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TOTAL SYNTHESIS OF (±)-OUDEMANSIN

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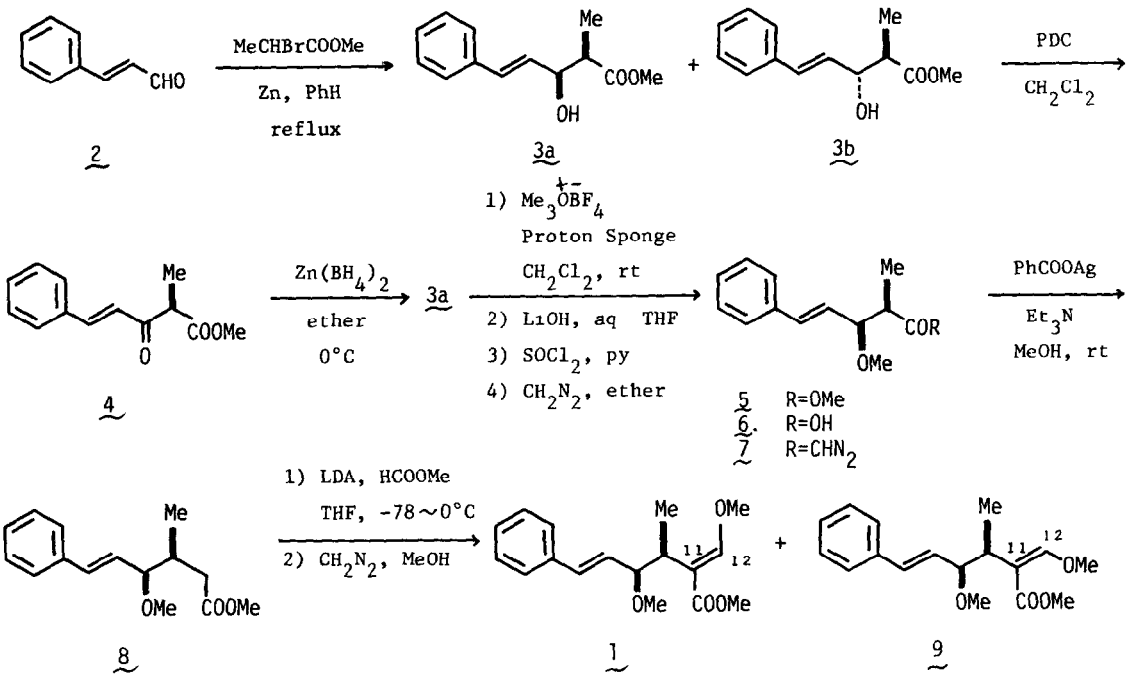
Summary (±)-Oudemansin has been synthesized starting from trans-cinnamaldehyde by a route involving the stereoselective $Zn(BH_4)_2$ reduction of β-keto ester.

Oudemansin (1), isolated from mycelial cultures of Oudemansiella mucida, is an antibiotic exhibiting strong antifungal activities.[1] The structure and the relative configurations have been determined by X-ray analysis.[1] Oudemansin contains a styryl, erythro-CH(OMe)-CHMe-, and a methyl (E)-β-methoxy acrylate units in its structure We have recently developed a method for the preparation of erythro-α-methyl-β-hydroxy esters by $Zn(BH_4)_2$ reduction of the corresponding β-keto esters[2] We now report the stereoselective synthesis of (±)-oudemansin (1) by a route involving this stereoselective reduction.

Reformatsky reaction of trans-cinnamaldehyde (2) and methyl α-bromo propionate gave a ca 1 1 mixture of erythro- and threo-hydroxy esters (3a and 3b), which was oxidized directly with PDC[3] in CH_2Cl_2 to the β-keto ester (4)[4][NMR ($CDCl_3$) δ 1.45 (d, J=7 1 Hz, Me), 1.95 (s, Me)] in 68% yield from 2. As described in the previous paper,[2] $Zn(BH_4)_2$ reduction of 4 gave the erythro-hydroxy ester (3a)[72% yield, NMR ($CDCl_3$) δ 3 72 (s, COOMe), 4 59 (ddd, J=5 5, 4, 1 Hz, CH-OH)] along with a small amount of the threo-isomer (3b)(7% yield), which is separable by carrying out preparative TLC repeatedly. On treatment of $Me_3\overset{+}{O}\bar{B}F_4$ and 1, 8-bis(dimethylamino)naphthalene (Proton Sponge) in CH_2Cl_2,[5] the erythro-hydroxy ester (3a) was effectively methylated to the β-methoxy ester (5)[72% yield, IR (CCl_4) 1740 cm^{-1}, NMR ($CDCl_3$)· δ 3 32 (s; OMe), 3.66 (s, COOMe)].[6] The β-methoxy ester (5) was hydrolyzed with LiOH in aq. THF to give the carboxylic acid (6)[97% yield, IR (CCl_4) 1710 cm^{-1}, NMR ($CDCl_3$) δ 3 38 (s; OMe)]. Treatment of 6 with $SOCl_2$ in pyridine, followed by the addition of CH_2N_2 gave the diazoketone (7). Wolff rearrangement of 7 with silver benzoate in MeOH containing a small amount of Et_3N[7] afforded the ester (8)[IR (CCl_4). 1735 cm^{-1}, NMR ($CDCl_3$). δ 3.31 (s, OMe), 3.64 (s, COOMe)] in 54% yield from 6. Formylation of 8 with LDA and methyl formate in THF at -78 to 0°C, followed by treatment with CH_2N_2-MeOH produced a 2.9 1 mixture[8] of (E)- and (Z)-isomers (1 and 9), readily separable by preparative TLC, in 28% combined yield [1 mp 69-70°C, IR($CHCl_3$) 1695, 1640 cm^{-1}, NMR ($CDCl_3$) δ 1 26 (d, J=6.8 Hz; Me), 3.32 (s, OMe), 3.64 (s; OMe), 3.77 (s, OMe), 7 18 (s, C_{12}-H), 9 IR ($CHCl_3$) 1700, 1640 cm^{-1}, NMR ($CDCl_3$). δ 1.19 (d, J=7.3 Hz; Me), 3 31 (s, OMe), 3 71 (s, OMe), 3.78 (s, OMe), 6.43 (s, C_{12}-H)]. The geometry of the C_{11}-C_{12} double bond in the isomers was determined by the NMR spectra, The chemical shift of C_{12}-H [δ 7.18 in the major isomer (1) and δ 6.43 in the minor isomer (9)] indicates that the C_{12}-H is cis-oriented to the carbonyl group in 1, and trans in 9 The spectral data (IR and NMR) of the synthetic (±)-1 were identical with those of natural oudemansin.



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References and Notes

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2. T Nakata and T. Oishi, Tetrahedron Lett , 21, 1641 (1980).
3 E. J. Corey and G Schmidt, ibid., 399 (1979).
4. The β-keto ester (4) existed as an equilibrium mixture of keto and enol forms (ca 4 1 ratio from the NMR spectrum in $CDCl_3$)
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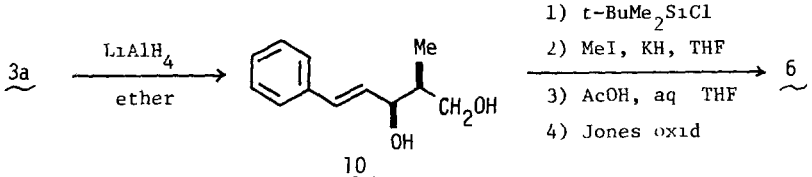
6. O-methylation of the related β-hydroxy ester with KH-MeI gave only an intractable mixture. Therefore, methylation was carried out after conversion to the base stable diol (10)(ca 40% overall yield of 6 from 3a). However, five steps are required in this route



7. V Lee and M S Newman, Org Syn., 50, 77 (1970)
8. Formylation of 8, followed by treatment with NaH and Me_2SO_4 in DMF gave only an (E)-isomer (1), but rather in low yield (13%)

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