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The transannular Diels–Alder strategy: applications to total synthesis

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1. Introduction

Transannular processes are among the most impressive transformation types in organic synthesis. They can be employed to generate a high degree of complexity with spectacular selectivity, including an entire array of chemo-, regio- and diastereoselectivities, as the result of conformational restrictions paralleled with entropic activation arising from the macrocyclic environment. Futhermore, the Diels–Alder reaction is regarded[1] as one of the most efficient reactions in terms of atom economy and broad versatility. Indeed, it is particularly well suited for transannular processes, requiring only heat for activation. Its rate can be tuned with catalysts, solvent effects, or pressure. When these features are coupled in the transannular Diels–Alder (TADA) reaction,[2] an impressive outcome is anticipated. When applied to an (m+n+2)-membered cyclotriene substrate (Fig. 1), it will generate an A.B.C [m.6.n] tricycle possessing up to four new stereogenic centers with the simultaneous formation of a central double bond.

Enthalpic and entropic activation from the macrocyclic environment allow the application of the TADA process

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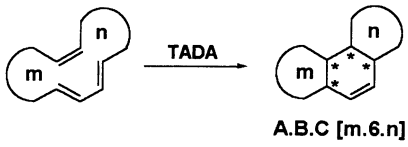

Figure 1.

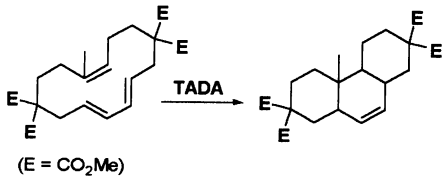

Figure 2.

to tetrasubstituted dienophiles[3] without activation and alkyne dienophiles,[4] as well as terminally substituted dienes,[5] to afford highly functionalized tricycles. These coupling partners are often not well tolerated in intermolecular or other intramolecular settings.[6,7] Moreover, the macrocyclic environment can enforce a high level of stereofacial control arising from conformational restrictions.

In Table 1, the eight possible geometrical isomers of the Diels–Alder precursors and the corresponding relative stereochemistries of the resulting cycloadducts are predicted, arranged from intermolecular to intramolecular to transannular settings. Included also are the results of a TADA model study conducted on a full set of 14-membered macrocycles according to Fig. 2.[8] This study provided the opportunity to make several noteworthy observations:

(1) The results are in good agreement with the predictions. (2) Although CC dienes (entries 3 and 7) are not compatible with the Diels–Alder reaction in general,[9] CT and TC dienes (entries 1, 5 and 2, 6, respectively) can be applied efficiently in the TADA reaction, in contrast to their inter- and intramolecular counterparts. (3) TT dienes (entries 4 and 8) are particularly reactive as they can reach the prerequisite *s-cisoid* geometry easily. (4) TAT tricycles cannot be prepared directly by the TADA reaction. However, this approach is complemented by the tandem cationic[10] and radical[11] polycyclizations where TAT tricycles are the major products (nevertheless, TAT tricycles can be obtained indirectly from the TADA reaction as already demonstrated,[12] by thermodynamic epimerization of a ring junction). (5) A high degree of facial selectivity can be expected. Even in those cases where the TADA reaction can provide a mixture of isomers, a relatively small methyl group on the dienophile is sufficient to induce a partial (entry 4) or full (entry 8) control (in the latter case, the malonates also play a crucial role in orienting the transition state; see Section 4.2).

It follows that, with appropriately located asymmetric centers, high diastereofacial control can also be achieved. In principle, with an orchestrated accord of double bond stereochemistry and steric, as well as electronic influences, limitless numbers of highly functionalized chiral polycycles are within reach. *Thus, the complexity and power of the TADA strategy arises from a 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.* An accurate analysis of the possible transition states will allow the one-step formation of a tricycle possessing four controlled stereogenic centers from a trienic macrocycle.

Furthermore, the special nature of the TADA reaction predestines it to be used as a mechanistic probe for the Diels–Alder reaction itself.[13] Moreover, as an additional benefit, the unsaturations along the chain will facilitate the macrocyclization of the TADA substrate by decreasing the conformational freedom, while partially eliminating the transannular steric repulsions. However, like all

Table 1.

Entry	Triene geometry[a]	Diels–Alder geometry[b]			Transannular experimental[c]	t (°C)
		Prediction				
		Intermolecular	Intramolecular	Transannular		
1	CTT	CAC+TAT	CAC	CAC	√	300
2	TCT	CAC+TAT	CAC+TAT	CAC	√	350
3	CCT	CAT+TAC	CAT	–	Rearr.[d]	300
4	TTT	CAT+TAC	CAT+TAC	CAT+TAC	1:2[e]	<80[f]
5	CTC	CSC+TSC	CST	CST	√	300
6	TCC	CSC+TSC	CST+TSC	TSC	√	300
7	CCC	CSC+TST	CSC	CSC	Rearr.[d]	365
8	TTC	CSC+TST	CSC+TST	CSC+TST	TST	<80[f]

[a] *cis* (C) or *trans* (T) refer to unsaturations 1–3 in the order depicted in the scheme.
[b] *cis* (C), *trans* (T), *anti* (A) and *syn* (S) in the order depicted in the scheme.
[c] Corresponding to the full set of TADA reactions shown in Fig. 2.
[d] Rearrangement, primarily by 1,5 H-shifts, resulting in a mixture of TADA products.
[e] Ratio of CAT and TAC tricycles.
[f] TADA reaction under macrocyclization conditions.

transannular processes, for the TADA reaction to reach its full potential depends upon the availability of the requisite macrocycles. Although the macrocyclization occasionally remains a limiting factor, contributions from the flourishing field of the total synthesis of macrocyclic natural products continuously offer an ever increasing variety of new macrocyclization methods.[14]

As a result, the TADA reaction has the potential to rapidly establish its position among the synthetic tools for the construction of polycyclic frameworks. In this report, applications of the TADA reaction to the total synthesis of polycyclic products are reviewed with a literature background search conducted in August 2000.

We chose to group the applications of the TADA strategy according to triene geometry, since this geometry determines the relative stereochemistry of the newly formed tricycles. Inside each section, subsections are dedicated to a single synthetic target. Only the TADA reactions performed within the frame of a specific total synthesis are detailed in this document. Although a succinct retrosynthetic analysis outlining the major bond forming steps of the macrocycles is indicated, our primary concerns are the issue of the TADA reaction, and the identification of key stereocontrol elements that orient the transition state towards the observed product(s).

2. TADA Reactions of *trans-trans-trans* (TTT) trienes

Medium-sized (10- to 14-membered) macrocycles are relatively difficult to prepare, both for entropic and enthalpic reasons.[15] Consequently, macrocyclic trienes containing three *trans* unsaturations, which add strain to the system, were long considered very difficult to reach. Recently, however, new methods involving β-ketoester alkylation,[16] Stille coupling,[17] ring-contraction methodology,[18] and ring-closing metathesis[19] have been used successfully to macrocyclize TTT trienes.

On the other hand, the TADA step itself usually involves a low activation energy, with the reaction occurring at temperatures typically between rt and 120°C in the TTT series, even when the dienophile is not activated. This low activation energy is readily explained by the observation that the TT diene easily adopts the *s-cisoid* geometry. Difficulty lies in the fact that two isomers (i.e. CAT and TAC tricycles; see Table 1, entry 4) are accessible from TTT trienes. Moreover, having a stereogenic center on the macrocycle doubles the number of possible products to four. In Fig. 3, the four possible chair–boat–chair transition states **2**–**5**[20,21] are depicted (other conformations are also possible, depending upon the substitution pattern on the macrocycle, e.g. chair–boat–boat,[22] etc.), as well as the corresponding TADA adducts **6**–**9**.

As indicated in Table 1 (entry 4), the presence of a methyl group on the dienophile creates a sufficient steric bias to give some advantage to the TAC cycloadduct, but does not allow a complete discrimination between the TAC and the CAT tricycles. Thus, before considering this strategy, a careful examination of the possible transition states is necessary, with the knowledge that substituent R_1 is able to bring a preference for one or the other transition state, assuming the pseudo-axial (**2** and **5**) or pseudo-equatorial (**3** and **4**) orientation.

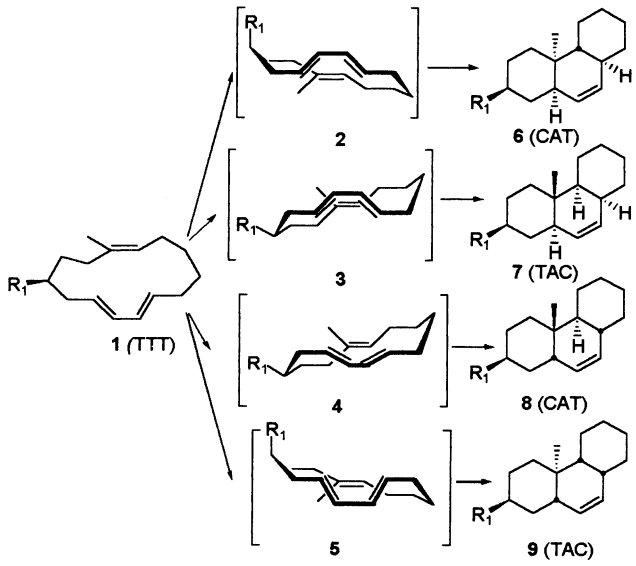

Figure 3.

2.1. Enantioselective total synthesis of (−)-oblongolide

A few studies directly compare the intramolecular Diels–Alder (IMDA) and TADA strategies for the synthesis of polycyclic products. In their enantioselective total synthesis of the boring/feeding deterrent oblongolide (**10**, Fig. 4),[23] Shing and Yang approached the tricyclic lactone via both ways, i.e. from acyclic ester **12** and 13-membered lactone **11**, respectively,[24] which were synthesized from (−)-citronellol.

The result of the IMDA reaction on acyclic triene **12** (Fig. 5) was a mixture of oblongolide **10** (from subsequent in situ lactonization) possessing the desired TAC stereochemistry, and bicycle **13** with the opposite CAT stereochemistry (ratio 2:1), arising from *endo* and *exo* transition states respectively. In this case, steric interactions counterbalanced secondary orbital interactions in the transition state.[25] Leaving the reaction mixture at 210°C for an extended period of time (76 h) smoothly converted **13** into the thermodynamically more stable oblongolide **10**, providing evidence for the reversibility of this IMDA process.

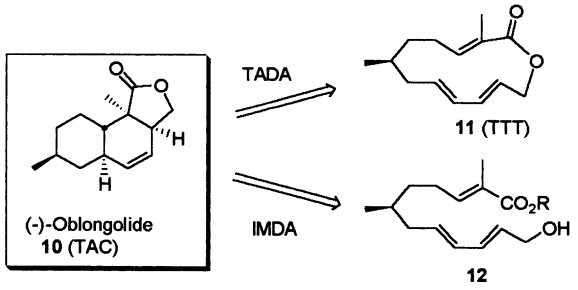

Figure 4.

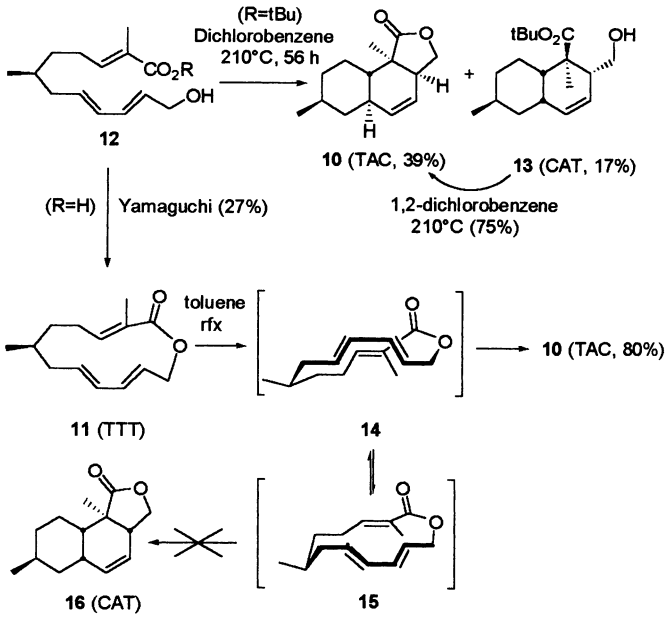

Figure 5.

In comparison, the authors managed to perform a difficult macrocyclization via the Yamaguchi procedure[26] to yield the TTT 13-membered lactone **11** (in a reasonable 27% yield given the high level of difficulty). They subsequently showed that the cyclic triene undergoes the TADA reaction at lower temperature and more selectively than its acyclic counterpart, leading only to natural oblongolide **10** in 80% yield. The desired TAC tricycle was produced selectively, while the alternative CAT isomer **16** was not formed.

The observed selectivity[24] arises primarily from three factors: firstly, the pseudo-equatorial orientation of the methyl group controls the diastereoselectivity via a chair-like conformation of ring A in transition state **14**; secondly, there is an unfavorable interaction between the diene and the methyl group on the dienophile in the competing transition state **15**; and finally, there is a preference for *endo* transition state **14**. All of these factors add up to strongly favor transition state **14**, leading exclusively to the natural product.

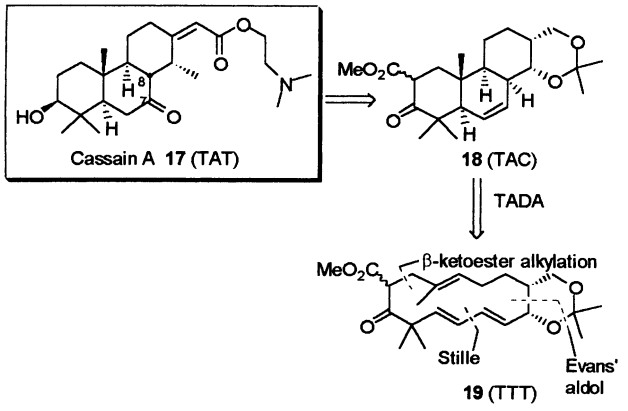

Figure 6.

2.2. Enantioselective synthesis of the cassain A skeleton

In their enantioselective approach to the cardioactive alkaloid cassain A[27] (**17**, Fig. 6), Deslongchamps et al.[16] found the right stereochemical factors to control the strategic TADA step, while significantly increasing the convergence of the strategy via proper connection of three building blocks. They approached the target via TAC tetracycle **18**, itself the result of a TADA reaction on TTT trienic macrocycle **19**.

The TADA step at 90°C provided selectively the desired TAC tetracycle **18** in 83% yield (Fig. 7), presumably via boat–boat–chair transition state **20**. The two substituents at C13 and C14 oriented **19** towards the desired conformation. At slightly higher temperature (125°C), this substituent effect was not sufficient and a mixture of TAC and CAT products **18** and **22** was obtained (ratio 72:20, **18** being more than 50% decarboxylated and **22** being completely decarboxylated), revealing a small energy difference between competing transition states **20** and **21**. Similarly to previous studies, they showed that when the substituents

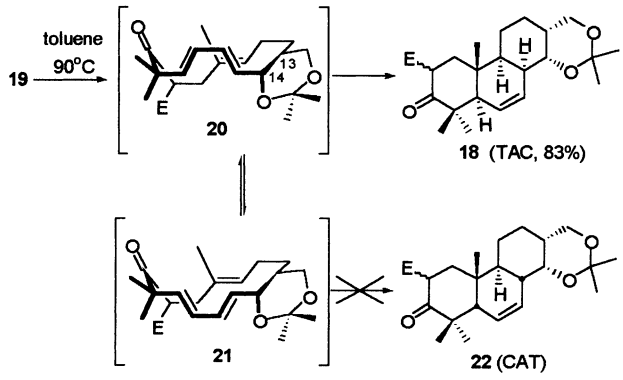

Figure 7.

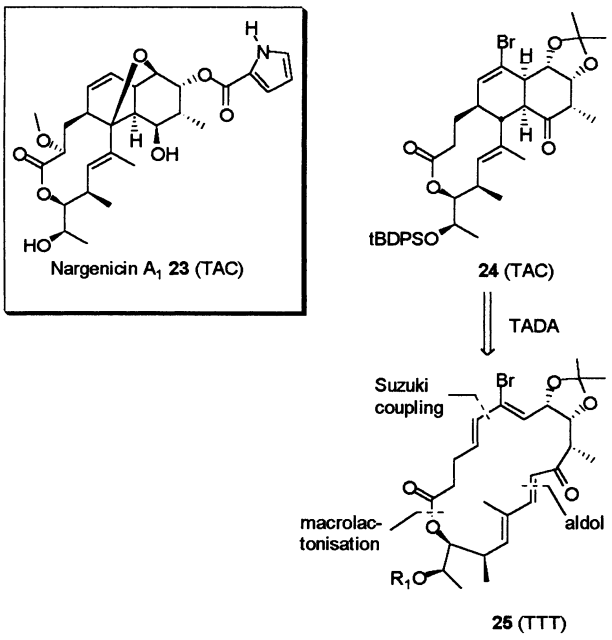

Figure 8.

at C13 and C14 were in the *anti* orientation, no stereocontrol was observed and a mixture of CAT and TAC tricycles was obtained.[28] Further functionalization involved decarboxylation, followed by ketone reduction at C4 to the desired β-alcohol. Oxidative functionalization at C7 and subsequent epimerization at C8 to the thermodynamically more stable TAT geometry should afford the target skeleton en route towards cassain A.

2.3. Synthesis of the nargenicin A1 skeleton

The conformational behavior of large rings is difficult to predict owing to the increased number of degrees of freedom to be considered. In their approach to the [10.6.6] tricyclic structure of the antibiotic nargenicin A1 (**23**, Fig. 8),[29] Roush et al. had to analyze very carefully the possible conformations of 18-membered tetraenic lactone **25**.[30] On the one hand, a larger ring is in principle an easier candidate for macrocyclization; on the other hand its conformations are difficult to analyze and may result in several TADA adducts, particularly in the TTT series. The authors boldly considered model [10.6.6] TAC tricycle **24** to be within reach from macrolactone **25** via a TADA reaction. The latter was constructed from three main fragments, with a macrolactonization to close the large ring.

When tetraene **26** (R_2=H, R_3=$COC_6H_2Cl_3$) was submitted to macrolactonization conditions (DMAP, toluene, 100°C), no macrolactone **25** was isolated (Fig. 9). Instead, the TADA adduct **24** was directly obtained, with the desired TAC stereochemistry (plus a small amount of its C10 epimer) in an overall 79% yield. The selectivity of the TADA reaction was predicted through a careful examination of the possible transition states. As commonly observed with TTT trienes, the TADA reaction occurred during the macrocyclization. However, four diastereomeric tetracycles were theoretically accessible.

In order to orient the transition state towards the requisite TAC configuration (transition state **27**), the authors made use of a bromine substituent at C6 on the diene.[31] This extra substituent prefers the β orientation (*syn* with respect to the C8 proton), a situation preferable to the bromine being oriented α and *syn* to the bulkier C8–C9 acetonide. Additionally, in transition state **27**, C5(H) does not interact with C2(H) as would be the case with the bromine possessing the α orientation. Moreover, the proton at C16 is eclipsed with the C14–C15 unsaturation, a situation preferable to the C16 methyl group eclipsing the unsaturation and creating a severe allylic strain. The C16 methyl group has the additional benefit of being in the pseudo-equatorial orientation. Based on this thorough analysis,[30] Roush et al. deduced transition state **27** to be favored, a hypothesis fully corroborated by experience. Tricycle **24** and its C10 epimer were obtained as the sole products in a combined 79% yield.

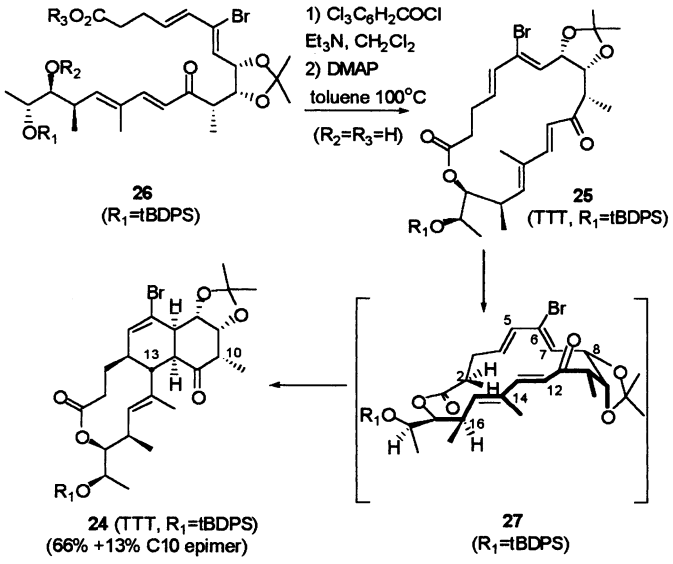

Figure 9.

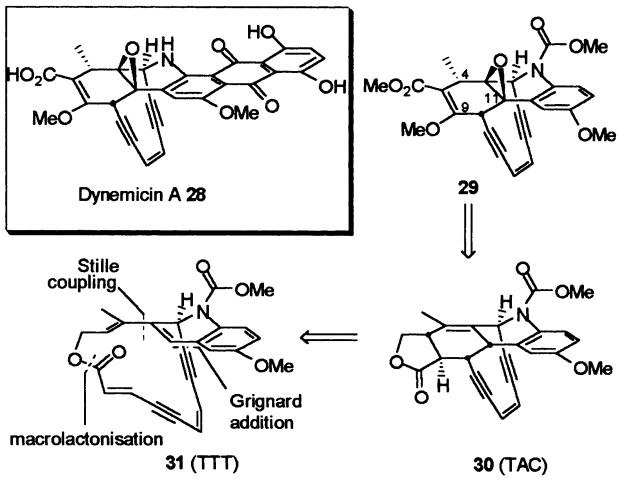

Figure 10.

Interestingly, the authors compared the TADA reaction with its intramolecular counterpart, and performed the cycloaddition on acyclic triene **26** (R_2=TES, R_3=Bn). The outcome of the cycloaddition was dramatically different, resulting in a 2:1 mixture of undesired CAT and desired TAC adducts, respectively, showing a superior stereocontrol with the TADA approach.[30] The same authors report other attempts to synthesize the desired skeleton via IMDA reaction, resulting in an opposite sense of stereochemistry.[32] Further effort aiming at the introduction of the oxygen atom at C13 did not allow for the desired transformation.[30]

2.4. Synthesis of the enediyne-bridged tricylic core of dynemicin A

The enediyne antibiotics have been the subject of intense research efforts, owing both to their exceptional biological properties and particularly intriguing structures.[33] Schreiber et al. approached the enediyne-bridged tricyclic core **29** of dynemicin A **28** via the TADA strategy (Fig. 10).[34] The first key step in the formation of the tricyclic core relied on the tandem macrolactonization–TADA reaction of TTT trienic macrolactone **31**, followed by subsequent elaboration of cycloadduct **30**.

It is noteworthy that the TADA cycloaddition occurred in situ at ambient temperature during the macrolactonization step (Fig. 11), revealing the very close proximity between the diene and the dienophile. The stereochemical outcome of the cycloaddition is readily explained by considering transition state **33**. The diene is embedded into the dihydroquinoline system and therefore has a fixed orientation with respect to the enediyne moiety, and shows an excellent alignment and proximity with the dienophile. This translates into a very low activation energy for the cycloaddition. Also, in this very rigid structure, the dienophile can either have the orientation shown on **33** or be perpendicular to the diene, which is unproductive. For this reason, the CAT stereochemistry in the cycloadduct is out of reach, and the exclusive product of the TADA reaction is TAC adduct **30**. The overall yield for the tandem macrolactonization–TADA steps was 51%. It should be noted that no IMDA reaction on acyclic triene **32** (R_1=TBS, R_2=Me) occurred up to 180°C, and decomposition was observed at higher temperatures. This observation emphasizes the importance of transannular activation.

The authors further secured the stereochemistry of the C4 methyl group (see **29**, Fig. 10) via epimerization at C9, benzylic oxidation, formation of a diazene at the C11 position, then stereospecific [1,5] sigmatropic rearrangement of the diazene to introduce the desired stereochemistry at C4.[34]

2.5. Synthesis of 5β-steroids

In their synthesis of the steroid skeleton **34** (Fig. 12), Takahashi et al.[35] made use of the TADA reaction on TTT macrocyclic triene **35**, giving the CATAT skeleton **34**. The TADA step could in principle have resulted in four products (see Fig. 13).

Examination of the transition states reveals that only two are accessible, namely **36** and **37**, each leading to a different product. The two other possible transition states would correspond to the methyl group on the dienophile adopting the α-orientation, which would confer onto ring C a boat conformation and a strong flagpole interaction with the

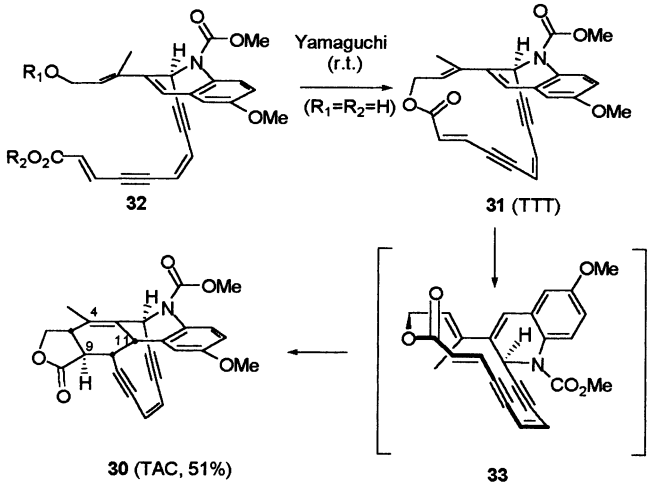

Figure 11.

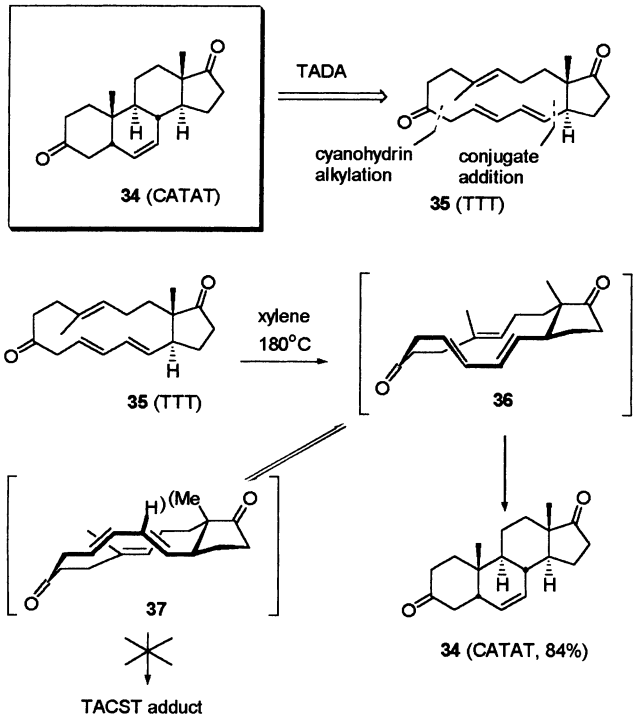

Figure 12.

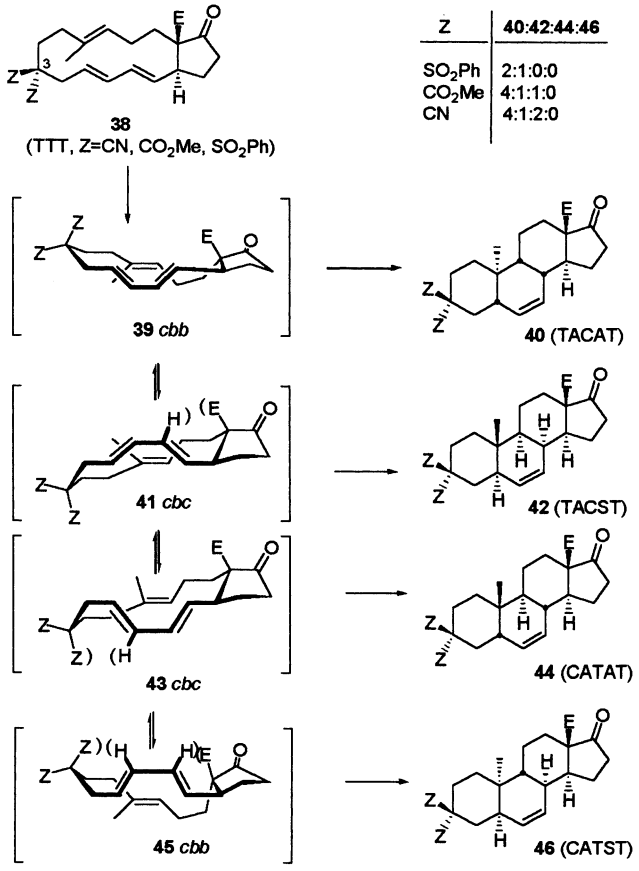

Figure 13.

methyl group on ring D (see **39** and **45** in Fig. 13, E=Me). Transition state **36** is favored over **37**, the latter suffering from a steric interaction between the diene and the tertiary methyl group. The outcome of the TADA reaction at 180°C was, indeed, exclusively CATAT tetracycle **34** (84% yield).

In order to illustrate the fundamental role played by substituents on the TADA reaction, it is relevant to compare these results to a contrasting study (Fig. 13).[36] The influence of the C3 substituents on the outcome of the TADA reaction on TTT trienic macrocycle **38** was studied, leading to the conclusion that the malonate moiety at C3 orients the TADA step in a completely different way than that observed by Takahashi et al. Indeed, with a large Z group ($Z=SO_2Ph$), two products were obtained: TACAT tetracycle **40** and TACST **42** (ratio of 2:1). In these cases, the axial Z group consistently preferred to adopt the *anti* orientation with respect to the diene (transition states **39** and **41**). With smaller Z groups ($Z=CO_2Me$ or CN), increasing proportions of the CATAT adduct **44** (from transition state **43**) were observed, as a result of the decreasing interaction between the Z group and the diene, agreeing with the observations of Takahashi et al. and ab initio calculations (see also Section 5.4).[35] The last transition state **45** suffers from two steric interactions and is not accessible. Once

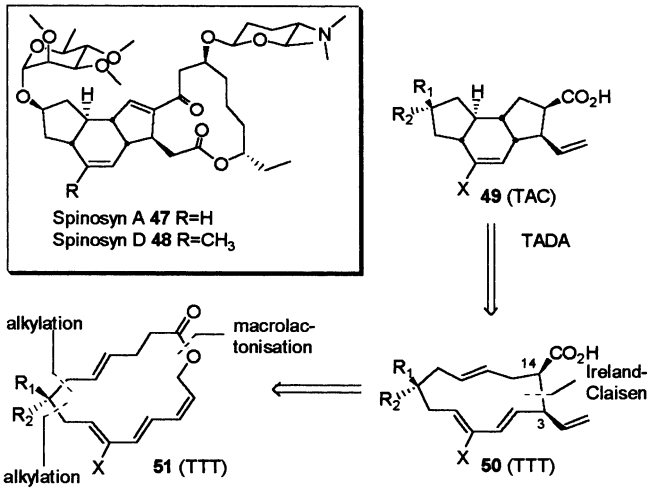

Figure 14.

again, it is clear from this comparison that substituent effects and transannular repulsions play a fundamental role in orienting the reaction towards the preferred product.

2.6. Synthesis of the decahydroindacene skeleton

The synthesis of 11- and 12-membered TTT macrocyclic trienes is extremely difficult by direct cyclization methods, as evidenced by several authors.[37] In their approach towards the decahydroindacene ring system found in (−)-spinosyns A and D (**47** and **48**)[38] as well as ikarugamycin and capsimycin,[39] Roush et al. circumvented the problem via a ring contraction methodology (Fig. 14).[18] Their approach relies on the formation of macrocyclic lactone **51**, which subsequently undergoes an Ireland–Claisen rearrangement to give the highly strained TTT 12-membered ring **50**. The latter was supposed to undergo a TADA reaction to give the desired TAC [5.6.5] ring system **49** found in these natural products.

Experimentally (Fig. 15), the authors proved the concept on a model system (**51**, $X=R_1=R_2=H$).[40] Accordingly, Ireland–Claisen rearrangement indeed occurred to give the desired 12-membered macrocyclic triene **50** ($X=R_1=R_2=H$) as a transient intermediate. As expected, the TADA reaction occurred in situ to give the decahydroindacene ring system **53** ($X=R_1=R_2=H$), albeit with a different stereochemistry from that of the natural product, in a ca. 4:1 mixture of isomers. The newly formed major tricycle possessed the CAT stereochemistry, as opposed to the desired TAC found in the above mentioned natural products. On a more elaborate substrate **51** (X=H, $R_1=R_2=CO_2t$Bu), the results were essentially identical.[18] The outcome of the cycloaddition step was interpreted using molecular mechanics calculations. The results showed transition state **52** ($X=R_1=R_2=H$) to be lower in energy by 0.8 kcal mol^{-1} over transition state **54**, the latter being disfavored due to a steric interaction between H12 and the C14 carboxyl group. The authors further reasoned that by introducing a directing group X (X=TMS or Br) on the diene, as already employed in other studies,[31a] they would be able to bias the transition state towards **54** with enforcement of a *trans* ring junction on the same side as the X substituent. This would lead to the desired TAC ring system **49**, in agreement with molecular mechanics calculations.[18] Further studies in this direction will hopefully confirm the hypothesis.

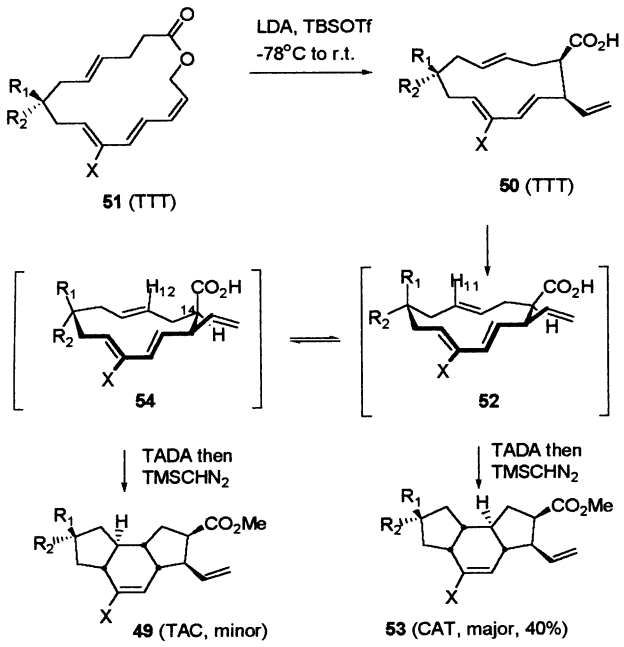

Figure 15.

3. TADA Reactions of furan dienes

The furan heterocycle has been used on many occasions as a TT diene in Diels–Alder reactions,[41] and was among the first dienes investigated by Diels and Alder.[42] Intramolecular reactions are a well documented subdivision of furan Diels–Alder chemistry.[43] However, only a few examples are reported where the dienophile is tethered to both sides of the furan to form a macrocycle and lock the system into an ideal conformation (Fig. 16). Accordingly, although TTT furanophane **55** cyclized to [7.6.7] tetracycle **56** under forcing conditions at high pressure, the product proved to be unstable and reverted to **55** spontaneously by a retro-TADA reaction.[44] In contrast, in their furanocembranoid synthetic studies, Marshall et al. found that TTC furanophane **57a** underwent a quantitative TADA reaction to give [6.6.6] tetracycle **58a** upon heating at 80°C for 3 h.[45a] Additionally, its analogue **57b** underwent the TADA spontaneously at rt in quantitative yield, giving TST [5.6.5] tetracycle **58b**.[45b] Further studies showed that a TADA reaction on TTC furanophane **59** exhibited less selectivity at 80°C and produced a mixture of [6.6.5] TST and CSC tetracycles **60** and **61**, respectively, in a 95:5 ratio.[45a]

To date, only one synthetic application of the TADA reaction to a furan diene has been reported, as outlined below.

3.1. Synthetic studies toward chatancin

Chatancin (**62**, Fig. 17) is a tetracyclic diterpene known to antagonize the platelet activation factor, making it an interesting biological target.[46] Its structure suggests at least two potentially biomimetic approaches via the TADA strategy,

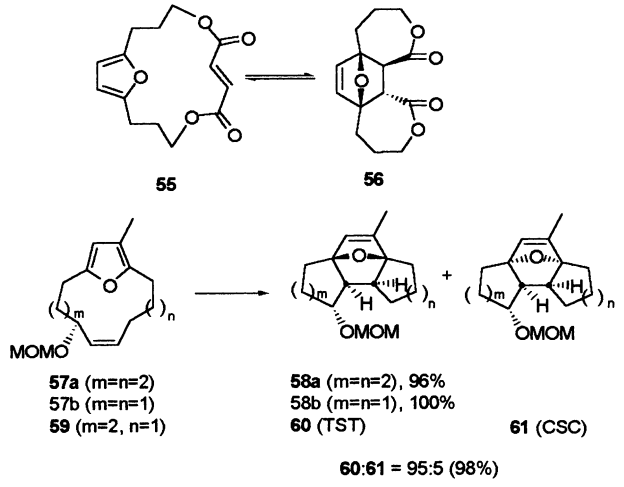

Figure 16.

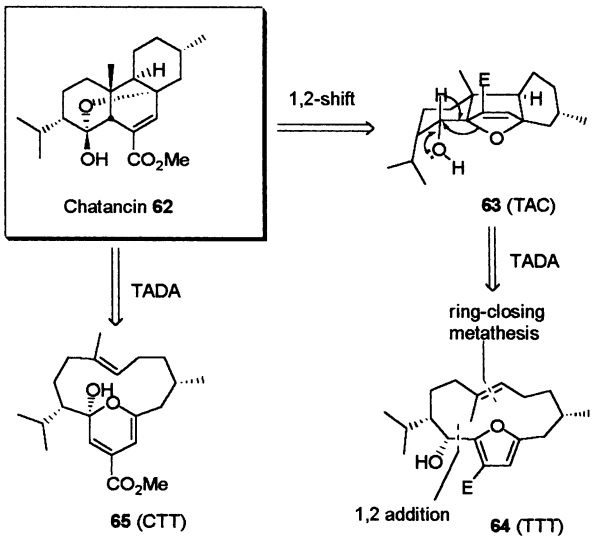

Figure 17.

both of which are being explored by Deslongchamps et al. In the first approach,[47] two key steps are considered: a TADA reaction on quasi-furanocembranoid **64** leading to tetracyclic adduct **63**, followed by a hydride shift-mediated oxygen transposition to give the desired product.

This first hypothesis was initially investigated on a model series (Fig. 18),[47b] where furanocycle **66** bearing a malonate connector was synthesized in 12 steps from homogeranyl pivalate. The TADA reaction turned out to be strongly solvent-dependent. In the more favorable conditions (DMSO:H_2O 1:2, 105°C), tetracycles **68** and **70** were produced (90:10 ratio, 80% overall yield), in favor of **68** possessing the chatancin stereochemistry. The authors speculated that an internal H-bond between the hydroxyl and ester groups oriented the TADA reaction towards transition state **69**, leading to minor adduct **70**. Water supposedly disrupted this H-bond, leading rather to adduct **68** via transition state **67**. This hypothesis is consistent with the increasing proportion of the unwanted tetracycle **70** as a function of the decreasing protic character of the solvent (in toluene, the **68**:**70** ratio was reversed to 29:71). Although the other two possible transition states leading to CAT tricycles are highly disfavored due to a repulsive interaction between the lone pairs of the furan oxygen and the dienophile methyl group, a quasi-equatorial hydroxyl group gives preference to transition state **67** and TAC tetracycle **68** ultimately, when the internal H-bond between this hydroxyl and the carbomethoxy group is broken.

When the malonate functionality was replaced with the requisite α-methyl group in furanophane **64** arising from ring closing metathesis (Figs. 17 and 19),[48] perfect diastereofacial control was achieved under similar conditions. However, only 67% conversion could be reached due to the reversibility of the reaction, as confirmed when heating the isolated tetracycle **63** in refluxing toluene. A Lewis acid-induced hydride shift occurred easily on **63**; however, the acid-sensitive target **62** dehydrated to known anhydrochatancin **71**.[46] Interestingly, the *trans* dienophiles were relatively easy to isomerize to *cis* dienophiles, which gave no TADA adducts.

In a parallel approach (Fig. 17),[49] the same authors proposed a TADA reaction on pyranophane pseudobase **65**. This conceptually more ambitious approach would give access more rapidly to chatancin. The synthesis of macrocyclic enedione **73** from *trans-trans* farnesol **72** is described (Fig. 19), featuring two enantioselective catalytic hydrogenations using Noyori's catalyst.[50] Further studies will ascertain if this is a realistic route to the desired target **62** via the intermediacy of pyranophane pseudobase **65**.

4. TADA Reactions of *trans-trans-cis* (TTC) trienes

Similarly to the TTT series, TTC macrocycles greatly benefit from the ready availability of the diene *s-cisoid*

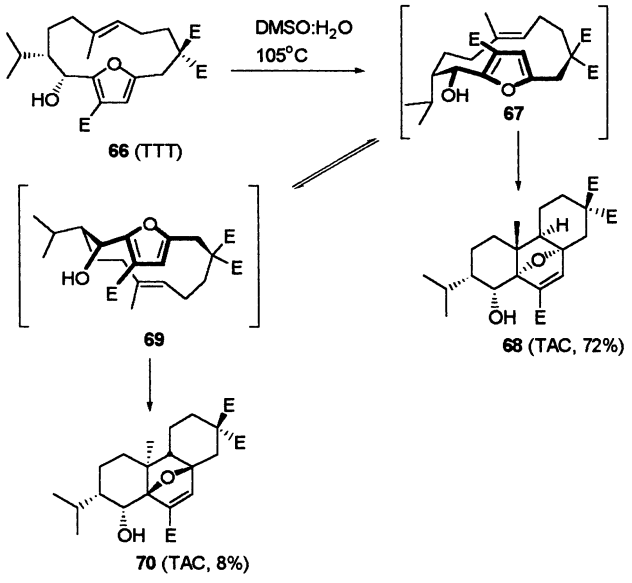

Figure 18.

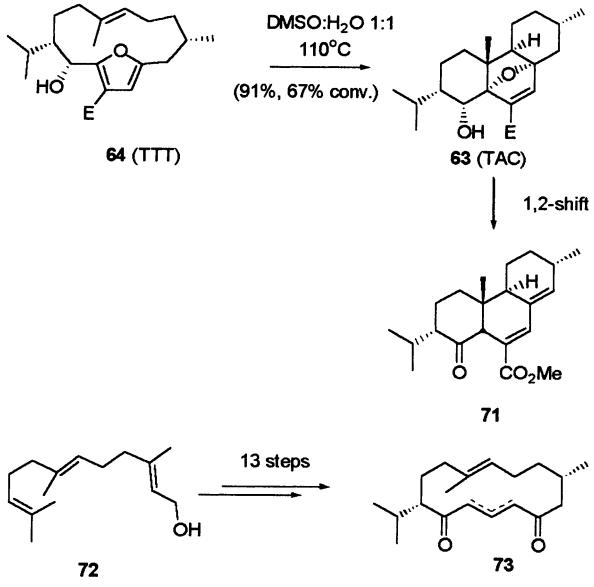

Figure 19.

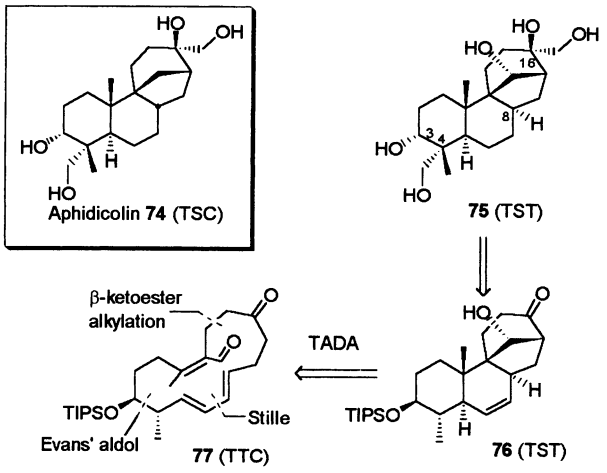

Figure 20.

geometry. This geometry results in a low activation energy with the possibility of forming two adducts having the TST and CSC geometries, with the former usually being predominant (see Table 1, entry 8).

4.1. Enantioselective total synthesis of 8-*epi*-(11*R*)-hydroxyaphidicolin

Aphidicolin (**74**, Fig. 20) has been the subject of intense research, due in part to its promising therapeutic potential for cancer treatment,[51] and to its complex tetracyclic structure.[52] The enantioselective total synthesis of unnatural 8-*epi*-(11*R*)-hydroxyaphidicolin **75** was recently reported, via a tandem TADA-adol strategy[53] on 15-membered TTC macrocyclic triene **77**.

The power of the approach lies in the key tandem TADA-aldol step (Fig. 21), which formed four new rings and six chiral centers in a one-pot process (i.e. **77** to **76**), all controlled by the methyl and siloxy substituents at C3 and C4.[54] The relative geometry of the A, B, C ring junctions was secured by the use of TTC macrocyclic triene **77**, which gave only the TST adduct. In this case, only the desired *endo* adduct was observed, arising from transition state **78**, in competition with *exo* transition state **80**, which would have led to CSC tricycle **81**. The direct TADA product **79** was observed to a small extent, as most of it underwent the subsequent intramolecular aldol reaction in situ to yield tetracycle **76**. The two other possible TST and CSC adducts were not observed, for the conformation of their transition states imposes a pseudo-axial orientation on substituents in C3 and C4. The authors also found an efficient and original solution to the long-standing problem of C16 functionalization. However, they encountered serious difficulties in final elaboration of ring A.

In principle, the correct C8 stereochemistry found in aphidicolin was within reach by using the analogous TCC macrocyclic triene. When attempted, the authors found the latter to be reluctant to undergo the cycloaddition and provide the desired TSC tricycle possessing the aphidicolane backbone, using thermal or Lewis acid activation.[54b] In a model study, a similar TCC 15-membered macrocyclic triene **82** with an activated trisubstituted dienophile

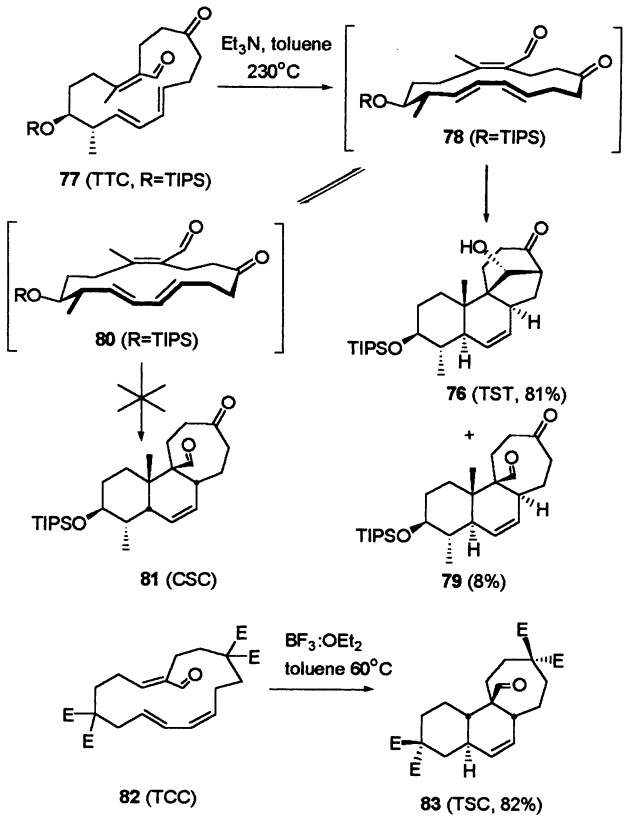

Figure 21.

lacking the methyl group had smoothly undergone the BF_3-catalyzed TADA reaction to give the desired TSC tricycle **83** in 82% yield.[54a]

4.2. Total synthesis of momilactone A

Several diterpenes possess the TST geometry of momilactone A (**84**, Fig. 22).[55] Its tricyclic ring system is directly accessible from TTC macrocyclic triene **87** and further elaboration of TADA adduct **86**.[56] The macrocyclization step involved alkylation of the malonate, a procedure used extensively in model studies of the TADA reaction.[8] Usually, malonates impede further progress towards total syntheses, requiring multiple transformations with often

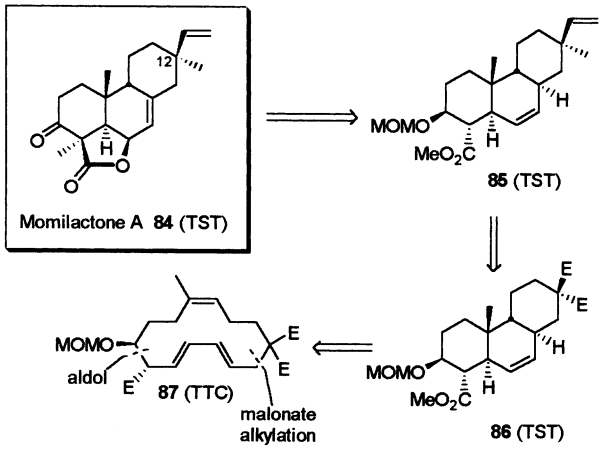

Figure 22.

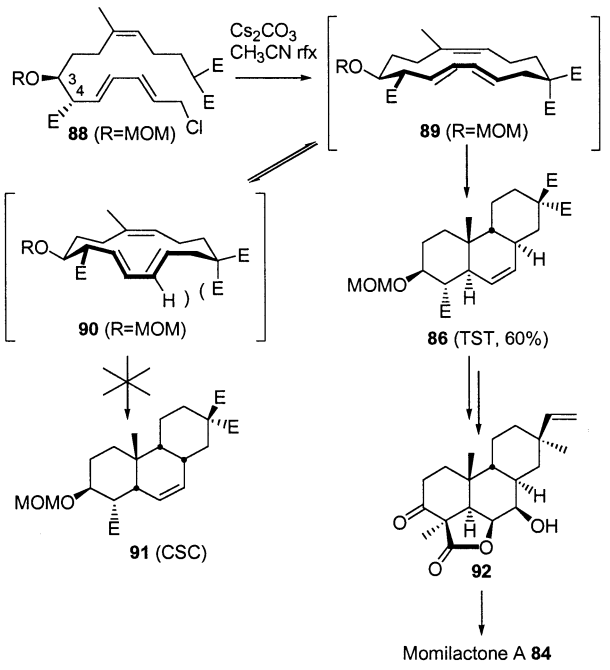

Figure 23.

low yields for further elaboration. In the present case, however, the malonate moiety was taken advantage of in order to introduce both exocyclic substituents on C12.[57]

Two stereocontrol elements were sufficient to bias the system towards the desired tricycle out of four possible products. Starting from TTC acyclic triene **88** (Fig. 23), the TADA reaction occurred in situ during the macrocyclization step, via transient macrocycle **89**. The malonate connector forced the diene into the β orientation in transition state **89** by sterically blocking the α orientation that would have led to CSC tricycle **91** (transition state **90**). The ester in C4 controlled the diastereoselectivity of the process by adopting the pseudo-equatorial geometry; a pseudo-axial orientation leads to a severe 1,3-diaxial interaction with the dienophile methyl group. The only TADA product isolated from the reaction was tricycle **86**, which was further elaborated to 7-hydroxymomilactone **92**. Also, it is noteworthy that the 3,4-*syn* isomer of **88** gave comparable results during the tandem macrocyclization–TADA steps. Dehydration of **92** led to the target momilactone A **84**.

5. TADA Reactions of *trans-cis-cis* (TCC) trienes

Undoubtedly, one of the main assets of the TADA strategy is its ability to efficiently manage TC dienes, which otherwise react poorly, if at all, in intermolecular and intramolecular settings (see Table 1, entries 1, 2, 5, 6).[8,12] Even methyl-substituted TC dienes are tolerated in the transannular version.[5] The temperatures required for cycloaddition are obviously higher than in the case of *trans-trans* dienes, reflecting the difficulty to reach the *s-cisoid* geometry. Molecular calculations showed the TADA step to go via an asynchronous transition state in the case of activated dienophiles,[13,58] allowing the diene to diverge from the purely *s-cisoid* geometry, thus lowering the activation energy required to reach the transition state.

5.1. Enantioselective total synthesis of (+)-maritimol

In model studies directed towards the total synthesis of (+)-maritimol[59] (Fig. 24), Deslongchamps et al.[60] observed that the stereochemical outcome of the key TADA step was governed exclusively by the orientation of the nitrile substituent.

The exact role of the nitrile substituent has not been completely elucidated; however, on TCC macrocycle **93**, the nitrile preferred to be inside the transition state pocket of **94**, leading to the TSC skeleton **95** exclusively. Quite spectacularly, on diastereomeric macrocyle **96** the nitrile was able to overcome the steric bias conferred by the C3 triisopropylsiloxy and the C4 methyl groups, leading to structural isomer **98** via transition state **97** (the A ring in this case could also adopt a boat-like conformation).

In essence, this intriguing role of the nitrile group directed their approach towards a more concise enantioselective total synthesis of maritimol **99**, in which the chiral appendages at C3 and C4 were replaced by the natural product subtituents (Fig. 25).[61] The authors targeted diketone **100**, a known intermediate in the synthesis of stemodanes.[52] The latter was obtained in four steps from TSC tricycle **101**, itself synthesized from TCC triene **102**.

As already explained, this approach via TCC trienic macrocyle **102** (Fig. 26) led exclusively to TSC tricyle **101** and eventually culminated in the first enantioselective total synthesis of (+)-maritimol **99**. This total synthesis demonstrates, at its best, the power of the TADA strategy. Indeed, a tetrasubstituted dienophile reacted here with a TC diene, under the perfect stereocontrol of a remote small nitrile group. The overall approach is exceptionally convergent for a diterpene synthesis.

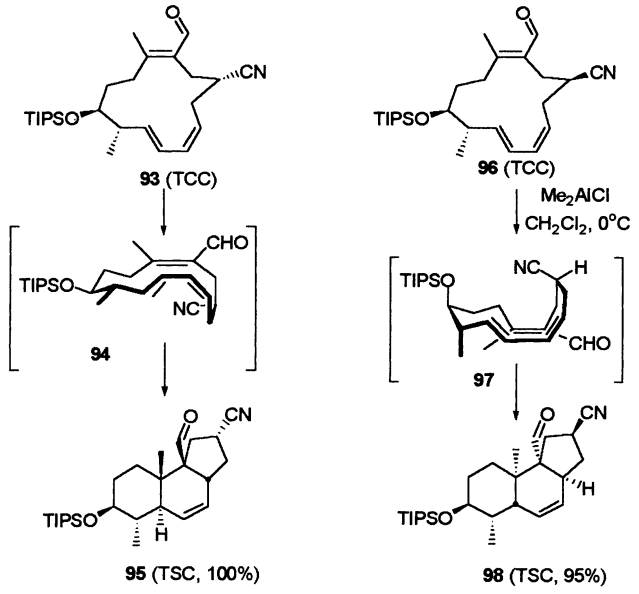

Figure 24.

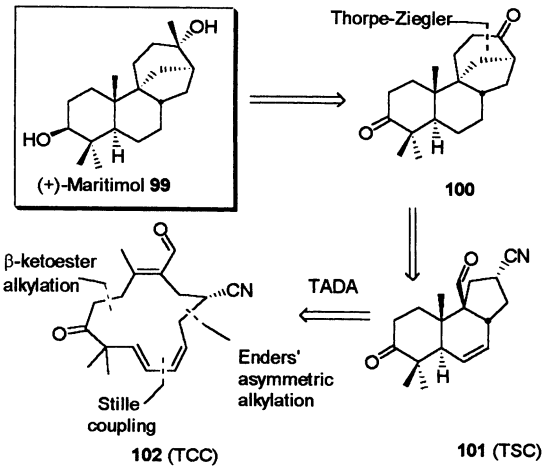

Figure 25.

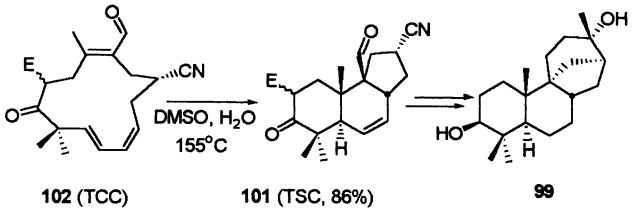

Figure 26.

5.2. Synthetic studies toward 14β-hydroxysteroids

Following model studies aiming at the synthesis of TSC [6.6.5] tricycles,[62] the TADA approach was applied to the synthesis of rings B, C, D of 14β-hydroxysteroids (Fig. 27).[63] Studies using TCC macrocyclic triene **103** led to the identification of one stereocontrol element at position C17. Indeed, the bulky siloxy substituent is oriented outside of the transition state cavity in **104**, in order to minimize steric repulsion with the forming bond. In the event, the ester substituent in C16 seemed to play a minor role, with the *syn* and *anti* orientations being equally tolerated with respect to the siloxy group. TSC tricyle **105** was obtained exclusively (94% yield), opening a new approach towards 14β-hydroxysteroids. Further studies incorporating an aromatic A ring[64] extended the concept and TCC macrocyle **106** led to TSC tetracycle **108** via transition state **107**. To be noted in this case, the macrocyclization was performed by intramolecular Pd-catalyzed substitution of an allylic pivaloate by a β-ketoester.

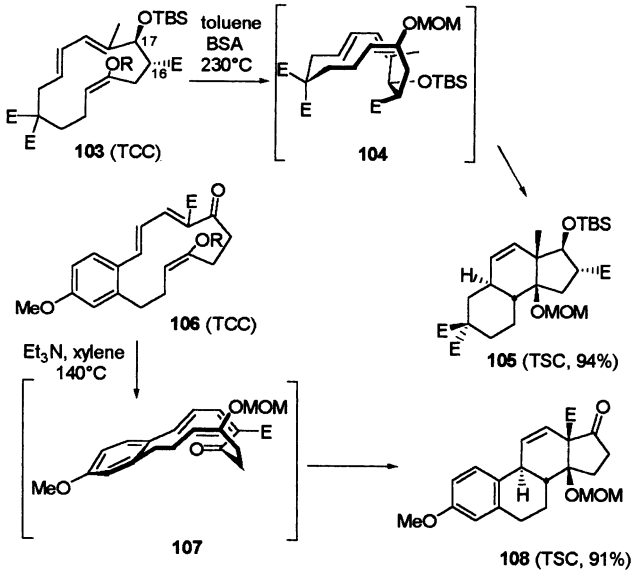

Figure 27.

5.3. Synthesis of 5α-steroids

The TAT geometry is one of the most common ring junctions found in natural diterpenes and steroids. However, it is the only geometry which is directly inaccessible with the TADA strategy (vide supra). Indirect methods are thus mandatory, such as epimerization of certain angular positions. This approach was successfully applied to the steroidal A.B.C ring system exemplified by aldosterone (**109**, Fig. 28).[65] Tetracyclic analogue **110** was synthesized from TSCAT tetracycle **111**, with the TADA adduct being derived from TCC triene **112**.

When macrocycle **112** was subjected to thermolysis at 225°C (Fig. 29), the expected TSCAT tetracycle **111** was obtained in 80% yield, with the *trans* orientation of

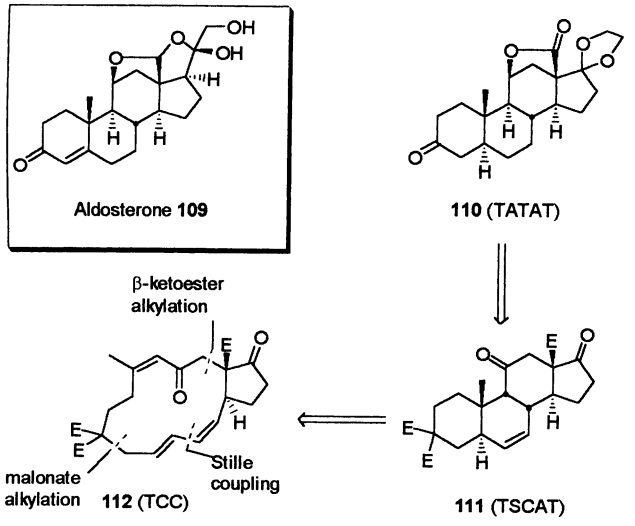

Figure 28.

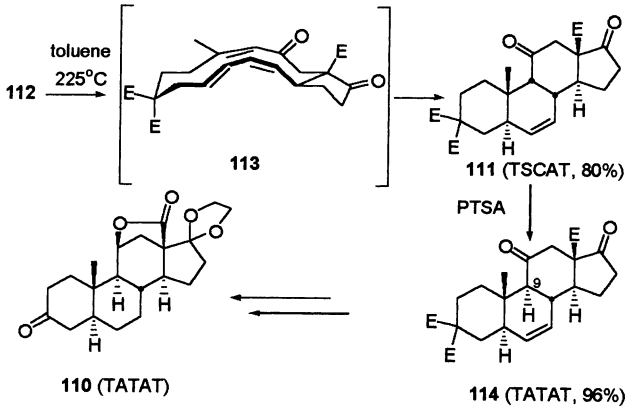

Figure 29.

substituents on the cyclopentanone controlling very well the diastereoselectivity of the process. Since the precursor cyclopentanone is accessible in optically active form,[66] this constitutes a potentially enantioselective approach to steroids. Subsequent epimerization at position C9 (steroid numbering) furnished quasi-quantitatively TATAT steroid **114**, offering easy access to the geometry of a large number of steroids. Further functional group elaboration allowed for the production of steroid **110** through malonate degradation.[65b]

5.4. Synthesis of 5α-3-azasteroids

The broad versatility of the TADA approach allows access to unnatural derivatives of natural products, such as heteroatom-substituted steroids known to possess interesting biological properties.[67] The method was successfully applied to the synthesis of two types of 3-azasteroids, via the strategy outlined in Fig. 30.[68] In the first series, 5α-3-aza-11-oxo derivative **117** having the TSCAT geometry was obtained by the TADA reaction of TCC trienic macrocycle **115**. The outcome of the TADA step is readily explained by invoking the same reasoning as in the previous section (vide supra). In the same TCC series, however, triene **118** did not yield any TADA reaction product; instead, [6.8.5] tricycle **119** was obtained, presumably via base-catalyzed elimination of the tosylamide moiety and subsequent IMDA reaction of the resulting tetraene. In a second approach towards 5β-3-azasteroids, TTT macrocyle analogous to TCC macrocycle **115** gave two TADA adducts having, respectively, the CATAT and the TACST in a 5:1 ratio (see Section 2.5 for a detailed analysis of the outcome of the TADA reaction).

5.5. Synthesis of the quassinoid skeleton

In addition to a good tolerance for TC dienes, the TADA strategy accepts alkyl-substituted dienes as well. These TC dienes give access to polycycles possessing angular quaternary centers such as quassin (**120**, Fig. 31)[69] that are otherwise difficult to reach. Model studies towards the quassinoid skeleton **121** led to the synthesis of TCC triene **122** bearing a methyl-substituted TC diene.[70]

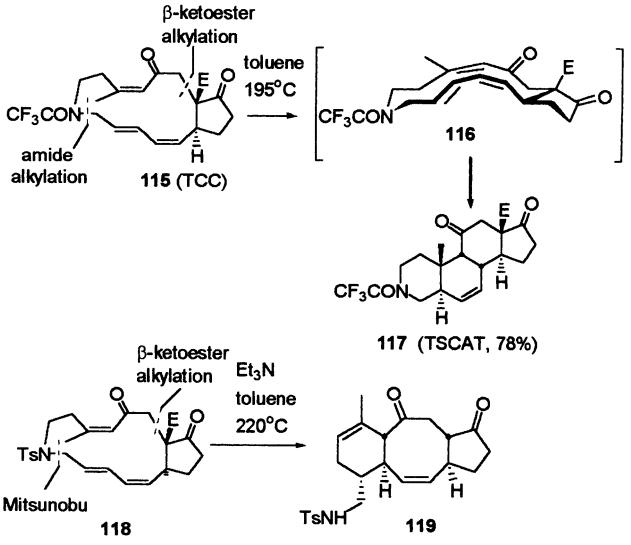

Figure 30.

When submitted to thermal TADA conditions (220°C, 20 h), triene **122** underwent the TADA reaction and gave exclusively the desired tricycle **121** having the expected TSC geometry (Fig. 32).

The fact that the triene adopted transition state conformation **123** instead of conformation **124** was readily explained by invoking a pseudo-1,3-diaxial interaction in conformer **124**, in addition to two pseudo-axial substituents in *pro*-ring A. Tricycle **121** was obtained in 90% yield, emphasizing here the easy use of functionalized TC dienes, usually unreactive in the Diels–Alder reaction. As is often the case with the TADA reaction, electronic effects were overruled by transannular steric repulsions. *Exo* transition state **123** was thus the only productive pathway. Consistently, the authors found TCC macrocyclic triene **122** to be insensitive to Lewis acid catalysis. This result is in agreement with the hypothesis that the carbonyl group is not conjugated with the dienophile in the macrocycle at the transition state, preventing Lewis acid activation.

6. Conclusions and future prospects

To broaden the scope of application of the TADA reaction, one may envision the possibility of applying the TADA

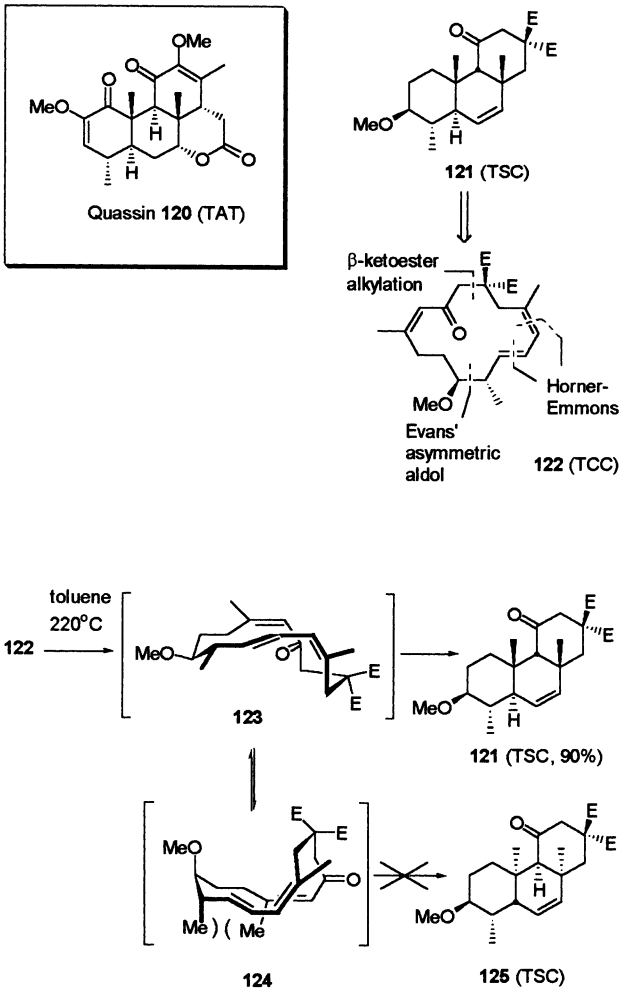

Figure 32.

strategy on a solid phase, eventually leading to libraries of polycyclic molecules. Preliminary studies in this direction have been reported recently.[71]

Furthermore, the possible existence of biogenetic pathways that incorporate TADA reactions has been put forward by several authors as discussed now.

The occurrence of a Diels–Alderase enzyme has been suggested,[72] and the first example of such an enzyme being able to catalyze an IMDA process has been reported very recently.[73] In a given system, in case no enzyme is able to orient a triene towards the one transition state among several that leads to the desired natural product, this bias has to be conferred by the substrate itself. This hypothesis has been formulated by Roush et al.[18] and constitutes the cornerstone concept of the TADA strategy, whereby exocyclic substituents alone orient the conformation of the macrocyclic triene towards the desired transition state.

Recently, Sorensen et al.[74] postulated a hetero-TADA[75] biogenetic pathway to the cytotoxic substance WS988 B (**126**, Fig. 33). The hypothesis, under scrutiny, relies on a TADA reaction on dienone **127**, with the substrate orienting the TADA reaction towards hexacycle **126** only. Venkateswarlu et al.[76] also proposed a TADA approach for the biosynthesis of diterpenoid mandapamate **128** from TTT triene **129**. This hypothesis is strengthened by the fact that furanocembranoid pukalide and a related diester furanocembranoid have been isolated from the same *Sinularia dissecta* soft corals that produce mandapamate.[77] A TADA-based approach has also been proposed by Deslongchamps et al. for the biosynthesis of chatancin **62** from quasi-furanocembranoid **64** (Fig. 17),[47] and one may reasonably consider a similar approach for the related tetracyclic diterpenoid sarcophytin **130**.[78] This hypothesis is supported by the close resemblance between their precursor macrocyclic furanophanes and known furanocembranoids, some of which have been shown to easily undergo TADA reactions.[45,79] Finally, Ito and Hirata proposed a TADA-based biosynthesis of ikarugamycin **131** from TTT triene **132**,[80] a hypothesis explored by Roush et al.[18]

As is now clear, the TADA strategy is a robust and versatile approach for the synthesis of polycyclic compounds such as di- and triterpenes. Its superiority in terms of stereocontrol over inter- and intramolecular versions comes from the easy use of TC or TT dienes in conjunction with unactivated dienophiles, as these unsaturations control perfectly the relative stereochemistry of the newly formed tricycle. Likewise, the diastereo- and enantioselectivities of the process can be controlled by a judicious choice of substituents on the macrocycle, which bias the transition state towards the desired product. A single stereogenic center can control the overall stereochemistry of the cycloaddition, as observed in several cases.

The price to pay for such additional benefits as compared to the other Diels–Alder versions is the building of a trienic macrocycle. It seems from the preceding examples that it is worth dedicating an effort towards macrocycle elaboration, as all direct studies between IMDA and TADA give a clear advantage in terms of selectivity to the latter. Nevertheless, the approaches employed by the various authors to build the macrocycle will determine the convergence of the overall synthesis, hence its efficiency. Macrolactonization has been used in a number of cases (Sections 2.1, 2.3, 2.4, 2.6), and is a well established macrocyclization strategy, but is not suitable for all targets. Malonate alkylation was sufficient for model studies, but its applicability is restricted (Sections 4.2, 5.3, 5.5). β-Ketoester alkylation has also been used in several instances, but is limited to ketones which cannot readily conjugate with the diene (Sections 2.2, 4.1, 5.1, 5.2). Ring-closing metathesis does not necessarily guarantee a good control of the stereochemistry of the newly formed unsaturation (Section 3.1). Clearly, a large density of functionality has to be present in the macrocycle, in order to reduce the number of post-TADA chemical steps. This requires an efficient strategy to assemble the macrocycle components, but more importantly a robust strategy for macrocyclization is mandatory, which is both general in application and tolerant to a broad variety of functionalities. When comparing the variety of possible trienic macrocycle precursors, one realizes that the only common element to all is the diene moiety and that disconnection of the latter gives a lot of flexibility to the approach (Fig. 34). Deslongchamps

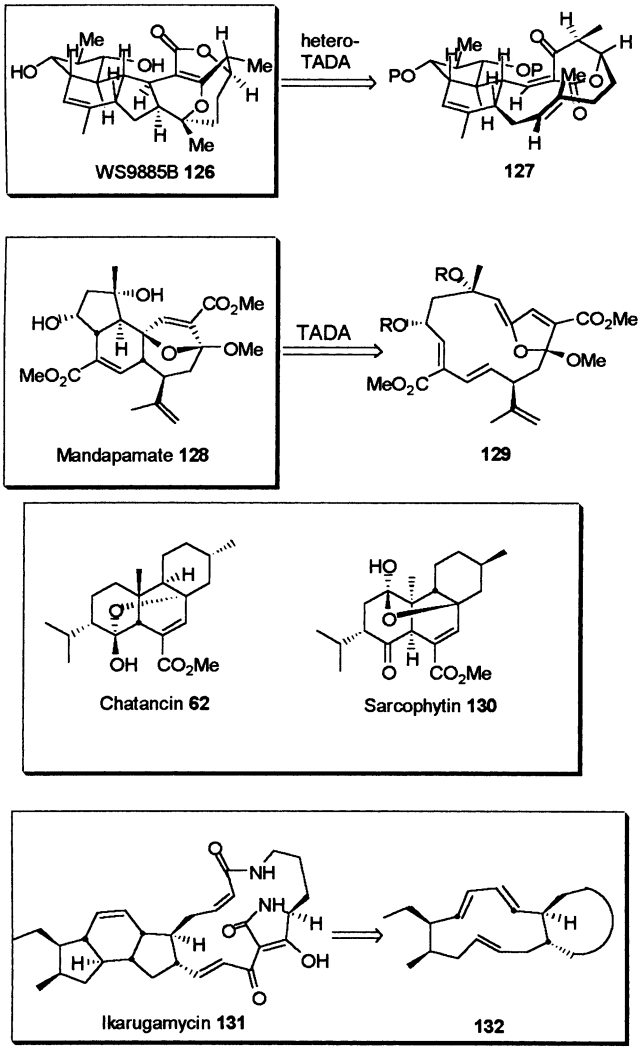

Figure 33.

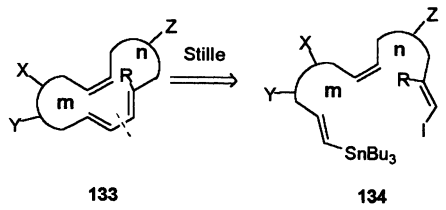

Figure 34.

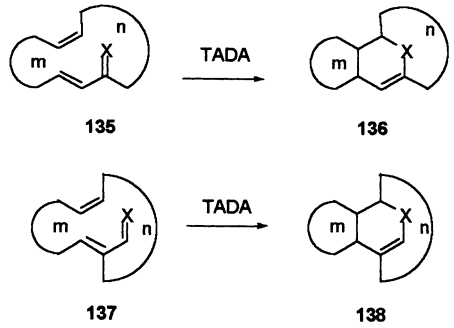

Figure 35.

et al. recently reported the synthesis of six 14-membered trienes incorporating T and C dienophiles, as well as TC and TT dienes, substituted or not, via Stille macrocyclization of acyclic trienes of type **134** to macrocycles **133**.[14d,17] All the desired macrocyclic trienes were obtained in yields equal or superior to those obtained by classical malonate alkylation as already used to build the same macrocycles. This paves the way to a higher convergence in the elaboration of macrocycles in future works.

In addition, the scope of the TADA strategy could be broadened significantly via the intermediacy of new types of dienes (Fig. 35), such as **135** and **137**. Cycloaddition on these macrocycles would lead to tricycles of type **136** and **138**, in a process that one may call type II TADA (see also Fig. 33).

Acknowledgements

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Biographical sketch

Eric Marsault was born in France in 1971. After undergraduate studies at ESCOM (Ecole Supérieure de Chimie Organique et Minérale, Paris), he earned his Ph.D. under the supervision of Prof. George Just (McGill University, Montreal), on the diastereoselective synthesis of DNA phosphorothioates. He then moved to Italy, where he worked as a researcher at the Sanofi–Winthrop pharmaceutical company. He then joined Prof. Deslongchamps' team as a postdoctoral fellow, working on an enantioselective approach towards norzoanthamine via the TADA strategy for 18 months, then almost one year as a research assistant. He recently joined Néokimia, a company founded by Prof. Deslongchamps. His main areas of interest are the synthesis of natural and unnatural products and the way they interact with living systems.

Pawel Nowak received his undergraduate education at the University of Adam Mickiewicz (Poznan, Poland). After graduating in 1992 he moved to the University of Saskatchewan (Saskatoon, Canada) and worked under the direction of Dr Marek Majewski on various aspects of enantioselective deprotonation of cyclic ketones. He earned his Ph.D. in 1998 and moved to the University of Sherbrooke (Sherbrooke, Canada) where he worked in the group of Dr Pierre Deslongchamps on the synthesis of (+)-maritimol via a transannular Diels–Alder reaction. In 2000 he joined the group of Dr Yoshito Kishi at Harvard University (Cambridge, USA) where he is further pursuing his research interests in the total synthesis of natural products.

András Toró was born in Hungary and received his University Doctorate degree from Eötvös Loránd University, Budapest, Hungary in 1992. He joined Prof. Deslongchamps' group in 1993 and investigated the TADA reaction for seven years, first as a NATO-NSERC postdoctoral fellow then as a research assistant. His work with Prof. Deslongchamps culminated in the total enantioselective synthesis of maritimol, as well as an elegant approach towards chatancin. Now, he is working for Array BioPharma as a Research Scientist. His research interest remains the design and construction of complex molecules with biological relevance.

Pierre Deslongchamps was born in Canada and received his B.Sc. from the University of Montreal (1959), then his Ph.D. from the University of New Brunswick in 1964 (Prof. Z. Valenta). In 1965, he spent one year at Harvard University as a postdoctoral fellow with the late R. B. Woodward. He then was appointed assistant professor at the University of Montreal and moved to the Université de Sherbrooke in 1967 where he became full professor in 1972.

Over the last 30 years, Professor Deslongchamps has made outstanding contributions in the area of the total synthesis of complex natural products and in the development of the concept of *stereoelectronic effects* in organic chemistry. His most famous work includes the total synthesis of Ryanodol and Erythromycin A and the design of two general strategies for the construction of complex terpenes and steroids (via the transannular Diels–Alder reaction as well as a new anionic polycyclization process).

His seminal contributions to the concept of *Stereoelectronic Effects in Organic Chemistry* led to the publication in 1983 of his classic textbook on the subject.

Prof. Deslongchamps' numerous contributions to organic chemistry led to a large number of international awards and distinctions, among others the Alfred P. Sloan Fellowship (1971–72), E. W. R. Steacie Fellowship (1971–74), Merck Sharp and Dohme Award (1976), and the Canada Gold Medal for Science and Engineering (1993).

He was made a Fellow of the famous Royal Society of London (UK) in 1983, and became the first selected Canadian member of the 'Académie des Sciences de Paris' (France) in 1995.