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New total synthesis of (+)-cystothiazole A based on palladium-catalyzed cyclization–methoxycarbonylation☆

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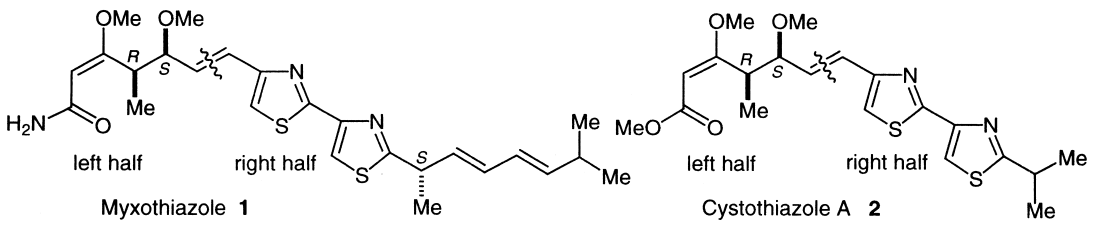
Abstract—Palladium-catalyzed cyclization-methoxycarbonylation of (2*R*,3*S*)-3-methylpenta-4-yne-1,2-diol (**6**) derived from (2*R*,3*S*)-epoxy butanoate **7** followed by methylation gave the tetrahydro-2-furylidene acetate (−)-**10**, which was converted to the left-half aldehyde (+)-**3**. A Wittig reaction between (+)-**4** and the phosphoranylide derived from the bithiazole-type phosphonium iodide **4** using lithium bis(trimethylsilyl)amide afforded the (+)-cystothiazole A (**2**). © 2003 Elsevier Science Ltd. All rights reserved.

Antifungal substances, myxothiazole (**1**)[2] and cystothiazole A (**2**),[3] were isolated from different strains of myxobacterium *Myxococcus fulvus* and *Cystobacter fuscus*, respectively. They are related to the oudemansins A,[4] B,[5] C[6] and melithiazoles,[7] which are naturally occurring congeners of β-methoxyacrylic acid. These antibiotics (**1** and **2**) possessing a bis-thiazole skeleton as well as a β-methoxyacrylate moiety and cystothiazole (**2**) have indicated potent antifungal activity against the phytopathogenic fungus, *Phytophthora capsici* (2 μg/disk), and have shown activity against a broad range of additional fungi with no effect on bacterial growth.[3] The fungicidal activity of these β-methoxyacrylate (MOA) inhibitors (**1**, **2**) has been shown to be due to their ability to inhibit mitochondrial respiration by blocking electron transfer between cytochrome b and cytochrome c.[8] The absolute structure of cystothiazole A (**2**) was established by a combination of spectroscopic analysis and chemical degradation of the natural product.[3] Total synthesis of a diastereomeric mixture of myxothiazole (**1**) has been achieved, but chiral synthesis of the left-half part possessing two chiral centers has not been carried out.[9] Another racemic synthesis of the left-half part of **1** starting from benzyloxyacetaldehyde is also reported.[10] Chiral synthesis of cystothiazoles A (**2**) and C based on the asymmetric Evans aldol process was reported.[11] In this paper, we describe a new chiral synthesis of (+)-cystothiazole A (**2**) based on a catalytic synthesis of the β-methoxyacrylate moiety including the adjacent chiral centers (Scheme 1).

Retrosynthetically, the synthesis of **2** can be achieved by Wittig condensation of the left-half aldehyde **3** and the right-half phosphonium iodide **4**. The aldehyde **3** can be derived from the tetrahydro-2-furylidene acetate **5**, which can be obtained by oxidative cyclization–methoxycarbonylation of (2*R*,3*S*)-3-methylpenta-4-yn-1,2-diol (**6**) in the presence of Pd(II)/*p*-benzoquinone in MeOH under a carbon monoxide atmosphere. The synthesis of the chiral diol **6** can be achieved by the reaction of (2*R*,3*S*)-epoxy butanoate **7**[12] and silyl-acetylide followed by reduction. An important chiral synthon (2*R*,3*S*)-**7** has been synthesized by us based on the lipase-catalysed asymmetric hydrolysis of



Scheme 1.

☆ See Ref. 1.

Keywords: (+)-cystothiazole A; cyclization; methoxycarbonylation.

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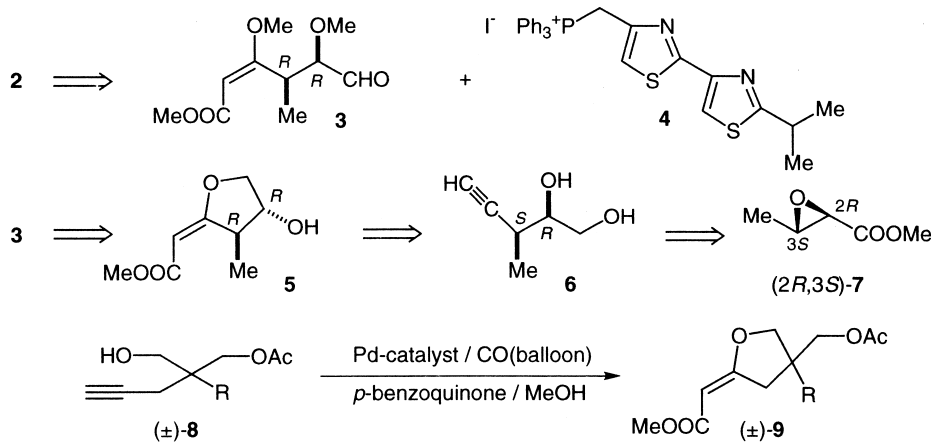
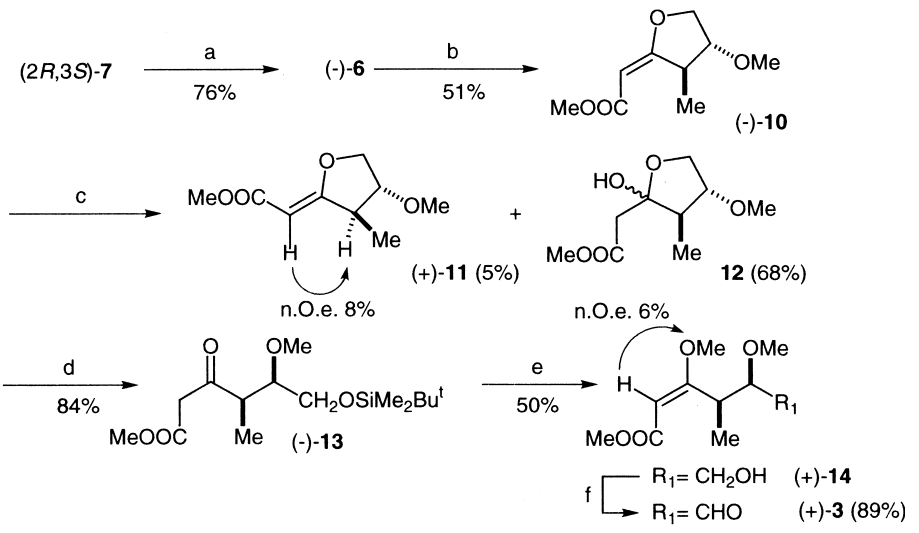


Scheme 2.

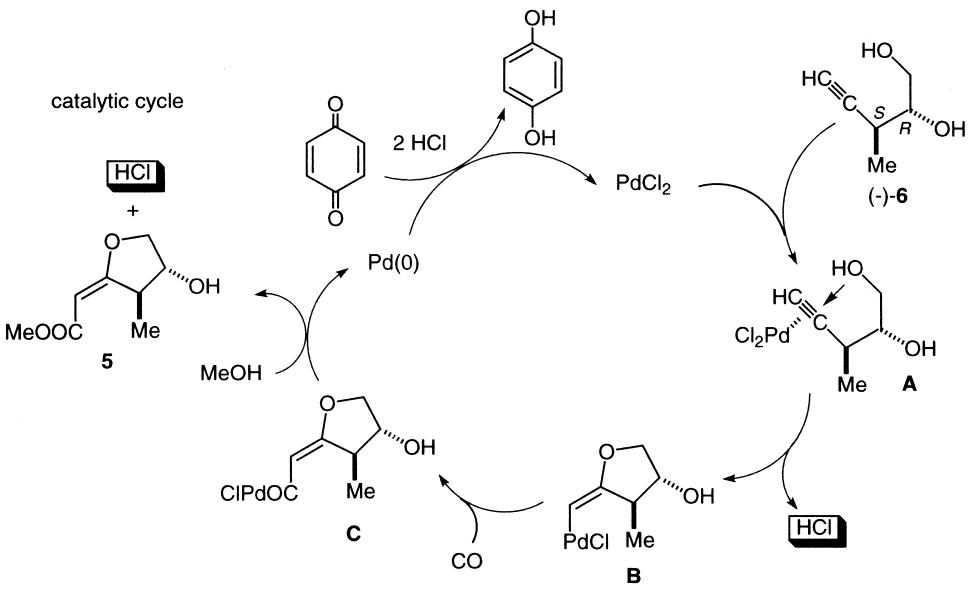
(±)-(2,3)-*trans*-3-acetoxy-2-chloro-butanoate.[12] A catalytic conversion of **6** into **5** is a key step in this total synthesis, and this type reaction was previously reported as shown in Scheme 2.[13] The oxidative cyclization-methoxycarbonylation of acyclic-4-yne-1-ols (±)-**8** affords (*E*)-cyclic-β-alkoxyacrylates (±)-**9** in good to excellent yields.[13] In this reaction, *p*-benzoquinone is found to be a very efficient reagent for trapping a proton of hydrogen chloride arising from the catalytic cycle and oxidative transfer of the generated Pd(0) species to a Pd(II) species.

By applying the previously reported procedure,[5b] the reaction of (2*R*,3*S*)-epoxy butanoate **7**[12] and lithium silylacetylide in the presence of Et_2AlCl followed by consecutive desilylation and reduction gave (−)-**6** ($[\alpha]_D$−36.8 (*c*=0.93, $CHCl_3$)) in 76% overall yield. The oxidative cyclization–methoxycarbonylation of (−)-**6** in the presence of $PdCl_2$ (5 mol%)/*p*-benzoquinone (1.1 equiv.) in MeOH at 0°C under a carbon monoxide atmosphere (balloon) gave a crude secondary alcohol **5**,[14] which was immediately subjected to methylation using MeI in the presence of Ag_2O to afford the methoxy compound (−)-**10** ($[\alpha]_D$−69.9 (*c*=1.06, $CHCl_3$)) in 51% overall yield. Acid treatment of (−)-**10** provided a hemiketal **12** (68%) along with the isomerized product (+)-**11** (5%). The geometry of (+)-**11** was confirmed to be *Z*-form because of n.O.e. enhancement for the olefinic proton and methine proton (8%); thence, that of (−)-**10** was deduced to be *E*-form. Silylation of **12** in DMF at 80°C gave a silyl ether (−)-**13** ($[\alpha]_D$−18.8 (*c*=1.02, $CHCl_3$)) in 84% yield, which was subjected to consecutive methylation (Me_2SO_4/K_2CO_3) and desilylation ($Et_3N(HF)_3$) to afford an alcohol (+)-**14** ($[\alpha]_D$+76.1 (*c*=0.7, $CHCl_3$)) in 50% overall yield. The (*E*)-geometry of (+)-**14** was confirmed by the n.O.e. enhancement for the olefinic proton and the methoxyl group (6%). Dess–Martin periodinane oxidation of (+)-**14** afforded the desired aldehyde >(+)-**3** ($[\alpha]_D$+104.7 (*c*=0.55, $CHCl_3$)) in 89% yield, whose NMR spectra were identical with those of the reported (±)-**3** (Scheme 3).[10]

As the reaction mechanism, the following path is plausible based on the precedents (Scheme 4).[15] Coordination of the triple bond of the substrate (−)-**6** to the Pd(II) species enables the inner primary hydroxyl group to attack the unsaturated bond, giving rise to σ-Pd complex **B**. It is well documented that the C–Pd bond undergoes CO insertion to generate intermediate **C**, which is reacted with MeOH to provide the product **5**. It is a well-established feature of the



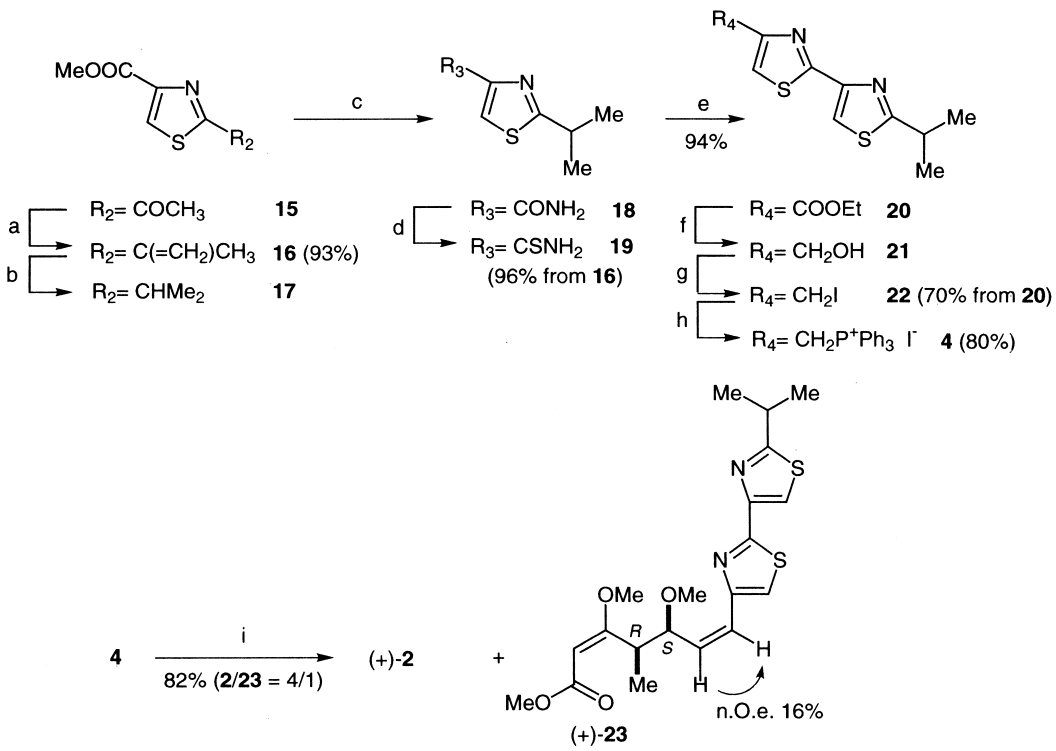
Scheme 3. a; 1) $Li^+ {}^-C{\equiv}C{-}SiMe_3/Et_2AlCl$ 2) $Bu_4N^+F^-$ 3) $LiBH_4$ b; 1) $PdCl_2$(5 mol%)/CO (balloon)/*p*-benzoquinone/MeOH 2) MeI/Ag_2O c; dil. HCl/THF d; $^tBuMe_2SiCl$/imidazole/DMF e; 1) Me_2SO_4/K_2CO_3/acetone 2) $Et_3N(HF)_3/CH_2Cl_2$ f; Dess-Martin periodinane.



Scheme 4.

reactions initiated by intramolecular nucleophilic attack on the triple bond coordinated to Pd(II) that the attack is anti with respect to palladium.[16] The exclusive occurrence of *E* stereochemistry in product **5** is clearly in agreement with this mechanistic hypothesis.

Wittig olefination of methyl ketone **15**[17] gave an *exo*-olefin **16** in 93% yield. A catalytic hydrogenation of **16** followed by consecutive treatment with NH_3/MeOH and Lawesson's reagent yielded a thioamide **19** in 96% overall yield from **16**. The reaction of **19** and α-bromopyruvate gave a bithiazole **20** in 94% yield, which was subjected to consecutive treatment with $LiBH_4$ and I_2/Ph_3P/imidazole to provide an iodide **22** in 70% overall yield from **20**. The reaction of **22** and triphenylphosphine gave a phosphonium salt **4** in 80% yield, which was condensed with (+)-**3** in the presence of lithium bis(trimethylsilyl)amide in THF to afford a mixture ((+)-(*E*)-**2**/(+)-(*Z*)-**23**=4/1) of olefins in 82% yield. Both isomers were isolated by silica-gel column chromatography to provide (+)-**2** (colorless needles from *n*-hexane/AcOEt (20/1), mp 110–111°C, $[\alpha]_D$+109.3 (*c*=0.53, $CHCl_3$)) and (+)-**23** ($[\alpha]_D$+240.5 (*c*=0.65, $CHCl_3$)). The (*Z*)-geometry of (+)-**23** was confirmed by the n.O.e. enhancement for the olefinic protons (16%).



Scheme 5. a; Ph_3P^+-Me Br^-/*t*-BuOK/toluene b; H_2/5% Pd-C/MeOH c; NH_3/MeOH d; Lawesson's reagent/benzene e; $BrCH_2COCOOEt$/EtOH f; $LiBH_4$ g; I_2/Ph_3P/imidazole h; Ph_3P/benzene i; $Li^+N^-(SiMe_3)_2$/(+)-**3**/THF.

The physical data of the synthetic (+)-**2** were identical with those (mp 111–112°C, $[\alpha]_D$=+109 (c=0.24, $CHCl_3$), NMR) of the reported natural product (+)-**2** (Scheme 5).[3]

In conclusion, palladium-catalyzed cyclization–methoxycarbonylation of (2*R*,3*S*)-3-methylpenta-4-yne-1,2-diol (**6**) derived from (2*R*,3*S*)-epoxy butanoate **7** followed by methylation gave the tetrahydro-2-furylidene acetate (−)-**10**, which was converted to the left-half aldehyde (+)-**3**. A Wittig reaction between (+)-**3** and the phosphoranylide derived from the bithiazole-type phosphonium iodide **4** using lithium bis(trimethylsilyl)amide afforded the (+)-cystothiazole A (**2**), whose spectral data were identical with those of the natural product (+)-**2**.

1. Experimental

1.1. General

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. High-resolution mass spectra (HRMS) and the 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. 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.

1.1.1. (−)-(2*R*,3*S*)-3-Methylpenta-4-yn-1,2-diol (6). *n*-Butyllithium (*n*-BuLi, 1.6 M in hexane, 28.4 ml, 45 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*)-**7** (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. To a solution of the above oily product in THF (30 ml) was added tetrabutylammonium fluoride (TBAF) in 1 M 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 (80 g, *n*-hexane/AcOEt=20:1) to afford methyl (2*R*,3*R*)-2-hydroxy-3-methyl-4-pentynoate (3.24 g, 80% yield) as a colorless oil. ^1H 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).

To a solution of above 2-hydroxy ester (1.104 g,78 mmol) in THF (15 ml) was added $LiBH_4$ (1.7 g, 78 mmol) at 0°C and the whole mixture was stirred for 30 min at room temperature. The reaction mixture was diluted with AcOEt (150 ml) and H_2O (15 ml), and the whole mixture was stirred for 12 h at the same temperature. The generated precipitate was filtered off with the aid of celite to afford the filtrate. Evaporation of the filtrate gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane/AcOEt=5:1) to provide a colorless oil (−)-**6** (0.842 g, 95%). (−)-**6**: $[\alpha]_D^{24}$ −36.8 (c=0.93, $CHCl_3$); IR (KBr): 3377 cm^{-1}; ^1H NMR: δ 1.26 (3H, d, J=6.8 Hz), 2.14 (1H, d, J=2.4 Hz), 2.57–2.65 (1H, m), 3.17 (2H, brs), 3.60 (1H, dt, J=3, 7.2 Hz), 3.70 (1H, dd, J=7.2, 11.2 Hz), 3.85 (1H, dd, J=3, 11.2 Hz). ^{13}C NMR: δ 17.0, 29.5, 64.5, 70.7, 74.6, 85.2. Anal. calcd for $C_6H_{10}O_2$: C, 63.14; H, 8.83. Found: C, 62.86; H, 8.94. MS (FAB) m/z: 115 (M^++1).

1.1.2. (−) Methyl α-[(3*R*,4*R*)-3-methyl-4-methoxy-tetrahydro-(2*E*)-furylidene]acetate (10). A 100 ml two-necked round-bottomed flask, containing a magnetic stirring bar, $PdCl_2$ (8 mg, 0.044 mmol), *p*-benzoquinone (95 mg, 0.88 mmol) and MeOH (5 ml), was fitted with a rubber septum and three-way stopcock connected to a balloon filled with carbon monoxide. The apparatus was purged with carbon monoxide by pumping-filling via the three-way stopcock. A solution of (−)-**6** (100 mg, 0.88 mmol) in MeOH (5 ml) was added to the stirred above mixture via a syringe at 0°C. After being stirred for 3 h, the reaction mixture was diluted with CH_2Cl_2 (20 ml), washed with 5% aqueous NaOH (50 ml), and dried over $MgSO_4$. Evaporation of the organic solvent gave a crude residue, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt=5:1) to provide a homogeneous oil **5** (114 mg, 76%); IR (KBr): 3445, 1704, 1644 cm^{-1}; **5**: ^1H NMR (acetone-d_4): δ 1.14 (3H, d, J=7.6 Hz), 3.58 (3H, s), 3.62 (1H, q, J=7.6 Hz), 4.16 (1H, d, J=10.2 Hz), 4.21 (1H, d, J=3.2 Hz), 4.35 (1H, brs), 4.39 (1H, dd, J=3.2, 10.2 Hz), 5.18 (1H, s). ^{13}C NMR (acetone-d_4): δ 15.7, 46.9, 50.5, 76.0, 78.0, 89.4, 168.2, 181.6. HRMS (FAB) (m/z): calcd for $C_8H_{13}O_4$ (M^++1): 173.0814. Found: 173.0844.

A mixture of the above oil (231 mg, 1.34 mmol), methyl iodide (1.94 g, 13 mmol) and Ag_2O (622 mg, 2.68 mmol) in DMF (2 ml) was stirred for 16 h at room temperature. The reaction mixture was diluted with AcOEt (30 ml) and filtered off with the aid of celite. Concentration of the filtrate gave a crude residue, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt=40:1) to provide a homogeneous oil (−)-**10** (246 mg, 99%). $[\alpha]_D^{27}$ −69.9 (c=1.06, $CHCl_3$); IR (KBr): 1701, 1648 cm^{-1}; ^1H NMR (acetone-d_4): δ 1.18 (3H, d, J=7.2 Hz), 3.28 (3H, s), 3.59 (3H, s), 3.71 (1H, q, J=7.6 Hz), 3.82 (1H, d, J=3.2 Hz), 4.30 (1H, d, J=10.6 Hz), 4.36 (1H, dd, J=3.2, 10.6 Hz), 5.16 (1H, s). ^{13}C NMR (acetone-d_4): δ 16.0, 43.3, 50.6, 56.2, 74.7, 85.4, 89.6, 168.3, 181.2. HRMS (FAB) (m/z): calcd for $C_9H_{15}O_4$ (M^++1): 187.0970. Found: 187.0939.

1.1.3. Acid treatment of (−)-10. To a solution of (−)-**10** (100 mg, 0.54 mmol) in THF (1 ml) was added 10% aqueous HCl (2 ml) and the whole mixture was stirred for 5 h at room temperature. 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 residue, which was chromatographed on silica gel (5 g) to provide a homogeneous oil **12** (75 mg, 68%) from *n*-hexane/AcOEt=

20:1 elution and a homogeneous oil (+)-**11** (5 mg, 5%) from *n*-hexane/AcOEt=10:1 elution. (+)-**11**: $[\alpha]_D^{24}$+34.5 (c=0.55, $CHCl_3$); IR (KBr): 1712, 1653 cm^{-1}; ^1H NMR (acetone-d_4): δ 1.18 (3H, d, J=7.6 Hz), 2.29 (1H, dq, J=2, 7.6 Hz), 3.30 (3H, s), 3.54 (3H, s), 3.74 (1H, dt, J=2, 4 Hz), 4.33 (1H, dd, J=1.6, 10.4 Hz), 4.44 (1H, dd, J=4, 10.4 Hz), 4.80 (1H, s). ^{13}C NMR (acetone-d_4): δ 17.7, 45.6, 50.3, 56.6, 76.3, 84.3, 88.4, 166.0, 176.7. Anal. calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 58.14; H, 7.55. MS (FAB) *m/z*: 187 (M^++1).

Compound **12**. IR (KBr): 3900, 1714, 1651, 1556, 1096 cm^{-1}; ^1H NMR (acetone-d_4) (major diastereomer): δ 1.08 (3H, d, J=7.2 Hz), 2.10 (1H, dq, J=6.4, 7.26 Hz), 2.64 (1H, d, J=14.8 Hz), 2.74 (1H, d, J=14.8 Hz), 3.27 (3H, s), 3.58 (1H, dd, J=4, 9 Hz), 3.65 (3H, s), 3.74 (1H, dt, J=4, 6 Hz), 4.03 (1H, dd, J=6.4, 9 Hz), 4.91 (1H, brs). ^{13}C NMR (acetone-d_4) (major diastereomer): δ 12.6, 42.9, 48.5, 51.9, 57.5, 70.4, 87.7, 105.1, 172.2. HRMS (FAB) (*m/z*): calcd for $C_9H_{17}O_5$ (M^++1): 205.1076. Found: 205.1041.

1.1.4. (−) Methyl (4*R*,5*R*)-6-*tert*-butyldimethylsiloxy-5-methoxy-4-methyl-3-oxohexanoate (13). A mixture of **12** (414 mg, 2.03 mmol), *tert*-butyldimethylsilyl chloride (TBDMSCl, 611 mg, 4.05 mmol) and imidazole (414 mg, 6.08 mmol) in DMF (10 ml) was stirred for 2 h at 80°C. 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 residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt=80:1) to provide a colorless oil (−)-**13** (542 mg, 84%). (−)-**13**: $[\alpha]_D^{26}$−18.8 (c=1.02, $CHCl_3$); IR (KBr): 1752, 1715, 1653, 1254, 1097 cm^{-1}; ^1H NMR: δ 0.06 (6H, s), 0.90 (9H, s), 1.14 (3H, d, J=6.8 Hz), 2.91–2.98 (1H, m), 3.41 (3H, s), 3.48 (1H, q, J=5.2 Hz), 3.54–3.67 (4H, m), 3.73 (3H, s). Anal. calcd for $C_{15}H_{30}O_5Si$: C, 56.57; H, 9.49. Found: C, 56.55; H, 9.49. MS (FAB) *m/z*: 319 (M^++1).

1.1.5. (+) Methyl (4*R*,5*R*)-6-hydroxy-3,5-dimethoxy-4-methyl-(2*E*)-hexenoate (14). A mixture of (−)-**13** (888 mg, 2.79 mmol), Me_2SO_4 (1.67 g, 13.2 mmol) and K_2CO_3 (1.02 g, 7.38 mmol) in acetone (20 ml) was stirred for 2 h at reflux. 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 residue. To a solution of the crude residue in CH_2Cl_2 (25 ml) was added hydrogen fluoride–triethylamine (HF–Et_3N, 1.9 g, 11.8 mmol), and the whole mixture was stirred for 9 h at room temperature. The reaction mixture was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Concentration of the organic layer gave a crude residue, which was chromatographed on silica gel (20 g, *n*-hexane/AcOEt=6:1) to provide a colorless oil (+)-**14** (291 mg, 50%). (+)-**14**: $[\alpha]_D^{24}$+76.1 (c=0.7, $CHCl_3$); IR (KBr): 3450, 1711, 1623, 1150 cm^{-1}; ^1H NMR: δ 1.19 (3H, d, J=6.8 Hz), 2.76 (1H, brs), 3.24–3.32 (1H, m), 3.44–3.48 (1H, m), 3.45 (3H, s), 3.63 (3H, s), 3.67–3.73 (1H, m), 3.69 (3H,s), 4.07–4.15 (1H, m), 5.05 (1H, s). ^{13}C NMR: δ 14.5, 36.0, 51.2, 55.6, 58.1, 61.4, 83.6, 91.4, 168.6, 176.5. HRMS (FAB) (*m/z*): calcd for $C_{10}H_{19}O_5$ (M^++1): 219.1232. Found: 219.1191.

1.1.6. (+) Methyl (4*R*,5*R*)-3,5-dimethoxy-4-methyl-(2*E*)-6-oxohexenoate (3). A mixture of (+)-**14** (142 mg, 0.65 mmol) and Dess–Martin reagent (708 mg, 1.67 mmol) in CH_2Cl_2 (6 ml) was stirred for 2 h at room temperature. The reaction mixture was diluted with ether. The organic layer was washed with 7% aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of organic solvent gave a crude residue, which was chromatographed on silica gel (5 g, *n*-hexane/AcOEt=9:1) to provide a colorless oil (+)-**3** (125 mg, 89%). (+)-**3**: $[\alpha]_D^{23}$+104.7 (c=0.55, $CHCl_3$); IR (KBr): 1712, 1628, 1441, 1149, 1095 cm^{-1}; ^1H NMR: δ 1.20 (3H, d, J=7.2 Hz), 3.43 (3H, s), 3.56 (1H, dd, J=2.4, 6.8 Hz), 3.64 (3H, s), 3.68 (3H, s), 4.48 (1H, dq, J=6.8, 7.2 Hz), 5.07 (1H, s), 9.59 (1H, q, J=2.4 Hz). ^{13}C NMR: δ 13.9, 36.5, 51.0, 55.7, 58.6, 87.4, 91.9, 167.6, 174.4, 202.1. HRMS (FAB) (*m/z*): calcd for $C_{10}H_{17}O_5$ (M^++1): 217.1076. Found: 217.1079.

1.1.7. 2-Isopropylidenethiazole-4-carboxylic acid methyl ester (16). A mixture of $Ph_3P^+MeBr^-$ (2.41 g, 6.7 mmol) and *tert*-BuOK (455 mg, 4.1 mmol) in toluene (20 ml) was stirred under reflux for 1 h under argon. A solution of methyl ketone **15** (500 mg, 2.7 mmol) in toluene (5 ml) was added to the above yellow solution ($Ph_3P{=}CH_2$) at 0°C and the whole mixture was stirred for 1 h at the same temperature. The reaction mixture was diluted with saturated aqueous NH_4Cl and extracted with AcOEt. 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 (10 g, *n*-hexane/AcOEt=80:1) to afford colorless compound **16** (460 mg, 93%). Recrystallization of **16** from *n*-hexane afforded a colorless needles **16**. **16**: mp 65–67°C; IR (KBr): 1724 cm^{-1}; ^1H NMR: δ 2.28 (3H, s), 3.95 (3H, s), 5.39 (1H, s), 5.89 (1H, s), 8.09 (1H, s). ^{13}C NMR: δ 20.6, 52.4, 118.1, 127.0, 137.7, 147.0, 161.7, 170.1. Anal. calcd for $C_8H_9NO_2S$: C, 52.44; H, 4.95; N, 7.64. Found: C, 52.38; H, 4.99; N, 7.67. MS (FAB) *m/z*: 184 (M^++1).

1.1.8. 2-Isopropylthiazole-4-thioamide (19). A solution of **16** (1.06 g, 5.8 mmol) in MeOH (20 ml) was subjected to catalytic hydrogenation in the presence of 5% Pd–C (250 mg) under hydrogen atmosphere. The reaction mixture was filtered off with the aid of celite and the filtrate was condensed to give a crude **17**, which was treated with the saturated NH_3 in MeOH (10 ml) and the whole mixture was left to stand for 3 days at room temperature. After cooling, the reaction mixture was concentrated to afford a crude amide **18**. To a solution of crude **18** in benzene (30 ml) was added Lawesson's reagent (2.4 g, 5.9 mmol) and the whole mixture was stirred for 1 h at reflux. The reaction mixture was diluted with H_2O and extracted with AcOEt. 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 (10 g, *n*-hexane/AcOEt=40:1) to afford a pale yellow compound **19** (1.034 g, 96%). Recrystallization of **19** from *n*-hexane afforded pale yellow needles **19**. **19**: mp 83–85°C; IR (KBr): 3290, 3155, 1634 cm^{-1}; ^1H NMR: δ 1.40 (6H, d, J=6.9 Hz), 3.28 (1H, sept, J=6.9 Hz), 7.79 (1H, brs), 8.32 (1H, s), 8.70 (1H, brs). ^{13}C NMR: δ 22.9, 33.3, 85.1, 126.4, 152.5, 177.7, 190.9. Anal. calcd for $C_7H_{10}N_2S_2$: C, 45.13; H, 5.41; N, 15.04. Found: C, 45.13; H, 5.36; N, 15.01. MS (FAB) *m/z*: 187 (M^++1).

1.1.9. 2′-Isopropyl[2,4′]bithiazolyl-4-carboxylic acid ethyl ester (20). A solution of **19** (0.99 g, 5.3 mmol) and ethyl bromopyruvate (1.14 g, 5.8 mmol) in absolute EtOH (30 ml) was stirred for 1 h at reflux. The reaction mixture was diluted with 7% aqueous $NaHCO_3$ and extracted with Et_2O. 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 (30 g, *n*-hexane/AcOEt=30:1) to afford **20** (1.41 g, 94%). Recrystallization of **20** from *n*-hexane provided colorless needles **20**. **20**: mp 76–77°C; IR (KBr): 1729 cm^{-1}; ^1H NMR: δ 1.43 (3H, d, J=7.1 Hz), 1.44 (6H, d, J=6.9 Hz), 3.36 (1H, sept, J=6.9 Hz), 4.44 (2H, q, J=7.1 Hz), 8.02 (1H, s), 8.16 (1H, s). ^{13}C NMR: δ 14.4, 23.1, 33.4, 61.5, 116.1, 127.4, 147.5, 147.6, 161.3, 163.5, 178.4. Anal. calcd for $C_{12}H_{14}N_2O_2S_2$: C, 51.04; H, 5.00; N, 9.92. Found: C, 50.89; H, 5.02; N, 9.96. MS (FAB) *m/z*: 283 (M^++1).

1.1.10. 2′-Isopropyl[2,4′]bithiazolyl-4-methyleneiodide (22). A mixture of **20** (1.787 g, 6.3 mmol) and $LiBH_4$ (0.69 g, 31.6 mmol) in THF (20 ml) was stirred for 2 h at room temperature. The reaction mixture was diluted with H_2O (10 ml) and the whole was stirred for 5 h at the same temperature. The reaction mixture was extracted with AcOEt and washed with brine, and dried over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt=5:1) to afford **21** (1.506 g, 99%). Recrystallization of **21** from *n*-hexane provided colorless needles **21**. **21**: mp 56–58°C; IR (KBr): 3247, 1536, 1447 cm^{-1}; ^1H NMR: δ 1.44 (6H, d, J=7.2 Hz), 3.25–3.40 (1H, brs), 3.37 (1H, sept, J=7.2 Hz), 4.81 (2H, s), 7.19 (1H, t, J=0.8 Hz), 7.84 (1H, s). ^{13}C NMR: δ 23.1, 23.1, 33.4, 60.9, 115.0, 115.2, 148.4, 157.2, 163.7, 178.8. Anal. calcd for $C_{10}H_{12}N_2OS_2$: C, 49.97; H, 5.03; N, 11.66%. Found: C, 50.27; H, 5.19; N, 11.43. MS (FAB) *m/z*: 241 (M^++1).

To a mixture of **21** (1.0 g, 4.2 mmol), triphenylphosphine (1.1 g, 4.2 mmol) and imidazole (0.375 g, 5.5 mmol) in THF (25 ml) was added I_2 (1.08 g, 4.3 mmol) under argon atmosphere and the whole mixture was stirred for 30 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 over $MgSO_4$. The organic layer was evaporated to give a crude residue, which was chromatographed on silica gel (10 g, *n*-hexane/AcOEt=40:1) to afford **22** (1.05 g, 72%). Recrystallization of **22** from *n*-hexane provided colorless needles **22**. **22**: mp 99–100°C; IR (KBr): 1653, 1506 cm^{-1}; ^1H NMR: δ 1.44 (6H, d, J=6.8 Hz), 3.37 (1H, sept, J=6.8 Hz), 4.56 (2H, s), 7.26 (1H, s), 7.86 (1H, s). ^{13}C NMR: δ 23.1, 23.1, 33.3, 85.1, 115.2, 116.7, 148.4, 154.0, 163.3, 178.7. Anal. calcd for $C_{10}H_{11}IN_2S_2$: C, 34.29; H, 3.17; N, 8.00. Found: C, 34.34; H, 3.19; N, 7.96. MS (FAB) *m/z*: 351 (M^++1).

1.1.11. 2′-Isopropyl[2,4′]bithiazolyl-4-methylenetriphenylphosphonium Iodide (4). A mixture of **22** (0.80 g, 2.2 mmol) and triphenylphosphine (0.63 g, 2.4 mmol) in benzene (7 ml) was stirred for 12 h at reflux. After cooling, the resulting colorless needles **4** (1.12 g, 80%) were obtained by filtration. **4**: mp 295–297°C; ^1H NMR: δ 1.40 (6H, d, J=6.9 Hz), 3.32 (1H, sept, J=6.9 Hz), 5.49 (2H, d, J=13.6 Hz), 7.27 (1H, s), 7.63–7.68 (6H, m), 7.77–7.84 (9H, m), 8.06 (1H, s). Anal. calcd for $C_{28}H_{26}IN_2PS_2$: C, 54.90; H, 4.28; N, 4.57. Found: C, 55.19; H, 4.28; N, 4.50. MS (FAB) *m/z*: 485 (M^++1–I).

1.1.12. Wittig condensation of (+)-3 and 4. To a solution of **4** (0.582 g, 0.95 mmol) in THF (5 ml) was added lithium bis(trimethylisilyl)amide (1 M solution in THF, 0.95 ml, 0.95 mmol) at 0°C under argon atmosphere and the whole mixture was stirred for 20 min at the same temperature. A solution of (+)-**3** (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 15 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 (5 g, *n*-hexane/AcOEt=20:1) to give (+)-**2** (129 mg, 66%) and a colorless oil (+)-**23** (32 mg, 16%) in elution order. Recrystallization of (+)-**2** from *n*-hexane/AcOEt (20/1) provided colorless needles **2**. (+)-**2**: mp 111–112°C; $[\alpha]_D^{23}$+109.3 (c=0.53, $CHCl_3$); IR (KBr): 2929, 1711, 1624, 1441, 1147 cm^{-1}; ^1H NMR: δ 1.22 (3H, d, J=6.8 Hz), 1.44 (6H, d, J=6.8 Hz), 3.33 (3H, s), 3.38 (1H, sept, J=6.8 Hz), 3.60 (3H, s), 3.67 (3H, s), 3.81 (1H, t, J=7.6 Hz), 4.18 (1H, dq, J=6.8, 7.6 Hz), 4.97 (1H, s), 6.41 (1H, dd, J=7.6, 16 Hz), 6.58 (1H, d, J=16 Hz), 7.09 (1H, s), 7.85 (1H, s). ^{13}C NMR: δ 14.1, 23.2, 23.2, 33.3, 39.8, 50.8, 55.5, 57.0, 84.4, 91.1, 114.8, 115.0, 125.6, 131.6, 148.7, 154.4, 162.6, 167.7, 176.7, 178.6. HRMS (FAB) (*m/z*): calcd for $C_{20}H_{27}O_4N_2S_2$ (M^++1): 423.1412. Found: 423.1440. (+)-**23**: $[\alpha]_D^{23}$+240.5 (c=0.65, $CHCl_3$); IR (KBr): 2932, 1715, 1623, 1457, 1146 cm^{-1}; ^1H NMR: δ 1.25 (3H, d, J=6.8 Hz), 1.45 (6H, d, J=6.8 Hz), 3.33 (3H, s), 3.34 (3H, s), 3.38 (1H, sept, J=6.8 Hz), 3.67 (3H, s), 4.22 (1H, dq, J=6.8, 9.2 Hz), 4.92 (1H, s), 5.10 (1H, t, J=9.2 Hz), 5.59 (1H, dd, J=9.2, 12 Hz), 6.58 (1H, d, J=12 Hz), 7.21 (1H, s), 7.82 (1H, s). ^{13}C NMR: δ 14.8, 23.2, 23.2, 33.4, 39.3, 50.8, 55.1, 56.3, 78.6, 91.1, 114.6, 117.8, 125.4, 132.6, 148.9, 153.6, 161.6, 167.8, 176.6, 178.8. HRMS (FAB) (*m/z*): calcd for $C_{20}H_{27}O_4N_2S_2$ (M^++1): 423.1412. Found: 423.1398.

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