Synthesis of Cystothiazole E and Formal Syntheses of Cystothiazoles A and C by Pd^0-Catalyzed Cross-Coupling Reactions

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Abstract: The synthesis of the naturally occurring bithiazole (+)-cystothiazole E (**1e**) is described starting from oxazolidinone **2**. It proceeded in 10 steps and an overall yield of 37%. The key reaction of the sequence was a Suzuki cross-coupling between bromobithiazole **4** and the (*E*)-alkenylboronic acid derived from alkyne **18** (94% yield). Prior to the synthesis, more general investigations related to the cross-coupling of bromobithiazole **4** were undertaken. Whereas Heck reactions failed Suzuki and Stille cross-coupling reactions were successfully conducted. By this means, the alkenylboronic acid derived from alkyne **11** and stannane **12** could be transformed into the corresponding alkenylbithiazoles **13** (92%) and **14** (52%). The Stille cross-coupling of compound **4** and stannane **5** allowed access to aldehyde **21** (97% yield) and paved the way for an alternative route to (+)-cystothiazole E (**1e**). In addition, aldehyde **21** was transformed into aldol product **22** (72%) which has been used in previous syntheses of cystothiazole A (**1a**) and C (**1c**). In this respect, the preparation of compound **21** represents a formal total synthesis of these cystothiazoles.

Keywords: aldol reaction · asymmetric synthesis · cross-coupling · heterocycles · total synthesis

Introduction

In 1998 Sakagami et al. reported on the isolation and structure elucidation of a series of structurally related bithiazoles from the myxobacterium *Cystobacter fuscus*.[1] The compounds were named cystothiazoles (**1**) and differ from each other in the substitution at three positions around a central skeleton (Figure 1). All cystothiazoles except cystothiazole E (**1e**) contain at one terminus (R in Figure 1) a β-methoxyacrylate moiety which is a frequently encountered motif in natural products isolated from myxobacteria.[2] The constitution and configuration of these cystothiazoles (**1a–d**, **f**) was deduced from spectroscopic analyses and comparison with known data. As no comparable spectral data were available for the ketone cystothiazole **1e** its configuration remained unclear and only its constitution had been established so far. All cystothiazoles display antifungal activity and inhibit the growth of a phytopathogenic fungus, *Phytophthora capsici*. The activity decreases in the order **1a** > **1f** > **1b** > **1e** ≅ **1c** ≅ **1d** with compound **1a** being 100 times more potent in the chosen assay than the least active compound **1d**.[1a]

Synthetic efforts towards cystothiazoles have been reported by the groups of Williams,[3] Akita,[4] Panek,[5] and by ourselves.[6] In a preliminary communication we reported on the first synthesis of a cystothiazole, cystothiazole E (**1e**).[6] We were able to elucidate its relative and absolute configuration based on NMR data and on the optical rotation. The syntheses of cystothiazoles A and C were reported shortly thereafter.[3, 4] Strategically, our retrosynthetic considerations were based on a disconnection directly at the 4-position of a 2′-alkyl-4-bromo-2,4′-bithiazole which was in turn obtained from 2,4-dibromothiazole by regioselective cross-coupling reactions. Contrary to that, the other reported syntheses[3, 4] employed the Hantzsch reaction for the bithiazole formation and established the crucial connection of the bithiazole by

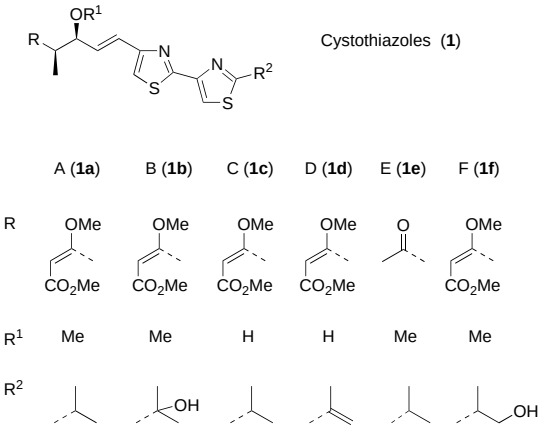

Figure 1. The structure of naturally occurring cystothiazoles (**1**) found in the myxobacterium *Cystobacter fuscus*.[1]

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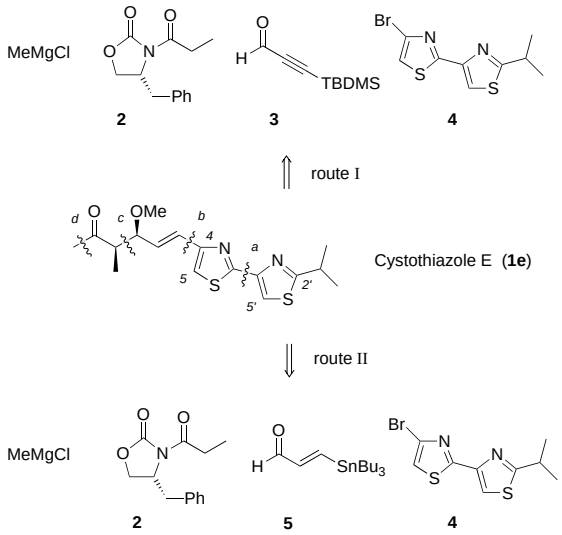
carbonyl olefination at the α-carbon atom of a preformed 4-substituted bithiazole.

In this paper we provide a full account on our endeavour directed towards the synthesis of cystothiazoles. Two pathways have been explored which differ in the order of events and which are depicted for cystothiazole E as possible target in Scheme 1. Both routes rely on the readily available 2′-isopropyl-4-bromo-2,4′-bithiazole (**4**). Its synthesis has been



Scheme 1. Retrosynthetic strategy for the preparation of cystothiazole E (**1e**) from precursors **2**–**5**.

optimized[7] and it is available from 2,4-dibromothiazole in 70% overall yield. Crucial to the success of all pathways is the cross-coupling at the 4-position of this substrate. The reactivity at this position is low and careful experimentation was necessary to find suitable conditions which allowed for a C–C-bond formation. In route I which has already been published in preliminary form[6] we followed a convergent approach and tried to establish bond *b* as late as possible in the synthesis. As it turned out, the aldol reaction of the *N*-propionyl oxazolidinone **2** and aldehyde **3** proceeded readily (bond *c*) but it was not sensible from a practical point of view to establish bond *d* prior to the cross-coupling (see below). Route II has been developed more recently which aimed at a bond construction in the order *a*-*b*-*c*-*d*. Although more linear than route I it was appealing to us because it allowed for a formal access to other cystothiazoles such as cystothiazoles A (**1a**) and C (**1c**). Stannane **5**[8] proved to be the key building block in this strategy.

Abstract in German: *Die Synthese des natürlich vorkommenden Bithiazols (+)-Cystothiazol E (**1e**) wird ausgehend von Oxazolidinon **2** beschrieben. Sie verläuft in 10 Stufen und einer Gesamtausbeute von 37%. Schlüsselschritt der Sequenz ist eine Suzuki-Kreuzkupplung zwischen Brombithiazol **4** und der von Alkin **18** abgeleiteten (E)-Alkenylboronsäure (94% Ausbeute). Im Vorfeld der Synthese wurden Untersuchungen zur Kreuzkupplung von Brombithiazol **4** durchgeführt. Während Heck-Reaktionen scheiterten, waren Suzuki- und Stille-Kreuzkupplungen erfolgreich. Auf diese Weise konnten die von Alkin **11** abgeleitete Alkenylboronsäure und das Stannan **12** in die entsprechenden Alkenylbithiazole **13** (92%) und **14** (52%) umgewandelt werden. Die Stille-Kreuzkupplung zwischen Verbindung **4** und Stannan **5** erlaubte einen Zugang zu Aldehyd **21** (97% Ausbeute) und eröffnete damit einen alternativen Syntheseweg zu (+)-Cystothiazol E (**1e**). Aldehyd **21** wurde überdies in das Aldolprodukt **22** umgewandelt (72%), das in bekannten Synthesen der Cystothiazole A (**1a**) und C (**1c**) als Intermediat verwendet worden war. Folglich repräsentiert die Herstellung von **21** eine formale Totalsynthese dieser Cystothiazole.*

Results and Discussion

Attempted cross-coupling reactions with substrate 4: Previous work in our group had revealed that a Pd-catalyzed cross-coupling with a 2-arylsubstituted 4-bromothiazole is not easy to achieve.[9, 10] Suzuki reactions with arylboronic acids, however, have been shown to work quite well.[11] In addition, there was literature precedence for successful Stille and Sonogashira cross-coupling reactions[12] conducted with 4-bromothiazoles[13, 14] and with the activated 4,4′-dibromo-2,2′-bithiazole.[15] Stannylations at 4-bromothiazoles with hexamethylditin had also been reported.[16] We were most intrigued by the fact that Heck reactions had been carried out with 4-bromothiazole although the reported yields were low (5–19%).[14a] In fact, a Heck reaction would have allowed for a connection between a complete aldol fragment and bithiazole **4**. Preliminary experiments were conducted with alkenes **6**, **7**, and **8** (Figure 2) but there was no indication for a successful coupling to bithiazole **4**. Conditions [$Pd(OAc)_2$, $P(o\text{-Tol})_3$, K_2CO_3 in *N*,*N*-dimethylacetamide (DMA)], which in our hands facilitated a rapid and smooth Heck reaction of acrylate **8** with bromobenzene, failed completely for the 4-bromobithiazole **4**.

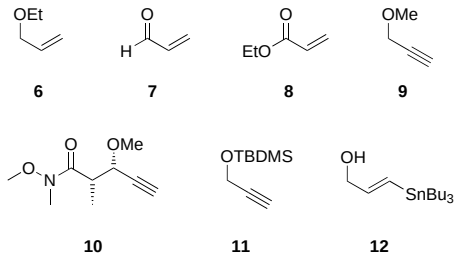


Figure 2. Potential reaction partners **6**–**12** for a Heck reaction or a cross-coupling reaction with bithiazole **4**.

We next tried to employ the Suzuki cross-coupling as an alternative C–C-bond forming reaction. Hydroboration of an alkyne with catecholborane and subsequent hydrolysis[17] was expected to deliver an *E*-alkenyl boronic acid which could be attached to the bithiazole fragment by Pd^0 catalysis. As the hydroborating reagent also reduces carbonyl groups the strategy required appropriate protection of ketones and aldehydes. Initial attempts with propargyl methyl ether (**9**)

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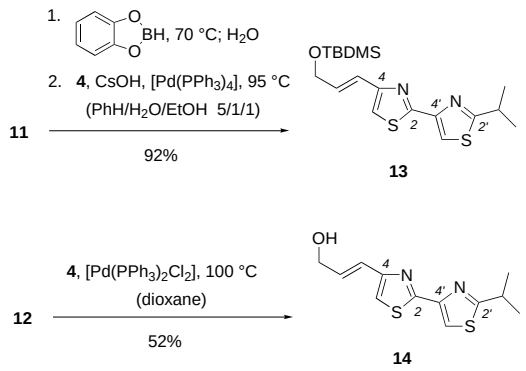
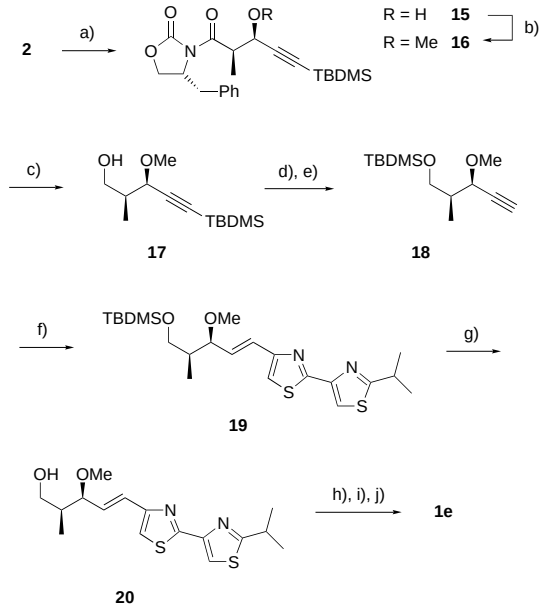
were hampered by its volatility. Cross-coupling products were not observed and there were indications that the hydroboration reaction itself had not properly worked. This suspicion was confirmed when we used the more sophisticated alkyne **10** which was available from the corresponding aldol product (see below). Under a wide variety of conditions a hydroboration of this substrate with catecholborane could not be achieved. In all instances unreacted starting material was recovered almost completely. NMR spectra of crude product gave no indication for a hydroboration. Luckily, we had also employed the *tert*-butyldimethylsilyl (TBDMS) ether **11**[18] in parallel experiments. Its hydroboration proceeded smoothly. The success of the hydroboration was proven by cross-coupling of the corresponding alkenyl boronic acid to bromobenzene. The reaction proceeded nicely following a standard protocol[19] {[$Pd(PPh_3)_4$], K_2CO_3, PhH/H_2O/EtOH 5:1:1, 90 °C} in 71 % yield. 4-Bromobithiazole (**4**), however, remained inert towards a cross-coupling with the same alkenyl boronic acid under identical conditions. Since the counterion of the hydroxide base used in Suzuki cross-coupling reactions has been shown to strongly affect the velocity of the reaction[20] we varied the base. Indeed, this variation led to a reliable and high-yielding protocol for the Suzuki cross-coupling of 4-bromobithiazoles which was also employed in the synthesis of cystothiazole E. The key to the success was the use of CsOH as the base. The reaction of compounds **11** and **4** to product **13** is depicted in Scheme 2.



Scheme 2. The two most relevant cross-coupling reactions conducted in model studies with bithiazole **4**.

A final set of experiments was directed towards a Stille cross-coupling of bithiazole **4** with appropriate stannanes. Test reactions conducted with alkenylstannane **12**[21] and [$Pd(PPh_3)_4$] in *N*,*N*-dimethyl acetamide (DMA) did not yield the desired product. Modifications of the reaction conditions were also successful in this instance and the clean formation of alcohol **14** was observed with [$PdCl_2(PPh_3)_2$] in dioxane at 100 °C (Scheme 2, 52 % yield). Even more remarkably, the same conditions were applicable to the cross-coupling of stannane **5**. The implementation of the latter reaction step in route II to cystothiazoles will be discussed in one of the following sections.

Synthesis of (+)-cystothiazole E according to route I: Based on the cross-coupling of an alkenyl boronic acid with bithiazole **4** we executed the synthesis of cystothiazole E as outlined in Scheme 1 (route I). Since we had determined the absolute configuration of the target in our preliminary work[6] we chose the oxazolidinone **2**[22] which is derived from (*R*)-phenylalanine to finally obtain the naturally occurring (+)-cystothiazole E. The sequence of steps is depicted in Scheme 3. Within usual limits the yields we achieved were identical to the yields previously reported for the synthesis of (−)-cystothiazole E (*ent*-**1e**). The previously reported synthesis commenced with oxazolidinone *ent*-**2** derived from (*S*)-phenylalanine.



Scheme 3. Individual steps and yields in the synthesis of (+)-cystothiazole E (**1e**) according to route I: a) i) Bu_2BOTf (1.1 equiv), $EtNiPr_2$ (1.2 equiv) in CH_2Cl_2, 0 °C, 45 min; ii) aldehyde **3** (1.35 equiv) in CH_2Cl_2, −78 → −10 °C, 1 h, 86 %; b) $Me_3O^+BF_4^-$ (2.1 equiv), 1,8-bis(*N*,*N*-dimethylamino)naphthalene (1.4 equiv) in CH_2Cl_2, RT, 2 d, 61 %; c) $LiAlH_4$ (1.1 equiv) in THF, 0 °C, 2 h, quant.; d) TBAF (1.2 equiv) on silica in THF, RT, 1 h; e) TDBDMSCl (1.2 equiv), imidazole (2.5 equiv) in DMF/CH_2Cl_2, RT, 1 d, quant. (two steps); f) i) catecholborane (1.5 equiv), neat, RT → 95 °C, 3 h; ii) **4** (0.3 equiv), [$Pd(PPh_3)_4$] (0.015 equiv), CsOH (1.2 equiv) in H_2O/EtOH/PhH, RT → 95 °C, 16 h, 94 % (relative to **4**); g) PPTS (0.5 equiv) in EtOH, 55 °C, 24 h, 82 %; h) Dess–Martin periodinane (1.2 equiv) in CH_2Cl_2, RT, 2 h, quant.; i) MeMgCl (4 equiv) in THF, RT, 1 h, 91 %; j) Dess–Martin periodinane (1.3 equiv) in CH_2Cl_2, RT, 3 h, quant.

Aldol reaction[23] of oxazolidinone **2** with aldehyde **3** provided access to the diastereomerically pure aldol product **15** (*syn*/*anti* > 98:2; > 95 % *de*).[24] Methylation with the Meerwein salt trimethyloxonium tetrafluoroborate in the presence of the proton sponge 1,8-bis(*N*,*N*-dimethylamino)-naphthalene[25] converted the secondary alcohol into its methyl ether **16**. Attempts to employ other methylating agents (methyl iodide, dimethyl sulfate, methyl triflate) for this conversion were unsuccessful. Methylation was achieved with MeI and K_2CO_3 in refluxing acetone but partial epimerization occurred. Reduction of the *N*-acyloxazolidinone with lithium aluminium hydride yielded the primary alcohol **17** and the recoverable auxiliary. Subsequent protec-

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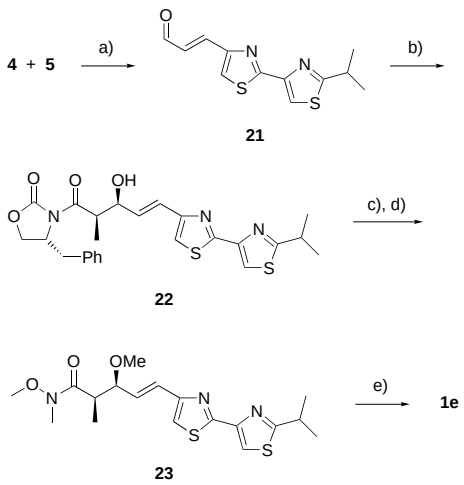
tive group manipulations included the cleavage of the TBDMS group from intermediate **16** (tetrabutylammonium fluoride, TBAF) to liberate the free alkyne and the installation of a protective group at the hydroxy group. For the latter purpose the TBDMS group was selected. Alkyne **18** underwent a smooth hydroboration with catecholborane. After hydrolysis the intermediate alkenyl boronic acid was not isolated but directly subjected to the Suzuki cross-coupling reaction with bithiazole **4**. The reaction which was conducted in full analogy to the transformation **11** → **13** produced the desired cystothiazole precursor **19** in excellent yield (94%). As the fluoride promoted deprotection of the silyl ether in compound **19** failed (e.g. TBAF in THF at RT, TBAF on silica gel in THF at RT, or TBAF/HOAc in THF at RT) we employed acidic conditions (pyridinium *p*-toluenesulfonate, PPTS) to generate the primary alcohol **20**. Oxidation under Dess–Martin conditions[26] yielded the corresponding aldehyde to which methyl magnesium chloride was added. The resulting secondary alcohol was obtained as a mixture of diastereoisomers (d.r. 3:1) which were not separated but oxidized directly to the desired product, (+)-cystothiazole E (**1e**). Its identity with the natural product was proven by comparison with reported NMR data. The optical rotation was positive as expected for the (3*R*,4*S*)-stereoisomer {$[\alpha]_D^{20} = +17.6$ ($c = 0.12$, $CHCl_3$)} and compared well with the optical rotation determined for the natural product {$[\alpha]_D^{20} = +17.8$ ($c = 0.2$, $CHCl_3$)}.[1a] Overall, the synthesis of cystothiazole E along route I proceeded in 10 steps and 37% yield starting from the oxazolidinone **2**.

Synthesis of cystothiazole E and formal syntheses of cystothiazoles A and C according to route II: Whereas the order of bond connection in route I was—according to Scheme 1—(*c*/*a*)/*b*/*d* we considered in a second route the linear bond connection in the order *a*/*b*/*c*/*d* which would enable facile access to other cystothiazoles. Key intermediate was aldehyde **21** (Scheme 4) which can be directly employed for an aldol reaction with chiral enolate equivalents and which has been previously synthesized.[3] The synthesis of this aldehyde based on cross-coupling methodology was possible from the corresponding alcohol **14** by Swern oxidation (89% yield). Alcohol **14** was available either directly from bithiazole **4** by Stille cross-coupling (Scheme 2) or from silyl ether **13** by deprotection (TBAF in THF, RT; 78% yield). In attempts to find a shorter route to aldehyde **21** we discovered that the Stille cross-coupling reaction of β-stannyl acrolein **5** and bithiazole **4** was a facile reaction which proceeded in 97% yield. By this means, key intermediate **21** was accessible in three consecutive cross-coupling steps from 2,4-dibromothiazole in a total yield of 68%.

The aldol reaction of aldehyde **21** with the *O*-(*Z*)-boron enolate derived from *N*-propionyloxazolidinone (**2**) proceeded smoothly and yielded the known *syn*-aldol product **22** (*syn*/*anti* > 98:2; > 95% *de*).[3] Its conversion to cystothiazole E was achieved in three steps which were not further optimized. Following the standard protocol[27] the oxazolidinone was substituted by *N*-methoxy-*N*-methylamine in the presence of trimethylaluminium. After O-methylation of the secondary alcohol the intermediate Weinreb amide **23** could be directly converted into the desired product by nucleophilic attack with magnesium methyl chloride.[28] Despite its linearity, route II requires less steps than route I as it completely lacks any protective group manipulations. In this respect, it is straightforward and includes only seven synthetic transformations starting from the readily available 2,4-dibromothiazole. It is, however, hampered by the low yields achieved in the methylation step (30–35%).



Scheme 4. Individual steps and yields in the synthesis of (+)-cystothiazole E (**1e**) acording to route II: a) **4** (1 equiv), **5** (3 equiv), NEt_3 (2 equiv), $[PdCl_2(PPh_3)_2]$ (0.05 equiv) in dioxane, 100 °C, 16 h, 97%; b) i) Bu_2BOTf (1.2 equiv), $EtNiPr_2$ (1.5 equiv) in CH_2Cl_2, 0 °C, 45 min; ii) aldehyde **21** (0.75 equiv) in CH_2Cl_2, −78 °C → −10 °C, 1 h, 86% (relative to **21**); c) i) $AlMe_3$ (9 equiv), HNMe(OMe)·HCl (9 equiv) in THF, 0 °C, 30 min; ii) **22** (1 equiv) in THF, −15 °C → RT, 1 h; d) $Me_3O^+BF_4^-$ (6.4 equiv), 1,8-bis(*N*,*N*-dimethylamino)naphthalene (6.4 equiv) in CH_2Cl_2, RT, 2 d, 17%. (two steps); e) MeMgCl (6.5 equiv) in Et_2O/THF, RT, 1 h, 95%.

Intermediate **22** has been elegantly converted to cystothiazoles A and C in recent syntheses by Williams et al. (Scheme 5).[3, 29] Cystothiazole A (**1a**) was obtained in 41% yield and cystothiazole C (**1c**) in 29% yield starting from aldol product **22**.

Scheme 5. Syntheses of cystothiazole A (**1a**) and cystothiazole C (**1c**) from intermediate **22** according to Williams et al.[3]

In view of these results, our synthesis of intermediate **22** represents a formal access to these cystothiazoles. The calculated overall yield for cystothiazole A is 20% in eleven steps and 14% for cystothiazole C in twelve steps starting from 2,4-dibromothiazole.

Conclusion

In summary, the 4-bromobithiazole (**4**) was shown to be a versatile building block for the syntheses of cystothiazoles A, C, and E. The starting material is available from 2,4-dibromothiazole in two consecutive cross-coupling reactions (70% yield). The pivotal cross-coupling at the 4-position of

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4-bromobithiazole (**4**) was closely studied. The Suzuki cross-coupling with alkenyl boronic acids and the Stille cross-coupling with alkenyl stannanes proceeded well under optimized conditions. Suzuki cross-coupling of bithiazole **4** with the boronic acid derived from aldol fragment **18** (94% yield) allowed for a convergent synthesis of cystothiazole E (route I). A linear but equally efficient pathway to the same target was paved by the Stille cross-coupling of bithiazole **4** and alkenyl stannane **5** (97% yield). The aldehyde **21** thus obtained is a versatile intermediate for the synthesis of cystothiazoles. Based on the presented cross-coupling methodology other biologically active bithiazoles should be equally well accessible. Studies along these lines are currently underway in our laboratory.

Experimental Section

General: All reactions involving water-sensitive chemicals were carried out in flame-dried glassware with magnetic stirring under Ar. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from potassium immediately prior to use. *N,N*-Diisopropylethylamine was distilled from calcium hydride. $[Pd(PPh_3)_4]$,[30] $[PdCl_2(PPh_3)_2]$,[31] and $[Pd_2(dba)_3]$,[32] and dppf[33] were prepared according to literature procedures. All other chemicals were either commercially available or prepared according to the cited references. TLC: Merck glass sheets (0.25 mm silica gel 60, F_{254}), eluent given in brackets. Detection by UV or coloration with ceric ammonium molybdate (CAM). Optical rotation: Perkin–Elmer 241 MC. Melting points (uncorrected): Reichert hot bench. NMR: Bruker spectrometers ARX-200, AC-250, AC-300 and AX-500. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature unless stated otherwise. Chemical shifts are reported relative to tetramethylsilane as internal standard or distinguished solvent signals. Apparent multiplets which occur as a result of the accidental equality of coupling constants of magnetically nonequivalent protons are marked as virtual (virt.). IR: Bruker IFS 200 or Perkin–Elmer 1600 FT-IR. MS: Varian CH7 (EI) or Finnigan MAT 8200 (EI, CI). HRMS: Finnigan MAT 8200 (EI). GC-MS: Agilent 6890 (GC system), Agilent 5973 (Mass selective detector, EI), Column: HP 5MS (30 m). Elemental analysis: Microanalytical laboratory Beller (Göttingen). Flash chromatography:[34] Merck silica gel 60 (230–400 mesh, ca. 50 g for 1 g of material to be separated), eluent given in brackets. Eluents [Et_2O, ethyl acetate (EtOAc) and pentane (P)] were distilled prior to use.

(4*S*)-Benzyl-3-[5-(*tert*-butyldimethylsilyl)-(3*S*)-hydroxy-(2*S*)-methyl-4-pentynyl]-oxazolidin-2-one (*ent*-15):[24] A 1M solution of di-*n*-butylboron-triflate in dichloromethane (14.0 mL, 14.0 mmol) and *N,N*-diisopropylethylamine (2.00 g, 15.5 mmol) were carefully added to a solution of the oxazolidinone *ent*-**2** (3.00 g, 12.9 mmol)[22] in dichloromethane (30 mL) so that the temperature remained between 0 and 5 °C. After 45 min the reaction mixture was cooled to −78 °C and a solution of aldehyde **3** (2.90 g. 17.5 mmol) in dichloromethane (10 mL) was added over a period of 1 h through a syringe pump. After 1 h at −78 °C the mixture was stirred for one additional hour at −10 °C before it was quenched by successive addition of pH 7 phosphate buffer (15 mL), methanol (42 mL) and a 1:2 mixture of 30% H_2O_2/MeOH (45 mL) keeping the temperature between 0 and 10 °C. After 1 h the mixture was concentrated in vacuo and the resultant slurry was extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and filtered. After removal of the solvent the crude residue was purified by flash chromatography (P/EtOAc 80:20) to afford *ent*-**15** (4.42 g, 86%) as a white solid. $R_f = 0.27$ (P/EtOAc 80:20); m.p. 85 °C; $[\alpha]_D^{20} = 65.8$ ($c = 0.40$ in CH_2Cl_2); ^1H NMR (250 MHz): $\delta = 0.11$ [s, 6H; $Si(CH_3)_2$], 0.93 [s, 9H; $SiC(CH_3)_3$], 1.43 (d, $^3J = 7.1$ Hz, 3H; $CHCH_3$), 2.81 (dd, $^2J = 13.3$ Hz, $^3J = 9.3$ Hz, 1H; $PhCHH$), 3.24 (dd, $^2J = 13.3$ Hz, $^3J = 3.3$ Hz, 1H; $PhCHH$), 3.96 (dq, $^3J = 7.1$ Hz, $^3J = 4.4$ Hz, 1H; $CHCH_3$), 4.19–4.23 (m, 2H; $NCHCH_2O$), 4.68–4.73 (m, 2H; $NCHCH_2O$, $CHOH$), 7.19–7.36 (m, 5H; CH_{ar}); ^{13}C NMR (62.9 MHz): $\delta = -4.8$ [$Si(CH_3)_2$], 12.3 ($NCOCHCH_3$), 16.4 [$SiC(CH_3)_3$], 26.0 [$SiC(CH_3)_3$], 37.7 ($PhCH_2$), 44.0 (NCOCH), 55.1 ($PhCH_2CH$), 63.7 (OCH_2CHN), 66.2 (CHOH), 88.8 (C≡CSi), 104.4 (C≡CSi), 127.4 (CH_{ar}), 128.9 (CH_{ar}), 129.4 (CH_{ar}), 134.9 (C_{ar}), 152.9 (OCONCO), 175.2 (OCONCO); IR (KBr): $\tilde{\nu} = 3494$ (br s; OH), 2931 (m; CH_{al}), 2860 (m; CH_{al}), 1801 (s), 1670 (s; C=O), 1385 (s), 1210 cm^{-1} (s); MS (CI, isobutane): *m/z* (%): 401 (4) [M^+]; elemental analysis calcd (%) for $C_{22}H_{31}NO_4Si$ (401.58): C 65.80, H 7.78; found: C 65.85, H 7.69.

(3*S*)-Methoxy-(2*S*)-methylpentyncarboxylic acid-*N*-methoxy-*N*-methyl-amide (10): A 2M solution of trimethylaluminium in hexane (2.25 mL, 4.50 mmol) was added at 0 °C to a slurry of *N,O*-dimethylhydroxylamine hydrochloride (439 mg, 4.50 mmol) in THF (12 mL). After 30 min the resulting solution was cooled to −15 °C and a solution of oxazolidinone *ent*-**15** (200 mg, 500 μmol) in THF (10 mL) was added. The temperature was kept at −15 °C for 1 h and at 0 °C for 1 h. After additional stirring at room temperature for 3 h the reaction was quenched by the careful addition of dichloromethane (19 mL) and a 0.5M aqueous HCl solution (12.5 mL). The aqueous layer was extracted with dichloromethane (3 × 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 and filtered. After removal of the solvent the crude residue was purified by flash chromatography (P/EtOAc 70:30) to afford the Weinreb amide (100 mg, 70%) as a white solid. $R_f = 0.34$ (P/EtOAc 70:30); ^1H NMR (250 MHz): $\delta = 0.11$ [s, 6H; $Si(CH_3)_2$], 0.94 [s, 9H; $SiC(CH_3)_3$], 1.36 (d, $^3J = 7.0$ Hz, 3H; $NCOCHCH_3$), 3.20 (s, 3H; NCH_3), 3.74 (s, 3H; OCH_3), 4.08–4.16 (m, 1H; $NCOCHCH_3$), 4.72 (virt. t, $^3J \cong 3.1$ Hz, 1H; $CHOH$); MS (EI, 70 eV): *m/z* (%): 270 (3) [$M^+ - Me$], 228 (100) [$M^+ - t$Bu].

A solution of the obtained Weinreb amide (100 mg, 350 μmol) in dichloromethane (3 mL) was submitted to methylation by addition of proton sponge (375 mg, 1.75 mmol) and trimethyloxonium tetrafluoroborate (259 mg, 1.75 mmol). After stirring at room temperature for 2d the resulting slurry was filtered and the solvent was removed in vacuo. The residue was purified by flash chromatography (P/EtOAc 80:20) and the desired methyl ether (51.8 mg, 51%) was obtained as a colorless oil. $R_f = 0.18$ (P/EtOAc 80:20); $[\alpha]_D^{20} = -78.6$ ($c = 0.79$ in CH_2Cl_2); ^1H NMR (250 MHz): $\delta = 0.06$ [s, 6H; $Si(CH_3)_2$], 0.90 [s, 9H; $SiC(CH_3)_3$], 1.20 (d, $^3J = 6.7$ Hz, 3H; $NCOCHCH_3$), 3.16 (s, 3H; NCH_3), 3.11–3.26 (m, 1H; $NCOCHCH_3$), 3.41 (s, 3H; $CHOCH_3$), 3.70 (s, 3H; $NOCH_3$), 4.08 (d, $^3J = 9.2$ Hz, 1H; $CHOCH_3$); ^{13}C NMR (62.9 MHz): $\delta = -4.7$ [$Si(CH_3)_2$], 14.1 ($NCOCHCH_3$), 16.4 [$SiC(CH_3)_3$], 26.0 [$SiC(CH_3)_3$], 32.1 (NCH_3), 41.4 ($NCOCHCH_3$), 56.6 ($CHOCH_3$), 61.5 ($NOCH_3$), 72.9 ($CHOCH_3$), 89.4 (CCSi), 104.0 (CCSi), 174.3 ($NCOCHCH_3$); IR (neat): $\tilde{\nu} = 2933$ (m; CH_{al}), 2171 (w; C≡C), 1666 (s; C=O), 1463 (m), 1102 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 284 (6) [$M^+ - Me$], 268 (4) [$M^+ - OMe$], 242 (100) [$M^+ - t$Bu]; elemental analysis calcd (%) for $C_{15}H_{29}NO_3Si$ (299.48): C 60.16, H 9.76; found: C 60.30, H 9.89.

To cleave off the TBDMS group a solution of the obtained methyl ether (24.0 mg, 80.1 μmol) in THF (2 mL) was treated with tetrabutylammonium fluoride (TBAF) on silica (100 mg, ≈100 μmol). The slurry was stirred for 2 h at room temperature. After the solvent had been removed in vacuo, the residue was purified by flash chromatography (P/EtOAc 70:30) and the desired terminal alkyne **10** (14.8 mg) was obtained as a colorless oil. $R_f = 0.48$ (P/EtOAc 80:20); $[\alpha]_D^{20} = 46.3$ ($c = 0.52$ in CH_2Cl_2); ^1H NMR (360 MHz): $\delta = 1.19$ (d, $^3J = 7.1$ Hz, 3H; $NCOCHCH_3$), 2.42 (d, $^4J = 2.0$ Hz, 1H; C≡CH), 3.16 (s, 3H; NCH_3), 3.16–3.22 (m, 1H; $NCOCHCH_3$), 3.39 (s, 3H; $CHOCH_3$), 3.69 (s, 3H; $NOCH_3$), 4.05 (dd, $^3J = 9.0$ Hz, $^4J = 2.0$ Hz, 1H; $CHOCH_3$); ^{13}C NMR (90 MHz): $\delta = 14.1$ ($NCOCHCH_3$), 31.9 (NCH_3), 41.3 ($NCOCHCH_3$), 56.8 ($CHOCH_3$), 61.5 ($NOCH_3$), 72.5 ($CHOCH_3$), 74.4 (C≡CH), 81.5 (C≡CH), 174.1 (NCOCH); IR (neat): $\tilde{\nu} = 3242$ (s, C≡CH), 2939 (s, CH_{al}), 2111 (w, C≡C), 1651 (s, C=O), 1462 (m), 1100 (m), 997 cm^{-1} (m); MS (EI, 70 eV): *m/z* (%): 170 (8) [$M^+ - Me$], 125 (46) [$M^+ - N(CH_3)OCH_3$], 69 (100) [$CH(OCH_3)CCH^+$]; HRMS: *m/z* calcd for $C_8H_{12}NO_3$ [$M^+ - Me$]: 170.0817, found: 170.0818.

4-[3-(*tert*-Butyldimethylsiloxy)-propenyl]-2′-isopropyl-2,4′-bithiazole (13): Catecholborane (989 mg, 8.25 mmol) was slowly added to 3-(*tert*-butyldimethylsiloxy)-1-propyne (**11**)[18] (935 mg, 5.50 mmol) and after 5 min the temperature was raised to 70 °C for 1 h and then to 95 °C for additional 2 h. After cooling to room temperature, water (8.25 mL) was added rapidly and the resulting slurry was stirred for 1 h. Ethanol (12 mL) was added to dilute the white precipitate. The obtained solution of the boronic acid was quantitatively given to a mixture of bromobithiazole **4** (612 mg, 2.12 mmol), $[Pd(PPh_3)_4]$ (120 mg, 106 μmol) and a 50% (*w/w*) aqueous CsOH solution (953 mg, 6.36 mmol) in benzene (60 mL). The blue solution was heated to 95 °C for 16 h. After cooling to room temperature, water

(20 mL) was added and the aqueous layer was extracted with pentane (2 × 50 mL) and dichloromethane (2 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4 and filtered. After removal of the solvent the crude residue was purified by flash chromatography (P/EtOAc 98:2) to afford **13** (742 g, 92%) as a yellow oil. $R_f = 0.18$ (P/EtOAc 97:3); ^{1}H NMR (360 MHz): $\delta = 0.11$ [s, 6H; Si(CH$_3$)$_2$], 0.94 [s, 9H; SiC(CH$_3$)$_3$], 1.43 [d, $^3J = 6.9$ Hz, 6H; CH(CH$_3$)$_2$], 3.36 [sept, $^3J = 6.9$ Hz, 1H; CH(CH$_3$)$_2$], 4.38 (d, $^3J = 3.9$ Hz, 2H; OCH$_2$), 6.60–6.75 (m, 2H; OCH$_2$CHCH), 7.04 (s, 1H; CH$_{ar}$), 7.86 (s, 1H; CH′$_{ar}$); ^{13}C NMR (90 MHz): $\delta = -5.2$ [Si(CH$_3$)$_2$], 18.5 [SiC(CH$_3$)$_3$], 23.1 [CH(CH$_3$)$_2$], 26.0 [SiC(CH$_3$)$_3$], 33.3 [CH(CH$_3$)$_2$], 63.3 (OCH$_2$CHCH), 114.8 (CH$_{ar}$), 114.9 (CH$_{ar}$), 122.0 (OCH$_2$CHCH), 132.4 (OCH$_2$CHCH), 148.7 (4′-C$_{ar}$), 154.7 (4-C$_{ar}$), 162.7 (NCS-thiazole), 178.6 (NCS-*i*Pr); IR (neat): $\tilde{\nu} = 3102$ (w; CH$_{ar}$), 2953 (m; CH$_{al}$), 1497 (m), 1255 (m), 1111 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 380 (42) [M^+], 323 (100) [$M^+ - t$Bu], 249 (63) [$M^+ -$ OTBDMS]; elemental analysis calcd (%) for $C_{18}H_{28}N_2OS_2Si$ (380.65): C 56.80, H 7.41; found: C 56.72, H 7.36.

4-(3-Hydroxypropenyl)-2′-isopropyl-2,4′-bithiazole (14) from silyl ether 13: A 1M solution of tetrabutylammonium fluoride (TBAF) in THF (0.60 mL, 0.60 mmol) was added to a solution of silyl ether **13** (150 mg, 394 μmol) in THF (5 mL) and the mixture was stirred for 3 h at ambient temperature. After the solvent had been removed in vacuo, the residue was purified by flash chromatography (P/Et$_2$O 30:70). The known compound **14**[3] (82.0 mg, 78%) was obtained as a white solid. $R_f = 0.23$ (P/Et$_2$O 30:70); ^{1}H NMR (250 MHz): $\delta = 1.41$ [d, $^3J = 6.9$ Hz, 6H; CH(CH$_3$)$_2$], 2.08 (br s, 1H; OH), 3.34 [sept, $^3J = 6.9$ Hz, 1H; CH(CH$_3$)$_2$], 4.33 (d, $^3J = 4.8$ Hz, 2H; OCH$_2$), 6.62 (d, $^3J = 15.6$ Hz, 1H; OCH$_2$CHCH), 6.75 (dt, $^3J = 4.8$ Hz, $^3J = 15.6$ Hz, 1H; OCH$_2$CHCH), 7.05 (s, 1H; CH$_{ar}$), 7.85 (s, 1H; CH′$_{ar}$); ^{13}C NMR (62.9 MHz): $\delta = 23.1$ [CH(CH$_3$)$_2$], 33.3 [CH(CH$_3$)$_2$], 63.1 (OCH$_2$CHCH), 115.0 (CH$_{ar}$), 115.4 (CH$_{ar}$), 123.4 (OCH$_2$CHCH), 131.8 (OCH$_2$CHCH), 148.5 (4′-C$_{ar}$), 154.2 (4-C$_{ar}$), 162.9 (NCS-thiazole), 178.7 (NCS-*i*Pr); MS (EI, 70 eV): *m*/*z* (%): 266 (15) [M^+], 237 (100).

4-(3-Hydroxypropenyl)-2′-isopropyl-2,4′-bithiazole (14) by Stille coupling between bithiazole 4 and stannane 12: Bromobithiazole (**4**; 42.1 mg, 145 μmol), tributylstannyl-2-propen-1-ol (**12**)[21] (157 mg, 453 μmol) and [PdCl$_2$(PPh$_3$)$_2$] (5.1 mg, 7.3 μmol) in dioxane (8 mL) were heated to 100 °C for 16 h. After the solvent had been removed in vacuo, the residue was purified by flash chromatography (P/Et$_2$O 30:70). **14** (20.0 mg, 52%) was obtained as a white solid. The spectroscopical data were identical to those obtained for the deprotection product of **13**.

(4*R*)-Benzyl-3-[5-(*tert*-butyldimethylsilyl)-(3*R*)-hydroxy-(2*R*)-methyl-4-pentynyl]-oxazolidin-2-one (15): Aldol product **15** was prepared as described for its enantiomer starting from **2** (1.00 g, 4.30 mmol), di-*n*-butylborontriflate (1M in CH$_2$Cl$_2$, 4.67 mL, 4.67 mmol), *N*,*N*-diisopropylethylamine (667 mg, 5.17 mmol) and aldehyde **3** (967 mg, 5.83 mmol). After purification by flash chromatography (P/EtOAc 80:20) product **15** (1.47 g, 86%) could be obtained as a white solid. $R_f = 0.27$ (P/EtOAc 80:20); m.p. 85 °C; $[\alpha]_D^{20} = -66.1$ ($c = 0.53$ in CH$_2$Cl$_2$). The spectroscopic data were identical to those of *ent*-**15**.

(4*R*)-Benzyl-3-[5-(*tert*-butyldimethylsilyl)-(3*R*)-methoxy-(2*R*)-methyl-4-pentynyl]-oxazolidin-2-on (16): Proton sponge (3.34 g, 15.6 mmol) and trimethyloxonium tetrafluoroborate (3.50 g, 23.4 mmol) were added to a solution of the alcohol **15** (4.50 g, 11.1 mmol) in dichloromethane (80 mL). After stirring at room temperature for 2 d the resultant slurry was filtered and the solvent was removed in vacuo. The residue was purified by flash chromatography (P/EtOAc 90:10) and the desired methyl ether **16** (2.79 g, 61%) was obtained as a white solid. $R_f = 0.57$ (P/EtOAc 80:20); m.p. 135 °C; $[\alpha]_D^{20} = -34.2$ ($c = 0.61$ in CH$_2$Cl$_2$); ^{1}H NMR (250 MHz): $\delta = 0.10$ [s, 6H; Si(CH$_3$)$_2$], 0.92 [s, 9H; SiC(CH$_3$)$_3$], 1.35 (d, $^3J = 6.4$ Hz, 3H; NCOCHCH$_3$), 2.79 (dd, $^2J = 16.0$ Hz, $^3J = 9.6$ Hz, 1H; PhCHH), 3.28 (dd, $^2J = 16.0$ Hz, $^3J = 3.1$ Hz, 1H; PhCHH), 3.42 (s, 3H; CHOCH$_3$), 4.14–4.25 (m, 4H; CH$_3$CHCHOCH$_3$, NCHCH$_2$O), 4.64–4.69 (m, 1H; NCHCH$_2$O), 7.19–7.29 (m, 5H; CH$_{ar}$); ^{13}C NMR (62.9 MHz): $\delta = -4.3$ [Si(CH$_3$)$_2$], 13.9 (NCOCHCH$_3$), 16.9 [SiC(CH$_3$)$_3$], 26.4 [SiC(CH$_3$)$_3$], 38.2 (PhCH$_2$), 43.3 (NCOCH), 55.8 (OCH$_2$CHN), 56.8 (CHOCH$_3$), 66.5 (OCH$_2$CHN), 72.7 (CHOCH$_3$), 87.5 (C≡CSi), 90.6 (C≡CSi), 127.7 (CH$_{ar}$), 129.3 (CH$_{ar}$), 129.8 (CH$_{ar}$), 135.6 (C$_{ar}$), 153.4 (OCONCO), 173.9 (OCONCO); IR (KBr): $\tilde{\nu} = 2934$ (m; CH$_{al}$), 1769 (s; C=O), 1684 (s; C=O), 1384 (m), 1208 cm^{-1} (m); MS (EI, 70 eV): *m*/*z* (%): 415 (2) [M^+], 400 (5) [$M^+ -$ Me], 358 (100) [$M^+ - t$Bu]; elemental analysis calcd (%) for $C_{23}H_{33}NO_4Si$ (415.60): C 66.47, H 8.00; found: C 66.41, H 7.95.

5-(*tert*-Butyldimethylsilyl)-(3*R*)-methoxy-(2*S*)-methyl-4-pentyn-1-ol (17): A solution of oxazolidinone **16** (2.67 g, 6.43 mmol) in THF (40 mL) was added at 0 °C to a slurry of lithium aluminium hydride (268 mg, 7.10 mmol) in THF (100 mL) over a period of 1 h through syringe pump. After stirring for 1 h at 0 °C, water (267 μL), 15% aqueous NaOH (800 μL), water (800 μL) and some Na_2SO_4 were successively added. The mixture was filtered, the solvent was removed in vacuo and the resulting residue was purified by flash chromatography (P/EtOAc 70:30). **17** (1.56 g, quant.) was obtained as a light red oil. $R_f = 0.33$ (P/EtOAc 85:15); $[\alpha]_D^{20} = -71.2$ ($c = 1.10$ in CH$_2$Cl$_2$); ^{1}H NMR (360 MHz): $\delta = 0.11$ [s, 6H; Si(CH$_3$)$_2$], 0.93 [s, 9H; SiC(CH$_3$)$_3$], 0.95 (d, $^3J = 7.5$ Hz, 3H; CHCH$_3$), 2.06–2.14 (m, 1H; CHCH$_3$), 3.40 (s, 3H; CHOCH$_3$), 3.55 (dd, $^2J = 10.9$ Hz, $^3J = 3.8$ Hz, 1H; HOCHH), 3.80 (dd, $^2J = 10.9$ Hz, $^3J = 7.5$ Hz; HOCHH), 4.07 (d, $^3J = 4.0$ Hz, 1H; CHOCH$_3$); ^{13}C NMR (90 MHz): $\delta = -4.6$ [Si(CH$_3$)$_2$], 12.7 [CH(CH$_3$)], 16.5 [SiC(CH$_3$)$_3$], 26.1 [SiC(CH$_3$)$_3$], 39.7 [CH(CH$_3$)], 56.9 (CHOCH$_3$), 65.6 (HOCH$_2$), 76.1 (CHOCH$_3$), 91.1 (CCSi), 102.8 (CCSi); IR (neat): $\tilde{\nu} = 3373$ (b; OH), 2929 (s; CH$_{al}$), 2857 (s; CH$_{al}$), 2169 (m; C≡C), 1471 (s), 1250 (s), 1096 cm^{-1} (s); MS (CI, isobutane): *m*/*z* (%): 243 (6) [M^++H].

1-*tert*-Butyldimethylsiloxy-(3*R*)-methoxy-(2*R*)-methyl-4-pentyne (18): To cleave off the TBDMS group a solution of alcohol **17** (1.00 g, 4.13 mmol) in THF (40 mL) was treated with tetrabutylammonium fluoride (TBAF) on silica (5.00 g, ≈5.00 mmol). The slurry was stirred for 1 h at room temperature. After the solvent had been removed in vacuo, the residue was purified by flash chromatography (P/Et$_2$O 50:50) and the desired terminal alkyne (529 mg, quant.) was obtained as a colourless oil. $R_f = 0.52$ (P/EtOAc 50:50). The resulting alcohol was diluted in DMF (35 mL). Dichloromethane (15 mL), imidazole (703 mg, 10.3 mmol) and a 2.9M solution of *tert*-butyldimethylsilylchloride in toluene (1.71 mL, 4.96 mmol) were added. After stirring for 1 d at room temperature, water (100 mL) was added and the aqueous layer was extracted with dichloromethane (2 × 150 mL) and pentane (2 × 150 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and filtered. After removal of the solvent the crude residue was purified by flash chromatography (P/Et$_2$O 98:2) to afford **18** (1.00 g, quant.) as a colorless oil. $R_f = 0.67$ (P/Et$_2$O 95:5); $[\alpha]_D^{20} = 53.9$ ($c = 0.54$ in pentane); ^{1}H NMR (250 MHz): $\delta = 0.02$ [s, 6H; Si(CH$_3$)$_2$], 0.87 [s, 9H; SiC(CH$_3$)$_3$], 0.97 (d, $^3J = 7.0$ Hz, 3H; CHCH$_3$), 1.84–1.97 (m, 1H; CHCH$_3$), 2.40 (d, $^4J = 2.1$ Hz, 1H; C≡CH), 3.38 (s, 3H; CHOCH$_3$), 3.52 (dd, $^2J = 9.8$ Hz, 1H; SiOCHH), 3.61 (dd, $^2J = 9.8$ Hz, $^3J = 5.8$ Hz, 1H; SiOCHH), 4.04 (dd, $^3J = 4.6$ Hz, $^4J = 2.1$ Hz, 1H; CHOCH$_3$); ^{13}C NMR (62.9 MHz): $\delta = -5.5$ [Si(CH$_3$)$_2$], 11.6 [CH(CH$_3$], 18.3 [SiC(CH$_3$)$_3$], 25.9 [SiC(CH$_3$)$_3$], 41.0 [CH(CH$_3$], 57.0 (CHOCH$_3$), 65.2 (SiOCH$_2$), 71.6 (C≡CH), 74.1 (CHOCH$_3$), 82.2 (C≡CH); IR (neat): $\tilde{\nu} = 2929$ (m; CH$_{al}$), 2858 (m; CH$_{al}$), 1472 (m), 1258 cm^{-1} (s); MS (CI, isobutane): *m*/*z* (%): 243 (100) [M^++H].

4-[5-(*tert*-Butyldimethylsiloxy)-(3*S*)-methoxy-(4*R*)-methylpent-1-enyl]-2′-isopropyl-2,4′-bithiazole (19): Catecholborane (673 mg, 5.60 mmol) was slowly added to alkyne **18** (905 mg, 3.74 mmol) and after 5 min the temperature was raised to 70 °C for 1 h and then to 95 °C for further 2 h. After cooling to room temperature, water (7.5 mL) was added rapidly and the resulting slurry was stirred for 1 h. Ethanol (12 mL) was added to dilute the white precipitate. The obtained solution of the boronic acid was quantitatively given to a mixture of bromobithiazole **4** (314 mg, 1.10 mmol), [Pd(PPh$_3$)$_4$] (87.0 mg, 55.0 μmol) and a 10% (*w*/*w*) aqueous CsOH solution (7.50 mL, 4.50 mmol) in benzene (70 mL). This blue solution was heated to 95 °C for 16 h. After cooling to room temperature, water (40 mL) was added and the aqueous layer was extracted with pentane (2 × 100 mL) and dichloromethane (2 × 100 mL). The combined organic layers were washed with brine (100 mL), dried over Na_2SO_4 and filtered. After removal of the solvent the crude residue was purified by flash chromatography (P/Et$_2$O 95:5) to afford **19** (448 g, 94%) as a yellow oil. $R_f = 0.35$ (P/EtOAc 90:10); $[\alpha]_D^{20} = 8.9$ ($c = 0.40$ in pentane); ^{1}H NMR (250 MHz): $\delta = 0.02$ [s, 6H; Si(CH$_3$)$_2$], 0.88 [s, 9H; SiC(CH$_3$)$_3$], 0.92 (d, $^3J = 6.2$ Hz, 3H; SiOCH$_2$CHCH$_3$), 1.41 [d, $^3J = 6.9$ Hz, 6H; CH(CH$_3$)$_2$], 1.77–1.87 (m, 1H; SiOCH$_2$CHCH$_3$), 3.31 (s, 3H; CHOCH$_3$), 3.33 [sept, $^3J = 6.9$ Hz, 1H; CH(CH$_3$)$_2$], 3.48 (dd, $^2J = 9.7$ Hz, $^3J = 5.7$ Hz, 1H; SiOCHH), 3.60 (dd, $^2J = 9.7$ Hz, $^3J = 6.7$ Hz, 1H; SiOCHH), 3.85 (virt. t, $^3J \cong 5.0$ Hz, 1H; CHOCH$_3$), 6.45–6.61 (m, 2H; CH$_3$OCHCHCH), 7.05 (s, 1H; CH$_{ar}$), 7.84 (s, 1H; CH′$_{ar}$); ^{13}C NMR (62.9 MHz): $\delta = -5.5$ [Si(CH$_3$)$_2$], 11.6 (SiOCH$_2$CHCH$_3$), 18.2 [SiC(CH$_3$)$_3$], 23.1 [CH(CH$_3$)$_2$], 25.9 [SiC(CH$_3$)$_3$], 33.3 [CH(CH$_3$)$_2$], 41.0 (SiOCH$_2$CH), 57.1 (CHOCH$_3$), 64.8 (SiOCH$_2$), 82.1

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(*C*HOCH$_3$), 114.9 (CH′$_{ar}$), 115.0 (CH$_{ar}$), 124.8 (CH$_3$OCHCH*C*H), 132.2 (CH$_3$OCH*C*HCH), 148.7 (4′-C$_{ar}$), 154.4 (4-C$_{ar}$), 162.7 (NCS-thiazole), 178.6 (NCS-*i*Pr); IR (neat): $\tilde{\nu}$ = 3110 (w; CH$_{ar}$), 2928 (m; CH$_{al}$), 2856 (m; CH$_{al}$), 1463 (s), 1255 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 452 (12) [*M*$^+$], 437 (8) [*M*$^+$ – Me], 395 (50) [*M*$^+$ – *t*Bu], 305 (41), 289 (27), 279 (100) [*M*$^+$ – TBDMSOCH$_2$CH(Me)]; HRMS: *m*/*z* calcd for $C_{22}H_{36}N_2O_2S_2Si$: 452.1988, found: 452.1982.

5-(2′-Isopropyl-2,4′-bithiazolyl-4-yl)-(3*S*)-methoxy-(2*S*)-methyl-4-penten-1-ol (20): Silyl ether **19** (410 mg, 905 μmol) and pyridinium *para*-toluenesulfonate (PPTS) (116 mg, 450 μmol) in ethanol (20 mL) were heated to 55 °C for 24 h. After removal of the solvent the residue was purified by flash chromatography (P/Et$_2$O 50:50). **20** (250 mg, 82 %) was obtained as a colourless oil. R_f = 0.28 (P/Et$_2$O 30:70); $[\alpha]_D^{20}$ = 41.9 (*c* = 0.83 in diethyl ether); ^{1}H NMR (250 MHz): δ = 0.93 (d, ^3J = 7.0 Hz, 3H; HOCH$_2$CHC*H*$_3$), 1.42 [d, ^3J = 7.0 Hz, 6H; CH(C*H*$_3$)$_2$], 2.05–2.11 (m, 1H; HOCH$_2$C*H*CH$_3$), 3.33 (s, 3H; CHOC*H*$_3$), 3.34 [sept, ^3J = 7.0 Hz, 1H; C*H*(CH$_3$)$_2$], 3.58 (dd, ^2J = 10.8 Hz, ^3J = 4.3 Hz, 1H; HOCH*H*), 3.73 (dd, ^2J = 10.8 Hz, ^3J = 7.5 Hz, 1H; HOC*H*H), 3.90 (virt. t, $^3J \cong$ 4.9 Hz, 1H; C*H*OCH$_3$), 6.50–6.65 (m, 2H; CH$_3$OCHC*H*C*H*), 7.10 (s, 1H; CH$_{ar}$), 7.89 (s, 1H; CH′$_{ar}$); ^{13}C NMR (62.9 MHz): δ = 12.2 (HOCH$_2$CH*C*H$_3$), 23.1 [CH(*C*H$_3$)$_2$], 33.3 [*C*H(CH$_3$)$_2$], 39.8 (HOCH$_2$*C*H), 57.0 (CHO*C*H$_3$), 66.0 (HO*C*H$_2$), 85.6 (*C*HOCH$_3$), 115.3 (CH′$_{ar}$), 115.7 (CH$_{ar}$), 126.1 (CH$_3$OCHCH*C*H), 130.0 (CH$_3$OCH*C*HCH), 148.4 (4′-C$_{ar}$), 153.8 (4-C$_{ar}$), 163.0 (NCS-thiazole), 178.7 (NCS-*i*Pr); IR (neat): $\tilde{\nu}$ = 3420 (br s; OH), 3122 (w; CH$_{ar}$), 2971 (s; CH$_{al}$), 1498 (m), 1081 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 338 (10) [*M*$^+$], 323 (13) [*M*$^+$ – Me], 279 (100) [*M*$^+$ – HOCH$_2$CHMe]; elemental analysis calcd (%) for $C_{16}H_{22}N_2O_2S_2$ (338.49): C 56.77, H 6.55; found: C 57.01, H 6.66.

(+)-Cystothiazole E (1e): Dess–Martin periodinane[26] (93.1 mg, 220 μmol) was added to a solution of alcohol **20** (62.0 mg, 183 μmol) in dichloromethane (2 mL). After being stirred at ambient temperature for 2 h, the reaction was quenched by the addition of diethyl ether (12 mL) and a saturated aqueous solution of NaHCO$_3$ containing 5 % Na$_2$S$_2$O$_3$ (4 mL). After additional 15 min the aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic phases were washed with brine (10 mL), dried over Na$_2$SO$_4$ and filtered. After removal of the solvent the crude residue was purified by flash chromatography (P/Et$_2$O 60:40) to afford the desired aldehyde (61.0 mg, quant.) as a yellow oil. R_f = 0.39 (P/Et$_2$O 50:50); ^{1}H NMR (250 MHz): δ = 1.18 (d, ^3J = 7.0 Hz, 3H; OHCCHC*H*$_3$), 1.44 [d, ^3J = 6.9 Hz, 6H; CH(C*H*$_3$)$_2$], 2.62–2.67 (m, 1H; OHCC*H*CH$_3$), 3.35 [sept, ^3J = 6.9 Hz, 1H; C*H*(CH$_3$)$_2$], 3.36 (s, 3H; CHOC*H*$_3$), 4.19 (dd, ^3J = 4.3 Hz, ^3J = 7.0 Hz, 1H; C*H*OCH$_3$), 6.53 (dd, ^3J = 7.0 Hz, ^3J = 15.6 Hz, 1H; CH$_3$OCHC*H*CH), 6.67 (d, ^3J = 15.6 Hz, 1H; CH$_3$OCHCH*C*H), 7.14 (s, 1H; CH$_{ar}$), 7.88 (s, 1H; CH′$_{ar}$), 9.82 (d, ^3J = 1.2 Hz, 1H; O*H*CCHCH$_3$); ^{13}C NMR (62.9 MHz): δ = 8.7 (OHCCH*C*H$_3$), 23.1 [CH(*C*H$_3$)$_2$], 33.3 [*C*H(CH$_3$)$_2$], 51.1 (OHC*C*HCH$_3$), 57.0 (CHO*C*H$_3$), 81.5 (*C*HOCH$_3$), 115.1 (CH′$_{ar}$), 116.2 (CH$_{ar}$), 126.4 (CH$_3$OCHCH*C*H), 129.4 (CH$_3$OCH*C*HCH), 148.5 (4′-C$_{ar}$), 153.6 (4-C$_{ar}$), 163.0 (NCS-thiazole), 178.7 (NCS-*i*Pr), 203.8 (OH*C*CHCH$_3$); IR (neat): $\tilde{\nu}$ = 3215 (m; CH$_{ar}$), 2969 (m; CH$_{al}$), 1727 (s; C=O), 1617 (s), 1079 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 336 (4) [*M*$^+$], 321 (4) [*M*$^+$ – Me], 279 (100) [*M*$^+$ – OHCCHMe].

To a solution of the aldehyde (61.0 mg, 182 μmol) in THF (5 mL) a 3 M solution of methyl magnesium chloride in THF (242 μL, 726 μmol) was added at room temperature. After stirring for 1 h, a saturated aqueous solution of NH$_4$Cl (5 mL) was added. The aqueous phase was extracted with diethyl ether (3 × 20 mL). The combined organic phases were washed with brine (15 mL), dried over Na$_2$SO$_4$ and filtered. After removal of the solvent the crude residue was purified by flash chromatography (P/Et$_2$O 60:40) to afford the desired secondary alcohol (58.2 mg, 91 %) as a yellow oil. It was obtained as a 3:1 mixture of diastereoisomers. R_f = 0.15 and 0.18 (P/Et$_2$O 50:50); ^{13}C NMR (62.9 MHz): *major* diastereoisomer: δ = 12.8 (HOCHCH*C*H$_3$), 20.9 (*C*H$_3$CHOH), 23.1 [CH(*C*H$_3$)$_2$], 43.7 (HOCH*C*HCH$_3$), 56.8 (OCH$_3$), 70.8 (HOCH), 86.9 (*C*HOCH$_3$), 115.0 (CH′$_{ar}$), 115.7 (CH′$_{ar}$), 125.2 (CH$_3$OCHCH*C*H), 131.1 (CH$_3$OCH*C*HCH), 148.4 (4′-C$_{ar}$), 153.9 (4-C$_{ar}$), 162.9 (NCS-thiazole), 178.6 (NCS-*i*Pr); *minor* diastereoisomer: δ = 15.2 (HOCHCH*C*H$_3$), 21.5 (*C*H$_3$CHOH), 23.1 [CH(*C*H$_3$)$_2$], 44.1 (HOCH*C*HCH$_3$), 56.9 (OCH$_3$), 69.8 (HOCH), 85.5 (*C*HOCH$_3$), 115.0 (CH′$_{ar}$), 115.6 (CH′$_{ar}$), 126.3 (CH$_3$OCHCH*C*H), 129.4 (CH$_3$OCH*C*HCH), 148.4 (4′-C$_{ar}$), 153.8 (4-C$_{ar}$), 162.8 (NCS-thiazole), 178.6 (NCS-*i*Pr); IR (KBr): $\tilde{\nu}$ = 3440 (br s; OH), 3124 (m; CH$_{ar}$), 2970 (s; CH$_{al}$), 1498 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 352 (8) [*M*$^+$], 337 (6) [*M*$^+$ – Me], 279 (84) [*M*$^+$ – MeCH(OH)CH(Me)], 261 (100); HRMS: *m*/*z* calcd for $C_{17}H_{24}N_2O_2S_2$: 352.1279, found: 352.1282.

The mixture of alcohols (48.0 mg, 137 μmol) was dissolved in dichloromethane (5 mL) and the Dess–Martin periodinane (76.3 mg, 180 μmol) was added. After being stirred at ambient temperature for 3 h, the reaction was quenched by the addition of diethyl ether (20 mL) and a saturated aqueous solution of NaHCO$_3$ containing 5 % Na$_2$S$_2$O$_3$ (6 mL). After further 15 min the aqueous phase was extracted with diethyl ether (2 × 20 mL). The combined organic phases were washed with brine (20 mL), dried over Na$_2$SO$_4$ and filtered. After removal of the solvent the crude residue was purified by flash chromatography (P/Et$_2$O 70:30) to afford (+)-cystothiazole E (**1e**) (48.0 mg, quant.) as a yellow oil. R_f = 0.65 (P/Et$_2$O 50:50); $[\alpha]_D^{20}$ = 17.6 (*c* = 0.12 in CHCl$_3$); ^{1}H NMR (360 MHz): δ = 1.19 (d, ^3J = 7.0 Hz, 3H; CH$_3$COCHC*H*$_3$), 1.44 [d, ^3J = 7.0 Hz, 6H; CH(C*H*$_3$)$_2$], 2.20 (s, 3H; CH$_3$CO), 2.79 (virt. quin, $^3J \cong$ 6.5 Hz, 1H; CH$_3$COC*H*), 3.34 (s, 3H; CHOC*H*$_3$), 3.37 [sept, ^3J = 7.0 Hz, 1H; C*H*(CH$_3$)$_2$], 4.02 (virt. t, $^3J \cong$ 6.6 Hz, 1H; C*H*OCH$_3$), 6.46 (dd, ^3J = 7.2 Hz, ^3J = 15.8 Hz, 1H; CH$_3$OCHC*H*CH), 6.61 (d, ^3J = 15.8 Hz, 1H; CH$_3$OCHCHC*H*), 7.11 (s, 1H; H$_{ar}$), 7.87 (s, 1H; H′$_{ar}$); ^{13}C NMR (90 MHz): δ = 11.8 (CH$_3$COCH*C*H$_3$), 23.0 [CH(*C*H$_3$)$_2$], 29.8 (*C*H$_3$COCHCH$_3$), 33.3 [*C*H(CH$_3$)$_2$], 51.9 (CH$_3$CO*C*HCH$_3$), 56.9 (CHO*C*H$_3$), 82.6 (*C*HOCH$_3$), 115.0 (5′-CH$_{ar}$), 115.7 (5-CH$_{ar}$), 126.1 (CH$_3$OCHCH*C*H), 130.1 (CH$_3$OCH*C*HCH), 148.5 (4′-C$_{ar}$), 153.8 (4-C$_{ar}$), 162.8 (NCS-thiazole), 178.5 (NCS-*i*Pr), 210.3 (CH$_3$*C*O); IR (neat): $\tilde{\nu}$ = 3103 (m; CH$_{ar}$), 2970 (s; CH$_{al}$), 2932 (s; CH$_{al}$), 1712 cm^{-1} (s; C=O); MS (EI, 70 eV): *m*/*z* (%): 350 (2) [*M*$^+$], 335 (12) [*M*$^+$ – Me], 279 (89) [*M*$^+$ – MeCOCHMe], 275 (100); elemental analysis calcd (%) for $C_{17}H_{23}N_2O_2S_2$ (350.50): C 58.25, H 6.33; found: C 58.06, H 6.13.

3-(2′-Isopropyl-2,4′-bithiazolyl-4-yl)-propenal (21): Bromobithiazole **4** (217 mg, 751 μmol), tributylstannyl-2-propen-1-al (**5**)[8] (777 mg, 2.25 mmol) triethylamine (152 mg, 1.50 mmol) and [PdCl$_2$(PPh$_3$)$_2$] (26.4 mg, 37.6 μmol) in dioxane (40 mL) were heated at 100 °C for 16 h. After the solvent had been removed in vacuo, the residue was purified by flash chromatography (P/Et$_2$O 70:30). The known aldehyde **21**[3] (192 mg, 97 %) was obtained as a yellow solid. R_f = 0.48 (P/EtOAc 75:25); ^{1}H NMR (250 MHz): δ = 1.42 [d, ^3J = 7.0 Hz, 6H; CH(C*H*$_3$)$_2$], 3.34 [sept, ^3J = 7.0 Hz, 1H; C*H*(CH$_3$)$_2$], 7.05 (dd, ^3J = 7.9 Hz, ^3J = 15.6 Hz, 1H; OHCC*H*CH), 7.42 (d, ^3J = 15.6 Hz, 1H; OHCCHC*H*), 7.55 (s, 1H; CH$_{ar}$), 7.88 (s, 1H; CH′$_{ar}$), 9.71 (d, ^3J = 7.9 Hz, 1H; O*H*CCHCH); ^{13}C NMR (62.9 MHz): δ = 23.1 [CH(*C*H$_3$)$_2$], 33.3 [*C*H(CH$_3$)$_2$], 116.0 (CH′$_{ar}$), 123.4 (CH$_{ar}$), 130.5 (OHC*C*HCH), 143.6 (OHCCH*C*H), 147.9 (4′-C$_{ar}$), 152.2 (4-C$_{ar}$), 163.9 (NCS-thiazole), 178.9 (NCS-*i*Pr), 193.6 (OH*C*CHCH); MS (EI, 70 eV): *m*/*z* (%): 264 (64) [*M*$^+$], 236 (100) [*M*$^+$ – CO], 221 (95) [*M*$^+$ – *i*Pr].

(4*R*)-Benzyl-3-[(3*S*)-hydroxy-5-(2′-isopropyl-2,4′-bithiazolyl-4-yl)-(2*R*)-methyl-4-pentenoyl]-oxazolidin-2-one (22): A 1 M solution of di-*n*-butylborontriflate in dichloromethane (370 μL, 370 μmol) and *N*,*N*-diisopropylethylamine (61.5 mg, 476 μmol) were carefully added to a solution of the oxazolidinone **2** (74.0 mg, 318 μmol) in dichloromethane (4 mL) so that the temperature was between 0 and 5 °C. After 45 min the reaction mixture was cooled to −78 °C and a solution of aldehyde **21** (64.0 mg, 242 mmol) in dichloromethane (2 mL) was added over a period of 1 h through syringe pump. After 1 h the mixture was stirred for 2 h at 0 °C before it was quenched by successive addition of pH 7 phosphate buffer (1 mL), methanol (2 mL) and a 1:2 mixture of 30 % H$_2$O$_2$/MeOH (2 mL) keeping the temperature between 0 and 10 °C. After 1 h the mixture was concentrated in vacuo and the resulting slurry was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with brine (30 mL), dried over Na$_2$SO$_4$ and filtered. After removal of the solvent the crude residue was purified by flash chromatography (P/EtOAc 60:40) to afford the known aldol product **22**[3] (87.0 mg, 72 %) as a white foam. R_f = 0.33 (P/EtOAc 50:50); ^{13}C NMR (90 MHz): δ = 11.2 (NCOCH*C*H$_3$), 23.1 [CH(*C*H$_3$)$_2$], 33.2 [*C*H(CH$_3$)$_2$], 37.6 (PhCH$_2$), 42.6 (NCO*C*HCH$_3$), 55.1 (PhCH$_2$*C*H), 66.1 (PhCH$_2$CH*C*H$_2$), 71.9 (CHOH), 115.2 (CH$_{ar}$), 115.9 (CH$_{ar}$), 123.9 (HOCHCH*C*H), 127.3 (CH$_{Ph}$), 128.9 (CH$_{Ph}$), 129.4 (CH$_{Ph}$), 131.7 (HOCH*C*HCH), 134.9 (C$_{Ph}$), 148.3 (4′-C$_{ar}$), 153.0 (O*C*ONCO), 153.9 (4-C$_{ar}$), 162.8 (NCS-thiazole), 176.6 (OCON*C*O), 178.7 (NCS-*i*Pr).

5-(2′-Isopropyl-2,4′-bithiazolyl-4-yl)-(3*S*)-methoxy-(2*R*)-methylpent-4-en-carboxylic acid-*N*-methoxy-*N*-methylamide (23): A 2 M solution of trimethylaluminium in hexane (0.79 mL, 1.58 mmol) was added at 0 °C to a slurry of *N*,*O*-dimethylhydroxylamine hydrochloride (154 mg, 1.58 mmol) in THF (5 mL). After 30 min the resulting solution was cooled to −15 °C and a solution of aldol product **22** (87.0 mg, 175 μmol) in THF (5 mL) was added.

The temperature was kept at $-15\,^{\circ}C$, $0\,^{\circ}C$ and ambient temperature for 1 h. The reaction was stopped by the careful addition of a 0.5 M aqueous HCl solution (4 mL) at $0\,^{\circ}C$. The aqueous phase was extracted with dichloromethane (2×15 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4 and filtered. After removal of the solvent the crude residue was purified by flash chromatography (P/EtOAc 40:60) to afford a mixture (85.0 mg) of the Weinreb amide and the Evans auxiliary as a yellow oil which still contained some EtOAc. $R_f = 0.18$ (P/EtOAc 50:50); ^1H NMR (360 MHz): $\delta = 1.22$ (d, $^3J = 7.3$ Hz, 3H; NCOCHCH_3), 1.44 [d, $^3J = 6.9$ Hz, 6H; CH(CH_3)$_2$], 2.87 (m, 1H; NCOCHCH$_3$), 3.22 (s, 3H; NCH_3), 3.38 [sept, $^3J = 6.9$ Hz, 1H; CH(CH$_3$)$_2$], 3.73 (s, 3H; OCH_3), 4.12 (m, 1H; CHOH), 6.62 (dd, $^3J = 4.6$ Hz, $^3J = 15.4$ Hz, 1H; HOCHCHCH), 6.76 (d, $^3J = 15.4$ Hz, 1H; HOCHCHCH), 7.09 (s, 1H; CH_{ar}), 7.87 (s, 1H; CH'_{ar}); ^{13}C NMR (90 MHz): $\delta = 10.4$ (NCOCHCH$_3$), 23.0 [CH(CH$_3$)$_2$], 31.7 (CH$_3$NCO), 33.2 [CH(CH$_3$)$_2$], 38.9 (NCOCHCH$_3$), 61.6 (H$_3C$ONCH$_3$), 71.3 (CHOH), 114.9 (CH_{ar}), 115.6 (CH_{ar}), 123.3 (HOCHCHCH), 131.9 (HOCHCHCH), 148.4 (4′-C_{ar}), 154.1 (4-C_{ar}), 162.6 (NCS-thiazole), 177.6 (H$_3$CNCO), 178.6 (NCS-*i*Pr).

Proton sponge (240 mg, 1.12 mmol) and trimethyloxonium tetrafluoroborate (166 mg, 1.12 mmol) were added to a solution of the above mixture (85 mg) in dichloromethane (5 mL). After stirring at room temperature for 2 d the resulting slurry was filtered and the solvent was removed in vacuo. The residue was purified by flash chromatography (P/EtOAc 50:50) and the desired methyl ether **23** (12.0 mg, 17%) was obtained as a yellow oil. $R_f = 0.37$ (P/EtOAc 50:50); $[\alpha]_D^{20} = 20.0$ ($c = 0.13$ in diethyl ether); ^1H NMR (250 MHz): $\delta = 1.23$ (d, $^3J = 7.3$ Hz, 3H; NCOCHCH_3), 1.42 [d, $^3J = 6.9$ Hz, 6H; CH(CH_3)$_2$], 3.11 (s, 3H; NCH_3), 3.16 (m, 1H; NCOCHCH$_3$), 3.31 (s, 3H; CHOCH_3), 3.34 [sept, $^3J = 6.9$ Hz, 1H; CH(CH$_3$)$_2$], 3.64 (s, 3H; CH$_3$NOCH_3), 3.86 (m, 1H; CHOCH$_3$), 6.48 (dd, $^3J = 4.6$ Hz, $^3J = 15.4$ Hz, 1H; CH$_3$OCHCHCH), 6.72 (d, $^3J = 15.4$ Hz, 1H; CH$_3$OCHCHCH), 7.09 (s, 1H; CH_{ar}), 7.84 (s, 1H; CH'_{ar}); ^{13}C NMR (62.9 MHz): $\delta = 14.2$ (NCOCHCH$_3$), 23.1 [CH(CH$_3$)$_2$], 32.3 (H$_3$CONCH$_3$), 33.3 [CH(CH$_3$)$_2$], 41.1 (NCOCHCH$_3$), 57.1 (CHOCH$_3$), 61.5 (H$_3$CONCH$_3$), 83.7 (CHOCH$_3$), 115.0 (CH_{ar}), 115.6 (CH_{ar}), 126.0 (CH$_3$OCHCHCH), 131.2 (CH$_3$OCHCHCH), 148.6 (4′-C_{ar}), 154.1 (4-C_{ar}), 162.6 (NCS-thiazole), 177.6 (H$_3$CNCO), 178.6 (NCS-*i*Pr); IR (neat): $\tilde{\nu} = 3102$ (m; CH_{ar}), 2969 (m; CH_{al}), 1654 (s; C=O), 1458 (m), 1181 (m), 1094 cm^{-1} (s); MS (EI, 70 eV): *m*/*z* (%): 395 (24) [M^+], 380 (16) [$M^+ -$ Me], 279 (100) [$M^+ -$ MeON(Me)COCHMe); HRMS: *m*/*z* calcd for $C_{18}H_{25}N_3O_3S_2$: 395.1337, found: 395.1339.

Cystothiazole E (1e): A 3 M solution of methyl magnesium chloride in THF (50.0 μL, 150 μmol) was added to a solution of the Weinreb amide **23** (9.0 mg, 23.0 μmol) in diethyl ether (2 mL) at $0\,^{\circ}C$. After stirring at $0\,^{\circ}C$ for 1 h, a saturated aqueous solution of NH_4Cl (2 mL) was added and the aqueous layer was extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine (10 mL), dried over Na_2SO_4 and filtered. The solvent was removed in vacuo to yield pure (+)-cystothiazole E (**1e**) (8.0 mg, 95%) as a yellow oil. The spectroscopical data were identical with those determined for the product obtained according to route I and with those reported for the natural product.

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