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Tandem Radical Cyclizations Promoted by O-Stannyl Ketyls

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Abstract: This work summarizes an investigation of tandem radical cyclizations triggered by O-stannyl ketyls. This organometallic reactive intermediate is prepared from the reaction of tributyltin hydride (nBu3SnH) with a carbonyl functional group by a free radical chain mechanism. Several precursor substrates leading to "separated," "spiro," and "fused" cyclopentaniod ring systems were investigated which collectively have good synthetic potential for the construction of a wide array of substituted polycyclic products. © 1997 Elsevier Science Ltd.

INTRODUCTION

Tandem radical cyclizations, involving the formation of two or more consecutive rings from one initial radical, have become a popular method to generate sophisticated carbon skeletons.[1] This general methodology rapidly lends itself to the synthesis of complex natural products such as linear- and angular-fused triquinianes,[2] steroids,[3] milbemycin,[4] prostaglandins,[5] and other ring constructions.[1,6] The carbon-centered radical which initiates the tandem process has been classically generated with tributyltin hydride (nBu3SnH) and a variety of precursor functionalities such as halides, thiocarbonyl amides, and alkenes. However, until recently, little attention has been paid to tandem one-electron reactions using carbonyl precursors such as ketones and aldehydes and tributyltin radical. Upon reaction with tributyltin hydride and an initiator, a carbonyl precursor **1** bearing suitable alkene appendages can lead to an O-stannyl ketyl intermediate **2**, bearing a tributyltin alkoxide with an adjacent carbon-centered radical, by a free radical chain mechanism as shown in Scheme 1.[7-10] The intial ketyl **2** allows for sequential carbon-carbon bond constructions, and upon workup, leads to a secondary or tertiary alcohol in the product. The organotin alkoxide or the hydroxyl can be a useful scaffolding for subsequent synthetic manipulations. Moreover, the alkoxy tin species are not directly afforded by other currently available free radical chain methods.

This work focuses specifically on tandem radical cyclizations promoted by metal-associated ketyls from ketone and aldehyde precursors. In these studies, all of the precursors were completely acyclic and lacked templating rings which have functioned as stereochemical control elements in radical cyclizations in many previous

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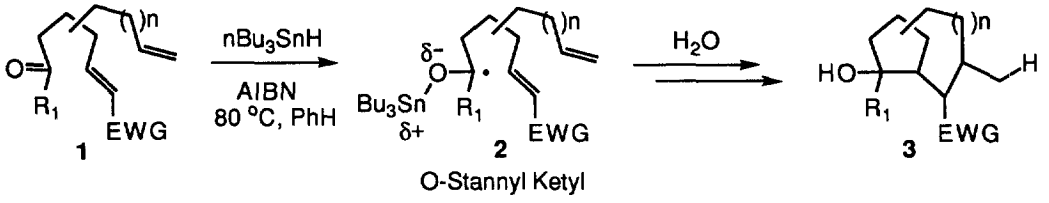
studies.[1-6] Different activating substituents on the intermediate olefin radicophiles were examined. In one case, only one cyclization was observed, rather than the tandem sequence of two closures. This study will examine several variables in the reaction which control the regiochemistry of cyclization, stereochemistry, and yield of the polycyclic alkanol products.[8(c)]

Scheme 1



O-Stannyl ketyls have been used in several studies of monocyclizations and have been used to cleave cyclopropyl rings.[8] Studies of simple alkene/carbonyl couplings demonstrated that an O-stannyl ketyl was effective in cyclizations of both aldehydes and ketones.[8(a)] Moreover, activated olefins functioned best in monocyclizations, whereas nonactivated olefins often produced low yields and gave acyclic alcohol products. Monocyclizations of allylic O-stannyl ketyls have been investigated where α,β-unsaturated ketones were reduced by the tributyltin radical to give a resonance stabilized radical and enolate species.[8(b)] From these initial efforts, it appears that O-stannyl ketyls are potentially very versatile, yet much synthetic utility remains to be discovered.[10]

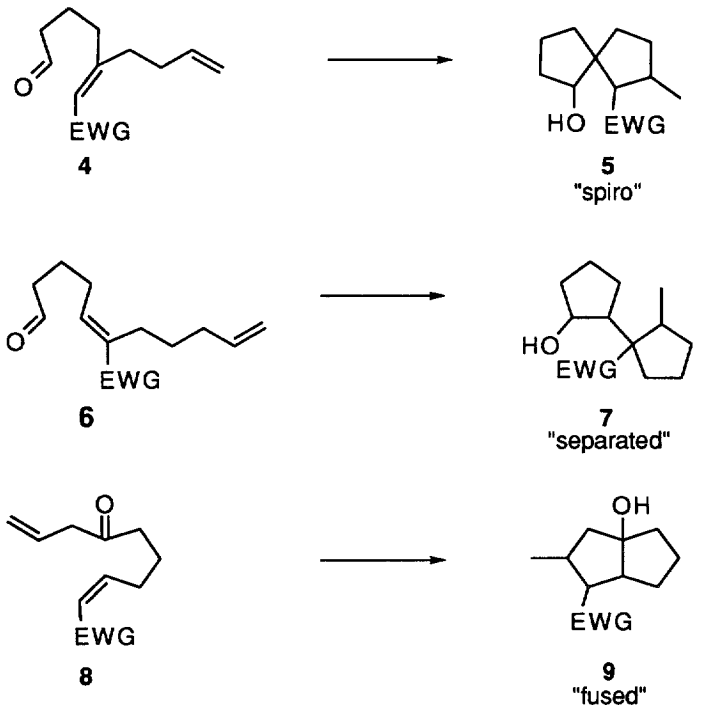
RESULTS AND DISCUSSION

By simply varying both the positions and electronic properties of two olefins along with the length of a carbon tether in an acyclic precursor molecule, a wide variety of bis-cyclopentanoid substrates might be constructed, as shown in Scheme 2. We initially envisioned the three acyclic precursor substrates, **4**, **6**, and **8**, which could be easily constructed by a combination of Grignard reactions, oxidations, and Wittig olefinations. These were specifically designed to generate the ring systems of the "spiro," **5**, "separated," **7**, and "fused" **9** bicyclic pentanols, respectively, provided the tandem reaction was successful in each case. Additionally, the activating capacity of styrene (EWG = Ph), a poorly studied radical acceptor,[11] and α,β–unsaturated esters (EWG = CO_2CH_3) were investigated. This allowed for a direct comparison of the activating capacity of each functionality. Note the central alkene bearing the EWG in **4**, **6**, and **8**, will act as the "middle man" in these cyclizations and must function in both capacities as a one-electron acceptor from the O-stannyl ketyl and donor in the last 5-hexenyl cyclization in the tandem sequence.[12]

The central alkene also provides a direct avenue for the distonic separation of the radicaloid and alkoxide nature of the initial O-stannyl ketyl species. This separation of the one- and two-electron nature of the ketyl creates the potential for the individual reactivity of either species in subsequent reactions from one initial carbonyl function group precursor.[13] The sequencing of one-and two-electron reactions is rapidly growing as new synthetic tool and a few studies indicate that sequencing reactions may be useful with O-stannyl ketyls.[8,14]

Because the first ring-forming reaction of the tandem sequence should function best with an activated central alkene, the precursor substrates were designed with this feature (EWG). The second alkene in tandem 5-hexenyl radical cyclization in the series will not require an activating group, so unsubstituted terminal alkenes were used and they appeared to function well.

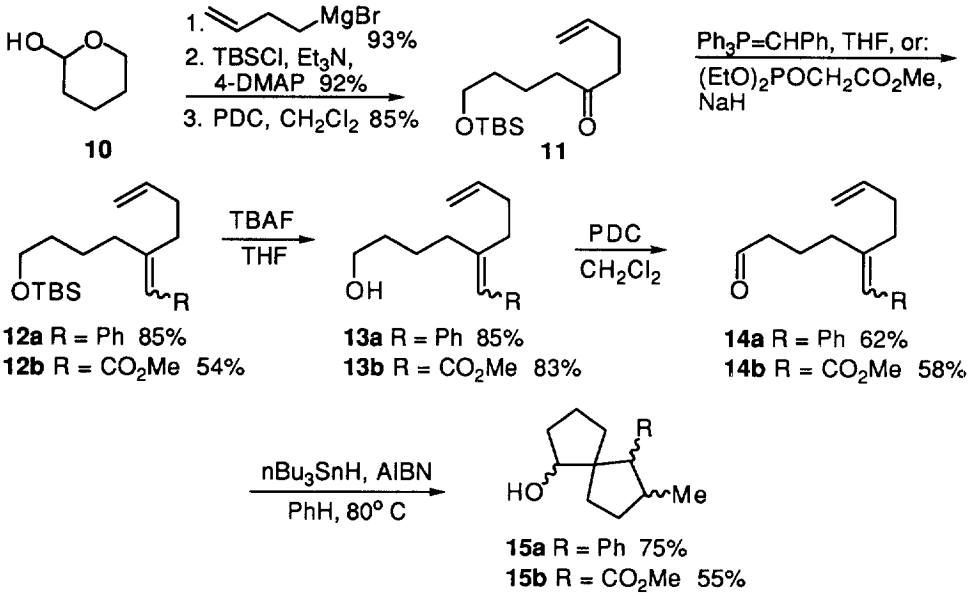
Scheme 2



In a typical tandem cyclization with O-stannyl ketyls, the precursor was dissolved in dilute benzene (0.1 to 0.03 M) and nBu3SnH (2-4 equiv.) with AIBN (0.1-0.2 equiv.) were added. The mixture was degassed with argon and then heated at 80 °C for 12-24 h. Some substrates required additional amounts of AIBN (0.1-0.2 equiv.) as well as nBu3SnH (1-2 equiv.) to consume the starting material where the ease of the reduction-

cyclization varied somewhat from substrate to substrate. We found the "spiro" **5** and "fused" **9** ring-systems were readily obtained in the tandem cyclizations and resulted in the desired polycyclic products in yields of 54-75%.

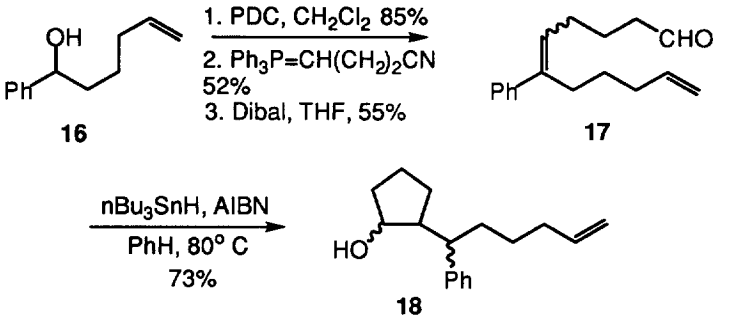
Scheme 3



The "spiro" ring skeleton **5** was first examined, with its two precursor substrates synthesized from a six-step sequence, shown in Scheme 3. Ketone **11** was used to synthesize both a styrene and an α,β-unsaturated ester, and a bifurcation in the reaction sequence was utilized in subsequent steps. The ketone was readily prepared in good yield from the treatment of lactol **10** with the three step sequence of excess butenyl Grignard, selective t-butyldimethylsilyl protection of the primary alcohol and oxidation of the secondary alcohol to a ketone. Separate Wittig reactions to elaborate the activated alkenes in **12a** and **12b** were utilized. The styrene product **12a** was synthesized in 85% yield and the α,β-unsaturated ester **12b** was constructed in an analogous manner in 54% yield. This was followed by the standard transformations of deprotection and oxidation to prepare the cyclization precursors **14a** and **14b** which were each isolated as a ca. 1:1 chromatographically inseparable mixture of geometric olefin isomers.

When subjected to treatment with tin hydride, both aldehydes **14a** and **14b** gave successful results, producing the expected spiro-[4.4]-ring system. From the styrene precursor **14a**, **15a** was obtained in 75% yield as four diastereomers in a ratio of *ca.* 5 : 5 : 6 : 2. The α,β-unsaturated ester **14b** led to **15b** in a ratio of *ca.* 6 : 2 : 2 : 1 : 1 in 55% yield. No monocyclized products were observed in either reaction.

Scheme 4



The next series of reactions examined the tandem O-stannyl ketyl reaction to construct the "separated" ring substrate **7**; where interestingly, only monocyclization was observed. The starting substrate **17** was prepared as a 1 : 1 inseparable mixture of geometric isomers by a series of reactions shown in Scheme 4 in an overall yield of 21%. A four-step sequence, starting with the reaction of benzaldehyde and pentenyl Grignard to prepare **16**, was adapted. The tandem ketyl reaction afforded **18** as two monocyclic diastereomers, in a ca. 1 : 1 ratio in 73% yield.

There are plausible mechanistic reasons for the difference in behavior between the conversion of **17** to **18** and the similar reaction of **14a** to **15a** from Scheme 3. The contrast between the "separated" and "spiro" cases can best be illustrated by their intermediate carbon-centered radical species **19** and **20** respectively, as shown in

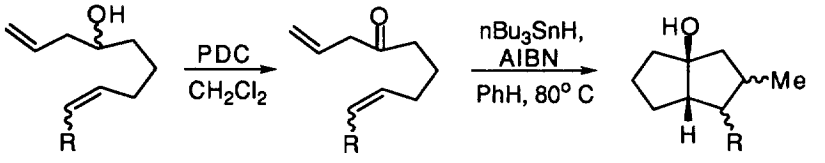
Figure 1

Figure 1. Bulky substituents at the precursor radical center usually have less effect on the rate of cyclization than substituents on the acceptor alkene,[1] however, the pendant olefin in **19** has substantially reduced steric access to the radical center, and the 5-exo-trig transition state conformation is not achieved. Hydrogen atom transfer from tin hydride to **19** becomes faster than cyclization. In the "spiro" case, benzylic radical **20** has less difficulty approaching the olefin, because it is a secondary, rather than a tertiary carbon-centered radical. Replacement of the phenyl with an ester in **19** likely would have improved chances for a successful cyclization.

The cyclization of the bicyclo[3.3.0]octane "fused" alcohol of type **9** proved to be particularly challenging. The synthesis of both precursor compounds possessing α, β-unsaturated ketone tethered to either a styrene unit in

22a or an α,β-unsaturated ester in **22b** are shown in Scheme 5. Alcohol **21a**, readily prepared in 80% yield from 6-phenyl-5-hexenal[15] and allylmagnesium bromide, was oxidized with PDC to styrene ketone **22a** as a 2.3 : 1, trans : cis mixture of geometric isomers in 52% yield. The α,β-unsaturated ester ketone **22b** was prepared in a similar manner from **21b**[16] in 56% yield as a 15 : 1, trans : cis mixture.

Scheme 5



21a R = Ph
21b R = CO_2Me

22a R = Ph 52%
22b R = CO_2Me 70%

23a R = Ph (no cyclization)
23b R = CO_2Me 54%

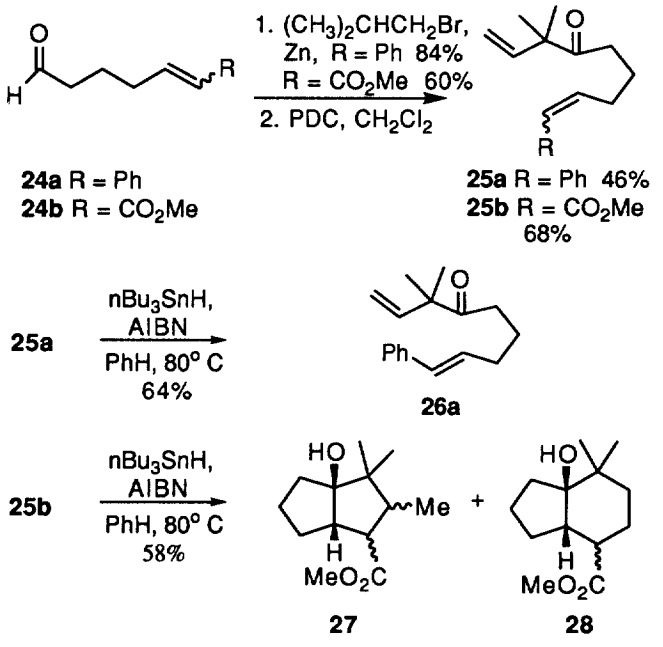
The styrene and ester ketones **22a** and **22b** were subjected to the tandem cyclization reaction with nBu3SnH. Inspection of the reaction mixture from styrene **22a** indicated that it did not cyclize to **23a**, but instead gave products exhibiting migration of the terminal unsturated bond into conjugation with the ketone. Thus, the styrene case appears to be resistant to cyclization, and additional equivalents of nBu3SnH only increased the number of unidentifiable products. It is also interesting to note that the phenyl substituted alkene in **14a**, which readily produced tandem cyclized product **15a**, differs from the reaction of **22a** above in a key respect. The ketyl leading to product in **14a** is a less-hindered secondary radical, compared to the tertiary radical formed from **22a**, and allows for a more efficient cyclization. This difference in the two substrates, demonstrates the steric variation in reactivity between ketyls prepared from ketones vs. aldehydes.

In marked contrast to styrene **22a**, ester **22b**, differing only in the olefin activation group, behaved differently and readily produced fused ring system **23b**. A minor byproduct from this example was also the result of double bond migration, however it was less prevalent than in the styrene example **22a**. Two diastereoisomers were obtained in 1 : 1 ratio and chromatographically isolated in a 54% yield. These results indicate that the α,β-unsaturated ester was better at "promoting" the cyclization in a manner superior to the styrene system. Nucleophilic radicals, such as O-stannyl ketyls, are electron-rich radicals with high-lying SOMOs and will preferentially interact with the LUMOs of electron-poor olefins.[17] Here the ester is more effective at lowering the energy of the olefin acceptor LUMO, providing a superior activating group for the olefin in these studies.

In order to prevent double bond migration, new compounds were examined in which potential olefin migration and conjugation was blocked by a gem-dimethyl group. Prenyl bromide and zinc dust, were used to introduce a dimethylallyl appendage in good yields to the appropriate aldehyde precursor, bearing a styrene in **24a** or an ester in **24b**, as shown in Scheme 6. Oxidation of each alcohol to ketones **25a** and **25b** provided the desired cyclization precursors.

When subjected to the tandem cyclization conditions with nBu3SnH, styrene ketone **25a**, prepared as a 2 : 1 mixture of trans : cis geometric isomers, paralleled the behavior of the nonblocked styrene compound **22a** and gave exclusively the acyclic trans-styrene product **26a** in 64% yield. This was the only product observed by thin layer chromatography and GC analysis. Equilibration of the styrene olefin from cis to trans was probably a result of reversible hydrostannylation with tin hydride. Ester **25b** (6 : 1, trans : cis mixture), in contrast, cyclized to form two isomers of **27** and a single isomer of bicyclic indane **28** in a 1 : 1 : 2 ratio, respectively, isolated in 58% yield. The formation of indane **28**, the result of tandem 6-membered ring formation in the second cyclization, was interesting. Bicyclic product **28** was not observed in a similar reaction in Scheme 5 and it had to arise from a 6-endo-trig cyclization. In this case the steric hindrance of the gem-dimethyl group probably slowed the usually highly-favored 5-exo-trig cyclization. Because only a 5-exo-trig cyclization pathway was observed in the otherwise identical compound **22b** lacking the gem-dimethyl substitution we can conclude that this is a clear comparative example of steric hinderence influencing free radical cyclizations in a position adjacent to the olefin acceptor. This is supportive of the established concept that regioselectivity in free radical reactions is governed by steric hindrance at the acceptor alkene.[1]

Scheme 6



CONCLUSION

These studies indicate that the O-stannayl ketyl induced tandem cyclization is effective, however, the reaction depends markedly on the starting substrate and the activating group. Activated alkenes such as styrenes and α,β-unsaturated esters were compared and contrasted to study the likelihood of the tandem cyclization. Interestingly, the phenyl group does not always appear to sufficiently activate the olefin and some substrates which contained this unit were resistant to cyclization. It is also clear that the activating groups did not make a great difference in the "spiro" ring example; but the functioned differently in the "fused" example. By simply varying the types of activated alkene acceptors, their relative positioning, and the tethers, potentially useful bicyclic alcohol products can be obtained.

EXPERIMENTAL

General. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra are reported in wave numbers (cm-1). Chemical shifts for NMR are reported in ppm down field (δ) relative to tetramethylsilane $(CH_3)_4Si$ as an internal standard in $CDCl_3$. All GC experiments were performed on a Varian 3500 capillary gas chromatograph using a J & W fused silica capillary column (DB5-30W; film thickness 0.25 micron). Elemental analysis was performed by Atlantic Microlab, Inc., Norcross, GA 30091.

All reactions were run under an inert atmosphere of argon using flame-dried apparatus. All reactions were monitored by thin layer chromatography (TLC) and judged complete when starting material was no longer visible in the reaction mixture as spotted on TLC. All yields reported refer to isolated material judged to be homogeneous by thin layer chromatography and NMR spectroscopy. Temperatures above and below ambient temperature refer to bath temperatures unless otherwise stated. Solvents and anhydrous reagents were dried according to established procedures by distillation under nitrogen from an appropriate drying agent: ether, benzene, and THF from benzophenone ketyl; dichloromethane from CaH_2. Other solvents were used as received from the manufacturer.

Analytical TLC was performed using E. Merck precoated silica gel plates (0.25 mm) using phosphomolybdic acid in ethanol as an indicator. Column chromatography was performed using E. Merck silica gel 60 (230-400 mesh) by standard flash and suction chromatographic techniques.[18]

1-t-Butyldimethylsiloxynon-8-ene-5-one (11). To a stirred solution of lactol **10**[19] (1.0 g, 9.79 mmol) in THF (19.6 mL; 0.5 M) at 0 °C was added a solution of 1-butenylmagnesium bromide (prepared by the addition of 1-butenyl bromide to magnesium turnings) (13.0 mL, 19.58 mmol). The reaction was stirred at room temperature for 1.5 h and was quenched with NH_4Cl (aq. sat., 5 mL), and then extracted with diethylether. The solvents were removed under reduced pressure and the residue was purified over silica gel to yield 1.4 g (93 %) of 8-nonene-1,5-diol a clear oil: Rf 0.22 (35% THF:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 5.85 (m, 1 H), 5.00 (m, 2 H), 3.65 (t, 3 H, J = 2.1 Hz), 2.19 (m, 2 H), 1.75 (s, 1 H), 1.74 (m, 2 H), 1.40-1.65 (m, 8 H); 75

MHz ^{13}C NMR ($CDCl_3$) δ 138.6, 114.6, 70.9, 62.1, 36.5, 36.4, 32.3, 30.0, 21.8; IR (neat) 3319, 2919, 2860, 1631, 1437, 1049, 908; mass spectrum (CI) m/z (relative intensity), 159 (m+1, 73), 141 (100); Exact mass (C.I.) for $C_9H_{19}O_2$ (M+1) calcd 159.1385; found 159.1387.

The purified 8-nonene-1,5-diol (984 mg, 6.22 mmol) was diluted with methylene chloride (12.4 mL; 0.5 M) and triethylamine (2.60 mL, 18.7 mmol), 4-dimethylaminopyridine (75.6 mg, 0.622 mmol) and t-butyldimethylsilyl chloride (1.03 g, 6.84 mmol) were added. After 2 h the reaction was quenched $NaHCO_3$ (aq. sat., 5 mL) and extracted with diethylether. The combined ether extracts were dried over anh. Na_2SO_4 and the solvents was removed under reduced pressure to give an oil. The oil was purified by column chromatography to give 1.56 g (92%) of 1-t-butyldimethylsiloxy-5-hydroxynon-8-ene a clear oil: Rf 0.78 (35% THF:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 5.79 (m, 1 H), 5.96 (m, 2 H), 3.56 (t, 3 H, J = 6.3 Hz), 2.11 (m, 2 H), 1.50 (m, 8 H), 0.85 (s, 9H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 138.6, 114.7, 71.4, 63.1, 37.2, 36.1, 32.7, 30.0, 26.0, 25.9, 21.9, 18.3; IR (neat) 3357, 2930, 2858, 1471, 1462, 1255, 1100, 1005, 909, 836, 809, 755; mass spectrum (EI), m/z (relative intensity) no m+ peak observed, 85 (100), 75 (17); Anal. calcd: C, 66.11; H, 11.84; found C, 66.10; H, 11.80.

The purified 1-t-butyldimethylsiloxy-5-hydroxynon-8-ene (2.37 g, 8.69 mmol) was dissolved in methylene chloride (18 mL; 0.5 M). Pyridinium dichromate (6.5 g, 17.39 mmol) and ground 4 Å molecular sieves (0.5 g) and acetic acid (200 μL) were added and the mixture was stirred 3 h and then diluted with diethyl ether (50 mL) and allowed to stir 12h. The solution was then filtered through a plug of celite and the solvent was removed "in vacuo." The residue was purified by suction chromatography to give 2.0 g (85 %) 1-t-butyldimethylsiloxynon-8-ene-5-one as a clear oil: Rf 0.73 (20% diethylether:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 5.75 (m, 1 H), 4.94 (m, 1 H), 3.56 (t, 1 H, J = 6.3 Hz), 2.45 (t, 2 H, 6.6 Hz), 2.39 (t, 2 H, 7.5 Hz), 2.28 (m, 2 H), 1.57 (m, 2 H), 1.46 (m, 2 H), 0.85 (s, 9 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 210.1, 137.1, 115.1, 62.8, 42.6, 41.7, 32.2, 27.8, 25.9, 25.9, 20.3, 18.3; IR (neat) 2930, 2857, 1716, 1471, 1462, 1361, 1255, 1099, 1005, 912; mass spectrum (EI), m/z (relative intensity) 270 (m+, 2), 213 (51), 171 (26), 129 (83), 115 (31); Anal. calcd: C, 66.61; H, 11.18; found C, 66.61; H, 11.27.

(E,Z)-1-t-Butyldimethylsiloxy-5-benzylidenenon-8-ene (12a). Benzyltriphenylphosphonium bromide (6.72 g, 15.5 mmol) was stirred in THF (15.5 mL; 1 M) and cooled to 0 °C. n-Butyllithium (5.4 mL, 13.6 mmol) was added dropwise and the solution turned bright red. After 30 min, ketone **11** (1.05 g, 3.88 mmol), dissolved in THF (2 mL), was added and the solution was refluxed 12h. The reaction was quenched with ethanol, and then diluted with ether and the $Ph_3P{=}O$ was removed by suction. Removal of solvents and chromatography yielded 1.13 g (85.0 %) of an oil. Physical data are for the 1:1 inseparable mixture of syn and anti isomers: Rf 0.79 (10 % diethylether:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 6.27 (s, 1 H), 5.77 (m, 1 H), 4.96 (m, 2 H), 3.62 (t, 1 H, J = 5.7 Hz), 3.54 (t, 1 H, J = 5.7 Hz), 2.20 (m, 6 H), 1.50 (m, 4 H), 0.870 (d, 9 H, J = 6.0 Hz), 0.015 (d, 6 H, J = 10 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 142.6, 142.5, 138.56, 138.5, 138.3, 133.9, 129.1, 128.7, 128.5, 128.1, 126.0, 125.7, 125.6, 114.7, 114.6, 63.1, 62.8, 37.0, 36.5, 32.9, 32.6, 32.6, 32.5, 30.4, 30.0, 26.2, 26.1, 26.0, 24.5, 24.4, 18.5, 18.4; IR (neat) 2956, 2848, 1643,

1472, 1249, 1096; mass spectrum (EI), m/z (relative intensity) 344 (m+, 0.69), 288 (20), 287(77); Anal. calcd: C, 76.68; H, 10.53; found C, 76.43; H, 10.32.

(E,Z)-5-Benzylidenon-8-ene-1-ol (13a). Alcohol **12a** (1.09 g, 3.16 mmol) was dissolved in THF (2.11 mL; 0.50 M) and cooled to 0 °C. Tetrabutylammonium fluoride (3.81 mL, 3.81 mmol) was added dropwise to the solution and the reaction was warmed to 23 °C. After 2 h the reaction was quenched with $NaHCO_3$ (aq. sat., 5 mL) and extracted with diethylether. The combined extracts were dried over anh. Na_2SO_4 and concentrated under reduced pressure Subsequent chromatography yielded 616 mg (85 %) of an oil as a 1:1 inseparable mixture of E and Z isomers: Rf 0.60 (35% THF:hexanes) ; 300 MHz ^1H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 6.30 (s, 1 H), 5.82 (m, 1 H), 5.01 (m, 2 H), 3.69 (t, 1 H, J = 6.0 Hz), 3.59 (t, 1 H, J = 6.3 Hz), 2.25 (m, 6 H), 1.59 (m, 5 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 142.4, 142.3, 138.5, 138.4, 138.4, 138.2, 128.7, 128.1, 126.0, 125.8, 125.7, 114.7, 114.6, 62.8, 62.6, 36.9, 36.4, 32.6, 32.5, 32.4, 30.4, 29.9, 24.4, 24.3; IR (neat) 3346, 2933, 2862, 1069, 911, 734, 698; mass spectrum (EI), m/z (relative intensity) 320 (m+, 6.20), 129 (100), 115 (25), 91 (40) ; Anal. calcd: C, 83.43; H, 9.63; found C, 83.30; H, 9.68.

(E,Z)-5-Benzylidenon-8-enal (14a). Alcohol **13a** (675 mg, 2.93 mmol) was dissolved in methylene chloride. Pyridinium dichromate (2.20 g, 5.86 mmol), acetic acid (200μL) and ground 4 Å molecular sieves (0.3 g) were added and the mixture was stirred at 23 °C for 1.5 h. The solution was diluted with ether and stirred 12 h. The mixture was filtered through celite and the solvent was removed under reduced pressure. The residue was subjected to chromatography to give 347 mg (52 %) as a clear oil. Physical data are for a 1:1 inseparable mixture of E and Z isomers: Rf 0.40 (35% THF:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 9.80 (t, 0.50H, J = 1.5 Hz), 9.69 (t, 0.50 H, J = 1.2 Hz), 7.24 (m, 5 H), 6.32 (d, 1 H, J = 12.6 Hz), 5.80 (m, 1 H), 5.01 (m, 2 H), 2.50 (d of t, 1 H, J = 7.3 Hz, 1.4 Hz), 2.26 (m, 7 H), 1.84 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 202.3, 202.0, 141.3, 141.3, 141.3, 138.2, 138.0, 128.6, 128.1, 126.5, 126.5, 126.2, 114.8, 114.7, 43.5, 43.3, 36.3, 36.1, 32.4, 32.3, 29.9, 29.8, 20.5, 20.5; IR (neat) 2933, 1725, 7640, 1445, 914, 747, 699 ; mass spectrum (EI), m/z (relative intensity) 228 (m+, 12), 169 (97), 143 (100), 141 (71); Anal. calcd: C, 84.16; H, 8.83; found C, 83.88; H, 8.85.

(E,Z)-Methyl-3-(3-butene)-7-t-butyldimethylsiloxyhept-2-eneoate (12b). Sodium hydride (395 mg, 9.88 mmol) was placed in a flame-dry flask, washed three times with pentane, and diluted with THF (2.5 mL). Then methyl diethylphosphonoacetate (1.7 mL, 9.29 mmol) was added dropwise to the flask. The mixture was stirred for 15 min and then ketone **11** (838 mg, 3.09 mmol) diluted with THF (0.5 mL) and added to the flask. The mixture was refluxed overnight and quenched with water (2 mL). Extraction and subsequent evaporation of the dried solvent gave an oil. The oil was subjected to column chromatography to yield 520 mg (54%) of product and 350 mg of recovered starting material. Physical data are for a 1 : 1, E and Z geometric mixture of isomers: Rf 0.68 (20% diethylether:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 5.80 (m, 1 H), 5.60 (d, 1 H, J = 3.9 Hz), 4.97 (m, 2 H), 3.63 (s, 1.5 H), 3.63 (s, 1.5 H), 3.57 (m, 2 H), 2.62 (m, 2 H), 2.19 (m, 4 H), 1.49 (m, 4 H), 0.849 (s, 4.5 H), 0.845 (s, 4.5 H), 0.00 (s, 6 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 166.8, 163.7, 163.6, 138.0, 137.3, 115.3, 114.7, 62.8, 62.7, 50.7, 38.1, 37.4, 32.8, 32.7, 32.3, 31.7, 31.7, 31.4, 25.9,

25.9, 24.7, 23.8, 18.3; IR (neat) 2930, 2858, 1720, 1642, 1471, 1462, 1434, 1386, 1255, 1229, 1191, 1168, 1148, 1102, 1031, 1006, 912, 836, 810, 776; mass spectrum (CI), m/z (relative intensity) 327 (m+1, 100), 295 (93), 269 (48), 209 (35); Exact mass (C.I.) for $C_{18}H_{35}SiO_3$ calcd: 327.2355, found: 327.2340.

(E,Z)-Methyl-3-(3-butene)-7-hydroxyhept-2-eneoate (13b). Alkene **12b** (1.18 g, 3.74 mmol) was dissolved in THF (3 mL, 2.24 M) and cooled to 0 °C. Then tetrabutylammonium fluoride (4.86 mL, 4.86 mmol) was added dropwise. The reaction was allowed to warm up to 23 °C and was monitored by TLC. After the reaction was complete, it was quenched with NH_4Cl (aq. sat., 2 mL). The reaction was extracted with ether and the combined layers were dried over anh. Na_2SO_4. Removal of the solvents under reduced pressure yielded an oil. Column chromatography gave 657 mg (83%) of an oil. Physical data are for a 1:1 inseparable E and Z mixture of isomers: Rf 0.41 (35% THF:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 5.83 (m, 1 H), 5.67 (s, 0.50 H), 5.65 (s, 0.50 H), 5.01 (m, 2 H), 3.70 (m, 2 H), 3.68 (s, 3 H), 2.70 (m, 2 H), 2.60 (m, 2 H), 2.21 (m, 4 H), 1.58 (m, 4 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 167.0, 166.8, 164.2, 163.6, 137.9, 137.1, 115.3, 115.0, 114.7, 62.1, 61.7, 50.8, 50.8, 38.0, 37.6, 32.6, 32.2, 32.1, 31.5, 31.5, 31.3, 24.6, 23.7; IR (neat) 3389, 2931, 2860, 1707, 1637, 1431, 1372, 1225, 1195, 1161, 1061, 1025, 908; mass spectrum (EI), m/z (relative intensity) 212 (m+, 0.76), 181 (25), 180 (24), 152 (30); Exact mass (C.I.) for $C_{12}H_{21}O_3$ (m+1) calcd: 213.1490; found: 213.1487.

(E,Z)-Methyl 3-(3-butene)-7-alhept-2-eneoate (14b). Alcohol **13b** (572 mg, 2.73 mmol) was dissolved in methylene chloride (5.0 mL; 0.54 M) and pyridinium dichromate (2.00 g, 5.46 mmol) was added. Crushed 4 Å molecular sieves (100 mg), and acetic acid (30μL) were added. The reaction was stirred overnight and then diluted with a large volume of diethyl ether and allowed to stir for 4 h. The slurry was filtered through celite and the resulting liquor was evaporated to give a residue which was then purified by column chromatography to give 330 mg of an oil (58%). Physical data are for a 1:1 mixture of isomers: Rf 0.76 (35% THF-hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 9.70 (m, 1 H), 5.75 (m, 1 H), 5.62 (s, 0.50 H), 5.59 (s, 0.50 H), 4.94 (m, 2 H), 3.61 (s, 1.5 H), 3.60 (s, 1.5 H), 2.59 (m, 2 H), 2.42 (q, 2 H, J = 7.5 Hz), 2.17 (m, 4 H), 1.70 (m, 2 H); 75 MHz ^{13}C NMR δ 202.1, 201.4, 166.6, 166.5, 162.3, 162.2, 137.7, 137.1, 116.0, 116.0, 115.4, 114.9, 50.8, 43.5, 43.0, 37.3, 32.6, 31.6, 31.2, 31.1, 20.8, 19.8; IR (neat) 2948.4, 1720.1, 1642.3, 1434.8, 1231.7, 1193.3, 1188.9, 1032.9, 915.2; mass spectrum (C.I.) m/z (relative intensity) 211 (m + 1, 23), 207 (29), 193 (100), 179 (32), 133 (50); Exact mass (C.I.) for $C_{12}H_{19}O_3$ (m + 1) calcd 211.1334, found 211.1314.

6-Methyl-5-phenylspiro[4.4]nonanol (15a). Aldehyde **14a** (120 mg, 0.526 mmol) was dissolved in benzene (16 mL; 0.1 M). TBTH (0.340 mL, 1.26 mmol) and AIBN (17 mg, 0.105 mmol) were added. The mixture was degassed with a stream of argon for 30 minutes. After removing the degassing tube, the solution was heated at 80 °C overnight. Removal of the solvent under reduced pressure and column chromatography of the residue gave 91 mg (75%) of 5 : 5 : 6 : 2 ratio (G.C.) corresponding to high : middle : low R_f isomers, respectively, on TLC. The low R_f fraction contained the last two isomers which were inseparable by column chromatography. Physical data for the high R_f isomer: Rf 0.32 (20% ether:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 3.31 (m, 1 H), 2.32 (m, 2H), 1.97 (m, 2 H), 1.50 (m, 4H), 1.27 (m, 4 H),

1.09 (d, 1 H, J = 7.8 Hz), 0.81 (d, 3 H, J = 6.0 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 141.2, 129.1, 128.1, 126.2, 75.3, 61.6, 55.8, 39.5, 37.1, 33.0, 31.8, 30.6, 19.0, 18.7; IR (neat) 3443, 2952, 2865, 1452, 1064, 703; mass spectrum (EI), m/z (relative intensity) 230 (m+, 18), 212 (83), 170 (100), 157 (34), 139 (23), 118 (27), 117 (35), 115 (28), 97 (36). Exact mass (E.I.) for $C_{16}H_{22}O$ calcd 230.1670, found 230.1673.

Physical data for middle R_f isomer: Rf 0.28 (20% ether:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 3.82 (t, 1 H, J = 4.8 Hz), 2.82 (d, 1 H, J = 11.1 Hz), 2.22 (m, 1 H), 1.92 (m, 2 H), 1.51 (m, 6H), 1.34 (m, 2 H), 1.29 (d, 1 H, J = 5.4 Hz), 0.89 (d, 3 H, J = 6.6 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 129.7, 128.0, 125.9, 82.4, 58.2, 58.1, 42.6, 38.4, 33.3, 33.0, 20.4, 18.9; IR (neat) 3418, 2949, 2865, 702 ; mass spectrum (EI), m/z (relative intensity) 230 (73), 161 (29), 157 (24), 139 (48), 129 (29), 117 (33), 115 (27), 97 (50), 91 (72), 84 (100). Exact mass (E.I.) for $C_{16}H_{22}O$ calcd 230.1670, found 230.1671. Physical data for the mixture of low R_f isomers: Rf 0.19 (20% ether:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 3.86 (d, 0.25 H, J = 5.0 Hz), 3.65 (t, 0.5 H, J = 8.2 Hz), 3.27 (d, 0.15 H, J = 7.29 Hz), 2.69 (d, 0.15 H, J = 7.29 Hz), 2.46 (d, 0.50 H, J = 11.5 Hz), 2.32 (m, 0.50 H), 2.0 (m, 3 H), 1.50 (m, 8 H), 0.97 (m, 1 H), 0.91 (d, 2 H, J = 6.3 Hz), 0.70 (m, 1 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 18.3, 18.9, 20.7, 29.9, 30.0, 31.1, 31.4, 32.2, 32.4, 33.4, 36.6, 38.0, 38.2, 38.8, 54.2, 56.4, 58.5, 76.1, 79.9, 80.6, 126.1, 127.6, 127.9, 129.6, 130.2, 140.6, 142.3; IR (neat) 3382, 2953, 2869, 1453, 1077, 702; mass spectrum (EI), m/z (relative intensity) 230 (m+, 60), 212 (27), 170 (36), 157 (44); Exact mass (E.I.) for $C_{16}H_{22}O$ calcd 230.1670, found 230.1673.

1-Methylcarboxy-2-methylspiro[4.4]nonan-5-ol (15b). Aldehyde **14b** (132 mg, 0.628 mmol) was dissolved in benzene (19 mL) and nBu_3SnH (0.405 mL, 1.51 mmol) and AIBN (21 mg, 0.13 mmol) were added and the mixture was degassed for 30 minutes with a stream of argon. The degassing tube was removed and the reaction was refluxed overnight. The solvent was then removed under reduced pressure and the residue purified by column chromatography to give 73 mg (55%) of a 6 : 2 : 2 : 1 : 1 ratio (G.C.) as an isomeric mixture. The major high R_f isomer could be separated but the minor 4 low R_f isomers could not be separated by column chromatography. Physical data for high R_f isomer: R_f 0.36 (35% THF:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 3.75 (m, 1 H), 3.73 (s, 3 H), 2.84 (d, 1 H, J = 3.0 Hz), 2.22 (m, 2 H), 2.13 (m, 1 H), 1.88 (m, 3 H), 1.59 (m, 3 H), 1.30 (m, 3 H), 1.00 (d, 3 H, J = 6 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 177.4, 76.7, 60.5, 55.9, 51.8, 40.9, 37.9, 33.4, 30.1, 23.4, 18.9, 18.2; IR (neat) 3524, 2952, 2869, 1714, 1436, 1373, 1301, 1268, 1198, 1160, 1082. Physical data for low R_f isomers: Rf 0.26 (35% THF:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 3.80 (m, 1 H), 3.64, 3.607, 3.58, 3.57 (s, 3 H), 3.00, 2.66 (d, 1 H, J = 6.9 Hz, 5.1 Hz), 2.30 (m, 2 H), 1.84 (m, 3 H), 1.63 (m, 2 H), 1.47 (m, 3 H), 1.19 (m, 2 H), 0.948 (m, 3 H); IR (neat) 3454, 2953, 2870, 1731, 1453, 1435, 1376, 1269, 1195, 1158, 1091, 1039, 733; mass spectrum (CI), m/z (relative intensity) 213 (m+1, 16), 195 (100); Exact mass (C.I.) for $C_{12}H_{21}O_3$ (m+1) calcd 213.1490, found 213.1491.

1-Phenyl-5-hexen-1-ol (16). 4-Pentenyl magnesium bromide (47.2 mL, 23.61 mmol) was added dropwise to a solution of benzaldehyde (2.00 mL, 19.67 mmol) in THF (19.7 mL, 1.0 M) at 0 °C. After stirring at 23 °C for 12h the reaction was quenched by the addition of aqueous saturated ammonium chloride solution (5

mL). The aqueous layer was extracted with ether and the combined ether extracts were dried over anh. sodium sulfate. Removal of the solvent under reduced pressure gave an oil, which was chromatographed to yield 3.17 g (92%) of a clear oil: Rf 0.31 (20% ether:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 5.71 (m, 1 H), 4.88 (m, 2 H), 4.57 (m, 1 H), 2.00 (m, 3 H), 1.68 (m, 2 H), 1.37 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 144.8, 138.6, 128.4, 127.5, 125.9, 114.7, 74.5, 38.5, 33.6, 25.1; IR (neat) 3356, 2935, 2860, 1640, 1493, 1453, 1063, 1027, 994, 911; mass spectrum (EI) m/z (relative intensity), 176 (m+, 12), 133 (44), 120 (24), 107 (100), 79 (56); Anal. calcd: C, 81.77; H, 9.15; found C, 81.82, H, 9.21.

(E,Z)-6-Phenyl-5,11-dodecadienal (17). Alcohol **16** (1.68 g, 9.54 mmol) was dissolved in methylene chloride (19.0 mL; 0.50 M). Pyridinium dichromate (7.18 g, 19.1 mmol) and crushed 4 Å molecular sieves (300 mg) and acetic acid (50 μL) were added. The reaction was stirred overnight and then diluted with diethyl ether and stirred for 2 h. The slurry was filtered through celite and the solvent was removed under reduce pressure. Chromatography yielded 1.47 g (89%) of 1-phenylhex-5-enone as an oil: Rf 0.62 (20% ether:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2 H), 7.50 (m, 3 H), 5.81 (m, 1 H), 5.01 (m, 2 H), 2.97 (t, 2 H, J = 7.4 Hz), 2.17(m, 2 H), 1.85 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 200.2, 138.0, 137.0, 132.9, 128.5, 128, 115.3, 37.7, 33.2, 23.3; IR (neat) 2934, 1686, 1448, 1232, 1001, 913, 753, 736, 690; mass spectrum (EI) m/z (relative intensity), 174 (m+, 8), 120 (46), 77 (31); Anal. calcd: C, 82.72; H, 8.10; found C, 82.95, H, 8.06.

Iodo-5-triphenylphosphoniumpentanenitrile (654.3 mg, 1.32 mmol) was placed in a flame dry flask and diluted with THF (1.7 mL; 0.77 M). The slurry was cooled to 0 °C and n-BuLi (0.495 mL, 1.14 mmol) was added dropwise resulting in a bright orange solution. After 20 min, 1-phenyl-5-hexen-1-one was diluted with THF (0.5 mL) and then added to the solution. After 30 more min, the reaction was warmed to 23 °C and allowed to stir for 72 h. Then the reaction was quenched with ethanol and stirred with 80% hexanes:ether until a white precipitate of Ph_3P=O formed which was filtered through celite and removed. The solvent was removed under reduced pressure and purified by column chromatography to give 72 mg (52%) of (E,Z)-6-Phenyl-5,11-dodecadienenitrile as an oil as a 1 : 1 geometric mixture: Rf 0.42 and 0.35 (20% ether:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 5.74 (m, 1 H), 5.54 (t, 0.50 H, J = 7.3 Hz), 5.36 (t, 0.50 H, J = 7.3 Hz), 4.95 (m, 2 H), 2.51 (t, 1 H, J = 8.0 Hz), 2.34 (m, 2 H), 2.17 (t, 1 H, J = 7.4 Hz), 2.03 (m, 3 H), 1.78 (m, 1 H), 1.63 (m, 1 H), 1.40 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 143.4, 142.7, 142.4, 140.7, 138.6, 138.4, 128.2, 126.9, 126.7, 126.4, 126.1, 124.5, 119.6, 114.8, 114.6, 38.8, 33.5, 33.2, 29.3, 27.8, 27.4, 27.2, 25.8, 25.6, 16.7, 16.5; IR (neat) 2930, 2858, 1438, 1119, 912, 721, 700, 542; mass spectrum (EI) m/z (relative intensity), 239 (m+, 2), 144 (45), 143 (23), 129 (25), 118 (100); Anal. calcd: C, 85.31, H, 8.84; found C, 85.44, H, 8.89.

(E,Z)-6-Phenyl-5,11-dodecadienenitrile (72 mg, 0.300 mmol) was placed in a flask and diluted with THF (0.60 mL; 0.5 M) and cooled to -78 °C. Dibal (0.90 mL, 0.90 mmol) was slowly added dropwise to the flask. The flask was immediately warmed to 0 °C. After 1.5 hours it was cooled again to -78 °C and quenched by the slow addition of methanol. The mixture was diluted with ether (50 mL) and then poured into a saturated solution of Rochelle's salt and stirred vigorously for two h. The mixture was extracted with ether and the combined ether layers were dried over anh. Na_2SO_4. The solvent was removed under reduced pressure purified by column

chromatography to give 40 mg (55%) of (E,Z)-6-Phenyl-5,11-dodecadienal as a 1 : 1 mixture of isomers: Rf 0.37 and 0.40 (20% ether:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 9.82 (s, 0.50 H), 9.70 (s, 0.50 H), 7.3 (m, 5 H), 5.79 (m, 1 H), 5.61 (t, 0.50 H, J = 7.2 Hz), 5.42 (t, 0.50 H, J = 7.5 Hz), 4.95 (m, 2 H), 2.51 (m, 2 H), 2.35 (t, 2 H, J = 7.5 Hz), 2.27 (m, 1 H), 2.02 (m, 3 H), 1.81 (m, 1 H), 1.66 (m, 1 H), 1.43 (m, 2 H) ; 75 MHz ^{13}C NMR ($CDCl_3$) δ 202.5, 202.3, 143.0, 142.2, 141.3, 141.0, 138.7, 138.5, 128.3, 128.2, 128.1, 127.6, 126.7, 126.5, 126.3, 125.9, 114.7, 114.5, 43.4, 43.3, 38.7, 33.5, 33.2, 29.2, 28.1, 27.8, 27.3, 22.4, 22.3; IR (neat) 2931, 2859, 1725, 1292, 1454, 1441, 911, 761, 701; mass spectrum (EI) m/z (relative intensity), 242 (m+, 0.85), 144 (60), 129 (50), 105 (100), 91 (43); Exact mass (C.I.) for $C_{17}H_{22}O$ (m+1) calcd 242.1670, found 242.1663.

2-(1'-Phenylhex-5'-ene)cyclopentanol (18). Aldehyde **17** (93 mg, 0.384 mmol) was dissolved in benzene (9.0 mL) and nBu_3SnH (0.247 mL, 0.919 mmol) and AIBN (12 mg, 0.076 mmol) were added to the flask and the mixture was degassed for 30 minutes with a stream of Ar gas. The degassing tube was removed and the mixture was refluxed 12h. Removal of the solvents and chromatography gave 68 mg (73%) of two diastereomers. Physical data for higher Rf isomer: Rf 0.60 (35% THF:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 5 H), 5.65 (m, 1 H), 4.95 (m, 2 H), 4.41 (q, 1 H, J = 3.9 Hz), 2.63 (dt, 1 H, J = 11.1, 3.3 Hz), 2.01 (m, 3 H), 1.87 (m, 3 H), 1.75 (m, 2 H), 1.45 (m, 1 H), 1.26 (m, 5 H); 75 MHz 13C NMR (CDCl3) δ 145.1, 139.1, 128.2, 128.0, 125.9, 114.3, 73.4, 52.3, 45.7, 35.3, 34.1, 33.7, 28.1, 26.4, 21.3; IR (neat) 3385, 2931, 2859, 1639, 1493, 1452, 991, 909, 700; mass spectrum (EI) m/z (relative intensity), 244 (m+, 1), 183 (20), 172 (20), 117 (59), 105 (20), 91 (100); Exact mass (C.I.) for $C_{17}H_{24}O$ (M+1) calcd 244.1827, found 244.1827. Physical data for the lower Rf isomer: Rf 0.40 (35% THF:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 5 H), 5.76 (m, 1 H), 4.93 (m, 2 H), 3.99 (m, 1 H), 2.62 (m, 1 H), 2.46 (m, 1 H), 2.35 (m, 2 H), 2.02 (m, 3 H), 1.67 (m 5 H), 1.22 (m, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 144.0, 138.9, 128.4, 128.4, 128.1, 126.0, 114.3, 77.3, 54.2, 49.1, 35.7, 34.0, 33.7, 29.2, 27.0, 22.3; IR (neat) 3345, 2932, 2861, 1494, 1452, 909, 702; mass spectrum (EI) m/z (relative intensity), 244 (m+, 0.44), 160 (43), 159 (29), 117 (31), 104 (42), 91 (100); Exact mass (C.I.) for $C_{17}H_{24}O$ (M+1) calcd 244.1827, found 244.1827.

(E,Z)-9-Phenyl-1,8-nonadien-4-ol (21a). (E,Z)-6-Phenyl-5-hexenal (283 mg, 1.62 mmol) was dissolved in THF (0.5 mL) and NH_4Cl (aq.sat.) (2.11 mL; 0.76 M). Then allyl bromide (0.184 mL, 2.11 mmol) and zinc dust (138 mg, 2.11 mmol) were added and the mixture was stirred open to the atmosphere for 3 h. The mixture was extracted with diethyl ether and the combined layers were dried over anhydrous sodium sulfate. The solvent was removed "in vacuo" and the residue was purified by column chromatography to give 278 mg (80%) of an oil. Physical data are for a 2.3 : 1 geometric mixture: Rf 0.25 (35% THF:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 6.39 (m, 1 H), 6.24 (dt, 0.66 H, J = 15.9 Hz,6.9 Hz), 5.84 (m, 1 H), 5.68 (dt, 0.33 H, J = 11.2 Hz, 7.2 Hz), 5.14 (m, 2 H), 3.70 (m, 1 H), 2.31 (m, 3 H), 2.17 (m, 1 H), 1.68 (m, 2 H). 1.55 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 137.8, 137.7, 134.9, 132.7, 130.6, 130.2, 129.2, 128.8, 128.5, 128.2, 126.9, 126.5, 126.0, 118.1, 70.6, 70.5, 42.0, 36.4, 36.3, 33.0, 28.5, 26.0, 25.5; IR (neat) 3383, 3024, 2031,

2859, 1494, 1447, 995, 964, 914, 693; mass spectrum (EI), m/z (relative intensity) 217 (m+, 8), 199 (27), 176 (30),175 (100); Exact mass (E.I.) for $C_{15}H_{21}O$ calcd 217.1592, found 217.1590.

(E,Z)-9-Phenyl-1,8-nonadiene-4-one (22a). Alcohol **21a** (61.0 mg, 0.281 mmol) was dissolved in methylene chloride (1 mL; 0.3 M) and pyridinium dichromate (212 mg, 0.563 mmol) was added. Crushed 4 Å molecular sieves (50 mg) were added and the mixture was stirred 12h. The mixture was diluted with ethyl ether and then filtered through celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography to yield 31 mg (52%) of an oil. Physical data are for an inseparable 2.3 : 1 geometric mixture of isomers. Rf 0.48 (20% ether:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 6.33 (d, 0.33 H, J = 11.7 Hz), 6.28 (d, 0.66 H, J = 15.8 Hz), 6.06 (dt, 0.66 H, J = 15.8 Hz, 6.9 Hz) 5.79 (m, 1 H), 5.50 (dt, 0.33 H, J = 11.7 Hz, 7.3 Hz), 5.05 (m, 2 H), 3.02 (dd, 2 H, J = 13.9 Hz, 7.0 Hz), 2.35 (dt, 2 H, J = 12.6 Hz, 7.3 Hz), 2.22 (dq, 1 H, J = 7.4 Hz, 1.8 Hz), 2.11 (m, 1 H), 1.66 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 208.5, 208.4, 137.6, 137.5, 131.9, 130.7, 130.7, 129.8, 129.7, 128.7, 128.6, 128.5, 128.3, 128.2, 127.0, 126.5, 126.0, 118.7, 47.8, 47.8, 41.6, 41.4, 32.3, 27.9, 23.7, 23.1; IR (neat) 2933, 1715, 1493, 1447, 966, 918, 694; mass spectrum (CI), m/z (relative intensity) 215 (100, m+1), 214 (31), 213 (19), 197 (99); Exact mass (C.I.) for $C_{15}H_{19}O$ (m+1) calcd 215.1435, found 215.1439.

(E)-Methyl 7-hydroxy-2,9-decadienoate (21b). 2-Hydroxy-6-allyltetrahydropyran[16] (706 mg, 5.97 mmol) was dissolved in chloroform (12 mL; 0.50 M). Benzoic acid (50 mg) and methyl(triphenylphosphoranylidene)acetate (4.40 g, 13.1 mmol) were added to the reaction. After stirring 12h, the reaction was diluted with diethyl ether and filtered through celite. The solvent was removed under reduced pressure and the resulting residue purified by suction chromatography to give 910 mg of an oil (77%) as a 15:1, E and Z mixture of geometric isomers. Physical data for the E isomer: Rf 0.56 (10% ether:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.97 (dt, 1 H, J = 15.9 Hz, 6.9 Hz), 5.84 (m, 2 H), 5.13 (m, 2 H), 3.72 (s, 3 H), 3.68 (bs, 1 H), 2.23 (m, 4 H), 1.57 (m, 5 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 167.0, 149.2, 134.6, 121.1, 118.0, 70.3, 51.3, 42.0, 36.1, 32.0, 24.1; IR (neat) 3439, 2934, 1724, 1656, 1437, 1314, 1274, 1202, 1038, 915, 733; mass spectrum (CI), m/z (relative intensity) 199 (100, m+1), 181 (72); Anal. calcd: C, 66.64, H, 9.15; found C, 66.61, H, 9.17.

(E)-Methyl-7-one-2,9-decadienoate (22b). Alcohol **21b** (760 mg, 3.83 mmol) was dissolved in methylene chloride (7.6 mL; 0.50 M). Then, pyridinium dichromate (2.89 g, 7.67 mmol) and acetic acid (40 μL) and ground 4 Å molecular sieves (50 mg) were added to the reaction mixture. After stirring 12h, the reaction was diluted with diethyl ether and filtered through celite. The solvent was removed "in vacuo" and the resulting residue purified by suction chromatography to give 525 mg (77%) of an oil: Rf 0.64 (10% hexanes:ether); 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.97 (dt, 1 H, J = 15.6 Hz, 6.9 Hz), 5.84 (m, 2 H), 5.13 (m, 2 H), 3.64 (s, 3 H), 3.16 (dt, 2 H, J = 7.0 Hz, 1.26 Hz), 2.22 (q, 1 H, J = 7.2 Hz), 2.21 (q, 1 H, J = 7.31 Hz), 1.76 (m, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 207.7, 166.7, 148.3, 130.4, 121.5, 118.7, 51.3, 47.7, 41.0, 31.2, 21.6; IR (neat) 2951, 1720, 1657, 1437, 1408, 1315, 1207, 1178, 1027, 980, 921; mass spectrum (EI), m/z (relative intensity)

196 (m+, 1) 165 (41), 155 (80), 127 (39), 123 (95), 95 (100), 85 (87), 81(43), 71 (43), 69 (39), 68 (53), 67 (59), 59 (67), 55 (53); Anal. calcd: C, 67.32, H, 8.22; found: C, 67.11, H, 8.17.

Bicyclic ester 23b. Ketone **22b** (127 mg, 0.648 mmol) was dissolved in benzene (6.5 mL; 0.10 M) and nBu_3SnH (0.436 mL, 1.62 mmol) and AIBN (21.0 mg, 0.129 mmol) were added and the mixture was degassed with a stream of argon. The reaction was heated at 80 °C overnight. The solvent was removed under reduced pressure and the resulting residue purified by column chromatography to give two diastereomeric products (69 mg, 54%) in a ca. 1 : 1 ratio. Physical data for the higher Rf isomer: Rf 0.32 (20% THF:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 3.60 (s, 3 H), 2.80 (s, 1 H), 2.55 (dd, 1 H, J = 2.1 Hz, 6.9 Hz), 2.39 (m, 2 H), 2.00 (m, 3 H), 1.67 (m, 4 H), 1.24 (m, 1 H), 0.99 (d, 3 H, J = 6.6 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 176.7, 90.3, 55.9, 54.6, 51.3, 48.9, 42.0, 36.9, 33.2, 25.9, 16.2; IR (neat) 3454, 2944, 2861, 1730, 1433, 1368, 1273, 1201, 1160, 994; mass spectrum (EI), m/z (relative intensity) no m+ observed, 156 (50), 125 (36), 124 (54), 97 (55), 69 (58), 55 (58); Exact mass (C.I.) for $C_{11}H_{19}O_3$ (M+1) calcd 199.1334, found 199.1317.

Physical data for the lower Rf isomer: Rf 0.21 (20% THF:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 3.70 (s, 3 H), 2.45 (m, 2 H), 2.05 dd, 1 H, J = 6.0 Hz, 13.5 Hz), 1.91 (dd, 1 H, 9.3 Hz, 10.8 Hz), 1.80 (m, 2 H), 1.60 (m, 2 H), 1.45 (m, 1 H), 1.31 (t, 2 H, J = 12.9 Hz), 1.02 (d, 3 H, J = 6.6 Hz), 0.89 (m, 1 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 175.6, 90.2, 59.5, 57.6, 51.6, 49.8, 41.2, 38.7, 31.3, 25.6, 17.9; IR (neat) 3437, 2952, 2868, 1736, 1436, 1377, 1310, 1292, 1213, 1170, 1027; mass spectrum (EI), m/z (relative intensity),198 (m+, 4), 156 (100), 139 (62), 124 (71), 121 (25), 100 (44), 97 (85), 83 (28), 69 (27); Anal. calcd: C, 66.64, H, 9.15; found: C, 66.76, H, 9.17.

(E,Z)-3,3-Dimethyl-9-phenyl-1,8-nonadiene-4-one (25a). (E,Z)-6-Phenyl-5-hexenal[15] (400 mg, 2.29 mmol) was dissolved in THF (0.5 mL) and NH_4Cl (aq.sat.) (2.29 mL; 1.0 M) was added. Then prenyl bromide (0.344 mL, 2.98 mmol) and zinc dust (195 mg, 2.98 mmol) were added and the mixture was stirred open to the atmosphere for 3 hours. The mixture was extracted with diethyl ether and the combined layers were dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue was purified by column chromatography to give 472 mg of (E,Z)-3,3-dimethyl-9-phenyl-1,8-nonadiene-4-ol an oil (84%). Physical data are for a 2.3:1 mixture of isomers: Rf 0.25 (35% THF:hexanes); 300 MHz ^1H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 6.25 (m, 1 H), 6.11 (dt, 0.66 H, J = 15.9 Hz, 6.6 Hz), 5.69 (dt, 1 H, J = 17.4 Hz, 10.8 Hz), 5.55 (dt, 0.33 H, J = 11.7 Hz, 7.2 Hz), 4.95 (m, 2 H), 3.15 (dd, 0.66 H, J = 10.5 Hz, 3.3 Hz), 3.09 (dd, 0.33 H, J = 10.2 Hz, 3.0 Hz), 2.22 (m, 2 H), 1.56 (m, 5 H), 1.20 (m, 1 H), 0.920 (s, 3.96 H), 0.880 (s, 1.98 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 145.5, 137.9, 132.9, 130.8, 130.1, 129.0, 128.8, 128.5, 128.2, 126.8, 126.5, 126.0, 113.3, 78.1, 78.1, 41.7, 41.7, 33.0, 31.0, 31.0, 28.6, 27.4, 26.8, 23.1, 23.1, 23.0, 22.2; IR (neat) 3454, 2944, 2865, 1493, 1448, 1073, 965; mass spectrum (CI), m/z (relative intensity) 245 (m+1, 17), 227 (99), 176 (59), 175 (64); Exact mass (C.I.) for $C_{17}H_{25}O$ (M+1) calcd 245.1905, found 245.1900.

The purified (E,Z)-3,3-Dimethyl-9-phenyl-1,8-nonadiene-4-ol (256 mg, 1.04 mmol) was dissolved in methylene chloride (4 mL; 0.25 M) and pyridinium dichromate (788 mg, 2.09 mmol) was added. Crushed 4 Å

molecular sieves (50 mg) and acetic acid (20μL) were added and the mixture was stirred 12h. The mixture was diluted with ethyl ether and then filtered through celite. The solvent was removed under reduced pressure and the residue was purified by column chromatography to give 118 mg (47%) of a thick oil. Physical data are for an inseparable 2:1, E : Z mixture of geometric isomers: Rf 0.83 (35% THF:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) d 7.20 (m, 5 H), 6.33 (d, 0.33 H, J = 11.6 Hz), 6.27 (d, 0.66 H, J = 15.8 Hz), 6.06 (dt, 0.66 H, J = 15.8 Hz, 6.8 Hz), 5.7 (m, 1 H), 5.51 (dt, 0.33 H, J = 11.0 Hz, 5.0 Hz), 5.05 (m, 2 H), 2.38 (m, 2 H), 2.19 (m, 1 H), 2.07 (q, 1 H, J = 7.0 Hz), 1.59 (m, 2 H), 1.12 (s, 4 H), 1.09 (s, 2 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 212.7, 212.7, 142.6, 142.6, 137.7, 137.6, 132.1, 130.5, 130.1, 129.5, 128.7, 128.6, 128.5, 128.1, 126.9, 126.6, 126.0, 114.2, 50.8, 50.7, 36.8, 36.5, 32.4, 28.0, 24.2, 23.5, 23.5; IR (neat) 2970, 1708, 1447, 965, 919, 698; mass spectrum (CI) m/z (relative intensity) 243 (94, m+1), 242 (31), 225 (100), 159 (25); Exact mass (C.I.) for $C_{17}H_{23}O$ (M+1) calcd 243.1748, found 243.1746.

(E)-Methyl-8,8-dimethyl-7-one-9,2-decadieneoate (25b). (E,Z)-Methyl-2-hexenaloate was dissolved in THF (2 mL; 5.0 M) and diluted with a NH_4Cl (aq.sat.) (8 mL) in a flask open to the air. Prenyl bromide (1.25 mL, 10.8 mmol) and zinc dust (708 mg, 10.8 mmol) were added and heat was evolved. The reaction was stirred for 1h and then extracted with ether. The ether extracts were combined and evaporated to give an oil which was subjected to chromatography to yield 1.36 g (76%) of (E)-methyl-8,8-dimethyl-7-hydroxy-9,2-decadieneoate as a clear oil as a 6:1, E:Z geometric mixture of isomers. Physical data are for the E isomer: Rf 0.68 (35% THF:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.97 (dt, 1 H, J = 15.0 Hz, 6.92 Hz), 5.81 (m, 2 H), 5.08 (m, 2 H), 3.63 (s, 3 H), 3.61 (s, 0.5 H), 3.14 (dd, 1 H, J = 10.2 Hz, 2.3 Hz), 2.15 (m, 2 H), 1.70 (m, 2 H), 1.45 (m, 2 H), 1.20 (m, 1 H), 1.0 (s, 6 H); 75 MHz 13C NMR (CDCl3) δ 167.1, 150.7, 149.4, 145.4, 145.3, 120.9, 119.3, 113.3, 113.1, 77.9, 77.7, 51.3, 50.9, 41.6, 32.1, 30.8, 30.8, 28.8, 26.3, 25.4, 22.9, 22.8, 22.2, 22.2, 22.1; IR (neat) 3508, 2950, 2867, 1726, 1656, 1437, 1313, 1273, 1200, 1076, 1040, 984, 913; mass spectrum (EI), m/z (relative intensity) no m+ observed, 157 (35), 125 (100), 70 (96), 69 (25), 55 (30), 41 (25); Anal. calcd: C, 68.99, H, 9.80; found: C, 68.71, H, 9.70.

The purified (E)-methyl-8,8-dimethyl-7-hydroxy-9,2-decadieneoate (1.36 g, 6.00 mmol) was dissolved in methylene chloride (12 mL). Then pyridinium dichromate (4.50 g, 12.0 mmol) and crushed 4 Å molecular sieves (200 mg) and acetic acid (100 μL) were added. The mixture was allowed to stir 12h and then diluted with diethyl ether. The resulting slurry was filtered through celite. The solvent was removed under reduced pressure and the residue purified by chromatography to give 910 mg (68 %) of an oil: Rf 0.71 (35% THF:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 6.92 (dt, 1 H, J = 15.6 Hz, 6.9 Hz), 5.84 (m, 2 H), 5.13 (m, 2 H), 3.74 (s, 3 H), 3.70 (s, 0.50 H), 2.47 (t, 2 H, J = 7.1 Hz), 2.16 (m, 2 H), 1.70 (m, 2 H), 1.21 (s, 6 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 212.1, 166.8, 148.5, 142.3, 121.4, 114.3, 51.3, 50.7, 36.2, 31.3, 28.3, 23.4, 22.1; IR (neat) 2950, 1713, 1657, 1461, 1436, 1411, 1378, 1364, 1317, 1272, 1199, 1096, 1071, 1041, 1016, 994, 920; mass spectrum (EI), m/z (relative intensity) no m+ observed, 155 (42), 127 (54), 123 (100), 95 (98), 85 (94), 69 (40), 67 (43), 41 (71); Anal. calcd: C, 69.61, H, 8.99; found: C, 69.39, H, 8.85.

Bicyclic esters 27 and 28. Ketone **25b** (159 mg, 0.709 mmol) was dissolved in benzene (14.7 mL; 0.05 M). Tributyltin hydride (0.476 mL, 1.77 mmol) and AIBN (23 mg, 0.14 mmol) were added and the mixture was degassed with Ar for 0.5 h. The degassing tube was removed and the reaction was heated to 80 °C for 18 h. The solvent was evaporated and the crude oil subjected to column chromatography. Three products in a ratio of ca. 1 : 1 : 2, collectively weighing 79 mg (58%), and recovered starting material (23 mg) were obtained. These were, respectively, 2 diastereomers of **27** as oils and a single diastereomer of **28**, which crystallized upon standing.

Physical data for higher Rf isomer of **27**: Rf 0.45 (35% THF:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.66 (s, 3 H), 2.68 (m, 1 H), 2.46 (dd, 1 H, J = 6.3 Hz, 4.5 Hz), 2.15 (m, 2 H), 1.90 (m, 1 H), 1.70 (m, 3 H), 1.50 (m, 2 H), 0.925 (d, 6 H, J = 4.8 Hz), 0.875 (d, 3 H, J = 7.2 Hz); 75 MHz ^{13}C NMR ($CDCl_3$) δ 175.8, 94.4, 52.5, 52.2, 51.3, 45.3, 43.3, 35.6, 31.8, 24.7, 22.7, 18.1, 11.4; IR (neat) 3507, 2954, 2876, 1732, 1436, 1377, 1279, 1160; mass spectrum (CI), m/z (relative intensity) 227 (m +1, 4), 218 (81), 209 (98), 149 (100); Exact mass (C.I.) for $C_{13}H_{23}O_3$ (M+1) calcd 227.1647, found 227.1654.

Physical data for lower Rf isomer of **27**: Rf 0.35 (35% THF:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.61 (s, 3 H), 2.25 (m, 2 H), 2.00 (dd, 1 H, J = 9.3 Hz, 2.1 Hz), 1.90 (m, 1 H), 1.80 (m, 2 H), 1.40 (m, 2 H), 1.25 (m, 2 H), 0.910 (s, 3 H), 0.820 (d, 3 H, J = 6.9 Hz), 0.715 (s, 3 H); 75 MHz ^{13}C NMR (CDCl3) δ 176.3, 94.3, 57.4, 55.2, 51.6, 48.6, 45.3, 35.7, 32.1, 27.2, 23.4, 19.6, 13.1; IR (neat) 3478, 2956, 2873, 1732, 1453, 1438, 1376, 1281, 1198, 1177; mass spectrum (CI), m/z (relative intensity) 227 (m+1, 3), 209 (37), 156 (20), 149 (100); Exact mass (C.I.) for $C_{13}H_{23}O_3$ (M+1) calcd 227.1647, found 227.1650.

Physical data for **28** (mp. 90-91 °C): Rf 0.52 (35% THF:hexanes); 300 MHz ^{1}H NMR ($CDCl_3$) δ 3.66 (s, 3 H), 2.50 (dt, 1 H, J = 11.7 Hz, 3.8 Hz), 1.90 (m, 1 H), 1.70 (m, 5 H), 1.50 (m, 4 H), (1.20, 1 H), 1.03 (s, 1 H), 1.00 (s, 3 H), 0.898 (s, 3 H); 75 MHz ^{13}C NMR ($CDCl_3$) δ 176.8, 83.7, 51.3, 43.8, 43.4, 36.6, 35.1, 32.6, 26.5, 25.7, 25.5, 22.8, 19.5; IR (neat) 3515, 2970, 2948, 2872, 1713, 1449, 1439, 1372, 1320, 1274, 1209, 1179, 1164, 1136, 992; mass spectrum (CI), m/z (relative intensity) 227 (m + 1, 76), 218 (97), 209 (100); Exact mass (C.I.) for $C_{13}H_{23}O_3$ (M+1) calcd 227.1647, found 227.1654.

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