Articles

A Novel Synthetic Method of the (±)-(3aα,8aα)-Ethyl 8*β*-Hydroxy-6*β*-methyl-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate and Its Chemical Transformation to (±)-(3aα,8aα)-3α,6*β*-Dimethyl-3,3a,4,5,6,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one, (+)- and (−)-7*β*-(2-Acetoxy-1α-methylethyl)-4*β*-methyl-2-cyclohepten-1*β*-ol, and (+)- and (−)-7*β*-(2-Acetoxy-1α-methylethyl)-4*β*-methyl-2-cyclohepten-1-one. Possible Common Synthetic Intermediates for Pseudoguaianolides, 4,5-Secopseudoguaianolides, Guaianolides, 4,5-Secoguaianolides, and Octalactins

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The catalytic hydrogenation of ethyl 8-hydroxy-6-methyl-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (**6**), which was derived regioselectively from 4-methyltropolone (**1**) in four steps in 62% overall yield, gave (3aα,8aα)-ethyl 8*β*-hydroxy-6*β*-methyl-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**8b**) in 45% yield. It is noteworthy that four asymmetric centers newly introduced on the seven-membered ring of **8b** were controlled to be syn-oriented by the single operation. The latter was transformed to (3aα,8aα)-3α,6*β*-dimethyl-3,3a,4,5,6,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one (**17a**) in 77% overall yield in five steps. Reduction of **17a** with $LiAlH_4$ gave (±)-7*β*-(2-hydroxy-1α-methylethyl)-4*β*-methyl-2-cyclohepten-1*β*-ol (**22**), whose enantioselective acetylation was achieved by vinyl acetate in the presence of Lipase PS to give (+)-7*β*-(2-acetoxy-1α-methylethyl)-4*β*-methyl-2-cyclohepten-1*β*-ol (**24**) in 48% yield (93% ee) or in 52% yield (77% ee) and (−)-**22** in 52% yield (70% ee) or 44% yield (89% ee). Oxidation of (+)-**24** with MnO_2 gave (−)-7*β*-(2-acetoxy-1α-methyl ethyl)-4*β*-methyl-2-cyclohepten-1-one (−)-(**25**). Similarly, acetylation of (−)-**22** followed by oxidation of resulting (−)-**24** gave (+)-**25**.

Pseudoguaianolides, 4,5-secopseudoguaianolides, guaianolides, and 4,5-secoguaianolides are rapidly expanding groups of natural products comprising to date ca. 1000 varieties.[1] Some of them have been shown to exhibit high biological activities such as antitumor,[2−15] antiulcer,[15] cardiotonic,[15] antisistosomal,[2,16,17] anthelmintic,[18] contraceptive,[19,20] immunomodulation,[21] root-growth stimulatory,[2,22,23] root-growth and germination inhibitory activities,[2,3,12,13,14,24,25] and preventive or curative activities for

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crop diseases.[3,14] Although the total syntheses of these natural products were reported by many research groups,[26,27] their efficient and systematic syntheses from easily available compounds are still very important because of the diverse biological activities of these compounds and since they are available from natural sources often in only small quantities. A large number of pseudoguaianolides,[27] 4,5-secopseudoguaianolides, 4,5-secoguaianolides, and some guaianolides have a cis-fused α-methylene γ-lactone moiety at the C-6,7 position and a methyl group at C-10 which is oriented to the same side of the γ-lactone ring as a common structural feature. The stereocontrolled introduction of these groups at C-6,7 and C-10 is critical in the syntheses of these compounds.

Recently potent cytotoxic eight-membered lactones, octalactins A and B, were isolated from natural marine sources.[28] For the syntheses of these compounds, we envisioned Baeyer−Villiger oxidation of appropriately functionalized cycloheptanone derivatives mentioned below.

In connection with the general synthetic strategy of these natural products, we envisioned common synthetic intermediates **A**, **B**, and **C** by the retrosynthetic analyses (Figure 1). The intermediates may be prepared from compound **II**, whose all-cis stereochemistry of substituents on the seven-membered ring may be introduced by the catalytic hydrogenation of unsaturated γ-lactone derivative **I**. The regioselective synthesis of **I** may be achieved by the application of tropolone chemistry[29] from 4-methyltropolone (**1**).[30,31]

In this paper we report the result of the regio- and stereoselective syntheses of common synthetic intermedi-

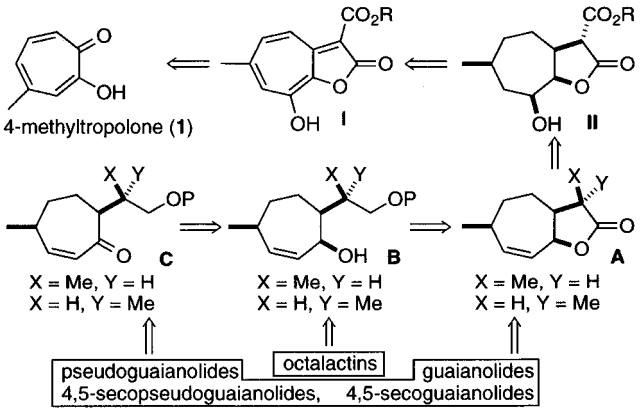
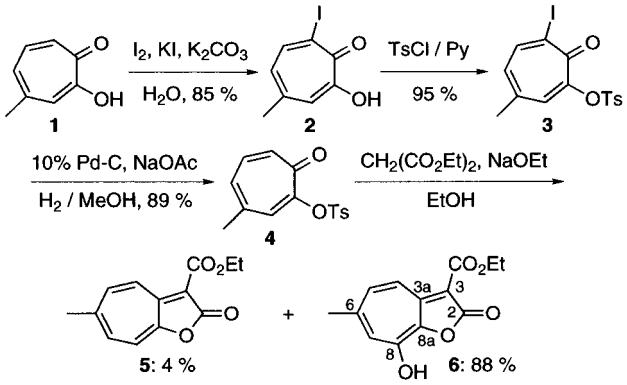


Figure 1. Retrosynthetic analyses and possible synthetic routes of natural products from common synthetic intermediates.

Figure 2. Rapid tautomeric mixtures of 4-methyltropolone (**1**) and 7-iodo-4-methyltropolone (**2**).

Scheme 1



ates **A**, **B**, and **C**. We also report the result of the syntheses of optically active intermediates **B** and **C** by the enantioselective acetylation of (±)-diol **B** (P = H) and subsequent oxidation of **B** (P = Ac).

Results and Discussion

Regioselective Synthesis of Ethyl 8-Hydroxy-6-methyl-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (6). We chose 4-methyltropolone (**1**) as a starting material on the basis of the above-mentioned retrosynthetic analyses and examined the regioselective synthesis of **6** via 4-methyl-2-(tosyloxy)tropone (**4**) (Scheme 1). The attempt of tosylation of **1** gave a 1:1 mixture of **4** and its regioisomer, 6-methyl-2-(tosyloxy)tropone. The result is well explained from the fact that **1** exists in a tautomeric mixture of **1a** and **1b** (Figure 2).[32] The regioselective tosylation of **1** to **4** was achieved via 7-iodo-4-methyltropolone (**2**), which was prepared by the treatment of **1** with I_2 in the presence of K_2CO_3 in H_2O in 85% yield. Tosylation of **2** gave 7-iodo-4-methyl-2-(tosyloxy)tropone

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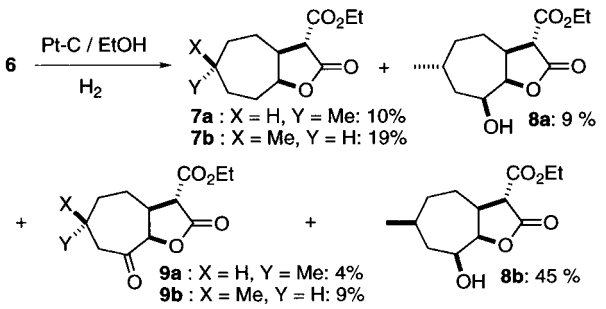
Scheme 2



(**3**) exclusively. The result was explained by the approach of TsCl from the less hindered hydroxyl group of **2a** in a tautomeric mixture of **2a** and **2b**. Hydrogenolysis of **3** in methanol in the presence of 10% Pd−C under H_2 gave the desired 4-methyl-2-(tosyloxy)tropone (**4**) in 89% yield. Condensation of **4** with diethyl malonate in ethanol in the presence of NaOEt gave **6** regioselectively in 88% yield.

Catalytic Hydrogenation of 6. We investigated the reduction conditions of **6** to (3aα,8aα)-ethyl 8*β*-hydroxy-6*β*-methyl-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**8b**) (Scheme 2). The best result was given by catalytic hydrogenation performed at atmospheric pressure in ethanol in the presence of Pt−C catalyst that was generated in the reaction mixture of 18% PtO_2 and 72% of activated carbon by weight on **6**. Under this condition, **6** gave the desired product **8b** in 45% yield accompanied by the minor five products, (3aα,8aα)-ethyl 6α-methyl-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**7a**) in 10% yield, (3aα,8aα)-ethyl 6*β*-methyl-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**7b**) in 19% yield, (3aα,8aα)-ethyl 8*β*-hydroxy-6α-methyl-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**8a**) in 9% yield, (3aα,8aα)-ethyl 6α-methyl-2,6-dioxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**9a**) in 4% yield, and (3aα,8aα)-ethyl 6*β*-methyl-2,6-dioxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**9b**) in 9% yield.

The minor products **7a** and **7b** were generated by the hydrogenolysis of C_8−OH group under this condition. The stereoselectivity of the cis *γ*-lactone moiety at the C-3a,8a position vs the methyl group at the remote C-6 position is 2:1 for the 8-deoxy derivatives **7b** and **7a**, 5:1 for 8-hydroxy derivatives **8b** and **8a**, and 2:1 for 8-oxo derivatives **9b** and **9a**, respectively, and the syn products were predominantly produced. The ratio of 8-deoxy derivatives **7a** and **7b** vs the 8-oxygenated compounds (8-hydroxy derivatives **8a** and **8b** plus 8-oxo derivatives **9a** and **9b**) is 1:2.3. The ratio depended on the pressure of H_2, and the yield of 8-deoxy derivatives (**7a** and **7b**) was increased to 50% and the yield of 8-oxygenated derivatives (**8a**, **8b**, **9a**, and **9b**) was decreased to 32% at 30 atm.

Although the yield of desired product **8b** was moderate and accompanied by five byproducts, **8b** was easily separated from the mixture by column chromatography and conveniently functionalized for the syntheses of a wide variety of natural products possessing seven-membered ring.[33]

Chemical Correlation and Stereochemistry of the Products of Catalytic Hydrogenation of 6. The stereochemistry of the products was determined by the following chemical transformation and the analyses of their NMR spectra. Oxidation of **8a** and **8b** with PCC

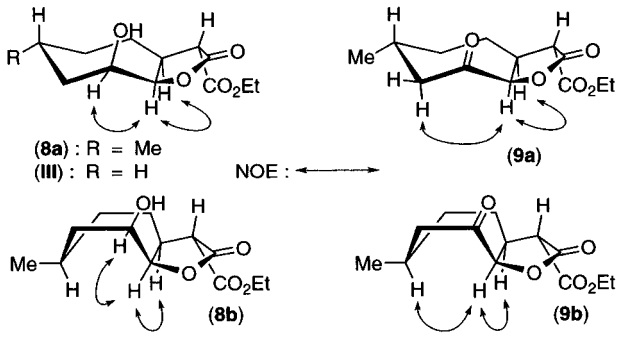


Figure 3. Stereostructure of compounds **III**, **8a**, **8b**, **9a**, and **9b** and the results of their NOE experiments.

gave **9a** and **9b** in 96% and 91% yields, respectively. The stereochemistry of the ring junction of these compounds was deduced to be cis from the coupling constant between C_{3a}-H and C_{8a}-H which was smaller than those of trans-fused compounds[34] and confirmed by the measurement of the NOE between C_{3a}-H and C_{8a}-H (Figure 3).

The stereochemistry of the substituent at C-3 of these compounds was deduced to be α-orientation by the fact that NOE between C_3-H and C_{3a}-H was not observed. The stereochemistry of the substituent at C-3 could not be determined by the coupling constant because this value was largely influenced by the mode of substitution at C-8 and the conformation of seven-membered as well as *γ*-lactone rings.[34] The stereochemistry of the substituent at C-3 of **8a** and **8b** was finally determined by the fact that the acid (HBr in acetic acid) or base (NaOEt in EtOH) treatment of **8a** and **8b** gave the recovery of starting material intactly. These experimental results strongly suggested that the compounds **8a** and **8b** were thermodynamically more stable than the corresponding C_3-epimers. The inspection of Dreiding model showed that the compounds possessing the substituent of α-configuration at C-3 were more stable than the corresponding *β*-epimers which had serious steric interaction between the C_3-substituent and the C_{3a}−C_4 bond.

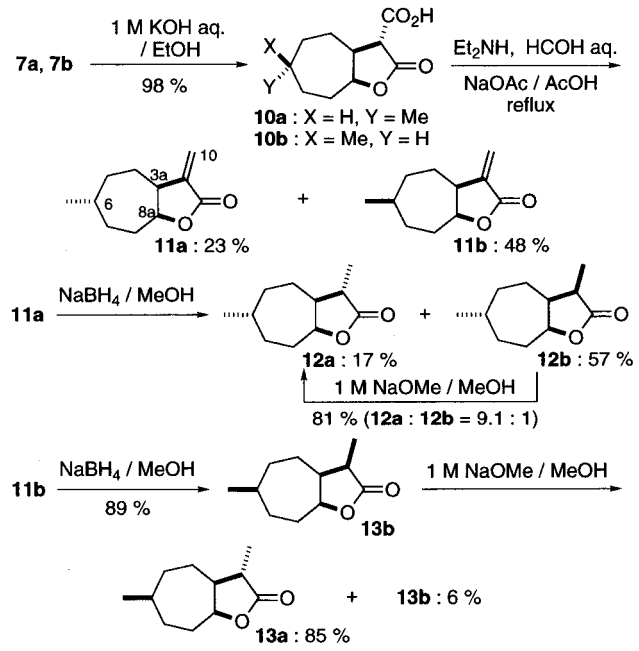
The stereochemistry of the hydroxyl group at C-8 of **8a** and **8b** was deduced to be the *β*-configuration from the values of the coupling constant between C_8-H and C_{8a}-H (J = 1.5 and 1.9 Hz, respectively) and the result of NOE experiments.

The stereochemistry of the methyl group at the C-6 position of **9b** was deduced to be the *β*-orientation from the fact that an NOE was observed between C_6-H and C_{8a}-H. The result of this NOE experiment and the chemical correlation between **8b** and **9b** suggested that the stereochemistry of the C-6 methyl group of **8b** was also the *β*-orientation. Since two pairs of compounds, (**8a**, **8b**) and (**9a**, **9b**), are stereoisomeric concerning the methyl group at C-6 from the result of the analyses of ^{1}H NMR spectra mentioned above, the C-6 methyl groups of **8a** and **9a** must be in the α-configuration, opposite to those of **8b** and **9b**. The ^{1}H NMR spectrum of **III**[34] resembles closely that of **8a** and differs from that of **8b**. This observation as well as the result of NOE experi-

(33) We have already completed the syntheses of two ambrosanolides, hymenolin and parthenin from the intermediate **C**, and the synthesis of the C-1−C-8 part of octalactins A and B (formal total syntheses of these compounds) from intermediate **B**. These results will appear in the following papers of this series.

(34) Ando, M.; Kataoka, N.; Yasunami, M.; Takase, K.; Hirata, N.; Yanagi, Y. *J. Org. Chem.* **1987**, *52*, 1429.

Scheme 3



ments suggests that the conformation of the seven-membered ring of **8a** is the chair form, the same as **III**, and that of **8b** is the boat form as depicted in Figure 3.

The stereochemistries of **7a** and **7b** were determined by chemical correlation with **8a** and **8b** (Scheme 3). Hydrolysis of an inseparable mixture of **7a** and **7b** (1:2) with a 1 M aqueous solution of KOH in ethanol followed by treatment with Et_2NH and 35% formalin in acetic acid gave α-methylene γ-lactones **11a** and **11b** in 23% and 48% yields. Reduction of **11a** with $NaBH_4$ gave an epimeric mixture of α-methyl γ-lactones, **12a** and **12b**, in 17% and 57% yields, respectively. Since the treatment of **12b** with 1 M NaOMe in MeOH gave a 9.1:1 mixture of **12a** and **12b**, the former was found to be the thermodynamically more stable 3α-methyl γ-lactone derivative.

Analogously, reduction of **11b** with $NaBH_4$ in MeOH gave **13b** as the sole isolated product in 89% yield. Since the treatment of **13b** with 1 M NaOMe in MeOH gave a 14.2:1 mixture of **13a** and **13b**, it was found that **13a** was the thermodynamically more stable 3α-isomer and **13b** was the thermodynamically less stable 3β-isomer. Catalytic hydrogenation of **17b** in a solution of benzene and ethanol in the presence of $(Ph_3P)_3RhCl$ gave **13b**. From this chemical correlation, the stereochemistry of the methyl group at C-6 of **7a** and **7b** was assigned to be the α- and β-orientation, respectively.

Syntheses of the Common Synthetic Intermediates of Types A, B, and C from 8b. Treatment of **8b** with 2.8 molar equiv of NaH in THF in the presence of 0.03 molar equiv of imidazole followed by 5 molar equiv of CS_2 and CH_3I resulted in concomitant introduction of the methyl group at C-3 and transformation of the C-8 hydroxyl group into a (methylthio)(thiocarbonyl)oxy group to give xanthate ester **14** (Scheme 4) in 91% yield.[35] The stereochemistry of the newly introduced methyl group at C-3 was deduced to be the α-configuration by the consideration that the reagent approached from the less hindered convex α-face of the enolate anion of the

(35) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

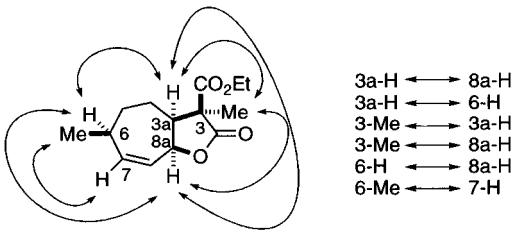
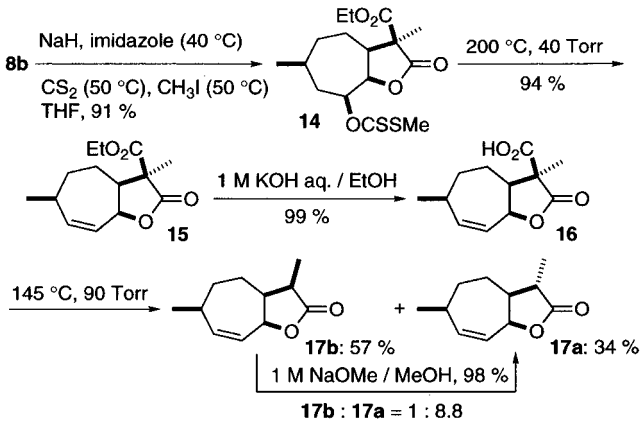


Figure 4. NOESY experiment of **15** at 500 MHz.

Scheme 4



substrate and finally confirmed by an NOESY experiment (Figure 4).

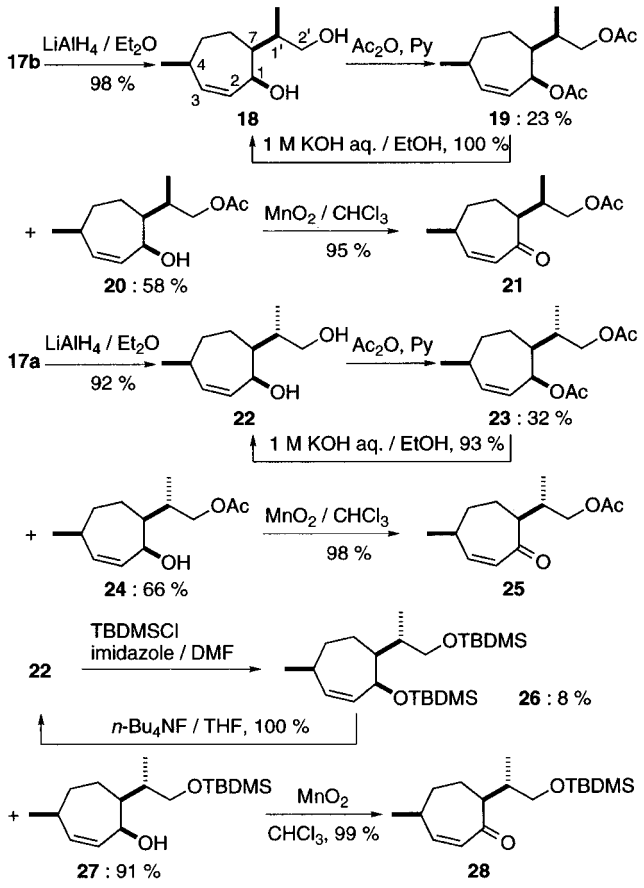
The pyrolysis of **14** at 200 °C under reduced pressure gave the desired 7,8-unsaturated γ-lactone **15** regioselectively in 94% yield. Hydrolysis of **15** with a 1 M aqueous solution of KOH in ethanol and successive thermal decarboxylation of the carboxylic acid **16** under reduced pressure gave a mixture of stereoisomers concerning C-3, **17a** and **17b**, in 34% and 57% yields, respectively. Since the treatment of **17b** with 1 M NaOMe in methanol gave an 8.8:1 mixture of **17a** and **17b**, it was found that **17a** was the thermodynamically more stable 3α-methyl γ-lactone and **17b** was the thermodynamically less stable 3β-methyl γ-lactone.

Reduction of **17b** with $LiAlH_4$ in ether gave the diol **18** in 98% yield (Scheme 5). Acetylation of **18** with Ac_2O and pyridine gave the desired monoacetate **20** in 58% yield accompanied by the undesired diacetate **19** in 23% yield. Since the latter was hydrolyzed with 1 M KOH in ethanol to give **18** in a quantitative yield, the undesired diacetate **19** could be recycled to **20**. Oxidation of **20** with MnO_2 in $CHCl_3$ gave the enone **21** in 95% yield. No change in configuration was observed in these three steps, and the stereochemistry at C-1′ of **18**, **19**, **20**, and **21** is the β-configuration.

Analogously reduction of **17a** with $LiAlH_4$ in ether gave the diol **22** in 92% yield. Acetylation of **22** with Ac_2O and pyridine gave the desired monoacetate **24** in 66% yield accompanied by the undesired diacetate **23** in 32% yield. The latter was recycled to **24** by hydrolysis and subsequent acetylation of resulting **22**. Oxidation of **24** with MnO_2 in $CHCl_3$ gave the enone **25** in 98% yield. The stereochemistry at C-1′ of **22**, **23**, **24**, and **25** is the α-configuration and opposite to that of the corresponding **18**, **19**, **20**, and **21**.

Then we attempted the selective silylation of the primary hydroxyl group of **22**. Silylation of **22** with *t*-$BuMe_2SiCl$ in DMF in the presence of imidazole gave

Scheme 5

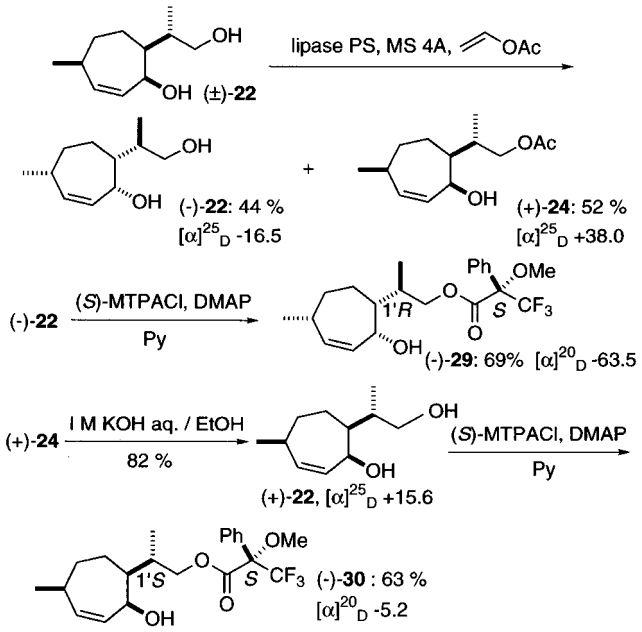


the desired monosilyl ether **27** in 91% yield accompanied by disilyl ether **26** in 8% yield. Oxidation of **27** with MnO_2 in $CHCl_3$ gave the desired enone **28** in a quantitative yield.

Syntheses of the Optically Active Compounds (+)- and (−)-22, (+)- and (−)-24, and (+)- and (−)-25. The optical resolution of (±)-**22** was achieved by enzymatic acetylation (Scheme 6). The most promising results were obtained with Lipase PS in an alcohol−lipase−sieves ratio (3.7:1.2:1) in vinyl acetate solution. The resolution was carried out at 23 °C, and the diol−monoacetate ratio was monitored by GC. The enantiomeric excess (ee) of the diol **22** and the monoacetate **24** in the reaction course was determined after the separation of a part of the reaction mixture by HPLC. The monoacetate (+)-**24** ($[\alpha]^{25}_D$ +46.1, 93% ee) and the diol (−)-**22** ($[\alpha]^{25}_D$ −13.0, 70% ee) were obtained in 48% and 52% yields, respectively, after 4.5 h. If we desired higher optical purity of diol (−)-**22**, we could get the desired (−)-**22** ($[\alpha]^{25}_D$ −16.5, 89% ee) in 44% yield by the prolongation of the reaction time accompanied by monoacetate (+)-**24** ($[\alpha]^{25}_D$ +38.0, 77% ee) in 52% yield. The absolute configuration and the optical yield were determined as follows.

(−)-**22** ($[\alpha]^{25}_D$ −16.5) was converted to the corresponding (*S*)-(−)-MTPA ester, (−)-**29**, according to Mosher's method[36] (Scheme 6). In the NMR spectra, the magnitude of lanthanide induced shift by Eu(fod)$_3$ for the OMe group of the (*S*)-(−)-MTPA ester of (1′*S*)-carbinol is expected to be larger than that of (1′*R*)-carbinol, since the (*S*)-(−)-MTPA ester of (1′*S*)-carbinol, (−)-**30**, forms a more stable Eu(fod)$_3$ complex than those of the (*S*)-(−)-MTPA ester of (1′*R*)-carbinol, (−)-**29**.[37] From the chemical shift and integration values of −OMe signals of (*S*,*R*) and (*S*,*S*) Mosher's esters, the stereochemistry of C-1′ and the enantiomeric excess of (−)-**22** were determined to be *R* and 89% ee. Since the relative stereochemistry of (±)-**22** has already been determined, the absolute configurations of (+)- and (−)-**22** were established as depicted in Scheme 6. This conclusion was also supported by the observed positive sign of the CD curve of *p*-bromobenzoate of (+)-**24**, which is in agreement with the expected sign from the exiton chirality rule applied to cyclic allylic alcohols.[38]

Scheme 6



The acetate, (+)-**24** ($[\alpha]^{25}_D$ +38.0), was hydrolyzed by a 1 M aqueous solution of KOH to give (+)-**22** ($[\alpha]^{25}_D$ +15.6), which was converted to the corresponding (*S*)-(−)-MTPA ester, (−)-**30**. By the analogous method mentioned above, the stereochemistry of C-1′ and the enantiomeric excess of (+)-**24** were determined to be *S* and 77% ee.

Oxidation of (+)-**24**, which was obtained by the above-mentioned enzymatic acetylation, with MnO_2 in $CHCl_3$ gave (−)-**25** ($[\alpha]^{20}_D$ −108.4) in 91% yield (Scheme 7). Analogously, acetylation of (−)-**22**, which was obtained by the enzymatic acetylation mentioned above as the recovered diol, and subsequent oxidation of the resulting monoacetate (−)-**24** ($[\alpha]^{25}_D$ −45.3) with MnO_2 in $CHCl_3$ gave (+)-**25** ($[\alpha]^{20}_D$ +129.6) in 55% overall yield.

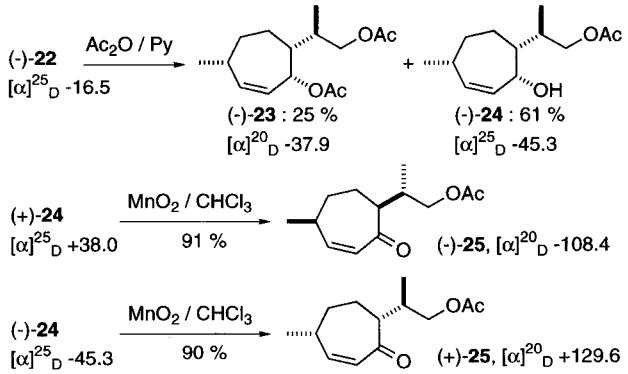
Biological Activities. 1. Cell Growth Inhibitory Activity of Compounds to P-388 Lymphocytic Leukemia.[39] The compounds **11a** and **11b** showed signifi-

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

(37) (a) Yasuhara, F.; Yamaguchi, S. *Tetrahedron Lett.* **1977**, 4085. (b) Yamaguchi, S. *Asymmetric Synthesis*, Vol. 1; Morrison, J. D., Ed.; Academic Press: 1983, pp 125−152. (c) Sugimoto, Y.; Sakita, T., Moriyama, Y.; Murae, T.; Tsuyuki, T.; Takahashi, T. *Tetrahedron Lett.* **1978**, 4285. (d) Sugimoto, Y.; Sakita, T.; Ikeda, T.; Moriyama, Y.; Murae, T.; Tsuyuki, T.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 3027. (e) Sugimoto, Y.; Tsuyuki, T.; Moriyama, Y.; Takahashi, T. *Bull. Chem. Soc. Jpn.* **1980**, *52*, 3027.

(38) (a) Harada, N.; Iwabuchi, J.; Yokota, Y.; Uda, H.; Nakanishi, K. *J. Am. Chem. Soc.* **1981**, *103*, 5590. (b) Nakanishi, K.; Berova, N. *Circular Dichroism, Principles and Applications*, Chapter 10; Nakanishi, K., Berova, N., Woody, R. W., Eds.; VCP Publishers: Cambridge, U.K., 1994, and references cited therein.

Scheme 7



cant cell growth inhibitory activity against murine lymphocytic leukemia (P-388) in vitro. The growth inhibition ratios of **11a** and **11b** are 50% and 69% at a concentration of 1 μg/mL, respectively.

2. Control of Crop Diseases.[40] The preventive and curative activities in controlling crop diseases were examined by pot test. The α-methylene γ-lactones **11a** and **11b** showed significant preventive activities in controlling damping-off of cucumber caused by *Pythium aphanidermatum*. The evaluation of disease control is 70−80% for **11a** and 100% for **11b** at 500 ppm.

3. Herbicide Test.[41] The α-methylene γ-lactone **11b** showed significant growth inhibitory activity against *Echinochloa flumentacea* (Japanese millet) and *Avena sativa* (oat) in field. The evaluation of the growth inhibition was 100% for *E. flumentacea* and 70−80% for *A. sativa* at a concentration of 8 g per 100 m^2 by posttreatment.

Experimental Section

General Experimental Procedure. All melting points are uncorrected. ^{1}H NMR spectra were recorded at 200 MHz and ^{13}C NMR spectra at 50 MHz in $CDCl_3$ unless otherwise stated. The assignments of ^{1}H NMR spectra were determined by decoupling and H−H COSY experiments. The assignments of ^{13}C NMR spectra were determined by DEPT, C−H COSY, HMQC, and HMBC experiments. Reactions were run under an atmosphere of N_2 or Ar. THF and ether were distilled from sodium benzophenone ketyl. $CHCl_3$ was dried over $CaCl_2$ and distilled. Benzene was dried over $CaCl_2$, distilled, and stored in a bottle with Na wire equipped with a mercury seal. CH_2Cl_2, DMF, and pyridine were distilled from CaH_2. MeOH and EtOH were distilled from $Mg(OMe)_2$ and $Mg(OEt)_2$, respectively. To describe HPLC conditions, the column, solvent, and flow rate are designated in this order. The column codes are as follows: A, 30 × 2 cm i.d. stainless column packed with 15−25 μm silica gel; B, 25 × 0.8 cm i.d. stainless column packed with 10 μm silica gel; C, 30 × 1 cm i.d. glass column packed with 10 μm silica gel; D, 25 × 0.4 cm i.d. stainless column packed with 10 μm silica gel. Silica gel (230−400 mesh) was employed for flash chromatography, and 70−230 mesh silica gel was employed for column chromatography. To describe the conditions of column and flash chromatographies, the weight of silica gel, column i.d., and solvent are designated in this order.

7-Iodo-4-methyltropolone (2). Into a stirred solution of 4-methyltropolone (50 g, 0.367 mol) and K_2CO_3 (104.7 g, 0.754 mol) in H_2O (750 mL) was slowly added a solution of I_2 (95.3 g, 0.376 mol) and KI (102.8 g, 0.616 mol) in H_2O (300 mL) at 0 °C. The mixture was stirred at rt for 20 h and filtered. The crystalline material separated by filtration was dissolved in $CHCl_3$ (500 mL) and stirred for 1 h with a mixture of $NaHSO_3$ (3.5 g, 19.7 mmol), 6 M H_2SO_4 (290 mL), and H_2O (80 mL). The chloroform layer was dried (Na_2SO_4) and concentrated. The residue was dissolved in MeOH (200 mL) and treated with activated carbon (10 g) at the refluxing temperature. The mixture was filtered and concentrated to give spectroscopically pure **2** (46.0 g, 48%).

The aqueous layer was also treated with a mixture of $NaHSO_3$ (10.0 g, 56.2 mmol) and 6 M H_2SO_4 (200 mL) at pH 1−2 and extracted with $CHCl_3$. The extracts were treated in the above-mentioned manner to give additional **2** (35.8 g, 37%) as a spectroscopically pure crystalline material.

The analytical sample of **2** was obtained by recrystallization from Et_2O as pale brown prisms: mp 118−120 °C; IR ($CHCl_3$) 3012, 1612 cm^{-1}; ^{1}H NMR δ 2.45 (3 H, s, C_4-Me), 6.59 (1 H, dd, J = 10.6, 1.0 Hz, C_5-H), 7.26 (1 H, br s, C_3-H), 8.32 (1 H, d, J = 10.6 Hz, C_6-H); ^{13}C NMR δ 14.7 (q, C_4-Me), 106.5 (s, C-7), 121.5 (d, C-3), 127.8 (d, C-5), 147.9 (d, C-6), 150.1 (s, C-4), 161.6 (s, C-2), 172.2 (s, C-1). Anal. Calcd for $C_8H_7O_2I$: C, 36.67; H, 2.69. Found: C, 36.86; H, 2.69.

7-Iodo-4-methyl-2-(tosyloxy)tropone (3). Into a stirred solution of **2** (90.0 g, 0.343 mol) in pyridine (850 mL) was added TsCl (115.5 g, 0.515 mol) at 0 °C. The solution was stirred at 0 °C for 3 h and then at rt for 11 h and poured into cold water (10 L) under vigorous stirring. The pale brown crystalline material was collected by filtration under reduced pressure and dried in a desiccator under reduced pressure to give spectroscopically pure **3** (136.2 g, 0.327 mol, 95%) as a crystalline material. A part of this crystalline material was recrystallized from Et_2O to give pale brown microcrystals: mp 140−142 °C; IR (KBr) 1604, 1380, 1360, 1182 cm^{-1}; ^{1}H NMR δ 2.36 (3 H, s, C_4-Me), 2.46 (3 H, s, Ts-Me), 6.60 (1 H, dd, J = 9.6, 1.3 Hz, C_5-H), 7.36 (2 H, d, J = 8.4 Hz, *m*-Hs of Ph), 7.44 (1 H, d, J = 1.3 Hz, C_3-H), 7.94 (2 H, d, J = 8.4 Hz, *o*-Hs of Ph), 8.38 (1 H, d, J = 9.6 Hz, C_6-H); ^{13}C NMR δ 21.8 (q, Ts-Me), 26.2 (q, C_4-Me), 122.9 (s, C-7), 128.7 (d, C-2′ of Ph), 129.7 (d, C-3′ of Ph), 131.6 (d, C-5), 132.9 (s, C-1′ of Ph), 133.1 (d, C-3), 143.2 (s, C-4), 145.7 (s, C-4′ of Ph), 146.9 (d, C-6), 147.1 (s, C-2), 174.6 (s, C-1). Anal. Calcd for $C_{15}H_{13}O_4SI$: C, 43.28; H, 3.14. Found: C, 43.55; H, 3.26.

4-Methyl-2-(tosyloxy)tropone (4). A mixture of **3** (50.0 g, 0.120 mol), 10% Pd−C (5.0 g), NaOAc (15.1 g, 0.180 mol), and MeOH (1.5 L) was stirred vigorously under 1 atm of H_2. Hydrogen uptake (3.2 L, 0.14 mol) was ceased after 80 min, and the mixture was filtered through Celite. The filtrate was concentrated to 300 mL and poured into water (1.3 L). The crystalline material was filtered under reduced pressure to give spectroscopically pure **4** (31.1 g, 89%) as a pale brown crystalline material, a part of which was recrystallized from Et_2O to give pale brown microcrystals: mp 110 °C; IR (KBr) 1636, 1602, 1584, 1366, 1192 cm^{-1}; ^{1}H NMR δ 2.39 (3 H, s, C_4-Me), 2.45 (3 H, s, Ts-Me), 6.94 (1 H, ddd, J = 8.0, 2.8, 1.4 Hz, C_5-H), 7.02 (1 H, dd, J = 12.0, 2.8 Hz, C_7-H), 7.11 (1 H, d, J = 12.0, 8.0 Hz, C_6-H), 7.36 (2 H, d, J = 8.4 Hz, *m*-Hs of Ph), 7.39 (1 H, d, J = 1.4 Hz, C_3-H), 7.95 (2 H, d, J = 8.4 Hz, *o*-Hs of Ph); ^{13}C NMR δ 21.8 (q, Ts-Me), 26.5 (q, C_4-Me), 128.6 (d, C-2′ of Ph), 129.6 (d, C-3′ of Ph), 133.0 (d, C-5), 133.5 (s, C-1′ of Ph), 133.8 (d, C-3), 136.6 (d, C-7), 138.8 (d, C-6), 142.3 (s,

(39) Murine lymphocytic leukemia cells (p388) were incubated with compounds at 37 °C in a humidified atmosphere of 5% CO_2 for 48 h. After incubation, the cell number was counted with a Coulter counter, and the cell growth inhibition ratio (%) was calculated according to

$$\text{cell growth inhibition ratio} = \left(1 - \frac{T - C_0}{C - C_0}\right) \times 100$$

where T = cell count after culture with compound, C = cell count after culture without compound, and C_0 = cell count at the start of culture.

(40) Test samples, which were formulated as emulsifiable in water, were applied by spraying to the plants or drenching to soil before or after incubation. The plants were inoculated with spores or hypa of fungal pathogens. After incubation, disease severity of test plants was observed under desirable conditions for 4−15 days. The tested crop diseases are as follows; blast of rice, sheath blight of rice, powdery mildew of wheat, damping off of cucumber, dawny mildew of grape, late blight of tomato, scab of apple.

(41) In 8−10 days after sowing, test samples, which were formulated as emulsifiable in water, were applied by spraying to the plants and the degree of the growth inhibition of plants was observed.

C-4), 145.4 (s, C-4′ of Ph), 153.8 (s, C-2), 178.8 (s, C-1). Anal. Calcd for $C_{15}H_{14}O_4S$: C, 62.05; H, 4.86. Found: C, 61.91; H, 4.86.

Ethyl 6-Methyl-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (5) and Ethyl 8-Hydroxy-6-methyl-2-oxo-2*H*-cyclohepta[*b*]furan-3-carboxylate (6). To a stirred solution of **4** (44.0 g, 0.152 mol) and diethyl malonate (45.3 mL, 0.300 mol) in EtOH (200 mL) was added a 1 M solution of NaOEt in EtOH (300 mL, 0.300 mol). The solution was stirred at 0 °C for 20 min, stored in a refrigerator overnight, poured into water (2 L), and extracted with benzene. The combined extracts were washed with a saturated aqueous solution of NaCl, dried (Na_2SO_4), and concentrated to 50 mL. The residue was diluted with ether to give spectroscopically pure **5** (1.50 g, 4%). A part of **5** was recrystallized from MeOH to give yellow prisms: mp 144 °C. Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.29; H, 5.29.

The aqueous layer was adjusted at pH 3 with 6 M HCl (90 mL) to form a yellow crystalline material, which was separated by filtration, washed with water, and dried to give spectroscopically pure **6** (32.9 g, 88%), a part of which was recrystallized from EtOH to give yellow microcrystals: mp 186 °C; IR (KBr) 3460, 1745, 1734, 1684 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.29 (3 H, t, J = 7.1 Hz, Et-C**H**$_3$), 2.50 (3 H, s, C_6-Me), 4.23 (2 H, q, J = 7.1 Hz, Et-C**H**$_2$), 7.48 (1 H, br s, C_7-H), 7.55 (1 H, d, J = 11.4 Hz, C_5-H), 8.62 (1 H, d, J = 11.4 Hz, C_4-H); ^{13}C NMR (DMSO-d_6) δ 14.3 (q, Et-**C**H$_3$), 26.8 (q, C_6-Me), 59.0 (t, Et-**C**H$_2$), 88.8 (s, C-8a), 129.3 (d, C-4), 130.4 (d, C-7), 138.9 (d, C-5), 141.9 (s), 146.2 (s, C-6), 148.7 (s), 150.7 (s), 163.6 (s), 164.1 (s). Anal. Calcd for $C_{13}H_{12}O_5$: C, 62.90; H, 4.87. Found: C, 63.10; H, 4.94.

Catalytic Hydrogenation of 6. A mixture of **6** (10.0 g, 40.3 mmol), PtO_2 (1.8 g), and activated carbon (7.2 g) in EtOH (590 mL) was stirred vigorously under 1 atm of hydrogen. Hydrogen uptake (6.5 L) ceased after 2 h and 50 min, and the mixture was filtered. The filtrate was concentrated under reduced pressure to give an oily crude product (ca. 12 g), which was subsequently chromatographed over silica gel [350 g; 6.5 cm i.d.; EtOAc−hexane (2:8)].

The first fraction gave an inseparable 1:2 mixture of (±)-(3aα,8aα)-ethyl 6α-methyl-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**7a**) and (±)-(3aα,8aα)-ethyl 6*β*-methyl-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**7b**) (2.8 g, 29%) as a colorless oil. The elemental analysis of the mixture was performed instead of those of pure **7a** and **7b**. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.77; H, 8.62.

The second fraction gave spectroscopically pure (±)-(3aα,8aα)-ethyl 8*β*-hydroxy-6α-methyl-2-oxooctahydro-2*H*-cyclohepta[*b*]-furan-3α-carboxylate (**8a**) (970 mg, 9%) as a crystalline material, which was recrystallized from a mixture of EtOAc−hexane to give colorless needles: mp 78−80 °C. Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.80; H, 8.16.

The third fraction gave a 1:2 mixture of (±)-(3aα,8aα)-ethyl 6α-methyl-2,8-dioxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**9a**) and (±)-(3aα,8aα)-ethyl 6*β*-methyl-2,8-dioxooctahydro-2*H*-cyclohepta[*b*]furan-3α-carboxylate (**9b**) (1.33 g, 13%) as a crystalline material. The repeated separation of this mixture by HPLC [column D; EtOAc−hexane (3:7); 3.0 mL/min] gave pure **9b** (faster running) and **9a** (slower running). **9a**: colorless prisms ($CHCl_3$): mp 55−57 °C. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.13. Found: C, 61.11; H, 7.11. **9b**: colorless needles (EtOAc−hexane): mp 71−72 °C. Anal. Calcd for $C_{13}H_{18}O_5$: C, 61.41; H, 7.13. Found: C, 61.13; H, 7.09.

The fourth fraction gave spectroscopically pure (±)-(3aα,8aα)-ethyl 8*β*-hydroxy-6*β*-methyl-2-oxooctahydro-2*H*-cyclohepta[*b*]-furan-3α-carboxylate (**8b**) (4.61 g, 45%) as colorless plates (EtOAc−hexane): mp 58−60 °C; IR ($CHCl_3$) 3500, 1782, 1736 cm^{-1}; ^1H NMR δ 0.99 (3 H, d, J = 6.1 Hz, C_6-Me), 1.32 (3 H, t, J = 7.2 Hz, Et-C**H**$_3$), 3.16 (1 H, dddd, J = 8.5, 6.1, 6.1, 4.7 Hz, C_{3a}-H), 3.46 (1 H, d, J = 6.1 Hz, C_3-H), 4.06 (1 H, br d, J = 8.6 Hz, C_8-H), 4.26 (2 H, q, J = 7.2 Hz, Et-C**H**$_2$), 4.95 (1 H, dd, J = 8.5, 1.9 Hz, C_{8a}-H); ^{13}C NMR δ 14.1 (q, Et-**C**H$_3$), 22.9 (q, C_6-Me), 27.7 (t), 31.7 (t), 32.3 (d, C-6), 39.4 (t), 39.8 (d, C-3a), 53.5 (d, C-3), 62.3 (t, Et-**C**H$_2$), 71.5 (d, C-8), 85.5 (d, C-8a), 167.9 (s), 171.8 (s). Anal. Calcd for $C_{13}H_{20}O_5$: C, 60.92; H, 7.87. Found: C, 60.68; H, 8.21.

(±)-(3aα,8aα)-Ethyl 8*β*-((Methylthio)(thiocarbonyl)-oxy)-3α,6*β*-dimethyl-2-oxooctahydro-2*H*-cyclohepta[*b*]furan-3*β*-carboxylate (14). A solution of **8b** (930 mg, 3.63 mmol) in THF (45 mL) containing imidazole (7.6 mg, 0.11 mmol) was slowly added to NaH [prepared from 55% NaH dispersion in mineral oil (455 mg, 1.02 mmol) by being washed with pentane] and stirred at 40 °C for 2.5 h. Then CS_2 (1.11 mL, 18.3 mmol) was added into the mixture, and the solution was stirred at 50 °C for 30 min. Finally MeI (1.14 mL, 18.2 mmol) was added into the mixture, and the solution was stirred at 50 °C for 30 min. After cooling, the reaction was quenched by the addition of AcOH (0.6 mL). The mixture was worked up as usual to give an oily crude product (1.43 g), which was chromatographed over silica gel [45 g; 3.1 cm i.d.; EtOAc−hexane (3:7)] to give **14** (1.19 g, 91%) as colorless prisms (ether−hexane): mp 107−108 °C; IR ($CHCl_3$) 1790, 1734 cm^{-1}; ^1H NMR δ 0.97 (3 H, d, J = 6.5 Hz, C_6-Me), 1.32 (3 H, t, J = 7.2 Hz, Et-C**H**$_3$), 1.63 (3 H, s, C_3-Me), 1.89 (1 H, m, C_7-H), 2.08 (1 H, m, C_7-H), 2.58 (3 H, s, OCS_2C**H**$_3$), 2.63 (1 H, m, C_{3a}-H), 4.25 (1 H, dq, J = 11.7, 7.2 Hz, Et-C**H**$_2$), 4.29 (1 H, dq, J = 11.7, 7.2 Hz, Et-C**H**$_2$), 4.99 (1 H, br d, J = 6.7 Hz, C_{8a}-H), 5.95 (1 H, dd, J = 11.4, 1.7 Hz, C_8-H); ^{13}C NMR δ 14.0 (q, Et-**C**H$_3$), 18.9 (q, C_3-Me), 21.5 (q, C_6-Me), 22.7 (q, OCS_2**C**H$_3$), 27.2 (t), 31.6 (t), 33.1 (d, C-6), 35.1 (t), 47.2 (d, C-3a), 55.0 (s, C-3), 61.8 (t, Et-**C**H$_2$), 80.9 (d), 81.4 (d), 169.1 (s, **C**O$_2$Et), 174.8 (s, C-2), 215.2 (s, O**C**S$_2$CH$_3$). Anal. Calcd for $C_{16}H_{24}O_5S_2$: C, 53.31; H, 6.71. Found: C, 53.76; H, 6.92.

(±)-(3aα,8aα) Ethyl 3α,6*β*-Dimethyl-2-oxo-3,3a,4,5,6,8a-hexahydro-2*H*-cyclohepta[*b*]furan-3*β*-carboxylate (15). Xanthate **14** (2.14 g, 5.94 mmol) in Kügelrohr distillation apparatus was heated at 200 °C for 10 h under reduced pressure (40 Torr) and then distilled at this temperature at 2 Torr to give a pale yellow oil, which was purified by flash chromatography [15 g; 2.2 cm i.d.; EtOAc−hexane (1:9)] to give a crystalline material, which was recrystallized from a mixture of EtOAc−hexane to give **15** (1.41 g, 94%) as colorless needles: mp 53−54 °C; IR ($CHCl_3$) 1775, 1742 cm^{-1}; ^1H NMR δ 1.06 (3 H, d, J = 6.8 Hz, C_6-Me), 1.27 (3 H, t, J = 7.2 Hz, Et-C**H**$_3$), 1.48 (3H, s, C_3-Me), 2.37 (1 H, m, C_6-H), 2.41 (1 H, ddd, J = 13.0, 9.2, 4.0 Hz, C_{3a}-H), 4.14 (1 H, dq, J = 11.0, 7.2 Hz, Et-C**H**$_2$), 4.21 (1 H, dq, J = 11.0, 7.2 Hz, Et-C**H**$_2$), 5.34 (1 H, ddd, J = 10.5, 5.5, 3.0 Hz, C_7-H), 5.40 (1 H, dddd, J = 9.2, 3.0, 3.0, 1.4 Hz, C_{8a}-H), 5.64 (1 H, ddd, J = 10.5, 3.3, 2.2 Hz, C_8-H); ^{13}C NMR δ 14.0 (q, Et-**C**H$_3$), 20.6 (q, C_3-Me), 21.4 (q, C_6-Me), 22.8 (t), 29.2 (t), 31.3 (d, C-6), 47.3 (d, C-3a), 54.1 (s, C-3), 61.7 (t, Et-**C**H$_2$), 78.5 (d, C-8a), 127.2 (d, C-8), 132.8 (d, C-7), 169.5 (s, **C**O$_2$Et), 176.1 (s, C-2). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.64; H, 7.99. Found: C, 66.68; H, 8.13.

(±)-(3aα,8aα)-3α,6*β*-Dimethyl-2-oxo-3,3a,4,5,6,8a-hexahydro-2*H*-cyclohepta[*b*]furan-3*β*-carboxylic Acid (16). A solution of **15** (3.52 g, 14.0 mmol) and a 1 M aqueous solution of KOH (28 mL) in ethanol (55 mL) was stirred at rt for 4 h, poured into a mixture of 2 M aqueous solution of HCl (28 mL) and a saturated aqueous solution of NaCl (250 mL), and extracted with EtOAc. The combined extracts were treated in the usual manner to give **16** (3.11 g, 99%) as colorless needles ($CHCl_3$): mp 109−111 °C; IR (KBr) 3500−2300, 1775, 1715 cm^{-1}; ^1H NMR δ 1.07 (3 H, d, J = 6.8 Hz, C_6-Me), 1.44 (3 H, s, C_3-Me), 2.45 (1 H, m, C_6-H), 3.02 (1 H, ddd, J = 10.5, 7.8, 4.9 Hz, C_{3a}-H), 5.40−5.62 (3 H, C_7-, C_8-, and C_{8a}-Hs), 8.91 (1 H, br s, CO_2**H**); ^{13}C NMR δ 16.5 (q, C_3-Me), 20.9 (t), 21.2 (q, C_6-Me), 30.0 (t), 31.1 (d, C-6), 44.2 (d, C-3a), 54.3 (s, C-3), 80.1 (d, C-8a), 125.0 (d, C-8), 135.0 (d, C-7), 175.3 (s), 176.1 (s). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.27; H, 7.19. Found: C, 64.00; H, 7.35.

(±)-(3aα,8aα)-3α,6*β*-Dimethyl-3,3a,4,5,6,8a-hexahydro-2*H*-cyclohepta[*b*]furan-2-one (17a) and (±)-(3aα,8aα)-3*β*,6*β*-Dimethyl-3,3a,4,5,6,8a-hexahydro-2*H*-cyclohepta-[*b*]furan-2-one (17b). The carboxylic acid **16** (517 mg, 2.31 mmol) was heated in a Kügelrohr distillation apparatus at 145 °C (90 Torr). After evolution of CO_2 ceased in 35 min, the residue was distilled under reduced pressure (1 Torr) at 145

°C to give a 1:1.7 mixture of **17a** and **17b** (513 mg), which was separated by HPLC [column A; EtOAc−hexane (1:9); 28.5 mL/min].

The first peak (t_R 7.4 min) gave **17a** (141 mg, 34%) as colorless oil: IR ($CHCl_3$) 3028, 1772, 1668 cm^{-1}; ^1H NMR δ 1.07 (3 H, d, J = 7.0 Hz, C_6-Me), 1.24 (3 H, d, J = 6.9 Hz, C_3-Me), 2.25−2.38 (2 H, C_3-, and C_{3a}-Hs), 2.40 (1 H, m, C_6-H), 5.32 (1 H, ddd, J = 8.0, 4.3, 2.8 Hz, C_{8a}-H), 5.41 (1 H, ddd, J = 11.0, 4.3, 2.3 Hz, C_7-H), 5.53 (1 H, ddd, J = 11.0, 2.8, 1.8 Hz, C_8-H); ^{13}C NMR δ 14.3 (q, C_3-Me), 21.8 (q, C_6-Me), 26.5 (t), 29.8 (t), 32.6 (d, C-6), 40.6 (d), 44.6 (d), 79.4 (d, C-8a), 126.4 (d, C-8), 135.0 (d, C-7), 179.3 (s, C-2). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.15; H, 9.14.

The second peak (t_R 12.0 min) gave spectroscopically pure **17b** (238 mg, 57%) as a colorless crystalline material, which was recrystallized from EtOAc−hexane to give colorless needles: mp 32.5−33.0 °C; IR (KBr) 3050, 1768 cm^{-1}; ^1H NMR δ 1.04 (3 H, d, J = 6.8 Hz, C_6-Me), 1.18 (3 H, d, J = 7.3 Hz, C_3-Me), 2.49 (1 H, m, C_6-H), 2.65 (1 H, m, C_{3a}-H), 2.86 (1 H, dq, J = 7.3, 7.3 Hz, C_3-H), 5.24 (1 H, br dd, J = 6.0, 2.0 Hz, C_{8a}-H), 5.47 (1 H, ddd, J = 11,2, 5.2, 2.0 Hz, C_7-H), 5.60 (1 H, ddd, J = 11.2, 2.0, 2.0 Hz, C_8-H); ^{13}C NMR δ 10.7 (q, C_3-Me), 19.5 (t), 21.1 (q, C_6-Me), 30.2 (d, C-6), 31.6 (t), 39.5 (d), 40.8 (d), 81.1 (d, C-8a), 124.6 (d, C-8), 135.8 (d, C-7), 178.6 (s, C-2). Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 72.93; H, 8.94.

Isomerization of (±)-17b. A solution of **17b** (2.82 g, 15.7 mmol) in 1 M NaOMe/MeOH (50 mL) was stirred at rt for 4 h and poured into a mixture of 2 M HCl (30 mL) and a saturated aqueous solution of NaCl (70 mL). The mixture was worked up as usual to give an oily crude product (2.80 g), which was separated by HPLC [column A; EtOAc−hexane (1:9); 28.5 mL/min].

The first peak (t_R 6.6 min) gave **17a** (2.49 g, 88%).

The second peak (t_R 13.8 min) gave **17b** (294 mg, 10%).

Conversion of (±)-17b to (±)-13b. The solution of **17b** (55.7 mg, 0.309 mmol), $(Ph_3P)_3RhCl$ (14 mg, 0.015 mmol) in benzene (2 mL), and EtOH (2 mL) was stirred under an H_2 atmosphere. H_2 uptake (12 mL) ceased after 5.4 h. The reaction mixture was filtered, passed through short column of silica gel (0.3 g), and purified by HPLC [column B; EtOAc−hexane (1:9); 3.1 mL/min; t_R 6.2 min] to give **13b** (49.1 mg, 87%).

(±)-7β-(2-Hydroxy-1β-methylethyl)-4β-methyl-2-cyclohepten-1β-ol (18). A solution of **17b** (215 mg, 1.19 mmol) in ether (2 mL) was added into a mixture of $LiAlH_4$ (32 mg, 0.84 mmol) and ether (3 mL). The mixture was refluxed for 45 min under stirring and worked up as usual to give a crude product, which was purified by column chromatography [15 g; 2.0 cm i.d.; EtOAc−hexane (1:1)] to give **18** (218 mg, 98%) as colorless prisms (EtOAc−hexane): mp 41−43 °C; IR ($CHCl_3$) 3400 cm^{-1}; ^1H NMR (90 MHz) δ 0.96 (3 H, d, J = 7.1 Hz, C_1'-Me), 1.07 (3 H, d, J = 7.4 Hz, C_4-Me), 2.32 (1 H, m, $W_{h/2}$ = 18 Hz, C_4-H), 3.42 (1 H, dd, J = 11.4, 4.8 Hz, C_2'-H), 3.61 (1 H, dd, J = 11.4, 7.5 Hz, C_2'-H), 4.35 (1 H, br d, J = 4.2 Hz, C_1-H), 5.60 (1 H, dd, J = 14.4, 2.7, C_3-H), 5.77 (1 H, ddd, J = 14.4, 4.2, 2.3 Hz, C_2-H). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.57; H, 10.94.

Acetylation of (±)-18. A solution of **18** (93 mg, 0.50 mmol) and acetic anhydride (71 μL, 0.75 mmol) in pyridine (3 mL) was stirred at rt for 18 h and worked up as usual to give an oily crude product (109 mg), which was separated by preparative HPLC [column A; EtOAc−hexane (1:9); 28.5 mL/min].

The first peak (t_R 5.2 min) gave diacetate **19** (31 mg, 23%) as a colorless oil.

The second peak (t_R 10.2 min) gave monoacetate **20** (66 mg, 58%) as colorless needles (EtOAc−hexane): mp 46−47 °C; IR (KBr) 3460, 1710 cm^{-1}; ^1H NMR δ 1.06 (3 H, d, J = 7.4 Hz, C_4-Me), 1.08 (3 H, d, J = 6.8 Hz, C_1'-Me), 2.04 (3 H, s, Ac), 2.30 (1 H, m, $W_{h/2}$ = 23 Hz, C_4-H), 3.91 (1 H, dd, J = 11.0, 6.2 Hz, C_2'-H), 4.16 (1 H, dd, J = 11.0, 4.4 Hz, C_2'-H), 4.51 (1 H, br d, J = 4.8 Hz, C_1-H), 5.51 (1 H, dd, J = 11.6, 2.6 Hz, C_3-H), 5.71 (1 H, ddd, J = 11.6, 4.8, 1.7 Hz, C_2-H). Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.59; H, 9.75.

Hydrolysis of (±)-19. A solution of **19** (126 mg, 0.468 mmol) and a 1 M aqueous solution of KOH (0.8 mL) in ethanol (2 mL) was stirred at 21 °C for 1 h and worked up as usual to give **18** (86 mg, 100%) as colorless prisms.

(±)-7β-(2-Acetoxy-1β-methylethyl)-4β-methyl-2-cyclohepten-1-one (21). A mixture of **20** (226 mg, 1.00 mmol), MnO_2 (1.15 g), and $CHCl_3$ (11 mL) was stirred for 23 h and filtered through Celite under reduced pressure. The filtrate was concentrated to give spectroscopically pure **21** (214 mg, 95%) as a colorless oil: IR ($CHCl_3$) 1730, 1678 cm^{-1}; ^1H NMR (90 MHz) δ 0.97 (3 H, J = 6.6 Hz, C_1'-Me), 1.17 (3 H, d, J = 7.4 Hz, C_4-Me), 2.02 (3 H, s, Ac), 2.50 (3 H, m, C_1'-, C_7-, and C_4-Hs), 4.03 (2 H, d, J = 5.6 Hz, C_2'-H), 5.91 (1 H, dd, J = 12.0, 2.6 Hz, C_2-H), 6.61 (1 H, dd, J = 12.0, 3.2 Hz, C_3-H); EIMS *m/e* (relative intensity) 224 (M^+, 2.4), 165 (12.6), 124 (100).

(±)-7β-(2-Hydroxy-1α-methylethyl)-4β-methyl-2-cyclohepten-1β-ol (22). A solution of **17a** (1.24 g, 6.88 mmol) in ether (10 mL) was added into a mixture of $LiAlH_4$ (261 mg, 6.88 mmol) and ether (30 mL). The mixture was refluxed under stirring for 1 h and worked up as usual to give a crude crystalline material (1.3 g), which was separated by column chromatography [15 g; 2.3 cm i.d.; EtOAc−hexane (3:7)] to give **22** (1.16 g, 92%) as colorless needles ($CHCl_3$): mp 74−76 °C; IR (KBr) 3250 (br) cm^{-1}; ^1H NMR δ 0.93 (3 H, d, J = 6.8 Hz, C_1'-Me), 1.04 (3 H, d, J = 7.1 Hz, C_4-Me), 2.27 (1 H, m, C_4-H), 3.45 (1 H, dd, J = 11.4, 5.2 Hz, C_2'-H), 3.80 (1 H, dd, J = 11.4, 3.1 Hz, C_2'-H), 4.62 (1 H, m, C_1-H), 5.44 (1 H, ddd, J = 11.2, 3.7, 2.0 Hz, C_3-H), 5.65 (1 H, dddd, J = 11.2, 4.5, 2.5, 1.0 Hz, C_2-H); ^{13}C NMR δ 16.6 (q, C_1'-Me), 23.3 (q, C_4-Me), 30.0 (t), 30.6 (t), 33.9 (d), 34.2 (d), 44.4 (d, C-7), 67.2 (t, C-2′), 74.0 (d, C-1), 134.5 (d, C-2), 136.6 (d, C-3). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.89; H, 11.00.

Acetylation of (±)-22. A solution of **22** (63.2 mg, 0.343 mmol) and acetic anhydride (43.4 μL, 0.446 mmol) in pyridine (2 mL) was stirred for 29 h. Since recovered diol **22** was detected by TLC, acetic anhydride (10 μL, 0.103 mmol) was added into the reaction mixture, which was stirred for a further 12 h. The reaction mixture was worked up as usual to give a colorless oil (88 mg), which was separated by flash chromatography (7.5 g; 1.6 cm i.d.).

The faster running [EtOAc−hexane (1:9)] gave diacetate **23** (29.9 mg, 32%) as a colorless oil. Anal. Calcd for $C_{15}H_{24}O_4$: C, 67.14; H, 9.02. Found: C, 67.25; H, 9.14.

The slower running [EtOAc−hexane (3:7)] gave monoacetate **24** (50.9 mg, 66%) as a colorless oil: IR ($CHCl_3$) 3620, 1730, 1250 cm^{-1}; ^1H NMR δ 0.96 (3 H, d, J = 6.7 Hz, C_1'-Me), 1.05 (3 H, d, J = 7.2 Hz, C_4-Me), 2.06 (3 H, s, Ac), 2.29 (1 H, m, C_4-H), 4.01 (1 H, dd, J = 11.0, 7.1 Hz, C_2'-H), 4.32 (1 H, dd, J = 11.0, 4.3 Hz, C_2'−H), 4.58 (1 H, br d, J = 3.9 Hz, C_1-H), 5.50 (1 H, ddd, J = 11.2, 3.5, 1.6 Hz, C_3-H), 5.68 (1 H, ddd, J = 11.2, 4.9, 2.5 Hz, C_2-H); ^{13}C NMR δ 15.8 (q, C_1'-Me), 21.0 (q, Ac-**C**H_3), 23.2 (q, C_4-Me), 28.5 (t), 30.7 (t), 32.4 (d, C-1′), 33.8 (d, C-4), 43.4 (d, C-7), 68.6 (t, C-2′), 73.8 (d, C-1), 133.3 (d, C-2), 137.6 (d, C-3), 171.3 (s, Ac-**C**O); HREIMS *m/e* calcd for $C_{13}H_{22}O_3$ 226.1569, found 226.1578.

Hydrolysis of (±)-23. A solution of **23** (10.3 mg, 0.0384 mmol) and a 1 M aqueous solution of KOH (77 μL) in ethanol (0.2 mL) was stirred at rt for 2.3 h and worked up as usual to give a crude oil (8.5 mg), which was purified by flash chromatography to give **22** (6.6 mg, 93%).

(±)-7β-(2-Acetoxy-1α-methylethyl)-4β-methyl-2-cyclohepten-1-one (25). A mixture of **24** (46 mg, 0.203 mmol), MnO_2 (265 mg, 3.1 mmol), and $CHCl_3$ (2.5 mL) was stirred for 9 h. The mixture was worked up as usual to give a crude oil (50 mg), which was purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (1:9)] to give **25** (44.4 mg, 98%) as a colorless oil: IR ($CHCl_3$) 1734, 1668, 1252 cm^{-1}; ^1H NMR (500 MHz) δ 0.91 (3 H, d, J = 6.8 Hz, C_1'-Me), 1.17 (3 H, d, J = 7.3 Hz, C_4-Me), 2.04 (3 H, s, Ac), 2.52 (1 H, m, C_1'-H), 2.56−2.62 (2 H, C_4-, and C_7-Hs), 3.95 (1 H, dd, J = 12.4, 6.5 Hz, C_2'-H), 3.97 (1 H, dd, J = 12.4, 6.5 Hz, C_2'-H), 5.96 (1 H, dd, J = 12.0, 2.7 Hz, C_2-H), 6.33 (1 H, ddd, J = 12.0, 3.4, 0.5 Hz, C_3-H); ^{13}C NMR (125 MHz) δ 13.3 (q, C_1'-Me), 20.9 (q, Ac-**C**H_3), 22.0 (q, C_4-Me), 23.2 (t), 32.7 (d, C-1′), 33.2 (t), 33.7 (d, C-4),

52.1 (d, C-7), 67.4 (t, C-2′), 131.7 (d, C-2), 151.0 (d, C-3), 171.1 (s, Ac-**C**O), 205.1 (s, C-1). Anal. Calcd for $C_{13}H_{20}O_3$: C, 69.61; H, 8.99. Found: C, 69.37; H, 9.11.

(±)-7*β*-[2-((*tert*-Butyldimethylsilyl)oxy)-1α-methylethyl]-4*β*-methyl-2-cyclohepten-1*β*-ol (27). A solution of diol **22** (1.85 g, 10.0 mmol), TBDMSCl (1.66 g, 11.0 mmol), and imidazole (3.47 g, 50.0 mmol) in DMF (7.5 mL) was stirred at rt for 80 min and worked up as usual to give a crude oil (3.2 g), which was separated by flash chromatography (150 g; 4.5 cm i.d.).

The fraction which was eluted by hexane gave disilyl ether **26** (335 mg, 8%) as a colorless oil. Anal. Calcd for $C_{23}H_{48}O_2Si_2$: C, 66.92; H, 11.72. Found: C, 66.80; H, 11.71.

The fraction which was eluted by a mixture of EtOAc−hexane (5:95) gave **27** (2.71 g, 91%) as a colorless oil: IR ($CHCl_3$) 3396, 3028 cm^{-1}; ^1H NMR δ 0.09 (6 H, s, Si−Me), 0.89 (3 H, d, J = 5.6 Hz, C_1′-Me), 0.91 (9 H, s, TBDMS/*t*-Bu), 1.03 (3 H, d, J = 7.1 Hz, C_4-Me), 2.27 (1 H, m, C_4-H), 3.53 (1 H, dd, J = 10.5, 5.1 Hz, C_2′-H), 3.81 (1 H, dd, J = 10.5, 3.1 Hz, C_2′-H), 4.50 (1 H, br s, $W_{h/2}$ = 7.0 Hz, C_1-H), 5.40 (1 H, br dd, J = 11.3, 3.6 Hz, C_3-H), 5.67 (1 H, ddd, J = 11.3, 5.0, 2.3 Hz, C_2-H); ^{13}C NMR δ −5.5 (q, Si−Me), −5.4 (q, Si−Me), 16.7 (q, C_1′-Me), 18.3 [s, Si**C**$(CH_3)_3$], 23.3 (q, C_4-Me), 25.8 [q, SiC(**C**$H_3)_3$], 30.4 (t), 30.5 (t), 33.9 (d), 34.1 (d), 45.0 (d, C-7), 68.0 (t, C-2′), 73.4 (d, C-1), 135.6 (d, C-2), 135.8 (d, C-3). Anal. Calcd for $C_{17}H_{34}O_2Si$: C, 68.39; H, 11.48. Found: C, 67.98; H, 11.50.

Desilylation of Disilyl Ether (±)-26. A solution of disilyl ether **26** (2.11 g, 5.11 mmol) and *n*-Bu_4NF (1 M in THF, 15.3 mL) in THF (30 mL) was stirred at rt for 18.5 h, poured into a saturated aqueous solution of NH_4Cl (100 mL), and worked up as usual to give a pale yellow oil (4.0 g), which was purified by flash chromatography [52 g; 3 cm i.d.; EtOAc−hexane (3:7)] to give diol **22** (937 mg, 100%) as colorless needles.

(±)-7*β*-[2-((*tert*-Butyldimethylsilyl)oxy)-1α-methylethyl]-4*β*-methyl-2-cyclohepten-1-one (28). A mixture of allylic alcohol **27** (2.39 g, 8.01 mmol), MnO_2 (13.9 g, 160 mmol), and $CHCl_3$ (70 mL) was stirred at rt for 48 h. The mixture was worked up as usual to give **28** (2.34 g, 99%) as a colorless oil: IR (neat) 3080, 1674 cm^{-1}; ^1H NMR δ 0.02 (3 H, s, Si−Me), 0.03 (3 H, s, Si−Me), 0.83 (3 H, d, J = 7.0 Hz, C_1′-Me), 0.87 (9 H, s, TBDMS/*t*-Bu), 1.16 (3 H, d, J = 7.2 Hz, C_4-Me), 2.33 (1 H, m, C_1′-H), 2.59 (1 H, m, C_4-H), 2.74 (1 H, m, C_7-H), 3.41 (1 H, dd, J = 9.9, 6.6 Hz, C_2′-H), 3.49 (1 H, dd, J = 9.9, 5.8 Hz, C_2′-H), 5.95 (1 H, dd, J = 12.0, 2.6 Hz, C_2-H), 6.29 (1 H, dd, J = 12.0, 3.2 Hz, C_3-H); ^{13}C NMR δ −5.50 (q, Si−Me), −5.45 (q, Si−Me), 13.0 (q, C_1′-Me), 18.2 [s, Si**C**$(CH_3)_3$], 22.1 (q, C_4-Me), 22.8 (t), 25.9 [q, SiC(**C**$H_3)_3$], 33.3 (t), 33.7 (d), 35.4 (d), 51.4 (d, C-7), 65.9 (t, C-2′), 132.0 (d, C-2), 150.4 (d, C-3), 206.3 (s, C-1). Anal. Calcd for $C_{17}H_{32}O_2Si$: C, 68.86; H, 10.88. Found: C, 69.18; H, 11.07.

Optical Resolution of (±)-22 by Enzymatic Acetylation. 1. A mixture of (±)-**22** (91.9 mg, 0.499 mmol), Amano Lipase PS (30.1 mg), powdered molecular sieves 4A (25.2 mg), and vinyl acetate (5 mL) was stirred at rt. The reaction was monitored by GC analysis. After 4.5 h, the ratio of diol/monoacetate became ca. 1:1, and the reaction mixture was filtered through Celite and concentrated to give a crude mixture. The mixture was separated by HPLC [column C; EtOAc−hexane (3:7); 3.0 mL/min].

The first peak (t_R 14.4 min) gave (+)-**24** (53.6 mg, 48%) as a colorless oil, $[\alpha]^{25}_D$ +46.1 (*c* 3.96, $CHCl_3$), whose IR and ^1H and ^{13}C NMR were identical with those of (±)-**24**.

The second peak (t_R 32.2 min) gave (−)-**22** (47.4 mg, 52%) as a colorless oil, $[\alpha]^{25}_D$ −13.0 (*c* 3.65, $CHCl_3$), whose IR and ^1H and ^{13}C NMR were identical with those of (±)-**22**.

Optical Resolution of (±)-22 by Enzymatic Acetylation. 2. A mixture of (±)-**22** (201 mg, 1.09 mmol), Amano Lipase PS (59 mg), powdered molecular sieves 4A (101 mg), and vinyl acetate (10 mL) was stirred at rt for 8.5 h. The reaction mixture was treated as usual to give a crude mixture, which was separated by HPLC by the conditions mentioned above.

The first peak (t_R 14.4 min) gave (+)-**24** (127.9 mg, 52%) as a colorless oil: $[\alpha]^{25}_D$ +38.0 (*c* 1.11, $CHCl_3$), whose IR and ^1H and ^{13}C NMR were identical with those of (±)-**24**.

The second peak (t_R 32.2 min) gave (−)-**22** (88.9 mg, 44%) as a colorless oil: $[\alpha]^{25}_D$ −16.5 (*c* 1.42, $CHCl_3$), whose IR and ^1H and ^{13}C NMR were identical with those of (±)-**22**.

Formation of (*S*)-(−)-MTPA Ester, (−)-(29), from (−)-22 and (*S*)-(−)-MTPACl. A solution of (−)-**22** (7.3 mg, 0.04 mmol), DMAP (2.4 mg, 0.02 mmol), and (*S*)-(−)-MTPACl (11 μL, 0.06 mmol) in pyridine (0.15 mL) was stirred for 1.5 h. The reaction mixture was treated as usual to give a pale yellow oil (33 mg), which was separated by flash chromatography (2 g; 1.2 cm i.d.).

The eluent by EtOAc−hexane (5:95) gave *di*-MTPA ester of (−)-**22** (6.4 mg, 26%) as a colorless oil.

The eluent by a mixture of EtOAc−hexane (1:9) gave *mono*-MTPA ester (−)-**29** (11.0 mg, 69%) as a colorless oil: $[\alpha]^{20}_D$ −63.5 (*c* 0.64, $CHCl_3$); ^1H NMR δ 0.96 (3 H, d, J = 6.8 Hz, C_1′-Me), 1.04 (3 H, d, J = 7.2 Hz, C_4-Me), 1.94 (1 H, m, C_6-H), 2.05−2.35 (2 H, C_1′-, and C_4-Hs) 3.56 (3 H, br s, -OMe), 4.4−4.5 (2 H, C_2′-Hs), 4.56 (1 H, br s, $W_{h/2}$ = 7.0 Hz, C_1-H), 5.48 (1 H, ddd, J = 11.3, 3.5, 1.7 Hz, C_3-H), 5.63 (1 H, ddd, J = 11.3, 4.7, 2.5 Hz, C_2-H), 7.36−7.45 (3 H, Ph), 7.45−7.58 (2 H, Ph).

From the analysis of the magnitude of shift induced by Eu(fod)$_3$ and the integration values for OMe of (−)-**29**, the absolute configuration (1′*R*) and the enantiomeric excess of (−)-**22** (89% ee) were determined (see text). Since (−)-**22** of 89% ee showed $[\alpha]^{25}_D$ −16.5 (*c* 1.42, $CHCl_3$), the $[\alpha]^{25}_D$ of enantiomerically pure (−)-**22** was estimated as −18.5.

Hydrolysis of (+)-24 with a 1 M Aqueous Solution of KOH. A solution of (+)-**24** (19.7 mg, 0.087 mmol) and a 1 M aqueous solution of KOH (174 μL) in EtOH (0.4 mL) was stirred at rt for 2.5 h and poured into a mixture of a 2 M aqueous solution of HCl (0.2 mL) and a saturated aqueous solution of NaCl (1 mL). The mixture was worked up as usual to give a crude oily product (16 mg), which was purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (2:8)] to give (+)-**22** (13.2 mg, 82%): $[\alpha]^{25}_D$ +15.6 (*c* 0.89, $CHCl_3$).

Formation of (*S*)-(−)-MTPA Ester of (+)-22. A solution of (+)-**22** (11.5 mg, 0.062 mmol) and DMAP (3.9 mg, 0.03 mmol) in pyridine (0.2 mL) was stirred for 2 min, and then (*S*)-(−)-MTPACl (17.0 μL, 0.094 mmol) was added. The mixture was stirred at rt for 1 h, and then additional (*S*)-(−)-MTPACl (5.7 μL, 0.031 mmol) was added. After 40 min, additional (*S*)-(−)-MTPACl (5.7 μL, 0.031 mmol) was added. Stirring for a further 50 min completed the reaction, and the reaction mixture was worked up as usual to give an oily crude product (71 mg), which was separated by flash chromatography (2.5 g; 1.2 cm i.d.).

The eluent by EtOAc−hexane (5:95) gave *di*-MTPA ester (14.2 mg, 37%) as a colorless oil.

The eluent by EtOAc−hexane (1:9) gave the desired *mono*-MTPA ester, (−)-**30** (15.6 mg, 63%), as a colorless oil: $[\alpha]^{20}_D$ −5.2 (*c* 1.06, $CHCl_3$); ^1H NMR δ 0.92 (3 H, d, J = 6.9 Hz, C_1′-Me), 1.04 (3 H, d, J = 7.1 Hz, C_4-Me), 3.45 (3 H, br s, -OMe), 4.32 (1 H, dd, J = 10.9, 6.1 Hz, C_2′-H), 4.58 (1 H, dd, J = 10.9, 3.9 Hz, C_2′-H), 4.59 (1 H, m, C_1-H), 5.50 (1 H, ddd, J = 11.3, 3.6, 1.7 Hz, C_3-H), 5.66 (1 H, ddd, J = 11.3, 4.7, 2.2 Hz, C_2-H), 7.36−7.46 (3 H, Ph), 7.46−7.58 (2 H, Ph).

From the analysis of the magnitude of the shift induced by Eu(fod)$_3$ of (−)-**30**, the absolute configuration (1′*S*) and enantiomeric excess (% ee) of (+)-**24** (77% ee) were determined (see text). Since (+)-**24** of 77% ee showed $[\alpha]^{25}_D$ +38.0 (*c* 1.11, $CHCl_3$), the $[\alpha]^{25}_D$ of enantiomerically pure (+)-**24** was estimated as +49.4.

(1′*S*)-(−)-7*β*-(2-Acetoxy-1α-methylethyl)-4*β*-methyl-2-cyclohepten-1-one (−)-(25). A mixture of (+)-**24** ($[\alpha]^{25}_D$ +38.0, 77% ee, 17.9 mg, 0.079 mmol), MnO_2 (104 mg, 1.19 mmol), and $CHCl_3$ (1.5 mL) was stirred for 9 h. The mixture was worked up as usual to give a pale yellow crude oil (17.8 mg) which was purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (1:9)] to give enone (−)-**25** (16.1 mg, 91%) as a colorless oil, $[\alpha]^{20}_D$ −108.4 (*c* 1.02, $CHCl_3$), which was identical with (±)-**25** in IR and ^1H NMR.

(1′*R*)-(+)-7α-(2-Acetoxy-1*β*-methylethyl)-4α-methyl-2-cyclohepten-1-one (+)-(25). A solution of (−)-**22** ($[\alpha]^{25}_D$ −16.5, 89% ee, 32.6 mg, 0.18 mmol) and Ac_2O (22.4 μL, 0.23 mmol) in pyridine (1 mL) was stirred at rt for 31.5 h.

Additional Ac_2O (5.0 μL, 0.05 mmol) was added into the reaction mixture, and the solution was stirred for a further 2 h. The reaction mixture was worked up as usual to give an oily crude product (41 mg), which was separated by flash chromatography (7.5 g; 1.6 cm i.d).

The first running which was eluted with a mixture of EtOAc−hexane (1:9) gave optically active diacetate (−)-**23** (11.9 mg, 25%), $[\alpha]^{20}_D$ −37.9 (*c* 0.88, $CHCl_3$), which was identical with (±)-**23** in IR and ^{1}H NMR.

The second running which was eluted with a mixture of EtOAc−hexane (3:7) gave optically active monoacetate (−)-**24** (24.3 mg, 61%), $[\alpha]^{25}_D$ −45.3 (*c* 1.32, $CHCl_3$), which was identical with (±)-**24** in IR and ^{1}H NMR.

A mixture of (−)-**24** ($[\alpha]^{25}_D$ −45.3, 24.3 mg, 0.107 mmol), MnO_2 (140 mg, 1.61 mmol), and $CHCl_3$ (1.5 mL) was stirred for 12 h. The mixture was worked up as usual to give a crude oil (23.2 mg), which was purified by flash chromatography [2.5 g; 1.2 cm i.d.; EtOAc−hexane (1:9)] to give enone (+)-**25** (21.5 mg, 90%) as a colorless oil, $[\alpha]^{20}_D$ +129.6 (*c* 1.27, $CHCl_3$), which was identical with (±)-**25** in IR and ^{1}H NMR.

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Supporting Information Available: Table of the comparison of ^{1}H NMR spectral data of **8a**, **8b**, **9a**, **9b**, and **III**; data table of the time progress of kinetic resolution of (±)-**22** by vinyl acetate in the presence of Lipase PS (Amano); ^{1}H NMR charts and stereostructures of (*S*)-(−)-MTPA esters of (−)-**22** and (+)-**22** for determination of absolute configuration and enantiomeric excess by the lanthanide-induced shift by Eu(fod)$_3$ for the -OMe group; CD curve of *p*-bromobenzoate and the stereostructure of *p*-bromobenzoate of (+)-**24**; spectral data of **5**, **7a** and **7b**, **8a**, **9a**, **9b**, **19**, **23**, **26**, *di*-MTPA ester of (+)- and (−)-**22** and Experimental Section for the preparation of **9a** and **9b**, **10a** and **10b**, **11a** and **11b**, **12a** and **12b**, **13b**, and isomerization of **12b** and **13b** (11 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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