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Transannular Diels-Alder Reaction of *Trans-Trans-Trans* 15-Membered Macrocyclic Trienes

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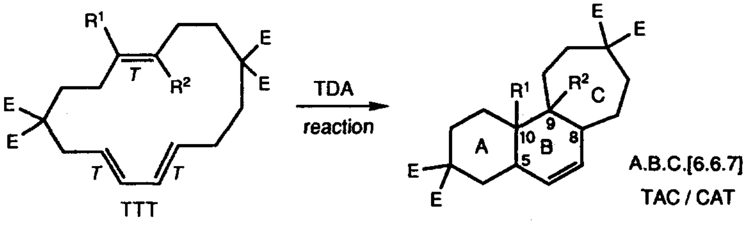
ABSTRACT: *The transannular Diels-Alder reaction of trans-trans-trans 15-membered macrocyclic trienes 1-5 leading to A.B.C.[6.6.7] tricyclic compounds is described.*

In the preceding communication[1] we reported the results of a study on the transannular Diels-Alder (TDA) reaction of *trans-trans-cis* (TTC) 15-membered macrocyclic trienes leading to A.B.C.[6.6.7] tricyclic compounds. It was shown that the position of a formyl substituent on the dienophile has a crucial influence on the observed diastereoselection by affecting the geometry of the transition states through the hypothesis of a concerted but asynchronous mechanism. We have also studied the TDA reaction of *trans-trans-trans* (TTT) macrocyclic trienes which can lead to other interesting A.B.C.[6.6.7] tricyclic diastereomers. More specifically, macrocycles **1-5** (Scheme 1) containing a *trans* (relative to the longest chains) trisubstituted dienophile bearing an alkyl or a formyl substituent were investigated.

1 $R^1 = CH_3$, $R^2 = H$
2 $R^1 = CH_2OMOM$, $R^2 = H$
3 $R^1 = H$, $R^2 = CH_2OMOM$
4 $R^1 = CHO$, $R^2 = H$
5 $R^1 = H$, $R^2 = CHO$

$E = CO_2CH_3$

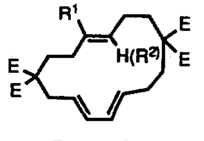


SCHEME 1

The synthesis of macrocycles **2** to **5** was previously described (Scheme 2, preceding communication[1]). In addition, macrocycle **1** was also prepared by coupling the appropriate T-dienophile and the same TT-diene synthon in the usual fashion.

In principle, each TTT macrocyclic triene can lead to two tricyclic diastereomers, namely *trans-anti-cis* (TAC) and CAT. The results of TDA reactions of TTT macrocycles **1-5** are summarized in the Table.[2] Pro-10 methyl-substituted macrocycle **1** gave a 88:12 ratio of TAC **1a** and CAT **1b** tricycles respectively (entry 1), the former resulting from an *endo* approach (relative to R^1). Similarly, CH_2OMOM-substituted macrocycle **2** furnished a 90:10 ratio of products again favoring TAC tricycle **2a** (entry 2) whose stereochemistry was established by X-ray analysis.[3] Inspection of the CAT transition state (Scheme 2) reveals a severe 1,3-diaxial steric interaction between the pseudo-axial ester function of ring A in a chair conformation and the sp^2 carbon (C6) of ring B. Such an interaction is absent in the TAC transition state and therefore the formation of greater proportions of TAC tricycles **1a** and **2a** over CAT tricycles **1b** and **2b** is well explained.

TABLE. TDA Reactions of 15-Membered Macrocyclic TTT Trienes.



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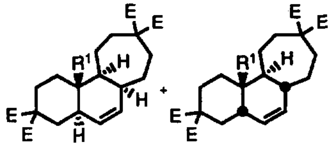
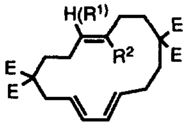
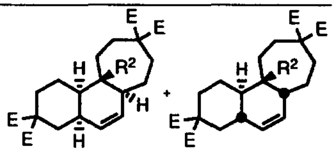


TAC *(endo)* CAT *(exo)*

Entry	Macrocyclic substrate	Method[a]	Temp., Time	Yield[b]	Products[c] and ratios[d]		
	1 $R^1 = CH_3$ (pro-10)				**1a**		**1b**
1		thermal	200°C, 4.5 h	63%		88:12	
	2 $R^1 = CH_2OMOM$ (pro-10)				**2a**		**2b**
2		thermal	200°C, 4 h	60%		90:10	
	4 $R^1 = CHO$ (pro-10)				**4a**		**4b**
3		thermal	130°C, 5 h[e]			100:0[f,g]	
4		thermal	300°C, 3 min	90%		100:0[f,g]	
5		$AlCl_3$, C_6H_6	r.t., 1.5 h			no reaction	
6		$SnCl_4$, C_6H_6	65°C, 4 h			g	



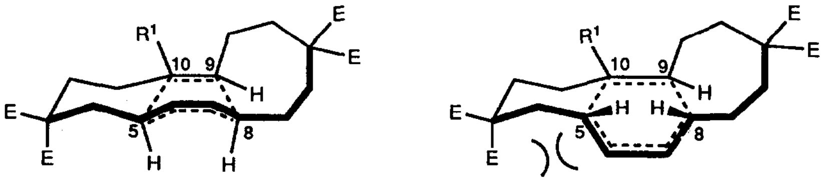
E = CO_2CH_3



CAT *(endo)* TAC *(exo)*

	3 $R^2 = CH_2OMOM$ (pro-9)				**3a**		**3b**
7		thermal	205°C, 6.5 h	98%		22:78	
	5 $R^2 = CHO$ (pro-9)				**5a**		**5b**
8		thermal	320°C, 1.5 min			23:77[g]	
9		thermal	150°C, 5.5 h			g	
10		$AlCl_3$, CH_2Cl_2	r.t., 2 h			16:84[g]	
11		$AlCl_3$, C_6H_6	r.t., 1 h[e]			16:84	

[a] Thermal reactions were performed neat or in C_6H_6 into a dried pyrex tube sealed under vacuum. Acid-catalyzed reactions used excess Lewis acids and could be accomplished either in CH_2Cl_2 or C_6H_6. [b] Total yields of isolated products except entries 4 and 7 (crude yields of products, non separated). [c] Diastereomeric pairs are all separable on silica gel. [d] Diastereomeric ratios were determined by ^1H nmr analysis of crude products. [e] At this point, the reaction is 40% completed for entry 3 and 85% for entry 11. [f] Minor isomer could not be detected by ^1H nmr.[g] Percentage of TDA products resulting from TTT → TTC *in situ* isomerization: entry 3: 50%, entry 4: 25%, entry 6: 100%, entry 8: 40%, entry 9: >90%, entry 10: 40%.

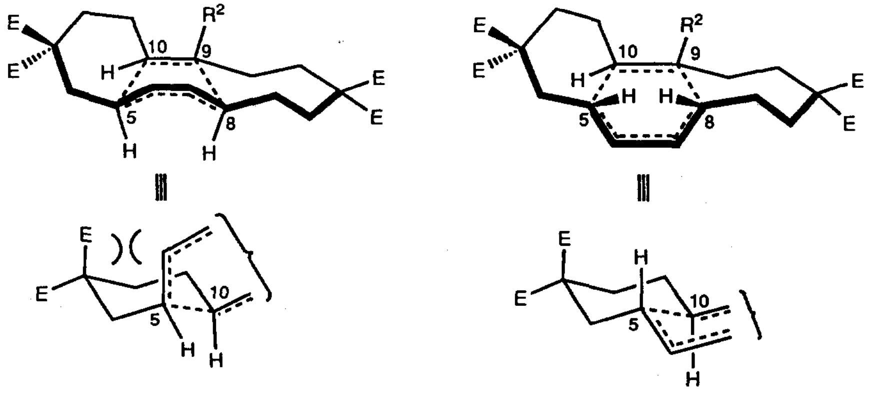


TAC *(endo)* transition state CAT *(exo)* transition state

SCHEME 2

The propensity at which TTT macrocyles **4** and **5** were found to isomerize into the corresponding TTC macrocycles[1,4] led us to use reaction conditions preventing isomerization of the conjugated dienophile prior to the Diels-Alder reaction. However, this problem could never be totally avoided.[5] Upon catalysis by $SnCl_4$ in benzene at 65°C, TTT macrocycle **4** led exclusively to the known TDA products of the corresponding TTC isomer (entry 6). However, under thermal activation only, the isomerization process was limited to the extent of 25-50%, allowing us to obtain TAC tricycle **4a** as the sole TDA reaction product from TTT macrocycle **4** (entries 3 and 4). This result can be rationalized using the same theoretical argumentation as before,[1] *i.e.*, the "asynchronous transition state" hypothesis for unsymmetrically activated dienophiles. Indeed, the presence of a formyl substituent (R^1) at the pro-10 position results in transition states having a short C9-C8 and a longer C10-C5 distance; a logical consequence of faster bonding development at the site bearing the larger β-LUMO coefficient. The magnitude of steric interactions around the short C9-C8 incipient bond is then raised, conferring to these interactions a decisive role in transition state discrimination. When such a situation happens, as for the TTC isomer of macrocycle **4**, a trend towards the obtention of a *cis* B.C.[6.7] ring junction seems to occur.[1] Compared to **1** and **2**, this supplementary factor further favors the TAC transition state of **4** and explains the unique obtention of the corresponding tricycle **4a** because the CAT transition state still suffers from the same unfavorable steric interaction encountered in macrocycles **1** and **2**.

Macrocyclic triene **3** bearing a CH_2OMOM substituent (R^2) at the pro-9 position gave a 22:78 ratio of products favoring TAC tricycle **3b** over CAT **3a** (entry 7). Thus, by moving the substituent on the dienophile from the pro-10 position as in **1**, **2**, and **4** to the pro-9 position, a reversal of *endo*/*exo* selectivity occurred. The analysis of transition states (Scheme 3) shows that the previously encountered steric interaction due to the pseudo-axial ester function of ring A is now present in the *endo* transition state leading to CAT tricycle **3a**. This interaction is absent in the *exo* approach, hence explaining the preponderance of the TAC tricycle **3b** in this case.



CAT *(endo)* transition state

TAC *(exo)* transition state

SCHEME 3

The thermal TDA reaction of macrocycle **5** (R^2 = CHO) gave a CAT **5a** / TAC **5b** ratio of 23:77 (entry 8) still accompanied by a large amount of the known Diels-Alder product[1] coming from *in situ* TTT → TTC isomerization. As in the TTC series,[1] the TDA reaction being faster when the more advanced incipient bond is closing the 6-membered ring, the Lewis acid catalyzed reaction of macrocycle **5** could be carried out at a lower temperature compared to isomer **4**. Contrary to dichloromethane (entry 10), the use of a non-polar solvent like benzene, at room temperature, has essentially stopped the competing isomerization and a 16:84 ratio of products favoring TAC tricycle **5b** was obtained (entry 11). It is known from the intramolecular Diels-Alder (IMDA) reaction[6] that the effect of Lewis acid catalysis on carbonyl-activated dienophiles is twofold: a) secondary orbital interactions become substantially more important as a large increase in *endo* selectivity is generally observed; b) the asynchronicity of concerted bond formation is enhanced, both effects arising from the accentuation of the size difference already present between the LUMO coefficients on both the carbonyl and the olefin.[7] These two effects are opposing each other in the transition states of macrocycle **5** because further shortening of the C10-C5 distance increases the key pseudo 1,3-diaxial interaction in the *endo* (CAT) transition state. Actually, this steric factor is even found to overcome secondary orbital interactions as the *endo* selectivity is decreased upon use of a Lewis acid (compare entry 8 *vs* 10, 11).

In summary, the stereoselectivity of the TDA reaction of TTT 15-membered macrocyclic trienes and their TTC congeners[1] was found to be strongly controlled by steric interactions originating from the substituents on the connecting chains. Moreover, a formyl group on the dienophile can alter the geometry of transition states through an asynchronous mechanism, hence controlling diastereoselection by affecting the extent of these steric interactions. This consequence of asynchronicity is further increased by Lewis acids, which were also found necessary to make the *endo* effect operative. In the case of macrocycle **5**, these two stereocontrolling factors are opposing each other.

Thus, the stereoselectivity observed in these model studies, spanning from good to specific, confirms the TDA reaction of 15-membered macrocyclic trienes as a valuable synthetic approach to natural products containing the A.B.C.[6.6.7] tricyclic skeleton. The tools to define a predictive model being well in hand, such applications are now under examination in our laboratory.[8]

REFERENCES AND NOTES

1. See following accompanying communication, and references cited therein.
2. 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.
3. Drouin, M.; Michel, A.; Université de Sherbrooke, Unpublished results.
4. Molecular modeling followed by semi-empirical (AM1) calculations have given a lower ΔH°_f (4 kcal/mol) for the TTC isomer.
5. Heat and Lewis acids can promote double bond isomerization: Sonnet, P.E.; *Tetrahedron* **1980**, *36*, 557-604.
6. Craig, D.; *Chem. Soc. Rev.* **1987**, *16*, 187-238.
7. (a) Fleming, I.; *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, **1976**, p. 163. (b) Birney, D.M.; Houk, K.N.; *J. Am. Chem. Soc.* **1990**, *112*, 4127.
8. Financial support of this work by NSERCC (Ottawa) and "FCAR (Québec)" is gratefully acknowledged.

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