Organic LETTERS

Letter

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Total Synthesis of Nannocystin A

Zhantao Yang,[†,‡] Xiaolong Xu,[†] Chun-Hua Yang,[†,‡] Yunfeng Tian,[†] Xinyi Chen,[†] Lihui Lian,[†] Wenwei Pan,[†] Xuncheng Su,[§] Weicheng Zhang,[*,†] and Yue Chen[*,†]

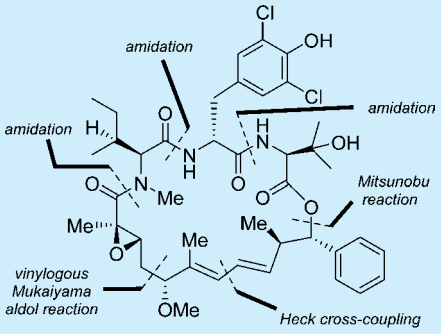
[†]State Key Laboratory of Medicinal Chemical Biology, College of Pharmacy, and Tianjin Key Laboratory of Molecular Drug Research, Nankai University, Tianjin 300353, P. R. China

[‡]College of Chemistry and Chemical Engineering, Anyang Normal University, Anyang 455000, P. R. China

[§]State Key Laboratory of Elemento-organic Chemistry, Nankai University, Tianjin 300071, P. R. China

Supporting Information

ABSTRACT: Nannocystin A is a 21-membered cyclodepsipeptide showing remarkable anticancer properties. Described is the total synthesis of nannocystin A, which features an asymmetric vinylogous Mukaiyama aldol reaction for efficient assembly of the penultimate open-chain precursor and a pivotal intramolecular Heck cross-coupling for the final macrocyclization.



Secondary metabolites from microorganisms constitute a large reservoir of valuable chemotherapeutic agents such as antibiotics and anticancer drugs.[1] Recently, a class of cyclic depsipeptides named nannocystins were isolated independently by two research teams through cultivation of the myxobacterial strains *Nannocystis* sp. ST201196 and *Nannocystis* sp. MB1016, respectively.[2,3] Nannocystin A (**1**) features a 21-membered polyketide−tripeptide macrocycle bearing a novel α,β-epoxy amide substructure, along with nine chiral centers and two continuous *E*-configured alkenes (Figure 1). Brönstrup et al. showed that **1** displayed potent antiproliferative activities toward 14 cancer cell lines at low nanomolar levels, and it retained excellent inhibitory effect against the drug-resistant cell line MDA-A1 (IC_{50} 12 nM) compared to the related cell line MDA-MB231 (IC_{50} 6.5 nM).[2] In contrast, the reference drug docetaxel suffered a considerable drop (nearly 2000-fold) in activity against MDA-A1 (IC_{50} 570 nM) with respect to MDA-MB231 (IC_{50} 0.3 nM). These results demonstrated the potential of **1** as a novel lead compound for the development of anticancer drugs.

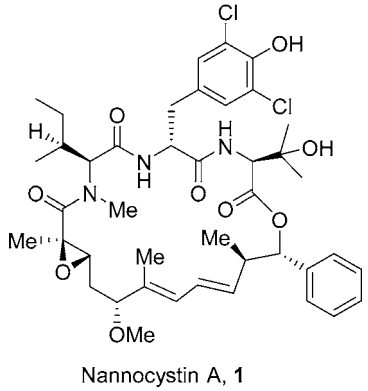


Figure 1. Structure of nannocystin A (**1**).

Parallel to Brönstrup's research,[2] Hoepfner et al. found that **1** displayed differential inhibitive properties (IC_{50} values ranging from 0.5 μM to 5 nM) against 472 cancer cell lines.[3] Different from some known actin-binding cyclodepsipeptides such as chondramide C,[4] jasplakinolide,[5] seragamide A,[6] and miuraenamide,[7] the primary target of **1** was identified to be the eukaryotic translation elongation factor (eEF1α).

To date, only preliminary studies have been carried out on their mechanism of action and pharmaceutical applications. Moreover, the issue regarding whether the epoxide moiety in **1** is a critical component of the pharmacophore is still unknown.[2,3] Hence, there is an urgent need to explore the chemical synthesis of nannocystin A, the leading species from the natural nannocystin congeners. More important, systematic structure variations will ensue to gain insight into key structural elements that account for its high antiproliferative properties and aid in developing more potent eEF1α-targeting analogues. As the first step toward this aim, we report herein the total synthesis of nannocystin A (**1**) in an efficient route.[8]

Retrosynthetically, the steric environment of the 6*E*,8*E*-diene from the southern polyketide segment is less congested than

Received: September 10, 2016
Published: October 13, 2016

DOI: 10.1021/acs.orglett.6b02729
Org. Lett. 2016, 18, 5768−5770

that of the northern tripeptide segment in **1** (Figure 2). Accordingly, the C7−C8 bond tethering the two *E*-alkenes is

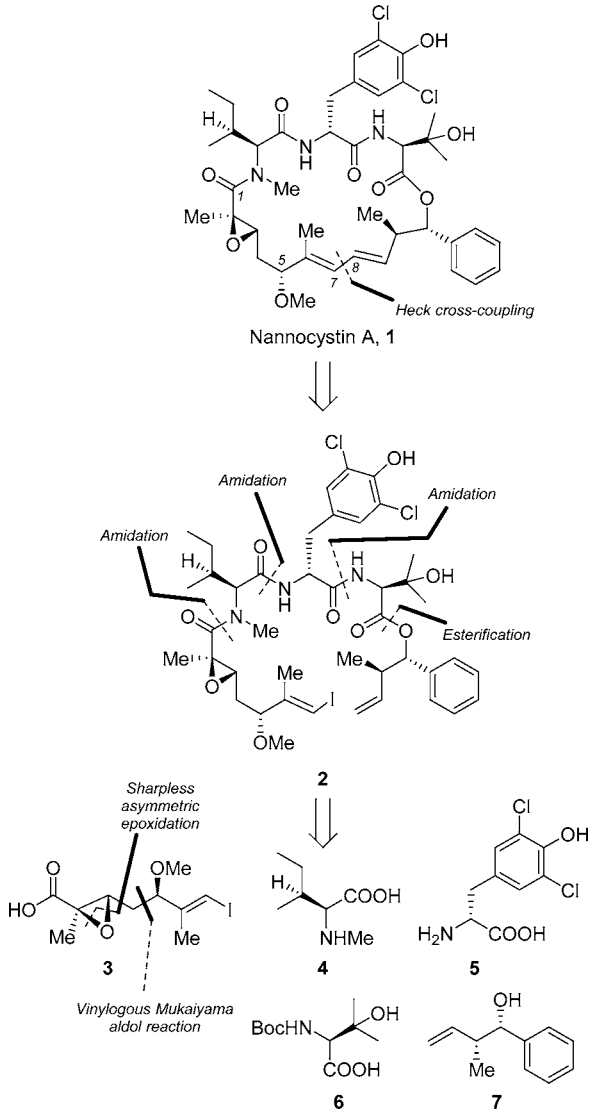
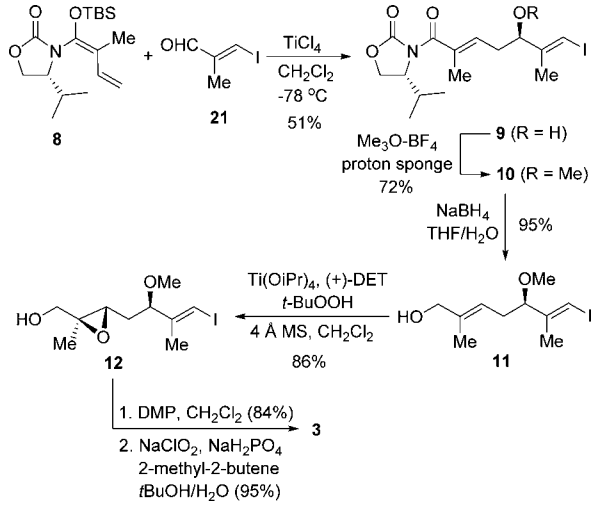


Figure 2. Retrosynthetic analysis of nannocystin A (**1**).

our preferred site for macrocyclization. In the synthetic direction, a ring-closing intramolecular *E*-selective Heck cross-coupling was envisioned to fulfill the task.[9,10] Further disconnection of the open-chain precursor **2** gave rise to five building blocks, including the vinyl iodide bearing epoxy acid **3**, *N*-methyl-L-isoleucine **4**, 3,5-dichloro-D-tyrosine **5**, *N*-Boc-3-hydroxy-D-valine **6**, and homoallylic alcohol **7**. The synthesis of **3** called for an asymmetric vinylogous Mukaiyama aldol reaction[11] to construct the carbon skeleton and a Sharpless asymmetric epoxidation[12] to install the chiral epoxide group. The other fragments **4**—**7** were easily accessible according to the literature.[13]

The forward synthesis commenced with the preparation of **3** (Scheme 1). Following Kobayashi's protocol,[11] **8** was subjected to $TiCl_4$-mediated vinylogous Mukaiyama aldol condensation with (*E*)-3-iodo-2-methylacrylaldehyde (**21**). Efficient control of stereoselectivity (dr >10:1) was observed in the reaction, with the predominant isomer **9** isolated in 51% yield after silica gel flash chromatography.[14] After methylation and reduction,

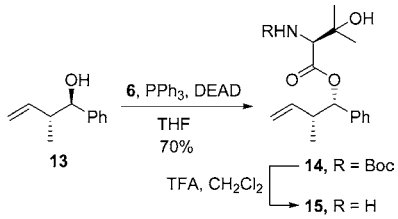
Scheme 1. Synthesis of the Polyketide Fragment 3



the allylic alcohol **11** was converted to **12** via Sharpless asymmetric epoxidation with excellent stereoselectivity (dr >10:1). Formation of **3** was secured through stepwise oxidations.

Next, union of *N*-Boc-3-hydroxy-D-valine (**6**) and homoallylic alcohol **7** was pursued. Unfortunately, condensation of **6** and **7** under standard esterification conditions (EDC/DMAP, DIC/DMAP)[15] failed to give the desired product, presumably due to steric hindrance. Hence, we turned our attention to the Mitsunobu reaction,[16] which required the use of *anti*-homoallylic alcohol **13**[17] as the coupling partner (Scheme 2).

Scheme 2. Synthesis of 3-Hydroxy-D-valine Homoallylic Ester (15) TFA Salt



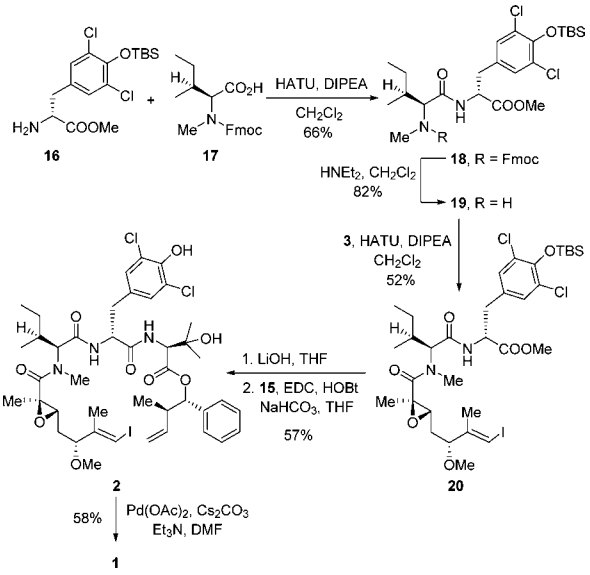
To our delight, Mitsunobu reaction between **13** and **6** proceeded smoothly to give **14** in 70% yield. The Boc group of **14** was then removed with TFA to liberate the amine moiety ready to be coupled to the tyrosine carboxyl group.

With the key building blocks **3** and **15** in hand, the next stage was the preparation of the Heck precursor **2** via amide coupling reactions. Incorporation of **3** into the tripeptide derivative turned out to be a nontrivial task. The major challenge was the development of a suitable peptide coupling sequence that is compatible with the potentially reactive epoxy group. By testing different coupling strategies, we eventually found a satisfactory approach to **2** as shown in Scheme 3.

Starting from TBS-protected tyrosine derivative **16**, which was prepared from commercially available D-tyrosine in three steps,[18] coupling of **16** and *N*-methyl-*N*-Fmoc-L-isoleucine (**17**) followed by Fmoc deprotection produced the dipeptide **19**. A second amide coupling was accomplished in 52% yield under standard condensation conditions using HATU and DIPEA. Treatment of the resulting **20** with lithium hydroxide led to the hydrolysis of both the methyl ester and the TBS

DOI: 10.1021/acs.orglett.6b02729
Org. Lett. 2016, 18, 5768−5770

Scheme 3. Completion of the Total Synthesis of 1



group, which was accompanied by a third amide condensation with **15** to afford the penultimate open-chain intermediate **2**. Finally, intramolecular Heck macrocyclization proceeded smoothly to give the product **1** in 58% yield. It was noteworthy that the labile epoxy group was well tolerated in the Heck macrocyclization conditions. The spectra (^{1}H NMR, ^{13}C NMR, HRMS) of our synthetic **1** are in good agreement with the literature data,[3] thus completing the total synthesis of nannocystin A.

In summary, total synthesis of nannocystin A **1** was achieved from readily available starting materials in 4.1% overall yield and 10 steps for the longest linear sequence. On the basis of the established route, synthesis and biological evaluation of structural analogues of **1** are currently in progress and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02729.

Detailed experimental procedures, spectroscopic data, and ^{1}H and ^{13}C NMR spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: zhangweicheng@nankai.edu.cn.
*E-mail: yuechen@nankai.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was kindly supported by the National Natural Science Foundation of China (NNSFC) (No. 81573282), Program for New Century Excellent Talents in University to Y.C., and Hundred Young Academic Leaders Program of Nankai University to Y.C.

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DOI: 10.1021/acs.orglett.6b02729
Org. Lett. 2016, 18, 5768−5770