Tetrahedron 64 (2008) 11822–11830

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Initiating radical cyclizations by H• transfer from transition metals

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ARTICLE INFO

Article history:
Received 2 October 2008
Accepted 10 October 2008
Available online 17 October 2008

Keywords:
Radical cyclization
Hydrogen atom transfer
Transition-metal hydrides
Acrylates

ABSTRACT

$CpCr(CO)_3H$ and $HV(CO)_4(P–P)$ (where P–P is a chelating diphosphine) can be used to initiate radical cyclizations by transferring H• to activated terminal olefins. $CpCr(CO)_3H$ can *catalyze* reductive cyclizations, with H_2 as the ultimate reductant. Appropriate substrates can be assembled by the Morita–Baylis–Hillman reaction of methyl acrylate with an aldehyde. Six- as well as five-membered rings can be formed, and a tandem cyclization to decalin can be effected.

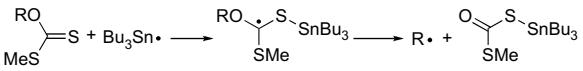
1. Introduction

Methods involving carbon-centered radicals are extensively used in synthesis, particularly in cyclization reactions. Such radicals can be generated in many ways, the most common being the abstraction of X• by an organotin radical (Eq. 1), where X is Br, I, occasionally Cl, or PhSe or PhS.[1] The radical R•, often after cyclization or rearrangement, then abstracts H• from a tin hydride (typically Bu_3SnH), regenerating the tin radical (Eq. 2) and continuing the chain.

$$R–X + Bu_3Sn• \longrightarrow R• + Bu_3SnX \quad (1)$$

$$R'• + Bu_3SnH \longrightarrow R'–H + Bu_3Sn• \quad (2)$$

Related methods begin with the addition of a tin radical to the C=S double bond in a xanthate (Eq. 3) or thiohydroxamate (Eq. 4) ester.[1,2] The resulting intermediates then give R• by β-scission and decarboxylation (Eq. 4).



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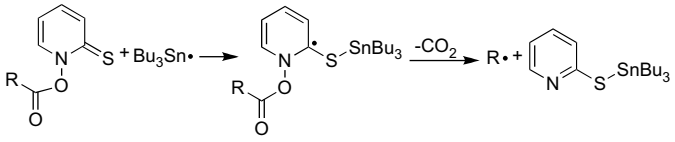

(4)

Such methods are necessarily stoichiometric both in tin and in another heavy element (Br, I, Se, S). In the laboratory, special care is required to handle trialkyltin hydrides and the waste they generate, and standard purification techniques often leave toxic levels of tin compounds in the product.[3] The industrial application of these methods has been hindered by the need to remove such tin-containing byproducts. In order to ameliorate this problem, methods catalytic in tin have been developed,[4–6] and tin hydride reagents modified to make their removal easier.[7–13] However, the need for alternatives to tin remains as evidenced by reviews such as 'Flight from the Tyranny of Tin'.[14–17] Substitutes such as *N*-ethylpiperidinium hypophosphite,[18] $(Me_3Si)_3SiH$,[19] Bu_3GeH,[20] $HGaCl_2$,[21] and $HInCl_2$[22] contain a bond to hydrogen stronger than the 78 kcal/mol one in Bu_3SnH[23] and are therefore likely to be less reactive at H• transfer.

Bonds to hydrogen weaker than Sn–H are common in transition-metal hydrides. Although an Os–H bond >82 kcal/mol has been reported,[24] most M–H bonds lie between 60 and 65 kcal/mol.[25] We have found V–H bonds (see below) as weak as 55 kcal/mol.[26] These weak bonds enable transition-metal hydrides to generate radicals in ways not available to tin hydrides. In 1977 Sweany and Halpern concluded, after observing CIDNP and an inverse H/D isotope effect, that the hydrogenation of α-methylstyrene by $HMn(CO)_5$ (Eqs. 5 and 6) begins with the reversible transfer of H• from Mn to the olefin.[27] (They presumed the new C–H bond to have a frequency of

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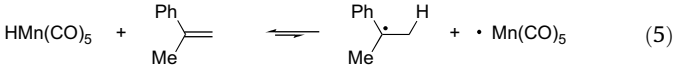
0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.10.030

'$\sim$3000 cm^{-1}', and implied that the inverse isotope effect arose from the *equilibrium* in Eq. 5. However, such C–H bonds are weakened by an adjacent radical center,[28] and ΔH for Eq. 5 is *endothermic*, +8 to 10 kcal/mol,[29,30] which raises the possibility[31] that the observed inverse effect has a *kinetic* origin.[32]).



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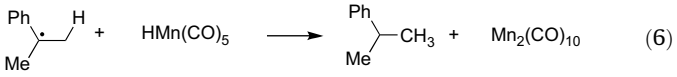


(6)

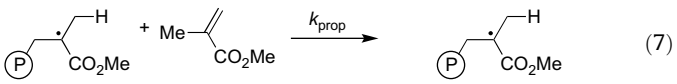
Some years ago we showed that $CpCr(CO)_3H$ (**1**) and related Cr hydrides could serve as H• donors to methyl methacrylate and styrene.[29,30] However, these Cr–H bonds are 62–64 kcal/mol and their H• transfer reactions were not fast. We considered where we might find weaker M–H bonds, and noted (1) the unusually efficient transfer of H• to a carbon radical from an anionic vanadium hydride,[33] (2) a number of papers in which vanadium hydrides appeared to transfer H• onto various dienes,[34,35] and (3) a calculation on the hypothetical VH_5 that gave it the weakest M–H bond of any of the hydride complexes considered.[36] We therefore prepared a series of vanadium hydrides $HV(CO)_4$(P–P) (P–P=$Ph_2P(CH_2)_nPPh_2$, with n=1 (dppm), n=2 (dppe), n=3 (dppp), and n=4 (dppb)) (**2a**–**d**),[37,38] determined the strength of their V–H bonds, and found that these bonds are indeed weak (Table 1).[39]

Table 1
Bond dissociation energies of some chromium and vanadium hydrides

M–H	M–H BDE (kcal/mol)
(η^5-C_5H_5)$Cr(CO)_3H$ (**1**)	62.2
$HV(CO)_4$(dppm) (**2a**)	57.9
$HV(CO)_4$(dppe) (**2b**)	57.5
$HV(CO)_4$(dppp) (**2c**)	56.0
$HV(CO)_4$(dppb) (**2d**)	54.9

The V–H bonds in **2a**–**d** transfer H• more rapidly than does the Cr–H bond in **1**, although the increase in rate is not as large as one would expect from the decrease in M–H bond strength. $HV(CO)_4$(dppe) (**2b**) transfers H• to styrene about 10 times more rapidly than does **1**.[39] Presumably, the steric bulk of the chelating ligand undermines the effect of the weaker bond.

Such H• transfer reactions are familiar as part of the catalytic cycle for chain transfer during radical polymerizations (Eq. 7). In the first step of that cycle, Eq. 8, H• is removed from the chain-carrying radical; its transfer to fresh monomer (Eq. 9) begins a new chain.[40] The competition between Eq. 8 and propagation (Eq. 7) reduces the chain length and molecular weight of the polymer.



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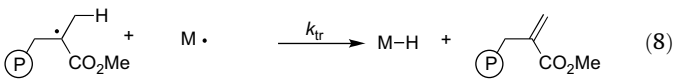

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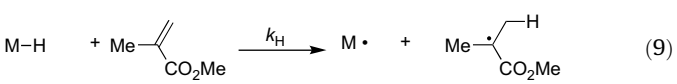


(9)

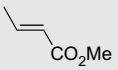
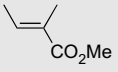
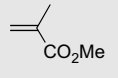
Metalloradicals M• have proven to be effective catalysts for chain transfer. The original catalysts were macrocyclic cobalt(II) complexes,[40] but their hydrides are unobservable during the catalytic cycle, apparently because they are so efficient in transferring H• back to monomer (Eq. 9). We have found that Cr metalloradicals are almost as effective while offering the advantage that their hydrides are stable enough to be observed during catalysis. For the polymerization of methyl methacrylate, $(C_5Ph_5)Cr(CO)_3$• is a good chain transfer catalyst, $CpCr(CO)_3$• (in equilibrium with its dimer) is a much better one,[41] and the vanadium metalloradical $V(CO)_4$(dppe)• shows respectable activity.[42] This effectiveness implies that the corresponding hydrides ($(C_5Ph_5)Cr(CO)_3H$, **1**, and **2b**) are efficient in transferring H• back to methyl methacrylate.

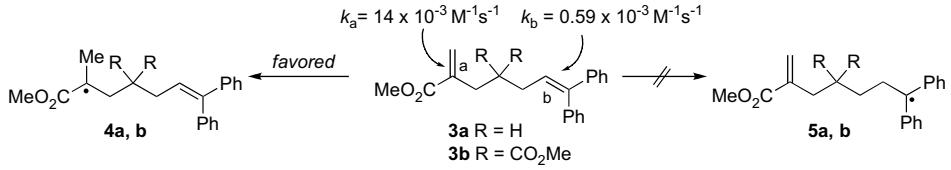
The effectiveness with which M–H bond strengths can control rates of H• transfer is illustrated by the recent work of O'Connor and Friese on Bergman cycloaromatizations. They found that $CpW(CO)_3H$, with an M–H bond strength of 72 kcal/mol,[25] does not react with an enediyne but does transfer H• to the diradical formed by its cyclization.[43]

Using H• transfer to selectively generate radicals requires that we know the relative rates at which such transfers occur to various olefins. There has been virtually no information on the rate constants k_H with which different double bonds accept H•. We have therefore examined the reactivity of $CpCr(CO)_3H$ (**1**) toward the nine olefins in Table 2, determining k_H from either the rate of H/D exchange or the rate of hydrogenation.[26]

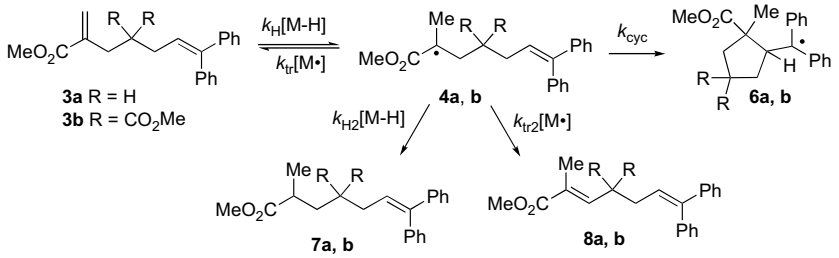
The stability of the resulting radical has a large effect on k_H: olefins bearing phenyl substituents (entries 1–3 and 8) accept H• more readily than do olefins bearing CO_2Me substituents (entries 4, 6, and 9), although the latter accept H• more readily than do olefins bearing methyl substituents. Additional methyl or phenyl substituents on the α carbon—which provide additional stabilization for the radical being generated—increase the rate further.

Table 2
Rate constants k_H for H• transfer from $CpCr(CO)_3H$ to various olefins at 323 K

Entry	Olefin	k_H ($\times10^{-3}$) (M^{-1} s^{-1})	Relative rate
1		0.59 (2)	1
2		460 (60)	780
3		79 (3)	134
4		$\leq3.2\times10^{-4}$	$\leq5\times10^{-4}$
5		$\leq1.1\times10^{-4}$	$\leq2\times10^{-4}$
6		$(0.8–1.6)\times10^{-2}$	$\approx$0.02
7		$\leq3.2\times10^{-3}$	$\leq$0.005
8		15.8 (6)	27
9		14 (3)	24



Scheme 1. H• transfer to dienes **3a** and **3b**.



Scheme 2. Pathways available to radicals **4a** and **4b**.

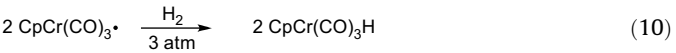
A methyl substituent on the β carbon (the one receiving the H•) reduces the rate substantially, presumably as a result of steric hindrance to the transfer. The results in Table 2 have enabled us to design substrates that can be cyclized by transition-metal hydrides.

2. Results and discussion

According to Table 2, the 'a' double bond in **3** (Scheme 1) should be kinetically favored (25 times faster) for H• transfer, yielding radical **4** rather than radical **5**.

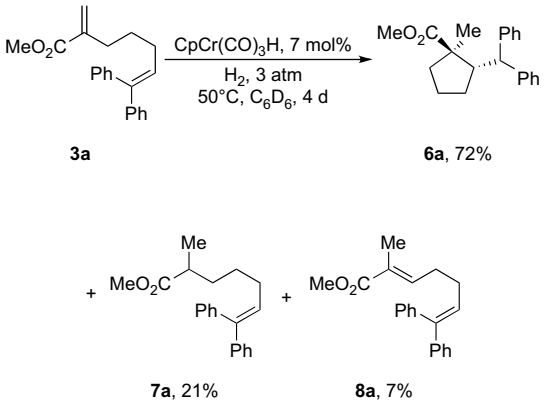
Several reactions, all shown in Scheme 2, are available to **4**. Such radicals are known to cyclize rapidly, with rate constants (k_{cyc})>10^5 s^{-1}.[44] However, they can also undergo back transfer (k_{tr}[M•]), hydrogenation (k_{H2}[M–H]), and isomerization by H• abstraction from the adjacent carbon (k_{tr2}[M•]).

Back transfer and isomerization require M•, and can be avoided if we convert M• back to M–H—a transformation that has the advantage of making the overall reaction *catalytic*. If M• is $CpCr(CO)_3$•, we can convert it back to $CpCr(CO)_3H$ (**1**) with modest hydrogen pressures (3 atm H_2, Eq. 10). (This transformation was reported by Fischer and co-workers in 1955, but under a pressure of 150 atm at 70 °C![45]) Unfortunately, we have as yet been unable to regenerate the vanadium hydrides **2** from the corresponding vanadoradicals, so they can only be used as *stoichiometric* reagents.



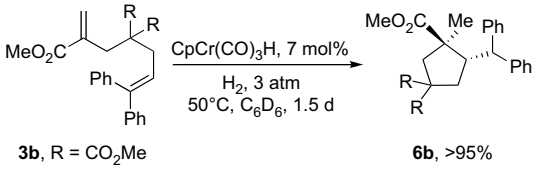
(10)

With **1** under 3 atm of H_2, we can carry out (Eq. 11) the catalytic and tin-free cyclization of **3a** to **6a**, although we also observe some hydrogenation (to **7a**) and isomerization (to **8a**).[46] The reaction is slow but conversion is complete. The transfer of H• to the cyclized radical gives the observed product **6a** as two diastereomers (only the major one is shown). An increase in the H_2 pressure favors (as we would expect) **7a** over **8a**, while a decrease in the pressure has the opposite effect (see Section 4.2).



(11)

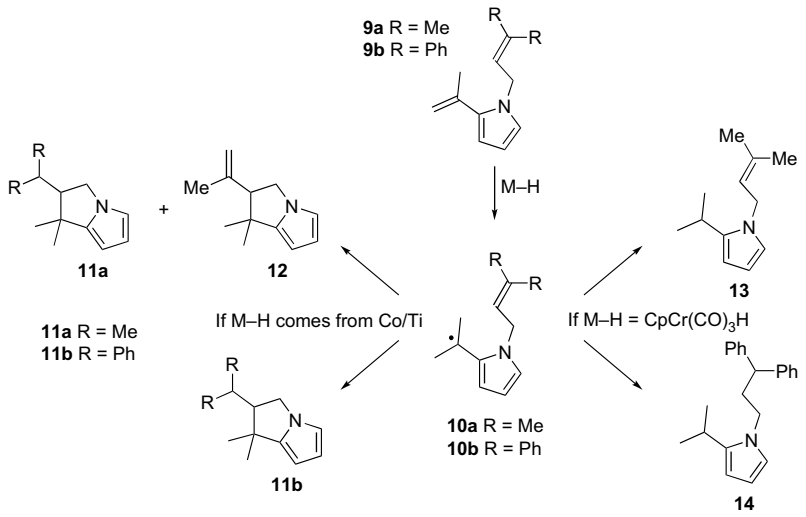
When we increase k_{cyc}, by placing two substituents on the γ carbon (**3b**, Eq. 12) to take advantage of the Thorpe–Ingold effect,[47] the reaction becomes fast and quantitative.[46]



(12)

Stoichiometric use of the vanadium hydrides **2** gave similar results with **3a** and **3b**, but *more quickly even at lower temperatures*.[39] For example, treatment of **3a** with **2b** yielded **6a** in 77% yield in 24 h, while treatment of **3b** with **2a–d** gave **6b** quantitatively in 6–24 h.

There have been previous reports on the use of organometallic complexes to effect the cyclization of 1,6-dienes. Cp^*_2YH (generated in situ) under H_2 reductively cyclizes some terminal dienes,[48] Ni and Pd allyls cyclize other dienes to unsaturated products,[49] and Ru and Rh catalysts cyclize heterocycle-substituted dienes.[50] Rh(I) catalysts under H_2 effect the reductive cyclization of diynes and enynes.[51] In none of these cases has evidence been reported for a radical mechanism.



Scheme 3. Treatment of **9a** and **9b** with B_{12}/Ti(III) (van der Donk) versus treatment with chromium hydride **1**.

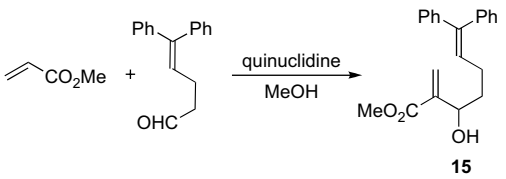
2.1. Substrates that generate pyrrole-stabilized radicals

Van der Donk and co-workers have reported the cyclization of **9a** and **9b** (Scheme 3), with Vitamin B_{12} as a catalyst and Ti(III) citrate as the ultimate reductant.[52,53] The substrates **9** closely resemble α-methylstyrene, and should be attractive recipients for H• transfer from transition metals (recall Eq. 5). It seems likely that the reported reaction involves H• transfer from a transient cobalt hydride with a very weak Co–H bond. We have treated **9a** and **9b** with **1** under H_2, but obtained only the hydrogenated products **13** and **14**.

These results (from treating **9a** and **9b** with **1**/H_2) imply that the radicals **10a** and **10b** cyclize more slowly than radicals **4a** and **4b**. The cyclizations of **10a** and **10b** are plainly slower than that of **4a** (which gave only 21% hydrogenation with **1** in Eq. 11) and that of **4b** (which gave a quantitative yield of the cyclization product **6b** with **1** in Eq. 12). The cause of this slow cyclization is probably the planar pyrrole ring, which places 120° angles in the '5-hexenyl' radical of **10** and makes it difficult to form products **11** and **12** by a 5-*exo*-*trig* pathway.[47]

2.2. Substrates from the Morita–Baylis–Hillman reaction

Additional α-substituted acrylates related to our original substrates **3** are readily assembled by the Morita–Baylis–Hillman reaction,[54,55] but necessarily bear an additional hydroxyl group. For example, diene **15** is available in 98% yield (Eq. 13) by treatment of the known aldehyde[56] 5,5-diphenylpent-4-enal with methyl acrylate and quinuclidine[57] at room temperature.

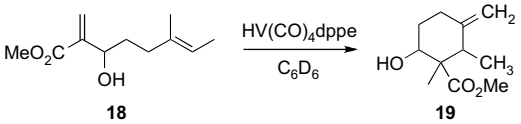


(13)

Our cyclization reaction has proven tolerant of the additional substituent. Treatment of diene **15** with a *catalytic* amount (7 mol%) of $Cp(CO)_3CrH$ in C_6D_6 under 3 atm H_2 generated the substituted cyclopentanol **16** after 3 days at 50 °C. Alternatively, treatment of **15** with a *stoichiometric* amount of the vanadium hydride **2b** gave **16** in 77% yield after 3 h at room temperature, a yield similar to that obtained (see above) with **2b** and substrates **3a** and **3b**. Apparently, a β-hydroxy substituent has little influence on k_{cyc}, which is not surprising in view of a literature report[58] that a β-methoxy substituent slows down the cyclization of a 6,6-Ph_2-5-hexenyl radical by only a factor of two.

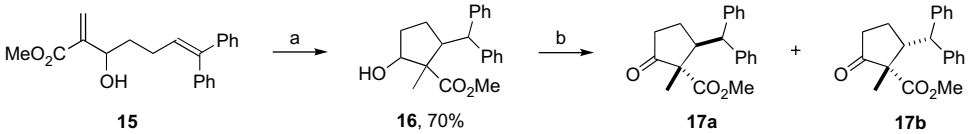
By NMR, we were able to observe four diastereomers of the cyclopentanol **16**. Jones oxidation deleted the alcohol stereocenter and gave a separable mixture of two diastereomers, **17a** and **17b**, in a 3:2 ratio (Scheme 4).

We have also changed the substituents on the trisubstituted double bond of **15** in an effort to encourage cyclization to a six-membered ring ('6-*endo*-*trig*'). Cyclization of 5-hexenyl radicals is normally slower to six-membered rings than to five-membered ones,[59] but can be encouraged by removing the two phenyl substituents from **3**/**15** and placing a methyl substituent on C-5 of the radical.[60,61] We have therefore prepared **18** and treated it with the vanadium hydride **2b** (Eq. 14).



(14)

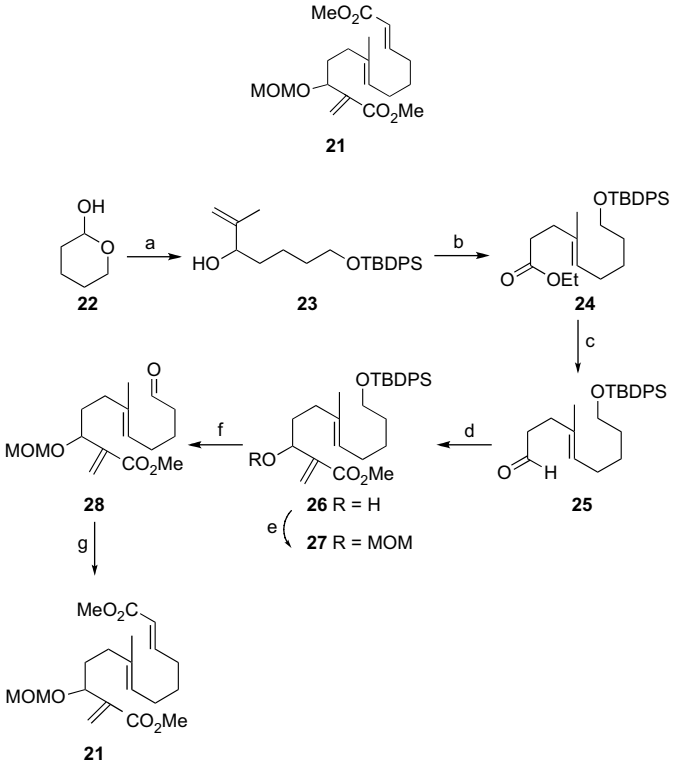
After 6 h, the acrylate methylene signal (^{1}H NMR) of **18** was gone, and the resulting mixture contained a single diastereomer of the 6-*endo*-*trig* cyclization product **19** (15%) along with material containing unreacted trisubstituted olefin (51%). The *exo* double bond of **19** echoes one obtained by Breslow and co-workers (apparently via a radical) after treating geranyl acetate with DBPO, CuCl, and $Cu(O_2CPh)_2$.[62] The regeneration of unsaturation in **19**



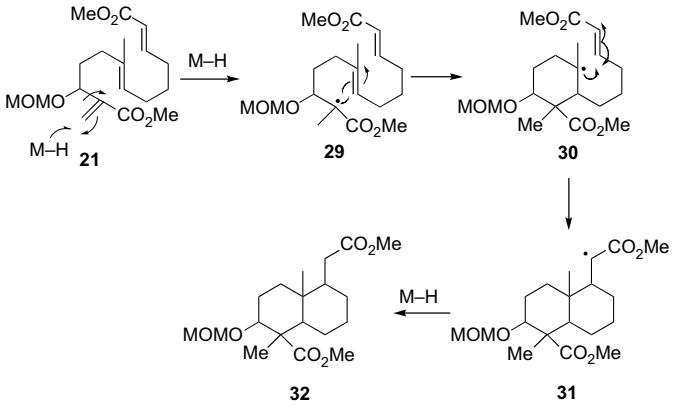
Scheme 4. Synthesis of cyclopentanones **17a** and **17b**. (a) $HV(CO)_4$(dppe), C_6D_6, 3 h; (b) CrO_3, aq H_2SO_4, acetone.

suggests that it may be possible to make our cyclization reactions catalytic in hydride even without hydrogen.

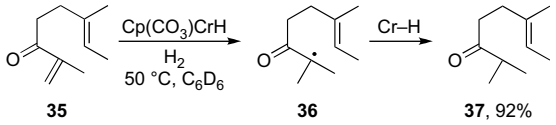
We then considered as a substrate **21**, an elaboration of **18** with an additional double bond to trap the radical formed by the initial cyclization. Triene **21** contains many features of polyolefins that have given terpene natural product substructures by radical mechanisms.[63–69]



Scheme 5. Synthesis of cyclization precursor **21**. (a) (1) Isopropenylmagnesium bromide, THF; (2) TBDPSCl, TEA, DMAP, CH_2Cl_2, 97% over two steps; (b) triethyl orthoacetate, propionic acid, reflux, 96%; (c) DIBAL, CH_2Cl_2, −78 °C, 88%; (d) methyl acrylate, quinuclidine, methanol, 81%; (e) MOMCl, DIPEA, TBAI, CH_2Cl_2, 70%; (f) (1) TBAF, AcOH (aq), THF, 78%; (2) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 50%; (g) methyl (triphenylphosphoranylidene)acetate, CH_2Cl_2, 76%.



Scheme 6. Proposed mechanism for the formation of **32**.



Scheme 8. Hydrogenation of **35**.

The synthesis of **21** (Scheme 5) began with the addition of isopropenyl magnesium bromide to the known[69] lactol **22**. The primary alcohol of the resulting diol was protected as the silyl ether before treatment with triethyl orthoacetate at reflux in the presence of a catalytic amount of propionic acid. The Johnson–Claisen product **24** was reduced to the aldehyde **25**, and the latter treated with methyl acrylate to give the alcohol **26** in a Morita–Baylis–Hillman reaction. Alcohol **26** was protected as the methoxy methyl ether, desilylated, and oxidized to the aldehyde **28**. Wittig olefination was then effected with *E* selectivity by treatment with methyl (triphenylphosphoranylidene)acetate, giving the cyclization substrate **21**.

The treatment of **21** with a catalytic amount of $CpCr(CO)_3H$ under H_2 for 6 days gave the cyclization product **32** in 23% isolated yield, presumably by the mechanism in Scheme 6. Alternatively, treatment of **21** with a *stoichiometric* amount of the vanadium hydride **2b** gave **32** in 35% yield overnight at room temperature. According to Scheme 6, the initial H• transfer will occur to the α-substituted acrylate, giving radical **29**. The 6-*endo*-*trig* cyclization of **29** gives tertiary radical **30**, which forms decalin **32** by intramolecular addition to its *E* double bond.

The resulting **32** was a mixture of one major diastereomer and two minor ones, in the ratio 62:24:14. Deprotection, followed by oxidation of the resulting alcohol **33** (Scheme 7), gave a 3:1 mixture of two diastereomeric decalones **34**. From this result we infer that, while **32** contains material with different configurations at the hydroxyl-bearing stereocenter, the resulting **34** consists of two diastereomers with different configurations elsewhere.

A minor product of the reaction contained an exo $=CH_2$, suggesting that M• abstracted some H• from the first cyclized radical **30** in competition with the second cyclization (to **31**).

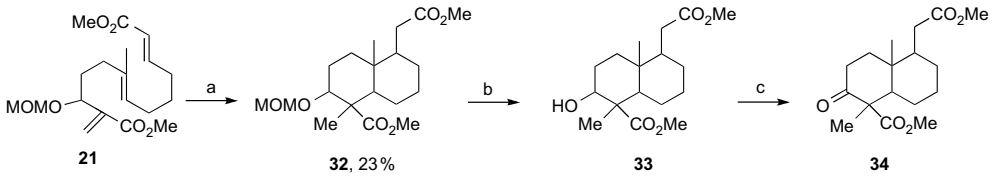
2.3. Can α,β-unsaturated ketones serve as substrates?

Acyl substituents stabilize radicals more effectively than carboalkoxy ones,[70] suggesting that an α,β-unsaturated ketone can also serve as an H• acceptor. We therefore prepared **35** and placed it under 3 atm H_2 with a catalytic amount of the Cr hydride **1**. However, the result was exclusively hydrogenation—a 92% yield of the isopropyl ketone **36** (Scheme 8).

Presumably, the radical **36** is formed but does not cyclize before it receives a second H•. The low k_{cyc} of **36** probably arises from its stability.[70]

3. Conclusion

$CpCr(CO)_3H$ (**1**) and $HV(CO)_4(P–P)$ (**2**) can be used to initiate radical cyclizations by transferring H• to activated terminal olefins. However, the resulting radical must cyclize quickly; competing reactions include transfer of a second H• (resulting in



Scheme 7. Synthesis of decalones **34** from acyclic precursor **21**. (a) $Cp(CO)_3CrH$, 7 mol %, C_6D_6, 50 °C; (b) HCl, MeOH, 65 °C; (c) CrO_3, aq H_2SO_4, acetone.

hydrogenation) and removal of an H• (resulting in isomerization). $Cp(CO)_3CrH$ (**1**) is relatively slow at H• transfer, but can be regenerated with H_2 gas, enabling it to carry out reductive cyclization *catalytically*; vanadium hydrides $HV(CO)_4(P–P)$ (**2**) are faster but operate stoichiometrically. Substrates (1,6-dienes) can be prepared by the Morita–Baylis–Hillman reaction of methyl acrylate with appropriate unsaturated aldehydes. Six- as well as five-membered rings can be formed, and a tandem cyclization to a decalin can be effected.

4. Experimental section

4.1. Materials and methods

All reactions were carried out under an atmosphere of argon in glassware that had been flame-dried under vacuum and backfilled with Argon. High pressure reactions were carried out in a Fisher & Porter bottle equipped with a pressure gauge, gas inlet, and pressure release valve. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Deuterated benzene (C_6D_6) was purified by vacuum transfer from sodium–benzophenone ketyl. THF, Et_2O, toluene, and CH_2Cl_2 were dried by filtration through alumina. $CpCr(CO)_3H$[71] (**1**) and $HV(CO)_4(P–P)$[72,73] (**2a–d**) were stored and manipulated in an inert argon atmosphere dry box (O_2 <1 ppm). $CpCr(CO)_3H$ was sublimed prior to use. Reaction mixtures involving **1** and **2a–d** were prepared in the drybox. ^1H NMR and ^{13}C NMR spectra were recorded at ambient temperature at 400 or 300 MHz and 100 or 75 MHz, respectively, using a Bruker DRX400 or DRX 300 spectrometer. The data are reported as follows: chemical shift in parts per million from internal tetramethylsilane on the δ scale, integration, multiplicity (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, qn=quintet, m=multiplet), and coupling constants (Hz). High-resolution mass spectra were acquired on a JOEL JMS-HX110 HF mass spectrometers, and were obtained by peak matching.

4.2. Methyl 2-benzhydryl-1-methylcyclopentane-carboxylate (6a)

A stock solution of $CpCr(CO)_3H$ in C_6D_6 (0.05 M, 0.18 mL) was stirred under H_2 pressure as specified in the table below. After 30 min, a solution of diene substrate **3a** (40 mg, 0.13 mmol) and hexamethylcyclotrisiloxane (0.074 M, 80 μL) in C_6D_6 (0.83 mL) was added (1.0 mL total volume). The reaction mixture was again pressurized with H_2 according to the table below and stirred at 50 °C. After NMR analysis indicated that the reaction was complete, yields of **6a** (as a pair of diastereomers) and byproducts **7a** (hydrogenation) and **8a** (isomerization) were determined from integration versus the hexamethylcyclotrisiloxane standard.

H_2 pressure (psi)	Time (days)	SM (**3a**) (%)	**6a** (%)	**7a** (%)	**8a** (%)
8	7	5	55	20	20
30	4	—	62	26	12
80	1.5	5	55	31	9

4.3. 2-Isopropyl-1-(3-methylbut-2-enyl)-1*H*-pyrrole (12)

A stock solution of $CpCr(CO)_3H$ in C_6D_6 (0.038 M, 0.51 mL) was stirred under 80 psi of H_2 for 30 min. A solution of diene **9a** (50 mg, 0.29 mmol) and hexamethylcyclotrisiloxane (0.074 M, 0.21 mL) in C_6D_6 (1.7 mL) was added to the reaction mixture (2.2 mL total volume). The reaction mixture was pressurized to 80 psi of H_2 and stirred at 50 °C. After NMR analysis indicated that the starting material was consumed (6 days), the reaction mixture was filtered through a silica plug and concentrated in vacuo to yield hydrogenated product **12** (100%, determined by NMR). ^1H NMR (400 MHz, $CDCl_3$): δ 6.56–6.55 (1H, m), 6.08–6.09 (1H, m), 5.91–5.90 (1H, m), 5.31–5.28 (1H, m), 4.43 (2H, d, J=6.8 Hz), 2.93–2.87 (1H, m), 1.75 (6H, s), 1.24 (6H, d, J=6.8 Hz); HRMS (FAB^+) calcd for $C_{12}H_{19}N$ $[M]^+$: 177.1517, found 177.1514, $C_{12}H_{19}N$.

4.4. 1-(3,3-Diphenylpropyl)-2-isopropyl-1*H*-pyrrole (13)

The above procedure was followed with **9b** (77.9 mg, 0.26 mmol), $CpCr(CO)_3H$ in C_6D_6 (0.038 M, 0.46 mL), and hexamethylcyclotrisiloxane (0.074 M, 0.21 mL) in C_6D_6 (1.94 mL total volume) to yield hydrogenated product **13** in 4 days (100%, determined by NMR). ^1H NMR (400 MHz, $CDCl_3$): δ 7.32–7.18 (10H, m), 6.52–6.51 (1H, m), 6.09–6.08 (1H, m), 5.89–5.87 (1H, m), 3.89 (1H, t, J=15.6 Hz), 3.78–3.75 (2H, m), 2.68–2.58 (1H, m), 2.50 (2H, q, J=8 Hz), 1.14 (6H, d, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.3, 140.1, 129.1, 128.1, 126.9, 119.7, 107.3, 103.2, 48.9, 44.9, 37.7, 30.1, 25.7, 23.7; HRMS (FAB^+) calcd for $C_{22}H_{25}N$ $[M]^+$: 303.1987, found 303.1997, $C_{22}H_{25}N$.

4.5. Methyl 3-hydroxy-2-methylene-7,7-diphenylhept-6-enoate (15)

Methyl acrylate (0.46 mL, 5.11 mmol), methanol (0.13 mL, 3.08 mmol), and quinuclidine (0.12 g, 1.08 mmol) were added to the known[56] 5,5-diphenylpent-4-enal (1.00 g, 4.24 mmol) at room temperature. The mixture was stirred for 3 days, at which point TLC indicated completion. Solvent was evaporated under reduced pressure, and the crude product was subjected to flash chromatography to give acrylate **15** (1.35 g, 4.18 mmol, 98%). ^1H NMR (400 MHz, $CDCl_3$): δ 7.37–7.15 (10H, m), 6.16 (1H, s), 6.08 (1H, t, J=7.2 Hz), 5.71 (1H, s), 4.40–4.35 (1H, m), 3.74 (3H, s), 2.32–2.15 (2H, m), 1.87–1.70 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 142.7, 142.4, 142.2, 140.1, 129.9, 128.9, 128.3, 128.2, 127.3, 127.1, 127.0, 125.2, 71.1, 51.9, 36.4, 26.2; HRMS (FAB^+) calcd for $C_{21}H_{23}O_3$ $[M+H]^+$: 323.1642, found 323.1661, $C_{21}H_{23}O_3$.

*4.5.1. Methyl 2-benzhydryl-5-hydroxy-1-methylcyclopentanecarboxylate (**16**)*

To diene **15** (10 mg, 0.031 mmol) and hexamethyltrissiloxane (0.074 M, 23 μL) in C_6D_6 (1.16 mL) was added $(dppe)(CO)_4VH$ (35 mg, 0.062 mmol). The reaction mixture was set at room temperature until completion (3 h) to give cyclopentanol **16** as a mixture of diastereomers (70%, determined by NMR). Isolated product from preparative runs with 7 mol% $CpCr(CO)_3H$ was characterized. HRMS (FAB^+) calcd for $C_{21}H_{25}O_3$ $[M+H]^+$: 325.1798, found 325.1796, $C_{21}H_{25}O_3$.

*4.5.2. Methyl 2-benzhydryl-1-methyl-5-oxocyclopentanecarboxylate (**17**)*

Jones reagent was added dropwise to a mixture of cyclopentanol diastereomers **16** (67 mg, 0.21 mmol) dissolved in acetone (1.75 mL) until the orange color remained. 2-Propanol was added until the solution turned green. Water was added and the reaction mixture was extracted with ether. The collected organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give a separable mixture of cyclopentanone diastereomers **17a** (24 mg, 0.074 mmol), **17b** (15 mg, 0.046 mmol, 57% combined yield). ^1H NMR (400 MHz, $CDCl_3$) δ major product: 7.37–7.16 (10H, m), 3.76–3.73 (2H, m), 3.34 (3H, s), 2.39–2.35 (2H, m), 1.91–1.84 (1H, m), 1.54–1.52 (1H, m), 1.18 (3H, s); minor product: 7.37–7.16 (10H, m), 3.90 (1H, d, J=15.2 Hz), 3.72 (3H, s), 3.03–2.93 (1H, m), 2.60–2.50 (1H, m), 2.33–2.20 (1H, m), 1.92–1.85 (2H, m), 0.871 (3H, s). Proposed stereochemistry confirmed by 2D NOESY.

4.6. (*E*)-Methyl 3-hydroxy-6-methyl-2-methyleneoct-6-enoate (18)

Methyl acrylate (0.26 mL, 2.89 mmol), methanol (73 μL, 1.80 mmol), and quinuclidine (67 mg, 0.60 mmol) were added to the known[74,75] (*E*)-4-methylhex-4-enal (0.27 g, 2.4 mmol). The mixture was stirred for 2 days until completion based on TLC at which point the solvents were evaporated. Flash chromatography gave the desired acrylate **18** (0.372 g, 1.87 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.19 (1H, s), 5.78 (1H, s), 5.24–5.21 (1H, m), 4.35 (1H, br), 3.74 (3H, s), 2.76 (1H, br), 2.10–1.98 (2H, m), 1.79–1.62 (2H, m), 1.57 (3H, s), 1.53 (3H, d, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.0, 142.7, 135.2, 125.0, 119.0, 71.2, 51.9, 35.9, 34.5, 15.6, 13.4; HRMS (FAB^+) calcd for $C_{11}H_{19}O$ $[M+H]^+$: 199.1329, found 199.1328, $C_{11}H_{19}O_3$.

4.7. Methyl 6-hydroxy-1,2-dimethyl-3-methylenecyclohexanecarboxylate (19)

To diene **18** (4.3 mg, 0.023 mmol) and hexamethyltrissiloxane (0.074 M, 18 μL) in C_6D_6 (1 mL) was added (dppe)$(CO)_4$VH (28 mg, 0.050 mmol). The reaction mixture was set at room temperature until completion (6 h) to give cyclohexanol **19** (15%, determined by NMR). Isolated product from preparative runs with 7 mol% $CpCr(CO)_3H$ was characterized. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.89 (1H, s), 4.67 (1H, s), 4.23–4.15 (1H, m), 3.75 (3H, s), 2.51 (1H, q, J=7.8 Hz), 2.39–2.32 (1H, m), 2.20–2.10 (1H, m), 1.90–1.82 (1H, m), 0.96 (1H, s), 0.91 (3H, d, J=6.6 Hz); LRMS ($APCI^+$) found $[M+H]^+$: 199.1.

4.8. Synthesis of tandem cyclization substrate

4.8.1. 6-Methylhept-6-ene-1,5-diol

A solution of tetrahydro-2*H*-pyran-2-ol[69] (0.81 g, 7.97 mmol) in THF (11 mL) was added dropwise to a solution of isopropenylmagnesium bromide in THF (0.50 M, 28.7 mL, 14.3 mmol) at 0 °C. After 20 min, more Grignard reagent was added (0.2 equiv) and the reaction was slowly warmed to room temperature. Upon completion as indicated by TLC, the reaction mixture was poured into a saturated NH_4Cl solution and extracted several times with ether. The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude diol was used in the subsequent step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.93 (1H, s), 4.83 (1H, s), 4.06 (1H, t, J=6.4 Hz), 3.65 (2H, t, J=6.4 Hz), 1.71 (3H, s), 1.63–1.54 (6H, m).

*4.8.2. 7-(tert-Butyldiphenylsilyloxy)-2-methylhept-1-en-3-ol (**23**)*

To a solution of the crude diol from above (1.37 g, 9.51 mmol) in CH_2Cl_2 (10 mL) were added *tert*-butylchlorodiphenylsilane (12.2 mL, 47 mmol), Et_3N (6.6 mL, 47 mmol), and DMAP (60 mg, 0.50 mmol) at room temperature. The reaction mixture was stirred and monitored by TLC until completion (3 h). The reaction mixture was then diluted, saturated NH_4Cl solution was added, and the organic layer was separated. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Silica gel purification of the crude product gave the silyl ether **23** (2.97 g, 7.77 mmol, 97% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.65 (4H, m), 7.42–7.35 (6H, m), 4.93 (1H, s), 4.83 (1H, s), 4.04 (1H, t, J=6.4 Hz), 3.67 (2H, t, J=6.4 Hz), 1.71 (3H, s), 1.63–1.51 (6H, m), 1.05 (9H, s).

*4.8.3. (E)-Ethyl 9-(tert-butyldiphenylsilyloxy)-4-methylnon-4-enoate (**24**)*

Five drops of propionic acid were added to a mixture of the silyl ether **23** (1.24 g, 3.24 mmol) and triethyl orthoacetate (3.5 mL, 19.1 mmol) at room temperature. The reaction mixture was brought to reflux and monitored by TLC. After 1.5 h, the reaction mixture was cooled to room temperature, and placed under vacuum to remove excess triethyl orthoacetate. Silica gel chromatography of the crude mixture gave the ester **24** (2.00 g, 4.40 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71–7.69 (4H, m), 7.44–7.38 (6H, m), 5.17 (1H, t, J=7.2 Hz), 4.14 (2H, q, J=7.2 Hz), 3.68 (2H, t, J=6.4 Hz), 2.44–2.40 (2H, m), 2.36–2.30 (2H, m), 1.99 (2H, q, J=7.2 Hz), 1.61 (3H, s), 2.36–2.30 (2H, m), 1.47–1.40 (2H, m), 1.26 (2H, t, J=7.2 Hz), 1.08 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 135.4, 133.9, 133.2, 129.3, 127.4, 125.2, 63.6, 60.0, 34.5, 33.1, 32.0, 27.4, 26.7, 25.7, 19.0, 15.7, 14.1; HRMS (FAB^+) calcd for $C_{28}H_{41}O_3Si$ $[M+H]^+$: 453.2819, found 453.2819, $C_{28}H_{41}O_3Si$.

*4.8.4. (E)-9-(tert-Butyldiphenylsilyloxy)-4-methylnon-4-enal (**25**)*

To a solution of ester **24** (1.25 g, 2.77 mmol) in CH_2Cl_2 (4.5 mL) at −78 °C was added DIBAL (1.0 M in CH_2Cl_2, 2.77 mL) dropwise. When the reaction reached completion as indicated by TLC, EtOAc (10 μL) was added dropwise, followed by saturated Rochelle's solution (4.7 mL). The mixture was stirred vigorously overnight until two clear phases separated. The aqueous layer was then extracted with CH_2Cl_2 and the collected organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Silica gel purification gave the desired aldehyde **25** (1.00 g, 2.45 mmol, 88%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.75 (1H, s), 7.68–7.65 (4H, m), 7.42–7.35 (6H, m), 5.14 (1H, t, J=7.2 Hz), 3.65 (2H, t, J=6.4 Hz), 2.50 (2H, t, J=7.6 Hz), 2.31 (2H, t, J=7.6 Hz), 1.97 (2H, q, J=6.8 Hz), 1.54 (3H, s), 1.59–1.54 (2H, m), 1.44–1.38 (2H, m), 1.05 (9H, s).

*4.8.5. (E)-Methyl 11-(tert-butyldiphenylsilyloxy)-3-hydroxy-6-methyl-2-methyleneundec-6-enoate (**26**)*

To the neat aldehyde **25** (260 mg, 0.64 mmol) were added methyl acrylate (69 μL, 0.76 mmol), methanol (22 μL, 0.48 mmol), and quinuclidine (18 mg, 0.16 mmol) at room temperature. The mixture was stirred for 2 days until completion as indicated by TLC. The flask was placed under vacuum to remove excess solvent and purified by flash chromatography to yield the Baylis–Hillman adduct **26** (0.26 g, 0.52 mmol, 81%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.66 (4H, m), 7.42–7.36 (6H, m), 6.24 (1H, s), 5.81 (1H, s), 5.17 (1H, t, J=6.8 Hz), 4.41–4.36 (1H, m), 3.78 (3H, s), 3.66 (2H, t, J=6.4 Hz), 2.18–2.04 (2H, m), 1.98 (2H, q, J=7.2 Hz), 1.83–1.68 (2H, m), 1.59 (3H, s), 1.59–1.53 (2H, m), 1.44–1.37 (2H, m), 1.05 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.5, 142.5, 135.7, 134.6, 134.3, 129.6, 127.7, 125.5, 125.2, 71.6, 64.0, 52.0, 36.1, 34.6, 32.4, 27.8, 27.0, 26.1, 19.4, 16.1; HRMS (FAB^+) calcd for $C_{30}H_{43}O_4Si$ $[M+H]^+$: 495.2925, found 495.2932, $C_{30}H_{43}O_4Si$.

*4.8.6. (E)-Methyl 11-(tert-butyldiphenylsilyloxy)-3-(methoxymethoxy)-6-methyl-2-methyleneundec-6-enoate (**27**)*

To a solution of alcohol **26** (0.50 g, 1.01 mmol) in CH_2Cl_2 (2 mL) were added chloromethyl methyl ether (155 μL, 2.02 mmol), diisopropylethylamine (0.485 mL, 2.53 mmol), and $[Bu_4N]^+I^-$ (0.186 g, 0.5 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 1 h and then stirred overnight at room temperature. Upon completion, the mixture was diluted with CH_2Cl_2 and washed with 5% $NaHCO_3$ solution. The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash chromatography to give the methoxymethyl ether **27** (0.38 g, 0.70 mmol, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.65 (4H, m), 7.42–7.35 (6H, m), 6.31 (1H, s), 5.85 (1H, s), 5.14 (1H, t, J=6 Hz), 4.61–4.55 (2H, m), 4.49–4.44 (1H, m), 3.76 (3H, s), 3.65 (2H, t, J=6.3 Hz), 3.38 (3H, s), 2.14–2.03 (2H, m), 1.97 (2H, q, J=6.9 Hz), 1.86–1.64 (2H, m), 1.57 (3H, s), 1.57–1.52 (2H, m), 1.44–1.37 (2H, m), 1.04 (9H, s).

4.8.7. (E)-Methyl 11-hydroxy-3-(methoxymethoxy)-6-methyl-2-methyleneundec-6-enoate

A premixed solution of acetic acid (0.2 mL) and $[Bu_4N]^+F^-$ (1.0 M in THF, 3.48 mL) was added to **27** (0.38 g, 0.70 mmol) at 0 °C, and the solution allowed to stir overnight at room temperature. Upon completion, water was added and the aqueous layer was extracted with CH_2Cl_2. The collected organic fractions were washed with 5% $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography gave the free alcohol (0.16 g, 0.54 mmol, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.30 (1H, s), 5.85 (1H, s), 5.13 (1H, t, J=7.2 Hz), 4.60–4.55 (2H, m), 4.48–4.45 (1H, m), 3.76 (3H, s), 3.38 (3H, s), 3.63 (2H, t, J=6.6 Hz), 2.17–2.02 (4H, m), 1.90–1.54 (4H, m), 1.44–1.37 (2H, m), 1.60 (3H, s).

*4.8.8. (E)-Methyl 3-(methoxymethoxy)-6-methyl-2-methylene-11-oxoundec-6-enoate (**28**)*

To a solution of alcohol from above (0.16 g, 0.54 mmol) in CH_2Cl_2 (3.6 mL) were added $NaHCO_3$ (68 mg, 0.81 mmol) and Dess–Martin periodinane (0.46 g, 1.08 mmol) at room temperature. The reaction mixture was stirred vigorously for 1.5 h and then water was added. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were separately washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography gave the desired aldehyde **28** (80 mg, 0.27 mmol, 50%), along with some unreacted alcohol (19 mg). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.76 (1H, s), 6.30 (1H, s), 5.85 (1H, s), 5.13 (1H, t, J=7.6 Hz), 4.60–4.55 (2H, m), 4.48–4.45 (1H, m), 3.76 (3H, s), 3.38 (3H, s), 2.42 (2H, t, J=7.2 Hz), 2.18–2.11 (2H, m), 2.04 (2H, q, J=7.6 Hz), 1.85–1.76 (2H, m), 1.70–1.64 (2H, m), 1.59 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 203.0, 166.7, 141.4, 135.9, 125.6, 123.7, 95.2, 74.6, 56.0, 52.0, 43.5, 35.8, 34.4, 27.6, 22.5, 16.2; HRMS (FAB^+) calcd for $C_{16}H_{26}O_5Na$ $[M+Na]^+$: 321.1672, found 321.1694, $C_{16}H_{26}O_5Na$.

*4.8.9. (2E,7E)-Dimethyl 11-(methoxymethoxy)-8-methyl-12-methylenetrideca-2,7-dienedioate (**21**)*

To aldehyde **28** (80 mg, 0.27 mmol) in CH_2Cl_2 (0.9 mL) was added methyl (triphenylphosphoranylidene)acetate (90 mg, 0.27 mmol) at room temperature. The mixture was stirred overnight until completion was indicated by TLC. Solvent was evaporated at reduced pressure and the crude mixture was purified by preparative TLC (silica, 1 mm) to give the desired acrylate **21** (73 mg, 0.21 mmol, 76%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00–6.93 (1H, m), 6.30 (1H, s), 5.85 (1H, s), 5.81 (1H, d, J=14 Hz), 5.13 (1H, t, J=6.8 Hz), 4.60–4.55 (2H, m), 4.48–4.45 (1H, m), 3.76 (3H, s), 3.72 (3H, s), 3.38 (3H, s), 2.19 (2H, q, J=7.6 Hz), 2.01 (2H, q, J=8 Hz), 1.85–1.76 (2H, m), 1.70–1.62 (2H, m), 1.59 (3H, s), 1.50 (2H, qn, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.4, 166.6, 149.7, 141.5, 135.4, 125.5, 124.1, 121.1, 95.2, 74.6, 56.0, 51.9, 51.5, 35.7, 34.4, 31.8, 28.2, 27.4, 16.2; HRMS (FAB^+) calcd for $C_{19}H_{30}O_6Na$ $[M+Na]^+$: 377.1935, found 377.1941, $C_{19}H_{30}O_6Na$.

*4.8.10. Methyl 5-(2-methoxy-2-oxoethyl)-2-(methoxymethoxy)-1,4a-dimethyldecahydronaphthalene-1-carboxylate (**32**)*

A solution of $CpCr(CO)_3H$ (0.04 M in C_6D_6, 0.14 mL) was added to acrylate **21** (23 mg, 0.065 mmol) in C_6D_6 (0.41 mL) in a Fisher & Porter high pressure apparatus. The apparatus was charged with 30 psi H_2 and placed in a heat bath at 50 °C. The reaction mixture was stirred until completion as indicated by NMR (6 days). The solvent was evaporated and the crude product was subjected to flash chromatography to give decalin **32** (5.4 mg, 0.015 mmol, 23%). Alternatively, acrylate **21** (3.7 mg, 0.014 mmol) was mixed with $(dppe)(CO)_4VH$ (12 mg, 0.028 mmol) in C_6D_6 (0.6 mL) overnight to give decalin **32** (35%, determined by NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ major product: 4.57 (1H, dd, J=6.8, 52.4 Hz), 3.95 (1H, dd, J=4.4, 12 Hz), 3.68 (3H, s), 3.66 (3H, s), 3.28 (3H, s), 2.43 (1H, dd, J=3.2, 14.8 Hz), 1.16 (3H, s), 0.83 (3H, s); minor product: 4.57 (1H, dd, J=6.8, 52.4 Hz), 3.89 (1H, dd, J=4.4, 11.6 Hz), 3.72 (3H, s), 3.67 (3H, s), 3.29 (3H, s), 2.31 (1H, dd, J=8.4, 15.4 Hz), 1.16 (3H, s), 1.14 (3H, s).

*4.8.11. Methyl 2-hydroxy-5-(2-methoxy-2-oxoethyl)-1,4a-dimethyldecahydronaphthalene-1-carboxylate (**33**)*

One drop of concentrated HCl was added to decalin **32** (5.4 mg, 0.015 mmol) in MeOH (0.15 mL), and the vessel was heated to 65 °C until completion as indicated by TLC. The solvent was evaporated and the crude alcohol **33** was used in the subsequent step. ^{1}H NMR (400 MHz, $CDCl_3$) δ major product: 3.99 (1H, dd, J=4, 11.8 Hz), 3.70 (3H, s), 3.65 (3H, s), 2.43 (1H, dd, J=3.2, 14.8 Hz), 1.14 (3H, s), 0.82 (3H, s); minor product: 3.92 (1H, dd, J=5.2, 11 Hz), 3.7 (3H, s), 3.67 (3H, s), 2.32 (1H, dd, J=8.4, 15.4 Hz), 1.12 (3H, s), 1.1 (3H, s).

*4.8.12. Methyl 5-(2-methoxy-2-oxoethyl)-1,4a-dimethyl-2-oxodecahydronaphthalene-1-carboxylate (**34**)*

Jones reagent was added dropwise to the crude alcohol **33** (2.1 mg) from above dissolved in acetone (0.15 mL) until the orange color remained. 2-Propanol was added until the solution turned green. Water was added and the reaction mixture was extracted with ether. The collected organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give decalone **34** (1.3 mg, 4.1 μmol, 70% over two steps) after preparative TLC (silica, 500 μm). ^{1}H NMR (400 MHz, $CDCl_3$) δ major product: 3.72 (3H, s), 3.67 (3H, s), 2.69–2.32 (4H, m), 2.03–1.65 (5H, m), 1.48–1.39 (4H, m), 1.35 (3H, s), 0.99 (3H, s); minor product: 3.73 (3H, s), 3.68 (3H, s), 2.69–2.32 (4H, m), 2.03–1.65 (5H, m), 1.48–1.39 (4H, m), 1.32 (3H, s), 1.28 (3H, s); HRMS (FAB^+) calcd for $C_{17}H_{27}O_5$ $[M+H]^+$: 311.1853, found 311.1871, $C_{17}H_{27}O_5$.

4.9. (*E*)-*N*-Methoxy-*N*-4-dimethylhex-4-enamide

To a thin slurry of *N*,*O*-dimethylhydroxylamine hydrochloride (1.03 g, 10.58 mmol) in CH_2Cl_2 (90 mL) was added dimethylaluminum chloride (1.0 M in CH_2Cl_2, 10.6 mL) at 0 °C. The mixture was stirred for 1 h while warming to room temperature. Known[67] (*E*)-ethyl 4-methylhex-4-enoate (0.55 g, 3.53 mmol) was added dropwise. After 30 min, 35 mL of phosphate buffer (pH 8) was added and the aqueous layer was extracted with CH_2Cl_2. The collected organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was used in the subsequent step. ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.23 (1H, q, J=5.6 Hz), 3.66 (3H, s), 3.15 (3H, s), 2.49 (1H, t, J=7.6 Hz), 2.27 (2H, t, J=8.4 Hz), 1.60 (3H, s), 1.55 (1H, d, J=6.8 Hz).

4.10. (*E*)-2,6-Dimethylocta-1,6-dien-3-one (35)

To a solution of crude Weinreb amide **10** from above in THF (18 mL) was added isopropenylmagnesium bromide (0.5 M in THF, 14 mL) dropwise at −78 °C. The reaction mixture was stirred at 0 °C until completion as indicated by TLC. Saturated NH_4Cl solution was added and the mixture was extracted with ether. The combined organic fractions were washed with brine, dried over $MgSO_4$, filtered, and concentrated. Flash chromatography gave enone **35** (0.52 g, 3.41 mmol, 96% over two steps). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.93 (1H, s), 5.73 (1H, s), 5.23–5.17 (1H, m), 2.75 (2H, t, J=7.6 Hz), 2.26 (2H, t, J=7.6 Hz), 1.85 (3H, s), 1.59 (3H, s), 1.54 (3H, d, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 202.0, 144.6, 134.7, 124.4, 119.0, 36.4, 34.4, 17.8, 15.8, 13.4; LRMS ($APCI^+$) found $[M+H]^+$: 152.9.

4.11. (*E*)-2,6-Dimethyloct-6-en-3-one (37)

A solution of $CpCr(CO)_3H$ (0.04 M in C_6D_6, 0.625 mL) was added to diene **35** (55 mg, 0.36 mmol) in C_6D_6 in a Fisher & Porter high

pressure apparatus. The apparatus was charged with 30 psi H_2 and placed in a heat bath at 50 °C. The reaction mixture was stirred until completion as indicated by NMR. The solvent was evaporated and the crude product was subjected to flash chromatography to give ketone **36** (51 mg, 0.33 mmol, 92%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.23–5.17 (1H, m), 2.64–2.50 (3H, m), 2.22 (1H, t, J=8.1 Hz), 1.59 (3H, s), 1.55 (3H, d, J=6.6 Hz), 1.08 (3H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 214.7, 134.7, 119.0, 41.0, 39.2, 33.6, 18.4, 15.9, 13.5; HRMS (FAB$^+$) calcd for $C_{10}H_{18}O$ $[M]^+$: 154.1358, found 154.1369, $C_{10}H_{18}O$.

Acknowledgements

This work was supported by US Department of Energy Grant DE-FG02-97ER14807. The authors are grateful to Profs. M. Greenberg, S. Danishefsky, and W. van der Donk for helpful discussions.

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