Tetrahedron Letters 49 (2008) 7024–7026

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

First synthesis of (+)-myxothiazol A

Yuki Iwaki [a,b], Masahiro Kaneko [a], Hiroyuki Akita [a,*]

[a] Faculty of Pharmaceutical Sciences, Toho University, 2-2-1, Miyama, Funabashi, Chiba 274-8510, Japan
[b] Research Institute, Novartis Pharma K.K., 8 Ohkubo, Tsukuba, Ibaraki 300-2611, Japan

ARTICLE INFO

Article history:
Received 28 August 2008
Accepted 22 September 2008
Available online 25 September 2008

Keywords:
Myxothiazol A
Antibiotic
Total synthesis
Asymmetric synthesis
Modified Julia olefination

ABSTRACT

First convergent synthesis of (+)-myxothiazol A (**1**) was achieved based on modified (one-pot) Julia olefination between (3,5*R*)-dimethoxy-(4*R*)-methyl 6-oxo-(2*E*)-hexenamide (**2**), corresponding to left-side of the final molecule, and *E*-4-2′-(1*S*,6-dimethylheptadiene)-(2,4′-bis-thiazole)-4-methybenzothiazole sulfone (**4**) corresponding to right-side.

1. Introduction

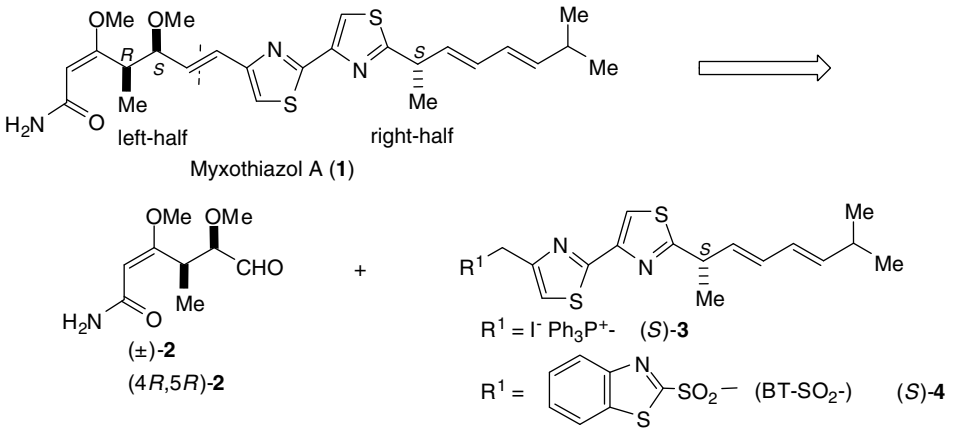
Myxothiazol A (**1**) possessing a bithiazole skeleton as well as a β-methoxyacrylate moiety was isolated from the myxobacterium *Myxococcus fulvus* strain Mxf16.[1] Myxothiazol A is active against many filamentous fungi and completely inhibits growth of *Mucor hiemalis* at a concentration of 2 μg/ml.[1] The fungicidal activity of the β-methoxyacrylate (MOA) inhibitors has been shown to be due to their ability to inhibit mitochondrial respiration by blocking electron transfer between cytochrome *b* and cytochrome *c*.[2] The structure of myxothiazol A (**1**) was established by a combination of chemical degradation and NMR study, and its absolute configuration at C(14)–carbon was determined by X-ray analysis of its degradation product.[3] The synthesis of a diasteromeric mixture of **1** was achieved based on a Wittig coupling between racemic aldehyde (±)-**2** (left half) and chiral phosphonium salt (*S*)-**3** (right half)[4] (Scheme 1). Chiral synthesis of **1** was not achieved so far, and we now report the first synthesis of (+)-**1** based on modified (one-pot) Julia olefination between a chiral aldehyde (4*R*,5*R*)-**2** and a chiral benzothiazole sulfone (*S*)-**4**.

2. Synthesis of left-half (4*R*,5*R*)-2

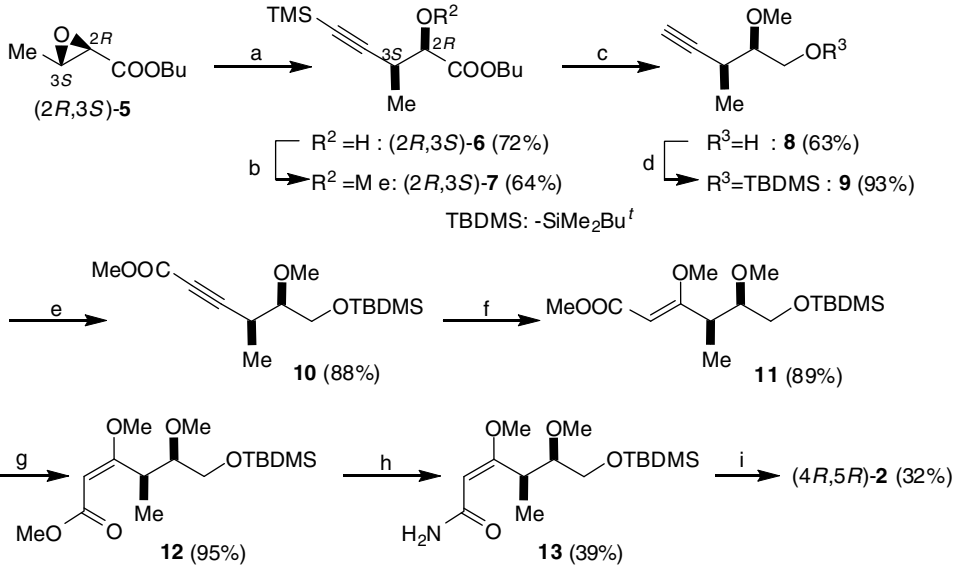
The synthesis of (±)-**2** was achieved in overall 1% yield (9 steps) based on a condensation reaction between cinnamaldehyde and the dianion derived from methyl 3-oxopentanoate followed by several synthetic steps.[4] In this case, the preparation of chiral form of **2** was possible due to the optical resolution of the intermediate. The preparation of (4*R*,5*R*)-**2** was achieved by the following synthetic route. By applying the previously reported procedure,[5] the reaction of (2*R*,3*S*)-epoxy butanoate **5**[6]and lithium silyl-acetylide in the presence of Et_2AlCl gave **6** {$[\alpha]_D^{24}$ −7.57 (*c* 1.09, $CHCl_3$)} in 72% yield. Methylation of **6** followed by consecutive desilylation and reduction afforded **8** {$[\alpha]_D^{27}$ −27.6 (*c* 1.05, $CHCl_3$)} in 40% overall yield.[7] Silylation of **8** afforded the silyl ether **9** {93%, $[\alpha]_D^{25}$ −4.74 (*c* 1.06, $CHCl_3$)}, which was treated with *n*-BuLi and methyl chloroformate to give an acetylenecarboxylate **10** ($[\alpha]_D^{24}$ − 15.1 (*c* 0.86, $CHCl_3$)) in 88% yield. Conjugate addition of MeOH to acetylenecarboxylate **10** in the presence of a catalytic amount of Bu_3P afforded a single isomer, (*Z*)-β-methoxy-α,β-unsaturated ester **11** {$[\alpha]_D^{25}$ −15.6 (*c* 0.96, $CHCl_3$)} in 89% yield. The (*Z*)-geometry of **11** was confirmed by the NOE enhancement for the olefinic proton and the methine proton (8.6%). Isomerization of (*Z*)-**11** to (*E*)-**12** was carried out by the following procedure. When a solution of (*Z*)-**11** in $CDCl_3$ (chloroform-*d* + 1% v/v TMS (D, 99.8%) + SILVER FOIL) from Cambridge Isotope Laboratories, Inc.) was allowed to react for 3 d at room temperature, (*E*)-**12** was exclusively obtained in 95% yield. The overall yield of (*E*)-**12** from (2*R*,3*S*)-**5** was 20% (7 steps), and was found to be improved in comparison to that of the desilylated **12** from methyl (2*R*,3*S*)-epoxy butanoate (11% overall yield, 8 steps).[8] In addition, a solution of (*Z*)-**11** in $CHCl_3$ was treated with a small amount of 4 M HCl in dioxane to give (*E*)-**12** in 81% yield. This experiment indicates proton (H^+)-assisted isomerization of (*Z*)-**11** to the thermodynamically more stable (*E*)-**12**. Conversion of ester group to amide was carried out by the following procedure. Alkaline hydrolysis of the crude (*E*)-**12** followed by acid treatment gave carboxylic acid. Treatment of this acid with water-soluble carbodiimide hydrochloric acid salt (WSCD·HCl) in the presence

* Corresponding author. Tel.: +81 474 72 1805.
E-mail address: akita@phar.toho-u.ac.jp (H. Akita).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.125



Scheme 1.

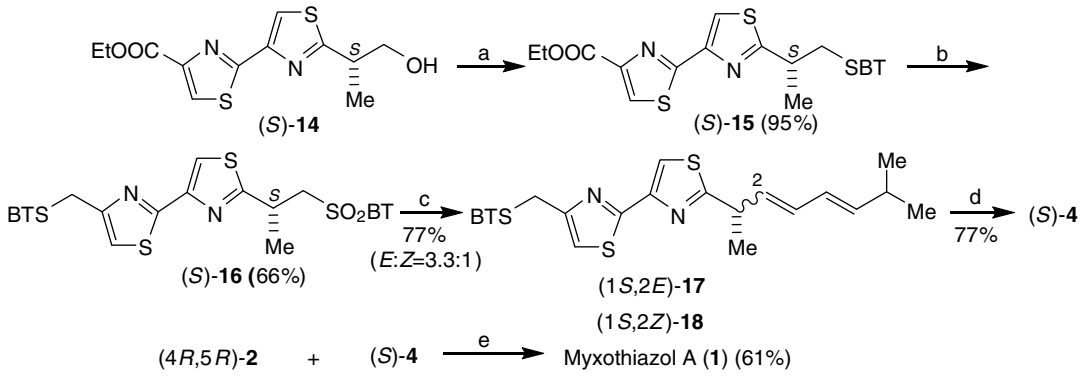


Scheme 2. Reagents and conditions: (a) trimethylsilylacetylene/*n*-BuLi/Et_2AlCl/THF; (b) MeI/Ag_2O/DMF; (c) (1) *n*-$Bu_4N^+F^-$/THF, (2) $LiBH_4$; (d) TBDMSCl/imidazole/DMF; (e) *n*-BuLi/ClCOOMe; (f) Bu_3P/MeOH; (g) $CDCl_3$ or 4 M-HCl in dioxane/$CHCl_3$; (h) (1) $Ba(OH)_2{\cdot}8H_2O$/MeOH, 70 °C (2) 0.5 M HCl (3) WSCD·HCl/HOAt/Et_3N/DMF; (4) 28% aqueous NH_3; (i) (1) HF–pyridine (2) TPAP/NMO/MS-4A/CH_2Cl_2.

of 1-hydroxy-7-aza-benzotriazole (HOAt) followed by addition of aqueous NH_3 gave the desired amide **13** {$[\alpha]_D^{27}$ +35.7 (*c* 0.84, $CHCl_3$)} in 39% overall yield from (*E*)-**12**. Desilylation of **13** with HF–pyridine followed by oxidation with tetrapropylammonium perruthenate (TPAP) in the presence of 4-methylmorpholine *N*-oxide (NMO) and MS-4A afforded the desired aldehyde (4*R*,5*R*)-**2** in 32% overall yield. ^{1}H NMR data of the synthetic (4*R*,5*R*)-**2** were consistent with those of the reported (±)-**2**[4b] (see Scheme 2).

3. Synthesis of right-half (*S*)-4 and Myxothiazol A (1)

We previously obtained the starting chiral alcohol (*S*)-**14** based on lipase-assisted asymmetric hydrolysis of racemic acetate of **14**.[9] Treatment of (*S*)-**14** with 2-mercaptobenzothiazole (BTSH) in the presence of Ph_3P and diethylazodicarboxylate (DEAD) gave the corresponding sulfide (*S*)-**15** {$[\alpha]_D^{26}$ −92.97 (*c* 1.48, $CHCl_3$)} in 95% yield. $LiBH_4$ reduction of (*S*)-**15** followed by oxidation with 35% H_2O_2 in the presence of hexaammonium heptamolybdate tetrahydrate {$Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$} provided the corresponding sulfone-alcohol, which was again treated with BTSH in the presence of Ph_3P and DEAD to afford the corresponding sulfide (*S*)-**16** {$[\alpha]_D^{26}$ −74.4 (*c* 0.77, $CHCl_3$)} in 66% overall yield. The reaction of (*S*)-**16** and (2*E*)-4-methylpentenal in the presence of lithium bis(trimethylsilyl)amide (LHMDS) in THF gave a mixture (*E*/*Z* = 3.3/1) of coupled products, which were separated to give (*E*)-**17** {$[\alpha]_D^{27}$ +7.83 (*c* 0.525, $CHCl_3$)} (59%) and (*Z*)-**18** {$[\alpha]_D^{27}$ −82.3 (*c* 0.81, $CHCl_3$)} (18%). Oxidation of (*E*)-**17** with 35% H_2O_2 in the presence of $Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$ provided the desired (*S*)-**4** {$[\alpha]_D^{25}$ −3.6 (*c* 0.6, $CHCl_3$)} in 77% yield. The overall yield of (*S*)-**4** from the reported (*S*)-**14** was 28% (4 steps). In contrast, the overall yield of (*S*)-**3** from the commercially available (2*R*)-3-hydroxy-2-methylpropanoate was 1% (19 steps).[4] Finally, modified (one-pot) Julia olefination between the chiral aldehyde (4*R*,5*R*)-**2** and the chiral benzothiazole sulfone (*S*)-**4** in the presence of LHMDS afforded (+)-myxothiazol A (**1**) {$[\alpha]_D^{26}$ +33.5 (*c* 0.70, MeOH)} in 61% yield. The spectral data of the synthetic **1** were identical with those of natural (+)-myxothiazol A (**1**) {$[\alpha]_D^{25}$ +43.4 (*c* 6.0, MeOH)} [3a] including the sign of a specific rotation (see Scheme 3).



Scheme 3. Reagents and conditions: (a) 2-mercaptobenzothiazol (BTSH)/DEAD/Ph_3P/THF; (b) (1) $LiBH_4$/THF (2) H_2O_2/$Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$/EtOH (3) BTSH/DEAD/$Ph_3P$/THF; (c) LHMDS/(2*E*)-4-methylpentenal/THF; (d) H_2O_2/$Mo_7O_{24}(NH_4)_6{\cdot}4H_2O$/EtOH; (e) LHMDS/THF.

4. Conclusion

The first convergent synthesis of (+)-myxothiazol A (**1**) was achieved based on modified (one-pot) Julia olefination between the chiral aldehyde (4*R*,5*R*)-**2**, corresponding to left-side of the final molecule, and chiral benzothiazole sulfone (*S*)-**4**, bearing a bithiazole moiety corresponding to right-side, respectively. The desired chiral aldehyde (4*R*,5*R*)-**2** was obtained from the starting epoxy ester (2*R*,3*S*)-**5** in an overall 2.5% yield (9 steps). Moreover, the desired chiral benzothiazole sulfone (*S*)-**4** was obtained from (*S*)-4-ethoxycarbonyl-2′-(1-hydroxymethylethyl)-2,4′-bithiazole (**14**) in an overall yield of 28% (4 steps). Finally, modified (one-pot) Julia olefination between (4*R*,5*R*)-**2** and (*S*)-**4** afforded (+)-myxothiazol A (**1**) in 61% yield. The coupling yield was comparably better than that of the reported Wittig procedure (22% yield).[4b]

Acknowledgments

We would like to thank Dr Ryoichi Akaishi of Osaka Yuki Kagaku Kogyo Co., Ltd (Japan) for providing *n*-butyl (2*R*,3*S*)-epoxy butyrate (**5**).

References and notes

1. Gerth, K.; Irschik, H.; Reichenbach, H.; Trowitzsch, W. *J. Antibiotics* **1980**, *33*, 1474–1479.
2. Thierbach, G.; Reichenbach, H. *Biochim. Biophys. Acta* **1981**, *638*, 282–289.
3. (a) Trowitzsch, W.; Reifenstahl, G.; Wray, V.; Gerth, K. *J. Antibiotics* **1980**, *33*, 1480–1490; (b) Trowitzsch, W.; Höfle, G.; Sheldrick, W. S. *Tetrahedron Lett.* **1981**, *22*, 3829–3832.
4. (a) Martin, B. J.; Clough, J. M.; Pattenden, G.; Waldron, I. R. *Tetrahedron Lett.* **1993**, *34*, 5151–5154; (b) Clough, J. M.; Dube, H.; Martin, B. J.; Pattenden Reddy, K. S. G.; Waldron, I. R. *Org. Biomol. Chem.* **2006**, *4*, 2906–2911.
5. Akita, H.; Matsukura, H.; Oishi, T. *Tetrahedron Lett.* **1986**, *27*, 5397–5400.
6. Chemenzymatic synthesis of methyl (2*R*,3*S*)-epoxy butanoate was reported: (a) Akita, H.; Kawaguchi, T.; Enoki, Y.; Oishi, T. *Chem. Pharm. Bull.* **1990**, *38*, 323–328; (b) Kato, K.; Ono, M.; Akita, H. *Tetrahedron* **2001**, *57*, 10055–10062. Now, *n*-butyl (2*R*,3*S*)-epoxy butyrate (**5**) is commercially available from Osaka Yuki Kagaku Kogyo Co., Ltd (Japan). Japan Kokai Tokkyo Koho JP 3095539.
7. Satisfactory analytical data were obtained for all new compounds.
8. Kato, K.; Nishimura, A.; Yamamoto, Y.; Akita, H. *Tetrahedron* **2003**, *43*, 643–645.
9. (a) Akita, H.; Nozawa, M.; Nagumo, S. *Chem. Pharm. Bull.* **1994**, *42*, 1208–1212; (b) Akita, H.; Iwaki, Y.; Kato, K.; Qi, J.; Ojika, M. *Tetrahedron: Asymmetry* **2007**, *18*, 513–519. Now, both (*S*)-**14** and (*R*)-**14** were obtained by optical resolution of (±)-**14** using HPLC separation {Chiralcel OD-H (2 × 25 cm), eluent; 20% 2-propanol in hexane, 10 mL/min, (*S*)-**14**; t_R = 30 min, (*R*)-**14**; t_R = 50 min}.