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Theoretical study of the molecular mechanism of the domino pathways for squarate ester sequential reactions

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ABSTRACT: The PM3 semiempirical method was selected to study the stereoselectivity along the domino pathways corresponding to the twofold addition of the chiral (*R*)-3-*tert*-butylcyclopentenyllithium **2** and the achiral cyclopentenyllithium **5** to dimethyl squarate ester **1** as a model for squarate ester sequential reactions. Stationary points, reactants, intermediates, transition structures and products, on the reactive potential energy surface were characterized with analytical gradient techniques. The main steps of this consecutive chemical reaction can be classified as follows: (1) addition of **2** to **1** to obtain the ketoalkoxide products **3** and **4**; (ii) a domino sequence corresponding to an initial addition of **5** to these products to yield dialkoxide intermediates **IN1** and **IN2**; subsequent C—C bond breaking processes of **IN1** and **IN2**, associated with electrocyclic four-membered ring cleavage, to yield the *endo* and *exo* octatetraene rotamers **IN3** and **IN4**, respectively; the final cyclizations give the cyclooctatriene products **6** and **7**, respectively; and (iii) hydrolysis and subsequent intramolecular aldolic condensation of these cyclooctatrienes to obtain the final products. The theoretical results show that the step controlling the product stereochemisty corresponds to the conrotatory cyclization of the *exo* octatetraene intermediate **IN4**. The large value of the barrier height associated with the cyclization of the *endo* octatetraene **IN3** together with the easy interconversion between the octatetraene rotamers **IN3** and **IN4** indicate that the cyclization process takes place only through the *exo* octatetraene **IN4**. Copyright © 1999 John Wiley & Sons, Ltd.

KEYWORDS: squarate esters; sequential reactions; domino reactions; PM3 semiempirical method

INTRODUCTION

The development of synthetic methodologies combining the simultaneous formation of several bonds in a single sequence (domino processes) represents an attractive field of research, belonging to a growing family of reactions that allow the regio-and stereo-controlled formation of several carbon–carbon bonds and/or ring systems in a single operation.[1–9] A striking feature of this type of rearrangement is that whereas both starting reagents can be achiral, products containing several contiguous stereogenic centers can be formed. In particular, the squarate ester cascade associated with the twofold addition of cyclopentenyllithium to a squarate ester triggers a domino of chemical events with concomitant formation of polycyclic products. This type of chemical reaction has been systematically studied by Paquette and co-workers[10–12] and can be considered as a useful synthetic transformation in organic chemistry.[13,14] A schematic representation of the stages of the overall process is presented in Scheme 1.

Although the sequence of the major steps is known from experimental work,[10–14] there have been no theoretical investigations on the detailed molecular mechanism. As a part of our ongoing research program to study the family of consecutive inter- and intramolecular domino reactions,[15–17] in this paper we report on a first theoretical study in which all stationary points related to the co-addition of a chiral alkyl-substituted and an achiral cyclopentenyllithium to a squarate ester were characterized on model compounds having the essential group elements intervening in the chemistry of this system. The aim of this work was to contribute to a better understanding of the mechanistic features of this domino reaction process, especially by identifying the step in the domino sequence that controls the product sterochemistry.

COMPUTATIONAL METHODS AND MODELS

Owing to the large size of the present systems, studies at the *ab initio* level are exceedingly expensive. However, semiempirical methods have progressed over the past few

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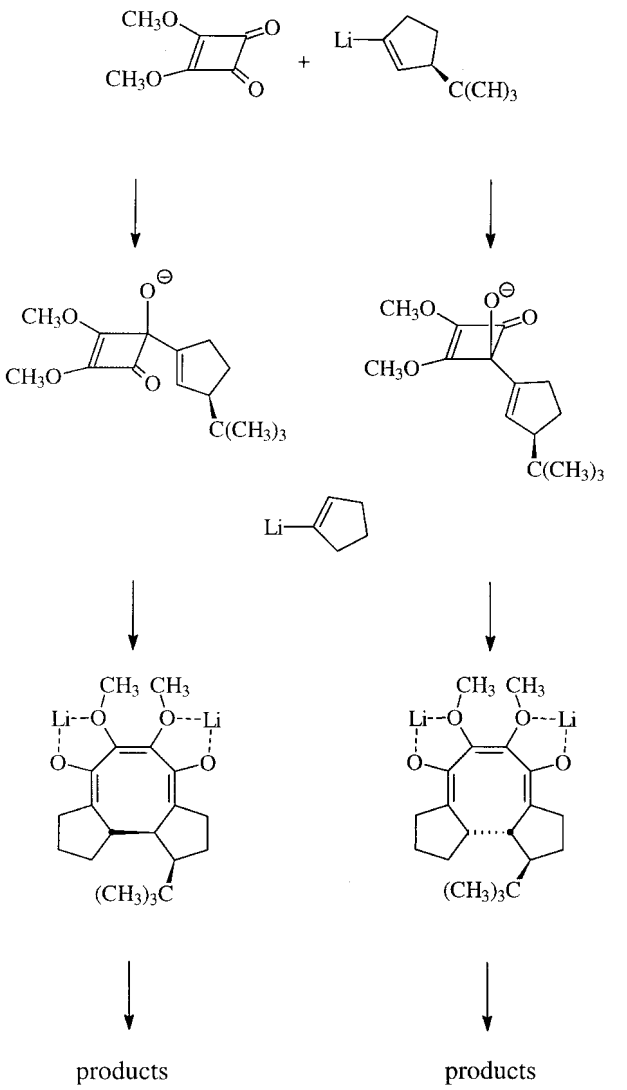

Scheme 1. Schematic representation of the twofold addition of the chiral and achiral cyclopentenyllithium **2** and **5** to the squarate ester **1** following Paquette's *et al.* scheme[11]

years to a surprising level of accuracy and reliability, considering the limitations of the underlying approximations;[18,19] even simple calculations at moderate levels of theory such as semiempirical procedures give useful information on the molecular mechanism of different chemical reactions. Accordingly, the PM3 semiempirical procedure[20] was selected to carry out the calculations with the MOPAC93 package of programs.[21] This method renders a reliable parameter set for Li and it has been applied to study different organic compounds.[22–30]

Theoretical characterization of the properties of stationary points, reactants, intermediates (IN), transition structures (TSs) and products, located on reactive potential energy surfaces (PES) of great complexity can be achieved satisfactorily by using semiempirical procedures.[31] The PES associated with the molecular mechanism, following the sequential stages proposed by Paquette *et al.*,[11] for the twofold addition of **2** and **5** to **1** was

Table 1. Heats of formation (ΔH_f, kcal mol^{-1}) for intermediates (**IN1, IN2, IN3, IN4**), transition structures (**TS1, TS2, TS3, TS4, TS5, TS6, TSint, TS7, TS8**) and products (**3, 4, 6, 7**) and relative energies with respect to reactants

Species	*Endo*	Species	*Exo*
TS1	−362.5 (10.8)	**TS2**	−364.0 (9.3)
3	−409.1 (−35.8)	**4**	−409.2 (−35.9)
TS3	−385.2 (−11.9)	**TS4**	−384.5 (−11.2)
IN1	−426.6 (−53.3)	**IN2**	−425.8 (−52.5)
TS5	−418.3 (−45.0)	**TS6**	−416.6 (−43.3)
IN3	−454.1 (−80.8)	**IN4**	−454.3 (−81.0)
TSint	−441.4 (−68.1)		
TS7	−408.4 (−35.1)	**TS8**	−421.6 (−48.3)
6	−437.0 (−63.7)	**7**	−446.6 (−73.3)

Table 2. Heats of formation (kcal mol^{-1}) for intermediates (**IN5, IN6**), transitions states (**TS9, TS10**) and products (**8, 9**), and relative energies with respect to **IN5**

Species	ΔH_f (kcal mol^{-1})
IN5	−138.9 (0.0)
IN6	−138.5 (0.4)
TS9	−116.0 (22.9)
TS10	−117.1 (21.8)
8	−177.4 (−38.5)
9	−178.9 (−40.0)

calculated in detail to ensure that all relevant stationary points were located and properly characterized. The optimizations were carried out using the eigenvalue following routine[32,33] and the requested convergence for the gradients of energy was 0.5 kcal mol^{-1} Å^{-1} or kcal mol^{-1} rad^{-1} (1 kcal = 4.184 kJ). The nature of each stationary point was checked by diagonalizing the Hessian matrix to determine the number of imaginary frequencies (zero for local minima and one for TSs). This type of analysis provides valuable information that complements that obtained by experimental organic work. Following recent experimental and theoretical work, we included in our calculations two or three molecules of dimethyl ether in order to complete the preferential four coordination number of the Li atom.[30,34,35]

RESULTS AND DISCUSSION

The domino pathways for the squarate ester sequential reactions include several steps and subtleties, and it is not an easy task to produce a sensible theoretical mechanism involving all aspects, which remains a challenging problem in theoretical physical organic chemistry. The different stationary points characterized on the reactive PES are depicted in Fig. 1 and the heats of formation are presented in Tables 1 and 2. Three reactants, **1, 2** and **5**,

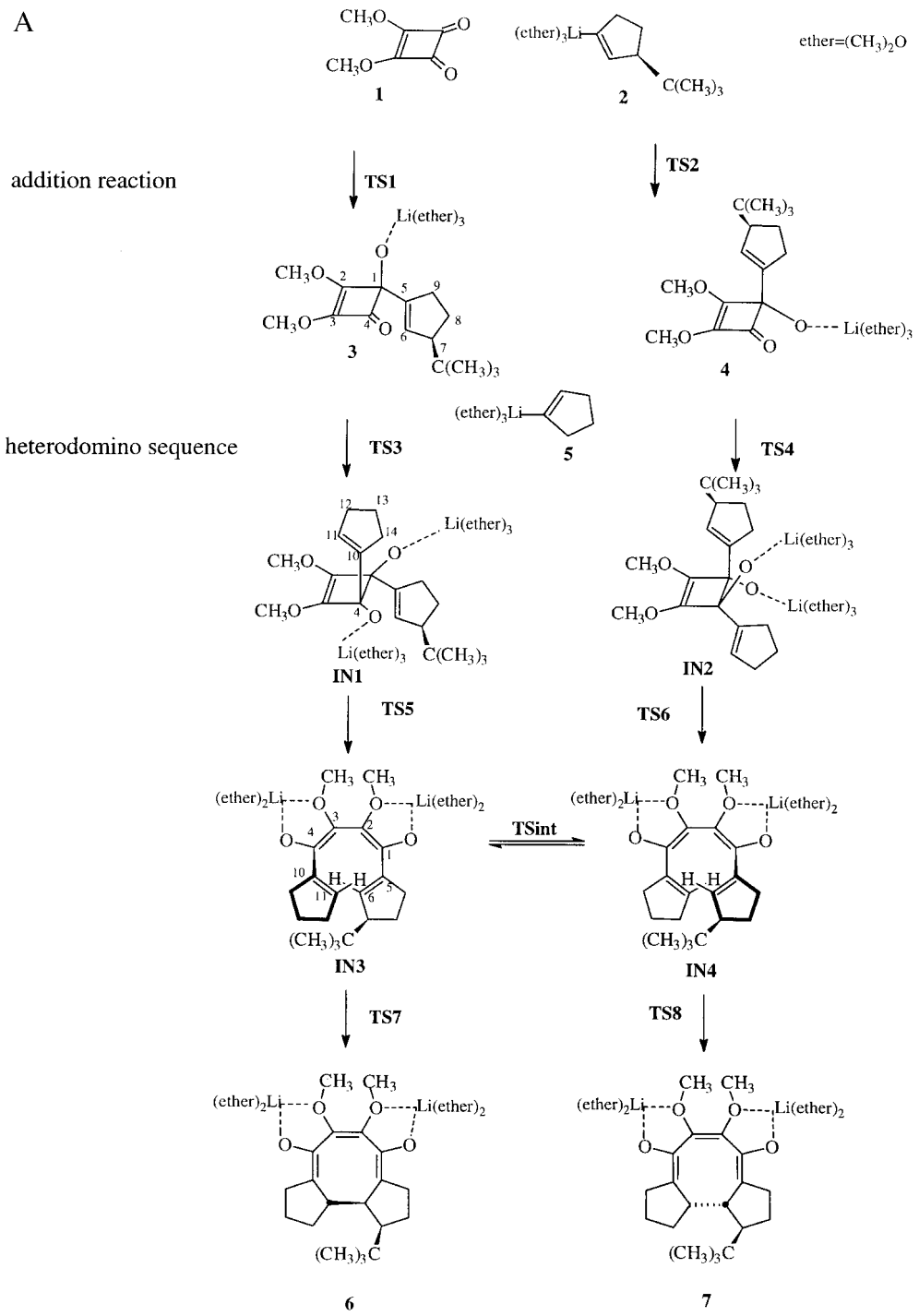

Figure 1. Stationary points along the reaction pathway. (a) Addition step and heterodomino sequence. (b) Hydrolysis and intramolecular aldol condensation

six intermediates, **IN1, IN2, IN3, IN4, IN5** and **IN6**, 11 TS, **TS1, TS2, TS3, TS4, TS5, TS6, TSint, TS7, TS8, TS9** and **TS10**, and six products, **3, 4, 6, 7, 8** and **9**, were located on the PES.

The analysis of the results shows that the overall reactions can be dissected into a series of three consecutive steps: (i) addition of the chiral (*R*)-3-*tert*-butylcyclopentenyllithium **2** to the squarate ester **1**, to give the ketoalkoxides **3** and **4**; (ii) a second process associated with a heterodomino sequence; addition of the achiral cyclopentenyllitium **5** to ketoalkoxides **3** and **4** gives the intermediates **IN1** and **IN2**, respectively, which by means of ring cleavage and subsequent cyclization afford the cyclooctatrienes **6** and **7** via the intermediates **IN3** and **IN4**; and (iii) hydrolysis and subsequent intramolecular aldolic condensation of these dienolates

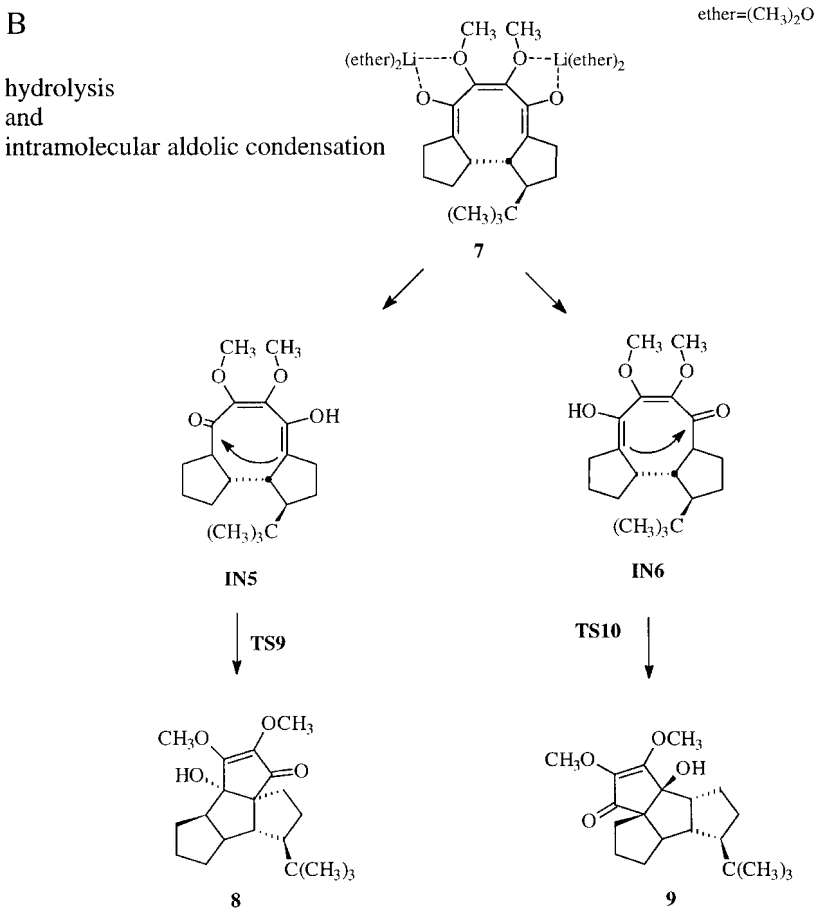

Figure 1. continued

to give the final products. We studied only the hydrolysis of **7**, to yield **8** and **9**, since the dienolate **6** is obtained experimentally in very small amounts and **7** is purified before the process continues.

Addition of the chiral cyclopentenyllithium 2 to squarate ester 1

Monoaddition of the chiral (*R*)-*tert*-butylcyclopentenyllitium **2** to the dimethyl squarate ester **1** corresponds to a nucleophilic attack of the anionic C-5 center of **2** to one of two faces of the carbonyl groups of the squarate ester **1** to give the diastereoisomeric ketoalkoxides **3** and **4**, via the transition structures **TS1** and **TS2**, respectively. Because of the presence of a symmetry plane in the squarate ester **1**, only two competitive diastereoisomeric pathways take place, along these diastereoisomeric transition structures. Owing to the chiral character of the cyclopentenyl system, two diastereoisomeric products **3** and **4** can be obtained. Both pairs of stereoproducts **3** and **4**, and transition structures **TS1** and **TS2**, have similar energies owing to a similar arrangement of the *tert*-butyl substituent in the two pairs of diastereostructures. The corresponding barrier heights are in the range 9.3–10.8 kcal mol^{-1}. The C-1—C-5 forming bond lengths at **TS1** and **TS2** are 2.357 and 2.294 Å, respectively, and the C-5—C-1—O angles of attack are 103.3° and 104.5°, respectively. In Fig. 2 a pictorial representation of **TS2** geometry is given and selected geometrical parameters for **TS1, TS2, 3** and **4** are given in Table 3.

Heterodomino sequence

The first step of the heterodomino process is the addition of the achiral cyclopentenyllithium **5** to the ketoalkoxides **3** and **4**, to give the intermediates **IN1** and **IN2** (*anti* attack), via a similar molecular mechanism to the previous nucleophilic addition. *Syn* attack was not considered because the corresponding final products were not detected experimentally; we adopted Paquette's *et al*. proposal.[11]

The presence of two bulky groups (cyclopentenyl and lithium alkoxide solvated) in ketoalkoxides **3** and **4** makes this addition take place at the opposite face of the chiral cyclopentenyl substituent, to give two diastereoisomeric dialkoxides, **IN1** and **IN2**, with similar energies, via the transition structures **TS3** and **TS4**, respectively.

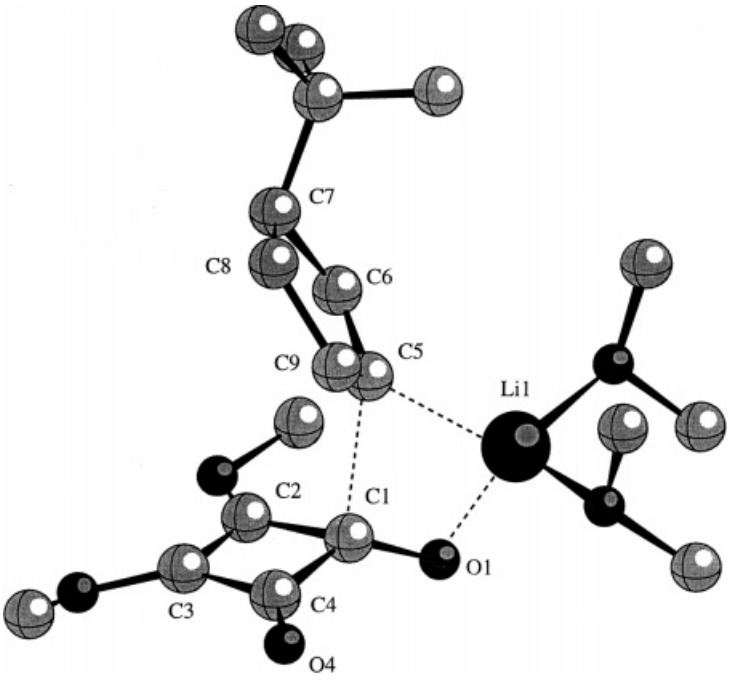

Figure 2. Schematic representation of **TS2** (without hydrogens), showing the C-5—C-1—O angle of attack (104.5°) and the lithium coordination with two ether molecules, with C-1 and with O-1 centers

Table 3. Selected geometric parameters (bond lengths in Å, angles in degrees) for **TS1, TS2, 3** and **4**

Bond	**TS1**	**TS2**	**3**	**4**
C1—O1	1.238	1.241	1.330	1.330
Li1—O1	1.928	1.923	1.712	1.711
C1—C5	2.357	2.294	1.505	1.506
Li1—C5	2.102	2.125	3.943	3.929
C1—C4	1.580	1.580	1.619	1.618
C1—C2	1.529	1.534	1.596	1.598
C2—C3	1.374	1.374	1.366	1.366
C3—C4	1.513	1.508	1.498	1.496
C5—C1—O1	103.29	104.52	114.69	114.41
Li1—O1—C1	98.43	97.85	173.52	176.92
C5—C1—C2—C3	97.86	261.96	109.99	250.39
C5—C1—O1—Li1	3.59	8.62	242.49	125.62
C4—C3—C2—C1	358.93	0.14	359.90	359.87

Both TSs also have similar energies (−285.2 and −284.5 kcal mol^{-1}).

At these TSs, the C-4—C-10 forming bond lengths are 2.237 and 2.217 Å, respectively, and the C-10—C-4—O attack bond angles are 101.9° and 101.5°, respectively. The two dialkoxides **IN1** and **IN2** present large values of C-1—C-4 bond lengths, 1.767 and 1.748 Å, respectively, owing to a stereoelectronic repulsive interactions between the bulky substituents located on the C-1 and C-4 atoms. These bond lengths are longer than for ketoalkoxides **3** and **4** (1.619 Å) and for the squarate ester **1** (1.564 Å), and consequently the ring cleavage is promoted.

The subsequent domino steps are the electrocyclic ring cleavages of the dialkoxyde intermediates **IN1** and **IN2** to give the octatetraenes **IN3** and **IN4**, via the transition structures **TS5** and **TS6**, respectively. Both transition structures take place along similar barrier heights (see Tables 1 and 2) and the C-1—C-4 breaking bond lengths in **TS5** and **TS6** are 2.323 and 2.306 Å, respectively. In this respect, the two terminal cyclopentenyl rings present a perpendicular arrangement relative to the C-1—C-4 breaking bond, promoting the ring opening process (see Fig. 3). Moreover, the stabilizing effect of the two cyclopentenyl rings causes the outward rotation of the oxide groups to be later than the opening process. The C-2—C-3 bond lengths in **TS5** and **TS6** are 1.374 and 1.376 Å, respectively. These bonds are slightly longer than the corresponding bonds in intermediates **IN1** and **IN2** (1.355 Å) but shorter than those in the octatetraenes **IN3** and **IN4** (1.462 and 1.456 Å, respectively). These results indicate that the ring cleavage processes correspond to a non-concerted electrocyclic mechanism, where the breaking bond process is more advanced than the conrotatory process to give the octatretaene conjugated system.

During the ring cleavages there is a change in hybridization from sp^3 to sp^2 on the C-1 and C-4 centers. Therefore, as soon as the intermediates **IN3** and **IN4** are formed, the temporal stereochemical information along the pathway on centers C-1 and C-4 is lost, but the diastereomeric distinction persists owing to the outward rotation of the oxide groups, which only lead to a *cis* C-2—C-3 and C-4—C-5 arrangement.

The intermediates **IN3** and **IN4** are two rotamers with

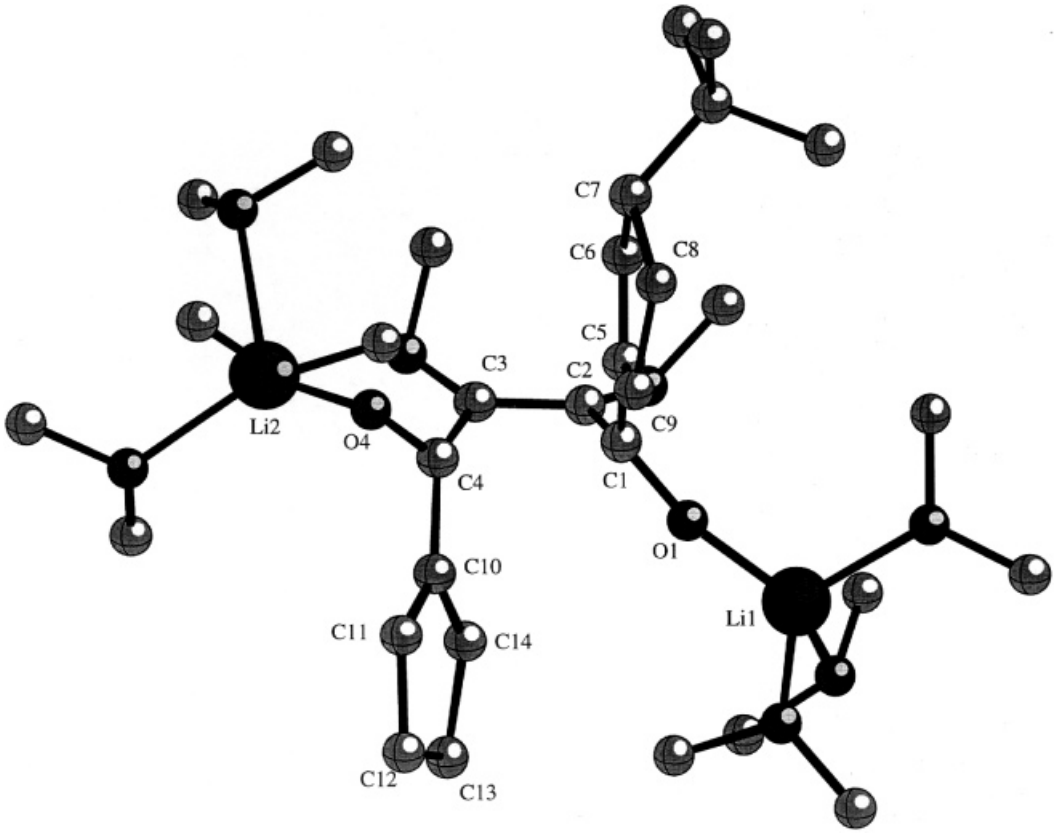

Figure 3. Schematic representation of **TS6** (without hydrogens), showing the perpendicular arrangement of the two cyclopentenyl rings relative to the C-1—C-4 breaking bond

similar energies (−454.1 and −454.3 kcal mol^{-1}, respectively), which can be connected by means of different rotations around the C—C single bonds of the octatetraene system. There are alternative ways connecting the two intermediates, and one of them (**TSint**) was selected in order to compare its barrier height (12.9 kcal mol^{-1}) with those in **TS7** and **TS8** (45.7 and 32.7 kcal mol^{-1}, respectively). Therefore, there is an easy interconversion between **IN3** and **IN4** and the Curtin–Hammett principle[36–39] has to be taken into account during the reactive sequence.

The helical arrangement of these intermediates favors the p atomic orbital overlap of the carbon chain and concomitant electron delocalization through the 8π system of the octatetraene. Hence these favorable interactions promote the electrocyclization of the octatetraenes **IN3** and **IN4** to give the products **6** and **7**, via the transition structures **TS7** and **TS8**, respectively (see Fig. 4). However, the presence of the *tert*-butyl substituent on the cyclopentenyl ring plays an important role in these electrocyclic closures. The presence of the *endo tert*-butyl group hinders the bond-making process between C-6 and C-11 in rotamer **IN3** and consequently the energy of **TS7** is higher than that of **TS8** (13.2 kcal mol^{-1}), the C-6—C-11 forming bond lengths being 2.150 and 2.072 Å, respectively. Therefore, only the *exo* rotamer **IN4** undergoes subsequent electrocyclization to obtain cyclooctatriene **7**. The chirality control of the hetero-domino sequence is kinetically dominated by the pathway **IN4** → **TS8** and the steric bulk effect of the *endo* alkyl group of the cyclopentenyl at transition structure **TS7** modulates the absolute configuration of the product. The sterochemical outcome is decided at this stage. Selected geometric parameters for **TS3, TS4, IN1, IN2, TS5, TS6, IN3, IN4, TSint, TS7, TS8, 6** and **7** are given in Tables 4 and 5.

Intramolecular aldolic condensation of cyclooctatriene 7

The last chemical process to transform the cyclooctatriene **7** into the polycyclic systems **8** and **9** [see Fig. 1(b)] demands the previous hydrolysis of the lithium dienolate **7**. A plausible mechanism would take place through the enols **IN5** and **IN6** with similar energies (see Tables 1 and 2). Both enols could afford the tetracyclic systems **8** and **9**, via the transition structures **TS9** and **TS10**, respectively, and further protonation–deprotonation processes. The similar energies of **IN5** and **IN6** and the similar barrier heights associated with **TS9** and **TS10** are in agreement with the fact that in aqueous hydrolysis

Table 4. Selected geometric parameters (bond lengths in Å, angles in degrees) for **TS3, TS4, IN1, IN2, TS5** and **TS6**

Bond	TS3	TS4	IN1	IN2	TS5	TS6
C4—O4	1.256	1.259	1.340	1.340	1.305	1.307
Li2—O4	1.875	1.867	1.703	1.698	1.726	1.717
C4—C10	2.237	2.217	1.506	1.507	1.469	1.471
Li2—C10	2.143	2.150	3.651	3.708	3.708	3.742
C1—C4	1.689	1.699	1.767	1.748	2.323	2.306
C1—C2	1.578	1.580	1.561	1.562	1.476	1.475
C2—C3	1.362	1.362	1.355	1.355	1.374	1.376
C3—C4	1.522	1.521	1.557	1.561	1.476	1.474
C10—C4—O4	101.93	101.49	112.27	112.56	116.70	116.56
Li2—O4—C4	102.06	102.75	161.87	163.66	162.06	164.48
C10—C4—C3—C2	10.61	243.70	110.47	248.23	80.09	280.37
C10—C4—O4—Li2	3.05	5.42	23.63	319.30	24.36	329.01
C4—C3—C2—C1	359.22	1.18	0.70	359.50	10.76	348.37
C10—C4—C1—C5	148.02	211.02	135.59	225.85	131.82	227.02
O1—C1—C4—O4	251.24	111.13	229.39	130.96	232.31	125.48

Table 5. Selected geometric parameters (bond lengths in Å, angles in degrees) for **IN3, IN4, TS7, TS8, 6** and **7**

Bond	IN3	IN4	TSint	TS7	TS8	6	7
C1—C2	1.383	1.381	1.388	1.436	1.428	1.497	1.492
C2—C3	1.462	1.456	1.460	1.408	1.418	1.365	1.370
C3—C4	1.385	1.384	1.388	1.439	1.427	1.399	1.490
C4—C10	1.478	1.480	1.475	1.410	1.414	1.365	1.365
C10—C11	1.342	1.343	1.345	1.399	1.400	1.492	1.489
C11—C6	3.968	4.146	3.452	2.150	2.072	1.559	1.558
C6—C5	1.340	1.341	1.340	1.403	1.399	1.502	1.490
C5—C1	1.481	1.481	1.478	1.410	1.415	1.359	1.365
C4—C3—C2—C1	84.32	279.75	24.40	15.61	317.01	355.36	333.95
C10—C11—C6—C5	103.95	245.47	71.47	122.88	238.72	115.16	245.06
C7—C6—C11—C10	312.47	56.66	312.54	236.04	122.19	229.32	124.84

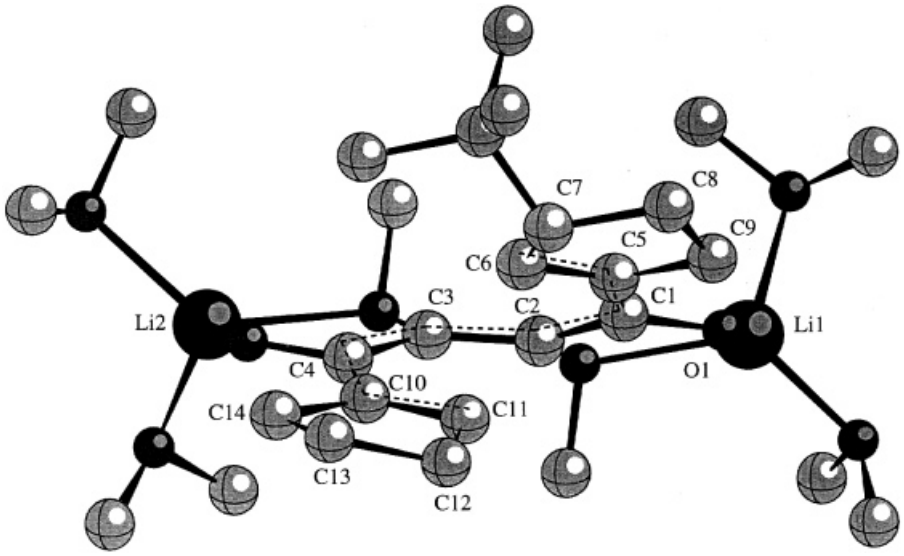

Figure 4. Schematic representation of **TS8** (without hydrogens), showing the helical arrangement favouring the p atomic orbital overlap of carbon chain and concomitant electronic delocalization through the π system. Dashed lines indicate the helical carbon chain

conditions, the tetracyclic systems **8** and **9** are obtained at similar rates.

The transition structures **TS9** and **TS10** correspond to intramolecular aldolic condensation processes. The C-4—C-5 and C-1—C-10 forming bond lengths in **TS9** and **TS10** are 1.869 and 1.912 Å, respectively. The arrangement of the *tert*-butyl substituent does not lead to any asymmetric induction during these chemical processes, giving two tetracyclic compounds with similar yields, in agreement with the experimental data. Nevertheless, more studies are being conducted in order to obtain a detailed explanation of the steps in the overall process, and the results will be reported elsewhere.

CONCLUSIONS

A theoretical study of the molecular mechanism for the co-addition of a chiral and an achiral cyclopentenyllithium to a squarate ester has been carried out. The reaction pathways were studied using the PM3 semiempirical method. Specific details of the overall process may change at higher levels of theory (e.g. *ab initio* methods), but despite the approximate nature of the calculations employed here, some important features were clarified in order to establish new mechanistic insights into the molecular mechanism of domino pathways of squarate ester sequential reactions. The following conclusions can be drawn from the results obtained in this study: (i) the step in the domino process responsible for the stereochemical control of the global process corresponds to the conrotatory electrocyclization of the *exo* octatetraene **IN4**; (ii) the large value the of the barrier height associated with the cyclization of the *endo* octatetraene **IN3** and the easy interconversion between the helical octatetraene rotamers **IN3** and **IN4** can explain the formation of a unique product, the cyclooctatriene **7**, in agreement with experimental data; the Curtin–Hammett principle is operative in this reactive sequence; and (iii) the electrocyclic opening of **4** and **5** intermediates is an asymmetric process; the ring opening process is more advanced than the disrotatory motion of cyclopentenyl rings in the corresponding transition structures, **TS5** and **TS6**, respectively.

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