JOC Article

First Experimental and Theoretical Evidence of a Deactivating Enone Dienophile in the Transannular Diels−Alder Reaction

Élyse Bourque,[†] Pierre Deslongchamps,*[,†] and Yves L. Dory*[,‡]

Département de chimie, Institut de Pharmacologie, Université de Sherbooke, 3001, 12e avenue nord, Sherbrooke, Québec J1H 5N4, Canada

pierre.deslongchamps@usherbrooke.ca; yves.dory@usherbrooke.ca

Received October 2, 2002

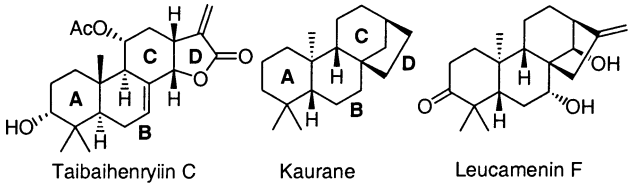
A thorough study of the transannular Diels−Alder (TADA) reaction of trans-trans-trans macrocyclic trienes was carried out. It led to a better understanding of various parameters that govern the TADA reaction in particular and the Diels−Alder reaction in general. Thus, carbonyl activation of the dienophile is thoroughly discussed in light of new experimental and theoretical data. An enone dienophile is found to deactivate the reaction, although it remains planar at the transition state. This unusual result was discussed in terms of tether substituents that provoke destabilization of the transition state.

I. Introduction

It is widely accepted that enones are activated dienophiles.[1] Accordingly, they undergo fast Diels−Alder [4+2] cycloaddition reactions, when compared to the corresponding simple alkene dienophiles.[2] There are no exceptions to this rule in intermolecular and very few in usual intramolecular environments.[3] However, the transannular Diels−Alder (TADA) strategy offers a much better way to control the approach of the diene and dienophile.[4,5] Indeed, the TADA reaction corresponds to a conformationally very restricted intramolecular Diels−Alder (IMDA) reaction, since the two reacting partners are held together by means of two tethers instead of only one. With this powerful probe as a tool, we have gathered experimental and theoretical data that unequivocally prove that enones can sometimes turn into deactivating dienophiles.

The geometry features of the transition state for the acrolein-butadiene Diels−Alder have been calculated at various RHF levels of ab initio theory.[6] In all cases, the transition state appears to be asymmetric with the following characteristics: (a) the short bond is located at the end of the acrolein molecule (2.09 Å for 3-21G calculations), (b) the long bond is next to the carbonyl (2.35 Å), and (c) the acrolein skeleton remains flat to ensure proper C=C/C=O conjugation and so to lower the energy of the dienophile LUMO. These geometry requirements can be fought in two ways: (a) by preventing the enone system from remaining flat or (b) by adding steric congestion or strain at the short bond site. Since we are currently interested in synthesizing molecules such as Taibaihenryiin C,[7] Odonicin,[8] members of the Kaurane family, like Leucamenin F,[9] and other di- and triterpenes in which the A ring is sterically congested (Chart 1), we thought that we should take that opportunity to study the aforementioned subject. Those compounds could originate from TAC (trans-anti-cis) tricycles obtained by TADA reaction of TTT (trans-trans-trans) 14-membered macrocyclic trienes (Chart 2). Since another tricycle of CAT (cis-anti-trans) geometry could be obtained as well from the same triene precursor, there are therefore two questions that we wanted to answer in model series. First, is the desired TAC adduct going to be the major product of the TADA reaction? If this is not so, then what can be done in terms of substituents to get the right bias?

CHART 1. Selected Targets for TADA Strategy



[†] Laboratoire de synthèse organique.
[‡] Laboratoire de synthèse supramoléculaire.

(1) Kistiakowsky, G. B.; Lacher, J. R. *J. Am. Chem. Soc.* **1936**, *58*, 123.

(2) Houk, K. N.; Li, Y.; Evanseck, J. D. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 682 and references therein.

(3) (a) Craig, D. *Chem. Soc. Rev.* **1987**, *16*, 187. (b) Jung, M. E.; Halweg, K. M. *Tetrahedron Lett.* **1981**, *22*, 3929. (c) Smith, D. A.; Sakan, K.; Houk, K. N. *Tetrahedron Lett.* **1986**, *27*, 4877.

(4) (a) Lamothe, S.; Ndibwami, A.; Deslongchamps, P. *Tetrahedron Lett.* **1988**, *29*, 1639. (b) Marsault, E.; Toró, A.; Nowak, P.; Deslongchamps, P. *Tetrahedron* **2001**, *57*, 4243.

(5) (a) Takahashi, T.; Katsuya, S.; Doi, T.; Tsuji, J. *J. Am. Chem. Soc.* **1988**, *110*, 2674. (b) Wood, J. L.; Porco, J. A.; Taunton, J.; Lee, A. Y.; Vlardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 5898. (c) Marshall, J. A.; Wang, X.-J. *J. Org. Chem.* **1992**, *57*, 3387. (d) Jung, S. H.; Lee, Y. S.; Park, H.; Kwon, D.-S. *Tetrahedron Lett.* **1995**, *36*, 1051. (e) Roush, W. R.; Works, A. B. *Tetrahedron Lett.* **1996**, *37*, 8065. (f) Jones, P.; Li, W.-S.; Pattenden, G.; Thomson, N. M. *Tetrahedron Lett.* **1997**, *38*, 9069.

(6) (a) Loncharich, R. J.; Brown, F. K.; Houk, K. N. *J. Org. Chem.* **1989**, *54*, 1129. (b) Dory, Y. L.; Hall, D. G.; Deslongchamps, P. *Tetrahedron* **1998**, *54*, 12279.

(7) Li, B.-L.; Pan, Y.-J.; Yu, K.-B. *Tetrahedron Lett.* **2002**, *43*, 3845.

(8) Fujita, E.; Node, M. *Prog. Chem. Org. Nat. Prod.* **1984**, *46*, 77.

(9) (a) Yoshio, T.; Tetsuro, F.; Akira, U. *Chem. Lett.* **1981**, 1229. (b) Manes, L. V.; Crews, P.; Kernan, M. R.; Faulkner, D. J. *J. Org. Chem.* **1988**, *53*, 570.

10.1021/jo0265129 CCC: $25.00
Published on Web 02/21/2003

CHART 2. Macrocyclic Trienes and Their Corresponding TADA Transition States

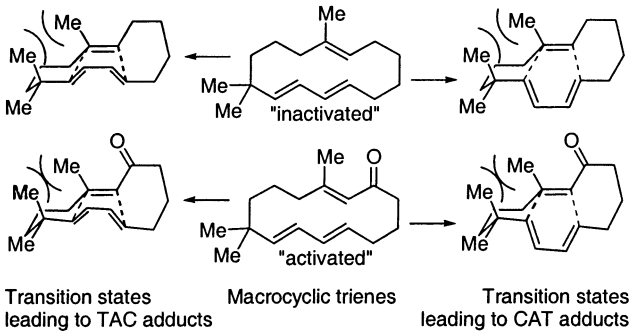
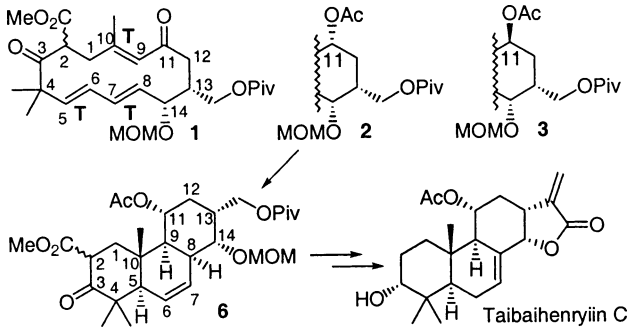


CHART 3. "Activated" and "Inactivated" Triene Models for the Synthesis of Taibaihenryiin C

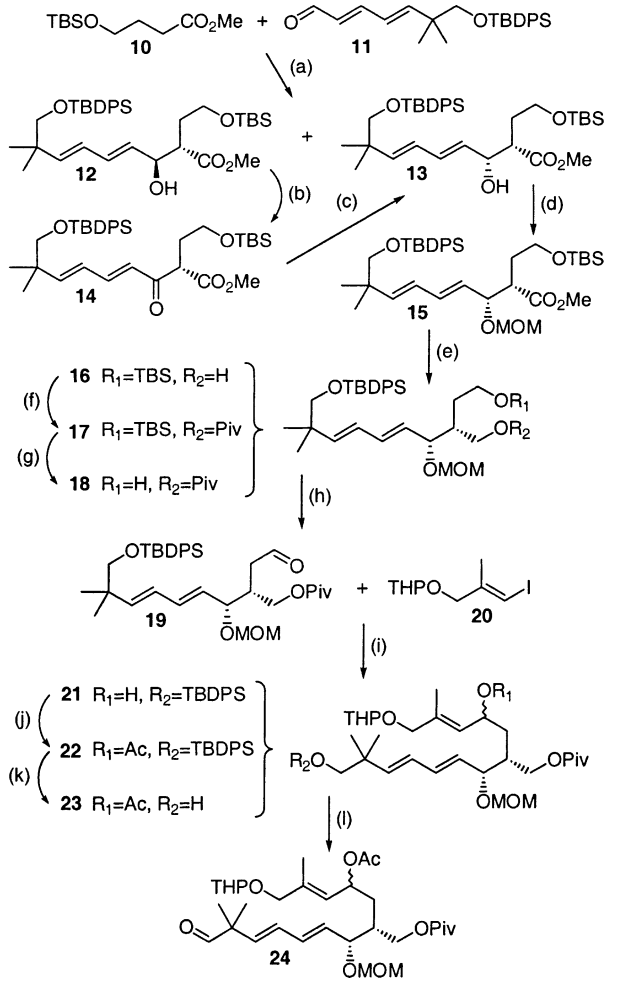


Second, is the *gem*-dimethyl group going to add too much steric hindrance, so that much higher reaction temperatures will be required? This latter aspect is very interesting, because this destabilizing steric effect could be enhanced by adding a carbonyl (at position 11) next to the dienophile, so that a normally very activated dienophile could turn out to be deactivating. Indeed, the methyl group of the dienophile and the axial methyl group of the *gem*-dimethyl could collide very strongly at the transition state, when the dienophile is conjugated with a carbonyl group, because the corresponding transition state distance shortens from 2.21 Å (calculated 3-21G distance for the ethylene/butadiene Diels−Alder transition state) to 2.09 Å.[6] In the case of the conjugated dienophile, the TADA reaction would then demand more energy despite the "activation".

Accordingly, we designed macrocycles **1**, **2**, and **3** to study this phenomenon as well as to pursue the synthesis of Taibaihenryiin C in particular, since an interesting key TAC tricyclic intermediate **6** could be easily obtained (Chart 3). The TADA experiments on the three macrocycles **1**, **2**, and **3** showed that the activation energy is larger for the trienone **1** than it is for the triene **2**. Ab initio theoretical calculations were therefore carried out to untangle all the different factors that could be responsible for such an a priori unexpected result. We wish to show these new results that complete our work on TT dienes within 14-membered macrocycles in TADA reactions (the first part was dealing with inactivated and activated cis dienophiles)[10] and that shed new light on the mechanism of the Diels−Alder reaction.

(10) Fortin, S.; Barriault, L.; Dory, Y. L.; Deslongchamps, P. *J. Am. Chem. Soc.* **2001**, *123*, 8216.

SCHEME 1[a]



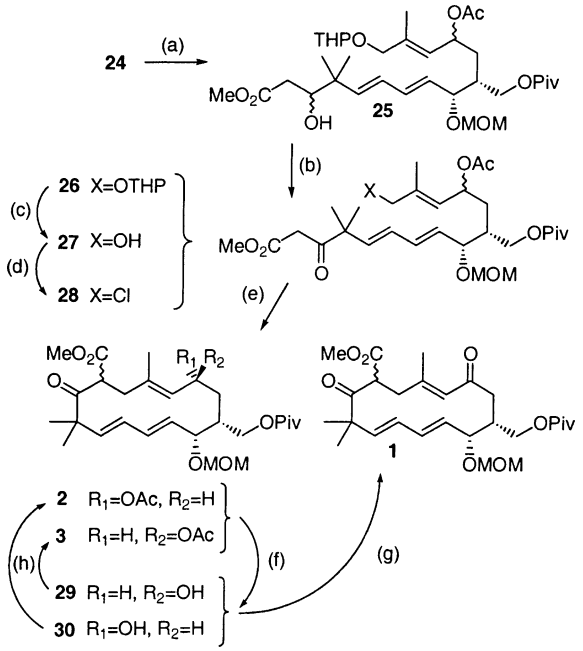
[a] Reagents and conditions: (a) KHMDS, THF, −78 °C, 84% (**12**:**13**, 52:48). (b) TPAP, NMMO, MS 4 Å, CH_2Cl_2, rt, 61%. (c) $NaBH_4$, $MnCl_2$, MeOH, 0 °C, 83% (**12**:**13**, 25:75). (d) MOMCl, DIEA, CH_2Cl_2/hex (9:1), rt, 80%. (e) $LiBH_4$, EtOH, Et_2O, rt, 89%. (f) PivCl, Py, DMAP, CH_2Cl_2, rt, 92%. (g) PPTS, MeOH, rt, 92%. (h) TPAP, NMMO, MS 4 Å, CH_2Cl_2, rt, 86% (i) (i) **20**, *t*BuLi, Et_2O, −78°C; (ii) **19**, 82%. (j) AcCl, Py, DMAP, CH_2Cl_2, rt, 99%. (k) TBAF, THF, rt, 87%. (l) TPAP, NMMO, MS 4 Å, CH_2Cl_2, rt, 89%.

II. Experimental and Theoretical Details

A. Synthesis. Synthesis of these macrocycles follows the highly convergent general strategy developed in our laboratory.[11] The diene fragment **11**[12] was coupled with the known ester **10**[13] via an aldol condensation to afford a 48:52 mixture of the desired *erythro* adduct **13** and the *threo* adduct **12** with a total yield of 84%. These compounds could be easily separated by flash chromatography (Scheme 1). The *threo* isomer **12** was oxidized to the *β*-ketoester **14** with TPAP and *N*-methyl morpholine oxide (NMMO)[14] (61% yield) and recycled to the *erythro* isomer **13** by reduction, using sodium borohydride-manganese chloride complex (yield 83%, 75:25 mixture

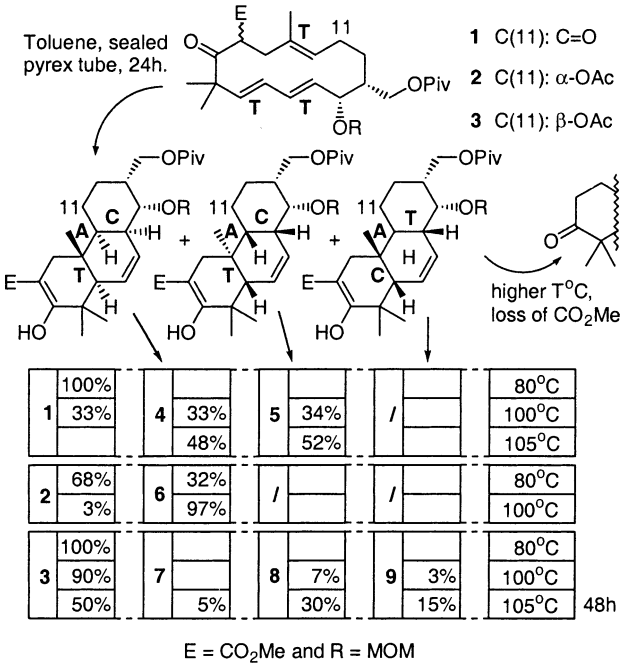
(11) Deslongchamps, P. *Pure Appl. Chem.* **1992**, *64*, 1831.
(12) Phoenix, S.; Bourque, E.; Deslongchamps, P. *Org. Lett.* **2000**, *2*, 4149.
(13) Solladié, G.; Almario, A. *Tetrahedron: Asymmetry* **1995**, *6*, 559.
(14) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625. (b) Griffith, W. P.; Ley, S. V. *Aldrichim. Acta* **1990**, *23*, 13.

SCHEME 2[a]



[a] Reagents and conditions: (a) MeOAc, LDA, THF, −78 °C, 87%. (b) Dess−Martin periodinane, CH_2Cl_2, rt, 86%. (c) PPTS, MeOH, rt, 88%. (d) Hexachloroacetone, Ph_3P, THF, −30 °C, 99%. (e) Cs_2CO_3, CsI, MeCN, **28** (2×10^{-3} M), 80 °C, 18 h, 60%. (f) K_2CO_3, MeOH, 76%. (g) Dess−Martin periodinane, CH_2Cl_2, rt, 84%. (h) AcCl, Py, CH_2Cl_2, rt, 65% and 71%.

SCHEME 3



of **13**:**12**).[15] The methoxymethyl ether **15** was obtained by protection of the alcohol **13** with MOM chloride and diisopropyl ethylamine (yield of 80%). The methyl ester **15** was reduced with lithium borohydride and with a yield of 89%. The resulting alcohol **16** was protected as its pivaloate ester **17** with a yield of 92%. The *tert*-butyldimethylsilyl group was selectively removed by mild acidic conditions with PPTS in methanol to yield the primary alcohol **18** (yield 92%), which was subsequently oxidized with TPAP to the aldehyde **19** with a yield of 86%. The dienophile part was then added by nucleophilic attack of the aldehyde **19** with the organolithium intermediate issued from the known iodide **20**.[16] The alcohol **21** was obtained in 82% yield and was protected as the acetate ester **22** with the excellent yield of 99%. The *tert*-butyldiphenylsilyl group was removed by a treatment with tetrabutylammonium fluoride to afford the alcohol **23** with a yield of 87%. The alcohol group was then oxidized to the aldehyde **24** (yield 89%) by means of TPAP.

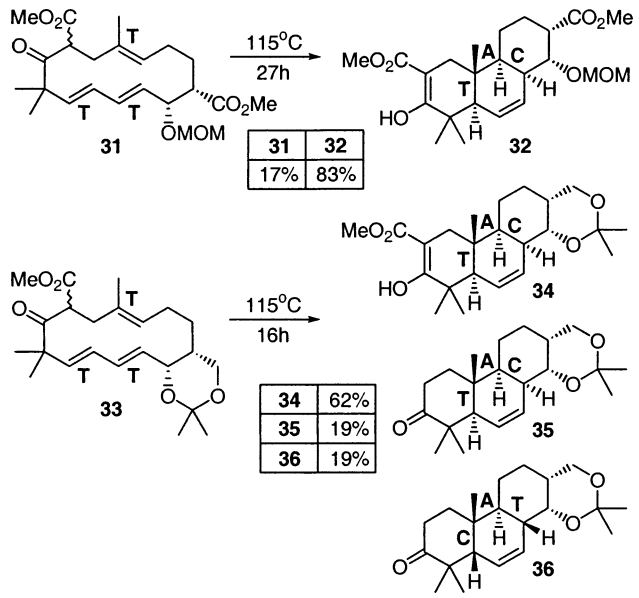
The β-ketoester moiety was further elaborated by aldol condensation of methyl acetate with the aldehyde **24** to give the alcohol **25** (yield 87%). That alcohol was immediately oxidized with Dess−Martin periodinane[17] to give the corresponding β-ketoester **26** with a yield of 86% (Scheme 2). The alcohol **27** was set free from its tetrahydropyranyl protecting group with PPTS and with a yield of 88%. Finally, the alcohol **25** was almost quantitatively (99%) transformed into the allylic chloride macrocyclization precursor **28** following Magid's procedure.[18] **28** was then submitted to macrocyclization high-dilution conditions using cesium carbonate in acetonitrile to yield an inseparable mixture of the macrocyclic acetates **2** and **3** with a total yield of 60% when the reaction medium was kept rigorously anhydrous; otherwise hydrolysis of the acetate group occurred and further led to degradation products.

The acetate group was removed by a treatment with potassium carbonate to afford the alcohols **29** and **30** as a 1:1 mixture (76% yield). Alcohols **30** and **29** were separated and each transformed back into their corresponding acetate **2** and **3** esters with the respective yields of 65% and 71%. In addition, a mixture of both alcohols was oxidized with the Dess−Martin reagent to afford the macrocyclic trienone **1** with a yield of 84%. **1** was crystallized and X-ray crystallography proved its structure.[19]

The thermal TADA reaction of macrocycle **1** was carried out in toluene in a sealed Pyrex tube (Scheme 3). The best result was obtained when **1** was heated at 105 °C for 24 h and gave two tricyclic TAC adducts **4** and **5** in almost equal portions (48:52). Nothing happened at 80 °C, but some decarboxymethylated product related to tricycle **4** was observed at higher temperature. These experiments suggest that the minimal activation temperature stands between 100 and 105 °C. The structure of **4** was established by X-ray crystallography;[20] and that of the other TADA adduct **5** was determined by NMR correlation experiments and spectral comparisons with

(15) Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1991**, *43*, 6147.
(16) Liu, F.; Negishi, E. I. *J. Org. Chem.* **1997**, *62*, 8591.
(17) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155.
(18) Magid, R. M.; Fruchey, O. S.; Johnson, W. L.; Allen, T. G. *J. Org. Chem.* **1979**, *44*, 359.
(19) Cambridge Data Bank reference for X-ray of macrocycle **1**: CCDC 190392. Formula: $C_{27}H_{40}O_8$. Unit cell parameters: a = 5.993(5) Å, b = 19.071(5) Å, c = 12.063(5) Å, β = 96.130(5)°. Space group *P*21.
(20) Cambridge Data Bank reference for X-ray of tricycle **5**: CCDC 190393. Formula: $C_{27}H_{40}O_8$. Unit cell parameters: a = 15.8491(11) Å, b = 9.845(17) Å, c = 17.9449(12) Å, β = 106.430(6)°. Space group *P*21/*c*.

SCHEME 4



a similar tricycle **32** obtained by TADA reaction of the macrocycle **31** at an optimal temperature slightly above 115 °C (Scheme 4).[12] Thus, the carbonyl function at C-11 of the trienone **1** lowers the TADA temperature by only 10 °C by comparison with the nonactivated series **31**. This almost nonexistent activation is further demonstrated by the inability of Lewis acids to catalyze the reaction:[3c,21] When the macrocycle **1** was treated for 3 h with tin tetrachloride in toluene at −20 °C, no trace of tricycle was observed, and at room temperature, only degradation products were obtained. The two other "inactivated" trienes **2** and **3** were also submitted to the TADA reaction conditions. The 11-α-acetoxy-isomer **2** starts reacting at 80 °C and yields only one adduct, the TAC tricycle **6**. The 11-*β*-isomer **3** reacts less readily, since no significant amounts of TADA adducts **7**, **8**, and **9** are obtained below 105 °C.

The structure of compound **6** was confirmed by crystal X-ray diffraction analysis[22] and that of compound **8** was determined by NMR correlation with the known tricycles **32** and **34** (Scheme 4).[12] Compounds **7** and **8** could not be separated because they have the same polarity in various solvents. In the same way **9** could not be separated from the starting material **3**. According to the shape of the ^{1}H NMR C*H*OAc signals for the tricycles, **7** has an equatorial acetate (wide multiplet signal), whereas **8** and **9** have an axial acetate (narrow multiplet signal). The respective relative geometry of the three tricycles was then easily attributed according to these observations and to a previous experiment carried out on related macrocycle **33**. In that experiment, **36**, the only CAT adduct obtained, has the same geometry as **9** and the TAC adduct **34** corresponding to **8** is also the most abundant product (Scheme 4).

B. Theoretical Procedures. Although most triene systems undergoing TADA reactions could be adequately handled by low-level calculations (semiempirical AM1 and PM3 methods),[23] it quickly appeared that the TTT case could not be treated as easily. In fact, reproducing the TAC:CAT adduct ratio experimentally observed proved impossible without the addition of empirical corrections.[24] We looked for a better way to model the different effects arising in the competing transition states (TSs) leading to the TAC and CAT TADA adducts, to put sufficiently accurate figures on all the different interactions involved. We calculated the different transition states (TSs) corresponding to the TADA reactions at the RHF/3-21G theory level[25] by means of GAMESS.[26] The zero-point energy corrections were not applied due to the large size of the systems, which always prevented such calculations. However, these corrections are known not to affect the relative energies between TSs in a significant way.[27] To estimate the activation energy corresponding to each case, it was necessary to locate the lowest energy macrocyclic conformers. We first performed a systematic conformational search of each a the macrocycles using the maximin2 force field within SYBYL.[28] All conformers having a relative energy below 4 kcal/mol were then individually calculated at the RHF/3-21G ab initio level. No conformers having an s-cis diene were found. Only the lowest energy conformers were selected to calculate the activation energy, because all other conformers were less stable by at least 2 kcal/mol (apart from two macrocycles where competing conformers were found with relative energies of 0.44 and 1.11 kcal/mol in one case and 1.28 kcal/mol in the other case). Although the RHF/3-21G method is not sophisticated by current standards, we have already proven that it was very efficient for our transannular systems.[10] Moreover, numerous calculations have to be carried out on rather large systems, so that the RHF/3-21G theory level appears to be the ideal compromise. We first validated its ability to deal with our TTT systems by modeling the prototype reaction from the triene **37** that yields a 67:33 mixture of TAC and CAT adducts **38** and **39** (Chart 4).[29] AM1 calculations give a 29:71 ratio, whereas a ratio of 72:28 is obtained by means of 3-21G calculations.[30] This latter ratio is therefore in excellent agreement with the experimental results. Furthermore, these calculations allow us to characterize the geometry of the favored transition states. Thus, both adducts **38** and **39** must have issued from chair-boat-chair (cbc) transition structures (46% and 28% respectively), but a fair share of the TAC adduct should form through a chair-boat-boat (cbb) transition

(21) (a) Yates, P.; Eaton, P. *J. Am. Chem. Soc.* **1960**, *82*, 4436. (b) Inukai, T.; Kojima, T. *J. Org. Chem.* **1971**, *36*, 924. (c) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976; Chapter 4. (d) Yamabe, S.; Dai, T.; Minato. T. *J. Am. Chem. Soc.* **1995**, *117*, 10994.

(22) Cambridge Data Bank reference for X-ray of tricycle **6**: CCDC 190394. Formula: $C_{116}H_{176}O_{36}$. Unit cell parameters: a = 13.676(5) Å, b = 16.9509(16) Å, c = 13.899(3) Å, β = 113.728(19)°. Space group *P*21/*n*.

(23) Dory, Y. L.; Soucy, P.; Drouin, M.; Deslongchamps, P. *J. Am. Chem. Soc.* **1995**, *117*, 518.

(24) Takahashi, T.; Sakamoto, Y.; Doi, T. *Tetrahedron Lett.* **1992**, *33*, 3519.

(25) Binkley, J. S.; Pople, J. A.; Hehre, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 939.

(26) Schmidt, M. W.; Baldridge, K. K.; Boatz, J. A.; Elbert, S. T.; Gordon, M. S.; Jensen, J. H.; Koseki, S.; Matsuraga, N.; Nguyen, K. A.; Su, S. J.; Windus, T. L.; Dupuis, M.; Montgomery, J. A. *J. Comput. Chem.* **1993**, *14*, 1347.

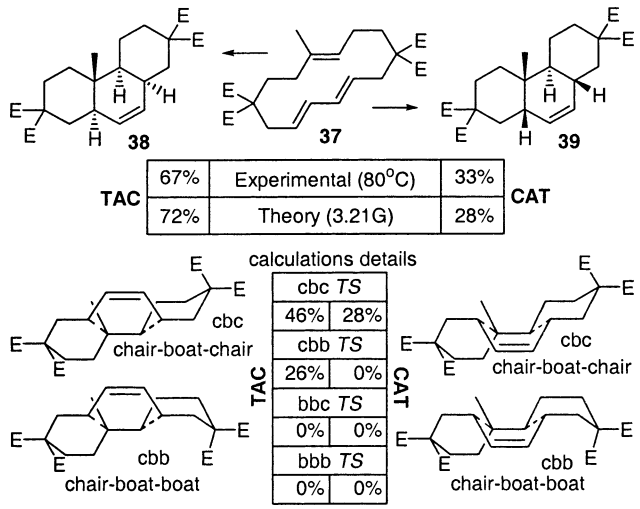
(27) García, J. I.; Martínez-Merino, V.; Mayoral, J. A.; Salvatella, L. *J. Am. Chem. Soc.* **1998**, *120*, 2415.

(28) Tripos Inc.: 1699 South Hanley Road, St. Louis, MO 63144-2913.

(29) Ndibwami, A.; Lamothe, S.; Soucy, P.; Goldstein, S.; Deslongchamps, P. *Can. J. Chem.* **1993**, *71*, 714.

(30) Zefirov, N. S. *Tetrahedron* **1977**, *33*, 2719.

CHART 4. TTT Model Study Results



structure (26%). The cbb *TS* structure leading to the CAT adduct, on the other hand, is much less stable (0%), and confirms the rule that states that a boat tether ring (ring C in this case) is not favored when the corresponding ring junction bond undergoing formation (bond b) is trans (ring junction BC here).[10,23,31] The other competing bbc and bbb TS structures are even less stable.

Therefore, this particular difficult case was successfully handled, and all of our previous work indicates that the RHF/3-21G level of ab initio theory is well suited for the current problem. All possible transition states dealing with the TTT systems under scrutiny have been calculated. The results of these calculations have been drawn up at the eight corners of a cube to ease the analysis and the comparisons necessary to fully understand all the various factors at work (Chart 5). Thus, the four back transition structures **A**−**D** correspond to systems without carbonyl at position 3, whereas the four structures **E**−**H** display a carbonyl at that position. The four right structures **A**, **C**, **E**, and **F** have no *gem*-dimethyl at position 4, contrary to the four structures **B**, **D**, **G**, and **H** on the left side. Finally the difference between the four bottom transition structures **A**, **B**, **E**, and **G** and the four top structures **C**, **D**, **F**, and **H** resides in the absence of a carbonyl at position 11 in the former case and in its presence in the latter. The transition structure **G** matches rather closely to the experimental TADA reactions carried out from the macrocyclic trienes **2** and **3**, and **H** corresponds to the conjugated case **1**. The major difference between the theoretical calculation and the true experiments consists of the removal of some pendant groups that would lead to unreasonably long computer times: (i) the methyl ester at position 2, (ii) the acetate at position 11 (cases corresponding to **2** and **3**), (iii) the CH_2OPiv group at position 13, and (iv) the MOM ether at position 14. We are well aware of the importance of the methyl ester at position 2, because the ketone at position 3 stands truly as a ketone in the macrocycles (as shown in the crystal structure of **1** and in the NMR data) but it prefers to exist in its enol form in the tricyclic adducts. Nevertheless, it is impossible to identify the exact nature of that ketone (either ketone or enol) at the transition state. We made the assumption that the ketone form would still give a fair representation of the systems at the transition state. The removal of all other groups is less dramatic, so that the overall discussion should be very meaningful. The aim of this study is to discover the trends of three selected groups, separately at first, in regards to their effect on the TADA selectivity, then to see the results of their combinations, leading to either synergism or antagonism. The three groups of particular interest are (i) a carbonyl at position 3, (ii) a *gem*-dimethyl at position 4, and (iii) a carbonyl at position 11 that could activate the dienophile.

For the forthcoming discussion, the bond that is formed between rings A and B, in front of the methyl group of the dienophile, will be called **a**, and the one that forms at the BC ring junction will be designed as **b**. Let us now analyze carefully each of the eight systems **A**−**H**.

A: The macrocycle **A**[32] corresponds to the parent system; its TADA reaction at 100 °C would theoretically lead to 56% (55 + 1) of CAT adduct and 44% (38 + 6) of TAC adduct. In this reference case, the TS cbc geometry is always favored, although the TAC cbb geometry is not negligible. This again confirms that a boat tether ring is possible when it connects a cis ring junction. The mean **a** bond value is 2.25 Å and that of bond **b** is 2.22 Å.

B: By adding a *gem*-dimethyl group at position 4 in the macrocycle **A**,[33] the cbc TSs are still favored but there is even more TAC adduct arising from a cbb geometry. The *gem*-dimethyl now favors the TAC adduct (95% = 63% + 30% + 2%) over the CAT adduct (5%) and the activation energy has increased by 3.48 kcal/mol; it can be assumed that this value corresponds roughly to the destabilizing effect of the axial methyls facing each other across the forming bond **a**. Indeed, this interaction looks like a 1,3 diaxial steric interaction, although it is slightly less severe than that found in 1,3 diaxial dimethyl cyclohexane (3.7 kcal/mol).[35] Addition of the *gem*-dimethyl group leads also to concomitant lengthening of bond **a** by 0.05 Å (now 2.30 Å) and shortening of bond **b** by 0.04 Å (2.18 Å). The presence of some TAC bbc adduct (2%) demonstrates that there could exist some steric hindrance in the cbc and cbb TSs because of the colliding axial methyl groups at positions 4 and 10 (see Chart 2). This effect is not present in a bbc transition state, where the methyl group at 4 is no longer axial.

C: From the reference system **A**, a carbonyl group is added at position 11 to see its sole effect;[34] the resulting dienone **C** requires less energy (−1.56 kcal/mol). The bond lengths are inverted; **a** is now the shorter at 2.11 Å (bond shortened by 0.14 Å) and **b** the longer at 2.34 Å (increase of 0.12 Å). The selectivity effect is the same as that of a *gem*-dimethyl at position 4 (**B**), since the TAC adduct is also favored (79% = 12% + 67%) over the CAT adduct (21% = 19% + 2%). It is worth noting that the most favored TAC transition state (67%) assumes a chair-

(31) (a) Coe, J. W.; Roush, W. R. *J. Org. Chem.* **1989**, *54*, 915. (b) Marshall, J. A.; Grote, J.; Audia, J. E. *J. Am. Chem. Soc.* **1987**, *109*, 1186. (c) Dory, Y. L.; Ouellet, C.; Berthiaume, S.; Favre, A.; Deslongchamps, P. *Bull. Soc. Chim. Fr.* **1994**, *131*, 121.

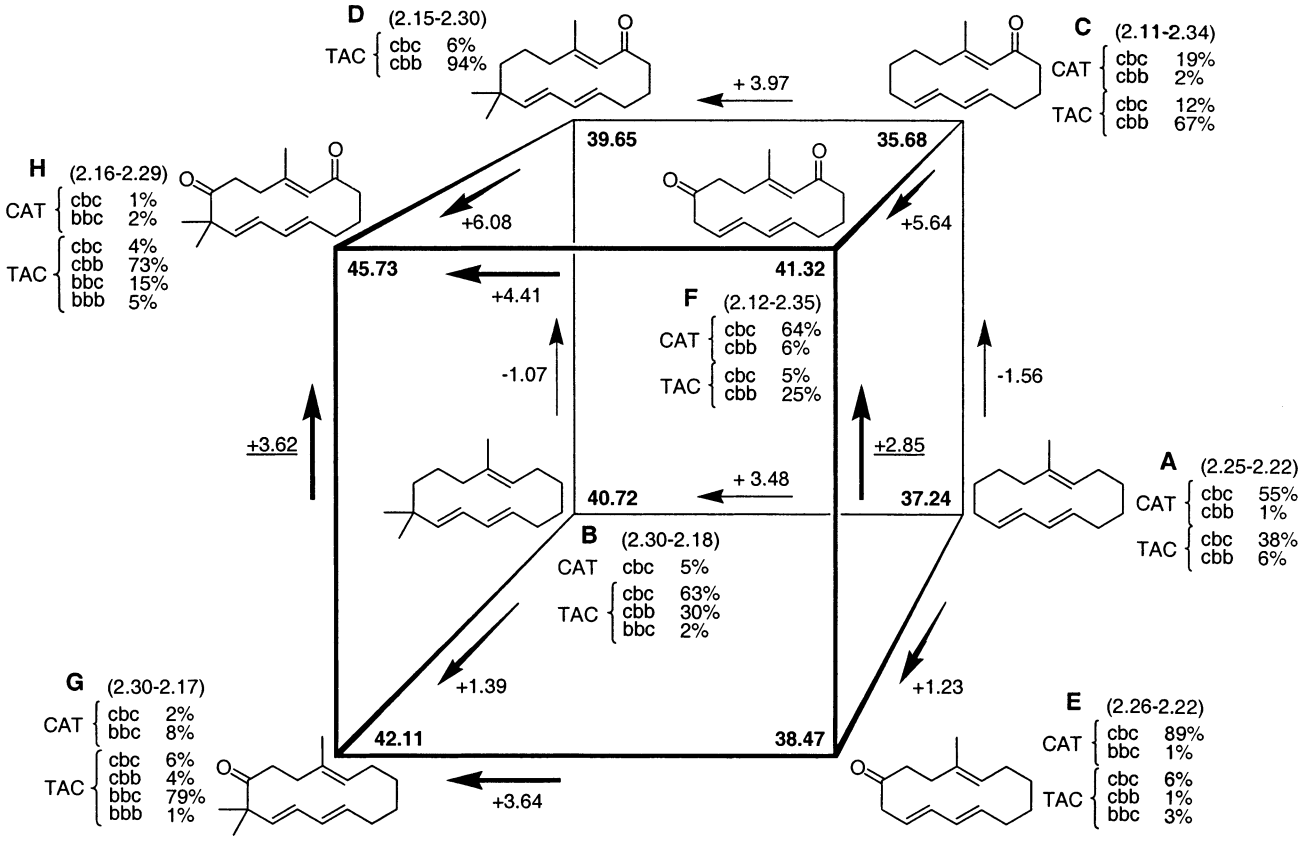
(32) The third calculated conformation with a relative energy of 2.78 kcal/mol corresponds to the crystal structure of macrocycle **1**.

(33) The third calculated conformation with a relative energy of 2.45 kcal/mol corresponds to the crystal structure of macrocycle **1**.

(34) The lowest calculated conformation corresponds to the crystal structure of macrocycle **1**.

(35) Allinger, N. L.; Miller, M. A. *J. Am. Chem. Soc.* **1961**, *83*, 2145.

CHART 5. Results of the Calculations[a]



[a] Each corner of the cube corresponds to a particular macrocyclic system among **A**-**H**. For each system the population of the expected products at 100 °C is indicated based on the calculated relative energies of the TSs.[30] The figures in brackets are the average lengths for the TS bonds **a** and **b** (Å). The bold figures at the corners are the activation energies ($\Delta\Delta E$) for the most favored TSs (kcal/mol). The figures along the vertices of the cube are differences of activation energies. For example, in the vertex connecting TSs **A** and **B**, the arrow goes from **A** to **B**, the difference of activation energy is therefore equal to 40.72 − 37.24 = +3.48 kcal/mol; this positive energy indicates that the introduction of a gem dimethyl at position 4 led to an increase of the activation energy as expected. On the contrary, the differences of activation energies that are underlined are unexpected from currently accepted rules.

boat-boat conformation. These calculations that are directly supported by experimental data obtained from the same macrocycle **C**[24,36] add further credit to our molecular modeling results.

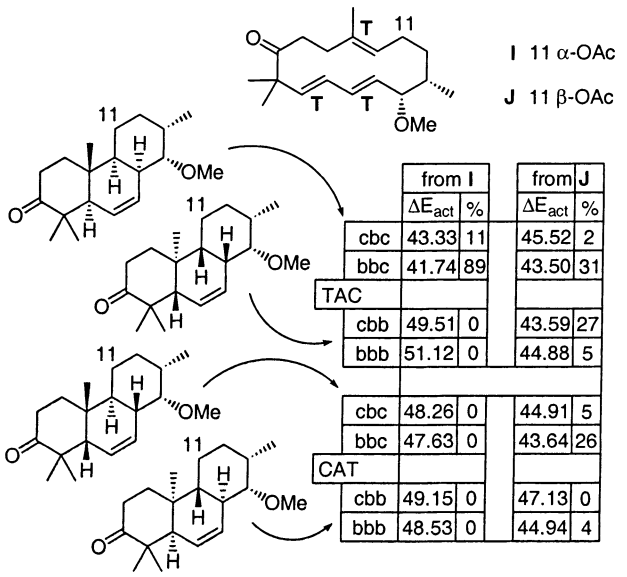
D: In system **D**,[34] the *gem*-dimethyl group at 4 and the carbonyl at 11 are both present. Since they both individually favor the TAC adduct, their effects are now synergetic and no CAT should be obtained with this macrocycle. The preferred TS geometry is a cbb as in **B**. On going from **C** to **D** the activation energy increases by 3.97 kcal/mol, virtually the same energy as that found between **A** and **B**. From **B** to **D**, the activation of the dienophile by a carbonyl is evidenced by the decrease of activation energy of 1.07 kcal/mol. This activation gap is not very different from that observed between **A** and **C** (1.56 kcal/mol).

E: In the macrocycle **E**,[34] we can probe the "pure" effect of a carbonyl at position 3. The tendency is now to favor the CAT TS (90% = 89% +1%) mostly via the cbc geometry (89%); this has no effect on the **a** and **b** bond distances (see **A** and **E**). However, the activation energy increases by 1.23 kcal/mol. This could come from the C2−C3−C4 angle, which is larger in **E** (around 120°) than in **A** (109.5°). The effect of a large angle inside the tether ring A (particularly at positions 2 or 3) could be to hold the diene and the dienophile at larger distances so that closing of the bond **a** (its formation) becomes less easy.

F: This explanation seems to gain credit in the case of **F**,[34] in which the carbonyl at position 11 shortens the bond **a** (**E**, 2.26 Å; **F**, 2.12 Å), while the effect of the carbonyl at position 3 is precisely to prevent that bond from shortening. A direct consequence of both opposing effects is to drastically increase the energy of activation by 5.64 kcal/mol from **C** to **F** and by 2.85 kcal/mol from **E** to **F**. The latter increase is very impressive because, from **E** to **F**, one normally expects the activation energy to decrease, as it did on going from **A** to **C**, the dienophile being more reactive. This constitutes therefore the first evidence of an enone behaving as a deactivating dienophile, and this theoretical assertion is strongly supported by our experimental data. In terms of adduct selection, the effects of both carbonyls are antagonistic so that there is more CAT adduct in the case of **F** (70% = 64% + 6%) than in the case of **C** (21%) and less in **F** than in **E** (90%). The geometrical features of **E** and **F** indicate that the bonds **a** and **b** are only influenced by the groups at positions 4 (none or gem dimethyl) and 11 (none or carbonyl). Consequently, **E** and **F** are geometrically

(36) Roush, W. R.; Warmus, J. S.; Works, A. B. *Tetrahedron Lett.* **1993**, *34*, 4427.

CHART 6. Calculation Results for Systems I and J



similar to **A** and **C**, respectively, and the same rule can be applied to the two remaining systems **G** and **H** that look like **B** and **D**.

G: For **G**,[34] there are also two opposing effects: the carbonyl at position 3 that gives more CAT adduct (10% = 2% + 8%) than in **B** (5%), where that carbonyl is not present, and the *gem*-dimethyl group at position 4, yielding more TAC adduct than in the case of **E** (10%), which bears no *gem*-dimethyl. The 90:10 TAC:CAT theoretical ratio matches well with the experimental results of **2** and **3** where no or little CAT adducts were isolated. In this case again, the additive effect of the factors is further evidenced by the differences of activation energies which are equivalent for the couples **AE**/**BG** (1.23 kcal/mol/1.39 kcal/mol) and **AB**/**EG** (3.48 kcal/mol/3.64 kcal/mol).

H: Finally, in **H**[34] all three factors are at work, two of which favor TAC selectivity. As a consequence, there is more TAC adduct in **H** (97% = 4% + 73% + 15% + 5%) than there was in **G** (90% = 6% + 4% + 79% + 1%). The deactivating effect of a carbonyl at position 11 becomes very severe in this case, since the activation energy increases by 3.62 kcal/mol from **G** to **H**.

Systems **G** and **H** are obviously good mimics of the TADA reaction for the macrocyclic trienes **1**−**3**. However, **2** and **3** behave very differently from each other, in terms of temperature of reaction and selectivity, although they both have been simplified by the same macrocycle **G** for the calculations. Clearly, the acetate at position 11, which is either α in **2** or *β* in **3**, has a drastic influence on the outcome of their TADA reactions. The methyl pivaloate substituent at position 13 and the methoxymethyl ether at position 14 must also play a significant role in the matter. Thus, to gain further confidence in the validity of our theoretical approach, we wanted to check if calculations could properly model both systems; so we examined macrocycles **I** and **J** (Chart 6) and calculated all their corresponding TSs. In **I** and **J**, the acetate at position 11 is explicitly there, but the methyl pivaloate at 13 and the MOM ether at 14 are replaced by a methyl and a methyl ether, respectively. These simplifications become necessary because the real macrocycles **2** and **3** would be too heavy for 3-21G ab initio calculations and the number of rotamers would unduly complicate the problem.

There are 16 competing TSs in each case, but the eight that bear an axial methyl group at position 13 have been discarded because their energies are on the whole exceedingly high. For system **I**[34] that resembles closely the case of macrocycle **2**, the calculations predict that only one TAC adduct would be obtained over a total of four possibilities. This TAC adduct would mostly be formed via a bbc TS geometry, and it corresponds exactly to the one experimentally observed (**6**). In the case of **J**,[37] the calculations indicate that three adducts should be equally formed: the two possible TAC adducts and one CAT adduct over two possibilities. Noteworthy, this CAT geometry theoretically found had been experimentally observed in another TADA experiment involving a closely related macrocyclic triene (compound **36** in Scheme 4).[19] System **J** mimics closely the case of macrocycle **3**, it yields theoretical predictions that reasonably match the experimental results (**7**/**8**/**9** ratio at 105 °C calcd 34/34/32, found 10/60/30). Moreover, the relative reactivity of both systems is correctly modeled, since the lowest activation energy for **I** is 41.74 kcal/mol and that for **J** is 43.50 kcal/mol. These figures match the fact that the α acetate macrocycle **2** already reacts at 80 °C whereas its *β* epimer **3** does not produce significant amounts of products before 105 °C.

III. Conclusions

An enone is usually known to behave as an activated dienophile, but we could prove that in special environments, the results of the activation could be surmounted by other factors so that deactivation would in fact ensue. To achieve this reverse activation effect, the enone dienophile and the diene were rigidly held in 14-membered macrocycles by means of two four-carbon tethers. On the side of the short forming bond, away from the ketone, a methyl group was placed on the dienophile and a *gem*-dimethyl group was added next to diene as part of the tether. Theoretical calculations showed that the resulting steric interaction, almost equivalent to 1−3 interaction, was not as strong as expected. In fact, these calculations suggest two important geometrical features in regard to the introduction of these three methyl groups: (a) a methyl on the dienophile acts as a donor and the bond that forms away from it becomes naturally shorter (2.22 Å) with concomitant lengthening of the bond directly linked to it (2.25 Å) and (b) a *gem*-dimethyl group next to the diene acts in exactly the same way by shortening the bond that forms further away from it. In the systems studied here, both effects tend to open the same forming bond, the one that is close to these methyls (2.30 Å). However, when a carbonyl becomes conjugated to the dienophile, it shortens this forming bond (2.15 Å) in such a way that the hydrogen atoms of the methyl groups give rise to steric repulsion (shortest H−H distance calculated at 1.91 Å instead of 2.02 Å without carbonyl) for chair-shaped tethers. Nevertheless, these

(37) The second calculated conformation with a relative energy of 2.02 kcal/mol corresponds to the crystal structure of macrocycle **1** (this comes as no surprise since the pseudoaxial acetate experiences strong transannular interaction).

calculations indicate that methyl−methyl 1−3 steric interactions across a TS forming bond remain usually moderate, precisely because those partially formed bonds are sufficiently long to accommodate rather bulky groups. Moreover, this steric interaction can be avoided when the tether (short bond side) assumes a boat conformation (shortest H−H distance calculated at 2.29 Å). On the other hand, a carbonyl at position 3 proved excessively efficient at antagonizing the activating effect of the enone dionophile. This effect went as far as turning the enone into a deactivating dienophile. The tether ketone is more effective than steric interactions because it affects the geometry of the tether, contrary to weaker steric nonbonding interactions. The resulting tether wants to hold the reactants further apart because the ketone internal angle of 120° is more open than a CH_2 having a angle of 109.5°. It is very likely that such unexpected results could not be reproduced in intermolecular cases, where the reactants can easily adjust their trajectories to avoid all detrimental steric and electronic interactions.

This work also puts us closer to the synthesis of Kaurane or diterpines such as Taibaihenryiin C having a carbonyl at position 3. The required TAC tricycle is the sole TADA adduct issued from macrocycle **2** having an α-acetoxy group at position 11. Theoretical calculations indicate that all three additional competing adducts would be obtained through much more energetic TS, contrary to macrocycles **1** and **3** that give mixtures of tricycles.

Acknowledgment. Financial help from NSERC-Canada and FCAR-Quebec (fellowship to Elyse Bourque) is highly appreciated. We are also grateful to Marc Drouin for the X-ray analysis.

Supporting Information Available: Experimental procedures and spectral data of compounds **1**−**9**, **12**−**19**, and **21**−**30** and crystal structure of macrocycle **1** and tricycles **4** and **6**; Cartesian coordinates, energies, and populations of the macrocycles and TSs calculated at the 3.21G level of ab initio theory (Charts 5 and 6). CIF file corresponding to the three crystal structures **1**, **5,** and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0265129