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TOTAL SYNTHESIS OF (4*R*,5*S*)-MELITHIAZOL C AND (3*R*,4*S*)-CYSTOTHIAZOLE E

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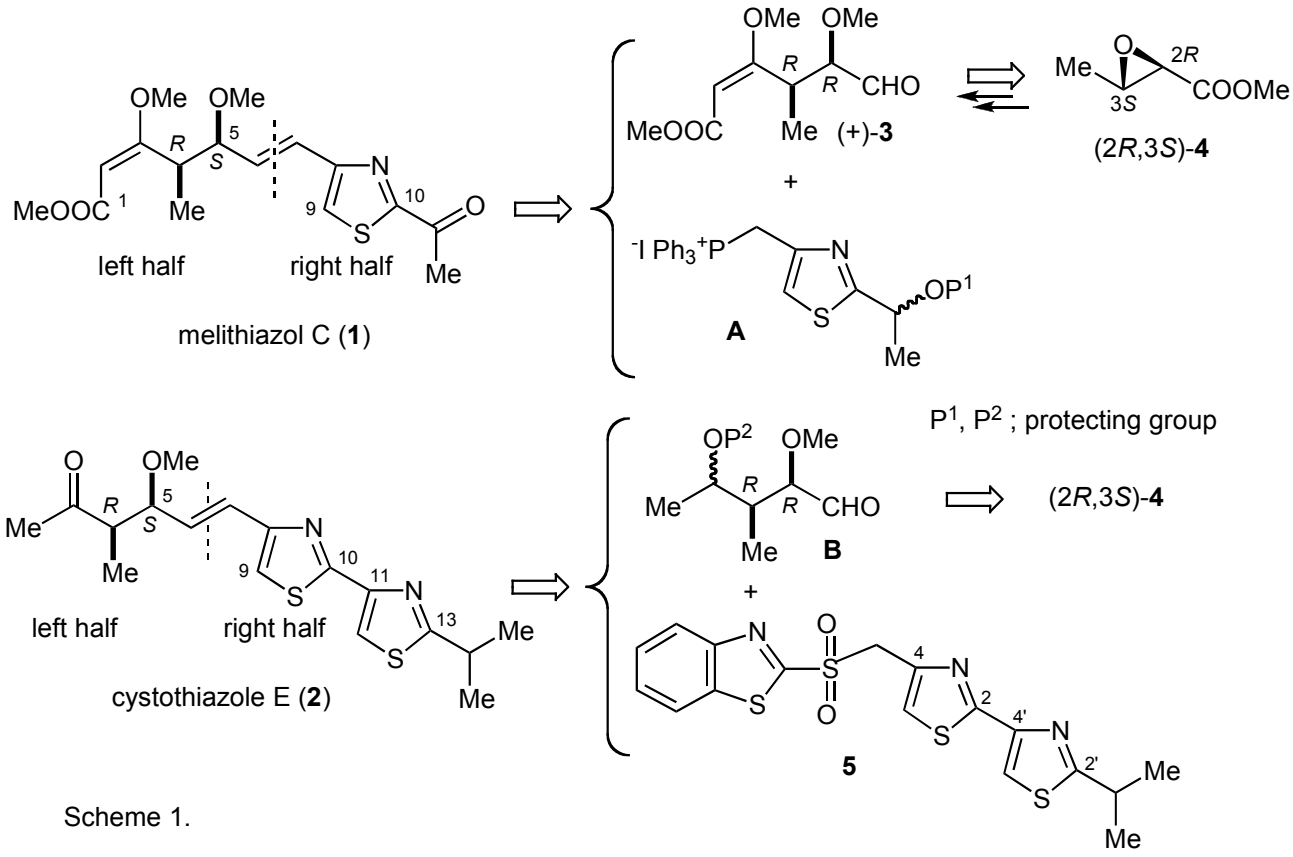
Abstract- A Wittig reaction between (+)-chiral aldehyde (4*R*,5*R*)-**3** and the phosphoranylide derived from the mono-thiazole-type phosphonium iodide [(±)-**10**] using lithium bis(trimethylsilyl)amide afforded the (+)-melithiazol C (**1**), whose spectral data were identical with those of the natural product [(+)-**1**]. Moreover, the Julia's coupling of aldehyde (**21**) and the bithiazole-type sulfone (**5**) followed by the consecutive deprotection and Dess-Martin oxidation gave the (+)-cystothiazole E (**2**), whose spectral data were identical with those of the natural product [(+)-**2**].

Melithiazol C (**1**)[1] and cystothiazole E (**2**)[2] were isolated from different strains of myxobacterium *Melittangium lichenicola*, strain Me 126 and *Cystobacter fuscus* strain AJ-13278, respectively. These myxobacterium are reported to produce antifungal antibiotics possessing a bis-thiazole skeleton as well as β-methoxy acrylate moiety. The structure of melithiazol C (**1**) was confirmed by an expeditious synthesis from myxothiazol A.[3] The absolute structure of cystothiazole E (**2**) was confirmed by the synthesis of antipodal **2**.[4] Meanwhile, we reported the total synthesis of an antifungal substance named cystothiazole A from the myxobacterium *Cystobacter fuscus* strain AJ-13278[5] in addition to the synthesis of (4*R*,5*S*)-melithiazols B and M.[6] This paper describes the total synthesis of (4*R*,5*S*)-melithiazol C (**1**) and cystothiazole E (**2**). (Scheme 1.)

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

Retrosynthetically, the synthesis of **1** can be achieved by Wittig condensation of the left-half aldehyde (**3**) and the right-half phosphonium iodide **A**. The synthesis of (+)-chiral aldehyde [(4*R*,5*R*)-**3**] from (2*R*,3*S*)-epoxy butanoate (**4**) was achieved in the total synthesis of cystothiazole A.[5]

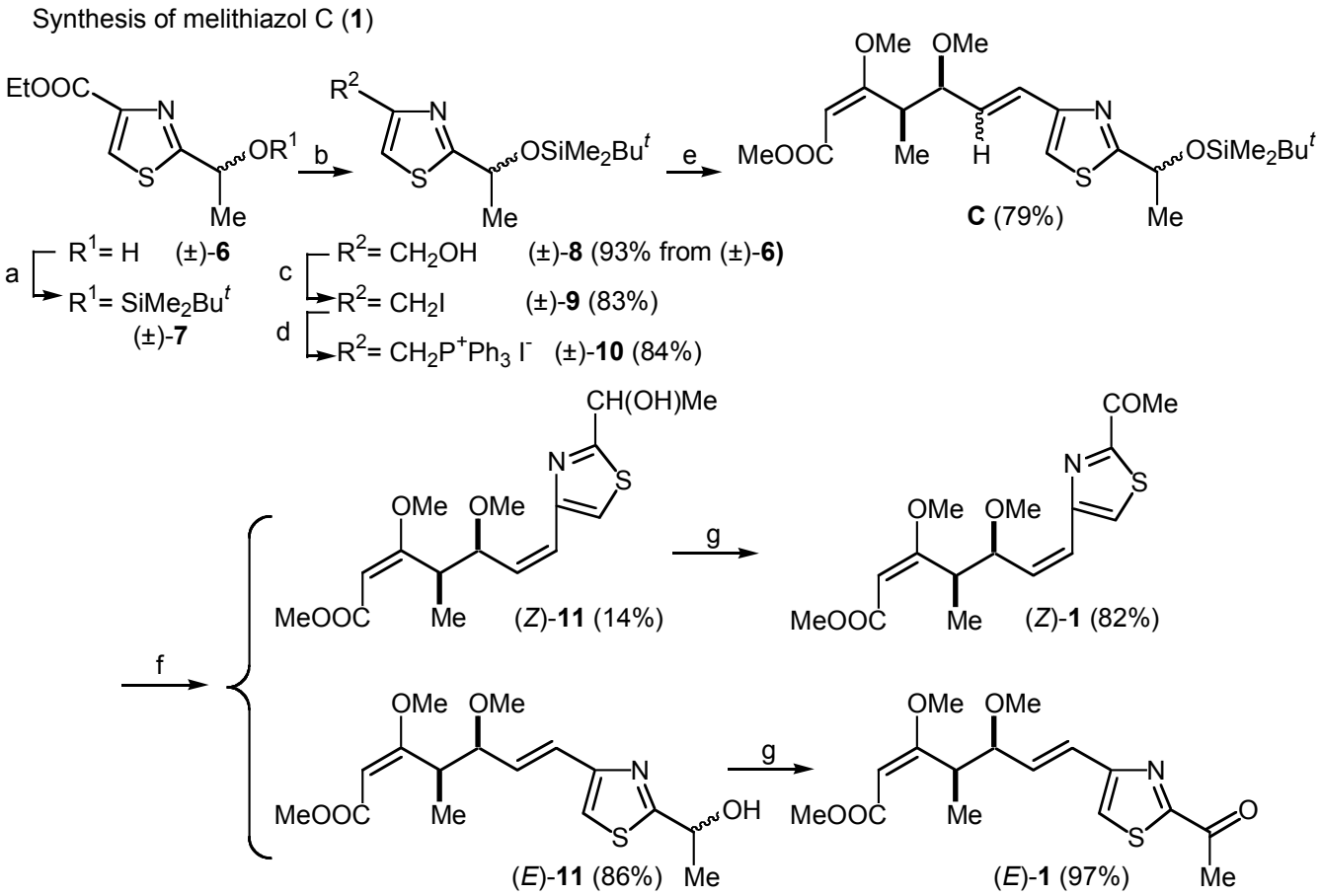


Scheme 1.

The synthesis of the right part (**10**) is shown in Scheme 2. Silylation of the reported alcohol (±)-**6**[7] followed by reduction with $LiBH_4$ gave an alcohol [(±)-**8**] in 93% overall yield from (±)-**6**. Treatment of (±)-**8** with I_2/Ph_3P/imidazole provided an iodide [(±)-**9**] in 83% yield. The reaction of (±)-**9** with triphenylphosphine gave a phosphonium salt [(±)-**10**] in 84% yield, which was condensed with (+)-(4*R*,5*R*)-**3** in the presence of lithium bis(trimethylsilyl)amide in THF to afford a mixture of olefins **C** in 79% yield. Deprotection of silyl group of mixture **C** gave (*Z*)-**11** (14%) and (*E*)-**11** (86%). The structure of (*Z*)-**11** and (*E*)-**11** was confirmed by the coupling constant ((*Z*)-**11**; *J*=12.0 Hz, (*E*)-**11**; *J*=15.6 Hz) due to olefinic protons, respectively. Dess-Martin oxidation of (*Z*)-**11** and (*E*)-**11** afforded methyl ketones (*Z*)-**1** (82%) and (*E*)-**1** (97%), respectively. The specific rotation and NMR data of the synthetic (*E*)-**1** ($[\alpha]_D$ +158.5° (c=0.41, MeOH)) were identical with those of natural melithiazol C (**1**) ($[\alpha]_D$ +169.0° (c=0.35, MeOH)).[3] (Scheme 2.)

Synthesis of (4*R*,5*S*)-cystothiazole E (2)

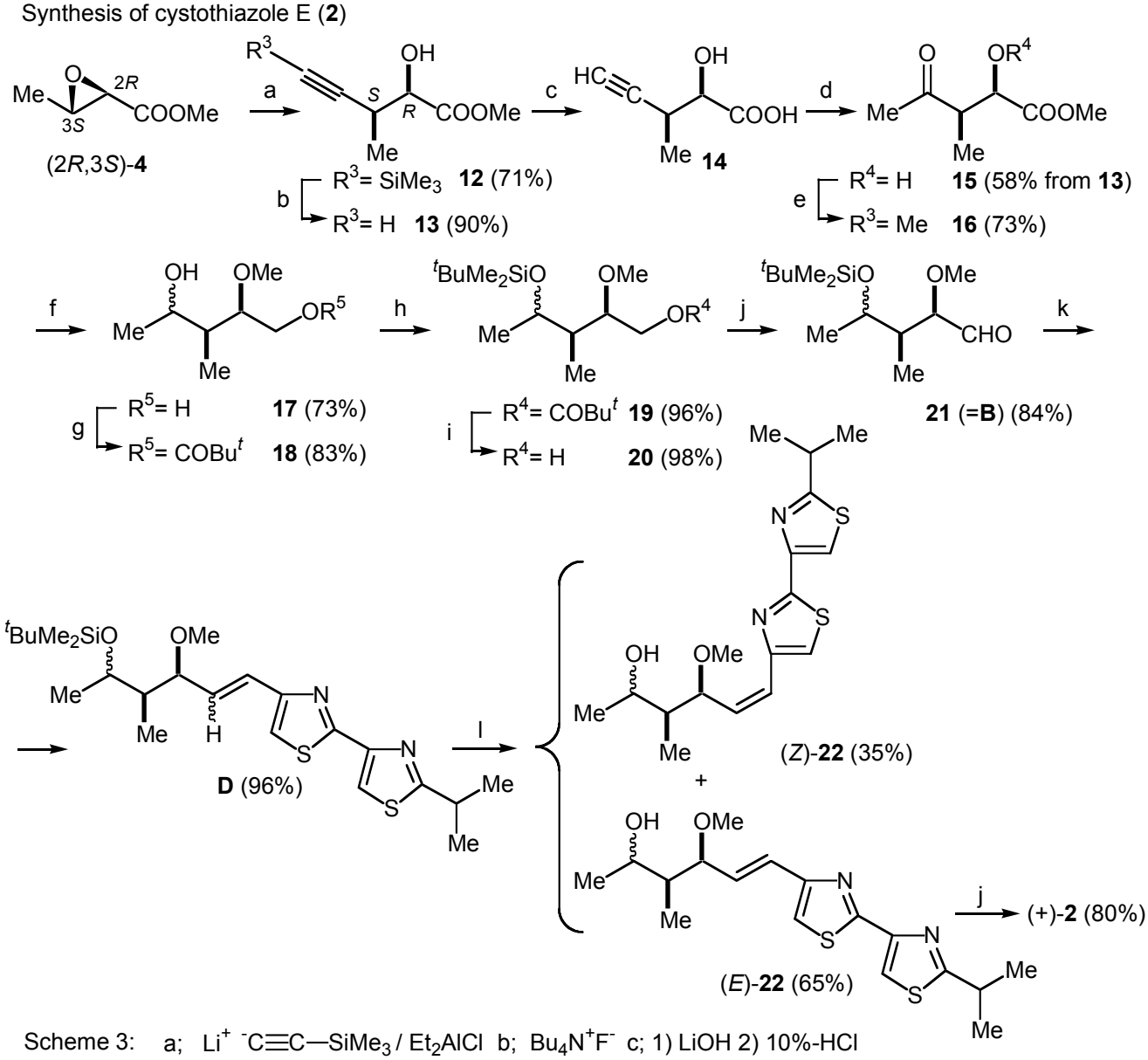
Retrosynthetically, the synthesis of **2** can be achieved by the double bond formation between the left-half aldehyde **B** (**21**) and the reported right-half sulfone (**5**) by us.[5c] By applying the previously reported procedure,[5b] the reaction of (2*R*,3*S*)-epoxy butanoate (**4**) and lithium silyl-acetylide in the presence of Et_2AlCl gave **12** in 71% yield. Desilylation of **12** followed by hydrolysis gave an acetylenic α-hydroxy-carboxylic acid (**14**), which was treated with 5 mol % of $Pd(MeCN)_2Cl_2$ and Et_3N in MeOH to



Scheme 2: a; ^{t}BuMe$_2$SiCl / imidazole / DMF b; LiBH$_4$ c; I$_2$/Ph$_3$P/imidazole d; Ph$_3$P
e; (+)-**3**/LHMDS f; Bu$_4$N$^+$F$^-$/THF g; Dess-Martin periodinane

give methyl ketone (**15**) in 58% yield from **13**. Methylation of **13** gave α-methoxy ester (**16**) (73%), which was subjected to reduction to afford a diastereomeric mixture of diol (**17**) in 73% yield. Selective protection of primary hydroxyl group in **17** followed by silylation gave a diastereomeric mixture of **19** in 96% yield. Reductive deprotection of vivaloyl group in **19** gave a diastereomeric mixture of **20** in 98% yield, which was subjected to the Dess-Martin oxidation to afford a diastereomeric mixture of aldehyde (**21**) in 84% yield. The Julia's coupling[8] of the sulfone (**5**) and aldehyde (**21**) in the presence of lithium bis(trimethylsilyl)amide in THF to afford a mixture of olefins **D** in 96% yield. Deprotection of silyl group of mixture **D** gave the less polar **22** (35%) and the more polar **22** (65%). The geometry of the less polar **22** was found to be *Z*-form by the coupling constant (*J*=12.0 Hz) due to olefinic proton and thence that of the more polar **22** was deduced to be (*E*)-form. Dess-Martin oxidation of (*E*)-**22** afforded methyl ketones [(*E*)-**2**] (80%). The specific rotation and NMR data of the synthetic (*E*)-**2** ([α]$_D$ +17.8° (c=0.66, $CHCl_3$)) were identical with those of natural cystothiazole E (**2**) ([α]$_D$ +17.8° (c=0.2, $CHCl_3$)).[2] (Scheme 3.) Low *E*/*Z* selectivity in the double bond formation might be explained by the more small bulkiness of left-half **B** than that of the left-half (+)-**3**.

Synthesis of cystothiazole E (**2**)



Scheme 3: a; $Li^+ {}^-C{\equiv}C{-}SiMe_3$ / Et_2AlCl b; $Bu_4N^+F^-$ c; 1) LiOH 2) 10%-HCl
d; $Pd(MeCN)_2Cl_2$ (5 mol %) / Et_3N / MeOH e; MeI / Ag_2O f; $LiAlH_4$
g; ^{t}BuCOCl / pyridine h; ^{t}BuMe$_2$SiCl / imidazole / DMF i; $(i\text{-Bu})_2AlH$
j; Dess-Martin periodinane k; **5** / LHMDS l; $Bu_4N^+F^-$ / THF

CONCLUSION

A Wittig reaction between (+)-(4*R*,5*R*)-**3** and the phosphoranylide derived from the mono-thiazole-type phosphonium iodide [(±)-**10**] using lithium bis(trimethylsilyl)amide afforded the (+)-melithiazol C (**1**), whose spectral data were identical with those of the natural product [(+)-**1**]. Moreover, the Julia's coupling of aldehyde (**21**) and the sulfone (**5**) followed by the consecutive deprotection and Dess-Martin oxidation gave the (+)-cystothiazole E (**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. ^{1}H- 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 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. All evaporations were performed under reduced pressure. For column chromatography, silica gel (Kieselgel 60) was employed.

(±) 2-(1-^{t}Butyldimethylsiloxyethyl)-4-hydroxymethylthiazole (8)

i) A solution of (±)-**6** (1.98 g, 9.8 mmol), imidazole (2.0 g, 29.5 mmol) and ^{t}butyldimethylsilyl chloride (TBDMSCl, 2.97 g, 19.7 mmol) in DMF (40 mL) was stirred for 3 h at rt. The reaction mixture was diluted with brine and extracted with *n*-hexane. The organic layer was dried over $MgSO_4$ and evaporated to give a crude (±)-**7**, which was used for the next reaction without further purification.

ii) A mixture of the crude (±)-**7** and $LiBH_4$ (0.86 g, 39.3 mmol) in THF (40 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 residue, which was chromatographed on silica gel (40 g, *n*-hexane:AcOEt=5:1) to afford a colorless needles (±)-**8** (2.503 g, 93% from (±)-**6**). (±)-**8**: mp 56-57°C (*n*-hexane/AcOEt), IR (KBr): 3228, 1156, 1028, 837 cm^{-1}; ^{1}H-NMR: δ 0.09 (3H, s), 0.12 (3H, s), 0.94 (9H, s), 1.54 (3H, d, *J*=6.4 Hz), 2.95 (1H, br. s), 4.72 (2H, s), 5.09 (1H, q, *J*=6.4 Hz), 7.08 (1H, s). ^{13}C-NMR: δ -5.1, -4.7, 18.1, 25.4, 25.7 (C3), 60.9, 69.5, 114.3, 156.0, 179.0. Anal. Calcd for $C_{12}H_{23}NO_2SSi$: C, 52.70; H, 8.48; N, 5.12. Found: C, 52.66; H, 8.35; N, 5.05. MS (FAB) m/z: 274 (M^++1).

(±) 2-(1-^{t}Butyldimethylsiloxyethyl)-4-iodomethylthiazole (9)

To a mixture of (±)-**8** (2.50 g, 9.1 mmol), triphenylphosphine (2.65 g, 10.0 mmol) and imidazole (0.94 g, 13.7 mmol) in THF (40 mL) was added I_2 (2.57 g, 10.0 mmol) under argon atmosphere and the whole mixture was stirred for 10 min at rt. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was washed with 1% aqueous $Na_2S_2O_3$ and brine, and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (30 g, *n*-hexane:AcOEt=10:1) to afford (±)-**9** (2.897 g, 83%) as a pale yellow oil. (±)-**9**: IR (KBr): 1117, 835 cm^{-1}; ^{1}H-NMR: δ 0.09 (3H, s), 0.13 (3H, s), 0.94 (9H, s), 1.56 (3H, d, *J*=6.4 Hz), 4.45 (2H, s), 5.10 (1H, q, *J*=6.4 Hz), 7.14 (1H, s). ^{13}C-NMR: δ -5.1, -4.7, -1.1, 18.1, 25.4, 25.7 (C3), 69.5, 115.6, 152.0, 178.6. Anal. Calcd for $C_{12}H_{22}NOISSi$: C, 37.60; H, 5.78; N, 3.65. Found: C, 37.56; H, 5.63; N, 3.58. MS (FAB) m/z: 384 (M^++1).

(±) 2-(1-^{t}Butyldimethylsiloxyethyl)-4-methylenetriphenylphosphonium iodide (10)

A mixture of (±)-**9** (2.17 g, 5.66 mmol) and triphenylphosphine (1.63 g, 6.23 mmol) in benzene (30 mL) was stirred for 30 h at reflux. After cooling, the resulting colorless powder (±)-**10** (3.08 g, 84%) was obtained by filtration. (±)-**10**: mp 84-85°C (benzene); IR (KBr): 1112, 837, 689 cm^{-1}; ^{1}H-NMR: δ 0.02 (3H, s), 0.05 (3H, s), 0.90 (9H, s), 1.24 (3H, d, *J*=6.4 Hz), 4.82 (1H, q, *J*=6.4 Hz), 5.23 (1H, t, *J*=14.4 Hz), 5.66 (1H, t, *J*=14.4 Hz), 7.27 (1H, s), 7.61-7.66 (6H, m), 7.75-7.80 (9H, m). Anal. Calcd for $C_{30}H_{37}NOIPSSi$: C, 55.81; H, 5.78; N, 2.17. Found: C, 55.44; H, 5.78; N, 2.01. MS (FAB) m/z: 519 (M^++1-I).

Wittig condensation of (+)-3 and (±)-10

i) To a solution of (±)-**10** (0.675 g, 1.04 mmol) in THF (5 mL) was added lithium bis(trimethylisilyl)amide (1M solution in THF, 1.05 mL, 1.05 mmol) at 0°C under argon atmosphere and the whole mixture was stirred for 10 min at the same temperature. A solution of (+)-**3** (0.113 g, 0.52 mmol) in THF (2 mL) was added to the above reaction mixture at 0°C and the whole mixture was stirred for 10 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 (10 g, *n*-hexane:AcOEt=15:1) to give a diastereomeric mixture **C** (0.187 g, 79%, (*E*)-**11** : (*Z*)-**11**=6.3:1) as a colorless oil.

ii) To a solution of the mixture **C** (0.185 g, 0.40 mmol) in THF (5 mL) was added 1M-tetrabutylammonium fluoride ($Bu_4N^+F^-$) solution (0.61 mL, 0.61 mmol) at 0°C and the whole mixture was stirred for 10 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 (15 g, *n*-hexane:AcOEt=7:1) to give (*Z*)-**11** (0.019 g, 14%, colorless oil) and (*E*)-**11** (0.119 g, 86%, colorless oil) in elution order. (*Z*)-**11**: IR (KBr): 3420, 2925, 1627, 1465, 1387, 1272, 1150, 1092, 928, 688 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.22 (3H, d, *J*=6.8 Hz), 1.65 (3H, d, *J*=6.8 Hz), 3.28 (3H, s), 3.37 (3H, s), 3.67 (3H, s), 4.19 (1H, dq, *J*=9.0, 6.6 Hz), 4.92 (1H, s), 5.00 (1H, dd, *J*=9.8, 9.0 Hz), 5.12 (1H, q, *J*=6.8 Hz), 5.56 (1H, dd, *J*=12.0, 9.8 Hz), 6.52 (1H, d, *J*=12.0 Hz), 7.27 (1H, s). ^{13}C-NMR ($CDCl_3$): δ 14.5, 24.0, 39.2, 50.9, 55.1, 56.1, 68.0, 78.4, 91.1, 117.3, 125.2, 132.5, 152.3, 167.9, 174.3, 176.6. MS (FAB) m/z: 342 (M^++1). (*E*)-**11**: IR (KBr): 3415, 2934, 1708, 1622, 1448, 1380, 1271, 1150, 1091, 971, 927, 827 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.20 (3H, d, *J*=6.8 Hz), 1.62 (3H, d, *J*=6.8 Hz), 3.31 (3H, s), 3.59 (3H, s), 3.66 (3H, s), 3.78 (1H, t, *J*=8.0 Hz), 4.14 (1H, dq, *J*=8.0, 6.8 Hz), 4.96 (1H, s), 5.11 (1H, q, *J*=6.8 Hz), 6.33 (1H, dd, *J*=15.6, 8.0 Hz), 6.50 (1H, d, *J*=15.6 Hz), 7.02 (1H, s). ^{13}C-NMR ($CDCl_3$): δ 14.1, 24.1, 39.8, 50.8, 55.5, 57.0, 68.1, 84.3, 91.1, 114.4, 125.3, 131.6, 153.2, 167.8, 175.5, 176.7. MS (FAB) m/z: 342 (M^++1).

(4*R*,5*S*,6*E*)-Melithiazol C (1)

To a solution of (*E*)-**11** (0.082 g, 0.24 mmol) in CH_2Cl_2 (3 mL) was added Dess-Martin reagent (0.66 g, 1.55 mmol) at rt and the whole mixture was stirred for 150 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 (5 g, *n*-hexane:AcOEt=10:1) to afford (+)-(6*E*)-**1** (0.079 g, 97%). (+)-(6*E*)-**1**: $[\alpha]_D^{22}$ +158.5° (c=0.41, MeOH) (cf. $[\alpha]_D$ +169.0° (c=0.35, MeOH) [3]), IR (KBr): 2925, 2874, 1708, 1603, 1454, 1372, 1275, 1148, 1089, 930, 814, 600 cm^{-1}; ^{1}H-NMR: δ 1.19 (3H, d, *J*=6.8 Hz), 2.69 (3H, s), 3.32 (3H, s), 3.58 (3H, s), 3.64 (3H, s), 3.80 (1H, t, *J*=7.6 Hz), 4.16 (1H, dq, *J*=7.6, 6.8 Hz), 4.95 (1H, s), 6.44 (1H, dd, *J*=15.6, 7.6 Hz), 6.57 (1H, d, *J*=15.6 Hz), 7.37 (1H, s). ^{13}C-NMR: δ 14.0, 26.0, 39.8, 50.8, 55.5, 57.1, 84.2, 91.2, 121.4, 124.7, 133.2, 155.6, 166.5, 167.7, 176.6, 191.9. HRMS (FAB) (m/z): Calcd for $C_{16}H_{22}NO_5S$ (M^++1): 340.1218. Found: 340.1208. MS (FAB) m/z: 362 (M^++Na).

(4*R*,5*S*,6*Z*)-Melithiazol C (1)

To a solution of (*Z*)-**11** (0.019 g, 0.05 mmol) in CH_2Cl_2 (1.5 mL) was added Dess-Martin reagent (0.142 g, 0.33 mmol) at rt and the whole mixture was stirred for 3 h 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 (5 g, *n*-hexane:AcOEt=10:1) to afford (+)-(6*Z*)-**1** (0.015 g, 82%) as a colorless oil. (+)-(6*Z*)-**1**: $[\alpha]_D^{25}$ +259.7° (c=0.15, MeOH), IR (KBr): 2928, 1697, 1621, 1448, 1375, 1272, 1147, 1091, 930, 822 cm^{-1}; ^{1}H-NMR: δ 1.22 (3H, d, *J*=6.8 Hz), 2.72 (3H, s), 3.31 (3H, s), 3.31 (3H, s), 3.65 (3H, s), 4.20 (1H, dq, *J*=8.8, 6.8 Hz), 4.90 (1H, s), 5.03 (1H, dd, *J*=10.0, 8.8 Hz), 5.67 (1H, dd, *J*=12.0, 10.0 Hz), 6.56 (1H, d, *J*=12.0 Hz), 7.52 (1H, s). ^{13}C-NMR: δ 14.7, 26.0, 39.2, 50.9, 55.0, 56.4, 78.4, 91.2, 124.4, 124.5, 134.2, 154.7, 165.8, 167.7, 176.4, 191.7. HRMS (FAB) (m/z): Calcd for $C_{16}H_{22}NO_5S$ (M^++1): 340.1218. Found: 340.1206. MS (FAB) m/z: 362 (M^++Na).

Methyl (2*R*,3*R*)-3-methyl-2-methoxy-4-oxopentanoate (16)

i) *n*-Butyllithium (*n*-BuLi, 1.6 M in hexane, 28.4 mL, 43 mmol) was added to a stirred solution of trimethylsilylacetylene (4.19 g, 43 mmol) in toluene (80 mL) at –40°C under an argon atmosphere and the mixture was stirred for 1 h at 0°C. A solution of (2*R*,3*S*)-**4** (3.3 g, 28 mmol) in toluene (10 mL) was added to the above reaction mixture and the whole mixture was stirred for 3 h at 5-10°C. The reaction mixture was diluted with H_2O (20 mL) at 0°C and the generated white precipitate was filtered off with the aid of celite. The precipitate was washed with AcOEt and the washing and filtrate were combined. The extracted organic layer was dried over $MgSO_4$ and evaporated to give an oily product, which was chromatographed on silica gel (60 g, *n*-hexane:AcOEt=30:1) to afford methyl (-)-**12** (4.32 g, 71% yield) as a colorless oil. (-)-**12**: $[\alpha]_D^{25}$ –24.1° (c=1.07, $CHCl_3$); IR (neat): 3482, 2168, 1741 cm^{-1}; ^{1}H-NMR: δ

0.15 (9H, s), 1.21 (3H, d, *J*=7.2 Hz), 2.86-2.93 (1H, m), 3.81 (3H, s), 4.21 (1H, d, *J*=4.4 Hz). ^{13}C-NMR: δ -0.07, 15.8, 32.3, 52.4, 73.5, 86.9, 106.1, 173.1. HRMS (FAB) Calcd for $C_{10}H_{19}O_3Si$ (M^++1): 215.1104. Found m/z: 215.1106.

ii) To a solution of (-)-**12** (4.32 g, 20.2 mmol) in THF (30 mL) was added 1M tetrabutylammonium fluoride (TBAF) in THF solution (30 mL, 30 mmol) at 0°C and the whole mixture was stirred for 30 min at 0°C. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt=20:1) to afford the reported **13** (3.239 g, 90% yield) as a colorless oil. **13**: ^{1}H-NMR: δ 1.22 (3H, d, *J*=7.2 Hz), 2.17 (1H, d, *J*=2.8 Hz), 2.94-2.97 (1H, m), 3.17 (1H, d, *J*=6.4 Hz), 3.82 (3H, s), 4.26-4.28 (1H, m).

iii) To a solution of **13** (0.500 g, 3.5 mmol) in a mixed solvent (THF (7 mL) and H_2O (7 mL)) was added LiOH (0.443 g, 10. 5 mmol) at 0°C and the whole mixture was stirred for 1 h at 0°C. The reaction mixture was diluted with 10% HCl and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and evaporated to give a crude **14**, which was used for the next reaction without further purification. To a solution of crude **14** in MeOH (10 mL) was added Et_3N (0.053 g, 0.53 mmol) and $Pd(MeCN)_2Cl_2$ (0.046 g, 0.18 mmol) and the whole mixture was stirred at reflux. The reaction mixture was evaporated to give a residue, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt=5:1) to afford (+)-**15** (0.329 g, 58% yield) as a pale yellow oil. (+)-**15**: $[\alpha]_D^{23}$ +5.1° (c=0.73, $CHCl_3$); IR (neat): 3477, 1740, 1712 cm^{-1}; ^{1}H-NMR: δ 1.16 (3H, d, *J*=7.4 Hz), 2.24 (3H, s), 2.95 (1H, dq, *J*=7.4, 3.4 Hz), 3.09 (1H, br. s), 3.82 (3H, s), 4.61 (1H, d, *J*=3.4 Hz). ^{13}C-NMR: δ 10.5, 28.3, 50.0, 52.8, 71.0, 173.8, 209.2. HRMS (FAB) Calcd for $C_7H_{12}O_4$ (M^++1): 161.0814. Found m/z: 161.0808.

iv) A mixture of (+)-**15** (0.85 g, 5.3 mmol), methyl iodide (6.03 g, 42 mmol) and Ag_2O (1.47 g, 6.34 mmol) in DMF (10 mL) was stirred for 15 h at rt. The reaction mixture was diluted with AcOEt (30 ml) and filtered off with the aid of celite. The filtrate was diluted with H_2O and extracted with n-hexane. The organic layer was dried over $MgSO_4$. Concentration of the organic layer gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane:AcOEt=10:1) to provide (+)-**16** (0.673 g, 73%) as a pale yellow oil. (+)-**16**: $[\alpha]_D^{24}$ +43.5° (c=0.69, $CHCl_3$); IR (neat): 1746, 1712 cm^{-1}; ^{1}H-NMR: δ 1.28 (3H, d, *J*=7.2 Hz), 2.21 (3H, s), 2.91 (1H, dq, *J*=7.2, 5.4 Hz), 3.44 (3H, s), 3.77 (3H, s), 4.13 (1H, d, *J*=5.4 Hz). ^{13}C-NMR: δ 11.4, 28.4, 49.4, 52.1, 59.1, 80.8, 171.9, 208.7. HRMS (FAB) Calcd for $C_8H_{14}O_4$ (M^++1): 175.0971. Found: 175.0960.

(2*R*,3*S*,*4RS*)-3-Methyl-2-methoxy-4-^{t}butyldimethylsiloxypentanal (21)

i) To a solution of (+)-**16** (0.179 g, 1.0 mmol) in THF (5 mL) was added $LiAlH_4$ (0.078 g, 2.0 mmol) at 0°C and the whole mixture was stirred for 10 min at 0°C. The reaction mixture was diluted with H_2O and extracted with AcOEt. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which

was chromatographed on silica gel (6 g, *n*-hexane:AcOEt=1:2) to provide a 1:2 diastereomeric mixture (**17**) (0.111 g, 73%) as a colorless oil. **17**: IR (neat): 3376, 1712 cm^{-1}; HRMS (FAB) Calcd for $C_7H_{16}O_3$ (M^++1): 149.1178. Found: 149.1190. major product; ^{1}H-NMR: δ 0.95 (3H, d, *J*=7.2 Hz), 1.20 (3H, d, J=6.4 Hz), 3.44 (3H, s). ^{13}C-NMR: δ 8.2, 21.1, 40.3, 57.6, 60.7, 67.2, 84.5. minor product; ^{1}H-NMR: δ 0.89 (3H, d, *J*=7.2 Hz), 1.18 (3H, d, J=6.4 Hz), 3.50 (3H, s). ^{13}C-NMR: δ 13.1, 21.9, 40.1, 58.2, 61.5, 70.1, 85.8.

ii) To a solution of **17** (0.099 g, 0.67 mmol) in pyridine (2 mL) was added pivaloyl chloride (0.088 g, 0.72 mmol) at 0°C and the whole mixture was stirred for 16 h at rt. The reaction mixture was evaporated under reduced pressure to a residue, which was chromatographed on silica gel (6 g, *n*-hexane:AcOEt=5:1) to provide a 1:2 diastereomeric mixture (**18**) (0.128 g, 83%) as a pale yellow oil. **18**: IR (neat): 3445, 1729 cm^{-1}; HRMS (FAB) Calcd for $C_{12}H_{24}O_4$ (M^++1): 233.1753. Found: 233.1769. major product; ^{1}H-NMR: δ 0.96 (3H, d, *J*=6.8 Hz), 1.21 (9H, s), 1.23 (3H, d, *J*=6.4 Hz), 348 (3H, s). ^{13}C-NMR: δ 6.3, 20.9, 27.2, 38.7, 40.8, 58.6, 65.2, 70.6, 83.4, 178.3. minor product; ^{1}H-NMR: δ 0.93 (3H, d, *J*=7.2 Hz), 1.18 (3H, d, *J*=6.4 Hz), 1.22 (9H, s), 3.48 (3H, s). ^{13}C-NMR: δ 12.0, 21.9, 27.1, 38.7, 41.5, 58.6, 64.8, 70.2, 81.2, 178.3

iii) A solution of **18** (0.212 g, 0.91 mmol), imidazole (0.205 g, 1.8 mmol) and ^{t}butyldimethylsilyl chloride (TBDMSCl, 0.205 g, 1.3 mmol) in DMF (5 mL) was stirred for 15 h at rt. The reaction mixture was diluted with brine and extracted with *n*-hexane. The organic layer was dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed on silica gel (7 g, *n*-hexane:AcOEt=50:1) to afford a 1:2 diastereomeric mixture (**19**) (0.304 g, 96%) as a pale yellow oil. **19**: IR (neat): 1733 cm^{-1}; HRMS (FAB) Calcd for $C_{18}H_{38}O_4Si$ (M^++1): 347.2618. Found: 347.2629. **19** major product; ^{1}H-NMR: δ 0.04 (3H, s), 0.06 (3H, s), 0.88 (9H, s), 0.94 (3H, d, *J*=6.8 Hz), 1.14 (3H, d, *J*=6 Hz), 1.22 (9H, s), 3.42 (3H, s). ^{13}C-NMR: δ -4.8, -4.0, 10.1, 18.1, 21.0, 25.9 (3C), 27.2 (3C), 38.8, 42.5, 58.5, 65.4, 69.3, 80.0, 178.5. minor product; ^{1}H-NMR: δ 0.06 (3H, s), 0.07 (3H, s), 0.86 (3H, d, *J*=8 Hz), 0.89 (9H, s), 1.12 (3H, d, *J*=6 Hz), 1.21 (9H, s), 3.43 (3H, s). ^{13}C-NMR: δ -5.0, -3.9, 9.6, 18.1, 21.0, 25.9 (3C), 27.1 (3C), 38.8, 43.5, 58.5, 65.4, 69.6, 78.6, 178.5.

iv) To a solution of **19** (0.304 g, 0.87 mmol) in toluene (6 mL) was added 1M diisobutylaluminum hydride (DIBAL-H) in toluene solution (0.87 mL, .87 mmol) at -78°C and the reaction mixture was stirred for 30 min at the same temperature. The reaction mixture was quenched with a trace of H_2O and filtered with the aid of Celite. The filyrate was evaporated to give a residue, which was chromatographed on silica gel (7 g, *n*-hexane:AcOEt=5:1) to afford a 1:2 diastereomeric mixture (**20**) (0.226 g, 98%) as a colorless oil. **20**: IR (neat): 3387 cm^{-1}; HRMS (FAB) Calcd for $C_{13}H_{30}O_3Si$ (M^++1): 263.2042. Found: 263.2051. major product; ^{1}H-NMR: δ 0.07 (3H, s), 0.07 (3H, s), 0.89 (9H, s), 0.96 (3H, d, *J*=6.8 Hz), 1.15 (3H, d, *J*=6.4 Hz), 3.41 (3H, s). ^{13}C-NMR: δ -4.9, -4.2, 12.0, 18.1, 20.1, 25.9 (3C), 42.4, 58.1, 62.3,

70.1, 83.4. minor product; ^{1}H-NMR: δ 0.06 (3H, s), 0.06 (3H, s), 0.90 (9H, s), 0.91 (3H, d, *J*=7.2 Hz), 1.13 (3H, d, *J*=6.4 Hz), 3.43 (3H, s). ^{13}C-NMR; δ -4.9, -4.2, 11.3, 18.1, 20.8, 25.8 (3C), 42.3, 58.5, 62.7, 70.1, 82.7.

v) To a solution of **20** (0.223 g, 0.85 mmol) in CH_2Cl_2 (6 mL) was added Dess-Martin reagent (0.722 g, 1.74 mmol) at rt and the whole mixture was stirred for 30min at the same temperature. The reaction mixture was evaporated under reduced pressure to give a residue, which was chromatographed on silica gel (5 g, *n*-hexane:AcOEt=10:1) to afford a 1:2 diastereomeric mixture (**21**) (0.188 g, 84%) as a colorless oil. **21**: IR (KBr): 2928, 1697, 1621, 1448, 1375, 1272, 1147, 1091, 930, 822 cm^{-1}; HRMS (FAB) (m/z): Calcd for $C_{16}H_{22}NO_5S$ (M^++1): 340.1218. Found: 340.1206. MS (FAB) m/z: 362 (M^++Na). major product; ^{1}H-NMR: δ 0.05 (3H, s), 0.05 (3H, s), 0.89 (9H, s), 0.94 (3H, d, *J*=7.2 Hz), 1.14 (3H, d, *J*=6 Hz), 3.40 (3H, s), 9.61 (1H, d, *J*=2 Hz). ^{13}C-NMR: δ -4.8, -4.2, 10.8, 18.1, 20.1, 25.9 (3C), 42.5, 58.3, 69.2, 86.7, 203.1. minor product; ^{1}H-NMR: δ 0.07 (3H, s), 0.09 (3H, s), 0.83 (3H, d, *J*=7.2 Hz), 0.90 (9H, s), 1.18 (3H, d, *J*=6 Hz), 3.43 (3H, s), 9.67 (1H, d, *J*=1 Hz). ^{13}C-NMR: δ -4.8, -4.2, 10.7, 18.1, 21.6, 25.9 (3C), 42.5, 58.3, 69.2, 85.2, 204.3.

Double bond formation between 5 and 21 based on modified Julia's method

To a solution of **5** (0.412 g, 0.98 mmol) in THF (6 mL) was added lithium bis(trimethylisilyl)amide (1M solution in THF, 0.98 mL, 0.98 mmol) at 0°C under argon atmosphere and the whole mixture was stirred for 15 min at the same temperature. A solution of **21** (0.170 g, 0.65 mmol) in THF (2 mL) was added to the above reaction mixture at 0°C and the whole mixture was stirred for 10 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 residue, which was chromatographed on silica gel (10 g, *n*-hexane:AcOEt=20:1) to afford a diastereomeric mixture **D** (0.294 g, 96%) as a pale yellow oil.

ii) To a solution of the mixture **D** (0.04 g, 0.086 mmol) in THF (2 mL) was added 1M-tetrabutylammonium fluoride ($Bu_4N^+F^-$) solution (0.086 mL, 0.086 mmol) at 0°C and the whole mixture was stirred for 4 h 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 subjected to preparative thin-layer chromatogram on silica gel (*n*-hexane:AcOEt=2:1) to give (*Z*)-**22** (0.011 g, 35%) as a less polar compound and (*E*)-**22** (0.020 g, 65%) as a more polar compound. (*Z*)-**22**; HRMS (FAB) Calcd for $C_{17}H_{24}N_2O_2S_2$ (M^++1): 353.1357. Found: 353.1332. major product; ^{1}H-NMR: δ 1.14 (3H, d, *J*=6.8 Hz), 1.19 (3H, d, *J*=6.4 Hz), 1.43 (6H, d, *J*=7.2 Hz), 1.58-1.62 (1H, m), 3.22 (3H, s), 3.36 (1H, sept, *J*=7.2 Hz), 4.14-4.16 (1H, m), 4.67 (1H, t, *J*=9.4 Hz), 5.16 (1H, br. S), 5.57 (1H, dd, *J*=12.0, 9.4 Hz), 6.67 (1H, d, *J*=12.0 Hz), 7.17 (1H, s), 7.90 (1H, s). minor product; ^{1}H-NMR: δ 0.98 (3H, d, *J*=7.2 Hz), 1.27 (3H, d, *J*=6.4 Hz), 1.44 (6H, d, *J*=6.8 Hz), 1.916-1.924 (1H, m), 3.33 (3H, s), 3.39 (1H, sept, *J*=7.2 Hz), 3.85 (1H, dq, *J*=6.4, 7.2 Hz), 5.48 (1H, dd, *J*=8.8, 3.2 Hz), 5.80

(1H, dd, *J*=12.0, 8.8 Hz), 6.56 (1H, d, *J*=12.0 Hz), 4.14-4.16 (1H, m), 7.17 (1H, s), 7.90 (1H, s). (*E*)-**22**; HRMS (FAB) Calcd for $C_{17}H_{24}N_2O_2S_2$ (M^++1): 353.1357. Found: 353.1389. major product; ^{1}H-NMR: δ 1.03 (3H, d, *J*=7.2 Hz), 1.19 (3H, d, *J*=6.4 Hz), 1.37-1.42 (1H, m), 1.45 (6H, d, *J*=7.2 Hz), 3.37 (3H, s), 3.35-3.42 (1H, m), 3.98 (1H, dq, *J*=6.4, 3.8 Hz), 4.35 (1H, t, *J*=7 Hz), 6.56-6.63 (2H, m), 7.12 (1H, s), 7.88 (1H, s). minor product; ^{1}H-NMR: δ 0.95 (3H, d, *J*=6.8 Hz), 1.20 (3H, d, *J*=6.4 Hz), 1.37-1.42 (1H, m), 1.45 (6H, d, *J*=7.2 Hz), 3.37 (3H, s), 3.35-3.43 (1H, m), 3.70 (1H, t, *J*=6 Hz), 4.13 (1H, dd, *J*=6.4, 2 Hz), 6.56-6.63 (2H, m), 7.12 (1H, s), 7.89 (1H, s).

(3*R*,4*S*,5*E*)-Cystothiazole E (2)

To a solution of (*E*)-**22** (0.020 g, 0.056 mmol) in CH_2Cl_2 (5 mL) was added Dess-Martin reagent (0.036 g, 0.085 mmol) at rt and the whole mixture was stirred for 30 min at the same temperature. The reaction mixture was evaporated under reduced pressure to afford a residue, which was chromatographed on silica gel (5 g, *n*-hexane:AcOEt=10:1) to afford (+)-**2** (0.015 g, 80%) as a colorless oil. (+)-**2**: $[\alpha]_D^{25}$ +17.8° (c=0.66, $CHCl_3$) (cf. $[\alpha]_D$ +17.8° (c=0.2, $CHCl_3$) [2]), IR (KBr): 1709 cm^{-1}; ^{1}H-NMR: δ1.20 (3H, d, *J*=7.2 Hz), 1.44 (6H, d, *J*=6.8 Hz), 2.20 (3H, s), 2.79 (1H, dq, *J*=6.8, 6.0 Hz), 3.34 (3H, s), 3.37 (1H, sept, *J*=6.8 Hz), 4.02 (1H, t, *J*=6.4 Hz), 6.46 (1H, dd, *J*=15.6, 7.2 Hz), 6.61 (1H, d, *J*=15.6 Hz), 7.11 (1H, s), 7.87 (1H, s). ^{13}C-NMR: 11.9, 23.1, 29.9, 33.3, 52.0, 57.0, 82.7, 115.0, 116.0, 126.2, 130.2, 148.6, 153.9, 162.9, 178.7, 210.5. HRMS (FAB) (m/z): Calcd for $C_{17}H_{22}N_2O_2S_2$ (M^++1): 351.1200. Found: 351.11727.

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