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THE ABSOLUTE CONFIGURATION OF OUDEMANSIN
TOTAL SYNTHESIS OF (-)-OUDEMANSIN

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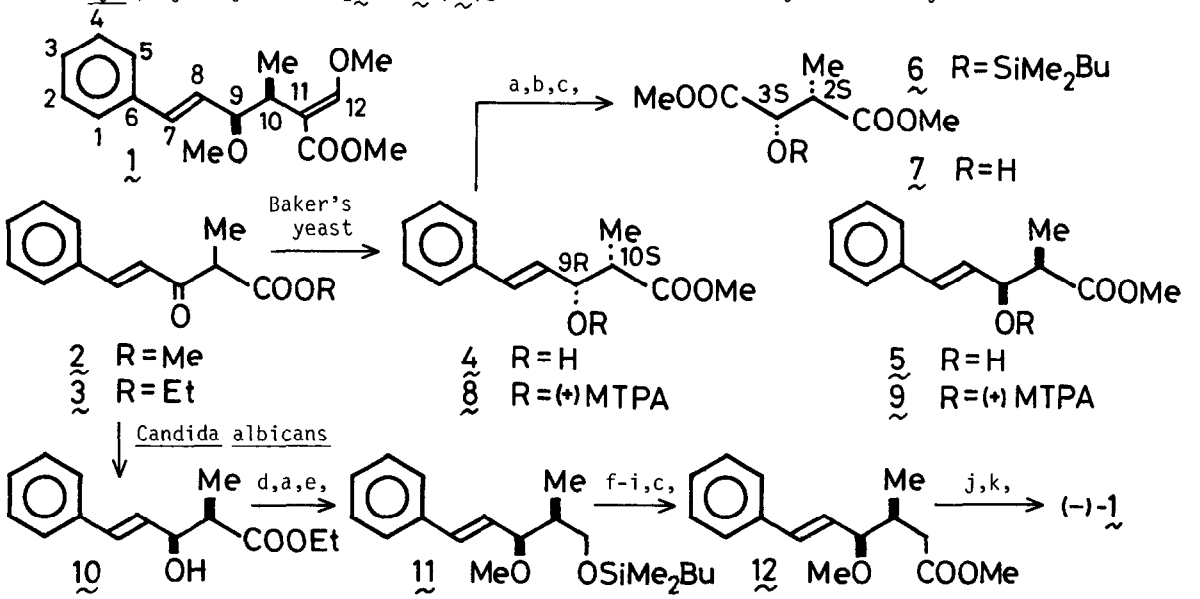
Summary: (-)-Oudemansin (1) was synthesized from the optically active intermediate 10 obtained by microbiological asymmetric reduction of β-keto ester 3. Oudemansin was found to have the 9S, 10S absolute configuration.

Oudemansin (1), an antibiotic isolated from mycelial cultures of Oudemansiella mucida, exhibits strong antifungal properties[3]. The structure and the relative configuration of 1 have been determined by X-ray analysis, but the absolute configuration of its two chiral centers is not known yet. The total synthesis of (±)-1 has already been achieved in this laboratory[4]. We now report that 1 was synthesized in optically active form and its absolute configuration was unequivocally determined as 9S, 10S.

The most intriguing point of the present synthesis is in the preparation of the optically active syn-β-hydroxy esters [4 or 5 (10)]. This was successfully achieved by the use of micro-



a) t-BuMe$_2$SiCl, imidazole, DMF; b) O_3-H_2O_2, CH_2Cl_2; c) CH_2N_2, Et_2O; d) $LiAlH_4$, Et_2O; e) MeI-KH, THF; f) AcOH-H_2O-THF; g) TsCl-Pyridine; h) NaCN, DMSO; i) KOH, EtOH; j) HOOMe, LDA, THF, -78°-0°C; k) CH_2N_2, MeOH;

biological asymmetric reduction of the corresponding α-methyl-β-keto esters (2, 3). This type of microbiological reduction has been extensively studied by us in the related systems[5].

Reduction of the β-keto methyl ester 2[4] with baker's yeast (Saccharomyces cerevisiae) gave the β-hydroxy methyl ester, although the yield was poor (7%). The structure of the reduction product was assigned as 4 (9R, 10S) from the fact the silyl diester 6 ($[\alpha]_D^{23}$-23.67°) derived from it in three steps (a, b, c) was identical with the authentic sample 6 prepared from the known 2S, 3S alcohol 7[6]. The reduction product 4 was then converted into the (+)-α-methoxy-α-trifluoromethyl-phenylacetate 8 ((+)-MTPA-8), which was contaminated with a small amount of (+)-MTPA-9. The NMR(400 MHz) signals due to ester methyl of this mixture were compared with those of the authentic samples (8 and 9, δ 3.666 and 3.609, respectively) prepared from 2 [1) $Zn(BH_4)_2$[4]; 2) (+)MTPACl]. Taking into account of the small peak due to the isomer 9, the optical purity of 8 derived from the reduction product 4 was calculated as 95% ee.

Then, the reduction of the β-keto ethyl ester 3 using various yeasts was examined. Among them, Candida albicans was found to afford the syn-β-hydroxy ethyl ester 10 (35% yield, $[\alpha]_D^{22}$ -11.52°, IR(CCl_4): 3525 cm^{-1}, NMR($CDCl_3$): δ 1.229 (d; C_{10}-Me), 4.570 (dd; C_9-H)) in much better yield than the previous case along with 10% of the corresponding anti-ester and 32% of starting material 3. These are readily separable by simple chromatography. The structure of the main product was assigned as 10 (9S, 10R) and its optical purity (97% ee) was determined in the same way as described in the case of 4. The remarkable feature of the present reduction is that the absolute configuration of 10 derived from the ethyl ester 3 is just opposite to that of 4 derived from methyl ester 2, which shows that the stereochemistry of the reduction is strictly governed by the structure of the substrates and the species of yeasts.

The 9S, 10R β-hydroxy ester 10 thus obtained was converted to the β-methoxy silyl ether 11 ($[\alpha]_D^{23.5}$+5.18°, 68% overall yield from 10) in three steps (d, a, e). Conversion of 11 into the methoxy ester 12 [IR(CCl_4): 1735 cm^{-1}, NMR($CDCl_3$): δ 3.308 (s; OMe), 3.631 (s; COOMe)] was achieved by the standard procedure (five steps, f-i, c) in overall 34% yield. Formylation of 12 with LDA and methyl formate in THF at -78° to 0°C, followed by treatment with CH_2N_2-MeOH produced the optically active oudemansin (1) (26% yield, $[\alpha]_D^{24}$-15.27° (C=1.67, EtOH), mp 40-44°C, NMR ($CDCl_3$) δ 1.265 (d; J=6.8 Hz; Me), 3.319 (s; OMe), 3.636 (s; COOMe), 3.768 (s; OMe), 7.181 (s; C_{12}-H)) after purification by HPLC. The spectral data ($[\alpha]_D$, mp and NMR) of the synthetic (-)-1 were identical with those of natural oudemansin (1)[3]. The 9S, 10S absolute configuration of natural oudemansin (1) was thus established.

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References and Notes

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