Chem. Pharm. Bull. 36(4)1358—1365(1988)

Preparation of Chiral, Highly Functionalized Cyclopentenones

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(Received October 5, 1987)

During a detailed examination on the cyclization of 1,4-diketones to cyclopentenones, we have found that two oxygenated products (**4** and **5**) are formed when the purification by column chromatography on silica gel takes a long time. The highly functionalized cyclopentenone (**4a**) obtained as the major product in this manner seems to be an attractive synthon for the synthesis of natural products. For example, the chiral synthon (1*S*,4*S*)-4-benzyloxycarbonyl-1,4-dihydroxy-2-methoxycarbonyl-3-methyl-2-cyclopentene ((+)-**7**) with high optical purity was obtained by microbial reduction with *Rhodotorula rubra* CCY 20-7-1, and the absolute stereochemistry was established independently by using the exciton chirality method and the chemical method.

Keywords——air-oxidation; 2,3,4,4-tetrasubstituted cyclopentenone; microbial reduction; kinetic resolution; silica-gel column chromatography

Chiral, highly functionalized cyclopentenones seem to be attractive synthons for the synthesis of biologically active compounds containing a five-membered ring, such as prostaglandins (PGs),[1] brefeldin A,[2] and cuparenones.[3] We wish to report that cyclopentenones prepared from 1,4-diketones undergo a facile air-oxidation to afford two oxygenated products, and chiral compounds could be obtained by microbial reduction of the products.

Previously, we reported a preparation[4] of 1,4-diketones (**1**) and the facile cyclization to the cyclopentenones (**2**), which could be stereospecifically hydrogenated with H_2/Pd–C to 2,3-*trans*-2,4-*trans*-trisubstituted cyclopentanone (**3**). During a more detailed examination on the cyclization of **1**, we have found that different products are obtained, depending on the time taken for column chromatography on silica gel. In the cyclization of **1** with $KHCO_3$/MeOH at room temperature to 40 °C, the usual work-up afforded crude **2**. Rapid silica-gel column chromatography of the crude **2** using benzene–Et_2O as the eluent gave **2** in 56—59% yield. However, in the case when elution with hexane–AcOEt required about 5 h, two oxygenated products (**4** and **5**) were obtained in 43—48% and 16—21% yields, respectively, and **2** could not be isolated at all (Chart 1).

The structures of **4a** and **5a** were confirmed on the basis of spectroscopic analysis. In the mass spectra (MS), **4a** and **5a** showed the molecular ion peak at *m/z* 304, suggesting that air-oxidation of **2a** (molecular weight 288) had occurred. The infrared (IR) spectra showed the absorption band of OH at 3450 cm^{-1}, in addition to the signals of hydroxy protons at δ 4.02 in **4a** and at δ 3.80 in **5a** in the proton nuclear magnetic resonance (^{1}H-NMR) spectra. The position of the hydroxy function was deduced on the basis of the ^{1}H-NMR spectra. While the signals of the C_5-geminal protons in **2a** and **4a** were observed at δ 2.73, 2.75 (1H each) and δ 2.68, 2.90 (1H each) as separate peaks, respectively, the C_5-geminal protons in **5a** appeared at lower field (δ 3.34) as signals with homoallylic coupling (J=2 Hz) between C_5-H_5 and C_3-CH_3. Furthermore, **5a** was converted into the carboxylic acid (**6a**) by oxidation with $NaIO_4$. From these results, it was concluded that the hydroxy function in **4a** and **5a** should be at C_4

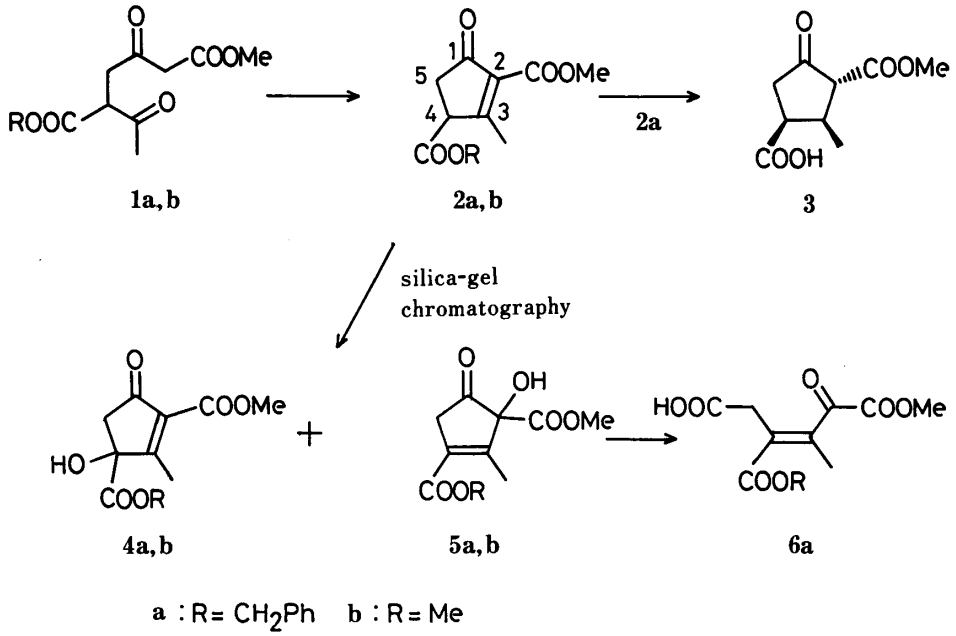


Chart 1

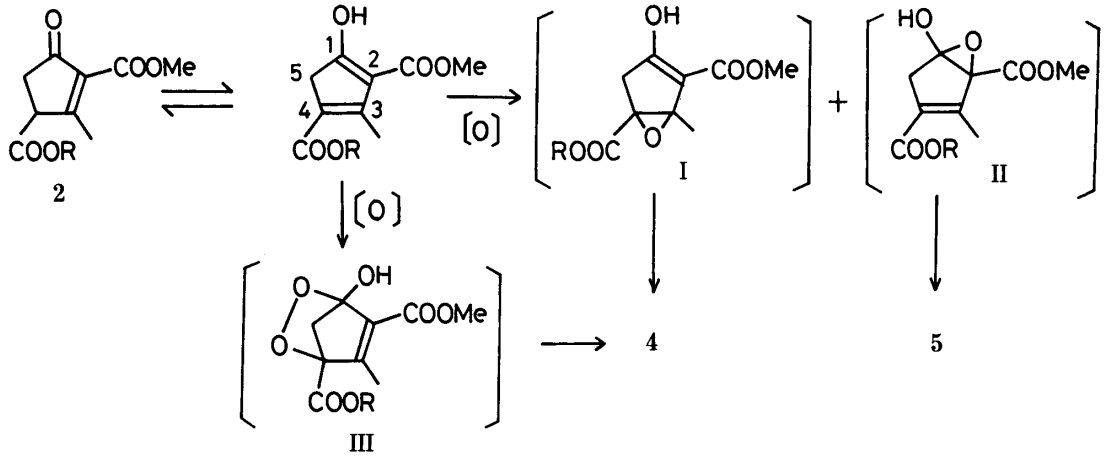


Chart 2

and at C_2, respectively.

The oxidation mechanism is tentatively proposed to be as shown in Chart 2. Product **4** or **5** may be produced *via* the intermediate I or II, formed by air-oxidation of $C_1=C_2$ or $C_3=C_4$. It also seems possible to assume the intermediate III for **4**. Rearrangement of the C_2-OH to the C_4 position or of the C_4-OH to the C_2 position in silica-gel chromatography was not observed.

These readily available and highly functionalized cyclopentenones (**4**) seem to have attractive functional groups for the synthesis of natural products. That is to say, these compounds have a conjugated enone (required for 1,4-addition) and a masked carbonyl function convertible to the carbonyl function by $LiAlH_4$ reduction and subsequent oxidation with $NaIO_4$. In addition, it is also possible to introduce appropriate substituents at each position on the five-membered ring.

The above structural advantages prompted us to prepare chiral **4a** by microbial reduction. On screening of microbial reduction of (±)-**4a** using 40 species of yeasts, *Rhodotorula rubra* CCY 20-7-1 was found to be effective for the kinetic resolution. On large-

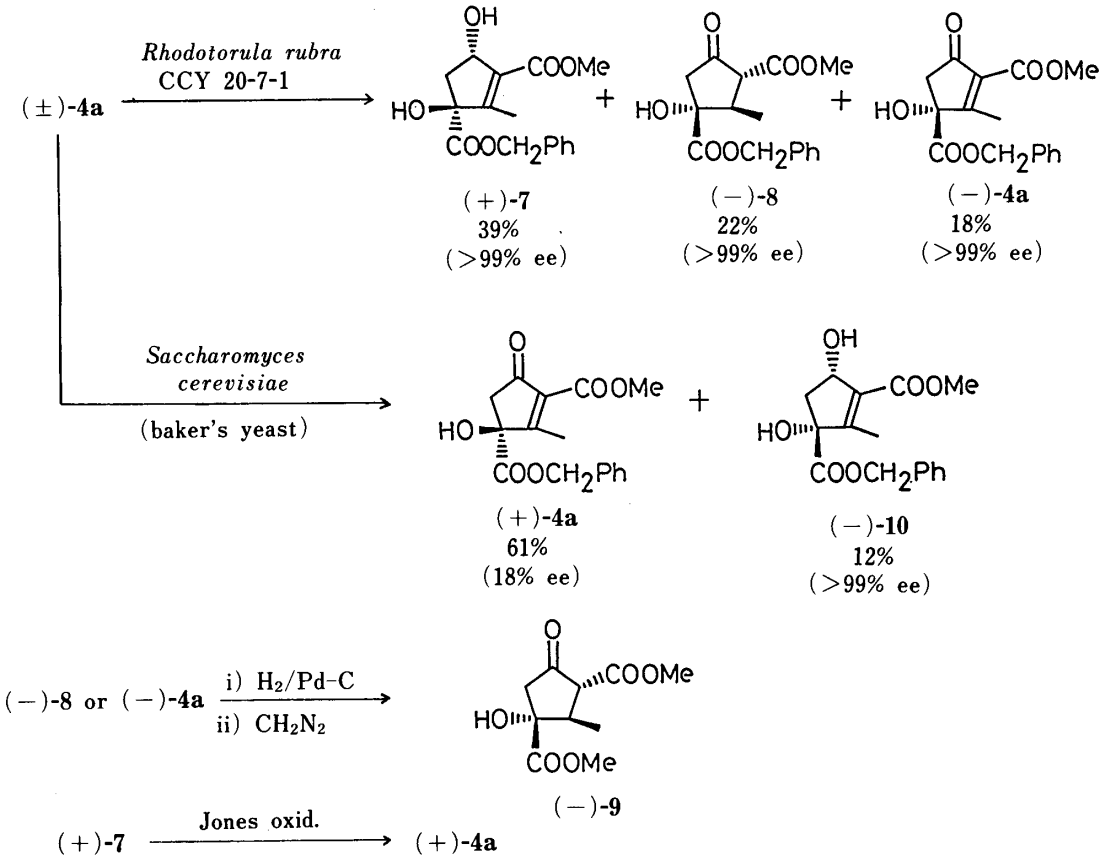
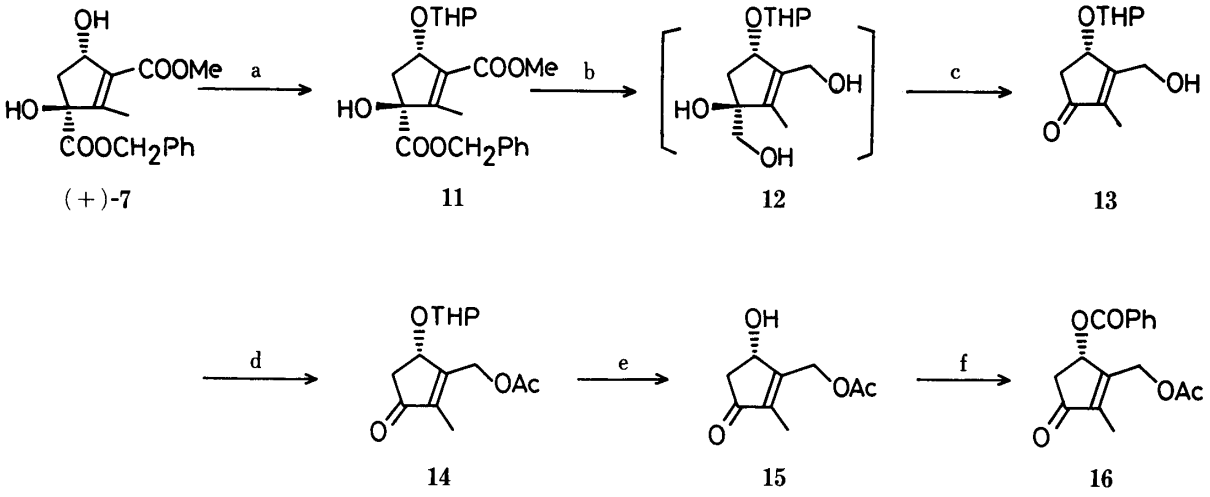


Chart 3

scale reduction using 13 g of the substrate (±)-**4a**, *R. rubra* CCY 20-7-1 gave (−)-**4a** (18%, >99% ee)[5] as a recovered substrate, and (+)-**7** (39%, >99% ee) and (−)-**8** (22%, >99% ee) as reduction products (Chart 3).

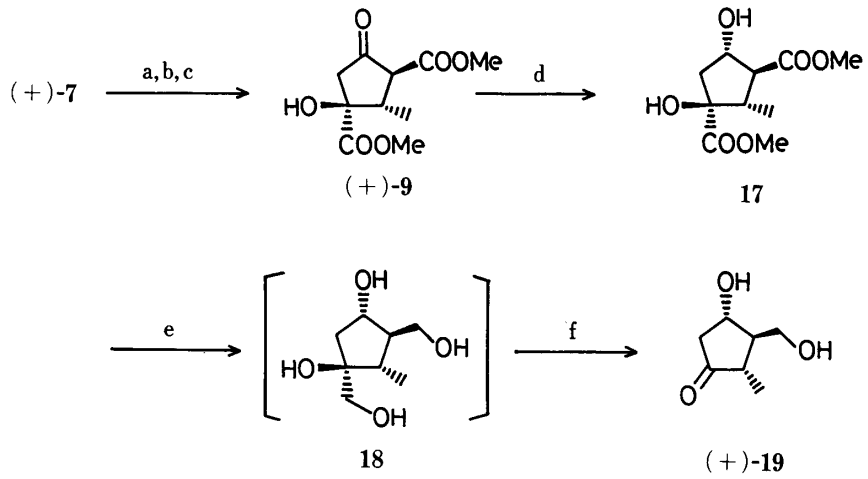
Chemical correlations of these products were achieved in the following ways. 1) Compound (−)-**8** could be converted into the crystalline dimethyl ester ((−)-**9**) *via* Pd-catalyzed hydrogenolysis and subsequent esterification with CH_2N_2. The relative configuration of each substituent in (−)-**9** was determined as 2*R**,3*R**,4*R** by X-ray analysis. 2) Jones oxidation of (+)-**7** afforded (+)-**4a**, the enantiomer of the recovered substrate (−)-**4a**. 3) The relative configuration of the diol in (+)-**7** was established to be 1,4-*trans* by comparison of the ^{1}H-NMR spectrum[6] with that of the 1,4-*cis*-diol ((−)-**10**), which was obtained by reduction of (±)-**4a** with baker's yeast. 4) Pd-catalyzed hydrogenation of (−)-**4a**, followed by esterification with CH_2N_2, afforded only (−)-**9**. This stereospecific hydrogenation is considered to proceed in a manner similar to that described in the previous paper.[4]

Next, the absolute stereochemistries of these products were determined independently by chemical and spectroscopic means. The absolute stereochemistry of the C_1 position in (+)-**7** was established by the exciton chirality method[7] as follows. After selective protection of C_1-OH in (+)-**7** with 3,4-dihydro-2*H*-pyran (DHP)/*p*-toluenesulfonic acid (*p*-TsOH), the tetrahydropyranyl ether (**11**) was subjected to reduction with $LiAlH_4$, followed by oxidation with $NaIO_4$ to afford the enone (**13**, 25% yield from (+)-**7**). Usual acetylation (Ac_2O/pyridine) of **13**, followed by deprotection with aqueous AcOH and then benzoylation (PhCOCl/Py), afforded the benzoate (**16**, 47% yield from **13**) (Chart 4). The circular dichroism (CD) spectrum of **16** showed a negative first Cotton effect. Therefore, the absolute stereochemistry of **16** could be concluded to be *S*. This result indicated that the absolute stereochemistry of (+)-**7**, (−)-**4**, and (−)-**8** should be (1*S*,4*S*), (*R*), and (2*R*,3*R*,4*R*), re-



a) DHP, *p*-TsOH b) $LiAlH_4$ c) $NaIO_4$ d) Ac_2O, pyridine e) aq. AcOH f) PhCOCl, pyridine

Chart 4



a) Jones oxid. b) H_2/Pd-C c) CH_2N_2 d) $NaBH_4$ e) $LiAlH_4$ f) $NaIO_4$

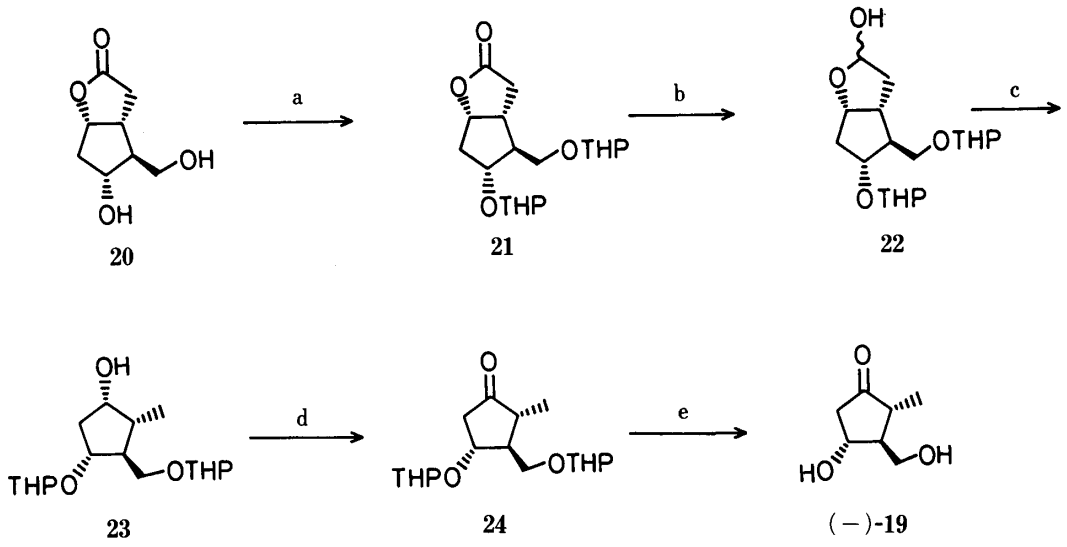
Chart 5

spectively.

The absolute stereochemistry of (+)-**7** was also determined by a chemical method. Compound (+)-**9** derived from (+)-**7** was reduced stereoselectively with $NaBH_4$ in MeOH at $-15°C$ to afford the 1,4-*trans*-diol (**17**, 87% yield).[6] The *trans*-diol (**17**) could be converted into the keto-diol ((+)-**19**, 13% from **17**) by $LiAlH_4$ reduction and subsequent $NaIO_4$ oxidation (Chart 5).

On the other hand, (−)-(2*R*,3*S*,4*R*)-**19** was obtained from the optically active Corey lactone diol (**20**) *via* a sequence of reactions as shown in Chart 6. Treatment of the diol (**20**) with DHP/*p*-TsOH followed by reduction with diisobutylaluminum hydride (DIBAL-H) afforded the lactol (**22**, 79% from **20**). Decarbonylation of **22** with RhCl $(PPh_3)_3$ followed by Collins oxidation gave the ketone (**24**), which was deprotected with aqueous AcOH to afford (−)-**19** (45% from **22**). This finding is in agreement with the conclusion from the exciton chirality method.

Thus, optically active and highly functionalized cyclopentenone derivatives could be



a) DHP, *p*-TsOH b) DIBAL-H c) $RhCl(PPh_3)_3$ d) Collins oxid. e) aq. HCl

Chart 6

easily prepared. The application of these new chirons for the synthesis of PGs and cuparenones is under investigation.

Experimental

IR spectra were measured on a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured on a JEOL JNM-PS-100 spectrometer unless otherwise stated. MS were taken on a JEOL JMS-D 300 spectrometer. Specific rotations were measured on a JASCO DIP-360 polarimeter. CD spectra were measured on a JASCO J-500 C spectrometer. X-Ray diffractions were measured on a Rigaku AFC-5R apparatus. For column chromatography, silica gel (Merck, Kieselgel, 70-230 mesh) was used. All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate.

(±)-4-Benzyloxycarbonyl-2-methoxycarbonyl-3-methylcyclopent-2-en-1-one (2a)——$KHCO_3$ (12.6 g) was added to a stirred solution of **1a**[4] (11.0 g) in MeOH (55 ml) at room temperature. After being stirred for 5.5 h, the reaction mixture was poured into 3% aqueous HCl (200 ml), and extracted with AcOEt. The AcOEt extract was washed and dried. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on silica gel (40 g). The fraction eluted with 5% Et_2O in benzene (v/v) afforded **2a** (6.12 g, 59%) as a colorless oil. IR (neat): 1710—1760 (br), 1435, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.35 (3H, s, C_3-CH_3), 2.73 (1H, d, J=7 Hz, C_5-H), 2.75 (1H, d, J=3 Hz, C_5-H), 3.60 (1H, m, C_4-H), 5.19 (2H, s, OCH_2Ph), 7.36 (5H, m, aromatic H). MS *m/z*: 288 (M^+), 256, 212.

Compound **2b** was prepared in a similar manner from **1b** in 56% yield. IR (neat): 1700—1760 (br), 1435, 1245 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (3H, s, C_3-CH_3), 2.71 (2H, m, C_5-H), 3.69 (1H, m, C_4-H), 3.73, 3.81 (3H each, s, $COOCH_3$). MS *m/z*: 212 (M^+), 168, 115.

(±)-4-Benzyloxycarbonyl-4-hydroxy-2-methoxycarbonyl-3-methylcyclopent-2-en-1-one ((±)-4a) and (±)-4-Benzyloxycarbonyl-2-hydroxy-2-methoxycarbonyl-3-methylcyclopent-3-en-1-one ((±)-5a)——The crude extract of **2a** obtained by the above procedure was chromatographed on silica gel (150 g). The fraction was eluted slowly (>5 h) with 12% AcOEt in hexane (v/v), and (±)-**5a** (2.30 g, 21%) was obtained as colorless needles, mp 108—110 °C (AcOEt–hexane). IR (Nujol): 3450, 1760, 1730, 1715, 1645, 1240 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, t, J=2 Hz, C_3-CH_3), 3.34 (2H, q, J=2 Hz, C_5-H), 3.80 (1H, br, OH), 3.81 (3H, s, $COOCH_3$), 5.26 (2H, s, OCH_2Ph). MS *m/z*: 304 (M^+), 213, 195. *Anal.* Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.21; H, 5.24. The fraction eluted with 20% AcOEt–hexane (v/v) afforded (±)-**4a** (5.25 g, 48%) as colorless needles, mp 76.5—78.5 °C (AcOEt–hexane). IR (Nujol): 3450, 1710—1760 (br), 1235 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.16 (3H, s, C_3-CH_3), 2.68, 2.90 (1H each, d, J=18 Hz, C_5-H), 3.86 (3H, s, $COOCH_3$), 4.02 (1H, br, OH), 5.24 (2H, s, OCH_2Ph). MS *m/z*: 304 (M^+), 273, 169. *Anal.* Calcd for $C_{16}H_{16}O_6$: C, 63.15; H, 5.30. Found: C, 63.19; H, 5.39.

Compounds (±)-**4b** and (±)-**5b** were obtained in a similar manner from **2b** in 43% and 16% yields, respectively. (±)-**4b**: colorless needles, mp 66—68.5 °C (Et_2O). IR (Nujol): 3440, 1700—1740 (br), 1635, 1435, 1340, 1190 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.25 (3H, s, C_3-CH_3), 2.71, 2.91 (1H each, d, J=18 Hz, C_5-H), 3.83, 3.88 (3H each, s, $COOCH_3$), 4.10 (1H, br, OH). MS *m/z*: 228 (M^+), 197, 169. *Anal.* Calcd for $C_{10}H_{12}O_6$: C, 52.63; H, 5.30. Found: C,

52.50; H, 5.38. (±)-**5b**: colorless solid. IR (Nujol): 3450, 1700—1740 (br), 1640, 1430, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.13 (3H, t, J=2 Hz, C_3-CH_3), 3.35, 3.37 (1H each, dq, J=22, 2 Hz, C_5-H), 3.75 (1H, br, OH), 3.81, 3.83 (3H each, s, $COOCH_3$). FD-MS m/z: 228 (M^+), 196, 169. *Anal.* Calcd for $C_{10}H_{12}O_6$: C, 52.63; H, 5.30. Found: C, 52.48; H, 5.25.

$NaIO_4$ Oxidation of (±)-5a——$NaIO_4$ (173 mg) in H_2O (2 ml) was added to a stirred solution of (±)-**5a** (113 mg) in acetone (2 ml) at room temperature. After being stirred for 2 h, the reaction mixture was diluted with CH_2Cl_2 (50 ml). The resulting precipitate was filtered off, and the filtrate was washed and dried. The solvent was removed *in vacuo* to give an oily residue, which was chromatographed on silica gel (3 g). The fraction eluted with 15% AcOEt in hexane (v/v) afforded **6a** (63 mg, 53%) as a colorless oil. IR (neat): 3380, 1720—1760, 1500, 1435 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 2.11 (3H, t, J=2 Hz, C_4-CH_3), 3.48, 3.51 (1H each, q, J=2 Hz, C_2-H), 3.89 (3H, s, $COOCH_3$), 5.18 (1H, br, COOH). FD-MS m/z: 321 (M^++1), 303, 260.

Screening of Yeasts——The microorganisms described in a previous paper[8] were examined for reduction of (±)-**4a**. Test tubes (25×200 mm) containing 10 ml of the culture medium (5% glucose, 0.1% KH_2PO_4, 0.1% $(NH_4)_2SO_4$, 0.05% urea, 0.05% $MgSO_4 \cdot 7H_2O$, 0.1% yeast extract and tap water (pH 6.5) were inoculated with microorganisms and cultured at 30°C for 3 d with continuous shaking. Then, the substrate (*ca.* 5 mg of (±)-**4a**) was added to the test tube, which was further incubated for 3 d under the same conditions. The mixture was extracted with AcOEt. The AcOEt extract was dried and concentrated *in vacuo*. Monitoring of the residue by thin layer chromatography (TLC) indicated that only two strains of yeast (listed in Chart 3) were effective for the reduction of (±)-**4a**.

Microbial Reduction of (±)-4a on a Preparative Scale——The above-mentioned seed culture of *Rhodotorula rubra* CCY 20-7-1 (2 ml) was transferred to 900 ml of the same culture medium. After cultivation at 30°C for 3 d, the substrate (±)-**4a** (1 g) was added to this seed culture, and cultivation was continued for a further 3 d under the same conditions. Similar reduction of (±)-**4a** on a preparative scale (1 g×13) was carried out. The reaction mixture was filtered with the aid of celite, and the filtrate was extracted with AcOEt. The AcOEt extract was washed and dried, then concentrated *in vacuo* to leave an oily residue, which was chromatographed on silica gel (200 g). The fraction eluted with 5% AcOEt in benzene (v/v) afforded (−)-**8** (2.90 g, 22%, >99% ee) as a colorless solid, mp 50—51 °C. $[\alpha]_D^{26}$ −70° (c=1.00, $CHCl_3$). IR (Nujol): 3480, 1720—1760 (br), 1450, 1220 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, J=6 Hz, C_3-CH_3), 2.73, 2.80 (1H each, d, J=18 Hz, C_5-H), 2.95 (1H, dq, J=11, 6 Hz, C_3-H), 3.23 (1H, d, J=11 Hz, C_2-H), 3.65 (1H, br, OH), 3.77 (3H, s, $COOCH_3$). FD-MS m/z: 306 (M^+), 275, 203. *Anal.* Calcd for $C_{16}H_{18}O_6$: C, 62.74; H, 5.92. Found: C, 62.85; H, 5.95. The fraction eluted with 10—15% AcOEt in benzene (v/v) afforded (−)-**4a** (2.34 g, 18%, >99% ee). $[\alpha]_D^{26}$ −155° (c=1.04, $CHCl_3$). The fraction eluted with 15—25% AcOEt in benzene (v/v) afforded (+)-**7** (5.10 g, 39%, >99% ee) as a colorless oil. $[\alpha]_D^{26}$ +105° (c=3.87, $CHCl_3$). IR (neat): 3470, 1700—1740 (br), 1435, 1220 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.94 (3H, d, J=1 Hz, C_3-H), 2.35 (1H, d, J=4 Hz, C_5-H), 2.36 (1H, d, J=6 Hz, C_5-H), 2.81, 3.70 (1H each, br, OH), 3.81 (3H, s, $COOCH_3$), 5.17 (1H, m, C_1-H). FD-MS m/z: 306 (M^+), 278, 179.

(2*R*,3*R*,4*R*)-(−)-4-Hydroxy-2,4-bis(methoxycarbonyl)-3-methylcyclopentanone ((−)-9)——A solution of (−)-**8** (409 mg) was hydrogenated in the presence of 10% Pd–C (500 mg) under an H_2 atmosphere for 2 h at 0°C. The catalyst was filtered off and the filtrate was concentrated *in vacuo* to afford an oily residue, which was treated with CH_2N_2 in the usual manner. The crude product was purified by column chromatography on silica gel (6 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded (−)-**9** (178 mg, 58%) as colorless needles, mp 124—125 °C (acetone–hexane). $[\alpha]_D^{26}$ −124° (c=0.80, $CHCl_3$). IR (Nujol): 3440, 1735, 1715, 1455, 1215 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, J=7 Hz, C_3-CH_3), 2.73, 2.81 (1H each, d, J=18 Hz, C_5-H), 2.97 (1H, dq, J=11, 7 Hz, C_3-H), 3.31 (1H, d, J=11 Hz, C_2-H), 3.67 (1H, br, OH), 3.79, 3.84 (3H each, s, $COOCH_3$). MS m/z: 230 (M^+), 212, 180. *Anal.* Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.02; H, 6.11. Crystal data: $C_{10}H_{14}O_6$, M_r 230.2, monoclinic, space group $P2_1$, Z=2, D_x=1.39 g cm^{-3}, a=7.516 (1), b=12.948 (1), c=5.939 (1) Å, U=550.5 Å^3, β=107.70 (1)°, R=0.048.

Compound (−)-**9** was also obtained from (−)-**4a** in a similar manner in 62% yield.

Compound (+)-4a from (+)-7——The Jones reagent (0.4 ml) was added dropwise to a stirred solution of (+)-**7** (100 mg) in acetone (3 ml) at 0°C. After 4 h, isopropanol (0.5 ml) was added to decompose excess reagent. The whole was diluted with Et_2O (50 ml), and washed with 5% aqueous $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel (3 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded (+)-**4a** (75 mg, 76%). $[\alpha]_D^{23}$ +147° (c=0.73, $CHCl_3$).

Reduction of (±)-4a with Baker's Yeast——Compound (±)-**4a** (386 mg) was added to a stirred mixture of sucrose (10 g), baker's yeast (10 g) and H_2O (50 ml), and the whole was stirred for 2 d at 30 °C. AcOEt (100 ml) was added to the reaction mixture, and the precipitate was filtered off. The aqueous layer of the filtrate was again extracted with AcOEt (50 ml×2), and the combined extracts were washed and dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by column chromatography on silica gel (16 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded (+)-**4a** (235 mg, 61%, 18% ee)[5] as recovered substrate. $[\alpha]_D^{26}$ +24° (c=1.06, $CHCl_3$). The fraction eluted with 25% AcOEt in hexane (v/v) afforded (−)-**10** (46 mg, 12%, >99% ee)[5] as a colorless oil. $[\alpha]_D^{25}$ −116° (c=0.63, $CHCl_3$). IR (neat): 1.92 (3H, s, C_3-CH_3), 1.93 (1H, dd, J=5, 14 Hz, $C_{5\alpha}$-H), 2.79 (1H, dd, J=7, 14 Hz, $C_{5\beta}$-H). 3.08, 3.87 (1H each, br, OH), 3.82 (3H, s, $COOCH_3$), 4.99 (1H, m, C_1-H). MS m/z: 306 (M^+),

288, 171.

Compound (−)-**10** could be converted into (−)-**4a** by a method similar to that used in the conversion of (+)-**7** into (+)-**4a**.

(+)-α-Methoxy-α-trifluoromethylphenylacetic Acid (MTPA)[9] Esters of (+)- and (−)-9——MTPA chloride (100 mg) was added to a mixture of **9** (25 mg) and 4-(*N*,*N*-dimethyl)aminopyridine (5 mg) in pyridine (1 ml) at 10 °C. After being stirred for 48 h at room temperature, the whole was diluted with 3% aqueous HCl (50 ml) and extracted with Et_2O. The Et_2O extract was successively washed with 5% aqueous $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was purified by preparative TLC in AcOEt–hexane (1 : 1) to afford the pure ester (41 mg, 84%) as a pale yellow oil. 270 MHz ^{1}H-NMR ($CDCl_3$) δ: (+)-MTPA ester of (+)-**9**: 3.634, 3.839 (3H each, s, C_2- and C_4-$COOCH_3$). (+)-MTPA ester of (−)-**9**: 3.595, 3.827 (3H each, s, C_2- and C_4-$COOCH_3$).

(1*S*,4*S*)-4-Benzyloxycarbonyl-4-hydroxy-2-methoxycarbonyl-3-methyl-1-(tetrahydropyran-2-yl)oxy-2-cyclopentene (11)——DHP (166 mg) in CH_2Cl_2 (1 ml) was added dropwise to a stirred solution of (+)-**7** (245 mg) in CH_2Cl_2 (3 ml) in the presence of *p*-TsOH (5 mg) at 5 °C. After 1 h, the reaction mixture was poured into brine (50 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 extract was dried. Removal of the solvent *in vacuo* gave an oily residue, which was purified by column chromatography on silica gel (4 g). The fraction eluted with 7% AcOEt in hexane (v/v) afforded **11** (278 mg, 89%) as a colorless oil. IR (neat): 3470, 1710—1740 (br), 1210, 1030 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, s, C_3-CH_3), 2.38 (2H, m, C_5-H), 3.74 (1H, s, OH), 3.78 (3H, s, $COOCH_3$), 4.70, 4.82 (0.5H each, m, OCHO), 5.12 (1H, m, C_1-H). MS *m/z*: 391 (M^+), 289, 255.

(*S*)-3-Hydroxymethyl-2-methyl-4-(tetrahydropyran-2-yl)oxycyclopent-2-en-1-one (13)——A solution of **11** (437 mg) in Et_2O (10 ml) was added dropwise to a stirred suspension of $LiAlH_4$ (94 mg) in Et_2O (15 ml) at −15 °C. The mixture was stirred for 15 min, H_2O (0.2 ml) was added and the precipitate was filtered off. The filtrate was concentrated *in vacuo* and the residue was dissolved in acetone (15 ml). $NaIO_4$ (1.2 g) in H_2O (10 ml) was added to the solution at room temperature. After being stirred for 29 h, the whole was diluted with acetone (100 ml) and the precipitate was filtered off. The filtrate was concentrated *in vacuo* to afford an oily residue, which was diluted with CH_2Cl_2 (100 ml). The solution was washed and dried. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on silica gel (6 g). The fraction eluted with 20—25% AcOEt in hexane (v/v) afforded **13** (73 mg, 29%) as a pale yellow oil. IR (neat): 3420, 1700, 1650, 1430, 1120, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.76 (3H, s, C_2-CH_3), 2.51 (1H, dd, J=2, 19 Hz, $C_{5\alpha}$-H), 2.66 (1H, br, OH), 2.76 (1H, dd, J=6, 19 Hz, $C_{5\beta}$-H), 4.57 (2H, br s, C_3-CH_2), 4.83 (1H, m, OCHO), 4.93 (1H, m, C_4-H). MS *m/z*: 226 (M^+), 208, 106.

(*S*)-3-Acetoxymethyl-2-methyl-4-(tetrahydropyran-2-yl)oxycyclopent-2-en-1-one (14)——Compound **14** was obtained from **13** as a colorless oil in a usual manner (Ac_2O/pyridine) in 95% yield. IR (neat): 1740, 1708, 1660, 1220, 1030 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.81 (3H, s, C_2-CH_3), 2.11 (3H, s, CH_3COO), 2.50 (1H, dd, J=2, 19 Hz, $C_{5\alpha}$-H), 2.79 (1H, dd, J=6, 19 Hz, $C_{5\beta}$-H), 4.75 (2H, m, OCHO, C_4-H), 4.97 (2H, m, C_3-CH_2). FD-MS *m/z*: 268 (M^+), 185, 85.

(*S*)-3-Acetoxymethyl-4-hydroxy-2-methylcyclopent-2-en-1-one (15)——Compound **14** (54 mg) was added to a mixed solution of AcOH (4 ml), tetrahydrofuran (THF, 2 ml) and H_2O (1 ml). After being stirred for 5 h at 40 °C, the reaction mixture was diluted with 5% aqueous $NaHCO_3$ (70 ml), and extracted with AcOEt. The AcOEt extract was washed and dried. Removal of the solvent *in vacuo* gave an oily residue, which was chromatographed on silica gel (2 g). The fraction eluted with 40% AcOEt in hexane (v/v) afforded **15** (28 mg, 76%) as a colorless oil. $[\alpha]_D^{19}$ −52.5° (c=1.40, $CHCl_3$). IR (neat): 3400, 1730, 1695, 1650, 1230 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.80 (3H, s, C_2-CH_3), 2.15 (3H, s, CH_3COO), 2.37 (1H, dd, J=2, 19 Hz, $C_{5\alpha}$-H), 2.73 (1H, br, OH), 2.79 (1H, dd, J=6, 19 Hz, $C_{5\beta}$-H), 4.87 (1H, m, C_4-H), 5.00, 5.07 (1H each, d, J=14 Hz, C_3-CH_2). MS *m/z*: 184 (M^+), 166, 124.

(*S*)-3-Acetoxymethyl-4-benzoyloxy-2-methylcyclopent-2-en-1-one (16)——Compound **16** was obtained from **15** as a colorless oil in a usual manner (PhCOCl/pyridine) in 65% yield. CD (c=2.07 × 10^{-5}, MeOH) $\Delta\varepsilon^{25}$: −46.6 (233.5) (negative maximum), +3.29 (216.5) (positive maximum). ^{1}H-NMR ($CDCl_3$) δ: 1.90 (3H, s, C_2-CH_3), 2.01 (3H, s, CH_3COO), 2.46 (1H, dd, J=2, 19 Hz, $C_{5\alpha}$-H), 3.02 (1H, dd, J=6, 19 Hz, $C_{5\beta}$-H), 5.03 (2H, s, C_3-CH_2), 6.10 (1H, m, C_4-H). MS *m/z*: 288 (M^+), 183, 105.

(1*S*,2*S*,3*S*,4*S*)-2,4-Bis(methoxycarbonyl)-1,4-dihydroxy-3-methylcyclopentane (17)——$NaBH_4$ (33 mg) was added to a stirred solution of (+)-**9** (196 mg) in MeOH (10 ml) at −15 °C. After 10 min, H_2O (0.2 ml) was added, and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (4 g). The fraction eluted with 50% AcOEt in hexane (v/v) afforded **17** (173 mg, 87%) as a colorless oil. $[\alpha]_D^{27}$ +29.9° (c=1.58, MeOH). IR (neat): 3450, 1700—1730 (br), 1435, 1250 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, J=7 Hz, C_3-CH_3), 2.27 (1H, dd, J=7, 14 Hz, C_5-H), 2.32 (1H, dd, J=8, 14 Hz, C_5-H), 2.35 (1H, m, C_3-H), 2.68 (1H, m, C_2-H), 2.77, 3.44 (1H each, br, OH), 3.75, 3.86 (3H each, s, $COOCH_3$), 4.54 (1H, m, C_1-H). MS *m/z*: 233 (M^++1), 214, 155.

(2*S*,3*R*,4*S*)-4-Hydroxy-3-hydroxymethyl-2-methylcyclopentanone ((+)-19)——The keto-diol ((+)-**19**) was prepared as a colorless oil, in 13% yield, from **17** in a manner similar to that described for the synthesis of **13** from **11**. $[\alpha]_D^{27}$ +87° (c=0.42, MeOH). IR (neat): 3400, 1730, 1450, 1160, 1075 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=7 Hz, C_2-CH_3), 1.73—2.00 (2H, m, C_2-, C_3-H), 2.29 (1H, dd, J=8, 19 Hz, C_5-H), 2.77 (1H, dd, J=7, 19 Hz, C_5-H), 2.34, 3.06 (1H each, br, OH), 3.78, 4.08 (1H each, dd, J=7, 10 Hz/J=3, 10 Hz, C_3-CH_2), 4.36 (1H, m, C_4-H). MS

m/z: 144 (M^+), 126, 114.

(1*S*,5*R*,6*S*,7*R*)-7-(Tetrahydropyran-2-yl)oxy-6-(tetrahydropyran-2-yl)oxymethyl-2-oxabicyclo[3.3.0]octan-3-one (21)——DHP (2.2 g) in CH_2Cl_2 (10 ml) was added dropwise to a stirred solution of **20** (1.85 g) in CH_2Cl_2 (15 ml) in the presence of *p*-TsOH (24 mg) at 0°C. The whole was stirred for 1.5 h at room temperature, then poured into brine (100 ml) and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed and dried. The solvent was removed *in vacuo* to afford an oily residue, which was chromatographed on silica gel (50 g). The fraction eluted with 20—40% AcOEt in hexane (v/v) afforded **21** (3.11 g, 84%) as a colorless oil. IR (neat): 1770, 1350, 1120, 1025 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.20—4.32 (7H, m, C_6-CH_2, C_7-H, $OCH_2 \times 2$), 4.56, 4.68 (1H each, m, OCHO), 5.00 (1H, m, C_1-H). MS *m/z*: 340 (M^+), 255, 239.

(1*S*,3*RS*,5*R*,6*S*,7*R*)-7-(Tetrahydropyran-2-yl)oxy-6-(tetrahydropyran-2-yl)oxymethyl-2-oxabicyclo[3.3.0]octan-3-ol (22)——DIBAL-H (1.0 M, 7 ml) was added to a stirred solution of **21** (1.76 g) in Et_2O (20 ml) at −78°C. The mixture was stirred for 20 min, H_2O (5 ml) was added and the precipitate was filtered off. The filtrate was dried and concentrated *in vacuo* to afford an oily residue, which was purified by column chromatography on silica gel (30 g). The fraction eluted with 30—40% AcOEt in hexane (v/v) afforded **22** (1.67 g, 94%) as a colorless oil. IR (neat): 3400, 1730, 1435, 1350, 1120 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 3.36—4.20 (7H, m, C_6-CH_2, C_7-H, $OCH_2 \times 2$), 4.50—4.70 (3H, m, $OCHO \times 2$, C_1-H), 5.53 (1H, m, C_3-H). FD-MS *m/z*: 342 (M^+), 325, 324.

(1*S*,2*R*,3*S*,4*R*)-2-Methyl-4-(tetrahydropyran-2-yl)oxy-3-(tetrahydropyran-2-yl)oxymethylcyclopentan-1-ol (23)——A mixture of **22** (1.66 g) and RhCl $(PPh_3)_3$ (9.03 g) in benzene (40 ml) was refluxed for 11 h under an N_2 atmosphere. After removal of the solvent *in vacuo*, the residue was treated with EtOH (50 ml), then the precipitate was filtered off. The filtrate was concentrated *in vacuo* to afford a yellow oil, which was purified by column chromatography on silica gel (30 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded **23** (935 mg, 61%) as a pale yellow oil. IR (neat): 3460, 1440, 1350, 1200, 1120, 1020 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=7 Hz, C_2-CH_3), 3.08—4.12 (7H, m, C_3-CH_2, C_4-H, $OCH_2 \times 2$), 4.22 (1H, m, C_1-H), 4.60, 4.72 (1H each, m, OCHO). FD-MS *m/z*: 314 (M^+), 286, 165.

(2*R*,3*S*,4*R*)-2-Methyl-4-(tetrahydropyran-2-yl)oxy-3-(tetrahydropyran-2-yl)oxymethylcyclopentanone (24)——Compound **23** (102 mg) in CH_2Cl_2 (3 ml) was added to a solution of the Collins reagent [prepared from CrO_3 (229 mg) and pyridine (359 mg) in CH_2Cl_2 (2 ml)] at 0°C. After being stirred for 19 h at room temperature, the whole was diluted with Et_2O (50 ml) and the precipitate was filtered off. The filtrate was successively washed with 2% aqueous HCl, 5% aqueous $NaHCO_3$ and brine, then dried. Removal of the solvent gave an oily residue, which was purified by column chromatography on silica gel (3 g). The fraction eluted with 5—10% AcOEt in hexane (v/v) afforded **24** (95 mg, 94%) as a colorless oil. IR (neat): 1742, 1350, 1130, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.17 (3H, d, J=7 Hz, C_2-CH_3), 2.00—2.32 (2H, m, C_2-H, $C_{5\alpha}$-H), 2.78 (1H, dd, J=7, 18 Hz, $C_{5\beta}$-H), 4.36 (1H, m, C_4-H), 4.65 (2H, m, OCHO). FD-MS *m/z*: 312 (M^+), 227, 85.

(2*R*,3*R*,4*R*)-Compound (−)-19 for 24——Aqueous HCl (0.01 N, 1.5 ml) was added to a solution of **24** (88 mg) in THF (1.5 ml) and the whole was stirred for 3 d at room temperature. $NaHCO_3$ (10 mg) was added to the reaction mixture, and the solvent was removed *in vacuo*. The residue was chromatographed on silica gel (2 g). The fraction eluted with 50% AcOEt in hexane afforded (−)-**19** (36 mg, 88%) as a colorless oil. $[\alpha]_D^{28}$ −99° (c=1.27, MeOH). ^{1}H-NMR, IR, and MS were identical with those of (+)-**19**.

Acknowledgement The authors are grateful to Sankyo Co., Ltd. for measurement of CD spectra, and X-ray analysis.

References and Notes

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