

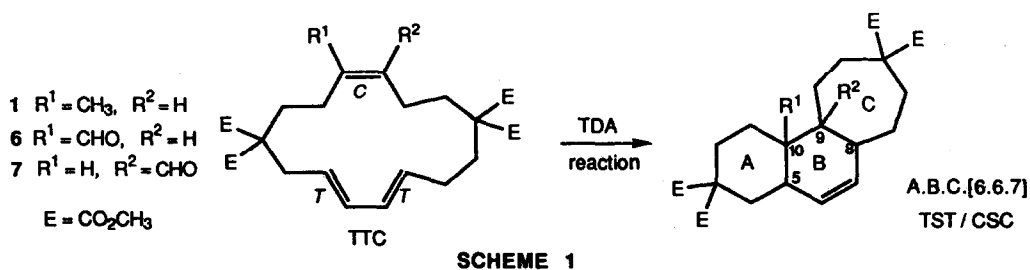
## Transannular Diels-Alder Reaction of *Trans-Trans-Cis* 15-Membered Macrocyclic Trienes. Evidence for Asynchronous Transition State.

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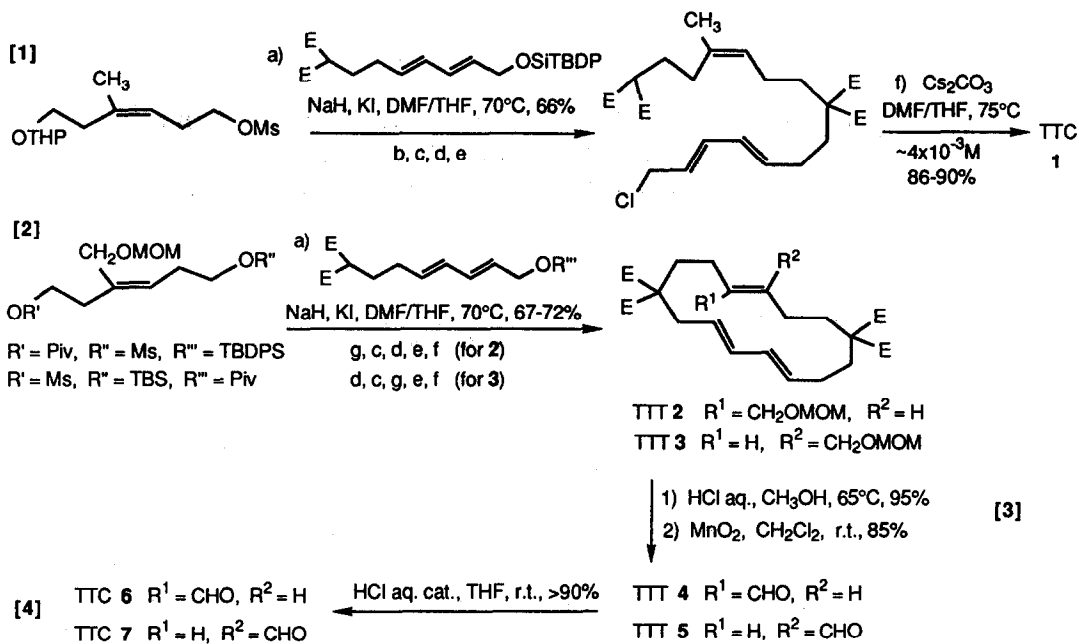
**ABSTRACT:** The transannular Diels-Alder reaction of *trans-trans-cis* 15-membered macrocyclic trienes **1**, **6**, and **7** leading to A.B.C.[6.6.7] tricyclic compounds is described.

We have previously reported complete studies featuring the power of the transannular Diels-Alder (TDA) reaction on 13- and 14-membered macrocyclic trienes as a general synthetic approach to A.B.C.[6.6.5] and [6.6.6] tricyclic compounds possessing various ring junction stereochemistry.<sup>1</sup> Although less frequent, the [6.6.7] tricyclic skeleton is found in some interesting natural products like the stemodanes, kauranes, stachanes, and aphidicolin.<sup>2</sup> In view of extending the scope of our methodology to these type of compounds, we have first studied macrocyclic trienes having a *trans-trans* (TT) diene geometry and a trisubstituted *cis* (C) dienophile. More precisely, as outlined in Scheme 1, *trans-trans-cis* (TTC) macrocycles **1**, **6**, and **7**, bearing a methyl or a formyl substituent on the dienophile were synthesized and the outcome of their TDA reaction is reported herein.



The desired macrocyclic trienes were obtained from our standard convergent approach.<sup>1</sup> Thus, methyl-substituted *C*-dienophile was coupled with the TT-diene-malonate leading to TTC macrocycle **1** after functional group transformations and macrocyclization (eq. [1] in Scheme 2). Similarly, MOMOCH<sub>2</sub>-substituted dienophile of *trans* geometry (with respect to the longest chains) was coupled at either end with the same diene leading to pro-10 substituted TTT macrocycle **2** or the pro-9 regioisomer **3** (eq. [2]) whose structure was ascertained by X-ray analysis.<sup>3</sup> Formyl-substituted TTT macrocycles **4** and **5** were obtained from TTT macrocycles **2** and **3** respectively through MOM cleavage followed by MnO<sub>2</sub> oxidation of the resulting alcohols (eq. [3]). Fast and complete acid-catalyzed *trans/cis* isomerization of the enal moiety of **4** and **5** then furnished TTC macrocycles **6** and **7** respectively (eq. [4]).<sup>4</sup>

The results of TDA reactions of TTC macrocycles **1**, **6**, and **7** are summarized in the Table.<sup>5</sup> Each TTC macrocyclic triene can afford in principle, two tricyclic diastereomers; one of *trans-syn-trans* (TST) stereochemistry by means of an *endo* approach (relative to CH<sub>3</sub> or CHO) and one of *cis-syn-cis* (CSC) stereochemistry from an *exo* approach. Methyl-substituted macrocyclic triene **1** provided a 86:14 ratio of products favoring TST

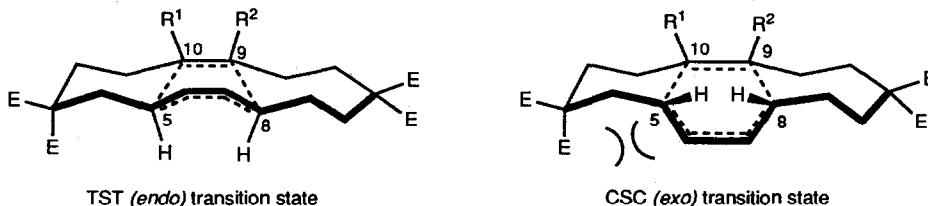


b) PPTS, *i*PrOH, 80°C, 1 h, 80%; c) i) MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, quant.; ii) NaCH(CO<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, KI, DMF/THF, 70°C, 92%; d) Bu<sub>4</sub>NF, THF, r.t., 3 h, 90%; e) MsCl, LiCl, collidine, DMF, 0°C, 1.5 h, 84%; g) CH<sub>3</sub>ONa, CH<sub>3</sub>OH, r.t., 78%.

SCHEME 2


tricycle **1a** (entry 1). Comparison of the two transition states mentioned above (Scheme 3) reveals, in the CSC case, the presence of a severe 1,3-diaxial steric interaction between the pseudo-axial ester function of ring A in a chair conformation and one of the sp<sup>2</sup> carbons (C6). Such an interaction being absent in the TST transition state, the preferential formation of TST tricycle **1a** over that of CSC tricycle **1b** is readily explained.

Compared to macrocycle **1** and contrasting to the known behavior of carbonyl-activated dienophiles, macrocycle **6** having an aldehyde function (R<sup>1</sup>) at the pro-10 position led to a decrease in *endo*-selectivity giving a **6a/6b** ratio of 76:24 (entries 2 and 3). An explanation of this result relies on the "concerted asynchronous transition state" hypothesis for unsymmetrical Diels-Alder substrates.<sup>6,7</sup> Indeed, when R<sup>1</sup> = CHO, as in acrolein-type dienophiles, the largest LUMO coefficient lies at the β-site (C9),<sup>8</sup> resulting at the transition state level in a short C9-C8 and a longer C10-C5 distance indicating that the incipient bonding is more advanced in the former case. Therefore, it follows that the importance of steric interactions in the vicinity of C10 and C5



SCHEME 3

TABLE. TDA Reaction of 15-Membered Macrocyclic TTC Trienes.



Entry	Macrocyclic substrate	Method <sup>a</sup>	Temp., Time	Yield <sup>b</sup>	Products <sup>c</sup> and ratios <sup>d</sup>
1	R <sup>1</sup> = CH <sub>3</sub> (pro-10) R <sup>2</sup> = H				<b>1a</b> <b>1b</b>
1	<b>6</b> R <sup>1</sup> = CHO (pro-10) R <sup>2</sup> = H	thermal	200°C, 4 h	63%	<b>6a</b> 86:14 <b>6b</b>
2		thermal	200°C, 7 h	60%	76:24
3		thermal	150°C, 5 h <sup>e</sup>		76:24
4		AlCl <sub>3</sub>	r.t., 20 h		no reaction
5		SnCl <sub>4</sub> , C <sub>6</sub> H <sub>6</sub>	80°C, 2 h		87:13
	<b>7</b> R <sup>1</sup> = H R <sup>2</sup> = CHO (pro-9)				<b>7a</b> <b>7b</b>
6		thermal	145°C, 5 h	85%	100:0 <sup>f</sup>
7		AlCl <sub>3</sub>	r.t., <30 min	95%	100:0 <sup>f</sup>

<sup>a</sup> Thermal reactions were performed neat or in C<sub>6</sub>H<sub>6</sub> into a dried pyrex tube sealed under vacuum. Acid-catalyzed reactions used excess Lewis acids and could be accomplished either in CH<sub>2</sub>Cl<sub>2</sub> or C<sub>6</sub>H<sub>6</sub>. <sup>b</sup> Total yields of isolated products. <sup>c</sup> Diastereomeric pairs are all separable on silica gel. <sup>d</sup> Diastereomeric ratios were determined by <sup>1</sup>H nmr analysis of crude reaction products. <sup>e</sup> At this point, the reaction is 65% completed. <sup>f</sup> Minor isomer could not be detected by <sup>1</sup>H nmr.

must be diminished, including the key pseudo 1,3-diaxial interaction which is taking place in the CSC transition state as mentioned above. Consequently, as this steric interaction is weakened, the formation of a slightly greater proportion of CSC tricycle **6b** compared to that of **1b** is well understood.<sup>9</sup> Thus, as previously observed in the thermal intramolecular Diels-Alder (IMDA) reaction,<sup>7</sup> the *endo* effect, leading to stabilizing secondary orbital interactions in this transition state, must also have a reduced influence in the transannular variant. On the other hand, the use of SnCl<sub>4</sub> led to a raise in *endo* selectivity with an obtained **6a/6b** ratio of 87:13 (entry 5). Again, this result parallels similar observations in the IMDA reaction<sup>7</sup> where Lewis acids were usually found very effective in promoting *endo* selectivity.

Macrocyclic regioisomer **7** gave TST tricycle **7a** exclusively, under both thermal and acid-catalyzed conditions (entries 6 and 7). In principle, owing to its spatial orientation, a permutation of the formyl group from the pro-10 to the pro-9 position should not affect the balance of steric interactions encountered in both transition states. However, in this case the aldehyde function being at the pro-9 position, the larger β-LUMO coefficient is now at C10 and a reversed situation to that encountered with macrocycle **6** should occur, *i.e.*, transition states will be characterized by a short C10-C5 and a longer C9-C8 distance. On this basis, the pseudo 1,3-diaxial interaction discussed above is now magnified in the CSC transition state of **7**, thus precluding the formation of the corresponding tricycle **7b**.

Also, the TDA reaction of macrocyclic triene **7** is significantly faster compared to that of **6**, as exemplified by entries 3 and 6 (thermal) and entries 4 and 7 (acid catalyzed). Assuming that a 6-membered ring closure is faster than that of a 7-membered ring at transition state level, this observation is also in line with the above theo-

retical arguments. Indeed, the TDA reaction of **7** gives rise to the 6-membered ring A by closure at the most advanced bonding site (C10-C5) whereas the fastest developing bond of **6** (C9-C8) rather involves the 7-membered ring C closure. Clearly, only an asynchronous mechanism can account for such observations.

In contrast to TTC (and TTT) 14-membered macrocyclic trienes which undergo the TDA reaction at less than 80°C,<sup>1</sup> the 15-membered homologs described here required a much higher temperature (up to 200°C). Thus, an additional methylene group makes a significant difference indicating that proximity effects play an important role in the TDA reaction, allowing isolation of these 15-membered macrocycles. Those effects are further substantiated by the fact that the corresponding TTC and TTT acyclic trienes do not undergo the IMDA reaction when heated at 200°C for 20 h.<sup>10</sup>

This study of Diels-Alder reaction on TTC 15-membered macrocyclic trienes has shown for the first time examples of Lewis acid catalysis applied to such a transannular process. Moreover, it was found that the position of the formyl substituent on the dienophile can alter the geometry of the transition state, influencing the extent of steric interactions which in turn resulted in different diastereomeric excess. Finally, the diastereoselectivity displayed in this model study on the TDA reaction of 15-membered macrocyclic trienes confirms its synthetic potential for the elaboration of A.B.C.[6.6.7] tricyclic structures.<sup>11</sup> The following communication describes the results obtained with TTT macrocyclic analogs.

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1. Deslongchamps, P.; *Aldrichimica Acta* **1991**, *24*, 43-56, and references cited therein.
2. (a) Devon, T.K.; Scott, A.I.; *Handbook of Naturally Occurring Compounds*; Vol. II: Terpenes. Academic Press: New York, 1972. (b) Kametani, T., Ed.; *Heterocycles*, Supplement no 2; June 1983.
3. Drouin, M.; Michel, A.; Université de Sherbrooke, Unpublished results.
4. Macrocyclic triene **7** has also been synthesized from a pre-formed *cis* dienophile.
5. All macrocyclic substrates and tricyclic products gave spectroscopic datas (NMR, IR, MS) in agreement with the assigned structures and control experiments have ascertained the kinetic nature of the diastereomeric ratios. Complete experimental details of this work will be reported elsewhere.
6. For related discussions on the mechanism of the Diels-Alder reaction including semi-empirical calculations: (a) Dewar, M.J.S.; Olivella, S.; Stewart, J.J.P.; *J. Am. Chem. Soc.* **1986**, *108*, 5771, and references cited therein. (b) For a review, see: Sauer, J.; Sustmann, R.; *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779-807.
7. Many reports using this hypothesis to account for results in the intramolecular Diels-Alder (IMDA) reaction has appeared. For a review on the IMDA reaction, see: Craig, D.; *Chem. Soc. Rev.* **1987**, *16*, 187-238.
8. Fleming, I.; *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, **1976**, p. 163.
9. This slightly greater proportion of CSC isomer when R<sup>1</sup> = CHO may also be explained by the fact that a B.C.[6.7] *cis* ring junction might be more easily formed, since the C9-C8 incipient bond (the most advanced and shortest at this level) has a crucial role in transition state discrimination.
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11. Financial support of this work by NSERCC (Ottawa) and "FCAR (Québec)" is gratefully acknowledged.

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