Sequenced Reactions with Samarium(II) Iodide. Sequential Intermolecular Carbonyl Addition/Intramolecular Nucleophilic Acyl Substitution for the Preparation of Seven-, Eight-, and Nine-Membered Carbocycles

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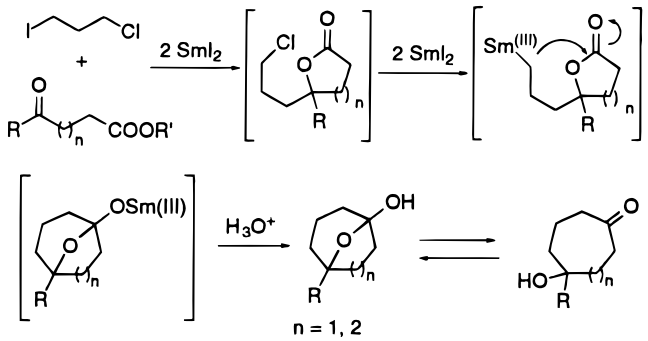
Samarium(II) iodide has been employed to promote a tandem intermolecular carbonyl addition/intramolecular nucleophilic acyl substitution sequence, generating seven- through nine-membered monocyclic, bicyclic, and tricyclic ring systems with good yields and high diastereoselectivities. This tandem reaction consists of an intermolecular reaction followed by an intramolecular ring expansion that results in a formal [$m + n$] cycloaddition, starting from extremely simple, readily available substrates. The regioselectivity and stereoselectivity of the process arise from a tuning of the reducing power of samarium(II) iodide with nickel(II) iodide in the first step and irradiation with visible light in the second. By using this method, a variety of structural motifs have been assembled rapidly in good yields.

Medium-sized carbocycles are structural units present in a wide range of natural products, existing either as isolated rings or forming part of bicyclic or tricyclic frameworks.[1] The synthesis of these structures is often quite challenging, mainly because the application of carbon−carbon bond-forming reactions to macrocycle synthesis is not always straightforward. Entropic factors, together with transannular interactions that inhibit cyclization, conspire to make the construction of medium-sized rings difficult.[2] As evidence of this, the number of general methods for preparing medium-sized carbocycles by cyclization or cycloaddition (annulation) reactions from acyclic precursors is relatively small.[1a,3]

We have previously demonstrated that SmI_2 in the presence of catalytic Fe(III) promotes the intramolecular nucleophilic acyl substitution of haloalkyl-substituted carboxylic acid derivatives.[4] In particular, we have reported a powerful method for obtaining medium-sized ring systems from appropriate haloalkyl-substituted lactones through a ring expansion employing this process.[4a]

In the present contribution we outline a novel way of obtaining medium ring hydroxy ketones by a more efficient, sequenced process. The reducing power of samarium(II) iodide (SmI_2) can be tuned by using a variety of solvents and additives or by a change in the reaction conditions. The chemoselectivity of this reductant is therefore highly adjustable.[5] Moreover, excellent diastereoselectivities are associated with many SmI_2-promoted reactions. These characteristics have made SmI_2 an excellent reagent for promoting sequential organic reactions.[5d,6] We reasoned that the intermolecular reaction between a chloroiodoalkane and a keto ester would yield a chloroalkyl-substituted lactone via an initial carbonyl addition reaction (Scheme 1). Preferential reactivity of the iodide over the chloride would be necessary to lead the process along a regioselective pathway. High selectivity for reaction at aldehydes or ketones in preference to the ester would be required.[7] Upon initial carbonyl addition, the formation of a lactone would be critical for the success of the annulation. This lactone would serve as a template, providing structural constraints to permit the medium-sized ring to be generated by a ring expansion process through what would formally be a five- or six-membered transition structure. Thus, reaction of the chloroalkyl-substituted lactone via an intramolecular nucleophilic acyl substitution would afford the desired carbocyclic hydroxy ketone.

Scheme 1



(1) (a) Petasis, N. A.; Patane, M. A. *Tetrahedron* **1992**, *48*, 5757 and references therein. (b) Oishi, T.; Ohtsuka, Y. In *Studies in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. 3, p 73 and references therein. (c) Rigby, J. H. In *Studies in Natural Products Synthesis*; Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1993; Vol. 12, p 233.

(2) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95.

(3) Molander, G. A. *Acc. Chem. Res.* In press.

(4) (a) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1993**, *58*, 7216. (b) Molander, G. A.; Shakya, S. R. *J. Org. Chem.* **1994**, *59*, 3445.

(5) For general reviews, see: (a) Soderquist, J. A. *Aldrichimica Acta* **1991**, *24*, 15. (b) Molander, G. A. *Chem. Rev.* **1992**, *92*, 29. (c) Molander, G. A. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1994; Vol. 46, p 211. (d) Molander, G. A.; Harris, C. R. *Chem. Rev.* **1996**, *96*, 307.

(6) (a) Molander, G. A.; Harris, C. R. *Tetrahedron.* In press. (b) Molander, G. A.; Kenny, C. *J. Org. Chem.* **1991**, *56*, 1439. (c) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1992**, *57*, 3132. (d) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1996**, *118*, 4059. (e) Molander, G. A.; del Pozo Losada, C. *J. Org. Chem.* **1997**, *62*, 2935. (f) Molander, G. A.; Alonso-Alija, C. *Tetrahedron* **1997**, *53*, 8067.

(7) (a) Kagan, H. B.; Machrouhi, F.; Hamann, B. *Synlett* **1996**, 633. (b) Csuk, R.; Hu, S.; Abdou, M.; Kratky, C. *Tetrahedron* **1991**, *47*, 7037. (c) Molander, G. A.; McKie, J. A. *J. Org. Chem.* **1991**, *56*, 4112.

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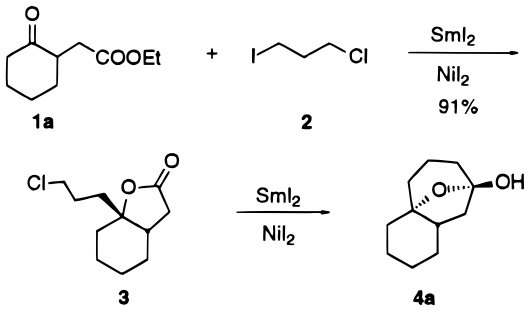
Scheme 2



There were some potential pitfalls associated with the proposed process and some obvious restrictions as well. For example, 1,2-dihaloalkanes could not be utilized because of the certainty of rapid β-elimination upon reaction with SmI_2,[5c] and cyclopropane formation from iodochloropropanes would have to be avoided.[8] It was anticipated that only five- and six-membered lactones would be formed efficiently after the initial carbonyl addition. In the final step of the overall process, the intramolecular nucleophilic acyl substitution was expected to take place in good yields only when a five- or six-membered transition structure was involved.

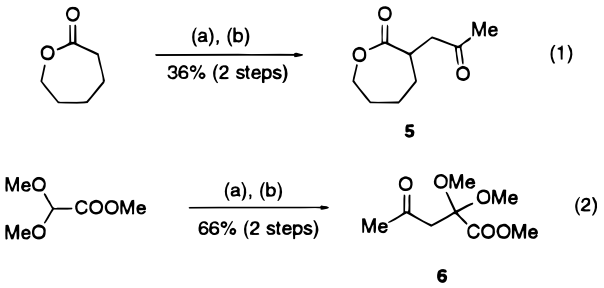
Interestingly, the reactions described in this paper have been successfully sequenced in the reverse order previously (i.e., nucleophilic acyl substitution followed by carbonyl addition).[9] The domino reaction developed herein establishes a formal [$m + n$] annulation between a dihaloalkane and a keto ester, generating seven-, eight-, and even nine-membered rings in an efficient manner.

Results and Discussion

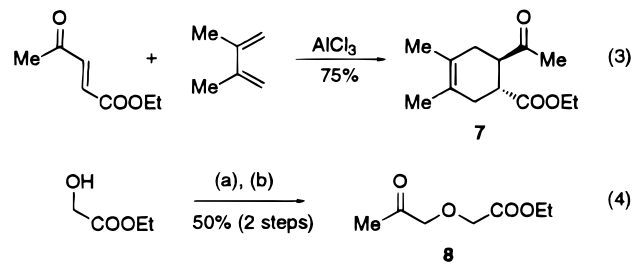
The desired process was initially tested by treating commercially available ethyl 2-oxocyclohexaneacetate (**1a**) and 1-chloro-3-iodopropane (**2**) with SmI_2 (Scheme 2). The intermediate chloroalkyl-substituted lactone **3** was smoothly formed within minutes and could be isolated in high yield and stereoselectivity when a catalytic amount of NiI_2 (2%) was used in the reaction.[7a] The second step of the sequenced process did not take place directly under these reaction conditions. An adjustment of the reaction conditions was required in order to promote the reduction of the terminal chloride. Addition of an excess of hexamethylphosphoramide (HMPA)[10] to the reaction mixture provided the desired bicyclic hydroxy ketone **4a** with excellent diasteroselectivity, although the yields were moderate even after 12 h of reaction. Large amounts of the intermediate lactone **3** remained unreacted. Using HMPA as a cosolvent from the beginning of the reaction led only to complex mixtures because under these conditions the necessary chemoselectivity of the SmI_2 was lost.

Irradiation with visible light has been reported to enhance the reducing ability of SmI_2, enabling the efficient reduction of organic chlorides.[11] This procedure proved to be very useful in the present study. Irradiation of lactone **3** with visible light in the presence of SmI_2 promoted the reduction of the chloride, and subsequent nucleophilic acyl substitution ensued to provide the desired hydroxy ketone. In this way, the method for the efficient one-pot synthesis of cyclic hydroxy ketones via a sequenced annulation process was established. Addition of the keto ester to a solution of SmI_2 containing 2% of NiI_2, followed by the dropwise addition of a THF solution of the chloroiodoalkane and subsequent irradiation of the reaction mixture with visible light for 3 h, afforded the desired hydroxy ketone **4a** in equilibrium with its hemiacetal. The desired product could be isolated after aqueous workup in good yield and with total diastereoselectivity. The advantages of the use of light as a promoter of SmI_2 reactions over using HMPA are obvious in terms of cost, safety, and cleanliness of the reactions.

The scope of the reaction with regard to the keto ester partners was next examined. The synthesis of several 4-keto esters was accomplished by alkylation of the appropriate ester or lactone with 3-bromo-2-methylpropene and subsequent ozonolysis (eqs 1 and 2). Alternatively, the alkylation of a ketone with ethyl bromoacetate led to complementary 4-keto esters. The keto ester **7** was synthesized by a Diels−Alder cycloaddition reaction (eq 3).[12] Ether **8** was generated by alkylation of ethyl glycolate with 3-bromo-2-methylpropene followed by ozonolysis (eq 4). Several 1,5-keto esters were easily prepared via Michael addition reactions.[13]



Key: (a) LDA, HMPA, $BrCH_2C(CH_3)=CH_2$; (b) O_3, then DMS.



Key: (a) NaH, $BrCH_2C(CH_3)=CH_2$; (b) O_3, then DMS.

Application of the standard experimental procedure developed to the reaction between 1-chloro-3-iodopropane

(8) (a) Connor, D. S.; Wilson, E. R. *Tetrahedron Lett.* **1967**, 4925. (b) Semmler, K.; Szeimies, G.; Belzner, J. *J. Am. Chem. Soc.* **1985**, *107*, 6410. (c) Bailey, W. F.; Gagnier, R. P. *Tetrahedron Lett.* **1982**, *23*, 5123. (d) Wiberg, K. B.; Lampman, G. M. *Tetrahedron Lett.* **1963**, 2173. (e) House, H. O.; Lord, R. C.; Rao, H. S. *J. Org. Chem.* **1956**, *21*, 1487. (f) Wiberg, K. B.; William, V. Z. *J. Org. Chem.* **1970**, *35*, 369.

(9) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705.

(10) Inanaga, J.; Ishikawa, M.; Yamaguchi, M. *Chem. Lett.* **1987**, 1485.

(11) (a) Skene, W. G.; Scaiano, J. C.; Cozens, F. L. *J. Org. Chem.* **1996**, *61*, 7918. (b) Ogawa, A.; Sumino, Y.; Nanke, T.; Ohya, S.; Sonoda, N.; Hirao, T. *J. Am. Chem. Soc.* **1997**, *119*, 2745. (c) Ogawa, A.; Ohya, S.; Hirao, T. *Chem. Lett.* **1997**, 275.

(12) For preparation of the dienophile, see: McMurry, J. E.; Blaszczak, L. C. *J. Org. Chem.* **1974**, *39*, 2217.

Table 1. Sequential SmI_2-Promoted Carbonyl Addition/Nucleophilic Acyl Substitution between Keto Esters and 1-Chloro-3-iodopropane (2)

entry	substrate	product	% isolated yield (ds)	entry	substrate	product	% isolated yield (ds)
1	**9a**, n = 1	**10a**	78	11	**19**	--[f]	
2	**9b**, n = 2	**10b**	74	12	**20**	--[f]	
3	**9c**, n = 3	--[a]		13	**21**	**22**	80
4	**1b**, n = 1	**4b**	58[c]				
5	**1a**, n = 2	**4a**[b]	70[c]	14	**5**	**23**	45 (8:1)[g]
6	**11a**, n = 1	**12a**	52[c]				
7	**11b**, n = 2	**12b**	66[c]	15	**6**	**24**	51
8	**13**	**14**	60[d]	16	**7**	--[f]	
9	**15**	**16**	64	17	**8**	--[f]	
10	**17**	**18**	44[e]				

[a] Simple addition of the organosamarium to the carbonyl without formation of the lactone. [b] Characterized after acylation. [c] A single diastereomer was detected. [d] Yield after acylation of the crude product with acetic anhydride/pyridine/DMAP. [e] Yield when using 2 equiv of dihaloalkane and 8 equiv of SmI_2. [f] Complex mixture obtained. [g] Stereochemistry not assigned.

and several of these 4-keto ester and 5-keto ester substrates afforded the expected cyclic hydroxy ketones, for the most part isolated as hemiacetals (Table 1). Simple seven- and eight-membered carbocycles were efficiently formed from both keto esters and the corresponding aldehydes. As anticipated, the size of the intermediate lactone was limited to five or six members, with no formation of a seven-membered lactone evident when the dihaloalkane was reacted with a 6-keto ester (entry 3). Substitution α to the ketone was not well tolerated (entries 10 and 16). In these cases, simple reduction of the carbonyl group was a competing reaction. On the contrary, substitution α to the ester group appeared to present few problems (entries 13 and 15). α,β-Unsaturated ketones **19** and **20**[14] (entries 11 and 12) afforded only complex mixtures in the first step of the reaction, and the synthesis of oxygen heterocycles also failed in the chlorolactone formation step (entry 17). Keto lactones (entry 14) turned out to be suitable substrates for the reaction, although the nucleophilic acyl substitution step was much slower than that in other cases.

Bicyclo[5.3.0], -[6.3.0], -[5.4.0], and -[6.4.0] ring systems were obtained in good yield and with complete diastereoselectivity. Single-crystal X-ray analysis of compound **12b** confirmed the expected trans fusion between the two carbocyclic rings resulting from attack of the organosamarium species trans to the side chain on the cyclic keto ester in the first step of the reaction.

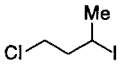
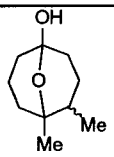
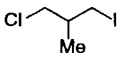
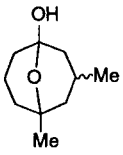
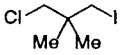
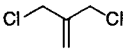
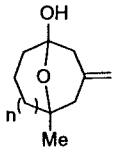
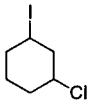
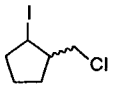
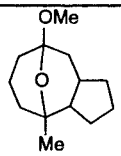
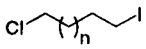
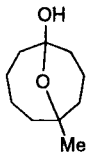
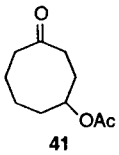
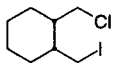
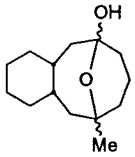
The synthesis of several different 1-chloro-3-iodoalkanes was carried out starting from α,β-unsaturated ketones (Scheme 3). Addition of hydrogen chloride to the conjugated double bond afforded the corresponding 3-chloro ketones, which were immediately reduced to the corresponding alcohols **25** and **27** with lithium aluminum hydride. Conversion of the resultant hydroxy group into an iodide provided an efficient way of synthesizing the 1-chloro-3-iodoalkanes **26** and **28**.

An alternative route utilized for the preparation of 1-chloro-3-iodoalkanes is shown in Scheme 4. The diol **29** was monotosylated in good yield, and the resulting

(13) (a) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223. (b) Stork, G.; Brizzolara, A.; Landesman, H.; Smuszkovicz, J.; Terrell, R. *J. Am. Chem. Soc.* **1963**, *85*, 207.

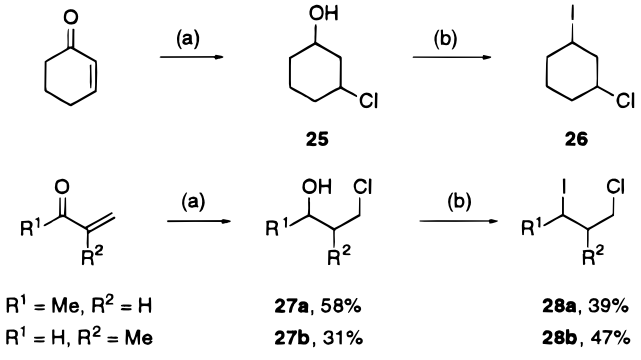
(14) Ziegler, F. E.; Piwinski, J. J. *J. Am. Chem. Soc.* **1982**, *104*, 7181.

Table 2. Sequential SmI_2-Promoted Carbonyl Addition/Nucleophilic Acyl Substitution between Ethyl 5-Oxohexanoate (9b) and Several Dihalo Compounds

entry	substrate	product	% isolated yield (ds)
1	 **28a**	 **33**	62 (1:1)
2	 **28b**	 **34**	38 (1:1)
3	 **35**	--[a]	
4	 **36**	 **37a**, n = 1	54
5		**37b**, n = 0[b]	46
6	 **26**	--[c]	
7	 **32**	 **38**	36 (1:1)[d]
8	 **39a**, n = 1	 **40**	65
9	**39b**, n = 2	--[e]	
10	**39c**, n = 3	--[f]	
11	**39a**[g]	 **41**	45
12	 **45b**	 **46**[h]	48 (3:1)

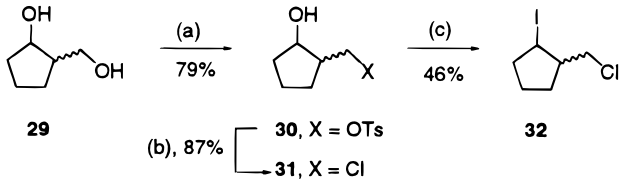
[a] The major compound isolated was δ-caprolactone. [b] Ethyl 4-oxopentanoate (**9a**) was used as the keto ester. [c] The major compound isolated was 5-cyclohexyl-δ-caprolactone. [d] Yield after methylation of the crude product with methyl orthoformate/PTSA in methanol. Stereochemistry not determined. [e] A nonreproducible mixture of the ten-membered ring and 5-pentyl-δ-caprolactone was isolated. [f] 5-Hexyl-δ-caprolactone was the only compound isolated. [g] Reaction with *n*-butyl 4-oxobutyrate (**13**). [h] The major diastereomer was characterized as the acylated compound (acetic anhydride/DMAP).

Scheme 3



Key: (a) HCl in Et_2O; then $LiAlH_4$; (b) PPh_3, imidazole, I_2.

Scheme 4



Key: (a) TsOH, pyr; (b) LiCl; (c) PPh_3, imidazole, I_2.

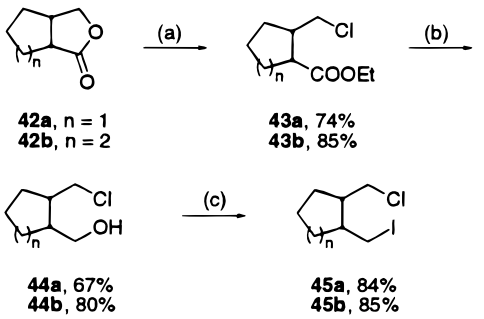
tosylate **30** was subsequently heated at reflux with lithium chloride in DMF to obtain the chloro alcohol **31**.[15] This was converted into the chloroiodoalkane **32**, a suitable substrate for the SmI_2-induced reaction.

The reaction between ethyl 5-oxopentanoate (**9b**) and several of these 1,3-dihaloalkanes was tested as shown in Table 2. Secondary iodides reacted efficiently under the standard reaction conditions, and the cyclization was completed in good yield (entry 1). However, the reduction of secondary chlorides with SmI_2 and visible light took place very slowly. In these cases, the only isolated products were the result of simple reduction of the chloride to the alkane prior to the cyclization (entry 6). 2-Substituted-1,3-dihalo compounds reacted rather inefficiently. One substituent in this position provided the desired product, although in modest yield (entry 2). Presumably, the chloroiodoalkane was partially consumed via the formation of cyclopropane side products. This effect was much more dramatic in 2,2-disubstituted compounds such as **35**,[16] wherein the Barbier reaction did not take place and the only isolated product was the δ-caprolactone. The latter was generated as a result of simple reduction and lactonization of the keto ester **9b** (entry 3). The reaction of compound **32** allowed the isolation of the bicyclo[6.3.0] product, albeit in moderate yield (entry 7). The diallylic dichloride **36** was sufficiently activated to afford the desired products without

(15) Falorni, M.; Lardicci, L.; Giacomelli, G. *J. Org. Chem.* **1986**, *51*, 5291.

(16) (a) Castro, B.; Selve, C. *Bull. Soc. Chim. Fr.* **1974**, 3004. (b) Castro, B.; Selve, C. *Bull. Soc. Chim. Fr.* **1974**, 3009.

Scheme 5



Key: (a) $SOCl_2$, cat. HCl (neat); then EtOH; (b) $LiAlH_4$, -78 °C; (c) PPh_3, imidazole, I_2.

the need for irradiation (entries 4 and 5). The isolation of these products in their hemiacetal forms prevented the isomerization of the double bond which has been observed in related reactions reported previously.[4a,9]

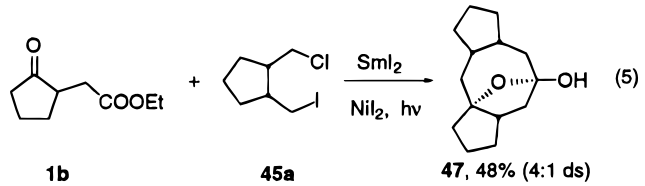
While establishing the practical limits of the reaction, we observed an unexpected annulation utilizing 1,4-dihaloalkane **39a** as a substrate. This one-pot process allowed the efficient synthesis of a nine-membered ring (entry 8). It is noteworthy that the ring expansion step must take place through a seven-membered transition structure in the attack of the organosamarium onto the lactone moiety. This example is not an isolated case, as the reaction of compound **13** with 1-chloro-4-iodobutane (**39a**) afforded the corresponding 4-acetoxycyclooctanone **41** in a comparable yield after acylation of the crude material (entry 11).

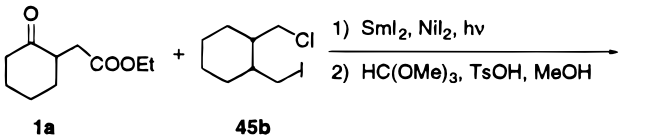
The scope of this unexpected cyclization with respect to the chain length of the dihalide substrates was briefly explored. Unfortunately, it was determined to be limited to 1,3- and 1,4-dihalides. For example, the reaction of **9b** with 1-chloro-5-iodopentane gave irreproducible mixtures of the desired ten-membered ring and simple dehalogenated lactone (entry 9), and 1-chloro-6-iodohexane showed only dehalogenation of the intermediate chlorolactone in the reaction with **9b** (entry 10).

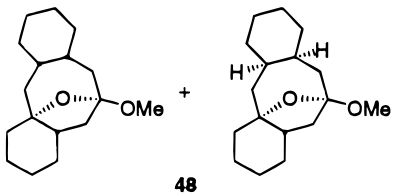
The synthesis of some novel 1-chloro-4-iodoalkanes was accomplished as depicted in Scheme 5. Ring opening of the cyclic *cis*-lactones **42a**[17] and **42b**[17a,e] with neat thionyl chloride and further addition of ethanol provided the 3-chloroesters **43** in a convenient one-pot reaction.[18] These compounds were reduced with lithium aluminum hydride at low temperature to afford the 4-chloro alcohols **44**. Finally, conversion of the hydroxy group into an iodide provided the requisite 1,4-chloroiodoalkanes **45**.[19]

The cyclic 1,4-dihalide **45b** reacted with the keto ester **9b** to afford the desired bicyclic keto alcohol, although in moderate yield as displayed in entry 12. Approximately 10% of the simple dehalogenated lactone was also formed in this case.

In light of these results, we investigated the synthesis of tricyclic frameworks via the sequenced reaction between a cyclic keto ester and a cyclic 1-chloro-4-iodoalkane (eqs 5 and 6). The reaction takes place to provide the desired carbotricyclics in moderate yield. Both ring fusions in the molecules are effectively set: one ring fusion is trans because of the diastereoselectivity of the initial carbonyl addition reaction and the stereochemistry of the second is fixed by the dihalide starting material. Only the relative stereochemistry between the two sets of stereocenters remains variable. For compound **47**, the relative stereochemistry of the major isomer was determined by single-crystal X-ray diffraction techniques. The net outcome of the SmI_2-sequenced, one-pot method provides an extremely simple way of constructing the 5:8:5 ring system that comprises the framework of several complex naturally occurring structures.[20]







Conclusions

The SmI_2-promoted carbonyl addition/nucleophilic acyl substitution sequence provides an efficient method for synthesizing seven- to nine-membered monocyclic, bicyclic, and tricyclic hydroxy ketones by intermolecular reactions between readily available keto esters and dihaloalkanes. Irradiation with visible light enhances the reducing power of SmI_2 and is of vital importance for completing this sequence. Noteworthy is the facile synthesis of the 5:8:5 ring system in a one-pot process utilizing this new method.

Experimental Section

Reagents. Tetrahydrofuran (THF) was distilled immediately prior to use from benzophenone ketyl under Ar. Samarium metal was purchased form Cerac Inc., Milwaukee, WI, and was stored under an inert atmosphere. Nickel(II) iodide (NiI_2) and iodine were purchased from Aldrich Chemicals. Hexamethylphosphoramide (HMPA) was purchased from Aldrich Chemicals and was distilled from CaH_2 at 0.04 mmHg and stored over 4 Å molecular sieves under Ar. Standard benchtop techniques were employed for handling air-sensitive reagents,[21] and all the reactions were carried out under Ar.

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(1*R,3*S**,8*R**)-1-Acetoxy-12-oxatricyclo[6.3.1.0^{3,8}]-dodecane (4a′). General Procedure for the Synthesis of Hydroxy Cycloalkanones.** THF (30 mL) was added to a mixture of samarium metal (519 mg, 3.45 mmol) and iodine (761 mg, 3.00 mmol). The brown slurry was stirred for 2 h at room temperature, while its color changed to yellow, green, and dark blue. NiI_2 (20 mg, 0.06 mmol) was added, and the mixture was cooled to 0 °C. After the solution was stirred for 5 min, 92 mg (0.50 mmol) of ethyl 2-cyclohexanoneacetate (**1**) was added, followed immediately by the dropwise addition of 112 mg (0.55 mmol) of 1-chloro-3-iodopropane (**2**) in 5 mL of THF over 30 min. When the addition of the substrates was complete, the reaction mixture was irradiated with visible light (250 W krypton lamp) for 3 h, while the temperature was maintained below 25 °C. The resultant mixture was quenched with a saturated aqueous solution of Rochelle's salt.[22] A 10% aqueous solution of potassium carbonate was added, the mixture was extracted several times with diethyl ether, and the organic materials were washed with brine and dried over anhydrous magnesium sulfate. Flash chromatography with 25% ethyl acetate:hexanes and Kugelrohr distillation afforded 64 mg (70% yield) of (1*R**,7*S**)-7-hydroxybicyclo[5.4.0]undecan-3-one (**4a**) as a single diastereomer (determined by GC), isolated as a hemiacetal:hydroxy ketone mixture. Further treatment of the product with an excess of acetic anhydride and pyridine in dichloromethane in the presence of a catalytic amount of DMAP[23] allowed the isolation of the title compound: mp 64−65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.69 (dd, J = 13.5, 8.0 Hz, 1H), 2.14 (m, 1H), 2.02 (s, 3H), 1.92 (m, 1H), 1.81−1.63 (m, 4H), 1.59−1.25 (m, 8H), 1.19 (m, 1H), 1.07 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 109.2, 81.4, 43.3, 39.1, 36.6, 33.7, 32.9, 32.3, 23.2, 21.7, 20.4, 18.9; IR (neat) 2933, 1738 cm^{-1}; LRMS (EI$^+$) *m*/*z* 224 (2.7), 206 (3.0), 182 (56), 164 (72), 154 (40), 136 (52), 122 (50), 111 (80), 94 (76), 79 (22), 67 (26), 55 (40), 43 (100). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 70.02; H, 9.14.

(1*R,6*S**)-1-(3-Chloropropyl)-9-oxabicyclo[4.3.0]nonan-8-one (3).** The procedure described above for the synthesis of **4a** was followed, except that the reaction was quenched immediately after the addition of the substrates. Flash chromatography over silica gel with 15% ethyl acetate:hexanes and Kugelrohr distillation afforded 98 mg (91% yield) of the title compound **3** as a single diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.57−3.45 (m, 2H), 2.53 (dd, J = 17.0, 8.0 Hz, 1H), 2.42 (dd, J = 17.0, 9.0 Hz, 1H), 2.30 (m, 1H), 1.90−1.72 (m, 5H), 1.68−1.61 (m, 2H), 1.59−1.51 (m, 2H), 1.46−1.40 (m, 2H), 1.33−1.26 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.3, 86.3, 45.1, 39.0, 34.8, 34.4, 32.0, 26.5, 25.9, 21.6, 20.6; IR (neat) 2937, 1770 cm^{-1}; LRMS (EI$^+$) *m*/*z* 218 (4.0), 216 (12), 175 (11), 173 (33), 139 (100), 111 (54), 67 (29), 55 (65), 41 (87). Anal. Calcd for $C_{11}H_{17}ClO_2$: C, 60.97; H, 7.91. Found: C, 61.34; H, 8.05.

(1*R,5*S**)-5-Methyl-8-oxabicyclo[3.2.1]octan-1-ol (10a).** Following the general procedure described above, 72 mg (0.50 mmol) of ethyl 4-oxopentanoate (**9a**) and 112 mg (0.55 mmol) of 1-chloro-3-iodopropane (**2**) provided 55 mg (78% yield) of the title compound **10a** after flash chromatography with 30% ethyl acetate:hexanes: mp 71−72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (bs, 1H), 2.05−1.98 (m, 1H), 1.81−1.58 (m, 7H), 1.45−1.29 (m, 2H), 1.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.8, 81.1, 36.1, 36.0, 35.7, 34.3, 26.7, 19.4; IR (neat) 3385, 2945, 1101 cm^{-1}; LRMS (EI$^+$) *m*/*z* 142 (12), 114 (24), 99 (66), 71 (83), 55 (62), 43 (100). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.17; H, 9.93.

5-Methyl-9-oxabicyclo[3.3.1]nonan-1-ol (10b). Following the general procedure described for the preparation of **4a**, 79 mg (0.50 mmol) of ethyl 5-oxohexanoate (**9b**) and 112 mg (0.55 mmol) of 1-chloro-3-iodopropane (**2**) provided 58 mg (74% yield) of the title compound **10b** after flash chromatography with 30% ethyl acetate:hexanes: mp 73−74 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.58 (s, 1H), 2.08 (m, 2H), 1.86 (m, 2H), 1.66−1.45 (m, 8H), 1.18 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 95.4, 75.4, 35.4, 34.5, 31.6, 20.6; IR (neat) 3390, 2934, 1202 cm^{-1}; LRMS (EI$^+$) *m*/*z* 156 (39), 128 (69), 110 (31), 95 (26), 82 (53), 71 (80), 69 (100), 56 (37), 43 (72). Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found: C, 69.58; H, 10.45.

(1*R,3*R**,7*S**)-1-Hydroxy-11-oxatricyclo[5.3.1.0^{3,7}]-undecane (4b).** Following the general procedure described for the preparation of **4a**, 85 mg (0.50 mmol) of ethyl 2-oxocyclopentaneacetate (**1b**)[9] and 112 mg (0.55 mmol) of 1-chloro-3-iodopropane (**2**) provided 49 mg (58% yield) of the title compound **4b** after flash chromatography with 25% ethyl acetate:hexanes as a single diastereomer as determined by GC: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.96 (bs, 1H), 2.31 (dd, J = 12.5, 9.0 Hz, 1H), 2.17 (m, 1H), 1.98−1.20 (m, 13H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 106.0, 92.9, 44.9, 44.5, 37.2, 35.5, 34.9, 32.7, 25.6, 20.1; IR (neat) 3386, 2946, 1103 cm^{-1}; LRMS (EI$^+$) *m*/*z* 168 (18), 150 (8.0), 140 (10), 108 (56), 97 (19), 94 (19), 81 (83), 80 (100), 67 (27), 55 (35), 41 (39). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.08; H, 9.64.

(1*R,4*R**,8*S**)-1-Hydroxy-12-oxatricyclo[6.3.1.0^{4,8}]-dodecane (12a).** Following the general procedure described for the preparation of **4a**, 85 mg (0.50 mmol) of methyl 3-(2-oxocyclopentyl)propionate (**11a**)[13a] and 112 mg (0.55 mmol) of 1-chloro-3-iodopropane (**2**) provided 48 mg (52% yield) of the title compound **12a** after flash chromatography with 25% ethyl acetate:hexanes as a single diastereomer as determined by GC: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 (bs, 1H), 1.96−1.86 (m, 2H), 1.84−1.35 (m, 15H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 95.7, 84.7, 41.7, 40.4, 36.9, 33.6, 32.2, 32.1, 24.1, 22.2, 19.9; IR (neat) 3390, 2943 cm^{-1}; LRMS (EI$^+$) *m*/*z* 182 (29), 154 (33), 136 (71), 122 (42), 108 (29), 94 (100), 79 (58), 67 (76), 55 (39), 41 (82). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.24; H, 10.09.

(1*R,4*R**,9*S**)-1-Hydroxy-13-oxatricyclo[7.3.1.0^{4,9}]-tridecane (12b).** Following the general procedure described for the preparation of **4**, 92 mg (0.50 mmol) of methyl 3-(2-oxocyclohexyl)propionate (**11b**)[13b] and 112 mg (0.55 mmol) of 1-chloro-3-iodopropane (**2**) provided 65 mg (66% yield) of the title compound **12b** after flash chromatography with 17% ethyl acetate:hexanes as a single diastereomer as determined by GC: mp 117−118 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70 (bs, 1H), 2.37 (m, 1H), 2.12 (m, 1H), 1.87 (m, 1H), 1.82−1.51 (m, 8H), 1.50−1.19 (m, 7H), 1.18−1.08 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 95.7, 75.9, 40.5, 37.6, 36.3, 36.1, 31.8, 28.7, 27.5, 25.7, 21.2, 21.1; IR (neat) 3418, 2931, 985 cm^{-1}; LRMS (EI$^+$) *m*/*z* 196 (41), 168 (56), 150 (46), 108 (98), 98 (59), 81 (72), 67 (53), 55 (58), 41 (100). Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.82; H, 10.41.

4-Acetoxycycloheptanone (14). The preparation of this compound was accomplished by following the general procedure described for the preparation of **4a**, except that 79 mg (0.50 mmol) of *n*-butyl 4-oxobutyrate (**13**) and 112 mg (0.55 mmol) of 1-chloro-3-iodopropane (**2**) were added simultaneously as a solution in 5 mL of THF. Acylation of the crude material in dichloromethane with an excess of acetic anhydride and pyridine and a catalytic amount of DMAP provided 51 mg (60% yield) of the title compound **14** after flash chromatography with 25% ethyl acetate:hexanes: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.93 (m, 1H), 2.58 (m, 1H), 2.46 (m, 2H), 2.39 (m, 1H), 2.00 (s, 3H), 1.92−1.82 (m, 4H), 1.80−1.73 (m, 1H), 1.67−1.58 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.3, 170.1, 73.2, 43.4, 37.6, 34.7, 28.8, 21.2, 18.8; IR (neat) 2944, 1732, 1704, 1244 cm^{-1}; LRMS (EI$^+$) *m*/*z* 155 (0.1), 152 (0.2), 128 (4.8), 110 (44), 100 (15), 82 (35), 68 (26), 55 (30), 43 (100). Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.19; H, 8.33.

5-Tridecyl-9-oxabicyclo[3.3.1]nonan-1-ol (16). Following the general procedure described for the preparation of **4a**, 156 mg (0.50 mmol) of methyl 5-oxooctadecanoate (**15**) and 112 mg (0.55 mmol) of 1-chloro-3-iodopropane (**2**) provided 104 mg (64% yield) of the title compound **16** after flash chromatography with 17% ethyl acetate:hexanes: mp 70−71 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70 (bs, 1H), 2.10 (m, 2H), 1.94 (m, 2H), 1.76−1.68 (m, 2H), 1.66−1.45 (m, 8H), 1.42−1.22 (m, 22H), 0.90 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 95.1, 77.2, 45.1, 35.9, 32.5, 31.9, 30.3, 29.7−29.6 (6), 29.3, 23.1, 22.7, 20.5, 14.1; IR (neat) 3335, 2918, 977 cm^{-1}; LRMS (EI$^+$) *m*/*z*

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324 (6.5), 296 (7.5), 156 (44), 128 (100), 110 (21), 95 (28), 83 (32), 69 (48), 55 (56), 41 (76). Anal. Calcd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42. Found: C, 77.66; H, 12.67.

(1*R,5*S**)-5-Isopropyl-8-oxabicyclo[3.2.1]octan-1-ol (18).** Following the general procedure outlined for the preparation of **4a** [except that 4.0 mmol of SmI_2 was prepared from 661 mg (4.4 mmol) of Sm and 1.015 g (4.0 mmol) of I_2], 86 mg (0.50 mmol) of ethyl 5-methyl-4-oxohexanoate (**17**) and 204 mg (1.00 mmol) of 1-chloro-3-iodopropane (**2**) provided 37 mg (44% yield) of the title compound **18** after flash chromatography with 20% ethyl acetate:hexanes: mp 66−67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.70 (bs, 1H), 2.03 (m, 1H), 1.85−1.53 (m, 8H), 1.40−1.33 (m, 2H), 0.91 (d, J = 7.0 Hz, 3H), 0.86 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 104.7, 86.4, 36.5, 36.1, 35.7, 31.0, 29.4, 19.1, 17.6, 17.0; IR (neat) 3386, 2959 cm^{-1}; LRMS (EI$^+$) *m*/*z* 170 (29), 142 (43), 127 (81), 99 (92), 83 (62), 71 (100), 55 (43), 41 (76). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.39; H, 10.84.

(1*R,5*S**)-7-Pentamethylene-5-methyl-7,11-oxabicyclo[3.2.1]octan-1-ol (22).** Following the general procedure described for the preparation of **4a**, 99 mg (0.50 mmol) of methyl 1-(2-oxopropyl)cyclohexanecarboxylate (**21**) and 112 mg (0.55 mmol) of 1-chloro-3-iodopropane (**2**) provided 84 mg (80% yield) of the title compound **22** after flash chromatography with 20% ethyl acetate:hexanes: mp 108−109 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.79 (bs, 1H), 1.80 (m, 1H), 1.77−1.02 (m, 17H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 105.1, 77.3, 47.0, 43.8, 35.4, 32.3, 31.7, 30.3, 28.0, 25.9, 24.3, 21.8, 18.9; IR (neat) 3401, 2934 cm^{-1}; LRMS (EI$^+$) *m*/*z* 210 (16), 123 (100), 107 (10), 96 (40), 81 (89), 67 (51), 55 (36), 43 (60). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.07; H, 10.60.

(1*R,5*S**,7*R**/*S**)-7-(4-Hydroxybutyl)-5-methyl-8-oxabicyclo[3.2.1]octan-1-ol (23).** Following the general procedure described for the preparation of **4a** (except that the irradiation time was 6 h), 85 mg (0.50 mmol) of 2-(2-oxopropyl)-ϵ-caprolactone (**5**) and 112 mg (0.55 mmol) of 1-chloro-3-iodopropane (**2**) provided 48 mg (45% yield) of the title compound **23** as an 8:1 diastereomeric mixture epimeric at C-7 (stereochemistry unassigned) after flash chromatography with neat ethyl acetate. The title compound was isolated as a hemiacetal:dihydroxy ketone mixture: ^{1}H NMR (500 MHz, $CDCl_3$) (major diastereomer, hemiacetal) δ 3.63 (m, 2H), 2.30 (bs, 2H), 2.01−1.87 (m, 2H), 1.75−1.25 (m, 12H), 1.25 (s, 3H), 1.12 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (major diastereomer, hemiacetal) δ 104.4, 78.7, 62.5, 44.1, 42.4, 36.3, 35.3, 32.6, 31.1, 27.1, 23.4, 18.8; IR (neat) 3390, 2936, 1770 cm^{-1}; HRMS calcd for $C_{12}H_{22}O_3$ 214.1569, found 214.1588; LRMS (EI$^+$) *m*/*z* 214 (3.6), 196 (11), 168 (13), 142 (31), 109 (49), 95 (31), 81 (49), 71 (64), 55 (64), 43 (100).

(1*R,5*S**)-5-Methyl-7,7-dimethoxy-8-oxabicyclo[3.2.1]octan-1-ol (24).** Following the general procedure outlined for the preparation of **4a**, 95 mg (0.50 mmol) of methyl 2,2-dimethoxy-4-oxopentanoate (**6**) and 112 mg (0.55 mmol) of 1-chloro-3-iodopropane (**2**) provided 52 mg (51% yield) of the title compound **24**, after flash chromatography with 25% ethyl acetate:hexanes: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (s, 1H), 3.28 (s, 3H), 3.24 (s, 3H), 2.05−1.91 (m, 2H), 1.81 (m, 1H), 1.75−1.66 (m, 3H), 1.49 (m, 1H), 1.36 (m, 1H), 1.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 106.0, 102.7, 76.2, 50.6, 48.5, 43.1, 35.3, 30.0, 27.5, 18.5; IR (neat) 3540, 2966, 2840 cm^{-1}; LRMS (EI$^+$) *m*/*z* 202 (1.7), 187 (5.8), 139 (10), 129 (48), 115 (100), 85 (13), 43 (41). Anal. Calcd for $C_{10}H_{18}O_4$: C, 59.39; H, 8.97. Found: C, 59.28; H, 9.10.

(1*R,4*R**/*S**,5*S**)-4,5-Dimethyl-9-oxabicyclo[3.3.1]nonan-1-ol (33).** Following the general procedure described for the preparation of **4a**, 79 mg (0.50 mmol) of ethyl 5-oxohexanoate (**9b**) and 120 mg (0.55 mmol) of 1-chloro-3-iodobutane (**28a**) provided 53 mg (62% yield) of the title compound **33** after flash chromatography with 25% ethyl acetate:hexanes, as a 1:1 diastereomeric mixture, as determined by GC: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02 (bs, 1H), 2.86 (bs, 1H), 2.28 (m, 1H), 2.10−1.26 (m, 21H), 1.17 (s, 3H), 1.13 (s, 3H), 1.02 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 6.5 Hz, 3H),; ^{13}C NMR (75 MHz, $CDCl_3$) δ 95.4, 95.0, 78.4, 38.6, 36.9, 35.8, 35.7, 35.4, 34.3, 31.9, 29.9 (2), 29.5, 28.6, 28.2, 20.7, 20.5, 17.2, 16.8; IR (neat) 3398, 2936, 1196 cm^{-1}; LRMS (EI$^+$) *m*/*z* 170 (9.0), 142 (22), 128 (60), 113 (27), 95 (34), 85 (43), 71 (100), 55 (29), 43 (80). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.18; H, 10.71.

(1*R,3*R**/*S**,5*S**)-3,5-Dimethyl-9-oxabicyclo[3.3.1]nonan-1-ol (34).** Following the general procedure described for the preparation of **4a**, 79 mg (0.50 mmol) of ethyl 5-oxohexanoate (**9b**) and 120 mg (0.55 mmol) of 1-chloro-3-iodo-2-methylpropane (**28b**) provided 32 mg (38% yield) of the title compound **34** after flash chromatography with 25% ethyl acetate:hexanes, as a 1:1 diastereomeric mixture, as determined by GC: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.85 (two bs, 2H), 2.36 (m, 1H), 2.07 (m, 1H), 1.96 (m, 1H), 1.89 (m, 1H), 1.84−1.25 (m, 14H), 1.22 (s, 3H), 1.21 (s, 3H), 1.14−0.94 (m, 4H), 0.89 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 96.1, 95.6, 75.4, 73.5, 44.7, 44.2, 42.3, 40.4, 38.0, 36.5, 35.2, 34.3, 31.7, 31.3, 26.9, 24.0, 23.8, 20.6, 20.4, 18.1; IR (neat) 3355, 2955 cm^{-1}; LRMS (EI$^+$) *m*/*z* 170 (13), 142 (11), 128 (27), 113 (16), 83 (70), 69 (47), 55 (27), 43 (100). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.41; H, 10.43.

(1*R,5*S**)-5-Methyl-3-methylene-9-oxabicyclo-[3.3.1]nonan-1-ol (37a).** The same general procedure was used as for the preparation of **4a**, except that the mixture was stirred at 0 °C for 3 h without being irradiated with light. By following this procedure, 79 mg (0.50 mmol) of ethyl 5-oxohexanoate (**9b**) and 69 mg (0.55 mmol) of 3-chloro-2-chloromethyl-1-propene (**36**) provided 45 mg (54% yield) of the title compound **37a** after flash chromatography with 30% ethyl acetate:hexanes: mp 102−103 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (m, 2H), 2.86 (bs, 1H), 2.58 (d, J = 14.0 Hz, 1H), 2.38−2.20 (m, 4H), 1.87 (m, 1H), 1.60−1.43 (m, 4H), 1.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3, 109.0, 96.0, 75.6, 44.7, 43.7, 36.5, 35.6, 30.8, 19.6; IR (neat) 3340, 2973, 1107 cm^{-1}; LRMS (EI$^+$) *m*/*z* 168 (37), 153 (26), 125 (24), 113 (37), 93 (43), 85 (40), 67 (26), 55 (29), 43 (100). Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.63; H, 9.61.

(1*R,5*S**)-5-Methyl-6-methylene-8-oxabicyclo-[3.2.1]octan-1-ol (37b).** The same general procedure was used as for the preparation of **4a**, except that the mixture was stirred at 0 °C for 3 h without being irradiated with light. By following this procedure, 72 mg (0.50 mmol) of ethyl 4-oxopentanoate (**9a**) and 69 mg (0.55 mmol) of 3-chloro-2-chloromethyl-1-propene (**36**) provided 35 mg (46% yield) of the title compound **37b** after flash chromatography with 30% ethyl acetate:hexanes: mp 89−90 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.83 (m, 2H), 3.36 (s, 1H), 2.40 (s, 2H), 2.19 (d, J = 13.5 Hz, 1H), 2.01 (d, J = 13.5 Hz, 1H), 1.99−1.94 (m, 1H), 1.75−1.59 (m, 3H), 1.36 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.2, 112.2, 105.0, 80.5, 46.2, 46.0, 36.5, 34.8, 26.2; IR (neat) 3305 cm^{-1}; LRMS (EI+) *m*/*z* 154 (10), 139 (7.5), 125 (7.0), 109 (24), 99 (96), 93 (16), 79 (16), 71 (24), 55 (24), 43 (100). Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.39; H, 9.30.

1-Methoxy-8-methyl-12-oxatricyclo[6.3.1.0^{3,7}]-dodecane (38). Following the general procedure described for the preparation of **4a**, 79 mg (0.50 mmol) of ethyl 5-oxohexanoate (**9b**) and 134 mg (0.55 mmol) of 2-chloromethyl-1-iodocyclopentane (**32**) were reacted with SmI_2. The crude product was stirred overnight at room temperature with 265 mg (2.5 mmol) of methyl orthoformate and a catalytic amount of TsOH in 10 mL of dry methanol to afford 38 mg (36%) of the title compound **38** after flash chromatography with 5% ethyl acetate:hexanes, as a 1:1 mixture of diastereomers (out of the four possible, stereochemistry unassigned): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.33 (s, 3H), 3.29 (s, 3H), 2.10 (dd, J = 14.0, 5.0 Hz, 1H), 1.92−0.90 (m, 31H), 1.19 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 98.8, 98.6, 76.0, 74.3, 54.4, 48.6, 48.3, 48.2, 40.3, 38.9, 38.7, 37.2, 37.1, 34.6, 31.4 (2), 29.9, 28.6, 28.3, 26.8, 25.7, 24.8, 22.5, 21.5, 20.0, 17.3; IR (neat) 2953, 1076 cm^{-1}; LRMS (EI$^+$) *m*/*z* 210 (24), 182 (16), 168 (13), 150 (25), 139 (25), 122 (22), 109 (100), 93 (49), 81 (63), 67 (59), 55 (35), 43 (66). Anal. Calcd for $C_{13}H_{22}O_2$: C, 74.24; H, 10.54. Found: C, 74.40; H, 10.66.

(1*R,6*S**)-6-Methyl-10-oxabicyclo[4.3.1]decan-1-ol (40).** Following the general procedure described for the preparation of **4a**, 79 mg (0.50 mmol) of ethyl 5-oxohexanoate (**9b**) and 120 mg (0.55 mmol) of 1-chloro-3-iodobutane (**39a**) provided 55 mg

(65% yield) of the title compound **40**, after flash chromatography with 30% ethyl acetate:hexanes: mp 66−67 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.55 (bs, 1H), 2.06 (m, 1H), 1.94−1.68 (m, 6H), 1.59−1.32 (m, 6H), 1.24 (m, 1H), 1.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 97.9, 74.8, 36.1, 35.0, 34.2, 33.3, 30.2, 19.2, 18.9, 18.5; IR (neat) 3296, 2940 cm^{-1}; LRMS (EI+) *m*/*z* 170 (11), 141 (38), 128 (38), 113 (22), 95 (25), 82 (100), 69 (62), 55 (46), 43 (53). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.76; H, 10.76.

4-Acetoxycyclooctanone (41). The preparation of this compound was accomplished by following the general procedure described for the synthesis of **4a**, except that 79 mg (0.50 mmol) of *n*-butyl 4-oxobutyrate (**13**) and 120 mg (0.55 mmol) of 1-chloro-3-iodobutane (**39a**) were added simultaneously as a solution in 5 mL of THF. Acylation of the crude material in dichloromethane with an excess of acetic anhydride and pyridine and a catalytic amount of DMAP provided 41 mg (45% yield) of the title compound **41**, after flash chromatography with 17% ethyl acetate:hexanes: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (m, 1H), 2.49−2.40 (m, 3H), 2.38−2.31 (m, 1H), 2.19−2.12 (m, 1H), 2.10−2.02 (m, 1H), 1.98 (s, 3H), 1.85−1.77 (m, 2H), 1.69−1.45 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 216.4, 170.2, 73.2, 40.5, 38.9, 30.2, 28.1, 27.9, 22.4, 21.2; IR (neat) 2940, 1738, 1732, 1246 cm^{-1}; LRMS (EI$^+$) *m*/*z* 185 (0.1), 142 (7.0), 124 (66), 113 (15), 95 (42), 80 (58), 67 (38), 55 (42), 43 (100). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 64.92; H, 8.62.

(1*R/*S**,3*R**,8*S**,10*R**/*S**)-1-Acetoxy-10-methyl-14-oxatricyclo[8.3.1.0^{3,8}]tetradecane (46′).** Following the general procedure described for the preparation of **4a**, 79 mg (0.50 mmol) of ethyl 5-oxohexanoate (**9b**) and 150 mg (0.55 mmol) of *cis*-1-chloromethyl-2-iodomethylcyclohexane (**45b**) provided 54 mg (48% yield) of the corresponding bicyclic compound **46** as a 3:1 mixture of diastereomers, as a hemiacetal:hydroxy ketone mixture. The product was acylated with an excess of acetic anhydride and DMAP in dichloromethane, and the title compound **46′** was isolated after flash chromatography with 10% ethyl acetate:hexanes. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.42 (m, 1H), 2.21−2.03 (s, 3H), 2.02 (s, 3H), 1.90−1.65 (m, 3H), 1.60−1.26 (m, 10H), 1.24−1.13 (m, 2H), 1.23 (s, 3H), 1.06 (dd, J = 14.5, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.2, 106.8, 75.3, 39.5, 37.3, 34.9, 33.0, 31.0, 30.6, 30.4, 28.9, 28.5, 22.7, 21.6 (2), 18.1; IR (neat) 2932, 1731 cm^{-1}; HRMS calcd for $C_{14}H_{24}O_2$ (M − C_2H_2O)$^+$ 224.1776, found 224.1756; LRMS (EI$^+$) *m*/*z* 224 (3.8), 206 (18), 189 (8.6), 163 (11), 135 (13), 111 (29), 96 (37), 81 (48), 67 (28), 55 (39), 43 (100).

(1*R,3*S**,7*R**,9*S**,11*S**)-9-Hydroxy-15-oxatetracyclo[7.5.1.0^{1,11}.0^{3,7}]pentadecane (47).** Following the general procedure described for the preparation of **4a**, 85 mg (0.50 mmol) of ethyl 2-oxocyclopentaneacetate (**1b**) and 150 mg (0.55 mmol) of *cis*-1-chloromethyl-2-iodomethylcyclopentane (**45a**) provided 53 mg (48% yield) of the title compound **47** and its minor diastereomer (due to the two relative ring fusions) in a 4:1 ratio. Further flash chromatography with 20% ethyl acetate:hexanes afforded the title compound **47**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.72 (bs, 1H), 2.60−2.49 (m, 2H), 2.23 (m, 1H), 2.09 (m, 1H), 1.96 (m, 1H), 1.89−1.33 (m, 14H), 1.31−1.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 106.1, 92.5, 46.1, 45.0, 44.7, 42.0, 40.9, 39.7, 36.0, 34.9, 34.6, 34.2, 23.8, 22.8; IR (neat) 2923 cm^{-1}; HRMS calcd for $C_{14}H_{22}O_2$ 222.1620, found 222.1620; LRMS (EI$^+$) *m*/*z* 222 (11), 205 (8.8), 162 (22), 122 (35), 107 (27), 95 (41), 81 (82), 67 (77), 55 (54), 41 (100).

(1*R,3*S**/*R**,8*R**/*S**,10*S**,12*S**)-10-Methoxy-17-oxatetracyclo[8.6.1.0^{1,12}.0^{3,8}]heptadecane (48).** Following the general procedure described for the preparation of **4a**, 92 mg (0.50 mmol) of ethyl 2-cyclohexanoneacetate (**1a**) and 150 mg (0.55 mmol) of *cis*-1-chloromethyl-2-iodomethylcyclohexane (**45b**) were reacted with SmI_2. The crude product was stirred overnight at room temperature with 265 mg (2.5 mmol) of methyl orthoformate and a catalytic amount of TsOH in 10 mL of dry methanol to afford 50 mg (40% yield) of the title compound **48** as a 1:1 mixture of diastereomers. Higher R_f diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.33 (s, 3H), 2.37 (dd, J = 13.5, 6.5 Hz, 1H), 2.30 (dd, J = 13.5, 10.0 Hz, 1H), 1.99−1.84 (m, 3H), 1.75−1.02 (m, 20H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.6, 82.8, 49.2, 47.7, 44.0, 40.9, 39.7, 37.5, 37.2, 34.8, 32.5, 29.7, 28.9, 26.3, 24.7, 22.3, 21.6; IR (neat) 2923, 2860 cm^{-1}; LRMS (EI+) *m*/*z* 264 (12), 232 (6.5), 207 (7.8), 190 (14), 168 (32), 153 (100), 121 (74), 95 (53), 81 (42), 67 (40), 55 (39), 41 (40). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.49; H, 10.83. Lower R_f diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.29 (s, 3H), 2.32−2.20 (m, 3H), 2.04 (m, 1H), 1.91−1.76 (m, 3H), 1.72−1.08 (m, 18H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 108.5, 81.3, 49.2, 44.6, 42.9, 42.5, 40.1, 37.2, 36.8, 35.4, 32.1, 29.6, 29.5, 28.0, 24.9, 21.9, 21.6; IR (neat) 2926, 2852 cm^{-1}; HRMS calcd for $C_{17}H_{28}O_2$ 264.2089, found 264.2092 LRMS (EI$^+$) *m*/*z* 264 (7.6), 232 (6.3), 190 (12), 168 (27), 166 (29), 153 (100), 121 (74), 95 (71), 81 (49), 67 (56), 55 (55), 41 (62).

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Supporting Information Available: Experimental details and characterizations for compounds **5**−**8**, **28**, **31**, **32**, and **43**−**45** (53 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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