# Total Synthesis and Stereochemistry of Alternaric Acid

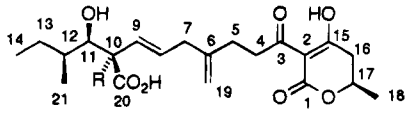
Hiroyasu Tabuchi, Taisuke Hamamoto, Shokyo Miki, Tsuyoshi Tejima, and Akitami Ichihara*

*Department of Bioscience and Chemistry, Faculty of Agriculture, Hokkaido University, Sapporo 060, Japan*

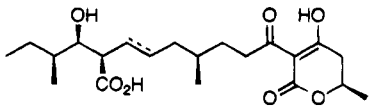
*Received March 2, 1994*®

Determination of the stereochemistry and the total synthesis of alternaric acid **1** has been achieved. The stereostructure of **1** has been elucidated by stereoselective synthesis of four diastereoisomers of the C(9)—C(14) fragment **6**, which had been obtained as a degradation product during structural studies. Key reactions of the total synthesis of **1** include the Julia olefination of tertiary aldehyde **6** and phenylsulfone **7** and novel one-pot construction of 3-acyl-4-hydroxy-5,6-dihydro-2-pyrone *via* Fries-type rearrangement of the *O*-enol acyl group of β-keto-δ-valerolactone toward the α-position of the δ-lactone. The absolute configuration of alternaric acid has been shown to be that illustrated in structure **1**. The modified Fries-type rearrangement method has also been extended to the synthesis of some other compounds containing a tricarbonylmethane structure.

Alternaric acid (**1**) was isolated over 40 years ago by Brian and co-workers from *Alternaria solani*, which is a causal fungus of early blight disease on potato and tomato plants.[1a–c] In 1960, the chemical structure of **1** was determined by using classical chemical methods,[1d–f] but the stereochemistry of **1** has not been determined.*A. solani* also produces several secondary metabolites, some of which were isolated in our laboratory.[2] Subsequently, alernaric acid (**1**) was shown to contribute to disease development of host by *A. solani* in a manner similar to the mode of action of the group of compounds classified as host-specific toxins, although all of the requirements as a primary disease determinant were not fulfilled.[3] This phytotoxin **1** was also shown to delay the occurrence of hypersensitive death of potato cells infected by an incompatible race of *Phytophthora infestans*.[4] Recently, we disclosed the isolation, structural elucidation, and determination of the stereochemistries of three new metabolites **2**, **3**, and **4** related to alternaric acid (**1**).[5]



**1**; R = OH (alternaric acid)
**2**; R = H



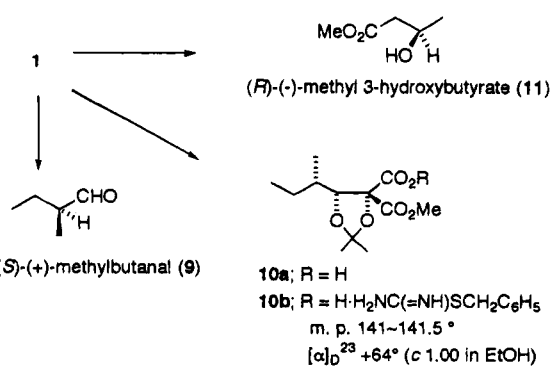
**3**; C8,C9 -CH=CH- (*E*)
**4**; C8,C9 $-CH_2CH_2-$

In this paper, we would like to present the determination of the complete stereochemistry and a total synthesis of alternaric acid (**1**).[6,7]

## Results and Discussion

**Synthetic Plan.** Retrosynthetic analysis of **1** generated three building blocks: aldehyde **6** (segment A), phenylsulfone **7** (segment B), and β-keto δ-valerolactone **8** (segment C) (Scheme 1), in which aldehyde **6** is considered to be combined with phenylsulfone **7** by Julia olefination.[8] This condensation is challenging, because aldehyde **6** is tertiary and has a methoxycarbonyl group, which could be easily attacked by a nucleophilic reagent. There may be no precedents for such a case in Julia olefination.[8] Construction of the 3-acyl-4-hydroxy-5,6-dihydro-2-pyrone from carboxylic acid **5** and β-keto-δ-valerolactone **8** *via* Fries-type rearrangement of the *O*-enol acyl group of β-keto-δ-valerolactone toward the α-position of the δ-lactone was achieved using the newly developed procedure utilizing DCC and DMAP.[7]

From the values of the optical rotations of the degradation products **9** and **11** of **1**,[1e,f] the stereochemistry at C(12) and C(17) positions was presumed to be 12-*S* and 17-*R*. Since the stereochemistry at C(10) and C(11) positions was not known, we have elucidated the stereochemistry of **1** through the synthesis of four possible diasteroisomers of the degradation product **10**, C(9)–C(14) fragment, of **1**.



(*S*)-(+)-methylbutanal (**9**)

(*R*)-(-)-methyl 3-hydroxybutyrate (**11**)

**10a**; R = H
**10b**; R = H·$H_2NC(=NH)SCH_2C_6H_5$
m. p. 141~141.5 °
$[\alpha]_D^{23}$ +64° (*c* 1.00 in EtOH)

® Abstract published in *Advance ACS Abstracts*, August 1, 1994.

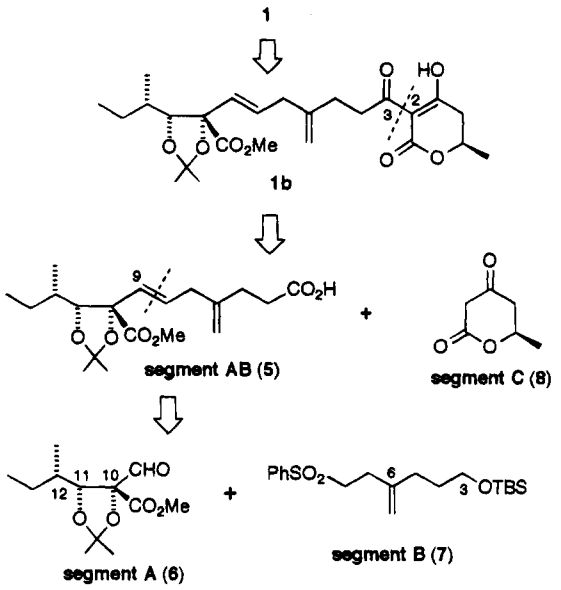
(1) (a) Brian, P. W.; Curtis, P. J.; Hemming, H. G.; Unwin, C. H.; Wright, J. M. *Nature* **1949**, *164*, 534. (b) Brian, P. W.; Curtis, P. J.; Hemming, H. G.; Jefferys, E. G.; Unwin, C. H.; Wright, J. M. *J. Gen. Microbiol.* **1951**, *5*, 619. (c) Brian, P. W.; Elson, G. W.; Hemming, H. G.; Wright, J. M. *Ann. Appl. Biol.* **1952**, *39*, 308. (d) Grove, J. F. *J. Chem. Soc.* **1952**, 4056. (e) Bartels-Keith, J. R. *J. Chem. Soc.* **1960**, 860. (f) Bartels-Keith, J. R. *J. Chem. Soc.* **1960**, 1662.

(2) Solanapyrones: (a) Ichihara, A.; Tazaki, H.; Sakamura, S. *Tetrahedron Lett.* **1983**, *24*, 5373. (b) Ichihara, A.; Miki, M.; Sakamura, S. *Tetrahedron Lett.* **1985**, *26*, 2453. (c) Ichihara, A.; Miki, M.; Tazaki, H.; Sakamura, S. *Tetrahedron Lett.* **1987**, *28*, 1175. Zinnolide: (d) Ichihara, A.; Tazaki, H.; Sakamura, S. *Agric. Biol. Chem.* **1985**, *49*, 2811.

(3) (a) Furuichi, N.; Nishimura, S. *Ann. Phytopathol. Soc. Jpn.* **1984**, *50*, 128. (b) Furuichi, N.; Nishimura, S.; Kimura, Y.; Hamazaki, H.; Tomiyama, K.; Okamoto, H. *Ann. Phytopathol. Soc. Jpn.* **1984**, *50*, 412. (c) Langsdorf, G.; Furuichi, N.; Nishimura, S. *J. Phytopathol.* **1990**, *128*, 271.

0022-3263/94/1959-4749$04.50/0 

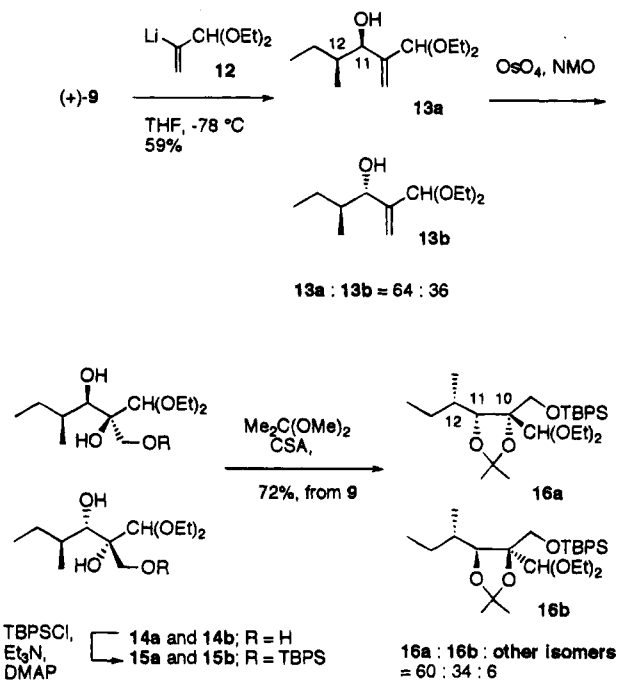
**Scheme 1**



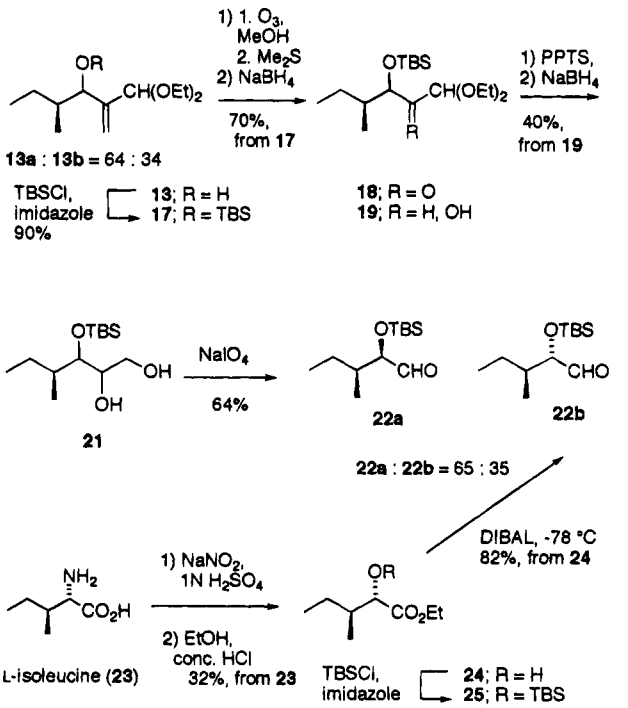

**Synthesis of Segment A and Stereochemistry of Alternaric Acid.** The determination of stereochemistry at the C(10) and C(11) positions was achieved through the synthesis of four possible diastereoisomers of the degradation product **10** of **1**.

The starting material, (*S*)-(+)-2-methylbutanal (**9**), was prepared by Swern oxidation[9] or nitroxyl radical oxidation[10] (2,2,6,6-tetramethylpiperidin-1-oxyl, NaOCl, pH 9.5, KBr, 0−15 °C) of (*S*)-(−)-2-methylbutanol. Condensation of aldehyde **9** with vinyllithium reagent **12** which was prepared from 1.7 equiv of 2-bromo-3,3-diethoxy-1-propene[11] and 1.7 equiv of *n*-butyllithium yielded a diastereomeric mixture of **13a** and **13b** in a ratio of 64:36 (59% yield) (Scheme 2).[12,13] The stereochemistry of newly arisen stereocenters at C(11) in **13a** and **13b** was confirmed by chemical correlation of **13b** with L-isoleucine (**23**) (Scheme 3). Thus, protection of the mixture of **13a** and **13b** with *tert*-butyldimethylsilyl chloride furnished silyl ether **17**. Ozonolysis of the vinyl group in **17** and following reductive cleavage with dimethyl sulfide afforded ketone **18**. Reduction of the ketone **18** with sodium borohydride yielded alcohol **19**. By hydrolysis of **19** with pyridinium *p*-toluenesulfonate and subsequent reduction of the resultant aldehyde **20** with sodium borohydride, the alcohol **19** was converted to diol **21**. Treatment of the diol **21** with sodium periodate gave the

**Scheme 2**




**Scheme 3**




mixture of diastereoisomers **22a** and **22b** in a ratio of 65:35,[12] whose ratio reflected that of **13a** and **13b**. The $^1$H-NMR spectrum of the aldehyde **22b** was identical with that of the authentic sample, (2*S*,3*S*)-2-[(*tert*-butyldimethylsilyl)oxy]-3-methylpropanal, which was prepared from L-isoleucine through hydroxy ester **24**. This indicated that **13a** and **13b** have the stereochemistry as shown in Scheme 2.

Dihydroxylation of the mixture of **13a** and **13b**, followed by selective protection of the primary hydroxyl group as the silyl ether and subsequent acetonide formation, furnished a mixture of four diastereoisomers in 72% overall yield (**16a**:**16b**:other diastereoisomers = 60:34:6). The mixture was separated by flash silica gel column chromatography to give pure **16a** and **16b**. The relative configuration of the stereocenters at C(10) and C(11) in

(4) Furuichi, N.; Nishimura, S.; Langsdorf, G. *Ann. Phytopathol. Soc. Jpn.* **1992**, *58*, 1.
(5) Tabuchi, H.; Ichihara, A. *J. Chem. Soc., Perkin Trans. 1* **1994**, 125.
(6) (a) Tabuchi, H.; Ichihara, A. *Tetrahedron Lett.* **1992**, *33*, 4933. (b) Tabuchi, H.; Hamamoto, T.; Miki, S.; Tejima, T.; Ichihara, A. *Tetrahedron Lett.* **1993**, *34*, 2327.
(7) Tabuchi, H.; Hamamoto, T.; Ichihara, A. *Synlett* **1993**, 651.
(8) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, 4833. For a recent review see: (b) Kocienski, P. *Phosphorus Sulfur* **1985**, *24*, 97. (c) Simpkins, N. S. *Sulphones in Organic Synthesis*, Pergamon Press: New York, 1993.
(9) Mancuso, A. J.; Huang, S.-L.; Swern, D. *J. Org. Chem.* **1978**, *43*, 2480.
(10) (a) Golubev, V. A.; Rozantsen, E. G.; Neiman, M. B. *Bull. Acad. Sci. USSR* **1965**, 1898. (b) Anelli, P. L.; Montanari, F.; Quici, S. *Org. Synth.* **1990**, *69*, 212.
(11) (a) Ficini, J.; Depezay, J. C. *Tetrahedron Lett.* **1969**, 4797. (b) Smith, A. B., III; Levenberg, P. A.; Jerris, P. J.; Scarborough, R. M., Jr.; Wovkulich, P. M. *J. Am. Chem. Soc.* **1981**, *103*, 1501.
(12) The ratio was determined by $^1$H NMR (500 MHz) spectrum.
(13) It is known that the condensation of the vinyllithium reagent **12** and chiral α-methyl aldehyde gives Cram (*syn*) adduct as the major product (61:39−63:37). Kinoshita, M.; Nakata, M. *Yuki Gosei Kagaku Kyokai-Shi* **1986**, *44*, 206.

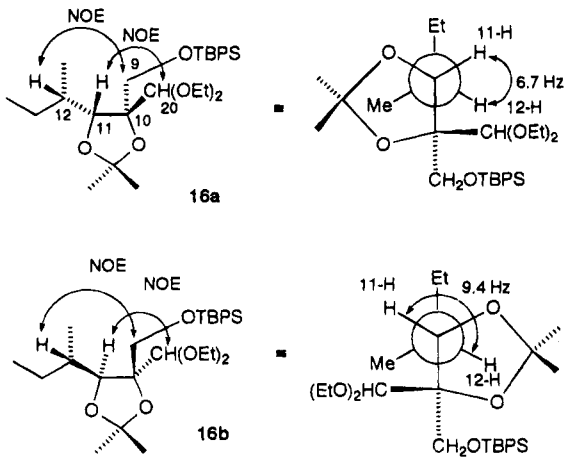


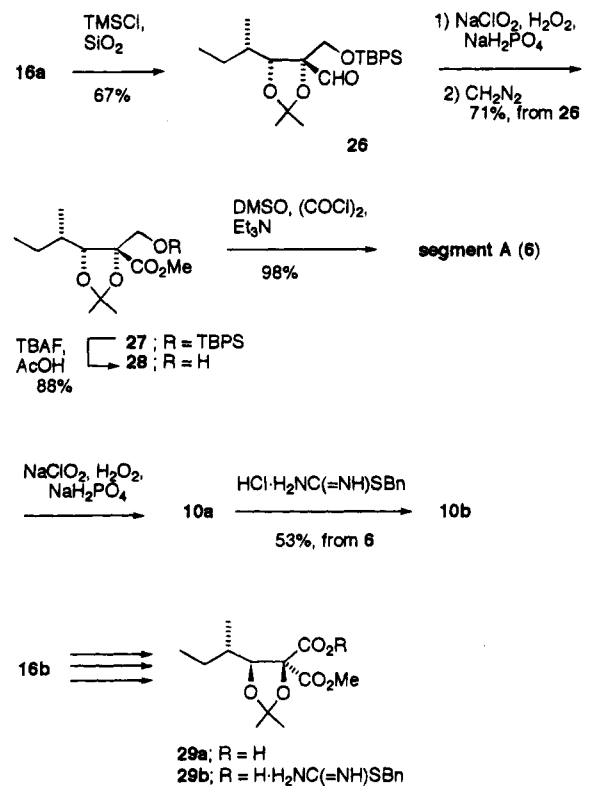

**Figure 1.** NOE experiments and coupling constants of **16a** and **16b**.

**16a** and **16b** was elucidated by difference NOE experiments in the $^1$H-NMR spectrum. Thus, the NOE was observed between 9-H and 12-H and between 11-H and 20-H on **16a** and **16b** (Figure 1). These stereochemical assignments are consistent with the expectation according to Kishi's empirical formulation[14] that dihydroxylation of **13a** and **13b** with osmium tetraoxide would occur from the opposite side of the allylic hydroxyl group to give **14a** and **14b**, respectively. In addition, the coupling constants due to 11-H, $J$ = 6.7 Hz in **16a** and 9.4 Hz in **16b**, are in accordance with stable conformers arising from previously assigned configurations of **13a** and **13b** as shown in Figure 1.

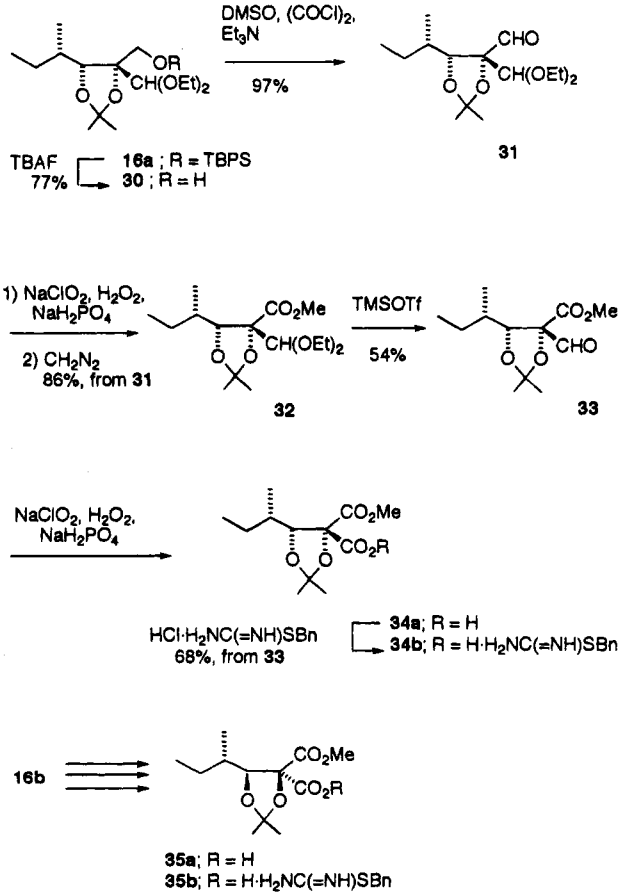
Selective removal of the diethyl acetal group and silyl ether group and subsequent oxidative reactions on both of acetonide **16a** and **16b** afforded the four possible diastereoisomers of the degradation product of **1**. Thus, hydrolysis of **16a** (TMSCl, $SiO_2$, acetone, rt, 8 h) gave aldehyde **26** (Scheme 4). In this step, treatment of **16a** with protonic acid failed to give **26** because of hydrolysis of the acetonide moiety. Sodium chlorite oxidation[15] of the resultant aldehyde **26** followed by methylation with diazomethane afforded methyl ester **27**. Removal of the silyl protecting group ($n$-$Bu_4NF$, AcOH, THF, rt, 44 h) of methyl ester **27** and subsequent Swern oxidation of the alcohol **28** provided aldehyde **6**. In the removal of the silyl protecting group, acetic acid is necessary to prevent the hydrolysis of the methyl ester group because of the basicity of tetrabutylammonium fluoride. Sodium chlorite oxidation of the resultant aldehyde **6** yielded carboxylic acid **10a**, which was treated with an aqueous solution of 2-benzyl-2-thiopseudourea hydrochloride to give the corresponding salt **10b**. Similarly, using the reactions from **16a** to **10b**, acetonide isomer **16b** was converted to **29b**.

On the other hand, removal of the silyl protecting group of **16a** gave alcohol **30** which was converted to **34**, the C-10 epimer of **10**, as follows (Scheme 5). Thus, Swern oxidation of the resultant alcohol **30** led to aldehyde **31**. Sodium chlorite oxidation of the aldehyde **31** followed by methylation with diazomethane afforded methyl ester **32**. Oxidation of the resultant aldehyde **33**

**Scheme 4**




**Scheme 5**




provided carboxylic acid **34a**, which was treated with an aqueous solution of 2-benzyl-2-thiopseudourea hydrochloride, affording the corresponding salt **34b**. Following to the procedure used to convert **16a** to **34b**, acetonide isomer **16b** was converted to **35b**. The optical rotations and melting points of **10b** and all other diastereomers

(14) (a) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3943. (b) Christ, W. J.; Cha, J. K.; Kishi, Y. *Tetrahedron Lett.* **1983**, *24*, 3947. (c) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

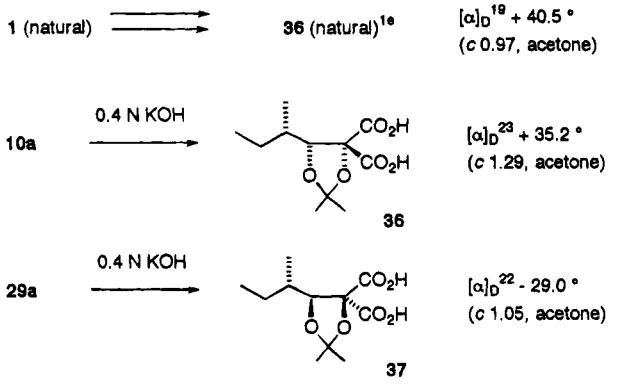
(15) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888. (b) Kudesia, V. P. *Bull. Soc. Chim. Belg.* **1972**, *81*, 623. (c) Dalcanale, E.; Montanari, F. *J. Org. Chem.* **1986**, *51*, 567.

**Table 1. Optical Rotations and Melting Points of Salts 10b, 29b, 34b, and 35b**

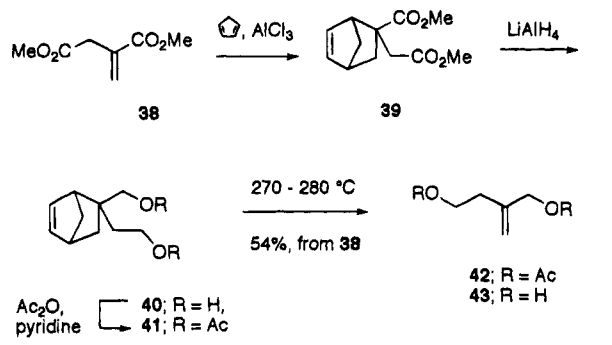
| salts | optical rotation[a] $[\alpha]_D$ (EtOH) | mp (°C) |
|---|---|---|
| **10b** (natural)[1e] | +64° | 141~141.5 |
| **10b** | +59.2° | 139~141 |
| **29b** | −40.4° | 136~138 |
| **34b** | +24.7° | 127~129 |
| **35b** | −15.3° | 143~145 |

[a] Optical rotations were measured at 22 °C for salts **10b**, **29b**, **35b** and at 23 °C for salts **10b** (natural) and **34b**.

**Scheme 6**



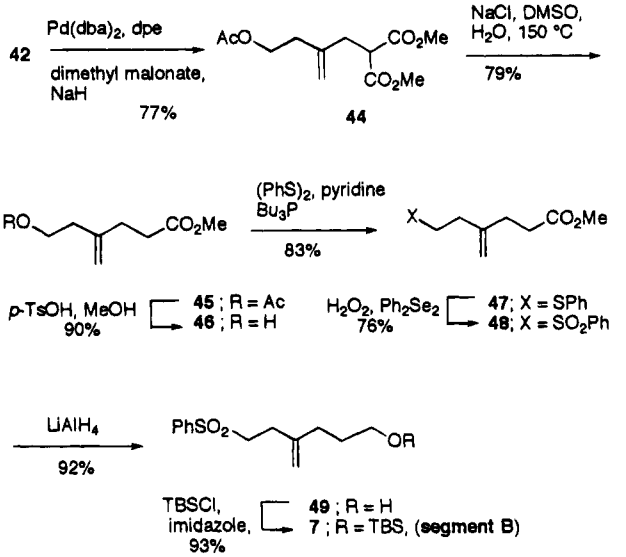

**Scheme 7**




thus obtained are summarized in Table 1, in which the physical data of **10b** are in fair agreement with those of the degradation product **10b** (natural) of alternaric acid (**1**). In addition, hydrolysis of **10a** and **29a** gave dicarboxylic acids **36**, $[\alpha]^{23}_D$ +35.2° (*c* 1.29, acetone), and **37**, $[\alpha]^{22}_D$ −29.0° (*c* 1.05, acetone), respectively (Scheme 6). The optical rotation of **36** was close to that of the authentic sample, $[\alpha]^{19}_D$ +40.5° (*c* 0.97, acetone).[1e] From the above results, we concluded that the absolute configuration of alternaric acid must be as depicted in **1**.

**Synthesis of Segment B.** As shown in Scheme 7, segment B (**7**) was synthesized from dimethyl itaconate (**38**). Direct reduction of **38** failed to give the corresponding diol **43** because of its ready 1,4-reduction. This problem was surmounted by protection of the olefin moiety according to a retro-Diels–Alder procedure.[16] Diels–Alder reaction of **38** with cyclopentadiene gave a diastereomeric mixture of adduct **39**. Without isolation, reduction of **39** with lithium aluminum hydride and subsequent acetylation yielded diacetate **41**. Deprotection of **41** by heating (270–280 °C) furnished olefin **42** (54% yield, four steps). Palladium-catalyzed allylic alkylation[17] of **42** with sodium dimethyl malonate gave

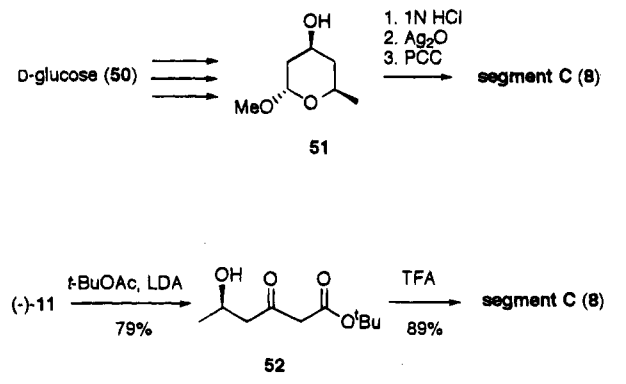
**Scheme 8**







**Scheme 9**

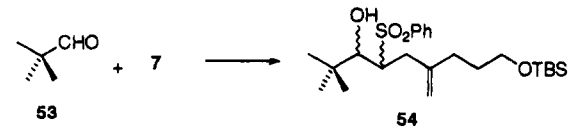



dimethyl ester **44**, and decarboxylation of **44** by heating with sodium chloride in wet DMSO at 150 °C afforded the corresponding ester **45** without hydrolysis of methyl ester (Scheme 8).[18] The acetoxyl group of **45** was converted into the phenylsulfonyl group *via* three conventional reactions. Thus, treatment of **45** with *p*-toluenesulfonic acid in methanol yielded alcohol **46**, and treatment of **46** with diphenyl disulfide and tri-*n*-butylphosphine in pyridine[19] followed by selective oxidation of the sulfide group of **47** with diphenyl diselenide and hydrogen peroxide provided phenylsulfone **48**.[20] Reduction of the ester group of **48** with lithium aluminum hydride and protection with *tert*-butyldimethylsilyl chloride provided C(3)–C(8) phenylsulfone **7** (segment B).

**Synthesis of Segment C.** β-Keto-δ-valerolactone **8**, segment C, was prepared in two ways. One route prepared the acetal **51** from D-glucose (**50**), but this involves many steps. Accordingly, the carbon skeleton of segment C was constructed according to the literature.[21] Claisen condensation of (*R*)-(−)-methyl 3-hydroxybutanoate ((−)-**11**) and lithium *tert*-butyl acetate gave δ-hydroxy β-keto ester **52** (79% yield),[21] and hydrolysis of keto ester **52** with trifluoroacetic acid afforded β-keto-δ-valerolactone **8**, segment C, in 89% yield (Scheme 9). Evidently, the latter route is more effective because of its number of steps and overall yield.

(16) (a) Ichihara, A. *Synthesis* **1987**, 207. (b) Lasne, M. C.; Ripoll, J. L. *Synthesis* **1985**, 121. (c) Ripoll, J. L.; Rouessac, A.; Rouessac, F. *Tetrahedron* **1978**, *34*, 19.
(17) Fiaud, J. C.; Malleron, J. L. *Tetrahedron Lett.* **1980**, *21*, 4437.
(18) Krapcho, A. P.; Lovey, A. J. *Tetrahedron Lett.* **1973**, *12*, 957.
(19) Nakagawa, I.; Hata, T. *Tetrahedron Lett.* **1975**, *16*, 1409.
(20) (a) Reich, H. J.; Chow, F.; Peake, S. L. *Synthesis* **1978**, 299. (b) Edwards, M. P.; Ley, S. L.; Lister, S. G.; Palmer, B. D.; Williams, D. J. *J. Org. Chem.* **1984**, *49*, 3503.
(21) Deschenaux, P.-F.; Kallimopoulos, T.; Stoeckli-Evans, H.; Jacot-Guillarmod, A. *Helv. Chim. Acta* **1989**, *79*, 731.

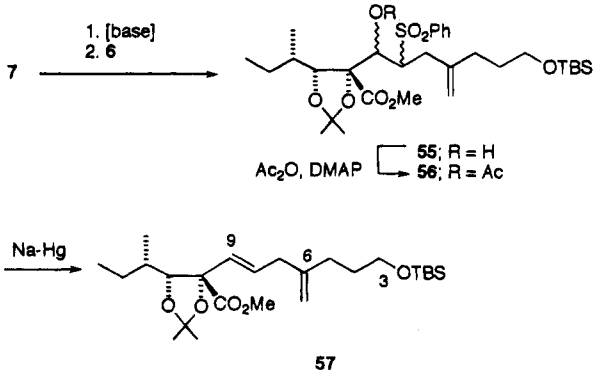
**Table 2. Coupling of Compound 7 and Pivalaldehyde**




53 54

| | conditions (solvent, $T$ (°C)) | yield (%) |
|---|---|---|
| 1. | $n$-BuLi/THF, −78 | 30 |
| 2. | $s$-BuLi/THF, −78 | 18 |
| 3. | LDA/THF, −78 | 96 |
| 4. | LDA/THF−$n$-hex = 1:1, −78 | 96 |

**Table 3. Condensation of Segments A and B**



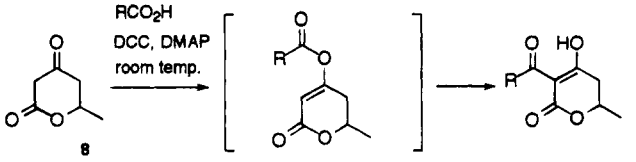

57

| | conditions (solvent, $T$ (°C)) | yield (%) |
|---|---|---|
| 1. | $Et_2NLi$/THF, −78 | <3 (1 step) |
| 2. | LDA/THF, −78 | <4 (1 step) |
| 3. | LDA/THF−$n$-hex = 1:1, −78 | 16 (3 steps) |
| 4. | LDA/ether−$n$-hex = 1:1, −78 | 41 (3 steps) |

**Julia Coupling of Segments A and B.** The next steps involves Julia olefination[8] of aldehyde **6** (segment A) and phenylsulfone **7** (segment B). In general, the addition of sulfone anions to aldehydes can be a capricious process and depends on base, solvent, and auxiliary reagents.[22] In our case, segment A (**6**) is a tertiary aldehyde and has a methoxycarbonyl group at the vicinal carbon, C(10). In model experiments using pivalaldehyde (**53**), the reaction proceeds in good yield when using a lithium dialkylamide rather than an alkyllithium as base (Table 2). However, in the coupling of segment A (**6**) and B (**7**), the reaction yields not only depend on base but also on the solvents (Table 3). Thus, the reaction proceeds more smoothly in the presence of $n$-hexane as cosolvent, and the following conditions gave good results; treatment of phenylsulfone **7** with 1.5 equiv of lithium diisopropylamide at −78 °C in ether−$n$-hexane (1:1) afforded the corresponding sulfone anion, which reacted with aldehyde **6** to give the corresponding β-hydroxy sulfones **55** as a mixture of diastereomers. The mixture was acetylated to afford β-acetoxy sulfones **56**, and **56** was subjected to elimination with sodium amalgam.[8] The product **57** was obtained in 41% overall yield and consisted of a 14:1 mixture of $E$ and $Z$ isomers. These were separated by MPLC to give the desired major isomer **57**.

**Construction of the 3-Acyl-4-hydroxy-5,6-dihydro-2-pyrone Structure.** Several methods for construction of 3-acyl-4-hydroxy-5,6-dihydro-2-pyrones have been reported.[23] However, most of them are not convenient, since they require several steps, and the starting materials are not readily available. We discovered that 3-acyl-4-hydroxy-5,6-dihydro-2-pyrones are prepared directly from carboxylic acids and β-keto-δ-valerolactones under mild conditions. This reaction involves Fries-type rearrangement of the $O$-enol acyl group of the β-keto-δ-valerolactone toward the α-position of the lactone. Thus, a solution of the carboxylic acid, β-keto-δ-valerolactone (1 equiv), DCC (1.1 equiv), and DMAP (0.1 equiv) in $CH_2Cl_2$ was stirred at room temperature to give the product in good yield.

**Table 4. Synthesis of 3-Acyl-5,6-dihydro-4-hydroxy-2-pyrones from Carboxylic Acids and β-Keto-δ-valerolactone 8**




8

| entry | R | solvent | time (h) | yield (%) |
|---|---|---|---|---|
| 1. | MEMO$(CH_2)_2C(=CH_2)(CH_2)_2$ | $CH_2Cl_2$ | 24 | 65[a] |
| 2. | | acetone | 24 | 50[a] |
| 3. | | THF | 24 | 29[a] |
| 4. | $CH_3$ | $CH_2Cl_2$ | 53 | 77[b] |
| 5. | $CH_3CH_2$ | $CH_2Cl_2$ | 48 | 85[b] |
| 6. | $CH_3(CH_2)_6$ | $CH_2Cl_2$ | 10 | 78[a] |
| 7. | $(CH_3)_2CH$ | $CH_2Cl_2$ | 72 | 25[a] |
| 8. | $(CH_3)_3C$ | $CH_2Cl_2$ | 7 days | N.R.[c] |
| 9. | $CH_3(CH_2)_7CH=CH(CH_2)_7$ | $CH_2Cl_2$ | 24 | 86[a] |
| 10. | $CH_3(CH_2)_4CH=CHCH_2CH=CH(CH_2)_7$ | $CH_2Cl_2$ | 24 | 89[a] |

[a] Yield after purification of product by flash chromatography. [b] Yield after recrystallization of product. [c] $O$-Acylation proceeds in quantitative yield.

Several examples are summarized in Table 4.[7]

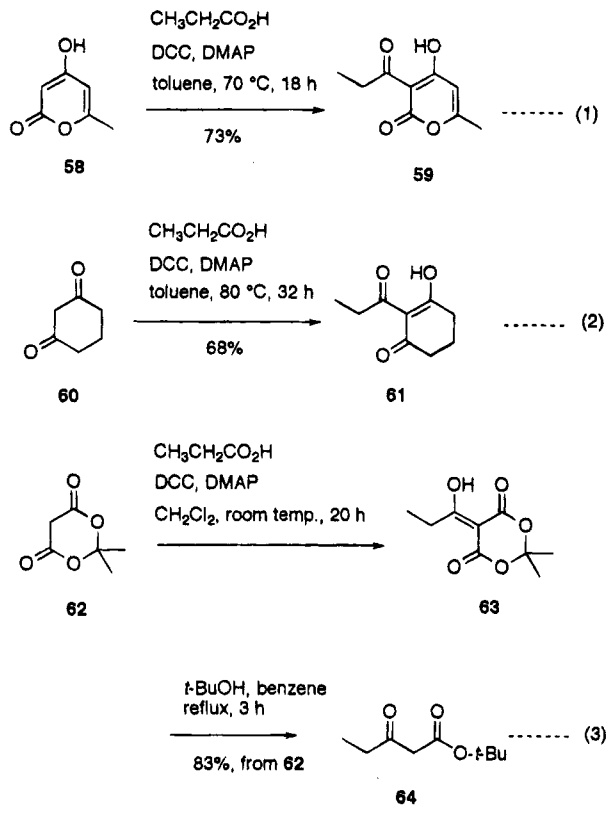
In addition, this method can be also applied to the construction of 3-acyl-4-hydroxy-2-pyrones, 2-acyl-3-hydroxy-2-cyclohexen-1-ones, and 5-acyl-2,2-dimethyl-1,3-dioxane-4,6-diones (acyl Meldrum's acids). Thus, treatment of 4-hydroxy-6-methyl-2-pyrone (**58**) with 1 equiv of propionic acid in the presence of DCC (1.1 equiv) and DMAP (0.12 equiv) in toluene at 70 °C for 18 h gives 3-propionyl-4-hydroxy-6-methyl-2-pyrone (**59**) in 73% yield (eq 1). Treatment of 1,3-cyclohexanonedione (**60**) with 1 equiv of propionic acid in the presence of DCC (1.1 equiv) and DMAP (0.1 equiv) in toluene at 80 °C for 32 h gives 2-propionyl-3-hydroxy-2-cyclohexen-1-one (**61**) in 68% yield (eq 2). In both cases, the reaction proceeds slowly at room temperature, but smoothly rearranges at 70−80 °C in toluene within 32 h. Acyl Meldrum's acids are well known as versatile synthons, because of their easy conversion to β-keto ester by alcoholysis.[24] When a $CH_2Cl_2$ solution of Meldrum's acid (**62**) was treated with 1 equiv of propionic acid in the presence of DCC (1.1 equiv) and DMAP (0.1 equiv) at room temperature for 20 h, acyl Meldrum's acid **63** was isolated in almost quantitative yield.[25] Following Yonemitsu's method,[24] alcoholysis of the crude acyl Meldrum's acid **63** gave *tert*-butyl 3-oxopentanoate (**64**) in 83% yield from **62** (eq 3).

(22) For recent examples, see: (a) Isobe, M.; Ichikawa, Y.; Bai, D.-L.; Masaki, H.; Goto, T. *Tetrahedron* **1987**, *43*, 4767. (b) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368. (c) Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001.

(23) (a) Gelin, S.; Gelin, R. *Bull. Soc. Chim. Fr.* **1968**, 288. (b) Tanabe, Y.; Miyakado, M.; Ohno, N.; Yoshioka, H. *Chem. Lett.* **1982**, 1543.

(24) (a) Oikawa, Y.; Sugana, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087. (b) Melillo, D. G.; Shinkai, I.; Liu, T.; Ryan, K.; Sletzinger, M. *Tetrahedron Lett.* **1980**, *21*, 2783.

(25) The $^1H$ NMR spectrum ($CDCl_3$) shows clearly that **63** is present completely in its enol form.

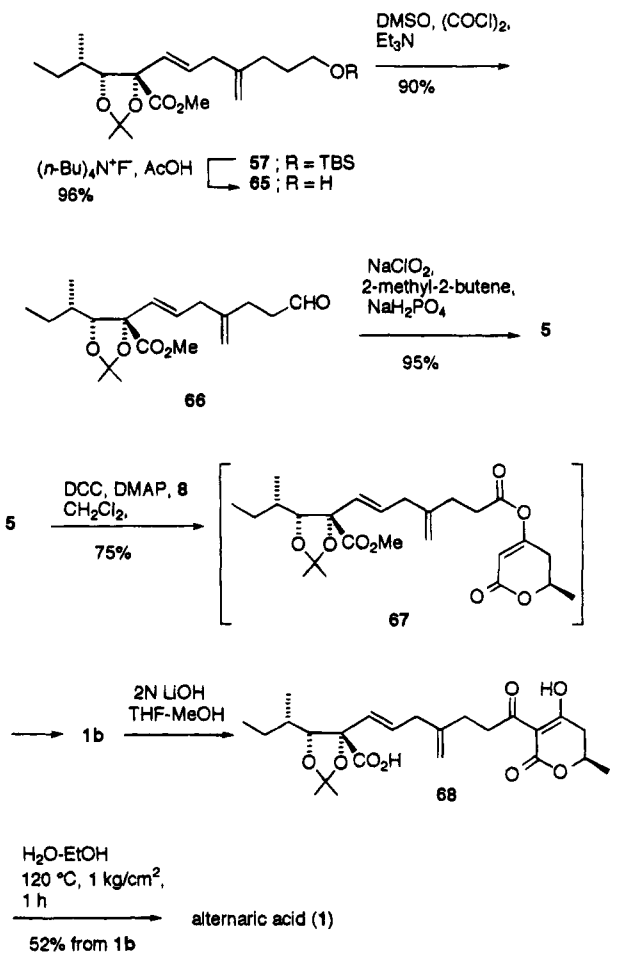



This improved method was applied to the synthesis of alternaric acid (**1**). Thus, removal of the silyl protecting group on **57** yielded alcohol **65** (Scheme 10). Swern oxidation of the alcohol **65** and sodium chlorite oxidation of aldehyde **66** furnished carboxylic acid **5** (segment AB). *O*-Enolacylation of β-keto-δ-valerolactone **8** (segment C) with carboxylic acid **5** in the presence of DCC and DMAP afforded 3-acyl-4-hydroxy-5,6-dihydropyrone **68**, $[\alpha]^{26}_D$ −3.8° (*c* 3.70, EtOH) [natural, $[\alpha]^{25}_D$ −5.2° (*c* 3.68, EtOH)],[1f] in good yield (75%).

**Deprotection and Total Synthesis of Alternaric Acid.** The hydrolysis of **1b** was not easy because of its instability to acid. Acetonide hydrolysis of **1b** with 1 N hydrochloric acid in methanol–THF gave the corresponding diol in only 21% yield, which could not be converted to the target compound by further hydrolysis. Eventually, the problem was overcome by changing the order of hydrolysis reactions (Scheme 10). Thus, hydrolysis of the methyl ester of **1b** with 2 N lithium hydroxide in methanol–THF (1:2) smoothly yielded the corresponding carboxylic acid **68** and acetonide hydrolysis by heating at 120 °C in autoclave provided alternaric acid (**1**), $[\alpha]^{24}_D$ 0° (*c* 1.00, acetone) [natural, optically inactive],[1d] in 45% yield (two steps). In the acetonide, increased pressure and the presence of the carboxyl group were essential. The reaction proceeds without adding acid or base under mild and neutral conditions. The spectroscopic data of synthetic **1** thus obtained were identical in all respects with those of natural **1**.

In saummary, the determination of the stereochemistry and the first total synthesis of alternaric acid **1** have been accomplished. In addition, an advanced method for the construction of tricarbonylmethane structures was developed. These studies make possible the synthesis of analogs of alternaric acid for the study of their structure–activity relationship and also the synthesis of other bioactive compounds containing a tricarbonylmethane structure.

**Scheme 10**




## Experimental Section

**General Methods.** Chemical shifts are reported in ppm with tetramethylsilane as an internal standard. Splitting patterns are designed as "s, d, t, m, and br"; these symbols indicate "singlet, doublet, triplet, multiplet, and broad," respectively. Unless otherwise noted, nonaqueous reactions were carried out under an argon atmosphere. Ether, THF, and benzene were distilled from sodium metal/benzophenone ketyl. *n*-Hexane, $CH_2Cl_2$, DMSO, and DMF were distilled from calcium hydride. MeOH was distilled from magnesium methoxide. Ethyl acetate was distilled from diphosphorus pentaoxide. Acetone was distilled from Drierite. All other commercially obtained reagents and solvents were used as received. Analytical TLC was carried out using precoated silica gel plates (DC-Fertigplatten Kieselgel 60 $F_{254}$ Art. 5554 0.2 mm, E. Merk). Silica gel used for column chromatographies was Merck Kiesel gel 60 (0.04–0.063 mm).

**(3*SR*,4*S*)-1,1-Diethoxy-3-hydroxy-4-methyl-2-methylenehexane (13a and 13b).** To a stirred solution of 2-bromo-3,3-diethoxy-1-propane[11] (18.6 g, 89.0 mmol) in dry THF (129 mL) at −78 °C was added *n*-butyllithium (1.6 M solution in hexane: 55 mL, 88 mmol) dropwise to give a mixture of **12**. After being stirred at the same temperature for 17 min, a solution of aldehyde **11** (4.50 g, 52.3 mmol) in dry THF (18 mL) was added to the mixture over a period of 5 min, and stirring was continued at the same temperature for 25 min. The reaction mixture was quenched by adding saturated $NH_4Cl$ solution and extracted with ether (×3). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with *n*-hexane–ether (9:1) yielded a mixture of diastereomeric allyl alcohols **13a** and **13b** in a ratio of 64:36 (6.64 g, 59%) as a colorless oil: IR (thin film) 3450, 1050 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 5.36 (s, 2/3 H), 5.34 (s, 1/3 H), 5.24 (s, 2/3 H), 5.22 (s, 1/3 H), 4.89 (s, 1/3 H), 4.87 (s, 2/3 H), 4.03 (t, *J* = 5.9 Hz, 2/3 H), 3.87 (t, *J* = 5.7 Hz, 1.3

H), 3.46~3.76 (m, 4 H), 2.69 (d, $J$ = 6.0 Hz, 1/3 H), 2.38 (d, $J$ = 6.0 Hz, 2/3 H), 1.78 (1/3 H, m, 4'-H), 1.65 (2/3 H, m, 4-H), 1.10–1.47 (2 H, m, 5- and 5'-H), 1.21–1.25 (m, 6 H), 0.83–0.93 (m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 146.3, 145.8, 115.3, 114.5, 102.8, 102.6, 77.7, 75.9, 62.55, 62.49, 62.2, 61.9, 38.35, 38.32, 26.5, 24.4, 15.8, 15.12, 15.11, 13.7, 11.6, 11.2; MS (FI) $m/z$ 217 ($M^+$ + H), 159, 57; HRMS (EI) $m/z$ 171.1384 ($M^+$ − OEt calcd for $C_{10}H_{19}O_2$ 171.1385). Anal. Calcd for $C_{12}H_{24}O_3$: C, 66.63; H, 11.18. Found: C, 66.70; H, 10.92.

**(4*R*,5*R*,1'*S*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4-(diethoxymethyl)-2,2-dimethyl-5-(1'-methylpropyl)-1,3-dioxolane (16a) and (4*S*,5*S*,1'*S*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-4-(diethoxymethyl)-2,2-dimethyl-5-(1'-methylpropyl)-1,3-dioxolane (16b).** To a stirred solution of allyl alcohol **13** (4.0 g, 18.5 mmol) in acetone (25 mL) and deionized water (25 mL) was added *N*-methylmorpholine *N*-oxide (3.75 g, 32.0 mmol). A solution of osmium tetraoxide (0.1 M in water: 8.47 mL, 0.85 mmol) was then introduced. The reaction mixture was quenched after 24 h by adding saturated aqueous sodium bisulfite (50 mL) and stirring vigorously for 30 min. The biphasic mixture was separated, and the aqueous layer was extracted with ethyl acetate (×5). The combined organic layers were washed with 1 N HCl and water, dried ($Na_2SO_4$), and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with *n*-hexane–ethyl acetate (7:3, 0.05% triethylamine) yielded the diastereomeric triols **14** (4.37 g).

To a solution of unpurified diastereomeric triols **14** (4.37 g) in $CH_2Cl_2$ (78 mL) were added triethylamine (3.68 mL, 26.2 mmol), DMAP (214 mg, 1.75 mmol), and *tert*-butyldiphenylsilyl chloride (6.5 mL, 25.0 mmol). The reaction mxiture was stirred at room temperature for 35 h, washed with saturated $NaHCO_3$ and saturated $NH_4Cl$, and evaporated *in vacuo* to yield the crude silyl ethers **15** (10 g).

To a solution of the crude diastereomeric diols **15** (10 g) in dry acetone (88 mL) were added 2,2-dimethoxypropane (17.2 mL, 140 mmol) and D-camphorsulfonic acid (200 mg, 0.87 mmol). The resulting solution was stirred at room temperature for 5 h and quenched with triethylamine (4.4 mL), and the organic solvents were removed *in vacuo*. Water was added, followed by extraction with ether (×3). The combined organic layers were dried ($Na_2SO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with *n*-hexane–ether (98:2) yielded acetonides **16a** (4.24 g, 43.4%) and **16b** (2.40 g, 24.6%) and other diastereoisomers (424 mg, 4.3%) (total yield 72.3% from **13**) as colorless oils. **16a**: $[\alpha]^{25}_D$ −10.0° (*c* 2.02, $CH_2Cl_2$); IR (thin film) 1110, 1070 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.72 (m, 4 H), 7.34–7.42 (m, 6 H), 4.89 (s, 1 H), 4.10 (d, $J$ = 6.7 Hz, 1 H), 3.85 (m, 1 H), 3.84 (d, $J$ = 10.0 Hz, 1 H), 3.77 (m, 2 H), 3.64 (d, $J$ = 10.0 Hz, 1 H), 3.52 (m, 1 H), 1.58–1.65 (m, 2 H), 1.40 (s, 3 H), 1.35 (s, 3 H), 1.23 (t, $J$ = 7.1 Hz, 3 H), 1.20 (t, $J$ = 7.0 Hz, 3 H), 1.12 (m, 1 H), 1.06 (s, 9 H), 0.82 (d, $J$ = 6.6 Hz, 3 H), 0.78 (t, $J$ = 7.3 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 135.9, 135.7, 133.8, 133.3, 129.5, 127.6, 127.5, 106.9, 102.6, 86.1, 80.4, 67.0, 65.1, 64.6, 33.7, 28.5, 27.1, 26.9, 26.2, 19.3, 15.9, 15.2, 11.1; MS (FI) $m/z$ 529 ($M^+$ + H), 471, 57; HRMS (EI) $m/z$ 513.3055 ($M^+$ − Me calcd for $C_{30}H_{45}O_5Si$ 513.3037). Anal. Calcd for $C_{31}H_{48}O_5Si$: C, 70.41; H, 9.15. Found: C, 70.37; H, 9.23.

**16b**: $[\alpha]^{25}_D$ + 7.7° (*c* 1.54, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.72 (m, 4 H), 7.35–7.42 (m, 6 H), 4.85 (s, 1 H), 4.00 (d, $J$ = 9.3, 1 H), 3.88 (m, 1 H), 3.84 (d, $J$ = 10.3 Hz, 1 H), 3.80 (m, 1 H), 3.73 (m, 1 H), 3.65 (d, $J$ = 10.3 Hz, 1 H), 3.56 (m, 1 H), 1.61–1.63 (m, 2 H), 1.38 (s, 3 H), 1.34 (s, 3 H), 1.20–1.24 (t, $J$ = 7.1 Hz, 6 H), 1.10–1.18 (m, 1 H), 1.07 (s, 9 H), 0.92 (d, $J$ = 6.6 Hz, 3 H), 0.81 (t, $J$ = 7.4 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 135.9, 135.7, 133.6, 133.2, 129.6, 127.6, 127.5, 106.4, 102.6, 86.1, 81.2, 66.7, 64.9, 33.2, 28.5, 27.0, 26.6, 26.0, 19.3, 16.1, 15.3, 10.3.

**(4*R*,5*R*,1'*S*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2,2-dimethyl-4-formyl-5-(1'-methylpropyl)-1,3-dioxolane (26).** To a solution of acetonide **16a** (3.08 g, 5.83 mmol) in dry acetone (15 mL) were added trimethylsilyl chloride (2.2 mL, 17.5 mmol) and silica gel (Kieselgel, 7.5 g). The resulting mixture was stirred at room temperature for 3 h and then filtered with Ceritepad. The filtrate was washed with saturated $NaHCO_3$, and the aqueous layer was extracted with ether (×3). The combined organic layers were dried ($Na_2SO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with *n*-hexane–ether (98:2) yielded aldehyde **26** (1.77 g, 67%) as a colorless oil: $[\alpha]^{22}_D$ −8.1° (*c* 1.04, $CHCl_3$); IR (thin film) 1740, 1110 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.74 (s, 1 H), 7.69 (m, 4 H), 7.36–7.44 (m, 6 H), 4.01 (d, $J$ = 10.8 Hz, 1 H), 3.77 (d, $J$ = 9.2 Hz, 1 H), 3.74 (d, $J$ = 10.8 Hz, 1 H), 1.60 (m, 1 H), 1.48 (s, 3 H), 1.41 (s, 3 H), 1.40–1.43 (m, 1 H), 1.03 (s, 9 H), 0.90–0.96 (m, 1 H), 0.93 (d, $J$ = 6.5 Hz, 3 H), 0.76 (t, $J$ = 7.4 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 202.1, 135.8, 135.6, 132.95, 132.85, 129.8, 129.7, 127.70, 127.67, 108.9, 87.9, 81.3, 63.9, 34.0, 27.6, 26.8, 25.9, 25.5, 19.2, 16.2, 10.9; HRMS (FI) $m/z$ 455.2658 ($M^+$ + H calcd for $C_{27}H_{39}O_4Si$ 455.2618).

**(4*R*,5*R*,1'*S*)-4-[[(*tert*-Butyldiphenylsilyl)oxy]methyl]-2,2-dimethyl-4-(methoxycarbonyl)-5-(1'-methylpropyl)-1,3-dioxolane (27).** To a solution of aldehyde **26** (1.93 g, 4.25 mmol) in acetonitrile (4.3 mL) and sodium phosphate, monobasic monohydride (171 mg) in water (1.7 mL), and 30% hydrogen peroxide (496 mL, 4.42 mmol) was added a solution of sodium chlorite (86% purity, 680 mg, 6.47 mmol) in water (6.0 mL) dropwise at 3–5 °C. After the solution was stirred at room temperature for 1.5 h, sodium sulfite (43 mg) was added. The solution was extracted with ethyl acetate (×3). The combined organic layers were dried ($Na_2SO_4$) and evaporated *in vacuo*. The crude acid was the dissolved in ether (5 mL) and treated with an excess of an ethereal solution of diazomethane. The mixture was concentrated *in vacuo*, and the residue was chromatographed on silica gel with *n*-hexane–ether (98:2) to yield methyl ester **27** (1.46 g, 71%) as a colorless oil: $[\alpha]^{23}_D$ −8.2° (*c* 1.02, $CHCl_3$); IR (thin film) 1740, 1250, 1110 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.69 (m, 4 H), 7.35–7.43 (m, 6 H), 4.07 (d, $J$ = 7.9 Hz, 1 H), 4.01 (d, $J$ = 10.3 Hz, 1 H), 3.754 (d, $J$ = 10.3 Hz, 1 H), 3.753 (s, 3 H), 1.78 (m, 1 H), 1.58 (m, 1 H), 1.45 (s, 3 H), 1.43 (s, 3 H), 1.11 (m, 1 H), 1.04 (s, 9 H), 0.93 (d, $J$ = 6.5 Hz, 3 H), 0.80 (t, $J$ = 7.4 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 172.6, 135.8, 135.7, 133.2, 133.0, 129.69, 129.68, 128.3, 127.67, 127.6, 108.6, 85.7, 83.3, 65.0, 52.3, 33.8, 27.6, 26.8, 26.3, 25.2, 19.2, 15.9, 11.0; MS (FI) $m/z$ 485 ($M^+$ + H), 427; HRMS (EI) $m/z$ 469.2414 ($M^+$ − Me calcd for $C_{27}H_{37}O_5Si$ 469.2411).

**(4*R*,5*R*,1'*S*)-2,2-Dimethyl-4-(hydroxymethyl)-4-(methoxycarbonyl)-5-(1'-methylpropyl)-1,3-dioxolane (28).** To a solution of methyl ester **27** (1.34 g, 2.77 mmol) in THF (14 mL) were added tetrabutylammonium fluoride (1 M in THF, 5.54 mL, 5.54 mmol) and acetic acid (317 mL, 554 mmol). The mixture was stirred at room temperature for 44 h, and water was added. The aqueous layer was extracted with ether (×3). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with *n*-hexane–ether (6:4) yielded alcohol **28** (602 mg, 88%) as a colorless oil: $[\alpha]^{21}_D$ −20.0° (*c* 1.23, $CH_2Cl_2$); IR (thin film) 3480, 1740, 1250, 1060 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 4.00 (d, $J$ = 9.3 Hz, 1 H), 3.97 (dd, $J$ = 11.5, 8.7 Hz, 1 H), 3.80 (s, 3 H), 3.69 (dd, $J$ = 11.5, 4.7 Hz, 1 H), 2.14 (dd, $J$ = 8.7, 4.7 Hz, 1 H), 1.75 (m, 1 H), 1.47–1.53 (m, 1 H), 1.50 (s, 3 H), 1.48 (s, 3 H), 1.06 (m, 1 H), 1.02 (d, $J$ = 6.5 Hz, 3 H), 0.89 (t, $J$ = 7.4 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 172.7, 109.3, 84.6, 84.5, 63.1, 52.8, 33.6, 28.0, 25.5, 25.1, 16.3, 10.8; MS (FD) $m/z$ 247 ($M^+$ + H), 231; HRMS (EI) $m/z$ 231.1223 ($M^+$ − Me calcd for $C_{11}H_{19}O_5$ 231.1232). Anal. Calcd for $C_{12}H_{22}O_5$: C, 58.52; H, 9.00. Found: C, 58.37; H, 9.05.

**(4*R*,5*R*,1'*S*)-2,2-Dimethyl-4-formyl-4-(methoxycarbonyl)-5-(1'-methylpropyl)-1,3-dioxolane (6).** To a cooled (−60 °C), stirred solution of oxalyl chloride (0.31 mL, 3.55 mmol) in dry $CH_2Cl_2$ (2.5 mL) was added a solution of DMSO (0.475 mL, 8.99 mmol) in dry $CH_2Cl_2$ (2.5 mL) dropwise over a 5-min period. After an additional 10 min, a solution of alcohol **28** (215 mg, 0.874 mmol) in dry $CH_2Cl_2$ (0.8 mL) was added dropwise *via* cannula. The resulting white heterogeneous mixture was stirred at the same temperature for 15 min, and then triethylamine (2.0 mL, 14.3 mmol) was added to produce a thick white slurry. The reaction temperature was allowed to rise to room temperature. Water (15 mL) was added, and the mixture was extracted with $CH_2Cl_2$ (×3). The combined organic layers were dried ($Na_2SO_4$) and evaporated *in vacuo*.

Flash column chromatography of the residue on silica gel with *n*-hexane–ether (8:2) yielded aldehyde **6** (210 mg, 98%) as a colorless oil: $[\alpha]^{23}_D$ +40.7° (*c* 1.13, $CH_2Cl_2$); IR (thin film) 1740, 1250, 1220, 1090 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.69 (s, 1 H), 4.39 (d, $J$ = 7.6 Hz, 1 H), 3.83 (s, 3 H), 1.76 (m, 1 H), 1.60 (s, 3 H), 1.54 (m, 1 H), 1.44 (s, 3 H), 1.22 (m, 1 H), 0.97 (d, $J$ = 6.5 Hz, 3 H) and 0.91 (t, $J$ = 7.4 Hz, 33 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 196.7, 169.1, 111.4, 87.8, 86.2, 53.1, 34.2, 26.9, 25.9, 24.9, 15.7, 11.0; MS (FD) *m/z* 245 ($M^+$ + H); HRMS (EI) *m/z* 229.1067 ($M^+$ − Me calcd for $C_{11}H_{17}O_5$ 229.1076).

**(4*S*,5*R*,1′*S*)-*S*-Benzylthiouronium 2,2-Dimethyl-4-(methoxycarbonyl)-5-(1′-methylpropyl)-1,3-dioxolane-4-carboxylate (10b).** To a solution of aldehyde **6** (92.4 mg, 0.379 mmol) in acetonitrile (0.43 mL) and sodium phosphate, monobasic monohydride (40.2 mg) in water (0.40 mL), and 30% hydrogen peroxide (125 mL, 1.11 mmol) was added a solution of sodium chlorite (86% purity, 165 mg, 1.57 mmol) in water (1.4 mL) dropwise at 3–5 °C. After the solution was stirred at room temperature for 3 h, sodium sulfite (83 mg) was added. The solution was extracted with ethyl acetate (×3). The combined organic layers were washed with 9% $NaHCO_3$ (×6). The aqueous layers were acidified with 2 N $H_2SO_4$ with ice–water cooling and then extracted with ethyl acetate (×3). The combined organic extracts were dried ($Na_2SO_4$) and evaporated *in vacuo*. The crude acid **10a** then obtained was employed in the next experiment without purification.

The crude acid **10a** (prepared in the previous experiment) was dissolved in 1 N NaOH (0.2 mL), and the pH was adjusted to 3 with 1.2 N HCl. This was added with stirring to a solution of benzylisothiourea hydrochloride (45 mg, 0.222 mmol) in water (0.23 mL). After 1.5 h at 0 °C, the precipitate of salt **10b** was collected (69.4 mg, 53% from **6**). Recrystallization from 50% aqueous EtOH raised the mp to 139–141 °C: $[\alpha]^{22}_D$ +59.2° (*c* 1.05, EtOH); IR (KBr) 3280, 1740, 1650, 1600, 1250, 1100 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$ 7.32–7.43 (m, 5 H), 4.62 (d, $J$ = 5.5 Hz, 1 H), 4.43 (s, 2 H), 3.72 (s, 3 H), 1.85 (m, 1 H), 1.64 (m, 1 H), 1.51 (s, 3 H), 1.23 (s, 3 H), 1.18 (m, 1 H), 0.93 (d, $J$ = 6.7 Hz, 3 H), 0.90 (t, $J$ = 7.4 Hz, 3 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 206.7, 174.3, 171.9, 135.3, 130.13, 130.05, 129.4, 110.4, 88.9, 84.2, 52.8, 36.7, 36.2, 28.9, 27.1, 25.7, 15.1, 12.0; HRMS (FAB) *m/z* 427.1926 ($M^+$ + H calcd for $C_{20}H_{31}O_6N_2S$ 427.1903).

**(4*R*,5*S*,1′*S*)-*S*-Benzylthiouronium 2,2-Dimethyl-4-(methoxycarbonyl)-5-(1′-methylpropyl)-1,3-dioxolane-4-carboxylate (29b).** This salt was prepared from **16b** by the use of a procedure (Scheme 4) similar with that described for the preparation of **10b**: mp 136–138 °C (EtOH-water); $[\alpha]^{22}_D$ −40.4° (*c* 1.38, EtOH); IR (KBr) 3250, 3000, 1730, 1640, 1590, 1240, 1080 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3OD$) $\delta$ 7.31–7.43 (m, 5 H), 4.48 (d, $J$ = 7.7, 1 H), 4.44 (s, 2 H), 3.73 (s, 3 H), 1.79 (m, 1 H), 1.69 (m, 1 H), 1.51 (s, 3 H), 1.25 (s, 3 H), 1.17 (m, 1 H), 1.00 (d, $J$ = 6.7 Hz, 3 H), 0.87 (t, $J$ = 7.5 Hz, 3 H); $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta$ 206.3, 173.4, 171.9, 135.1, 130.1, 130.0, 129.4, 110.5, 88.2, 52.9, 36.4, 36.2, 27.1, 26.3, 25.6, 16.9, 11.1; HRMS (FAB) *m/z* 427.1938 ($M^+$ + H calcd for $C_{20}H_{31}O_6N_2S$ 427.1903).

**(4*R*,5*R*,1′*S*)-4-(Diethoxymethyl)-2,2-dimethyl-4-(hydroxymethyl)-5-(1′-methylpropyl)-1,3-dioxolane (30).** To a solution of acetonide **16a** (610 mg, 1.16 mmol) in THF (6.1 mL) was added a solution of tetrabutylammonium fluoride (1 M in THF, 2.38 mL, 2.38 mmol), and the mixture was stirred at 30–40 °C for 12 h. After addition of TBAF (1 M, 1 mL), the mixture was stirred for a further 12 h, and the reaction mixture was concentrated *in vacuo* to give a residue. Flash column chromatography on silica gel with *n*-hexane–ether (9:1 → 8:2) yielded alcohol **30** (259 mg, 77%) as a colorless oil: $[\alpha]^{25}_D$ −4.9° (*c* 1.23, $CH_2Cl_2$); IR (thin film) 3470, 2980, 2880, 1450, 1180, 1100, 1070 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 4.54 (s, 1 H), 4.05 (d, $J$ = 6.6 Hz, 1 H), 3.74–3.83 (m, 3 H), 3.58–3.68 (m, 3 H), 2.36 (t, $J$ = 7.5 Hz, 1 H), 1.71 (m, 1 H), 1.63 (m, 1 H), 1.44 (s, 3 H), 1.40 (s, 3 H), 1.24 (t, $J$ = 7.2 Hz, 3 H), 1.22 (t, $J$ = 7.2 Hz, 3 H), 1.19 (m, 1 H), 0.98 (d, $J$ = 6.6 Hz, 3 H), 0.88 (t, $J$ = 7.5 Hz, 3 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 107.0, 104.1, 85.3, 81.1, 66.5, 65.4, 62.8, 33.5, 28.6, 27.4, 26.1, 15.9, 15.3, 11.2; HRMS (EI) *m/z* 275.1857 ($M^+$ − Me calcd for $C_{14}H_{27}O_3$ 271.1859).

**(4*S*,5*R*,1′*S*)-4-(Diethoxymethyl)-2,2-dimethyl-4-formyl-5-(1′-methylpropyl)-1,3-dioxolane (31).** To a cooled (−60 °C), stirred solution of oxalyl chloride (0.144 mL, 1.65 mmol) in dry $CH_2Cl_2$ (1.5 mL) was added a solution of DMSO (0.23 mL, 2.78 mmol) in dry $CH_2Cl_2$ (1.5 mL) dropwise over 5 min under argon atmosphere. After the solution was stirred for an additional 10 min, a solution of alcohol **30** (121 mg, 0.42 mmol) in dry $CH_2Cl_2$ (0.52 mL) was added dropwise *via* cannula and stirred for 15 min at −60 °C. To the mixture was added dropwise triethylamine (0.97 mL, 6.95 mmol) and then water (8 mL) at room temperature. The separated aqueous layer was extracted with $CH_2Cl_2$ (×3), and the combined organic layers were dried ($Na_2SO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with *n*-hexane–ether (9:1) yielded aldehyde **31** (117 mg, 97%) as a colorless oil: $[\alpha]^{26}_D$ +14.4° (*c* 1.17, $CH_2Cl_2$); IR (thin film) 2980, 2930, 2880, 1740, 1450, 1170, 1110, 1070; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.75 (s, 1 H), 4.63 (s, 1 H) 4.16 (d, $J$ = 5.5 Hz, 1 H), 3.81 (m, 2 H), 3.61 (m, 2 H), 1.84 (m, 1 H), 1.56 (m, 1 H), 1.55 (s, 3 H), 1.46 (s, 3 H), 1.26 (m, 1 H), 1.23 (t, $J$ = 7.1 Hz, 3 H), 1.21 (t, $J$ = 7.0 Hz, 3 H), 0.92 (t, $J$ = 7.3 Hz, 3 H), 0.89 (d, $J$ = 6.8 Hz, 3 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) 202.3, 109.7, 104.1, 89.8, 83.7, 66.5, 65.5, 33.8, 27.8, 27.2, 26.1, 15.3, 15.2, 11.3; HRMS (EI) *m/z* 273.1723 ($M^+$ − Me calcd for $C_{14}H_{25}O_5$ 273.1702).

**(4*S*,5*R*,1′*S*)-4-(Diethoxymethyl)-2,2-dimethyl-4-(methoxycarbonyl)-5-(1′-methylpropyl)-1,3-dioxolane (32).** To a solution of aldehyde **31** (126 mg, 0.438 mmol) in acetonitrile (0.4 mL) and sodium phosphate, monobasic monohydride (37 mg) in water (0.36 mL), and 30% hydrogen peroxide (109 mL, 1.11 mmol) was added a solution of sodium chlorite (86% purity, 110 mg, 1.05 mmol) in water (13 mL) dropwise at 10 °C. After stirring for 1.5 h at room temperature, sodium sulfite (50 mg) was added, and the mixture was extracted with ether (×3). The combined organic layers were dried ($Na_2SO_4$) and evaporated *in vacuo* to yield the crude acid. The acid was treated with an excess of an ethereal solution of diazomethane. The reaction mixture was concentrated *in vacuo*, and flash column chromatography of the residue on silica gel with *n*-hexane–ether (19:1 → 4:1) yielded methyl ester **32** (120 mg, 80%) as a colorless oil: $[\alpha]^{28}_D$ +12.3° (*c* 1.20, $CH_2Cl_2$); IR (thin film) 2980, 2930, 2880, 1760, 1740, 1110, 1070 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 4.80 (s, 1 H), 4.01 (d, $J$ = 6.5 Hz, 1 H), 3.89 (m, 1 H), 3.81 (m, 1 H), 3.71 (s, 3 H), 3.57 (m, 2 H), 1.52–1.58 (m, 2 H), 1.54 (s, 3 H), 1.41 (s, 3 H), 1.22 (t, $J$ = 6.9 Hz, 3 H), 1.14 (t, $J$ = 7.1 Hz, 3 H), 1.17 (m, 1 H), 0.88 (t, $J$ = 7.3 Hz, 3H), 0.87 (d, $J$ = 6.9 Hz, 3H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 171.7, 109.5, 103.0, 88.5, 82.9, 66.6, 65.2, 52.0, 34.7, 26.8, 25.9, 15.4, 15.3, 15.0, 11.2; HRMS (EI) *m/z* 303.1807 ($M^+$ − Me calcd for $C_{15}H_{27}O_6$ 303.1807).

**(4*S*,5*R*,1′*S*)-2,2-Dimethyl-4-formyl-4-(methoxycarbonyl)-5-(1′-methylpropyl)-1,3-dioxolane (33).** To a solution of methyl ester **32** (45 mg, 0.14 mmol) in dry acetone (1 mL) was added trimethylsilyl triflate (32.3 mL, 0.168 mmol), and the mixture was stirred for 1 h at room temperature. After addition of a saturated bicarbonate solution, the reaction mixture was extracted with ethyl acetate (×3). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with *n*-hexane–ether (7:3 → 1:1) yielded aldehyde **33** (18.8 mg, 54%): $[\alpha]^{22}_D$ −18.3° (*c* 0.94, $CH_2Cl_2$); IR (thin film) 3200, 2930, 2860, 1730, 1120, 1070 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 9.82 (s, 1 H), 4.01 (d, $J$ = 8.4 Hz, 1 H), 3.83 (s, 3 H), 1.52–1.65 (m, 2 H), 1.61 (s, 3 H), 1.40 (s, 3 H), 1.08 (m, 1 H), 0.99 (d, $J$ = 6.5 Hz, 3 H), 0.89 (t, $J$ = 7.4 Hz, 3 H); HRMS (EI) *m/z* 185.1800 ($M^+$ − Me calcd for $C_{10}H_{17}O_3$ 303.1807185.1177).

**(4*R*,5*R*,1′*S*)-*S*-Benzylthiouronium 2,2-Dimethyl-4-(methoxycarbonyl)-5-(1′-methylpropyl)-1,3-dioxolane-4-carboxylate (34b).** This salt was prepared from **33** by the use of a procedure similar with that described for **10b**: mp 127–129 °C (EtOH–water); $[\alpha]^{23}_D$ +24.7° (*c* 0.98, EtOH); IR (KBr) 3300, 3050, 2950, 1740, 1650, 1600, 1430, 1370, 1090 $cm^{-1}$; $^1H$ NMR (500 MH, $CD_3OD$) $\delta$ 7.33–7.42 (m, 5 H), 4.51 (d, $J$ = 5.9 Hz, 1 H), 4.41 (s, 2 H), 3.70 (s, 3 H), 1.76 (m, 1 H), 0.91 (t, $J$ = 7.4 Hz, 3 H), 0.86 (d, $J$ = 6.5 Hz, 3 H); $^{13}C$ NMR (125 MHz, $CD_3OD$) $\delta$ 206.8, 173.0, 171.6, 135.1, 130.00, 129.96,

129.3, 109.9, 89.2, 85.8, 52.4, 36.09, 36.07, 28.5, 27.1, 26.0, 15.0, 12.0; HRMS (FAB) *m/z* 427.1942 ($M^+$ + H calcd for $C_{20}H_{31}O_6N_2S$ 427.1903).

**(4*S*,5*S*,1′*S*)-*S*-Benzylthiouronium 2,2-Dimethyl-4-(methoxycarbonyl)-5-(1′-methylpropyl)-1,3-dioxolane-4-carboxylate (35b).** This salt was prepared from **16b** by the use of a procedure (Scheme 5) similar with that described for the preparation of **34b**: mp 143–145 °C (EtOH–water); $[\alpha]^{22}_D$ −15.3° (*c* 0.59, EtOH); IR (KBr) 3250, 3000, 1730, 1640, 1590, 1410, 1090 $cm^{-1}$; $^1H$ NMR (500 MHz, $CD_3OD$) δ 7.33–7.42 (m, 5 H), 4.41 (s, 2 H), 4.40 (d, *J* = 6.7 Hz, 3 H), 0.88 (t, *J* = 7.5 Hz, 3 H); $^{13}C$ NMR (125 MHz, $CD_3OD$) δ 206.6, 172.9, 171.8, 135.0, 129.99, 129.97, 129.4, 109.8, 86.4, 82.2, 52.0, 36.1, 36.0, 27.2, 26.7, 26.0, 16.6, 11.1; HRMS (FAB) *m/z* 427.1938 ($M^+$ + H calcd for $C_{20}H_{31}O_6N_2S$ 427.1903).

**(5*R*,1′*S*)-2,2-Dimethyl-5-(1′-methylpropyl)-1,3-dioxolane-4,4-dicarboxylic Acid (36).** To a solution of 0.4 N KOH (0.88 mL) was added methyl ester **10a** (13.9 mg, 0.054 mmol), and the mixture was allowed to stand for 20 h at room temperature. The reaction mixture was washed with ether (×3) and extracted immediately with ether after acidification by 2 N $H_2SO_4$ under ice cooling. The combined organic layers were dried ($Na_2SO_4$) and evaporated *in vacuo* to give dicarboxylic acid **36** (12.9 mg, 98%): $[\alpha]^{22}_D$ +35.2° (*c* 1.29, acetone); IR (thin film) 3100 br, 2970, 2920, 2920, 2600, 1720, 1450, 1170, 1100, 1060 $cm^{-1}$; $^1H$ NMR (270 MH, $CDCl_3$) δ 4.48 (d, *J* = 6.6 Hz, 1 H), 1.81 (m, 1 H), 1.63 (s, 3 H), 1.59 (m, 1 H) 1.46 (s, 3 H), 1.26 (m, 1 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 0.92 (t, *J* = 7.3 Hz, 3 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 171.0, 170.6, 111.8, 85.1, 84.6, 34.9, 26.8, 26.6, 24.7, 14.7, 11.2; HRMS (FAB) *m/z* 247.1190 ($M^+$ + H calcd for $C_{11}H_{19}O_6$ 247.1182).

**(5*S*,1′*S*)-2,2-Dimethyl-5-(1′-methylpropyl)-1,3-dioxolane-4,4-dicarboxylic Acid (37).** This dicarboxylic acid (20.9 mg, 92%) was prepared from **29a** (24 mg, 0.092 mmol) by the use of a procedure similar with that described for the preparation of **36**: $[\alpha]^{22}_D$ −29.0° (*c* 1.05, acetone); IR (thin film) 3100 br, 2970, 2920, 2600, 1720, 1450, 1370, 1210, 1170, 1100, 1060 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 4.41 (d, *J* = 6.6 Hz, 1 H), 1.81 (m, 1 H), 1.63 (s, 3 H), 1.59 (m, 1 H) 1.46 (s, 3 H), 1.26 (m, 1 H), 0.97 (d, *J* = 9.2 Hz, 1H), 1.74 (m, 2 H), 1.61 (s, 3 H), 1.46 (s, 3 H), 1.26 (m, 1 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 0.90 (t, *J* = 7.3 Hz, 3 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 171.5, 111.7, 85.5, 84.9, 34.8, 26.6, 25.9, 24.9, 15.5, 10.2; HRMS (FAB) *m/z* 247.1190 ($M^+$ + H calcd for $C_{11}H_{19}O_6$ 247.1182).

**1,4-Diacetoxy-2-methylenebutane (42).** To a stirred solution of dimethyl itaconate (**38**) (20 g, 15 mmol) in benzene (100 mL) was added freshly distilled cyclopentadiene (11 mL, 134 mmol) in one portion. Aluminum chloride powder (2 g, 15 mmol) was added to the solution with water cooling. The reaction mixture was stirred at room temperature for 2.5 h and quenched with water to give a yellow solid. The solution was filtered off, and the filtrate was extracted with ethyl acetate (×3). The extracts were washed with brine, dried ($Na_2SO_4$), and evaporated *in vacuo* to yield crude adduct **39** (26.8 g) as a yellow oil. The product was employed without further purification in the subsequent step: IR (thin film) 1735, 1195 $cm^{-1}$.

To a stirred solution of lithium aluminum hydride (LAH) (4.7 g, 724 mmol) in dry ether (150 mL) was added a solution of the crude adduct **39** (26.8 g) in dry ether (100 mL) dropwise at −78 °C. The reaction was allowed to rise to room temperature. After 4 h, water was added dropwise until the excess LAH was completely hydrolized. The reaction mixture was neutralized with 1 N HCl and extracted with ethyl acetate (×3). The combined extracts were washed with brine, dried ($Na_2SO_4$), and evaporated *in vacuo* to give crude diol **40** (19.2 g) as an oil. The product was employed without further purification in the subsequent step; IR (thin film) 3300, 1030 $cm^{-1}$.

To a solution of the crude diol **40** (19.2 g) in pyridine (15 mL) was added acetic anhydride (7.5 mL). After 12 h, the reaction mixture was evaporated *in vacuo* to yield crude diacetate **41** (26 g) as an oil: IR (thin film) 1730, 1220 $cm^{-1}$.

The crude diacetate **41** (26 g) was heated at 300 °C in a vessel which was fitted with a Vigreux column (20 cm). After 10 min, cyclopentadiene was collected as the monomer (<50 °C/760 mmHg). The remaining oil was further distilled *in vacuo* to afford diacetate **42** (123–125 °C/21 mmHg, 12.7 g, 54% from **38**) as an oil: IR (thin film) 1730, 1220 $cm^{-1}$; $^1H$ NMR (90 MHz, $CDCl_3$) δ 5.09 (s, 1 H), 4.98 (s, 1 H), 4.52 (s, 2 H), 4.15 (t, *J* = 7.0 Hz, 2 H), 2.38 (t, *J* = 7.0 Hz, 2 H), 2.07 (s, 3 H), 2.02 (s, 3 H); MS (FI) *m/z* 186 ($M^+$); HRMS (EI) *m/z* 187.0962 ($M^+$ + H calcd for $C_9H_{15}O_4$ 187.0970).

**Methyl 6-Acetoxy-2-(methoxycarbonyl)-4-methylenehexanoate (44).** A solution of diacetate **42** (718 mg, 3.86 mmol), bis(diphenylphosphino)ethane (15.2 mg, 0.038 mmol), and bis(dibenzylideneacetone)palladium (22 mg, 0.038 mmol) in dry THF (7 mL) was stirred for 10 min. To this solution was added in one portion another solution of the sodium salt of dimethyl malonate in dry THF (14 mL), generated from dimethyl malonate (980 mg, 7.43 mmol) and sodium hydride (ca. 60% in oil; 201 mg, 5.03 mmol). The resultant mixture was stirred for 19 h at room temperature, quenched with saturated $NH_4Cl$, and evaporated *in vacuo*. The aqueous solution was extracted with ethyl acetate (×3). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated *in vacuo*. Column chromatography of the residue on silica gel with benzene–ethyl acetate (97:3) yielded diester **44** (775 mg, 78%) as a colorless oil: IR (thin film) 1730, 1220 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.87 (s, 1 H), 4.86 (s, 1 H), 4.18 (t, *J* = 6.8 Hz, 2 H), 3.75 (s, 3 H), 3.74 (s, 3 H), 3.63 (t, *J* = 7.8 Hz, 1 H), 2.67 (d, *J* = 7.8 Hz, 2 H), 2.37 (t, *J* = 6.8 Hz, 2 H), 2.04 (s, 3 H); MS (FI) *m/z* 258 ($M^+$); HRMS (EI) *m/z* 198.0891 ($M^+$ − AcOH calcd for $C_{10}H_{14}O_4$ 198.0890).

**Methyl 6-Acetoxy-4-methylenehexanoate (45).** To a solution of diester **44** (715 mg, 2.77 mmol) in DMSO (2.9 mL) was added sodium chloride (86 mg, 3.18 mmol) and water (0.2 mL). The mixture was refluxed for 5 h. Sodium chloride (86 mg, 3.18 mmol) and water (0.2 mL) were added again, and the resultant mixture was further refluxed for 5 h. The reaction mixture was diluted with water and extracted with ethyl acetate (×3). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated *in vacuo*. Column chromatography of the residue on silica gel with benzene–ethyl acetate (97:3) yielded ester **45** (464 mg, 79%) as a colorless oil: IR (thin film) 1730, 1230 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 4.83 (s, 2 H), 4.18 (t, *J* = 6.9 Hz, 2 H), 3.68 (s, 3 H), 2.33–2.52 (m, 6 H), 2.04 (s, 3 H); $^{13}C$ NMR (68 MHz, $CDCl_3$) δ 173.5, 171.0, 143.9, 111.6, 62.7, 51.6, 35.1, 32.3, 30.9, 21.0; MS (FI) *m/z* 200 ($M^+$); HRMS (EI) *m/z* 201.1120 ($M^+$ + H calcd for $C_{10}H_{17}O_4$ 201.1125).

**Methyl 6-Hydroxy-4-methylenehexanoate (46).** To a solution of ester **45** (345 mg, 1.73 mmol) in methanol (7 mL) was added *p*-toluenesulfonic acid monohydrate (119 mg, 0.636 mmol). After the solution was stirred at room temperature for 1 h, *p*-toluenesulfonic acid monohydrate (60 mg) was added again. The mixture was further stirred for 30 min and concentrated *in vacuo* to 1/3 volume. The mixture was neutralized with saturated $NaHCO_3$ and extracted with ethyl acetate (×3). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated *in vacuo*. Column chromatography of the residue on silica gel with *n*-hexane–ether (7:3) yielded alcohol **46** (246 mg, 90%) as a colorless oil: IR (thin film) 3410, 1740, 1170 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) δ 4.83 (s, 1 H), 4.81 (s, 1 H), 3.69 (t, *J* = 6.4 Hz, 2 H), 3.63 (s, 3 H), 2.47 (t, *J* = 7.5 Hz, 2 H), 2.32 (t, *J* = 7.5 Hz, 2 H), 2.27 (t, *J* = 6.4 Hz, 2 H), 2.13 (br s, 1 H); $^{13}C$ NMR (68 MHz, $CDCl_3$) δ 173.6, 144.5, 111.4, 60.3, 51.4, 39.2, 32.0, 30.3; MS (FI) *m/z* 158 ($M^+$); HRMS (EI) *m/z* 159.1011 ($M^+$ + H calcd for $C_8H_{15}O_3$ 159.1020).

**Methyl 4-Methylene-6-(phenylthio)hexanoate (47).** To a stirred solution of alcohol **46** (2.05 g, 13.0 mmol) and diphenyl disulfide (4.43 g, 20.3 mmol) in pyridine (3.2 mL) was added dropwise tri-*n*-butylphosphine (5.0 mL, 20.1 mmol) at 0 °C. After 4.5 h at room temperature, the mixture was diluted with ether, washed with 10% $NaHCO_3$ and brine, dried ($Na_2SO_4$), and evaporated *in vacuo*. Column chromatography of the residue on silica gel with *n*-hexane–ether (9:1) yielded phenyl sulfide **47** (2.72 g, 83%) as a colorless oil: IR (thin film) 1720, 1150 $cm^{-1}$; $^1H$ NMR (270 MHz, $CDCl_3$) δ 7.16–7.35 (m, 5 H), 4.82 (s, 1 H), 4.81 (s, 1 H), 3.65 (s, 3 H), 3.02 (t, *J* = 7.6 Hz, 2 H), 2.45 (m, 2 H), 2.32–2.38 (m, 4 H); MS (FI) *m/z* 250 ($M^+$);

HRMS (EI) *m/z* 250.1031 ($M^+$ $C_{14}H_{18}O_2S$ 250.1027). Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.17; H, 7.25. Found: C, 67.25; H, 7.41.

**Methyl 4-Methylene-6-(phenylsulfonyl)hexanoate (48).** To a solution of phenyl sulfide **47** (545 mg, 2.18 mmol) in 15% $CH_2Cl_2$–ether (11 mL) was added at 0 °C diphenyl diselenide (620 mg, 1.99 mmol). 30% Hydrogen peroxide (1.24 mL) was added dropwise at the same temperature. After 30 min, 30% hydrogen peroxide (1.24 mL) was added again, and the mixture was stirred for 20 min. The mixture was diluted with ethyl acetate before washing with saturated $NaHCO_3$, 5% $NaHSO_3$, and brine. The organic solution was dried ($Na_2SO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with *n*-hexane–ether (1:1) yielded phenylsulfone **48** (465 mg, 76%) as a colorless oil: IR (thin film) 1720, 1270, 1190 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.57–7.93 (m, 5 H), 4.79 (s, 1 H), 4.75 (s, 1 H), 3.66 (s, 3 H), 3.21–3.24 (m, 2 H), 2.42–2.45 (m, 4 H), 2.29 (t, $J$ = 7.5 Hz, 2 H); MS (FI) *m/z* 282 ($M^+$); HRMS (EI) *m/z* 250.0675 ($M^+$ – MeOH calcd for $C_{13}H_{14}O_3S$ 250.0664). Anal. Calcd for $C_{14}H_{18}O_4S$: C, 59.55; H, 6.43. Found: C, 59.31; H, 6.43.

**4-Methylene-6-(phenylsulfonyl)-1-hexanol (49).** To a solution of LAH (175.3 mg, 4.61 mmol) in dry ether (1.0 mL) was added dropwise phenylsulfone **48** (1.28 g, 4.54 mmol) at −40 °C under nitrogen. After 20 min, the mixture was quenched by adding water and extracted with ethyl acetate (×3). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with chloroform–methanol (99:1) yielded alcohol **49** (465 mg, 76%) as a colorless oil: IR (thin film) 3500, 1300, 1140 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.57–7.93 (m, 5 H), 4.81 (s, 1 H), 4.72 (s, 1 H), 3.61 (t, $J$ = 6.4 Hz, 2 H), 3.21–3.24 (m, 2 H), 2.43 (m, 2 H), 2.06 (t, $J$ = 7.7 Hz, 2 H), 1.83 (br s, 1 H), 1.62–1.67 (m, 2 H); MS (FI) *m/z* 254 ($M^+$); HRMS (EI) *m/z* 254.0999 ($M^+$ calcd for $C_{13}H_{18}O_3S$ 254.0977).

**1-[(*tert*-Butyldimethylsilyl)oxy]-4-methylene-6-(phenylsulfonyl)hexane (7).** To a stirred solution of alcohol **49** (78.1 mg, 0.31 mmol) in dry DMF (0.5 mL) were added imidazole (31.6 mg, 0.46 mmol) and *tert*-butyldimethylsilyl chloride (56 mg, 0.37 mmol). After 3.5 h at room temperature, water was added and the mixture was extracted with ether (×3). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with *n*-hexane–ether (8:2) yielded silyl ether **7** (105.6 mg, 93%) as a colorless oil: IR (thim film) 1280, 1240, 1140, 1090 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.51–7.88 (m, 5 H), 4.74 (s, 1 H), 4.64 (s, 1 H), 3.52 (t, $J$ = 6.3 Hz, 2 H), 3.15–3.18 (m, 2 H), 2.35–2.38 (m, 2 H), 1.97 (t, $J$ = 7.7 Hz, 2 H), 1.53 (m, 2 H), 0.83 (s, 9 H), 0.03 (s, 6 H); $^{13}C$ NMR (68 MHz, $CDCl_3$) $\delta$ 144.2, 138.1, 132.7, 128.3, 127.1, 109.9, 61.4, 53.9, 31.2, 29.7, 27.8, 24.9, 17.3, −6.3; MS (FI) *m/z* 369 ($M^+$ + H); HRMS (EI) *m/z* 311.1132 ($M^+$ – *t*-Bu calcd for $C_{15}H_{23}O_3SSi$ 311.1138). Anal. Calcd for $C_{19}H_{32}O_3SSi$: C, 61.91; H, 8.75; S, 8.70. Found: C, 61.91; H, 8.86; S, 8.59.

**(6*R*)-Dihydro-6-methyl-2*H*-pyran-2,4(3*H*)-dione (8).** To a solution of $\beta$-keto ester **52**[21] (35.9 mg, 0.178 mmol) in $CH_2Cl_2$ (3 mL) was added trifluoroacetic acid (20 mg, 0.175 mmol) at 10 °C. The solution was stirred at room temperature for 24 h and evaporated *in vacuo*. Column chromatography of the residue on Sephadex LH-20 with chloroform–methanol (7:3) yielded $\beta$-keto lactone **8** (105.6 mg, 93%) as colorless crystals. The $\beta$-keto lactone **8** was recrystallized from MeOH–water: mp 113–115 °C; $[\alpha]^{25}_D$ −147.3° (*c* 2.10, EtOH); IR (KBr) 1680, 1580, 1210 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 4.80 (m, 1 H), 3.57 (d, $J$ = 18.9 Hz, 1 H), 3.44 (d, $J$ = 18.9 Hz, 1 H), 2.47 (dd, $J$ = 18.3, 11.4 Hz, 1 H), 2.37 (dd, $J$ = 18.3, 2.7 Hz, 1 H), 1.53 (d, $J$ = 6.3 Hz, 3 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 200.0, 167.3, 71.9, 46.8, 45.0, 20.5; MS (FI) *m/z* 128 ($M^+$); HRMS (EI) *m/z* 128.0468 ($M^+$ calcd for $C_6H_8O_3$ 128.0473). Anal. Calcd for $C_6H_8O_3$: C, 56.25; H, 6.29. Found: C, 55.78; H, 6.12.

**(6*E*,8*S*,9*R*,10*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]-8,9-(isopropylidenedioxy)-8-(methoxycarbonyl)-10-methyl-4-methylene-6-dodecene (57).** To a solution of diisopropylamine (782 $\mu$l, 5.58 mmol) in dry ether (2.1 mL) at −78 °C under argon was added *n*-butyllithium (1.6 M in hexane, 3.48 mL, 5.57 mmol) dropwise. The resulting solution was warmed to −5 to −7 °C and stirred for 20 min. In separate flask, sulfone **7** (284 mg, 0.772 mmol) was azeotropically dried by addition and evaporation of toluene (×3), dissolved in ether and *n*-hexane (1:1, 8.7 mL), and cooled to −78 °C. To the sulfone solution was added the LDA solution (886 $\mu$L, 1.158 mmol) dropwise over a 5-min period. The canary yellow solution thus obtained was warmed to −50 °C and stirred for 50 min before being recooled to −78 °C. In a third flask, aldehyde **6** (187.4 mg, 0.768 mmol) was azeotropically dried with toluene (×2) and dissolved in ether and *n*-hexane (1:1, 3.4 mL). The aldehyde solution was then introduced dropwise to the sulfone anion solution by cannula over 8 min. After 40 min at −78 °C, the reaction was quenched by addition of saturated $NH_4Cl$. The two layers were separated, and the aqueous phase was extracted with ether (×3). The combined organic layers were dried ($Na_2SO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with benzene–ethyl acetate (99:1) yielded the crude diastereomeric hydroxy sulfones **55**, sulfone **7** (118 mg, 42%), and alcohol **28** (19 mg, 10%).

To a solution of the crude hydroxy sulfone **55** in dry $CH_2Cl_2$ (7.3 mL) were added DMAP (693 mg, 5.68 mmol) and acetic anhydride (442 $\mu$L, 4.68 mmol). The mixture was stirred for 9 h at room temperature and concentrated to an oil with a flow of nitrogen. The resultant residue was dissolved THF (7.9 mL) and water (7.9 mL) and stirred for 20 min. The solution was diluted with ethyl acetate (30 mL) and acidified with 1.2 N HCl. The two layers were separated, and the aqueous phase was extracted with ethyl acetate (×3). The combined organic layers were washed with saturated $NaHCO_3$, water, and brine, dried ($Na_2SO_4$), and evaporated *in vacuo* to afford the crude acetoxy sulfone **56** which was employed without further purification in the subsequent step.

To a cooled (−40 to −50 °C) solution of the acetoxy sulfones **56** in dry methanol (12 mL) and dry ethyl acetate (5.4 mL) was added sodium amalgam (5%, 5.05 g, 13.15 mmol). The mixture was stirred vigorously at this temperature for 50 min. The reaction was quenched by pipet transfer of the supernatant into a rapidly stirred and cooled (0 °C) mixture consisting of ethyl acetate and pH 2–3 aqueous $NaHSO_4$ (4:6, 150 mL). After the aqueous layer was further acidified to pH 4–5 with 0.1 N $NaHSO_4$, the two layers were separated and the aqueous extract was washed with ethyl acetate (×2). The combined organic extracts were dried ($Na_2SO_4$) and evaporated *in vacuo*. The residue was first passed through silica gel (eluting with *n*-hexane–ether 9:1) to remove polar impurities, and then the olefin isomers were separated by MPLC (Löber prepackcolumn Si 60, Grőss B (310–25) × 2, *n*-hexane–ether 9:1] to afford pure *E*-isomer **57** (133.5 mg, 38% from **6**) and *Z*-isomer (9.5 mg, 2.7% from **6**). **57**: $[\alpha]^{26}_D$ +26.8° (*c* 0.41, $CHCl_3$); IR (thin film) 1740, 1250, 1100 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 5.92 (dt, $J$ = 15.3, 7.0 Hz, 1 H), 5.64 (d, $J$ = 15.3 Hz, 1 H), 4.77 (br s, 1 H), 4.74 (br s, 1 H), 4.11 (d, $J$ = 7.7 Hz, 1 H), 3.77 (s, 3 H), 3.60 (t, $J$ = 6.6 Hz, 2 H), 2.80 (d, $J$ = 7.0 Hz, 2 H), 2.05 (t, $J$ = 7.7 Hz, 2 H), 1.65 (m, 3 H), 1.52 (s, 3 H), 1.51 (m, 1 H), 1.43 (s, 3 H), 1.14 (m, 1 H), 0.97 (d, $J$ = 6.7 Hz, 3 H), 0.892 (s, 9 H), 0.891 (t, $J$ = 7.4 Hz, 3 H), 0.04 (s, 6 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 173.3, 147.5, 130.7, 127.3, 110.4, 109.0, 85.4, 85.0, 62.8, 52.6, 39.1, 35.1, 32.3, 30.8, 27.4, 26.1, 26.0, 25.1, 18.4, 15.6, 11.2, −5.3; MS (FD) *m/z* 455 ($M^+$ + H), 397; HRMS (FI) *m/z* 455.3191 ($M^+$ + H calcd for $C_{25}H_{47}O_5Si$ 455.3192).

**(6*E*,8*S*,9*R*,10*S*)-8,9-(Isopropylidenedioxy)-8-(methoxycarbonyl)-10-methyl-4-methylene-6-dodecen-1-ol (65).** To a solution of olefin **57** (73.7 mg, 0.162 mmol) in THF (0.8 mL) were added tetrabutylammonium fluoride (1 M in THF, 0.486 mL, 0.486 mmol) and acetic acid (27.8 $\mu$L, 0.486 mmol). The mixture was stirred at room temperature for 48 h, concentrated *in vacuo*, and then added to water. The aqueous layer was extracted with ether (×3). The combined organic layers were dried ($Na_2SO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with *n*-hexane–ether (6:4) yielded alcohol **65** (53.2 mg, 96%) as a colorless oil: $[\alpha]^{26}_D$ +39.5° (*c* 0.53, $CHCl_3$); IR (thin film) 3400, 1730, 1140, 1050 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 5.91 (dt, $J$ = 15.3, 7.1 Hz, 1 H), 5.66 (d, $J$ = 15.3 Hz, 1 H), 4.80 (br s, 1 H), 4.77 (br s, 1 H), 4.12 (d, $J$ = 7.7 Hz, 1 H), 3.77 (s, 3 H), 3.64 (t, $J$ =

6.5 Hz, 2 H), 2.82 (d, $J$ = 7.0 Hz, 2 H), 2.10 (t, $J$ = 7.6 Hz, 2 H), 1.71 (m, 2 H), 1.66 (m, 1 H), 1.52 (s, 3 H), 1.50 (m, 1 H), 1.43 (s, 3 H), 1.13 (m, 1 H), 0.98 (d, $J$ = 6.6 Hz, 3 H), 0.89 (t, $J$ = 7.4 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.3, 147.3, 130.6, 127.4, 110.8, 109.0, 85.4, 84.9, 62.6, 52.7, 39.1, 35.0, 32.2, 30.5, 27.3, 26.0, 25.0, 15.6, 11.1; MS (FD) $m/z$ 341 ($M^+$ + H); HRMS (FI) $m/z$ 281.2114 ($M^+$ − $CO_2Me$ calcd for $C_{17}H_{29}O_3$ 281.2117).

**(6*E*,8*S*,9*R*,10*S*)-8,9-(Isopropylidenedioxy)-8-(methoxycarbonyl)-10-methyl-4-methylene-6-dodecen-1-al (66).** To a cooled (−60 °C), stirred solution of oxalyl chloride (51.4 mL, 0.589 mmol) in dry $CH_2Cl_2$ (0.42 mL) was added a solution of DMSO (79.5 $\mu$L, 1.51 mmol) in dry $CH_2Cl_2$ (0.42 mL) dropwise over 5 min. After an additional 10 min, a solution of alcohol **65** (52 mg, 0.153 mmol) in dry $CH_2Cl_2$ (0.24 mL) was added by cannula. The resulting mixture was stirred at this temperature for 25 min, and then triethylamine (0.337 mL, 2.42 mmol) was added to produce a thick slurry. The reaction temperature was allowed to rise to room temperature. Water was added, and the mixture was extracted with ether (×3). The combined organic layers were dried ($Na_2SO_4$) and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with *n*-hexane−ether (8:2) yielded aldehyde **66** (46.4 mg, 90%) as an oil: $[\alpha]^{24}_D$ +40.0° (*c* 1.13, $CHCl_3$); IR (thin film) 1730, 1250 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 9.76 (t, $J$ = 1.6 Hz, 1 H), 5.91 (dt, $J$ = 15.3, 7.0 Hz, 1 H), 5.68 (d, $J$ = 15.3 Hz, 1 H), 4.82 (br s, 1 H), 4.77 (br s, 1 H), 4.12 (d, $J$ = 7.8 Hz, 1 H), 3.77 (s, 3 H), 2.83 (d, $J$ = 7.0 Hz, 2 H), 2.58 (dt, $J$ = 7.5, 1.6, 2 H), 2.35 (t, $J$ = 7.5 Hz, 2 H), 1.65 (m, 1 H), 1.52 (s, 3 H), 1.50 (m, 1 H), 1.44 (s, 3 H), 1.13 (m, 1 H), 0.97 (d, $J$ = 6.6 Hz, 3 H), 0.89 (t, $J$ = 7.4 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 176.7, 173.2, 145.8, 130.1, 127.9, 111.3, 109.1, 85.4, 84.9, 52.6, 41.8, 39.4, 35.1, 28.1, 27.4, 26.0, 25.0, 15.3, 11.1; MS (FD) $m/z$ 339 ($M^+$ + H); HRMS (FI) $m/z$ 323.1878 ($M^+$ − Me calcd for $C_{18}H_{27}O_5$ 323.1858).

**(6*E*,8*S*,9*R*,10*S*)-8,9-(Isopropylidenedioxy)-8-(methoxycarbonyl)-10-methyl-4-methylene-6-dodecen-1-oic Acid (5).** To a solution of aldehyde **66** (46.4 mg, 0.137 mmol), 2-methyl-2-butene (64 $\mu$L) and sodium phosphate (16.5 mg, 0.138 mmol) in a mixture of 2-methyl-2-propanol (0.98 mL) and water (0.27 mL) was added sodium chlorite (86% purity, 42.4 mg, 0.552 mmol) portionwise. After the solution was stirred at 10 °C for 50 min, water was added, and the resulting mixture was acidified with 0.1 N HCl and extracted with ethyl acetate (×3). The combined organic layers were washed with brine, dried ($Na_2SO_4$), and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with chloroform−methanol (98:2) yielded carboxylic acid **5** (46.2 mg, 95%) as an oil: $[\alpha]^{26}_D$ +32.5° (*c* 2.11, $CHCl_3$); IR (thin film) 3200, 1720, 1220 cm$^{-1}$; $^1$H NMR (270 MHz, $CDCl_3$) $\delta$ 5.91 (dt, $J$ = 15.2, 7.3 Hz, 1 H), 5.67 (d, $J$ = 15.2 Hz, 1 H), 4.81 (br s, 1 H), 4.80 (br s, 1 H), 4.12 (d, $J$ = 7.3 Hz, 1 H), 3.77 (s, 3 H), 2.83 (d, $J$ = 7.3 Hz, 2 H), 2.51 (t, $J$ = 7.6 Hz, 2 H), 2.34 (t, $J$ = 7.6 Hz, 2 H), 1.66 (m, 1 H), 1.52 (s, 3 H), 1.46−1.58 (m, 1 H), 1.43 (s, 3 H), 1.13 (m, 1 H), 0.97 (d, $J$ = 6.6 Hz, 3 H), 0.89 (t, $J$ = 7.3 Hz, 3 H); $^{13}$C NMR (68 MHz, $CDCl_3$) $\delta$ 178.1, 173.2, 145.8, 130.2, 127.8, 111.1, 109.1, 85.4, 84.9, 52.6, 39.3, 35.0, 32.2, 30.5, 27.3, 26.0, 25.0, 15.5, 11.1; MS (FI) $m/z$ 355 ($M^+$ + H); HRMS (EI) $m/z$ 339.1810 ($M^+$ − Me calcd for $C_{18}H_{27}O_5$ 339.1808).

**Methyl *O*,*O*-Isopropylidenealternarate (1b).** A solution of carboxylic acid **5** (46.2 mg, 0.131 mmol), $\beta$-keto lactone **8** (18 mg, 0.141 mmol), DMAP (3.6 mg, 0.0295 mmol), and DCC (43 mg, 0.209 mmol) in dry $CH_2Cl_2$ (1.5 mL) was stirred at room temperature for 36 h. The mixture was filtered, and the filtrate was washed with saturated $NH_4Cl$, dried ($MgSO_4$), and evaporated *in vacuo*. Flash column chromatography of the residue on silica gel with chloroform yielded dihydropyrone **1b** (45.5 mg, 75%) as an oil: $[\alpha]^{26}_D$ −6.2° (*c*, 4.06, EtOH); UV (EtOH) $\lambda$ 216 ($\epsilon$ 8000), 274 nm (8000); IR (thin film) 3400, 1720, 1560, 1260, 1060 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 17.84 (br s, 1 H), 5.91 (dt, $J$ = 15.4, 6.9 Hz, 1 H), 5.67 (d, $J$ = 15.4 Hz, 1 H), 4.81 (br s, 1 H), 4.79 (br s, 1 H), 4.53 (m, 1 H), 4.12 (d, $J$ = 7.8 Hz, 1 H) 3.77 (s, 3 H), 3.22 (m, 1 H), 3.18 (m, 1 H), 2.85 (d, $J$ = 6.9 Hz, 2 H), 2.67 (dd, $J$ = 17.1, 11.7 Hz, 1 H), 2.62 (dd, $J$ = 17.1, 4.0 Hz, 1 H), 2.36 (m, H), 1.65 (m, 1 H), 1.45−1.54 (m, 1 H), 1.52 (s, 3 H), 1.47 (d, $J$ = 6.3 Hz, 3 H), 1.43 (s, 3 H), 1.13 (m, 1 H), 0.97 (d, $J$ = 6.5 Hz, 3 H), 0.89 (t, $J$ = 7.4 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 203.9, 194.5, 173.2, 164.2, 146.0, 130.3, 127.7, 111.2, 109.0, 85.4, 85.0, 70.3, 52.6, 39.2, 39.1, 37.0, 35.0, 30.6, 29.7, 27.4, 26.0, 25.1, 20.6, 15.6, 11.1; MS (FD) $m/z$ 465 ($M^+$ + H); HRMS (EI) $m/z$ 405.2279 ($M^+$ − $CO_2Me$ calcd for $C_{23}H_{33}O_6$ 405.2277).

**Alternaric Acid (1).** Dihydropyrone **1b** (40.6 mg, 0.0875 mmol) was dissolved in 2 N lithium hydroxide−methanol−THF (1:1:2, 0.98 mL) under ice−water cooling. The mixture was kept at room temperature for 50 min and neutralized with 1 N HCl, and the organic solvents were removed *in vacuo*. The resulting aqueous solution was extracted with ethyl acetate (×5). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated *in vacuo* to afford crude acid **68**. This material was employed without further purification in the subsequent step.

A solution of crude acid **68** in ethanol (10 mL) and water (10 mL) was heated for 1 h in an autoclave (120 °C, 1 kg/cm$^2$). The reaction mixture was extracted with ethyl acetate (×3). The combined organic extracts were washed with saturated $NH_4Cl$ and brine, dried ($MgSO_4$), and evaporated *in vacuo*. Recrystallization of the residue from benzene yielded alternaric acid (**1**) (16.3 mg, 52%, from **1b**) as colorless crystals: mp 135−136 °C (MeOH−water) (natural, 135 °C);[1d] $[\alpha]^{24}_D$ 0° (*c* 1.00, acetone) (natural, optically inactive);[1d] CD (EtOH) $\lambda$ 214 ($\Delta\epsilon$ +5.9), 227 (0), 260 nm (−3.1) [natural, CD (EtOH) $\lambda$ 213 ($\Delta\epsilon$ +6.9), 228 (0), 260 nm (−4.2)]; IR (thin film) 3450, 1720, 1250, 1050 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 17.88 (br s, 1 H), 5.97 (dt, $J$ = 15.4, 6.6 Hz, 1 H), 5.78 (d, $J$ = 15.4 Hz, 1 H), 4.86 (br s, 1 H), 4.83 (br s, 1 H), 4.56 (m, 1 H), 3.94 (d, $J$ = 2.0 Hz, 1 H), 3.25 (ddd, $J$ = 13.8, 10.8, 5.1 Hz, 1 H), 2.92 (ddd, $J$ = 13.8, 10.9, 5.3, 1 H), 2.85 (dd, $J$ = 14.6, 6.7, 1 H), 2.81 (dd, $J$ = 14.6, 6.1 Hz, 1 H), 2.69 (dd, $J$ = 17.6, 9.2 Hz, 1 H), 2.65 (dd, $J$ = 17.6, 5.9 Hz, 1 H), 2.44 (ddd, $J$ = 14.7, 10.7, 5.1 Hz, 1 H), 2.26 (ddd, $J$ = 14.7, 10.8, 5.2 Hz, 1 H), 1.84 (m, 1 H), 1.47 (d, $J$ = 6.3 Hz, 3 H), 1.45 (m, 1 H) 1.31 (m, 1 H), 0.89 (t, $J$ = 7.4 Hz, 3 H), 0.87 (t, $J$ = 6.6 Hz, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 203.8, 195.3, 176.4, 165.4, 145.3, 130.2, 129.7, 112.4, 112.4, 102.8, 78.4, 76.7, 70.8, 39.3, 38.9, 37.3, 34.9, 31.9, 31.2, 27.7, 20.6, 12.4, 11.8; HRMS (FAB) $m/z$ 409.1886 ($M^-$ − H calcd for $C_{21}H_{29}O_8$ 409.1863).

**Typical Procedure of Modified Fries-Type Rearrangement.** A solution of propionic acid (90 mg, 1.21 mmol), $\beta$-keto-$\delta$-valerolactone **8** (155 mg, 1.21 mmol), DMAP (7 mg, 0.057 mmol), and DCC (274 mg, 1.33 mmol) in dry $CH_2Cl_2$ (2.5 mL) was stirred at room temperature until rearrangement was complete (usually 48 h). The *N*,*N*-dicyclohexylurea was filtered, and the filtrate was washed with saturated $NH_4Cl$ and brine, dried ($Na_2SO_4$), and evaporated *in vacuo* to give the pyrone, 3-propionyl-5,6-dihydro-4-hydroxy-2-pyrone, which was purified by recrystallization from petroleum ether−chloroform to give the product (190 mg, 85%).

**Acknowledgment.** We are grateful to Mr. K. Watanabe and Mrs. E. Fukushi in our department for analysis of MS spectra and Dr. T. Tsuge, Faculty of Agriculture, Nagoya University, for the *Alternaria solani* strain.

**Supplementary Material Available:** NMR spectra of those compounds lacking combustion data (25 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.