

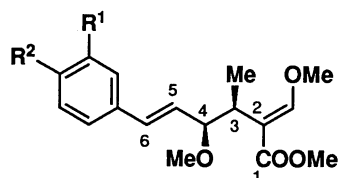
Total Synthesis of Antibiotic (-)-Oudemansin X Utilizing L-Quebrachitol as a Chiral Pool

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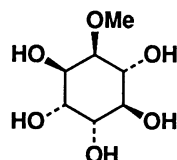
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The stereoselective conversion of naturally occurring optically active cyclitol, L-quebrachitol (**2**), into antifungal (*E*)- β -methoxyacrylate, oudemansin X is described. This synthesis fully confirmed the proposed absolute configuration of the antibiotic and revealed the usefulness of **2** as a versatile chiral pool.

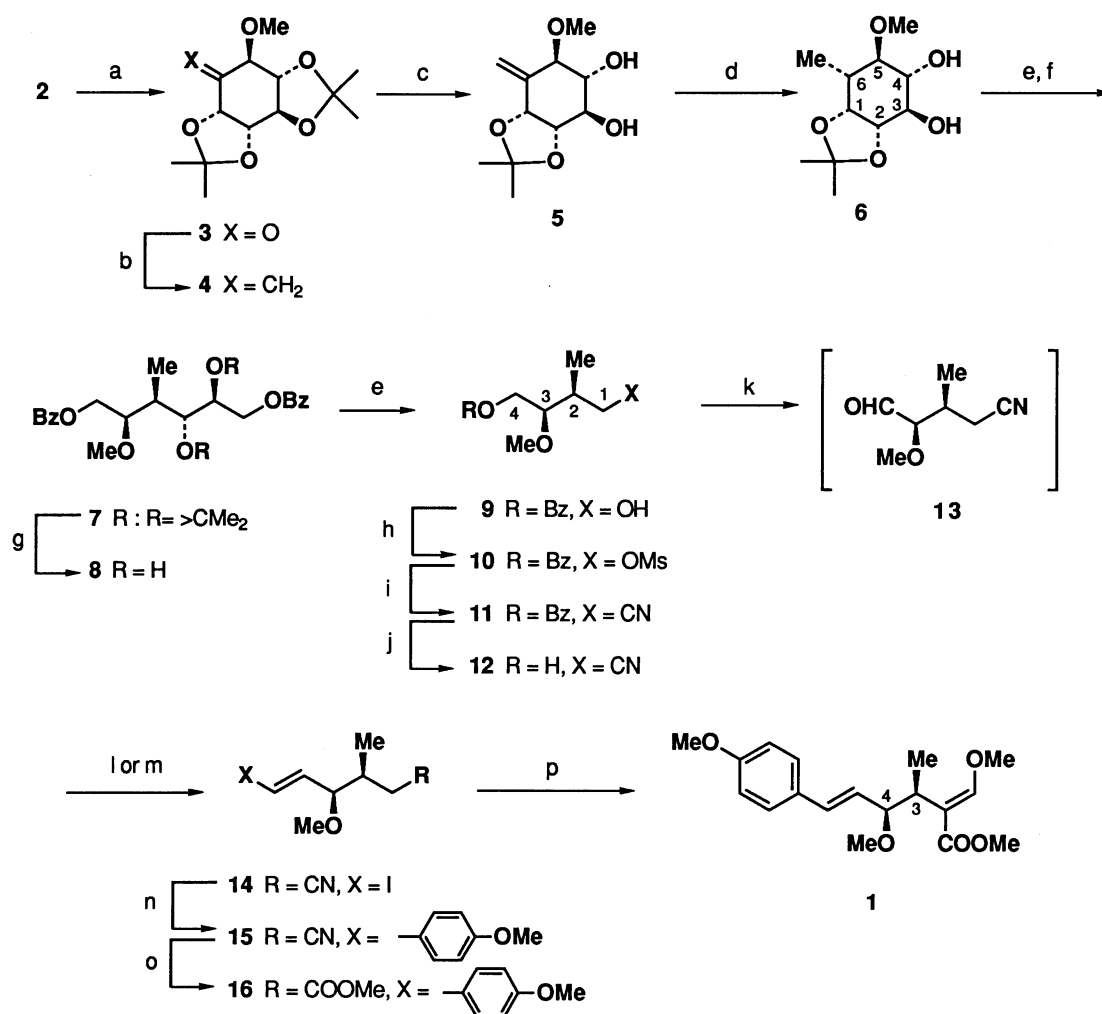
Oudemansin X (**1**) is an antibiotic recently isolated by Steglich and his co-workers from mycelial culture of *Oudemansiella radicata* and is reported to show high antifungal activities.¹⁾ The structure of **1** including the absolute configuration (3*S*,4*S*) has been deduced¹⁾ from a comparison of its ¹H NMR, CD, and mass spectra with those of the known structurally relating antibiotics, oudemansins A²⁾ and B.³⁾ Oudemansins are reported to possess the high antifungal activity, which is caused by a strong inhibition of eukaryotic respiration, and inhibitory activity for the incorporation of thymidine, uridine, and leucine into DNA, RNA, and protein of Ehrlich ascitic carcinoma cells.¹⁻³⁾ These novel biological activities as well as intriguing structures of oudemansins which include two chiral centers, (*E*)-styryl- and β -methoxyacrylate functions have stimulated the synthetic efforts, and several reports on syntheses of oudemansin A and B in racemic form⁴⁾ and in optically active form⁵⁾ have appeared, however, total synthesis of **1** has not been achieved so far. In this communication, as a part of our continuous study to explore the usefulness of L-quebrachitol (**2**), an optically active cyclitol readily obtained from the serum of the rubber tree,⁶⁾ as a chiral starting material for the natural product synthesis,^{7,8)} we wish to report the stereoselective first total synthesis of **1** starting from **2**, which fully confirmed the proposed absolute stereochemistry of the natural product.



R¹ = H, R² = OMe; oudemansin X (**1**)
 R¹ = R² = H; oudemansin A
 R¹ = OMe, R² = Cl; oudemansin B

L-quebrachitol (**2**)

The Peterson alkenation,⁹⁾ using trimethylsilylmethylmagnesium chloride followed by KH treatment, of the known ketone (**3**),^{7b)} prepared from **2** in 2 steps and in 83% yield, afforded the *exo*-methylene derivative (**4**) in 57% yield. Mild acid treatment of **4** cleaved the *trans*-*O*-isopropylidene group selectively and gave **5** in 80% yield. Hydrogenation of **5** in the presence of Raney-Ni proceeded highly stereoselectively to provide the single



Bz = -COPh, Ms = -SO₂Me. Reagents and conditions: a, see Ref. 7b; b, Me₃SiCH₂MgCl, THF, rt, then KH, THF, rt; c, *p*-TsOH (1 mol%), MeOH, 0 °C; d) H₂, Raney-Ni, EtOH; e) NaIO₄, NaHCO₃, acetone-H₂O, 0 °C, then NaBH₄, MeOH, 0 °C; f) BzCl, pyridine, 0 °C; g) 80% AcOH, 70 °C; h) MsCl, pyridine; i) NaCN, DMF, 50 °C, 6 h; j) NaOMe, MeOH; k) PCC, CH₂Cl₂; l) (**13**→**14**) CHI₃, CrCl₂, DMF-THF, rt; m) (**13**→**15**) Ph₃P⁺CH₂C₆H₄(*p*-OMe)Cl⁻, *n*-BuLi, THF, 0 °C, then PhSH, AIBN, benzene, reflux; n) (*p*-OMe)C₆H₄MgBr, Pd(PPh₃)₄ (5 mol%), benzene, rt; o) i) DIBAL, CH₂Cl₂, 0 °C, 2 h, then acidic (aq H₂SO₄) work up, ii) NaClO₂, NH₂SO₃H, NaH₂PO₄, *t*-BuOH-H₂O, rt, iii) CH₂N₂, ether-CH₂Cl₂; p) i) (Me₃Si)₂NLi, THF, -78 - -40 °C, 1 h, then HCOOMe, -78 - 0 °C, ii) (MeO)₂SO₂, K₂CO₃, acetone, rt.

product, 1L-(1,2,4,6/3,5)-6-methyl-1,2,3,4,5-cyclohexanepentol derivative (**6**, mp 131-133 °C), in 76% yield. The observed coupling constants of compound **6** in its ¹H NMR spectrum (*J*_{1,6} = 3.9, *J*_{5,6} = 10.7, and *J*_{4,5} = 9.3 Hz) strongly suggested that the methyl group at C-6 and the methoxy group at C-5 took an equatorial orientation, supporting the assigned structure of **6**. Periodate oxidation of **6**, followed by reduction of the resulting aldehyde functions with NaBH₄, gave a diol, which was isolated after *O*-benzoylation to afford **7** in 76% yield. Removal of the remaining *O*-isopropylidene group (80% acetic acid) gave **8** (95% yield). Glycol cleavage of **8** with sodium periodate, followed by NaBH₄ treatment, provided the mono-benzoate (**9**), which would be a suitable four-carbon unit for the synthesis of **1**, possessing two defined (2*S*-methyl and 3*R*-methoxy) stereocenters as well as distinguished two primary alcohol functions, in 79% yield. *O*-Methanesulfonylation of **9**

gave the mesylate (**10**) in 94% yield, which was then treated with sodium cyanide in *N,N*-dimethylformamide (DMF) at 50 °C to afford the nitrile (**11**), quantitatively. Removal of the *O*-benzoyl group (MeONa-MeOH) gave a primary alcohol (**12**) in 89% yield, which was oxidized with pyridinium chlorochromate (PCC) in dichloromethane to give the aldehyde (**13**). To construct the β -styryl moiety of **1**, Wittig alkenation of **13** was attempted. Thus, reaction of **13** with (4-methoxyphenylmethylene)triphenylphosphorane [generated from its corresponding phosphonium chloride¹⁰] and *n*-BuLi in tetrahydrofuran (THF)] provided a mixture of *E*-olefin (**15**) and its *Z*-isomer in a ratio of *ca.* 1:1, in 73% yield from **12**. Although the ratio of **15** and its *Z*-isomer was not improved by a change of the reaction solvent (benzene), fortunately, it was found that isomerization of *Z*-isomer of **15** using thiophenol¹¹) proceeded very efficiently. Namely, treatment of a benzene solution of a 1:1 mixture of **15** and its *Z*-isomer with thiophenol (10 mol%) and 2,2'-azobis(isobutyronitrile) (AIBN, 10 mol%) at reflux for 4 h afforded the isomerically pure **15** in 95% yield. Alternatively, **15** was also obtained stereoselectively in two step reactions. Reaction of the aldehyde (**13**) with iodoform and CrCl₂ in THF-DMF (Takai reaction)¹²) gave *E*-vinyl iodide derivative (**14**) and its *Z*-isomer in a ratio of >10:1 in 50% yield. Palladium-catalyzed cross-coupling reaction¹³) of **14** with (4-methoxyphenyl)magnesium bromide in the presence of 5 mol% of Pd(PPh₃)₄ in benzene at room temperature afforded **15** in 61% yield. The cross-coupling of **14** with (4-methoxyphenyl)tributyltin¹⁴) in the presence of Pd(PPh₃)₄ or Pd(OAc)₂/PPh₃ gave less satisfactory results (yields up to 27%).

Achieving the stereoselective construction of a β -styryl moiety, the requisite operations for the total synthesis would be a conversion of the nitrile group in **15** into a methoxycarbonyl moiety and an introduction of a methoxymethylene function. Although the attempted hydrolysis of the compound **15** (KOH in H₂O-EtOH, reflux) gave many unidentified products, reduction of **15** with diisobutylaluminum hydride (DIBAL), followed by acidic hydrolysis (aqueous H₂SO₄ work up) of the resulting imine, and subsequent oxidation (NaClO₂) afforded the corresponding carboxylic acid, which was esterified with diazomethane to provide **16** in 51% overall yield from **15**. Trapping the lithium ester enolate of **16**, generated by the treatment of **16** with lithium bis(trimethylsilyl)amide in THF, with methyl formate,^{5c}) followed by *O*-methylation of the product with dimethyl sulfate/K₂CO₃^{5c,15}) in acetone provided **1** in 51% yield (**16** recovered in 39% yield). The spectral [¹H (in MeOH-*d*₄), ¹³C (in DMSO-*d*₆) NMR and IR] and physical properties of synthetic **1** {syrup, [α]_D²⁶ -20° (*c* 0.16, EtOH); lit.¹) [α]_D -20° (*c* 0.14, EtOH)} were all identical with those of natural oudemansin X.

In summary, the first total synthesis of (-)-oudemansin X (**1**) has been achieved. From this synthesis, the absolute stereochemistry of natural oudemansin X was determined to be 3*S*,4*S*, which is the same as that of oudemansin A and B. This synthesis also revealed that L-quebrachitol (**2**) should be a useful starting material for the synthesis of a natural product in an optically active form.

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