A Total Synthesis of (+)-Hirsutic Acid

Mayumi NISHIDA,[1] Katsuhiko ISEKI,[2] Masakatsu SHIBASAKI,[1] and Shiro IKEGAMI*

Faculty of Pharmaceutical Sciences, Teikyo University, Sagamiko, Kanagawa 199-01, Japan. *Received April 17, 1990*

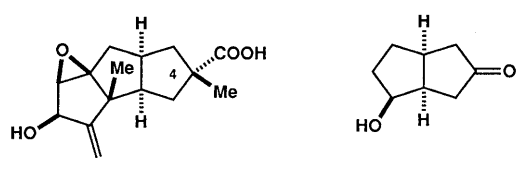
The first asymmetric total synthesis of (+)-hirsutic acid has been accomplished in a highly stereocontrolled manner, including a novel method for the preparation of (1*S*,5*R*,6*S*)-6-hydroxy-*cis*-bicyclo[3.3.0]octan-3-one and a stereospecific Simmons–Smith reaction controlled by the participation of a relatively remote hydroxyl group.

Keywords asymmetric synthesis; (+)-2-cyclopenteneacetic acid; (+)-di-3-pinanylborane; Simmons–Smith reaction; potassium pyrosulfate; Wacker-type oxidation; chelation-controlled reaction

(+)-Hirsutic acid (**1**) was first isolated from *Stereum hirsutum* by Heatley *et al.* in 1947,[3] and its structure was determined by Comer *et al.* in 1967.[4] The interesting antibacterial activity and the fascinating chemical structure possessing the highly functionalized *cis,anti,cis*-tricyclo[6.3.0.0^{2,6}]undecane ring system have generated considerable interest in the synthesis of **1**. Although several elegant total syntheses of *dl*-hirsutic acid have appeared,[5] it seems to us that research on a simple, highly stereocontrolled synthesis of (+)-**1** is still of great interest. Herein we present a detailed account of the total synthesis of (+)-hirsutic acid (**1**).[6]

For the efficient synthesis of (+)-**1**, there are two serious problems which have to be solved. One is the stereocontrolled construction of the C_4 chiral center, which possesses the carboxyl group on the convex face of the molecule along with the *endo*-oriented methyl group. Trost and his coworkers solved this problem by using a rigid bridged bicyclic template.[5b] However, their synthetic route to **1** is fairly lengthy. It was assumed that this synthetic problem could be easily solved by utilizing a chelation-controlled carbon–carbon bond-forming reaction, such as the Simmons–Smith method. Accordingly, the ketone **2** having the *endo*-hydroxyl group was selected as the key synthetic intermediate for our present purpose. The other problem is how to obtain the key intermediate in the naturally occurring absolute configuration. Since we knew that the ketone **2** could be converted to hirsutic acid with high stereochemical control from studies using the racemic compounds[7] we first concentrated our attention on the efficient preparation of (1*S*,5*R*,6*S*)-6-hydroxy-*cis*-bicyclo[3.3.0]octan-3-one (**2**).

Synthesis of (1*S*,5*R*,6*S*)-6-Hydroxy-*cis*-bicyclo[3.3.0]-octan-3-one In the first place, conversion of the hydroxy-ester **3** having the known absolute configuration to the target molecule **2** was attempted. According to the reported method,[8] methyl 5-cyclopentadieneacetate was treated with (−)-di-3-pinanylborane followed by alkaline hydrogen peroxide oxidation to yield the hydroxy-ester **3**, $[\alpha]_D^{25}$ +136° (c=0.98, MeOH), 92% optical purity. In order to remove the hydroxyl group of **3**, **3** was first treated with carbon tetrabromide and triphenylphosphine in methylene chloride, resulting in a complex mixture. However, **3** was cleanly converted to the crystalline phenoxythiocarbonyl derivative **4**, $[\alpha]_D^{25}$ +48° (c=1.18, MeOH), in nearly quantitative yield.[9] Optically pure **4**, $[\alpha]_D^{25}$ +52° (c=0.88, MeOH), was efficiently obtained by single crystallization from ethanol (72% yield). Reductive removal of the phenoxythiocarbonyloxy group was achieved readily when tributyltin hydride in toluene at 75 °C with a catalytic amount of 2-2′-azobisisobutyronitrile (AIBN) as an initiator was used.[9] Alkaline hydrolysis of methyl 2-cyclopenteneacetate (**5**) afforded 2-cyclopenteneacetic acid (**6**) in 50—60% yield, $[\alpha]_D^{25}$ +113° (c=0.51, $CHCl_3$).[10] Conversion of (+)-2-cyclopenteneacetic acid (**6**) to (+)-**11** was carried out according to the method reported by Vandewalle and his coworkers.[11] Namely, transformation to the acid chloride **7**, followed by condensation with Meldrum's acid in pyridine–dichloromethane and solvolysis with MeOH, gave the β-keto ester **8**, $[\alpha]_D^{25}$ +98° (c=1.03, $CHCl_3$), in 85% overall yield. Subsequent treatment with *p*-tosyl azide and triethylamine provided the diazo compound **9**, which was converted to the tricycle **10** by refluxing in toluene with copper(II) acetylacetonate as a catalyst in 77% overall yield from **8**, $[\alpha]_D^{25}$ +38° (c=1.00, $CHCl_3$). Solvolysis with acetic acid containing sylfuric acid at room temperature afforded the acetate **11** in 80% yield, $[\alpha]_D^{25}$ +19° (c=1.35, $CHCl_3$). Demethoxycarbonylation of **11** was successfully carried out by treatment with acetic acid containing a small amount of sulfuric acid at reflux temperature for 0.5 h to give **12**. Alkaline hydrolysis of **12** furnished the *exo*-alcohol **13**, $[\alpha]_D^{25}$ −60° (c=1.14, $CHCl_3$) in 50% overall yield from **11**, which was then subjected to the Mitsunobu reaction.[12] Finally, the benzoate **14** was converted to optically pure (1*S*,5*R*,6*S*)-6-hydroxybicyclo[3.3.0]octan-3-one (**2**), $[\alpha]_D^{25}$ +55° (c=1.00, $CHCl_3$), in 54% overall yield from **13**; this product was identical with an authentic sample except for optical rotation.[13] Confirmation of the optical purity of this product **2** was performed by converting it to the α-methoxy-α-trifluoromethylphenylacetate **15**. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **15** (270 MHz) clearly indicated the absence of the diastereoisomer. Thus, a chiral synthesis of the key synthetic intermediate **2** for (+)-hirsutic acid (**1**) was accomplished starting with cyclopentadiene.



1 2

Fig. 1

Although the optically pure key intermediate **2** can be obtained by the route described above, this route is still unsatisfactory from the practical point of view because of the low overall yield. Therefore, a more practical synthesis

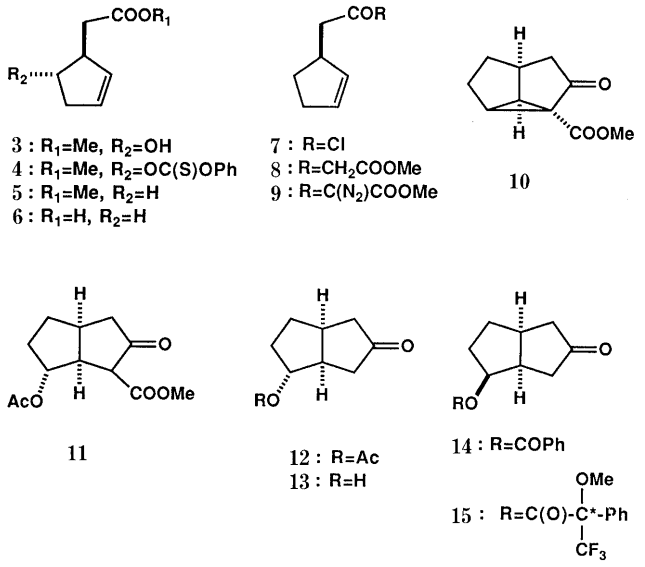


Chart 1

of (+)-**2** was sought. It is generally known that *cis*-bicyclo[3.3.0]octene skeletons undergo the hydroboration reaction predominantly from the convex face of molecules.[14] Accordingly, on the basis of the mechanism of asymmetric hydroboration using (+)-di-3-pinanylborane (**24**),[15] it was assumed that reaction of *dl*-**16** with **24**, followed by oxidation with alkaline hydrogen peroxide, would afford the alcohol **17** corresponding to high enantiomeric excess along with **18** having the opposite absolute configuration. This was found to be the case. Treatment of *dl*-**16** with 1.3 eq of (+)-di-3-pinanylborane (**24**) in tetrahydrofuran (THF) at 0—6 °C for 24 h, followed by alkaline hydrogen peroxide oxidation, resulted in the formation of the alcohols, which were roughly separated from (+)-isopinocampheol by silica gel column chromatography. Oxidation of the mixture of the alcohols with pyridinium chlorochromate (PCC) in methylene chloride afforded the easily separable ketones **19** and **22**. The more polar product was assigned as the desired ketone **19**, $[\alpha]_D^{25}$ +11° (c=1.18, $CHCl_3$), obtained in 35% yield from *dl*-**16**. On the other hand, the less polar ketone was found to be **22**, formed in 40% overall yield from *dl*-**16**. The enantiomeric excess of **22**, $[\alpha]_D^{25}$ −73° (c=0.43, $CHCl_3$), was determined by using the chiral shift reagent {tris[3-heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III)} to be 60%. The desired ketone **19** was subjected to hydrogenolysis over 5% Pd–C in MeOH to afford (+)-**2**, $[\alpha]_D^{25}$ +44° (c=0.30, $CHCl_3$), in quantitative yield. Based on the optical rotation of optically pure **2**, $[\alpha]_D^{25}$ +55° ($CHCl_3$), the hydroxy-ketone thus obtained was concluded to possess the 1*S*,5*R*,6*S* absolute configuration and to have 80% optical purity. Thus, (+)-**2**, the key intermediate for the chiral synthesis of (+)-hirsutic acid (**1**), became available in large quantities and high enantiomeric purity. It should also be noted that the undesired ketone **22** could be converted to (+)-**2**, so that the whole process described above is enantioconvergent.

The following mechanism seems to be reasonable for this interesting resolution method. The most stable conformation of (+)-di-3-pinanylborane is presumed to be **24**, where

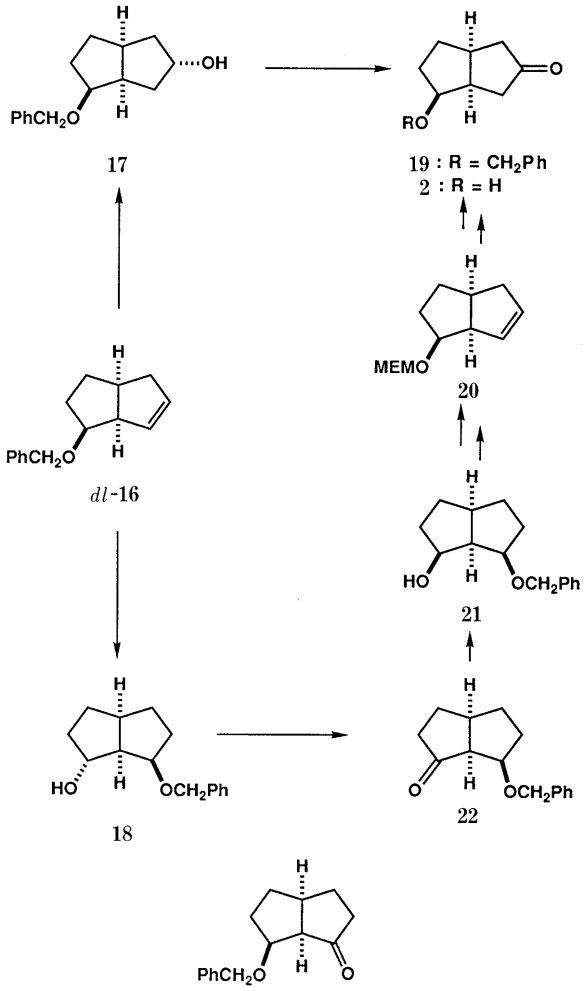


Chart 2

the borane group and the *trans*-methyl group on the pinane moiety have a diequatorial arrangement, with an anti- or nearly antiparallel orientation of the two methyl groups.[15] Accordingly, there is a greater steric repulsion in transition state A leading to the minor product **23** than in transition state B leading to the major ketone **19**, since in transition state A there is a fairly serious interaction between the methine in **16** and the methylene of the pinane moiety. Likewise, there is also a greater steric repulsion in transition state C than in transition state D. Thus, it seems likely that (+)-di-3-pinanylborane could differentiate the enantiomers of *dl*-**16** to give the optically active alcohols, which, after oxidation, were led to **19** and **22** in good to excellent optical purities.

Synthesis of (+)-Hirsutic Acid (1) Here we describe the highly stereocontrolled transformation of (+)-**2** into (+)-hirsutic acid (**1**). In order to construct the C_4 chiral center with high stereocontrol, (+)-**2**, $[\alpha]_D^{25}$ +44° (c=0.30, $CHCl_3$), 80% optical purity, was first converted to the enol ether **25** in 60—70% yield based on the recovery of (+)-**2** (20—25%). It is well known that in five- and six-membered rings, the Simmons–Smith reaction produces the corresponding cyclopropane derivatives with very high stereochemical control in allylic and homoallylic alcohols, but when a hydroxy group is located at the third carbon from the double bond, the control is largely lost.[16] Nevertheless,

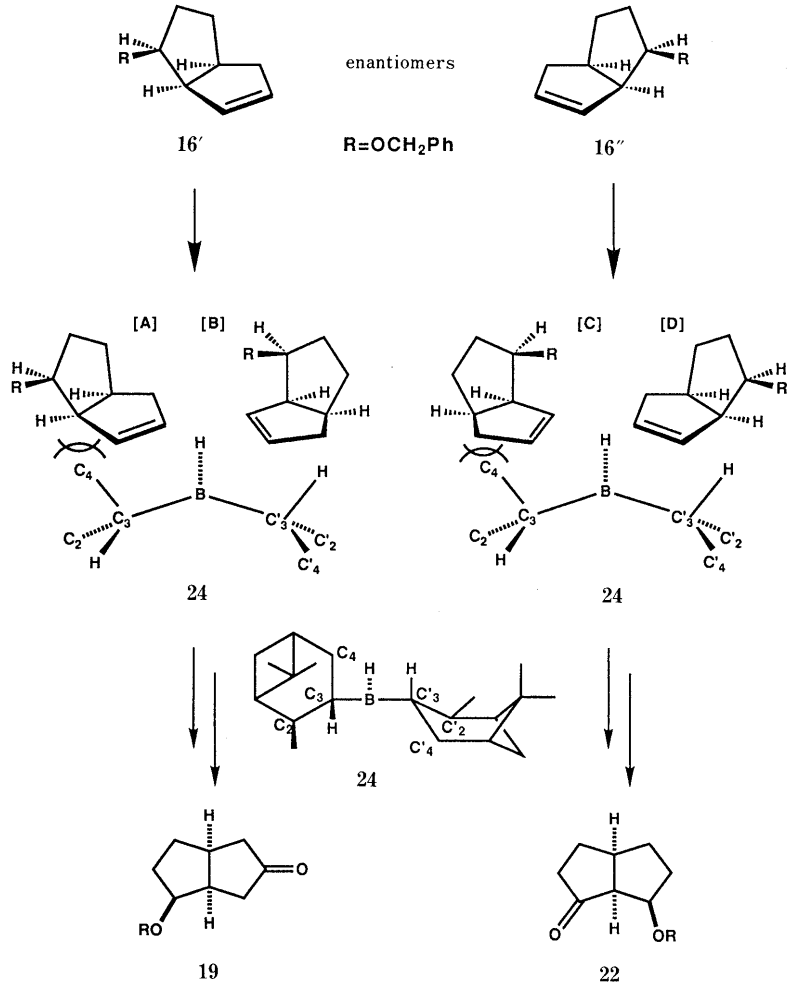


Chart 3

we assumed that in **25**, the methylene transfer would occur at the *endo*-face, where the hydroxy group plays an important role in the stereocontrolled approach of a reagent.

Indeed, treatment of **25** with methylene iodide and zinc–copper couple in ether containing a catalytic amount of iodine (reflux temperature)[16] afforded the cyclopropane derivative **27** with high stereochemical control (>98%) in 73% yield. The structure of **27** was determined as follows. Protection of **27** as the benzyl ether, followed by treatment with HCl in aqueous MeOH at reflux temperature, gave the aldehyde **28** without concomitant formation of the stereoisomer. Likewise, the cyclopropane derivatives **30** formed in *ca.* 0.7% yield afforded the single aldehyde **29**, which was cleanly converted to the lactone **32** by a series of reactions, allowing unequivocal determination of the structure of the cyclopropane derivative **27**. As was expected, in the case of the benzyl ether **26**, the methylene transfer took place predominantly at the *exo*-face to give **31** as a major product. Oxidation of **27** with PCC produced the ketone **33** in nearly quantitative yield, and this was treated with HCl (35% HCl–MeOH) at reflux temperature for 4 h to provide the aldehyde **34**. Oxidation of **34** with Jones reagent, followed by treatment with diazomethane, afforded **35**, $[\alpha]_D^{25}$ −137° (c=0.99, $CHCl_3$), in 50% overall yield from **33**.

Treatment of **35** with 1.2 eq of methyllithium in ether at −78 °C gave the *tert*-alcohol **36**. Dehydration of **36** under various reaction conditions afforded a mixture of regioisomers. However, treatment of **36** with potassium pyrosulfate[17] at 120—125 °C for 0.5 h resulted in the

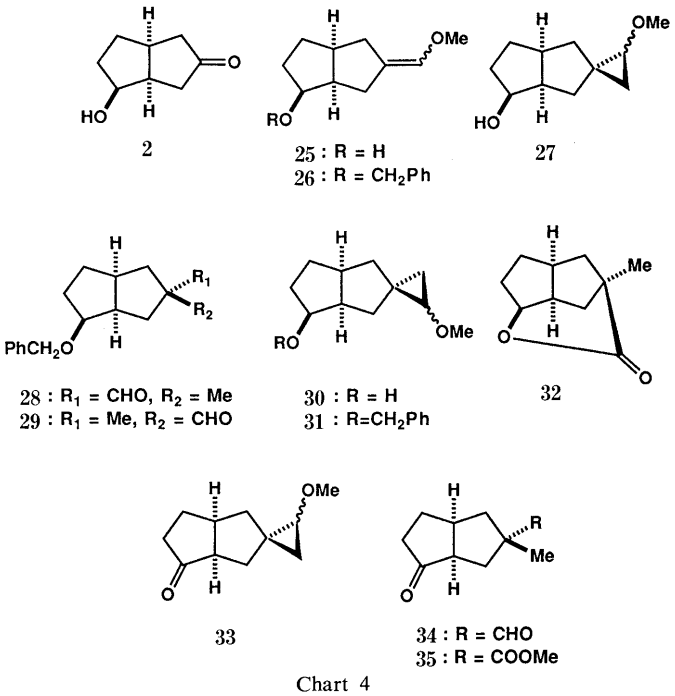


Chart 4

formation of **37** with high regiochemical control (76% overall yield from **35**). Hydroboration of **37**, followed by direct oxidation with PCC, gave the ketone **38** in 61% yield.[18] The spectral data of **38** were fairly different from those of **39**.[5d] Thus, as was expected, hydroboration reaction of **37** was found to proceed predominantly from the convex face of the molecule. The ketone **38** was treated with 1.1 eq of sodium hydride in 1,2-dimethoxyethane (DME), followed by the addition of allyl bromide, giving the desired allyl-ketone **40**, $[\alpha]_D^{25}$ +8° (c=1.28, $CHCl_3$), in *ca.* 70% yield. No other isomer was detected in the reaction mixture on careful thin-layer chromatographic analysis. The stereo- and regiochemistry of **40**, which could be anticipated from a literature precedent,[19] were unequivocally determined by the fact that **40** was successfully converted to (+)-hirsutic acid (**1**). The allyl-ketone **40** was subjected to Wacker-type oxidation[20] to afford the methyl-ketone **41**, $[\alpha]_D^{25}$ −31° (c=1.31, $CHCl_3$), in 74% yield. In this reaction, one by-product **42** was formed in *ca.* 5% yield. Cyclization of **41** by treatment with base (potassium *tert*-butoxide, *tert*-butyl alcohol) resulted in the formation of the known tricycle **43**, $[\alpha]_D^{25}$ +50° (c=1.87, $CHCl_3$), in 79% yield, and this is a key intermediate for the synthesis of *dl*-hirsutic acid reported by Matsumoto *et al.*[5a] Comparison of its spectral data with those of the *dl*-tricycle **43** confirmed their identity.

Introduction of an α-methylene functionality into the tricycle **43** was achieved in the following manner. The tricycle **43** was methylated in THF using 2 eq of lithium diisopropylamide (LDA) and 8 eq of methyl iodide (−78—0 °C) to give **44** in 85% yield. The methyl-ketone **44** was further treated with 2 eq of LDA at −78 °C for 0.5 h, followed by the addition of 3.2 eq of phenylselenenyl bromide (−78—0 °C), to provide the selenide **45**, which was oxidized with 30% hydrogen peroxide and a small amount of acetic acid in THF at 0 °C, giving the α-methylene-enone **46**, $[\alpha]_D^{25}$ +76.9° (c=0.37, $CHCl_3$), in 51% overall yield from **44**. Subsequently, the carboxylic acid **47**, $[\alpha]_D^{25}$ +67.7° (c=0.42, $CHCl_3$), was obtained in 88% yield by treatment of **46** with 15 eq of anhydrous lithium iodide in refluxing *N,N*-dimethylformamide (DMF).[5a] Conversion of **47** to the epoxide **48**, $[\alpha]_D^{25}$ −66.9° (c=0.26, $CHCl_3$), was performed by reaction with 30% hydrogen peroxide in MeOH–H_2O containing 3 eq of sodium hydroxide at −50——36 °C (40% yield).[5a] Finally, reduction of **48** with sodium borohydride in ethanol at 0 °C provided crystalline (+)-hirsutic acid (**1**), mp 170°, $[\alpha]_D^{25}$ +91° (c=1.38, $CHCl_3$), in 74% yield. The spectral data of (+)-**1** thus obtained were superimposable on those reported by Heatley and his coworkers.[3] Recrystallization from ether twice afforded optically pure (+)-hirsutic acid (**1**), $[\alpha]_D^{25}$ +114° (c=0.11, $CHCl_3$) [lit.[3] $[\alpha]_D^{25}$ +116° (c=1.05, $CHCl_3$)], mp 174—176 °C [lit.[3] mp 179—180 °C)].

In this way, the first asymmetric total synthesis of (+)-hirsutic acid (**1**) has been accomplished in a highly stereocontrolled manner, including a novel, efficient method for the preparation of optically active *cis*-bicyclo[3.3.0]octane derivatives.

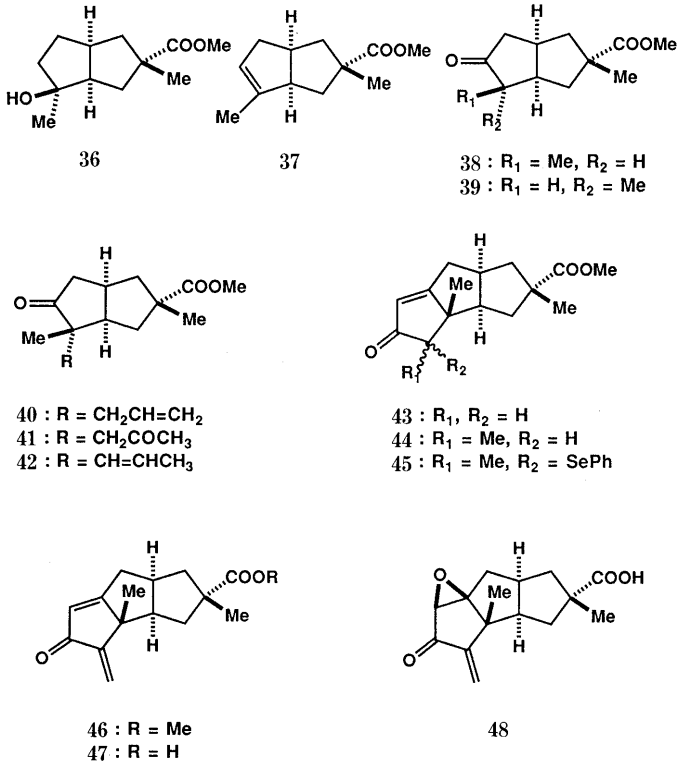


Chart 5

Experimental

Melting points are uncorrected. Infrared (IR) spectra were measured on a Hitachi 215 grating infrared spectrophotometer. ^{1}H-NMR spectra were recorded with a Varian EM360A NMR spectrometer or a Varian XL-100-12 NMR spectrometer in $CDCl_3$ solution with tetramethylsilane as an internal standard. Low resolution mass spectra (MS) were obtained with a JEOL JMS-D300 mass spectrometer and high resolution (HR) mass spectra with a JEOL JMS-01SG-2 mass spectrometer. Optical rotations were determined using a Jasco DIP-181 digital polarimeter.

In general, reactions were carried out under an argon atmosphere.

Methyl (1*R*,5*R*)-5-Phenoxythiocarbonyl-2-cyclopentenylacetate (4) A mixture of the hydroxy-ester **3**, $[\alpha]_D^{25}$ +136° (c=0.98, MeOH), 92% optical purity, (4.00 g, 26 mmol), phenyl chlorothionocarbonate (5.36 g, 31 mmol) and 4-dimethylaminopyridine (7.62 g, 62 mmol) in acetonitrile (50 ml) was stirred at room temperature for 12 h. The reaction mixture was diluted with ether, and the suspension was washed with H_2O and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* afforded an oily residue, which was purified by silica gel column chromatography (ether–hexane, 1 : 6) to give **4**, $[\alpha]_D^{25}$ +48° (c=1.18, MeOH), as a pale yellow viscous oil (8.60 g, 95% yield). IR (film, cm^{-1}): 3060, 2950, 1735, 1590, 1490, 1435, 1015, 810, 770, 684. ^{1}H-NMR ($CDCl_3$) δ: 2.30—3.54 (5H, m), 3.70 (3H, s), 5.60 (1H, m), 5.82 (2H, br s), 7.00—7.64 (5H, m). MS *m/z*: 292, 261, 215. The phenoxythiocarbonate **4** could be crystallized from ethanol to provide optically pure **4** (72% yield), $[\alpha]_D^{25}$ +52° (c=0.88, MeOH), mp 41.5—42 °C. *Anal.* Calcd for $C_{15}H_{16}O_4S$: C, 61.62; H, 5.53. Found: C, 61.51; H, 5.51.

(*S*)-2-Cyclopentenylacetic Acid (6) A mixture of optically pure **4** (6.78 g, 23 mmol) and tributyltin hydride (10.19 g, 35 mmol) in toluene (50 ml) containing a catalytic amount of AIBN was stirred at 75 °C for 2.5 h. After evaporation of the solvent *in vacuo*, the residual oil was roughly purified by silica gel column chromatography (ether–hexane, 1 : 6) to give **5**, which was dissolved in MeOH (15 ml) and 10% aqueous NaOH (7.5 ml). The mixture was stirred at room temperature for 2 h. MeOH was then removed *in vacuo* to give the aqueous layer, which was washed with ether to remove tributhyltin bromide. The aqueous layer was then acidified with 10% aqueous HCl, and extracted with ether. The combined organic extracts were washed with brine. Concentration of the dried extract ($MgSO_4$) afforded an oily residue, which was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 95 : 5) to give **6**, $[\alpha]_D^{25}$ +113° (c=0.51, $CHCl_3$), as a pale yellow oil (1.59 g, 55% yield). IR (film, cm^{-1}): 1705, 1410, 1290, 925, 720. ^{1}H-NMR ($CDCl_3$) δ: 1.24—1.80 (1H, m), 1.90—2.70 (5H, m), 2.90—3.34 (1H, m), 5.52—5.96 (2H, m). The spectral data of (+)-**6** thus obtained were identical with those of commercially available (±)-**6**.

Methyl (*S*)-3-Oxo-4-(2-cyclopentenyl)butyrate (8) A solution of optically pure *S*-(+)-**6** (1.712 g, 13.5 mmol) in thionyl chloride (1.8 ml,

14.9 mmol) was stirred at 60 °C for 1 h. The crude acid chloride was distilled *in vacuo* to afford pure **7** (1.791 g, 91%), bp 65 °C (15 mmHg). A solution of the acid chloride (1.719 g) in CH_2Cl_2 (5 ml) was gradually added to Meldrum's acid (1.868 g, 14.7 mmol) in pyridine (2 ml) and CH_2Cl_2 (3 ml) at 0 °C. After being stirred for 2 h at 20 °C, the reaction mixture was diluted with 90 ml of CH_2Cl_2. The organic layer was successively washed with 4 N aqueous HCl and H_2O, and dried over $MgSO_4$. Concentration of the dried solution afforded an oily residue, which was dissolved in MeOH (12 ml). This solution was stirred for 2 h at reflux temperature, then concentrated *in vacuo* to afford an oily residue, which was purified by silica gel column chromatography (ether–hexane, 1 : 6) to give **8**, $[\alpha]_D^{25}$ +98° (c = 1.03, $CHCl_3$), as a colorless oil (1.92 g, 85% yield from **7**). IR (film, cm^{-1}): 1760, 1730, 1660, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.05—2.70 (6H, m), 2.76—3.30 (1H, m), 3.38 (*ca.* 2H, s), 3.67 (3H, s), 5.40—5.80 (2H, m). MS *m/z*: 182, 67.

Methyl (1*R*,2*R*,5*S*,8*S*)-Tricyclo[3.3.0.0^{2,8}]octan-3-one-2-carboxylate (10) A solution of *p*-toluenesulfonyl azide (2.113 g, 10.7 mmol) in acetonitrile (6 ml) was added to a mixture of the optically pure β-keto ester **8** (1.928 g, 10.6 mmol) and triethylamine (1.5 ml, 10.8 mmol) in acetonitrile (16 ml) at 0 °C. After being stirred for 12 h at 20 °C, the reaction mixture was concentrated *in vacuo* to afford a residue, which was dissolved in ether. The organic layer was washed with 10% aqueous KOH and H_2O, and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* afforded a residue, which was taken up in toluene (200 ml). Copper(II) acetylacetonate (200 mg) was then added to the toluene solution, and the mixture was heated at reflux temperature under vigorous stirring for 2 h. Concentration of the mixture *in vacuo* afforded a residue, which was dissolved in $CHCl_3$. This solution was washed with aqueous 10% H_2SO_4 and H_2O. Evaporation of the dried ($MgSO_4$) solution afforded an oily residue, which was purified by silica gel column chromatography (hexane–ether, 2 : 3) to yield the tricycle **10**, $[\alpha]_D^{25}$ +38° (c = 1.00, $CHCl_3$), as a yellow oil (1.464 g, 77% yield). IR (film, cm^{-1}): 1750—1720 (broad absorption). ^{1}H-NMR ($CDCl_3$) δ: 1.34—3.35 (9H, m), 3.70 (3H, s). MS *m/z*: 180, 148.

Methyl (1*S*,4*RS*,5*S*,6*R*)-6-Acetoxy-*cis*-bicyclo[3.3.0]octan-3-one-4-carboxylate (11) A solution of the optically pure tricycle **10** (1.464 g, 8.12 mmol) and concentrated H_2SO_4 (0.5 ml) in acetic acid (7.5 ml) was stirred at 20 °C for 2 h, followed by the gradual addition of sodium acetate (3 g, 36.6 mmol). The reaction mixture was concentrated *in vacuo*, and the residue was taken up in ether. The organic layer was successively washed with saturated aqueous $NaHCO_3$ and brine, and dried over $MgSO_4$. Concentration of the solution *in vacuo* afforded an oily residue, which was purified by silica gel column chromatography (hexane–AcOEt, 4 : 1) to give **11**, $[\alpha]_D^{25}$ +19° (c = 1.35, $CHCl_3$), as a colorless oil (1.522 g, 78% yield). IR (film, cm^{-1}): 1730, 1660, 1620. ^{1}H-NMR ($CDCl_3$) δ: 1.30—3.40 (9H, m), 2.03 (3H, s), 3.74 (3H, s), 5.08 (1H, m). MS *m/z*: 209, 180, 148.

(1*S*,5*R*,6*R*)-6-Hydroxy-*cis*-bicyclo[3.3.0]octan-3-one (13) A solution of the optically pure β-keto ester **11** (931 mg, 3.88 mmol) in acetic acid (9 ml) containing concentrated H_2SO_4 (1%) was refluxed for 0.5 h, then allowed to cool. Sodium acetate (4 g, 48.8 mmol) was added, and the reaction mixture was concentrated *in vacuo* to afford an oily residue. The residue was then diluted with brine, and the resulting aqueous layer was extracted with AcOEt three times. The solvent was evaporated off *in vacuo* to give the ketone **12**, which was treated with potassium carbonate (1.1 g, 7.96 mmol) and MeOH (3 ml). The mixture was stirred at 20 °C for 2 h, and quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with AcOEt three times, and the combined organic extracts were washed with brine. Concentration of the dried extract afforded a residue, which was purified by silica gel column chromatography (ether–MeOH, 98 : 2) to give **13**, $[\alpha]_D^{25}$ −60° (c = 1.14, $CHCl_3$), as a pale yellow oil (273 mg, 50% yield). IR (film, cm^{-1}): 3400, 1735. ^{1}H-NMR ($CDCl_3$) δ: 1.05—3.25 (11H, m), 3.88—4.15 (1H, m). MS *m/z*: 140, 122, 83.

(1*S*,5*R*,6*S*)-6-Hydroxy-*cis*-bicyclo[3.3.0]octan-3-one (2) A solution of diethyl azodicarboxylate (210 mg, 1.20 mmol) in THF (3 ml) was gradually added to a mixture of the optically pure alcohol **13** (84 mg, 0.60 mmol), triphenylphosphine (316 mg, 1.20 mmol) and benzoic acid (147 mg, 1.20 mmol) in THF (8 ml) at room temperature. After being stirred for 14 h, the mixture was concentrated *in vacuo* to afford a syrupy residue, which was roughly purified by silica gel column chromatography (hexane–ether, 1 : 3) to give **14**. The benzoate **14** was then treated with potassium carbonate (1.1 g, 7.96 mmol) and MeOH (3 ml) at 20 °C for 2 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with AcOEt three times, and the combined organic extracts were washed with brine, then concentrated to afford an oily residue, which was purified by silica gel column chromatography (ether–hexane, 1 : 3) to provide **2**, $[\alpha]_D^{25}$ +55° (c = 1.00, $CHCl_3$) as a colorless oil (45 mg, 54% yield). IR (film, cm^{-1}): 3450, 1730, 1400, 1170. ^{1}H-NMR ($CDCl_3$) δ: 1.12—3.15 (11H, m), 4.10—4.42 (1H, m). MS *m/z*: 140, 122, 96, 80. HR-MS *m/z*: 140.0836 (Calcd for $C_8H_{12}O_2$, 140.0837, M^+). The hydroxy-ketone **2** thus obtained was converted to the α-methoxy-α-trifluoromethylphenylacetate **15**. Although the ^{1}H-NMR spectrum of the α-methoxy-α-trifluoromethylphenylacetate prepared from *dl*-**2** and optically pure α-methoxy-8α-trifluoromethylphenylacetyl chloride displayed two multiplets (δ 5.39 and 5.43, C<u>H</u>–O–CO), whose intensities were in a ratio of 1 : 1, the spectrum of **15** obtained from **2**, $[\alpha]_D^{25}$ +55° (c = 1.00, $CHCl_3$), showed only one multiplet (δ 5.43, C<u>H</u>–O–CO).

Reaction of *dl*-8-Benzyloxy-*cis*-bicyclo[3.3.0]oct-2-ene (16) with (+)-Di-3-pinanylborane and the Oxidation Products Borane–THF complex (0.96 M solution in THF, 3.80 ml, 3.65 mmol) was added to (−)-α-pinene (1.09 g, 8 mmol), $[\alpha]_D^{25}$ −47.5° (neat) at 0 °C. The reaction mixture was stirred under the same conditions for 13 h, then a solution of the olefin **16** (600 mg, 2.80 mmol) in THF (4 ml) was added to the colorless suspension, and the whole mixture was stirred for an additional 24 h at the same temperature, followed by the dropwise addition of 3 N aqueous NaOH (3 ml) and 30% aqueous H_2O_2 (3 ml), and by further stirring for 0.5 h. The organic layer was separated from the aqueous layer, which was further extracted with ether. The combined organic extracts were washed with saturated aqueous $Na_2S_2O_3$ and brine. Concentration of the dried ($MgSO_4$) extract afforded an oily residue, which was purified by silica gel column chromatography (ether–petroleum ether, 1 : 1) to give a mixture of the alcohols **17** and **18** (*ca.* 550 mg). A brown suspension of the alcohols **17** and **18**, Celite (0.88 g) and PCC (0.88 g, 4.1 mmol) in CH_2Cl_2 (10 ml) was stirred at room temperature for 2 h, and then diluted with ether. The suspension was filtered through a short pad of Florisil, and additional ether was used to rinse the Florisil. The filtrate was concentrated *in vacuo* to afford an oily residue, which was purified by silica gel column chromatography (ether–petroleum ether, 1 : 2), giving the desired ketone **19** (193 mg, 35% yield from *dl*-**16**) and **22** (276 mg, 40% yield from *dl*-**16**). The spectral data of **19** were as follows. $[\alpha]_D^{25}$ +11° (c = 1.18, $CHCl_3$). IR (film, cm^{-1}): 3025, 2945, 1735, 1600, 1580, 1500, 1450, 1160, 1105, 1060, 738, 698. ^{1}H-NMR ($CDCl_3$) δ: 1.10—2.10 (10H, m), 3.90—4.15 (1H, m), 4.51 (2H, ABq, J = 12 Hz), 7.34 (5H, s), MS *m/z*: 230, 212, 202, 186, 173, 170, 157, 139, 124, 107, 97, 91. Rf = 0.4 (AcOEt–hexane, 1 : 4). The spectral data of **22** were as follows. $[\alpha]_D^{25}$ −73° (c = 0.43, $CHCl_3$). IR (film, cm^{-1}): 3025, 2945, 1735, 1600, 1580, 1500, 1450, 1110, 1082, 1060, 738, 698. ^{1}H-NMR ($CDCl_3$) δ: 1.20—2.10 (10H, m), 4.10—4.36 (1H, m), 4.53 (2H, s), 7.30 (5H, s). MS *m/z*: 230, 212, 202, 186, 173, 170, 157, 139, 124, 107, 97, 91. Rf = 0.3 (AcOEt–hexane, 1 : 4). The ^{1}H-NMR spectrum (270 MHz) of 0.48 ml of $CDCl_3$ solution containing the ketone **22** (31.1 mg, 0.135 mmol, 0.3 M solution) and tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (1.66 mg, 0.014 mmol) displayed two singlets (C<u>H</u>–OPh), whose intensities were in a ratio of 4 : 1.

Hydrogenolysis of (1*S*,5*R*,6*S*)-6-Benzyloxy-*cis*-bicyclo[3.3.0]octan-3-one (19) A suspension of **19** (159 mg, 0.68 mmol), $[\alpha]_D^{25}$ +11° (c = 1.18, $CHCl_3$), and 5% Pd–C (100 mg) in MeOH (3 ml) was stirred at room temperature for 16 h under hydrogen. The suspension was filtered, washed thoroughly with MeOH, and concentrated *in vacuo* to give an oily residue, which was purified by silica gel column chromatography (ether) to provide **2**, $[\alpha]_D^{25}$ +44° (c = 0.30, $CHCl_3$), as a colorless oil (95 mg, 100% yield). The spectral data of (+)-**2** thus obtained were identical with those of an authentic sample.

Conversion of (−)-22 to (+)-2 Sodium borohydride (88 mg, 2.33 mmol) was added to the ketone **22** (531 mg, 2.31 mmol), $[\alpha]_D^{25}$ −73° (c = 0.43, $CHCl_3$), in MeOH (2.66 ml) at −25 °C, and the mixture was stirred for 0.5 h under the same conditions. The reaction was quenched by the addition of 10% aqueous HCl. The solvent was evaporated off *in vacuo* to afford the residue, to which brine was added. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine. Concentration of the dried ($MgSO_4$) extract afforded an oily residue, which was purified by silica gel column chromatography (ether–hexane, 1 : 3) to yield the alcohol **21** (434 mg, 82% yield) as a nearly colorless oil. A mixture of the alcohol **21** (434 mg, 1.87 mmol), methoxyethoxymethyl (MEM) chloride (1.395 g, 11.2 mmol) and *N,N*-diisopropylethylamine (1.448 g, 11.2 mmol) in CH_2Cl_2 (8.68 ml) containing a catalytic amount of 4-dimethylaminopyridine was stirred at room temperature for 30 h. The reaction was quenched by the addition of saturated aqueous $NaHCO_3$, followed by extraction with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and concentrated. Purification by silica gel column chromatography (ether–hexane, 1 : 5) afforded the MEM ether

(552 mg, 92% yield) as a nearly colorless oil. A suspension of the MEM ether (626 mg, 1.96 mmol) and 5% Pd–C (100 mg) in MeOH (6.3 ml) was stirred at room temperature for 40 h under a hydrogen atmosphere. Filtration, evaporation of the solvent *in vacuo* and purification of the residue by silica gel column chromatography (ether–hexane, 1 : 3) afforded the alcohol (390 mg, 86% yield) as a nearly colorless oil. A solution of the alcohol (370 mg, 1.61 mmol) in ether (15 ml) was added to a suspension of sodium hydride (78 mg, 3.23 mmol) in ether (5 ml), and the reaction mixture was heated to reflux for 10 h. After 3 h of this period, carbon disulfide (490 mg, 6.44 mmol) was added *via* a syringe; after 6 h, methyl iodide (910 mg, 6.44 mmol) was added. The reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by extraction with ether. The combined ether extracts were washed with brine, dried over $MgSO_4$, and concentrated by evaporation to afford the crude xanthate (*ca.* 520 mg), which was directly subjected to pyrolysis at *ca.* 200 °C *in vacuo* using a Kugelrohr apparatus. After purification by silica gel column chromatography (ether–hexane, 1 : 6), the desired olefin **20** (250 mg, 73% yield) was obtained as a pale yellow oil, $[\alpha]_D^{25}$ −92° (*c* = 1.03, $CHCl_3$). IR (film, cm^{-1}): 2945, 1450, 1365, 1200, 1180, 1120, 1050, 1000, 940, 850, 720. ^{1}H-NMR ($CDCl_3$) δ: 1.24—2.40 (5H, m), 2.48—2.90 (2H, m), 3.18—3.83 (5H, m), 3.41 (3H, s), 4.02—4.30 (1H, m), 4.80 (2H, s), 5.54—5.90 (2H, m). MS *m/z*: 212, 137, 136, 106. *N*-Bromosuccinimide (43 mg, 0.24 mmol) was added to a solution of **20** (43 mg, 0.20 mmol) in dimethyl sulfoxide (DMSO)–H_2O (50 : 1, 1 ml) at 0 °C. After being stirred for 0.5 h at room temperature, the reaction mixture was diluted with brine. The aqueous layer was extracted with AcOEt, and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated by evaporation *in vacuo*. The residue was purified by silica gel column chromatography (ether–hexane, 1 : 3) afforded the bromohydrin (63 mg). A mixture of the bromohydrin (63 mg) and tributyltin hydride (80 mg, 0.30 mmol) in benzene (2 ml) containing a catalytic amount of AIBN was heated to reflux for 0.5 h. After evaporation of the solvent *in vacuo*, the residual oil was purified by silica gel column chromatography (ether–hexane, 1 : 3) to yield the alcohol (40 mg). A mixture of the alcohol (40 mg), sodium acetate (6 mg, 0.072 mmol) and PCC (39 mg, 0.18 mmol) in CH_2Cl_2 (1 ml) was stirred at room temperature for 2 h. The reaction mixture was diluted with ether, and then filtered. The filtrate was concentrated *in vacuo* to afford an oily residue, which was purified by silica gel column chromatography (ether–hexane, 1 : 5) to yield the ketone (31 mg, 67% yield from **20**) as a pale yellow oil. A solution of the ketone (31 mg) in 1% H_2SO_4 (acetone–H_2O, 7 : 1, 10 ml) was stirred at 50 °C for 2 d, and the reaction was quenched by the addition of H_2O. The aqueous layer was extracted with ether, and the combined ether extracts were successively washed with H_2O and brine, dried ($MgSO_4$) and concentrated by evaporation to afford an oily residue, which was purified by silica gel column chromatography (ether–hexane, 1 : 3) to give (+)-**2**, $[\alpha]_D^{25}$ +32° (*c* = 0.77, $CHCl_3$), as a nearly colorless oil (19 mg, 90% yield). The spectral data of (+)-**2** thus obtained were identical with those of an authentic sample.

(1*R*,2*S*,5*S*)-2-Hydroxy-7-methoxymethylene-*cis*-bicyclo[3.3.0]octane (25) Butyllithium (1.4 M hexane solution, 14.2 ml) was added to a solution of diethylamine (1.463 g, 20 mmol) in 25 ml of THF at −78 °C, and the mixture was stirred under the same conditions for 10 min and then without a cooling bath for 10 min. The resulting lithium diethylamide solution was added to a suspension of (methoxymethyl)triphenylphosphonium chloride (7.16 g, 21 mmol) in 50 ml of toluene at 0 °C, and the reaction mixture was stirred for 10 min under the same conditions. The ketone **2** (1.327 g, 9.5 mmol, 80% optical purity), $[\alpha]_D^{25}$ +44° (*c* = 0.30, $CHCl_3$), in 10 ml of toluene was injected *via* a syringe into the reddish suspension and the whole was stirred for 0.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with ether and the combined ether extracts were washed with brine, dried ($MgSO_4$) and concentrated by evaporation to afford an oily residue, which was purified by silica gel column chromatography (ether) to yield **25** as a pale yellow oil (715 mg, 60% yield based on the recovery of **2**). IR (film, cm^{-1}): 3400, 2930, 1690, 1450, 1355, 1220, 1198, 1115. ^{1}H-NMR ($CDCl_3$) δ: 1.18—2.74 (11H, m), 3.58 (3H, s, $OC\underline{H}_3$), 4.10—4.30 (1H, m, $C\underline{H}$–O), 5.80—5.96 (1H, m, olefinic proton). MS *m/z*: 168, 151, 150, 122, 109, 105, 95, 91, 79. HR-MS *m/z*: 168.1151 (Calcd for $C_{10}H_{16}O_2$, 168.1150, M^+). From the reaction mixture, the starting ketone (334 mg, 25% recovery) was recovered.

(1*S*,3*S*,5*S*,6*S*)-6-Hydroxy-3,3-methoxyethano-*cis*-bicyclo[3.3.0]octane (27) A mixture of Zu–Cu couple (1.10 g, 17 mg atom), methylene iodide (3.40 g, 12.7 mmol) and a catalytic amount of iodine in 10 ml of ether was heated at reflux for 0.5 h, followed by the addition of **25** (849 mg, 5 mmol, 80% optical purity). After being stirred for 1 h at reflux temperature, the cooled reaction mixture was treated with saturated aqueous NH_4Cl, and filtered through Celite. The Celite pad was washed thoroughly with ether. From the combined filtrates the organic layer was separated. The aqueous layer was further extracted with ether, and the ether extracts were washed with brine, dried ($MgSO_4$) and concentrated by evaporation to afford an oily residue, which was purified by silica gel column chromatography (petroleum ether–ether, 1 : 1) to furnish the cyclopropane derivative **27** as a colorless oil (757 mg, 82%) and **30** (8 mg, 1%). The spectral data of **27** were as follows. IR (film, cm^{-1}): 3400, 2930, 1450, 1200, 1120, 1090, 1065, 990. ^{1}H-NMR ($CDCl_3$) δ: 0.40—0.75 (2H, m, protons of the cyclopropane ring), 0.75—2.86 (11H, m), 3.00 (2H, dd, *J* = 6.0, 2.5 Hz, $C\underline{H}OCH_3$), 3.35 (3H, s, $OC\underline{H}_3$), 4.00—4.40 (1H, m, $C\underline{H}$–O). MS *m/z*: 182, 164, 149, 135, 98, 91. HR-MS *m/z*: 182.1305 (Calcd for $C_{11}H_{18}O_2$, 182.1307, M^+). The spectral data of **30** were as follows. IR (film, cm^{-1}): 3400, 2930, 1450, 1200, 1120, 1090, 1065, 990. ^{1}H-NMR ($CDCl_3$) δ: 0.40—0.75 (2H, m, protons of the cyclopropane ring), 0.75— 2.86 (11H, m), 3.00 (1H, dd, *J* = 6.0, 2.5 Hz, $C\underline{H}OCH_3$), 3.35 (3H, s, $OC\underline{H}_3$), 4.00—4.40 (1H, m, $C\underline{H}$–O). MS *m/z*: 182, 164, 149, 135, 98, 91. HR-MS *m/z*: 182.1305 (Calcd for $C_{11}H_{18}O_2$, 182.1307, M^+).

(1*S*,3*S*,5*R*)-3,3-Methoxyethano-*cis*-bicyclo[3.3.0]octan-6-one (33) PCC (1.36 g, 6.3 mmol) was added to a stirred suspension of **27** (765 mg, 4.2 mmol, 80% optical purity), Celite (1.36 g) and sodium acetate (103 mg, 1.3 mmol) at room temperature. After being stirred for 2 h, the reaction mixture was diluted with ether, followed by filtration through a short pad of Florisil. Additional ether was used to rinse the Florisil. The filtrate was concentrated *in vacuo* to yield the oily ketone **33** (690 mg, 91% yield), which was directly used for the next reaction without further purification. IR (film, cm^{-1}): 2930, 1740, 1450, 1210, 1140, 990. ^{1}H-NMR ($CDCl_3$) δ: 0.34—0.77 (2H, m, protons of the cyclopropane ring), 1.20—2.17 (10H, m), 2.17—2.87 (1H, m, $C\underline{H}OCH_3$), 3.34 (3H, s, $OC\underline{H}_3$). MS *m/z*: 180, 165, 150, 135, 121. HR-MS *m/z*: 180.1511 (Calcd for $C_{11}H_{16}O_2$, 180.1510, M^+).

Methyl (1*S*,3*S*,5*R*)-3-Methyl-6-oxo-*cis*-bicyclo[3.3.0]octan-3-carboxylate (35) A solution of the cyclopropane derivative **33** (200 mg, 1.1 mmol, 80% optical purity) in MeOH–concentrated aqueous HCl, (1 : 1, 6 ml) was heated at reflux for 4 h, and the reaction mixture was diluted with H_2O. The aqueous layer was extracted with ether, and the combined ether extracts were successively washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated by evaporation to afford the aldehyde **34** (154 mg) as a pale yellow oil, which was used for the next reaction without further purification. A solution of the aldehyde **34** (154 mg, 0.93 mmol) in ether (40 ml) was poured into a mixture of chromium trioxide (1.60 g, 16 mmol), $MnSO_4 \cdot 5H_2O$ (7.72 g, 32 mmol) and concentrated H_2SO_4 (1.78 ml, 32 mmol) in H_2O (40 ml). The mixture was stirred at room temperature for 3 h, then the organic layer was separated from the aqueous layer, which was further extracted with ether. The combined ether extracts were successively washed with water and brine, dried ($MgSO_4$) and concentrated by evaporation to afford an oily residue (the carboxylic acid), which was dissolved in ether (3 ml). The ether solution was treated with ethereal diazomethane. After purification by silica gel column chromatography (ether–petroleum ether, 1 : 4), the desired ester **35** (110 mg, 50% yield from **33**) was obtained as a colorless oil, $[\alpha]_D^{25}$ −137° (*c* = 0.99, $CHCl_3$). IR (film, cm^{-1}): 2950, 1730, 1460, 1190, 1160, 1110. ^{1}H-NMR ($CDCl_3$) δ: 1.30 (3H, s, $C\underline{H}_3$), 1.50—3.20 (10H, m), 3.70 (3H, s, $COOC\underline{H}_3$). MS *m/z*: 196, 168, 164, 151, 140, 137, 109, 96, 93, 81. HR-MS *m/z*: 196.1099 (Calcd for $C_{11}H_{16}O_3$, 196.1099, M^+).

Transformation of the Minor Cyclopropane Derivative 30 to the Lactone 32 The cyclopropane derivative **31** (73 mg, 0.27 mmol), which was prepared from **30** by reaction with sodium hydride and benzyl bromide in DMF (50% yield), was subjected to the same reaction conditions as described for the conversion of **33** to **34**, giving the single aldehyde **29** (17 mg, 22% yield) as a nearly colorless oil. IR (film, cm^{-1}): 3025, 2945, 1720, 1450, 1350, 1100, 1015, 940, 735, 695. ^{1}H-NMR ($CDCl_3$) δ: 0.50—3.30 (10H, m), 1.10 (3H, s), 3.50—4.10 (1H, m), 4.50 (2H, s), 7.35 (5H, s), 9.50 (1H, s). MS *m/z*: 258, 240, 235, 211, 176, 167, 152, 139, 121, 105. HR-MS *m/z*: 258.1617 (Calcd for $C_{17}H_{22}O_2$, 258.1620, M^+). On the other hand, the spectral data of **28** were as follows. IR (film, cm^{-1}): 3025, 2945, 1720, 1450, 1350, 1100, 1015, 940, 735, 695. ^{1}H-NMR ($CDCl_3$) δ: 0.50—3.00 (10H, m), 1.18 (3H, s), 3.50—4.10 (1H, m), 4.50 (2H, s), 7.35 (5H, s), 9.50 (1H, s). MS *m/z*: 258, 240, 230, 211, 167, 149, 137, 121, 105. HR-MS *m/z*: 258.1617 (Calcd for $C_{17}H_{22}O_2$, 258.1620, M^+). The aldehyde **29** (17 mg) was subjected to the same reaction conditions as described for the oxidation of **34**, giving the corresponding acid, which was treated with ethereal diazomethane. The obtained ester underwent hydrogenolysis over 5% Pd–C to furnish the hydroxy-ester, which was

treated with a catalytic amount of *p*-toluenesulfonic acid in benzene at reflux temperature for 0.5 h. The lactone **32** (10 mg) was obtained after purification by silica gel column chromatography (ether–petroleum ether, 1 : 2). IR (film, cm^{-1}): 2950, 1725, 1460, 1360, 1160, 1100, 980. ^{1}H-NMR ($CDCl_3$) δ: 1.20—3.00 (10H, m), 1.30 (3H, s), 4.70—4.88 (1H, m). MS *m/z*: 166, 148, 139, 122, 107. HR-MS *m/z*: 166.0991 (Calcd for $C_{10}H_{14}O_2$, 166.0994, M^+).

Methyl (1*R*,5*S*,7*S*)-2,7-Dimethyl-*cis*-bicyclo[3.3.0]oct-2-ene-7-carboxylate (37) Methyllithium (1.05 M diethyl ether solution, 14.3 ml) was injected *via* a syringe into a solution of the ketone **35** (2.455 g, 12.5 mmol, 80% optical purity) in ether (50 ml) at −78 °C. The mixture was stirred for 10 min under the same conditions, then the reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine, dried ($MgSO_4$) and concentrated by evaporation to afford an oily alcohol **26** (2.557 g), which was used for the next reaction without further purification. A mixture of the crude alcohol (2.557 g) and finely ground potassium pyrosulfate (2.50 g), which was prepared by fusing potassium hydrogensulfate, was heated at 120 °C for 0.5 h. The reaction was quenched by the addition of water, and the aqueous solution was extracted with ether. The combined ether extracts were successively washed with 2 N aqueous Na_2CO_3 and brine. Concentration of the dried ($MgSO_4$) extract afforded an oily residue, which was purified by silica gel column chromatography (AcOEt–petroleum ether, 1 : 4) to give the olefin **37** as a colorless oil [1.824 g, 82% overall yield from **35** based on the recovery of **35** (9%)]. IR (film, cm^{-1}): 3025, 2925, 1725, 1443, 1195, 1160, 1085. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, s, $C\underline{H}_3$), 1.50—3.20 (8H, m), 3.70 (3H, s, $COOC\underline{H}_3$), 5.04—5.20 (1H, m, olefinic proton). MS *m/z*: 194, 94, 79. HR-MS *m/z*: 194.1304 (Calcd for $C_{12}H_{18}O_2$, 194.1307, M^+).

Methyl (1*R*,2*R*,5*R*,7*S*)-2,7-Dimethyl-3-oxo-*cis*-bicyclo[3.3.0]octane-7-carboxylate (38) Borane–THF complex (1.25 M solution in THF, 10 ml) was added to a solution of **37** (1.827 g, 9.4 mmol, 80% optical purity) in THF (4 ml) at 0 °C. The mixture was stirred for 20 min under the same conditions, then the solvent was evaporated off *in vacuo* to give an oily residue, which was dissolved in CH_2Cl_2 (100 ml). Celite (20 g) and PCC (20 g, 94 mmol) were added to this solution at room temperature. Stirring was continued for 2 h, then the black suspension was diluted with ether. Filtration through a short pad of Florisil, followed by concentration of the filtrate *in vacuo*, afforded an oily residue, which was purified by silica gel column chromatography (hexane–AcOEt, 4 : 1), giving the ketone **38**, $[\alpha]_D^{25}$ −4.8° (*c* = 15.4, $CHCl_3$), as a colorless oil in 61% yield. IR (film, cm^{-1}): 2950, 1735, 1460, 1375, 1305, 1160. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, d, *J* = 7 Hz, $C\underline{H}_3$), 1.33 (3H, s, $C\underline{H}_3$), 1.60—3.20 (9H, m), 3.76 (3H, s, $COOC\underline{H}_3$). MS *m/z*: 210, 178, 123, 110, 101. HR-MS *m/z*: 210.1256 (Calcd for $C_{12}H_{18}O_3$, 210.1256, M^+).

Methyl (1*R*,2*S*,5*R*,7*S*)-2-Allyl-2,7-dimethyl-3-oxo-*cis*-bicyclo[3.3.0]-octane-7-carboxylate (40) A solution of the ketone **38** (132 mg, 0.66 mmol, 80% optical purity) in DME (2 ml) was added to sodium hydride (18 mg, 0.76 mmol) at 0 °C. The resulting suspension was stirred at room temperature for 1 h, followed by the addition of allyl bromide (798 mg, 6.6 mmol) at 0 °C. The mixture was stirred for an additional 3 h at room temperature, then the reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with ether, and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated by evaporation *in vacuo* to give an oily residue, which was purified by silica gel column chromatography (hexane–AcOEt, 4 : 1), giving **40**, $[\alpha]_D^{25}$ +8° (*c* = 1.28, $CHCl_3$), as a colorless oil (109 mg, 70% yield). IR (film, cm^{-1}): 3080, 2950, 1735, 1720, 1640, 1450, 1375, 1300, 1105, 990, 915. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, s, $C\underline{H}_3$), 1.32 (3H, s, $C\underline{H}_3$), 1.80—3.20 (10H, m), 3.72 (3H, s, $COOC\underline{H}_3$), 4.94—5.30 (2H, m, olefinic protons), 5.50—5.90 (1H, m, olefinic proton). MS *m/z*: 250, 217, 190, 149, 121, 110, 95. HR-MS *m/z*: 250.1567 (Calcd for $C_{15}H_{22}O_3$, 250.1569, M^+).

Methyl (1*R*,2*S*,5*R*,7*S*)-2,7-Dimethyl-3-oxo-2-(2-oxypropyl)-*cis*-bicyclo-[3.3.0]octane-7-carboxylate (41) A suspension of cuprous chloride (131 mg, 1.33 mmol) and palladium(II) chloride (47 mg, 0.27 mmol) in DMF–H_2O (3 ml, 1 : 1) was stirred at room temperature for 2 h under an oxygen atmosphere, and then this suspension was added in one portion to the allyl-ketone **40** (105 mg, 0.42 mmol, 80% optical purity). The reaction mixture was stirred at room temperature for 5 h under oxygen, and then poured into 3 N aqueous HCl, followed by extraction with CH_2Cl_2. The combined organic extracts were successively washed with saturated aqueous $NaHCO_3$ and brine, dried ($MgSO_4$) and concentrated by evaporation *in vacuo* to afford an oily residue, which was purified by silica gel column chromatography (AcOEt–hexane, 1 : 3) to give the ketone **41**, $[\alpha]_D^{25}$ −31° (*c* = 1.31, $CHCl_3$), as a colorless oil (88 mg, 74% yield). IR (film, cm^{-1}): 2950, 1740—1700 (broad absorption), 1460, 1360, 1160, 1100, 1070. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, s, $C\underline{H}_3$), 1.33 (3H, s, $C\underline{H}_3$), 2.07 (3H, s, $COC\underline{H}_3$), 2.70 (2H, s, $C\underline{H}_2COCH_3$), 1.05—3.05 (10H, m), 3.66 (3H, s, $COOC\underline{H}_3$). MS *m/z*: 266, 223, 220, 209, 191, 149, 121. HR-MS *m/z*: 266.1518 (Calcd for $C_{15}H_{22}O_4$, 266.1518, M^+). From the reaction mixture, the olefin **42** was also isolated as a nearly colorless oil (5 mg, 5%). IR (film, cm^{-1}): 2950, 1725, 1450, 1375, 1300, 1195, 1160, 1100, 735. ^{1}H-NMR ($CDCl_3$) δ: 1.03 (3H, s, $C\underline{H}_3$), 1.30 (3H, s, $C\underline{H}_3$), 1.64 (3H, d, *J* = 5 Hz, $C\underline{H}_3$), 1.05—3.50 (8H, m), 3.66 (3H, s, $OC\underline{H}_3$), 5.00—5.60 (2H, m, olefinic protons). MS *m/z*: 250, 190, 149, 121, 110, 95. HR-MS *m/z*: 250.1567 (Calcd for $C_{15}H_{22}O_3$, 250.1569, M^+).

Methyl (1*S*,2*R*,4*S*,6*S*)-1,4-Dimethyl-10-oxotricyclo[6.3.0.0^{2,6}]undec-8-ene-4-carboxylate (43) Potassium *tert*-butoxide in *tert*-butyl alcohol (0.7 M *tert*-butyl alcohol solution, 0.24 ml) was added to the ketone (89 mg, 0.33 mmol, 80% optical purity) at room temperature, and the resulting solution was stirred for 10 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the aqueous layer was extracted with ether. The combined organic extracts were washed with brine, and dried over $MgSO_4$. Evaporation of the solvent *in vacuo* afforded an oily residue, which was purified by silica gel column chromatography (ether–petroleum ether, 1 : 2) to yield **43**, $[\alpha]_D^{25}$ +50° (*c* = 1.87, $CHCl_3$), as a colorless oil (65 mg, 79% yield). IR (film, cm^{-1}): 2950, 1730—1690 (broad absorption), 1630, 1465, 1305, 1160, 1090. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, s, $C\underline{H}_3$), 1.38 (3H, s, $C\underline{H}_3$), 1.00—3.10 (8H, m), 3.68 (3H, s, $COOC\underline{H}_3$), 5.70 (1H, d, *J* = 2 Hz, olefinic proton). MS *m/z*: 248, 233, 220, 188, 173, 160, 145, 120, 108, 91, 80. HR-MS *m/z*: 248.1412 (Calcd for $C_{15}H_{22}O_3$, 248.1412, M^+).

Methyl (1*S*,2*R*,4*S*,6*S*,11*RS*)-1,4,11-Trimethyl-10-oxotricyclo-[6.3.0.0^{2,6}]undec-8-ene-4-carboxylate (44) A solution of the tricyclic enone (229 mg, 0.93 mmol, 80% optical purity) in THF (2 ml) was added to LDA in THF (7.58 ml, 2 mmol) at −78 °C. The mixture was stirred for 10 min under the same conditions, then methyl iodide (1.37 g, 9.64 mmol) was added. The reaction mixture was gradually warmed up to 0 °C over 0.5 h, and the reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with ether, and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated by evaporation *in vacuo* to afford the methyl ketone **44** as a pale yellow oil (202 mg, 83% yield), which was used for the next reaction without further purification. IR (film, cm^{-1}): 2970, 1730, 1705, 1640, 1470, 1375, 1310, 1240, 1200, 1170, 1095. ^{1}H-NMR ($CDCl_3$) δ: 1.06 (3H, d, *J* = 8 Hz, $C\underline{H}_3$), 1.13 (3H, s, CH_3), 1.37 (3H, s, $C\underline{H}_3$), 1.00—3.00 (9H, m), 3.68 (3H, s, $COOC\underline{H}_3$), 5.65 (1H, m, olefinic proton). MS *m/z*: 262, 247, 202, 187, 159, 145, 134, 122, 107, 105, 94, 79. HR-MS *m/z*: 262.1567 (Calcd for $C_{16}H_{22}O_3$, 262.1569, M^+).

Methyl (1*S*,2*R*,4*S*,6*S*)-1,4-Dimethyl-11-methylene-10-oxotricyclo-[6.3.0.0^{2,6}]undec-8-ene-5-carboxylate (46) A solution of the methyl enone **44** (202 mg, 0.77 mmol, 80% optical purity) in THF (3 ml) was added to LDA in THF (5.68 ml, 1.5 mmol) at −78 °C, and the resulting mixture was stirred under the same conditions for 0.5 h. Subsequently phenylselenenyl bromide in THF (1.02 ml, 2.4 mmol) was injected *via* a syringe. After being stirred for 10 min at −78 °C, the reaction mixture was gradually warmed to 0 °C over 0.5 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by extraction with ether. The combined ether extracts were washed with brine, and dried over $MgSO_4$. Evaporation of the solvent afforded an oily residue, which was roughly purified by silica gel column chromatography (AcOEt–petroleum ether, 1 : 3) to yield the selenide **45** (207 mg). H_2O_2 (30% solution in H_2O, 0.39 ml) was gradually added to a solution of **45** (207 mg) in THF (3 ml) containing glacial acetic acid (0.078 ml) at 0 °C. The resulting mixture was stirred under the same conditions for 0.5 h, followed by the successive addition of saturated aqueous $NaHCO_3$ and aqueous NH_4Cl. The aqueous layer was extracted with ether, and the combined ether extracts were washed with brine, dried ($MgSO_4$) and concentrated by evaporation to afford an oily residue, which was purified by silica gel column chromatography (AcOEt–hexane, 1 : 4) to afford **46**, $[\alpha]_D^{25}$ +76.9° (*c* = 0.37, $CHCl_3$) as a colorless oil (103 mg, 55% yield from **44**). IR (film, cm^{-1}): 2955, 1720, 1700, 1620, 1465, 1300, 1260, 1200, 1160. ^{1}H-NMR ($CDCl_3$) δ: 1.19 (3H, s, $C\underline{H}_3$), 1.39 (3H, s, $C\underline{H}_3$), 1.10—3.00 (8H, m), 3.66 (3H, s, $COOC\underline{H}_3$), 5.18 (1H, s, olefinic proton), 5.90 (2H, s, olefinic protons). MS *m/z*: 260, 232, 201, 185, 173, 157, 145, 132, 121, 115, 91. HR-MS *m/z*: 260.1411 (Calcd for $C_{16}H_{20}O_3$, 260.1412, M^+).

(1*S*,2*R*,4*S*,6*S*)-1,4-Dimethyl-11-methylene-10-oxotricyclo[6.3.0.0^{2,6}]-undec-8-ene-5-carboxylic acid (47) A mixture of the ester **46** (103 mg, 0.4 mmol, 80% optical purity) and lithium iodide (772 mg, 6 mmol), which had been dried *in vacuo* at 100 °C for 2 d, in DMF (7 ml) was heated at

reflux for 36 h, and then diluted with water. After acidification with 10% aqueous HCl, the aqueous layer was extracted with ether. The combined ether extracts were washed with water, and dried over $MgSO_4$. Evaporation of the solvent afforded an oily residue, which was purified by silica gel column chromatography (AcOEt–hexane, 1 : 1) to give the acid **47**, $[\alpha]_D^{25}$ +67.7° (c=0.42, $CHCl_3$), as a colorless solid (86 mg, 88% yield). IR (film, cm^{-1}): 2955, 1690, 1640, 1620, 1465, 1305, 1260, 1150, 940, 905, 860. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, s, C$\underline{H}_3$), 1.42 (3H, s, C$\underline{H}_3$), 1.10—3.10 (8H, m), 5.18 (1H, s, olefinic proton), 5.90 (2H, s, olefinic protons). MS m/z: 246, 201, 157, 145, 131, 91. HR-MS m/z: 264.1254 (Calcd for $C_{15}H_{18}O_3$, 246.1256, M^+).

(1*R*,2*R*,4*S*,6*R*,8*S*,9*S*)-8,9-Epoxy-1,4-dimethyl-11-methylene-10-oxotricyclo[6.3.0.0^{2,6}]undecane-4-carboxylic acid (48) H_2O_2 (30% in H_2O, 0.35 ml) and 1 N aqueous NaOH (1.05 mmol 1.05 ml) were successively added to the dienone (86 mg, 0.35 mmol, 80% optical purity) in MeOH (5 ml) at −50 °C, and the reaction mixture was gradually warmed to −36 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl, followed by extraction with ether. The combined ether extracts were washed with brine, and dried over $MgSO_4$. Evaporation of the solvent afforded an oily residue, which was purified by silica gel column chromatography (hexane–AcOEt, 1 : 1) to afford **48**, $[\alpha]_D^{25}$ −66.9° (c=0.26, $CHCl_3$), as a colorless solid (37 mg, 40% yield). IR (film, cm^{-1}): 2960, 2760, 1725, 1690, 1640, 1465, 950. ^{1}H-NMR ($CDCl_3$) δ: 1.18 (3H, s, C$\underline{H}_3$), 1.42 (3H, s, C$\underline{H}_3$), 1.00—3.00 (8H, m), 3.42 (1H, s, C$\underline{H}$–O), 6.08 (1H, s, olefinic proton), 6.30 (1H, s, olefinic proton). MS m/z: 262, 247, 244, 233, 216, 205, 159, 131, 119, 105, 91. HR-MS m/z: 262.1002 (Calcd for $C_{15}H_{18}O_4$, 262.1205, M^+).

(+)-Hirsutic Acid (1) Sodium borohydride (6 mg, 0.16 mmol) was added to a solution of **48** (37 mg, 0.14 mmol, 80% optical purity) in ethanol (4 ml) at 0 °C. The mixture was stirred for 10 min under the same conditions, then the reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous layer was extracted with AcOEt, and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated by evaporation *in vacuo* to afford a solid residue, which was purified by silica gel column chromatography (AcOEt–hexane, 2 : 1) to give **1**, $[\alpha]_D^{25}$ +91° (c=1.38, $CHCl_3$), as a colorless solid (28 mg, 74% yield), mp 170 °C. IR ($CHCl_3$, cm^{-1}): 3450, 3400, 2400, 1700, 1670, 915, 890. ^{1}H-NMR ($CDCl_3$) δ: 1.15 (3H, s, C$\underline{H}_3$), 1.43 (3H, s, C$\underline{H}_3$), 1.10—3.00 (8H, m), 3.53 (1H, br s, C$\underline{H}$–O), 4.67 (1H, m, C$\underline{H}$–OH), 5.07 (1H, d, J=2.5 Hz, olefinic proton), 5.34 (1H, J=2.0 Hz, olefinic proton). MS m/z: 264, 246, 235, 201, 189, 149, 138, 109. HR-MS m/z: 264.1362 (Calcd for $C_{15}H_{20}O_4$, 264.1361, M^+). Recrystallization from ether twice afforded optically pure (+)-hirsutic acid (**1**), $[\alpha]_D^{25}$ +114° (c=0.11, $CHCl_3$) [lit.[3] $[\alpha]_D^{25}$ +116° (c=1.05, $CHCl_3$)], mp 174—176 °C (lit.[3] mp 179—180 °C).

Acknowledgement We are grateful to Professors T. Matsumoto, Tokai University, and H. Shirahama, Hokkaido University, for providing the spectral data of the tricyclic enone **43**. We also thank Mrs. Miwa Saimoto for her technical assistance. Our thanks are due to the members of the central analysis room of this faculty for spectral measurements. The financial support of this research by the Japan Foundation for Optically Active Compounds, by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture and by Suzuken, Kenzo Memorial Foundation is gratefully acknowledged. K.I. is grateful to Drs. S. Hata and Y. Morinaka for their encouragement.

References and Notes

1) Present address: *Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan.*
2) Present address: *Pharmaceuticals Laboratory, Research Center, Mitsubishi Kasei Corporation, 1000, Kamoshida, Midori-ku, Yokohama 227, Japan.*
3) N. G. Heatley, M. A. Jennings, and H. W. Florey, *Brit. J. Exptl. Path.*, **28**, 31 (1947).
4) *a*) F. W. Comer, F. McCapra, I. H. Qureshi, and A. I. Scott, *Tetrahedron*, **23**, 4761 (1967); *b*) F. W. Comer and J. Trotter, *J. Chem. Soc.*, (B), **1966**, 11.
5) *a*) H. Hashimoto, K. Tsuzuki, F. Sakan, H. Shirahama, and T. Matsumoto, *Tetrahedron Lett.*, **1974**, 3745; *b*) B. M. Trost, C. D. Shuey, and F. DiNinno, *J. Am. Chem. Soc.*, **101**, 1284 (1979); *c*) P. T. Lansbury, N. Y. Wang, and J. E. Rhodes, *Tetrahedron Lett.*, **1972**, 2053; *d*) M. Yamazaki, M. Shibasaki, and S. Ikegami, *Chemistry Lett.*, **1981**, 1245; *e*) A. E. Greene, M.-J. Luche, and J.-P. Deprés, *J. Am. Chem. Soc.*, **105**, 2435 (1983); *f*) P. Magnus, C. Exon, and P. Albaugh-Robertson, *Tetrahedron*, **41**, 5861 (1985); *g*) P. F. Schuda, J. L. Philips, and T. M. Morgan, *J. Org. Chem.*, **51**, 2742 (1986).
6) M. Shibasaki, M. Yamazaki, K. Iseki, and S. Ikegami, *Tetrahedron Lett.*, **23**, 5311 (1982). (+)-Hirustic acid has also been synthesized by Greene and coworkers. See: A. E. Greene, M.-J. Luche, and A. A. Serra, *J. Org. Chem.*, **50**, 3957 (1985).
7) M. Nishida, M. Shibasaki, and S. Ikegami, unpublished result.
8) *a*) J. J. Partridge, N. K. Chadha, and M. R. Uskokovič, *J. Am. Chem. Soc.*, **95**, 7171 (1973); *b*) *Idem. ibid.*, **95**, 532 (1973).
9) M. J. Robins and J. S. Wilson, *J. Am. Chem. Soc.*, **103**, 932 (1981).
10) K. Mislow and I. V. Steinberg, *J. Am. Chem. Soc.*, **77**, 3807 (1955).
11) P. Callant, H. D. Wilde, and M. Vandewalle, *Tetrahedron*, **37**, 2079 (1981).
12) O. Mitsunobu, *Synthesis*, **1981**, 1.
13) Prepared from the known bromohydrin,[19b] 2-*endo*-bromo-3-*exo*-hydroxy-8-*endo*-benzyloxy-*cis*-bicyclo[3.3.0]octane, by successive treatment with Bu_3SnH, PCC and H_2 (Pd–C).
14) I. Tabushi, K. Fujita, and R. Oda, *J. Org. Chem.*, **35**, 2383 (1970).
15) H. C. Brown, P. K. Jadhav, and A. K. Mandal, *Tetrahedron*, **37**, 3547 (1981).
16) H. E. Simmons, T. L. Cairns, and S. A. Vladuchick, *Organic Reactions*, **20**, 1 (1973).
17) J. K. Whitesell, R. S. Matthews, M. A. Minton, and A. M. Helbling, *J. Am. Chem. Soc.*, **103**, 3468 (1981).
18) R. D. Little and G. W. Muller, *J. Am. Chem. Soc.*, **103**, 2744 (1981).
19) *a*) S. Nozoe, J. Furukawa, U. Sankawa, and S. Shibata, *Tetrahedron Lett.*, **1976**, 195; *b*) K. Iseki, M. Yamazaki, M. Shibasaki, and S. Ikegami, *Tetrahedron*, **37**, 4411 (1981).
20) J. Tsuji, I. Shimizu, and K. Yamamoto, *Tetrahedron Lett.*, **1976**, 2975.