Theoretical and Experimental Determination of the Effects Governing the Transannular Diels−Alder Reaction of Trans−Trans−Cis Systems with or without Activation of the Dienophile

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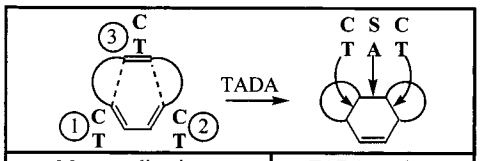
Abstract: A thorough study of the transannular Diels−Alder (TADA) reaction of trans−trans−cis macrocyclic trienes was carried out. It led to a better understanding of various parameters that govern the TADA reaction in particular and the Diels−Alder reaction in general. Thus, carbonyl activation of the dienophile and substitution of the diene are discussed, as well as the presence of substituents on the macrocycle and their respective effects at the transition-state level.

Introduction

Transannular reactions are very impressive methods for the synthetic organic chemists. This general approach coupled with the use of the Diels−Alder reaction leads to a very powerful strategy known as the transannular Diels−Alder (TADA) strategy.[1] It is therefore not surprising that several research groups have already used this impressive tool in their synthetic efforts.[2] During our own systematic and general studies of the TADA reaction,[3] we considered the eight possible combinations as regards the geometry of the diene and dienophile, each insaturation being either cis or trans. On a few occasions, competing 1,5-hydrogen shifts[4] and ene reactions[5] led to side products, but on the whole, the outcome of the reaction is highly predictable, as indicated in Table 1. This predictability can be used to design and carry out syntheses of natural products[6] or their analogues.[7] Thus, cis−cis dienes are of no use (cis−cis−cis, cis−cis−trans) because they always lead to rearranged products. This comes from the fact that the cisoid conformation of the diene is energetically very high. On the contrary, the cisoid conformation requires less energy in the cis−trans and trans−cis diene systems; only small amounts of rearranged side products are sometimes observed beside the expected adduct. It is worth noting that in all those cases (cis−trans−cis, cis−trans−trans, trans−cis−cis, trans−cis−cis) predictions are straightforward because there is always only one possible TADA adduct. Such is not the case for the trans−trans dienes (trans−trans−cis, trans−trans−trans), which can theoretically lead to the formation of two adducts each due to easy flipping of the plane constituted by the diene in its flat cisoid conformation (Scheme 1). In those cases, the ratio of TADA adducts is rather difficult to forecast because it is influenced by so many factors such as steric effects from various groups on the macrocyclic rings;[8] the problem can become even more complicated when the dienophile is activated since the so-called endo effect[9] can either antagonize all other effects or act in a synergic way.[10] The purpose of this work is precisely to untangle these

Table 1. Macrocyclic Trienes and Their Corresponding Tricyclic TADA Adducts. Nomenclature Used To Describe the Double Bond Stereochemistry of the Reactant: Diene Geometry (Cis C or Trans T) Followed by Dienophile Geometry



Macrocyclic triene		TADA product	
diene ① ②	dienophile ③	Theory	Experimental
CC (cis-cis)	C (cis)	CSC	none
	T (trans)	none	
CT (cis-trans)	C	CST (cis-syn-trans)	
	T	CAC (cis-anti-cis)	
TC (trans-cis)	C	TSC (trans-syn-cis)	
	T	CAC	
TT	C	TST and/or CSC	
	T	TAC and/or CAT	

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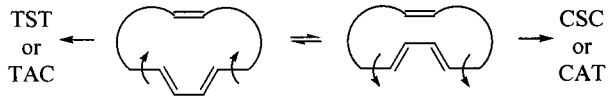
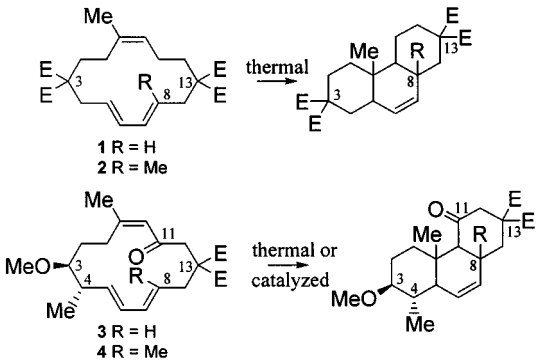
Scheme 1



Scheme 2

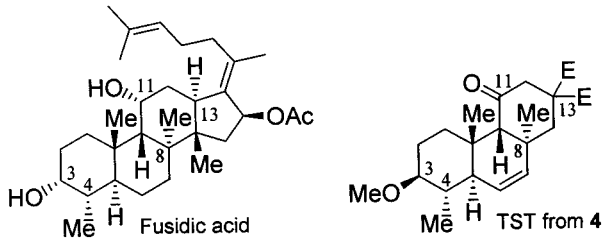


various factors in the case of trans−trans−cis macrocyclic trienes.

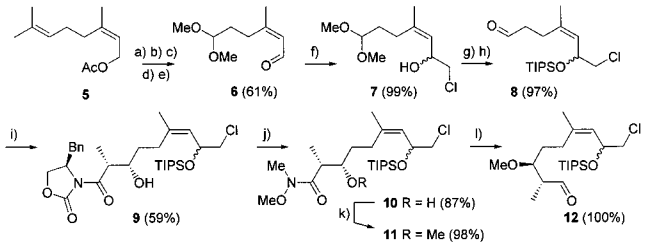
Choice of Models

To understand the activation of the dienophile by a carbonyl, one must first understand the behavior of the trans−trans−cis system without that activating carbonyl. In fact, compounds **1** and **2** (Scheme 2), which could allow such study, have already been prepared by us.[4,11] These two compounds differ only from each other by a methyl group at position 8 (numbering corresponding to the steroid-like adducts). The reason those two models had been made comes from the fact that many potential polycyclic natural product targets exist with or without a methyl substituent at that position.[12] It is also worth noting that many natural products have either an alcohol or a carbonyl group at position 11, hence the reason for studying the effect of a carbonyl at that position in **3** and **4**. The use of a carbonyl at position 11 is also meant to fix a particular problem: trans−trans−cis macrocyclic compounds such as **2** that have a methyl group at position 8 necessitate high temperatures to yield the corresponding tricyclic adducts. In the process, side reactions have been observed but carbonyl activation of the dienophile should sufficiently reduce the temperature of reaction so that all unwanted side reactions could be eradicated. Beside the addition of a carbonyl at position 11 in **3** and **4**, a methoxy group at position 3 and a methyl group at position 4 (instead of the malonate group at position 3 in **1** and **2**) have also been added in order to induce chirality in the TADA adducts and also because these two substituents are found in many natural products. Compounds such as fusidic acid[13] (Chart 1) and other fusidanes such as cephalosporin P1[14] and helvolic acid could result from the TADA reaction of **4** (or related macrocycles) provided that the trans−syn−trans tricyclic adduct could be obtained selectively.

Chart 1. Two Natural Products Suitable for the TADA Strategy



Scheme 3[a]



[a] Conditions: (a) *m*-CPBA, CH_2Cl_2, 0 °C; (b) $NaIO_4$, HCl, THF/H_2O, room temperature. (c) HCl, MeOH, room temperature. (d) K_2CO_3, MeOH, room temperature. (e) $(COCl)_2$, DMSO, CH_2Cl_2; then Et_3N, −78 °C. (f) $BrCH_2Cl$, Li, THF, − 78 °C. (g) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C. (h) TFA, CH_2Cl_2/H_2O, room temperature. (i) (*R*)-3-(1-Oxopropyl)-4-benzyl-2-oxazolidinone, $^nBu_2BOTf$, CH_2Cl_2, 0 to −78 °C. (j) $AlMe_3$, NH(OMe)Me·HCl, CH_2Cl_2, 0 °C. (k) MeI, NaH, THF/DMF, °C. (l) DIBAL-H, THF, − 78 °C.

Synthesis

The synthesis of the macrocycles **3** and **4** was started with the selective epoxidation of neryl acetate **5** followed by opening of the epoxide and cleavage of the resulting diol leading to the corresponding aldehyde (Scheme 3).[15] The aldehyde was protected as a dimethoxy acetal and the acetate was hydrolyzed; the resulting allylic alcohol was oxidized[16] to furnish the aldehyde **6**. A 1,2 addition on the aldehyde **6** with chlorobromomethane and lithium gave the chlorohydrin **7**.[17] Protection of the alcohol[18] and hydrolysis of the acetal led to the aldehyde **8**. Evans asymmetric aldolization[19] was performed on that aldehyde to give the adduct **9**. The chiral auxiliary was removed via transamidation, according to Weinreb's technique,[20] yielding the amide **10**. The alcohol was protected as a methyl ether **11**,[21] and the amide was then quantitatively reduced to give the aldehyde **12**. Horner−Emmons reactions[22] with the phosphonates $(E)(MeO)_2POCH_2CH{=}CHCO_2Me$ and $(E)(MeO)_2POCH_2$-$CH{=}C(Me)CO_2Me$ led respectively to the trans−trans diene **13** and to the substituted trans−trans diene **14** (Scheme 4). An identical six-step sequence was then applied to **13** and **14** to obtain the two precursors of cyclization **25** and **26**, respectively. Thus, reduction of the methyl ester **13** gave the alcohol **15** that

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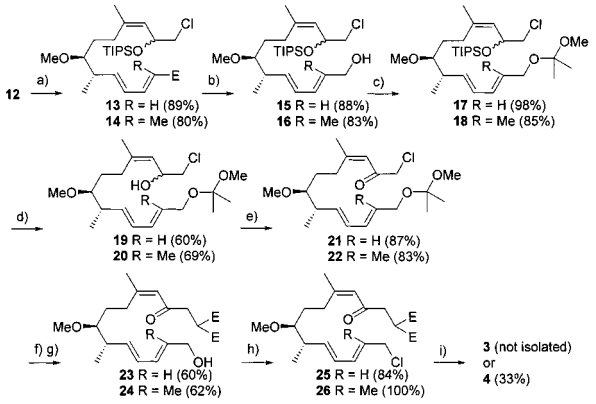
Scheme 4[a]

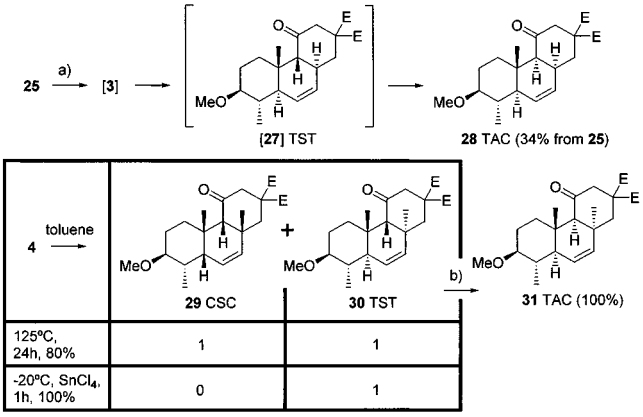


[a] Conditions: (a) $(E)(MeO)_2P(O)CH_2CH{=}CHCO_2Me$ (to **13**) or $(E)(MeO)_2P(O)CH_2CH{=}C(Me)CO_2Me$ (to **14**), BuLi, Et_2O, −20 °C. (b) DIBAH, THF, − 78 °C. (c) 2-Methoxypropene, PPTS, CH_2Cl_2. (d) TBAF, THF. (e) TPAP, NMO, CH_3CN, room temperature. (f) Dimethyl malonate, NaH, NaI, DMF, room temperature. (g) AcOH, THF/H_2O, room temperature. (h) Hexachloroacetone, PPh_3, 2,6-lutidine, THF, − 40 °C. (i) Cs_2CO_3, NaI, CH_3CN, 85 °C.

was transformed into the acetal **17**. Deprotection of the silyl ether with tetrabutylammonium fluoride yielded the alcohol **19**. The chloroketone **21** was obtained by oxidation of the resulting secondary alcohol.[23] The dimethylmalonate connector was introduced by SN_2 alkylation of the chloroketone **21**. Subsequent hydrolysis of the acetal group with aqueous acetic acid yielded the allylic alcohol **23**. The alcohol was transformed into the allylic chloride **25** according to Schreiber's chlorination method.[24] **25** was obtained from **13** with an overall yield of 23%; similarly, the other allylic chloride **26** was obtained from **14** with the overall yield of 25% for the six consecutive reactions.

The macrocyclization of **25** to obtain the macrocycle **3** was carried out under the usual conditions by means of cesium carbonate at 85 °C in acetonitrile.[25] As previously observed with trans−trans dienes having no additional substituents, the expected macrocycle was not isolated; rather, the TADA reaction took place during the macrocyclization reaction.[26] Thus, the trans−anti−cis tricycle **28** (structure established by X-ray diffraction analysis) was obtained in 34% yield from the allylic chloride **25** (Scheme 5). However, a trans−anti−cis tricycle cannot issue directly from the TADA reaction of a trans−trans−cis macrocycle (Table 1), instead a trans−syn−trans or a cis−syn−cis tricyclic adduct (or both) should have been obtained.[3a] Therefore, this result shows that only the trans−syn−trans tricycle **27** must have been produced and directly isomerized with cesium carbonate present in the reaction medium to the more stable trans−anti−cis tricycle **28** as shown in Scheme 5. Alternatively, the same adduct **28** could have arisen from IMDA (intramolecular Diels−Alder)[27] reaction of the trienone **25** immediately followed by malonate cyclization of the resulting bicyclic adduct to produce **27** then **28**. However, this route can be ruled out since there exist many IMDA precedents that demonstrate clearly that **25** cannot be expected to react below 150 °C.[2e,28]

Scheme 5[a]



[a] Conditions: (a) see Scheme 4. (b) TFA, $CHCl_3$, room temperature.

In the case of the substituted trans−trans diene series, it was possible to isolate the macrocycle **4** from **26** with the rather poor yield of 33%. The TADA reaction with **4** was then carried out under two types of conditions: thermal and catalyzed. When heated at 125 °C in toluene (sealed tube) for 24 h, the two possible cis−syn−cis and trans−syn−trans TADA adducts **29** and **30** were obtained as a 1:1 mixture and with a yield of 80% (the two compounds were separated by chromatography). The identity of **29** was established by X-ray diffraction analysis. As for **30**, the compound was treated with TFA to provoke epimerization at position 9. The resulting more stable trans−anti−cis tricycle **31** was obtained quantitatively, and its identity was also established by X-ray diffraction analysis. On the other hand, under catalytic ($SnCl_4$) conditions, only the trans−syn−trans exo adduct **30** was obtained in 100% yield. This latter result is extremely interesting since it opens a route to fusidic acid for which the ABC ring system is in a trans−syn−trans arrangement (Chart 1).

Theoretical Rationalization

Beside the obvious interest in total synthesis of suitable targets by means of the TADA reaction, we are also very much interested in shedding new light on the famous, but also not yet fully understood, Diels−Alder reaction. Clearly the transannular environment can provide an excellent tool to study reactions in general, Diels−Alder in particular, since mobility of the reactants is greatly reduced. Under such conditions, entropy (a factor not easily monitored) should be minimized. Therefore, the results should be mostly influenced by enthalpy, which can be discussed in terms of disfavored steric interactions and disfavored or favored electrostatic or stereoelectronic interactions. The five correlated experimental data are shown in Table 2. They cannot be easily rationalized because there are at least three questions that are difficult to address in a simple and satisfactory manner: (i) Why is the trans−syn−trans tricycle the only product in the unsubstituted cases (entries 1 and 3) ? (ii) Why does the cis−syn−cis adduct appear in the presence of a methyl on the diene at position 8 (entries 2 and 4)? (iii) Why is Lewis acid catalysis favoring the trans−syn−trans exo product (entries 4 and 5)?

To put sufficiently accurate figures on all those interactions, we calculated the different transition states (TSs) corresponding to these reactions at the RHF/3-21G theory level[29] by means of

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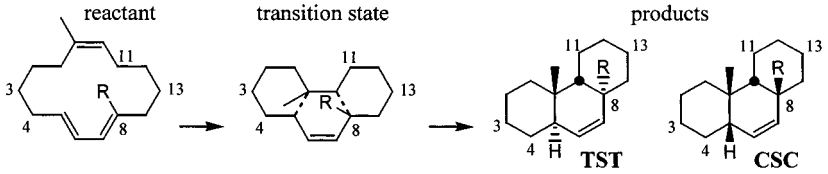
Table 2. Experimental Results



position							products		
3	4	8	11	13	macrocyle	conditions	TST	CSC	entry
E_2	E_2	H	H_2	E_2	**1**	80 °C	100	0	1
E_2	E_2	Me	H_2	E_2	**2**	310 °C	85	15	2
β-MeO	α-Me	H	$_{11}$C=O	E_2	**3**	85 °C	100	0	3
β-MeO	α-Me	Me	$_{11}$C=O	E_2	**4**	125 °C	50	50	4
β-MeO	α-Me	Me	$_{11}$C=O	E_2	**4**	$SnCl_4$, −25 °C	100	0	5

GAMESS.[30] The zero point energy corrections were not applied due to the large size of the systems, which always prevented us from calculating them. However, these corrections are known not to affect the relative energies between TSs in a significant way.[31]

We also reasoned that it should be possible to deconvolute the effect of each substituent found at positions 3, 4, 8, 11, and 13. We can safely assume that the substituents in ring A and the ones in ring C that act in an antagonistic or synergistic way can be studied separately. Thus, the calculations to be carried out were selected according to this purpose. The most influential factors with a direct impact on the TADA reaction mechanism itself should be the presence or the absence of a carbonyl at position 11 (with the possibility of Lewis acid catalysis with the carbonyl) and then the substitution of the diene at position 8. All the other substituents, which are away from the reaction site, should be less influential but can still modulate the effect of the substituents at positions 11 and 8.

The best way of analyzing the problem would be to isolate each factor that influences the TADA reaction. Thus, the factors that we must account for are the following: (a) the geometry of the macrocycle at the TS which can be cbc (chair−boat−chair), bbc, cbb, or even bbb; (b) the effect of the most influential substituents at positions 11 and 8; and (c) the effect of the substituents far away from the reaction site at positions 3, 4, and 13.

The theoretical study that follows is precisely intended to isolate all these various factors; the results of the calculations are shown in the Tables 3 and 4. Table 3 relates to not-activated TADA reactions (CH_2 at position 11) and corresponds to the experimental results of the macrocycles **1** and **2**. Table 4 relates to reactions with a dienophile activated by a carbonyl at position 11; it corresponds to the experimental results of the macrocycles **3** and **4** under purely thermal conditions and to the macrocycle **4** catalyzed by a Lewis acid.

(a) Influence of the Geometry of the Macrocycle at the Transition State. For the five studied cases, it was initially necessary to determine by calculation which TS would have been the probable pathway without the presence of the various substituents at positions 3, 4, and 13. These results indicated in the left-hand column of Tables 3 and 4 show that the cbc geometry is generally favored. However, it is sometimes possible that the cbb geometry (better described as chair−boat−twist boat from calculations) must be taken into account (11% for a cbb cis−syn−cis TS in Table 3) or is even preferred to the cbc geometry (see Table 4: cbc cis−syn−cis TS, 3.83 kcal/mol vs cbb cis−syn−cis TS, 3.36 kcal/mol) because there are no major detrimental 1,4 interactions in those cases. Such is not the case for the geometry bbc (twist boat−boat−chair) in which the methyl of the dienophile (position 10) always leads to a severe steric 1,4 interaction with the substituents in position 3 even if those are hydrogens. The bbc geometry is on average destabilized by 6.28 kcal/mol and is therefore omitted in the tables. The bbb (twist boat−boat−twist boat) geometry was not considered for the same reasons. The theoretical results also show that the cbb trans−syn−trans TSs cannot really compete with the cbc trans−syn−trans TSs; indeed, the differences in energies ($E_{cbb} - E_{cbc}$) calculated in these cases are 5.11, 5.22 (6.55−1.33), 2.41, 3.91, and 6.11 kcal/mol. For the cis−syn−cis TSs, the situation is quite different because the differences in energy ($E_{cbb} - E_{cbc}$) are now much smaller with values of 3.95 (4.86−0.91), 2.13, 0.17 (2.32−2.15), −0.47 (3.36−3.83; cbb more stable), and 1.10 kcal/mol (4.99−3.89). These figures confirm that a boat conformation for the tether ring is only possible close to a cis junction but not trans. According to this principle, only the transition states trans−syn−trans cbc, cis−syn−cis cbc, and cis−syn−cis cbb can lead to adducts.

(b) Influence of the Substitution on the Diene at Position 8. When there are no substituents at position 8, the cbc trans−syn−trans geometry is favored by 0.91 kcal/mol compared to the cbc cis−syn−cis geometry (Table 3, top, Ra = H and Rc = H) because the latter has two diene−H interactions that are not found in the trans−syn−trans geometry. For this reason, trans−syn−trans adducts are naturally favored when the diene is not substituted. That is also confirmed in the case of an activated dienophile (Table 4, top, R = H and Rc = H) since the trans−syn−trans adduct is now more stable than the cis−syn−cis adduct by as much as 2.15 kcal/mol. The addition of a methyl in position 8 introduced a methyl−H interaction into the cbc trans−syn−trans geometry (Table 3, bottom, Ra = H and Rc = H), but it is also necessary to mention the appearance of an interaction undoubtedly much more severe between the methyl of the diene and the pseudoaxial hydrogen in position 11. Calculations reveal indeed that one of the hydrogens of this methyl group and the axial hydrogen in position 11 are very close in space with a separation of only 1.98 Å (two van der Waals radii of H, 2.2 Å). There is also evidence of such an unfavorable steric interaction in the distances *b* (distance between C8 and C9) in the transition state. Thus, it should be noted that this distance *b* is 0.04 Å (2.28 − 2.24 Å) shorter in the cbc cis−syn−cis TS (Table 3, bottom) compared to the cbc

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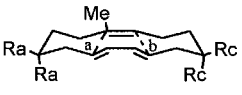
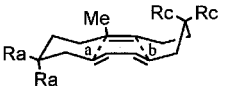
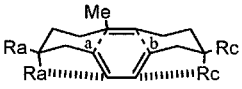
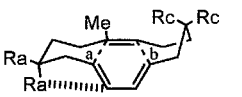
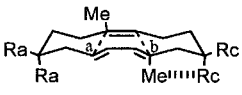
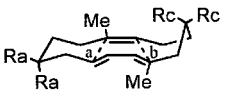
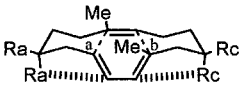
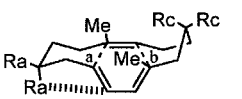
Table 3. Theoretical and Experimental Results: TADA of **1** (H at position 8) (80 °C) (top) and TADA of **2** (Me at position 8)(310 °C) (bottom)

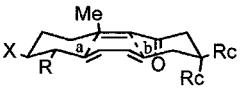
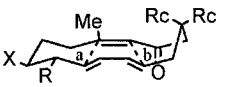
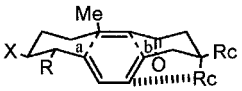
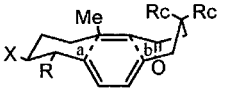
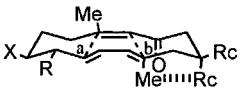
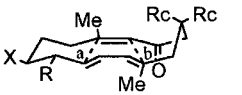
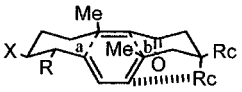
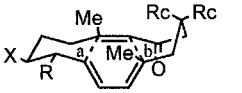
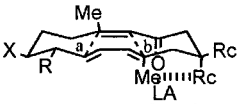
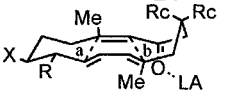
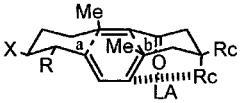
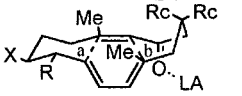
Transition state				Calculations				Experimental
				Ra=H (3) Rc=H (13)	Ra=E (3) Rc=H (13)	Ra=H (3) Rc=E (13)	Ra=E (3) Rc=E (13)	
TST		cbc	E (Kcal/mol)	**0.00**	**0.00**	**0.00**	**0.00**	100%
			population	78%			95%	
			a - b (Å)	2.27 - 2.20			2.26 - 2.21	
		cbb	E (Kcal/mol)	**5.11**	/	**6.21**	/	
			population	0%				
			a - b (Å)	2.25 - 2.20				
CSC		cbc	E (Kcal/mol)	**0.91**	**1.65**	**1.55**	**2.12**	0%
			population	22%			5%	
			a - b (Å)	2.29 - 2.19			2.29 - 2.18	
		cbb	E (Kcal/mol)	**4.86**	/	**4.26**	/	
			population	0%				
			a - b (Å)	2.23 - 2.22				
TST		cbc	E (Kcal/mol)	**1.33**	**0.65**	**1.46**	**0.29**	15%
			population	22%			37%	
			a - b (Å)	2.22 - 2.28			2.21 - 2.30	
		cbb	E (Kcal/mol)	**6.55**	/	**6.45**	/	
			population	0%				
			a - b (Å)	2.23 - 2.26				
CSC		cbc	E (Kcal/mol)	**0.00**	**0.00**	**0.00**	**0.00**	85%
			population	67%			48%	
			a - b (Å)	2.25 - 2.24			2.26 - 2.22	
		cbb	E (Kcal/mol)	**2.13**	/	**1.36**	**1.38**	
			population	11%			15%	
			a - b (Å)	2.25 - 2.24			2.23 - 2.26	

trans−syn−trans TS whereas there is no difference (0.01 Å = 2.20 − 2.19 Å) when the diene is not substituted (Table 3, top). As a result from this methyl(8)−H(11) interaction the cbc cis−syn−cis TS is now favored by 1.33 kcal/mol.

(c) Influence of a Carbonyl in Position 11. (Table 4, Column R = H and Rc = H). Thus, trans−syn−trans adducts are intrinsically preferred during the TADA reaction of a trans−trans−cis macrocycle. This tendency can be reversed by adding a methyl on the diene in position 8 because a significant transannular interaction appears between the methyl of the diene and the axial hydrogen at C11. By introducing a carbonyl at C11, the length of bond *b* in formation increases in the TS (toward 2.3−2.5 Å without catalysis and 2.8−3.2 Å with catalysis). Consequently, any transannular interaction on both sides of bond *b* should be reduced particularly in the case of the catalyzed reaction; in this case, the only observed adduct has the trans−syn−trans geometry (bottom). Obviously, when there are no substituents on the diene, the trans−syn−trans adduct is also favored (top). On the other hand, this effect is not so clear in the intermediate case, i.e., when the methyl in position 8 of the diene is found adjacent to the carbonyl at C11 in the geometry of the cbc trans−syn−trans TS and under thermal conditions (middle). In this case, indeed, calculations show that the unfavorable transannular interaction has not really disappeared because the C═O··· H−CH_2C8 distance, 2.20 Å, is still definitely smaller than the sum of the van der Waals radii of O and H (2.45 Å). In fact, in this case, this factor should support adduct cis−syn−cis; but a more complete examination of the transition states calculated show than the addition of a carbonyl at C11 introduced a new and more severe interaction between the carbonyl and the axial hydrogen at position 1 of pro-ring A. This interaction, which seems equivalent for both the trans−syn−trans and the cis−syn−cis cases, is more unfavorable in the cbc cis−syn−cis TS geometry. Thus; the C═O··· Hax−C1 distance for the cbc trans−syn−trans TSs is 2.18 (top), 2.24 (middle), and 2.18 Å (bottom); whereas for the competing cbc cis−syn−cis TSs this distance takes the following values: 2.15, 2.10, and 2.09 Å. The fact that the distance differences and the energy differences between the corresponding TSs vary in a similar way (0.03 Å/2.15 kcal/mol; 0.14 Å/3.83 kcal/mol; 0.10 Å/3.89 kcal/mol) indicates that this factor is particularly significant to explain the trans−syn−trans selectivity when there is a carbonyl at position 11. No improvements are observed for the trans−syn−trans cbb structures (2.18, 2.23, and 2.15 Å), and their energies are always definitely higher than the trans−syn−trans cbc structures. On the contrary, cbb cis−syn−cis structures really make it possible to slacken the tension of this steric interaction with respective distances of 2.21, 2.22, and 2.16 Å; that explains why the cbb cis−syn−cis TSs become significant and can even be more stable than the cbc cis−syn−cis TSs. However, in all cases, the cbc trans−syn−trans TSs are energetically favored.

(d) Influence of Substituents on Rings A and C at Positions 3, 4, and 13. To this point, calculations without the substituents on pro-rings A and C do not give an exact representation of the experimental results, which suggests that these substituents must bring a considerable influence on the selectivity. Thus, although the tendencies are in general well predicted (Tables 3 and 4, left column), the case of the thermal TADA reaction of the macrocycle **4** is particularly far away from reality (Table 4,

Table 4. Theoretical and Experimental Results: TADA of **3** (H at Position 8) (85 °C) (Top) and TADA of **4** (Me at Position 8) (125 °C) (Middle) and TADA of **4** (−25 °C, LA = BF_3 in Calculations and $SnCl_4$ in Experiments) (Bottom)

Transition state				Calculations X=H (3)				Experimental X=OMe (3)
				R=H (4) Rc=H (13)	R=Me (4) Rc=H (13)	R=H (4) Rc=E (13)	R=Me (4) Rc=E (13)	
TST		cbc	E (Kcal/mol)	**0.00**	**0.00**	**0.00**	**0.00**	100%
			population	90%			99%	
			a - b (Å)	2.14 - 2.33			2.13 - 2.34	
		cbb	E (Kcal/mol)	**2.41**	/	**3.83**	**3.86**	
			population	3%			0%	
			a - b (Å)	2.11 - 2.34			2.12 - 2.31	
CSC		cbc	E (Kcal/mol)	**2.15**	**2.62**	**7.45**	/	0%
			population	4%				
			a - b (Å)	2.15 - 2.32				
		cbb	E (Kcal/mol)	**2.32**	/	**3.12**	**3.48**	
			population	3%			1%	
			a - b (Å)	2.12 - 2.33			2.13 - 2.32	
TST		cbc	E (Kcal/mol)	**0.00**	**0.00**	**2.12**	**1.73**	50%
			population	97%			9%	
			a - b (Å)	2.08 - 2.45			2.12 - 2.40	
		cbb	E (Kcal/mol)	**3.91**	/	**1.61**	**1.29**	
			population	1%			15%	
			a - b (Å)	2.04 - 2.50			2.05 - 2.45	
CSC		cbc	E (Kcal/mol)	**3.83**	**4.41**	**6.85**	/	50%
			population	1%				
			a - b (Å)	2.09 - 2.41				
		cbb	E (Kcal/mol)	**3.36**	/	**0.00**	**0.00**	
			population	1%			76%	
			a - b (Å)	2.10 - 2.37			2.11 - 2.36	
TST		cbc	E (Kcal/mol)	**0.00**	**0.00**	**0.00**	**0.00**	100%
			population	100%			88%	
			a - b (Å)	1.97 - 3.18			2.00 - 3.15	
		cbb	E (Kcal/mol)	**6.11**	/	**3.99**	**3.98**	
			population	0%			0%	
			a - b (Å)	1.99 - 3.05			1.98 - 3.02	
CSC		cbc	E (Kcal/mol)	**3.89**	**4.40**	**4.10**	**4.70**	0%
			population	0%			0%	
			a - b (Å)	2.02- 2.93			2.06 - 2.92	
		cbb	E (Kcal/mol)	**4.99**	/	**0.57**	**1.01**	
			population	0%			12%	
			a - b (Å)	2.01 - 2.91			2.01 - 2.88	

middle). The subsequent theoretical study consists of the progressive introduction of these substituents to check their individual impact.

According to the study carried out on macrocycles **1** and **2**, one first notes that the effect of a gem diester in position 3 (Table 3, column Ra = E and Rc = H) is always to disadvantage the cbc cis−syn−cis TSs compared to the cbc trans−syn−trans TSs by a value close to 0.7 kcal/mol (1.65 − 0.91 and 1.33 − 0.65 kcal/mol) because of a diene−ester interaction in the cbc cis−syn−cis structures. As expected, the effect is the same for a gem diester in position 13 (Table 3, top, column Ra = H and Rc = E, 1.55 − 0.91 kcal/mol) because a diene−ester interaction is also present. These calculations also indicate that a Me(8)−ester interaction in a cbc trans−syn−trans TS is equivalent to a diene−ester interaction found in a cbc cis−syn−cis TS because the relative energies of these transition states remained similar whether they are substituted at position 13 (Table 3, bottom, column Ra = H and Rc = E, 1.46 kcal/mol) or not (column Ra = H and Rc = H, 1.33 kcal/mol). It is particularly interesting to note that the cbb cis−syn−cis TS can easily accommodate a gem diester in 13 since that enables the avoidance of the unfavorable diene−ester interaction. When two gem diesters are present at positions 3 and 13 (Table 3, column Ra = E and Rc = E), the calculations correspond to the real cases and the theoretical results reproduce the experimental results well. When the two diene−ester interactions energies (0.7 kcal/mol each) are added to the basic cbc cis−syn−cis TS energy (0.91 kcal/mol, Table 3), the resulting value (2.31 kcal/mol) is very close to the computed value for the cbc cis−syn−cis TS with four methyl esters (2.12 kcal/mol). In this case, the

calculated trans−syn−trans/cis−syn−cis ratio is 95:5 whereas it is 100:0 experimentally. For the macrocycle **2**, this experimental ratio is 15:85 (trans−syn−trans/cis−syn−cis); calculations give a ratio of 37:73 once again in excellent agreement with reality.

For the macrocycles **3** and **4**, there is no gem diester at position 3 but a methyl ether at this position and a methyl group in position 4. Since these two groups can be placed easily in an equatorial position on the tether in a chair conformation, we considered it useless to study the effect of the methoxy group in 3. On the other hand, the methyl in position 4 is directly adjacent with the diene and should thus exert a certain influence to be defined. Indeed, calculations (Table 4, rows cbc, column R = H and Rc = H and column R = Me and Rc = H) show that in all cases the trans−syn−trans TSs are favored by ∼0.5 kcal/mol (2.62 − 2.15, 4.41 − 3.83, 4.40 − 3.89 kcal/mol) when one adds an equatorial methyl in **4**. The effect of a gem diester in position 13 was already described, and it is accentuated even more here since the cbc cis−syn−cis TSs (column R = H and Rc = E) are now impossible. Thus, the series of macrocycle **3** (top) is very well represented since the theory (column R = Me and Rc = E) predicts a trans−syn−trans/cis−syn−cis ratio of 99:1 for an experimental ratio of 100:0. For the macrocycle **4** (without its methyl group at position 4) under thermal conditions (middle) or under Lewis acid catalysis (bottom), the cbb trans−syn−trans TS geometry allows to avoid a doubly unfavorable methyl−ester and carbonyl−ester interaction; the approximate relative energy gain of 2.2 kcal/mol (middle, 3.91 − 1.61 kcal/mol; bottom, 6.11 − 3.99 kcal/mol) is sufficient for the cbb trans−syn−trans TS to become more favored than the cbc trans−syn−trans TS under thermal conditions (middle). However, this substantial profit of energy does not make it possible for the cbb trans−syn−trans TS to become the major under catalysis (bottom) because the basic cbb trans−syn−trans TS (without substituents) is much too penalized (6.11 kcal/mol). By finally adding the methyl at position 4 (which favors trans−syn−trans TSs by ∼0.5 kcal/mol), one obtains the final theoretical trans−syn−trans/cis−syn−cis ratios of 24:76 (thermal) and 88:12 (catalysis) which represent well the experimental ratios of 50:50 and 100:0.

Conclusion

The TADA reaction of trans−trans−cis 14-membered ring trienes having a methyl on the dienophile can lead to two adducts: a trans−syn−trans tricycle and a cis−syn−cis tricycle. Rules concerning the outcome of this particular reaction were drawn out from experimental and theoretical data. These rules can be summarized as follows:

(a) The trans−syn−trans tricycle is inherently favored over the cis−syn−cis tricycle by less than 1 kcal/mol. This slight difference can therefore be supported or fought by other factors. The most influential factors are the substituents that are directly situated on the site of the reaction at positions 8 and 11.

(b) A methyl on the diene at position 8 favors the cis−syn−cis tricycle adduct. No cis−syn−cis adducts were ever observed in series not having a methyl at that position. This factor is considered to be the only one that can force the trans−syn−trans tricycle to become disfavored.

(c) A carbonyl at position 11 activates the dienophile; its most important effect is to relieve transannular interactions across the BC ring junction at the transition state. This effect is very strong with Lewis acids, and a methyl at position 8 which usually favors the cis−syn−cis adduct because of those transannular interactions has no effect any more. On the whole, the trans−syn−trans adduct is favored, despite the fact that it corresponds to an exo approach at the transition state. This result confirms once more that the Diels−Alder endo rule may be exaggerated.[32]

(d) Axial substituents at positions 3 and 13 enhance the natural tendency to lead to the trans−syn−trans adducts because cis−syn−cis transition states suffer diaxial interaction with the diene.

(e) An equatorial methyl group next to the diene at position 4 also enhances the trans−syn−trans preference by ∼0.5 kcal/mol for no obvious reasons.

(f) The cbc macrocycle geometry is usually favored at the transition state, but the cbb geometry can also be found mostly in the transition states leading to cis−syn−cis adducts. The cbb geometry is normally disfavored in the trans−syn−trans transition states.

All these elements will now allow us to pursue our synthesis of fusidic acid and related compounds. The trans−syn−trans tricycle is required for that purpose, and our experimental data (Table 2) have already shown that this tricycle can be obtained as the sole TADA adduct from **4**. Nevertheless, the calculations also suggest that the cis−syn−cis adduct is not very much disfavored because the gem diester at position 13 destabilizes the trans−syn−trans transition state. The presence of a gem diester can in fact become a burden for the rest of the synthesis, and we can see that removing it before the TADA reaction would be very advantageous because the trans−syn−trans adduct would become so much favored (4.40 kcal/mol instead of 1.01 kcal/mol by calculations, Lewis acid catalysis) so that we could introduce other necessary substituents (e.g., at position 14) without losing the trans−syn−trans selectivity.

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Supporting Information Available: Experimental procedures and data, X-ray structures of tricycles **28**, **29**, and **31**, and Cartesian coordinates (supplied as a ZIP file) of the TSs calculated at the 3.21G level of ab initio theory (left and right columns of Tables 3 and 4). See any current masthead page for ordering information and Web access instructions. This material is available free of charge via the Internet at http://pubs.acs.org.

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