Synthesis of α-Methylenecyclobutanones. The First Preparation of Norsarkomycin Methyl Ester

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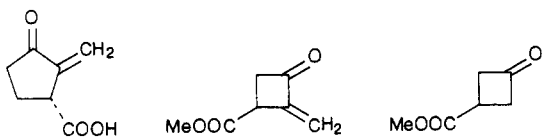
α-Methylenecyclobutanones were synthesized from cyclobutanones via two different routes. In the first route, the aldol condensation of methyl 3-oxocyclobutanecarboxylate (**3**) with monomeric formaldehyde yielded the ketol **4**, which was carried on to the norsarkomycin methyl ester by treatment with $MeSO_2Cl/2\ Et_3N$. The second route, utilizing α-(alkoxymethyl)cyclobutanones, was found to be the most convenient: cyclobutanone silyl enol ethers were alkylated with $ROCH_2Cl$ in the presence of $ZnBr_2$. Treatment of the resulting α-(alkoxymethyl)-cyclobutanones with $KHSO_4$ at high temperature and under reduced pressure led to α-methylenecyclobutanones **2**, **15**, and **19** in satisfactory yields. The importance of the choice of the R group will be discussed.

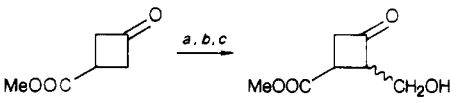
In the course of our research program on the synthesis of sarkomycin (**1**) and of related compounds, we had previously reported the synthesis of several five- to seven-membered-ring compounds.[1] In order to complete our



1 **2** **3**

work in this area, we attempted to prepare the four-membered-ring analogue, norsarkomycin methyl ester (**2**). We thought that obtaining it should be easy when starting from methyl 3-oxocyclobutanecarboxylate (**3**). Contrary to our expectations, methylenation α to the carbonyl group of cyclobutanones is not easy and general methods such as the reaction with paraformaldehyde in the presence of *N*-methylanilinium trifluoroacetate[2] did not occur from a cyclobutanone.[2a] Only two reports of α-methylenation on cyclobutanones have been documented in the literature.[3,4] In the first case, the Mannich reaction with cyclobutanone[3] resulted in a mixture of mono- and bis-aminomethylation products along with the starting material and this mixture led to α-methylenecyclobutanone in low overall yield and in several steps. In the second case, the aldol condensation between α,α,β-trisubstituted cyclobutanones and formalin[4] occurred but the yields of the α-methylenated compounds obtained through the intermediate ketols were not indicated. One can surmise that they were low due to the formation of polyhydroxymethyl compounds which are formed under similar conditions.[5] Therefore α-methylenecyclobutanones are rather obtained, in the literature, by cycloadditions between either ketenes and allenes[6] or synthetic equivalents of methyleneketene and olefins,[7] by ring expansion of cyclopropane derivatives,[8] and by other indirect routes.[9]

Table I. Aldol Condensation between Formaldehyde and Methyl 3-Oxocyclobutanecarboxylate (3)



3 **4**

entry[d]	activation	rctn time, min	quenching	yield,[e] %
1	without	7	aqueous NH_4Cl	10
2	$MgBr_2$ (0.5 equiv)	2.5	aqueous NH_4Cl	14[f]
3	$MgBr_2$ (0.5 equiv)	4	aqueous NH_4Cl	22
4	$MgBr_2$ (0.5 equiv)	4	CH_3COOH (2.2 equiv)/Et_2O	30
5	$ZnCl_2$ (0.5 equiv)	4	aqueous NH_4Cl	22
6	HMPA (1.2 equiv)	1.25	aqueous NH_4Cl	15
7	HMPA (1.2 equiv)	1.5	CH_3COOH (2.2 equiv)/Et_2O	35
8	HMPA (1.2 equiv)	1	HCl/Et_2O	40

[a] LDA, THF. [b] HCHO, Et_2O, −78 °C with or without activation. [c] Quenching. [d] Solvents: THF:Et_2O = 1:2 except for entry 8 (1:1). [e] Of isolated product. [f] Starting material recovered.

As a few aldol condensations with cyclobutanones were described,[4,5,10] we tried to obtain ketol **4** (Table I) by condensation of the lithium enolate of **3** with monomeric formaldehyde.[11] These reactions were carried out both with and without additives ($MgBr_2$,[12] $ZnCl_2$,[12] or hexamethylphosphoramide (HMPA)[10]). Comparison of the results of these experiments (Table I) showed the expected trend of increased yield and faster rate in the presence of an additive. $ZnCl_2$ and $MgBr_2$ gave similar results (entries 3 and 5), but the best yield was obtained by the use of HMPA, particularly when nonaqueous quenching was carried out with CH_3COOH/Et_2O or HCl/Et_2O (entries 7 and 8), the HCl resulting in a cleaner product. Under

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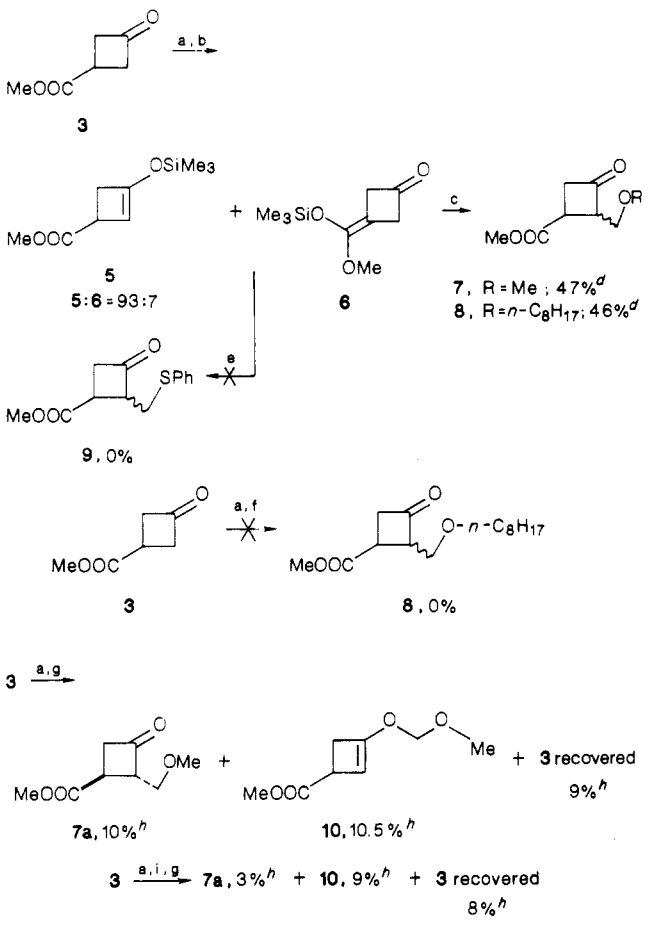
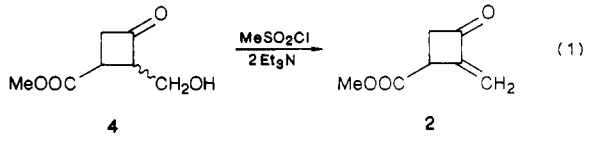
Scheme I[a]



[a] (a) LDA; (b) $SiMe_3Cl$; (c) $ROCH_2Cl$, $ZnBr_2$; (d) yield of isolated product from **3**; (e) $PhSCH_2Cl$, $TiCl_4$ or $ZnBr_2$; (f) n-$C_8H_{17}OCH_2Cl$; (g) $MeOCH_2I$; (h) yield of isolated product; (i) 1 equiv of HMPA.

our best conditions (entry 8), the ketol **4** was obtained in moderate yield of 40% as a rather unstable mixture of both diastereomers which progressively decomposed to unidentified products. Freshly prepared ketol **4** was treated with mesyl chloride in the presence of 2 equiv of triethylamine[13] (eq 1), to give the α-methylene compound **2** in 74% crude yield (**2** was not purified further).



(1)

The two drawbacks of this procedure are the use of monomeric formaldehyde at low temperature and the instability of ketol **4**. Therefore, other methods such as alkoxymethylation[14] or phenylthiomethylation[15] were examined (Scheme I). Enolization of **3** by lithium diisopropylamide followed by reaction with chlorotrimethylsilane gave, after a nonaqueous workup,[16] a mixture of silyl enol ether **5** and ketene acetal **6**, in the ratio 93:7, as determined by GC/MS analysis. Alkylation of this crude mixture with $MeOCH_2Cl$ or n-$C_8H_{17}OCH_2Cl$ in the presence of $ZnBr_2$ gave the corresponding alkylation products

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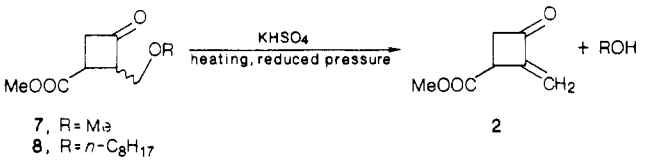
Table II. ROH Elimination from 7 and 8. Formation of Norsarkomycin Methyl Ester (2)

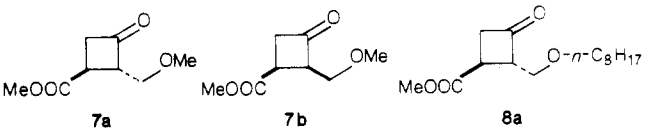


7, R = Me
8, R = n-C_8H_{17}

		rctn condns			
entry	starting material	temp, °C	time (min) for heating under 760 mm	pressure for trapping,[a] mm	product(s) (except ROH)
1	**7a**	160	2	3	**7a**
2	**7a**	200	2	3	**2**:**7a** = 43:57
3	**7a**:**7b** = 30:70	160	2	2	**2**:**7a** = 63:37
4	**7a**:**7b** = 30:70	180	1.3	6	**2**:**7a** = 53:47[b]
5	**7a**	185	2	22	**2**:**7a** = 53:47[c]
6	**8a**	172	0.8	6	**2**[d]
7	**8a**	175	0.5	22	**2**[e]

[a] Products were trapped in solution (pentane, −78 °C) as soon as they were formed. [b] Yield of isolated **2**: 47% (75% when **7a** + **7b** recovered is taken into account). [c] Yield of isolated **2**: 47% (88% when **7a** recovered is taken into account). [d] Yield of isolated **2**: 57%. [e] Yield of isolated **2**: 56%.

7 and **8** in satisfactory overall isolated yields for the three steps (47% and 46%, respectively). Compound **7** was



obtained after bulb to bulb distillation, as a mixture of both diastereomers **7a**/**7b** in the ratio 51:49 as determined by GC analysis. These diastereomers were partially separated by column chromatography, but some epimerization occurred during the separation (see Experimental Section). Similar epimerization of 2,3-disubstituted cyclobutanones has precedent in the literature.[17] In the case of **8**, the ^{13}C NMR spectrum showed only one diastereomer, which was assigned as **8a**.

Unexpectedly, the alkylation of the crude mixture of the compounds **5** and **6** with $PhSCH_2Cl$ in the presence of $ZnBr_2$ or $TiCl_4$ totally failed to produce the desired phenylthiomethylated compound **9**, yielding instead only complex mixtures in which none of the product **9** could be detected. In the same way, reaction of the lithium enolate of **3** with chloromethyl octyl ether also led to a complex mixture. Reactions with iodomethyl methyl ether[18] with or without HMPA gave only small amounts of C- and O-alkylation products **7a** and **10**, in addition to unidentified products and small amounts of starting material. This tendency of cyclobutanones to undergo O-alkylation has been previously documented.[19]

It was anticipated that heating **7** and **8** under reduced pressure in the presence of $KHSO_4$[14b] would lead to the corresponding elimination product. This reaction was found to be more facile from **7b** than from **7a** (Table II). Even though the yield was satisfactory (entry 5, 47% yield of isolated **2**; 88% when the amount of recovered **7a** is

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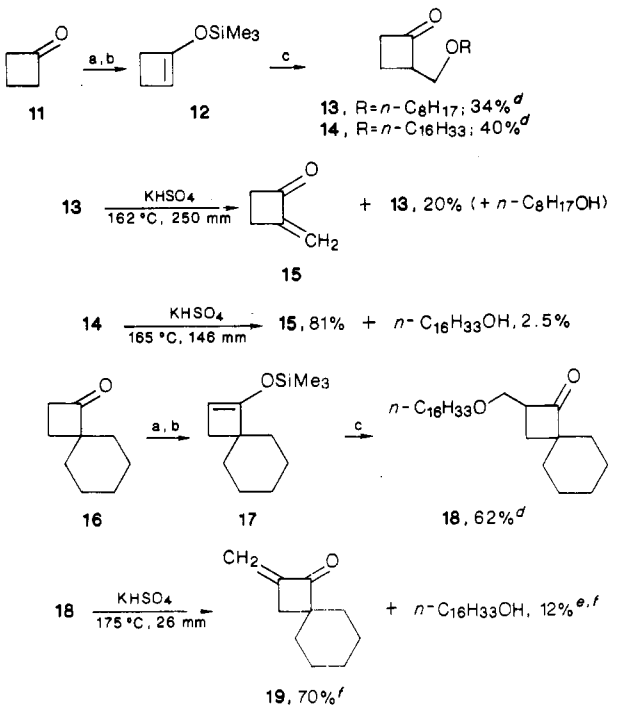
Scheme II[a]



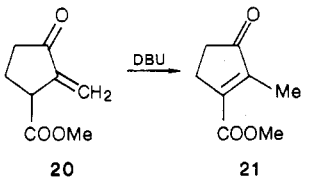
[a] (a) LDA; (b) $ClSiMe_3$; (c) $ROCH_2Cl$, $ZnBr_2$; (d) yield of isolated product from the starting cyclobutanone; (e) most of the alcohol remained in the distillation flask; (f) yield of isolated product from 18.

taken into account), it was impossible to obtain a complete conversion of **7**. This impossibility was due to the small difference in boiling point between **7** and **2**. However, when the *n*-octyl ether **8a** was subjected to the same reaction with $KHSO_4$, the starting **8a** was completely consumed, leaving only the desired compound **2** and *n*-octanol. In order to facilitate the separation of compound **2**, we treated the crude product mixture with CH_3COCl/pyridine before column chromatography, compound **2** being obtained free of *n*-octyl acetate in a 57% isolated yield from **8a** (entry 6). Thus, the easily polymerizable enone **2** can be obtained by a high-temperature reaction utilizing strong acid, provided that the product can be quickly distilled from the reaction mixture and trapped as a cold pentane solution.

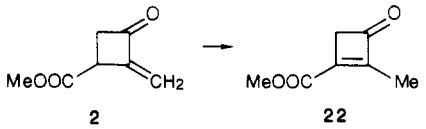
This method was extended to the synthesis of 2-methylenecyclobutanone (**15**). Whereas the octyl ether **13** (Scheme II) led to the mixture consisting of 49% of **15**, 20% of unreacted **13** and of *n*-octanol, the ether **14** (R = n-$C_{16}H_{33}$) was completely consumed and resulted in an 81% yield of **15** in addition to only 2.5% of n-$C_{16}H_{33}OH$. The volatile and easily polymerizable[3,8a,9a] product **15** was not purified further, and the yields, in both cases, were determined by NMR. *n*-Hexadecyl chloromethyl ether necessary for this reaction was obtained in 95% yield by reaction between *n*-hexadecyl alcohol methoxymethyl ether and BCl_3.[20] This result represents a vast improvement for the preparation of enone **15**, which was synthesized[3] in a five-step sequence from cyclobutanone yielding less than 11% of the desired compound (the yield of the last step was not given). Substance **19** could also be prepared from **16** in the same way; the overall yield of isolated product was 43.5%. This compound could not yet be prepared by another method.[2a]

When concentrated to neat solutions, compounds **2**, **15**, and **19** progressively polymerized at room temperature; therefore they were stored as solutions in low temperature. This behavior is similar to that mentioned in our preceding report on related products.[1] When aqueous solutions of **2** or sarkomycin methyl ester (**20**) were maintained at 38 °C, a progressive decrease in absorbance for the enone was observed by UV spectroscopy (λ_{max} 232 nm for **20**, 230 nm for **2**). The half-lives were 10.95 and 72.68 for **2** and **20**, respectively.

In a previous publication,[21] we have shown that the sarkomycin nitrile was isomerized by DBU. When the sarkomycin methyl ester (**20**) was treated with DBU, the same isomerization was observed (eq 2). Contrary to a recent report[22] on the thermodynamic isomerization of methylcyclobutenes to methylenecyclobutanes, treatment of the compound **2** with DBU resulted in a complete conversion to the cyclobutene **22** (eq 3). Apparently, the increased conjugation in **22** is more important than the increase of strain in the molecule.

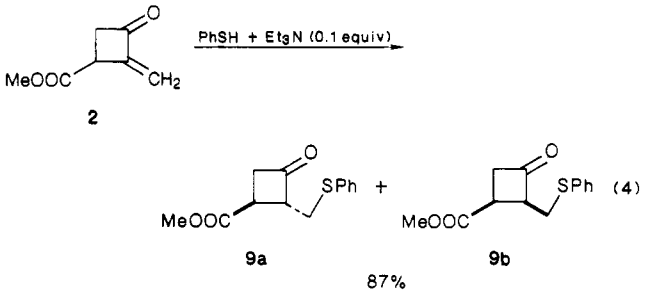


(2)



(3)

The reaction between **2** and PhSH in the presence of Et_3N gave both diastereomers of **9** in the ratio **9a**:**9b** = 70:30 and a combined yield of 87% for the isolated products (eq 4). It was shown earlier in this study that **9** was



(4)

not formed in the reaction between the silyl enol ethers **5** + **6** with $PhSCH_2Cl$ in the presence of $ZnBr_2$ or $TiCl_4$. Since we have now obtained **9** in an 87% isolated yield, it serves to illustrate that the failure of the first reactions to obtain the phenylthiomethylated compound was not due to the instability of the resulting compound.

In this work, we have demonstrated that α-methylenecyclobutanones are obtained in fair to high yields by the heating of α-(alkoxymethyl)cyclobutanones with $KHSO_4$ and the rapid distillation and trapping of the product at low temperature. This method, which represents probably the best route for methylenation α to the carbonyl group of cyclobutanones to date, has allowed for the first preparation of norsarkomycin methyl ester (**2**).

Experimental Section

NMR spectra were obtained on either a Perkin-Elmer R32 (90 MHz, proton) or a Brucker AM 250 instrument (proton and

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carbon). Mass spectra were recorded on a Girdel-Nermag R10-10 mass spectrometer. Accurate mass measurements were obtained on a double focusing VG 70-250 instrument.[23] IR spectra were determined on a Perkin-Elmer 682 instrument. UV spectra were recorded on a LKB Ultrospec II instrument. Microanalyses were performed by the service de microanalyse, CNRS, ICSN, Gif-sur-Yvette. The preparative column chromatographies were run on silica gel SDS 70–230 mesh.

Preparation of a Solution of Monomeric Formaldehyde in Diethyl Ether.[11] Dry paraformaldehyde (0.370 g, 12.3 mmol) was heated at 150 °C under argon to generate gaseous, monomeric HCHO, and the mixture of HCHO and argon was bubbled through 12 mL (entry 8, Table I) or 25 mL (entries 1–7, Table I) of Et_2O at −78 °C. Approximately 0.270 g (9 mmol) of HCHO was dissolved in the Et_2O and 0.100 g of $(HCHO)_n$ remained on the path.

Methyl 2-(Hydroxymethyl)-3-oxocyclobutanecarboxylate (4). Experimental Conditions for Entry 8, Table I. A solution of lithium diisopropylamide was prepared by dropwise addition of diisopropylamine (0.296 g, 2.92 mmol) to a stirred solution of *n*-butyllithium (1.80 mL of a 1.55 M solution in hexane; 2.79 mmol) in THF (8 mL), at −5 °C, under argon. After 10 min, the mixture was cooled to −78 °C and a solution of methyl 3-oxocyclobutanecarboxylate (**3**)[24] (0.320 g, 2.50 mmol) in THF (4 mL) was added dropwise (45 min). Then the mixture was stirred for 15 min at −78 °C and 15 min at 0 °C and cooled again to −78 °C, and 0.520 mL (2.99 mmol) of HMPA was added. After 5 min of stirring, a freshly prepared solution of monomeric HCHO in Et_2O (see above) (12 mL, ≃9 mmol of HCHO) kept at −78 °C was cannulated under argon pressure into the preceding mixture in 17 s. Reaction proceeded for 1 min, and a solution of HCl in Et_2O (5.3 mL of a 1.04 M solution; 5.5 mmol) was quickly added at −78 °C. The cooling bath was removed, and the mixture was allowed to warm up to room temperature. The white precipitate of LiCl was removed by vacuum filtration through a sintered-glass funnel and washed with Et_2O (3 mL), and the filtrate was evaporated. Purification of the crude product by column chromatography on 30 g of silica gel (pentane/ether, 60:40) gave 0.271 g (40%) of a mixture of both diastereomers of methyl 2-(hydroxymethyl)-3-oxocyclobutanecarboxylate (**4**). These products were unstable and had to be prepared just before they were used in the next step: ^1H NMR ($CDCl_3$) δ 3.25–4.15 (m, comprising two s (3.70, 3.80)); IR ($CDCl_3$) 3610, 1792, 1730 cm^{-1}; MS, *m/e* (relative intensity) (EI) 39 (41), 41 (43), 42 (43), 43 (42), 55 (100), 99 (62), 127 (45), (chemical ionization, NH_3) 159 (MH^+, 4), 176 (MNH_4^+, 100).

Experimental Conditions for Entries 1–7, Table I. In these experiments, a more diluted solution of monomeric HCHO in ether was used (25 mL, ≃9 mmol of HCHO). In the case of entries 6 and 7, HMPA was used as additive as for entry 8. In the case of entries 2–5, ether solutions of $MgBr_2$ (0.5 mL of a 2.5 M solution, 1.3 mmol) (entries 2–4) or $ZnCl_2$ (0.95 mL of a 1.4 M solution, 1.3 mmol) (entry 5) were used instead of HMPA. In the case of entry 1, no additive was used. For all cases (entries 1–7), the reaction time is given in Table I.

Quenching was run either by pouring the reaction mixture into saturated aqueous NH_4Cl (30 mL, 0 °C) followed by extraction of the aqueous phase with ether (4 × 15 mL), drying (Na_2SO_4), and evaporation or by using 330 mg (5.5 mmol) of CH_3COOH in ether (10 mL) instead of HCl/Et_2O. In this case (CH_3COOH/Et_2O), the precipitate of CH_3COOLi was washed with 2 × 3 mL of ether (instead of 3 mL of entry 8).

Methyl 2-Methylene-3-oxocyclobutanecarboxylate (2). A mixture of 0.100 g (0.63 mmol) of methyl 2-(hydroxymethyl)-3-oxocyclobutanecarboxylate (**4**) (mixture of both diastereomers), CH_2Cl_2 (3.5 mL), and 0.137 g (1.36 mmol) of Et_3N was cooled to 0 °C. Then 55 μL (0.081 g, 0.71 mmol) of $MeSO_2Cl$ was added dropwise with stirring. After 2 h at 0 °C, CH_2Cl_2 (4 mL) was added and the solution was successively washed with iced water (4 mL), iced 5% aqueous HCl (4 mL), and iced 10% aqueous $NaHCO_3$. The aqueous phases were extracted with ether (3 mL). The combined organic phases were dried (Na_2SO_4) and evaporated. Thus, 66 mg (74%) of practically pure methyl 2-methylene-3-oxocyclobutanecarboxylate (**2**) were obtained as an oil: ^1H NMR ($CDCl_3$) δ 3.13 (dd, *J* = 18.3, 9.1 Hz, 1 H), 3.38 (dd, *J* = 18.3, 6.8 Hz, 1 H), 3.73 (s, 3 H), 3.80 (dddd, *J* = 9.1, 6.8, 2.9, 2.4 Hz (verified by spin decoupling), 1 H), 5.29 (dd, *J* = 2.4, 1.5 Hz, 1 H), 5.82 (dd, *J* = 2.9, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 38.71 (d), 48.08 (t), 52.43 (q), 114.72 (t), 158.24 (s), 171.52 (s), 194.49 (s); IR ($CDCl_3$) 1780, 1740, 1650 cm^{-1}; UV (H_2O) λ_{max} 230 nm (ε 5400); MS, *m/e* (relative intensity) (EI) 53 (100), 54 (98), 55 (44), 82 (41), 112 (82), 113 (29), 140 (M^+, 0.4); accurate mass (EI), *m/e* 112.0546 (calcd for $M^+ - CO$, $C_6H_8O_2$, 112.0524), (FAB, Xe) *m/e* 141.0557 (calcd for MH^+, $C_7H_9O_3$, 141.0552).

Methyl 3-[(Trimethylsilyl)oxy]-2-cyclobutenecarboxylate (5) and 3-[Methoxy[(trimethylsilyl)oxy]methylene]cyclobutanone (6). Freshly distilled $ClSiMe_3$ (1.66 g, 15.3 mmol), 0.51 mL (0.364 g, 3.6 mmol) of anhydrous Et_3N, and THF (1.9 mL) were mixed under argon, and the mixture was centrifuged. The resulting solution was quickly added, with stirring, at 0 °C and under argon to the lithium enolate corresponding to 0.628 g (4.90 mmol) of methyl 3-oxocyclobutanecarboxylate (**3**) which was prepared as indicated above (see paragraph on methyl 2-(hydroxymethyl)-3-oxocyclobutanecarboxylate (**4**)). After 30 min of stirring at 0 °C and 10 min at room temperature and evaporation, anhydrous pentane (23 mL) was added. Suction filtration on a dried sintered-glass funnel to remove LiCl and washing of LiCl with pentane (3.5 mL) led to a clear pentane solution, which was evaporated again to give 0.978 g of a mixture of practically pure methyl 3-[(trimethylsilyl)oxy]-2-cyclobutenecarboxylate (**5**) and 3-[methoxy[(trimethylsilyl)oxy]methylene]cyclobutanone (**6**). (When LiCl was not totally removed the first time, the same workup was used once again.) Spectral data of **5**: ^1H NMR ($CDCl_3$) δ 0.09 (s, 9 H), 2.54–2.69 (m, 2 H), 2.91–3.09 (m, 1 H), 3.51 (s, 3 H), 4.49 (br s, 1 H); IR ($CDCl_3$) 1742, 1630 cm^{-1}; in ^1H NMR and IR spectra, peaks for **5** appear with others due to **6**; MS, *m/e* (relative intensity) (EI) 73 (100), 89 (16), 141 (48), 200 (M^+, 11). Compound **6** was detected by GC/MS; MS (**6**), *m/e* (relative intensity) (EI) 73 (65), 89 (100), 141 (90), 200 (M^+, 11). Ratio **5**:**6** by GC/MS = 93:7.

Methyl 2-(Methoxymethyl)-3-oxocyclobutanecarboxylate (7). The crude preceding mixture of **5** and **6** was dissolved in CH_2Cl_2 (15 mL), 0.050 g (0.22 mmol) of $ZnBr_2$ was added to the solution, and the mixture was cooled to −40 °C under argon. Then 0.530 g of $MeOCH_2Cl$ (6.58 mmol) was added dropwise at this temperature with stirring. The reaction mixture was allowed to warm up slowly to room temperature, and the disappearance of the silyl enol ether **5** as well as the formation of $ClSiMe_3$ was observed by ^1H NMR (signals at 0.09 and 0.4 ppm, respectively). After 3 h, the reaction was complete and CH_2Cl_2 (5 mL) was added. The organic phase was washed with water (2 × 5 mL), the aqueous phases were extracted with ether (2 × 2 mL), and the combined organic phases were dried (Na_2SO_4) and evaporated to leave 0.735 g of an orange oil. Bulb to bulb distillation led to two fractions. The first one (45 °C, 0.1 mm) (0.060 g) contained mainly methyl 3-oxocyclobutanecarboxylate (**3**) and the second one (60 °C, 0.1 mm) (0.400 g) both stereoisomers of methyl 2-(methoxymethyl)-3-oxocyclobutanecarboxylate (**7a** and **7b**) (47% from **3**) in the ratio **7a**:**7b** = 51:49 measured by vapor-phase chromatography (3.5% OV 101 + 0.35% Carbowax 20 M on Chromosorb W 80–100 mesh, acid washed; 130 °C). A residue of 0.269 g did not distill until 150 °C. The alkylation product corresponding to **6** was not detected.

When the mixture of **7a** and **7b** was chromatographed on 13 g of silica gel (pentane/ether, 80:20), 107 mg of **7a** was eluted at first and then 280 mg of a mixture of **7a** and **7b** in the ratio **7a**:**7b** = 63:37. Thus 97% of **7a** + **7b** was recovered but the ratio of the whole **7a** + **7b** increased to 71:29; this result shows that epimerization occurred during this chromatography. Separation of both stereoisomers (94 mg of a mixture **7a**:**7b** = 50:50) was possible by column chromatography on 3 g of silica gel (pentane/ether, 80:20, then pentane/ether, 20:80); 56 mg of **7a** and 38 mg of **7b** were thus obtained. **7a**: ^1H NMR (C_6D_6) δ 2.82 (ddd, *J* = 15.9, 8.5, 2.8 Hz, 1 H), 3.00 (s, 3 H), 3.03–3.23 (m, 3 H),

(23) We thank Dr. A. Gouyette, Institut Gustave Roussy, Villejuif, for these measurements.

(24) (a) Avram, M.; Nenitzescu, C. D.; Maxim, M. *Chem. Ber.* **1957**, *90*, 1424. (b) Wiberg, K. B.; Lampman, G. M.; Cuila, R. P.; Connor, D. S.; Schertler, P.; Lavanish, J. *Tetrahedron* **1965**, *21*, 2749. (c) Caputo, J. A.; Fuchs, R. *J. Org. Chem.* **1968**, *33*, 1959. Methyl 3-hydroxycyclobutanecarboxylate (prepared according to ref 24b) was oxidized to methyl 3-oxocyclobutanecarboxylate by Swern's method (Mancuso, A. J.; Swern, D. *Synthesis* **1981**, 165) in 90% yield.

3.34–3.53 (m, 2 H), 3.40 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 30.5 (d), 48.9 (t), 52.1 (q) 58.9 (d), 64.8 (q), 68.1 (t), 174.8 (s), 205.7 (s); MS, *m/e* (relative intensity) (EI) 53 (100), 54 (33), 55 (37), 59 (37), 81 (28), 112 (60), (chemical ionization, NH_3) 173 (mH^+, 22), 189 (20), 190 (MNH_4^+, 100). **7b**: ^{1}H NMR (C_6D_6) δ 2.65 (ddd, *J* = 17.8, 10.0, 2.8 Hz, 1 H), 2.94 (s, 3 H), 3.03–3.25 (m, 3 H), 3.25–3.55 (m, 2 H), 3.43 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 30.5 (d), 48.7 (t), 51.7 (q), 58.6 (d), 63.3 (q), 67.2 (t), 172.9 (s), 206.5 (s); MS, *m/e* (relative intensity) (EI) 53 (100), 54 (34), 55 (39), 59 (39), 81 (30), 112 (68) (chemical ionization, NH_3) 172 (55), 173 (MH^+, 82), 189 (24), 190 (MNH_4^+, 100). **7a + 7b**: IR ($CDCl_3$) 1797, 1735 cm^{-1}. Anal. (**7a + 7b**). Calcd for $C_8H_{12}O_4$: C, 55.81; H, 7.02. Found: C, 55.91; H, 7.02.

Stereochemical assignments are based on the preceding results concerning epimerization on silica gel (trans-2,3-disubstituted cyclobutanones are more stable than cis isomers[17]) and on ^{13}C NMR spectra (^{13}C NMR of **3** ($CDCl_3$): δ 203.8 (s), 174.5 (s, *C*OOMe), 51.9 (q, COO*Me*), 51.2 (t), 26.7 (d)); this spectrum led to the following assignments for **7a** and **7b** spectra: COO*Me*, 52.1 and 51.7; *C*OOMe, 174.8 and 172.9; *C*H_2OMe, 68.1 and 67.2; CH_2O*Me*, 64.8 and 63.3, respectively. (As the less sterically crowded carbons should appear at lower field, **7a** should be the trans isomer.)

Methyl 2-[(Octyloxy)methyl]-3-oxocyclobutanecarboxylate (8a). The reaction was run according to the procedure described for the preparation of **7a + 7b** at −35 °C by starting from 0.551 g (4.30 mmol) of methyl 3-oxocyclobutanecarboxylate (**3**) and in the presence of 0.080 g (0.35 mmol) of $ZnBr_2$. The crude product was chromatographed on 37 g of silica gel (hexane/ether, 85:15), and 0.537 g (46% from **3**) of methyl 2-[(octyloxy)methyl]-3-oxocyclobutanecarboxylate (**8a**) was obtained. The alkylation product corresponding to the ketene acetal **6** was not detected. Spectral data of **8a**: ^{1}H NMR (CCl_4) δ 0.74–1.04 (m, 3 H), 1.13–1.67 (br s, 12 H), 2.93–3.67 (m, 8 H), 3.94 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 13.94 (q), 22.54, 25.95, 29.14, 29.28, 29.34, 30.77, 31.71, 49.28 (t), 52.17 (q), 65.20 (d), 66.39 (t), 71.48 (t), 174.48 (s), 205.21 (s); IR (CCl_4) 1795, 1737 cm^{-1}; MS, *m/e* (relative intensity) (EI) 43 (70), 55 (51), 57 (44), 71 (89), 99 (100), 113 (53), 270 (M^+, 1.8). Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.56; H, 9.51.

Reaction of Lithium Enolate of Methyl 3-Oxocyclobutanecarboxylate (3) with Iodomethyl Methyl Ether. The lithium enolate corresponding to 0.265 g (2.07 mmol) of methyl 3-oxocyclobutanecarboxylate (**3**) was prepared as indicated above (see paragraph on methyl 2-(hydroxymethyl)-3-oxocyclobutanecarboxylate (**4**)). Then 0.400 g (2.13 mmol) of iodomethyl methyl ether[18] was added quickly at −78 °C. After 1 h of stirring at −78 °C, water (2 mL) and ether (3 mL) were added and the mixture was warmed to room temperature. Decantation, extraction (3 × 3 mL of ether), drying (Na_2SO_4), and evaporation gave the crude product, which was chromatographed on 7.3 g of silica gel (hexane/ether, 80:20, then 60:40, then 0:100); 0.024 g (9%) of **3** was recovered and 0.036 g (10%) of **7a** and 0.037 g (10.5%) of methyl 3-(methoxymethoxy)-2-cyclobutenecarboxylate (**10**) and a colored residue, which was not eluted. Spectral data of **10**: ^{1}H NMR ($CDCl_3$) δ 2.78–2.89 (m, 2 H), 3.25–3.44 (m, 1 H), 3.44 (s, 3 H), 3.69 (s, 3 H), 4.71 (s, 1 H), 4.96 (d, *J* = 1 Hz, 2 H); IR ($CDCl_3$) 1730, 1637 cm^{-1}; MS, *m/e* (relative intensity) (chemical ionization, NH_3) 112 (48), 173 (MH^+, 48), 190 (MNH_4^+, 100).

In another experiment, 0.371 g (2.07 mmol) of HMPA was introduced before the iodomethyl methyl ether. The same workup as above led to 0.021 g (8%) of **3**, 0.011 g (3%) of **7a**, and 0.032 g (9%) of **10**.

Methyl 2-Methylene-3-oxocyclobutanecarboxylate (2) via α-(Alkoxymethyl)cyclobutanones 7 and 8. Experimental Conditions for Entry 4, Table II. Crushed $KHSO_4$ (11.6 mg) was heated at 180 °C for 20 min under reduced pressure (6 mm) in a small distillation apparatus. The heating bath was removed, and 46.9 mg (0.27 mmol) of a mixture **7a**:**7b** = 30:70 was introduced in 45 s under atmospheric pressure. The mixture was heated at 180 °C for 1.3 min, and the reaction was allowed to proceed under reduced pressure (6 mm). The distillate was trapped (ca. 3 min) in pentane (0.6 mL) at −78 °C. Pentane and methanol were evaporated, and the mixture was separated by column chromatography on 2 g of silica gel (pentane/ether, 95:5). Methyl 2-methylene-3-oxocyclobutanecarboxylate (**2**) (17 mg, 45%) and **7a + 7b** (19 mg) were thus obtained (yield of **2** when the starting material recovered is taken into account: 75%).

Experimental Conditions for Entry 7, Table II. Crushed $KHSO_4$ (247 mg) was heated at 175 °C for 20 min under reduced pressure (22 mm) in a small distillation apparatus. The heating bath was removed, and **8a** (591 mg, 2.19 mmol) was introduced during 1 min under atmospheric pressure. The mixture was heated at 175 °C for 30 s, and the reaction was allowed to proceed under reduced pressure (22 mm). The distillate was trapped (10 min) in pentane (1 mL) at −78 °C. After evaporation, the crude product, which was a mixture of *n*-octanol and **2**, was dissolved in CCl_4 (3 mL) and cooled to 0 °C. Pyridine (0.173 g, 0.176 mL, 2.19 mmol) was quickly added with stirring, and 0.180 g (0.163 mL, 2.29 mmol) of acetyl chloride was added dropwise at 0 °C. After 15 min of stirring at 0 °C, pyridinium chloride was removed by vacuum filtration and washed with pentane (2 × 1 mL). The combined filtrates were evaporated and chromatographed on 10.5 g of silica gel (pentane/ether, 75:25). Methyl 2-methylene-3-oxocyclobutanecarboxylate (**2**) (0.171 g, 56%) was thus obtained.

1-[(Trimethylsilyl)oxy]cyclobutene (12). Cyclobutanone (0.409 g, 5.84 mmol) in THF (6 mL) was added dropwise (25 min) under argon to a stirred solution of LDA (6.08 mmol) in THF (8 mL) (see paragraph on methyl 2-(hydroxymethyl)-3-oxocyclobutanecarboxylate (**4**)) at −78 °C. After 20 min of stirring at −78 °C and 20 min at 0 °C, a centrifuged mixture of THF (2 mL), $ClSiMe_3$ (2 mL), and Et_3N (0.5 mL) was introduced. The mixture was stirred for 15 min at 0 °C and 10 min at room temperature. Volatile products were removed by distillation under reduced pressure (150 mm), and pentane (7 mL) was added to the residue. LiCl was removed by vacuum filtration and washed with pentane (2 × 1 mL). Volatile products of filtration were distilled (150 mm), pentane (7 mL) was added to the residue, and the remaining LiCl was removed. After distillation of pentane (150 mm), 0.735 g (88%) of crude 1-[(trimethylsilyl)oxy]cyclobutene (**12**) was obtained. It was sufficiently pure to be used in the next step: ^{1}H NMR ($CDCl_3$) δ 0.28 (s, 9 H), 2.03 (t, *J* = 3 Hz, 2 H), 2.61 (t, *J* = 3 Hz, 2 H), 4.60 (br s, 1 H); IR ($CDCl_3$) 1625 cm^{-1}; MS, *m/e* (relative intensity) (EI) 73 (64), 75 (100), 127 (69), 142 (M^+, 29) (results in agreement with literature[25]).

2-[(Octyloxy)methyl]cyclobutanone (13). The crude preceding 1-[(trimethylsilyl)oxy]cyclobutene (**12**) (0.735 g, 5.14 mmol) was dissolved in CH_2Cl_2 (11 mL); 0.110 g (0.49 mmol) of $ZnBr_2$ was added to the solution, and the mixture was cooled to −20 °C under argon. Then 1.10 mL (1.01 g, 5.40 mmol) of n-$C_8H_{17}OCH_2Cl$ (purity, 95%) was added dropwise at this temperature with stirring. The reaction mixture was slowly allowed to warm up to 20 °C (1.5 h), and after a further 30 min at this temperature, CH_2Cl_2 (10 mL) was added. The organic phase was washed with water (2 × 5 mL), and the aqueous phases were extracted with ether (2 × 2 mL). The combined organic phases were dried (Na_2SO_4) and evaporated to give the crude product, which was purified by column chromatography on 31 g of silica gel (hexane/ether, 80:20). 2-[(Octyloxy)methyl]cyclobutanone (0.421 g, 34% from **II**) was thus obtained: ^{1}H NMR (CCl_4) δ 0.70–1.00 (m, 3 H), 1.15–1.60 (m, 12 H), 1.95–2.20 (m, 3 H), 2.80–3.05 (m, 2 H), 3.27–3.65 (m, 4 H); IR (CCl_4) 1790 cm^{-1}; MS, *m/e* (relative intensity) (EI) 41 (64), 43 (60), 55 (100), 56 (95), 57 (69), 70 (71), (chemical ionization, NH_3) 229 (26), 213 (MH^+, 18), 230 (MNH_4^+, 100). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.78; H, 11.48.

2-[(Hexadecyloxy)methyl]cyclobutanone (14). n-$C_{16}H_{33}OCH_2Cl$ was prepared[20] by dropwise addition of 3.4 mL (3.4 mmol) of a 1 M solution of BCl_3 in CH_2Cl_2 to a stirred solution of 2.85 g (9.96 mmol) of $C_{16}H_{33}OCH_2OCH_3$ at 0 °C under argon. After 20 min of stirring at the same temperature and 2 h at room temperature, the mixture was evaporated and 2.76 g (95%) of crude $C_{16}H_{33}OCH_2Cl$ was obtained. It was sufficiently pure to be used in the next step: ^{1}H NMR ($CDCl_3$) δ 0.78–1.04 (m, 3 H), 1.22–1.62 (m, 28 H), 3.68 (t, *J* = 6.5 Hz, 2 H), 5.49 (s, 2 H). For another preparation, see, for instance, ref 26. Crude 1-[(tri-

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methylsilyl)oxy]cyclobutene (**12**) (0.493 g, 3.44 mmol) (obtained from 3.92 mmol of cyclobutanone (**11**)) was dissolved in CH_2Cl_2 (7 mL); 0.085 g (0.38 mmol) of $ZnBr_2$ was added to the solution, and 1.14 g (3.92 mmol) of crude n-$C_{16}H_{33}OCH_2Cl$ was added dropwise with stirring at room temperature under argon. After 1.5 h, CH_2Cl_2 (10 mL) and water (3 mL) were added. The aqueous phase was extracted with ether (2 × 2 mL). The combined organic phases were dried (Na_2SO_4) and evaporated. The purification by column chromatography on 30 g of silica gel (hexane/ether, 95:5) gave 0.510 g (40% from **11**) of 2-[(hexadecyloxy)methyl]-cyclobutanone as an oil, which crystallized in the refrigerator: ^1H NMR (CCl_4) δ 0.75–1.05 (m, 3 H), 1.10–1.40 (m, 28 H), 1.72–2.35 (m, 3 H), 2.81–3.05 (m, 2 H), 3.17–3.70 (m, 4 H); IR (CCl_4) 1795 cm^{-1}; MS, m/e (relative intensity) (chemical ionization, NH_3) 314 (26), 325 (MH^+, 18), 341 (33), 342 (MNH_4^+, 100), 343 (73), 344 (17). Anal Calcd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42. Found: C, 77.61; H, 12.35.

2-Methylenecyclobutanone (15). Crushed $KHSO_4$ (17.4 mg) was heated at 162 °C for 20 min under reduced pressure (20 mm) in a small distillation apparatus. The heating bath was removed, and 0.105 g (0.495 mmol) of **13** was introduced during 45 s under atmospheric pressure; the mixture was heated at 162 °C for 10 s. The reaction was allowed to proceed under reduced pressure (250 mm). The distillate was trapped (3 min) in $CDCl_3$ (0.5 mL) at −50 °C. The ^1H NMR analysis in the presence of 25.1 mg of $CHCl_3$ showed that the yield of nonisolated **15** was 49%; 20% of unreacted **13** was also trapped as well as n-octanol. In another experiment, 0.165 g (0.509 mmol) of **14** was used. The reaction in the presence of 63.3 mg of $KHSO_4$ at 165 °C under 145 mmHg gave a distillate, which was trapped in $CDCl_3$. The ^1H NMR analysis in the presence of $CHCl_3$ showed that two products were trapped, 2-methylenecyclobutanone (**15**) (0.411 mmol, 81%) and n-$C_{16}H_{33}OH$ (0.012 mmol, 2.5%). IR and ^1H NMR (45–100 MHz) data for **15** are in agreement with the literature:[3,8a,27] ^1H NMR ($CDCl_3$) (90 MHz) δ 2.59–2.93 (m, 2 H), 2.95–3.23 (m, 2 H), 5.12 (t, J = 2.5 Hz, 1 H), 5.77 (t, J = 2.8 Hz, 1 H); ^1H NMR ($CDCl_3$) (250 MHz) δ 2.67 (tdd, J = 8.4, 2.8, 2.5 Hz, 2 H), 2.99 (t, J = 8.4 Hz, 2 H), 5.07 (t, J = 2.5 Hz, 1 H), 5.72 (t, J = 2.8 Hz, 1 H); IR ($CDCl_3$) 1760, 1660 cm^{-1}; MS, m/e (relative intensity) (EI) 26 (32), 39 (82), 53 (40), 54 (100), 82 (M^+, 66).

2-Methylenespiro[3.5]-1-nonanone (19). (See also the preceding paragraphs for experimental procedures.) 1-[(Trimethylsilyl)oxy]spiro[3.5]-1-nonene (**17**) was prepared by starting from 0.388 g (2.81 mmol) of spiro[3.5]-1-nonanone.[28] (In this case, silylation was run at −60 °C.) Practically pure **17** (0.602 g, 2.81 mmol) was obtained: ^1H NMR ($CDCl_3$) δ 0.22 (s, 9 H), 0.88–1.70 (m, 10 H), 1.78 (s, 2 H), 4.53 (br s, 1 H); IR ($CDCl_3$) 1625 cm^{-1}; MS, m/e (relative intensity) (EI) 73 (100), 75 (53), 155 (31), 181 (30), 210 (M^+, 37). This crude product (0.602 g) gave by alkylation with $C_{16}H_{33}OCH_2Cl$ in the presence of $ZnBr_2$ (2.5 h, room temperature) the crude 2-[(hexadecyloxy)methyl]spiro[3.5]-1-nonanone (**18**), which was purified by column chromatography on 39 g of silica gel (hexane/ether, 95:5) to give 0.691 g (62% from **16**) of **18** as an oil: ^1H NMR ($CDCl_3$) δ 0.80–1.09 (m, 3 H), 1.27 (br s, 28 H), 1.62 (br s, 10 H), 1.75–2.04 (m, 2 H), 3.29–3.69 (m, 5 H); IR ($CDCl_3$) 1770 cm^{-1}; MS, m/e (relative intensity) (chemical ionization, NH_3) 123 (31), 168 (24), 393 (MH^+, 13), 410 (MNH_4^+, 100), 411 (44). Anal. Calcd for $C_{26}H_{48}O_2$: C, 79.53; H, 12.32. Found: C, 79.62; H, 12.52. The reaction of 0.232 g (0.591 mmol) of **18** in the presence of 98.8 mg of $KHSO_4$ (175 °C, 0.5 min at atmospheric pressure and 8 min under 26 mmHg, trapping in $CDCl_3$ at −50 °C) gave crude **19**, which was purified by column chromatography on 5 g of silica gel (pentane/ether, 95:5) to give 0.062 g (70% from **18**) of pure **19** and another fraction of 0.018 g (12%) of n-$C_{16}H_{33}OH$. Spectral data of **19**: ^1H NMR ($CDCl_3$) δ 1.25–1.90 (m, 10 H), 2.44 (t, J = 3 Hz, 2 H), 5.11 (t, J = 3 Hz, 1 H), 5.79 (t, J = 3 Hz, 1 H); IR ($CDCl_3$) 1770, 1660 cm^{-1}; MS, m/e (relative intensity) (EI) 39 (64), 41 (61), 67 (91), 68 (88), 79 (100), 81 (79), 150 (M^+, 14); accurate mass (EI),[29] m/e 150.1045 (calcd for M^+, $C_{10}H_{14}O$: 150.1045).

Stabilities of 2 and 20 in Water Measured by UV Spectroscopy. Aqueous solutions of **2** (1.93×10^{-4} M) or **20** (1.91×10^{-4} M) were poured into thermostated UV cells at 38 °C, and UV spectra were recorded to follow the rate of disappearance of **2** (λ_{max} 230 nm) or **20** (λ_{max} 232 nm). A first-order decomposition reaction occurred for at least 6 h in the case of **2** and 28 h in the case of **20**. The corresponding rate constants were 1.08×10^{-3} min^{-1} ($t_{1/2}$ = 10.95 h) and 1.62×10^{-4} min^{-1} ($t_{1/2}$ = 72.68 h), respectively.

Methyl 2-Methyl-3-oxo-1-cyclobutenecarboxylate (22). DBU (5 μL, 0.033 mmol) was added dropwise at room temperature and with stirring to 24.5 mg (0.175 mmol) of methyl 2-methylene-3-oxo-1-cyclobutanecarboxylate (**2**) in CH_2Cl_2 (2 mL). After 5 min, the total disappearance of **2** was observed by TLC (pentane/ether, 40:60; R_f (**2**) 0.42, (**22**) 0.56) and CH_2Cl_2 (5 mL) and water (1 mL) were added. The aqueous phase was neutralized (10% aqueous HCl), decanted, and extracted with CH_2Cl_2 (1 mL). The combined organic phases were dried (Na_2SO_4) and evaporated. The column chromatography on 1 g of silica gel (pentane/ether, 90:10) gave 11.0 mg (46%) of methyl 2-methyl-3-oxo-1-cyclobutenecarboxylate (**22**): ^1H NMR (CCl_4) δ 1.92 (t, J = 2.2 Hz, 3 H), 3.30 (q, J = 2.2 Hz, 2 H), 3.80 (s, 3 H); IR (CCl_4) 1775, 1720, 1635 cm^{-1}; UV (H_2O) λ_{max} 230 nm (ϵ 5400); MS, m/e (relative intensity) (EI) 43 (23), 51 (22), 53 (100), 54 (22), 112 (39), 140 (M^+, 15).

Methyl 3-Oxo-2-[(phenylthio)methyl]cyclobutanecarboxylates 9a and 9b. Thiophenol (95 μL, 0.92 mmol) and Et_3N (12 μL, 0.09 mmol) were successively added at −30 °C to 0.120 g (0.96 mmol) of methyl 2-methylene-3-oxocyclobutanecarboxylate (**2**) in Et_2O (10 mL). After 25 min of stirring at −30 °C, the total disappearance of **2** was observed by TLC (pentane/ether, 75:25; R_f (**2**) 0.25, (**9**) 0.17) and Et_2O (5 mL) and water (3 mL) were added. The mixture was allowed to warm up to room temperature, the aqueous phase was extracted with Et_2O (3 × 2 mL), and the combined organic phases were dried (Na_2SO_4) and evaporated. The column chromatography on 5 g of silica gel gave 0.187 g (87%) of methyl 3-oxo-2-[(phenylthio)methyl]cyclobutanecarboxylates **9a** and **9b** in the ratio 70:30 (by vapor-phase chromatography). They were not separated, and the most abundant **9a** was assigned as the trans isomer:[17] ^1H NMR (**9a** + **9b**) ($CDCl_3$) δ 2.85–3.45 (m, 5 H), 3.70–4.00 (m, 4 H, comprising 2 s (3.70, 1.8 H; 3.72, 1.2 H)), 7.17–7.50 (m, 5 H); IR ($CDCl_3$) (**9a** + **9b**) 1795, 1737 cm^{-1}; GC/MS, m/e (relative intensity) (EI) (**9a**) 53 (54), 66 (51), 109 (72), 110 (100), 112 (45), 250 (M^+, 2.4), (**9b**) 53 (48), 66 (34), 109 (52), 110 (100), 112 (39), 250 (M^+, 2.5). Anal. (**9a** + **9b**). Calcd for $C_{13}H_{14}O_3S$: C 62.38; H, 5.64; S, 12.81. Found: C, 62.51; H, 5.73; S, 12.78.

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Registry No. 1 (methyl ester), 111465-64-6; **2**, 112139-41-0; **3**, 695-95-4; *trans*-**4**, 112139-40-9; *cis*-**4**, 112139-39-6; **5**, 112139-42-1; **6**, 112139-43-2; **7a**, 112139-44-3; **7b**, 112139-45-4; **8a**, 112139-46-5; **9a**, 112139-54-5; **9b**, 112139-55-6; **10**, 112139-47-6; **12**, 54623-41-5; **13**, 112139-48-7; **14**, 112139-49-8; **15**, 17714-43-1; **17**, 112139-50-1; **18**, 112139-51-2; **19**, 112139-52-3; **22**, 112139-53-4; $H_3C(CH_2)_7O$-CH_2Cl, 24566-90-3; $H_3C(CH_2)_{15}OCH_2Cl$, 13497-63-7; HCHO, 50-00-0; cyclobutane, 1191-95-3; spiro[3,5]-1-nonanone, 185-02-4.

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