59.81; H, 7.03; N, 9.78.

The crude NMR spectrum prior to silica gel chromatography showed the presence of 1,4-dimethyl-6-(phenylsulfonyl)-1,4-diazacyclooct-6-ene (**20**): NMR ($CDCl_3$, 90 MHz) $\delta$ 2.25 (s, 3 H), 2.30–2.85 (m, 4 H), 2.45 (s, 3 H), 3.40 (d, 2 H, $J$ = 6.0 Hz), 3.85 (s, 2 H), 7.05 (t, 1 H, $J$ = 6.0 Hz), and 7.25–7.85 (m, 5 H). Unfortunately, all attempts to isolate a pure sample of **20** failed as it readily rearranged to piperazine **18**.

**Reaction of 2,3-Bis(phenylsulfonyl)-1,3-butadiene (1) with *N,N'*-Dimethyl-1,3-propanediamine (21).** To a solution containing 250 mg of 2,3-bis(phenylsulfonyl)-1,3-butadiene (**1**) in 20 mL of methylene chloride at 0 °C was added 76 mg of *N,N'*-dimethyl-1,3-propanediamine (**21**). After stirring for 5 min, 76 mg of triethylamine was added, and the reaction was stirred at 0 °C under a nitrogen atmosphere for an additional 3 h. The reaction mixture was washed once with water, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue consisted of a 2:1 mixture of 1,5-dimethyl-7-(phenylsulfonyl)-1,5-diazacyclonon-7-ene (**22**) and 1,4-dimethyl-5-(1-(phenylsulfonyl)ethenyl)-1,4-diazepine (**23**). Heating the reaction mixture in refluxing benzene for 4 h afforded a 9:1 mixture of **22** and **23**. Flash chromatography of the reaction mixture on a silica gel column using a 90% chloroform–methanol mixture as the eluent resulted in the isolation of cyclononene **22** (155 mg (70% yield)) as a pale yellow solid (mp 124–125 °C) whose structure was assigned on the basis of its spectral properties: IR ($CHCl_3$) 3010, 2950, 2930, 2845, 2800, 1450, 1305, 1220, 1150, 1085, and 690 $cm^{-1}$; NMR ($CDCl_3$), 300 MHz) $\delta$ 1.41 (m, 2 H), 1.92 (s, 3 H), 2.08 (t, 2 H, $J$ = 6.5 Hz), 2.19 (s, 3 H), 2.24 (t, 2 H, $J$ = 7.6 Hz), 3.12 (s, 2 H), 3.35 (d, 2 H, $J$ = 5.7 Hz), 7.17 (t, 1 H, $J$ = 5.7 Hz), 7.52 (t, 2 H, $J$ = 7.2 Hz), 7.59 (t, 1 H, $J$ = 7.2), and 7.86 (d, 2 H, $J$ = 7.2 Hz). Anal. Calcd for $C_{15}H_{22}N_2O_2S$: C, 61.20; H, 7.53; N, 9.51. Found: C, 61.11; H, 7.39; N, 9.34. Diazepine **23** showed the following NMR characteristics: NMR ($CDCl_3$, 300 MHz) $\delta$ 6.18 (s, 1 H) and 6.45 (s, 1 H). Unfortunately, a pure sample of diazepine **23** could not be obtained as it was readily converted to **22** upon silica gel chromatography.

**Reaction of 2,3-Bis(phenylsulfonyl)-1,3-butadiene (1) with 2-(Ethylamino)ethanol.** To a solution containing 250 mg of 2,3-bis(phenylsulfonyl)-1,3-butadiene (**1**) in 20 mL of methylene chloride at 25 °C was added 67 mg of 2-(ethylamino)ethanol. After stirring for 5 min, 76 mg of triethylamine was added, and the reaction was stirred at 25 °C under a nitrogen atmosphere for an additional 16 h. The reaction mixture was washed once with water, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue was subjected to flash chromatography on a silica gel column, using a 90% chloroform–methanol mixture as the eluent. The major fraction contained 151 mg (72% yield) of a yellow oil whose structure was assigned as 4-ethyl-2-(1-(phenylsulfonyl)ethenyl)morpholine (**25**) on the basis of its spectral properties: IR (neat) 3080, 2985, 2880, 2820, 1445, 1310, 1220, 1180, 1155, 1110, 1085, and 970 $cm^{-1}$; NMR ($CDCl_3$, 300 MHz) $\delta$ 1.00 (t, 3 H, $J$ = 7.2 Hz), 1.84 (dd, 1 H, $J$ = 11.1 and 10.1 Hz), 2.06 (m, 1 H), 2.35 (q, 2 H, $J$ = 7.2 Hz), 2.66 (m, 1 H), 3.02 (m, 1 H), 3.53 (m, 1 H), 3.78 (m, 1 H), 4.18 (m, 1 H), 6.19 (s, 1 H), 6.54 (s, 1 H), 7.45–7.70 (m, 3 H), and 7.87 (d, 2 H, $J$ = 7.4 Hz). Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98. Found: C, 59.71; H, 6.59; N, 4.92. The initial crude NMR spectrum showed only the presence of 4-ethyl-7-(phenylsulfonyl)-1,4-oxazacyclooct-6-ene (**24**) whose structure was assigned on the basis of its characteristic NMR spectrum: NMR ($CDCl_3$, 300 MHz) $\delta$ 1.03 (t, 3 H, $J$ = 7.2 Hz), 2.25 (q, 2 H, $J$ = 7.2 Hz), 2.37 (t, 2 H, $J$ = 5.0 Hz), 3.33 (s, 2 H), 3.39 (d, 2 H, $J$ = 6.6 Hz), 3.47 (t, 2 H, $J$ = 5.0 Hz), 7.14 (t, 1 H, $J$ = 6.6 Hz), 7.45–7.70 (m, 3 H), and 7.88 (d, 2 H, $J$ = 7.4 Hz). Unfortunately, all attempts to isolate a pure sample of **24** failed as it readily rearranged to **25**.

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# Iterative Synthesis of Selectively Substituted $\alpha,\beta$-Unsaturated and Saturated Medium-Ring Lactones

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Chloro, chloromethyl, and chlorofluoro carbenoids, generated by reaction of a base on the corresponding halides, were added to trimethylsilyl enol ethers derived from lactones, to give 1-[(trimethylsilyl)oxy]-2-chlorobicyclo-[*n*.1.0]oxanes. Thermal rearrangement of these adducts led to the $\alpha,\beta$-ethylenic lactones, corresponding to a one-carbon ring expansion of the starting lactones. After hydrogenation, with the same iterative sequence a new one-carbon ring expansion could be performed. This method allowed the preparation in good yields of hitherto unknown medium-ring lactones. Spectroscopic and physicochemical properties of the isomeric unsaturated lactones were examined. For the 9- and 10-membered series, the trans isomers could be readily isomerized by $I_2$ into the cis isomers or gave diolides under acidic conditions.

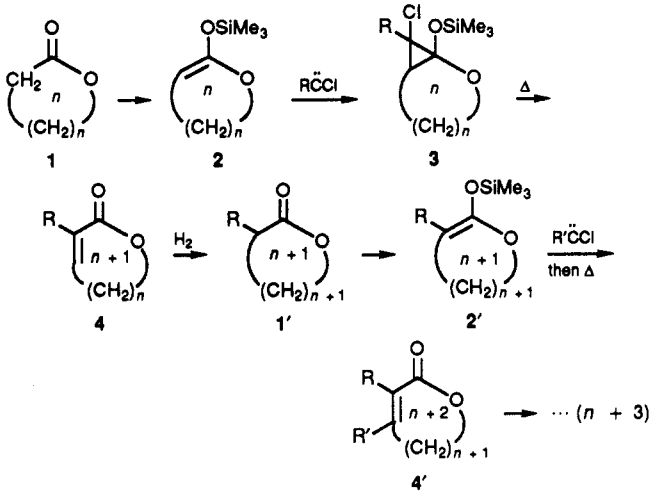
The synthesis of medium-ring lactones has been the subject of active investigation recently, as many of these compounds possess diverse and significant biological activities. In the case of macrolide preparation,[1] the main synthetic methods leading to these compounds begin from either linear or cyclic precursors. Starting with linear precursors, ring closure can be effected by generation of the C(O)–O– moiety;[1] the main drawback of such a process, disfavored on entropy grounds, is the need for dilution in order to avoid intermolecular condensations. However, lactonizations by enzymic methods have been described in a few cases[2]. Ring closure can also be obtained through carbon–carbon bond formation by various methods,[3]

(1) (a) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (b) Back, T. G. *Tetrahedron* **1977**, *33*, 3041. (c) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (d) Boeckman, R. K.; Goldstein, S. W. *The Total Synthesis of Natural Products*, Wiley: New York, 1988; Vol. 7, Chapter 1.

(2) (a) Gatfield, I. L. *Ann. N.Y. Acad. Sci.* **1984**, *434*, 569. (b) Makita, A.; Nikira, T.; Yamada, Y. *Tetrahedron Lett.* **1987**, *28*, 805.

0022-3263/90/1955-4807$02.50/0 

**Scheme I**



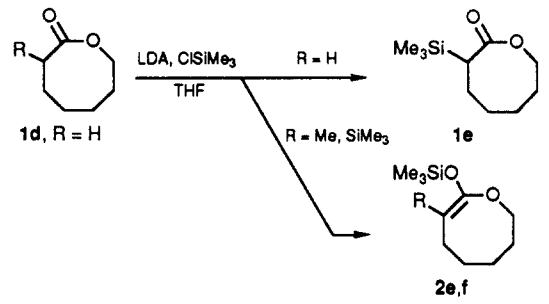
among which intramolecular Wittig or Wittig-like reactions[4a,b] lead to 12-membered and higher membered $\alpha,\beta$-unsaturated lactones. Such a methodology has recently been studied in the case of medium-ring compounds.[4c]

Potential cyclic precursors include ketones whose Baeyer–Villiger oxidation[1a,b,5] exhibits a high regioselectivity, but only when bearing $\alpha$-substitutents. Enzymic Baeyer–Villiger[6] reaction has been applied to the formation of 7-membered lactones. Fragmentation of the bridged bond of bicyclic compounds may also lead to medium-sized lactones,[1,7-10] as may intramolecular Claisen rearrangements of cyclic ketene acetals.[11] Preformed lactones or thiolactones can also be precursors of these compounds: Whereas acyl transfer from hydroxyalkyl lactones is restricted to the formation of 11- or 12-membered-rings,[12] the same process starting with hydroxyalkyl thiolactones can generate smaller rings.[13]

In many cases, classical chemical transformations (such as double-bond generation $\alpha$ to the CO group by selenoxide chemistry or alkyl substitution via enolates formed by conjugate addition to $\alpha,\beta$-unsaturated lactones) have been used to prepare $\alpha,\beta$-unsaturated medium-ring lactones or to introduce substituents $\alpha$ or $\beta$ to the carbonyl group.[5]

The reactions of carbenes with ketene acetals have been studied in our laboratory;[14] the cyclopropanes thus formed lead easily to $\alpha$-substituted $\alpha,\beta$-unsaturated esters. This

**Scheme II**



reaction has been applied to a cyclic ketene acetal related to a 6-membered lactone,[14b] as well as to the synthesis of pyrenophorol.[15] The extension of such a process would appear interesting (see Scheme I) since it allows the introduction of a selected substituent $\alpha$ to the carbonyl group of an $\alpha,\beta$-unsaturated lactone **4**, depending on the nature of the carbene reagent, starting from a smaller ring saturated ($n$) lactone such as **1**. Moreover, this method should be iterative, since after hydrogenation another saturated lactone, **1'** ($n + 1$), ring-expanded by one carbon unit and substituted at will, should be obtained. Another cycle should then lead to new $n + 2$ lactones **4'**, bearing the desired substituents at the $\alpha$- and $\beta$-positions (Scheme I).

Such ring "growing" possibilities were already described by Masamune et al.,[1c] using $CH_2N_2$ and medium-ring cyclanones. Recently, a radical process was developed for a ring expansion of ketones by one carbon or more.[16]

In the present work, we examine the extent to which the iterative methodology can be applied to the synthesis of diversely substituted saturated and $\alpha,\beta$-unsaturated medium-ring lactones. The spectral properties as well as the conformations of several of these lactones will be discussed. The application of this methodology to a short and efficient synthesis of (*S*)-phoracantholide I has already been published.[17]

## Results and Discussion

**1-[(Trimethylsilyl)oxy]-2-chlorobicyclo[*n*.1.0]oxanes.** According to the planned iterative method, saturated lactones **1** were transformed into cyclic ketene acetals **2** by the action of LDA and $ClSiMe_3$ in THF according to Corey and Gross,[18] but avoiding any aqueous workup. The products were purified by distillation and characterized by $^1H$ NMR, IR, MS. The cyclic ketene acetals **2** so prepared are listed in Table I. In all cases, a single isomer was obtained to which the *E* configuration was assigned on the basis of $^1H$ NMR data, in agreement with literature values.[14b,18]

Heptanolide **1d** was transformed into the C-silylated analogue **1e** by the same treatment, even after reaction conditions were modified.[19] However, $\alpha$-substitution of lactone **1d** suppressed this side reaction, and **1e** and **1f** were thus transformed into ketene acetals **2e** and **2f** (Scheme II).

Cyclopropanation was performed as previously described:[14a-c] $NaN(SiMe_3)_2/CH_2Cl_2$/pentane at −15 °C (R

(3) (a) Takahashi, T.; Hashiguchi, S.; Kasuga, K.; Tsuji, J. *J. Am. Chem. Soc.* **1978**, *100*, 7424. (b) Wada, M.; Shigehisa, T.; Akiba, K. *Tetrahedron Lett.* **1985**, *26*, 5191. (c) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1979**, *101*, 1595; *J. Am. Chem. Soc.* **1980**, *102*, 4743. (d) Tsuji, T.; Mandai, T. *Tetrahedron Lett.* **1978**, *21*, 1817. (e) Porter, N. A.; Chang, V. H. T. *J. Am. Chem. Soc.* **1987**, *109*, 4976.

(4) (a) Stork, G.; Nakamura, E. *J. Org. Chem.* **1979**, *44*, 4010. (b) Bestmann, H. J.; Schobert, R. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 780. (c) Yvergnaux, F.; Le Floc'h, Y.; Grêe, R.; Toupet, L. *Tetrahedron Lett.* **1989**, *30*, 7393.

(5) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981.

(6) (a) Walsh, C. T.; Chen, Y. C. J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 333 and quoted references. (b) Taschner, M. J.; Black, D. J. *J. Am. Chem. Soc.* **1988**, *110*, 6892. (c) Ouazzani-Chahdi, J.; Buisson, D.; Azerad, R. *Tetrahedron Lett.* **1987**, *28*, 1109.

(7) Wakalmatsu, T.; Akasaka, K.; Ban, Y. *J. Org. Chem.* **1979**, *44*, 2008.

(8) Stach, H.; Hess, M. *Tetrahedron* **1988**, *44*, 1573 and quoted references.

(9) Suginome, H.; Yamada, S. *Tetrahedron* **1987**, *43*, 3371.

(10) Ono, N.; Miyake, H.; Kaji, A. *J. Org. Chem.* **1984**, *49*, 4997.

(11) Petrzilka, M. *Helv. Chim. Acta* **1978**, *61*, 3075.

(12) Corey, E.; Brunelle, D. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1977**, *99*, 7359.

(13) Vedejs, E.; Powell, D. W. *J. Am. Chem. Soc.* **1982**, *104*, 2046.

(14) (a) Slougui, N.; Rousseau, G.; Conia, J. M. *Synthesis* **1982**, *58*. (b) Slougui, N.; Rousseau, G. *Tetrahedron* **1985**, *41*, 2643 and quoted references. (c) Rousseau, G.; Slougui, N. *Tetrahedron* **1985**, *41*, 2653. (d) Blanco, L.; Rousseau, G. *Bull. Soc. Chim. Fr.* **1985**, 455.

(15) Hirao, T.; Fujihara, Y.; Kurokawa, K. *J. Org. Chem.* **1986**, *51*, 2830.

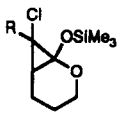
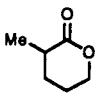
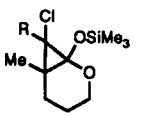
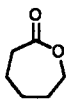
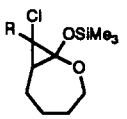
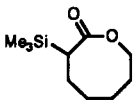
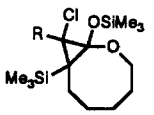
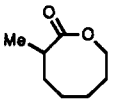
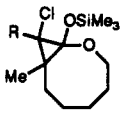
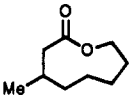
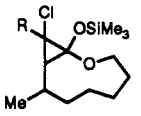
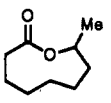
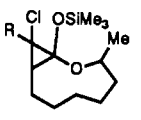
(16) (a) Dowd, P.; Choi, S.-C. *Tetrahedron* **1989**, *45*, 77. (b) Beckwith, A. L. J.; O'Shea, D. M.; Westwood, S. W. *J. Am. Chem. Soc.* **1988**, *110*, 2565.

(17) Fouque, E.; Rousseau, G. *Synthesis* **1989**, 661.

(18) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495.

(19) Various conditions used: LDA, THF/hexane, −40 °C; lithium tetramethylpiperidide, THF, −70 °C; Na- or K-HMDS, THF, −70 °C; LDA, DME, −70 °C. In all the cases less than 10% of the expected ketene acetal was formed. For a similar observation, see: Gilbert, J. C.; Kelly, T. A. *Tetrahedron Lett.* **1989**, *30*, 4193.

**Table I. Obtainment of 2-Chlorobicyclo[*n*.1.0]oxanes 3**

| entry | | starting lactone | ketene acetal (yield, %) | cyclopropyl compound: structure | R | no. | cis/trans[a] |
|---|---|---|---|---|---|---|---|
| 1 | 1a |  | 2a (85)[14b] |  | H | 3aI | 33/67 |
| 2 | | | | | $CH_3$ | 3aII | 40/60 |
| 3 | 1b |  | 2b (87) |  | H | 3bI | 46/54 |
| 4 | | | | | $CH_3$ | 3bII | 32/68 |
| 5 | | | | | F | 3bIII | 56/44 |
| 6 | 1c |  | 2c (82)[35] |  | H | 3cI | 43/57 |
| 7 | | | | | $CH_3$ | 3cII | 37/63 |
| 8 | | | | | F | 3cIII | 50/50 |
| 9 | 1e |  | 2e (92) |  | H | 3eI | 39/61 |
| 10 | | | | | F | 3eIII | 20/80 |
| 11 | 1f |  | 2f (89) |  | H | 3fI | 77/23 |
| 12 | | | | | $CH_3$ | 3fII | 40/60 |
| 13 | | | | | F | 3fIII | 50/50 |
| 14 | 1g |  | 2g (92) |  | H | 3gI | 55/45[b] |
| 15 | | | | | $CH_3$ | 3gII | 45/55[c] |
| 16 | | | | | F | 3gIII | *d* |
| 17 | 1h |  | 2h (94)[17] |  | H | 3hI[17] | 55/45[b] |
| 18 | | | | | $CH_3$ | 3hII | *d* |
| 19 | | | | | F | 3hIII | *d* |

[a] For R = H, the cis/trans assignment relies on the shielding of the R proton when it lies in the endo position, relative to the exo in $^1H$ NMR. For R = $CH_3$, the cis/trans assignment is made by $^1H$ NMR by comparison of the ASIS effects on $SiMe_3$ signals ($\delta_{CCl_4} - \delta_{C_6D_6}$), which are larger for the cis than for the trans isomers.[24] For R = F the cis/trans assignment is accomplished by $^{19}F$ NMR: $^3J_{H-F}$ values for **3cIII**[36] and $^{19}F$ shielding when F is located in the endo relative to the exo position, as well as use of shift increments.[37] [b] *E* isomer characterized next to the ring-expanded lactone formed from the *Z* isomer (estimated ratio). [c] *Z*/*E* ratio determined after thermal rearrangement. [d] No chloro compounds characterized at room temperature. α,β-Unsaturated lactones **4gIII**, **4hII**, and **4hIII** are formed in situ.

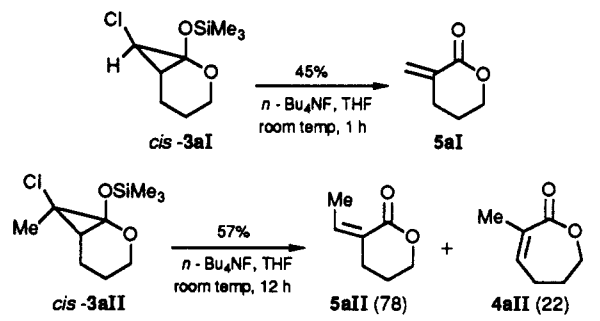
= H, series I), *n*-BuLi/$CH_3CHCl_2$/$Et_2O$ at −30 °C (R = $CH_3$, series II), KO*t*-Bu/$CHFCl_2$/hexane at −78 °C[14d] (R = F, series III), under an inert gas atmosphere. The chlorobicyclo[*n*.1.0]oxanes **3I**, **3II**, and **3III** (Table I) were obtained as cis/trans mixtures (cis and trans being defined by the relative configuration of the C–Cl and C–$OSiMe_3$ bonds in the cyclopropane). Because of their low stabilities, most products were not purified but were identified by $^1H$ NMR and IR spectra of the crude reaction mixtures (vide infra). (*Z*)-**3gI**, (*Z*)- and (*E*)-**3gIII**, (*Z*)-**3hI**, (*Z*)- and (*E*)-**3hII** and (*Z*)- and (*E*)-**3hIII** (Table II, entries 14–19) were too unstable to be characterized at room temperature and were transformed in situ into the corresponding α,β-unsaturated lactones, in the presence of added $Et_3N$ in order to avoid oligomerizations (vide infra).

The estimated yields of compounds **3** were generally high, although it was necessary to use 3 or 4 equiv of carbene precursor and base when starting from 8- or 9-membered ketene acetals (**2e–h**; Table II, entries 9–19). As expected,[14] the cyclopropanation reaction showed poor stereoselectivity in all but two cases (Table I, entries 10 and 11).

**Unsaturated and Saturated Lactones.** Thermolysis of **3** in refluxing toluene or xylene, occasionally in the presence of $Et_3N$, generally led to α,β-unsaturated lactones **4** (Table II) whose structural assignments were made on the basis of their physicochemical properties (vide infra).

When starting from chlorobicyclo[*n*.1.0]heptanes (cis/trans mixtures, **3a** and **3b**), lactones (*Z*)-**4aI**, (*Z*)-**4aII**, (*Z*)-**4bI**, and (*E*)-**4bIII** were obtained in moderate yields,

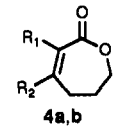
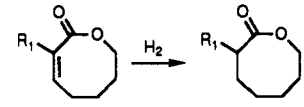
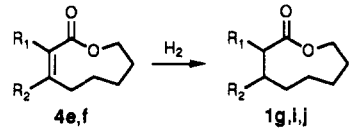
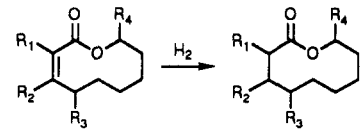
**Scheme III**




along with recovered cyclopropane precursors *cis*-**3a** and -**3b** (Table II, entries 1–3) or side products (Table II, entry 5). The lactones were separated by flash chromatography on $SiO_2$. In one case (entry 4), treatment with *n*-$Bu_4NF$ in THF gave (*Z*)-**4bII** in better yield than simple heating (54% after 2.3 h in refluxing xylene). *cis*-**3aI** and **3aII** were not transformed into lactones under thermal conditions; and the action of *n*-$Bu_4NF$ in THF led to the known exo methylene lactones **5aI**[20] and **5aII**[21] accompanied by small amounts of the ring-expanded lactone **4aII** when the starting material was *cis*-**3aII** (Scheme III).

(20) Mori, M.; Washioka, Y.; Urayama, T.; Yoshiura, K.; Chiba K.; Ban, Y. *J. Org. Chem.* **1983**, *48*, 4058.
(21) Ksander, G. M.; Mc Murry, J. E.; Johnson, M. *J. Org. Chem.* **1977**, *42*, 1180.

**Table II. Lactone Syntheses**

| entry | cyclopropyl intermediate | rearrangement conditions | R gps | $\alpha,\beta$-unsatd lactones (yield, %)[a] | hydrogenation conditions | satd lactones[d] (yield, %) |
|---|---|---|---|---|---|---|
| | | | 7-Membered Lactones | | | |
| | | |  **4a,b** | | | |
| 1 | **3aI** | xylene, 7 h | $R_1 = R_2 = H$ | **4aI**[34] (39)[b] | | |
| 2 | **3aII** | xylene, 7 h | $R_1 = Me$; $R_2 = H$ | **4aII**[14b] (65)[b] | | |
| 3 | **3bI** | xylene, 5 h | $R_1 = H$; $R_2 = Me$ | **4bI** (48)[b] | | |
| 4 | **3bII** | *n*-$Bu_4N^+F^-$, THF, 1 h | $R_1 = R_2 = Me$ | **4bII** (72) | | |
| 5 | **3bIII** | xylene, 1 h | $R_1 = F$; $R_2 = Me$ | **4bIII** (39)[c,d] | | |
| | | | 8-Membered Lactones | | | |
| | | |  **4c** **1f** | | | |
| 6 | **3cI** | toluene, 25 h | $R_1 = H$ | **4cI** (81) | | |
| 7 | **3cII** | xylene, 10 h | $R_1 = Me$ | **4cII** (81) | 4 atm, 3 h | **1f** (95) |
| 8 | **3cIII** | xylene, 4 h | $R_1 = F$ | **4cIII** (77) | | |
| | | | 9-Membered Lactones | | | |
| | | |  **4e,f** **1g,i,j** | | | |
| 9 | **3eI** | xylene, 1 h | $R_1 = H$; $R_2 = SiMe_3$ ($E/Z$ = 65/35) | **4eI** (75) | *E*: 4 atm, 48 h<br>*Z*: 4 atm, 96 h | **1i** (95)<br>**1i** (97) |
| 10 | **3eIII** | benzene/$NEt_3$, 2 h | $R_1 = F$; $R_2 = SiMe_3$ ($E/Z$ = 81/19) | **4eIII** (41) | *E*: 4 atm, 4 h<br>*Z*: 4 atm, 4 h | **1j** (96) (cis/trans = 97/3)<br>**1j** (93) (cis/trans = 6/94) |
| 11 | **3fI** | xylene, 2 h | $R_1 = H$; $R_2 = Me$ ($E/Z$ = 38/62) | **4fI** (80) | *E* + *Z*: 4 atm, 24 h | **1g** (95) |
| 12 | **3fII** | xylene, 2.5 h | $R_1 = R_2 = Me$ ($E/Z$ = 38/62) | **4fII** (54) | | |
| 13 | **3fIII** | xylene, 2 h | $R_1 = F$; $R_2 = Me$ ($E/Z$ = 60/40) | **4fIII** (78) | | |
| | | | 10-Membered Lactones | | | |
| | | |  **4g,h** **1k,q** | | | |
| 14 | **3gI** | toluene/$NEt_3$, 0.5 h | $R_1 = R_2 = R_4 = H$; $R_3 = Me$ ($E/Z$ = 47/53) | **4gI** (74) | *E*: 1 atm, 2 h<br>*Z*: 1 atm, 2 h | **1k** (97)<br>**1k** (95) |
| 15 | **3gII** | toluene/$NEt_3$, 0.5 h | $R_1 = R_3 = Me$; $R_2 = R_4 = H$ ($E/Z$ = 50/50) | **4gII** (66) | *E*: 1 atm, 0.5 h<br>*Z*: 1 atm, 2 h | **1l** (93) (cis/trans = 92/8)<br>**1l** (93) (cis/trans = 83/17) |
| 16 | [**3gIII**] | toluene/$NEt_3$, 0.5 h | $R_1 = F$; $R_2 = R_4 = H$; $R_3 = Me$ ($E/Z$ = 70/30) | **4gIII** (75) | *E* + *Z*: 1 atm, 2 h | **1m** (94) (cis/trans = 91/9) |
| 17 | **3hI** | toluene/$NEt_3$, 0.5 h | $R_1 = R_2 = R_3 = H$; $R_4 = Me$ ($E/Z$ = 52/48) | **4hI** (70) | *E*: 1 atm, 0.25 h<br>*Z*: 1 atm, 1.5 h | **1o**[17] (96)<br>**1o**[17] (91) |
| 18 | [**3hII**] | toluene/$NEt_3$, 1 h | $R_1 = R_4 = Me$; $R_2 = R_3 = H$ ($E/Z$ = 52/48) | **4hII**[17] (75) | *E*: 1 atm, 0.25 h<br>*Z*: 1 atm, 3 h | **1p**[26] (93) (cis/trans = 83/17)<br>**1p**[26] (96) (cis/trans = 68/32) |
| 19 | [**3hIII**] | toluene/$NEt_3$, 0.25 h | $R_1 = F$; $R_2 = R_3 = H$; $R_4 = Me$ ($E/Z$ = 52/48) | **4hIII** (64) | *E*: 1 atm, 1 h<br>*Z*: 1 atm, 0.25 h | **1q** (95) (cis/trans = 96/4)<br>**1q** (95) (cis/trans = 81/19) |

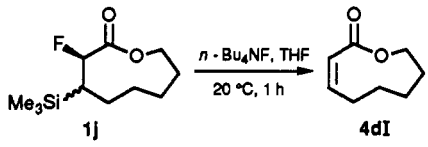
[a] Isolated yield calculated from enoxysilanes **2**. [b] Unchanged cis cyclopropanes **3** present in the reaction mixture. [c] 6.5% of 2-(chlorofluoromethyl)-2-methylpentanolide (**4'bIII**) and 19.5% of 2-chloro-3-methyl-2-hexenolide (**4''bIII**) were also isolated. [d] Treatment by *n*-$Bu_4NF$ in THF led to **4bIII** next to 2-(chlorofluoromethyl)-2-pentanolide (**4'bIII**) in a 84/16 ratio (yield 64%). [d] Determination of the ratios of cis and trans isomers by GPC.

**Table III. Trans–Cis Lactone Isomerizations by $I_2$ in Refluxing Benzene**

| starting lactone | $t_{1/2}$, h | reaction time, h | product (yield, %)[a] |
|---|---|---|---|
| (*Z*)-**4eI** | 3 | 150 | (*E*)-**4eI** (85) |
| (*E*)-**4fI** | 2.5 | 140 | (*Z*)-**4fI** (87) |
| (*E*)-**4gI** | 48 | 350 | (*Z*)-**4gI** (42)[b] |
| (*E*)-**4gII** | 0.5 | 93 | (*Z*)-**4gII** (80) |

[a] Yield of purified compound. [b] Diolide **6gI** is also formed (27%).

**Scheme IV**




**1j** **4dI**

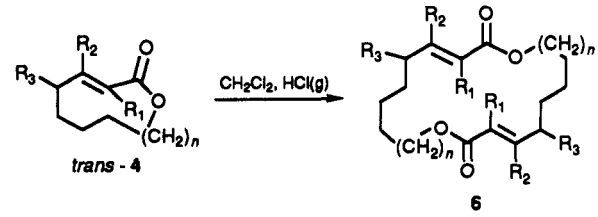
In the [5.1.0] series **3c**, the yields of unsaturated lactones **4cI**, **4cII**, and **4cIII** were higher, all of the cyclopropane precursors being transformed after a sufficiently long reflux period (Table II, entries 6–8). This result is probably due to the ring opening of *cis*-**3c** into unsaturated trans lactones, which undergo rapid isomerization to the cis compounds. Such behavior finds precedent in the alicyclic series; (*E*)-cyclooctenones have only been characterized at low temperature.[22]

From larger ring derivatives **3e–h**, cis and trans $\alpha,\beta$-unsaturated lactones **4eI**, **4eIII**, **4fI–III**, **4gI–III**, and **4hI–III** were obtained in a 50:50 to 70:30 ratio in moderate to good yields. The mixtures were separated by $SiO_2$ flash chromatography. Thermolysis of **3eIII**, **3g,h** had to be performed in the presence of $Et_3N$ in order to avoid oligomerization of the cis lactones.[23] The observed product isomer ratios of **4** are close to the estimated cis:trans ratios in chlorocyclopropane precursors **3**, in agreement with the stereospecificity of the ring opening of 1-(silyloxy)-2-chlorocyclopropanes.[14c,d,24,25] The nearly 1:1 ratio of isomers obtained in most cases is due to the poor stereoselectivity of the cyclopropanation reaction[14] (vide infra).

Moreover, as has already been found in some related cases, *cis*-**3g** and -**3h** always undergo cyclopropane ring opening faster than the corresponding trans compounds. Finally, trans → cis isomerizations of lactones (*Z*)-**4eI**, (*E*)-**4fI**, (*E*)-**4gI**, and (*E*)-**4gII** could easily be accomplished by the action of catalytic amounts of $I_2$ in refluxing benzene (Table III), thus making possible the regio- and stereoselective synthesis of cis-$\alpha,\beta$-unsaturated, substituted medium-membered lactones **4** by our method.

Hydrogenation of $\alpha,\beta$-unsaturated lactones **4** was performed on Pd/C in ethyl acetate at room temperature at 1–4 atm of pressure. Trans isomers were hydrogenated faster than cis (entries 9, 15, and 17–19, Table II). When stereoisomers could be formed, one was always predominant (Table II, entries 10, 15, 16, 18, and 19). The configuration of some of the isomers obtained has been assigned by $^1H$ NMR ($^3J_{FH}$ values for **1i**: comparison with $^1H$ NMR spectra of *cis*-**1p**[26]). From entry 10, it appears that syn hydrogenation of the double bond is, as expected,[27] the favored process. This observation is the basis for the assignment of cis geometry to the major isomers in **1l**, **1m**, and **1q**, assuming syn hydrogenation of the double bond from the face of the molecule opposite to the substituent.

**Scheme V**




*trans*-**4** **6**

From a mixture of *cis*- and *trans*-**1j** or from pure *cis*-**1j** (isolated by flash chromatography from the cis/trans mixture), fluoro desilylation by the action of *n*-$Bu_4NF$ in THF led to the 9-membered unsaturated lactone **4dI** (Scheme IV). This compound could not be prepared since the 8-membered precursor **1d** was not transformed into the corresponding ketene acetal **2d** (vide supra). This alternative process may overcome the earlier limitation on our methodology.

**Diolide Formation.** It has been reported in regard to the 9- and 10-membered series (vide supra) that the thermolysis of the chlorocyclopropane precursors often had to be performed in the presence of $Et_3N$. Indeed, in the absence of such a base, no trans isomers are formed along with the cis-unsaturated lactones **4eIII**, **4gI–III**, and **4hI–III**. Instead of monomeric trans lactones, the corresponding diolides **6eIII**, **6gI–III**, and **6hI–III** can be characterized together, in some cases, with small amounts of triolide. When pure trans lactones were treated with gaseous HCl in $CH_2Cl_2$, these oligomers were also formed; pure diolides **6eI**, **6fI**, **6gI–III**, and **6hI–II** were isolated from the reaction mixture by column chromatography (Scheme V). The trans configuration of the double bonds was assigned by IR and, in some instances, by $^1H$ NMR. This dimerization process appears to be a good way to access the macrocyclic bis(lactones), a new class of interesting natural products.[28] Under the same conditions, we did not observe any change of the cis lactones.

**Physicochemical Properties of Unsaturated Lactones. 7- and 8-Membered Lactones.** Single cis isomers were obtained in all cases studied (**4aI–cI**, **4aII–cII**, **4bIII,cIII**). By comparison with carbocyclic systems,[22] trans isomers in these systems are presumed to be unstable at room temperature. The IR carbonyl (1700–1730 $cm^{-1}$) and carbon–carbon double bond (1640–1672 $cm^{-1}$) absorptions of the products (taking into account when necessary the influence of the methyl or the fluoro substituents on the position of the bands)[29] are in agreement with the planar geometry expected to result from conjugation of the two double bonds. The $^1H$ and $^{19}F$ NMR data ($^3J_{HH}$, $^3J_{FH}$, $^4J_{FH}$, and $\delta$)[30] also confirm this configuration.

**9- and 10-Membered Lactones.** The various isomers obtained can be classified within two series A and B according to their polarity (TLC on $SiO_2$, eluent ether–hexane, GPC on OV101 column), those in series A being

(22) (a) Corey, E. J.; Tada, M.; LaMahieu, R.; Libit, L. *J. Am. Chem. Soc.* **1965**, *87*, 2051. (b) Eaton, P. E.; Lin, K. *J. Am. Chem. Soc.* **1964**, *86*, 2087; *J. Am. Chem. Soc.* **1965**, *87*, 2052.

(23) Seebach, D.; Brändli, U.; Schnurren Berger, P.; Przybylski, M. *Helv. Chim. Acta* **1988**, *71*, 155 and quoted references.

(24) Blanco, L. Thèse d'Etat, Orsay, 1982.

(25) (a) Depuy, C. H.; Schnack, L. G.; Hauser, J. M.; Wiedemann, W. *J. Am. Chem. Soc.* **1965**, *87*, 4006. (b) Depuy, C. H.; Schnack, L. G.; Hauser, J. M. *J. Am. Chem. Soc.* **1966**, *88*, 3343.

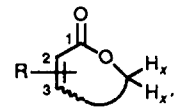
(26) We are grateful to Prof. Still for providing the NMR spectrum of *cis*-**1p**.[5]

(27) (a) Rylander, P. *Catalytic hydrogenation in organic syntheses*; Academic Press: New York, 1979. (b) Farina, M.; Morandi, C.; Mantica, E.; Botta, D. *J. Chem. Soc. Chem. Commun.* **1976**, 816.

(28) Keck, G. E.; Boden, E. P.; Wiley, M. R. *J. Org. Chem.* **1989**, *54*, 896. Yvergnaux, F.; Le Floc'h, Y.; Grée, R. *Tetrahedron Lett.* **1989**, *30*. 7397.

(29) Conia, J. M.; Doucet, J. P.; Goré, J. *Structure et Propriétés moléculaires VIII Fonctions Divalentes*; Masson: Paris, 1973.

**Table IV. IR (Film) and NMR Parameters ($CDCl_3$) of 9- and 10-Membered Lactones**



| series | no. | $\gamma_{C=O}$, $cm^{-1}$ | $\gamma_{C=C}$, $cm^{-1}$ | $\lvert\delta_{H_x} - \delta_{H_{x'}}\rvert$, ppm | $\delta_{H_2}$ | $\delta_{H_3}$ | δ: found (calcd) $C_1$ | $C_2$ | $C_3$ |
|---|---|---|---|---|---|---|---|---|---|
| A | (*Z*)-**4dI** | 1720 | 1620 | 0 | 5.89 | 6.51 | 170.01 | 123.86 | 148.28 |
| A | (*Z*)-**4fI** | 1711 | 1631 | 0 | 5.72 | | 170.16 | 118.42 | 158.69 |
| | | | | | | | | (116) | (158.9) |
| B | (*E*)-**4fI** | 1737 | 1653 | 0.43 | 5.98 | | 169.74 | 117.74 | 146.35 |
| A | (*E*)-**4eI** | 1718 | 1590 | ~0 | 6.12 | | 169.43 | 128.80 | 164.75 |
| | | | | | | | | (130.6) | (164.1) |
| B | (*Z*)-**4eI** | 1755[a] | | ~0.4 | 6.50 | | 170.22 | 131.93 | 151.71 |
| A | (*Z*)-**4fII** | 1710 | 1630 | 0 | | | | | |
| B | (*E*)-**4fII** | 1742 | 1660[a] | 0.37 | | | | | |
| | | 1750[a] | | | | | | | |
| A | (*E*)-**4fIII** | 1733 | 1654 | ~0 | | | 164.49 | 145.49 | 133.74 |
| | | | | | | | | (143.3) | (125.6) |
| B | (*Z*)-**4fIII** | 1749 | 1699 | 0.12 | | | 162.73 | 144.72 | 121.47 |
| | | | | | | | | (142.6) | (112.0) |
| A | (*E*)-**4eIII** | 1737 | 1610 | 0 | | | 163.79 | 152.66 | 133.00 |
| | | 1740[a] | | | | | | (153.7) | (130.4) |
| B | (*Z*)-**4eIII** | 1755 | 1638 | ~0.1 | | | 162.88 | 149.84 | 120.10 |
| | | | | | | | | (156.8) | (117.4) |
| A | (*Z*)-**4gI** | 1720 | 1623 | 0.96 | 5.76 | 6.06 | 167.18 | 121.32 | 153.76 |
| B | (*E*)-**4gI** | 1745[a] | 1652[a] | 0.39 | 6.25 | 6.02 | 170.99 | 119.58 | 148.46 |
| A | (*Z*)-**4hI** | 1717 | 1623 | | 5.85 | 6.32 | 167.31 | 123.73 | 145.10 |
| B | (*E*)-**4hI** | 1740[a] | 1650[a] | | 6.09–6.30 | | 170.12 | 122.71 | 142.63 |
| A | (*Z*)-**4gII** | 1718 | 1637 | 0.66 | | 5.75 | 169.35 | 128.67 | 146.66 |
| | | | | | | | | (131.9) | (145.9) |
| B | (*E*)-**4gII** | 1744 | 1665 | ~0 | | 5.38 | 174.65 | 126.43 | 138.77 |
| | | 1751[a] | | | | | | (130.2) | (140.7) |
| A | (*Z*)-**4hII** | 1711 | 1638 | | | 5.95 | 169.74 | 131.61 | 136.95 |
| | | | | | | | | (134.3) | (137.2) |
| B | (*E*)-**4hII** | 1747[a] | 1670[a] | | | 5.60 | 174.14 | 128.79 | 133.36 |
| | | | | | | | | (133.3) | (134.7) |
| A | (*E*)-**4gIII** | 1745 | 1653 | 1.13 | | 5.77 | 161.15 | 147.91 | 128.57 |
| | | | | | | | | (146.2) | (119.5) |
| B | (*Z*)-**4gIII** | 1742 | 1695 | 0.59 | | 5.16 | 164.38 | 148.45 | 123.09 |
| | | | | | | | | (144.5) | (114.3) |
| A | (*E*)-**4hIII** | 1740 | 1654 | | | 6.07 | 160.85 | 149.77 | 121.20 |
| | | | | | | | | (148.6) | (110.8) |
| B | (*Z*)-**4hIII** | 1740 | 1698 | | | 5.38 | 164.05 | 150.27 | 117.29 |
| | | | | | | | | (147.6) | (108.3) |

[a] $CCl_4$ solution.

more readily eluted than those in series B. The principal IR and NMR parameters are listed in Table IV. The cis or trans structural assignment about the lactone cyclic double bond is unequivocal[30] for (*Z*)-**4gI** and (*E*)-**4gI**, (*Z*)-**4hI** and (*E*)-**4hI** (for both, $^3J_{H_2H_3}$ = 11.3 (*Z*) and 16.5 Hz (*E*)), (*Z*)-**4fI** and (*E*)-**4fI** (NOE effect on $H_2$ after $CH_3$ irradiation: +9.4% (*Z*), 0% (*E*)), (*E*)-**4gIII** and (*Z*)-**4gIII** ($^3J_{FH}$ = 20.7 Hz (*E*) and 38.1 Hz (*Z*)), and (*E*)-**4hIII** and (*Z*)-**4hIII** ($^3J_{FH}$ = 20.6 Hz (*E*) and 38.4 Hz (*Z*)). Moreover, the calculated $H_2$ chemical shift for (*E*)-**4eI** and (*Z*)-**4eI** using tabulated parameters[30,31] gives 6.13 ppm (*E* isomer, experimental value 6.12 ppm) and 6.34 ppm (*Z* isomer, experimental value 6.50 ppm). Parametric calculations of $^{13}C$ $C_3$ and $C_2$ chemical shifts[32] also agree with the cis and trans assignments in methyl- or trimethylsilyl-substituted α,β-unsaturated lactones (*Z*)-**4fI**, (*E*)-**4eI**, (*Z*)- and (*E*)-**4gII**, and (*Z*)- and (*E*)-**4hII**.

All the lactones of the A series are characterized by $\gamma_{C=O}$ and $\gamma_{C=C}$ IR absorptions at low frequencies, indicative of a high degree of conjugation between these two double bonds.[29] In the $^1H$ NMR spectra, $H_2$ resonates at higher field and $H_3$ at lower field than in the B series. While there is no general trend in $C_1$ and $C_2$ chemical shifts, for a given *Z*/*E* couple, $C_3$ always resonates at lower field in the A than in the B series, which is also in agreement with a more effective charge delocalization through conjugation[32] in the former series. Similar conclusions may be drawn from the UV spectra[29] of (*Z*)- and (*E*)-**4hI**, -**4hII**, and -**4hIII** (see the Experimental Section).

According to all these criteria, a cis configuration around the endocyclic double bond is assigned to all members of the A series, thus presenting a nearly planar arrangement of the $C_3$, $C_2$, $C_1$, O segment.

In contrast, for (*E*)-**4gI**, (*E*)-**4hI**, (*E*)-**4fI**, (*Z*)-**4gIII**, and (*Z*)-**4hIII**, which display the trans configuration, the $\nu_{C=O}$ and $\gamma_{C=C}$ IR absorptions, as well as the $H_2$, $H_3$, and $C_3$ chemical shifts and UV spectra, are closer to the spectral parameters observed for isolated C=O and C=C double bonds. These results may be extended to other members of series B; in these compounds, the two C=C and C=O double bonds do not lie in the same plane.

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MM2 calculations[33] have been performed on four pairs of 9- and 10-membered lactones: **4fI**, **4gI**, **4gII**, and **4hI**. In all cases, the cis isomers display a favored conformation that is 10 kcal/mol (9-membered ring) or 5 kcal/mol (10-membered ring) more stable than the most stable conformer of the trans isomer; this is in agreement with the isomerization experiments.

The calculated value of the $C_3$–$C_2$–$C_1$–O dihedral angle of the most stable conformer in the 9-membered (*Z*)-**4fI** is ~126°, which is far from coplanarity as deduced from the IR and NMR parameters. However, in the cis 10-membered rings (*Z*)-**4gI**, (*Z*)-**4gII**, and (*Z*)-**4hII**, this calculated value is around 170°. On the other hand, in trans 10-membered systems, several conformers, close in energy, are found, with $C_3$–$C_2$–$C_1$–O dihedral angles being around 70, 80, or 130°, in agreement with the lack of coplanarity deduced from the spectral parameters. The presence of several conformers is also revealed by shoulders on the C=O absorption band in a few cases, as well as the splitting of $C_2$ and $C_9$ signals in the $^{13}C$ spectrum of (*Z*)-**4fI**.

The results obtained with the α-fluoro 9- and 10-membered lactones (series III) also deserve comment. The IR spectra of the cis compounds (series A) (*E*)-**4fIII**, (*E*)-**4eIII**, (*E*)-**4gIII**, and (*E*)-**4hIII** display a $\gamma_{C=O}$ absorption between 1733 and 1745 $cm^{-1}$ (i.e., at frequencies close to those of α-fluoro α,β-unsaturated esters[14d]). The $\gamma_{C=C}$ resonates at a slightly lower frequency (1654 $cm^{-1}$ as opposed to 1670 $cm^{-1}$), probably due to ring strain. In the trans isomers, the $\gamma_{C=O}$ frequency depends on the ring size: It is shifted to higher frequency relative to the cis isomer in the 9-membered compounds (*Z*)-**4fIII** and (*Z*)-**4eIII** ($\gamma_{C=O}$: 1749 and 1755 $cm^{-1}$) while it resonates in the same range in the 10-membered (*Z*)-**4gIII** and (*Z*)-**4hIII** (1742 and 1740 $cm^{-1}$). However, in all of these compounds, the $\gamma_{C=C}$ is shifted to higher frequency relative to the corresponding cis isomers by around 40 $cm^{-1}$, the poor conjugation between the two bonds also being evidenced by their UV spectra (Experimental Section).

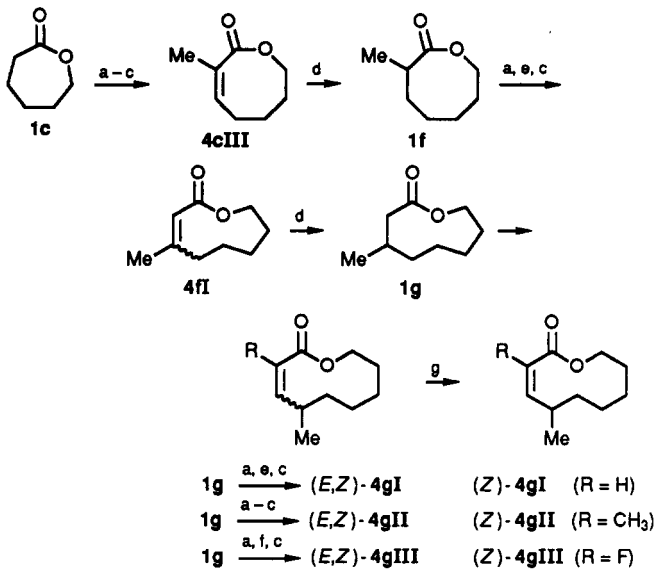
Moreover, while the calculated $^{13}C$ $C_2$ chemical shifts are not very different from the experimental ones, there is a sizable deviation to additivity for $C_3$ (10 ppm), which is probably due, as in the case of the unexpected $\gamma_{C=O}$ variation, to conjugative interactions between the fluorine lone pairs and the double bonds, which might be both conformation and ring size dependent. Finally, the significant nonequivalence of $H_\alpha$ protons in (*E*)-**4fI**, (*Z*)-**4eI**, (*E*)-**4fII**, (*Z*)-**4gI**, (*E*)-**4gI**, (*Z*)-**4gII**, (*E*)-**4gIII**, and (*Z*)-**4gIII** is indicative of the presence of a highly preferred conformer.

## Concluding Remarks

In this work, hitherto unknown α,β-unsaturated and saturated substituted lactones have been prepared from commercially available or easily synthesized *n*-membered lactone precursors, by iterative one-carbon ring enlargement. This multistep process has been applied to the syntheses of α,γ-substituted α,β-unsaturated lactones **4gI**, **4gII**, and **4gIII** from readily available 7-membered ε-caprolactone **1c** (see Scheme VI).

The limitations on this pathway are the moderate yield in rearrangements in the [4.1.0] series leading to 7-membered lactones and the need for an excess of carbene precursors and of base when the ring size increases beyond 10-membered systems. Nevertheless, this sequence seems to be among the most convenient for obtaining 8–10-membered substituted lactones **4** and **1**.

**Scheme VI**[a]




[a] Reagents: (a) $ClSiMe_3$, LDA; (b) $CH_3CHCl_2$, *n*-BuLi; (c) reflux in toluene or xylene; (d) $H_2$, Pd/C; (e) $CH_2Cl_2$, NaHMDS; (f) $CHCl_2F$, KO-*t*-Bu; (g) $I_2$, benzene.

## Experimental Section

Nuclear magnetic resonance spectra were recorded on Perkin-Elmer R-32A, Bruker AC 200, and Brucker AM250 spectrometers at 90, 200, or 250 MHz for proton and 62.86 MHz for carbon and on a Perkin-Elmer R-32A spectrometer for fluorine (84.6 MHz). Mass spectra were determined with a Nermag R10-10 spectrometer at an ionizing voltage of 70 eV. In some cases, chemical ionization was accomplished with ammonia. Infrared spectra were recorded on a Perkin-Elmer 682 spectrometer. Melting points were determined on a Reichert microscope. GLPC spectra were recorded on a Intersmat IGC 120FB with 10% SE-30 2-m column. Column chromatography was performed with SDS silica gel (230–240 mesh; flash chromatography). Thin-layer chromatography was performed on 0.25-mm silica gel (Merck 60 $F_{254}$).

Dry solvents were obtained as follows: Diethyl ether was distilled over $LiAlH_4$, tetrahydrofuran over sodium–benzophenone, and hexane over phosphoric anhydride. Triethylamine and diisopropylamine were purified by distillation over calcium hydride and chlorotrimethylsilane by distillation over quinoline under argon.

Lactone trimethylsilyl enol ethers **2a–c,e–h** were prepared according to a literature procedure.[18] The same method gave the 2-(trimethylsilyl)heptanolide **1e** from heptanolide[38] **1d**.

**3,4-Dihydro-6-(trimethylsiloxy)-2*H*-pyran (2a)**:[14b] 85% yield; bp 75–77 °C (15 mmHg).

**3,4-Dihydro-5-methyl-6-(trimethylsiloxy)-2*H*-pyran (2b)**: 87% yield; bp 100 °C (10 mmHg); $^1H$ NMR (90 MHz, $CCl_4$) δ 3.94 (m, 2 H), 2.09–1.62 (m, 4 H), 1.49 (s, 3 H), 0.16 (s, 9 H); IR (film, $cm^{-1}$) 1710 (CC); MS, *m/e* 187 ($M^+$ + 1, 15), 186 ($M^+$, 50), 185 (14), 171 (49), 143 (45), 101 (28), 75 (46), 73 (100), 41 (37).

**2,3,4,5-Tetrahydro-7-(trimethylsiloxy)oxepine (2c)**:[35] 82% yield; bp 80 °C (12 mmHg).

**3,4,5,6-Tetrahydro-8-(trimethylsiloxy)-7-(trimethylsilyl)-2*H*-oxocine (2e)**: 92% yield; bp 52 °C ($10^{-2}$ mmHg); $^1H$ NMR (250 MHz, $CDCl_3$) δ 3.87 (m, 2 H), 2.11 (m, 2 H), 1.76–1.40 (m, 6 H), 0.22 (s, 9 H); 0.07 (s, 9 H); IR (film, $cm^{-1}$) 1632 (CC);

(33) Molecular calculations were performed by using the Macro-Model program of W. C. Still based on MM2 developed by Allinger: Allinger, N. J. *J. Am. Chem. Soc.* **1977**, *99*, 8127.

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MS, *m/e* 272 ($M^+$, 0.6), 217 (9), 147 (50), 75 (14), 73 (100), 55 (86), 45 (15). Anal. Calcd for $C_{13}H_{28}O_2Si_2$: C, 57.27; H, 10.36. Found: C, 57.61; H, 10.53.

**3,4,5,6-Tetrahydro-7-methyl-8-(trimethylsiloxy)-2*H*-oxocine (2f)**: 89% yield; bp 98 °C (14 mmHg); $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 3.85–3.65 (m, 2 H), 2.10–1.85 (m, 2 H), 1.44 (s, 3 H), 1.75–1.35 (m, 6 H), 0.17 (s, 9 H); IR (film, $cm^{-1}$) 1710 (CC); MS, *m/e* 214 ($M^+$, 8), 199 (2), 143 (15), 75 (29), 73 (100), 69 (37), 41 (20).

**2,3,4,5,6,7-Hexahydro-7-methyl-9-(trimethylsiloxy)oxonine (2g)**: 91% yield; bp 39 °C ($5 \times 10^{-2}$ mmHg); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 3.96–3.84 (m, 2 H), 3.74 (d, $J$ = 7.9 Hz, 1 H), 2.54–2.35 (m, 1 H), 1.78–1.63 (m, 2 H), 1.63–1.38 (m, 5 H), 1.38–1.17 (m, 2 H), 0.94 (d, $J$ = 6.6 Hz, 3 H), 0.22 (s, 9 H); IR (film, $cm^{-1}$) 1685 (CC); MS, *m/e* 228 ($M^+$, 20), 213 (6), 185 (13), 172 (16), 171 (84), 143 (27), 75 (44), 73 (100), 69 (62), 41 (24). Anal. Calcd for $C_{12}H_{24}O_2Si_2$: C, 63.08; H, 10.60. Found: C, 63.30; H, 10.73.

**2,3,4,5,6,7-Hexahydro-2-methyl-9-(trimethylsiloxy)oxonine (2h)**:[17] 94% yield; bp 50–51 °C ($4 \times 10^{-2}$ mmHg).

**2-(Trimethylsilyl)heptanolide (1e)**: 80% yield; bp 42 °C (0.04 mmHg); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.65–4.51 (m, 1 H), 3.98–3.84 (m, 1 H), 2.00 (dd, $J$ = 10.5 and 4.8 Hz, 1 H), 1.95–1.57 (m, 6 H), 1.57–1.20 (m, 2 H), 0.10 (s, 9 H); IR (film, $cm^{-1}$) 1727 (CO); MS, *m/e* 185 (5), 129 (23), 117 (41), 75 (86), 73 (100), 55 (28). Anal. Calcd for $C_{10}H_{20}O_2Si$: C, 59.93; H, 10.07. Found: C, 59.80; H, 10.00.

Published procedures were used for the preparation of (*n* + 3)-chloro-2-oxa-1-(trimethylsiloxy)bicyclo[*n*.1.0]alkanes **3I**,[14b] of (*n* + 3)-chloro-(*n* + 3)-methyl-2-oxa-1-(trimethylsiloxy)bicyclo[*n*.1.0]alkanes **3II**,[14a] and (*n* + 3)-chloro-(*n* + 3)-fluoro-2-oxa-1-(trimethylsiloxy)bicyclo[*n*.1.0]alkanes **3III**.[14d] For 1 equiv of enol ethers 2 equiv of base and dichloroalkanes were used for the formation of 7- and 8-membered lactones; 3 equiv was used for 9-membered lactones and 4 equiv for greater than 9-membered lactones. See Table I for the diastereoselectivity in the carbenoid additions.

**7-Chloro-2-oxa-1-(trimethylsiloxy)bicyclo[4.1.0]heptane (3aI)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 3.80–3.20 (m, 2 H), 3.04 (d, $J$ = 9 Hz, 0.67 H (*E* isomer)), 2.73 (d, $J$ = 5.2Hz, 0.33H (*Z* isomer)), 2.00–1.10 (m, 5 H), 0.19 (s, 3 H (*Z* isomer)), 0.15 (s, 6 H (*E* isomer)).

**7-Chloro-6-methyl-2-oxa-1-(trimethylsiloxy)bicyclo[4.1.0]heptane (3bI)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$. 3.90–3.15 (m, 2 H), 2.79 (s, 0.46 H (*E* isomer)), 2.63 (s, 0.54 H (*Z* isomer)), 1.11 (s, 1.6 H (*Z* isomer)), 1.07 (s, 1.4 H (*E* isomer)), 2.00–1.05 (m, 4 H), 0.13 (s, 4.1 H (*E* isomer)), 0.12 (s, 4.9 H (*Z* isomer)).

**8-Chloro-2-oxa-1-(trimethylsiloxy)bicyclo[5.1.0]octane (3cI)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 3.95–3.25 (m, 2 H), 2.89 (d, $J$ = 9 Hz, 0.57 H (*E* isomer)), 2.66 (d, $J$ = 4.5 Hz, 0.43H (*Z* isomer)), 2.10–0.90 (m, 9 H), 0.19 (s, 3.9 H (*Z* isomer)), 0.15 (s, 5.1 H (*E* isomer)).

**9-Chloro-2-oxa-1-(trimethylsiloxy)-8-(trimethylsilyl)bicyclo[6.1.0]nonane (3eI)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 4.00–3.15 (m, 2 H), 2.65 (s, 0.61 H (*E* isomer)), 2.53 (s, 0.39H (*Z* isomer)), 2.10–0.90 (m, 8 H), 0.20 (s, 3.5 H (*Z* isomer)), 0.15 (s, 5.5 H (*E* isomer)), 0.11 (s, 3.5 H (*Z* isomer)), 0.03 (s, 5.5 H (*E* isomer)).

**7-Chloro-7-methyl-2-oxa-1-(trimethylsiloxy)bicyclo[4.1.0]heptane (3aII)**: $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 3.90–3.79 (m, 0.6 H (*E* isomer)), 3.79–3.70 (m, 0.4 H (*Z* isomer)), 3.62–3.45 (m, 1 H), 1.62 (s, 1.8 H (*E* isomer)), 1.61 (s, 1.2 H (*Z* isomer)), 2.10–0.70 (m, 5 H), 0.25 (s, 3.6 H (*Z* isomer)), 0.23 (s, 5.4 H (*E* isomer)).

**7-Chloro-6,7-dimethyl-2-oxa-1-(trimethylsiloxy)bicyclo[4.1.0]heptane (3bII)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 3.90–3.20 (m, 2 H), 1.52 (s, 1 H (*Z* isomer)), 1.46 (s, 2 H (*E* isomer)), 1.13 (s, 1 H (*Z* isomer)), 1.04 (s, 2 H (*E* isomer)), 2.05–0.80 (m, 4 H), 0.16 (s, 9 H).

**8-Chloro-8-methyl-2-oxa-1-(trimethylsiloxy)bicyclo[5.1.0]octane (3cII)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 4.10–3.30 (m, 2 H), 1.54 (s, 1.7 H (*E* isomer)), 1.51 (s, 1.3 H (*Z* isomer)), 2.10–0.75 (m, 7 H), 0.15 (s, 3.3 H (*Z* isomer)), 0.14 (s, 5.7 H (*E* isomer)). $^1H$ NMR for (*Z*)-**3cII** (250 MHz, $CDCl_3$) $\delta$ 4.08–3.95 (m, 1 H), 3.86–3.73 (m, 1 H), 2.20–2.05 (m, 1 H), 1.58 (s, 3 H), 1.90–0.80 (m, 6 H), 0.23 (s, 9 H).

**9-Chloro-8,9-dimethyl-2-oxa-1-(trimethylsiloxy)bicyclo[6.1.0]nonane (3fII)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 4.00–3.30 (m, 2 H), 1.55 (s, 1.2 H (*Z* isomer)), 1.47 (s, 1.8 H (*E* isomer)), 1.02 (s, 1.8 H (*E* isomer)), 0.91 (s, 1.2 H (*Z* isomer)), 2.15–0.80 (m, 8 H), 0.22 (s, 3.6 H (*Z* isomer)), 0.17 (s, 5.4 H (*E* isomer)).

**7-Chloro-7-fluoro-6-methyl-2-oxa-1-(trimethylsiloxy)bicyclo[4.1.0]heptane (3bIII)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 4.00–3.20 (m, 2 H), 1.33 (s, 0.56 H (*Z* isomer)), 1.18 (s, 0.44 H (*E* isomer)), 2.10–0.75 (m, 4 H), 0.22 (s, 9 H); $^{19}F$ NMR (84.6 MHz, $CCl_4$) $\delta$ –72.6 (s, 0.44 F), –76.2 (s, 0.56 F).

**8-Chloro-8-fluoro-2-oxa-1-(trimethylsiloxy)bicyclo[5.1.0]octane (3cIII)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 4.20–3.50 (m, 2 H), 2.40–0.80 (m, 7 H), 0.22 (s, 4.5 H), 0.18 (s, 4.5 H); $^{19}F$ NMR (84.6 MHz, $CCl_4$) $\delta$ –61.1 (d, $J$ = 22.6 Hz, 0.5 F (*E* isomer)), –80.1 (s, 0.5 F (*Z* isomer)).

**9-Chloro-9-fluoro-8-methyl-2-oxa-1-(trimethylsiloxy)bicyclo[6.1.0]nonane (3fIII)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 4.10–3.40 (m, 2 H), 1.32 (s, 1.5 H), 1.02 (d, $J$ = 1 Hz, 1.5 H), 2.10–0.80 (m, 8 H), 0.26 (s, 4.5 H (*Z* isomer)), 0.19 (d, $J$ = 1 Hz, 4.5 H (*E* isomer)).

**9-Chloro-9-fluoro-2-oxa-1-(trimethylsiloxy)-8-(trimethylsilyl)bicyclo[6.1.0]nonane (3eIII)**: $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$. 4.06–3.93 (m, 1 H), 3.82–3.70 (m, 1 H), 0.28 (s, 9 H), 0.18 (s, 9 H).

**Preparation of $\alpha,\beta$-Unsaturated Lactones 4a–h.** The crude chloro(trimethylsiloxy)bicyclo[*n*.1.0]alkanes **3** were heated under the conditions indicated in Table II. Usually 1 mL of solvent/mmol of compound was used. When necessary, 10% (v/v) triethylamine was added before heating. The reactions were followed by TLC and the lactones purified by flash chromatography ($SiO_2$, ether–hexane).

**3-Methyl-2-hexenolide (4bI)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 5.69 (s, 1 H), 4.30–4.05 (m, 2 H), 1.91 (s, 3 H), 2.55–1.82 (m, 4 H); IR (film, $cm^{-1}$) 1700 (CO), 1640 (CC); MS, *m/e* 126 ($M^+$, 14.5), 112 (21), 111 (100), 95 (33), 85 (87), 81 (46), 69 (46), 67 (66), 41 (51), 39 (55). Anal. Calcd for $C_7H_{10}O_2$: C, 66.63; H, 7.99. Found: C, 66.90; H, 8.18.

**2-Fluoro-3-methyl-2-hexenolide (4bIII)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 4.33–4.05 (m, 2 H), 2.57–2.23 (m, 2 H), 1.92 (d, $J$ = 4.5 Hz, 3 H), 2.23–1.78 (m, 2 H); IR (film, $cm^{-1}$) 1715 (CO), 1620 (CC); MS, *m/e* 144 ($M^+$, 16), 129 (6), 113 (11), 98 (15), 85 (100), 51 (16), 43 (16), 39 (21). Anal. Calcd for $C_7H_9O_2F$: C, 58.31; H, 6.30. Found: C, 58.52; H, 6.49.

**2-Chloro-3-methyl-2-hexenolide (4′bIII)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 4.17 (t, $J$ = 6.4 Hz, 2 H), 2.58–2.28 (m, 2 H), 2.07 (s, 3 H), 2.22–1.88 (m, 2 H); IR (film, $cm^{-1}$) 1738 (CO), 1627 (CC); MS, *m/e* 162 ($M^+$, 3), 160 ($M^+$, 10), 145 (1), 85 (100), 67 (24), 43 (20).

**2-(Chlorofluoromethyl)-2-methylpentanolide (4″bIII)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 6.48 (d, $J$ = 4.9 Hz, 0.9 H (one diastereoisomer)), 6.38 (d, $J$ = 5.1 Hz, 0.1 H (second diastereoisomer)), 4.49–4.10 (m, 2 H), 2.43–1.60 (m, 4 H), 1.45 (s, 0.3 H), 1.30 (s, 2.7 H).

**2-Heptenolide (4cI)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 6.21 (dt, $J$ = 5.2 Hz, 1 H), 5.61 (dt, $J$ = 13 and 2 Hz, 1 H), 4.40–4.23 (m, 2 H), 2.60–2.20 (m, 2 H), 2.10–1.50 (m, 4 H); IR (film, $cm^{-1}$) 1715 (CO), 1640 (CC); MS, *m/e* 126 ($M^+$, 2), 98 (12), 85 (13), 81 (14), 68 (100), 55 (21), 39 (30). Anal. Calcd for $C_7H_{10}O_2$: C, 66.63; H, 7.99. Found: C, 67.01; H, 8.20.

**2-Methyl-2-heptenolide (4cII)**: $^1H$ NMR (200 MHz, $CDCl_3$) $\delta$ 5.93 (tq, $J$ = 6.2 Hz, 1 H), 4.45–4.34 (m, 2 H), 2.30–2.15 (m, 2 H), 1.95 (d, $J$ = 1.5 Hz, 3 H), 2.01–1.81 (m, 2 H), 1.72–1.56 (m, 2 H); IR (film, $cm^{-1}$) 1720 (CO), 1655 (CC); MS, *m/e* 140 ($M^+$, 16), 112 (20), 97 (13), 95 (42), 85 (39), 84 (30), 83 (17), 82 (100), 79 (19), 71 (24), 69 (51), 68 (44), 67 (42), 54 (46), 41 (53), 39 (53). Anal. Calcd for $C_8H_{12}O_2$: C, 68.53; H, 8.63. Found: C, 68.70; H, 8.60.

**2-Fluoro-2-heptenolide (4cIII)**: $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 5.98 (dt, $J$ = 23.5 and 7 Hz, 1 H), 4.60–4.30 (m, 2 H), 2.50–2.15 (m, 2 H), 2.05–1.50 (m, 4 H); $^{19}F$ NMR (84.6 MHz, $CCl_4$) $\delta$ –37.9 (dt, $J$ = 23.5 and 4.7 Hz, 1 F); IR (film, $cm^{-1}$) 1730 (CO), 1672 (CC); MS, *m/e* 144 ($M^+$, 21), 116 (16), 99 (59), 97 (29), 86 (88), 85 (54), 72 (44), 71 (87), 59 (30), 58 (100), 57 (76), 42 (47), 41 (62). Anal. Calcd for $C_7H_9O_2F$: C, 58.31; H, 6.30. Found: C, 58.47; H, 6.42.

**3-(Trimethylsilyl)-2-octenolide (4eI). *E* isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 6.12 (s, 1 H), 4.44 (t, $J$ = 5.4 Hz, 2 H), 2.70–2.60 (m, 2 H), 1.87–1.73 (m, 2 H), 1.62–1.40 (m, 4 H), 0.13 (s, 9 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 66.72 (t), 31.48 (t), 28.34 (t), 28.16 (t), 24.69 (t), –2.55 (q); MS, *m/e* 212 ($M^+$, 9), 197 (4), 169 (12), 153 (15), 122 (13), 75 (57), 73 (100), 45 (17).

Anal. Calcd for $C_{11}H_{20}O_2Si$: C, 62.21; H, 9.49. Found: C, 62.16; H, 9.52. **Z isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 6.50 (s, 1 H), 4.62–4.36 (m, 1 H), 4.19–3.96 (m, 1 H), 2.89–2.68 (m, 2 H), 2.50–1.75 (m, 2 H), 1.40–1.00 (m, 3 H), 0.22 (s, 9 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 73.94 (t), 40.30 (t), 30.62 (t), 29.17 (t), 28.85 (t), -1.15 (q); MS, *m/e* 212 ($M^+$, 0.5), 197 (2), 169 (14), 79 (10), 75 (75), 73 (100), 45 (21). Anal. Calcd for $C_{11}H_{20}O_2Si$: C, 62.21; H, 9.49. Found: C, 62.29; H, 9.40.

**2-Fluoro-3-(trimethylsilyl)-2-octenolide (4eIII). Z isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.47 (t, $J$ = 5.8 Hz, 2 H), 2.66–2.55 (m, 2 H), 1.86–1.73 (m, 2 H), 1.63–1.36 (m, 4 H), 0.21 (d, $J$ = 1.3 Hz, 9 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 68.46 (t), 31.27 (t), 28.30 (t), 25.23 (td, $J$ = 9 Hz), 22.70 (t), -1.12 (q); MS, *m/e* 230 ($M^+$, 0.6), 171 (21), 93 (12), 79 (32), 77 (100), 73 (71), 55 (14). Anal. Calcd for $C_{11}H_{19}O_2FSi$: C, 59.15; H, 5.42; F, 8.51. Found: C, 59.25; H, 5.49; F, 8.70. **E isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.47–4.33 (m, 2 H), 2.95 (tdd, $J$ = 12.1, 12.1, and 4.8 Hz, 1 H), 2.58–1.05 (m, 7 H), 0.23 (s, 9 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 74.52 (td), 29.85 (t), 27.81 (td), 22.71 (t), -0.94 (q); MS, *m/e* 230 ($M^+$, 1.6), 171 (38), 93 (12), 91 (12), 79 (24), 77 (100), 73 (59), 55 (21). Anal. Calcd for $C_{11}H_{19}O_2FSi$: C, 59.15; H, 5.42; F, 8.51. Found: C, 59.30; H, 5.48; F, 8.60.

**3-Methyl-2-octenolide (4fI). Z isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 5.72 (brs), 4.38 (t, $J$ = 5.7 Hz, 1 H), 2.67–2.55 (m, 2 H), 1.93 (d, $J$ = 1.4 Hz, 3 H), 1.86–1.72 (m, 2 H), 1.68–1.51 (m, 2 H), 1.51–1.38 (m, 2 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 66.78 (t), 31.99 (t), 30.01 (t), 28.55 (t), 27.39 and 27.26 (q), 23.73 (t); MS, *m/e* 154 ($M^+$, 7), 111 (17), 109 (17), 98 (25), 97 (32), 96 (89), 95 (100), 94 (31), 86 (20), 85 (36), 83 (54), 82 (62), 68 (44), 67 (43), 55 (40), 40 (45). Anal. Calcd for $C_9H_{14}O_2$: C, 70.08; H, 9.16. Found: C, 70.25; H, 9.23. **E isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.43 (t, 1 H), 4.00 (dt, $J$ = 12.8 and 3.1 Hz, 1 H), 2.43–2.03 (m, 4 H), 1.87 (s, 3 H), 1.95–1.75 (m, 1 H), 1.20–0.88 (m, 2 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 73.78 (t), 40.28 (t), 29.93 (t), 29.81 (t), 27.38 (t), 18.78 (q); MS, *m/e* 154 ($M^+$, 0.9), 111 (16), 109 (16), 98 (25), 97 (30), 96 (91), 95 (100), 94 (25), 86 (28), 85 (45), 83 (66), 82 (60), 81 (31), 70 (31), 69 (40), 68 (59), 67 (23), 56 (68), 55 (76), 54 (47), 42 (52), 40 (61). Anal. Calcd for $C_9H_{14}O_2$: C, 70.08; H, 9.16. Found: C, 70.20; H, 9.31.

**2,3-Dimethyl-2-octenolide (4fII). Z isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.35 (t, $J$ = 5.8 Hz, 2 H), 2.55–2.45 (m, 2 H), 1.87 (s, 3 H), 1.83 (s, 3 H), 1.95–1.70 (m, 2 H), 1.70–1.40 (m, 4 H); MS, *m/e* 168 ($M^+$, 24), 153 (15), 125 (17), 110 (20), 109 (100), 108 (52), 98 (14), 96 (32), 95 (52), 94 (36), 83 (35), 82 (37), 81 (44), 79 (28), 67 (74), 55 (46), 43 (72), 39 (47). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59. Found: C, 71.50; H, 9.58. **E isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.37 (ddd, $J$ = 9.8 and 1.5 Hz, 1 H), 4.00 (ddd, $J$ = 13.2, 5.2, and 2.6 Hz, 1 H), 2.57 (m, 1 H), 2.04 (s, 3 H), 1.81 (s, 3 H), 2.30–0.98 (m, 7 H); MS, *m/e* 168 ($M^+$, 12), 153 (16), 125 (17), 123 (24), 109 (99), 108 (49), 96 (54), 95 (78), 94 (44), 81 (65), 80 (47), 67 (100), 55 (60), 54 (46). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59. Found: C, 71.43; H, 9.66.

**2-Fluoro-3-methyl-2-octenolide (4fIII). E isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.42 (t, $J$ = 6.0 Hz, 2 H), 2.65–2.53 (m, 2 H), 1.90 (d, $J$ = 4.1 Hz, 3 H), 1.85–1.72 (m, 2 H), 1.68–1.55 (m, 2 H), 1.46–1.34 (m, 2 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 68.50 (t), 30.48 (t), 29.39 (t), 28.52 (t), 22.56 (t), 18.33 (qd, $J$ = 8 Hz); MS, *m/e* 172 ($M^+$, 14), 114 (48), 113 (100), 100 (18), 73 (26), 72 (24), 58 (100), 56 (24), 55 (24), 40 (25). Anal. Calcd for $C_9H_{13}O_2F$: C, 62.76; H, 7.61. Found: C, 62.80; H, 7.75. **Z isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.56–4.33 (m, 2 H), 2.98–2.82 (m, 1 H), 2.50–2.30 (m, 1 H), 1.80 (d, $J$ = 3.6 Hz, 3 H), 2.10–1.75 (m, 3 H), 1.55–1.08 (m, 3 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 73.97 (td, $J$ = 6 Hz), 29.99 (t), 29.18 (t), 27.86 (t), 25.84 (t), 15.57 (q); MS, *m/e* 172 ($M^+$, 9), 114 (50), 113 (100), 100 (28), 86 (36), 85 (30), 73 (37), 72 (56), 68 (27), 56 (33), 55 (36), 42 (31), 40 (36). Anal. Calcd for $C_9H_{13}O_2F$: C, 62.76; H, 7.61. Found: C, 62.90; H, 7.50.

**4-Methyl-2-nonenolide (4gI). Z isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 6.06 (dd, $J$ = 7.5 Hz, 1 H), 5.76 (dd, $J$ = 11.3 and 1.7 Hz, 1 H), 4.82 (ddd, $J$ = 4.9 and 2.3 Hz, 1 H), 3.86 (td, $J$ = 11, 11, and 4.4 Hz, 1 H), 3.27 (heptet, 1 H), 1.90–1.52 (m, 4 H), 1.52–1.30 (m, 3 H), 1.06 (d, $J$ = 6.3 Hz, 3 H), 1.26–1.00 (m, 1 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 64.84 (t), 36.85 (t), 30.24 (d), 27.05 (t), 23.16 (t), 21.19 (q); MS, *m/e* 168 ($M^+$, 8), 113 (100), 112 (16), 95 (65), 82 (62), 81 (41), 67 (36), 55 (39), 43 (80), 41 (56), 40 (30), 39 (22). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59. Found: C, 71.15; H, 9.70. **E isomer**: see Table IV; solid; mp 63 °C; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 6.25 (d, 1 H), 6.02 (dd, $J$ = 16.5 and 9.6 Hz, 1 H), 4.56 (ddd, $J$ = 10.5 and 2.7 Hz, 1 H) 4.16 (dt, $J$ = 13.2 and 4.2 Hz, 1 H), 2.40–2.18 (m, 1 H), 1.10 (d, $J$ = 1.1 Hz, 3 H), 1.95–0.90 (m, 8 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 65.03 (t), 40.94 (d), 34.18 (t), 29.48 (t), 24.38 (t), 21.91 (t), 18.75 (q); MS, *m/e* 168 ($M^+$, 1), 96 (27), 95 (41), 94 (20), 82 (100), 81 (56), 71 (21), 69 (36), 68 (51), 67 (39), 55 (52), 54 (30), 53 (26), 43 (25), 41 (71), 39 (31). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.38; H, 9.59. Found: C, 71.49; H, 9.68.

**2,4-Dimethyl-2-nonenolide (4gII). Z isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 5.75 (dq, $J$ = 7.7 and 1.5 Hz, 1 H), 4.65 (ddd, $J$ = 4.6 and 2.3 Hz, 1 H), 3.99 (td, $J$ = 11 and 3.7 Hz, 1 H), 3.01 (heptet, 1 H), 1.91 (s, 3 H), 1.87–1.14 (m, 8 H), 1.03 (d, $J$ = 6.5 Hz, 3 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 65.14 (t), 36.72 (t), 30.28 (d), 26.88 (t), 26.01 (t), 23.44 (t), 21.44 (q), 16.64 (q); MS, *m/e* 182 ($M^+$, 8), 113 (100), 112 (52), 109 (52), 96 (16), 95 (30), 67 (25), 43 (50), 41 (39). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.47; H, 9.96. Found: C, 72.60; H, 9.80. **E isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 5.38 (dq, $J$ = 10.8 Hz, 1 H), 4.17–4.04 (m, 2 H), 2.55–2.33 (m, 1 H), 1.97 (d, $J$ = 1.6 Hz, 3 H), 2.00–1.57 (m, 4 H), 1.50–1.38 (m, 4 H), 1.03 (d, $J$ = 6.5 Hz, 3 H), 1.08–0.82 (m, 2 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 65.72 (t), 36.00 (t), 35.75 (d), 27.05 (t), 21.61 (t), 19.71 (q), 15.12 (q); MS, *m/e* 182 ($M^+$, 2), 113 (44), 112 (30), 109 (34), 96 (100), 95 (82), 85 (55), 81 (32), 69 (42), 68 (45), 67 (59), 43 (42), 41 (89), 39 (28).

**2-Fluoro-4-methyl-2-nonenolide (4gIII). E isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 5.77 (dd, $J$ = 20.7 and 8.3 Hz, 1 H), 5.00 (ddd, $J$ = 5.1 and 2.2 Hz, 1 H), 3.87 (td, $J$ = 11.0 and 4.3 Hz, 1 H), 3.25 (heptet, 1 H), 1.97–1.55 (m, 4 H), 1.55–1.21 (m, 3 H), 1.09 (d, $J$ = 6.9 Hz, 3 H), 1.21–0.91 (m, 1 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 66.02 (t), 36.93 (t), 27.78 (d), 27.34 (t), 25.88 (t), 23.24 (t), 21.70 (q); $^{19}F$ NMR (84.6 MHz, $CCl_4$) $\delta$ -45.2 (d, $J$ = 20.7 Hz); MS, *m/e* 186 ($M^+$, 7), 117 (37), 113 (71), 100 (56), 99 (49), 97 (31), 81 (27), 72 (78), 69 (68), 68 (55), 55 (58), 43 (35), 41 (100), 39 (56). Anal. Calcd for $C_{10}H_{15}O_2F$: C, 64.48; H, 8.12; F, 10.21. Found: C, 64.70; H, 8.50; F, 10.01. **Z isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 5.16 (dd, $J$ = 38.1 and 11.3 Hz, 1 H), 4.88–4.71 (m, 1 H), 4.27–4.14 (m, 1 H), 3.00–2.75 (m, 1 H), 1.08 (d, $J$ = 6.8 Hz, 3 H), 2.10–0.85 (m, 8 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 66.21 (t), 32.63 (d), 29.41 (t), 27.46 (t), 25.63 (t), 23.73 (t), 22.23 (t), 19.40 (q); MS, *m/e* 186 ($M^+$, 1), 127 (21), 118 (34), 100 (91), 99 (55), 86 (50), 85 (56), 72 (100), 69 (98), 68 (32), 55 (27), 41 (27), 40 (86), 38 (36). Anal. Calcd for $C_{10}H_{15}O_2F$: C, 64.48; H, 8.12. Found: C, 64.33; H, 8.28.

**2-Methyl-2-decen-9-olide (4hII). Z isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 5.95 (tq, $J$ = 8.6 and 1.5 Hz, 1 H), 5.20–5.04 (m, 1 H), 2.56–2.38 (m, 1 H), 2.14–1.95 (m, 1 H), 1.92 (br s, 3 H), 1.31 (d, $J$ = 6.7 Hz, 3 H), 1.84–1.17 (m, 8 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 72.13 (d), 33.54 (t), 27.30 (t), 26.10 (t), 25.82 (t), 21.21 (t), 20.30 (q), 19.58 (q); UV (isooctane) $\lambda_{max}$ 216.1 nm ($\epsilon$ = 5775 $mol^{-1}$ $cm^{-1}$); MS, *m/e* 182 ($M^+$, 16), 125 (18), 112 (23), 111 (23), 109 (25), 96 (71), 95 (100), 82 (67), 81 (50), 80 (30), 69 (34), 68 (48), 67 (80), 55 (70), 39 (41). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.47; H, 9.96. Found: C, 72.30; H, 9.51. **E isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 5.66–5.54 (m, 1 H), 4.37–4.22 (m, $J$ = 6.6 and 2.5 Hz, 1 H), 1.95 (s, 3 H), 1.33 (d, $J$ = 5.8 Hz, 3 H), 2.26–0.82 (m, 10 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 74.06 (d), 34.89 (t), 28.35 (t), 26.94 (t), 26.29 (t), 22.86 (t), 20.99 (q), 14.71 (q); UV (isooctane) $\lambda_{max}$ 199.2 nm ($\epsilon$ = 4125 $mol^{-1}$ $cm^{-1}$); MS, *m/e* 182 ($M^+$, 3), 112 (16), 109 (17), 96 (45), 95 (100), 85 (78), 82 (49), 81 (46), 80 (35), 69 (38), 68 (37), 67 (79), 55 (75), 41 (79). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.47; H, 9.96. Found: C, 72.59; H, 10.05.

**2-Decen-9-olide (4hI).**[17] **Z isomer**: UV (isooctane) $\lambda_{max}$ 206.5 nm ($\epsilon$ = 11 670 $mol^{-1}$ $cm^{-1}$). **E isomer**: UV (isooctane) $\lambda_{max}$ 200.3 nm ($\epsilon$ = 5730 $mol^{-1}$ $cm^{-1}$).

**2-Fluoro-2-decen-9-olide (4hIII). E isomer**: see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 6.07 (dt, $J$ = 20.6 and 9.1 Hz, 1 H), 5.35–5.21 (m, 1 H), 2.98–2.79 (m, 1 H), 2.08–1.91 (m, 1 H), 1.35 (d, $J$ = 6.3 Hz, 3 H), 1.87–0.97 (m, 8 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 72.35 (d), 33.96 (t), 27.29 (t), 25.52 (t), 22.23 (tq, $J$ = 5 Hz), 20.41 (t), 19.69 (q); UV (isooctane) $\lambda_{max}$ 216.4 nm ($\epsilon$ = 8250 $mol^{-1}$ $cm^{-1}$); MS *m/e* 186 ($M^+$, 2), 99 (27), 86 (49), 81 (35), 72 (30), 67 (31), 58 (42), 54 (100), 43 (30), 41 (68), 39 (36). Anal. Calcd

for $C_{10}H_{15}O_2F$: C, 64.48; H, 8.12. Found: C, 64.80; H, 8.28. ***Z* isomer:** see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 5.38 (ddd, $J$ = 38.4, 12.2, and 5.4 Hz, 1 H), 5.07–4.90 (m, 1 H), 2.64–2.43 (m, 1 H), 1.37 (d, $J$ = 6.4 Hz, 3 H) 2.22–0.95 (m, 9 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 74.33 (dd, $J$ = 10 Hz), 36.55 (t), 26.56 (t), 26.33 (t), 25.36 (t), 23.70 (t), 21.60 (q); UV (isooctane) $\lambda_{max}$ 199.1 nm ($\epsilon$ = 4205 $mol^{-1}$ $cm^{-1}$); MS $m/e$ 186 ($M^+$, 2), 100 (17), 99 (84), 86 (72), 85 (40), 81 (66), 80 (29), 79 (28), 72 (75), 68 (39), 67 (34), 58 (53), 55 (100), 54 (31), 43 (46), 41 (77). Anal. Calcd for $C_{10}H_{15}O_2F$: C, 64.48; H, 8.12. Found: C, 64.18; H, 8.25.

**Preparation of 2,3-Dimethyl-2-hexenolide (4bII).** To a solution of **3bII** (2.2 mmol) in THF (2 mL) was added a tetrabutylammonium fluoride solution in THF (1 M, 2.4 mL, 2.4 mmol) over a 5-min period. After 1 h, water was added (3 mL) and the product was extracted with ether (3 × 3 mL). The extract was dried ($Na_2SO_4$), and after the solvent was removed, the product was purified by column chromatography on silica gel (ether/hexane, 25/75): yield 72%; IR (film, $cm^{-1}$) 1721 (C=O), 1650 (CC); $^1H$ NMR (90 MHz, $CCl_4$) $\delta$ 4.13 (t, $J$ = 6 Hz, 2 H), 1.91 (br s, 3 H), 1.87 (br s, 3 H), 2.40–1.75 (m, 4 H); MS, $m/e$ 140 ($M^+$, 15), 125 (29), 85 (100), 84 (58), 83 (21), 82 (16), 67 (53), 66 (40), 55 (22), 41 (27). Anal. Calcd for $C_8H_{12}O_2$: C, 68.53; H, 8.63. Found: C, 68.88; H, 8.89.

Similar experimental conditions were used for the reactions of *cis*-**3aI**, *cis*-**3aII**, and *cis*-**1j** with tetrabutylammonium fluoride which led, respectively, to the formation of **5aI**,[20] **5aII**,[21] and **4dI**.

**2-Octenolide ((*Z*)-4dI):** see Table IV; $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 6.51 (dt, $J$ = 8.2 Hz, 1 H), 5.89 (d, $J$ = 11.5 Hz, 1 H), 4.41 (t, $J$ = 5.7 Hz, 2 H), 2.66–2.51 (m, 2 H), 1.82–1.72 (m, 2 H), 1.52–1.39 (m, 2 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 67.03 (t), 30.49 (t), 28.34 (t), 26.26 (t), 23.68 (t); MS, $m/e$ 140 ($M^+$, 1.7), 85 (42), 82 (26), 81 (100), 80 (30), 68 (59), 67 (34), 55 (30), 53 (32), 41 (26), 39 (44).

**Trans–Cis Lactone Isomerizations by Iodine.** To a solution of trans lactone (1 mmol) in benzene (15 mL) was added iodine (10 mg). The mixture was heated under reflux (the isomerization was followed by TLC), and after the time indicated in Table III, 10% sodium thiosulfate (15 mL) was added. The organic phase was separated, dried ($Na_2SO_4$), and concentrated to give the product, which was purified by liquid chromatography on silica gel.

**Hydrogenation of $\alpha,\beta$-Unsaturated Lactones 4.** A mixture of **4** (1 mmol) and 10% Pd on charcoal (8 mg) in ethyl acetate (3 mL) was stirred under an atmosphere of hydrogen for 0.25–96 h (see Table II). The reaction mixture was then filtered through Celite and concentrated to give lactones **1**.

**2-Methylheptanolide (1f):** bp 32–35 °C (0.035 mmHg); IR (film, $cm^{-1}$) 1740 (CO); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.49 (ddd, $J$ = 6.3 and 4.6 Hz, 1 H), 4.28 (ddd, $J$ = 12.1, 7.9, and 4.2 Hz, 1 H), 2.85–2.67 (m, 1 H), 1.97–1.35 (m, 8 H), 1.16 (d, $J$ = 6.6 Hz, 3 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 179.82 (s), 67.29 (t), 38.80 (t), 35.87 (d), 31.64 (t), 25.93 (t), 25.03 (t), 17.03 (q); MS, $m/e$ 142 ($M^+$, 2.2), 100 (45), 84 (24), 70 (23), 69 (100), 68 (76), 56 (80), 55 (75), 41 (50). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.79; H, 10.13.

**2-(Trimethylsilyl)octanolide (1i):** IR (film, $cm^{-1}$) 1740 (CO); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.60 (td, $J$ = 10.9 and 4.4 Hz, 1 H), 4.00 (dt, $J$ = 10.9 and 4 Hz, 1 H), 2.29 (dd, $J$ = 3.6 Hz, 1 H), 2.02 (dd, $J$ = 11.7 and 13.3 Hz, 1 H), 1.87–1.10 (m, 8 H), 0.93–0.80 (m, $J$ = 13.3, 3.6, 6.5, and 4.4 Hz, 1 H), 0.00 (s, 9 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 176.51 (s), 64.29 (t), 36.28 (t), 30.77 (t), 17.64 (t), 24.85 (t), 24.58 (d), 22.19 (t), –3.63 (q); MS, $m/e$ 199 (5), 171 (13), 129 (13), 117 (35), 75 (60), 73 (100), 55 (18). Anal. Calcd for $C_{11}H_{22}O_2Si$: C, 72.42; H, 12.17. Found: C, 72.58; H, 12.28.

**2-Fluoro-3-(trimethylsilyl)octanolides 1j.** The cis and trans isomers were separated by liquid chromatography on silica gel (hexane/ethyl acetate/ether, 95/2.5/2.5). ***cis*-1j:** IR (film, $cm^{-1}$) 1772 (CO); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 5.14 (dd, $J$ = 48.3 and 2.8 Hz, 1 H), 4.48 (dt, $J$ = 4.2 Hz, 1 H), 4.39–4.25 (m, $J$ = 10.7, 9.8, and 4.9 Hz, 1 H), 1.90–1.13 (m, 8.5 H), 1.05–0.95 (m, 0.5 H), 0.10 (s, 9 H); MS, $m/e$ 232 ($M^+$, 0.1), 95 (16), 85 (31), 81 (48), 77 (53), 73 (100), 68 (39), 67 (27), 55 (37). ***trans*-1j:** IR (film, $cm^{-1}$) 1744 (CO); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.89 (td, $J$ = 11.0 and 3.2 Hz, 1 H), 4.72 (dd, $J$ = 48.3 and 11.6 Hz, 1 H), 3.97–3.86 (m, $J$ = 11.0 Hz, 1 H), 1.91–0.81 (m, 9 H), 0.10 (s, 9 H); MS, $m/e$ 232 ($M^+$, 0.1), 95 (10), 86 (15), 82 (20), 81 (46), 77 (56), 73 (100), 71 (40), 67 (23), 55 (38). Anal. Calcd for $C_{11}H_{21}O_2FSi$: C, 56.84; H, 9.11. Found (cis and trans mixture): C, 56.96; H, 9.33.

**Table V. IR ($CCl_4$) and NMR Parameters ($CDCl_3$) of Diolides 6**

| trans lactone | diolide (yield, %) | $\gamma_{C=O}$, $cm^{-1}$ | $\gamma_{C=C}$, $cm^{-1}$ | $\delta_{H_1}$ | $\delta_{H_2}$ | $\delta_{CH_2O}$ |
|---|---|---|---|---|---|---|
| (*E*)-**4fI** | **6fI** (70)[a] | 1720 | 1650 | 5.66 | | 4.09 |
| (*Z*)-**4eI** | **6eI** (80)[a] | 1722 | 1600 | 6.26 | | 4.10 |
| (*Z*)-**4fII** | **6fII** (90) | 1730 | 1665 | | | 4.21 |
| (*E*)-**4gI** | **6gI** (70) | 1724 | 1654 | 5.77[b] | 6.86 | 4.12 |
| (*E*)-**4gII** | **6gII** (70) | 1718 | 1650 | | 6.52 | 4.11 |

[a] ~5% of triolide was also formed. [b] $J$ = 15.7 Hz.

**3-Methyloctanolide (1g):** IR (film, $cm^{-1}$) 1745 (CO); $^1H$ NMR (250 MHz; $CDCl_3$) $\delta$ 4.50 (td, $J$ = 7.0 Hz, 1 H), 4.07 (dt, $J$ = 10.8 and 4.9 Hz, 1 H), 2.36 (dd, $J$ = 3.7 Hz, 1 H), 2.00 (t, $J$ = 10.2 Hz, 1 H), 2.07–1.82 (m, 1 H), 1.82–1.18 (m, 8 H), 1.01 (d, $J$ = 6.6 Hz, 3 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 174.65 (s), 64.20 (t), 43.01 (t), 32.90 (t), 32.32 (d), 27.36 (t), 27.04 (t), 23.64 (q), 23.40 (t); MS, $m/e$ 156 ($M^+$, 0.6), 113 (14), 99 (53), 98 (22), 97 (26), 96 (55), 83 (38), 82 (59), 81 (25), 70 (80), 69 (100), 68 (47), 57 (40), 56 (94), 55 (66), 42 (83). Anal. Calcd for $C_9H_{16}O_2$: C, 69.18; H, 10.33. Found: C, 69.51; H, 10.10.

**4-Methylnonanolide (1k):** IR (film, $cm^{-1}$) 1735 (CO); $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.49–4.29 (m, 1 H), 4.26–4.16 (m, $J$ = 10.5, 7.1, and 3.2 Hz, 1 H), 2.52–2.40 (m, 1 H), 2.32–2.19 (m, 1 H), 1.70–1.40 (m, 9 H), 1.30–1.10 (m, 2 H), 0.90 (d, $J$ = 6.4 Hz, 3 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 173.77 (s), 66.15 (t), 32.79 (t), 32.19 (d), 29.84 (t), 27.87 (t), 25.82 (t), 24.34 (t), 22.18 (t), 20.50 (q); MS, $m/e$ 170 ($M^+$, 1), 141 (16), 114 (26), 110 (28), 108 (33), 98 (44), 97 (29), 83 (66), 69 (40), 55 (100), 41 (45). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.53; H, 10.66. Found: C, 70.30; H, 10.91.

**2,4-Dimethylnonanolides 1l.** ***cis*-1l:** IR (film, $cm^{-1}$) 1736 (CO); $^1H$ NMR (250 MHz, $C_6D_6$) $\delta$ 4.16–4.05 (m, 1 H), 3.93–3.80 (m, 1 H), 2.48–2.34 (m, 1 H), 1.04 (d, $J$ = 6.9 Hz, 3 H), 1.62–0.92 (m, 11 H), 0.74 (d, $J$ = 6.6 Hz, 3 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 176.60 (s), 66.00 (t), 36.38 (2 C), 30.11 (t), 29.05 (d), 25.87 (t), 24.72 (t), 22.99 (t), 20.85 (q), 17.12 (q); MS, $m/e$ 184 ($M^+$, 3), 141 (24), 124 (15), 123 (21), 112 (45), 111 (52), 97 (70), 95 (31), 82 (33), 69 (100), 56 (38), 42 (65). ***trans*-1l:** MS, $m/e$ 184 ($M^+$, 4), 141 (27), 112 (33), 111 (46), 110 (17), 97 (52), 95 (36), 83 (24), 82 (31), 70 (25), 69 (100), 56 (45), 55 (98), 41 (68). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.68; H, 10.95. Found (cis and trans mixture): C, 71.89; H, 11.30.

**2-Fluoro-4-methylnonanolides 1m.** ***cis*-1m:** $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.93 (ddd, $J$ = 53.3, 8.4, and 5.2 Hz, 1 H), 4.72 (ddd, $J$ = 4 Hz, 1 H), 3.98 (td, $J$ = 10.4 and 3.8 Hz, 1 H), 2.23–1.10 (m, 11 H), 1.00 (d, $J$ = 6.9 Hz, 3 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 170.04 (d, $J_F$ = 24 Hz), 88.53 (dd, $J_F$ = 173 Hz), 66.37 (t), 37.44 (dt, $J_F$ = 19 Hz), 32.17 (t), 27.17 (dd, $J_F$ = 6 Hz), 24.83 (t), 24.44 (t), 23.38 (t), 22.05 (q); MS, $m/e$ 173 ($M^+$, 0.6), 141 (13), 116 (24), 101 (20), 95 (26), 73 (30), 69 (71), 68 (35), 67 (26), 55 (100), 41 (84). ***trans*-1m:** MS, $m/e$ 141 (17), 123 (19), 112 (40), 111 (39), 97 (61), 70 (26), 69 (89), 56 (34), 55 (100), 41 (75). Anal. Calcd for $C_{10}H_{17}O_2F$: C, 63.79; H, 9.11. Found (cis and trans mixture): C, 64.01; H, 9.29.

**2-Methyl-9-decanolide (1p).**[5,26] ***Cis* and *Trans* Mixture:** $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 5.07–4.90 (m, 1 H (cis and trans)), 1.27 (d, $J$ = 6.2 Hz, methyl (trans)), 1.25 (d, $J$ = 6.6 Hz, methyl (cis)), 1.18 (d, $J$ = 7.2 Hz, methyl (trans)), 1.13 (d, $J$ = 6.9 Hz, methyl (cis)), 2.15–0.80 (m, 18 H); IR (film, $cm^{-1}$) 1732 (CO); MS, (*cis*-**1p**), $m/e$ 184 ($M^+$, 6), 140 (14), 113 (30), 98 (100), 84 (29), 83 (31), 74 (26), 70 (50), 69 (85), 56 (80), 55 (97), 42 (41), 41 (68); MS (*trans*-**1p**), $m/e$ 184 ($M^+$, 10), 112 (27), 111 (32), 98 (74), 97 (21), 83 (27), 74 (31), 70 (44), 68 (78), 56 (80), 55 (100), 43 (43), 42 (40), 41 (63).

**2-Fluoro-4-methylnonanolides 1q.** ***cis*-1q:** $^1H$ NMR (250 MHz, $CDCl_3$) $\delta$ 4.93 (ddd, $J$ = 53.3, 8.4, and 5.2 Hz, 1 H), 4.72 (ddd, $J$ = 4 Hz, 1 H), 3.98 (td, $J$ = 10.4 and 3.8 Hz, 1 H), 2.23–1.10 (m, 11 H), 1.00 (d, $J$ = 6.9 Hz, 3 H); $^{13}C$ NMR (62.8 MHz, $CDCl_3$) $\delta$ 170.04 (d, $J_F$ = 24 Hz), 88.53 (dd, $J_F$ = 173 Hz), 66.37 (t), 37.44 (dt, $J_F$ = 19 Hz), 32.17 (t), 27.17 (dd, $J_F$ = 6 Hz), 24.83 (t), 24.44 (t), 23.38 (t), 22.05 (q); MS, $m/e$ 173 ($M^+$, 0.6), 116 (24), 101 (20), 96 (20), 95 (26), 81 (40), 73 (30), 69 (71), 68 (35), 55 (100), 41 (84). ***trans*-1q:** $^1H$ NMR (250 MHz) 5.02 (ddd, $J$ = 46, 5.2 and 2.1

Hz, 1 H), 0.93 (d, $J$ = 6.4 Hz, 3 H); MS, $m/e$ 141 (17), 123 (19), 112 (41), 111 (39), 97 (61), 95 (28), 82 (34), 70 (26), 69 (89), 55 (100), 41 (75). Anal. Calcd for $C_{10}H_{17}O_2F$: C, 63.79; H, 9.11. Found (cis and trans mixture): C, 63.98; H, 9.10.

**Diolide Formation. General Experimental Procedure.** To HCl gas in solution (5%, w/w) in methylene chloride (5 mL) was added lactone (*E*)-**4fI** (0.8 mmol). After 30 min, the solvent was removed and the residue purified by liquid chromatography on silica gel ($CH_2Cl_2/CH_3COOEt$, 90/10–50/50). Diolide **6fI** ($R_1$ = $R_3$ = H, $R_2$ = Me; Scheme V): 70% yield; MS (chemical ionization, $NH_3$), $m/e$ 326 ($M^+$ + 18, 11), 309 (100), 208 (19), 190 (40), 155 (37). The main spectroscopic characteristics of diolides **6** prepared are reported in Table V. The other signals are similar to those of the monomeric lactones.

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# Displacement of Halogen of 2-Halogeno-Substituted Benzonitriles with Carbanions. Preparation of (2-Cyanoaryl)arylacetonitriles

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(2-Cyanoaryl)arylacetonitriles are obtained by displacement of halogen of 2-halobenzonitriles with phenylacetonitrile anions. The method also applies to a number of heteroaromatics with ortho-situated halogen and cyano groups and to heteroarylacetonitrile anions. The anions were generated by using potassium *tert*-butoxide or potassium carbonate. Calculated electron densities of the electrophilic centers reflect the reactivity in the displacement reaction. The calculations indicate that the potassium ion complexes with the cyano group of the 2-halobenzonitriles in nonpolar solvents, thus promoting competitive addition of the anion to the cyano group. Carbanions derived from acids with $pK_a$ ca. 19–23 similarly displaced the halogen of 2-halobenzonitriles.

(2-Cyanophenyl)phenylacetonitriles **3** are useful intermediates for the construction of five- and six-membered rings as described in the following paper. A conceivable route to (2-cyanophenyl)phenylacetonitriles involves treatment of (2-cyanophenyl)phenylhalomethanes with cyanide ions. Of these, only the parent bromo compound has been described.[1] It was prepared by treatment of (2-cyanophenyl)phenylmethane with bromine, conditions that are not compatible with the presence of alkyl groups or electron-donating substituents at the aromatic rings. Therefore, we attempted to prepare (2-cyanophenyl)-phenylchloromethanes by treatment of (2-cyanophenyl-phenyl)hydroxymethanes **5**, available through sodium borohydride reduction of benzophenones, with thionyl chloride. However, the cyano group takes part in the reaction, giving rise to iminolactones, which hydrolyze during workup to lactones **8**, which were isolated in good yields.[1,2]

Another approach to (2-cyanophenyl)phenylacetonitriles **3** is displacement of activated aromatic halogen with the anion of (2-cyanophenyl)acetonitrile (**6**, R = H) (Scheme I). Early attempts to generate this anion and to alkylate it failed since the anion rather adds to unchanged (2-cyanophenyl)acetonitrile.[3] If, however, the anion is generated by using potassium hydroxide in pyridine, it can displace the halogen of nitro-activated halobenzenes **7**.[4] The restrictions of this approach are set by the limited availability of the (2-cyanophenyl)acetonitrile (**6**) and the substituted nitro-activated halobenzenes. The resulting nitro-substituted (2-cyanophenyl)phenylacetonitriles do not undergo further alkylation, the basis for many useful applications of (2-cyanophenyl)phenylacetonitriles.[5] These limitations have been overcome by an approach in which the halogen of 2-halobenzonitriles **1** is displaced by anions from phenylacetonitrile. Although examples of nitro, ester, or cyano group activation of halogen-substituted aromatic rings toward addition of N, O, and S nucleophiles at the position occupied by halogen are abundant,[6] activation by the cyano group toward addition of carbon nucleophiles has only been observed in polycyanochlorobenzenes. Thus 1,4-dichloro-2,3,5,6-tetracyanobenzene and 1,3,5-trichloro-2,4,6-tricyanobenzene both react with carbanions derived from diethyl malonate, malononitrile, or ethyl acetoacetate.[7,8]

The present study reveals that the chlorine of 2-chlorobenzonitrile can be displaced by stabilized benzylic carbanions, notably the phenylacetonitrile anion. The reaction was performed by mixing a solution of the 2-chlorobenzonitrile **1** and the phenylacetonitrile **2** with 2 equiv of a strong base, the second equivalent being required to deprotonate the product (**3**). The reaction is sensitive to the nature of the base, the solvent, the leaving group, the substituents at the rings, and to the kind of rings. In most cases, potassium *tert*-butoxide in dimethylformamide and chlorine serve best as base, solvent, and leaving group, respectively.

Neutral substituents at position 3 of the 2-halobenzonitriles do not influence the reactivity toward addition of nucleophiles at the position occupied by halogen. Thus 2,3-dichlorobenzonitrile reacts smoothly (Table II, entry 2). Electron-donating groups at C-3 and C-5 lead to deactivation. Thus conversion of 2-chloro-5-methoxy-

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