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TETRAHEDRON

SEQUENCED REACTIONS WITH SAMARIUM(II) IODIDE. INTERMOLECULAR KETYL-OLEFIN COUPLING / INTRAMOLECULAR NUCLEOPHILIC ACYL SUBSTITUTION FOR THE PREPARATION OF SIX-, SEVEN-, AND EIGHT-MEMBERED CARBOCYCLES.

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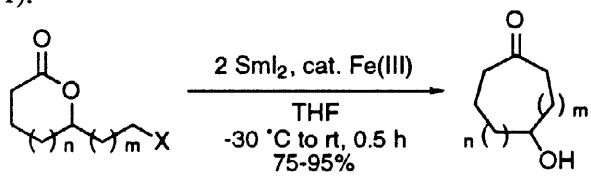
ABSTRACT

A samarium(II) iodide-promoted sequence consisting of an intermolecular ketyl-olefin coupling followed by an intramolecular nucleophilic acyl substitution is described. This process leads to functionalized six- to eight-membered monocyclic and bicyclic ring systems in moderate to good yields.

INTRODUCTION

The development of novel synthetic methods that allow an efficient entrée into medium-sized carbocycles is a particularly valuable endeavor. Although a host of important natural products incorporate such units within their overall structure, in fact the number of general methods for preparing medium-sized carbocycles by cyclization or cycloaddition (annulation) reactions from acyclic precursors is relatively small.[1]

Several methods for medium-ring synthesis have evolved utilizing samarium(II) iodide (SmI_2) as a promoter of both cyclization[2] and ring expansion reactions.[3] The ring expansion mode in particular has proven extremely valuable as a simple route to seven-, eight-, and even nine-membered rings. In SmI_2-promoted reactions, ring expansions take the form of nucleophilic acyl substitution reactions on appropriately functionalized lactones (eq 1).



(1)

More efficient are processes wherein two carbon-carbon bonds are formed in a single reaction.[4] For a ring expansion protocol with SmI_2 this can be accomplished in several ways. For example, a nucleophilic acyl substitution reaction followed by carbonyl addition provides ready access to polycyclic ring systems (eq 2).[5] The initial nucleophilic acyl substitution reaction generates a ketone that takes part in the subsequent carbonyl addition reaction. The selectivity exhibited by SmI_2 permits the initial generation of an organosamarium exclusively from the alkyl iodide. This nucleophilic acyl substitution reaction is followed by reaction of the

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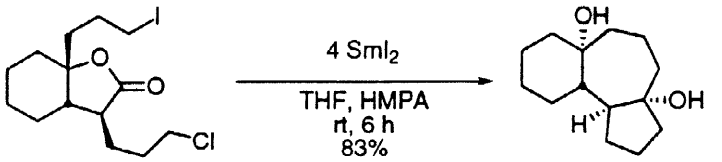
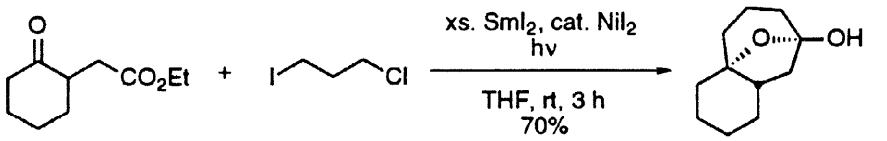
alkyl chloride with SmI_2 to generate a second organosamarium intermediate that undergoes carbonyl addition with the ketone created in the first reaction.



(2)

Related transformations can be carried out to accomplish cycloaddition-type processes that lead directly from acyclic precursors to medium-membered ring systems. One such protocol involves reactions of alkyl dihalides with keto esters, resulting in the construction of cyclic hydroxy ketones (eq 3).[6] In these annulations, intermolecular carbonyl addition of the organosamarium species generated from the iodide induces lactone formation. The lactone then reacts by a ring expansion with the organosamarium created from the alkyl chloride.



(3)

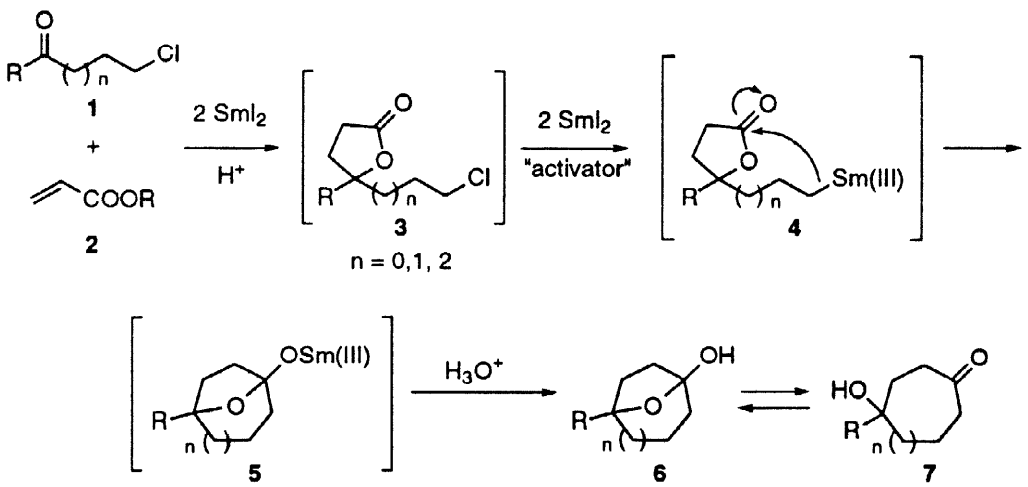
Noteworthy in all of these examples is the exquisite selectivity demonstrated by SmI_2 in reactions with multifunctional substrates. In fact, the reducing characteristics of SmI_2 can be modulated by the addition of catalysts,[7] solvent additives,[8] and even irradiation of the reaction mixture.[9] The flexibility afforded by these options allows a sequencing of events that might not be possible otherwise with this or other reducing agents.

Another advantage of SmI_2 is its versatility. Samarium(II) iodide is capable of promoting a vast range of one step and sequenced carbon-carbon bond-forming reactions.[4,10] Ketyl-olefin coupling reactions constitute one class of such reactions that have been widely studied.[4,10,11] When α,β-unsaturated esters are employed as radical acceptors in these processes, lactones are the observed products of the reactions. Because lactones are also intermediates in SmI_2-promoted ring expansion reactions, we envisioned that ketyl-olefin coupling reactions could be utilized as the initial component of a two-step sequence leading to medium ring compounds.

Herein we describe the results of these studies, outlining a novel combination of ketyl-olefin coupling and nucleophilic acyl substitution resulting in the synthesis of medium-ring hydroxy ketones (Scheme 1). The process involves the initial formation of a lactone **3** through an intermolecular ketyl-olefin coupling. By being able to utilize chloro ketone starting materials, it was anticipated that intramolecular Barbier-type reactions could be avoided. This ketyl-olefin coupling would be followed by an intramolecular nucleophilic acyl substitution to afford ring-expanded products. As mentioned above, the ability to make adjustments in the reaction conditions would permit the SmI_2 to be activated at this stage of the sequence for formation of the organosamarium intermediate from the alkyl chloride. One significant challenge posed by this sequence was the requirement of the presence of a proton source (1 equiv) during the SmI_2-promoted ketyl-olefin coupling reaction. This proton source was necessary to quench the ester enolate generated in the first carbon-carbon bond-forming step of the reaction, but at the same time threatened to interrupt the two-step sequence by

quenching the organosamarium species generated in the second step of the process. The fact that the sequence can be carried out as described attests to the remarkable properties of SmI_2 as a reductive coupling agent.

Scheme 1



RESULTS AND DISCUSSION

To study the feasibility of this reaction, a variety of halo ketones were employed as starting materials (eq 4). The results of their Sm(II)-promoted reaction with *n*-butyl acrylate are shown in Table 1.

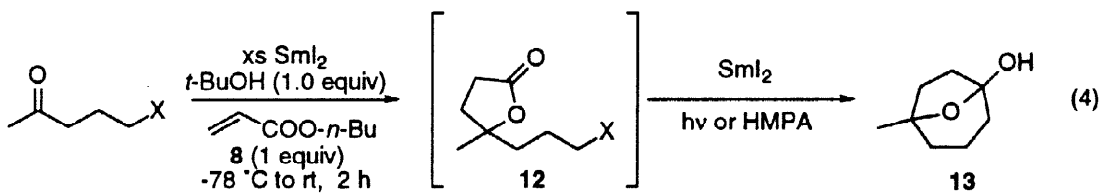
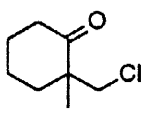
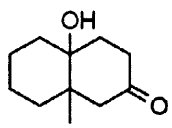
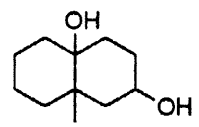
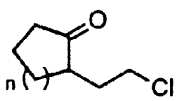
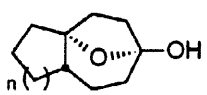
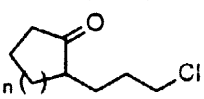
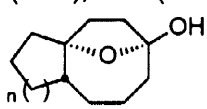
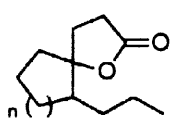
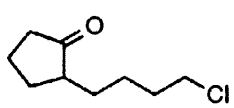
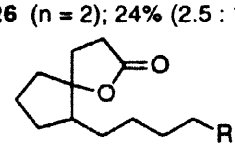
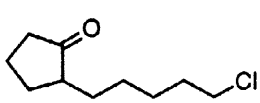
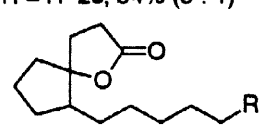


Table 1. Sequential SmI_2-Promoted Ketyl-Olefin Coupling / Nucleophilic Acyl Substitution Between 5-Halo-2-pentanones and *n*-Butyl Acrylate (8).

entry	substrate	X	activator	temp (°C)	time (h)	% isoltd yield
1	**9**	Cl	visible light	0-25	8.0	73
2	**9**	Cl	HMPA	rt	12.0	61
3	**10**	Br	visible light	0-25	5.0	68
4	**10**	Br	HMPA	rt	3.0	61
5	**11**	I	visible light	0-25	0.5	66
6	**11**	I	HMPA	rt	1.0	59

For each substrate, sequential reductive cyclization proceeded smoothly to afford seven-membered carbocycles **13** in one pot. The first step in the sequence, formation of the lactone, appeared to be facile in all cases as determined by TLC analysis. However, the efficiency of the second step, nucleophilic acyl substitution, was variable and depended upon the halogen species used and on whether visible light or the cosolvent HMPA was used to activate the SmI_2. Iodide **11** was consumed in the shortest time, but the yield of **13** was slightly lower than with the other halo ketones. Chloride **9** required a longer reaction time for complete conversion to **13** (it is less easily reduced to the corresponding organometallic), but the yield of **13** was good. In general, the use of visible light gave higher yields than the analogous HMPA method.

Table 2. Sequential SmI_2-Promoted Ketyl-Olefin Coupling/Nucleophilic Acyl Substitution Between Halo Ketones and *n*-Butyl Acrylate (8).

entry	substrate	product; isoltd yield (ds)	
1	 **14**	 **15**; 26%	 **16a,b**; 33% (1 : 1)[a]
2	 **17** (n = 1)	 **18** (n = 1); 65% (9:1)[b,c]	
3	**19** (n = 2)	**20a,b** (n = 2); 72% (1.4 : 1)[a,c]	
4	 **21** (n = 1)	 **22** (n = 1); 34% (18 : 1)[b,c]	 **23** (n = 1); 32% (18 : 1)[b]
5	**24** (n = 2)	**25a,b** (n = 2); 56% (1.3 : 1)[a,c]	**26** (n = 2); 24% (2.5 : 1)[b]
6	 **27**		 R = Cl **28** R = H **29**; 54% (5 : 1)[b]
7	 **30**		 R = Cl **31** R = H **32**; 72% (10 : 1)[b]

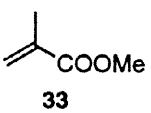
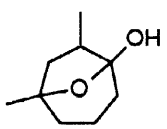
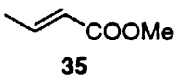
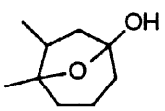
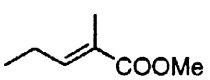
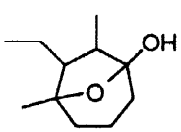
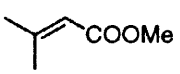
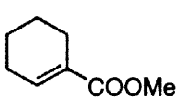
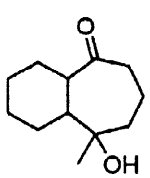
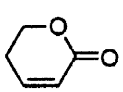
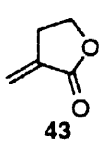
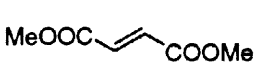
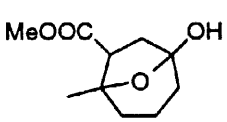
[a] The ratio is based on the weight of the isolated isomers. [b] The ratio was determined by GC analysis.
[c] The stereochemistry of the major isomer was assigned by comparison with products reported in ref. 6.

The study was continued by applying the experimental procedure developed for chloro ketone **9** to the reaction between *n*-butyl acrylate and a series of chloro ketones (Table 2). Six- and seven-membered carbocycles were formed in good yield (entries 1, 2, and 3), while eight-membered carbocycles (entries 4 and 5) were prepared only in modest yield. Some diol product **16**, resulting from an overreduction of the initially-formed hydroxy ketone **15**, was observed. This is perhaps due to the fact that the intermediate hydroxy

ketone was not "protected" as an intramolecular hemiacetal as were all of the other hydroxy ketone products formed in this study. The spirocyclic lactones **23** and **26** were the major side products formed from **21** and **24** (entries 4 and 5, respectively). Nine- and ten-membered carbocycles were not observed (entries 6 and 7). In these cases, the only isolated products were spirocyclic lactones **29** and **32**, the result of reduction of the intermediate chloro lactones **28** and **31** to the corresponding alkanes.

The reaction between 5-chloro-2-pentanone (**9**) and a series of substituted α,β-unsaturated esters and lactones was explored next (Table 3).

Table 3. Sequential SmI_2-Promoted Ketyl-Olefin Coupling / Nucleophilic Acyl Substitution Between 5-Chloro-2-pentanone (9) and Several α,β-Unsaturated Esters.

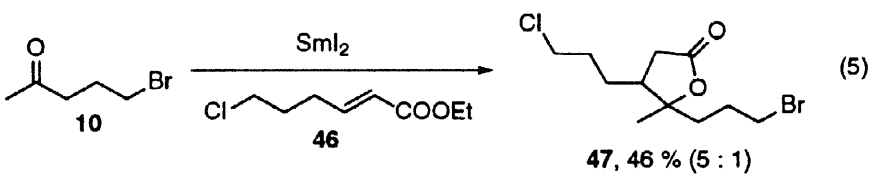
entry	substrate	product	isoltd yield (ds)
1	 **33**		**34a,b**; 74% (1.4 : 1)[a]
2	 **35**		**36**; 71% (2 : 1)[b]
3	 **37**		**38a,b**; 62% (1.7 : 1)[a]
4	 **39**	— c	
5	 **40**		**41a,b**; 59% (1.1 : 1)[a]
6	 **42**	— c	
7	 **43**	— c	
8	 **44**		**45**; 64% (1 : 1)[b]

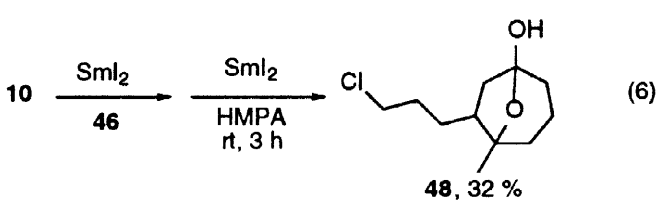
[a] The ratio is based on the weight of isolated isomers. [b] Ratios were determined by ^{1}H-NMR and ^{13}C-NMR.
[c] A complex mixture was obtained.

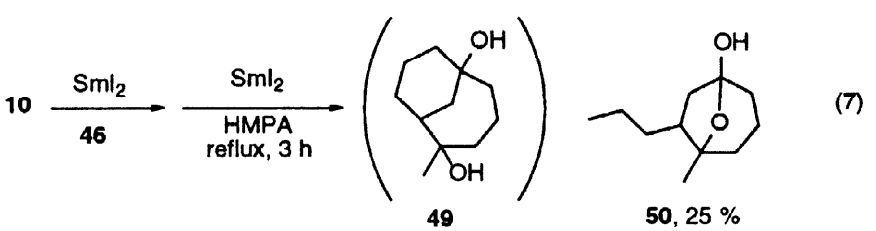
In these reactions, lactone formation was slow in comparison to the cases where *n*-butyl acrylate (**8**) was used as a ketyl radical acceptor. Interestingly, and in contrast to the examples in Table 1, the yield using HMPA as an activator in these cases was superior to the yields using the visible light method. The fact that HMPA addition led to complete consumption of starting material may have contributed positively to the higher yields.[11b] Using HMPA as a cosolvent in the sequential reaction with α- or β-monosubstituted acrylates and **9** gave substituted seven-membered carbocycles in good yield as mixtures of diastereomers (entries 1 and 2). Utilizing α,β-disubstituted acrylate **37** provided the corresponding disubstituted seven-membered carbocycle, once again as a diastereomeric mixture (entry 3). The ketone reduction product, 5-chloro-2-pentanol, was isolated as a main product when β,β-disubstituted acrylate **39** was used as a radical acceptor (entry 4). In this case, simple reduction of the ketone carbonyl competed sucessfully with lactone formation. This problem was not corrected when NiI_2 was added as an activator.[7]

When the cyclic carboxylate **40** was used as an acceptor, the corresponding seven-membered carbocycles **41a** and **41b** were produced as diastereomeric hydroxy ketones in moderate yield (entry 5). The α,β-unsaturated lactones **42** and **43** afforded only complex mixtures (entries 6 and 7). Dimethyl fumarate (**44**) provided the seven-membered carboxylic ester **45** in good yield (entry 8). In this case, the remaining ester group in the product **45** could serve as a handle for further functionalization.

Finally, the reaction between 5-bromo-2-pentanone (**10**) and chloro-substituted α,β-unsaturated ester **46** was examined. Initial exposure to SmI_2 resulted in lactone **47** (eq 5). Subsequent addition of HMPA effected nucleophilic acyl substitution to give the cyclic chloride **48** as a single diastereomer (eq 6). If the mixture was heated at reflux, reduction of the chloro functionality to the corresponding samarium carbanion group occurred. Unfortunately, the desired ketone addition reaction to give **49** did not occur. Instead, the samarium(III) carbanion was simply protonated to afford **50** (eq 7).







CONCLUSIONS

Herein we have demonstrated that a samarium(II) iodide-promoted ketyl-olefin coupling/intramolecular nucleophilic acyl substitution sequence is a useful method for synthesizing substituted six-, seven- and eight-membered cyclic hydroxy ketones from readily available halo ketones and α,β-unsaturated esters. These tandem reactions proceed in moderate to good yield in a one-pot procedure using either visible light or HMPA as activators for SmI_2. The tandem intermolecular ketyl-olefin coupling/intramolecular nucleophilic acyl substitution reaction sequence with SmI_2 and visible light has the advantage of being efficient and safe. Using HMPA with SmI_2 accelerates the ketyl-olefin coupling reaction in some cases and permits chemoselective halide activation.

ACKNOWLEDGMENTS

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EXPERIMENTAL SECTION

Reagents. Tetrahydrofuran (THF) was distilled from $LiAlH_4$ under argon and then redistilled from sodium-benzophenone ketyl immediately prior to use. Samarium metal was purchased from Cerac, Inc., Milwaukee, WI and stored under Ar. Iodine was purchased from Aldrich. HMPA was purchased from Aldrich and was distilled from CaH_2 and stored over 4Å molecular sieves under Ar. *t*-BuOH was purchased from Aldrich and was distilled from magnesium and stored over 4Å molecular sieves under Ar. *n*-Butyl acrylate and 5-chloro-2-pentanone was purchased from Aldrich and was distilled and stored over 4Å molecular sieves under Ar. All solvents were distilled prior to use. Commercially available reagents were used with no further purification. Standard benchtop techniques were employed for handling air-sensitive reagents,[12] and all reactions were performed under Ar.

Preparation of the SmI_2 Solution. Samarium metal (496.3 mg, 3.3 mmol) was added under a flow of argon to an oven-dried, round-bottomed two-necked flask containing a magnetic stirring bar and a septum inlet. Iodine (761.4 mg, 3.0 mmol) was added to a vigorously stirred suspension of samarium metal in THF (25 mL). The mixture was stirred vigorously for 3 h at rt. The resultant deep blue-green solution was used directly to effect the following sequential reactions.

General Procedure for the Synthesis of Hydroxy Cycloalkanones.

Method 1: To the SmI_2 (3.0 mmol) in THF (25 mL) at -78 °C, a solution of the halo ketone (0.5 mmol), α,β-unsaturated ester (0.5 mmol), and *t*-BuOH (0.5 mmol) in 5 mL of THF were added slowly dropwise over 20 min. The mixture was stirred at -78 °C for 30 min and then allowed to warm to rt. After the starting material was consumed and the intermediate lactone was formed, the reaction mixture was irradiated with visible light (250 W krypton lamp) for 8 h. The temperature was maintained below 25 °C. TLC analysis revealed the consumption of intermediate lactone. The reaction was quenched with a saturated aqueous solution of Rochelle's salt.[13] The organic phase was extracted with diethyl ether, washed with brine, and dried over anhydrous magnesium sulfate. The products were purified by silica gel flash chromatography.

Method 2: To the SmI_2 (3.0 mmol) in THF (25 mL) at -78 °C, a solution of the halo ketone (0.5 mmol), α,β-unsaturated ester (0.5 mmol), and *t*-BuOH (0.5 mmol) in THF (5 mL) were added slowly dropwise over 20 min. The mixture was stirred at -78 °C for 30 min and then allowed to warm to rt. After the starting material was consumed and the intermediate lactone was formed, HMPA (1 mL) was added to the reaction mixture at 0 °C. The mixture was stirred at 0 °C for 30 min and then allowed to warm to rt. TLC analysis revealed the consumption of the intermediate lactone. The reaction mixture was quenched with a saturated aqueous solution of Rochelle's salt.[13] The organic materials were extracted with diethyl ether, washed with brine, and dried over anhydrous magnesium sulfate. The products were purified by silica gel flash chromatography.

5-Methyl-8-oxabicyclo[3.2.1]octan-1-ol (13) was prepared from 5-chloro-2-pentanone (**9**, 60.3 mg, 0.5 mmol) and *n*-butyl acrylate (**8**, 64.0 mg, 0.5 mmol) according to the general procedure (method 1) described above to afford after flash chromatography (30% ethyl acetate/hexanes), **13** (52.1 mg 73% yield).

13: colorless crystals; mp 70-72 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 1.36-1.52 (m, 2H), 1.64-1.90 (m, 7H), 1.96-2.10 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.3 (t), 26.7 (q), 34.3 (t), 35.6 (t), 35.9 (t), 36.0 (t), 81.1 (s), 104.9 (s); IR (neat) 3390, 2947, 1100 cm^{-1}; LRMS (EI) *m/z* 142 (M^+), 124, 114, 99, 82, 71 (base); HRMS (EI) calcd for $C_8H_{14}O_2$: 142.0994, found 142.0998.

1-Hydroxy-6-methylbicyclo[4.4.0]-decan-4-one (15) a n d 6-Methylbicyclo[4.4.0]decan-1,4-diol (16a,b) were prepared from **14** (80.3 mg, 0.5 mmol) and *n*-butyl acrylate (**8**, 64.0 mg, 0.5 mmol) according to the general procedure (method 1) described above to afford, after flash chromatography (30% ethyl acetate/hexanes), the less polar compound **15** (23.6 mg, 26% yield), the more polar compound **16a** (15.8 mg, 17% yield), and **16b** (14.9 mg, 16% yield).

15: colorless crystals; mp 84-86 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (s, 3H), 1.00-1.77 (m, 9H), 1.83 (dd, *J* = 13.8, 2.1 Hz, 1H), 1.92 (td, *J* = 13.1, 5.4 Hz, 1H), 2.27 (ddt, *J* = 15.0, 5.7, 2.1 Hz, 1H), 2.75 (ddd, *J* = 15.0, 13.1, 7.8 Hz, 1H), 2.78 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.2 (t), 21.0 (t), 22.0 (q), 33.7 (t), 34.8 (t), 35.5 (t), 37.5 (t), 40.6 (s), 51.4 (t), 72.0 (s), 214.1 (s); IR (neat) 3474, 2940, 2864, 1700 cm^{-1}; LRMS (EI) *m/z* 182 (M^+), 167, 164, 153, 139, 125, 122, 112 (base); HRMS (EI) calcd for $C_{11}H_{18}O_2$: 182.1307, found 182.1305.

16a: colorless crystals; mp 161-163 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00-1.26 (m, 3H), 1.28 (s, 3H), 1.44-1.74 (m, 8H), 1.82 (dd, *J* = 14.4, 3.9 Hz, 1H), 1.96 (td, *J* = 13.7, 4.2 Hz, 1H), 2.16 (tt, *J* = 13.7, 4.2 Hz, 1H), 4.17 (tt, *J* = 4.2, 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.9 (t), 21.0 (t), 23.0 (q), 28.7 (t), 29.9 (t), 34.0 (t), 34.6 (t), 36.3 (s), 42.1 (t), 67.6 (d), 73.1 (s); IR (neat) 3418, 2924, 1017, 992, 960 cm^{-1}; LRMS (EI) *m/z* 184 (M^+), 166, 151, 148, 128, 112, 95, 82 (base); HRMS (EI) calcd for $C_{11}H_{20}O_2$: 184.1463, found 184.1454.

16b: colorless crystals; mp 163-165 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.12-2.14 (m, 14H), 4.00 (tt, *J* = 10.2, 5.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2 (t), 21.7 (t), 23.3 (q), 33.0 (t), 35.4 (t), 36.6 (t), 38.0 (s), 42.9 (t), 42.9 (t), 67.5 (d), 72.7 (s); IR (neat) 3381, 2932, 2864, 1158 cm^{-1}; LRMS (EI) *m/z* 184 (M^+), 166, 151, 137, 128, 123, 112 (base); HRMS (EI) calcd for $C_{11}H_{20}O_2$: 184.1463, found 184.1469.

1-Hydroxy-11-oxatricyclo[6.2.1.0^{4,8}]undecane (18) was prepared from **17** (73.3 mg, 0.5 mmol) and *n*-butyl acrylate (**8**, 64.0 mg, 0.5 mmol) according to the general procedure (method 1) described above to

afford, after flash chromatography (30% ethyl acetate/hexanes), **18** (54.7 mg, 65% yield) as a 9:1 mixture of diastereomers as determined by GC.

18: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) major compound: δ 1.44-1.94 (m, 13H), 2.00-2.14 (m, 2H), 3.90 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) major compound: δ 21.1 (t), 21.6 (t), 28.0 (t), 30.9 (t), 32.6 (t), 34.3 (t), 34.8 (t), 43.0 (d), 90.5 (s), 104.0 (s); IR (neat) 3390, 2942, 1732, 1093 cm^{-1}; LRMS (EI) *m/z* 168 (M^+), 150, 140, 122 (base), 108, 95, 80; HRMS (EI) calcd for $C_{10}H_{16}O_2$: 168.1150, found 168.1149.

1-Hydroxy-12-oxatricyclo[7.2.1.0^{4,9}]dodecane (20a and **20b)** were prepared from **19** (80.3 mg, 0.5 mmol) and *n*-butyl acrylate (**8**, 64.0 mg, 0.5 mmol) according to the general procedure (method 1) described above to afford, after flash chromatography (30% ethyl acetate/hexanes), the less polar compound **20a** (27.7 mg, 30% yield) and the more polar compound **20b** (38.4 mg, 42% yield).

20a: colorless crystals; mp 78-80 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82-0.97 (m, 2H), 1.15-2.05 (m, 15H), 3.48 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.8 (t), 25.6 (t), 25.9 (t), 27.8 (t), 32.7 (t), 35.0 (t), 36.0 (t), 37.0 (t), 39.7 (d), 82.2 (s), 105.4 (s); IR (neat) 3382, 2932, 1733 cm^{-1}; LRMS (EI) *m/z* 182 (M^+), 164, 154, 136, 122, 111, 94 (base); HRMS (EI) calcd for $C_{11}H_{18}O_2$: 182.1307, found 182.1315.

20b: colorless crystals; mp 103-106 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82-1.03 (m, 2H), 1.10-1.34 (m, 4H), 1.40-2.03 (m, 11H), 3.83 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.4 (t), 25.7 (t), 26.6 (t), 29.3 (t), 29.9 (t), 35.5 (t), 36.8 (t), 37.5 (t), 42.5 (d), 83.5 (s), 104.2 (s); IR (neat) 3374, 2925, 1456, 1344 cm^{-1}; LRMS (EI) *m/z* 182 (M^+), 164, 154, 136 (base), 122, 111, 94; HRMS (EI) calcd for $C_{11}H_{18}O_2$: 182.1307, found 182.1303.

1-Hydroxy-12-oxatricyclo[7.2.1.0^{5,9}]dodecane (22) and **6-Propyl-1-oxaspiro[4.4]nonan-2-one (23)** were prepared from **21** (73.3 mg, 0.5 mmol) and *n*-butyl acrylate (**8**, 64.0 mg, 0.5 mmol) according to the general procedure (method 1) described above to afford, after flash chromatography (30% ethyl acetate/hexanes), **22** (31.0 mg, 34% yield) as an 18 : 1 mixture of diastereomers as determined by GC. **23** (29.2 mg, 32% yield) was also prepared as an 18 : 1 mixture of diastereomers as determined by GC.

22: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) major compound: δ 1.25-2.22 (m, 17H), 3.54 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) major compound: δ 24.2 (t), 24.8 (t), 31.2 (t), 34.1 (t), 35.3 (t), 38.9 (t), 40.6 (t), 40.6 (t), 51.4 (d), 91.3 (s), 107.6 (s); IR (neat) 3394, 2932, 2862, 1452, 1065 cm^{-1}; LRMS (EI) *m/z* 182 (M^+), 164, 154, 140, 136, 122, 108, 94 (base); HRMS (EI) calcd for $C_{11}H_{18}O_2$: 182.1307, found 182.1317.

23: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) major compound: δ 0.91 (t, J = 6.6 Hz, 3H), 1.20-2.28 (m, 13H), 2.52-2.63 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) major compound: δ 14.3 (q), 21.3 (t), 21.6 (t), 29.6 (t), 29.7 (t), 29.8 (t), 30.3 (t), 39.4 (t), 48.9 (d), 95.7 (s), 177.1 (s); IR (neat) 2957, 2872, 1770, 1225 cm^{-1}; LRMS (EI) *m/z* 182 (M^+), 164, 153, 140, 122, 111 (base); HRMS (EI) calcd for $C_{11}H_{18}O_2$: 182.1307, found 182.1310.

1-Hydroxy-13-oxatricyclo[8.2.1.0^{5,10}]tridecane (25a and 25b) and **6-Propyl-1-oxaspiro[5.4]decan-2-one (26)** were prepared from **24** (87.3 mg, 0.5 mmol) and *n*-butyl acrylate (**8**, 64.0 mg, 0.5 mmol) according to the general procedure (method 1) described above to afford, after flash chromatography (30% ethyl acetate/hexanes), the less polar compound **25a** (23.5 mg, 24% yield) and the more polar compound **25b** (31.4 mg, 32% yield). **26** (23.5 mg, 24% yield) was also prepared as a 2.5 : 1 mixture of diastereomers as determined by GC.

25a: colorless crystals; mp 74-76 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10-2.20 (m, 19H), 3.03 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7 (t), 23.0 (t), 25.8 (t), 28.8 (t), 30.6 (t), 36.2 (t), 40.2 (t), 40.4 (t), 42.3 (t), 44.7 (d), 84.1 (s), 107.8 (s); IR (neat) 3392, 2928, 2858, 1448, 1060 cm^{-1}; LRMS (EI) *m/z* 196 (M^+), 178, 168, 154, 139, 136, 123, 111, 108 (base); HRMS (EI) calcd for $C_{12}H_{20}O_2$: 196.1463, found 196.1456.

25b: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.82-2.17 (m, 19H), 2.93 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 23.8 (t), 24.4 (t), 25.6 (t), 27.7 (t), 31.3 (t), 31.8 (t), 40.1 (t), 41.8 (t), 42.1 (t), 49.5 (d), 86.1 (s), 106.4 (s); IR (neat) 3392, 2932, 1456 cm^{-1}; LRMS (EI) *m/z* 196 (M^+), 178, 168, 154, 150, 136, 123, 108 (base); HRMS (EI) calcd for $C_{12}H_{20}O_2$: 197.1463, found 196.1475.

26: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) major compound: δ 0.90 (t, J = 6.9 Hz, 3H), 1.14-1.95 (m, 14H), 2.22 (ddd, J = 13.2, 9.9, 8.1 Hz, 1H), 2.46-2.72 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) major compound: δ 14.2 (q), 20.5 (t), 22.4 (t), 24.1 (t), 27.2 (t), 28.9 (t), 30.7 (t), 31.4 (t), 38.0 (t), 44.5 (d), 88.3 (s), 177.1 (s); IR (neat) 2935, 2864, 1770, 1176 cm^{-1}; LRMS (EI) *m/z* 196 (M^+), 178, 167, 153, 140, 136, 125, 122, 111 (base); HRMS (EI) calcd for $C_{12}H_{20}O_2$: 196.1463, found 196.1471.

6-Butyl-1-oxaspiro[4.4]nonan-2-one (29) was prepared from **27** (87.3 mg, 0.5 mmol) and *n*-butyl acrylate (**8**, 64.0 mg, 0.5 mmol) according to the general procedure (method 1) described above to afford, after flash chromatography (30% ethyl acetate/hexanes), **29** (52.6 mg, 54% yield) as a 5 : 1 mixture of diastereomers as determined by GC.

29: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) major compound: δ 0.90 (t, J = 6.6 Hz, 3H), 1.20-2.28 (m, 15H), 2.54-2.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) major compound: δ 14.0 (q), 21.2 (t), 22.9 (t), 27.7 (t), 29.5 (t), 29.7 (t), 29.8 (t), 30.6 (t), 39.3 (t), 49.0 (d), 95.8 (s), 177.2 (s); IR (neat) 2956, 2872, 1773, 1167 cm^{-1}; LRMS (EI) *m/z* 196 (M^+), 178, 167, 153, 136, 122, 111 (base); HRMS (EI) calcd for $C_{12}H_{20}O_2$: 196.1463, found 196.1476.

6-Pentyl-1-oxaspiro[4.4]nonan-2-one (32) was prepared from **30** (94.2 mg, 0.5 mmol) and *n*-butyl acrylate (**8**, 64.0 mg, 0.5 mmol) according to the general procedure (method 1) described above to afford, after flash chromatography (30% ethyl acetate/hexanes), **32** (76.1 mg, 72% yield) as a 10 : 1 mixture of diastereomers as determined by GC.

32: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) major compound: δ 0.89 (t, J = 6.6 Hz, 3H), 1.20-2.28 (m, 17H), 2.51-2.64 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) major compound: δ 14.0 (q), 21.2 (t), 22.5 (t), 28.0 (t), 28.1 (t), 29.5 (t), 29.7 (t), 29.8 (t), 32.0 (t), 39.3 (t), 49.1 (d), 95.8 (s), 177.2 (s); IR (neat) 2931, 2859, 1774, 1166 cm^{-1}; LRMS (EI) *m/z* 210 (M^+), 192, 181, 167, 150, 140, 122, 111 (base); HRMS (EI) calcd for $C_{13}H_{22}O_2$: 210.1620, found 210.1638.

5,7-Dimethyl-8-oxabicyclo[3.2.1]octan-1-ol (34a and **34b)** were prepared from 5-chloro-2-pentanone (**9**, 60.3 mg, 0.5 mmol) and methyl methacrylate (**33**, 50.1 mg, 0.5 mmol) according to the general procedure (method 2) described above to afford, after flash chromatography (30% ethyl acetate/hexanes), the less polar compound **34a** (24.2 mg, 31% yield) and the more polar compound **34b** (33.2 mg, 43% yield).

34a: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (d, J = 7.2 Hz, 3H), 1.20-1.50 (m, 3H), 1.28 (s, 3H), 1.60-1.80 (m, 4H), 2.00-2.20 (m, 2H), 3.06 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.4 (q), 18.8 (t), 27.2 (q), 35.4 (t), 35.7 (t), 38.5 (d), 44.3 (t), 78.3 (s), 104.2 (s); IR (neat) 3630, 2920, 1735, 1458 cm^{-1}; LRMS (EI) *m/z* 156 (M^+), 141, 138, 128, 123, 113, 110, 98, 96, 85 (base); HRMS (EI) calcd for $C_9H_{15}O_2$ $(M-H)^+$: 155.1073, found 155.1084.

34b: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (d, J = 7.2 Hz, 3H), 1.20-1.40 (m, 3H), 1.32 (s, 3H), 1.44-1.65 (m, 2H), 1.70-1.88 (m, 2H), 1.94-2.22 (m, 2H), 3.54 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.0 (q), 18.6 (t), 27.1 (q), 30.9 (t), 35.7 (t), 41.4 (t), 43.2 (d), 79.2 (s), 105.3 (s); IR (neat) 3384, 2964, 1702, 1206, 1113 cm^{-1}; LRMS (EI) *m/z* 156 (M^+), 141, 138, 128, 123, 113, 110, 98, 96, 85, 83 (base); HRMS (EI) calcd for $C_9H_{16}O_2$: 156.1150, found 156.1159.

5,6-Dimethyl-8-oxabicyclo[3.2.1]octan-1-ol (36) was prepared from 5-chloro-2-pentanone (**9**, 60.3 mg, 0.5 mmol) and methyl crotonate (**35** 50.1 mg, 0.5 mmol) according to the general procedure (method 2) described above to afford, after flash chromatography (30% ethyl acetate/hexanes), **36** (55.3 mg, 71% yield) as a 2:1 mixture of diastereomers as determined by ^{1}H- and ^{13}C-NMR.

36: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.99 (d, J = 6.9 Hz, 3H), 1.01 (d, J = 6.9 Hz, 3H), 1.20 (s, 3H), 1.22 (s, 3H), 1.30-1.60 (m, 6H), 1.60-1.80 (m, 8H), 1.90-2.40 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) major compound: δ 13.4 (q), 19.3 (t), 25.5 (q), 30.9 (t), 35.4 (t), 41.6 (d), 43.4 (t), 83.6 (s), 103.9 (s), minor compound: δ 18.8 (t), 19.1 (q), 22.4 (q), 35.1 (t), 37.0 (t), 37.5 (d), 45.8 (t), 82.4 (s), 103.3 (s); IR (neat) 3380, 2963, 1734, 1095 cm^{-1}; LRMS (EI) *m/z* 156 (M^+), 141, 137, 128, 113, 99, 98, 85 (base); HRMS (EI) calcd for $C_9H_{16}O_2$: 156.1150, found 156.1165.

5,7-Dimethyl-6-ethyl-8-oxabicyclo[3.2.1]octan-1-ol (38a and **38b)** were prepared from 5-chloro-2-pentanone (**9**, 60.3 mg, 0.5 mmol) and methyl (*E*)-2-methyl-2-pentenoate (**37**, 64.1 mg, 0.5 mmol) according to the general procedure (method 2) described above to afford, after flash chromatography (30% ethyl acetate/hexanes), the less polar compound **38a** (36.0 mg, 39% yield) and the more polar compound **38b** (21.0 mg, 23% yield).

38a: colorless crystals; mp 60-62 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (t, J = 7.5 Hz, 3H), 1.05 (d, J = 7.2 Hz, 3H), 1.21 (s, 3H), 1.28-1.51 (m, 5H), 1.62-1.86 (m, 5H), 3.21 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.7 (q), 17.7 (q), 18.7 (t), 21.9 (t), 26.5 (q), 30.8 (t), 35.4 (t), 44.5 (d), 59.4 (d), 80.6 (s), 103.2 (s); IR (neat) 3391, 2964, 1734, 1069 cm^{-1}; LRMS (EI) *m/z* 184 (M^+), 169, 155, 141, 126, 113, 97 (base); HRMS (EI) calcd for $C_{11}H_{20}O_2$: 184.1463, found 184.1474.

38b: colorless crystals; mp 82-84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3H), 1.15 (d, J = 7.2 Hz, 3H), 1.21 (s, 3H), 1.26-1.90 (m, 10H), 3.10 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6 (q), 13.5 (q), 18.0 (t), 22.7 (q), 26.5 (t), 30.6 (t), 37.0 (t), 51.2 (d), 51.4 (d), 81.2 (s), 103.8 (s); IR (neat) 3378, 2964, 1718, 1111 cm^{-1}; LRMS (EI) *m/z* 184 (M^+), 155, 141, 126, 113, 97 (base), 85, 71; HRMS (EI) calcd for $C_{11}H_{20}O_2$: 184.1463, found 184.1479.

2-Hydroxy-2-methylbicyclo[5.4.0]undecan-6-one (41a and **41b)** were prepared from 5-chloro-2-pentanone (**9**, 60.3 mg, 0.5 mmol) and methyl cyclohexenylcarboxylate (**40**, 70.1 mg, 0.5 mmol) according to the general procedure (method 2) described above to afford, after flash chromatography (30% ethyl acetate/hexanes), the less polar compound **41a** (27.5 mg, 28% yield) and the more polar compound **41b** (30.4 mg, 31% yield).

41a: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.20-2.00 (m, 13H), 2.37 (ddd, J = 12.3, 7.1, 4.2 Hz, 1H), 2.44 (td, J = 11.7, 3.6 Hz, 1H), 2.62 (td, J = 10.2, 7.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 17.8 (t), 25.5 (t), 26.2 (t), 26.6 (t), 29.4 (q), 30.1 (t), 40.4 (t), 42.2 (t), 47.5 (d), 51.9 (d), 73.8 (s), 216.3 (s); IR (neat) 3454, 2930, 2855, 1694, 1450 cm^{-1}; LRMS (EI) *m/z* 196 (M^+), 181, 178, 162, 153, 138, 125, 111, 43 (base); HRMS (EI) calcd for $C_{12}H_{20}O_2$: 196.1463, found 196.1480.

41b: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3H), 1.17-2.03 (m, 13H), 2.90 (brt, J = 12.9 Hz, 1H), 2.29 (dt, J = 11.7, 5.4 Hz, 1H), 2.74 (ddd, J = 11.7, 10.2, 6.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.8 (t), 22.5 (q), 25.8 (t), 26.1 (t), 26.2 (t), 31.4 (t), 39.2 (t), 44.0 (t), 48.5 (d), 55.1 (d), 74.6 (s), 216.2 (s); IR (neat) 3372, 2925, 2855, 1694, 1446 cm^{-1}; LRMS (EI) *m/z* 196 (M^+), 181, 178, 168, 153, 138, 125, 111 (base); HRMS (EI) calcd for $C_{12}H_{20}O_2$: 196.1463, found 196.1476.

6-Methoxycarbonyl-5-methyl-8-oxabicyclo[3.2.1]octan-1-ol (45) was prepared from 5-chloro-2-pentanone (**9**, 60.3 mg, 0.5 mmol) and dimethyl fumarate (**44**, 79.3 mg, 0.5 mmol) according to the general procedure (method 2) described above to afford, after flash chromatography (30% ethyl acetate/hexanes), **45** (64.1 mg, 64% yield) as a 1:1 mixture of diastereomers as determined by ^{1}H- and ^{13}C-NMR.

45: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.48 (s, 3H), 1.40-1.90 (m, 10H), 2.08 (t, J = 12.9 Hz, 1H), 2.22 (dd, J = 13.5, 9.0 Hz, 1H), 2.30 (dd, J = 13.5, 7.8 Hz, 1H), 2.62 (dd, J = 13.5, 6.0 Hz, 1H), 2.81 (dd, J = 9.0, 6.3 Hz, 1H), 3.05 (dd, J = 12.3, 6.3 Hz, 1H), 3.60-3.80 (m, 2H), 3.71 (s, 3H), 3.72 (s, 3H), 4.06 (brs, 1H), 4.18 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.8 (t), 18.9 (t), 23.1 (q), 26.8 (q), 32.5 (t), 34.1 (t), 35.5 (t), 36.9 (t), 38.0 (t), 40.0 (t), 49.8 (d), 51.8 (q), 51.8 (q), 51.9 (d), 82.1 (s), 83.0 (s), 103.9 (s), 104.3 (s), 172.1 (s), 175.1 (s); IR (neat) 3412, 2954, 1732, 1435, 1349, 1204, 1107, 1043, 1026 cm^{-1}; LRMS (EI) *m/z* 200 (M^+), 182, 172, 154, 140, 129, 122, 113 (base), 97, 87; HRMS (EI) calcd for $C_{10}H_{16}O_4$: 200.1049, found 200.1036.

5-(3-Bromopropyl)-4-(3-chloropropyl)-5-methyltetrahydrofuran-2-one (47). To the SmI_2 (3.0 mmol) in THF at -78 °C, **10** (164.9 mg, 0.25 mmol), **46** (40.6 mg, 0.25 mmol), and *t*-BuOH (0.25 mmol) in 5 mL of THF were added slowly dropwise over 20 min. The mixture was stirred at -78 °C for 30 min and then allowed to warm to rt. After the starting material was consumed, the reaction was quenched with a saturated aqueous solution of Rochelle's salt.[13] The organic phase was extracted with diethyl ether, washed with brine, and dried over anhydrous magnesium sulfate. Silica gel flash chromatography gave **47** (33.9 mg, 46% yield) as a 5 : 1 mixture of diastereomers as determined by GC.

47: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) major compound: δ 1.44 (s, 3H), 1.46-2.16 (m, 9H), 2.27-2.39 (m, 1H), 2.60-2.70 (m, 1H), 3.37-3.52 (m, 2H), 3.58 (brt, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) major compound: δ 24.5 (q), 26.4 (t), 26.6 (t), 31.2 (t), 33.4 (t), 33.9 (t), 34.6 (t), 44.4 (t), 46.2 (d), 87.5 (s), 175.1 (s); IR (neat) 2934, 1766, 1446, 1385, 1242 cm^{-1}; LRMS (EI) *m/z* 297 $(M+1)^+$, 283, 281, 267, 265, 219, 175 (base); HRMS (EI) calcd for $C_{11}H_{19}BrClO_2$: $(M+H)^+$: 297.0257, found 297.0251.

6-(3-Chloropropyl)-5-methyl-8-oxabicyclo[3.2.1]octan-1-ol (48). To the SmI_2 (3.0 mmol) in THF at -78 °C, **10** (164.9 mg, 0.25 mmol), **46** (40.6 mg, 0.25 mmol), and *t*-BuOH (0.25 mmol) in 5 mL of THF were added slowly dropwise over 20 min. The mixture was stirred at -78 °C for 30 min and then allowed to warm to rt. After the starting material was consumed and the intermediate lactone was formed, HMPA (1 mL) was added to the reaction mixture at 0 °C. The mixture was stirred at 0 °C for 30 min and then at rt for 3 h. TLC analysis revealed the consumption of intermediate lactone. The reaction was quenched with a saturated aqueous solution of Rochelle's salt.[13] The organic materials were extracted with diethyl ether, washed with brine, and dried over anhydrous magnesium sulfate. Silica gel flash chromatography gave **48** (17.4 mg, 32% yield) as a single isomer.

48: colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (s, 3H), 1.40-2.08 (m, 13H), 3.56 (t, J = 6.3 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.6 (t), 25.9 (q), 26.5 (t), 31.2 (t), 32.3 (t), 35.4 (t), 42.0 (t), 45.0 (t),

47.2 (d), 83.3 (s), 103.9 (s); IR (neat) 3382, 2934, 1450, 1378, 1348, 1271, 1226, 1107 cm^{-1}; LRMS (EI) *m/z* 218 (M^+), 200, 190, 183, 175, 154, 141, 128, 113, 95, 83, 71, 43 (base); HRMS (EI) calcd for $C_{11}H_{19}ClO_2$: 218.1074, found 218.1087.

5-Methyl-6-propyl-8-oxabicyclo[3.2.1]octan-1-ol (50). To the SmI_2 (3.0 mmol) in THF at -78 °C, **10** (164.9 mg, 0.25 mmol), **46** (40.6 mg, 0.25 mmol), and *t*-BuOH (0.25 mmol) in 5 mL of THF were added slowly dropwise over 20 min. The mixture was stirred at -78 °C for 30 min and then allowed to warm to rt. After the starting material was consumed and the intermediate lactone was formed, HMPA (1 mL) was added to the reaction mixture at 0 °C. The mixture was stirred at 0 °C for 30 min and then at rt for 3 h. TLC analysis revealed the consumption of intermediate lactone. The reaction mixture was heated at reflux for 3 h. The reaction was quenched with a saturated aqueous solution of Rochelle's salt.[13] The organic phase was extracted with diethyl ether, washed with brine, and dried over anhydrous magnesium sulfate. Silica gel flash chromatography gave **50** (11.5 mg, 25% yield) as a single isomer.

50: colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, J = 6.9 Hz, 3H), 1.23 (s, 3H), 1.25-1.80 (m, 11H), 1.98-2.10 (m, 2H), 3.30 (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3 (q), 19.6 (t), 22.5 (t), 26.0 (q), 31.3 (t), 31.6 (t), 35.6 (t), 42.3 (t), 47.8 (d), 83.4 (s), 103.9 (s); IR (neat) 3380, 2928, 1098 cm^{-1}; LRMS (EI) *m/z* 184 (M^+), 166, 156, 151, 141, 128, 114 (base); HRMS (EI) calcd for $C_{11}H_{20}O_2$: 184.1463, found 184.1476.

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