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Synthetic Studies on Tautomycin Synthesis of 2,3-Disubstituted Maleic Anhydride Segment

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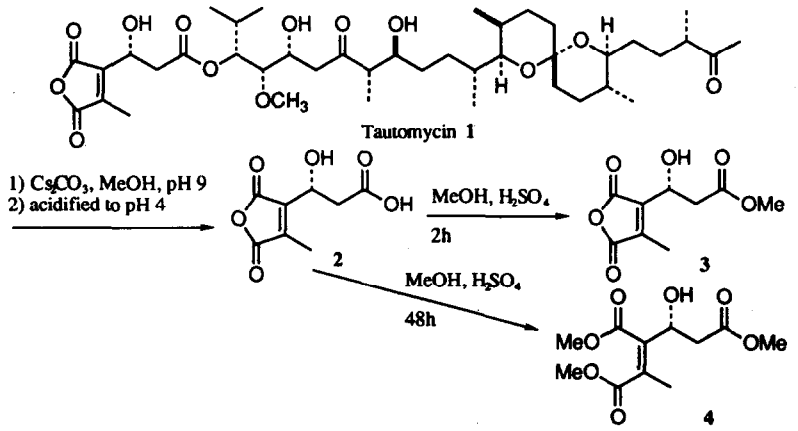
Abstract: The 2,3-disubstituted maleic anhydride segment of tautomycin has been synthesized in optically active form. Oxidation of 3,4-disubstituted furan employing singlet oxygen completes the construction of the maleic anhydride moiety. Esterification of the maleic anhydride segment without protecting anhydride moiety resulted in the successful coupling reaction with fragment derived from tautomycin.

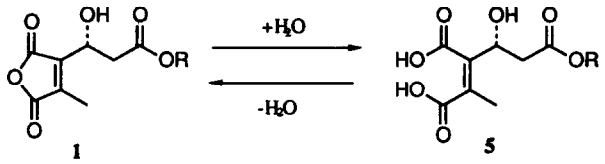
In 1987 Isono and co-workers reported isolation of tautomycin **1** from *Streptomyces spiroverticillatus* as a new antibiotic with strong antifungal activity against *Sclerotinia sclerotiorum*.[1] This antibiotic induces the morphological change (bleb formation) in human leukemia cells K562, and inhibits type 1 and type 2A protein phosphatases.[2] This interesting biological activity prompted us to contribute the chemical transformation and establishing the stereochemistry as shown below.[3] In these structural studies, Isono and co-workers also reported isolation of the 2,3-disubstituted maleic anhydride segment **3** and its trimethyl ester **4** derived from **1** as shown in Scheme 1.[4]



Scheme 1

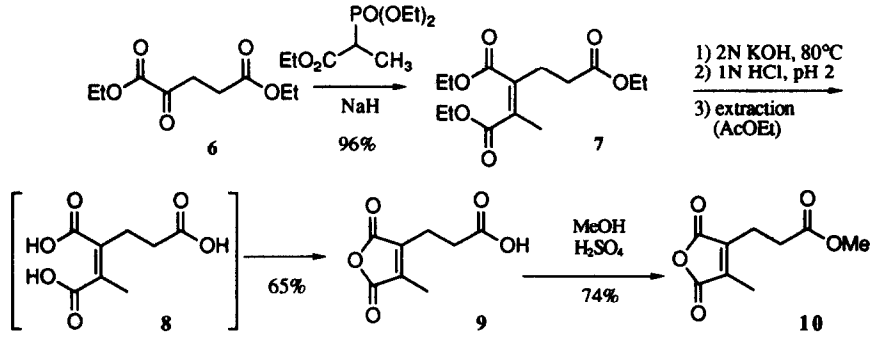
The important biological activities as well as its interesting structure led us to study the synthesis of this molecule. This manuscript reports the synthesis of the 2,3-disubstituted maleic anhydride segment **3** and its opposite enantiomer in optically active form.[5]

Synthesis of the Model Compound. The maleic anhydride moiety of tautomycin showed an interesting chemical behavior: purified tautomycin gave two peaks on HPLC due to equilibrium between anhydride **1** and diacid **5** in aqueous media.[1]



1 **5**

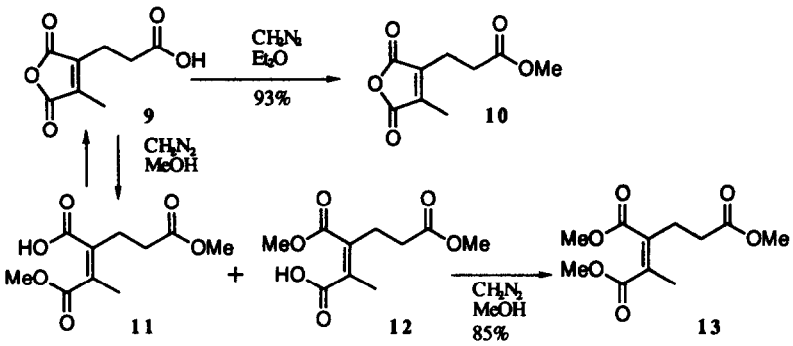
At the beginning of this work, we synthesized a model compound with 2,3-disubstituted maleic anhydride structure to confirm the chemical properties of the anhydride (Scheme 2). Stereoselective Horner-Emmons condensation of α-ketoester has been used for the construction of the maleic acid structure.[6] Accordingly, reaction of diethyl 2-ketoglutarate **6** with triethyl α-phosphonopropionate exclusively provided the maleic ester **7** in 96% yield. This triester **7** was hydrolyzed with aqueous 2N potassium hydroxide in ethanol at 80 °C for 2.5 h. In the work-up of this hydrolysis, pH adjustment of the reaction mixture to lower than pH 4 was crucial for isolating **9** with an anhydride structure.[7] In fact, adjustment of the reaction mixture to pH 2 with 1N hydrogen chloride and extraction with ethyl acetate resulted in the ring closure of the maleic acid **8** to furnish the 2,3-disubstituted maleic anhydride **9** in 65% yield. Esterification of **9** with a mixture of methanol and conc. sulfuric acid (10:1)[4] provided the monomethyl ester **10** in 74% yield. The structure of compound **10** was evident from spectroscopic data [UV (CH_3CN) λ_{max} 250 nm; IR (KBr) ν_{max} 1830, 1760 cm^{-1}] which supported the existence of the 2,3-disubstituted maleic anhydride moiety.[3]



6 **7** **8** **9** **10**

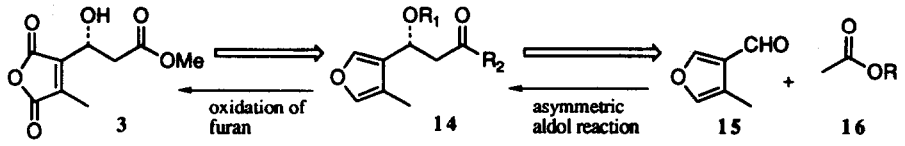
Scheme 2

The esterification procedure required a drastic condition using conc. sulfuric acid (Scheme 2). Scheme 3 illustrates an alternative esterificaton using diazomethane under neutral condition. Reaction of the acid **9** with diazometnane in ether solvent furnished the monomethyl ester **10** in 93% yield. Use of methanol as solvent provided the trimethyl ester **13** in 85% yield. These different products depending on the solvent are due to the fact that the anhydride ring opened by attack of methanol, and the half ester either **11** or **12** were subsequently esterified with diazomethane.



Scheme 3

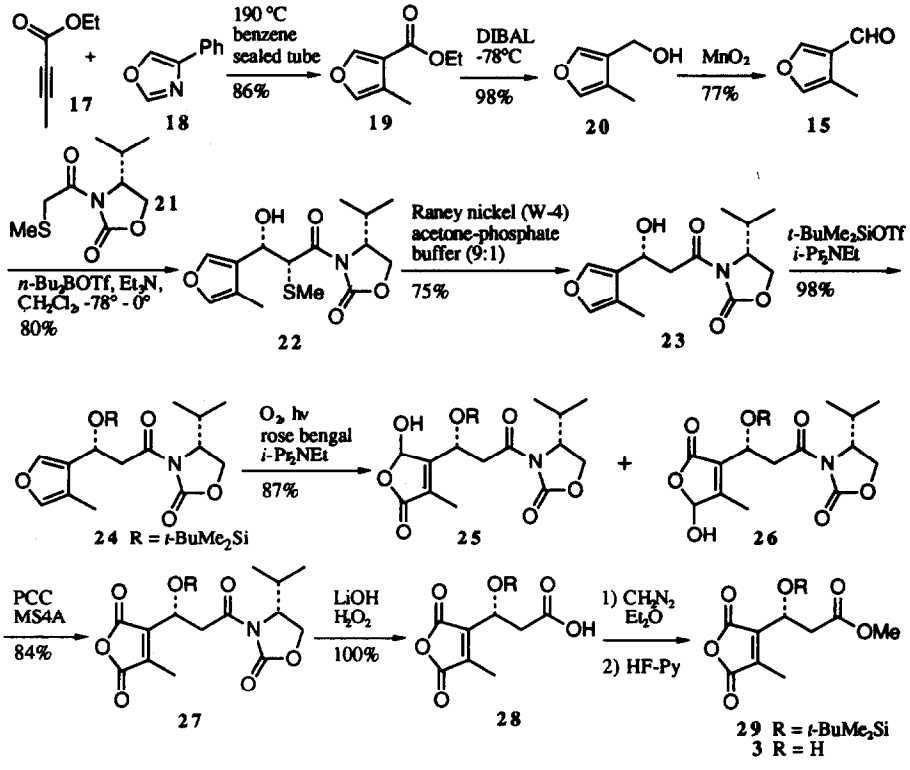
Synthesis of the 2,3-Disubstituted Maleic Anhydride Segment 3. The 2,3-disubstituted maleic anhydride segment **3** is highly oxygenated molecule with three carboxylic groups and one hydroxy group. From the standpoint of synthesis, it is desirable to prepare the anhydride moiety at the final stage of the synthesis. Moreover, we need both enantiomers of this segment for investigating the structure-activity relationship to the protein phosphatase inhibition. On the basis of these background, we planned to construct the 2,3-disubstituted maleic anhydride moiety through oxidation of 3,4-disubstituted furan **14**, and the asymmetric center could be set up by asymmetric aldol reaction between aldehyde **15** and ester **16** (Scheme 4). The synthesis along this line is depicted in Scheme 5.



Scheme 4

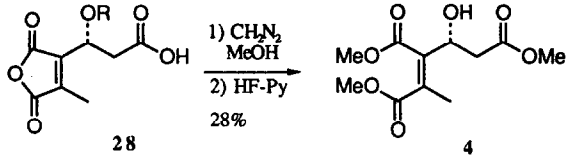
Diels-Alder addition of ethyl tetrolate **17** with 4-phenyloxazole **18** and spontaneous retro-Diels-Alder reaction with elimination of benzonitrile proceeded at a temperature of 190 °C for 24 h to furnish the 3,4-disubstituted furan **19** in 86% yield.[8] Reduction of the ester **19** with diisobutylaluminum hydride and subsequent oxidation with activated manganese (IV) oxide gave the aldehyde **15** in 75% yield. We chose asymmetric aldol condensation involving chiral oxazolidinone boron enolate developed by Evans.[9] Accordingly, the aldol reaction between boron enolate of chiral *N*-acetyloxazolidinone **21** (prepared from D-valine)[10] and the aldehyde **15** exclusively provided the aldol adduct **22** in 80% yield. Desulfurizaion of **22** using Raney nickel (W-4 type) in acetone resulted in affording a mixture of **23** and β-elimination product. This side reaction was avoided by employing a mixture of acetone and pH 7 phosphate buffer (9:1) as the reaction media, in which only **23** was obtained in 75% yield. The stereochemical assignment of the alcohol **23** was initially made to be *R* based on the paper of Evans. This assignment was further confirmed by using modified Mosher's method (see the experimental section).[11] Protection of the hydroxy group as *t*-butyldimethylsilyl ether gave **24** quantitatively. Photosensitized oxidation of the furan **24** by a 500W tungsten incandescent lamp under oxygen atmosphere in the presence of rose bengal and diisopropylethylamine at -20 °C gave a regioisomeric mixture of 2,3-disubstituted-4-hydroxy-butenolides **25** and **26** (4:1) in 87% combined yield.[12] Pyridinium chlorochromate oxidation of the mixture **25** and **26** in the presence of powdered and activated molecular sieves 4A furnished the maleic anhydride **27** in 84% yield. Removal of the auxiliary with lithium hydroperoxide gave the acid **28**, which was in turn esterified with

diazomethane in ether to provide the monomethyl ester **29**. Finally *t*-butyldimethylsilyl group was removed with pyridinium poly(hydrogen fluoride)pyridine complex to furnish the 2,3-disubstituted maleic anhydride segment **3**. The spectroscopic data (UV, IR, NMR) and TLC behavior of our synthetic material proved it to be identical with those of authentic sample derived from natural tautomycin.

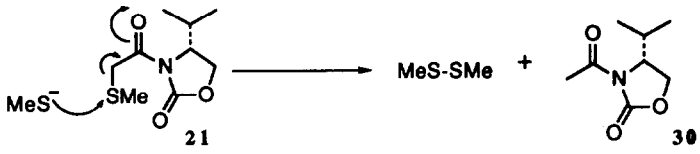


Scheme 5

Finally the acid **28** was transformed into the trimethyl ester **4** by treatment with diazomethane in methanol and deprotection of *t*-butyldimethylsilyl group with pyridinium poly(hydrogen fluoride)pyridine in 28% yield. The spectroscopic data (IR, ^{1}H and ^{13}C NMR) and the optical rotation ($[\alpha]_D^{27}$ -16.7°, *c* 0.49 in $CHCl_3$) were identical with those reported by Ubukata ($[\alpha]_D^{25}$ -16.3°, *c* 0.3 in $CHCl_3$).[4] This confirmed the structure of our synthetic material as well as naturally occurring maleic anhydride segment **3** to be *R* configuration.

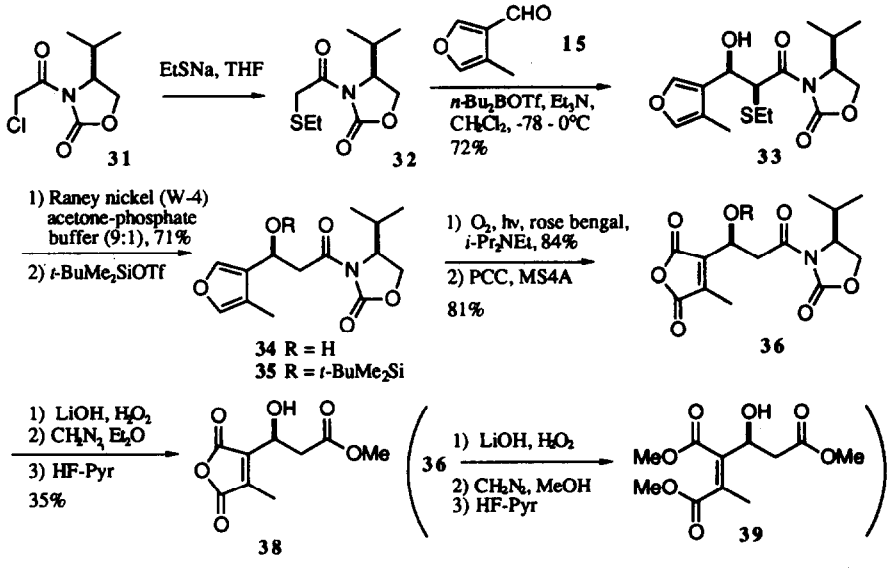


Synthesis of the (S)-Enantiomer of Segment 3. During preparation of the oxazolidinone **21**, we observed that use of methanethiol sometimes resulted in variable yields due to the unstable nature of **21** under reaction conditions. This may be explained by a nucleophilic attack of the excess methanethiolate on sulfur of **21** to afford the reduction product **30** as shown below.[14]



21 **30**

To avoid this problem, stoichiometric amount of thiolate was necessary. In this context, we used ethanethiolate for the preparation of chiral oxazolidinone, because methanethiol was volatile and difficult to handle. Thus, in the synthesis of (*S*)-enantiomer **38**, we used the oxazolidinone **32** prepared from L-valine. The synthesis along this line is shown in Scheme 6. Aldol reaction of boron enolate derived from dibutylboron triflate and chiral oxazolidinone **32** with aldehyde **15** furnished aldol adduct **33** in 72% yield. Removal of ethylsulfide moiety of **33** by Raney nickel (W-4) in a mixture of acetone and pH 7 phosphate buffer provided **34** in 71% yield. Further transformation of **34** furnished the (*S*)-enantiomer **38** by the identical procedure described in Scheme 5. The trimethyl ester **39** derived from **36** showed positive sign in an optical rotation ($[\alpha]_D^{25}$ +18.4°, *c* 0.21, $CHCl_3$) to show opposite enantiomer of natural form.

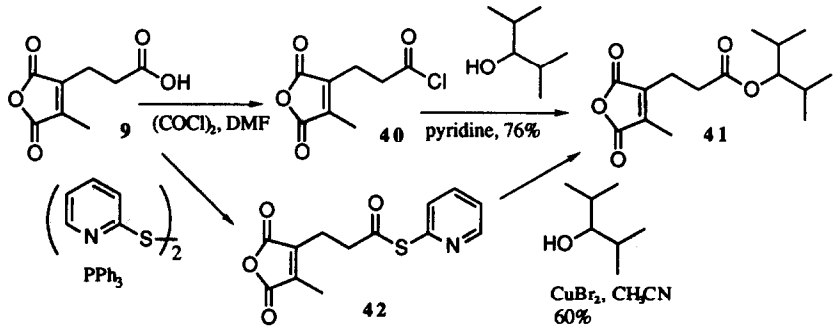


31 **32** **33** **36** **38** **39**

Scheme 6

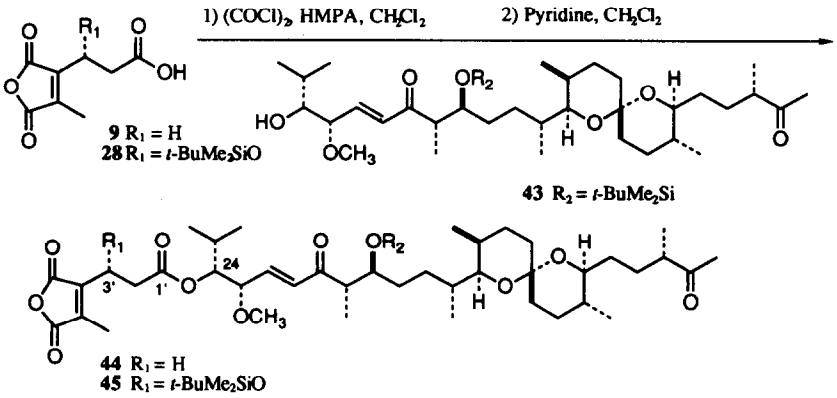
Coupling Reaction. The free acid of model compound **9** has to be more activated than the anhydride moiety for the subsequent coupling with alcohol segment. Two methods for activation of the model compound **9** were initially examined (Scheme 7). Reaction of **9** with oxalyl chloride in the presence of a catalytic amount of dimethylformamide completed the conversion into the corresponding acid chloride **40**.[15] Esterification of this acid chloride **40** with 2,4-dimethyl-3-pentanol and pyridine proceeded smoothly to provide the ester **41** in

76% yield from the acid **9**. Secondly, copper ion promoted esterification of the *S*-2-pyridyl thioate **42** also provided **41** in 60% yield from the acid **9**.[16]



Scheme 7

Based on these experiments using 2,4-dimethyl-3-pentanol as a model alcohol, esterification of **43** prepared from natural tauomycin was secured.[17] Two methods shown in Scheme 7 failed with no detectable coupling product, and only formate of **43** was isolated in the coupling reaction between the acid chloride **40** and the alcohol **43**. After these trials, we found that the acid chloride **40** prepared by oxalyl chloride with a catalytic amount of hexamethylphosphoramide[18] successfully reacted with **43** to furnish the coupling product **44** in 88% yield [**44**: ^{1}H NMR δ 4.97 (1H, dd, *J* = 7, 5 Hz, H-24), FABMS *m/z* 847 (M^++H)]. The reaction of the 2,3-disubstituted maleic anhydride segment **28** and **43** also provided the coupling product **45** in 29% yield [**45**: ^{1}H NMR δ 4.91 (1H, dd, *J* = 8, 4 Hz, H-24), 5.13 (1H, m, H-3'), FABMS *m/z* 977 (M^++H); IR ν_{max} 1850, 1770 cm^{-1}].



Scheme 8

These experiments clearly demonstrated the efficiency of the coupling reaction by activating the acid **28** without protection of the maleic anhydride moiety. Further synthetic studies along this line is now under investigation.

Experimental Section

General: Melting points were recorded on a Yanaco MP-S3 melting point apparatus and are not corrected. Infrared spectra were recorded on a JASCO FT/IR-8300 spectrophotometer and are reported in wave number (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a JEOL EX-270 and a BRUKER ARX-400 spectrometer. Low resolution mass spectra (EI) were recorded on a JEOL JMS-D 100 spectrometer. High-resolution mass spectra (HRMS) were recorded on a JEOL DX-705L spectrometer and reported in *m/z*. Elemental analysis were performed by Mr. S. Kitamura in Analytical Laboratory at Faculty of Agriculture, Nagoya University to whom the authors gratefully acknowledge.

Diethyl 2,3-Disubstituted Malelate 7. To a suspension of sodium hydride (0.98 g, 24.5 mmol, washed with hexane three times) in tetrahydrofuran (120 ml) was added a solution of phosphoryl propionate (7.14 g, 30 mmol) in tetrahydrofuran (20 ml). After the evolution of hydrogen ceased, a solution of diethyl ketoglutarate **6** (4 g, 20 mmol) in tetrahydrofuran (20 ml) was added, and stirring was continued for 30 min. The solution was poured into saturated aq. NH_4Cl and extracted with ether. The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford the crude product (8.3 g). Purification by silica gel chromatography with a mixture of ether/hexane (2:1) afforded triethyl ester **7** (5.5 g, 96%, colorless oil). UV (CH_3CN) λ_{max} (log ε) 210 (4.0) nm. IR (KBr) ν_{max} 1730, 1650 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.26 (3H, t, J = 7.5 Hz, CH_2CH_3), 1.29 (6H, t, J = 7.5 Hz, CH_2CH_3 × 2), 2.00 (3H, s, C=C-CH_3), 2.40-2.60 (4H, m, $CH_2CH_2CO_2Et$), 4.14 (2H, q, J = 7.5 Hz, CH_2CH_3), 4.22 (2H, q, J = 7.5 Hz, CH_2CH_3), 4.23 (2H, q, J = 7.5 Hz, CH_2CH_3). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 13.9 (× 2), 14.1, 15.4, 24.9, 32.2, 60.5, 61.00, 61.03, 134.7, 135.5, 167.9, 168.6, 172.2. EI-MS *m/z* 286 (M^+). Anal. Calcd for $C_{16}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 58.77; H, 7.70.

2,3-Disubstituted Maleic Anhydride 9. A solution of triethyl ester **7** (2 g, 7 mmol) dissolved in a mixture of 2 N aq. KOH (17 ml, 35 mmol) and ethanol (60 ml) was heated under reflux for 1 h. The resulting solution was diluted with water, and ethanol was removed by evaporation. The aqueous solution was washed with dichloromethane and acidified with 1 N aq. HCl to pH 2. The resulting aqueous solution was extracted with ethyl acetate. Concentration under reduced pressure gave the crude product (1.2 g), which was recrystallized from dichloromethane/hexane to provide maleic anhydride **9** (0.84 g, 65%, white needle). Mp 96-97 °C. UV (CH_3CN) λ_{max} (log ε) 201 (4.1), 252 (3.9) nm. IR (KBr) ν_{max} 1820, 1760 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 2.13 (3H, s, C=C-CH_3), 2.80 (4H, s, $CH_2CH_2CO_2H$), 10.2 (1H, brd, CO_2H). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 9.6, 19.5, 30.7, 141.8, 142.4, 165.5, 165.7, 177.4. Anal. Calcd for $C_8H_8O_5$: C, 52.18; H, 4.38. Found: C, 52.10; H, 4.39.

2,3-Disubstituted Maleic Anhydride Monomethyl Ester 10. A solution of **9** (50 mg, 0.27 mmol) dissolved in methanol (2 ml) was stirred for 4 h under nitrogen in the presence of 1 N H_2SO_4 (methanol solution, 0.05 ml, 0.05 mmol). The solvent was removed by evaporation, and the residue was diluted with water. The aqueous solution was extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and concentrated to afford the residue (51 mg). Purification by silica gel chromatography with a mixture of ether/hexane (2:1) afforded monomethyl ester **10** (40 mg, 74%, an oil).

A solution of **9** (20 mg, 0.11 mmol) in ether (1 ml) was treated with a solution of diazomethane in ether at 0 °C until the starting material disappeared (checked by TLC analysis). Acetic acid (1 drop) was added to the solution to quench the excess diazomethane. Concentration under reduced pressure afforded an oil (22 mg), which was purified by silica gel chromatography with a mixture of ether/hexane (1:1) to give monomethyl ester **10** (20 mg, 93%). UV (CH_3CN) λ_{max} (log ε) 204 (4.1), 249 (3.8) nm. IR (KBr) ν_{max} 1830, 1770, 1730, 1680 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 2.14 (3H, s, C=C-CH_3), 2.66-2.82 (4H, m, $CH_2CH_2CO_2Me$), 3.69 (3H, s, CO_2CH_3). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 9.6, 19.8, 30.8, 52.0, 142.18, 142.23, 165.5, 165.8, 172.0. EI-MS *m/z* 198 (M^+), 167 (M^+-31). Anal. Calcd for $C_9H_{10}O_5$: C, 54.55; H, 5.09. Found: C, 54.48; H, 5.25.

Trimethyl Ester of Model Compound 13. To a solution of **9** (20 mg, 0.11 mmol) in methanol (1 ml) was added a solution of diazomethane at 0 °C until the solution became yellow. The solution was stirred for 15 min and acetic acid (1 drop) was added. Concentration of the solvent provided an oil (27 mg), which was purified by silica gel chromatography with a mixture of ether/hexane (1:1) to afford trimethyl ester **13** (23 mg, 85 %). IR (film) ν_{max} 1770, 1730, 1650 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 2.01 (3H, s, C=C-C*H*$_3$), 2.48 (2H, t, J = 8 Hz, C*H*$_2$), 2.68 (2H, t, J = 8 Hz, C*H*$_2$), 3.69 (3H, S, CO_2CH_3), 3.76 (6H, s, $CO_2CH_3 \times 3$). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 15.5, 35.7, 31.9, 51.7, 52.20, 52.24, 135.1, 135.3, 168.4, 169.2, 172.6. Anal. Calcd for $C_{11}H_{16}O_6$: C, 54.09; H, 6.60. Found: C, 54.16; H, 6.72.

3-Methyl-4-(Ethoxycarbonyl)furan 19. A sealed-tubed flask was charged with 4-phenyloxazole (14.5 g, 0.1 mol), ethyl tetrolate (11.2 g, 0.1 mol), dihydroquinone (100 mg, 0.53 mmol) and benzene (10 ml). The reaction mixture was heated at 190 °C for 24 h, and then concentrated under reduced pressure. Purification of the resulting residue by silica gel chromatography with a mixture of ether/hexane (1:20 to 1:5) provided 3-methyl-4-ethoxycarbonyl furan **19** (11.9 g, 77%). UV (CH_3CN) λ_{max} 207 nm. IR (KBr) ν_{max} 3150, 2990, 1710 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 1.35 (3H, t, J = 8 Hz, CH_2CH_3), 2.20 (3H, d, J = 1 Hz, Ar-C*H*$_3$), 4.29 (2H, q, J = 8 Hz, C*H*$_2$CH$_3$), 7.21 (1H, m, Ar), 7.95 (1H, d, J = 2 Hz, Ar). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 9.0, 14.2, 59.9, 120.4 (× 2), 140.8, 148.5, 163.6. EI-MS *m/z* 154 (M^+). HRMS calcd for $C_8H_{10}O_3$; 154.0630, found 154.0617.

3-Methyl-4-(Hydroxymethyl)furan 20. Diisobutylaluminum hydride (1 M solution in hexane, 11.4 ml, 11.4 mmol) was added to a solution of **19** (795 mg, 5.2 mmol) in dichloromethane (25 ml) at -78 °C under argon atmosphere. After stirring at -78 °C for 10 min, the cooling bath was removed and stirring was continued at room temperature for 50 min. The solution was neutralized with 1N HCl, and saturated aq. potassium sodium tartrate was added. The aqueous layer was extracted with ether, and combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford a residue (610 mg), which was purified by silica gel chromatography with ether to furnish 3-methyl-4-(hydroxymethyl)furan **20** (569 mg, 98%). IR (KBr) ν_{max} 3290, 2920, 1550 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 2.01 (3H, d, J = 1 Hz, Ar-C*H*$_3$), 2.54 (1H, brd, O*H*), 4.44 (2H, s, C*H*$_2$OH), 7.16 (1H, m, Ar), 7.31 (1H, s, Ar). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 7.7, 51.1, 119.4, 125.1, 140.0, 140.5. EI-MS *m/z* 112 (M^+). HRMS calcd for $C_6H_8O_2$; 112.0524, found 112.0519.

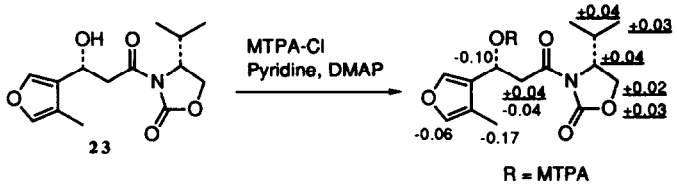
3-Methyl-4-Formylfuran 15. A solution of **20** (4.45 g, 41 mmol) and activated manganese(IV) oxide (51.5 g, 0.4 mol) in dichloromethane (100 ml) was stirred vigorously at room temperature for 22 h under nitrogen atmosphere. The reaction mixture was filtered and the filtrate was concentrated under reduced pressure to afford 3-methyl-4-formylfuran **15** (3.4 g, 77%). UV (CH_3CN) λ_{max} 204, 256 nm. IR (KBr) ν_{max} 1690, 1540 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 2.21 (3H, d, J = 1 Hz, Ar-C*H*$_3$), 7.22 (1H, m, Ar), 7.97 (2H, d, J = 2 Hz, Ar), 9.93 (1H, s, C*H*O). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 8.7, 119.1, 127.7, 141.8, 152.9, 185.6. HRMS calcd for $C_6H_6O_2$; 110.0368, found 110.0360.

Aldol Reaction between Chiral Oxazolidinone 21 and Furan 15 to Aldol Adduct 22. To a cooled solution of oxazolidinone **21** (929 mg, 4.28 mmol) in dichloromethane (10 ml) under argon atmosphere at 0 °C was added dropwise dibutylboron triflate (1.0 M solution in dichloromethane, 5.14 ml, 5.14 mmol) and triethylamine (0.77 ml, 5.56 mmol) in this sequence. After stirring at 0 °C for 30 min, the solution was cooled to -78 °C, and 3-methyl-4-formylfuran **15** (518 mg, 4.71 mmol) in dichloromethane (2 ml) was added. The reaction mixture was stirred for 20 min at -78 °C, and then for 1 h at 0 °C. The mixture was quenched by the addition of pH 7 aqueous phosphate buffer (5 ml) and methanol (15 ml). To this solution was added a mixture of 2 : 1 methanol/30% hydrogen peroxide (15 ml) at such a rate as to keep the internal temperature below +10 °C. After stirring for an additional 1 h, the methanol was removed under reduced pressure, and the resulting slurry was extracted with ether. The combined organic extracts were washed with 5% aq. $NaHCO_3$ and brine and concentrated to afford crude oil (1.46 g), which was purified by silica gel chromatography with a mixture of ether/hexane (1:1) to furnish aldol adduct **22** (1.13 g, 80%). Mp 90-91 °C. UV (CH_3CN) λ_{max} (log ε) 209 (4.1), 268 (3.1) nm. IR (KBr) ν_{max} 3500, 1770, 1690 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (3H, d, J = 6 Hz, $CH(CH_3)_2$), 0.94 (3H, d, J = 6 Hz, $CH(CH_3)_2$), 2.07

(3H, s, Ar-C*H*$_3$), 2.19 (3H, s, SC*H*$_3$), 2.33 (1H, m, C*H*(CH$_3$)$_2$), 3.08 (1H, brd, O*H*), 4.21 (2H, m, OC*H*$_2$CH*i*-Pr), 4.38 (1H, dt, *J* = 7, 4 Hz, NC*Hi*-Pr), 4.98 (1H, d, *J* = 9 Hz, C*H*SMe), 5.23 (1H, d, *J* = 9 Hz, C*H*OH), 7.15 (1H, m, Ar), 7.39 (1H, d, *J* = 1 Hz, Ar). ^{13}C NMR (CDCl$_3$, 67.9 MHz) δ 8.4, 12.2, 14.5, 17.8, 28.2, 49.8, 58.0, 62.7, 63.0, 119.3, 124.4, 140.3, 141.2, 153.4, 168.9. EI-MS *m/z* 327 (M$^+$). $[\alpha]_D^{27}$ -36.8° (*c* 0.21, CHCl$_3$). Anal. Calcd for $C_{15}H_{21}O_5NS$: C, 55.03; H, 6.47; N, 4.28. Found: C, 55.15; H, 6.42; N, 4.14.

Desulfrization of the Aldol Adduct 22 to Furan 23 with Raney Nickel. Raney nickel (W-4, 4g) was added to a solution of **22** (1 g, 3.06 mmol) in a mixture of acetone (45 ml) and pH 7 phosphate buffer (5 ml) under nitrogen. After stirring for 30 min at room temperature, the reaction mixture was filtered to remove Raney nickel. Concentration of the filtrate afforded a crude product (902 mg), which was purified by recrystallization from acetone and hexane to yield furan **23** (648 mg, 75%, white needle). Mp 99-100 °C. UV (CH$_3$CN) λ_{max} (log ε) 204 (4.2) nm. IR (KBr) ν_{max} 3350, 1780, 1710 cm^{-1}. ^{1}H NMR (CDCl$_3$, 270 MHz) δ 0.87 (3H, d, *J* = 7 Hz, CH(C*H*$_3$)$_2$), 0.93 (3H, d, *J* = 7 Hz, CH(C*H*$_3$)$_2$), 2.06 (3H, d, *J* = 1 Hz, Ar-C*H*$_3$), 2.39 (1H, m, C*H*(CH$_3$)$_2$), 3.20 (1H, brd, O*H*), 3.28 (1H, dd, *J* = 17, 3 Hz, C*H*2CON), 3.51 (1H, dd, *J* = 17, 9.5 Hz, C*H*2CON), 4.26 (2H, m, OC*H*$_2$CH*i*-Pr), 4.47 (1H, dt, *J* = 7.5, 3.5 Hz, NC*Hi*-Pr), 5.11 (1H, dd, *J* = 9.5, 3 Hz, C*H*OH), 7.16 (1H, m, Ar), 7.36 (1H, s, Ar). ^{13}C NMR (CDCl$_3$, 67.9 MHz) δ 8.4, 14.6, 17.9, 28.4, 42.2, 58.4, 62.9, 63.6, 118.8, 127.0, 139.7, 140.3, 154.0, 172.2. EI-MS *m/z* 281 (M$^+$). $[\alpha]_D^{27}$ -22.3° (*c* 0.24, CHCl$_3$). Anal. Calcd for $C_{14}H_{19}O_5N$: C, 59.78; H, 6.81; N, 4.98. Found: C, 60.05; H, 6.55; N, 4.82.

Stereochemical Assignment of Furan 23. Furan **23** was transformed into the corresponding (*S*)- and (*R*)-MTPA esters by standard conditions. Examination of the Δδ values (δ_S - δ_R) obtained for the (*S*)- and (*R*)-MTPA esters are summarized below. These Δδ values clearly determined the stereogenic center to be *R* configuration based on the model of MTPA plane.[11]



***t*-Butyldimethylsilyl Ether 24.** To a solution of **23** (300 mg, 1.07 mmol) and diisopropylethylamine (0.37 ml, 2.14 mmol) in dichloromethane (10 ml) cooled to 0 °C under argon atmosphere was added *t*-butyldimethylsilyl trifluoromethanesulfonate (0.37 ml, 1.61 mmol). After stirring for 30 min at 0 °C, the reaction mixture was quenched by the addition of saturated aq. NH$_4$Cl. The separated aqueous layer was extracted with dichloromethane and the combined organic extracts were washed with water, dried (Na$_2$SO$_4$), and concentrated to afford a residue (550 mg), which was purified by silica gel chromatography with a mixture of ether/hexane (1:2) to afford *t*-butyldimethylsilyl ether **24** (440 mg, quantitatively, colorless oil). UV (CH$_3$CN) λ_{max} (log ε) 203 (4.2) nm. IR (KBr) ν_{max} 1760, 1700 cm^{-1}. ^{1}H NMR (CDCl$_3$, 270 MHz) δ -0.09 (3H, s, SiC*H*$_3$), 0.04 (3H, s, SiC*H*$_3$), 0.83 (9H, s, Si*t-Bu*), 0.86 (3H, d, *J* = 7 Hz, CH(C*H*$_3$)$_2$), 0.91 (3H, d, *J* = 7 Hz, CH(C*H*$_3$)$_2$), 2.08 (3H, d, *J* = 1 Hz, Ar-C*H*$_3$), 2.37 (1H, m, C*H*(CH$_3$)$_2$), 3.28 (1H, dd, *J* = 16.5, 4.5 Hz, C*H*2COON), 3.58 (1H, dd, *J* = 16.5, 8.5 Hz, C*H*2COON), 4.21 (2H, m, OC*H*$_2$CH*i*-Pr), 4.40 (1H, dt, *J* = 7, 4 Hz, NC*Hi*-Pr), 5.26 (1H, dd, *J* = 8.5, 4.5 Hz, C*H*OTBDMS), 7.12 (1H, m, Ar), 7.26 (1H, d, *J* = 1.5 Hz, Ar). ^{13}C NMR (CDCl$_3$, 67.9 MHz) δ -5.3, -4.9, -3.0, 8.7, 14.5, 18.0, 25.7, 28.2, 44.6, 58.4, 63.2, 63.6, 118.8, 127.9, 139.9, 140.3, 154.0, 170.2. EI-MS *m/z* 395 (M$^+$). $[\alpha]_D^{27}$ -13.7° (*c* 0.23, CHCl$_3$). Anal. Calcd for $C_{20}H_{33}O_5NSi$: C, 60.73; H, 8.41; N, 3.54. Found: C, 60.82; H, 8.60; N, 3.42.

2,3-Disubstituted Maleic Anhydride 27. To a solution of **24** (355 mg, 0.9 mmol) and diisopropylethylamine (0.31 ml, 0.18 mmol) in dichloromethane (10 ml) containing rose bengal sensitizer (10 mg, 0.009 mmol) was stirred at -20 °C under oxygen atmosphere and irradiated with a 500W tungsten

incandescent lamp until starting material consumed (ca. 2 h, checked by TLC analysis). The reaction was quenched by the addition of saturated aq. NH_4Cl, and separated organic phase was washed with water and dried (Na_2SO_4). Concentration under reduced pressure afforded an oil (392 mg), which was purified by silica gel chromatography with a mixture of ether/hexane (1:1) to furnish a 4:1 mixture of 2,3-dialkyl-4-hydroxybutenolides **25** and **26** (332 mg, 87% combined yield).

To a stirred solution of 4-hydroxybutenolides **25** and **26** (285 mg, 0.67 mmol) and activated molecular sieves 4A (1 g) in dichloromethane (10 ml) was added pyridinium chlorochromate (286 mg, 1.34 mmol), and the mixture was stirred at room temperature for 1.75 h. The resulting suspension was filtered, and the filtrate was concentrated under reduced pressure to afford a brown solid (594 mg). Purification by silica gel chromatography with a mixture of ether/hexane (1:1) gave the white solid, which was recrystallized from a mixture of ether and dichloromethane to provide maleic anhydride **27** (240 mg, 84%, white needle). Mp 115-117 °C. UV (CH_3CN) λ_{max} (log ε) 202 (4.4), 250 (3.8) nm. IR (KBr) ν_{max} 2960, 1860, 1770, 1710 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 0.03 (3H, s, $SiCH_3$), 0.14 (3H, s, $SiCH_3$), 0.86 (9H, s, Si*t*-*Bu*), 0.87 (3H, d, J = 7 Hz, $CH(CH_3)_2$), 0.91 (3H, d, J = 7 Hz, $CH(CH_3)_2$), 2.24 (3H, d, J = 1 Hz, Ar-CH_3), 2.35 (1H, m, $CH(CH_3)_2$), 3.27 (1H, dd, J = 17, 6.0 Hz, CH_2COON), 3.59 (1H, dd, J = 17, 7 Hz, CH_2COON), 4.26 (2H, m, OCH_2CH*i*-Pr), 4.39 (1H, dt, J = 7, 4 Hz, NC*Hi*-Pr), 5.25 (1H, t, J = 7 Hz, *CH*OTBDMS). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ -5.2, -4.9, 10.3, 14.5, 18.0, 25.6, 28.2, 42.2, 58.5, 62.8, 63.4, 142.6, 143.7, 154.0, 164.3, 167.0, 168.8. EI-MS *m/z* 425 (M^+). $[\alpha]_D^{25}$ -15.5 (*c* 0.26, $CHCl_3$). Anal. Calcd for $C_{20}H_{31}O_7NSi$: C, 56.45; H, 7.34; N, 3.29. Found: C, 56.58; H, 7.33; N, 3.26.

Removal of Chiral Auxiliary to Carboxylic acid 28. A dry flask was charged with **27** (50 mg, 0.12 mmol) and tetrahydrofuran (0.8 ml), and the mixture was cooled to 0 °C under nitrogen atmosphere. Hydrogen peroxide (30 %, 0.06 ml, 0.6 mmol) and aq. lithium hydroxide (0.8 M, 0.71 ml, 0.58 mmol) was added and the mixture was stirred for 1 h at 0 °C. Excess hydrogen peroxide was reduced by the addition of Na_2SO_3 (74 mg, 0.6 mmol), and the mixture was extracted with dichloromethane to remove the oxazolidinone auxiliary. The resulting aqueous layer was acidified to pH 3 with 1 N HCl and then was extracted with ethyl acetate. In each extraction, the aqueous layer maintained at pH 3 by the addition of 1 N HCl. The combined extracts were dried (Na_2SO_4) and concentrated under reduced pressure to afford crude carboxylic acid **28** (37 mg, 100%). This material was used for the next reaction without further purification.

2,3-Disubstituted Maleic Anhydride Segment Monomethyl Ester 3. A solution of **28** (37 mg, ca. 0.12 mmol) in ether (1 ml) was treated with a solution of diazomethane in ether at 0 °C until the starting material disappeared (checked by TLC analysis). Acetic acid was added to quench the excess diazomethane, and the mixture was concentrated under reduced pressure. The resulting residue dissolved in tetrahydrofuran (1 ml) was transferred into a Teflon tube, and pyridinium poly(hydrogen fluoride) (25 drops) was added to the solution at room temperature. After stirring for 4 h, the mixture was neutralized with saturated aq. $NaHCO_3$, acidified with 1N HCl to pH 3, and then extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4) and concentrated to afford an oil (35.6 mg) which was purified by silica gel chromatography with a mixture of ether/hexane (3:1) to afford monomethyl ester **3** (9.2 mg, 36% from **27**, 3 steps). UV (CH_3CN) λ_{max} (log ε) 202 (4.1), 251 (3.8) nm. IR (KBr) ν_{max} 3520, 1830, 1770, 1740 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 2.28, (3H, d, J = 1 Hz, C=C-CH_3), 2.87 (2H, m, CH_2CO_2Me), 3.54 (1H, brd, *OH*), 3.76 (3H, s, CO_2CH_3), 5.13 (1H, m, *CH*OH). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 10.0, 39.1, 52.3, 63.8, 141.6, 143.1, 164.6, 165.5, 171.7. EI-MS *m/z* 215 (M^++H). $[\alpha]_D^{27}$ +50.6° (*c* 0.3, $CHCl_3$). Anal. Calcd for $C_9H_{10}O_6$: C, 50.47; H, 4.71. Found: C, 50.50; H, 4.55.

2,3-Disubstituted Maleic Anhydride Segment Trimethyl Ester 4. Crude carboxylic acid **28** (7.8 mg, *ca.* 0.12 mmol) dissolved in methanol (0.5 ml) cooled to 0 °C was treated with a solution of diazomethane until the starting material consumed (checked by TLC analysis). Acetic acid was added to quench the excess diazomethane. The mixture was neutralized with saturated aq. $NaHCO_3$, and then concentrated under reduced pressure. The resulting residue dissolved in tetrahydrofuran (0.5 ml) was transferred into a Teflon tube, and pyridinium poly(hydrogen fluoride) (10 drops) was added at room temperature. After stirring for 2 h, the reaction mixture was neutralized with saturated aq. $NaHCO_3$ and extracted with ethyl acetate. The organic extracts were dried (Na_2SO_4) and concentrated to afford the residue

which was purified by silica gel chromatography with a mixture of ether/hexane (5:1) to yield trimethyl ester **4** (1.8 mg, 28%). UV (CH_3CN) λ_{max} (log ε) 206 (4.4) nm. IR (KBr) ν_{max} 3510, 1720, 1650 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 2.00, (3H, s, C=C-C*H*$_3$), 2.57 (1H, dd, *J* = 16.5, 3.5 Hz, C*H*$_2CO_2Me$), 2.95 (1H, dd, *J* = 16.5, 9.5 Hz, C*H*$_2CO_2Me$), 3.23(1H, brd, O*H*), 3.73 (3H, s, CO_2CH_3), 3.76 (3H, s, CO_2CH_3), 3.80 (3H, s, CO_2CH_3), 5.08 (1H, dd , *J* = 9.5, 3.5 Hz, C*H*OH). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 14.9, 39.8, 52.0, 52.36, 52.44, 66.2, 132.2, 139.5, 167.9, 171.8. $[\alpha]_D^{25}$ -16.7° (*c* 0.49, $CHCl_3$). Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.15. Found: C, 50.65; H, 6.14. Reported data of compound **4**:[3,4] UV (CH_3CN) λ_{max} (log ε) 225 (33) nm. IR (film) ν_{max} 1720 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 2.00, (3H, s), 2.58 (1H, dd, *J* = 17, 4 Hz), 2.95 (1H, dd, *J* = 17, 10 Hz), 3.72 (6H, s), 3.80 (3H, s), 5.10 (1H, dd , *J* = 10, 4 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.0, 39.5, 51.5, 52.0, 66.0, 131.0, 140.0, 167.5, 171.5. $[\alpha]_D^{25}$ -16.3° (*c* 0.3, $CHCl_3$). Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.15. Found: C, 50.62; H, 6.31.

(α-Ethylthioacetyl)oxazolidinone 32. A solution of ethanethiol (0.036 ml, 0.049 mmol) dissolved in tetrahydrofuran (2 ml) cooled to 0 °C was treated with sodium methoxide (5 N solution in methanol, 0.1 ml, 0.05 mmol) under nitrogen atmosphere for 10 min. The resulting solution was cooled to -78 °C and then a solution of (α-chloroacetyl)-oxazolidinone **31** (100 mg, 0.049 mmol) in tetrahydrofuran (1 ml) was added. After stirring for 30 min, the solution was quenched by the addition of saturated aq. NH_4Cl, and aqueous layer was extracted with ether. The organic extracts were concentrated under reduced pressure to give an oil (87 mg), which was purified by silica gel chromatography with a mixture of ether/hexane (1:1) to afford (α-ethylthioacetyl)oxazolidinone **32** (74 mg, 66%). IR (KBr) ν_{max} 1870, 1700 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 0.89 (3H, d, *J* = 5 Hz, CH(C*H*$_3$)$_2$), 0.92 (3H, d, *J* = 5 Hz, CH(C*H*$_3$)$_2$), 1.25 (3H, t, *J* = 7 Hz, SCH$_2$C*H*$_3$), 2.37 (1H, m, C*H*(CH$_3$)$_2$), 2.60 (2H, q, *J* = 7.0 Hz, C*H*$_2$CH$_3$), 3.71 (1H, d, *J* = 14 Hz, SC*H*$_2$CON), 3.95 (1H, d, *J* = 14 Hz, SC*H*$_2$CON), 4.26 (2H, m, *i*-PrCHC*H*$_2$O), 4.43 (1H, dt, *J* = 8, 3.5 Hz, OCH$_2$C*Hi*-Pr). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 14.2, 14.5, 17.8, 26.1, 28.2, 34.1, 58.3, 63.3, 153.7, 169.3. EI-MS *m/z* 231 (M^+). $[\alpha]_D^{23}$ +90.5° (*c* 0.22, $CHCl_3$). HRMS calcd for $C_{10}H_{17}NO_3S$; 231.0929, found 231.0913.

Aldol Reaction between Chiral Oxazolidinone 32 and Furan 15 to Aldol Adduct 33. To a solution of α-(ethylthioacetyl)oxazolidinone **32** (2 g, 8.66 mmol) in dichloromethane (20 ml) cooled to 0°C under argon atmosphere was added a solution of dibutylboron triflate (1.0 M solution in dichloromethane, 8.66 ml, 8.66 mmol) and triethylamine (1.57 ml, 11.3 mmol) dropwise. After stirring for 30 min, the solution was cooled to -78 °C and a solution of aldehyde (1.05 g, 9.55 mmol) in dichloromethane (5 ml) was added dropwise. After stirring for 20 min at -78 °C and then for 1 h at 0 °C, the reaction mixture was quenched by the addition of pH 7 phosphate buffer (9.5 ml) and methanol (28.5 ml). To this solution was added a 2:1 mixture of methanol/30% hydrogen peroxide (28.5 ml) at such a rate as to keep the internal temperature below + 10°C. After stirring for 1 h, methanol was removed by evaporation, and the resulting slurry was extracted with ether. The organic extracts were washed with 5 % aq. $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated to afford the residue (3.85 g). Purification by silica gel chromatography with a mixture of ether/hexane (1:1) provided aldol adduct **33** (2.2 g, 72%). UV (CH_3CN) λ_{max} (log ε) 207 (4.1), 268 (3.1) nm. IR (KBr) ν_{max} 3500, 1770, 1690 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 0.91 (3H, d, *J* = 6 Hz, CH(C*H*$_3$)$_2$), 0.93 (3H, d, *J* = 6 Hz, CH(C*H*$_3$)$_2$), 1.26 (3H, t, *J* = 7.5 Hz, SC*H*$_2$CH$_3$), 2.06 (3H, d, *J* = 1 Hz, Ar-C*H*$_3$), 2.33 (1H, m, C*H*(CH$_3$)$_2$), 2.50 (1H, brd, O*H*), 2.66 (1H, dd, *J* = 12, 7.5 Hz, SC*H*$_2$CH$_3$), 2.80 (1H, dd, *J* = 12, 7.5 Hz, -SC*H*$_2$CH$_3$), 4.19 (2H, m, OCH$_2$C*Hi*-Pr), 4.37 (1H, ddd, *J* = 6.5, 5, 4 Hz, C*Hi*-Pr), 4.95 (1H, d, *J* = 9 Hz, C*H*SEt), 5.24 (1H, d, *J* = 9 Hz, C*H*OH), 7.14 (1H, m, Ar), 7.38 (1H, d, *J* = 1.5 Hz, Ar). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 8.4, 14.1, 17.8, 22.6, 28.1, 50.5, 58.0, 63.1, 64.1, 119.2, 124.5, 140.3, 141.2, 153.5, 170.1. EI-MS *m/z* 341 (M^+). $[\alpha]_D^{25}$ +10.4 ° (*c* 0.35, $CHCl_3$). Anal. Calcd for $C_{16}H_{23}O_5NS$: C, 56.29; H, 6.79; N, 4.10. Found: C, 56.21; H, 6.70; N, 4.17.

Desulfrization of the Aldol Adduct 33 to Furan 34 with Raney Nickel (Enantiomer of 23). Raney nickel (W-4, 4 g) was added to a solution of **33** (1.5 g, 4.4 mmol) in a mixture of acetone (36 ml) and pH 7 phosphate buffer (4 ml) under nitrogen at room temperature. The reaction mixture was stirred until the starting material disappeared (checked by TLC analysis). Raney nickel was removed by filtration, and the filtrate was concentrated under reduced pressure. The resulting residue was recrystallized from

dichloromethane/hexane to afford furan **34** (891 mg, 71%, white needle). Mp 99-100 °C. UV (CH_3CN) λ_{max} (log ε) 202 (4.3) nm. IR (KBr) ν_{max} 3350, 1780, 1710 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 0.87 (3H, d, J = 7 Hz, -CH(CH_3)$_2$), 0.93 (3H, d, J = 7 Hz, CH(CH_3)$_2$), 2.06 (3H, d, J = 1 Hz, Ar-CH_3), 2.39 (1H, m, CH(CH_3)$_2$), 3.21 (1H, brd, OH), 3.28 (1H, dd, J = 17, 3 Hz, CH_2CON), 3.51 (1H, dd, J = 17, 9.5 Hz, CH_2CON), 4.26 (2H, m, OCH_2CH*i*-Pr), 4.47 (1H, dt, J = 7.5, 3.5 Hz, NCH*i*-Pr), 5.11 (1H, dd, J = 9.5, 3 Hz, CHOH), 7.16 (1H, m, Ar), 7.36 (1H, s, Ar). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 8.4, 14.6, 17.9, 28.4, 42.2, 58.4, 62.9, 63.6, 118.8, 127.0, 139.7, 140.3, 154.0, 172.2. EI-MS *m/z* 281 (M^+). $[\alpha]_D^{24}$ +24.7° (*c* 0.43, $CHCl_3$). Anal. Calcd for $C_{14}H_{19}O_5N$: C, 59.78; H, 6.81; N, 4.98. Found: C, 59.79; H, 6.78; N, 4.80.

***t*-Butyldimethylsilyl Ether 35 (Enantiomer of 24).** Starting from alcohol **34** (700 mg, 2.49 mmol), diisopropylethylamine (0.86 ml, 3.34 mmol), dichloromethane (23 ml) and *tert*-butyldimethylsilyl trifluoromethanesulfonate (0.87 ml, 4.98 mmol), *t*-butyldimethylsilyl ether **35** (982 mg, colorless oil) was obtained quantitatively by the same procedure described before. $[\alpha]_D^{27}$ +12.6° (*c* 0.50, $CHCl_3$). Anal. Calcd for $C_{20}H_{33}O_5NSi$: C, 60.73; H, 8.41; N, 3.54. Found: C, 60.61; H, 8.73; N, 3.46.

Maleic Anhydride 36 (Enantiomer of 27). Starting from furan **35** (900 mg, 2.29 mmol), diisopropylethylamine (0.79 ml, 4.58 mmol), rose bengal (40 mg, 0.039 mmol) and dichloromethane (40 ml), a mixture of hydroxy-butenolides (842 mg, 83%, 4:1) was isolated by the same procedure described before.

Starting from a mixture of the hydroxybutenolides (842 mg, 4:1), pyridinium chlorochromate (633 mg, 2.9 mmol), activated molecular sieves 4A (3 g) and dichloromethane (30 ml), maleic anhydride **36** (676 mg, white needle) was obtained by the same procedure described before in 81% yield. $[\alpha]_D^{24}$ +16.5° (*c* 0.43, $CHCl_3$). Anal. Calcd for $C_{20}H_{31}O_7NSi$: C, 56.45; H, 7.34; N, 3.29. Found: C, 56.51; H, 7.30; N, 3.13.

Monomethyl Ester 38 (Enantiomer of 3). Starting from oxazolidinone **36** (50 mg, 0.12 mmol), lithium hydroxide (0.71 ml, 0.58 mmol), 30% hydrogen peroxide (0.06 ml, 0.59 mmol) and tetrahydrofuran (0.8 ml), crude carboxylic acid (37 mg, 100 %) was obtained by the same procedure described before.

Starting from crude carboxylic acid (42 mg, *ca.* 0.12 mmol), diazomethane solution in ether, ether (5 ml), tetrahydrofuran (1 ml) and pyridinium poly(hydrogen fluoride) (25 drops), monomethyl ester **38** was isolated (8.7 mg, 35% yield) by the same procedure described before. $[\alpha]_D^{27}$ -49.1° (*c* 0.41, $CHCl_3$). Anal. Calcd for $C_9H_{10}O_6$: C, 50.47; H, 4.71. Found: C, 50.52; H, 4.57.

Trimethyl Ester 39 (Enantiomer of 4). Starting from crude carboxylic acid (38 mg, *ca.* 0.12 mmol) prepared from **36**, diazomethane solution in ether, methanol (1 ml), tetrahydrofuran (1 ml) and pyridinium poly(hydrogen fluoride) (25 drops), trimethyl ester **39** (4.2 mg, 14 %) was obtained by the same procedure described before. $[\alpha]_D^{25}$ +18.4° (*c* 0.21, $CHCl_3$). Anal. Calcd for $C_{11}H_{16}O_7$: C, 50.77; H, 6.20. Found: C, 50.65; H, 6.14.

2,4-Dimethyl-3-pentyl Ester 41. To a solution of **9** (50 mg, 0.27 mmol) and *N,N*-dimethylformamide (1 drop) dissolved in dichloromethane (1 ml) was added oxalyl chloride (0.036 ml, 0.41 mmol). After stirring for 1 h, the solvent was removed under reduced pressure to afford acid chloride **40** (63.8 mg), which was used for the next reaction without further purification.

The resulting acid chloride **40** (63.8 mg) was dissolved in dichloromethane (1 ml), and 2,4-dimethyl-3-pentanol (0.046 ml, 0.33 mmol) and pyridine (0.033 ml, 0.4 mmol) was added. After stirring for 1 h, the mixture was quenched by the addition of saturated aq. NH_4Cl. The mixture was acidified with 1 N HCl to pH 2, and extracted with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), and concentrated under reduced pressure. Purification of the resulting oil (72.5 mg) by silica gel chromatography with a mixture of ether/hexane (1:1) afforded 2,4-dimethyl-3-pentyl ester **41** (58.2 mg, 76%, pale yellow oil). UV (CH_3CN) λ_{max} 203, 253 nm. IR ν_{max} 1820, 1770, 1730 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 0.84 (12H, t, J = 7 Hz, CH(CH_3)$_2$ × 4), 1.89 (2H, m, CH(CH_3)$_2$ × 2), 2.13 (3H, s, C=C-CH_3), 2.76 (4H, m, $CH_2CH_2CO_2$), 4.85 (1H, t, J = 6.5 Hz, CO_2CH). ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 9.7, 17.1, 19.4, 20.1, 29.2, 30.9, 83.6, 142.1, 142.4, 165.8, 171.8. Anal. Calcd for $C_{15}H_{22}O_5$: C, 63.81; H, 7.85. Found: C, 63.81; H, 7.79.

***S*-2-Pyridyl Thioate 42.** A solution of **9** (30 mg, 0.16 mmol), 2,2'-dipyridyl disulfide (36 mg, 0.16 mol) and triphenylphosphine (43 mg, 0.16 mmol) dissolved in acetonitrile (1 ml) was stirred at room

temperature for 30 min. Concentration of the reaction mixture provided the residue, which was purified by silica gel chromatography with a mixture of ether/hexane (1:1) to afford *S*-2-pyridyl thioate **42** (35.6 mg, 79%). UV (CH_3CN) λ_{max} (log ε) 246 (2.77) nm. IR (KBr) ν_{max} 1830, 1760, 1710, 1570, 1450, 1420, 1280 cm^{-1}. ^1H NMR ($CDCl_3$, 270 MHz) δ 2.11 (3H, s, C=C-C*H*$_3$), 2.83 (2H, t, *J* = 7 Hz, *CH*$_2$CH$_2$COS), 3.12 (2H, t, *J* = 7 Hz, CH$_2$*CH*$_2$COS), 7.33 (1H, ddd, *J* = 7.5, 5, 1 Hz, H-5), 7.57 (1H, d, *J* = 8 Hz, H-3), 7.77 (1H, ddd, *J* = 8, 7.5, 2 Hz, H-3), 8.61 (1H, ddd, *J* = 5, 2, 1 Hz, H-6). ^{13}C NMR ($CDCl_3$, 69.7 MHz) δ 9.7, 19.8, 40.2, 123.9, 141.5, 142.4, 150.5, 165.5, 165.7, 194.8. FAB-MS *m/z* 278 (M^++H). HRMS calcd for $C_{13}H_{12}O_4NS$; 278.3049, found 278.0469.

To a solution of **42** (39 mg, 0.15 mmol) and cupric bromide (47 mg, 0.22 mmol) dissolved in acetonitrile (1 ml) was added 2,4-dimethyl-3-propanol (39 μl, 0.28 mmol), and stirring was continued at room temperature for 14 h. The mixture was poured into saturated aq. NH_4Cl, and then acidified to pH 3 with 1 N HCl. The precipitate was filtered and the filtrate was extracted with dichloromethane, dried (Na_2SO_4) and concentrated to provide a green oil (34 mg). Purification by silica gel chromatography with a mixture of ether/hexane (1: 2, and then 1:1) afforded ester **41** (23.8 mg, 60%).

Coupling Product with Deoxy-segment 44. To a solution of **9** (20 mg, 0.11 mmol) and hexamethylphosphorous triamide (1 μl, 5.7 μmol) dissolved in dichloromethane (0.5 ml) cooled to 0 °C under argon atmosphere was added oxalyl chloride (15 μl, 0.18 mmol) dropwise. The cooling bath was removed, and stirring was continued for 3 h. The reaction mixture was concentrated under reduced pressure, and excess oxalyl chloride was removed in vacuum. The resulting acid chloride **40** was dissolved in dichloromethane (0.5 ml), and to this solution was added **43** (10 mg, 0.015 mmol) and pyridine (9 μl, 0.11 mmol) in dichloromethane (0.5 ml). After stirring for 1 h, the reaction mixture was quenched by addition of saturated aq. NH_4Cl. The aqueous layer was extracted with dichloromethane, and combined organic extracts were dried (Na_2SO_4), and concentrated under reduced pressure to give a residue (29 mg), which was purified by silica gel chromatography with a mixture of ether/hexane (1:1) to afford coupling product **44** (11 mg, 88%). IR (film) ν_{max} 1840, 1770, 1730, 1720 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (3H, s, SiC*H*$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.80 (3H, d, *J* = 6.5 Hz, C*H*$_3$), 0.84 (9H, s, *t-Bu*), 0.87 (3H, d, *J* = 6.5 Hz, C*H*$_3$), 0.88 (3H, d, *J* = 6.5 Hz, C*H*$_3$), 0.91 (3H, d, *J* = 7 Hz, C*H*$_3$), 0.98 (3H, d, *J* = 6.5 Hz, C*H*$_3$), 1.02 (3H, d, *J* = 7 Hz, C*H*$_3$), 1.09 (3H, d, *J* = 7 Hz, C*H*$_3$), 1.16-1.74 (16H, m), 1.85 (1H, m, H-13), 1.89 (1H, qn, *J* = 6.5 Hz, H-16), 2.03 (1H, tt, *J* = 13, 4.5 Hz, H-12), 2.11 (3H, s, 5'-C*H*$_3$), 2.14 (3H, s, H-1), 2.55 (1H, sext, *J* = 7 Hz, H-3), 2.62-2.77 (4H, m, H-2',3'), 2.99 (1H, qn, *J* = 7 Hz, H-19), 3.17 (1H, dt, *J* = 10, 2 Hz, H-6), 3.26 (1H, dd, *J* = 10, 2 Hz, H-14), 3.28 (3H, s, 23-OC*H*$_3$), 3.82 (1H, dd, *J* = 7.5, 7 Hz, H-23), 3.98 (1H, dt, *J* = 7, 5 Hz, H-18), 4.90 (1H, dd, *J* = 7, 5 Hz, H-24), 6.36 (1H, dd, *J* = 16, 1 Hz, H-21), 6.59 (1H, dd, *J* = 16, 7 Hz, H-22). $[\alpha]_D^{25}$ +23.6 ° (*c* 0.58, $CHCl_3$). FAB-MS *m/z* 847 (M^++H). HRMS calcd for $C_{47}H_{79}O_{11}Si$; 847.5391, found 847.5368.

Coupling Product with 2,3-Disubstituted Maleic Anhydride Segment 45. To a solution of **28** (15.3 mg, 44 μmol) and hexamethylphosphoramide (2 μl, 11 μmol) dissolved in dichloromethane (0.5 ml) at 0 °C was added oxalyl chloride (8 μl, 88 μmol), and the reaction mixture was stirred for 3 h. The solvent and excess oxalyl chloride were removed in vacuum, and a dichloromethane (0.5 ml) solution of **43** (10 mg, 15 μmol) and pyridine (36 μl, 24 μmol) was added. After stirring for 6 h, the reaction was quenched by the addition of water. The mixture was acidified with 1 N HCl to pH 3 and then extracted with dichloromethane. The organic extracts were dried (Na_2SO_4) and concentrated. The resulting oil was purified by silica gel chromatography with a mixture of ether/hexane (1:2) to afford coupling product **45** (4.2 mg, 29%). IR (film) ν_{max} 1850, 1770, 1750, 1710, 1690, 1460, 1380, 1250 cm^{-1}. ^1H NMR ($CDCl_3$, 400 MHz) δ 0.00 (3H, s, SiC*H*$_3$), 0.02 (3H, s, SiC*H*$_3$), 0.05 (3H, s, SiC*H*$_3$), 0.12 (3H, s, SiC*H*$_3$), 0.81 (3H, d, *J* = 7 Hz, C*H*$_3$), 1.81 (3H, d, *J* = 7 Hz, C*H*$_3$), 0.83-0.91 (6H, m, C*H*$_3$ × 2), 0.84 (9H, s, *t-Bu*), 0.90 (9H, s, *t-Bu*), 0.92 (3H, d, *J* = 6 Hz, C*H*$_3$), 0.99 (3H, d, *J* = 7 Hz, C*H*$_3$), 1.02 (3H, d, *J* = 7 Hz, C*H*$_3$), 1.09 (3H, d, *J* = 7 Hz, C*H*$_3$), 1.18-1.72 (18H, m), 1.86 (1H, m, H-13), 2.03 (1H, tt, *J* = 13, 4 Hz, H-12), 2.15 (3H, s, H-1), 2.21 (3H, s, 5'-C*H*$_3$), 2.56 (1H, sext, *J* = 7 Hz, H-3), 2.70-3.03 (3H, m, H-19, H-2'), 3.17 (1H, dt, *J* = 10, 2 Hz, H-6), 3.26 (3H, s, 23-OC*H*$_3$), 3.27 (1H, m, H-23), 3.82 (1H, ddd, *J* = 7, 2, 1 Hz, H-23), 3.99 (1H, m, H-18), 4.91 (1H, dd, *J* = 8.4 Hz, H-24), 5.13 (1H, m, H-3'), 6.36 (1H, dd, *J* = 16, 1 Hz, H-21), 6.59 (1H, dd, *J* = 16, 7 Hz, H-22). FAB-MS *m/z* 977 (M^++H). HRMS calcd for $C_{53}H_{93}O_{12}Si_2$ 977.6205, found 977.6185.

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