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Synthetic Studies on Spirovetivane Phytoalexins. II. Stereoselective Synthesis of (2*RS*,5*RS*,6*SR*,8*RS*,10*SR*)-6-Hydroxymethyl-8-methoxymethoxy-10-methyl-2-pivaloyloxyspiro[4.5]decane

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(2*RS*,5*RS*,6*SR*,8*RS*,10*SR*)-6-Hydroxymethyl-8-methoxymethoxy-10-methyl-2-pivaloyloxyspiro[4.5]decane (**4a**), a key intermediate for the synthesis of the spirovetivane sesquiterpenes, *i.e.* (±)-lubiminol and (±)-oxylubimin, was synthesized. A stereoselective 1,2-reduction of the enone (**6**) followed by oxygenation of the C_6-methyl group afforded **10**. Subsequent hydrogenation of C_6–C_7 double bond in **10** gave **4a** exclusively.

Keywords——spiro[4.5]decane; spirovetivane sesquiterpene; phytoalexin; catalytic hydrogenation; hydride reduction; ^{13}C-NMR; γ-effect

Since solavetivone (**1**),[1] lubimin (**2**),[2] and oxylubimin (**3**)[2] were isolated as phytoalexins in 1974, many highly oxygenated spirovetivane sesquiterpenes have been reported.[3] Structurally, these compounds have the *trans* relationship between the C_1–C_5 and C_{10}-Me bonds in a spiro[4.5]decane system containing five or six asymmetric carbon centers. Biologically, these compounds are considered to be biosynthetic intermediates of rishitin, which exibits strong antifungal activity.[4] From the viewpoint of their biosynthetic interest and biological activity, it is very significant to synthesize highly oxygenated spirovetivane phytoalexins. In this paper we describe the stereoselective synthesis of (2*RS*, 5*RS*, 6*SR*, 8*RS*, 10*SR*)-6-hydroxymethyl-8-methoxymethoxy-10-methyl-2-pivaloyloxyspiro[4.5]decane (**4a**), which would serve as a key intermediate for the synthesis of the highly oxygenated phytoalexins, starting from the spiroenone (**5**) synthesized previously.[5]

The important points for the transformation of **5** into **4a** are as follows: i) the hydroxy group at C-8 must be *cis* to the C_{10}-methyl group; ii) oxidation of the C_6-methyl group has to be done prior to the reduction of the C_6–C_7 double bond; iii) stereoselective reduction of the C_6–C_7 double bond is required.

First of all, compound **5** was converted to the pivaloyl ester (**6**) followed by the reduction with sodium dihydrobis(2-methoxyethoxy)aluminate (Red-Al) in ether at −78 °C to afford a single diastereoisomeric alcohol (**7**) in 85% yield. The orientation of the newly formed hydroxy group is presumed to be equatorial, that is, *cis* to the C_{10}-methyl substituent.[6,7] The structural assignment of **7** was confirmed by its transformation into **4a** and **4b** later. The methoxymethyl (MOM) ether (**8**) obtained from **7** was oxidized with selenium dioxide to give the aldehyde (**9**) in 88% yield along with the corresponding alcohol (**10**). Hydrogenation of **9** on Raney Ni (W2) afforded the saturated alcohols (**4a** and **4b**) in 56 and 17% yields, respectively. On the other hand, the allylic alcohol (**10**), obtained by reduction of the aldehyde (**9**) with sodium borohydride, was hydrogenated on various catalysts, and the results are summarized in Table I. Compound **10** gave the desired alcohol (**4a**) exclusively under the conditions in entry 5 (H_2–PtO_2 in EtOH–AcOEt).

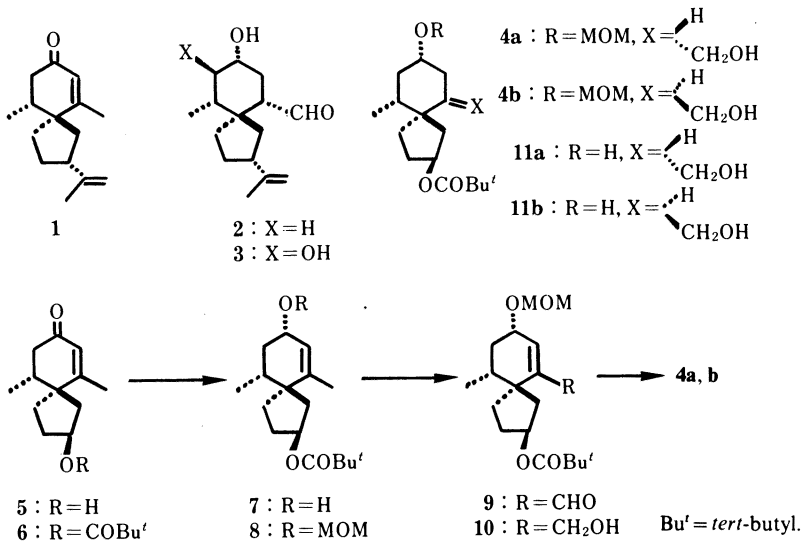

Chart 1

TABLE I. Hydrogenation of the C_6–C_7 Double Bond of **9** and **10** on Various Catalysts

Entry	Starting material	Conditions	Yield (%)	Ratio (**4a**/**4b**)
1	**9**	Raney Ni (W_2), EtOH	73	3.3 : 1
2	**10**	Raney Ni (W_2), EtOH	85	4.8 : 1
3	**10**	Pd/C, EtOH	0[a]	—
4	**10**	PtO_2, EtOH	80	**4a** only
5	**10**	PtO_2, AcOEt–EtOH	90	**4a** only

a) Only hydrogenolysis proceeded.

TABLE II. ^{13}C-NMR Data[a] for **11a** and **11b**

Compound	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	CH_2OH	C_{10}-Me
11a	39.6	76.0	33.6	23.2	46.4	49.1	35.8	69.8	41.1	41.4	64.0	16.8
11b	39.0	76.3	33.7	29.5	46.9	45.5	31.9	66.2	40.5	34.2	62.3	17.2

a) Data obtained for $CDCl_3$ solutions; shieldings in ppm from internal tetramethylsilane.

The stereochemistry of **4a** and **4b** was determined as follows. The half-band widths of C_8-H in **4a** and **4b** are 22 and 24 Hz, respectively, indicating that the protons at C_8 are oriented axially. On the other hand, **4a** and **4b** were hydrolyzed under acidic conditions to give **11a** and **11b**, respectively. Their carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectra revealed clearly the difference of configuration of the C_6-hydroxymethyl group. Significant upfield shifts are seen for the signals of C-8, C-10, and the hydroxymethyl carbon in **11b** due to the γ-effect, together with a downfield shift for that of C-4, all relative to the corresponding signals in **11a** (Table II), thereby establishing the orientation of the hydroxymethyl group of **11b** to be axial.[8]

Thus, we have synthesized the desired intermediate (**4a**) stereoselectively and also determined its stereochemistry by spectral comparison with its isomer **4b**.

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 JNM-GX400 (400 MHz) and ^{13}C-NMR spectra were taken on a Hitachi R-900 instrument 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 (High MS) were obtained with a JEOL JMS-D300 mass spectrometer. For column chromatography, Merck Kieselgel 60 (70—230 mesh) was used, and for preparative thin layer chromatography (PTLC), Merck Kieselgel 60 PF_{254} was used. High-performance liquid chromatography (HPLC) was carried out on a Waters instrument (μ-Porasil, semi prep. (3.9 mm × 30 cm) × 2). The extracts were dried over $MgSO_4$.

(2*RS*,5*RS*,10*SR*)-6,10-Dimethyl-2-pivaloyloxyspiro[4.5]dec-6-en-8-one (6)——Pivaloyl chloride (0.39 ml, 3.20 mmol) was added to a mixture of **5** (520 mg, 2.68 mmol) and pyridine (6 ml) at 0 °C, and the mixture was heated for 30 min at 50 °C. After cooling, the reaction mixture was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O. The extract was washed with saturated $NaHCO_3$ solution, water, saturated $CuSO_4$ solution, and brine, then dried, and evaporated. The residue was purified by column chromatography with benzene–AcOEt (1 : 1) to give **6** (688 mg, 92%) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1721, 1670, 1615. UV λ_{max}^{EtOH} nm (ε): 240 (11000). ^{1}H-NMR (CCl_4) δ: 1.02 (3H, d, J = 6 Hz, C_{10}-Me), 1.15 (9H, s, *tert*-Bu), 1.89 (3H, s, C_6-Me), 5.10 (1H, m, C_2-H), 5.59 (1H, s, C_7-H). MS *m*/*z* (%): 278 (M^+, 15), 176 (48), 134 (100). High MS *m*/*z*: 278.1889 (Calcd for $C_{17}H_{26}O_3$: 278.1882).

(2*RS*,5*RS*,8*RS*,10*SR*)-8-Hydroxy-6,10-dimethyl-2-pivaloyloxyspiro[4.5]dec-6-ene (7)——A solution of Red-Al (70% in toluene, 1.09 g, 3.77 mmol) in dry Et_2O (25 ml) was added dropwise to a mixture of **6** (670 mg, 2.41 mmol) and Et_2O (25 ml) at −78 °C and the resulting solution was stirred for 5 h at this temperature. After the addition of saturated potassium sodium tartrate, the mixture was extracted with Et_2O. The organic layer was washed with water and brine, then dried, and evaporated. The crude product was purified by column chromatography with benzene–AcOEt (1 : 1) to give **7** (571 mg, 85%) as a colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3600, 3420, 1720, 1655. ^{1}H-NMR (CCl_4) δ: 1.02 (3H, d, J = 6 Hz, C_{10}-Me), 1.15 (9H, s, *tert*-Bu), 1.73 (3H, s, C_6-Me), 4.14 (1H, m, C_8-H), 4.98 (1H, m, C_2-H), 5.22 (1H, s, C_7-H). MS *m*/*z* (%): 280 (M^+, 4.4), 178 (10), 121 (14), 94 (100). High MS *m*/*z*: 280.2018 (Calcd for $C_{17}H_{28}O_3$: 280.2036).

(2*RS*,5*RS*,8*RS*,10*SR*)-8-Methoxymethoxy-6,10-dimethyl-2-pivaloyloxyspiro[4.5]dec-6-ene (8)——*N*,*N*-Diethylaniline (0.060 ml, 0.39 mmol) and MOM-Cl (0.030 ml, 0.39 mmol) were added to a solution of **7** (73 mg, 0.26 mmol) in dry CH_2Cl_2 (2 ml) at 0 °C, and the resulting solution was stirred for 12 h at room temperature. The mixture was quenched with saturated $NaHCO_3$ solution and extracted with Et_2O. The ethereal phase was washed with saturated $NaHCO_3$ solution, water, and brine, then dried, and evaporated. The residue was purified by column chromatography with benzene–AcOEt (1 : 1) to give **8** (67 mg, 79%) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720, 1655, 1005. ^{1}H-NMR (CCl_4) δ: 1.02 (3H, d, J = 6 Hz, C_{10}-Me), 1.16 (9H, s, *tert*-Bu), 1.72 (3H, s, C_6-Me), 3.27 (3H, s, –OCH_2OMe), 3.95 (1H, m, C_8-H), 4.52 (2H, s, –OCH_2OMe), 4.98 (1H, m, C_2-H), 5.24 (1H, br s, C_7-H). MS *m*/*z* (%): 324 (M^+, 10), 222 (26), 177 (52), 161 (39), 128 (100). High-MS *m*/*z*: 324.2296 (Calcd for $C_{19}H_{32}O_4$: 324.2298).

(2*RS*,5*RS*,8*RS*,10*SR*)-8-Methoxymethoxy-10-methyl-2-pivaloyloxyspiro[4.5]dec-6-ene-6-carbaldehyde (9) and (2*RS*,5*RS*,8*RS*,10*SR*)-6-Hydroxymethyl-8-methoxymethoxy-10-methyl-2-pivaloyloxyspiro[4.5]dec-6-ene (10)——A) From **8**: SeO_2 (1.46 g, 13.1 mmol) and $CaCO_3$ (263 mg, 2.63 mmol) were added to a mixture of **10** (854 mg, 2.63 mmol) and dry xylene (15 ml), and the mixture was refluxed for 1 h. After cooling, the resulting mixture was filtered to remove inorganic substances, and the filtrate was evaporated. The crude product was purified by PTLC with benzene–AcOEt (2 : 1) to give **9** (781 mg, 88%) and **10** (47 mg, 5%).

B) From **9**: A solution of $NaBH_4$ (35 mg, 0.93 mmol) in MeOH (0.5 ml) was added to a mixture of **9** (314 mg, 0.93 mmol) and MeOH (4 ml) at 0 °C, and the resulting solution was stirred for 10 min at 0 °C. After removal of MeOH and addition of water, the mixture was extracted with AcOEt. The organic phase was washed with water and brine, then dried, and evaporated. The residue was purified by PTLC with benzene–AcOEt (2 : 1) to give **10** (261 mg, 83%) as a colorless oil. **9**: A colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1730, 1700, 1635. UV λ_{max}^{EtOH} nm (ε): 232 (11800). ^{1}H-NMR (CCl_4) δ: 1.06 (3H, d, J = 7 Hz, C_{10}-Me), 1.13 (9H, s, *tert*-Bu), 3.33 (3H, s, –OCH_2OMe), 4.27 (1H, m, C_8-H), 4.62 (2H, s, –OCH_2OMe), 5.41 (1H, m, C_2-H), 6.40 (1H, br s, C_7-H), 9.41 (1H, s, –CHO). MS *m*/*z* (%): 338 (M^+, 2.5), 192 (63), 174 (100). High MS *m*/*z*: 338.2085 (Calcd for $C_{19}H_{30}O_5$: 338.2090). **10**: A colorless oil. IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3620, 3450, 1720, 1658. ^{1}H-NMR (CCl_4) δ: 1.01 (3H, d, J = 7 Hz, C_{10}-Me), 1.13 (9H, s, *tert*-Bu), 3.28 (3H, s, –OCH_2OMe), 3.8—4.2 (3H, m, C_2-H and C_6-CH_2OH), 4.55 (2H, s, –OCH_2OMe), 5.00 (1H, m, C_2-H), 5.59 (1H, br s, C_7-H). MS *m*/*z* (%): 310 ($M^+ - CH_2O$, 4.3), 309 (21), 177 (36), 176 (100), 148 (42). High MS *m*/*z*: 310.2141 (Calcd for $C_{18}H_{30}O_4$ ($M^+ - CH_2O$): 310.2141).

(2*RS*,5*RS*,6*SR*,8*RS*,10*SR*) and (2*RS*,5*RS*,6*RS*,8*RS*,10*SR*)-6-Hydroxymethyl-8-methoxymethoxy-10-methyl-2-pivaloyloxyspiro[4.5]decane (4)——A) From **9**: Raney Ni (W2, 10 mg) was added to a solution of **9** (40 mg, 0.12 mmol) in EtOH (10 ml) and hydrogenation was carried at 1 atm pressure at room temperature. After the reaction completed, the reaction mixture was filtered, and the filtrate was evaporated to obtain the crude product, which was

purified by column chromatography with benzene–AcOEt (1 : 1) to give **4a** and **4b** (29 mg, 73%). **4a** and **4b** were separated by HPLC (AcOEt : hexane = 1 : 1).

B) General Procedure for Catalytic Hydrogenation of **10**: Hydrogenations were carried out at 1 atm pressure and room temperature using catalyst equivalent to 10% by weight of the substrates and the reaction mixtures were worked up as described above. **4a**: IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3630, 3475, 1720, 1110. ^{1}H-NMR (CCl_4) δ: 0.95 (3H, d, J = 6 Hz, C_{10}-Me), 1.16 (9H, s, *tert*-Bu), 3.27 (3H, s, $-OCH_2O\underline{Me}$), 3.2—3.8 (3H, m, C_8-H and C_6-C$\underline{H}_2$OH), 4.53 (2H, s, $-OC\underline{H}_2OMe$), 4.87 (1H, m, C_2-H). ^{13}C-NMR ($CDCl_3$) δ: 16.9 (q), 23.1 (t), 27.1 (q), 33.0 (t), 33.7 (t), 38.6 (s), 38.9 (t), 39.6 (d), 41.1 (t), 46.7 (s), 49.1 (d), 55.1 (q), 63.9 (t), 74.9 (d), 76.1 (d), 94.4 (t), 178.2 (s). MS *m/z* (%): 312 ($M^+ - CH_2O$, 7.9), 178 (33), 148 (100), 107 (25), 94 (25), 57 (52). High MS *m/z*: 312.2292 (Calcd for $C_{18}H_{32}O_4$ ($M^+ - CH_2O$): 312.2298). **4b**: IR $\nu_{max}^{CCl_4}$ cm^{-1}: 3630, 3475, 1725, 1110. ^{1}H-NMR (CCl_4) δ: 0.94 (3H, d, J = 6 Hz, C_{10}-Me), 1.14 (9H, s, *tert*-Bu), 3.27 (3H, s, $-OCH_2O\underline{Me}$), 3.3—3.8 (3H, m, C_8-H and C_6-C$\underline{H}_2$OH), 4.51 (2H, s, $-OC\underline{H}_2OMe$), 5.00 (1H, m, C_2-H). ^{13}C-NMR ($CDCl_3$) δ: 17.2 (q), 27.2 (q), 29.6 (t), 31.3 (t), 32.1 (t), 34.5 (d), 37.8 (t), 38.6 (s), 39.1 (t), 45.2 (d), 47.1 (s), 55.1 (q), 62.6 (t), 71.9 (d), 76.3 (d), 94.7 (t), 178.3 (s). MS *m/z* (%): 312 ($M^+ - CH_2O$, 3.2), 310 (7), 292 (12), 178 (49),148 (51), 107 (41), 94 (32), 57 (100). High MS *m/z*: 312.2295 (Calcd for $C_{18}H_{32}O_4$ ($M^+ - CH_2O$): 312.2298).

11a and **11b** were obtained from **4a** and **4b**, respectively, by treatment with 6 N HCl solution. **11a**: colorless crystals, mp 155.0—156.5 °C. IR ν_{max}^{KBr} cm^{-1}: 3340, 1725. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (3H, d, J = 6.8 Hz, C_{10}-Me), 1.17 (9H, s, *tert*-Bu), 1.71 (1H, dd, J = 5.9, 14.8 Hz, C_1-H), 2.03 (1H, dd, J = 7.3, 14.8 Hz, C_1-H), 3.39 (1H, dd, J = 6.6, 10.3 Hz, C_6-CH_2OH), 3.66 (1H, m, $W_{1/2}$ = 22 Hz, C_8-H), 3.79 (1H, dd, J = 3.0, 10.3 Hz, C_6-CH_2OH), 5.01 (1H, m, C_2-H). MS (CI) *m/z*: 299 ($M^+ + 1$, 18), 197 (100), 179 (65), 161 (29). *Anal.* Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.23; H, 10.04. **11b**: Colorless crystals, mp 127.5—129.0 °C. IR ν_{max}^{KBr} cm^{-1}: 3280, 1725. ^{1}H-NMR ($CDCl_3$) δ: 0.97 (3H, d, J = 7.0 Hz, C_{10}-Me), 1.17 (9H, s, *tert*-Bu), 3.61 (1H, dd, J = 8.6, 10.7 Hz, C_6-CH_2OH), 3.75 (1H, dd, J = 4.1, 10.7 Hz, C_6-CH_2OH), 3.86 (1H, m, $W_{1/2}$ = 24 Hz, C_8-H), 5.12 (1H, m, C_2-H). MS (CI) *m/z*: 299 ($M^+ + 1$, 18), 197 (95), 179 (100), 161 (48). *Anal.* Calcd for $C_{17}H_{30}O_4$: C, 68.42; H, 10.13. Found: C, 68.36; H, 10.15.

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