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Formal total syntheses of *Myxothiazols* by three different approaches starting from benzyloxyacetaldehyde†

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Abstract

An efficient entry into the key intermediate for the total synthesis of myxothiazol A[1] and related structures is described. We investigated three different approaches for building up the carbon framework starting from benzyloxyacetaldehyde and subjecting this to an aldol reaction, a titanium tetrachloride-mediated aldol reaction of a protected β-ketoester and a Barbier-type reaction using zinc or indium, respectively. The latter proved to be the longer (seven steps), but more efficient route, with 15% overall yield. © 2000 Elsevier Science Ltd. All rights reserved.

Myxothiazol **1**,[2] melithiazols A–N **2**[3] and cystothiazols **3**[4] are natural products which have been isolated from different strains of myxobacteria. They all possess a potent antifungal activity and are inhibitors of the bc1 segment of the respiratory chain (complex III-inhibitors).[5] Structurally, they are similar to the strobilurins — for example, oudemansin A **4** — which inhibit the same target and have already been developed as commercial fungicides.[6] Whereas myxothiazol is highly cytotoxic, it has been shown that this toxicity is not associated with the β-methoxyacrylate moiety but with the side chain instead.[3] For this reason, we envisioned the synthesis of the precursor **5**, which has been successfully transformed into myxothiazol A by Pattenden et al.,[1] with the goal of preparing analogues with a potential use as fungicides.[7] Retrosynthetically, the aldehyde **5** can be derived from a protected precursor **6**, which itself can be obtained from commercially available benzyloxyacetaldehyde **7**. As we were interested in testing all stereoisomers we did not focus on developing a stereoselective synthesis in particular, but on one that would allow us to prepare a reasonable amount of material to synthesize analogues (Scheme 1).

Reaction of the dianion of methyl propionylacetate with benzyloxyacetaldehyde **7** afforded the corresponding β-ketoester which was treated without further purification with potassium hydride and dimethylsulfate to give the (*E*)-configurated enol ether **8**, albeit only with 25% yield (*syn*:*anti*=1:1). The yield of the *O*-alkylated product is low, due to the competing double alkylation, *C*-alkylation,

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† Dedicated to Dr. Pol Bamelis on the occasion of his 60th Birthday.

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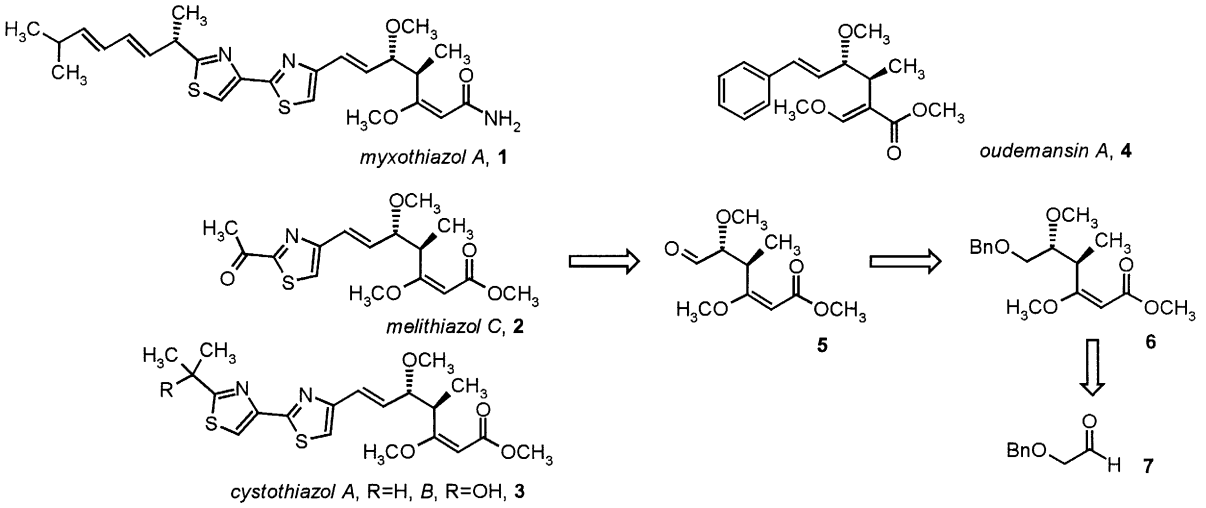


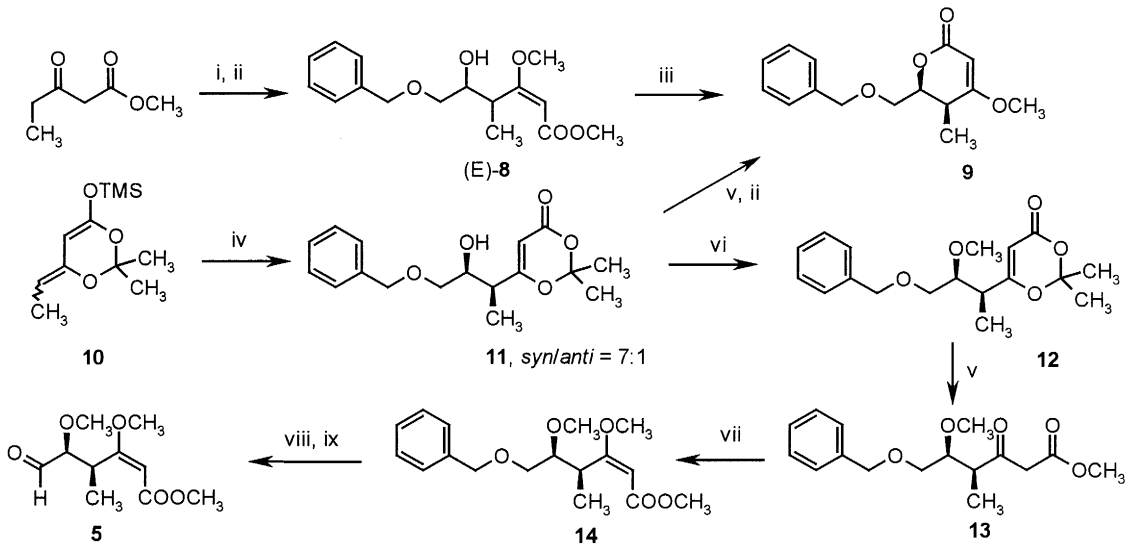
Scheme 1.

elimination and ring closure. Because of the instability of **8**, it was not possible to methylate the hydroxyl functionality either; even the mild Purdie methylation[8] conditions afforded only the cyclized enolether **9**.

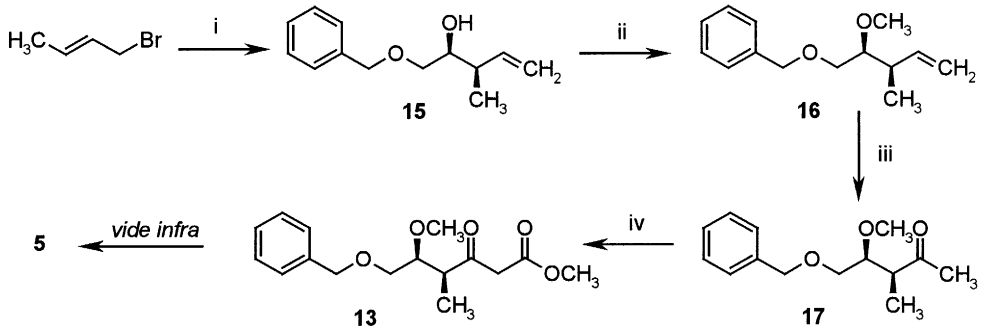
To circumvent this problem we used β-ketoester **10** which was protected as the corresponding acetonide as described earlier by Sato et al.[9] The titanium tetrachloride-mediated aldol reaction afforded the corresponding alcohol **11** in good yield (65%) and a *syn*-selectivity of 7:1. The stereochemistry was confirmed by transforming the aldol product into the cyclic enolether **9** which allowed the differentiation of the stereoisomers by means of coupling constants and NOESY effects in the ^{1}H NMR spectra.[10] The alcohol functionality was then methylated under Purdie conditions to give the precursor **12**. After opening the acetonide with methanol the β-ketoester functionality was recovered to give **13**. As the alcohol functionality was already methylated, no side reactions occurred when reacting **13** with potassium hydride and dimethyl sulfate, in this case yielding the corresponding (*E*)-configurated enolether **14** in 77% yield. Finally, the benzyl protecting group was removed by hydrogenation and the volatile and unstable alcohol was oxidized with Dess–Martin periodinane to give the desired aldehyde **5**.[11] The only drawback of this reaction sequence is the fact that the alkylation giving rise to **12** could not be scaled-up and only gave satisfactory yields when performed on a millimolar scale (Scheme 2).

We, therefore, chose a third, linear reaction sequence to get the required amount of material. Benzyloxyacetaldehyde was treated with crotyl bromide in a Barbier-type reaction using zinc[12] or indium[13] in an aqueous medium to give the homoallylic alcohol **15**[14] in good yield. After alkylating the alcohol under standard conditions, the olefin **16** was subjected to a Wacker oxidation giving methylketone **17** in good (76%) yield. The conversion into the β-ketoester was then achieved by deprotonation with sodium hydride and reaction with methyl cyanoformate affording **13** in 80% yield. The conversion of olefin **16** into **13** was also accomplished by oxidation with sodium periodate/ruthenium(III) chloride to yield the corresponding acid and subsequent reaction with carbonyldiimidazole/potassium monomethylmalonate and magnesium bromide, but in a lower overall yield (17%) (Scheme 3).

Overall, the approach using silylenol ether **10** yielded the desired aldehyde **5** in six steps, 8% overall yield and a *syn*-selectivity of 7:1 compared to the approach using the Barbier-type reaction with a total of seven steps, an overall yield of 15% and no stereoselectivity. Although being a step longer and not stereoselective, the latter route was more convenient for us as we were able to synthesize intermediate **14** on a 30 g scale and the diastereoisomers could be separated by chromatography.



Scheme 2. Reagents: (i) NaH, *n*-BuLi, THF, 0°C the **7**, then; (ii) KH, Me_2SO_4, DMPU, 12% (two steps); (iii) NaH, MeI, DMF or Ag_2O, MeI, DMF; (iv) **7**, $TiCl_4$, CH_2Cl_2, −78°C, 65%; (v) MeOH, toluene, Δ, 79%; (vi) MeI, Ag_2O, Et_2O, 57%; (vii) KH, Me_2SO_4, THF/DMPU, 75%; (viii) H_2, Pd–C, EtOAc, 38%; (ix) Dess–Martin periodinane, CH_2Cl_2, rt, quant.



Scheme 3. Reagents: **(**i) Zn or In H_2O/THF, 80–95%; (ii) NaH, MeI, THF, 92%; (iii) $PdCl_2$ (cat.), $CuCl_2$ (cat.), O_2, DMF, 76%; (iv) $LiN(SiMe_3)_2$, CNCOOMe, THF, 80%

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10. ^{1}H NMR (400 MHz, $CDCl_3$), syn-isomer: δ=1.10 (d, J=7.1 Hz, 3H, CHC*H*$_3$), 2.53 (qd, J=7.1/3.4 Hz, 1H, C*H*CH$_3$), 3.63 (dd, J=9.7/7.5 Hz, 1H, OC*H*HCH), 3.73 (s, 3H, OCH_3), 3.74 (m, 1H, OCH*H*CH), 4.50–4.65 (m, 2H, OCH_2Ph), 4.60 (m, 1H, CHO), 5.08 (s, 1H, *H*CCOCH_3), 7.28–7.40 (m, 5H, CHar); strong NOE of C*H*CH$_3$ with C*H*O and O*CH*$_2$CHO ppm. Anti-isomer: δ=1.19 (d, J=7.1 Hz, 3H, CHC*H*$_3$), 2.88 (qd, J=7.1/7.1 Hz, 1H, C*H*CH$_3$), 3.71 (m, 2H, O*CH*$_2$CH), 3.71 (s, 3H, OCH_3), 4.22 (ddd, J=7.3/4.4/3.0 Hz, 1H, CHO), 4.50–4.65 (m, 2H, OCH_2Ph), 5.09 (s, 1H, *H*CCOCH_3), 7.28–7.40 (m, 5H, CHar) ppm; strong NOE of CHC*H*$_3$ with CHO and C*H*CH$_3$ with C*H*O and OCH_3.
11. ^{1}H NMR spectra (400 MHz, $CDCl_3$, syn-isomer): δ=1.20 (d, J=7.1 Hz, 3H, CHC*H*$_3$), 3.43 (s, 3H, OCH_3), 3.57 (dd, J=6.9/2.4 Hz, 1H, C*H*CH$_3$), 3.64 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3) 4.49 (dt, J=7.1/7.1 Hz, 1H, C*H*OCH_3), 9.10 (d, J=2.5 Hz, 1H, CHO) ppm.
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