Nickel-Catalyzed Cyclizations of Enoate Equivalents: Application to the Synthesis of Angular Triquinanes

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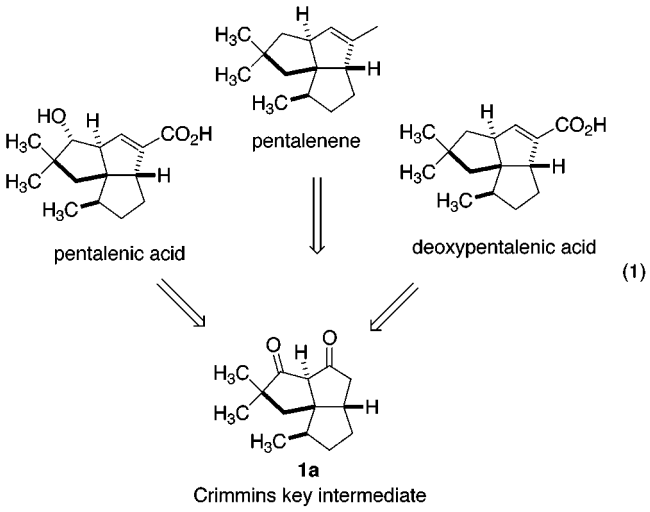
Unsaturated acyloxazolidinones and α′-silyloxy enones were found to be effective substrates in nickel-catalyzed organozinc-promoted cyclizations. Both groups served as convenient enoate equivalents, whereas methyl enoates themselves were inefficient substrates. A five-step procedure for the conversion of dimethylcyclopentenone into a highly functionalized angular triquinane was developed utilizing this observation. The key step of the procedure involves a nickel-catalyzed reductive cyclization/Dieckmann condensation sequence involving a cyclic enone tethered to an unsaturated acyloxazolidinone or α′-silyloxy enone. The method was applied in a formal synthesis of pentalenene, pentalenic acid, and deoxypentalenic acid.

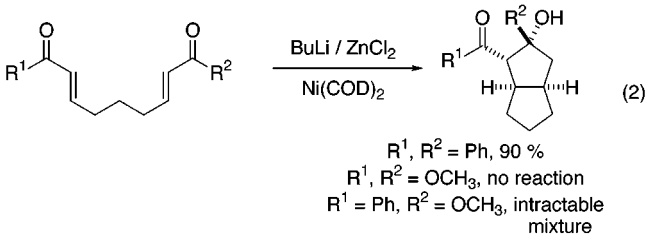
Introduction

The angularly fused triquinane carbocyclic skeleton is a common structural motif in a variety of naturally occurring terpenes such as pentalenene, pentalenic acid, and deoxypentalenic acid. Numerous synthetic approaches to natural products within this class have been reported, and several excellent reviews have appeared.[1] Of the numerous attractive approaches that have been described, two strategies involved metal-catalyzed couplings of enynes with carbon monoxide as a key step. The zirconium-catalyzed approach from Negishi[2] and the cobalt-catalyzed approach from Schore[3] both demonstrated that metal-templated processes allowed efficient assembly of the compact carbocyclic framework of the triquinanes. An approach from Crimmins,[4] in which several members of the pentalenene family of triquinanes were prepared from a common intermediate, is also noteworthy in that pentalenene, pentalenic acid, and deoxypentalenic acid were prepared from common 1,3-dicarbonyl intermediate **1a**, which was the target of the studies reported herein (eq 1).



(1)

An efficient method for preparing [3.3.0] bicycles involving a nickel-catalyzed reductive cyclization of bis-enones was recently reported from our laboratories (eq 2).[5−7] The process involves a reductive coupling of the enone β-carbons followed by an intramolecular aldol addition. Starting from a cyclic enone tethered to an acyclic enoate, we envisioned that the reaction could be applied to the synthesis of structurally complex triquinanes. Relative to the simple examples reported in our preliminary studies, additional concerns included whether quaternary centers could be introduced during the nickel-catalyzed cyclization, whether unsymmetrical bis-enones could undergo efficient cyclizations, and whether the reductive cyclization could be coupled with a Dieckmann condensation rather than an aldol addition to provide access to more synthetically versatile products. Earlier studies showed that, even with simple systems, reductive cyclizations involving methyl enoates were significantly less effective than the corresponding alkyl



(2)

(1) For excellent reviews of approaches to these and related natural products, see: (a) Mehta, G.; Srikrishna, A. *Chem. Rev.* **1997**, *97*, 671. (b) Paquette, L. A. *Top. Curr. Chem.* **1979**, *79*, 41. (c) Paquette, L. A. *Top. Curr. Chem.* **1984**, *119*, 1.

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(3) Rowley, E. G.; Schore, N. E. *J. Org. Chem.* **1992**, *57*, 6853.

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(5) (a) Savchenko, A. V.; Montgomery, J. *J. Org. Chem.* **1996**, *61*, 1562−1563. (b) Montgomery, J.; Oblinger, E.; Savchenko, A. V. *J. Am. Chem. Soc.* **1997**, *119*, 4911−4920.

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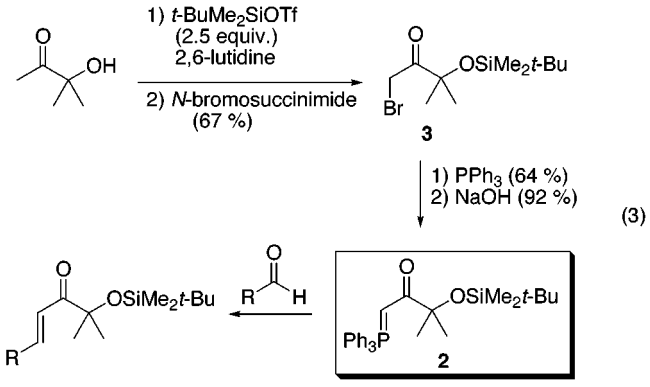
or aryl enones. Herein, we report that a highly direct synthetic entry to the angular triquinane skeleton may be achieved through the use of unsaturated acyl oxazolidinones or α′-silyloxyenones as enoate equivalents.

Results and Discussion

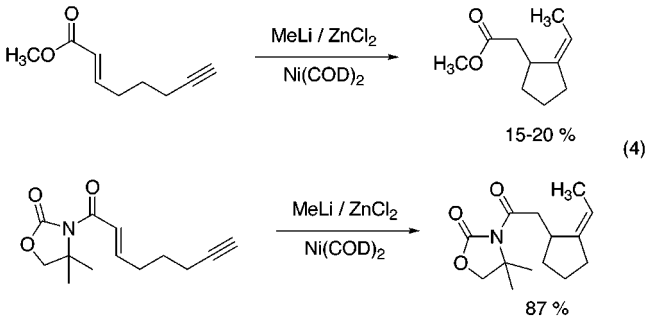
Choice of Enoate Equivalents. In the context of aldol additions, Heathcock demonstrated that α-silyloxy ketones are convenient enoate equivalents since oxidative cleavage with periodic acid directly affords products in the carboxylic acid oxidation state.[8] Therefore, we envisioned that enones possessing the α′-silyloxy functionality would serve well as enoate synthetic equivalents in conjugate addition processes and related reactions. To provide convenient access to the desired α′-silyloxy enones, we prepared a new reagent, 3-(*tert*-butyldimethylsilyloxy)-3-methyl-1-triphenylphosphoranylidene-2-butanone (**2**) (eq 3). Bis-silylation of 3-hydroxy-3-methyl-



(3)

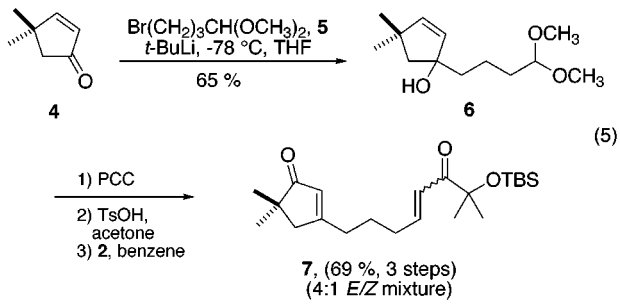
2-butanone with *t*-BuMe$_2$SiOTf followed by bromination of the enoxysilane with *N*-bromosuccinimide cleanly afforded α-bromoketone **3** in 67% yield. Treatment of **3** with triphenylphosphine followed by a basic workup afforded **2** in 59% yield. Aldehydes were readily transformed to the desired α′-silyloxy enones upon treatment with **2**, typically as a 5:1 mixture of trans and cis isomers. We anticipated that enones of this class would participate cleanly in nickel-catalyzed cyclizations as well as other conjugate addition processes that are limited by the relative lack of reactivity of enoates (vide infra).

Acyloxazolidinones also typically display enhanced reactivity relative to simple enoates in conjugate addition processes.[9] Prior to studying the performance of unsaturated acyloxazolidinones in the synthesis of triquinanes, we examined a simpler cyclization of an unsaturated acyl oxazolidinone tethered to an alkyne since the efficiency of this class of reactions typically parallels that of bisenone cyclizations.[5] In contrast to the poor results obtained with enoates tethered to alkynes, the corresponding unsaturated acyloxazolidinone cyclization was very satisfactory (eq 4).[10] Therefore, participation of the oxazolidinone unit in the preparation of triquinanes by a reductive cyclization/Dieckmann condensation sequence appeared promising.



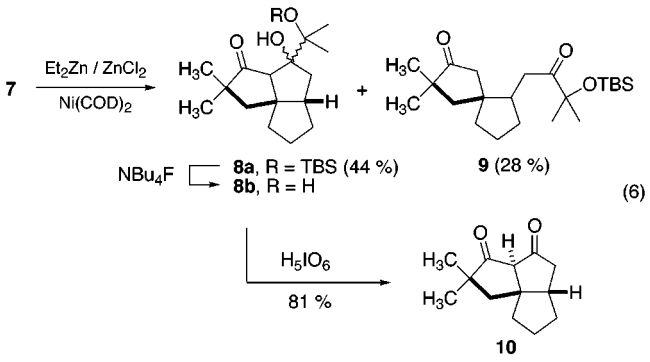
(4)

Application to Triquinane Synthesis. Our initial studies focused on the preparation of a triquinane that lacked the C-ring methyl group. The requisite precursor for a reductive cyclization/Dieckmann condensation sequence was prepared in direct analogy to a related method reported by Fukumoto (eq 5).[11] Accordingly, the alkyllithium derived from **5**[12] underwent 1,2-addition to 4,4-dimethyl-2-cyclopenten-1-one **(4)**.[13] The resulting tertiary allylic alcohol **6** smoothly underwent oxidation with allylic transposition in the presence of PCC.[14] Acetal deprotection with TsOH and Wittig olefination with reagent **2** afforded a readily separable 4:1 *E*/*Z* mixture of enone **7** in 45% overall yield from dimethylcyclopentenone.



(5)

Cyclization of **7** with Et$_2$Zn/ZnCl$_2$ and 10 mol % Ni(COD)$_2$ in THF afforded a 44% yield of triquinane **8a** as a mixture of two diastereomers that are epimeric at the tertiary hydroxyl center (eq 6). Spirocyclic compound



(6)

9 (of undetermined relative stereochemistry) was also

(8) (a) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066. (b) Heathcock, C. H. *Science* **1981**, *214*, 395. (c) Heathcock, C. H. *Aldrichim. Acta* **1990**, *23*, 99.

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(11) Ihara, M.; Katogi, M.; Fukumoto, K.; Kametani, T. *J. Chem. Soc., Chem. Commun.* **1987**, 721.

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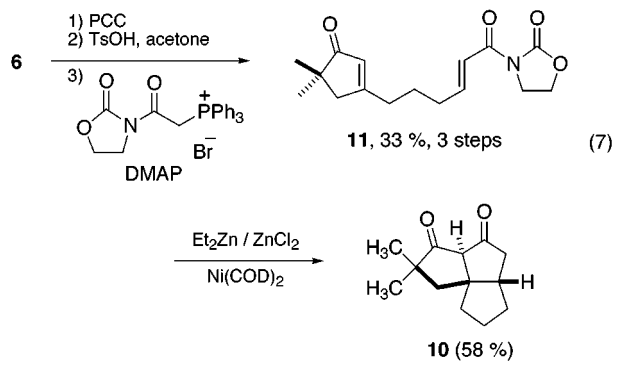
(14) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682.

obtained in 28% isolated yield. The diastereomeric mixture of **8a** was then treated with NBu_4F in THF to afford a 57% isolated yield of a single diastereomer of the expected diol **8b** and a 31% yield of a single diastereomer of recovered **8a**. Apparently, deprotection of the two diastereomers of **8a** occurs at significantly different rates, and complete deprotection was not realized. The diol **8b** was then treated with periodic acid in ether to afford triquinane **10** in 81% isolated yield with the desired 1,3-dicarbonyl functionality intact. This strategy demonstrates the utility of α′-silyloxyenones as enoate equivalents; however, we realized that the postcyclization oxidative manipulation would be avoided with the use of an acyloxazolidinone instead.

Again starting with allylic alcohol **6**, PCC oxidation, acetal deprotection with TsOH, and Wittig olefination with an oxazolidinone-based Wittig reagent[15] afforded the nickel-cyclization substrate **11**. Treatment of **11** with a 3:1 mixture of diethylzinc/zinc chloride in the presence of 10 mol % $Ni(COD)_2$ in THF at 0 °C directly afforded **10** in 58% isolated yield, thus providing a convenient preparation of a synthetically versatile triquinane intermediate in five steps from dimethylcyclopentenone (eq 7).



The oxazolidinone-based route was then selected as the most efficient, and the procedure was applied in the formal synthesis of pentalenene, pentalenic acid, and deoxypentalenic acid by converging with the Crimmins strategy. Preparation of substrate **13** proceeded as described for **11** (Scheme 1). The nickel-catalyzed cyclization proceeded with reasonable efficiency, although high levels of diastereoselectivity were not realized. At best, a 1:1 ratio of diastereomers of **1a** and **1b** in 49% yield was obtained, and in some instances, the undesired epimer **1b** predominated with diastereomeric ratios up to >3:1. Numerous variables that were studied in an attempt to improve diastereoselectivities included Lewis acid structure, solvent composition, structure and method of preparation of the organozinc, and variation of the enoate equivalent (Table 1).

Conclusions

In summary, unsaturated acyloxazolidinones and α′-silyloxyenones were demonstrated to be efficient enoate equivalents in nickel-catalyzed cyclizations. Utilizing these groups, a direct and efficient method for the preparation of angularly fused triquinanes has been developed. The method was demonstrated in the formal synthesis of three members of the pentalenene class of triquinanes. While the inherent stereoselectivity within the triquinane core is quite high, the overall control of diastereoselectivity from preexisting chirality was poor. Nonetheless, this procedure provides one of the most direct entries to angular triquinanes and should be useful in the synthesis of other structurally compact carbocyclic ring systems.

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Scheme 1

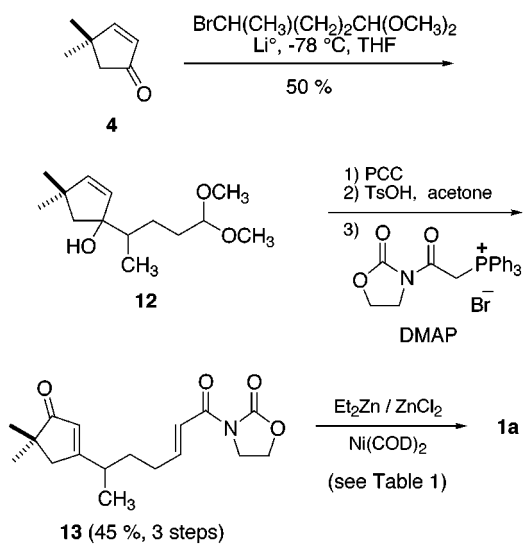
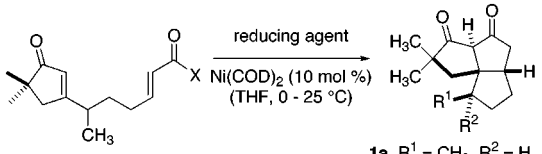
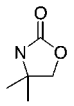


Table 1. Reductive Cyclization of 13



entry	reducing agent	X	yield (%)	**1a** : **1b** ratio
(1)	BuLi / $ZnCl_2$		49	1:1
(2)[a]	BuLi / $ZnCl_2$	"	46	1 : 2.4
(3)[b]	BuLi / $ZnCl_2$	"	48	1 : 1.1
(4)	$AlEt_3$	"	0	--
(5)	Et_2Zn / $ZnCl_2$	"	34	1 : 3.3
(6)	BuLi / $ZnCl_2$ $Ti(O\textit{i}pr)_4$	"	56	1 : 1.6
(7)	BuLi / $ZnCl_2$	OCH_3	24	1 : 1.8
(8)	BuLi / $ZnCl_2$		0	--

[a] A 1:1 THF/toluene mixture was used as the solvent. [b] 25 mol % $Ni(COD)_2$ was used.

Experimental Section

1-Bromo-3-(*tert*-butyldimethylsilyloxy)-3-methyl-2-butanone (3). A 100 mL CH_2Cl_2 solution of *tert*-butyldimethylsilyl trifluoromethanesulfonate (34.71 g, 131 mmol) was treated with 2,6-lutidine (19.2 g, 180 mmol) at 0 °C, and the resulting mixture was stirred for 10 min. 3-Hydroxy-3-methyl-

2-butanone (5.3 g, 52 mmol) was added to the mixture via syringe at 0 °C. The mixture was stirred for 2 h, and 50 mL of 1.0 M NaOH was then added at 0 °C. The aqueous phase was extracted with CH_2Cl_2 three times, and the organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The remaining yellow oil was then taken up in THF (100 mL). *N*-Bromosuccinimide (9.2 g, 52 mmol) was added to the solution at 0 °C, and stirring was continued 4 h. The reaction mixture was quenched with saturated aqueous $NaHCO_3$, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with brine, dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (SiO_2, 20:1 hexane/EtOAc) to afford bromoketone **3** (10.3 g, 67%) as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.40 (s, 2H), 1.41 (s, 6H), 0.91 (s, 9H), 0.15 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.1, 80.6, 33.7, 27.7, 25.7, 18.0, −2.3; IR (film) 1741, 1717, 1258 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_7H_{14}O_2SiBr$ 236.9946, found 236.9945 ((M − *t*-Bu)$^+$).

3-(*tert*-Butyldimethylsilyloxy)-3-methyl-2-oxobutyltriphenylphosphonium Bromide. A 50 mL THF solution of triphenylphosphine (9.2 g, 35 mmol) was treated with neat **3** (10.3 g, 35 mmol), and the solution was stirred at 50 °C for 14 h. The reaction mixture was concentrated under reduced pressure, and the resulting white precipitate was washed with toluene, hexanes, and cold THF and was vacuum-dried to afford 12.5 g (64%) of product as a white solid: mp 188−188.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.4−7.7 (m, 15H), 6.13 (d, *J* = 12.6 Hz, 2H), 1.40 (s, 6H), 0.78 (s, 9H), 0.10 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.5, 134.7 (d, *J* = 3.3 Hz), 133.9 (d, *J* = 11.1 Hz), 130.1, (d, *J* = 13.3 Hz), 118.9, (d, *J* = 89.4 Hz), 80.4, 34.6 (d, *J* = 58.5 Hz), 26.4, 25.6, 17.9, −2.2.

3-(*tert*-Butyldimethylsilyloxy)-3-methyl-1-triphenylphosphoranylidene-2-butanone (2). The bromide salt prepared above (9.3 g, 16.7 mmol) was dissolved in 60 mL of THF and 20 mL of water at 0 °C, and aqueous NaOH (2 M, 10 mL) was added slowly via syringe. The resulting white suspension was stirred for 1 h at 0 °C, and the reaction mixture was concentrated to approximately 25 mL under reduced pressure. The resulting aqueous phase was extracted with CH_2Cl_2, and then hexane was added to the combined organic phases. The organic phases were dried over Na_2SO_4 and filtered, and the solution was then concentrated to dryness under reduced pressure to afford an off-white solid (7.3 g, 92%): mp 129.5−130 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.7−7.4 (m, 15H), 4.38 (d, *J* = 28 Hz, 1H), 1.41 (s, 6H), 0.90 (s, 9H), 0.12 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.3, 133.0 (d, *J* = 10.1 Hz), 131.8 (d, *J* = 2.8 Hz), 128.7 (d, *J* = 12 Hz), 127.7 (d, *J* = 90.5 Hz), 79.1 (d, *J* = 11.1 Hz), 46.9 (d, *J* = 108 Hz), 28.9, 26.1, 18.3, −2.0; IR (KBr) 1716, 1708 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{25}H_{28}O_2PSi$ 419.1597; found 419.1602 ((M − *t*-Bu)$^+$). Anal. Calcd for $C_{29}H_{37}O_2PSi$: C, 73.07; H, 7.82. Found: C, 72.87; H, 7.84.

3-(2-[(*Z*)-2-Ethylidenecyclopentyl]-acetyl)-4,4-dimethyl-2-oxazolidinone. A 2 mL THF solution of $ZnCl_2$ (91 mg, 0.67 mmol) was stirred at 0 °C, and MeLi (0.72 mL, 1.0 mmol of a 1.4 M diethyl ether solution) was added by syringe followed by stirring for 15 min at 0 °C. A 0.5 mL THF solution of Ni(COD)$_2$ (3 mg, 0.01 mmol) was added by cannula, and the resultant pale yellow solution was immediately transferred by cannula to a 1.5 mL THF solution of the unsaturated *N*-acyloxazolidinone (51 mg, 0.22 mmol, prepared as described for compound **11**) at 0 °C. After consumption of starting material by TLC analysis, the reaction mixture was subjected to an extractive workup (NH_4Cl/NH_4OH pH = 8 buffer/EtOAc) followed by flash chromatography on SiO_2 (6:1 hexanes/EtOAc) to produce 47 mg (87%) of product as a light yellow oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.03 (tq, *J* = 2.0, 7.0 Hz, 1H), 3.99 (s, 2H), 3.18−3.08 (m, 1H), 3.01 (dd, *J* = 4.0, 17.0 Hz, 1H), 2.79 (dd, *J* = 11.0, 17.0 Hz, 1H), 2.29 (quintet of t, *J* = 2.0, 6.0 Hz, 1H), 2.16 (quintet of t, *J* = 1.5, 7.0 Hz, 1H), 1.86 (dq, *J* = 7.5, 13.0 Hz, 1H), 1.71−1.61 (m, 1H), 1.61 (dquintet, *J* = 1.5, 7.0 Hz, 3H), 1.58−1.49 (m, 1H), 1.56 (s, 6H), 1.47−1.40 (m, 1H); ^{13}C NMR (125 MHz) δ 173.5, 154.1, 145.8, 116.0, 75.2, 60.4, 41.0, 35.8, 33.1, 32.4, 24.9, 24.8, 24.0, 14.5; IR (film) 1777, 1700 cm^{-1}; HRMS (EI) *m*/*e* calcd for $C_{14}H_{21}NO_3$ 251.1521, found 251.1525 (M$^+$).

1-(4,4-Dimethoxybutyl)-4,4-dimethylcyclopent-2-en-1-ol (6). *t*-BuLi (2.47 mL, 3.85 mmol of a 1.56 M pentane solution) was added dropwise to a −78 °C solution of 4-bromo-1,1-dimethoxybutane (**5**)[12] (0.40 g, 2.03 mmol) in THF (3 mL). After being stirred for 20 min at −78 °C, the mixture was warmed to 0 °C over 10 min. The solution was cooled again to −78 °C, and a solution of 4,4-dimethylcyclopent-2-enone (**4**)[13] (0.11 g, 1.0 mmol) in THF (3.0 mL) was added dropwise. After being stirred for 30 min, the mixture was quenched with 30 mL of buffered NH_4Cl solution (pH 8), extracted with Et_2O, washed with brine, dried over $MgSO_4$, and concentrated. The residue was chromatographed (SiO_2, 3:1 hexanes/EtOAc), providing 0.147 g (65%) of **6** as a colorless oil that was homogeneous by TLC analysis: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (d, *J* = 5.5 Hz, 1H), 5.52 (d, *J* = 5.5 Hz, 1H), 4.36 (t, *J* = 6.0 Hz, 1H), 3.31 (s, 6H), 1.84 (d, *J* = 13.5 Hz, 1H), 1.72 (d, *J* = 14.0 Hz, 1H), 1.57−1.66 (m, 4H), 1.55 (m, 1H), 1.40−1.47 (m, 2H), 1.15 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 133.1, 104.5, 86.3, 52.8, 52.7, 44.6, 41.5, 32.9, 30.6, 29.2, 19.7; IR (film) 3446 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{13}H_{22}O_2$ 210.1620, found 210.1623 ((M − H_2O)$^+$).

(4-*E*)-8-(5,5-Dimethyl-1-oxocyclopent-2-en-3-yl)-2-(*tert*-butyldimethylsilyloxy)-2-methyloct-4-en-3-one [(*E*)-7]. A solution of the tertiary alcohol **6** (0.45 g, 1.97 mmol) in 8 mL of CH_2Cl_2 was added dropwise to a stirred suspension of PCC (1.7 g, 7.88 mmol) and Florisil (1.7 g) in 6 mL of CH_2Cl_2 at 0 °C. The reaction mixture was stirred for 80 min at 0 °C, diluted with CH_2Cl_2, and filtered through a pad of Florisil. The solid was rinsed with CH_2Cl_2 and then Et_2O. After concentration, the residue was treated with TsOH (0.225 g, 1.18 mmol) in acetone/water (3:1, 40 mL) for 6 h at 25 °C. The reaction mixture was subjected to an extractive workup ($NaHCO_3$/Et_2O). The crude aldehyde thus obtained was dissolved in benzene (4 mL) and was treated with compound **2** (1.4 g, 2.94 mmol) at 70 °C for 2 days. Evaporation and flash chromatography (SiO_2, 1:5 hexanes/Et_2O) afforded, in order of elution, 0.102 g (14%) of (*Z*)-**7** as a colorless oil and 0.41 g (55%) of (*E*)-**7** as a pale yellow oil that were both homogeneous by TLC analysis. For (*E*)-**7**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.92 (dt, *J* = 15.5, 6.5 Hz, 1H), 6.80 (dt, *J* = 15.8, 1.0 Hz, 1H), 5.85 (s, 1H), 2.41 (m, 2H), 2.39 (t, *J* = 7.8 Hz, 2H), 2.28 (dq, *J* = 1.0, 7.0 Hz, 2H), 1.76 (quintet, *J* = 7.5 Hz, 2H), 1.33 (s, 6H), 1.09 (s, 6H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 202.5, 178.4, 146.5, 126.9, 124.7, 79.0, 48.1, 44.0, 32.8, 32.0, 27.0, 25.8, 25.3, 25.1, 18.1, −2.4; IR (film) 1705, 1622 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{18}H_{29}O_3Si$ 321.1886, found 321.1886 ((M − C_4H_9)$^+$). For (*Z*)-**7**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.71 (dt, *J* = 11.5, 1.8 Hz, 1H), 6.19 (dt, *J* = 11.5, 7.5 Hz, 1H), 5.85 (t, *J* = 1.3 Hz, 1H), 2.65 (dq, *J* = 1.5, 7.5 Hz, 2H), 2.43 (m, 2H), 2.40 (t, *J* = 7.8 Hz, 2H), 1.72 (quintet, *J* = 7.8 Hz, 2H), 1.32 (s, 6H), 1.09 (s, 6H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.4, 204.6, 179.0, 148.1, 126.8, 123.4, 79.3, 48.1, 44.1, 33.1, 29.0, 27.0, 26.5, 25.8, 25.1, 18.1, −2.4; IR (film) 1703, 1617 cm^{-1}; HRMS (EI) *m*/*z* calcd for $C_{18}H_{29}O_3Si$ 321.1886, found 321.1887 ((M − C_4H_9)$^+$).

1,2,3a,5,5a,6,7,8-Octahydro-4-[1-(*tert*-butyldimethylsilyloxy)-1-methylethyl]-4-hydroxy-2,2-dimethylcyclopenta[*c*]pentalen-3-one (8a). Et_2Zn (41 μL, 0.397 mmol) was added dropwise to $ZnCl_2$ (18 mg, 0.132 mmol) in 2 mL of THF at 0 °C followed by stirring for 30 min at 0 °C. A 2 mL THF solution of Ni(COD)$_2$ (4 mg, 0.0132 mmol) was added, and the resultant mixture was immediately transferred by cannula to a solution of enone **7** (50 mg, 0.132 mmol) in 2.5 mL of THF at 0 °C and was allowed to warm to 25 °C. After being stirred for 2 h at 25 °C, the reaction mixture was subjected to an extractive workup (NH_4Cl/NH_4OH pH = 8 buffer/Et_2O), followed by flash chromatography (9:1 hexanes/Et_2O) to afford, in order of elution, 22.2 mg (44%) of **8a** (6:4:1 mixture of diastereomers) as a pale yellow oil and 13.8 mg (28%) of **9** as a pale yellow oil that were both homogeneous by TLC analysis. Compound **8a** was not fully characterized, but was directly

carried through to diol **8b**. For **8a**: IR (film) 1740, 1720 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{31}O_3Si$ 323.2042, found 323.2042 ($(M - C_4H_9)^+$). For **9**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.64 (d, J = 2.5 Hz, 1H), 2.63 (s, 1H), 2.32 (d, J = 17.5 Hz, 1H), 2.20 (d, J = 18.0 Hz, 1H), 2.18 (m, 1H), 1.88 (m, 1H), 1.81 (d, J = 13.0 Hz, 1H), 1.62−1.71 (m, 4H), 1.53−1.59 (m, 1H), 1.33 (s, 3H), 1.29 (s, 3H), 1.16−1.20 (m, 1H) 1.10 (s, 3H), 1.05 (s, 3H), 0.91 (s, 9H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 223.8, 215.8, 81.0, 51.0, 47.0, 45.9, 45.8, 44.0, 39.4, 38.1, 30.9, 27.9, 27.8, 26.9, 26.5, 22.1, 18.8, −1.48, −1.52; IR (film) 1740, 1719 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{18}H_{31}O_3Si$ 323.2042, found 323.2046 ($(M - C_4H_9)^+$).

1,2,3a,5,5a,6,7,8-Octahydro-4-(1-hydroxy-1-methylethyl)-4-hydroxy-2,2-dimethylcyclopenta[*c*]pentalen-3-one (8b). NBu_4F (0.29 mL, 0.29 mmol, 1.0 M in THF) was added dropwise to a solution of **8a** (22.2 mg, 0.0584 mmol) in 0.4 mL of THF at 0 °C. After being stirred for 6 h, the reaction mixture was subjected to an extractive workup (NH_4Cl/NH_4OH pH = 8 buffer/Et_2O). The residue was chromatographed (SiO_2, 6:1 hexanes/Et_2O) to afford, in order of elution, 6.8 mg (31%) of recovered **8a** as a colorless oil and 8.9 mg (57%) of diol **8b** as a white crystalline solid: mp 120−120.5 °C (recrystallized from Et_2O/hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 3.82 (m, 1H), 3.27 (d, J = 2.5 Hz, 1H), 2.84 (s, 1H), 2.59 (q, J = 8.5 Hz, 1H), 2.37 (d, J = 13.0 Hz, 1H), 2.01 (dd, J = 13.3, 7.8 Hz, 1H), 1.89 (dd, J = 12.8, 1.3 Hz, 1H), 1.85−1.89 (m, 1H), 1.67−1.76 (m, 2H), 1.52−1.63 (m, 2H), 1.36 (s, 3H), 1.34−1.37 (m, 2H), 1.14 (s, 3H), 1.06 (s, 3H), 1.04 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 229.3, 89.2, 75.0, 67.7, 56.8, 54.9, 52.0, 50.4, 46.1, 44.7, 32.9, 27.7, 27.0, 26.2, 24.9, 24.4; IR (film) 3445, 3410, 1712 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{16}H_{26}O_3$ 266.1882, found 266.1882 (M^+).

(3aα,5a*β*,8a*β*)-1,2,3a,5,5a,6,7,8-Octahydro-2,2-dimethylcyclopenta[*c*]pentalene-3,4-dione (10). A solution of H_5IO_6 (5.7 mg, 0.025 mmol) in 4.5 mL of Et_2O was added dropwise to a solution of diol **8b** (6.0 mg, 0.0225 mmol) in 1 mL of Et_2O at 25 °C, and the mixture was stirred until the starting material was consumed as judged by TLC analysis. After the mixture was filtered and concentrated, the residue was chromatographed (SiO_2, 4:1 hexanes/Et_2O) to produce 3.7 mg (81%) of **10** as a white crystalline solid: mp 65−66 °C (recrystallized from hexane); ^1H NMR (500 MHz, $CDCl_3$) δ 2.95 (s, 1H), 2.64 (dd, J = 19.5, 9.0 Hz, 1H), 2.45 (m, 1H), 2.25 (ddd, J = 19.3, 3.3, 1.3 Hz, 1H), 1.84−2.06 (m, 5H), 1.64−1.80 (m, 2H), 1.34 (m, 1H), 1.11 (s, 3H), 1.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 210.4, 70.8, 53.7, 51.4, 48.7, 47.0, 45.6, 42.6, 34.8, 26.3, 26.1, 25.3; IR (film) 1765, 1706 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{13}H_{18}O_2$ 206.1307, found 206.1310 (M^+).

3-[(2-*E*)-6-(5,5-Dimethyl-1-oxocyclopent-2-en-3-yl)-1-oxohex-2-enyl]-2-oxazolidinone (11). A solution of the tertiary alcohol **6** (0.147 g, 0.645 mmol) in 3 mL of CH_2Cl_2 was added dropwise to a mixture of PCC (0.42 g, 1.94 mmol) and Florisil (0.42 g) in 2.5 mL of CH_2Cl_2 at 0 °C followed by stirring for 80 min at 0 °C. The mixture was diluted with CH_2Cl_2, filtered through a pad of Florisil, and rinsed with CH_2Cl_2 and then Et_2O. After concentration, the residue was treated with TsOH (74 mg, 0.387 mmol) in acetone/water (3:1, 12 mL) at 25 °C followed by stirring for 4 h at 25 °C. The reaction mixture was subjected to an extractive workup ($NaHCO_3/Et_2O$) to provide the crude aldehyde that was directly used in the following step without further purification. A solution of 3-[2-(triphenylphosphonio)acetyl]oxazolidin-2-one bromide salt (0.395 g, 0.86 mmol) and DMAP (0.21 g, 1.72 mmol) in 4 mL of $CHCl_3$ was added dropwise to the aldehyde in 1 mL of $CHCl_3$ at 25 °C. After being stirred for 1 h at 60 °C, the mixture was cooled to 25 °C and was stirred at 25 °C for 20 h. The reaction mixture was quenched with 1.0 M $NaHSO_4$, extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was chromatographed (SiO_2, 1:1 hexanes/EtOAc) to produce 60.9 mg (33% for three steps) of **11** as a colorless oil that was homogeneous by TLC analysis: ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (dt, J = 15.5, 1.8 Hz, 1H), 7.11 (dt, J = 15.5, 7.0 Hz, 1H), 5.85 (t, J = 1.3 Hz, 1H), 4.42 (t, J = 8.0 Hz, 2H), 4.06 (t, J = 8.3 Hz, 2H), 2.42 (m, 2H), 2.40 (t, J = 7.0 Hz, 2H), 2.34 (dq, J = 1.5, 7.3 Hz, 2H), 1.78 (quintet, J = 7.5 Hz, 2H), 1.08 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.3, 178.3, 165.0, 153.5, 149.8, 127.0, 120.9, 62.1, 48.1, 44.1, 42.7, 32.7, 32.1, 25.3, 25.1; IR (film) 1776, 1698, 1637, 1616 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{16}H_{21}NO_4$ 291.1470, found 291.1470 (M^+).

(3aα,5a*β*,8a*β*)-1,2,3a,5,5a,6,7,8-Octahydro-2,2-dimethylcyclopenta[*c*]pentalene-3,4-dione (10). Et_2Zn (32 μL, 0.309 mmol) was added dropwise to $ZnCl_2$ (14 mg, 0.103 mmol) in 2 mL of THF at 0 °C followed by stirring for 20 min at 0 °C. A 2 mL portion of a THF solution of $Ni(COD)_2$ (3 mg, 0.0103 mmol) was added, and the resultant mixture was immediately transferred by cannula to a solution of enone **11** (30 mg, 0.103 mmol) in 1 mL of THF at 0 °C and then allowed to warm to 25 °C. After being stirred for 6 h at 25 °C, the reaction mixture was subjected to an extractive workup (NH_4Cl/NH_4OH pH = 8 buffer/Et_2O) followed by flash chromatography (5:1 hexanes/EtOAc) on silica gel to produce 12.2 mg (58%) of **10** (spectral data reported above).

1-(4,4-Dimethoxy-1-methylbutyl)-4,4-dimethylcyclopent-2-en-1-ol (12). A suspension of high purity lithium foil (0.125 g, 17.8 mmol) in 7 mL of THF containing 4,4-dimethylcyclopent-2-en-1-one (**4**)[13] (0.325 g, 2.96 mmol) and 4-bromo-1,1-dimethoxypentane[12] (1.2 g, 5.69 mmol) was sonicated for 2 h in a 10 °C bath. The mixture was filtered and was subjected to an extractive workup (NH_4Cl/NH_4OH pH = 8 buffer/Et_2O). The residue was chromatographed (SiO_2, 2:1 hexanes/Et_2O), providing 0.36 g (50%) of **12** (1:1 mixture of diastereomers) as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 5.67 (d, J = 5.5 Hz, $1H_{\text{single isomer}}$), 5.66 (d, J = 6.0 Hz, $1H_{\text{single isomer}}$), 5.53 (d, J = 5.0 Hz, $1H_{\text{single isomer}}$), 5.52 (d, J = 5.0 Hz, $1H_{\text{single isomer}}$), 4.35 (m, 1H), 3.309, 3.307, 3.305, 3.302 (4 singlets, 6H), 1.82 (d, J = 13.5 Hz, $1H_{\text{single isomer}}$), 1.81 (d, J = 14.0 Hz, $1H_{\text{single isomer}}$), 1.73 (m, 2H), 1.65 (d, J = 14.0 Hz, $1H_{\text{single isomer}}$), 1.61 (d, J = 14.5 Hz, $1H_{\text{single isomer}}$), 1.46−1.58 (m, 3H), 1.16 (s, 3H), 1.05 (m, 4H), 0.95 (d, J = 7.0 Hz, $3H_{\text{single isomer}}$), 0.86 (d, J = 7.0 Hz, $3H_{\text{single isomer}}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0, 144.7, 132.7, 132.3, 104.8, 104.7, 89.6, 89.5, 52.8, 52.5, 52.4, 49.8, 49.1, 44.4, 44.3, 41.9, 41.7, 31.0, 30.9, 30.8, 29.1, 29.0, 27.1, 26.2, 15.1, 14.2; IR (film) 3471 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{14}H_{24}O_2$ 224.1776, found 224.1777 ($(M - H_2O)^+$).

3-[(2-*E*)-6-(5,5-Dimethyl-1-oxocyclopent-2-en-3-yl)-1-oxohept-2-enyl]-2-oxazolidinone (13). The procedure for compound **11** was followed starting with **12** to afford 0.2 g of **13** as a white solid (45% for three steps) on a 1.45 mmol scale: mp 72−73 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.22 (dt, J = 15.5, 1.5 Hz, 1H), 7.09 (dt, J = 15.5, 7.0 Hz, 1H), 5.84 (s, 1H), 4.42 (t, J = 8.0 Hz, 2H), 4.05 (t, J = 8.3 Hz, 2H), 2.56 (m, 1H), 2.44 (dd, J = 18.0, 1.8 Hz, 1H), 2.40 (dd, J = 18.0, 1.8 Hz, 1H), 2.26 (m, 2H), 1.74 (m, 1H), 1.61 (m, 1H), 1.15 (d, J = 7.0 Hz, 3H), 1.09 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 182.7, 165.0, 153.4 149.8, 126.3, 120.6, 62.0, 45.5, 43.8, 42.6, 36.5, 32.9, 30.1, 25.1, 25.0, 18.6; IR (film) 1775, 1700, 1686, 1635, 1611 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{17}H_{23}NO_4$ 305.1627, found 305.1632 (M^+).

(3aα,5a*β*,8*β*,8a*β*)-1,2,3a,5,5a,6,7,8-Octahydro-2,2,8-trimethylcyclopenta[*c*]pentalene-3,4-dione (1a). *n*-BuLi (0.25 mL, 0.59 mmol, 2.39 M hexane solution) was added dropwise to a 0 °C solution of $ZnCl_2$ (54 mg, 0.393 mmol) in 2.5 mL of THF. After the solution was stirred for 30 min at 0 °C, a 2 mL THF solution of $Ni(COD)_2$ (4 mg, 0.0131 mmol) was added, and the resultant mixture was immediately transferred by cannula to a solution of enone **13** (40 mg, 0.131 mmol) in 2 mL of THF at 0 °C and was allowed to warm to 25 °C. After being stirred for 20 h at 25 °C, the reaction mixture was subjected to an extractive workup (NH_4Cl/NH_4OH pH = 8 buffer/Et_2O), followed by flash chromatography (4:1 hexanes/EtOAc) on silica gel, to produce 14 mg (49%) of **1a** and **1b** (1:1 molar ratio based on ^1H NMR integration). The key intermediate **1a** was partially isolated by recrystallization from pentane (mp 69−70 °C (lit.[4] mp 71−72 °C)), and compound **1b** as a colorless oil was also partially isolated by flash chromatography (6:1 hexanes/EtOAc). For **1a**: ^1H NMR (500 MHz, $CDCl_3$) δ 2.97 (s, 1H), 2.70 (dd, J = 19.0, 9.0 Hz, 1H), 2.57 (m, 1H), 2.27 (ddd, J = 18.8, 4.0, 1.3 Hz, 1H), 2.22 (dd, J = 14.0, 1.5 Hz, 1H), 2.20 (m, 1H), 2.10 (m, 1H), 1.91 (dquintet, J = 8.8,

6.8 Hz, 1H), 1.72 (d, J = 14.0 Hz, 1H), 1.51 (qt, J = 8.3, 5.5 Hz, 1H), 1.34 (qt, J = 9.0, 5.5 Hz, 1H), 1.13 (s, 3H), 1.10 (s, 3H), 1.04 (d, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 212.6, 209.6, 69.3, 56.7, 47.6, 46.3, 44.4, 42.7, 41.8, 33.6, 30.8, 25.6, 25.3, 16.1; IR (film) 1761, 1716 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1464 (M^+). The ^{1}H NMR spectrum of **1a** matched that provided by Professor M. T. Crimmins. For **1b**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.10 (s, 1H), 2.80 (dd, J = 19.5, 10.0 Hz, 1H), 2.66 (m, 1H), 2.15 (ddd, J = 19.5, 4.5, 1.0 Hz, 1H), 2.07 (d, J = 14.0 Hz, 1H), 1.95−2.02 (m, 2H), 1.90 (m, 1H), 1.83 (m, 1H), 1.50 (m, 1H), 1.17 (m, 1H), 1.14 (s, 3H), 1.06 (s, 3H), 0.92 (d, J = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 213.0, 210.2, 64.9, 55.7, 50.3, 46.9, 46.8, 46.5, 45.2, 33.0, 32.9, 26.1, 25.2, 15.0; IR (film) 1762, 1717 cm^{-1}; HRMS (EI) m/z calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1464 (M^+).

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Supporting Information Available: Copies of ^{1}H NMR spectra for **1a**,**b** and **6**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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