CHEMISTRY LETTERS, pp. 687-690, 1992.

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

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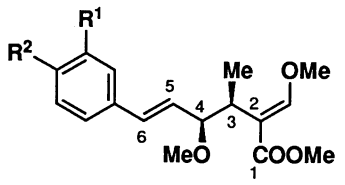
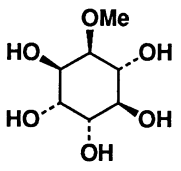
The stereoselective conversion of naturally occurring optically active cyclitol, L-quebrachitol (**2**), into antifungal (*E*)-β-methoxyacrylate, oudemansin X is described. This synthesis fully confirmed the proposed absolute configuration of the antibiotic and revealed the usefulness of **2** as a versatile 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 deduced[1] from a comparison of its ^{1}H NMR, CD, and mass spectra with those of the known structurally relating antibiotics, oudemansins A[2] 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 Ehrich 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 form[4] and in optically active form[5] 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.

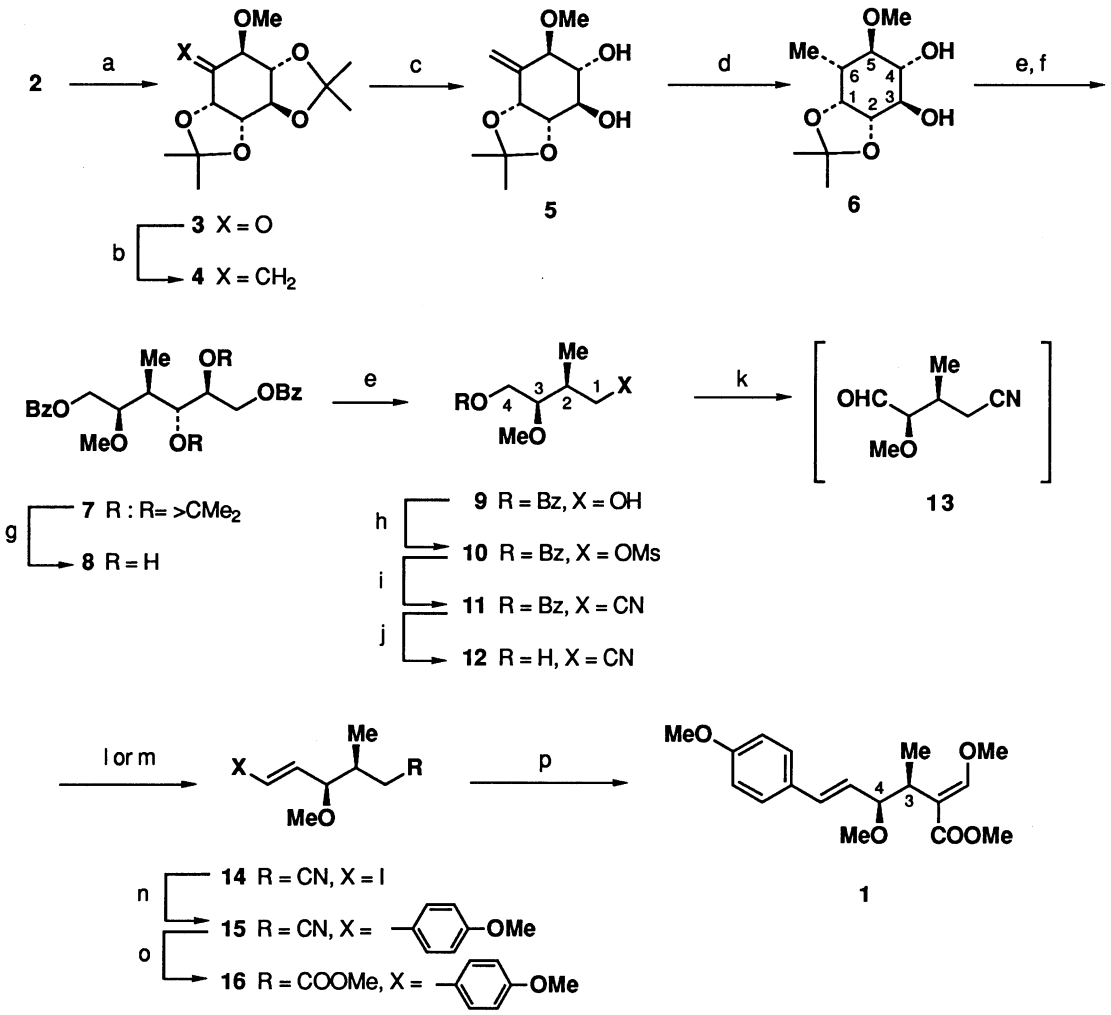


R^1 = H, R^2 = OMe; oudemansin X (**1**)
R^1 = R^2 = H; oudemansin A
R^1 = OMe, R^2 = Cl; oudemansin B



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 = $-SO_2Me$. Reagents and conditions: a, see Ref. 7b; b, Me_3SiCH_2MgCl, THF, rt, then KH, THF, rt; c, *p*-TsOH (1 mol%), MeOH, 0 °C; d) H_2, Raney-Ni, EtOH; e) $NaIO_4$, $NaHCO_3$, acetone-H_2O, 0 °C, then $NaBH_4$, 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, CH_2Cl_2; l) (**13**→**14**) CHI_3, $CrCl_2$, DMF-THF, rt; m) (**13**→**15**) $Ph_3P^+CH_2C_6H_4$(*p*-OMe)Cl^-, n-BuLi, THF, 0 °C, then PhSH, AIBN, benzene, reflux; n) (*p*-OMe)C_6H_4MgBr, $Pd(PPh_3)_4$ (5 mol%), benzene, rt; o) i) DIBAL, CH_2Cl_2, 0°C, 2 h, then acidic (aq H_2SO_4) work up, ii) $NaClO_2$, NH_2SO_3H, NaH_2PO_4, t-BuOH-H_2O, rt, iii) CH_2N_2, ether-CH_2Cl_2; p) i) $(Me_3Si)_2NLi$, THF, -78 – -40°C, 1 h, then HCOOMe, -78 – 0°C, ii) $(MeO)_2SO_2$, K_2CO_3, 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 $NaBH_4$, 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 $NaBH_4$ 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 chloride[10] 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 thiophenol[11] 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 $CrCl_2$ in THF-DMF (Takai reaction)[12] gave *E*-vinyliodide derivative (**14**) and its *Z*-isomer in a ratio of >10:1 in 50% yield. Palladium-catalyzed cross-coupling reaction[13] of **14** with (4-methoxyphenyl)magnesium bromide in the presence of 5 mol% of $Pd(PPh_3)_4$ in benzene at room temperature afforded **15** in 61% yield. The cross-coupling of **14** with (4-methoxyphenyl)tributyltin[14] in the presence of $Pd(PPh_3)_4$ or $Pd(OAc)_2/PPh_3$ 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 H_2O-EtOH, reflux) gave many unidentified products, reduction of **15** with diisobutylaluminum hydride (DIBAL), followed by acidic hydrolysis (aqueous H_2SO_4 work up) of the resulting imine, and subsequent oxidation ($NaClO_2$) 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/K_2CO_3[5c,15] in acetone provided **1** in 51% yield (**16** recovered in 39% yield). The spectral [^1H (in MeOH-d_4), ^{13}C (in DMSO-d_6) NMR and IR] and physical properties of synthetic **1** {syrup, $[\alpha]_D^{26}$ -20° (*c* 0.16, EtOH); lit.[1] $[\alpha]_D$ -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.

We express our sincere thanks to Professor W. Steglich (Institut für Organishe Chemie und Biochemie der Universität, Germany) for providing us with copies of ^1H, ^{13}C NMR, and IR spectra of natural oudemansin X. Financial support from Yokohama Rubber Co. Ltd., (Tokyo) is gratefully acknowledged.

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15) In previous oudemansin A syntheses, it has been reported that *O*-methylation of the β-formyl ester with K_2CO_3-dimethyl sulfate gave only *E*-vinyl ether whereas that with diazomethane afforded a mixture of *E*- and *Z*-isomers (see Refs. 4a, 4e, and 5c), and also reported that the vinyl proton of *E*-vinyl ether resonated at δ 7.18 and that of Z-isomer was appeared at δ 6.43 (see Ref. 4a). The observed chemical shift (δ 7.28) of the vinyl proton in oudemansin X supported the *E*-geometry of the vinyl ether moiety.

(Received January 31, 1992)