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Dimethyl 2-(Tosylmethyl)fumarate: An Allyl Sulfone as Electrophilic Reagent for the Synthesis of Itaconate Ester Derivatives

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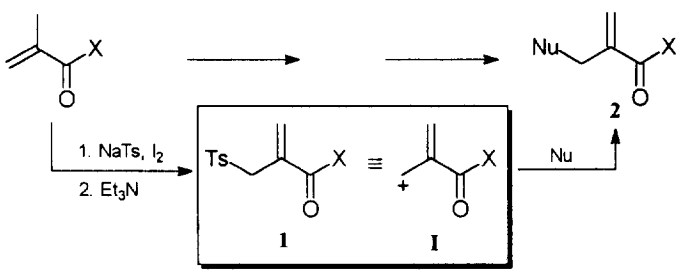
Abstract: The reaction of dimethyl 2-(tosylmethyl)fumarate (**6**), prepared by iodosulfonylation-dehydroiodination of dimethyl itaconate, with carbonucleophiles or sodium methoxide allows the direct synthesis of 3-substituted itaconate ester derivatives **8** via a S_N2' pathway. When sodium thiolates are used as nucleophiles dimethyl 2-(alkylthiomethyl)fumarates **9** or alkylthiomethylene butanoates **10** are obtained via a double S_N2' process. In the case of pyrrolidine and cyclopentanone enamine, the corresponding diamino derivative **11** and the bicyclic[3.2.1]ketones **12** are obtained, respectively.

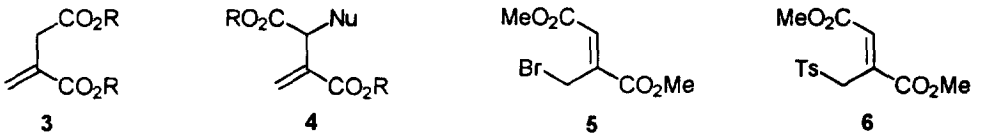
INTRODUCTION

Direct nucleophilic allylic substitution of a sulfonyl group takes place in the case of allyl sulfones only when an electron-withdrawing group is present at the β-position. A good example are α-(tosylmethyl)acrylic acid derivatives of the type **1**[1,2] which afford directly α-methylene esters and amides **2** starting from methacrylic derivatives[1], in which the allyl sulfone acts as a cationic synthon of the type **I** (Scheme 1).



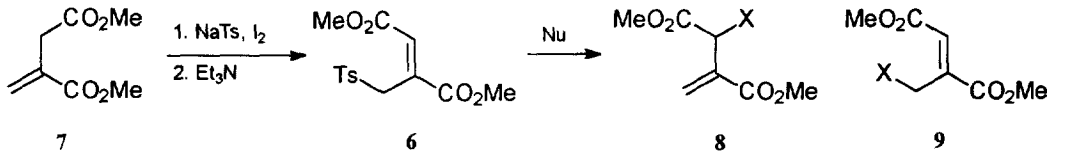
Scheme 1

Applying this methodology it could be possible to transform itaconate ester derivatives **3** into 3-substituted itaconate esters **4**. This type of compounds has been previously prepared using mainly the allylic bromide **5**[3,4], prepared by allylic bromination of mesaconate methyl ester[3]. The substitution of the bromine occurs at the α (S_N2 process) or γ (S_N2' process) position depending on the nucleophile. For instance, with potassium acetate[3], methanolic potassium hydroxide[4b], alkyl cuprates[4b], lithiated allyl sulfones[4a], enamines[4c] or 1,3-diketones[4d] a S_N2' reaction is mainly observed. When sodium benzenesulfinate[4a], dimethyl sulfide[4e-h] or 2-thiobenzothiazole[4i] are used, 2-substituted fumarate ester derivatives are mainly obtained. We describe herein the direct transformation of itaconate dimethyl ester **7** into 3-substituted derivatives **8** using dimethyl 2-(tosylmethyl)fumarate (**6**) as electrophilic reagent.



RESULTS AND DISCUSSION

The starting sulfone, dimethyl 2-(tosylmethyl)fumarate (**6**)[5], was prepared on a multigram scale from dimethyl itaconate (**7**) in 65% yield by a sequential *in situ* iodosulfonylation-dehydroiodination procedure[6]. Sulfone **6** was a crystalline compound (Scheme 2) which was stable during several months at room temperature, its stereochemistry being confirmed by NOE experiments. When this allyl sulfone **6** was allowed to react with different carbo- and hetero-nucleophiles, itaconate derivatives **8** from a S_N2' process were mainly obtained. However, in some cases 2-substituted fumarates **9** were also isolated resulting from an apparent S_N2 process; sometimes it was possible to switch the regioselectivity depending on the reaction conditions (Scheme 2 and Table 1).



Scheme 2

When 1.1 equiv. of a nucleophile as sodium dimethyl malonate was added to a solution of sulfone **6** (method A), a mixture of S_N2'/S_N2 products **8a/9a** in a 3/1 molar ratio was obtained (Table 1, entry 1). This resulting **8a/9a** ratio was reversed when a solution of sulfone **6** was added to 2 equiv. of nucleophile (method B), obtaining a **8a/9a**: 1/10 molar ratio (Table 1, entry 2). However, when the temperature was lowered to -40°C, formation of the S_N2' product **8a** was favored to give a **8a/9a**: 10:1 molar ratio although method B was now used (Table 1, entry 3). When sodium methyl acetoacetate was used as nucleophile, S_N2'-derived compound **8b** was almost exclusively obtained in a **8b/9b**: 24/1 molar ratio (Table 1, entry 4, method A). However, the use of method B increased the amount of the observed S_N2-type compound **9b** affording a **8b/9b**: 5/1 molar ratio (Table 1, entry 5). All these ratios were determined by GLC and the regioisomers separated by flash chromatography for analytical purposes.

The possibility of the occurrence of a S_N2' pathway in sulfone **6** is enhanced by the increased electrophilicity of the double bond caused by conjugation with the ester function. Thus, this route could also be looked upon as a Michael addition-tosyl elimination process. Most probably the simultaneous formation of the S_N2' and S_N2-type products by reaction with these stabilized carbanions reflects the competition between initial *O*-attack and *C*-attack at the 3-position of **6**. The intermediate product of *O*-alkylation in a S_N2' fashion would suffer Claisen rearrangement to give the *C*-alkylated product **9** as it has been observed in the reaction of cyclic 1,3-diketones with bromide **5**[4d] (Scheme 3).

Table 1. Reaction of Sulfone **6** with Nucleophiles (E = CO_2Me).

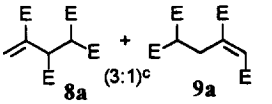
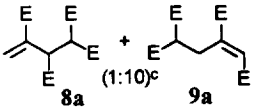
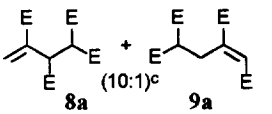
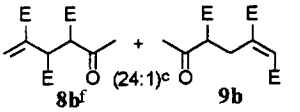
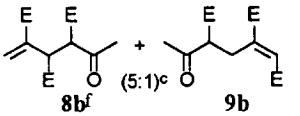
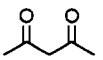
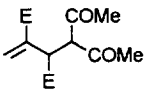
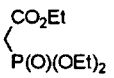
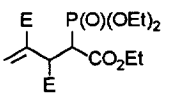
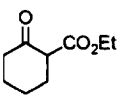
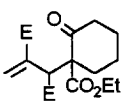
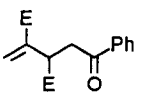
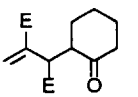
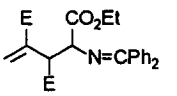
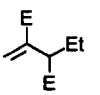
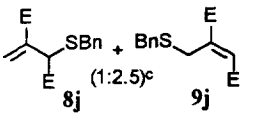
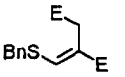
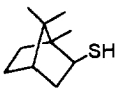
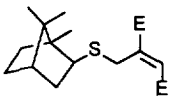
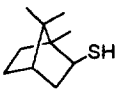
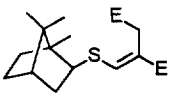
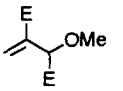
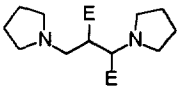
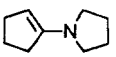
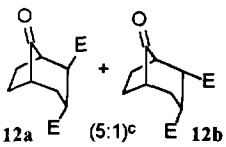
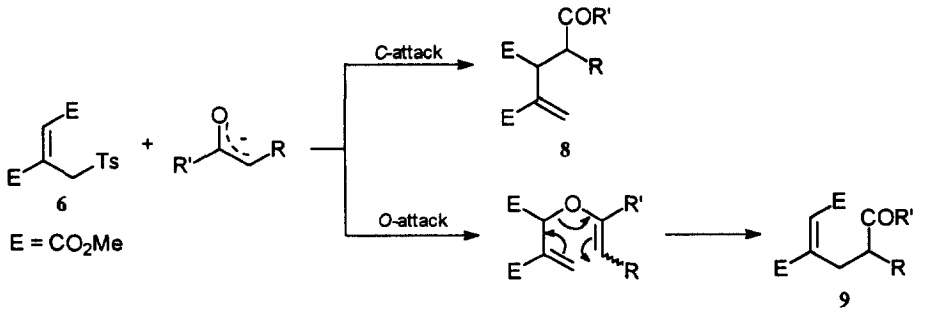
	Reaction Conditions					Products	
Entry	NuH or Nu	Base	Method[a]	T (°C)	Time (h)	Formula and No.	Yield (%)[b]
1		NaH	A	rt	3	 **8a** (3:1)[c] **9a**	86
2		NaH	B	rt	3	 **8a** (1:10)[c] **9a**	80[d]
3		NaH	B	-40	8	 **8a** (10:1)[c] **9a**	72[e]
4		NaH	A	rt	2	 **8b**[f] (24:1)[c] **9b**	79
5		NaH	B	rt	2	 **8b**[f] (5:1)[c] **9b**	76
6		NaH	A[g]	rt	3	 **8c**	73
7		NaH	A	rt	3	 **8d**[h]	58
8		NaH	A	rt	3	 **8e**[i]	42
9		LDA	-	-78→-10	-	 **8f**	75
10		LDA	-	-78→-10	-	 **8g**[i]	76
11		LHMDS	-	-78→-10	-	 **8h**[j]	81
12	EtMgCl	-	-	-30	3	 **8i**	67

Table 1. (Continued)

	Reaction Conditions					Products	
Entry	NuH or Nu	Base	Method[a]	T (°C)	Time (h)	Formula and No.	Yield (%)[b]
13	BnSH	NaH	A	rt	1	 **8j** (1:2.5)[c] **9j**	53[k]
14	BnSH	NaH	C	rt	2	 **10j**	39
15		NaH	A	rt	3	 **9k**[l]	32
16		NaH	C	rt	2	 **10k**[m]	50
17	NaOMe	-	-	rt	3	 **8k**	31
18		-	-	rt	24	 **11j**	81
19		-	-	80	2	 **12a** (5:1)[c] **12b**	60

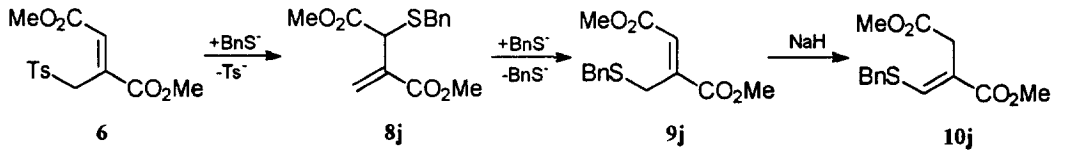
[a] THF was used as solvent. Method A: 1.1 eq of Nu was added over the sulfone; Method B: The sulfone was slowly added over 2 equiv. of NuH or Nu; Method C: Like Method A but an additional excess of 0.2 eq of NaH was used. [b] Isolated global yield after flash chromatography (silica gel) based on starting sulfone. [c] GLC. [d] **9a**: 40% isolated yield. [e] **8a**: 30% isolated yield. [f] Diastereomeric mixture: 2:1 (GLC). [g] A mixture of THF/DMF: 3/2 was used as solvent. [h] Diastereomeric mixture: 3/2 (GLC). [i] Diastereomeric mixture: 10/1 (GLC). [j] Diastereomeric mixture: 7/1 (GLC). [k] Compounds **8j** and **9j** were obtained in 19% and 31% yield respectively after chromatographic separation. [l] $[\alpha]_D^{30}$ = +27 (*c*, 0.6, $CHCl_3$). [m] $[\alpha]_D^{30}$ = +123 (*c*, 1.6, $CHCl_3$).

Reaction of **6** with sodium enolate derived from acetylacetone at room temperature yielded itaconate ester derivative **8c** in 73% yield (Table 1, entry 6); reaction with sodium enolates derived from triethyl phosphonoacetate and ethyl 2-cyclohexanonecarboxylate afforded exclusively derivatives **8d** and **8e** in 58 and 42% isolated yield and in 7:1 and 10:1 diastereomeric ratio respectively (Table 1, entries 7 and 8). In addition, when the reaction was carried out with lithium enolates from acetophenone, cyclohexanone and *N*-(diphenylmethylene)glycine ethyl ester, only S_N2' compounds **8f**, **8g** and **8h** were isolated in 75-81% yield, compounds **8g** and **8h** being obtained as a mixture of diastereoisomers in a 10:1 and 7:1 molar ratio, respectively (Table 1, entries 9-11). Using the Grignard reagent ethylmagnesium chloride as nucleophile, the S_N2'-derived product **8i**[4b] was exclusively obtained in 67% yield (Table 1, entry 12).



Scheme 3

The synthesis of alkylthiomethyl fumarates has only been accomplished by reaction of base-sensitive bromoester **5** with unpleasant dimethyl sulfide since the use of strongly basic thiolate anions was ruled out[4e-h]. However, when sodium benzylthiolate was employed with sulfone **6** using method A, a mixture of S_N2' and S_N2 products **8j** and **9j** was obtained in a 1:2.5 ratio and in 50% overall yield (Table 1, entry 13). In this case, no Claisen rearrangement is possible, so firstly formed compound **8j** suffers probably a second S_N2' attack in which the benzylthiolate now acts as a leaving group (Scheme 4), although an allylic rearrangement is also possible[7]. When this reaction was carried out following method A, but in the presence of a small excess of free sodium hydride (method C), compound **10j** was the only isolated product in 39% yield (Table 1, entry 14), its stereochemistry being confirmed by NOE experiments. This derivative seems to be produced from compound **9j** by further base-induced isomerization. Moreover, when a crude mixture of **8j** and **9j** was treated with a small amount of sodium hydride, only isomerized compound **10j** was obtained. Using the sodium salt of (1*S*-*exo*)-2-bornanethiol[8] as sulfur nucleophile and following method A, only the S_N2-type product **9k** was isolated in 32% yield (Table 1, entry 15). As above, the presence of a small amount of free sodium hydride (method C) allowed the preparation of the isomer **10k** in 50% isolated yield (Table 1, entry 16).

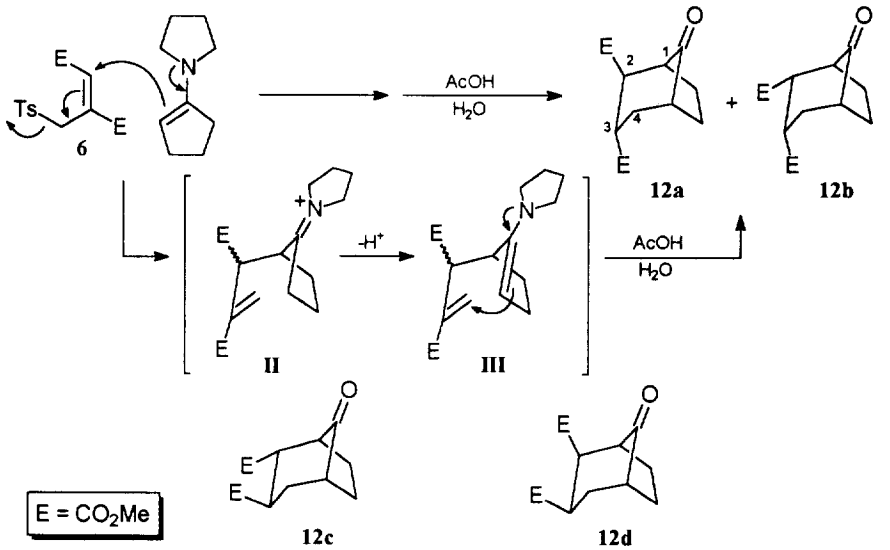


Scheme 4

The use of alcoholates as nucleophiles under different reaction conditions produced decomposition of the starting sulfone. The only exception was when sodium methoxide in methanol was employed, affording the itaconate derivative **8k**[4b] in 31% isolated yield (Table 1, entry 17). On the other hand, when an excess (3 equiv.) of pyrrolidine was used as a nitrogen nucleophile, compound **11** was the only isolated product in 81% yield as a result of a successive S_N2'-attack followed by Michael addition (Table 1, entry 18).

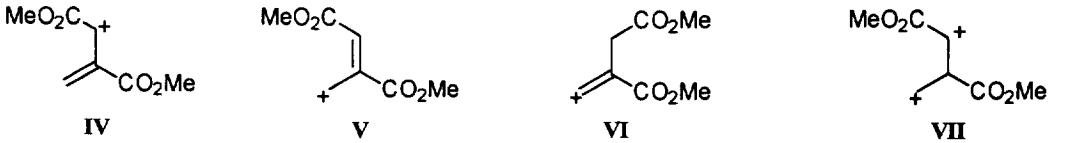
Reaction of starting sulfone **6** with the pyrrolidino enamine of cyclopentanone in refluxing acetonitrile afforded, after hydrolysis of the imine salt with acetic acid, a mixture of 2-*exo*,3-*endo* and 2-*endo*,3-*endo* bicyclic[3.2.1]ketones **12a** and **12b** in 60% total yield and in a 5:1 ratio (Table 1, entry 19). The

stereochemistry of **12a** and **12b** was determined by one- and two-dimensional ^{1}H-NMR spectroscopy and NOE experiments. The absence of observed large *anti* coupling constants between hydrogens at C2, C3 and C4 would indicate 2-*exo*,3-*endo* and 2-*endo*,3-*endo* configurations for these compounds. Also, molecular mechanics calculations[9] showed torsion angles and coupling constants for the more stable conformations in more agreement with the observed coupling constants for H1, H2, H3 and H4 in **12a** and **12b** than the corresponding for the possible 2-*endo*,3-*exo* (**12c**) or 2-*exo*,3-*exo* (**12d**) isomers[10]. These compounds would be obtained through a S_N2' alkylation-Michael pathway in which the enamine acts as a 1,3-dianion ketone equivalent[4c] (Scheme 5) and with a ratio only dependent on the relative orientation of the enamine and ester fragments in the intermediate **II**. Proton transfer to re-form enamine intermediate **III** followed by Michael reaction and protonation of the formed enolate from the least hindered side of the molecule would afford the mixture of isomers **12a** and **12b**. This reaction has been previously carried out using bromide **5**[4c]: the isolation of a mixture of the 2-*exo*,3-*endo* adduct **12a** and a small amount of the 2-*exo*,3-*exo* product **12d** *via* an alkylation-Michael pathway has been reported. In our case a similar mechanism would involve direct allylic substitution of the tosyl group of **6** at the first step, something more difficult than in the case of a bromide group.



Scheme 5

In conclusion, in this paper we have demonstrated that dimethyl 2-(tosylmethyl)fumarate (**6**), very stable and easily prepared from dimethyl itaconate, can be mainly used as cationic synthon of the type **IV** with different carbonucleophiles and sodium methoxide, and of the type **V** or **VI** with sodium thiolates as well as dicationic synthon type **VII** with pyrrolidine and cyclopentanone enamine.



EXPERIMENTAL

General. Melting points were obtained with a Reichert Thermovar apparatus and are uncorrected. Optical rotations were measured with a Jasco DIP-1000 polarimeter. FT-IR spectra were obtained on a Nicolet Impact 400D spectrophotometer. NMR spectra were determined on a Bruker AC-300 (300 MHz for ^1H and 75 MHz for ^{13}C) using $CDCl_3$ as solvent and TMS as internal standard; chemical shifts are given in δ (ppm) and the coupling constants (*J*) are measured in Hz. ^{13}C-NMR assignments were made on the basis of DEPT experiments. Mass spectra (EI, 70eV) were obtained on a Shimadzu GC/MS QP-5000 spectrometer. High resolution mass spectra (EI) were determined by the corresponding Service at the University of Zaragoza. Thin layer chromatography (TLC) was carried out on Schleicher & Schuell F1500/LS 254 plates coated with a 0.2 mm layer of silica gel and UV visualization. Flash chromatography was performed using silica gel 60 of 230-400 mesh (hexane/EtOAc). All starting materials were commercially available (Aldrich, Fluka) of the best grade and were used without further purification. THF was dried over benzophenone ketyl under an argon atmosphere and distilled before use.

***Iodosulphonylation-dehydroiodination[6] of Dimethyl Itaconate. Preparation of Dimethyl 2-(Tosylmethyl)fumarate* (6).** Iodine (15.3 g, 60 mmol) was added to a suspension of dimethyl itaconate (8.4 mL, 60 mmol) and sodium *p*-toluenesulfinate monohydrate (16.2 g, 83 mmol) in CH_2Cl_2 (400 mL). The mixture was stirred at room temperature for 3 days and then triethylamine (25 mL, 180 mmol) was slowly added at 0°C. The resulting solution was stirred at room temperature for 2 h and then successively washed with water (2x100 mL), 1N HCl (2x100 mL), saturated aqueous $NaHCO_3$ (100 mL) and 0.1M aqueous $Na_2S_2O_3$ (100 mL). The organic layer was dried (Na_2SO_4) and distilled (15 Torr) to afford the crude title compound, which was purified by elution through a plug of silica gel (hexane/ethyl acetate: 1/1) and precipitation with ether (12.2 g, 65%): mp 111°C (hexane/CH_2Cl_2); R_f 0.54 (hexane/EtOAc: 1/1); ν 3022, 1648 (C=CH), 1720 and 1734 cm^{-1} (C=O); δ_H 2.44 (s, 3H, ArCH_3), 3.63, 3.74 (2s, 6H, 2xOCH_3), 4.89 (s, 2H, CH_2), 6.94 (s, 1H, C=CH), 7.33 and 7.72 (2d, *J*=7.9, 4H, ArH); δ_C 21.46 (ArCH_3), 51.98, 52.99, 53.30 (2xOCH_3, CH_2), 128.65, 129.48, 134.21, 135.50 (ArC), 131.91 (C=CH), 144.77 (*C*=CH), 164.60 and 165.11 (2xC=O); *m/z* 312 (M^+, 0.8%), 157 (13), 155 (21), 126 (51), 98 (10), 91 (100), 89 (10), 68 (14), 67 (10), 65 (43), 63 (12) and 58 (30) (Found: M^+ 312.0670. Calcd. for $C_{14}H_{16}O_6S$: 312.0668).

Reaction of Sulfone* 6 *with Sodium Enolates and Alkylthiolates. General Procedures. The following methods were used (see Table 1):

Method A: To a solution of sulfone **6** (156 mg, 0.5 mmol) in THF (2 mL) was added dropwise a mixture of sodium hydride (60% dispersion in mineral oil, 22 mg, 0.55 mmol) and the corresponding ester or thiol (0.55 mmol) in THF (3 mL) at room temperature. The suspension was stirred until the reaction was completed (TLC) and then water (5 mL) was added. The resulting solution was extracted with ether (3x10 mL), the organic layer was washed with brine (5 mL), dried (Na_2SO_4) and evaporated to give crude products **8** and/or **9** (see Table 1), which were purified by column chromatography (hexane/ethyl acetate gradients).

Method B: To a suspension of sodium hydride as a 60% dispersion in mineral oil (40 mg, 1 mmol) and the corresponding ester or thiol (1 mmol) was added dropwise a solution of **6** (156 mg, 0.5 mmol) in THF (3 mL) over *ca.* 20 min at room temperature or -40°C (see Table 1). The reaction was stirred until completed (TLC) and then quenched, extracted and purified as in method A.

Method C: As in method A, but an additional amount of sodium hydride (*ca.* 8 mg, 0.2 mmol) was used.

Dimethyl 2-Methylene-3,4-(dimethoxycarbonyl)pentanedioate (**8a**): R_f 0.48 (hexane/EtOAc: 1/1); ν 3004, 1632 (C=CH) and 1739 cm^{-1} (C=O); δ_H 3.65, 3.69 (2s, 6H, 2xOCH_3), 3.78 (s, 6H, 2xCHCO$_2$CH_3), 4.14, 4.28 (2d, *J*=11.3, 2H, 2xCH), 5.84 and 6.39 (2s, 2H, C=CH_2); δ_C 47.14 (*C*HCO$_2$Me), 52.26, 52.60, 52.64, 52.85, 53.00 [4xOCH_3, *C*H(CO$_2$Me)$_2$], 130.12 (C=*C*H$_2$), 135.34 (*C*=CH$_2$), 135.4, 167.51, 168.06 and

170.92 (4xC=O); *m/z* 273 (M^+-CH_3, 0.2%), 256 (16), 229 (10), 225 (13), 224 (61), 197 (92), 196 (14), 185 (28), 169 (17), 157 (88), 139 (17), 137 (11), 129 (29), 113(12), 111 (40), 83 (13), 79 (22), 75 (25), 69 (16), 68 (18), 59 (100), 53 (18), 52 (14) and 51 (21) (Found: M^+ 273.0613. Calcd. for $C_{12}H_{16}O_8$-CH_3: 273.0610).

Dimethyl (E)-*3,5-(Dimethoxycarbonyl)-2-hexenedioate* (**9a**): R_f 0.55 (hexane/EtOAc: 1/1); ν 3004, 1647 (C=CH), 1721, 1736 and 1752 cm^{-1} (C=O); δ_H 3.37 (d, *J*=8.0, 2H, CH_2), 3.75 (t, *J*=8.0, 1H, CH), 3.71 [s, 6H, $CH(CO_2CH_3)_2$], 3.78, 3.82 (2s, 6H, 2xC=CCO_2CH_3) and 6.87 (s, 1H, C=CH); δ_C 26.56 (CH_2), 52.48 [2x$CH(CO_2CH_3)_2$], 50.62, 51.91, 52.67 (CH, 2xC=CCO_2CH_3), 128.83 (C=*C*H), 143.19 (*C*=CH), 165.54, 166.50 and 168,88 (3xC=O); *m/z* 288 (M^+, 0.7%), 257 (21), 256 (24), 225 (30), 224 (97), 197 (47), 193 (17), 169 (90), 165 (23), 156 (12), 137 (13), 123 (12), 111 (14), 79 (24), 75 (12), 69 (21), 68 (12), 59 (100), 55 (19), 53 (17), 52 (12) and 51 (17) (Found: M^+ 288.0865. Calcd. for $C_{12}H_{16}O_8$: 288.0845).

Dimethyl 2-Acetyl-4-methylene-3-(methoxycarbonyl)pentanedioate (**8b**): R_f 0.59 (hexane/EtOAc: 1/1); ν 3003, 1631 (C=CH), 1734 and 1723 cm^{-1} (C=O); major diastereomer in the mixture: δ_H 2.37 (s, 3H, $COCH_3$), 3.65 (s, 6H, 2xOCH_3), 3.78 (s, 3H, OCH_3), 4.33, 4.38 (2d, *J*=11,3, 2H, 2xCH), 5.84 and 6.37 (2s, 2H, C=CH_2); δ_C 30.15 ($COCH_3$), 47.32 (CH), 52.60 (2xOCH_3), 52.82 (OCH_3), 59.85 (CH), 135.61 (C=*C*H_2), 165.71 (*C*=CH_2), 167.19 (OC=O), 171.34 (2xOC=O) and 200.32 (C=O); minor diastereomer in the mixture: δ_H 2.21 (s, 3H, $COCH_3$), 3.68, 3.77, 3.79 (3s, 9H, 3xOCH_3), 4.33, 4.38 (2d, *J*=11.3, 2H, 2xCH), 5.83 and 6.38 (2s, 2H, C=CH_2); δ_C 30.36 ($COCH_3$), 46.42 (CH), 52.22 (2xOCH_3), 52.31 (OCH_3), 60.30 (CH), 130.40 (C=*C*H_2), 135.20 (*C*=CH_2), 165.71, 165.79, 168.24 (3xOC=O) and 200.81 (C=O); major diastereomer in the mixture: *m/z* 240 (M^+-33, 4%), 209 (16), 208 (12), 198 (37), 181 (20), 166(42), 139 (68), 138 (15), 111 (23), 79 (10), 59 (26), 51 (10) and 43 (100).

Dimethyl (E)-*4-Acetyl-3-(methoxycarbonyl)-2-hexenedioate* (**9b**): R_f 0.59 (hexane/EtOAc: 1/1); ν 3002, 658 (C=CH), 1741 and 1723 cm^{-1} (C=O); δ_H 2.25 (s, 3H, CH_3), 3.27, 3.33 (2dd, *J*=14.0, 7.5, 2H, CH_2), 3.78 (m, 1H, CH), 3.78 (s, 3H, OCH_3) and 6.83 (s, 1H, C=CH); δ_C 28.71 (CH_3), 39.72 (CH_2), 52.03, 52.46, 52.99 (3xOCH_3), 58.41 (CH), 128.46 (*C*H=C), 144.02 (CH=*C*), 165.68, 166.95, 169.33 (3xOC=O) and 201.74 (C=O); *m/z* 272 (M^+, 2%), 208 (11), 199 (51), 198 (25), 167 (27), 166 (41), 153 (28), 139 (13), 59 (28), 53 (11), 44 (11) and 43 (100).

Dimethyl 2-(Diacetylmethyl)-3-methylenebutanedioate (**8c**): R_f 0.54 (hexane/EtOAc: 1/1); ν 3004, 1631 (C=CH), 1703 and 1735 cm^{-1} (C=O); δ_H 2.12, 2.34 (2s, 6H, 2x$COCH_3$), 3.65, 3.79 (2s, 6H, 2xOCH_3), 4.44, 4.55 (2d, *J*=11.3, 2H, 2xCH), 5.82 and 6.37 (2s, 2H, C=CH_2); δ_C 29.42, 30.46 (2x$COCH_3$), 47.58 (*C*HCO_2Me), 52.38, 52.71 (2xOCH_3), 69.16 (*C*HCOMe), 130.55 (C=*C*H_2), 135.25 (*C*=CH_2), 165.82, 171.40 (2xOC=O) and 201.30 (2xC=O); *m/z* 256 (M^+, 0.1%), 182 (16), 150 (14), 139 (23), 123 (20), 95 (13), 59 (11) and 43 (100) (Found: M^+ 256.0954. Calcd. for $C_{12}H_{16}O_6$: 256.0947).

1-Ethyl, 5-Methyl 2-(Diethylphosphono)-4-methylene-3-(methoxycarbonyl)pentanedioate (**8d**): R_f 0.36 (hexane/EtOAc: 1/1); ν 1633 (C=C) and 1736 cm^{-1} (C=O); major diastereomer in the mixture: δ_H 1.18-1.39 (m, 9H, 3xCH_3), 3.66, 3.77 (2s, 6H, 2xOCH_3), 4.00-4.30 (m, 8H, 2xCH, 3xCH_2), 5.94 and 6.45 (2s, 2H, C=CH_2); minor diastereomer in the mixture: δ_H 1.18-1.39 (m, 9H, 3xCH_3), 3.72, 3.79 (2s, 6H, 2xOCH_3), 4.00-4.30 (m, 8H, 2xCH, 3xCH_2), 5.89 and 6.38 (2s, 2H, C=CH_2); diastereomeric mixture (very complicated spectrum): δ_C 13.86, 13.97, 16.06, 16.15, 16.25 (5xCH_3), 43.34, 45.73, 47.29, 47.47 (4xCH), 52.04, 52.34, 52.66 (OCH_3), 61.67, 62.66, 62.70, 62.75, 62.78, 63.11 (6xCH_2), 128.00, 130.60 (2xC=*C*H_2), 135.59, 136.78 (2x*C*=CH_2), 165,65, 165,79, 168,42, 168,49, 171,29 and 171,58 (6xC=O); major diastereomer in the mixture: *m/z* 380 (M^+, 3.3%), 321 (53), 293 (12), 275 (17), 247 (16), 219 (19), 201 (19), 187 (19), 185 (11), 161 (16), 159 (11), 157 (25), 152 (11), 151 (16), 139 (100), 133 (20), 125 (35), 123 (12), 115 (23), 111 (43), 109 (25), 107(11), 99 (11), 97 (29), 96 (15), 95 (11), 91 (12), 83 (26), 82 (17), 81 (57), 79 (29), 69 (12), 68 (15), 65 (27), 59 (58), 55 (11), 53 (22), 52 (12), 51 (15) and 45 (13) (Found: M^+ 380.1225. Calcd. for $C_{15}H_{25}O_9P$: 380.1236).

Dimethyl 2-[1-(Ethoxycarbonyl)-2-(oxocyclohexyl)]-3-methylenebutanedioate (**8e**): R_f 0.67 (hexane/EtOAc: 1/1); ν 1626 (C=C), 1715 and 1729 cm^{-1} (C=O); major diastereomer in the mixture: δ_H 1.26 (t, *J*=7,

3H, CH_2CH_3), 1.58-1.96 (m, 5H, CH_2), 2.40 (m, 3H, CH_2), 3.67, 3.74 (2s, 6H, 2xOCH_3), 4.14 (m, 2H, OCH_2), 5.55 and 6.46 (2s, 2H, C=CH_2); δ_C 13.81 (CH_3), 22.41, 25.70, 30.14, 40.96 (4xCH_2), 47.10 (CH), 52.12, 52.33 (2xOCH_3), 61.98 (OCH_2), 62.31 (CCO_2Et), 129.72 (C=CH_2), 134.29 (*C*=CH_2), 166.28, 169.65, 171.87 (3xOC=O) and 205.74 (C=O); minor diastereomer in the mixture (detectable signals): δ_H 3.67, 3.79 (2s, 6H, 2xOCH_3), 4.33 (s, 1H, CH), 5.89 and 6.50 (2s, 2H, C=CH_2); δ_C 13.87, 22.00, 24.91, 25.58, 26.72, 33.90, 40.65, 61.51, 63.28, 130.82, 170.51; major diastereomer in the mixture: *m/z* 295 (M^+-CH_3O, 3%), 221 (11), 193 (13), 192 (21), 189 (14), 165 (11), 164 (13), 161 (12), 158 (41), 157 (49), 151 (12), 141 (16), 137 (10), 135 (13), 133 (23), 126 (50), 123 (30), 113 (10), 105 (43), 95 (13), 91 (23), 81 (11), 79 (41), 78 (14), 77 (48), 68 (15), 67 (23), 66 (13), 65 (27), 59 (100), 55 (43), 53 (24), 51 (11), 45 (16), 43 (17), 42 (44) and 41 (33) (Found: M^+ 295.1176. Calcd. for $C_{16}H_{19}O_7$-CH_3O: 295.1182).

Dimethyl 2-(Benzylthio)-3-methylenebutanedioate (**8j**): R_f 0.75 (hexane/EtOAc: 1/1); ν 1632, 3028 (C=CH) and 1728 cm^{-1} (C=O); δ_H 3.70, 3.75 (2s, 6H, 2xOCH_3), 3.78, 3.89 (2d, *J*=13.1, 2H, CH_2S), 4.32 (s, 1H, CH), 6.02, 6.45 (2s, 2H, C=CH_2) and 7.25-7.33 (m, 5H, ArH); δ_C 36.34 (CH_2), 46.57 (CH), 52.24, 52.64 (2xOCH_3), 127.30, 129.02, 129.09, 135.14, 136.69 (ArC, C=CH_2), 165.66 and 170.50 (2xC=O); *m/z* 248 (M^+-32, 3%), 158 (49), 126 (45), 123 (24), 91 (100), 65 (19) and 45 (40).

Dimethyl (E)-*(Benzylthiomethyl)-2-butenedioate* (**9j**): R_f 0.76 (hexane/EtOAc: 1/1); ν 1640, 3028 (C=CH) and 1724 cm^{-1} (C=O); δ_H 3.73 (s, 2H, CH_2C=C), 3.74, 3.81 (2s, 6H, 2xOCH_3), 3.94 (s, 2H, CH_2Ph), 6.73 (s, 1H, C=CH) and 7,30 (m, 5H, ArH); δ_C 27.61, 36.63 (2xCH_2), 51.84, 52.67 (2xOCH_3), 125.67, 126.96, 128.32, 128.88, 137.79 (ArC, C=*C*H), 144.25 (*C*=CH), 165.71 and 166.45 (2xC=O); *m/z* 280 (M^+, 5%), 248 (11), 157 (15), 123 (18), 92 (13), 91 (100), 65 (20), 59 (12) and 45 (44) (Found: M^+ 280.0765. Calcd. for $C_{14}H_{16}O_4S$: 280.0769).

Dimethyl (E)-*2-(Benzylthiomethylene)butanedioate* (**10j**): R_f 0.67 (hexane/EtOAc: 1/1); ν 1653, 3028 (C=CH), 1701 and 1739 cm^{-1} (C=O); δ_H 3.36 (s, 2H, CH_2C=C), 3.67, 3.71 (2s, 6H, 2xOCH_3), 4.06 (s, 2H, CH_2Ph), 7.27-7.35 (m, 5H, ArH) and 7.72 (s, 1H, C=CH); δ_C 33.66, 38.45 (2xCH_2), 51.92, 51.99 (2xOCH_3), 120.66 (*C*=CH), 127.72, 128.74, 128.82, 136.43 (ArC), 145.13 (C=*C*H), 165.15 and 170.38 (2xC=O); *m/z* 280 (M^+, 2%), 189 (12), 91 (100) and 65 (15) (Found: M^+ 280.0762. Calcd. for $C_{14}H_{16}O_4S$: 280.0769).

Dimethyl (E)-*2-{*[(1S)-exo]-*Bornylthiomethyl}-2-butenedioate* (**9k**): R_f 0.74 (hexane/EtOAc: 1/1); ν 1640 (C=C) and 1725 cm^{-1} (C=O); δ_H 0.80, 0.90, 0.99 (3s, 9H, 3xCH_3), 1-64-1,84 (m, 7H, 3xCH_2, CH), 2.66 (dd, *J*=8.9, 6.1, 1H, CHS), 3.78, 3.83 (2s, 6H, 2xOCH_3), 3.87, 4.00 (2d, *J*=13.1, 2H, CH_2S) and 6,70 (s, 1H, C=CH); δ_C 13.18, 19.93 (3xCH_3), 26.89, 29.36, 37.81 (3xCH_2), 40.35 (CH_2S), 45.39, 46.78 (2xC), 51.48, 52.24 (2xOCH_3), 53.36 (CHS), 124.54 (C=*C*H), 144.48 (*C*=CH), 165,58 and 166,25 (2xC=O); *m/z* 326 (M^+, 7%), 169 (29), 158 (15), 137 (61), 135 (10), 109 (13), 95 (27), 93 (18), 81 (100), 79 (17), 77 (11), 69 (26), 67 (35), 59 (18), 57 (12), 55 (24), 53 (14), 45 (17), 43 (28) and 41 (63) (Found: M^+ 326.1549. Calcd. for $C_{17}H_{26}O_4S$: 326.1552).

Dimethyl (E)-*2-{*[(1S)-exo]-*Bornylthiomethylene}butanedioate* (**10k**): R_f 0.78 (hexane/EtOAc: 1/1); ν 1587 (C=C), 1708 and 1743 cm^{-1} (C=O); δ_H 0.85, 0.93, 0.95 (3s, 9H, 3xCH_3), 1.17-1.28 (m, 3H, CH_2, CH), 1.75-1.99 (m, 4H, 2xCH_2), 3.11 (dd, *J*=9.2, 5.8, 1H, CHS), 3.36 (s, 2H, CH_2=C), 3.68, 3.73 (2s, 6H, 2xOCH_3) and 7.71 (s, 1H, C=CH); δ_C 13.93, 20.08, 20.14 (3xCH_3), 27.16, 33.64, 38.11 (3xCH_2), 39.59 (CH_2C=C), 47.40 (*C*HCMe$_2$), 45.64, 49.64 (2xC), 51,85, 51.93 (2xOCH_3), 58.01 (CHS), 118.59 (*C*=CH), 148.79 (C=*C*H), 165.54 and 170.66 (2xC=O); *m/z* 326 (M^+, 4%), 137 (59), 95 (20), 81 (100), 69 (18), 67 (24), 55 (11), 43 (17) and 41 (32) (Found: M^+ 326.1550. Calcd. for $C_{17}H_{26}O_4S$: 326.1552).

Reaction of Sulfone 6 with Lithium Enolates. Synthesis of Itaconate Derivatives 8f and 8g. To a solution of diisopropylamine (70 μL, 0.5 mmol) in THF (3 mL) cooled to -78°C was added n-butyllithium (1.6 M in hexanes, 312 μL, 0.5 mmol) and the mixture was stirred at this temperature for 30 min. Acetophenone or cyclohexanone (0.5 mmol) was then added and the mixture was stirred for 30 min at the same temperature. To the resulting solution was added dropwise the sulfone **6** (156 mg, 0.5 mmol)

dissolved in THF (2 mL) at -78°C and the temperature was allowed to rise to -10°C. Water was added (5 mL) and the mixture was extracted with ether (3x15 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4), evaporated (15 Torr) and the residue was purified by flash chromatography (hexane/EtOAc: 4/1) affording compounds **8f** (104 mg, 75%) or **8g** (97 mg, 76%) as a mixture of diastereomers.

Dimethyl 2-(Benzoylmethyl)-3-methylenebutanedioate (**8f**): R_f 0.68 (hexane/EtOAc: 1/1); ν 3027, 1630 (C=CH), 1686, 1721 and 1736 cm^{-1} (C=O); δ_H 3.26 (dd, *J*=18, 5.5, 1H, C*H*HCOPh), 3.77 (dd, *J*=18, 7.9, 1H, CH*H*COPh), 3.71, 3.78 (2s, 6H, 2xOCH$_3$), 4.28 (dd, *J*=7.9, 5.5, 1H, CH), 5.82, 6.36 (2s, 2H, C=CH$_2$), 7.47 (m, 2H, *m*-ArH), 7.56 (m, 1H, *p*-ArH), 7.96 (m, 2H, *o*-ArH); δ_C 40.31 (CH), 42.66 (CH$_2$), 52.14, 52.32 (2xOCH$_3$), 128.02, 128.53, 133.22, 136.37, 137.82, 166.12 (ArC, C=CH$_2$), 172.80 (2xOC=O) and 197.16 (C=O); *m/z* 276 (M^+, 0.3%), 105 (100), 77 (59) and 51 (15) (Found: M^+ 276.1000. Calcd. for $C_{15}H_{16}O_5$: 276.0998).

Dimethyl 2-Methylene-3-(2-oxocyclohexyl)butanedioate (**8g**): R_f 0.78 (hexane/EtOAc: 1/1); ν 1629 (C=C), 1713 and 1732 cm^{-1} (C=O); major diastereomer in the mixture: δ_H 1.68-2.44 (m, 8H, 4xCH$_2$), 2.92 (m, 1H, CH), 3.68, 3.80 (2s, 6H, 2xOCH$_3$), 4.09 (d, *J*=7.3, 1H, CHCO$_2$Me), 5.68 and 6.33 (2s, 2H, C=CH$_2$); δ_C 24.92, 27.36, 30.63 (3xCH$_2$), 42.03 (*C*H$_2$CO), 45.22 (*C*HCO$_2$Me), 51.97 (*C*HCO), 52.23, 52.82 (2xOCH$_3$), 126.47 (C=*C*H$_2$), 137.29 (*C*=CH$_2$), 166.70, 172.79 (2xOC=O) and 208.61 (C=O); major diastereomer in the mixture: *m/z* 244 (13), 171 (10), 105 (100), 77 (49), and 51 (15).

***Synthesis of 1-Ethyl, 5-Methyl 2-Diphenylmethyleneamino-3-(ethoxycarbonyl)-4-methylenepentanedioate* (8h).** To a solution of hexamethyldisilazane (105 μL, 0.5 mmol) in THF (3 mL) cooled at -78°C was added n-butyllithium (1.6 M in hexanes, 312 μL, 0.5 mmol) and the mixture was stirred at this temperature during 30 min. A solution of *N*-(diphenylmethylene)glycine ethyl ester (134 mg, 0.5 mmol) in THF (2 mL) was then added and the mixture was stirred for 30 min at -78°C. To the resulting deep yellow solution was added dropwise the sulfone **6** (156 mg, 0.5 mmol) dissolved in THF (2 mL) at -78°C and the temperature was allowed to rise to -20°C. Water was added (5 mL) and the mixture was extracted with ether (3x15 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4), evaporated (15 Torr) and the residue was purified by flash chromatography (hexane/EtOAc: 4/1) affording the title compound **8h** as a mixture of diastereomers in a 7/1 ratio (171 mg, 81%): R_f 0.78 (hexane/EtOAc: 1/1); ν 3024, 1624 (C=CH, C=C) and 1739 cm^{-1} (C=O); major diastereomer in the mixture: δ_H 1.29 (t, *J*=7, 3H, CH$_2$C*H*$_3$), 3.55, 3.62 (2s, 6H, 2xOCH$_3$), 4.21 (q, *J*=7, 2H, C*H*$_2$CH$_3$), 4.46, 4.68 (2d, *J*=9.2, 2H, CH$_2$CO$_2$Et), 5.82, 6.36 (2s, 2H, C=CH$_2$) and 7.19-7.55 (m, 10H, ArH); δ_C 13.97 (CH$_2$*C*H$_3$), 50.17 (CH), 51.84, 52.08 (2xOCH$_3$), 61.32 (OCH$_2$), 65.75 (CH), 127.90, 127.95, 128.15, 128.20, 128.27, 128.40, 128.75, 128.88, 128.95, 130.33, 130.45, 135.27, 135.57, 139.45 (ArC, C=CH$_2$), 165.80 (C=N), 170.43, 171.37 and 171.98 (3xC=O); minor diastereomer in the mixture: δ_H 1.21 (t, *J*=7.3, 3H, CH$_2$C*H*$_3$), 3.68, 3.71 (2s, 6H, 3xOCH$_3$), 4.12 (q, *J*=7.3, 2H, CH$_2$), 4.50, 4.61 (2d, *J*=7.3, 2H, CH$_2$CO$_2$Et), 5.79, 6.38 (2s, 2H, C=CH$_2$) and 7.19-7.55 (m, 10H, ArH); δ_C 25.53 (CH$_2$*C*H$_3$), 49.17 (CH), 52.08, 52.12 (2xOCH$_3$), 66.96 (OCH$_2$), 67.88 (CH), 127.6, 128.61, 129.97, 130.39, 132.34, 135.48, 135.94, 139.29 (ArC, C=CH$_2$), 166.26 (C=N), 169.80, 171.15 and 172.28 (3xC=O); major diastereomer in the mixture: *m/z* 364 (M^+-CO$_2$Me, 25%), 266 (12), 265 (22), 193 (31), 192 (18), 166 (14), 165 (70), 77 (23), 59 (100), 51 (18) and 45 (10).

***Synthesis of Dimethyl 2-Ethyl-3-methylenebutanedioate* (8i)[4b].** To a solution of ethylmagnesium chloride (25% in THF, 355 μL, 1 mmol) in 3 mL of THF kept at -30°C was added a solution of sulfone **6** (156 mg, 0.5 mmol) in THF (3 mL) during *ca.* 15 min. and the mixture was stirred at this temperature for 3 h. The reaction was quenched with aqueous saturated ammonium chloride (5 mL) and extracted with ether (2x20 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4) and evaporated (15 Torr) affording crude title compound which was purified by flash chromatography (hexane/EtOAc: 9/1) (62 mg, 67%): R_f 0.53 (hexane/EtOAc: 4/1); ν 1634 (C=C) and 1734 cm^{-1} (C=O), δ_H 0.93 (t, *J*=7.3, 3H, CH$_2$C*H*$_3$), 1.71, 1.93

(2dq, *J*=13.7, 7.3, 2H, CH_2), 3.43 (dd, *J*=8.2, 7.3, 1H, CH), 3.69, 3.77 (2s, 6H, 2xOCH_3), 5.75 and 6.37 (2s, 2H, C=CH_2); δ_C 11.94 (CH_2CH_3), 24.31 (CH_2), 48.14 (CH), 51.89, 52.03 (2xOCH_3), 126.71 (C=CH_2), 138.09 (*C*=CH_2), 166.65 and 173.62 (2xC=O); *m/z* 157 (M^+-CH_2CH_3, 81%), 155 (12), 127 (15), 126 (13), 111 (10), 95 (28), 67 (100), 65 (14), 59 (79), 55 (16), 53 (28), 45 (11) and 41 (44).

***Synthesis of Dimethyl 2-Methylene-3-methoxybutanedioate* (8k)**[4b]. To the sulfone **6** (125 mg, 0.4 mmol) dissolved in dry methanol (5 mL) was added a solution of sodium methoxide (25 mg, 0.44 mmol) in methanol (2 mL) at room temperature. The mixture was stirred for 3 h and the solvent was evaporated (15 Torr). Water (10 mL) was then added and the mixture was extracted with ether (2x15 mL). The organic layer was washed with brine (5 mL), dried (Na_2SO_4), evaporated (15 Torr), and the residue chromatographed (hexane/EtOAc: 9/1) yielding compound **8k** (23 mg, 31%): R_f 0.46 (hexane/EtOAc: 1/1); ν 1636 (C=C) and 1731 cm^{-1} (C=O); δ_H 3.45 (s, 3H, OCH_3), 3.77, 3.80 (2s, 6H, 2xCO_2CH_3), 4.67 (d, *J*=0.9, 1H, CH), 6.00, 6.46 (2d, *J*=0,6, 2H, C=CH_2); δ_C 52.19, 52.39 (2xCO_2CH_3), 58.12 (OCH_3), 78.64 (CH), 128.50 (C=CH_2), 136.09 (*C*=CH_2), 165.51 and 170.11 (2xC=O); *m/z* 156 (M^+-MeOH, 10%), 129 (64), 75 (100), 59 (13), 47 (21) and 45 (11).

***Reaction of Sulfone* 6 *with Pyrrolidine. Synthesis of Dimethyl 2-Pyrrolidino-3-pyrrolidinomethyl-butanoate* (11).** To a solution of sulfone **6** (125 mg, 0.4 mmol) in acetonitrile (5 mL) was added pyrrolidine (100 μL, 1.2 mmol) and the mixture was stirred during 24 h. The solvent was evaporated (15 Torr), water (10 mL) was added and the suspension was extracted with ethyl acetate (2x15 mL). The organic layer was dried (Na_2SO_4) and evaporated (15 Torr) affording the title compound as a mixture of diastereomers in a 7:1 ratio (97 mg, 81%): ν 1736 (C=O); major diastereomer in the mixture: δ_H 1.72 (m, 8H, 4xCH_2CH_2N), 2.42-2.79 [m, 9H, 4xCH_2N, $CHN(CH_2)_4$], 2.93 [dd, *J*=11.9, 9.2, 1H, $CHN(CH_2)_4$], 3.04 (dt, *J*=10.0, 4.3, $CHCO_2Me$), 3.67 (s, 6H, 2xOCH_3) and 3.78 (d, *J*=10.0, 1H, CHN); δ_C 23.65 (2xCH_2CH_2N), 23.85 (2xCH_2CH_2N), 46.41 ($CHCO_2Me$), 48.86 (2xCH_2N), 50.95, 51.59 (2xOCH_3), 54.44 (2xCH_2N), 55.75 [$CH_2N(CH_2)_4$], 63.26 (CHN), 171.33 and 174.41 (2xC=O); major diastereoisomer in the mixture: *m/z* 298 (M^+, 2%), 170 (20), 168 (27), 156 (41), 142 (18), 124 (26), 85 (17), 84 (100), 83 (10), 82 (10), 71 (11), 70 (35), 55 (29), 43 (20), 42 (50) and 41 (30).

***Reaction of Sulfone* 6 *with 1-Pyrrolidino-1-cyclopentene. Preparation of Bicyclic Ketones* 12a *and* 12b**[4c]. To a solution of sulfone **6** (156 mg, 0.5 mmol) in acetonitrile (3 mL) was added 1-pyrrolidino-1-cyclopentene (88 μL, 0.6 mmol) in THF (2 mL) and the resulting mixture was refluxed under argon for 2 h. Then, 2 drops of aqueous 5% acetic acid were added and the mixture was refluxed again for 2 h. Water (5 mL) was added and the mixture was extracted with ether (3x15 mL). The organic layer was washed with 2N HCl (2x10 mL), saturated $NaHCO_3$ (10 mL) and brine (5 mL). Evaporation of the dried (Na_2SO_4) solvent and flash chromatography of the resulting residue (hexane/EtOAc: 9/1) afforded ketone **12a** (48 mg, 40%) as the major isomer and ketone **12b** (9 mg, 8%) as the minor one.

Dimethyl Bicyclo[3.2.1]octan-8-one-2-exo,*3*-endo-*dicarboxylate* (**12a**): R_f 0.62 (hexane/EtOAc: 1/1); ν 1755 and 1732 cm^{-1} (C=O); δ_H 1.94-1.85 (m, 4H, 2xCH_2CHCO), 2.24 (m, 1H, CHCHCO), 2.50 (dddd, *J*=14.4, 8.2, 3.4, 0.9, 1H, $CH_{exo}H_{endo}CHCO_2Me$), 2.64 (m, 1H, CH_2CHCH_2), 2.75 (ddt, *J*=14.4, 3.9, 2.1, 1H, $CH_{exo}H_{endo}CCO_2Me$), 3.14 (dt, *J*=7.9, 1.8, 1H, $CH_{exo}CO_2Me$), 3.74, 3.80 (2s, 6H, 2xOCH_3) and 3.93 (dt, *J*=3.4, 1.8, 1H, $CH_{endo}CO_2Me$); δ_C 20.76, 21.19 (2xCH_2CH), 35.34 (CH_2CHCO_2Me), 36.30, 42.94 (2xCHCO), 44.89 (CH_2CHCO_2Me), 52.43 (2xOCH_3), 53.34 (CHCHCO), 172.81, 174.40 (2xOC=O) and 217.15 (C=O); *m/z* 240 (M^+, 6%), 212 (13), 209 (21), 208 (19), 181 (21), 180 (100), 177 (15), 154 (34), 153 (26), 152 (47), 149 (15), 148 (18), 139 (25), 126 (14), 124 (13), 122 (15), 121 (30), 120 (19), 113 (18), 111 (13), 95 (12), 94 (29), 93 (93), 92 (33), 91 (42), 83 (16), 81 (23), 79 (39), 78 (12), 77 (46), 74 (10), 69 (11),

68 (22), 67 (21), 66 (18), 65 (23), 59 (54), 55 (76), 54 (10), 53 (36), 51 (13), 45 (17), 43 (14), 41 (74) and 40 (17).

Dimethyl Bicyclo[3.2.1]octan-8-one-2-endo,*3*-endo-*dicarboxylate* (**12b**): R_f 0.62 (hexane/EtOAc: 1/1); ν 1755 and 1732 cm^{-1} (C=O); δ_H 1.57 (m, 2H), 1.92 (m, 1H), 2.26 (m, 3H), 2.73 (m, 2H), 3.10 (1H, dd, *J*=7.0, 2.4, CHC*H*CO_2Me), 3.29 (1H, br t, *J*=7.0, CH_2CHCO_2Me), 3.71 and 3.75 (2s, 6H, 2xOCH_3); δ_C 19.60, 21.26 (2xCH_2CHCO), 35.89 (CH_2CHCO$_2$Me), 38.04, 43.23, 45.05, 49.84 (4xCH), 51.99, 52.26 (2xOCH_3), 171.63, 173.45 (2xOC=O) and 219.05 (C=O); *m/z* 240 (M^+, 10%), 209 (25), 208 (10), 181 (18), 180 (39), 176 (14), 159 (76), 153 (18), 152 (23), 148 (19), 135 (16), 127 (26), 126 (21), 121 (34), 120 (18), 114 (10), 113 (27), 96 (10), 95 (19), 94 (23), 93 (100), 92 (29), 91 (40), 82 (46), 81 (24), 79 (36), 78 (11), 77 (40), 69 (12), 68 (23), 67 (21), 66 (16), 65 (22), 59 (52), 55 (67), 53 (34), 51 (12), 45 (17), 43 (14), 41 (72) and 40 (15).

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5. The corresponding phenylsulfonyl derivative has been prepared from bromide **5** by reaction with sodium benzenesulfinate in DMF at room temperature[4a].
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9. PCMODEL for Windows from Serena Software was used for these calculations.
10. Selected calculated[9] and observed coupling constants for compounds **12a-d**:

Compound	$J_{1,2}$[a]	$J_{2,3}$[a]	$J_{3,4\text{-}exo}$[a]	$J_{3,4\text{-}endo}$[a]
12a	2.3 (1.8)	0.4 (1.8)	8.1 (7.9)	0.9 (≈0)
12b	3.7 (2.4)	8.6 (7)	8.6 (7)	1 (≈0)
12c	2.4	13	11.7	5.1
12d	2.4	6	12	4.7

[a] Observed values in parenthesis.

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