Utilisation of L-Quebrachitol in Natural Product Synthesis. Total Synthesis and Absolute Configuration of (−)-Oudemansin X

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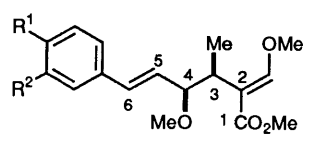
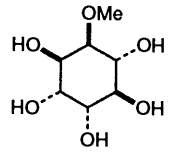
The stereoselective conversion of the naturally occurring optically active cyclitol, L-quebrachitol **2**, into antifungal β-methoxyacrylate, oudemansin X **1** is described. This first total synthesis of **1** fully confirmed the proposed absolute configuration of the antibiotic and showed the importance of **2** as a versatile chiral starting material in natural product syntheses.

L-Quebrachitol **2**, readily available from the serum of the rubber tree,[1] is an optically active cyclitol and has been used as a starting material for the synthesis of optically active cyclitol and aminocyclitol derivatives,[2] and as a chiral auxiliary for asymmetric reactions.[3] By regioselective ring cleavage of the cyclohexane ring, the pentanol **2** is expected to be a versatile chiral starting material for the preparation of highly oxygenated acyclic or heterocyclic natural products.[4] Based on this methodology, syntheses of several natural products from L-quebrachitol **2** have been reported from these laboratories.[5] In this article, as a part of our continuous study to explore the usefulness of **2**, we report the stereoselective first total synthesis of (−)-oudemansin X **1** starting from **2**, which fully confirmed the proposed absolute structure of the natural product.[6]



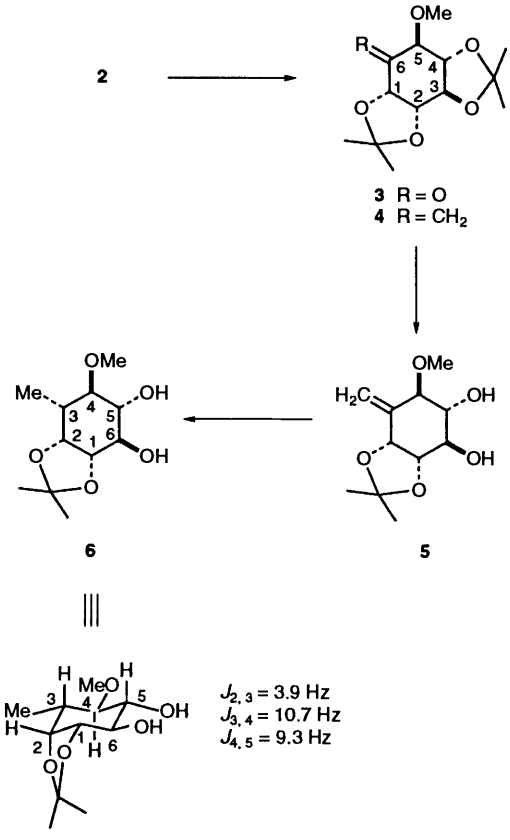
R^1 = OMe, R^2 = H: Oudemansin X **1**
R^1 = R^2 = H: Oudemansin A
R^1 = Cl, R^2 = OMe: Oudemansin B



L-Quebrachitol **2**

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.[7] The structure of compound **1** including the absolute configuration (3*S*,4*S*) has been deduced by Steglich[7] from a comparison of its ^{1}H NMR, CD, and mass spectra with those of the known structurally related antibiotics, oudemansins A[8] and B.[9] Oudemansins are reported to exhibit high antifungal activity, which is due to a strong inhibition of eukaryotic respiration.[7–10] This novel biological activity as well as intriguing structures of oudemansins which embody two chiral centres, (*E*)-styryl- and β-methoxyacrylate functions have stimulated the synthetic efforts, and several reports on syntheses of oudemansin A and B in racemic form[11] and in an optically active form[12] have appeared. Earlier successful syntheses of oudemansin A and B[11,12] as well as our retrosynthetic analysis suggested that a four-carbon unit possessing two chiral centres, such as compound **10**, should be a suitable intermediate for the synthesis of previously unprepared oudemansin X. Therefore, preparation of the stereo-defined four-carbon unit from **2** was first examined.

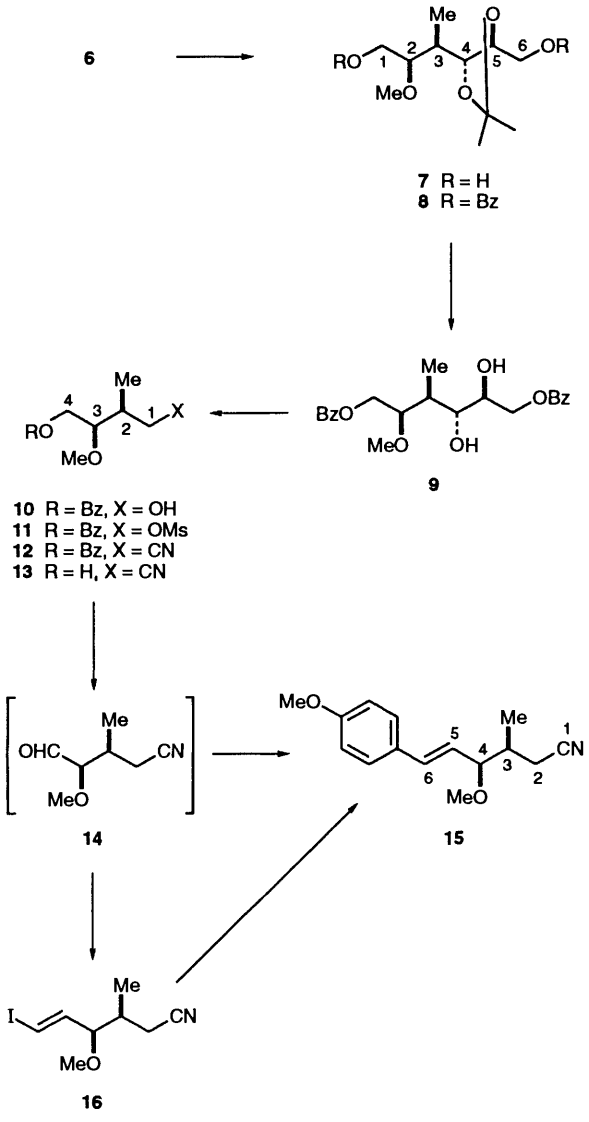
The Peterson alkenation[13] of the known ketone **3**,[2a] prepared from the pentol **2** in two steps (83% overall yield), afforded the *exo*-methylene compound **4** in 57% yield (Scheme 1). The Wittig reaction of ketone **3** with methylenetriphenylphosphorane was



Scheme 1

not reproducible and gave less satisfactory results (yield up to 47%). Mild acid treatment of the alkene **4** cleaved the *trans*-*O*-isopropylidene group selectively and provided the diol **5** in 80% yield. Hydrogenation of the diol **5** in the presence of Raney-Ni proceeded with high stereoselectivity to give the single product **6** in 76% yield. The observed coupling constants of the diol **6** in its ^{1}H NMR spectrum ($J_{2,3}$ = 3.9, $J_{3,4}$ = 10.7 and $J_{4,5}$ = 9.3 Hz) showed that both the newly formed 6-methyl group and the 5-methoxy group are equatorial, supporting the assigned structure of the diol **6**. As expected, addition of hydrogen took place from the less hindered, convex face of the dioxabicyclo-[4.3.0] system.

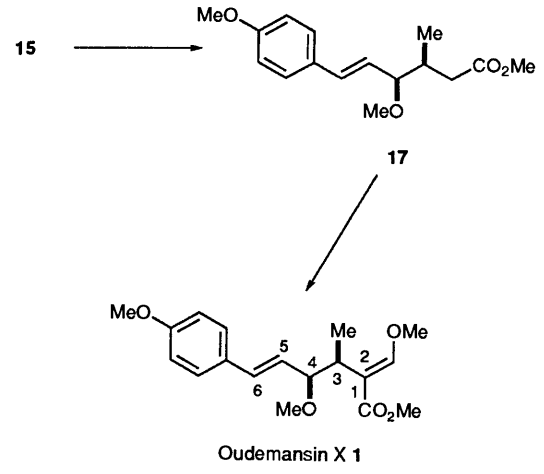
Periodate oxidation of the diol **6**, followed by successive reduction of the resulting aldehyde functions with $NaBH_4$, provided the diol **7** in 79% yield (Scheme 2). After *O*-benzoylation of the diol **7**, the remaining *O*-isopropylidene group was removed with 80% aqueous acetic acid to afford the diol **9**. Glycol cleavage of compound **9** with sodium periodate,



Scheme 2 Bz = COPh, Ms = SO_2Me

followed by reduction with $NaBH_4$ provided the mono-benzoate **10**, which is a suitable four-carbon unit for the synthesis of **1**, possessing two defined (2*S*-methyl and 3*R*-methoxy) stereocentres as well as two distinct primary alcohol functions in 79% yield. For one carbon homologation, the mono-benzoate **10** was converted into the nitrile **12** *via* the mesylate **11** (94% overall yield). Removal of the *O*-benzoyl group gave a primary alcohol **13** in 89% yield, which was then oxidised with pyridinium chlorochromate (PCC) to afford the aldehyde **14**. For a construction of the β-styryl moiety of compound **1**, Wittig alkenation of the aldehyde **14** was first attempted. Reaction of the aldehyde **14** with (4-methoxyphenylmethylene)triphenylphosphorane in tetrahydrofuran (THF) provided a mixture of the *E*-olefin **15** and its *Z*-isomer in a ratio of *ca.* 1:1 in 73% yield from the nitrile **13**. The geometries of the double bond in **15** and its *Z*-isomer were unambiguously determined from the coupling constants of vinyl protons observed in their ^1H NMR spectra ($J_{5,6}$ = 16.1 Hz in **15** and 11.7 Hz in the *Z*-isomer). Treatment of the mixture of *E*-isomer **15** and its *Z*-isomer with catalytic amount of thiophenol and 2,2′-azo(isobutyronitrile) (AIBN)[14] in refluxing benzene caused the isomerization of the double bond and afforded the isomerically pure *E*-isomer **15** in 95% (70% overall from the nitrile **13**) yield. Alternatively, the alkene **15** was also synthesized stereoselectively *via* a two-step route. Reaction of the alcohol **13** with iodoform and $CrCl_2$ in THF–*N*,*N*-dimethylformamide (DMF) (Takai reaction)[15] afforded the *E*-vinyl iodide **16** and its *Z*-isomer in a ratio of >20:1 in 50% yield. Several cross-coupling reactions[16] of the iodide **16** with (4-methoxyphenyl)metals were investigated (Table 1). Reaction of the iodide **16** with aryl Grignard reagent in the presence of a catalytic amount of $Pd(PPh_3)_4$ provided the isomerically pure alkene **15** in 61% (31% overall from **13**) yield.

Having achieved the stereoselective construction of the β-styryl moiety, the requisite operation for the total synthesis would be a conversion of the nitrile function in compound **15** into a methoxycarbonyl moiety and an introduction of a methoxymethylene functionality (Scheme 3). Although an



Scheme 3

attempted alkaline hydrolysis of the nitrile group in compound **15** gave many unidentified products, reduction of compound **15** with diisobutylaluminium hydride (DIBAL), followed by acidic hydrolysis of the resulting imine, and subsequent oxidation afforded the corresponding carboxylic acid, which was treated with diazomethane to provide the ester **17** in 51% overall yield from **15**. For a construction of a β-methoxyacrylate group, we adopted the literature procedure which had been reported for the total synthesis of oudemansin A and B,[11a,12a–c] with slight modification. Trapping the lithium ester enolate of **17**, generated by the action of lithium bis(trimethylsilyl)amide, with methyl formate, followed by *O*-methylation of the product with dimethyl sulfate–potassium carbonate in acetone* provided oudemansin X **1** in 51% yield, along with the recovery of the starting material (39%). The spectral (^1H and ^{13}C NMR, and IR) data were fully identical with those of the natural product, kindly provided by Professor Steglich, and the optical rotational value of synthetic **1** showed a good accord with that reported in the literature.

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

* In previous syntheses of oudemansin A, it has been reported that *O*-methylation of the α-formyl ester with dimethyl sulfate–potassium carbonate in acetone gave only *E*-vinyl ether whereas that with diazomethane afforded a mixture of *E*- and *Z*-isomers [see, refs. 11(*a*), 11(*e*) and 12(*b*)], and also reported that the vinyl proton of *E*-vinyl ether resonated at δ 7.18 and that of *Z*-isomer was observed at δ 6.43 [see, ref. 11(*a*)]. The observed chemical shift (δ 7.28) of the vinyl proton in **1** supported the *E*-geometry of the vinyl ether moiety.

Table 1 The cross-coupling reaction of vinyl iodide **16** with aryl metals[a]

Aryl metal[b] (equiv.)	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield of **15**[c] (%)
$ArSnBu_3$ (2.0)	$(Ph_3P)_4Pd$	THF	Reflux	1	27
$ArSnBu_3$ (2.0)	$(Ph_3P)_4Pd$	Toluene	80	2	24
$ArSnBu_3$ (2.0)	$Pd(OAc)_2$[d]	THF	Reflux	1	21
ArMgBr (1.5)	$(Ph_3P)_4Pd$	Benzene	r.t.	1	61
ArMgBr (1.8)	$NiCl_2(dppp)$[e]	Ether	r.t.	2	0[f]

[a] All reactions were carried out under Ar in the presence of catalyst (5 mol%). [b] Ar = $(p\text{-MeO})C_6H_4$. [c] Isolated yield after silica gel chromatography. [d] Ph_3P (10 mol%) was added. [e] dppp = $Ph_2PCH_2CH_2CH_2PPh_2$. [f] Decomposition of **16** was observed.

Experimental

M.p.s were determined on a Mitamura-riken micro hot stage and are uncorrected. ^1H NMR spectra were measured with a JEOL JNM EX-90 (90 MHz) and a JEOL JNM-GSX 270 (270 MHz) spectrometers, with tetramethylsilane as the internal standard for solutions in deuteriochloroform, unless otherwise noted, and J values are given in Hz. ^{13}C NMR spectra were taken on a JEOL JNM-GSX 270 (67 MHz) spectrometer. High resolution mass spectra were measured by a JEOL JMS-DX-302 spectrometer with EI mode (70 eV). Optical rotations were measured with a JASCO DIP-370 instrument and values of $[\alpha]_D$ are recorded in units of 10^{-1} deg cm^2 g^{-1}. IR spectra were taken with a JASCO IR-810 spectrometer. Organic extracts were dried over anhydrous Na_2SO_4 and concentrated below 40 °C under reduced pressure. Ether refers to diethyl ether.

1L-(1,2,4/3,5)-1,2:3,4-*Di*-O-*isopropylidene*-5-O-*methyl*-6-*methylenecyclohexane*-1,2,3,4,5-*pentol* **4**.—To a stirred solution of 2L(2,3,5/4,6)-2,3:4,5-di-*O*-isopropylidene-6-*O*-methylpentahydroxycyclohexanone **3**, prepared from **2** by the method reported by Paulsen[2a] (35 mg, 0.13 mmol) in THF (1 cm^3) under Ar at 0 °C was added a solution of trimethylsilylmethylmagnesium chloride in diethyl ether (1 mol dm^{-3}; 0.65 cm^3, 0.65 mmol). After being stirred at room temp. for 3 h, the reaction mixture was quenched by the addition of saturated aq. NH_4Cl at 0 °C, and the products were extracted with EtOAc. The extract was washed with brine and then dried. Evaporation of the solvent left crude tertiary alcohol derivatives as an oil, which was dissolved in THF (1 cm^3). To this solution under Ar at 0 °C was added potassium hydride (35% dispersion in oil; 74 mg, 0.65 mmol) and the resulting mixture was stirred at room temp. for 30 min. Saturated aq. NH_4Cl was added to the reaction mixture at 0 °C and the product was extracted with EtOAc. The extract was washed with brine, dried and concentrated to give a residue, which was chromatographed on a column of silica gel (3 g) with EtOAc–toluene (1:35; v/v) as eluent, to give the title compound **4** (20 mg, 57%) as a crystalline residue, m.p. 93 °C (from ethanol) (Found: C, 62.2; H, 8.0. $C_{14}H_{22}O_5$ requires C, 62.2; H, 8.2%); $[\alpha]_D^{28}$ +52 (*c* 0.8 in $CHCl_3$); δ_H(270 MHz) 1.40, 1.44, 1.53 and 1.59 [each 3 H, 4 s, $2C(CH_3)_2$], 3.46 (3 H, s, OCH_3), 3.57–3.61 (2 H, m, 3-H, 4-H), 4.01 (1 H, m, 5-H), 4.32 (1 H, m, 2-H), 4.77 (1 H, d, *J* 6.4, 1-H) and 5.41 and 5.56 (each 1 H, 2 d, *J* 1.5, CH_2=C).

1L-(1,2,4/3,5)-1,2-O-*Isopropylidene*-5-O-*methyl*-6-*methylene-cyclohexane*-1,2,3,4,5-*pentol* **5**.—To a stirred solution of compound **4** (161 mg, 0.593 mmol) in MeOH (3 cm^3) at 0 °C was added toluene-*p*-sulfonic acid-mono hydrate (1.1 mg, 5.9 μmol). After being stirred at 0 °C for 5 h, the reaction mixture was neutralized by the addition of triethylamine and concentrated to give a residue. Silica gel chromatography (4 g) of the residue with EtOAc–toluene (1:3; v/v) as eluent, gave starting material **4** (16 mg, 10% recovery). Further elution with MeOH–$CHCl_3$ (1:10; v/v) afforded the title compound **5** (109 mg, 80%) as a colourless syrup [Found: $(M + 1)^+$, 231.1236. $C_{11}H_{19}O_5$ requires (M + 1), 231.1233]; $[\alpha]_D^{28}$ −34 (*c* 1.6 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3450 (OH); δ_H(270 MHz) 1.40 and 1.54 [each 3 H, 2 s, $C(CH_3)_2$], 2.54 (2 H, m, OH), 3.42 (1 H, dd, *J* 8.3 and 8.3, 4-H), 3.49 (3 H, s, OCH_3), 3.76–3.88 (2 H, m, 3-H, 5-H), 4.08 (1 H, dd, *J* 5.9 and 6.3, 2-H), 4.66 (1 H, d, *J* 5.9, 1-H) and 5.42 and 5.49 (each 1 H, 2 d, *J* 1.5, CH_2=C).

1D-(1,2,3,5/4,6)-1,2-O-*Isopropylidene*-3-*methyl*-4-O-*methyl-cyclohexane*-1,2,4,5,6-*pentol* **6**.—A mixture of the alkene **5** (19 mg, 0.083 mmol) and Raney-Ni (W-4; *ca.* 0.5 cm^3) in EtOH (1 cm^3) was stirred under an atmospheric pressure of H_2 at room temp. for 18 h. The catalyst was removed by filtration, and the filtrate was concentrated to give a residue, which was chromatographed on a silica gel column (1 g), with MeOH–$CHCl_3$ (1:20; v/v) as eluent, to give compound **6** (15 mg, 76%) as a crystalline residue, m.p. 131–133 °C (from EtOH) (Found: C, 56.7; H, 8.4. $C_{11}H_{20}O_5$ requires C, 56.9; H, 8.7%); $[\alpha]_D^{27}$ −35 (*c* 1.1 in $CHCl_3$); ν_{max}(KBr)/cm^{-1} 3450 (OH); δ_H(270 MHz) 1.24 (3 H, d, *J* 6.8, 3-Me), 1.35 and 1.51 [each 3 H, 2 s, $C(CH_3)_2$], 1.85 (1 H, m, 3-H), 2.68–2.80 (2 H, m, 2-H), 3.08 (1 H, dd, *J* 9.3 and 10.7, 4-H), 3.33 (1 H, dd, *J* 9.3 and 9.8, 5-H), 3.58 (3 H, s, OCH_3), 3.64 (1 H, dd, *J* 7.8 and 9.8, 6-H), 3.91 (1 H, dd, *J* 4.9 and 7.8, 1-H) and 4.12 (1 H, dd, *J* 3.9 and 4.9, 2-H).

3-*Deoxy*-4,5-O-*isopropylidene*-3-C-*methyl*-2-O-*methyl*-L-*altritol* **7**.—To a stirred solution of the diol **6** (100 mg, 0.43 mmol) in acetone (3 cm^3) at 0 °C was added an aq. solution (3 cm^3) of sodium periodate (461 mg, 2.15 mmol) dropwise. The pH of the reaction mixture was maintained at 6–7 (pH paper) by the addition of solid sodium hydrogen carbonate. After being stirred at 0 °C for 4 h, the mixture was concentrated to give a residue, which was diluted with EtOAc and then washed with brine, and dried. Removal of the solvent gave a crude dialdehyde derivative, which was dissolved in methanol (2 cm^3). To this solution at 0 °C was added sodium borohydride (33 mg, 0.86 mmol), and the mixture was stirred at 0 °C for 2 h. The reaction mixture was neutralized by adding resin (IR-120B, H^+ form) and insoluble materials were removed by filtration. The filtrate was concentrated to give a residue, which was chromatographed on a column of silica gel (5 g), with MeOH–$CHCl_3$ (1:50, v/v) as eluent, to afford compound **7** (80 mg, 79%) as a colourless syrup [Found: $(M + 1)^+$, 235.1550. $C_{11}H_{23}O_5$ requires (M + 1), 235.1546]; $[\alpha]_D^{26}$ −66 (*c* 0.4 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3400 (OH); δ_H(270 MHz) 0.91 (3 H, d, *J* 6.8, 3-Me), 1.39 and 1.49 [each 3 H, 2 s, $C(CH_3)_2$], 1.52–2.05 (3 H, m, 3-H and 2 OH), 3.50 (3 H, s, OCH_3), 3.54–3.71 (5 H, m, 1-, 1′-, 2-, 6- and 6′-H), 4.12 (1H dd, *J* 5.4 and 10.3, 4-H) and 4.15 (1 H, m, 5-H).

1,6-*Di*-O-*benzoyl*-3-*deoxy*-4,5-O-*isopropylidene*-3-C-*methyl*-2-O-*methyl*-L-*altritol* **8**.—A solution of the diol **7** (70 mg, 0.30 mmol) and benzoyl chloride (0.087 cm^3, 0.75 mmol) in pyridine (1 cm^3) was stirred at room temp. for 1 h. After addition of MeOH, the reaction mixture was concentrated to give a residue, which was diluted with EtOAc and washed successively with aq. HCl (1 mol dm^{-3}), saturated aq. sodium hydrogen carbonate and brine, and dried. Removal of the solvent left a syrup, which was chromatographed on a column of silica gel (4 g), with EtOAc–toluene (1:4; v/v) as eluent, to afford compound **8** (127 mg, 96%) as a colourless syrup (Found: C, 67.9; H, 6.8. $C_{25}H_{30}O_7$ requires C, 67.9; H, 6.8%); $[\alpha]_D^{29}$ −16 (*c* 1.0 in

$CHCl_3$); ν_{max}(neat)/cm^{-1} 1710 (C=O); δ_H(270 MHz) 1.01 (3 H, d, *J* 6.8, 3-Me), 1.41 and 1.48 [each 3 H, 2 s, $C(CH_3)_2$], 2.05 (1 H, m, 3-H), 3.57 (3 H, s, OCH_3), 4.01 (1 H, ddd, *J* 2.4, 4.9 and 6.8, 2-H), 4.27 (1 H, dd, *J* 4.9 and 10.7, 1-H), 4.30 (1 H, dd, *J* 6.8 and 10.7, 1'-H), 4.32 (1 H, dd, *J* 5.4 and 11.7, 6-H), 4.42 (1 H, m, 5-H), 4.45 (1 H, dd, *J* 4.9 and 10.7, 4-H), 4.46 (1 H, dd, *J* 2.9 and 11.7, 6'-H) and 7.32–8.04 (10 H, m, phenyl).

1,6-*Di*-O-*benzoyl*-3-*deoxy*-3-C-*methyl*-2-O-*methyl*-L-*altritol* **9**.—A solution of compound **8** (395 mg, 0.892 mmol) in acetic acid–water (4:1; v/v; 4 cm^3) was stirred at 70 °C for 6 h. The reaction mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (15 g), with EtOAc–toluene (1:5; v/v) as eluent, to afford compound **9** (343 mg, 95%) as a colourless syrup (Found: C, 65.6; H, 6.4. $C_{22}H_{26}O_7$ requires C, 65.7; H, 6.5%); $[\alpha]_D^{25}$ −1 (*c* 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3470 (OH) and 1715 (C=O); δ_H(270 MHz) 1.14 (3 H, d, *J* 6.8, 3-Me), 2.26 (1 H, m, 3-H), 3.03 and 3.47 (each 1 H, 2 br s, OH), 3.56 (3 H, s, OCH_3), 3.84 (1 H, m, 4-H), 4.00 (1 H, m, 5-H), 4.04 (1 H, td, *J* 2.4 and 6.8, 2-H), 4.40–4.50 (2 H, m, 1-H_2), 4.52 (1 H, dd, *J* 6.4 and 11.7, 6-H), 4.70 (1 H, dd, *J* 2.9 and 11.7, 6'-H) and 7.40–8.12 (10 H, m, phenyl).

4-O-*Benzoyl*-2-*deoxy*-2-C-*methyl*-3-O-*methyl*-L-*threitol* **10**.—To a stirred solution of the diol **9** (117 mg, 0.29 mmol) in acetone (2 cm^3) at 0 °C was added an aq. solution (2 cm^3) of sodium periodate (310 mg, 1.45 mmol) dropwise. After being stirred at 0 °C for 4 h, the mixture was concentrated to give a residue, which was diluted with EtOAc and then washed with brine, and dried. Removal of the solvent gave a crude aldehyde derivative, which was dissolved in methanol (1 cm^3). To this solution at 0 °C was added sodium borohydride (27 mg, 0.72 mmol), and the mixture was stirred at 0 °C for 1 h. The reaction mixture was neutralized by adding resin (IR-120B, H^+ form) and insoluble materials were removed by filtration. The filtrate was concentrated to give a residue, which was purified by preparative TLC with acetone–hexanes (1:2; v/v) to afford compound **10** (54 mg, 79%) as a colourless syrup (Found: M^+, 238.1210. $C_{13}H_{18}O_4$ requires *M*, 238.1205); $[\alpha]_D^{27}$ +7 (*c* 1.0 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3430 (OH) and 1715 (C=O); δ_H(270 MHz) 1.01 (3 H, d, *J* 7.3, 2-Me), 2.18 (1 H, m, 2-H), 3.53 (3 H, s, OCH_3), 3.68–3.74 (3 H, m, 3-H and 1-H_2), 4.41 (1 H, dd, *J* 6.4 and 11.7, 4-H), 4.51 (1 H, dd, *J* 4.4 and 11.7, 4'-H) and 7.42–8.12 (5 H, m, phenyl).

4-O-*Benzoyl*-2-*deoxy*-1-O-*methylsulfonyl*-2-C-*methyl*-3-O-*methyl*-L-*threitol* **11**.—To a solution of the alcohol **10** (105 mg, 0.441 mmol) in pyridine (1 cm^3) at 0 °C was added methanesulfonyl chloride (0.068 cm^3, 0.88 mmol), and the mixture was stirred at 0 °C for 1 h. After addition of MeOH, the reaction mixture was concentrated and diluted with EtOAc, and washed successively with aq. HCl (1 mol dm^{-3}), saturated aq. sodium hydrogen carbonate and brine, and dried. Removal of the solvent left a syrup, which was chromatographed on a column of silica gel (5 g), with EtOAc–toluene (1:25, v/v) as eluent, to afford compound **11** (130 mg, 94%) as a colourless syrup (Found: C, 52.75; H, 6.3. $C_{14}H_{20}SO_6$ requires C, 53.15; H, 6.4%); $[\alpha]_D^{25}$ +2 (*c* 1.6 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1710 (C=O) and 1350 (SO_2); δ_H(270 MHz) 1.04 (3 H, d, *J* 6.8, 2-Me), 2.25 (1 H, m, 2-H), 3.03 (3 H, s, SO_2CH_3), 3.52 (3 H, s, OCH_3), 3.67 (1 H, td, *J* 3.4 and 5.9, 3-H), 4.16 (1 H, dd, *J* 6.4 and 9.8, 1-H), 4.29 (1 H, dd, *J* 7.8 and 9.8, 1'-H), 4.42 (2 H, d, *J* 5.9, 4-H_2) and 7.43–8.11 (5 H, m, phenyl).

(3S,4R)-5-*Benzoyloxy*-4-*methoxy*-3-*methylpentanenitrile* **12**.—A solution of the mesylate **11** (93 mg, 0.29 mmol) and sodium cyanide (43 mg, 0.88 mmol) in DMF (1 cm^3) was stirred at 50 °C for 6 h. The reaction mixture was diluted with EtOAc and washed with water, and dried. Removal of the solvent left an oil, which was chromatographed on a column of silica gel (5 g), with EtOAc–toluene (1:30; v/v) as eluent, to give compound **12** (77 mg, 100%) as a colourless syrup (Found: C, 67.7; H, 6.8; N, 5.65. $C_{14}H_{17}NO_3$ requires C, 68.0; H, 6.9; N, 5.7%); $[\alpha]_D^{28}$ +3 (*c* 0.6 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2250 (CN) and 1715 (C=O); δ_H(270 MHz) 1.13 (3 H, d, *J* 6.8, 3-Me), 2.23 (1 H, m, 3-H), 2.37 (1 H, dd, *J* 7.3 and 16.6, 2-H), 2.55 (1 H, dd, *J* 6.9 and 16.6, 2'-H), 3.53 (3 H, s, OCH_3), 3.60 (1 H, td, *J* 3.4 and 5.4, 4-H), 4.41 (2 H, d, *J* 5.4, 5-H_2) and 7.42–8.11 (5 H, m, phenyl).

(3S,4R)-5-*Hydroxy*-4-*methoxy*-3-*methylpentanenitrile* **13**.—To a mixture of the benzoate **12** (20 mg, 0.081 mmol) in MeOH (0.5 cm^3) was added NaOMe in methanol (1 mol dm^{-3}; 0.16 cm^3, 0.16 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the reaction mixture was neutralized by adding resin (IR-120B, H^+ form). Insoluble materials were removed by filtration and the filtrate was concentrated to give a residue, which was chromatographed on a column of silica gel (1 g), with EtOAc–toluene (1:3; v/v) as eluent, to give compound **13** (11 mg, 89%) as a colourless syrup (Found: M^+, 143.0935. $C_7H_{13}NO_2$ requires *M*, 143.0946); $[\alpha]_D^{25}$ +3 (*c* 0.4 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 3430 (OH) and 2250 (CN); δ_H(270 MHz) 1.11 (3 H, d, *J* 6.8, 3-Me), 1.83 (1 H, br s, OH), 2.25 (1 H, m, 3-H), 2.31 (1 H, dd, *J* 7.8 and 16.6, 2-H), 2.52 (1 H, dd, *J* 5.4 and 16.6, 2'-H), 3.24 (1 H, m, 4-H), 3.46 (3 H, s, OCH_3) and 3.63 and 3.74 (each 1 H, 2 m, 5-H_2).

(E)-(3S,4R)-4-*Methoxy*-6-(4-*methoxyphenyl*)-3-*methylhex*-5-*enenitrile* **15**.—To a stirred suspension of pyridinium chlorochromate (PCC) (258 mg, 1.20 mmol) and powdered molecular sieves 4 Å (250 mg) in dichloromethane (1.5 cm^3) was added a solution of the nitrile **13** (34 mg, 0.24 mmol) in dichloromethane (1.5 cm^3) dropwise at room temp. After being stirred at room temp. for 30 min, the reaction mixture was concentrated and chromatographed on a silica gel column (2 g), with ether as eluent, to give crude aldehyde **14**, which was used immediately in the next reaction without further purification.

To a stirred suspension of (4-methoxyphenyl)methyltriphenylphosphonium chloride[17] (301 mg, 0.719 mmol) in THF at 0 °C under Ar was added butyllithium (1.46 mol dm^{-3} solution in hexanes; 0.41 cm^3, 0.59 mmol), and the resulting mixture was stirred at 0 °C for 1 h. To this solution at 0 °C was added a solution of the crude aldehyde **14** in THF (1.5 cm^3). After being stirred at 0 °C for 1 h, the reaction mixture was quenched by the addition of saturated aq. NH_4Cl, and the products were extracted with EtOAc. The organic extract was washed with brine and dried. Removal of the solvent left a syrup, which was chromatographed on a column of silica gel (3 g), with EtOAc–toluene (1:15; v/v) as eluent, to give a mixture (*ca.* 1:1) of compound **15** and its *Z*-isomer (43 mg, 73%) as a colourless syrup. A solution of this mixture, thiophenol (0.0025 cm^3, 0.024 mmol) and AIBN (3.9 mg, 0.024 mmol) in benzene (1.5 cm^3) was heated under reflux for 4 h. The mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (5 g), with EtOAc–toluene (1:15; v/v) as eluent, to give compound **15** (41 mg, 70% overall) as a crystalline residue, m.p. 54 °C (from EtOH) (Found: C, 73.3; H, 7.5; N, 5.7. $C_{15}H_{19}NO_2$ requires C, 73.4; H, 7.8; N, 5.7%); $[\alpha]_D^{28}$ −35 (*c* 0.3 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2250 (CN) and 1610 (*p*-substituted phenyl); δ_H(270 MHz) 1.13 (3 H, d, *J* 6.8, 3-Me), 2.13 (1 H, m, 3-H), 2.28 (1 H, dd, *J* 7.3 and 16.6, 2-H), 2.52 (1 H, dd, *J* 5.4 and 16.6, 2'-H), 3.31 (3 H, s, OCH_3), 3.66 (1 H, dd, *J* 5.4 and 8.3, 4-H), 3.82 (3 H, s, OCH_3), 5.87 (1 H, dd, *J* 8.3 and 16.1, 5-H), 6.56 (1 H, d, *J* 16.1, 6-H) and 6.88 and 7.36 (each 2 H, 2 m, phenyl).

(E)-(3S,4R)-6-*Iodo*-4-*methoxy*-3-*methylhex*-5-*enenitrile* **16**.—To a stirred suspension of chromium(II) chloride (393 mg, 3.20 mmol) in THF (1.5 cm^3) under Ar at room temp. was added DMF (0.248 cm^3, 3.20 mmol), and the mixture was stirred at room temp. for 30 min. To this mixture was added a solution of the crude aldehyde **14** [prepared from **13** (57 mg, 0.40 mmol) similarly as described for preparation of compound **15**] and iodoform (315 mg, 0.80 mmol) in THF (2 cm^3) at room temp. After being stirred at room temp. for 4 h, the mixture was diluted with EtOAc and washed successively with saturated aq. sodium thiosulfate and brine, and dried. Removal of the solvent afforded an oil, which was chromatographed on a column of silica gel (5 g), with acetone–hexanes (1:20; v/v) as eluent, to give a >20:1 mixture of compound **16** and its *Z*-isomer (54 mg, 50%) as a colourless syrup (Found: M^+, 264.9954. $C_8H_{12}NOI$ requires *M*, 264.9965); $[\alpha]_D^{20}$ +14 (*c* 0.9 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 2250 (CN); δ_H(270 MHz, for the major isomer) 1.08 (3 H, d, *J* 6.8, 3-Me), 2.04 (1 H, m, 3-H), 2.24 (1 H, dd, *J* 7.3 and 16.6, 2-H), 2.49 (1 H, dd, *J* 5.9 and 16.6, 2'-H), 3.30 (3 H, s, OCH_3), 3.56 (1 H, dd, *J* 4.4 and 4.9, 4-H), 6.38 (1 H, dd, *J* 4.9 and 14.9, 5-H) and 6.46 (1 H, d, *J* 14.9, 6-H).

Preparation of **15** *from Vinyl Iodide* **16**.—To a stirred solution of compound **16** (10 mg, 0.039 mmol) in benzene (0.5 cm^3) at room temp. under Ar was added tetrakis(triphenylphosphine)-palladium(0) (2.4 mg, 0.0020 mmol) and 4-methoxyphenyl-magnesium bromide (1.0 mol dm^{-3} solution in THF; 0.060 cm^3, 0.060 mmol). After being stirred at room temp. for 1 h, saturated aq. NH_4Cl was added and the products were extracted with EtOAc. The organic extract was washed with brine and dried. Removal of the solvent afforded a residue, which was chromatographed on a column of silica gel (1 g), with EtOAc–toluene (1:15; v/v) as eluent, to give compound **15** (5.8 mg, 61%) as a crystalline residue. The physical properties of compound **15** were fully identical with those of **15** obtained from **13** by Wittig reaction followed by isomerization (*vide supra*).

Methyl (E)-(3S,4R)-4-*Methoxy*-6-(4-*methoxyphenyl*)-3-*methylhex*-5-*enoate* **17**.—To a stirred solution of **15** (12 mg, 0.048 mmol) in dichloromethane (0.4 cm^3) at 0 °C under Ar was added DIBAL (1.5 mol dm^{-3} solution in toluene; 0.064 cm^3, 0.095 mmol). After being stirred at 0 °C for 2 h, saturated aq. NH_4Cl (0.07 cm^3) was added, and the mixture was stirred at room temp. for 30 min. To this solution, 5% aq. sulfuric acid (0.10 cm^3) was added. After being stirred at room temperature for 6 h, the mixture was diluted with dichloromethane and washed with water, and dried. Removal of the solvent left a residue, which was dissolved in *tert*-butyl alcohol (0.8 cm^3) and water (0.8 cm^3). To this solution at room temp. were added sulfamic acid (14 mg, 0.14 mmol), sodium phosphate-monobasic dihydrate (15 mg, 0.095 mmol) and sodium chlorite (13 mg, 0.14 mmol), and the mixture was stirred at room temp. for 10 min. The mixture was diluted with dichloromethane and washed with brine, and dried. Removal of the solvent gave a crude carboxylic acid, which was dissolved in dichloromethane (1 cm^3) and treated with an excess of ethereal diazomethane at 0 °C for 20 min. The reaction mixture was concentrated to give a residue, which was chromatographed on a column of silica gel (1 g), with EtOAc–hexanes (1:20; v/v) as eluent, to give compound **17** (6.8 mg, 51%) as a colourless syrup (Found: C, 69.0; H, 7.7. $C_{16}H_{22}O_4$ requires C, 69.0; H, 8.0%); $[\alpha]_D^{28}$ +25 (*c* 0.2 in $CHCl_3$); ν_{max}(neat)/cm^{-1} 1730 (C=O) and 1610 (*p*-substituted phenyl); δ_H(270 MHz) 1.00 (3 H, d, *J* 6.8, 3-Me), 2.14 (1 H, dd, *J* 8.3 and 14.7, 2-H), 2.27 (1 H, m, 3-H), 2.54 (1 H, dd, *J* 5.4 and 14.7, 2'-H), 3.30 (3 H, s, OCH_3), 3.55 (1 H, dd, *J* 5.4 and 7.8, 4-H), 3.63 (3 H, s, CO_2CH_3), 3.82 (3 H, s, OCH_3), 5.90 (1 H, dd, *J* 7.8 and 16.1, 5-H), 6.48 (1 H, d, *J* 16.1, 6-H) and 6.86 and 7.35 (each 2 H, 2 m, phenyl).

Oudemansin X **1**.—To a stirred solution of the ester **17** (20 mg, 0.070 mmol) in THF (1 cm^3) at −78 °C under Ar was added lithium bis(trimethylsilyl)amide (1.0 mol dm^{-3} solution in THF; 0.56 cm^3, 0.56 mmol). The mixture was gradually warmed up to −40 °C over 1 h and then recooled to −78 °C. To this solution was added methyl formate (0.052 cm^3, 0.84 mmol) and the resulting mixture was gradually warmed up to room temp. over 2.5 h, and then diluted with dichloromethane and washed successively with diluted aqueous HCl and brine, and dried. Removal of the solvent left an oil, which was dissolved in acetone (1 cm^3). To this solution at room temp., potassium carbonate (39 mg, 0.28 mmol) and dimethyl sulfate (0.99 cm^3, 1.05 mmol) were added, and the mixture was stirred at room temp. for 14 h. The mixture was diluted with EtOAc and washed with water and dried. Removal of the solvent afforded a residue, which was purified by preparative TLC (EtOAc–hexanes; 1:9) to afford the starting material **17** (7.7 mg, 39% recovered) and oudemansin X **1** (11.4 mg, 51%) as amorphous solid, m.p. 36 °C (Found: C, 67.2; H, 7.35%; M^+, 320.1631. Calc. for $C_{18}H_{24}O_5$: C, 67.5; H, 7.55%; *M*, 320.1624); $[\alpha]_D^{26}$ −20 (*c* 0.2 in EtOH) [lit.,[7] −20.35 (*c* 0.14 in EtOH)]; ν_{max}(neat)/cm^{-1} 1705 (C=O), 1640 (C=C) and 1600 (*p*-substituted phenyl); δ_H(270 MHz in CD_3OD) 1.22 (3 H, d, *J* 6.8, 3-Me), 2.94 (1 H, dq, *J* 6.8 and 9.8, 3-H), 3.29 (3 H, s, OCH_3), 3.61 (3 H, s, CO_2CH_3), 3.81 (3 H, s, OCH_3), 3.92 (1 H, dd, *J* 8.8 and 9.8, 4-H), 5.69 (1 H, dd, *J* 8.8 and 15.6, 5-H), 6.35 (1 H, d, *J* 15.6, 6-H), 6.84 and 7.24 (each 2 H, 2 m, phenyl) and 7.28 [1 H, s, C=C*H*(OMe)]; δ_C{67 MHz in [$^2H_6$]DMSO; ($^{13}CD_3$)S=O as internal standard (δ_C 39.7)} 16.0, 35.4, 51.0, 55.3, 56.0, 61.7, 84.7, 111.2, 114.2, 126.8, 127.7, 129.2, 131.9, 159.1, 160.0 and 167.6. The ^1H and ^{13}C NMR, and IR spectroscopic data were fully identical with those of the natural product.

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References

1 (*a*) J. van Alphen, *Ind. Eng. Chem.*, 1951, **43**, 141; (*b*) N. Chida, M. Suzuki, M. Suwama and S. Ogawa, *J. Carbohydr. Chem.*, 1989, **8**, 319.
2 (*a*) H. Paulsen and F. R. Heiker, *Liebigs Ann. Chem.*, 1981, 2180; (*b*) S. Ogawa and A. Isaka, *Carbohydr. Res.*, 1991, **210**, 105; T. Akiyama, N. Takechi and S. Ozaki, *Tetrahedron Lett.*, 1990, **31**, 1433; T. Akiyama, H. Shima and S. Ozaki, *Tetrahedron Lett.*, 1991, **32**, 5593; T. Akiyama, M. Ohnari, H. Shima and S. Ozaki, *Synlett*, 1991, 831; W. Tegge and C. E. Ballou, *Proc. Natl. Acad. Sci. U.S.A.*, 1989, **86**, 94; A. P. Kozikowski, A. H. Fauq, I. A. Aksoy, M. J. Seewald and G. Powis, *J. Am. Chem. Soc.*, 1990, **112**, 7403; A. P. Kozikowski, A. H. Fauq, G. Powis and D. C. Meilder, *J. Am. Chem. Soc.*, 1990, **112**, 4528; C. Liu, S. R. Nahorski and B. V. L. Potter, *J. Chem. Soc., Chem. Commun.*, 1991, 1014; N. Chida, K. Yamada and S. Ogawa, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1131.
3 T. Akiyama, H. Nishimoto and S. Ozaki, *Tetrahedron Lett.*, 1991, **32**, 1335; T. Akiyama, K. Okada and S. Ozaki, *Tetrahedron Lett.*, 1992, **33**, 5763.
4 S. J. Angyal and R. M. Hosinson, *Methods Carbohydr. Chem.*, 1963, **2**, 87.
5 N. Chida, M. Suzuki, M. Suwama and S. Ogawa, ref. 1(*b*); N. Chida, K. Yamada, M. Suzuki and S. Ogawa, *J. Carbohydr. Chem.*, 1992, **11**, 137; N. Chida, T. Tobe and S. Ogawa, *Tetrahedron Lett.*, 1991, **32**, 1063; N. Chida, T. Tobe, M. Suwama, M. Ohtsuka and S. Ogawa, *J. Chem. Soc., Perkin Trans. 1*, 1992, 2667.
6 Preliminary communication of this work, see N. Chida, K. Yamada and S. Ogawa, *Chem. Lett.*, 1992, 687.
7 T. Anke, A. Werle, M. Bross and W. Steglich, *J. Antibiot.*, 1990, **43**, 1010.

8 T. Anke, H. J. Hecht, G. Schramm and W. Steglich, *J. Antibiot.*, 1979, **32**, 1112.
9 T. Anke, H. Besl, U. Mocek and W. Steglich, *J. Antibiot.*, 1983, **36**, 661.
10 W. F. Becker, G. Von Jagow, T. Anke and W. Steglich, *FEBS Lett.*, 1981, **132**, 329.
11 Synthesis of racemic oudemansin A, see (*a*) T. Nakata, T. Kuwabara, Y. Tani and T. Oishi, *Tetrahedron Lett.*, 1982, **23**, 1015; (*b*) K. Mikami, K. Azuma and T. Nakai, *Chem. Lett.*, 1983, 1379; (*c*) C. J. Kowalski, M. S. Haque and K. W. Fields, *J. Am. Chem. Soc.*, 1985, **107**, 1429. Synthesis of racemic oudemansin A and B, see (*d*) J. Kallmerten and M. D. Wittman, *Tetrahedron Lett.*, 1986, **27**, 2433; (*e*) M. D. Wittman and J. Kallmerten, *J. Org. Chem.*, 1987, **52**, 4303.
12 Synthesis of (−)-oudemansin A, see (*a*) H. Akita, H. Koshiji, A. Furuichi, K. Horikoshi and T. Oishi, *Tetrahedron Lett.*, 1983, **24**, 2009; *Chem. Pharm. Bull.*, 1984, **32**, 1242. Synthesis of (+)-oudemansin A (antipode of the natural product) and its epimer, see (*b*) H. H. Meyer, *Liebigs Ann. Chem.*, 1984, 791. Synthesis of (−)-oudemansin B, see (*c*) H. Akita, H. Matsuoka and T. Oishi, *Tetrahedron Lett.*, 1986, **27**, 5397.
13 D. J. Ager, *Org. React.*, 1990, **38**, 1.
14 M. Schwarz, G. F. Graminski and R. M. Waters, *J. Org. Chem.*, 1986, **51**, 260.
15 K. Takai, N. Nitta and K. Utimoto, *J. Am. Chem. Soc.*, 1986, **108**, 7408.
16 For a review of metal-catalysed coupling reactions between sp^2 carbon centres, see D. W. Knight, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 3, p. 481.
17 R. Ketcham and D. Jambotkar, *J. Org. Chem.*, 1962, **27**, 4666.

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