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Asymmetric synthesis of novel β-substituted β-methoxyacrylates bearing a chiral 1,2-*cis*-disubstituted cyclopropane substructure

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Abstract—The first asymmetric synthesis of β-substituted β-methoxyacrylate bearing a chiral 1,2-*cis*-disubstituted cyclopropane ring as a 'conformationally locked' substructure, by Claisen condensation and *E*-selective Wittig reaction was successfully achieved.

β-Methoxyacrylates (MOAs) including strobilurins (**1**) and oudemansins (**2**) inhibit the mitochondrial respiration pathway by interfering with the function of the cythochrome bc_1 complex.[1] Although these natural MOAs exhibit a broad spectrum of fungicidal activity, they could not be used as practical fungicides because of their photoinstability and high volatility. Extensive screenings of a number of analogues have, therefore, been carried out to overcome these problems, and Azoxystrobin (**3**), Kresoxim-methyl (**4**) etc., were developed as potent agricultural disinfectants.[2,3] However, the prevalence of resistant strains against these aromatic analogues has recently been reported as a serious problem.[4] On the other hand, β-substituted β-methoxyacrylates such as cystothiazoles (**5**)[5] and melithiazoles (**6**)[6], were recently isolated from nature as a new type of MOAs (Fig. 1). Both of these β-substituted MOAs include an oudemansin-type *syn*-9-methoxy-10-methyl substructure at the position corresponding to the 9-10 position of the original strobilurin skeleton. However, we assumed that this 'conformationally unlocked' 9-10 linkage is not ideal for their antifungal activities. Therefore, several studies to develop a novel and effective 9-10 linkage are now in progress in our laboratory. In the previous paper, the synthesis and antifungal activity of novel 9-methoxystrobilurin-type β-substituted MOAs was reported, and the superiority of 'conformationally locked' 9-methoxystrobilurin-type analogue compared with the corresponding oudemansin-type analogue was clearly demonstrated.[7,8] In this paper, we would like to describe the first and asymmetric synthesis of β-substituted MOAs bearing a chiral 1,2-*cis*-disubstituted cyclopropane ring as a 'conformationally locked' substructure (Fig. 2). While a similar interesting work concerning α-substituted MOAs was recently reported by Rossi et al.,[9] our present study can provide

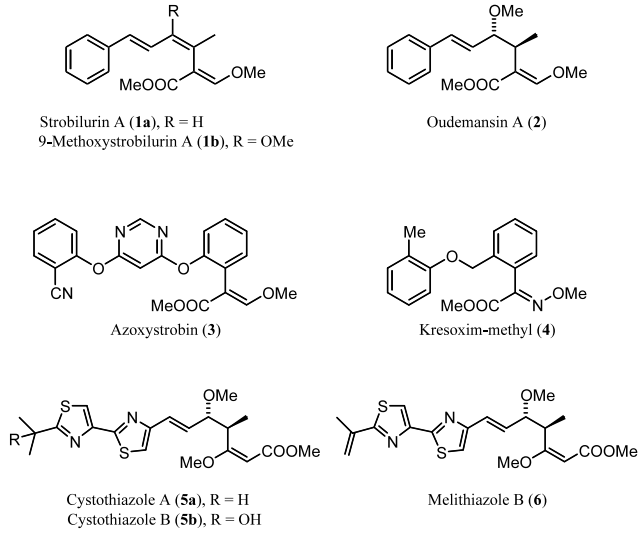

Figure 1. Structure of MOAs analogues.

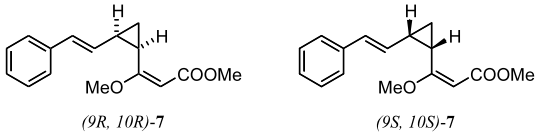

Figure 2. Structure of target molecules.

Keywords: β-substituted MOAs; cyclopropane.

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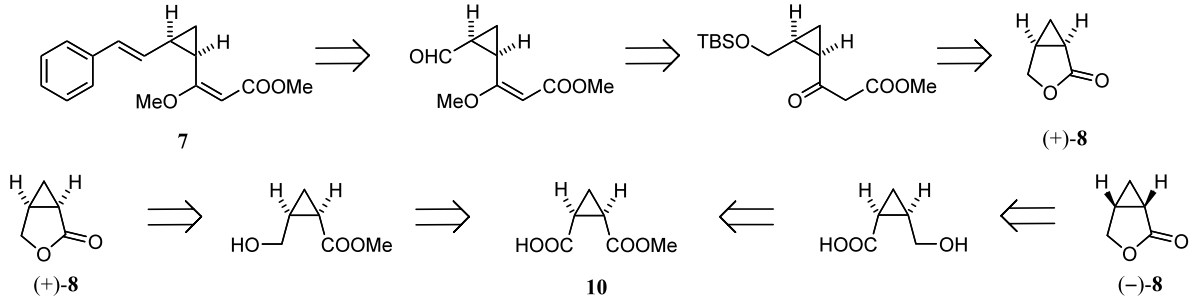
more precise information on the structure–activity relationships of the β-substituted analogues through the synthesis of chiral molecules.

A synthetic strategy for **7** from chiral cyclopropane **10** is shown in Scheme 1. The crucial steps in this strategy are (i) Claisen condensation of chiral lactone **8** with lithium enolate of methyl acetate, and (ii) efficient introduction of an aromatic moiety by *E*-selective Wittig reaction. The starting chiral lactone (+)-**8** and (−)-**8** would be easily prepared from dimethyl *meso*-cyclopropane-1,2-dicarboxylate **9** via an enzymatic enantioselective hydrolysis utilizing PLE (Porcine liver esterase)[10] and successive chemoselective reduction.

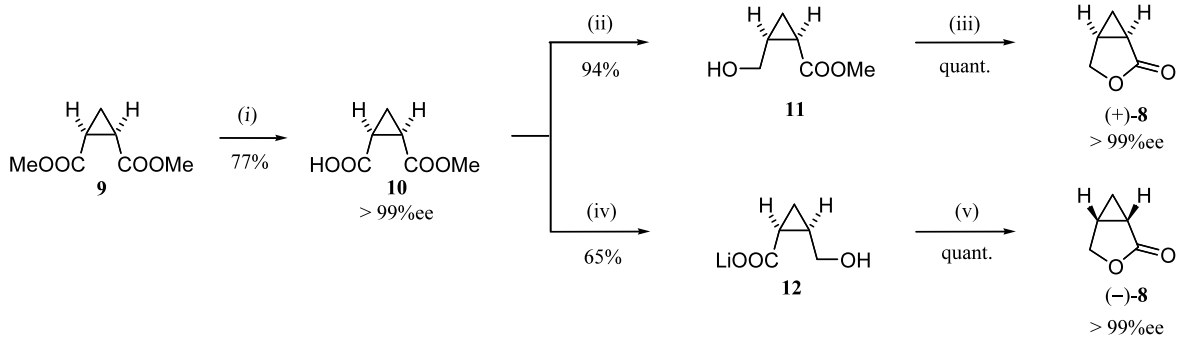
Chiral monoester **10** was prepared according to reported procedure, and a carboxylic acid moiety of **10** was selectively reduced by BH_3·THF to give the corresponding γ-hydroxylester **11**. The ester **11** was then treated with *p*-TsOH to obtain the chiral lactone (+)-**8** in quantitative yield. On the other hand, the ester moiety of **10** was also selectively reduced by $LiBH_4$ to afford the alcohol **12**, and was transformed to (−)-**8** quantitatively. The optical purities of (+)-**8** and (−)-**8** were determined as >99% ee[10,11] (Scheme 2).

With chiral lactones (+)-**8** and (−)-**8** in hand, we turned our attention to the formation of the β-substituted β-methoxyacrylate moiety. A reaction of the chiral lactone (+)-**8** with lithium enolate generated from methyl acetate was carried out. However, the desired β-ketoester was not isolated, and a cyclic ketal **13** was obtained only in 11% yield. The low yield might be due to the high water-solubility of **13**, and we attempted to trap the intermediate anion as the *tert*-butyldimethylsilyl ether. As a result, TBS-protected β-ketoester **15** and TBS-protected silyl enol ether **14** were obtained in 52 and 39% yields, respectively. The chemoselective desilylation of the silyl enol ether moiety of **14** was performed by stirring in THF–H_2O at room temperature for 9 h to give the TBS-protected β-ketoester **15**. For the formation of an *E*-β-methoxyacrylates moiety, TBS-protected β-ketoester **15** was treated with *tert*-BuOK and dimethyl sulfate in HMPA, and the desired *O*-methylated product **16** was obtained in 67% yield. On the other hand, when the same reaction was carried out in THF, an undesired *C*-methylated product was exclusively produced. Then, the silyl ether moiety of **16** was deprotected by the addition of $Et_3N(HF)_3$ in CH_2Cl_2 to give the corresponding alcohol **17** in 88% yield. The resulting alcohol **17** was converted to the aldehyde **18** by PCC oxidation. The aromatic moiety was finally introduced by *E*-selective Wittig reaction with phosphonium ylide prepared from benzyl tributyl phosphonium bromide and KHMDS.[12] The desired product (+)-**7**[13] was stereoselectively (*E*/*Z* >50/1) obtained in 63% yield (two steps). The synthesis of the enantiomer (−)-**7**[13] was also achieved from (−)-**8** by a similar procedure.

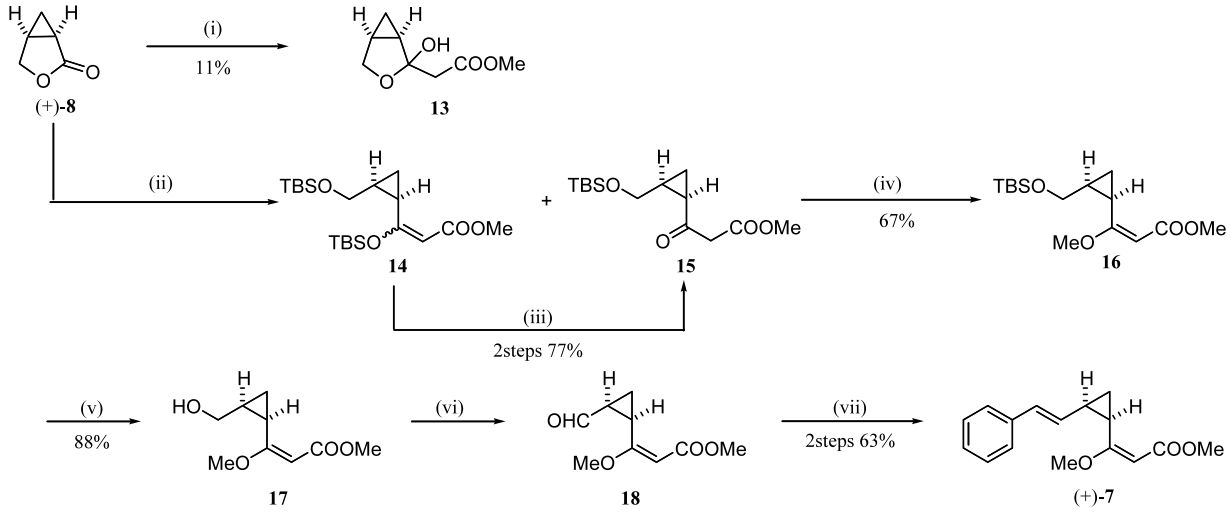
In conclusion, asymmetric synthesis of a 'conformationally locked' β-substituted β-methoxyacrylate bearing a chiral 1,2-*cis*-disubstituted cyclopropane substructure was successfully achieved. It is noted that the present synthetic method for the β-substituted MOAs starting from readily available chiral lactone would be applicable to the synthesis of various analogues having other types of 9-10 linkage by use of



Scheme 1. Retrosynthetic analysis of **7**.



Scheme 2. *Reagents and conditions*: (i) PLE, $NaHCO_3$, buffer pH 8, rt; (ii) BH_3·THF, THF, −20°C to rt; (iii) cat. TsOH, benzene, reflux; (iv) $LiBH_4$, THF, −20°C to rt; (v) TsOH, benzene, reflux.



Scheme 3. *Reagents and conditions*: (i) LDA, methyl acetate, THF, −78°C; (ii) LDA, methyl acetate, THF, −78°C, then TBSCl, HMPA, (iii) THF, H_2O, rt; (iv) Me_2SO_4, *tert*-BuOK, HMPA, rt; (v) $Et_3N(HF)_3$, CH_2Cl_2, rt; (vi) PCC, NaOAc, MS3A, CH_2Cl_2, rt; (vii) KHMDS, benzyltributylphosphoniumbromide, toluene, 0°C.

appropriate lactones. Further investigations on the structure–activity relationships of β-substituted MOAs and development of a novel pharmacologically superior analogue are now in progress (Scheme 3).

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11. Physical data of synthesized (+)-**8** and (−)-**8**; ^{1}H NMR (δ, 400 MHz, $CDCl_3$) 0.89 (dt, 1H, $J=3.4$, 4.6 Hz) 1.28 (ddd, 1H, $J=4.9$, 7.6, 9.0 Hz) 2.08 (m, 1H) 2.24 (m, 1H) 4.24 (d, 1H, $J=9.3$ Hz) 4.36 (dd, 1H, $J=4.8$, 9.3 Hz) ^{13}C NMR (δ, 100.4 MHz, $CDCl_3$) 12.3, 17.4, 17.6, 69.5, 176.5; $[\alpha]_D^{24}=+67.8$ (+)-**8** (*c* 1.20, $CHCl_3$), $[\alpha]_D^{27}=-68.0$ (−)-**8** (*c* 2.50, $CHCl_3$); HRMS calcd for $C_5H_6O_2$ (M^+) 98.0368, found 98.0383.
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13. Physical data of synthesized (+)-**7** and (−)-**7**; ^{1}H NMR (δ, 500 MHz, $CDCl_3$) 1.22 (dt, 1H, $J=4.9$, 8.2 Hz) 1.44 (dt, 1H, $J=4.9$, 6.4 Hz) 2.17 (ddt, 1H, $J=6.4$, 8.9, 9.2 Hz) 3.40 (dt, 1H, $J=6.7$, 8.6 Hz) 3.65 (s, 3H) 3.67 (s, 3H) 5.13 (s, 1H) 5.95 (dd, 1H, $J=9.2$, 15.6 Hz) 6.53 (d, 1H, $J=15.6$ Hz) 7.15–7.34 (m, 5H); ^{13}C NMR (δ, 125.6 MHz, $CDCl_3$) 12.6, 21.0, 25.0, 50.7, 55.2, 92.0, 125.7, 126.7, 128.5, 128.7, 130.7, 137.7, 168.4, 173.0; $[\alpha]_D^{24}=+683$ (+)-**7** (*c* 0.040, $CHCl_3$), $[\alpha]_D^{24}=-639$ (−)-**7** (*c* 0.548, $CHCl_3$); HRMS calcd for $C_{16}H_{18}O_3$ (M^+) 258.1256, found 258.125.