Ruthenium-Catalyzed Alder Ene Type Reactions. A Formal Synthesis of Alternaric Acid

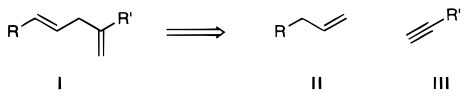
Barry M. Trost,* Gary D. Probst, and Andreas Schoop

Contribution from the Department of Chemistry, Stanford University, Stanford, California 94305-5080

Received May 4, 1998

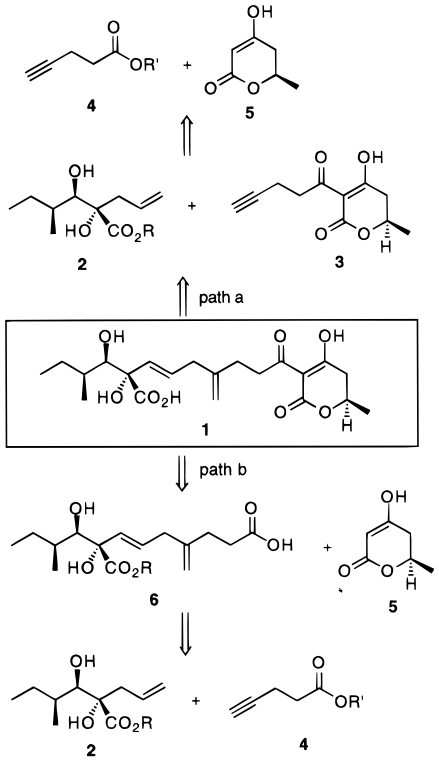
Abstract: Alternaric acid, a nanomolar fungal germination inhibitor, is typified by a 1,4-diene, consisting of a terminal methylene and an (*E*)-1,2-disubstituted alkene. A new strategy for the synthesis of natural products containing such functionality stems from the development of a ruthenium-catalyzed addition of terminal alkenes with terminal alkynes. The alkyne substrate, 4-pentynoic acid, is commercially available or can be prepared in two steps by alkylation of *tert*-butyl acetate. The alkene substrate is prepared from commercially available (*S*)-2-methyl-1-butanol. This synthesis involves formation of a geometically defined trisubstituted alkene by involving Pd-catalyzed cross-coupling and asymmetric dihydroxylation. The ruthenium-catalyzed coupling proceeds best in the absence of alcohol protecting groups to maximize regioselectivity. The examples of this addition illustrated herein help elucidate some of the important factors controlling regioselectivity. They also illustrate the excellent chemoselectivity. The acyclic unit of alternaric acid, which is simply coupled to a dihydropyrone fragment to complete the synthesis, is available in only 11 steps and 27% overall yield compared to the one extant synthesis also starting from (*S*)-2-methyl-1-butanol which proceeds in 26 steps and 0.003% overall yield. This new reaction provides a powerful tool in streamlining this synthesis and should prove more generally useful.

A number of biologically interesting natural products possess the diene fragment **I**[1] whose access normally involves multistep olefination protocols. A particularly attractive approach to such natural products derives from an equivalent of an Alder ene type reaction between a terminal alkene **II** and a terminal alkyne **III**.[2] While such intermolecular reactions, with unactivated



substrates, do not proceed thermally, we have developed a Ru-catalyzed process that effects such reactions. To explore the scope and limitations of this process as well as its ability to facilitate syntheses of natural products, we chose alternaric acid (**1**) as our target (Scheme 1). This natural product, initially isolated in 1949 from *Alternaria solani*,[3,4] exhibits extreme specificity for inhibition of germination in certain strains of fungi at 100 nM concentrations.[5] Some fungal strains exhibit stunting of their hyphae at 5−10 nM concentrations. In addition to antifungal activities, alternaric acid displays selective phytotoxic activities as well.[6] This effect derives from an increased rate of transpiration compared to water uptake resulting in dehydration.

Scheme 1. Retrosynthetic Analyses of Alternaric Acid



The magnitude of the challenge is illustrated by the one extant synthesis which required 29 steps with an overall yield of less than 0.001%.[7] The development of our Ru-catalyzed Alder ene

(1) For a recent class of interesting antitumor macrolides bearing this unit, the amphidinolides, see: Kobayashi, J.; Ishibashi, M. *Chem. Rev.* **1993**, *93*, 1753. Ishibashi, M.; Kobayashi, J. *Heterocycles* **1997**, 543. Also, see: Ishibashi, M.; Takahashi, M.; Kobayashi, J. *Tetrahedron* **1997**, *53*, 7827. Kobayashi, J.; Yamaguchi, N.; Ishibashi, M. *J. Org. Chem.* **1994**, *59*, 4698.

(2) (a) Trost, B. M.; Indolese, A. F.; Muller, T.; Treptow, B. *J. Am. Chem. Soc.* **1995**, *117*, 615. (b) Trost, B. M.; Martinez, J. A.; Kulawiec, R. J.; Indolese, A. *J. Am. Chem. Soc.* **1993**, *115*, 10402. (c) Trost, B. M.; Indolese, A. *J. Am. Chem. Soc.* **1993**, *115*, 4361.

(3) Brian, P. W.; Curtis, P. J.; Hemming, H. G.; Unwin, C. H.; Wright, J. M. *Nature* **1949**, *164*, 534. For structural studies, see: Tabuchi, H.; Ichihara, A. *Tetrahedron Lett.* **1992**, *33*, 4933. Bartels-Keith, J. R. *Chem. Soc.* **1960**, 1662, 860. Grove, J. F. *J. Chem. Soc.* **1952**, 4056.

(4) Also, see: Tabuchi, H.; Ichihara, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 125.

(5) Brian, P. W.; Curtis, P. J.; Hemming, H. G.; Jefferys, E. G.; Unwin, C. H.; Wright, J. M. *J. Gen. Microbiol.* **1951**, *5*, 619.

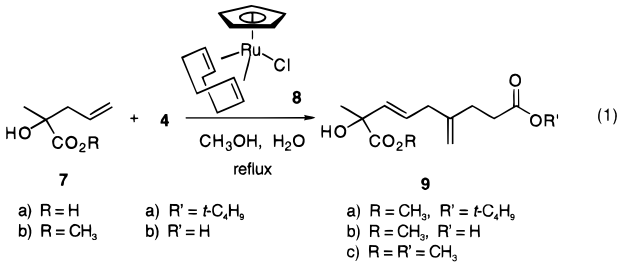
(6) Brian, P. W.; Elson, G. W.; Hemming, H. G.; Wright, J. M. *Ann. Appl. Biol.* **1952**, *39*, 308.

S0002-7863(98)01540-6 CCC: $15.00
Published on Web 08/29/1998

type reaction suggested two convergent strategies. Path a of Scheme 1 envisions linking the two halves **2** and **3** by creating the branched 1,4-diene unit using our Ru reaction. The latter half **3** would derive from standard C-acylation of the dihydropyrone. The pyrone **5** requires just three steps from commercially available poly (*R*)-3-hydroxybutanoate and *tert*-butyl acetate.[7,8] Path b follows the strategy of Ichihara et al. Their synthesis of the diene fragment **6** employed the Julia olefination[9] and required 26 steps with an overall yield of 0.003%. The existence of the Ru-catalyzed reaction suggests the ene **2** and yne **4** as precursors. Either path ultimately requires the same three fragments, **2**, **4**, and **5**. If the Ru-catalyzed reaction is successful, the conciseness of the route depends on the efficiency of the synthesis of **2**.

Model Studies

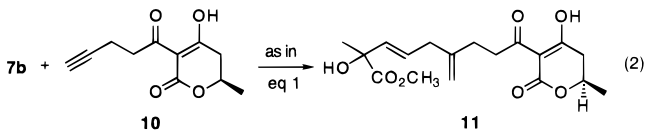
To probe which of the two strategies would prove most promising, we performed several model studies. Lactic acid was converted to the allylated derivative **7** by simple alkylation. Reacting the acid **7a** with *tert*-butyl 4-pentynoate (**4a**)[10] in the presence of 5 mol % of the ruthenium complex **8** gave only a small amount of the adduct **9** (R = H, R′ = *t*-C_4H_9) (eq 1). On



(1)

the other hand, the corresponding methyl ester **7b**, under identical conditions, gives a 49% GC yield (46% isolated yield) of the diene **9a** as a single isomer. Performing the same reaction of **7b** with the acid **4b** causes a lower conversion to the acid **9b**. Working up the reaction by esterfication with diazomethane led to a 20% isolated yield of diester **9c**.

These results suggest that carboxylic acids can inhibit the reaction but that free hydroxyl groups are well tolerated. To probe this point further, we prepared alkyne **10** by standard acylation of dihydropyrone **5** with acid **4b** as a substrate. With 10 mol % of complex **8** as catalyst, the reaction gave a 21% yield of the desired adduct **11** as a single regioisomer (eq 2).

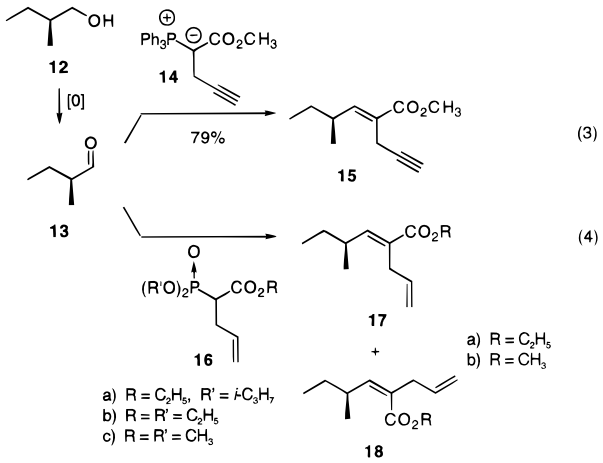


(2)

Again, only a low conversion can be realized. It appears that relatively acidic substrates such as carboxylic acids and acyldihydropyrones that can generate good coordinating anions are catalyst inhibitors. These model studies focused our efforts on the synthetic strategy of path b rather than path a of Scheme 1.

Synthesis of Alkene Partner

The commercial availability of the alcohol **12** in enantiomerically pure form led us to consider olefination of the corresponding aldehyde **13**[11] followed by asymmetric dihydroxylation to create the three stereogenic centers of **2**. As shown in eq 3, the reaction of the ylide **14**[12] gave the desired *E*-alkene **15** as the only geometric isomer in a rather slow reaction that required 3.5 days in refluxing chloroform. Un-



fortunately, significant racemization accompanied this reaction.[13] The anion derived from the phosphonate **16** (eq 4) underwent reaction at −78° to room temperature but gave an *E*:*Z* ratio of **17** and **18**, depending upon the phosphonate, ranging from 1:1.2 for **16a** to 1:4 for **16b** or **16c**. In the case of **16a**, KHMDS in THF−toluene at −78° (87% yield) was employed. For **16b**, the Roush−Masamune conditions[14] (DBU or Hunig's base, LiCl, CH_3CN, room temperature, 28−58% yields) were used. The yields in these reactions were not optimized since the ratios were deemed unsatisfactory.

An alternative synthesis involved oxidation and in situ olefination with the parent Wittig reagent as shown in eq 5. In our hands, oxidation of the alcohol was best performed using the Moffatt-Swern method.[15] Addition of the stabilized parent Wittig reagent gave the alkene **19** without racemization as shown by comparison to the literature[16] and by subsequent analysis of **24**.[17] Bromination−dehydrobromination gave nearly a quantitative yield of the vinyl bromide **20** as a single geometric isomer. Stille cross-coupling[18] generated **17b** as a single geometric isomer whose geometry is readily established by NMR spec-

(7) Tabuchi, H.; Hamamoto, T.; Miki, S.; Tejima, T.; Ichihara, A. *J. Org. Chem*. **1994**, *59*, 4749. Tabuchi, H.; Hamamoto, T.; Miki, S.; Tejima, T.; Ichihara, A. *Tetrahedron Lett.* **1993**, *34*, 2327. For review, see: Ichihara, A. *J. Synth. Org. Chem. Jpn.* **1995**, *53*, 975.

(8) Hoffman, R. W.; Dressely, S. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 189.

(9) Kocienski, P. *Phosphorus Sulfur* **1985**, *24*, 97. Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: New York, 1993.

(10) Atkinson, R. S.; Grimshire, M. J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 1215.

(11) Anelli, P. L.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, *69*, 212.

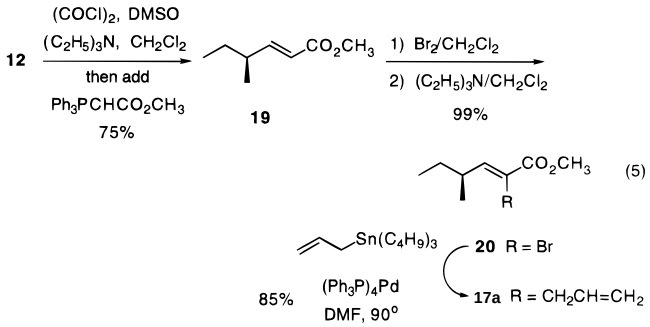
(12) Prepared in 67% yield by alkylation of methyl (triphenylphosphoranylidene)acetate with propargyl bromide in ethyl acetate at reflux.

(13) Determined by reduction of the ester of **15** (LAH) to form the primary alcohol and formation of the *O*-methylmandelate ester (DCC, DMAP) which showed a 1.2:1 ratio of diastereomers.

(14) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfield, A. P.; Masamune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(15) Mancuso, A. J.; Juang, S. L.; Swern D. *J. Org. Chem.* **1978**, *41*, 2480.

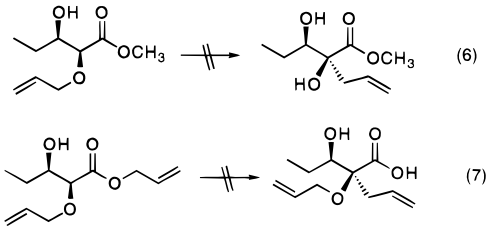
(16) Baker, R.; Head, J. C.; Swain, C. J., *J. Chem. Soc., Perkin Trans. 1* **1988**, 85. Guerriero, A.; D'Ambrosio, M.; Cuomo, V.; Vanzanella, F.; Pietra, F. *Helv. Chim. Acta* **1989**, *72*, 438.



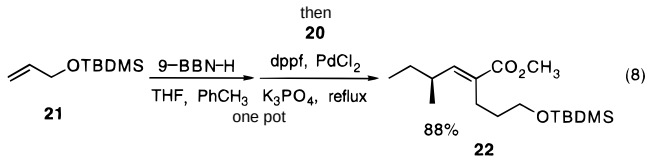
troscopy since both geometric isomers were available by the Emmons−Wadsworth−Horner reaction.

These substrates were synthesized to test the chemoselectivity of the osmium-catalyzed dihydroxylations. Surprisingly, enyne **15** was inert toward all catalytic dihydroxylations, both achiral and chiral. The literature suggests that trisubstituted alkenes bearing a carbonyl group are readily dihydroxylated; whereas, monosubstituted alkenes are not.[19] However, dihydroxylation of **17b** led only to reaction at the nonconjugated alkene. Reduction of the electron-withdrawing nature of the ester by conversion to a carboxylate salt had no effect on this chemoselectivity.

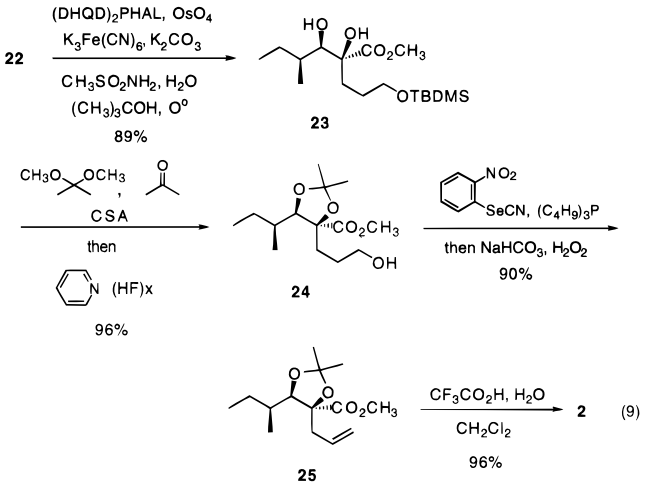
The fact that **19** undergoes asymmetric dihydroxylation without difficulty and that such diols can also be accessed by aldol strategies led us to examine Wittig and Claisen rearrangements as shown in eqs 6 and 7, respectively. In neither case were the desired products observed.



A straightforward resolution of this impasse used a primary alcohol as a surrogate for the monosubstituted alkene. Suzuki cross-coupling[20] of the organoborane derived from the *tert*-butyldimethylsilyl ether of allyl alcohol **21** with vinyl bromide **20** gave **22** as a single geometric isomer in 88% isolated yield (eq 8). Use of cesium carbonate as base or DMF as solvent

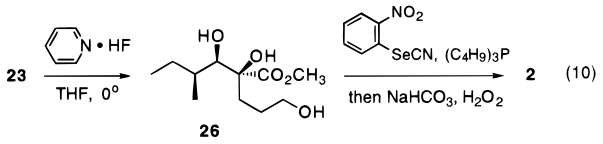


gave poor results. Asymmetric dihydroxylation proceeded uneventfully to give an 89% yield of diol **23** with a diastereomeric excess (de) of 98% (eq 9). Acetonide formation was



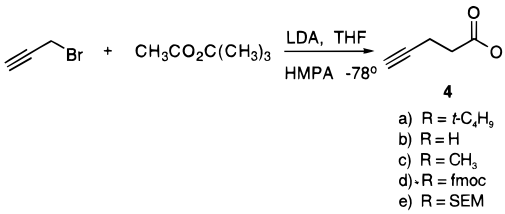
accompanied by desilylation by addition of pyridine·hydrofluoride. The primary alcohol completed its role as an alkene surrogate and was eliminated to form the monosubstituted alkene **25** via the Grieco method.[21] Acid solvolysis removed the acetonide to provide the desired alkene substrate **2**. In this way, substrate **2** is available in 8-steps from commercially available alcohol.

In examining the sequence, the employment of the acetonide was to maintain differentiation among the three hydroxyl groups present in **26**. However, chemoselective substitution of the primary alcohol to form the selenide should be feasible in the presence of the secondary and tertiary alcohols. Indeed, exposing the triol to the standard conditions proceeds smoothly to give the diol **2** in 77% overall yield (eq 10). The net result



is eliminating one step and providing alkene **2** in only seven steps from commercially available alcohol **12** although the overall yield of 45−50% was virtually unchanged.

The alkyne partner **4b** was originally synthesized from propargylated malonate by hydrolysis and decarboxylation. A convenient alternative involving fewer steps proved to be the direct alkylation of the enolate of *tert*-butyl acetate with propargyl bromide (eq 11) to give the *tert*-butyl ester **4a** in 66% yield, which was easily solvolyzed (TFA, CH_2Cl_2, 74%) to form the acid **4b**. This acid is also commercially available. The methyl ester **4c** was prepared by esterification of the acid with diazomethane.



Ru-Catalyzed Coupling

Initial attempts to perform the Alder ene reaction focused on the protected form of the ene component **25** with the *tert*-butyl ester **4a**. Heating an approximately 1:1 mixture of the two substrates with 10 mol % of complex **8** in 1:1 DMF−water at

(17) Converting **19** derived from both (***S***)-**12** and racemic **12** to **24** allows ready analysis of the diastereomeric purity which, since the asymmetric dihydroxylation proceeds with 98% ee and translates into the enantiopurity of **19**.

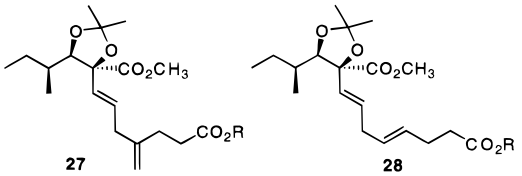
(18) Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

(19) Kolb, H. C.; VanNieuwenhze M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1993**, *115*, 7047.

(20) Oh-e, T.; Miyaura, N.; Suzuki, A. *J. Org. Chem.* **1993**, *58*, 2201. Johnson, C. R.; Braun, M. P. *J. Am. Chem. Soc.* **1993**, *115*, 11014. Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Suzuki, A. *J. Am. Chem. Soc.* **1989**, *111*, 314.

(21) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

Table 1. Ru-Catalyzed Reaction of Acetonide Ene **25** and Alkynes **4**[a]



a) R = $C(CH_3)_3$, b) R = H, c) R = CH_3, d) R = fmoc

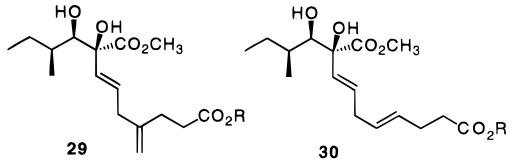
Entry	Alkyne	Ratio **4a**:**25**	% **8**	Additive	Solvent	Temp	Time (h)	Isolated Yield	**27** : **28**[b]
1	**4a**	1.04	9.8	none	DMF:H_2O	100°	2.5	26	1.6
2	**4a**	1.09	15.9	none	CH_3OH:H_2O[c]	reflux	14	49	2.2
3	**4a**	1.05	13.1	none	CH_3OH:H_2O[d]	95°	14	18	1.1
4	**4a**	1.19	10.5	pH7 phosphate buffer	CH_3OH:H_2O[c]	75°	5	16	1.7
5	**4a**	1.19	13.8	$(C_2H_5)_3NHPF_6$	CH_3OH:H_2O[c]	reflux	5	51	N.D.
6	**4a**	1.18	10.4	NH_4PF_6	CH_3OH:H_2O[c]	reflux	9	58	1.6
7	**4a**	1.18	11.1	$AgPF_6$	CH_3OH:H_2O[c]	reflux	4.5	41	2.8
8	**4a**	1.10	10.5	Ag_2SO_4	CH_3OH:H_2O[c]	reflux	4.5	54	2.2
9	**4a**	1.47	16.1	$In(OSO_2CF_3)_3$	CH_3OH:H_2O[c]	reflux	4.5	47	1.6
10	**4b**	1.03	10.0	NH_4PF_6	CH_3OH	reflux	4	43	1.2
11	**4b**[e]	1.20	14.9	NH_4PF_6	CH_3OH	R.T.	1	39	1.4
12	**4d**	1.01	11.1	NH_4PF_6	CH_3OH	reflux	4	15	3.9
13	**4d**[e]	1.30	15.0	NH_4PF_6	CH_3OH	R.T.	1	28	3.6
14	**4d**[e]	1.24	16.3[f]	CSA	CH_3OH	R.T.	1	30	3.8

[a] All reactions were run at 0.1 M under nitrogen. [b] Determined by ^1H NMR spectroscopy. [c] 1:1 ratio. [b] 1:3 ratio. [e] Reaction performed at 7−8 kbar at room temperature. [f] $CpRu(Ph_3P)$(2-methallyl) was used at catalyst.

100 °C gave a 26% yield of a 1.6:1 ratio of **27a**:**28a** (see Table 1, entry 1). Replacing DMF−water with 1:1 methanol:water increased the yield to 49% and the **27a**:**28a** ratio to 2.2 (Table 1, entry 2). The reaction appears to be sensitive to pH (Table 1, entries 2 and 4−6). The yield increases with increasing acidity. Stronger acids were not explored because of the assumed sensitivity of the product to acid, but may be generally beneficial. The effect of chloride ion was explored by the addition of strong (Table 1, entries 7 and 8) and moderate (Table 1, entry 9) chloride scavengers. Except for silver sulfate, these did not influence the reaction. The effect of silver sulfate may be related to pH since addition of a pH 7 phosphate buffer to the reaction of entry 4 saw the yield plummet to 16%. Thus, under the best reaction conditions (Table 1, entries 6 and 8), a 58% yield of the desired ene type adducts were obtained but, surprisingly, with disappointing regioselectivity.

Because of the rather polar hydroxylic nature of the solvent, we hypothesized that the highly lipophilic substrate **25** may be adopting conformations that attenuated the regioselectivity. The use of alcoholic solvents suggested that the free diol itself **2** would be an acceptable substrate. Table 2 summarizes the results of its ruthenium-catalyzed reaction with various 4-pentynoate acceptors to give the adducts **29** and **30**. Using conditions similar to entry 6 of Table 1, except that pure methanol was employed (see Table 2, entry 1), a nearly quantitative yield (based upon recovered starting material, brsm) of the adducts was obtained. Furthermore, the branched-to-linear ratio improved to 6.1. The problem that remained was conversion. In all cases, significant quantities of unreacted starting material remained although it was not always recovered. In those cases where it was recovered, the yields based upon recovered starting material were always high and frequently quantitative. Adding a second batch of catalyst after 15 min (Table 2, entry 2) nearly doubled the conversion and retained the excellent yield. On the other hand, initiating the reaction with twice the amount of catalyst did not significantly improve the turnover (Table 2, entry 3 vs 1). Addition of indium triflate improved the branched-to-linear ratio but at the expense of conversion (Table 2, entry 4). A significant difference occurred upon performing the reaction under high pressure at ambient temperature (Table 2, entry 5) which nearly doubled the branched-to-linear ratio. The yield was high based upon total mass recovery but was complicated by the fact that some transesterification occurred to produce the methyl ester **29c**. The methyl ester **4c** participated in a fashion similar to the *tert*-butyl ester **4a** as shown in entries 6 and 7, Table 2. The slightly higher regioselectivity may derive from a steric effect.

Table 2. Ru-Catalyzed Reaction of Diol Ene *2* and Alkynes *4*[a]

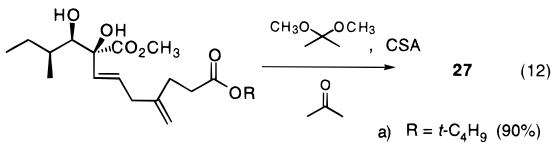


a) R = *t*-C$_4$H$_9$ b) R = H c) R = CH$_3$ d) R = fmoc

entry	alkyne	ratio **4a**:**2**	**8** (%)	additive	temp.	time (h)	isolated yield (%)	ratio **29**:**30**
1	**4a**	1.06	12.0	NH_4PF_6[g]	reflux	2	35(99)[d]	6.1
2[c]	**4a**	1.05	2 × 10.9	NH_4PF_6[g]	reflux	2	60(100)[d]	4.9
3	**4a**	1.20	23	NH_4PF_6[g]	reflux	2	41	6.7
4	**4a**	1.22	10.8	NH_4PF_6[g] + $In(OSO_2CF_3)_3$	reflux	2	25	8.8
5[e]	**4a**	1.14	10.9	NH_4PF_6[g]	rt	24	65(100)	12.5
6	**4c**	1.52	10.1	NH_4PF_6[f]	reflux	2	25(79)	7.4
7	**4c**	1.00	10.9	NH_4PF_6[g]	reflux	2	33	7.0
8	**4d**	0.96	10.6	NH_4PF_6	reflux	2.5	52	4.9
9[h]	**4d**	1.02	12.3	NH_4PF_6	rt	2	47(90)[d]	6.7
10[i]	**4d**	1.03	14.5	NH_4PF_6	rt	1	58(92)[d]	6.9
11[i]	**4d**	1.17	15.4	NH_4PF_6 + CF_3CO_2H	rt	1	48	5.4
12[i,j]	**4d**	1.11	11.7	NH_4PF_6	rt	1	39(55)	7.7
13[j,k]	**4d**	1.20	18.5	NH_4PF_6	rt	1.5	51	8.9
14[k,l]	**4d**	1.36	16.7	NH_4PF_6	rt	1.5	33	5.2

[a] All reactions were run at 0.1 M in methanol. [b] Determined by ^{1}H NMR spectroscopy. [c] The reaction was initially charged with 10.9 mol % **8** and no NH_4PF_6; after 15 min, an additional 10.9 mol % **8** and 40 mol % NH_4PF_6 were added. [d] Yields in parentheses based upon recovered starting material. [e] Reaction performed at 8−9 kbar. [f] 5.9 equiv relative to catalyst used. [g] 2.2 equiv relative to catalyst used. [h] Reaction performed at 5 kbar. [i] Reaction performed at 7−8 kbar. [j] Reaction run in 1:1 acetone:methanol. [k] Reaction performed at 11−13 kbar. [l] Reaction performed in acetone.

Having both the methyl and *tert*-butyl esters of the acyclic fragment available, we only require the acid **27b** to complete the formal synthesis since the coupling with the dihydropyrone and hydrolysis that completes the synthesis has been previously accomplished in only three steps. Formation of the acetonides **27a** and **27b** proceeds uneventfully under standard conditions (eq 12). Surprisingly, neither could be hydrolyzed in our hands



a) R = *t*-C$_4$H$_9$ (90%)
b) R = H
c) R = CH$_3$ (96%)
d) R = fmoc (97%)

to the desired acid **27b**. In the case of the *tert*-butyl ester, acid conditions led to decomposition. Cleavage of the methyl ester by either base or by dealkylation suffered from low chemoselectivity between the two esters.

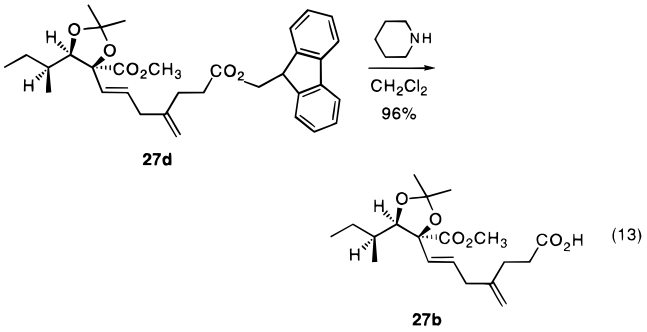
We, therefore, examined the ruthenium-catalyzed addition of 4-pentynoic acid with the alkene partner. The extraordinary polarity of a diol carboxylic acid led us to examine the reaction of the acetonide **25** with this acid to form **27b** directly. As shown in Table 1, entry 10, the reaction proceeded in somewhat lower yield than the *tert*-butyl ester (cf entry 6) and the regioselectivity was still poor. Running at high pressure (Table 1, entry 11) did not have a favorable effect on the reaction.

Since the substrates **27a** and **27c** showed sensitivity to acid and the lack of chemoselectivity with nucleophilic base, we considered the use of an ester that could be removed selectively with a nonnucleophilic base. For this purpose, we chose the trimethylsilylethyl (SEM) and 9-fluorenylmethyl (fmoc) esters. Coupling 4-pentynoic acid with 2-trimethylsilylethanol and 9-fluorenylmethanol with DCC and DMAP gave the corresponding esters **4e** and **4d** in 85% and 71% yields respectively (eq 11). The SEM ester did not survive the ruthenium-catalyzed addition. On the other hand, the fmoc ester **4d** did participate (see Table 1, entries 12−14, and Table 2, entries 8−14).

Studies with the acetonide alkene **25** under standard conditions (Table 1, entry 12) gave a low conversion resulting in a low isolated yield of the desired adducts **27d** and **28d**. Interestingly, the branched-to-linear ratio improved by about a factor of 2. Given our earlier success with high pressure, we examined its effect here (Table 1, entry 13). While the conversion improved, even though we were operating at room temperature, the regioselectivity was unchanged.

The diol alkene **2** proved to be a more satisfactory substrate in the reactions of the fmoc ester **4d** as in all other cases. An excellent yield at about 50% conversion is obtained under almost all conditions. The bulky fmoc ester does appear to have a slight effect on regioselectivity causing it to diminish somewhat (Table 2, entry 8). The reaction, when performed under high pressure, proceeds at ambient temperature (Table 2, entries 9 and 10). While the regioselectivity improved somewhat, the effect was much smaller than that seen with the *tert*-butyl ester (Table 2, entry 5). Increasing acidity by adding a trace of trifluoroacetic acid decreased the selectivity (Table 2, entry 11). Decreasing the polarity of the solvent by using a 1:1 mixture of acetone−methanol caused a small increase in regioselectivity (Table 2, entry 12) which further increased by raising the pressure to about 13 kbar (Table 2, entry 13). On the other hand, using only acetone as solvent caused the regioselectivity to diminish (Table 2, entry 14).

With the fmoc ester of the intact acyclic fragment of alternaric acid in hand, the corresponding acetonide **27d** (eq 12) was formed in standard fashion, setting the stage for the final step, the deesterification. Subjecting the fmoc ester **27d** to piperidine in methylene chloride led to smooth cleavage to the free acid **27b** in nearly quantitative yield (eq 13).



27d **27b** (13)

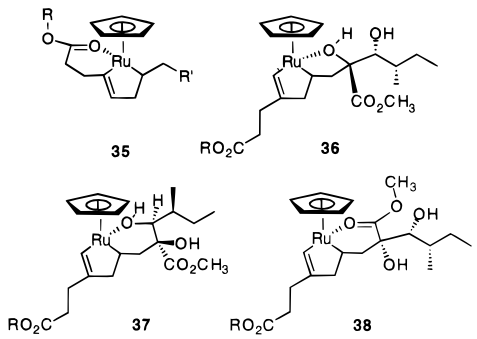
Discussion

New methodology provides an opportunity to consider synthetic strategies that formerly did not exist. The examination of the structural fragment **I** present in natural products normally led to a retrosynthetic analysis based upon olefination protocols such as the Wittig, Peterson, and Julia olefinations. Application of such methods suffers from the need to juggle the functionality in order to make it compatible and the requirement of multiple steps with dienes such as **I**. The synthesis of alternaric acid highlights this point. The creation of the ruthenium-catalyzed reaction led to a synthesis of the acyclic unit in 10 linear steps and 38% overall yield from commercially available (*S*)-2-methyl-1-butanol and the fmoc ester of 4-pentynoic acid, the latter available in one step from the commercially available acid in 71% unoptimized yield. Thus, from commercially available materials, a total of 11 steps and 27% overall yield were required as a result of the availability of the ruthenium-catalyzed reaction. In fact, we can cut one step from our sequence by simply adding triethylamine to the in situ generated dibromide to make it a total of 10 steps from commercially available materials or nine linear steps. The fact that the yield for the one-step conversion of alkene to vinyl bromide was in the 70−80% range compared to quantitative for the two-step process led us to favor the latter. It contrasts quite favorably with the previously recorded synthesis (vide supra) which also employed (*S*)-2-methyl-2-butanol as one starting material but relied upon established methodologies. Our route requires only about one-third the number of steps.

Further reduction of the number of linear steps were thwarted by racemization during olefination and by the reverse chemoselectivity in the dihydroxylation of the diene **20b**. To reduce the length of the longest linear sequence, we explored the use of alkylated stabilized olefination agents. With the Wittig reagent **14** (eq 3), addition to (*S*)-2-methylbutanal gave nearly racemic product. Since the addition of ylide **14** to the aldehyde was very slow, we believe that its low nucleophilicity led to the domination of an acid−base reaction which effects racemization. Using the less stabilized phosphonate anions might resolve this problem. Unfortunately, the enolates from **16a**−**c** led only to *E*−*Z* olefinic mixtures. Since we suspected that other alkyl-bearing olefinating agents would show similar behavior, they were not pursued. Work by the Sharpless group established that monosubstituted alkenes react at a significantly slower rate than trisubstituted alkenes.[19] Further, they report that α,β-unsaturated esters are excellent substrates.[22] While the electron-withdrawing nature of the ester function decreases the reactivity of the trisubstituted double bond, the question of whether the loss in reactivity would make it slower than a monosubstituted double bond was not answered. To our chagrin, the answer is that excellent chemoselectivity resides in the opposite direction of our requirement. This result raises the question of whether a ligand environment can be found for osmium to impart more nucleophilicity and thereby reverse such a chemoselectivity. That the trisubstituted double bond bearing the ester functionality can participate in the asymmetric dihydroxylation is illustrated by the reaction of **22**, which proceeds in good yields and with excellent reagent controlled diastereoselectivity.

It is interesting to note that the acetonide is not required for the synthesis of the acyclic fragment. The chemoselectivity of the dehydration sequence (eq 10) and the ruthenium-catalyzed addition of alkene **2** with alkyne **4** do not require such protection. Thus, the acyclic fragment is actually available in only nine linear steps. Indeed, one of the strengths of the ruthenium reaction is its chemoselectivity, and the substrates examined herein illustrate that point.

Scheme 2 outlines the mechanistic rationale for the ruthenium-catalyzed addition. The equivalent of a triply coordinatively unsaturated ruthenium cationic complex is generated by the ionization of the chloride and the removal of the COD ligand by a [2 + 2 + 2] cycloaddition with the alkyne. The result of this activation event is to consume an amount of the alkyne equivalent to the amount of the ruthenium complex. Thus, the alkyne:alkene ratios depicted in the tables must be adjusted to take into account the consumption of the alkyne. For example, in Table 1, entry 1, the adjusted **4**:**25** ratio is 0.94 and the alkyne is the limiting substrate. The regioselectivity is determined by the ratio of ruthenacycle **33** (leading to branched product) to ruthenacycle **34** (leading to linear product). Normally, regioisomer **33** dominates, presumably because it minimizes steric congestion around the ruthenium compared to **34**. On the other hand, in the present case, the ester is poised to occupy the open coordination site on ruthenium otherwise occupied by solvent (or some other external ligand) in **33** and **34** as depicted in **35**.

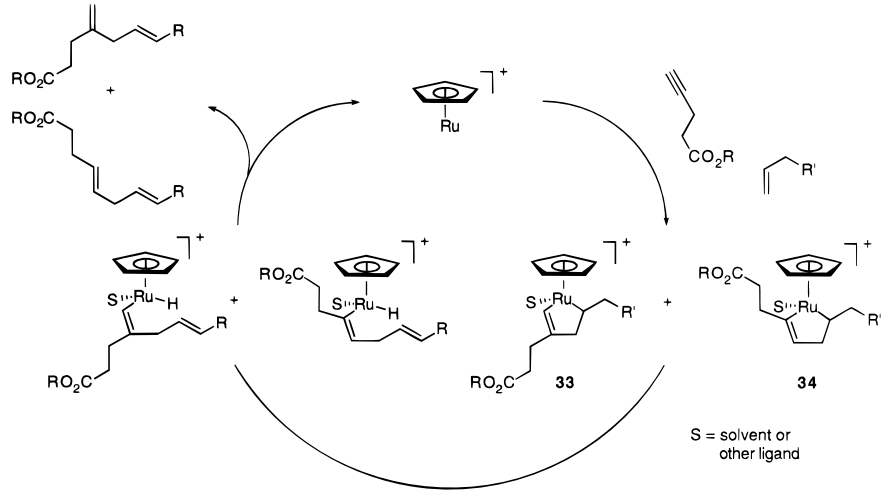


35 **36** **37** **38**

This competitive internal coordination compromises the intrinsic preference for branched product leading to a low selectivity for the reactions with acetonide **25**. Removal of the acetonide then leads to the prospect of internal coordination with the functionality present in the alkene. Either hydroxyl group (via **36** or **37**) or even the ester (via **38**) may compete with the alkyne ester for the open coordination site on ruthenium, thereby restoring the selectivity for the branched product. Since ester coordination as in **38** is also possible in the acetonide **25**, this motif may seem less likely although steric hindrance imposed by the acetonide may account for the failure of the methoxycarbonyl group to effectively participate in this case. Increasing pressure should increase participation by the oxygens as depicted in **36**−**38**. Since it is reasonable to expect that transition states involving such coordination would have lower volumes of activation, an increased selectivity for the branched product

(22) Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.; Kwang, H.; Morikawa, K.; Wang, Z.; Xu, D.; Zhang, X. *J. Org. Chem.* **1992**, *57*, 2768.

Scheme 2. Mechanistic Rationale of Ru-Catalyzed Addition



would be expected and is observed. In support of this interpretation, high-pressure had no effect on the regioselectivity of the addition of the acetonide **25** which precludes such coordination. Exploitation of these coordination effects constitutes an important direction for further study.

The ruthenium-catalyzed additions of alkenes and alkynes provide a powerful new paradigm for the construction of complex organic molecules. The example of alternaric acid is an excellent illustration of its potential impact. The strength of the methodology stems to a considerable extent from its extraordinary chemoselectivity. Except for basic amines (which can be "protected" as an amide or by protonation), and phosphines, no other groups have yet been found to be incompatible. Divalent sulfur, notorious as a catalyst poison, does not interfere.[23] The compatibility with aqueous media also bodes well for the prospect of employing just water as solvent with appropriate substrates, thereby making this reaction more environmentally benign. The ability of the reaction to form the new 1,2-disubstituted double bond adjacent to a quaternary center is noteworthy since the reaction has shown extreme sensitivity to steric factors with respect to substitution on the alkene. While many aspects of the reaction remain to be explored, the current study helps establish its utility even in its current stage of development.

Experimental Section

Reactions were generally conducted under a positive pressure of dry nitrogen within flame-dried glassware. Reactions were sealed with red rubber septa and magnetically stirred. THF and diethyl ether were distilled from sodium/benzophenone ketyl prior to use. Methylene chloride and acetonitrile were distilled from calcium hydride prior to use. Methanol was distilled from magnesium methoxide prior to use. Common reagents and materials were purchased from commercial sources and purified by recrystallization or distillation. Anhydrous solvents and reaction mixtures were transferred by oven-dried syringe or cannula. Flash chromatography employed ICN silica gel (Kiesselgel 60, 230−400 mesh). Analytical TLC was performed with 0.2 mm coated commercial silica plates (E. Merck, DC-Platten Kieselgel 60 F_{254}). Melting points were determined on a Thomas-Hoover oil bath apparatus and were not corrected. Analytical gas chromatography was performed on a Varian star 3600 gas chromatograph with a 10 m × 0.25 mm poly(dimethylsiloxane) column.

***tert*-Butyl (*E*)-8-Hydroxy-8-(methoxycarbonyl)-4-methylene-6-nonenoate (9a).** To a solution of 72.1 mg (0.5 mmol) of methyl 2-hydroxy-2-methyl-4-pentenoate (**7b**) and 77.1 mg (0.5 mmol) of *tert*-butyl 4-pentynoate (**4a**) in 2.5 mL of water and 1.5 mL of methanol was added 7.8 mg (0.025 mmol) of CpRu(COD)Cl in 1 mL of methanol. The mixture was heated at 70 °C for 8 h. Water (5 mL) was added, and the mixture was extracted with ether (3 × 15 mL). The organic phase was washed with brine (3 × 2 mL), dried ($MgSO_4$), and evaporated in vacuo. Chromatography (ethyl acetate:hexane = 1:4) of the residue yielded 68 mg (46%) of the product **9a**. IR (neat): 3512, 1731, 1647, 1452, 1437 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.84 (td, J = 6.9, 15.4 Hz, 1H), 5.64 (d, J = 15.4 Hz, 1H), 4.75 (s, 2H), 3.78 (s, 3H), 2.75 (d, J = 6.9 Hz, 2H), 2.38−2.24 (m, 4H), 1.48 (s, 3H), 1.43 (s, 9H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 176.23, 172.50, 146.30, 133.36, 128.17, 110.61, 80.25, 74.26, 53.00, 38.91, 33.77, 30.99, 28.08, 25.94. Anal. Calcd for $C_{16}H_{26}P_5$: C, 64.41; H, 8.78. Found: C, 64.42; H, 8.54.

(*E*)-(6*R*,8′*R*)-5,6-Dihydro-4-hydroxy-6-methyl-3-(8-(methoxycarbonyl)-4-methylene-8-hydroxy-6-nonenol)pyrane-2-one (11). To a solution of 64.5 mg (0.31 mmol) of alkene **7b** and 44.6 mg (0.31 mmol) of compound **10** in 1.5 mL of water and 1.5 mL of methanol was added 9.6 mg (0.031 mmol) of CpRu(COD)Cl, and the mixture was heated at 70 °C for 1 h. Brine (3 mL) was added, and the mixture was extracted with ether (4 × 3 mL). The organic phase was dried ($MgSO_4$) and evaporated in vacuo. After purification by chromatography (ethyl acetate:hexane = 1:1 and dichloromethane:methanol = 95:5) 23 mg (21%) of product **11** was obtained. $[\alpha]_D^{28} = 24.8$ (c = 2.0, $CHCl_3$). IR (neat): 3506, 1737, 1715, 1573, 1558, 1454 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.85 (td, J = 6.8, 15.4 Hz, 1H), 5.66 (d, J = 15.4 Hz, 1H), 4.80−4.77 (m, 2H), 4.58−4.47 (m, 1H), 3.78 (s, 3H), 3.31 (s, 1H), 3.27−3.07 (m, 2H), 2.79 (m, 2H), 2.67−2.63 (m, 2H), 2.35 (m, 2H), 1.49 (s, 3H), 1.46 (d, J = 6.4 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 203.81, 194.50, 176.20, 164.22, 146.03, 133.54, 128.08, 111.28, 103.13, 74.30, 70.32, 52.98, 39.15, 38.79, 37.01, 30.58, 25.89, 20.59. Anal. Calcd for $C_{18}H_{24}O_7$: C, 61.35; H, 6.87; MW, 352.1522. Found: C, 61.10; H, 6.96; MW, 352.1518.

(2*Z*,4*S*)-Methyl-2-bromo-4-methylhex-2-enoate (20a). Bromine (0.07 mL, 1.36 mmol) was slowly added dropwise to **19** (142 mg, 0.999 mmol) in 2 mL of methylene chloride at 0 °C. After 2 h of stirring, the solution was diluted with saturated sodium thiosulfate, extracted with diethyl ether, the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was diluted with 2 mL of methylene chloride. Triethylamine (0.70 mL, 5.02 mmol) was then added, and the reaction was stirred for 24 h. The heterogeneous mixture was concentrated under reduced pressure, and the residue was flash chromatographed with 49:1 pentane:diethyl ether as the eluant to yield 218 mg (99% yield) of a clear liquid, R_f = 0.42 (19:1 hexanes:ethyl acetate), $[\alpha]_D^{28} = +17.88$ (c = 10.0, toluene). When this reaction was performed using 5.92 g (41.6 mmol) of **19**, 2.6 mL (50.5 mmol) of bromine in 84 mL of methylene chloride followed by 11.7 mL (83.9 mmol) of triethylamine in 210 mL of methylene chloride, 7.09 g (77% yield) of **20a** was obtained. IR (thin

(23) Trost, B. M.; Shi, Z.-P. *J. Am. Chem. Soc.* **1994**, *116*, 7459.

film): 1735, 1623, 1459, 1436 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, J = 9.6 Hz, 1H), 3.83 (s, 3H), 2.67 (m, 1H), 1.44 (m, 2H), 1.05 (d, J = 6.9 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 164.83, 153.28, 116.12, 54.67, 39.95, 30.23, 19.83, 13.09. Anal. Calcd for $C_8H_{13}BrO_2$: C, 43.46; H, 5.93. Found: C, 43.39; H, 6.00.

(2*E*,4*S*)-Methyl-2-(3-*tert*-butyldimethylsiloxypropyl)-4-methylhex-2-enoate (22). Borane dimethyl sulfide (10 M, 200 μL, 2.00 mmol) was added to a solution of 1,5-cyclooctadiene (245 μL, 2.00 mmol) in 4 mL of THF at 0 °C. The reaction was subsequently heated to reflux for 2.5 h. After cooling to room temperature, **21** (336.2 mg, 1.95 mmol) was added and the reaction was stirred for 22 h at which time tribasic potassium phosphate (641.8 mg, 3.02 mmol) and bis-1,1′-(diphenylphosphino)ferrocenepalladium(II) chloride (36.6 mg, 0.0500 mmol) was added. The mixture was heated to reflux during which time it became dark. Vinyl bromide **20a** (206.9 mg, 0.936 mmol) was added, and the mixture was heated at reflux for 13 h. The mixture was diluted with water, extracted with diethyl ether, the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was flashed chromatographed with 49:1 pentane:diethyl ether as the eluant to yield 257.7 mg (88%) of a clear liquid, R_f = 0.44 (19:1 hexanes:ethyl acetate), $[\alpha]_D^{28}$ = +17.87 (c = 10.0, CH_2Cl_2). Performing this reaction with 5.84 g (26.4 mmol) of **20a**, 9.10 g (52.8 mmol) of **21**, 53.0 mmol of 9-BBN-H, and 0.98 g (1.34 mmol) of bis-1,1-(diphenylphosphinol)ferrocene in 106 mL of THF gave 6.54 g (79% yield) of **22**. IR (thin film): 1717, 1645, 1462, 1436, 1253 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 6.52 (d, J = 10.2 Hz, 1H), 3.72 (s, 3H), 3.60 (t, J = 6.3 Hz, 2H), 2.44 (m, 1H), 2.34 (t, J = 7.5 Hz, 2H), 1.60 (m, 2H), 1.36 (m, 2H), 0.99 (d, J = 6.9 Hz, 3H), 0.90 (s, 9H), 0.85 (t, J = 7.5 Hz, 3H), 0.05 (s, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 170.27, 150.35, 132.19, 64.15, 53.02, 36.04, 34.24, 31.08, 27.31, 24.78, 21.41, 19.66, 13.33, −3.94. HRMS: calcd for $C_{16}H_{31}O_3Si$ ($M^+ - CH_3$) 299.2043, found 299.2051.

(2*R*,3*S*,4*S*)-Methyl 2-(3-*tert*-Butyldimethylsiloxypropyl)-2,3-dihydroxy-4-methylhexanoate (23). A heterogeneous mixture of potassium carbonate (8.74 g, 63.2 mmol), potassium ferricyanide (20.61 g, 62.6 mmol), $(DHQD)_2PHAL$ (1.55 g, 1.99 mmol), 4% osmium tetraoxide (5.4 mL, 0.817 mmol) in water, methanesulfonamide (1.99 g, 20.9 mmol), and **22** (6.54 g, 20.8 mmol) in *tert*-butyl alcohol (105 mL) and water (105 mL) was stirred for 6 days at 0 °C. The heterogeneous mixture was diluted with saturated aqueous sodium dithionite, stirred until the solution became homogeneous, extracted with diethyl ether, the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was flash chromatographed with 1:1 pentane:diethyl ether as the eluant to yield 6.44 g (89%) of a clear liquid, R_f = 0.51 (7:3 hexanes:ethyl acetate), $[\alpha]_D^{28}$ = +3.46 (c = 5.0, CH_2Cl_2). IR (thin film): 3506, 1736, 1463, 1445 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.75 (s, 1H), 3.61 (m, 2H), 2.14 (d, J = 10.8 Hz, 1H), 1.65 (m, 4H), 1.35 (m, 3H), 0.91 (m, 6H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 176.91, 80.80, 76.43, 62.97, 52.98, 35.09, 32.28, 28.28, 27.03, 25.80, 18.19, 12.69, 11.86, −5.47. Anal. Calcd for $C_{17}H_{36}O_5Si$: C, 58.58; H, 10.41. Found: C, 58.62; H, 10.20.

(4*S*,5*R*,1′*S*)-2,2-Dimethyl-4-(3-hydroxypropyl)-4-(methoxycarbonyl)-5-(1′-methylpropyl)-1,3-dioxolane (24). CSA (60.9 mg, 262 μmol) was added to a solution of **23** (0.41 g, 1.18 mmol) and 2,2-dimethoxypropane (1.45 mL, 11.8 mmol) in 11.8 mL of acetone. After 24 h of stirring, pyridine:hydrofluoride (0.60 mL) was added at 0 °C, and the reaction was stirred for 1 h. The solution was diluted with water, extracted with diethyl ether, the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was flash chromatographed with 1:1 pentane:diethyl ether as the eluant to yield 0.31 g (96%) of a clear liquid, R_f = 0.41 (1:1 hexanes:ethyl acetate), $[\alpha]_D^{23}$ = 31.13 (c = 10.0, CH_2Cl_2). IR (thin film): 3450, 2965, 2937, 2878, 1740, 1455 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 3.87 (d, J = 9.0 Hz, 1H), 3.76 (s, 3H), 3.64 (m, 2H), 1.99 (m, 1H), 1.60 (m, 7H), 1.45 (s, 6H), 1.01 (d, J = 6.6 Hz, 3H), 0.86 (t, J = 7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.85, 108.75, 85.42, 85.03, 62.88, 52.53, 33.72, 28.47, 27.87, 27.12, 25.20, 24.87, 16.13, 10.61. HRMS: calcd for $C_{13}H_{23}O_5$ ($M^+ - CH_3$) 259.1546, found 259.1548.

(4*S*,5*R*,1′*S*)-2,2-Dimethyl-4-(methoxycarbonyl)-5-(1′-methylpropyl)-4-(prop-2-enyl)-1,3-dioxolane (25). Tri-*n*-butylphosphine (3.4 mL, 13.6 mmol) was added to a solution of **24** (757.5 mg, 2.76 mmol) and *o*-nitrophenylselenocyante (3.08 g, 13.6 mmol) in 28 mL of THF, and the solution immediately turned dark brown. After 12 h of stirring, sodium bicarbonate (1.1429 g, 13.6 mmol) was added followed by the addition of 30% hydrogen peroxide (2.8 mL, 27.4 mmol). After 8 h of stirring, the heterogeneous mixture was diluted with 10% aqueous hydrochloric acid, extracted with diethyl ether, the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was flash chromatographed with 19:1 pentane:diethyl ether as the eluant to yield 640 mg (90%) of a clear liquid, R_f = 0.50 (9:1 hexanes:ethyl acetate), $[\alpha]_D^{23}$ = −54.97 (c = 3.8, CH_2Cl_2). IR (thin film): 1740, 1642, 1457, 1437 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.84 (m, 1H), 5.13 (m, 1H), 5.09 (s, 1H), 3.91 (d, J = 9.0 Hz, 1H), 3.74 (s, 3H), 2.65 (dd, J = 13.8 Hz, 7.2 Hz, 1H), 2.35 (dd, J = 13.8 Hz, 6.9 Hz, 1H), 1.75 (m, 1H), 1.54 (m, 2H), 1.47 (s, 3H), 1.44 (s, 3H), 1.06 (m, 1H), 1.03 (d, J = 6.6 Hz, 3H), 0.88 (t, J = 7.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.33, 133.01, 118.68, 108.84, 85.04, 84.89, 52.35, 37.05, 33.84, 27.79, 25.13, 16.12, 10.69. Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.71; H, 9.19.

(4*S*,5*R*,6*S*)-4,5-Dihydroxy-4-(methoxycarbonyl)-6-methyl-1-octene (2). Method A: Compound **25** (0.68 g, 2.65 mmol) was dissolved in 4 mL of dichloromethane, 4 mL of trifluoroacetic acid, and 0.3 mL of water. After 10 h of stirring, the solution was concentrated under reduced pressure. The residue was flash chromatographed with 4:1 pentane:diethyl ether as the eluant to yield 0.57 g (99%) of a clear liquid.

Method B: Pyridine·hydrofluoride (0.55 mL) was added to a solution of **23** (366.8 mg, 1.05 mmol) in 11 mL of THF. After 14 h of stirring, the solution was concentrated on to silica gel in vacuo and passed through a plug of silica with 2:3 hexanes:ethyl acetate as the eluant. The pure triol was diluted with 10 mL of THF, and *o*-nitrophenylselenocyanate (681.1 mg, 3.00 mmol) was added followed by the addition of tri-*n*-butylphosphine (0.75 mL, 3.01 mmol). After 1 h stirring, sodium bicarbonate (2.52 g, 30.0 mmol) and 30% peroxide hydrogen (3.1 mL, 30.3 mmol) was added. After 14 h of stirring, the heterogeneous mixture was diluted with 10% aqueous hydrochloric acid, extracted with diethyl ether, the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was flash chromatographed with 4:1 pentane: diethyl ether as the eluant to yield 176 mg (77% overall) of a clear liquid, R_f = 0.46 (7:3 hexanes:ethyl acetate), $[\alpha]_D^{23}$ = −10.16 (c = 6.3, CH_2Cl_2). IR (thin film): 3505, 1736, 1642, 1460, 1440 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.71 (m, 1H), 5.13 (d, J = 3.9 Hz, 1H), 5.08 (s, 1H), 3.8 (d, J = 1.8 Hz, 1H), 3.79 (s, 3H), 2.41 (d, J = 7.5 Hz, 2H exchangeable protons), 1.70 (dsextet, J = 6.9, 1.8 Hz, 1H), 1.44 (m, 1H), 1.35 (m, 1H), 0.92 (m, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 176.19, 131.88, 119.34, 80.80, 75.94, 52.99, 40.26, 35.05, 28.25, 12.66, 11.83. HRMS: calcd for $C_{11}H_{21}O_4$ (MH^+) 217.1440, found 217.1440.

(6*E*,8*R*,9*R*,10*S*)-*tert*-Butyl 8,9-(Isopropylidenedioxy)-8-(methoxycarbonyl)-10-methyl-4-methylene-6-dodecenoate (27a). From **25**: Methanol (0.50 mL) and water (0.50 mL) was added to a mixture of **4a** (18.1 mg, 117 umol), **25** (25.4 mg, 99.1 mmol), CpRu(COD)Cl (3.2 mg, 10.3 umol), and ammonuim hexafluorophosphate (9.1 mg, 55.8 umol), and the resulting mixture was heated to reflux. After 9 h, the solution was concentrated in vacuo, and the residue was flash chromatographed (9:1 pentane:diethyl ether) to yield 24 mg (58%) of a clear liquid.

From **29a**: CSA (7.0 mg, 30.1 umol) was added to a solution of **29a** (96.3 mg, 260 umol) and 2,2-dimethoxypropane (0.32 mL, 2.60 mmol) in 2.6 mL of acetone. After 16 h of stirring, the solution was concentrated in vacuo, and the residue was flash chromatographed with 9:1 pentane:diethyl ether as the eluant to yield 96 mg (90%) of a clear liquid, R_f = 0.48 (4:1 hexanes:ethyl acetate), $[\alpha]_D^{23}$ = +31.5 (c = 2.7, CH_2Cl_2). IR (thin film): 2971, 2934, 2878, 1732, 1647, 1457, 1436 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 5.90 (dt, J = 15.3 Hz, 6.9 Hz, 1H), 5.66 (d, J = 15.3 Hz, 1H), 4.78 (s, 1H), 4.77 (s, 1H), 4.11 (d, J = 7.5 Hz, 1H), 3.76 (s, 3H), 3.66 (s, 3H), 2.81 (d, J = 6.9 Hz, 2H),

2.46 (m, 2H), 2.33 (m, 2H), 1.65 (m, 1H), 1.51 (s, 3H), 1.47 (m, 1H), 1.43 (s, 3H), 1.14 (m, 1H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.89 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 173.73, 173.39, 146.21, 130.32, 127.78, 110.96, 109.09, 85.41, 84.94, 52.62, 51.53, 39.15, 34.98, 32.32, 30.82, 27.26, 25.92, 24.95, 15.46, 11.01. HRMS: calcd for $C_{21}H_{35}O_4$ ($M^+ - CO_2CH_3$) 353.1965, found 353.1964.

(6*E*,8*R*,9*R*,10*S*)-*tert*-Butyl 8,9-Dihydroxyl-8-(methoxycarbonyl)-10-methyl-4-methylene-6-dodecenoate (29a). Methanol (11.0 mL) was added to a mixture of **4a** (172.9 mg, 1.12 mmol), **2** (241.9 mg, 1.12 mmol), CpRu(COD)Cl (34.8 mg, 112 umol), and ammonuim hexafluorophosphate (36.5 mg, 224 umol), and the resulting mixture was heated to reflux. After 2 h, the solution was concentrated in vacuo and the residue was flash chromatographed with 4:1 pentane:diethyl ether as the eluant to yield 168 mg (45%) of a white solid, mp = 65 °C, $[\alpha]_D^{23} = +35.01$ ($c = 1.5$, CH_2Cl_2). IR (thin film): 3549, 1728, 1648, 1459, 1437 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.99 (dt, J = 15.3 Hz, 7.2 Hz, 1H), 5.55 (dd, $J = 1.2$ Hz, 15.3 Hz, 1H), 4.76 (s, 1H), 4.74 (s, 1H), 3.92 (dd, $J = 2.1$ Hz, 11.1 Hz, 1H), 3.83 (s, 3H), 3.57 (s, 1H, D_2O exchangeable), 2.78 (d, $J = 7.2$ Hz, 2H), 2.35 (m, 2H), 2.27 (m, 2H), 2.07 (d, $J = 11.1$ Hz, 1H, D_2O exchangeable), 1.66 (m, 1H), 1.42 (s, 9H), 1.25 (m, 1H), 0.89 (m, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.65, 172.59, 146.41, 129.61, 129.13, 110.71, 81.32, 80.26, 75.92, 53.41, 38.93, 35.30, 33.62, 31.01, 28.20, 28.00, 12.74, 11.71. Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.93; H, 9.46.

(6*E*,8*R*,9*R*,10*S*)-9-Fluorenylmethyl 8,9-Dihydroxy-8-methoxycarbonyl-10-methyl-4-methylene-6-dodecenoate. Method A. Methanol (2.0 mL) was added to a mixture of **4d** (57.5 mg, 208 μmol), **2** (47.0 mg, 217 μmol), CpRu(COD)Cl (7.1 mg, 22.9 μmol), and ammonium hexafluorophosphate (10.4 mg, 63.8 μmol), and the mixture was heated to reflux. After 2.5 h, the solution was concentrated in vacuo, and the residue was flash chromatographed with 1:1 pentane:diethyl ether as the eluant to yield 48 mg (52%) of a clear liquid.

Method B. Compounds **4d** (35.8 mg, 130 μmol), **2** (23.3 mg, 108 μmol), CpRu(COD)Cl (6.2 mg, 20.0 μmol), and ammonium hexafluorophosphate (6.9 mg, 42.3 μmol) were sequentially added to plastic tube sealed with a glass rod on one end. Acetone (0.55 mL) and methanol (0.55 mL) were added, and the open end of the plastic tube was sealed with a glass rod by using a heat gun. The tube was placed in a high-pressure apparatus, and the pressure was gradually increased to 13 kbar over a 15 min period. After 1.5 h, the pressure fell to 11 kbar, the tube was removed, the contents were concentrated in vacuo, and the residue was flash chromatographed with 1:1 pentane:diethyl ether as the eluant to yield 27 mg (51%) of a clear liquid, $R_f = 0.26$ (7:3 hexanes:ethyl acetate), $[\alpha]_D^{23} = +24.12$ ($c = 3.05$, CH_2Cl_2). IR (thin film): 3505, 1736, 1647, 1450 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, $J = 7.5$ Hz, 2H), 7.59 (d, $J = 7.5$ Hz, 2H), 7.41 (m, 2H), 7.32 (dt, $J = 1.2$ Hz, 7.5 Hz, 2H), 6.00 (m, 1H), 5.56 (d, J = 15.3 Hz, 1H), 4.76 (s, 2H), 4.40 (d, $J = 7.2$ Hz, 2H), 4.20 (t, $J = 7.2$ Hz, 1H), 3.92 (dd, $J = 11.1$ Hz, 1.8 Hz, 1H), 3.81 (s, 3H), 3.60 (s, 1H), 2.78 (d, $J = 7.2$ Hz, 2H), 2.53 (m, 2H), 2.32 (m, 2H), 2.11 (d, J = 11.1 Hz, 1H), 1.65 (m, 1H), 1.43 (m, 1H), 1.30 (m, 1H), 0.88 (m, 6H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 175.60, 173.19, 146.11, 143.91, 141.43, 129.42, 129.29, 127.89, 127.19, 125.07, 120.12, 110.93, 81.22, 75.81, 66.31, 53.44, 46.78, 39.96, 35.31, 32.42, 30.71, 28.20, 12.74, 11.72. HRMS: calcd for $C_{30}H_{35}O_5$ ($M^+ - OH$) 475.2486, found 475.2486.

(6*E*,8*R*,9*R*,10*S*)-9-Fluorenylmethyl 8,9-(Isopropylidenedioxy)-8-(methoxycarbonyl)-10-methyl-4-methylene-6-dodecenoate (27d). CSA (1.4 mg, 6.03 umol) was added to a solution of **29d** (34.9 mg, 70.1 umol) and 2,2-DMP (0.09 mL, 732 umol) in acetone (0.71 mL). After 48 h of stirring, the solution was concentrated under reduced pressure and the residue was flash chromatographed with 9:1 pentane:diethyl ether as the eluant to yield 37 mg (97%) of a clear liquid, $R_f = 0.54$ (4:1 hexanes:ethyl acetate), $[\alpha]_D^{23} = +23.43$ ($c = 2.10$, CH_2Cl_2). IR (thin film): 1736, 1647, 1610, 1478, 145 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, $J = 7.5$ Hz, 2H), 7.59 (d, $J = 7.5$ Hz, 2H), 7.41 (m, 2H), 7.32 (dt, $J = 1.2$ Hz, 7.5 Hz, 2H), 5.92 (m, 1H), 5.67 (d, J = 15.3 Hz, 1H), 4.79 (s, 1H), 4.77 (s, 1H), 4.39 (d, $J = 7.2$ Hz, 2H), 4.20 (d, $J = 7.2$ Hz, 1H), 4.12 (d, $J = 7.8$ Hz, 1H), 3.75 (s, 3H), 2.82 (d, $J = 6.9$ Hz, 2H), 2.54 (m, 2H), 2.34 (m, 2H), 1.65 (m, 2H), 1.52 (s, 3H), 1.43 (s, 3H), 1.15 (m, 1H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 174.88, 174.71, 147.65, 145.44, 142.93, 131.76, 129.37, 128.70, 126.61, 121.61, 112.51, 110.62, 86.93, 86.44, 67.82, 54.14, 48.28, 40.64, 36.48, 33.97, 32.30, 28.79, 27.43, 26.46, 16.99, 12.54. HRMS: calcd for $C_{32}H_{37}O_6$ ($M^+ - CH_3$) 517.2591, found 517.2590.

(6*E*,8*R*,9*R*, 10*S*)-8,9-(Isopropylidenedioxy)-8-(methoxycarbonyl)-10-methyl-4-methylene-6-dodecen-1-oic Acid (27b). Piperidine (0.02 mL, 202 μmol) was added to a solution of **29d** (36.5 mg, 68.5 μmol) in methylene chloride (0.70 mL). After 48 h of stirring, the solution was diluted with 10% HCl, extracted with methylene chloride, the combined organic extracts were dried over magnesium sulfate, filtered, and concentrated under reduced pressure. The residue was flash chromatographed with 99:1 methylene chloride:methanol as the eluant then with 9:1 methylene chloride:methanol as the eluant to yield 23 mg (96% yield) of a film. The spectral properties are in agreement with those previously recorded.[7] $[\alpha]_D^{27} = +25.6$ ($c = 1.16$, CH_2Cl_2). IR (thin film): 3200, 1739, 1712, 1648, 1455, 1436 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.90 (m, 1H), 5.67 (d, $J = 15.3$ Hz, 1H), 4.81 (s, 1H), 4.79 (s, 1H), 4.12 (d, $J = 7.8$ Hz, 1H), 3.76 (s, 3H), 2.82 (d, $J = 6.9$ Hz, 2H), 2.51 (m, 2H), 2.33 (t, $J = 7.5$ Hz, 2H), 1.64 (m, 1H), 1.52 (s, 3H), 1.50 (m, 1H), 1.43 (s, 3H), 1.12 (m, 1H), 0.97 (d, $J = 6.6$ Hz, 3H), 0.88 (t, $J = 7.5$ Hz, 3H). ^{13}C NMR (500 MHz, $CDCl_3$): δ 178.44, 173.18, 145.74, 130.13, 127.73, 111.02, 109.04, 85.39, 84.88, 52.67, 39.26, 35.03, 32.16, 30.49, 27.31, 25.97, 25.02, 15.56, 11.10. TLC $R_f = 0.40$ (19:1 methylene chloride:methanol).

Acknowledgment. We thank the National Institutes of Health, General Medical Sciences Institute, and the National Science Foundation for their generous support of our programs. A.S. was supported by a NATO Grant. Mass spectra were provided by the Mass Spectrometry Facility, University of San Francisco, supported by the NIH Division of Research Resources.

Supporting Information Available: Experimental procedures for preparation of **4d** and **9c** (1 page, print/PDF). See any current masthead page for ordering information and Web access instructions.

JA981540N