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Catalytic asymmetric synthesis of key intermediate for scytophycin C

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ABSTRACT

We achieved a formal total synthesis of scytophycin C. The synthesis demonstrates the utility of the catalytic asymmetric direct thioamide-aldol reaction for the preparation of polyketide structures, and was accomplished via diastereoselective allylation, and allylative cyclization as other key transformations. The reported process accesses Miyashita's key fragment corresponding to the C7–C18 framework in fewer steps (14 steps) than in previously reported syntheses.

Introduction

Scytophycins are cytotoxic and antifungal 22-membered macrolides of marine origin discovered from the terrestrial blue-green alga *Scytonema pseudohofmanni*. Scytophycin C (**1**) reported by Moore and coworkers in 1986 particularly exhibits outstanding antiproliferative activity against solid tumor cell lines.[1] Both Paterson and Miyashita[2–5] independently reported the total syntheses of scytophycin C, which has intriguing biologic activity and a complex structural nature. In Miyashita's synthesis, C7–C18 fragment **2** is a key intermediate from which the carbon framework was constructed via Mukaiyama aldol reaction and Horner–Wadsworth–Emmons reaction. The fragment **2** was also prepared in the synthetic study of the same natural product reported by Yadav et al.[3a] Both syntheses of **2** commence with the chiral starting material and require relatively long reaction sequences (18 steps for Miyashita's synthesis and 17 steps for Yadav's synthesis), which prompted us to develop an alternative route using a catalytic asymmetric aldol strategy studied extensively in our group to shorten the scheme (Fig. 1, bottom). In this Letter, we describe a new synthesis of key intermediate **2** for scytophycin C using the catalytic asymmetric thioamide-aldol reaction to furnish the requisite stereocontrol.

Results and discussion

The catalytic asymmetric direct thioamide-aldol reaction shown in Scheme 1 was previously reported by our group, and is characterized by the selective deprotonation of thioamide over more acidic aldehyde rationalized by the activation by the soft Lewis acidic copper complex with a bidentate phosphine ligand (Ph-BPE) and hard Brønsted base precursor (chromanol derivative, **7**). This reaction is advantageous due to its atom-economical proton transfer process without the need for preactivation of a prenucleophile by a structural modification (i.e., formation of silylenol ether), and the feasibility of the thioamide substructure transformation into variety of functionalities. The reaction was effective for the enantio- and diastereoselective synthesis of natural products and clinical drugs such as thuggacin,[6] (−)-membrenones,[7] caprazamycin B,[8] and atorvastatin.[9] The present formal total synthesis of scytophycin C started with the catalytic asymmetric thioamide-aldol reaction using **5** and **6** as the substrates (Scheme 1). Although this combination of substrates was reported in our synthesis of thuggacin,[6] the enantioselectivity was improved from 93% ee to 95% ee in the present case.

Next, the secondary hydroxyl group of thioamide-aldol adduct **8** was protected as TBS ether **9**, followed by conversion of the thioamide moiety into a primary alcohol to afford **10** in good yield (Scheme 2). Then, the hydroxy group was converted to PMB ether **11**, from which the TBDPS group was removed to give the substrate for the catalytic stereoselective allylation reaction (**12**) developed by Krische and coworkers.[10] The catalyst generated in situ with $[Ir(cod)Cl]_2$, (*S*)-Cl-MeO-BIPHEP ((*S*)-(−)-5,5′-dichloro-6,6′-dimethoxy-2,2′-bis(diphenylphosphino)-1,1′-biphenyl), Cs_2CO_3,

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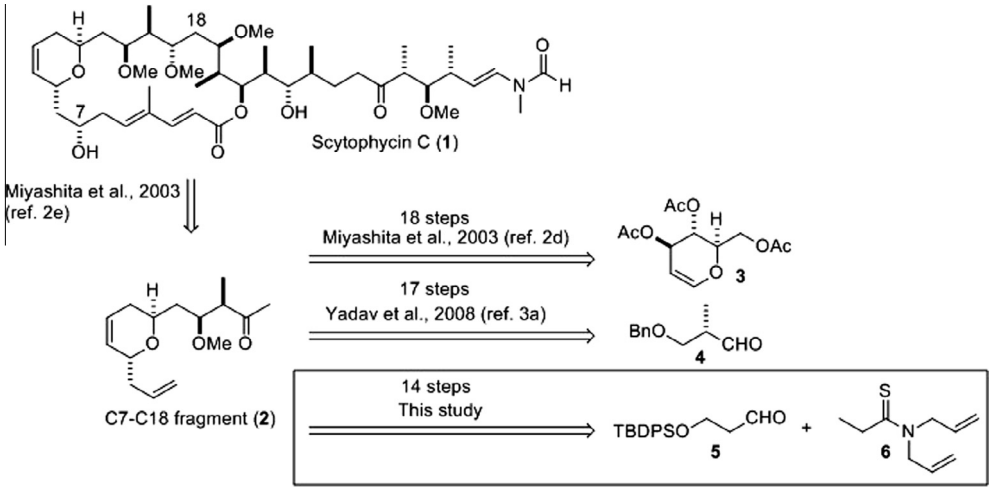
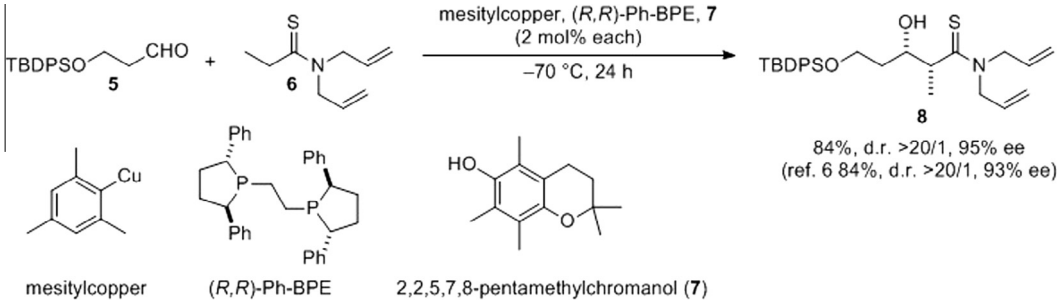
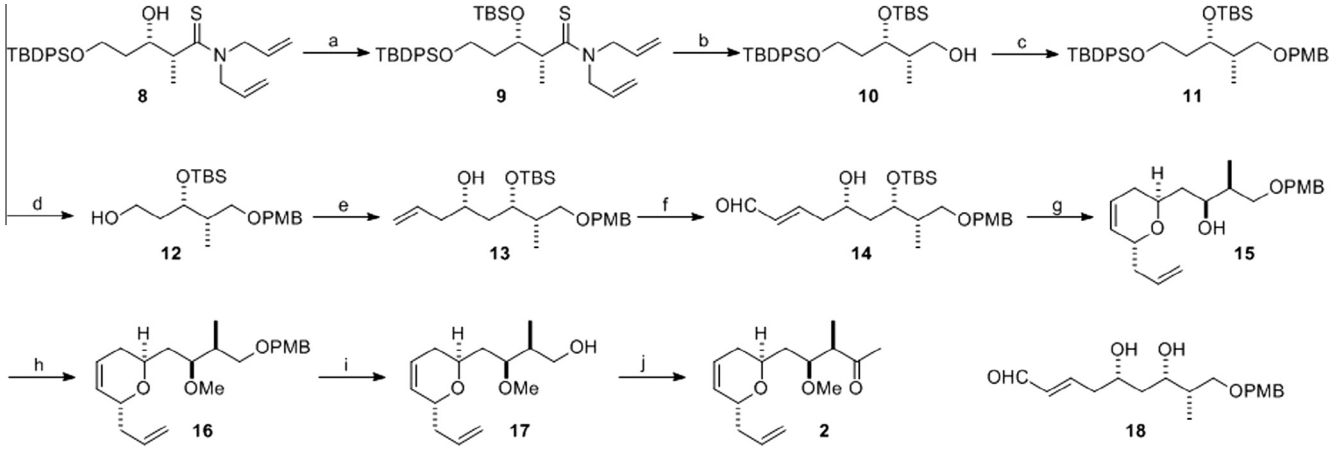


Figure 1. Scytophycin C; structure and strategies toward its formal total synthesis.



Scheme 1. Catalytic asymmetric direct thioamide-aldol reaction of **5** and **6**.



Scheme 2. Formal total synthesis of scytophycin C; synthesis of the Miyashita's key intermediate **2**. Reagents and conditions: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C–rt, 3 h, 98%; (b) (1) MeOTf, Et_2O, 0 °C–rt, 5.5 h, then $LiAlH(Ot\text{-}Bu)_3$, 4 h, −78 °C; (2) $NaBH_4$, EtOH, −20 °C, 3 h, 78% (2 steps); (c) 4-methoxybenzyl-2,2,2-trichloroacetimidate, $La(OTf)_3$, toluene, rt, 3 h, 96%; (d) NH_4F, MeOH, 50 °C, 4 h, 82%; (e) allyl acetate, $[Ir(cod)Cl]_2$, (*S*)-Cl-MeO-BIPHEP, Cs_2CO_3, 4-Cl-3-NO_2-BzCl, THF, 100 °C, 26 h, 80%, dr >20:1; (f) Hoveyda–Grubbs II, acrolein, CH_2Cl_2, rt, 30 min, 96%; (g) allyltrimethylsilane, I_2, CH_2Cl_2, 0 °C–rt, 1 h, then MeOH, rt, 3 h, 67%; (h) NaH, MeI, 15-crown-5, THF, 0 °C–rt, 20 h, 90%; (i) DDQ, CH_2Cl_2, H_2O, rt, 30 min, 96%; (j) (1) IBX, AcOEt, 80 °C, 2.5 h; (2) MeLi, THF, −78 °C, 30 min; (3) DMP, $NaHCO_3$, CH_2Cl_2, rt, 30 min, 71% (3 steps).

and 4-Cl-3-NO_2-BzCl, which was reported in Krische and coworkers' synthesis of premisakinolide A,[10b] was effective for the present system to afford homoallylic alcohol **13** as the sole product in 80% yield. The subsequent cross metathesis with acrolein proceeded uneventfully in the presence of a Hoveyda–Grubbs 2nd generation catalyst to afford the enal **14**.

In the first synthetic plan, the subsequent allylative cyclization to construct the dihydropyran (DHP) ring system was conducted according to Yadav's protocol with slight modification[3a,11] using a catalytic amount of $InBr_3$ (10 mol %) and allyltrimethylsilane with diol **18** as the substrate. In this condition, one of the hydroxy groups takes part in the reaction with the enal moiety activated by the catalyst to generate an oxocarbenium intermediate that is attacked by allylsilane to afford DHP systems accompanied by allylation. Although the Bn congener (instead of PMB ether) was successfully cyclized in his report, the conditions did not work in our system, while acetalized byproducts were produced between the 1,3-diol and the formyl group in an intermolecular manner. Changing the protecting group to TBDPS ether gave almost the same results without any trace amount of

the desired DHP product. To avoid acetalization, the logical and straightforward solution was protection of either of the hydroxy groups; TBS ether **14** was examined for the cyclization reaction. After the screening, the I_2-mediated protocol of Yadav[12] was effective with the allylative cyclization occurring smoothly, and TBS ether was partially removed in the DHP product detected by TLC. Interestingly, addition of MeOH produced the completely desilylated product **15**, probably due to the generation of HI in situ, which plays a role in the desilylation.[13] Stereochemistry was confirmed by NOE between H9 and H14 protons (scytophycin numbering).

The remaining transformation was straightforward; the secondary hydroxy group was masked by a methyl group, followed by deprotection of the primary alcohol, oxidation to aldehyde, methylation, and oxidation to complete the synthesis of Miyashita's C7–C18 fragment (**2**). The structure, including the stereochemistry, was unequivocally confirmed by ^1H and ^{13}C NMR, and optical rotation.[2d]

Conclusion

In conclusion, a formal total synthesis of scytophycin C was achieved via catalytic asymmetric direct thioamide-aldol reaction followed by diastereoselective allylation, and allylative cyclization. With the present process, Miyashita's key intermediate **2** is accessible in fewer steps (14 steps) compared to the precedents. Synthetic studies to expand the scope of applicability of the enantioselective process for efficient supply of precious natural products are under way.

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Supplementary data

Supplementary data (characterization of new data, and experimental procedures) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2015.12.051.

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