Modeling the Stereoselectivity of the Johnson−Claisen Rearrangements in the Danishefsky Synthesis of Gelsemine

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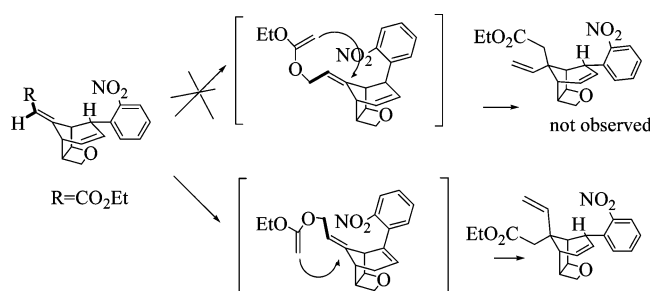
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The stereochemistries of [3,3] sigmatropic Johnson−Claisen (J−C) rearrangements of six intermediates studied in the synthesis of gelsemine were modeled using DFT methodology. The possible origins of the rearrangement stereoselectivity are explored and compared with the experimentally suggested rationalizations by Danishefsky et al. (*J. Am. Chem. Soc.* **2002**, *124*, 9812−9824). In the intermediate used for the J−C rearrangement in the Danishefsky synthesis (**3**), the closure is inhibited by the repulsive interactions between the enolate terminus and the carbon atoms of the double bond as well as with the hydrogen on C7. The closure is favored by stabilizing interactions between the enolate terminus and the H's of the oxetane ring.

Introduction

Gelsemine (**1**), the major alkaloid component of *Gelsemium sempervirens*, was isolated in the 1870s (Figure 1).[1,2] After 80 years of extensive studies, the structure was solved in 1959 by both NMR and X-ray spectroscopic methods.[3] The highly functionalized hexacyclic skeleton of gelsemine stimulated intensive synthetic efforts throughout the world.[4] Ng, Lin, and Danishefsky found a facial stereoselectivity of the Johnson−Claisen (J−C) rearrangement in the total synthesis of gelsemine.[5,6]

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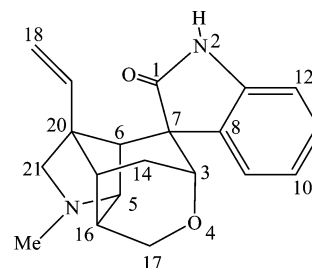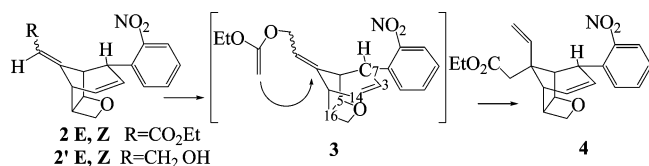

FIGURE 1. Gelsemine.

In the total synthesis of gelsemine, one of the key steps is the J−C rearrangement of **2** to **4** (Scheme 1). The stereoisomers **2E** and **2Z** were converted by reduction to their allylic alcohol counterparts **2′E** and **2′Z**, respectively. These isomers were individually treated with

SCHEME 1. Johnson−Claisen Rearrangement of 3

2 E, Z R=CO$_2$Et
2' E, Z R=CH$_2$OH

SCHEME 2. Johnson−Claisen Rearrangement of 5

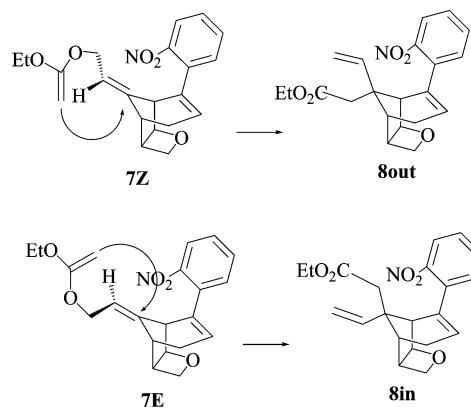**SCHEME 3. Johnson−Claisen Rearrangement of 7E and 7Z**
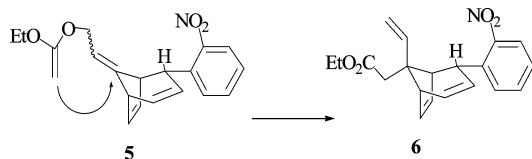
triethylorthoacetate. Each allylic alcohol gave rise to a single γ,δ-unsaturated ester **4** by a J−C process via intermediate **3**. The ester, **4**, had the β-vinyl and α-carboxymethyl functions at C20 as required for the synthesis.

Danishefsky et al. attribute this stereochemical convergence to the tendency of the enolate-like migrating component of the Claisen rearrangement step to pass over the cyclopentane ring fused to the oxetane, rather than cyclohexene. They claim the facial selectivity of **3Z** to arise from a steric effect of the axial proton at C7.[5] On the other hand, the facial selectivity of **3E** has been rationalized by considering an electrostatic repulsion of the enolate-like migrating group by the C3−C14 system. Still another factor thought to be operating in the same direction was the attraction of the migrating enolate-like group by the electron-withdrawing C5−C16 bond. Additional cases (i.e., **5** and **7**) were evaluated by Danishefsky et al. to distinguish between possible steric and electronic factors in directing the face selectivity of the migrating step.

Isomers **5E** and **5Z** separately subjected to J−C rearrangement gave a single rearrangement product, **6** (Scheme 2). In this case, the authors argue that there is less steric hindrance upon migration across the cyclopentene face of the bicyclic.[5]

One pair of isomers gave different behavior (Scheme 3). When compound **7Z** was subjected to J−C rearrangement conditions, a single product, **8out**, in which the migration occurred across the two-carbon cyclopentane face, formed. When **7E** was subjected to J−C rearrangement conditions, a single product, identified as **8in** and differing from **8out**, was obtained. Though not subjected to rigorous structural proof, the compound was formulated as **8in**.

This result could be explained by the interaction between the highly polarized C7−C3 olefin and the electron-rich enolate. In the transition state of **7E** the electronegative enolate terminus was reported to be closer to the electropositive end (C3) of the olefin. By contrast, in the transition state of **7Z**, the enolate was claimed to be closer to the electronegative end (C7) of the olefin.

In this study, we have explored the origins of the facial stereoselectivity in the rearrangement of compounds **3**, **5**, and **7** using DFT methodology.

Computational Methodology

The geometry optimizations were carried out with B3LYP/6-31G*. B3LYP/6-31+G**[7] and MPW1K/6-31+G**[8] have been used to refine the energetics. The nature of the transition structures was confirmed by the presence of one imaginary frequency, which was traced with IRC calculations. The nonscaled frequencies were used to compute zero-point energies. It is known that the modified Perdew−Wang 1-parameter model for kinetics (MPW1K) reduces the mean unsigned error in reaction barrier heights by a factor of 3 over B3LYP, and thus this methodology has been used for compound **7** where the experimental findings were not completely reproduced with B3LYP. For the calculation of atomic charges we have employed Mulliken population analysis (MPA)[9] and natural population analysis (NPA).[10,11] Solvent effects were modeled using the integral equation formalism polarized continuum model of Tomasi et al.[12] within self-consistent reaction field theory by means of single-point calculations based on the gas-phase geometries. All calculations were performed with Gaussian 98.[13]

The chair conformation was assumed for all the transition structures sketched here. Chairlike transition structures are known to be formed except when there is a great deal of steric hindrance on these transition states.[14−18] In substrates **3**, **5**, and **7**, the ethoxy group on the enolate was replaced by a methoxy group. The cyclohexene face of the rearrangement of the compounds **3**, **5**, and **7** is denoted as "**in**", and the cyclopentene face of the rearrangement of the same compounds

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TABLE 1. Bond Lengths in the Reactants, Transition States, and Products for the Claisen Rearrangements of the Compounds 3, 5, 7, and AVE(B3LYP/6-31G*)

	1−2	2−3	3−4	4−5	5−6	1−6
AVE-reactant	1.34	1.36	1.42	1.50	1.33	
AVE-TS	1.38	1.29	1.90	1.40	1.38	2.31
AVE-product	1.51	1.21		1.33	1.50	1.53
3Z	1.34	1.35	1.43	1.50	1.33	
3E	1.34	1.35	1.43	1.50	1.33	
TS-3Z-4out	1.38	1.27	1.97	1.39	1.38	2.60
TS-3E-4out	1.38	1.27	1.97	1.40	1.38	2.61
4out	1.52	1.21		1.33	1.52	1.55
5Z	1.34	1.35	1.43	1.50	1.33	
5E	1.34	1.35	1.43	1.50	1.33	
TS-5Z-6out	1.38	1.28	1.92	1.40	1.38	2.55
TS-5E-6out	1.38	1.28	1.94	1.40	1.38	2.55
6out	1.52	1.21		1.33	1.52	1.55
7Z	1.34	1.35	1.43	1.50	1.33	
7E	1.34	1.35	1.43	1.50	1.33	
TS-7Z-8out	1.38	1.27	2.00	1.39	1.38	2.60
TS-7E−8out	1.38	1.27	2.00	1.39	1.38	2.63
8out	1.52	1.22		1.33	1.52	1.57

is denoted as "**out**". Thus, the product for the J−C rearrangement of the **Z** isomer of compound **3** is called **4in**, and the transition state for the cyclohexene face rearrangement of **3Z** to **4in** is called **TS-3Z-4in**. The global minima have been considered for the compounds of interest. The geometrical parameters and charges for the reactants, the "**out**" products, and the corresponding transition structures are displayed in Tables 1 and 2.

Results

All the transition states are very similar and resemble allyl vinyl ether (**AVE)-TS**. For compounds **3**, **5**, and **7**, the transition state bond lengths vary between 1.92 and 2.00 Å for the breaking C−O bond and 2.55−2.63 Å for the forming C−C bond. In the case of **AVE**, these values are 1.90 and 2.31 Å, respectively. The −OCH$_3$ group at C2 is known to reduce the bond length at O3−C4, and the alkyl groups at C6 are known to increase the bond length at O3−C4.[19−21] In the transition states of compounds **3**, **5**, and **7**, these two opposite effects cause bond lengthening at O3−C4. The −OCH$_3$ group at C2 and the alkyl groups at C6 have been reported to increase the bond length of C1−C6. These two similar effects cause bond lengthening for C1−C6 in the transition states of compounds **3**, **5**, and **7**.

In all of the transition states of the compounds **3**, **5**, and **7**, the charge separation between the allyl and the oxy-allyl sides is larger than the one for **AVE** (Table 2). This charge separation is due to the electron-donating groups at C2 (OCH$_3$) and C6 (R, R′) (Scheme 4). In all the transition states, the bond breaking of the C−O bond exceeds the formation of the C−C bond. The charge separation between the allyl and oxy-allyl groups suggests a polarized transition state.[14,15,17] Note also that the charge separation between the two moieties is more or less independent of the methodology used.

The "**in**" products resulting from the cyclopentane side attack are thermodynamically slightly preferred (1 kcal/mol) over the "**out**" products for **3** and **7**. However, the barrier heights for the rearrangement of these compounds are in favor of the "**out**" products. Note that including the thermal corrections and the entropies of activation does not alter the trend observed with the electronic energies at 0 K (Table 3).

Compounds 3 and 5. The Mulliken charge distributions of the reactive centers in the transition states have been used to consider the repulsive and attractive interactions between atoms in close proximity to each other and to rationalize the facial selectivity of the Claisen rearrangement. A large number of these interactions are found to be important for each transition structure. The charge distributions and critical distances are more or less similar for "**Z**" and "**E**" isomers, so that only the parameters of the "**Z**" conformers will be discussed. The interactions of the enolate terminus (C1 and H1) with the carbon atoms of the closest double bond (C3 and C14) and the carbon and hydrogens of the closest polarized C−C bond (C5, C16, H(C5), H(C16)) and H* on C7 have been considered.

In the case of compound **3**, for the "**in**" closure (**TS-3Z-4in**), C1 (*−0.42*) on the electronegative enolate terminus and the carbons of the C3 (*−0.11*)−C14 (*−0.12*) double bond (∼3.3 Å away from C1) repel each other. In the "**out**" transition structure, C1 (*−0.42*) is in close proximity (∼3.3 Å) with C5 (*0.17*) and C16 (*−0.17*). The repulsion between C1 and C16 is almost equal to the attraction between C1 (*−0.42*) and C5 (*0.17*). Stabilizing interactions are also present in the "**out**" closure for C1 (*−0.42*)−H(C5) (*0.15*) (∼3.01 Å) and C1 (*−0.42*)−H(C16) (*0.14*) (∼2.9 Å).

Regarding the interactions of H1 with its neighbors in compound **3**, in the "**out**" closure, H1 (*0.14*) on the electronegative enolate terminus and C16 (*−0.17*) (∼2.9 Å) attract each other, whereas H1 (*0.14*) and C5 (*0.17*) (∼2.9 Å) repel each other. Furthermore, destabilizing interactions are present between H1 (*0.15*)−H(C5) (*0.15*) (∼2.46 Å) and H1 (*0.15*)−H(C16) (0.17) (∼2.43 Å). In the

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TABLE 2. MPA[16] and NPA[14,15] (in Parentheses) Charges on the Critical Atoms (Charges of H's Are Summed into Heavy Atoms) for Compounds 3, 5, 7, and AVE

	1	2	3	7	8	oxallyl	4	5	6	allyl
AVE-TS	−0.04	0.29	−0.46			−0.21	0.13	0.08	0.00	0.21
	(−0.04)	(0.37)	(−0.56)			(−0.24)	(−0.09)	(0.09)	(0.24)	(0.24)
3Z	−0.22	0.62	−0.48	−0.46	0.26	−0.28	0.26	−0.09	0.18	0.35
	(−0.23)	(0.65)	(−0.54)	(−0.53)	(0.32)	(−0.33)	(0.35)	(−0.01)	(−0.01)	(0.33)
3E	−0.22	0.62	−0.48	−0.46	0.26	−0.28	0.24	−0.06	0.17	0.35
	(−0.23)	(0.65)	(−0.54)	(−0.53)	(0.32)	(−0.33)	(0.349)	(0.00)	(0.00)	(0.33)
TS-3Z-4out	−0.14	0.62	−0.52	−0.49	0.26	−0.27	0.13	0.00	0.14	0.27
	(−0.11)	(0.67)	(−0.60)	(−0.57)	(0.32)	(−0.29)	(0.25)	(−0.08)	(0.09)	(0.25)
TS-3E−4out	−0.14	0.63	−0.52	−0.49	0.25	−0.27	0.11	0.03	0.14	0.28
	(−0.10)	(0.66)	(−0.60)	(−0.58)	(0.31)	(−0.29)	(0.24)	(−0.07)	(0.09)	(0.26)
4out	−0.03	0.64	−0.49	−0.45	0.29	−0.04	−0.05	0.07	0.04	0.06
	(−0.01)	(0.84)	(−0.61)	(−0.55)	(0.34)	(0.01)	(0.02)	(0.02)	(−0.07)	(−0.03)
5Z	−0.22	0.62	−0.48	−0.46	0.26	−0.28	0.25	−0.09	0.20	0.36
	(−0.23)	(0.64)	(−0.54)	(−0.53)	(0.32)	(−0.33)	(0.34)	(−0.02)	(0.01)	(0.33)
5E	−0.22	0.62	−0.48	−0.46	0.27	−0.27	0.24	−0.08	0.20	0.36
	(−0.23)	(0.64)	(−0.54)	(−0.53)	(0.32)	(−0.33)	(0.34)	(−0.02)	(0.01)	(0.33)
TS-5Z-6out	−0.12	0.62	−0.52	−0.49	0.25	−0.26	0.13	0.00	0.15	0.28
	(−0.08)	(0.66)	(−0.59)	(−0.57)	(0.32)	(−0.27)	(0.24)	(−0.09)	(0.09)	(0.24)
TS-5E−6out	−0.11	0.61	−0.51	−0.49	0.25	−0.25	0.11	0.02	0.15	0.28
	(−0.07)	(0.65)	(−0.59)	(−0.58)	(0.31)	(−0.27)	(0.23)	(−0.08)	(0.09)	(0.24)
6out	−0.02	0.63	−0.49	−0.45	0.29	−0.04	−0.06	0.07	0.04	0.05
	(0.00)	(0.84)	(−0.62)	(−0.55)	(0.33)	(0.01)	(0.01)	(0.02)	(−0.06)	(−0.04)
7Z	−0.23	0.62	−0.48	−0.46	0.26	−0.29	0.24	−0.09	0.20	0.35
	(−0.24)	(0.65)	(−0.53)	(−0.53)	(0.32)	(−0.33)	(0.34)	(0.01)	(0.00)	(0.34)
7E	−0.22	0.62	−0.48	−0.46	0.26	−0.28	0.23	−0.06	0.18	0.35
	(−0.24)	(0.65)	(−0.54)	(−0.53)	(0.32)	(−0.33)	(0.35)	(0.00)	(−0.01)	(0.34)
TS-7Z-8out	−0.15	0.63	−0.52	−0.49	0.25	−0.28	0.13	0.02	0.15	0.30
	(−0.10)	(0.67)	(−0.60)	(−0.58)	(0.31)	(−0.30)	(0.23)	(−0.05)	(0.09)	(0.27)
TS-7E−8out	−0.14	0.62	−0.52	−0.49	0.25	−0.28	0.10	0.05	0.14	0.29
	(−0.11)	(0.67)	(−0.60)	(−0.58)	(0.32)	(−0.30)	(0.25)	(−0.07)	(0.09)	(0.27)
8out	−0.02	0.63	−0.49	−0.44	0.29	−0.03	−0.07	0.10	0.01	0.04
	(−0.02)	(0.84)	(−0.62)	(−0.54)	(0.34)	(0.00)	(0.01)	(0.03)	(−0.06)	(−0.03)

SCHEME 4. Numbering System Used in the Johnson−Claisen Rearrangement of 3, 5, and 7
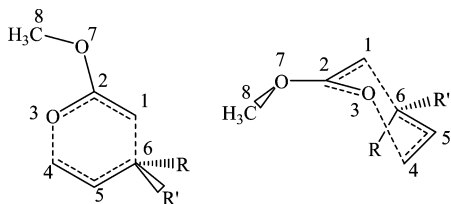
"**in**" transition structures weak stabilizing interactions are present between H1 (*0.15*)−C3 (*−0.12*) (∼2.9 Å) and H1 (*0.15*)−C14 (*−0.12*) (∼3.1 Å). However, there are unique repulsive interactions between H1 (*0.15*) and H* (*0.20*) on C7 and (∼2.4 Å) that disfavor the "**in**" closure over the "**out**".

In summary, for compound **3**, the repulsive interactions between C1−C3, C1−C14, and H*−H1 disfavor the "**in**" closure, but on the other hand, the attractive interactions between C1−H(C5) and C1−H(C16) stabilize the "**out**" transition structures.

In compound **5**, C1 (*−0.42*) has repulsive interactions with C3 (*−0.12*) and C14 (*−0.09*) in the "**in**" transition structures (∼3.3 Å) and also with C5 (*−0.10*) and C16 (*−0.09*) in the "**out**" transition structures (∼3.3 Å). On the other hand, the C1 (*−0.42*)−H(C5) (*0.14*) (∼3.9 Å) and C1 (*−0.42*)−H(C16) (*0.18*) (∼4.0 Å) attractive interactions stabilize the "**out**" closure.

As to the interactions of H1 with its neighbors in compound **5**, for the "**in**" closure, the stabilizing interactions are H1 (*0.15*)−C3 (*−0.12*) (∼3.1 Å) and H1 (*0.14*)− C14 (*−0.09*) (∼3.0 Å) for the "**out**" closure. The H1

(*0.14*)−H(C5) (*0.14*) (∼3.4 Å); H1 (*0.15*)−C5 (*−0.10*) (∼3.9 Å); H1 (*0.15*)−C16 (*−0.09*) (∼3.1 Å) and H1 (*0.14*)− H(C16) (*0.18*) (∼3.5 Å) interactions all cancel each other. As in compound **3**, the unique repulsive interaction between H*(*0.18*) on C7 and H1 (*0.15*) (∼2.5 Å) disfavors the "**in**" transition states.

In summary, for compound **5**, the repulsive interactions between C1−C3, C1−C14, and H*−H1 disfavor the "**in**" closure. Even though stabilizing interactions due to H1− C3 and H1−C14 in the "**in**" structures are not counterbalanced, these are smaller in magnitude than those of the former. (Figure 2).

Compound 7. A similar charge analysis has also been carried out for the transition structures of compound **7**. As mentioned earlier, the interactions of the enolate terminus (C1 and H1) with C3, C7 for the "**in**" closure, and C5, C16, H(C5), and H(C16) for the "**out**" closure have been rationalized. C1 (*−0.47*) has attractive interactions with C7 (*0.13*) (∼3.3 Å) and C5 (*0.17*) (∼3.2 Å) and repulsive interactions with C3 (*−0.14*) (∼3.3 Å) and C16 (*−0.18*) (∼3.2 Å). The magnitudes of these interactions are almost equal such that they cancel each other. H1 (*0.18*) also has attractive interactions with C3 (*−0.14*) (∼2.8 Å) and C16 (*−0.18*) (∼3.0 Å) and repulsive interactions with C7 (*0.13*) (∼3.0 Å) and C5 (*0.17*) (∼2.9 Å), which cancel each other. The transition structures of the "**out**" closure bear attractive interactions between C1 (*−0.47*)−H(C5) (*0.16*) (∼2.8 Å) and C1 (*−0.47*)−H(C16) (*0.15*) (∼2.9 Å). Due to the magnitude of the charge on C1, these stabilizing interactions overcome the repulsive interactions due to H1 (*0.18*)−H(C5) (*0.16*) (∼2.4 Å) and H1− H(C16) (*0.15*) (∼2.5 Å).
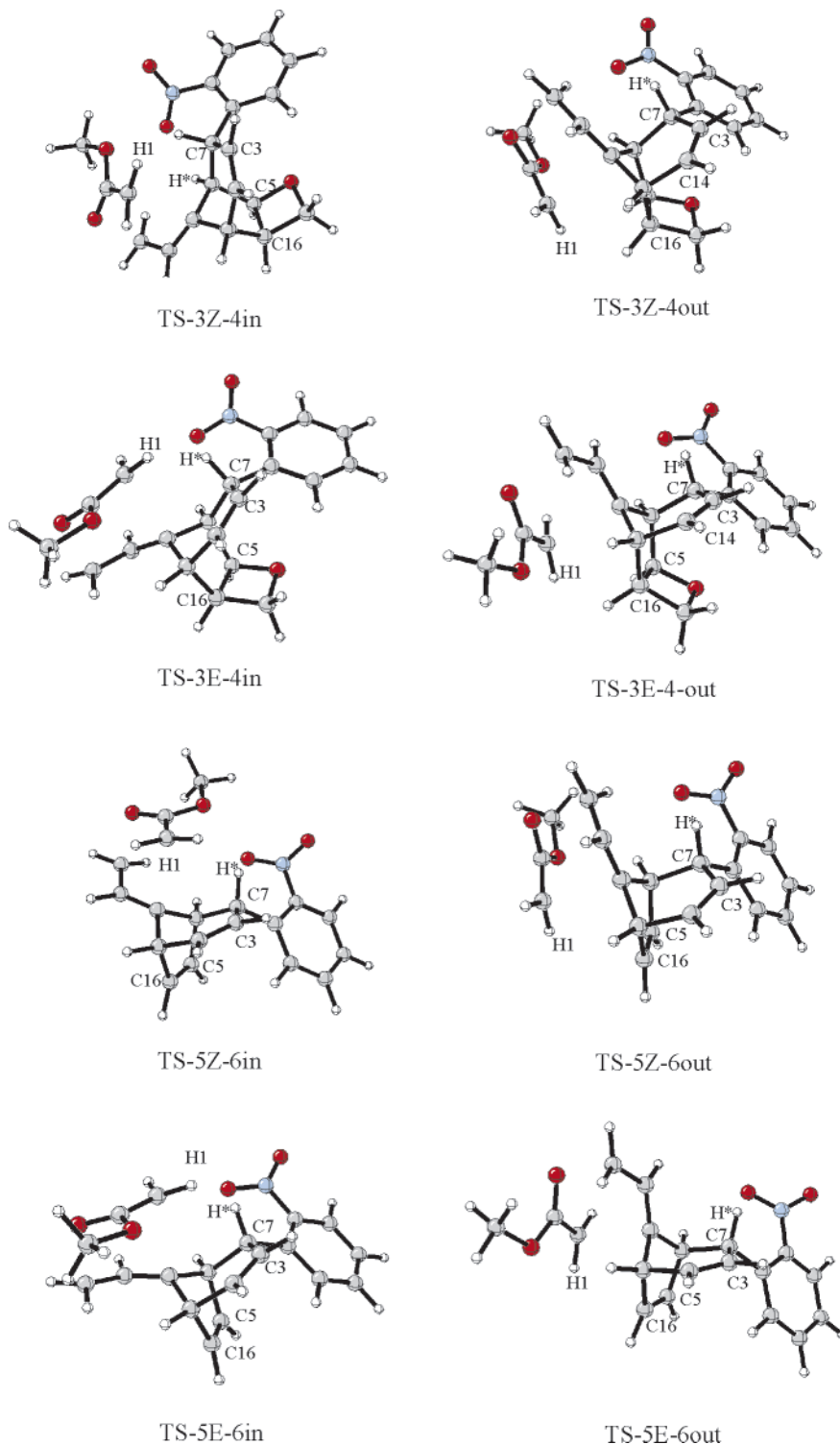
FIGURE 2. Transition structures for ompounds **3** and **5**.

The major repulsive interaction disfavoring the "**in**" closure is the one between H1 (*0.18*) and H*(C14) (*0.18*) (~2.5 Å). There is no similar disfavoring interaction in the "**out**" closure.

Overall, in the transition structures of compound **7**, as in the ones for compound **3**, attractive interactions between C1−H(C5) and C1−H(C16) favor the "**out**" closure, whereas the repulsion between H*(C14) with H1 on the enolate terminus disfavors the "**in**" closure (Figure 3).

Whereas theory and experiment are in accord for five of the cases, the reversal in selectivity postulated for **7E** was not found computationally (Tables 3 and 4). The energies for the transition states of compounds **7Z** and **7E** were refined with B3LYP/6-31+G**//B3LPY/6-31+G** and MPW1K/6-31+G**//MPW1K/6-31+G** calculations,[11,12] but no change in selectivity was predicted (Tables 5 and 6). Furthermore, the effect of the media has been taken into account by carrying out single-point calculations in solution for two different solvents: water
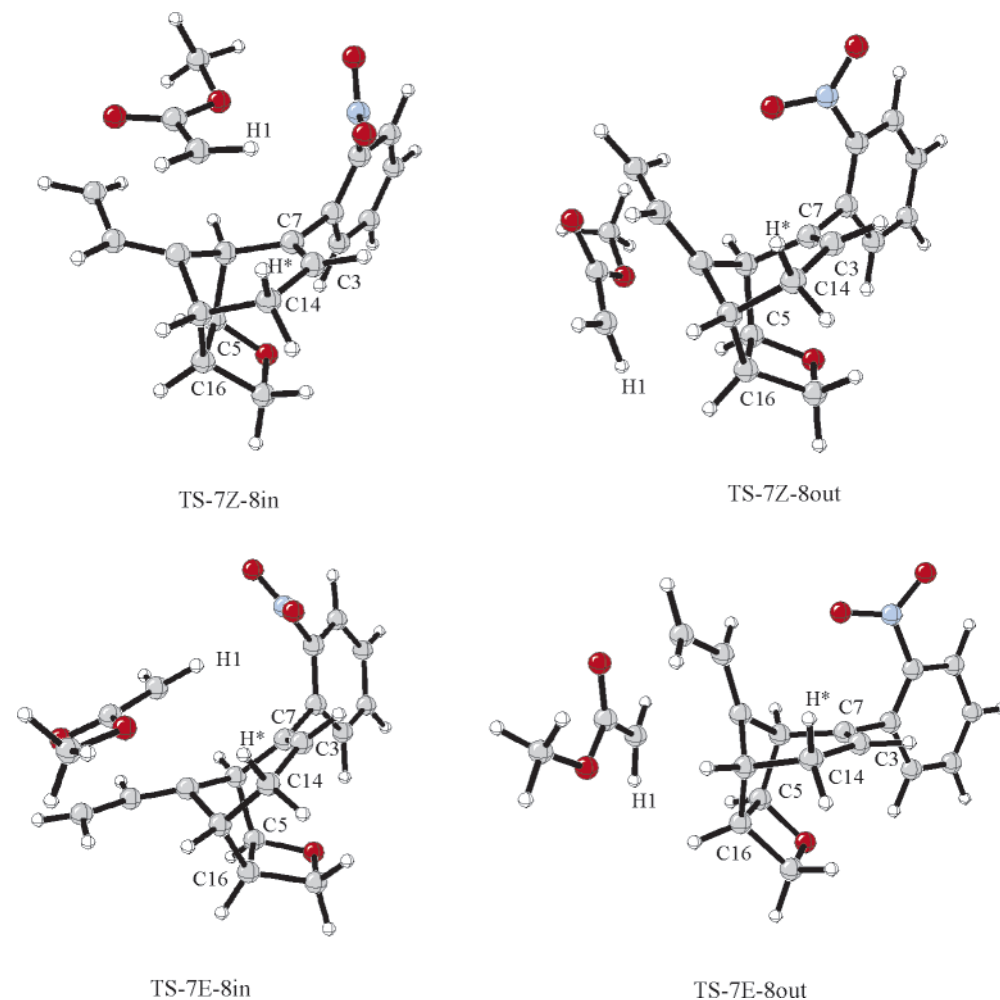
FIGURE 3. Transition structures for compound **7**.

TABLE 3. Activation Energies (ΔE‡), Activation Free Energies (ΔG‡), and Reaction Enthalpies (ΔH$_{rxn}$) (kcal/mol) for Compounds 3, 5, and 7[a]

	ΔE‡	ΔG‡	ΔH$_{rxn}$
3Z → 4in	24.1	26.4	−28.2
3Z → 4out	19.7	21.5	−27.4
3E → 4in	23.3	25.1	−28.7
3E → 4out	20.1	21.7	−27.8
5Z → 6in	24.0	25.7	−29.4
5Z → 6out	20.2	21.6	−30.5
5E → 6in	23.9	25.8	−29.5
5E → 6out	20.6	22.1	−30.6
7E → 8in	24.7	26.6	−27.9
7E → 8out	20.0	21.5	−26.9
7Z → 8in	25.6	28.0	−27.0
7Z → 8out	21.3	22.6	−26.0

[a] Electronic energies include zero-point energies (B3LYP/6-31G*).

TABLE 4. Relative Energies for the Transition States (kcal/mol) for Compounds 3, 5, and 7[a]

	Δ[E‡ (in) − E‡ (out)]	Δ[G‡ (in) − G‡ (out)]
TS-3Z-4	4.4	4.9
TS-3E-4	3.2	3.4
TS-5Z-6	3.8	4.1
TS-5E-6	3.3	3.7
TS-7Z-8	4.3	5.4
TS-7E-8	4.7	5.1

[a] Electronic energies include zero-point energies (B3LYP/6-31G*).

phenyl-2-adamantylidene)ethyl vinyl ether and allyl (5-fluoro-2-adamantylidene) methyl ether.[22] Hehre et al. have assigned face stereoselectivity to the transition state for a [3,3] sigmatropic migration by matching the more electron-rich face of the "nucleophilic" allylic component with the more electron-poor face of the "electrophilic" component in a chairlike transition structure for the Claisen rearrangement.[23]

Conclusion

The facial selectivities in all cases are controlled by steric repulsions between H1 on the enolate group and H*, which disfavor the "**in**" closure. In compounds **3** and **5**, the repulsions between C1 on the enolate moiety and

and toluene. These calculations have allowed us to confirm our findings that, the stereoselectivity is not changed by the polarity of the medium.

Our calculations have shown electrostatic as well as steric effects to direct the facial selectivity of the J–C rearrangement in the synthesis of gelsemine. Electrostatic and steric effects have already been encountered in the literature to direct facial stereoselectivity. A uniform face selectivity has been observed in the [3,3] sigmatropic shifts of the Claisen rearrangement of 2-(5-

TABLE 5. Electronic Energies E_{el} (B3LYP/6-31+G//B3LYP/6-31+G**) (hartrees) and Relative Energies E_{el} (Rel) (kcal/mol) for the Transitions States for Compound 7 in Vacuum ($\epsilon = 1$), Toluene ($\epsilon = 2.24$), and Water ($\epsilon = 78.5$)**

$\epsilon = 1$ (vacuum)	E_{el}	E_{el} (Rel)
TS-7E-8in	−1205.4499345	4.80
TS-7E-8out	−1205.4575858	0.00
TS-7Z-8in	−1205.4489860	4.77
TS-7Z-8out	−1205.4565910	0.00
$\epsilon = 2.24$ (toluene)	E_{el}	E_{el} (Rel)
TS-7E-8in	−1205.442553	4.76
TS-7E-8out	−1205.450136	0.00
TS-7Z-8in	−1205.440118	5.44
TS-7Z-8out	−1205.44878	0.00
$\epsilon = 78.5$ (water)	E_{el}	E_{el} (Rel)
TS-7E-8in	−1205.453206	5.10
TS-7E-8out	−1205.461331	0.00
TS-7Z-8in	−1205.449871	6.37
TS-7Z-8out	−1205.460023	0.00

TABLE 6. Electronic Energies E_{el} (MPW1K/6-31+G//MPW1K/6-31+G**) (Hartrees) and Relative Energies E_e (Rel) (kcal/mol) for the Transitions States for Compound 7 in Vacuum ($\epsilon = 1$), Toluene ($\epsilon = 2.24$), and Water ($\epsilon = 78.5$)**

$\epsilon = 1$ (vacuum)	E_{el}	E_{el} (Rel)
TS-7E-8in	−1205.0782317	3.67
TS-7E-8out	−1205.0840859	0.00
TS-7Z-8in	−1205.0781802	3.47
TS-7Z-8out	−1205.0837049	0.00
$\epsilon = 2.24$ (toluene)	E_{el}	E_{el} (Rel)
TS-7E-8in	−1205.073601	3.56
TS-7E-8out	−1205.079267	0.00
TS-7Z-8in	−1205.071241	4.16
TS-7Z-8out	−1205.077877	0.00
$\epsilon = 78.5$ (water)	E_{el}	E_{el} (Rel)
TS-7E-8in	−1205.084086	3.94
TS-7E-8out	−1205.090363	0.00
TS-7Z-8in	−1205.080562	5.29
TS-7Z-8out	−1205.088991	0.00

the C3−C14 double bond inhibit the "**in**" closure. In compounds **3** and **7**, the "**out**" closure is also promoted by the attractive interactions between C1 and the H's of the oxetane ring. The experimental selectivity for the rearrangement of the compounds **3E**, **3Z**, **5E**, **5Z**, and **7Z** is reproduced by the calculations. However, the selectivity predicted for compound **7E** is the same as that for the other compounds, while experiments suggest that this rearrangement follows a different course.

Supporting Information Available: Cartesian coordinates and energetics of the compounds discussed in the text. This material is available free of charge via the Internet at http://pubs.acs.org.

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