentres present in macrocycle **59** nicely controlled the stereochemical outcome of the TADA reaction, affording only the desired *trans*–anti-*cis*-perhydrophenanthrene tricycle **61** in 76% yield by heating the macrocycle to 123 °C in toluene in a sealed tube (Scheme 9). A possible transition state is shown in Scheme 9. The two original stereocentres are used to set four new ones in the critical TADA reaction, three of which were of the correct configuration, while the fourth centre was epimerised at a later stage in order to arrive at (+)-cassaine.




**Scheme 8** TADA reaction used by both Sorensen and Evans in the total synthesis of FR182877.

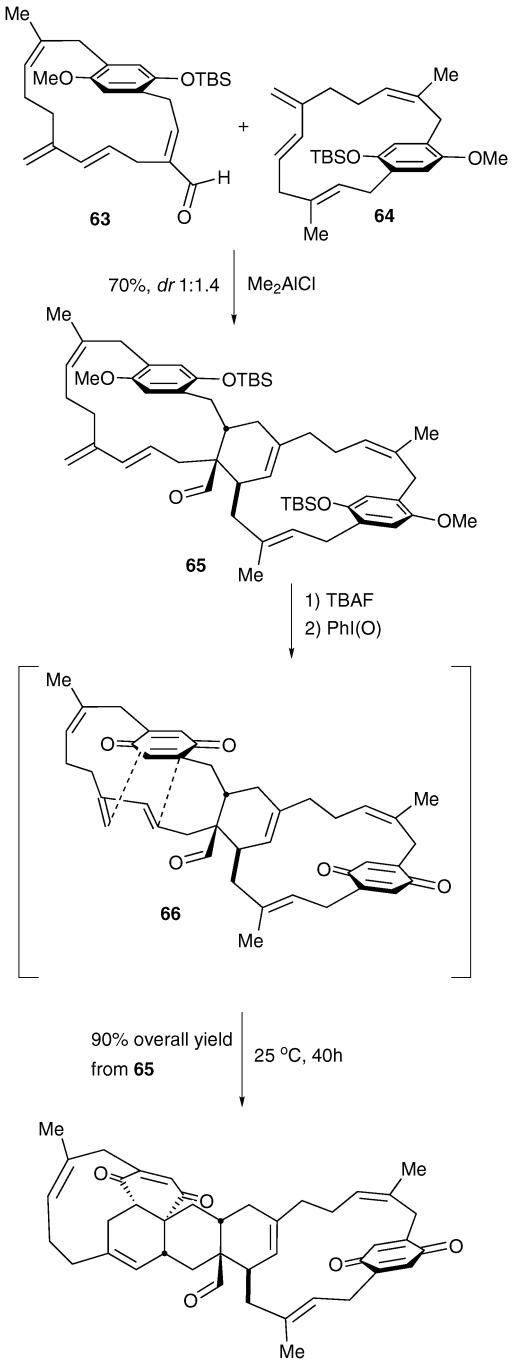
### Biomimetic transannular Diels–Alder reaction

An interesting biomimetic proposal for Nature's synthesis of the unusual heptacyclic topology of longithorone A (**67**) was suggested by its discoverers, Schmitz and co-workers, in 1994.[21] The idea relied on the merger of two very similar [12]-paracyclophanes through an *endo*-selective intermolecular DA reaction, followed by a TADA reaction between a quinone, serving as the dienophile, and a diene. Several clues to the viability of the proposal were at hand. First of all was the isolation of longithorone B, a [12]-paracyclophane structurally similar to the ones proposed by Schmitz to participate in the intermolecular DA reaction. Secondly, the isolation of longithorone I, what could be called a [12]-cyclophane dimer or DA adduct was also isolated, which did not contain the diene moiety, seen in **65**, and could therefore not participate in the TADA reaction. Further support for the biomimetic hypothesis came in 2002 when the research group of Shair reported an enantioselective total synthesis based on these same DA reactions.[22] These researchers designed and executed a concise synthesis of the




**Scheme 9** The Deslongchamps total synthesis of cassaine, *via* a TADA reaction.

two non-trivial atropisomerically pure cyclophanes **63** and **64**. The first intermolecular DA reaction was promoted by Lewis acid activation using dimethylaluminium chloride ($Me_2AlCl$) and proceeded in 70% yield as a 1 : 1.4 mixture of diastereomers, in which the minor product was the desired isomer. The reaction was completely *endo* selective, the lack of diastereomeric control being due to poor facial selectivity. (The disappointing diastereomeric substrate control, as well as the need for Lewis acid activation, could indicate the involvement of a Diels–Alderase enzyme in Nature to promote the reaction and control the stereochemical outcome by fixation of the substrate in the active site.) Subsequent removal of the *tert*-butyldimethylsilyl groups and oxidation state adjustment afforded bisquinone **66**. Pleasingly, it was found that the activated bisquinone **66** underwent the desired TADA reaction upon standing at room temperature for 40 h without any additives in an impressive 90% overall yield from **65**, thereby completing the first total synthesis of longithorone A (Scheme 10).

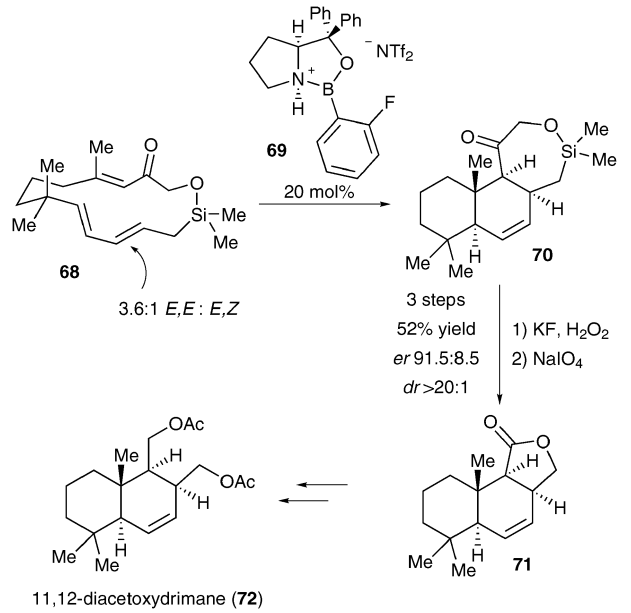



**Scheme 10** Shair's route to longithorone, with TADA as a key step.

## Enantioselective transannular Diels–Alder reactions

The field of TADA chemistry is constantly expanding and many recent innovative and elegant contributions within diastereoselective transannular cyclisations have been reported, as can be seen in the highlighted examples in the previous sections. A novel contribution to the field was provided by Jacobsen and Balskus in their report disclosing their solution to the challenge of performing enantioselective TADA reactions.[23] After extensive screening, Corey's cationic proline-derived oxazaborolidine catalyst **69**, shown in Scheme 11, was found to promote the TADA event, with a variety of macrolactones and macrocyclic ketones with good er (92.5 : 7.5–96 : 4) and dr (5 : 1–>19 : 1) values, as well as reasonable yields across the board. As is often the case, the usefulness of the developed strategy was demonstrated by incorporating the catalytic enantioselective TADA as the key step in a total synthesis. The sesquiterpene natural product 11,12-diacetoxydrimane (**72**) was chosen as the target structure. The silicon-containing TADA precursor **68** was accessed *via* eight synthetic transformations, but unfortunately, the diene-configuration was isolated with an *E*,*E*/*E*,*Z*-ratio of only 3.6 : 1 (Scheme 11). Exposure of macrocycle **68** to oxazaborolidine catalyst **69** resulted in full conversion of the *E*,*E*-isomer to afford the TADA product in greater than 20 : 1 dr. A possible transition state is shown in Fig. 7. The




**Scheme 11** Jacobsen's TADA reaction involving enantioselective catalysis for the synthesis of 11,12-diacetoxydrimane.

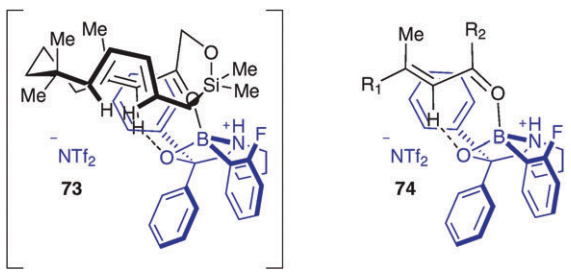
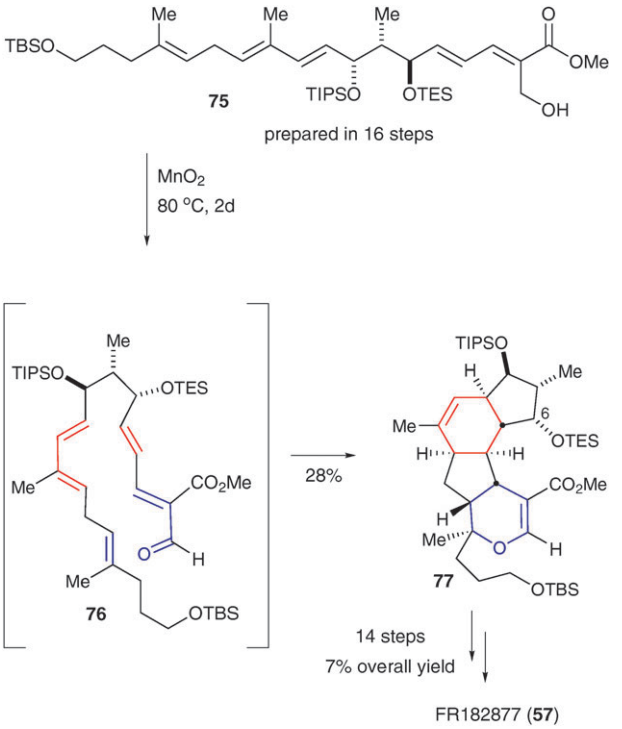



**Fig. 7** Proposed transition state for the enantioselective formation of **70** (Scheme 11).

enantiomeric ratio was determined after two subsequent manipulations. The crude product of the TADA reaction was subjected to a Tamao-oxidation and subsequent oxidative cleavage to arrive at tricyclic lactone **71** in 52% overall yield for the three step sequence. The enantiomeric ratio was determined at this point to be 91.5 : 8.5. As can be seen from the proposed transition state model, the controlling element for this cationic oxazaborolidine catalyst is a two point binding motif to the dienophile, one between the carbonyl oxygen and boron and the other between the oxazaborolidine oxygen and the dienophiles hydrogen attached to the $sp^2$-hybridised carbon α to the carbonyl.[24] The synthesis of 11,12-diacetoxydrimane was then completed *via* three straightforward transformations.

## Comparing the IMDA and TADA approaches in the total synthesis of natural products: FR182877 revisited

The structural complexity of the bioactive secondary metabolite, FR182877 (**57**, see Scheme 8), allows for a wide diversity in synthetic approaches for its construction. Very recently,




**Scheme 12** Cascade sequence of IMDA reactions used by Nakada for the total synthesis of FR182877.

Nakada and co-workers reported a cascade sequence comprising an IMDA and an intramolecular hetero-Diels–Alder (IMHDA) reaction as the key step.[25]

Nakada and co-workers prepared alcohol **75** in 16 steps and purposely incorporated the wrong stereochemistry at C6, as shown in Scheme 12. The stereochemistry shown was crucial in achieving the correct stereoisomer in the IMDA reaction.[26] In order to promote the cascade reaction sequence alcohol **75** was oxidised to the corresponding aldehyde (**76**) using manganese oxide at elevated temperature. Under these conditions aldehyde **76** underwent a thermal cascade IMDA–IMHDA reaction sequence to afford **77** in 28% yield as a single diastereomer. This impressive transformation generated no less than seven stereocentres as well as three carbon–carbon bonds, and one carbon–oxygen bond in a single operation. The synthesis was completed *via* an additional fourteen steps, two of which were used to correct the stereochemistry at C6. The total number of steps for Nakada's synthesis of FR182877 (**57**) was 31, which can be compared to the Sorensen (22 steps) and Evans (19 steps) approaches. The step-count notwithstanding, all three syntheses testify to the extraordinary puissance of the Diels–Alder reaction in the "one-pot" generation of molecular complexity.

## Conclusions

Since the initial disclosure in 1928, the Diels–Alder reaction has continued to thrive and to pique the imagination of synthetic chemists engaged in the assembly of complex molecular structures, in particular biologically significant natural products. As is hopefully obvious from the small selection of examples presented above, the IMDA and TADA versions of this

exquisite cycloaddition process provide rich opportunities for the rapid and selective generation of molecular complexity.

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