Evaluation of *exo-endo* Ratios in the Halolactonization of *ω*-Unsaturated Acids

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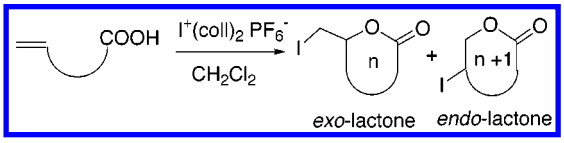
The reaction of 2-(*ω*−alkenyl)benzoic acids with bis(collidine)iodine and bis(collidine)bromine hexafluorophosphate was examined. Except with 2-but-3-enylbenzoic acid, for which only the *exo* lactone was obtained, for the other acids a mixture of *exo-endo* lactones was always obtained. The proportion of *endo* lactone was important for the acid chain length of 11 carbons (formation of a 12-membered ring *endo* lactone) and for the acid chain lengths higher than 14 carbons. The formation of the *endo* lactones was explained, on the base of molecular calculations, by competition between electronic and steric effects. These latter were developed by transannular interactions (for the acid chain lengths 8−11) and/or the conformations adopted by the chains (for the acid chain lengths ≥ 14,) which disfavored the formation of the *exo* lactones. The larger proportion of *endo* lactones observed with the bromo reagent compared to the iodo reagent seemed due to electronic factors.

Introduction

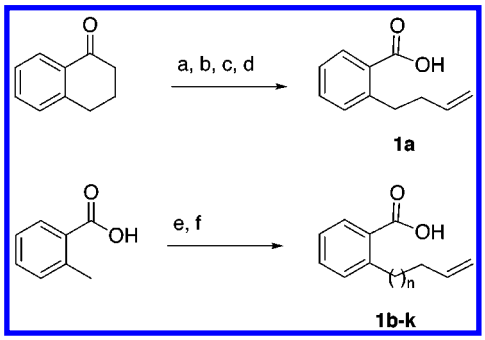
We have previously reported that bis(collidine)iodine(I) hexafluorophosphate was an excellent electrophile for the preparation of medium ring lactones.[1] We found that structural modifications of the carbon chain were necessary in order to form these lactones in acceptable yields. The influence of an oxygen atom,[1a] *gem*-dialkyl,[1b] and conformational constraints upon the lactonization reaction were previously studied.[1c] In general, we observed a competition between the *exo* mode and the *endo* mode of cyclization for the formation of medium sized lactone rings. This event occurred even in the absence of substituents on the terminal carbon of the double bond (Scheme 1). Similar observations were reported in the case of selenium reagents.[2]

Electrophilic cyclization of acids leading to four- to six-membered lactone rings, where the terminal carbon of the double bond is unsubstituted, was observed to proceed exclusively by an *exo* process.[3] These results are in agreement with Baldwin's rules,[4] which state that 3−7 *exo-trig* cyclizations are favored. Our previous results[1] indicate that longer acid carbon chains favor the formation of lactones by the *endo* cyclization mode. We wondered if the observed trend would hold true for the formation of macrolactones. We therefore investigated the halolactonization of *ω*-unsaturated acids. The results obtained for the macrolactone formation are compared those we previously obtained as there are very few similar literature examples.

Scheme 1



Scheme 2[a]



[a] (a) $HC(OMe)_3$MeOH, cat. TsOH; (b) O_3, CH_2Cl_2; (c) $Ph_3P{=}CH_2$; (d) OH^-, then H_3O^+; (e) 2 LDA, THF/heptane; (f) $Br(CH_2)_nCH{=}CH_2$.

Results

For this study, 2-substituted benzoic acids were used as they were expected to give good lactone yields for all ring sizes investigated. The formation of 7- to 20-membered lactone rings were consequently synthesized, using bis(collidine)iodine and bis(collidine)bromine hexafluorophosphate as reagents. 2-(But-3-enyl)benzoic acid **1a**[5] was obtained from 1-tetralone. The alkenylbenzoic acids **1b**−**k** were prepared by alkylation of the dianion of 2-methylbenzoic acid with unsaturated bromides (Scheme 2).

These alkylations were efficient when the dianion was prepared by reaction of lithium diisopropylamide in tetrahydrofuran at −30 °C in the presence of 20%

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Scheme 3

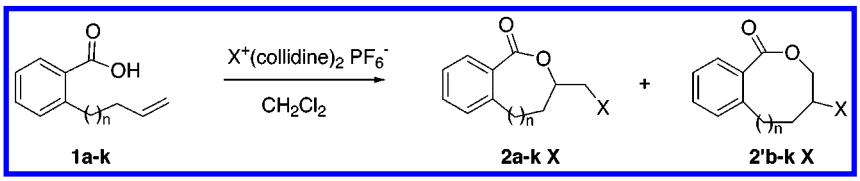


Table 1. Halolactonization of Acids 1a−k

acid	ring size of *exo-endo* lactones	iodo lactones: overall yield (%)	iodo lactones: *exo*:*endo* ratio	bromo lactones: overall yield (%)	bromo lactones: *exo*:*endo* ratio
1a	7:8	**2aI:2′aI** (93)	100:0	**2aBr:2′aBr** (95)	100:0
1b	8:9	**2bI:2′bI** (80)	98:2	**2bBr:2′bBr** (78)	80:20
1c	9:10	**2cI:2′cI** (84)	69:31	**2cBr:2′cBr** (50)	66:34
1d	10:11	**2dI:2′dI** (52)	60:40	**2dBr:2′dBr** (40)	52:48
1e	11:12	**2eI:2′eI** (46)	53:47	**2eBr:2′eBr** (35)	47:53
1f	12:13	**2fI:2′fI** (48)	82:18	**2fBr:2′fBr** (35)	64:36
1g	13:14	**2gI:2′gI** (55)	84:16	**2gBr:2′gBr** (40)	72:28
1h	14:15	**2hI:2′hI** (62)	85:15	**2hBr:2′hBr** (40)	75:25
1i	15:16	**2iI:2′iI** (55)	81:19	**2iBr:2′iBr** (45)	70:30
1j	16:17	**2jI:2′jI** (46)	76:24	**2jBr:2′jBr** (30)	66:34
1k	19:20	**2kI:2′kI** (53)	67:33	**2kBr:2′kBr** (35)	50:50

heptane.[6] In the absence of this cosolvent, lower yields were observed. The subsequent halolactonizations were carried out by slow addition (12 h) of the acids **1a**−**k** to a methylene chloride solution of bis(collidine)iodine or bis(collidine)bromine hexafluorophosphate. The products were separated by column chromatography on silica gel after the reactions were judged completed. The structures of the *exo* lactones **2a**−**kX** and *endo* lactones **2′b**−**kX** (Scheme 3) were determined by ^{1}H NMR and ^{13}C NMR, with the results reported in Table 1.

The halolactonizations of acid **1a** led only to *exo* lactones **2aX**. Similar results have been previously reported with 6-heptenoic acids.[1a] This is also the case for the iodolactonization of 2-allyl and 2-vinylbenzoic acids, which were found to lead to six- and five-membered ring lactones, respectively.[7] When the length of the acid's unsaturated chain of **1** was increased, we observed a mixture of *exo* lactones **2** and *endo* lactones **2′** formed. The maximum ratio of *endo* to *exo* lactonization was observed with acid **1e** and then decreased to a minimum for acid **1h**. With further chain elongation, the ratio was observed to increased once again. The evolution of *endo* lactones as a function of acid chain length **1** is reported in Figure 1.

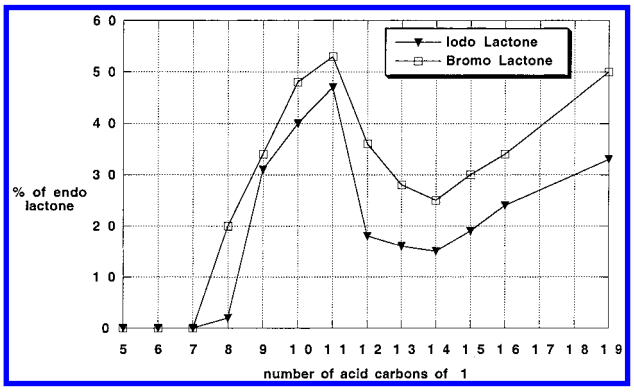
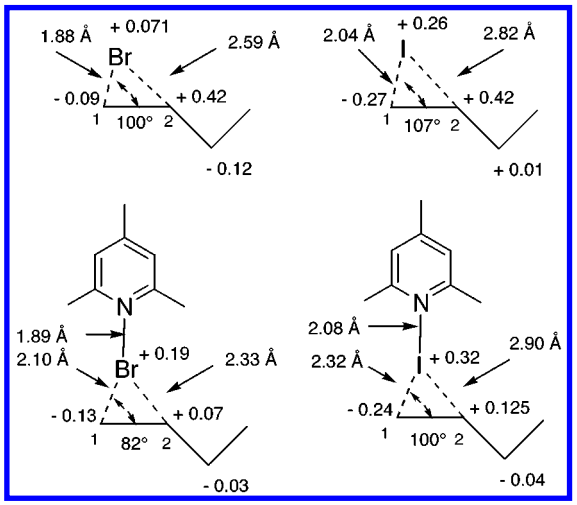


Figure 1. *Endo* lactone **2′X** ratio as a function of the number of acid carbons.

Scheme 4. Results from MNDO Calculations of Halonium Intermediates Formed from 1-Butene



Discussion

Considering only electronic factors, the regio addition of an electrophile on a unsymmetrically substituted carbon−carbon double bond should always give the Markovnikov product. For halolactonizations, the exclusive formation of *exo*-mode cyclization lactones should be observed and is the case for butyro- and valerolactones halolactonization.[3] *Endo*-mode cyclization products are obtained only if the carbon−carbon double bond is terminally substituted by a carbocation stabilizing group, i.e., an aryl group.[3] Calculations of charge distributions on the two carbons in the bromonium and the iodonium bridges formed as intermediates with 1-butene support this assumption. These calculations were done with MNDO semiempirical method on the proposed naked halonium intermediate and the halonium intermediate on which one molecule of collidine was fixed. The formation of the collidine−halonium intermediate has been recently established[8] when this kind of reagent is used in halocyclizations. The results obtained from the semiempirical calculations are reported in Scheme 4.

These calculations illustrate the influence of collidine on the intermediate formed during the lactonization reaction. Scheme 4 shows quite clearly that the participation of collidine led to less asymmetric halonium intermediates. In all cases, carbon 2 bears a greater positive charge relative to carbon 1. The results obtained from the calculations are in agreement with those previously reported for haloniums formed from propene.[9] They

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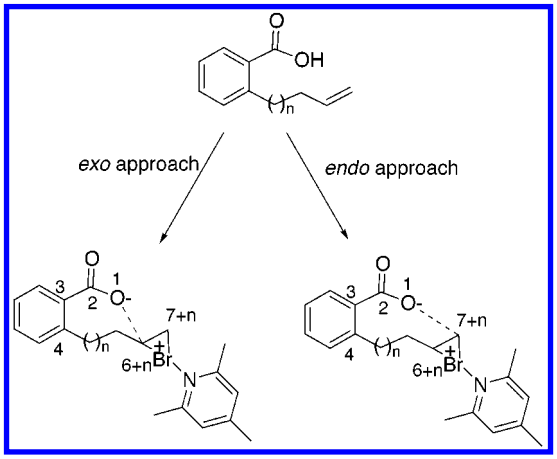
Table 2. Calculated Relative Energies of *exo* and *endo* Transition States and Lactones

			relative transition state stability[a]				
entry	acid		naked bromonium	collidinobromonium	relative lactone stability[a]	lactone ring size	exptl *exo*:*endo* ratio
a	**1a**	*exo*	0	0	0	7	100
b	**1a**	*endo*	10.7	5.4	7.2	8	0
c	**1e**	*exo*	0	0	3.4	11	47
d	**1e**	*endo*	0.9	0.7	0	12	53
e	**1h**	*exo*	0	0	3.0	14	75
f	**1h**	*endo*	1.5	1.7	0	15	25
g	**1k**	*exo*	0	0	5.8	19	50
h	**1k**	*endo*	0.1	0	0	20	50

[a] $\Delta(\Delta H_f)$ in kcal mol^{-1}.

Scheme 5



also imply *endo*-mode lactone cyclization should a priori be disfavored. However, since this is not the case observed with increasing acid chain length, a steric factor must be present and therefore considered. For intermediate sized rings, transannular interactions (H/H repulsions for CH_2 groups across the ring) exist and are minimized principally at the expense of distorting rotational angles. The observed increase in *endo* lactone ratio with chain length ring sizes 8−11 implies steric hindrance induced by an *endo* approach is lower than those in an *exo* approach. Therefore, these transannular interactions supersede the electronic factor. However, for larger rings the transannular interactions are assumed to decrease to the point where they eventually become insignificant relative to other effects.[10] The decrease in the *endo* lactone ratio for chain length 12−14 (Figure 1) can be justified by this decrease. The increase of *endo* lactone ratio observed for chain lengths greater than 14 is more surprising and seems to be due to the formation of other steric interactions. These interactions disfavor again the *exo* approaches in the halonium stabilized intermediates.

Further computational studies were undertaken to validate our hypothesis for the different *endo* and *exo* ratios observed. Calculations were carried out on the bromine compounds. The relative stabilities of the *exo* versus the *endo* transition states were first examined (Scheme 5). We hypothesize that the carboxylates and not the acid functions participate in the transition state. The appropriate chain conformations were determined by molecular dynamic simulations with molecular mechanic calculations (MM2 force field type) including two constraints. One involved locking the *exo* (or *endo*) dihedral angle $O_1C_{6+n}C_{7+n}Br$ (or $O_1C_{7+n}C_{6+n}Br$) at 180°. This value takes into account the antiperiplanar position of the carboxylate function and the bromine atom encountered in the transition state. The second constraint concerned the $O_1\cdots C_{6+n}$ (or $O_1\cdots C_{7+n}$) distance. A distance of 2.2 Å was selected as it represents the transition state distance. To confirm our model, Hessian calculations (in the case of **1a**) were carried out after fully location of the transition structures by MNDO method for the *exo* and *endo* approaches. Although this type of calculations is assumed to have better correlation for ground-state structures than for transition states, the results showed that our model corresponded well to a transition structure, i.e., a first-order saddle point with the Hessian having only one negative eigenvalue. All the transition states were subsequently minimized with the MNDO method using only the second constraint. The relative stabilities of the *exo* and *endo* lactones **2** and **2′** were also examined by molecular dynamic simulations with molecular mechanic calculations (MM2 force field type) and minimization by MNDO method. Our results are reported in Table 2. Calculations of the relative transition state stabilities did not agree with our experimental results when the acid functions, instead of the carboxylates, were investigated. This suggest that the reaction process can involve a deprotonated intermediate.

An energy difference of 7.2 Kcal mol^{-1} between the *exo* and *endo* lactones from **1a** (Table 2, entries a and b) would exclusively form the *exo* lactone, which also agrees well with our experimental data. However, this does not hold true for the other acids. The *endo* lactones appear to be more stable. If cyclization occurred under thermodynamic control, *endo* products should exclusively be formed. However, this is not the case. In fact, we have previously reported that halolactonizations occur under kinetic control with bis(collidine)iodine hexafluorophosphate.[1] So, the relative stability of the *endo* and *exo* lactones cannot be used as criteria for predicting the *endo* and *exo* product ratios. The calculations provide evidence that the halolactonizations occur under kinetic control. The relative stability of the calculated *exo* and *endo* transition states correlates well with our experimental results. The results are consistent regardless of the intermediate used in calculating the transition state. This is due in fact to the large distance (3.70−4.10 Å) between the halogen and the collidine nitrogen atom in the complexed transition states. With acid **1e** (Table 2, entries c and d) and acid **1k** (entries g and h) a small difference between the energy of the two transition states was found and are in agreement with our experimental data. A larger difference was observed in the case of acid **1h** (entries e and f). For acid **1k**, the steric constraints developed in the *exo* approach are due to "curling" of the

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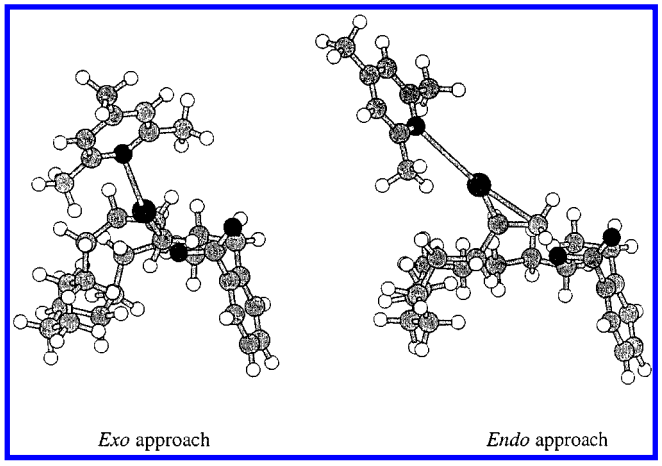
Scheme 6. Conformation of the Bromoniums Derivated from Acid 1k in the *exo* and *endo* Transition States



cycle, which offsets the Markovnikov electronic effect (Scheme 6). Such an effect was not observed in other cases. These new steric interactions occur with large rings as the *Z* conformation of the lactone function is more stable than the *E* conformation.[11] Consequently, this imposes a less favorable conformation on the carbon chain in the *exo* approach.

During these cyclizations, the proportion of *endo* lactone was always higher with the bromo reagent than with the iodo reagent (Figure 1). The electronic factor explains these results (Scheme 4) where the difference in charges calculated on carbons 1 and 2 are greater in the case of the iodonium than in the case of the bromonium.

Conclusion

We report that the *endo*:*exo* ratio observed during the electrophilic cyclization of ω-unsaturated acids depends of the size of the lactones formed. For the first time, we report the different factors responsible for control of the cyclization of unsaturated acids leading to medium and large lactone rings. A maximum of *endo* lactone was observed for ring sizes comprising 10 and 11 members. The proportion of *endo* lactone appears also to depend of the nature of the electrophile used for the cyclization. The unique formation of *exo* lactones in small rings (≤7) is mainly controlled by electronic factors (Markovnikov effect) and the fact that steric hindrance disfavors *endo* approaches. The formation of *endo* lactones for ring sizes 8−13 seems to involve transannular interactions, and these are more important in the *exo* than in the *endo* approaches. *Exo* lactone formation appears again disfavored for large ring sizes (≥14). Steric interactions that disfavor the *exo* approaches are a result of conformations adopted by the carbon chains. At least, we can notice a reasonably good description of these halolactonizations was obtained using an unsophisticated computional model.

Experimental Section

General. Proton and ^{13}C NMR spectra were recorded on a 250 MHz apparatus. Solvents were dried and purified prior to use. Tetrahydrofuran was distilled from benzophenone/sodium, and dichloromethane from calcium hydride. Reactions were generally carry out under argon and in the dark for the iodolactonizations. 4-Bromo-but-1-ene, 5-bromo-pent-1-ene, 6-bromo-hex-1-ene and 7-bromo-hept-1-ene were prepared according to ref 12.

Computational Analysis. Molecular dynamic simulations using molecular mechanic calculations and structure minimization using MNDO method were carried out with Hyperchem 5.1 system.

8-Bromooct-1-ene.[13] 1,8-Dibromooctane (0.1 mol, 27.2 g) was added dropwise (4 h) to a solution of KO^{t}Bu (0.13 mol, 14.56 g) in THF at reflux. After cooling the solvent was removed under vacuum, and water (50 mL) was added to the residue. The aqueous phase was extracted with ether (3 × 50 mL). The organic phase was dried and concentrated under vacuum. The crude bromide was purified by distillation under vacuum: yield 9.6 g (50%); bp 92 °C/24 mmHg. 9-Bromonon-1-ene[14] and 12-bromododec-1-ene[15] were prepared following the same procedure (55% yields).

10-Bromodec-1-ene.[16] This compound was obtained in two steps from commercially available 9-decen-1-ol by reaction of its mesylate with LiBr in *N*-methylpyrrolidinone[17] (overall yield: 56%). 11-Bromo-undec-1-ene[18] was obtained in the same way (75%) from 10-undecen-1-ol. 15-Bromo-pentadec-1-ene[19] was prepared in three steps from *tert*-butyl 14-pentadecenoate [20] by $LiAlH_4$ reduction in THF (99% yield) followed by transformation of the alcohol in bromide using the above procedure (80%).

2-But-3-enylbenzoic acid 1a.[5] This acid was obtained in two steps from methyl 2-(3-oxopropyl)benzoate[21] by Wittig reaction (methyltriphenylphosphonium bromide, ^{n}BuLi in ether (46%)) followed by saponification of the ester function (KOH/MeOH, 90%).

General Procedure for the Preparation of Acids 1b−1k. A dry three-necked flask equipped with a magnetical stirrer, a thermometer and a rubber septum was charged with dry THF (42 mL). The flask was cooled to −50 °C and 1.6 M *n*-butyllithium in hexane (42 mL, 0.052 mol) was added, followed by diisopropylamine (7.3 mL, 0.052 mol). After 30 min at −50 °C, the mixture was warmed to −30 °C and a solution containing *o*-toluic acid (2.79 g, 0.0205 mol), THF (20 mL) and dry heptane (20 mL) was added in 2 h. To the deep red reaction mixture was added the bromoalkene (0.029 mol) diluted in THF (15 mL). After 2 h at −30 °C, water was added (100 mL), and the organic phase was extracted twice with water (50 mL). The aqueous phase was acidified (pH 2) with 2 N HCl and then extracted with ether (3 × 150 mL). The combinated organic phases were dried ($MgSO_4$) and concentrated under vacuum. The different acids were used for the halolactonizations without further purification.

2-Pent-4-enylbenzoic Acid 1b.[1c] 48%; ^1H NMR ($CDCl_3$) 12.00 (bs, 1H), 8.05 (d, J = 6.6 Hz, 1H), 7.10−7.40 (m, 1H), 7.40−7.20 (m, 2H), 6.00−5.80 (m, 1H), 5.10−4.90 (m, 2H), 3.05 (t, J = 8.3 Hz, 2H), 2.20−2.10 (m, 2H), 1.80−1.60 (m, 2H). Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.85; H, 7.50.

2-Hex-5-enylbenzoic Acid 1c.[1c] 80%; ^1H NMR ($CDCl_3$) 12.00 (bs, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.60−7.40 (m, 1H), 7.40−7.20 (m, 2H), 6.00−5.70 (m, 1H), 5.20−4.80 (m, 2H), 3.05

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(t, J = 8.3 Hz, 2H), 2.20−2.00 (m, 2H), 1.80−1.50 (m, 4H). Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.55; H, 8.20.

2-Hept-6-enylbenzoic Acid 1d.[1c] 70%; ^{1}H NMR ($CDCl_3$) 12.00 (bs, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.55−7.40 (m, 1H), 7.40−7.20 (m, 2H), 5.90−5.70 (m, 1H), 5.10−4.90 (m, 2H), 3.05 (t, J = 8.3 Hz, 2H), 2.15−1.90 (m, 2H), 1.75−1.55 (m, 4H). Anal. Calcd for $C_{14}H_{18}O_2$: C, 77.02; H, 8.31. Found: C, 77.15; H, 8.40.

2-Oct-7-enylbenzoic Acid 1e. 65%; ^{1}H NMR ($CDCl_3$) 12.00 (bs, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.55−7.45 (m, 1H), 7.30−7.20 (m, 2H), 5.90−5.70 (m, 1H), 5.10−4.90 (m, 2H), 3.05 (t, J = 8.5 Hz, 2H), 2.10−2.00 (m, 2H), 1.70−1.50 (m, 2H), 1.50−1.35 (m, 6H); ^{13}C NMR ($CDCl_3$) 173.6, 145.9, 139.1, 132.7, 131.6, 131.1, 128.0, 125.7, 114.1, 34.5, 33.7, 31.6, 29.5, 28.9, 28.8. Anal. Calcd for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.45; H, 8.61.

2-Non-8-enylbenzoic Acid 1f. 60%; ^{1}H NMR ($CDCl_3$) 12.00 (bs, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.55−7.45 (m, 1H), 7.30−7.20 (m, 2H), 6.00−5.70 (m, 1H), 5.10−4.90 (m, 2H), 3.05 (t, J = 8.5 Hz, 2H), 2.20−1.95 (m, 2H), 1.75−1.50 (m, 2H), 1.50−1.20 (m, 8H); ^{13}C NMR ($CDCl_3$173.7, 145.9, 139.2, 133.3, 131.7, 131.2, 128.0, 125.7, 114, 34.5, 33.7, 31.7, 29.6, 29.2, 29.1, 29.0. Anal. Calcd: C, 77.55; H, 8.68. Found: C, 77.45; H, 8.61. Anal. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 78.25; H, 9.11.

2-Dec-9-enylbenzoic Acid 1g. 85%; ^{1}H NMR ($CDCl_3$) 12.00 (bs, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.60−7.40 (m, 1H), 7.35−7.20 (m, 2H), 6.00−5.70 (m, 1H), 5.10−4.90 (m, 2H), 3.05 (t, J = 8.5 Hz, 2H), 2.20−1.95 (m, 2H), 1.70−1.50 (m, 2H), 1.50−1.20 (m, 10H); ^{13}C NMR ($CDCl_3$) 173.8, 146.0, 139.2, 132.8, 131.6, 131.18, 128.0, 125.7, 114, 34.5, 33.8, 31.7, 29.6, 29.4, 29.3, 29.1, 28.9. Anal. Calcd for $C_{17}H_{24}O_2$: C, 78.46; H, 9.23. Found: C, 78.42; H, 9.22.

2-Undec-10-enylbenzoic Acid 1h. 70%; ^{1}H NMR ($CDCl_3$) 12.00 (bs, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.60−7.40 (m, 1H), 7.40−7.25 (m, 2H), 6.00−5.70 (m, 1H), 5.10−4.90 (m, 2H), 3.05 (t, J = 8.5 Hz, 2H), 2.15−1.90 (m, 2H), 1.80−1.50 (m, 2H), 1.50−1.20 (m, 12H); ^{13}C NMR ($CDCl_3$) 173.7, 146.0, 139.1, 132.7, 131.6, 131.2, 130.5, 128.1, 125.7, 114.0, 34.5, 33.7, 31.7, 29.8, 29.6, 29.5, 29.1, 28.9. Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.79; H, 9.55. Found: C, 78.67; H, 9.32.

2-Dodec-11-enylbenzoic Acid 1i. 90%; ^{1}H NMR ($CDCl_3$) 12.00 (bs, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.55−7.40 (m, 1H), 7.30−7.10 (m, 2H), 6.00−5.70 (m, 1H), 5.10−4.90 (m, 2H), 3.05 (t, J = 8.5 Hz, 2H), 2.20−2.00 (m, 2H), 1.70−1.55 (m, 2H), 1.70−1.20 (m, 14H); ^{13}C NMR ($CDCl_3$) 28.9, 29.1, 29.4, 29.5, 29.6, 29.7, 29.8, 31.7, 33.8, 34.6, 114.0, 125.7, 127.1, 128.1, 130, 131.6, 139.1, 146.0, 173.7. Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.16; H, 9.72. Found: C, 79.18; H, 9.77.

2-Tridec-12-enylbenzoic Acid 1j. 80%; ^{1}H NMR ($CDCl_3$) 12.00 (bs, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.6−7.4 (m, 1H), 7.3−7.15 (m, 2H), 6.00−5.70 (m, 1H), 5.10−4.90 (m, 2H), 3.05 (t, J = 8.5 Hz, 2H), 2.20−1.90 (m, 2H), 1.8−1.55 (m, 2H), 1.5−1.15 (m, 16H). Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.62; H, 9.82.

2-Hexadec-15-enylbenzoic Acid 1k. 80%; ^{1}H NMR ($CDCl_3$) 12.00 (bs, 1H), 8.05 (d, J = 7.5 Hz, 1H), 7.6−7.4 (m, 1H), 7.4−7.2 (m, 2H), 6.00−5.70 (m, 1H), 5.10−4.90 (m, 2H), 3.05 (t, J = 8.5 Hz, 2H), 2.10−2.20 (m, 2H), 1.70−1.5 (m, 2H), 1.5−1.1 (m, 22H); ^{13}C NMR ($CDCl_3$) 28.1, 28.7, 28.9, 29.1, 29.4, 29.5, 29.6, 31.7, 32.8, 33.8, 33.9, 34.5, 114.0, 125.7, 125.8, 128.0, 131.1, 131.6, 131.8, 132.8, 139.1, 146, 173.7.

Halolactonization: Representative Procedure. To a methylene chloride solution (35 mL) of bis(collidine)bromine(I) hexafluorophosphate[22] (2.6 mmol, 1.21 g) was added in 10 h at room temperature using a push-syringe, the 2-alkenylbenzoic acid (2 mmol) in solution in methylene chloride (10 mL). At the end of the addition silica gel was added (2 g), and the solvent was removed under vacuum. The resulting powder was placed on the top of a silica gel column, and the products were isolated by liquid chromatography over silica gel (elution pentane/ether 95:5 to 99:1 in function of the product polarity). The same procedure was used with bis(collidine)iodine(I) hexafluorophosphate, except the reaction was conducted in absence of light. The subsequent chromatography was conducted without special case. The yields in lactones **2** and **2′** are reported in Table 1.

4,5-Dihydro-3-iodoomethyl-(3*H*)-benzo[*c*]oxepin-1-one 2aI. Oil; ^{1}H NMR ($CDCl_3$) 7.70 (d, J = 7 Hz, 1H), 7.60−7.45 (m, 1H), 7.45−7.30 (m, 1H), 7.20 (d, J = 7 Hz, 1H), 4.20−4.00 (m, 1H), 3.50−3.15 (m, 2H), 3.10−2.90 (m, 1H), 2.90−2.70 (m, 1H), 2.40−2.00 (m, 2H); ^{13}C NMR ($CDCl_3$) 169.9, 137.4, 132.7, 130.9, 130.0, 128.6, 127.3, 77.0, 33.7, 29.3, 5.5. Anal. Calcd for $C_{11}H_{11}IO_2$: C, 43.70; H, 3.64.Found: C, 43.79; H, 3.68.

3-Bromomethyl-4,5-dihydro-(3*H*)-benzo[*c*]oxepin-1-one 2aBr. Oil; ^{1}H NMR ($CDCl_3$) 7.75 (d, J = 7 Hz, 1H), 7.60−7.40 (m, 1H), 7.40−7.30 (m, 1H), 7.37−7.15 (m, 1H), 4.45−4.15 (m, 1H), 3.70−3.40 (m, 2H), 3.10−2.25 (m, 2H), 2.20−2.05 (m, 2H); ^{13}C NMR ($CDCl_3$) 170.1, 137.4, 132.7, 130.9, 130.0, 128.6, 127.4, 77.5, 32.7, 32.3, 29.2. Anal. Calcd for $C_{11}H_{11}BrO_2$: C, 51.76; H, 4.35. Found: C, 51.58; H, 4.35.

7-Iodomethyl-6-oxa-7,8,9,10-tetrahydrobenzocycloocten-5-one 2bI. Already described.[1c]

8-Iodo-6-oxa-8,9,10,11-tetrahydro(7*H*)benzocyclononen-5-one 2b′I. Oil; ^{1}H NMR ($CDCl_3$) 7.85 (dd, J = 6 and 1 Hz, 1H), 7.50−7.10 (m, 3H), 5.00 (dd, J = 10 and 3 Hz, 1H), 4.45 (t, J = 10 Hz, 1H), 4.40−4.10 (m, 1H), 3.10 (dd, J = 11 and 4 Hz, 1H), 2.65−2.40 (m, 1H), 2.20−1.20 (m, 4H). Anal. Calcd for $C_{12}H_{13}IO_2$: C, 45.59; H, 4.14. Found: C, 45.68; H, 4.31.

7-Bromomethyl-6-oxa-7,8,9,10-tetrahydrobenzocycloocten-5-one 2bBr. Oil; ^{1}H NMR ($CDCl_3$) 7.60−7.40 (m, 2H), 7.40−7.30 (m, 1H), 4.50−4.30 (m, 1H), 3.50 (dd, J = 11 and 8 Hz, 1H), 3.35 (dd, J = 11 and 8 Hz, 1H), 3.00−2.70 (m, 2H), 2.20−1.80 (m, 3H), 1.70−1.50 (m, 2H); ^{13}C NMR ($CDCl_3$) 170.7, 140.0, 131.9, 130.7, 129.8, 128.5, 79.4, 35.1, 33.0, 32.4, 26.1, 19.1. Anal. Calcd for $C_{12}H_{13}BrO_2$: C, 53.55; H,0.4.87. Found: C, 53.76; H, 4.76.

8-Bromo-6-oxa-8,9,10,11-tetrahydro(7*H*)benzocyclononen-5-one 2b′Br. Oil; ^{1}H NMR ($CDCl_3$) 7.85 (dd, J = 6 and 1 Hz, 1H), 7.50−7.40 (m, 1H), 7.35 (t, J = 8 Hz, 1H), 7.20 (t, J = 6 Hz, 1H), 5.00 (dd, J = 12 and 2 Hz, 1H), 4.40 (t, J = 8 Hz, 1H), 4.35−4.20 (m, 1H), 3.20−2.90 (m, 2H), 2.50−2.30 (m, 1H), 2.30−1.90 (m, 3H); ^{13}C NMR ($CDCl_3$) 169.0, 144.8, 132.3, 130.9, 130.7, 130.0, 126.6, 69.1, 47.00, 38.8, 35.9, 30.6. Anal. Calcd for $C_{12}H_{13}BrO_2$: C, 53.55; H,0.4.87. Found: C, 53.81; H, 4.62.

7-Iodomethyl-6-oxa-8,9,10,11-tetrahydro(7*H*)benzocyclononen-5-one 2cI. Already described.[1c]

7,8,9,10,11,12-Hexahydro-8-iodo-6-oxabenzocyclodecen-5-one 2′cI. Already described.[1c]

7-Bromomethyl-6-oxa-8,9,10,11-tetrahydro(7*H*)benzocyclononen-5-one 2cBr. Oil; ^{1}H NMR ($CDCl_3$) 7.90 (d, J = 7 Hz, 1H), 7.50−7.35 (m, 1H), 7.35−7.20 (m, 2H), 5.35−5.15 (m, 1H), 3.75−3.40 (m, 3H), 2.75−2.55 (m, 1H), 2.20−1.40 (6H); ^{13}C NMR ($CDCl_3$) 170.1, 144.8, 132.3, 131.3, 130.8, 130.4, 126.3, 76.3, 34.8, 34.0, 31.1, 30.4, 23.1; HRMS calcd for $C_{13}H_{15}{}^{79}BrO_2$ (M^+) 282.0256, found 282.0256.

8-Bromo-7,8,9,10,11,12-hexahydro-6-oxabenzocyclodecen-5-one 2′cBr. Oil; ^{1}H NMR ($CDCl_3$) 7.85 (d, J = 7 Hz, 1H), 7.50−7.35 (m, 1H), 7.35−7.20 (m, 2H), 5.05 (dd, J = 12 and 1 Hz, 1H), 4.30−4.00 (m, 2H), 3.38−3.20 (m, 1H), 2.70−2.50 (m, 1H), 2.50−2.30 (m, 2H), 2.00−1.30 (m, 4H); ^{13}C NMR ($CDCl_3$) 167.9, 143.4, 132.3, 131.4, 130.5 (2C), 126.2, 68.3, 46.0, 34.9, 32.1, 29.4, 26.5; HRMS calcd for $C_{13}H_{15}{}^{79}BrO_2$ (M^+) 282.0256, found 282.0256.

7,8,9,10,11,12-Hexahydro-7-iodomethyl-6-oxabenzocyclodecen-5-one 2dI. Already described.[1c]

8,9,10,11,12,13-Hexahydro-8-iodo-6-oxa(7*H*)benzocycloundecen-5-one 2′dI. Already described.[1c]

7-Bromomethyl-7,8,9,10,11,12-hexahydro-6-oxabenzocyclodecen-5-one 2dBr. Oil; ^{1}H NMR ($CDCl_3$) 7.75 (dd, J = 7 and 1 Hz, 1H), 7.45−7.30 (m, 1H), 7.30−7.10 (m, 2H), 5.40−5.20 (m, 1H), 3.70−3.40 (m, 2H), 3.15−3.00 (m, 1H), 2.60−2.40 (m, 1H), 2.05−1.40 (m, 8H); ^{13}C NMR ($CDCl_3$) 168.6, 143.2, 131.6, 130.8, 130.7, 129.9, 126.0, 74.7, 33.3, 32.7, 29.6,

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28.8, 27.4, 20.0; HRMS calcd for $C_{14}H_{17}{}^{79}BrO_2$ (M^+) 296.0412, found 296.0412.

8-Bromo-8,9,10,11,12,13-hexahydro-6-oxa(7*H*)benzocycloundecen-5-one 2′dBr. Oil; ^{1}H NMR ($CDCl_3$) 7.85 (dd, J = 7 and 1 Hz, 1H), 7.55−7.40 (m, 1H), 7.40−7.20 (m, 2H), 5.10−4.90 (m, 1H), 4.50−4.30 (m, 2H), 3.20−3.00 (m, 1H), 2.75−2.55 (m, 1H), 2.30−2.00 (m, 2H), 2.00−1.50 (m, 6H); ^{13}C NMR ($CDCl_3$) 168.3, 143.2, 132.0, 131.3, 130.8, 130.2, 126.0, 67.9, 47.0, 35.7, 31.5, 29.8, 25.9, 24.8; HRMS calcd for $C_{14}H_{17}{}^{79}BrO_2$ (M^+) 296.0412, found 296.0412.

8,9,10,11,12,13-Hexahydro-7-iodomethyl-6-oxa(7*H*)-benzocycloundecen-5-one 2eI. Already described.[1c]

8-Iodo-7,8,9,10,11,12,13,14-octahydro-6-oxabenzocyclododecen-5-one 2′eI. Already described.[1c]

7-Bromomethyl-8,9,10,11,12,13-hexahydro-6-oxa(7*H*)-benzocycloundecen-5-one 2eBr. Oil; ^{1}H NMR ($CDCl_3$) 7.70 (dd, J = 8 and 1 Hz, 1H), 7.55−7.35 (m, 1H), 7.35−7.15 (m, 2H), 5.50−5.30 (m, 1H), 3.59 (d, J = 8 Hz, 2H), 3.20−3.00 (m, 1H), 2.75−2.55 (m, 1H), 2.10−1.10 (m, 10H); ^{13}C NMR ($CDCl_3$) 168.9, 142.2, 131.3, 131.0, 129.9, 129.2, 125.8, 73.8, 34.8, 32.1, 30.4, 30.0, 24.8, 24.3, 22.8. Anal. Calcd for $C_{15}H_{19}BrO_2$: C, 57.89; H, 6.15. Found: C, 57.98; H, 6.22.

8-Bromo-7,8,9,10,11,12,13,14-octahydro-6-oxabenzocyclododecen-5-one 2e′Br. Oil; ^{1}H NMR ($CDCl_3$) 7.78 (dd, J = 8 and 2 Hz, 1H), 7.55−7.35 (m, 1H), 7.35−7.20 (m, 2H), 4.90 (dd, J = 3 and 10 Hz, 1H), 4.65−4.45 (m, 1H), 4.30 (t, J = 11 Hz, 1H), 3.60−3.35 (m, 1H), 3.23 (dt, J = 6 and 13 Hz, 1H), 2.40−2.50 (m, 1H), 2.20−2.05 (m, 2H), 1.75−1.20 (m, 7H); ^{13}C NMR ($CDCl_3$) 168.4, 142.7, 131.7, 130.9, 130.8, 130.0, 125.7, 68.2, 46.6, 35.4, 30.8, 30.3, 25.1, 24.2, 23.2. Anal. Calcd for $C_{15}H_{19}BrO_2$: C, 57.89; H, 6.15. Found: C, 57.78; H, 6.25.

7-Iodomethyl-7,8,9,10,11,12,13,14-octahydro-6-oxabenzocyclododecen-5-one 2fI. Oil; ^{1}H NMR ($CDCl_3$) 7.75 (dd, J = 8 and 2 Hz, 1H), 7.50−7.32 (m, 1H), 7.32−7.20 (m, 2H), 5.25 (m, 1H), 3.50−3.30 (m, 2H), 3.15−3.00 (m, 1H), 2.90−2.70 (m, 1H), 2.10−1.90 (m, 2H), 1.70−1.20 (m, 10H); ^{13}C NMR ($CDCl_3$) 168.7, 142.5, 131.6, 131.3, 130.7, 129.8, 125.6, 74.6, 30.7, 30.4, 29.3, 25.3 (2C), 22.6, 21.5, 7.0. Anal. Calcd for $C_{16}H_{21}IO_2$: C, 59.09; H, 6.51. Found: C, 59.20; H, 6.62.

8-Iodo-8,9,10,11,12,13,14,15-octahydro-(7*H*)-6-oxabenzocyclotridecen-5-one 2′fI. Oil; ^{1}H NMR ($CDCl_3$) 7.70 (dd, J = 8 and 2 Hz, 1H), 7.50−7.32 (m, 1H), 7.32−7.20 (m, 2H), 4.82 (dd, J = 11 and 2 Hz, 1H), 4.48 (t, J = 10 Hz, 1H), 4.40−4.25 (m, 1H), 3.15−3.00 (m, 1H), 2.85−2.60 (m, 1H), 2.25−1.95 (m, 2H), 1.70−1.20 (m, 10H); ^{13}C NMR ($CDCl_3$) 168.5, 142.7, 131.7, 131.4, 130.7, 130.3, 125.8, 69.6, 36.0, 33.4, 30.0, 27.4, 25.3, 25.2, 24.0, 21.6. Anal. Calcd for $C_{16}H_{21}IO_2$: C, 59.09; H, 6.51. Found: C, 59.38; H, 6.81.

8-Bromo-8,9,10,11,12,13,14,15-octahydro-(7*H*)-6-oxabenzocyclotridecen-5-one 2′fBr. ^{1}H NMR ($CDCl_3$) 7.75 (dd, J = 9 and 2 Hz, 1H), 7.50−7.35 (m, 1H), 7.35−7.20 (m, 2H), 4.75 (dd, J = 11 and 3 Hz, 1H), 4.45 (t, J = 10 Hz, 1H), 4.35−4.20 (m, 1H), 3.20−3.00 (m, 1H), 2.80−2.60 (m, 1H), 2.30−2.15 (m, 1H), 2.15−1.95 (m, 1H), 1.70−1.20 (m, 10H); ^{13}C NMR ($CDCl_3$) 168.9, 142.8, 131.7, 130.7, 130.4, 129.9, 125.8, 67.6, 48.3, 34.6, 33.4, 30.0, 27.4, 24.9, 24.1, 23.9; HRMS calcd for $C_{16}H_{21}{}^{79}BrO_2$ (M^+) 324.0725, found 324.0725.

7-Bromomethyl-7,8,9,10,11,12,13,14-octahydro-6-oxabenzocyclododecen-5-one 2fBr. Oil; ^{1}H NMR ($CDCl_3$) 7.70 (dd, J = 9 and 2 Hz, 1H), 7.50−7.35 (m, 1H), 7.35−7.20 (m, 2H), 5.35−5.20 (m, 1H), 3.65−3.45 (m, 2H), 3.15−3.00 (m, 1H), 2.90−2.65 (m, 1H), 2.10−1.90 (m, 2H), 1.70−1.20 (m, 10H); ^{13}C NMR ($CDCl_3$) 168.9, 142.6, 131.7, 131.4, 130.7, 129.9, 125.6, 74.8, 33.4, 30.7, 30.5, 28.2, 25.3, 25.2, 22.6, 21.9; HRMS calcd for $C_{16}H_{21}{}^{79}BrO_2$ (M^+) 324.0725, found 324.0724.

7-Iodomethyl-8,9,10,11,12,13,14,15-octahydro-(7*H*)-6-oxabenzocyclotridecen-5-one 2gI. Oil; ^{1}H NMR ($CDCl_3$) 7.75 (dd, J = 2 and 7 Hz, 1H), 7.42 (t, J = 7 Hz, 1H), 7.35−7.20 (m, 2H), 5.35−5.22 (m, 1H), 3.43 (d, J = 7 Hz, 2H), 3.15 (dt, J = 7 and 12 Hz, 1H), 2.75 (dt, J = 7 and 12 Hz, 1H), 2.00−1.85 (m, 1H), 1.85−1.74 (m, 1H), 1.74−1.10 (m, 12H); ^{13}C NMR ($CDCl_3$) 168.5, 142.7, 131.1, 130.4, 130.4, 129.2, 125.4, 73.5, 32.7, 31.4, 30.6, 26.3, 26.2, 25.4, 25.2, 23.3, 7.7. Anal. Calcd for $C_{17}H_{23}IO_2$: C, 52.86; H, 6.00. Found: C, 52.95; H, 6.05.

7,8,9,10,11,12,13,14,15,16-Decahydro-8-iodo-6-oxabenzocyclotetradecen-5-one 2′gI. Oil; ^{1}H NMR ($CDCl_3$) 7.70 (dd, J = 2 and 7 Hz, 1H), 7.47−7.35 (m, 1H), 7.35−7.18 (m, 2H), 4.87 (q, J = 7 Hz, 1H), 4.50 (m, 2H), 3.15−3.00 (m, 1H), 2.90−2.75 (m, 1H), 2.75−1.15 (m, 14H); ^{13}C NMR ($CDCl_3$) 168.1, 143.2, 131.9, 131.5, 130.4; 129.7, 125.6, 68.7, 32.9, 32.0, 31.4, 29.2, 26.9, 25.9, 25.8, 24.7, 24.3. Anal. Calcd for $C_{17}H_{23}IO_2$: C, 52.86; H, 6.00. Found: C, 53.11; H, 6.21.

7-Bromomethyl-8,9,10,11,12,13,14,15-octahydro-(7*H*)-6-oxabenzocyclotridecen-5-one 2gBr. Oil; ^{1}H NMR ($CDCl_3$) 7.70 (d, J = 7 Hz, 1H), 7.48−7.35 (m, 1H), 7.35−7.18 (m, 2H), 5.57−5.38 (m, 1H), 3.58 (d, J = 6 Hz, 2H), 3.20 (dt, J = 6 and 12 Hz, 1H), 2.80−2.65 (m, 1H), 1.96−1.18 (m, 14H); ^{13}C NMR ($CDCl_3$) 168.8, 142.7, 131.2, 130.5 (2C), 129.2, 125.5, 73.5, 34.3, 31.4 (2C), 30.6, 26.4, 26.3, 25.4, 25.2, 23.4. Anal. Calcd for $C_{17}H_{23}BrO_2$: C, 60.18; H, 6.83. Found: C, 60.33; H, 6.98.

8-Bromo-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxabenzocyclotridecen-5-one 2′gBr. Oil; ^{1}H NMR ($CDCl_3$) 7.70 (dd, J = 1 and 7 Hz, 1H), 7.50−7.38 (m, 1H), 7.35−7.20 (m, 2H), 4.75 (q, J = 8 Hz, 1H), 4.50−4.35 (m, 1H), 3.25−3.00 (m, 1H), 2.88−2.68 (m, 1H), 2.10−1.15 (m, 15H); ^{13}C NMR ($CDCl_3$) 166.6, 143.3, 132.0, 131.6, 130.5, 129.8, 125.6, 66.8, 49.3, 32.0, 31.9, 31.2, 26.9, 25.9, 24.5 (2C), 23.2. Anal. Calcd for $C_{17}H_{23}BrO_2$: C, 60.18; H, 6.83. Found: C, 60.55; H, 7.23.

7,8,9,10,11,12,13,14,15,16-Decahydro-7-iodomethyl-6-oxabenzocyclotetradecen-5-one 2hI. Oil; ^{1}H NMR ($CDCl_3$) 7.85 (d, J = 7 Hz, 1H), 7.50−7.35 (m, 1H), 7.45−7.20 (m, 2H), 5.25−5.10 (m, 1H), 3.55−3.30 (m, 2H), 2.75−2.60 (m, 1H), 2.05−1.00 (m, 17H); ^{13}C NMR ($CDCl_3$) 167.9, 143.6, 131.4, 130.8, 130.4, 129.8, 125.5, 71.3, 33.3, 31.3, 31.2, 26.9, 25.8, 25.5, 25.4, 24.8, 21.8, 8.7; HRMS calcd for $C_{18}H_{25}IO_2$ (M^+) 400.0901, found 400.0902.

8,9,10,11,12,13,14,15,16,17-Decahydro-8-iodo-(7*H*)-6-oxabenzocyclopentadecen-5-one 2′hI. Oil; ^{1}H NMR ($CDCl_3$) 7.75 (d, J = 7 Hz, 1H), 7.50−7.35 (m, 1H), 7.35−7.15 (m, 2H), 4.80 (dd, J = 11 and 4 Hz, 1H), 4.50 (t, J = 8 Hz, 1H), 4.40−4.25 (m, 1H), 3.20−3.05 (m, 1H), 3.05−2.85 (m, 1H), 2.10−1.00 (m, 16H); ^{13}C NMR ($CDCl_3$) 167.5, 143.9, 131.8, 131.2, 130.8, 129.5, 125.7, 68.9, 34.0, 33.7, 30.1, 30.0, 26.5, 25.8, 25.6, 25.5, 25.0, 24.2; HRMS calcd for $C_{18}H_{25}IO_2$ (M^+) 400.0901, found 400.0899.

7-Bromomethyl-7,8,9,10,11,12,13,14,15,16-decahydro-6-oxabenzocyclotetradecen-5-one 2hBr. Oil; ^{1}H NMR ($CDCl_3$) 7.80 (dd, J = 9 and 2 Hz, 1H), 7.50−7.45 (m, 1H), 7.45−7.20 (m, 2H), 5.55−5.40 (m, 1H), 3.70−3.52 (m, 2H), 3.50−3.30 (m, 1H), 2.80−2.60 (m, 1H), 1.95−1.00 (m, 16H); ^{13}C NMR ($CDCl_3$) 168.0, 143.7, 131.5, 130.8, 130.5, 129.8, 125.5, 71.4, 34.9, 31.8, 31.3, 31.2, 26.9, 25.8, 25.5, 25.3, 24.8, 21.8; HRMS calcd for $C_{18}H_{25}{}^{79}BrO_2$ (M^+) 352.1038, found 352.1038.

8-Bromo-8,9,10,11,12,13,14,15,16,17-decahydro-(7*H*)-6-oxabenzocyclopentadecen-5-one 2′hBr. Oil; ^{1}H NMR ($CDCl_3$) 7.75 (d, J = 9 and 2 Hz, 1H), 7.50−7.48 (m, 1H), 7.48−7.15 (m, 2H), 4.75 (dd, J = 11 and 4 Hz, 1H), 4.50 (t, J = 9 Hz, 1H), 4.32−4.15 (m, 1H), 3.20−2.80 (m, 2H), 2.22−2.00 (m, 1H), 1.80−1.00 (m, 15H); ^{13}C NMR ($CDCl_3$) 167.8, 144.0, 131.9, 131.2, 130.4, 129.6, 125.8, 67.1, 50.3, 34.1, 32.8, 30.3, 26.8, 26.7, 25.9, 24.9, 24.2, 23.6; HRMS calcd for $C_{18}H_{25}{}^{79}BrO_2$ (M^+) 352.1038, found 352.1027.

8,9,10,11,12,13,14,15,16,17-Decahydro-7-iodomethyl-(7*H*)-6-oxabenzocyclopentadecen-5-one 2iI. Oil; ^{1}H NMR ($CDCl_3$) 7.90 (dd, J = 7 and 1 Hz, 1H), 7.55−7.35 (m, 1H), 7.35−7.15 (m, 2H), 5.30−5.15 (m, 1H), 3.70−3.50 (m, 1H), 3.50−3.30 (m, 2H), 2.60−2.40 (m, 1H), 2.00−1.65 (m, 2H), 1.65−1.10 (m, 16H); ^{13}C NMR ($CDCl_3$) 167.7, 144.2, 131.6, 130.8, 130.2, 130.1, 125.6, 72.2, 34.9, 33.7, 30.9, 26.9, 26.7 (2C), 25.9, 24.4, 24.2, 23.4, 8.6; HRMS calcd for $C_{19}H_{27}IO_2$ (M^+) 414.1057, found 414.1055.

7,8,9,10,11,12,13,14,15,16,17,18-Dodecahydro-8-iodo-6-oxabenzocyclohexadecen-5-one 2′iI. Oil; ^{1}H NMR ($CDCl_3$) 7.90 (dd, J = 7 and 1 Hz, 1H), 7.55−7.35 (m, 1H), 7.35−7.15 (m, 2H), 4.70 (dd, J = 11 and 4 Hz, 1H), 4.55 (dd, J = 10 and 5 Hz, 1H), 4.50−4.30 (m, 1H), 3.70−3.40 (m, 2H), 3.10−2.95 (m, 2H), 2.10−1.10 (m, 16H); ^{13}C NMR ($CDCl_3$) 167.0, 144.6, 131.9, 131.4, 130.5, 130.1, 125.6, 68.0, 35.4, 33.5, 31.0, 29.7,

29.3, 27.2, 26.5, 26.4, 25.7, 25.6, 24.6; HRMS calcd for $C_{19}H_{27}IO_2$ (M^+) 414.1057, found 414.1055.

7-Bromomethyl-8,9,10,11,12,13,14,15,16,17-decahydro-(7*H*)-6-oxabenzocyclopentadecen-5-one 2iBr. Oil; ^{1}H NMR ($CDCl_3$) 7.85 (dd, J = 7 and 1 Hz, 1H), 7.55−7.35 (m, 1H), 7.35−7.15 (m, 2H), 5.55−5.35 (m, 1H), 3.70−3.45 (m, 3H), 2.60−2.40 (m, 1H), 1.90−1.65 (m, 3H), 1.65−1.10 (m, 15H); ^{13}C NMR ($CDCl_3$) 167.8, 144.1, 131.6, 130.5, 130.0, 129.1, 125.6, 72.2, 35.0, 33.7, 33.4, 30.9, 26.9, 26.7, 26.4, 25.7, 24.1, 24.0, 23.4. Anal. Calcd for $C_{19}H_{27}BrO_2$: C, 62.13; H, 7.41. Found: C, 62.55; H, 7.28.

8-Bromo-7,8,9,10,11,12,13,14,15,16,17,18-dodecahydro-6-oxabenzocyclohexadecen-5-one 2′iBr. Oil; ^{1}H NMR ($CDCl_3$) 7.90 (dd, J = 7 and 1 Hz, 1H), 7.55−7.35 (m, 1H), 7.35−7.15 (m, 2H), 4.75 (dd, J = 11 and 6 Hz, 1H), 4.55 (dd, J = 11 and 6 Hz, 1H), 4.40−4.35 (m, 1H), 3.15−2.95 (m, 2H), 2.10−1.80 (m, 2H), 1.60−1.10 (m, 16H); ^{13}C NMR ($CDCl_3$) 167.4, 144.8, 132.0, 130.8 (2C), 130.6, 125.7, 66.5, 50.6, 34.2, 33.6, 31.2, 27.3, 27.0, 26.4, 26.0, 25.7, 24.9, 24.1. Anal. Calcd for $C_{19}H_{27}BrO_2$: C, 62.13; H, 7.41. Found: C, 62.41; H, 7.38.

7,8,9,10,11,12,13,14,15,16,17,18-Dodecahydro-7-iodomethyl-6-oxabenzocyclohexadecen-5-one 2jI. Oil; ^{1}H NMR ($CDCl_3$) 8.00 (dd, J = 8 and 1 Hz, 1H), 7.50−7.40 (m, 1H), 7.35−7.15 (m, 2H), 5.75−5.05 (m, 1H), 3.70−3.55 (m,1H), 3.48 (dd, J = 11 and 5 Hz, 1H), 3.38 (dd, J = 11 and 5 Hz, 1H), 2.70−2.40 (m, 1H), 2.05−1.85 (m, 2H), 1.85−1.00 (m, 18H); ^{13}C NMR ($CDCl_3$) 166.9, 145.2, 131.8, 130.8 (2C), 129.1, 125.6, 71.2, 34.1, 33.2, 30.6, 27.2, 27.1, 26.8 (2C), 26.5, 25.8, 25.0, 24.4, 9.1; HRMS calcd for $C_{20}H_{29}IO_2$ (M^+) 428.1214, found 428.1210.

8,9,10,11,12,13,14,15,16,17,18,19-dodecahydro-8-iodo-6-oxa(7*H*)benzocycloheptadecen-5-one 2′jI. Oil; ^{1}H NMR ($CDCl_3$) 7.90 (dd, J = 8 and 1 Hz, 1H), 7.50−7.40 (m, 1H), 7.35−7.15 (m, 2H), 5.10−4.90 (m, 1H), 4.70−4.50 (m, 1H), 4.45−4.30 (m, 1H), 3.20−2.90 (m, 2H), 1.70−1.00 (m, 20H); ^{13}C NMR ($CDCl_3$) 167.1, 144.8, 139.0, 132.0, 130.9, 128.9, 125.6, 69.0, 34.4, 33.7, 30.4, 29.8, 29.4, 29.0, 28.8, 28.6, 27.5, 27.4, 27.3, 26.2; HRMS calcd for $C_{20}H_{29}IO_2$ (M^+) 428.1214, found 428.1210.

7-Bromomethyl-7,8,9,10,11,12,13,14,15,16,17,18-dodecahydro-6-oxabenzocyclohexadecen-5-one 2jBr. Oil; ^{1}H NMR ($CDCl_3$) 7.85 (d, J = 7 Hz, 1H), 7.50−7.35 (m, 1H), 7.35−7.15 (m, 2H), 5.55−5.35 (m, 1H), 3.70−3.40 (m, 3H), 2.60−2.40 (m, 1H), 1.90−1.00 (m, 20H); ^{13}C NMR ($CDCl_3$) 167.0, 145.3, 131.9, 130.9, 130.7, 129.2, 125.7, 71.3, 35.2, 33.8, 32.8, 31.1, 27.2, 27.1, 26.8 (2C), 26.5, 25.4, 25.1, 24.4; HRMS calcd for $C_{20}H_{29}{}^{79}BrO_2$ (M^+) 380.1351, found 380.1345.

8-Bromo-8,9,10,11,12,13,14,15,16,17,18,19-dodecahydro-(7*H*)-6-oxabenzocycloheptadecen-5-one 2′jBr. Oil; ^{1}H NMR ($CDCl_3$) 7.95 (dd, J = 8 and 2 Hz, 1H), 7.55−7.40 (m, 1H), 7.40−7.20 (m, 2H), 4.75 (dd, J = 10 and 3 Hz, 1H), 4.55 (dd, J = 14 and 3 Hz, 1H), 4.40−4.25 (m, 1H), 3.15−2.95 (m, 2H), 2.10−1.80 (m, 2H), 1.70−1.00 (m, 18H); ^{13}C NMR ($CDCl_3$) 167.2, 144.8, 132.1, 131.0, 130.9, 129.0, 125.7, 67.6, 51.0, 34.2, 34.1, 30.8, 28.1, 27.5, 26.7, 26.5, 26.4, 26.3, 25.9, 25.4; HRMS calcd for $C_{20}H_{29}{}^{79}BrO_2$ (M^+) 380.1351, found 380.1347.

7-Iodomethyl-6-oxa-8,9,10,11,12,13,14,15,16,17,18,19,-20,21-tetradecahydro-(7*H*)benzocyclononadecen-5-one 2kI. Oil; ^{1}H NMR ($CDCl_3$) 8.05−7.90 (m, 1H), 7.55−7.35 (m, 1H), 7.35−7.15 (m, 2H), 5.10−4.90 (m, 1H), 3.60−3.35 (m, 3H), 3.35−3.15 (m, 1H), 2.85−2.15 (m, 1H), 2.00−1.00 (m, 25H); ^{13}C NMR ($CDCl_3$) 167.0, 144.7, 131.9, 130.9, 130.8, 129.5, 125.7, 72.5, 34.6, 34.2, 31.8, 29.4, 28.5, 28.2, 27.5 (2C), 27.4, 27.2, 27.0, 26.5, 26.1, 24.7, 8.7; HRMS calcd for $C_{23}H_{35}IO_2$ (M^+) 470.1683, found 470.1679.

7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22-Hexadecahydro-8-iodo-6-oxabenzocycloeicosen-5-one 2′kI. Oil; ^{1}H NMR ($CDCl_3$) 8.05−7.90 (m, 1H), 7.55−7.35 (m, 1H), 7.35−7.15 (m, 2H), 4.55 (d, J = 9 Hz, 2H), 4.50−4.30 (m, 1H), 3.60−3.42 (m, 1H), 3.10−2.90 (m, 2H), 2.00−1.00 (m, 25H); ^{13}C NMR ($CDCl_3$) 167.1, 144.8, 131.9, 130.9, 130.8, 129.2, 125.7, 69.5, 34.3, 34.0, 32.8, 30.7, 29.7, 29.1, 28.7, 28.6 (2C), 27.7, 27.6, 27.1, 26.8, 26.6, 22.7; HRMS calcd for $C_{23}H_{35}IO_2$ (M^+) 470.1683, found 470.1679.

7-Bromomethyl-6-oxa-8,9,10,11,12,13,14,15,16,17,18,19,-20,21-tetradecahydro-(7*H*)-benzocyclononadecen-5-one. Oil; ^{1}H NMR ($CDCl_3$) 7.95 (dd, J = 7 and 1 Hz, 1H), 7.55−7.35 (m, 1H), 7.35−7.15 (m, 2H), 5.40−5.25 (m, 1H), 3.70−3.55 (m, 2H), 3.50−3.40 (m, 2H), 3.30−3.10 (m, 1H), 2.85−2.60 (m, 1H), 2.10−1.20 (m, 24H); ^{13}C NMR ($CDCl_3$) 167.1, 144.7, 131.9, 130.8, 130.7, 129.5, 125.7, 72.7, 34.7, 34.0, 32.8, 32.5, 31.8, 29.6, 29.4, 28.7, 28.5, 28.1, 27.6, 27.3, 26.4, 26.1, 24.7; HRMS calcd for $C_{23}H_{35}{}^{79}BrO_2$ (M^+) 422.1820, found 422.1820.

8-Bromo-7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22-hexadecahydro-6-oxabenzocycloeicosen-5-one 2′kBr. Oil; ^{1}H NMR ($CDCl_3$) 7.95 (dd, J = 7 and 1 Hz, 1H), 7.55−7.35 (m, 1H); 7.35−7.15 (m, 2H), 4.65−4.45 (m, 2H), 4.45−4.25 (m, 1H), 3.60−3.45 (m, 1H), 3.10−2.85 (m, 2H), 2.10−1.10 (m, 25H); ^{13}C NMR ($CDCl_3$) 167.4, 144.6, 132.0, 130.9, 130.7, 129.2, 125.7, 68.1, 51.3, 34.5, 34.4, 31.9, 29.5, 29.2, 28.6, 27.8, 27.6, 27.4, 27.3, 27.0, 26.8, 26.6, 26.4; HRMS calcd for $C_{23}H_{35}{}^{79}BrO_2$ (M^+) 422.1820, found 422.1820.

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