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Selective "One-Pot" Synthesis of Functionalized Cyclopentenones

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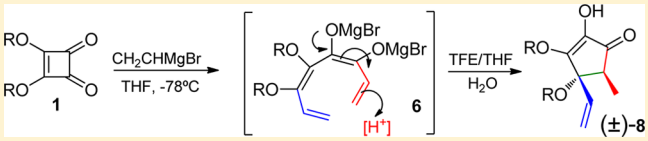
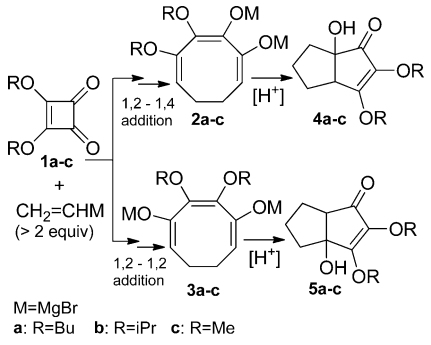
Supporting Information

ABSTRACT: Double addition (1,2−1,4) of vinyl magnesium bromide to squaric acid derivatives allows the preparation of polyoxygenated cyclopentenones (8) in a "one-pot" procedure. The reaction occurs through the intermediate formation of octatetraenes (6). Protonation of this latter intermediate at −78 °C with TFE occurs selectively at the vinyl CH_2 closer to the metallic centers. DFT studies of the cyclization step justify the observed diastereoselectivity.



The double addition of alkenyl magnesium or lithium derivatives to squarate esters **1** is a suitable route for the preparation of a variety of cyclic compounds containing the cyclopentenone moiety. The substitution pattern of this ring depends on the regioselectivity attained in the double 1,2−1,2 or 1,2−1,4 addition process.[1,2] Our group has reported that the addition of vinyl magnesium to **1** leads mainly to the corresponding bicyclooctenones **4** besides minor amounts of their regioisomers **5** (Scheme 1). The **4**:**5** ratio depends on the size of the alkoxy group in **1** and the reaction conditions, in particular the solvent and the reaction temperature.[1] The formation of these compounds occurs through the protonation of an intermediate cyclooctatriene **2** or **3**. On the other hand, the double 1,2-addition of different alkenyl lithium derivatives to **1** has been widely used and applied to the synthesis of a great variety of compounds related with **5** containing the 4-hydroxycyclopentenone ring.[2]

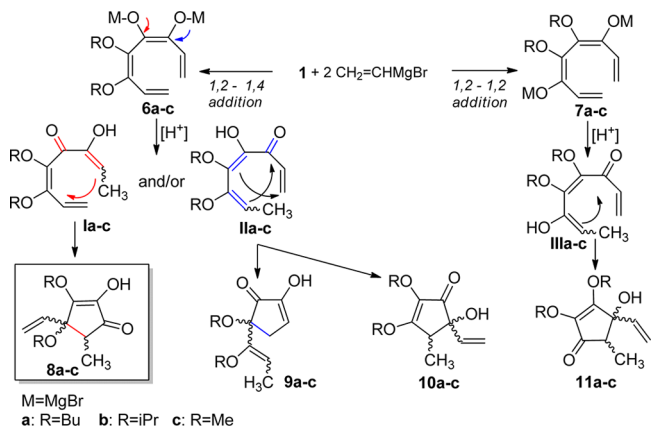
Scheme 1



The synthesis of cyclopentenones has been recently subject of numerous reviews[3] in the literature because this structure is present in a variety of natural products and derivatives of therapeutic interest and it is also important in the construction of more complex organic structures such as carbofuranoses[4] and a wide range of derivatives.[5]

In this context, we realized that the regular course of these reactions after the 1,2−1,2 or 1,2−1,4 double addition to **1** could be shifted toward the synthesis of different types of monocyclic cyclopentenones. In this sense, the octatetraene intermediates **6** and **7** resulting from the double addition step should be protonated before the subsequent cyclization which results in the formation of cyclooctatrienes **2** and **3**, respectively (Scheme 2).

Scheme 2



In this way, new reaction intermediates **I**−**III** similar to those described by Tius[6] (Scheme 3) in the Nazarov base catalyzed cyclization of unsaturated diketones would be obtained. Nazarov's reaction is usually carried out in acid medium, and it is considered an excellent route to generate the cyclopentenone ring.[7]

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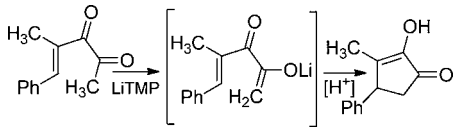
Scheme 3



Dialkoxy octatetraene **6** results as the major intermediate product in the double addition of vinylmagnesium bromide to squarates **1**,[1] and it could produce, at first, different isomeric unsaturated α-hydroxyketones **8**−**10** due to the presence of two different enolate groups in this structure (see intermediates **I** and **II**, Scheme 2). On the other hand, the addition of the vinyl reagent to the carbonyl groups of the squarate **1** would form the cyclopentenone **11** through the symmetric octatetraene **7**. This could constitute an easy "one pot" synthetically useful route to oxyfunctionalized cyclopentenones from commercially available squaric acid esters if the reaction could be conducted in a regioselective way.

According to this approach, and as it was expected based on our previous results,[1] commercial dibutyl squarate **1a** reacted with 2 equiv of vinyl magnesium bromide in THF at −78 °C to afford bicyclic compounds **4a** and **5a** with high regioselectivity (ratio >9:1) after hydrolysis at room temperature (see entry 1, Table 1). In aiming to avoid the formation of bicyclooctenones **4** and **5** by ring closure of the intermediate cyclooctatrienes **2** and **3**, in a parallel experiment, the reaction mixture was quenched at −78 °C with aqueous ammonium chloride (entry 2). NMR analysis of the crude reaction mixture revealed the formation of a single vinyl cyclopentenone as the major product besides a minor amount of bicyclooctenone **5a** formed in spite of the low temperature protonation. Three of the cyclopentenone isomers shown in Scheme 2 (compounds **8**, **10**, and **11**) meet this characteristic.

Table 1. Selectivity of the Reactions of Squarates 1 with Vinylmagnesium bromide in THF at −78°C

entry	substrate	protonation conditions[a]	selectivity[b] 4:5:8	product (yield)[c]
1	**1a**	A	92:8 0	
2	**1a**	B	0:15:85[d]	
3	**1a**	C	0:9:91	
4	**1a**	D	0:8:92	**8a** (78%)
5	**1b**	D	0:20:80	**8b** (70%)
6	**1c**	D	0:7:93	**8c** (84%)
7	**1a**	D[e]	55:10:35	
8	**1a**	D[f]	89:11:0	

[a]A: NH_4Cl/H_2O, rt. B: NH_4Cl/H_2O, −78 °C. C: TFA/THF, −78 °C. D: TFE/THF −78 °C. [b]Based on NMR and/or GC. [c]Determined by NMR from the crude. Yields of isolated compounds are given in the Experimental Section. [d]NMR spectra showed a complex mixture. [e]Before hydrolysis, the reaction mixture was allowed to reach 0 °C, maintained at this temperature for 2 h, and cooled down again to −78 °C. [f]Before hydrolysis, the reaction mixture was allowed to reach room temperature, maintained at this temperature for several hours, and cooled down again to −78 °C.

Hydrolysis with trifluoroacetic acid or trifluoroethanol in THF at −78 °C of a similar reaction mixture obtained from squarate **1a** and vinyl magnesium bromide gave a single cyclopentenone and less than 10% of **5a** (entries 3, 4, Table 1). The reaction product was hard to purify by column chromatography due to the lack of stability of vinyl cyclopentenones. Compound (±)-**8b** (R = ^{i}Pr) was obtained under similar conditions as a crystalline solid and its crystal structure determined by X-ray diffraction showing the relative cis configuration of the 4-vinyl and 5-methyl groups (Figure 1). The NMR spectra of the compounds obtained from **1a** and **1b** showed a similar pattern, which allows proposition of the structure **8a** (R = Bu) to the ketone derived from **1a.**

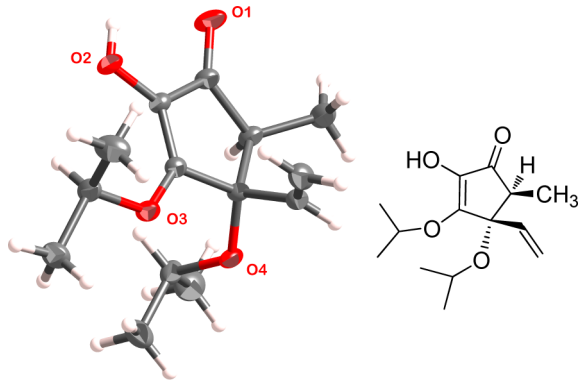


Figure 1. X-ray ellipsoid plot of **8b** (one enantiomer) 50% probability level.

Aiming at a better understanding of the protonation step, charges and HOMO coefficients in a minimum energy structure of magnesium dialkoxy octatetraene intermediate **6c** (R = Me) were calculated. The terminal carbon atom next to the alkoxy groups showed both the highest coefficient and electronic density in the HOMO, confirming this position as the most reactive in the protonation step (see Figure 2).

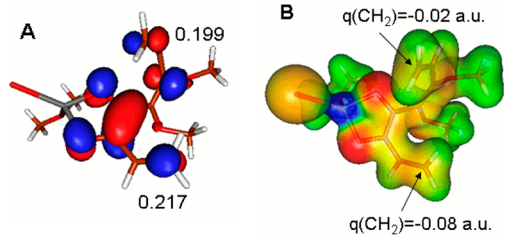


Figure 2. Minimum energy structure of magnesium dialkoxy octatetraene intermediate **6c** (R = Me) showing HOMO coefficients (A) and charges (B) at the terminal CH_2.

In addition, the formation of **8** occurs with complete diastereoselectivity because only cyclopentenones with cis disposition of the 4-vinyl and 5-methyl groups were formed in all cases. To ascertain this result, we carried out a theoretical study of the cyclization step (DFT level) from octatetraenes **6**. The cyclization of these intermediates can be viewed as an intramolecular Michael-type attack of the enolate on the α,β-unsaturated carbonyl moiety (Figure 3A). This process, however, should be ascribed to a [5-endotrig] cyclization, an unfavored transformation according to the Baldwin rules.[8] Alternatively, the cyclization step can be envisaged as a four-electron electrocyclization because the in-phase combination of the HOMO of the enolate (highlighted in red in Figure 3B) and the LUMO of the acrylic moiety (shown in blue in Figure 3B) yields an orbital topology that enforces the conrotatory cyclization to yield the cyclopentenone ring.[9] Different aspects of the selectivity in

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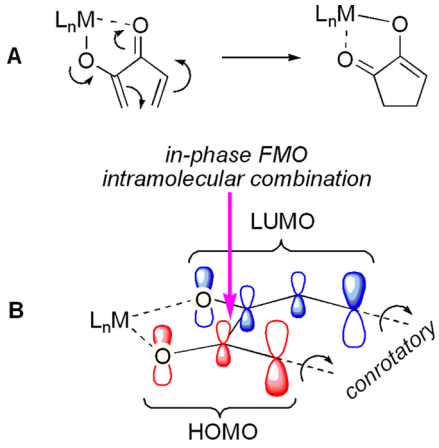


Figure 3. (A) Cyclization of a model compound possessing an enolate moiety and an electrophilic α,β-unsaturated carbonyl group. (B) Frontier molecular orbital (FMO) diagram showing the origin of the conrotatory topology for this cyclization.

related $4\pi e^-$ electrocyclic ring closure reactions have been theoretically studied by De Lera.[10]

Our calculations (B3LYP/6-31G* level of theory, vide infra) on the model transition structures gathered in Figure 4 show

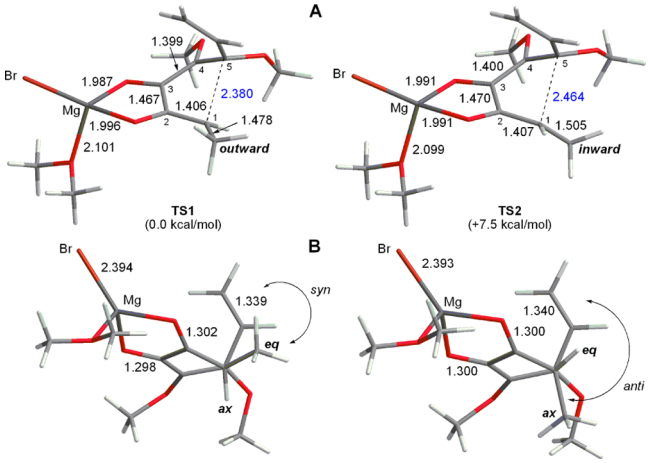


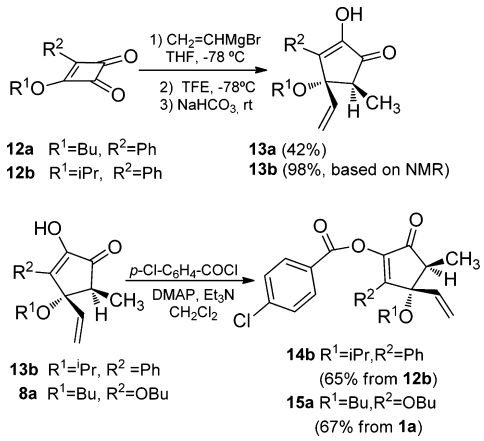
Figure 4. Fully optimized (B3LYP/6-31G* level of theory) transition structures associated with the formation of *syn*- and *anti*-2-hydroxy-3,4-dimethoxy-5-methyl-4-vinylcyclopent-2-enone. Bond distances are given in Å. Numbers in parentheses are the relative energies, computed at the B3LYP/6-31G*+ΔZPVE level.

geometries compatible with conrotatory electrocyclizations. It is interesting to note that TS1, which has a methyl group in an equatorial disposition with respect to the cyclopentenone ring being formed, is ca. 7 kcal/mol more stable than TS2, in which the methyl group occupies a more sterically demanding axial position. In addition, the electron-releasing methyl group occupies an outward disposition in TS1, whereas in TS2 this methyl group is inward. Because, according the torquoelectronic theory for conrotatory electrocyclizations,[11] electron releasing groups prefer to be outward, TS1 must be more stable than TS2, a result in nice agreement with our calculations and with the experimental findings.

Several additional experiments (Table 1, entries 7–8) showed that cyclizations to afford bicyclic compounds **4** only occurs at a feasible reaction rate at temperatures above −78 °C and can be inhibited when the temperature of the reaction is maintained at this value until protonation. Formation of cyclopentenones **11**, which would be derived from intermediate **7**, was not observed in any case. On the other hand, use of vinyl lithium instead of vinyl magnesium in the preliminary addition steps did not give rise to the formation of any type of monocyclic cyclopentenones and only bicycles **5** were obtained.[12]

Total selectivity toward the formation of cyclopentenones **13** (Scheme 4) was achieved in the addition of vinyl magnesium to

Scheme 4



unsymmetrically substituted squarates **12** bearing alkyl substituents. Formation of ketones **13** takes place in nearly quantitative yield based on the NMR analysis of the crude reaction product. However, partial decomposition occurs in any attempt of further purification of these vinyl cyclopentenones by the usual chromatographic methods. To obtain more stable derivatives, different methods were tested to protect the enol group. The best results were obtained upon acylation of the crude hydroxyketones **13** with *p*-chlorobenzoyl chloride in the presence of DMAP and triethylamine. Ester **14b** was isolated after column chromatography in 65% yield from **12b** (see ^{1}H and ^{13}C NMR spectra of the crude corresponding to the obtention of **14b** from **12b** in Supporting Information). Acylation under similar conditions of the crude reaction from **1a** (entry 4, Table1) gave in 67% yield the *p*-chlorobenzoyl ester **15a**, which is much more stable than the parent cyclopentenone **8a**.

The above results indicate that formation of polysubstituted cyclopentenones **8** or **13** is completely regioselective, involving a good selectivity not only in the attack to the squarate of the 2 equiv of vinylmagnesium bromide (first 1,2 and then 1,4) but also in the protonation step, which occurs exclusively at the vinyl methylene group adjacent to the alkoxy groups.

In conclusion, highly functionalized cyclopentenones can be prepared from readily available and convenient cyclobutenedione precursors through a 1,2−1,4 double addition of vinyl magnesium bromide. Regardless of the presence of several reactive sites in the enol intermediate resulting from the addition step, the protonation occurs with high regioselectivity to afford a single α-hydroxy unsaturated vinyl ketone. Selective cyclization of this later intermediate leads to a single polysubstituted cyclopentenone.

EXPERIMENTAL SECTION

General Procedure 1: Obtaining α-Hydroxycyclopentenones by Addition of Vinylmagnesium Bromide to Cyclobutenediones. A solution of vinylmagnesium bromide (8 mmol) in anhydrous

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THF (40 mL) was cooled and stirred at −78 °C in a jacketed two-neck round-bottom flask under N_2. Then, a solution of the squarate **1** (1 mmol) in anhydrous THF (20 mL), maintained also at −78 °C in a jacketed addition funnel, was slowly added under N_2. Both stirring and the N_2 flow were maintained at this temperature for 4 h before quenching with a cold solution (−78 °C) of trifluoroethanol (0.73 mL, 10 mmol) in dry THF (10 mL). After 10 min stirring at −78 °C, the reaction mixture was allowed to reach room temperature and a saturated sodium bicarbonate solution (5 mL) was added. After 30 min, the organic layer was separated, and the aqueous layer was extracted three times with ethyl acetate. The combined organic extracts were washed with brine, dried over Na_2SO_4, and filtered. After concentration, the resulting residue was analyzed by NMR and/or GC before purification by chromatography. NMR spectra of the crude reaction mixtures showed in all cases (entries 4−6, Table 1) compounds **8** as the main products.

*(4S,5S)-3,4-Dibutoxy-2-hydroxy-5-methyl-4-vinylcyclopent-2-en-1-one (**8a**).* Following the general procedure 1, 145 mg (0.52 mmol, 52% yield) of cyclopentenone **8a** were obtained as an oil from **1a** (1 mmol) after purification by flash chromatography (silica gel, 9:1 hexane/ethyl acetate). (±)-**8a**: ^{1}H NMR ($CDCl_3$) δ 0.84 (3H, t, J = 7.4 Hz), 0.86 (3H, t, J = 7.4 Hz), 0.98 (3H, d, J = 7.5 Hz), 1.25−1.42 (4H, m), 1.44−1.57 (2H, m), 1.60−1.70 (2H, m), 2.60 (1H, q, J = 7.5 Hz), 3.32 (2H, m), 4.47 (2H, m), 5.24 (1H, dd, J_1 = 10.5 Hz, J_2 = 1.5 Hz), 5.27 (1H, dd, J_1 = 17.3 Hz, J_2 = 1.5 Hz), 5.60 (1H, dd, J_1 = 10.5 Hz, J_2 = 17.3 Hz). ^{13}C NMR ($CDCl_3$) δ 10.8, 13.7, 13.9, 18.7, 19.3, 31.9, 32.2, 45.2, 63.1, 71.6, 82.6, 116.8, 133.0, 136.6, 159.4, 199.5. IR ν (cm^{-1}) 3300, 2959, 2875, 1711, 1633, 1432, 1310. MS (EI$^+$) m/z (relative intensity) 282 (M^+, 21%), 208 (14%), 185 (45%), 142 (18%), 129 (56%), 111 (53%), 57 (100%). HRMS: calcd for $C_{16}H_{26}O_4$, 282.1831; found, 282.1838.

*(4S,5S)-2-Hydroxy-3,4-diisopropoxy-5-methyl-4-vinylcyclopent-2-en-1-one (**8b**).* Following the general procedure 1, 179 mg (0.71 mmol, 35% yield) of cyclopentenone **8b** were obtained as a white solid from **1b** (2 mmol) after purification by column chromatography (silica gel, 9:1 hexane/ethyl acetate). (±)-**8b**: mp 78−80 °C. ^{1}H NMR ($CDCl_3$) δ 0.97 (3H, d, J = 7.4 Hz), 1.09 (3H, d, J = 6.1 Hz), 1.11 (3H, d, J = 6.1 Hz), 1.29 (3H, d, J = 6.1 Hz), 1.30 (3H, d, J = 6.1 Hz), 2.57 (1H, q, J = 7.4 Hz), 3.70 (1H, sept, J = 6.1 Hz), 5.18 (1H, d, J = 10.5 Hz), 5.21 (1H, d, J = 17.5 Hz), 5.31 (1H, sept, J = 6.1 Hz), 5.61 (1H, dd, J = 17.5 Hz, J_2 = 10.5 Hz), 6.95 (1H, s, 1 OH). ^{13}C NMR ($CDCl_3$) δ 10.2, 22.6, 22.9, 24.3, 24.8, 46.7, 66.0, 74.4, 82.8, 116.7, 132.1, 137.4, 159.3, 199.6. IR ν (cm^{-1}) 3292, 2977, 2936, 1703, 1632, 1384, 1304. MS (FAB$^+$) m/z (relative intensity) 255 ([M + H]$^+$, 52%), 213 (10%), 195 (26%), 169 (21%), 153 (100%). HRMS-FAB: calcd for $C_{14}H_{23}O_4$, 255.1596; found, 255.1628.

*(4S,5S)-2-Hydroxy-3,4-dimethoxy-5-methyl-4-vinylcyclopent-2-en-1-one (**8c**).* Following the general procedure 1, 55.4 mg (0.28 mmol, 28% yield) of cyclopentenone **8c** were obtained as an oil from **1c** (1 mmol) after purification by column chromatography (calcined silica gel, 12:1 hexane/ethyl acetate,). (±)-**8c**: ^{1}H NMR ($CDCl_3$) δ 1.00 (3H, d, J = 7.3 Hz), 2.64 (1H, q, J = 7.3 Hz), 3.23 (3H, s), 4.18 (3H, s), 5.28 (1H, dd, J_1 = 17.5 Hz, J_2 = 1.3 Hz), 5.29 (1H, dd, J_1 = 10.5 Hz, J_2 = 1.3 Hz), 5.59 (1H, dd, J_1 = 17.5 Hz, J_2 = 10.5 Hz), 6.60 (1H, bs, OH). ^{13}C NMR ($CDCl_3$) δ 10.8, 44.4, 51.1, 59.4, 83.0, 117.2, 133.7, 135.8, 159.2, 199.4. IR ν (cm^{-1}) 3357, 2959, 1763, 1711, 1613, 1455, 1380, 1261. MS(EI$^+$) m/z (relative intensity) 198 (M^+, 37%), 183 (17%), 167 (50%), 155 (23%), 138 (43%), 95 (95%), 67 (100%). HRMS: calcd for $C_{10}H_{14}O_4$, 198.0892; found, 198.0900.

*(4S,5S)-4-Butoxy-2-hydroxy-5-methyl-3-phenyl-4-vinylcyclopent-2-en-1-one (**13a**).* Following the procedure described in the literature,[13] 0.75 g of cyclobutenedione **12a** (3.24 mmol, 54% yield) were obtained as a yellow solid from squarate **1a** (6 mmol) after purification by flash column chromatography (silica gel, 9:1 hexane/ethyl acetate). General procedure 1 was then applied to **12a** (1 mmol), and NMR spectra of the crude reaction mixture showed **13a** as the only product. Isolation by column chromatography (silica gel, hexane/ethyl acetate, 4:1) was difficult due to partial decomposition of the product in the column allowing to isolate 121 mg (0.42 mmol, 42% yield) of cyclopentenone **13a** as an oil. **12a**: mp 100−102 °C. ^{1}H NMR ($CDCl_3$) δ 0.99 (3H, t, J = 7.4 Hz), 1.45 (2H, m), 1.88 (2H, m), 4.91 (2H, dt, J_1 = 6.5 Hz, J_2 = 0.6 Hz), 7.50 (3H, m), 8.05 (2H, m). ^{13}C NMR ($CDCl_3$) δ 13.6, 18.5, 31.9, 75.2, 127.6 (2C), 127.7, 129.1 (2C), 132.6, 173.6, 192.5, 192.8, 194.6. IR ν (cm^{-1}) 2978, 2955, 2934, 2871, 1782, 1742, 1610, 1599, 1587. MS(EI$^+$) m/z 230 (M^+), 202, 145 (100%), 117, 89, 85. (±)-**13a**: ^{1}H NMR ($CDCl_3$) δ 0.82 (3H, t, J = 6.6 Hz), 1.14 (3H, d, J = 6.7 Hz), 1.30 (2H, m), 1.45 (2H, m), 2.9 (1H, q, J = 7.3 Hz), 3.15 (1H, m), 3.30 (1H, m), 5.23 (1H, dd, J_1 = 10.7 Hz, J_2 = 1 Hz), 5.32 (1H, dd, J_1 = 17.5 Hz, J_2 = 1 Hz), 5.82 (1H, dd, J_1 = 17.5 Hz, J_2 = 10.7 Hz), 7.35 (3H, m), 8.17 (2H, d, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 10.3, 13.8, 19.2, 31,9, 45.6, 62.0, 85.1, 115.9, 128.0 (2C), 129.0, 129.6 (2C), 131.9, 137.1, 139.8, 149.2, 202.0. IR ν (cm^{-1}) 3388, 3054, 2954, 2925, 2868, 1705, 1616, 1593, 1490, 1445, 1380, 1355, 1264, 1156. MS(EI$^+$) m/z (relative intensity) 286 (M^+, 33%), 258 (15%), 202 (100%), 105 (40%). HRMS: calcd for $C_{18}H_{22}O_3$, 286.1569; found, 286.1561.

*(4S,5S)-2-Hydroxy-4-isopropoxy-5-methyl-3-phenyl-4-vinylcyclopent-2-en-1-one (**13b**).* Following the procedure described in the literature,[13] 0.88 g of cyclobutenedione **12b** (3.9 mmol, 65% yield) were obtained as a yellow solid from squarate **1b** (6 mmol) after purification by flash column chromatography (silica gel, 15:1 hexane/ethyl acetate). General procedure 1 was then applied to **12b** (1,2 mmol), and 328 mg were obtained as an oil were the only product observed by NMR was cyclopentenone **13b**. All our attempts of isolation by column chromatography led to degradation of **13b**, which only could be further purified after derivatization (see compound **14b**). **12b**: mp 114 °C (lit 113−114 °C).[13] ^{1}H NMR (CDCl3) δ 1.54 (6H, d, J = 6.2 Hz), 5.59 (1H, sept, J = 6.2 Hz), 7.50 (3H, m), 8.02 (2H, m). ^{13}C NMR ($CDCl_3$) δ 22.9, 80.1, 127.5 (2C), 127.8, 129.0 (2C), 132.5, 173.9, 192.4, 192.8, 194.2. IR ν (cm^{-1}) 2983, 2937, 2780, 1751, 1603, 1587, 1496, 1399, 1340, 1091, 1015, 904, 774, 695. (±)-**13b** (from crude reaction): ^{1}H NMR ($CDCl_3$) δ 0,67 (3H, d, J = 6.0 Hz), 1.06 (3H, d, J = 6.0 Hz), 1.07 (3H, d, J = 7.3 Hz), 2.8 (1H, q, J = 7.3 Hz), 3.56 (1H, m), 5.17 (1H, dd, J_1 = 10.7 Hz, J_2 = 1.1 Hz), 5.20 (1H, dd, J_1 = 1.1 Hz, J_2 = 17.5 Hz), 5.82 (1H, dd, J_1 = 17.5 Hz, J_2 = 10.7 Hz), 7.23−7.31 (3H, m), 8.00 (2H, d, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 10.0, 23.4, 25.2, 47.5, 65.6, 85.4, 116.0, 127.8 (2C), 128.9, 130.4 (2C), 131.7, 137.5, 140.7, 148.9, 201.4.

General Procedure 2:[14] Formation of Benzoylated Derivatives 14 and 15. Triethylamine (0.30 mmol) and 4-nitrobenzoyl chloride (0.21 mmol) were added under N_2 to a solution of the corresponding hydroxycyclopentenone (0.15 mmol) and DMAP (0.15 mmol) in anhydrous CH_2Cl_2 (10 mL). After being stirred at rt for 2 h, the mixture was washed with 5% HCl until pH 2, then with a 1N NaOH solution until pH 12, and then with a $NaHCO_3$ solution until pH 8−9, and finally with brine. Then, the organic layer was dried and concentrated. The residue was purified by flash chromatography on silica gel (elution with hexane/ethyl acetate)

*(3S,4S)-3-Isopropoxy-4-methyl-5-oxo-2-phenyl-3-vinylcyclopent-1-enyl 4-Chlorobenzoate (**14b**).* Following the general procedure 2 starting from 275 mg of crude **13b**, 267 mg (0.65 mmol, 65% yield) of the OH-protected cyclopentenone **14b** were obtained as an oil after purification by column chromatography (silica gel, 99:1 hexane/ethyl acetate). (±)-**14b**: ^{1}H NMR ($CDCl_3$) δ 0.51 (3H, t, J = 6.0 Hz), 1.07 (3H, d, J = 6.0 Hz), 1.08 (3H, d, J = 7.1 Hz), 3.01 (1H, q, J = 7.1 Hz), 3.64 (1H, sept, J = 6.0 Hz), 5.30 (1H, d, J = 11.3 Hz), 5.45 (1H, d, J = 17.1 Hz), 5.83 (1H, dd, J_1 = 11.3 Hz, J_2 = 17.1 Hz), 7.27 (2H, m), 7.38 (2H, d, J = 8.7 Hz), 7.71 (2H, m), 7.89 (1H, m), 7.99 (2H, d, J = 8.5 Hz). ^{13}C NMR ($CDCl_3$) δ 9.0, 23.1, 25.0, 49.2, 66.5, 85.7, 116.8, 126.6, 128.2 (2C), 129.0 (2C), 129.8 (2C), 131.8 (2C), 140.1, 145.1, 155.0, 162.6, 197.6. IR ν (cm^{-1}) 2959, 2875, 1723, 1633, 1462, 1380. MS (EI$^+$) m/z (relative intensity) 410 (M^+, 5%), 229 (11%), 184 (4%), 141 (32%), 139 (100%), 111 (15%). HRMS: calcd for $C_{24}H_{23}O_4Cl$, 410.1285; found, 410.1279.

*(3S,4S)-2,3-Dibutoxy-4-methyl-5-oxo-3-vinylcyclopent-1-enyl 4-Chlorobenzoate (**15a**).* Cyclopentenone **8a** was obtained by following the general procedure 1 from **1a** (1 mmol), and the crude reaction was submitted to the above-described benzoylation conditions (general procedure 2). 281 mg (0.67 mmol, 67% yield) of cyclopentenone **15a** were obtained as an oil after purification by column chromatography (silica gel, 15:1 hexane/ethyl acetate). (±)-**15a**: ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, t, J = 7.4 Hz), 0.92 (3H, t, J = 7.4 Hz), 1.08 (3H, d, J = 7.3 Hz), 1.23−1.40 (4H, m), 1,56−1.67 (4H, m), 2.83 (1H, q, J = 7.3 Hz), 3.40

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(1H, dt, J = 8.9 and 7.4 Hz), 3.60 (1H, dt, dt, J = 8.9 and 7.4 Hz), 4.30 (2H, t, J = 6.5 Hz)), 5.35 (1H, dd, J = 10.8 and 1.2 Hz), 5.45 (1H, dd, J = 17.4 and 1.2 Hz), 5.76 (1H, dd, J = 17.4 and 10.8 Hz), 7.44 (2H, d, J = 8.8 Hz), 8.03 (2H, d, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$) δ 10.2, 13.5, 13.9, 18.7, 19.3, 31.4, 32.2, 45.9, 63.5, 71.8, 83.0, 117.4, 126.7, 127.5, 129.0 (2C), 130.9 (2C), 131.8, 135.9, 140.6, 162.7, 169.6, 195.8. IR ν (cm^{-1}) 2960, 2874, 1747, 1724, 1644, 1594, 1488, 1402, 1323, 1253, 1089. MS (FAB$^+$) m/z (relative intensity) 421 ([M + H]$^+$, 30%), 139 (100%). HRMS-FAB: calcd for $C_{23}H_{30}O_5Cl$, 421.1782; found, 421.1789.

Computational Methods. All the calculations reported in this paper were obtained with the GAUSSIAN 03 suite of programs.[15] Electron correlation was partially taken into account using the hybrid functional usually denoted as B3LYP[16] and the standard 6-31G* basis set.[17] Zero point vibrational energy (ZPVE) corrections were computed at the B3LYP/6-31+G* level and were not scaled. Reaction intermediates were characterized by frequency calculations,[18] and have positive definite Hessian matrices. Transition structures (TSs) show only one negative eigenvalue in their diagonalized force constant matrices, associated with nuclear motion along the reaction coordinate being studied. Atomic charges were computed using the natural bond orbital (NBO) method.[19]

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

General experimental methods, ^{1}H and ^{13}C NMR spectra of compounds (±)-**8a**−**c**, **12a**,**b**, (±)-**13a**,**b**, (±)-**14b**, and (±)-**15a**, computational data, and crystallographic information file (CIF) for compound (±)-**8b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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