# Enantiomerically Pure Acetals in Organic Synthesis. 2. Diastereoselective Alkylation of Enantiomeric Lithio Alkyl Lactyl Tetrahydropyranosides and Related Enolates

Eugene A. Mash* and James A. Fryling

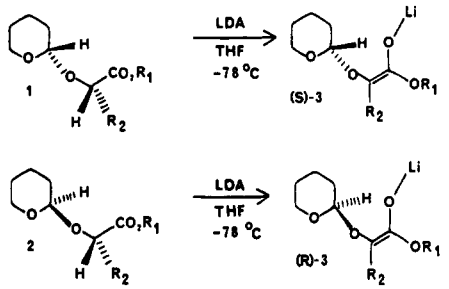
*Department of Chemistry, University of Arizona, Tucson, Arizona 85721*

*Received March 29, 1990*

A concise approach for the rapid synthesis of enantiomerically pure α-alkylated derivatives of lactate esters and of other enantiomerically pure α-hydroxy esters is presented. This methodology, which makes use of enantiomeric lithium enolates prepared from diastereomeric tetrahydropyranyl ethers derived from alkyl lactates and other α-hydroxy esters, is used to prepare both enantiomers of frontalin from (*S*)-(−)-methyl lactate.

A number of useful synthetic methods for the synthesis of enantiomerically pure α-hydroxy acids and derivatives have recently been described.[1] Several of these methods make use of enolates rendered asymmetric by attachment to an enantiomerically pure auxiliary.[1,2] Such methodology normally requires some investment of time and materials in construction, attachment, use, detachment, and recovery of the auxiliary. Where the required investment is minimized, less impediment to use of the methodology exists.

We recently described a general chromatographic separation of diastereomeric tetrahydropyranyl (THP) ethers of α-hydroxy esters, including **1** and **2**.[3] We wondered if




such diastereomeric ester acetals could be deprotonated to give enantiomeric enolates (*S*)-**3** and (*R*)-**3**[4] and whether such enolates would exhibit diastereoselectivity upon alkylation. Results of studies bearing on these questions are presented herein.

## Alkylation Studies

Deprotonations of diastereomeric ester acetals **1** and **2** were accomplished by using lithium diisopropylamide in tetrahydrofuran (THF) solvent at −78 °C. The resulting enolates **3**[4] were treated with various electrophiles[5] as summarized in Table I. As discussed below, diastereomeric THP ethers of a wide variety of enantiomerically pure α-hydroxy esters could be chromatographically separated,[3] deprotonated, and alkylated, albeit with fair to poor diastereoselectivity. However, in most cases the product diastereomers were themselves chromatographically separable, so that diastereomerically pure alkylated products could be obtained via chromatography.

Enolate (*S*)-**3a**, produced by deprotonation of the less polar diastereomeric THP ether derived from (*S*)-(−)-methyl lactate,[3] did not react with allyl chloride at −78 °C but did react with allyl iodide at this temperature in THF to give, in 85% yield, a 4:1 mixture of the chromatographically inseparable diastereomers **4a** and **4b** as determined by 62.9-MHz $^{13}C$ NMR spectroscopy[6] (entry 2, Table I). Stereochemistries are assigned to the products by analogy with assignments made to diastereomers **11a–d** from the syntheses of (+)- and (−)-frontalin described below.

Allylation under similar conditions of enolates (*S*)-**3b**, (*S*)-**3c**, and racemic **3d**, derived from (*S*)-ethyl, (*S*)-isopropyl, and (*S*)-*tert*-butyl lactates, gave in 85–92% yields and with comparable diastereoselectivity pairs of diastereomeric products **5a** and **5b**, **6a** and **6b**, and **7a/c** and **7b/d**, respectively. Use of allyl bromide in place of allyl iodide for alkylation of enolate (*S*)-**3c** gave inseparable diastereomers **6a** and **6b** in lower yield and with poorer diastereoselectivity (compare entries 5 and 7). Substitution of the non-coordinating solvent toluene for THF increased the observed diastereoselectivity for allylation of enolate (*S*)-**3a** but reduced the yield (compare entries 2 and 3).

Enolate (*R*)-**3a** reacted with benzyl bromide in THF at −78 °C to give, in 93% yield, a 3:1 mixture of the chromatographically separable diastereomers **8c** and **8d** (entry 8). Enolate (*S*)-**3a** reacted with benzyl bromide under similar conditions, but in the presence of 2.5 equiv of hexamethylphosphoric triamide (HMPA), to produce diastereomers **8a** and **8b** in a comparable yield and with slightly attenuated diastereoselectivity (entry 9).

Alkylation of racemic enolate **3a** using iodomethane or iodononane was sluggish in THF at −78 °C (entries 10 and 11). At higher temperatures alkylation was more rapid but was accompanied by considerable decomposition of both

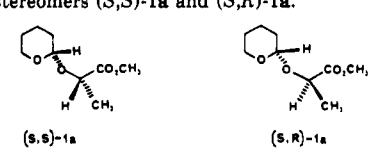
(1) (a) Ojima, I.; Miyazawa, Y.; Kumagai, M. *J. Chem. Soc., Chem. Commun.* **1976**, 927–928. (b) Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313–1324. (c) Whitesell, J. K.; Lawrence, R. M.; Chen, H.-H. *J. Org. Chem.* **1986**, *51*, 4779–4784. (d) Ludwig, J. W.; Newcomb, M.; Bergbreiter, D. E. *Tetrahedron Lett.* **1986**, *27*, 2731–2734. (e) Pearson, W. H.; Cheng, M.-C. *J. Org. Chem.* **1986**, *51*, 3746–3748. (f) References cited in ref 1a–e.

(2) (a) Meyers, A. I.; Knaus, G.; Kendall, P. M. *Tetrahedron Lett.* **1974**, *39*, 3495–3498. (b) Eliel, E. L.; Koskimies, J. K.; Lohri, B. *J. Am. Chem. Soc.* **1978**, *100*, 1614–1616. (c) Whitesell, J. K.; Bhattacharya, A.; Henke, K. *J. Chem. Soc., Chem. Commun.* **1982**, 988–989. (d) Kelly, T. R.; Arvanitis, A. *Tetrahedron Lett.* **1984**, *25*, 39–42. (e) Enomoto, M.; Ito, Y.; Katsuki, T.; Yamaguchi, M. *Ibid.* **1985**, *26*, 1343–1344. (f) Frye, S. V.; Eliel, E. L. *Ibid.* **1985**, *26*, 3907–3910. (g) Boireau, G.; Korenova, A.; Deberly, A.; Abenhaim, D. *Ibid.* **1985**, *26*, 4181–4182.

(3) Mash, E. A.; Arterburn, J. B.; Fryling, J. A.; Mitchell, S. H. *J. Org. Chem.*, previous article in this issue.

(4) The *Z* enolate geometry is presumed to predominate, see: Heathcock, C. H.; Pirrung, M. C.; Young, S. D.; Hagen, J. P.; Jarvi, E. T.; Badertscher, U.; Marki, H.-P.; Montgomery, S. H. *J. Am. Chem. Soc.* **1984**, *106*, 8161–8174.

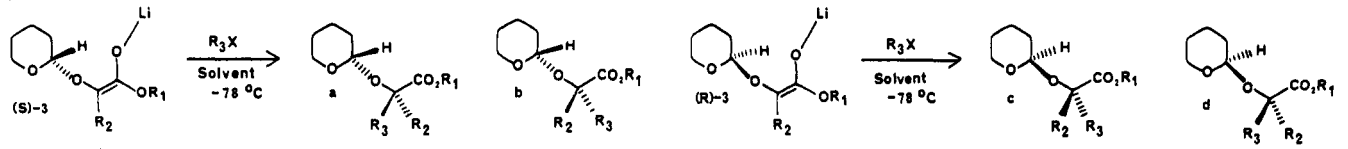
(5) Reprotonation of enolate (*S*)-**3a** at −78 °C using acetic acid or methanol as the proton source gave a 1:1 mixture of chromatographically separable diastereomers (*S,S*)-**1a** and (*S,R*)-**1a**.




(6) Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.* **1977**, *18*, 2183–2186.

0022-3263/91/1956-1094$02.50/0 

**Table I. Diastereoselective Alkylations of Enolates Derived from Lactyl Tetrahydropyranyl Ethers and Related Compounds**




| entry | enolate[a] | $R_1$ | $R_2$ | solvent | $R_3X$ | products | yields, % | diastereomer ratio, a:b or c/d[b] | $\alpha$[c] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | (*S*)-**3a** | $CH_3$ | $CH_3$ | THF | $CH_2$=$CHCH_2Cl$ | **4a, 4b** | no reaction | | |
| 2 | (*S*)-**3a** | $CH_3$ | $CH_3$ | THF | $CH_2$=$CHCH_2I$ | **4a, 4b** | 85 | 4:1 | 1.00 |
| 3 | (*S*)-**3a** | $CH_3$ | $CH_3$ | $PhCH_3$ | $CH_2$=$CHCH_2I$ | **4a, 4b** | 37 | 6:1 | 1.00 |
| 4 | (*S*)-**3b** | $CH_2CH_3$ | $CH_3$ | THF | $CH_2$=$CHCH_2I$ | **5a, 5b** | 85 | 5:1 | 1.00 |
| 5 | (*S*)-**3c** | $CH(CH_3)_2$ | $CH_3$ | THF | $CH_2$=$CHCH_2I$ | **6a, 6b** | 85 | 6:1 | 1.00 |
| 6 | (*R*/*S*)-**3d** | $C(CH_3)_3$ | $CH_3$ | THF | $CH_2$=$CHCH_2I$ | **7a/c, 7b/d** | 92 | 4:1 | 1.00 |
| 7 | (*S*)-**3c** | $CH(CH_3)_2$ | $CH_3$ | THF | $CH_2$=$CHCH_2Br$ | **6a, 6b** | 66 | 2:1 | 1.00 |
| 8 | (*R*)-**3a** | $CH_3$ | $CH_3$ | THF | $PhCH_2Br$ | **8c, 8d** | 93 | 4:1 | 0.91 |
| 9 | (*S*)-**3a** | $CH_3$ | $CH_3$ | THF/HMPA | $PhCH_2Br$ | **8a, 8b** | 92 | 3:1 | 0.91 |
| 10 | (*R*/*S*)-**3a** | $CH_3$ | $CH_3$ | THF | $CH_3I$ | **9a, 9c** | 50 | | |
| 11 | (*R*/*S*)-**3a** | $CH_3$ | $CH_3$ | THF | $CH_3(CH_2)_8I$ | **10a/c, 10b/d** | 16 | not determined | 0.95 |
| 12 | (*R*/*S*)-**3a** | $CH_3$ | $CH_3$ | THF/HMPA | $CH_3(CH_2)_8I$ | **10a/c, 10b/d** | 59 | 3:2 | 0.95 |
| 13 | (*S*)-**3a** | $CH_3$ | $CH_3$ | THF/HMPA | $CH_3C(=CH_2)(CH_2)_3I$ | **11a, 11b** | 83 | 2:1 | 0.92 |
| 14 | (*R*)-**3a** | $CH_3$ | $CH_3$ | THF/HMPA | $CH_3C(=CH_2)(CH_2)_3I$ | **11c, 11d** | 84 | 3:2 | 0.92 |
| 15 | (*R*/*S*)-**3a** | $CH_3$ | $CH_3$ | $PhCH_3$ | $CH_3C(=CH_2)(CH_2)_3I$ | **11a/c, 11b/d** | 14 | 4:1 | 0.92 |
| 16 | (*R*/*S*)-**3c** | $CH(CH_3)_2$ | $CH_3$ | THF/HMPA | $CH_3C(=CH_2)(CH_2)_3I$ | **12a/c, 12b/d** | 46 | 3:1 | 1.00 |
| 17 | (*S*)-**3e** | $CH_3$ | $CH_2Ph$ | THF | $CH_2$=$CHCH_2I$ | **13a, 13b** | 60 | 4:1 | 1.07 |
| 18 | (*R*)-**3e** | $CH_3$ | $CH_2Ph$ | THF | $CH_2$=$CHCH_2I$ | **13c, 13d** | 50 | 4:1 | 1.07 |
| 19 | (*S*)-**3f** | $CH_3$ | $CH_2CH(CH_3)_2$ | THF | $CH_2$=$CHCH_2I$ | **14a, 14b** | 30 | 1:1 | 1.08 |
| 20 | (*R*)-**3f** | $CH_3$ | $CH_2CH(CH_3)_2$ | THF | $CH_2$=$CHCH_2I$ | **14c, 14d** | 54 | 1:1 | 1.08 |
| 21 | (*S*)-**3g** | $CH_2C(CH_3)_2$ | | THF | $CH_2$=$CHCH_2I$ | **15a, 15b** | 30 | 3:1 | 1.30 |
| 22 | (*S*)-**3g** | $CH_2C(CH_3)_2$ | | THF/HMPA | $CH_2$=$CHCH_2I$ | **15a, 15b** | 37 | 2:1 | 1.30 |
| 23 | (*S*)-**3h** | $CH_3$ | Ph | THF | $CH_2$=$CHCH_2I$ | **16a, 16b** | 82 | 12:1 | 1.11 |
| 24 | (*S*)-**3h** | $CH_3$ | Ph | THF/HMPA | $CH_3I$ | **17a, 17b** | 89 | 5:1 | 1.15 |

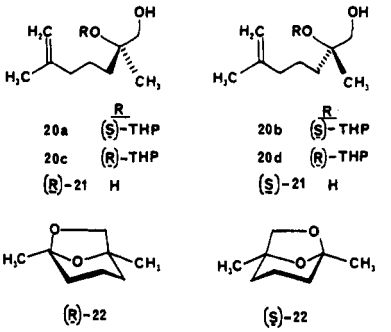
[a] The *Z* enolate geometry is presumed; see ref 4. [b] Determined by 62.9-MHz $^{13}C$ NMR spectroscopy. [c] The separation factor, $\alpha$, is the ratio of $R_f$ values for diastereomers **a** and **b** (or **c** and **d**) on 0.25-mm silica gel 60 analytical TLC plates (Merck, 70–230 mesh) eluted with 20% ethyl acetate in hexanes.

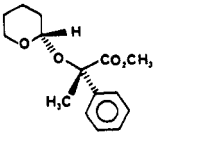
products and starting materials (presumably via carbonyl condensation reactions). However, in the presence of 1 equiv of HMPA, added after the alkylating agent, reaction of enolate (*R*/*S*)-**3a** with iodononane proceeded more smoothly at −78 °C to provide, in 59% yield, a 3:2 mixture of pairs of chromatographically separable diastereomers **10a/c** and **10b/d** (entry 12). Enolate (*S*)-**3a** was subsequently alkylated in the presence of 2.4 equiv of HMPA using 5-iodo-2-methyl-1-pentene (**18**) as the electrophile to produce, in 83% yield, a 2:1 mixture of chromatographically separable diastereomers **11a** and **11b** (entry 13). Alkylation of enolate (*R*)-**3a** with iodide **18** under the same conditions gave similar but enantiomeric results (entry 14). Structures were assigned to diastereomers **11a–d** by conversion of each to a particular enantiomer of frontalin (vide infra).

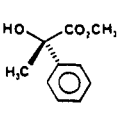
In an effort to improve upon the diastereoselectivity obtained above, the alkylation of enolate (*R*/*S*)-**3a** with iodide **18** was run in toluene (entry 15). As before, better diastereoselectivity was observed in this solvent but was offset by a lower yield. Substitution of enolate **3c** for **3a** also gave enhanced diastereoselectivity and a lower yield (entry 16).

Alkylations of enolates of diastereomeric THP ethers derived from other enantiomerically pure $\alpha$-hydroxy esters were also examined. Enolates (*R*)-**3e** and (*S*)-**3e**, derived from (*S*)-(+)-methyl 3-phenyllactate,[3] reacted with allyl iodide in THF at −78 °C to give in 50 and 60% yields 4:1 mixtures of pairs of separable diastereomers **13a** and **13b**, and **13c** and **13d**, respectively (entries 17 and 18). Allylation of enolates (*R*)-**3f** and (*S*)-**3f**, derived from (*S*)-(+)-methyl 2-hydroxy-4-methylvalerate,[3] gave 1:1 mixtures of separable pairs of diastereomers **14a** and **14b**, and **14c** and **14d**, in 30% and 54% yields, respectively (entries 19 and 20). Enolate (*S*)-**3g**, derived from (*R*)-(−)-pantolactone,[3] was similarly allylated to produce a 3:1 mixture of separable diastereomers **15a** and **15b** in 30% yield (entries 21 and 22). Enolate (*S*)-**3h**, derived from (*S*)-(+)-methyl mandelate,[3] was allylated to give in 82% yield a 12:1 mixture of separable diastereomers **16a** and **16b** (entry 23). Reaction of this last enolate (*S*)-**3h** with iodomethane at −78 °C in THF in the presence of 2.5 equiv. of HMPA gave, in 89% yield, a 5:1 mixture of separable diastereomers **17a** and **17b** (entry 24). The identity of the major diastereomer **17a** was confirmed by its conversion to (*S*)-(+)-methyl atrolactate (**19**).[7]

**Chart I**





17a


19

(7) Bonner, W. A.; Zderic, J. A.; Casaletto, G. A. *J. Am. Chem. Soc.* **1952**, *74*, 5086–5089.

## Synthesis of (+)- and (-)-Frontalin (22)

As a test of the utility of this methodology, and in order to assign structures to some of the alkylated products, we have prepared both enantiomers of frontalin (**22**)[8] from esters **11a–d** (Table I). Each ester was independently reduced with use of LAH to the corresponding alchol **20a–d** (Chart I) and subsequently hydrolyzed to the known[8o] diols (*R*)-(+)-**21** and (*S*)-(-)-**21** (ca. 35% yield of each enantiomeric diol starting from (*S*)-(-)-methyl lactate over four steps). Ozonolysis[8o] of (*S*)-(-)-**21** provided in 66% yield (*S*)-(-)-frontalin, $[\alpha]_D$ −50.3° (*c* 2.3, $Et_2O$), lit.[8o] $[\alpha]_D$ −54.8° (*c* 0.52, $Et_2O$), while ozonolysis of (*R*)-(+)-**21** gave (*R*)-(+)-frontalin, thus establishing the structures of **11a–d**.

## Experimental Section

Toluene was distilled from calcium hydride and diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl under an inert atmosphere. Diisopropylamine was distilled from calcium hydride under reduced pressure and stored over 3-Å molecular sieves. HMPA (*caution! carcinogen*) was stored over 3-Å molecular sieves. The purity of all title compounds was judged to be ≥95% by $^1H$ and $^{13}C$ NMR spectral determinations. $^1H$ and $^{13}C$ NMR spectra were recorded at 250 and at 62.9 MHz, respectively. In NMR spectral data for mixed diastereomers, signals belonging to the major diastereomer are underlined. Elemental analyses were performed by Desert Analytics, Tucson, AZ. Thin layer chromatographic analyses were performed on Merck silica gel 60 plates (0.25 mm, 70–230-mesh ASTM). Column chromatography was performed on Merck silica gel 60 (gravity driven, 70–230 mesh ASTM; flash, 230–400-mesh ASTM). Gas chromatography was performed on a 2.5 mm i.d. × 3 m glass column packed 230–400 mesh 15% Carbowax 20M on Chromasorb W-HP (60–80 mesh). Helium was used as the carrier gas.

**General Procedure for Alkylations.** All glassware was flame-dried under vacuum and cooled under argon. A solution of diisopropylamine (160 mg, 1.6 mmol) in dry THF (10 mL) under argon was stirred and cooled to 0 °C, and *n*-butyllithium (0.9 mL of 1.6 M solution in hexanes, 1.4 mmol) was added via syringe. The reaction was stirred for 20 min and then cooled to −78 °C, and the THP-protected α-hydroxy ester (1 mmol) was added via syringe. After stirring for 1 h, the alkylating agent (1–3 equiv) was added via syringe. Progress of the reaction was monitored by TLC. The reaction was quenched at −78 °C with saturated $NaHCO_3$ (10 mL) and diluted with diethyl ether (100 mL). The ether phase was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo. The concentrate was chromatographed on silica gel eluted with 5–10% EtOAc in hexanes to afford the products as colorless oils. When the product diastereomers were inseparable (**4–7** and **12**), the spectral data were obtained on the diastereomeric mixture. Diastereomers **8–11** and **13–17** were separated by chromatography and characterized individually. The reactants, products, and results are presented in the following abbreviated format (see Table I also): enolate, alkyl halide (equiv), product (diastereomer ratio, percent yield).

**Methyl 2-Methyl-2-(tetrahydropyranyloxy)pent-4-enoates (4a and 4b, Entry 2).** (*S*)-**3a**, allyl iodide (2.7), **4a** and **4b** (4:1, 85%). Spectral data for the mixture ($R_f$ 0.385, 20% EtOAc/hexanes): IR ($CHCl_3$) $cm^{-1}$ 2950, 1729, 1433, 1118, 1074; $^1H$ NMR ($CDCl_3$) δ 1.40 and 1.48 (3, s), 1.47–1.92 (6, m), 2.51 and 2.55 (1, bs), 2.51 and 2.58 (1, bs), 3.37–3.50 (1, m), 3.70 (3, s), 3.87–3.99 (1, m), 4.73–4.77 and 4.77–4.82 (1, m), 5.05–5.09 (1, s), 5.10–5.15 (1, m), 5.69–5.90 (1, m); $^{13}C$ NMR ($CDCl_3$) δ 19.92 and 20.04 ($CH_2$), 20.70 and 22.24 ($CH_3$), 25.06 and 25.17 ($CH_2$), 31.16 ($CH_2$), 42.93 and 43.72 ($CH_2$), 51.77 ($CH_3$), 62.90 and 63.27 ($CH_2$), 78.73 and 80.12 (C), 94.83 and 95.88 (CH), 118.14 and 118.52 ($CH_2$), 132.64 (CH), 174.01 and 174.26 (C).

**Ethyl 2-Methyl-2-(tetrahydropyranyloxy)pent-4-enoates (5a and 5b, Entry 4).** (*S*)-**3b**, allyl iodide (2.7), **5a** and **5b** (5:1, 85%). Spectral data for the mixture ($R_f$ 0.426, 20% EtOAc/hexanes): IR ($CHCl_3$) $cm^{-1}$ 2943, 1725, 1121, 1074, 1032; $^1H$ NMR ($CDCl_3$) δ 1.27 and 1.28 (3, t, $J$ = 7.1 Hz), 1.39 and 1.48 (3, s), 1.48–1.93 (6, m), 2.49–2.60 (2, m), 3.37–3.50 (1, m), 3.89–3.99 (1, m), 4.10–4.30 (2, m), 4.72–4.82 (1, m), 5.05–5.17 (2, m), 5.70–5.93 (1, m); $^{13}C$ NMR ($CDCl_3$) δ 13.98 and 14.07 ($CH_3$), 19.95 and 20.04 ($CH_2$), 21.02 and 22.21 ($CH_3$), 25.12 and 25.21 ($CH_2$), 31.24 ($CH_2$), 42.77 and 43.98 ($CH_2$), 60.71 ($CH_2$), 62.89 and 63.22 ($CH_2$), 78.82 and 80.12 (C), 95.00 and 96.01 (CH), 118.11 and 118.46 ($CH_2$), 132.70 and 132.80 (CH), 173.57 and 173.83 (C).

**Isopropyl 2-Methyl-2-(tetrahydropyranyloxy)pent-4-enoates (6a and 6b, Entry 5).** (*S*)-**3c**, allyl iodide (2.8), **6a** and **6b** (6:1, 85%). Spectral data for the mixture ($R_f$ 0.511, 20% EtOAc/hexanes): IR ($CHCl_3$) $cm^{-1}$ 2943, 1720, 1102, 1073, 1031; $^1H$ NMR ($CDCl_3$) δ 1.24 and 1.25 (6, d, $J$ = 6.3 Hz), 1.37 and 1.47 (3, s), 1.46–1.95 (6, m), 2.46–2.52 (2, m) and 2.56 (2, d, $J$ = 7.3 Hz), 3.37–3.47 (1, m), 3.90–3.99 (1, m), 4.71–4.74 and 4.75–4.79 (1, m), 5.02 (1, m, $J$ = 6.3 Hz), 5.07–5.16 (2, m), 5.72–5.91 (1, m): $^{13}C$ NMR ($CDCl_3$) δ 20.05 and 20.24 ($CH_2$), 21.39 ($CH_3$), 21.50 ($CH_3$), 21.60 ($CH_3$), 21.68 ($CH_3$), 22.22 ($CH_3$), 25.17 and 25.24 ($CH_2$), 31.31 and 31.40 ($CH_2$), 42.60 and 44.27 ($CH_2$), 62.97 and 63.42 ($CH_2$), 68.18 (CH), 79.00 and 80.21 (C), 95.35 and 96.23 (CH), 118.10 and 118.40 ($CH_2$), 132.75 and 132.96 (CH), 173.13 and 173.36 (C).

Anal. Calcd for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44. Found: C, 65.53; H, 9.49.

***tert*-Butyl 2-Methyl-2-(tetrahydropyranyloxy)pent-4-enoates (7, Entry 6).** Racemic **3d**, allyl iodide (3.2), **7a/c** and **7b/d** (4:1, 92%). Spectral data for the mixture ($R_f$ 0.519, 20% EtOAc/hexanes): IR ($CHCl_3$) $cm^{-1}$ 2944, 1719, 1368, 1152, 1030; $^1H$ NMR ($CDCl_3$) δ 1.34 and 1.44 (3, s), 1.456 and 1.462 (9, s), 1.45–1.93 (6, m), 2.45–2.50 and 2.52–2.58 (2, m), 3.38–3.51 (1, m), 3.90–4.00 (1, m), 4.74–4.78 and 4.78–4.81 (1, m), 5.05–5.16 (2, m), 5.72–5.94 (1, m); $^{13}C$ NMR ($CDCl_3$) δ 20.04 and 20.16 ($CH_2$), 21.60 and 22.31 ($CH_3$), 25.22 and 25.30 ($CH_2$), 27.83 and 27.95 (3 $CH_3$), 31.40 and 31.50 ($CH_2$), 42.74 and 44.44 ($CH_2$), 62.89 and 63.24 ($CH_2$), 79.37 and 80.38 (C), 80.85 and 81.03 (C), 95.15 and 96.12 (CH), 117.94 and 118.24 ($CH_2$), 132.98 and 133.20 (CH), 172.69 and 173.01 (C).

**Methyl 2-Methyl-3-phenyl-2-(tetrahydropyranyloxy)-propanoates (8c and 8d, Entry 8).** (*R*)-**3a**, benzyl bromide (2.7), **8d** (19%) and **8c** (74%). Spectral data for **8c** ($R_f$ 0.32): $[\alpha]^{26}_D$ + 68.71° (*c* 1.32, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 3009, 1729, 1453, 1117; $^1H$ NMR ($CDCl_3$) δ 0.84–1.95 (6, m), 1.32 (3, s), 3.04 (1, d, $J$ = 13.4 Hz), 3.12 (1, d, $J$ = 13.4 Hz), 3.35–3.45 (1, m), 3.70 (3, s), 3.89–3.99 (1, m), 4.75–4.82 (1, m), 7.18–7.30 (5, m); $^{13}C$ NMR ($CDCl_3$) δ 19.08 ($CH_3$), 20.06 ($CH_2$), 25.13 ($CH_2$), 31.07 ($CH_2$), 45.26 ($CH_2$), 51.86 ($CH_3$), 63.33 ($CH_2$), 78.85 (C), 94.42 (CH), 126.55 (CH), 127.87 (CH), 130.52 (CH), 136.13 (C), 174.09 (C). For **8d** ($R_f$ 0.35, 20% EtOAc/hexanes): $[\alpha]^{24}_D$ + 54.2° (*c* 1.84, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 3009, 1729, 1452, 1116, 1023; $^1H$ NMR ($CDCl_3$) δ 1.48 (3, s), 1.49–1.95 (6, m), 3.01 (1, d, $J$ = 13.5 Hz), 3.08 (1, d, $J$ = 13.5 Hz), 3.35–3.45 (1, m), 3.65 (3, s), 3.72–3.82 (1, m), 4.80 (1, dd, $J$ = 3.5, 3.7 Hz), 7.20–7.29 (5, m); $^{13}C$ NMR ($CDCl_3$) δ 19.60 ($CH_2$), 22.25 ($CH_3$), 25.35 ($CH_2$), 31.21 ($CH_2$), 46.09 ($CH_2$), 51.83 ($CH_3$), 62.32 ($CH_2$), 81.14 (C), 95.82 (CH), 126.58 (CH), 127.75 (CH), 130.58 (CH), 136.11 (C), 174.48 (C).

(8) For previous enantioselective syntheses of frontalin, see: (a) Mori, K. *Tetrahedron* **1975**, *31*, 1381–1384. (b) Hicks, D. R.; Fraser-Reid, B. *J. Chem. Soc., Chem. Commun.* **1976**, 869–870. (c) Ohrui, H.; Emoto, S. *Agric. Biol. Chem.* **1976**, *40*, 2267–2270. (d) Magnus, P.; Roy, G. *J. Chem. Soc., Chem. Commun.* **1978**, 297–298. (e) Sakito, Y.; Mukaiyama, T. *Chem. Lett.* **1979**, 1027–1028. (f) Jarosz, S.; Hicks, D. R.; Fraser-Reid, B. *J. Org. Chem.* **1982**, *47*, 935–940. (g) Fuganti, C.; Grasselli, P.; Servi, S. *J. Chem. Soc., Perkin Trans. I* **1983**, 241–244. (h) Barner, R.; Hubscher, J. *Helv. Chim. Acta* **1983**, *66*, 880–890. (i) Meister, C.; Scharf H.-D. *Liebigs Ann. Chem.* **1983**, 913–921. (j) Naef, R.; Seebach, D. *Ibid.* **1983**, 1930–1936. (k) Lee, A. W. M. *J. Chem. Soc., Chem. Commun.* **1984**, 578–579. (l) Johnston, B. D.; Oehlschlager, A. C. *Can. J. Chem.* **1984**, *62*, 2148–2154. (m) Yadav, J. S.; Joshi, B. V.; Sahasrabudhe, A. B. *Synth. Commun.* **1985**, *15*, 797–805. (n) Hosokawa, T.; Makabe, Y.; Shinohara, T.; Murahashi, S. *Chem. Lett.* **1985**, 1529–1530. (o) Whitesell, J. K., Buchanan, C. M. *J. Org. Chem.* **1986**, *51*, 5443–5445. (p) Ohwa, M.; Eliel, E. L. *Chem. Lett.* **1987**, 41–44. (q) Trinh, M.-C.; Florent, J.-C.; Monneret, C. *J. Chem. Soc., Chem. Commun.* **1987**, 615–616. (r) Sato, T.; Maeno, H.; Noro, T.; Fujisawa, T. *Chem. Lett.* **1988**, 1739–1742. (s) Trinh, M.-C.; Florent, J.-C.; Monneret, C. *Tetrahedron* **1988**, *44*, 6633–6644. (t) Wershofen, S.; Classen, A.; Scharf, H.-D. *Liebigs Ann. Chem.* **1989**, 9–18.

**Methyl 2-Methyl-3-phenyl-2-(tetrahydropyranyloxy)-propanoates (8a and 8b, Entry 9).** (*S*)-**3a**, HMPA (2.5), benzyl bromide (2.2), **8b** (21%) and **8a** (71%).

**Methyl 2-Methyl-2-(tetrahydropyranyloxy)propanoates (9a and 9c, Entry 10).** Racemic **3a**, iodomethane (1.3), **9a** and **9c** (50%). Spectral data: IR ($CHCl_3$) $cm^{-1}$ 1727, 1153, 1074, 1030; $^1H$ NMR ($CDCl_3$) $\delta$ 1.39–1.95 (6, m), 1.45 (3, s), 1.50 (3, s), 3.39–3.49 (1, m), 3.72 (3, s), 3.89–3.97 (1, m), 4.70–4.74 (1, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.21 ($CH_2$), 24.95 ($CH_3$), 25.10 ($CH_2$), 25.39 ($CH_3$), 31.29 ($CH_2$), 51.88 ($CH_3$), 63.26 ($CH_2$), 77.18 (C), 95.82 (CH), 175.02 (C).

**Methyl 2-Methyl-2-(tetrahydropyranyloxy)undecanoates (10, Entry 11).** Racemic **3a**, 1-iodononane (1.3), **10a–d** (16%).

**Methyl 2-Methyl-2-(tetrahydropyranyloxy)undecanoates (10a/c and 10b/d, Entry 12).** Racemic **3a**, 1-iodononane (1.2), HMPA (1 equivalent), **10a/c** and **10b/d** (3:2, 59%). Spectral data for the product mixture (**10a/10c** $R_f$ 0.492, **10b/d** $R_f$ 0.521, 20% EtOAc/hexanes): $^1H$ NMR ($CDCl_3$) $\delta$ 0.88 (3, t, $J$ = 6.4 Hz), 1.20–1.85 (25, m), 3.35–3.50 (1, m), 3.697 and 3.708 (3, s), 3.88–3.97 (1, m), 4.67–4.71 and 4.73–4.77 (1, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.04 ($CH_3$), 20.25 ($CH_2$), 20.60 ($CH_3$), 22.54 ($CH_3$), 22.61 ($CH_2$), 23.49 ($CH_2$), 25.18 ($CH_2$), 25.28 ($CH_2$), 29.24 ($CH_2$), 29.39 ($CH_2$), 29.45 ($CH_2$), 29.69 ($CH_2$), 29.78 ($CH_2$), 31.37 ($CH_2$), 31.83 ($CH_2$), 38.52 ($CH_2$), 39.89 ($CH_2$), 51.82 ($CH_3$), 63.18 ($CH_2$), 63.45 ($CH_2$), 79.27 (C), 80.61 (C), 94.71 (CH), 96.24 (CH), 174.78 (C), 175.16 (C).

**5-Iodo-2-methyl-1-pentene (18).** 4-Methyl-4-penten-1-yl *p*-toluenesulfonate[9] (1.7 g, 6.68 mmol) was dissolved in 50 mL of acetone under argon. Sodium iodide (10.04 g, 67 mmol) was added and the mixture was stirred for 45 min. The reaction mixture was then warmed to 50 °C for 1 min, at which time TLC showed no remaining tosylate. The mixture was diluted with water (250 mL) and extracted with ether (2 × 125 mL). The combined ether extracts were dried ($MgSO_4$) and filtered, and the solvent was removed in vacuo. The residue was chromatographed on silica gel 60 (50 g) eluted with 10% ether/pentane to afford the iodide **18** (1.4 g, quantitative) as a pale yellow oil: $^1H$ NMR ($CDCl_3$) $\delta$ 1.72 (3, s), 1.89–2.01 (2, m), 2.12 (2, t, $J$ = 7 Hz), 3.18 (2, t, $J$ = 7 Hz), 4.72 (1, bs), 4.76 (1, bs); $^{13}C$ NMR ($CDCl_3$) $\delta$ 6.42 ($CH_2$), 22.26 ($CH_3$), 31.21 ($CH_2$), 38.23 ($CH_2$), 111.08 ($CH_2$), 143.69 (C).

**Methyl 2,6-Dimethyl-2-(tetrahydropyranyloxy)hept-6-enoates (11a and 11b, Entry 13).** (*S*)-**3a**, 5-iodo-2-methyl-1-pentene (**18**) (1.1), HMPA (2.4), **11a** and **11b** (2:1, 82.8%). Spectral data for **11a** ($R_f$ 0.42): $[\alpha]^{24}_D$ −51.9° (*c* 3.575, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 2948, 1729, 1646, 1118, 1074, 1032; $^1H$ NMR ($CDCl_3$) $\delta$ 1.23–1.91 (10, m), 1.42 (3, s), 1.70 (3, s), 2.01 (2, t, $J$ = 7.3 Hz), 3.38–3.47 (1, m), 3.70 (3, s), 3.90–3.99 (1, m), 4.67 (1, bs), 4.70 (1, bs), 4.74–4.78 (1, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.16 ($CH_2$), 20.66 ($CH_3$), 21.30 ($CH_2$), 22.07 ($CH_3$), 25.10 ($CH_2$), 31.28 ($CH_2$), 37.71 ($CH_2$), 37.89 ($CH_2$), 51.80 ($CH_3$), 63.36 ($CH_2$), 79.09 (C), 94.68 (CH), 110.06 ($CH_2$), 145.23 (C), 174.61 (C). For **11b** ($R_f$ 0.46, 20% EtOAc/hexanes): $[\alpha]^{25}_D$ −65.38° (*c* 1.50, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 2944, 1735, 1118, 1074, 1030; $^1H$ NMR ($CDCl_3$) 1.26–1.91 (10, m), 1.49 (3, s), 1.70 (3, s), 2.00 (2, t, $J$ = 7.2 Hz), 3.40–3.50 (1, m), 3.71 (3, s), 3.90–3.99 (1, m), 4.67–4.74 (3, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.20 ($CH_2$), 21.37 ($CH_2$), 22.16 ($CH_3$), 22.64 ($CH_3$), 25.30 ($CH_2$), 31.37 ($CH_2$), 37.62 ($CH_2$), 39.39 ($CH_2$), 51.87 ($CH_3$), 63.13 ($CH_2$), 80.49 (C), 96.20 (CH), 110.13 ($CH_2$), 145.34 (C), 175.10 (C).

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.56; H, 9.83.

**Methyl 2,6-Dimethyl-2-(tetrahydropyranyloxy)hept-6-enoates (11c and 11d, Entry 14).** (*R*)-**3a**, 5-iodo-2-methyl-1-pentene (**18**) (1.2), HMPA (2.4), **11c** and **11d** (3:2, 83.8%). Spectral data for **11c** ($R_f$ 0.42): $[\alpha]^{25}_D$ +49.5° (*c* 4.82, $CHCl_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.20 ($CH_2$), 20.69 ($CH_3$), 21.34 ($CH_2$), 22.10 ($CH_3$), 25.14 ($CH_2$), 31.32 ($CH_2$), 37.75 ($CH_2$), 37.93 ($CH_2$), 51.84 ($CH_3$), 63.41 ($CH_2$), 79.15 (C), 94.73 (CH), 110.09 ($CH_2$), 145.29 (C), 174.67 (C). For **11d** ($R_f$ 0.46, 20% EtOAc/hexanes): $[\alpha]^{25}_D$ +64.59° (*c* 3.44, $CHCl_3$); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.19 ($CH_2$), 21.36 ($CH_2$), 22.15 ($CH_3$), 22.63 ($CH_3$), 25.30 ($CH_2$) 31.36 ($CH_2$), 37.62 ($CH_2$), 39.38 ($CH_2$), 51.86 ($CH_3$), 63.12 ($CH_2$) 80.49 (C), 96.20 (CH), 110.13 ($CH_2$), 145.34 (C), 175.10 (C).

**Isopropyl 2,6-Dimethyl-2-(tetrahydropyranyloxy)hept-6-enoates (12a/c and 12b/d, Entry 16).** Racemic **3c**, 5-iodo-2-methyl-1-pentene (**18**) (1.1), HMPA (1.2), **12a/c** and **12b/d** (3:1, 46%). Spectral data for the mixture ($R_f$ 0.477, 20% EtOAc/hexanes): $^1H$ NMR ($CDCl_3$) $\delta$ 1.25 (6, d, $J$ = 6.3 Hz), 1.39–1.90 (10, m), 1.39 and 1.47 (3, s), 1.70 (3, s), 2.00 (2, t, $J$ = 7.4 Hz), 3.36–3.48 (1, m), 3.89–3.99 (1, m), 4.67 (1, bs), 4.70 (1, bs), 4.80–4.87 (1, m), 4.97–5.09 (1, m, $J$ = 6.3 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.27 and 20.34 ($CH_2$), 21.26 ($CH_3$), 21.46 ($CH_2$), 21.54 ($CH_3$), 21.66 ($CH_3$), 22.18 ($CH_3$), 25.25 and 25.33 ($CH_2$), 31.42 and 31.54 ($CH_2$), 37.63 and 37.71 ($CH_2$), 37.94 and 39.81 ($CH_2$), 63.12 and 63.46 ($CH_2$), 68.06 and 68.15 (CH), 79.48 and 80.59 (C), 95.14 and 96.46 (CH), 110.02 ($CH_2$), 145.49 (C), 173.72 (C).

**Methyl 2-(Phenylmethyl)-2-(tetrahydropyranyloxy)-pent-4-enoates (13a and 13b, Entry 17).** (*S*)-**3e**, allyl iodide (1.8), **13a** and **13b** (4:1, 60%). Spectral data for **13a** ($R_f$ 0.52, 20% EtOAc/hexanes): $[\alpha]^{26}_D$ −41.45° (*c* 2.75, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 2947, 1736, 1434, 1026; $^1H$ NMR ($CDCl_3$) $\delta$ 1.28–1.95 (6, m), 2.66–2.71 (2, m), 3.05 (2, s), 3.40–3.50 (1, m), 3.59 (3, s), 3.88–3.98 (1, m), 4.90 (1, dd, $J$ = 3, 5 Hz), 5.13–5.19 (2, m), 5.88–6.06 (1, m), 7.18–7.27 (5, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 19.92 ($CH_2$), 25.25 ($CH_2$), 31.09 ($CH_2$), 39.57 ($CH_2$), 42.44 ($CH_2$), 51.56 ($CH_3$), 63.04 ($CH_2$), 83.38 (C), 95.82 (CH), 118.77 ($CH_2$), 126.47 (CH), 127.72 (2 CH), 130.35 (2 CH), 133.11 (CH), 136.25 (C), 173.25 (C). For **13b** ($R_f$ 0.49): $[\alpha]^{26}_D$ −67.12° (*c* 0.76, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 2948, 1730, 1440, 1030; $^1H$ NMR ($CDCl_3$) $\delta$ 1.26–1.92 (6, m), 2.45 (1, dd, $J$ = 6.9, 16.4 Hz), 2.68 (1, dd, $J$ = 7, 15.8 Hz), 3.20 (2, d, $J$ = 2.7 Hz), 3.39–3.48 (1, m), 3.68 (3, s), 3.92–4.01 (1, m), 4.90–4.94 (1, m), 5.09–5.21 (2, m), 5.77–5.93 (1, m), 7.20–7.30 (5, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.12 ($CH_2$), 25.18 ($CH_2$), 31.10 ($CH_2$), 36.18 ($CH_2$), 41.36 ($CH_2$), 51.76 ($CH_3$), 63.47 ($CH_2$), 81.64 (C), 94.86 (CH), 118.72 ($CH_2$), 126.64 (CH), 128.05 (2 CH), 130.43 (2 CH), 132.72 (CH), 135.90 (C), 173.04 (C).

Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 70.84; H, 7.97.

**Methyl 2-(2-Methylpropyl)-2-(tetrahydropyranyloxy)-pent-4-enoates (14a and 14b, Entry 19).** (*S*)-**3f**, allyl iodide (3), **14a** and **14b** (1:1, 30%). Spectral data for **14a** ($R_f$ 0.59, 20% EtOAc/hexanes): $[\alpha]^{27}_D$ −51.96° (*c* 1.40, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 2951, 1735, 1073, 1029; $^1H$ NMR ($CDCl_3$) $\delta$ 0.84 (3, d, $J$ = 6.3 Hz), 0.92 (3, d, $J$ = 6.4 Hz), 1.25–1.90 (9, m), 2.55–2.74 (2, m), 3.40–3.50 (1, m), 3.70 (3, s), 3.90–3.99 (1, m), 4.81–4.85 (1, m), 5.05–5.15 (2, m), 5.78–5.95 (1, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.24 ($CH_2$), 23.69 ($CH_3$), 23.86 ($CH_3$), 24.02 (CH), 25.28 ($CH_2$), 31.34 ($CH_2$), 40.72 ($CH_2$), 45.27 ($CH_2$), 51.62 ($CH_3$), 63.32 ($CH_2$), 82.86 (C), 95.89 (CH), 118.28 ($CH_2$), 133.35 (CH), 174.48 (C). For **14b** ($R_f$ 0.54): $[\alpha]^{27}_D$ −65.9° (*c* 1.34, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 2952, 1727, 1230, 1033; $^1H$ NMR ($CDCl_3$) $\delta$ 0.86 (3, d, $J$ = 6.4 Hz), 0.91 (3, d, $J$ = 6.3 Hz), 1.27–1.92 (9, m), 2.53–2.80 (2, m), 3.39–3.48 (1, m), 3.68 (3, s), 3.90–4.00 (1, m), 4.81–4.86 (1, m), 5.07–5.17 (2, m), 5.70–5.87 (1, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.07 ($CH_2$), 23.36 ($CH_3$), 23.71 (CH), 24.07 ($CH_3$), 25.19 ($CH_2$), 31.21 ($CH_2$), 37.60 ($CH_2$), 43.75 ($CH_2$), 51.63 ($CH_3$), 63.25 ($CH_2$), 81.18 (C), 94.20 (CH), 118.09 ($CH_2$), 133.02 (CH), 173.86 (C).

Anal. Calcd for $C_{15}H_{26}O_4$: C, 66.64; H, 9.69. Found: C, 66.42; H, 9.76.

**2-(2-Propenyl)-2-*O*-(tetrahydropyranyl)pantolactones (15a and 15b, Entry 22).** (*S*)-**3g**, allyl iodide (2), HMPA (1), **15a** and **15b** (2:1, 37%). Spectral data for **15a** ($R_f$ 0.43, 20% EtOAc/hexanes): $[\alpha]^{27}_D$ +56.0° (*c* 2.77, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 2945, 1766, 1259, 1032; $^1H$ NMR ($CDCl_3$) $\delta$ 1.09 (3, s), 1.17 (3, s), 1.42–1.90 (6, m), 2.28 (1, dd, $J$ = 9.5, 15.8 Hz), 2.96 (1, dm, $J$ = 15.8 Hz), 3.51–3.60 (1, m), 3.73 (1, d, $J$ = 8.0 Hz), 3.93–4.02 (1, m), 4.09 (1, d, $J$ = 8.0 Hz), 5.03 (1, d, $J$ = 4.8 Hz), 5.10–5.12 (1, m), 5.12–5.19 (1, dm, $J$ = 11.6 Hz), 5.96–6.13 (1, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 18.04 ($CH_3$), 19.81 ($CH_2$), 21.66 ($CH_3$), 25.04 ($CH_2$), 31.29 ($CH_2$), 33.89 ($CH_2$), 43.92 (C), 63.44 ($CH_2$), 77.43 ($CH_2$), 81.36 (C), 94.69 (CH), 117.67 ($CH_2$), 132.61 (CH), 175.57 (C). For **15b** ($R_f$ 0.33): $[\alpha]^{27}_D$ −52.0° (*c* 1.46, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 2945, 1766, 1260, 1031; $^1H$ NMR ($CDCl_3$) $\delta$ 1.08 (3, s), 1.15 (3, s), 1.49–1.90 (6, m), 2.24 (1, dd, $J$ = 8.8, 16.0 Hz), 2.86 (1, dm, $J$ = 16.0 Hz), 3.46–3.56 (1, m), 3.74 (1, d, $J$ = 8.1 Hz), 3.78–3.90 (1, m), 4.235 (1, d, $J$ = 8.1 Hz), 4.95–4.99 (1, m), 5.12–5.15 (1, m), 5.17 (1, d, $J$ = 9.6 Hz), 5.82–6.00 (1, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 17.90 ($CH_3$), 20.28 ($CH_2$), 22.51 ($CH_3$), 25.00 ($CH_2$), 31.08 ($CH_2$), 33.24 ($CH_2$), 44.21 (C), 63.76 ($CH_2$), 77.13 ($CH_2$), 79.35 (C), 94.26 (CH), 118.29 ($CH_2$), 131.82 (CH), 176.34 (C).

(9) Mazzocchi, P. H.; Wilson, P.; Khachik, F.; Klingler, L.; Minamikawa, S. *J. Org. Chem.* **1983**, *48*, 2981–2989.

**Methyl 2-Phenyl-2-(tetrahydropyranyloxy)pent-4-enoates (16a and 16b, Entry 23).** (*S*)-**3h**, allyl iodide (2), **16a** (75.3%) and **16b** (6.3%). Spectral data for **16a** ($R_f$ 0.423, 20% EtOAc/hexanes): IR ($CHCl_3$) $cm^{-1}$ 2948, 1730, 1243, 1032; $^1H$ NMR ($CDCl_3$) $\delta$ 1.25–2.03 (6, m), 2.40–2.52 (1, m), 3.00–3.04 (2, m), 3.69 (3, s), 3.93–4.03 (1, m), 4.81 (1, t, $J$ = 3.7 Hz), 4.86–4.89 (1, m), 4.93 (1, s), 5.49–5.67 (1, m), 7.20–7.47 (5, m); $^{13}C$ NMR ($CDCl_3$) 19.63 ($CH_2$), 25.15 ($CH_2$), 31.18 ($CH_2$), 41.89 ($CH_2$), 52.32 ($CH_3$), 63.01 ($CH_2$), 84.53 (C), 96.19 (CH), 118.26 ($CH_2$), 125.91 (CH), 127.40 (CH), 127.84 (CH), 132.40 (CH), 139.49 (C), 172.72 (C). For **16b** ($R_f$ 0.382): $^1H$ NMR ($CDCl_3$) $\delta$ 1.25–2.03 (6, m), 2.40–2.52 (1, m), 3.00–3.04 (2, m), 3.64 (3, s), 3.93–4.03 (1, m), 4.81 (1, t, $J$ = 3.7 Hz), 4.86–4.89 (1, m), 4.93 (1, s), 5.49–5.67 (1, m), 7.20–7.47 (5, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 19.74 ($CH_2$), 25.21 ($CH_2$), 30.95 ($CH_2$), 39.27 ($CH_2$), 52.15 ($CH_3$), 63.13 ($CH_2$), 82.18 (C), 94.31 (CH), 118.35 ($CH_2$), 125.79 (CH), 127.67 (CH), 128.11 (CH), 132.48 (CH), 140.20 (C), 173.19 (C).

**Methyl 2-Phenyl-2-(tetrahydropyranyloxy)propanoates (17a and 17b, Entry 24).** (*S*)-**3h**, iodomethane (2), HMPA (2), **17a** and **17b** (5:1, 89%). Spectral data for **17a** ($R_f$ 0.41, 20% EtOAc/hexanes): $[\alpha]^{27}_D$ −85.5° (*c* 4.80, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 2946, 1732, 1256, 1117, 1031; $^1H$ NMR ($CDCl_3$) $\delta$ 1.27–2.04 (6, m), 1.83 (3, s), 3.47–3.56 (1, m), 3.68 (3, s), 3.94–4.03 (1, m), 4.85 (1, t, $J$ = 3.7 Hz), 7.22–7.38 (3, m), 7.50–7.56 (2, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 19.64 ($CH_2$), 25.21 ($CH_2$), 25.45 ($CH_3$), 31.27 ($CH_2$), 52.30 ($CH_3$), 62.56 ($CH_2$), 82.15 (C), 96.26 (CH), 125.02 (2 CH), 127.49 (CH), 128.08 (2 CH), 142.22 (C), 173.57 (C). For **17b** ($R_f$ 0.361): $[\alpha]^{27}_D$ −58.8° (*c* 1.07, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 2948, 1729, 1269, 1125, 1034; $^1H$ NMR ($CDCl_3$) $\delta$ 1.26–2.02 (6, m), 1.82 (3, s), 3.35–3.44 (1, m), 3.67 (3, s), 3.91–4.00 (1, m), 4.79 (1, t, $J$ = 4 Hz), 7.24–7.38 (3, m), 7.43–7.51 (2, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 19.87 ($CH_2$), 23.20 ($CH_3$), 25.16 ($CH_2$), 31.21 ($CH_2$), 52.24 ($CH_3$), 63.02 ($CH_2$), 80.30 (C), 94.47 (CH), 125.52 (2 CH), 127.67 (CH), 128.16 (2 CH), 141.90 (C), 173.69 (C).

**(*S*)-(+)-Methyl Atrolactate (19).**[7] The pyran **17a** (170.1 mg, 0.643 mmol) was placed in a 5-mL flask with a stir bar under argon and cooled to 0 °C. A solution (1 mL), which was 90% $CH_3OH$, 9% $H_2O$, and 1% concentrated HCl, was added and the progress of the hydrolysis monitored by TLC. After 1 h the reaction was diluted with 20 mL of diethyl ether and washed with 3 mL of saturated $NaHCO_3$, and the aqueous phase was extracted with an additional 10 mL of ether. The combined ether extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel 60 (50 g) eluted with 5% EtOAc/hexanes to afford the alcohol **19** (110.0 mg, 95%) as a colorless oil. Spectral data for **19** ($R_f$ 0.32, 20% EtOAc/hexanes): $[\alpha]^{27}_D$ +4.92° (*c* 2.84, EtOH), $[\alpha]^{26}_D$ +54.5° (*c* 2.84, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 3497, 2951, 1729, 1445, 1259; $^1H$ NMR ($CDCl_3$) $\delta$ 1.78 (3, s), 3.76 (3, s), 3.82 (1, s), 7.25–7.39 (3, m), 7.52–7.56 (2, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 26.60 ($CH_3$), 53.15 ($CH_3$), 75.70 (C), 125.08 (2 CH), 127.73 (CH), 128.26 (2 CH), 142.64 (C), 176.01 (C).

**2,6-Dimethyl-2-(tetrahydropyranyloxy)hept-6-en-1-ol (20d).** Ester **11d** (125.5 mg, 0.464 mmol) was dissolved in dry ether (10 mL) under argon and cooled to 0 °C in an ice bath. Lithium aluminum hydride (20.0 mg, 0.527 mmol) was added with stirring in one portion, and the reaction was allowed to warm to room temperature. After 30 min the reaction was quenched by the sequential addition of 20 μL of water, 20 μL of 4 M NaOH, and 60 μL of water. The solution was filtered through a Pasteur pipette plugged with glass wool and the solid rinsed with ether. The filtrate was concentrated in vacuo and chromatographed on silica gel (50 g) eluted with 20% EtOAc/hexanes to afford **20d** (102.4 mg, 91%) as a colorless oil. Spectral data ($R_f$ 0.244, 20% EtOAc/hexanes): $[\alpha]^{25}_D$ +54.5° (*c* 2.60, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 3450, 2947, 1073, 1023; $^1H$ NMR ($CDCl_3$) $\delta$ 1.19 (3, s), 1.71 (3, s), 1.26–1.90 (10, m), 2.02 (2, t, $J$ = 6 Hz), 3.34 (1, dd, $J$ = 8.0, 12.3 Hz), 3.46–3.57 (2, m), 3.70 (1, t, $J$ = 6.3 Hz), 3.97–4.05 (1, m), 4.63–4.68 (1, m), 4.68 (1, bs), 4.72 (1, bs); $^{13}C$ NMR ($CDCl_3$) $\delta$ 20.95 ($CH_2$), 21.25 ($CH_2$), 22.19 (2 $CH_3$), 25.00 ($CH_2$), 32.13 ($CH_2$), 33.28 ($CH_2$), 38.01 ($CH_2$), 64.74 ($CH_2$), 68.06 ($CH_2$), 79.56 (C), 94.18 (CH), 110.11 ($CH_2$), 145.35 (C).

**2,6-Dimethylhept-6-ene-1,2-diol [(*R*)-21].**[8o] Alcohol **20d** was placed in a 100-mL flask with a stir bar under argon and cooled to 0 °C in an ice bath. A solution that was 1% concentrated HCl, 9% $H_2O$, and 90% $CH_3OH$ (1 mL) was added via syringe, and the reaction was stirred for 2 h. The solution was diluted with ether (30 mL) and washed with saturated $NaHCO_3$ (5 mL), and the ether layer was separated, dried ($MgSO_4$), filtered, and concentrated in vacuo. The residue was chromatographed on silica gel (50 g) eluted with 50% EtOAc/hexanes to afford (*R*)-**21** (62.4 mg, 93%) as a pale yellow oil. Spectral data ($R_f$ 0.17, 50% EtOAc/hexanes): $[\alpha]^{26}_D$ +2.4° (*c* 3.11, $CHCl_3$); IR ($CHCl_3$) $cm^{-1}$ 3579, 3441, 2941, 1044; $^1H$ NMR ($CDCl_3$) $\delta$ 1.15 (3, s), 1.43–1.52 (4, m), 1.71 (3, s), 1.99–2.05 (2, m), 2.9–3.3 (1, bs), 3.32–3.47 (3, m), 4.68 (1, bs), 4.71 (1, bs); $^{13}C$ NMR ($CDCl_3$) 21.56 ($CH_2$), 22.22 ($CH_3$), 22.91 ($CH_3$), 38.06 (2 $CH_2$), 69.51 ($CH_2$), 73.00 (C), 109.99 ($CH_2$), 145.49 (C).

**2,6-Dimethylhept-6-ene-1,2-diol [(*S*)-21].**[8o] LAH reduction and acid hydrolysis of **11c** (as for **11d** but without chromatographic purification of the alcohol **20c**) afforded (*S*)-**21** in 89% yield for the two steps. The product was identical with (*R*)-**21** obtained above but gave the opposite rotation.

Similarly treated, **11a** gave (*R*)-**21**, while **11b** gave (*S*)-**21**.

**(*S*)-Frontalin (22).**[8o] Diol (*S*)-**21** (106.0 mg, 0.67 mmol) was dissolved in 10 mL of dry methanol and cooled to −78 °C. Ozone in oxygen was bubbled through the solution until the blue color persisted, and the excess ozone was removed by bubbling oxygen through the solution until the blue color disappeared. Dimethyl sulfide (355 mg, 5.7 mmol) was added and the reaction stirred for 30 min. The reaction mixture was then warmed to 0 °C and stirred for an additional 1 h. The resulting dimethyl acetal was hydrolyzed by addition of 0.1 mL of aqueous 10% HCl. After 15 min the reaction was quenched with saturated $NaHCO_3$ (5 mL) and then diluted with $Et_2O$ (100 mL) and water (50 mL). The layers were separated and the ether extracts were dried ($MgSO_4$), filtered, and concentrated to ca. 1 mL by distillation at ambient pressure. The residue was chromatographed on silica gel (50 g) eluted with 20% $Et_2O$/pentane. Fractions containing the product were collected and concentrated by distillation at ambient pressure to ca. 0.75 mL. The residue was further purified by GLC (94 °C column temperature gave a 7-min retention time) to afford the product **22** (62.9 mg, 66%) as a colorless oil. Spectral data: $[\alpha]^{14}_D$ −50.3° (*c* 2.3, $Et_2O$), lit.[8o] $[\alpha]_D$ −54.8° (*c* 0.52, $Et_2O$); $^1H$ NMR ($CDCl_3$) 1.33 (3, s), 1.44 (3, s), 1.47–1.71 (5, m), 1.78–1.99 (1, m), 3.46 (1, dd, $J$ = 1.5, 6.7 Hz), 3.92 (1, d, $J$ = 6.7 Hz).

**(*R*)-Frontalin (22).**[8o] Diol (*R*)-**21** was similarly treated to afford (*R*)-frontalin, which had identical spectral characteristics but opposite rotation.

**Acknowledgment.** Partial support of this research by Research Corporation, by the Elsa U. Pardee Foundation, by the American Heart Association, Arizona Affiliate, by the American Cancer Society, and by the University of Arizona Foundation and the Office of the Vice President for Research is gratefully acknowledged.

**Supplementary Material Available:** $^1H$ NMR and $^{13}C$ NMR spectra of all new compounds (68 pages). Ordering information is given on any current masthead page.