SYNTHESIS OF A KEY INTERMEDIATE FOR D-BIOTIN VIA 1,3-CYCLOADDITION OF A THIOCARBONYL YLIDE AND SILA-PUMMERER REARRANGEMENT

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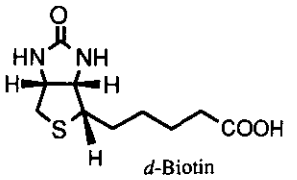
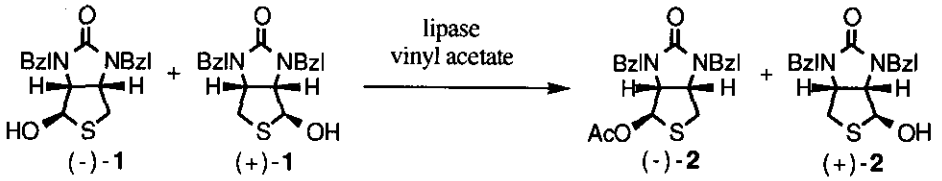
Abstract--An efficient preparation of a *d*-biotin intermediate, (±)-(3aα,4α,6aα)-1,3-dibenzyl-3a,4,6,6a-tetrahydro-4-hydroxy-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one was accomplished by use of 1,3-cycloaddition of a thiocarbonyl ylide, Curtius rearrangement and sila-Pummerer rearrangement. Addition of *p*-toluenesulfonic acid was found to be effective to promote sila-Pummerer rearrangement of sterically unfavorable *anti*-2-trimethylsilyl sulfoxide.

D-Biotin referred to as vitamin H or coenzyme R is widely distributed in animals and plants. Recently its functions, such as amino acid metabolism, carbohydrate metabolism, the maintenance of skin, hair and nerves and growth promotion, have been recognized[1] and these findings have led to renewed interest in the total synthesis of *d*-biotin.[2]



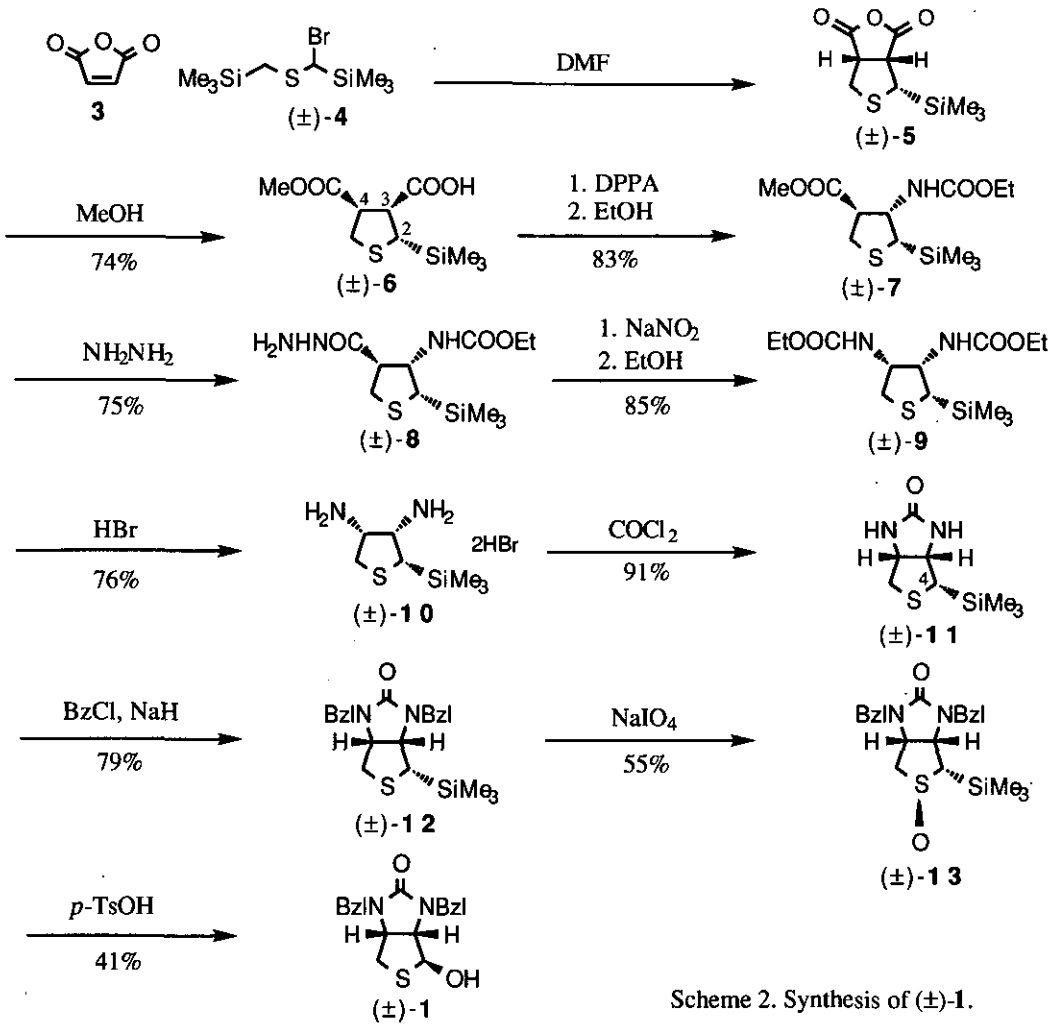
d-Biotin

We have recently developed the effective optical resolution of (±)-(3aα,4α,6aα)-1,3-dibenzyl-3a,4,6,6a-tetrahydro-4-hydroxy-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one [(±)-**1**],[3] which is a key intermediate for *d*-biotin,[4] by use of lipoprotein lipase from *Pseudomonas aeruginosa* TE3285.[5] (Scheme 1)



Scheme 1. Optical resolution of (±)-**1**. 46%, 99%e.e.

Having established the effective optical resolution of (±)-**1**, the preparation of racemic (±)-**1** has become a focal point of current interest. We wish to report here a novel preparation of a *d*-biotin intermediate [(±)-1]. The synthesis of *d*-biotin is complicated by the fact that it contains three chiral centers. We assumed that the introduction of the chiral centers keeping their relative configuration *cis* is crucial. It seems in our view that the 1,3-cycloaddition of a thiocarbonyl ylide, reported by Achiwa *et al.*,[6] meets our requirements. Hence, the *d*-biotin intermediate [(±)-**1**] was produced starting from the 1,3-cycloaddition reaction. (Scheme 2)



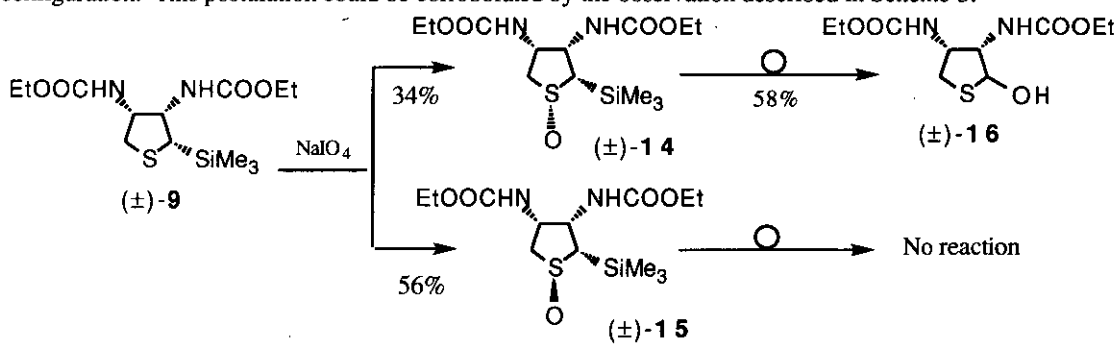
Scheme 2. Synthesis of (±)-**1**.

The 1,3-cycloaddition of maleic anhydride [**3**] with bromo(trimethylsilylmethylthio)methyltrimethylsilane [(±)-**4**] gave the tetrahydrothiophane [(±)-**5**],[6] and its methanolysis produced (2*RS*, 3*RS*, 4*SR*)-4-methoxycarbonyl-1-trimethylsilylthiophane-3-carboxylic acid [(±)-(**6**)]. Despite the excellent stereoselectivities of the 1,3-

cycloaddition, the relative configuration of C(2) and C(3) of (±)-(**5**) was not established. We have independently determined it to be *cis* based on ^{1}H nmr analysis of (±)-**6** in which NOE was observed between C(2)-H and C(3)-H; C(2)-H and C(4)-H. In addition, X-ray analysis of the sulfoxide [(±)-**14**],[7] which is an oxidation product of the diamino compound [(±)-**9**], also supported its *cis* configuration.

Next, (±)-**6** was converted into the diamino compound [(±)-**9**] by stepwise Curtius rearrangements. Thus, treatment of (±)-**6** with diphenylphosphoryl azide (DPPA) followed by ethanolysis led to the introduction of an amino group on C(3). The methoxycarbonyl group of (±)-**7** was readily converted to a carboethoxyamino group through the carboxyhydrazide [(±)-**8**] by use of Curtius rearrangement. Treatment of (±)-**8** with 48% hydrobromic acid afforded the diamine [(±)-**9**], which was next cyclized by the reaction with phosgene to give (±)-(3aα,4β,6aα)-3a,4,6,6a-tetrahydro-4-trimethylsilyl-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one [(±)-**11**]. Then amino groups were protected with benzyl groups by a conventional procedure.

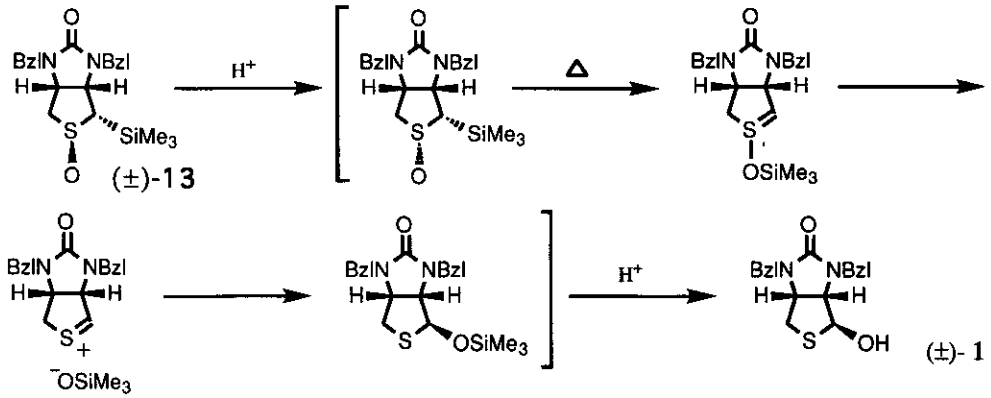
The silyl group of (±)-**11** was successfully converted into a hydroxyl group by using sila-Pummerer rearrangement,[8,9] – a previously hardly tried method of obtaining α-hydroxy sulfides. The thiophane was oxidized with sodium metaperiodate to give an *anti*-sulfoxide[10] [(±)-**12**] as a sole product. As a preliminary experiment, the *anti*-sulfoxide [(±)-**12**] was subjected to sila-Pummerer rearrangement by heating according to the Brook's procedure;[9] it, however, has proved unsuccessful. This low reactivity seems to be attributed to its *anti* configuration. This postulation could be corroborated by the observation described in Scheme 3.



Scheme 3. Sila-Pummerer rearrangement of (±)- **14** and (±)-**15**

The sulfoxide [(±)-**14**] having *syn*-configuration[10] gave a rearranged product [(±)-**16**]. However, the *anti*-sulfoxide [(±)-**15**] didn't afford a rearranged product. After some preliminary experiments, we found that the addition of *p*-toluenesulfonic acid was effective to promote the rearrangement of *anti*-sulfoxide [(±)-**13**].[11] A plausible explanation would appear to involve the *p*-toluenesulfonic acid-catalyzed epimerization of the

sulfoxide.[12] The epimerization would enable the trimethylsilyl group to migrate to oxygen to give a siloxysulfonium ylide, which itself rearranges by the Pummerer pathway to give α-siloxy sulfide. (Scheme 4)



Scheme 4. Possible reaction mechanism.

The rearranged product [(±)-**1**] had 4α configuration which is readily explained by the attack of the siloxymethyl anion on the less hindered *exo*-face of the sulfur-stabilized carbocation.

In summary, a *d*-biotin intermediate [(±)-**1**] was prepared from maleic anhydride by using 1,3-cycloaddition of thiocarbonyl ylide, Curtius rearrangement and sila-Pummerer rearrangement catalyzed *p*-toluenesulfonic acid.

EXPERIMENTAL

All melting points (mp) were uncorrected. Ir were obtained on a Shimadzu IR-260-10 infrared spectrophotometer. Nmr spectra were recorded on JEOL JNM-GX400 (400 MHz), JEOL JNM-GSX270 (270 MHz), Varian XL-200 (200 MHz) and Hitachi R-90H (90 MHz) spectrometers using tetramethylsilane (TMS) as an internal reference. Ms were measured with a JEOL JMS-AX-505W.

(2*RS*,3*RS*,4*SR*)-4-Methoxycarbonyl-2-trimethylsilylthiophane-3-carboxylic acid [(±)-6]. A solution of maleic anhydride (33.2 g, 0.38 mol) and bromo(trimethylsily)methyl trimethylsilylmethyl sulfide (151.7 g, 0.532 mol) in dimethylformamide (DMF) (150 ml) was heated at 130 °C for 2 h. Evaporation of the solvent gave a crude (±)-**5**, which without purification was dissolved in methanol (900 ml). To this solution *p*-toluenesulfonic acid (1.3 g) was added, and the mixture was stirred at refluxing temperature for 1.5 h. The resulting mixture was concentrated *in vacuo* to give an oil, which was subjected to silica gel column chromatography (hexane : ethyl acatate, 1 : 1) to give (±)-**6** (65.0 g, 74%): mp 95-105 °C; Anal. Calcd for

$C_{10}H_{18}O_4SSi$: C, 45.77; H, 6.91; S, 12.22. Found: C, 45.75; H, 6.77; S, 12.32; ir (KBr) 2950, 1750, 1700, 1250, 1200, 840 cm^{-1}; ^1H nmr (400 MHz, $CDCl_3$) δ: 0.14 (9H, s), 2.88 (1H, d, *J*=5.5 Hz), 3.15 (1H, ddd, *J*=5.5, 9.2 and 10.3 Hz), 3.23 (1H, t-like, *J*=9.2 Hz), 3.46 (1H, t-like, *J*=10.3 Hz), 3.64 (1H, t, *J*=5.5 Hz), 3.70 (3H, s); ^{13}C nmr ($CDCl_3$) δ: -2.35, 30.85, 37.26, 50.90, 52.10, 53.10, 171.21, 177.70.

(2*RS*,3*SR*,4*SR*)-3-Carboethoxyamino-4-methoxycarbonyl-2-trimethylsilylthiophane [(±)-7].

Diphenylphosphoryl azide (DPPA) (730 mg, 2.65 mmol) was added to a solution of (±)-**6** (700 mg, 2.67 mmol) and triehtylamine (0.386 ml, 2.77 mmol) in toluene (2.0 ml), and the mixture was stirred at 80 °C for 2 h. Then ethanol (0.315 ml) was added to the reaction mixture. After stirring at the same temperature for 6 h, the solvent was evaporated to give an oil, which was diluted with dichloromethane, washed successively with 0.025N NaOH and water. The mixture was dried over Na_2SO_4 and concentrated *in vacuo* to give (±)-**7** as white crystals (679 mg, 83%): mp 58-59 °C; Anal. Calcd for $C_{12}H_{23}NO_4SSi$: C, 47.18; H, 7.59; N, 4.59; S, 10.50. Found: C, 47.42; H, 7.62; N, 4.73; S, 10.25; ir (KBr) 3380, 1730, 1710, 1520, 1235, 840 cm^{-1}; ^1H nmr (90 MHz, DMSO-d_6) δ: 0.02 (9H, s), 1.13 (3H, t, *J*=7.0 Hz), 2.80 (1H, d, *J*=4.0 Hz), 2.9-3.3 (3H, m), 3.54 (3H, s), 3.98 (2H, q, *J*=7.0 Hz), 4.82 (1H, m), 6.74 (1H, br d, *J*=10.5 Hz).

(2*RS*,3*SR*,4*SR*)-3-Carboethoxyamino-2-trimethylsilylthiophane-4-carboxyhydrazide [(±)-8].

The mixture of 98% hydrazine hydrate (1.0 ml, 20 mmol) and (±)-**7** (608 mg, 2.00 mmol) was stirred at 90 °C for 1.5 h. After coling, the precipitate was collected and washed with water to afford (±)-**7** (454 mg, 75%) as white crystals: mp 141-148 °C; Anal. Calcd for $C_{11}H_{23}N_3O_3SSi$: C, 43.25; H, 7.59; N, 13.76; S, 10.50. Found: C, 42.89; H, 7.76; N, 13.48; S, 10.58; ir (KBr) 3300, 1700, 1655, 1535, 1250, 845 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 0.11 (9H, s), 1.23 (3H, t, *J*=7.0 Hz), 2.73 (1H, d, *J*=3.7 Hz), 3.00 (1H, dd, *J*=8.8 Hz and 10.5 Hz), 3.15 (1H, d, *J*=8.8 Hz), 3.29 (1H, t, *J*=10.5 Hz), 3.8-4.2 (2H, m) 4.12 (2H, q, *J*=7.0 Hz), 4.85 (1H, dt, *J*=3.7 and 10.5 Hz), 5.39 (1H, br d, *J*=10.2 Hz), 8.15 (1H, br s).

(2*RS*,3*SR*,4*RS*)-3,4-Bis(carboethoxyamino)-2-trimethylsilylthiophane [(±)-9].

To a mixture of (±)-**8** (207 mg, 0.696 mmol), chloroform (5.0 ml) and 1N hydrochloric acid (7.0 ml), a solution of sodium nitrite (56 mg, 0.81 mmol) in water (5.0 ml) was added dropwise at 0 °C over a period of 5 min. After being stirred additional 10 min, the organic layer was separated and water layer was extracted with chloroform. The combined extracts were dried over Na_2SO_4 at 0 °C. Then ethanol (7.0 ml) was added, and the mixture was

stirred at refluxing temperature for 1.5 h. The mixture was concentrated *in vacuo* to give an oil, which was subjected to silica gel chromatography (chloroform : ethanol, 20 : 1) to afford (±)-**9** (192 mg, 85%) as white crystals: mp 100-101 °C; Anal. Calcd for $C_{13}H_{26}N_2O_4SSi$: C, 46.68; H, 7.83; N, 8.37; S, 9.59. Found: C, 46.67; H, 7.96; N, 8.40; S, 9.57; ir (KBr) 3340, 1685, 1535, 1250, 1040, 840 cm^{-1}; ^1H nmr (90 MHz, $CDCl_3$) δ: 0.11 (9H, s), 1.24 (3H, t, *J*=7.1 Hz), 1.26 (3H, t, *J*=7.1 Hz), 2.39 (1H, t, *J*=10 Hz), 2.71 (1H, d, *J*=3.4 Hz), 3.26 (1H, t-like, *J*=10 Hz), 4.11 (4H, q, *J*=7.1 Hz), 4.17 (1H, m), 4.52 (1H, m), 4.7-5.2 (2H, m).

(2*RS*,3*SR*,4*RS*)-3,4-Diamino-2-trimethylsilylthiophane hydrobromide [(±)-10].

A mixture of (±)-**9** (1.42 g) and 47% hydrobromic acid (14 ml) was stirred at 100 °C for 45 min. After cooling, the precipitates were collected and washed with dioxane to afford (±)-**10** (1.13g, 76%): mp 239-244 °C; Anal. Calcd for $C_7H_{20}N_2Br_2SSi$: C, 23.87; H, 5.72; N, 7.95; S, 9.10. Found: C, 23.90; H, 5.88; N, 8.00; S, 9.19; ir (KBr) 3400, 2900, 1600, 1500, 1060, 850 cm^{-1}; ^1H nmr (90 MHz, DMSO-d_6) δ: 0.16 (9H, s), 2.77 (1H, t, *J*=10.5 Hz), 3.06 (1H, d, *J*=3.0 Hz), 3.20 (1H, t-like *J*=10.5Hz), 3.85 (1H, m), 4.17 (1H, t-like, *J*=3.0 Hz), 7.7-8.8 (6H, br s)

(±)-(3aα,4β,6aα)-3a,4,6,6a-Tetrahydro-4-trimethylsilyl-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one [(±)-11].

A solution of phosgene (6.0 g) in carbon tetrachloride (20 ml) was added to a solution of (±)-**10** (5.00 g) and sodium carbonate (7.85 g) in water (125 ml) at 0 °C. After being stirred for 20 min, ethyl acetate (70 ml) was added to this mixture, and stirring was continued at room temperature. After 1.5 h, the mixture was then quenched with aqueous NaOH. The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure to afford (±)-**11** (2.8 g, 91%) as crystals: mp 190 °C (decomp.); Anal. Calcd for $C_8H_{16}N_2OSSi$: C, 44.41; H, 7.45; N, 12.95; S, 14.82. Found C, 44.15; H, 7.43; N, 12.80; S, 15.09; ir (KBr) 3280, 2920, 1685, 1460, 1260, 850 cm^{-1}; ^1H nmr (90 MHz, DMSO-d_6) δ: 0.09 (9H, s), 2.20 (1H, d, *J*=3.3 Hz), 2.67 (2H, m), 4.37 (2H, m), 4.7-5.5 (1H, br s), 5.9-6.6 (1H, br s).

(±)-(3aα,4β,6aα)-1,3-Dibenzyl-3a,4,6,6a-tetrahydro-4-trimethylsilyl-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one [(±)-12].

Benzyl bromide (2.12 ml, 17.8 mmol) and (±)-**11** (1.28 g, 5.93 mmol) was added to a solution of sodium hydride (60% oil dispersion, 460 mg, 11.5 mmol) in tetrahydrofuran (40 ml) at room temperature and the mixture was stirred at refluxing temperature for 6.5 h. After removal of the solvent, the residue was dissolved in

ether and washed with water. The mixture was concentrated under reduced pressure to give an oil, which was subjected to silica gel column chromatography (hexane : etyl acetate, 3 : 1) to yield (±)-**12** (1.86g, 79.4%) as an oil: Ms (EI), m/z (M^+) 396; ir (KBr) 1695, 1455, 1240, 1260, 840 cm^{-1}; ^1H nmr (90 MHz, $CDCl_3$) δ: 0.26 (9H, s), 2.24 (1H, d, *J*=4.6 Hz), 2.51 (1H, dd, *J*=4.6 and 12.8 Hz), 2.92 (1H, d, *J*=12.8 Hz), 3.87, 4.01, 4.93, 5.19 (each 1H, d, *J*=15.5 Hz), 4.05 (2H, m), 7.28 (10H, m).

(±)-(3aα,4β,6aα)-1,3-Dibenzyl-3a,4,6,6a-tetrahydro-4-trimethylsilyl-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one-5-oxide [(±)-13].

To a solution of (±)-**12** (230 mg, 0.581 mmol) in methanol (10 ml), sodium metaperiodate (137 mg, 0.643 mmol) dissolved in water (5.0 ml) was added at 0 °C, and the mixture was stirred at the same temperature for 44 h. After removal of methanol *in vacuo*, the mixture was diluted with ethyl acetate, washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography (hexane : ethyl acetate, 1 : 1) to yield (±)-**12** (132 mg , 55%) as an oil: Ms (EI), m/z (M^+) 412; ir (KBr) 1700, 1455, 1255, 1035, 850 cm^{-1}; ^1H nmr (270 MHz, CDCl3, 50 °C) δ: 0.21 (9H, s), 2.62 (1H, dd, *J*=6.3 and 14.1 Hz), 3.15 (2H, m), 3.73, 4.17, 4.73, 5.16 (each 1H, d, *J*=15.2 Hz), 4.38 (1H, m), 4.83 (1H, m), 7.29 (1H, m).

(±)-(3aα,4α,6aα)-1,3-Dibenzyl-3a,4,6,6a-tetrahydro-4-hydroxy-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one [(±)-1].

To a solution of (±)-**13** (300 mg) in tetrahydrofuran (9.0 ml), *p*-toluenesulfonic acid (14 mg) was added, and the mixture was refluxed for 3.5 h. After removal of the solvent, the residue was subjected to silica gel column chromatography (hexane : ethyl acetate, 1 : 1) to afford (±)-**1** (101 mg, 41%): Anal. Calcd for $C_{19}H_{20}N_2O_2S$: C, 67.03; H, 5.92; N, 8.23; S, 9.42. Found: C, 67.08; H, 5.86; N, 8.21; S, 9.10; ir (KBr) 3300, 1660, 1460, 1250 cm^{-1}; ^1H nmr (200 MHz, $CDCl_3$) δ: 2.17 (1H, br s), 2.85 (1H, d, *J*=12.7 Hz), 3.08 (1H, dd, *J*=4.7 and 12.7 Hz), 4.02 (1H, d, *J*=7.9 Hz), 4.22 (1H, m), 4.21, 4.31, 4.66, 4.74 (each 1H, d, *J*=15.5 Hz), 5.18 (1H, s), 7.3 (10H, m).

(2*RS*,3*SR*,4*RS*)-3,4-Bis(carboethoxyamino)-2-trimethylsilylthiophaneoxides [(±)-14 and (±)-15].

To a solution of (±)-**9** (716 mg, 2.14 mmol) in methanol (35 ml), sodium metaperiodate (500 mg, 2.34 mmol) dissolved in water (17 ml) was added at 0°C, and the mixture was stirred for 10 h at 10 °C. Then chloroform and water were added to the mixture. The organic layer was separated, dried over Na_2SO_4 and concentrated *in vacuo*.

The residue was subjected to silica gel column chromatography to afford (±)-**14** (257 mg, 34%) and (±)-**15** (417 mg, 56%). (±)-**14**: mp 126-127 °C; Anal. Calcd for $C_{13}H_{26}N_2O_5SSi$: C, 44.55; H, 7.48; N, 7.99; S, 9.15. Found: C, 44.53; H, 7.35; N, 8.09; S, 8.93; ir (KBr); 3360, 1715, 1513, 1250, 1000, 840 cm^{-1}; ^{1}H-nmr (400 MHz, $CDCl_3$) δ: 0.30 (9H, s), 1.24 (3H, t, *J*=7.1 Hz), 1.26(3H, t, *J*=7.2 Hz), 1.86 (1H, d, *J*=4.8 Hz), 2.70 (1H, dd, *J*=7.9 and 14.3 Hz), 3.87 (1H, dd, *J*=9.4 and 14.3 Hz), 4.14 (4H, m), 4.37 (1H, m), 4.93 (1H, dt, *J*=4.8 and 9.4 Hz), 5.57 (1H, d, *J*=6.8 Hz), 6.26 (1H, d, *J*=9.4 Hz). The crystal data are as follows: a = 12.589 (4), b = 15.080 (3), c = 10.390 (4) Å, α = 96.46 (3), β = 95.83 (3), γ = 77.10 (3)°, V = 1904 (1)Å^3, triclinic, Space Group $P\bar{1}$, Z = 4, Density = 1.223 g cm^{-3}. (±)-**15**: mp 81-83 °C; Anal. Calcd for $C_{13}H_{26}N_2O_5SSi$: C, 44.55; H, 7.48; N, 7.99; S, 9.15. Found: C, 44.31; H, 7.47; N, 7.76; S, 9.23; ir (KBr) 3300, 1720, 1535, 1245, 1000, 840 cm^{-1}; ^{1}H nmr (270 MHz, $CDCl_3$ + D_2O, 50 °C) δ: 0.23 (9H, s), 1.24 (6H, t, *J*=7.0 Hz), 2.50 (1H, d, *J*=6.2 Hz), 2.90 (1H, m), 3.22 (1H, dd-like, *J*=6.5 and 14.2 Hz), 4.13 (4H, m), 4.9 (2H, m).

(2*RS*,3*RS*,4*SR*)-3,4-Bis(carboethoxyamino)-2-hydroxythiophane [(±)-16].

A solution of (±)-**14** (500 mg, 1.43 mmol) in tetrahydrofuran (5.0 ml) was refluxed for 11 h, and the solvent was removed under reduced pressure. Then methanol (25 ml) and citric acid (1.25 g) were added to the redidue and the resulting mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the residue was dissolved in ethyl acetate, washed with water and dried over Na_2SO_4. The resulting mixture was concentrated to give an oil, which was purified by silica gel column chromatography (hexane : ethyl acetate, 1 : 1) to afford (±)-**16** as white crystals (229 mg, 58%): mp 130-131°C; Anal. Calcd for $C_{10}H_{18}N_2O_5S$: C, 43.15; H, 6.52; N, 10.06. Found: C, 43.32; H, 6.60; N, 10.06; ir (KBr) 3370, 1730, 1690, 1520, 1240 cm^{-1}; ^{1}H nmr (270 MHz, $CDCl_3$ + D_2O, 50 °C) δ: 1.25 (3H, t, *J*=7.1 Hz), 1.26 (3H, t, *J*=7.1 Hz), 2.99 (1H, dd, *J*=1.3 and 11.5 Hz), 3.19 (1H, dd, *J*=5.6 and 11.5 Hz), 4.12 (2H, q, *J*=7.1 Hz), 4.15 (2H, q, *J*=7.1 Hz), 4.15 (1H, m), 4.61 (1H, m), 5.39 (1H, d, *J*=4.6 Hz), 5.46 (1H, br d, *J*=8.0 Hz), 5.91 (1H, br d, *J*=9.6 Hz).

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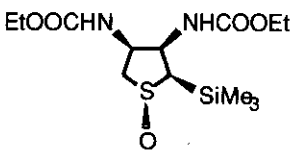
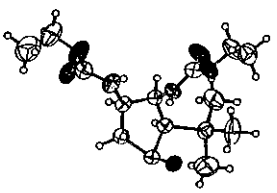
7. 

(±)-**14**

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