Synthesis of Racemic and Optically Active Cispentacin (FR109615) Using Intramolecular Nitrone–Olefin Cycloaddition

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Synthesis of racemic and optically active cispentacin ((−)-1) is described. Intramolecular nitrone–olefin cycloaddition of the alkenyl nitrone 7 gave *cis*-isoxazolidine (±)-8, which was transformed into (±)-1 by sequential reactions involving catalytic hydrogenolysis and oxidation. Similarly, the optically active nitrone (*R*)-22, which was derived from the ketone 15 *via* lipase-catalyzed hydrolysis of the acetate (±)-17, underwent intramolecular cycloaddition to give (+)-25 with high stereoselectivity (15 : 1). The cycloadduct (+)-25 was transformed in 4 steps into optically active natural cispentacin.

Keywords cispentacin; FR109615; nitrone; cycloaddition; lipase-catalyzed hydrolysis

Cispentacin ((−)-**1**) is an antifungal antibiotic that was isolated by Konishi *et al.* from the culture broth of a *Bacillus cereus* strain.[1] The same compound was independently isolated from the culture broth of a *Streptomyces setonii* strain and named FR109615 by Iwamoto *et al.*[2] The synthesis of the racemate of this compound had been achieved[3–5] before the isolation of cispentacin; this racemate was utilized as a probe for determination of the spatial dimension in γ-aminobutyric acid (GABA) receptors.[6] The configuration of naturally occurring cispentacin was determined to be 1*R*,2*S* by X-ray crystallographic analysis of the *N*-(*N*-phenylthiocarbamoyl-L-phenylalanyl) derivatives of cispentacin and its (+)-enantiomer.[7] Despite its simple chemical structure, cispentacin was shown to exhibit significant *in vivo* therapeutic efficacy against various models of systemic mycoses in mice.[8] Synthetic studies in this area therefore seem important.[9] In this paper, we describe a synthesis of racemic and optically active cispentacin.

Racemic Cispentacin There are essentially two known procedures for the synthesis of racemic cispentacin ((±)-**1**) (Chart 1). Plieninger and Schneider[4] synthesized (±)-**1** using Hofmann degradation of the half amide (±)-**2**, which is obtainable from *cis*-cyclopentanedicarboxylic acid anhydride. Konishi *et al.*[1] and Kawabata *et al.*[7] prepared (±)-**1** by cleaving the β-lactam ring in (±)-**3**, which was obtained by cycloaddition of cyclopentene and chlorosulfonyl isocyanate.[3] Our plan for the synthesis of (±)-**1** was based on the intramolecular nitrone–olefin cycloaddition,[10] as depicted in Chart 2.

The commercially available starting material, 5-hexen-1-ol (**5**), was transformed into the aldehyde **6** by Collins oxidation. Since the aldehyde **6** is water-soluble and volatile, the supernatant of the reaction mixture was used for the next reaction after being filtered through Florisil. Treatment of the crude solution of **6** in dichloromethane–ether with *N*-benzylhydroxylamine afforded the nitrone **7**, which was heated in benzene at 70 °C for 2.5 h to give the fused isoxazolidine (±)-**8** in 81% overall yield from **5**. Since the cyclization reaction of the related 5-alkenyl-substituted nitrones has been reported to form only *cis*-fused [3.3.0]bicyclic isoxazolidines,[11] the fused rings in (±)-**8** were presumed to be in the *cis* configuration; this was later confirmed by transforming (±)-**8** into (±)-cispentacin. Cleavage of the N–O bond and removal of the benzyl protecting group in (±)-**8** were effected by catalytic hydrogenolysis with 10% palladium/carbon in acetic acid

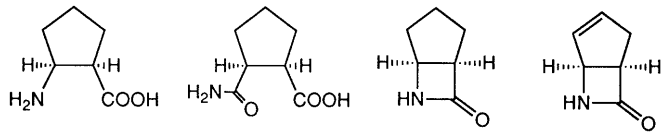


Chart 1

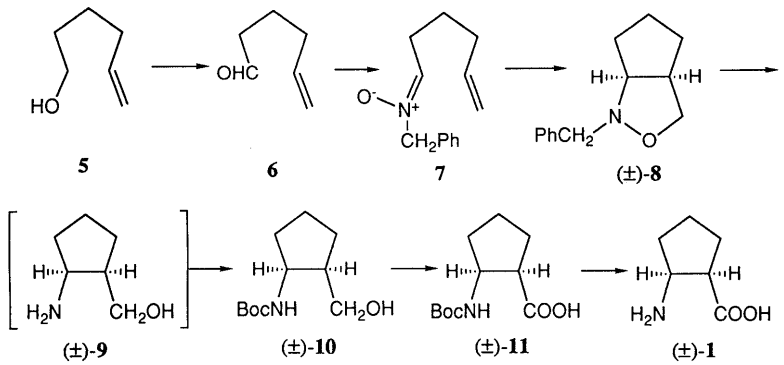


Chart 2

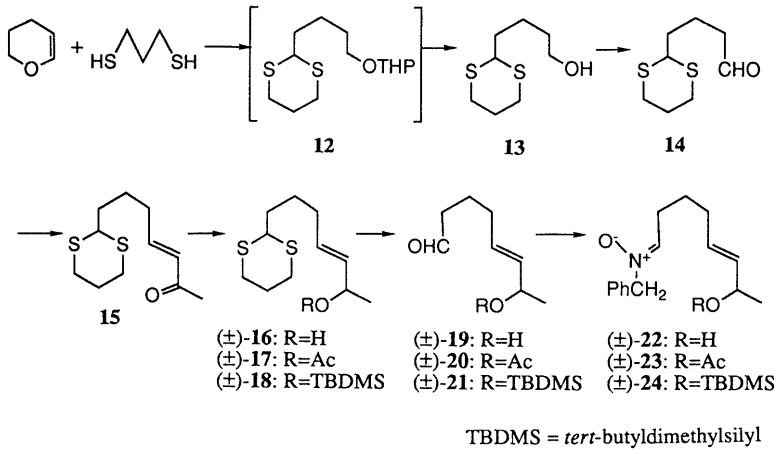
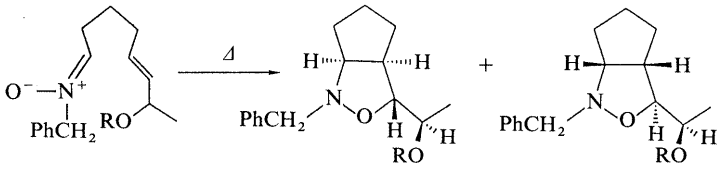


Chart 3

TABLE I. Intramolecular [3+2] Cycloaddition of the Nitrones (±)-**22**, **23**, and **24**



(±)-**22**: R=H
(±)-**23**: R=Ac
(±)-**24**: R=TBDMS[a]

(±)-**25**: R=H
(±)-**26**: R=Ac
(±)-**27**: R=TBDMS

(±)-**25′**: R=H
(±)-**26′**: R=Ac
(±)-**27′**: R=TBDMS

Nitrone	R	Solvent	Temp. (°C)	Time (h)	Yield[b] (%)	Product ratio
(±)-**22**	H	Benzene	80	6	95	(±)-**25**:(±)-**25′**=15:1
(±)-**23**	Ac	Benzene	80	6	80	(±)-**26**:(±)-**26′**= 1:2
(±)-**24**	TBDMS	Toluene	110	3	71	(±)-**27**:(±)-**27′**= 1:1

a) TBDMS=*tert*-butyldimethylsilyl. *b*) Combined yields of the cyclization products (±)-**25**—**27** and (±)-**25′**—**27′** from the corresponding aldehyde precursors (±)-**19**—**21**.

to produce the aminoalcohol (±)-**9**, which underwent N-protection by treatment with di-*tert*-butyl dicarbonate and triethylamine in tetrahydrofuran (THF) to afford (±)-**10** in 85% yield from (±)-**8**. Jones oxidation of (±)-**10** gave the carboxylic acid (±)-**11** in 84% yield. Finally, the *tert*-butoxycarbonyl (Boc) protecting group was removed by treatment with HCl in dioxane to furnish racemic cispentacin ((±)-**1**) in 76% yield. The ^{1}H-NMR, ^{13}C-NMR, and mass spectra of (±)-**1** thus synthesized were in accord with those reported for cispentacin ((−)-**1**).[1,2]

Optically Active Cispentacin Optically active cispentacin ((−)-**1**) has been prepared by means of optical resolution of the N-Cbz derivative[1] and methyl ester[7] of (±)-cispentacin, or by means of whole cell-catalyzed resolution of the β-lactam precursor (±)-**4**,[12] but no asymmetric synthesis of (−)-**1** has so far been reported. In order to synthesize cispentacin in optically active form, an optically active appendage was planned to be attached to the nitrone **7**. There are some reports that describe diastereoselective intramolecular nitrone–olefin cycloaddition of related chiral nitrones into optically active bicyclo[3.3.0] ring systems; in these literature precedents, the chiral centers were situated adjacent to the nitrone nitrogen atom[13] or on the carbon bridge linking the nitrone and the olefin moieties.[14] We assumed that differentiating the two enantiotopic faces of the olefin moiety in **7** would effectively introduce high enantioselectivity in the cycloaddition reaction, and decided to prepare the nitrones **22**—**24** possessing a subsequently removable chiral center adjacent to the terminal carbon of the olefin moiety. In order to evaluate their effectiveness for diastereoselective intramolecular nitrone–olefin cycloaddition, these nitrones were first obtained as racemates in the following steps (Chart 3).

Treatment of dihydropyran with 1,3-propanedithiol in dichloromethane in the presence of a catalytic amount of boron trifluoride etherate afforded the tetrahydropyranyl ether **12**, which was methanolyzed to give the alcohol **13** in 78% yield from 1,3-propanedithiol. Swern oxidation of the alcohol **13** gave the aldehyde **14** in 83% yield. Conversion of the aldehyde **14** into the (*E*)-enone **15** was carried out in 91% yield by reaction with 1-(triphenylphosphoranylidene)-2-propanone in refluxing benzene. The enone **15** was reduced by treatment with $NaBH_4$–$CeCl_3 \cdot 7H_2O$[15] in ethanol to give the alcohol (±)-**16** in 97% yield. The dithiane protecting group in (±)-**16** was cleaved by treatment with mercury(II) chloride in the presence of calcium carbonate in acetonitrile–H_2O to afford the aldehyde (±)-**19**. Analogously, the aldehydes (±)-**20** and (±)-**21** were prepared from the corresponding dithianes (±)-**17** and (±)-**18**, which were obtained from the alcohol (±)-**16** by acetylation and silylation, respectively.

Treatment of the aldehydes (±)-**19**—**21** with *N*-

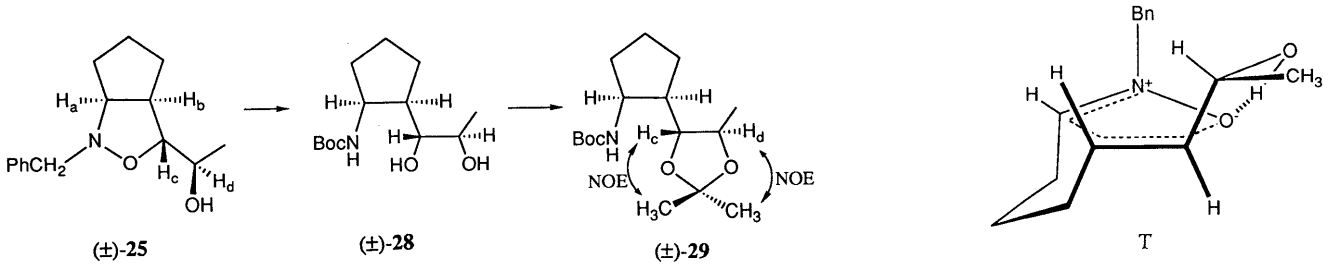


Chart 4

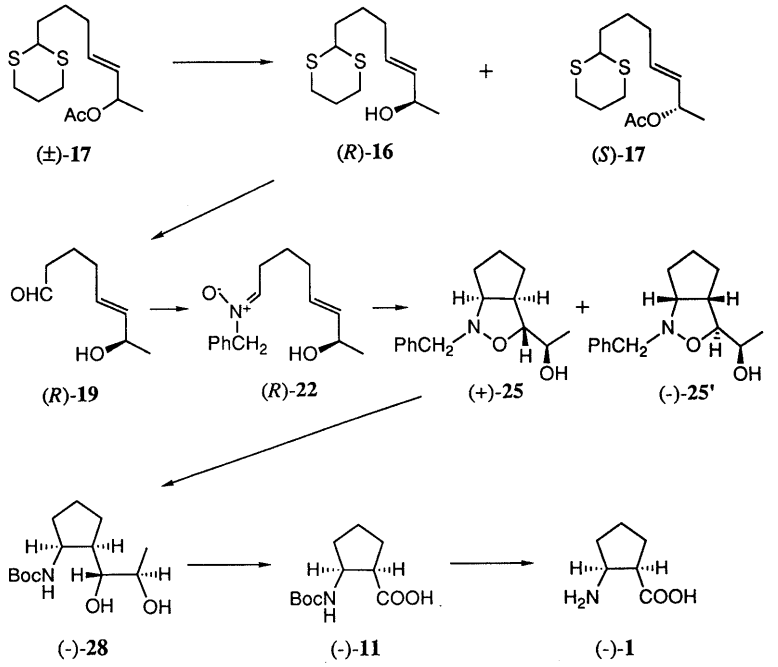


Chart 5

benzylhydroxylamine in chloroform or benzene, followed by heating of the resulting nitrones (±)-**22**—**24** in benzene or toluene, afforded mixtures of the fused isoxazolidine products (±)-**25**—**27** and their diastereomers (±)-**25'**—**27'**. The yields and the diastereomeric ratios are listed in Table I. Among the cyclization precursors investigated, the alcohol (±)-**22** was found to afford the best yield (95%), with significantly high diastereoselectivity [(±)-**25**:(±)-**25'** = 15:1].

The relative configurations of the chiral centers in the cyclization product (±)-**25** was determined as follows (Chart 4). The hydrogen atoms H_a and H_b were presumed to be in the *cis* orientation because only *cis*-fused isoxazolidines are reported to be formed from the related 5-alkenyl-substituted nitrones[11]; this presumption was later confirmed by leading (+)-**25** to cispentacin. The *trans* orientation of the hydrogen atoms H_b and H_c was deduced from the (*E*) configuration of the olefin precursor (±)-**22** because nitrone–olefin cycloaddition proceeds with retention of configuration of the olefin geometry.[16] In order to determine the relative orientation of the hydrogen atoms H_c and H_d, the cyclization product (±)-**25** was transformed, in a manner similar to that described above for the conversion of (±)-**8** into (±)-**10**, into the Boc-protected aminodiol (±)-**28**, which was converted into the acetonide (±)-**29**. Nuclear Overhauser effect (NOE) in the ^{1}H-NMR spectrum of (±)-**29** was observed between the protons shown by the arrows, thus verifying the *trans* orientation of the methine protons H_c and H_d in the dioxolane ring. Accordingly, the relative configuration of the four asymmetric centers in (±)-**25** was determined to be as depicted. The structures of the other cyclization products (±)-**26** and (±)-**27** were respectively ascertained by leading them to (±)-**25** through deacetylation and desilylation.

The reason for the high diastereoselectivity observed in the cyclization of (±)-**22** is unclear, but the hydrogen bond between the hydroxyl group and the nitrone moiety in (±)-**22** presumably played a role in stabilizing the transition state that leads to the diastereomer (±)-**25**, as illustrated in T.

Having found that the nitrone (±)-**22** undergoes diastereoselective cyclization reaction, our attention was next directed to the preparation of the optically active material of **22** and its conversion to optically active cispentacin. For this purpose, lipase-catalyzed kinetic resolution[17] was applied to the acetate (±)-**17** (Chart 5). Treatment of the racemic acetate (±)-**17** with lipase PS "Amano" (available from Amano Pharmaceutical Co., Ltd.) in acetone–water gave the optically active alcohol (*R*)-**16** in >97% enantiomeric excess (ee) in 36% yield, along with a 59% recovery of the optically active acetate (*S*)-**17** (51% ee). Optical purity of the alcohol (*R*)-**16** was

determined by high performance liquid chromatographic (HPLC) analysis of its (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionic acid (MTPA) ester, and that of the acetate (*S*)-**17** was determined by leading it to the alcohol (*S*)-**16** by treatment with potassium carbonate in methanol–water. The absolute configuration of (*R*)-**16** could not be determined at this stage, but it was later determined to be *R* by leading this alcohol to natural (−)-cispentacin.

The optically active alcohol (*R*)-**16** (>97% ee) thus obtained was transformed, in a manner similar to that described above for the transformation of the racemic alcohol (±)-**16** into (±)-**28**, into the Boc-protected aminodiol (−)-**28** in 4 steps (Chart 5). The diol moiety in (−)-**28** was cleaved by treatment with a catalytic amount of potassium permanganate in the presence of excess sodium metaperiodate in phosphate buffer solution to afford the carboxylic acid (−)-**11** in 91% yield. Removal of the Boc protecting group as above afforded optically active cispentacin ((−)-**1**), $[\alpha]_D^{25}$ −9.1° (c=1.23, H_2O), whose IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra were in accord with those reported in the literature.[1,2] The sign of rotation coincided with that of naturally occurring cispentacin,[1,2] thereby showing that the absolute configuration of the above-mentioned optically active substances **16** and **17**, as well as that of the derivatives thereof, is as indicated above and as illustrated in Chart 5.

Experimental

Melting points are not corrected. IR spectra were recorded on a Jasco A-102 spectrometer or on a Nic 5SXC spectrometer, ^{1}H-NMR spectra on a Varian EM-360L spectrometer (60 MHz), or a JEOL GX-270 spectrometer (270 MHz) using tetramethylsilane as the internal standard, and mass spectra (MS) and high-resolution mass spectra (HRMS) on a JEOL JMS D300 spectrometer. Preparative TLC was performed on TLC plates, Silica gel $60F_{254}$ precoated, layer thickness 2 mm (E. Merck). Chromatography columns were prepared with silica gel (60—110 mesh, Kanto Chemical Co., Inc.) and flash chromatography columns were prepared with silica gel (230—400 mesh, E. Merck). The amount of silica gel used and the developing solvents are shown in parentheses. Lobar® columns used were pre-packed LiChroprep® Si 60 columns (E. Merck, Größe A or B). The abbreviations used are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

(1*S,5*R**)-2-Benzyl-3-oxa-2-azabicyclo[3.3.0]octane ((±)-8)** CrO_3 (12.0 g, 0.12 mol) was added to a stirred solution of pyridine (19.0 g, 0.24 mol) in dichloromethane (300 ml) over a period of 15 min. After the solution had been stirred at room temperature for additional 30 min, a solution of 5-hexen-1-ol (2.00 g, 0.02 mol) in CH_2Cl_2 (8 ml) was added with stirring and ice-cooling, and the whole was stirred for 50 min at 0 °C. Powdered $KHSO_4$ was then added to allow the excess oxidant to precipitate, and the supernatant fluid was filtered through a column of Florisil. The precipitates were washed several times with a total of *ca.* 0.9 l of ether, and the washings were filtered through the same column. The combined filtrates (*ca.* 1.2 l), containing 5-hexenal (**6**), were used for the next reaction without concentration because of the volatility of **6**. In a separate experiment, formation of **6** was ascertained by partial removal of the solvent from the filtrate, giving a concentrated, crude solution of **6** in a mixture of CH_2Cl_2 and ether. IR (neat): 1730 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.7—2.5 (6H, m), 4.8—4.9 (1H, m), 5.0—5.2 (1H, m), 5.4—6.2 (1H, m), 9.82 (1H, t, J=2 Hz).

N-Benzylhydroxylamine (2.20 g, 18 mmol) was added to the solution of **6** obtained as described above, and the mixture was allowed to stand at room temperature for 2 h. After removal of the solvent *in vacuo*, the resulting crude solid nitrone **7** was heated at 70 °C in benzene (100 ml) for 2.5 h. The solvent was removed *in vacuo*, and the residue was purified by silica gel column chromatography (70 g, EtOAc : hexane = 3 : 17) to afford (±)-**8** (3.28 g, 81% overall yield from **5**) as an oil. IR ($CHCl_3$): 2970, 2890, 1605, 1500, 1455, 1030, 1015, 700 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.4—1.8 (6H, m), 3.02 (1H, m), 3.37 (1H, m), 3.43 (1H, dd, J=9, 6 Hz), 3.88 and 3.96 (each 1H, ABq, J=13 Hz), 4.14 (1H, t, J=9 Hz), 7.30—7.45 (5H, m). MS m/z: 203 (M^+), 160, 149, 126, 112, 91 (100%). HRMS Calcd for $C_{13}H_{17}NO$: 203.1305. Found: 203.1309.

(1*R,2*S**)-1-(*tert*-Butoxycarbonylamino)-2-hydroxymethylcyclopentane ((±)-10)** A mixture of (±)-**8** (3.39 g, 16.7 mmol), 10% palladium/carbon (1.70 g), and AcOH (110 ml) was stirred under an H_2 atmosphere (1 atm) at room temperature for 18 h. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to give an oily residue, which was treated with triethylamine (9.00 g, 89 mmol) and di-*tert*-butyl dicarbonate (7.50 g, 35 mmol) in THF (50 ml) at room temperature for 1 h. The mixture was diluted with AcOEt, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave a solid, which was recrystallized from hexane to give (±)-**10** (2.70 g) as colorless needles, mp 111—112 °C. *Anal.* Calcd for $C_{11}H_{21}NO_3$: C, 61.36; H, 9.83; N, 6.51. Found: C, 61.60; H, 9.63; N, 6.49. IR ($CHCl_3$): 3460, 2960, 1685, 1502, 1368, 1160 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3+D_2O$) δ: 1.13 (1H, m), 1.46 (9H, s), 1.40—1.75 (4H, m), 1.99 (1H, m), 2.13 (1H, m), 3.38 (1H, t, J=12 Hz), 3.58 (1H, dd, J=12, 4 Hz), 4.10 (1H, q-like, J=6 Hz). MS m/z: 216 (M^++1), 185, 158, 141, 129, 119, 98, 81, 57 (100%). Purification of the concentrated mother liquor by column chromatography (60 g, AcOEt : hexane = 1 : 3) afforded an additional amount of (±)-**10** (0.34 g, total yield = 85%) as a solid.

(1*R,2*S**)-2-(*tert*-Butoxycarbonylamino)cyclopentane-1-carboxylic Acid ((±)-11)** A solution of Jones reagent, prepared from CrO_3 (634 mg, 6.3 mmol), 98% H_2SO_4 (0.55 ml), and H_2O (2.4 ml), was added dropwise to an ice-cooled solution of (±)-**10** (339 mg, 1.58 mmol) in acetone (34 ml). After the solution had been stirred at 0 °C for 50 min, 2-propanol was added to decompose the excess oxidant. The mixture was diluted with AcOEt, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by column chromatography (5 g, AcOEt : benzene = 1 : 9) to afford (±)-**11** (305 mg, 84%) as an oil. IR ($CHCl_3$): 3450, 3320, 2980, 1705, 1500, 1408, 1370, 1165 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3+D_2O$) δ: 1.45 (9H, s), 1.40—1.75 (2H, m), 1.75—2.20 (4H, m), 3.0—3.2 (1H, br), 4.0—4.3 (1H, br). MS m/z: 228 (M^+−1), 172, 170, 156, 138, 127, 100, 67, 57 (100%). HRMS Calcd for $C_{11}H_{18}NO_4$ (M^+−1): 228.1219. Found: 228.1212.

(1*R,2*S**)-2-Aminocyclopentane-1-carboxylic Acid ((±)-1)** A mixture of (±)-**11** (692 mg, 3.0 mmol) and a 4 N HCl solution in dioxane (6 ml, 24 mmol) was stirred at room temperature for 1 h. The mixture was concentrated *in vacuo* to dryness and the residual solid was charged on a column of cation exchange resin, IR-120B (H^+ form, 50—100 mesh, 20 ml), washed with H_2O, and then eluted with 0.5 N ammonia solution. The eluates were evaporated *in vacuo* to dryness and the residual solid was recrystallized from acetone–H_2O to afford (±)-**1** (296 mg, 76%) as a powder, mp 201 °C (dec.). *Anal.* Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.50; H, 8.35; N, 10.57. IR (KBr): 2975, 2872, 1629, 1521, 1463, 1452, 1244 cm^{-1}. The ^{1}H-NMR, ^{13}C-NMR, and mass spectra were in accord with those of natural cispentacin reported in the literature.[1,2]

4-(1,3-Dithian-2-yl)butanol (13) A solution of 1,3-propanedithiol (8.6 g, 80 mmol), 3,4-dihydro(2*H*)pyran (14.0 g, 168 mmol), and boron trifluoride etherate (0.5 ml, 4 mmol) in CH_2Cl_2 (50 ml) was stirred at room temperature for 40 min. MeOH (30 ml) was then added and the whole was stirred at room temperature for 4 h. A diluted aqueous solution of $NaHCO_3$ was added and the mixture was extracted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. Concentration of the extract and purification of the residual oil by distillation afforded **13** (10.3 g) as an oil, bp 173—183 °C (5 Torr). IR (neat): 3400, 2934, 2902, 2860, 1422 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3+D_2O$) δ: 1.2—2.2 (8H, m), 2.5—3.1 (4H, m), 3.4—3.9 (2H, m), 4.05 (1H, t, J=7 Hz). MS m/z: 192 (M^+), 145, 133, 119 (100%). HRMS Calcd for $C_8H_{16}OS_2$: 192.0638. Found: 192.0638. The distillate with lower boiling point (150—173 °C (5 Torr)) and the residual oil were combined and purified by column chromatography (50 g, AcOEt : hexane = 2 : 3) to afford an additional amount of **13** (2.8 g, 78% combined yield from 1,3-propanedithiol) as an oil.

4-(1,3-Dithian-2-yl)butanal (14) Dimethyl sulfoxide (6.5 g, 83 mmol) was added to a solution of oxalyl chloride (9.93 g, 78 mmol) in CH_2Cl_2 (150 ml) at −70 °C with stirring. After 15 min, a solution of **13** (7.52 g, 39 mmol) in CH_2Cl_2 (30 ml) was added dropwise to the mixture and the whole was stirred at −70 °C for 40 min. Triethylamine (17 g, 168 mmol) was then added and the mixture was allowed to warm to −5 °C over a period of 2 h. The mixture was diluted with CH_2Cl_2, washed with brine, and dried over Na_2SO_4. Evaporation of the solvent gave an oily residue, which was purified by column chromatography (100 g, benzene) to afford **14** (6.15 g, 83%) as an oil. IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.4—2.2 (6H, m), 2.2—2.7 (2H, m), 2.7—3.0 (4H, m), 4.04 (1H,

t-like, $J=7$ Hz), 9.82 (1H, t, $J=2$ Hz). MS *m/z*: 190 (M^+), 145, 133, 119 (100%). HRMS Calcd for $C_8H_{14}OS_2$: 190.0481. Found: 190.0480.

(*E*)-7-(1,3-Dithian-2-yl)-3-hepten-2-one (15) A solution of **14** (100 mg, 0.53 mmol) and 1-(triphenylphosphoranylidene)-2-propanone (180 mg, 0.57 mmol) in benzene (2 ml) was refluxed for 6.5 h. The solvent was evaporated *in vacuo* and the residue was purified by column chromatography (2 g, AcOEt : benzene = 1 : 19) to afford **15** (110 mg, 91%) as an oil. IR ($CHCl_3$): 2960, 1680, 1630, 1430, 1365, 1260, 980 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.2—2.3 (8H, m), 2.24 (3H, s), 2.5—3.0 (4H, m), 4.02 (1H, t-like, $J=7$ Hz), 6.05 (1H, d-like, $J=16$ Hz), 6.78 (1H, dt, $J=16$, 6 Hz). MS *m/z*: 230 (M^+), 191, 187, 175, 172, 145, 119 (100%). HRMS Calcd for $C_{11}H_{18}OS_2$: 230.0794. Found: 230.0797.

(±)-(*E*)-7-(1,3-Dithian-2-yl)-3-hepten-2-ol ((±)-16) Sodium borohydride (0.95 g, 28 mmol) was added portionwise to a solution of **15** (4.50 g, 20 mmol) and cerium(III) chloride heptahydrate (7.65 g, 21 mmol) in EtOH (70 ml) at 0 °C with stirring. After 40 min, a saturated aqueous solution of NH_4Cl was added and the mixture was extracted with AcOEt. The extract was dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to leave an oily residue, which was purified by column chromatography (60 g, AcOEt : benzene = 1 : 19) to afford (±)-**16** (4.40 g, 97%) as an oil. IR ($CHCl_3$): 3450, 3000, 2950, 1425, 1280, 970 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3+D_2O$) δ: 1.24 (3H, d, $J=6$ Hz), 1.3—2.3 (9H, m), 2.7—3.0 (4H, m), 4.05 (1H, t, $J=7$ Hz), 3.9—4.5 (1H, m), 5.5—5.7 (2H, m). MS *m/z*: 232 (M^+), 214, 191, 167, 157, 145, 134, 119 (100%). HRMS Calcd for $C_{11}H_{20}OS_2$: 232.0951. Found: 232.0954.

(±)-(*E*)-7-(1,3-Dithian-2-yl)-3-hepten-2-yl Acetate ((±)-17) A solution of (±)-**16** (5.80 g, 25 mmol) and acetic anhydride (12.0 ml, 163 mmol) in pyridine (50 ml) was stirred at room temperature overnight. After addition of MeOH (20 ml) at 0 °C, the mixture was stirred for 15 min at the same temperature. The mixture was diluted with AcOEt, washed with brine, and then dried over Na_2SO_4. The solvent was evaporated *in vacuo* to leave an oily residue, which was purified by flash chromatography (80 g, benzene) to afford (±)-**17** (6.50 g, 95%) as an oil. IR ($CHCl_3$): 2950, 1720, 1372, 1250, 1040 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 1.27 (3H, d, $J=6$ Hz), 1.4—2.4 (8H, m), 2.01 (3H, s), 2.6—3.0 (4H, m), 4.05 (1H, t-like, $J=7$ Hz), 5.1—5.8 (3H, m). MS *m/z*: 274 (M^+), 231, 214, 167, 145, 134, 119 (100%). HRMS Calcd for $C_{13}H_{22}O_2S_2$: 274.1060. Found: 274.1059.

(±)-2-[(*E*)-6-(*tert*-Butyldimethylsilyloxy)-4-heptenyl]-1,3-dithiane ((±)-18) A solution of (±)-**16** (62 mg, 0.27 mmol), imidazole (40 mg, 0.59 mmol), and *tert*-butylchlorodimethylsilane (60 mg, 0.40 mmol) in *N*,*N*-dimethylformamide (DMF, 1.2 ml) was stirred at room temperature for 1.2 h. The mixture was diluted with benzene, and washed successively with an aqueous solution of $NaHCO_3$, water, and brine. The extract was dried over Na_2SO_4, and the solvent was evaporated to leave an oily residue, which was purified by column chromatography (2 g, AcOEt : benzene = 1 : 49) to afford (±)-**18** as an oil. IR ($CHCl_3$): 2940, 2800, 1730, 1460, 1250, 970, 835 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.04 (6H, s), 0.88 (9H, s), 1.16 (3H, d, $J=6$ Hz), 1.3—2.3 (8H, m), 2.6—3.0 (4H, m), 4.03 (1H, t, $J=7$ Hz), 3.9—4.5 (1H, m), 5.4—5.6 (2H, m). MS *m/z*: 346 (M^+), 331, 289, 221, 181, 165, 149, 125, 87, 81, 75 (100%). HRMS Calcd for $C_{17}H_{34}OS_2Si$: 346.1815. Found: 346.1814.

(±)-(*E*)-7-Hydroxy-5-octenal ((±)-19) A suspension of (±)-**16** (133 mg, 0.57 mmol), $HgCl_2$ (340 mg, 1.3 mmol), and $CaCO_3$ (250 mg, 2.5 mmol) in a mixture of CH_3CN (4 ml) and H_2O (1 ml) was heated under reflux for 5 h. After being cooled, the mixture was diluted with AcOEt and the resulting precipitates were removed by filtration. The filtrate was washed with brine and dried over Na_2SO_4. The concentrated extract was chromatographed on silica gel (2 g, AcOEt : hexane = 1 : 19—1 : 4) to afford (±)-**16** (40 mg, 30% recovery) and (±)-**19** (41 mg, 50%) as oils in that order of elution. The spectral data of (±)-**19** are as follows. IR ($CHCl_3$): 3430, 2920, 1720, 968 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3+D_2O$) δ: 1.26 (3H, d, $J=6$ Hz), 1.73 (2H, quintet, $J=7$ Hz), 2.08 (2H, m), 2.45 (2H, t d, $J=7$, 2 Hz), 4.27 (1H, quintet, $J=6$ Hz), 5.5—5.7 (2H, m), 9.77 (1H, t, $J=2$ Hz). MS *m/z*: 141 (M^+-1), 124, 96, 83, 81, 71, 43 (100%). HRMS Calcd for $C_8H_{13}O_2$ (M^+-1): 141.0907. Found: 141.0904.

(±)-(*E*)-7-Acetoxy-5-octenal ((±)-20) Following a procedure similar to that described above for the conversion of (±)-**16** to (±)-**19**, (±)-**17** (40 mg, 0.15 mmol) was treated with $HgCl_2$ (129 mg, 0.48 mmol) and $CaCO_3$ (106 mg, 1.06 mmol) in a mixture of CH_3CN (2.3 ml) and H_2O (0.7 ml) to afford, after purification by column chromatography (0.5 g, benzene), (±)-**20** (26 mg, 97%) as an oil. IR ($CHCl_3$): 1730 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, $J=6$ Hz), 1.73 (2H, quintet, $J=7$ Hz), 2.01 (3H, s), 2.08 (2H, m), 2.45 (2H, t d, $J=7$, 2 Hz), 5.1—5.8 (3H, m), 9.77 (1H, t, $J=2$ Hz). MS *m/z*: 183 (M^+-1), 142, 123 (100%). HRMS Calcd for $C_{10}H_{15}O_3$ (M^+-1): 183.1008. Found: 183.1012.

(±)-(*E*)-7-(*tert*-Butyldimethylsilyloxy)-5-octenal ((±)-21) Following a procedure similar to that described above for the conversion of (±)-**16** to (±)-**19**, (±)-**18** (80 mg, 0.23 mmol) was treated with $HgCl_2$ (200 mg, 0.74 mmol) and $CaCO_3$ (150 mg, 1.5 mmol) in a mixture of CH_3CN (5 ml) and H_2O (1 ml) to afford, after purification by column chromatography (2 g, AcOEt : benzene = 1 : 49), (±)-**21** (48 mg, 87%) as an oil. IR ($CHCl_3$): 2940, 1720, 1460, 1355, 975 cm^{-1}. ^{1}H-NMR (60 MHz, $CDCl_3$) δ: 0.06 (6H, s), 0.90 (9H, s), 1.18 (3H, d, $J=6$ Hz), 1.2—2.4 (4H, m), 2.42 (2H, t-like, $J=6$ Hz), 4.0—4.5 (1H, m), 5.4—5.6 (2H, m), 9.82 (1H, t, $J=2$ Hz). MS *m/z*: 255 (M^+-1), 239, 199 (100%), 75. HRMS Calcd for $C_{14}H_{27}O_2Si$ (M^+-1): 255.1771. Found: 255.1768.

(1*S,4*R**,5*R**)-2-Benzyl-4-[(*R**)-1-hydroxyethyl]-3-oxa-2-azabicyclo-[3.3.0]octane ((±)-25) and (1*R**,4*S**,5*S**)-2-Benzyl-4-[(*R**)-1-hydroxyethyl]-3-oxa-2-azabicyclo[3.3.0]octane ((±)-25′)** A solution of (±)-**19** (41 mg, 0.29 mmol) and *N*-benzylhydroxylamine (37 mg, 0.30 mmol) in $CHCl_3$ (3 ml) was concentrated *in vacuo*. Addition of benzene and evaporation were repeated three times in order to remove water azeotropically. The resulting crude nitrone (±)-**22** was heated in benzene (4 ml) at 80 °C for 6 h. Column chromatography (1 g, AcOEt : hexane = 1 : 9) of the crude product afforded a 15 : 1 mixture of (±)-**25** and (±)-**25′** (68 mg, 95%) as an oil. The ratio was determined by ^{1}H-NMR (270 MHz). Further purification using a Lobar® column (Größe A, AcOEt : $CHCl_3$ = 1 : 10) afforded (±)-**25′** (4 mg, 6%) as the more mobile isomer and (±)-**25** (60 mg, 84%) as the less mobile one, each as an oil.

(±)-**25**: IR ($CHCl_3$): 3450, 2590, 2880, 1660, 1500, 1455, 1030 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3+D_2O$) δ: 1.17 (3H, d, $J=6.5$ Hz), 1.30—1.70 (5H, m), 2.60—2.70 (1H, m), 3.25—3.40 (1H, br), 3.43 (1H, t, $J=6.5$ Hz), 3.75 (1H, quintet, $J=6.5$ Hz), 3.93 and 4.00 (1H each, ABq, $J=13$ Hz), 7.2—7.4 (5H, m). MS *m/z*: 247 (M^+), 232, 204, 202, 162, 146, 136, 106, 91 (100%). HRMS Calcd for $C_{15}H_{21}NO_2$: 247.1563. Found: 247.1560.

(±)-**25′**: IR ($CHCl_3$): 3450, 2950, 2870, 1600, 1590, 1448, 1360, 1030 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3+D_2O$) δ: 1.14 (3H, d, $J=7$ Hz), 1.3—1.7 (5H, m), 1.82 (1H, m), 2.94 (1H, br q, $J=7$ Hz), 3.1—3.3 (1H, br), 3.50 (1H, dd, $J=7$, 3 Hz), 3.96 (2H, s), 4.03 (1H, qd, $J=7$, 3 Hz). MS *m/z*: 247 (M^+), 232, 204, 202, 162, 146, 106, 91 (100%). HRMS Calcd for $C_{15}H_{21}NO_2$: 247.1563. Found: 247.1559.

(1*S,4*R**,5*R**)-4-[(*R**)-1-Acetoxyethyl]-2-benzyl-3-oxa-2-azabicyclo-[3.3.0]octane ((±)-26) and (1*R**,4*S**,5*S**)-4-[(*R**)-1-Acetoxyethyl]-2-benzyl-3-oxa-2-azabicyclo[3.3.0]octane ((±)-26′)** Following a procedure similar to that described above for the conversion of (±)-**19** to a mixture of (±)-**25** and (±)-**25′**, (±)-**20** (23 mg, 0.12 mmol) was condensed with *N*-benzylhydroxylamine (15 mg, 0.12 mmol) in benzene (5 ml), and the resulting nitrone (±)-**23** was heated in benzene (2 ml) at 80 °C for 6 h to afford, after purification by chromatography (0.5 g, benzene), an inseparable 1 : 2 mixture of (±)-**26** and (±)-**26′** (27 mg, 80%) as an oil. The ratio was determined by ^{1}H-NMR. The spectral data of this mixture were as follows. IR ($CHCl_3$): 2950, 1720 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.25 (3H × (2/3), d, $J=6$ Hz), 1.26 (3H × (1/3), d, $J=6$ Hz), 1.2—1.9 (6H, m), 2.04 (3H, s), 2.6—2.8 (1H, m), 3.2—3.3 (1H, m), 3.5—3.7 (1H, m), 3.85 and 4.08 (1H × (1/3) each, ABq, $J=13$ Hz), 3.88 and 4.04 (1H × (2/3) each, ABq, $J=13$ Hz), 5.0—5.1 (1H, m), 7.2—7.4 (5H, m).

Deacetylation of (±)-26 and (±)-26′ K_2CO_3 (30 mg, 0.22 mmol) was added to an ice-cooled, stirred solution of a 1 : 2 mixture of (±)-**26** and (±)-**26′** [24 mg, 0.083 mmol, obtained as described above by cyclization of (±)-**23**] in MeOH (2 ml) and the mixture was allowed to warm to room temperature over a period of 2.5 h. The mixture was diluted with AcOEt, washed with brine, and dried over Na_2SO_4. The solvent was evaporated to leave an oily residue, which was purified by using a Lobar® column (Größe A, AcOEt : $CHCl_3$ = 1 : 10) to afford (±)-**25′** (12.6 mg, 61%) as the more mobile isomer and (±)-**25** (5.3 mg, 26%) as the less mobile one, each as an oil. The spectral data were in accord with those of (±)-**25** and (±)-**25′** obtained as described above from (±)-**19** *via* (±)-**22**.

(1*S,4*R**,5*R**)-2-Benzyl-4-[(*R**)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3-oxa-2-azabicyclo[3.3.0]octane ((±)-27) and (1*R**,4*S**,5*S**)-2-Benzyl-4-[(*R**)-1-(*tert*-butyldimethylsilyloxy)ethyl]-3-oxa-2-azabicyclo[3.3.0]octane ((±)-27′)** Following a procedure similar to that described above for the conversion of (±)-**19** to a mixture of (±)-**25** and (±)-**25′**, (±)-**21** (49 mg, 0.19 mmol) was condensed with *N*-benzylhydroxylamine (24 mg, 0.19 mmol) in benzene (5 ml), and the resulting nitrone (±)-**24** was heated in toluene (4 ml) at 110 °C for 3 h to afford, after purification using a Lobar® column (Größe A, AcOEt : hexane = 1 : 19), an inseparable 1 : 1 mixture of (±)-**27** and (±)-**27′** (49 mg, 71% combined yield) as an oil. The ratio was determined by ^{1}H-NMR. The spectral data of this mixture were as follows. IR ($CHCl_3$): 2960, 1255, 835 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 0.02 (3H × (1/2), s), 0.04 (3H × (1/2), s), 0.06 (3H × (1/2), s), 0.09 (3H × (1/2),

s), 0.85 (9H × (1/2), s), 0.90 (9H × (1/2), s), 1.13 (3H × (1/2), J=6 Hz), 1.14 (3H × (1/2), J=6 Hz), 1.1—2.1 (5H, m), 2.5—2.7 (1H, m), 2.8—3.0 (1H, m), 3.1—3.3 (1H, m), 3.37 (1H × (1/2), dd, J=7, 5 Hz), 3.49 (1H × (1/2), dd, J=7, 6 Hz), 3.7—4.1 (3H, m), 7.2—7.4 (5H, m).

Desilylation of (±)-27 and (±)-27′ A solution of a 1 : 1 mixture of (±)-**27** and (±)-**27′** [20 mg, 0.055 mmol, obtained as described above by cyclization of (±)-**24**], AcOH (4 mg, 0.067 mmol), Bu_4NF (1.0 N solution in THF, 0.11 ml, 0.011 mmol) was stirred at room temperature overnight. The mixture was charged on a column of silica gel (1 g) and eluted with AcOEt. The concentrated eluates were further purified by chromatography (0.5 g, AcOEt : hexane = 1 : 10) to afford an oily product (13 mg, 95%), which was shown by ^{1}H-NMR to be a 1 : 1 mixture of the above-described alcohols (±)-**25** and (±)-**25′**.

(1*S,2*R**)-1-(*tert*-Butoxycarbonylamino)-2-[(1*R**,2*R**)-1,2-dihydroxypropyl]cyclopentane ((±)-28)** Following a procedure similar to that described above for the conversion of (±)-**8** into (±)-**10**, (±)-**25** (55 mg, 0.22 mol) was hydrogenolyzed and *tert*-butoxycarbonylated to afford, after purification by column chromatography (2 g, AcOEt : benzene = 3 : 7), (±)-**28** (47 mg, 82%) as an oil. IR ($CHCl_3$): 3450, 2970, 1680, 1500, 1330, 1160, 990 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3 + D_2O$) δ: 1.25 (1H, m), 1.27 (3H, d, J=6 Hz), 1.46 (9H, s), 1.53—1.65 (2H, m), 1.65—1.85 (2H, m), 1.85—2.03 (1H, m), 2.03—2.20 (1H, m), 3.15 (1H, dd, J=10, 2 Hz), 3.67 (1H, qd, J=6, 2 Hz), 4.12 (1H, q-like, J=6 Hz), 4.51 (1H, br d, J=7 Hz). MS m/z: 260 ($M^+ + 1$), 228, 214, 185, 158, 114, 57 (100%). HRMS Calcd for $C_{13}H_{26}NO_4$ ($M^+ + 1$): 260.1844. Found: 260.1850.

(4*R,5*R**)-4-[(1*R**,2*S**)-2-(*tert*-Butoxycarbonylamino)cyclopentyl]-2,2,5-trimethyl-1,3-dioxolane ((±)-29)** A solution of (±)-**28** (25 mg, 0.096 mmol), 2,2-dimethoxypropane (1 ml), and pyridinium *p*-toluenesulfonate (1 mg, 0.004 mmol) in acetone (1 ml) was stirred at room temperature for 3 h. The mixture was diluted with AcOEt, washed successively with an aqueous solution of $NaHCO_3$ and brine, and dried over Na_2SO_4. The solvent was evaporated to leave an oily residue, which was purified by column chromatography (0.5 g, AcOEt : benzene = 1 : 9) to afford (±)-**29** (26 mg, 90%) as an oil. IR ($CHCl_3$): 3400, 2970, 1700, 1500, 1265, 1165 cm^{-1}. ^{1}H-NMR (270 MHz, $CDCl_3$) δ: 1.27 (3H, d, J=6 Hz), 1.38 (3H, s), 1.42 (3H, s), 1.44 (9H, s), 1.5—2.1 (7H, m), 3.64 (1H, dd, J=8, 6 Hz), 3.91 (1H, dq, J=8, 6 Hz), 4.02 (1H, m), 5.6 (1H, br). In the differential NOE spectrum, the methine signals at δ 3.64 and 3.91 respectively appeared upon irradiating the methyl signals at δ 1.38 and 1.42. MS m/z: 300 ($M^+ + 1$), 284, 270, 254, 228, 185, 168, 124 (100%), 57. HRMS Calcd for $C_{16}H_{30}NO_4$ ($M^+ + 1$): 300.2157. Found: 300.2161.

Enantioselective Hydrolysis of (±)-17 Using Lipase. (*R*)-(*E*)-7-(1,3-Dithian-2-yl)-3-hepten-2-ol ((*R*)-16) and (*S*)-(*E*)-7-(1,3-Dithian-2-yl)-3-hepten-2-yl Acetate ((*S*)-17) A mixture of (±)-**17** (6.60 g, 24 mmol), Lipase PS "Amano" (available from Amano Pharmaceutical Co., Ltd., 6.60 g), KH_2PO_4 (3.37 g, 25 mmol), K_2HPO_4 (4.35 g, 25 mmol), acetone (400 ml), and H_2O (50 ml) was stirred at room temperature for 12 h. Further lipase (6.00 g) was added and the whole was vigorously stirred at 35—40 °C for 18 h. The mixture was filtered by suction, and the filtrate was diluted with AcOEt, washed with brine, and dried over Na_2SO_4. The solvent was evaporated to leave an oily residue, which was purified by column chromatography (60 g, AcOEt : benzene = 0 : 1—1 : 19) to afford (*S*)-**17** [3.90 g, 59% recovery, $[\alpha]_D^{25}$ −22.9° (c = 1.76, $CHCl_3$), 51% ee] and (*R*)-**16** [2.00 g, 36% yield, $[\alpha]_D^{25}$ +6.3° (c = 1.06, $CHCl_3$), >97% ee] as oils in that order of elution. The IR, ^{1}H-NMR, and mass spectra of (*R*)-**16** and (*S*)-**17** were in accord with those of the corresponding racemates described above.

Determination of the Optical Purity of (*R*)-16 A solution of (*R*)-**16** [10.6 mg, 0.064 mmol, $[\alpha]_D^{25}$ +6.3° (c = 1.06, $CHCl_3$), obtained above by enzymatic hydrolysis of (±)-**17**] and (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropionyl chloride (20 mg, 0.079 mmol) in pyridine (0.4 ml) was stirred at room temperature for 1 h. TLC revealed that the starting alcohol (*R*)-**16** was all esterified. The mixture was directly analyzed by HPLC, and the diastereomeric purity of the MTPA ester formed was determined to be >97% de, thereby showing that the optical purity of the starting alcohol (*R*)-**16** had been >97% ee. HPLC conditions: immobile phase, Shim-pack CLC-SIL (M) (4.6 mm i.d. × 25 cm), Shimadzu, Kyoto, Japan; column temperature, 23 °C; mobile phase, hexane : AcOEt = 97 : 3; flow rate, 1.0 ml/min; detection, UV at 254 nm. The retention times of the diastereomers were as follows: minor isomer, 19.9 min; major isomer, 20.7 min.

Determination of the Optical Purity of (*S*)-17 A solution of (*S*)-**17** [23 mg, 0.084 mmol, $[\alpha]_D^{25}$ −22.9° (c = 1.76, $CHCl_3$), recovered as described above from the reaction mixture of the enzymatic hydrolysis of (±)-**17** to (*R*)-**16**] and K_2CO_3 (50 mg, 0.36 mmol) in a mixture of MeOH (1 ml) and H_2O (0.5 ml) was stirred at room temperature for 1.5 h. The mixture was diluted with AcOEt, washed twice with brine, and dried over Na_2SO_4. The solvent was evaporated *in vacuo* to leave an oily residue, which was purified by chromatography (0.5 g, AcOEt : benzene = 1 : 19) to afford (*S*)-**16** (19.6 mg, 100%) as an oil, $[\alpha]_D^{25}$ −3.2° (c = 1.33, $CHCl_3$). The IR, ^{1}H-NMR, and mass spectra were in accord with those of the corresponding racemate (±)-**16** described above. The optical purity of (*S*)-**16** was determined to be 51% ee by HPLC of its MTPA ester, following a procedure similar to that described above for the determination of the optical purity of (*R*)-**16**. The optical purity of the starting acetate (*S*)-**17** was therefore shown to have been 51% ee.

(*R*)-(*E*)-7-Hydroxy-5-octenal ((*R*)-19) Following a procedure similar to that described for the racemate, the optically active alcohol (*R*)-**16** [$[\alpha]_D^{25}$ +6.3°, >97% ee, obtained above by enzymatic hydrolysis of (±)-**17**] was heated with $HgCl_2$ (8.0 g, 29 mmol) and $CaCO_3$ (7.5 g, 75 mmol) in a mixture of CH_3CN (80 ml) and H_2O (32 ml) under reflux for 7 h to afford, after purification by column chromatography (20 g, AcOEt : hexane = 1 : 4), (*R*)-**19** (1.14 g, 93%) as an oil, $[\alpha]_D^{25}$ +24.4° (c = 1.26, $CHCl_3$). The IR, ^{1}H-NMR, and mass spectra were in accord with those of the racemic material (±)-**19** described above.

(1*S*,4*R*,5*R*)-2-Benzyl-4-[(*R*)-1-hydroxyethyl]-3-oxa-2-azabicyclo[3.3.0]-octane ((+)-25) and (1*R*,4*S*,5*S*)-2-Benzyl-4-[(*R*)-1-hydroxyethyl]-3-oxa-2-azabicyclo[3.3.0]octane ((−)-25′) Following a procedure similar to that described above for the racemates, the optically active aldehyde (*R*)-**19** (1.13 g, 7.95 mmol) was condensed with *N*-benzylhydroxylamine (970 mg, 7.89 mmol) in benzene (20 ml), and the resulting crude nitrone (*R*)-**22** was heated in benzene (100 ml) under reflux for 3 h to afford, after purification by flash column chromatography (30 g, AcOEt : $CHCl_3$ = 1 : 49), a 15 : 1 (determined by ^{1}H-NMR) mixture of (+)-**25** and (−)-**25′** (1.67 g, 85%) as an oil. Further purification using a Lobar® column (Größe B, AcOEt : $CHCl_3$ = 1 : 10) afforded (−)-**25′** (50 mg, 3%) as the more mobile isomer, $[\alpha]_D^{25}$ −71.6° (c = 2.26, $CHCl_3$), and (+)-**25** (1.17 g, 60%) as the less mobile isomer, $[\alpha]_D^{25}$ +60.4° (c = 1.61, $CHCl_3$), each as an oil. The IR, ^{1}H-NMR, and mass spectra were in accord with those of the racemates (±)-**25** and (±)-**25′** described above.

(1*S*,2*R*)-1-(*tert*-Butoxycarbonylamino)-2-[(1*R*,2*R*)-1,2-dihydroxypropyl]cyclopentane ((−)-28) Following a procedure similar to that described above for the racemate, the optically active isoxazolidine (+)-**25** (1.17 g, 3.94 mmol) was hydrogenolyzed with 10% palladium/carbon (1.7 g) in AcOH (35 ml), and then treated with triethylamine (3.65 g, 36 mmol) and di-*tert*-butyl dicarbonate (4.23 g, 19.4 mmol) in a mixture of THF (30 ml) and benzene (10 ml) to afford, after purification by column chromatography (40 g, AcOEt : benzene = 3 : 7), (−)-**28** (0.95 g, 93%) as an oil, $[\alpha]_D^{25}$ −34.1° (c = 1.07, $CHCl_3$). The IR, ^{1}H-NMR, and mass spectra were in accord with those of the corresponding racemate (±)-**28** described above.

(1*R*,2*S*)-2-(*tert*-Butoxycarbonylamino)cyclopentane-1-carboxylic Acid ((−)-11) A solution of $NaIO_4$ (2.7 g, 13 mmol) and $KMnO_4$ (70 mg, 0.44 mmol) in H_2O (30 ml) was added to an ice-cooled solution of (−)-**28** (0.92 g, 3.6 mmol), KH_2PO_4 (1.63 g, 12 mmol), and K_2HPO_4 (2.09 g, 12 mmol) in a mixture of acetone (60 ml) and H_2O (12 ml). Stirring was continued for 3 h, during which time the mixture was allowed to warm to room temperature. Further $KMnO_4$ (70 mg, 0.44 mmol) was added and the whole was stirred at room temperature for 1.5 h. The mixture was diluted with AcOEt, acidified with HCl, washed with brine, and dried over Na_2SO_4. The solvent was evaporated and the residue was purified by chromatography (20 g, AcOEt : benzene = 1 : 9) to afford (−)-**11** (740 mg, 91%) as an oil, $[\alpha]_D^{25}$ −29.6° (c = 1.56, $CHCl_3$). The IR, ^{1}H-NMR, and mass spectra were in accord with those of the corresponding racemate (±)-**11** described above.

(1*R*,2*S*)-2-Aminocyclopentane-1-carboxylic Acid (Cispentacin, (−)-1) Following a procedure similar to that described above for the racemate, the optically active acid (−)-**11** (419 mg, 1.83 mmol) was treated with a 4 N HCl solution in dioxane (15 ml, 60 mmol). Concentration of the reaction mixture to dryness and purification using a column of cation exchange resin, IR-120B (H^+ form, 50—100 mesh, 50 ml), afforded a crude solid, which was recrystallized from acetone–H_2O to afford (−)-**1** (139 mg) as a powder, mp 227 °C (dec.), $[\alpha]_D^{25}$ −9.1° (c = 1.23, H_2O) [lit. $[\alpha]_D^{25}$ −10.7° (c = 1.0, H_2O),[1] $[\alpha]_D^{25}$ −9.8° (c = 1.0, H_2O)[2]]. *Anal.* Calcd for $C_6H_{11}NO_2$: C, 55.80; H, 8.58; N, 10.84. Found: C, 55.71; H, 8.55; N, 10.80. Recrystallization of the mother liquor afforded an additional amount of (−)-**1** (49 mg, total yield = 80%) as a powder, mp 220 °C (dec.). The IR, ^{1}H-NMR, ^{13}C-NMR, and mass spectra were in accord with those of cispentacin (FR109615) reported in the literature.[1,2]

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