Oxygen Effect in the Iodo Lactonization of Unsaturated Carboxylic Acids Leading to 7- to 12-Membered Ring Lactones

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The reaction of ω-alkenoic acids with bis(*sym*-collidine)iodine(I) hexafluorophosphate led to (iodomethyl) ε-caprolactones in good yields (49–75%) and medium ring iodo lactones in low yields (4–5%). The latter compounds have been obtained after introduction of an oxygen atom in the carbon chain. The position of the oxygen appeared important. This oxygen effect was explained by the stabilization of the intermediate iodonium ion by the oxygen atom.

An increasing number of natural products possessing a medium-size heterocyclic skeleton have been isolated, particularly in the last 5 years. These include ethers (mainly of marine origin), lactones, amines, and lactams.[1,2] In the case of lactones numerous methods have been reported. The more widely studied methods are certainly the cyclization of hydroxy acids and esters, which generally give unsatisfactory yields for these ring sizes.[3] These disappointing results have led to the development of other methods. One of the oldest is the Claisen rearrangement of vinylketene acetal,[4] recently applied as key step for the synthesis of natural products.[5] We can also cite the fragmentation of bicyclic compounds,[6] intramolecular Diels–Alder reactions,[7] intramolecular trapping of ketenes by alcohols,[8] reactions of allyl ethers with dichloroketene,[9] double Michael reactions,[10] one[11] or several carbon[12] ring expansions starting from lactones or ketones, and electrophilic ring enlargement of ethers or acetals.[13] Cyclizations of linear precursors under anionic,[14] radical,[15] and neutral[16] conditions were also reported. The studies of novel methods for preparing these ring sizes seem therefore useful.

Before we started our work on the cyclization of linear compounds to obtain 7-membered and medium heterocycles using electrophilic reagents, few examples were reported in the literature. ε-Caprolactones have been obtained by phenylseleno lactonization,[17] and some particular halo lactones have also been reported.[18] However, attempts to generalize these reactions were unsuccessful.[19] Our interest in the chemistry of medium-ring lactones[11] led us to reinvestigate this electrophilic cyclization. We chose iodine as the electrophile due to the easy conversion of iodide derivatives to other functions and its low toxicity compared to electrophiles which could, *a priori*, be used such as selenium, mercury, or thallium.[20]

In a preliminary study we tested the cyclization of 4-oxahept-6-enoic acid (**1a**) using bis(*sym*-collidine)iodine(I) perchlorate, and we obtained 25% yield.[18c] With common iodine reagents[21] such as I_2/CH_3CN, ICl/CH_2Cl_2, and NIS/AgOTf no iodo lactone was obtained. Different bis(aromatic amine)iodine(I) hexafluorophosphates **2** were

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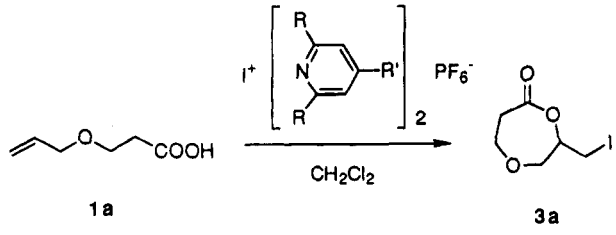
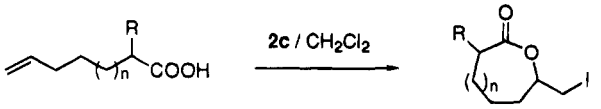
Table 1. Iodo Lactonization of Acid 1a



1a 3a

R, R′	no.	yield (%); reaction time (h)
R = R′ = H	**2a**	20; 6
R = OMe, R′ = H	**2b**	10; 48
R = R′ = Me	**2c**	59; 6

Table 2. Iodo Lactonization of ω-Alkenoic Acids 4a-4f



4a-4f 5a-5f

alkenoic acid			reaction	ring	lactones	
n	R	no.	time (h)	size	yield[a] (%)	no.
1	H	**4a**	18	7	76	**5a**
2	H	**4b**	4	8	5	**5b**
5	H	**4c**	16	11	4	**5c**
1	Me	**4d**	20	7	49[b]	**5d**
1	*c*-hexyl	**4e**	13	7	79[b]	**5e**
1	*tert*-butyl	**4f**	4	7	72[b]	**5f**

[a] Yield of purified product. [b] Isolated as a *trans*–*cis* mixture (57–43).

thus prepared using the method reported for bis(*sym*-collidine)iodine(I) perchlorate[22] and allowed to react with acid **1a** in methylene chloride at reflux. Our results are reported in Table 1. The iodo complexes of 2,6-di-*tert*-butylpyridine and 2,2′-dipyridyl could not be obtained.

It appeared that bis(*sym*-collidine)iodine(I) hexafluorophosphate (**2c**) was the best reagent. The nature of the solvent was then examined. In acetonitrile or THF, no reaction was observed, while in chloroform or toluene low yields were obtained (24 and 31% yields, respectively). The best yields were obtained in the 10^{-2}–7×10^{-2} M concentration range. At higher concentration, oligomerization became the major pathway, while at lower concentration no cyclization was observed. We have observed no noticable changes in yields whether the reactions were carried at room temperature or at reflux.

Iodo Lactonization of ω-Alkenoic Acids 4a-4f. After optimization of the reaction conditions, we tested the reactivity of ω-alkenoic acids **4** in the preparation of 7–11 ring size lactones. The starting acids were either commercially available (**4a**, **4c**) or easily prepared by conventional methods (**4b**, **4d-4f**). These alkenoic acids were subjected to the electrophilic reaction of the iodo complex **2c** according to the protocol developed for acid **1a**. The results are summarized in Table 2.

With 6-heptenoic acids **4a**, **4e**, and **4f**, we observed the formation of ϵ-caprolactones in high yields, while with 7-octenoic acid (**4b**) and 10-undecenoic acid (**4c**) the yields of iodo lactones **5b**, and **5c** were low. These different lactones were characterized by analysis of their ^{1}H and ^{13}C NMR spectra. Their ^{1}H NMR spectra showed in particular a multiplet at ~3.30 ppm which could be attributed to the methylene bearing the iodine atom.

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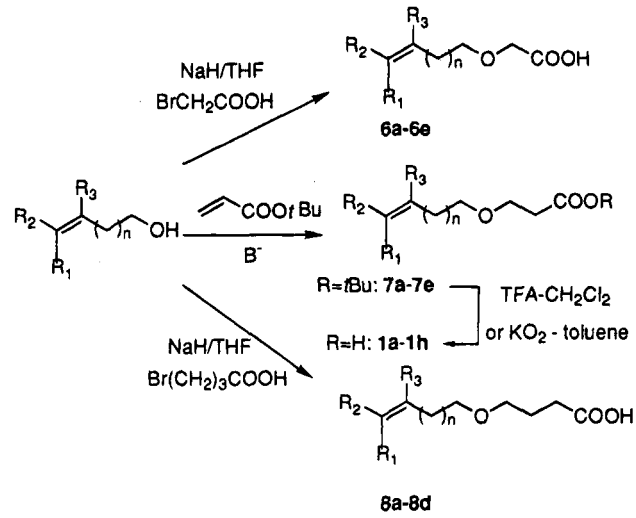
Scheme 1



Lactones **5d-5f** were isolated as a mixture of two diastereoisomers. The major isomers were found to be *trans* after examination of their COSY and NOESY spectra. Introduction of a bulky group α to the acid function did not modify the diastereoselectivity of the cyclization. However, diastereoselective modifications have been observed in the synthesis of five- and six-membered heterocycles proceeding under thermodynamic conditions.[20]

Oxygen Atom Influence on the Iodo Lactonization of Alkenoic Acids. The beneficial influence of the oxygen atom in the cyclization of linear compounds to obtain medium ring cycles has been known for a long time[23] and has been mainly explained by a decrease of C–H–H–C intramolecular nonbonding interactions.[24] Comparison of the properties of hydrocarbon medium ring compounds with their oxygenated homologues have confirmed this explanation.[25] The oxygen effect has been also observed in the preparation of medium[26] and normal[27] ring ethers.[28]

The acids **1**, **6**, and **8** used for this study have been prepared as outlined in Scheme 1. Thus, 2-(*n*-alkenoxy)-ethanoic acids **6a-6e** were readily obtained by reaction of *n*-alkenoates with bromoacetic acid (52–90%).[29] 3-(*n*-Alkenoxy)propanoic acids **1a-1h** were obtained in two steps by Michael addition of alkenoates on *tert*-butyl acrylate, followed by hydrolysis of the ester function (50–90%).[30] 4-(*n*-Alkenoxy)butanoic acids **8a-8d** were formed (10–28%) by reaction of alkenoates with 4-bromobutanoic acid; the low yields observed in these latter reactions are due to facile crotonic acid formation. These different acids were subjected to the iodo lactonization reaction according to the protocol developed for acid **1a**. The results are summarized in Table 3.

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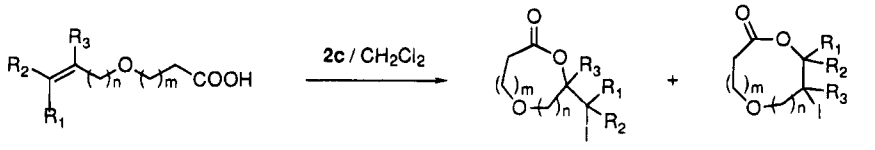
Table 3. Iodo Lactonization of *n*-Oxa-ω-alkenoic Acids 1, 6, and 8

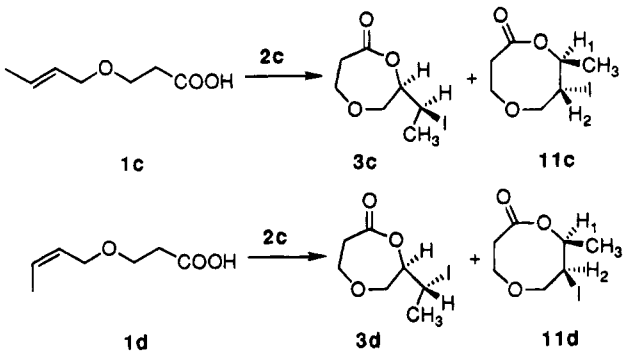


1, 6, 8 3, 9, 10 11, 12, 13

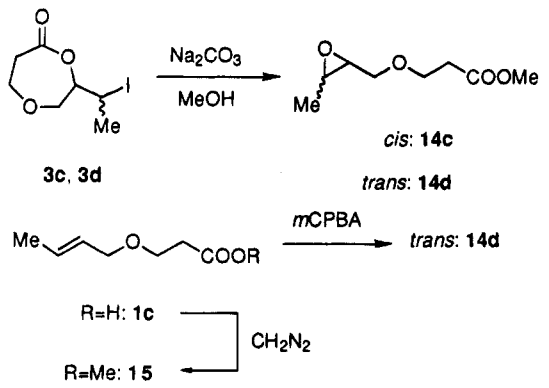
	alkenoic acid						reaction	*exo* cyclization			*endo* cyclization		
entry	*m*	*n*	R^1	R^2	R^3	no.	time (h)	ring size	no.	yield[a] (%)	ring size	no.	yield[a] (%)
a	1	1	H	H	H	**1a**	6	7	**3a**	59			
b	1	1	H	H	Me	**1b**	5	7	**3b**	70			
c	0	2	H	H	H	**6a**	6	7	**9a**	75			
d	0	2	H	H	Me	**6b**	4	7	**9b**	75			
e	1	1	Me	H	H	**1c**	6	7	**3c**	45[b]	8	**11c**	45[b]
f	1	1	H	Me	H	**1d**	6	7	**3d**	40[b]	8	**11d**	40[b]
g	1	1	Me	Me	H	**1e**	6	7	**3e**	5	8	**11e**	39
h	0	3	H	H	H	**6c**	13	8	**9c**	23	9	**12c**	23
i	1	2	H	H	H	**1f**	16	8	**3f**	40	9	**11f**	5
j	1	2	H	H	Me	**1g**	17	8	**3g**	45[c]			
k	2	1	H	H	H	**8a**	10	8	**10a**	8[c]			
l	2	1	H	H	Me	**8b**	24	8	**10b**	2[c]	9	**13b**	1[c]
m	1	3	H	H	H	**1h**	15	9	**3h**	2[d]			
n	2	2	H	H	H	**8c**	10	9	**10c**	24[c]	10	**13c**	24[c]
o	0	5	H	H	H	**6d**	16	10	**9d**	18[c]	11	**12d**	18[c]
p	0	6	H	H	H	**6e**	17	11	**9e**	7[c]	12	**12e**	21[c]
q	2	5	H	H	H	**8d**	10	12	**10d**	16[c]	13	**13d**	16[c]

[a] Yield in purified product. [b] Only one diastereoisomer was isolated. [c] Alkenoic acid was recovered in part. [d] Formation of 2-(iodomethyl)tetrahydrofuran.

Scheme 2



Scheme 3



As we have seen previously, ϵ-caprolactones were obtained in good yields (entries a-f) even if comparison of the result for the cyclization of 4-oxahept-6-enoic acid (**1a**) with 6-heptenoic acid (**4a**) shows the existence of a slight *negative* oxygen effect which seems specific to this ring size.[26] Introduction of a methyl in the ω-1 position on the carbon–carbon double bond increases the yield of the cyclization of the acid **1b** (entry b) compared to the nonsubstituted one (entry a). An improved yield was also observed when the oxygen atom was closer to the acid function (entries c and d). Substitution of the hydrogen(s) fixed on the terminal carbon of the double bond by one or two methyl groups favored the *endo* mode cyclization[31] (entries e–g). The structure of these lactones was deduced from their ^1H and ^{13}C NMR spectra.

Cyclization of acid **1c** (entry e) led to a mixture of two lactones which were identified with the diastereoisomers obtained from acid **1d** (entry f; see Scheme 2). The stereochemistry of the lactones **3c** and **3d** was established by chemical correlation. Thus, their reaction with sodium carbonate in methanol led stereoselectively[32] to the corresponding epoxides **14**, whose spectra were compared with those obtained by the epoxidation of ester **15** (Scheme 3). This correlation showed that the *trans* epoxide **14d** obtained by the epoxidation of ester **15** was identical with the epoxide obtained by opening of ϵ-caprolactone **3c**, formed during the iodo lactonization of the acid **1c** (Scheme 3). The stereochemistry of the two lactones **11c** and **11d** was confirmed by analysis of their ^1H NMR spectra. Particularly revealing was the coupling constant J_{H1H2} which was found to be 2.0 Hz for the *cis* isomer and 6.2 Hz for the *trans* isomer. We can deduce from these results that the iodolactonization reactions occurred under kinetic control.[33]

The obtention of lactones **9c**, **3f**, and **3g** indicated that the preparation of 8-membered lactones by an *exo*-mode cyclization is possible with acceptable yields (entries h–j). The proximity of the oxygen atom to the carboxylic function favored the *endo* cyclization (compare entries h and i). As for the formation of 7-membered ring lactones,

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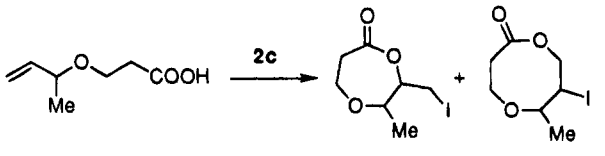
Scheme 4



if the oxygen atom is far from the acidic group, we observed dramatic decrease in yields (entries k and l). Entries n–q indicated that higher ring sizes could be obtained in moderate yields. For these 9–12 ring sizes we observed a competition between the *exo* and *endo* mode of cyclizations. Such a competition was precedently reported for the selenocyclization of unsaturated acids leading to large ring lactones.[34] The low yield observed for the reaction of acid **1h** (entry m) is due to a competitive iodo etherification which favored the five-membered ring ether.

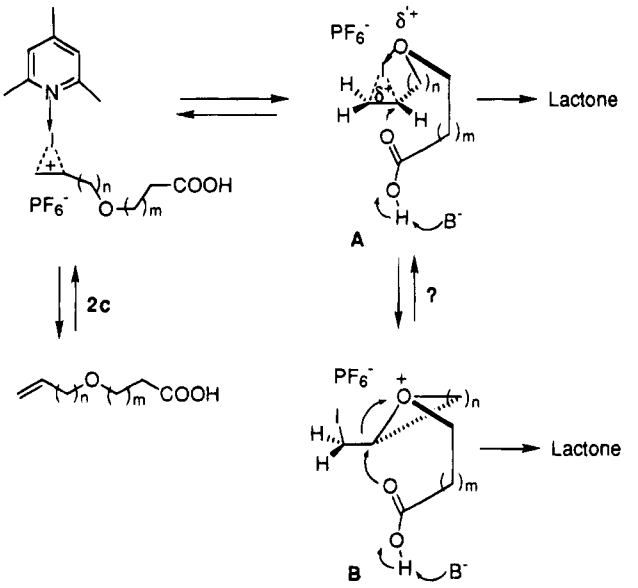
Iodo lactonization of acid **1i** was also examined (Scheme 4). After 40 h at reflux in methylene chloride, two lactones (**16**, **17**) were isolated (36% yield; ratio 22:78). Each lactone was diastereoisomerically pure. However, their stereochemistries could not be determined. Apparently, for steric reasons, the presence of a substituent in α position of the carbon–carbon double bond makes the *exo*-mode cyclization unfavorable.

Discussion

The results show that the substitution of a carbon atom by an oxygen atom in the chain at a specific position favors the formation of medium ring lactones. This is the first general report concerning the possibility to obtain medium ring heterocycles using an electrophilic reagent.

This oxygen effect can, *a priori*, be due to four different (but not necessary independent) effects: (1) an enthalpic effect; (2) an electronic inductive effect; (3) an entropic effect; and (4) a chelating effect. (1) In their study Illuminati and Mandolini[28] found, for the reactions they have examined, that the oxygen effect is principally enthalpic (release of CH–CH nonbonding interactions). Such an explanation cannot be used in our case. Indeed, the reactions appear to proceed under kinetic conditions (see the reactions with acids **1c**, **1d**, and **1i**) where the release of CH–CH nonbonding interactions cannot be the main factor. This claim was confirmed by our results from the study of the *gem*-dimethyl effect.[35] We have shown that the introduction of a *gem*-dimethyl group favored the formation of medium ring iodolactones, although nonbonding interactions in the products increased. (2) The inductive effect of the oxygen atom should slightly favor or disfavor the cyclization, depending on its position in the chain. When the oxygen atom was near the acid function the yields in iodo lactones increased (compare entries a and c), whereas when this atom was near the CC double bond the yields decreased. However, this effect appears to be limited. (3) Also, the entropic effect can be also considered as minor since the geometrical modification introduced by the oxygen atom is insignificant. (4) If all these contributing effects are judged to be insufficient, then we can consider a chelating

Scheme 5



effect due to the oxygen atom. Contrary to the charge transfer mechanism postulated to explain the results of iodocyclization using iodine as a reagent,[36] the use of bis(collidine)iodine hexafluorophosphate implies the intervention of an iodonium ion intermediate (at least in a first step). The oxygen atom probably induces a well-known[37] stabilization effect (Scheme 5). The consequence of this oxygen participation is probably a decrease in entropy, due to the formation of a chelate (A) or oxonium (B) intermediate, which subsequently favors the cyclization. This effect was optimal with 2-(*n*-alkenoxy)ethanoic acids for which we can postulate a 5- (intermediate B) or a 6- (intermediate A) membered cyclic intermediate (Scheme 5).

In conclusion, this work showed that the use of bis(*sym*-collidine)iodine hexafluorophosphate allows the formation of ε-caprolactones in high yields, a reaction which was not possible with other iodo reagents. Additionally, we have been able to obtain medium ring lactones in moderate yields if an oxygen atom is present in the chain. We explained these results in terms of the stabilization of the ionic intermediate by the oxygen atom.

Experimental Section

^{1}H NMR spectra were recorded at 200 MHz. Mass spectra were determined at an ionizing voltage of 70 eV. Column chromatography was performed with silica gel (70–230 mesh). TLC was performed on 0.25 mm silica gel (Merck 60 F_{254}). Bis(*sym*-collidine)iodine(I) hexafluorophosphate was prepared in two steps (91% overall yield) according to Lemieux and Morgan.[22] $Ag^+(collidine)_2PF_6^-$: white solid; mp 204 °C. Anal. Calcd for $C_{16}H_{22}AgF_6N_2P$: C, 38.81; H, 4.48; Ag, 21.78. Found: C, 39.05; H, 4.36; Ag, 22.38. $I^+(collidine)_2PF_6^-$: white solid; mp 147 °C. Anal. Calcd for $C_{16}H_{22}IF_6N_2P$: C, 37.35; H, 4.31; I, 24.69. Found: C, 37.42; H, 4.29; I, 24.66. 6-Heptenoic acid (**4a**) and 10-undecenoic acid (**4c**) were commercially available. 7-Octenoic acid (**4b**) was obtained in three steps by condensation of 6-bromo-1-octene with diethyl malonate followed by hydrolysis of the ester functions and heating (60% overall yield). The 6-heptenoic acids **4d-4e** were obtained by

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(36) (a) Chamberlin, A. R.; Mulholland, R. L.; Kahn, S. D.; Hehre, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 672. (b) Doi, J. T.; Luehr, G. W.; Carmen, D. del.; Lippsmeyer, B. C. *J. Org. Chem.* **1989**, *54*, 2764.
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alkylation of, respectively, propanoic acid (**4d**[38]), cyclohexylacetic acid (**4e**), and 3,3-dimethylbutanoic acid (**4f**) with 4-bromo-1-pentane (70–80% yields).The iodo lactonizations were conducted in the dark. However, the iodo lactones were stable enough to be purified without special care.

2-*tert*-Butyl-6-heptanoic acid (4f): ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9H), 1.30–1.75 (m, 4H), 2.04 (m, 3H), 4.97 (bd, J = 9.9 Hz, 1H), 5.03 (bd, J = 12.0 Hz, 1H), 5.80 (m, 1H), 8.00–9.50 (m, 1H); mass spectrum (EI) m/z (relative intensity) 169 (M-15, 3), 127 (13), 116 (14), 101 (32), 73 (32), 69 (36), 68 (20), 58 (12), 57 (100), 56 (18), 55 (21), 54 (10), 43 (11), 41 (50), 39 (16).

2-Cyclohexyl-6-heptenoic acid (4e): ^{1}H NMR ($CDCl_3$) δ 0.87–1.75 (m, 16H), 1.97–2.30 (m, 3H), 4.95 (bd, J = 9.9 Hz, 1H), 5.01 (bd, J = 12.0 Hz, 1H), 5.80 (m, 1H), 8.00–10.00 (m, 1H); mass spectrum (EI) m/z (relative intensity) 210 (M^+, 7), 142 (89), 128 (24), 110 (22), 99 (28), 87 (14), 86 (16), 83 (40), 82 (43), 81 (38), 79 (15), 73 (82), 70 (13), 69 (75), 68 (48), 67 (38), 56 (40), 55 (100), 54 (14), 53 (15), 41 (66), 39 (26).

Preparation of 6-(Iodomethyl)hexanolide (5a). Representative Procedure A. To a solution of 0.2 g (1.5 mmol) of 6-heptenoic acid in CH_2Cl_2 (20 mL) was added 1.5 g (3 mmol) of bis(*sym*-collidine)iodine(I) hexafluorophosphate. The flask was heated at 40 °C. After complexion of the reaction (18 h), the mixture was cooled at rt and ether (30 mL) was added. The organic phase was washed with 6 N HCl (6 × 20 mL) and dried over Na_2SO_4. After concentration of the solution, the crude product was purified over silica gel (hexane–ether, 7/3–1/1), and 0.213 g of lactone **5a** was obtained (76% yield) as an orange oil: IR ($CDCl_3$) 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.50–1.85 (m, 3H), 1.89–2.10 (m, 2H), 2.24 (m, 1H), 2.68 (m, 2H), 3.33 (m, 2H), 4.35 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 8.0 (t), 22.5 (t), 27.4 (t), 34.3 (t), 34.5 (t), 78.9 (d), 173.7 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 272 (M^+ + 18, 100); mass spectrum (EI) m/z (relative intensity) 254 (M^+, 5), 127 (48), 113 (18), 109 (16), 85 (20), 84 (20), 81 (31), 67 (27), 56 (28), 55 (100), 54 (31), 43 (35), 42 (26), 41 (71), 39 (30). Anal. Calcd for $C_7H_{11}O_2I$: C, 33.07; H, 4.36. Found: C, 33.35; H, 4.48. Lactones **5b-5e** were obtained using this procedure.

7-(Iodomethyl)heptanolide (5b): orange oil; IR ($CDCl_3$) 1737 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.35 (m, 3H), 1.52–1.88 (m, 5H), 2.38 (bt, J = 6.4 Hz, 2H), 3.26 (bd, J = 5.9 Hz, 2H), 4.85 (m, 1H); mass spectrum (Cl, NH_3) m/z (relative intensity) 287 (21), 286 (M^+ + 18, 100), 269 (M^+ + 1, 10); mass spectrum (EI) m/z (relative intensity) 268 (M^+, 1), 141 (54), 123 (40), 98 (22), 97 (24), 95 (50), 81 (55), 80 (18), 70 (21), 69 (44), 56 (17), 55 (100), 54 (15), 43 (37), 42 (45), 41 (79), 39 (34). Anal. Calcd for $C_8H_{13}O_2I$: C, 35.84; H, 4.89. Found: C, 35.88; H, 5.04.

10-(Iodomethyl)decanolide (5c): white solid; mp 62 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (m, 10H), 1.67 (m, 4H), 2.36 (m, 2H), 3.27 (dd, J = 6.3, 1.6 Hz, 2H), 4.82 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 8.1 (t), 25.0 (t), 25.5 (t), 29.2 (2t), 29.7 (2t), 34.0 (t), 34.9 (t), 72.1 (d), 171.4 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 329 (34), 328 (M^+ + 18, 100), 203 (22), 202 (38), 183 (16); mass spectrum (EI) m/z (relative intensity) 310 (M^+, 1), 183 (19), 165 (17), 147 (21), 123 (23), 98 (21), 97 (20), 95 (22), 84 (17), 83 (32), 81 (61), 69 (38), 57 (15), 56 (17), 55 (100), 54 (37), 43 (31), 42 (27), 41 (68), 40 (21). Anal. Calcd for $C_{11}H_{19}O_2I$: C, 42.60; H, 6.17. Found: C, 42.91; H, 5.89.

***cis*-6-(Iodomethyl)-2-methylhexanolide (*cis*-5d):** orange oil; IR ($CDCl_3$) 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.21 (d, J = 6.7 Hz, 3H), 1.51–1.82 (m, 3H), 1.96 (m, 1H), 2.17 (m, 1H), 2.69$_5$ (m, 1H), 3.26 (dd*, J = 10.3, 6.0 Hz), 3.37 (dd*, J = 10.30 Hz, 5.9 Hz, 1H), 4.42 (bdd, 1H); ^{13}C NMR ($CDCl_3$) δ 7.6 (t), 18.5 (q), 27.4 (t), 31.8 (t), 34.0 (t), 37.8 (d), 78.7 (d), 176.0 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 286 (M^+ + 18, 100), 269 (M^+ + 1, 7); mass spectrum (EI) m/z (relative intensity) 268 (M^+, 4), 141 (75), 127 (14), 98 (10), 95 (22), 81 (20), 69 (19), 56 (12), 55 (100), 43 (43), 42 (27), 41 (63), 39 (26). Anal. Calcd for $C_8H_{13}O_2I$: C, 35.84; H, 4.89. Found: C, 35.76; H, 5.01.

***trans*-6-(Iodomethyl)-2-methylhexanolide (*trans*-5d):** orange paste; IR ($CDCl_3$) 1727 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 7.4 Hz, 3H), 1.60 (m, 1H), 1.70–1.96 (m, 3H), 2.12 (m, 1H), 3.02 (qd, 1H), 3.35 (m, 2H), 4.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 6.7 (t), 16.0 (q), 21.7 (t), 29.1 (t), 33.4 (t), 41.3 (d), 77.8 (d), 175.6 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 286 (M^+ + 18, 100), 269 (M^+ + 1, 9); mass spectrum (EI) m/z (relative intensity) 268 (M^+, 2), 141 (66), 127 (15), 98 (25), 95 (21), 81 (25), 69 (21), 56 (15), 55 (100), 43 (52), 42 (36), 41 (73), 39 (29). Anal. Calcd for $C_8H_{13}O_2I$: C, 35.84; H, 4.89. Found: C, 35.84; H, 4.78.

***cis*-6-(Iodomethyl)-2-cyclohexylhexanolide (*cis*-5e):** orange paste; IR ($CDCl_3$) 1742 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.83–1.44 (m, 7H), 1.48–1.77 (m, 6H), 1.78–1.98 (m, 3H), 2.10$_5$ (dd, J = 9.8, 4.4 Hz, 1H), 2.29 (ddd, J = 10.8, 5.3, 1.9 Hz, 1H), 3.22 (dd*, J = 10.3, 6.10 Hz, 1H), 3.31 (dd*, J = 10.3, 5.7 Hz, 1H), 4.38 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 8.0 (t), 25.5 (t), 26.2 (t), 26.3 (t), 26.4 (t), 27.0 (t), 28.6 (t), 31.1 (t), 33.7 (t), 39.1 (d), 48.2 (d), 77.8 (d), 173.7 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 355 (19), 354 (M^+ + 18, 100), 337 (M^+ + 1, 8), 353 (22); mass spectrum (EI) m/z (relative intensity) 254 (M^+ – 56, 44), 127 (19), 109 (27), 84 (14), 83 (12), 81 (100), 73 (33), 69 (10), 67 (31), 55 (41), 54 (11), 43 (11), 41 (39), 39 (13). Anal. Calcd for $C_{13}H_{21}O_2I$: C, 46.44; H, 6.30. Found: C, 46.64; H, 6.23.

***trans*-6-(Iodomethyl)-2-cyclohexylhexanolide (*trans*-5e):** orange solid; mp 81 °C; IR ($CDCl_3$) 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (bs, 1H), 1.01–1.34 (m, 4H), 1.52–1.88 (m, 11H), 1.96–2.16 (m, 1H), 2.63 (m, 1H), 3.21 (bs*, 1H), 3.24$_5$ (d*, J = 1.5 Hz, 1H), 4.49 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 7.8 (t), 21.6 (t), 24.4 (t), 25.8 (t), 25.9 (t), 30.8 (t), 31.1 (t), 34.2 (t), 36.0 (d), 53.9 (d), 77.0 (d), 174.2 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 355 (20), 354 (M^+ + 18, 100), 353 (24), 337 (M^+ + 1, 11), 228 (355 – I, 16); mass spectrum (EI) m/z (relative intensity) 336 (M^+, 1), 254 (M^+ – 82, 40), 127 (21), 109 (30), 95 (13), 84 (36), 83 (32), 81 (100), 79 (14), 73 (26), 69 (17), 67 (44), 55 (67), 54 (14), 53 (12), 43 (12), 41 (54), 39 (18). Anal. Calcd for $C_{13}H_{21}O_2I$: C, 46.44; H, 6.30. Found: C, 46.26; H, 6.01.

***cis*-6-(Iodomethyl)-2-*tert*-butylhexanolide (*cis*-5f):** orange paste; IR ($CDCl_3$) 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.05 (bs, 9H), 1.51–1.73 (m, 3H), 1.90–2.07 (m, 2H), 2.14–2.30 (m, 2H), 3.24$_5$ (dd*, J = 10.3, 6.6 Hz, 1H), 3.35 (dd*, J = 10.3, 5.3 Hz, 1H), 4.46 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 7.9 (t), 25.3 (t), 27.0 (q), 27.4 (t), 33.0 (s), 33.8 (t), 51.9 (d), 77.9 (d), 173.7 (q); mass spectrum (CI, NH_3) m/z (relative intensity) 329 (27), 328 (M^+ + 18, 100), 311 (M^+ + 1, 8); mass spectrum (EI) m/z (relative intensity) 254 (M^+ – 56, 35), 183 (17), 127 (24), 109 (29), 84 (40), 83 (21), 81 (100), 73 (53), 69 (34), 67 (23), 57 (72), 55 (74), 53 (13), 43 (31), 41 (59), 39 (20). Anal. Calcd for $C_{11}H_{19}O_2I$: C, 42.60; H, 6.17. Found: C, 42.74; H, 6.42.

***trans*-6-(Iodomethyl)-2-*tert*-butylhexanolide (*trans*-5f):** orange solid; mp 36 °C; IR ($CDCl_3$) 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (bs, 9H), 1.42–1.67 (m, 2H), 1.77–2.03 (m, 4H), 2.76 (bdd, J = 10.5, 8.6 Hz, 1H), 3.28 (bd, J = 6.04 Hz, 2H), 4.77 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 5.8 (t), 20.6 (t), 22.5 (t), 28.3 (q), 32.3 (t), 34.1 (s), 58.5 (d), 74.8 (d), 172.9 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 329 (26), 328 (M^+ + 18, 100), 311 (M^+ + 1, 12), 202 (329 – I, 13); mass spectrum (EI) m/z (relative intensity) 310 (M^+, 1), 254 (M^+ – 56, 24), 183 (29), 127 (24), 109 (24), 97 (15), 84 (86), 83 (35), 81 (92), 73 (44), 69 (50), 67 (27), 57 (100), 56 (14), 55 (97), 54 (13), 53 (16), 43 (51), 41 (76), 39 (24). Anal. Calcd for $C_{11}H_{19}O_2I$: C, 42.60; H, 6.17. Found: C, 42.51; H, 6.46.

Preparation of 2-(*n*-alkenoxy)ethanoic acids 6a-6e was made following a report procedure.[29] **2-(3-Butenoxy)ethanoic acid (6a)** and **2-(3-methyl-3-butenoxy)ethanoic acid (6b)** have already been described.[39]

2-(4-Pentenoxy)ethanoic acid (6c): 90% yield; IR (film) 3600–2500, 1730, 1650 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.75 (q, J = 7.2 Hz, 2H), 2.17 (bq, J = 7.2 Hz, 2H), 3.59 (t, J = 7.3 Hz, 2H), 4.13 (s, 2H), 4.99 (d, J = 8.9 Hz, 1H), 5.06 (d, J = 14.9 Hz, 1H), 5.82 (m, 1H), 12.5–13.0 (m, 1H); mass spectrum (CI, NH_3) m/z (relative intensity) 162 (M + 18, 100); mass

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spectrum (EI) m/z (relative intensity) 68 (100), 67 (67), 61 (13), 57 (11), 41 (35), 39 (15).

2-(6-Heptenoxy)ethanoic acid (6d): 76% yield; bp 97–101 °C/0.05 mmHg; IR (film) 3600–2400, 1735, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.40 (m, 4H), 1.64 (bq, J = 6.80, 6.60 Hz, 2H), 2.06 (btd, J = 12.61, 6.5 Hz, 2H), 3.56 (t, J = 6.60 Hz, 2H), 4.12 (s, 2H), 4.93 (bd, J = 9.2 Hz, 1H), 5.01 (bd, J = 13.9 Hz, 1H), 5.81 (m, 1H), 8.40–9.20 (m, 1H); mass spectrum (CI, NH_3) m/z (relative intensity) 191 (11), 190 (M + 18, 100); mass spectrum (EI) m/z (relative intensity) 172 (M^+, 0.1), 96 (20), 81 (33), 68 (52), 67 (68), 61 (24), 57 (13), 55 (100), 54 (62), 43 (12), 41 (47), 39 (23).

2-(7-Octenoxy)ethanoic acid (6e): 52% yield; bp 118 °C/0.05 mmHg; IR (film) 3600–2400, 1730, 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.38 (m, 6H), 1.65 (m, 2H), 2.07 (btd, 2H, J = 12.6, 6.5 Hz), 3.58 (t, J = 6.60 Hz, 2H), 4.13 (s, 2H), 4.95 (bd, J = 9.2 Hz, 1H), 5.03 (bd, J = 13.9 Hz, 1H), 5.82 (m, 1H), 8.40–9.20 (m, 1H); mass spectrum (CI, NH_3) m/z (relative intensity) 206 (14), 205 (27), 204 (M + 18, 100); mass spectrum (EI) m/z (relative intensity) 110 (20), 95 (22), 82 (37), 81 (58), 70 (22), 69 (92), 68 (96), 67 (100), 66(14), 61 (33), 60 (17), 59 (11), 57 (21), 56 (22), 55 (77), 54 (65), 43 (18), 42 (26), 41 (88), 39 (30).

Preparation of 3-(*n*-alkenoxy)propanoic Acids 1a-1i has already been reported.[30]

Preparation of 4-(*n*-alkenoxy)butanoic Acids 8a-8d. Representative Procedure. Under argon at 0 °C, ether (20 mL) was added to NaH (3.7 g at 50% in oil; 77 mmol) previously washed with hexane. To this suspension was added dry allylic alcohol (2.4 mL, 38 mmol) dropwise over 30 min, followed by a solution of 4-bromobutanoic acid (6.0 g, 35 mmol) in THF (10 mL). The mixture was heated for 2 h at reflux and then hydrolyzed by a saturated NaCl solution (100 mL). The aqueous phase was washed with ether (2 × 20 mL), acidified at pH 1 (6 N HCl), and extracted with ether (6 × 50 mL). The organic phases were washed with water (30 mL) and saturated NaCl solution (50 mL) and dried over Na_2SO_4. After concentration of the solution under vacuum the crude mixture was distilled under vacuum to give 1.40 g of 4-(2-propenoxy)butanoic acid (**8a**) (28%; bp 114 °C/0.35 mmHg); IR (film) 3600–2400, 1715, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.94 (q, J = 6.50 Hz, 2H), 2.50 (t, J = 7.20 Hz, 2H), 3.50 (t, J = 5.78 Hz, 2H), 3.98 (bd, J = 5.80 Hz, 2H), 5.19 (dd, J = 1.4 Hz, 10.7 Hz), 5.27 (dd, J = 1.4, 17.3 Hz), 5.83 (m, 1H), 10.0–12.0 (m, 1H); mass spectrum (CI, NH_3) m/z (relative intensity) 162 (M + 18, 54), 145 (M + 1, 100); mass spectrum (EI) m/z (relative intensity) 87 (42), 85 (32), 58 (11), 57 (22), 45 (35), 43 (40), 42 (13), 41 (100), 39 (26).

4-(2-Methyl-2-propenoxy)butanoic acid (8b): bp 87 °C/0.15 mmHg; IR (film) 3600–2400, 1715, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.94 (q, J = 6.7 Hz, 2H), 2.50 (t, J = 7.20 Hz, 2H), 3.48 (t, J = 6.0 Hz, 2H), 3.88 (bs, 2H), 4.93 (bd, J = 15.0 Hz), 10.4–12.2 (m, 1H); mass spectrum (CI, NH_3) m/z (relative intensity) 176 (M + 18, 65), 159 (M + 1, 100); mass spectrum (EI) m/z (relative intensity) 87 (100), 85 (35), 72 (77), 71 (42), 69 (24), 57 (47), 56 (27), 55 (57), 45 (40), 43 (77), 42 (13), 41 (40), 39 (31). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.92; H, 9.11.

4-(3-Butenoxy)butanoic acid (8c): bp 84 °C/0.15 mmHg; IR (film) 3600–2400, 1715, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.92 (q, J = 6.35 Hz, 2H), 2.35 (bq, J = 6.35 Hz, 2H), 2.49 (t, J = 6.35 Hz, 2H), 3.50 (2 t, J = 6.35 Hz, 4H), 5.04 (bd, J = 8.65 Hz, H), 5.10 (bd, J = 16.9 Hz, H), 5.82 (m, 1H), 10.0–12.0 (m, 1H); mass spectrum (CI, NH_3) m/z (relative intensity) 176 (M + 18, 17), 159 (M + 1, 100); mass spectrum (EI) m/z (relative intensity) 87 (100), 55 (24), 45 (47), 43 (66), 42 (12), 41 (39), 39 (16). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.98; H, 9.01.

4-(6-Heptenoxy)butanoic acid (8d): bp 115 °C/0.15 mmHg; IR (film) 3600–2400, 1715, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.38 (m, 4H), 1.58 (q, J = 6.7 Hz, 2H), 1.91 (q, J = 6.35 Hz, 2H), 2.06 (btd, 2H, J = 12.6, 6.5 Hz), 2.49 (t, J = 6.5 Hz, 2H), 3.42 (t, J = 6.5 Hz, 4H), 3.48 (t, J = 6.5 Hz, 2H), 4.94 (bd, J = 10.0 Hz, 1H), 5.00 (bd, J = 16.8 Hz, 1H), 5.82 (m, 1H), 10.0–11.7 (m, 1H); mass spectrum (CI, NH_3) m/z (relative intensity) 218 (M + 18, 66), 201 (M + 1, 100); mass spectrum (EI) m/z (relative intensity) 103 (14), 96 (17), 87 (80), 85 (38), 81 (17), 68 (28), 67 (38), 55 (100), 54 (31), 45 (29), 43 (45), 41 (46), 39 (18). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.22; H, 10.21.

Iodo Lactonization of *n*-Oxa-ω-alkenoic Acids. Representative Procedure B. The reaction was conducted under the conditions described in procedure A. After complexion of the reaction conducted on 1.5 mmol of acid **6a**, $NaS_2O_3{\cdot}5H_2O$ (1.6 g, 6 mmol) and oxalic acid (0.45 g, 3.5 mmol) were added. After 2 h at room temperature the mixture was filtered over Celite and concentrated. The residue was purified by column chromatography over silica gel (ether–hexane, 4/1) to give 0.293 g of 6-(iodomethyl)-3-oxahexanolide (**9a**) as a yellow paste (75%): IR (film) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.28 (m, 2H), 3.40 (m, 2H), 3.82 (m, 1H), 4.08 (m, 1H), 4.39 (dd, 2H), 4.67 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 6.7 (t), 35.7 (t), 69.8 (t), 70.8 (t), 77.4 (t), 170.1 (s); mass spectrum (CI, NH_3)-m/z (relative intensity) 274 (M^+ + 18, 100); mass spectrum (EI) m/z (relative intensity) 256 (M^+, 2), 129 (14), 55 (100).

The lactones **3a-3h, 9b-9c, 10a-10c, 11c-f, 12c, 13b,** and **13c** were isolated using this procedure.

6-(Iodomethyl)-4-oxahexanolide (3a): white solid; mp 102 °C; already described.[18c]

6-(Iodomethyl)-6-methyl-3-oxahexanolide (3b): yellowish oil; IR (film) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.75 (s, 3H), 2.31 (m, 1H), 2.51 (m, 1H), 3.46 (d, 1H), 3.70 (d, 1H), 3.97 (m, 2H), 4.38 (dd, 2H); ^{13}C NMR ($CDCl_3$) δ (ppm) 14.0 (t), 26.0 (q), 36.4 (t), 65.5 (t), 68.7 (t), 81.4 (s), 171.3 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 306 (100), 288 (M^+ + 18, 43), 162 (45); mass spectrum (EI) m/z (relative intensity) 185 (20), 128 (32), 127 (28), 101 (33), 85 (40), 71 (84), 58 (55), 57 (48), 55 (34), 43 (100), 41 (57). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.11. Found: C, 31.21; H, 4.15.

(6*RS*,7*SR*)-6-(1-Iodoethyl)-4-oxahexanolide (3c): yellow paste; IR ($CDCl_3$) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (d, J = 6.2 Hz, 3H), 2.78 (ddd, J = 14.6, 4.9, 1.0 Hz, 1H), 3.07 (ddd, J = 14.6, 11.0, 3.2 Hz, 1H), 3.71 (m, 2H), 4.03 (ddd, J = 12.2, 4.4, 3.2 Hz, 1H), 4.17 (qd, J = 6.7, 2.0 Hz, 1H), 4.25 (bd, J = 12.2 Hz, 1H), 4.32 (dd, J = 7.3, 4.9 Hz, 1H); mass spectrum (CI, NH_3) m/z (relative intensity) 288 (M^+ + 18, 58), 162 (25), 143 (M^+ − 127, 100); mass spectrum (EI) m/z (relative intensity) 270 (M^+, 10), 184 (12), 101 (12), 87 (12), 86 (88), 73 (22), 71 (100), 58 (45), 57 (29), 56 (17), 55 (73), 45 (18), 44 (14), 43 (56), 42 (29), 41 (59), 39 (20). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.11. Found: C, 31.29; H, 4.16.

(6*RS*,7*RS*)-6-(1-Iodoethyl)-4-oxahexanolide (3d): white solid; mp 91 °C; IR ($CDCl_3$) 1737 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.92 (bd, J = 6.7 Hz, 3H), 2.79 (bdd, J = 15.0, 4.7 Hz, 1H), 3.07 (ddd, J = 15.0, 11.3, 3.1 Hz, 1H), 3.71 (m, 2H), 4.00–4.27 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 22.0 (d), 23.9 (q), 39.4 (t), 65.1 (t), 75.4 (t), 82.7 (d), 171.9 (s); mass spectrum (EI) m/z (relative intensity) 270 (M^+, 3), 87 (12), 86 (77), 73 (22), 71 (100), 58 (29), 57 (20), 55 (80), 43 (32), 42 (14), 41 (33). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.10. Found: C, 31.36; H, 4.11.

6-(1-Iodo-1-methylethyl)-4-oxahexanolide (3e): orange oil; ^1H NMR ($CDCl_3$) δ 1.42 (s, 3H), 1.46 (s, 3H), 2.68 (t, J = 6.2 Hz, 2H), 3.81 (bt, J = 6.2 Hz, 2H), 3.92 and 3.98 (2dd*, J = 8.2, 6.2, 4.5 Hz, 2H), 4.28 (dd, J = 6.2, 4.5 Hz, 1H); mass spectrum (CI, NH_3) m/z (relative intensity) 302 (M^+ + 18, 100); mass spectrum (EI) m/z (relative intensity) 226 (88), 212 (19), 182 (38), 154 (96), 99 (27), 85 (35), 73 (15), 71 (15), 69 (19), 68 (15), 67 (19), 59 (19), 58 (15), 57 (19), 56 (31), 55 (100), 53 (27), 43 (35), 42 (15), 41 (77), 39 (31). Anal. Calcd for $C_8H_{13}O_3I$: C, 33.82; H, 4.61. Found: C, 33.95; H, 4.68.

7-(Iodomethyl)-4-oxaheptanolide (3f): white solid; mp 61 °C; IR ($CDCl_3$) 1730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.74 (m, 1H), 2.27 (m, 1H), 2.53 (m, 1H), 3.00 (m, 1H), 3.34 (m, 3H), 3.77 (m, 1H), 4.10 (m, 2H), 4.84 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 6.0 (t), 35.6 (t), 37.6 (t), 67.7 (t), 70.2 (t), 76.6 (d), 173.3 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 351 (100), 350 (23), 306 (10), 288 (M^+ + 18, 15), 162 (31). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.10. Found: C, 31.26; H, 4.10.

7-(Iodomethyl)-7-methyl-4-oxaheptanolide (3g): white solid; mp 78 °C; IR ($CDCl_3$) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48 (s, 3H), 1.86 (dd, J = 16.0, 4.0 Hz, 1H), 2.31 (dd, J = 16.0, 9.8 Hz, 1H), 2.43–2.64 (m, 2H), 3.50 (d, J = 10.3 Hz, 1H), 3.65 (dd, J = 13.2, 9.6 Hz, 1H), 3.81 (ddd, J = 11.5, 9.2, 5.5 Hz,

1H), 3.98 (m, 1H), 3.99 (d, J = 10.3 Hz, 1H), 4.12 (ddd, J = 11.6, 6.6, 3.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.8 (t), 26.4 (q), 38.6 (t), 38.8 (t), 71.2 (t), 72.9 (t), 80.5 (s), 174.6 (s); mass spectrum (EI) m/z (relative intensity) 284 (M^+, 1), 194 (72), 157 (31), 103 (16), 85 (27), 73 (34), 71 (59), 57 (17), 55 (100), 43 (73), 42 (18), 41 (27), 39 (21). Anal. Calcd for $C_8H_{13}O_3I$: C, 33.82; H, 4.61. Found: C, 33.87; H, 4.87.

8-(Iodomethyl)-4-oxaoctanolide (3h): orange paste; ^{1}H NMR ($CDCl_3$) δ 1.57 (m, 1H), 1.77 (m, 2H), 2.08 (m, 1H), 2.53 (m, 1H), 2.70 (m, 1H), 3.30 (m, 2H), 3.49 (m, 1H), 3.81 (m, 3H), 5.02 (m, 1H); mass spectrum (EI) m/z (relative intensity) 284 (M^+, 1), 194 (19), 158 (10), 103 (20), 88 (16), 87 (62), 86 (24), 73 (58), 72 (24), 71 (89), 68 (33), 55 (100), 43 (54), 42 (36), 41 (39), 39 (17). Anal. Calcd for $C_8H_{13}O_3I$: C, 33.82; H, 4.61. Found: C, 33.88; H, 4.69.

6-(Iodomethyl)-6-methyl-4-oxahexanolide (9b): white solid; mp 45 °C; IR ($CHCl_3$) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.56 (s, 3H), 2.93 (t, J = 3.0 Hz, 2H), 3.48 (s, 2H), 3.83–4.05 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 9.8 (t), 23.3 (q), 40.1 (t), 65.5 (t), 76.2 (t), 80.3 (s), 170.9 (s); mass spectrum (EI) m/z (relative intensity) 270 (M^+, 1), 184 (13), 86 (100), 58 (22), 43 (48), 41 (11). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.10. Found: C, 31.34; H, 4.09. Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.10. Found: C, 31.17; H, 4.24.

7-(Iodomethyl)-3-oxaheptanolide (9c): white solid; mp 56 °C; IR ($CDCl_3$) 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.72 (bd, J = 15.7 Hz, 1H), 1.83 (dd, J = 13.2, 12.0 Hz, 1H), 2.02 (qt, 1H), 2.14 (tt, 1H), 3.24, 3.28 (2m*, 2H), 3.75 (bd, J = 12.0 Hz, 1H), 4.00 (td, J = 12.3, 3.5 Hz, 1H), 4.15 (d*, J = 17.9 Hz, 1H), 4.68 (d*, J = 17.9 Hz, 1H); 5.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 7.5 (t), 22.7 (t), 33.5 (t), 69.2 (t), 72.1 (d), 77.7 (t), 171.3 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 288 (M^+ + 18, 100); mass spectrum (EI) m/z (relative intensity) 270 (M^+, 1), 143 (56), 71 (52), 41 (100). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.10. Found: C, 31.23; H, 4.09.

7-(Iodomethyl)-5-oxaheptanolide (10a): white solid; mp 41 °C; 90% of the acid **8a** was recovered; IR ($CDCl_3$) 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.87 (m, 2H), 2.32 (t, J = 6.1 Hz, 2H), 3.54 (dd, J = 9.6, 5.2 Hz, 1H), 3.64 (t, J = 10.4 Hz, 1H), 3.95 (m, 1H), 4.18 (m, 1H), 4.27 (t, J = 10.4 Hz, 1H), 4.38 (m, 1H), 4.79 (ddd, J = 9.6, 4.3, 1.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.6 (t), 32.7 (t), 69.0 (t), 71.1 (t), 77.6 (d), 172.6 (s). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.10. Found: C, 31.18; H, 4.20.

7-(Iodomethyl)-7-methyl-5-oxaheptanolide (10b): yellow oil; 90% of the acid **8b** was recovered; ^{1}H NMR ($CDCl_3$) δ 1.57 (s, 3H), 2.02 (m, 2H), 2.41 (dd, J = 6.9, 5.9 Hz, 2H), 3.57 (m, 3H), 3.76 (m, 2H), 3.83 (d, J = 11.8 Hz, 1H); mass spectrum (Cl, NH_3) m/z (relative intensity) 193 (17), 192 (M^+ + 18, 100), 176 (17), 175 (M^+ + 1, 89), 174 (M^+, 31), 157 (20); mass spectrum (EI) m/z (relative intensity) 174 (M^+, 10), 143 (23), 100 (38), 87 (28), 74 (20), 72 (23), 70 (48), 69 (38), 59 (14), 57 (22), 55 (29), 45 (27), 42 (100), 41 (44), 39 (17). Anal. Calcd for $C_8H_{13}O_3I$: C, 33.82; H, 4.61. Found: C, 33.92; H, 4.46.

8-(Iodomethyl)-5-oxaoctanolide (10c): yellow solid; mp 43 °C; 25% of the acid **8c** was recovered; ^{1}H NMR ($CDCl_3$) δ 1.73–2.17 (m, 4H), 2.35 (m, 2H), 3.35 (m, 2H), 3.53 (m, 2H), 3.84 (m, 2H), 5.06 (m, 1H); mass spectrum (CI, NH_3) m/z (relative intensity) 302 (M^+ + 18, 100), 285 (M^+ + 1, 10), 176 (22); mass spectrum (EI) m/z (relative intensity) 157 (11), 117 (12), 56 (17), 55 (18), 54 (19), 43 (89), 42 (52), 41 (100). Anal. Calcd for $C_8H_{13}O_3I$: C, 33.82; H, 4.61. Found: C, 33.96; H, 4.88.

(6*RS*,7*SR*)-6-Iodo-7-methyl-4-oxaheptanolide (11c): yellow paste; ^{1}H NMR ($CDCl_3$) δ 1.69 (d, J = 6.8 Hz, 3H), 2.57 (ddd, J = 13.0, 4.5, 2.4 Hz, 1H), 2.95 (ddd, J = 13.3 Hz, J = 10.5, 4.3 Hz, 1H), 3.76 (bdd, J = 14.0, 1.8 Hz, 1H), 3.93 (ddd, J = 12.6, 10.5, 2.3 Hz, 1H), 4.01–4.23 (m, 3H), 4.97 (qd, J = 6.2, 6.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 20.7 (q), 35.3 (d), 35.7 (t), 69.7 (t), 74.4 (t), 77.1 (d), 173.5 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 288 (M^+ + 18, 100), 162 (55), 160 (27), 145 (36), 143 (M^+ − 127, 64); mass spectrum (EI) m/z (relative intensity) 270 (M^+, 14), 226 (23), 154 (90), 143 (38), 103 (100), 99 (15), 73 (17), 71 (29), 55 (61), 45 (17), 43 (88), 42 (54), 41 (88), 39 (30). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.10. Found: C, 31.38; H, 4.33.

(6*SR*,7*SR*)-6-Iodo-7-methyl-4-oxaheptanolide (11d): yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.46 (d, J = 5.8 Hz, 3H), 2.54 (ddd, J = 12.7, 3.6, 1.1 Hz, 1H), 2.98 (m, 1H), 3.38 (dd, J = 14.8, 12.7 Hz, 1H), 3.75 (m, 1H), 4.10–4.40 (m, 4H); mass spectrum (EI) m/z (relative intensity) 270 (M^+, 7), 168 (32), 154 (51), 103 (44), 73 (17), 71 (100), 55 (44), 43 (36), 42 (18), 41 (33). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.10. Found: C, 31.23; H, 4.35.

7,7-Dimethyl-6-iodo-4-oxaheptanolide (11e): orange oil; ^{1}H NMR ($CDCl_3$) δ 1.59 (s, 3H), 1.95 (s, 3H), 2.54 (m*, 2H), 3.79 (m, 2H), 4.21 (ddd, J = 14.0, 7.5, 2.4 Hz, 1H), 4.39 (dd, J = 16.4, 2.4 Hz, 1H), 4.62 (dd, J = 12.5, 2.4 Hz, 1H); mass spectrum (CI, NH_3) m/z (relative intensity) 302 (M^+ + 18, 100); mass spectrum (EI) m/z (relative intensity) 143 (21), 85 (87), 77 (17), 73 (37), 71 (100), 69 (50), 68 (46), 67 (54), 55 (25), 53 (33), 49 (17), 45 (25), 43 (21), 42 (25), 41 (58), 40 (67), 39 (37). Anal. Calcd for $C_8H_{13}O_3I$: C, 33.82; H, 4.61. Found: C, 34.06; H, 4.89.

7-Iodo-4-oxaoctanolide (11f): yellow paste; IR ($CDCl_3$) 1750 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.33 (m, 2H), 2.64 (ddt, 2H), 3.67 (m*, 1H), 3.78 (m*, 1H), 3.84 (dd, J = 6.5, 6.0 Hz, 2H), 4.36 (dd, J = 17.4, 10.7 Hz, 1H), 4.41 (m, 1H), 4.75 (dd, J = 17.4, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.5 (d), 36.6 (t), 40.6 (t), 67.2 (t), 70.6 (t), 73.2 (t), 171.3 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 288 (M^+ + 18, 100), 271 (M^+ + 1, 13), 162 (17); mass spectrum (EI) m/z (relative intensity) 270 (M^+, 1), 143 (56), 113 (27), 71 (48), 55 (16), 43 (26), 41 (100), 39 (20). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.10. Found: C, 31.28; H, 4.37.

7-Iodo-3-oxaoctanolide (12c): yellow paste; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.68 (m, 2H), 1.78 (m, 1H), 2.12 (m, 1H), 3.24 (m, 2H), 3.84 (dd, J = 14.8, 7.8 Hz, 1H), 4.02 (m, 2H), 4.75 (d, J = 13.6 Hz, 1H), 4.90 (d, J = 13.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.5 (d), 36.6 (t), 40.6 (t), 67.2 (t), 70.6 (t), 73.2 (t), 171.3 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 288 (M^+ + 18, 100). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.10. Found: C, 31.41; H, 4.48.

7-Iodo-7-methyl-5-oxaoctanolide (13b): yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.06 (s, 3H), 1.94 (m, 2H), 2.38 (ddd, J = 7.9, 5.6, 2.8 Hz, 2H), 3.38 (d, J = 10.4 Hz, 1H), 3.53 (m, 1H), 3.72 (dd, J = 10.4, 1.4 Hz, 1H), 3.83 (d, J = 12.7 Hz, 1H), 4.12 (m, 1H), 4.85 (dd, J = 12.7, 1.4 Hz); mass spectrum (CI, NH_3) m/z (relative intensity) 193 (19), 192 (M^+ + 18, 100), 175 (M^+ + 1, 67); mass spectrum (EI) m/z (relative intensity) 174 (M^+, 15), 143 (51), 101 (29), 100 (100), 97 (12), 87 (49), 74 (25), 71 (55), 70 (52), 69 (59), 58 (29), 57 (29), 55 (32), 45 (22), 43 (64), 42 (69), 41 (36). Anal. Calcd for $C_8H_{13}O_3I$: C, 33.82; H, 4.61. Found: C, 33.97; H, 4.59.

8-Iodo-5-oxanonanolide (13c): yellow solid; mp 64 °C; IR ($CDCl_3$) 1740 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.74 (m, 1H), 2.12 (m, 2H), 2.38 (m, 3H), 3.34 (m, 1H), 3.48 (m, 1H), 3.68 (m, 2H), 4.16 (dd, J = 10.5, 4.6 Hz, 1H), 4.59 (m, 1H), 4.77 (dd, J = 10.5, 2.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 24.0 (d), 25.0 (t), 33.7 (t), 40.6 (t), 68.6 (t), 69.5 (t), 70.3 (t), 173.2 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 302 (M^+ + 18, 100), 285 (M^+ + 1, 10), mass spectrum (EI) m/z (relative intensity) 284 (M^+, 1), 157 (13), 127 (19), 87 (71), 71 (33), 43 (33), 41 (100). Anal. Calcd for $C_8H_{13}O_3I$: C, 33.82; H, 4.61. Found: C, 33.75; H, 4.80.

The iodolactones 9d, 9e, 10d, 12d, 12e, and 13d were obtained using procedure A.

9-(Iodomethyl)-3-oxanonanolide (9d): yellow solid; mp 110 °C; 20% of the acid **6d** was recovered; IR ($CDCl_3$) 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.25–1.45 (m, 3H), 1.60–1.98 (m, 4H), 2.10 (m, 1H), 3.38 (m, 3H), 3.80 (m, 12H), 4.34 (d, 1H), 4.92 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 5.8 (t), 22.5 (t), 22.9 (t), 27.3 (t), 30.6 (t), 69.7 (t), 70.4 (t), 76.2 (t), 171.6 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 316 (M^+ + 18, 100); mass spectrum (EI) m/z (relative intensity) 298 (M^+, 1), 95 (24), 69 (10), 67 (17), 55 (100), 41 (23). Anal. Calcd for $C_9H_{15}O_3I$: C, 36.26; H, 5.07. Found: C, 36.41; H, 5.21.

10-(Iodomethyl)-3-oxadecanolide (9e): yellow oil; 40% of the acid **6e** was recovered; IR ($CDCl_3$) 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.16–1.78 (m, 7H), 1.82–2.10 (m, 3H), 3.27–3.53 (m, 3H), 3.82 (m, 1H), 3.90 (d, J = 17 Hz, 1H), 4.30 (d, J = 17 Hz, 1H), 4.83 (m, 1H); ^{13}C NMR ($CDCl_3$) δ (ppm) 6.7 (t), 20.5

(t), 23.4 (t), 25.0 (t), 27.6 (t), 30.3 (t), 70.1 (t), 70.7 (t), 74.9 (t), 171.4 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 330 ($M^+ + 18$, 100). Anal. Calcd for $C_{10}H_{17}O_3I$: C, 38.48; H, 5.49. Found: C, 38.51; H, 5.62.

11-(Iodomethyl)-5-oxaundecanolide (10d): yellow oil; 30% of the acid **8d** was recovered; IR ($CDCl_3$) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.21–1.97 (m, 9H), 2.07–2.52 (m, 3H), 3.25 (d*, J = 5.9 Hz, 2H), 3.28–3.49 (m, 3H), 3.62 (ddd, J = 9.0, 4.1, 3.7 Hz, 1H), 5.11 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 7.8 (t), 20.6 (t), 23.4 (t), 25.9 (t), 26.9 (t), 31.2 (t), 33.4 (t), 69.3 (t), 70.5 (d), 71.1 (t), 173.1 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 344 ($M^+ + 18$, 100), 343 (34), 325 (29), 326 (M^+, 10); mass spectrum (EI) m/z (relative intensity) 326 (M^+, 4), 199 ($M^+ - 127$, 10), 97 (16), 95 (59), 87 (100), 85 (16), 71 (19), 69 (14), 67 (19), 55 (62), 43 (25), 41 (26). Anal. Calcd for $C_{11}H_{19}O_3I$: C, 40.51; H, 5.87. Found: C, 40.69; H, 5.57.

9-Iodo-3-oxadecanolide (12d): yellow oil; IR (CCl_4) 1745 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.31–1.50 (m, 2H), 1.56–1.69 (m, 2H), 1.69–1.79 (m, 2H), 3.22–3.46 (m, 2H), 3.47–3.62 (m, 2H), 4.10 (m, 2H), 4.94 (m, 1H); mass spectrum (Cl, NH_3) m/z (relative intensity) 316 ($M^+ + 18$, 100); mass spectrum (EI) m/z (relative intensity) 171 (11), 113 (18), 95 (78), 69 (11), 67 (21), 55 (100), 54 (10), 43 (12), 41 (44), 39 (17); exact mass calcd for $C_9H_{15}O_3I$ H^+ 299.0147, found 299.0161.

10-Iodo-3-oxaundecanolide (12e): yellowish solid, mp 92 °C; IR ($CDCl_3$) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ (ppm) 1.30–1.51 (m, 3H), 1.51–1.58 (m, 3H), 1.58–1.84 (m, 2H), 3.32 (m, 2H), 3.54 (m, 2H), 4.31 (bs, 1H), 4.91 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 7.1 (d), 24.9 (t), 26.0 (t), 28.8 (t), 29.3 (t), 33.9 (t), 68.8 (t), 71.8 (t), 73.2 (t), 170.1 (s); mass spectrum (EI) m/z (relative intensity) 330 ($M^+ + 18$, 100). Anal. Calcd for $C_{10}H_{17}O_3I$: C, 38.48; H, 5.49. Found: C, 38.62; H, 5.68.

11-Iodo-5-oxadodecanolide (13d): yellow oil; ^1H NMR ($CDCl_3$) δ 1.37 (m, 3H), 1.58 (m, 2H), 1.70 (m, 2H), 1.93 (m, 2H), 2.45 (m, 2H), 3.31 (m, 2H), 3.42 (m, 4H), 4.21 (m, 2H), 4.74 (m, 1H); mass spectrum (Cl, NH_3) m/z (relative intensity) 469 (49), 344 ($M^+ + 18$, 100), 343 (20), 327 (47), 218 (13), 199 ($M^+ - 127$, 26); mass spectrum (EI) m/z (relative intensity) 326 (M^+, 5), 325 ($M^+ - 1$, 35), 96 (12), 95 (100), 67 (17), 55 (58), 43 (20), 41 (45). Anal. Calcd for $C_{11}H_{19}O_3I$: C, 40.51; H, 5.87. Found: C, 40.77; H, 6.05.

Preparation of Methyl 3-(*trans*-2,3-Epoxybutanoxy)-propanoate (14c) from the Ester 15. To CH_2Cl_2 (2.5 mL) cooled at 0 °C was added successively methyl (*E*)-3-(2-butenoxy)propanoate (**15**) (220 mg, 1.4 mmol) and *m*-chloroperbenzoic acid (500 mg at 50%, 1.45 mmol). The mixture was stirred for 2 h at 20 °C, and a 10% $Na_2S_2O_3$ solution (3 mL) was added followed by aqueous Na_2CO_3 solution. After separation of the organic phase, the aqueous phase was extracted with dichloromethane (3 × 5 mL). The organic phases were dried over Na_2SO_4. After filtration and concentration, the crude epoxide was obtained (200 mg) as a *cis*:*trans* mixture in the ratio 6:94 (90%). **14c:** IR (film) 1740 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.32 (d, J = 5.2 Hz, 2H), 2.60 (t, J = 6.4 Hz, 2H), 2.86 (ddd, J = 6.5, 2.4, 2.2 Hz, 1H), 2.89 (dq, J = 5.2, 2.2 Hz, 1H), 3.43 (dd, J = 11.4, 5.5 Hz, 1H), 3.69 (s, 1H), 3.70 (dd, J = 11.4, 3.4 Hz, 1H), 3.74 (t, J = 6.4 Hz, 1H), 3.77 (t, J = 6.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.0 (q), 34.7 (t), 51.4 (d), 51.7 (d), 57.6 (d), 66.5 (d), 71.0 (q), 171.6 (q); mass spectrum (EI) m/z (relative intensity) 159 (1), 103 (12), 88 (12), 87 (100), 72 (16), 71 (47), 59 (45), 57 (14), 55 (42), 45 (52), 43 (78), 41 (16). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.57; H, 8.55.

Preparation of Methyl 3-(*trans*-2,3-Epoxybutanoxy)-propanoate (14c) from the Iodo Lactone 3c. To methanol (0.2 mL) cooled at 0 °C was added successively the iodo lactone **3c** (53 mg; 0.2 mmol) and Na_2CO_3 (62 mg, 0.6 mmol). After 15 h at 20 °C the methanol was distilled under vacuum and the residue was taken off with saturated $NaHCO_3$ solution (2 mL). The aqueous phase was extracted with CH_2Cl_2 (5 × 5 mL). The organic phases were dried over Na_2SO_4 and concentrated under vacuum to give pure *trans* epoxide **14c** (34 mg, yield 99%).

Methyl 3-(*cis*-2,3-Epoxybutanoxy)propanoate (14d) was prepared from the iodo lactone **3d** following the procedure reported for the preparation of the *trans* epoxide **14c** (99%); ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 (d, J = 5.5 Hz, 2H), 2.63 (t, J = 6.3 Hz, 2H), 3.11 (m, 2H), 3.53 (m, J = 10.0, 5,0 Hz, 1H), 3.67 (d, J = 10.0, 3.5 Hz, 1H), 3.70 (s, 1H), 3.79 (t, J = 6.3 Hz, 1H), 3.81 (t, J = 6,3 Hz, 1H); mass spectrum (EI) m/z (relative intensity) 129 (15), 117 (14), 103 (32), 88 (100), 87 (80), 73 (29), 71 (49), 61 (15), 59 (41), 57 (74), 56 (22), 55 (25), 45 (42), 43 (21), 41 (25). Anal. Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.50; H, 8.65.

Preparation of 6-(Iodomethyl)-5-methyl-4-oxahexanolide (16) and 6-Iodo-5-methyl-4-oxaheptanolide (17). The iodo lactonization of acid **1i** was conducted following procedure B: overall yield 36%; 30% of acid **1i** was recovered. **Lactone 16**: yellow oil; ^1H NMR ($CDCl_3$) δ 1.52 (d, J = 6.2 Hz, 3H), 2.64 (m, 1H), 3.05 (m, 1H), 3.52 (qd, 1H), 3.78 (m, 1H), 4.38 (m, 1H, 4.00 (m, 1H,), 4.97 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 3.0 (t), 14.2 (q), 38.9 (t), 58.8 (t), 81.0 (d), 82.5 (d), 173.1 (s); mass spectrum (CI, NH_3) m/z (relative intensity) 320 (14), 288 ($M^+ + 18$, 100), 271 (9), 192 (43), 176 (38), 175 (17), 162 (75), 160 (14), 159 (27), 145 (22), 122 (29); mass spectrum (EI) m/z (relative intensity) 199 (8), 131 (86), 88 (15), 87 (100), 71 (15), 59 (50), 55 (19), 45 (20), 44 (18), 43 (51). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.10. Found: C, 31.38; H, 4.24. **Lactone 17**: yellow oil; ^1H NMR ($CDCl_3$) δ 1.26 (d, J = 6.2 Hz, 3H), 2.49 (ddd, J = 13.6, 3.4, 1.4 Hz, 1H), 2.78 (ddd, J = 13.6, 6.0, 2.2 Hz, 1H), 3.07 (ddd, J = 13.2, 12.1, 4.5 Hz, 1H), 3.80 (ddd, J = 13.2, 12.9, 1.4 Hz, 1H), 4.18 (m, 1H), 4.29 (m, 1H), 4.46 (dd, J = 12.2, 5.3 Hz, 1H), 4.74 (dd, ^2J = 12.2, 11.9 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 23.9 (q), 35.3 (t), 38.3 (d), 68.1 (t), 70.4 (t), 73.2 (d), 173.5 (s); mass spectrum (CI, NH_3): 288 ($M^+ + 18$, 100), 271 ($M^+ + 1$, 7), 162 (16); mass spectrum (EI) m/z (relative intensity) 270 (M^+, 4), 154 (65), 143 (51), 99 (49), 73 (55), 72 (16), 71 (90), 55 (44), 53 (13), 44 (25), 43 (100), 42 (33), 41 (63), 39 (25). Anal. Calcd for $C_7H_{11}O_3I$: C, 31.13; H, 4.10. Found: C, 31.50; H, 4.38.

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