Total synthesis of myxothiazols, novel bis-thiazole β-methoxyacrylate-based anti-fungal compounds from myxobacteria†

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Convergent total syntheses of myxothiazols A and Z are described. The syntheses are based on elaboration of the (*S*)-*E*,*E*-diene thioamide **22**, conversion of **22** into the bis-thiazole **27** and Wittig reactions between **27c** and the aldehyde **30**. The substituted β-methoxyacrylate aldehyde **30** was produced *via* an Evans asymmetric aldol protocol or *via* the 2H-pyran-2-one **31**. An *E*-selective Wittig reaction between the ylide derived from the phosphonium salt **27c** and the (+)-aldehyde **30** led to (+)-myxothiazol Z (**1b**), and a corresponding reaction with the (±)-acrylamide aldehyde **44** gave (±)-myxothiazol A (**1a**). Complementary studies led to synthesis of the ester **47b**, corresponding to myxothiazol R and myxothiazol S.

Introduction

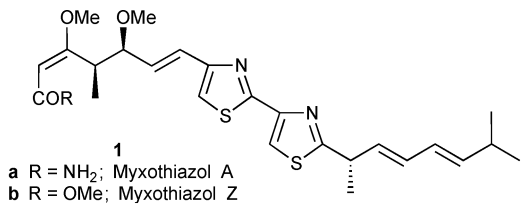
Myxothiazol is the generic name used to describe a family of fungicides isolated from myxobacteria, *e.g. Myxococcus fulvus*, *Angiococcus disciformis*, and characterised by the presence of a novel and unusual β-methoxyacrylate pharmacophore linked to a 2,4-disubstituted bis-thiazole unit. Myxothiazol A (**1a**) was the first member to be isolated, in 1980,[1] and myxothiazol Z (**1b**) was described in the primary literature in 1999.[2] In 1988, Hőfle and Sakagami and their respective co-workers[3] reported a different group of β-methoxyacrylate fungicides from various species of myxobacteria which were named melithiazols, *e.g.* melithiazol A (**2**), and cystothiazols, *e.g.* **3a** and **3b**. Interestingly, the secondary metabolites **1**, **2**, and **3** are related to the strobilurins, *e.g.* **4**, and the oudemansins, *e.g.* **5**, produced by various fungi.[4]

All of the aforementioned β-methoxyacrylates act as inhibitors of mitochondrial respiration by blocking electron transfer between cytochrome b and cytochrome c_1.[5] An exciting range of synthetic analogues of strobilurin has now been brought to the market as agricultural fungicides,[6] and synthetic studies within the melithiazols and cystothiazols have been vigorous in recent years.[7] Before these recent endeavours, however, in 1993, we described the first, and only, synthesis of (±)-myxothiazol A (**1a**).[8] Since this time, we have carried out further synthetic investigations towards the myxothiazols, and in this paper we draw together these studies, culminating in total syntheses of several of their members.

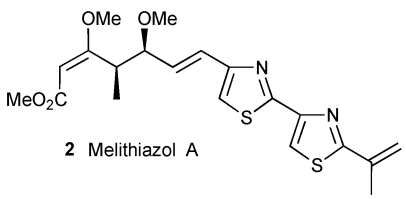
Results and discussion

Synthetic strategies

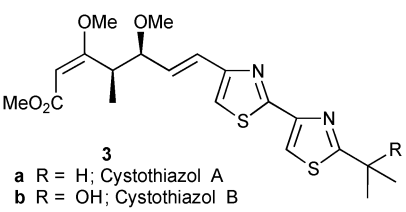
The myxothiazol structure **1** accommodates a substituted β-methoxyacrylate left-hand side, *viz.* **6**, linked to a bis-thiazole by an *E*-butenyl unit, carrying two stereogenic centres. The bis-thiazole in **1** is further substituted on the right-hand side by a conjugated *E*,*E*-heptadienyl unit, *viz.* **8**, carrying a third stereogenic centre. The presence of these structural units in the myxothiazols **1** suggested a straightforward strategy to their synthesis based on (i) synthesis of the *E*,*E*-heptadienyl side chain, **8**, followed by (ii) conversion into the substituted bis-thiazole **7**, and finally (iii) linking the left-hand side β-methoxyacrylate residue **6**. In our



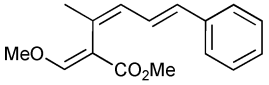
1
a R = NH_2; Myxothiazol A
b R = OMe; Myxothiazol Z



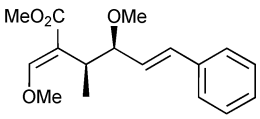
2 Melithiazol A



3
a R = H; Cystothiazol A
b R = OH; Cystothiazol B



4 Strobilurin A



5 Oudemansin A

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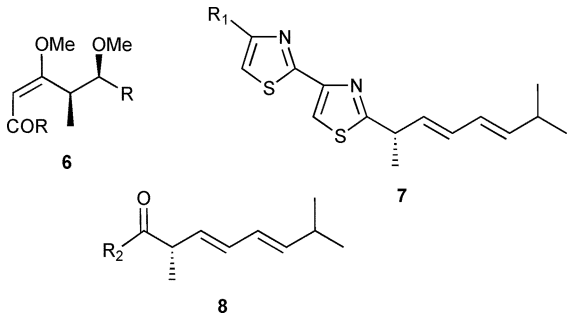
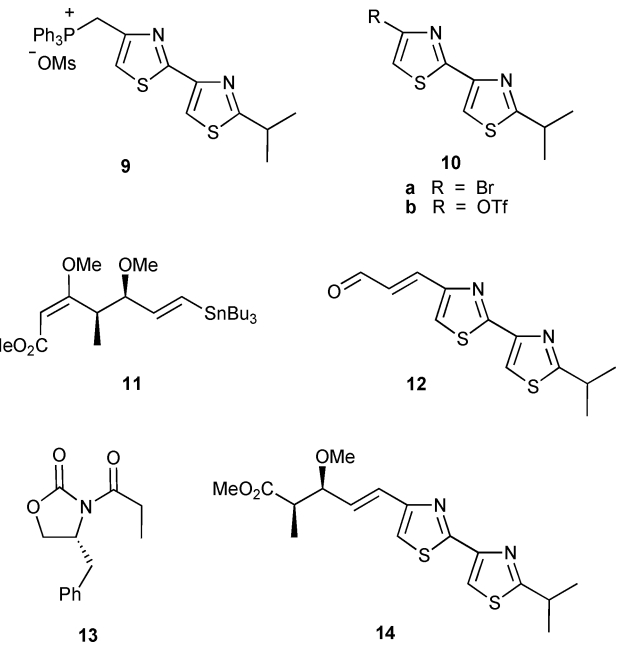


earlier studies,[8] we synthesised the bis-thiazole unit **7** and attached the left-hand side chain in the structure **1** using a Wittig reaction between the ylide derived from the bis-thiazole phosphonium salt **7** and the aldehyde **6** (R = CHO). This strategy was later

$$(R_1 = CH_2\overset{+}{P}Ph_3\ \overset{-}{I})$$

applied by Charette and Deroy[7b] and by Akita and co-workers[7a] in their syntheses of cystothiazols A (**3a**) and B (**3b**) using the phosphonium salt **9**. In other studies Bach and Heuser[7d] developed a Suzuki cross-coupling reaction from the 4-bromo bis-thiazole **10a** to synthesise cystothiazol E, and Shao and Panek,[7e] in 2004, applied the Stille cross-coupling reaction between **10b** and **11** in their synthesis of cystothiazols. By contrast, Williams *et al.*[7c] produced the left-hand side chain in their synthesis of cystothiazols A and C using an asymmetric aldol reaction between the α,β-unsaturated aldehyde **12** and the Evans oxazolidinone **13**, leading ultimately to **14**. This general strategy was also later used by Ojika *et al.*[7f] in another synthesis of cystothiazol A.



In our own studies, we explored a number of complementary pathways to elaborate the interesting substituted β-methoxyacrylate side chain, *viz.* **6**, in the myxothiazols. These methods, alongside procedures to synthesise the right-hand side chain **8** attached to the bis-thiazole unit **7**, together with the assembly of these units leading to syntheses of myxothiazol A (**1a**) and Z (**1b**), and also the methyl ester corresponding to myxothiazols R and S, will now be described.

The (*S*)-*E*,*E*-heptadienyl side chain 8

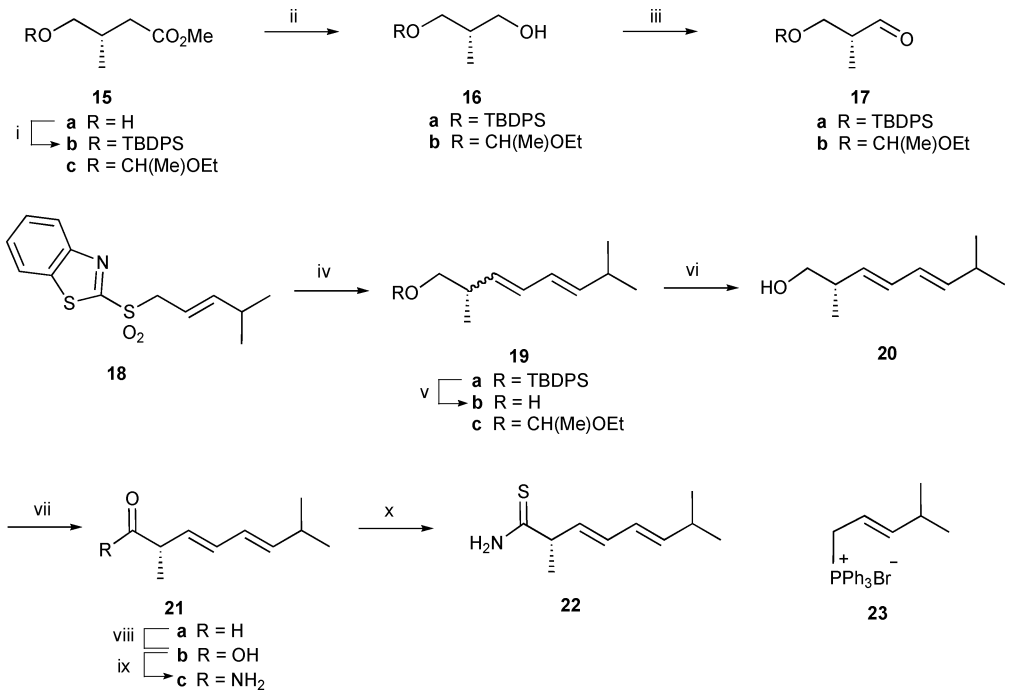
The heptadienyl side chain in the myxothiazols, appropriately functionalised as a thioamide, *i.e.* **22**, was conveniently synthesised starting from commercially available (*R*) methyl 3-hydroxy-2-methylpropionate **15a** (Scheme 1). Thus, protection of **15a** as its TBDPS ether, followed by reduction of the ester group in **15b**, to the corresponding carbinol **16a** and oxidation first gave the aldehyde **17a** as a low-melting solid. A Julia olefination reaction[9] between the aldehyde **17a** and the *E*-benzothiazole sulfone **18** derived from *E*-4-methylpent-2-en-1-ol,[10] in the presence of sodium bis(trimethylsilylamide) at −78 °C next led to the conjugated diene **19a**, which was produced as a 4 : 1 mixture of *E*- and *Z*-isomers at the newly introduced alkene bond. Deprotection of the TBDPS group in **19a**, followed by treatment of the resulting diene alcohol **19b** (4 : 1 mixture of *E*-3, *E*-5 and *Z*-3, *E*-5 isomers) with iodine in refluxing diethyl ether under ultraviolet light irradiation, and chromatography, gave the geometrically pure *E*-3, *E*-5 diene alcohol **20** as a colourless liquid. A Mosher's ester analysis gave an ee > 98%,[11] and the *E*-3, *E*-5 geometry of the conjugated diene followed conclusively from examination of the magnitude of the vicinal couplings for the olefinic protons in the ^{1}H NMR spectrum of **20**. The same diene alcohol **20** was also obtained *via* a Wittig reaction between the l-ethoxyethyl derivative **17b**, and the phosphonium salt **23**, using *n*-BuLi in diethyl ether at −10 °C, which first gave the conjugated diene **19c**, also as a 4 : 1 mixture of *E*-3, *E*-5 and *Z*-3, *E*-5 isomers. Deprotection of **19c**, followed by iodine-catalysed equilibration of the resulting diene alcohol then gave the *E*-3, *E*-5 diene alcohol **20** in a similar overall yield as the alternative Julia olefination protocol. The *E*-3, *E*-5 diene alcohol **20** was next smoothly converted into the corresponding thioamide **22** in four straightforward steps, *i.e.* oxidation to the carboxylic acid **21b** using Dess–Martin periodinane followed by buffered sodium chlorite; conversion of the acid **21b** into the amide **21c** and, finally, treatment of **21c** with Lawesson's reagent in THF.

The substituted bis-thiazole 7

A useful variety of methods is now available for making 2,4-disubstituted thiazoles, including the Hantzsch method[12] described as early as 1887, and a more biomimetic approach which proceeds *via* thiazoline intermediates produced from cysteinyl peptide precursors.[13] Both of these general methods can be used in an iterative manner to make bis-thiazoles of the type found in myxothiazols and the related natural products **2** and **3**. More recently, Pd-catalysed cross-coupling reactions between 4-bromo-, 4-stannyl, and 4-triflyl thiazoles[7] have been used to synthesise bis-thiazoles *en route* to cystothiazols.

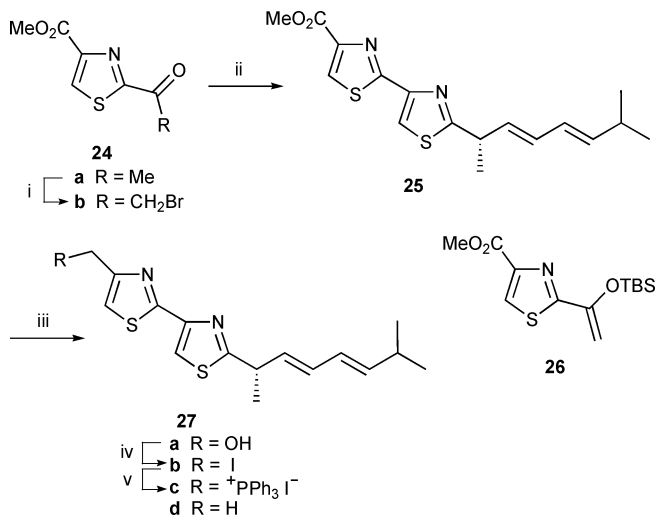
In our own studies we examined a variety of complementary routes to the bis-thiazole unit **7** in the myxothiazols.[14] Ultimately, we found that a Hantzsch condensation between the thioamide **22** and the 2,4-disubstituted thiazole bromoketone **24b**, carried out under the conditions described by Holzapfel and Bredenkamp,[15] provided the most reliable procedure for preparing the particular substituted bis-thiazole **25**.

The thiazole α-bromoketone **24b** is a known compound obtained by bromination of the corresponding methyl ketone **24a** using NBS in refluxing CCl_4.[16] We experienced difficulty in



Scheme 1 *Reagents and conditions*: i) ^{t}BuMe$_2$SiCl, imidazole (95%); ii) LiBH$_4$, THF (85%); iii) DMSO, (COCl)$_2$, −78 °C (60%); iv) LiHMDS, **17**, −78 °C (75%); v) Bu$_4$NF, THF (94%); vi) I$_2$, Et$_2$O, *hν* (74%); vii) Dess–Martin periodinane, NaHCO$_3$, then viii) NaClO$_2$, NaHPO$_4$ (61%); ix) (COCl)$_2$ then NH$_3$ (74%); x) Lawesson's reagent, THF (87%).

obtaining reproducible yields using these conditions, and ultimately produced the bromoketone **24b** by bromination of the intermediate enol silyl ether **26** derived from **24a**, using NBS in THF at 0 °C (Scheme 2). The bis-thiazole ester **25** was obtained as colourless prisms, with $[\alpha]_D^{25}$ +1.96 (*c* 1.53 in CHCl$_3$). Reduction of the ester **25** using DIBAL-H in THF next gave the primary carbinol **27a**. Analysis of the corresponding Mosher's ester of **27a** gave an ee > 95%.



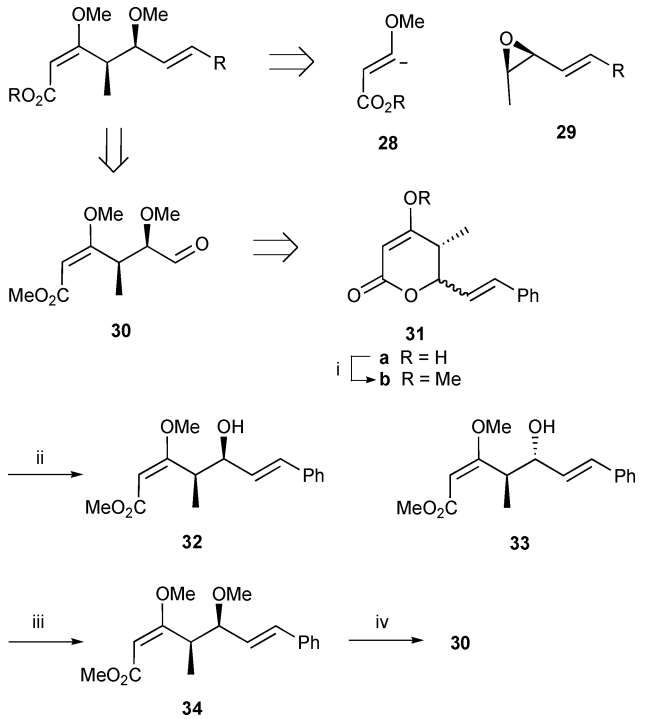
Scheme 2 *Reagents and conditions*: i) NBS, CCl$_4$ or NBS, THF then **26** (54%); ii) **24b** and **22**, NaHCO$_3$ at −20 °C, then TFA, pyridine (59%); iii) DIBAL-H, THF, −78 °C (56%); iv) I$_2$, PPh$_3$, imidazole, 0 °C (78%); v) PPh$_3$, C$_6$H$_6$ (80%).

With the overall intention of linking the β-methoxyacrylate side chain **6** to the bis-thiazole unit **7** using a Wittig reaction, we next treated the alcohol **27a** with I$_2$/PPh$_3$/imidazole at 0 °C under a nitrogen atmosphere, which led to the corresponding iodide **27b**, as a solid, in 78% yield. Treatment of the iodide **27b** with triphenylphosphine in benzene at room temperature then gave the corresponding phosphonium salt **27c**, which was obtained as a colourless powder.

The substituted β-methoxyacrylate unit 6, and end game

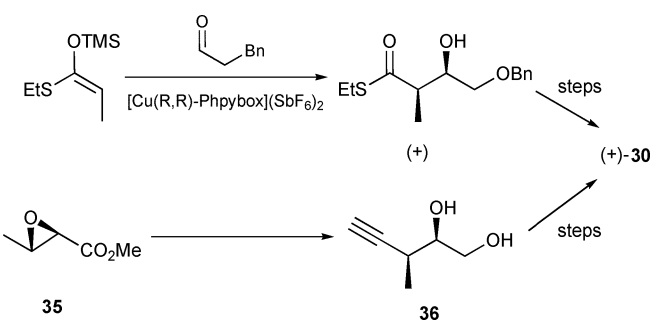
We discussed earlier the variety of synthetic approaches that have been applied, by others, to introduce the substituted β-methoxyacrylate left-hand side chain, *viz*. **6**, in endevours towards the related cystothiazols, *i.e.* **2** and **3**. We examined a number of complementary synthetic routes to the β-methoxyacrylate side chain in myxothiazols in our studies, including those based on regioselective ring opening of chiral epoxides, *i.e.* **29**, by both substituted lithium acetylides and vinyl anions *e.g.* **28**, but to no avail. Ultimately, we decided to synthesise the aldehyde **30** and carry out a Wittig reaction with **27c** leading to **1b**. A synthetic approach to the β-methoxyacrylate aldehyde **30** that was attractive was *via* the 2H-pyran-2-one **31** (Scheme 3). The pyranone **31** was chosen since it incorporated a masked δ-hydroxy ester functionality, in addition to a β-methoxyacrylate residue with the required *E*-configuration. Furthermore, the styryl side chain in **31b** acted as precursor to the sensitive aldehyde functionality in the β-methoxyacrylate aldehyde **30**.

Thus, a condensation between cinnamaldehyde and the dianion produced from methyl 3-oxopentanoate,[17] using NaH and *n*-BuLi in THF at 0 °C, first gave the pyran-2-one **31a** which, on methylation with Me$_2$SO$_4$–K$_2$CO$_3$, produced a 1 : 1 mixture of

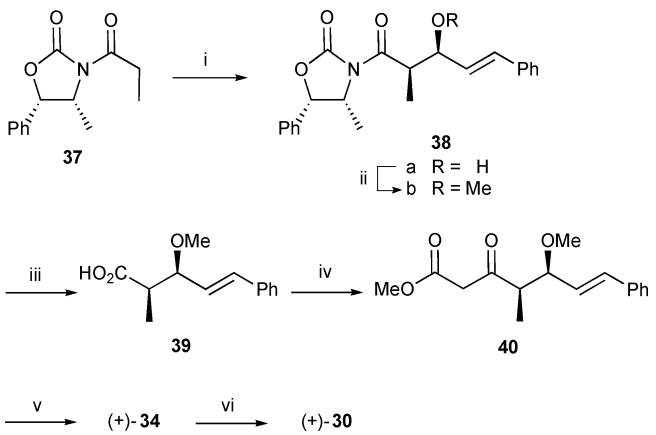


Scheme 3 *Reagents and conditions*: i) Me_2SO_4, K_2CO_3 (65%); ii) KOH, H_2O, 100 °C, then CH_2N_2, then chromatography (9%); iii) MeI, Ag_2O (55%); iv) OsO_4, NMO, Me_2CO–H_2O (9 : 1), then $NaIO_4$, THF–H_2O (1 : 3) (65%).

syn- and *anti*-diastereoisomers of the corresponding methyl ether **31b**. The diastereoisomers of **31b** could be separated by HPLC and their relative stereochemistries followed from inspection of the magnitude of their vicinal coupling between C5 and C6 in the ^{1}H NMR spectra, and comparison of these data with those obtained for similar compounds in the literature.[18] Thus, the *syn*-diasteroisomer of **31b** displayed vicinal coupling of 3.6 Hz between the hydrogen atoms at C5 and C6 whereas the corresponding *anti*-diastereoisomer showed vicinal coupling of 7.1 Hz between the same hydrogens. For the related compound kawain-5-ol the corresponding vicinal couplings have been recorded as 3.0 Hz (*syn*-diastereoisomer) and 7.0 Hz (*anti*-diastereoisomer).[18] Preparative HPLC separation of the diastereoisomers of **31b** was avoided in the synthetic scheme at this point, however, and instead the mixture of diastereoisomers was heated with 1.2 equivalents of KOH in H_2O at 100 °C followed by treatment with diazomethane leading to the *syn* and *anti* β-methoxyacrylate secondary alcohols **32** and **33** respectively, which could be easily separated by routine column chromatography. Methylation of the *syn*-diastereoisomer **32** using MeI and Ag_2O in diethyl ether finally led to the 3*RS*, 5*RS* methyl ether diastereoisomer **34** as a colourless oil. Oxidative cleavage of **34** *via* the corresponding isolated intermediate vicinal diol, using OsO_4–NMO, followed by $NaIO_4$, finally gave the (±)-β-methoxyacrylate aldehyde **30**, as a labile liquid.

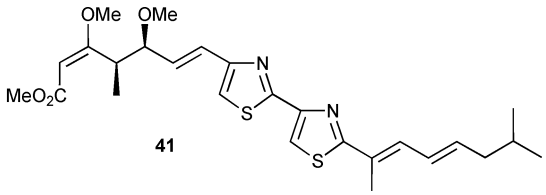


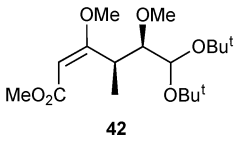
The same β-methoxyacrylate aldehyde **30** was later synthesised by Backhaus[19] using aldol chemistry starting from benzyloxyacetaldehyde, and Deroy and Charette[7b] developed an Evans enantiopure asymmetric aldol protocol to afford the (+)-aldehyde **30**. Akita *et al.*[7a] also developed a route to enantiopure **30** from the chiral acetylenic alcohol **36** produced from ring opening of the 2*R*, 3*S* epoxy butanoate **35**. We also synthesised the enantiopure β-methoxyacrylate aldehyde **30** by first using an Evans aldol reaction between the auxiliary **37** and cinnamaldehyde, which gave the *syn*-aldol **38a** with >98% ee (Scheme 4).[20] O-Methylation of **38a**, followed by conversion of the intermediate methyl ether **38b** into the corresponding carboxylic acid **39** and treatment of the latter with $LiCH_2CO_2Me$ next led to the β-ketoester **40**. Deprotonation of the β-ketoester **40**, using NaH in DMPU, followed by addition of dimethyl sulfate then led to the enantiopure (+)-β-methoxyacrylate **34**. Oxidative cleavage of the styryl alkene bond in **34**, using the same conditions as those used with the racemic material, finally gave the (+) β-methoxyacrylate aldehyde **30**, as an oil $[a]_D^{25}$ +105 (*c* 0.55 in $CHCl_3$).

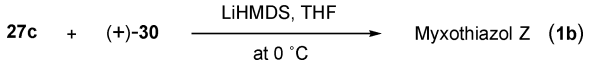


Scheme 4 *Reagents and conditions*: i) *n*-Bu_2BOTf, **37**, then PhCH=CH·CHO (90%); ii) 2,6-^{t}$Bu_2C_5H_3N$, MeOTf (72%); iii) LiOH, H_2O_2 (98%); iv) NNCD, then $LiCH_2CO_2Me$, −78 °C (85%); v) NaH, Me_2SO_4, DMPU (66%); vi) OsO_4, NMO, Me_2CO–H_2O (9 : 1), then $NaIO_4$, THF–H_2O (1 : 3) (65%). (DMPU = *N*,*N*′-dimethylpropylene urea; NNCD = 2-chloro-4-nitro-1-benzenediazonium 2-naphthalenesulfonate.)

With both the phosphonium salt **27c**, and racemic and enantiopure β-methoxyacrylate aldehyde **30** in hand, we were now in a position to examine their coupling to give myxothiazol Z (**1b**). This Wittig reaction between **27c** and **30** proved to be somewhat temperamental. For example, when the salt **27c** was treated with KOBu^t in THF at 0 °C followed by addition of the (±)-aldehyde **30**, only the product **27d** resulting from hydrolysis of the phosphonium salt was isolated. Furthermore, when a mixture of **27c** and (±)-**30** was treated with KOBu^t in THF only the positional isomer **41** of myxothiazol Z and the di-*t*-butyl acetal **42** of the aldehyde **30** were isolated. After more experimentation, use of the less basic



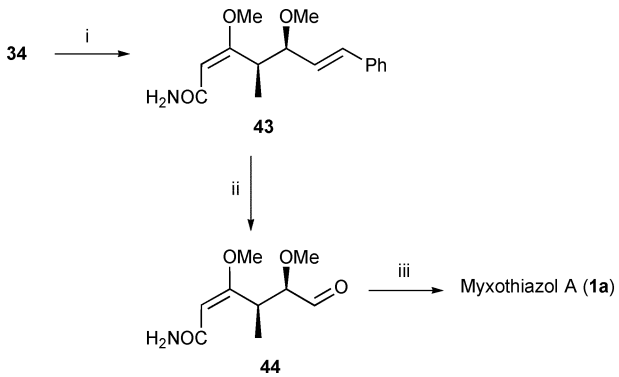




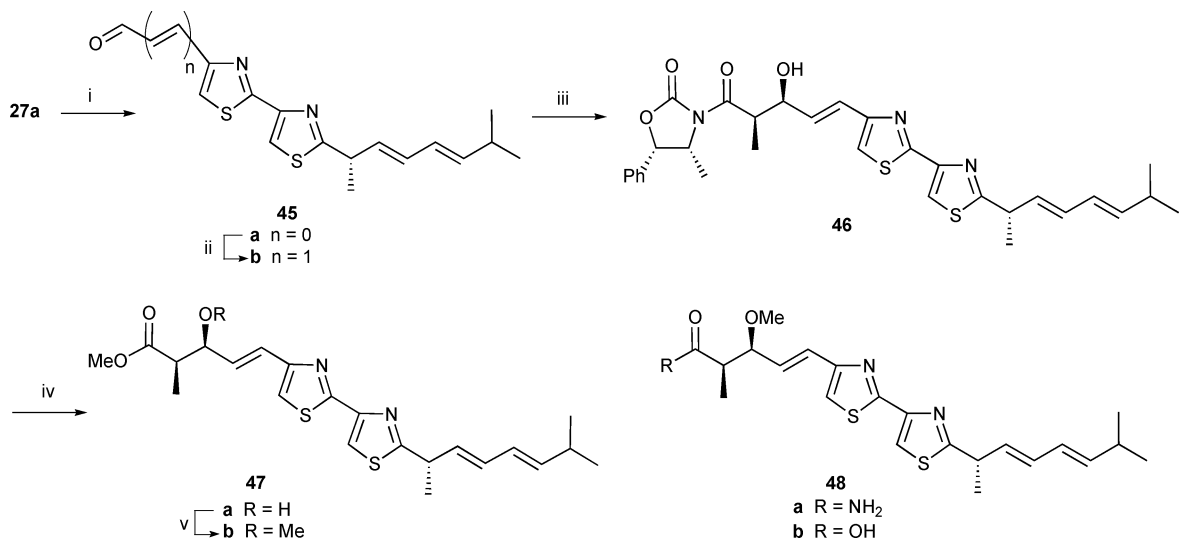
sodium methoxide in THF at 0 °C finally delivered myxothiazol Z (**1b**), which was obtained as a single alkene geometrical isomer after HPLC purification, in 11% yield. The synthetic myxothiazol showed spectroscopic data which were identical to those described for myxothiazol Z isolated from myxobacteria, even though this structure was not published as a natural product until some time after the completion of this work. A corresponding Wittig reaction between the bis-thiazole salt **27c** and the enantiopure (+)-aldehyde **30**, using lithium hexamethyldisilazide as the base in THF at 0 °C, proceeded much more smoothly and led to (+)-myxothiazol Z in 74% yield. A small amount of the corresponding *Z*-alkene was produced concurrently during the condensation which could be largely removed by HPLC. The synthetic myxothiazol Z had $[a]_D^{25}$ +118.8 (*c* 1.44 in $CHC1_3$) whereas Ahn *et al.* give $[a]_D^{25}$ +152, and Hőfle and co-workers $[a]_D^{22}$ +79.2 for naturally derived material.[2]

Attempts were now made to convert myxothiazol Z (**1b**) into myxothiazol A (**1a**) using Weinreb's conditions, *i.e.* Me_2AlNH_2 in CH_2Cl_2. However, these attempts failed, and instead only starting material was recovered. However, treatment of the β-methoxyacrylate **34** with Me_2AlNH_2 gave the corresponding amide **43** in 40% yield (Scheme 5). Oxidative cleavage of the styryl alkene bond in **43**, using OsO_4–$NaIO_4$ then gave the β-methoxyacrylamide aldehyde **44**. Gratifyingly, a Wittig reaction between this aldehyde and the phosphonium salt **27c** using LiHMDS in THF at 0 °C was found to be *E*-selective and led to 7*R*, 18*SR*, 19*RS* myxothiazol A (**1a**), albeit in only 12% yield. The synthetic myxothiazol A showed spectroscopic data which were completely superimposable on those of the natural product derived from *M. fulvus*.

As a corollary to the aforementioned synthetic work, we also examined a synthetic approach to the bis-thiazole metabolites **48a** and **48b** known as myxothiazol R and myxothiazol S respectively, which co-occur with the β-methoxyacrylate myxothiazols A and Z in myxobacteria.[21] Thus, a Wittig reaction between the bis-thiazole aldehyde **45a** produced from the alcohol **27a**, and (formylmethylene) triphenylphosphorane first gave the corresponding α, β-unsaturated aldehyde **45b** as a pale yellow solid in 72% yield (Scheme 6). An Evans aldol condensation between **37** and the aldehyde **45b** in the presence of *n*-Bu_2BOTf next gave the β-hydroxy amide **46**, which was then converted into the methyl ester **47a** using MeMgBr in MeOH at 0 °C. Treatment of **47a** with NaOH–MeI gave the corresponding methyl ether **47b** which is the methyl ester analogue of the amide **48a**, *i.e.* myxothiazol R, and the carboxylic



Scheme 5 *Reagents and conditions*: i) Me_2AlNH_2, CH_2Cl_2 (40%); ii) OsO_4, Me_2CO–H_2O (9 : 1), then $NaIO_4$, THF–H_2O (1 : 3) (32%); iii) LiHMDS, THF added to **44** and **27c** (22%).



Scheme 6 *Reagents and conditions*: i) PDC, CH_2Cl_2 (58%); ii) OHC·CH=PPh_3, C_6H_6 (72%); iii) **37**, *n*-Bu_2BOTf, Et_3N, 0 °C, then **45** (93%); iv) MeMgBr, MeOH, 0 °C (52%); v) MeI, NaOH, DMSO–H_2O (2 : 1) (45%).

acid **48b**, *i.e.* myxothiazol S. Unfortunately, the dearth of synthetic materials did not allow us to realise the syntheses of myxothiazols R and S from the methyl ester **47b**.

Acknowledgements

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