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Synthesis of (4*R*,5*S*)-Melithiazols F and I

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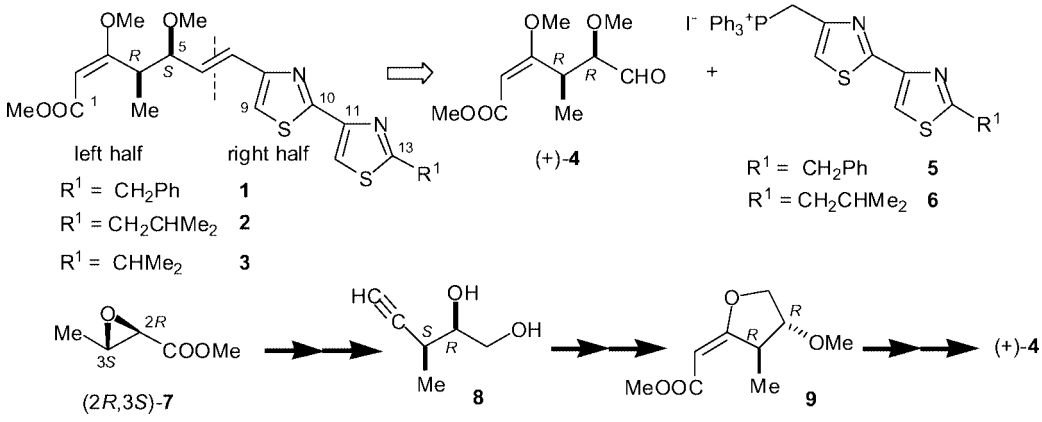
Palladium-catalyzed cyclization-methoxycarbonylation of (2*R*,3*S*)-3-methylpenta-4-yne-1,2-diol (**8**) derived from the (2*R*,3*S*)-epoxybutanoate **7** followed by methylation gave the tetrahydro-2-furylidene acetate (–)-**9**, which was converted into the left-half aldehyde (+)-**4**. A Wittig reaction between (+)-**4** and the phosphoranylide derived from the bithiazole-type phosphonium iodide **5** using lithium bis(trimethylsilyl)-amide afforded (+)-(4*R*,5*S*)-melithiazol F (**1**), whose spectroscopic data were identical with those of the natural product **1**. Moreover, the synthesis of (+)-(4*R*,5*S*)-melithiazol I (**2**), was achieved by the same synthetic strategy as that of (+)-(4*R*,5*S*)-melithiazol F (**1**). The antifungal activity of the synthetic melithiazols F (**1**) and I (**2**) against the phytopathogenic fungus, *Phytophthora capsici*, was evaluated by using a paper disc assay method.

Melithiazols F (**1**) and I (**2**) have been isolated from myxobacterium, *Myxococcus stipitatus*, strain Mx s64, and exhibit antifungal and cytotoxic activities, and inhibition of NADH oxidation.[1] The structures of F (**1**) and I (**2**) were established on the basis of spectroscopic analysis, and the absolute configurations of F (**1**) and I (**2**) were deduced as (4*R*,5*S*) by similarity to melithiazol E (**3**).[1] Compound **3** was found to be identical to an antifungal substance named cystothiazole A (**3**)[1] from the myxobacterium *Cystobacter fuscus* strain AJ-13278 by using an inhibition assay against the phytopathogenic fungus, *Phytophthora capsici*.[2,3] Meanwhile, we reported the total synthesis of cystothiazole A (**3**) based on a chemoenzymatic method.[4,5] Synthesis of melithiazols B and C based on transformation from natural myxothiazol A was reported,[6,7] while earlier reports have documented the independent total synthesis of cystothiazoles A,[8–10] B,[10,11] C,[8,9] E[12] and G.[13] This paper describes the synthesis of (4*R*,5*S*)-melithiazols F (**1**) and I (**2**) and the antifungal activity of melithiazols F (**1**) and I (**2**).

Retrosynthetically, the synthesis of **1** can be achieved by Wittig condensation of the left-half aldehyde **4** and the right-half phosphonium iodide **5** (Scheme 1). The synthesis of chiral aldehyde **4** was achieved in the total synthesis of cystothiazole A (**3**).[4,5] Palladium-catalyzed cyclization-methoxycarbonylation of (2*R*,3*S*)-3-methylpenta-4-yne-1,2-diol (**8**) derived from the (2*R*,3*S*)-epoxybutanoate **7** followed by methylation gave the tetrahydro-2-furylidene acetate (**9**), which was converted into the left-half aldehyde (+)-**4**.[4,5] The synthesis of **5**, the right part, is shown in Scheme 2.



Scheme 1.

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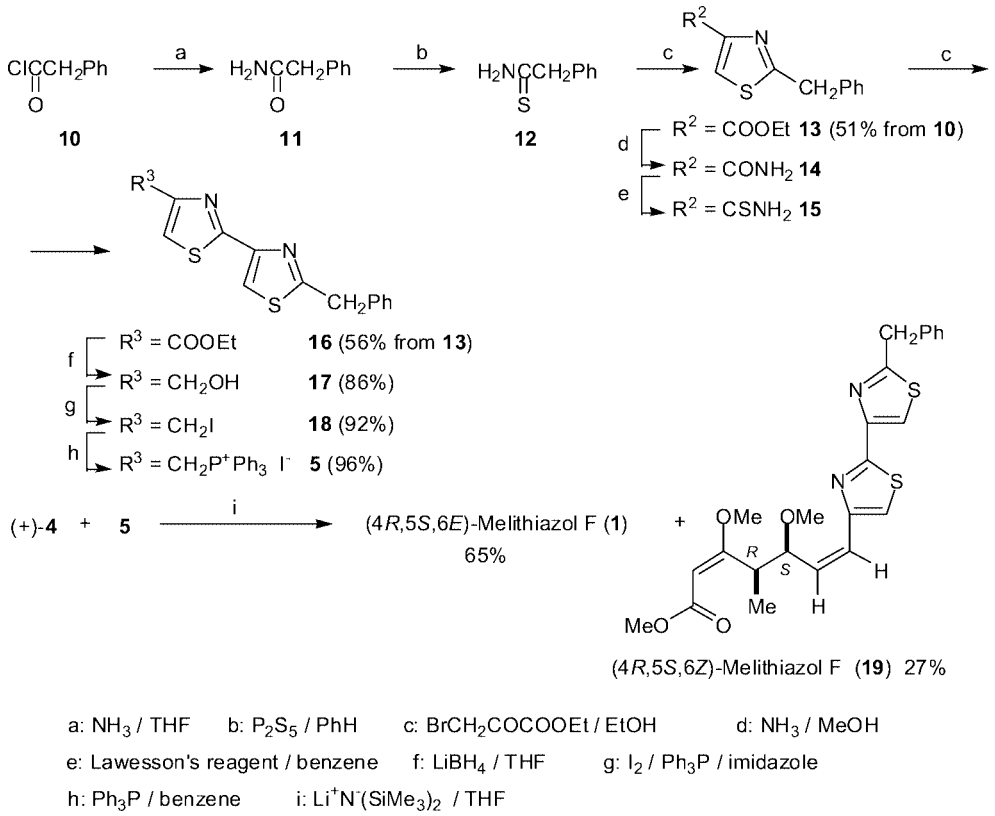
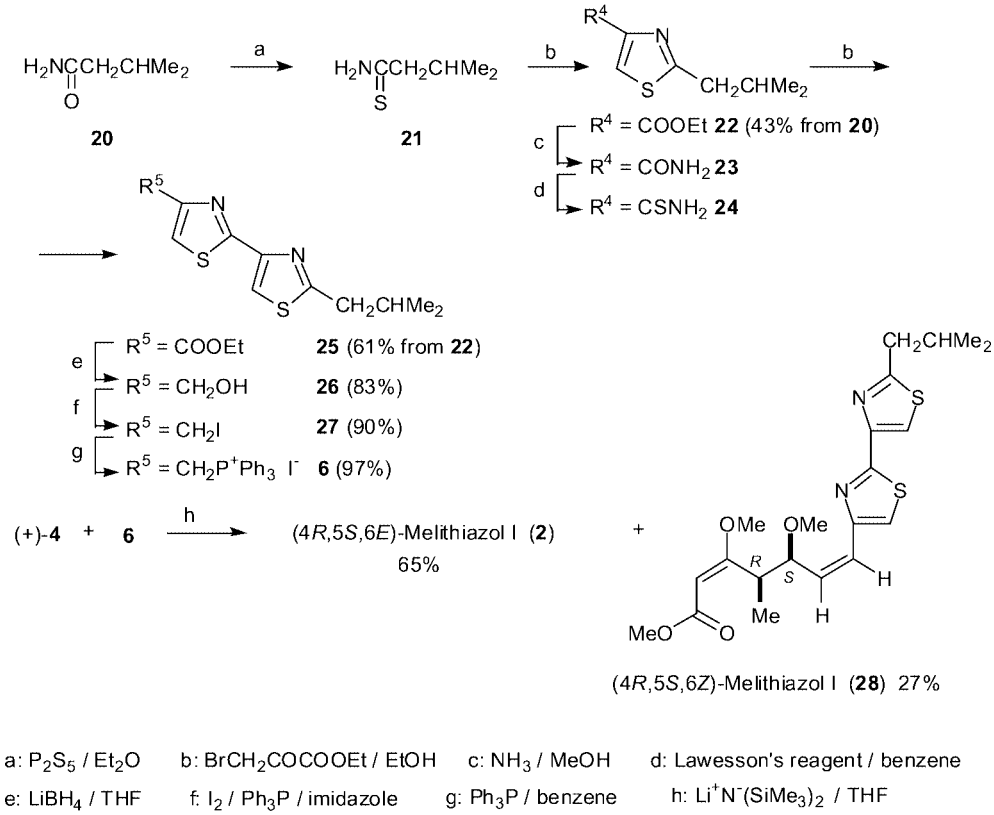


Scheme 2.

Commercially available phenylacetyl chloride (**10**) was treated with NH_3/THF to give the corresponding amide **11**. Treatment of **11** with P_4S_{10} gave the corresponding thioamide **12**, which was reacted with α-bromopyruvate to afford a mono-thiazole ester **13** in 51% overall yield from **10**. Treatment of **13** with NH_3/MeOH followed by thioamidation with Lawesson's reagent yielded thioamide **15**, which was reacted with α-bromopyruvate to afford the 2,4′-bithiazole ester **16** in 56% overall yield from **13**. $LiBH_4$ reduction [alcohol **17**: 86% yield] of **16** followed by treatment with I_2/Ph_3P/imidazole provided the iodide **18** in 92% yield. The reaction of **18** and triphenylphosphane gave the phosphonium salt **5** in 96% yield, which was condensed with (+)-**4** in the presence of lithium bis(trimethylsilyl)amide in THF to afford a mixture [(+)-(*E*)-**1**/(+)-(*Z*)-**19** = 2.33:1] of olefins in 92% yield. Both isomers were isolated by means of preparative HPLC to provide (+)-**1** as a colorless oil {$[\alpha]_D$ +79.9 (*c* = 0.925, $CHCl_3$)} and (+)-**19** as a colorless oil {$[\alpha]_D$ +231.4 (*c* = 1.41, $CHCl_3$)}. The (*Z*)-geometry of (+)-**19** was confirmed by the coupling constant (*J* = 12.0 Hz) of the olefinic protons. The physical data [^{1}H NMR ($CDCl_3$)] of the synthetic (+)-**1** were identical with those of the reported melithiazol (+)-**1**. Then the synthesis of melithiazol I (**2**) was carried out. Retrosynthetically, the synthesis of **2** can be achieved by Wittig condensation of the left-half aldehyde **4** and the right-half phosphonium iodide **6**. The synthesis of **6**, the right part, is shown in Scheme 3.

Treatment of commercially available isobutylamide **20** with P_4S_{10} gave the corresponding thioamide **21**, which was reacted with α-bromopyruvate to afford the mono-thiazole ester **22** in 43% overall yield from **20**. Treatment of **22** with NH_3/MeOH followed by thioamidation with Lawesson's reagent yielded thioamide **24**, which was reacted with α-bromopyruvate to afford the bithiazole ester **2** in 61% overall yield from **22**. $LiBH_4$ reduction (alcohol **26**: 83% yield) of **25** followed by treatment with I_2/Ph_3P/imidazole provided the iodide **27** in 90% yield. The reaction of **27** and triphenylphosphane gave the phosphonium salt **6** in 97% yield, which was condensed with (+)-**4** in the presence of lithium bis(trimethylsilyl)amide in THF to afford a mixture [(+)-(*E*)-**2**/(+)-(*Z*)-**28** = 2.83:1] of olefins in 92% yield. Both isomers were isolated by means of preparative HPLC to provide (+)-**2** as a colorless oil {$[\alpha]_D$ +91.6 (*c* = 0.63, $CHCl_3$)} and (+)-**28** as a colorless oil {$[\alpha]_D$ +245.7 (*c* = 1.46, $CHCl_3$)}. The (*Z*)-geometry of (+)-**28** was confirmed by the coupling constant (*J* = 12.0 Hz) of the olefinic protons. The physical data [^{1}H NMR($CDCl_3$)] of the synthetic (+)-**2** were identical with those of the reported melithiazol I (**2**). The antifungal activity of the synthetic melithiazols F (**1**) and I (**2**) against the phytopathogenic fungus, *Phytophthora capsici*, was evaluated by using a paper disc assay method as reported previously.[3,4] The minimum dose applied on a paper disc to inhibit the fungal growth was 1 μg/disc. The synthetic melithiazols F (**1**) and I (**2**) also showed the activities at a similar level of dosage (0.2 μg/disc and



Scheme 3.

0.04 μg/disc, respectively) in comparison to that (0.2 μg/disc) of cystothiazole A (**3**).[14] According to the recent studies on antifungal tests using the phytopathogenic fungus, *Phytophthora capsici*, synthetic cystothiazole A (**3**) [(4*R*,5*S*)-**3**] showed activity up to a dose of 0.04 μg/disc. However, not only the enantiomer (4*S*,5*R*)-**3**, but also the two diastereomers, (4*S*,5*S*)-**3** and (4*R*,5*R*)-**3**, showed no antifungal activity up to 100 μg/disc. This result was not expected at all, because all the stereoisomers possess the β-methoxyacrylate unit that is regarded as the binding site to the target molecules.[15]

In conclusion, palladium-catalyzed cyclization–methoxycarbonylation of (2*R*,3*S*)-3- methylpenta-4-yne-1,2-diol (**8**) derived from the (2*R*,3*S*)-epoxybutanoate **7** followed by methylation gave the tetrahydro-2-furylidene acetate (–)-**9**, which was converted into the left-half aldehyde (+)-**4**. Wittig reaction between (+)-**4** and the phosphoranylide derived from the bithiazole-type phosphonium iodide **5** using lithium bis(trimethylsilyl)amide afforded (+)-(4*R*,5*S*)-melithiazol F (**1**), the spectroscopic data of which were identical with those of the natural product. Moreover, the synthesis of (+)-(4*R*,5*S*)-melithiazol I (**2**) was achieved by the same synthetic strategy as that of (+)-(4*R*,5*S*)-melithiazol F (**1**). The absolute structure of natural melithiazols F (**1**) and I (**2**) might be confirmed as (4*R*,5*S*)-configuration because both natural products and synthetic products indicate antifungal activity, although the tested microorganisms were different.

Experimental Section

General: All melting points were measured on a Yanaco MP-3S micro melting point apparatus and are uncorrected. ^{1}H- and ^{13}C NMR spectra were recorded with a JEOL AL 400 spectrometer in $CDCl_3$. Carbon substitution degrees were established by DEPT pulse sequence experiments. High-resolution mass spectra (HRMS) and fast atom bombardment mass spectra (FAB MS) were obtained with a JEOL JMS 600H spectrometer. IR spectra were recorded with a JASCO FT/IR-300 spectrometer. The preparative HPLC system was composed of a detector (Shodex RI-1) and a pump (JASCO PU-2080 Plus). HPLC analysis conditions were as follows; column: YMC-Pack ProC_{18} [150 × 20 mm and Precolumn (50 × 20 mm)], solvent: MeOH/H_2O (80:20), flow rate: 5 mL/min. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

Ethyl 2-Phenethylthiazole-4-carboxylate (13): 1) NH_3 gas was bubbled into a solution of commercially available **10** (1.0 g, 6.46 mmol) in anhydrous THF (20 mL) for 10 min at room temp. The reaction mixture was diluted with H_2O and extracted with AcOEt. Evaporation of the organic solvent gave a crude amide (**11**), which was used without further purification. 2) To a solution of phosphorus pentasulfide (P_4S_{10}; 0.288 g, 0.65 mmol) in benzene (35 mL) was added crude **11** and the whole mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with brine and extracted with AcOEt. The organic layer was dried with $MgSO_4$ and evaporated to give crude **12**. 3) A mixture of crude **12** and ethyl α-bromopyruvate (1.22 g, 6.47 mmol) in EtOH (20 mL)

was refluxed for 60 min. The reaction mixture was evaporated, diluted with AcOEt, and washed with 7% aqueous $NaHCO_3$. The organic layer was dried with $MgSO_4$ and evaporated to give a crude oil, which was purified by chromatography on silica gel (20 g, *n*-hexane/AcOEt, 10:1) to afford **13** as a pale yellow oil (0.816 g, 51% overall yield from **10**). **13**: IR (KBr): $\tilde{\nu}$ = 1719 cm^{-1}. ^1H NMR: δ = 1.41 (t, *J* = 7.2 H, 3 H), 4.39 (s, 2 H), 4.43 (q, *J* = 7.2 Hz, 2 H), 7.27–7.37 (m, 5 H), 8.05 (s, 1 H) ppm. ^{13}C NMR: δ = 14.4, 39.9, 61.5, 127.5, 127.8, 129.0 (2 C), 129.2 (2 C), 137.3, 146.9, 161.5, 171.9 ppm. MS (FAB): *m*/*z* = 248 [M^+ + 1].

Ethyl 2′-Phenethyl-2,4′-bithiazolyl-4-carboxylate (16): 1) A mixture of **13** (0.78 g, 3.5 mmol) and NH_3-saturated MeOH (100 mL) in a sealed tube stood for 2 d at room temp. After cooling, the reaction mixture was evaporated to afford crude amide **14**. To a solution of crude **14** in benzene (10 mL) was added Lawesson's reagent (0.65 g, 1.6 mmol) and the whole mixture was refluxed for 1 h. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried with $MgSO_4$. The organic layer was evaporated to give crude thioamide **15**. A solution of **15** and ethyl α-bromopyruvate (0.62 g, 3.1 mmol) in absolute EtOH (10 mL) was stirred for 1.5 h at reflux. The reaction mixture was evaporated, diluted with 7% aqueous $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with brine and dried with $MgSO_4$. The organic layer was evaporated to give a crude residue, which was purified by chromatography on silica gel (20 g, *n*-hexane/AcOEt, 10:1) to afford **16** (0.581 g, 56%). Recrystallization of **16** from *n*-hexane/AcOEt provided colorless needles. **16**: m.p. 92–94 °C. IR (KBr): $\tilde{\nu}$ = 1721 cm^{-1}. ^1H NMR: δ = 1.43 (t, *J* = 7.2 Hz, 3 H), 4.37 (s, 2 H), 4.44 (q, *J* = 7.2 Hz, 2 H), 7.27–7.37 (m, 5 H), 8.03 (s, 1 H), 8.17 (s, 1 H) ppm. ^{13}C NMR: δ = 14.4, 39.6, 61.5, 117.6, 127.4, 127.7, 128.9 (2 C), 129.1 (2 C), 137.2, 147.9, 148.2, 161.5, 163.4, 171.5 ppm. $C_{16}H_{14}N_2O_2S_2$: calcd. C 58.16, H 4.27, N 8.48; found C 58.19, H 4.26, N 8.10. MS (FAB): *m*/*z* = 331 [M^+ + 1].

4-Hydroxymethyl-2′-phenethyl-2,4′-bithiazol (17): A mixture of **16** (1.54 g, 5.45 mmol) and $LiBH_4$ (0.51 g, 2.72 mmol) in THF (20 mL) was stirred for 1.5 h at room temperature. The reaction mixture was diluted with H_2O (10 mL) and the whole mixture was stirred for 5 h at the same temperature. The reaction mixture was extracted with AcOEt, washed with brine, and the organic layer dried with $MgSO_4$. The organic layer was evaporated to give a crude residue, which was purified by chromatography on silica gel (16 g, *n*-hexane/AcOEt, 1:1) to afford **17** (1.16 g, 86%). Recrystallization of **17** from *n*-hexane/AcOEt provided colorless needles. **17**: m.p. 121–123 °C. IR (KBr): $\tilde{\nu}$ = 3391, 3114 cm^{-1}. ^1H NMR: δ = 4.37 (s, 2 H), 4.81 (s, 2 H), 7.20 (s, 1 H), 7.28–7.36 (m, 5 H), 7.83 (s, 1 H) ppm. ^{13}C NMR: δ = 39.7, 61.0, 115.2, 116.4, 127.4, 128.9 (2 C), 129.1 (2 C), 137.3, 148.9, 157.2, 163.3, 171.6 ppm. $C_{14}H_{12}N_2OS_2$: calcd. C 58.31, H 4.19, N 9.71; found C 58.38, H 4.20, N 9.58. MS (FAB): *m*/*z* = 289 [M^+ + 1].

4-Iodomethyl-2′-phenethyl-2,4′-bithiazol (18): To a mixture of **17** (0.40 g, 1.38 mmol), triphenylphosphane (0.40 g, 1.52 mmol), and imidazole (0.141 g, 2.0 mmol) in THF (10 mL) was added I_2 (0.383 g, 1.52 mmol) under argon and the mixture was stirred for 10 min at room temperature. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried with $MgSO_4$. The organic layer was evaporated to give a crude residue, which was purified by chromatography on silica gel (10 g, *n*-hexane/AcOEt, 5:1) to afford **18** (0.507 g, 92%). Recrystallization of **18** from *n*-hexane provided pale yellow needles. **18**: m.p. 129–131 °C. IR (KBr): $\tilde{\nu}$ = 1499 cm^{-1}. ^1H NMR: δ = 4.37 (s, 2 H), 4.56 (s, 2 H), 7.26–7.36 (m, 5 H), 7.27 (s, 1 H), 7.89 (s, 1 H) ppm. ^{13}C NMR: δ = –1.60, 39.7, 116.7, 116.8, 127.4, 128.9 (2 C), 129.1 (2 C), 137.4, 148.7, 154.1, 162.9, 171.5 ppm. $C_{14}H_{11}IN_2S_2$: calcd. C 42.22, H 2.78, N 7.03; found C 42.27, H 2.81, N 6.50. MS (FAB): *m*/*z* = 399 [M^+ + 1].

[2′-Phenethyl-2,4′-bithiazolyl-4-yl)methyl]triphenylphosphonium Iodide (5): A mixture of **18** (0.507 g, 1.27 mmol) and triphenylphosphane (0.368 g, 1.4 mmol) in benzene (10 mL) was refluxed for 15 h. After cooling, the resulting colorless powder **5** (0.81 g, 96%) was obtained by filtration. **5**: m.p. 224–226 °C. ^1H NMR: δ = 4.32 (s, 2 H), 5.52 (d, *J* = 13.6 Hz, 2 H), 7.25 (s, 1 H), 7.27–7.37 (m, 5 H), 7.26–7.66 (m, 6 H), 7.75–7.84 (m, 9 H), 8.11 (s, 1 H) ppm. $C_{32}H_{26}IN_2PS_2$: calcd. C 58.18, H 3.97, N 4.24; found C 58.13, H 3.92, N 3.63. MS (FAB): *m*/*z* = 533 (M^+ – I).

Wittig Condensation of (+)-4 and 5: To a solution of **5** (0.608 g, 0.92 mmol) in THF (5 mL) was added lithium bis(trimethylisilyl)-amide (1 M in THF, 0.92 mL, 0.92 mmol) at 0 °C under argon and the mixture was stirred for 20 min. A solution of (+)-**4** (0.10 g, 0.46 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 with $MgSO_4$ and evaporated to afford a crude product which was purified by chromatography on silica gel (5 g, *n*-hexane/AcOEt, 20:1) to give a mixture [(*E*)/(*Z*) = 2.33:1] of isomers of **1** (0.20 g, 92%). This mixture was subjected to preparative HPLC to afford (+)-**1** (0.140 g, 58%) as a colorless oil and (+)-**19** (0.06 g, 27%) as a colorless oil. (+)-**1**: $[\alpha]_D^{28}$ = +79.9 (*c* = 0.925, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2925, 1711, 1627, 1450, 1146 cm^{-1}. ^1H NMR: δ = 1.21 (d, *J* = 7.0 Hz, 3 H), 3.30 (s, 3 H), 3.60 (s, 3 H), 3.66 (s, 3 H), 3.81 (t, *J* = 7.6 Hz, 1 H), 4.16 (dq, *J* = 7.6, 7.0 Hz, 1 H), 4.38 (s, 2 H), 4.96 (s, 1 H),6.41 (dd, *J* = 15.8, 7.6 Hz, 1 H), 6.58 (d, *J* = 15.8 Hz, 1 H), 7.10 (s, 1 H), 7.28–7.40 (m, 5 H), 7.85 (s, 1 H) ppm. ^{13}C NMR: δ = 14.0, 39.7, 39.8, 50.8, 55.5, 57.0, 84.4, 91.1, 115.0, 116.3, 125.5, 127.4, 128.9 (2 C), 129.1 (2 C), 131.8, 137.4, 149.2, 154.5, 162.2, 167.7, 171.4, 176.7 ppm. HRMS (FAB): (*m*/*z*) calcd. for $C_{24}H_{26}N_2O_4S_2$: 471.1412 [M^+ + 1]; found 471.1431. (+)-**19:** $[\alpha]_D^{29}$ = +231.4 (*c* = 1.41, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2925, 1710, 1621, 1449, 1378, 1267, 1146, 925, 817, 703 cm^{-1}. ^1H NMR: δ = 1.24 (d, *J* = 7.2 Hz, 3 H), 3.32 (s, 3 H), 3.34 (s, 3 H), 3.67 (s, 3 H), 4.22 (dq, *J* = 9.4, 7.2 Hz, 1 H), 4.39 (s, 2 H), 4.92 (s, 1 H), 5.08 (t, *J* = 9.4 Hz, 1 H), 5.60 (dd, *J* = 12.0, 9.4 Hz, 1 H), 6.59 (d, *J* = 12.0 H, 1 H), 7.24 (s, 1 H), 7.28–7.40 (m, 5 H), 7.83 (s, 1 H) ppm. ^{13}C NMR (CD_3OD): δ = 14.8, 39.3, 39.7, 50.8, 55.1, 56.3, 78.5, 91.1, 116.0, 117.9, 125.4, 127.4, 128.9 (2 C), 129.1 (2 C), 132.7, 137.4, 149.2, 153.6, 161.3, 167.8, 171.6, 176.6 ppm. HRMS (FAB): (*m*/*z*) calcd. for $C_{24}H_{26}N_2O_4S_2$ [M^+ + 1]: 471.1412; found 471.1372.

Ethyl 2-Isobutyl-1,3-thiazole-4-carboxylate (22): 1) To a solution of phosphorus pentasulfide (P_4S_{10}; 0.872 g, 1.9 mmol) in Et_2O (20 mL) was added commercially available isobutylamide **20** (1.98 g 19.6 mmol), and the mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with brine and extracted with Et_2O. The organic layer was dried with $MgSO_4$ and evaporated to give crude thioamide **21**, which was used for the next reaction without further purification. 2) A mixture of crude **21** and ethyl α-bromopyruvate (3.82 g, 19.6 mmol) in EtOH (30 mL) was refluxed for 2 h. The reaction mixture was evaporated, diluted with AcOEt, and washed with 7% aqueous $NaHCO_3$. The organic layer was dried with $MgSO_4$ and evaporated to give a crude oil, which was purified by chromatography on silica gel (40 g, *n*-hexane/AcOEt, 10:1) to afford **22** as a pale yellow oil (1.99 g, 48% overall yield from **20**). **22**: IR (KBr): $\tilde{\nu}$ = 1728 cm^{-1}. ^1H NMR: δ = 1.00 (d, *J* = 6.8 Hz, 6 H), 1.40 (t, *J* = 7.2 Hz, 3 H), 2.14 (m, 1 H), 2.93

(d, J = 7.2 Hz, 2 H), 4.42 (q, J = 7.2 Hz, 2 H), 8.06 (s, 1 H) ppm. ^{13}C NMR: δ = 14.4, 22.3 (2 C), 29.9, 42.4, 61.4, 126.9, 146.8, 161.5, 171.2 ppm. MS (FAB): m/z = 214 [M^+ + 1].

Ethyl 2′-Isobutyl-2,4′-bithiazolyl-4-carboxylate (25): 1) A mixture of **22** (1.99 g, 9.3 mmol) and NH_3-saturated MeOH (100 mL) in a sealed tube stood for 2 d at room temperature. After cooling, the reaction mixture was evaporated to afford crude amide **23**. To a solution of crude **23** in benzene (25 mL) was added Lawesson's reagent (1.72 g, 4.3 mmol) and the mixture was refluxed for 20 min. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried with $MgSO_4$. The organic layer was evaporated to give crude thioamide **24**. A solution of crude thioamide **24** and ethyl α-bromopyruvate (1.82 g, 9.3 mmol) in absolute EtOH (40 mL) was refluxed for 1 h. The reaction mixture was evaporated, diluted with 7% aqueous $NaHCO_3$, and extracted with AcOEt. The organic layer was washed with brine and dried with $MgSO_4$. The organic layer was evaporated to give a crude residue, which was purified by chromatography on silica gel (40 g, *n*-hexane/AcOEt, 10:1) to afford **25** (1.6981 g, 61%). Recrystallization of **25** from *n*-hexane provided colorless needles. **25**: m.p. 83–84 °C. IR (KBr): $\tilde{\nu}$ = 1722 cm^{-1}. ^{1}H NMR: δ = 1.03 (d, J = 6.8 Hz, 6 H), 1.43 (t, J = 7.2 Hz, 3 H), 2.16 (m, 1 H), 2.91 (d, J = 7.2 Hz, 2 H), 4.44 (q, J = 7.2 Hz, 1 H), 8.03 (s, 1 H), 8.16 (s, 1 H)ppm. ^{13}C NMR: δ = 14.4, 22.3 (2 C), 29.7, 42.2, 61.5, 116.7, 127.6, 147.9, 148.0, 161.5, 163.7, 171.1 ppm. $C_{13}H_{16}N_2O_2S_2$: calcd. C 52.68, H 5.44, N 9.45; found C 52.54, H 5.36, N 9.17. MS (FAB): m/z = 297 [M^+ + 1].

4-Hydroxymethyl-2′-isobutyl-2,4′-bithiazol (26): A mixture of **25** (1.0 g, 4.4 mmol) and $LiBH_4$ (0.486 g, 22.3 mmol) in THF (30 mL) was stirred for 2 h at room temperature. The reaction mixture was diluted with H_2O (20 mL) and stirred for 15 h at the same temperature. The reaction mixture was extracted with AcOEt, washed with brine, and the organic layer was dried with $MgSO_4$. The organic layer was evaporated to give a crude residue, which was purified by chromatography on silica gel (20 g, *n*-hexane/AcOEt, 2:1) to afford **26** (0.92 g, 83%). Recrystallization of **26** from *n*-hexane/AcOEt provided colorless needles. **26**: m.p. 118–119 °C. IR (KBr): $\tilde{\nu}$ = 3402, 2925 cm^{-1}. ^{1}H NMR: δ = 1.02 (d, J = 6.8 Hz, 6 H), 2.15 (m, 1 H), 2.91 (d, J = 7.2 Hz, 2 H), 3.49 (br. s, 1 H), 4.81 (s, 2 H), 7.20 (s, 1 H), 7.85 (s, 1 H) ppm. ^{13}C NMR: δ = 22.3 (2 C), 29.7, 42.2, 60.8, 115.3, 115.5, 148.6, 157.2, 163.6, 171.2 ppm. $C_{11}H_{14}N_2OS_2$: calcd. C 51.94, H 5.55, N 11.01; found C 51.87, H 5.49, N 10.86. MS (FAB): m/z = 255 [M^+ + 1].

4-Iodomethyl-2′-isobutyl-2,4′-bithiazol (27): To a mixture of **26** (0.77 g, 3.0 mmol), triphenylphosphane (0.875 g, 3.33 mmol), and imidazole (0.309 g, 4.54 mmol) in THF (15 mL) was added I_2 (0.847 g, 3.33 mmol) under argon and the mixture was stirred for 10 min at room temp. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine and dried with $MgSO_4$. The organic layer was evaporated to give a crude residue, which was purified by chromatography on silica gel (10 g, *n*-hexane/AcOEt, 5:1) to afford **27** (0.99 g, 90%). Recrystallization of **27** from *n*-hexane provided pale yellow needles. **27**: m.p. 116–117 °C. IR (KBr): $\tilde{\nu}$ = 1500 cm^{-1}. ^{1}H NMR: δ = 1.01 (d, J = 6.8 Hz, 6 H), 2.15 (m, 1 H), 2.91 (d, J = 7.2 Hz, 2 H), 4.56 (s, 2 H), 7.25 (s, 1 H), 7.87 (s, 1 H) ppm. ^{13}C NMR: δ = –1.50, 22.3 (2 C), 29.7, 42.2, 115.8, 116.7, 148.5, 154.0, 163.2, 171.1 ppm. $C_{11}H_{13}IN_2S_2$: calcd. C 36.27, H 3.60, N 7.69; found C 36.15, H 3.58, N 7.26. MS (FAB): m/z = 365 [M^+ + 1].

[2′-Isobutyl-2,4′-bithiazolyl-4-yl)methyl]triphenylphosphonium Iodide (6): A mixture of **27** (0.815 g, 2.24 mmol) and triphenylphosphane (0.646 g, 2.46 mmol) in benzene (20 mL) was refluxed for 20 h. After cooling, the resulting colorless powder **6** (1.34 g, 97%) was obtained by filtration. **6**: m.p. 222–223 °C. ^{1}H NMR: δ = 0.99 (d, J = 6.8 Hz, 6 H), 2.10 (m, 1 H), 2.85 (d, J = 7.2 Hz, 2 H), 5.44 (d, J = 13.6 Hz, 2 H), 7.25 (s, 1 H), 7.63–7.66 (m, 6 H), 7.75–7.81 (m, 9 H), 8.01 (s, 1 H) ppm. $C_{29}H_{28}IN_2PS_2$: calcd. C 55.59, H 4.50, N 4.47; found C 55.52, H 4.44, N 3.99. MS (FAB): m/z = 499 (M^+ – I).

Wittig Condensation of (+)-4 and 6: To a solution of **6** (0.463 g, 0.74 mmol) in THF (45 mL) was added lithium bis(trimethylisilyl)-amide (1 M in THF, 0.74 mL, 0.74 mmol) at 0 °C under argon and the mixture was stirred for 20 min. A solution of (+)-**4** (0.08 g, 0.37 mmol) in THF (2 mL) was added 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 with $MgSO_4$ and evaporated to afford a crude product which was purified by chromatography on silica gel (10 g, *n*-hexane/AcOEt, 20:1) to give a mixture [(*E*)/(*Z*) = 2.5:1] of isomers of **2** (0.151 g, 93%). This mixture was subjected to preparative HPLC to afford (+)-**2** (0.108 g, 66%) as a colorless oil and (+)-**28** (0.043 g, 26%) as a colorless oil. (+)-**2**: $[\alpha]_D^{26}$ = +91.6 (c = 0.63, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2925, 1711, 1626, 1457, 1376, 1146 cm^{-1}. ^{1}H NMR: δ = 1.02 (d, J = 6.4 Hz, 6 H), 1.22 (d, J = 6.8 Hz, 3 H), 2.10–2.20 (m, 1 H), 2.92 (d, J = 7.2 Hz, 2 H), 3.33 (s, 3 H), 3.60 (s, 3 H), 3.67 (s, 3 H), 3.81 (t, J = 7.6 Hz, 1 H), 4.17 (dq, J = 7.6, 6.8 Hz, 1 H), 4.97 (s, 1 H),6.41 (dd, J = 16.0, 7.6 Hz, 1 H), 6.57 (d, J = 16.0 Hz, 1 H), 7.09 (s, 1 H), 7.86 (s, 1 H) ppm. ^{13}C NMR: δ = 14.1, 22.3 (2 C), 29.7, 39.8, 42.2, 50.8, 55.5, 57.0, 84.4, 91.1, 115.0, 115.4, 125.6, 131.7, 149.0, 154.5, 162.5, 167.7, 171.0, 176.7 ppm. HRMS (FAB): (m/z) calcd. for $C_{21}H_{28}N_2O_4S_2$: 437.1569 [M^+ + 1]; found 437.1576. (+)-**28:** $[\alpha]_D^{29}$ = +245.7 (c = 1.46, $CHCl_3$). IR (KBr): $\tilde{\nu}$ = 2925, 1711, 1628, 1457, 1146 cm^{-1}. ^{1}H NMR: δ = 1.03 (d, J = 6.8 Hz, 6 H), 1.25 (d, J = 6.8 Hz, 3 H), 2.10–2.23 (m, 1 H), 2.93 (d, J = 7.2 Hz, 2 H), 3.33 (s, 3 H), 3.34 (s, 3 H), 3.67 (s, 3 H), 4.23 (dq, J = 9.4, 6.8 Hz, 1 H), 4.92 (s, 1 H), 5.09 (t, J = 9.4 Hz, 1 H), 5.60 (dd, J = 12.0, 9.4 Hz, 1 H), 6.59 (d, J = 12.0 Hz, 1 H), 7.23 (s, 1 H), 7.83 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 14.8, 22.3 (2 C), 29.7, 39.3, 42.3, 50.8, 55.1, 56.3, 78.6, 91.1, 115.1, 117.8, 125.4, 132.7, 149.0, 153.5, 161.6, 167.8, 171.2, 176.6 ppm. HRMS (FAB): (m/z) calcd. for $C_{21}H_{28}N_2O_4S_2$ [M^+ + 1]: 437.1569; found 437.1595.

Supporting Information Available (see footnote on the first page of this article): NMR charts for (+)-(4*R*,5*S*,6*E*)-melithiazol F (**1**), (+)-(4*R*,5*S*,6*Z*)-melithiazol F (**19**), (+)-(4*R*,5*S*,6*E*)-melithiazol I (**2**), and (+)-(4*R*,5*S*,6*Z*)-melithiazol I (**28**) are available on the WWW under http://www.eurjoc.org.

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