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Chemistry of the β-Thiolactones: Substituent and Solvent Effects on Thermal Decomposition and Comparison with the β-Lactones.

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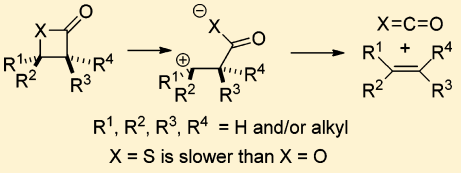
Supporting Information

ABSTRACT: The synthesis of a series of di-, tri-, and tetraalkyl β-thiolactones and β-lactones is described as well as their thermal decomposition with extrusion of carbon oxysulfide and carbon dioxide in two solvents of opposite polarities. The β-thiolactones are considerably more thermally stable than the β-lactones and require higher temperatures for efficient decomposition in both solvents, whatever the degree of substitution. The results are interpreted in terms of a zwitterionic mechanism for fragmentation with a change in the rate-determining step between the two series.



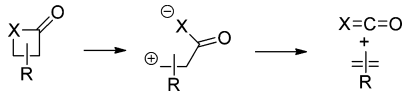
INTRODUCTION

The β-lactones (2-oxetanones) have enjoyed considerable interest from the synthetic organic and medicinal chemistry communities over a period of many years because of their interesting and varied reactivity patterns.[1−8] Interest in the medicinal chemistry of the β-lactones continues apace with the recent discovery of potent proteasome inhibitors based upon them,[9−20] and their recent application as potent inhibitors for a number of bacterial virulence factors.[21−23] Indeed, it is this interest that is currently driving efforts toward more effective stereocontrolled syntheses of this class of molecule.[11,24−27]

In our laboratory, on the other hand, we are interested in the possible use of β-thiolactones as surrogates for β-lactones and β-lactams in bioorganic and medicinal chemistry.[28,29] The chemistry of the β-thiolactones (2-thietanones) has been much less investigated than that of the β-lactones and β-lactams but has the potential to be equally rich and varied,[30,31] with possible applications in bioorganic and medicinal chemistry. Toward this end, we have synthesized a series of cognate β-lactones, β-thiolactones, and β-lactams and have investigated their relative abilities to inhibit porcine pancreatic lipase,[29] cysteine proteases (cathepsins B and L),[28] and the proliferation of various human cancer cell lines.[28,29] In earlier work, the β-thiolactones have been exploited as β-mercaptopropionamide precursors by virtue of their ability to acylate amines.[32−37] They also were shown to undergo nucleophilic ring-opening on prolonged exposure to hydrogen sulfide in the presence of base,[38] although it is not known whether this process takes place by acylation of sulfide anion or by S_N2-like attack of sulfide at C4, as has been shown to be the case for thiolate anions.[36] In order to better understand the relative reactivities of β-lactones and β-thiolactones toward external nucleophiles and to identify their relative merits for application in biological systems, we conducted a systematic comparison of the reactivities and regioselectivities of simple model β-lactones and β-thiolactones toward ring-opening by thiols and amines.[39]

In furtherance of our studies on the bioorganic and medicinal chemistry of the β-thiolactones, we now turn to a comparison of the thermal stability of the β-thiolactones and of the β-lactones with respect to the extrusion of carbon oxysulfide and carbon dioxide, respectively. Since it was postulated by Erlenmeyer in 1880[40] and observed by Einhorn in 1883,[41] one of the most-studied reactions of the β-lactones is the thermal extrusion of carbon dioxide to give alkenes with retention of configuration.[1−4,8] The decarboxylation mechanism, which is first-order in β-lactone,[42,43] has been widely studied and, while both concerted pathways and diradical intermediates have been considered and excluded,[44,45] is widely held on the basis of solvent,[46−48] reaction volume,[48] substituent,[45,49−53] kinetic,[49] and computational evidence[54−56] to involve a zwitterionic intermediate formed by initial cleavage of the O1−C4 bond (Scheme 1, X = O).

Scheme 1. Zwitterion Mechanism for β-Lactone and β-Thiolactone Fragmentation



The complementary extrusion of carbon oxysulfide (COS) from a β-thiolactone was first suggested by Staudinger for the case of tetraaryl β-thiolactones formed by the cycloaddition of diarylthioketones with diphenyl ketene.[57] Subsequent work by Kohn et al. confirmed this result[58] and corrected an earlier report suggesting that the initial cycloaddition proceeded to

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give the 3-thietanone regioisomer rather than the β-thiolactones.[59] Notably, 3,3-bis(4-dimethylaminophenyl)-4,4-diphenyl-2-thietanone was shown to afford the tetraaryl alkene on heating to 60 °C in a sealed tube.[58] The extrusion of COS in ethanol at reflux from a spirocyclic β-thiolactone generated by cycloaddition of diphenyl ketene with *N*-methyl monothiophthalimide was later shown by Coyle et al. to take place quantitatively in ethanol at reflux.[60] The formal loss of COS from peraryl-β-thiolactones may also be induced by nucleophilic attack on the carbonyl carbon, albeit through an alternative mechanism involving cleavage of the C1−C4 bond, followed by elimination of a thiocarboxylate.[61] Formal loss of COS from tetraphenyl β-thiolactone is also observed on treatment with Raney nickel and its equivalents and, in low yield, on oxidation with *m*CPBA.[61]

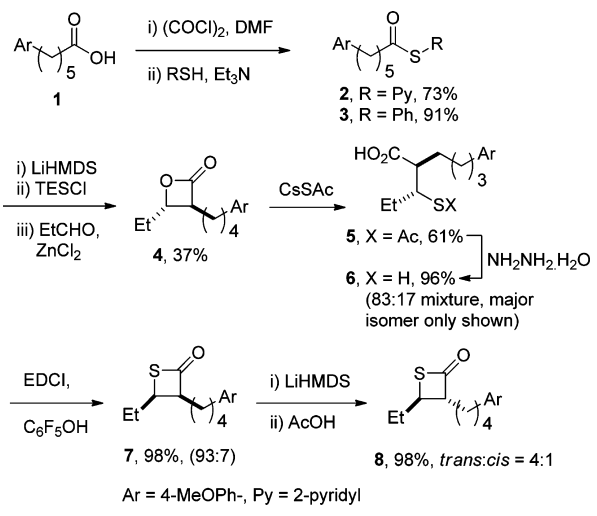
In spite of these reports on the extrusion of COS from β-thiolactones carrying multiple aromatic substituents, to the best of our knowledge, there are no comparable studies on the parallel decomposition of alkyl-substituted β-thiolactones. Accordingly, in this article, we direct our attention to the synthesis and thermal decomposition of the alkyl-substituted β-thiolactones and cognate β-lactones. In addition to providing information on the thermal stability of the β-thiolactones, the solvent dependence of the decomposition of the β-thiolactones and β-lactones provides a means of probing the mechanisms of extrusion of COS and CO_2 (Scheme 1, X = S and O, respectively).

RESULTS AND DISCUSSION

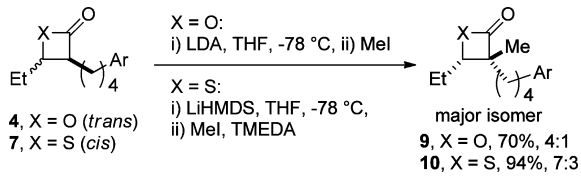
Synthesis. 6-(*p*-Anisyl)hexanoic acid **1** was converted in the standard manner to the 2-pyridyl thioester **2** and the phenyl thioester **3**. Following the method of Romo et al.,[62] **2** was converted to the corresponding *O*-triethylsilyl monothio ketene acetal and then allowed to react with propanal in the presence of zinc chloride to afford a 3,4-*trans*-disubstituted β-lactone **4** (Scheme 2). The configuration of the *trans*-lactone **4** was deduced by NOESY measurements; in particular, the methylene group of the ethyl substituent was correlated with the enolizable hydrogen adjacent to the carbonyl group, whereas the two lactone ring hydrogens were only very weakly correlated with each other. Invertive nucleophilic ring-opening[29,63−66] of β-lactone **4** with cesium thioacetate in DMF afforded the 3-acetylthio acid **5**, which was converted to the corresponding thiol acid **6** with hydrazine hydrate so as to avoid competing elimination. Nevertheless, thiol acid **6** was obtained as a 83:17 mixture of diastereomers, which arose from either a base-catalyzed epimerization or an elimination−readdition pathway. Carbodiimide ring closure of a diastereomerically enriched sample of **6** in the presence of pentafluorophenol, going via the intermediacy of the pentafluorophenyl ester, then gave the *cis*-configured β-thiolactone **7** as a 93:7 mixture of *cis*:*trans*-isomers in excellent yield. The relative stereochemistry of **7** rests on the strong correlation between the two lactone ring protons and that between the two methylene groups directly appended to the lactone in the NOESY spectrum. On deprotonation with LiHMDS and quenching at −78 °C with acetic acid, **7** was converted to an inseparable 4:1 mixture of β-thiolactones **7** and **8** favoring the *trans*-isomer **8** (Scheme 2). In light of subsequent alkylations of **4** and **7**, it is probable that this selectivity is the result of equilibration during the work-up procedure.

The *trans*-disubstituted β-lactone **4** and the *cis*-disubstituted β-thiolactone **7** were deprotonated with lithium amide bases and the resulting enolates were alkylated with methyl iodide at −78 °C to the corresponding 3,3,4-trisubstituted systems **9** and **10** as inseparable mixtures of stereoisomers (Scheme 3) in good yield. In both cases, the alkylation took place with moderate selectivity on the opposite face of the enolate from the existing C4 substituent, as was confirmed for both compounds by NOESY measurements. A regioisomeric 3,4,4-trisubstituted-β-lactone **11** was readily accessed in good yield by reaction of the lithium enolate of **3** with 2-butanone according to the method of Danheiser and Nowick (Scheme 4).[67]

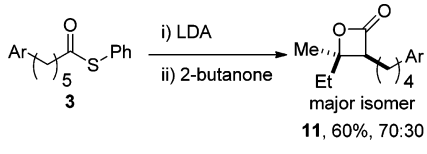
Scheme 2. Preparation of *cis*- and *trans*-3,4-Disubstituted β-Lactones 4 and β-Thiolactones 7 and 8



Scheme 3. Synthesis of 3,3,4-Trisubstituted β-Lactone 9 and β-Thiolactone 10



Scheme 4. Synthesis of 3,4,4-Trisubstituted β-Lactone 11



Condensation of the lithium enolate of *tert*-butyl 6-(*p*-anisyl)hexanoate **12** with 2-adamantanone and with 2-adamantanethione[68] gave the β-hydroxy and β-mercapto esters **13** and **14**, which were converted to the corresponding acids **15** and **16** with trifluoroacetic acid in dichloromethane (Scheme 5). Intriguingly, attempted isolation of the mercapto ester **14** resulted in considerable retro-thioaldolization, and it was, therefore, converted in situ to the acid **16**. In contrast, the corresponding hydroxyl ester **13** was readily isolated and characterized. The difference in reactivity between the hydroxyl

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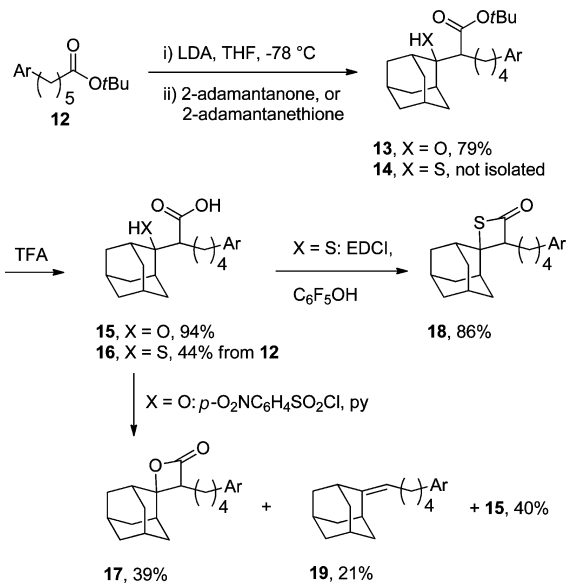
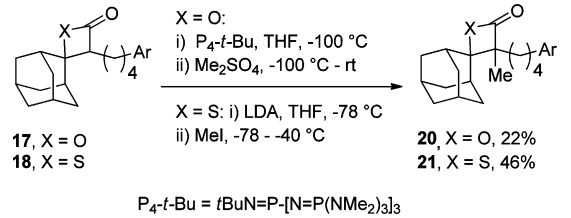
Scheme 5. Synthesis of 3,4,4-Trisubstituted β-Lactone 17 and β-Thiolactone 18



and mercapto series was also evident in the cyclization step. Thus, whereas cyclization of the hydroxyl acid **15** to the β-lactone **17** required considerable optimization and screening of coupling reagents, the formation of the β-thiolactone **18** from the mercapto acid **16** proceeded smoothly under the same conditions applied to obtain the less substituted system **7**. Furthermore, even under the optimal conditions using 4-nitrobenzenesulfonyl chloride as condensation reagent, cyclization of **15** to give the β-lactone was accompanied by the formation of the formal extrusion product **19** (Scheme 5).

Alkylation of the trisubstituted systems **17** and **18** was then employed to access the tetraalkyl substituted β-lactone **20** and the β-thiolactone **21** (Scheme 6). Again, a significant difference

Scheme 6. Synthesis of Tetrasubstituted β-Lactone 20 and β-Thiolactone 21



in reactivity was apparent with attempted alkylation of **17**, being attended by extensive decarboxylation under the conditions applied successfully to **18** (Scheme 6). Ultimately, alkylation of **17** was achieved by use of the phosphazene base P_4-*t*-Bu[69] at −100 °C, as recommended by Schwesinger[70] and employing dimethyl sulfate as alkylating agent,[71] but nevertheless with a very modest yield (Scheme 6).

In this manner, a series of di-, two sets of tri-, and one pair of tetraalkyl substituted β-lactones and the corresponding β-thiolactones were prepared for studies of thermal stability. Although the chemistry employed in these preparations was mostly straightforward, several interesting points emerged, most notably for the 3,4,4-trisubstituted and the tetrasubstituted systems where both ring closure and alkylation were notably easier in the thiolactone case.

Extrusion Reactions. Studies on the thermal stability of the various β-lactones and β-thiolactones were conducted in dilute solution in two solvents: fluorinert [Fc-70, $(C_5F_{11})_3N$] and 1-butyl-3-methylimidazolium hexafluorophosphate [BMIM PF_6], the one being extremely nonpolar and the other highly polar,[72] with neither being miscible with toluene. An experimental protocol was established whereby the substrate was heated in dilute solution in the reaction solvent to the temperature of choice in the presence of the internal standard 1,3,5-trimethoxybenzene, and aliquots were withdrawn periodically for examination. The analytical procedure involved extraction of the aliquot at room temperature with a standard volume of toluene, concentration under vacuum, and dissolution in acetonitrile before examination by RP-UPLC with detection by UV and mass spectrometry with atmospheric pressure chemical ionization (APCI). Experiments conducted on a larger scale enabled the isolation and characterization of the olefinic products resulting from extrusion of CO_2 or COS and, thus, the provision of authentic samples for the kinetic runs.

After a preliminary survey of decomposition temperatures of the various substrates at hand, 120 °C was selected as the most appropriate for the comparison as it provoked fragmentation of most substrates on a practical time scale. Fragmentations were conducted in duplicate in dilute solution, leading to the first-order rate constants and half-lives presented in Table 1. With the exception of β-thiolactones **8** and **10**, which did not fragment under these conditions, all pyrolyses conducted in this manner were clean with the anticipated olefin being the only observable product. No evidence was found for alternative modes of decomposition such as those that are known to occur for the β-thiolactones on photolysis.[73]

Rate constants for the various β-lactones studied at 120 °C span a range of more than 2 orders of magnitude with the 3,4-disubstituted and 3,3,4-trisubstituted systems **4** and **9** having the longest half-lives and the tetrasubstituted system **20** the shortest (Table 1, entries 1−10). An interesting pattern of solvent dependence was observed for the β-lactones with the 3,4-disubstituted system **4** showing no measurable change in extrusion rate with solvent (Table 1, entries 1 and 2) and the 3,3,4-trisubstituted system **9** showing only a modest acceleration on going to the more polar solvent (Table 1, entries 3 and 4), while the 3,4,4-trisubstituted system **11** displayed a much greater correlation between solvent polarity and reaction rate (Table 1, entries 5 and 6). This pattern of reactivity is most consistent with a mechanism for extrusion that displays little change in polarization between the substrate and the transition state, namely, a concerted mechanism, with polar character, as in Scheme 1, only becoming apparent when stepwise cleavage of a tertiary C−O bond is involved. The 3,4,4-trisubstituted β-lactone **17**, based on the adamantylidene skeleton, showed only a modest solvent dependence (Table 1, entries 7 and 8), reflecting the greater degree of substitution of the intermediate cation than that derived from the acyclic counterpart **11** (Table 1, entries 5 and 6). The higher degree of substitution in the adamantylidene system provides additional stabilization to any intermediate cation and shields it to a greater extent from the surrounding medium, thereby reducing dependence on solvent polarity, consistent with earlier work documenting the lack of solvent participation in the solvolysis of 2-adamantanyl derivatives[74] and with the greater stability of the 2-adamantanyl cations than simple tertiary aliphatic carbenium ions.[75−80]

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Table 1. First-Order Rate Constants and Half-Lives for the Thermal Fragmentation of β-Lactones and β-Thiolactones at 120 °C[a]

Entry	Substrate	Solvent	k, h^{-1}	$t_{1/2}$, h	Product
1		Fc-70	0.07	9.48	
2		BMIM PF_6	0.07	9.48	
3[a]		Fc-70	0.06	11.95	
4[a]		BMIM PF_6	0.12	5.91	
5[a]		Fc-70	0.78	0.89	
6[a]		BMIM PF_6	15.14	0.05	
7		Fc-70	3.10	0.22	
8		BMIM PF_6	3.81	0.18	
9		Fc-70	5.50	0.13	
10		BMIM PF_6	14.57	0.05	
11[a]		Fc-70	/	/	
12[a]		BMIM PF_6	/	/	
13[a]		Fc-70	/	/	
14[a]		BMIM PF_6	/	/	
15		Fc-70	0.02	44.47	
16		BMIM PF_6	0.04	17.45	
17		Fc-70	0.07	10.66	
18		BMIM PF_6	0.07	10.02	

[a]Substrate employed as a mixture of stereoisomers, leading to a mixture of stereoisomeric products reflecting the initial substrate mixture.

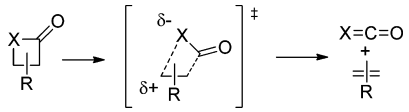
Interestingly, however, a significant solvent dependence returned with the tetrasubstituted system **20**, which is nevertheless based on the adamantylidene framework (Table 1, entries 9 and 10) to which we return below.

In the β-thiolactone series, neither the 3,4-di- nor the 3,3,4-trisubstituted systems **8** and **10**, respectively (Table 1, entries 11−14) showed any appreciable decomposition at the standard temperature of 120 °C in either solvent. In further experiments intended to determine the decomposition temperature of compounds **8** and **10**, both were found to be stable on heating neat at 230 °C under an inert atmosphere for multiple hours. The 3,4,4-trisubstituted system **18** underwent decomposition to the alkene in both solvents at this temperature (Table 1, entries 15 and 16), albeit more than a hundred-fold more slowly than the β-lactone analogue **17** (Table 1, entries 7 and 8). The decomposition of **18** showed only a modest solvent dependence, consistent with that seen with the β-lactone congener **17**. Finally, the tetrasubstituted β-thiolactone **21** underwent decomposition (Table 1, entries 17 and 18) more rapidly than the trisubstituted analogue **18** but, again, more than 100-fold more slowly than the direct β-lactone analogue **20**. Unexpectedly, in view of the high solvent dependence observed for the tetrasubstituted β-lactone **20** (Table 1, entries 9 and 10), decomposition of the tetrasubstituted β-thiolactone **21** was not influenced by the polarity of the solvent (Table 1, entries 17 and 18).

In general, it is very clear that the β-thiolactones, whatever their degree of substitution, are much more thermally stable than comparable β-lactones. It is also clear that the alkyl-substituted β-thiolactones studied here decompose by thermal extrusion of carbon oxysulfide to give alkenes and that the alternative pathway considered by early workers in the field with conjugated systems according to which thioketones and ketenes are the main products is not operative. The pattern of solvent effects observed is noteworthy and reveals differences between the β-lactones and the β-thiolactones. Most noteworthy is the manner in which the tetrasubstituted β-thiolactone **21** shows no solvent dependence (Table 1, entries 17 and 18), while its β-lactone analogue **20** (Table 1, entries 9 and 10) decomposes considerably faster in the more polar solvent. In contrast with these observations, the two 3,4,4-trisubstituted systems **17** and **18** both show a modest solvent dependence (Table 1, entries 7, 8, 15, and 16).

The ensemble is best considered in terms of either a stepwise mechanism with a zwitterionic intermediate (Scheme 1) or a concerted mechanism with a highly asynchronous transition state (Scheme 7). The differences between the various systems

Scheme 7. Concerted Mechanism and Asynchronous Transition State for Decomposition of β-Lactones and β-Thiolactones



can then be accounted for either by changes in the rate-determining step for the stepwise mechanism or by changes in the degree of asynchronicity for the concerted mechanism.

For the stepwise mechanism with the zwitterionic intermediate, solvent effects can be expected to operate on both reaction steps. The use of a more polar solvent is expected to accelerate the initial cleavage of the C−X bond through stabilization of the polar zwitterion. However, for a given carbon skeleton, the accelerating effect of the polar solvent on this first step is expected to be less important for the β-thiolactones than for the β-lactones as thiocarboxylates are

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more stable than carboxylates[81,82] and, therefore, less susceptible to stabilization by polar solvents. Fragmentation of the zwitterionic intermediates to the alkenes and O=C=X also will be influenced by solvent polarity in a different manner according to X. Thus, for X = O, this step, which proceeds with a loss of polarity, should be faster in less polar solvents. On the other hand, when X = S, the products retain substantial polarity owing to the formation of carbon oxysulfide with its dipole moment of 0.72 D units,[83] leading to the prediction of accelerated fragmentation in polar solvents. Overall, for the β-lactones, the two individual steps in the stepwise mechanism are expected to experience opposite effects from an increase in solvent polarity and, therefore, the nature of the observed effect will depend on which step is rate-limiting. In the case of the β-thiolactones, both steps of the stepwise mechanism are expected to be accelerated in the more polar medium.

The weakness of C−S σ-bonds compared to their C−O counterparts[84,85] and the higher acidity of thioacids than carboxylic acids[81,82] suggest that heterolysis of the C−S bond in the β-thiolactones will be considerably easier than that of the C−O bond in the β-lactones. On the other hand, the thiocarbonyl bond in carbon oxysulfide (73.7 kcal·mol^{-1})[84] is much weaker than the carbonyl bond in carbon dioxide (127.2 kcal·mol^{-1}),[84] indicating that loss of COS from a β-thiolactone-derived zwitterionic intermediate will be slower than that of CO_2 from the analogous β-lactone-derived zwitterion. It is conceivable, therefore, that there is a change of rate-limiting step in the stepwise mechanism on replacement of the ring oxygen by a sulfur atom. In the case of the β-lactone, the initial cleavage of the C−O leading to the zwitterion would be rate-limiting and followed by rapid loss of CO_2, whereas, in the case of the β-thiolactone, rapid C−S bond scission leads to a zwitterion whose decomposition to the alkene and COS is slow and rate-limiting. In both cases, formation of the zwitterion is expected to be reversible.

Regarding the concerted mechanism with the asynchronous transition state, fragmentation of both the β-lactones and the β-thiolactones is expected to be accelerated in polar solvents owing to stabilization of the polar transition state.

The lack of a consistent pattern of solvent effects for either the β-lactones or the β-thiolactones suggests that the concerted mechanism is not operative. Rather, it seems likely that the stepwise mechanism with the zwitterionic intermediates is the preferred pathway with changes in the rate-determining step being caused by subtle changes in substrate structure and possibly by solvent.

CONCLUSION

The di-, tri-, and tetraalkyl substituted β-thiolactones require significantly higher temperature than the corresponding β-lactones for the thermal extrusion of carbon oxysulfide and carbon dioxide, respectively. This finding, coupled with differences in the influences of solvent polarity on the extrusion reactions, suggests that the decomposition of the β-thiolactones and of the β-lactones is best interpreted in terms of stepwise fragmentation mechanisms involving zwitterionic intermediates with the rate-determining step, ring-opening, or expulsion of COS or CO_2 being dependent on the nature of the heteroatom, S or O.

EXPERIMENTAL SECTION

***S*-Pyridin-2-yl 6-(4-Methoxyphenyl)hexanethioate (2).** To a stirred solution of 6-(4-methoxyphenyl)hexanoic acid[86] (3.6 g, 16.2 mmol) in CH_2Cl_2 (81 mL) were added oxalyl chloride (2.12 mL, 24.3 mmol) and a catalytic amount of anhydrous DMF at room temperature, and the reaction mixture was stirred for 30 min. The solvent was evaporated under reduced pressure. To the oil residue was added a solution of 2-mercaptopyridine (2.16 g, 19.4 mmol) in CH_2Cl_2 (81 mL), followed by Et_3N (4.52 mL, 32.4 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then quenched with 1 M HCl and neutralized by washing with saturated $NaHCO_3$. The organic layers were combined and evaporated. After purification by flash chromatography (80:20 heptane/AcOEt), the desired product was obtained as a yellow oil (3.7 g, 73%); IR υ_{max} (cm^{-1}) 2929, 2854, 1704, 1611, 1572, 1511; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.61 (d, J = 4.3 Hz, 1 H), 7.73 (t, J = 7.6 Hz, 1 H), 7.59 (d, J = 7.6 Hz, 1 H), 7.25−7.32 (m, 1 H), 7.08 (d, J = 8.1 Hz, 2 H), 6.82 (d, J = 8.1 Hz, 2 H), 3.79 (s, 3 H), 2.69 (t, J = 7.6 Hz, 2 H), 2.55 (t, J = 7.6 Hz, 2 H), 1.76 (quint., J = 7.6 Hz, 2 H), 1.61 (quint., J = 7.6 Hz, 2 H), 1.40 (quint., J = 7.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 196.5 (C), 157.7 (C), 151.7 (C), 150.4 (CH), 137.1 (CH), 134.5 (C), 130.1 (CH), 129.2 (2 CH), 123.4 (CH), 113.7 (2 CH), 55.3 (CH_3), 44.1 (CH_2), 34.7 (CH_2), 31.3 (CH_2), 28.5 (CH_2), 25.3 (CH_2); MS (ES$^+$) m/z (%) 316.1 (100, [M + H]$^+$); ESI-TOF-HRMS calcd for $C_{18}H_{22}NO_2S$ (M + H) 316.1371, found 316.1375.

***S*-Phenyl 6-(4-Methoxyphenyl)hexanethioate (3).** To a stirred solution of (**1**)[86] (4 g, 18.00 mmol) in CH_2Cl_2 (90 mL) were added oxalyl chloride (2.4 mL, 27.96 mmol) and a catalytic amount of anhydrous DMF at room temperature. The reaction mixture was stirred for 30 min, and the solvent was evaporated under reduced pressure. To the stirred oil residue was added thiophenol (2.21 mL, 21.59 mmol) in CH_2Cl_2 (90 mL), followed by Et_3N (5 mL, 35.87 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h and then quenched with 1 M HCl and neutralized by washing with saturated $NaHCO_3$. The organic layers were combined and evaporated. After purification by flash chromatography (50/50 heptane/CH_2Cl_2), the desired product was obtained as a yellow oil (5.16 g, 91%); IR υ_{max} (cm^{-1}) 2933, 2857, 1707, 1612, 1584, 1512; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (s, 5 H), 7.09 (d, J = 8.3 Hz, 2 H), 6.83 (d, J = 8.3 Hz, 2 H), 3.79 (s, 3 H), 2.65 (t, J = 7.5 Hz, 2 H), 2.57 (t, J = 7.5 Hz, 2 H), 1.74 (quint, J = 7.5 Hz, 2 H), 1.62 (quint, J = 7.5 Hz, 2 H), 1.42 (quint., J = 7.5 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.5 (C), 157.7 (C), 134.5 (C, 2 CH), 129.3 (2 CH), 129.2 (C, 2 CH), 129.1 (CH), 113.7 (2 CH), 55.3 (CH_3), 43.6 (CH_2), 34.7 (CH_2), 31.3 (CH_2), 28.5 (CH_2), 25.4 (CH_2); MS (ES$^+$) m/z (%) 332.1 (100, [M + NH_4]$^+$); ESI-TOF-HRMS calcd for $C_{19}H_{26}NO_2S$ (M + NH_4) 332.1684, found 332.1670.

***trans*-4-Ethyl-3-(4-(4-methoxyphenyl)butyl)oxetan-2-one (4).** To a stirred solution of 1 M LiHMDS in hexane (3.7 mL, 3.7 mmol) at −78 °C was added dropwise a solution of (**2**) (500 mg, 1.6 mmol) in CH_2Cl_2 (8 mL). The reaction mixture was stirred for 30 min at −78 °C, and TESCl (0.54 mL, 3.2 mmol) was added dropwise. The reaction mixture was stirred at −78 °C for 1 h and then quenched with a pH 7 buffer solution. The organic layer was separated, dried over Na_2SO_4, and evaporated. Propanal (0.1 mL, 1.39 mmol) and a solution of crude *S*-pyridin-2-yl 6-(4-methoxyphenyl)hexanethioate triethylsilyl enol ether (680 mg, 1.58 mmol) in CH_2Cl_2 (7.2 mL) were added dropwise to a suspension of $ZnCl_2$ (393 mg, 2.88 mmol, freshly fused under vacuum) at room temperature. The reaction mixture was stirred at room temperature for 2.5 h. A PBS buffer (pH 7) was added to the reaction mixture, which was stirred for 25 min. The product was extracted with CH_2Cl_2 and dried over Na_2SO_4, and the solvents were evaporated. After purification on silica (80:20 heptane/AcOEt), the desired product was obtained as a colorless oil (155.3 mg, 37%); IR υ_{max} (cm^{-1}) 2930, 1814, 1611, 1511; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, J = 8.3 Hz, 2 H), 6.83 (d, J = 8.3 Hz, 2 H), 4.10−4.18 (m, 1 H), 3.79 (s, 3 H), 3.11−3.20 (m, 1 H), 2.57 (t, J = 7.7 Hz, 2 H), 1.78−1.95 (m, 2 H), 1.69−1.78 (m, 2 H), 1.53−1.69 (m, 2 H), 1.32−1.53 (m, 2 H), 0.99 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4 (C), 157.8 (C), 134.1 (C), 129.2 (2 CH), 113.8 (2 CH), 79.1 (CH), 55.6 (C), 55.3 (CH), 34.6 (CH_2), 31.3 (CH_2), 27.8 (CH_2), 27.5 (CH_2), 26.5 (CH_2), 9.1 (CH_3); MS (ES$^+$) m/z (%) 547.3 (10,

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[2M + Na]$^+$), 285.1 (100, [M + Na]$^+$); ESI-TOF-HRMS calcd for $C_{16}H_{22}NaO_3$ (M + Na) 285.1467, found 285.1473.

(*S)-2-((*S**)-(1-(Acetylthio)propyl)-6-(4-methoxyphenyl)-hexanoic Acid (5).** To a solution of (**4**) (531 mg, 2.02 mmol) in DMF (4.04 mL) was added cesium ethanethioate (1.05 g, 5.07 mmol), and the reaction mixture was stirred at room temperature for 22 h. The mixture was acidified with 1 M HCl and was then extracted with ether and dried over Na_2SO_4. The desired product was obtained after purification on a silica cartridge (70:30 heptane/AcOEt) as a yellow oil (418.8 mg, 61%); IR υ_{max} (cm^{-1}) 3100, 2932, 1705, 1690; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (br s, 1 H), 7.08 (d, J = 8.0 Hz, 2 H), 6.82 (d, J = 8.0 Hz, 2 H), 4.13 (q, J = 7.2 Hz, 0.1 H, AcOEt), 3.78 (s, 3 H), 3.70−3.77 (m, 1 H), 2.50−2.65 (m, 3 H), 2.34 (s, 3 H), 2.05 (s, 0.1 H, AcOEt), 1.71−1.82 (m, 2 H), 1.54−1.67 (m, 4 H), 1.30−1.49 (m, 2 H), 0.97 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.1 (C), 179.4 (C), 157.7 (C), 134.5 (C), 129.2 (2 CH), 113.7 (2 CH), 60.4 (2 CH_2, AcOEt), 55.3 (CH_3), 49.5 (CH), 47.4 (CH), 34.7 (CH_2), 31.5 (CH_2), 30.7 (CH_3), 29.5 (CH_2), 27.1 (CH_2), 25.5 (CH_2), 14.2 (2 CH_3, AcOEt) 11.5 (CH_3); MS (ES$^-$) m/z (%) 337.1 (100, [M − H]$^-$); ESI-TOF-HRMS calcd for $C_{18}H_{25}O_4S$ (M − H) 337.1474, found 337.1459.

(*S)-2-((*S**)-1-Mercaptopropyl)-6-(4-methoxyphenyl)-hexanoic Acid (6).** To a solution of (**5**) (410 mg, 1.2 mmol) in CH_3CN (24 mL) was added hydrazine monohydrate (0.12 mL, 2.4 mmol), and the reaction mixture was stirred at 0 °C for 1.5 h. The mixture was acidified with 1 M HCl. The product was extracted with CH_2Cl_2 and dried over Na_2SO_4, and the solvent was evaporated. The desired product was obtained as a yellow oil (*S**,*S**/*S**,*R** = 83/17) without further purification (342.4 mg, 96%); IR υ_{max} (cm^{-1}) 3100, 2929, 2856, 1703, 1612; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.67 (br s, 1 H), 7.08 (d, J = 8.1 Hz, 2 H), 6.82 (d, J = 8.1 Hz, 2 H), 3.78 (s, 3 H), 2.92−3.03 (m, 1 H), 2.73−2.60 (m, 3 H), 2.00 (s, 1 H), 1.69−1.83 (m, 2 H), 1.21−1.68 (m, 6 H), 1.05 (t, J = 7.4 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.3(C), 157.6 (C), 134.5 (C), 129.2 (2 CH), 113.7 (2 CH), 55.2 (CH_3), 52.4 (CH), 44.3 (CH), 34.7 (CH_2), 31.5 (CH_2), 29.8 (CH_2), 28.9 (CH_2), 27.1 (CH_2), 11.8 (CH_3); MS (ES$^-$) m/z (%) 589.3 (100, [2M − 3H]$^-$); ESI-TOF-HRMS calcd for $C_{32}H_{45}O_6S_2$ (2M − 3H) 589.2658, found 589.2648.

***cis*-4-Ethyl-3-(4-(4-methoxyphenyl)butyl)thietan-2-one (7).** To a solution of (**6**) (330 mg, 1.11 mmol) in CH_2Cl_2 (5.6 mL) were added to EDCI·HCl (427.3 mg, 2.23 mmol) and pentafluorophenol (246.1 mg, 1.34 mmol) at 0 °C and the mixture was stirred at 0 °C for 1 h 30. The mixture was quenched with 1 M HCl and extracted with CH_2Cl_2, dried over Na_2SO_4 and the solvent was removed. The desired product was obtained after purification on a silica cartridge (90:10 heptane/AcOEt) as a colorless oil (302.8 mg, 98%) in the form of a 93/7 *cis*/*trans* mixture; IR υ_{max} (cm^{-1}) 2932, 2858, 1749, 1612, 1512; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 4.12 (q, J = 7.5 Hz, 1 H), 3.79 (s, 3 H), 3.53 (ddd, J = 11.4, 7.4, 4.1 Hz, 1 H), 2.56 (t, J = 7.6 Hz, 2 H), 1.27−2.08 (m, 8 H), 1.06 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3 (C), 157.7 (C), 134.3 (C), 129.2 (2 CH), 113.7 (2 CH), 70.4 (CH), 55.2 (CH_3), 40.9 (CH), 34.6 (CH_2), 31.5 (CH_2), 27.4 (CH_2), 26.2 (CH_2), 25.8 (CH_2), 13.1 (CH_3); MS (ES$^+$) m/z (%) 579.3 (15, [2M + Na]$^+$), 301.1 (100, [M + Na]$^+$), 296.2 (60, [M + NH_4]$^+$); ESI-TOF-HRMS calcd for $C_{16}H_{22}NaO_2S$ (M + Na) 301.1238, found 301.1236.

***trans*-4-Ethyl-3-(4-(4-methoxyphenyl)butyl)thietan-2-one (8).** To a −78 °C solution of (**7**) (270 mg, 0.97 mmol) in THF (26.9 mL) was added 1 M LiHMDS in hexane (1.46 mL, 1.46 mmol), and the reaction mixture was stirred at −78 °C for 1 h. Tetramethylethylenediamine (0.22 mL, 1.46 mmol) was then added at −78 °C, and the mixture was stirred for an additional 30 min, after which the solution was quenched with acetic acid (0.17 mL, 2.97 mmol). The reaction mixture was neutralized with a saturated Na_2CO_3, and the product was extracted with ether. The solvent was removed under vacuo. The desired product was obtained as a mixture of *cis*/*trans* thiolactones (20/80) and as a colorless oil (263.8 mg, 98%); IR υ_{max} (cm^{-1}) 2930, 2856, 1747, 1612, 1583, 1511; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 4.12 (q, J = 7.9 Hz, 0.2 H), 3.79 (s, 3 H), 3.62 (ddd, J = 8.4, 6.4, 3.6 Hz, 0.8 H), 3.53 (ddd, J = 11.2, 7.4, 3.6 Hz, 0.2 H), 3.15 (ddd, J = 8.9, 5.6, 3.5 Hz, 0.8 H), 2.56 (t, J = 7.5 Hz, 2 H), 1.53−2.05 (m, 6 H), 1.50−1.36 (m, 2 H), 1.03 (t, J = 7.5 Hz, 0.6 H), 1.01 (t, J = 7.5 Hz, 2.4 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.3 (0.2 C), 194.4 (0.8 C), 157.7 (C), 134.2 (C), 129.2 (2 CH), 113.7 (2 CH), 73.9 (0.8 CH), 70.4 (0.2 CH), 55.2 (CH_3), 42.4 (0.8 CH_2), 40.9 (0.2 CH_2), 34.7 (CH_2), 31.4 (CH_2), 30.7 (CH_2), 27.4 (0.2 CH_2), 26.2 (0.8 CH_2), 25.9 (0.8 CH_2), 25.8 (0.2 CH_2), 13.1 (0.2 CH_3), 13.0 (0.8 CH_3); MS (ES$^+$) m/z (%) 579.3 (15, [2M + Na]$^+$), 301.1 (100, [M + Na]$^+$), 296.2 (60, [M + NH_4]$^+$); ESI-TOF-HRMS calcd for $C_{16}H_{22}NaO_2S$ (M + Na) 301.1238, found 301.1236.

4-Ethyl-3-(4-(4-methoxyphenyl)butyl)-3-methyloxetan-2-one (9). A solution of 0.6 M LDA (7.5 mL, 4.5 mmol) in THF was added dropwise to a solution of (**4**) (534 mg, 2.0 mmol) in THF (6.7 mL) at −78 °C. The reaction mixture was stirred at this temperature for 30 min, and freshly distilled MeI (0.44 mL, 6.9 mmol) was added. The reaction was slowly warmed up to room temperature for 2.5 h. The mixture was then cooled down to −78 °C, and acetic acid was added. The mixture was extracted with AcOEt, washed with saturated Na_2CO_3 and then brine, and dried over Na_2SO_4. The solvent was removed under vacuo. The desired product was obtained after purification on a silica cartridge (85:15 heptane/AcOEt) as a colorless oil (394.6 mg, 70%, *unlike*/*like* 4:1); IR υ_{max} (cm^{-1}) 2937, 1815, 1612, 1512; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.0 Hz, 2 H), 6.83 (d, J = 8.0 Hz, 2 H), 4.17 (dd, J = 9.1 Hz, 5.5 Hz, 0.2 H), 4.11 (dd, J = 9.6 Hz, 4.6 Hz, 0.8 H), 3.78 (s, 3 H), 2.50−2.63 (m, 2 H), 1.47−1.85 (m, 8 H), 1.38 (s, 2.4 H), 1.24 (s, 0.6 H), 1.03 (t, J = 7.3 Hz, 2.4 H), 1.01 (t, J = 7.3 Hz, 0.6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0 (C), 157.7 (C), 134.2 (0.8 C), 134.1 (0.2 C), 129.2 (2 CH), 113.7 (2 CH), 85.4 (0.8 CH), 82.8 (0.2 CH), 57.0 (0.2 C), 56.4 (0.8 C), 55.2 (CH_3), 35.7 (0.2 CH_2), 34.7 (0.8 CH_2), 32.0 (0.8 CH_2), 31.7 (0.2 CH_2), 30.0 (CH_2), 23.8 (CH_2), 23.4 (0.8 CH_2), 19.8 (CH_2), 14.1 (0.2 CH_2), 10.0 (0.8 CH_3), 9.9 (0.2 CH_3); MS (APCI) m/z (%) 277.2 (85, [M + H]$^+$), 318.2 (100, [M + H + CH_3CN]$^+$); ESI-TOF-HRMS calcd for $C_{17}H_{25}O_3$ (M + H) 277.1804, found 277.1794.

4-Ethyl-3-(4-(4-methoxyphenyl)butyl)-3-methylthietan-2-one (10). To a solution of (**7**) (168 mg, 0.6 mmol) in THF (16.7 mL) was added 1 M LiHMDS in hexane (0.9 mL, 0.93 mmol) at −78 °C, and the mixture was stirred at this temperature for 1 h. TMEDA (0.14 mL, 0.93 mmol) and distilled MeI (0.19 mL, 3.0 mmol) were added at −78 °C, and the reaction mixture was allowed to warm up to −40 °C and was stirred at this temperature for 12 h. Acetic acid was added at this temperature. The organic layer was washed with saturated Na_2CO_3 and dried over Na_2SO_4, and the solvent was removed in vacuo. The desired product was obtained as a yellow oil without further purification (164.7 mg, 94%, 7:3 *unlike*/*like*); IR υ_{max} (cm^{-1}) 2934, 2856, 1740, 1612, 1511; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.4 Hz, 2 H), 6.82 (d, J = 8.4 Hz, 2 H), 3.79 (s, 3 H), 3.24 (dd, J = 10.6, 4.5 Hz, 0.3 H), 3.17 (dd, J = 11.5, 4.1 Hz, 0.7 H), 2.50−2.64 (m, 2 H), 1.41−2.02 (m, 8 H), 1.35 (s, 2.1 H), 1.24 (s, 0.9 H), 1.00 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7 (0.3 C), 198.4 (0.7 C), 157.7 (C), 134.4 (0.7 C), 134.3 (0.3 C), 129.2 (2 CH), 113.7 (2 CH), 74.7 (0.3 C), 74.2 (0.7 C), 55.2 (CH_3), 49.9 (0.7 CH), 46.9 (0.3 CH), 37.9 (CH_2), 34.7 (CH_2), 32.2 (0.7 CH_2), 32.1 (0.3 CH_2), 25.8 (0.7 CH_2), 25.0 (0.3 CH_2), 24.3 (0.7 CH_2), 23.4 (0.3 CH_2), 22.3 (0.7 CH_3), 16.5 (0.3 CH_3), 13.3 (CH_3); MS (ES$^+$) m/z (%) 310.2 (100, [M + NH_4]$^+$); ESI-TOF-HRMS calcd for $C_{17}H_{28}NO_2S$ (M + NH_4) 310.1841, found 310.1827.

4-Ethyl-3-(4-(4-methoxyphenyl)butyl)-4-methyloxetan-2-one (11). To a stirred solution of 0.6 M LDA in THF (4.7 mL, 2.82 mmol) at −78 °C was added dropwise a solution of (**3**) (809 mg, 2.57 mmol) in THF (1.2 mL). The reaction mixture was stirred for 30 min at −78 °C, and 2-butanone (0.23 mL, 2.57 mmol) was added dropwise. The reaction was stirred at −78 °C for 30 min and then allowed to warm up to 0 °C. The reaction was quenched with half-saturated aqueous ammonium chloride. The mixture was poured into a separatory funnel containing hexane/water (1:1). The aqueous layer was extracted with hexane, and the combined organic layers were washed successively with aqueous $NaHCO_3$ and brine and then was dried over Na_2SO_4 and evaporated. After a purification on a silica

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cartridge (95:5 heptane/AcOEt), the desired product was obtained as a mixture of *unlike/like* (70:30) isomers and as a colorless oil (425 mg, 60%); IR υ_{max} (cm^{-1}) 2973, 2934, 2859, 1811, 1612, 1512; ^1H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 3.80 (s, 3 H), 3.20 (t, J = 8.0 Hz, 0.3 H), 3.15 (t, J = 8.0 Hz, 0.7 H), 2.59 (t, J = 7.5 Hz, 2 H), 1.09−2.56 (m, 7 H), 1.54 (s, 1 H), 1.44 (s, 2 H), 1.25−1.42 (m, 1 H), 1.04 (t, J = 7.3 Hz, 1 H), 0.98 (t, J = 7.3 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (C), 157.8 (C), 134.1 (C), 129.2 (2 CH), 113.7 (2 CH), 82.6 (0.7 C), 82.3 (0.3 C), 58.9 (0.3 CH), 56.5 (0.7 CH), 55.2 (CH_3), 34.6 (CH_2), 33.7 (0.7 CH_2), 31.4 (0.3 CH_2), 31.3 (0.7 CH_2), 27.9 (0.3 CH_2), 27.2 (0.3 CH_2), 27.0 (0.7 CH_2), 24.9 (0.7 CH_2), 24.2 (0.3 CH_2), 24.1 (0.3 CH_3), 18.9 (0.7 CH_3), 8.4 (0.7 CH_3), 7.9 (0.3 CH_3); MS (ES^+) m/z (%) 277.1 (100, $[M + H]^+$); ESI-TOF-HRMS calcd for $C_{17}H_{25}O_3$ (M + H) 277.1804, found 277.1802.

***tert*-Butyl 6-(4-Methoxyphenyl)hexanoate (12).** To a stirred solution of 6-(4-methoxyphenyl)hexanoic acid (4.8 g, 21.6 mmol) in CH_2Cl_2 (108 mL) were added oxalyl chloride (2.8 mL, 32.1 mmol) and a catalytic amount of anhydrous DMF at room temperature. The reaction mixture was stirred for 30 min, and the solvent was evaporated under reduced pressure. To the stirred oil residue was added *tert*-butanol (108 mL), followed by Et_3N (6.0 mL, 43.0 mmol), at room temperature. The reaction mixture was stirred at this temperature for 2 h and then quenched with 1 M HCl and neutralized by washing with saturated $NaHCO_3$. The organic layer was evaporated. The desired product was obtained as a yellow oil (5.51 g, 92%); IR υ_{max} (cm^{-1}) 2977, 2932, 2857, 1728, 1613, 1513; ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.4 Hz, 2 H), 6.82 (d, J = 8.4 Hz, 2 H), 3.78 (s, 3 H), 2.55 (t, J = 7.5 Hz, 2 H), 2.20 (t, J = 7.5 Hz, 2 H), 1.53−1.67 (m, 4 H), 1.43 (s, 9 H), 1.23−1.40 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2 (C), 157.6 (C), 134.7 (C), 129.2 (2 CH), 113.6 (2 CH), 79.9 (C), 55.2 (CH_3), 35.5 (CH_2), 34.8 (CH_2), 31.4 (CH_2), 28.6 (CH_2), 28.1 (3 CH_3), 25.0 (CH_2); MS (ES^+) m/z (%) 296.2 (100, $[M + NH_4]^+$); ESI-TOF-HRMS calcd for $C_{17}H_{30}NO_3$ (M + NH_4) 296.2226, found 296.2221.

***tert*-Butyl 2-(2-Hydroxyadamantan-2-yl)-6-(4-methoxyphenyl)hexanoate (13).** To a solution of (**12**) (1 g, 3.59 mmol) in dry THF (8.2 mL) at −78 °C was added 0.6 M LDA in THF (6.4 mL, 3.84 mmol). The mixture was stirred at −78 °C for 40 min. A solution of adamantan-2-one (573 mg, 3.81 mmol) in THF (9.6 mL) was added. The cold bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2, and 1 M HCl was added. The product was extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified on a silica cartridge (95:5 heptane/AcOEt) to give the desired product as a colorless oil (1.22 g, 79%); IR υ_{max} (cm^{-1}) 3500, 2906, 2857, 1699, 1612, 1512; ^1H NMR (300 MHz, $CDCl_3$) δ 7.07 (d, J = 8.4 Hz, 2 H), 6.81 (d, J = 8.4 Hz, 2 H), 3.77 (s, 3 H), 3.48 (br s, 1 H), 2.99 (dd, J = 11.4, 4.0 Hz, 1 H), 2.54 (t, J = 7.9 Hz, 2 H), 2.31 (d, J = 13.2 Hz, 1 H), 2.23 (d, J = 13.2 Hz, 1 H), 1.85−2.12 (m, 4 H), 1.47−1.85 (m, 12 H), 1.43 (s, 9 H), 1.18−1.36 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8 (C), 157.7 (C), 134.5 (C), 129.2 (2 CH), 113.7 (2 CH), 81.4 (C), 75.1 (C), 55.2 (CH_3), 49.0 (CH), 38.3 (CH_2), 38.0 (CH), 34.8 (CH_2), 34.2 (CH_2), 33.7 (CH_2), 33.4 (2 CH_2), 33.1 (CH_2), 32.6 (CH_2), 31.5 (CH_2), 28.2 (3 CH_3), 27.3 (CH_2), 27.11 (CH), 27.08 (CH), 25.7 (CH_2); MS (ES^+) m/z (%) 355.2 (75, $[M - OH - C_4H_8]^+$), 451.3 (100, $[M + Na]^+$); ESI-TOF-HRMS calcd for $C_{27}H_{40}NaO_4$ (M + Na) 451.2824, found 451.2806.

2-(2-Hydroxyadamantan-2-yl)-6-(4-methoxyphenyl)-hexanoic Acid (15). To a solution of (**13**) (1.19 g, 2.78 mmol) in CH_2Cl_2 (1.9 mL) was added TFA (1.9 mL). The reaction mixture was stirred at room temperature for 1 h, and the solvent was evaporated. The residue was treated with CH_2Cl_2 and concentrated to dryness, and the process was repeated twice. After purification on a silica cartridge (85:15 heptane/AcOEt), the desired product was obtained as a white solid (972.7 mg, 94%, mp = 93.9−95.3 °C); IR υ_{max} (cm^{-1}) 3500, 2908, 2858, 1699, 1612, 1511; ^1H NMR (300 MHz, $CDCl_3$) δ 9.51 (br s, 1 H), 7.07 (d, J = 8.5 Hz, 2 H), 6.82 (d, J = 8.5 Hz, 2 H), 3.78 (s, 3 H), 3.17 (dd, J = 11.7, 3.7 Hz, 1 H), 2.50−2.61 (m, 2 H), 2.22 (br d, J = 13.2 Hz, 1 H), 2.16 (br d, J = 13.2 Hz, 1 H), 1.97 (br s, 2 H), 1.50−1.89 (m, 15 H), 1.29−1.46 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.2 (C), 157.7 (C), 134.5 (C), 129.2 (2 CH), 113.7 (2 CH), 75.4 (C), 55.2 (CH_3), 49.0 (CH), 38.1 (CH), 37.8 (CH_2), 34.8 (CH_2), 34.3 (CH), 33.7 (CH_2), 33.4 (CH), 33.0 (CH_2), 32.6 (CH_2), 31.6 (CH_2), 27.4 (CH_2), 27.1 (CH), 26.9 (CH), 25.5 (CH_2); MS (ES^-) m/z (%) 371.2 (100, $[M - H]^-$), 743.5 (15, $[2M - H]^-$); ESI-TOF-HRMS calcd for $C_{23}H_{31}O_4$ (M − H) 371.2222, found 371.2223.

2-(2-Mercaptoadamantan-2-yl)-6-(4-methoxyphenyl)-hexanoic Acid (16). To a solution of (**12**) (315.7 mg, 1.13 mmol) in dry THF/cyclohexane (4:1, 2.6 mL) at −78 °C was added 0.6 M LDA in THF (2 mL, 1.2 mmol). The mixture was stirred at −78 °C for 40 min, and a solution of adamantan-2-thione (200 mg, 1.2 mmol) in THF (3.6 mL) was added. The cold bath was removed, and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was diluted with CH_2Cl_2, and 1 M HCl was added. The organic phase was extracted with CH_2Cl_2 and washed with brine, dried over Na_2SO_4, filtered, and concentrated. To this crude product in CH_2Cl_2 (0.5 mL) was added TFA (0.5 mL). The reaction mixture was stirred at room temperature for 2 h. CH_2Cl_2 was added and the mixture was concentrated to dryness; this was repeated twice. After purification on a silica cartridge (90:10 heptane/AcOEt), the desired product was obtained as a white solid (193.2 mg, 44%, mp = 134.1−134.4 °C); IR υ_{max} (cm^{-1}) 3100, 2941, 2908, 2866, 1697, 1512; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (br s, 1 H), 7.08 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 3.78 (s, 3 H), 3.44 (dd, J = 11.6, 2.4 Hz, 1 H), 2.52−2.69 (m, 3 H), 2.50 (s, 1 H), 2.35 (br d, J = 13.7 Hz, 2 H), 1.91−2.03 (m, 3 H), 1.87 (br s, 2 H), 1.20−1.76 (m, 12 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5 (C), 157.7 (C), 134.5 (C), 129.2 (2 CH), 113.7 (2 CH), 57.1 (C), 55.3 (CH_3), 50.4 (CH), 39.1 (CH_2), 38.7 (CH), 35.5 (CH), 34.8 (CH_2), 34.4 (CH_2), 34.0 (CH_2), 33.01 (CH_2), 32.97 (CH_2), 31.7 (CH_2), 27.7 (CH_2), 27.4 (CH), 27.1 (CH_2), 26.7 (CH); MS (ES^-) m/z (%) 387.2 (100, $[M - H]^-$); ESI-TOF-HRMS calcd for $C_{23}H_{31}O_3S$ (M − H) 387.1994, found 387.1994.

3′-(4-(4-Methoxyphenyl)butyl)spiro[adamantane-2,2′-oxetan]-4′-one (17). 4-Nitrobenzenesulfonyl chloride (357.3 mg, 1.61 mmol) and triethylamine (0.37 mL, 2.65 mmol) were added to a solution of (**15**) (500 mg, 1.34 mmol) in CH_2Cl_2 (6.7 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 2 h and at room temperature overnight. The mixture was quenched with 1 M HCl and extracted with CH_2Cl_2. The solution was dried over Na_2SO_4, and the solvent was removed. The desired product was obtained, after purification on a silica cartridge (90:10 heptane/AcOEt), as a white solid (186 mg, 39%, mp = 82.7−83.5 °C); IR υ_{max} (cm^{-1}) 2909, 2856, 1810, 1612, 1511; ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 3.78 (s, 3 H), 3.04 (dd, J = 10.5, 5.3 Hz, 1 H), 2.52−2.64 (m, 2 H), 2.14 (br s, 1 H), 2.10 (br d, J = 13.2 Hz, 1 H), 2.04 (br d, J = 13.2 Hz, 1 H), 1.58−1.94 (m, 16 H), 1.43−1.54 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (C), 157.7 (C), 134.4 (C), 129.2 (2 CH), 113.7 (2 CH), 86.5 (C), 57.5 (CH), 55.2 (CH_3), 38.8 (CH), 36.6 (CH_2), 34.8 (CH), 34.7 (CH_2), 34.4 (CH_2), 33.3 (CH_2), 33.0 (CH_2), 32.9 (CH_2), 31.6 (CH_2), 27.1 (CH_2), 26.8 (CH), 26.2 (CH), 24.5 (CH_2) ; MS (APCI) m/z (%) 355.2 (70, $[M + H]^+$), 396.3 (100, $[M + H + CH_3CN]^+$); ESI-TOF-HRMS calcd for $C_{23}H_{31}O_3$ (M + H) 355.2273, found 355.2270, calcd for $C_{25}H_{34}NO_3$ (M + H + CH_3CN) 396.2539, found 396.2540.

2-(5-(4-Methoxyphenyl)pentylidene)adamantane (19). This compound was obtained as a byproduct on formation of **17** described above. It was isolated after purification on a silica cartridge (95:5 heptane/AcOEt) as a colorless oil (349.9 mg, 70%); IR υ_{max} (cm^{-1}) 2906, 2848, 1613, 1512; ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.7 Hz, 2 H), 6.82 (d, J = 8.7 Hz, 2 H), 5.01 (t, J = 7.3 Hz, 1 H), 3.79 (s, 3 H), 2.79 (br s, 1 H), 2.54 (t, J = 7.6 Hz, 2 H), 2.30 (br s, 1 H), 1.51−2.06 (m, 16 H), 1.35 (quint., J = 7.6 Hz, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6 (C), 147.5 (C), 135.0 (C), 129.2 (2 CH), 116.1 (CH), 113.6 (2 CH), 55.2 (CH_3), 40.6 (CH), 39.9 (2 CH_2), 39.0 (CH), 37.4 (CH_2), 34.9 (CH_2), 32.1 (2 CH_2), 31.2 (CH_2), 29.9 (CH_2), 28.7 (2 CH), 26.3 (CH_2); MS (APCI) m/z (%) 310.2 (100, $[M^{+\cdot}]$), 311.2 (92, $[M + H]^+$), 328.2 (90, $[M + NH_4]^+$), 352.3 (85, [M

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+ H + $CH_3CN]^+$); ESI-TOF-HRMS calcd for $C_{22}H_{30}O$ ($M^{+\cdot}$) 310.2297, found 310.2297.

3′-(4-(4-Methoxyphenyl)butyl)spiro[adamantane-2,2′-thietan]-4′-one (18). A solution of (**16**) (90 mg, 0.23 mmol) in CH_2Cl_2 (1 mL) was added to EDCI·HCl (155.3 mg, 0.81 mmol) and C_6F_5OH (44.7 mg, 0.24 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 5 h. The mixture was quenched with 1 M HCl and extracted with CH_2Cl_2 and dried over Na_2SO_4, and the solvent was removed. The desired product was obtained after purification on a silica cartridge (98:2 heptane/AcOEt) as a white solid (73.3 mg, 86%, mp = 79.2−80.7 °C); IR υ_{max} (cm^{-1}) 2906, 2853, 1739, 1612, 1511; ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.6 Hz, 2 H), 6.82 (d, J = 8.6 Hz, 2 H), 3.79 (s, 3 H), 3.47 (dd, J = 10.1, 5.5 Hz, 1 H), 2.47−2.66 (m, 2 H), 2.27 (br s, 1 H), 1.97−2.10 (m, 2 H), 1.68−1.97 (m, 15 H), 1.53−1.68 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.9 (C), 157.7 (C), 134.5 (C), 129.2 (2 CH), 113.7 (2 CH), 73.3 (CH), 59.6 (C), 55.2 (CH_3), 42.2 (CH), 37.14 (CH_2), 37.07 (CH_2), 36.3 (CH_2), 35.7 (CH_2), 35.1 (CH), 34.8 (CH_2), 33.7 (CH_2), 31.8 (CH_2), 27.32 (CH_2), 27.25 (CH), 27.1 (CH_2), 25.9 (CH); MS (APCI) m/z (%) 371.2 (100, $[M + H]^+$); ESI-TOF-HRMS calcd for $C_{23}H_{31}O_2S$ (M + H) 371.2045, found 371.2034.

3′-(4-(4-Methoxyphenyl)butyl)-3′-methylspiro[adamantane-2,2′-oxetan]-4′-one (20). Dimethyl sulfate (0.11 mL, 1.16 mmol) was added to a solution of (**17**) (132 mg, 0.37 mmol) in THF (1.2 mL), and the mixture was cooled to −100 °C. Phosphazene base P_4-*t*-Bu (1 M in hexane) (0.75 mL, 0.75 mmol) was added at this temperature, and the reaction mixture was stirred for 1 h and allowed to warm up to room temperature for 18 h. The reaction was quenched at room temperature with acetic acid. After extraction with CH_2Cl_2, the organic phase was washed with saturated aqueous Na_2CO_3 and then brine and dried over Na_2SO_4. The solvent was removed under vacuo. The desired product was obtained, after purification on a silica cartridge (95:5 heptane/AcOEt), followed by HPLC (95:5 heptane/AcOEt), as a white solid (30.2 mg, 22%, mp = 72.3−73.6 °C); IR υ_{max} (cm^{-1}) 2916, 2858, 1810, 1612, 1512; ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.4 Hz, 2 H), 6.82 (d, J = 8.4 Hz, 2 H), 3.78 (s, 3 H), 2.48−2.66 (m, 2 H), 2.27 (br s, 1 H), 2.22 (br s, 1 H), 1.44−2.15 (m, 18 H), 1.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5 (C), 157.8 (C), 134.5 (C), 129.2 (2 CH), 113.8 (2 CH), 89.5 (C), 57.4 (C), 55.3 (CH_3), 36.6 (CH_2), 35.1 (CH_2), 35.0 (CH_2), 34.9 (CH_2), 33.9 (CH), 33.67 (CH_2), 33.65 (CH_2), 33.4 (CH), 32.4 (CH_2), 31.6 (CH_2), 26.5 (CH), 26.1 (CH), 24.4 (CH_2), 15.1 (CH_3); MS (APCI) m/z (%) 323.2 (99, $[M - CO_2H]^+$), 324.2 (25, $[M - CO_2]^+$), 369.2 (100, $[M + H]^+$); ESI-TOF-HRMS calcd for $C_{24}H_{33}O_3$ (M + H) 369.2430, found 369.2433.

3′-(4-(4-Methoxyphenyl)butyl)-3′-methylspiro[adamantane-2,2′-thietan]-4′-one (21). LDA in THF 0.6 M (5.0 mL, 3.00 mmol) and MeI (0.93 mL, 15.1 mmol) were added to a 0.2 M solution of (**18**) (559 mg, 1.51 mmol) in THF (7.5 mL) at −78 °C, and the mixture was allowed to warm up to −40 °C and stirred for 3 h at that temperature. The reaction was quenched with acetic acid, and the organic phase was washed with saturated Na_2CO_3, which was extracted with CH_2Cl_2. After evaporation of the solvent, the product was purified using HPLC (95:5 heptane/AcOEt). The desired product was obtained as a colorless oil (265.1 mg, 46%); IR υ_{max} (cm^{-1}) 2908, 2853, 1729, 1612, 1584, 1511; ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.7 Hz, 2 H), 6.82 (d, J = 8.7 Hz, 2 H), 3.78 (s, 3 H), 2.48−2.65 (m, 2 H), 2.40 (br s, 1 H), 2.30 (br s, 1 H), 1.69−2.00 (m, 14 H), 1.49−1.68 (m, 4 H), 1.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.9 (C), 157.5 (C), 134.3 (C), 129.0 (2 CH), 113.5 (2 CH), 72.7 (C), 64.8 (C), 55.0 (CH_3), 37.7 (CH_2), 37.4 (CH_2), 37.2 (CH), 37.1 (CH_2), 35.9 (CH_2), 35.7 (CH), 35.1 (CH_2), 34.7 (CH_2), 34.5 (CH_2), 32.3 (CH_2), 26.8 (CH), 26.0 (CH), 24.3 (CH_2), 17.4 (CH_3); MS (APCI) m/z (%) 384.2 (25, $[M^{+\cdot}]$), 385.2 (75, $[M + H]^+$), 426.2 (100, $[M + H + CH_3CN]^+$), 769.4 (10, $[2M + H]^+$); ESI-TOF-HRMS calcd for $C_{24}H_{33}O_2S$ (M + H) 385.2201, found 385.2206.

***(E)*-1-Methoxy-4-(oct-5-en-1-yl)benzene (22).** Compound (**4**) (30 mg, 0.11 mmol) was heated neat at 150 °C for 4 h to give the desired product as a yellow oil (18.6 mg, 75%); IR υ_{max} (cm^{-1}) 2930, 1612, 1512; ^1H NMR (300 MHz, $CDCl_3$) δ 7.09 (d, J = 8.7 Hz, 2 H), 6.82 (d, J = 8.7 Hz, 2 H), 5.27−5.51 (m, 2 H), 3.79 (s, 3 H), 2.55 (t, J = 7.1 Hz, 2 H), 1.93−2.05 (m, 4 H), 1.52−1.65 (m, 2 H), 1.36−1.44 (m, 2 H), 0.96 (t, J = 7.7 Hz, 3 H); ^1H NMR (500 MHz, C_6D_6) 7.01 (d, J = 8.2 Hz, 2 H), 6.81 (d, J = 8.2 Hz, 2 H), 5.36−5.50 (ABt, J = 14.8, 5.4 Hz, 2 H), 3.35 (s, 3 H), 2.48 (t, J = 7.7 Hz, 2 H), 1.90−2.01 (m, 4 H), 1.56 (quint., J = 7.7 Hz, 2 H), 1.36 (quint., J = 7.7 Hz, 2 H), 0.95 (t, J = 7.7 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6 (C), 134.9 (C), 132.1 (CH), 129.2 (2 CH), 129.1 (CH), 113.7 (2 CH), 55.3 (CH_3), 34.9 (CH_2), 32.4 (CH_2), 31.2 (CH_2), 29.2 (CH_2), 25.6 (CH_2), 14.0 (CH_3); MS (APCI) m/z (%) 218.2 (100, $[M^{+\cdot}]$), 219.2 (30, $[M + H]^+$); ESI-TOF-HRMS calcd for $C_{15}H_{22}O$ ($M^{+\cdot}$) 218.1671, found 218.1671.

1-Methoxy-4-(5-methyloct-5-en-1-yl)benzene (23). Compound (**9**) (*unlike/like* 80:20) (53.2 mg, 0.19 mmol) was heated in FC-70 (1 mL) at 120 °C overnight to give, after purification on a silica cartridge (98:2 heptane/AcOEt), the desired product as a colorless oil (11.4 mg, 26%, *Z*/*E* (80:20)) and the starting material (38.8 mg); IR υ_{max} (cm^{-1}) 2960, 1613, 1512; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J = 8.4 Hz, 2 H), 6.83 (d, J = 8.4 Hz, 2 H), 5.12 (t, J = 7.3 Hz, 1 H), 3.79 (s, 3 H), 2.56 (t, J = 7.8 Hz, 2 H), 1.91−2.08 (m, 4 H), 1.66 (s, 2.4 H), 1.50−1.62 (m, 2.6 H), 1.34−1.48 (m, 2 H), 0.93 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6 (C), 134.9 (C), 134.7 (C), 129.2 (2 CH), 127.1 (0.8 CH), 126.4 (0.2 CH), 113.7 (2 CH), 55.3 (CH_3), 39.4 (0.2 CH_2), 35.0 (CH_2), 31.5 (1.6 CH_2), 31.3 (0.2 CH_2), 27.6 (0.8 CH_2), 27.5 (0.2 CH_2), 23.4 (CH_3), 21.15 (0.8 CH_2), 21.07 (0.2 CH_2), 14.7 (0.8 CH_3), 14.4 (0.2 CH_3); MS (APCI) m/z (%) 274.2 (100, $[M + H + CH_3CN]^+$), 232.2 (30, $[M^{+\cdot}]$), 233.2 (20, $[M + H]^+$); ESI-TOF-HRMS calcd for $C_{16}H_{25}O$ ($[M + H]^{+\cdot}$) 233.1905, found 233.1915.

1-Methoxy-4-(6-methyloct-5-en-1-yl)benzene (24). Compound (**11**) (*unlike/like* 70:30) (57.9 mg, 0.21 mmol) was heated in FC-70 (1 mL) at 120 °C overnight to give, after purification on a silica cartridge (98:2 heptane/AcOEt), the desired product as a colorless oil (29.4 mg, 60%, *Z*/*E* (70:30)) and the starting material (23.2 mg); IR υ_{max} (cm^{-1}) 2963, 2928, 1613, 1512; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 5.05−5.16 (m, 1 H), 3.79 (s, 3 H), 2.56 (t, J = 7.7 Hz, 2 H), 1.94−2.08 (m, 4 H), 1.68 (s, 1 H), 1.54−1.67 (m, 2 H), 1.60 (s, 2 H), 1.29−1.44 (m, 2 H), 0.99 (t, J = 7.5 Hz, 2 H), 0.97 (t, J = 7.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6 (C), 137.1 (0.3 C), 136.9 (0.7 C), 135.0 (C), 129.2 (2 CH), 124.3 (0.3 CH), 123.1 (0.7 CH), 113.7 (2 CH), 55.2 (CH_3), 35.0 (CH_2), 32.4 (0.3 CH_2), 31.4 (CH_2), 29.7 (0.3 CH_2), 29.5 (0.7 CH_2), 27.7 (0.7 CH_2), 27.5 (0.3 CH_2), 24.8 (0.7 CH_2), 22.9 (0.7 CH_3), 15.9 (0.3 CH_3), 12.8 (CH_3); MS (APCI) m/z (%) 274.2 (100, $[M + H + CH_3CN]^+$), 233.2 (50, $[M + H]^+$), 232.2 (30, $[M^{+\cdot}]$); ESI-TOF-HRMS calcd for $C_{16}H_{25}O$ (M + H) 233.1905, found 233.1907.

2-(6-(4-Methoxyphenyl)hexan-2-ylidene)adamantane (25). Compound (**20**) (55.3 mg, 0.15 mmol) was heated in FC-70 (1 mL) at 200 °C overnight to give, after purification on a silica cartridge (98:2 heptane/AcOEt), the desired product as a colorless oil (34 mg, 70%); IR υ_{max} (cm^{-1}) 2905, 2847, 1613, 1512; ^1H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J = 8.6 Hz, 2 H), 6.83 (d, J = 8.6 Hz, 2 H), 3.79 (s, 3 H), 2.83 (br s, 2 H), 2.56 (t, J = 7.6 Hz, 2 H), 2.02 (t, J = 7.6 Hz, 2 H), 1.81 (br s, 2 H), 1.77−1.88 (m, 6 H), 1.51−1.73 (m, 6 H), 1.61 (s, 3 H), 1.31−1.44 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6 (C), 140.1 (C), 135.0 (C), 129.2 (2 CH), 120.5 (C), 113.6 (2 CH), 55.3 (CH_3), 39.3 (2 CH_2), 38.9 (2 CH_2), 37.3 (CH_2), 35.0 (CH_2), 33.4 (CH_2), 32.9 (CH), 32.7 (CH), 31.5 (CH_2), 28.4 (CH_2), 28.2 (2 CH), 17.6 (CH_3); MS (APCI) m/z (%) 324.2 (100, $[M^{+\cdot}]$), 325.2 (90, $[M + H]^+$), 366.3 (30, $[M + H + CH_3CN]^+$); ESI-TOF-HRMS calcd for $C_{23}H_{33}O$ (M + H) 325.2531, found 325.2516.

■ ASSOCIATED CONTENT

Supporting Information

Copies of the ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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