Alkylation of Position C-5 of Triacetic Acid Lactone by [2,3] Sigmatropic Rearrangement of Sulphonium Ylides

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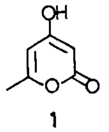
Reactions of the 4-methoxy-6-(phenylthiomethyl)-2*H*-pyran-2-ones **4** with three different diazo compounds under copper or rhodium catalysis give the corresponding sulphonium ylides, which through [2,3] sigmatropic rearrangement and further prototropy afford the pyrones **6**, functionalized at the difficultly accessible position C-5. Desulphurations of products **6** with deactivated Raney nickel give the pyrones **17**–**19**. The influence of the experimental conditions on the competition between [2,3] sigmatropic and Stevens rearrangement has been studied for the reaction of 4-methoxy-6-(phenylthiomethyl)-2*H*-pyran-2-one (**4a**) and dimethyl diazomalonate. Several products (**9**, **10**, and **11**) arising from sulphonium ylides equilibration and radical recombination have been found in addition to the [2,3] sigmatropic and the Stevens rearrangement products **6d** and **8**.

Alkylierung der 5-Stellung von Triessigsäurelacton durch [2,3]-sigmatrope Umlagerung von Sulfonium-Yliden

Die Reaktionen von 4-Methoxy-6-(phenylthiomethyl)-2*H*-pyran-2-onen **4** mit drei verschiedenen Diazoverbindungen unter Kupfer- oder Rhodium-Katalyse liefern entsprechende Sulfonium-Ylide, die durch [2,3]-sigmatrope Umlagerung und nachfolgende Prototropie die Pyrone **6**, die an der schwer zugänglichen 5-Stellung funktionalisiert sind, ergeben. Entschwefelung von **6** mit desaktiviertem Raney-Nickel ergibt die Pyrone **17**–**19**. Der Einfluß der experimentellen Bedingungen auf die Konkurrenz von [2,3]-sigmatroper und Stevens-Umlagerung wurde bei der Reaktion von 4-Methoxy-6-(phenylthiomethyl)-2*H*-pyran-2-on (**4a**) mit Diazomalonsäure-dimethylester studiert. Zusammen mit den aus [2,3]-sigmatroper und Stevens-Umlagerungen abgeleiteten Verbindungen **6d** und **8** wurden noch andere Produkte (**9**, **10** und **11**), die über Sulfonium-Ylid-Gleichgewichtseinstellung und Radikalverknüpfung entstehen, isoliert.

Triacetic acid lactone (**1**; 4-hydroxy-6-methyl-2*H*-pyran-2-one) is one of the most simple polyketides[1] and is also easily available on multigram scale by deacetylation of commercially available dehydroacetic acid (**2**)[2]. Since **2** is accessible in ton quantities at reasonable cost, both, **1** and **2**, are attractive starting materials in organic synthesis. Moreover, many natural products of polyketide biogenesis have the basic 4-hydroxy-(or 4-methoxy-)-2*H*-pyran-2-one structure complemented with biogenetically logical groups R^1, R^2, and R^3 at C-3, C-5, and C-6 positions, as indicated in **3**.



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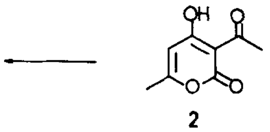

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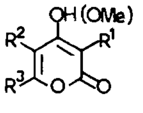

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To prepare products of the general type **3**, three synthetic transformations in either **1**, **2**, or derivatives thereof should be possible: a) alkylation at C-3 position, b) alkylation at C-5 position; and c) lengthening of the chain at C-6. Although many electrophiles react at C-3 of **1** and its methyl ether, alkylations of **1** under conventional conditions produce large amounts of ethers at C-4. To overcome this difficulty, we have developed a method of broad applicability for C-3 alkylation of **1**[3]. Also, the lengthening of the chain at C-6 has been accomplished by means of dianion or trianion chemistry[4–6] and through Wittig reactions[7,8]. However, alkylations at C-5 have met with little success. Bromination of **2** at C-5 has been achieved by Harris[9]. This has enabled us to prepare a complete set of 5-bromopyrones related to **1** and **2**[10]. However, lithiation of the methyl ether **3** (R^1 = H, R^2 = Br, R^3 = CH_3) followed by reaction with electrophiles did not result in functionalization at C-5[11]. A Claisen rearrangement from the reaction of methyl ether **3** (R^1 = R^2 = H, R^3 = CH_2OH) with ethyl orthoacetate produces the methyl ether **3** (R^1 = H, R^2 = $CH_3CH_2OCOCH_2$, R^3 = CH_3) in good yield[7], but the method is far from being general. Finally, methods to alkylate C-3 and C-5 of these types of pyrones based on the use of transition metals are presently being developed in our laboratories[12].

With all the above considerations in mind we reasoned that transfer of functionality from position C-6 to position C-5 was a possible approach if a general rearrangement could be found. Sulphur ylides are being used increasingly in synthetic chemistry by means of their [2,3] sigmatropic rearrangement. Ando and coworkers[13] have thoroughly investigated the formation and rearrangements of sulphur ylides. In the last years much work has been done on the preparation of these ylides[14] and some products, i.e. betweenanenes[15], sarkomycin[16], and khellin derivatives[17], have been synthesized through the Sommelet-Hauser [2,3] sigmatropic rearrangement of sulphur ylides. Therefore, our choice was the [2,3] sigmatropic rearrangement of sulphonium ylides, since the carbon-sulphur bond can be hydrogenolyzed at a further stage without affecting the unsaturated ring[3]. Two short reports have already been published[11,18] by us and, in the sequel, we want to give full details of this investigation.

Thus, the reaction (Scheme 1) between 4-methoxy-6-(phenylthiomethyl)-2*H*-pyran-2-one (**4a**), prepared according to a described procedure[11], and ethyl diazoacetate in toluene using $Cu(acac)_2$ as catalyst (Table 1, entry 1) afforded a mixture of **5a** (as shown by the presence of two ^1H-NMR absorptions between δ = 4.55 and 4.90) and **6a**. The mixture was treated with silica gel in dichloromethane to afford a 41% yield of pure 5-[(ethoxycarbonyl)(phenylthio)methyl]-4-methoxy-6-methyl-2*H*-pyran-2-one (**6a**). In addition, 11% yield of **4a** was recovered.

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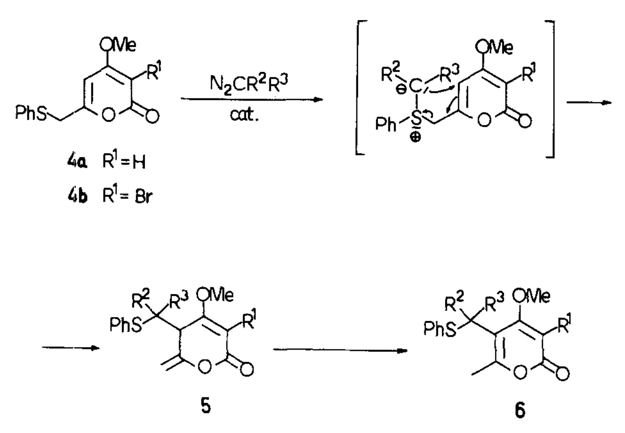
Table 1. Reactions of pyrones **4** with diazo compounds

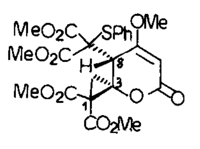
Run	Pyrone	R^2	R^3	$4/N_2CR^2R^3$	Solvent (°C)	Catalyst	Products (% yield)
1	**4a**	H	CO_2Et	1/2	toluene (90)	$Cu(acac)_2$	**6a** (41)[a,c]
2	**4b**	H	CO_2Et	1/2	toluene (90)	$Cu(acac)_2$	**6b** (40)[a,c]
3	**4a**	H	CO_2Et	1/1.2	toluene (90)	$Rh_2(OAc)_4$	**6a** (46)[a,c]
4	**4a**	H	CO_2Et	1/2	toluene (90)	$Rh_2(OAc)_4$	**6a** (55)[a,c]
5	**4a**	H	C_6H_5	1/2.5	toluene-diglyme (90)	$Cu(acac)_2$	**6c** (40)[b,d]
6	**4a**	H	n-C_3H_7	1/6	toluene (90)	$Cu(acac)_2$	**7** (13), unidentified compound (12)
7	**4a**	CO_2Me	CO_2Me	1/2	diglyme (140)	Cu	**6d** (24), **8** (24), **9** (5), **10** (6), **11** (14)
8	**4a**	CO_2Me	CO_2Me	1/2	toluene (90)	$Rh_2(OAc)_4$	**5d** (17), **16** (53)
9	**4a**	CO_2Me	CO_2Me	1/1.2	toluene (90)	$Rh_2(OAc)_4$	**5d** (89), **16** (8)

[a] Products **5a** and **5b**, originally formed, were spectroscopically characterized and isomerized in separate runs to **6a** and **6b**. — [b] Product **5c** was spectroscopically characterized and isomerized to **6c**. The yield is the overall from **4a** to **6c** (see Experimental). — [c] Yield of recrystallized and pure **6** (see Experimental). — [d] Yield of recrystallized and pure **19** (see Experimental).

Scheme 1



5,6	R^1	R^2	R^3
a	H	H	CO_2Et
b	Br	H	CO_2Et
c	H	H	Ph
d	H	CO_2Me	CO_2Me



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A similar reaction (entry 2) starting from 3-bromo-4-methoxy-6-(phenylthiomethyl)-2*H*-pyran-2-one[11] (**4b**) afforded a mixture containing **5b** (as shown by the presence of two doublets at δ = 4.65 and 4.90 with J ca. 2 Hz) and **6b**, which after isomerization gave 3-bromo-5-[(ethoxycarbonyl)(phenylthio)methyl]-4-methoxy-6-methyl-2*H*-pyran-2-one (**6b**) in 40% yield of purified product. Again some starting material was recovered (18%).

The adoption of rhodium acetate[19] as catalyst improved the results. By using about equimolar amounts of **4a** and diazo ester (entry 3), after isomerization, the yield in **6a** was now 46%, and when twice as much of ethyl diazoacetate was used (entry 4), the yield increased to 55%. The starting pyrone **4a** was also recovered in 43 and 30% yields, respectively.

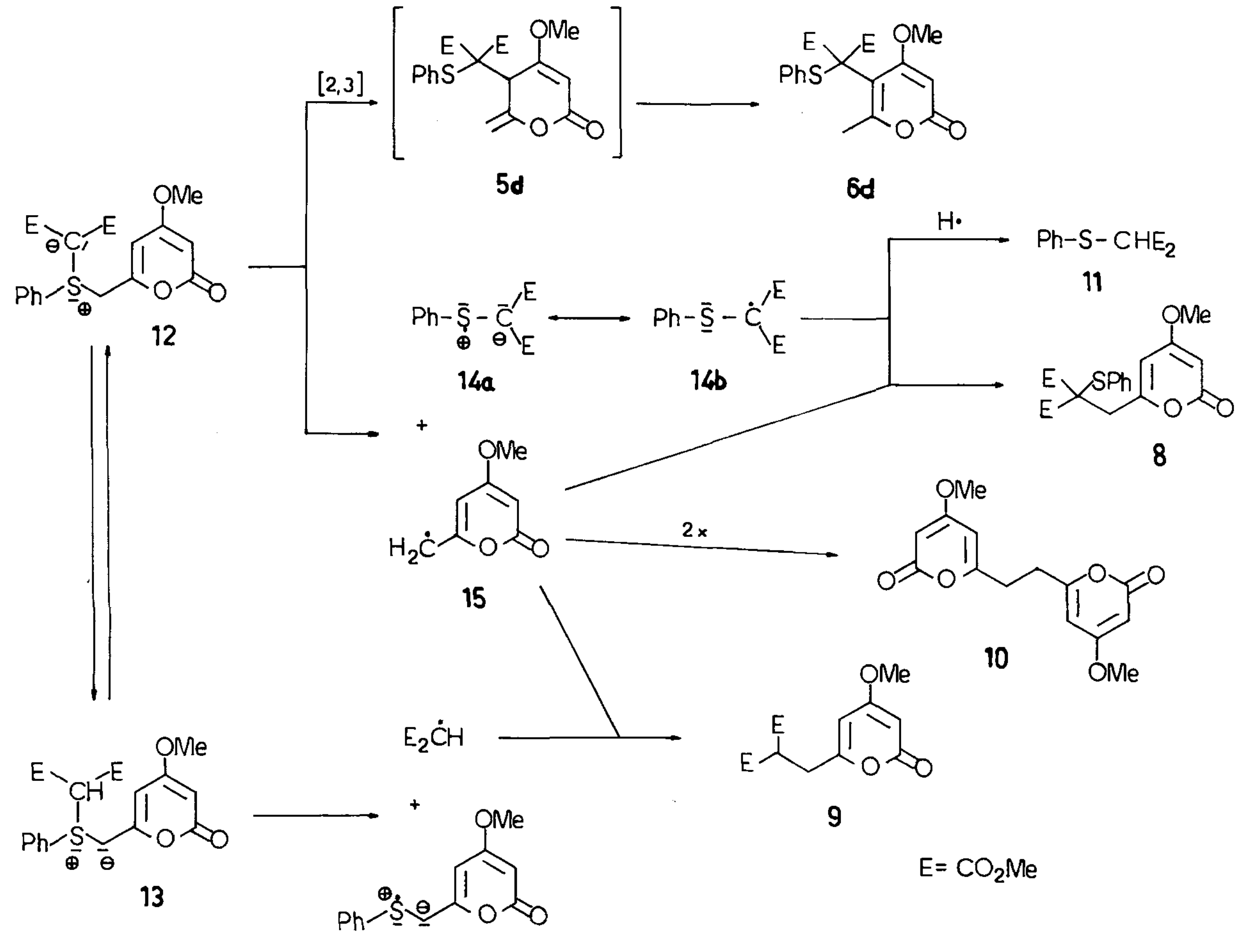
Phenyldiazomethane[20] was the next diazo compound to be studied. Under catalysis by $Cu(acac)_2$ (entry 5), the diastereoisomers **5c** were formed. Good ^{1}H-NMR spectra were registered for mixtures enriched in both of them presenting, among others, absorptions at $\delta(CDCl_3)$ = 3.41 and 3.75 (s, OCH_3), δ = 4.53 (d, J = 6.2 Hz), and δ = 4.53 (d, J = 6.2 Hz) for the methine benzylic protons, and pairs of doublets (J = 2.5 Hz) at δ = 4.20 and 4.87 and at δ = 4.44 and 4.90 for the exocyclic methylene groups. As before, products **5c** were isomerized to give 4-methoxy-6-methyl-5-[(phenyl)(phenylthio)methyl]-2*H*-pyran-2-one (**6c**). The isomerization was carried out with DABCO in refluxing THF since silica gel in dichloromethane at room temperature gave no reaction. Product **6c** was very difficult to purify from the contaminating **4a**. The yield given in Table 1 is based on the recrystallized and pure desulphurated compound **19**. Since all the above yields are based on recrystallized pure products which involved one or two further transformations from **5**, they should be considered as lower limits.

The reaction of **4a** with diazobutane[20] took a different course (entry 6). The only identified product was 4-methoxy-6-[(2-phenylthio)pentyl]-2*H*-pyran-2-one (**7**; see Scheme 3) in an isolated yield of 13%. Pyrone **7** arises from the Stevens rearrangement, process which is known to compete with [2,3] sigmatropic rearrangements of sulphonium ylides[13]. A second oily product, an isomer of **7**, was also isolated, but it could not be identified.

We next studied the behaviour of dimethyl diazomalonate[21]. Its reaction with **4a** under copper powder catalysis required temperatures as high as 140°C (entry 7). Under these conditions the reaction was not synthetically useful, but mechanistically meaningful. Products **6d** (24%), **8** (24%), **9** (5%), **10** (6%), and **11** (14%) were isolated and identified (Scheme 2).

The Stevens rearrangement of onium ylides is formally a [1,2] rearrangement, forbidden in its stereochemically acceptable *supra-supra* version[22]. There are evidences that the Stevens rearrangement occurs through free-radical formation by homolytic cleavage of the carbon—sulphur bond followed by recombination in an alternative way. Whereas most of the evidences arise from CIDNP experiments[13,23], in some cases side products arising from radicals coupling have been identified[13,23a,23b,24]. The array of products formed in our reaction (entry 7) can be explained by accepting free

Scheme 2



radical formation and recombination and also an equilibration of the initially formed sulphonium ylide **12** with a second ylide **13**, in which the negative charge is differently placed (Scheme 2). One example of this type of equilibration has been recently considered to explain some experimental facts[14e].

Thus, 5-[bis(methoxycarbonyl)(phenylthio)methyl]-4-methoxy-6-methyl-2*H*-pyran-2-one (**6d**) is the product resulting from the [2,3] sigmatropic rearrangement to **5d** followed by conversion into the most stable tautomer. 6-[2,2-Bis(methoxycarbonyl)-2-(phenylthio)ethyl]-4-methoxy-2*H*-pyran-2-one (**8**) is the result of the Stevens rearrangement. The formed radicals **14** and **15** are the key intermediates. The recombination of **15** with **14** affords **8**; uptake of a hydrogen atom by **14** produces dimethyl phenylthiomalonate (**11**); recombination of two radicals **15** gives **10**. Finally, the formation of 6-[2,2-bis(methoxycarbonyl)ethyl]-4-methoxy-2*H*-pyran-2-one (**9**) requires the combination of **15** with the dimethyl malonyl radical, which is probably formed by homolytic cleavage of the sulphonium ylide **13**.

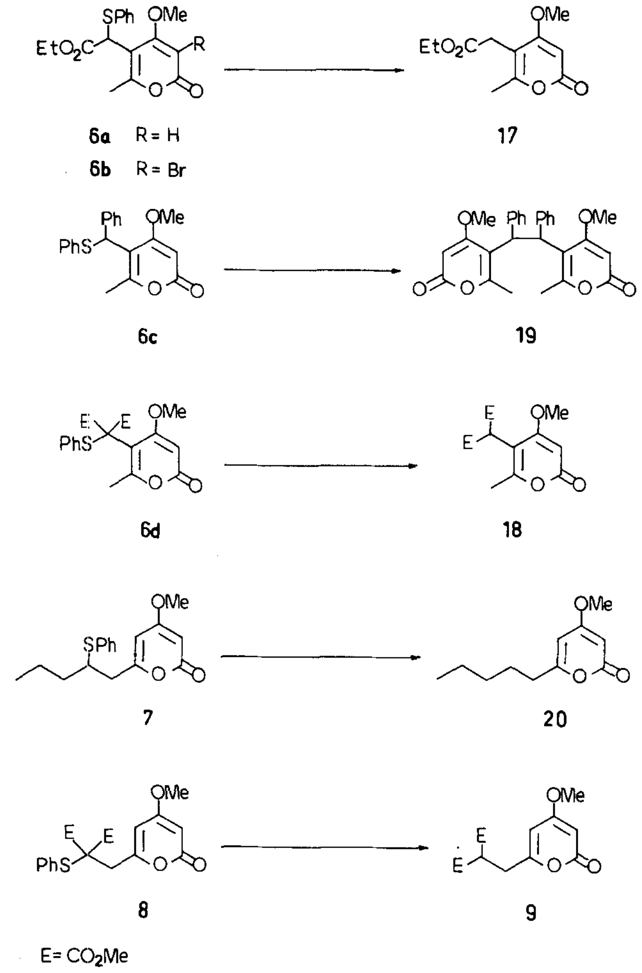
The use of rhodium acetate gave better synthetic results. By using nearly equimolar amounts of **4a** and dimethyl diazomalonate, 5-[bis(methoxycarbonyl)(phenylthio)methyl]-5,6-dihydro-4-methoxy-6-methylene-2*H*-pyran-2-one (**5d**) which arises directly from the [2,3] sigmatropic rearrangement was formed in 89% yield (entry 9). It could be isolated and fully identified (see Experimental). A small amount of a second product involving two equivalents of diazomalonate was also produced. This product was the major one when two equivalents of diazomalonate were used (entry 8). An X-ray analysis[18] revealed the spiro compound **16** (Scheme 1). Product **16** arises from cyclopropanation of the exocyclic double bond of **5d** by the less hindered side. In an independent experiment **5d** was isomerized to give **6d** by treatment with silica gel in ethyl acetate-methanol.

Desulphurations of products **6** were performed by treatment with deactivated Raney nickel W-2 in ethanol, as previously described for similar pyrones substituted at C-3[3]. Deactivation of the catalyst by boiling in acetone for 30–45 minutes is necessary to prevent hydrogenation of the pyrone ring.

Thus, hydrogenolysis of **6a** and **6b** (Scheme 3) led to the same product **17** in practically quantitative yields. The concomitant debromination of **6b** to afford **17** is important since the route to **4b** is easier than the route to **4a**[10]. The thioether **6d** afforded 5-[bis(methoxycarbonyl)methyl]-4-methoxy-6-methyl-2*H*-pyran-2-one (**18**) also in quantitative yield.

As previously mentioned, compound **6c** was difficult to purify from contaminating **4a**. A mixture of both gave after treatment with Raney nickel the products of desulphurative

Scheme 3



dimerization of **6c**: *meso-* and *rac-***19**. This surprising result does not seem to depend on the concentration, since a second reaction with lower concentration of **6c** gave the same result. The contaminating **4a** gave the methyl ether **3** (R^1 = R^2 = H, R^3 = CH_3). Both diastereoisomers **19** were isolated, and their constitutions were independently assigned, although no efforts were made to attribute the correct stereochemistry to them.

Products **7** and **8**, arising from Stevens rearrangements, were also submitted to desulphurative processes. Thus, **7** afforded **20**, and **8** afforded **9**.

In summary, the described experiments demonstrate the possibility of functionalization of 2-pyrones at C-5 through [2,3] sigmatropic rearrangements, and the influence of the reaction conditions on the outcome of the processes.

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Experimental

M.p.'s (uncorrected): Kofler block (Reichert). – IR spectra: Perkin-Elmer Infracord 720, Perkin-Elmer 1310. – NMR spectra: Bruker WP 80 SY (in ^{1}H-NMR spectra tetramethylsilane was the standard). – Mass spectra: Hewlett-Packard 5985 B (ionization energy 70 eV). – HPLC: Perkin-Elmer Series 2. – Column chromatography: SiO_2, 230–400 mesh (Merck). – Ethyl diazoacetate was purchased from Fluka, and rhodium acetate was obtained from Johnson Matthey Chemicals Limited.

5-[(Ethoxycarbonyl)(phenylthio)methyl]-4-methoxy-6-methyl-2H-pyran-2-one (**6a**). – A) (*Table 1, entry 1*): A magnetically stirred mixture of **4a**[11] (0.993 g, 4 mmol), bis(2,4-pentanedionato)copper (a catalytic amount), and anhydrous toluene (5 ml) was heated at 90°C under argon atmosphere. Ethyl diazoacetate (0.912 g, 8 mmol) in toluene (1.5 ml) was added dropwise to the above mixture during 3 h, the required volume of N_2 being released. The solution was refluxed for another hour, cooled to room temperature and methanol (2 ml) was added. The solvents were evaporated and the residue was partitioned between methylene chloride and diluted aqueous ammonia. The organic layer was washed with water, dried with Na_2SO_4 and evaporated. Since the residue showed absorption in the ^{1}H-NMR spectrum in the range δ = 4.55–4.90 due to **5a**, it was dissolved in methylene chloride (50 ml) and treated under stirring for 72 h with silica gel. Finally the silica was filtered off and the solvent evaporated to afford 1.674 g of a mixture which was chromatographed under pressure in a silica gel column, the following products being eluted: a mixture of by-products derived from toluene and ethoxycarbonylcarbene (0.306 g) with methylene chloride:hexane (4:1); starting material **4a** (112 mg, 11%) with methylene chloride:ethyl acetate (98:2); and **6a** (687 mg, 51%) with methylene chloride:ethyl acetate (94:6) which was recrystallized from ether/pentane to afford 553 mg (41% yield) of pure **6a**, m.p. 105°C. – IR (KBr): ν = 1740 cm^{-1}, 1700, 1640. – ^{1}H NMR ($CDCl_3$): δ = 1.24 (t, J = 7 Hz, 3H, CH_3), 1.87 (s, 3H, 6-CH_3), 3.79 (s, 3H, OCH_3), 4.22 (q, J = 7 Hz, 2H, OCH_2), 4.91 (s, 1H, SCH), 5.45 (s, 1H, 3-H), 7.17–7.53 (m, 5H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 13.9 (CH_3), 17.3 (6-CH_3), 48.5 (OCH_3), 55.9/61.9 (OCH_2/SCH), 87.9 (C-3), 109.2 (C-5), 128.6/128.9/133.0/134.8 (Ph), 160.7 (C-6), 162.9 (lactone C=O), 168.70/168.74 (C-4/ester C=O). – MS: m/z (%) = 334 (M^+, 20), 226 (13), 225 (100), 197 (22), 179 (28), 169 (16), 153 (15), 125 (11), 109 (38), 43 (22).

$C_{17}H_{18}O_5S$ (334.3) Calcd. C 61.06 H 5.42
Found C 61.08 H 5.64

B) (*Table 1, entry 4*): The same procedure was repeated using rhodium acetate as catalyst and a ratio pyrone:diazo compound of 1:2. The catalyst was eliminated by partitioning the residue between methylene chloride and 10% hydrochloric acid solution. The yield of **6a** was 55%, and 30% of the starting material **4a** was recovered. This represents a yield of 78% based on reacted pyrone **4a**.

C) (*Table 1, entry 3*): The reaction was run under the same conditions described in experiment B), except for the molar ratio of pyrone:diazo compound (in this reaction 1:1.2). In this case the pyrone **6a** was isolated in 46% yield and the starting material **4a** was recovered in 43% yield. Based on reacted pyrone **4a** this represents a yield of 80%.

3-Bromo-5-[(ethoxycarbonyl)(phenylthio)methyl]-4-methoxy-6-methyl-2H-pyran-2-one (**6b**): This was prepared as described above for **6a** (section A) from pyrone **4b**[11] (0.981 g, 3 mmol) and ethyl diazoacetate (0.684 g, 6 mmol) (Table 1, entry 2). The following products were isolated by pressure chromatography in a silica gel column: a mixture of by-products derived from toluene and ethoxycarbonylcarbene (0.224 g) with hexane:ethyl acetate (95:5); pyrone **6b** (0.727 g, 59%) with hexane:ethyl acetate (82:18); and starting material **4b** (0.180 g, 18%) with hexane:ethyl acetate (80:20). Lactone **6b** was recrystallized to afford 503 mg (40% yield), m.p.

97–98 °C (ether/pentane). – IR (KBr): ν = 1730 cm^{-1}, 1625. – ^{1}H NMR (CDCl$_3$): δ = 1.27 (t, J = 8 Hz, 3 H, CH$_3$), 1.72 (s, 3 H, 6-CH$_3$), 4.14 (s, 3 H, OCH$_3$), 4.23 (q, J = 8 Hz, 2 H, OCH$_2$), 4.81 (s, 1 H, SCH), 7.15–7.56 (m, 5 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 13.8 (CH$_3$), 17.0 (6-CH$_3$), 49.9 (OCH$_3$), 61.8/62.2 (OCH$_2$/SCH), 94.3 (C-3), 112.9 (C-5), 128.9/129.1/132.6/134.9 (Ph), 159.0 (C-6), 159.8 (lactone C=O), 167.5/168.2 (C-4/ester C=O). – MS: m/z (%) = 414 (11), 412 (M$^+$, 13), 305 (81), 303 (78), 277 (19), 275 (24), 259 (19), 257 (18), 233 (16), 231 (17), 205 (20), 203 (18), 189 (18), 178 (16), 109 (49), 43 (100).

$C_{17}H_{17}BrO_5S$ (413.3) Calcd. C 49.40 H 4.14
Found C 49.46 H 4.38

4-Methoxy-6-methyl-5-[(phenyl)(phenylthio)methyl]-2H-pyran-2-one (**6c**): A solution of **4a**$^{11)}$ (1.489 g, 6 mmol) and a catalytic amount of bis(2,4-pentanedionato)copper in anhydrous toluene (6 ml) under argon atmosphere was heated at 90 °C (Table 1, entry 5). A solution of phenyldiazomethane$^{20)}$ in diglyme was added during 4 h, and 375 ml of nitrogen was evolved (15.5 mmol). After another 1.5 h at 90 °C the solution was partitioned between methylene chloride and diluted aqueous ammonia. The organic layer was washed with water to neutrality, dried with anhydrous Na$_2$SO$_4$, the methylene chloride was evaporated, and the diglyme was distilled. The residue was taken up in THF (25 ml), and after addition of a catalytic amount of DABCO it was refluxed for 5 h. This solution was partially evaporated and partitioned between methylene chloride and 2% hydrochloric acid, the organic layer was dried with Na$_2$SO$_4$, and the solvent was evaporated. This crude was chromatographed affording the following fractions: a mixture of stilbene and other hydrocarbons derived from phenylcarbene (2.32 g) with hexane:ethyl acetate (95:5); and a mixture of starting material **4a** and pyrone **6c** (1.83 g) with hexane:ethyl acetate (82:18). The separation of these compounds was very difficult, and only after three column chromatography separations a pure sample of **6c** was obtained. The yield of this reaction was calculated after the desulphuration of **6c** (vide infra). – M.p. 105–115 °C (ethanol/hexane). – IR (KBr): ν = 1710 cm^{-1}, 1635, 1560. – ^{1}H NMR (CDCl$_3$): δ = 2.01 (s, 3 H, 6-CH$_3$), 3.70 (s, 3 H, OCH$_3$), 5.52 (s, 1 H, 3-H), 5.68 (s, 1 H, SCH), 7.04–7.54 (m, 10 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 18.1 (6-CH$_3$), 47.5 (OCH$_3$), 55.7 (SCH), 87.8 (C-3), 112.9 (C-5), 126.8/127.1/128.1/128.7/131.9/135.2/138.2 (Ph), 160.5 (C-6), 163.1 (C=O), 169.2 (C-4). – MS: m/z (%) = 338 (M$^+$, 18), 230 (16), 229 (100), 187 (24), 127 (11), 43 (12).

$C_{20}H_{18}O_3S$ (338.4) Calcd. C 70.98 H 5.36
Found C 70.83 H 5.40

4-Methoxy-6-[(2-phenylthio)pentyl]-2H-pyran-2-one (**7**): A solution of **4a**$^{11)}$ (500 mg, 2 mmol) and a catalytic amount of bis(2,4-pentanedionato)copper in anhydrous toluene (3 ml) was heated under argon atmosphere at 90 °C (Table 1, entry 6). A solution of diazobutane$^{20)}$ in toluene was added during 3 h, and 290 ml of nitrogen was formed (12.1 mmol). After another hour at 90 °C, the solution was partitioned between methylene chloride and dilute aqueous ammonia. The organic layer was washed with water to pH = 7, dried with Na$_2$SO$_4$, and chromatographed on a silica gel column to give the following fractions: a mixture of aliphatic compounds (412 mg) derived from propylcarbene with hexane:ethyl acetate (95:5); a mixture of compound **7** and an unidentified substance with formula $C_{17}H_{20}O_3S$ (335 mg) with hexane:ethyl acetate (80:20); and starting material **4a** (119 mg, 24%) with hexane:ethyl acetate (75:25). The second fraction was submitted to preparative HPLC [column Perkin-Elmer 0258–0051, length 20 cm, temp. 35 °C, Φ = 25 ml/min, eluent methanol:water (65:35), λ_{det} = 225 nm] to afford 79 mg of pure **7** (oil, 13% yield), 74 mg of the unidentified product $C_{17}H_{20}O_3S$ (oil, 12% yield), and 170 mg of a mixture of both.

7: IR (KBr): ν = 1720 cm^{-1}, 1640, 1560. – ^{1}H NMR (CDCl$_3$): δ = 0.9 (t, J = 6 Hz, 3 H, CH$_3$), 1.55 (m, 4 H), 2.67 (d, J = 7 Hz, 2 H, allylic CH$_2$), 3.55 (m, 1 H, SCH), 3.78 (s, 3 H, OCH$_3$), 5.35 (d, J = 2.5 Hz, 1 H, 3-H), 5.80 (d, J = 2.5 Hz, 1 H, 5-H), 7.14–7.48 (m, 5 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 13.6 (CH$_3$), 19.8/36.5/40.0 (3 × CH$_2$), 46.0 (OCH$_3$), 55.6 (SCH), 87.8 (C-3), 101.7 (C-5), 127.1/128.8/132.3/134.2 (Ph), 162.3 (C-6), 164.2 (C=O), 170.7 (C-4). – MS: m/z (%) = 304 (M$^+$, 20), 195 (33), 165 (55), 153 (43), 140 (40), 125 (31), 123 (100), 109 (22), 69 (49).

$C_{17}H_{20}O_3S$ (304.3) Calcd. C 67.08 H 6.62
Found C 67.15 H 6.63

Unidentified Compound $C_{17}H_{20}O_3S$: IR (KBr): ν = 1720 cm^{-1}, 1630, 1555. – ^{1}H NMR (CDCl$_3$): δ = 0.87 (t, J = 6 Hz, 3 H), 1.09–1.58 (m, 2 H), 1.75–2.11 (m, 5 H), 3.75 (s, 3 H), 3.89–4.36 (m, 1 H), 5.39 (s, 1 H), 7.09–7.44 (m, 5 H). – ^{13}C NMR (CDCl$_3$): δ = 13.5, 17.8, 21.2, 36.4, 46.5 (broad), 55.8, 88.2, 112.1, 127.8, 128.8, 133.7, 135.2, 159.4 (broad), 163.5, 170.4. – MS: m/z (%) = 304 (M$^+$, 3), 261 (3), 195 (69), 153 (100), 109 (12), 43 (30). – MS (CI with NH$_3$): m/z = 305 (M + 1)$^+$, 322 (M + 18)$^+$.

$C_{17}H_{20}O_3S$ (304.3) Calcd. C 67.08 H 6.62
Found C 66.88 H 6.85

Reaction between **4a** *and Dimethyl Diazomalonate under Copper Powder Catalysis:* A mixture of **4a**$^{11)}$ (993 mg, 4 mmol), a catalytic amount of copper powder and anhydrous diglyme (5 ml) was heated at 140 °C (Table 1, entry 7). A solution of dimethyl diazomalonate$^{21)}$ (1.264 g, 8 mmol) in anhydrous toluene (1.5 ml) was added during 7 h, the required volume of nitrogen being evolved. The cooled mixture was filtered, diluted with methylene chloride, and washed with dilute aqueous ammonia. The organic layer was dried with anhydrous Na$_2$SO$_4$, and the solvents were eliminated. Ethyl acetate was added to the residue (2.06 g), and the insoluble material was identified as the bispyrone **10** (31 mg, 6% yield). The ethyl acetate portion was chromatographed through a silica gel column affording the following compounds: dimethyl phenylthiomalonate (**11**, 134 mg, 14% yield) with hexane:ethyl acetate (90:10), which was purified by distillation (b.p. 120 °C/2 Torr); pyrone **8** (363 mg, 24% yield) with hexane:ethyl acetate (75:25); and pyrone **9** (58 mg, 5% yield) followed by pyrone **6d** (377 mg, 24% yield) with hexane:ethyl acetate (70:30).

6d: M.p. 116–118 °C (methanol). – IR (KBr): ν = 1755 cm^{-1}, 1710, 1615. – ^{1}H NMR (CDCl$_3$): δ = 1.87 (s, 3 H, CH$_3$), 3.50 (s, 3 H, OCH$_3$), 3.78 (s, 6 H, 2 × OCH$_3$), 5.25 (s, 1 H, 3-H), 7.08–7.59 (m, 5 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 19.5 (CH$_3$), 53.7/55.8 (2 × OCH$_3$), 66.5 (CH), 87.5 (C-3), 109.9 (C-5), 128.2/129.9/137.7 (Ph), 161.9 (C-6), 162.6 (lactone C=O), 166.7/168.4 (C-4/ester C=O). – MS: m/z (%) = 378 (M$^+$, 2), 319 (4), 269 (58), 237 (100), 167 (41), 109 (47), 69 (23), 65 (22), 59 (28), 43 (44).

$C_{18}H_{18}O_7S$ (378.3) Calcd. C 57.13 H 4.79
Found C 56.86 H 4.67

8: M.p. 120–122 °C (methylene chloride/pentane). – IR (KBr): ν = 1725 cm^{-1}, 1710, 1645, 1560. – ^{1}H NMR (CDCl$_3$): δ = 3.20 (s, 2 H, CH$_2$), 3.77 (s, 9 H, 3 × OCH$_3$), 5.43 (d, J = 2.5 Hz, 1 H, 3-H), 5.90 (d, J = 2.5 Hz, 1 H, 5-H), 7.23–7.63 (m, 5 H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 38.5 (CH$_2$), 53.2/55.7 (2 × OCH$_3$), 62.9 (CS), 88.4 (C-3), 103.1 (C-5), 128.6/128.9/130.1/136.8 (Ph), 159.0 (C-6), 163.2 (lactone C=O), 167.6/170.4 (C-4/ester C=O). – MS: m/z (%) = 378 (M$^+$, 17), 269 (23), 237 (87), 207 (21), 179 (36), 125 (100), 109 (28), 91 (11), 69 (62), 59 (43).

$C_{18}H_{18}O_7S$ (378.3) Calcd. C 57.13 H 4.79
Found C 57.19 H 4.92

9: M.p. 57–59°C (methylene chloride/hexane). – IR (KBr): ν = 1730 cm^{-1}, 1650, 1565. – ^1H NMR ($CDCl_3$): δ = 3.04 (d, *J* = 7.5 Hz, 2H, CH_2), 3.76 (s, 6H, 2 × OCH_3), 3.78 (s, 3H, OCH_3), 3.86 (t, *J* = 7.5 Hz, 1H, CH), 5.40 (d, *J* = 2.5 Hz, 1H, 3-H), 5.86 (d, *J* = 2.5 Hz, 1H, 5-H). – ^{13}C NMR ($CDCl_3$): δ = 32.6 (CH_2), 48.8/52.7/55.7 (OCH_3/OCH_3/CH), 88.2 (C-3), 101.3 (C-5), 160.7 (C-6), 163.8 (lactone C=O), 168.2/170.8 (C-4/ester C=O). – MS: *m/z* (%) = 270 (M^+, 22), 239 (19), 211 (100), 179 (65), 125 (80), 69 (40), 59 (43).

$C_{12}H_{14}O_7$ (270.2) Calcd. C 53.34 H 5.22
Found C 53.09 H 5.20

10: IR (KBr): ν = 1715 cm^{-1}, 1640, 1555. – ^1H NMR ($CDCl_3$): δ = 2.69 (s, 4H, CH_2), 3.69 (s, 6H, OCH_3), 5.34 (d, *J* = 2.5 Hz, 2H, 3-H), 5.87 (d, *J* = 2.5 Hz, 2H, 5-H). – MS: *m/z* (%) = 278 (M^+, 40), 153 (54), 125 (100), 111 (36), 69 (99), 53 (31), 43 (20).

11: IR (film): ν = 1735 cm^{-1}, 1470. – ^1H NMR ($CDCl_3$): δ = 3.76 (s, 6H, OCH_3), 4.53 (s, 1H, CH), 7.20–7.66 (m, 5H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 53.3/55.7 (CH/OCH_3), 129.3/129.9/133.4/133.7 (Ph), 167.4 (C=O). – MS: *m/z* (%) = 240 (M^+, 49), 181 (17), 149 (32), 121 (100), 110 (13), 109 (39), 69 (22), 65 (20).

Reaction between **4a** *and Dimethyl Diazomalonate under Rhodium Acetate Catalysis:* A) A mixture of **4a**[11] (1.242 g, 5 mmol), a catalytic amount of rhodium acetate and anhydrous toluene (5 ml) was heated at 90°C (Table 1, entry 8). A solution of dimethyl diazomalonate[21] (1.58 g, 10 mmol) in anhydrous toluene (2 ml) was added over a period of 2 h, the required volume of nitrogen being evolved. The crude was partitioned between methylene chloride and 10% hydrochloric acid. The organic layer was washed to pH = 7, dried with anhydrous Na_2SO_4, and the solvent eliminated to afford a crude (2.68 g), which was chromatographed through a silica gel column affording the following compounds: i) *5-[bis(methoxycarbonyl)(phenylthio)methyl]-5,6-dihydro-4-methoxy-6-methylene-2H-pyran-2-one* (**5d**, 486 mg, 26% yield) with hexane:ethyl acetate (85:15). After recrystallization in methanol the yield was 17% (318 mg). ii) *Dimethyl (3SR,8RS)-8-[bis(methoxycarbonyl)(phenylthio)methyl]-7-methoxy-5-oxo-4-oxaspiro[2.5]oct-6-ene-1,1-dicarboxylate* (**16**, 1.78 g, 70% yield) with hexane:ethyl acetate (79:21). Recrystallization from ethyl acetate yielded 1.35 g of pure material (53% yield).

5d: M.p. 124–125°C (methanol). – IR (KBr): ν = 1725 cm^{-1}, 1650, 1625. – ^1H NMR ($CDCl_3$): δ = 3.56 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 3.76 (s, 3H, OCH_3), 4.31 (s, 1H, 5-H), 4.84 (d, *J* = 2.5 Hz, 1H, =CH_2), 5.05 (d, *J* = 2.5 Hz, 1H, =CH_2), 5.33 (s, 1H, 3-H), 7.20–7.67 (m, 5H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 47.0 (C-5), 52.8/52.9 (2 × ester OCH_3), 56.3 (4-OCH_3), 67.1 (C-SPh), 92.5 (C-3), 102.8 (=CH_2), 128.6/129.8/130.0/136.3 (Ph), 148.7 (C-6), 162.5/166.2/166.3/169.2 (C-4/lactone C=O/2 × ester C=O). – MS: *m/z* (%) = 378 (M^+, 13), 269 (17), 255 (16), 239 (39), 207 (64), 179 (100), 109 (85), 69 (65), 59 (74).

$C_{18}H_{18}O_7S$ (378.3) Calcd. C 57.13 H 4.79
Found C 56.95 H 4.57

16: M.p. 139–140°C (ethyl acetate). – IR (KBr): ν = 1735 cm^{-1}, 1720, 1610. – ^1H NMR ($CDCl_3$): δ = 2.22 (dd, *J* = 7.5 Hz, *J'* = 3.7 Hz, 2H, cyclopropane CH_2), 3.47 (s, 3H, OCH_3), 3.65 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 3.75 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 4.48 (s, 1H, 8-H), 5.36 (s, 1H, 6-H), 7.19–7.72 (m, 5H, Ph). – ^{13}C NMR ($CDCl_3$): δ = 24.2 (cyclopropane CH_2), 38.8/42.7 [C-8/cyclopropane $C(CO_2Me)_2$], 52.5/52.8/53.4/55.9 (5 × OCH_3), 65.8/67.6 (CS/C-3), 93.2 (C-6), 128.6/129.6/130.4/135.8 (Ph), 164.4/165.1/166.5/166.7/167.3/170.4 (lactone C=O/C-7/4 × ester C=O). – MS: *m/z* (%) = 508 (M^+, 2), 477 (2), 399 (6), 367 (14), 307 (18), 269 (15), 239 (38), 227 (37), 207 (100), 179 (98), 125 (39), 109 (80), 69 (61), 59 (90).

$C_{23}H_{24}O_{11}S$ (508.5) Calcd. C 54.33 H 4.76
Found C 54.49 H 4.74

B) The reaction was carried out under the same conditions as in A) and with the same quantity of starting material, except that dimethyl diazomalonate was used only in 20% excess (Table 1, entry 9). The workup procedure was also identical. Compound **5d** was isolated in 89% yield (1.825 g) and the pyrone **16** in 8% yield (210 mg).

Isomerization of the Dihydropyrone **5d** *to the Pyrone* **6d**: Silica gel (35 g) was added to a solution of compound **5d** (1.02 g, 2.7 mmol) in ethyl acetate (60 ml) and ethanol (1 ml). The mixture was stirred for 24 h at room temperature. The silica gel was filtered off and washed, and the residue was chromatographed affording *5-[bis(methoxycarbonyl)(phenylthio)methyl]-4-methoxy-6-methyl-2H-pyran-2-one* (**6d**) (780 mg, 76% yield). For spectroscopic data see above.

5-Ethoxycarbonylmethyl-4-methoxy-6-methyl-2H-pyran-2-one (**17**): A) A suspension of 5 ml of Raney nickel W-2 in ethanol was rinsed with acetone (3 × 15 ml) and then refluxed in acetone (20 ml) for 45 min. The solvent was changed for ethanol (20 ml), and a solution of **6a** (402 mg, 1.2 mmol) in ethanol (15 ml) was added. The mixture was refluxed for 45 min and the catalyst was filtered off and washed with ethyl acetate. The solvents were evaporated, and a residue (319 mg) was obtained, which was chromatographed yielding **17** (270 mg, 100% yield) with hexane:ethyl acetate (70:30) as eluent; m.p. 91–92°C (ref.[7] m.p. 91–93°C). Spectroscopic data were identical to those reported previously[7].

B) When the identical procedure was applied to the bromopyrone **6b** (413 mg, 1 mmol), with a refluxing time of 2 h, the same product **17** was isolated (216 mg, 96% yield).

5-[Bis(methoxycarbonyl)methyl]-4-methoxy-6-methyl-2H-pyran-2-one (**18**): Raney nickel W-2 (3 ml) was deactivated following the above described procedure, and **6d** (265 mg, 0.7 mmol) was reduced. The reaction was stopped after 1.75 h, and the residue (241 mg) was chromatographed to afford **18** (188 mg, 99% yield) with hexane:ethyl acetate (1:1). – M.p. 116–118°C (ethyl acetate:pentane, 50:50). – IR (KBr): ν = 1720 cm^{-1}, 1710, 1640, 1565. – ^1H NMR ($CDCl_3$): δ = 2.24 (s, 3H, 6-CH_3), 3.76 (s, 6H, 2 × OCH_3), 3.81 (s, 3H, OCH_3), 4.75 (s, 1H, 5-CH), 5.46 (s, 1H, 3-H). – ^{13}C NMR ($CDCl_3$): δ = 18.1 (CH_3), 47.1 (5-CH), 52.8/56.3 (2 × OCH_3), 87.9 (C-3), 105.2 (C-5), 161.9 (C-6), 163.0 (lactone C=O), 167.4/168.9 (C-4/ester C=O). – MS: *m/z* (%) = 270 (M^+, 57), 242 (47), 211 (58), 183 (100), 179 (43), 109 (70), 69 (34), 59 (72), 43 (73).

$C_{12}H_{14}O_7$ (270.2) Calcd. C 53.34 H 5.22
Found C 53.21 H 5.03

meso- and (±)-5,5'-(1,2-Diphenyl-1,2-ethanediyl)bis(4-methoxy-6-methyl-2H-pyran-2-one) (**19**): Raney nickel (10 ml) was deactivated following the above described procedure. A mixture of **4a** and **6c** (1.83 g) resulting from the reaction of **4a** (6 mmol) with phenyldiazomethane (vide supra) was refluxed in an ethanolic suspension of Raney nickel for 1.5 h. Chromatography of the residue (1.566 g) afforded the following compounds: triacetic acid lactone methyl ether (**3**, R^1 = R^2 = H, R^3 = CH_3, 360 mg) with hexane:ethyl acetate (70:30) as eluent; and a diastereomeric mixture of **19** (537 mg, 39% yield based on starting material **4a**) with hexane:ethyl acetate (20:80). Careful chromatography of **19** allowed the isolation of pure samples of both diastereoisomers, **19a** and **19b**.

19a: M.p. 288 – 295 °C (dec.) (methylene chloride/pentane). – IR (KBr): ν = 1705 cm^{-1}, 1630, 1545. – ^{1}H NMR (CDCl$_3$): δ = 2.20 (s, 6H, CH$_3$), 3.76 (s, 6H, OCH$_3$), 5.08 (broad s, 2H, CHPh), 5.31 (s, 2H, 3-H), 7.16 (s, 10H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 18.1 (CH$_3$), 45.9 (CHPh), 55.6 (OCH$_3$), 88.9 (C-3), 112.8 (C-5), 126.8/128.1/128.2/140.9 (Ph), 159.3 (C-6), 163.3 (C=O), 170.7 (C-4).

$C_{28}H_{26}O_6$ (458.5) Calcd. C 73.35 H 5.71
Found C 72.53 H 5.70

19b: M.p. 258 – 260 °C (methylene chloride/pentane). – IR (KBr): ν = 1710 cm^{-1}, 1625, 1545. – ^{1}H NMR (CDCl$_3$): δ = 2.36 (broad s, 6H, CH$_3$), 3.70 (s, 6H, OCH$_3$), 5.14 (broad s, 2H, CHPh), 5.35 (s, 2H, 3-H), 7.14 (s, 10H, Ph). – ^{13}C NMR (CDCl$_3$): δ = 17.6 (CH$_3$), 43.9 (CHPh), 55.5 (OCH$_3$), 88.8 (C-3), 113.2 (C-5), 126.0/127.6/128.3/140.3 (Ph), 158.8 (C-6), 162.9 (C=O), 170.2 (C-4).

$C_{28}H_{26}O_6$ (458.5) Calcd. C 73.35 H 5.71
Found C 72.50 H 5.67

19a + **19b**: MS: *m/z* (%) = 458 (M$^+$, 2), 319 (1), 230 (21), 229 (100), 187 (18), 127 (11).

4-Methoxy-6-pentyl-2H-pyran-2-one (**20**): Compound **7** (60 mg, 0.2 mmol) was desulphurated with deactivated Raney nickel W-2 (see above). After 1.5 h the crude (48 mg) was chromatographed to afford 32 mg of an oily material, that was characterized by its mass spectrum (*m/z* = 196, M$^+$).

6-[2,2-Bis(methoxycarbonyl)ethyl]-4-methoxy-2H-pyran-2-one (**9**): An analogous procedure (see above) was carried out with **8** (152 mg, 0.4 mmol), and the reaction time was 1.25 h. Chromatography yielded **9** (108 mg, 100% yield), m.p. 57 – 59 °C. Spectroscopic data are described above.

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[1] R. Bentley, P. M. Zwitkowits, *J. Am. Chem. Soc.* **89** (1967) 676 and 681.

[2] J. N. Collie, *J. Chem. Soc.* **59** (1891) 607.

[3] M. Moreno-Mañas, R. Pleixats, *Synthesis* **1984**, 430.

[4] M. P. Wachter, T. M. Harris, *Tetrahedron* **26** (1970) 1685.

[5] T. M. Harris, C. M. Harris, M. P. Wachter, *Tetrahedron* **24** (1968) 6897.

[6] R. Bacardit, M. Moreno-Mañas, *J. Chem. Ecol.* **9** (1983) 703.

[7] R. Bacardit, M. Moreno-Mañas, R. Pleixats, *J. Heterocycl. Chem.* **19** (1982) 157.

[8] C. Suzuki, R. Hamajima, S. Inoue, *Synthesis* **1975**, 192.

[9] T. M. Harris, C. M. Harris, C. K. Brush, *J. Org. Chem.* **35** (1970) 1329.

[10] P. de March, M. Moreno-Mañas, R. Pi, I. Ripoll, F. Sánchez-Ferrando, *J. Heterocycl. Chem.* **22** (1985) 1537.

[11] P. de March, M. Moreno-Mañas, I. Ripoll, *Synth. Commun.* **14** (1984) 521.

[12] [12a] J. Cervelló, J. Marquet, M. Moreno-Mañas, J. Ribas, A. Virgili, presented at the XIIth European Colloquium on Heterocyclic Chemistry, Communication P 39. Reims (France), 1986. – [12b] J. Cervelló, J. Marquet, M. Moreno-Mañas, *J. Chem. Soc., Chem. Commun.* **1987**, 644.

[13] [13a] W. Ando, *Acc. Chem. Res.* **10** (1977) 179. – [13b] W. Ando, *The Chemistry of Diazonium and Diazo Groups*, Chapter 9, p. 341, (S. Patai, Ed.), Wiley, New York 1978.

[14] [14a] M. P. Doyle, W. H. Tamblyn, V. Bagheri, *J. Org. Chem.* **46** (1981) 5094. – [14b] Z. Kosarych, T. Cohen, *Tetrahedron Lett.* **23** (1982) 3019. – [14c] M. P. Doyle, J. H. Griffin, M. S. Chinn, D. van Leusen, *J. Org. Chem.* **49** (1984) 1917. – [14d] H. Storflor, J. Skramstad, S. Nordenson, *J. Chem. Soc., Chem. Commun.* **1984**, 208. – [14e] A. Padwa, J. Gasdaska, *J. Org. Chem.* **51** (1986) 2857.

[15] A. Nickon, A. Rodriguez, V. Shirhatti, R. Ganguly, *Tetrahedron Lett.* **25** (1984) 3555.

[16] T. Cohen, Z. Kosarych, K. Suzuki, L. C. Yu, *J. Org. Chem.* **50** (1985) 2965.

[17] R. B. Gammil, *J. Org. Chem.* **49** (1984) 5035.

[18] P. de March, M. Moreno-Mañas, I. Ripoll, F. Florencio, S. García-Blanco, S. Martínez-Carrera, *Tetrahedron Lett.* **27** (1986) 3673.

[19] R. Paulissen, H. Reimlinger, E. Hayez, A. J. Hubert, Ph. Teyssie, *Tetrahedron Lett.* **1973**, 2233.

[20] G. M. Kaufman, J. A. Smith, G. G. Vanderstouw, H. Shechter, *J. Am. Chem. Soc.* **87** (1965) 935.

[21] M. Rosenberger, P. Yates, J. B. Hendrickson, W. Wolf, *Tetrahedron Lett.* **1964**, 2285.

[22] R. W. Jemison, T. Laird, W. D. Ollis, I. O. Sutherland, *J. Chem. Soc., Perkin Trans. 1*, **1980**, 1436.

[23] [23a] U. Schöllkopf, G. Ostermann, J. Schossig, *Tetrahedron Lett.* **1969**, 2619. – [23b] J. E. Baldwin, W. F. Erickson, R. E. Hackler, R. M. Scott, *J. Chem. Soc., Chem. Commun.* **1970**, 576. – [23c] H. Iwamura, M. Iwamura, T. Nishida, M. Yoshida, J. Nakayama, *Tetrahedron Lett.* **1971**, 63. – [23d] W. Ando, T. Yagihara, S. Tozune, I. Imai, J. Suzuki, T. Toyana, S. Nakaido, T. Migita, *J. Org. Chem.* **37** (1972) 1721.

[24] J. E. Baldwin, R. E. Hackler, *J. Am. Chem. Soc.* **91** (1969) 3646.

[78/87]