Pergamon

Tetrahedron Letters 42 (2001) 4531–4534

TETRAHEDRON LETTERS

Asymmetric total synthesis of 9-methoxystrobilurin K

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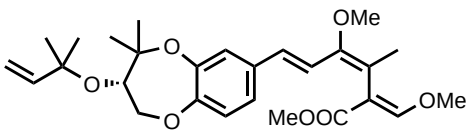
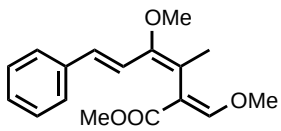
Received 5 April 2001; revised 8 May 2001; accepted 11 May 2001

Abstract—Asymmetric total synthesis of a potent antifungal and cytostatic 9-methoxystrobilurin K was achieved by developing a convergent and versatile synthetic route.

9-Methoxystrobilurin K (**1**) was first isolated from a mycelial culture of the *Favolaschia* by Anke and co-workers in 1995[1] as a new and potent analogue of β-methoxyacrylate antibiotics (MOAs). The compound was originally proposed as another structure;[1] however, Blunt and Munro et al. claimed a benzodioxepin-type structure **1** in 1997.[2] Recently, Anke and Steglich et al. formally revised the structure to **1** by the comparison of the synthetic benzodioxepin moiety with the degradation product of natural strobilurin K.[3]



9-Methoxystrobilurin K (1)



9-Methoxystrobilurin A (2)

9-Methoxystrobilurin K (**1**) exhibits strong antifungal activities toward a wide variety of fungi by specific binding to the Qo-center of cytochrome b and inhibiting mitochondrial respiration in a similar manner as other natural and artificial MOAs. In addition, **1** shows remarkable cytostatic activity toward human-derived tumor cell lines at very low concentration without showing any significant cytotoxity. The interesting cytostatic property of 9-methoxystrobilurin K would be closely related to the structure of an extended side-chain moiety from the 1,5-benzodioxepin ring system because strobilurin D and E having similar part on aromatic ring also exhibit cytostatic activities.[4] Study of the structure–activity relationship on the side-chain moiety is expected for the development of new anti-tumor agents; however, asymmetric synthesis of 9-methoxystrobilurin K or its derivative has not yet been developed.

In our previous paper, a total synthesis of 9-methoxystrobilurin A (**2**), which is the simplest 9-methoxystrobilurin-type MOA, was reported.[5] In this communication, we would like to describe the first total synthesis of the more complicated and potent analogue 9-methoxystrobilurin K by a convergent and applicable method including efficient construction of an enantiomerically pure 1,5-benzodioxepin ring system having a hindered and acid-sensitive allylic tertiary-secondary ether linkage.

Our synthetic strategy for the benzodioxepin-type 9-methoxystrobilurin analogue is shown in Scheme 1. A convergent synthetic route was strongly desired for future studies of the structure–activity relationships of the side-chain moiety. A key-step of our approach is the Heck reaction of aryl bromide with vinyl ketone, and optically active 7-bromo-4,4-dimethyl-3,4-dihydro-1,5-benzodioxepin-3-ol **6** was decided as the first synthetic target. The 1,5-benzodioxepin skeleton in **6** might be constructed by a Lewis acid-mediated intramolecular cyclization[6] of the chiral epoxy phenol **5**.

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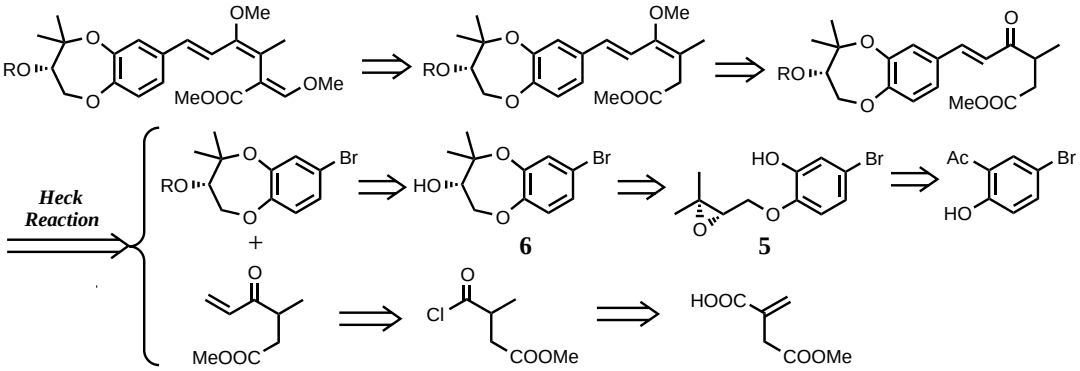


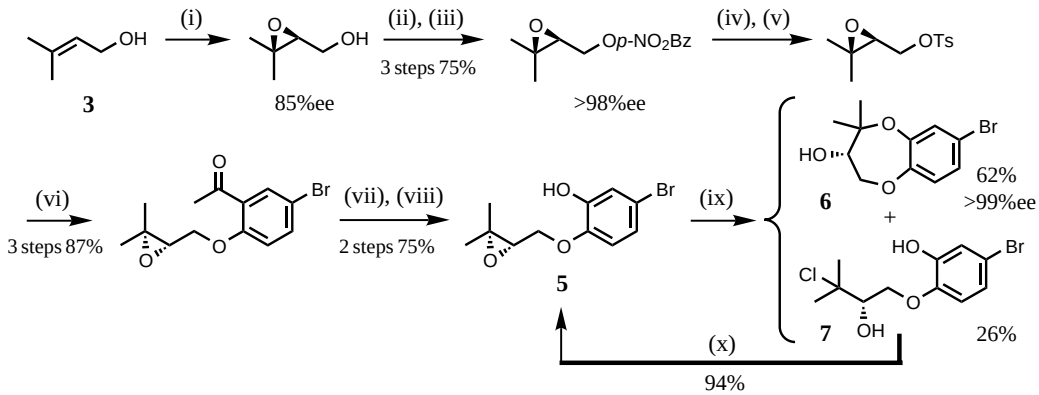
Scheme 1. Synthetic strategy for benzodioxepin-type 9-methoxystrobilurins.

The desired chiral epoxy phenol **5** was successfully prepared from prenyl alcohol **3** using Sharpless asymmetric epoxidation (Scheme 2). However, in the synthesis of 7-bromo-type benzodioxepin, the yield of the desired 7-*endo*-cyclized product **6** significantly decreased because of several undesirable side reactions. The major side reaction was tin(IV) chloride-mediated 1,2-hydride migration of epoxy phenol **5** followed by an intramolecular acetalization resulting in the corresponding hemiketal of isopropyl ketone. This is probably due to the lowering of nucleophilicity of the phenolic hydroxyl group on the bromo-substituted aromatic ring.

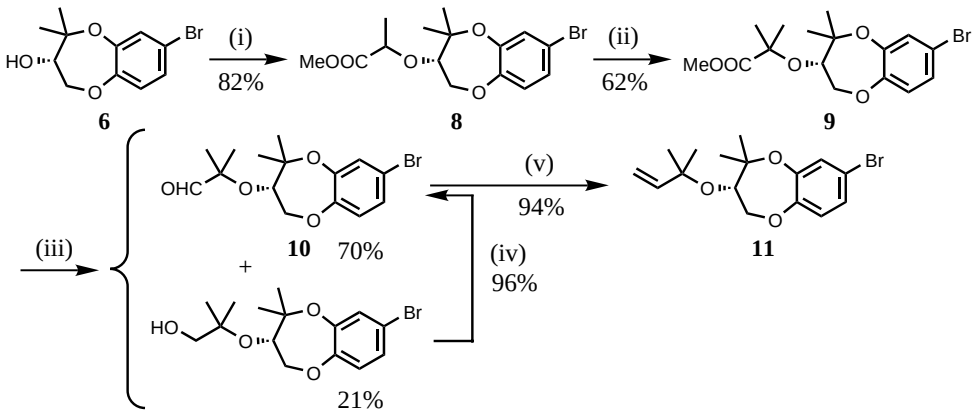
Therefore, several reaction conditions for the 7-*endo* selective cyclization were examined and the yield was greatly improved by use of diethyl ether as solvent at 0°C. Interestingly, a major by-product under these conditions was a chlorohydrin **7** produced by ring-opening and chlorine-transfer from tin(IV) chloride. It is noted that the chlorohydrin **7** was efficiently converted in high yield to the starting epoxy phenol **5** by a treatment with potassium *tert*-butoxide at 0°C.

Next, construction of a hindered and allylic secondary–tertiary ether linkage was studied. Several attempts for direct ether synthesis utilizing 1,5-benzodioxepin-3-ol **6** and isoprene under acidic conditions were unsuccessful because of exclusive polymerization of isoprene; therefore, a stepwise approach was attempted. A Williamson-type coupling reaction of methyl 2-bromopropionate with sodium alkoxide of **6** smoothly proceeded to give the corresponding α-alkoxyester **8** in good yield. The thus-obtained α-monomethylester **8** was further methylated with sodium bis(trimethylsilyl)amide-methyl iodide to afford the corresponding α,α-dimethylester **9** and the desired secondary-tertiary ether linkage was successfully constructed. The ester **9** was converted to the corresponding aldehyde **10,** and the following Wittig reaction gave the 7-bromo-4,4-dimethyl-1,5-benzodioxepin **11** equipped with the natural-type side-chain moiety (Scheme 3).

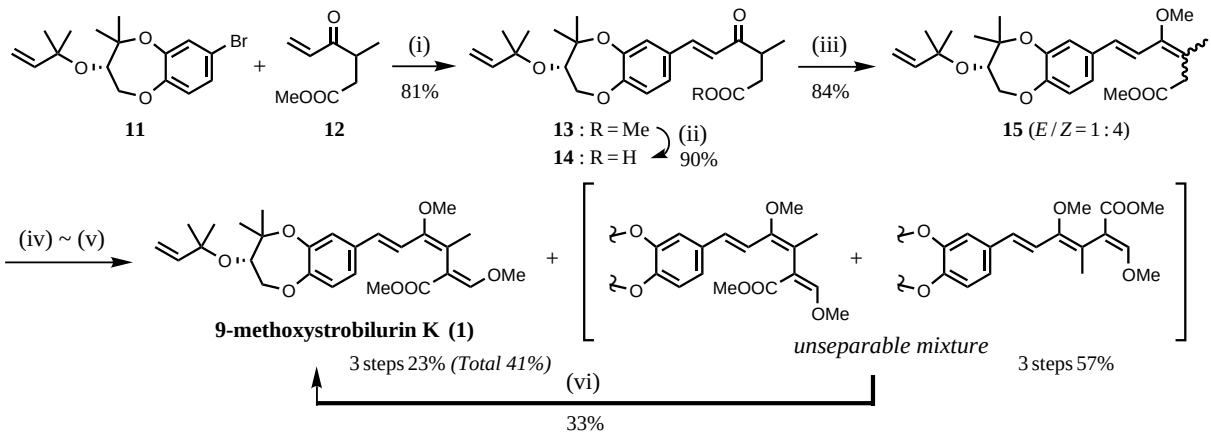
Heck reaction of the above 7-bromo-4,4-dimethyl-1,5-benzodioxepin **11** with 2 equivalents of vinyl ketone **12**[5] prepared from methyl itaconate was tried to obtain the corresponding α,β-unsaturated ketone **13** (Scheme 4). The reaction proceeded smoothly, and the desired coupling product **13** was prepared in high yield (81%). The conversion of enone **13** to the corresponding methyl enol ether **15** was then examined; however, the allylic and tertiary ether linkage was completely cleaved under the acidic condition employed for the synthesis of 9-methoxystrobilurin A.[5] On the other hand, *O*-alkyla-



Scheme 2. Synthesis of optically active 7-bromo-1,5-benzodioxepin-3-ol. (i) TBHP, $Ti(O^iPr)_4$, (+)-DIPT, CH_2Cl_2, –40°C; (ii) *p*-NO_2BzCl, Et_3N, 0°C; (iii) recryst. from Et_2O; (iv) NaOMe, MeOH, Et_2O, 0°C; (v) TsCl, DMAP, CH_2Cl_2, Et_3N, 0°C; (vi) K_2CO_3, 5-bromo-2-hydroxyacetophenone **3**, DMF, rt; (vii) mCPBA, benzene, 60°C; (viii) DIBAH, THF, –78°C; (ix) $SnCl_4$, Et_2O, 0°C; (x) KO^{t}Bu, THF, –15°C.



Scheme 3. Construction of hindered allylic tertiary-secondary ether linkage. (i) NaH, methyl 2-bromopropionate, THF, 0°C; (ii) NaHMDS, MeI, THF, −78°C; (iii) DIBAH, CH_2Cl_2, −78°C; (iv) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −60°C; (v) $Ph_3P{=}CH_2$, DMSO–THF, rt.



Scheme 4. Total synthesis of 9-methoxystrobilurin K. (i) 20 mol% $Pd(OAc)_2$, PPh_3, Et_3N, 100°C; (ii) aq. NaOH–MeOH, rt then HCl; (iii) KO^{t}Bu, MeI, DMF, −45 to −15°C; (iv) NaH, HCOOMe, rt; (v) K_2CO_3, Me_2SO_4, HCOOMe, rt; (vi) *hv* (λ: 365 nm), acetone–benzene, rt.

tion of enolate under several basic conditions (e.g. potassium bis(trimethylsilyl)amide-methyl triflate) gave complex mixtures. We assumed that an undesirable side reaction occurred after intramolecular lactonization of the enolic hydroxyl group. In order to prevent the intramolecular reaction, a stepwise double methylation was attempted. First, the ester **13** was hydrolyzed to afford the corresponding carboxylic acid **14**. A dianion was generated by treatment of the carboxylic acid **14** with potassium *tert*-butoxide in dimethylformamide at −45°C. By the addition of excess dimethyl sulfate to the dianion at −45 to −15°C, the double methylation proceeded successively and methyl enol ether **15** was obtained in good yield. Treatment of the enol ether **15** with sodium hydride–methyl formate, followed by the addition of dimethyl sulfate and potassium carbonate gave a mixture of the geometrical isomers of 9-methoxystrobilurin K (**1**). The mixture was isomerized twice by irradiation with an ultraviolet lamp (λ: 365 nm) and the desired **1** was successfully obtained (three steps total 41% yield) along with other isomerization-incomplete isomers.[7] The physical data of the synthetic 9-methoxystrobilurin K[8] were in good accordance with those of the natural product reported by Anke's group.[1]

Thus, the first asymmetric total synthesis of 9-methoxystrobilurin K was successfully achieved. It should be emphasized that the present methodology could be applied to the synthesis of various 9-methoxystrobilurin-type β-MOAs. Further investigation into the structure–activity relationships and development of a new and pharmacologically superior analogue are now in progress.

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7. The irradiation condition has not yet been optimized in terms of the light density.
8. Physical data of synthesized 9-methoxystrobilurin K (**1**): ^{1}H NMR (δ, 300 MHz, $CDCl_3$) 1.23 (s, 3H), 1.32 (s, 6H), 1.43 (s, 3H), 1.89 (s, 3H), 3.65 (s, 3H), 3.68 (dd, 1H, $J=3.3$, 7.9 Hz), 3.71 (s, 3H), 3.81 (s, 3H), 3.98 (dd, 1H, $J=7.7$, 12.3 Hz), 4.22 (dd, 1H, $J=3.3$, 12.3 Hz), 5.15 (d, 1H, $J=10.6$ Hz), 5.17 (d, 1H, $J=17.6$ Hz), 5.88 (dd, 1H, $J=10.8$, 17.6 Hz), 6.37 (d, 1H, $J=15.8$ Hz), 6.63 (d, 1H, $J=15.9$ Hz), 6.82 (d, 1H, $J=8.6$ Hz), 6.93 (dd, 1H, $J=2.0$, 8.8 Hz), 6.94 (d, 1H, $J=2.0$ Hz), 7.39 (s, 1H); ^{13}C NMR (δ, 75.5 MHz, $CDCl_3$) 16.3, 21.8, 26.3, 26.7, 28.1, 51.5, 59.5 61.8, 71.8, 75.5, 76.1, 81.6, 110.5, 114.4, 118.1, 120.1, 120.3, 121.5, 122.5, 126.8, 132.9, 143.5, 146.4, 150,6, 152.6, 159.4, 168.1; $[\alpha]_D^{24}=-8.87$ ($c=0.860$, $CHCl_3$); HRMS calcd for $C_{27}H_{36}O_7$ (M^+) 472.2461, found 472.2437.