Communications to the Editor

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THE USE OF A VERSATILE BUILDING BLOCK HAVING TWO CHIRAL CENTERS A TOTAL SYNTHESIS OF (-)-OUDEMANSIN

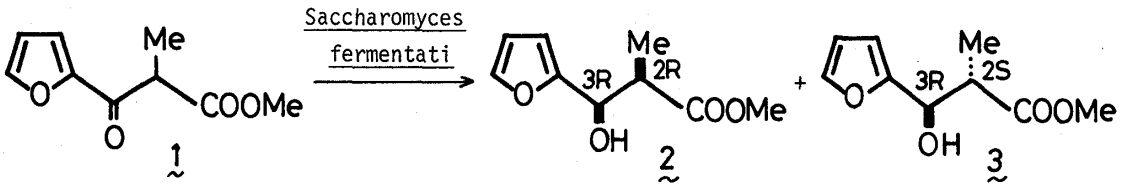
Hiroyuki Akita,*[a] Hiroko Koshiji,[a] Akiya Furuichi,[a] Koki Horikoshi,[b] and Takeshi Oishi*[a]

Synthetic Organic Chemistry Laboratory,[a] and Laboratory of Bacteriology and Ecology,[b] The Institute of Physical and Chemical Research (Riken Institute), 2-1 Hirosawa, Wako-shi, Saitama 351, Japan

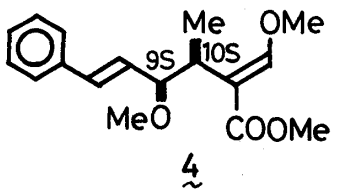
(-)-Oudemansin (4) has been synthesized from the chiral synthon 2 obtained by microbiological asymmetric reduction of the prochiral β-keto ester 1.

KEYWORDS——total synthesis; antibiotic; cleavage of furan; α-methyl β-hydroxy ester

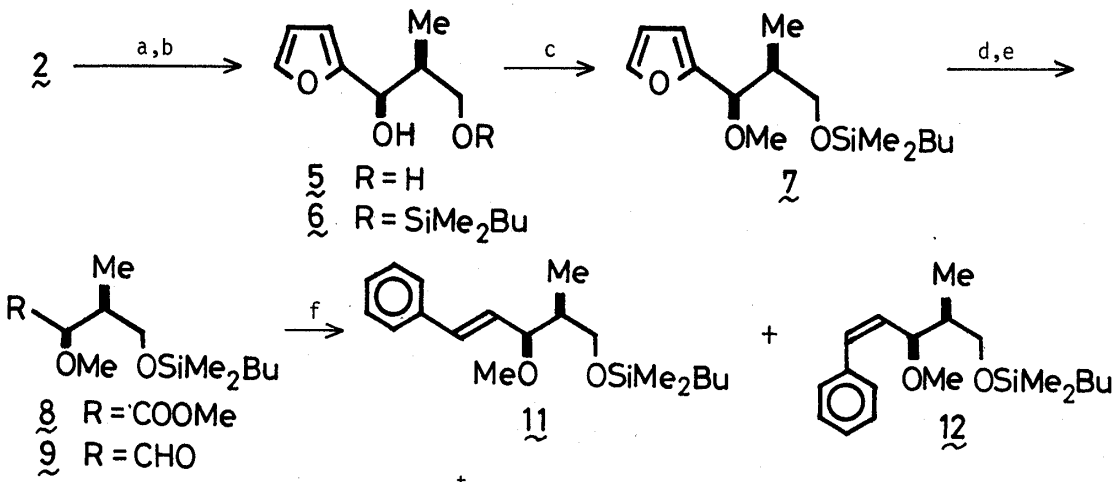
In the course of our synthesis studies of optically active chiral synthons useful for the synthesis of polyoxo macrolide antibiotics or related natural products, we reported previously that the reduction of 3-(2-furyl)-2-methyl-3-oxopropionate 1 with Saccharomyces fermentati yielded a 1:1 mixture of the corresponding 2,3-syn (2)- and anti (3)-2-methyl-3-hydroxy esters in total 77% yield.[1] The enantioselectivity of the present reduction was remarkably high: in particular, syn-2 was obtained in more than 99% e.e. and thus, this compound was expected to be a versatile building block for the synthesis of the natural products having syn-2-methyl-3-hydroxy functions in their molecules.



We now report the total synthesis of (-)-oudemansin (4),[2,3] an antibiotic isolated from mycelial cultures of Oudemansiella mucida, starting from syn-2.



Reduction of 2 with $LiAlH_4$ in Et_2O afforded diol 5 [IR (CCl_4): 3430 cm^{-1}] in quantitative yield. Diol 5 was treated with one equivalent of tert-butyldimethylsilylchloride in the presence of imidazole in DMF afforded the mono-silyl ether 6 [IR (CCl_4): 3480 cm^{-1}; NMR ($CDCl_3$): δ 0.917 (s, tert-Bu)] in 80% yield. Methylation of secondary hydroxyl group in 6 with MeI in the presence of NaH in DMF yielded the methoxy silyl ether 7 [$[\alpha]_D^{21}$+44.30° (c=5.0, $CHCl_3$), NMR ($CDCl_3$): δ 3.232 (s, OMe), 4.192 (d, $J_{2,3}$=6.4 Hz; 3-H)] in 91% yield. Ozonolysis of 7 in CH_2Cl_2 under dry ice-acetone cooling and the subsequent oxidation of the product with 30% H_2O_2 gave a crude carboxylic acid, which was esterified with CH_2N_2 to afford the methoxy ester 8 [$[\alpha]_D^{21}$+37.45° (c=4.95, $CHCl_3$), IR (CCl_4): 1752 cm^{-1}, NMR ($CDCl_3$): δ 3.762 (s;



a; $LiAlH_4/Et_2O$ b; $^tBuMe_2SiCl$/imidazole/DMF c; MeI/NaH/DMF

d; 1) O_3/CH_2Cl_2 2) 30% H_2O_2 3) CH_2N_2 e; $HAl(iso\text{-}Bu)_2/Et_2O$

f; $PhCH_2P^+Ph_3Br^-$ 10/n-BuLi/THF

COOMe)] in 29% yield. The DIBAL reduction of 8 provided aldehyde 9 [56% yield, $[\alpha]_D^{27}$+43.90° (c= 7.2, $CHCl_3$), IR (CCl_4): 1730 cm^{-1}, NMR ($CDCl_3$): δ 8.456 (d, J=1.6 Hz; CHO)], which was treated with phosphonium salt 10 in the presence of n-BuLi producing a 43:57 mixture of (E)- and (Z)-isomers 11 and 12 in 94% yield. This mixture was separated by HPLC into two fractions. The more polar fraction 11 [$[\alpha]_D^{27}$+5.24° (c=5.0, $CHCl_3$), NMR ($CDCl_3$): δ 6.117 (dd, $J_{3,4}$=7.7 Hz, $J_{4,5}$=16 Hz; 4-H), 6.530 (d, $J_{4,5}$=16 Hz; 5-H)] was identical with the authentic specimen 11[3c] in every respect (IR, NMR, and $[\alpha]_D$). The less polar fraction 12 [$[\alpha]_D^{27}$+86.80° (c=5.0, $CHCl_3$), NMR ($CDCl_3$): δ 5.658 (dd, $J_{3,4}$=9.6 Hz, $J_{4,5}$=12 Hz; 4-H), 6.653 (dd, $J_{3,5}$=1.0 Hz, $J_{4,5}$=12 Hz; 5-H)] was found to be Z-isomer 12 from the NMR spectra. The optically active trans isomer 11 thus obtained has already been converted to (-)-oudemansin (4) in 7 steps.[3c]

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