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The Preparation of Synthetically Useful Carbonyl-Protected δ- and ε-Lithio Ketones via Reductive Lithiation

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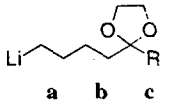
Abstract: The aromatic radical-anion induced reductive lithiation of the acetals or thioacetals of δ- and ε-(phenylthio)ketones provides δ- and ε-lithioketone equivalents. Primary and tertiary organolithiums have been generated and the ketone function may be part of a ring. The major synthetic use demonstrated in this report is the conversion to mixed heterocuprates which react with acyl chlorides to yield mono-protected 1,6- or 1,7-diketones. The cuprates also undergo conjugate addition to enones.

INTRODUCTION

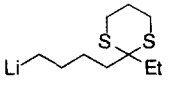
Since its introduction,[1] reductive lithiation of phenyl thioethers[2] using aromatic radical-anions has become one of the most versatile methods known for generating organolithiums, largely because of the great ease of introducing the phenylthio group into organic molecules. Such reductive lithiation of the acetals of 3- and 4-(phenylthio)ketones has led to a great expansion of the previously limited methodology for preparing β- and γ- lithio ketone (homoenolate[3] and bishomoenolate[4]) equivalents.

However, at present the only available δ-lithio masked carbonyl compounds are linear and primary (**1a–d** and **2**). Recently, Yus and co-workers[5] have prepared **1a-c** and **2** in widely varying yields by treatment of 5-chloroacetals at low temperature with a large excess of lithium under naphthalene catalysis. An earlier example, **1d**, was prepared by Mandai and co-workers[6] by treatment of the corresponding iodoacetal with *tert*-butyllithium at -83 °C and was used *in situ* for the synthesis of isocarbacyclin.



a b c d

1 R = H Et Ph TMS



2

We now report that reductive lithiation of carbonyl-protected δ- and ε-(phenylthio)ketones is a general and versatile method for the preparation of δ- and ε-lithioketone equivalents. The phenylthio group can be easily placed at a position δ or ε to the protected carbonyl function of ketones. Among methods to accomplish this is the addition of thiophenol in a Markovnikoff or anti-Markovnikoff manner (1) to the allylation products of ketones and enones, followed by acetal or thioacetal formation or (2) to ε-allylacetals or thioacetals. Primary and tertiary organolithiums are generated in this way and the protected ketone function can be a part of a ring.

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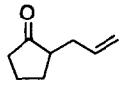
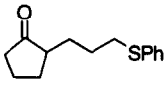
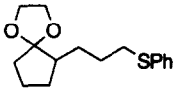
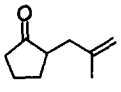
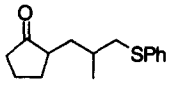
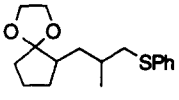
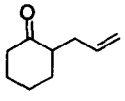
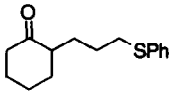
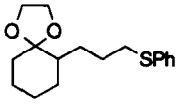
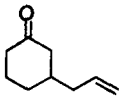
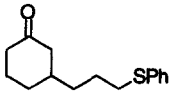
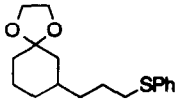
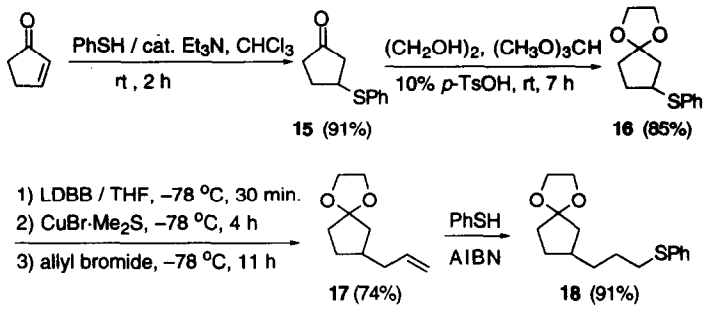
RESULTS AND DISCUSSION

Preparation of Carbonyl-Protected δ- and ε-(Phenylthio)ketones

In most cases, the δ- and ε-(phenylthio)acetals were prepared by the radical addition[7] of thiophenol to the alkene linkage of an allylated ketone, followed by acetal formation (Table 1). The allylations were performed on suitable enolate derivatives of the ketone, using an allylic halide, or on a conjugated enone, using allyltrimethylsilane under acid catalysis. Thus, 2-allylcyclopentanone (**3**) and 2-methallylcyclopentanone (**6**) were prepared by direct allylation, using allyl bromide or methallyl bromide, of the lithium enolate of cyclopentanone in the presence of cuprous cyanide.[8] 2-Allylcyclohexanone (**9**) was prepared by allylation of cyclohexanone with allyl bromide via the potassium enoxytrialkylborate.[9] 3-Allylcyclohexanone (**12**) was prepared by conjugate addition of allyltrimethylsilane to 2-cyclohexen-1-one in the presence of $TiCl_4$.[10,11] Unfortunately, this procedure was unsuccessful for the preparation of 3-allylcyclopentanone. In this case, the ketal (**18**) of an ε-(phenylthio)ketone was prepared by radical addition of thiophenol to the alkene - acetal **17**. The latter was in turn prepared by the attack of allyl bromide on the cuprate derived from the lithium homoenolate equivalent[3] prepared by reductive lithiation of **16** using lithium 4,4'-di-*tert*-butylbiphenylide (LDBB)[12] (Scheme 1).

Table 1. Radical Addition of PhSH to Ketoalkenes and Formation of Acetals

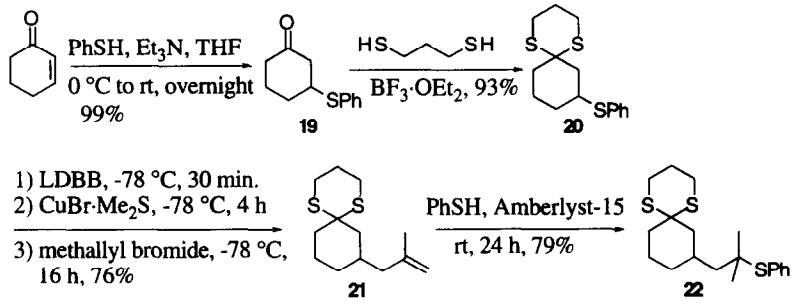
α-Olefins	Product	Yields	Product	% Yields
 **3**	 **4**	96%	 **5**	97%
 **6**	 **7**	84% (1:1)	 **8**	97% (1:1)
 **9**	 **10**	96%	 **11**	98%
 **12**	 **13**	98%	 **14**	84%



Scheme 1

The yields in the addition of thiophenol to the alkenes in the presence of the radical initiator 2,2'-azobis(2-methylpropionitrile) (AIBN), whether in a molecule bearing a ketone (Table 1) or an acetal (Scheme 1) function, were good to excellent as were the yields in the protection of the ketones to acetals.

In order to demonstrate that tertiary as well as primary organolithiums could be generated at the δ-position to a protected ketone function, we took advantage of the acid-induced Markovnikoff addition to an alkene. Since it was assumed that acid catalyzed addition of thiophenol to 3-methallylcyclohexanone would lead to phenyl thioacetal formation as well as addition to the alkene, thiophenol was added instead to the carbonyl protected alkene **21**. The protecting group would have to be a thioacetal since an acetal would react with the thiophenol under acidic addition to yield the phenyl thioacetal that would undergo reductive lithiation in the subsequent production of the organolithium. The procedure for the preparation of the reductive lithiation substrate **22** is shown in Scheme 2.

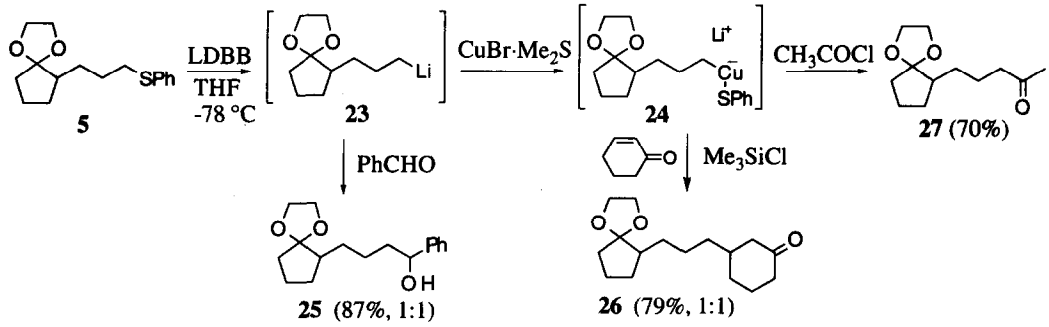


Scheme 2

The high yields and great ease of production of these varied reductive lithiation substrates provides a convincing demonstration of the value of using phenyl thioethers as precursors to organolithium compounds.

Reductive Lithiation of Carbonyl-Protected δ- and ε-(Phenylthio)ketones

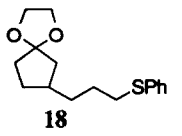
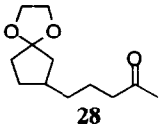
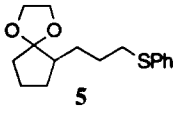
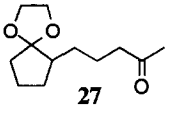
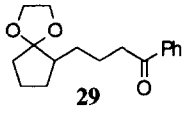
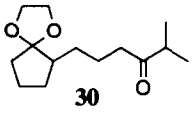
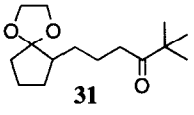
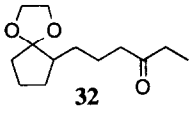
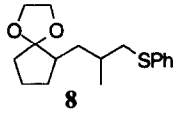
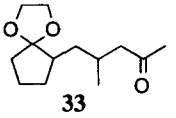
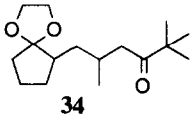
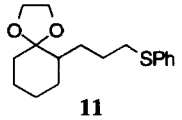
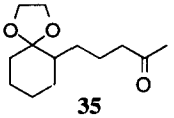
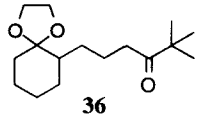
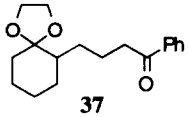
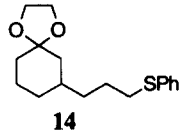
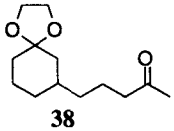
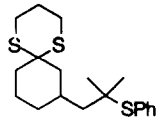
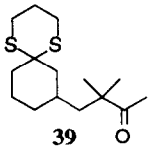
Reductive lithiation of the carbonyl-protected δ- and ε-(phenylthio)ketones with LDBB provided the carbonyl-protected δ- and ε-lithioketones. Scheme 3 outlines some of the exemplary reactions undergone by **23**, the reductive lithiation product of **5**. The addition of benzaldehyde to the organolithium **23** provides the acetal alcohol **25** in 87% yield. The mixed heterocuprates (e.g. **24**), containing thiophenoxide ion, obtained by treatment of the carbonyl-protected δ- and ε-lithioketones with $CuBr•Me_2S$ are particularly useful synthetically. For example, conjugate addition of **24** to 2-cyclohexen-1-one occurs readily to yield a mono-protected 1,8-diketone, **26**. Acetylation with acetyl chloride yields the monoprotected 1,6-diketone **27** in good yield.



Scheme 3

In order to demonstrate the generality of this type of procedure, most of the other phenyl thioacetals were converted to organolithiums in the same way and the derived heterocuprates were acylated by several acyl chlorides. The results are displayed in Table 2. In general, the yields were moderate for these unoptimized reactions. The results in Scheme 3 suggest that the yields would be better for direct capture by an aldehyde but the cuprates are particularly versatile. Reductive lithiation differs sharply from conventional methods of carbanion production, the removal of a proton or other electrophile with a strong base, in that the less stable the carbanion the more readily it is produced, a consequence of the rate determining production of a radical intermediate. As a result, very unstable tertiary carbanions are generated instantaneously at -78 °C and they can be captured by an electrophile before decomposition occurs. An example is shown in Table 2 for reduction of **22** and acylation of the resulting tertiary organocuprate; this is one of a large number of tertiary carbanions that have been generated by reductive lithiation of phenyl thioethers and used successfully in synthesis.[2-4,13] The resulting monoprotected 1,6- and 1,7-diketones, and their analogues generated from other phenylthio-substituted acetals and other acyl halides, should be of considerable use in synthesis as should the monoprotected diketones with still greater separation of the two functions (e.g. **26**) generated by conjugate addition of the cuprates to enones.

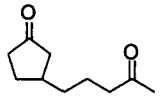
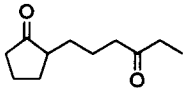
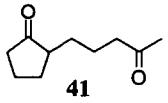
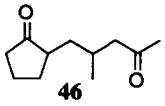
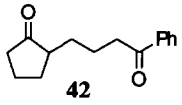
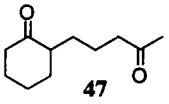
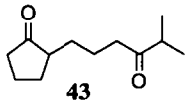
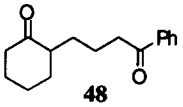
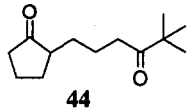
Table 2. Results of Acylation of Lithio Acetals and Thioacetals

Phenylthio Ethers	Products of Reductive Lithiation and Electrophile Capture (Yield)
 **18**	 (55%) **28**
 **5**	 (70%) **27**;  (59%) **29**;  (73%) **30**
	 (52%) **31**;  (71%)[a] **32**
 **8**	 (70%) (1:1) **33**;  (52%) (1:1) **34**
 **11**	 (68%) **35**;  (66%) **36**;  (70%) **37**
 **14**	 (67%) **38**
 **22**	 (68%) **39**

[a] Total yield of **32** (50%) and the diketone **45** (21%). Some hydrolysis occurred during workup.

The mono-protected diketones are versatile intermediates in that the unprotected carbonyl group can be manipulated before deprotection of the other one, or the diketones can be generated by ready hydrolysis in high yield performed by mixing them with acetone, water and Amberlyst-15[14] and stirring the mixture at room temperature for about 1 hour. The results of the hydrolyses of a number of the acetals are presented in Table 3.

Table 3. Results of the Hydrolyses of Acetals and Thioacetals

Products	Yield	Products	Yield
 **40**	96%	 **45**	97%
 **41**	96%	 **46**	90% (1:1)
 **42**	96%	 **47**	96%
 **43**	99%	 **48**	95%
 **44**	96%		

Our method for preparing 1,6-diketones represents a substantial improvement over methods in the literature. For example, the reported syntheses of **41** and **42** involve a long series of reactions in which the yields and the method of preparation of starting materials were not reported,[15] whereas the syntheses reported here proceed in yields of 37% and 31%, respectively, in 5 steps from commercial materials. The reported synthesis of **45** involves 8 steps from commercial materials; while the yields in all the steps are not specified, the yield of a close analogue, prepared by the same series of reactions, was 2%;[16] the overall yield of the 5-step synthesis of **45** reported here is 33%.

CONCLUSIONS

It is shown in the present paper that a wide variety of carbonyl-protected δ- and ε-lithioketones can be generated by reductive lithiation of carbonyl-protected δ- and ε-(phenylthio)ketones which are easily prepared by the addition of thiophenol to the alkene linkage of unsaturated ketones. Not only can primary and tertiary organolithiums be generated in this way but the protected carbonyl function can be in a ring. Some of these species have been previously inaccessible. These organolithiums and the derived mixed hetero cuprates are capable of reaction with a wide variety of electrophiles. This technology should find wide use in organic synthesis.

EXPERIMENTAL SECTION

All reactions were carried out in flame- or oven-dried glassware under an atmosphere of prepurified Ar. All solvents were dried by using standard procedures and were distilled freshly. A dry ice / acetone slush bath was used to obtain a temperature of –78 °C and an ice bath was used to obtain 0 °C. When a temperature of –78 °C was needed for an extended period of time, an FTS Systems, Inc Model TC-10 Flexicool probe was used. Infrared spectra were recorded using an IBM IR / 32 or Mattson Cygnus 100 FTIR spectrometer. ^{1}H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded either on a Brucker WH-300 or a Brucker AF-300 spectrometer. Chemical shift data are reported in units of δ (ppm) relative to solvents ($CDCl_3$ δ 7.27 or C_6D_6 δ 7.15 for ^{1}H NMR and $CDCl_3$ δ 77.09 or C_6D_6 δ 125.00 for ^{13}C NMR) as internal standards. ^{1}H NMR data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant, integration and assignment. ^{13}C spectra are not reported for several mixtures of diastereomers; the spectra are not very informative since they have many overlapping and coincident peaks. High resolution EI or CI mass spectra were recorded on a CH-5 double focusing Varian Mat mass spectrometer or on a VG 70-6 mass spectrometer. Exact mass values determined by high resolution mass spectrometry were considered satisfactory if there are no other structures within 35 ppm which are consistent with the method of preparation or the spectral data. Thin layer chromatograms were developed on glass supported 250 μm silica gel GF plates (Analtech). TLC plates were visualized using 7% phosphomolybdic acid in ethanol or 5% *p*-anisaldehyde in ethanol. Flash Chromatography was performed using 40–63 μm silica gel 60 (Merck). Capillary gas liquid chromatographic analyses were performed on a Hewlett-Packard 5890 gas chromatograph utilizing a 0.20 mm fused silica capillary column (Carbowax 20M) and a flame ionization detector. Except when otherwise stated, all chromatographed samples were pure by NMR and/or mass spectrometry.

Formation of Lithium 4,4'-di-*tert*-butylbiphenylide (LDBB). A typical experiment is described. To a flame-dried three necked flask, equipped with a glass-coated stirring bar, rubber septum and Ar inlet, were added 4,4'-di-*tert*-butylbiphenyl (DBB; 1.604 g, 6.02 mmol) and 20 mL of THF. Lithium ribbon was prepared by scraping the dark oxide coating off of the surface while it was immersed in mineral oil. The shiny metal was dipped in hexanes in order to remove the oil and then weighed (49.5 mg, 7.13 mmol) in a tared beaker containing mineral oil. The metal was sliced into small pieces while it was still immersed in mineral oil. The lithium pieces were dipped again in hexanes prior to addition to the mixture of THF and DBB, while the flask was rapidly being purged with Ar. The reaction mixture was stirred at room temperature for about 5 min until a dark-blue color appeared on the lithium surface, and then it was cooled to 0 °C and stirred for 4 to 5 h. The resulting dark-blue LDBB solution (6.02 mmol, 0.30 M) was ready for use in reductive lithiation (~3 mmol scale). It appears to lose a few percent of its reactivity per week when stored in a freezer at -20 °C in the absence of air and moisture. It was usually prepared fresh for each experiment. The actual amount of LDBB is usually less than that indicated due to impurities on the lithium ribbon and the decomposition of LDBB. In experiments in which LDBB solutions were used, a solution of phenylthio ether (amount known) in ~9 mL of THF was added dropwise to the LDBB solution until the color of the solution changed from blue-green to yellow-red. The amount of the phenylthio ether used was calculated from the amount of the solution added.

2-(3-(Phenylthio)propyl)cyclopentanone (4). A mixture of 0.593 g (4.77 mmol) of 2-allylcyclo-pentanone (**3**),[8] 91.0 mg (0.550 mmol) of AIBN, and 2.0 mL (20 mmol) of thiophenol was heated, under Ar at 86–92 °C for 5 h. After being cooled, the mixture was diluted with ether, washed with 1 N NaOH solution and water, and dried over Na_2SO_4. The solvent was removed by rotary evaporation. The crude

product was purified by flash chromatography (10% ethyl acetate / hexanes, R_f 0.20) yielding 1.07 g (96%) of **4**. ^{1}H NMR ($CDCl_3$) δ 7.33–7.13 (m, 5 H, arom.), 2.99–2.83 (m, 2 H, CH_2S), 2.30–1.33 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 220.9, 136.6, 129.0, 128.9, 125.8, 48.7, 38.0, 33.5, 29.6, 28.9, 27.2, 20.7; IR (neat, NaCl) 3056 (m), 2959 (s), 2863 (s), 1736 (s), 1154 (m), 741 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 234 (95, M^+), 125 (90), 110 (100), 55 (90); exact mass calculated for $C_{14}H_{18}OS$ 234.1078, found 234.1075.

6-(3-(Phenylthio)propyl)-1,4-dioxaspiro[4.4]nonane (5). A mixture of 1.04 g (4.43 mmol) of 2 (3-(phenylthio)propyl)cyclopentanone (**4**), 1.7 mL (31 mmol) of ethylene glycol, 1.4 mL (13 mmol) of trimethyl orthoformate and 90.0 mg (0.47 mmol) of *p*-toluenesulfonic acid was stirred at room temperature for 6 h. The reaction mixture was diluted with ether and washed with a saturated solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The crude oily product was purified by flash chromatography (5% ethyl acetate / hexanes, R_f 0.17) to yield 1.20 g (97%) of **5**. ^{1}H NMR ($CDCl_3$) δ 7.32–7.09 (m, 5 H, arom.), 3.89–3.78 (m, 4 H, OCH_2CH_2O), 2.92–2.85 (m, 2 H, H_2CS), 1.91–1.80 (m, 2 H), 1.75–1.54 (m, 7 H), 1.36–1.24 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 136.9, 128.8, 125.6, 118.0, 64.5, 64.4, 45.6, 35.7, 33.7, 29.4, 28.2, 27.9, 20.6; IR (neat, NaCl) 3058 (m), 2948 (s), 2874 (m), 1584 (m), 1480 (m), 1028 (m), 739 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 278 (45, M^+), 99 (100); exact mass calculated for $C_{16}H_{22}O_2S$ 278.1341, found 278.1332.

2-Methallylcyclopentanone[17] **(6).** The procedure used by Posner and Lentz[8] to prepare 2-allylcyclopentanone (**3**) was used. To 5.0 mL (36 mmol) of diisopropylamine in 7.5 mL of dry THF under Ar at –78 °C was added 22.5 mL of 1.6 M *n*-butyllithium (36 mmol). Cyclopentanone (2.65 mL, 29.8 mmol) in 17.5 mL of THF was added to the lithium diisopropylamide dropwise over 1 h. The solution was allowed to stir for another 2 h, at which time CuCN (270 mg, 3.02 mmol) and 5.15 mL of HMPA (29.7 mmol) in 2.5 mL of THF were added. After 1 h, 6.61 mL (65.5 mmol) of methallyl bromide and 400 mg of lithium iodide dissolved in 1 mL of THF were added. The reaction mixture was allowed to stir at –78 °C for 7 h, the reaction was quenched with solid ammonium chloride, and the mixture was allowed to warm slowly to 25 °C and to stir overnight. Water (20 mL) was added. The organic layer was dried over $MgSO_4$ and the solvents were removed by rotary evaporation. The crude product was distilled under aspirator pressure to give 3.42 g (83%) of crude 2-methallylcyclopentanone. The product was purified by flash chromatography (5% ethyl acetate / hexanes) yielding 1.94 g (47%) of **6**. ^{1}H NMR ($CDCl_3$) δ 4.76 (s, 1 H, C=C*H*H), 4.70 (s, 1 H, C=CH*H*), 2.55–2.50 (m, 1 H, ring CH), 2.37–1.78 (m, 8 H, ring CH_2, CH_2), 1.71 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 220.8, 143.4, 111.6, 47.3, 38.0 (two carbons), 29.3, 22.0, 20.5; IR (neat, NaCl) 3075 (m), 2965 (s), 2878 (s), 1738 (s), 1649 (m) cm^{-1}.

2-(2-Methyl-3-(phenylthio)propyl)cyclopentanone (7). A mixture of 0.148 g (1.07 mmol) of 2-methallylcyclopentanone (**6**), 34.2 mg (0.208 mmol) of AIBN, and 0.44 mL (4.3 mmol) of thiophenol was heated, under Ar, at 88–96 °C for 2.5 h. Another 30.6 mg of AIBN was added and the mixture was heated under the same conditions for another 2.5 h. After it had cooled, the mixture was diluted with ether, washed with 1 N NaOH solution and water, and dried over Na_2SO_4. The solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (10% ethyl acetate / hexanes, R_f 0.21) yielding 0.224 g (84%) a 1:1 mixture of two diastereomers. ^{1}H NMR ($CDCl_3$) δ 7.35–7.14 (m, 5 H, arom.), 3.02–2.67 (m, 2 H, CH_2S), 2.40–1.40 (m, 10 H), 1.08–1.01 (2 doublets, 3 H, CH_3); IR (neat, NaCl) 3055.6 (w), 2959.2

(s), 2924 (m), 2872 (m), 1736 (s), 1584 (w), 741 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 248 (50, M^+), 139 (55), 110 (100), 55 (65); exact mass calculated for $C_{15}H_{20}OS$ 248.1235, found 248.1248.

6-(2-Methyl-3-(phenylthio)propyl)-1,4-dioxaspiro[4.4]nonane (8). A mixture of 1.83 g (7.38 mmol) of 2-(2-methyl-3-(phenylthio)propyl)cyclopentanone (**7**), 3.0 mL (54 mmol) of ethylene glycol, 2.60 mL (23.8 mmol) of trimethyl orthoformate and 160 mg (0.84 mmol) of *p*-toluenesulfonic acid was stirred at room temperature for 10 h. The reaction mixture was diluted with ether and washed with a saturated solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The crude oily product was purified by flash chromatography (5% ethyl acetate / hexanes, R_f 0.19) to yield 2.09 g (97%) of a 1:1 mixture of two diastereomers. ^1H NMR ($CDCl_3$) δ 7.33–7.11 (m, 5 H, arom.), 3.92–3.79 (m, 4 H, OCH_2CH_2O), 3.03–2.62 (m, 2 H, H_2CS), 2.04–1.21 (m, 10 H), 1.07–1.00 (2 doublets, J = 6.6, 3 H, CH_3); IR (neat, NaCl) 2901 (s), 1572 (m), 1428 (m), 1196 (m), 1092 (s), 1024 (s), 733 (s), 687 (s) cm^{-1}; mass spectrum, *m / e* (relative intensity), 292 (37, M^+), 183 (100), 141 (45), 99 (83); exact mass calculated for $C_{17}H_{24}O_2S$ 292.1497, found 292.1500.

2-(3-(Phenylthio)propyl)cyclohexanone (10). A mixture of 0.766 g (5.55 mmol) of 2-allylcyclo-hexanone (**9**),[9] 98.8 mg (0.600 mmol) of AIBN, and 4.0 mL (39 mmol) of thiophenol was heated, under Ar, at 80–90 °C for 3 h. After it had cooled, the mixture was diluted with ether, washed with 1 N NaOH solution and water, and dried over Na_2SO_4. The solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (10% ethyl acetate / hexanes, R_f 0.27) yielding 1.33 g (96%) of **10**. ^1H NMR ($CDCl_3$) δ 7.30–7.09 (m, 5 H, arom.), 2.95–2.80 (m, 2 H, CH_2S), 2.38–2.18 (m, 3 H, CH_2COCH), 2.07–1.98 (m, 2 H), 1.88–1.78 (m, 2 H), 1.66–1.56 (m, 4 H), 1.37–1.27 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 212.9, 136.7, 128.8, 125.6, 50.2, 42.0, 33.9, 33.5, 28.6, 27.9, 26.7, 24.9; IR (neat, NaCl) 3056 (m), 2934 (s), 2860 (m), 1709 (s), 1584 (w), 1481 (m), 739 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 248 (40, M^+), 139 (100), 110 (45).

6-(3-(Phenylthio)propyl)-1,4-dioxaspiro[4.5]decane (11). A mixture of 1.10 g (4.44 mmol) of 2-(3-(phenylthio)propyl)cyclohexanone (**10**), 1.9 mL (34 mmol) of ethylene glycol, 1.5 mL (14 mmol) of trimethyl orthoformate and 110 mg (0.578 mmol) of *p*-toluenesulfonic acid was stirred at room temperature for 23 h. The reaction mixture was diluted with ethyl ether and washed with saturated solution of $NaHCO_3$. The organic layer was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The crude oily product was purified by flash chromatography (10% ethyl acetate / hexanes, R_f 0.32) to yield 1.267 g (98%) of the product. ^1H NMR ($CDCl_3$) δ 7.33–7.12 (m, 5 H, arom.), 3.98–3.85 (m, 4 H, OCH_2CH_2O), 2.98–2.82 (m, 2 H, H_2CS), 1.77–1.17 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 137.0, 128.8, 125.6, 110.7, 64.8, 64.7, 44.3, 34.7, 33.9, 29.1, 27.6, 27.3, 24.6, 23.8; IR (neat, NaCl) 3058 (w), 2935 (s), 2863 (m), 1584 (w), 1481 (m), 1089 (m), 738 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 292 (100, M^+), 183 (50), 99 (80); exact mass calculated for $C_{17}H_{24}O_2S$ 292.1497, found 292.1503.

3-(3-(Phenylthio)propyl)cyclohexanone (13). A mixture of 0.697 g (5.04 mmol) of 3-allylcyclo-hexanone (**12**),[10] 95.1 mg (0.579 mmol) of AIBN, and 4.0 mL (39 mmol) of thiophenol was heated, under Ar at 80–90 °C for 5 h. After it had cooled, the mixture was diluted with ether, washed with 1 N NaOH solution and water, and dried over Na_2SO_4. The solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (10% ethyl acetate / hexanes, R_f 0.14) yielding 1.23 g (98%) of the product. ^1H NMR ($CDCl_3$) δ 7.34–7.14 (m, 5 H, arom.), 2.90 (t, J = 7.1 Hz, 2 H, CH_2S), 2.42–2.23 (m, 4 H, CH_2COCH_2), 2.06–1.25 (m, 9 H); IR (neat, NaCl) 2915 (s), 1698 (s), 1570 (m), 1470

(m), 1431 (m), 735 (m), 687 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 248 (75, M^+), 123 (63), 110 (100), 97 (97), 69 (90); exact mass calculated for $C_{15}H_{20}OS$ 248.1235, found 248.1253.

7-(3-(Phenylthio)propyl)-1,4-dioxaspiro[4.5]decane (14). A mixture of 1.17 g (4.69 mmol) of 3-(3-(phenylthio)propyl)cyclohexanone (**13**), 1.9 mL (34 mmol) of ethylene glycol, 1.5 mL (14 mmol) of trimethyl orthoformate and 97 mg (0.51 mmol) of *p*-toluenesulfonic acid was stirred at room temperature for 5 h. The reaction mixture was diluted with ethyl ether and washed with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The crude oily product was purified by flash chromatography (10% ethyl acetate / hexanes, R_f 0.19) to yield 1.16 g (84%) of the product. ^1H NMR ($CDCl_3$) δ 7.32–7.15 (m, 5 H, arom.), 3.91 (m, 4 H, OCH_2CH_2O), 2.89 (t, J = 7.4 Hz, 2 H, H_2CS), 1.75–1.11 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 136.8, 128.8, 125.6, 109.2, 64.2, 64.1, 41.6, 36.0, 35.1, 34.8, 33.6, 31.6, 26.4, 23.1; IR (neat, NaCl) 3054 (w), 2928 (s), 1582 (m), 1478 (m), 1075 (s), 739 (s) cm^{-1}; mass spectrum, *m / e* (relative intensity), 292 (32, M^+), 183 (95), 141 (100), 99 (95); exact mass calculated for $C_{17}H_{24}O_2S$ 292.1497, found 292.1464.

7-Phenylthio-1,4-dioxaspiro[4.4]nonane[18] (16). A mixture of 0.680 g (3.54 mmol) of 3-(phenylthio)cyclopentanone[19] (**15**), 1.4 mL (25 mmol) of ethylene glycol, 1.2 mL (11 mmol) of trimethyl orthoformate and 0.066 g (0.350 mmol) of *p*-toluenesulfonic acid was stirred at room temperature for 19 h. The reaction mixture was diluted with ethyl ether and washed with saturated $NaHCO_3$. The organic layer was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The crude oily product was purified by flash chromatography (10% ethyl acetate / hexanes, R_f 0.22) to yield 0.710 g (85%) of 7-phenylthio-1,4-dioxaspiro[4.4]nonane (**16**). ^1H NMR ($CDCl_3$) δ 7.37–7.15 (m, 5 H, arom.), 3.86 (s, 4 H, OCH_2CH_2O), 3.65 (m, 1 H, HCS), 2.33–1.68 (m, 6 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 135.9, 130.4, 128.8, 126.3, 116.7, 64.4, 64.1, 43.5, 43.2, 35.3, 31.1; IR (neat, NaCl) 2952 (m), 2867 (m), 1572 (m), 1325 (s), 1107 (s), 1015 (s) cm^{-1}.

7-Allyl-1,4-dioxaspiro[4.4]nonane (17). A solution of 1.16 g (4.92 mmol) of 7-phenylthio-1,4-dioxaspiro[4.4]nonane (**16**) in 8 mL of THF was added dropwise via a syringe to a solution of LDBB (12.1 mmol, 0.40 M), prepared as above, at –78 °C. The reaction mixture, which changed from blue-green to yellow-red, was stirred for 30 min, and then was transferred via a double-ended needle to another flask containing 1.52 g (7.41 mmol) of CuBr•Me_2S. The resulting mixture was stirred for 4 h at –78 °C. A solution of 0.9 mL (10 mmol) of allyl bromide in 4 mL of THF was added dropwise. The resulting mixture was stirred for 11 h at –78 °C and quenched with 30 mL of saturated ammonium chloride solution; the mixture was filtered through celite and extracted with ethyl ether (4 × 75 mL). The organic layer was dried over $MgSO_4$ and the solvent removed by rotary evaporation. The crude product was purified by flash chromatography (5% ethyl acetate /hexanes, R_f 0.19) yielding 0.615 g (74%) of **17**. ^1H NMR ($CDCl_3$) δ 5.85–5.71 (m, 1 H, =CH), 5.05–4.96 (m, 2 H, $=CH_2$), 3.95–3.85 (m, 4 H, OCH_2CH_2O), 2.12–1.22 (m, 9 H); ^{13}C NMR ($CDCl_3$) δ 137.3, 117.7, 115.2, 64.1, 63.9, 42.2, 39.9, 37.1, 35.8, 29.8; IR (neat, NaCl) 3073 (m), 2961 (s), 2880 (s), 1119 (m) cm^{-1}.

7-(3-(Phenylthio)propyl)-1,4-dioxaspiro[4.4]nonane (18). A mixture of 0.605 g (3.60 mmol) of 7-allyl-1,4-dioxaspiro[4.4]nonane (**17**), 60.6 mg (0.369 mmol) of AIBN, and 1.5 mL (15 mmol) of thiophenol was heated, under Ar, at 88 °C for 6 h. After being cooled, the mixture was diluted with ether, washed with 1 N NaOH solution and water, and dried over Na_2SO_4. The solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (5% ethyl acetate / hexanes, R_f 0.09)

yielding 0.906 g (91%) of **18**. ^{1}H NMR ($CDCl_3$) δ 7.31–7.12 (m, 5 H, arom.), 3.89–3.81 (m, 4 H, OCH_2CH_2O), 2.89 (t, J = 7.2 Hz, 2 H, CH_2S), 1.98–1.19 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 136.8, 128.9, 125.7, 117.8, 64.3, 64.1, 42.8, 37.4, 36.0, 35.1, 33.6, 30.3, 27.8; IR (neat, NaCl) 2948 (s), 2861 (s), 1451 (m), 1063 (s), 907 (s) cm^{-1}; mass spectrum, *m / e* (relative intensity), 278 (20, M$^+$), 169 (41), 127 (83), 99 (100); exact mass calculated for $C_{16}H_{22}O_2S$ 278.1341, found 278.1359.

3-(Phenylthio)cyclohexanone (19).[3] To a solution of 2.8 mL (29 mmol) of 2-cyclohexen-1-one and 3.0 mL (29 mmol) of thiophenol in 6 mL of THF at 0 °C was added 0.12 mL (0.86 mmol) of triethylamine. The cooling bath was removed, and the solution was stirred at room temperature for 12 h, diluted with ether, and washed with 5% aqueous NaOH, H_2O, and saturated NaCl solution. After the mixture was dried over Na_2SO_4, the solvent was removed to give 5.92 g (99%) of 3-(phenylthio)cyclohexanone (**19**). ^{1}H NMR ($CDCl_3$) δ 7.45–7.26 (m, 5 H, arom.), 3.46–3.38 (m, 1 H, HCS), 2.72–2.66 (dd, J_1 = 14.3, J_2 = 4.5, 1 H), 2.42–2.09 (m, 5 H), 1.81–1.62 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 208.5, 133.0, 132.9, 128.9, 127.6, 47.6, 45.9, 40.7, 31.0, 23.8; IR (neat, NaCl) 3033 (m), 2919 (s), 1700 (s), 741 (s) cm^{-1}.

8-(Phenylthio)-1,5-dithiaspiro[5.5]undecane (20). To a mixture of 4.5 mL (45 mmol) of propane-1,3-dithiol and 5.35 g (25.9 mmol) of 3-(phenylthio)cyclohexanone (**19**) was added dropwise 4.8 mL (39 mmol) of $BF_3{\cdot}OEt_2$. The reaction mixture was stirred at room temperature for 30 min, diluted with ether and washed with 1 N NaOH solution. The aqueous phase was extracted with ether (2 × 30 mL). The combined ether extract was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The product was purified by flash chromatography (5% EtOAc / hexanes, R_f 0.28) yielding 7.18 g (93%) of **20**. ^{1}H NMR ($CDCl_3$) δ 7.42–7.19 (m, 5 H, arom.), 3.54–3.48 (m, 1 H, CHSPh), 2.91–2.67 (m, 5 H), 2.20–1.58 (m, 8 H), 1.31–1.25 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 134.2, 131.6, 128.9, 126.8, 50.2, 43.7, 41.8, 37.4, 32.7, 26.1, 25.8, 25.7, 22.0; IR (neat, NaCl) 3036 (m), 2905 (s), 1568 (m), 1464 (s), 1426 (s), 731 (s) cm^{-1}; mass spectrum, *m / e* (relative intensity), 296 (83, M$^+$), 187 (100), 113 (60), 79 (34); exact mass calculated for $C_{15}H_{20}S_3$ 296.0727, found 296.0724.

8-Methallyl-1,5-dithiaspiro[5.5]undecane (21). A solution of 0.968 g (3.26 mmol) of 8-(phenylthio)-1,5-dithiaspiro[5.5]undecane (**20**) in 9 mL of THF was added dropwise via a syringe to a solution of LDBB (6.53 mmol, 0.327 M) at –78 °C. The reaction mixture, which changed from blue-green to yellow-red, was stirred for 30 min, and then was transferred via a double-ended needle to another flask containing 1.03 g (5.01 mmol) of $CuBr{\bullet}Me_2S$. The resulting mixture was stirred for 4 h at –78 °C. A solution of 0.50 mL (5.0 mmol) of methallyl bromide in 4 mL of THF was added dropwise. The resulting mixture was stirred for 16 h at –78 °C and the reaction was quenched with 30 mL of saturated ammonium chloride solution; the mixture was filtered through celite and extracted with ethyl ether (4 × 60 mL). The organic layer was dried over $MgSO_4$ and the solvent removed by rotary evaporation. The crude product was purified by flash chromatography (3% ethyl acetate /hexanes, R_f 0.41) yielding 0.60 g (76%) of **21**. ^{1}H NMR ($CDCl_3$) δ 4.74 (s, 1 H, =C*H*H), 4.66 (s, 1 H, =CH*H*), 2.90–2.71 (m, 4 H), 2.33 (d, J = 13.4, 2 H, allylic CH_2), 2.01–1.85 (m, 6 H), 1.70 (s, 3 H, CH_3), 1.77–1.55 (m, 4 H), 1.26–1.15 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 143.4, 111.7, 50.3, 45.3, 43.9, 37.7, 32.8, 30.4, 26.0, 25.7, 25.6, 22.2, 22.0; IR (neat, NaCl) 3050 (m), 2905 (s), 1636 (m), 1431 (s) cm^{-1}; mass spectrum, *m / e* (relative intensity), 242 (70, M$^+$), 187 (100), 135 (72), 113 (92), 79 (80); exact mass calculated for $C_{13}H_{22}S_2$ 242.1163, found 242.1159.

8-(2-Methyl-2-(phenylthio)propyl)-1,5-dithiaspiro[5.5]undecane (22). A mixture of 0.597 g (2.46 mmol) of 8-methallyl-1,5-dithiaspiro[5.5]undecane (**21**), 3.0 mL (29 mmol) of thiophenol and

300 mg of Amberlyst-15 was stirred at room temperature for 24 h. The reaction mixture was diluted with ether and the Amberlyst-15 was removed by filtration. The mixture was washed with 1 N NaOH solution, water, and brine and dried over $MgSO_4$. The solvent was removed by rotary evaporation and the crude product was purified by flash chromatography (5% EtOAc / hexanes, R_f 0.29) yielding 0.685 g (79%) of **22.** ^1H NMR ($CDCl_3$) δ 7.53–7.51 (m, 2 H, arom.), 7.33–7.28 (m, 3 H, arom.), 2.88–2.85 (m, 2 H), 2.76 (m, 2 H), 2.48 (m, 1 H), 2.30 (m, 1 H), 2.12–2.07 (m, 1 H), 1.97 (m, 2 H), 1.80 (m, 2 H), 1.59–1.30 (m, 5 H), 1.25 (s, 6 H, CH_3), 1.03–0.94 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 137.5, 132.1, 128.6, 128.4, 50.6, 49.6, 49.2, 46.1, 37.3, 34.9, 29.8, 29.4, 29.2, 26.1, 25.8, 22.2; IR (neat, NaCl) 3056 (m), 2929 (s), 1423 (m), 1133 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 352 (42, M^+), 242 (65), 135 (100), 95 (50); exact mass calculated for $C_{19}H_{28}S_3$ 352.1353, found 352.1370.

6-(4-Hydroxyl-4-phenylbutyl)-1,4-dioxaspiro[4.4]nonane (25). A solution of 0.496 g (1.78 mmol) of 6-(3-(phenylthio)propyl)-1,4-dioxaspiro[4.4]nonane (**5**) in 4 mL of THF was added dropwise via a syringe to a solution of LDBB (6.0 mmol, 0.30 M) at –78 °C. The reaction mixture, which changed from blue-green to yellow-red, was stirred for 30 min, and then 0.36 mL (3.5 mmol) of benzaldehyde was added dropwise. The resulting mixture was stirred at –78 °C for 30 min and the reaction was quenched with 10 mL of water; the mixture was allowed to warm slowly to room temperature and extracted with ether (4 × 75 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was purified by flash chromatography (30% ethyl acetate /hexanes, R_f 0.28) yielding 0.427 g (87%) of a 1:1 mixture of two diastereomers. ^1H NMR ($CDCl_3$) δ 7.33–7.22 (m, 5 H, arom.), 4.67–4.61 (m, 1 H, PhC*H*), 3.84 (m, 4 H, OCH_2CH_2O), 2.20 (s, 1 H, OH), 1.85–1.17 (m, 13 H); IR (neat, NaCl) 3449 (s), 3063 (w), 3029 (w), 2940 (s), 2872 (s), 1105 (m), 1030 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 276 (10, M^+), 120 (32), 99 (100), 79 (31); exact mass calculated for $C_{17}H_{24}O_3$ 276.1725, found 276.1717.

6-(3-(3-Oxocyclohexyl)propyl)-1,4-dioxaspiro[4.4]nonane (26). A solution of 0.338 g (1.21 mmol) of 6-(3-(phenylthio)propyl)-1,4-dioxaspiro[4.4]nonane (**5**) in 5 mL of THF was added dropwise via syringe to a solution of LDBB (3.10 mmol, 0.26 M) at –78 °C. The mixture, which changed from blue-green to yellow-red, was stirred for 30 min, and then 0.408 g (1.99 mmol) of CuBr•Me_2S was added. The resulting mixture was stirred at –78 °C for 3 h, and a solution of 0.25 mL (2.0 mmol) of TMSCl in 2 mL of THF was added, followed by dropwise addition of a solution of 0.15 mL (1.6 mmol) of 2-cyclohexen-1-one in 4 mL of THF. The resulting mixture was stirred at –78 °C for 12 h and the reaction was quenched with 10 mL of 5% NaOH and 40% aqueous *n*-Bu_4NOH (10 drops); the mixture was filtered through celite and extracted with ether (4 × 75 mL). The organic layer was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude product was subjected to flash chromatography (20% ethyl acetate / hexanes, R_f 0.27) yielding 0.254 g (79%) of a 1:1 mixture of two diastereomers containing a trace of persistent impurity. ^1H NMR ($CDCl_3$) δ 3.89 (m, 4 H, OCH_2CH_2O), 2.42–2.20 (m, 4 H, CH_2COCH_2), 2.05–1.17 (m, 18 H); IR (neat, NaCl) 2919 (s), 1670 (s), 1103 (m), 727 (s) cm^{-1}; mass spectrum, *m / e* (relative intensity), 266 (36, M^+), 155 (27), 99 (100), 55 (26); exact mass calculated for $C_{16}H_{26}O_3$ 266.1882, found 266.1882.

6-(4-Oxopentyl)-1,4-dioxaspiro[4.4]nonane (27). A solution of 0.547 g (1.96 mmol) of 6-(3-(phenylthio)propyl)-1,4-dioxaspiro[4.4]nonane (**5**) in 6 mL of THF was added dropwise via a syringe to a solution of LDBB (6.0 mmol, 0.30 M), prepared as above, at –78 °C. The reaction mixture, which changed from blue-green to yellow-red, was stirred for 30 min, and then 0.550 g (2.68 mmol) of CuBr•Me_2S was added. The resulting mixture was stirred at –78 °C for 4 h and a solution of 0.200 g (2.55 mmol) of acetyl

chloride in 4 mL of THF was added dropwise. The resulting mixture was stirred at –78 °C for 12 h and the reaction was quenched with 20 mL of saturated ammonium chloride solution; the mixture was filtered through celite and extracted with ether (4 × 75 mL). The organic layer was dried over $MgSO_4$ and the solvent removed by rotary evaporation. The crude product was purified by flash chromatography (10% ethyl acetate /hexanes, R_f 0.07) yielding 0.290 g (70%) of **27**. ^1H NMR ($CDCl_3$) δ 3.93–3.85 (m, 4 H, OCH_2CH_2O), 2.43 (t, J = 7.3, 2 H, $COCH_2$), 2.14 (s, 3 H, CH_3), 1.92–1.21 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 208.7, 117.8, 64.3, 64.1, 45.6, 43.8, 35.4, 29.6, 29.1, 28.2, 22.2, 20.4; IR (neat, NaCl) 2946 (s), 2876 (s), 1713 (s), 1161 (m), 1103 (m), 1034 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 212 (68, M^+), 183 (52), 169 (75), 141 (78), 99 (100); exact mass calculated for $C_{12}H_{20}O_3$ 212.1412, found 212.1429.

7-(4-Oxopentyl)-1,4-dioxaspiro[4.4]nonane (28). The procedure was the same as that for the preparation of **27** except that 0.333 g (1.20 mmol) of 7-(3-(phenylthio)propyl)-1,4-dioxaspiro[4.4]nonane (**18**) in 6 mL of THF was added to LDBB (2.40 mmol, 0.160 M); 0.626 g (3.05 mmol) of CuBr•Me_2S was used for the metallation over 3 h and 0.15 mL (2.1 mmol) of acetyl chloride in 4 mL of THF was used. The product purification (R_f 0.18) yielded 0.140 g (55%) of **28**. ^1H NMR ($CDCl_3$) δ 3.94–3.86 (m, 4 H, OCH_2CH_2O), 2.43 (t, J = 7.4, 2 H, $CH_2C(O)$), 2.13 (s, 3 H, CH_3), 2.01–1.78 (m, 5 H), 1.59–1.54 (m, 2 H), 1.40–1.27 (m, 4 H); ^{13}C NMR ($CDCl_3$) δ 208.8, 117.6, 64.1, 63.8, 43.6, 42.5, 37.4, 35.8, 35.2, 30.1, 29.7, 22.2; IR (neat, NaCl) 2934 (s), 1713 (s), 1354 (m), 1121 (m), 1092 (m), 1036 (m) cm^{-1}.

6-(3-Benzoylpropyl)-1,4-dioxaspiro[4.4]nonane (29). The procedure was the same as that for the preparation of **27**. 0.866 g (3.11 mmol) of 6-(3-(phenylthio)propyl)-1,4-dioxaspiro[4.4]nonane (**5**) in 7 mL of THF was added to LDBB (6.6 mmol, 0.33 M); 0.995 g (4.84 mmol) of CuBr•Me_2S was used for the metal-lation over 3 h and 0.60 mL (5.2 mmol) of benzoyl chloride in 4 mL of THF was used. Product purification (R_f 0.18) yielded 0.501 g (59%) of **29**. ^1H NMR ($CDCl_3$) δ 7.95–7.92 (m, 2 H, arom.), 7.55–7.40 (m, 3 H, arom.), 3.92–3.82 (m, 4 H, OCH_2CH_2O), 2.95 (t, J = 7.4 Hz, 2 H, $COCH_2$), 1.94–1.28 (m, 11 H); ^{13}C NMR ($CDCl_3$) δ 200.3, 137.0, 132.8, 128.5, 128.0, 118.1, 64.5, 64.4, 45.9, 38.9, 35.7, 29.4, 28.7, 23.0, 20.7; IR (neat, NaCl) 2924 (s), 1673 (s), 1196 (m), 1136 (m), 1024 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 274 (15, M^+), 155 (25), 99 (100); exact mass calculated for $C_{17}H_{22}O_3$ 274.1569, found 274.1519.

6-(5-Methyl-4-oxohexyl)-1,4-dioxaspiro[4.4]nonane (30). The procedure was the same as that for the preparation of **27** except that 0.873 g (3.14 mmol) of 6-(3-(phenylthio)propyl)-1,4-dioxaspiro[4.4]nonane (**5**) in 8 mL of THF was added to LDBB (6.6 mmol, 0.26 M); 1.16 g (5.64 mmol) of CuBr•Me_2S was used for the metallation over 3 h and 0.50 mL (4.8 mmol) of isobutyryl chloride in 4 mL of THF was used. The procedure in experiment 1 was followed to generate LDBB (6.6 mmol, 0.26 M). The product purification (R_f 0.19) yielded 0.549 g (73%) of **30** (light yellow liquid). ^1H NMR ($CDCl_3$) δ 3.56–3.43 (m, 4 H, OCH_2CH_2O), 2.19–1.27 (m, 14 H), 0.90 (d, J = 6.8 Hz, 6 H, 2 CH_3); ^{13}C NMR ($CDCl_3$) δ 214.8, 118.1, 64.5, 64.3, 45.9, 40.7, 40.6, 35.7, 29.3, 28.6, 22.4, 20.6, 18.2; IR (neat, NaCl) 2944 (s), 2876 (s), 1712 (s), 1467 (m), 1109 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 240 (20, M^+), 99 (100); exact mass calculated for $C_{14}H_{24}O_3$ 240.1725, found 240.1722.

6-(5,5-Dimethyl-4-oxohexyl)-1,4-dioxaspiro[4.4]nonane (31). The procedure was the same as that for the preparation of **27** except that 1.66 g (5.98 mmol) of 6-(3-(phenylthio)propyl)-1,4-dioxaspiro[4.4]nonane (**5**) in 7 mL of THF was added to LDBB (12.6 mmol, 0.42 M); 1.73 g (8.41 mmol) of CuBr•Me_2S was used for the metallation over 4 h and 1.1 mL (8.9 mmol) of trimethylacetyl chloride in 4 mL of

THF was used, the mixture being allowed to stir for 15 h. The product purification (R_f 0.24) yielded 0.792 g (52%) of **31**. ^{1}H NMR ($CDCl_3$) δ 3.95–3.85 (m, 4 H, OCH_2CH_2O), 2.49 (t, J = 7.3 Hz, 2 H, $COCH_2$), 1.92–1.20 (m, 11 H), 1.15 (s, 9 H, 3 CH_3); ^{13}C NMR ($CDCl_3$) δ 216.0, 118.1, 64.5, 64.4, 45.9, 44.0, 36.7, 35.7, 29.3, 28.6, 26.4, 22.6, 20.6; IR (neat, NaCl) 2959 (s), 2874 (s), 1705 (s), 1148 (m), 1107 (m), 733 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 254 (11, M^+), 169 (18), 99 (100), 44 (48); exact mass calculated for $C_{15}H_{26}O_3$ 254.1882, found 254.1876.

6-(4-Oxohexyl)-1,4-dioxaspiro[4.4]nonane (32). The procedure was the same as that for the prepar-ation of **27**. 0.679 g (2.44 Mmol) of 6-(3-(phenylthio)propyl)-1,4-dioxaspiro[4.4]nonane (**5**) in 9 mL of THF was added to LDBB (6.00 mmol, 0.40 M); 0.750 g (3.65 mmol) of CuBr•Me_2S was used for the metallation over 3 h and 0.42 mL (4.9 mmol) of propionyl chloride in 2 mL of THF was used, the mixture being allowed to stir for 12 h. The product purification yielded 0.276 g (50%) of 6-(4-oxohexyl)-1,4-dioxaspiro[4.4]nonane (**32**) (R_f 0.11) and 0.092 g (21%) of 2-(4-oxohexyl)cyclopentanone (**45**) (R_f 0.07). The characterization of the latter is described below. **32** ^{1}H NMR (C_6D_6) δ 3.55–3.43 (m, 4 H, OCH_2CH_2O), 2.02–1.09 (m, 15 H), 0.92 (t, J = 7.2, 3 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 211.7, 118.1, 64.5, 64.4, 45.8, 42.7, 35.8, 35.6, 29.3, 28.5, 22.5, 20.6, 7.8; IR (neat, NaCl) 2930 (s), 1725 (s), 1449 (m), 1148 (m), 1065 (m), 729 (s) cm^{-1}; mass spectrum, *m / e* (relative intensity), 226 (9, M^+), 141 (18), 99 (100); exact mass calculated for $C_{13}H_{22}O_3$ 226.1569, found 226.1608.

6-(2-Methyl-4-oxopentyl)-1,4-dioxaspiro[4.4]nonane (33). The procedure was the same as that for the preparation of **27**. 0.711 g (2.43 Mmol) of 6-(2-methyl-3-(phenylthio)propyl)-1,4-dioxaspiro-[4.4]nonane (**8**) in 4 mL of THF was added to LDBB (10.4 mmol, 0.42 M); 0.701 g (3.41 mmol) of CuBr•Me_2S was used for the metallation over 3 h and 0.25 mL (3.5 mmol) of acetyl chloride in 4 mL of THF was used, the mixture being allowed to stir for 15 h. The product purification (R_f 0.09) yielded 0.281 g (70%) of a 1:1 mixture of two diastereomers. ^{1}H NMR ($CDCl_3$) δ 3.95–3.84 (m, 4 H, OCH_2CH_2O), 2.49–2.17 (m, 2 H, $COCH_2$), 2.13 (br singlet, 3 H, $COCH_3$), 2.06–1.18 (m, 10 H), 0.94–0.87 (2 doublets, J = 6.5 Hz, 3 H, $CHCH_3$); IR (neat, NaCl) 2944 (s), 1711 (s), 1362 (m), 1113 (m), 1036 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 226 (10, M^+), 141 (38), 99 (100); exact mass calculated for $C_{13}H_{22}O_3$ 226.1569, found 226.1569.

6-(2,5,5-Trimethyl-4-oxohexyl)-1,4-dioxaspiro[4.4]nonane (34). The procedure was the same as that for the preparation of **27** except that 0.785 g (2.68 mmol) of 6-(2-methyl-3-(phenylthio)propyl)-1,4-dioxaspiro[4.4]nonane (**8**) in 6 mL of THF was added to LDBB (6.60 mmol, 0.26 M); 0.948 g (4.61 mmol) of CuBr•Me_2S was used for the metallation over 3 h and 0.50 mL (4.1 mmol) of trimethylacetyl chloride in 4 mL of THF was used. The product purification (R_f 0.25) yielded 0.377 g (52%) of a 1:1 mixture of two diastereomers. ^{1}H NMR ($CDCl_3$) δ 3.91–3.81 (m, 4 H, OCH_2CH_2O), 2.38–2.26 (m, 2 H, $COCH_2$), 2.05–1.13 (m, 10 H), 1.07 (s, 9 H), 3 CH_3), 0.82 (d, J = 6.7 Hz, 1.5 H, $CHCH_3$), 0.78 (d, J = 6.7 Hz, 1.5 H, $CHCH_3$); IR (neat, NaCl) 2965.0 (s), 2874 (s), 1705 (s), 1113 (m), 1038 (m), 733 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 268 (46, M^+), 211 (40), 183 (44), 99 (100), 57 (58); exact mass calculated for $C_{16}H_{28}O_3$ 268.2038, found 268.2001.

6-(4-Oxopentyl)-1,4-dioxaspiro[4.5]decane (35). The procedure was the same as that for the preparation of **27** except that 0.932 g (3.19 mmol) of 6-(3-(phenylthio)propyl)-1,4-dioxaspiro[4.5]decane (**11**) in 6 mL of THF was added to LDBB (6.30 mmol, 0.32 M); 0.964 g (4.69 mmol) of CuBr•Me_2S was used for the metallation over 3 h and 0.32 mL (4.5 mmol) of acetyl chloride in 4 mL of THF was used. The product

purification (R_f 0.18) yielded 0.493 g (68%) of **35**. ^{1}H NMR ($CDCl_3$) δ 3.80 (m, 4 H, OCH_2CH_2O), 2.32–2.29 (ABX_2, 2 H, $COCH_2$), 2.00 (s, 3 H, CH_3), 1.66–0.94 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 208.9, 110.4, 64.5, 64.4, 44.2, 43.9, 34.4, 29.6, 28.8, 27.4, 24.3, 23.6, 21.6; IR (neat, NaCl) 2936 (s), 2872 (s), 1715 (s), 1358 (s), 1159 (m), 1092 (s) cm^{-1}; mass spectrum, *m / e* (relative intensity), 226 (12, M$^+$), 155 (21), 99 (100); exact mass calculated for $C_{13}H_{22}O_3$ 226.1569, found 226.1541.

6-(5,5-Dimethyl-4-oxohexyl)-1,4-dioxaspiro[4.5]decane (36). The procedure was the same as that for the preparation of **27** except that 0.753 g (2.58 mmol) of 6-(3-(phenylthio)propyl)-1,4-dioxaspiro[4.5]decane (**11**) in 12 mL of THF was added to LDBB (6.80 mmol, 0.34 M); 0.968 g (4.71 mmol) of CuBr•Me_2S was used for the metallation over 3 h and 0.57 mL (4.6 mmol) of trimethylacetyl chloride in 4 mL of THF was used. The product purification (R_f 0.23) yielded 0.455 g (66%) of **36**. ^{1}H NMR ($CDCl_3$) δ 3.94 (m, 4 H, OCH_2CH_2O), 2.42 (ABX_2, 2 H, $COCH_2$), 1.81–1.19 (m, 13 H), 1.13 (s, 9 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 216.0, 110.8, 64.8, 64.6, 44.5, 44.0, 36.9, 34.6, 28.9, 27.8, 11.6, 24.4, 23.8, 21.9; IR (neat, NaCl) 2894 (s), 1690 (s), 1439 (m), 1348 (m), 1082 (s) cm^{-1}; mass spectrum, *m / e* (relative intensity), 268 (65, M$^+$), 172 (28), 99 (100), 91 (80); exact mass calculated for $C_{16}H_{28}O_3$ 268.2038, found 268.2059.

6-(3-Benzoylpropyl)-1,4-dioxaspiro[4.5]decane (37). The procedure was the same as that for the preparation of **27** except that 0.287 g (0.981 mmol) of 6-(3-(phenylthio)propyl)-1,4-dioxaspiro[4.5]decane (**11**) in 4 mL of THF was added to LDBB (3.79 mmol, 0.38 M); 0.302 g (1.47 mmol) of CuBr•Me_2S was used for the metallation over 3 h and 0.20 mL (1.7 mmol) of benzoyl chloride in 4 mL of THF was used. The crude product was purified by flash chromatography (20% ethyl acetate / hexanes, R_f 0.34) yielding 0.198 g (70%) of **37**. ^{1}H NMR ($CDCl_3$) δ 7.96–7.94 (m, 2 H, arom.), 7.56–7.42 (m, 3 H, arom.), 3.98–3.84 (m, 4 H, OCH_2CH_2O), 2.94 (m, 2 H, $COCH_2$), 1.93–1.13 (m, 13 H); ^{13}C NMR ($CDCl_3$) δ 200.3, 137.0, 132.8, 128.5, 128.0, 110.7, 64.7, 64.6, 44.5, 39.0, 34.6, 29.0, 27.8, 24.4, 23.8, 22.3; IR (neat, NaCl) 2915 (s), 1673 (s), 1437 (m), 1084 (m), 727 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 288 (75, M$^+$), 245 (74), 183 (63), 99 (100); exact mass calculated for $C_{18}H_{24}O_3$ 288.1725, found 288.1721.

7-(4-Oxopentyl)-1,4-dioxaspiro[4.5]decane (38).[4] The procedure was the same as that for the preparation of **28** except that 0.956 g (3.27 mmol) of 7-(3-(phenylthio)propyl)-1,4-dioxaspiro[4.5]decane (**14**) in 13 mL of THF was added to LDBB (11.7 mmol, 0.47 M); 0.960 g (4.67 mmol) of CuBr•Me_2S was used for the metallation over 3 h and 0.42 mL (5.9 mmol) of acetyl chloride in 4 mL of THF was used. The product purification (R_f 0.16) yielded 0.492 g (67%) of **38**. ^{1}H NMR ($CDCl_3$) δ 3.86–3.80 (m, 4 H, OCH_2CH_2O), 2.33 (ABX_2, 2 H, $COCH_2$), 2.05 (s, 3 H, CH_3), 1.69–1.02 (m, 13 H) ; ^{13}C NMR ($CDCl_3$) δ 209.0, 109.2, 64.2, 64.0, 43.8, 41.5, 36.2, 35.2, 34.8, 31.5, 29.8, 23.1, 20.9; IR (neat, NaCl) 2934 (s), 1713 (s), 1356 (m), 1165 (m), 1076 (s) cm^{-1}; mass spectrum, *m / e* (relative intensity), 226 (7, M$^+$), 183 (40), 141 (85), 99 (100); exact mass calculated for $C_{13}H_{22}O_3$ 226.1569, found 226.1534.

8-(2,2-dimethyl-3-oxobutyl)-1,5-dithiaspiro[5.5]undecane (39). The procedure was the same as that for the preparation of **28** except that 0.378 g (1.07 mmol) of 8-(2-methyl-2-(phenylthio)propyl)-1,5-dithiaspiro[5.5]undecane (**22**) in 9 mL of THF was added to LDBB (2.14 mmol, 0.107 M); 0.343 g (1.67 mmol) of CuBr•Me_2S was used for the metallation over 3 h and 0.15 mL (2.11 mmol) of acetyl chloride in 4 mL of THF was used. The product purification (R_f 0.23) yielded 0.208 g (68%) of **39**. ^{1}H NMR ($CDCl_3$) δ 2.89–2.83 (m, 2 H), 2.73 (m, 2 H), 2.30–2.23 (m, 3 H), 2.15 (s, 3 H, $C(O)CH_3$), 2.02–1.96 (m, 3 H), 1.75–1.23 (m, 7 H), 1.13 (s, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 214.1, 50.3, 47.6, 46.5, 45.1, 37.5, 34.0, 30.1, 26.1, 26.0, 25.7, 25.2, 25.1, 25.0, 21.9; IR (neat, NaCl) 2921 (s), 1696 (s), 1433 (m), 729 (s) cm^{-1}.

3-(4-Oxopentyl)cyclopentanone (40).[20] To a solution of 0.130 g (0.612 mmol) of 7-(4-oxopentyl)-1,4-dioxaspiro[4.4]nonane (**28**) in 4.0 mL of acetone containing 0.12 g of water was added 80 mg of Amberlyst-15 ion-exchange resin and the mixture was stirred at room temperature for 1 h. The mixture was filtered to remove the resin and the acetone was removed by rotary evaporation. The mixture was washed with water and extracted with ethyl ether. The organic layer was dried over $MgSO_4$ and then the solvent was removed by rotary evaporation to give 0.099 g (96%) of **40**. ^1H NMR ($CDCl_3$) δ 2.44–2.12 (m, 4 H), 2.10 (s, 3 H, CH_3), 2.12–2.01 (m, 3 H), 1.80–1.34 (m, 6 H); ^{13}C NMR ($CDCl_3$) δ 219.7, 208.8, 45.0, 43.5, 38.4, 37.0, 35.0, 29.9, 29.3, 21.9.

2-(4-Oxopentyl)cyclopentanone (41). To a solution of 0.262 g (1.23 mmol) of 6-(4-oxopentyl)-1,4-dioxaspiro[4.4]nonane (**27**) in 6.0 mL of acetone containing 0.12 g of water was added 100 mg of Amberlyst-15 ion-exchange resin and the mixture was stirred at room temperature for 1 h. The reaction mixture was filtered to remove the resin. The acetone was removed by rotary evaporation. The mixture was washed with water and extracted with ethyl ether. The organic layer was dried over $MgSO_4$ and then the solvent was removed again by rotary evaporation. The product was purified by flash chromatography (20% ethyl acetate / hexanes, R_f 0.16) to give 0.199 g (96%) of **41**. ^1H NMR ($CDCl_3$) δ 2.45 (t, J = 7.2 Hz, 2 H, CH_3COCH_2), 2.29–2.16 (m, 3 H, ring CH_2COCH), 2.14 (s, 3 H, CH_3), 2.10–1.50 (m, 8 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 220.5, 208.2, 48.6, 43.1, 37.7, 29.5, 29.1, 28.7, 21.3, 20.4; IR (neat, NaCl) 2953 (s), 2872 (m), 1736 (s), 1360 (m), 1159 (m) cm^{-1}.

2-(3-Benzoylpropyl)cyclopentanone (42). To a solution of 0.467 g (1.70 mmol) of 6-(3-benzoyl-propyl)-1,4-dioxaspiro[4.4]nonane (**29**) in 6.0 mL of acetone containing 0.12 g of water was added 100 mg of Amberlyst-15 ion-exchange resin and the mixture was stirred at room temperature for 1 h. The reaction was worked up as for **40** to give 0.378 g (96%) of **42**. ^1H NMR ($CDCl_3$) δ 7.94–7.91 (m, 2 H, arom.), 7.56–7.41 (m, 3 H, arom.), 2.97 (t, J = 6.8, 2 H, $PhCOCH_2$), 2.33–2.15 (m, 2 H), 2.15–1.95 (m, 3 H), 1.90–1.61 (m, 4 H), 1.58–1.40 (m, 1 H), 1.40–1.25 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 221.2, 199.9, 136.8, 133.0, 128.6, 127.9, 49.1, 38 4, 38.1, 29.5, 29.3, 22.1, 20.7; IR (neat, NaCl) 2924 (m), 1727 (s), 1674 (s) cm^{-1}; mass spectrum, *m / e* (relative intensity), 230 (7, M^+), 120 (70), 105 (100); exact mass calculated for $C_{15}H_{18}O_2$ 230.1307, found 230.1312.

2-(5-Methyl-4-oxohexyl)cyclopentanone (43). To a solution of 0.537 g (2.24 mmol) of 6-(5-methyl-4-oxohexyl)-1,4-dioxaspiro[4.4]nonane (**30**) in 5.0 mL of acetone containing 0.12 g of water was added 120 mg of Amberlyst-15 ion-exchange resin and the mixture was stirred at room temperature for 1.5 h. The reaction was worked up as for **41** to give, after flash chromatography (R_f 0.28), 0.433 g (99%) of product. ^1H NMR ($CDCl_3$) δ 2.49 (m, 1 H), 2.37 (t, J = 7.0, 2 H), 2.25–2.06 (m, 2 H), 2.05–2.18 (m, 3 H), 1.77-1.37 (m, 5 H), 1.21–1.03 (m, 1 H), 0.97 (d, J = 6.9, 6 H, CH_3); ^{13}C NMR ($CDCl_3$) δ 220.9, 214.2, 48.9, 40.6, 40.0, 37.9, 29.3, 29.1, 21.5, 20.5, 18.1; IR (neat, NaCl) 2964 (s), 2937 (m), 2873 (s), 1737 (s), 1711 (s), 1468 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 196 (27, M^+), 107 (100), 55 (65); exact mass calculated for $C_{12}H_{20}O_2$ 196.1463, found 196.1456.

2-(5,5-Dimethyl-4-oxohexyl)cyclopentanone (44). To a solution of 0.616 g (2.42 mmol) of 6-(5,5-dimethyl-4-oxohexyl)-1,4-dioxaspiro[4.4]nonane (**31**) in 8.0 mL of acetone containing 0.14 g of water was added 150 mg of Amberlyst-15 ion-exchange resin and the mixture was stirred at room temperature for 1 h. The reaction was worked up as for **40** to give 0.488 g (96%) of **44**. ^1H NMR ($CDCl_3$) δ 2.51 (t, J = 7.1, 2 H, Me_3CCOCH_2), 2.29–1.16 (m, 11 H), 1.13 (s, 9 H, 3 CH_3); ^{13}C NMR ($CDCl_3$) δ 221.0, 215.4, 49.0, 43.9,

38.0, 36.2, 29.3, 29.1, 26.2, 21.7, 20.6; IR (neat, NaCl) 2930 (s), 1723 (s), 1694 (s), 1451 (m), 727 (s) cm^{-1}; mass spectrum, *m / e* (relative intensity), 210 (8, M^+), 153 (11), 135 (10), 107 (20), 57 (15), 28 (100); exact mass calculated for $C_{13}H_{22}O_2$ 210.1620, found 210.1651.

2-(4-Oxohexyl)cyclopentanone (45).[16] To a solution of 0.247 g (1.09 mmol) of 6-(4-oxohexyl)-1,4-dioxaspiro[4.4]nonane (**32**) in 7.0 mL of acetone containing 0.12 g of water was added 100 mg of Amberlyst-15 ion-exchange resin and the mixture was stirred at room temperature for 1 h. The reaction was worked up as for **40** to give 0.193 g (97%) of product. ^1H NMR (C_6D_6) δ 1.91–1.84 (m, 4 H), 1.71–0.99 (m, 11 H), 0.92 (t, J = 7.3, 3 H, CH_3); ^{13}C NMR (C_6D_6) δ 218.5, 209.1, 48.8, 42.1, 37.8, 35.6, 29.6, 22.0, 20.8, 7.9; IR (neat, NaCl) 2928 (m), 1727 (m), 1449 (m), 1150 (m) cm^{-1}.

2-(2-Methyl-4-oxopentyl)cyclopentanone (46). To a solution of 0.234 g (1.04 mmol) of 6-(2-methyl-4-oxopentyl)-1,4-dioxaspiro[4.4]nonane (**33**) in 5.0 mL of acetone containing 0.12 g of water was added 100 mg of Amberlyst-15 ion-exchange resin and the mixture was stirred at room temperature for 1 h. The reaction was worked up as for **41** to give, after flash chromatography (R_f 0.20), 0.170 g (90%) of a 1:1 mixture of two diastereomers. ^1H NMR ($CDCl_3$) δ 2.13 and 2.14 (2 overlapping singlets, 3 H, $COCH_3$), 2.46–2.01 (m, 8 H), 1.80–1.16 (m, 4 H), 0.94 -0.88 (2 overlapping doublets, J = 6.6, 3 H, $CHCH_3$); IR (neat, NaCl) 2945.7 (s), 1726.5 (s), 1356.1 (m), 1153.6 (m) cm^{-1}; mass spectrum, *m / e* (relative intensity), 182 (53, M^+), 124 (34), 84 (70); exact mass calculated for $C_{11}H_{18}O_2$ 182.1307, found 182.1318.

2-(4-Oxopentyl)cyclohexanone (47).[21] To a solution of 0.431 g (1.91 mmol) of 6-(4-oxopentyl)-1,4-dioxaspiro[4.5]decane (**35**) in 7.5 mL of acetone containing 0.12 g of water was added 150 mg of Amberlyst-15 ion-exchange resin and the mixture was stirred at room temperature for 2.5 h. The reaction was worked up as for **41** to give, after flash chromatography (R_f 0.28), 0.334 g (96%) of **47**. ^1H NMR ($CDCl_3$) δ 2.46–2.20 (m, 5 H, CH_2COCH and CH_2CO), 2.13 (s, 3 H, CH_3), 2.10–1.15 (m, 10 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 212.8, 208.7, 50.3, 43.5, 41.8, 33.7, 29.6, 28.6, 27.8, 24.7, 21.2; IR (neat, NaCl) 2934 (s), 2861 (m), 1711 (s), 1449 (m), 1364 (m) cm^{-1}.

2-(3-Benzoylpropyl)cyclohexanone (48). To a solution of 0.191 g (0.662 mmol) of 6-(3-benzoyl-propyl)-1,4-dioxaspiro[4.5]decane (**37**) in 4.0 mL of acetone containing 0.12 g of water was added 100 mg of Amberlyst-15 ion-exchange resin and the mixture was stirred at room temperature for 3 h. The reaction was worked up as for **41** to give, after flash chromatography (R_f 0.35), 0.154 g (95%) of **48**. ^1H NMR ($CDCl_3$) δ 7.95 (d, J = 7.2, 2 H, arom.), 7.57–7.42 (m, 3 H, arom.), 2.98 (t, J = 6.7, 2 H, $PhCOCH_2$), 2.37–1.62 (m, 11 H), 1.41–1.26 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 213.0, 200.1, 136.9, 132.9, 128.5, 127.9, 50.6, 42.0, 38.6, 33.8, 29.0, 28.0, 24.9, 21.8; mass spectrum, *m / e* (relative intensity), 210 (8, M^+), 153 (11), 135 (10), 107 (20), 57 (15), 28 (100); exact mass calculated for $C_{16}H_{20}O_2$ 244.1463, found 244.1445.

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