Eudistomidin D (4): yellow solid; mp 180 °C dec; IR (KBr) 3500, 3100, 1640, 1540, 1520, 1480, 1320, and 820 cm^{-1}; UV (MeOH) λ_{max} 211 (ϵ 13 600), 270 (9800), 315 (6800), and 416 (1800) nm; (MeOH + KOH) λ_{max} 254 (ϵ 7000), 299 (8600), 342 (sh), and 503 (700) nm; EIMS m/z 278 $(M + 2)^+$, 276 $(M)^+$, 234, 232, 198, 184, 183, and 168; FABMS m/z 279 $(M + 2 + H)^+$ and 277 $(M + H)^+$; HRFABMS m/z 276.9978 $((M + H)^+$, calcd for $C_{12}H_{10}ON_2Br$, 276.9976); ^1H NMR (CD_3OD) δ 9.21 (s, H-1), 9.10 (d, J = 5.4 Hz, H-4), 8.47 (d, J = 5.4 Hz, H-3), 7.66 (d, J = 8.7 Hz, H-7), 7.49 (d, J = 8.7 Hz, H-8), and 4.56 (s, 9-NCH_3); ^{13}C NMR (CD_3OD) δ 148.8 (d, C-1), 148.4 (s, C-6), 138.7 (d, C-3), 135.3 (s, C-9a), 134.7 (s, C-8a), 130.9 (s, C-4a), 121.6 (s, C-4b), 118.2 (D, C-7), 117.7 (d, C-4), 111.4 (d, C-8), 101.5 (s, C-5), and 37.0 (q, 9-NCH_3).

***O*-Methyleudistomidin D (16).** Treatment of eudistomidin D (4, 1.2 mg) with CH_2N_2 in MeOH gave the corresponding methylated compound (16, 1.2 mg): FABMS m/z 293 $(M + 2 + H)^+$ and 291 $(M + H)^+$; HRFABMS m/z 291.0146 $((M + H)^+$, calcd for $C_{13}H_{12}ON_2Br$, 291.0132); ^1H NMR ($CDCl_3$) δ 8.83 (d, J = 6.4 Hz, H-4), 8.62 (s, H-1), 7.88 (d, J = 9.0 Hz, H-8), 7.52 (d, J = 6.4 Hz H-3), 7.43 (d, J = 9.0 Hz, H-7), 4.35 (s, OCH_3), and 4.02 (s, NCH_3).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra, correlation spectra, and high-resolution mass spectra (15 pages). Ordering information is given on any current masthead page.

Synthesis of Optically Active 3(*R*)-[(Alkylsulfonyl)oxy]thiolanes from 2(*R*)-Hydroxy-4-(methylthio)butanoic Acid or D-Methionine

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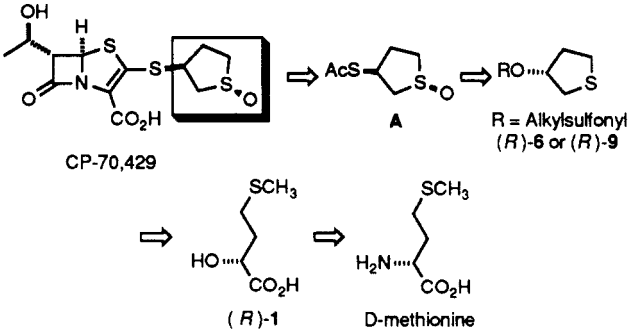
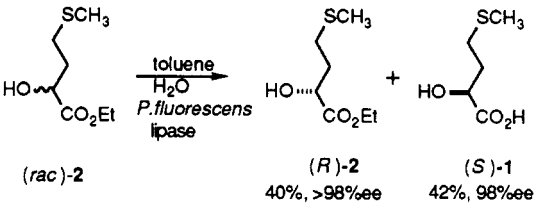
The highly active penem antibiotic CP-70,429 featured a 1(*R*)-oxo-3(*S*)-(thiolanylthio) substituent at carbon 2. The side-chain precursor, 1(*R*)-oxo-3(*S*)-(acetylthio)-thiolane (A), was synthesized initially by Volkmann et al.[1] starting from L-aspartic acid and through the intermediacy of 3(*R*)-[(methylsulfonyl)oxy]- or 3(*R*)-[(*p*-tolylsulfonyl)-oxy]thiolanes, (*R*)-**6** and (*R*)-**9**. An alternate approach to the synthesis of these optically active thiolanes is presented (Scheme I). We started from 2(*R*)-hydroxy-4-(methylthio)butanoic acid ((*R*)-**1**), which was prepared from D-methionine or, more efficiently, by a novel lipase hydrolysis of racemic ethyl 2-hydroxy-4-(methylthio)butyrate (*rac*-**2**).

For our initial work, the diazotization of D-methionine[2] provided a source of optically active 2(*R*)-hydroxy-4-(methylthio)butanoic acid ((*R*)-**1**), although the yield was low. Racemic 2-hydroxy-4-(methylthio)butanoic acid (*rac*-**1**) is readily available as its calcium salt, which is used

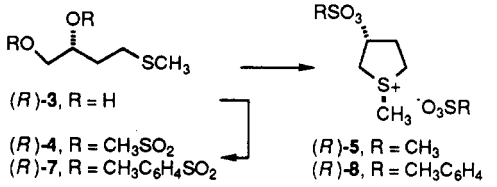
Scheme I



as a methionine substitute in animal feed. However, there have been no reports in the literature for the resolution of this material. The commercially available calcium salt of *rac*-**1** was esterified and the resulting racemic ethyl ester (*rac*-**2**) was resolved by stereospecific hydrolysis with the lipase from *Pseudomonas fluorescens*[3] to give the *R* ester and the *S* acid. While optically active acid (*R*)-**1** was reported also from microbiological reduction of 2-oxo-4-(methylthio)butanoic acid,[4] *the current resolution makes both (R)-2 and (S)-1 readily available chiral starting materials.*



Since the ester group in (*R*)-**2** was activated by the neighboring hydroxy group, the reduction to diol (*R*)-**3** could be accomplished with sodium borohydride. Diol (*R*)-**3** has been prepared previously through resolution of the racemic bis-phthalate half ester of *rac*-**3** with L-amphetamine.[5] The current synthesis afforded (*R*)-**3** with 96% ee, while the literature method yield (*R*)-**3** of 90% ee.



For the thiolane synthesis, diol (*R*)-**3** was converted to its dimesylate (*R*)-**4** with mesyl chloride in pyridine. Dimesylate (*R*)-**4** could be characterized by NMR and TLC but slowly cyclized to the sulfonium salt (*R*)-**5** upon standing. Heating (*R*)-**4** in benzene gave the crude sulfonium salt (*R*)-**5** in 70–80% yield from diol (*R*)-**3** with a trans/cis ratio of 5/2 (estimated by NMR). The pure trans diastereomer was isolated in 40% yield by recrystallization of the crude reaction mixture. Use of tosyl chloride gave similarly a 40% yield of one diastereomer (*R*)-**8** after crystallization, but the determination of the diastereomer ratio was not possible due to the presence of side products in the filtrate including 3-hydroxy-1-methylthiolanium tosylate. The latter was the result of cyclization of 2-

(1) Volkmann, R. A.; Bordner, J.; Foulds, G. H.; Girard, A. E.; Girard, D.; Gootz, T.; Jasy, V. J.; Kelbaugh, P. R.; Kellogg, M. S.; Hamanaka, E. S.; Lindner, D. L.; Nason, D. M.; Retsema, J. A.; Campbell, B. Interscience Conference on Antimicrobial Agents and Chemotherapy; Oct 23–26, 1988; Los Angeles, CA. Paper 220. Volkmann, R. A.; Lindner, D. L. U.S. Pat. 4 794 179, 1988.

(2) Kleemann, A.; Lehmann, B.; Martens, J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 797.

(3) Amano International Enzyme Co.; lipase P-30.

(4) Hummel, W.; Schütte, H.; Kula, M.-R. *Appl. Microbiol. Biotechnol.* **1985**, *21*, 7.

(5) Steadman, T. R.; Van Peppen, J. F.; Sifniades, S. *J. Agric. Food Chem.* **1975**, *23*, 1137.

0022-3263/90/1955-3670$02.50/0

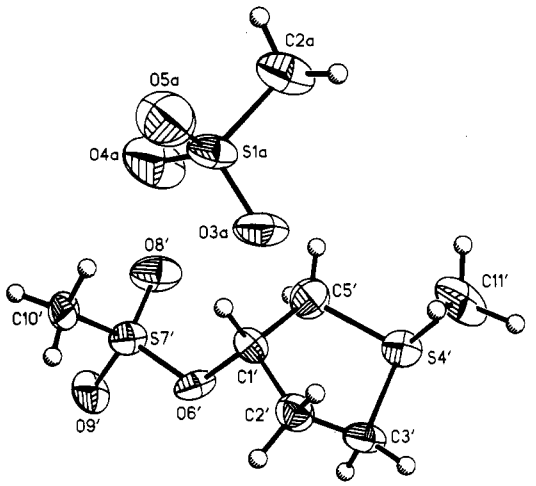
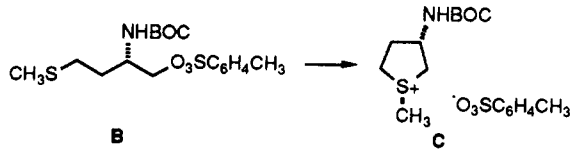


Figure 1.

(*R*)-hydroxy-1-[(*p*-tolylsulfonyl)oxy]-4-(methylthio)butane due to incomplete formation of ditosylate (*R*)-**7**.

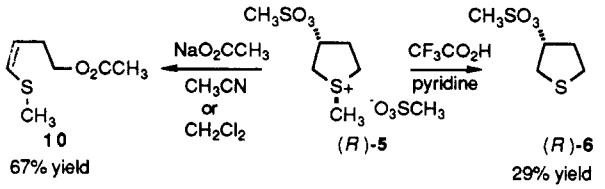
The absolute configuration of the major, optically active sulfonium salt was confirmed as trans by single-crystal X-ray analysis of 3(*S*)-[(methylsulfonyl)oxy]-1(*S*)-methylthiolanium methanesulfonate ((*S*)-**5**), which was made starting from the diazotization of L-methionine (Figure 1). The spectral data for the *S* intermediates were superimposable on those for the *R* intermediates.

N-BOC-L-methionine methyl ester has been converted over several steps into optically active thiolanium salt C by Otsuka et al.[6] The five-membered ring was formed as an 11:2 mixture of trans to cis isomers by cyclization of (*S*)-*tert*-butyl [1-(tosyloxy)-4-(methylthio)-2-butyl]carbamate (B), but they did not attempt to demethylate this sulfonium salt to afford the thiolane.

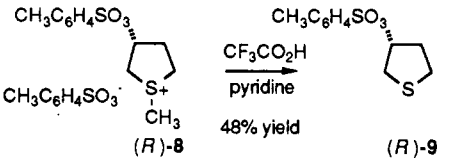


The final step in the thiolane synthesis required the selective demethylation of sulfonium salt (*R*)-**5** with a weak nucleophile that would not displace the sulfonate. Eliel and co-workers[7] had shown earlier that nucleophiles reacted with the parent *S*-methylthiolanium salt both at the ring methylene and the methyl group and that effective demethylation required substitution of both α methylenes with methyl groups as well as careful selection of the nucleophile. Also, both 1-methyl- and 1-ethylthiolanium salts have been used as reagents for the introduction of a 4-(methylthio)- or 4-(ethylthio)butyl group, respectively, via ring opening.[8]

The result of reaction of (*R*)-**5** with nucleophiles such as halide salts, acetate, and trifluoroacetate was found to depend upon solvent and conditions. Only the neutral reaction products that could be extracted into organic solvents were studied; materials that retained the sulfonium salt were water soluble and were not isolated. With either acetic or trifluoroacetic acid in pyridine at room temperature, the only nonpolar material isolated in 29% yield was the desired chiral thiolane mesylate (*R*)-**6**. Heating the reaction did not improve the yield and some 3-acetoxythiolane was formed.



In contrast, reaction of (*R*)-**5** with sodium acetate in either acetonitrile or methylene chloride at room temperature gave only the ring-opened product **10**, which was assigned by NMR as the cis isomer. In these solvents, sodium acetate was sufficiently basic to remove the acidic proton α to the sulfonium salt forming the ylide. The elimination of the mesylate from the ylide and nucleophilic attack at the other methylene group would give **10**. In the buffered trifluoroacetic acid/pyridine reaction, ylide formation was suppressed.



Seeking to improve the yield for the demethylation, we have found that the corresponding 1(*R*)-methyl-3(*R*)-[(*p*-tolylsulfonyl)oxy]thiolanium *p*-toluenesulfonate ((*R*)-**8**) was demethylated to 3(*R*)-[(*p*-tolylsulfonyl)oxy]thiolane ((*R*)-**9**) in 48% yield by trifluoroacetic acid in pyridine at room temperature, making this a practical process.

The thiolanes (*R*)-**6** and (*R*)-**9** were converted to the *trans*-sulfoxide with a peracid or potassium peroxymonosulfate[9] followed by reaction with potassium thioacetate to give A.[1]

Experimental Section

Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on either a Brucker WM 250 (250 MHz) or Brucker WM 300 (300 MHz) spectrometer in deuteriochloroform ($CDCl_3$) or deuterium oxide (D_2O). Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer. Mass spectra were determined with a Finnigan 4510 mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by the Analytical Chemistry Department, Pfizer Central Research. Lipase P was purchased from Amano Co. and 2-hydroxy-4-(methylthio)butyric acid calcium salt from Sigma Chemical Co.

Ethyl 2(*R*)-Hydroxy-4-(methylthio)butyrate ((*R*)-2) and 2(*S*)-Hydroxy-4-(methylthio)butanoic Acid ((*S*)-1). Racemic ethyl 2-hydroxy-4-(methylthio)butyrate (2 g, 11 mmol), prepared from the calcium salt by the method of Steadman,[5] was dissolved in toluene (20 mL) and water (40 mL). The pH was adjusted to 7.5 and Lipase P (0.2 g) was added. The reaction was stirred at room temperature and the pH was adjusted periodically to ca. 7.5 by the addition of 0.5 M NaOH. The extent of ester hydrolysis was estimated by the amount of NaOH used. When the desired conversion was achieved, the layers were separated. The ester was recovered from the toluene layer, while the aqueous layer was acidified to pH 1.5 and the acid extracted into ether. The ester was an oil that was suitable for use in the next step or could be purified by distillation. The acid was purified as its dicyclohexylamine salt from ether.[2] At ca. 60% hydrolysis, the ester (*R*)-**2** (0.77 g) was recovered in 38.5% yield: $[\alpha]_D$ +20.5° (c = 1.12, methanol); NMR ($CDCl_3$) δ 4.30–4.19 (m, 3), 2.68 (s, 1, OH), 2.60

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(9) Quallich, G. J. Private communication.

Table I. Single-Crystal X-ray Crystallographic Analysis

A. Crystal Parameters	
formula	$C_7H_{16}O_6S_3$ (292.4)
crystallization medium	2-propanol
crystal size, mm	0.14 × 0.16 × 0.34
cell dimensions	a = 5.934 (2) Å
	b = 6.959 (3) Å
	c = 15.494 (6) Å
	α = 81.18 (3)°
	β = 79.02 (3)°
	γ = 90.01 (3)°
	V = 620.4 (4) Å^3
space group	$P1$ (Z = 2)
molecules/unit cell	2
density calcd, g/cm^3	1.57
linear absorption factor, cm^{-1}	55.2
B. Refinement Parameters	
number of reflections	1323
nonzero reflections ($I > 3.0\sigma$)	1301
R index[a]	0.046
GOF[b]	1.13
scale factor	1.418 (2)
secondary extinction factor	NONE

[a] R index = $\sum||F_o| - |F_c||/\sum|F_o|$. [b] GOF = $[\sum w(F_o2 - F_c^2)^2/(m - s)]^{1/2}$ where $w = [\sigma^2(F) + |g|F^2]^{-1}$ and g = 0.00000.

(m, 3), 2.10 (s, 3, and m, 1), 1.91 (m, 1), 1.28 (t, 3). This was identical with the standard sample prepared from D-methionine according to ref 2. At ca. 40% hydrolysis, the dicyclohexylamine salt of (*S*)-**1** was isolated, 1.23 g, 33% yield: mp 127–9 °C; $[\alpha]_D$ −22.08° (c = 1.02, ethanol); [lit.[2] mp 128–9 °C; $[\alpha]_D$ −22.5° (c = 1, ethanol].

(*R*)-1,2-Dihydroxy-4-(methylthio)butane ((*R*)-3). The resolved ether ester (*R*)-**2** (8.19 g, 0.046 mol) in tetrahydrofuran (50 mL) and water (5 mL) was treated with sodium borohydride (2.1 g, 0.055 mol) at room temperature. After 18 h, the reaction was cooled in an ice bath while concentrated HCl (4.6 mL, 0.055 mol) was added dropwise. The reaction was concentrated in vacuo to remove most of the tetrahydrofuran and the residue was extracted with chloroform. The organic phase was washed with brine, dried over $MgSO_4$, and evaporated to an oil. The crude product was chromatographed over silica gel with $CHCl_3$/EtOAc (1/1 to 1/2) to afford the diol as a colorless oil, 4.4 g, 70% yield: $[\alpha]_D$ +39.9° (c = 1.62, methanol) [lit.[5] for *S*-diol $[\alpha]_D$ −41.4° (c = 2.5, methanol)]; NMR ($CDCl_3$) δ 1.67 (m, 2), 2.09 (s, 3), 2.60 (m, 2), 3.38–3.85 (m, 5).

(*R*)-1,2-Bis[(methylsulfonyl)oxy]-4-(methylthio)butane ((*R*)-4). (*R*)-**3** (2.14 g, 0.0157 mol) in dry pyridine (15 mL) at 10 °C was treated with methanesulfonyl chloride (4 g, 2.65 mL, 0.035 mol). After stirring at that temperature for 3.5 h, TLC (silica gel, ethyl acetate/hexanes, 1/1) showed that the reaction was complete. The reaction was diluted with ethyl acetate and washed with 1 N HCl (3 ×) and with brine, and dried over $MgSO_4$. The solution was filtered and was evaporated in vacuo to a faint yellow oil, 4.2 g, 91% yield. This material was characterized by NMR, although precipitation of the thiolanium salt was noted in the NMR tube and in the neat oil starting within an hour. NMR ($CDCl_3$): δ 5.01 (m, 1), 4.45 (q, 1), 4.30 (q, 1), 3.10 (s, 3), 3.08 (s, 3), 2.60 (m, 2), 2.10 (s over m, 4),1.98 (m, 1).

1(*R*)-Methyl-3(*R*)-[(methylsulfonyl)oxy]thiolanium Methanesulfonate ((*R*)-5). (*R*)-**4** (4.2 g, 0.014 mol) was refluxed in benzene for 8 h. The solvent was removed in vacuo and the residue was dissolved in hot isopropyl alcohol (20 mL) and allowed to stand at room temperature for 18 h. The crystalline product was recovered by filtration, washed with alcohol, and dried under high vacuum; 1.65 g, 39% yield; mp 132–4 °C; $[\alpha]_D$ +4.2° (c = 1.05, methanol); NMR (D_2O) δ 5.92 (m, 1), 4.20 (d, 1), 3.90–3.68 (m, 3), 3.32 (s, 3), 2.98 (s over m, 4), 2.83 (s, 3), 2.72 (m, 1). Anal. Calcd for $C_7H_{16}O_6S_3$: C, 28.76; H, 5.52. Found: C, 28.60; H, 5.64.

The filtrate was evaporated to dryness. NMR analysis indicated it was mainly a 2:1 mixture of the presumed cis isomer as the major component along with (*R*)-**5** and impurities.

1(*R*)-Methyl-3(*R*)-[(*p*-tolylsulfonyl)oxy]thiolanium *p*-Toluenesulfonate ((*R*)-8). Using the procedure described above for the synthesis of (*R*)-**5**, the diol (*R*)-**3** (0.4 g, 2.9 mmol) and *p*-toluenesulfonyl chloride (1.1 g, 6 mmol) were reacted in pyridine to give crude (*R*)-1,2-bis[(*p*-tolylsulfonyl)oxy]-4-(methylthio)butane ((*R*)-**7**), which was heated in benzene to yield 38% of (*R*)-**8** after recrystallization from ethyl acetate: mp 148–51 °C; $[\alpha]_D$ +7.34° (c = 1.04, methanol); NMR ($CDCl_3$) δ 7.75 (d, 2), 7.67 (d, 2), 7.33 (d, 2), 7.18 (d, 2), 5.50 (m, 1), 4.18 (dd, 1), 3.95 (d, 1), 3.72 (dd, 1), 3.48 (m, 1), 3.23 (s, 3), 2.70 (m, 1), 2.45 (m and s, 4), 2.35 (s, 3). Anal. Calcd for $C_{19}H_{24}O_6S_3$: C, 51.33; H, 5.44. Found: C, 50.67; H, 5.44.

Single-Crystal X-ray Analysis of (*S*)-5. A sample of 1-(*S*)-methyl-3(*S*)-[(methylsulfonyl)oxy]thiolanium methanesulfonate ((*S*)-**5**), prepared from L-methionine according to the above procedures, was submitted for a single-crystal X-ray study. A representative crystal was surveyed and a 1 Å data set (maximum sin θ/λ = 0.5) was collected on a Nicolet R3m/μ diffractometer. Atomic scattering factors were taken from the *International Tables for X-ray Crystallography*.[10] All crystallographic calculations were facilitated by the SHELXTL[11] system. All diffractometer data were collected at room temperature. Pertinent crystal, data collection, and refinement parameters are summarized in Table I.

A trial structure was obtained by direct methods. This trial structure refined routinely. Hydrogen positions were calculated wherever possible. The methyl hydrogens were located by difference Fourier techniques. The hydrogen parameters were added to the structure factor calculations but were not refined. The shifts calculated in the final cycle of least-squares refinement were all less than 0.1 of their corresponding standard deviations. The final R index was 0.046. A final difference Fourier revealed no missing or misplaced electron density.

The refined structure was plotted using the SHELXTL plotting package (Figure 1). The absolute configuration was determined by the method of Ibers and Hamilton.[12,13] Coordinates, anisotropic temperature factors, distances, and angles are available as supplementary material (TBles S1–S5).

3(*R*)-[(Methylsulfonyl)oxy]thiolane ((*R*)-6). The thiolanium salt (*R*)-**5** (0.21 g, 0.75 mmol) was added to a solution of trifluoroacetic acid (0.17 g, 0.115 mL, 1.5 mmol) in pyridine (2 mL). After the reaction was warmed briefly on a steam bath to give a solution, it was stirred overnight at room temperature. Ethyl acetate was added and the organics were washed with 1 N HCl (2×) and with brine and dried over $MgSO_4$. Evaporation of the ethyl acetate afforded (*R*)-**6** as an oil in high purity; 0.035 g, 29% yield. This was identical with the authentic sample.[1] $[\alpha]_D$ + 19.9° (c = 0.174, methanol); NMR ($CDCl_3$) δ 5.41 (m, 1), 3.19–2.90 (m with s at 3.04, 7), 2.46 (m, 1), 2.07 (m, 1).

3(*R*)-[(4-Tolylsulfonyl)oxy]thiolane ((*R*)-9). Following the same procedure with 1(*R*)-methyl-3(*R*)-[(*p*-tolylsulfonyl)oxy]-thiolanium *p*-toluenesulfonate ((*R*)-**8**) (0.145 g, 0.33 mmol) yielded 48% of (3*R*)-(*p*-tolylsulfonyl)oxy]thiolane ((*R*)-**9**) (0.040 g), identical with the authentic sample.[1] $[\alpha]_D$ + 16.76° (c = 0.63, methanol); NMR ($CDCl_3$) δ 7.79 (d, 2), 7.32 (d, 2), 5.18 (m, 1), 3.01–2.79 (m, 4), 2.44 (s, 3), 2.29 (m, 1), 1.92 (m, 1).

(*Z*)-1-Acetoxy-4-(methylthio)-3-butene (10). (*R*)-**5** (0.107 g, 0.37 mmol) and sodium acetate (0.1 g, 1 mmol) were stirred in methylene chloride (5 mL) at room temperature for 18 h. The solution was washed with water and with brine and dried over $MgSO_4$. Evaporation of the solvent gave **10** as an oil, 0.04 g, 67% yield: NMR ($CDCl_3$) δ 6.0 (dt, J = 9 and 1.4, 1), 5.50 (m, 1), 4.08 (t, J = 6.7, 2), 2.42 (dq, J = 6.9 and 1.4, 2), 2.25 (s, 3), 2.02 (s, 3); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 171.11, 129.73, 123.43, 63.14, 28.57, 20.98, 17.01.

Acknowledgment. We thank Dr. Jon Bordner for solving the single-crystal X-ray structure of (*S*)-**5**.

Supplementary Material Available: Tables of coordinates, antisotropic temperature factors, distances, and angles for (*S*)-**5** (5 pages). Ordering information is given on any current masthead page.

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