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Total Synthesis of the β-Methoxyacrylate-based Fungicide Myxothiazol

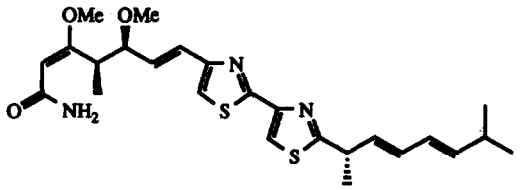
Bruce J. Martin, John M. Clough,† Gerald Pattenden,* and Ian R. Waldron

Department of Chemistry, The University, Nottingham NG7 2RD

†ICI Agrochemicals, Jealott's Hill Research Station, Bracknell, Berkshire RG12 6EY
(ICI Agrochemicals is part of Zeneca Ltd. in the UK)

Abstract: A total synthesis of the novel antifungal substance myxothiazol **1** isolated from the myxobacterium *Myxococcus fulvus* is described. The synthesis is based on elaboration of the *S-E,E*-diene thioamide **15** and the 2*RS*, 3*SR* amide aldehyde **25** as key intermediates, followed by conversion of **15** into the *bis*-thiazole **19** and a final Wittig coupling reaction between **25** and the salt **20c** leading to 7*S*,18*SR*, 19*RS* myxothiazol.

The antifungal substance myxothiazol **1** was first isolated in 1980 from the myxobacterium *Myxococcus fulvus*,[1] and later from other bacteria.[2] Myxothiazol is related to the strobilurins, *e.g.* **2**, and the oudemansins, *e.g.* **3**, which are also naturally occurring derivatives of β-methoxyacrylic acid produced, in this case, by various fungi.[3,4] Synthetic compounds related to the strobilurins are in development by industry as broad spectrum fungicides for use in agriculture.[5,6] The fungicidal activity of the strobilurins, oudemansins and myxothiazol has been shown to be due to their ability to inhibit mitochondrial respiration by blocking electron transfer between cytochrome b and cytochrome c.[7] Although a number of syntheses of the strobilurin and oudemansin structures have been reported,[8] hitherto no descriptions of synthetic work towards the more challenging structure, myxothiazol **1** have been forthcoming. In this *Letter* we describe a total synthesis of this intriguing structure.



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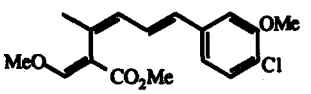

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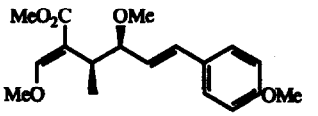
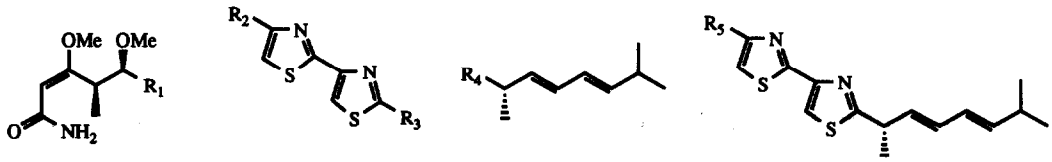


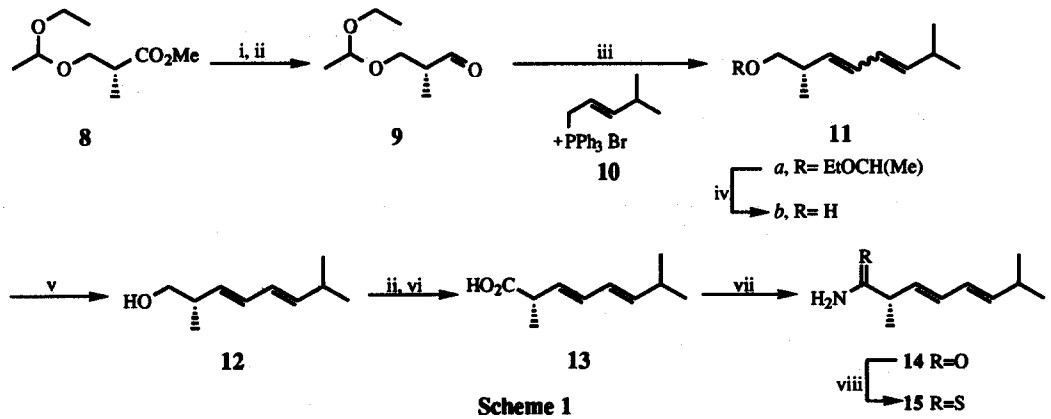
3

The structure of myxothiazol was established by a combination of chemical methods and n.m.r. techniques, and its absolute configuration followed from X-ray analysis of some of its degradation products.[9] The compound accommodates a highly substituted β-methoxyacrylamide left-hand side portion **4** and a heptadienyl right-hand segment **6**, which are separated by an interesting *bis*-thiazole unit **5**. The presence of these structural units in myxothiazol **1** suggested a strategy towards its synthesis based on: (*i*) synthesis of the *E,E*-heptadienyl unit **6**, appropriately functionalised (*i.e.* R_4=$CSNH_2$) for (*ii*) elaboration to the substituted *bis*-thiazole **7**, together with (*iii*) synthesis of the β-methoxyacrylamide residue **4**, and finally (*iv*) a Wittig coupling reaction between (**4**, R_1=CHO) and (**7**, R_5=$CHPPh_3$).



4 5 6 7

Thus, the homochiral *E,E*-diene thioamide **15** was first synthesised in readiness for elaboration to the substituted *bis*-thiazole **7**. The thioamide **15** was prepared from commercially available *R*-methyl 3-hydroxy-2-methylpropionate, following protection as the corresponding 1-ethoxyethyl derivative **8**, elaboration of **8** to the aldehyde **9**, a Wittig reaction between **9** and the *E*-phosphonium salt **10**[10] leading to the diene **11a**, and finally functional group manipulation of **11** to **15** *via* the carbinol **12**, the acid **13** and the amide **14**.[11] The Wittig reaction between **9** and **10** (BuLi, Et_2O, -10°C) led to a 4:1 mixture of *E,E*- and *Z,E*-geometrical isomers of the diene **11a**. Deprotection of this mixture, followed by irradiation of a solution of the resulting mixture of geometrical isomers of the dienol **11b** in benzene in the presence of iodine (300 watt sunlamp) gave the dienol **12** as a single enantiomer (Mosher ester analysis) of the pure *E,E*-diene (Scheme 1).[11]



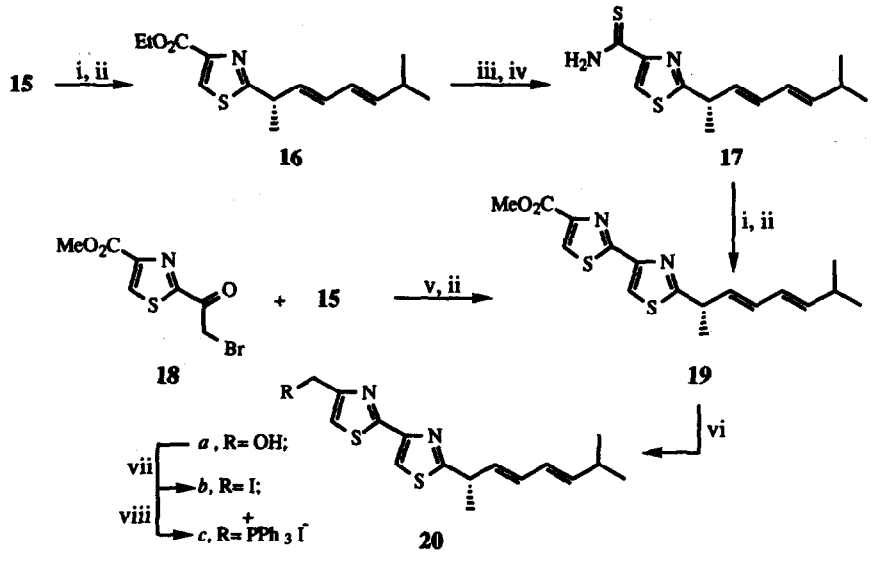
Scheme 1

Reagents: i, $LiAlH_4$, Et_2O (90%); ii, Dess-Martin periodinane, CH_2Cl_2; iii, *n*-BuLi, Et_2O, -10°C (60%); iv, HCl, THF/H_2O (93%); v, I_2(cat.), Et_2O, hν (89%); vi, $NaClO_2$, NaH_2PO_4, $^tBuOH/Me_2C$:CHMe (60%); vii, $(COCl)_2$, DMF(cat.),CH_2Cl_2 then NH_3, Et_2O (75%); viii, P_4S_{10}, PhH (49%).

Two complementary approaches to the substituted *bis*-thiazole **19** from the thioamide **15** were investigated (Scheme 2). In one approach the thioamide **15** was first subjected to a Hantzsch reaction with ethyl bromopyruvate leading to the thiazole ester intermediate **16**. Following manipulation of the ester functionality in **16** to the thioamide **17**, a second Hantzsch reaction with ethyl bromopyruvate then gave the *bis*-thiazole ester **19**. A more satisfactory sequence leading to **19** from **15** however involved condensation between **15** and the 2,4-disubstituted thiazole bromoketone **18** whose synthesis has been described earlier by Sakai *et al.*[12]

With the successful synthesis of the *bis*-thiazole **19**, substituted with the *S-E,E*-heptadiene (right-hand) side chain, we now required a synthesis of the left-hand side β-methoxyacrylamide unit **4** in order to complete the total synthesis of myxothiazol **1**. We planned to achieve this objective by a stereocontrolled Wittig reaction between the aldehyde **25** and the Wittig salt **20c** derived from **19** *via* the corresponding carbinol **20a** and the iodide **20b**.The carbinol **20a** was produced as a single enantiomer (Mosher's ester analysis). A number of complementary synthetic routes to the β-methoxyacrylamide aldehyde **25** were investigated simultaneously, and these routes will be discussed in detail in a full paper. In one approach, which we highlight here (Scheme 3), we elected to use the substituted 2*H*-pyran-2-one **22** as a key intermediate. This intermediate was chosen since: (*i*) it incorporated a masked δ-hydroxy ester functionality, (*ii*) it accommodated the β-methoxyacrylate residue in **25** in the required *E*-configuration, and (*iii*) the styryl side chain unit was a latent precursor to the sensitive

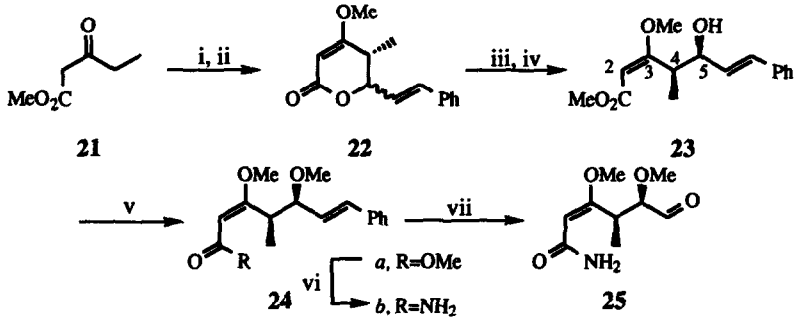
aldehyde functionality in **25**.



Scheme 2

Reagents: i, EtO 2C.CO.CH 2Br, KHCO 3, THF, 0°C; ii, TFAA, Py (59%); iii, NH 3, EtOH (78%); vi, Lawesson's reagent, PhH, Δ (47%); v, $KHCO_3$, THF, 0°C (65%); vi, DIBAL, THF, -78 to 0°C (80%); vii, PPh_3, imidazole, I_2 (78%); viii, PPh_3, PhH (80%).

The 2*H*-pyran-2-one **22** was smoothly produced from a condensation reaction between cinnamaldehyde and the dianion derived from methyl 3-oxopentanoate **21**,[13] followed by methylation using K_2CO_3-Me_2SO_4. This procedure led to the 2*H*-pyran-2-one methyl ether **22** as a 1:1 mixture of *syn*-(oil) and *anti*-(crystals, m.p. 113-114°C) diastereoisomers which could be separated by h.p.l.c.[14] For convenience however, the diastereoisomeric mixture of **22** was next treated with aqueous KOH followed by diazomethane to produce (41%) the acyclic *E,E*-diene **23** as a mixture of diastereoisomers. Chromatography then easily separated the diastereoisomers,[15] and the *syn* (4*RS*,5*SR*)-diastereoisomer **23** was next converted into the corresponding O-methyl ether **24a** (MeI, Ag_2O)and then into the amide **24b** (Me_2AlNH_2). Oxidative cleavage of **24b**, *via* the corresponding isolated *vicinal* diol (OsO_4, NMMO; then $NaIO_4$), was chemoselective and did not result in any epimerisation at the chiral centres, and led to the unstable and sensitive aldehyde-amide **25**.



Scheme 3

Reagents: i, NaH, n-BuLi, THF, 0°C, then PhCH:CHCHO, then H_3O^+; ii, Me_2SO_4- K_2CO_3, Me_2CO, Δ (70%); iii, KOH, H_2O then H $3O^+$; iv, CH_2N_2 (41%); v, MeI, Ag_2O, Et_2O (55%); vi, Me_2AlNH_2, CH $2Cl$ 2, Δ (77%); vii, OsO_4, NMMO, Me_2CO/H_2O (49%) then $NaIO_4$, THF/H $2O$ (32%).

A Wittig reaction between the aldehyde **25** and the phosphoranylide derived from the corresponding salt **20c** using lithium hexamethyldisilazide in THF at 0°C, was found to be *E*-selective, and led to 7*S*,18*SR*, 19*RS* myxothiazol which showed spectroscopic data which were completely superimposable on those of the natural (7*S*, 18*S*,19*R*) product derived from *Myxococcus fulvus*.

Acknowledgements

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15. Significant amounts of methyl all-*E* 3-methoxy-4-methyl-7-phenylhepta-2,4,6-trienoate were produced concurrently in the sequence leading to **23** from **22** unless reaction conditions were monitored closely.

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