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Stereoselective total synthesis of (+)-myriocin from D-mannose

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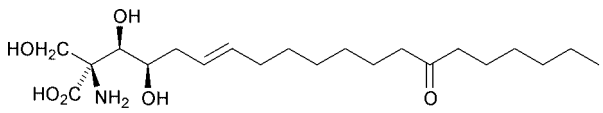
The stereoselective total synthesis of myriocin 1 from D-mannose is described; the carbon framework with three contiguous chiral centers including a tetra-substituted carbon with nitrogen was effectively constructed using Overman rearrangement as the key reaction.

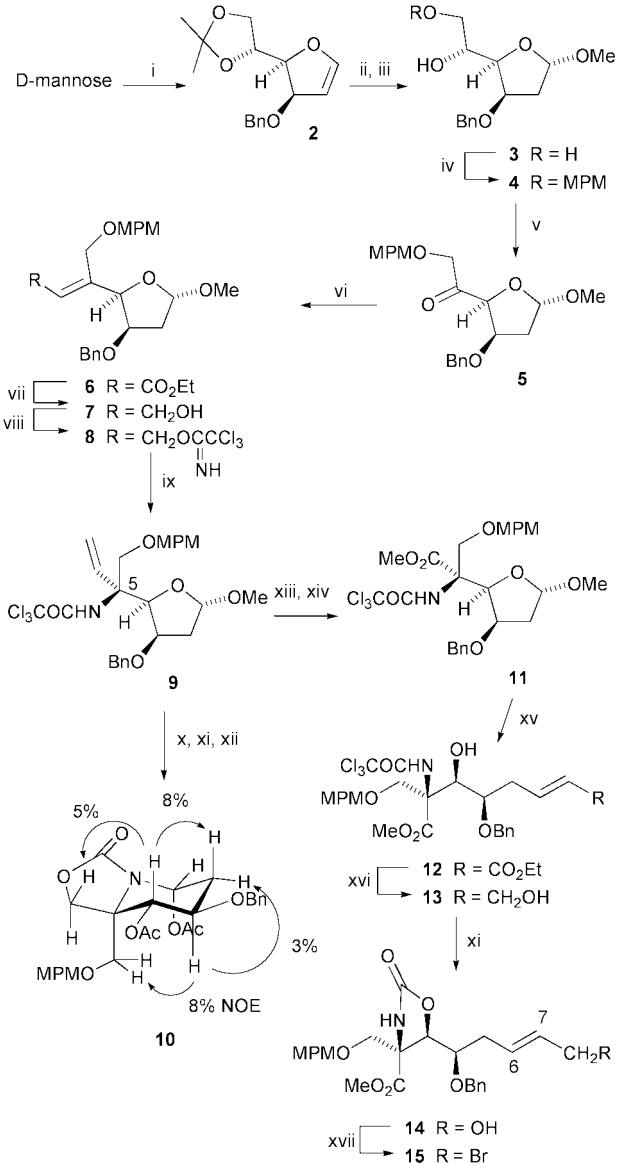
Myriocin[1] (also known as thermozymocidin[2] and ISP-I[3]) **1** (Fig. 1) is an α,α-disubstituted α-amino acid derivative isolated from the culture broth of *Myriococcus*,[1] *Mycelia*[2] and *Isalia*,[3] and reported to show antifungal[1,2] as well as immunosuppressive activities.[3] Its promising immunosuppressive properties[4] and unique structure have attracted much synthetic interest, and several total[5] and formal syntheses[6] of **1** have been reported to date. A structural feature of **1** is the unusual α,α-disubstituted α-amino acid framework with three contiguous chiral centers including a tetra-substituted carbon with nitrogen. For construction of the tetra-substituted carbon, previous syntheses adopted the Strecker synthesis,[6a] hydrocyanation of imines,[5a] the Darzen reaction,[5b,6c] Pd-catalyzed hydroxyamination of a vinyl epoxide,[6b] asymmetric aldol reaction of chiral dilactim ethers,[5c] and Lewis acid catalyzed cyclization of an epoxytrichloroacetimidate.[5d] Our previous success in total synthesis of lactacystin, a heterocyclic natural product with an α,α-disubstituted α-amino acid framework, from D-glucose[7] suggested that the rearrangement of an allylic trichloroacetimidate (Overman rearrangement)[8] derived from a furanose with proper functionalities would generate the tetra-substituted carbon stereoselectively. This methodology was also expected to provide an efficient approach to the highly functionalized part in **1**. Here we report the realization of this plan in a total synthesis of **1** from D-mannose.

The known glycal **2**[9] derived from D-mannose in three steps (80% overall yield) (Scheme 1) was converted into α-methyl furanoside **3**† by oxymercuration-reduction followed by acid treatment in 81% yield. The primary hydroxy group in **3** was selectively *p*-methoxybenzylated[10] to afford **4** (95% yield). Swern oxidation of **4** generated ketone **5**, which was submitted to the Horner–Emmons reaction to provide an inseparable mixture of (*E*)-alkene **6** and its (*Z*)-isomer (15 : 1) in 90% yield from **4**. DIBAL-H reduction of the mixture followed by chromatographic separation afforded geometrically pure (*E*)-allyl alcohol **7** and its (*Z*)-isomer in 93 and 6% isolated yields, respectively. Compound **7** was converted into trichloroacetimidate **8**, which, without isolation, was subjected to Overman rearrangement. Thus, a xylene solution of **8** was heated at 140 °C in the presence of K_2CO_3[11] in a sealed tube for 72 h to provide an inseparable mixture of rearranged products **9** and its C(5) epimer in a ratio of 7 : 1 (determined with 300 MHz ^{1}H NMR) in 90% yield from **7**.‡ The newly formed stereochemistry in **9** was determined to be *R* by NOE experiments



myriocin **1**

Fig. 1



Scheme 1 Bn = $-CH_2Ph$, MPM = $-CH_2C_6H_4$-*p*-OMe. *Reagents and conditions*: i see ref. 9; ii $Hg(OAc)_2$, $THF–H_2O$, room temp., then KI, $NaBH_4$, $THF–H_2O$, 0 °C; iii $AcOH–H_2O$ (3 : 2), room temp., then AcCl, MeOH, 0 °C; iv *n*-Bu_2SnO, toluene, reflux, then MPMCl, CsF, DMF, 70 °C; v $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, then Et_3N, 0 °C; vi $(MeO)_2P(O)CH_2CO_2Me$, LiBr, DBU, CH_3CN, −40 °C; vii DIBAL-H, toluene, −78 °C; viii Cl_3CCN, DBU, CH_2Cl_2, 0 °C; ix K_2CO_3, *o*-xylene, 140 °C; x O_3, MeOH, −78 °C, then $NaBH_4$, 0 °C; xi DBU, CH_2Cl_2, room temp.; xii 1 M aqueous HCl–THF (1 : 1), room temp., then Ac_2O, DMAP, pyridine, room temp.; xiii O_3, CH_2Cl_2, −78 °C, then Me_2S; xiv $NaClO_2$, NaH_2PO_4, $HOSO_2NH_2$, t-BuOH–H_2O, room temp., then Me_3SiCHN_2, MeOH, room temp.; xv 4 M aqueous HCl–THF (1 : 3), room temp., then $Ph_3P{=}CHCO_2Et$, toluene, room temp.; xvi DIBAL-H, THF–toluene, −15 °C; xvii MsCl, Et_3N, CH_2Cl_2, 0 °C, then LiBr, acetone, room temp.

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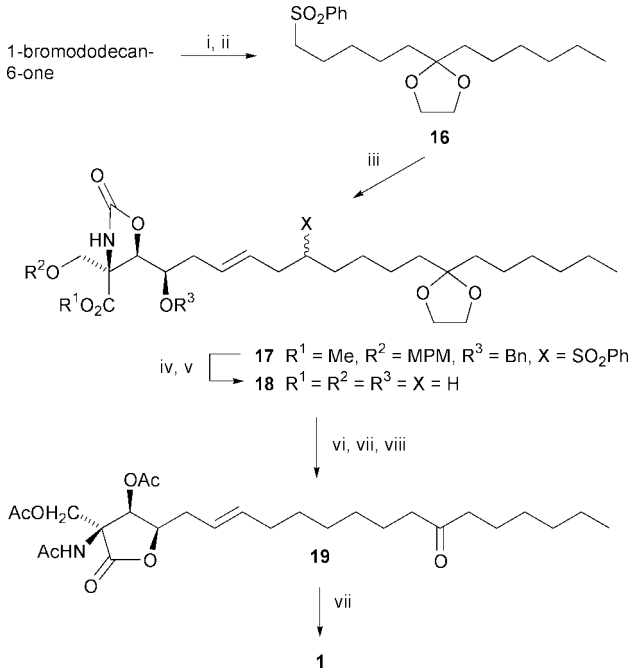
of bicyclic carbamate **10** derived from **9** in four steps (46% overall yield). Ozonolysis of the mixture of **9** and its C(5) epimer (Me_2S work-up) followed by oxidation and esterification, and subsequent chromatographic separation afforded **11** in a diastereochemically pure form (82% yield from the mixture of **9** and its epimer). Acid hydrolysis of **11** provided an anomeric mixture of lactol, which was then reacted with stabilized ylide to give (*E*)-alkene **12** as a single isomer in 71% yield. When compound **12** was treated with DIBAL-H in THF–toluene at −15 °C, only the α,β-unsaturated ester function was reduced to afford allyl alcohol **13** (75% yield), which was transformed into cyclic carbamate **14** in 86% yield. The observed coupling constant in **14** ($J_{6,7}$ = 15.6 Hz) clearly supported the (*E*)-geometry of the double bond. The primary hydroxy group in **14** was converted into corresponding bromide to furnish the highly functionalized moiety, allyl bromide **15** in 92% yield.

The hydrophobic part of myriocin, sulfone **16**, was prepared by treatment of 1-bromododecan-6-one§ with $PhSO_2Na$, followed by ketalization (82% yield) (Scheme 2). Sulfone **16** was lithiated with *n*-BuLi, and then reacted with the allyl bromide **15** to afford the coupling product **17** in 80% yield. Saponification of **17** and subsequent Birch reduction gave crude carboxylic acid **18**. Removal of the ketal group and carbamate function in **18** followed by conventional acetylation provided the known γ-lactone **19** {$[\alpha]_D^{20}$ +54 (*c* 0.7, $CHCl_3$); lit.[2a] $[\alpha]_D^{24}$ +57 (*c* 1.0, $CHCl_3$)} in 47% yield from **17**. The spectral data for **19** were identical in all respects to those kindly provided by Professor Hatakeyama.[5d] Finally, according to the precedent,[5d] saponification of **19** followed by neutralization with weak acidic resin (Amberlite IRC-76, H^+ form) furnished (+)-myriocin **1** in 82% yield. The spectroscopic (^1H and ^{13}C NMR) data for synthetic **1** were fully identical with those of natural myriocin, and the physical properties of **1** {mp 168–170 °C, $[\alpha]_D^{23}$ +5.1 (*c* 0.17, MeOH); lit.[3] mp 169–171 °C, $[\alpha]_D$ +4.8 (*c* 0.286, MeOH)} showed good agreement with those reported for the natural product.



Scheme 2 *Reagents and conditions*: i $PhSO_2Na$, DMF, room temp.; ii $(TMSOCH_2)_2$, TMSOTf, CH_2Cl_2, room temp.; iii *n*-BuLi, THF, −78 °C, then **15**, −78–0 °C; iv LiOH, H_2O–MeOH, room temp.; v Li, liq. NH_3, THF, −78 °C; vi 4 M aqueous HCl–THF (1:1), room temp.; vii 10% aqueous NaOH–MeOH (1:3), reflux; viii Ac_2O, pyridine, room temp.

This synthesis established an alternative and efficient pathway to myriocin **1** (24 linear steps and 4.9% overall yield from D-mannose), which showed almost the same efficiency as previous excellent approaches (2.4–5.1% overall yield).[5b–d] In addition, this work proved that the novel methodology, Overman rearrangement on a furanose scaffold,[7] is quite effective for the chiral synthesis of both acyclic and heterocyclic natural products possessing highly functionalized α,α-disubstituted α-amino acid structures. Additional applications of this methodology in natural product synthesis are now warranted and will be reported in due course.

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Notes and references

† All new compounds described in this paper were fully characterized by 300 MHz ^1H NMR, 75 MHz ^{13}C NMR, IR and mass spectrometric and/or elemental analyses.

‡ Overman rearrangement of an imidate derived from (*Z*)-allyl alcohol afforded **9** and its C(5) epimer in a ratio of 1:5 in 70% yield.

§ 1-Bromododecan-6-one was synthesized by essentially the same procedure reported by Just and Payette [see ref. 6(*a*)]. In place of cyclooctanone, cyclohexanone was employed as the starting material.

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