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A Highly Stereoselective Synthesis of the Versatile Chiral Synthons Possessing Two Stereogenic Centers, The Formal Total Syntheses of (-)-Oudemansins A, B, and X

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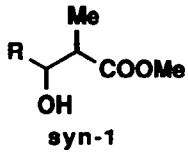
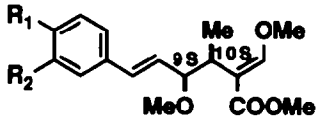
Abstract: A highly stereoselective synthesis of the versatile chiral synthons possessing two stereogenic centers, (2R,3R)-**8** and (2S,3S)-**8** was achieved and the application of (2R,3R)-**8** into the formal total syntheses of (-)-oudemansins A(**2**), B(**3**), and X(**4**) were described

In an effort to develop a better method for the synthesis of optically active *syn*-3-hydroxy-2-methyl ester **1** or its congener, a useful chiral synthon for the synthesis of polyoxomacrolide antibiotics or the related natural products, the stereoselective synthesis of the optically active form **1** based on a combination of the diastereoselective reduction with $Zn(BH_4)_2$ and the enantioselective hydrolysis using the lipase has aroused our interest. We now report the synthesis of two optically active building blocks, β-acetoxy esters (2R,3R)-**8** and (2S,3S)-**8** and the application of (2R,3R)-**8** into the formal total syntheses of the fungicide oudemansins A(**2**),[1] B(**3**),[2] X(**4**).[3] The optically active *syn*-3-hydroxy-3-*p*-methoxyphenyl-2-methyl propanoate **5** or its acetate **8** involving two stereogenic centers was selected as target molecule because *p*-methoxyphenyl group is convertible into a carboxylic acid or its congeners and benzylic oxygen functional group should be reduced to give a useful chiral synthon possessing one stereogenic center.[4]



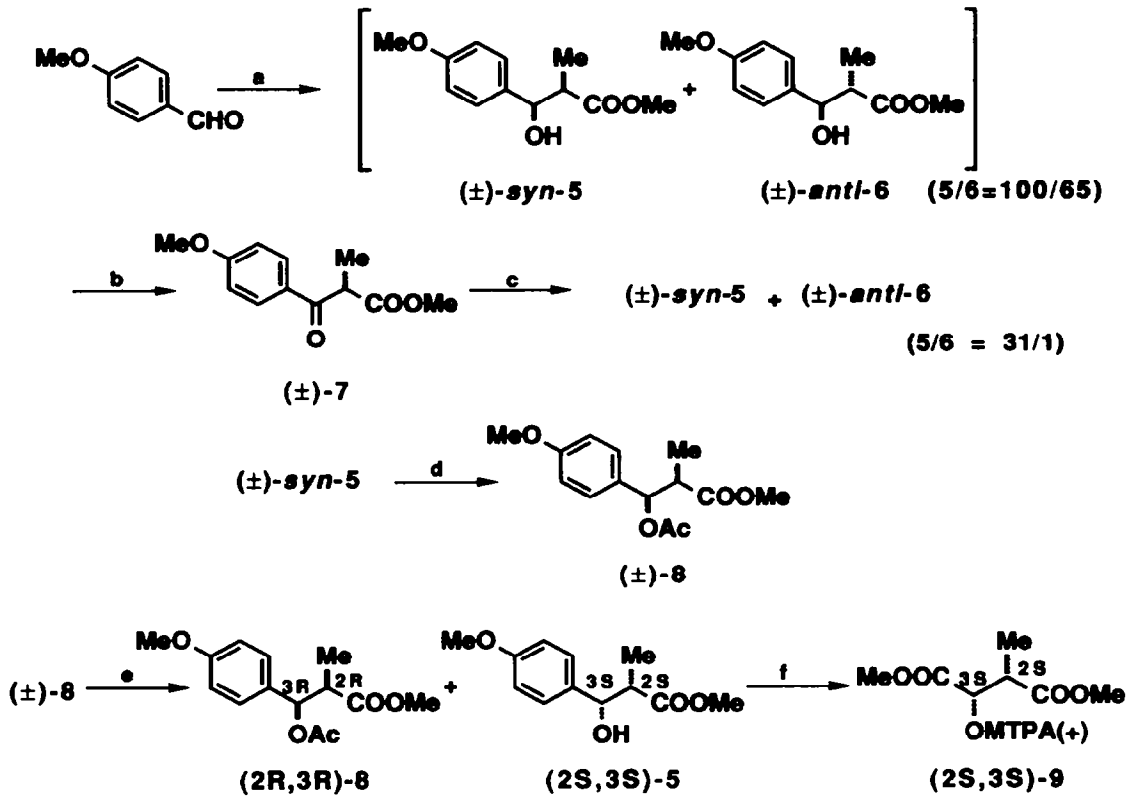
syn-1



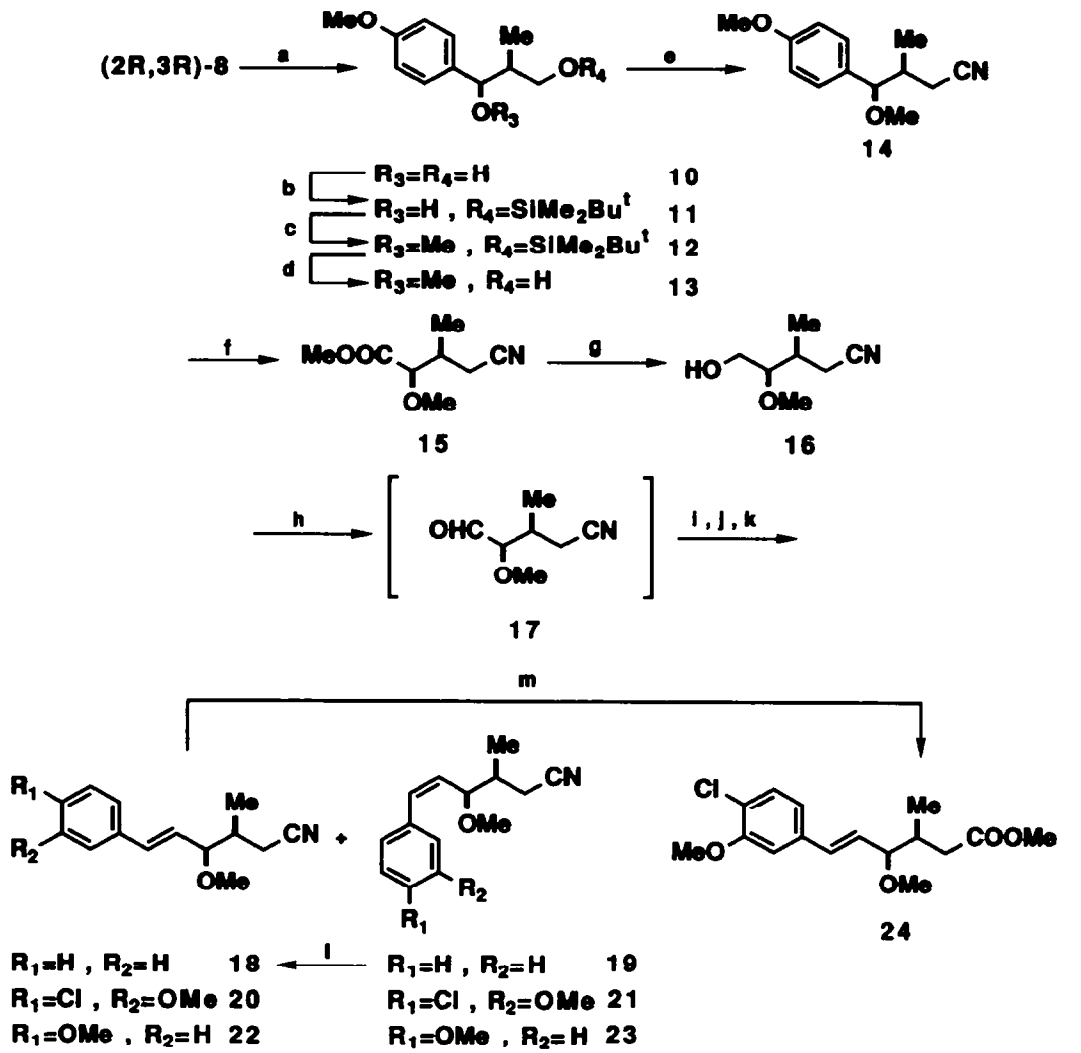
$R_1=R_2=H$	Oudemansin	A	2
$R_1=Cl$, $R_2=OMe$	Oudemansin	B	3
$R_1=OMe$, $R_2=H$	Oudemansin	X	4

Reformatsky reaction of *p*-methoxybenzaldehyde and α-bromopropionate gave a mixture of (±)-*syn*-**5** and (±)-*anti*-**6** (**5**/**6** = 100/65), which was oxidized with Jones' reagent to afford the β-keto ester **7**. Without further purification, by applying $Zn(BH_4)_2$ reduction procedure of α-methyl-β-keto ester,[5] the reduction of **7** produced as was expected the desired (±)-*syn*-**5**[6] in high diastereoselectivity (**5**/**6** = 31/1) and high overall yield (90%) from *p*-methoxybenzaldehyde. After small amounts of (±)-**6** was removed by SiO_2 column chromatography, (±)-**5** was converted into the corresponding (±)-acetate **8** in 97% yield. From a screening experiment, (±)-**8** was found to be hydrolyzed enantioselectively using the lipase "Amano A" from *Aspergillus niger* to afford alcohol **5** ($[\alpha]_D$ -16.4 (c=4.7, $CHCl_3$), 51% yield) in high enantiomeric excess (94% ee) along with the unchanged acetate **8** ($[\alpha]_D$ +47.3 (c=4.6, $CHCl_3$), 48% yield, >99% ee). The enantiomeric excesses of (-)-**5** and (+)-**8** were calculated based on NMR (400 MHz) data of the corresponding (+)-α-methoxy-α-trifluoromethylphenyl acetates[7] ((+)-MTPA esters: (+)-MTPA ester from (-)-**5**, δ 3.57, COOMe; (+)-MTPA

ester from (+)-**8**, δ 3.52, COOMe). The absolute structure of (-)-**5** was determined as follows. Ozonolysis of (-)-**5**-(+)-MTPA ester followed by the oxidative treatment and the subsequent esterification gave a diester **9**, whose NMR spectra were identical with those of the authentic (2S,3S)-**9**.[8] Consequently, (-)-**5** should possess (2S,3S)-configuration and thence the absolute configuration of (+)-**8** is determined to be 2R, 3R. For the purpose of enrichment of the enantiomeric purity of (-)-**5**, (-)-**5** was converted into the corresponding acetate **8**, which was recrystallized to give homochiral (2S,3S)-**8** (>99% ee).



Reduction of (2R,3R)-**8** gave the (+)-diol **10** ($[\alpha]_D$ +58.1 (c=1.04, $CHCl_3$), 94% yield), which was converted to the (+)-monosilyl ether **11** ($[\alpha]_D$ +31.5 c=1.52, $CHCl_3$), 97% yield). Methylation of (+)-**11** yielded the (+)-methoxy silyl ether **12** ($[\alpha]_D$ +44.9 (c=1.48, $CHCl_3$), 99% yield), which was converted to the (+)-methoxy alcohol **13** ($[\alpha]_D$ +7.67 (c=0.99, $CHCl_3$), 91% yield). Tosylation of (+)-**13** followed by treatment of NaCN afforded the (+)-methoxy nitrile **14** ($[\alpha]_D$ +34.4 (c=1.17, $CHCl_3$), in 94% overall yield). Ozonolysis of (+)-**14** followed by the oxidative treatment and the subsequent esterification provided the (+)-


(2R,3R)-8
a
MeO
Me
OR4
OR3
e
CN
OMe
14
b
R3=R4=H 10
R3=H , R4=SiMe2But 11
c
R3=Me , R4=SiMe2But 12
d
R3=Me , R4=H 13
f
MeOOC
g
HO
15
16
h
OHC
i , j , k
17
m
R1
R2
18
19
20
21
22
23
l
Cl
COOMe
24
a ; LiAlH4/THF b ; tBuMe2SiCl/imidazole/DMF c ; MeI/KH/THF d ; Bu4N+F- /THF
e ; 1) TsCl/pyridine 2) NaCN/DMSO f ; 1) O3/AcOEt 2) 30% H2O2 3) CH2N2 g ; LiBH4/THF
h ; PCC/CH2Cl2 i ; benzylphosphonium bromide/n-BuLi
j ; 4-chloro-3-methoxyphenylmethylene phosphonium bromide/n-BuLi
k ; 4-methoxyphenylmethylene phosphonium chloride/n-BuLi
l ; PhSH/AIBN/PhH,reflux m ; 1) KOH 2) H+ 3) CH2N2

methyl ester **15** ($[\alpha]_D$ +44.5 (c=1.18, $CHCl_3$)) in 39% overall yield, which was reduced to the alcohol **16** in 80% yield. Oxidation of **16** with pyridinium chlorochromate (PCC) followed by the individual treatment of phosphonium salt in the presence of n-BuLi produced a mixture of double bond formation products (**18-23**). That is to say, the Wittig reaction of **17** and benzylphosphonium bromide gave a mixture of (E)-**18** and (Z)-**19** in a ratio of ca 1:1 in 67% yield. This mixture was separated by SiO_2 column chromatography to (-)-**18** ($[\alpha]_D$ -32.9 (c=0.455, $CHCl_3$), $J_{7,8}$=16 Hz) and (+)-**19** ($[\alpha]_D$ +59.6 (c=0.305, $CHCl_3$), $J_{7,8}$=12 Hz). Isomerization of (Z)-**19** using thiophenol in the presence of 2,2'-azobisisobutyronitrile (AIBN) at reflux proceeded efficiently to afford (E)-**18** (70% yield) and the unchanged **19** (29% recovery yield). The physical data (IR and 400 MHz NMR) of the present obtained (E)-**18** were identical with those of the reported (E)-**18**.[1b] The Wittig alkenation of **17** and 4-chloro-3-methoxyphenylmethylene phosphonium bromide afforded a ca 1:1 mixture of (E)-**20** and (Z)-**21** in 57% yield, which was separated into (E)-**20** ([α]D -29.8 (c=1.05, $CHCl_3$), $J_{7,8}$=16 Hz) and (Z)-**21** ($[\alpha]_D$ +40.4 (c=0.91, $CHCl_3$), $J_{7,8}$=12 Hz). Conversionof (-)-**20** into the methyl ester **24** ($[\alpha]_D$ +10.1 (c=1.0, $CHCl_3$)) was achieved by the standard procedure (three steps) in overall 59% yield. The physical data (IR, NMR and $[\alpha]_D$) of the present synthesized (+)-**24** were identical with those of the reported (+)-**24** ($[\alpha]_D$ +10.23 ($CHCl_3$)).[2b] The third Wittig reaction of **17** and 4-methoxyphenylmethylene phosphonium chloride yielded a ca 1:1 mixture of (E)-**22** and (Z)-**23** in 73% yield, which was also separated into the (E)-**22** ($[\alpha]_D$ -35.0 (c=1.1, $CHCl_3$), $J_{7,8}$=16Hz) and (Z)-**23** ($[\alpha]_D$ +74.7 (c=1.08, $CHCl_3$), $J_{7,8}$=12 Hz). The physical data (IR,NMR and $[\alpha]_D$) of (-)-**22** were identical with those of the reported (-)-**22**.[3b,c] Conversion of (Z)-**23** into (E)-**22** was already reported.[3b] Thus obtained intermediates (-)-**18**, (-)-**20**, and (-)-**22** were already converted into the (-)-oudemansins A (**2**),[1b] B (**3**),[2b] and X (**4**)[3b,c], respectively.

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Reference and note

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