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Mechanism of the Carbonyl-Ene Reaction

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Abstract: The isolation of the ene adducts in the thermal reaction of allylbenzene and 3-phenylbut--1-ene with oxomalonic esters and cyclization or skeletal rearrangement products in the tin tetrachloride mediated addition has been interpreted as indicating a change of the mechanism from concerted (thermal) to an ionic one in the case of a catalyzed reaction.

Thermal carbonyl-ene reactions proceed according to a concerted mechanism, i.e. are single barrier processes[1]. On the other hand the mechanism of the Lewis acid promoted carbonyl-ene reactions is usually discussed in terms of the continuum from concerted to ionic mechanisms with the dipolar, Friedel - Crafts type intermediates[1] . An indication of the Friedel - Crafts type intermediates in the Lewis acid mediated carbonyl-ene reactions was obtained by the kinetic isotope effect measurements[2], effect of electron donating substituents[3], and isolation of the skeletal rearrangement[4] as well as cyclization products[5]. However, the occurrence of such products has been also interpreted as the result of the ene adduct rearrangement or/and cyclization catalyzed by the protic acid appearing in the reaction medium[3] . The proton donor could arise by the formation of the Lewis acid - ene adduct complex[6] . Therefore, the isolation of these side-products has been viewed as not conclusive proof of the occurrence of an ionic intermediate in the ene addition itself. Also isotope effects in $SnCl_4$ catalyzed reactions were interpreted as indicative of a concerted mechanism with variations in C-C bond formation and C-H bond cleavage[7].

To gain more evidence on the mechanism of the carbonyl-ene reaction we have examined the addition of allylbenzene (**1**) and 3-phenylbut-1-ene (**2**) to oxomalonic esters **3** and **4** . The choice of olefin **1** was inspired by the contradictory results reported in the literature on its $SnCl_4$ catalyzed reactions with diethyl oxomalonate (**4**)[7,8]. The isolation of different products led to disparate mechanistic interpretations.

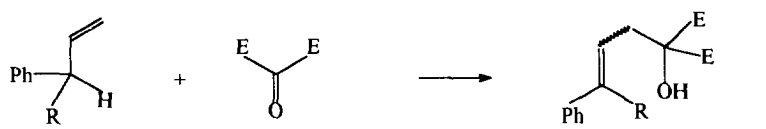
3-Phenylbut-1-ene (**2**) was selected because it was anticipated that its reaction with oxomalonate esters will allow to distinguish between the rearrangement or/and cyclization products resulting via the dipolar

intermediate or arising in a consecutive reaction from the ene adduct (*vide infra*). In the present paper we report on the results of these studies which strongly indicate a change in the mechanism of the carbonyl-ene reactions from concerted in thermal conditions to ionic in the $SnCl_4$ catalyzed case.

RESULTS and DISCUSSION

The thermal reaction (140°, 24 h) of allylbenzene (**1**) and 3-phenylbut-1-ene (**2**) with dimethyl oxomalonate (**3**) gave expected adducts **5a** and **6** respectively, as a mixture of *E* / *Z* isomers in 13.2 : 1 (**5a**) and 3.33 : 1 (**6**) ratios (^{1}H NMR). *E* and *Z* configuration of the **5a** isomers was apparent from the $J_{2,3}$ = 15.8 Hz and $J_{2,3}$ = 11.9 Hz coupling constants, corresponding to the *trans* and *cis* relation of olefinic protons, respectively. Assignment of the C_2 - C_3 double bond configuration of the isomers **6** was based on the downfield shift of the H-2 proton *cis* to the phenyl group.

Scheme 1

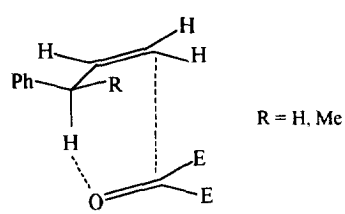


1 R = H
2 R = Me

3 E = CO_2Me
4 E = CO_2Et

5a R = H, E = CO_2Me
5b R = H, E = CO_2Et
6 R = Me, E = CO_2Me

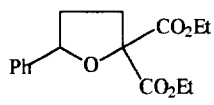
The prevailing formation of the (*E*) - **5a** and (*E*) - **6** adducts is consistent with the concerted mechanism favouring the *exo* position of the bulky substituent in the cyclic transition state (Figure). The higher *E* / *Z* ratio in the case of adduct **5a** than that for adduct **6** is in keeping with the larger difference in steric hindrance between the phenyl group and the hydrogen atom (adduct **5a**) relatively to this difference between the phenyl and methyl groups (adduct **6**).



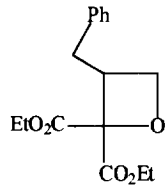
R = H, Me

Figure

Reactions of allylbenzene (**1**) with diethyl oxomalonate (**4**) catalyzed by Lewis acid ($SnCl_4$) were reported by Stephenson and Orfanopulos[7] as well as Kwart and Brechbiel[8]. However, these authors under similar reaction conditions have obtained entirely different products - namely derivatives of oxolane **7**[7] and oxetane **8**[8] respectively.



7



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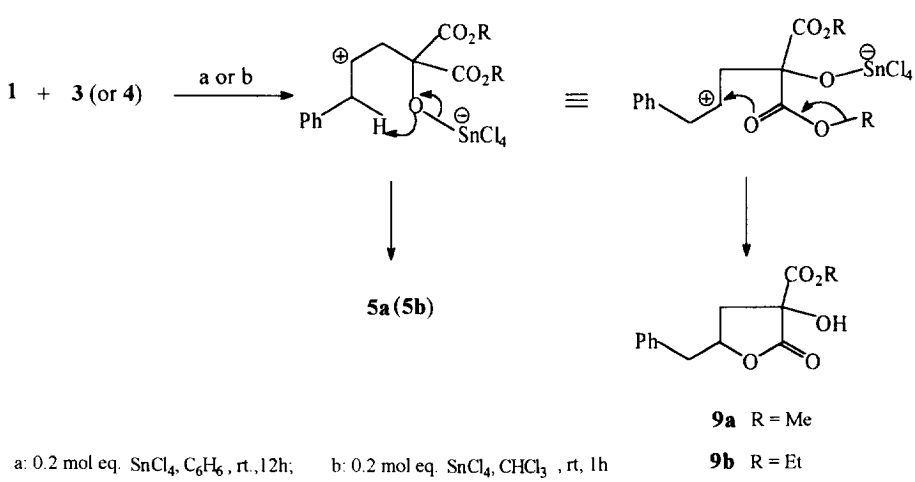
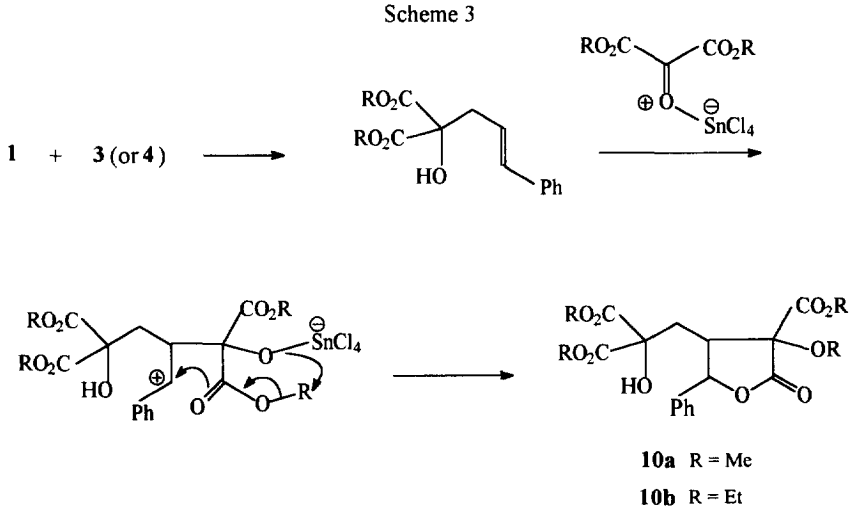
The reaction appears to be remarkably capricious because in our hands it gave again different products. Following the reported conditions we carried out the reaction of allylbenzene (**1**) with dimethyl oxomalonate (**3**) in the presence of 0.2 mol equiv. of $SnCl_4$ in benzene or in chloroform solution. To mimic the experimental conditions of the American authors and for the sake of comparison we have also used diethyl oxomalonate (**4**) as the enophile. Regardless of the solvent used and the reaction time the results appeared to be nearly identical. Silica gel flash chromatography of the reaction mixture yielded two products: ene adduct **5a** (or **5b**) and lactone **9a** (or **9b**) (Scheme 2).

Scheme 2



Structures of lactones **9a** and **9b** were in accord with ^{1}H NMR, IR and HRMS data (*cf.* Experimental). The formation of γ-lactones in the Lewis acid catalyzed oxomalonate esters reaction with olefins was noted before[3,5]. Careful chromatography of both the above mentioned reaction mixtures in each case afforded also minute amounts of the third, the least mobile in TLC, product. It was characterized only by the ^{1}H NMR spectrum and was tentatively assigned the structure **10a** or **10b**, products of one alkene to two enophile molecules addition. The manner of their formation is proposed in Scheme 3:

Scheme 3



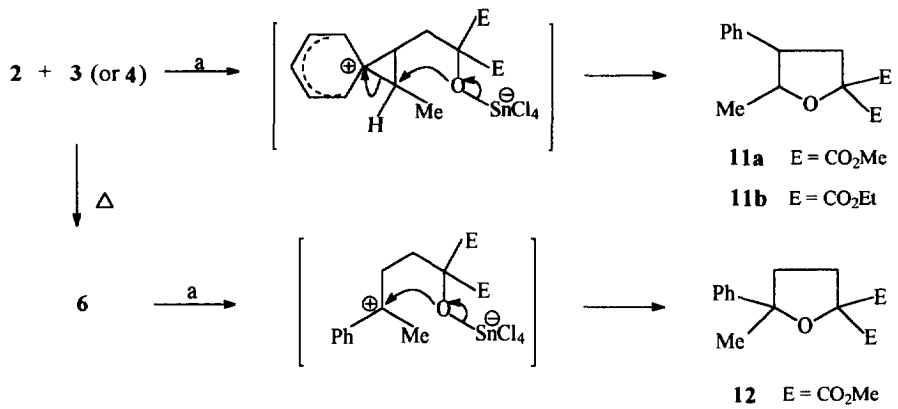
10a R = Me
10b R = Et

Since it was postulated that oxolane **7** resulted from the acid catalyzed cyclization of the ene adduct **5b**[7], we treated adducts **5a** and **5b** in chloroform solution with 0.2 mol equiv. of $SnCl_4$. Significantly, in each case the starting material was recovered and moreover, no cyclization or / and rearrangement products were detected. Therefore, it could be concluded that the formation of lactone **9a** or **9b** is a parallel reaction to the ene addition, both reactions proceeding *via* a common dipolar intermediate shown in Scheme 2.

Reaction of 3-phenylbut-1-ene (**2**) with dimethyl oxomalonate (**3**) carried out in the presence of 0.2 mol equiv. of $SnCl_4$ gave the oxolane derivative **11a** as a single product. The structure of compound **11a** was established on the basis of its ^{1}H and ^{13}C NMR data, proton decoupling and DEPT experiments. Under the above conditions diethyl oxomalonate (**4**) gave the analogous product **11b**. Significantly, treatment of the ene adduct **6**, obtained in the thermal reaction with 0.2 mol equiv. of $SnCl_4$ in benzene solution gave oxolane derivative **12** as the sole reaction product (Scheme 4).

Disappearance of the hydroxyl group (IR) and vinylic protons (^{1}H NMR) confirmed the cyclic structure, whereas absence in the ^{1}H NMR spectrum of a signal corresponding to a hydrogen atom α to an oxygen atom ruled out the skeletal rearrangement. This remarkable result can be rationalized by considering the mechanism

Scheme 4



a: 0.2 mol eq. $SnCl_4$, benzene, rt., 12h.

of the ene reaction which is depicted in Scheme 4. Compounds **11a** or **11b** arise directly from the dipolar intermediate, presumably with the phenonium ion structure (Scheme 4), without prior formation of the ene adduct **6**, whereas the protonation of the ene adduct catalyzed by tin tetrachloride led to the benzyl cation which cyclized to give oxolane **12** (Scheme 4). Thus, the isolated products indicate a change in the ene reaction mechanism from concerted for the thermal process to ionic in the case of the tin tetrachloride mediated reaction.

EXPERIMENTAL

B.p. refer to the air-bath temperature. ^1H and ^{13}C NMR spectra were recorded at 200 MHz and 50.3 MHz respectively on a Varian Gemini 2000 or Bruker AM 500 spectrometer using TMS as internal standard. IR spectra were recorded with a Perkin Elmer FT 2000 spectrophotometer. High resolution mass spectra (HRMS) were obtained on AMD 604 and Fimigan MAT 8200 mass spectrometers. Column chromatography was carried out on Merck Kieselgel 60 (230-400 mesh) and TLC was performed on silica gel 60 F_{254} aluminum precoated layer.

Dimethyl oxomalonate (**3**)[9], b. p. 96 °C / 18 Torr and 3-phenylbut-1-ene (**2**)[10] , b. p. 60 - 62 °C / 10 Torr, ^1H NMR (200 MHz, $CDCl_3$): δ : 7.32 - 7.12 (m, 5H, aromatic), 6.00 (ddd, J_{1t2} = 16.9, J_{1c2} =1.05, J_{23} = 6.4 Hz, 1H, H-2), 5.04 (dt, J_{1t2} = 16.8, $J_{1t1c} \approx J_{1t3}$ = 1.55 Hz, H-1^t), 5.02 (dt, J_{1c2} = 10.6, $J_{1t1c} \approx J_{1c3}$ = 1.55 Hz, H-1^c), 3.49 (apparent quint. t, J_{34} = 7.1 Hz, 1H, H-3), 1.35 (d, J = 7.0 Hz, 3H, CH_3), were obtained according to the literature procedures. Allylbenzene (**1**) and diethyl oxomalonate (**4**) were of commercial origin. Solvents and reagents were purified before use according to standard procedures[11].

General procedure: thermal ene reaction.

A toluene solution of dimethyl oxomalonate (**3**) (3.0 mmol), olefin (**1** or **2**) (4.0 mmol) and a trace of hydroquinone in toluene (4 cm^3) was sealed in glass vial and kept at 140°C for 24 h. Then the solvent was evaporated off and the residue flash chromatographed in hexane - ethyl acetate 5 : 2 solution. Homogeneous fractions (TLC) were combined, evaporated and kugelrohred to give **5a** (82%, 160°C/ 0.4 Torr) or **6** (80%, 145°C/ 0.3 Torr).

Dimethyl 2-hydroxy-2-(3-phenylprop-2-enyl)malonate (5a):
^{1}H NMR (200 MHz, $CDCl_3$), δ: *(E)* 7.32 - 7.21 (m, 5H, aromatic), 6.51 (dt, J_{23} = 15.8, J_{13} = 1.1 Hz, H-3), 6.14 (dt, J_{23} = 15.9, J_{12} = 6.3 Hz, H-2), 3.82 (s, 6H, 2 x OCH_3), 2.95 (dd, J_{23} = 7.3 Hz, 2H, H-1, H-1'). *(Z)*: 7.32 - 7.21 (m, 5H, aromatic), 6.61 (dt, J_{23} = 11.9, J_{13} = 1.6 Hz, 1H, H-3), 5.59 (dt, J_{23} = 11.8, J_{12} =6.3 Hz, 1H, H-2), 3.74 (s, 6H, 2x OCH_3), 3.10 (dd, J_{12} = 7.2, J_{13} = 1.8 Hz, 2H, H-1, H-1'); IR (CH_2Cl_2), ν_{max}: 3485, 1744, 1275, 1233 cm^{-1}; MS EIHR calculated for $C_{14}H_{16}O_5$ 264.09977, found 264.09958.

Dimethyl 2-hydroxy-2-(3-phenylbut-2-enyl)malonate (6):
^{1}H NMR (200 MHz, $CDCl_3$), δ: *(E)*: 7.37 - 7.13 (m, 5H, aromatic), 5.71 (tq, $J_{12} \approx J_{1'2}$ = 7.4, J_{24} = 1.3 Hz, 1H, H-2), 3.9 (s, 1H, OH), 3.8 (s, 6H, 2 x OCH_3), 2.98 (d, J_{12} = 7.5 Hz, 2H, H-1, H-1'), 2.06 (bs, 3H, CH_3). *(Z)* : 7.37 - 7.13 (m, 5H, aromatic), 5.43 (tq, $J_{12} \approx J_{1'2}$ = 7.24, J_{24} = 1.23 Hz, 1H, H-2), 3.84 (s, 1H, OH), 3.71 (s, 6H, 2 x-OCH_3), 2.76 (d, J_{12} = 7.1 Hz, 2H, H-1, H-1'), 2.03 (d, J_{24} = 1.1 Hz, 3H, CH_3); IR (CH_2Cl_2), ν_{max}: 3517, 1744, 1275, 1215, 1046 cm^{-1}; MS EIHR calculated for $C_{15}H_{18}O_5$ 278.1152, found 278.1147.

General procedure: tin tetrachloride catalyzed ene reaction.
A solution of oxomalonate ester (**3** or **4**) (5.0 mmol) and olefin (**1** or **2**) (6.0 mmol) in dry benzene or chloroform (10 cm^3) under nitrogen was cooled with an ice bath and tin tetrachloride (10 mmol) was added with a syringe. The resulting mixture was stirred at ambient temperature for 12 h, diluted with diethyl ether and neutralized with triethylamine. The organic layer was washed with water, dried ($MgSO_4$) and evaporated off. The residue was chromatographed in a hexane - ethyl acetate solution. Fractions homogeneous in TLC were combined and distilled. The reaction in chloroform solution was terminated after 1h. The obtained results are given in Table 1 and 2.

Table 1 .

Reactions with Allylbenzene.

Reagents	**Products** yield, b.p. (m.p.)		
1 + 3	**5a**, 37%, 160°C/ 0.4 Torr	**9a**, 15%,180°C/ 0.4 Torr	**10a**, 10%, 215°C/ 0.4 Torr
1 + 4	**5b**, 32%, 155°C/ 0.4 Torr	**9b**, 10%, 160°C/ 0.4 Torr	**10b**, 10%, 79-82 °C

Table 2 .

Reactions with 3-Phenylbut-1-ene.

Reagents	**Product,** yield, b.p.
2 + 3	**11a**, 45%, 145°C/ 0.3 Torr
2 + 4	**11b**, 45%, 145°C/ 0.3 Torr

Diethyl 2-hydroxy-2-(3-phenylprop-2-enyl)malonate (5b):
^{1}H NMR (200 MHz, $CDCl_3$), δ: 7.35 - 7.20 (m, 5H, aromatic), 6.50 (d, J_{23} = 15.9 Hz, 1H, H-3), 6.16 (dt, J_{23} = 15.9, J_{12} = 7.3 Hz, 1H, H-2), 4.35 - 4.15 (m, 4H, 2 x OCH_2), 3.85 (s, 1H, OH), 2.94 (d, J_{12} = 7.3 Hz, 2H, H-1), 1.28 (t, J = 7.1 Hz, 6H, 2 x CH_3); IR (CH_2Cl_2), ν_{max}: 3516, 1736, 1270 cm^{-1}; MS EIHR calculated for $C_{14}H_{16}O_5$ 292.13107, found 292.13097.

Methyl 3-hydroxy-2-oxo-5-phenylmethyloxolane-3-carboxylate (9a):
^{1}H NMR (200 MHz, $CDCl_3$), δ: 7.40 - 7.20 (m, 5H, aromatic), 4.86 (dq, J_d = 9.1, J_q = 6.2 Hz, 1H, H-5), 3.85 (s, 3H, OCH_3), 3.20 (dd, J = 13.9, J = 6.7 Hz, 1H, Ph-CH-), 2.96 (dd, J = 13.9, J = 6.5 Hz, 1H, Ph-CH'-), 2.73 (dd, J = 13.65, J = 6.2 Hz, 1H, H-4), 2.23 (dd, J = 13.6, J = 9.1 Hz, 1H, H-4'); IR (CH_2Cl_2), ν_{max}: 3450, 1785, 1746, 1250 cm^{-1}; MS m/z 250, 232, 206, 174, 104.

Ethyl 3-hydroxy-2-oxo-5-phenylmethyloxolane-3-carboxylate (9b):
^{1}H NMR (200 MHz, $CDCl_3$), δ: 7.40 - 7.20 (m, 5H, aromatic), 4.86 (dq, J_d = 9.0, J_q = 6.3 Hz, 1H, H-5), 4.30 (q, J = 7.1 Hz, 2H, OCH_2), 3.20 (dd, J = 13.9, J = 6.7 Hz, 1H, Ph-CH-), 3.01 (s, 1H, OH), 2.97 (dd, J = 13.9, J = 6.4 Hz, 1H, Ph-CH'-), 2.72 (dd, J = 13.6, J = 6.2 Hz, 1H, H-4), 2.22 (dd, J = 13.6, J = 9.0 Hz, 1H, H-4'), 1.30 (t, J = 7.1 Hz, 3H, CH_3); IR (CH_2Cl_2), ν_{max} : 3522, 1786, 1739, 1261 cm^{-1}.

Dimethyl 2-hydroxy-2-(4-methoxy-4-methoxycarbonyl-5-oxo-2-phenyltetrahydrofuran-3-ylmethyl)-malonate (10a):
^{1}H NMR (200 MHz, $CDCl_3$), δ: 7.40 - 7.20 (m, 5H, aromatic), 4,95 (d, J =9.8 Hz, 1H, H-5), 4.02 (s, 1H, OH), 3.85 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.33 (td, J_t = 10.0, J_d = 8.0 Hz, H-4), 2.96 (dd, J = 13.3, J = 7.9Hz, 1H, -C_αH-), 2.95 (s, 3H, OCH_3), 2.74 (dd, J = 13.3, J = 10.75 Hz, 1H, -C_αH'-).

Diethyl 2-hydroxy-2-(4-methoxy-4-methoxycarbonyl-5-oxo-2-phenyltetrahydrofuran-3-ylmethyl)-malonate (10b):
^{1}H NMR (200 MHz, $CDCl_3$), δ: 7.40 - 7.25 (m, 5H, aromatic), 4.97 (d, J = 9.83 Hz, 1H, H-5), 4.37 - 4.17 (m, 6H, 3 x OCH_2), 3.98 (s, 1H, OH), 3.67 (dq, J = 10.7, J = 7.1 Hz, 1H, OCH<), 3.33 (td, J = 10.4, J = 7.8 Hz, 1H, H-4), 2.98 (dd, J = 13.25, J = 7.9 Hz, 1H, -C_αH-), 2.97 (dq, J = 10.7, J = 7.2 Hz, 1H, OCH'<), 2.73 (dd, J = 13.2, J = 10.8 Hz, 1H, -C_αH'-), 1.56 (t, J = 7.1 Hz, 3H, CH_3), 1.32 (t, J = 7.05 Hz, 3H, CH_3), 1.28 (t, J = 7.1 Hz, 3H, CH_3), 0.82 (t, J = 7.2 Hz, 3H, CH_3).

Dimethyl 5-methyl-4-phenyloxolane-2,2-dicarboxylate (11a):
^{1}H NMR (500 MHz , $CDCl_3$), δ: 7.35 - 7.23 (m, 5H, aromatic), 4.21 (dq, J_{45} = 9.7, J_{5Me} = 5.95 Hz, 1H, H-5), 3.84 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 3.03 - 2.94 (m, 2H, H-3, H-4), 2.65 (m, 1H, H-3'), 1.29 (d, J_{5Me} = 6.0 Hz, 3H, CH_3); ^{1}H NMR (200 MHz, C_6D_6), oxolane ring protons, δ: 4.26 (dq, J_{45} = 9.4, J_{5Me} = 6.05 Hz, 1H, H-5), 3.10 (dd, $J_{33'}$ = 11.9, J_{34} = 7.1 Hz, 1H, H-3), 2.94 (ddd, J_{45} = 9.4, J_{34} = 7.1, $J_{3'4}$ = 10.7 Hz, 1H, H-4), 2.72 (dd, $J_{33'}$ = 11.9, $J_{3'4}$ = 10.7 Hz, 1H, H-3'); ^{13}C NMR (50.3 MHz, $CDCl_3$), δ:18.9 (CH_3), 42.7 (CH_3), 52.8 (C-4), 53.7 (OCH_3), 53.8 (OCH_3), 85.0 (C-5), 86.0 (C-2), 128.0 (*p*-C), 128.4 (2 x *m*-C), 129.5 (2 x *o*-C), 138.8 (*ipso* - C), 170.6 (C=O), 171.1 (C=O); IR (neat), ν_{max}: 1745, 1288, 1086 cm^{-1}; MS m/z 278, 263.

Diethyl 5-methyl-4-phenyloxolane-2,2-dicarboxylate (11b):
^{1}H NMR (200 MHz, $CDCl_3$), δ: 7.38 - 7.16 (m, 5H, aromatic), 4.36 - 4.23 (m, 4H, 2 x OCH_2), 4.22 (dq, J_{45} = 9.3, J_{5Me} = 6.0 Hz, 1H, H-5), 3.06 - 2.90 (m, 2H, H-3, H-4), 2.71 - 2.56 (m, 1H, H-3'), 1.34 (t, J = 7.1 Hz, 6H, 2x CH_3), 1.28 (d, J_{5Me} = 6.0 Hz, 3H, CH_3); IR (neat), ν_{max}: 1741, 1280, 1090 cm^{-1}; MS EIHR calculated for $C_{17}H_{22}O_5$ 306.14672, found 306,14687.

Dimethyl 5-methyl-5-phenyloxolane-2,2-dicarboxylate (12):
To a cooled with an ice-bath solution of adduct **6** (556 mg, 2 mmol) in benzene (5 cm^3) under nitrogen was added tin tetrachloride (104 mg, 0.4 mmol). The resulting mixture was stirred at ambient temperature. After 3 h when the substrate **6** disappeared (TLC), the reaction mixture was diluted with diethyl ether (50 cm^3), neutralized with triethylamine, washed with water, dried ($MgSO_4$) and evaporated to give **12**, b.p. 140°/0.3 Torr (yield 68%). ^1H NMR (200 MHz, $CDCl_3$), δ: 7.48 - 7.41 (m, 2H, aromatic), 7.36 - 7.17 (m, 3H, aromatic), 3.88 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 2.62 - 2.14 (m, 4H, H-4, H-4', H-3, H-3'), 1.64 (s, 3H, CH_3); IR (CH_2Cl_2), ν_{max}: 1746, 1287, 1249, 1085 cm^{-1} ; MS EIHR calculated for $C_{15}H_{18}O_5$ 278.11542, found 278.11573; MS EIHR calculated for $C_{14}H_{15}O_5$ (M - CH_3) 263.09195, found 263.09187.

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