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Three-Carbon Dowd−Beckwith Ring Expansion Reaction versus Intramolecular 1,5-Hydrogen Transfer Reaction: A Theoretical Study

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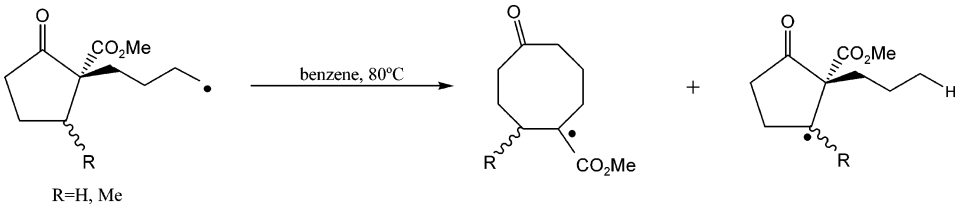

R=H, Me

The evolution of the primary radicals formed by addition of AIBN/$HSnBu_3$ to methyl 1-(3-iodopropyl)-5-oxocyclopentanecarboxylate, methyl (1*R**,2*R**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate, and methyl (1*R**,2*S**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate in benzene has been theoretically investigated by ROMP2/6-311++G(2d,2p)//UB3LYP/6-31G(d,p) calculations taking into account the effect of solvent through a PCM−UAHF model. According to the theoretical results, for methyl 1-(3-iodopropyl)-5-oxocyclopentanecarboxylate and methyl (1*R**,2*S**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate the major product is the cyclooctane derivative from the three-carbon ring expansion, whereas for methyl (1*R**,2*R**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate the major product is that corresponding to the 1,5-H transposition in agreement with the experimental findings. This different behavior is a consequence of several factors determining the relative energy barriers. The methyl substituent destabilizes the ring expansion process for methyl (1*R**,2*R**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate because of steric repulsion but favors it in the case of the β-trans-substituted substrate because it makes possible the evolution of the system along more favorable conformations. The methyl group also favors the 1,5-H transposition rendering the transposed product a tertiary radical. The second stage of the ring expansion process is stabilized by resonance.

Introduction

An attractive way to approach the synthesis of medium and large rings is to take advantage of existing cyclic structures through ring expansion reactions.[1] One of these synthetic strategies is the so-called Dowd−Beckwith free radical ring expansion which uses β-keto esters as starting materials.[2−4] The efficiency of this method has been experimentally proved for both one- and three-carbon ring expansions (see Scheme 1). However, in the case of the three-carbon expansion processes experimental work has identified a competing 1,5-hydrogen transfer which can become dominant for some substrates.

For methyl 1-(3-iodopropyl)-2-oxocyclopentanecarboxylate (**5** in Scheme 2) the ring expansion product **6** accounts for 77% of the products. In addition, 15% of the directly reduced product **8** and 8% of reduction product **7** with deuterium incorporated β to the carbonyl are formed, showing that 1,5-H transfer is occurring. For the β-trans-substituted precursor methyl (1*R**,2*R**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate, **9**, ring expansion (**10**), 1,5-hydrogen transfer (**11**), and direct reduction (**12**) products are formed in 8%, 86%, and 6% yields, respectively. In contrast, reaction of the β-cis-

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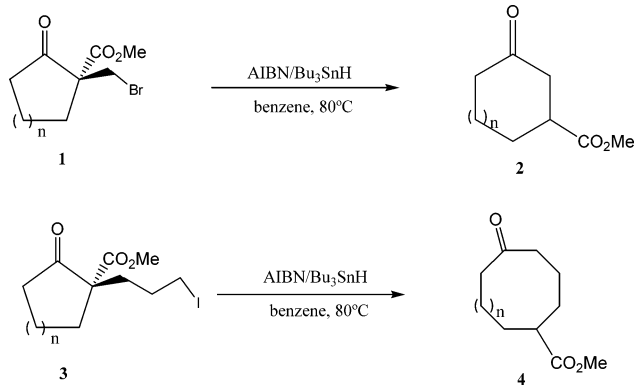
SCHEME 1



substituted compound **13** affords ring expansion (**14**) in excellent yield (93%), while direct reduction (**15**) is only a minor process (7%), and 1,5-hydrogen transfer is not observed.

In a previous work,[5] we have studied, by means of both density functional theory (DFT) and MP2 methods, the mechanism for one-carbon Dowd−Beckwith ring expansion of methyl 1-(bromomethyl)-2-oxocyclopentanecarboxilate **1** to yield methyl 3-oxo-cyclohexanecarboxylate **2**. In that investigation we have performed a comparative study of the two reaction mechanisms previously proposed for this process.[2,3] According to our findings, along the most favorable route formation of the primary radical by addition of a radical-generating reagent is followed by attack of the radical center on the ketone carbonyl to yield the ring-expanded product in a concerted way without fragmentation through a bicyclic transition state (TS).

As a further step, we report here a theoretical study of the three-carbon ring expansion and the 1,5-H transposition reactions of the primary radicals formed from 1-(3-iodopropyl)-2-oxocyclopentanecarboxylate, **5**, methyl (1*R**,2*R**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate, **9**, and methyl (1*R**,2*S**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate, **13**, trying to rationalize the experimental observations displayed in Scheme 2.

Methods

Quantum chemical computations were performed using the Gaussian 98 series of programs.[6] The geometries of the stable species and the TSs were fully optimized in the gas phase at the UB3LYP/6-31G(d,p) theory level[7] using Schlegel's algorithm.[8] Harmonic vibrational frequencies were also calculated at the UB3LYP/6-31G(d,p) theory level to characterize the critical points located and to evaluate the zero-point vibrational energy (ZPVE). Single-point calculations were also performed in the gas phase on the UB3LYP/6-31G(d,p)-optimized geometries at the ROMP2/6-311++G(2d,2p) level.[9] An NBO population analysis[10] was performed at the UB3LYP/6-311++G(d,p)//UB3LYP/6-31G(d,p) level.

ΔG values were computed in the gas phase using the UB3LYP/6-31G(d,p) frequencies within the ideal gas, rigid rotor, and harmonic oscillator approximations[11] at 1 atm and 353.15 K, which were the experimental conditions.

To take into account condensed-phase effects we used a self-consistent reaction field (SCRF) model proposed for quantum chemical computations on solvated molecules.[12−14] The solvent is represented by a dielectric continuum characterized by its relative static dielectric permittivity, ϵ. The solute, which is placed in a cavity created in the continuum after spending some cavitation energy, polarizes the continuum, which in turn creates an electric field inside the cavity. This interaction can be taken into account using quantum chemical methods by minimizing the electronic energy of the solute plus the Gibbs energy change corresponding to the solvation process. Addition to ΔG_{gas} of the solvation Gibbs energy gives $\Delta G_{solution}$. To calculate the electrostatic potential created by the polarized continuum in the cavity we employed the polarizable continuum model (PCM) with the united atom Hartree−Fock (UAHF) parametrization.[15] The solvation Gibbs energies $\Delta G_{solvation}$ along the reaction coordinates were evaluated from single-point PCM calculations on the gas-phase-optimized geometries at the UB3LYP/6-311++G(d,p) theory level. A relative permittivity of 2.247 was employed to simulate benzene as the solvent used in the experimental work.

Results and Discussion

We will present first the results obtained for the ring expansion and the 1,5-H transfer for the primary radical from methyl 1-(3-iodopropyl)-2-oxocyclopentanecarboxylate and then for its *β-trans*-methyl- and *cis*-methyl-substituted derivatives. Figures 1S, 2S, and 3S of the Supporting Information show the optimized geometries of the critical structures located along the reaction coordinates. Tables 1, 2, and 4 collect the electronic energy, the ZPVE, the Gibbs energy of solvation, and the Gibbs energy in the gas phase and in solution for all the critical structures for the three substrates, respectively, and Figures 1, 2, and 3 display the corresponding ROMP2/6-311++G(2d,2p)//UB3LYP/6-31G(d,p) Gibbs energy profiles in solution. Table 3 collects the most important NBO atomic spin densities for the two substituted substrates. Unless otherwise stated, ROMP2/6-311++G(2d,2p)//UB3LYP/6-31G(d,p) relative Gibbs energies in solution will be given in the text.

Evolution of the Primary Radical from Methyl 1-(3-Iodopropyl)-2-oxocyclopentanecarboxylate. According to our theoretical results, the ring expansion of the primary radical from methyl 1-(3-iodopropyl)-2-

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SCHEME 2

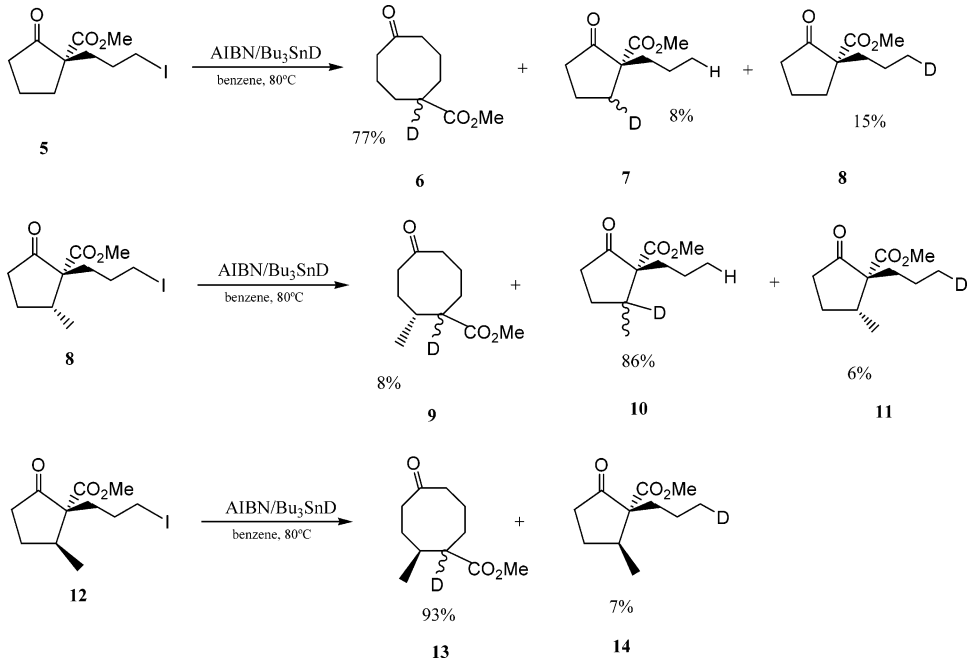

TABLE 1. Relative Electronic Energies, ZPVEs, Gibbs Energies of Solvation, and Gibbs Energies in the Gas Phase and in Solution for the Ring Expansion and 1,5-H Transfer for Methyl 1-(3-Iodopropyl)-5-oxocyclopentanecarboxylate

	UB3LYP/6-31G(d,p)					ROMP2/6-311++G(2d,2p)//UB3LYP/6-31G(d,p)		
structures	$\Delta(E_{elec})$	Δ(ZPVE)	$\Delta G_{gas-phase}$	$\Delta\Delta G_{solv}$[a]	$\Delta G_{solution}$	$\Delta(E_{elec})$	$\Delta G_{gas-phase}$	$\Delta G_{solution}$
R	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TS1E	10.0	0.9	12.7	−1.2	11.5	10.4	13.1	11.9
IE	−2.1	2.6	2.9	−0.8	2.1	2.1	7.1	6.3
TS2E	2.0	−0.8	4.1	−0.3	3.8	5.1	11.4	11.1
PE	−17.0	2.3	−13.7	−1.3	−15.0	−12.1	−8.7	−10.0
TS1T	5.5	−0.1	6.0	−0.2	5.8	5.8	6.3	6.1
IT	0.6	−0.3	−0.3	−0.4	−0.7	1.3	0.4	0.0
TS2T	14.0	−2.5	11.8	0.2	12.0	14.4	12.2	12.4
PT	−0.3	0.0	−0.5	0.3	−0.2	0.0	−0.1	0.2

[a] Evaluated at the UB3LYP/6-311++G(d,p) level.

TABLE 2. Relative Electronic Energies, ZPVEs, Gibbs Energies of Solvation, and Gibbs Energies in the Gas Phase and in Solution for the Ring Expansion and 1,5-H Transfer for Methyl (1*R,2*R**)-1-(3-Iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate**

	UB3LYP/6-31G(d,p)					ROMP2/6-311++G(2d,2p)//UB3LYP/6-31G(d,p)		
structures	$\Delta(E_{elec})$	Δ(ZPVE)	$\Delta G_{gas-phase}$	$\Delta\Delta G_{solv}$[a]	$\Delta G_{solution}$	$\Delta(E_{elec})$	$\Delta G_{gas-phase}$	$\Delta G_{solution}$
R′	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TS1E′	10.3	0.9	13.3	0.0	13.3	10.8	13.8	13.8
IE′	−0.9	2.6	4.8	−1.1	3.7	3.7	9.4	8.3
TS2E′	1.0	2.0	6.1	−1.4	4.7	8.6	13.7	12.3
PE′	−16.1	2.5	−11.9	−1.6	−13.5	−11.2	−7.0	−8.6
TS1T′	5.1	−0.1	6.4	−0.3	6.1	4.7	6.1	5.8
IT′	0.1	−0.3	0.0	0.0	0.0	0.2	0.1	0.1
TS2T′	11.3	−2.6	9.8	0.1	9.9	11.0	9.4	9.5
PT′	−8.3	0.0	−9.3	0.0	−9.3	−4.3	−5.3	−5.3

[a] Evaluated at the UB3LYP/6-311++G(d,p) level.

oxocyclopentanecarboxylate, **R**, is a two-step process without fragmentation (see Figure 1). **R**, in which the α unpaired electron is localized at C8 (total NBO spin density = +0.99), evolves through a TS **TS1E** (11.9 kcal/mol) for the nucleophilic attack of the radical carbon atom C8 on the carbon atom of the carbonyl group, C1, to form a bicyclic intermediate, **IE** (6.3 kcal/mol). At **TS1E**, the C8−C1 distance is 2.120 Å, the C1−C2 bond length has stretched from 1.567 to 1.603 Å, and the α unpaired spin is located mainly at C8 (+0.65) and O11 (+0.38), while C1 presents a slight spin polarization (−0.07).

At **IE**, the C8−C1 and C1−C2 bond lengths are 1.550 and 1.616 Å, respectively, and the α unpaired spin is

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TABLE 3. Most Important NBO Atomic Spin Densities along the Ring Expansion and 1,5-H Transfer for Methyl (1*R,2*R**)-1-(3-Iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate and Methyl (1*R**,2*S**)-1-(3-Iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate**

structure	C1	C2	C3	C8	O10	O11	H12
R′/R″				+0.99/+0.98			
TS1E′/TS1E″	−0.07/−0.06			+0.64/+0.70		+0.40/+0.36	
IE′/IE″			+0.11/+0.11			+0.86/+0.86	
TS2E′/TS2E″	−0.07/−0.07	+0.36/+0.36				+0.63/+0.63	
PE′/PE″		+0.75/+0.74			+0.15/+0.14		
TS1T′/TS1T″				+0.98/+0.99			
IT′/IT″				+0.98/+1.00			
TS2T′/TS2T″			+0.43/+0.44	+0.58/+0.56			−0.06/−0.06
PT′/PT″			+0.83/+0.84				

TABLE 4. Relative Electronic Energies, ZPVEs, Gibbs Energies of Solvation, and Gibbs Energies in the Gas Phase and in Solution for the Ring Expansion and 1,5-H Transfer for Methyl (1*R,2*S**)-1-(3-Iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate**

	UB3LYP/6-31G(d,p)					ROMP2/6-311++G(2d,2p)//UB3LYP/6-31G(d,p)		
structures	$\Delta(E_{elec})$	Δ(ZPVE)	$\Delta G_{gas-phase}$	$\Delta\Delta G_{solv}$[a]	$\Delta G_{solution}$	$\Delta(E_{elec})$	$\Delta G_{gas-phase}$	$\Delta G_{solution}$
R″	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
TS1E″	8.1	0.7	10.8	−1.0	9.8	8.4	11.0	10.0
IE″	−4.3	2.2	0.0	−0.5	−0.5	−0.1	4.2	3.7
TS2E″	−3.1	1.6	1.0	−0.8	0.2	4.1	8.1	7.3
PE″	−20.2	2.2	−17.0	−1.3	−18.3	−15.8	−12.6	−13.9
TS1T″	4.6	−0.6	5.1	−0.2	4.9	3.7	4.2	4.0
IT″	−2.0	−0.6	−3.4	0.3	−3.1	−3.7	−5.1	−4.8
TS2T″	21.5	−0.6	20.0	−0.1	19.9	18.0	16.6	16.5
PT″	−10.2	−0.3	−12.2	0.6	−11.6	−6.1	−8.0	−7.4

[a] Evaluated at the UB3LYP/6-311++G(d,p) level.

distributed between C5 (+0.11) and O11 (+0.85). Finally, **IE** yields the expanded product, **PE** (−10.0 kcal/mol), through the TS **TS2E** (11.1 kcal/mol) for the cleavage of the C1−C2 bond. At **TS2E**, the C1−C2 bond is strongly elongated (1.904 Å) and the α unpaired spin density is localized mainly at C2 (+0.36) and O11 (+0.62), while C1 is slightly spin polarized (−0.07). At **PE**, the α unpaired spin density is distributed between C2 (+0.74) and O10 (+0.14). This delocalization of spin density on O10 reflects the presence of the resonance >C•−C9=O10 ↔ >C=C9−O•10, which appreciably stabilizes the last part of the expansion energy profile. Therefore, the rate-determining step for this process is the formation of the bicyclic intermediate **IE** with an energy barrier of 11.9 kcal/mol. It is interesting to note that in this case no vestige of a mechanism with fragmentation was found for the ring expansion.

We also investigated the attack of the radical carbon center to the ester carbonyl group. The structures located along the reaction coordinate, and the corresponding energies, can be found, respectively, in Figure 4S and Table 4S of the Supporting Information. We found that the process renders a bicyclic structure through a concerted mechanism with a Gibbs energy barrier in solution of 15.7 kcal/mol at the UB3LYP/6-31G(d,p) level and of 17.0 kcal/mol at the ROMP2/6-311++G(2d,2p)//UB3LYP/6-31G(d,p) level. Therefore, this attack is not competitive with the addition to the keto carbonyl group, in agreement with experimental evidence.

From **R** the 1,5-H transposition takes place in two stages (see Figure 1). The first one consists of a conformational change in which the dihedral angle C2−C6−C7−C8 changes from −60.1° to 78.2° leading to the isomeric form of **R** appropriate for the H atom migration, **IT** (0.0 kcal/mol), through the TS **TS1T** (6.1 kcal/mol; dihedral angle C2−C6−C7−C8 = 3.2°). In **TS1T** and **IT** the α unpaired spin density is localized at C8 (+0.98). In the second step **IT** can undergo a 1,5-H migration through the TS **TS2T** (12.4 kcal/mol) to yield the final product **PT** (0.2 kcal/mol). At **TS2T**, the migrating H atom is situated at a distance of 1.345 Å from C3 and 1.366 Å from C8 and the α unpaired spin is located mainly at C3 (+0.49) and C8 (+0.55), the migrating H presenting a small polarization (−0.06). At **PT**, the α unpaired electron is mainly located at C3 (+0.90). Then the rate-determining TS for this process is **TS2T** with an energy barrier of 12.4 kcal/mol.[16]

Evolution of the Primary Radical from Methyl (1*R,2*R**)-1-(3-Iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate.** According to our results, the mechanisms for ring expansion and 1,5-H transposition of methyl (1*R**,2*R**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate, **R′**, are analogous to those found for methyl 2-propylcyclopentanone-2-carboxylate (see Figure

(16) To benchmark the theory level employed in the present work we performed geometry optimization of the reactant, the rate-determining TSs, **TS1E** and **TS2T**, and **PE** and **PT** products for the ring expansion and 1,5-H transposition in the primary radical from 1-(3-iodopropyl)-2-oxocyclopentanecarboxylate, **16**, at the UBHandHLYP/6-31G(d,p) theory level, and single-point ROMP2/6-311++G(2d,2p)//UBHandHLYP/6-31G(d,p) calculations. We found that, in general, bond lengths are slightly larger with the UBHandHLYP functional (the mean difference is about 0.01 Å). The ROMP2/6-311++G(2d,2p)//UBHandHLYP/6-31G(d,p) Gibbs energy barriers in solution are 11.7 kcal/mol for **TS1E** and 12.5 kcal/mol for **TS2T**. The reaction energies are −9.9 kcal/mol for the ring expansion and −0.9 kcal/mol for the 1,5-H transposition. Thus, the energy barriers obtained with the UBHandHLYP functional differ from those obtained with the B3LYP one only by 0.1−0.2 kcal/mol, whereas the largest difference was found for the reaction energy for the transposition (1.1 kcal/mol). Therefore, the ROMP2/6-311++G(2d,2p)//UB3LYP/6-31G(d,p) theory level used in this work seems to be adequate for the present study. The geometries and energies obtained in this benchmarking can be found in Figure 5S and Table 6S of the Supporting Information.

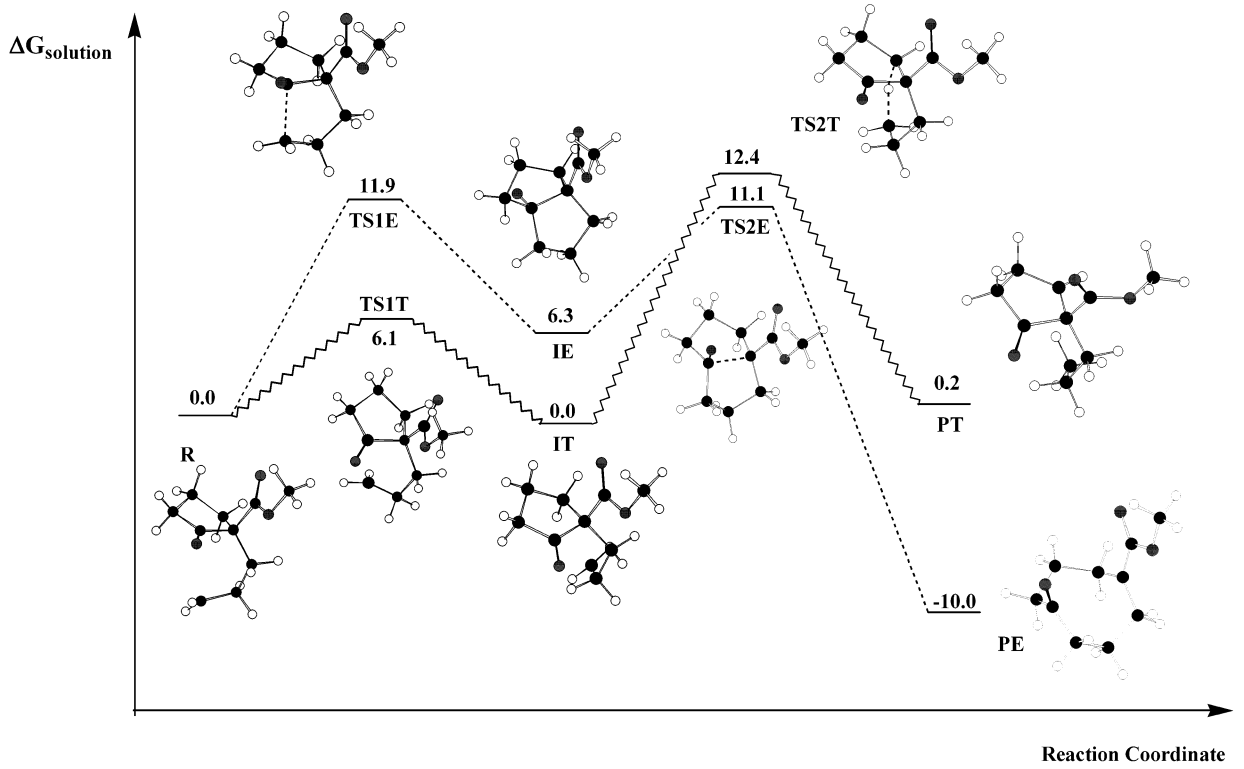

FIGURE 1. ROMP2 Gibbs energy profiles (kcal/mol) in solution for the ring expansion (plain line) and the 1,5-H transfer (curly line) for methyl 1-(3-iodopropyl)-5-oxocyclopentanecarboxylate.

2 and Tables 2 and 3). Along the ring expansion mechanism without fragmentation the primary radical **R′** evolves through **TS1E′** (13.8 kcal/mol) to give a bicyclic intermediate **IE′** (8.3 kcal/mol). At **TS1E′**, the C8−C1 distance is 2.115 Å and the C1−C2 bond length has stretched from 1.561 to 1.597 Å (see Figure 2S). Finally, **IE′** yields **PE′** (−8.6 kcal/mol) through **TS2E′** (12.3 kcal/mol). At **TS2E′**, the C1−C2 distance is 1.897 Å. NBO spin densities are similar to those found for the unsubstituted substrate (see Table 3). Therefore, the rate-determining step for this process is the first one with an energy barrier of 13.8 kcal/mol corresponding to **TS1E′**. No mechanism with fragmentation was found in this case either.

Along the 1,5-H transposition **R′** evolves through **TS1T′** (5.8 kcal/mol) to render the intermediate **IT′** (0.1 kcal/mol), which in turn transforms into the final product **PT′** (−5.3 kcal/mol) through **TS2T′** (9.5 kcal/mol). **TS2T′**, which is the rate-determining TS, displays an earlier structure (the distances from the migrating H atom to C3 and C8 are now 1.323 and 1.395 Å, respectively) than **TS2T** and, consequently, presents a lower energy barrier than it.

The NBO atomic spin densities for both processes are similar to those corresponding to the unsubstituted substrate (see Table 3).

Evolution of the Primary Radical from Methyl (1*R,2*S**)-1-(3-Iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate.** The primary radical **R″** evolves along a ring expansion mechanism without fragmentation through **TS1E″** (10.0 kcal/mol) to give a bicyclic intermediate **IE″** (3.7 kcal/mol). At **TS1E″**, the C8−C1 distance is 2.141 Å and the C1−C2 bond length is 1.604 Å (see Figure 3S). Finally, **IE″** evolves through **TS2E″** (7.3 kcal/mol) to yield the product **PE″** (−13.9 kcal/mol). NBO spin densities are similar to those corresponding to the two previous systems (see Table 3).

Along the 1,5-H transposition **R″** evolves through a TS, **TS1T″** (4.0 kcal/mol), for the conformational change required to reach the intermediate **IT″** (−4.8 kcal/mol) and make possible the H transposition. Finally, **IT″** transforms into the final product **PT″** (−7.4 kcal/mol) through **TS2T″** (16.5 kcal/mol).

Table 3 displays the most important NBO atomic spin densities for both processes, which are similar to those found for the unsubstituted and the β-cis-substituted substrates.

Discussion and Comparison with Experiment. Comparing the MP2 energies with the UB3LYP ones in Tables 1, 2, and 4, we see that the perturbation method renders the most strained structures along the ring expansion process, particularly structures **IE**, **IE′**, **IE″**, **TS2E**, **TS2E′**, **TS2E″**, **PE**, **PE′**, and **PE″**, about 4.5−7.5 kcal/mol less stable than the DFT ones.

The effect of solvent is rather similar for the analogous structures of the three substrates with the exception of **TS1E**, **TS1E″**, and **TS2E′**, which become about 1 kcal/mol more favored in solution than **TS1E′** and **TS2E**, respectively, and of **IT**, which is favored by solvent by 0.7 kcal/mol with respect to **IT″**.

From comparison of the figures in Tables 1, 2, and 4, we learn that the methyl substituent introduced in methyl 1-(3-iodopropyl)-2-oxocyclopentanecarboxylate pro-

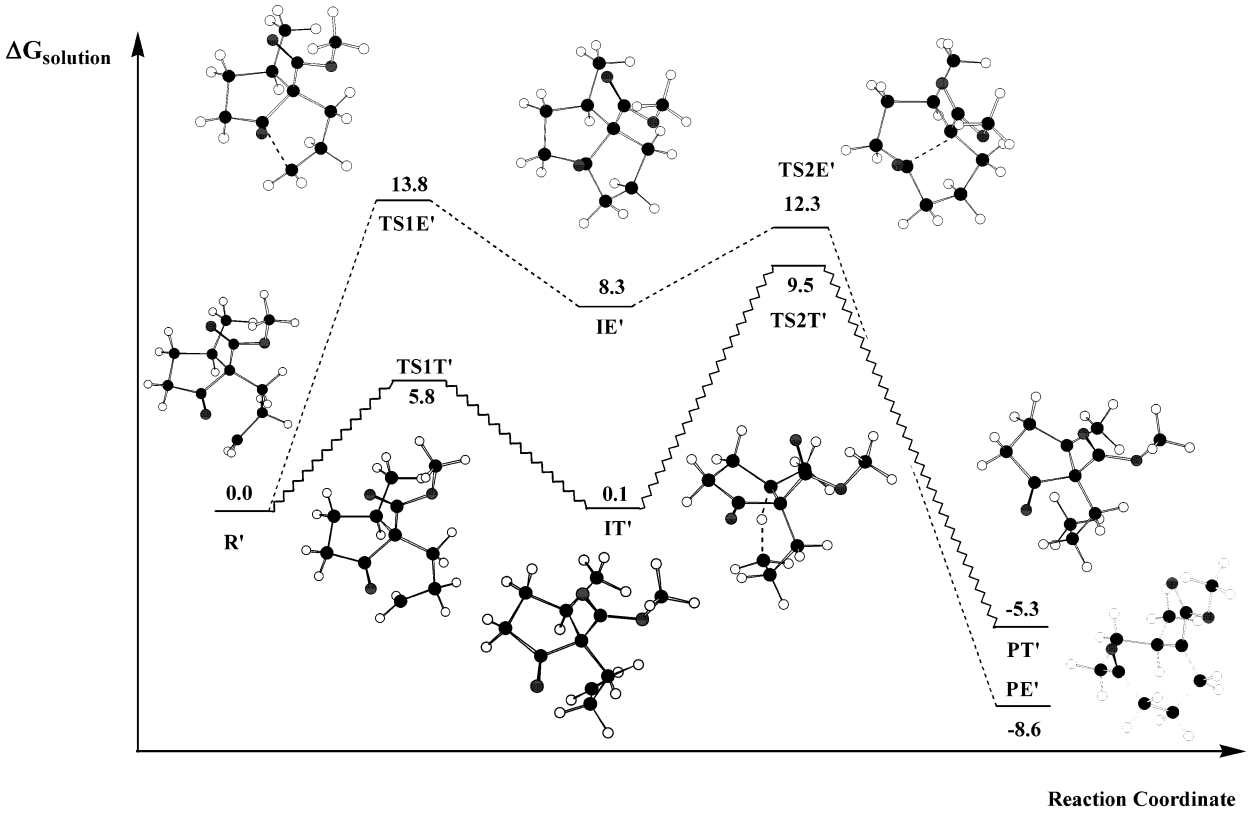

FIGURE 2. ROMP2 Gibbs energy profiles (kcal/mol) in solution for the ring expansion (plain line) and the 1,5-H transfer (curly line) for methyl (1*R**,2*R**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate.

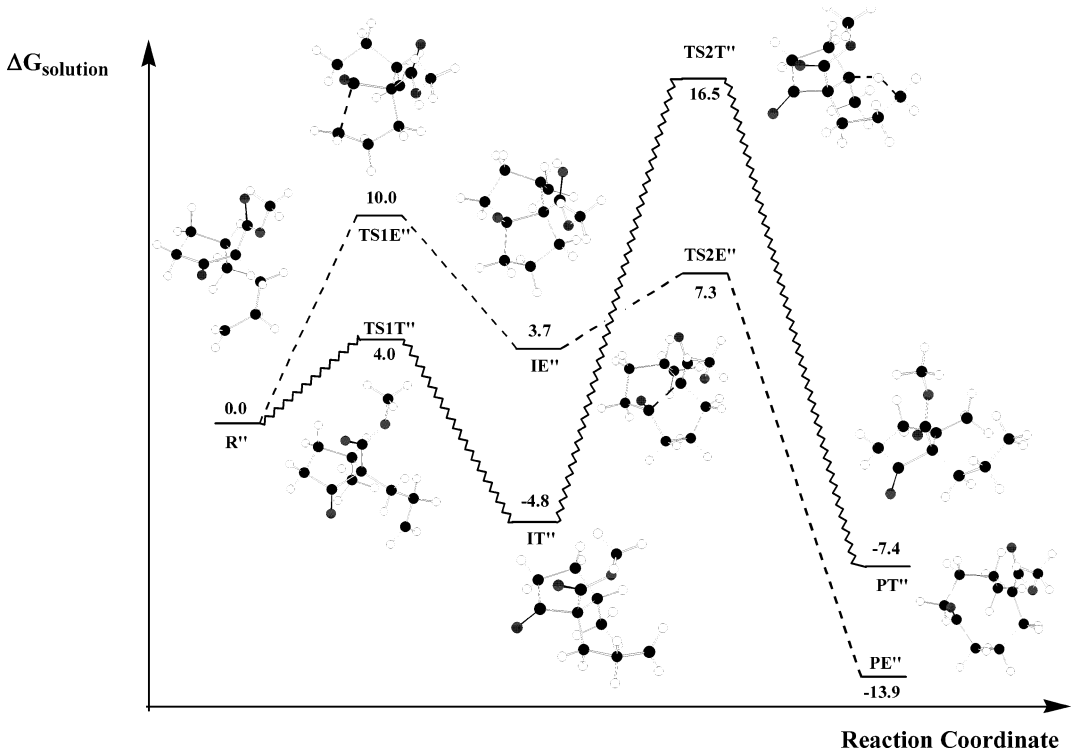

FIGURE 3. ROMP2 Gibbs energy profiles (kcal/mol) in solution for the ring expansion (plain line) and the 1,5-H transfer (curly line) for methyl (1*R**,2*S**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate.

duces the following main effects. On one hand, the energy profile for the ring expansion of methyl (1*R**,2*R**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate is about 1−2 kcal/mol higher than that for the unsubstituted system. This destabilization stems from the steric repulsion between the methyl substituent and the carboxylate

group, which disfavors the evolution of the system through bicyclic structures and the formation of the expanded ring. In contrast the *β-trans*-methyl substituent in (1*R**,2*S**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate seems to allow an evolution through more favorable conformations of the bicyclic structures yielding an energy profile for the ring expansion about 2−4 kcal/mol more favorable than that for the unsubstituted substrate. On the other hand, along the 1,5-H transposition path for the substituted systems **TS2T′**, **TS2T″**, **PT′**, and **PT″** become stabilized with respect to the corresponding initial reactants **R′** and **R″** by the methyl group because in this processes the original primary radical is transformed into a more stable tertiary radical. Another factor which plays an appreciable stabilizing role in the last stage of the ring expansion process is the presence of the resonance >C•−C9═O10 ↔ >C═C9−O•10 in **TS2E**, **TS2E′**, **TS2E″**, **PE**, **PE′**, and **PE″** as clearly indicated by the spin density analysis. This effect seems to decisively contribute to rendering the first stage of the three ring expansions the rate-determining one. Also, the steric hindrance met by the radical center C8 when approaching C5 to receive the migrating H atom in the *β*-trans-substituted substrate appreciably destabilizes the corresponding TS, **TS2T″**. As a consequence of the interplay of all these effects the expansion is kinetically the most favored process for the unsubstituted and the *β*-trans-substituted substrates, whereas the 1,5-H transposition is kinetically the most favored process for the *β*-cis-substituted substrate.

As mentioned in the Introduction, the experimental results indicate that for methyl 1-(3-iodopropyl)-5-oxocyclopentanecarboxylate the major product is the cyclooctane derivative (77%), whereas for methyl (1*R**,2*R**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate the major product is that corresponding to the 1,5-H transposition (86%). For methyl (1*R**,2*S**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate the major product is the cyclooctane derivative (93%) with a total absence of the transposed product. Our theoretical results allow us to rationalize these behaviors. From Tables 1, 2, and 4 we see that the ring expansion process is kinetically favored by 0.5 kcal/mol over the 1,5-H transposition for methyl 1-(3-iodopropyl)-5-oxocyclopentanecarboxylate and by 11.3 kcal/mol for methyl (1*R**,2*S**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate. In contrast, for methyl (1*R**,2*R**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate the 1,5-H transposition is kinetically favored by 4.3 kcal/mol over the expansion process.

In summary, according to ROMP2/6-311++G(2d,2p)//UB3LYP/6-31G(d,p) calculations taking into account the effect of solvent through a PCM−UAHF model, for methyl 1-(3-iodopropyl)-5-oxocyclopentanecarboxylate and methyl (1*R**,2*S**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate the major product is the cyclooctane derivative from the three-carbon ring expansion, whereas for methyl (1*R**,2*R**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate the major product is that corresponding to the 1,5-H transposition in accordance with the experimental results. This different behavior is a consequence of several acting factors which determine the relative energy barriers. The methyl substituent destabilizes the ring expansion process for methyl (1*R**,2*R**)-1-(3-iodopropyl)-2-methyl-5-oxocyclopentanecarboxylate because of steric repulsion but favors it in the case of the *β*-trans-substituted substrate because it makes possible the evolution of the system along more favorable conformations. The methyl group also favors the 1,5-H transposition rendering the transposed product a tertiary radical. The presence of the resonance >C•−C9═O10 ↔ >C═C9−O•10 stabilizes the second stage of the ring expansion process causing the rate-determining step to be the first one.

Supporting Information Available: Absolute electronic energies, ZPVEs, and Cartesian coordinates for all the critical structures located along the reaction paths; relative electronic energies and relative Gibbs energies in the gas phase and in solution for the radical attack on the ester carbonyl group and for the UBHandHLYP benchmarking calculations; gas-phase-optimized geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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