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SYNTHESIS OF (4R,5S)-MELITHIAZOLS B AND M

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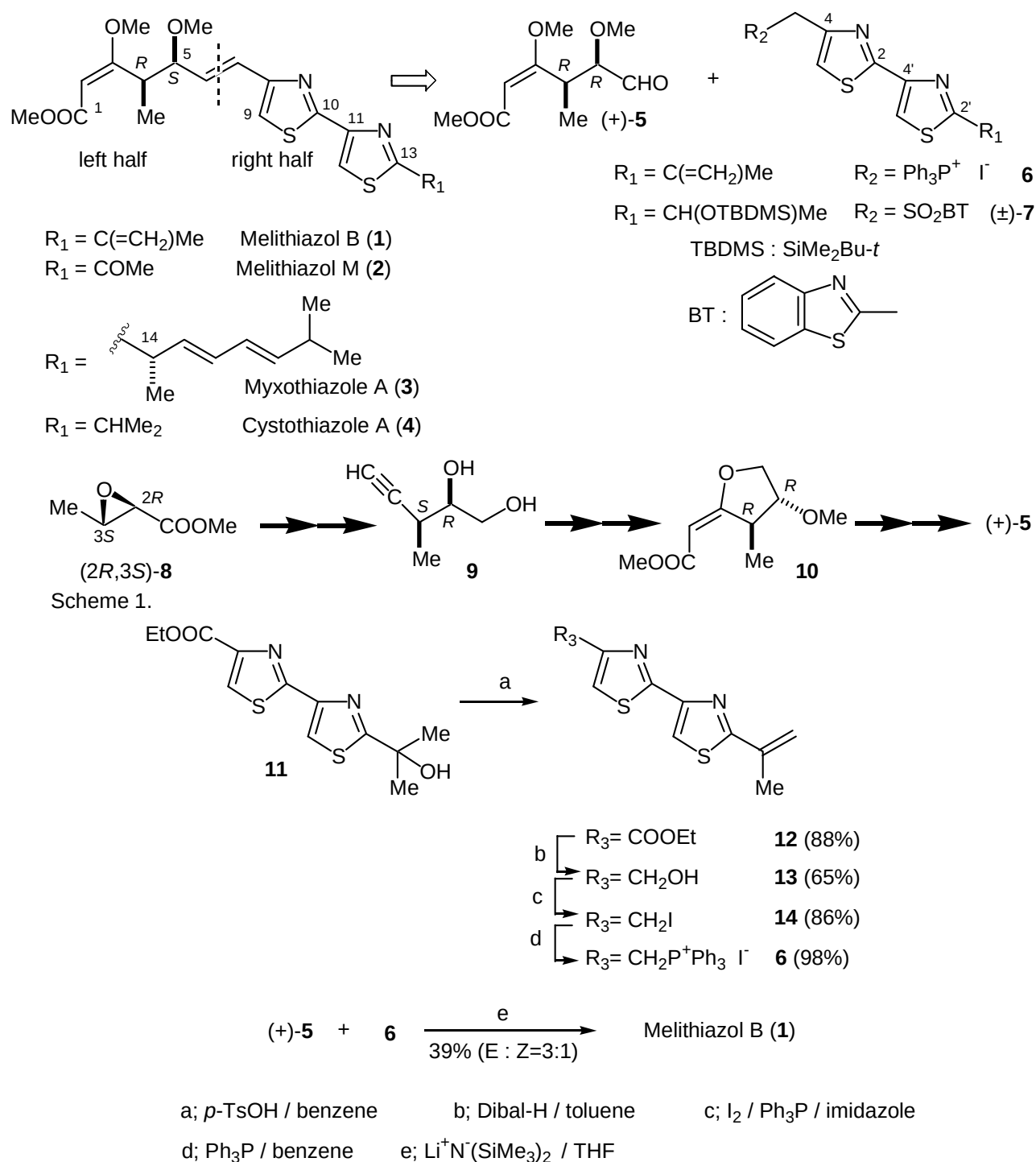
Abstract- A Wittig reaction between the reported (+)-chiral aldehyde [(4R,5R)-5] and the phosphoranylide derived from the bithiazole-type phosphonium iodide (6) using lithium bis(trimethylsilyl)amide afforded the (+)-melithiazol B (1), whose spectral data were identical with those of the natural (+)-1 from the myxobacterium *Archangium gephyra*, strain Ar 7747. Moreover, the selective olefin formation between (+)-(4R,5R)-5 and the bithiazole-type sulfone [(±)-7] followed by transformation gave the (+)-melithiazol M (2), whose spectral data were identical with those of the natural (+)-2 from the myxobacterium *Archangium gephyra*, strain Ar 7747.

Melithiazols B (1) and M (2) have been isolated from myxobacterium *Archangium gephyra*, strain Ar 7747, and exhibit antifungal and cytotoxic activity, inhibition of NADH oxidation.¹ The structures of B (1) and M (2) were established on the basis of spectroscopic analysis and the absolute configuration of B (1) was determined by CD spectroscopy.¹ Semisynthesis of B (1) and M (2) was achieved based on the chemical conversion from myxothiazol A (3) possessing (4R,5S,14S)-absolute configurations.² Meanwhile, we reported the total synthesis of an antifungal substance named cystothiazole A (4)³ from the myxobacterium *Cystobacter fuscus* strain AJ-13278. Cystothiazole A (4) was reported to exhibit an inhibitory activity against the phytopathogenic fungus, *Phytophthora capsici*.⁴ This paper describes the total synthesis of (4R,5S)-melithiazols B (1) and M (2). (Scheme 1.)

Synthesis of (4R,5S)-melithiazol B (1)

Retrosynthetically, the synthesis of 1 can be achieved by Wittig condensation of the left-half aldehyde (5) and the right-half phosphonium iodide (6). The synthesis of (+)-chiral aldehyde [(4R,5R)-5] was achieved in the total synthesis of cystothiazole A (4).⁴ Palladium-catalyzed cyclization-

methoxycarbonylation of (2*R*,3*S*)-3-methylpenta-4-yne-1,2-diol (**9**) derived from (2*R*,3*S*)-epoxy butanoate (**8**) followed by methylation gave the tetrahydro-2-furylidene acetate (**10**), which was converted to the left-half aldehyde [(+)-(4*R*,5*R*)-**5**].³ (Scheme 1.) The synthesis of the right part (**6**) is shown in Scheme 2.

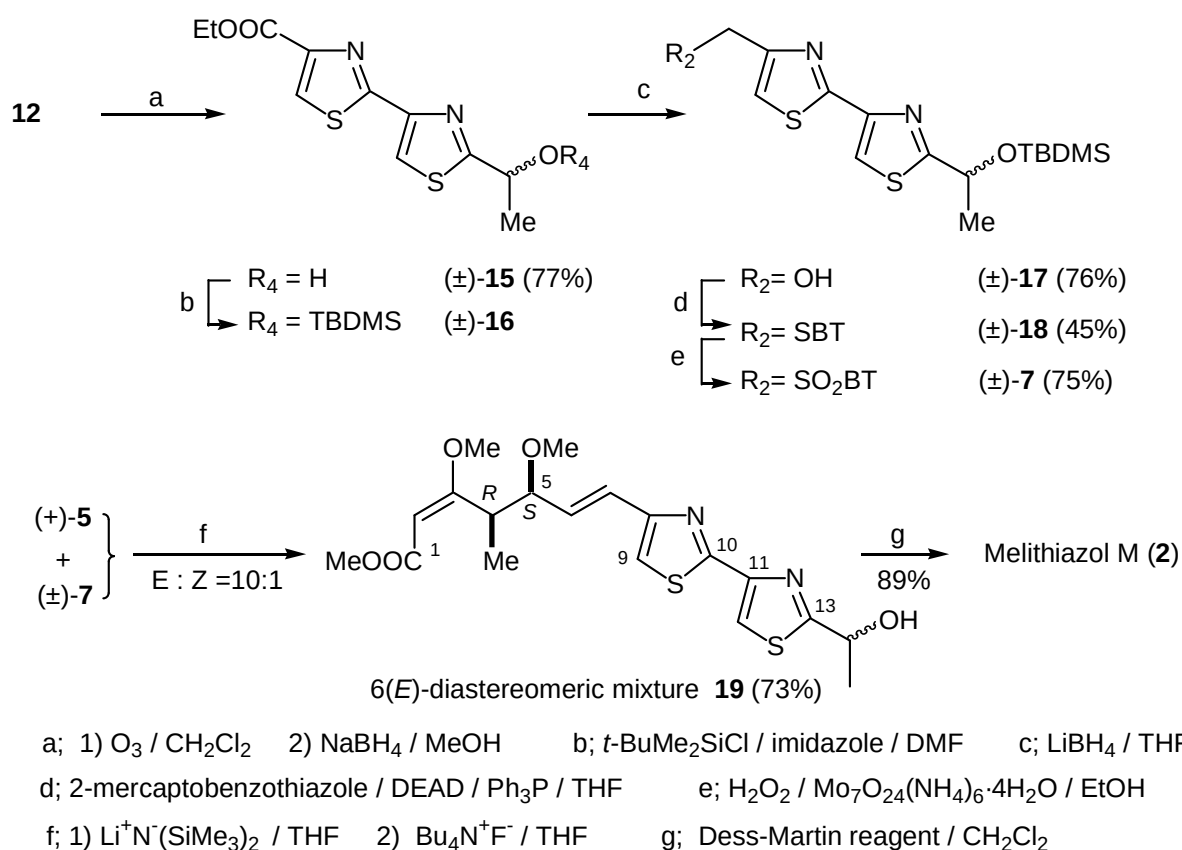


Treatment of the previously reported alcohol (**11**)⁵ with *p*-TsOH gave an olefin (**12**) in 88% yield, which was reacted with Dibal-H to afford a primary alcohol (**13**) in 65%. Treatment of **13** with

I_2/Ph_3P /imidazole provided an iodide (**14**) in 86% yield. The reaction of **14** with triphenylphosphine gave a phosphonium salt (**6**) in 98% yield, which was condensed with (+)-(4*R*,5*R*)-**5** in the presence of lithium bis(trimethylsilyl)amide in THF to afford a 3:1 ((*E*) / (*Z*)) mixture of olefins (**1**) in 39% yield. A part of this mixture was subjected to purification by means of preparative silica-gel thin-layer chromatography (CH_2Cl_2) to provide (+)-**1** as a colorless oil. The condensation yield was found to be unsatisfactory, but reaction conditions were not optimized at this time. The physical data of the synthetic (+)-**1** were identical with those of the reported melithiazol B (**1**).¹ Moreover, the physical data of the synthetic (+)-**1** ($[\alpha]_D +89.5^\circ$ ($c=0.43$, $CHCl_3$), 1H -NMR($CDCl_3$)) were identical with those ($[\alpha]_D +67^\circ$ ($c=0.036$, $CHCl_3$), 1H -NMR($CDCl_3$)) of melithiazol B [(+)-**1**] from the myxobacterium *Cystobacter fuscus* strain AJ-13278.⁶

Synthesis of (4*R*,5*S*)- melithiazol M (**2**)

Retrosynthetically, the synthesis of **2** can be achieved by the selective (*E*)-double bond formation between the left-half aldehyde (+)-[(4*R*,5*R*)-**5**] and the right-half sulphone [(±)-**7**]. The selective (*E*)-olefin formation could be achieved by applying the modified Julia olefination.⁷ The synthesis of the right part [(±)-**7**] is shown in Scheme 3.



Scheme 3.

Ozonolysis of the olefin (**12**) followed by $NaBH_4$ reduction gave secondary alcohol [(±)-**15**] in 77% yield. Silylation of (±)-**15** followed by reduction with $LiBH_4$ afforded the reported primary alcohol [(±)-**17**]⁸ in

76% yield from ($\pm$)-**15**. The reaction of ($\pm$)-**17** with 2-mercaptobenzothiazole in the presence of diethyl azocarboxylate (DEAD) and Ph_3P provided a sulfide [($\pm$)-**18**] in 45% yield. Oxidation of ($\pm$)-**18** with H_2O_2 in the presence of hexaammonium heptamolybdate tetrahydrate ($(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$) gave the corresponding sulfone [($\pm$)-**7**] in 75% yield, which was condensed with (+)-**5** in the presence of lithium bis(trimethylsilyl)amide in THF to afford a 10:1 (*E* / *Z*) mixture of olefins. Deprotection of the silyl group in this mixture with tetrabutylammonium fluoride (TBAF) gave an olefinic mixture (**19**), which was subjected to purification by means of preparative silica-gel thin-layer chromatography (*n*-hexane-AcOEt = 2:1) to provide a diastereomeric mixture of (*E*)-**19** as a colorless oil in 73% yield from (+)-**5**. Dess-Martin oxidation of (*E*)-**19** afforded (+)-**2** as a colorless oil in 89% yield. The physical data of the synthetic (+)-**2** were identical with those of the reported melithiazol M (**2**).¹ The specific rotation of the synthetic **2** ($[\alpha]_{\text{D}} +83.6^\circ$ ($c=0.99$, CHCl_3)) were identical with those ($[\alpha]_{\text{D}} +84^\circ$ ($c=0.11$, CHCl_3), $^1\text{H-NMR}(\text{CDCl}_3)$) of Professor Ojika's sample (+)-**2**.⁶

CONCLUSION

A Wittig reaction between (+)-(4*R*,5*R*)-**5** and the phosphoranylide derived from the bithiazole-type phosphonium iodide (**6**) using lithium bis(trimethylsilyl)amide afforded the (+)-melithiazol B (**1**), whose spectral data were identical with those of the natural product [(+)-**1**]. Moreover, the selective olefin formation between (+)-(4*R*,5*R*)-**5** and the sulfone [($\pm$)-**7**] followed by transformation gave the (+)-melithiazol M (**2**), whose spectral data were identical with those of the natural product [(+)-**2**].

EXPERIMENTAL

All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^1H - and ^{13}C -NMR spectra were recorded on JEOL AL 400 spectrometer in CDCl_3 . Carbon substitution degrees were established by DEPT pulse sequence. HRMS spectra and the FAB MS spectra were obtained with a JEOL JMS 600H spectrometer. IR spectra were recorded with a JASCO FT/IR-300 spectrophotometer. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. CD spectra were measured with a JASCO J-720 spectropolarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

4-Ethoxycarbonyl-2'-propenyl-2,4'-bithiazole (**12**)

A mixture of **11** (1.0 g, 3.35 mmol) and *p*-toluenesulphonic acid (*p*-TsOH, 0.701 g, 3.7 mmol) in benzene (30 mL) was refluxed for 2 h. The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over MgSO_4 and evaporated to give a crude **12**, which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt=10:1) to afford colorless crystal (**12**) (0.831 g, 88%). Recrystallization of **12** from *n*-hexane gave colorless needles (**12**). **12**: mp 122-123°C, IR (KBr): 1731 cm^{-1} ; $^1\text{H-NMR}$: δ

1.43 (3H, t, $J=7.2$ Hz), 2.28 (3H, s), 4.45 (2H, q, $J=7.2$ Hz), 5.39 (1H, s), 5.91 (1H, s), 8.07 (1H, s), 8.18 (1H, s). ^{13}C -NMR: δ 14.4, 20.4, 61.5, 117.0, 117.6, 127.8, 137.7, 147.9, 148.6, 161.5, 163.6, 167.0. Anal. Calcd for $\text{C}_{12}\text{H}_{12}\text{N}_2\text{O}_2\text{S}_2$: C, 51.41; H, 4.31; N, 9.99. Found: C, 51.32; H, 4.45; N, 9.82. MS (FAB) m/z : 281 (M^++1).

4-Hydroxymethyl-2'-propenyl-2,4'-bithiazole (13)

To a solution of **12** (2.07 g, 7.38 mmol) in toluene (40 mL) was added 1M-HAl(*i*-Bu)₂ toluene solution (18.5 mL, 18.5 mmol) with stirring at -78°C and the whole mixture was stirred for 30 min. The reaction mixture was diluted with AcOEt (40 mL) and H₂O (24 mL) and the generated precipitate was filtered off with the aid of Celite. The filtrate was extracted with AcOEt and the extract was washed with brine, and dried over MgSO₄. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (40 g, *n*-hexane:AcOEt=5:1) to afford **13** (0.95 g, 65%). Recrystallization of **13** from *n*-hexane provided colorless needles (**13**). **13**: mp 126-127 $^\circ\text{C}$; IR (KBr): 3259 cm^{-1} ; ^1H -NMR: δ 2.27 (3H, s), 4.81 (2H, s), 5.36 (1H, s), 5.91 (1H, s), 7.20 (1H, s), 7.88 (1H, s). ^{13}C -NMR: δ 20.4, 60.8, 115.5, 115.7, 117.5, 137.8, 149.3, 157.2, 163.6, 169.9. Anal. Calcd for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{OS}_2$: C, 50.39; H, 4.23; N, 11.75%. Found: C, 50.35; H, 4.21; N, 11.66. MS (FAB) m/z : 239 (M^++1).

4-Iodomethyl-2'-propenyl-2,4'-bithiazole (14)

To a mixture of **13** (1.16 g, 4.85 mmol), triphenylphosphine (1.40 g, 5.34 mmol) and imidazole (0.496 g, 7.3 mmol) in THF (25 mL) was added I₂ (1.35 g, 5.33 mmol) under argon atmosphere and the whole mixture was stirred for 30 min at rt. The reaction mixture was diluted with H₂O and extracted with AcOEt. The organic layer was washed with 1% aqueous Na₂S₂O₃ and brine, and dried over MgSO₄. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (30 g, *n*-hexane:AcOEt=20:1) to afford **14** (1.46 g, 86%). Recrystallization of **13** from *n*-hexane provided colorless needles (**14**). **14**: mp 137-138 $^\circ\text{C}$; IR (KBr): 1618 cm^{-1} ; ^1H -NMR: δ 2.27 (3H, s), 4.56 (2H, s), 5.37 (1H, s), 5.91 (1H, s), 7.27 (1H, s), 7.90 (1H, s). ^{13}C -NMR: δ -1.51, 20.4, 116.0, 116.9, 117.5, 137.7, 149.2, 154.0, 163.1, 169.9. Anal. Calcd for $\text{C}_{10}\text{H}_9\text{N}_2\text{IS}_2$: C, 34.49; H, 2.61; N, 8.04. Found: C, 34.55; H, 2.71; N, 7.79. MS (FAB) m/z : 349 (M^++1).

2'-Propenyl[2,4']bithiazolyl-4-methylenetriphenylphosphonium Iodide (6)

A mixture of **14** (1.18 g, 3.39 mmol) and triphenylphosphine (0.978 g, 3.73 mmol) in benzene (10 mL) was stirred for 8 h at reflux. After cooling, the resulting colorless powder (**6**) (2.04 g, 98%) was obtained by filtration. **6**: mp 266-267 $^\circ\text{C}$ (benzene); IR (KBr): 1490, 1434, 1110 cm^{-1} ; ^1H -NMR: δ 2.23 (3H, s), 5.36 (1H, s), 5.50 (2H, d, $J=14$ Hz), 5.87 (1H, s), 7.30 (1H, s), 8.09 (1H, s), 7.62-7.84 (15H, m). Anal. Calcd for $\text{C}_{28}\text{H}_{24}\text{N}_2\text{IPS}_2$: C, 55.08; H, 3.96; N, 4.59. Found: C, 55.16; H, 3.91; N, 4.26. MS (FAB) m/z :

483 ($M^+ - 1$).

Wittig condensation of (+)-5 and 6

To a solution of **6** (0.567 g, 0.93 mmol) in THF (5 mL) was added lithium bis(trimethylsilyl)amide (1M solution in THF, 0.86 mL, 0.86 mmol) at 0°C under argon atmosphere and the whole mixture was stirred for 20 min at the same temperature. A solution of (+)-**5** (0.090 g, 0.42 mmol) in THF (2 mL) was added to the above reaction mixture at 0°C and the whole mixture was stirred for 15 min at the same temperature. The reaction mixture was diluted with H₂O and extracted with AcOEt. The organic layer was dried over MgSO₄ and evaporated to afford a crude product which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt=20:1) to give a mixture ((*E*) : (*Z*)=3:1) of **1** (0.052 g, 39%). A part of this mixture (0.015 g) was subjected to thin-layer chromatography (silica-gel, CH₂Cl₂) to afford (+)-**1** (0.009 g) as a colorless oil. (+)-(4*R*,5*S*)-**1**: [α]_D²⁷ +89.5° (*c*=0.43, CHCl₃); UV (MeOH) $\lambda_{\max}$ 235 (ϵ 27785), 307 (ϵ 8641) nm; CD (MeOH) λ_{ext} 225 ($\Delta\epsilon$ -15.9), 253 (+20.4), 308 (-0.6) nm; IR (neat): 1713, 1625 cm⁻¹; ¹H-NMR (CDCl₃): δ 1.22 (3H, d, *J*=6.8 Hz), 2.28 (3H, s), 3.34 (3H, s), 3.61 (3H, s), 3.67 (3H, s), 3.82 (1H, t, *J*=7.8 Hz), 4.18 (1H, dq, *J*=7.6, 7.2 Hz), 4.97 (1H, s), 5.36 (1H, s), 5.91 (1H, s), 6.42 (1H, dd, *J*=7.6, 15.8 Hz), 6.57 (1H, d, *J*=15.8 Hz), 7.10 (1H, s), 7.90 (1H, s). ¹³C-NMR (CD₃OD): δ 14.1, 20.5, 39.8, 50.8, 55.6, 57.0, 84.4, 91.1, 115.3, 115.7, 117.3, 125.5, 131.7, 137.8, 149.6, 154.4, 162.5, 167.8, 169.8, 176.8. HRMS (FAB) (*m/z*): Calcd for C₂₀H₂₅N₂O₄S₂ ($M^+ + 1$): 421.1255. Found: 421.1314.

(±) 4-Ethoxycarbonyl-2'-(1-hydroxyethyl)-2,4'-bithiazole (15)

Ozone was passed through a solution of **12** (0.5 g, 1.78 mmol) in CH₂Cl₂ (20 mL) at -78°C for 5 h, then MeOH (5 mL) and NaBH₄ (0.1 g) were added to the ozonolysed product. The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over MgSO₄ and evaporated to give a residue, which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt=5:1) to afford a colorless crystal [(±)-**15**] (0.395 g, 77%). Recrystallization of (±)-**15** from *n*-hexane-AcOEt gave colorless needles [(±)-**15**]. (±)-**15**: mp 120-121°C, IR (KBr): 3316, 1727 cm⁻¹; ¹H-NMR: δ 1.43 (3H, t, *J*=7.2 Hz), 1.69 (3H, d, *J*=6.4 Hz), 3.13 (1H, s), 4.44 (2H, q, *J*=7.2 Hz), 5.20 (1H, q, *J*=6.4 Hz), 8.12 (1H, s), 8.16 (1H, s). ¹³C-NMR: δ 14.4, 24.1, 61.6, 68.2, 117.5, 127.7, 148.0, 148.1, 161.5, 163.4, 176.8. Anal. Calcd for C₁₁H₁₂N₂O₃S₂: C, 46.46; H, 4.25; N, 9.85. Found: C, 46.52; H, 4.35; N, 9.63. MS (FAB) *m/z*: 285 ($M^+ + 1$).

(±) 2'-(1-^tButyldimethylsiloxyethyl)-4-hydroxymethyl-2,4'-bithiazole (17)

i) A solution of (±)-**15** (0.925 mg, 3.25 mmol), imidazole (0.443 g, 6.61 mmol) and ^tbutyldimethylsilyl chloride (TBDMSCl, 0.736 g, 4.88 mmol) in DMF (5 mL) was stirred for 3 h at rt. The reaction mixture

was diluted with brine and extracted with AcOEt. The organic layer was dried over MgSO_4 and evaporated to give a crude ($\pm$)-**16**, which was used for the next reaction without further purification. ii) A mixture of the crude ($\pm$)-**16** and LiBH_4 (0.283 g, 13 mmol) in THF (5 mL) was stirred for 50 min at rt. The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried over MgSO_4 and evaporated to give a residue, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt=5:1) to afford a colorless crystal [($\pm$)-**17**] (0.891 g, 76%). Recrystallization of ($\pm$)-**17** from *n*-hexane gave colorless prisms [($\pm$)-**17**]. ($\pm$)-**17**: mp 82-83°C, IR (KBr): 3317, 3110 cm^{-1} ; ^1H -NMR: δ 0.11 (3H, s), 0.14 (3H, s), 0.96 (9H, s), 1.60 (3H, d, $J=6.4$ Hz), 4.81 (2H, s), 5.17 (1H, q, $J=6.4$ Hz), 7.19 (1H, s), 7.89 (1H, s). ^{13}C -NMR: δ -5.1, -4.7, 18.1, 25.3, 25.7 (X3), 61.0, 69.4, 115.0, 116.0, 148.8, 157.0, 163.6, 179.0. Anal. Calcd for $\text{C}_{15}\text{H}_{24}\text{N}_2\text{O}_2\text{S}_2\text{Si}$: C, 50.52; H, 6.78; N, 7.86. Found: C, 50.53; H, 6.80; N, 7.84. MS (FAB) m/z : 357 (M^++1).

2-Benzothiazolyl sulfide derivative (18)

To a solution of ($\pm$)-**17** (0.84 g, 2.36 mmol) in THF (10 mL) were added triphenylphosphine (1.24 g, 4.72 mmol), diethyl azocarboxylate (DEAD, 0.615 g, 3.54 mmol) and 2-mercaptobenzothiazole (0.788 g, 4.71 mmol) and the whole mixture was stirred for 1 h at rt. The reaction mixture was diluted with 2M-aqueous NaOH and extracted with ether. The organic layer was washed with brine and dried over MgSO_4 . The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt=6:1) to afford ($\pm$)-**18** (0.538 g, 45%) as a pale yellow oil. ($\pm$)-**18**: ^1H -NMR: δ 0.11 (3H, s), 0.14 (3H, s), 0.95 (9H, s), 1.59 (3H, d, $J=6.4$ Hz), 4.77 (2H, s), 5.17 (1H, q, $J=6.4$ Hz), 7.27-7.31 (1H, m), 7.34 (1H, s), 7.40-7.44 (1H, m), 7.73-7.76 (1H, m), 7.87 (1H, s), 7.89-7.92 (1H, m). ^{13}C -NMR: δ -5.1, -4.7, 18.1, 25.4, 25.7 (X3), 32.9, 69.4, 116.1, 117.4, 121.0, 121.6, 124.3, 126.0, 135.4, 148.8, 152.1, 153.1, 163.2, 165.9, 179.0. MS (FAB) m/z : 506 (M^++1).

2-Benzothiazolyl sulfone derivative (7)

To a solution of ($\pm$)-**18** (0.51 g, 1.01 mmol) in EtOH (5 mL) were added hexaammonium heptamolybdate tetrahydrate ($(\text{NH}_4)_6\text{Mo}_7\text{O}_{24}\cdot 4\text{H}_2\text{O}$, 0.124 g, 0.1 mmol) and 30% aqueous H_2O_2 (1 mL) at 0°C. The whole mixture was stirred for 22 h at rt. The reaction mixture was diluted with brine and extracted with AcOEt, and the extract was dried over MgSO_4 . The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (15 g, *n*-hexane:AcOEt=8:1) to afford ($\pm$)-**7** (0.41 g, 75%) as a colorless amorphous. ($\pm$)-**7**: mp 45-46°C; IR (KBr): 2936, 1335, 1157, 1118 cm^{-1} ; ^1H -NMR: δ 0.09 (3H, s), 0.12 (3H, s), 0.94 (9H, s), 1.55 (3H, d, $J=6.4$ Hz), 4.99 (2H, s), 5.11 (1H, q, $J=6.4$ Hz), 7.22 (1H, s), 7.35 (1H, s), 7.55-7.59 (1H, m), 7.62-7.67 (1H, m), 7.91-7.94 (1H, m), 8.26-8.28 (1H, m). ^{13}C -NMR: δ -5.1, -4.7, 18.1, 25.3, 25.7 (X3), 57.0, 69.3, 115.9, 121.3, 122.2, 125.6, 127.6, 128.0, 137.3, 142.7, 148.3,

152.7, 163.4, 165.1, 178.9. Anal. Calcd for $C_{22}H_{27}N_3O_3S_4Si$: C, 49.13; H, 5.06; N, 7.81. Found: C, 49.05; H, 5.06; N, 7.52. MS (FAB) m/z : 538 ($M^+ + 1$).

Double bond formation between (+)-5 and (±)-7 based on modified Julia's method

To a solution of (±)-7 (0.392 g, 0.73 mmol) in THF (5 mL) was added lithium bis(trimethylsilyl)amide (1M solution in THF, 0.73 mL, 0.73 mmol) at 0°C under argon atmosphere and the whole mixture was stirred for 15 min at the same temperature. A solution of (+)-5 (0.105 g, 0.49 mmol) in THF (2 mL) was added to the above reaction mixture at 0°C and the whole mixture was stirred for 20 min at the same temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product, which was used for the next reaction without further purification. ii) To a solution of the above-mentioned crude product in THF (4 mL) was added 1M-tetrabutylammonium fluoride ($Bu_4N^+F^-$) solution (0.48 mL, 0.48 mmol) at 0°C and the whole mixture was stirred for 40 min at the same temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product, which was chromatographed on silica gel (12 g, *n*-hexane:AcOEt=3:1) to give a mixture ((*E*) : (*Z*)=10:1) of **19**. This mixture was subjected to preparative thin-layer chromatography (silica gel, *n*-hexane:AcOEt = 2:1) to afford (*E*)-**19** (0.166 g, 73%) as a pale yellow amorphous. (*E*)-**19**: IR ($CHCl_3$): 3453, 1705, 1620 cm^{-1} ; 1H -NMR ($CDCl_3$): δ 1.22 (3H, d, $J=6.8$ Hz), 1.68 (3H, d, $J=6.4$ Hz), 3.33 (3H, s), 3.61 (3H, s), 3.66 (3H, s), 3.82 (1H, dd, $J=7.6, 8.0$ Hz), 4.17 (1H, dq, $J=7.2, 6.8$ Hz), 4.97 (1H, s), 5.19 (1H, q, $J=6.8$ Hz), 6.42 (1H, dd, $J=7.6, 16.0$ Hz), 6.58 (1H, d, $J=16.0$ Hz), 7.10 (1H, s), 7.96 (1H, s). ^{13}C -NMR (CD_3OD): δ 14.1, 24.1, 39.8, 50.8, 55.6, 57.0, 68.2, 84.4, 91.1, 115.1, 116.3, 125.3, 132.0, 148.9, 154.4, 162.2, 167.8, 176.6, 176.7. MS (FAB) m/z : 425 ($M^+ + 1$).

(4*R*,5*S*)-Melithiazol **M** (2)

To a solution of (*E*)-**19** (0.124 g, 0.29 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin reagent (0.186 g, 0.44 mmol) at rt and the whole mixture was stirred for 40 min at the same temperature. The reaction mixture was diluted with brine and extracted with ether. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt=10:1) to afford (+)-**2** (0.11 g, 89%) as a pale yellow oil. (+)-**2**: $[\alpha]_D^{23} +83.6^\circ$ ($c=0.99$, $CHCl_3$), IR (KBr): 1703, 1619 cm^{-1} ; 1H -NMR: δ 1.22 (3H, d, $J=6.8$ Hz), 2.78 (3H, s), 3.35 (3H, s), 3.62 (3H, s), 3.67 (3H, s), 3.84 (1H, t, $J=7.6$ Hz), 4.18 (1H, dq, $J=7.2, 6.8$ Hz), 4.98 (1H, s), 6.46 (1H, dd, $J=16.0, 7.6$ Hz), 6.59 (1H, d, $J=16.0$ Hz), 7.16 (1H, s), 8.30 (1H, s). ^{13}C -NMR: 14.0, 26.0, 39.9, 50.8, 55.6, 57.1, 84.3, 91.1, 115.8, 122.9, 125.1, 132.3, 151.2, 154.7, 161.3, 167.1, 167.7, 176.7, 191.4. HRMS (FAB) (m/z): Calcd for $C_{19}H_{23}N_2O_5S_2$ ($M^+ + 1$): 423.1049. Found: 423.1067. MS (FAB) m/z : 423 ($M^+ + 1$).

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6. According to private communication from Professor Ojika at Nagoya University, his group also isolated melithiazoles B (**1**) and M (**2**) from the myxobacterium *Cystobacter fuscus* strain AJ-13278. Melithiazol B (**1**): colorless oil, $[\alpha]_{\text{D}}^{25} +67^\circ$ ($c=0.036$, CHCl_3); UV (MeOH) λ_{max} 235 (ϵ 28000), 307 (ϵ 8500) nm, CD (MeOH) λ_{ext} 225 ($\Delta\epsilon$ -30), 253 (+35), 308 (-1.6) nm; IR (film): ν_{max} 3102, 1708, 1624, 1147, 1094, 1038, 971, 926, 826, 804, 759 cm^{-1} ; ^1H -NMR (CDCl_3 400 MHz): δ 1.22 (3H, d, $J=6.9$ Hz), 2.28 (3H, s), 3.34 (3H, s), 3.61 (3H, s), 3.67 (3H, s), 3.82 (1H, t, $J=7.7$ Hz), 4.18 (1H, dq, $J=7.7$, 6.9 Hz), 4.97 (1H, s), 5.36 (1H, s), 5.91 (1H, s), 6.42 (1H, dd, $J=7.7$, 15.7 Hz), 6.58 (1H, d, $J=15.7$ Hz), 7.10 (1H, s), 7.89 (1H, s). HRMS (ESI) (m/z): Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_4\text{S}_2$ (M^++1): 421.1250. Found: 421.1209, Calcd for $\text{C}_{20}\text{H}_{25}\text{N}_2\text{O}_4\text{S}_2$ Na: 443.1070. Found: 443.1082. melithiazol M (**2**): colorless oil, $[\alpha]_{\text{D}}^{25} +84^\circ$ ($c=0.11$, CHCl_3); UV (MeOH) λ_{max} 234 (ϵ 30300), 310 (ϵ 9400) nm; IR (film): ν_{max} 3108, 1709, 1694, 1623, 1271, 1147, 1094, 1056, 971, 928, 826, 806, 757 cm^{-1} ; ^1H -NMR (CDCl_3 400 MHz): δ 1.22 (3H, d, $J=6.9$ Hz), 2.78 (3H, s), 3.34 (3H, s), 3.61 (3H, s), 3.67 (3H, s), 3.83 (1H, t, $J=7.7$ Hz), 4.18 (1H, dq, $J=7.7$, 6.9 Hz), 4.98 (1H, s), 6.46 (1H, dd, $J=7.7$, 15.7 Hz), 6.58 (1H, d, $J=15.7$ Hz), 7.15 (1H, s), 8.29 (1H, s). HRMS (ESI) (m/z): Calcd for $\text{C}_{19}\text{H}_{23}\text{N}_2\text{O}_5\text{S}_2$ (M^++1): 423.1043. Found: 423.1005, Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_2\text{O}_5\text{S}_2$ Na: 445.0862. Found: 445.0819. On the other hand, the reported CD spectra ((CD (MeOH) λ_{max} ($\Delta\epsilon$)=237 nm (+2.8)) of melithiazol B (**1**) were found to be different from those Professor Ojika's sample (**1**) and synthetic melithiazol B (**1**).

But, according to the recent private communication from Professor G. Höfle, the spectral data (UV, ^1H -NMR and CD) of the reported melithiazol B (**1**) are fairly identical with those of Professor Ojika's sample (**1**) and synthetic (**1**). Consequently, the previously reported CD data (CD (MeOH) λ_{max} ($\Delta\epsilon$)=237 nm (+2.8)) of melithiazol B (**1**) should be changed to the present data.

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