Sequenced Reactions with Samarium(II) Iodide. Sequential Nucleophilic Acyl Substitution/Ketyl Olefin Coupling Reactions for the Preparation of Oxygen Heterocycles

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Samarium(II) iodide has been employed to promote a sequential intramolecular nucleophilic acyl substitution/intramolecular ketyl olefin coupling cyclization sequence to provide bicyclic, tricyclic, and spiro-fused oxygen heterocycles in excellent yield and with high diastereoselectivity.

Introduction

Since the initial development of samarium(II) iodide (SmI_2) as a reducing agent in the early 1980's, its ability to promote a variety of reductions and reductive coupling processes has been overwhelming.[1] Indeed, previous research from this laboratory and others has demonstrated SmI_2 to be an excellent reagent for performing a diverse array of reductive coupling processes. In each of these reactions, SmI_2 exhibits remarkable selectivity because its reactivity can be modulated through the addition of catalysts,[1c,2] solvent additives,[3] or through other variations of the reaction conditions.[4] It is the ability to alter the reactivity of SmI_2 that enhances the applicability of this reagent in complex synthetic operations, thereby providing the potential to make a major impact in many facets of synthetic chemistry.

Processes that generate multiple carbon−carbon or carbon−heteroatom bonds in a sequence of events without isolation of any intermediates represent a very powerful means to increase molecular complexity dramatically in a single operation.[5] Recent research from this laboratory has been directed toward developing SmI_2 into a useful reagent for such second-generation processes by asserting its ability to perform sequential reactions in both one- and two-electron processes, affording highly functionalized products from relatively simple precursors.[1a,6] For example, a sequential nucleophilic acyl substitution/Barbier-type coupling sequence leading to bicyclic and tricyclic ring systems has been reported.[6b] Additionally, a sequential nucleophilic acyl substitution/ketyl olefin coupling sequence has been developed.[6a]

Both tetrahydrofurans and tetrahydropyrans are becoming increasingly recognized as a common structural motif in many naturally occurring compounds.[7] This recognition, combined with our ongoing efforts aimed at utilizing SmI_2 in sequential processes, provided us with the impetus to apply this powerful ring-building strategy toward the generation of oxygen heterocycles. The sequence to be investigated involved the transformation of simple acyclic substrates to more complex heterocycles through a sequential nucleophilic acyl substitution/ketyl olefin coupling sequence, thus providing a unique entry to a multitude of bicyclic, tricyclic, and spiro-fused oxygen heterocycles. The problems associated with building these ring systems have been generally recognized.[8] The stereoselective synthesis of highly functionalized oxygen heterocycles by the protocol described herein posed a significant challenge as well. One inherent difficulty anticipated in constructing these heterocyclic systems during a sequential SmI_2-mediated process was the potential for α-deoxygenation of the initial α-heterosubstituted carbonyl system or, more likely, deoxygenation of the intermediate α-oxygenated ketone species.[9] Although it had been demonstrated repeatedly that SmI_2 is capable of promoting the rapid deoxygenation of both α-oxygenated ketones and esters (or lactones) even at −78 °C, we found that in the desired sequential coupling sequence the remarkable selectivity of SmI_2 allowed the

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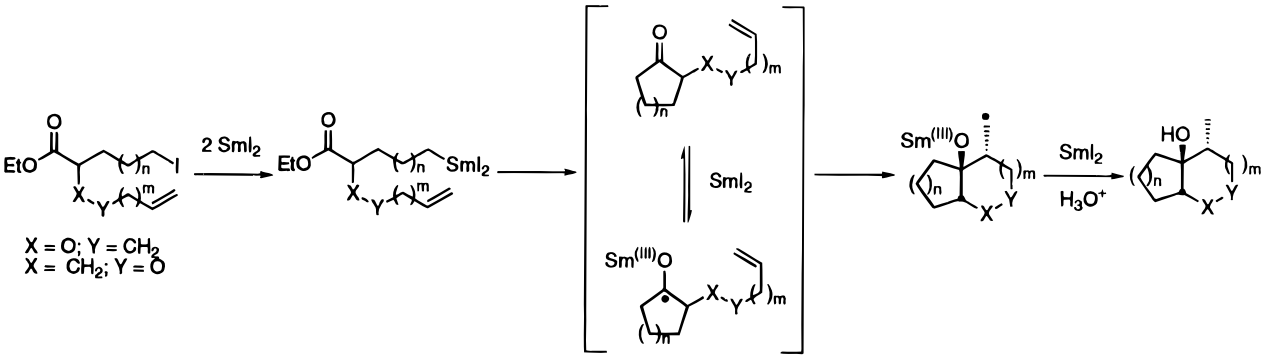
Scheme 1



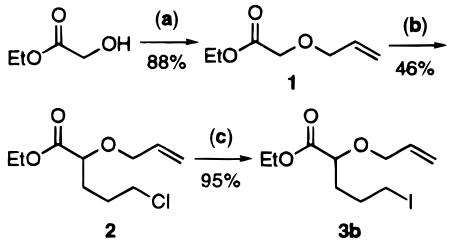
formation of the desired multi-ring, highly functionalized oxygen heterocycles while inducing little, if any, products derived from reductive cleavage of the oxygen species α to the ester or intermediate ketone.

Results and Discussion

Initial studies on the development of this sequential process concentrated primarily on ester functionalities containing both a pendant olefin and halogen chain, with one of these incorporating a remote oxygen ether functionality. A representative example is shown in Scheme 1. The cyclization is believed to proceed through the initial formation of an organosamarium species.[6b,10] Presumably, attack of the organosamarium species on the ester results in formation of a tetrahedral intermediate that collapses to liberate the cyclic ketone. The resultant olefinic ketone may then undergo either a 5-exo ($n = 0$) or 6-exo ($n = 1$) ketyl olefin coupling reaction.[6a,c,d,11] The resultant carbon-centered radical is rapidly reduced to an organosamarium species, generating the desired bicyclic oxygen heterocycle after an aqueous workup. The major diastereomers in both the 5-exo and 6-exo cyclizations are those with the developing radical center trans to the alkoxy group. The formation of this isomer avoids unfavorable stereoelectronic interactions in the radical cyclization.[6c,11]

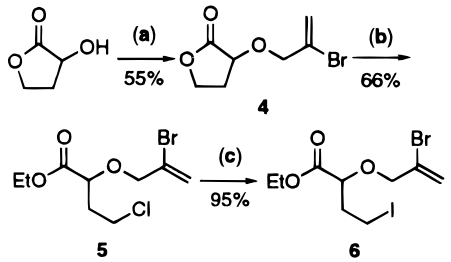
Initially, a series of olefinic esters was prepared to demonstrate the scope and limitations of this sequential process. The α-oxygenated substrates in these systems were prepared in one of two ways. A representative example is depicted in Scheme 2. Thus, ethyl glycolate was *O*-alkylated with an appropriate electrophile to generate the allyloxy carboxylate.[12] Subsequent alkylation of the resultant alkoxy ester with a second electrophile provided suitable substrates for SmI_2 chemistry.[13] Scheme 3 outlines an alternative strategy to these α-oxygenated substrates. As depicted in Scheme 3, Williamson ether synthesis beginning with α-hydroxybutyrolactone and an appropriate electrophile provided the desired allyloxy lactone. A one-pot lactone ring opening/ester generation with $SOCl_2$ (neat) followed by the addition of ethanol provided the α-oxygenated substrates. Finally, a Finkelstein reaction with NaI provided the requisite substrates in relatively few steps.

Scheme 2[a]



[a] Key: (a) NaH, allyl bromide, DMF; (b) LDA, 1-chloro-3-iodopropane; (c) NaI, acetone.

Scheme 3[a]



[a] Key: (a) NaH, $BrCH_2C(Br)=CH_2$, DMF; (b) $SOCl_2$, cat. HCl (neat); then EtOH; (c) NaI, acetone, reflux.

Optimum reaction conditions for these reactions involved the dropwise addition of the substrate to a solution of 4.4 equiv of SmI_2 in THF containing 5 equiv of hexamethylphosphoramide (HMPA) at 0 °C. The standard reaction conditions did not involve the intentional addition of a proton source to quench the final organosamarium intermediate. In general, these reactions were complete after 30−45 min.

In the event, cyclization of the α-oxygenated species (**3a**−**c**, **8**) provided the desired oxygen-containing heterocycles (**7a**−**c**, **9**) in very good yield as single isomers (^{1}H NMR) in most cases (eqs 1 and 2). One obvious challenge in these oxygenated systems was to acheive both individual reactions without inducing reductive cleavage of the oxygen heterosubstituent α to the carbo-

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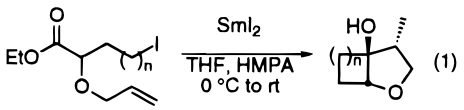
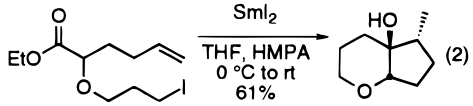


3a, n = 1
3b, n = 2
3c, n = 3

7a, 67%
7b, 83%
7c, 76% (7.3:1)

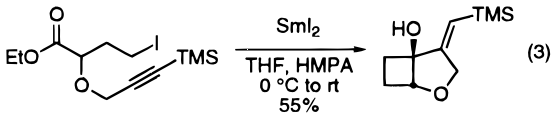


8 **9**

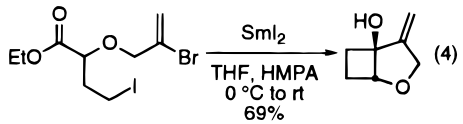
nyl. Surprisingly, only a very small amount of deoxygenated products (generally <5−10% of cyclopentanone/cyclohexanone species) was detectable, although it has been demonstrated repeatedly that SmI_2 promotes the rapid deoxygenation of both α-oxygenated ketones and esters (or lactones) even at −78 °C.[9] Apparently, the rate of the SmI_2-mediated organic halide reduction, nucleophilic acyl substitution, and the ensuing 5-exo ketyl olefin coupling reaction are much more rapid than α-heteroatom extrusion under these reaction conditions.

Unfortunately, substrates in which the terminating cyclization event involved a 6-exo ketyl olefin coupling reaction provided solely α-deoxygenated ketone products. This observation implies that the rate of 6-exo ketyl olefin coupling does not compete effectively with the α-heteroatom extrusion under these reaction conditions, and therefore, only products resulting from α-heteroatom cleavage of the intermediate cycloalkanone are generated.

Further investigation revealed the facility with which strained bicyclic systems could be generated in good yields and with high diastereoselectivity. For example, sequential cyclization of substrates **10** and **6** afforded the desired heterocycles **11** and **12**, respectively, in good yields (eqs 3 and 4).

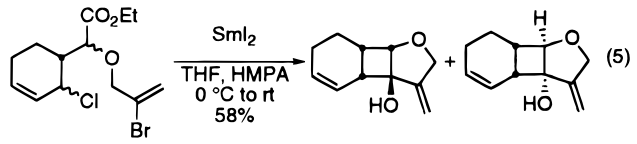


10 **11**

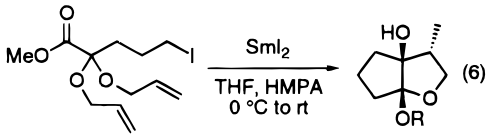


6 **12**

In an effort to probe further the ability of this reaction sequence to generate highly sophisticated and strained ring systems, substrates **13** and **17** (eqs 5 and 6) were subjected to the SmI_2-mediated sequential reaction conditions. The cyclization event in eq 5 (performed on a mixture of diastereomeric compounds **13**) afforded the strained tricyclic oxygenated ring systems in **14** containing an internal cyclobutane ring system as a 2:1 mixture of diastereomeric products in 58% combined yield. When the α-oxygenated species **17** in eq 6 was subjected to the standard reaction conditions, the desired hemiketal **18** was generated as a mixture of the allyl and methyl ketals in 57% combined yield as a single diastereomer. Apparently, some transketalization (*O*-allyl to *O*-methyl) results from the liberated methoxy group during either the reaction process or workup procedure.



13 **14**



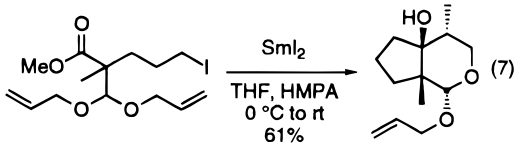
17

18a, 41%, R = allyl
18b, 16%, R = methyl

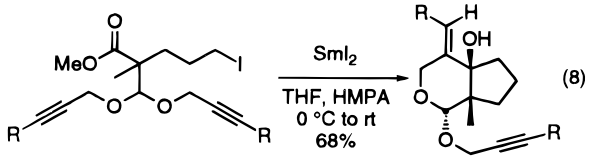
Substrate **17** was prepared as depicted in Scheme 4 from methyl 5-chloropentanoate using a sequence initiated by a Claisen condensation with propional, formation of the mesylate, and generation of the enoate, **15**, with DBU.[14] Finally, a Finkelstein reaction with NaI, ozonolysis with a reductive workup, and subsequent ketal generation with the trimethylsilyl ether of allyl alcohol in the presence of catalytic TMSOTf provided the requisite bis(allyl) ketal, **17**, in good overall yield.[15]

A second class of substrates in this series contained a *β*-substituted allylic ether functionality and pendant halogen chain. Such substrates would each terminate in a 6-exo ketyl olefin cyclization process. However, they do not possess the problematic α-deoxygenation reaction pathway, and hence, they were anticipated to work quite well under the standard sequential SmI_2 reaction conditions. The allylic ether-functionalized substrates in this series were prepared in one of two ways. One method involved substrate preparation from the *β*-formyl ester by Noyori-type ketalization as depicted in Scheme 5. Thus, the *β*-formyl ester (**20**) was treated with the trimethylsilyl ether of allyl alcohol (or propargyl alcohol) in the presence of catalytic TMSOTf to provide the bis(allyloxy) [or bis(propargyloxy)] acetal **21** (or **23**) in excellent yield.[11]

Cyclization of the *β*-formyl ester-derived substrates **21** and **23** provided the desired hemiacetal products (**22** and **24**) in good yield and with high diastereoselectivity (eqs 7 and 8).



21 **22**



23, R = TMS **24**

The anticipated stereochemistry of these highly functionalized molecules was verified by ^1H NMR. Thus, ^1H NMR chemical shifts of the cyclized oxygen heterocycles

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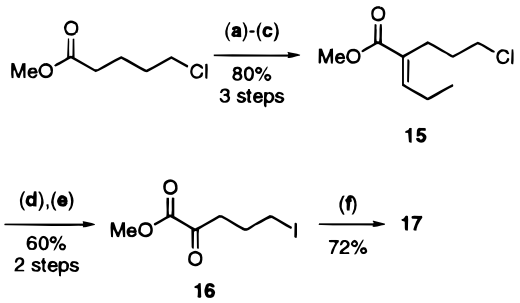
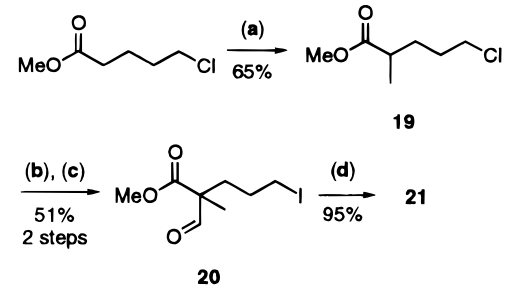
Scheme 4[a]



[a] Key: (a) LDA, propional, −78 °C; (b) MsCl, Et_3N, DMAP; (c) DBU, THF; (d) NaI, acetone; (e) O_3; DMS; (f) $TMSOCH_2CH{=}CH_2$, TMSOTf.

Scheme 5[a]



[a] Key: (a) LDA, MeI; (b) LDA, methyl formate; (c) NaI, acetone; (d) $CH_2{=}CHCH_2OTMS$, TMSOTf.

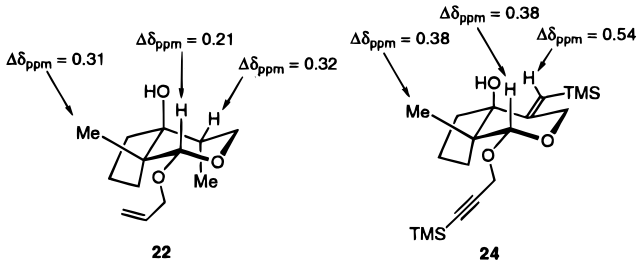
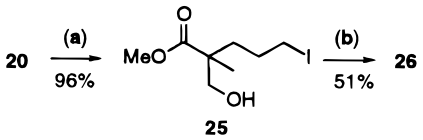


Figure 1. Interactions of the bridgehead hydroxyl group with the bridgehead methyl, 1,3-diaxially substituted methine, and vicinally substituted methine groups influencing solvent-induced chemical shift differences ($\delta_{pyr} - \delta_{CDCl_3}$) in compounds **22** and **24**.

observed in d_5-pyridine relative to those observed in $CDCl_3$ solvent (TMS internal standard) provided evidence for the indicated cis ring fused stereochemistry at the bridgehead of the oxabicyclo[4.3.0] systems, as well as evidence for the stereochemistry about the methine/hemiacetal position and the C-2 methyl of the cyclized products (Figure 1).[16] The protons about the bridgehead hydroxyl groups experience a large deshielding effect in these bridged bicyclic systems owing to coordination of pyridine at the hydroxyl functionality, which influences the chemical shift of protons positioned vicinally and 1,3-diaxially to the bridgehead alcohol in both **22** and **24**. The extent of vicinal deshielding about the bridgehead methyl group is a function of the dihedral angle of the $OCCCH_3$ unit, with the largest deshielding observed for dihedral angles approaching 0°. Thus, the solvent-induced chemical shift difference of a methyl (or methine) group experiencing a vicinally oriented diaxial interaction with a hydroxyl substituent ranges from approximately 0.0 ppm for a dihedral angle approaching 160−180° to 0.2−0.3 for a dihedral angle approaching 60° and an even

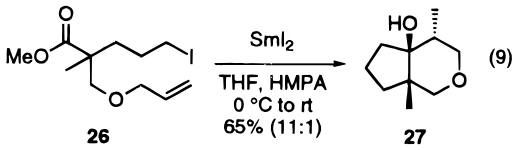
Scheme 6[a]



[a] Key: (a) $NaBH_4$, MeOH; (b) $CH_2{=}CHCH_2OC(NH)CCl_3$, $BF_3{\cdot}OEt_2$.

larger downfield shift observed for dihedral angles approaching 0°. Similarly, the solvent-induced chemical shift difference of a methine group experiencing a 1,3-diaxial interaction with a hydroxyl substituent is generally 0.20−0.40 ppm. As depicted in Figure 1, the bridgehead methyl group in both systems experiences a large downfield shift (0.31 ppm and 0.38 ppm for **22** and **24**, respectively) indicating a cis-fused bicyclic ring system. The results depicted in Figure 1 are also consistent with the 1,3-diaxial orientation between the acetal methine and the bridgehead hydroxyl group for both **22** (0.21 ppm downfield shift in pyridine solvent relative to the $CDCl_3$ solvent spectrum) and **24** (0.38 ppm downfield shift in pyridine solvent relative to the $CDCl_3$ solvent). Finally, a 0.32 ppm shift downfield in the C2-methine is indicative of a cis relationship between the bridgehead hydroxyl and C2-methine in **22**. Likewise, the 0.54 ppm shift downfield observed for the olefinic proton of **24** provides evidence for the *E*-stereochemistry about the olefin as depicted in Figure 1.

Additional substrates were prepared from *β*-hydroxy esters with allyl ether formation occurring *via* Schmidt-type chemistry as outlined in Scheme 6. Initial attempts to prepare these systems by *O*-alkylation of the corresponding *β*-hydroxy esters under Williamson ether-type conditions proved futile. Thus, as depicted in Scheme 6, the formyl ester **20** was reduced with $NaBH_4$ to provide the *β*-hydroxy ester **25**.[17] Allyl ether formation was accomplished *via* the Schmidt-type chemistry with the trichloroacetimidate of allyl alcohol and catalytic TMSOTf or catalytic $BF_3{\cdot}OEt_2$ to provide **26**.[18] Cyclization of the *β*-formyl ester-derived allylic ether **26** (eq 9) generated the desired [4.3.0]oxabicyclic **27** in good yield as an 11:1 mixture of diastereomers.



(9)

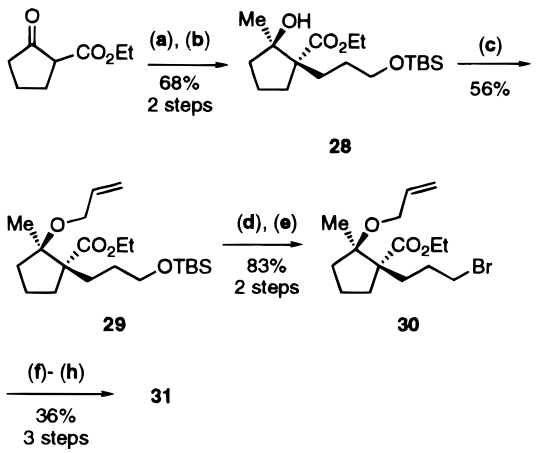
Likewise, it was discovered that the corresponding *β*-keto esters would not provide the requisite bis(allyl) ketals under several attempted reaction conditions. Consequently, an alternative strategy to these systems was sought. The overall strategy for this class of substrates is demonstrated in Scheme 7. Thus, ethyl 2-oxo-cyclopentanecarboxylate was alkylated with the TBS ether of 3-bromopropanol, and the resulting *β*-keto ester was treated with MeMgBr to provide the desired *β*-hydroxy ester **28** in nearly quantitative yield. Subsequently, treatment of **28** with the trichloroacetimidate of allyl alcohol in the presence of catalytic TMSOTf or catalytic $BF_3{\cdot}OEt_2$ provided the desired allyl ether in

(16) Demarco, P. V.; Farkas, E.; Doddrell, D.; Mylari, B. L.; Wenkert, E. *J. Am. Chem. Soc.* **1968**, *90*, 5480.

(17) Stevens, R. V.; Beaulieu, N.; Chan, W. H.; Daniewski, A. R.; Takeda, T.; Waldner, A.; Williard, P. G.; Zutter, V. *J. Am. Chem. Soc.* **1986**, *108*, 1039.

(18) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.

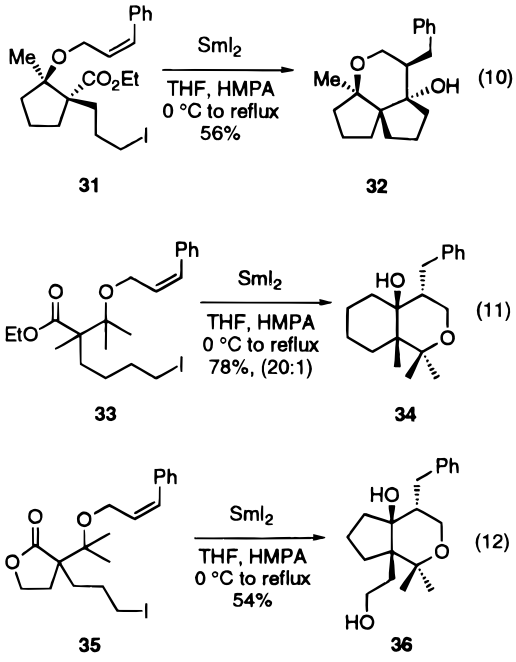
Scheme 7[a]



[a] Key: $Br(CH_2)_3OTBS$, NaH, DMF, 60 °C; (b) MeMgBr, −78 °C; (c) $CH_2{=}CHCH_2OC(NH)CCl_3$, TMSOTf; (d) Amberlyst-15, EtOH; (e) CBr_4, PPh_3, Et_2O/CH_3CN; (f) O_3; DMS; (g) $PhCH{=}PPh_3$; (h) NaI, acetone.

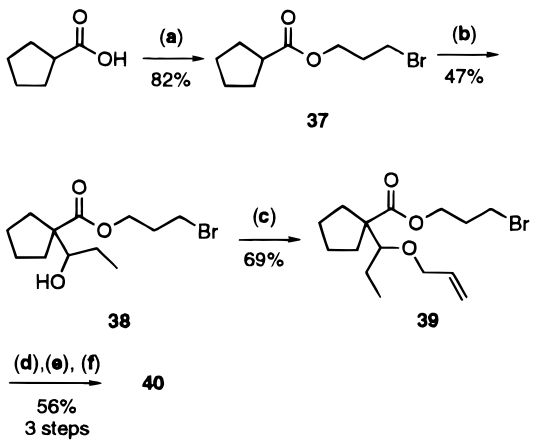
good yield.[18] Removal of the TBS ether in these systems was accomplished without lactonization by the use of EtOH (protic solvent) and Amberlyst-15 resin.[19] The substrates could be further elaborated by subsequent ozonolysis and Wittig reaction to provide the phenyl substituted olefin in fair overall yield.[17,20]

Cyclization of the substrates thus prepared proceeded in good yield and with excellent diastereoselectivity provided that the olefin was activated with an electron-withdrawing group (eqs 10−12). Without the activated



olefin present in the substrate, little or no desired bicyclic products were obtained, and the majority of the product mixture contained merely cyclic ketone from the initial intermediate or alcohol from reduction of the intermediate ketone. Replacement of the unactivated terminal olefin with the more activating phenyl-substituted alkene lowers the π^* orbital energy (LUMO) of the alkene and

Scheme 8[a]

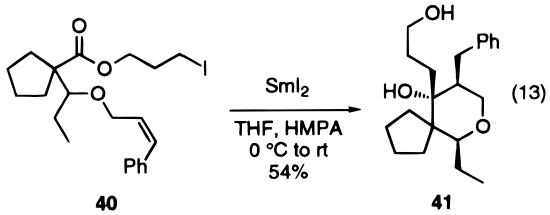


[a] Key: $BrCH_2CH_2CH_2OH$, EDCI, CH_2Cl_2; (b) LDA, propional, −78 °C; (c) $CH_2{=}CHCH_2OC(NH)CCl_3$, TMSOTf; (d) O_3; DMS; (e) $Ph_3P{=}CHPh$, THF; (h) NaI, acetone.

establishes more effective overlap with the ketyl radical anion SOMO.[21] Consequently, any ketyl generated through the pertinent equilibria would thus be more efficiently trapped by the alkene, facilitating the cyclization. In most instances, it was also necessary to heat the reaction mixture overnight in refluxing THF to provide acceptable yields of the desired cyclized oxygen heterocycles.

The anticipated stereochemistry of **32** was verified by comparing the ^1H NMR of **32** in pyridine-d_5 and $CDCl_3$. The bridgehead hydroxyl group in **32** causes both the bridgehead methyl group and vicinally substituted methine to experience a large deshielding effect owing to coordination of pyridine at the bridgehead hydroxyl group, thus causing a substantial downfield shift of both signals. Indeed, the bridgehead methyl **32** experiences a downfield shift of 0.25 ppm and the vicinally substituted methine experiences a 0.33 ppm downfield shift, all indicative of a cis relationship of the bridgehead hydroxyl, bridgehead methyl, and the vicinally substituted methine. Additionally, the stereochemistry of the cyclization product **32** in eq 10 was unambiguously determined by single-crystal X-ray diffraction, thus providing additional evidence for the predictability of the ketyl olefin cyclization stereochemistry. The reaction in eq 10 also provided a 35% yield of the spirocyclic intermediate ketone in addition to the desired angular, tricyclic oxygenated ring system.

The ability to prepare more elaborate spirocyclic ring systems was further demonstrated by the reaction depicted in eq 13. Substrate **40** was prepared similarly to



the above systems as illustrated in Scheme 8. Thus, the desired ester **37** was prepared from cyclopentanecarboxylic acid under Mitsunobu-type reaction conditions.[10b] The β-hydroxy ester functionality in **38** was prepared by a Claisen condensation of the ester with propional. Then,

(19) Use of TBAF/THF provided a mixture of both the cyclized lactone resulting from attack of the liberated primary alcohol on the ester and a minor amount of the desired primary alcohol.

(20) Bunnelle, W. H.; Rafferty, M. A.; Hodges, S. L. *J. Org. Chem.* **1987**, *52*, 1603.

(21) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley-Interscience: New York, 1976.

ether formation under Schmidt-type reaction conditions followed by ozonolysis with a reductive workup and subsequent Wittig reaction provided the desired substrate **40** after a Finkelstein reaction. Treatment of the desired substrate under the standard sequential reaction conditions provided the desired spirocycle **41** in fair yield as a single diastereomer (eq 13).

The stereochemistry of **41** was verified by pyridine-d_5 ^{1}H NMR studies that were consistent with the expected cyclization stereochemistry. Thus, comparison of the ^{1}H NMR spectrum of **41** in $CDCl_3$ and pyridine-d_5 revealed a 0.44 ppm shift in the C2-methine (indicative of a 1,3-diaxial orientation of the C2-methine and hydoxyl group) and no shift in the CH_2 ethyl protons. This observation is consistent with the stereochemistry depicted in **41** for a cis relationship between the C2-methine and hydroxyl functionality.

Conclusions

The SmI_2-promoted intramolecular nucleophilic acyl substitution/ketyl olefin cyclization sequence has been utilized to convert a variety of suitable substrates to bicyclic, tricyclic, and spiro-fused oxygen heterocycles efficiently, in high yield, and with excellent diastereoselectivity. Substrates for these sequential processes are readily prepared by classical alkylation chemistry in a relatively few steps. The overall transformation represents an effective means by which simple starting materials can be converted to highly sophisticated oxygen heterocycles in a one-pot process. The remarkable selectivity of SmI_2 in these sequential reaction processes allows formation of the desired bicyclic and tricyclic products while inducing little, if any, products derived from reductive cleavage of the heterosubstituents α to the ester (or lactone) or the intermediate ketone.

Experimental Section

Reagents. Tetrahydrofuran (THF) was distilled immediately prior to use from benzophenone ketyl under Ar. Samarium metal was purchased from Cerac Inc., Milwaukee, WI, and was weighed and stored under an inert atmosphere. CH_2I_2 was purchased from Aldrich Chemicals and was distilled prior to use and stored under argon over copper turnings. HMPA was purchased from either Aldrich or Sigma Chemicals and was distilled from either Na(0) or 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,[22] and all reactions were carried out under argon.

Ethyl 3-Oxa-5-hexenoate (1). General Procedure for the *O*-Alkylation of Alcohol Nucleophiles. Ethyl glycolate (4.16 g, 40.0 mmol) was added neat to a stirred slurry of NaH (1.76 g of a 60% dispersion in mineral oil, 44.0 mmol) in DMF at 0 °C. The resultant reaction mixture was stirred at rt for 2 h and then cooled to 0 °C, whereupon allyl bromide (5.32 g, 44.0 mmol) was added *via* syringe. After the addition of the electrophile, the reaction was allowed to come to rt and stir for 2 h. After this period, the reaction was quenched by the careful addition of saturated aqueous NH_4Cl. The reaction mixture was subjected to an aqueous workup. Shortpath distillation afforded the desired product **1** in 88% yield: bp 70−74 °C (20 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.26 (m, 2H), 4.20 (q, J = 7.08 Hz, 2H), 4.07 (m, 4H), 1.47 (t, J = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.34, 133.72, 118.19, 72.34, 67.17, 60.82, 14.16.

Ethyl 2-(3-Chloropropyl)-3-oxa-5-hexenoate (2). General Procedure For Alkylation of Ester Nucleophiles. Compound **2** was prepared according to the following general procedure. Ethyl 3-oxa-5-hexenoate (**1**) (4.32 g, 30.0 mmol) was added dropwise *via* cannula as a 1 M solution in THF to a solution of LDA (33.0 mmol, 1 M in THF) cooled to −78 °C. After the addition of the ester was complete, the reaction mixture was stirred at −78 °C for an additional 30−40 min before adding a solution of 1-chloro-3-iodopropane in 7.0 mL of HMPA rapidly dropwise *via* cannula and warming the reaction mixture to −30 °C. The reaction mixture was maintained at −30 °C for 12 h and then quenched with saturated aqueous NH_4Cl and subjected to an aqueous workup. Flash chromatography with 2−3% EtOAc/hexanes afforded **2** in 46% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.23 (m, 2H), 4.17 (m, 3H), 3.88 (m, 2H), 3.54 (m, 2H), 1.89 (m, 4H), 1.28 (t, J = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.42, 133.92, 117.90, 77.25, 71.38, 60.92, 44.60, 30.21, 28.41, 14.24.

Dihydro-3-(2-propenyloxy)furan-2(2*H*)-one was prepared from α-hydroxybutyrolactone by *O*-alkylation with allyl bromide according to the general procedure for the preparation of **1** to afford the desired allyl ether in 76% yield after flash chromatography with 25% EtOAc/hexanes and Kugelrohr distillation (ot 90−100 °C/10 mmHg): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.24 (m, 2H), 4.37 (m, 2H), 4.18 (m, 3H), 2.48 (m, 1H), 2.25 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.60, 133.56, 118.32, 72.51, 71.22, 65.40, 29.81.

Ethyl 2-(2-Chloroethyl)-3-oxa-5-hexenoate. General Procedure for One-Pot Lactone Opening/Halogenation/Ester Formation Reactions. Thionyl chloride (neat, 1.78 g, 15.0 mmol) and three drops of concd HCl were added neat to dihydro-3-(2-propenyloxy)furan-2(2*H*)-one (0.44 g, 3.0 mmol) in an argon-filled flask equipped with a drying tube and cooled to 0 °C in an ice bath. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at ambient temperature for 18 h. After this period of time, the reaction mixture was cooled to 0 °C, absolute ethanol (20 mL) was added *cautiously* in small portions, and the reaction mixture was stirred for an additional 1 h at 0 °C and 4 h at rt. Then, the reaction was quenched at 0 °C by *careful* addition of a saturated aqueous $NaHCO_3$ solution to afford the desired ester in 94% yield (0.58 g, 2.82 mmol) after an aqueous workup and flash chromatography with 5% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.22 (m, 2H), 4.17 (m, 2H), 4.10 (m, 1H), 3.93 (m, 1H), 3.68 (m, 1H), 3.68 (m, 2H), 2.15 (m, 2H), 1.28 (t, J = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.26, 133.81, 118.12, 74.56, 71.81, 61.10, 40.70, 35.65, 14.21.

Ethyl 2-(2-iodoethyl)-3-oxa-5-hexenoate (3a) was prepared from ethyl 2-(2-chloroethyl)-3-oxa-5-hexenoate according to the general procedure outlined for the preparation of **3b** to afford **3a** in 92% yield after flash column chromatography with 5% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.90 (m, 1H), 5.24 (m, 2H), 4.19 (m, 3H), 3.94 (m, 2H), 3.28 (m, 2H), 2.19 (m, 2H), 1.27 (t, J = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.98, 133.85, 118.19, 77.49, 71.83, 61.12, 36.47, 14.22, 11.42.

Ethyl 2-(3-Iodopropyl)-3-oxa-5-hexenoate (3b). General Finkelstein Procedure. Compound **3b** was prepared from **2** according to the following general procedure. A solution of **2** (0.56 g, 2.4 mmol) in 10 mL of acetone was heated at reflux for 12 h with NaI (3.6 g, 24.0 mmol) to afford **3b** in 95% yield after an aqueous workup and flash chromatography with 5% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.23 (m, 2H), 4.18 (m, 3H), 3.88 (m, 2H), 3.20 (t, J = 6.67 Hz, 2H), 1.89 (m, 4H), 1.28 (t, J = 7.13 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.79, 134.74, 116.84, 77.38, 71.25, 60.47, 33.86, 29.64, 14.20, 5.87.

Ethyl 2-(4-chlorobutyl)-3-oxa-5-hexenoate was prepared according to the general procedure outlined for the preparation of **2** by alkylation of **1** with 1-chloro-4-iodobutane to afford the desired chloride in 24% yield after flash chromatography with 2−3% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.23 (m, 2H), 4.18 (m, 3H), 3.88 (m, 2H), 3.51 (t, J = 6.63 Hz, 2H), 1.76 (m, 4H), 1.56 (m, 2H), 1.27 (t, J = 7.14 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.72, 134.02, 117.86, 77.79, 71.42, 60.84, 44.68, 32.22, 32.17, 22.69, 14.26.

Ethyl 2-(4-iodobutyl)-3-oxa-5-hexenoate (3c) was prepared from ethyl 2-(4-chlorobutyl)-3-oxa-5-hexenoate according to the general Finkelstein procedure outlined for the preparation of **3b** to afford **3c** in 74% yield after an aqueous workup

(22) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975.

and flash chromatography with 2% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.23 (m, 2H), 4.18 (m, 3H), 3.90 (m, 2H), 3.16 (t, J = 7.08 Hz, 2H), 1.79 (m, 4H), 1.53 (m, 2H), 1.27 (t, J = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.68, 134.02, 117.85, 77.74, 71.41, 60.84, 33.12, 31.79, 26.25, 14.28, 6.33.

Dihydro-3-[(2-bromo-2-propenyl)oxy]furan-2(2*H*)-one (4) was prepared according to the general procedure outlined for the preparation of **1** by *O*-alkylation of α-hydoxybutyrolactone with 2,3-dibromopropene to afford **4** in 66% yield after flash chromatography with 18% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (m, 1H), 5.67 (m, 1H), 4.42 (m, 3H), 4.25 (m, 2H), 2.52 (m, 1H), 2.32 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.55, 128.10, 119.29, 73.81, 72.33, 65.49, 29.68.

Ethyl 5-bromo-2-(2-chloroethyl)-3-oxa-5-hexenoate (5) was prepared from **4** according to the general procedure outlined for the lactone ring opening/ester formation as described for the preparation of ethyl 2-(2-chloroethyl)-3-oxa-5-hexenoate to afford **5** in 95% yield after flash chromatography with 5% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (m, 1H), 5.63 (m, 1H), 4.34−4.10 (m, 3H), 4.06 (m, 2H), 3.72 (m, 2H), 2.20 (m, 2H), 1.80 (t, J = 7.08 Hz, 3H).

Ethyl 5-bromo-2-(2-iodoethyl)-3-oxa-5-hexenoate (6) was prepared from **5** according to the general procedure outlined for the preparation of **3b** to afford **6** in 85% yield after flash chromatography with 5% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (m, 1H), 5.63 (m, 1H), 4.36 (d, J = 13.43 Hz, 1H), 4.20 (dq, J = 1.46, 7.08 Hz, 2H), 4.04 (m, 2H), 3.33 (t, J = 7.08 Hz, 2H), 2.25 (m, 2H), 1.28 (t, J = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.30, 128.37, 119.22, 77.66, 74.66, 61.35, 36.63, 14.21, 1.20.

(1*R,2*S**,5*S**)-2-Methyl-4-oxabicyclo[3.2.0]heptan-1-ol (7a)** was prepared from **3a** according to the general procedure outlined for the preparation of **7b** to afford **7a** as a single diastereomeric product in 67% yield after flash chromatography with 35% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.33 (m, 1H), 4.12 (dd, J = 4.15, 7.57 Hz, 1H), 3.53 (dd, J = 9.52, 10.99 Hz, 1H), 2.24−2.05 (m, 3H), 1.79−1.69 (m, 2H), 1.58−1.45 (m, 1H), 0.98 (d, J = 6.84 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.73, 83.61, 72.87, 42.68, 23.83, 18.50, 9.15; IR (neat) 3246.8 cm^{-1}; HRMS calcd for $C_7H_{12}O_2$ 128.0887, found 128.0837; LRMS (EI$^+$) m/z 128 (8), 113 (18), 100 (100), 85 (89), 67 (51), 57 (63), 43 (100), 29 (54). Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.38; H, 9.57.

(1*R,2*S**,5*S**)-2-Methyl-4-oxabicyclo[3.3.0]octan-1-ol (7b). General Procedure for Sequenced Nucleophilic Acyl Substitution/Ketyl Olefin Coupling Reactions Mediated by SmI_2.** Compound **7b** was prepared from **3b** according to the following general procedure. Diiodomethane (0.64 g, 2.39 mmol) was added to a vigorously stirred solution of Sm metal (0.40 g, 2.66 mmol) in 20 mL of dry THF. The resultant reaction mixture was stirred for 2 h at ambient temperature, and then HMPA (2.1 mL) was added, and the reaction mixture was cooled to 0 °C. Then, ethyl 2-(3-iodopropyl)-3-oxa-5-hexenoate (**3b**) (0.156 g, 0.478 mmol) in 10 mL of dry THF was added dropwise *via* cannula over 2 h to the 0 °C cooled solution. The reaction was monitored by TLC and found to be complete after addition of the substrate was complete. The reaction mixture was warmed to rt and quenched with saturated aqueous $NaHCO_3$ to afford **7b** as a single diastereomeric product in 83% yield after an aqueous workup and flash chromatography with 22% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (dd, J = 2.91, 6.01 Hz, 1H), 4.01 (t, J = 8.41 Hz, 1H), 3.39 (t, J = 8.97 Hz, 1H), 2.39 (m, 1H), 2.00 (m, 1H), 1.85 (m, 1H), 1.75 (m, 2H), 1.63 (m, 1H), 1.49 (m, 1H), 1.41 (s, 1H), 0.99 (d, J = 6.88 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 90.92, 90.50, 74.13, 44.52, 33.79, 32.87, 24.98, 10.62; IR (neat) 3417.5 cm^{-1}; HRMS calcd for $C_8H_{14}O_2$ 142.0994, found 142.0992; LRMS (EI$^+$) m/z 142 (2), 127 (10), 100 (100), 82 (46), 72 (51), 55 (48), 41 (98), 27 (78).

(1*R,6*S**,9*S**)-9-Methyl-7-oxabicyclo[4.3.0]nonan-1-ol (7c)** was prepared from **3c** according to the general procedure outlined for the preparation of **7b** to afford **7c** as a 7.3:1 mixture of diastereomeric products (epimeric at C9) in 76% combined yield after an aqueous workup, flash chromatography with 17% EtOAc/hexanes, and Kugelrohr distillation (ot 80 °C/0.1 mmHg). Major diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.07 (t, J = 8.55 Hz, 1H), 3.64 (m, 1H), 3.40 (t, J = 9.40 Hz, 1H), 2.25 (m, 1H), 1.86 (m, 1H), 1.64−1.36 (m, 8H), 0.90 (d, J = 6.84 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 80.36, 75.31, 71.87, 44.42, 28.35, 25.96, 20.69, 20.05, 9.31; IR ($CHCl_3$): 3886.0, 3690.0, 3607.3, 1087.9 cm^{-1}; HRMS calcd for $C_9H_{16}O_2$ 156.1150, found 156.1158; LRMS (EI$^+$) m/z 156 (13), 139 (10), 114 (86), 97 (34), 85 (48), 70 (100), 57 (78), 41 (77), 27 (52). Anal. Calcd for $C_9H_{16}O_2$ C, 69.19; H, 10.32. Found: C, 68.78; H, 10.53. Minor diastereomer: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.09 (t, J = 8.55 Hz, 1H), 3.70 (dd, J = 5.61, 8.06 Hz, 1H), 3.53 (t, J = 8.55 Hz, 1H), 2.25 (m, 1H), 1.86 (m, 1H), 1.64−1.36 (m, 8H), 0.95 (d, J = 6.84 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.04, 78.30, 72.68, 37.86, 32.78, 29.54, 22.30, 22.13, 10.55.

Ethyl 6-[(*tert*-butyldimethylsilyl)oxy]-3-oxahexanoate was prepared from ethyl glycolate by *O*-alkylation with *tert*-butyldimethylsilyl-protected 3-bromo-1-propanol[23] according to the general procedure outlined for the preparation of **1** to afford the desired TBS-protected alkoxy ester in 72% yield after flash chromatography with 8% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (q, J = 7.33 Hz, 2H), 4.04 (s, 2H), 3.69 (t, J = 6.10 Hz, 2H), 3.60 (t, J = 6.34 Hz, 2H), 1.81 (pent, J = 6.10 Hz, 2H), 1.26 (t, J = 7.08 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.51, 68.59, 68.48, 60.75, 59.69, 32.72, 25.89 (3), 18.27, 14.18, −5.41 (2).

Ethyl 2-(3-butenyl)-3-oxa-6-[(*tert*-butyldimethylsilyl)-oxy]hexanoate was prepared from ethyl 6-[(*tert*-butyldimethylsilyl)oxy]-3-oxahexanoate by alkylation with 4-bromo-1-butene according to the general alkylation procedure for preparation of **2** to afford the desired olefinic ester in 46% yield after flash chromatography with 7% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (m, 1H), 4.99 (m, 2H), 4.17 (m, 2H), 3.80 (t, J = 6.41 Hz, 1H), 3.71−3.61 (m, 3H), 3.40 (m, 1H), 2.16 (m, 2H), 1.78 (m, 4H), 1.26 (t, J = 7.17 Hz, 3H), 0.86 (s, 9H), 0.02 (s, 6H).

Ethyl 6-bromo-2-(3-butenyl)-3-oxahexanoate was prepared from ethyl 2-(3-butenyl)-3-oxa-6-[(*tert*-butyldimethylsilyl)oxy]hexanoate according to the following general procedure. To the ester (1.65 g, 5.0 mmol) dissolved in 10 mL of THF and cooled to 0 °C in an ice bath was added dropwise 6 mL of a 1.0 M (in THF) solution of tetrabutylammonium fluoride (TBAF), and the reaction mixture was allowed to warm to rt. TLC analysis of the reaction mixture after warming to rt showed complete consumption of the starting TBS ether. The reaction mixture was concentrated *in vacuo* and flashed through a short plug of silica gel with 50% EtOAc/hexanes to provide the desired primary alcohol, which was subjected immediately to halogenation according to the following procedure. The alcohol was dissolved in 10 mL of Et_2O, and then CBr_4 (3.32 g, 10.0 mmol) and PPh_3 (2.62 g, 10.0 mmol) were added successively, and the reaction mixture was stirred overnight at ambient temperature. After this period of time, the reaction mixture was diluted with pentane, filtered through a short plug of Celite to remove the resultant precipitate, concentrated *in vacuo*, and subjected to flash chromatography with 10% EtOAc/hexanes to afford the desired bromide (1.06 g, 3.80 mmol) in 76% yield (two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.77 (m, 1H), 5.01 (m, 2H), 4.19 (m, 2H), 3.82 (m, 1H), 3.69 (m, 1H), 3.53 (m, 3H), 2.15 (m, 4H), 1.78 (m, 2H), 1.27 (t, J = 7.15 Hz, 3H).

Ethyl 2-(3-butenyl)-6-iodo-3-oxahexanoate (8) was prepared from ethyl 6-bromo-2-(3-butenyl)-3-oxahexanoate according to the general procedure outlined for the preparation of **3** to afford **8** in 92% yield after flash chromatography with 10% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.78 (m, 1H), 5.01 (m, 2H), 4.19 (m, 2H), 3.81 (dd, J = 5.65, 7.21 Hz, 1H), 3.63 (m, 1H), 3.39 (m, 1H), 3.30 (m, 2H), 2.19−2.03 (m, 4H), 1.78 (m, 2H), 1.28 (t, J = 7.12 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.82, 137.36, 115.55, 78.41, 69.68, 60.68, 33.49, 32.11, 29.41, 14.28, 3.39.

(1*R,6*S**,9*R**)-9-Methyl-5-oxabicyclo[4.3.0]nonan-1-ol (9)** was prepared from **8** according to the general procedure outlined for the preparation of **7b** to afford **9** as a single

(23) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

diasteromeric product in 61% yield after flash chromatography with 20% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (m, 1H), 3.73 (m, 1H), 3.64 (m, 1H), 1.98−1.74 (m, 5H), 1.71−1.59 (m, 4H), 1.36 (m, 1H), 1.00 (d, J = 6.59 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.02, 76.21, 61.58, 42.26, 28.26, 26.69, 23.41, 21.20, 13.95; IR (neat) 3346.7 cm^{-1}; HRMS calcd for $C_9H_{16}O_2$ 156.1150, found 156.1131; LRMS (EI$^+$) m/z 156 (52), 114 (29), 100 (27), 86 (31), 71 (100), 55 (48), 43 (83), 27 (32). Anal. Calcd for $C_9H_{16}O_2$: C, 69.20; H, 10.32. Found: C, 68.97; H, 10.57.

Dihydro-3-(2-propynyloxy)furan-2(2*H*)-one was prepared from α-hydroxybutyrolactone by *O*-alkylation with propargyl bromide according to the general alkylation procedure given for the preparation of **1** to afford the propargyl ether in 72% yield after flash chromatography with 18% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (dd, J = 2.44, 13.67 Hz, 1H), 4.44−4.36 (m, 2H), 4.24 (m, 1H), 2.61−2.51 (m, 2H), 2.48 (t, J = 2.44 Hz, 1H), 2.35−2.22 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.65, 78.52, 75.56, 71.70, 65.38, 57.44, 29.63.

Dihydro-3-[[(3-(trimethylsilyl)-2-propynyl]oxy]furan-2(2*H*)-one was prepared according to the following general procedure. Dihydro-3-(2-propynyloxy)furan-2(2*H*)-one (0.56 g, 4.0 mmol), dissolved in 5 mL of dry THF, was added dropwise *via* cannula to a −78 °C cooled solution of LDA (4.4 mmol, 1 M in THF). The resultant reaction mixture was stirred for 5 min at reduced temperature, and then TMSCl (0.65 g, 6.0 mmol) was added rapidly. The reaction mixture was stirred for an additional 15 min, and then the reaction was quenched at −78 °C with saturated aqueous NH_4Cl. The silylated alkyne was obtained in 42% yield after an aqueous workup and flash chromatography with 18% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.46 (d, J = 5.13 Hz, 2H), 4.44 (m, 2H), 4.26 (m, 1H), 2.54 (m, 1H), 2.30 (m, 1H), 0.16 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.71, 100.11, 92.76, 71.56, 65.36, 58.31, 29.71, −0.26 (3).

Ethyl 2-(2-chloroethyl)-2-oxa-6-(trimethylsilyl)-5-hexynoate was prepared from dihydro-3-[3-(trimethylsilyl)-2-propynyl]oxy]furan-2(2*H*)-one according to the general lactone ring opening/ester formation procedure outlined for the preparation of **5** to afford the desired ester in 70% yield after flash chromatography with 15% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (d, J = 16.4 Hz, 1H), 4.35 (m, 1H), 4.19 (d, J = 16.1 Hz, 1H), 3.28 (t, J = 7.08 Hz, 2H), 3.65 (m, 2H), 2.17 (m, 2H), 1.27 (t, J = 7.08 Hz, 3H), 0.16 (s, 9H).

Ethyl 2-(2-iodoethyl)-2-oxa-6-(trimethylsilyl)-5-hexynoate (10) was prepared from ethyl 2-(2-chloroethyl)-2-oxa-6-(trimethylsilyl)-5-hexynoate according to the general procedure outlined for the preparation of **3** to afford **10** in 70% yield after flash chromatography with 10% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (d, J = 16.12 Hz, 1H), 4.34−4.16 (m, 3H), 3.65 (m, 1H), 3.28 (t, J = 7.08 Hz, 2H), 2.23 (m, 2H), 1.28 (t, J = 7.08 Hz, 3H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.45, 100.42, 92.56, 73.48, 76.39, 61.25, 58.52, 36.66, 14.21, −0.19 (3).

(1*R,5*S**,2*E*)-2-[(Trimethylsilyl)methylene]-4-oxabicyclo[3.2.0]heptan-1-ol (11)** was prepared from **10** according to the general procedure outlined for the preparation of **7b** to afford **11** in 55% yield after flash chromatography with 20% EtOAc/hexanes and Kugelrohr distillation (ot 100−110 °C/0.5 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.87 (t, J = 2.44 Hz, 1H), 4.68 (dd, J = 2.20, 14.41 Hz, 1H), 4.54 (dd, J = 2.44, 14.16 Hz, 1H), 4.45 (m, 1H), 2.06−1.97 (m, 4H), 1.56 (m, 1H), 0.10 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.73, 121.19, 84.10, 81.90, 69.71, 28.46, 18.21, −0.80 (3); IR (neat) 3383.3, 1634.0, 838.3 cm^{-1}; HRMS calcd for $C_{10}H_{17}O_2Si$ (M − H$^+$) 197.0998, found 197.0991; LRMS (EI$^+$) m/z 197 (61), 184 (74), 169 (100), 155 (96), 155 (96), 127 (32), 75 (100). Anal. Calcd for $C_{10}H_{18}O_2$-Si: C, 53.39; H, 7.24. Found: C, 53.34; H, 7.64.

(1*R,5*S**)-2-Methylene-4-oxabicyclo[3.2.0]heptan-1-ol (12)** was prepared from **6** according to the general procedure outlined for the preparation of **7b** to afford **25** in 69% yield after flash chromatography with 35% EtOAc/hexanes and Kugelrohr distillation (ot 100−110 °C/8 mmHg); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.34 (m, 1H), 5.15 (m, 1H), 4.61 (m, 1H), 4.46 (m, 1H), 2.16 (s, 1H), 2.10−2.03 (m, 3H), 1.63−1.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.43, 107.02, 85.05, 81.17, 70.50, 28.12, 18.27; IR (neat) 3418.0, 1668.1 cm^{-1}; HRMS calcd for $C_7H_{10}O_2$ 126.0681, found 126.0625; LRMS (EI) m/z 125 (19), 111 (100), 98 (99), 69 (84), 41 (96), 27 (36).

(1*R,6*S**,7*R**)-7-[(2-Bromo-2-propenyl)oxy]-9-oxabicyclo-[4.3.0]non-2-ene-8-one** was prepared from (1*R**,6*R**,7*S**/*R**)-7-hydroxy-9-oxabicyclo[4.3.0]non-2-en-8-one[24] according to the following general procedure. The α-hydroxylactone (0.928 g, 6.03 mmol) in 5 mL of dry DMF was added dropwise to a stirred, 0 °C, slurry of NaH (0.26 g of a 60% dispersion in mineral oil, 6.6 mmol) in 10 mL of dry DMF. The reaction mixture was maintained at 0 °C until H_2 evolution had ceased and substrate addition was complete. Then, the reaction mixture was warmed to rt and allowed to stir for 2 h. After this period of time, the reaction mixture was cooled to 0 °C, and 2,3-dibromopropene (1.81 g, 9.04 mmol) was added neat. The reaction mixture was warmed to rt and allowed to stir for 12 h at ambient temperature. After this period of stirring, the reaction mixture was quenched with saturated aqueous NH_4Cl and then subjected to an aqueous workup. Flash chromatography with 8% EtOAc/hexanes afforded a mixture of diastereomers epimeric at C-7 (1.21 g, 4.46 mmol) in 74% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.20 (m, 1H), 6.01 (m, 1H), 5.90 (m, 1H), 5.66 (m, 1H), 4.61 (m, 1H), 4.47 (m, 1H), 4.41 (m, 2H), 2.70 (m, 1H), 2.19 (m, 1H), 2.02−1.87 (m, 2H), 1.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.11, 136.22, 128.11, 121.66, 118.77, 76.59, 74.11, 70.98, 38.14, 23.11, 17.70.

(1*R,6*S**,7*S**)-7-[(2-Bromo-2-propenyl)oxy]-9-oxabicyclo-[4.3.0]non-2-ene-8-one:** ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.00 (m, 1H), 5.97 (m, 1H), 5.87 (m, 1H), 5.68 (m, 1H), 4.95 (m, 1H), 4.46 (m, 2H), 3.98 (d, J = 7.93 Hz, 1H), 2.71 (m, 1H), 2.13 (m, 2H), 1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.60, 133.08, 128.64, 124.02, 119.97, 74.34, 73.81, 73.77, 39.67, 21.01, 21.18.

Ethyl (1*R,2*R**/*S**)-5-bromo-2-(2-chloro-3-cyclohexenyl)-3-oxa-5-hexenoate (13)** was prepared from a mixture of the above bicyclic α-oxygenated lactones according to the general lactone ring opening/esterification procedure outlined for the preparation of **5** to afford an unseparable mixture of diastereomeric **13** in 52% yield after flash chromatography with 3% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96−5.68 (m, 3H), 5.62 (m, 1H), 4.82 (m, 0.34H), 4.56 (m, 0.66H), 4.23−4.18 (m, 3H), 4.08−3.81 (m, 2H), 2.64 (m, 0.66H), 2.43 (m, 0.34H), 2.15−1.86 (m, 3H), 1.71−1.42 (m, 1H), 1.29 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.93, 170.82, 130.88, 130.47, 130.14, 129.29, 128.95, 128.37, 128.08, 127.89, 119.04, 118.86, 80.98, 80.87, 78.35, 74.39, 74.36, 74.33, 61.18, 55.80, 55.00, 54.09, 45.78, 39.01, 37.73, 31.72, 31.08, 23.70, 23.55, 23.00, 19.83, 14.30, 14.22; HRMS calcd for $C_{13}H_{19}BrClO_2$ (M + H$^+$) 337.0206, found 337.0156; LRMS (EI$^+$) m/z 301 (100), 265 (82), 257 (80), 222 (98), 200 (71).

(1*R,2*S**/*R**,7*S**/*R**,8*R**)-9-Oxa-11-methylenetricyclo-[6.3.0^{2,7}]undec-3-ene-1-ol (14)** was prepared from a diastereomeric mixture of **13** according to the general procedure outlined for the preparation of **7b** to afford an inseparable 2:1 mixture of **14** in 58% combined yield after flash chromatography with 25% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.10 (m, 0.34H), 5.86 (m, 1H), 5.71 (m, 0.66H), 5.37 (t, J = 2.20 Hz, 0.34H), 5.17 (dt, J = 2.69, 5.13 Hz, 1.66H), 4.72−4.57 (m, 1.3H), 4.49−4.43 (m, 1.3H), 4.15 (d, J = 2.44 Hz, 0.40H), 2.81 (m, 1H), 2.67 (m, 0.60H), 2.26−2.00 (m, 2.4H), 1.86−1.5 (m, 1H), 1.70−1.58 (m, 1H), 1.47−1.30 (m, 1H). Major diastereomer: ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.17, 129.41, 125.16, 108.15, 85.30, 84.39, 74.33, 39.22, 30.37, 22.26, 18.92. Minor diastereomer ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.28, 132.05, 124.54, 107.63, 87.47, 82.62, 71.08, 38.14, 30.54, 21.43, 20.11; IR (neat) 3389.9, 3021.9, 1667.1, 1644.2 cm^{-1}; HRMS calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.1004; LRMS (NH_3) m/z 178 (41), 161 (71), 149 (100), 131 (34), 121 (80), 115 (28), 109 (58).

Methyl 3-Hydroxy-2-(3-chloropropyl)pentanoate. Methyl 5-chloropentanoate (6.02 g, 40.0 mmol) in 5 mL of dry THF was added slowly dropwise to a −78 °C 1 M solution of LDA (44.0 mmol). The reaction mixture was stirred at −78 °C for 0.5 h before propionaldehyde (2.90 g, 50 mmol) was added neat

(24) Lubineau, A.; Auge, J.; Grand, E.; Lubin, N. *Tetrahedron* **1994**, *50*, 10265.

via cannula. The resultant reaction mixture was stirred at −78 °C for 0.5 h and then quenched at −78 °C with saturated aqueous NH_4Cl. Kugelrohr distillation (ot 110−120 °C/0.05 mmHg) after an aqueous workup provided the desired *β*-hydroxy ester compound in 97% yield (8.07 g, 38.8 mmol): ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.70 (s, 3H), 3.58 (m, 1H), 3.52 (t, *J* = 6.11 Hz, 2H), 2.46 (m, 1H), 2.30 (bs, 1H), 1.79 (m, 4H), 1.46 (m, 2H), 0.95 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$), major, *δ* 175.50, 73.58, 51.69, 49.79, 44.41, 30.25, 28.32, 26.71, 10.00; ^{13}C NMR (100 MHz, $CDCl_3$), minor, *δ* 175.39, 73.38, 51.76, 49.95, 44.56, 30.59, 27.27, 24.32, 10.21.

Methyl 3-hydroxy-2-(3-chloropropyl)pentanoate, methanesulfonyl ester was prepared from methyl 3-hydroxy-2-(3-chloropropyl)pentanoate according to the following general procedure. To a solution of the alcohol (4.16 g, 20.0 mmol) in 30 of dry CH_2Cl_2 were added successively methanesulfonyl chloride (2.52 g, 22.0 mmol) and triethylamine (2.23 g, 22.0 mmol). The resultant reaction mixture was stirred at 0 °C for 0.5 h and then at rt for 2 h. The reaction mixture was quenched with 0.1 N HCl after this period of stirring and subjected to an aqueous workup to afford the desired mesylate (5.60 g, 19.5 mmol) in 98% yield: ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 4.85 (m, 1H), 3.71 (s, 3H), 3.52 (m, 2H), 3.02 (s, 3H), 2.68−2.84 (m, 1H), 1.83−1.71 (m, 6H), 0.99 (t, *J* = 7.57 Hz, 3H); IR (neat) 1731.8, 1455.5, 1337.9 cm^{-1}.

Methyl 2-(3-Chloropropyl)-2-pentenoate (15). The crude mesylate ester, (5.60 g, 19.5 mmol), was taken up in 20 mL of THF and cooled to 0 °C while DBU (3.3 g, 21.5 mmol) was added via syringe. The resultant reaction mixture was stirred at 0 °C for 1 h and then warmed to rt with continued stirring for 12 h. The reaction mixture was quenched after this period of time with saturated aqueous NH_4Cl and subjected to an aqueous workup. Flash chromatography with 2% EtOAc/hexanes afforded the desired olefin **15** (3.12 g, 16.4 mmol) in 84% yield: ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 6.79 (t, *J* = 7.57 Hz, 1H), 3.71 (s, 3H), 3.50 (t, *J* = 6.59 Hz, 2H), 2.42 (m, 2H), 2.21 (m, 2H), 1.86 (m, 2H), 1.04 (t, *J* = 6.59 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.13, 145.68, 129.96, 51.68, 44.62, 31.96, 23.97, 21.90, 13.30.

Methyl 2-(3-iodopropyl)-2-pentenoate was prepared from **15** according to the general procedure outlined for the preparation of **3** to afford the desired iodide in 91% yield after flash column chromatography with 3% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 6.58 (t, *J* = 7.55 Hz, 1H), 3.51 (s, 3H), 2.96 (t, *J* = 6.86 Hz, 2H), 2.18 (m, 2H), 2.02 (m, 2H), 1.72 (m, 2H), 1.07 (t, *J* = 6.86 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.10, 145.63, 129.79, 51.69, 33.01, 27.55, 22.03, 13.33, 6.36.

Methyl 5-Iodo-2-oxopentanoate (16). General Procedure for Ozonolysis of Olefins with Reductive Workup. Compound **16** was prepared from methyl 2-(3-iodopropyl)-2-pentenoate according to the following general procedure. Ozone was bubbled through a solution of the iodide (0.84 g, 3.0 mmol) in 10 mL of a 5:1 mixture of CH_2Cl_2/MeOH and catalytic $NaHCO_3$ until a blue color persisted. The reaction mixture was then purged with argon for 5 min before adding DMS (1.86 g, 30.0 mmol) and allowing the reaction mixture to warm to rt and stir for 18 h. After this period of time, the reaction mixture was concentrated in vacuo and subjected to flash chromatography with 10% EtOAc/hexanes to afford **16** (0.50 g, 1.95 mmol) in 66% yield: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.86 (s, 3H), 3.22 (t, *J* = 6.67 Hz, 2H), 3.00 (t, *J* = 6.96 Hz, 2H), 2.14 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 192.62, 161.03, 53.08, 39.93, 26.41, 5.06.

Methyl 5-iodo-2-oxopentanoate, diallyl ketal (17) was prepared from **16** according to the general procedure outlined for the preparation of **21** to afford **17** in 72% yield after flash chromatography with 4% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.90 (m, 2H), 5.33−5.15 (m, 4H), 4.01 (m, 4H), 3.78 (s, 3H), 3.15 (t, *J* = 6.69 Hz, 2H), 2.03 (m, 2H), 1.77 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 169.21, 133.71 (2), 117.03 (2), 101.53 (2), 63.63, 52.52, 35.63, 27.38, 5.85.

(1*R,2*S**,5*R**)-2-Methyl-4-oxa-5-(2-propenyloxy)bicyclo-[3.3.0]octan-1-ol (18a)** was prepared from **17** according to the general procedure outlined for the preparation of **7b** to afford **18a** and **18b** in 57% combined yield after flash chromatography with 10% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.92 (m, 1H), 5.24 (m, 1H), 5.12 (m, 1H), 4.20 (ddt, *J* = 1.61, 6.69 Hz, 12.85H), 4.02 (m, 2H), 3.37 (m, 1H), 2.48 (bs, 1H), 2.30 (m, 1H), 1.98 (m, 1H), 1.88−1.78 (m, 3H), 1.61 (m, 2H), 1.00 (d, *J* = 6.96 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 135.26, 115.90, 113.94, 87.66, 72.60, 64.59, 41.36, 32.53, 30.58, 21.54, 11.24; IR (neat) 3556.2, 1644.2, 1423.7 cm^{-1}; HRMS calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1253; LRMS (EI$^+$) *m*/*z* 198 (2), 181 (10), 157 (48), 140 (100), 115 (31), 97 (52), 55 (61), 41 (97).

(1*R,2*S**,5*R**)-2-Methyl-4-oxa-5-methoxybicyclo[3.3.0]-octan-1-ol (18b):** ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 3.99 (t, *J* = 8.30 Hz, 1H), 3.35 (s, 3H), 3.36 (m, 1H), 2.42 (bs, 1H), 2.25 (m, 1H), 1.96 (m, 1H), 1.86−1.77 (m, 3H), 1.65−1.57 (m, 2H), 0.99 (d, *J* = 6.96 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 114.10, 87.49, 72.54, 50.97, 41.40, 31.82, 30.75, 21.43, 11.25; IR (neat) 3550.6 cm^{-1}; HRMS calcd for $C_9H_{16}O_3$ 172.1094, found 172.1091; LRMS (EI$^+$) *m*/*z* 172 (11), 157 (15), 140 (100), 125 (34), 112 (68), 97 (94), 83 (99), 71 (74), 55 (83), 41 (95), 27 (41).

Methyl 5-chloro-2-methylpentanoate (19) was prepared according to the general procedure outlined for the preparation of **3** by alkylation of methyl 5-chloropentanoate with methyl iodide to afford **19** in 65% yield after flash chromatography with 5% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 3.66 (s, 3H), 3.50 (t, *J* = 6.35 Hz, 2H), 2.44 (m, 1H), 1.80−1.55 (m, 4H), 1.15 (d, *J* = 7.08 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 176.70, 51.61, 44.68, 38.79, 30.30, 30.22, 17.14.

Methyl 5-chloro-2-formyl-2-methylpentanoate was prepared according to the following general procedure. Methyl 5-chloro-2-methylpentanoate, **19** (1.65 g, 10.0 mmol), in 10 mL of dry THF was added slowly dropwise *via* cannula to a −78 °C cooled solution of LDA (11.0 mmol, 1 M in THF). After the addition of the ester was complete, the reaction mixture was stirred for an additional 0.5 h, and then ethyl formate (0.89 g, 12.0 mmol) was added rapidly. The resultant reaction mixture was stirred for 0.5 h at reduced temperature and then quenched with saturated aqueous NH_4Cl. The reaction mixture was subjected to an aqueous workup followed by flash chromatography with 15% EtOAc/hexanes to afford the desired formyl ester in 60% yield after Kugelrohr distillation (ot 120−140 °C/0.5 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 9.67 (s, 1H), 3.75 (s, 3H), 3.51 (t, *J* = 5.98 Hz, 2H), 2.01−1.68 (m, 4H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 198.85, 172.33, 57.15, 52.57, 44.58, 31.34, 27.46, 17.14.

Methyl 2-formyl-5-iodo-2-methylpentanoate (20) was prepared from methyl 5-chloro-2-formyl-2-methylpentanoate according to the general procedure outlined for the preparation of **3** to afford **20** in 85% yield after flash chromatography with 12% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 9.66 (s, 1H), 3.75 (s, 3H), 3.14 (m, 2H), 1.96−1.75 (m, 4H), 1.30 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 198.78, 172.26, 57.06, 52.59, 34.82, 28.28, 17.18, 5.44.

Methyl 2-Formyl-5-iodo-2-methylpentanoate, Bis(2-propenyloxy) Acetal (21). General Procedure for the Preparation of Bis(2-propenyloxy) Acetals. Trimethylsilyl triflate (TMSOTf) (86.0 mg, 0.38 mmol) was added *via* syringe to a 0 °C cooled solution of **20** (0.28 g, 1.0 mmol) and *O*-[(trimethylsilyl)allyl] ether (0.20 g, 1.5 mmol) in 3 mL of dry CH_2Cl_2. The reaction mixture was stirred subsequently for 1 h at 0 °C and then for 2 h at rt before adding successively *O*-[(trimethylsilyl)allyl] ether (0.20 g, 1.5 mmol) and TMSOTf (86.0 mg, 0.38 mmol). The reaction mixture was then stirred for 18−24 h at rt before quenching with saturated aqueous $NaHCO_3$ and subjecting the reaction mixture to an aqueous workup. Flash chromatography with 8% EtOAc/hexanes afforded the desired bis(allyloxy) hemiacetal **31** (0.36 g, 0.95 mmol) in 95% yield: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.84 (m, 2H), 5.30−5.11 (m, 4H), 4.66 (s, 1H), 4.23 (m, 2H), 4.04 (m, 2H), 3.65 (s, 3H), 3.11 (t, *J* = 6.56 Hz, 2H), 1.78 (m, 2H), 1.61 (m, 2H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 174.91, 134.27, 134.20, 117.02, 116.32, 106.80, 71.50, 71.37, 52.09, 51.76, 36.16, 28.73, 15.24, 6.65.

(1*R,2*S**,5*R**,6*R**)-5-(2-Propenyloxy)-4-oxa-2,6-dimethylbicyclo[4.3.0]nonan-1-ol (22)** was prepared according to the general procedure outlined for the preparation of **7b** to afford **22** as a 17:1 mixture of diastereomeric products in 71% combined yield (**22**, major diastereomer, 59% isolated yield) after flash chromatography with 8% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.87 (dq, *J* = 5.26, 15.77 Hz, 1H), 5.25 (dq, *J* = 1.71, 17.39 Hz, 1H), 5.11 (dq, *J* = 1.71, 10.44

Hz, 2H), 4.40 (s, 1H), 4.13 (ddt, J = 13.53, 4.47, 1.61 Hz, 1H), 3.82 (ddt, J =15.01, 5.30, 1.53 Hz, 1H), 3.40−3.32 (m, 2H), 2.15 (m, 1H), 1.91 (m, 1H), 1.75−1.66 (m, 3H), 1.57 (m, 1H), 1.44 (m, 1H), 1.07 (s, 3H), 0.83 (d, J = 6.82 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.61, 115.62, 105.11, 82.53, 68.17, 63.33, 48.95, 35.98, 33.87, 33.06, 20.56, 19.44, 10.86; IR (neat) 3345.0, 1640.6 cm^{-1}; HRMS calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1542; LRMS (EI$^+$) m/z 226 (100), 185 (72), 122 (52), 109 (54), 98 (72), 69 (48), 55 (37), 41 (100). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 69.24; H, 9.89.

Methyl 2-formyl-5-iodo-2-methylpentanoate, bis(2-propynyloxy) acetal was prepared from **20** according to the general procedure for the preparation of **21** (*O*-[(trimethylsilyl)-propargyl] ether) to afford the desired bis(propargyloxy) acetal in 96% yield after flash chromatography with 12% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.97 (s, 1H), 4.38 (m, 2H), 4.32 (m, 2H), 3.69 (s, 3H), 3.11 (t, J = 5.86 Hz, 2H), 2.49 (t, J = 2.44 Hz, 1H), 2.46 (t, J = 2.44 Hz, 1H), 1.81−1.57 (m, 4H), 1.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.50, 104.81, 79.17, 79.12, 75.29, 74.98, 57.49, 57.03, 51.90, 51.65, 36.16, 28.59, 15.30, 6.42.

Methyl 2-formyl-5-iodo-2-methylpentanoate, bis[[3-(trimethylsilyl)-2-propynyl]oxy] acetal (23) was prepared according to the general procedure outlined for the preparation of dihydro-3-[[3-(trimethylsilyl)-2-propynyl]oxy]furan-2(2*H*)-one except 2 equiv of LDA and 2 equiv of TMSCl were employed to afford **23** in 47% yield after flash chromatography with 5% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (s, 1H), 4.44−4.24 (m, 4H), 3.69 (s, 3H), 3.11 (m, 2H), 1.82−1.53 (m, 4H), 1.17 (s, 3H), 0.17 (s, 9H), 0.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.60, 104.56, 101.13, 101.01, 92.23, 91.92, 58.30, 57.72, 51.87, 51.68, 36.10, 28.70, 15.39, 6.39, −0.17 (3), −0.22 (3).

(1*R,2*E*, 5*R**,6*R**)-6-Methyl-4-oxa-2-[(trimethylsilyl)-methylene]-5-[[(3-(trimethylsilyl)-2-propynyl]oxy]bicyclo-[4.3.0]nonan-1-ol (24)** was prepared according to the general procedure outlined for the preparation of **7b** to afford **24** as a single diastereomeric product in 68% yield after flash chromatography with 6% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.77 (s, 1H), 4.60 (s, 1H), 4.33 (m, 1H), 4.20 (m, 2H), 2.33 (m, 1H), 1.78 (m, 3H), 1.54 (m, 2H), 1.41 (m, 1H), 1.21 (m, 1H), 0.99 (s, 3H), 0.12 (s, 9H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.82, 122.18, 103.96, 101.39, 91.25, 83.39, 62.07, 55.74, 52.14, 39.42, 33.20, 22.17, 19.23, 0.25 (3), −0.19 (3); IR (neat) 3499.9, 2177.3, 1620.8, 1614.5, 840.9 cm^{-1}; HRMS calcd for $C_{19}H_{34}O_3Si_2$ 366.2047, found 366.2057; LRMS (EI$^+$) m/z 366 (39), 351 (100), 336 (36), 321 (53), 305 (49), 239 (15), 195 (38), 98 (47), 73 (98). Anal. Calcd for $C_{19}H_{34}O_3Si_2$: C, 62.24; H, 9.35. Found: C, 62.49; H, 9.23.

Methyl 2-(hydroxymethyl)-5-iodo-2-methylpentanoate (25) was prepared from **20** according to the following general procedure. To a stirred solution of $NaBH_4$ (0.13 g, 3.50 mmol) in 5 mL of dry MeOH was added the substrate **20** (1.04 g, 3.82 mmol) dropwise in 2 mL of dry MeOH. The reaction mixture was then warmed to rt and allowed to stir for 8 h at ambient temperature. The reaction was quenched by the careful addition of saturated aqueous NH_4Cl. The desired alcohol **25** (1.04 g, 3.64 mmol) was obtained in 96% yield after an aqueous workup and flash column chromatography with 25% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.70 (s, 3H), 3.64 (dd, J = 7.23, 11.24 Hz, 1H), 3.53 (dd, J = 6.16, 11.24 Hz, 1H), 3.13 (t, J = 6.69 Hz, 2H), 2.25 (t, J = 6.42 Hz, 1H), 1.81−1.56 (m, 4H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.07, 68.08, 52.04, 47.28, 36.63, 28.51, 19.60, 6.30.

Methyl 2-(3-iodopropyl)-2-methyl-4-oxo-6-heptenoate (26) was prepared from **25** according to the following general procedure.[25] To **25** (1.04 g, 3.64 mmol) in 3 mL of dry CH_2Cl_2 cooled to 0 °C in an ice bath was added successively the trichloroacetimidate of allyl alcohol (0.80 mL of a 5 M solution in hexanes, 4.0 mmol) followed by 30 μL of BF_3·OEt_2. The resultant reaction mixture was stirred at 0 °C for 1 h and then warmed to rt and stirred at ambient temperature overnight. The reaction mixture was quenched after this period with saturated aqueous $NaHCO_3$ and subjected to an aqueous workup. Flash column chromatography with 4−5% EtOAc/hexanes afforded the desired allyl ether **26** (0.605 g, 1.85 mmol) in 51% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.19 (m, 2H), 3.94 (d, J = 5.62 Hz, 2H), 3.67 (s, 3H), 3.46 (d, J = 9.10 Hz, 1H), 3.39 (d, J = 8.83 Hz, 1H), 3.12 (m, 2H), 1.74 (m, 3H), 1.55 (m, 1H), 1.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.04, 134.66, 116.80, 75.21, 72.27, 51.87, 46.76, 36.66, 28.70, 19.97, 6.52.

(1*R,2*S**,6*R**)-2,6-Dimethyl-4-oxabicyclo[4.3.0]nonan-1-ol (27)** was prepared from **26** according to the general procedure outlined for the preparation of **7b** to afford **27** in 65% yield as an 11:1 mixture of diastereomeric products epimeric at C-2. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (ddd, J = 1.07, 5.09, 11.51 Hz, 1H), 3.38 (m, 1H), 3.14−3.02 (m, 2H), 2.01 (m, 1H), 1.92−1.51 (m, 5H), 1.27 (m, 1H), 1.13 (bs, 1H), 1.09 (s, 3H), 0.82 (d, J = 6.69 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 83.02, 75.72, 72.09, 46.16, 36.46, 33.83, 30.73, 18.80, 17.83, 10.65; IR (neat) 3452.1 cm^{-1}; HRMS calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1316; LRMS (EI$^+$) m/z 170 (42), 128 (24), 111 (96), 97 (33), 84 (38), 69 (100), 55 (53), 41 (77), 28 (26). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.14; H, 10.41.

Ethyl 2-Oxo-1-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]-cyclopentanecarboxylate. General Procedure for the Alkylation of β-Keto Esters and β-Keto Lactones. Ethyl 2-oxocyclopentanecarboxylate (6.25 g, 40.0 mmol) in 50 mL of dry DMF was added neat *via* syringe to a 0 °C cooled slurry of NaH (1.84 g of a 60% dispersion in mineral oil, 46.0 mmol), and the resultant reaction mixture was stirred at 0 °C for 1 h and then at rt for 2 h. Then, the resultant reaction mixture was cooled to 0 °C, and the TBS ether of 3-bromo-1-propanol was added (15.2 g, 60.0 mmol). The reaction mixture was warmed to rt, heated for 18 h at 50−60 °C, and then quenched after this period with saturated aqueous NH_4Cl. The desired alkylated keto ester (10.96 g, 30.1 mmol) was obtained in 75% yield after an aqueous workup and flash chromatography with 4% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (dq, J = 2.14, 3.48 Hz, 2H), 3.57 (m, 2H), 2.50 (m, 1H), 2.38 (m, 1H), 2.22 (m, 1H), 2.02−1.84 (m, 4H), 1.60−1.38 (m, 3H), 1.22 (t, J = 6.96 Hz, 3H), 0.86 (s, 9H), 0.01 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 214.93, 171.03, 63.01, 61.32, 60.18, 37.93, 32.79, 30.19, 28.21, 25.91 (3), 19.57, 18.29, 14.08, −5.34 (2).

Ethyl (1*R,2*S**)-1-[3-[(*tert*-Butyldimethylsilyl)oxy]propyl]-2-hydroxy-2-methylcyclopentanecarboxylate (28). General Procedure for the Addition of Grignard Reagents to β-Keto Esters and β-Keto Lactones.** Compound **28** was prepared from ethyl 2-oxo-1-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]cyclopentane carboxylate according to the following procedure. Methylmagnesium bromide (2.0 mL of a 3.0 M solution in Et_2O, 6.0 mmol) was added to the β-keto ester (1.83 g, 5.0 mmol) in 10 mL of dry THF cooled to −78 °C. The resultant reaction mixture was stirred at −78 °C for 0.5 h and then allowed to warm to rt. TLC analysis after reaching rt revealed the complete consumption of the starting keto ester and formation of a major, lower R_f product. The reaction mixture was quenched at rt by the careful addition of saturated aqueous NH_4Cl. Flash chromatography with 10% EtOAc/hexanes after an aqueous workup afforded **28** (1.55 g, 4.50 mmol) as a single diastereomeric product (^{1}H NMR) in 90% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.14 (m, 2H), 3.58 (m, 2H), 2.11 (m, 1H), 1.98 (s, 1H), 1.95 (m, 1H), 1.84 (m, 1H), 1.76−1.62 (m, 4H), 1.55−1.36 (m, 2H), 1.26 (t, J = 6.96 Hz, 3H), 1.22 (m, 1H), 1.19 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.73, 80.88, 63.34, 60.33, 59.44, 37.39, 29.21, 28.77, 28.07, 25.91 (3), 25.81, 18.29, 18.02, 14.30, −5.30 (2).

Ethyl (1*R,2*S**)-1-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]-2-methyl-2-(2-propenyloxy)cyclopentanecarboxylate (29)** was prepared from **28** according to the general procedure outlined for the preparation of **25** to afford **29** in 56% yield after flash chromatography with 2% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88 (m, 1H), 5.26 (m, 1H), 5.05 (m, 1H), 4.08 (m, 2H), 3.96−3.82 (m, 2H), 3.56 (m, 2H), 2.21 (m, 1H), 1.92 (m, 2H), 1.72−1.54 (m, 5H), 1.45−1.30 (m, 2H), 1.23 (t, J = 6.96 Hz, 3H), 1.14 (s, 3H), 0.87 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.89, 136.12, 114.61,

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85.83, 63.83, 62.99, 61.55, 60.21, 35.01, 31.82, 29.82, 27.58, 25.97 (3), 19.92, 19.24, 18.35, 14.19, −5.26 (2).

Ethyl (1*R,2*S**)-1-(3-Hydroxypropyl)-2-methyl-2-(2-propenyloxy)cyclopentanecarboxylate. General Procedure for the Removal of the TBS Protecting Group.** Amberlyst-15 was added to a stirred solution of **29** (0.10 g, 0.26 mmol) in 2 mL of of absolute ethanol at ambient temperature. After 3 h, TLC analysis of the reaction mixture showed complete consumption of the starting TBS ether and formation of a single, lower R_f product. The reaction mixture was filtered through a plug of Celite and then concentrated *in vacuo*. Flash chromatography with 25% EtOAc/hexanes afforded the desired primary alcohol (0.07 g, 0.26 mmol) in quantitative yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.87 (m, 1H), 5.25 (m, 1H), 5.07 (m, 1H), 4.10 (m, 2H), 3.88 (m, 2H), 3.60 (m, 2H), 2.21 (m, 1H), 1.96 (m, 2H), 1.74−1.47 (m, 6H), 1.37 (m, 2H), 1.24 (t, J = 7.32 Hz, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.90, 136.10, 114.78, 85.97, 63.47, 63.01, 61.58, 60.36, 34.82, 31.84, 29.24, 27.42, 20.03, 19.14, 14.19.

Ethyl (1*R,2*S**)-1-(3-Bromopropyl)-2-methyl-2-(2-propenyloxy)cyclopentanecarboxylate (30). General Procedure for the Preparation of Bromides from Alcohols.** Compound **30** was prepared from ethyl (1*R**,2*S**)-1-(3-hydroxypropyl)-2-methyl-2-(2-propenyloxy)cyclopentanecarboxylate according to the following general procedure. CBr_4 (0.37 g, 1.12 mmol) and PPh_3 (0.29 g, 1.12 mmol) were added to a solution of the alcohol (0.25 g, 0.93 mmol) in 10 mL of dry ether. The reaction mixture was allowed to stir overnight at ambient temperature. After this period of stirring, the reaction mixture was diluted with pentane, filtered through a short plug of Celite, concentrated *in vacuo*, and then subjected to flash column chromatography (2% EtOAc/hexanes) to afford the desired bromide **30** (0.26 g, 0.77 mmol) in 83% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.94−5.82 (m, 1H), 5.26 (ddt, J = 10.50, 19.04, 4.88 Hz, 1H), 5.08 (ddt, J = 10.50, 3.66, 1.95 Hz, 1H), 4.11 (m, 2H), 3.89 (qtd, J = 12.70, 4.88, 1.71 Hz, 2H), 3.37 (m, 2H), 2.17 (m, 1H), 2.00 (m, 2H), 1.80−1.55 (m, 7H), 1.25 (t, J = 7.08 Hz, 3H), 1.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.54, 135.96, 114.75, 85.98, 62.89, 61.40, 60.40, 34.66, 34.20, 31.97, 30.33, 29.64, 20.09, 19.03, 14.18.

Ethyl (1*R,2*S**)-1-(3-Bromopropyl)-2-methyl-2-(2-formylethoxy)cyclopentanecarboxylate. General Procedure for Ozonolysis with Reductive Workup.** This compound was prepared from **30** according to the general procedure outlined for the preparation of **16** to afford the desired aldehyde (1.53 g, 4.56 mmol) in 100% yield after flash column chromatography with 25−30% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.71 (s, 1H), 4.18−4.09 (m, 2H), 3.98 (d, J = 17.40 Hz, 1H), 3.39 (m, 2H), 2.23 (m, 1H), 2.05 (m, 1H), 1.87 (m, 1H), 1.79−1.62 (m, 6H), 1.22 (m, 1H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.96, 175.06, 86.95, 68.65, 61.14, 60.04, 34.81, 35.05, 31.76, 30.28, 29.42, 19.75, 19.19, 14.19.

Ethyl (1*R,2*S**)-1-(3-Iodopropyl)-2-methyl-2-[(3-phenyl-2(*Z*)-propenyl)oxy]cyclopentanecarboxylate (31). General Wittig Reaction Procedure.** Compound **31** was prepared from the above aldehyde according to the following general procedure. *n*-Butyllithium (3.6 mL of a 1.6 M solution in hexanes, 5.76 mmol) was added to a 0 °C solution of benzyltriphenylphosphonium chloride (2.24 g, 5.76 mmol) in 20 mL of dry THF. The resultant dark red solution was allowed to warm to rt and stir for 0.5 h before cooling to −78 °C. Then, the aldehyde (1.61 g, 4.80 mmol) was added in 10 mL of dry THF to the prepared Wittig reagent. The reaction mixture was maintained at −78 °C until the substrate addition was complete. After this period of time, the reaction mixture was allowed to warm to rt. TLC analysis at this time revealed the complete consumption of starting aldehyde and the formation of a single, higher R_f product. The reaction mixture was quenched at rt with saturated aqueous $NaHCO_3$ and subjected to an aqueous workup. Flash column chromatography with 3% EtOAc/hexanes afforded the desired olefin as a mixture of the bromide and chloride. The resultant mixture was taken up in acetone and heated at reflux overnight with NaI (7.2 g, 48.0 mmol). The reaction mixture was then subjected to an aqueous workup and flash column chromatography with 2% EtOAc/hexanes to afford the desired iodide **31** (0.79 g, 1.73 mmol) in 36% yield (two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.18 (m, 5H), 6.58 (m, 0.3H), 6.51 (m, 0.67H), 6.25 (dt, J = 5.36, 15.80 Hz, 0.30H), 5.79 (dt, J = 11.78, 6.16 Hz, 0.67H), 4.22−4.00 (m, 4H), 3.19−3.13 (m, 2H), 2.18 (m, 1H), 2.00 (m, 2H), 1.76−1.54 (m, 7H), 1.25 (m, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.51, 136.84, 130.30, 130.06, 128.67, 128.47, 128.17, 127.56, 127.31, 127.00, 126.32, 86.15, 62.69, 61.30, 61.18, 60.43, 60.40, 59.33, 34.83, 34.76, 32.71, 32.64, 32.02, 30.42, 30.33, 20.13, 20.10, 19.18, 14.24, 14.21, 7.34, 7.15; LRMS (EI$^+$) m/z 439 (21), 426 (82), 382 (11), 339 (19), 323 (97), 249 (83), 197 (26), 133 (68), 117 (100), 91 (64), 77 (69), 55 (42), 43 (92), 29 (71).

(1*R,2*S**,5*S**)-2-Benzyl-5-methyltricyclo[7.3.0^{5,9}]-dodecan-1-ol (32a)** was prepared from **31** (a 2:1 mixture of *Z* and *E* olefin isomers, respectively) according to the general procedure outlined for the preparation of **4** (except the reaction mixture was heated at reflux for 12 h after the addition of the substrate was complete) to afford **32a** as a single diastereomeric product in 56% yield along with the uncyclized intermediate (**32b**, 35% yield, a 2:1 mixture of *E* and *Z* olefin isomers, respectively) after flash column chromatography with 8% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70−7.64 (m, 5H), 4.19−4.06 (m, 2H), 3.42 (dd, J = 13.65, 4.55 Hz, 1H), 3.20 (m, 1H), 2.78 (dd, J = 13.39, 9.91 Hz, 1H), 2.67 (m, 1H), 2.42 (m, 1H), 2.23−2.03 (m, 8H), 1.95 (m, 1H), 1.83 (s, 3H), 1.80 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.50, 128.90 (2), 128.49 (2), 126.14, 81.26, 81.10, 66.89, 57.00, 45.77, 37.72, 37.45, 35.05, 33.86, 28.09, 26.82, 19.50, 18.19; IR (CCl_4) 3614.2, 1542.9, 1494.8, 1455.6 cm^{-1}; HRMS calcd for $C_{19}H_{26}O_2$ 286.1933, found 286.1928; LRMS (EI$^+$) m/z 286 (21), 271 (100), 253 (13), 244 (62), 238 (31), 229 (22), 223 (13), 191 (97), 177 (23), 135 (28), 108 (95), 91 (94), 79 (23), 67 (17), 55 (28), 43 (26), 28 (18).

6-Methyl-6-[(2*E*/*Z*)-3-phenyl-2-propenyl)oxy]spiro[4.4]-nonan-1-one (32b) (2:1 mixture of *E* and *Z* olefin isomers): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.18 (m, 5H), 6.58−6.49 (m, 1H), 6.26 (dt, J = 15.80, 5.36 Hz, 0.67H), 5.76 (dt, J = 11.78, 6.16 Hz, 0.33H), 4.09−3.98 (m, 2H), 2.38−1.98 (m, 3H), 1.99−1.81 (m, 4H), 1.80−1.65 (m, 4H), 1.19 (m, 1H), 1.16 (s, 2H), 1.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 215.86, 137.11, 136.85, 130.47, 130.25, 129.92, 128.67, 128.48, 128.19, 127.86, 127.31, 127.03, 126.31, 86.55, 63.34, 63.19, 61.82, 58.48, 39.62, 39.59, 35.22, 35.14, 34.17, 32.25, 32.21, 20.32, 20.23, 19.31, 19.26, 17.38, 17.31; IR (neat) 1728.6, 1599.7, 1576.7, 1494.4 cm^{-1}; HRMS calcd for $C_{19}H_{24}O_2$ 284.1776, found 284.1756; LRMS (EI$^+$) m/z 284 (22), 266 (48), 223 (28), 199 (83), 167.100, 151 (21), 133 (18), 117 (98), 107 (9), 91 (19), 79 (8), 67 (9), 55 (11), 43 (17), 28 (8).

Ethyl 2-acetyl-6-[(*tert*-butyldimethylsilyl)oxy]-2-methylhexanoate was prepared from ethyl 2-methylacetoacetate according to the general procedure outlined for the preparation of ethyl 2-oxo-1-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]cyclopentanecarboxylate to afford the desired β-keto ester in 52% yield after flash column chromatography with 2−3% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.16 (q, J = 7.23 Hz, 2H), 3.57 (t, J = 6.43 Hz, 2H), 2.12 (s, 3H), 1.85 (m, 1H), 1.74 (m, 1H), 1.49 (m, 2H), 1.30 (s, 3H), 1.23 (t, J = 7.23 Hz, 3H), 1.72 (m, 2H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.72, 173.02, 62.01, 61.18, 59.65, 34.52, 33.07, 26.09, 25.89 (3), 20.53, 18.71, 18.27, 14.03, −5.33 (2).

Ethyl 6-[(*tert*-butyldimethylsilyl)oxy]-2-(2-hydroxypropyl)-2-methylhexanoate was prepared from the above ethyl 2-acetyl-6-[(*tert*-butyldimethylsilyl)oxy]-2-methylhexanoate according to the general procedure outlined for the preparation of **28** to afford the desired tertiary alcohol (5.93 g, 17.1 mmol) in 86% yield: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (q, J = 7.32 Hz, 2H), 3.61 (s, 1H), 3.57 (t, J = 6.10 Hz, 2H), 2.08 (m, 1H), 1.57−1.33 (m, 4H), 1.28 (m, 1H), 1.27 (t, J = 7.32 Hz, 3H), 1.15 (s, 3H), 1.13 (s, 3H), 1.12 (s, 3H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.69, 73.92, 62.83, 60.75, 53.64, 33.53, 33.35, 26.82, 25.91 (3), 23.94, 21.57, 18.29, 17.81, 14.21, −5.32 (2).

Ethyl 2-[4-[(*tert*-butyldimethylsilyl)oxy]butyl]-4-oxa-2,3,3-trimethyl-6-heptenoate was prepared from ethyl 6-[(*tert*-butyldimethylsilyl)oxy]-2-(2-hydroxypropyl)-2-methylhexanoate according to the general procedure outlined for the preparation of **26** to afford the desired allyl ether in 72% yield after flash column chromatography with 2% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (m, 1H), 5.23 (m, 1H), 5.03

(m, 1H), 4.09 (m, 2H), 3.86 (m, 2H), 3.56 (t, J = 6.59 Hz, 2H), 1.92 (m, 1H), 1.51−1.44 (m, 2H), 1.42−1.31 (m, 2H), 1.25 (m, 4H), 1.20 (s, 3H), 1.18 (s, 3H), 1.17 (s, 3H), 0.86 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.68, 136.17, 114.26, 78.58, 63.08, 62.15, 60.04, 54.66, 33.81, 33.58, 25.93 (3), 21.70, 21.28, 20.93, 18.31, 17.04, 14.22, −5.30 (2).

Ethyl 2-(4-hydroxybutyl)-4-oxa-2,3,3-trimethyl-6-heptenoate was prepared from ethyl 2-[4-[(*tert*-butyldimethylsilyl)oxy]butyl]-4-oxa-2,3,3-trimethyl-6-heptenoate according to the general procedure outlined for the preparation of ethyl (1*R**,2*S**)-1-(3-hydroxypropyl)-2-methyl-2-(2-propenyloxy)cyclopentanecarboxylate to afford the desired primary alcohol in quantitative yield after flash column chromatography with 30% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (ddt, J = 17.09, 10.50, 4.64 Hz, 1H), 5.23 (m, 1H), 5.03 (m, 1H), 4.09 (q, J = 7.08 Hz, 2H), 3.86 (m, 2H), 3.62 (m, 2H), 1.98 (m, 1H), 1.59−1.49 (m, 2H), 1.43−1.32 (m, 2H), 1.24 (t, J = 7.08 Hz, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.15−0.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.77, 136.12, 114.31, 78.53, 62.69, 62.17, 60.18, 54.71, 33.40, 33.22, 21.53, 21.24, 20.93, 17.00, 14.21.

Ethyl 2-(4-bromobutyl)-4-oxa-2,3,3-trimethyl-6-heptenoate was prepared from ethyl 2-(4-hydroxybutyl)-4-oxa-2,3,3-trimethyl-6-heptenoate according to the general procedure outlined for the preparation of **30** to afford the desired bromide in 73% yield after flash column chromatography with 2% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.23 (m, 1H), 5.03 (m, 1H), 4.10 (q, J = 6.96 Hz, 2H), 3.86 (m, 2H), 3.38 (t, J = 6.69 Hz, 2H), 1.95 (m, 1H), 1.83 (m, 2H), 1.42−1.35 (m, 2H), 1.23 (t, J = 6.96 Hz, 3H), 1.19 (s, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.49, 136.10, 114.36, 78.46, 62.19, 60.22, 54.56, 33.68, 33.44, 32.94, 24.09, 21.25, 20.94, 17.05, 14.23.

Ethyl 2-(4-bromobutyl)-6-formyl-4-oxa-2,3,3-trimethyl-6-hexanoate was prepared from the above bromide, ethyl 2-(4-bromobutyl)-4-oxa-2,3,3-trimethyl-6-heptenoate, according to the general ozonolysis procedure described above to afford the desired aldehyde in 98% yield after flash column chromatography with 20% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H), 4.13 (q, J = 7.23 Hz, 2H), 3.90 (s, 2H), 3.39 (t, J = 6.69 Hz, 2H), 1.97 (m, 1H), 1.83 (m, 2H), 1.41 (m, 2H), 1.24 (t, J = 7.23 Hz, 3H), 1.22 (s, 3H), 1.21 (s, 3H), 1.20 (s, 3H), 1.16 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.44, 175.06, 79.71, 68.08, 60.46, 54.35, 33.60, 33.30, 33.01, 23.98, 21.31, 21.05, 17.08, 14.26.

Ethyl 2-(4-iodobutyl)-4-oxa-7-phenyl-2,3,3-trimethyl-6(*Z*)-heptenoate (33) was prepared from the above aldehyde, ethyl 2-(4-bromobutyl)-6-formyl-4-oxa-2,3,3-trimethyl-6-hexanoate, according to the general procedure outlined for the preparation of **31** to afford **33** as a 2:1 mixture of *Z* and *E* isomers, respectively, in 60% yield (two steps) after flash column chromatography with 2−3% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34−7.18 (m, 5H), 6.47 (d, J = 12.05 Hz, 1H), 5.74 (dt, J = 12.05, 6.16 Hz, 1H), 4.14−4.08 (m, 4H), 3.16 (t, J = 6.96 Hz, 2H), 1.94 (m, 1H), 1.79 (m, 2H), 1.39 (m, 2H), 1.23 (t, J = 7.23 Hz, 3H), 1.20 (s, 3H), 1.19 (s, 3H), 1.18 (s, 3H), 1.12 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.49, 136.92, 130.66, 129.97, 128.67 (2), 128.16, 126.95, 126.26, 78.73, 60.25, 58.79, 54.43, 34.18, 32.70, 26.42, 21.36, 21.07, 17.04, 14.29, 6.86; LRMS (EI$^+$) m/z 458 (5), 441 (16), 427 (19), 412 (22), 400 (100), 355 (83), 325 (52), 284 (30), 251 (40), 199 (18), 117 (73), 87 (64), 57 (73), 43 (100), 29 (65).

(1*R,2*S**,6*R**)-2-Benzyl-4-oxa-5,5,6-trimethylbicyclo-[4.4.0]decan-1-ol (34)** was prepared from **33** according to the general procedure outlined for the preparation of **7b** to afford **34** in 78% yield after flash column chromatography with 10% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.13 (m, 5H), 3.46 (m, 1H), 3.36 (m, 1H), 2.94 (d, J = 10.44, 1H), 2.14 (m, 2H), 1.96 (m, 1H), 1.70−1.47 (m, 7H), 1.43 (s, 3H), 1.14 (s, 3H), 1.13 (m, 1H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.83, 128.87 (2), 128.24 (2), 78.63, 73.23, 42.96, 30.92, 27.84, 27.67, 21.81; IR (neat) 3564.5, 1455.9, 1372.9, 1090.6 cm^{-1}; HRMS calcd for $C_{19}H_{27}O_2$ (M − H$^+$) 287.2011, found 287.1999; LRMS (EI$^+$) m/z 287 (100), 273 (98), 270 (42), 255 (48), 112 (48), 91 (78), 71 (99), 55 (48), 41 (92), 27 (68). Anal. Calcd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78. Found: C, 78.96; H, 9.88.

3-Acetyl-3-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]furan-2(2*H*)-one was prepared from 2-acetyl butyrolactone according to the general procedure outlined for the preparation of ethyl 2-oxo-1-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]cyclopentanecarboxylate to afford the desired β-keto lactone in 41% yield after flash column chromatography with 15% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.27 (dt, J = 3.17, 9.03 Hz, 1H), 4.13 (dt, J = 7.08, 9.28 Hz, 1H), 3.63−3.55 (m, 2H), 2.91 (ddd, J = 12.94, 7.08, 2.93 Hz, 1H), 2.32 (s, 3H), 2.26 (ddd, J = 4.88, 11.96, 14.16 Hz, 1H), 2.04−1.94 (m, 1H), 1.85−1.75 (m, 1H), 1.41−1.31 (m, 2H), 0.86 (s, 9H), 0.02 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.71, 175.50, 66.30, 62.08, 61.29, 31.56, 29.11, 28.19, 25.86 (3), 25.41, 18.23, −5.42 (2); IR (neat) 1772.0, 1716.5, 830.0 cm^{-1}.

3-[3-[(*tert*-Butyldimethylsilyloxy]propyl]-3-(2-hydroxypropyl)furan-2(2*H*)-one was prepared from 3-acetyl-3-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]furan-2(2*H*)-one according to the general procedure outlined for the preparation of ethyl 6-[(*tert*-butyldimethylsilyl)oxy]-2-(2-hydroxypropyl)-2-methylhexanoate to afford the desired tertiary alcohol in 74% yield after flash column chromatography with 20% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.24 (m, 2H), 3.64 (m, 1H), 3.54 (m, 1H), 3.01 (s, 1H), 2.33 (m, 1H), 2.17−1.99 (m, 2H), 1.62 (m, 1H), 1.47 (m, 2H), 1.26 (s, 3H), 1.24 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 181.79, 73.77, 65.81, 62.87, 53.68, 29.63, 29.37, 28.46, 26.71, 25.87 (3), 24.08, 18.26, −5.33, −5.38.

3-[[3-(*tert*-Butyldimethylsilyl)oxy]propyl]-3-[5-(5-methyl-4-oxa-2-hexenyl)]furan-2(2*H*)-one was prepared from 3-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]-3-(2-hydroxypropyl)-furan-2(2*H*)-one according to the general procedure outlined for the preparation of **26** to afford the desired allyl ether in 72% yield after flash column chromatography with 8% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (m, 1H), 5.19 (m, 1H), 5.04 (m, 1H), 4.22 (m, 1H), 3.89 (m, 2H), 3.63 (m, 1H), 3.54 (m, 1H), 2.62 (m, 1H), 2.10 (m, 1H), 1.71 (m, 1H), 1.55 (m, 2H), 1.43 (m, 1H), 1.35 (s, 3H), 1.22 (s, 3H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.92, 135.65, 114.99, 79.71, 65.81, 63.00, 62.28, 54.74, 29.77, 28.48, 28.36, 25.89 (3), 21.05, 19.83, 18.27, −5.30, −5.35.

3-(3-Hydroxypropyl)-3-[5-(5-methyl-4-oxa-2-hexenyl)]-furan-2(2*H*)-one was prepared from 3-[3-[(*tert*-butyldimethylsilyl)oxy]propyl]-3-[5-(5-methyl-4-oxa-2-hexenyl)]furan-2(2*H*)-one according to the general procedure outlined for the preparation of ethyl (1*R**,2*S**)-1-(3-hydroxypropyl)-2-methyl-2-(2-propenyloxy)cyclopentanecarboxylate to afford the desired primary alcohol in 83% yield after flash column chromatography with 50% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (m, 1H), 5.18 (m, 1H), 5.04 (m, 1H), 4.23 (m, 1H), 4.14 (m, 1H), 3.88 (m, 2H), 3.61 (m, 2H), 2.61 (m, 1H), 2.10 (m, 1H), 1.88 (m, 1H), 1.78 (m, 1H), 1.68−1.52 (m, 2H), 1.43 (m, 1H), 1.34 (s, 3H), 1.22 (s, 3H).

3-(3-Bromopropyl)-3-[5-(5-methyl-4-oxa-2-hexenyl)]furan-2(2*H*)-one was prepared from 3-(3-hydroxypropyl)-3-[5-(5-methyl-4-oxa-2-hexenyl)]furan-2(2*H*)-one according to the general procedure outlined for the preparation of **30** to afford the desired bromide in 100% yield after flash column chromatography with 15% EtOAc/hexanes: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (m, 1H), 5.13 (m, 1H), 5.06 (m, 1H), 4.26−4.12 (m, 2H), 3.90 (m, 2H), 3.45 (m, 1H), 3.31 (m, 1H), 2.64 (m, 1H), 2.08 (m, 1H), 1.89−1.66 (m, 4H), 1.35 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.59, 135.49, 115.16, 79.64, 69.86, 62.32, 54.57, 33.44, 32.07, 28.47, 28.44, 20.99, 19.91.

3-(3-Bromopropyl)-3-(4-methyl-3-oxapentanoyl)furan-2(2*H*)-one was prepared from 3-(3-bromopropyl)-3-[5-(5-methyl-4-oxa-2-hexenyl)]furan-2(2*H*)-one according to the general ozonolysis procedure outlined above to afford the desired aldehyde in 100% yield after flash column chromatography with 50% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.64 (s, 1H), 4.31 (m, 1H), 4.19 (m, 1H), 4.01 (s, 2H), 3.45 (m, 1H), 3.31 (m, 1H), 2.73 (m, 1H), 2.13 (m, 1H), 1.85 (m, 3H), 1.72 (m, 1H), 1.36 (s, 3H), 1.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.45, 179.16, 80.83, 67.92, 65.86, 54.37, 33.27, 32.13, 28.44, 28.30, 20.97, 19.99.

3-(3-Iodopropyl)-3-[5-(5-methyl-4-oxa-1-phenyl-1(*Z*)-hexenyl)]furan-2(2*H*)-one (35) was prepared from 3-(3-bromopropyl)-3-[4-methyl-3-oxapentanoyl]furan-2(2*H*)-one ac-

cording to the general procedure outlined for the preparation of **31** to afford **35** in 56% yield (two steps) as a 2:1 mixture of *Z* and *E* isomers, respectively, after flash column chromatography with 10% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83−7.64 (m, 5H), 6.99 (m, 1H), 6.66 (dt, J = 5.62, 15.80 Hz, 0.3H), 6.19 (dt, J = 6.43, 11.78 Hz, 0.67H), 4.70 (m, 1H), 4.62 (m, 2H), 4.54 (m, 1H), 3.71 (m, 1H), 3.56 (m, 1H), 3.12 (m, 1H), 2.55 (m, 1H), 2.75 (m, 3H), 2.12 (m, 1H), 1.88 (s, 2H), 1.83 (s, 2H), 1.78 (s, 1H), 1.73 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.56, 136.83, 136.64, 130.58, 129.69, 128.60, 128.48, 128.22, 127.45, 127.10, 126.97, 126.32, 79.84, 65.91, 62.17, 58.58, 54.48, 34.36, 34.31, 29.14, 29.11, 28.50, 21.10, 20.98, 20.21, 6.08; LRMS (EI$^+$) *m*/*z* 428 (100), 413 (13), 385 (19), 370 (9), 323 (11), 296 (68), 281 (97), 268 (10), 251 (14), 237 (12), 209 (13).

(1*R,2*S**,6*R**)-2-Benzyl-5,5-dimethyl-6-(2-hydroxyethyl)-4-oxabicyclo[4.3.0]nonan-1-ol (36)** was prepared from **35** according to the general procedure outlined for the preparation of **7b** (except the reaction mixture was heated at reflux for 12 h after addition of the substrate was complete) to afford **36** as a 20:1 mixture of diastereomeric products in 54% yield after flash column chromatography with 30% EtOAc/hexanes. Major diastereomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.20 (m, 5H), 4.11 (m, 1H), 3.81 (m, 1H), 3.48 (m, 1H), 3.37 (m, 1H), 3.11 (dd, J = 3.21, 13.65 Hz, 1H), 2.42 (m, 1H), 2.21−2.03 (m, 3H), 2.14 (bs, 2H), 1.96−1.79 (m, 3H), 1.68−1.59 (m, 3H), 1.27 (s, 3H), 1.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.84, 128.79 (2), 128.35 (2), 125.87, 83.58, 77.90, 62.71, 59.78, 54.73, 45.12, 37.58, 36.06, 35.81, 33.82, 28.16, 24.71, 20.83; IR (neat) 3360.6, 3061.9, 3024.8, 1651.4, 1603.2, 1495.6, 1470.3 cm^{-1}; HRMS calcd for $C_{19}H_{26}O_2$ (M − H_2O) 286.1933, found 286.1919; LRMS (EI$^+$) *m*/*z* 286 (12), 216 (19), 198 (21), 137 (48), 110 (37), 110 (37), 91 (100), 79 (26), 67 (28), 55 (48), 43 (72). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.49; H, 9.23.

3-Bromopropyl Cyclopentanecarboxylate (37). Cyclopentanecarboxylic acid (1.37 g, 12.0 mmol), EDCI (3.57 g, 12.0 mmol), 3-bromo-1-propanol (2.00 g, 14.4 mmol), and catalytic DMAP were stirred together for 18 h at ambient temperature. After this period of time, the reaction was quenched with saturated aqueous $NaHCO_3$ and subjected to an aqueous workup. Flash column chromatography with 5% EtOAc/hexanes afforded the desired ester **37** (2.46 g, 9.88 mmol) in 82% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.18 (t, J = 6.10 Hz, 2H), 3.44 (t, J = 6.59 Hz, 2H), 2.70 (m, 1H), 2.15 (m, 2H), 1.88−1.55 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.54, 61.90, 43.72 (2), 31.73, 29.96, 25.75 (2), 1.45.

3-Bromopropyl 1-(1-hydroxypropyl)cyclopentanecarboxylate (38) was prepared from **37** according to the following general procedure. The ester, **37** (2.32 g, 9.88 mmol), in 10 mL of dry THF was added dropwise via cannula to LDA (10.9 mmol) at −78 °C. After the addition of the ester was complete, the reaction was stirred at reduced temperature for an additional 0.5 h and then propionaldehyde (0.86 g, 14.82 mmol) was added neat via syringe. The reaction mixture was maintained at −78 °C for 0.5 h, and then quenched with saturated aqueous NH_4Cl. An aqueous workup followed by flash column chromatography with 10% EtOAc/hexanes afforded the desired product, **38** (1.35 g, 4.61 mmol), in 47% yield: ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (m, 2H), 3.43 (t, J = 6.35 Hz, 3H), 2.46 (d, J = 8.55 Hz, 1H), 2.21−1.85 (m, 5H), 1.67−1.57 (m, 4H), 1.54−1.44 (m, 2H), 1.24 (m, 1H), 0.99 (t, J = 7.08 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.32, 78.57, 62.35, 59.00, 34.23, 33.06, 31.47, 29.23, 26.61, 25.94, 25.47, 11.27; IR (neat) 3491.9, 1725.7 cm^{-1}.

3-Bromopropyl 1-(1-ethyl-2-oxa-4-pentenyl)cyclopentanecarboxylate (39) was prepared from **38** according to the general procedure outlined for the preparation of **26** to afford the desired allyl ether, **39**, in 69% yield after flash column chromatography with 2% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.89 (m, 1H), 5.23 (m, 1H), 5.11 (m, 1H), 4.19 (t, J = 5.89 Hz, 2H), 4.10 (dq, J = 10.98, 5.35 Hz, 2H), 3.48 (dd, J = 8.57, 3.75 Hz, 1H), 3.45 (t, J = 6.69 Hz, 2H), 2.19−2.13 (m, 2H), 2.10 (m, 1H), 1.95 (m, 1H), 1.74 (m, 1H), 1.64−1.39 (m, 7H), 0.95 (t, J = 7.23 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.58, 135.11, 116.17, 85.18, 73.97, 62.13, 60.01, 33.92, 31.62, 30.64, 29.49, 25.89, 25.30, 25.21, 11.65.

3-Bromopropyl 1-(1-ethyl-2-oxa-4-oxobutyl)cyclopentanecarboxylate was prepared from **39** according to the general ozonolysis procedure outlined above to afford the desired aldehyde, which was subjected immediately to the Wittig reaction conditions as below: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.69 (s, 1H), 4.22−4.16 (m, 4H), 3.57 (m, 2H), 3.45 (t, J = 6.69 Hz, 2H), 2.16 (m, 2H), 2.07 (m, 2H), 1.65−1.51 (m, 7H), 0.97 (t, J = 7.50 Hz, 3H).

3-Iodopropyl 1-(1-ethyl-2-oxa-5(*Z*)-phenyl-4-pentenyl)-cyclopentanecarboxylate (40) was prepared from the above aldehyde according to the general procedure outlined for the preparation of **31** to afford **40** in 56% yield (from **39**) after flash column chromatography with 2% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38−7.29 (m, 3H), 7.27 (m, 1H), 7.17 (m, 1H), 6.53 (d, J = 11.8 Hz, 1H), 5.83 (dt, J = 6.16, 11.8 Hz, 1H), 4.36 (ddq, J = 1.61, 6.16, 12.60 Hz, 2H), 4.08 (t, J = 6.16 Hz, 2H), 3.50 (dd, J = 3.74, 8.03 Hz, 1H), 3.18 (t, J = 6.96 Hz, 2H), 2.08 (m, 3H), 1.97 (m, 1H), 1.72 (m, 1H), 1.62−1.39 (m, 7H), 0.94 (t, J = 7.50 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.26, 136.74, 130.62, 129.56, 128.72, 128.51, 128.20, 127.10, 126.46, 85.51, 69.76, 64.04, 59.96, 33.88, 32.23, 30.81, 25.85, 25.32, 25.24, 11.69, 1.64.

(2*R,5*R**,6*S**)-5-Benzyl-2-ethyl-6-(3-hydroxypropyl)-3-oxaspiro[5.4.0]decan-6-ol (41)** was prepared from **40** according to the general procedure outlined for the preparation of **7b** to afford **41** as a single diastereomer in 54% yield after flash column chromatography with 40% EtOAc/hexanes: ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.82−3.73 (m, 3H), 3.57 (d, J = 11.51 Hz, 1H), 3.46 (d, J = 9.64 Hz, 1H), 2.81 (t, J = 13.12 Hz, 1H), 2.65 (m, 1H), 2.07 (m, 2H), 1.91−1.79 (m, 7H), 1.72 (m, 2H), 1.64−1.43 (m, 8H), 1.36−1.21 (m, 3H), 1.00 (t, J = 7.23 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.38, 129.26 (2), 128.35 (2), 125.97, 110.52, 83.21, 65.25, 63.47, 53.89, 44.95, 34.15, 31.23, 29.91, 29.34, 28.52, 26.59, 25.14, 23.41, 12.17; IR ($CHCl_3$) 3690.4, 3611.6, 3409.2, 1602.1, 1495.8 cm^{-1}; HRMS calcd for $C_{21}H_{32}O_3$ 332.2351, found 332.2372; LRMS (EI$^+$) *m*/*z* 332 (22), 314 (12), 285 (71), 273 (11), 255 (18), 205 (64), 165 (18), 110 (46), 91 (48). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.46; H, 9.77.

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Supporting Information Available: Copies of ^{1}H NMR and ^{13}C NMR spectra of compounds synthesized (148 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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