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Comparative Effects of Conjugated and Deconjugated Isomeric Enones on the Transannular Diels–Alder Reaction

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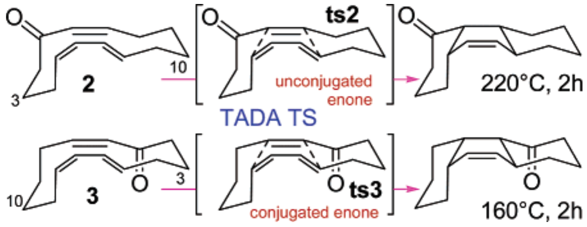
ABSTRACT



Two isomeric cyclic trienones 2 and 3 (with four methyl esters at positions 3 and 10) underwent transannular Diels–Alder (TADA) reaction at very different temperatures. This drastic difference could be traced to the capacity of the enone dienophile to be conjugated or unconjugated at the transition state. Molecular modeling could confirm this explanation. The calculated enone proved to be very distorted in transition state ts2, and the TADA reaction temperature was accordingly much higher than the one corresponding to ts3 in which the enone was flat.

The transannular environment provides a very powerful way to control the trajectories and the shapes of two reactive partners facing each other across macrocycles.[1] We could take advantage of this approach to design and carry out various syntheses of natural products, the reaction being a transannular Diels−Alder (TADA).[2] To further understand the rules governing this powerful reaction, we designed two isomeric macrocyclic trienones **2** and **3** (Figure 1) on the basis of their unactivated parent **1**. All these macrocycles have CTC (cis trans diene and cis dienophile) geometry, for the triene would yield TADA tricycle adducts having all the same CST (cis syn trans) framework.[3] Earlier studies of dienophile activation confirmed that an enone leads to a tight and a loose forming bond, at the transition state (TS), at the β and α positions of the enone, respectively.[4] It was then shown that bulky groups placed across the tight bond hinder the approach of the diene and dienophile, resulting in partial deactivation of the TADA reaction.[5] We now wish to demonstrate that the enone must adopt a flat shape at the TS for activation to take place.[6] Thus, macrocycles **2** and **3**, which differ only from each other by the relative position of the ketone group, would respectively fight or favor

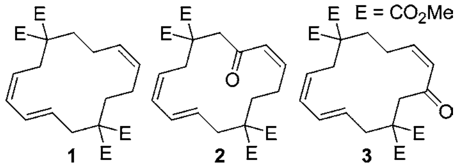


Figure 1. CTC macrocyclic trienes **1**−**3**.

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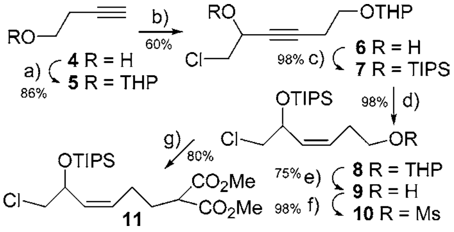
conjugation of the enone at the critical TS level. The results of this investigation constitute the topic of this letter.

Macrocycle **1** has already been prepared.[7] The two other macrocycles **2** and **3** were synthesized according to a similar general sequence of 13 linear steps starting from 3-butyn-1-ol **4** (Scheme 1).

Scheme 1[a]

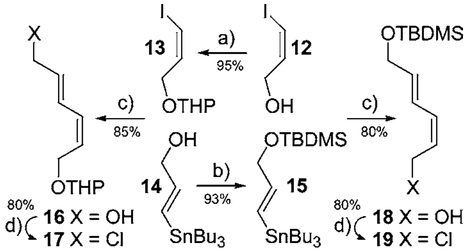


[a] Reaction conditions: (a) DHP, PTSA, CH_2Cl_2, 0 °C. (b) (i) *n*-BuLi, THF, −78 °C; (ii) $ClCH_2CHO$, THF, −60 °C. (c) TIPSOTf, 2,6-lutidine, THF, 0 °C. (d) H_2, Lindlar, Et_2O. (e) PTSA, MeOH. (f) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C. (g) $NaCH(CO_2Me)_2$, KI, THF, DMF, 80 °C.

Thus, **4** was protected as its corresponding THP ether **5** (86%).[8] The anion of **5** was prepared with *n*-butyllithium and treated with freshly prepared chloro-acetaldehyde (ozonolysis of allyl chloride) to yield the chlorohydrin **6** (60%), whose alcohol group was protected as a TIPS silyl ether in 98% yield. The resulting alkyne **7** was hydrogenated with Lindlar catalyst and hydrogen to afford the cis alkene **8** (98%).[9] The THP ether was cleaved with PTSA (75%), and the alcohol **9** was activated as its mesylate **10** with a yield of 98%. Subsequent coupling with dimethyl malonate anion gave the dienophile precursor **11** (80%) that was used to finally obtain both **2** and **3**.

The diene **17** is a known compound,[10] but we developed a new and more convergent synthesis (Scheme 2) from the allylic alcohol **12**.[11] Thus, the vinyl iodide **13**, obtained by THP protection of the alcohol **12** (95%), was coupled with the stannane **14**[12] by means of Pd(II)[13] to yield the desired diene **16** (yield: 85%) whose alcohol group was transformed into a chloride group to finally obtain the diene **17** in 80% yield. Having protected the alcohol **14** as its silyl ether **15** (93%), the same sequence was then applied to the vinyl iodide **12** and the stannane **15** to get the other required diene **19** in 64% overall yield for the two steps.

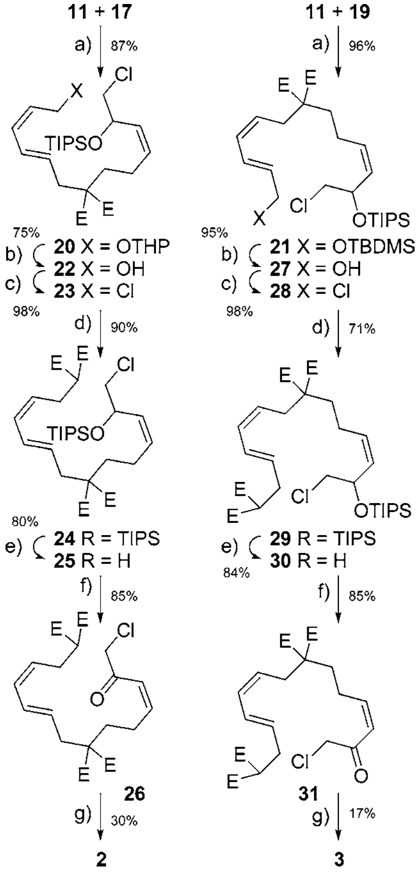
Scheme 2[a]



[a] Reaction conditions: (a) DHP, PTSA, CH_2Cl_2, 0 °C. (b) TBDMSCl, imidazole, CH_2Cl_2. (c) $(MeCN)_2PdCl_2$, DMF. (d) 2,4,6-Collidine, MsCl, LiCl, DMF, 0 °C.

The malonate **11** was either alkylated with the chloride **17** or **19** (Scheme 3) to yield the trienes **20** and **21**,

Scheme 3[a]



[a] Reaction conditions: (a) NaH, THF, DMF. (b) PTSA, MeOH. (c) Ph_3P, HCA, THF, −20 °C. (d) NaH, KI, CH_2E_2, THF, DMF, 80 °C. (e) TBAF, THF, −20 °C. (f) Dess−Martin periodinane, DIPEA, CH_2Cl_2. (g) CsI, Cs_2CO_3, MeCN.

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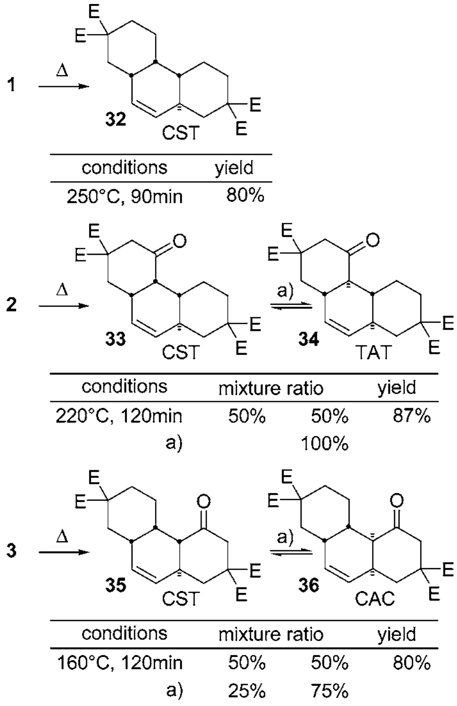
Scheme 4[a]



[a] Reaction conditions: (a) PTSA, toluene, reflux.

respectively (yields: 87 and 96%). The THP ether **20** was cleaved to yield the alcohol **22** (75%) that was transformed into the corresponding allylic chloride **23** by means of hexachloroacetone in 98% yield.[14] Dimethylmalonate was monoalkylated with the freshly prepared chloride **23** to afford the tetraester **24** (90%). Its silyl ether was cleaved with TBAF (80%), and the resulting alcohol **25** oxidized to the trienone **26** using Dess and Martin conditions (85% yield).[15] In summary, the triene **20** was transformed into the trienone **26** with an overall yield of 45%. The same five-step sequence was applied to the triene **21** to get the isomeric trienone **31** with an overall yield of 47%. Both chloroketones **26** and **31** were macrocyclized by slowly injecting them into a suspension of cesium carbonate in acetonitrile.[16] The corresponding desired macrocycles **2** and **3** were finally obtained with the rather poor yields of 30 and 17%, respectively.

The trienone **2** had to be heated at 220 °C for 120 min to produce tricycles **33** and **34** (Scheme 4). It is worth noting that these conditions are almost as drastic as the ones used to get the triene **1** to react (250 °C, 90 min). These results suggest that the activation of the dienophile by a ketone in macrocycle **2** is almost nonexistent or at best very weak. On the contrary, the isomeric trienone **3** shows marked activation of the dienophile, since it reacts at a much lower temperature (160 °C, 120 min) yielding tricycles **35** and **36**.

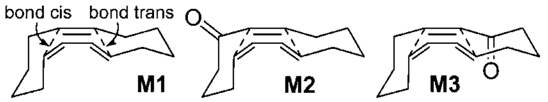


Figure 2. TSs of triene models **M1−3**.

In principle, all CTC macrocycles such as **1−3** should only give the CST adducts **32**, **33**, and **35**.[17] However, the ketones **33** and **35** can easily epimerize to give tricycles **34** and **36**, having TAT (trans anti trans) and CAC (cis anti cis) geometries, respectively. Under the TADA reaction conditions, partial epimerization occurred, yielding 1:1 mixtures of epimers in both cases. By treating these mixtures with PTSA in toluene at reflux, we proved that **34** and **36** were more stable than their epimers. This latter experiment helped us to obtain pure TAT tricycle **34**, from which we could clarify its identity by NMR spectrometry. The tricycle **35** was crystallized and its geometry proven by X-ray crystal analysis.

Ab initio calculations (3.21G)[18] were carried out on simple models **M1−3** (Figure 2) representing the macrocycles **1−3**, respectively, without their four methyl esters. In each case, the lowest energy conformation for the macrocycle was characterized together with the corresponding TSs (Table 1, no zero point energy corrections were applied). On the basis that a boat tether next to a trans ring junction is known to be disfavored,[19] we only considered TSs having either cbc (chair boat chair) or bbc (boat boat chair) conformations for the CST (cis syn trans) ABC ring systems under scrutiny. It was first observed that the bbc TSs were consistently more stable than their cbc competitors.

Table 1. Summary of Calculations[a]

		M1	M2	M3
macrocycle	θ (enone)		33°	37°
TS cbc	activation	*50.90*	*51.56*	*44.10*
	bond cis	2.27 Å	2.30 Å	2.16 Å
	bond trans	2.22 Å	2.18 Å	2.33 Å
	θ (enone)		138°	9°
TS bbc	activation	*50.78*	*49.51*	*42.94*
	bond cis	2.26 Å	2.45 Å	2.10 Å
	bond trans	2.20 Å	2.07 Å	2.36 Å
	θ (enone)		4°	15°

[a] θ: torsion of the enone. Energy (italics) in kcal/mol.

It was then possible to estimate and compare the reaction energy barriers (assuming that the entropy of reaction would be similar for all three systems).[20] The calculations proved

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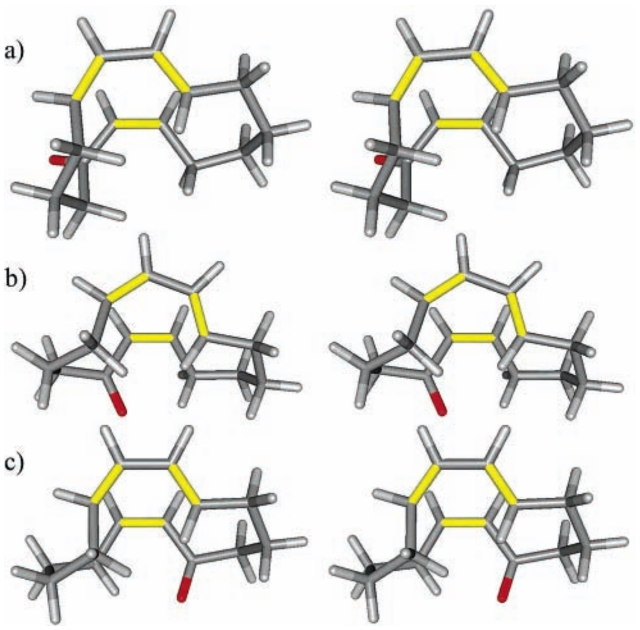

Figure 3. Stereoviews of TSs. (a) **M2** cbc, (b) **M2** bbc, (c) **M3** bbc. The twisted transoid enone in the **M2** cbc TS and the distorted **M2** bbc TS geometry are clearly visible.

to be very successful for modeling the three reactions as primarily shown by their energy barriers. An energy of 50.78 kcal/mol was associated with the no-activation case **M1**, very close to the energy calculated for **M2** (49.51 kcal/mol). Accordingly, the effect of the carbonyl in **2** should be marginal, and this is indeed the case as indicated by the temperatures of reaction: **2** reacts at 220 °C, only 30 °C lower than **1**. On the other hand, **3**, which reacts at 160 °C, must experience a strong activation from its carbonyl at the TS. Again, calculations agree with the experimental data since the activation energy for **M3** is now as low as 42.94 kcal/mol, a decrease of around 7 kcal/mol with regards to its isomeric trienone **M2**.

Inspection of the various TS geometries revealed interesting hints to explain the marked difference of reactivity of the isomeric enones **2** and **3** (Figure 3). The enone part of **M3** takes an almost flat cisoid shape both in its cbc (9°) and bbc (15°) conformations, hence its strong activation effect. On the contrary, the enone in **M2** cannot adopt such a flat arrangement in its cbc TS; in fact, its transoid conformation deviates substantially from planarity (42° = 180° − 138°). The activation energy corresponding to this cbc TS is accordingly high due to the lack of activation. In the bbc TS, the enone can assume a cisoid flat conformation. However, the energy remains rather high because the flat enone shape can only be reached through costly backbone strain, a fact clearly demonstrated by the overall conformation of the TS: the forming bonds are very asymmetric (2.45 and 2.07 Å instead of 2.30 and 2.18 Å for the cbc competing TS) and do not belong to the same plane, leading then to a very distorted Diels−Alder TS geometry.

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Supporting Information Available: Experimental procedures and full characterizations for new compounds, except for **33** and **36** (partial ^{1}H NMR assignments from mixtures), all coordinates (*xyz*) for **M1**−**3** (macrocycles and TSs), and a CIF file for **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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