Ruthenium-Catalyzed Synthesis of Butenolides and Pentenolides via Contra-Electronic α-Alkylation of Hydroxyalkynoates

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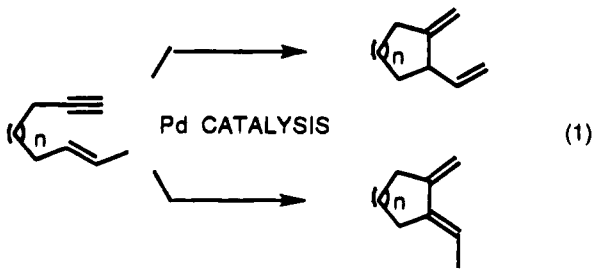
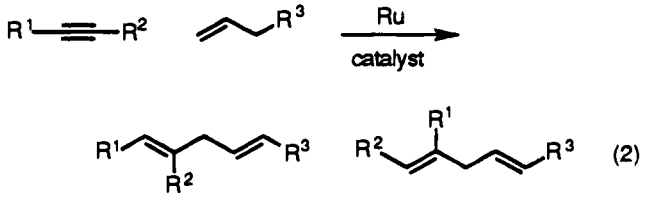
Abstract: The addition of alkenes to 4-hydroxy-2-alkynoates in an Alder−ene-type mode produces butenolides in the presence of a ruthenium catalyst. Among various ruthenium complexes, CpRu(COD)Cl appears to be most effective. The best results occur in aqueous DMF or methanol, with the latter preferred. The reaction proceeds with excellent chemoselectivity. Even nonreacting double bonds do not isomerize. The regioselectivity with respect to the alkene is with clean allyl inversion, i.e., in Alder−ene-type fashion. The regioselectivity with respect to the alkyne places the allyl group preferentially at the α-carbon in complete contrast to more normal behavior of alkynoates wherein β-alkylation strongly dominates. The sequence retains the stereochemical integrity of the propargylic position of the starting alkyne which becomes the 5-position of the product 2(5*H*)-furanones, a position prone to epimerization. Use of allyl alcohols as the alkene partners introduces a β-acylethyl group at the α-position of the butenolide, a net equivalent of a conjugate addition to a butenolide anion without requiring the very sensitive enones which are the normal Michael acceptors. The ready availability of 4-hydroxy-2-alkynoates by carbonyl addition of lithiated ethyl propiolate makes this approach to butenolides very practical. The addition of the latter to epoxides in the presence of $BF_3{\cdot}OEt_2$ provides ready access to 5-hydroxy-2-alkynoates. These substrates participate in a completely analogous fashion as above to form α-allylated and α-ketoethylated pentenolides. The mechanism of the reaction may be rationalized as invoking a ruthenacycle where coordinating and unusual electronic effects account for the observed selectivity. A synthesis of the simple acetogenin (+)-ancepsenolide results from commercially available 10-undecenal and methyl (*S*)-lactate in seven steps with 31% overall yield. This synthesis establishes the stereochemistry of this natural product as *S,S*.

Catalysis offers the prospect of realizing more of the potential of a formal Alder−ene reaction by expanding its scope and selectivity.[1] Initial efforts revolved around the use of Pd catalysis for the cycloisomerization of enynes.[2] The particular benefit of transition metal catalyzed versions is illustrated here since a process to form a 1,3-diene, which is structurally inaccessible via a thermal reaction, also evolved (eq 1).



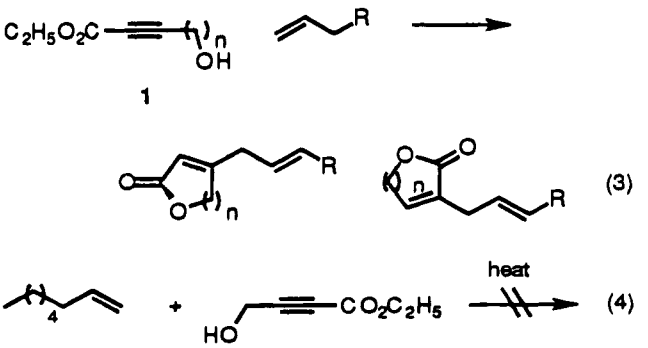
(1)

Extension to an intermolecular version succeeded when the catalyst was switched to ruthenium (eq 2).[1] An important issue is the question of regioselectivity with unsymmetrical acetylenes. With simple systems, steric factors appear to dominate.



(2)

The evolution of this process as a useful synthetic protocol requires a better definition of the factors that affect regioselectivity. Such studies are also important to provide an understanding of the mechanism of this reaction. We chose to explore these issues in the context of a new lactone synthesis according to eq 3 because (1) the substrates provide an opportunity to explore the competition of electronic, steric, and coordinative effects of substituents and (2) the products are important structural units of many biologically important molecules and versatile building blocks for further elaboration. The significance of a ruthenium-catalyzed process is emphasized by the failure of a thermal version as summarized in eq 4.



(3)

(4)

The Ru-catalyzed reaction of terminal alkenes and simple acetylenes is believed to involve a metallacycle such as **2**. If L

[⊗] Abstract published in *Advance ACS Abstracts,* January 15, 1995.

(1) For leading references, see: Trost, B. M.; Indolese, A. F.; Müller, T. J. J.; Treptow, B. *J. Am. Chem. Soc.*, in press.

(2) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34. For most recent references, see: Trost, B. M.; Romero, D. J.; Rise, F. *J. Am. Chem. Soc.* **1994**, *116*, 4268. Trost. B. M.; Tanoury, G. J.; Lautens, M.; Chan, C.; MacPherson, D. T. *J. Am. Chem. Soc.* **1994**, *116*, 4255.

(3) For a preliminary report of a portion of this work, see: Trost, B. M.; Müller, T. J. J. *J. Am. Chem. Soc.* **1994**, *116*, 4985.

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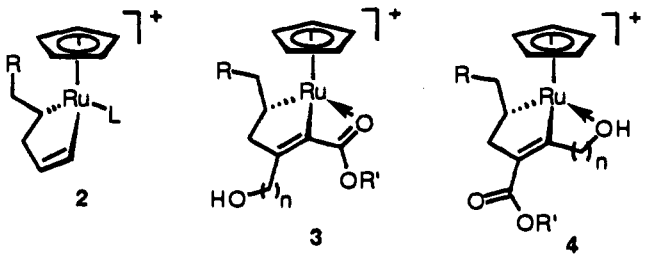
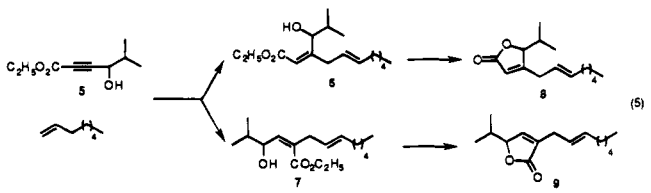
is a weakly coordinating ligand, its displacement by either the carbonyl oxygen as in **3** or hydroxyl oxygen as in **4** of the hydroxyalkynoate substrate **1** may be envisioned to play a significant role in determining the regioselectivity. On the other hand, the normal electronic bias for formation of new C−C bonds at the β-carbon of alkynoates should favor metallacycle **3**. In this paper, we (1) develop a butenolide and pentenolide synthesis with alkenes, (2) develop a variant with allyl alcohols to form (acylethyl)butenolides and -pentenolides, (3) establish that polarization of the alkyne does not play a significant role in these reactions, (4) establish the unusual regioselectivity, (5) establish the maintenance of the stereochemical integrity of the propargylic position, (6) illustrate the utility of this process in a simple synthesis of the simple acetogenin (+)-ancepsenolide which also establishes its absolute configuration.



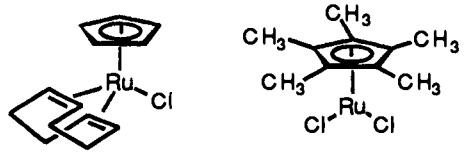
2 **3** **4**

Development of a Butenolide Synthesis. In order to develop a butenolide synthesis, the reaction of 1-octene and alkynoate **5** was chosen (eq 5). Using the ruthenium complex **10**[4] in

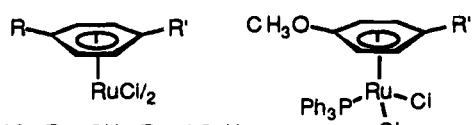


(5)

aqueous DMF (Table 1, entry 1) or methanol (Table 1, entry 3), which proved successful for the simple case, led to a mixture of the hydroxy ester **6** and the butenolide **9**. NMR spectroscopy clearly defines the structures of both products. For **6**, appearance



10 **11**



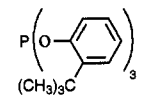
12 R = CH_3, R' = i-C_3H_7
13 R = OCH_3, R' = H

14

of the vinylic proton on the conjugated double bond as a singlet at δ 5.89 and the proton adjacent to the OH as a doublet (J = 5.0 Hz) coupled only to the isopropyl methine proton at δ 3.91 establishes the regiochemistry. An NOE between the vinyl proton at δ 5.89 and the protons of the doubly allylic methylene group at δ 3.04 and 3.48 establishes the Z geometry of the trisubstituted double bond. The 15.4 Hz coupling between the vinyl protons of the disubstituted double bond (δ 5.51 and 5.41) establishes its E geometry. For **9**, the appearance of its vinylic

(4) Albert, M. O.; Robinson, D. J.; Shaver, A.; Singleton, E. *Organometallics* **1986**, *5*, 2199.

Table 1. Effect of Reaction Parameters on Reaction of 1-Octene with Ethyl 4-Hydroxy-5-methyl-2-hexynoate (Eq 5)

entry	catalyst	solvent	additive	yield[a]	ratio[a]
1	**10**	DMF−H_2O		55	5.9
2	**10**	CF_3CH_2OH		59	2.3
3	**10**	CH_3OH		79	4.3 (6.7)[b]
4	**10**	CH_3OH		63	4.3
5	**10**	CH_3OH	$P(O\text{-}i\text{-}C_3H_2)_3$	64	5.4
6	**10**	CH_3OH	CO[c]	0	
7	**11**	CH_3OH		26	2.7
8	**12**	CH_3OH	NH_4PF_6	0	
9	**13**	CH_3OH	NH_4PF_6	0	
10	**14**	CH_3OH	NH_4PF_6	0	

[a] Yields and ratios based upon isolated products. [b] Ratio in parentheses based upon NMR spectrum of crude reaction mixture. [c] Reaction performed under 1 atm of CO.

Table 2. Variation of Substrates for Butenolide Synthesis (Eq 6)

entry	alkyne R^1	alkyne R^2	alkene R^3	isolated yield (%)	ratio **15**:**16**	compd no. suffix
1	H	H	CH_3CH_2	47	2.6[a]	**a**
2	CH_3	H	CH_3CH_2	83	4.5[b]	**b**
3	$(CH_3)_2CH$	H	CH_3CH_2	79	4.3[b] (6.7)[a]	**c**[d]
4	$-(CH_2)_4-$		CH_3CH_2	68	6.6[b]	**d**
5	$(CH_3)_3C$	CH_3	CH_3CH_2	60	only **15**	**e**
6	H	H	$CH_3O_2C(CH_2)_4$	51	2.9[a]	**f**
7	$(CH_3)_2CH$	H	$CH_3O_2C(CH_2)_4$	63	4.4[a]	**g**
8	$-(CH_2)_4-$		$CH_3O_2C(CH_2)_4$	67	12.2[b]	**h**
9	$-(CH_2)_4-$		$OHC(CH_2)_4$	80[c]	7.9[b]	i
10	$-(CH_2)_4-$		$HOCH_2(CH_2)_4$	71	only **15**	**j**
11	CH_3	H	$HOCH_2(CH_2)_4$	73	7.0[a]	**k**
12	CH_3	H	HO	53	4.9[a]	l
13	$(CH_3)_2CH$	H	$CH_3(CH_2)_7CH{=}CH$	59	only **15**	**m**

[a] Ratio determined by ^1H NMR spectroscopy. [b] Ratio determined by isolation of each pure product. [c] Product isolated as the dimethyl acetal. [d] Compound **15c** is the same as **8** and **16c** as **7**.

proton on the conjugated double bond at δ 6.97 as a dd (J = 1.6, 1.55 Hz) and the corresponding ^{13}C shift of this carbon at δ 146.8, as well as the signal for the proton on carbon-bearing oxygen at δ 4.66 as a dd (J = 5.8, 1.8 Hz), establish the regiochemistry. The 15.3 Hz coupling of the vinyl protons on the disubstituted double bond (δ 5.53 and 5.42) establish its E geometry. Neither **7** nor **8** has been detected.

The solvents that proved optimal in our previous work also are quite successful here. These regioselectivities appear to be minimal values since they were determined by isolation to be as close as possible to a synthetic protocol. Determining the regioselectivity on the initial crude reaction mixture in entry 3 showed the actual selectivity to be somewhat higher. In contrast to our previous work, methanol appears to be somewhat more beneficial than aqueous DMF. However, a significant change in regioselectivity occurs upon using the somewhat less polar trifluoroethanol although the yield remains good. Introduction of a phosphite ligand causes a slight enhancement of regioselectivity (Table 1, entry 5) if it is not too sterically demanding (Table 1, entry 4). On the other hand, introduction of CO shuts down reaction.

Using the sterically more demanding Cp*$RuCl_2$ (**11**)[5] slows reaction and decreases regioselectivity. The (arene)ruthenium complexes[6] either as their dimers (e.g., **12** and **13**)[7] or their monomers formed upon complexation with phosphine (e.g., **14**)[7]

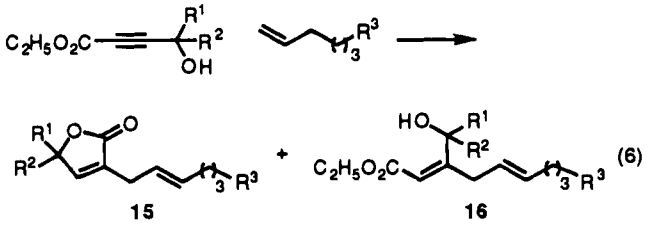
(5) Tilley, T. D.; Grubbs, R. H.; Bercaw, J. E. *Organometallics* **1984**, *3*, 274.

(6) For review, see: Le Bozec, H.; Touchard, D.; Dixneuf, P. H. *Adv. Organomet. Chem.* **1989**, *29*, 163.

(7) Bennett, M. A.; Smith, A. K. *J. Chem. Soc., Dalton Trans.* **1974**, *233*. Arthur, T.; Stephenson, T. A. *J. Organomet. Chem.* **1981**, *208*, 369.

failed to catalyze the reaction. Thus, use of complex **10** in methanol was adopted as our standard protocol.

The generality of this protocol was established with a variety of terminal alkenes and alkynes as summarized in eq 6 and Table 2. In each case, the reactions were performed using a 0.25 M solution of a 1:1 ratio of reactants with 5 mol % **10** in methanol at reflux for 3 h. The initial α-alkylation product always spontaneously lactonized to **15**, whereas the β-alkylation product **16** was always isolated uncyclized. This facilitated separation of the minor product chromatographically.

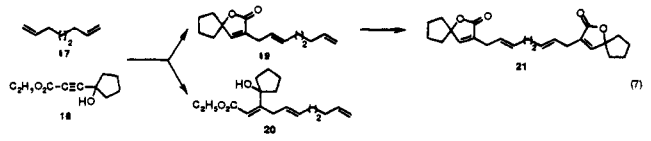


(6)

Perusal of Table 2 reveals the excellent chemoselectivity exhibited. Two examples require elaboration. A carboxaldehyde function undergoes *in situ* acetalization to give the dimethyl acetal of the product (entry 9). This simultaneous derivatization−butenolide annulation serves as an extra benefit since the aldehyde is then available either in a protected form or, if mild acid treatment is incorporated in the workup, as the free aldehyde. The much greater reactivity of the terminal alkene is illustrated by the compatibility of a disubstituted double bond (entry 13).

The good to excellent regioselectivity reflects the steric requirements of the propargylic position. Increasing steric hindrance increases the propensity for formation of the α-allylated butenolide **15** (α-alkylation) (cf. entries 1−5 and 6−8). Particularly noteworthy is the exclusive formation of the α-alkylation product **15** in the case of entry 13 (cf. entry 3). It appears that the second double bond not only did not have a negative effect on the chemoselectivity but that it had a significant positive effect on the regioselectivity.

An α,ω-diene in which both double bonds are monosubstituted may lead to bis-annulation (eq 7). Reacting a 1:1 ratio of diene **17** and alkyne **18** gave a 5.3:1:2 mixture of **19:20:21**. The 3:1 ratio of mono- to diannulation products indicates a significant rate difference for the second annulation. Thus, even with poly-monosubstituted alkenes, monoannulation can be synthetically useful. Increasing the alkyne to diene ratio to 2:1 produces a 5.3:1:13 mixture of **19:20:21** after the same time period of 3 h. In neither case was the diannulation product from the minor monoannulation product **20** isolated. Furthermore, the only isolated diannulation product was derived from bis-α-alkylation.


(7)

A Pentenolide Synthesis. The success of the butenolide synthesis and the easy availability of δ-hydroxy-α,β-alkynoates led us to pursue the prospect of a pentenolide synthesis (eq 8).

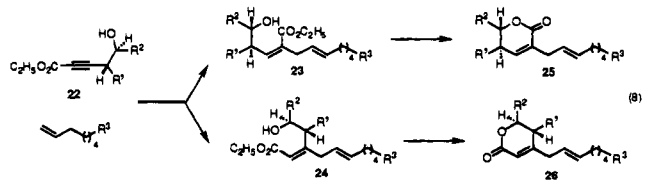
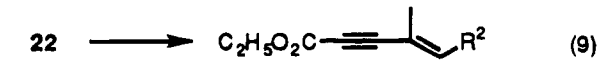

(8)

Table 3. Pentenolide Synthesis (Eq 8)

entry	alkyne R¹	alkyne R²	alkene R³	isolated yield[a] (%)	ratio[a] **25:26**	compd no. suffix
1	H	CH_3	CH_3	74	1.2	**a**
2	$-(CH_2)_4-$		CH_3	59	7.4	**b**
3	H	CH_3	$CH_3O_2C(CH_2)_3$	81	2.0	**c**
4	$-(CH_2)_4-$		$CH_3O_2C(CH_2)_3$	71	3.4	**d**

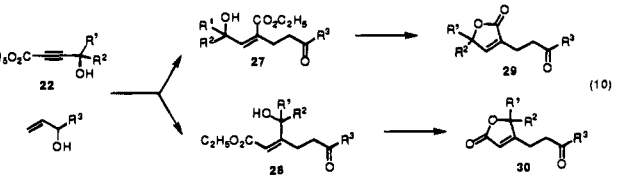
[a] Determined by isolation.

A major concern was the prospect for simple dehydration as in eq 9 arising from the activation provided by the alkynoate.


(9)

Gratifyingly, this fear proved totally unwarranted, again illustrating the chemoselectivity of the process. Using the same conditions as above (0.25 M solution of 1:1 ratio of alkyne **22** and alkene with 5 mol % **10** in methanol at reflux for 3 h) gave a mixture of **24** and **25** as the only isolated products as summarized in Table 3. As in the butenolide synthesis, the initial α-alkylation product **23** underwent spontaneous lactonization to **25**, whereas the β-alkylation product **24** showed no signs of lactonization to **26**. This differential rate of cyclization of the initial adducts greatly facilitated chromatographic separation of the regioisomers. The regioselectivity followed the same trend, with increasing steric hindrance strongly favoring the α-alkylation product.

Ketoethylation−Lactone Annulation. In considering the proposed metallacycle intermediates **3** and **4** in which the propargyl alcohol is envisioned to serve as a bidentate ligand, an intriguing question arises by introducing a competition for such coordination in the alkene partner. We previously proposed that an allyl alcohol serves as a bidentate coordinator toward ruthenium.[8,9] If the reaction of an allyl alcohol and a hydroxyalkynoate proceeds in similar fashion as above, the products will be keto lactones as illustrated in eq 10.[10]

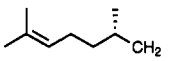
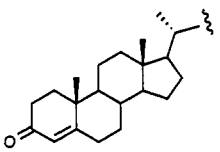

(10)

Our initial experiments examined the reaction of 3-buten-2-ol and ethyl 4-hydroxy-2-nonynoate Table 4, entry 1) with 4 mol % **10** as catalyst in 1:1 DMF/water at 60 °C. In contrast to the reactions of simple terminal olefins which were best performed in methanol, these reactions require the use of aqueous DMF for satisfactory results. Furthermore, only butenolides **29** and **30** were isolated. Neither hydroxy ester **27** nor **28** was detected. The steric effect of propargylic substituents was muted relative to the reactions with simple olefins although the trend is in the same direction.

This version of the butenolide annulation extrapolates to a pentenolide annulation as illustrated in eq 11. The same general conditions outlined above gave 62−65% isolated yields of the

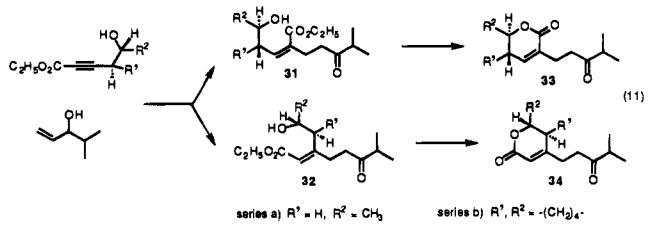
(8) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 5579.
(9) Trost, B. M.; Kulawiec, R. J. *J. Am. Chem. Soc.* **1993**, *115*, 2027.
(10) For some examples of similar behaviors in the Heck reaction of allyl alcohols, see: Larock, R. C.; Kuo, M. *Tetrahedron Lett.* **1991**, *32*, 569. Mandai, T.; Hasegawa, S.; Fujimoto, T.; Kawada, M.; Nokami, J.; Tsuji, J. *Synlett.* **1990**, *85*. Benhaddow, R.; Czernecki, S.; Ville, G. *Chem. Commun.* **1988**, 247. Yamada, F.; Hasegawa, T.; Wakita, M.; Sugiyama, M.; Somer, M. *Heterocycles* **1986**, *24*, 1223. Jeffrey, T. *J. Chem. Soc., Chem. Commun.* **1984**, 1287. Smadja, W.; Ville, G.; Cahiez, G. *Tetrahedron Lett.* **1984**, *25*, 1793. Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron* **1979**, *35*, 329.

Table 4. Ketoethylation–Butenolide Annulation[a]

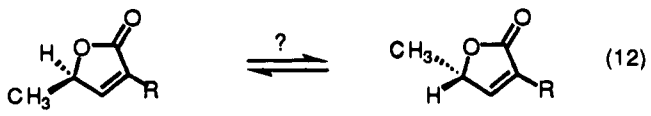
entry	alkyne R^1	alkyne R^2	alkene R^3	isolated yield (%)	ratio **29**:**30**	compd no. suffix
1[b]	*n*-C_5H_{11}	H	CH_3	59	4.4 (5.3)[c]	**a**
2	C_2H_5	$(CH_2)_4CO_2C_2H_5$	CH_3	66	4.5 (5.8)	**b**
3	H	H	$(CH_3)_2CH$	59	2.8 (3.7)	**c**
4	CH_3	H	$(CH_3)_2CH$	78	5.0 (4.1)	**d**
5	$(CH_3)_2CH$	H	$(CH_3)_2CH$	64	3.6 (4.7)	**e**
6		$-(CH_2)_4-$	$(CH_3)_2CH$	86	5.7 (7.4)	**f**
7	$(CH_3)_3C$	CH_3	$(CH_3)_2CH$	35	7.8 (7.3)	**g**
8	CH_3	H		49	3.1 (3.8)	**h**
9		$-(CH_2)_4-$		44	3.0	**i**

[a] All reactions performed with 5 mol % **10** in 1:1 DMF water at 100 °C for 2 h unless otherwise noted. [b] 4 mol % **10** at 60 °C. [c] Ratios derive from isolation of each butenolide. Ratios in parenthess were determined by ^1H NMR spectroscopy.

hydroxy esters **31** and **32** in ratios of 3.1 (series **a**) and 4.2 (series **b**) unaccompanied by *in situ* lactonization as observed in all previous cases for adducts analogous to **31**. Heating the initial adducts in benzene at reflux in the presence of 3 Å molecular sieves effects lactonization. In the case of series **b**, the two-step protocol from allyl alcohol and hydroxyalkynoate gave overall 40% isolated yield of lactone **33** and 16% isolated yield of lactone **34**.

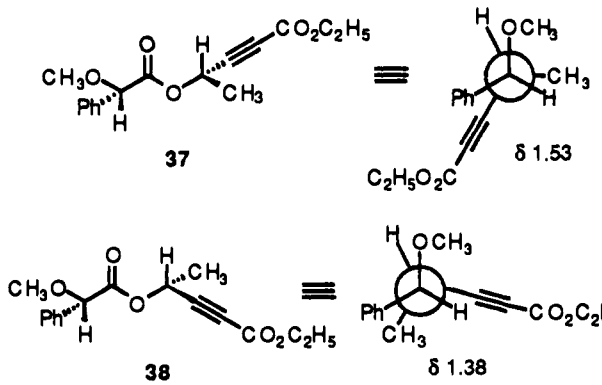


Stereochemistry of Propargyl Position. The direct generation of butenolides raises the specter of racemization under the reaction conditions because of the anticipated high acidity of (5*H*)-furanones especially in polar protic media like methanol. However, the synthetic utility would be greatly expanded if this stereogenic center remained unscathed. To test this propensity in the most synthetically meaningful way possible, as well as for subsequent synthetic objectives, we examined the methyl-substituted derivatives shown in eq 12.

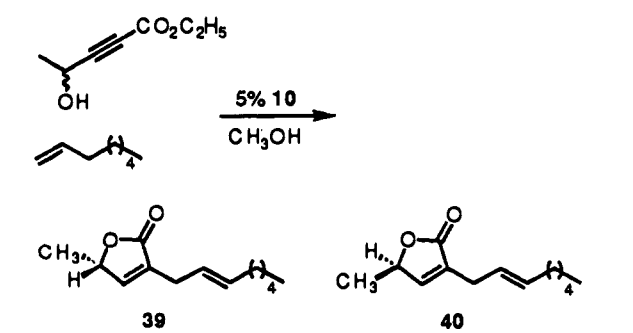


Enantiomerically pure ethyl (*S*)-4-hydroxy-2-pentynoate is readily available from the well-known TBDMS ether of (*S*)-lactaldehyde, itself derived in two steps from commercially available methyl (*S*)-lactate as outlined in Scheme 1.[11] Dibromomethylenation with triphenylphosphine and carbon tetrabromide provided the olefin **35**. Treatment with 2.4 equiv of *n*-butyllithium formed the lithium acetylide,[12] which was directly capped by adding ethyl chloroformate. Without purification, the product was worked up with aqueous acetic acid in warm THF to remove the TBDMS group to give the desired hydroxyalkynoate **36**. The overall yield of the latter from methyl (*S*)-lactate was 43%.

The prospect of racemization at several stages of the synthesis, particularly during the formation and subsequent olefination of the lactaldehyde, required the establishment of the enantiomeric purity of **36**. In order to do so, we prepared the racemic version of **36** and converted it to its *O*-methylmandelate esters **37** and **38**, which clearly show the expected chemical shifts for the secondary methyl groups with the *S,S*-isomer **37** at lower field than the *S,R*-isomer **38**.[13] Converting the alkynoate **36** from methyl (*S*)-lactate to the *O*-methylmandelate ester showed no detectable signals for **38** indicating that it possessed >95% ee.



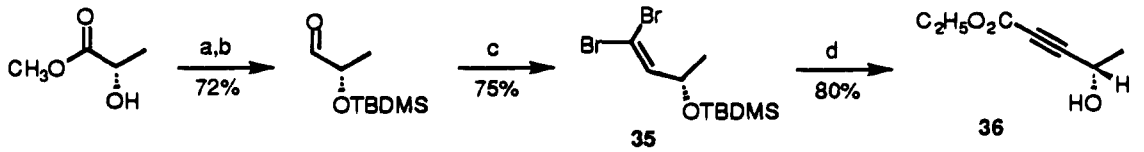
Reaction of racemic ethyl 4-hydroxy-2-pentynoate with 1-octene gave the corresponding butenolide as a racemate, **39** and **40** (eq 13). Using Eu(hfbc)$_3$, the methyl doublet at δ 1.39



nicely resolves into two distinct doublets between 0.25 and 0.40 equiv of shift reagent (e.g., δ 1.90 and 1.88 at 0.35 equiv). Performing the same reaction with enantiomerically pure **36**

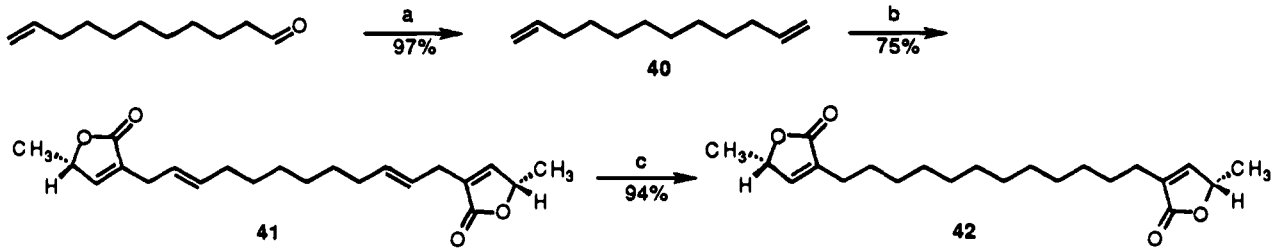
(11) Massad, S. K.; Hawkins, L. D.; Baker, D. C. *J. Org. Chem.* **1983**, *48*, 5180.
(12) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, *36*, 3769.
(13) Trost, B. M.; Belletire, J. L.; Godleski, S. A.; McDougal, P. G.; Balkovec, J. M.; Baldwin, J. J.; Christy, M. E.; Ponticello, G. S.; Varga, S. L.; Springer, J. P. *J. Org. Chem.* **1986**, *56*, 2370.

Scheme 1. Synthesis of Ethyl (*S*)-4-Hydroxy-2-pentynoate[a]



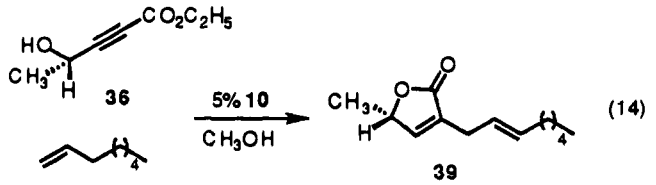
[a] (a) TBDMSCl, $(C_2H_5)_3N$, DMAP, THF; (b) DIBAL−H, hexane, −78 °C; (c) Ph_3P, CBr_4, CH_2Cl_2, −78 °C to room temperature; (d) *n*-C_4H_9Li, THF, −78 °C add $ClCO_2C_2H_5$, work up with THF, H_2O, HOAc, 60−70 °C.

Scheme 2. Synthesis of (+)-Ancepsenolide[a]



[a] (a) Ph_3PCH_3Br, *n*-C_4H_9Li, THF, −78 °C; (b) 10 mol % **10**, **36**, CH_3OH, reflux; (c) 10 mol % $(Ph_3P)_3RhCl$, 1 atm of H_2, PhH−C_2H_5OH (1:1), room temperature.

gave the corresponding butenolide **39**, which showed no detectable signals for the enantiomer **40** performing the same ^1H NMR shift study as in eq 14. Thus, the ruthenium-catalyzed



(14)

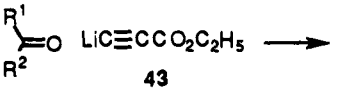
butenolide annulation fully maintains the stereochemical integrity of the propargylic position during and after its transition to the 5-position of the 2(5*H*)-furanone.

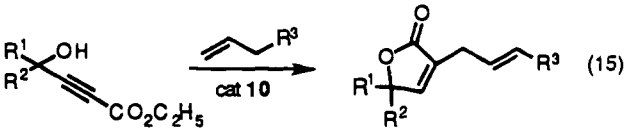
Synthesis of (+)-Ancepsenolide. The acetogenins represent a growing class of natural products whose biological activity, which includes cytotoxicity and antitumor, antimalaria, and immunosuppression activity, has generated great excitement.[14] Their structures typically possess a terminal butenolide attached to a long aliphatic chain punctuated by oxygen substituents. One of the earliest and simplest acetogenins, (+)-ancepsenolide (**42**), had its gross structure established but, prior to this work, was of unknown absolute configuration.[15,16] Furthermore, its reported rotation has varied from 7.7° to 47.6°. To further explore the role of a remote olefin substituent on regioselectivity, to develop a simple protocol to acetogenins, and to establish the absolute configuration of one of the earliest members of this class of compounds, we embarked upon a synthesis of (+)-ancepsenolide as outlined in Scheme 2.

Commercially available 10-undecenal was subjected to standard olefination to form 1,11-dodecadiene. Ru-catalyzed butenolide annulation using a 2.3:1 ratio of **36** to **40** gave rise to the bis-annulated product **41**, $[\alpha]_D$ 38.7° (*c* 1.8, $CHCl_3$), with no other regioisomers observed. Catalytic hydrogenation with Pd/C gave only over-reduction, whereas Wilkinson's catalyst in benzene or 3:1 benzene/ethanol gave mostly starting material. On the other hand, the latter catalyst in 1:1 benzene/ethanol gave smooth reduction to form (+)-ancepsenolide, mp 95.5−97.5 °C (lit.[15] mp 93−4 °C), $[\alpha]^{25}_D$ 39.6° (*c* 0.4, $CHCl_3$). The sign of rotation of the synthetic sample derived from (*S*)-lactic acid corresponds to that of the natural product, thereby establishing the configuration as *S*,*S*.

Discussion

The ruthenium-catalyzed addition of terminal alkenes with 4- and 5-hydroxy-2-alkynoates provides ready access to both butenolides and pentenolides. The ready availability of the acetylenic precursors via the reactions of lithiated ethyl propiolate (**43**)[17] imparts simplicity to this annulation protocol. Thus, α-allylated butenolides readily derive from aldehydes and ketones as outlined in eq 15. The addition of **43** to aldehydes





(15)

and ketones proceeded smoothly via the protocol of Midland et al.[17] Although **43** is thermally unstable, it readily opened epoxides in the presence of $BF_3{\cdot}OEt_2$[18] presumably in an S_N2 fashion as shown in eq 16. Propylene oxide reacts only at the primary carbon to give adduct **44** ($R^1 = CH_3$, $R^2 = H$) in 64% yield. Cyclohexene oxide gives only the *E* isomer as revealed by the 9.5 Hz coupling between H_a and H_b of **44**, $R^1,R^2 = (CH_2)_4$, in 89% yield. Thus, α-allylated pentenolides now derive in two steps from epoxides. To the extent the epoxides are available in enantiomerically pure form, this protocol constitutes an asymmetric synthesis of these useful lactones.

Employing an allyl alcohol as an alkene substrate provides a most useful extension of this protocol. Since the initial allylated

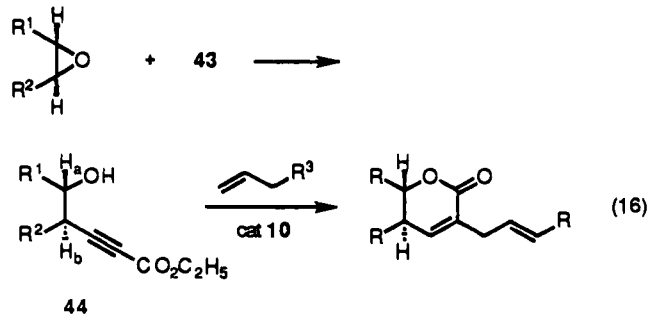
(14) Rupprecht, J. K.; Hui, Y.-H.; McLaughlin, J. L. *J. Nat. Prod.* **1990**, *53*, 237. Fang. X.-P.; Rieser, M. J.; Gu, Z.-M.; Zhao, G.-X.; McLaughlin, J.L. *Phytochem. Anal.* **1993**, *4*, 27. Reiser, M. J.; Hui, Y.-H.; Rupprecht, J. K.; Kozlowski, J. F.; Wood, K. V.; McLaughlin, J. L.; Hanson, P. R.; Zhuang, Z.; Hoye, T. R. *J. Am. Chem. Soc.* **1992**, *114*, 10203.

(15) Schmitz, F. J.; Lorance, E. D. *J. Org. Chem.* **1971**, *36*, 719. Schmitz, F. S.; Lorance, E. D.; Ciereszko, L. S. *J. Org. Chem.* **1969**, *34*, 1989. Schmitz, F. J.; Kraus, K. W.; Ciereszko, L. S.; Sifford, D. H.; Weinheimer, A. J. *Tetrahedron Lett.* **1966**, 97. Also see: Pawlik, F. J.; Fenical, W. *Mar. Ecol.: Prog. Ser.* **1992**, *87*, 183.

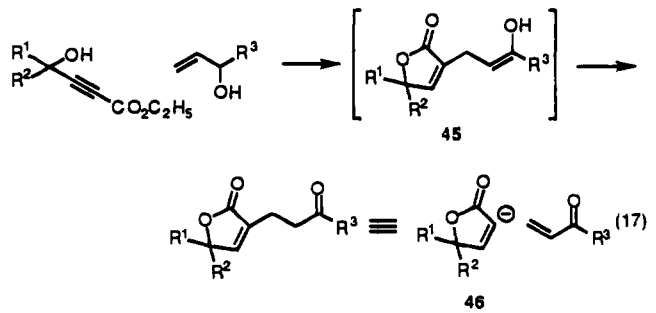
(16) For a synthesis of the racemate, see: Podraza, K. F.; Sneden, A. T. *J. Nat. Prod.* **1985**, *48*, 792.

(17) Midland, M. M.; Tramatano, A.; Cable, J. R. *J. Org. Chem.* **1980**, *45*, 28.

(18) See: Yamaguchi, M.; Hirao, I. *Tetrahedron Lett.* **1983**, *24*, 391. Anorbe, B.; Martin, V. S.; Palazón, J. M.; Triyillo, J. M. *Tetrahedron Lett.* **1986**, *27*, 4991. Soll, R. M.; Seitz, S. P. *Tetrahedron Lett.* **1987**, *28*, 5457. Askin, D. A.; Angst, C.; Danishefsky, S. *J. Org. Chem.* **1987**, *52*, 622. Kluge, A. F.; Kertesz, D. J.; Yang, C. O.; Wu, H. Y. *J. Org. Chem.* **1987**, *52*, 2860.

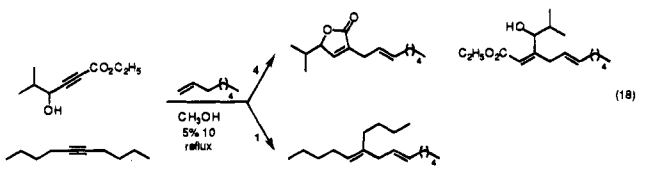


product **45** is an enol, it spontaneously tautomerizes to the keto butenolide as shown in eq 17 and analogously for the keto



pentenolide synthesis of eq 10. This reaction constitutes the equivalent of a Michael addition of the butenolide anion **46** to an α,β-unsaturated ketone.[10] The inaccessibility of Michael donors like **46** and the sensitivity of enones makes this ruthenium-catalyzed protocol quite attractive.

The reaction exhibits a high steric sensitivity with respect to the alkene, a fact that leads to high chemoselectivity for reaction with terminal alkenes in the presence of any other olefinic linkage. On the other hand, the reaction proceeds with a wide variety of acetylenes. To compare the effect of the polar substituents flanking the triple bond in this annulation protocol to a simple disubstituted acetylene, 5-decyne competed with ethyl 4-hydroxy-5-methyl-2-hexynoate as shown in eq 18. While



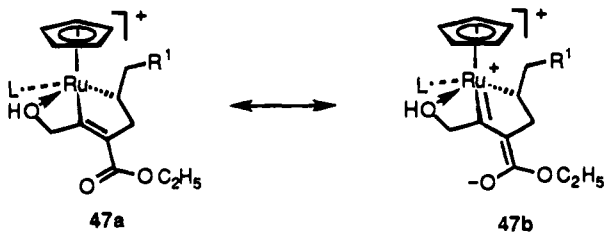
the polarized acetylene showed enhanced reactivity relative to a simple acetylene, the difference was not dramatic. To the extent that the increased steric hindrance associated with the hexynoate mitigates its reactivity, it will reduce this ratio. Nevertheless, the competition reveals that simple electronic effects do not exert a powerful influence on this reaction.

A most remarkable feature of this reaction is the regioselectivity. The reaction proceeds with clean allyl rearrangement with respect to the alkene (i.e., analogous to an Alder–ene process).[19] Strikingly, the reaction preferentially introduces the new C–C bond at the α-carbon of the alkynoate in complete opposition to the normal behavior of alkynoates even in the Alder–ene reaction.[20]

(19) Snider, B. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Paquette, L. A., Eds.; Pergamon Press: Oxford, U.K., 1991; Vol. 5, pp 1–28.

(20) For a similar regioselectivity in a palladium-catalyzed carbametallation–reduction sequence to butenolides, see: Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron* **1988**, *44*, 481.

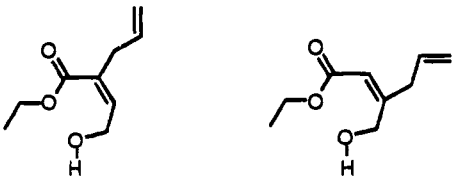
The ruthenacycle mechanism discussed for the simple acetylenes and outlined in Scheme 3 for the present case rationalizes most of the present results. Additional ligation may trigger the tautomerization of the initial enyne complex to the metallacycle. The most puzzling aspect to rationalize is the preference for path a in spite of the normal electronic bias of alkynoates to direct nucleophilic attack to the β-carbon. With simple alkynes, increasing steric hindrance at the propargylic position increased the propensity for C–C bond formation at the acetylenic carbon distal to that position.[1] This same trend is observed here in that increased steric hindrance at the propargylic position favors path a over path b. However, this argument seems insufficient to account for the higher selectivity observed here in comparison to a propargyl alcohol or a propiolate alone. There appears to be a synergistic effect of having both functionalities in the same substrate. A possible explanation may derive from an enhancement of the coordination of the hydroxyl group because of increased electrophilicity of ruthenium as a result of its conjugation with the ester represented in resonance structures **47a** and **47b**. The effect of solvent polarity on regioselectivity



is accommodated by this explanation. This coordination requires dissociation of chloride from ruthenium. In the less polar solvent, such ionization would be disfavored, therefore precluding coordination of the hydroxyl substituent. This electronic effect that may stabilize the 3-(ethoxycarbonyl)-ruthenacyclopentene compared to a 2-(ethoxycarbonyl)ruthenacyclopentene may account for the regiochemistry of a simple alkynoate such as methyl butynoate. Whereas steric effects should favor β-alkylation in that case, this electronic effect will favor α-alkylation. With neither effect dominating, the result is a nearly 1:1 regioisomeric mixture as observed.

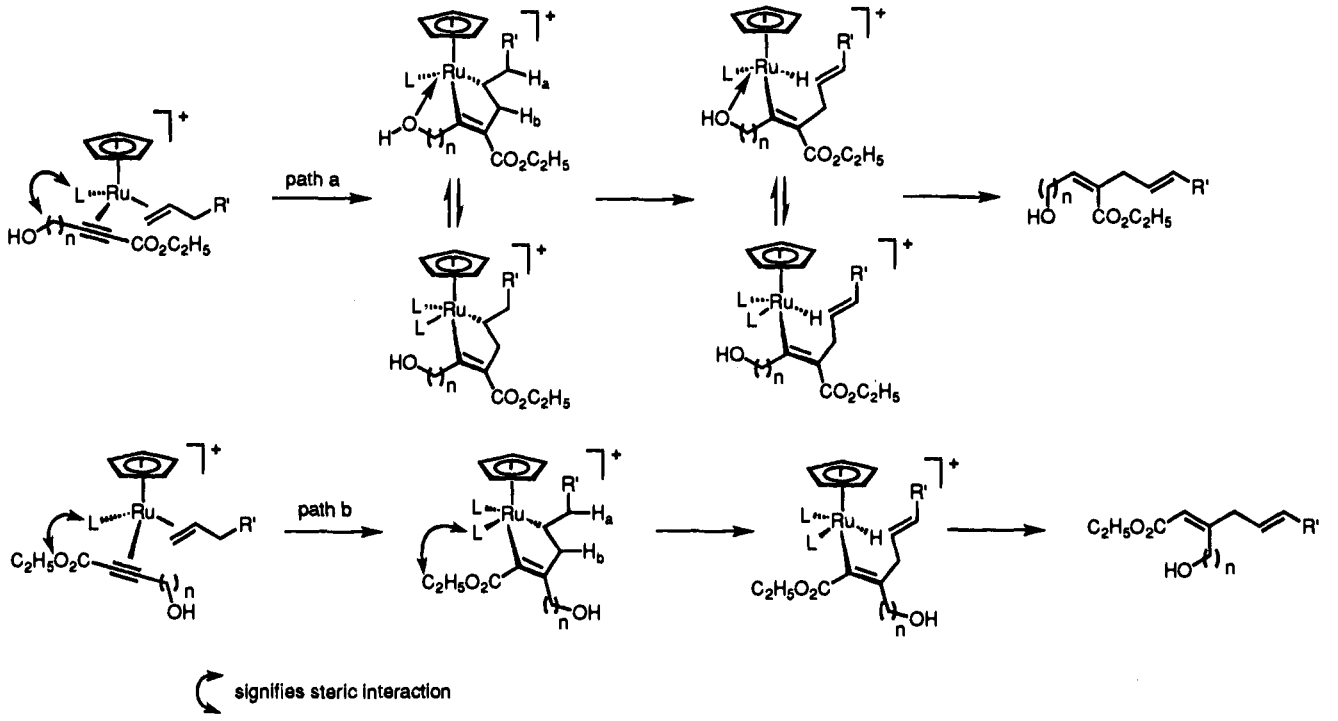
Collapse of the metallacycle by β-hydrogen elimination followed by reductive elimination as illustrated in Scheme 3 completes the sequence. The geometrical constraints imposed by the metallacycle preclude ready attainment of the required geometry for elimination of H_b whereas there are no geometrical constraints for elimination of H_a. Thus, only 1,4-dienes are observed as products. To probe the integrity of the purported ruthenium hydride intermediate, we performed the addition of 1-octene with ethyl 4-hydroxy-5-methyl-2-hexynoate (eq 5) in CD_3OD. No deuterium incorporation in either product was detected. Thus, reductive elimination is much faster than exchange of ruthenium hydride with solvent.

An intriguing ancillary question is the observation that the α-alkylated products directly lactonize but that the β-alkylated products do not. Molecular mechanics calculations using a



CAChe program on model systems **48** and **49** in the conformation required for lactonization as depicted (i.e., hydroxyl group

Scheme 3. A Rationale for Ru-Catalyzed Lactone Annulation



to approach carbonyl group at approximately the Burgi–Dunitz angle) indicate that **48** is more stable than **49** by 3.0 kcal/mol. Thus, the α-allylated product can more readily adopt the conformation necessary for cyclization, which will likely be reflected in the activation energies for the two cyclizations. While we cannot exclude a role for ruthenium in causing this difference, the fact that the initial uncyclized adducts are isolated for both isomers in eq 11 leads us to believe the simple explanation. A practical consequence of this rate difference is the ease by which the minor isomer is separated from the major isomer in those cases where both are formed.

In developing synthetic methodology, attention must focus on the twin issues of selectivity and atom economy. This ruthenium-catalyzed synthesis of butenolides and pentenolides does just that. Good chemo-, regio-, and diastereo- (in terms of olefin geometry) selectivity are observed. Transition metal catalysts may change the rules of selectivity. That is the case here with respect to regioselectivity. Thus, the usual preference for β-alkylation is reversed, with α-alkylation now dominating. A potentially easily epimerizable stereocenter maintains its stereointegrity. The process involves a simple addition of alkenes to 4- or 5-hydroxy-2-alkynoates with only the loss of a molecule of ethanol, a reasonably atom-economical reaction. Of special interest is the direct reaction of allyl alcohols to introduce an acylethyl group. By precluding the need to oxidize the allyl alcohol, which is readily available by simple carbonyl addition reactions, to an enone in order to achieve this oxidation level, enhanced synthetic efficiency as well as improved ease of operation by precluding the need to handle very sensitive enones also results. In this regard, this ruthenium-catalyzed reaction is analogous to the Heck reaction with allyl alcohols.[11] It appears that this facile new process should prove valuable in synthetic designs. One immediate application has been in the synthesis of acetogenins which are normally characterized by the presence of a 2-alkyl-4(*S*)-methylbutenolide (3-alkyl-5(*S*)-methyl-2(5*H*)-furanone). The synthesis of (+)-ancepsenolide reported herein illustrates the strategic simplification possible by the advent of this new annulation protocol. Thus, this ruthenium-catalyzed reaction expands the scope of the Alder–ene reaction not only by allowing a reaction to proceed that fails thermally but also by changing the rules of selectivity as a result of the metal making its imprint on the reaction pathway.

Experimental Section

Reactions were generally conducted under a positive pressure of dry nitrogen in glassware which had been flame-dried under a stream of dry nitrogen. Reaction flasks were sealed with red rubber septa and, unless otherwise mentioned, were magnetically stirred. Anhydrous solvents and reaction mixtures were transferred by oven-dried syringe or cannula. Flash chromatography employed E. Merck silica gel (Kieselgel 60, 230–400 mesh). Analytical TLC was performed with 0.2 mm coated commercial silica gel plates (E. Merck, DC-Plastikfolien, Kieselgel $60F_{254}$). ^1H NMR spectra were obtained and recorded from Gemini GEM-200 (200 MHz), Nicolet NT-300 (300 MHz), or Varian XL-400 (400 MHz) instruments with TMS as internal standard. ^{13}C NMR spectra were recorded on a Nicolet NT-300 (75 MHz) or a Varian XL-400 (100 MHz) instrument. Chemical shifts are reported in δ units, parts per million from the central peak of $CDCl_3$ (δ = 77.0) as an internal reference. IR spectra were performed by the NIH Mass Spectral Facility at the School of Pharmacy, University of California–San Francisco, on a Kratos MS-90 instrument with an ionizing current of 98 mA and an ionizing voltage of 70 eV. Microanalyses were performed by M-H-W Laboratories, Pheonix, AZ.

Ruthenium-Catalyzed Condensations of Terminal Alkenes and Ethyl 4-Hydroxy-2-alkynoates. General Procedure. Alkene, ethyl 4-hydroxy-2-alkynoate,[11] and degassed methanol were added by syringe to CpRu(COD)Cl under nitrogen. The resulting mixture was heated to reflux for 3 h. The cooled reaction mixture was diluted with 20 mL of ether and filtered through a short plug of silica gel. The solution was evaporated *in vacuo*, and the residue was purified by chromatography on silica gel. The details for each run are summarized in Table 5.

Characterization Data for Products of Table 5. 15a and 16a: IR (neat) 3480, 1756, 1714, 1652, 1452, 1348 cm^{-1}. **15a**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (t, J = 1.7 Hz, 1H), 5.32–5.60 (m, 2H), 4.74 (dt, J = 2.0, 2.1 Hz, 2H), 2.94 (d, J = 5.7 Hz, 2H), 1.92–2.02 (m, 2H), 1.19–1.35 (m, 6H), 0.85 (t, J = 6.9 Hz, 3H). Additional signals for **16a**: 5.95 (s, 1H), 4.15 (s, 2H), 4.14 (q, J = 7.1 Hz, 2H), 3.22 (d, J = 6.3 Hz, 2H), 0.83 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.09, 144.61, 134.21, 133.65, 124.09, 70.22, 32.37, 31.31, 28.91, 28.50, 22.44, 13.99. Additional signals for **16a**: 166.40, 159.29, 133.11, 125.82, 124.09, 113.54, 65.15, 59.71, 32.76, 28.97, 14.22. HRMS. Calcd for $C_{12}H_{18}O_2$ (**15a**): 194.1306. Found: 194.1287. Calcd for $C_{14}H_{24}O_3 - H_2O$ (**16a**): 222.1620. Found: 222.1622.

Table 5. Experimental Details for Table 2

entry	alkene (mg, mmol)	hydroxy ynoate (mg, mmol)	Cp(COD)RuCl (mg, mmol)	MeOH (mL)	yield (mg, %)		R_f (% EtOAc in hex)		compd no. suffix
					15	**16**	**15**	**16**	
1	57.7, 0.51	65.0, 0.51	7.9, 0.0255	4	50.0 (47)		0.28(14)	0.28(14)	**a**
2	58.1, 0.52	74.2, 0.52	8.1, 0.0261	2	73.9, 68	19.4, 15	0.29(0)	0.18(9)	**b**
3	55.7, 0.50	85.8, 0.50	7.7, 0.025	2	74.9, 64	21.0, 15	0.35(7.7)	0.23(7.7)	**c**
4	55.9, 0.51	91.2, 0.50	7.8, 0.0252	4	71.1, 59	13.2, 9	0.44(9)	0.18(9)	**d**
5	55.0, 0.50	99.4, 0.50	7.8, 0.0252	4	79.5, 60		0.46(9)		**e**
6	101.3, 0.51	65.4, 0.51	7.9, 0.0255	4	74.5, 51		0.21(20)	0.21(20)	**f**
7	99.6, 0.50	84.9, 0.50	7.8, 0.0255	2	102.9, 63		0.17(9)	0.17(9)	**g**
8	99.2, 0.50	91.1, 0.50	7.8, 0.0252	4	103.5, 62	9.7, 5	0.33(14)	0.22(14)	**h**
9	85.6, 0.51	92.8, 0.51	7.9, 0.0255	4	127.4, 71[a]	18.2, 9[a]	0.27(13)	0.16(13)	**i**
10	84.6, 0.50	91.2, 0.50	7.8, 0.0252	4	109.2, 71		0.19(25)		**j**
11	48.0, 0.28	40.0, 0.28	4.4, 0.014	2	54.3, 73		0.21(33)		**k**
12	39.8, 0.40	56.4, 0.40	6.5, 0.021	2	43.0, 53		0.18(50)	0.18(50)	**l**
13	110.5, 0.50	85.0, 0.50	7.7, 0.025	2	101.4, 59		0.18(6)		**m**

[a] Isolated as dimethyl acetal.

15b: IR (neat) 1756, 1655, 1457, 1375, 1320, 1197 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (dd, J = 1.5, 1.6 Hz, 1H), 5.53 (dt, J = 6.4, 15.2 Hz, 1H), 5.42 (dt, J = 6.5, 15.3 Hz, 1H), 4.96 (qq, J = 1.9, 6.8 Hz, 1H), 2.91 (d, J = 6.3 Hz, 2H), 1.98 (dt, J = 6.7, 7.0 Hz, 2H), 1.37 (d, J = 6.8 Hz, 3H), 1.19–1.33 (m, 6H), 0.84 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.44 (C), 149.39 (CH), 134.08 (CH), 133.41 (C), 124.19 (CH), 77.54 (CH), 32.36 (CH_2), 31.30 (CH_2), 28.90 (CH_2), 28.36 (CH_2), 22.42 (CH_2), 19.06 (CH_3), 13.98 (CH_3). Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.76; H, 9.58.

16b: IR (neat) 3457, 1716, 1648, 1456, 1371, 1318, 1245, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.97 (s, 1H), 5.50 (ddd, J = 6.0, 6.5, 15.4 Hz, 1H), 5.39 (ddd, J = 6.0, 6.5, 15.3 Hz, 1H), 4.31 (q, J = 6.5 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.52 (dd, J = 5.9, 13.3, 1H), 3.03 (dd, J = 6.6, 13.4 Hz, 1H), 1.95 (dt, J = 6.6, 6.9 Hz, 2H), 1.71 (br, 1H), 1.29 (d, J = 6.7 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.20–1.33 (m, 6H), 0.84 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ = 7.1 Hz, 3H), 1.20–1.33 (m, 6H), 0.84 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.60, 163.29, 132.97, 126.51, 114.01, 70.72, 59.81, 32.70, 32.43, 31.36, 29.04, 22.48, 22.22, 14.25, 14.04. HRMS. Calcd for $C_{15}H_{26}O_3 - H_2O$: 236.1776. Found: 236.1779.

15c: IR (neat) 1760, 1653, 1467, 1370, 1355, 1199, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (dd, J = 1.6, 1.6 Hz, 1H), 5.53 (td, J = 6.3, 15.3 Hz, 1H), 5.42 (td, J = 6.4, 15.3 Hz, 1H), 4.66 (dd, J = 1.8, 5.8 Hz, 1H), 2.92 (d, J = 6.8 Hz, 2H), 1.98 (dt, J = 6.6, 7.0 Hz, 2H), 1.91 (m, J = 6.1, 6.7 Hz, 1H), 1.21–1.35 (m, 6H), 0.97 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.8 Hz, 3H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.55, 146.83, 134.36, 134.00, 124.31, 85.91, 32.35, 31.74, 31.29, 28.89, 28.45, 22.43, 17.83, 17.60, 14.00. Anal. Calcd for $C_{15}H_{23}O_2$: C, 76.23; H, 10.24. Found: C, 76.29; H, 9.91.

16c: IR (neat) 3495, 1716, 1645, 1466, 1369, 1241, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.89 (s, 1H), 5.51 (ddd, J = 5.6, 6.5, 15.3 Hz, 1H), 5.41 (ddd, J = 5.8, 6.5, 15.4 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.91 (d, J = 5.0, 1H), 3.48 (dd, J = 5.8, 13.6, 1H), 3.04 (dd, J = 6.5, 13.3 Hz, 1H), 1.90–2.01 (m, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.20–1.42 (m, 6H), 0.93 (d, J = 6.9 Hz, 3H), 0.86 (d, J = 6.8 Hz, 3H), 0.85 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.39, 161.32, 132.86, 126.73, 115.91, 80.00, 59.80, 32.89, 32.43, 31.37, 31.09, 29.07, 22.50, 19.98, 16.18, 14.26, 14.05. HRMS. Calcd for $C_{17}H_{30}O_3 - H_2O$: 264.2089. Found: 264.2088.

15d: IR (neat) 1754, 1467, 1434, 1339, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.88 (t, J = 1.7 Hz, 1H), 5.52 (td, J = 6.3, 15.3 Hz, 1H), 5.42 (td, J = 6.4, 15.3 Hz, 1H), 2.89 (d, J = 6.3 Hz, 2H), 1.97 (q, J = 6.4 Hz, 2H), 1.73–2.01 (m, 8H), 1.16–1.35 (m, 6H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.99 (C), 151.00 (CH), 133.92 (CH), 132.44 (C), 124.33 (CH), 94.76 (C), 36.85 (CH_2), 32.37 (CH_2), 31.31 (CH_2), 28.89 (CH_2), 28.34 (CH_2), 24.51 (CH_2), 22.42 (CH_2), 14.00 (CH_3). HRMS. Calcd for $C_{16}H_{24}O_2$: 248.1776. Found: 248.1774.

16d: IR (neat) 3462, 1718, 1636, 1457, 1365, 1262, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.08 (s, 1H), 5.48 (td, J = 5.3, 15.4 Hz, 1H), 5.43 (td, J = 4.9, 15.4 Hz, 1H), 4.14 (q, J = 7.1 Hz, 3H), 3.32 (d, J = 3.9 Hz, 2H), 1.94 (dt, J = 6.3, 6.4 Hz, 2H), 1.60–1.97 (m, 8H), 1.26 (t, J = 7.1 Hz, 3H), 1.18–1.32 (m, 6H), 0.84 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.68 (C), 163.61 (C), 132.28 (CH), 127.89 (CH), 114.59 (CH), 85.59 (C), 59.78 (CH_2), 39.52 (CH_2), 33.42 (CH_2), 32.48 (CH_2), 31.38 (CH_2), 29.11 (CH_2), 24.01 (CH_2), 22.50 (CH_2), 14.28 (CH_3), 14.06 (CH_3). HRMS. Calcd for $C_{18}H_{30}O_3 - H_2O$: 276.2089. Found: 276.2077.

15e: IR (neat) 1759, 1467, 1456, 1375, 1278, 1210, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, J = 1.6 Hz, 1H), 5.51 (td, J = 6.4, 15.2 Hz, 1H), 5.40 (td, J = 6.4, 15.3 Hz, 1H), 2.90 (d, J = 7.1 Hz, 2H), 1.98 (q, J = 6.4 Hz, 2H), 1.35 (s, 3H), 1.21–1.32 (m, 6H), 0.92 (s, 9H), 0.83 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.35 (C), 151.94 (CH), 133.85 (CH), 132.83 (C), 124.49 (C), 91.33 (C), 36.88 (C), 32.34 (CH_2), 31.26 (CH_2), 28.89 (CH_2), 28.26 (CH_2), 25.42 (CH_3), 22.42 (CH_2), 20.03 (CH_3), 14.01 (CH_3). HRMS. Calcd for $C_{17}H_{28}O_2$: 264.2089. Found: 264.2082.

15f and 16f: IR (neat) 3510, 1739, 1718, 1652, 1437, 1366, 1349, 1249, 1198, 1175 cm^{-1}. **15f**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (d, J = 1.3 Hz, 1H), 5.30–5.57 (m, 2H), 4.16 (d, J = 4.2 Hz, 2H), 3.61 (s, 3H), 2.91 (d, J = 4.6 Hz, 2H), 2.24 (t, J = 7.5 Hz, 2H), 1.90–1.98 (m, 2H), 1.20–1.25 (m, 10H). Additional signals for **16f**: 5.94 (s, 1H), 4.73 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.60 (s, 3H), 3.20 (d, J = 5.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.37 (C), 174.24 (C), 144.67 (CH), 133.52 (CH), 132.83 (C), 124.20 (CH), 70.21 (CH_2), 51.36 (CH_3), 33.96 (CH_2), 32.31 (CH_2), 29.08 (CH_2), 28.95 (CH_2), 28.80 (CH_2), 28.45 (CH_2), 24.78 (CH_2). Additional signals for **16f**: 166.42 (C), 159.41 (C), 134.00 (CH), 126.04 (CH), 113.37 (CH), 64.97 (CH_2), 59.63 (CH_3), 32.22 (CH_2), 28.86 (CH_2), 28.64 (CH_2), 24.71 (CH_2), 14.18 (CH_3). HRMS. Calcd for $C_{16}H_{24}O_4$: 280.1675. Found: 280.1647. Calcd for $C_{18}H_{30}O_5 - H_2O$ (**16f**): 308.1899. Found: 308.1981.

15g and 16g: IR (neat) 3491, 1759, 1740, 1716, 1648, 1465, 1437, 1368, 1245, 1199, 1175 cm^{-1}. **15g**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (d, J = 1.6 Hz, 1H), 5.51 (ddd, J = 6.0, 6.4, 15.2 Hz, 1H), 5.41 (ddd, J = 6.1, 6.4, 15.3 Hz, 1H), 4.66 (dm, J = 5.8 Hz, 1H), 3.62 (s, 3H), 2.92 (d, J = 6.4 Hz, 2H), 2.26 (t, J = 7.6 Hz, 2H), 1.86–2.01 (m, 3H), 1.57 (m, 2H), 1.22–1.29 (m, 8H), 0.94 (d, J = 6.7 Hz, 3H), 0.93 (d, J = 6.7 Hz, 3H). Additional signals for **16g**: 5.88 (s, 1H), 4.25 (d, J = 6.0 Hz, 1H), 4.19 (q, J = 7.1 Hz, 2H), 1.00 (d, J = 6.7 Hz, 3H), 0.98 (d, J = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.23, 173.55, 146.84, 134.30, 133.85, 124.38, 85.91, 51.39, 33.98, 32.34, 31.72, 29.11, 28.99, 28.83, 28.43, 24.83, 17.59, 17.83. Additional signals for **16g**: 166.36, 161.38, 132.56, 126.82, 115.75, 79.69, 59.70, 34.13, 32.82, 30.98, 28.76, 19.94, 16.06, 13.93. HRMS. Calcd for $C_{19}H_{30}O_4$ (**15g**): 322.2144. Found: 322.2133. Calcd for $C_{21}H_{36}O_5 - H_2O$ (**16g**): 350.2457. Found: 350.2451.

15h: IR (neat) 1754, 1752, 1654, 1436, 1339, 1249, 1198, 1173, cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.87 (s, 1H), 5.52 (td, J = 5.6, 15.2 Hz, 1H), 5.40 (td, J = 5.8, 15.3 Hz, 1H), 3.61 (s, 3H), 2.88 (d, J = 5.5 Hz, 2H), 2.25 (t, J = 7.4 Hz, 2H), 1.75–1.99 (m, 10H), 1.56 (m, 2H), 1.20–1.25 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.17, 172.92, 150.97, 133.75, 132.39, 124.44, 94.71, 51.34, 36.85, 33.96, 32.34, 29.11, 28.92, 28.84, 28.33, 24.81, 24.49.

16h: IR (neat) 3496, 1740, 1716, 1637, 1438, 1367, 1248, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (s, 1H), 5.48 (dm, J = 15.3 Hz, 1H), 5.41 (dm, J = 15.4 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.64 (s, 3H), 3.31 (d, J = 2.5 Hz, 2H), 2.27 (t, J = 7.6 Hz, 2H), 1.57–1.95 (m, 10H), 1.49 (m, 2H), 1.23–1.28 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.34, 166.66, 163.64, 132.07, 128.01, 114.56, 85.54, 65.83,

Table 6. Experimental Details for Table 3

entry	alkene (mg, mmol)	hydroxy ynoate (mg, mmol)	Cp(COD)RuCl (mg, mmol)	MeOH (mL)	yield (mg, %) 25	yield (mg, %) 24	R_f (% EtOAc in hex) 25	R_f (% EtOAc in hex) 24	compd no. suffix
1	50.5, 0.45	69.2, 0.44	6.9, 0.0223	2	39.2(40)	50.0(47)	0.35(14)	0.18(14)	**a**
2	55.0, 0.49	96.9, 0.49	7.6, 0.0245	2	66.5(52)	10.5(7)	0.50(14)	0.25(14)	**b**
3	97.9, 0.49	74.9, 0.48	7.5, 0.0242	2	79.6(54)	45.6(27)	0.19(14)	0.46(33)	**c**
4	93.9, 0.47	92.9, 0.47	7.3, 0.0236	2	90.6(55)	29.0(16)	0.27(14)	0.48(33)	**d**

51.44, 39.46, 34.06, 32.56, 32.39, 29.26, 29.05, 28.98, 28.82, 24.87, 24.01, 14.27. Anal. Calcd for $C_{22}H_{36}O_5$: C, 69.44; H, 9.54. Found: C, 69.27; H, 9.66.

15i: IR (neat) 1756, 1463, 1345, 1191, 1128 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.86 (t, J = 1.5 Hz, 1H), 5.50 (td, J = 6.2, 14.2 Hz, 1H), 5.40 (td, J = 6.3, 15.3 Hz, 1H), 4.29 (t, J = 5.7 Hz, 1H), 3.25 (s, 6H), 2.88 (d, J = 5.8 Hz, 2H), 1.95 (t, 6.8 Hz, 2H), 1.73−1.97 (m, 8H), 1.53 (q, J = 6.6 Hz, 2H), 1.24−1.33 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.87 (C), 150.93 (CH), 133.79 (CH), 132.39 (C), 124.38 (CH), 104.45 (CH), 94.66 (C), 52.41 (CH_3), 36.83 (CH_2), 32.38 (CH_2), 32.33 (CH_2), 29.31 (CH_2), 29.24 (CH_2), 29.15 (CH_2), 28.94 (CH_2), 28.30 (CH_2), 24.48 (CH_2), 24.45 (CH_2). HRMS. Calcd for $C_{21}H_{34}O_4 - OCH_3$: 319.2273. Found: 319.2256.

16i: IR (neat) 3477, 1716, 1637, 1456, 1368, 1260, 1176, 1127 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.09 (s, 1H), 5.49 (dm, J = 15.3 Hz, 1H), 5.41 (dm, J = 15.1 Hz, 1H), 4.33 (t, J = 5.7 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.31 (d, J = 3.3 Hz, 2H), 3.29 (s, 6H), 1.51−1.95 (m, 12H), 1.18−1.36 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.68, 163.67, 132.15, 127.98, 114.57, 104.51, 85.55, 59.77, 52.55, 39.48, 32.58, 32.43, 29.70, 29.40, 29.32, 28.93, 24.54, 24.04, 14.29. HRMS. Calcd for $C_{23}H_{40}O_5 - CH_3OH$: 364.2614. Found: 364.2539.

15j: IR (neat) 3434, 2927, 2874, 2854, 1751, 1635, 1751, 1635, 1432, 1341, 1252, 1177, 1097, 1057, 987, 970 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.87 (t, J = 1.5 Hz, 1H), 5.51 (td, J = 6.3, 15.2 Hz, 1H), 5.41 (td, J = 6.2, 15.2 Hz, 1H), 3.58 (t, J = 6.6 Hz, 2H), 2.89 (d, J = 5.8 Hz, 2H), 1.96 (dt, J = 6.2, 6.7 Hz, 2H), 1.73−2.01 (m, 8H), 1.51 (tt, J = 6.8, 6.9 Hz, 2H), 1.20−1.31 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.02 (C), 151.06 (CH), 133.84 (CH), 132.39 (C), 124.38 (CH), 94.79 (C), 62.85 (CH_2), 36.85 (CH_2), 32.66 (CH_2), 32.37 (CH_2), 29.30 (CH_2), 29.18 (CH_2), 29.08 (CH_2), 28.97 (CH_2), 28.33 (CH_2), 25.63 (CH_2), 24.51 (CH_2). HRMS. Calcd for $C_{19}H_{30}O_3$: 306.2195. Found: 306.2188.

15k: mp = 37.5−38 °C (from ether); $[\alpha]_D$ 24.3 ± 0.4° (c 1.23, $CHCl_3$); IR (neat, solid state) 3265, 1739, 1705, 1654, 1470, 1425, 1377, 1324, 1118 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (t, J = 1.6 Hz, 1H), 5.54 (ddd, J = 6.3, 6.4, 15.3 Hz, 1H), 5.42 (ddd, J = 6.4, 6.5, 15.3 Hz, 1H), 4.98 (qq, J = 1.8, 6.8 Hz, 1H), 3.61 (t, J = 6.6 Hz, 2H), 2.92 (d, J = 6.6 Hz, 2H), 1.99 (dt, J = 6.6, 6.7 Hz, 2H), 1.49−1.55 (m, 2H), 1.45 (br, 1H), 1.38 (d, J = 6.7 Hz, 3H), 1.27−1.32 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.50 (C), 149.42 (CH), 134.03 (CH), 133.40 (C), 124.24 (CH), 77.58 (CH), 62.96 (CH_2), 32.71 (CH_2), 32.40 (CH_2), 29.30 (CH_2), 29.20 (CH_2), 29.00 (CH_2), 28.38 (CH_2), 25.66 (CH_2), 19.09 (CH_3). Anal. Calcd for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84; MW, 266.1882. Found: C, 72.37; H, 9.77; MW, 266.1882.

15l and 16l: IR (neat) 3424, 1748, 1648, 1448, 1374, 1321, 1196 cm^{-1}. **15l**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (dd, J = 1.6, 1.7 Hz, 1H), 5.51 (m, 2H), 4.97 (qq, J = 1.8, 6.8 Hz, 1H), 3.61 (t, J = 6.5 Hz, 2H), 2.92 (dt, J = 1.5, 6.0 Hz, 2H), 2.05−2.12 (m, 2H), 1.92 (br, 1H), 1.53−1.65 (m, 2H), 1.37 (d, J = 6.8 Hz, 3H). Additional signals for **16l**: 5.96 (d, J = 1.0 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.57 (t, J = 6.4 Hz, 2H), 3.50 (dd, J = 4.9, 13.4 Hz, 1H), 3.00 (dd, J = 5.4, 13.7 Hz, 1H), 1.26 (d, J = 6.5 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.52, 149.61, 133.11, 131.75, 124.97, 77.63, 62.17, 32.05, 28.69, 28.34, 19.04. Additional signals for **16l**: 166.64, 163.30, 127.23, 114.09, 70.54, 62.26, 59.80, 32.51, 28.89, 22.17, 14.20. HRMS. Calcd for $C_{16}H_{16}O_3$ (**15l**): 196.1100. Found: 196.1093. Calcd for $C_{13}H_{20}O_3$ ($M^+ - H_2O$) (**16l**): 224.1413. Found: 224.1404.

15m: IR (neat) 1761, 1652, 1469, 1389, 1370, 1355, 1297, 1198, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (t, J = 1.6 Hz, 1H), 5.25−5.58 (m, 4H), 4.66 (m, 1H), 2.93 (d, J = 5.8 Hz, 2H), 1.86−2.08 (m, 8H), 1.22 (m, 16H), 0.95 (d, J = 6.9 Hz, 3H), 0.94 (d, J = 6.9 Hz, 3H), 0.84 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.52, 149.92, 134.28, 133.32, 130.49, 128.69, 124.79, 85.92, 32.51, 31.85, 31.75, 29.55, 29.51, 29.28 (2), 28.45, 27.24, 26.91, 22.63, 17.84, 17.62, 14.07. HRMS. Calcd for $C_{23}H_{38}O_2$: 364.2872. Found: 346.2881.

Reaction of 1,7-Octadiene (17) and 1-[(Ethoxycarbonyl)ethynyl]-1-hydroxycyclopentane (18). 1:1 Ratio. Following the general procedure, 55.3 mg (0.50 mmol) of diene **17**, 91.0 mg (0.50 mmol) of alkyne **18**, and 7.8 mg (0.025 mmol) of **10** in 4 mL of methanol gave after flash chromatography (9−17% EtOAc in hexane) 42.7 mg (35% yield) of **19**, 9.6 mg (7% yield) of **20**, and 25.8 mg (14% yield) of **21**.

1:2 Ratio. Following the general procedure, 28.7 mg (0.26 mmol) of diene **17**, 94.7 mg (0.52 mmol) of alkyne **18**, and 4.0 mg (0.013 mmol) of **10** in 3 mL of methanol gave after flash chromatography 30.4 mg (24% yield) of **19**, 6.8 mg (5% yield) of **20**, and 58.2 mg (59% yield) of **21**.

19: R_f = 0.35 (9% ethyl acetate/hexane); IR (neat, solid state) 1753, 1640, 1434, 1339, 1256 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.88 (t, J = 1.6 Hz, 1H), 5.77 (tdd, J = 6.7, 10.2, 17.1 Hz, 1H), 5.53 (td, J = 6.4, 15.3 Hz, 1H), 5.44 (td, J = 6.4, 15.4 Hz, 1H), 4.99 (ddd, J = 1.5, 2.0, 17.5 Hz, 1H), 4.91 (dd, J = 1.0, 10.7 Hz, 1H), 2.99 (d, J = 5.4, 2H), 1.74−2.06 (m, 12H), 1.44 (dt, J = 7.3, 7.7 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.99, 151.04, 138.59, 133.44, 132.38, 124.80, 114.51, 94.78, 36.88, 33.14, 31.81, 28.42, 28.36, 24.53. HRMS. Calcd for $C_{16}H_{22}O_2$: 246.1620. Found: 246.1628.

21: R_f = 0.22 (17% ethyl acetate/hexane); IR (neat, solid state) 1747, 1736, 1653, 1449, 1420, 1325 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.90 (d, J = 1.5 Hz, 2H), 5.54 (td, J = 5.1, 15.4 Hz, 2H), 5.47 (td, J = 5.7, 15.4 Hz, 2H), 2.92 (d, J = 5.3 Hz, 4H), 2.10 (m, 4H), 1.75−1.98 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.97, 151.17, 132.84, 132.27, 125.20,94.82, 36.95, 32.19, 28.41, 24.60. HRMS. Calcd for $C_{24}H_{30}O_4$: 382.2144. Found: 382.2145.

Ruthenium-Catalyzed Condensation of Terminal Alkenes and Ethyl 5-Hydroxy-2-alkynoates. General procedure. Alkene and ethyl 5-hydroxy-2-alkynoate followed by methanol were added by syringe to CpRu(COD)Cl under nitrogen. The reaction mixture then was heated to reflux for 3 h. The cooled reaction mixture was diluted with 20 mL of ether and filtered through a short plug of silica gel. The solution was evaporated *in vacuo*, and the residue was purified by chromatography on silica gel. The experimental details for each run are summarized in Table 6.

25a: IR (neat) 2957, 2927, 2871, 2856, 1718, 1655, 1460, 1388, 1240, 1119, 1096, 958, 850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.50 (m, 1H), 5.48 (ddd, J = 6.0, 6.4, 15.3 Hz, 1H), 5.38 (ddd, J = 6.2, 6.5, 15.3 Hz, 1H), 4.48 (pd, J = 6.2, 9.5 Hz, 1H), 2.95 (d, J = 5.5 Hz, 2H), 2.30 (m, 1H), 2.27 (m, 1H), 1.97 (dt, J = 6.6, 6.8 Hz, 2H), 1.38 (d, J = 6.3 Hz, 3H), 1.21−1.34 (m, 6H), 0.85 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.60, 138.43, 133.69, 131.77, 125.66, 74.16, 33.34, 32.46, 31.37, 29.01, 22.47, 20.68, 14.04. HRMS. Calcd for $C_{14}H_{22}O_2$: 222.1620. Found: 222.1617.

24a: IR (neat) 3463, 1716, 1641, 1459, 1397, 1376, 1245, 1173 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (s, 1H), 5.50 (ddd, J = 6.6, 6.7, 15.3 Hz, 1H), 5.36 (ddd, J = 6.6, 6.7, 15.3 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.99 (ddq, J = 6.1, 6.2, 6.6 Hz, 1H), 3.41 (dd, J = 6.5, 13.3 Hz, 1H), 3.21 (dd, J = 6.7, 13.3 Hz, 1H), 2.13−2.27 (m, 2H), 1.95 (q, J = 6.8 Hz, 2H), 1.79 (br, 1H), 1.25 (t, J = 7.1 Hz, 3H), 1.19 (d, J = 6.1 Hz, 3H), 1.13−1.35 (m, 6H), 0.84 (t, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.05 (C), 158.10 (C), 133.35 (CH), 125.98 (CH), 118.08 (CH), 65.51 (CH), 59.71 (CH_2), 47.77 (CH_2), 35.47 (CH_2), 32.44 (CH_2), 31.34 (CH_2), 29.01 (CH_2), 23.27 (CH_3), 22.46 (CH_2), 14.23 (CH_3), 14.03 (CH_3). HRMS. Calcd for $C_{16}H_{28}O_3$: 268.2038. Found: 268.2026.

25b: IR (neat) 1713, 1677, 1467, 1450, 1378, 1233, 1160, 1102 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.26 (s, 1H), 5.47 (ddd, J = 6.0, 6.3, 15.4 Hz, 1H), 5.36 (ddd, J = 6.3, 6.5, 15.6 Hz, 1H), 3.87 (dt, J = 4.1, 11.5 Hz, 1H), 2.93 (d, J = 6.1 Hz, 2H), 1.71−2.08 (m, 7H), 1.53

Table 7. Experimental Details for Table 4

entry	alkene (mg, mmol)	alkyne (mg, mmol)	Cp(COD)RuCl (mg, mmol)	1:1 DMF/H_2O (mL)	yield (mg, %) 29	yield (mg, %) 30	R_f (% EtOAc in hex) 29	R_f (% EtOAc in hex) 30	compd no. suffix
1	59, 0.80	84, 0.45	6, 0.019	2[a]	43, 48	10, 11	0.56(67)[b]	0.32(89)[b]	**a**
2	36, 0.50	70, 0.25	4, 0.013	1.5[c]	41, 54	9, 12	0.25(67)[b]	0.14(89)[b]	**b**
3	51.4, 0.51	65.3, 0.51	7.9, 0.025	4	54.4(59)		0.13(25)	0.13(25)	**c**
4	43.9, 0.44	60.0, 0.42	6.5, 0.021	2	53.4, 65	10.3, 13	0.14(20)	0.21(33)	**d**
5	50.2, 0.50	85.1, 0.50	7.8, 0.025	4	55.6, 50	15.2, 14	0.11(13)	0.16(25)	**e**
6	51.0, 0.51	93.2, 0.51	7.9, 0.025	4	88.5, 74	15.6, 13	0.39(25)	0.28(25)	**f**
7	42.7, 0.43	84.6, 0.43	7.9, 0.025	4	33.5, 31	3.9, 4	0.44(25)	0.24(25)	**g**
8	76.7, 0.42	58.6, 0.41	6.4, 0.021	2	42.4, 37	13.5, 12	0.08(14)	0.12(20)	**h**
9	89.1, 0.25	45.6, 0.25	3.9, 0.013	3.5[d]	40.0, 33	13.2, 11	0.12(25)	0.41(50)	**i**

[a] Reaction performed for 3 h at 60 °C. [b] Percent ether in hexane. [c] Reaction performed for 2 h at 90 °C. [d] Reaction performed in 3:1 DMF/water at 100 °C for 14 h.

(dddd, J = 3.6, 3.8, 11.9, 12.4 Hz, 1H), 1.08−1.37 (m, 8H), 0.84 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.61, 144.13, 133.60, 131.62, 125.67, 81.57, 39.68, 33.27, 32.42, 31.32, 31.01, 29.07, 28.95, 25.15, 23.91, 22.44, 14.03. Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99; MW, 262.1933. Found: C, 78.01; H, 9.88; MW, 262.1923.

24b: IR (neat) 3455, 1714, 1639, 1449, 1396, 1244, 1172, 1147 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (s, 1H), 5.56 (td, J = 6.6, 15.3 Hz, 1H), 5.42 (td, J = 6.3, 15.3 Hz, 1H), 4.13 (q, J = 7.1 Hz, 2H), 3.58 (ddd, J = 4.3, 9.7, 10.0 Hz, 1H), 3.37 (dd, J = 6.0, 13.0 Hz, 1H), 3.28 (dd, J = 7.0, 13.0 Hz, 1H), 1.61−2.18 (m, 10H), 1.26 (t, J = 7.1 Hz, 3H), 1.07−1.36 (m, 7H), 0.84 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.30, 163.02, 133.44, 126.47, 116.74, 71.87, 59.74, 55.54, 34.93, 34.30, 32.47, 31.59, 31.37, 29.08, 25.55, 24.79, 22.49, 14.26, 14.05. HRMS. Calcd for $C_{19}H_{32}O_3$: 308.2351. Found: 308.2351.

25c: IR (neat) 1736, 1720, 1648, 1437, 1388, 1241, 1201, 1173, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.49 (dddd, J = 1.4, 1.6, 1.7, 3.8 Hz, 1H), 5.46 (td, J = 6.3, 15.4 Hz, 1H), 5.36 (td, J = 6.4, 15.4 Hz, 1H), 4.48 (qdd, J = 6.0, 6.1, 15.9 Hz, 1H), 3.62 (s, 3H), 2.93 (d, J = 5.4 Hz, 1H), 2.26 (t, J = 7.5 Hz, 2H), 1.98 (dt, J = 6.4, 6.6 Hz, 2H), 1.57 (m, 2H), 1.38 (d, J = 6.3 Hz, 3H), 1.25−1.40 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.29, 165.60, 138.47, 133.52, 131.71, 125.75, 74.16, 51.41, 34.02, 33.32, 32.43, 31.36, 29.21, 29.01 (2), 28.89, 24.85, 20.66. HRMS. Calcd for $C_{18}H_{28}O_4$: 308.1988. Found: 308.1986.

24c: IR (neat) 3467, 1739, 1716, 1642, 1438, 1375, 1245, 1176 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (s, 1H), 5.49 (td, J = 6.6, 15.3 Hz, 1H), 5.35 (ddd, J = 6.4, 6.7, 15.3 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.99 (qt, J = 6.2, 6.6 Hz, 1H), 3.63 (s, 3H), 3.40 (dd, J = 6.2, 13.3 Hz, 1H), 3.21 (dd, J = 6.6, 13.2 Hz, 1H), 2.26 (t, J = 7.7 Hz, 2H), 1.94 (dt, J = 6.4, 6.5 Hz, 2H), 1.85 (br, 1H), 1.57 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.18 (d, J = 6.1 Hz, 3H), 1.15−1.27 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.34 (C), 166.04 (C), 158.08 (C), 133.18 (CH), 126.09 (CH), 118.06 (CH), 65.51 (CH), 59.70 (CH_2), 51.43 (CH_3), 47.76 (CH_2), 35.47 (CH_2), 34.03 (CH_2), 32.41 (CH_2), 29.21 (CH_2), 29.01 (2 × CH_2), 28.85 (CH_2), 24.84 (CH_2), 23.26 (CH_3), 14.23 (CH_3). HRMS. Calcd for $C_{20}H_{34}O_5$ − H_2O: 336.2301. Found: 336.2307.

25d: IR (neat) 1736, 1722, 1449, 1436, 1383, 1362, 1231, 1193, 1160, 1127 cm^{-1}; ^{1}H NMR (300 MHz, $CDCL_3$) δ 6.24 (s, 1H), 5.44 (ddd, J = 5.8, 6.3, 15.4 Hz, 1H), 5.34 (ddd, J = 6.0, 6.3, 15.3 Hz, 1H), 3.86 (ddd, J = 4.1, 11.4, 11.5 Hz, 1H), 3.61 (s, 3H), 2.91 (d, J = 5.6 Hz, 2H), 2.24 (t, J = 7.5 Hz, 2H), 1.49−2.16 (m, 10H), 1.10−1.34 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.17 (C), 165.54 (C), 144.12 (CH), 133.39 (CH), 131.53 (C), 125.73 (CH), 81.52 (CH), 51.33 (CH_3), 39.63 (CH), 33.95 (CH_2), 33.24 (CH_2), 32.36 (CH_2), 30.97 (CH_2), 29.12 (CH_2) 29.03 (CH_2), 28.96 (2 × CH_2), 28.83 (CH_2), 25.11 (CH_2), 24.80 (CH_2), 23.86 (CH_2). Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; MW, 348.2301. Found: C, 72.18; H, 9.12; MW, 348.2302.

24d: IR (neat) 3506, 1738, 1716, 1639, 1448, 1367, 1246, 1174 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (s, 1H), 5.55 (ddd, J = 6.5, 6.6, 15.4 Hz, 1H), 5.41 (ddd, J = 6.3, 6.9, 15.3 Hz, 1H), 4.12 (q, J = 7.1 Hz, 2H), 3.63 (s, 3H), 3.54 (m, 1H), 3.28−3.41 (m, 2H), 2.26 (t, J = 7.6 Hz, 2H), 1.55−2.01 (m, 11H), 1.25 (t, J = 7.1 Hz, 3H), 1.12−1.30 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.31, 166.28, 163.00, 133.24, 126.56, 116.71, 71.84, 59.70, 55.50, 34.91, 34.31, 34.04, 32.44, 31.57, 29.28, 29.03 (2), 28.90, 25.54, 24.87, 24.77, 14.25. HRMS. Calcd for $C_{23}H_{38}O_5$ − H_2O: 376.2614. Found: 376.2615.

Ruthenium-Catalyzed Condensations of Allyl Alcohols and Ethyl 4-Hydroxy-2-alkynoates. Allyl alcohol and ethyl 4-hydroxy-2-alkynoate followed by a 1:1 mixture of degassed DMF/water were added by syringe to CpRu(COD)Cl under nitrogen. The reaction mixture was vigorously stirred at 100 °C for 2 h. The cooled reaction mixture was diluted with 20 mL of ether and filtered through a short plug of silica gel. The clear filtrate was evaporated *in vacuo*. The residue was diluted with 15 mL of ether and analyzed by GC. The solution was evaporated *in vacuo*, and the residue was purified by chromatography on silica gel. The experimental details for each run are summarized in Table 7.

29a: IR (neat) 1752, 1718, 1357, 1201, 1163; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.00−6.99 (m, 1H), 4.84−4.79 (m, 1H), 2.68 (t, J = 7.0 Hz, 2H), 2.08 (s, 3H), 1.65−1.52 (m, 3H), 1.38−1.18 (m, 5H), 0.81 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.96, 173.57, 149.52, 132.60, 81.33, 40.74, 33.34, 31.44, 29.85, 24.60, 22.40, 19.50, 13.90. Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.49; H, 9.12.

30a: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66−5.64 (m, 1H), 4.83−4.80 (m, 1H), 2.72 (t, J = 7.0 Hz, 2H), 2.53−2.43 (m, 2H), 2.15 (s, 3H), 1.89−1.82 (m, 2H), 1.51−1.15 (m, 6H), 0.82 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.71, 172.92, 171.77, 115.49, 84.16, 40.37, 32.11, 31.41, 29.93, 24.05, 22.40, 21.73, 13.93. HRMS. Calcd for $C_{13}H_{20}O_3$: 224.1412. Found: 224.1409.

29b: IR (neat) 1752, 1749, 1718, 1370, 1247, 1177, 1164 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.90 (s, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.75 (t, J = 7.0 Hz, 2H), 2.56 (t, J = 7.1 Hz, 2H), 2.29 (t, J = 7.3 Hz, 2H), 2.15 (s, 3H), 1.83−1.67 (m, 4H), 1.59 (quint, J = 7.6 Hz, 2H), 1.25 (t, J = 7.1 Hz, 5H), 0.80 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.85, 173.28, 173.14, 152.24, 132.77, 89.13, 60.24, 40.84, 36.40, 33.93, 30.01, 29.82, 24.84, 22.87, 19.49, 14.17, 7.68. Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44; MW, 310.1780. Found: C, 65.90; H, 8.61; MW, 310.1778.

30b: IR (neat) 1732, 1720, 1711, 1638, 1370, 1234, 1163 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (d, J = 1.7 Hz, 1H), 4.11 (q, J = 7.1 Hz, 2H), 2.80 (t, J = 7.2 Hz, 2H), 2.42−2.37 (m, 2H), 2.27 (t, J = 7.5 Hz, 2H), 2.24 (s, 3H), 1.98−1.85 (m, 2H), 1.71−1.54 (m, 4H), 1.25 (t, J = 7.2 Hz, 3H), 1.12−1.04 (m, 2H), 0.75 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 205.85, 173.32, 172.93, 116.16, 91.98, 60.31, 39.82, 36.02, 33.97, 30.02, 29.39, 24.77, 22.16, 21.02, 14.23, 6.92. HRMS. Calcd for $C_{17}H_{26}O_5$: 310.1780. Found: 310.1780.

29c and 30c: IR (neat) 1751, 1708, 1702, 1465, 1441, 1350, 1260 cm^{-1}. **29c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (t, J = 1.4 Hz, 1H), 4.72 (d, J = 1.8 Hz, 2H), 2.73 (t, J = 6.9 Hz, 2H), 2.55 (sept, J = 6.8 Hz, 1H), 2.53 (t, J = 6.9 Hz, 2H), 1.04 (d, J = 6.9 Hz, 6H). Additional signals for **30c**: 5.76 (t, J = 1.7 Hz, 1H), 4.74 (d, J = 1.7 Hz, 2H), 2.78 (t, J = 6.8 Hz, 2H), 2.64 (t, J = 6.9 Hz, 2H), 2.59 (sept, J = 6.9 Hz, 1H), 1.10 (d, J = 7.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.95, 174.06, 145.61, 132.82, 70.09, 40.73, 37.32, 19.55, 18.13. Additional signals for **30c**: 73.21, 22.13. HRMS. Calcd for $C_{10}H_{14}O_3$: 182.0943. Found: 182.0939.

29d: IR (neat) 1753, 1711, 1656, 1468, 1384, 1373, 1320, 1203, 1120 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.01 (q, J = 1.4 Hz, 1H), 4.95 (qq, J = 1.6, 6.8 Hz, 1H), 2.72 (t, J = 6.7 Hz, 2H), 2.49−2.60 (m, 3H), 1.35 (d, J = 6.8 Hz, 3H), 1.04 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.95, 173.46, 150.44, 132.62, 77.43, 40.75, 37.44, 19.47, 18.99, 18.13, 18.10. HRMS. Calcd for $C_{11}H_{16}O_3$: 196.1099. Found: 196.1107.

30d: IR (neat) 1754, 1713, 1639, 1468, 1384, 1322, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.67 (q, J = 1.6 Hz, 1H), 4.93 (dq, J = 1.7, 6.8 Hz, 1H), 2.75 (m, 2H), 2.45-2.66 (m, 3H), 1.44 (d, J = 6.8 Hz, 3H), 1.10 (d, J = 6.9 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.85, 173.22, 166.00, 114.91, 80.55, 40.85, 37.14, 21.59, 18.23 (2). HRMS. Calcd for $C_{11}H_{16}O_3$: 196.1099. Found: 196.1106.

29e: IR (neat) 1755, 1712, 1655, 1468, 1386, 1369, 1204, 1177 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (d, J = 1.4 Hz, 1H), 4.65 (q, J = 1.6, 6.4 Hz, 1H), 2.72 (t, J = 6.9 Hz, 2H), 2.55 (m, 1H), 2.53 (m, 2H), 1.90 (sept, J = 6.8 Hz, 1H), 1.040 (d, J = 6.8 Hz, 3H), 1.037 (d, J = 6.9 Hz, 3H), 0.911 (d, J = 6.8 Hz, 3H), 0.907 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.97, 173.59, 148.08, 133.52, 85.76, 40.73, 37.49, 31.65, 19.56, 18.15, 17.76, 17.47. HRMS. Calcd for $C_{13}H_{20}O_3$: 224.1412. Found: 224.1406.

30e: IR (neat) 1754, 1718, 1638, 1467, 1386, 1369, 1177 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (d, J = 1.7 Hz, 1H), 4.79 (s, 1H), 2.77 (t, J = 7.0 Hz, 2H), 2.62 (sept, J = 6.9 Hz, 1H), 2.52 (m, J = 1.4, 6.9 Hz, 2H), 2.12 (dsept, J = 2.4, 6.9 Hz, 1H), 1.15 (d, J = 7.0 Hz, 3H), 1.10 (d, J = 7.0 Hz, 6H), 0.69 (d, J = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.92, 173.23, 171.30, 115.89, 88.23, 40.84, 37.02, 29.70, 21.88, 19.87, 18.23, 13.52. HRMS. Calcd for $C_{13}H_{20}O_3$: 224.1412. Found: 224.1404.

29f: IR (neat) 1751, 1711, 1467, 1435, 1384, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.93 (s, 1H), 2.70 (t, J = 7.0 Hz, 2H), 2.54 (sept, J = 7.0 Hz, 1H), 2.50 (t, J = 7.0 Hz, 2H), 1.73–1.94 (m, 8H), 1.03 (d, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.05, 172.96, 152.11, 131.60, 94.62, 40.73, 37.59, 36.79, 24.50, 19.44, 18.07. HRMS. Calcd for $C_{14}H_{20}O_3$: 236.1412. Found: 236.1407.

30f: IR (neat) 1749, 1713, 1635, 1468, 1418, 1384, 1236, 1171 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.62 (t, J = 1.7 Hz, 1H), 2.81 (t, J = 6.7 Hz, 2H), 2.63 (sept, J = 6.9 Hz, 1H), 2.49 (dt, J = 1.7, 6.8 Hz, 2H), 1.80–1.98 (m, 8H), 1.11 (d, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.05, 173.63, 172.05, 114.59, 97.80, 40.89, 37.07, 36.51, 25.06, 20.73, 18.24. HRMS. Calcd for $C_{14}H_{20}O_3$: 236.1412. Found: 236.1418.

29g: mp 73.5–74 °C; IR (neat, solid state) 1737, 1708, 1660, 1474, 1455, 1371, 1264, 1131 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.06 (s, 1H), 2.73 (t, J = 6.9 Hz, 2H), 2.55 (sept, J = 6.9 Hz, 1H), 2.52 (t, J = 7.1 Hz, 2H), 1.34 (s, 3H), 1.05 (d, J = 6.9 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H), 0.81 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.08 (C), 173.41 (C), 153.40 (CH), 131.88 (C), 91.29 (C), 40.74 (CH), 37.56 (CH_2), 36.88 (C), 25.40 (CH_3), 19.97 (CH_3), 19.41 (CH_2), 18.17 (CH_3). HRMS. Calcd for $C_{15}H_{24}O_3$: 252.1725. Found: 252.1729.

30g: IR (neat) 1751, 1712, 1632, 1469, 1376, 1261, 1123 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.60 (t, J = 1.9 Hz, 1H), 2.78, 2.79 (tm, J = 6.6 Hz, 2H), 2.64 (sept, J = 6.9 Hz, 1H), 2.57 (m, 2H), 1.46 (s, 3H), 1.13 (d, J = 6.9 Hz, 3H), 1.12 (d, J = 6.9 Hz, 3H), 0.99 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.96, 176.19, 169.97, 115.55, 94.55, 40.93, 37.55, 37.23, 25.86, 23.32, 19.67, 18.28. HRMS. Calcd for $C_{15}H_{24}O_3$ + H: 253.1804. Found: 253.1809.

29h: IR (neat) 1755, 1713, 1656, 1451, 1376, 1320, 1248, 1202 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.03 (t, J = 1.5 Hz, 1H), 5.03 (pt, J = 1.4, 7.1 Hz, 1H), 4.95 (qq, J = 1.6, 6.8 Hz, 1H), 2.64–2.70 (m, 2H), 2.49–2.58 (m, 2H), 2.32–2.40 (m, 1H), 2.14–2.22 (m, 1H), 1.85–2.02 (m, 3H), 1.64 (d, J = 1.3 Hz, 3H), 1.55 (s, 3H), 1.35 (d, J = 6.8 Hz, 3H), 1.10–1.31 (m, 2H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.16, 173.46, 150.48, 132.57, 131.55, 124.16, 77.47, 50.15, 40.35, 36.91, 28.94, 25.66, 25.39, 19.68, 19.39, 19.01, 17.62. HRMS. Calcd for $C_{17}H_{26}O_3$: 278.1882. Found: 278.1889.

30h: IR (neat) 1753, 1716, 1639, 1450, 1376, 1321, 1177 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (t, J = 1.7 Hz, 1H), 5.03 (pt, J = 1.4, 7.1 Hz, 1H), 4.95 (qq, J = 1.6, 6.8 Hz, 1H), 2.64–2.70 (m, 2H), 2.49–2.58 (m, 2H), 2.32–2.40 (m, 1H), 2.14–2.22 (m, 1H), 1.85–2.02 (m, 3H), 1.64 (d, J = 1.3 Hz, 3H), 1.55 (s, 3H), 1.35 (d, J = 6.8 Hz, 3H), 1.10–1.31 (m, 2H), 0.84 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.97, 173.07, 172.66, 131.71, 124.04, 114.99, 80.52, 50.24, 40.06, 36.89, 28.97, 25.68, 25.38, 21.52, 19.70, 18.23, 17.64. HRMS. Calcd for $C_{17}H_{26}O_3$: 278.1882. Found: 278.1888.

29i: IR (neat) 1750, 1711, 1673, 1616, 1447, 1435, 1374, 1268, 1251, 1229, 1187 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.96 (s, 1H), 5.69 (s, 1H), 2.24–2.73 (m, 9H), 1.14 (s, 3H), 1.04 (d, J = 6.9 Hz, 3H), 0.84–1.97 (m, 24H), 0.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.77 (C), 199.49 (C), 171.21 (C), 152.48 (CH), 131.48 (C), 123.79 (CH), 94.65 (C), 55.10 (CH), 53.60 (CH), 51.94 (CH), 49.23 (CH), 42.54 (CH_2), 39.35 (C), 38.75 (CH_2) 38.49 (C), 36.81 (CH_2), 35.60 (CH_2), 35.47 (CH), 33.90 (CH_2), 32.77 (CH_2), 31.85 (CH_2), 27.37 (CH_2), 24.54 (CH_2), 24.29 (CH_2), 20.89 (CH_2), 19.26 (CH_2), 17.30 (CH_3), 16.35 (CH_3), 12.14 (CH_3). HRMS. Calcd for $C_{32}H_{44}O_4$: 492.3239. Found: 492.3239.

30i: IR (neat) 1751, 1713, 1673, 1639, 1616, 1448, 1374, 1330, 1268, 1230, 1170 cm^{-1}; ^1H NMR(300 MHz, $CDCl_3$) δ 5.70 (s, 1H), 5.63 (t, J = 1.6 Hz, 1H), 2.20–2.92 (m, 9H), 1.16 (s, 3H), 1.11 (d, J = 6.9 Hz, 3H), 0.87–2.03 (m, 24H), 0.73 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.76, 199.50, 173.59, 171.12, 161.42, 123.88, 114.62, 97.82, 55.15, 53.62, 51.92, 49.32, 42.63, 39.39, 38.48, 36.53, 35.65, 35.52, 33.92, 32.78, 31.87, 27.58, 25.05, 24.36, 20.92, 20.60, 17.34, 16.57, 12.17. Anal. Calcd for $C_{32}H_{44}O_4$: C, 78.01; H, 9.00. Found: C, 78.11; H, 8.86.

Ruthenium-Catalyzed Condensations of Ethyl 5-Hydroxy-2-alkynoates and Allyl Alcohols. General procedure. Allyl alcohol (0.5 mmol) and ethyl 5-hydroxy-2-alkynoate (0.5 mmol) followed by 2 mL of a 1:1 mixture of degassed DMF/water were added by syringe to 7 mg (0.023 mmol) of CpRu(COD)Cl under nitrogen. The reaction mixture was vigorously stirred at 100 °C for 2 h. The cooled reaction mixture was diluted with 20 mL of ether and filtered through a short plug of silica gel. The clear filtrate was evaporated *in vacuo*. The residue was diluted with 15 mL of ether and analyzed by GC. The solution was evaporated *in vacuo*, and the residue was purified by chromatography on silica gel to give the hydroxy esters **31** and **32**.

31a and 32a: 79.4 mg (65% yield); R_f = 0.28 (33% ethyl acetate/hexane); IR (neat) 3483, 1712, 1643, 1467, 1382, 1236, 1210, 1141 cm^{-1}. **31a**: ^1H NMR (300 MHz, $CDCl_3$) δ 6.01 (t, J = 7.7 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.84 (qt, J = 6.0, 6.1 Hz, 1H), 2.40–2.64 (m, 7H), 1.24 (t, J = 7.1 Hz, 3H), 1.15 (d, J = 6.3 Hz, 3H), 1.01 (d, J = 6.9 Hz, 6H). Additional signals for **32a**: 5.66 (s, 1H), 4.08 (q, J = 7.1 Hz, 2H), 1.22 (t, J = 6.9 Hz, 3H), 1.15 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 6.3 Hz, 6H). **31a**: ^{13}C NMR (75 MHz, $CDCl_3$) 213.72, 167.81, 138.98, 132.91, 67.31, 60.40, 40.82, 39.54, 38.77, 28.80, 23.29, 18.04, 14.14. Additional signals for **32a**: δ 213.16, 167.46, 159.83, 117.06, 67.44, 60.07, 42.08, 40.82, 37.72, 32.19, 24.46, 18.14, 14.14. HRMS. Calcd for $C_{14}H_{24}O_4$ + H: 257.1753. Found: 257.1747.

31b and 32b: 84.8 mg (62% yield); R_f = 0.19 (25% ethyl acetate/hexane); IR (neat) 3506, 1716, 1714, 1639, 1467, 1449, 1383, 1232, 1215 cm^{-1}. **31b**: ^1H NMR (300 MHz, $CDCl_3$) δ 5.70 (d, J = 9.9 Hz, 1H), 4.15 (q, J = 7.1 Hz, 2H), 3.16 (dt, J = 4.5, 9.9 Hz, 1H), 2.37–2.69 (m, 8H), 1.99 (m, 1H), 1.55–1.67 (m, 2H), 1.24 (t, J = 7.1 Hz, 3H), 1.10–1.22 (m, 3H), 1.00 (d, J = 7.0 Hz, 6H). Additional signals for **32b**: 5.61 (s, 1H), 4.08, 4.07 (q, J = 7.1 Hz, 2H), 1.04 (d, J = 7.0 Hz, 6H). **31b**: ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.70, 168.42, 145.11, 132.18, 73.71, 60.62, 46.15, 40.83, 39.46, 35.18, 31.53, 28.74, 24.72, 24.68, 18.00, 14.07. Additional signals for **32b**: 163.06, 116.84, 71.50, 59.99, 48.34, 40.88, 37.97, 36.09, 29.67, 25.32, 25.28, 24.90, 18.16. HRMS. Calcd for $C_{17}H_{28}O_4$: 296.1988. Found: 296.1993.

Lactonization of 31a and 32a. A mixture of 47.2 mg (0.18 mmol) of **31a** and **32a** in 2 mL of benzene and 30 mg of 3 Å molecular sieves was heated at reflux under nitrogen for 24 h. After cooling, the reaction mixture was filtered, and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (17% and 33% EtOAc/hexanes) to give 20.9 mg (55%) of **33** as a colorless oil and 9.5 mg (18%) of a 2.9:1 mixture of **34** and starting material.

33a: R_f = 0.14 (17% ethyl acetate/hexane); IR (neat) 1715, 1478, 1415, 1376, 1250, 1124 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.61 (ddt, J = 1.2, 1.7, 3.8 Hz, 1H), 4.46 (ddq, J = 6.2, 6.3, 15.7 Hz, 1H), 2.67 (m, 2H), 2.44–2.59 (m, 3H), 2.24–2.30 (m, 2H), 1.38 (d, J = 6.3 Hz, 3H), 1.04 (d, J = 7.0 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.71, 165.44, 140.07, 131.29, 74.31, 40.87, 38.76, 31.38, 25.54, 20.67, 18.15. HRMS. Calcd for $C_{12}H_{18}O_3$: 210.1256. Found: 210.1248.

31b and 32b: A mixture of a benzene solution (2 mL) of the crude product (derived from 47.1 mg (0.47 mmol) of 4-methyl-1-buten-3-ol, 90.2 mg (0.46 mmol) of (*E*)-1-[(ethoxycarbonyl)ethynyl]-2-hydroxycyclohexane, and 7.2 mg (0.023 mmol) of CpRu(COD)Cl in 2 mL of 1:1 DMF/water) and 30 mg of 3 Å molecular sieves was heated at reflux for 24 h. After workup and chromatography (17% EtOAc in hexane) as above, 46.0 mg (40% yield) of **33b** and 18.5 mg (16% yield) of **34b** were isolated as colorless oils.

33b: $R_f = 0.27$ (17% ethyl acetate/hexane); IR (neat) 1712, 1670, 1466, 1450, 1391, 1367, 1236, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.36 (s, 1H), 3.84 (dt, $J = 4.2$, 11.4 Hz, 1H), 2.37−2.74 (m, 5H), 1.05−2.24 (m, 9H), 1.03 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.57, 165.49, 145.72, 131.10, 81.74, 40.81, 39.66, 38.80, 31.00, 29.00, 25.40, 25.12, 23.88, 18.07. HRMS. Calcd for $C_{15}H_{22}O_3$: 250.1569. Found: 250.1569.

34b: $R_f = 0.09$ (17% ethyl acetate/hexane); IR (neat) 1712, 1629, 1466, 1450, 1383, 1287, 1255 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.68 (td, $J = 1.6$, 2.4 Hz, 1H), 3.94 (dt, $J = 4.2$, 11.3, 11.5 Hz, 1H), 2.41−2.66 (m, 5H), 1.04−2.25 (m, 9H), 1.09 (d, $J = 6.9$ Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 212.30, 164.81, 163.13, 115.44, 80.94, 41.93, 41.02, 36.69, 31.47, 26.39, 25.83, 25.34, 24.00, 18.22. HRMS. Calcd for $C_{15}H_{22}O_3$: 250.1569. Found: 250.1572.

1,1-Dibromo-3(*S*)-[(*tert*-butyldimethylsilyl)oxy]-1-butene (35). To a solution of 23.22 g (70 mmol) of carbon tetrabromide in 30 mL of dichloromethane under nitrogen at 0 °C was added a solution of 36.72 g (140 mmol) of triphenylphosphine in 90 mL of dichloromethane dropwise by syringe. After 15 min, the mixture was cooled to −78 °C and a solution of 6.59 g (35.0 mmol) of lactaldehyde *tert*-butyldimethylsilyl ether in 40 mL was added dropwise by syringe. The reaction mixture was stirred for 1 h at this temperature and allowed to come to room temperature, at which point 700 mL of pentane was added. After 30 min, the precipitate was separated by filtration through a short plug of silica and washed with pentane. The filtrate was concentrated *in vacuo* and redissolved in 30 mL of dichloromethane to which 150 mL of pentane was added. The suspension was filtered, the filtrate again concentrated *in vacuo*, and the residue dissolved in 20 mL of dichloromethane. After addition of 100 mL of pentane, the suspension was filtered again. The filtrate was concentrated *in vacuo* to give a clear oil (9.19 g, 77%). Further purification was achieved by vacuum distillation, bp 87−88 °C at 0.5 mmHg. IR (neat) 1619, 1472, 1463, 1370, 1362, 1253, 1137 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 6.34 (d, $J = 7.8$ Hz, 1H), 4.42, (dq, $J = 6.3$, 7.8 Hz, 1H), 1.20 (d, $J = 6.3$ Hz, 3H), 0.86 (s, 9H), 0.05 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.95, 87.52, 69.86, 25.78, 22.83, 18.06, −4.62, −4.88. HRMS. Calcd for $C_{10}H_{19}Br_2OSi$-C_4H_9: 286.8925. Found: 286.8938.

Ethyl 4(*S*)-Hydroxy-2-pentynoate (36). To a solution of 3.04 g (8.80 mmol) of **35** in 25 mL of THF under nitrogen was added 14 mL (21 mmol) of *n*-butyllithium in hexanes dropwise by syringe over a period of 20 min at −78 °C. After 1 h of stirring at −78 °C, 2.4 g (22 mmol) of ethyl chloroformate was added by syringe. After stirring at −78 °C for 10 min, the mixture was allowed to come to room temperature and poured into brine (20 mL). The aqueous layer was extracted with ether (50 mL). The combined organic layers were dried ($MgSO_4$). The solvents were removed *in vacuo* to give 2.61 g of a yellow-colored oil. This residue was dissolved in 5 mL of THF to which was added 5 mL of water and 14 mL of acetic acid. The reaction mixture was stirred overnight at 60−70 °C. The cooled mixture was neutralized with 30 mL of a saturated sodium bicarbonate solution and solid sodium bicarbonate. After addition of 100 mL of ether, the aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*, and the residue was purified by column chromatography on silica gel (25% ethyl acetate/hexane) to give 1.00 g (80% from **35**) of the titled compound: $R_f = 0.35$ (25% ethyl acetate/hexane); $[\alpha]^{25}_D$ −28.40 ± 0.2° (*c* 2.06, $CHCl_3$); IR (neat) 3410, 2245, 1715, 1449, 1369, 1251, 1125 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.61 (q, $J = 6.8$ Hz, 1H), 4.20 (q, $J = 7.1$ Hz, 2H), 2.72 (br, 1H), 1.48 (d, $J = 6.8$ Hz, 3H), 1.27 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.50, 88.49, 75.63, 62.19, 57.85, 23.15, 13.91. Anal. Calcd for $C_7H_{10}O_3$: C, 59.14; H, 7.09. Found: C, 58.93; H, 7.17.

1,11-Dodecadiene (40). To a suspension of 4.80 g (13.4 mmol) of methyltriphenylphosphonium bromide in 50 mL of THF was added 9 mL (14 mmol) of *n*-butyllithium in hexanes by syringe at −78 °C. After 15 min, the reaction mixture was allowed to come to room temperature. After an additional 10 min, the mixture was again cooled to −78 °C, at which point 2.25 g (13.4 mmol) of 10-undecenal was added dropwise by syringe to the suspension. After 15 min at −78 °C, the reaction mixture was allowed to come to room temperature and was stirred for 1 h. The suspension was filtered, and ~3 g of silica gel was added to the filtrate. The solvent was evaporated *in vacuo*, and the residue was slurried in 100 mL of hexane and filtered again. The solvent was removed *in vacuo* to give 2.16 g (97% yield) of the crude product, which may be further purified by vacuum distillation: bp = 65 °C (0.5 mmHg) (lit.[21] bp 80.7−81.2 °C at 9 mmHg); IR (neat) 1641, 1465, 1440, 992, 909 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.80 (ddt, $J = 6.7$, 10.2, 17.0 Hz, 2H), 5.04 (ddd, $J = 1.6$, 2.1, 17.2 Hz, 2H), 4.91 (ddd, $J = 1.1$, 1.2, 10.2 Hz, 2H), 2.02 (dt, J = 5.9, 6.9 Hz, 4H), 1.27−1.39 (m, 12H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 139.24, 114.09, 33.82, 29.44, 29.13, 28.94, HRMS. Calcd for $C_{12}H_{22} - C_2H_4$: 138.1409. Found: 138.1404.

3-{12-[5(*S*)-methyl-2-oxo-2,5-dihydro-3-furanyl]-2,10-dodecadienyl}-5(*S*)-methyl-2(5*H*)-furanone (41). Following the normal protocol, 52.8 mg (0.32 mmol) of **40** and 106.4 mg (0.75 mmol) of **36** followed by 2 mL of degassed methanol were added by syringe to 9.3 mg (0.030 mmol) of CpRu(COD)Cl. The reaction mixture was heated at reflux for 5.5 h. The cooled reaction mixture was diluted with 20 mL of ether and filtered through a short plug of silica gel. The solution was evaporated *in vavuo*, and the residue was purified by chromatography on silica gel (20−33% ethyl acetate/hexane) to give 85.6 mg (75% yield) of **41** as a colorless solid, which may be further purified by recrystallization from chloroform/pentane: mp 71.5−72.5 °C; $R_f = 0.20$ (25% ethyl acetate/hexane); $[\alpha]^{25}_D$ + 38.68 ± 0.5 °C (*c* 1.81, $CHCl_3$); IR (neat, solid state) 1740, 1654, 1467, 1426, 1324 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.97 (d, $J = 1.3$ Hz, 2H), 5.54 (td, $J = 6.2$, 15.6 Hz, 2H), 5.43 (td, $J = 6.3$, 15.6 Hz, 2H), 4.98 (dq, $J = 1.7$, 6.9 Hz, 2H), 2.92 (d, $J = 6.5$ Hz, 4H), 1.99 (dt, $J = 6.6$, 6.8 Hz, 4H), 1.38 (d, $J = 6.6$ Hz, 6H), 1.25−1.35 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.49 (C), 149.44 (CH), 133.98 (CH), 133.38 (C), 124.30 (CH), 77.58 (CH), 32.41 (CH_2), 29.19 (CH_2), 28.93 (CH_2), 28.41 (CH_2), 19.12 (CH_3). Anal. Calcd for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44; MW, 358.2144. Found: C, 73.60; H, 8.20; MW, 358.2132.

(*S,S*)-Ancepsenolide (42). A mixture of 40.4 mg (0.113 mmol) of **41** and 10.8 mg (0.012 mmol) of Wilkinson's catalyst ($RhCl(PPh_3)_3$) in 1.0 mL of 1:1 benzene/ethanol was placed in a thick-wall glass cylinder topped with a manometer and gas inlet. After three cycles of evacuation and filling with nitrogen, 28 psi (~2 atm) of hydrogen was pressed into the cylinder. The reaction mixture was stirred at room temperature for 18 h. After the pressure was released, 20 mL of chloroform was added, and the solution was filtered through a short plug of silica gel. The solvent was evaporated *in vacuo* and the residue was chromatographed (20% ethyl acetate/hexane) to give 38.8 mg (94% yield) of **42** as a solid: mp 95.5−97.5 °C (from $CHCL_3$/hexane); $R_f = 0.15$ (20% ethyl acetate/hexane); $[\alpha]^{25}_D$ + 39.6 ± 1° (*c* 0.40, $CHCl_3$); IR (neat, solid state) 1743, 1654, 1473, 1121 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.97 (q, $J = 1.5$ Hz, 2H), 4.98 (qq, $J = 1.7$, 6.9 Hz, 2H), 2.24 (ddt, $J = 1.4$, 1.6, 7.0 Hz, 4H), 1.52 (m, $J = 6.5$, 7.2 Hz, 4H), 1.38 (d, $J = 6.8$ Hz, 6H), 1.24−1.28 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.90, 148.86, 134.29, 77.41, 29.53, 29.46, 29.27, 29.15, 27.38, 25.15, 19.20. Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45; MW, 362.2457. Found: C, 72.63; H, 9.35; MW, 362.2471.

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