Synthetic Studies on Spirovetivane Phytoalexins. V.[1] A Stereoselective Total Synthesis of (±)-Oxylubimin[2]

Chuzo IWATA,* Yoshiji TAKEMOTO, Hitoshi KUBOTA, Takeshi KURODA, and Takeshi IMANISHI

Faculty of Pharmaceutical Sciences, Osaka University, 1–6 Yamadaoka, Suita, Osaka 565, Japan. *Received July 15, 1989*

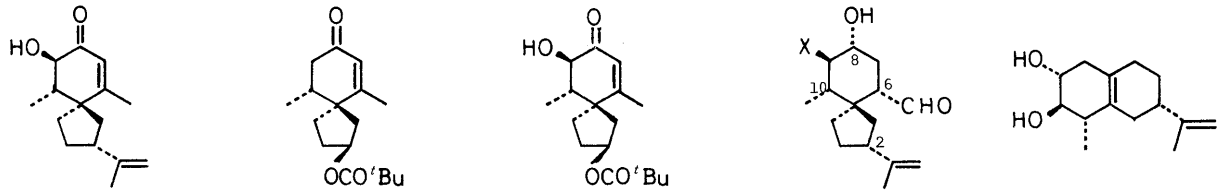
(±)-Oxylubimin (4), the most highly oxygenated spirovetivane phytoalexin, was synthesized stereoselectively from a key intermediate, (2*RS*,5*RS*,9*SR*,10*RS*)-9-hydroxy-6,10-dimethyl-2-pivaloyloxyspiro[4.5]dec-6-en-8-one (3). Its methoxymethyl ether (8) was reduced with $NaBH_4$ and $CeCl_3 \cdot 7H_2O$ to give predominantly the desired alcohol (9a) (9a/9b = 6.4). The alcohol (9a) was successfully transformed into oxylubimin (4) *via* several steps, involving introduction of a bis(ethoxycarbonyl)methyl group at the C_2, catalytic hydrogenation of the C_6–C_7 double bond, and pyridinium chlorochromate oxidation of the hydroxymethyl group at C_6.

Keywords spiro[4.5]decane; spirovetivane phytoalexin; sesquiterpene; total synthesis; α′-hydroxy-α,β-unsaturated ketone; 1,2-reduction; *trans*-glycol; chemoselective hydrogenation; methoxymethyl ether

In the preceding paper,[1] we described a synthesis of (±)-3-hydroxysolavetivone (**1**) using a crucial stereoselective triphenyl phosphite ozonide (TPPO) oxidation of the α,β-unsaturated ketone (**2**) to **3**. Herein we wish to report a stereoselective total synthesis of (±)-oxylubimin (**4**), the most highly oxygenated spirovetivane phytoalexin, from the same intermediate (**3**).

Oxylubimin (**4**), a spirovetivane sesquiterpene having six asymmetric carbon centers, was isolated from tuber tissue of white potatoes infected by *Phytophthora infestans*, along with lubimin (**5**) and rishitin (**6**).[3] This natural product is not only a representative spirovetivane phytoalexin from the viewpoints of its strong biological activity and the complex stereochemistry, but also a promising biosynthetic precursor of rishitin (**6**), which is known to show the strongest antifungal activity of this family.[4]

For synthesis of **4** from **3**, the first crucial step is reduction of the enone (**3**) to the *trans*-diol (**7a**). All attempts to reduce **3** under various conditions expected to favor 1,2-reduction of α,β-unsaturated ketone,[5] however, resulted in formation of a mixture of the diols (**7a** and **7b**) without satisfactory stereoselectivity (Table I, R = H). Especially in the case of run 1, the undesired isomer (**7b**) was mainly produced. This unsatisfactory result is probably attributable to five-membered chelation involving a metal ion (the reductant) and oxgen atoms (the hydroxy and ketone groups in the substrate).[6] Such chelation would lead to relative ease of equatorial attack of the hydride due to a torsional strain effect, affording the *cis*-glycol (**7b**) in a moderate amount (Fig. 1). Therefore, in order to obtained the isomer (**7a**) or its equivalent more efficiently, a decrease of the chelating character of the hydroxy group, prior to ketone reduction, must be achieved. Thus, the hydroxy group of **3** was initially protected as the methoxymethyl (MOM) ether, and the obtained **8** (84% yield) was reduced under various conditions. As expected, all the runs gave the desired stereoselectivity and the results are included in Table I (R = MOM), which shows that the ratio of **9a**/**9b** is



1 2 3 4 : X = OH 5 : X = H 6

Chart 1

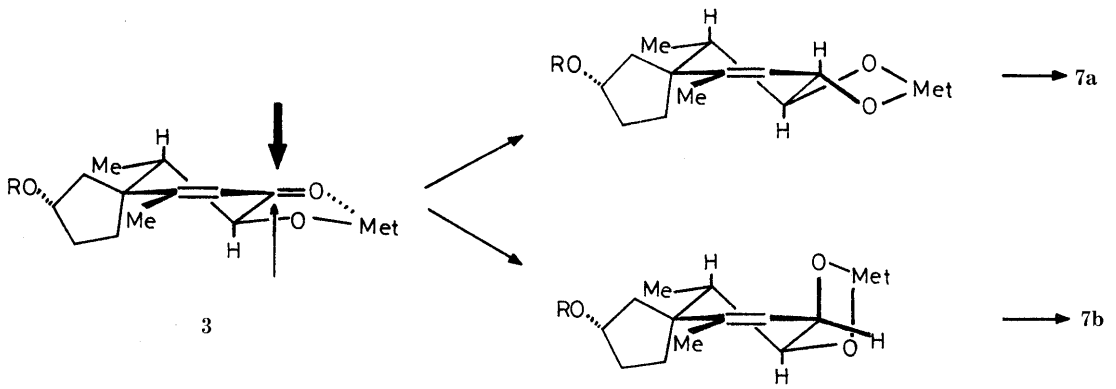


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Fig. 1

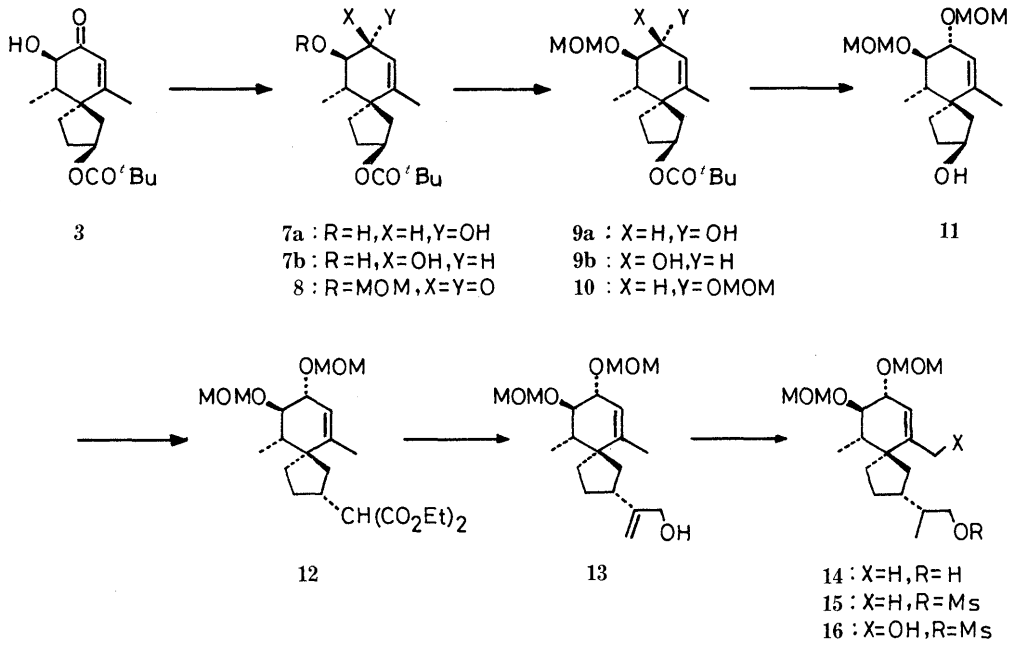

Chart 2

TABLE I. Reduction of α′-Hydroxy Enones (**3** and **8**) under Various Conditions

Run	Conditions	Yield of **7** (%) (Ratio of **7a**/**7b**)[a]	Yield of **9** (%) (Ratio of **9a**/**9b**)[a]
1	$Zn(BH_4)_2$, Et_2O, 0 °C[5a]	96 (0.81)	79 (1.9)
2	Red-Al, Et_2O, 0 °C	73[c] (2.4)	—
3	$LiBH_3$(*n*-Bu), toluene, hexane, −78 °C[5b]	—	84 (1.2)
4	$NaBH_3CN$, MeOH, 2 N HCl, r.t.[5c]	62 (1.9)	71 (5.6)
5	$NaBH_4$, $CeCl_3 \cdot 7H_2O$, MeOH, r.t.[5d]	70 (2.7)	90 (6.4)[b]

a) The ratio was based on isolated yields. *b*) The reaction was carried out at 0 °C. *c*) Based on the consumed starting material.

always higher than that of **7a**/**7b**. When the reduction was carried out under the conditions shown in run 5, that is, reduction with sodium borohydride–cerium(III) chloride[5d] in a polar solvent, the highest ratio of **9a**/**9b** was obtained and the desired product (**9a**) was isolable in 78% yield together with a small amount of the axial alcohol (**9b**).

Next, introduction of a three-carbon unit at the C_2 position in **9a** was accomplished according to the previous reports[1,7] as follows. The hydroxy group in **9a** was protected as the MOM ether, and the obtained compound (**10**) was reacted with methyllithium in ether to give the alcohol (**11**) in 86% yield. Mesylation of **11** and the subsequent *S*N2-type reaction with the enolate anion of diethyl malonate provided the desired product (**12**) in 95% yield. The bis(ethoxycarbonyl)methyl group in **12** was converted into the allylic alcohol (**13**) by using a modification of the Marshall conditions[8] [Red-Al in dimethoxyethane (DME) under reflux]. A chemoselective reduction of the disubstituted C–C double bond in **13** was achieved by treatment with sodium borohydride and cobalt(III) chloride in methanol,[9] affording **14** in 78% yield. The mesylate (**15**), prepared from **14** in the usual manner, was oxidized with

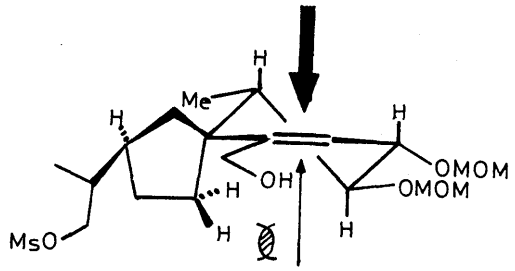

Fig. 2

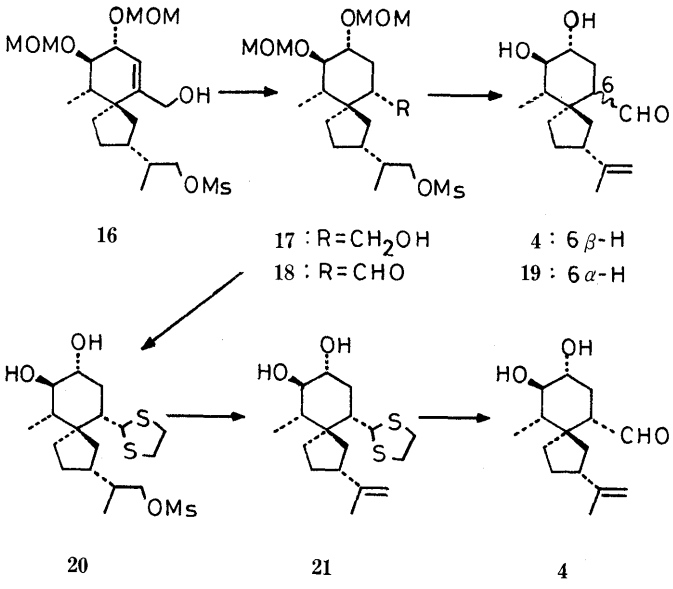

Chart 3

selenium dioxide in boiling xylene, followed by reaction with sodium borohydride to give the allylic alcohol (**16**) in 70% yield.

From an inspection on the steric environment of **16** and our previous experimental result[7a] in a total synthesis of

(±)-lubiminol, catalytic hydrogenation of the C_6–C_7 double bond in **16** was expected to take place from the top side because of steric hindrance of the methylene unit at the C_4 position (Fig. 2). In fact, hydrogenation of **16** over Raney Ni (W2) in ethanol gave only the saturated alcohol (**17**) in 90% yield.[10] After **17** had been subjected to pyridinium chlorochromate (PCC) oxidation to provide the saturated aldehyde (**18**) in 82% yield, treatment with 3 N hydrochloric acid in tetrahydrofuran (THF) followed by reaction with 1,8-diazabicyclo[5.4.0]undecene (DBU) and sodium iodide in boiling dimethoxyethane (DME) afforded (±)-oxylubimin (**4**) and, unexpectedly, (±)-10-epioxylubimin (**19**) in a ratio of 3:2. The formation of **19** would be owing to isomerization at C-6 during the reaction sequence.[11]

On the other hand, thioacetalization of **18** in the usual manner [ethanedithiol, borontrifluoride etherate, dichloromethane, 0 °C→room temperature] was accompanied with deprotection[12] of the MOM ether to give the diol (**20**) in 87% yield. This product was treated with DBU and sodium iodide to give the olefin (**21**) in 74% yield as a single diastereoisomer. Finally, on reaction with a large excess of methyl iodide in boiling aqueous acetonitrile in the presence of calcium carbonate, **21** was fairly effectively transformed into (±)-oxylubimin (**4**) without any formation of its C_6-isomer (**19**). The synthetic product (**4**) was proved to be identical with an authentic sample of natural oxylubimin by means of spectral comparison.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrophotometer. Ultraviolet (UV) spectra were recorded on a Hitachi 124 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Hitachi R-22 (90 MHz) or JEOL FX-90Q (90 MHz) with tetramethylsilane as an internal standard. The following abbreviations for the signal patterns are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad. Mass spectra (MS) and high-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D300 mass spectrometer. For column chromatography, Merck Kieselgel 60 (70—230 mesh) were used, and for preparative thin layer chromatography (TLC), Merck Kieselgel 60 PF_{254} was used. All organic extracts were dried over $MgSO_4$.

Reduction of (2*RS*,5*RS*,9*SR*,10*RS*)-9-Hydroxy-6,10-dimethyl-2-pivaloyloxyspiro[4.5]dec-6-en-8-one (3) a) Reduction with $Zn(BH_4)_2$: An ethereal solution of $Zn(BH_4)_2$ (an excess) was added to a solution of the enone (**3**) (11.6 mg, 0.039 mmol) in dry ether (0.2 ml) at 0 °C, and the mixture was stirred for 1 h at this temperature. The mixture was quenched with H_2O and 1 N HCl, and extracted with ether. The extract was washed with saturated $NaHCO_3$ solution, H_2O and brine, dried, and then evaporated. Purification of the residue by preparative TLC with benzene–ethyl acetate (2:1) afforded (2*RS*,5*RS*,8*SR*,9*SR*,10*RS*)-6,10-dimethyl-2-pivaloyloxyspiro[4.5]dec-6-ene-8,9-diol (**7a**) (5.0 mg, 43%) and (2*RS*,5*RS*,8*RS*,9*SR*,10*RS*)-6,10-dimethyl-2-pivaloyloxyspiro[4.5]dec-6-ene-8,9-diol (**7b**) (6.2 mg, 54%).

7a: A colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 1720, 1665. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, d, J=6 Hz, C_{10}-Me), 1.20 (9H, s, *tert*-Bu), 1.70 (3H, br s, C_6-H), 3.24 (1H, dd, J=8, 12 Hz, C_9-H), 3.96 (1H, d, J=8 Hz, C_8-H), 5.09 (1H, br s, C_7-H), 4.9—5.3 (1H, m, C_2-H). MS *m/z* (%): 278 (M^+ − 18, 1.8), 136 (100). HRMS Calcd for $C_{17}H_{28}O_4$: 296.1984. Found: 296.1976.

7b: Colorless needles, mp 141—142 °C (ether). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 1720, 1660. ^{1}H-NMR ($CDCl_3$) δ: 1.11 (3H, d, J=6 Hz, C_{10}-Me), 1.18 (9H, s, *tert*-Bu), 1.73 (3H, br s, C_6-Me), 3.45 (1H, dd, J=4, 11 Hz, C_9-H), 4.00 (1H, dd, J=4, 5 Hz, C_8-H), 4.8—5.2 (1H, m, C_2-H), 5.39 (1H, d, J=5 Hz, C_7-H). MS *m/z* (%): 296 (M^+, 1.2), 136 (100). HRMS Calcd for $C_{17}H_{28}O_4$: 296.1987. Found: 296.1987.

b) Reduction with Red-Al: A solution of the enone (**3**) (69.1 mg, 0.24 mmol) in dry ether (1.5 ml) was added dropwise to a solution of Red-Al (101.7 mg, 0.35 mmol) in dry ether (0.5 ml) at −78 °C. After being stirred for 30 min at this temperature, the mixture was treated with additional Red-Al (34.0 mg, 0.12 mmol) and stirred for another 30 min. Saturated potassium sodium tartrate aqueous solution was added and the resulting solution was extracted with ether. The organic phase was washed with H_2O and brine, dried, and then evaporated. The residue was purified by column chromatography with benzene–ethyl acetate (2:1) to give **7a** (21.8 mg), **7b** (9.3 mg), and the unchanged starting material (26.5 mg). Yields of **7a** and **7b**, based on the consumed starting material, were 51 and 22%, respectively.

c) Reduction with $NaBH_3CN$: A 2 N HCl solution was added to a mixture of the enone (**3**) (133.1 mg, 0.45 mmol), $NaBH_3CN$ (56.8 mg, 0.90 mmol), methyl orange (trace), and MeOH (1 ml) until the color of the mixture became permanently red, and then the mixture was stirred for 8 h at room temperature. After removal of the solvent and addition of water, the mixture was extracted with ether. The organic phase was washed with H_2O and brine, dried, and then evaporated. The residue was purified by preparative TLC with benzene–ethyl acetate (2:1) to afford **7a** (54.1 mg, 41%) and **7b** (28.3 mg, 21%).

d) Reduction with $NaBH_4$–$CeCl_3 \cdot 7H_2O$: $NaBH_4$ (3.4 mg, 0.091 mmol) was added in one portion to a solution of the enone (**3**) (26.8 mg, 0.091 mmol) and $CeCl_3 \cdot 7H_2O$ (33.9 mg, 0.091 mmol) in MeOH (1.5 ml) at room temperature, and the resulting mixture was stirred for 10 min at the same temperature. After removal of the solvent and acidification with dilute HCl aqueous solution, the resulting solution was extracted with ether. The ethereal layer was washed with H_2O and brine, dried, and then evaporated. The residue was purified by preparative TLC with benzene–ethyl acetate (2:1) to afford **7a** (13.6 mg, 51%) and **7b** (5.0 mg, 19%).

(2*RS*,5*RS*,9*SR*,10*RS*)-9-Methoxymethoxy-6,10-dimethyl-2-pivaloyloxyspiro[4.5]dec-6-en-8-one (8) A solution of the enone (**3**) (180.8 mg, 0.61 mmol), diisopropylethylamine (0.16 ml, 0.92 mmol), and MOM–Cl (0.061 ml, 0.80 mmol) in dry CH_2Cl_2 (1 ml) was stirred for 8 h at room temperature. Saturated $NaHCO_3$ solution was added under ice-water cooling, and the resulting mixture was extracted with ether. The extract was washed with H_2O and brine, dried, and evaporated. The residue was chromatographed with benzene–ethyl acetate (9:1) to give **8** (174 mg, 84%) as colorless needles. mp 84—85 °C (hexane). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1735, 1695, 1630. UV λ_{max}^{EtOH} nm (ε): 239 (13000). ^{1}H-NMR (CCl_4) δ: 1.11 (3H, d, J=6 Hz, C_{10}), 1.17 (9H, s, *tert*-Bu), 1.93 (3H, s, C_6-Me), 3.28 (3H, s, OMe), 3.68 (1H, d, J=9 Hz, C_9-H), 4.47 and 4.72 (each 1H, d, J=7 Hz, OCH_2O), 5.01 (1H, m, C_2-H), 5.56 (1H, s, C_7-H). MS *m/z* (%): 307 (M^+ − 31, 4), 134 (100). *Anal.* Calcd for $C_{19}H_{30}O_5$: C, 67.43; H, 8.94. Found: C, 67.04; H, 9.03.

Reduction of 8 a) Reduction with $Zn(BH_4)_2$: An ethereal solution of $Zn(BH_4)_2$ (an excess), prepared as described above, was added to a solution of the enone (**8**) (35.6 mg, 0.105 mmol) in dry ether (0.5 ml) at 0 °C, and the mixture was stirred for 1 h at the same temperature. Work-up as usual gave a crude product, which was purified by preparative TLC with benzene–ethyl acetate (9:1) to give (2*RS*,5*RS*,8*SR*,9*SR*,10*RS*)-9-methoxymethoxy-6,10-dimethyl-2-pivaloyloxyspiro[4.5]dec-6-en-8-ol (**9a**) (18.6 mg, 52%) and its C-8 isomer (**9b**) (9.7 mg, 27%).

9a: A colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3460, 1730, 1670, 1110. ^{1}H-NMR (CCl_4) δ: 1.08 (3H, d, J=6 Hz, C_{10}-Me), 1.18 (9H, s, *tert*-Bu), 1.76 (3H, d, J=1 Hz, C_6-Me), 2.96 (1H, dd, J=7, 11 Hz, C_9-H), 3.42 (3H, s, OMe), 3.85 (1H, d, J=7 Hz, C_8-H), 4.60 and 4.72 (each 1H, d, J=7 Hz, OCH_2O), 5.08 (1H, br s, C_7-H), 4.9—5.2 (1H, m, C_2-H). MS *m/z* (%): 340 (M^+, 0.3), 136 (100). HRMS Calcd for $C_{13}H_{32}O_5$: 340.2250. Found: 340.2251.

9b: A colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3575, 1730, 1665, 1110. ^{1}H-NMR (CCl_4) δ: 1.01 (3H, d, J=7 Hz, C_{10}-Me), 1.13 (9H, s, *tert*-Bu), 1.72 (3H, s, C_6-Me), 3.31 (3H, s, OMe), 3.35 (1H, dd, J=4 and 8 Hz, C_9-H), 3.96 (1H, t, J=4 Hz, C_8-H), 4.55 and 4.64 (each 1H, d, J=6 Hz, OCH_2O), 4.97 (1H, m, C_2-H), 5.22 (1H, d, J=4 Hz, C_7-H). MS *m/z* (%): 340 (M^+, 0.3), 136 (100). HRMS Calcd for $C_{19}H_{32}O_5$: 340.2247. Found: 340.2241.

b) Reduction with $LiBH_3$(*n*-Bu): $LiBH_3$(*n*-Bu) (0.25 M, 1.4 ml), prepared from borane–Me_2S (10 M, 0.10 ml) and *n*-BuLi (1.4 M, 0.69 ml), was added to a solution of the enone (**8**) (116 mg, 0.34 mmol) in dry toluene (1.5 ml) at −78 °C under nitrogen, and the mixture was stirred for 3 h at this temperature. After successive addition of water, 10% aqueous NaOH (1 ml), and 30% H_2O_2 solution (0.66 ml), the resulting mixture was stirred for 12 h at room temperature. Water was added, and the mixture was stirred for 12 h at room temperature. Water was added, and the mixture was extracted with ether. The extract was washed with H_2O, saturated $NaHSO_3$ solution, and brine, dried, and then evaporated. The residue was purified by column chromatography with benzene–ethyl acetate (9:1) to give **9a** (52.7 mg, 46%) and **9b** (43.5 mg, 38%).

c) Reduction with $NaBH_3CN$: A mixture of the enone (**8**) (358 mg, 1.06 mmol), $NaBH_3CN$ (133 mg, 2.12 mmol), methyl orange (trace), and MeOH (2 ml) was treated in the same manner as **7a**, and purification by

column chromatography with benzene–ethyl acetate (9 : 1) gave **9a** (218 mg, 60%) and **9b** (39.2 mg, 11%).

d) Reduction with $NaBH_4$–$CeCl_3 \cdot 7H_2O$: Enone (**8**) (306 mg, 0.90 mmol), $CeCl_3 \cdot 7H_2O$, and $NaBH_4$ (34.2 mg, 0.90 mmol) were reacted in the same manner as **7a**, except that the reaction was carried at 0 °C, and the obtained residue was chromatographed with benzene–ethyl acetate (5 : 1) to afford **9a** (240 mg, 78%) and **9b** (7.6 mg, 12%).

(2*RS*,5*RS*,8*SR*,9*SR*,10*RS*)-8,9-Bis(methoxymethoxy)-6,10-dimethyl-2-pivaloyloxyspiro[4.5]dec-6-ene (10) A mixture of the alcohol (**9a**) (227 mg, 0.67 mmol), diisopropylethylamine (0.17 ml, 1.00 mmol), and MOM–Cl (0.066 ml, 0.87 mmol) was treated in the same manner as described for **8**, and purification of the crude product by column chromatography with benzene–ethyl acetate (9 : 1) gave **10** (233 mg, 91%) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1725, 1660. ^{1}H-NMR ($CDCl_3$) δ: 1.04 (3H, d, J=7 Hz, C_{10}-Me), 1.16 (9H, s, *tert*-Bu), 1.72 (3H, s, C_6-Me), 3.35 and 3.39 (each 3H, s, OMe), 3.2—3.5 (1H, m, C_9-H), 3.98 (1H, d, J=7 Hz, C_8-H), 4.61 and 4.83 (each 1H, d, J=6 Hz, OCH_2O), 4.67 (2H, s, OCH_2O), 5.17 (1H, s, C_7-H), 4.9—5.3 (1H, m, C_2-H). MS *m/z* (%): 323 ($M^+ - 61$, 6), 159 (46), 57 (100). *Anal.* Calcd for $C_{21}H_{36}O_6$: C, 65.59; H, 9.44. Found: C, 65.55; H, 9.38.

(2*RS*,5*RS*,8*SR*,9*SR*,10*RS*)-8,9-Bis(methoxymethoxy)-6,10-dimethylspiro[4.5]dec-6-en-2-ol (11) An ethereal solution of MeLi (0.4 M, 2.9 ml) was added to a solution of the ester (**10**) (222 mg, 0.58 mmol) in dry ether (1 ml) at 0 °C under nitrogen, and the mixture was stirred for 5 min at the same temperature. The mixture was quenched with aqueous AcOH and extracted with ether, then the organic layer was washed with saturated $NaHCO_3$ solution, H_2O, and brine, dried, and then evaporated. The residue was chromatographed with benzene–ethyl acetate (2 : 1) to give **11** (165 mg, 95%) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620, 1668. ^{1}H-NMR (CCl_4) δ: 1.12 (3H, d, J=7 Hz, C_{10}-Me), 1.69 (3H, br s, C_6-Me), 2.60 (1H, br s, OH), 3.1—3.4 (1H, m, C_9-H), 3.31 and 3.35 (each 3H, s, OMe), 3.89 (1H, d, J=7 Hz, C_8-H), 4.18 (1H, m, C_2-H), 4.53 and 4.79 (each 1H, d, J=6 Hz, OCH_2O), 4.60 (2H, s, OCH_2O), 5.11 (1H, br s, C_7-H). MS *m/z* (%): 232 ($M^+ - 62$, 12), 198 (100). HRMS Calcd for $C_{14}H_{22}O_3$: 238.1569. Found: 238.1579.

Diethyl (2*RS*,5*SR*,8*RS*,9*RS*,10*SR*)-8,9-Bis(methoxymethoxy)-6,10-dimethylspiro[4.5]dec-6-en-2-ylmalonate (12) A mixture of the alcohol (**11**) (198 mg, 0.67 mmol), mesyl chloride (0.06 ml, 0.78 mmol), and pyridine (0.6 ml) was stirred for 12 h at 0 °C. The reaction mixture was diluted with saturated $NaHCO_3$ under ice-water cooling and extracted with ether. The extract was washed with saturated $NaHCO_3$ solution, saturated $CuSO_4$ solution, H_2O, and brine, and then dried. The solvent was evaporated off under reduced pressure to give the *O*-mesyl derivative of **11**. This material was used in the next step without further purification. A solution of the mesylate in dry DME (3 ml) was added to a DME solution of the enolate anion of diethyl malonate [prepared from NaH (132 mg, 3.3 mmol) and diethyl malonate (0.50 ml, 3.3 mmol) in dry DME (5 ml)] at 0 °C, and the mixture was refluxed for 7 h. Saturated NH_4Cl solution was added under cooling, and the resulting mixture was extracted with ethyl acetate. The extract was washed with H_2O and brine, and then dried. The solvent was removed under reduced pressure to afford an oily residue, which was purified by column chromatography with benzene–ethyl acetate (1 : 3) to give **12** (284 mg, 97%) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1758, 1740, 1660. ^{1}H-NMR (CCl_4) δ: 1.07 (3H, d, J=6 Hz, C_{10}-Me), 1.29 (6H, t, J=7 Hz, $COOCH_2\underline{CH_3} \times 2$), 1.72 (3H, s, C_6-Me), 3.05 (1H, d, J=10 Hz, $CH(COOEt)_2$), 3.32 and 3.34 (each 3H, s, OMe), 3.0—3.4 (1H, m, C_9-H), 3.91 (1H, d, J=6 Hz, C_8-H), 4.14 (4H, q, J=7 Hz, $COO\underline{CH_2}CH_3 \times 2$), 4.52 and 4.77 (each 1H, d, J=6 Hz, OCH_2O), 4.60 (2H, s, OCH_2O), 5.17 (1H, br s, C_7-H). MS *m/z* (%): 380 ($M^+ - 62$, 2), 180 (100). HRMS Calcd for $C_{21}H_{32}O_6$: 380.2199. Found: 380.2205.

(2*RS*,5*SR*,8*RS*,9*RS*,10*SR*)-2-(3-Hydroxypropen-2-yl)-8,9-bis(methoxymethoxy)-6,10-dimethylspiro[4.5]dec-6-ene (13) A suspension of **12** (158 mg, 0.36 mmol) and NaH (60% mineral oil, 21.6 mg, 0.54 mmol) in dry DME (3 ml) was stirred for 30 min at room temperature. A solution of Red-Al (70% toluene solution, 722 mg, 2.50 mmol) in dry DME (2 ml) was added and the resulting solution was refluxed for another 30-min period. The reaction mixture was diluted with 10% aqueous NaOH under ice-water cooling and extracted with ethyl acetate. The extract was washed with H_2O and brine, dried, and then evaporated. The residue was purified by preparative TLC with benzene–ethyl acetate (2 : 1) to afford the allylic alcohol (**13**) (89.7 mg, 74%) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620, 1650, 1110. ^{1}H-NMR (CCl_4) δ: 1.00 (3H, d, J=7 Hz, C_{10}-Me), 1.71 (3H, s, C_6-Me), 3.1—3.5 (1H, m, C_9-H), 3.30 (6H, s, OMe × 2), 3.98 (2H, br s, C=C–$C\underline{H_2}OH$), 3.7—4.0 (1H, m, C_8-H), 4.50 and 4.73 (each 1H, *d*, J=6 Hz, OCH_2O), 4.58 (2H, s, OCH_2O), 4.77 and 4.89 (each 1H, br s, C=CH), 5.11 (1H, br s, C_7-H). MS *m/z* (%): 278 ($M^+ - 62$, 12), 95 (59), 55 (100). HRMS Calcd for $C_{17}H_{26}O_3$: 278.1880. Found: 278.1880.

(2*RS*,5*SR*,8*RS*,9*RS*,10*SR*)-2-(2-Hydroxy-1-methylethyl)-8,9-bis(methoxymethoxy)-6,10-dimethylspiro[4.5]dec-6-ene (14) $NaBH_4$ (4.1 mg, 0.092 mmol) was added to a mixture of **13** (31.2 mg, 0.092 mmol), $CoCl_2 \cdot 6H_2O$ (10.9 mg, 0.046 mmol), and EtOH (0.4 ml) at 0 °C under nitrogen, and stirring was continued for 24 h at room temperature. The mixture was treated with water and extracted with ether. The organic phase was washed with 10% aqueous AcOH, H_2O, saturated $NaHCO_3$ solution, and brine. The dried extract was evaporated, and the residue was chromatographed with benzene–ethyl acetate (1 : 1) to give **14** (24.6 mg, 78%) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3630, 1655, 1110. ^{1}H-NMR (CCl_4) δ: 0.93 (6H, m, C_{10}-Me and CH-Me), 1.67 (3H, s, C_6-Me), 3.27 (6H, s, OMe × 2), 3.1—3.7 (3H, m, C_9-H and CH-$C\underline{H_2}OH$), 3.85 (1H, d, J=7 Hz, C_8-H), 4.48 and 4.70 (each 1H, d, J=6 Hz, OCH_2O), 4.56 (2H, s, OCH_2O), 5.07 (1H, br s, C_7-H). MS *m/z* (%): 280 ($M^+ - 62$, 14), 240 (100). *Anal.* Calcd for $C_{19}H_{34}O_5$: C, 66.63; H, 10.01. Found: C, 66.85; H, 9.67.

(2*RS*,5*SR*,8*RS*,9*RS*,10*SR*)-2-(2-Mesyloxy-1-methylethyl)-8,9-bis(methoxymethoxy)-6,10-dimethylspiro[4.5]dec-6-ene (15) A solution of the alcohol (**14**) (24.6 mg, 0.072 mmol) and mesyl chloride (0.007 ml, 0.09 mmol) in pyridine (0.3 ml) was stirred for 2 h at 0 °C. Saturated $NaHCO_3$ solution was added and the resulting mixture was extracted with ether. The ethereal phase was washed with saturated $NaHCO_3$ solution, saturated $CuSO_4$ solution, H_2O, and brine, dried, and then evaporated. The residue was purified by column chromatography with benzene–ethyl acetate (2 : 1) to give **15** as a colorless oil (24.0 mg, 79%). IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1655, 1370, 1350, 1180. ^{1}H-NMR (CCl_4) δ: 0.8—1.1 (6H, m, C_{10}-Me and CH-Me), 1.69 (3H, br s, C_6-Me), 2.85 (3H, s, SO_2Me), 3.28 (6H, s, OMe × 2), 3.0—3.4 (1H, m, C_9-H), 3.7—4.2 (3H, m, C_8-H and CH_2OMs), 4.48 and 4.70 (each 1H, d, J=6 Hz, OCH_2O), 4.56 (2H, s, OCH_2O), 5.09 (1H, br s, C_7-H). MS *m/z* (%): 358 ($M^+ - 62$, 10), 318 (100). *Anal.* Calcd for $C_{20}H_{36}O_7S$: C, 57.12; H, 8.63; S, 7.61. Found: C, 56.74; H, 8.63; S, 7.62.

(2*RS*,5*SR*,8*RS*,9*RS*,10*SR*)-6-Hydroxymethyl-2-(2-mesyloxy-1-methylethyl)-8,9-bis(methoxymethoxy)-10-methylspiro[4.5]dec-6-ene (16) A mixture of the mesylate (**15**) (36.3 mg, 0.086 mmol), SeO_2 (47.9 mg 0.43 mmol), $CaCO_3$ (8.6 mg, 0.086 mmol), and xylene (0.5 ml) was refluxed for 40 min with stirring. The cooled mixture was filtered to remove the inorganic substances, and the filtrate was concentrated. The residue was purified by preparative TLC with benzene–ethyl acetate (2 : 1) to afford the corresponding aldehyde (30.9 mg, 82%) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2705, 1690, 1625, 1360, 1340. UV λ_{max}^{EtOH} nm (ε) 233 (9300). ^{1}H-NMR (CCl_4) δ: 1.00 (6H, d, J=7 Hz, C_{10}-Me and CH-Me), 2.87 (3H, s, SO_2-Me), 3.0—3.4 (1H, m, C_9-H), 3.30 and 3.33 (each 3H, s, OMe), 3.9—4.1 (2H, m, CH_2OMs), 4.17 (1H, dd, J=2, 7 Hz, C_8-H), 4.51 and 4.73 (each 1H, d, J=6 Hz, OCH_2O), 4.67 (2H, s, OCH_2O), 6.28 (1H, d, J=2 Hz, C_7-H), 9.39 (1H, br s, CHO). MS *m/z* (%): 434 (M^+, 14), 163 (100). HRMS Calcd for $C_{20}H_{34}O_8S$: 434.1971. Found: 434.1958.

$NaBH_4$ (11.4 mg, 0.30 mmol) was added to a solution of the aldehyde (130.5 mg, 0.30 mmol) in MeOH (1 ml) at 0 °C. The mixture was stirred for 10 min at the same temperature. After removal of MeOH by evaporation, the residue was treated with water and extracted with ether. The ethereal phase was washed with H_2O and brine, dried, and then evaporated. The residue was purified by preparative TLC with benzene–ethyl acetate (2 : 1) to give **16** (115 mg, 88%) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 3450, 1370, 1350, 1185. ^{1}H-NMR (CCl_4) δ: 0.98 (6H, d, J=6 Hz, C_{10}-Me and CH-Me), 2.94 (3H, s, SO_2Me), 3.2—3.5 (1H, m, C_9-H), 3.36 (6H, s, OMe × 2), 3.8—4.4 (5H, m, C_6–$C\underline{H_2}OH$, C_8-H, and CH_2OMs), 4.62 and 4.82 (each 1H, d, J=6 Hz, OCH_2O), 4.69 (2H, s, OCH_2O), 5.53 (1H, br s, C_7-H). MS *m/z* (%): 418 ($M^+ - 18$, 0.2), 272 (100). HRMS Calcd for $C_{20}H_{36}O_8S$: 436.2132. Found: 436.2140.

(2*RS*,5*SR*,6*SR*,7*RS*,8*RS*,10*SR*)-10-Hydroxymethyl-2-(2-mesyloxy-1-methylethyl)-7,8-bis(methoxymethoxy)-6-methylspiro[4.5]decane (17) A solution of **16** (26.0 mg, 0.060 mmol) in EtOH (0.5 ml) was hydrogenated over Raney Ni (W2) at atmospheric pressure for 2 h at room temperature. The catalyst was filtered off and the filtrate was concentrated. The residue was purified by preparative TLC with ethyl alcetate to give **17** (23.6 mg, 90%) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3640, 1370, 1350, 1180, 1110. ^{1}H-NMR (CCl_4) δ: 0.9—1.1 (6H, m, C_6-Me and CH-Me), 2.50 (1H, s, OH), 2.89 (3H, s, SO_2Me), 3.1—3.4 (1H, m, C_7-H), 3.29 (6H, s, OMe × 2), 3.4—3.9 (3H, m, C_8-H and C_{10}–$C\underline{H_2}OH$), 3.9—4.2 (2H, m, CH_2OMs), 4.47 and 4.76 (each 1H, d, J=6 Hz, OCH_2O), 4.58 (2H, s, OCH_2O). MS *m/z* (%): 406 ($M^+ - 32$, 1), 107 (100). HRMS Calcd for $C_{19}H_{34}O_7S$: 406.2023. Found: 406.2012.

(2*RS*,5*SR*,6*SR*,8*RS*,9*RS*,10*SR*)-2-(2-Mesyloxy-1-methylethyl)-8,9-bis(methoxymethoxy)-10-methylspiro[4.5]decane-6-carbaldehyde (18) A mix-

ture of the alcohol (**17**) (22.0 mg, 0.050 mmol), NaOAc (1.2 mg, 0.015 mmol), PCC (16.2 mg, 0.075 mmol), and dry CH_2Cl_2 (0.5 ml) was stirred for 2 h at room temperature. The resulting mixture was diluted with ether and filtered through Florisil. The filtrate was concentrated and the residue was purified by preparative TLC with benzene–ethyl acetate (1 : 2) to give **18** (18.0 mg, 82%) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 2730, 1725, 1370, 1350, 1180, 1155, 1110. ^{1}H-NMR (CCl_4) δ: 0.98 (6H, d, J=6 Hz, C_{10}-Me and CH-Me), 2.88 (3H, s, SO_2Me), 2.7—3.0 (1H, m, C_9-H), 3.27 and 3.29 (each 3H, s, OMe), 3.42 (1H, m, C_8-H), 3.99 (2H, m, CH_2-OMs), 4.47 and 4.78 (each 1H, d, J=6 Hz, OCH_2O), 4.57 (2H, s, OCH_2O), 9.71 (1H, d, J=2.5 Hz, CHO). MS m/z (%): 435 (M^+-1, 0.2), 374 (1.6), 107 (100). HRMS Calcd for $C_{18}H_{30}O_6S$: 374.1760. Found: 374.1744.

(2*RS*,5*SR*,6*SR*,7*RS*,8*RS*,10*SR*)-10-Ethylenedithiomethyl-2-(2-mesyloxy-1-methylethyl)-6-methylspiro[4.5]decane-7,8-diol (20) Ethanedithiol (0.030 ml, 0.36 mmol) and $BF_3 \cdot Et_2O$ (1 drop) were added to a solution of the aldehyde (**18**) (31.6 mg, 0.072 mmol) in dry CH_2Cl_2 at 0 °C, and the mixture was stirred for 12 h at room temperature. After addition of 5% aqueous NaOH, the reaction mixture was extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated to afford an oily residue. The residue was chromatographed with benzene–ethyl acetate (1 : 2) to yield **20** (26.7 mg, 87%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 1360, 1335, 1180. ^{1}H-NMR ($CDCl_3$) δ: 0.9—1.1 (6H, m, C_6-Me and CH-Me), 2.96 (1H, t, J=11 Hz, C_7-H), 3.01 (3H, s, SO_2Me), 3.0—3.6 (5H, m, C_8-H and $SCH_2 \times 2$), 4.12 (2H, m, CH_2OMs), 4.92 (1H, s, C<u>H</u>$(SCH_2)_2$). MS m/z (%): 424 (M^+, 0.4), 105 (100). HRMS Calcd for $C_{18}H_{32}O_5S_3$: 424.1410. Found: 424.1387.

(2*RS*,5*SR*,6*SR*,7*RS*,8*RS*,10*SR*)-10-Ethylenedithiomethyl-2-isopropenyl-6-methylspiro[4.5]decane-7,8-diol (21) A mixture of NaI (12.5 mg, 0.083 mmol), the mesylate (**20**) (11.8 mg, 0.028 mmol), and dry DME (0.5 ml) was stirred for 10 min at room temperature. DBU (0.02 ml, 0.083 mmol) was added and the resulting mixture was refluxed for 3 h. The cooled reaction mixture was diluted with CH_2Cl_2 and the organic phase was washed with H_2O and brine, and then dried. Evaporation of the solvent left an oily residue, which was purified by preparative TLC with benzene–ethyl acetate (1 : 2) to give the unchanged starting material (1.5 mg) and **21** (6.0 mg, 66%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3575, 1645, 894. ^{1}H-NMR ($CDCl_3$) δ: 1.05 (3H, d, J=6.6 Hz, C_6-Me), 1.74 (3H, br s, C=C–Me), 2.8—3.7 (6H, m, C_7-H, C_8-H, and $SCH_2 \times 2$), 4.71 (2H, br s, $C=CH_2$), 4.99 (1H, s, C<u>H</u>$(SCH_2)_2$). MS m/z (%): 328 (M^+, 6), 105 (100). HRMS Calcd for $C_{17}H_{28}O_2S_2$: 328.1528. Found: 328.1525.

(±)-Oxylubimin (4) a) From **18**: A 3 N HCl solution (1 ml) was added to a solution of the aldehyde (**18**) (16.5 mg, 0.038 mmol) in THF (0.5 ml) at 0 °C, and the mixture was stirred for 6 h at room temperature. The resulting mixture was diluted with brine and extracted with ethyl acetate. The extract was washed with saturated $NaHCO_3$, H_2O, and brine, dried, and then evaporated. The residue was purified by preparative TLC with benzene–ethyl acetate (1 : 4) to afford a diol (9.0 mg, 68%) as a colorless oil. A mixture of the diol (9.0 mg, 0.026 mmol), DBU (0.012 ml, 0.080 mmol), and NaI (11.6 mg, 0.077 mmol) was treated in the same manner as described for **21** and the obtained crude product was purified by preparative TLC with ethyl acetate to give a mixture of (±)-oxylubimin (**4**) and (±)-10-epioxylubimin (**19**) (3.7 mg, 57%). ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, J=6.6 Hz, C_{10}-Me), 1.72 (3H, br s, C=C–Me), 3.04 (1H, m, C_9-H), 3.46 (1H, m, C_8-H), 4.69 (2H, s, $C=CH_2$), 9.80 (3/5H, d, J=2.6 Hz, –CHO), 9.87 (2/5H, s, –CHO).

b) From **21**: A suspension of 20 (14.0 mg, 0.043 mmol), $CaCO_3$ (8.5 mg, 0.085 mmol), and MeI (0.27 ml, 4.3 mmol) in 80% aqueous CH_3CN (1 ml) was refluxed. After being stirred for 1 h, additional MeI (0.2 ml, 3.2 mmol) was added, and reflux was continued. This operation was repeated twice more. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried, and then evaporated. The residue was purified by preparative TLC with benzene–ethyl acetate (1 : 2) to give the starting material (1.2 mg) and (±)-oxylubimin (**4**) (4.6 mg, 43%) as colorless needles. mp 78—80 °C (ether–hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3580, 3400, 2745, 1720, 1645, 895. ^{1}H-NMR ($CDCl_3$) δ: 1.07 (3H, d, J=6.6 Hz, C_{10}-Me), 1.71 (3H, s, C=C–Me), 3.04 (1H, t, J=9 Hz, C_9-H), 3.41 (1H, m, $W_{1/2}$=22 Hz, C_8-H), 4.70 (2H, s, $C=CH_2$), 9.83 (1H, d, J=2.9 Hz, CHO). MS m/z (%): 252 (M^+, 35), 234 (19), 216 (10), 136 (100). HRMS Calcd for $C_{15}H_{24}O_3$: 252.1725. Found: 252.1748. The IR and ^{1}H-NMR spectra of this product were identical with those of natural oxylubimin.

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References and Notes

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