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A STEREOSELECTIVE TOTAL SYNTHESIS OF (±)-OXYLUBIMIN

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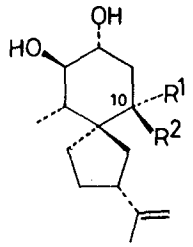
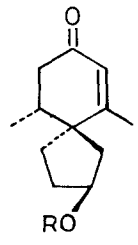
Summary: (±)-Oxylubimin (**1**), the highest oxidized spirovetivane-type phytoalexin, was totally synthesized with high stereoselectivity using a novel method for α'-hydroxylation of α,β-unsaturated ketones.

Oxylubimin (**1**), which was first isolated as a phytoalexin from tuber tissues of "white potatoes" (Solanum tuberlosum and S. demissum) infected by Phytophthora infestans,[1] is of great interest from viewpoint of the biogenetic intermediate for other phytoalexins, e.g. rishitin,[2] and the complex stereochemistry. Murai et al. have reported the first total synthesis of (±)-oxylubimin (**1**) and -10-epioxylubimin (**2**).[3] In this communication we describe an efficient total synthesis of (±)-**1** with high stereoselectivity starting from the known enone (**3**), a potential synthon for various spirovetivane sesquiterpenoids.[4]



1: R^1=CHO,R^2=H
2: R^1=H,R^2=CHO



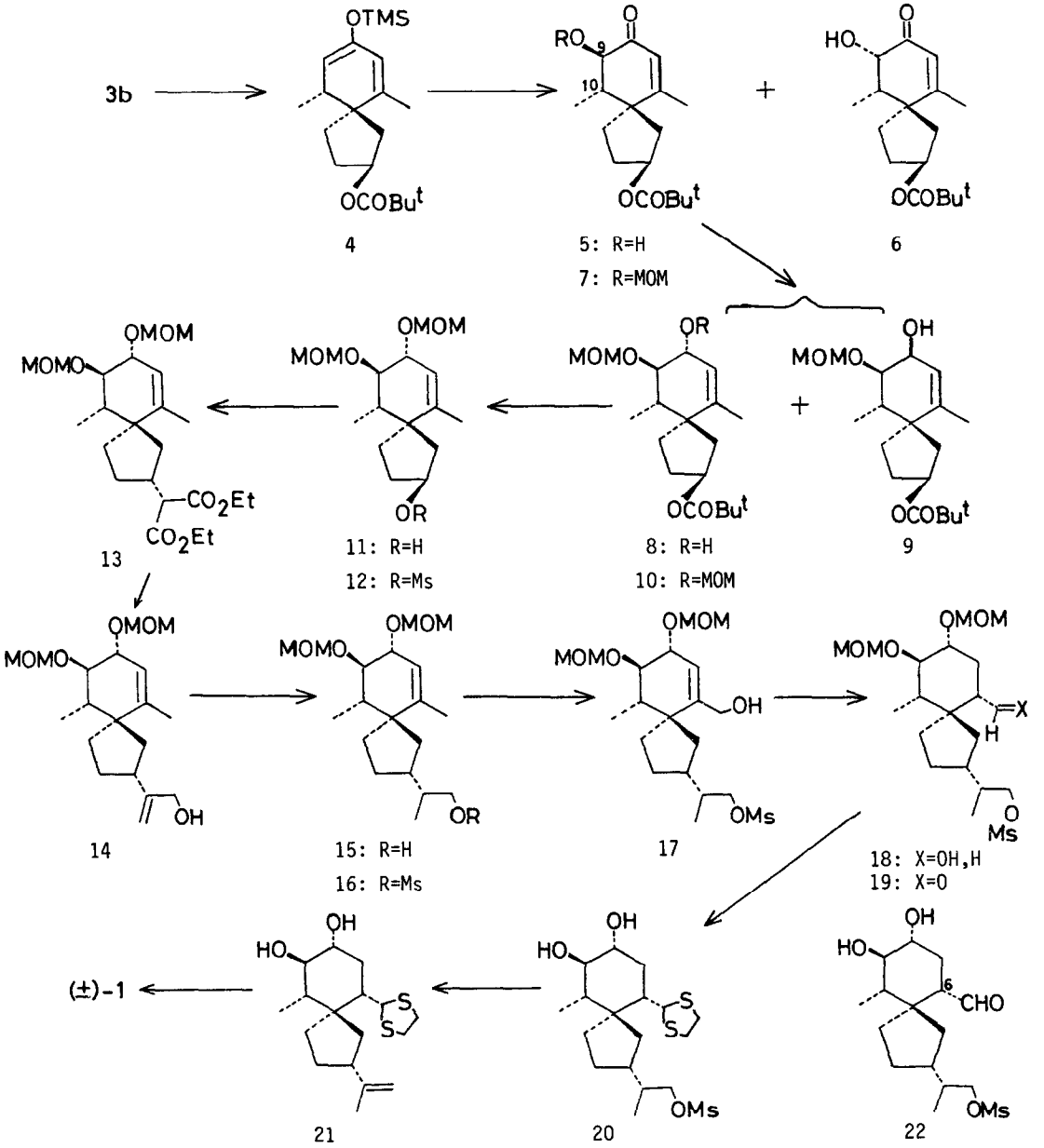
3a: R=H
b: R=COBu^t

One of crucial steps in the synthesis consists in a regio- and stereoselective α'-hydroxylation of the enone (**3**). In the preceding paper we have reported that TPPO oxidation of the silyl enol ethers of α,β-unsaturated ketones gave the regioselective α'-hydroxylated products with interesting stereoselectivity.[5] And the novel oxidation method has been found to be adequate for this purpose. Namely, the silyl enol ether (**4**), derived from the enone (**3b**)[4] in the usual way, was reacted with 1.5 equiv. of TPPO[6] in CH_2Cl_2 at -50°C and then treated with triphenyl phosphine to give a 8:1 mixture of diastereoisomer **5**[7] and **6**[7] in 71% yield from **3**.[8] On the other hand, the known oxidation methods [MCPBA,[9] MoOPH,[10] and $Mn(OAc)_3$[11]] were also examined for the oxidation but showed less stereoselectivity.[12]

The second difficulty to be solved, a reduction of the keto group in **5** to

the equatorial hydroxyl one, was overcome through a reduction of the MOM ether derivative (**7**) which was prepared from **5** in 84% yield.[13] Treatment of **7** with $NaBH_4$-$CeCl_3 \cdot 7H_2O$[14] in MeOH at 0°C provided the desired equatorial alcohol (**8**)[7] in 78% yield along with a small amount of the axial alcohol (**9**).

The hydroxyl group in **8** was protected as the MOM ether and the obtained **10** (91%) was reacted with 2 equiv. of methyllithium in ether to afford **11** in 95% yield. The mesylate (**12**), obtained from **11** by the usual procedure, was



subjected to a S_N2 reaction with sodium salt of diethyl malonate to give the malonate (**13**)[7] in 95% yield from **11**. Transformation of the malonyl group in **13** into the hydroxyisopropyl group was accomplished by the following stepwise procedure. Reduction of the sodium salt of **13** with Red-Al in DME gave the allylic alcohol (**14**) in 74% yield and then a regioselective reduction of the disubstituted olefinic double bond in **14** smoothly underwent on reaction with $NaBH_4$-$CoCl_3 \cdot 6H_2O$[15] yielding **15** in 78% yield. After **15** was derived into the corresponding mesylate (**16**), an allylic oxidation of **16** with selenium dioxide in boiling xylene was followed by treatment with $NaBH_4$ to give the allylic alcohol (**17**) in 70% yield. Catalytic hydrogenation of **17** over Raney Ni underwent highly stereoselectively to afford the saturated alcohol (**18**), which was subjected to PCC oxidation to provide the saturated aldehyde (**19**)[7] in 73% yield.

Thioacetalization of **19** under the usual condition [ethanedithiol, $BF_3 \cdot Et_2O$, CH_2Cl_2, r.t.] was accompanied with removal of the MOM protecting group to afford the glycol (**20**) in 87% yield. Treatment of **20** with DBU-NaI in boiling DME gave the olefin (**21**)[7] in 74% yield without any amount of other stereoisomers. Finally, dethioacetalization of **21** was successfully achieved by treatment with a large excess of methyl iodide in boiling aq. acetonitrile in the presence of $CaCO_3$[16] to furnish (±)-oxylubimin (**1**)[7] as a single stereoisomer.[17] The synthetic (±)-**1** was proved to be identical with the authentic sample by means of spectral comparisons.

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6. P.D. Bartlett and H.K. Chu, J. Org. Chem., **45**, 3000 (1980).
7. Physical and spectral data of representative compounds are given below. **5**: mp 97-98°C (from n-hexane); ν ($CHCl_3$) 3480, 1720, 1675, 1615; δ 1.15 (9H,

s), 1.28 (3H, d, J=7), 2.03 (3H, d, J=1), 3.72 (1H, d, J=12, C_9-H), 5.07 (1H, m), 5.69 (1H, d, J=1); m/z 294 (M^+), 134 (base); λ (EtOH) 238 nm (10,500). **6**: ν ($CHCl_3$) 3490, 1720, 1680, 1615; δ 0.78 (3H, d, J=7), 1.17 (9H, s), 1.89 (3H, d, J=1), 4.27 (1H, d, J=5, C_9-H), 5.16 (1H, m), 5.70 (1H, d, J=1); m/z 294 (M^+), 134 (base); λ (EtOH) 239 nm (10,800). **8**: ν 3460, 1730, 1670, 1110; δ 1.08 (3H, d, J=6), 1.18 (9H, s), 1.76 (3H, d, J=1), 2.96 (1H, dd, J=7, 11, C_9-H), 3.42 (3H, s), 3.85 (1H, br d, J=7, C_8-H), 4.60 (1H, d, J=7), 4.72 (1H, d, J=7), 5.08 (1H, br s, C_7-H); m/z 340 (M^+), 136 (base). **13**: ν 1758, 1740, 1660, 1100; δ 1.07 (3H, d, J=6), 1.29 (6H, t, J=7), 3.05 (1H, d, J=10), 3.32, 3.34 (each 3H, s), 3.0-3.4 (1H, m), 3.91 (1H, br d, J=6), 4.14 (4H, q, J=7), 4.52 (1H, d, J=6), 4.60 (2H, s), 4.77 (1H, d, J=6), 5.17 (1H, br s); m/z (CI) 380 (M^+-62). **19**: ν 2730, 1725, 1370, 1180, 1110; δ 0.98 (6H, br d, J=6), 2.88 (3H, s), 3.27, 3.29 (each 3H, s), 3.42 (1H, m), 3.99 (2H, m), 4.47 (1H, d, J=6), 4.57 (2H, s), 4.78 (1H, d, J=6), 9.71 (1H, d, J=2.5); m/z 435 (M^+-1), 107 (base). **21**: ν ($CHCl_3$) 3575, 1645, 895; δ ($CDCl_3$) 1.05 (3H, d, J=6.5), 1.74 (3H, s), 4.71 (2H, br s), 4.99 (1H, s); m/z 328 (M^+), 105 (base). (±)-**1**: mp 78-80°C (from n-hexane-ether); ν ($CHCl_3$) 3580, 3400, 3080, 2745, 1720, 1645, 895; δ ($CDCl_3$) 1.07 (3H, d, J=6.5), 1.71 (3H, s), 3.04 (1H, t, J=9), 3.41 (1H, ddd, J=6, 9, 11), 4.70 (2H, s), 9.83 (1H, d, J=3); m/z 252 (M^+), 234, 136 (base).

8. The desired isomer (**5**) was easily isolable by means of recrystallization. Stereochemistry of **5** and **6** was determined by their ^{1}H-NMR spectra: $J_{9,10}$ for **5** is larger (12 Hz) than that for **6** (5 Hz).
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12. Ratio of **5**/**6** was in the range of about 1/1 and 2/1.
13. Attempts to transform the hydroxy ketone (**5**) exclusively into the trans-glycol were unsuccessful, because a strong chelating ability of **5** would tend to increase the production of the cis-glycol.
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17. Although the yield of (±)**1** was low (47% yield), it was the only isolable product. An alternation route from **19** to (±)-**1** was also investigated. Without protection of the carbonyl group, initial treatment of **19** with an aqueous acid afforded the glycol (**22**) in an excellent yield. Conversion of **22** into (±)**1** by treatment with DBU, however, was found to be accompanied with isomerization at C-6, affording only a complex mixture.

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