Determination of the Absolute Stereochemistry of (−)-Galbonolide A

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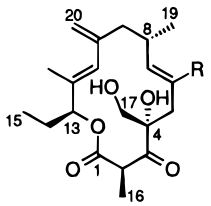
The absolute stereochemistry of (−)-galbonolide A (**1**) was assigned by chemical methods. First, **1** was degraded to diol **3**. After selective silylation of the primary alcohol, two independent methods were carried out to determine the chirality at C13. Both established its *S*-configuration. Using the methodology developed in the total synthesis of (−)-galbonolide B, diols **13(*S*,*S*)** and **13(*S*,*R*)** were prepared. Their (*R*)-MTPA esters, **14(*S*,*S*,*R*)** and **14(*S*,*R*,*R*)**, were compared with the analogous (*R*)-MTPA ester of the degradation product **3**, which subsequently established the *S*-chirality at C8. To determine the chirality at C4, two independent methods were carried out. One involved a comparison with the chirality of C4 of galbonolide B. The other involved a comparison of the degradation product of galbonolide A, **22**, with its synthetic equivalents. Both methods confirmed the *S*-configuration at C4. Since three of the four chiral centers of galbonolides A and B have been confirmed to be identical and since the two galbonolides share very similar conformations as suggested by their ^{1}H NMR spectra, the configurations at C2 of these two compounds should also be the same.

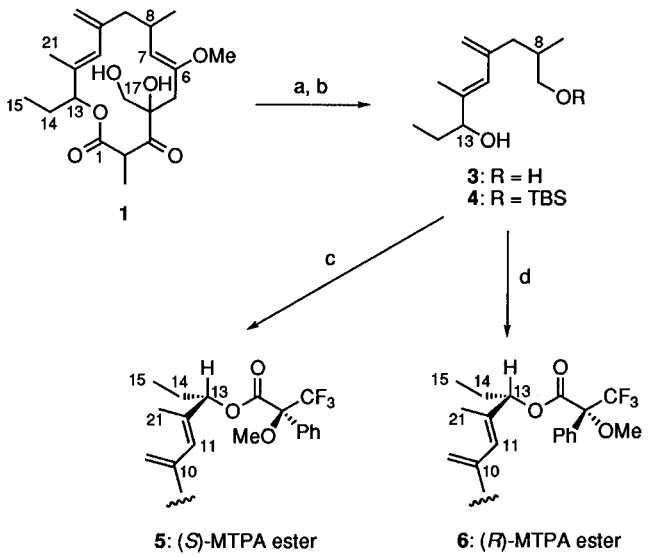
Galbonolide A (**1**) and B (**2**) were isolated as fungal metabolites from *Micromonospora chalcea* by Otake[1] and from *Streptomyces galbus* by Achenbach[2] independently. They exhibit antifungal activities against a large number of pathogens such as *Candida albicans*, *Botrytis cinerea*, and *Rhodotorula rubra*.[3] Of these two compounds, galbonolide A is the more potent antifungal agent. Recently, the first total synthesis of galbonolide B was accomplished. In addition, its absolute stereochemistry was determined.[4] Through a translactonization involving the tertiary alcohol at C4, the secondary alcohol at C13 was exposed for derivatization. Two independent methods were carried out to determine its chirality. Both established its *S*-configuration. Together with the relative stereochemistry determined by its crystal structure, the absolute stereochemistry was formally established. On the other hand, there is still no formal establishment of the absolute stereochemsitry of galbonolide A to our knowledge, though the connectivities of the atoms have been confirmed to be the same as that of galbonolide B.[1,2] Unlike galbonolide B, however, efforts to obtain an X-ray structure of galbonolide A or its derivatives have so far been unsuccessful in our laboratory. Thus, we turned to chemical methods to determine the absolute stereochemistry. This article describes the assignment of the absolute stereochemistry of galbonolide A by judicious modifications of the methodology developed in the total synthesis of galbonolide B.



1: Galbonolide A, R = OMe
2: Galbonolide B, R = Me

Chirality of C13. Being an enol ether, the C6−C7 double bond was expected to be the most electron-rich and thus most susceptible to ozonolysis. Indeed, selective cleavage of the C6−C7 olefin was successful. Immediate reduction of the aldehyde and subsequent treatment with NaOMe gave diol **3** in 72% yield (Scheme 1). In the absence of the relatively unstable enol ether moiety, diol **3** would be comparatively easier to handle and thus was

Scheme 1



Reagents and conditions: a. 1. O_3, CH_2Cl_2-MeOH, -78 °C, followed by Me_2S work-up. 2. $NaBH_4$, rt. 3. NaOMe, rt. b. TBSCl, NEt_3, DMAP, CH_2Cl_2, rt. c. (*R*)-MTPA-Cl, NEt_3, DMAP, CH_2Cl_2, rt. d. (*S*)-MTPA-Cl, NEt_3, DMAP, CH_2Cl_2, rt. If the chirality of C13 were *S* as drawn, with the shielding effects of the phenyl groups, one would predict an upfield shift of the protons on C11 and C21 from **5** to **6** and a downfield shift of the protons on C14 and C15. If the chirality were *R*, the opposite shifts would be observed.

(1) Abe, Y.; Nakayama, H.; Shimazu, A.; Furihata, K.; Ikeda, K.; Furihata, K.; Seto, H.; Otake, N. *J. Antibiot.* **1985**, *38*, 1810.
(2) Achenbach, H.; Muhlenfeld, A.; Fauth, U.; Zahner, H. *Tetrahedron Lett.* **1985**, *26*, 6167.
(3) Achenbach, H.; Muhlenfeld, A.; Fauth, U.; Zahner, H. *Ann. N.Y. Acad. Sci.* **1988**, *544*, 128.
(4) Tse, B. *J. Am. Chem. Soc.* **1996**, *118*, 7094.

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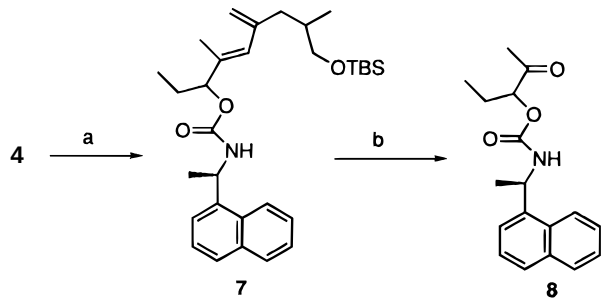
Table 1. Chemical Shifts of the Protons Adjacent to the (*S*)- and (*R*)-MTPA Esters Moieties (ppm) with $CDCl_3$ as the Solvent[a]

compound	C14-H	C15-H	C11-H	C21-H
5	1.60−1.78	0.80	5.91	1.75
6	1.64−1.82	0.88	5.83	1.60

[a] In comparison of the chemical shifts of the relevant signals of **5** to **6**, the downfield shifts of the protons on C14 and C15 and the upfield shifts of those on C11 and C21 indicated *S*-chirality at C13.

Scheme 2



Reagents and conditions: a. (*R*)-1-(1-naphthyl)ethyl isocyanate, DMAP, toluene, reflux. b. $NaIO_4$, $RuCl_3$, CCl_4-CH_3CN-H_2O, rt.

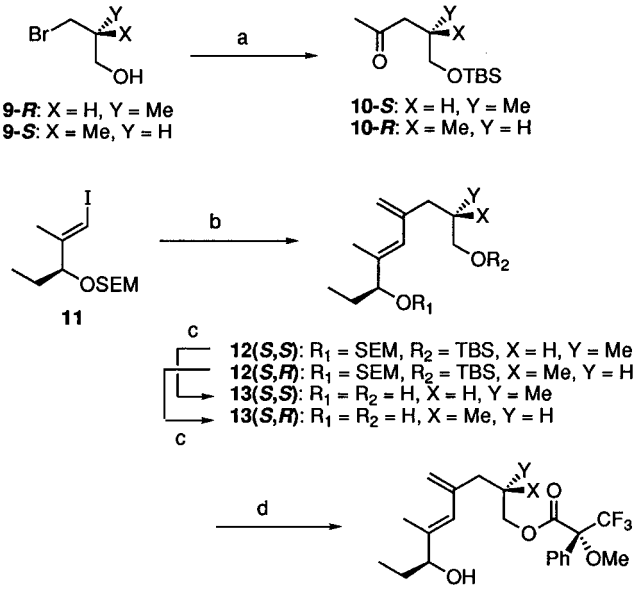
used for the determination of the configurations of C8 and C13. After selective silylation of the primary alcohol (91%), the secondary alcohol at C13 was derivatized. As in the case of galbonolide B, two independent methods were carried out to determine the configuration at C13, and both methods confirmed its *S*-chirality.

First, the standard Mosher method was employed, using the (*S*)-MTPA and the (*R*)-MTPA esters.[5] From the comparison of the chemical shifts of the pertinent signals as tabulated in Table 1, the *S*-chirality of C13 was indicated.

In the second method (Scheme 2), carbamate **7** was prepared (83% from **4**), which was degraded to methyl ketone **8** (59%). This degradation product was then compared with synthetic **8(*R*,*R*)** and **8(*S*,*R*)** as reported earlier.[4] The match of its ^1H NMR with that of **8(*S*,*R*)** confirmed the *S*-chirality at C13.

Chirality of C8. In the total synthesis of galbonolide B, methyl ketone **10-*S*** was synthesized from **9-*R*** (Scheme 3).[4] Similarly, **10-*R*** was prepared from **9-*S*** (*ca*. 60% over three steps). Following the same procedure to prepare **12(*S*,*S*)** from **10-*S*** as in the total synthesis, **12(*S*,*R*)** was obtained from **10-*R***. Both of the SEM and the TBS groups were cleaved by treatment with Et_4NF in DMSO at 90 °C (*ca*. 53%) to furnish **13(*S*,*S*)** and **13(*S*,*R*)**. Despite being diastereomers, ^1H NMR spectra of these two compounds were identical and thus could not be used for direct comparison with the degradation product **3**. However, using normal phase HPLC, it was found that **3** coeluted with **13(*S*,*S*)**, not with **13(*S*,*R*)**, indicating that **3** and **13(*S*,*S*)** were identical and that the chirality of C8 was *S*. In addition, when the (*R*)-MTPA esters of the primary alcohol were prepared, the two diastereomers **14(*S*,*S*,*R*)** and **14(*S*,*R*,*R*)** could be easily differentiated by ^1H NMR. When they were compared with the corresponding (*R*)-MTPA ester prepared from **3**, there was a match of its ^1H NMR with that of **14(*S*,*S*,*R*)** and a mismatch with **14(*S*,*R*,*R*)**. The *S*-configuration at C8 was thus confirmed.

Scheme 3



Reagents and conditions: a. 1. TBSOTf, *i*-Pr_2NEt, CH_2Cl_2, -78 °C. 2. LiI, THF, reflux. 3. Ethyl vinyl ether, *t*-BuLi, THF, rt, followed by acid workup. b. 1. *t*-BuLi, ether, -78 °C. 2. Methyl ketone **10-*S*** or **10-*R***, THF-ether, -78 °C. 3. Martin's sulfurane reagent, CH_2Cl_2, rt. c. Et_4NF, DMSO, powdered molecular sieves, 90 °C. d. (*S*)-MTPA-Cl, NEt_3, CH_2Cl_2, rt.

Chirality of C4. To determine the chirality of C4, two independent methods were carried out. The first method involved a comparison with the chirality of C4 of galbonolide B which had already been established. In the second method, a degradation product of galbonolide A containing C4 was prepared synthetically using a simple modification of the methodology developed in the total synthesis. A subsequent comparison between the degradation product and the synthetic material could then allow the assignment of the chirality at C4.

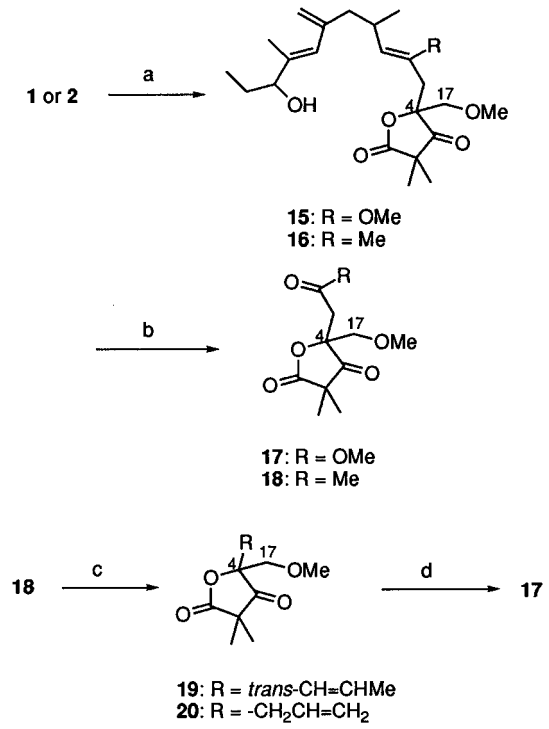
Compounds **1** and **2** were translactonized to **15** and **16**, respectively, upon treatment with NaH and MeI in DMF (*ca*. 70%) (Scheme 4). The extra methyl group at C2 eliminated any complications related to epimerization at C2. Upon ozonolysis, **17** and **18** were formed (*ca*. 95%), respectively. The methyl ketone of **18** could be reduced selectively by $LiHAl(Ot\text{-}Bu)_3$ to yield the corresponding secondary alcohol (95%), which was dehydrated to give a mixture of **19** and **20** (~6:1).[6] The mixture was cleaved oxidatively using Sharpless's procedure. After treatment with diazomethane, the product proved identical to **17** carrying the same optical rotation, thus establishing the chirality of C4 of galbonolide A to be the same as that of galbonolide B, *i.e.*, *S*.

In the second method, an (*S*)-MTPA ester was first derived from the C17 primary alcohol of galbonolide A (80%). Upon translactonization, **21** was obtained (60%), and was subsequently degraded to **22** by ozonolysis (84%) (Scheme 5). Compound **22** could be readily synthesized from the methodology developed in the total synthesis (Scheme 6). A modification of Seebach's and Ladner's contrasteric enolate chemistry was employed on **24** to

(5) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512.

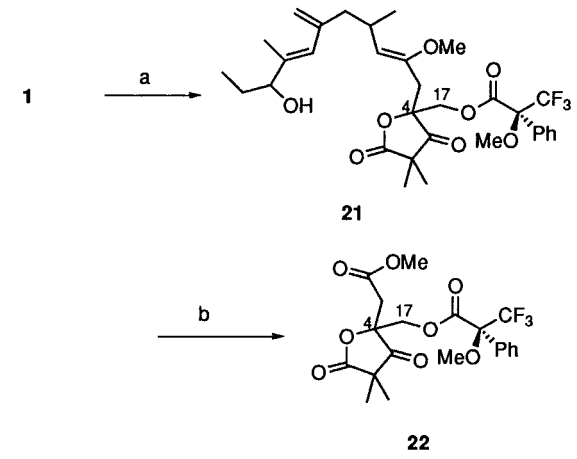
(6) Since the goal was to convert **18** to **17** regardless of the yield, no effort to optimize the ratio of **19**:**20** was carried out.

Scheme 4



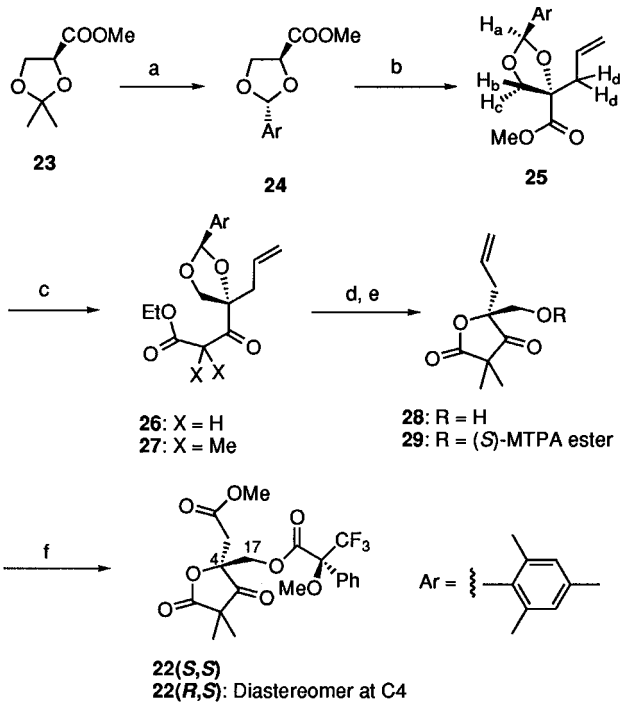
Reagents and conditions. a. MeI, NaH, DMF, rt. b. O_3, CH_2Cl_2-MeOH, -78 °C, followed by Me_2S work-up. c. 1. LiHAl(O*t*-Bu)$_3$, THF, -78 °C. 2. Martin's sulfurane reagent, CH_2Cl_2, rt. d. 1. $NaIO_4$, $RuCl_3$, CCl_4-CH_3CN-H_2O, rt. 2. CH_2N_2, ether, rt.

Scheme 5



Reagents and conditions: a. 1. (*R*)-MTPA-Cl, NEt_3, CH_2Cl_2, rt. 2. NaH, MeI, DMF, rt. b. O_3, CH_2Cl_2-MeOH, -78 °C, followed by Me_2S work-up.

Scheme 6



Reagents and conditions: a. 1. *p*-TsOH, MeOH-H_2O, rt. 2. ArCHO, Camphor sulfonic acid, $CHCl_3$, Dean-Stark. 3. Chromatography. b. Allyl bromide, LiHMDS, THF-HMPA, -78 °C. c. 1. EtOAc, LiHMDS, THF, -78 °C. 2. KO*t*-Bu, MeI, THF, 0 °C. d. *p*-TsOH, MeOH-H_2O, rt. e. (*R*)-MTPA-Cl, NEt_3, CH_2Cl_2, rt. f. 1. $NaIO_4$, $RuCl_3$, CCl_4-CH_3CN-H_2O, rt. 2. CH_2N_2, ether, rt.

install the chiral center at C4 in the total synthesis.[7,8] Using allyl bromide as the electrophile in this case, **25** was formed (79%).[9] After condensation with the lithium enolate of ethyl acetate and subsequent methylation at the C2 position, **27** was furnished (59% over two steps). Treatment with acid led to hydrolysis of the acetal as well as lactonization to provide **28** (82%), from which the (*S*)-MTPA ester **29** was prepared (89%). Upon subsequent oxidative cleavage of the double bond and methylation of the resultant carboxylic acid (62%), **22(*S,S*)** was obtained. Following the same procedure with the use of the enantiomer of **23** as the starting material, **22(*R,S*)** was furnished. When the ^{1}H NMR spectrum of **22** was compared with those of **22(*S,S*)** and **22(*R,S*)**, a match with the former and a mismatch with the latter were observed, thus confirming the configuration of C4 to be *S*. The results from these two independent methods were therefore consistent.

Chirality of C2. Thus, the chiralities of C4, C8 and C13 of galbonolide A have been assigned and found identical to those of galbonolide B. Since the asymmetric center at C2 was rather kinetically labile, no chemical methods were sought to determine its chirality. However, upon comparison of the ^{1}H NMR spectra of galbonolide A and galbonolide B and their C2-epimers,[10] one observes that the spectra of the two galbonolides are extremely similar (Table 2). A striking similarity was also noticed in the two C2-epimers. Thus, one can conclude that the two galbonolides share very similar conformations as do the two C2-epimers. Since the chiralities of three of the four chiral centers of the two galbonolides have been confirmed to be identical, the configurations at C2 of these two compounds should also be the same. The absolute stereochemistry is, therefore, fully established to be the structure shown in **1**.

(7) Seebach, D.; Aebi, J. D.; Gander-Coquoz, M.; Naef, R. *Helv. Chim. Acta* **1987**, *70*, 1194.

(8) Ladner, W. *Chem. Ber.* **1983**, *116*, 3413.

(9) The fact that NOE's were observed between H_a and H_c and between H_b and H_d's (Scheme 6) confirmed the configuration of **25**. The diastereoselectivity of the contrasteric attack of the lithium enolate of **24** on allyl bromide was 12:1.

(10) Galbonolides A and B and their C2-epimers did not equilibrate by themselves at room temperature, thus suggesting that there was sufficient geometrical constraint imposed by the macrocycle to prevent isomerization at C2. However, the two galbonolides and their C2-epimers were found to be in equilibrium in conditions such as DMAP in CH_2Cl_2 and pyridine-water mixture and were characterized by Dr. Mark Greenlee and Ms. Regina Black of this department. Both *epi* compounds have also been reported in the literature, *e.g.*, see ref 3.

Table 2. Chemical Shifts (ppm) with CD_3OD as the Solvent[a]

	1	C2-*epi*-1	2	C2-*epi*-2
C9-H	2.04, 2.20	1.90, 2.25	2.09, 2.19	1.92, 2.26
C11-H	5.62	5.88	5.63	5.87
C13-H	4.83	4.94	4.82	4.93
C16-H	1.38	1.17	1.40	1.17
C17-H	3.59, 3.90	3.50, 3.66	3.55, 3.89	3.52, 3.64
C19-H	0.73	0.91	0.71	0.87
C20-H	4.75, 4.97	4.87, 5.04	4.75, 4.98	4.87, 5.05
C15-H	0.90	0.85	0.91	0.84

[a] The characteristic shifts of signals from galbonolide A (**1**) to C2-*epi*-galbonolide A were also observed from galbonolide B (**2**) to C2-*epi*-galbonolide B.

Experimental Section

General. Reactions sensitive to moisture or air were performed under nitrogen using anhydrous solvents and reagents. Reagents and solvents were used as supplied otherwise. Na_2SO_4 was used for drying in the aqueous workups of reactions. ^1H and ^{13}C NMR spectra were obtained at 500 and 125 MHz, respectively. Chemical shifts are reported in parts per million, and residual solvent peaks were used as internal references. Coupling constants are reported in hertz. IR spectra were measured as films and the wavenumbers are reported in cm^{-1}. Analytical TLC was performed with E. Merck precoated TLC plates, silica gel 60F-254, layer thickness 0.25 mm. Preparative TLC (PTLC) separations were performed on E. Merck precoated TLC plates, silica gel 60F-254, layer thickness 0.50 mm. Flash chromatography was performed with E. Merck Kieselgel 60 (230−400 mesh) silica gel.

Diol 3. Galbonolide A (100.0 mg, 0.26 mmol) was dissolved in 3 mL of CH_2Cl_2 and 8 mL of MeOH. Ozone was periodically passed through this mixture at −78 °C. The course of the reaction was carefully monitored by TLC. Upon the completion of the reaction, nitrogen was passed through the mixture for 2 min, after which Me_2S (1 mL) was added. The mixture was stirred at −78 °C for 10 min. $NaBH_4$ (500 mg, 13.2 mmol) was added, and the mixture was stirred at room temperature for 1 h. NaOMe (3 mL of a 1 M solution in MeOH, 3 mmol) was added, and the mixture was stirred at room temperature overnight. After concentration *in vacuo*, aqueous workup and purification by PTLC, 37.5 mg (72%) of **3** was obtained: $[\alpha]^{25}_D$ +34.9° (*c* 0.30, $CHCl_3$). IR 3300. ^1H NMR ($CDCl_3$) δ 0.86 (3H, t, J = 7.5), 0.87 (3H, d, J = 6.8), 1.55−1.61 (2H, m), 1.73 (1H, m), 1.75 (3H, d, J = 1.4), 1.90 (1H, dd, J = 6.3, 13.6), 2.21 (1H, dd, J = 6.2, 13.4), 3.42 (1H, dd, J = 6.2, 10.5), 3.48 (1H, dd, J = 5.7, 10.5), 3.95 (1H, t, J = 6.5), 4.88 (1H, s), 5.03 (1H, t, J = 1.2), 5.78 (1H, s). ^{13}C NMR ($CDCl_3$) δ 10.0, 13.2, 16.5, 27.8, 34.5, 41.9, 68.0, 79.3, 115.2, 126.7, 140.0, 143.8.

TBS Ether 4. To a solution of diol **3** (35 mg, 0.177 mmol) in CH_2Cl_2 (3 mL) were added NEt_3 (0.074 mL, 0.531 mmol), TBSCl (53.3 mg, 0.354 mmol), and a catalytic amount of DMAP. The mixture was stirred overnight at room temperature. After purification by PTLC, 50.2 mg (91% yield) of **4** was obtained: $[\alpha]^{25}_D$ +42.7° (*c* 0.37, $CHCl_3$). IR 3350. ^1H NMR ($CDCl_3$) δ 0.01 (3H, s), 0.01 (3H, s), 0.82 (3H, d, J = 6.4), 0.86 (3H, t, J = 7.4), 0.87 (9H, s), 1.43 (1H, br s), 1.58 (2H, m), 1.64−1.72 (1H, m), 1.75 (3H, d, J = 1.4), 1.78 (1H, dd, J = 8.8, 13.6), 2.26 (1H, dd, J = 5.6, 13.4), 3.35 (1H, dd, J = 6.3, 9.7), 3.40 (1H, dd, J = 5.1, 9.8), 3.94 (1H, t, J = 6.5), 4.86 (1H, s), 5.00 (1H, t, J = 1.1), 5.77 (1H, s). ^{13}C NMR ($CDCl_3$) δ −5.4, −5.4, 10.0, 13.1, 16.5, 18.3, 25.9, 27.8, 34.5, 41.7, 67.9, 79.5, 115.1, 127.0, 139.5, 144.0.

(*S*)-MTPA Ester 5. To a solution of **4** (10.0 mg, 0.032 mmol) in CH_2Cl_2 (2 mL) were added NEt_3 (0.045 mL, 0.32 mmol), (*R*)-MTPA chloride (0.030 mL, 0.16 mmol), and a catalytic amount of DMAP. The mixture was stirred at room temperature overnight. After purification by PTLC, 13.9 mg (82% yield) of **5** was obtained: $[\alpha]^{25}_D$ −7.4° (*c* 0.18, $CHCl_3$). IR 1746. ^1H NMR ($CDCl_3$) δ 0.00 (3H, s), 0.00 (3H, s), 0.79 (3H, d, J = 6.6), 0.81 (3H, t, J = 7.6), 0.87 (9H, s), 1.60−1.80 (4H, m), 1.75 (3H, d, J = 1.3), 2.28 (1H, dd, J = 5.6, 13.4), 3.37 (2H, m), 3.50 (3H, d, J =1.1), 4.86 (1H, s), 5.04, (1H, s), 5.33 (1H, t, J =7.0), 5.91 (1H, s), 7.34−7.38 (3H, m), 7.45−7.49 (2H, m). ^{13}C NMR ($CDCl_3$) δ −5.4, 9.7, 13.4, 16.2, 18.3, 25.5, 25.9, 34.4, 41.4, 55.2, 67.9, 83.7, 115.8, 123.5, 127.4, 128.3, 129.5, 131.0, 132.5, 134.1, 143.5, 165.8.

(*R*)-MTPA Ester 6. The same procedure for the synthesis of **5** was followed with the use of (*S*)-MTPA chloride. From 10.0 mg of **4**, 13.8 mg (82% yield) of **6** was obtained: $[\alpha]^{25}_D$ +47.2° (*c* 0.14, $CHCl_3$). IR 1748. ^1H NMR ($CDCl_3$) δ 0.00 (3H, s), 0.01 (3H, s), 0.79 (3H, d, J = 6.7), 0.87 (9H, s), 0.88 (3H, t, J = 7.6), 1.60 (3H, s), 1.61−1.82 (4H, m), 2.24 (1H, dd, J = 5.3, 13.3), 3.36 (2H, m), 3.55 (3H, s), 4.82 (1H, s), 5.01 (1H, s), 5.27 (1H, t, J = 7.0), 5.83 (1H, s), 7.32−7.37 (3H, m), 7.46−7.49 (2H, m). ^{13}C NMR ($CDCl_3$) δ −5.4, −5.4, 9.9, 13.1, 16.3, 18.3, 25.5, 25.9, 34.4, 41.4, 55.5, 67.9, 83.8, 115.7, 123.6, 127.2, 128.3, 129.4, 130.8, 132.6, 133.9, 143.5, 165.7.

Carbamate 7. To a solution of **4** (10.0 mg, 0.032 mmol) in toluene (3 mL) were added (*R*)-1-(1-naphthyl)ethyl isocyanate (0.060 mL, 0.34 mmol) and a catalytic amount of DMAP. The mixture was refluxed overnight. After concentration *in vacuo* and purification by PTLC, 13.5 mg (83% yield) of **7** was obtained: $[\alpha]^{25}_D$ +35.7° (*c* 0.21, $CHCl_3$). IR 1707, 3324. ^1H NMR ($CDCl_3$) δ −0.01 (6H, s), 0.78 (3H, d, J = 6.0), 0.82−0.88 (3H, m), 0.85 (9H, s), 1.64−1.78 (11H, m), 2.20 (1H, dd, J = 5.5, 13.3), 3.30−3.37 (2H, m), 4.83 (1H, s), 4.97 (1H, t, J = 6.4), 4.98 (1H, s), 5.62 (1H, s), 5.76 (1H, s), 7.41−7.52 (4H, m), 7.76 (1H, d, J = 8.0), 7.84 (1H, d, J = 7.6), 8.08 (1H, d, J = 8.5). ^{13}C NMR ($CDCl_3$) δ −5.4, −5.4, 9.8, 13.8, 16.4, 18.3, 21.5, 25.9, 34.4, 41.5, 46.5, 67.8, 81.0, 115.2, 122.2, 123.3, 125.2, 125.7, 126.4, 128.2, 128.8, 131.2, 133.9, 135.6, 138.9, 143.9, 155.2. HRMS (EI) calcd for $C_{31}H_{47}N_1O_3Si_1$ 509.3325, found 509.3329.

Degradation Product 8. To a solution of carbamate **7** (9.0 mg, 0.018 mmol) in CCl_4 (1 mL) and CH_3CN (1 mL) was added H_2O (1.5 mL), $NaIO_4$ (42.0 mg, 0.20 mmol) and $RuCl_3$ (1 mg, 0.0048 mmol).[11] The mixture was stirred at room temperature for 4 h. After aqueous workup (CH_2Cl_2) and purification by PTLC, 3.1 mg (58% yield) of **8** was obtained. Its spectroscopic data was found to be identical to **8(*S*,*R*)**.

(*R*)-MTPA Ester 14(*S*,*S*,*R*). To a solution of **12(*S*,*S*)** (5.0 mg, 0.011 mmol) in DMSO (1.5 mL) were added Et_4NF (84 mg, 0.56 mmol) and 4 Å powdered molecular sieves (0.5 g). The mixture was stirred at 90 °C overnight. After acidification, aqueous workup (ether), and purification by PTLC, 1.1 mg of the diol was obtained, which was used directly in the next step. To a solution of this diol (1.1 mg, 0.0056 mmol) in CH_2Cl_2 (1.5 mL) were added NEt_3 (0.016 mL, 0.12 mmol) and (*S*)-MTPA chloride (0.010 mL, 0.053 mmol). The mixture was stirred at room temperature overnight. After purification by PTLC, 1.7 mg (36% overall yield) of **14(*S*,*S*,*R*)** was obtained: $[\alpha]^{25}_D$ +63.6° (*c* 0.082, $CHCl_3$). IR 1744, 3423. ^1H NMR ($CDCl_3$) δ 0.85 (3H, t, J = 7.5), 0.89 (3H, d, J = 6.4), 1.57 (3H, m), 1.74 (3H, s), 1.93 (2H, m), 2.14 (1H, m), 3.53 (3H, s), 3.93 (1H, t, J = 6.7), 4.13 (2H, m), 4.87 (1H, s), 4.96 (1H, s), 5.71 (1H, s), 7.39 (3H, m), 7.49 (2H, m). ^{13}C NMR ($CDCl_3$) δ 10.0, 13.2, 16.7, 27.8, 31.3, 41.4, 55.3, 70.5, 79.2, 116.0, 123.3, 126.2, 127.4, 128.4, 129.6, 132.3, 140.4, 142.7, 166.6. HRMS (EI) calcd for $C_{22}H_{29}O_4F_3$ 414.2018, found 414.2005.

(*R*)-MTPA Ester 14(*S*,*R*,*R*). To prepare **12(*S*,*R*)**, the same procedure for the synthesis of **12(*S*,*S*)** was adopted with the use of **9-*S*** as the starting material. To prepare **14(*S*,*R*,*R*)** from **12(*S*,*R*)**, the same procedure for the synthesis of **14(*S*,*S*,*R*)** from **12(*S*,*S*)** was adopted. From 6.5 mg of **12(*S*,*R*)**, 1.9 mg (31% overall yield) of **14(*S*,*R*,*R*)** was obtained: $[\alpha]^{25}_D$ +33.6° (*c* 0.15, $CHCl_3$). IR 1744, 3414. ^1H NMR ($CDCl_3$) δ 0.84 (3H, t, J = 7.5), 0.87 (3H, d, J = 6.4), 1.57 (3H, m), 1.74 (3H, s), 1.95 (2H, m), 2.13 (1H, m), 3.52 (3H, s), 3.93 (1H, t, J = 6.5), 4.00 (1H, dd, J = 5.9, 10.6), 4.24 (1H, dd, J = 4.7, 10.7), 4.89 (1H, s), 4.99 (1H, s), 5.72 (1H, s), 7.32 (3H, m), 7.49 (2H, m). ^{13}C NMR ($CDCl_3$) δ 9.9, 13.1, 16.7, 27.8, 31.3, 41.5, 55.4, 70.6, 79.3, 115.9, 123.3, 126.2, 127.4, 128.4, 129.6, 132.3, 140.4, 142.7, 166.6. HRMS (EI) calcd for $C_{22}H_{29}O_4F_3$ 414.2018, found 414.2033.

(11) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(*R*)-MTPA Ester of 3. The same procedure for the synthesis of **14(*S,S,R*)** from **13(*S,S*)** was adopted. From 7.4 mg of **3**, 11.6 mg (75% yield) of the corresponding (*R*)-MTPA ester was obtained. Its spectroscopic data was identical to that of **14(*S,S,R*)**, thus establishing the configuration of C8 to be *S*.

Translactonized Product 15. The same procedure for the preparation of **16** from **2** was followed.[4] From 200.0 mg of **1**, 152.0 mg (71% yield) of **15** was obtained: $[\alpha]^{25}_D$ +74.2° (*c* 0.43, $CHCl_3$). IR 1752, 1799, 3525. ^{1}H NMR ($CDCl_3$) δ 0.85 (3H, t, J = 7.5), 0.86 (3H, d, J = 4.6), 1.26 (3H, s), 1.28 (3H, s), 1.56 (2H, m), 1.71 (3H, d, J = 1.4), 1.98 (2H, m), 2.33 (1H, d, J = 14.9), 2.63 (1H, m), 2.66 (1H, d, J = 14.8), 3.28 (3H, s), 3.29 (3H, s), 3.46 (1H, d, J = 10.1), 3.60 (1H, d, J = 10.1), 3.93 (1H, t, J = 6.4), 4.58 (1H, d, J = 9.4), 4.82 (1H, s), 4.95 (1H, t, J = 0.9), 5.74 (1H, d, J = 0.9). ^{13}C NMR ($CDCl_3$) δ 9.9, 13.3, 20.6, 21.2, 21.5, 27.8, 28.9, 34.5, 44.6, 45.5, 56.6, 59.4, 75.2, 79.2, 90.1, 115.2, 124.7, 126.8, 139.5, 143.6, 146.3, 177.6, 213.1.

Degradation Product 17. Ozone was passed through a solution of **15** (150.0 mg, 0.37 mmol) in CH_2Cl_2 (5 mL) and MeOH (15 mL) at −78 °C. Upon the completion of the reaction as monitored by TLC, the excess ozone was removed by passing nitrogen through the mixture. Me_2S (1 mL) was added to the mixture. Stirring was continued for another 15 min at −78 °C, and the mixture was allowed to warm to room temperature. After concentration *in vacuo* and purification by PTLC, 86.0 mg (96% yield) of **17** was obtained: $[\alpha]^{25}_D$ −39.3° (*c* 0.18, $CHCl_3$). IR 1735, 1756, 1801. ^{1}H NMR ($CDCl_3$) δ 1.50 (3H, s), 1.36 (3H, s), 2.83 (1H, d, J = 17.4), 2.98 (1H, d, J = 17.4), 3.32 (3H, s), 3.52 (1H, d, J = 10.3), 3.60 (1H, d, J = 10.1), 3.64 (3H, s). ^{13}C NMR (CDCl3) δ 21.5, 22.3, 37.7, 45.1, 52.4, 59.5, 74.7, 87.8, 168.8, 177.7, 212.9. HRMS (EI) calcd for $C_{11}H_{16}O_6$ 244.0947, found 244.0946.

Degradation Product 18. The same procedure for the synthesis of **17** was followed using **16** as the starting material. From 200.0 mg of **16**, 110.5 mg (95%) of **18** was obtained: $[\alpha]^{25}_D$ −20.1° (*c* 0.29, $CHCl_3$). IR 1720, 1756, 1799. ^{1}H NMR ($CDCl_3$) δ 1.35 (3H, s), 1.59 (3H, s), 2.10 (3H, s), 3.10 (2H, AB q, J = 18.6), 3.32 (3H, s), 3.47 (1H, d, J = 10.3), 3.55 (1H, d, J = 10.5). ^{13}C NMR ($CDCl_3$) δ 21.7, 22.6, 29.5, 45.3, 47.0, 59.5, 74.7, 87.4, 177.9, 203.0, 213.0.

Conversion of 18 to 17. To a solution of **18** (50.0 mg, 0.22 mmol) in THF (5 mL) was added LiHAl(O*t*-Bu)$_3$ (0.24 mL of a 1 M solution in THF, 0.24 mmol) at −78 °C. The mixture was stirred at −78 °C for 2 h. After aqueous workup and purification by PTLC, 47.9 mg (95%) of the corresponding alcohol, which consisted of two diastereomers, was obtained.

To a solution of the alcohol obtained above (47.9 mg, 0.21 mmol) in CH_2Cl_2 (5 mL) was added Martin's sulfurane reagent at room temperature until TLC analysis indicated the completion of the reaction. After purification by PTLC, the inseparable mixture of **19** and **20** (~6:1) was obtained. To a solution of this mixture in CCl_4 (1 mL) and CH_3CN (1 mL) were added H_2O (1.5 mL), $NaIO_4$ (223.0 mg, 1.04 mmol), and $RuCl_3$ (0.011 mmol). The mixture was stirred at room temperature for 4 h. After aqueous workup (ether), the crude mixture was dissolved in 10 mL of ether. Ethereal CH_2N_2 was added until a steady yellow color was obtained. After stirring for an additional 5 min, the excess CH_2N_2 was removed by passing nitrogen through the mixture. After concentration *in vacuo* and purification, 7.2 mg (14% yield over three steps) of **17** was obtained, which was found to have the same optical rotation and spectroscopic data as the direct ozonolysis product from **15** as mentioned above.

(*S*)-MTPA Ester of 1. To a solution of **1** (65 mg, 0.17 mmol) in CH_2Cl_2 (7 mL) was added NEt_3 (0.48 mL, 3.44 mmol) and (*R*)-MTPA chloride (0.32 mL, 1.71 mmol). The mixture was stirred at room temperature overnight. After aqueous workup (CH_2Cl_2) and purification by PTLC, 82 mg (80% yield) of the corresponding (*S*)-MTPA ester was obtained: $[\alpha]^{25}_D$ −52.1° (*c* 0.53, $CHCl_3$). IR 1713, 1729, 1752, 3461. ^{1}H NMR (C_6D_6) δ 0.70 (3H, t, J = 7.5), 0.85 (3H, d, J = 6.6), 1.28 (3H, d, J = 6.9), 1.49 (1H, m), 1.71 (2H, t, J = 11.9), 1.77 (3H, s), 2.13 (1H, dd, J = 3.2, 12.8), 2.45 (1H, d, J = 14.7), 2.72 (1H, d, J = 14.9), 2.72 (1H, m), 2.90 (3H, s), 3.45 (3H, s), 3.73 (1H, q, J = 7.1), 4.46 (1H, d, J = 10.3), 4.68 (1H, d, J = 10.3), 4.86 (1H, d, J = 8.9), 4.97 (1H, s), 5.02 (1H, s), 5.08 (1H, t, J = 7.3), 5.91 (1H, s), 7.06 (5H, m), 7.70 (1H, d, J = 7.8). ^{13}C NMR (C_6D_6) δ 10.0, 12.2, 13.5, 23.0, 25.4, 33.1, 37.3, 46.5, 51.1, 55.3, 56.8, 71.5, 76.8, 82.6, 117.4, 124.3, 125.8, 127.9, 128.3, 128.6, 129.7, 132.7, 132.8, 136.0, 144.0, 149.1, 166.1, 172.8, 208.3. HRMS (EI) calcd for $C_{31}H_{39}O_8F_3$ 596.2597, found 596.2593.

Translactonized Product 21. To a solution of the (*S*)-MTPA ester of **1** obtained above (13.0 mg, 0.022 mmol) in DMF (0.5 mL) was added MeI (0.015 mL, 0.24 mmol), followed by NaH (2.0 mg of a 60% oil dispersion, 0.050 mmol). The mixture was stirred at room temperature for 2 h. After concentration *in vacuo* and purification by PTLC, 8.0 mg (60% yield) of **21** was obtained: $[\alpha]^{25}_D$ +31.5° (*c* 0.52, $CHCl_3$). IR 1675, 1759, 1806, 3484. ^{1}H NMR ($CDCl_3$) δ 0.85 (8H, m), 1.19 (3H, s), 1.56 (4H, m), 1.71 (3H, s), 1.97 (2H, d, J = 7.1), 2.42 (1H, d, J = 14.9), 5.33 (1H, d, J = 14.9), 2.63 (1H, m), 3.28 (3H, s), 3.50 (3H, s), 3.92 (1H, t, J = 6.5), 4.33 (1H, d, J = 11.9), 4.45 (1H, d, J = 11.9), 4.59 (1H, d, J = 9.3), 4.82 (1H, s), 4.95 (1H, s), 5.73 (1H, s), 7.35 (5H, m). ^{13}C NMR ($CDCl_3$) δ 9.9, 13.3,. 20.6, 21.0, 21.4, 27.9, 28.9, 35.4, 44.3, 45.4, 55.8, 56.7, 67.2, 79.2, 87.1, 115.3, 123.0, 125.6, 126.6, 126.9, 128.4, 129.8, 131.8, 139.7, 143.4, 145.4, 166.0, 176.7, 211.2.

Degradation Product 22. Ozone was passed through a solution of **21** (6.7 mg, 0.011 mmol) in CH_2Cl_2 (2 mL) and MeOH (5 mL) at −78 °C until TLC analysis indicated the completion of the reaction. Nitrogen was then passed through the mixture for 5 min to remove the excess ozone. Me_2S (0.25 mL) was added, and the mixture was stirred at −78 °C for another 15 min. After concentration *in vacuo* and purification by PTLC, 4.1 mg (84% yield) of **22** was obtained. Its spectroscopic data was identical to that of **22(*S,S*)** described below, thus confirming the configuration of C4 to be *S*.

Allylated Product 25. Compound **24** (800.0 mg, 3.2 mmol), which was prepared from the *S* isomer of **23**, was dissolved in THF (15 mL) and HMPA (5 mL). To this mixture was added allyl bromide (1.7 mL, 0.020 mol) followed by LiHMDS (4.8 mL of a 1 M solution in THF, 4.8 mmol) at −78 °C. The mixture was stirred at −78 °C for 1 h. After aqueous workup (ether) and chromatography, 733.1 mg (79% yield) of **25** was obtained: $[\alpha]^{25}_D$ −16.2° (*c* 0.57, $CHCl_3$). IR 1752. ^{1}H NMR (CD_3OD) δ 2.17 (3H, s), 2.32 (6H, s), 2.60 (1H, dd, J = 6.4, 14.2), 2.73 (1H, dd, J = 8.0, 14.2), 3.72 (3H, s), 3.96 (1H, d, J = 8.4), 4.13 (1H, d, J = 8.5), 5.06 (2H, m), 5.74 (1H, m), 6.11 (1H, s), 6.75 (2H, s). ^{13}C NMR (CD_3OD) δ 20.3, 21.0, 42.0, 53.0, 73.3, 84.9, 104.4, 119.6, 128.5, 130.9, 133.2, 139.4, 140.3, 174.6.

Compound 27. To a solution of EtOAc (1.36 mL, 0.014 mol) in THF (15 mL) at −78 °C was added LiHMDS (15.4 mL of a 1 M solution in THF, 15.4 mmol). The mixture was stirred at −78 °C for 10 min. Compound **25** (406.1 mg, 1.40 mmol) in THF (5 mL) was then added. The mixture was stirred at −78 °C for another 2 h. After aqueous workup (CH_2Cl_2) and chromatography, 399.3 mg (82% yield) of **26** was obtained, which was used directly in the next step.

To a solution of **26** (273.8 mg, 0.79 mmol) in DMF (10 mL) was added *t*-BuOK (0.79 mL of a 1 M solution in THF, 0.79 mmol) at 0 °C. The mixture was stirred at 0 °C for 5 min. MeI (0.20 mL, 3.2 mmol) was added, and the mixture was stirred at 0 °C for 1 h. The same procedure of adding *t*-BuOK followed by MeI was repeated three times over a period of 3 h. After aqueous workup and chromatography, 225.7 mg (76% yield) of **27** was obtained: $[\alpha]^{25}_D$ −22.0° (*c* 0.21, $CHCl_3$). IR 1705, 1744. ^{1}H NMR (CD_3OD) δ 1.07 (3H, t, J = 7.1), 1.27 (3H, s), 1.40 (3H, s), 2.17 (3H, s), 2.35 (6H, s), 2.62 (1H, dd, J = 6.9, 14.1), 2.71 (1H, dd, J = 7.7, 14.1), 3.89 (1H, d, J = 9.0), 4.02 (2H, m), 4.14 (1H, d, J = 8.9), 4.99 (2H, m), 5.65 (1H, m), 6.00 (1H, s), 6.75 (2H, s). ^{13}C NMR (CD_3OD) δ 14.2, 21.0, 21.1, 22.3, 23.9, 45.3, 55.0, 62.3, 74.4, 90.2, 105.8, 119.0, 128.9, 131.1, 133.9, 139.1, 140.1, 174.5, 211.4.

Lactone 28. To a solution of **27** (206.7 mg, 0.55 mmol) in MeOH (10 mL) was added *p*-TsOH (49.3 mg, 0.26 mmol). The mixture was stirred at room temperature for 30 min. NEt_3 (0.040 mL, 0.27 mmol) was added. After concentration *in vacuo* and chromatography, 84.4 mg (82% yield) of **28** was obtained: $[\alpha]^{25}_D$ −24.0° (*c* 0.56, $CHCl_3$). IR 1747, 1796, 3466. ^{1}H NMR ($CDCl_3$) δ 1.19 (3H, s), 1.26 (3H, s), 2.44 (2H, m), 3.41 (1H, br s), 3.77 (1H, d, J = 12.0), 3.82 (1H, d, J = 12.0),

5.13 (2H, m), 5.62 (1H, m). ^{13}C NMR ($CDCl_3$) δ 20.1, 20.8, 36.5, 44.7, 65.3, 93.5, 121.6, 129.3, 178.3, 213.9.

(*S*)-MTPA Ester 29. To a solution of **28** (33.7 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) was added NEt_3 (0.47 mL, 3.37 mmol) followed by (*R*)-MTPA chloride (0.23 mL, 1.23 mmol). The mixture was stirred at room temperature overnight. After aqueous workup (CH_2Cl_2) and purification by PTLC, 58.5 mg (89% yield) of **29** was obtained: $[\alpha]^{25}_D$ −47.0° (*c* 2.9, $CHCl_3$). IR 1644, 1759, 1798. ^{1}H NMR ($CDCl_3$) δ 0.80 (3H, s), 1.14 (3H, s), 2.50 (2H, d, J = 7.1), 3.46 (3H, s), 4.32 (1H, d, J = 11.9), 4.49 (1H, d, J = 11.9), 5.18 (2H, m), 5.64 (1H, m), 7.32 (5H, m). ^{13}C NMR ($CDCl_3$) δ 19.6, 21.1, 37.6, 44.0, 55.6, 67.0, 88.6, 122.5, 123.1, 126.8, 128.3, 129.7, 131.7, 165.7, 176.4, 211.5.

Synthetic 22(*S*,*S*). To a solution of **29** (21.0 mg, 0.051 mmol) in CCl_4 (2 mL) and CH_3CN (2 mL) were added H_2O (3 mL), $NaIO_4$ (54.2 mg, 0.25 mmol), and $RuCl_3$ (1.0 mg, 0.0048 mmol). The mixture was stirred at room temperature for 4 h. After aqueous workup (CH_2Cl_2), the crude mixture was dissolved in ether (5 mL). Ethereal CH_2N_2 was added until a steady yellow color was obtained. The mixture was stirred at room temperature for 5 min. The excess CH_2N_2 was removed by passing nitrogen through the mixture. After concentration *in vacuo* and purification by PTLC, 14.0 mg (62% yield) of **22-(*S*,*S*)** was obtained: $[\alpha]^{25}_D$ −87.2° (*c* 0.12, $CHCl_3$). IR 1729, 1759, 1806. ^{1}H NMR ($CDCl_3$) δ 1.04 (3H, s), 1.44 (3H, s), 2.90 (1H, d, J = 17.4), 3.02 (1H, d, J = 17.4), 3.53 (3H, s), 3.65 (3H, s), 4.34 (1H, d, J = 12.1), 4.48 (1H, d, J = 12.1), 7.38 (5H, m). ^{13}C NMR ($CDCl_3$) δ 21.2, 22.4, 38.4, 44.9, 52.6, 55.8, 66.5, 84.7, 123.0, 126.9, 128.5, 129.9, 131.6, 165.9, 168.5, 176.6, 211.1. HRMS (EI) calcd for $C_{20}H_{21}O_8F_3$ 446.1189, found 446.1205.

Synthetic 22(*R*,*S*). With the same procedure for the synthesis of **22(*S*,*S*)** using the *R* isomer of **23** as the starting material, **22(*R*,*S*)** was obtained: $[\alpha]^{25}_D$ +6.9° (*c* 0.49, $CHCl_3$). IR 1728, 1759, 1806. ^{1}H NMR ($CDCl_3$) δ 1.15, (3H, s), 1.46 (3H, s), 2.98 (2H, AB q, J = 17.6), 3.47 (3H, s), 3.63 (3H, s), 4.37 (1H, d, J = 12.1), 4.52 (1H, d, J = 12.1), 7.41 (5H, m). ^{13}C NMR ($CDCl_3$) δ 21.0, 22.6, 38.4, 45.0, 52.6, 55.6, 66.4, 84.9, 123.0, 127.1, 128.6, 130.0, 131.2, 165.9, 168.6, 176.2, 211.2. HRMS (EI) calcd for $C_{20}H_{21}O_8F_3$ 446.1189, found 446.1205.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all key compounds and NOE difference spectra of **25** (51 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.

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