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Macroring Contraction Methodology. 6. Transannular Diels-Alder Reaction of the 14-Membered (E,E,E)-Trienone

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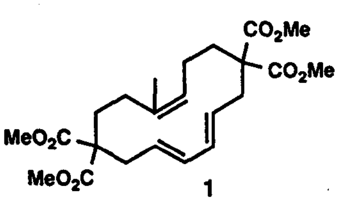
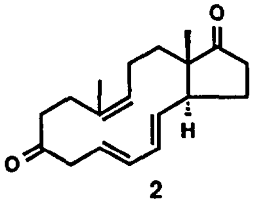
SUMMARY: Transannular Diels-Alder reaction of the 14-membered (E,E,E)-trienone **9** and a discussion of its high diastereoselectivity based on MM2 transition-state model are presented.

Macrocyclic reactions should follow a predictable course in organic syntheses[1), if preparations and rapid conformational analyses of macrocycles could be easily managed. Recently transannular Diels-Alder reactions of the (E,E,E)-trienes **1** and **2** were reported from P. Deslongchamps'[2a) and our laboratory[2b) respectively. In these studies, the reaction of **1** produced a 1 : 2 mixture of tricycles having the **cis-anti-trans** and the **trans-anti-cis** geometry in B-ring, while the reaction of **2** gave only the **cis-anti-trans** geometry. We report here transannular Diels-Alder reaction of the 14-membered (E,E,E)-trienone **4**, constructed by the intramolecular alkylation[3) of the cyanohydrin **3**, along with a discussion of the stereochemical prediction based on MM2 transition-state models. Macrocycles have the π-orbitals of the olefin oriented in the plane of the ring to minimize transannular nonbonded repulsions[4) (Fig. 1, 4). Therefore, if two reactive centers in **4** are rigidly locked at a short distance with two carbon chains, the transannular Diels-Alder reaction should give the tricyclic compound **5** in better chemical yield and with higher stereoselectivity in comparison with an acyclic Diels-Alder reaction like **3**, because of the stereoelectronic and entropy effects in a macrocyclic system.



1



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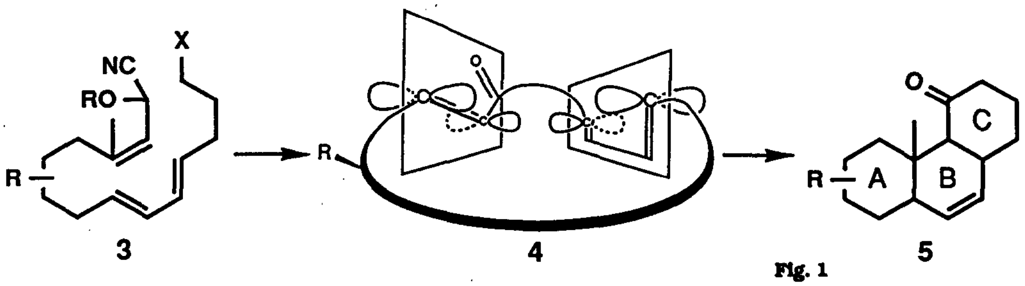
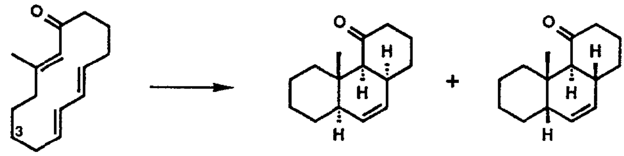


Fig. 1

The MM2 transition-state model[5] was obtained as follows ; the geometries of diene and dienophile moieties were fixed to that of the transition state in the Diels-Alder reaction of butadiene and ethylene obtained by *ab initio* calculations[6] and the rest of molecule was constructed by the ring making program (MMRS)[7], followed by energy optimization by the MM2 program[8]. In this calculation, however, the electronic effect, especially the secondary orbital effect found in the Diels-Alder reaction using the activated dienophile, is not included. At first, therefore, we examined the difference of product distributions between calculational and experimental results for the reaction of trienone **6**. MM2 calculations (Table 1) for the four possible transition states;[9] the endo transition states **6endo-chair**, **6endo-boat** and the exo transition states **6exo-chair**, **6exo-boat** provided the **trans-anti-cis 7** and the **cis-anti-trans 8**, respectively, and a Boltzmann distribution among these four transition states lead to an expected product ratio of 4 : 1 (endo **7** : exo **8**). On the other hand, Diels-Alder reaction of the trienone **6**[10] at 20 °C gave the endo and exo products **7** and **8** in a ratio of 27 : 1. Based on these calculation and experimental results, we introduce the correction value (1.15 Kcal/mol) to account for this additional endo preference. Indeed, subtraction of this correction value from the energy of the endo transition-state models led to quantitative agreement with the experimental ratio.

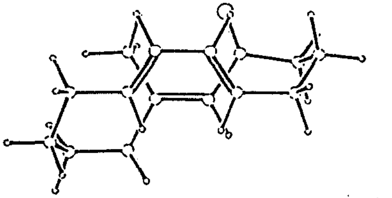
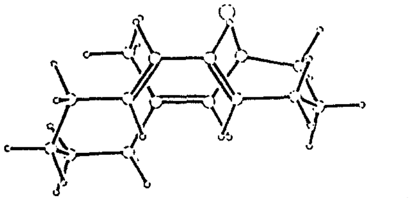
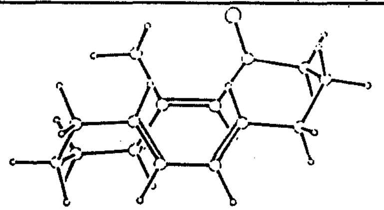
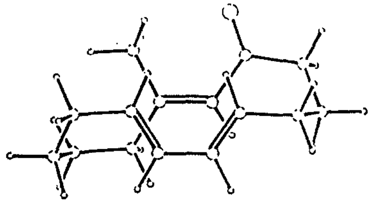
Then we examined the induced stereoselectivity from the alcohol stereogenic center in Diels-Alder reaction of the trienone **9** (Scheme 2). In this reaction there are four possible stereoisomers; two of them are endo products **10** and **11** having the **trans-anti-cis** relative stereochemistry in B-ring and other two are exo products **12** and **13** having the **cis-anti-trans** relative stereochemistry. MM2 calculations, including



6 **7** **8**

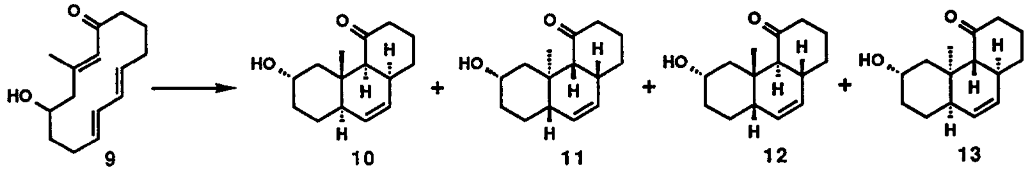
Scheme 1

Table 1. The MM2 transition-state models of the trienone **6**.

			Product
Endo	 **6endo-chair** 0.03 (-1.12)*	 **6endo-boat** 0.00 (-1.15)*	7
Exo	 **6exo-chair** 0.44	 **6exo-boat** 1.70 kcal/mol	8

* The energy values shown in parentheses already include the correction value.

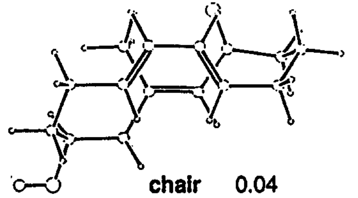
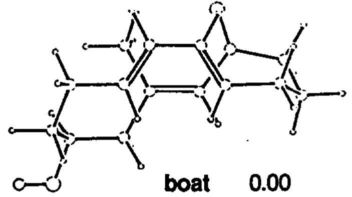
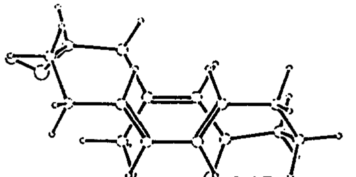
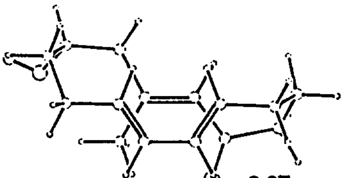
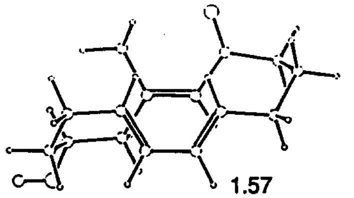
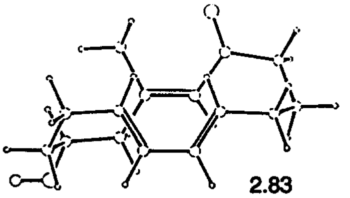
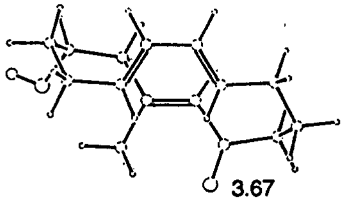
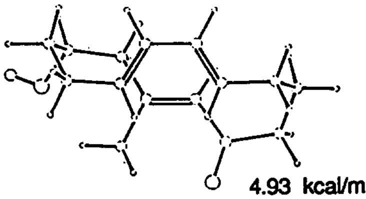
the correction value for endo effect, and a Boltzmann distribution of eight possible transition states (Table 2) suggested that the reaction of **9** should lead to an expected product ratio of 96 : 4 (endo **10**,**11** : exo **12**,**13**) and a ratio of 94 : 2 (β-Me **10**[11]: α-Me **11**) in the endo products.



Calculation 10 : 11 : 12 : 13 = 94 : 2 : 4 : 0
Experiment 10 : 11 : 12 : 13 = 93 : 0 : 7 : 0

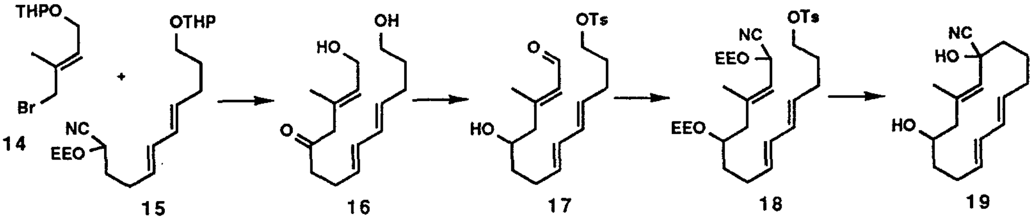
Scheme 2

Table 2. The MM2 transition-state models of the trienone **9**.

				Product
Endo	β-Me	 chair 0.04	 boat 0.00	10
	α-Me	 2.15	 2.07	11
Exo	β-Me	 1.57	 2.83	12
	α-Me	 3.67	 4.93 kcal/mol	13

Preparation of the trienone **9** and its Diels-Alder reaction were carried out as follows. Alkylation of the protected cyanohydrin **15** with **14** (LiN(TMS)$_2$/THF reflux), followed by acid and basic treatment (*p*-TsOH/MeOH, aq.NaHCO$_3$) gave the dihydroxy ketone **16** in 77% overall yield. The reduction of **16** (LiAlH$_4$), selective oxidation of the allylic alcohol (MnO$_2$) and selective tosylation of the primary alcohol gave the enal **17** in 67% overall yield. Cyanohydrin formation of the aldehyde in two steps (Me$_3$SiCN/KCN/18-crown-6, 1N HCl/THF) and protections of the resulting diol (ethyl vinyl ether/H$^+$) gave the protected cyanohydrin **18** in 78% overall yield. The cyclization of **18** with LiN(TMS)2 in dioxane at 70 °C and acid treatment (3N HCl/THF) of the cyclized product gave the free cyanohydrin **19** in 85% overall yield. The basic treatment (2% aq.NaOH) of **19** at 20 °C underwent spontaneous transannular Diels-Alder reaction to lead a 93 : 7 mixture of tricyclic compounds **10** and **12** quantitatively.

Thus these results demonstrate that MM2 transition-state models are useful in designing synthetic intermediates which show the C-O chirality in the macrocycle **9** can control the conformation of 14-membered ring and produce the **trans-anti-cis** relative stereochemistry in B-ring with a high stereoselectivity.



Scheme 3

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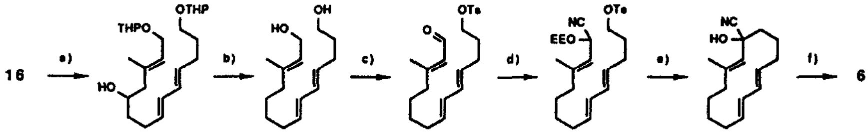
9) In both exo and endo transition states, the dominant conformation of A-ring takes the chair form because its boat conformation has the severe strain repulsion between the vinyl methyl and C3-methylene (steroidal numbering) groups. On the other hand, the C-ring has two possible chair and boat conformations within 1.26 Kcal/mol.

10) The macrocyclic enone **6** was prepared in the following way.



a) 1) DHP/H$^+$, 2) LiAlH$_4$, b) 1) TsCl/Py, 2) LiAlH$_4$, 3) H$^+$, c) 1) MnO$_2$, 2) TsCl/Py, d) 1) TMS(CN), 2) H$^+$, 3) EVE/H$^+$, e) 1) NaN(TMS)$_2$, 2) H$^+$, f) OH$^-$.

11) Satisfactory ^{1}H NMR and IR properties were obtained.

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