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Total synthesis of myriocin

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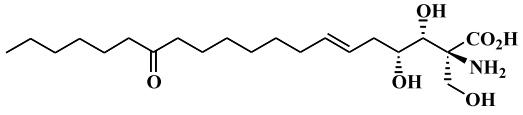
Abstract—A concise, stereocontrolled synthesis of myriocin was achieved. Key features involve diastereoselective oxazoline formation catalyzed by palladium(0), $MgBr_2$-promoted allylic stannane addition, and palladium(0)-catalyzed coupling of a vinyl iodide with an organozinc reagent.

Myriocin (Fig. 1, **1**)[1] was first isolated from the fermentation broth of the thermophilic fungi, *Myriococcus albomyces* and *Mycelia sterila* as an antifungal principle in 1972.[2] Recently, this potent immunosuppressant compound, shown to be 10∼100 times more potent than cyclosporin A, was also isolated from culture broth of *Isaria sinclairri* by a Fujita group.[3]

Myriocin has a quaternary center, three consecutive chiral centers, and *trans*-olefinic group in polar hydroxyl amine head group. A number of its synthetic approaches have been reported due to its novel structure and its interesting biological activity.[4]

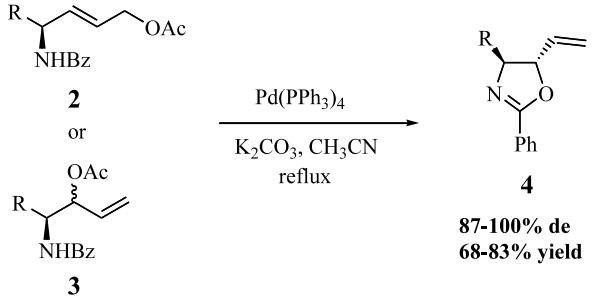
Recently, we have been investigating the stereoselective intramolecular cyclization of homoallyl benzamide via π-allylpalladium complex catalyzed by Pd(0) (Scheme 1).[5] In our laboratory, we have been exploring the utility of enantiopure oxazoline as chiral building blocks for the stereocontrolled synthesis of natural products. As part of this program, we developed a novel strategy for a concise synthesis of the myriocin. Herein we describe a novel asymmetric synthesis of myriocin that utilizes oxazoline as a chiral building block.

The synthesis proceeded as shown in Scheme 2. Oxidation of protected L-*N*-benzoyl-serinol **5** with Dess–Martin periodinane[5b,6] gave the corresponding aldehyde without racemization,[5b,6b] which was reacted with vinyl magnesium bromide in THF at 0°C to afford the allyl alcohol **6** as an ca. 1.1:1 mixture of *syn*/*anti* isomers (^{1}H NMR) in 70% yield.[7] Acetylation of hydroxyl group yielded the secondary allylic acetate. A standard oxazoline ring formation [$Pd(PPh_3)_4$, K_2CO_3, in CH_3CN] of the allylic acetate gave the desired *trans*-oxazoline **7** as a single isomer and in good yields (87%). Fluoride-induced removal of the silyl protection group, and the resulting alcohol was oxidized with ruthenium chloride[8] to afford the acid. The resulting carboxylic acid was converted to its methyl ester **8** with diazomethane in 68% yield for three steps. The hydroxymethylation of **8** with formaldehyde gave the *anti* hydroxymethylation[9] product **9** as the major isomer with high diastereoselectivity (20:1) and in modest yield (58%). Protection of **9** with MOMCl gave **10** in 90% yield.



Myriocin, 1

Figure 1.



Scheme 1.

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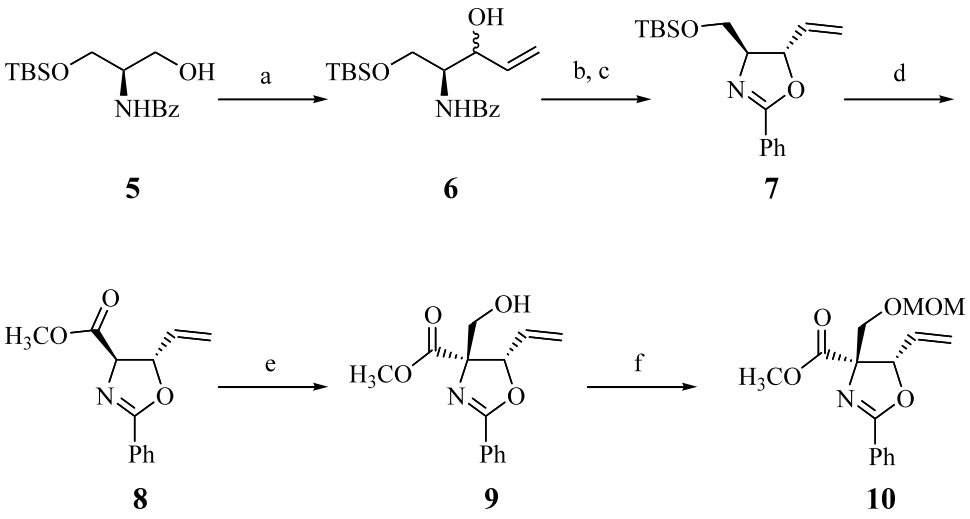
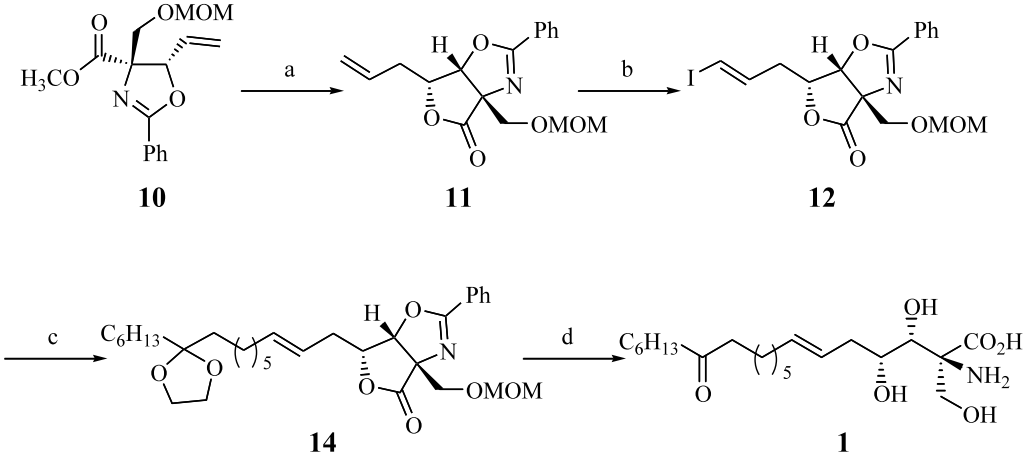


Scheme 2. *Reagents and conditions*: (a) (i) Dess–Martin periodinane, CH_2Cl_2; (ii) CH_2=CHMgBr, THF, 0°C, 70% for two steps; (b) Ac_2O, pyr., CH_2Cl_2, 95%; (c) $Pd(PPh_3)_4$, K_2CO_3, CH_3CN, 60°C, 87%; (d) (i) TBAF, THF, 99%; (ii) $RuCl_3$, $K_2S_2O_8$, 1 M NaOH, CH_3CN; (iii) CH_2N_2, Et_2O, 68% for two steps; (e) HCHO, KHMDS, HMPA, THF, −78°C, 58%; (f) MOMCl, Hünig base, CH_2Cl_2, 90%.

Ozonolysis of **10** gave the unstable aldehyde, which was treated with $MgBr_2{\cdot}OEt_2$ in CH_2Cl_2 at −20°C followed by allyl tributyltin[10] and warming to 25°C gave the allylating product **11** in 82% yield with >20:1 stereoselectivity.[11] Upon subjection of **11** to ozone and $CrCl_2$-mediated iodomethylenation,[12] vinyl iodide **12** was generated. Application of the Negishi protocol for palladium-catalyzed reaction of **12** with alkyl iodide **13**[13] provided the fully protected **14** in 71% yield.[14]

Removal of MOM group by 2N HCl in THF effected simultaneous hydrolysis of the ethylene ketal and oxazoline to give ketolactone. Finally, a base-promoted hydrolysis cleaved the lactone and the amide group, and subsequent neutralization with an acidic resin (Amberlite IRC-50) afforded myriocin. The spectroscopic (^1H and ^{13}C NMR) data for synthetic **1** were fully identical with those of synthetic myriocin,[4e] and the physical properties of **1** {mp 167–170°C, $[\alpha]_D^{25}$ of +4.0 (*c* 0.25, DMSO); lit.[4e] mp 165–168°C, $[\alpha]_D^{21}$ of +3.7 (*c* 0.26, DMSO)} showed good agreement with those reported (Scheme 3).

In summary, the asymmetric total synthesis of myriocin has been accomplished from L-serinol **5** with a high degree of stereocontrol. Our synthesis has demonstrated the versatility of oxazoline as a chiral building block. Work is in progress on the enantioselective synthesis of natural products using oxazoline as a chiral building block.



Scheme 3. *Reagents and conditions*: (a) (i) O_3, MeOH, −78°C, then DMS; (ii) $Bu_3SnCH_2CH{=}CH_2$, $MgBr_2$–Et_2O, CH_2Cl_2, 82% for two steps; (b) (i) O_3, MeOH, −78°C, then DMS; (ii) $CrCl_2$, CHI_3, THF, 63% for two steps; (c) **13**, *t*-BuLi, −78°C; then, $ZnCl_2$, −78°C ~ rt, $Pd(PPh_3)_4$, THF, 71%; (d) (i) 2N HCl, THF, 78%; (ii) 1N NaOH, reflux, 79%.

Acknowledgements

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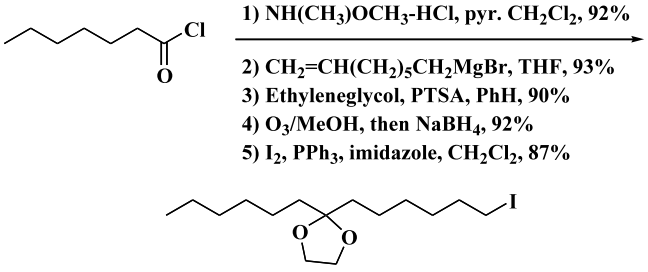
13. Preparation of alkyl iodide **13**:



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