Synthetic Routes to Allenic Acids and Esters and Their Stereospecific Conversion to Butenolides

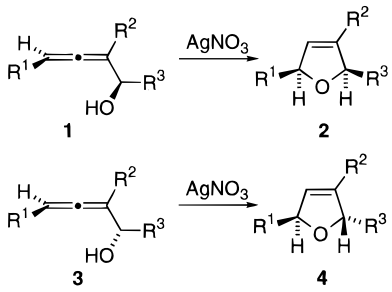
James A. Marshall,* Mark A. Wolf, and Eli M. Wallace

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22901

Received October 3, 1996[⊗]

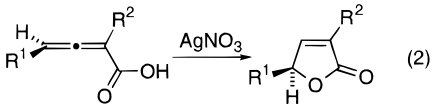
The synthesis of allenic acids and esters and their conversion to butenolides has been examined in some detail. Racemic butenolides **10** are efficiently prepared from the esters **8** through treatment with BCl_3 and exposure of the derived acid **9** to catalytic $AgNO_3$ in acetone. Conversion of the enantioenriched allenylstannane (*S*)-**17** to the acid **18** through lithiation and subsequent carboxylation with CO_2 afforded racemic product. The enantioenriched propargylic mesylates **16** and **22** afforded the allenic esters **19** and **23** with inversion of configuration through treatment with $Pd(Ph_3P)_4$, CO, and the appropriate alcohol in THF. These reactions proceeded with *ca.* 10% or less of racemization. The allenic esters **23** yielded the iodobutenolides **24** by reaction with IBr. Hydrogenolysis to the butenolide **25** was achieved with $Pd(PPh_3)_4$ and Bu_3SnH. Alternatively, the allenic acids **27** could be prepared directly from mesylates **22** with $Pd(PPh_3)_4$ and CO in aqueous THF. Cyclization to the butenolides **25** was achieved, as before, with catalytic $AgNO_3$.

In connection with ongoing projects relating to the synthesis of furanocembrane, pseudopterolide, and Annonaceous acetogenin natural products[1] we became interested in developing versatile and efficient routes to butenolides.[2] The approach that we chose to explore was based on our previous findings that allenylcarbinols **1**/**3** are smoothly and stereospecifically converted to 2,5-dihydrofurans **2**/**4** upon treatment with catalytic $AgNO_3$ in acetone, or supported on silica gel (eq 1).[3]



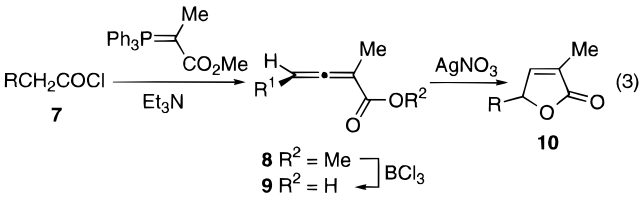
1 **2** (1) **3** **4**

Accordingly, we reasoned that allenic acids **5** might be expected to follow a similar course to afford butenolides **6** (eq 2).



5 **6** (2)

To test the feasibility of this cyclization approach we prepared the racemic allenic acids **9a**, **9b**, and **9c** by treatment of the acid chlorides **7a**, **7b**, and **7c** with methyl 2-(triphenylphosphoranylidene)propionate[4] and subsequent cleavage of the allenic esters **8a**, **8b**, and **8c** with BCl_3.[5] The resulting acids were smoothly converted to the butenolides **10a**, **10b**, and **10c** with 10% $AgNO_3$ in acetone (eq 3).[6]



R	7	8	yield, %	9	yield, %	10	yield, %
n-C_5H_{11}	**7a**	**8a**	95	**9a**	86	**10a**	90
CH_2=$CH(CH_2)_7$	**7b**	**8b**	91	**9b**	84	**10b**	80
c-C_6H_{11}	**7c**	**8c**	62	**9c**	67	**10c**	68

As an aside, saponification of the foregoing allenic esters with LiOH led to mixtures of allenic acids and alkynylacetic acids. In fact, when the sequence was carried out with the monosubstituted allenic esters **11a** and **11b**, obtained by treatment of acid chlorides **7a** and **7b** with methyl 2-(triphenylphosphoranylidene)acetate, the alkynylacetic acids **12a** and **12b** were the sole isolable saponification products. Interestingly, these acids were efficiently converted to the labile enol lactones **13a** and **13b** by catalytic $AgNO_3$ in acetone (eq 4).

In the next stage of these investigations, we explored possible routes to nonracemic allenic acids, as precursors to enantioenriched butenolides. We had previously found that chiral allenic stannanes of high ee could be prepared through S_N2' displacement of enantioenriched propargylic mesylates with a Bu_3Sn cuprate reagent.[3b] It therefore seemed worth attempting to convert such stannanes to the related acids through lithiation and carboxylation. To test this possibility we first prepared the racemic stannane **17** and subjected it to MeLi followed by CO_2. This sequence led to the racemic allenic acid **18** in 64% yield. Subsequently, enantioenriched alcohol **15** of 70% ee was prepared by reduction of the ketone **14** with

[⊗] Abstract published in *Advance ACS Abstracts,* January 1, 1997.

(1) *Cf.* (a) Marshall, J. A.; Bartley, G. S.; Wallace, E. M. *J. Org. Chem.* **1996**, *61*, 5729. (b) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1996**, *61*, 4247.

(2) For a recent review, see: Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287.

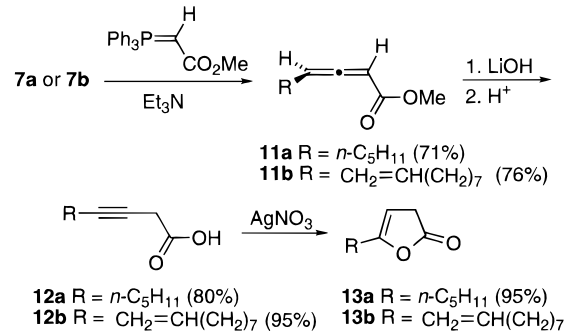
(3) (a) Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966. (b) Marshall, J. A.; Yu, R. H.; Perkins, J. F. *J. Org. Chem.* **1995**, *60*, 5550.

(4) Lang, R. W.; Hansen, H. J. *Helv. Chim. Acta* **1980**, *63*, 438.

(5) Manchand, P. S. *J. Chem. Soc., Chem. Commun.* **1971**, 667.

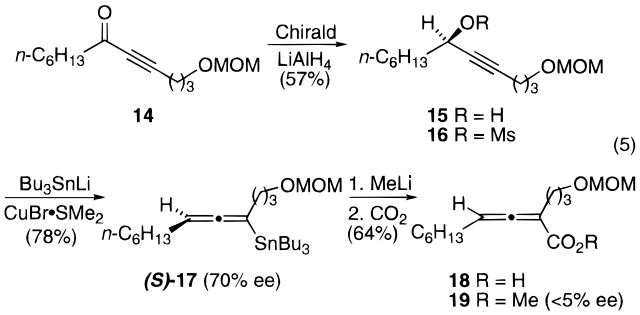
(6) For other Ag(I)-catalyzed cyclizations leading to exocyclic enol lactones, see: Pale, P.; Chuche, J. *Tetrahedron Lett.* **1987**, *28*, 6447. Dalla, V.; Pale, P. *Tetrahedron Lett.* **1994**, *35*, 3525.

S0022-3263(96)01874-9 CCC: $14.00



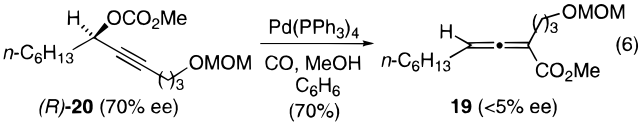
(4)

Chirald-LAH. The mesylate derivative **16** was converted to the nonracemic allenylstannane **17**, with inversion of configuration. The assignment is based on our previous findings.[3b] Treatment of stannane **17** with MeLi followed by CO_2 led to the allenic acid **18**. The derived methyl ester **19** was found to be racemic (eq 5).



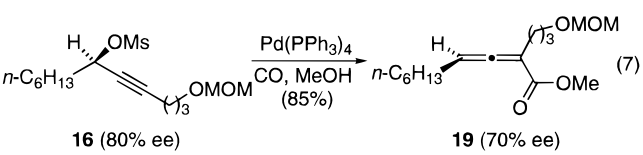
(5)

We next attempted to prepare ester **19** in nonracemic form through methoxycarbonylation of the carbonate derivative **20** of alcohol **15** following the procedure of Tsuji *et al.*[7] Treatment of this ester with CO in methanol−benzene in the presence of catalytic $Pd(PPh_3)_4$ at 50−60 °C gave ester **19**, but as a virtual racemate (eq 6).



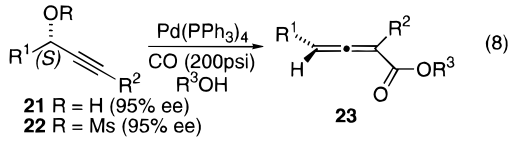
(6)

In view of the potential for Ph_3P-catalyzed racemization of allenic esters at elevated temperatures in the foregoing carbonylation sequence,[1a] we explored the use of the more reactive mesylate derivative **16** of alcohol **15**. We also increased the effective CO concentration by conducting the reaction at higher pressure (200 psi). With these modifications, we obtained ester **19** in high yield and significant ee (eq 7).



(7)

Encouraged by these results, we examined a number of representative propargylic mesylates with several different participating alcohols. These experiments were conducted with mesylates **22a**−**c** derived from alcohols **21a**−**c** of ∼95% ee. The alcohols were obtained through reduction of the acetylenic ketones with (*S*)-BINAL-H.[8] In all cases, enantioenriched allenic esters were formed in satisfactory yield by exposure of the mesylates **22** to CO and $Pd(PPh_3)_4$ in the presence of the alcohol (eq 8). Evaluation of ee was possible through analysis of the allenic ester product **23** or the derived iodobutenolide **24** (eq 9) by HPLC.



(8)

22	R^1	R^2	**23**	R^3	yield, %	ee, %[a]
22a	CH_3	*n*-C_7H_{15}	**23a**	Bn	84	80
22a	CH_3	*n*-C_7H_{15}	**23b**	TMSE[b]	80	84
22a	CH_3	*n*-C_7H_{15}	**23c**	CH_3	86	84
22b	*n*-C_5H_{11}	H	**23d**	TMSE	80	95
22b	*n*-C_5H_{11}	H	**23e**	Bn	80	93
22c	H	*n*-C_4H_9	**23f**	Bn	76	–

a determined by HPLC analysis of **23** or the derived iodobutenolides **24**
b TMSE = $Me_3SiCH_2CH_2OH$

Conversion of the propargylic mesylate **22b** to allenic esters **23d** or **23e** was highly enantioselective. The more substituted analogue **22a**, however, afforded allenic esters **23a**−**c** with partial racemization. This difference may be related to the configurational stability of the intermediate Pd species in the carbonylation reaction.[11] It could also reflect a slightly lower rate of CO insertion for this Pd species relative to the one derived from mesylate **22a**. The allenic esters **23a** and **23b** were unaffected by prolonged exposure to the carbonylation reaction conditions as determined by analysis of aliquots removed during the course of the reaction and beyond.

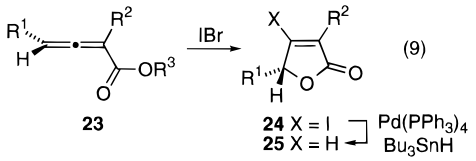
The conversion of allenic esters **23** to the butenolides **25** *via* the allenic acids proved troublesome. Treatment of ester **23c** of *ca.* 90% ee with BCl_3 and subsequent exposure to $AgNO_3$, as in eq 3, afforded butenolide **25a** of *ca.* 40% ee.[9] An alternative protocol involving cleavage of the TMSE ester **23b** of 65% ee with TBAF followed by esterification of the resulting acid with CH_2N_2 led to allenic ester **23c** of *ca.* 20% ee.

In view of these unpromising results, we examined an alternative two-step conversion of allenic esters **23** to the butenolides **25**. This could be efficiently accomplished by iodolactonization with IBr and subsequent hydrogenolysis (eq 9).[10] The ee values of the intermediate iodobutenolides **24**, as determined by HPLC analysis, were essentially identical to those of the starting allenic esters **23**. The iodobutenolides **24a**−**c** were converted to butenolides **25a**−**c** through Pd(0)-catalyzed hydrogenolysis with Bu_3SnH.[12]

The absolute stereochemistry of butenolide **25a** was determined through an unambiguous synthesis of the enantiomer *ent*-**25a** from the (*S*) propargylic alcohol **21a** of established configuration and ee (eq 10).[13,3b] The

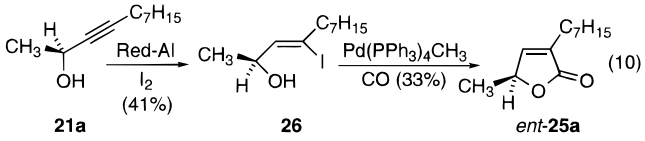
(7) Tsuji, J. Sugiura, T.; Minami, I. *Tetrahedron Lett.* **1986**, *27*, 731.
(8) Noyori, R.; Tomino, I.; Tanimoto, Y.; Nishizawa, M. *J. Am. Chem. Soc.* **1984**, *106*, 6709.

(9) In our preliminary work we determined the ee of ester **24c** through use of the $Eu(hfc)_3$ shift reagent and integration of the vinylic CH_3 signals in the ^1H NMR spectrum. The derived butenolide **25a** could likewise be analyzed through integration of the CH_3 signals. Subsequent analysis by HPLC was in close agreement.
(10) *Cf.* Smith, A. B., III; Duan, J. J.-W.; Hull, K. G.; Salvatore, B. A. *Tetrahedron Lett.* **1991**, *32*, 4855.
(11) Racemization of allenyl/propargyl Pd intermediates has previously been studied. Granberg, K. L.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1992**, *114*, 6858.
(12) Baillargeon, V. P.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 452.
(13) Noyori has shown that (*S*) propargylic alcohols are formed through reduction of acetylenic ketones with (*S*)-BINAL-H.[8]



23	R^1	R^2	R^3	24	ee, %	yield, %	25	yield, %
23a	CH_3	*n*-C_7H_{15}	Bn	**24a**	80	90		
23b	CH_3	*n*-C_7H_{15}	TMSE	**24a**	84	90	**25a**	70
23c	CH_3	*n*-C_7H_{15}	CH_3	**24a**	84	97	**25a**	96
23d	*n*-C_5H_{11}	H	TMSE	**24b**	95	89	**25b**	70
23e	*n*-C_5H_{11}	H	Bn	**24b**	93	93		
23f	H	*n*-C_4H_9	Bn	**24c**	—	83	**25b**	79

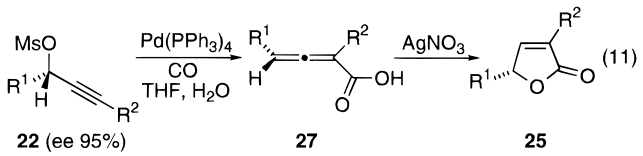
optical rotation of the two enantiomeric lactones **25a** and *ent*-**25a** were nearly equal but of opposite signs. Accordingly, the carbonylation reaction of mesylates **22** must proceed by a net *anti* S_E2' process. The stereoselectivity of this conversion was highest when minimal catalyst and Ph_3P ligand were employed.[11] With 10 mol % $Pd(PPh_3)_4$, significant erosion of ee was observed. Best results were obtained with 1 mol % of catalyst.



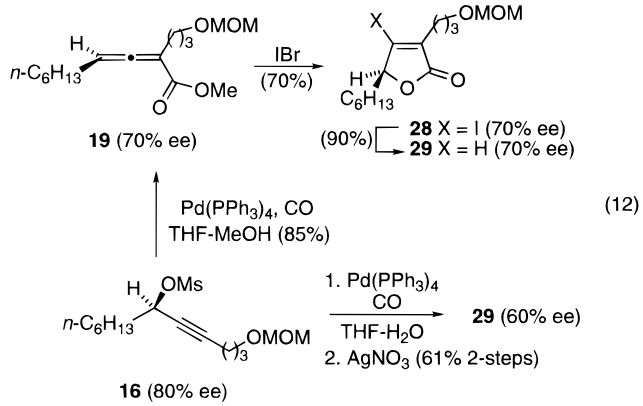
The correlation of butenolides **25a** and *ent*-**25a** also confirms that the hydrogenolysis of iodobutenolide **24a** proceeds without loss of ee. This conclusion is based on the reasonable assumption that the sequence leading to *ent*-**25a** does not affect the carbinyl stereocenter.

In a preliminary report of these results, we noted that allenic acids could be prepared from mesylates **22** by $Pd(PPh_3)_4$-catalyzed carbonylation in aqueous THF, but only in low yield.[14] However, by using minimal amounts of Pd catalyst and elevated CO pressures, we have considerably improved this process. Thus butenolide **25a** can be prepared in 62% overall yield with >90% enantioselectivity from mesylate **22a** by the two-step sequence (eq 11). Unfortunately significant racemization is seen with mesylates **22b** (eq 11) and **16** (eq 12). In these two cases, the three-step process *via* allenic esters **23d**/**e** and **19** proceeds in comparable yield and with higher ee than the direct hydroxycarbonylation−lactonization sequence.

In view of the ease with which nonracemic propargylic alcohols can be prepared from alkynones through reduction with chiral hydrides[8] or from chiral pool polyols,[15] the propargyl mesylate methodology offers an attractive route to nonracemic butenolides. Racemization is minimized when the carbonylation step is performed in the presence of alcohols to produce allenic esters. These can be converted to iodobutenolides through iodolactonization. Presumably, reactions other than hydrogenolysis could be carried out on the vinylic iodide function, if desired. Although the hydroxycarbonylation route to butenolides such as **25** is more direct, it suffers from partial racemization. Efforts to improve this process are currently in progress.



22	R^1	R^2	25	yield, %	ee, %
22a	CH_3	*n*-C_7H_{15}	**25a**	62	90
22b	*n*-C_5H_{11}	H	**25b**	91	60



Experimental Section[16]

(±)-Methyl 2-Methyl-2,3-nonadienoate (8a). A modification of the method of Lang and Hansen was employed.[4] Triethylamine (1.16 g, 1.60 mL, 11.52 mmol) was added to a stirred solution of methyl 2-(triphenylphosphoranylidene)-propionate (3.68 g, 10.57 mmol) in CH_2Cl_2 (50 mL) in the presence of 4 Å activated molecular sieves. Heptanoyl chloride (1.41 g, 1.46 mL, 9.49 mmol) was added, and the reaction mixture was stirred for 16 h. The reaction mixture was concentrated under reduced pressure and triturated twice with pentane. The residue was chromatographed on silica gel. Elution with 5% ethyl acetate in hexanes gave 1.40 g (95%) of allenic ester **8a** as an oil: IR (film) 1959, 1718 cm^{-1}; ^1H NMR δ 5.44 (tq, 1H, J = 5.4, 2.9 Hz), 3.71 (s, 3H), 2.08 (q, 2H, J = 7.1 Hz), 1.84 (d, 3H, J = 2.9 Hz), 1.42 (m, 2H), 1.31 (m, 4H), 0.87 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 210.0, 168.4, 95.2, 93.8, 51.9, 31.1, 28.4, 27.8, 22.4, 15.2, 14.0. Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.61; H, 10.00.

(±)-2-Methyl-2,3-nonadienoic Acid (9a). A modification of the method of Manchand was employed.[5] To a solution of allenic ester **8a** (0.396 g, 2.176 mmol) in 20 mL of CH_2Cl_2 with stirring at −78 °C was added 8.70 mL (8.70 mmol) of a 1.0 M BCl_3 solution in hexanes. After 5 min, the reaction mixture was quenched by the addition of a 10% NaOH solution and warmed to rt. The reaction mixture was extracted with Et_2O, and the aqueous layer was then acidified with 10% HCl. The acidified aqueous layer was extracted with Et_2O. The combined Et_2O extracts of the acidified aqueous layer were dried over $MgSO_4$ and concentrated under reduced pressure to give 0.314 g (86%) of acid **9a** as an oil: IR (film) 3077, 1959, 1682 cm^{-1}; ^1H NMR δ 5.51 (m, 1H), 2.08 (q, 2H, J = 7.1 Hz), 1.83 (d, 3H, J = 2.8 Hz), 1.43 (m, 2H), 1.30 (m, 4H), 0.87 (t, 3H, J = 7.1 Hz); ^{13}C NMR δ 211.2, 173.8, 95.2, 94.3, 31.1, 28.4, 27.7, 22.4, 14.8, 14.0. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.19; H, 9.62.

(±)-4-Hydroxy-2-methyl-2-nonenoic Acid Lactone (10a). To a solution of acid **9a** (0.381 g, 2.27 mmol) in 10 mL of acetone was added $AgNO_3$ (0.077 g, 0.45 mmol) with stirring. The reaction mixture was sealed under N_2, the flask was covered with foil, and stirring was continued for 16 h. The mixture was then diluted with Et_2O and dried over $MgSO_4$. Filtration of the solution through a pad of silica gel and concentration of the filtrate under reduced pressure gave 0.343

(14) Marshall, J. A.; Wolf, M. A. *J. Org. Chem.* **1996**, *61*, 3238.
(15) Yadav, J. S.; Chandler, M. C.; Rao, C. S. *Tetrahedron Lett.* **1989**, *30*, 5455. Takano, S.; Yoshimitsu, T.; Ogasawara, K. *Synlett* **1994**, 119.

(16) For a description of experimental protocols, see Marshall J. A.; Wang, X-j. *J. Org. Chem.* **1991**, *56*, 960. Unless otherwise stated, ^1H and ^{13}C NMR spectra were determined on dilute solutions of sample in $CDCl_3$ at 300 and 75 MHz, respectively.

g (90%) of butenolide **10a** as an oil that was pure according to the ^{1}H NMR spectrum. An analytical sample was obtained by bulb to bulb distillation: bath 85 °C (1 mmHg); IR (film) 2930, 1756, 1660, 1098 cm^{-1}; ^{1}H NMR δ 7.00 (q, 1H, J = 1.6 Hz), 4.82 (m, 1H), 1.86 (t, 3H, J = 1.8 Hz), 1.60 (m, 2H), 1.39 (m, 2H), 1.27 (m, 4H), 0.83 (t, 3H, J = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.4, 148.9, 129.7, 81.2, 33.4, 31.5, 24.7, 22.4, 13.9, 10.6. Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.20; H, 9.44.

(±)-Methyl 2,3-Nonadienoate (11a). The procedure described for allenic ester **8a** was employed with 2.50 mL (2.40 g, 16.16 mmol) of heptanoyl chloride and 5.94 g (17.78 mmol) of methyl (triphenylphosphoranylidene)acetate to afford 1.93 g (71%) allenic ester **11a** as an oil: IR (film) 1959, 1723 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.56 (m, 2H), 3.71 (s, 3H), 2.11 (m, 2H), 1.44 (m, 2H), 1.30 (m, 4H), 0.87 (t, 3H, J = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.4, 166.7, 95.4, 87.8, 51.9, 31.0, 28.3, 27.4, 22.3, 14.0.

3-Nonynoic Acid (12a). To a solution of allenic ester **11a** (0.227 g, 1.351 mmol) in a 1:1 mixture of THF−H_2O (10 mL) was added LiOH (0.162 g, 6.756 mmol). After 15 min, the reaction mixture was diluted with H_2O and extracted with Et_2O. The aqueous layer was acidified with 10% HCl and extracted with Et_2O. The combined Et_2O extracts of the acidified aqueous layer were dried over $MgSO_4$ and concentrated under reduced pressure to give 0.167 g (80%) of acid **12a** as an oil: IR (film) 3165, 1959, 1719 cm^{-1}; ^{1}H NMR δ 3.31 (t, 2H, J = 2.5 Hz), 2.18 (m, 2H), 1.49 (m, 2H), 1.31 (m, 4H), 0.88 (t, 3H, J = 7.1 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.3, 87.7, 70.5, 31.0, 28.3, 25.9, 22.1, 18.7, 13.9.

4-Hydroxy-3-nonenoic Acid Lactone (13a). The procedure described for butenolide **10a** was employed with acid **12a** (0.150 g, 0.974 mmol) to afford 0.142 g (95%) of enol lactone **13a** as an oil: IR (film) 1799, 1755, 1668 cm^{-1}; ^{1}H NMR δ 5.08 (app p, 1H, J = 1.2 Hz), 3.16 (q, 2H, J = 2.3 Hz), 2.26 (dt, 2H, J = 7.6, 1.4 Hz), 1.54 (m, 2H), 1.30 (m, 4H), 0.88 (t, 3H, J = 7.0 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 177.0, 157.2, 98.1, 33.9, 31.1, 28.1, 25.3, 22.3, 13.8.

(*R*)-(+)-12-(Methoxymethoxy)dodec-8-yn-7-ol (15). The procedure of Marshall and Wang[3b] was employed to prepare 1.84 g (57%) of enantioenriched alcohol **15** from ketone **14** (3.16 g, 13.07 mmol): $[\alpha]^{25}_D$ +4.2 ($CHCl_3$, *c* 1.20); IR (film) 3419, 2227, cm^{-1}; ^{1}H NMR δ 4.60 (s, 2H), 4.32 (tt, 1H, J = 6.6, 2.0 Hz), 3.60 (t, 2H, J = 6.2 Hz), 3.35 (s, 3H), 2.32 (tt, 2H, J = 7.1, 2.0 Hz), 1.77 (app p, 2H, J = 6.5 Hz), 1.71−1.17 (m, 11H), 0.87 (t, 3H, J = 6.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 96.2, 83.9, 82.0, 66.0, 62.4, 55.0, 38.1, 31.7, 28.9, 28.7, 25.1, 22.5, 15.4, 14.0. The ee of this alcohol was found to be 70% by ^{1}H NMR analysis of the (*R*)-*O*-methylmandelate derivative through integration of signals at 4.59, 4.56 ppm, 3.56, 3.49 ppm, and 2.30, 2.22 ppm.

(*S*)-(+)-1-(Methoxymethoxy)-4-(tributylstannyl)-4,5-dodecadiene (17). The procedure of Marshall and Wang[3b] was employed to prepare enantioenriched stannane **17** from alcohol **15** of 70% ee. To a flame-dried, argon-flushed, three-necked flask equipped with a side arm charged with 3.30 g (16.0 mmol) of $CuBr{\cdot}SMe_2$ were added 2.49 mL (17.7 mmol) of diisopropylamine and 40 mL of THF. To this stirring solution at 0 °C was added 4.32 mL of Bu_3SnH. After stirring 0.5 h, the reaction was cooled to −78 °C and the $CuBr{\cdot}SMe_2$ was added. After 1 h at −78 °C, a solution of 2.70 g (8.45 mmol) of mesylate **16** in 5 mL of THF was added with stirring. After 45 min at −78 °C, the reaction was quenched by pouring into a stirring solution of NH_4Cl-NH_4OH (9:1). This mixture was extracted with Et_2O, and the extracts were dried over $MgSO_4$. Following filtration and concentration under reduced pressure, the crude oil was purified by flash chromatography on silica gel to afford 3.37 g (78%) of allenyl stannane **17** as a colorless oil: $[\alpha]^{25}_D$ +59.1 ($CHCl_3$, *c* 0.83); IR (film) 1930 cm^{-1}; ^{1}H NMR δ 4.62 (m, 1H), 4.60 (s, 2H), 3.53 (t, 2H, J = 6.6 Hz), 3.34 (s, 3H), 2.09 (dt, 2H, J = 4.9, 3.0 Hz), 1.90 (q, 2H, J = 7.1 Hz), 1.72 (p, 2H, J = 7.3 Hz), 1.51−0.85 (m, 38H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 202.2, 96.4, 92.5, 82.8, 67.3, 55.0, 31.8, 30.0, 29.7, 29.4, 29.2, 29.03, 29.03, 27.3, 22.7, 14.1, 13.7, 10.0.

2-[3-(Methoxymethoxy)propyl]-2,3-decadienoic Acid (18). A. From Racemic Allenyl Stannane 17. To a stirred solution of allenyl stannane **17** (0.099 g, 0.192 mmol) in THF (5 mL) at −78 °C was added 0.38 mL of a 1.4 M solution of MeLi in hexanes. After 20 min, CO_2 was bubbled into the reaction mixture. After 2 h, CO_2 addition was stopped and the reaction mixture warmed to rt, diluted with H_2O, and extracted with Et_2O. The aqueous layer was acidified with 10% HCl and extracted with Et_2O. The combined Et_2O extracts of the acidified aqueous layer were dried over $MgSO_4$ and concentrated under reduced pressure to yield 0.033 g (64%) of allenic acid **18** as an oil: IR (film) 3204, 2650, 1952, 1679 cm^{-1}; ^{1}H NMR δ 5.57 (m, 1H), 4.59 (s, 2H), 3.53 (t, 2H, J = 6.5 Hz), 3.33 (s, 3H), 2.27 (dt, 2H, J = 7.8, 2.7 Hz), 2.09 (q, 2H, J = 7.1 Hz), 1.72 (app p, 2H, J = 7.1 Hz), 1.44−1.25 (m, 8H), 0.85 (t, 3H, J = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 210.8, 172.8, 99.7, 96.3, 95.8, 67.0, 55.1, 31.5, 28.8, 28.7, 28.2, 27.9, 24.9, 22.6, 14.0. Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.63; H, 9.69. Found: C, 66.54; H, 9.65.

B. From Enantioenriched Allenyl Stannane 17. The procedure described for allenic acid **18** was used with enantioenriched allenyl stannane **17** (70% ee). The ee of the derived acid was determined by analysis of the methyl ester **19**, prepared as follows: To a solution of the foregoing sample of allenic acid **18** (0.028 g, 0.104 mmol) in Et_2O (2 mL) at 0 °C was added CH_2N_2 (1.04 mmol) in Et_2O (2 mL). After 1 h, the cooling bath was removed, and N_2 was bubbled through the reaction mixture. The reaction mixture was dried over $MgSO_4$ and concentrated under reduced pressure to give 0.029 g (98%) of allenic ester **19** as an oil: ^{1}H NMR δ 5.51 (m, 1H), 4.59 (s, 2H), 3.70 (s, 3H), 3.52 (t, 2H, J = 6.5 Hz), 3.33 (s, 3H), 2.29 (dt, 2H, J = 7.1, 2.8 Hz), 2.08 (q, 2H, J = 7.1 Hz), 1.71 (app p, 2H, J = 6.8 Hz), 1.44−1.23 (m, 8H), 0.86 (t, 3H, J = 6.8 Hz); $[\alpha]_D$ 0.0 ($CHCl_3$, *c* 1.0).

Methyl 2-[3-(Methoxymethoxy)propyl]-2,3-decadienoate (19). A. From Carbonate 20. A modification of the method of Tsuji and co-workers was employed.[7] To a purple mixture of Pd_2dba_3 (0.028 g, 0.031 mmol) in C_6H_6 (1 mL) under argon was added Ph_3P (0.032 g, 0.123 mmol). The reaction mixture was stirred for 5 min, after which time it had turned yellow. A solution of carbonate **20** (0.184 g, 0.613 mmol, 70% ee) in 2 mL of 1:1 C_6H_6−MeOH was added. The reaction mixture was placed under 1 atm of CO (balloon) and stirred for 4.5 h at 50 to 60 °C. The reaction mixture was cooled to rt, diluted with Et_2O, and filtered through a pad of Celite 545. The residue was chromatographed on silica gel. Elution with 10% ethyl acetate in hexanes gave 0.122 g (70%) of allenic ester **19** as an oil: $[\alpha]^{25}_D$ +1.1 ($CHCl_3$, *c* 1.80). Anal. Calcd for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92. Found: C, 67.53; H, 9.98

B. From Mesylate 16. In a flame-dried, argon-flushed flask, a solution of 0.0023 g (0.0025 mmol) of Pd_2dba_3 and 0.0026 g (0.01 mmol) of Ph_3P in 2.5 mL of THF was stirred under a stream of CO gas for ∼2 min. This Pd(0) solution was transferred by syring to a Parr pressure reactor containing 0.160 g (0.50 mmol) of mesylate **16** (from alcohol **15** of 80% ee) in 2.5 mL of THF, and then 0.41 mL (10.0 mmol) of MeOH was added. The Parr reactor was charged with 200 psi of CO gas. After stirring for 1 h at rt, the reaction was quenched with brine and extracted with Et_2O. The extracts were washed with brine and dried over $MgSO_4$. Following filtration and concentration under reduced pressure, the crude residue was purified by flash chromatography on silica gel to afford 0.121 g (85%) of allenic ester **19** as a yellow oil: $[\alpha]_D$ +17.7 ($CHCl_3$, *c* 0.97). HPLC analysis on a Regis (*R*,*R*) Whelk-O column showed 70% ee for this sample.

(*R*)-(+)-Methyl 1-Hexyl-6-(methoxymethoxy)-2-hexynyl Carbonate (20). Alcohol **15** (0.20 g, 0.82 mmol) of 70% ee was added to a stirred slurry of hexane-washed KH (0.400 g of 35% KH by wt in oil) in THF (5 mL) and DMPU (1 mL) at 0 °C. After 1 h, methyl chloroformate (0.32 mL, 0.39 g, 4.10 mmol) was added and the reaction mixture was warmed to rt. After 16 h, the reaction mixture was quenched with H_2O and diluted with Et_2O. The layers were separated, and the Et_2O layer was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel. Elution with ethyl acetate in hexanes gave 0.19 g (76%) of carbonate **20** as an oil: $[\alpha]^{25}_D$ +54.7 ($CHCl_3$, *c* 1.80); IR (film) 2242, 1748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.13 (t, 1H, J = 6.3 Hz), 4.55 (s, 2H), 3.73 (s, 3H), 3.53 (t, 2H, J = 6.4 Hz), 3.29 (s, 3H), 2.28 (t, 2H, J = 6.6 Hz),

1.72 (m, 4H), 1.39−1.23 (m, 8H), 0.82 (t, 3H, J = 6.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.0, 96.3, 86.1, 77.5, 68.6, 65.9, 55.0, 54.7, 35.0, 31.6, 28.7, 28.5, 24.8, 22.5, 15.5, 14.0.

(*S*)-1-Methyl-2-decynyl Methanesulfonate (22a). To a solution of 0.84 g (0.50 mmol) of (*S*)-3-undecyn-2-ol of 95% ee[3b] in 3.3 mL of CH_2Cl_2 at −78 °C were added 0.14 mL (1.0 mmol) of Et_3N and 0.06 mL (0.75 mmol) of methanesulfonyl choride. After stirring for 1 h, the reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O. The extracts were washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. After filtration, the extract was concentrated under reduced pressure and used directly: ^{1}H NMR δ 5.20 (tq, 1H, J = 6.9, 1.8 Hz), 3.01 (s, 3H), 2.14 (dt, 2H, J = 6.9, 1.4 Hz), 1.52 (d, 3H, J = 6.9 Hz), 1.45−1.17 (m, 13H).

(*R*)-2-(Trimethylsilyl)ethyl 2-*n*-Heptyl-2,3-pentadienoate (23b). In a flame-dried, argon-flushed flask, a solution of 0.031 g (0.12 mmol) of Ph_3P, 0.014 g (0.015 mmol) of Pd_2dba_3, and 0.090 g (0.65 mmol) of K_2CO_3 in 4.0 mL of THF was stirred for 5 min at rt with an attendant color change from violet to yellow. The mixture was placed under a CO atmosphere (balloon), and a solution of 0.15 g (0.59 mmol) of mesylate **22b** in 1.9 mL of THF and 0.42 mL (2.95 mmol) of 2-(trimethylsilyl)ethanol was added; a progressive color change from yellow to red to green was observed. After stirring for 1 h at rt under CO, the reaction was quenched with water and extracted with hexanes. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to a volume of ∼6 mL. This solution was purified by flash chromatography to afford 0.14 g (80%) of ester **23b** as a yellow oil: IR (film) 2923, 1954, 1708 cm^{-1}; ^{1}H NMR δ 5.45 (m, 1H), 4.24 (ddd, 2H, J = 8.98, 5.68, 2.01 Hz), 2.20 (m, 2H), 1.75 (d, 3H, J = 7.15 Hz), 1.44−1.22 (m, 10H), 1.03−0.84 (m, 5H), 0.04 (s, 9H); ^{13}C NMR δ 210.3, 167.9, 100.2, 89.5, 62.9, 31.8, 29.1, 29.0, 28.5, 28.0, 22.6, 17.2, 14.1, 13.4, −1.5; $[\alpha]_D$ −19.2 ($CHCl_3$, c 0.64).

(*R*)-Methyl 2-*n*-Heptyl-2,3-pentadienoate (23c). In a flame-dried, argon-flushed flask, a solution of 2.0 mg (0.0022 mmol) of Pd_2dba_3 and 2.3 mg (0.0088 mmol) of Ph_3P in 2.2 mL of THF was stirred under a stream of CO gas for ∼2 min. This Pd(0) solution was transferred by syringe to a Parr pressure reactor containing 0.108 g (0.44 mmol) of mesylate **22a** in 2.2 mL of THF, and then 0.36 mL of MeOH was added. The Parr reactor was charged to 200 psi with CO gas. The mixture was stirred for 1 h at rt, the gas was vented, and the residue was extracted with Et_2O, washed with brine, and dried over $MgSO_4$. Following filtration and concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel to afford 0.079 g (86%) of ester **23c** as a colorless oil: IR (film) 2927, 1958, 1718, 1436, 1270, 1130, 1085, 799 cm^{-1}; ^{1}H NMR δ 5.47 (m, 1H), 3.71 (s, 3H), 2.19 (m, 2H), 1.74 (d, 3H, J = 7.2 Hz), 1.40−1.26 (m, 10H), 0.86 (t, 3H, J = 6.9 Hz); ^{13}C NMR δ 210.4, 168.1, 99.8, 89.6, 51.9, 31.8, 29.08, 28.97, 28.4, 28.0, 22.6, 14.0, 13.3; $[\alpha]_D$ −16.6 ($CHCl_3$, c 0.32). This ester showed a single peak on both of the aforementioned HPLC columns.

(*R*)-5-Methyl-3-*n*-heptyl-4-iodo-2(5*H*)-furanone (24a). To a solution of 0.070 g (0.33 mmol) of allenic ester **23c** in 3.3 mL of CH_2Cl_2 at −78 °C was added 0.50 mL of 1.0 M iodine monobromide in CH_2Cl_2. After being stirred for 1 h at −78 °C, the reaction was quenched with water and extracted with CH_2Cl_2. The extracts were washed with saturated $Na_2S_2O_3$ and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel to afford 0.103 g (97%) of iodobutenolide **23a** as a yellow oil: $[\alpha]_D$ 0.0 ($CHCl_3$, c 1.04); IR (film) 2917, 1763, 1641 cm^{-1}; ^{1}H NMR δ 4.92 (q, 1H, J = 6.8 Hz), 2.32 (t, 2H, J = 7.3 Hz), 1.49 (d, 3H, J = 6.8 Hz), 1.36−1.23 (m, 10H), 0.88 (t, 3H, J = 6.6 Hz); ^{13}C NMR 169.7, 139.0, 122.2, 82.2, 31.7, 29.3, 29.0, 27.4, 27.1, 22.7, 19.5, 14.1. Anal. Calcd for $C_{12}H_{19}O_2I$: C, 44.74; H, 5.94. Found: C, 44.81; H, 5.93. HPLC analysis on a Regis (*R*,*R*) Whelk-O column showed 85% ee for this sample.

(*R*)-5-Methyl-3-*n*-heptyl-2(5*H*)-furanone (25a). A. From Iodobutenolide 24a. In a flame-dried, argon-flushed flask, a solution of 5.7 mg (0.0062 mmol) of Pd_2dba_3 and 3 mg (0.050 mmol) of Ph_3P in 2.1 mL of THF was stirred for ∼5 min. A solution of 0.10 g (0.31 mmol) of iodobutenolide **24a** in 1.0 mL of THF was added, followed by 0.088 mL (0.32 mmol) of Bu_3SnH. After 40 min at rt the mixture was extracted with Et_2O, washed with brine, and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the crude product was purified by flash chromatography on silica gel to afford 0.058 g (96%) of butenolide **25a** as a yellow oil: $[\alpha]_D$ −37.9 ($CHCl_3$, c 0.33); IR (film) 3082, 1754, 1658 cm^{-1}; ^{1}H NMR δ 6.89 (m, 10H, 4.90 (m, 1H), 2.18 (m, 2H), 1.31 (d, 3H, J = 7.0 Hz), 1.21 (m, 10H), 0.79 (t, 3H, J = 7.0 Hz); ^{13}C NMR 173.7, 148.7, 134.1, 77.3, 31.7, 29.2, 29.0, 27.4, 25.2, 22.7, 19.3, 14.1. Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.30; H, 10.22. HPLC analysis on a Chiracel OB-H column showed 84% ee for this sample.

B. From Mesylate 22a. In a flame-dried, argon-flushed flask, a solution of 6.4 mg (0.0070 mmol) of Pd_2dba_3 and 0.014 g (0.056 mmol) of Ph_3P in 7.0 mL of THF was stirred under a stream of CO gas for ∼2 min. This Pd(0) solution was transferred by syringe to a Parr pressure reactor containing 0.342 g (1.39 mmol) of mesylate **22a** in 7.0 mL of THF, and then 1.0 mL of water was added. The Parr reactor was charged with 200 psi of CO gas. After 1 h at rt, the gas was vented and the mixture was extracted with EtOAc, washed with brine (2×), and dried over $MgSO_4$. After filtration, the extract was concentrated under reduced pressure at rt affording acid **27a** which was used directly.

The above acid was dissolved in 14 mL of hexanes, and the flask was covered in aluminum foil to exclude light. To this was added 0.47 g (0.28 mmol) of 10% $AgNO_3$ on silica gel. After stirring for 0.5 h, the reaction mixture was filtered through Celite. The filtrate was washed with saturated $NaHCO_3$ and brine and dried over $MgSO_4$. Following filtration and concentration under reduced pressure, the crude product was purified by flash chromatography to afford 0.168 g (62%) of butenolide **25a** as a yellow oil: $[\alpha]_D$ −41.1 ($CHCl_3$, c 0.76). HPLC analysis on a Chiracel OB-H column showed 90% ee for this sample.

(*S*)-5-Methyl-3-*n*-heptyl-2(5*H*)-furanone (*ent*-25a). In a flame-dried and argon-flushed flask, a solution of 0.077 g (0.29 mmol) of Ph_3P and 0.034 g (0.037 mmol) of Pd_2dba_3 in 0.74 mL of THF was stirred for 10 min at rt. To the resulting yellow-violet solution was added a solution of vinyl iodide **26** in 1.0 mL of THF. A color change from yellow-violet to red was observed. The reaction mixture was place under a CO atmosphere (balloon) and stirred for 25 h. The mixture was diluted with hexanes, washed with water and brine, and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the crude product was purified by flash chromatography to afford 0.048 g (33%) of butenolide *ent*-**25a**; $[\alpha]_D$ +43.8 ($CHCl_3$, c 0.63).

(*S*,*Z*)-4-Iodo-3-undecen-2-ol (26). To a solution of 0.37 g (2.0 mmol) of alcohol **21a** in 5.7 mL of THF at rt under a nitrogen atmosphere was added 0.97 mL (3.3 mmol) of 3.4 M Red-Al in toluene. After stirring overnight, the reaction mixture was cooled to −78 °C and 0.84 g (3.3 mmol) of iodine was added. After stirring for 20 min at −78 °C, the reaction mixture was diluted with Et_2O, washed with saturated $Na_2S_2O_3$ and brine, and dried over $MgSO_4$. After filtration and concentration under reduced pressure, the crude product was purified by flash chromatography to afford 0.24 g (41%) of iodo alcohol **26** as a colorless oil: $[\alpha]_D$ 0.0 ($CHCl_3$, c 0.35).

Acknowledgment. This work was supported by research grants R01-GM39998 and R01-GM29475 from the National Institutes of General Medical Sciences.

Supporting Information Available: ^{1}H NMR spectra for **9b**, **9c**, **11a**, **12a**, **13a**, **13b**, **15**, **15** (mandelate), **17**, **20**, **22a**, **22b**, **22c**, **23b**, **23f**, **24c**, **25b**, **25c**, **26**, **28**, **29**. Experimental procedures for **8b**, **8c**, **9b**, **9c**, **10b**, **10c**, **11b**, **12b**, **13b**, **15**, **17**, **22b**, **22c**, **23a**, **23d**, **23e**, **23f**, **24b**, **24c**, **25b**, **25c**, **28**, **29** (31 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO9618740