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Concise total synthesis of 9-methoxystrobilurin A

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Abstract

Total synthesis of a potent antifungal and cytostatic 9-methoxystrobilurin A was achieved by developing a concise and general route to β-methoxy acrylate.

9-Methoxystrobilurin A (**1**) was isolated by Anke and Steglich et al. in 1995[1] as a new and potent analogue of antifungal β-methoxyacrylates.[2] Structurally complicated strobilurin K (**2**)[1,3] and L (**3**)[6] were also isolated in 1996, and they have a unique triene moiety including two electron-rich and acid-sensitive methyl enol ethers as common substructures. Interestingly, this 9-methoxystrobilurin family was found to exhibit potent cytostatic activity toward human-derived tumor cell lines in addition to the originally reported antifungal activity. As an example, 9-methoxystrobilurin A and K inhibited the growth of HeLa S3 cell at very low concentration (the IC_{50} value reached 8.5 nM) without showing any significant cytotoxity (Fig. 1).

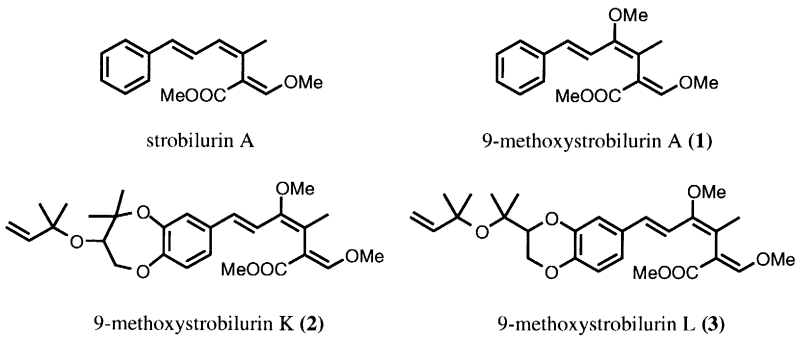

Fig. 1. Structures of strobilurin antibiotics

The total synthesis of strobilurin A has already been reported by several groups.[7] However, these approaches seem not be directly applicable to the synthesis of a 9-methoxy analogue since these

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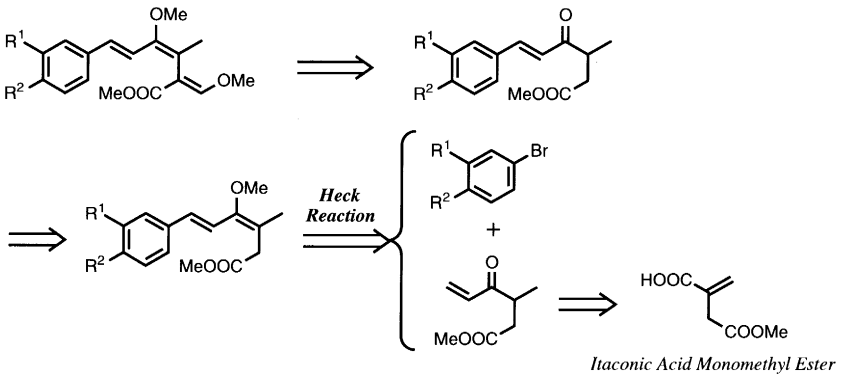
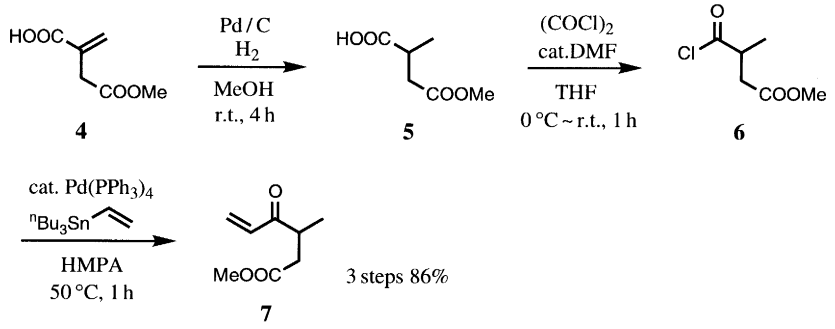
compounds have a different oxidation level in their triene moiety. In this paper, we would like to report the first total synthesis of 9-methoxystrobilurin A by a concise route which might be applicable to synthesis of **2** or **3**.

Our synthetic strategy for the 9-methoxystrobilurin analogue is shown in Scheme 1. A simple and convergent synthetic route was desired for future studies of the structure–activity relationships on the 9-alkoxy group and an oxygenated side chain attached to the hydrophobic aromatic ring. A key step of our convergent approach is the Heck reaction of aryl bromide with vinyl ketone. We expected that the mildness of the Heck reaction would be applicable for the coupling of vinyl ketone and aryl bromide with a highly oxygenated side chain such as for strobilurin K and L. Vinyl ketone might be prepared from commercially available monomethyl ester of itaconic acid.[8]



Scheme 1. Synthetic strategy of 9-methoxystrobilurins

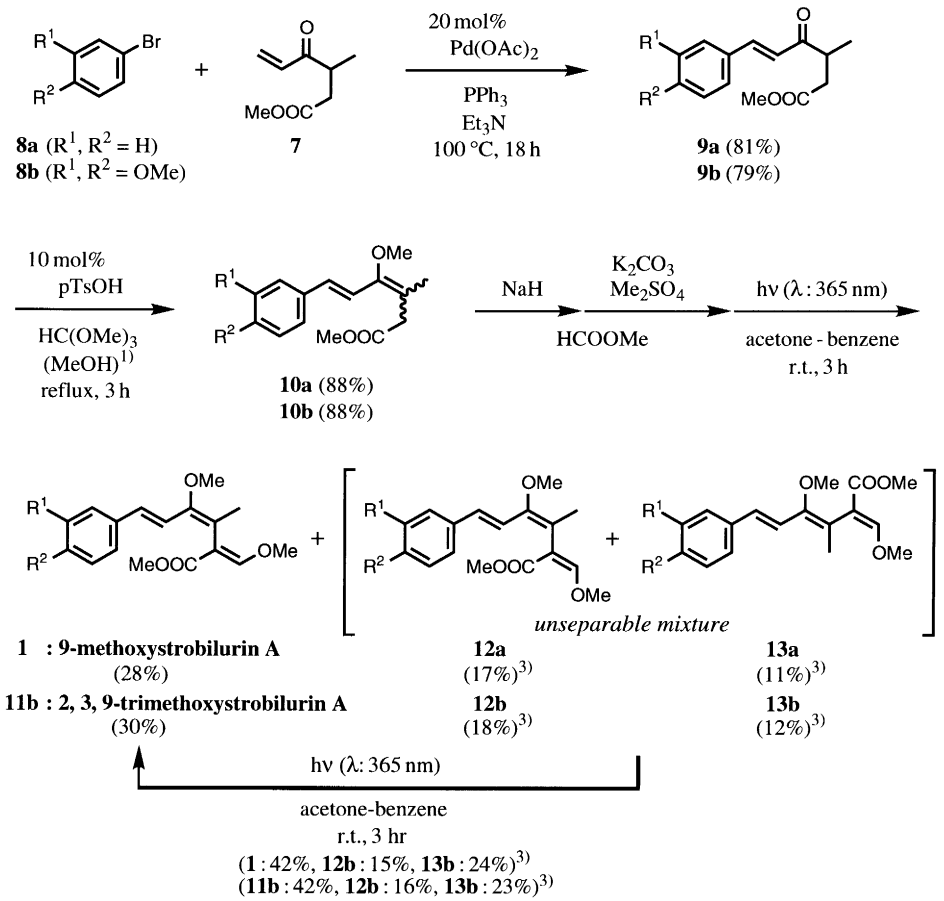
First, the olefin part of monomethyl itaconate **4** was hydrogenated and the resulting saturated monoester (monomethyl methylsuccinate) **5** was successively converted to the corresponding acid chloride **6** without isolation. Stille coupling reaction of the acid chloride with vinyl-tributylstannane[9] gave the desired vinyl ketone **7** in good yield (three steps, 86%). Thus, an efficient preparative method for the vinyl ketone **7** was developed (Scheme 2).



Scheme 2. Synthesis of vinyl ketone

Next, Heck reaction of the above vinyl ketone **7** with bromobenzene **8a** was tried to obtain the corresponding α,β-unsaturated ester. The reaction proceeded smoothly and the desired coupling product **9a** was obtained in high yield (81%) when 2 equivalents of vinyl ketone **7** were used.[10] In the presence of a catalytic amount of *p*-toluenesulfonic acid, the α,β-unsaturated ketone **9a** was refluxed for 1 h with trimethylorthoformate and methanol. After evaporation of volatile materials, trimethylorthoformate was added again to the residue, and refluxed for 2 h to obtain the corresponding methyl enol ether

10a as a geometrical mixture (ca. 1:1). Treatment of the **10a** with sodium hydride-methyl formate, followed by the successive addition of dimethylsulfate and potassium carbonate gave a mixture of the geometrical isomers of strobilurin A. The mixture was successively isomerized by the irradiation of an ultraviolet lamp (λ: 365nm) and the desired 9-methoxystrobilurin A (**1**) was isolated in 28% yield (three steps) along with unseparable mixture of other two isomers (28% yield, **12a**:**13a**=17:11) after silicagel column chromatography (Scheme 3).[11] The undesired isomers were again subjected to UV-mediated isomerization, affording **1** in 42% yield and 39% of starting mixture was recovered (**12a**:**13a**=15:24). Spectral data of the synthetic 9-methoxystrobilurin A[12] were in good accordance with those of the natural product reported by Anke's group.[1]



1) Refluxed for 1 h with MeOH and for 2 h without MeOH.
2) The yields are for 3 steps including the former reactions.
3) The ratio of **12** and **13** was determined by ^{1}H-NMR.

Scheme 3. Total synthesis of 9-methoxystrobilurin A

The present procedure was also applied to the synthesis of a dimethoxy analogue of 9-methoxystrobilurin A which is structurally more close to 9-methoxystrobilurin K (**2**) and L (**3**). All steps, including the Heck reaction, proceeded in a similar manner to give 2,3,9-trimethoxystrobilurin.[13]

Thus, the first total synthesis of 9-methoxystrobilurin A which is the simplest analogue of 9-methoxystrobilurins was successfully achieved. The concise and convergent approach developed by

the present study is noteworthy. Further investigations for the synthesis of the more complicated and biologically significant 9-methoxystrobilurin K, L and other analogues are now in progress.

References

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8. This compound was purchased from Tokyo Kasei Industries, Inc.
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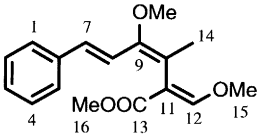
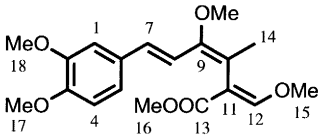
10. The yield of the coupling compound was moderate (61%) when 1.2 eqivalent of vinyl ketone was used, probably due to a thermal polymerization of vinyl ketone during the Heck reaction.
11. The irradiation condition has not yet been optimized in terms of the light density.
12. Spectral data of synthesized 9-methoxystrobilurin A (**1**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.91 (s, 3H, H-14), 3.68 (s, 3H, H-17), 3.72 (s, 3H, H-16), 3.82 (s, 3H, H-15), 6.52 (d, 1H, *J*=16.0 Hz, H-8), 6.71 (d, 1H, *J*=16.0 Hz, H-7), 7.20 (m, 1H, H-3), 7.30 (dd, 2H, *J*=7.3 Hz, 8.0 Hz, H-2 and H-4), 7.37 (d, 2H, *J*=7.2 Hz, H-1 and H-5), 7.40 (s, 1H, H-12); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.3 (C-14), 51.6 (C-16), 59.5 (C-17), 61.8 (C-15), 110.5 (C-11), 118.8 (C-10), 121.5 (C-8), 126.5 (C-1 C-5), 127.3 (C-3) 127.6 (C-7), 128.5 (C-2 C-4), 137.5 (C-6), 152.6 (C-9) 159.3 (C-12), 167.1 (C-13); EI-MS 288 (M^+).
13. Spectral data of synthesized 2,3,9-trimethoxystrobilurin A (**11b**): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.91 (s, 3H, H-14), 3.68 (s, 3H, H-17), 3.72 (s, 3H, H-16), 3.82 (s, 3H, H-15), 3.88 (s, 3H, *Me*O-Ar), 3.90 (s, 3H, *Me*O-Ar), 6.37 (d, 1H, *J*=16.0 Hz, H-8), 6.66 (d, 1H, *J*=16.0 Hz, H-7), 6.81 (d, 1H, *J*=8.3 Hz, H-4), 6.89 (d, 1H, *J*=1.7 Hz, H-1), 6.96 (dd, 1H, *J*=1.7, 8.3 Hz, H-5), 7.40 (s, 1H, H-12); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 16.2 (C-14), 51.5 (C-16), 55.9 (C-18 C-19), 59.5 (C-17), 61.8 (C-15), 109.4 (C-4), 110.6 (C-11), 111.1 (C-10), 117.8 (C-10), 119.4 (C-5), 119.7 (C-8) 127.4 (C-7), 130.6 (C-6) 148.6 (C-3), 148.9 (C-2), 152.7 (C-9), 159.3 (C-12), 168.2 (C-13); EI-MS 348 (M^+).



(**1**)



(**11b**)