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New total synthesis of (+)-cystothiazole A

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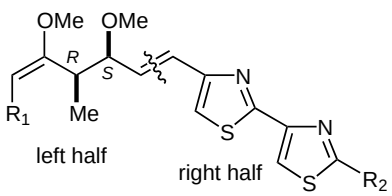
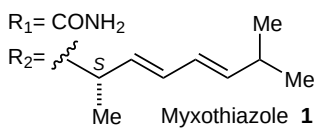
Abstract—Palladium-catalyzed cyclization–methoxycarbonylation of (2*R*,3*S*)-3-methylpenta-4-yne-1,2-diol (**7**) derived from (2*R*,3*S*)-epoxy butanoate **8** followed by methylation gave the tetrahydro-2-furylidene acetate (−)-**9**, which was converted to the left-half aldehyde (+)-**4**. A Wittig reaction between (+)-**4** and the phosphoranylide derived from the bithiazole-type phosphonium iodide **5** using lithium bis(trimethylsilyl)amide afforded the (+)-cystothiazole A (**2**).

Antifungal substances, myxothiazole (**1**)[1] and cystothiazole A (**2**),[2] were isolated from different strains of myxobacterium *Myxococcus fulvus* and *Cystobacter fuscus*, respectively. They are related to the oudemansins A (**3a**),[3] B (**3b**),[4] C (**3c**),[5] which are also naturally occurring congeners of β-methoxyacrylic acid produced by *Oudemansiella mucida*, *Xerula* species, *Oudemansiella radicata*, respectively. The fungicidal activity of these β-methoxyacrylate (MOA) inhibitors (**1**, **2**, **3a**,**b**,**c**) has been shown to be due to their ability to inhibit mitochondrial respiration by blocking electron transfer between cytochrome b and cytochrome c.[6] The absolute structure of cystothiazole A (**2**) was established by a combination of spectroscopic analysis and chemical degradation of the natural product.[2] Although a number of chiral syntheses of the β-methoxyacrylate moiety including the adjacent chiral centers have been achieved,[3b,4b,5b] a catalytic synthesis of the β-methoxyacrylate system has not been reported so far. 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.[7] Another racemic synthesis of the left-half part of **1** starting from benzyloxyacetaldehyde is also reported.[8] In this paper, we describe a new total synthesis of (+)-cystothiazole A (**2**) based on a catalytic synthesis of the β-methoxyacrylate moiety.[9]

Retrosynthetically, the synthesis of **2** can be achieved by Wittig condensation of the left-half aldehyde **4** and the right-half phosphonium iodide **5** by applying Martin's approach[7] in the total synthesis of myxothiazole (**1**). The aldehyde **4** can be derived from the tetrahydro-2-furylidene acetate **6**, which can be obtained by oxidative cyclization–methoxycarbonylation of (2*R*,3*S*)-3-methylpenta-4-yne-1,2-diol (**7**) in the presence of Pd(II)/*p*-benzoquinone in MeOH under a carbon monoxide atmosphere. The synthesis of the chiral diol **7** can be achieved by the reaction of (2*R*,3*S*)-epoxy butanoate **8**[10] and silyl-acetylide followed by reduction. An important chiral synthon (2*R*,3*S*)-**8** has been synthesized by us based on the lipase-catalyzed asymmetric hydrolysis of (±)-(2,3)-*anti*-3-acetoxy-2-chloro-butanoate.[10] A catalytic conversion of **7** into **6** is a key step in this total synthesis, and this type of reaction was previously reported.[11]

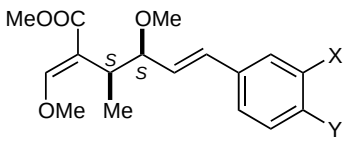




Myxothiazole **1**

R_1= COOMe R_2= $CHMe_2$

Cystothiazole A **2**



X = Y = H Oudemansin A **3a**
X = OMe Y = Cl Oudemansin B **3b**
X = H Y = OMe Oudemansin X **3c**

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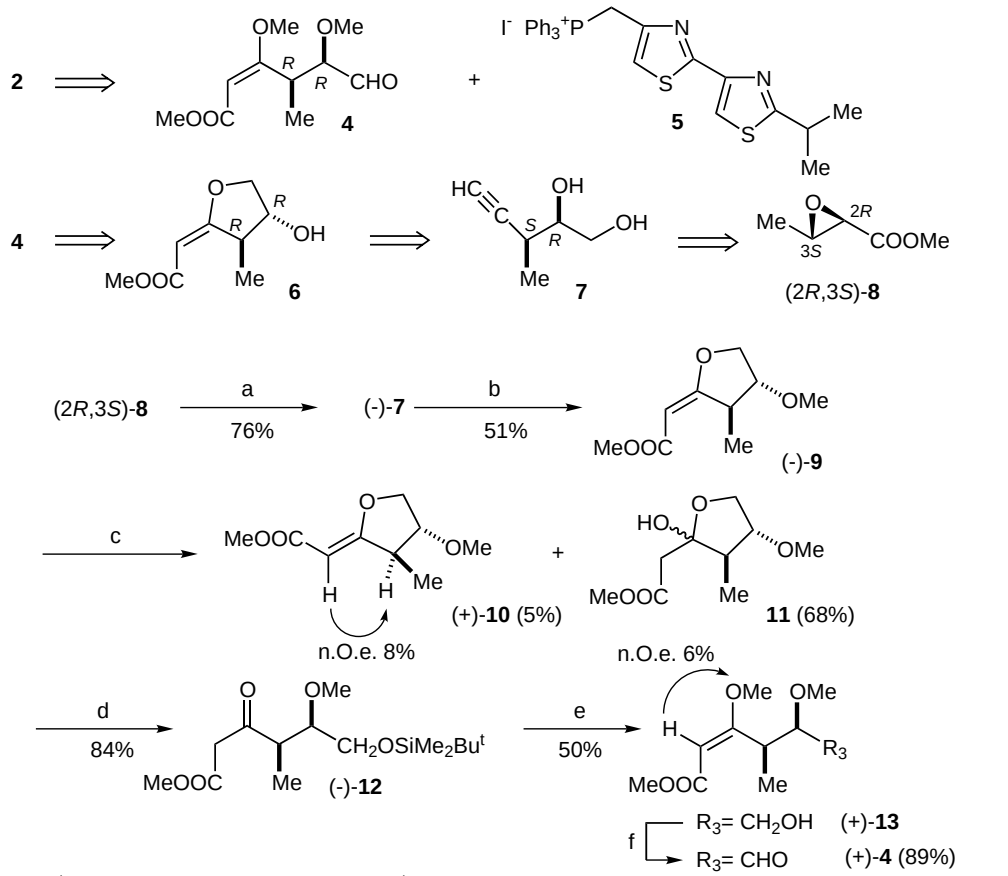
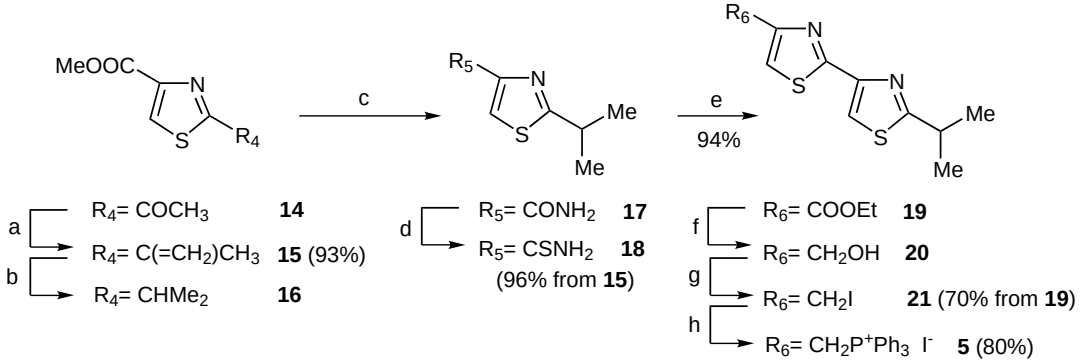
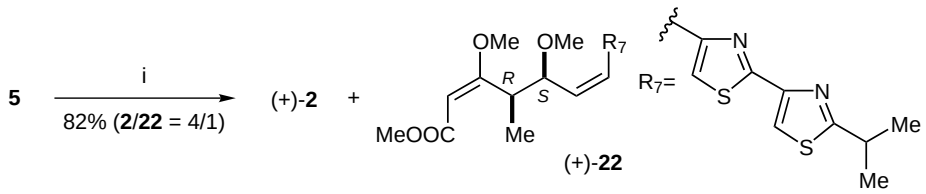


By applying the previously reported procedure,[4b] the reaction of (2*R*,3*S*)-epoxy butanoate **8**[10] and lithium silyl-acetylide in the presence of Et_2AlCl, followed by the consecutive desilylation and reduction gave (−)-**7** ($[\alpha]_D$ −36.8 ($c=0.93$, $CHCl_3$))[12] in 76% overall yield. The synthesis of an alcohol (±)-**13** corresponding to the left-half part from (±)-**7** was briefly reported,[11] total yield of (+)-**13** from (−)-**7** was improved in the chiral synthesis.

The oxidative cyclization–methoxycarbonylation of (−)-**7** in the presence of $Pd(OAc)_2$ (5 mol%)/*p*-benzoquinone (1.1 equiv.) in MeOH at 0°C under a carbon monoxide atmosphere (balloon) gave crude secondary alcohol **6**, which was immediately subjected to methylation using MeI in the presence of Ag_2O to afford the methoxy compound (−)-**9** ($[\alpha]_D$ −69.9 ($c=1.06$, $CHCl_3$)) in 51% overall yield.[13] Acid treatment of (−)-**9** provided a hemiketal **11** (68%) along with the isomerized product (+)-**10** (5%). The geometry of (+)-**10** was confirmed to be *Z*-form because of NOE enhancement for the olefinic proton and methine proton (8%); thence, that of (−)-**9** was deduced to be *E*-form. Silylation of **11** in DMF at 80°C gave a silyl ether (−)-**12** ($[\alpha]_D$ −18.8 ($c=1.02$, $CHCl_3$)) in 84% yield, which was subjected to consecutive methylation (Me_2SO_4/K_2CO_3) and desilyla-





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; $Li^+N^-(SiMe_3)_2$ / (+)-**4** / THF

tion ($Et_3N(HF)_3$) to afford an alcohol (+)-**13** ($[\alpha]_D$ +76.1 ($c=0.7$, $CHCl_3$)) in 50% overall yield. The (*E*)-geometry of (+)-**13** was confirmed by the NOE enhancement for the olefinic proton and the methoxyl group (6%). Dess–Martin periodinane oxidation of (+)-**13** afforded the desired aldehyde (+)-**4** ($[\alpha]_D$ +104.7 ($c=0.55$, $CHCl_3$)) in 89% yield, whose NMR spectra were identical with those of the reported (±)-**4**.[8]

Wittig olefination of methyl ketone **14**[14] gave an *exo*-olefin **15** in 93% yield. A catalytic hydrogenation of **15** followed by consecutive treatment with NH_3/MeOH and Lawesson's reagent yielded a thioamide **18** in 96% overall yield form **15**. The reaction of **18** and α-bromopyruvate gave a bithiazole **19** in 94% yield, which was subjected to consecutive treatment with $LiBH_4$ and I_2/Ph_3P/imidazole to provide an iodide **21** in 70% overall yield from **19**. The reaction of **21** and triphenylphosphine gave a phosphonium salt **5** in 80% yield, which was condensed with (+)-**4** in the presence of lithium bis(trimethylsilyl)amide in THF to afford a mixture ((+)-(*E*)-**2**/(+)-(*Z*)-**22** = 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 (+)-**22** ($[\alpha]_D$ +240.5 ($c=0.65$, $CHCl_3$)). 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**.[2]

In conclusion, palladium-catalyzed cyclization–methoxycarbonylation of (2*R*,3*S*)-3-methylpenta-4-yne-1,2-diol (**7**) derived from (2*R*,3*S*)-epoxy butanoate **8**[10] followed by methylation gave the tetrahydro-2-furylidene acetate (−)-**9**, which was converted to 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 the (+)-cystothiazole A (**2**), whose spectral data were identical with those of the natural product (+)-**2**.

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11. Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron Lett*. **2001**, *42*, 4203–4205.
12. Satisfactory analytical data were obtained for all new compounds.
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