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Formal Syntheses of (−)-α- and (+)-β-Cuparenones, Cuparene, and Laurene

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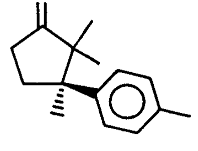
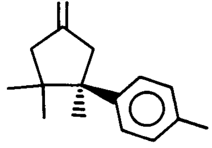
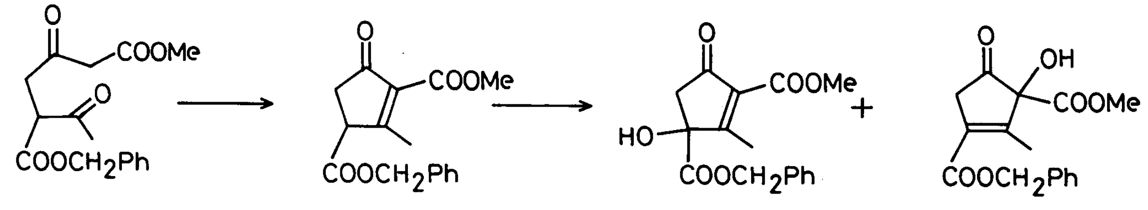
This paper describes formal syntheses of the title compounds from the easily prepared chiral synthon (+)-**5**. One of the structural features of the cuparene family is the presence of vicinal quaternary carbons on the five-membered ring. The quaternary carbon with the tolyl function could be constructed by stereoselective 1,4-addition of $(p\text{-tolyl})_2Zn$ to (+)-**5**. The key intermediate β-ketol (**13**), obtained from (+)-**5** *via* a sequence of reactions, was successfully applied to formal syntheses of the title compounds.

Keywords——(−)-α-cuparenone; cuparene; laurene; 1,4-addition; masked carbonyl; oxidative rearrangement; (+)-β-cuparenone

In the previous paper,[1] we reported that the cyclopentenone (**4**) obtained by cyclization of the 1,4-diketone (**3**) undergoes facile air-oxidation during silica-gel column chromatography to afford two oxygenated products, (**5**) and (**6**), in 48% and 21% yields, respectively, and optically pure **5** was obtained by microbial reduction using *Rhodotorula rubra* CCY 20-7-1. As a part of our synthetic studies on biologically active compounds based on a five-membered ring, we have undertaken the formal syntheses of the title compounds from the readily prepared chiral **5**. The highly functionalized **5** seems to have attractive functional groups for the syntheses of natural products containing a five-membered ring. For example, this compound has a conjugated enone, required for 1,4-addition to construct the quaternary carbon, and the C_4 center with two substituents of the alcohol and the ester can be regarded as a masked carbonyl function, which may be converted to the carbonyl function *via* reduction of the ester function and subsequent oxidation with $NaIO_4$. In addition, it is possible to


(−)-α-cuparenone (**1**)


(+)-β-cuparenone (**2**)

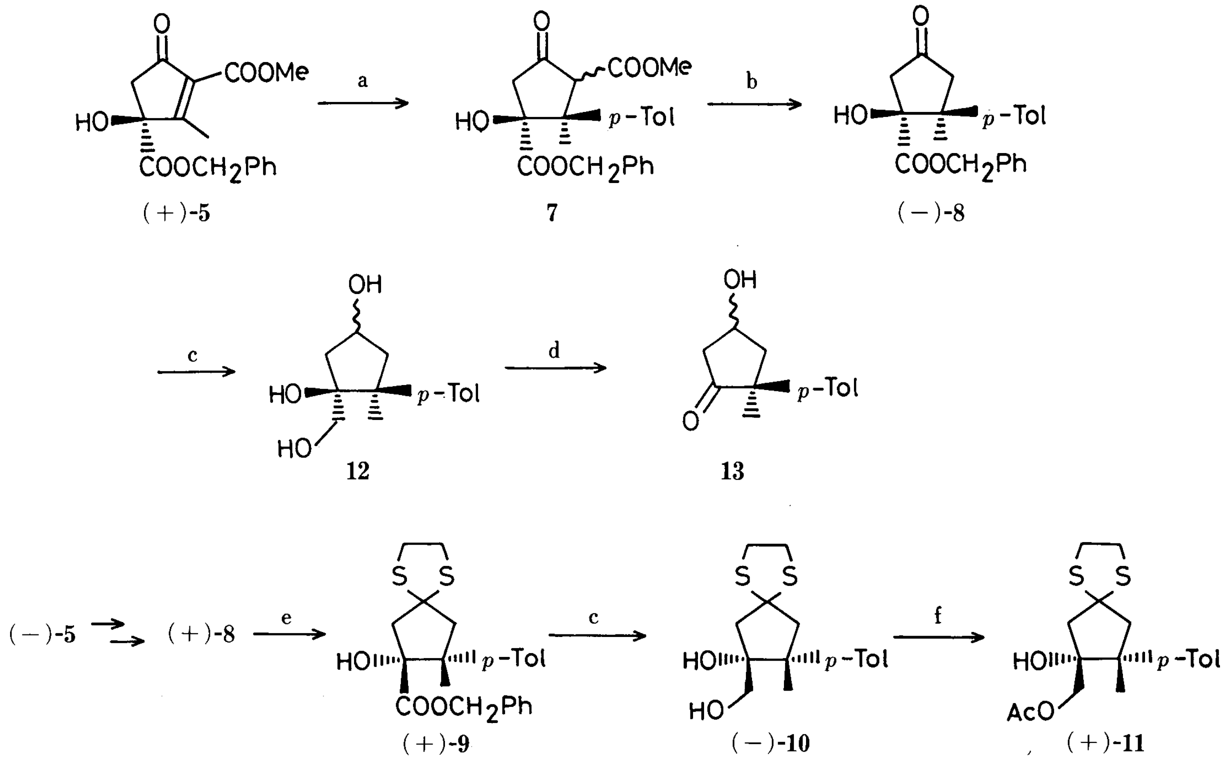


3 **4** **5** **6**

Chart 1

introduce appropriate substituents at each position on the five-membered ring. Thus, the structural advantages of **5** prompted us to use it to synthesize the title compounds (Chart 1).

(−)-α-Cuparenone (**1**) and (+)-β-cuparenone (**2**), sesquiterpenes isolated from the essential oil of the *Mayur Pankhi* tree[2a] and the liverwort *Mannia fragrans*,[2b] respectively, have been attractive targets for chemical synthesis,[3] because of their unique framework with vicinal quaternary centers. One of the difficulties in the synthesis of cuparenone is how to create these centers. In (+)-**5**, two electron-withdrawing groups (the ketone and the ester) should facilitate the introduction of the tolyl (Tol) function by 1,4-addition. However, attempts to achieve conjugate addition by using "cuprate reagents" such as $(p\text{-Tol})_2\text{CuLi}$ (with or without Me_3SiCl),[4] $(p\text{-Tol})\text{CuBF}_3$,[5] $(p\text{-Tol})_2\text{Cu(CN)Li}_2$[6] resulted in recovery of (+)-**5** or the formation of a complex mixture. However, this difficulty in the introduction of the tolyl function by conjugate addition was overcome by means of nickel-catalyzed conjugate addition of "zinc reagent".[7] Nickel acetylacetonate-catalyzed conjugate addition of $(p\text{-Tol})_2\text{Zn}$, which could be prepared by sonication of a mixture of lithium wire, *p*-bromotoluene, and zinc bromide in ether at room temperature, afforded that keto-ester (**7**) in 50% yield. Compound **7** gave a single spot on thin layer chromatography (TLC), but in the proton nuclear magnetic resonance (^{1}H-NMR) spectrum, the signal of the methyl ester appeared as two peaks (δ 3.54 and 3.65) attributable to the C_2-epimeric esters. Decarbomethoxylation of **7** by heating at 100 °C in the presence of NaI in dimethylsulfoxide (DMSO) afforded the ketone ((−)-**8**) as single product in 89% yield. The relative configuration of the tolyl function was determined to be *cis* relative to the C_4-OH by analysis of the nuclear Overhauser effect difference spectrum (NOEDS) of the monoacetate ((+)-**11**), which was prepared from the enantiomer (−)-**5** *via* conjugate addition of $(p\text{-Tol})_2\text{Zn}$, decarbomethoxylation to (+)-**8**, conversion by treatment with BF_3/ethanedithiol to the thioacetal ((+)-**9**), reduction with LiAlH_4 to the diol ((−)-**10**), and acetylation with Ac_2O/pyridine. This conjugate addition in a



a) $(p\text{-Tol})_2\text{Zn}$, Ni(acac)_2 b) NaI, DMSO c) LiAlH_4 d) NaIO_4 e) $(\text{CH}_2\text{SH})_2$, $\text{BF}_3\cdot\text{Et}_2\text{O}$
f) Ac_2O, pyridine

Chart 2

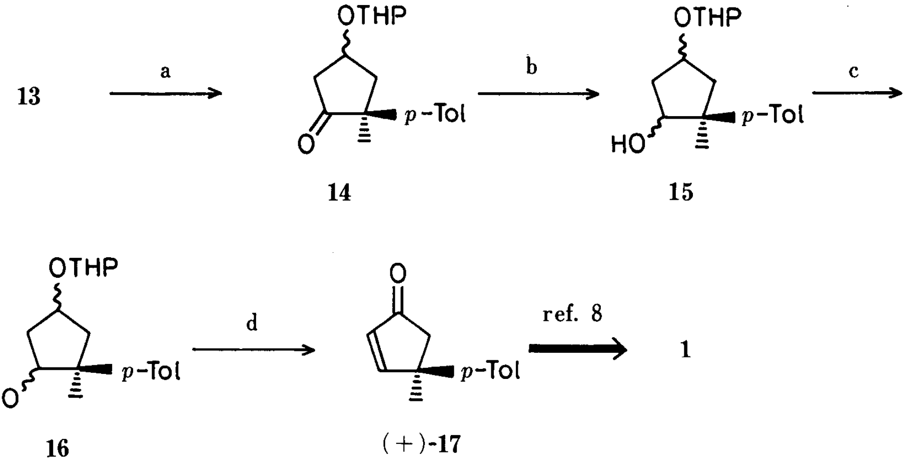
stereocontrolled manner may be induced by chelation between $(p\text{-Tol})_2Zn$ and the C_4-OH to afford the *cis*-adduct to the C_4-OH. The absolute stereochemistry[1] of compound (−)-**8** with the carbonyl and the masked carbonyl functions is favorable for the syntheses of the title compounds. With the object of the conversion of the masked carbonyl to the ketone, (−)-**8** was subjected to reduction with $LiAlH_4$ to afford the triol (**12**) as colorless needles, mp 159 °C, in 87% yield. Oxidation of **12** with $NaIO_4$ in aqueous acetone gave the *β*-ketol (**13**) in 97% yield. In the ^{1}H-NMR spectrum of **13**, the methyl signal appeared as two peaks (δ 1.39 and 1.49) of almost equal ratio. This seems to be caused by the C_1-epimeric alcohols, which were formed in the reduction of (−)-**8** with $LiAlH_4$ to **12**. The *β*-ketol (**13**) is a key intermediate for the synthesis of (−)-*α*-cuparenone (**1**), (+)-*β*-cuparenone (**2**), cuparene (**22**), and laurene (**23**).

Formal Synthesis of (−)-α-Cuparenone (1)

Conversion of **13** to the enone ((+)-**17**) was accomplished in the following way. Conversion of **13** to the tetrahydropyranyl (THP) ether (**14**) by treatment with 3,4-dihydro-2*H*-pyran (DHP)/pyridinium *p*-toluenesulfonate (PPTS) and subsequent reduction with $LiAlH_4$ afforded the alcohol (**15**) in 91% yield from **13**. By treatment with methanesulfonyl chloride (MsCl)/NEt_3 in benzene, **15** was converted to the mesylate (**16**) in 98% yield. In accordance with our expectation, Jones oxidation of **16** afforded directly (+)-**17** in 91% yield, *via* three concurrent reactions: i) removal of the THP function, ii) oxidation of the alcohol to the ketone, iii) elimination of the mesyl function. Compound (+)-**17** was identical in terms of the spectral data with Meyers' intermediate[8] in the synthesis of (−)-*α*-cuparenone (**1**).

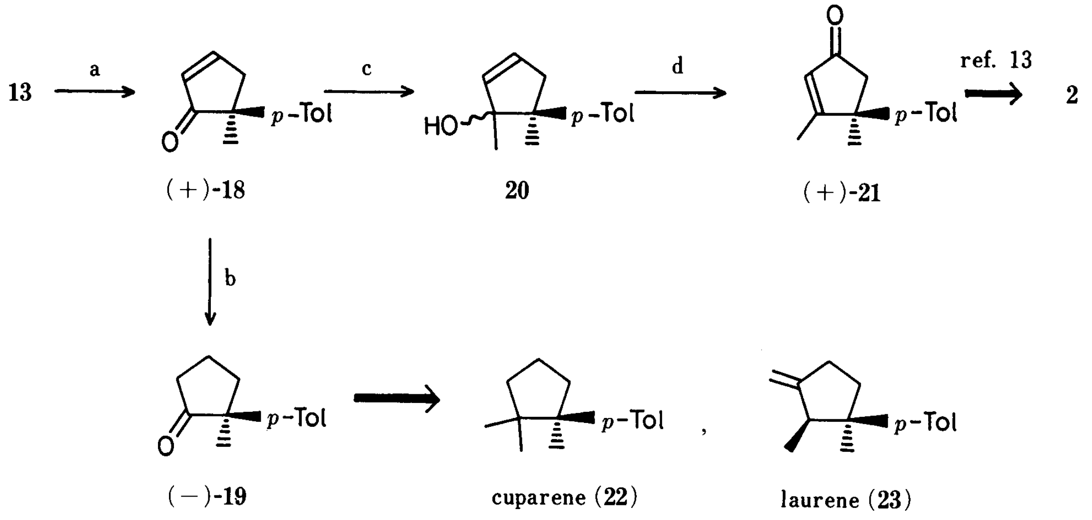
Formal Synthesis of (+)-β-Cuparenone (2), Cuparene (22), and Laurene (23)

Mesylation of **13** with MsCl/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene gave the *α*-enone ((+)-**18**), which showed signals at δ 6.26 (1H, dt, $J=5.9$, 2.2 Hz, C_2-H) and 7.77 (1H, dt, $J=5.9$, 2.7 Hz, C_3-H) in the ^{1}H-NMR spectrum, in addition to the absorption bands of 1705 and 1590 cm^{-1} in the infrared (IR) spectrum. Hydrogenation of (+)-**18** with Pd–C/H_2 afforded the *α*-ketone ((−)-**19**), $[\alpha]_D^{24}$ −79.8° ($CHCl_3$). Conversion of (±)-**19** to (±)-cuparene (**22**) was accomplished by Reetz *et al.*[9] Posner and Kogan[10] reported that the chiral (−)-**19** was completely racemized under the conversion conditions employed ($(Me)_2TiCl_2$) to afford (±)-cuparene (**22**). Compound (±)-**19** was also converted to (±)-laurene (**23**) by Taber and Anthony.[11] Treatment of (+)-**18** with MeLi afforded the tertiary alcohol (**20**), which was subjected to oxidative rearrangement[12] by Jones oxidation to give the cyclopentenone ((+)-



a) DHP, PPTS b) $LiAlH_4$ c) MsCl, NEt_3 d) Jones oxid.

Chart 3



a) MsCl, DBU b) H_2/Pd-C c) MeLi d) Jones oxid.

Chart 4

21), $[\alpha]_D^{24}$ +236° ($CHCl_3$), in 88% yield from (+)-**18**. After completion of the conversion of (+)-**21** to (+)-β-cuparenone (**2**) by using $(CH_3)_2Zn$, a similar conversion of (+)-**21** prepared by an alternative method into **2** was reported by Greene *et al.*[13)]

Experimental

IR spectra were measured with a JASCO A-202 spectrometer. ^{1}H-NMR spectra were measured on JEOL JNM-PS-100 and GX-270 spectrometers. Mass spectra (MS) were taken on a JEOL JMS-D 300 spectrometer. Optical rotations were measured on a JASCO DIP-4 polarimeter. For column chromatography, silica gel (Merck, Kieselgel 60, 70—230 mesh) was used. TLC was performed on Silica gel 60 F_{254} plates (Merck). All organic solvent extracts were washed with brine and dried over anhydrous sodium sulfate.

(2*RS*,3*S*,4*S*)-4-Benzyloxycarbonyl-4-hydroxy-2-methoxycarbonyl-3-methyl-3-*p*-tolyl-1-cyclopentanone (7)——A mixture of *p*-bromotoluene (18.3 g, 107 mmol), zinc bromide (12.1 g, 53.5 mmol), and lithium wire (1.49 g, 214 mmol) in ether (300 ml) was sonicated at room temperature for 2 h under an Ar atmosphere. A mixture of (+)-**5**[1)] (3.26 g, 10.7 mmol) and nickel acetylacetonate (118 mg, 0.43 mmol) in ether (30 ml) was added to the above reagents, and the whole was stirred for 20 h at room temperature. The reaction mixture was poured into 5% aqueous NH_4Cl and extracted with AcOEt (100 ml × 3). The AcOEt extract was washed, and dried, then removal of the solvent *in vacuo* afforded an oily residue (12.7 g), which was subjected to column chromatography on silica gel (50 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **7** as a colorless oil (1.80 g, 50%). IR (neat): 3550, 1765, 1730, 1660, 1615 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.43, 1.50 (3H, (1.4 : 1), s, C_3-CH_3), 2.33 (3H, s, Ar-CH_3), 2.57 (1H, m, OH), 2.65, 2.69 (1H, (1 : 1.4), d, J = 18 Hz, C_5-H), 3.53, 3.65 (3H, (1 : 1.4), s, $COOCH_3$), 5.20 (2H, m, OCH_2), 7.06 (4H, d, J = 4 Hz, Ar-H), 7.20—7.66 (5H, m, Ar-H). MS *m/z*: 396 (M^+), 378, 349, 320.

(3*S*,4*S*)-4-Benzyloxycarbonyl-4-hydroxy-3-methyl-3-*p*-tolyl-1-cyclopentanone (8)——A mixture of **7** (1.78 g, 4.54 mmol) and NaI (817 mg, 5.45 mmol) in DMSO (20 ml) was stirred for 3 h at 100 °C. After cooling, the reaction mixture was diluted with brine (10 ml) and extracted with AcOEt (30 ml × 3). The AcOEt extract was washed and dried, then concentrated *in vacuo* to afford an oily residue (1.55 g), which was subjected to column chromatography on silica gel (15 g). The fraction eluted with 10—15% AcOEt in hexane (v/v) afforded (−)-**8** (1.37 g, 89%) as colorless needles, mp 91—92 °C, recrystallized from benzene–hexane. $[\alpha]_D^{24}$ −85.0 °C (c = 1.00, $CHCl_3$). IR (Nujol): 3500, 1740, 1720, 1515 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, J = 0.82 Hz, C_3-CH_3), 2.33 (3H, s, Ar-CH_3), 2.36, 3.32 (1H each, d, J = 19 Hz, C_2-H), 2.62, 3.21 (1H each, d, J = 17 Hz, C_5-H), 2.68 (1H, s, OH), 5.25 (2H, s, OCH_2). MS *m/z*: 338 (M^+), 320, 247. *Anal.* Calcd for $C_{21}H_{22}O_4$: C, 74.53; H, 6.55. Found: C, 74.41; H, 6.59.

(1*RS*,3*S*,4*S*)-4-Hydroxymethyl-3-methyl-3-*p*-tolyl-1,4-cyclopentanediol (12)——Compound (−)-**8** (1.37 g, 4.05 mmol) in ether (20 ml) was added dropwise with stirring to a suspension of $LiAlH_4$ (154 mg, 4.05 mmol) in ether (20 ml) at 0 °C, and stirred for 40 min. Usual work-up afforded a crude semisolid, which was subjected to column chromatography on silica gel (20 g). The fraction eluted with AcOEt afforded **12** (829 mg, 87%) as colorless needles, mp 158—159 °C, recrystallized from AcOEt. IR (Nujol): 3270, 1515, 1450, 1100, 1050 cm^{-1}. ^{1}H-NMR (acetone-d_6) δ:

1.50 (3H, s, C_3-CH_3), 1.69 (1H, dd, J= 14, 2.8 Hz, C_5-H), 2.27 (3H, s, Ar-CH_3), 3.42—3.90 (4H, m), 4.59 (1H, m, C_1-H). MS m/z: 236 (M^+), 218, 200. *Anal.* Calcd for $C_{14}H_{20}O_3$: C, 71.16; H, 8.53. Found: C, 71.21; H, 8.49.

(2*S*,4*RS*)-4-Hydroxy-2-methyl-2-*p*-tolyl-1-cyclopentanone (13)——A solution of $NaIO_4$ (319 mg, 1.49 mmol) in H_2O (4 ml) was added dropwise to a stirred solution of **12** (293 mg, 1.24 mmol) in acetone (5 ml) at room temperature. The whole was stirred for 2.5 h, and the resulting precipitate was filtered off. The filtrate was concentrated *in vacuo* to afford an oily residue, which was diluted with brine (5 ml) and extracted with AcOEt (10 ml × 3). The AcOEt extract was washed and dried. The solvent was removed *in vacuo* to leave an oily residue, which was subjected to column chromatography on silica gel (5 g). The fraction eluted with 20—30% AcOEt in hexane (v/v) afforded **13** (250 mg, 98%) as a colorless oil. IR (neat): 3430, 1735, 1515, 1060 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.38, 1.49 (3H, (1 : 1), s, C_3-CH_3), 1.68 (1H, br s, OH), 1.94—3.00 (4H, m, C_2-, C_5-H), 2.32 (3H, s, Ar-CH_3), 4.57 (1H, m, C_1-H), 7.06—7.40 (4H, m, Ar-H). MS m/z: 204 (M^+), 186, 171. *Anal.* Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.58; H, 8.01.

(3*R*,4*R*)-4-Benzyloxycarbonyl-4-hydroxy-3-methyl-3-*p*-tolyl-1-cyclopentanone Ethylene Dithioacetal (9)—— Ethanedithiol (109 mg, 1.15 mmol) was added to a stirred solution of (+)-**8** (260 mg, 0.77 mmol) in CH_2Cl_2 (5 ml) in the presence of BF_3-etherate (0.03 ml, 0.23 mmol) at room temperature. After 1 h, the reaction mixture was diluted with brine (5 ml) and extracted with CH_2Cl_2 (10 ml × 3). The CH_2Cl_2 extract was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue (341 mg), which was subjected to column chromatography on silica gel (5 g). The fraction eluted with 5—10% AcOEt in hexane (v/v) afforded (+)-**9** (224 mg, 70%) as a colorless oil. $[\alpha]_D^{24}$ + 52.8° (c= 1.16, $CHCl_3$). IR (neat): 3550, 1730, 1520, 1265 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.50 (3H, s, C_3-CH_3), 1.54 (1H, s, OH), 2.30 (3H, s, Ar-CH_3), 2.54 (1H, d, J= 14 Hz, $C_{2\beta}$-H), 2.81 (1H, d, J= 15 Hz, $C_{5\beta}$-H), 3.20—3.60 (6H, m, $SCH_2 \times 2$, $C_{2\alpha}$-, $C_{5\alpha}$-H), 5.21 (2H, s, OCH_2). MS m/z: 414 (M^+), 322, 282.

(3*R*,4*R*)-4-Hydroxy-4-hydroxymethyl-3-methyl-3-*p*-tolyl-1-cyclopentanone Ethylene Dithioacetal (10)—— Compound (+)-**9** (220 mg, 0.53 mmol) in ether (5 ml) was added dropwise with stirring to a suspension of $LiAlH_4$ (25 mg, 0.65 mmol) in ether (10 ml) at 0 °C. The mixture was stirred for 0.5 h, then usual work-up afforded a semisolid, which was chromatographed on silica gel (3 g). The fraction eluted with AcOEt afforded (−)-**10** (86 mg, 52%) as colorless needles, mp 153—154 °C, recrystallized from AcOEt. $[\alpha]_D^{24}$ −11.7° (c= 0.48, $CHCl_3$). IR (Nujol): 3530, 3380, 1520 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.51 (3H, s, CH_3), 1.73—1.93 (2H, br, OH × 2), 2.33 (3H, s, Ar-CH_3), 2.49 (1H, d, J= 14 Hz, $C_{2\beta}$-H), 2.80 (2H, s, C_5-H), 3.24—3.51 (4H, m, $SCH_2 \times 2$), 3.56 (1H, d, J= 14 Hz, $C_{2\alpha}$-H), 3.63, 3.65 (1H each, d, J= 11 Hz, C_4-CH_2). MS m/z: 310 (M^+), 292, 274, 262. *Anal.* Calcd for $C_{16}H_{22}O_2S_2$: C, 61.91; H, 7.15. Found: C, 61.83; H, 7.22.

(3*R*,4*R*)-4-Acetoxymethyl-4-hydroxy-3-methyl-3-*p*-tolyl-1-cyclopentanone Ethylene Dithioacetal (11)——Acetic anhydride (0.1 ml) was added to a stirred solution of the diol (−)-**10** (12 mg, 0.04 mmol) in pyridine (1 ml) at room temperature. After 2 h, the reaction mixture was diluted with brine (3 ml) and extracted with AcOEt (5 ml × 3). The AcOEt extract was washed, and dried, then concentrated *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel (2 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded (+)-**11**(13.4 mg, 98%) as a colorless oil. $[\alpha]_D^{24}$ +8.6° (c= 1.26, $CHCl_3$). IR (neat): 3450, 1735, 1515, 1230 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.55 (3H, s, C_3-CH_3), 1.77 (1H, br, OH), 1.94 (3H, s, $OCOCH_3$), 2.33 (3H, s, Ar-CH_3), 2.49 (1H, d, J= 14 Hz, $C_{2\beta}$-H), 2.77 (1H, d, J= 15 Hz, $C_{5\alpha}$-H), 2.86 (1H, d, J= 15 Hz, $C_{5\beta}$-H), 3.25—3.48 (4H, m, $SCH_2 \times 2$), 3.59 (1H, d, J= 14 Hz, $C_{2\alpha}$-H), 4.18 (2H, s, C_4-CH_2). MS m/z: 352 (M^+), 334, 274.

(2*S*,4*RS*)-2-Methyl-2-*p*-tolyl-4-(tetrahydropyran-2-yl)oxy-1-cyclopentanone (14)——DHP (62 mg, 0.74 mmol) in CH_2Cl_2 (2 ml) was added to a stirred solution of **13** (126 mg, 0.62 mmol) in CH_2Cl_2 (2 ml) in the presence of a catalytic amount of PPTS. After 3.5 h, the reaction mixture was diluted with CH_2Cl_2 (10 ml). The organic layer was successively washed with aqueous $NaHCO_3$ and brine, the dried. The solvent was removed *in vacuo* to afford an oily residue (190 mg), which was subjected to column chromatography on silica gel (2 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **14** (177 mg, 99%) as a colorless oil. IR (neat): 1735, 1510, 1020 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.40, 1.46 (3H, (1 : 1), s, C_3-CH_3), 2.31 (3H, s, Ar-CH_3), 1.97—3.06 (4H, m, C_2-, C_5-H), 3.54, 3.80 (1H each, m, OCH_2), 4.23—4.86 (2H, m, OCHO, C_1-H). MS m/z: 288 (M^+), 204, 186.

(1*RS*,2*S*,4*RS*)-2-Methyl-2-*p*-tolyl-4-(tetrahydropyran-2-yl)oxy-1-cyclopentanol (15)——Compound **14** (100 mg, 0.35 mmol) in ether (5 ml) was added dropwise with stirring to a suspension of $LiAlH_4$ (13 mg, 0.35 mmol) in ether (5 ml) at 0 °C, and stirred for 4 h. Usual work-up afforded a crude oil (93 mg), which was subjected to column chromatography on silica gel (2 g). The fraction eluted with 20% AcOEt in hexane (v/v) afforded **15** (92 mg, 91%) as a colorless oil. IR (neat): 3450, 1520, 1020 cm^{-1}. ^1H-NMR ($CDCl_3$) δ: 1.43, 1.44 (3H, (1 : 1), s, C_3-CH_3), 2.26, 2.31 (3H, (1 : 1), s, Ar-CH_3), 3.55, 3.85 (1H each, m, OCH_2), 4.06—4.54 (2H, m, C_1-, C_4-H), 4.64 (1H, m, OCHO). MS m/z: 290 (M^+), 272, 206.

(1*RS*,3*S*,4*RS*)-4-Methanesulfonyloxy-3-methyl-3-*p*-tolyl-1-(tetrahydropyran-2-yl)oxycyclopentane (16)——MsCl (36 mg, 0.32 mmol) in benzene (2 ml) was added dropwise to a stirred solution of **15** (77 mg, 0.266mmol) in benzene (5 ml) in the presence of Et_3N (40 mg, 0.40 mmol) at room temperature. After 0.5 h, the reaction mixture was diluted with 3% aqueous HCl (5 ml) and extracted with AcOEt (10 ml × 3). The AcOEt extract was successively washed with 5% aqueous $NaHCO_3$ and brine, then dried. The solvent was removed *in vacuo* to afford an oily residue (115 mg), which was chromatographed on silica gel (2 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded **16**

(96 mg, 98%) as a colorless oil. IR (neat): 1520, 1450, 1350, 1175 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, s, C_3-CH_3), 2.32 (3H, s, Ar-CH_3), 2.89 (3H, s, OSO_2CH_3), 3.54, 3.86 (1H each, m, OCH_2), 4.31 (1H, m, C_1-H), 4.63 (1H, m, OCHO), 5.07 (1H, m, C_4-H). MS *m/z*: 368 (M^+), 340, 284.

(*R*)-4-Methyl-4-*p*-tolyl-2-cyclopenten-1-one (17)——The Jones reagent (0.2 ml) was added dropwise to a stirred solution of **16** (76 mg, 0.21 mmol) in acetone (5 ml) at 0 °C. After 4 h, the excess reagent was decomposed with isopropanol, and the reaction mixture was diluted with brine (5 ml), then extracted with AcOEt. The AcOEt extract was washed, and dried, then concentrated *in vacuo* to leave an oily residue (59 mg), which was subjected to column chromatography on silica gel (2 g). The fraction eluted with 10% AcOEt in hexane (v/v) afforded (+)-**17** (35 mg, 91%) as a colorless oil. $[\alpha]_D^{26}$ +139° (c = 1.18, EtOH), (lit.[8] $[\alpha]_D^{20}$ +114° (c = 1.36, EtOH)). IR (neat): 1705, 1580, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.62 (3H, s, C_4-CH_3), 2.33 (3H, s, Ar-CH_3), 2.56, 2.60 (1H each, d, J = 18 Hz, C_5-H), 6.19 (1H, d, J = 5.6 Hz, C_2-H), 7.15 (4H, s, Ar-H), 7.66 (1H, d, J = 5.6 Hz, C_3-H). MS *m/z*: 186 (M^+), 171, 143. High-MS for $C_{13}H_{14}O$ (M^+): Calcd *m/z* 186.1044; Found 186.1038.

(*S*)-5-Methyl-5-*p*-tolyl-2-cyclopenten-1-one (18)——MsCl (38 mg, 0.34 mmol) in benzene (5 ml) was added dropwise to a stirred solution of **13** (57 mg, 0.28 mmol) in benzene (5 ml) in the presence of DBU (128 mg, 0.84 mmol) at room temperature. After 4 h, the reaction mixture was diluted with brine (5 ml), and extracted with AcOEt. The AcOEt extract was successively washed with 3% aqueous HCl, 5% aqueous $NaHCO_3$, and brine, then dried. Removal of the solvent *in vacuo* afforded an oily residue, which was subjected to column chromatography on silica gel (5 g). The fraction eluted with 5—10% AcOEt in hexane (v/v) afforded (+)-**18** (51 mg, 98%) as a colorless oil. $[\alpha]_D^{24}$ +7.1° (c = 1.16, $CHCl_3$). IR (neat): 1705, 1590, 1515, 1190 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.51 (3H, s, C_5-CH_3), 2.30 (3H, s, Ar-CH_3), 2.87 (1H, ddd, J = 19.5, 2.7, 2.2 Hz, $C_{4\alpha}$-H), 3.08 (1H, ddd, J = 19.5, 2.7, 2.2 Hz, $C_{4\beta}$-H), 6.26 (1H, dt, J = 5.9, 2.2 Hz, C_2-H), 7.14 (4H, s, Ar-H), 7.77 (1H, dt, J = 5.9, 2.7 Hz, C_3-H). MS *m/z*: 186 (M^+), 171, 143.

(*S*)-2-Methyl-2-*p*-tolyl-1-cyclopentanone (19)——The enone (+)-**18** (50 mg, 0.27 mmol) in ethanol (5 ml) was hydrogenated in the presence of 5% Pd–C under an H_2 atmosphere at room temperature. The catalyst was filtered off, and the filtrate was concentrated *in vacuo* to afford an oily residue, which was subjected to column chromatography on silica gel (2 g). The fraction eluted with 5—10% AcOEt in hexane (v/v) afforded (−)-**19** (45 mg, 89%) as a colorless oil. $[\alpha]_D^{24}$ −79.8° (c = 1.04, $CHCl_3$). IR (neat): 1735, 1515, 1445, 1055 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (3H, s, C_2-CH_3), 1.63—2.17 (3H, m, $C_{3\alpha}$-H, C_4-H), 2.32 (3H, s, Ar-CH_3), 2.17—2.71 (3H, m, $C_{3\beta}$-H, C_5-H), 7.08—7.30 (4H, m, Ar-H). MS *m/z*: 188 (M^+), 145, 132. High-MS for $C_{13}H_{16}O$ (M^+): Calcd *m/z* 188.1200; Found 188.1210.

(1*RS*,5*S*)-1,5-Dimethyl-5-*p*-tolyl-2-cyclopenten-1-ol (20) and (*R*)-3,4-Dimethyl-4-*p*-tolyl-2-cyclopenten-1-one (21)——MeLi (0.89 M in ether, 0.37 ml) was added dropwise to a stirred solution of (+)-**18** (51 mg, 0.27 mmol) in ether (5 ml) under an N_2 atmosphere at −78 °C. After 1 h, the reaction mixture was diluted with 3% aqueous HCl (5 ml) and extracted with AcOEt (5 ml × 3). The AcOEt extract was washed and dried. Removal of the solvent *in vacuo* afforded an oily residue (**20**), which was subjected to the next oxidation reaction without further purification. IR (neat): 3420, 1590, 1515, 1100 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (6H, s, C_1-, C_5-CH_3), 1.58 (1H, br, OH), 2.33 (3H, s, Ar-CH_3), 2.10—2.48 (1H, m, C_4-H), 3.08—3.30 (1H, m, C_4-H), 5.68 (1H, m, C_3-H), 5.98 (1H, m, C_2-H), 6.97—7.34 (4H, m, Ar-H). MS *m/z*: 202 (M^+), 184, 171.

The Jones reagent (0.2 ml) was added dropwise to a stirred solution of crude **20** (83 mg) in acetone (5 ml) at 0 °C. After 10 min, the excess reagent was decomposed with isopropanol, and the reaction mixture was diluted with brine (5 ml), then extracted with AcOEt. The combined extracts were washed and dried. Removal of the solvent *in vacuo* afforded an oily residue (69 mg), which was subjected to silica-gel column chromatography (2 g). The fraction eluted with 5—10% AcOEt in hexane (v/v) afforded (+)-**21** (48 mg, 88% from (+)-**18**) as a colorless oil. $[\alpha]_D^{24}$ +236° (c = 1.02, $CHCl_3$), (lit.[13] $[\alpha]_D^{20}$ +253° (c = 1.7, $CHCl_3$)). IR (neat): 1700, 1615, 1510 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.63 (3H, s, C_4-CH_3), 1.83 (3H, d, J = 1.2 Hz, C_3-CH_3), 2.33 (3H, s, Ar-CH_3), 2.56, 2.63 (1H each, d, J = 18 Hz, C_5-H), 6.02 (1H, q, J = 1.2 Hz, C_2-H), 7.12 (4H, s, Ar-H). MS *m/z*: 200 (M^+), 185, 157. High-MS for $C_{14}H_{16}O$ (M^+): Calcd *m/z* 200.1200; Found 200.1208.

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