4-[(4′-Methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone as a New Four-Carbon Synthon for Substituted Divinyl Ketones

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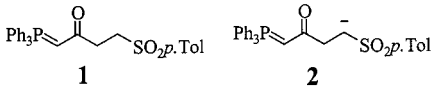
The title compound and the corresponding anion have been conveniently used as precursors of substituted divinylketones in both carbo- and heterocyclization reactions in one-pot, three-step sequences leading to a wide variety of substituted carbo- and heterocyclic ring systems, as well as to multifunctionalized linear carbon frameworks. The compounds generated through the use of this multi-coupling reagent represent useful synthons for the construction of natural compounds including (±)-epibatidine, (−)-anabasine and (±)-pyrenophorin.

Introduction

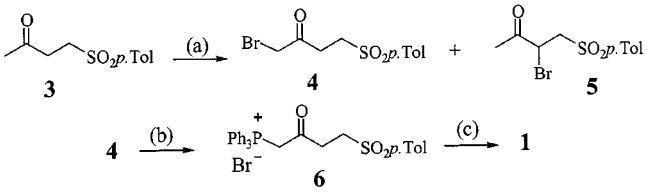
The development of one-pot, multiple bond-forming reactions for the stereoselective construction of complex molecules in just a few steps, coupling together small and simple components, continues to be a challenging goal in organic synthesis. Methods and reagents that allow for the formation of multiple carbon−carbon or carbon−heteroatom bonds are especially valuable.[1] We have recently introduced 4-[(4′-methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone (**1**) as a new four-carbon synthon for substituted divinyl ketones, able to participate in a domino reaction sequence initiated by a nitrogen- or carbon-centered nucleophile as a tool for building up six-membered heterocyclic and carbocyclic rings.[2]



1 **2**

This compound features a stabilized ylide function, useful for the installation of conjugated double bonds and able to act as a Michael acceptor, and a γ-keto sulfone system: a functionality stable in neutral or acidic media but susceptible to *p*-toluenesulfinic acid elimination under the basic conditions required in the initial event of the synthetic sequence. Moreover, the ylide function, acting temporarily as a deactivating factor in the electron-withdrawing character of the carbonyl group, permitted deprotonation at the α-position of the sulfone, thus creating an anion (**2**) able to react with different electrophiles at either terminus of its four carbon atom chain. Finally, the sulfone moiety can either be removed at the end of the synthetic sequence by various reductive desulfonylation methods, or be transformed into an oxygenated function.[3]

The preparation of **1** utilizes as starting material the Michael adduct **3** of sodium *p*-toluenesulfinate and 3-buten-2-one (Scheme 1). Bromination of **3** with pyridinium bromide perbromide produces a 3:1 mixture of **4** and its regioisomer **5**, which could be easily separated by column chromatography. Treatment of **4** with triphenylphosphane afforded the corresponding phosphonium salt **6**, which was quantitatively transformed into the solid phosphorane **1** by treatment with sodium hydroxide in methanol and subsequent precipitation with water (Scheme 1).



(a) $PyH^+ Br_3^-$, AcOH, 60%; (b) Ph_3P, C_6H_6, 80°C, 92%; (c) NaOH, $MeOH/H_2O$, 95%.

Scheme 1

Results and Discussion

In this full account we wish to report our studies on the reactivity of **1** and its anion **2**, as well as some applications which serve to demonstrate their synthetic versatility.

Reactions with Aldehydes

As expected, reaction between the stabilized ylide **1** and different aldehydes **7a−h** proceeded uneventfully, producing

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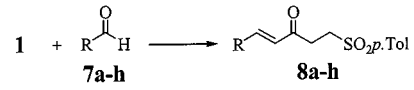


a: R = Me; **b**: R = Ph; **c**: R = C_9H_{19}; **d**: R = CH_2-N(Bn)-Boc; **e**: R = 2-Cl-5-pyridyl; **f**: R = 3-pyridyl; **g**: R = CO_2Me; **h**: R = 2,2-dimethyl-1,3-dioxolan-4-yl; **i**: R = $CH_2(CH_2)_2NH$-Boc; **l**: R = $CH_2(CH_2)_3NH$-Boc.

Scheme 2

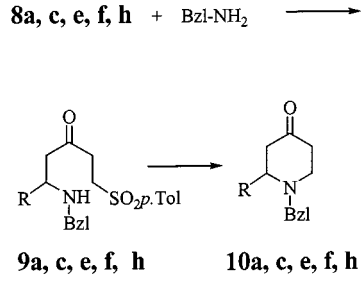
the corresponding enones **8a−h** in good to satisfactory yields under selected conditions, each substrate requiring a set of well defined reaction conditions (Scheme 2 and Table 1). The ylide did not react with ketones.

Table 1. Syntheses of enones **8** from ylide **1** and aldehydes **7**

	Compound **7** R	Yield of **8** (%)	Solvent	Time (h)
a	Me	90	Benzene	12
b		83	Toluene	2
c	CH_2-$(CH_2)_7$Me	88	Toluene	6
d	CH_2-N(Bn)-Boc	66	$CHCl_3$	16
e		94	Toluene	3
f		81	Benzene	12
g	-CO_2Me	76	$CHCl_3$	3
h		80	$CHCl_3$	12
i	CH_2-$(CH_2)_2$-NH-Boc	56	Toluene	3
l	CH_2-$(CH_2)_3$-NH-Boc	45	Toluene	3

Intermolecular Tandem Michael Reactions

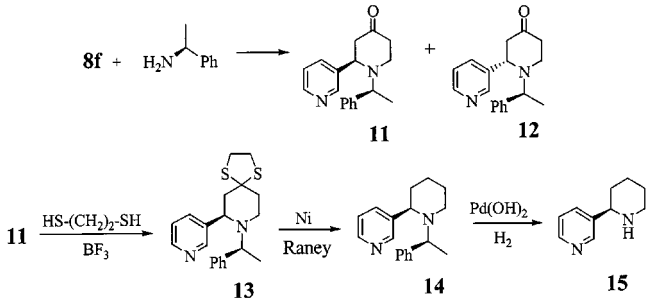
We anticipated that the unsaturated γ-keto sulfones described in the previous section would constitute interesting materials for further transformations. They easily underwent base-induced elimination of *p*-toluenesulfinic acid,



Scheme 3

generating a new double bond adjacent to the central carbonyl group, and giving rise to the formation of substituted divinyl ketone intermediates able to participate in a domino reaction sequence initiated by a nitrogen- or carbon-centered nucleophile. Thus, double Michael reaction occurred smoothly on treatment of **8a**, **8c**, **8e**, **8f**, and **8h** with a primary amine Michael donor such as benzylamine, affording the corresponding substituted piperidones **10** in good yield (Scheme 3).

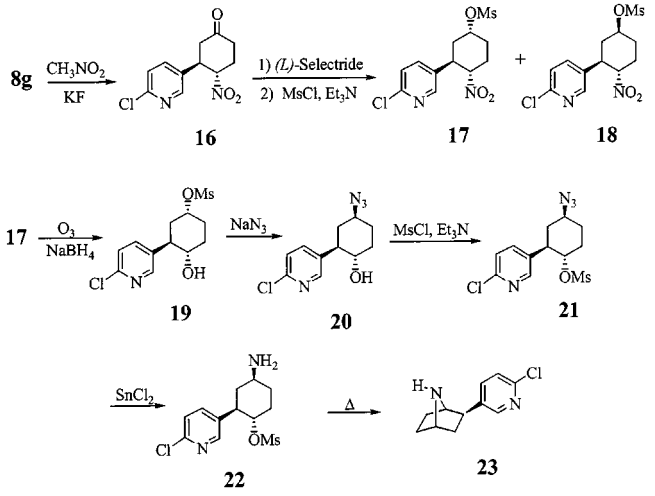
In the case of the substrate **8e**, it was observed that the mixture of reagents remained unchanged at 0 °C for several hours. When the temperature of the reaction mixture reached 15 °C, the Michael adduct **9e** was formed. The subsequent base-promoted elimination of *p*-toluenesulfinic acid produced the new Michael acceptor site, thus allowing the second Michael addition. At room temperature, the behavior of the amine as a nucleophile or as a base could not be differentiated. Interestingly, the reaction of **8f** with (*S*)-(−)-phenylethylamine produced a 3:1 mixture of diastereomers **11** and **12**, which were separated by flash chromatography. The most abundant isomer, **11**, was then transformed through two conventional reductive steps, involving the removal of the carbonyl group by Raney Ni desulfurization of the corresponding dithiane **13** and of the chiral auxiliary of the derived **14** by hydrogenolysis, affording the quite popular natural target (−)-anabasine **15**. Its identity was confirmed by derivatization to the known *N*-(4-nitrobenzoyl) derivative and comparison of analytical data.[4] The synthetic sequence is depicted in the Scheme 4.



Scheme 4

As an example of double Michael addition initiated by a carbon-centered nucleophile serving as a tool for the construction of substituted cyclohexanone derivatives, a very interesting application is offered by the easy preparation of the nitrocyclohexanone **16**, a valuable precursor along the route to the alkaloid (±)-epibatidine **23**,[5a] as already reported in preliminary form (Scheme 5).[5b]

The choice of the base to form the nitronate anion has been demonstrated to be of crucial importance: the best results were obtained using KF in THF/H_2O at room temperature. Use of stronger bases was detrimental, with the fast formation of the divinylketone resulting in the formation of polymeric material. With the intermediate **16** in hand, its diastereoselective reduction by treatment with L-Selectride produced a mixture (7:3, HPLC) of diastereomeric secondary alcohols; these were esterified by standard chemistry to afford the corresponding mesylates **17** and **18**, which were separated by flash chromatography (see exp. section). Submitting the most abundant nitro-substituted mesylate **17** to ozonolysis and quenching the reaction mixture with $NaBH_4$, we were able to achieve a clean conver-



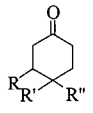
Scheme 5

sion of the nitro group into a hydroxy group, with complete retention of configuration of the center involved. The derived mesyloxy alcohol **19** underwent nucleophilic substitution with sodium azide to give the appropriate azido alcohol **20**, which was subsequently esterified to provide the azido mesylate **21**. Reduction of the latter with stannous chloride produced the amino mesylate **22**, which was heated in chloroform to give (±)-epibatidine **23**.

When the anions of diethyl malonate and ethyl cyanoacetate, generated using potassium *tert*-butoxide, were used as partners for the enones **8b** and **8f**, the substituted cyclohexanones **24a−c** were the reaction products (Table 2).

Table 2. Syntheses of cyclohexanones **24** from enones **8b**, **8f** and anions of diethyl malonate and ethyl cyanoacetate

Enone **8** R		Nucleophiles	Yield of **24** (%)	Time (h)
b	Ph	$(EtO_2C)_2CH^-$	60	48
f	3-Pyridyl	$(EtO_2C)_2CH^-$	71	24
		$EtO_2C(CN)CH^-$	85	24

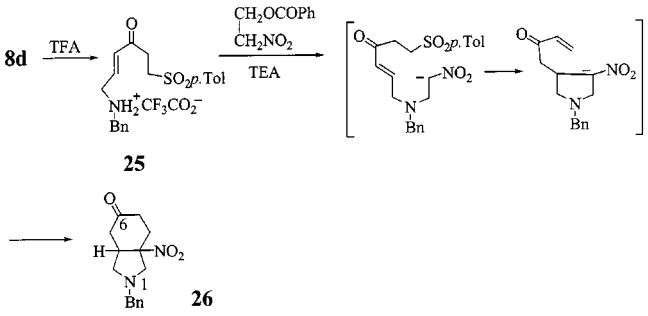


24

a: R = Ph; R' = R" = CO_2Et; **b**: R = 3-Pyridyl; R' = R" = CO_2Et; **c**: R = 3-Pyridyl; R' = CO_2Et; R" = CN

Triple Michael Reaction

An interesting extension of this chemistry is well exemplified by the one-step (homo-domino process) assemblage of a polycyclic system. Thus, the reaction between the unsaturated γ-keto sulfone **8d** and *O*-benzoyl-2-nitroethanol (which serves as a precursor of nitroethylene) proceeded at 60 °C over 24 h through three consecutive Michael additions, resulting in a single diastereoisomer of the substituted octahydroisoindolone **26** in 84% yield. The ring junction stereochemistry could not be assigned (Scheme 6).

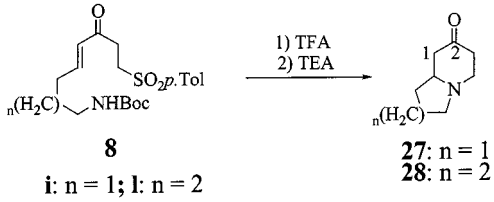


Scheme 6

In order that reaction could take place, it was necessary beforehand to remove the benzyloxycarbonyl protecting group from the nitrogen of **8d**, by treatment with trifluoroacetic acid. The corresponding base, freed from the trifluoroacetate salt **25** by treatment with triethylamine, added smoothly to nitroethylene, generated in turn from its precursor, initiating the first of three Michael additions.

Double Intramolecular Michael Addition

When the Michael donor was suitably positioned in the chain of the divinyl ketone precursor, an intramolecular Michael reaction could easily take place, furnishing substituted indolizidine and quinolizidine derivatives. Thus, successive treatment of **8i** and **8l** with trifluoroacetic acid and triethylamine, to free the amino groups, produced the indolizidinone **27** and the quinolizidone **28**, respectively (Scheme 7).



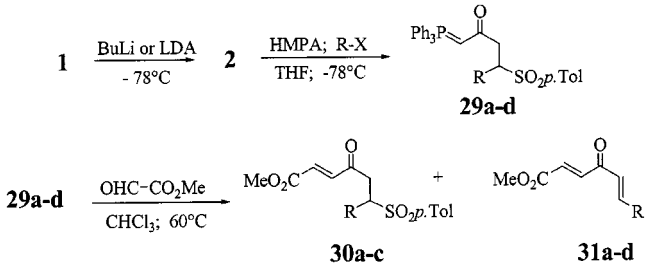
Scheme 7

Generation of the Anion 2

As anticipated, the ylide **1** can be deprotonated at the α-position of the sulfone moiety by treatment with strong bases, giving rise to a particularly reactive anion **2**. This is almost exclusively stabilized through inductive effects, the mesomeric effect being less important owing to the low contribution of the C=S of the sulfone moiety. Therefore, this anion may be considered as the kinetic anion of the phosphorane, thus allowing operations to be effected at the carbon atom activated by the sulfone group, rather than at that of the phosphorane. Thus, the anion **2** was easily generated by treatment of **1** with BuLi or LDA in THF at −78 °C. Its reactivity may be improved both by enhancing its nucleophilicity by addition of HMPA or/and TMEDA, or by enhancing the electrophilic potency of the partner by addition of Lewis acids.

Alkylation of 2

Treatment of **2** with different alkyl halides under the experimental conditions described above resulted in the formation of the alkylated products **29a−d**. These intermediates cannot be easily purified and were used without further purification in the subsequent Wittig reaction with methyl glyoxylate, affording a mixture of unsaturated γ-keto sulfones **30a−c** and divinyl ketones **31a−d**, easily separated by flash chromatography as indicated in Scheme 8. Table 3 summarizes the alkylating agents used and the yields obtained in these reactions.



a: R = Me; **b:** R = Et; **c:** R = Bn; **d:** R = $Me(CH_2)_9$

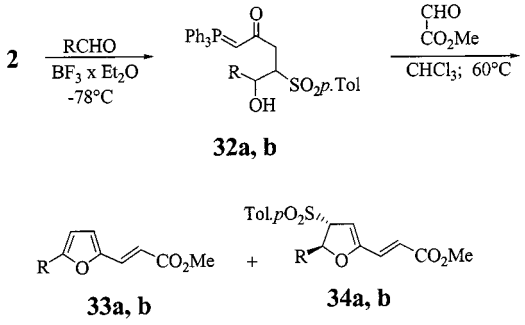
Scheme 8

Table 3. Alkyl halides used in the alkylation of anion **2**

RX	Product	Yield (%)
MeI	30a	36
	31a	36
EtBr	**30b**	34
	31b	43
BnBr	**30c**	46
	31c	37
$Me(CH_2)_9I$	**31d**	58

Aldol Condensation of 2

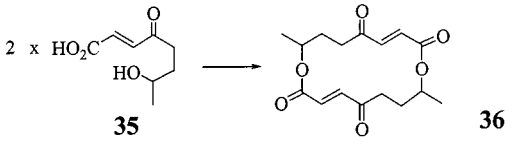
As a logical extension of the synthetic utility of the anion **2**, its reaction with aldehydes was next investigated. However, when this reaction was attempted under the experimental conditions already described for treatment of **2** with alkyl halides, no reaction took place. Aldol adducts could be obtained by adding one equivalent of boron trifluoride−diethyl ether, to enhance the electrophilic character of the carbonyl group, and quenching the reaction mixture (initially maintained at −78 °C) at −20 °C by adding water. Under these conditions, representative aldehydes such as ethanal and benzaldehyde produced the aldol adducts **32a** and **32b**, respectively; these were not isolated, but directly submitted to Wittig reaction with methyl glyoxylate to afford an easily separable mixture of furans **33a** and **33b**, and *trans*-dihydrofurans **34a** and **34b**,[6] in good yield (Scheme 9).



a: R = Me; **b**: R = Ph

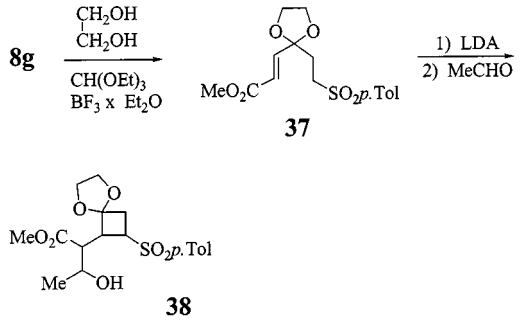
Scheme 9

These results paved the way to the development of a new approach to (±)-pyrenophorin[7] **36**, the macrolide antibiotic usually produced by dimerization of a suitably protected 7-hydroxy-4-oxo-2-octenoic acid (**35**, Scheme 10).



Scheme 10

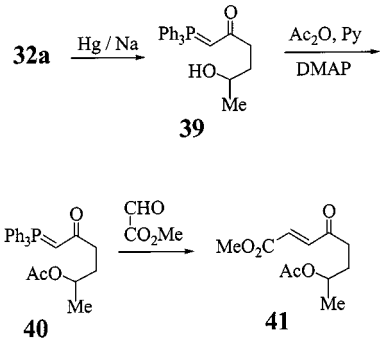
Considering that the heterocyclic derivatives **33a** and **34a** possessed the carbon atom framework and the functionalization of **35**, it became evident that a formal synthesis of **36** could easily be accomplished simply by avoiding their cyclization by protection of one of the two functions (the carbonyl or the hydroxyl group). To this end, the enone **8g** was transformed into the corresponding ketal **37** by treatment with ethylene glycol and triethyl orthoformate in the presence of boron trifluoride. Generation of the sulfonyl anion by treatment of **37** with LDA at −78 °C, followed by treatment with ethanal, resulted in the formation of the substituted cyclobutane derivative **38** as a complex diastereomeric mixture (Scheme 11).[8]



Scheme 11

Its formation could be accounted for trapping by ethanal of the anion originating from intramolecular Michael addition, since **37** remained unchanged in the absence of the electrophile. Therefore, we were forced to look at an alternative route, which began with the protection of the hydroxy

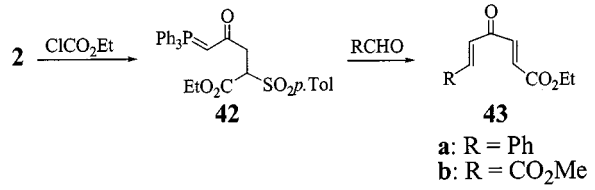
function of **39**, obtained by reductive desulfonylation of **32a** with sodium amalgam, to give the phosphorane **40**. This easily underwent Wittig reaction with methyl glyoxylate to give **41**: the protected hemipyrenophorin. The reaction sequence proceeded in 30% overall yield (Scheme 12).



Scheme 12

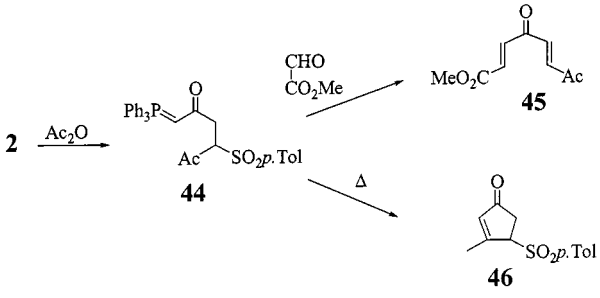
Acylation of 2

The anion **2**, generated using BuLi in the presence of TMEDA, underwent acylation with ethyl chloroformate to give **42**, which further reacted with benzaldehyde or methyl glyoxylate to produce dienones **43a** and **43b**, respectively (Scheme 13).



Scheme 13

The reaction of **2** with acetic anhydride gave rise to the initial formation of keto sulfone **44**, which, interestingly, could be transformed into the cyclopentenone derivative **46** by heating, the keto group being able successfully to undergo an intramolecular Wittig reaction, which had failed in the intermolecular version (Scheme 14). The keto sulfone **44** also reacted with methyl glyoxylate to give **45**.



Scheme 14

In conclusion, we have demonstrated that the readily available compound **1** can be considered as a convenient four-carbon synthon for substituted divinyl ketones, which are useful intermediates for the preparation of a wide variety of substituted carbo- or heterocyclic ring systems through a multiply convergent process centering, with great operational simplicity, on a three-step sequence initiated by reaction with a carbon- or nitrogen-centered nucleophile. We have also demonstrated that the highly functionalized carbon frameworks are particularly well suited for transformation into popular natural targets, allowing us to perform new formal syntheses of (±)-epibatidine, (−)-anabasine, and (±)-pyrenophorin.

Experimental Section

General Remarks: Melting points were determined on a Reichert−Kofler apparatus and are uncorrected. − Nuclear magnetic resonance spectra were recorded on a Bruker AC-200 spectrometer at 200 MHz (^{1}H NMR) or 50 MHz (^{13}C NMR) for solutions in $CDCl_3$, and chemical shifts are given in parts per million (δ) downfield from tetramethylsilane as an internal standard. Coupling constants are given in Hertz. − Infrared (IR) spectra were taken on a Perkin−Elmer model 297 and characteristic bands are in cm^{-1}. − Optical rotations [α] were determined using a Perkin−Elmer 241 polarimeter operating at 589 nm (sodium D line) at 20° C. Organic solutions were dried over anhydrous magnesium sulfate and evaporated using a rotary evaporator. Light petroleum refers to the fractions boiling in the range 40−60 °C, and ether to diethyl ether. − HPLC analysis was performed on a Bruker LC 313 UV variable wavelength detector. Recording and quantification were accomplished with an Epson computer system chromatographic data processor (QX-10). A Vydac C_{18} column (150 × 4.5 mm i.d., 5 μm particle size, flow rate 1 mL/min) was used. Analytical processes were carried out using a gradient made up of A = 10% acetonitrile in water and B = 60% acetonitrile in water, both containing 0.1% of TFA. A 25 min linear gradient was run from 0% to 50% of B, λ = 220 nm. Retention times (t_R) are reported in min. − Thin layer chromatography was performed using precoated plates of silica gel (Merck F-254), using the indicated solvent system. − Flash chromatography was carried out with Merck silica gel (230−400 mesh).

1-Bromo-4-[(4′-methylphenyl)sulfonyl]-2-butanone (4): To a solution of 4-[(4′-methylphenyl)sulfonyl]-2-butanone (**3**)[9] (4.344 g, 19.2 mmol) in glacial acetic acid (40 mL) was added pyridinium bromide perbromide (6.126 g, 19.2 mmol), and the stirred mixture was heated at 70 °C for 16 h. After removal of acetic acid in vacuum, the residual oil was purified by column chromatography (diethyl ether/light petroleum, 1:1) to give **4** and its regioisomer 3-bromo-4-[(4′-methylphenyl)sulfonyl]-2-butanone (**5**).

Compound 4: 3.981 g, 62%, white solid, m.p. 108−110 °C. − IR (nujol): $\tilde{\nu}$ = 1750, 1600, 1360, 1110 cm^{-1}. − ^{1}H NMR: δ = 2.48 (s, 3 H, CH_3), 3.17 (t, 2 H, J = 7 Hz, CH_2CO), 3.42 (t, 2 H, J = 7 Hz, CH_2S), 3.91 (s, 2 H, CH_2Br), 7.60 (dd, 4 H, Ph) (1.601 g, 27%). − ^{13}C NMR: δ = 21.7 (*C*C4′), 32.8, 33.8 (C1 and C3), 50.8 (C4), 128.0, 130.2, 135.7, 145.3 (C aromatic), 198.2 (C2). − $C_{11}H_{13}BrO_3S$ (305.1): calcd. C 43.29, H 4.29, Br 26.18, S 10.51; found C 43.16, H 4.31, Br 26.16, S 10.72.

Compound 5: 1.601 g, 27%, white solid, m.p. 78−80 °C. − ^{1}H NMR: δ = 2.32 (s, 3 H, CH_3), 2.48 (s, 3 H, CH_3Ph), 3.55 (dd, 1 H, J = 14.4 and 4 Hz, CHS), 4.15 (dd, 1 H, J = 14.4 and 9 Hz, CHS), 4.72 (dd, 1 H, J = 4 and 9 Hz, CHBr), 7.65 (dd, 4 H, Ph). − ^{13}C NMR: δ = 21.6 (*C*C4′), 31.2 (C1), 37.3 (C3), 50.8 (C4), 128.2, 130.3, 135.7, 145.9 (C aromatic), 192.5 (C2).

{4-[(4′-Methylphenyl)sulfonyl]-2-oxobutyl}triphenylphosphonium Bromide (6): A solution of 1-bromo-4-[(4′-methylphenyl)sulfonyl]-2-butanone (**4**) (4.119 g, 13.05 mmol) and triphenylphosphane

(3.422 g, 13.05 mmol) in dry benzene (100 mL) was stirred at 40 °C for 6 hours. The precipitated phosphonium salt **6** was collected by filtration as a white solid, m.p. 133° C (6.569 g, 92%). − IR (nujol): $\tilde{\nu}$ = 1710, 1600, 1360, 1110 cm^{-1}. − ^1H NMR: δ = 2.41 (s, 3 H, CH_3), 3.45−3.60 (m, 4 H, CH_2CO and CH_2S), 6.02 (d, 2 H, J = 12 Hz, CH_2P), 7.33−8.01 (m, 19 H, Ph). − ^{13}C NMR: δ = 21.5 (C5), 37.7 (d, J_{P-C3} = 7.2 Hz, C3), 38.4 (d, J_{P-C1} = 59 Hz, C1), 50.7 (C4), 118.1 (d, J = 88.4 Hz, CP aromatic), 127.9, 129.9, 130.1, 133.9, 134.7, 135.4, 144.8 (C aromatic), 198.9 (d, J_{P-C2} = 11.9 Hz, C2). − $C_{29}H_{28}BrO_3PS$ (567.5): calcd. C 61.38, H 4.97, Br 14.08, P 5.46, S 5.65; found C 61.29, H 4.86, Br 14.31, P 5.45, S 5.65.

4-[(4′-Methylphenyl)sulfonyl]-1-(triphenylphosphoranylidene)-2-butanone (1): To a cooled (0 °C) solution of the phosphonium salt **6** (3.178 g, 5.4 mmol) in methanol (20 mL) was added, drop by drop with stirring, a solution of sodium hydroxide in water (12% w/v) until pH = 8−9 was reached. Water (100 mL) was added and the precipitated phosphorane **1** (2.988 g, 88.5%) collected by filtration as white solid, m.p. 163−165 °C. − IR (nujol): $\tilde{\nu}$ = 1710, 1600, 1350, 1120 cm^{-1}. − ^1H NMR: δ = 2.42 (s, 3 H, CH_3), 2.69−2.71 (m, 2 H, CH_2CO), 3.42−3.50 (m, 2 H, CH_2S), 3.72 (d, 1 H, J = 24 Hz, HC=P), 7.30−7.89 (m, 19 H, 4 Ph). − ^{13}C NMR: δ = 21.5 (CH_3), 33.6 (d, J_{P-C3} = 16.7 Hz, C3), 51.8 (d, J_{P-C1} = 105.6 Hz, C1), 53.7 (C4), 126.4 (d, J = 90.5 Hz, CP aromatic), 128.1, 128.9, 129.7, 132.2, 133.0, 136.4, 144.8 (C aromatic), 187.3 (d, J_{P-C2} = 10 Hz, C2). − $C_{29}H_{27}O_3PS$ (486.6): calcd. C 71.59, H 5.59, P 6.37, S 6.59; found C 72.01, H 5.50, P 6.31, S 6.49.

Synthesis of 1-Substituted 5-[(4′-Methylphenyl)sulfonyl]-1-penten-3-ones (8a−l). − General Procedure: A mixture of the ylide **1** (5 mmol) and aldehyde **7a−h** (5 mmol) was heated in the appropriate solvent (15 mL) for the required time (see Table 1). At the end of the reaction (monitored by TLC), the solvent was removed under reduced pressure and the residual oil purified by flash column chromatography.

1-[(4′-Methylphenyl)sulfonyl]-4-hexen-3-one (8a): From **1** and **7a**. Solid, m.p. 74−77 °C. Eluent: ethyl acetate/cyclohexane, 1:1. − IR (nujol): $\tilde{\nu}$ = 1655, 1620, 1590, 1350, 1130 cm^{-1}. − ^1H NMR: δ = 1.91 (m, 3 H, CH_3), 2.37 (s, 3 H, CH_3Ph), 2.95 (t, 2 H, J = 7.9 Hz, CH_2CO), 3.32 (t, 2 H, J = 7.9 Hz, CH_2S), 6.00 (dq, 1 H, J = 1.5 and 15.9 Hz, HC=C), 6.88 (dq, 1 H, J = 6.8 and 15.9 Hz, HC=C), 7.39 (d, 2 H, J = 8 Hz, Ph), 7.82 (d, 2 H, J = 8 Hz, Ph). − ^{13}C NMR: δ = 18.2 (C6), 20.8 (*C*C4′), 31.1 (C2), 50.6 (C1), 125.1, 128.0, 128.5, 129.1, 130.0, 130.1, 134.0, 136.1, 143.9, 144.8 (C aromatic, C4, C5), 195.3 (C3). − $C_{13}H_{16}O_3S$ (252.3): calcd. C 61.88, H 6.39, S 12.71; found C 61.65, H 6.23, S 12.79.

5-[(4′-Methylphenyl)sulfonyl]-1-phenyl-1-penten-3-one (8b): From **1** and **7b**. Solid, m.p. 162−165 °C (ref.[10]: 147−149 °C). Eluent: ethyl acetate/cyclohexane, 1:2. − IR (nujol): $\tilde{\nu}$ = 1655, 1620, 1590, 1350, 1110 cm^{-1}. − ^1H NMR: δ = 2.45 (s, 3 H, CH_3), 3.21 (t, 2 H, J = 8 Hz, CH_2CO), 3.45 (t, 2 H, J = 8 Hz, CH_2S), 6.69 (d, 1 H, J = 16 Hz, HC=C), 7.37−7.87 (m, 10 H, Ph and HC=C). − ^{13}C NMR: δ = 21.7 (*C*C4′), 33.2 (C4), 51.0 (C5), 126.2, 126.5, 127.1, 128.9, 132.2, 135.0, 135.2, 141.6, 143.6 (C aromatic, C1, C2), 198.2 (C3). − $C_{18}H_{18}O_3S$ (252.3): calcd. C 68.76, H 5.77, S 11.20; found C 68.61, H 5.50, S 11.38.

1-[(4′-Methylphenyl)sulfonyl]-4-tetradecen-3-one (8c): From **1** and **7c**. Oil. Eluent: ethyl acetate/cyclohexane, 1:3. − IR (nujol): $\tilde{\nu}$ = 1670, 1625, 1600, 1320, 1150 cm^{-1}. − ^1H NMR: δ = 0.85 (t, 3 H, J = 6.3 Hz, CH_3), 1.18−1.65 (m, 14 H, aliphatic chain), 2.21 (q, 2 H, J = 6.6 Hz, aliphatic chain), 2.44 (s, 3 H, CH_3Ph), 3.01 (t, 2 H, J = 8 Hz, CH_2CO), 3.38 (t, 2 H, J = 8 Hz, CH_2S), 6.06 (d, 1 H, J = 16 Hz, HC=CCO), 6.85 (dt, 1 H, J = 16 and 6.6 Hz, HC=C), 7.34−7.77 (m, 2 H, Ph). − ^{13}C NMR: δ = 15.2, 22.0, 29.9, 30.1, 30.3, 30.5, 30.6, 30.9, 31.8, 32.3, 32.8 (C2, C6, C7, C8, C9, C10, C11, C12, C13, C14, *C*C4′), 47.9 (C1), 122.3, 129.9, 137.8, 140.0, 142.9, 146.1 (C aromatic, C4, C5), 197.7 (C3). − $C_{21}H_{32}O_3S$ (364.3): calcd. C 69.19, H 8.85, S 8.80; found C 68.95, H 8.83, S 8.91.

6-[Benzyl(*tert*-butoxycarbonyl)amino]-1-[(4′-methylphenyl)sulfonyl]-4-hexen-3-one (8d): From **1** and **7d**.[11] Oil. Eluent: ethyl acetate/cyclohexane, 1:3. − IR (nujol): $\tilde{\nu}$ = 1690, 1630, 1590, 1320, 1150 cm^{-1}. − ^1H NMR: δ = 1.46 (s, 9 H, CH_3), 2.42 (s, 3 H, CH_3Ph), 2.96 (t, 2 H, J = 8 Hz, CH_2), 3.36 (t, 2 H, J = 8 Hz, CH_2), 3.94 (m, 2 H, CH_2), 4.38 (m, 2 H, CH_2), 6.03 (d, 1 H, J = 16 Hz, HC=CCO), 6.62 (dt, 1 H, J = 16 and 5 Hz, HC=C), 7.16−7.85 (m, 9 H, Ph). − ^{13}C NMR: δ = 21.3 (*C*C4′), 28.2 (3 CH_3), 32.1 (C2), 49.9, 51.3, 52.6 (C1, CN, CN), 71.8 (CO), 125.9, 126.7, 128.2, 128.5, 129.0, 131.2, 136.0, 137.0, 140.8, 143.6 (C aromatic, C4, C5), 160.2 (C=O urethane), 197.5 (C3). − $C_{25}H_{31}NO_5S$ (457.6): calcd. C 65.62, H 6.83, N 3.06, S 7.01; found C 65.83, H 6.90, N 3.01, S 6.87.

1-[3′-(6′-Chloro)pyridyl]-5-[(4′-methylphenyl)sulfonyl]-1-penten-3-one (8e): From **1** and **7e**. Solid, m.p. 138−140 °C. Eluent: ethyl acetate. − IR (nujol): $\tilde{\nu}$ = 1655, 1620, 1590, 1575, 1550, 1350, 1150 cm^{-1}. − ^1H NMR: δ = 2.48 (s, 3 H, CH_3), 3.20 (t, 2 H, J = 6 Hz, CH_2CO), 3.45 (t, 2 H, J = 6 Hz, CH_2S), 6.75 (d, 1 H, J = 16.2 Hz, HC=C), 7.40 (d, 1 H, J = 7.2 Hz, HC=C), 7.41 (d, 2 H J = 8 Hz, Ph), 7.55 (d, 1 H, J = 16.2 Hz, pyridine), 7.8 (d, 2 H, J = 8 Hz, Ph), 7.81 (d, 1 H, J = 7.2 Hz, pyridine), 8.53 (d, 1 H, J = 2.4 Hz, pyridine). − ^{13}C NMR: δ = 21.1 (*C*C4′), 32.9 (C4), 50.7 (C5), 122.6, 126.5, 129.1, 130.8, 134.4, 134.7, 136.1, 142.5, 150.1, 150.7, 152.8 (C aromatic, C1, C2), 199.9 (C3). − $C_{17}H_{16}ClNO_5S$ (381.8): calcd. C 58.37, H 4.61, Cl 10.13, N 4.00, S 9.17; found C 58.13, H 4.56, Cl 10.12, N 3.92, S 3.38.

5-[(4′-Methylphenyl)sulfonyl]-1-(3′-pyridyl)-1-penten-3-one (8f): From **1** and **7f**. Solid, m.p. 113−115 °C. Eluent: ethyl acetate/cyclohexane, 1:1. − IR (nujol): $\tilde{\nu}$ = 1675, 1630, 1600, 1580, 1325, 1150 cm^{-1}. − ^1H NMR: δ = 2.46 (s, 3 H, CH_3), 3.20 (t, 2 H, J = 7 Hz, CH_2CO), 3.47 (t, 2 H, J = 7 Hz, CH_2S), 6.78 (d, 1 H, J = 16.4 Hz, HC=C), 7.35 (d, 2 H, J = 8 Hz, HC=C, Ph), 7.55 (d, 1 H, J = 16.4 Hz, pyridine), 7.65 (m, 1 H, pyridine), 7.82 (d, 2 H, J = 8, Ph), 7.9 (m, 1 H, pyridine), 8.63 (dd, 1 H, J = 5 and 1.4, pyridine), 8.76 (d, 1 H, J = 2 Hz, pyridine). − ^{13}C NMR: δ = 19.1 (*C*C4′), 30.9 (C4), 50.6 (C5), 124.0, 125.5, 131.7, 131.9, 134.9, 135.5, 135.7, 141.2, 143.5, 148.8, 149.9 C aromatics and C1, C2), 199.3 (C3). − $C_{17}H_{17}NO_3S$ (315.4): calcd. C 64.74, H 5.43, N 4.44, S 10.17; found C 64.89, H 5.36, N 4.49, S 10.52.

Methyl 6-[(4′-Methylphenyl)sulfonyl]-4-oxo-2-hexenoate (8g): From **1** and **7g**. Solid, m.p. 105−106 °C. Eluent: ethyl acetate/cyclohexane, 2:1. − IR (nujol): $\tilde{\nu}$ = 1720, 1680, 1640, 1600, 1320, 1150 cm^{-1}. − ^1H NMR: δ = 2.46 (s, 3 H, CH_3), 3.09 (t, 2 H, J = 7 Hz, CH_2CO), 3.43 (t, 2 H, J = 7 Hz, CH_2S), 3.82 (s, 3 H, CH_3O) 6.69 (d, 1 H, J = 16.2 Hz, HC=C), 7.04 (d, 1 H, J = 16.2 Hz, HC=C), 7.38 (d, 2 H, J = 8 Hz, Ph), 7.79 (d, 2 H, J = 8 Hz, Ph). − ^{13}C NMR: δ = 20.1 (*C*C4′), 31.2 (C2), 49.9, 50.4 (C1 and CO), 122.8, 126.6, 130.8, 131.0, 143.4, 145.8 (C aromatic, C2, C3), 163.2 (C1), 197.5 (C1). − $C_{14}H_{16}O_5S$ (296.3): calcd. C 56.74, H 5.44, S 10.82; found C 56.89, H 5.44, N 4.49, S 10.43.

1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-5-[(4′-methylphenyl)sulfonyl]-1-penten-3-one (8h): From **1** and **7h**.[12] Solid, m.p. 74−73 °C. Eluent: ethyl acetate/cyclohexane, 1:1. − $[\alpha]_D^{20}$ = +23.6 (c = 0.55, $CHCl_3$,). − IR (nujol): $\tilde{\nu}$ = 1670, 1630, 1590, 1320, 1150 cm^{-1}. − ^1H NMR:

δ = 1.41 (s, 3 H, CH_3 dioxolane), 1.45 (s, 3 H, CH_3 dioxolane), 2.46 (s, 3 H, *CH*$_3$Ph), 3.07 (t, 2 H, *J* = 8 Hz, CH_2CO), 3.40 (t, 2 H, *J* = 8 Hz, CH_2S), 4.20 (m, 1 H, dioxolane), 4.45 (m, 1 H, dioxolane), 4.67 (m, 1 H, dioxolane), 6.38 (dd, 1 H, *J* = 17 and 3 Hz, HC=C), 6.8 (dd, 1 H, *J* = 17 and 4.5 Hz, HC=C), 7.3 (d, 2 H, *J* = 8 Hz, Ph), 7.8 (d, 2 H, *J* = 8 Hz, Ph). − ^{13}C NMR: δ = 21.6 (*C*C4′), 25.6, 26.4 (2 CH_3), 33.1 (C4), 50.6 (C5), 68.6 (CO), 74.7 (CO), 110.3 (OCO), 127.9, 128.9, 130.0, 135.8, 144.1, 150.2 (C aromatic, C1, C2), 194.7 (C3). − $C_{17}H_{22}O_5S$ (338.4): calcd. C 60.33, H 6.55, S 9.48; found C 60.35, H 6.51, S 9.44.

8-[(*tert*-Butoxycarbonyl)amino]-1-[(4′-methylphenyl)sulfonyl]-4-octen-3-one (8i): From **1** and **7i**.[13] Oil. Eluent: ethyl acetate/cyclohexane, 1:2. − IR (neat): ṽ = 3350, 1750, 1690, 1600, 1321, 1120 cm^{-1}. − ^{1}H NMR: δ = 1.55 (s, 9 H, 3 CH_3 of Boc), 1.58−69 (m, 2 H, CH_2), 2.19−2.36 (m, 2 H, CH_2), 2.46 (s, 3 H, CH_3), 2.81−2.99 (m, 2 H, CH_2), 3.13 (t, 2 H, *J* = 7.5 Hz, CH_2), 3.45 (t, 2 H, *J* = 7.5 Hz, CH_2), 4.69 (br. s, 1 H, NH), 6.00 (dt, 1 H, *J* = 16 and 3 Hz, HC=C), 6.82 (dt, 1 H, *J* = 16 and 5.4, HC=C), 7.47 (d, 2 H, *J* = 8 Hz, Ph), 7.86 (d, 2 H, *J* = 8 Hz, Ph). − ^{13}C NMR: δ = 20.7 (CC4′), 28.6, (3 CH_3), 30.0, 31.5, 32.9 (C2, C6, C7), 43.4 (C8), 50.0 (C1), 71.1 CO), 125.8, 127.4, 130.5, 136.7, 142.6, 142.8 (C aromatic, C4, C5), 159.9 (CO urethane), 198.3 (C3). − $C_{20}H_{29}NO_5S$ (395.5): calcd. C 60.73, H 7.39, N 3.54, S 8.11; found C 60.91, H 7.52, N 3.61, S 9.01.

9-[(*tert*-Butoxycarbonyl)amino]-1-[(4′-methylphenyl)sulfonyl]-4-nonen-3-one (8l): From **1** and **7l**.[14] Oil. Eluent: ethyl acetate/cyclohexane, 1:2. − IR (neat): ṽ = 3300, 1750, 1700, 1600 cm^{-1}. − ^{1}H NMR: δ = 1.51 (s, 9 H, 3 CH_3 of Boc), 1.48−1.52 (m, 4 H, CH_2), 2.00−2.10 (m, 2 H, CH_2), 2.46 (s, 3 H, CH_3), 2.89−2.98 (m, 2 H, CH_2), 3.10 (t, 2 H, *J* = 8 Hz, CH_2), 3.40 (t, 2 H, *J* = 8 Hz, CH_2), 4.61 (br. s, 1 H, NH), 6.0 (dt, 1 H, *J* = 16 and 2.7 Hz, HC=C), 6.88 (dt, 1 H, *J* = 16 and 5.2 Hz, HC=C), 7.41 (d, 2 H, *J* = 8 Hz, Ph), 7.85 (d, 2 H, *J* = 8 Hz, Ph). − ^{13}C NMR: δ = 20.6 (CC4′), 28.4, (3 CH_3), 27.5, 30.2, 30.5, 33.0 (C2, C6, C7, C8), 43.9 (C9), 50.8 (C1), 71.0 CO), 123.5, 126.9, 130.3, 137.1, 142.6, 142.9 (C aromatic, C4, C5), 159.7 (CO urethane), 198.8 (C3). − $C_{21}H_{31}NO_5S$ (409.5): calcd. C 61.59, H 7.63, N 3.42, S 7.83; found C 61.71, H 7.85, N 3.54, S 7.51.

Synthesis of *N*,2-Substituted Piperidones 10a, 10c, 10f, 10h, 11, 12. − General Procedure: A mixture of γ-keto sulfone **8** (0.4 mmol) and benzylamine or (*S*)-(−)-*N*-1-phenylethylamine (0.8 mmol) in THF (10 mL) was stirred at 25 °C for 15−20 h. At the end of the reaction (monitored by TLC), the solvent was removed under reduced pressure, and the residual oil dissolved in ethyl acetate and washed with aqueous $NaHCO_3$. After the usual workup, the product was purified by column flash chromatography.

***N*-Benzyl-2-methyl-4-piperidone (10a):** Oil. Yield 75%. Eluent: ethyl acetate/cyclohexane, 1:1. − IR (neat): ṽ = 1710, 1655, 1600, 1590, 1545, 1490 cm^{-1}. − ^{1}H NMR: δ = 1.17 (d, 3 H, *J* = 6.4 Hz, CH_3CN), 2.28−2.39 (m, 3 H, piperidine), 2.51−2.56 (m, 2 H, piperidine), 2.95−3.01 (m, 2 H, piperidine), 3.43 (d, 1 H, *J* = 13.3 Hz, CH_2Ph), 3.95 (d, 1 H, *J* = 13.3 Hz, CH_2Ph), 7.28−7.36 (m, 5 H, Ph). − ^{13}C NMR: δ = 13.0 (CH_3), 40.9, 46.2, 47.5, 48.4, 55.6 (C2, C3, C5, C6, CN), 126.9, 128.3, 129.9, 137.4 (C aromatic), 208.1 (C4). − $C_{13}H_{17}NO$ (203.1): calcd. C 76.81, H 8.43, N 6.89; found C 77.05, H 8.53, N 6.99.

***N*-Benzyl-2-nonyl-4-piperidone (10c):** Oil. Yield 65%. Eluent: ethyl acetate/cyclohexane, 1:3. − IR (neat): ṽ = 1710, 1655, 1600, 1590, 1545, 1490 cm^{-1}. − ^{1}H NMR: δ = 0.87 (t, 3 H, *J* = 6.2 Hz, CH_3), 1.10−1.51 (m, 16 H, piperidine and aliphatic chain), 2.28−2.44 (m, 3 H, piperidine and aliphatic chain), 2.52−2.80 (m, 2 H, piperidine and aliphatic chain), 2.89−3.18 (m, 2 H, piperidine and aliphatic chain) 3.62 (d, 1 H, *J* = 13.3 Hz, CH_2Ph), 3.87 (d, 1 H, *J* = 13.3 Hz, CH_2Ph), 7.25−7.34 (m, 5 H, Ph). − ^{13}C NMR: δ = 14.2, 20.1, 23.4, 29.3, 29.4, 29.6, 30.0, 33.3, 34.2 (2-nonyl), 45.0, 47.3, 47.4, 53.1, 57.9 (C2, C3, C5, C6, CN), 127.8, 128.0, 130.1, 137.8 (C aromatic), 207.1 (C4). − $C_{21}H_{33}NO$ (315.5): calcd. C 79.95, H 10.54, N 4.44; found C 79.60, H 10.22, N 4.51.

***N*-Benzyl-2-[3′-(6′-chloro)pyridyl]-4-piperidone (10e):** Oil. Yield 55%. Eluent: ethyl acetate. − IR (neat): ṽ = 1711, 1605, 1573, 1482 cm^{-1}. − ^{1}H NMR: δ = 2.33−2.51 (m, 1 H, piperidine), 2.60−2.81 (m, 1 H, piperidine), 2.89 (dd, 1 H, *J* = 17.1 and 7.4 Hz, piperidine), 3.15 (dd, 1 H, *J* = 17.2 and 5.5 Hz, piperidine), 3.37 (d, 1 H, *J* = 13.0 Hz, CH_2Ph), 3.60 (dd, 1 H, *J* = 15.6 and 2.2 Hz, piperidine), 3.83 (d, 1 H, *J* = 13.0 Hz, CH_2Ph), 4.13 (dd, 1 H, *J* = 15.5 and 2.1 Hz, piperidine), 4.22 (dd, 1 H, *J* = 7.5 and 5.4 Hz, piperidine), 7.22−7.59 (m, 5 H, Ph), 7.68−7.98 (m, 2 H, pyridine), 8.56−8.88 (m, 2 H, pyridine). − ^{13}C NMR: δ = 43.1, 45.9, 50.1, 55.5, 56.7 (C2, C3, C5, C6, CN), 122.0, 123.8, 126.2, 128.1, 129.5, 137.1, 151.3, 152.3, 158.6 (C aromatic), 209.3 (C4). − $C_{17}H_{17}ClN_2O$ (300.8): calcd. C 67.88, H 5.70, Cl 11.79, N 9.30; found C 68.00, H 5.89, Cl 11.63, N 9.44.

***N*-Benzyl-2-(3-pyridyl)-4-piperidone (10f):** Oil. Yield 50%. Eluent: ethyl acetate. − IR (neat): ṽ = 1710, 1600, 1570, 1490 cm^{-1}. − ^{1}H NMR: δ = 2.35−2.46 (m, 1 H, piperidine), 2.68−2.79 (m, 1 H, piperidine), 2.99 (dd, 1 H, *J* = 17.3 and 7.5 Hz, piperidine), 3.05 (dd, 1 H, *J* = 17.6 and 5.6 Hz, piperidine), 3.35 (d, 1 H, *J* = 13.3 Hz, CH_2Ph), 3.66 (dd, 1 H, *J* = 15.5 and 2 Hz, piperidine), 3.76 (d, 1 H, *J* = 13.3, CH_2Ph), 4.05 (dd, 1 H, *J* = 15.5 and 2 Hz, piperidine), 4.16 (dd, 1 H, *J* = 7.5 and 5.6, piperidine), 7.25−7.54 (m, 5 H, Ph), 7.71−8.01 (m, 2 H, pyridine), 8.56−8.77 (m, 2 H, pyridine). − ^{13}C NMR: δ = 41.3, 43.9, 49.5, 49.9, 61.9 (C2, C3, C5, C6, CN), 124.1, 126.6, 128.0, 128.2, 133.9, 138.1, 142.8, 149.0, 149.9 (C aromatic), 207.7 (C4). − $C_{17}H_{18}N_2O$ (266.3): calcd. C 76.66, H 6.81, N 10.52; found C 77.00, H 6.99, N 10.41.

1-Benzyl-2-(2,2-dimethyl-1,3-dioxolan-4-yl)-4-piperidone (10h): Oil. Overall yield 76%. Eluent: ethyl acetate/cyclohexane, 1:2. − IR (nujol): ṽ = 1720, 1655, 1600, 1590, 1545, 1490 cm^{-1}. − Diastereomer with higher R_f. Yield 27%. − $[\alpha]_D^{20}$ = +3.9 (*c* = 2.7, $CHCl_3$). − ^{1}H NMR: δ = 1.34 (s, 3 H, CH_3 dioxolane), 1.41 (s, 3 H, CH_3 dioxolane), 2.19 (dd, 1 H, *J* = 5.56 and 14.7 Hz, piperidine and dioxolane), 2.33−2.58 (m, 2 H, piperidine and dioxolane), 2.61 (dd, 1 H, *J* = 5.5 and 14.7 Hz, piperidine and dioxolane), 2.80−2.85 (dt, 1 H, *J* = 6.5 and 12.7 Hz, piperidine and dioxolane), 3.17 (m, 2 H, piperidine and dioxolane), 3.70 (t, 1 H, *J* = 7.8 Hz, piperidine and dioxolane), 3.82 (d, 1 H, *J* = 13.8 Hz, piperidine and dioxolane), 3.99 (t, 1 H, *J* = 6.5 Hz, piperidine and dioxolane), 4.32 (q, 1 H, *J* = 6.5 Hz, piperidine and dioxolane), 7.25−7.41 (m, 5 H, Ph). − Diastereoisomer with lower R_f. Yield 49%. − $[\alpha]_D^{20}$ = −8.79 (*c* = 6.5, $CHCl_3$). − ^{1}H NMR: δ = 1.28 (s, 3 H, dioxolane), 1.32 (s, 3 H, dioxolane), 2.29−2.51 (m, 4 H, piperidine and dioxolane), 2.95 (m, 1 H, piperidine and dioxolane), 3.07−3.15 (m, 2 H, piperidine and dioxolane), 3.58 (dd, 1 H *J* = 7 and 8.3 Hz, piperidine and dioxolane), 3.85 (s, 2 H, piperidine and dioxolane), 4.0 (dd, 1 H, *J* = 7 and 8.3 Hz, piperidine and dioxolane), 4.30 (dt, 1 H, *J* = 7 and 4.4 Hz, piperidine and dioxolane), 7.25−7.41 (m, 5 H, Ph). − ^{13}C NMR: δ = 25.3, 26.1 (2 CH_3), 39.8, 44.0, 47.1, 50.6, 56.5 (C2, C3, C5, C6, CN), 70.7, 80.3 (2 CO), 102.9 (COC), 126.6, 128.5, 129.4, 139.8 (C aromatic), 206.5 (C4). − $C_{17}H_{23}NO_3$ (289.2): calcd. C 70.56, H 8.01, N 4.84; found C 70.58, H 8.12, N 4.85.

(2*R*/*S*)-*N*-[(1*S*)-1-Phenylethyl]-2-(3-pyridyl)-4-piperidones (11 and 12): From (*S*)-(−)-*N*-1-phenylethylamine. Overall yield 70%. Elu-

ent: ethyl acetate/cyclohexane, 9:1. − IR (nujol): $\tilde{\nu}$ = 1710, 1590, 1570, 1490 cm^{-1}.

11 (diastereomer with higher R_f): ^1H NMR: δ = 1.33 (d, 3 H, *J* = 6.8 Hz, CH_3), 2.31−2.92 (m, 5 H, piperidine and *CH*Ph), 2.99−3.15 (m, 1 H, piperidine and *CH*Ph), 4.00 (q, 1 H, *J* = 6.8 Hz, piperidine and *CH*Ph), 4.16 (dd, 1 H, *J* = 9 and 4.5 Hz, piperidine and *CH*Ph), 7.23−7.64 (m, 6 H, Ph and pyridine), 7.95 (m, 1 H, pyridine), 8.65 (m, 1 H, pyridine), 8.75 (m, 1 H, pyridine). − ^{13}C NMR: δ = 10.2 (CH_3), 41.4, 43.8, 49.1, 55.3, 61.8 (C2, C3, C5, C6, CN), 123.9, 126.9, 127.2, 128.2, 134.7, 137.6, 143.2, 149.1, 149.3 (C aromatic), 207.8 (C4). − $C_{18}H_{20}N_2O$ (280.2): calcd. C 77.11, H 7.19, N 9.99; found C 77.01, H 7.12, N 10.23.

12 (diastereomer with lower R_f): ^1H NMR: δ = 1.57 (d, 3 H, *J* = 6.6 Hz, CH_3), 2.39−2.81 (m, 4 H, piperidine and *CH*Ph), 2.84−2.93 (m, 1 H, piperidine and *CH*Ph), 3.30−3.38 (m, 1 H, piperidine and *CH*Ph), 3.95 (q, 1 H, *J* = 6.6 Hz, piperidine and *CH*Ph), 4.02−4.10 (m, 1 H, piperidine and *CH*Ph), 7.32−7.69 (m, 6 H, Ph and pyridine), 7.63−7.77 (m, 1 H, pyridine), 8.46−8.55 (m, 1 H, pyridine), 8.66−8.76 (m, 1 H, pyridine). − ^{13}C NMR: δ = 10.1 (CH_3), 41.8, 42.9, 49.1, 55.1, 61.0 (C2, C3, C5, C6, CN), 124.5, 127.0, 127.5, 128.1, 134.7, 137.4, 143.9, 149.3, 150.8, (C aromatic), 206.9 (C4).

Dithiolane 13: To a mixture of piperidone **11** (476 mg, 1.7 mmol) and ethane-1,2-dithiol (0.17 mL, 2.1 mmol) in CH_2Cl_2 (15 mL) containing 5-Å molecular sieves (1 g), was added $BF_3{\cdot}OEt_2$ (0.85 mL, 6.8 mmol) at 0 °C. After 1 h, the temperature was allowed to rise to 25 °C and the mixture was stirred for 12 h. The suspension was diluted with CH_2Cl_2 (25 mL), filtered, and washed consecutively with saturated, aqueous $NaHCO_3$ and H_2O. Workup yielded the dithiolane **13** in quantitative yield; it was used in the next step without further purification. − IR: $\tilde{\nu}$ = 1600, 1590, 1570, 1490 cm^{-1}. − ^1H NMR: δ = 1.25 (d, 3 H, *J* = 6.8 Hz, CH_3), 2.04−2.70 (m, 6 H, 3 CH_2), 3.11−3.44 (m, 4 H, CH_2), 3.69−3.98 (m, 2 H, CH_2), 7.25−7.67 (m, 6 H, Ph and pyridine), 7.88 (m, 1 H, pyridine), 8.54 (m, 1 H, pyridine), 8.74 (m, 1 H, pyridine). − ^{13}C NMR: δ = 12.1 (CH_3), 34.9 (2 CS), 38.8, 39.7, 40.1, 46.1, 50.0, 54.7 (C2, C3, C5, C6, CN), 57.1 (C4), 126.9, 128.0, 128.1, 129.8, 130.2, 136.9, 137.0, 138.4, 149.1 (C aromatic).

(2*S*)-*N*-[(1*S*)-1-Phenylethyl]-2-(3-pyridyl)-4-piperidine (14): Raney Ni (2 g) was added to a solution of the dithiolane **13** (519 mg, 1.6 mmol) in 15 mL of 95% ethanol, and the mixture was refluxed for 12 h. After this time, the suspension was filtered through Celite and concentrated in vacuo. The residual oil was diluted with ethyl acetate (25 mL) and washed with saturated, aqueous Na_2CO_3 and then with H_2O. Workup yielded the product **14** in quantitative yield; it was used in the next step without further purification. − IR: $\tilde{\nu}$ = 1600, 1590, 1570, 1490 cm^{-1}. − ^1H NMR: δ = 1.23 (d, 3 H, *J* = 7 Hz, CH_3), 1.25−1.85 (m, 6 H, 3 CH_2), 2.45−2.56 (m, 1 H), 3.30−3.33 (m, 1 H), 3.58−3.65 (m, 1 H), 3.96 (q, 1 H, *J* = 7 Hz), 7.20−7.60 (m, 6 H, Ph and pyridine), 7.82 (m, 1 H, pyridine), 8.45−8.61 (m, 1 H, pyridine), 8.65−8.74 (m, 1 H, pyridine). − ^{13}C NMR: δ = 11.6 (CH_3), 22.1, 26.9, (C4, C5), 33.1 (C3), 47.8, 52.4, 55.1 (C2, C5, CN), 127.0, 128.2, 128.9, 129.5, 130.3, 136.1, 136.4, 138.9, 149.7 (C aromatic).

(2*S*)-*N*-4′-Nitrobenzoyl-2-(3-pyridyl)piperidine (*N*-4′-nitrobenzoyl derivative of 15): $Pd(OH)_2$ (21 mg) was added to a solution of **14** (300 mg, 1.1 mmol) in 20 mL of methanol and the mixture was vigorously stirred under H_2 at 3.5 atm. in a Parr apparatus. The suspension was filtered through Celite and the filtrate concentrated in vacuo. A solution of the oily residue (156 mg) in CH_2Cl_2 (10 mL) was treated with Et_3N (2 mL) and 4-nitrobenzoyl chloride (370 mg, 2 mmol), and stirred at room temp. for 2 h. Additional CH_2Cl_2 (10 mL) was added and the organic layer was washed with H_2O. The crude product obtained upon workup was purified by flash chromatography (eluent: ethyl acetate) to afford the *N*-4′-nitrobenzoyl derivative of **15** as a white solid, m.p. 120−123 °C. − $[\alpha]_D^{20}$ = −125 (*c* = 1.3, MeOH) [ref.[4]: m.p. 127−128 °C, $[\alpha]_D^{20}$ = −130 (*c* = 3, MeOH)]. − $C_{10}H_{14}N_2$ (162.2): calcd. C 74.03, H 8.70, N 17.27; found C 73.99, H 8.70, N 17.25.

(3α,4β)-3-(6-Chloro-3-pyridyl)-4-nitrocyclohexan-1-one (16): Nitromethane (0.15 mL, 2.8 mmol) in THF (50mL) was added to a solution of **8g** (1 g, 2.8 mmol) containing a catalytic amount of KF (165 mg 0.28 mmol) dissolved in 1 mL of water, and the mixture was stirred for 72 h at 30 °C. The solvents were removed in vacuo, and the residue dissolved in ethyl acetate and washed with water. The crude product obtained upon workup was purified by flash chromatography (ethyl acetate/cyclohexane, 3:1) to give **16** (527 mg, 71%) as a solid, m.p. 120−121 °C. − IR (nujol): $\tilde{\nu}$ = 1720, 1590, 1550 cm^{-1}. − ^1H NMR: δ = 2.48−2.76 (m, 6 H, 3 CH_2), 3.73 (dt, 1 H, *J* = 5.7 and 11.4 Hz, CH), 5.02 (dt, 1 H, *J* = 11.4 and 2 Hz, $HCNO_2$), 7.34 (d, 1 H, *J* = 8.2 Hz, pyridine), 7.55 (dd, 1 H, *J* = 8.2 and 2.6, pyridine), 8.31 (d, 1 H, *J* = 2.6 Hz, pyridine). − ^{13}C NMR: δ = 22.1, 32.1, 36.9, 46.4 (C2, C3, C5, C6), 88.8 (CN), 123.5, 132.8, 138.1, 147.7, 150.8 (pyridine). − $C_{11}H_{11}ClN_2O_3$ (254.7): calcd. C 51.88, H 4.35, Cl 13.92, N 11.00; found C 52.13, H 4.66, Cl 14.50, N 10.55.

(1α,4α,2β)- and (1α,2β,4β)-3-(6-Chloro-3-pyridyl)-4-methylsulfonyloxy-1-nitrocyclohexane (17, 18): L-Selectride solution (1.0 M in THF, 1.74 mL) was added to a cooled (−78 °C) solution of the ketone **16** (578 mg, 2.27 mmol) in 30 mL of dry THF. After stirring for 0.5 h at −78 °C and 1.5 h at room temp., the mixture was evaporated in vacuo and the residue diluted with water and extracted with ethyl acetate. The dried organic layers were evaporated and the solid residue was utilized in the next step without purification. An HPLC analysis gave a diastereoisomer ratio of 7:3 (t_R = 13.27 and 13.66).

To a solution of this crude mixture (508 mg, 1.98 mmol) in CH_2Cl_2 (20 mL), were added Et_3N (0.33 mL, 2.38 mmol) and methanesulfonyl chloride (0.18 mL, 2.38 mmol) at −5 °C . After stirring for 0.5 h at room temp., the reaction mixture was washed with water. After adjusting the pH to 7, the aqueous phase was extracted once with CH_2Cl_2. The crude mixture of the diastereomeric mesylates was separated by flash chromatography (ethyl acetate/cyclohexane, 4:1) to yield **17** (362 mg, 47.6%) and **18** (155 mg, 20.4%).

Compound 17: White solid, m.p. 135−136 °C. − IR (KBr): $\tilde{\nu}$ = 1550, 1340, 1170 cm^{-1}. − ^1H NMR: δ = 1.71−2.02 (m, 2 H, CH_2), 2.24−2.55 (m, 4 H, 2 CH_2), 3.14 (s, 3 H, CH_3), 3.68−3.74 (m, 1 H, CH), 4.71−3.75 (m, 1 H, $HCNO_2$), 5.08−5.13 (m, 1 H, HCO), 7.23 (d, 1 H, *J* = 8.2 Hz, pyridine), 7.55 (dd, 1 H, *J* = 8.2 and 2.6 Hz, pyridine), 8.29 (d, 1 H, *J* = 2.6 Hz, pyridine). − ^{13}C NMR: δ = 25.8, 28.8, 36.6, 38.5 (C2, C3, C5, C6), 74.7, 88.4 (CO, CN), 124.5, 133.5, 137.6, 148.7, 150.8 (pyridine). − $C_{12}H_{15}ClN_2O_5S$ (334.8): calcd. C 43.05, H 4.52, N 8.37, S 9.58; found C 43.14, H 4.53, N 8.44, S 10.01.

Compound 18: White solid, m.p. 156−158 °C. − IR (KBr): $\tilde{\nu}$ = 1556, 1338, 1171 cm^{-1}. − ^1H NMR: δ = 1.65−1.95 (m, 2 H, CH_2), 2.04−2.48 (m, 4 H, 2 CH_2), 3.05 (s, 3 H, CH_3), 3.29−3.45 (m, 1 H, CH), 4.61−4.75 (m, 1 H, $HCNO_2$), 4.77−4.93 (m, 1 H, HCO), 7.31 (d, 1 H, *J* = 8.1 Hz, pyridine), 7.53 (dd, 1 H, *J* = 8.1 and 2.4 Hz, pyridine), 8.28 (d, 1 H, *J* = 2.4 Hz, pyridine). − ^{13}C NMR: δ = 26.7, 28.0, 37.0, 39.6 (C2, C3, C5, C6), 77.1, 86.3 (CO, CN), 124.2, 135.3, 138.9, 147.6, 153.3 (pyridine).

(1α,4α,2β)-2-(6-Chloro-3-pyridyl)-4-(methylsulfonyloxy)cyclohexan-1-ol (19): Ozone was bubbled at −78 °C for 1 h through a solution of **17** (535 mg, 1.6 mmol) and potassium *tert*-butoxide (187 mg, 1.6 mmol) in 10 mL of methanol. After this time, N_2 was passed through the solution to remove the excess of O_3 and dimethylsulfide (1.5 mL) was added, followed by 500 mg of $NaBH_4$. The temperature of the stirred mixture was slowly allowed to rise (3 h) to 20 °C. The methanol was removed in vacuo, the reaction mixture diluted with H_2O (5 mL) and extracted with ethyl acetate. After the usual workup, the alcohol **19** (380 mg, 80%) was obtained as a colorless oil by flash chromatography (ethyl acetate). − IR (neat): $\tilde{\nu}$ = 3300, 1330, 1160 cm^{-1}. − ^1H NMR: δ = 1.63−2.04 (m, 4 H, 2 CH_2), 2.21−2.27 (m, 2 H, CH_2), 2.85−2.96 (m, 1 H, CH), 3.02 (s, 1 H, OH), 3.07 (s, 3 H, CH_3), 3.55−3.75 (m, 1 H, HCO), 5.01−5.12 (m, 1 H, HCOMs), 7.26 (d, 1 H, *J* = 8.2 Hz, pyridine), 7.55 (dd, 1 H, *J* = 8.2 and 2.5 Hz, pyridine), 8.19 (d, 1 H *J* = 2.5 Hz, pyridine). − ^{13}C NMR: δ = 29.0, 29.8 (C5, C6), 36.9, 38.7, 43.2 (C2, C3, CH_3), 72.6, 76.7 (C1, C4), 124.3, 136.6, 138.4, 149.4, 149.7 pyridine). − $C_{12}H_{16}ClNO_4S$ (305.8): calcd. C 47.13, H 5.27, Cl 11.59, N 4.58, S 10.49; found C 47.89, H 5.55, Cl 12.00, N 4.23, S 10.52.

(1α,2β,4β)-4-Azido-2-(6-chloro-3-pyridyl)cyclohexan-1-ol (20):. A mixture of the alcohol **19** (428 mg, 1.4 mmol) in DMF (20 mL) and sodium azide (396 mg, 6.1 mmol) was stirred at 55 °C for 12 h. After removing the DMF in vacuum, the residual slurry was diluted with H_2O (7 mL) and extracted with ethyl acetate. After the usual workup, the azido derivative **20** (0.3 g, 90%) was purified by flash chromatography (ethyl acetate). − IR (neat): $\tilde{\nu}$ = 3300, 2100 cm^{-1}. − ^1H NMR: δ = 1.50−1.79 (m, 4 H, 2 CH_2, cyclohexane), 2.07−2.55 (m, 3 H, cyclohexane and OH), 2.59−2.65 (m, 1 H, cyclohexane), 3.41−3.66 (m, 1 H, cyclohexane), 3.69−3.81 (m, 1 H, cyclohexane), 7.28 (d, 1 H, *J* = 8.2 Hz, pyridine), 7.55 (dd, 1 H, *J* = 8.2 and 2.4 Hz, pyridine), 8.24 (d, 1 H *J* = 2.4 Hz, pyridine). − ^{13}C NMR: δ = 29.8, 29.9, 37.8, 44.5 (C2, C3, C5, C6), 50.5, 74.6 (C1, C4), 124.3, 133.1, 135.4, 137.0, 149.4 (pyridine). − $C_{11}H_{13}ClN_4O$ (252.7): calcd. C 52.28, H 5.19, Cl 14.03, N 22.17; found C 52.64, H 5.21, Cl 14.25, N 22.21.

(1α,2β,4β)-4-Azido-2-(6-chloro-3-pyridyl)-1-(methylsulfonyloxy)-cyclohexane (21): To a solution of **20** (303 mg, 1.2 mmol) and Et_3N (0.22 mL, l.6 mmol) in 10 mL of CH_2Cl_2 was added methanesulfonyl chloride (0.13 mL, 1.6 mmol) at −5 °C, and the reaction mixture was stirred at room temp. for 1 h. The mixture was washed with H_2O and, after the usual workup, the mesyl derivative **21** (360 mg, 89%) was obtained by flash chromatography (ethyl acetate) as a solid, m.p. 119−120 °C. − IR (KBr): $\tilde{\nu}$ = 2100 cm^{-1}. − ^1H NMR: δ = 1.22−1.86 (m, 3 H, cyclohexane), 2.15−2.29 (m, 3 H, cyclohexane), 2.49−2.58 (m, 1 H, cyclohexane), 2.52 (s, 3 H, CH_3, Ms), 2.83−2.94 (m, 1 H, CHN_3), 4.56 (dt, 1 H, *J* = 10.7 and 4.4 Hz, CHO), 7.36 (d, 1 H, *J* = 8.2 Hz, pyridine), 7.69 (dd, 1 H, *J* = 8.2 and 2.6 Hz, pyridine), 8.29 (d, 1 H, *J* = 2.4 Hz, pyridine). − ^{13}C NMR: δ = 29.7, 29.9, 37.6, 45.1 (C2, C3, C5, C6), 50.2, 71.1 (C1, C4), 122.9, 132.9, 135.5, 137.4, 149.0 (pyridine). − $C_{12}H_{15}ClN_4O_3S$ (330.8): calcd. C 43.57, H 4.57, Cl 10.72, N 16.94, S 9.69; found C 43.40, H 4.50, Cl 10.93, N 16.99, S 9.68.

(±)-Epibatidine 23: An excess of $SnCl_2 \cdot 2\,H_2O$ (2.2 g, 10 mmol) was added to a solution of **21** (0.33 g, 1 mmol) in methanol/THF, 1:1 (30 mL), and the reaction mixture was refluxed for 24 h. After cooling, the pH was adjusted to 9 with NH_4OH (37% in H_2O), and the reaction mixture was concentrated under reduced pressure and extracted with $CHCl_3$. The dried $CHCl_3$ solution of the amine **22** was refluxed for 20 h under argon to afford, after the usual workup and purification by flash chromatography ($CHCl_3$/MeOH/NH_4OH, 10:1:0.1), 193 mg (84%) of epibatidine **23** with spectral data in agreement with those in the literature.[5a]

Cyclohexanones 24a−c. − General Procedure: To a solution of **8a−c** (1 mmol) in freshly distilled THF (5 mL) was added the potassium salt of the corresponding anion (2 mmol), and the mixture was stirred at room temp. When **8** had disappeared (TLC), the mixture was evaporated in vacuo and the residue chromatographed with the pertinent eluent to give **24a−c** as oils. See Table 2. The potassium salts of diethyl malonate and ethyl cyanoacetate were prepared by adding an equimolecular amount of potassium *tert*-butoxide to a solution of the ester in *tert*-butyl alcohol. The salts were recovered by filtration as white solids in almost quantitative yield, washed with ether, dried, and used without further purification..

Ethyl 4-Oxo-2-phenyl-1,1-cyclohexanedicarboxylate (24a): From **8b** and potassium diethyl malonate. Eluent: Et_2O/petroleum ether, 1:2). Oil. Yield: 60%. − IR (neat): $\tilde{\nu}$ = 1717, 1740 cm^{-1}. − ^1H NMR: δ = 1.12 (t, 3 H, *J* = 7.2, CH_3), 1.25 (t, 3 H, *J* = 7.1 Hz, CH_3), 2.25−2.82 (m, 5 H, cyclohexane), 3.21 (dd, 1 H *J* = 6.4 and 15.3, cyclohexane), 3.91−4.12 (m, 3 H, OCH_2 and cyclohexane), 4.6 (q, 2 H, *J* = 7 Hz, OCH_2), 7.07−7.27 (m, 5 H, Ph). − ^{13}C NMR: δ = 11.4, 12.1 (2 CH_3), 23.4, 31.6, 36.9 40.0 (C2, C3, C5, C6), 58.4, 59.8, 63.4 (2 C−O, C1), 125.4, 127.9, 128.1, 138.1 (Ph), 175.2, 178.1 (2 C=O), 208.2 (C4). − $C_{18}H_{22}O_5$ (318.4): calcd. C 67.91, H 6.97; found C 67.95, H 7.11.

Ethyl 4-Oxo-2-(3-pyridyl)-1,1-cyclohexanedicarboxylate (24b): From **8f** and potassium diethyl malonate. Eluent: AcOEt/Et_2O, 1:1). Oil. Yield: 71%. − IR (neat): $\tilde{\nu}$ = 1717, 1738 cm^{-1}. − ^1H NMR: δ = 1.15 (t, 3 H, *J* = 7, CH_3), 1.22 (t, 3 H, *J* = 7, CH_3), 2.37−2.6 (m, 4 H, cyclohexane), 2.83 (dd, 1 H, *J* = 6.3 and 16.1 Hz, cyclohexane), 3.1 (dd, 1 H, *J* = 6.5 and 16.1 Hz, cyclohexane), 3.98−4.14 (m, 3 H, OCH_2 and cyclohexane), 4.24 (q, 2 H, *J* = 7 Hz, OCH_2), 7.20−7.26 (m, 1 H, pyridine), 7.50−7.55 (m, 1 H, pyridine), 8.39 (m, 1 H, pyridine), 8.5 (m, 1 H, pyridine). − ^{13}C NMR: δ = 11.9, 12.5 (2 CH_3), 22.9, 30.6, 37.1 41.1 (C2, C3, C5, C6), 58.4, 59.7, 63.6 (2 C−O, C1), 123.9, 138.6, 136.6, 146.5, 149.7 (pyridine), 174.3, 177.9 (2 C=O), 206.5 (C4). − $C_{17}H_{21}NO_5$ (319.4): calcd. C 63.94, H 6.63, N 4.39; found C 64.55, H 7.00, N 4.23.

Ethyl 1-Cyano-2-(3-pyridyl)-4-oxo-1-cyclohexanecarboxylate (24c, diastereomeric mixture): From **8f** and potassium ethyl cyanoacetate. Eluent: AcOEt/Et_2O, 1:1). Oil. Yield: 85%. − IR (neat): $\tilde{\nu}$ = 2245, 1742, 1714 cm^{-1}. − ^1H NMR: δ = 1.20 (dt, 3 H, *J* = 7 Hz, CH_3), 2.43−2.92 (m, 5 H, cyclohexane), 3.12−3.29 (m, 1 H, cyclohexane), 3.55−3.85 (m, 1 H, cyclohexane), 4.16 (dq, 2 H, *J* = 7 Hz, OCH_2), 7.30−7.82 (m, 2 H, pyridine), 8.49−8.62 (m, 2 H, pyridine). − ^{13}C NMR: δ = 12.9, 13.1 (CH_3), 21.1, 21.5, 29.6, 30.4, 35.6, 36.5, 42.7, 43.8, 49.9, 50.1, 59.2, 60.1 (C2, C3, C1, C5, C6, C−O), 122.1, 122.3, 132.3, 132.4, 139.3, 140.5, 147.8, 148.9, 151.0, 153.1 (pyridine), 207.1, 208.8 (C1). − $C_{15}H_{16}N_2O_3$ (272.3): calcd. C 66.16, H 5.92, N 10.29; found C 66.25, H 6.10, N 10.33.

Benzyl{6-[(4-methylphenyl)sulfonyl]-4-oxo-2-hexenyl}ammonium Trifluoroacetate (25): A solution of **8d** (594 mg, 1.3 mmol) in trifluoroacetic acid/ dichloromethane, 1:4 (5 mL) was prepared at 0 °C and stirred for 2h at room temp. The solvent was evaporated in vacuo, and the residue dissolved in dichloromethane (20 mL) and evaporated again. The crude product **25** was utilized in the next step without further purification.

Isoindole 26: To a solution of **25** (610 mg, 1.3 mmol) in $CHCl_3$/EtOH, 1:1 (10mL), were added *O*-benzoyl-2-nitroethanol (251 mg,

1.3 mmol) and Et_3N (0.18 mL, 1.3 mmol), and the mixture was stirred at 50 °C for 3 h. A second equivalent (0.18 mL) of Et_3N was added, and after 12 h a third equivalent was added. After 24 h the solvent was evaporated in vacuo, and the residue dissolved in $CHCl_3$ and washed with saturated, aqueous $NaHCO_3$ and H_2O. After usual workup, the product was purified by flash chromatography, (eluent: ethyl acetate/cyclohexane, 1:2) to give *cis*- or *trans*-**26** (470 mg, 84%) as a yellow oil. − IR: $\tilde{\nu}$ = 1730, 1600, 1550 cm^{-1}. − ^1H NMR: δ = 2.22−2.58 (m, 5 H), 2.61−2.75 (m, 2 H), 2.93 (d, 1 H, *J* = 10.6 Hz), 2.98 (m, 1 H), 3.32 (d, 1 H, *J* = 10.6 Hz), 3.44 (m, 1 H), 3.61 (AB system, 2 H, *J* = 13 Hz), 7.21−7.36 (m, 5 H, Ph). − ^{13}C NMR: δ = 21.5, 33.2, 37.8, 39.3, 47.2, 57.5, 59.9, (C2, C4, C5, C7, C8, C9, *C*Ph), 88.5 (*C*NO*2*), 125.6, 127.1, 130.5, 138.8 (Ph), 207.4 (C6). − $C_{15}H_{18}N_2O_3$ (274.3): calcd. C 65.68, H 6.61, N 10.21; found C 65.44, H 6.77, N 10.30.

Hexahydroindolizidinone 27:[15] A solution of **8i** (593 mg, 1.5 mmol) in trifluoroacetic acid/dichloromethane, 1:4 (10 mL) was prepared at 0 °C and stirred for 2 h at room temperature. The solvent was evaporated in vacuo, and the residue dissolved in dichloromethane (20 mL) and evaporated again. To the residue, dissolved in ethanol (20 mL), was added Et_3N (0.4 mL) and the solution was stirred for 24 h. After evaporation, the crude product was purified by flash chromatography (eluent: ethyl acetate/methanol/NH_4OH, 9:1:0.1) to afford **27** (81 mg, 38%) as a yellow oil. − IR (neat): $\tilde{\nu}$ = 1720 cm^{-1}. − ^1H NMR: δ = 1.52−1.95 (m, 4 H), 2.29−2.40 (m, 5 H), 2.45−2.61 (m, 2 H), 3.11−3.38 (m, 2 H). − ^{13}C NMR: δ = 22.3 (C7), 31.5 (C8), 40.2 (C3), 47.1 (C1), 49.8, 53.1 (C6, C4), 63.8 (C9), 207.8 (C2). − $C_8H_{13}NO$ (139.2): calcd. C 69.03, H 9.41, N 10.06; found C 69.61, H 9.57, N 10.28.

Octahydroquinolizidinone 28:[16] Starting from **8h** (406 mg, 1.2 mmol) and following the same procedure as reported above for **27**, the quinolizidinone **28** (101 mg, 55%) was obtained as an oil. − IR (neat): $\tilde{\nu}$ =1725 cm^{-1}. − ^1H NMR: δ = 1.15−1.95 (m, 6 H), 2.01−2.94 (m, 7 H), 3.00−3.25 (m, 2 H). − ^{13}C NMR: δ = 22.9, 25.3 (C7, C8), 33.4 41.4 47.7 (C9, C1, C3), 55.1 55.3 62.0 (C6, C3, C10), 208.4 (C2). − $C_9H_{15}NO$ (153.2): calcd. C 70.55, H 9.87, N 9.14; found C 70.84, H 10.01, N 9.15.

Alkylation of Anion 2. − General Procedure: To a cooled (−78 °C) solution of phosphorane **1** (199 mg, 0.41 mmol) in dry THF (4 mL) was added a solution of butyllithium (2.5 M in hexane, 0.3 mL, 0.82 mmol). Stirring was continued for 10 minutes. To the dark red mixture were added HMPA (0.41 mmol) and the alkylating agent (0.41 mmol), and the temperature was slowly allowed to rise to 25 °C. The solvent was evaporated and the residue extracted with H_2O (5 mL) and $CHCl_3$ (7 mL). To the dried chloroform solution of **29a−d** was added methyl glyoxylate (36 mg, 4.1 mmol), and the solution was warmed at 60 °C for 3 h. After evaporation, the residue was purified by column chromatography.

Methyl 6-[(4′-Methylphenyl)sulfonyl]-4-oxo-2-heptenoate (30a): Oil. Yield 36%. Eluent: ethyl acetate/cyclohexane, 1:1.5. − IR (neat): $\tilde{\nu}$ = 1740, 1680 cm^{-1}. − ^1H NMR: δ = 1.26 (d, 3 H, *J* = 7 Hz, CH_3CS), 2.46 (s, 3 H, CH_3Ph), 2.87 (dd, 1 H, *J* = 16.3 and 9.5 Hz, CH), 3.43 (dd, 1 H, *J* = 16.3 and 2.6 Hz, CH), 3.65 (m, 1 H, CH), 3.82 (s, 3 H, OCH_3), 6.68 (d, 1 H, *J* = 16 Hz, HC=C), 7.05 (d, 1 H, *J* = 16 Hz, HC=C), 7.37 (d, 2 H, *J* = 8 Hz, Ph), 7.77 (d, 2 H, *J* = 8.6 Hz, Ph). − ^{13}C NMR: δ = 10.1 (CH_3), 20.8 (*C*H_3Ph), 37.1 (C5), 48.6, 50.1 (C6, C−O), 126.5, 131.1, 135.4, 136.2, 141.0, 142.8 (C2, C3, Ph), 163.2 (C=O), 197.4 (C=O). − $C_{15}H_{18}O_5S$ (310.4): calcd. C 58.05, H 5.85, S 10.33; found C 57.92, H 5.98, S 10.45.

Methyl 4-Oxo-2,5-heptadienoate (31a): Oil. Yield 36.5%. Eluent: ethyl acetate/cyclohexane, 1:1.5. − IR (neat): $\tilde{\nu}$ = 1740, 1680 cm^{-1}. − ^1H NMR: δ = 1.97 (dd, 3 H, *J* = 6.7 and 1.7 Hz, CH_3), 3.82 (s, 3 H, OCH_3), 6.37 (dq, 1 H, *J* = 16.3 and 1.7 Hz, HC=CCO), 6.78 (d, 1 H, *J* = 16 Hz, HC=C), 7.05 (dq, 1 H, *J* = 16.3 and 6.7 Hz, $HC=CCH_3$), 7.35 (d, 1 H, *J* = 16 Hz, HC=C). − ^{13}C NMR: δ = 15.5 (C7), 50.3 (OCH_3), 132.2, 137.9, 142.6, 148.0 (C2, C3, C5, C6), 163.9 (C=O), 189.1 (C=O). − $C_8H_{10}O_3$ (154.2): calcd. C 62.33, H 6.54; found C 63.05, H 6.71.

Methyl 6-[(4′-Methylphenyl)sulfonyl]-4-oxo-2-octenoate (30b): Oil. Yield 33.7%. Eluent: ethyl acetate/cyclohexane, 1:2. − IR (neat): $\tilde{\nu}$ = 1740, 1680, 1600 cm^{-1}. − ^1H NMR: δ = 0.94 (t, 3 H, *J* = 7.44 Hz, CH_3), 1.65 (m, 2 H, CH_2), 2.43 (s, 3 H, CH_3Ph), 2.90 (dd, 1 H, *J* = 17.6 and 8 Hz), 3.35 (dd, 1 H, *J* = 17.6 and 5.3 Hz), 3.70−3.80 (m, 1 H), 3.82 (s, 3 H, OCH_3), 6.7 (d, 1 H, *J* = 16 Hz, HC=C), 7.04 (d, 1 H, *J* = 16 Hz, HC=C), 7.38 (d, 2 H, *J* = 8 Hz, Ph), 7.79 (d, 2 H, *J* = 8 Hz, Ph). − ^{13}C NMR: δ = 10.2 (CH_3), 18.5 (C7), 20.8 (*C*H_3Ph), 36.8 (C5), 50.2, 53.6 (C6, OCH_3), 125.9, 131.0, 134.6, 134.7, 142.9, 150.1 (C2, C3, Ph), 164.9 (C=O), 189.9 (C=O). − $C_{16}H_{20}O_5S$ (324.4): calcd. C 59.24, H 6.21, S 9.88; found C 59.33, H 6.31, S 10.00.

Methyl 4-Oxo-2,5-octadienoate (31b): Oil. Yield 43%. Eluent: ethyl acetate/cyclohexane, 1:2. − IR (neat): $\tilde{\nu}$ = 1740, 1680 cm^{-1}. − ^1H NMR: δ = 1.13 (t, 3 H, *J* = 7.4 Hz, CH_3), 2.32 (dq, 2 H, *J* = 6.4 and 1.1, $CH_2C=C$), 3.82 (s, 3 H, OCH_3), 6.44 (dt, 1 H, *J* = 16 and 1.1, HC=C), 6.74 (d, 1 H, *J* = 15.7 Hz, HC=C), 7.11 (dt, 1 H, *J* = 16 Hz, *J* = 6.4 Hz, HC=C), 7.42 (d, 1 H, *J* = 15.7 Hz, HC=C). − ^{13}C NMR: δ = 13.5 (C8), 26.6 (C7), 50.4 (OCH_3), 132.6, 136.8, 144.8, 150.9.0 (C2, C3, C5, C6), 165.7 (C=O), 188.4 (C=O). − $C_9H_{12}O_3$ (168.2): calcd. C 64.27, H 7.19; found C 63.22, H 7.23.

Methyl 6-[(4′-Methylphenyl)sulfonyl]-4-oxo-7-phenyl-2-heptenoate (30c): Oil. Yield 46%. Eluent: ethyl acetate/cyclohexane, 1:1.5. − IR (neat): $\tilde{\nu}$ = 3050, 1740, 1680, 1600 cm^{-1}. − ^1H NMR: δ = 2.49 (s, 3 H, CH_3Ph), 2.70 (dd, 1 H, *J* = 15 and 5 Hz), 2.78 (dd, 1 H, *J* = 18 and 9.5 Hz), 3.25 (dd, 1 H, *J* = 15 and 4.5 Hz), 3.31 (dd, 1 H, *J* = 18 and 3 Hz), 3.82 (s, 3 H, OCH_3), 4.14 (m, 1 H, HCS), 6.52 (d, 1 H, *J* = 16 Hz, HC=C), 6.85 (d, 1 H, *J* = 16 Hz, HC=C), 7.00−7.41 (m, 7 H, Ph), 7.77 (d, 2 H, *J* = 8.2 Hz, Ph). − ^{13}C NMR: δ = 20.8 (*C*H_3Ph), 32.2, 36.8 (C5, C7), 50.0, 55.0 (C6, OCH_3), 125.1, 126.5, 127.9, 128.3, 130.7, 135.8, 135.9, 139.5, 144.1 (C2, C3, 2 Ph), 165.4 (C=O), 196.9 (C=O). − $C_{21}H_{22}O_5S$ (386.5): calcd. C 65.27, H 5.74, S 8.30; found C 65.26, H 5.77, S 8.21.

Methyl 4-Oxo-7-phenyl-2,5-heptadienoate (31c): Oil. Yield 37%. Eluent: ethyl acetate/cyclohexane, 1:1.5. − IR (neat): $\tilde{\nu}$ = 3080, 3050, 1740, 1680 cm^{-1}. − ^1H NMR: δ = 3.62 (dd, 2 H, *J* = 6.7 and 1.3 Hz, CH_2), 3.82 (s, 3 H, OCH_3), 6.38 (dt, 1 H, *J* = 16 and 1.3 Hz, HC=C), 6.75 (d, 1 H, *J* = 15.7 Hz, HC=C), 7.15 (dt, 1 H, *J* = 16 and 6.7 Hz, HC=C), 7.17−7.49 (m, 6 H, Ph and HC=C). − ^{13}C NMR: δ = 39.4 (C7), 50.1 (OCH_3), 124.9, 127.8, 129.4, 133.5, 139.9, 144.1, 147.7 149.3 (C2, C3, C5, C6, Ph), 165.9 (C=O), 187.1 (C=O). − $C_{14}H_{14}O_3$ (230.3): calcd. C 73.03, H 6.13; found C 73.55, H 6.33.

Methyl 4-Oxo-2,5-hexadecadienoate (31d): Oil. Yield 58%. Eluent: ethyl acetate/cyclohexane, 1:1.5. − IR (neat): $\tilde{\nu}$ = 1740, 1680 cm^{-1}. − ^1H NMR: δ = 0.87 (t, 3 H, *J* = 6 Hz, CH_3), 1.13−1.66 (m, 16 H, 8 CH_2), 2.25 (ddt, 2 H, *J* = 6.4 and 7 and 1 Hz, $CH_2C=C$), 3.82 (s, 3 H, OCH_3), 6.25 (dt, 1 H, *J* = 16 and 1 Hz, HC=C), 6.75 (d, 1 H, *J* = 15.7 Hz, HC=C), 7.01 (dt, 1 H, *J* = 16 and 6.4 Hz, HC=C), 7.43 (d, 1 H, *J* = 15.7 Hz, HC=C). − ^{13}C NMR: δ = 12.2, 23.1 (C15, C16), 29.9, 30.1, 30.5, 30.6, 30.7, 31.2, 32.4, 32.9 (C7, C8, C9, C10, C11, C12, C13, C14), 50.0 (CH_3O), 132.4, 143.9, 146.8, 151.3 (C2, C3, C5, C6), 163.2 (C=O), 189.2 (C=O). −

$C_{17}H_{28}O_3$ (280.4): calcd. C 72.82, H 10.06; found C 72.89, H 10.97.

General Procedure for the Aldol Condensation of 2: To a cooled (−78 °C) solution of phosphorane **1** (199 mg, 0.41 mmol) in dry THF (7 mL) was added a solution of butyllithium (2.5 M in hexane, 0.3 mL, 0.82 mmol). The reaction mixture was stirred for 10 minutes. To the dark red solution were added $BF_3{\cdot}Et_2O$ (0.05 mL) and the aldehyde (0.41 mmol). The temperature was maintained at −78 °C for 10 minutes and then slowly allowed to rise to −20 °C. Water (a few drops) was added and the mixture stirred at room temperature for 15 minutes. The solvent was evaporated and the residue, diluted with H_2O (3mL), extracted with $CHCl_3$ (8 mL). To the dried organic solution of **32a** or **32b** was added methyl glyoxylate (36 mg, 0.41 mmol), and the solution was heated at 60 °C for 3 h. After evaporation, the residue was purified by flash chromatography.

Methyl 3-(5′-Methyl-2′-furanyl)propenoate (33a): Oil. Yield 70%. Eluent: ethyl acetate/cyclohexane, 1:1. − IR (neat): $\tilde{\nu}$ = 1680 cm^{-1}. − ^1H NMR: δ = 2.35 (s, 3 H, CH_3), 3.77 (s, 3 H, OCH_3), 6.06 (d, 1 H, *J* = 3.2 Hz, HC=C), 6.22 (d, 1 H, *J* = 15.6 Hz, HC=C), 6.58 (d, 1 H, *J* = 3.2 Hz, HC=C), 7.43 (d, 1 H, *J* = 15.6 Hz, HC=C). − ^{13}C NMR: δ = 16.8 (CH_3), 50.6 (OCH_3), 107.6, 111.1 (C3′, C4′), 128.9, 140.3, 152.8, 154.2 (C2, C3, C2′, C5′), 168.4 (C=O). − $C_9H_{19}O_3$ (175.2): calcd. C 65.05, H 6.07; found C 66.01, H 6.64.

Methyl *trans*-3-[4′,5′-Dihydro-5′-methyl-4′-(4-methylphenyl)sulfonyl-2′-furanyl]propenoate (34a): Oil. Yield 21.7%. Eluent: ethyl acetate/cyclohexane, 1:1. − IR (neat): $\tilde{\nu}$ = 1680, 1600 cm^{-1}. − ^1H NMR: δ = 1.34 (d, 3 H, *J* = 6.4 Hz, CH_3), 2.45 (s, 3 H, CH_3Ph), 3.75 (s, 3 H, OCH_3), 4.16 (dd, 1 H, *J* = 2.1 and 5 Hz, HCS), 5.14 (dq, 1 H, *J* = 5 and 6.4 Hz, HCO), 5.22 (d, 1 H, *J* = 5 Hz, HC=C), 6.17 (d, 1 H, *J* = 15.6 Hz, HC=C), 7.04 (d, 1 H, *J* = 15.6 Hz, HC=C), 7.38 (d, 2 H, *J* = 8 Hz, Ph), 7.79 (d, 2 H, *J* = 8 Hz, Ph). − ^{13}C NMR: δ = 19.9, 20.5 (CH_3Ph, CH_3-C5′), 50.6 (OCH_3), 60.2, 68.7 (C4′, C5′), 99.8 (C3′), 125.6, 126.8, 131.5, 136.9, 142.8, 143.0, 155.9 (Ph, C2, C3, C2′, C3′), 164.8 (C=O). − $C_{16}H_{18}O_5S$ (322.4): calcd. C 59.61, H 5.63, S 9.95; found C 60.12, H 5.77, S 9.62.

Methyl 3-(5′-Phenyl-2′-furanyl)propenoate (33b): Oil. Yield 70%. Eluent: ethyl acetate/cyclohexane, 1:1. − IR (neat): $\tilde{\nu}$ = 3080, 1680, 1600 cm^{-1}. − ^1H NMR: δ = 3.81 (s, 3 H, CH_3O), 6.05 (d, 1 H, *J* = 2.5 Hz, furan), 6.39 (d, 1 H, *J* = 15.5 Hz, HC=C), 6.52 (d, 1 H, *J* = 2.5 Hz, furan), 7.24−7.41 (m, 6 H, Ph and HC=C). − ^{13}C NMR: δ = 50.6 (OCH_3), 105.6, 109.5 (C3′, C4′), 125.3, 126.8, 127.1, 128.5, 135.6, 141.0 (Ph, C2, C3), 155.3, 158.9 (C2′, C5′), 166.5 (C=O). − $C_{14}H_{12}O_3$ (228.2): calcd. C 73.67, H 5.31; found C 72.84, H 5.03.

Methyl 3-[4′,5′-Dihydro-4′-[(4-methylphenyl)sulfonyl]-5′-phenyl-2′-furanyl]propenoate (34b): Oil. Yield 26.4%. Eluent: ethyl acetate/cyclohexane, 1:1. − IR (neat): $\tilde{\nu}$ = 3080, 1680, 1600 cm^{-1}. − ^1H NMR: δ = 2.45 (s, 3 H, CH_3Ph), 3.82 (s, 3 H, CH_3O), 4.51 (dd, 1 H, *J* = 6.2 and 5 Hz, HCS), 5.0 (d, 1 H, *J* = 6.2 Hz, CHO), 6.3 (d, 1 H, *J* = 5 Hz, SCHC=C), 6.75 (d, 1 H, *J* = 15.6 Hz, HC=C), 7.22−7.49 (m, 7 H, Ph), 7.6 (d, 1 H, *J* = 15.6 Hz, HC=C), 7.79 (d, 2 H, *J* = 8 Hz, Ph). − ^{13}C NMR: δ = 20.1 (CH_3Ph), 50.2 (OCH_3), 68.7, 73.2 (C4′, C5′), 95.5 (C3′), 126.3, 126.5, 127.3, 128.2, 128.6, 129.7, 139.6, 140.1, 140.3, 142.0, 144.2, 158.5 (C2, C3, C2′, C3′, 2 Ph), 168.4 (C=O). − $C_{21}H_{20}O_5S$ (384.4): calcd. C 65.61, H 5.24, S 8.34; found C 65.79, H 5.30, S 8.18.

Methyl 4-(1,3-Dioxolan-2-yl)-6-[(4′-methylphenyl)sulfonyl]-2-hexenoate (37): A solution of the ester **8g** (741 mg, 2.5 mmol) in dry benzene (15 mL) with ethylene glycol (0.28 mL, 5.07 mmol), triethyl chloroformate (0.82 mL, 5.02 mmol), and a few drops of $BF_3{\cdot}Et_2O$ was refluxed for 24 h, cooled, and washed with a solution of $NaHCO_3$. After the usual workup, the residue was purified by flash chromatography, eluent: ethyl acetate/cyclohexane, 1:1, to give **37** as a white solid, m.p. 118−120 °C. − IR (nujol): $\tilde{\nu}$ = 1680, 1640, 1600, 1320, 1150 cm^{-1}. − ^1H NMR: δ = 0.10 (m, 2 H, CH_2C), 2.44 (s, 3 H, CH_3Ph), 3.19 (m, 2 H, CH_2S), 3.81−4.11 (m, 4 H, 2 CH_2 dioxolane), 3.82 (s, 3 H, CH_3O), 6.05 (d, 1 H, *J* = 15.4 Hz, HC=C), 6.64 (d, 1 H, *J* = 15.4 Hz, HC=C), 7.35 (d, 2 H, *J* = 8 Hz, Ph), 7.77 (d, 2 H, *J* = 8 Hz, Ph). − ^{13}C NMR: δ = 20.3 (CH_3), 31.2 (C6), 44.0 (C6), 50.2 (OCH_3), 72.3 (2 C−O), 116.8, 121.4, 126.3, 132.0, 135.9, 142.8, 145.6 (C2, C3, C4, Ph), 168.9 (C=O). − $C_{16}H_{20}O_6S$ (340.4): calcd. C 56.46, H 5.92, S 9.42; found C 55.94, H 6.04, S 9.96.

Spiro Compound 38 (diastereomeric mixture): A solution of butyllithium (1.6 M in hexane, 1.05 mL, 1.72 mmol) was added to a cooled (−78 °C) solution of diisopropylamine (0.24 mL, 1.72 mmol in dry THF (2 mL). After 5 minutes, a solution of the ester **37** (585 mg, 1.72 mmol) in dry THF (6 mL) was added dropwise, followed, after 10 minutes, by the addition of $BF_3{\cdot}Et_2O$ (0.14 mL, 1.15 mmol) and ethanal (64 mg, 1.15 mmol). The mixture was maintained at −78 °C for 15 minutes and then slowly allowed to rise to −20 °C. Water (a few drops) was added and the mixture was stirred at room temperature for 15 minutes. After evaporation of the solvent, water (5 mL) was added to the residue and the slurry extracted with $CHCl_3$ (twice with 10 mL). After the usual workup, the residue was purified by chromatography, eluent: ethyl acetate/cyclohexane, 2:1, to give **38** (166 mg, 37.6%) as a diastereomeric mixture.

Data for the most abundant diastereoisomer: IR (neat): $\tilde{\nu}$ = 3450, 3080, 1720, 1600, 1320, 1150 cm^{-1}. − ^1H NMR: δ = 1.27 (d, 3 H, *J* = 6.4 Hz, CH_3), 1.71 (br. s, 1 H), 2.29−2.39 (m, 1 H), 2.44 (s, 3 H, CH_3Ph), 2.56−2.63 (m, 1 H), 2.65−2.71 (m, 1 H), 3.25 (m, 1 H), 3.45 (m, 1 H), 3.73 (s, 3 H, CH_3O), 3.75−3.90 (m, 4 H, 2 CH_2 dioxolane), 4.15 (m, 1 H), 7.35 (d, 2 H, *J* = 8 Hz, Ph), 7.81 (d, 2 H, *J* = 8 Hz, Ph). − ^{13}C NMR: δ = 14.6, (C3′ cyclobutane), 20.3, 20.5 (CH_3Ph, CH_3 ethyl), 35.9, 36.9, 49.7 (C2 and C1′, C4′ cyclobutane), 50.8 (OCH_3), 64.6 (C−OH), 71.2 (2 C−O dioxolane), 109.9 (OCO dioxolane), 126.3, 130.5, 135.9, 144.9 (Ph), 185.9 (C=O). − $C_{18}H_{24}O_7S$ (384.4): calcd. C 56.23, H 6.29, S 8.34; found C 56.38, H 6.54, S 8.22.

Methyl 7-Acetoxy-4-oxo-2-octenoate (41): A solution of butyllithium (2.5 M in hexane, 0.75 mL, 2.05 mmol) was added to a cooled (−78 °C) and stirred solution of the phosphorane **1** (499 mg, 1.02 mmol) in dry THF (15 mL). After 10 minutes, $BF_3{\cdot}Et_2O$ (0.1 mL) and ethanal (0.05 mL, 1.02 mmol) were added to the dark red solution, which was maintained at −78 °C for 10 minutes and then allowed to warm slowly to −20 °C. Water (a few drops) was added and the mixture stirred at room temperature for 15 minutes. After evaporation of the solvent, H_2O (3 mL) was added and the slurry extracted twice with 10 mL of $CHCl_3$ to obtain, after solvent removal, **32a.** To a cooled (−20 °C) solution of the crude **32a** in methanol (8 mL) were added anhydrous Na_2HPO_4 (2.95 g, 20.6 mmol) and 6% Na/Hg (7.72 g), and the slurry was stirred overnight. The mixture was filtered and evaporated. Water (5 mL) was added and the slurry extracted with $CHCl_3$, dried, and concentrated. The crude residue **39** was dissolved in CH_2Cl_2 (6 mL) containing a few crystals of DMAP and treated with pyridine (0.33 mL, 4.12 mmol) and acetic anhydride (0.19 mL, 2.06 mmol). After being stirred for 1 h at room temp., the reaction mixture was washed with saturated, aqueous NH_4Cl (5 mL). The dried organic solution of **40** was treated with methyl glyoxylate (90 mg, 1.03 mmol) and refluxed for 3 h. After evaporation, the residue was purified by flash chromatography, (eluent: ethyl acetate/cyclohex-

ane, 1:1.5) to give **41** (82 mg, 35%) as an oil. − IR (neat): $\tilde{\nu}$ = 1740, 1720, 1680 cm^{-1}. − ^1H NMR: δ = 1.24 (d, 3 H, *J* = 6.7 Hz, CH_3CO), 1.99 (m, 2 H, CH_2), 2.12 (s, 3 H, $CH_3C{=}O$), 2.68 (t, 2 H, *J* = 7.2 Hz, CH_2), 3.82 (s, 3 H, CH_3O), 4.92 (m, 1 H, CH), 6.68 (d, 1 H, *J* = 16 Hz, HC=C), 7.08 (d, 1 H, *J* = 16 Hz, HC=C). − ^{13}C NMR: δ = 15.9, 18.5 (CH_3, C8), 31.5, 35.9 (C5, C6), 50.2 (OCH_3), 70.0 (C7), 135.9, 143.2 (C2, C3), 169.8, 170.4 (C=O esters), 198.3 (C4). − $C_{11}H_{16}O_5$ (228.2): calcd. C 57.88, H 7.07; found C 58.35, H 7.36.

Acylation of Anion 2. − General Procedure: A solution of butyllithium (1.6 M in hexane, 0.78 mL, 1.24 mmol) was added to a cooled (−78 °C) and stirred solution of the phosphorane **1** (302 mg, 0.62 mmol) in dry THF (7 mL) containing TMEDA (0.09 mL, 0.62 mmol). After 10 minutes, the dark red solution was treated with freshly distilled ethyl chloroformate (0.04 mL, 1.24 mmol) and the temperature allowed to rise slowly to 25 °C. The flow of N_2 was increased to remove the THF and, without purification of **42**, aldehyde (0.62 mmol) in $CHCl_3$ (5 mL) was added and the mixture refluxed for 3 h. After evaporation of the solvent, the residue was purified by flash chromatography.

Ethyl 4-Oxo-6-phenyl-2,5-hexadienoate (43a): Oil. Yield 42%. Eluent: ethyl acetate/cyclohexane, 1:1.5. − IR (neat): $\tilde{\nu}$ = 3080, 1680, 1620, 1600 cm^{-1}. − ^1H NMR: δ = 1.42 (t, 3 H, *J* = 7 Hz, CH_3), 4.35 (q, 2 H, *J* = 7 Hz, CH_2), 6.85 (d, 2 H, *J* = 15 Hz, 2 HC=C), 7.31−7.58 (m, 7 H, Ph and 2 HC=C). − ^{13}C NMR: δ = 13.3 (CH_3), 61.2 (C−O), 127.1, 128.6, 128.7, 129.9, 134.7, 142.4, 143.5, 155.6 (C2, C3, C5, C6, Ph), 166.2 (C1), 194.2 (C4). − $C_{14}H_{14}O_3$ (230.3): calcd. C 73.03, H 5.70; found C 73.13, H 5.71.

Ethyl Methyl 4-Oxo-2,5-heptadienedioate (43b): Oil. Yield 40%. Eluent: ethyl acetate/cyclohexane, 1:1.5. − IR (neat): $\tilde{\nu}$ = 1735, 1590 cm^{-1}. − ^1H NMR: δ = 1.45 (t, 3 H, *J* = 7 Hz, CH_3), 3.99 (s, 3 H, CH_3O), 4.37 (q, 2 H, *J* = 7 Hz, CH_2), 6.85 (d, 2 H, *J* = 15 Hz, 2 HC=C), 7.38 (d, 1 H, *J* = 15 Hz, HC=C), 7.4 (d, 1 H, *J* = 15 Hz, HC=C). − ^{13}C NMR: δ = 13.5 (CH_3), 50.1 (OCH_3), 59.9 (CH_2−O), 142.8, 144.4, 146.3, 146.5 (C2, C3, C5, C6), 165.1, 165.4 (C1, C7), 190.0 (C4). − $C_{10}H_{12}O_5$ (212.2): calcd. C 56.60, H 5.70; found C 57.35, H 5.89.

Methyl 4,7-Dioxo-2,5-octadienoate (45): Following the general procedure and using freshly distilled acetic anhydride (0.07 mL, 0.62 mmol) as alkylating agent, the product **45** was obtained in 33% yield as an oil. Eluent: ethyl acetate/cyclohexane, 1:1. − IR (neat): $\tilde{\nu}$ = 1730, 1680, 1650, 1590 cm^{-1}. − ^1H NMR: δ = 1.37 (s, 3 H, $CH_3C{=}O$), 3.83 (s, 3 H, CH_3O), 6.57 (d, 1 H, *J* = 15.6 Hz, HC=C), 6.8 (d, 1 H, *J* = 15.9 Hz, HC=C), 7.0 (d, 1 H, *J* = 15.9 Hz, HC=C), 7.4 (d, 1 H, *J* = 15.6 Hz, HC=C). − ^{13}C NMR: δ = 22.3 (CH_3), 50.3 (CH_3O), 145.1, 145.9, 149.6, 150.2 (C2, C3, C5, C6), 165.5 (C1), 190.0, 195.8 (C4, C7). − $C_9H_{10}O_4$ (182.2): calcd. − C 59.34, H 5.53; found C 59.78, H 5.65.

3-Methyl-4-[(4′-methylphenyl)sulfonyl]cyclo-2-penten-1-one (46): A solution of butyllithium (1.6 M in hexane, 0.77 mL, 1.23 mmol) was added to a cooled (−78 °C) and stirred solution of diisopropylamine (0.172 mL, 1.23 mmol) in dry THF (7 mL). After 15 minutes, the phosphorane **1** (199 mg, 0.41 mmol) was added to the mixture. After 10 minutes, the dark red solution was treated with freshly distilled acetic anhydride (0.07 mL, 0.62 mmol) and the temperature allowed to rise slowly to 25 °C. The flow of N_2 was increased to remove the THF and toluene (20 mL) was added to the mixture, which was refluxed for 20 h. After evaporation of the solvent, the residue was purified by flash chromatography (ethyl acetate/cyclohexane, 2:1). The cyclopentenone **46** (61 mg, 60%) was obtained as an oil. − IR (neat): $\tilde{\nu}$ = 1710, 1685 cm^{-1}. − ^1H NMR: δ = 2.42 (s, 3 H, CH_3), 2.45 (s, 3 H, CH_3), 2.62−2.76 (m, 2 H, CH_2), 4.4 (m, 1 H, CH), 6.1 (s, 1 H, HC=C), 7.4 (d, 2 H, *J* = 8, Ph), 7.8 (d, 2 H, *J* = 8, Ph). − ^{13}C NMR: δ = 20.1, 21.6 (2 CH_3), 39.5 (C5), 61.5 (C4), 123.9, 125.9, 131.4, 135.6, 143.0, 149.1 (C2, C3, Ph), 199.8 (C1). − $C_{13}H_{14}O_3S$ (250.3): calcd. C 62.38, H 5.64, S 12.81; found C 63.00, H 5.88, S 13.02.

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[1] L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115−136.
[2] A. Barco, S. Benetti, C. De Risi, P. Marchetti, G. P. Pollini, V. Zanirato, *Tetrahedron Lett.* **1998**, *39*, 1973−1976.
[3] H. S. Simpkins, in "*Sulphones in Organic Synthesis*" Tetrahedron Organic Chemistry Series, Pergamon Press, **1993**, *Vol. 10*.
[4] E. J. Späth, F. Kesztler, *Ber. Dtsch. Chem. Ges.* **1937**, *70*, 704.
[5] [5a] T. F. Spande, H. M. Garraffo, M. W. Edwards, H. J. C. Yeh, L. Pannel, J. W. Daly, *J. Am. Chem. Soc.* **1992**, *114*, 3475−3478. − [5b] E. Albertini, A. Barco, S. Benetti, C. De Risi, G. P. Pollini, R. Romagnoli, V. Zanirato, *Tetrahedron Lett.* **1994**, *35*, 9297−9300.
[6] The relative stereochemistry was assigned on the basis of the vicinal coupling constants of 4-H and 5-H.
[7] Y. Kobayashi, M. Nakano, G. K. Kumar, K. Kishihara, *J. Org. Chem.* **1998**, *63*, 7505−7515.
[8] The cyclobutane ring was inferred from the infrared spectrum of a sample of **38** treated with water/H_2SO_4 (absorption for C=O stretching at 1775 cm^{-1}).
[9] S. Fayos, J. Clardy, L. J. Dolby, T. Farnham, *J. Org. Chem.* **1997**, *42*, 1349−1352.
[10] P. Messinger, *Arch. Pharmaz.* **1973**, *306*, 603−610.
[11] The aldehyde **7d** was prepared in situ by Swern oxidation (R. E. Ireland, D. W. Norberck, *J. Org. Chem.* **1985**, *50*, 2198−2200) of the corresponding alcohol (A. P. Krapcho, M. J. Maresh, J. Lunn, *Sinth. Commun.* **1993**, *23*, 2443−2450).
[12] W. R. Roush, B. B. Brown, B. Bradley, *J. Am. Chem. Soc.* **1993**, *115*, 2268−2278.
[13] A. R. Chamberlein, H. D. Nguyen, J. Y. L. Chung, *J. Org. Chem.* **1984**, *49*, 1682−1688.
[14] R. K. Dieter, R. R. Sharma, *J. Org. Chem.* **1996**, *61*, 4180−4184.
[15] O. Pollet, G. Cordonnier, C. Bengourina, C. Randria, H. Sliwa, *Heterocycles* **1996**, *43*, 1391−1402.
[16] A. Brandi, S. Garro, A. Guarna, A. Goti, F. Cordero, F. De Sarlo, *J. Org. Chem.* **1988**, *53*, 2430−2434.

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