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A Formal Total Synthesis of (−)-Oudemansin B

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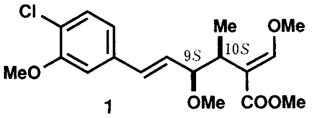
(−)-Oudemansin B (1) was formally synthesized from the (2*S*,3*R*)-3-hydroxy lactone 5 obtained by microbial asymmetric reduction as a key step.

Keywords total synthesis; (−)-oudemansin B; antibiotic; microbial reduction; Wittig reaction; hydroxy γ-lactone

Oudemansin B (**1**) is an antibiotic isolated from mycelial cultures of *Xerula melanotricha* and inhibits the growth of a wide variety of saprophytic and phytopathogenic fungi at very low concentration.[2)] The structure was elucidated by spectroscopic methods and the absolute configuration of its two chiral centers was reported by us[3)] to be 9*S*, 10*S*. The most intriguing point in the synthesis of optically active **1** is how to obtain the optically active *syn*-2-methyl-3-hydroxy moiety **A**. We reported previously that the reduction of the commercially available diethyl 2-methyl-3-oxosuccinate **2** with *Candida albicans* yielded a mixture of the corresponding 2,3-*syn*-(**3**)- and *anti*-(**4**)-2-methylmalates in 90% total yield.[4)] The enantioselectivity of the present reduction was remarkably high: in particular, *syn*-**3** was obtained in more than 99% ee, and thus this mixture was converted into the hydroxy γ-lactones (**5**—**8**) which were separated into each lactone by silica gel column chromatography.[4)] Among them, the lctones **5** and **6** are expected to be versatile building blocks for the synthesis of natural products having the *syn*-2-methyl-3-hydroxy moiety **A** in their molecules.

We now report the formal total synthesis of (−)-oudemasin B (**1**) from the (2*S*,3*R*)-3-hydroxy γ-lactone **5**. The lactone **5** was treated with MeI in the presence of Ag_2O to give a methoxy compound **9** in 58% yield.[5)] Diisobutylaluminum hydride (DIBAL-H) reduction of **9** provided a lactol **10** (IR (CCl_4) 3400, 3600 cm^{-1}) in 72% yield and this product, without further purification, was subjected to the Wittig reaction with the phosphonium salt **11** in the presence of *n*-BuLi to afford a mixture of *Z*-**12** (NMR δ 6.73, d, $J_{4,5}=12$ Hz, 5-H, δ 5.70, dd, $J_{3,4}=10$ Hz, $J_{4,5}=12$ Hz, 4-H) and *E*-**13** (NMR δ 6.53, d, $J_{4,5}=16$ Hz, 5-H, δ 6.15, dd, $J_{3,4}=8$ Hz, $J_{4,5}=16$ Hz, 4-H) in 6% and 20% yields,[6)] respectively, both of which were separated into pure forms by column chromatography. Conversion of the present *E*-isomer **13** into the one-carbon homologa-



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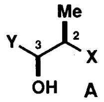


A

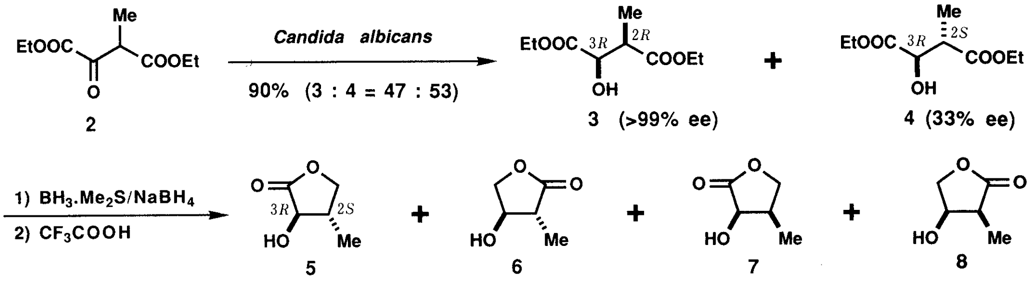
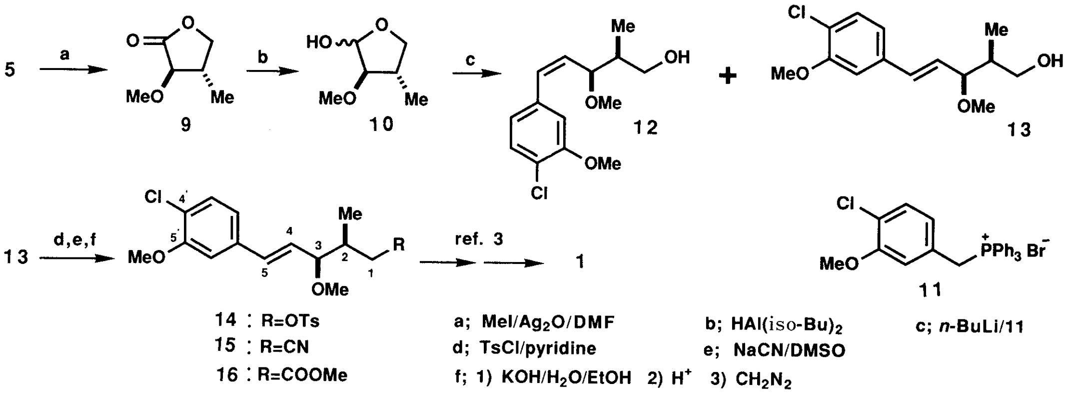


Chart 1



14 : R=OTs
15 : R=CN
16 : R=COOMe

a; MeI/Ag_2O/DMF b; HAl(iso-Bu)$_2$ c; *n*-BuLi/11
d; TsCl/pyridine e; NaCN/DMSO
f; 1) KOH/H_2O/EtOH 2) H^+ 3) CH_2N_2

Chart 2

tion product **16** ($[\alpha]_D$ +10.17° ($c=7.2$, $CHCl_3$), NMR ($CDCl_3$) δ 1.00, d, $J=7$ Hz, 2-Me, δ 3.32, s, 3-OMe, δ 3.64, s, COOMe, δ 3.93, s, 5′-OMe) was achieved by the standard procedure (tosylation, **14** (52%); CN substitution, **15** (89%); hydrolysis and methylation, **16** (79%)). The present methyl ester **16** was identical in terms of IR, NMR and $[\alpha]_D$ with the previously reported authentic sample **16** ($[\alpha]_D$ +10.23° ($c=3.1$, $CHCl_3$)). The optically active *trans* isomer **16** thus obtained has already been converted to (−)-oudemansin B (**1**) by us.[3]

Experimental

IR spectra (CCl_4) were measured on a JASCO A-3 spectrophotometer. NMR spectra were measured on a JEOL GX-400 instrument. Spectra were taken with 5—10% (W/V) solutions in $CDCl_3$ with Me_4Si as an internal reference. High-resolution mass spectra (HRMS) were obtained with a JEOL JMS-D 300 spectrometer. Optical rotations were measured on a Perkin-Elmer model 241 MC polarimeter. All the reactions were carried out in an atmosphere of argon. For column chromatography, silica gel (Wakogel C-200) was employed. All organic solvent extracts were washed with saturated brine and dried over anhydrous magnesium sulfate ($MgSO_4$). All evaporations were performed under reduced pressure.

(2*S*,3*R*)-2-Methyl-3-methoxy-1-butanolide (9)[7] A mixture of **5** (1.16 g), MeI (2.84 g) and Ag_2O (4.62 g) in *N*,*N*-dimethylformamide (DMF) (5 ml) was stirred for 5 h at room temperature. The resulting precipitate was filtered off with the aid of Celite and the filtrate was diluted with H_2O and extracted with AcOEt. Evaporation of the organic solvent gave an oily product which was chromatographed on silica gel (60 g) to afford a homogeneous oil **9** (749 mg, 58% yield) and C_3-epimerized methoxy lactone (68 mg, 5% yield) from the 20% AcOEt in *n*-hexane eluate. **9**: MS *m/z*: 130 (M^+). $[\alpha]_D^{21}$ +124.7° ($c=4.6$, $CHCl_3$). IR: 1785 cm^{-1}. NMR δ: 1.22 (3H, d, $J=7$ Hz, 2-Me), 3.65 (3H, s, 3-OMe), 3.63 (1H, d, $J_{2,3}=10$ Hz, 3-H). C_3-Epimerized methoxy lactone: MS *m/z*: 130 (M^+). IR: 1785 cm^{-1}. NMR δ: 1.09 (3H, d, $J=7$ Hz, 2-Me), 3.56 (3H, s, 3-OMe).

5-(4′-Chloro-5′-methoxyphenyl)-(2*S*)-methyl-(3*R*)-methoxy-(4*Z*)-penten-1-ol (12) and 5-(4′-Chloro-5′-methoxyphenyl)-(2*S*)-methyl-(3*R*)-methoxy-(4*E*)-penten-1-ol (13) A solution of **9** (501 mg) and 1 M DIBAL-H/*n*-hexane solution (4.7 ml) in anhydrous toluene (5 ml) was stirred under dry ice acetone cooling for 20 min. Water was added to the reaction mixture and the resulting precipitates were filtered off with the aid of Celite. The filtrate was extracted with AcOEt.

Evaporation of the organic solvent gave an oil **10** (364 mg, 72% yield). **10**: IR: 3400, 3600 cm^{-1}. A 1.36 M *n*-BuLi/*n*-hexane solution (6.1 ml) was added to a solution of the phosphonium salt **11** (2.06 g) in dry tetrahydrofuran (THF) (30 ml) at 0 °C with stirring for 30 min. A solution of **10** (364 mg) in dry THF (3 ml) was added to the above reaction mixture at 0 °C. The whole was stirred for 15 min at 0 °C and for 12 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was concentrated to give an oily product, which was chromatographed on silica gel (50 g) to yield a colorless oil **12** (46 mg, 6% yield) from the 10% AcOEt in *n*-hexane eluate and a homogeneous oil **13** (145 mg, 20% yield) from the 20% AcOEt in *n*-hexane eluate. **12**: *Anal.* HRMS Calcd for $C_{14}H_{19}O_3Cl$ (M^+) *m/z*: 270.1023. Found: 270.1031. $[\alpha]_D^{22}$ +51.23° ($c=1.3$, $CHCl_3$). IR: 3640, 3500 cm^{-1}. NMR δ: 0.98 (3H, d, $J=7$ Hz, 2-Me), 3.20 (3H, s, 3-OMe), 3.91 (3H, s, 5′-OMe), 4.33 (1H, dd, $J_{3,4}=10$ Hz, $J_{2,3}=4$ Hz, 3-H), 5.70 (1H, dd, $J_{3,4}=10$ Hz, $J_{4,5}=12$ Hz, 4-H), 6.73 (1H, d, $J_{4,5}=12$ Hz, 5-H). **13**: *Anal.* HRMS Calcd for $C_{14}H_{19}O_3Cl$ (M^+) *m/z*: 270.1023. Found: 270.1028. $[\alpha]_D^{22}$ +27.54° ($c=2.4$, $CHCl_3$). IR: 3600, 3500 cm^{-1}. NMR δ: 0.93 (3H, d, $J=7$ Hz, 2-Me), 3.34 (3H, s, 3-OMe), 3.88 (1H, dd, $J_{2,3}=4$ Hz, $J_{3,4}=8$ Hz, 3-H), 3.94 (3H, s, 5′-OMe), 6.15 (1H, dd, $J_{3,4}=8$ Hz, $J_{4,5}=16$ Hz, 4-H), 6.53 (1H, d, $J_{4,5}=16$ Hz, 5-H).

5-(4′-Chloro-5′-methoxyphenyl)-(2*S*)-methyl-(3*R*)-methoxy-1-tosyloxy-(4*E*)-pentene (14) A mixture of **13** (172 mg), TsCl (182 mg) in pyridine (1 ml) was stirred for 20 h at room temperature. The reaction mixture was diluted with H_2O and extracted with ether. Evaporation of the ether afforded an oily residue, which was chromatographed on silica gel (25 g) to provide a homogeneous oil **14** (140 mg, 52% yield) from the 10% AcOEt in *n*-hexane eluate. **14**: IR: 1370, 1180 cm^{-1}. NMR δ: 0.95 (3H, d, $J=7$ Hz, 2-Me), 2.42 (3H, s, aromatic Me), 3.23 (3H, s, 3-OMe), 3.92 (3H, s, 5′-OMe), 5.95 (1H, dd, $J_{3,4}=7$ Hz, $J_{4,5}=16$ Hz, 4-H), 6.49 (1H, d, $J_{4,5}=16$ Hz, 5-H).

5-(4′-Chloro-5′-methoxyphenyl)-(2*S*)-methyl-(3*R*)-methoxy-1-cyano-(4*E*)-pentene (15) A solution of **14** (149 mg), NaCN (52 mg) in dimethyl sulfoxide (DMSO) (2 ml) was heated at 90—95 °C for 3 h with stirring. The reaction mixture was diluted with H_2O and extracted with ether. The ether layer was evaporated to give an oily product, which was chromatographed on silica gel (25 g) to afford a homogeneous oil (82 mg, 89% yield) from the 10% AcOEt in *n*-hexane eluate. **15**: IR: 2250 cm^{-1}. NMR δ: 1.13 (3H, d, $J=7$ Hz, 2-Me), 3.34 (3H, s, 3-OMe), 3.93 (3H, s, 5′-OMe), 5.99 (1H, dd, $J_{3,4}=7$ Hz, $J_{4,5}=16$ Hz, 4-H), 6.60 (1H, d, $J_{4,5}=16$ Hz, 5-H).

5-(4′-Chloro-5′-methoxyphenyl)-(2*S*)-methyl-(3*R*)-methoxy-1-methoxycarbonyl-(4*E*)-pentene (16) A solution of **15** (82 mg), aqueous KOH (KOH (1 g)/H_2O (4 ml)) in EtOH (2 ml) was refluxed for 16 h with stirring. The reaction mixture was diluted with H_2O and extracted with ether. The water layer was acidified with 10% aqueous HCl and then re-extracted with $CHCl_3$. Evaporation of the $CHCl_3$ provided an oily residue, which was treated with CH_2N_2/ether solution. Evaporation of the solvent gave an oily product, which was chromatographed on silica gel (25 g) to yield a homogeneous oil **16** (72 mg, 79% overall yield) from the 10% AcOEt in *n*-hexane eluate. **16**: *Anal.* HRMS Calcd for $C_{16}H_{21}O_4Cl$ (M^+) *m/z*: 312.1126. Found: 312.1111. $[\alpha]_D^{22}$ +10.17° ($c=7.2$, $CHCl_3$). IR: 1735 cm^{-1}. NMR δ: 1.00 (3H, d, $J=7$ Hz, 2-Me), 3.32 (3H, s, 3-OMe), 3.59 (1H, dd, $J_{2,3}=5$ Hz, $J_{3,4}=8$ Hz, 3-H), 3.64 (3H, s, COOMe), 3.93 (3H, s, 5′-OMe), 6.04 (1H, dd, $J_{3,4}=8$ Hz, $J_{4,5}=16$ Hz, 4-H), 6.50 (1H, d, $J_{4,5}=16$ Hz, 5-H).

References and Notes

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2) T. Anke, H. Besl, U. Mocek and W. Steglich, *J. Antibiotics*, **36**, 661 (1983).
3) H. Akita, H. Matsukura and T. Oishi, *Tetrahedron Lett.*, **27**, 5397 (1986).
4) H. Akita, H. Matsukura and T. Oishi, *Chem. Pharm. Bull.*, **34**, 2656 (1986).
5) In this process, the C_3-epimerized methoxy γ-lactone was obtained in 5% yield.
6) Reaction conditions were not optimized.
7) According to the IUPAC rule, nomenclature of **9** is (2*R*,3*S*)-3-methyl-2-methoxy-4-butanolide, but the carbon numbering of **9** is compatible with that of the final compound **16** in the present case.