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Rong Liu, Mengwei Xia, Yanhui Zhang, Shaomin Fu, Bo Liu

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Graphical Abstract

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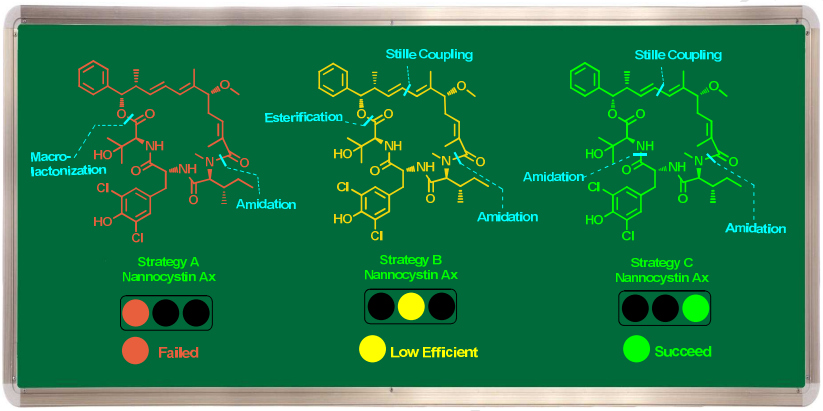
Rong Liu [a], Mengwei Xia [a], Yanhui Zhang [a], Shaomin Fu [a]*, Bo Liu [a, b]*,
[a] *College of Chemistry, Sichuan University, Chengdu 610064, PR China*
[b] *State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, PR China*



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The Journey of Total Synthesis Toward Nannocystin Ax

Rong Liu [a], Mengwei Xia [a], Yanhui Zhang [a], Shaomin Fu [a*], Bo Liu [a,b]*,

[a]*Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, PR China*
[b]*State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, PR China*

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ABSTRACT

Herein we describe present the detail on our full investigations that led to the achievement of the total synthesis of nannocystin Ax, a 21-membered macrocyclic natural product composing of a tripeptide fragment and a polyketide fragment, which featured in 8 longest linear steps in with 13.9 % total overall yield. The key synthetic strategy relied on the late-stage stille coupling for the macrolactonization to construct the 21-membered ring, while direct connection between the tripeptide fragment and the polyketide fragment failed. ^{1}H NMR experiments reveal that nannocystin Ax should exist as conformational mixtures in deuterated solvents.

1. Introduction

Natural products had provided unlimited sources for the development of new drugs [1]. Nearly one half of small molecule drugs are natural products or their derivatives. In 2015, Brönstrup`s group and Hoepfiner`s group independently identified natural compounds of nannocystin family [2], which were isolated from the fermentation of *Myxobacterial genus, Nannocystis sp*. Structurally, nannocystins feature a novel 21-membered macro-cyclic scaffold with more than 7 stereocenters containing tripeptide and polyketide (**Scheme 1**). Biological study revealed their outstanding cytotoxicity to numerous cancer cell lines, such as HCT116 cell lines (2.5-10 nM). In addition, nannocystin A exhibited a strong antifungal effect, inhibiting the growth of *C. albicans* (IC_{50} = 73 nM). Moreover, it was found that the activity target of nannocystins is EF-1α of eukaryotes, which is identical to that of a drug candidate, dehydrodidemnin B, although nannocystins show much better cytotoxicity. Undoubtedly, the novel molecular structures and remarkable bioactivities of nannocystin family have stimulated numerous passion and endeavor among synthetic chemists. To construct the challenging 21-membered macrocycle of this natural family, Wang 's group [3b] and Fürstner ' s group [3g] favored the ring-closing metathesis (RCM) strategy, while Ye 's group [3a] and Chen 's group [3c] resorted to the Suzuki coupling and Heck reaction to fulfill this transformation, respectively. In addition, our group utilized the Stille coupling in this key cyclization process, [3d] and He's group, as well as Kalesse`s group, selected amidation as the final step for macrocyclization[3e,3f]. Herein, we present our efforts toward total synthesis of nannocystin Ax in detail.

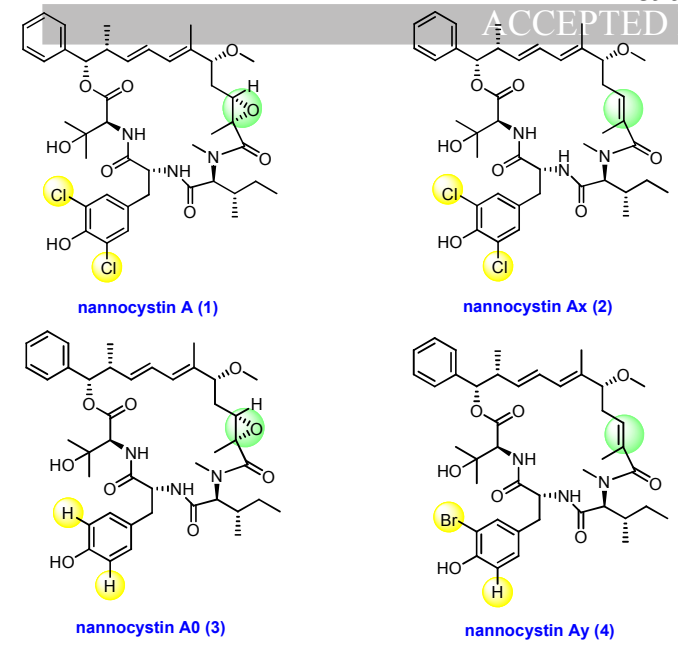
2. Results and Disccusions

2.1 Total Synthesis of Nannocystin Ax - Strategy A

Considering macro-lactonization is a powerful method to forge macrolide,[4] we made the first retrosynthetic analysis via disconnecting the tripeptide moiety and polyketide moiety in nannocystin Ax to get compounds **5** and **6**（**Scheme 2**）Then, the polyketide **5** can be formed by asymmetric Mukaiyama aldol reaction between unsaturated aldehyde **7** and vinylketene silyl *N, O*-acetal **8** [6]. The tripeptide **6** can be constructed via double amidation from three known compounds [5].

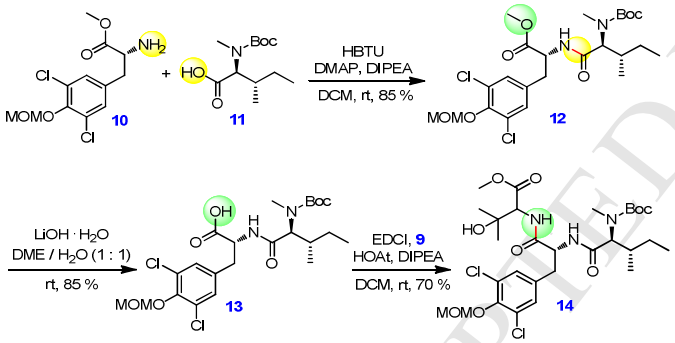
*[a]*Key Laboratory of Green Chemistry & Technology of Ministry of Education, College of Chemistry, Sichuan University, Chengdu 610064, PR China*
[b]*State Key Laboratory of Natural Medicines, China Pharmaceutical University, Nanjing 210009, PR China*

e-mail: *chembliu@scu.edu.cn*; *fsm09@aliyun.com*; *http://chem.scu.edu.cn./liubo/*; Fax:*+86 28 85413712*; Tel: *+86 28 85413712*



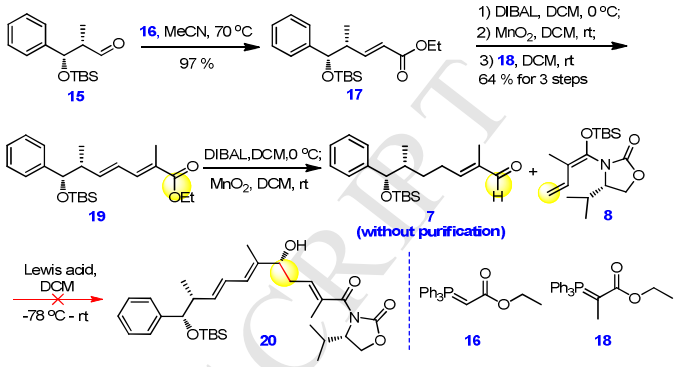
Scheme 1 Structures of selected nannocystins

According to the above retrosynthetic analysis, we geared up for the tripeptide **6** at first. The dipeptide **12** can be obtained in the presence of HBTU, DMAP and DIPEA. Hydrolysis of **12** with LiOH•H_2O afforded **13** in 85% yield. Subsequent amidation with **9** resulted in the tripeptide **14** in 70% yield. (**Scheme 3**).



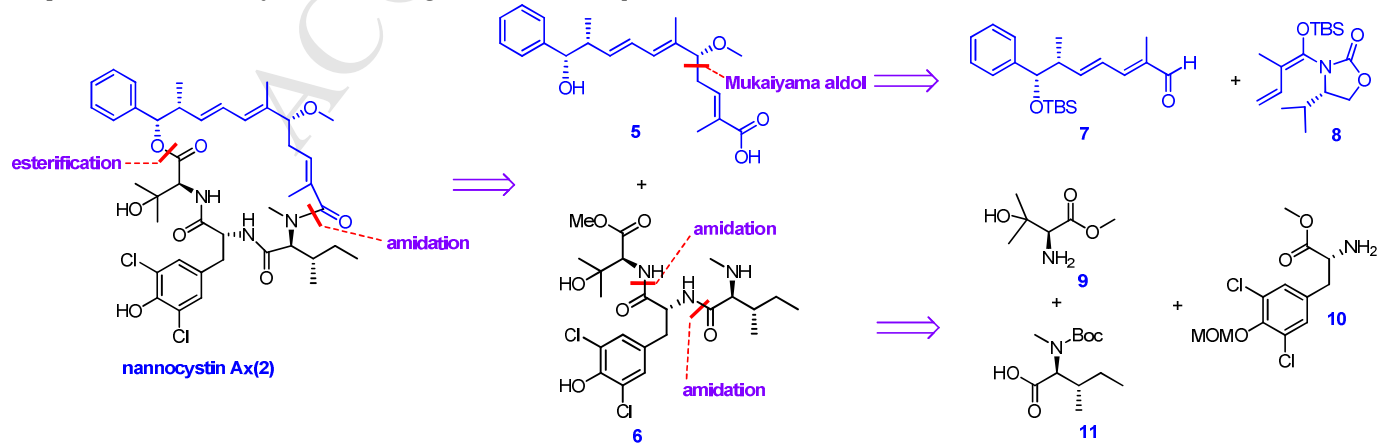
Scheme 3 Synthesis of compound 14

Then, we turned our attention to synthesize the polyketide moiety **5**. The known compound **15**[7] was transformed to compound **17** in 97% yield via Wittig reaction. Subsequent reduction of **17** followed by oxidation and Wittig reaction, generated **19** in 64% yield for 3 steps.[8] Reduction of **19** and oxidation of the resultant allylic alcohol with MnO_2 gave the corresponding aldehyde **7**. Due to its instability, we exposed **7** without further purification to the next Mukaiyama aldol reaction to examine the feasibility of this process. Unfortunately, both reactants decomposed rapidly under Lewis acid conditions such as $TiCl_4$ *et al*. Thus, we set about for an alternative route to achieve this polyketide (**Scheme 4**).

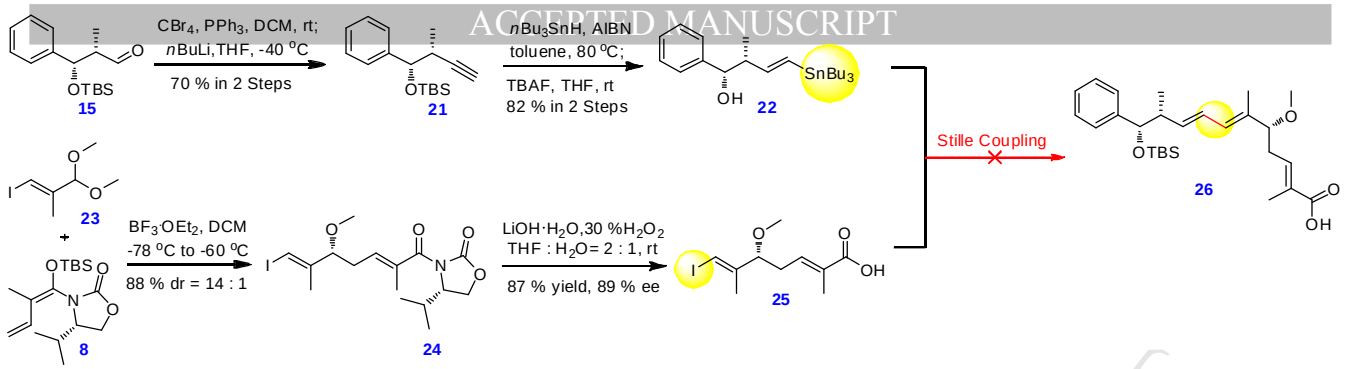


Scheme 4 Attempts to polyketide moiety by Asymmetric Aldol

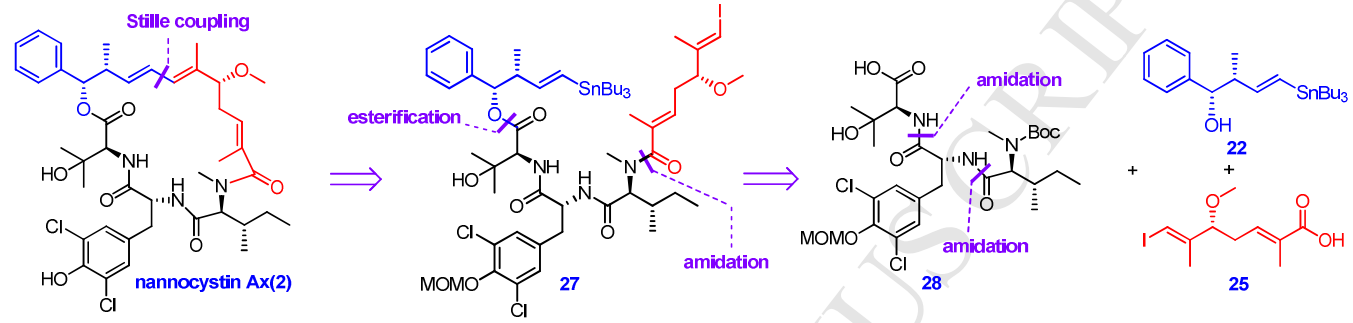
Witnessing comprehensive application of cross-coupling reactions in total synthesis, we conceived a Stille cross-coupling strategy between a vinyl iodide segment and an organostannane segment to acquire the polyketide fragment. Accordingly, we first attempted to make the corresponding vinyl iodide segment. So, an asymmetric Mukaiyama-type aldol reaction between vinylketene silyl N, O-acetal **8** and acetal **23** was utilized to achieve compound **24** by following Kobayashi and Hosokawa's methodology.[9] Delightfully, this asymmetric aldol reaction underwent smoothly with high yield and good diastereoselectivity (88% yield, 14: 1 dr). Subsequent removal of the chiral auxiliary group of **24** resulted in the acid **25** with satisfactory yield and retained ee value. Furthermore, after Corey-Fuchs alkynylation of the chiral aldehyde **15**, the resultant compound **21** underwent hydrostannation and deprotection of the TBS group to afford the organostannane segment **22**[10]. However, the desired Stille coupling did not take place between the unsaturated acid **25** and secondary alcohol **22** under various reaction conditions[11]. (**Scheme 5**)



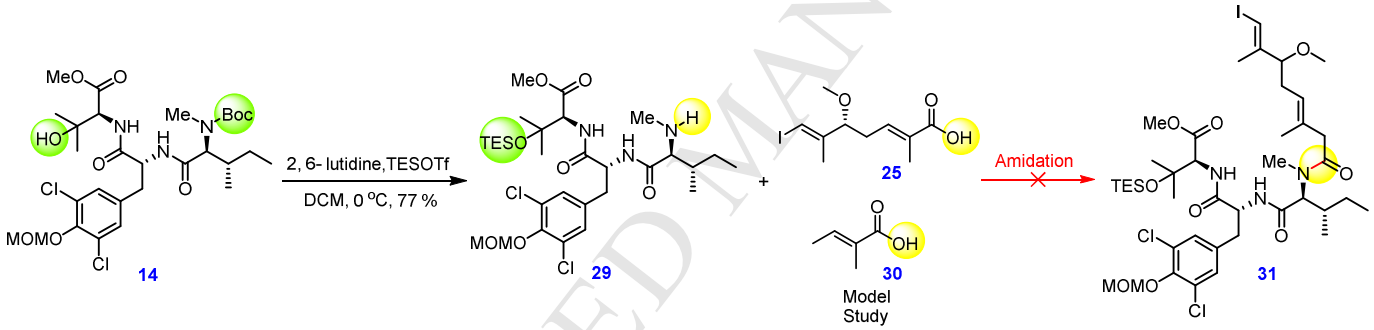
Scheme 2 Strategy A based on macrolactonization



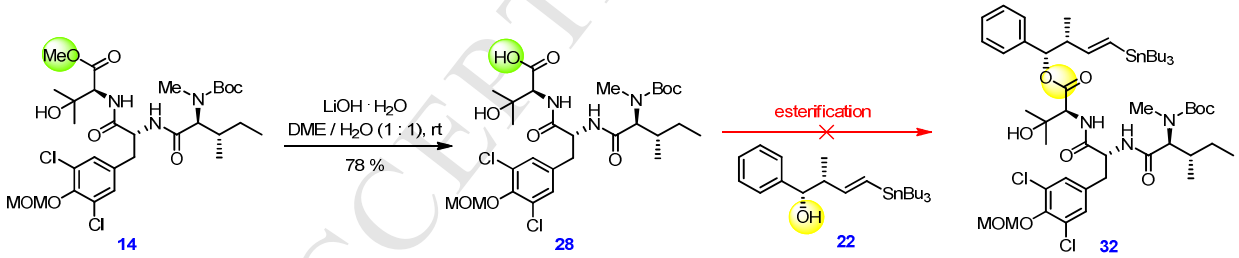
Scheme 5 Attempts to compound 26



Scheme 6 Strategy B Based on Stille Coupling



Scheme 7 Attempts to compound 31



Scheme 8 Synthetic attempts to compound 32

2.2 Total Synthesis of Nannocystin Ax - Strategy B

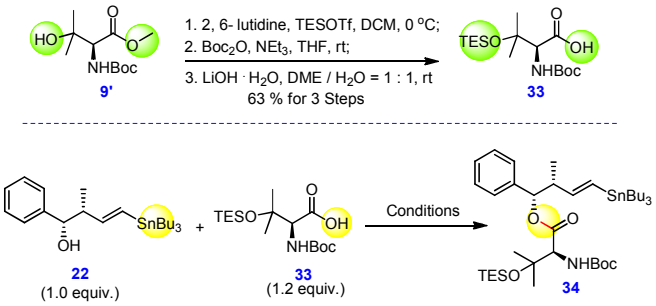
Besides the macrolactonization, metal-catalyzed Stille couplings are efficacious tool reactions as well in constructing macro-membered rings [14]. So, we considered the stille coupling to cyclize the 21-membered macrocycle. To make full use of the synthesized moiety from Strategy A, we disconnected nannocystin Ax retrosynthetically via esterification and amidation of the tripeptide **28** before Stille coupling of **27** (**Scheme 6-Strategy B**).

First, we tried amidation of the tripeptide with **25** ahead of esterification with **22**. Deprotection of Boc and protection of OH group in compound **14** [12] gave the resulting tripeptide **29**, which was subsequently subjected to amidation reaction with the unsaturated aicd **25**. Although numerous activating reagents, such as HBTU, HATU, EDCI, PivCl, $(COCl)_2$ and Ghosez regent, [13] were examined, all conditions failed to achieve the desired product (see SI for details). Amazingly, even the model reaction between tiglic acid **30** with the amine **29** could not furnish the corresponding amidation product (**Scheme 7**). We ascribed this difficulty in amidation to some special conformational folding of the tripeptide.

With these in mind, we began to attempt esterification of the tripeptide ahead of its amidation, by hydrolysis of the tripeptide **14** using LiOH•H_2O [15] to afford the acid **28**. However, esterification between **28** and **22** in numerous conditions proved infertile without compound **32** generated (see SI for details), but resulted in decomposition of the substrate (**Scheme 8**). We

speculated that the inefficient esterification between the acid **28** and the secondary alcohol **22** could be ascribed to the steric hinderance between them. The rate of esterification was so low that the vinyltin moiety of **22** had decomposed before the desired reaction took place. To test this possibility, compound **22** was prepared and its esterification with **33**, a much smaller compound than **28**, was examined. The tertiay alcohol of the known compound **9′**, [5h] was protected under TESOTf/lutidine condition, which led to partial deprotection of Boc amide. After treatment of the resultant mixture with Boc_2O and lithium hydroxide, comopound **33** was obtained in satisfactory yield. Notably, protection of the tertiary alcohol is necessary to prevent dehydration in the coupling reaction between **22** and **33** (**Table 1**). After screening various reaction conditions to promote the esterification, the best yield achieved is just 21%, albeit better than that in coupling reaction between **22** and **28**.

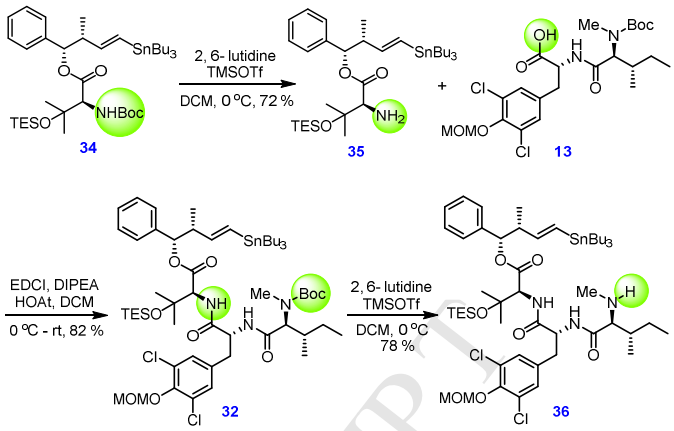
Table 1 Screening of Esterification between 22 and 33



Entry[a]	Condensing Reagent (equiv.)[b]	Additive (equiv.)	Yield (%)
1	DCC (3.0)	DMAP (0.2)	0 [e]
2	EDCI (3.0), HOAt (3.0)	DIPEA (4.0)	0 [f]
3	EDCI (3.0), HOBt (3.0)	NEt_3 (3.0)	0 [f]
4	$(COCl)_2$ (0.6)	DMF (cat), NEt_3 (3.0)	C.M. [g]
5	Yamaguchi reagent (1.5) [c]	DMAP (0.2), NEt_3 (3.0)	trace
6	MNBA (1.5)	DMAP (0.2), NEt_3 (3.0)	0 [e]
7	HATU (3.0), HOAt (3.0)	DIPEA (4.0)	C.M. [g]
8	HBTU (3.0)	DMAP (0.2), DIPEA (3.0)	21

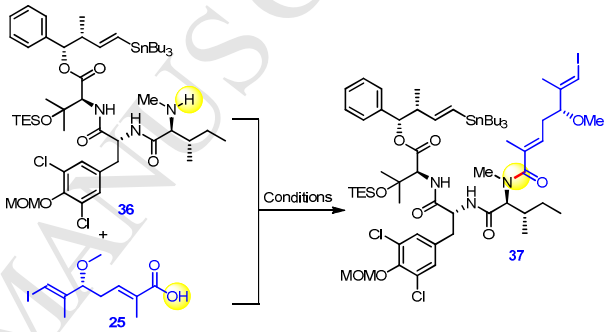
[a] Scale of the reactions ranged from 0.04 to 0.12 mmol. [b] Reactions were conducted in DCM (0.1 M) at room temperature unless otherwise stated. [c] Reaction was conducted in toluene (0.1 M) at room temperature; [d] Yamaguchi reagent: 2,4,6-trichloro-benzoyl choride. [e] No reaction with all starting material recovered. [f] The substrate **22** decomposed. [g] C.M.: complex mixture.

Although the yield of **34** was unsatisfactory, we still planned to move farward to examine the practicability of strategy B. Removing the Boc protection of **34** under the condition of TMSOTf and 2,6-lutidine in DCM [16] could give the free amine **35** in 72% yield. Then amidation of **35** and **13** gave rise to **32** in 82% yield which further underwent Boc deprotection to generate the amine **36** (**Scheme 9**). The following pivotal amidation reaction was examined with lots of condensing methods (**Table 2**). All initial attempts, such as utilizing DCC or EDCI as condensing reagent, activating the unsaturated acid **25** with $(COCl)_2$, PivCl, Yamaguchi reagent and Ghosez reagent, afforded no desired amidation product. We then paid our attention to utilize HATU or HBTU as the reagents. Fortunately, we could obtain **37** in 10 % yield in the presence of HBTU, DIPEA and DMAP, while only trace amount of **37** could be detected under HATU/HOAt/DIPEA condition (**Table 2**). Pleasingly, exposure of trace amount of **37** in typical Stille cross-coupling conditions, such as $Pd(PPh_3)_4$/LiCl in THF and $Pd(MeCN)_2Cl_2/Ph_3As$/CuI in DMF, afforded the cyclized product detectable through LC-MS, which inspired us to override the obstacles toward efficient total synthesis of nannocystin Ax.



Scheme 9 Synthesis of compound 36

Table 2 Screening of Amidation between 25 and 36

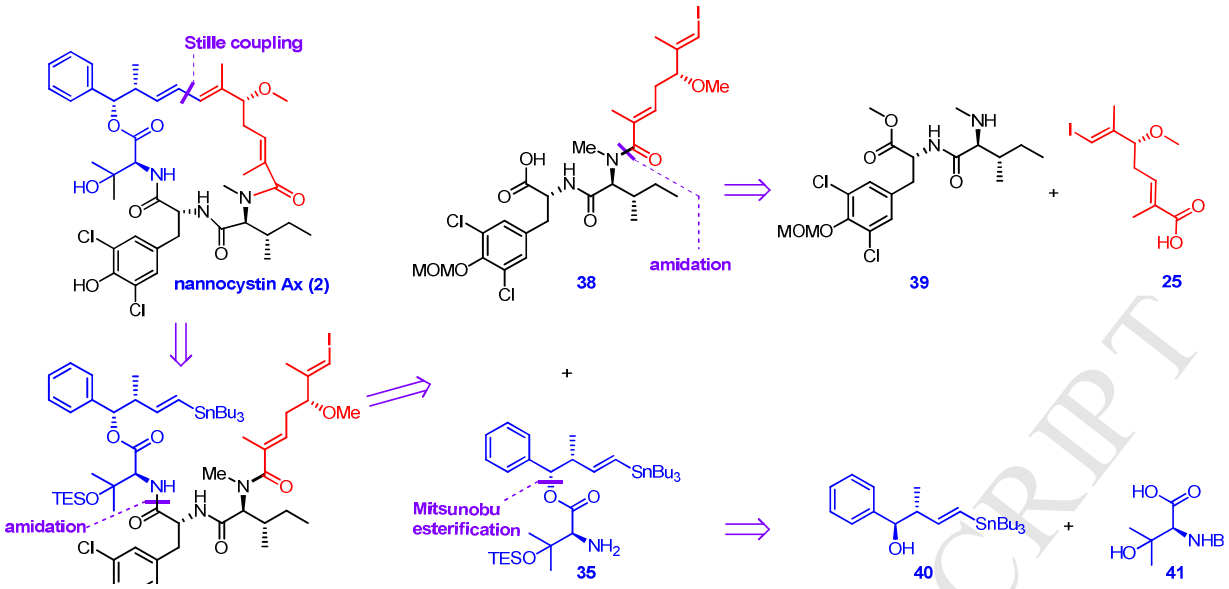


Entry[a]	Condensing Reagent (equiv.)[b]	Addictive (equiv.)	Yield (%)
1	DCC (3.0)	DMAP (0.2)	0 [e]
2	EDCI (3.0), HOAt (3.0)	DIPEA (3.0)	0 [e]
3	EDCI (3.0), HOBt (3.0)	DIPEA (3.0)	0 [e]
4	$(COCl)_2$ (0.6)	DMF (0.2), NEt_3 (3.0)	0 [f]
5	PivCl (1.2)	DMAP (0.2), NEt_3 (3.0)	0 [f]
6	Yamaguchi Reagent (1.5) [c]	DMAP (0.2), NEt_3 (3.0)	0 [f]
7	Yamaguchi Reagent (1.2)	NEt_3 (3.0)	0 [f]
8	HATU (3.0), HOAt (3.0)	DIPEA (3.0)	Trace
9	HBTU (3.0)	DMAP (0.2), DIPEA (3.0)	10

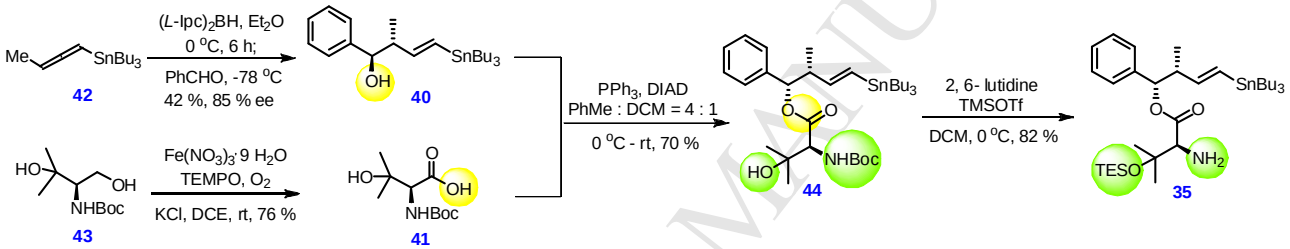
[a] Scale of the reactions ranged from 0.02 to 0.05 mmol. [b] Reaction were conducted in DCM (0.1 M) at room temperature unless otherwise stated. [c] Reaction was conducted in toluene (0.1M) at room temperature. [d] No reaction with the substrates recovered. [e] None product was detected and compound **36** partially decomposed. Yamaguchi Reagent: 2,4,6-trichorol-benzylchoride;

2.3 Total Synthesis of Nannocystin Ax - Strategy C

The above successful macrocyclization of **37** through Stille cross-coupling ensured us on the feasibility of this strategy in total synthesis. Failure in efficient connection between **25** and **29** or **36** indicated the possible presence of destructive function of conformation of the tripeptide on the amidation. Furthermore, we noticed that the amidation between the amine **35** and the acid **13** proceeded smoothly. Thus, we conceived a synthetic strategy involving forge of the tripeptide at the late stage of total synthesis, which retrosynthetically led to compound **38** and compound **35** from compound **37**, a Stille cross-coupling precursor toward the target molecule (**Scheme10-Strategy C**). Amidation between **25** and the dipeptide **39** might be feasible. Since direct esterification between compound **22** and compound **33** had been proved in low efficacy, a Mitusnobo-type esterification toward **35** from **40** and **41** was devised. Accordingly, based on asymmetric crotylboration of aldehyde developed by Roush's group [17], the secondary alcohol **40** was prepared smoothly with 85% ee. The acid **41** could be prepared by direct oxidation of the known



Scheme 10 Strategy C based on Stille coupling

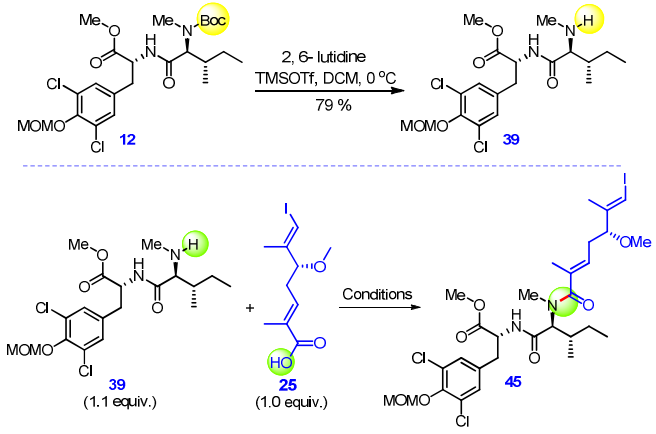


Scheme 11 Synthesis of compound 35

compound **43**. [18] Interestingly, when the reaction was performed in Mitsunobu condition in THF, [19] no product could be detected. But the reaction underwent well in toluene and dichloromethane and afforded **44** in 70% yield. Subsequent removal of Boc group provided the amine **35** in 82% yield (**Scheme 11**). Deprotection of **12** under 2,6-lutidine and TMSOTf could generate the amidation precursor **39** in 79% yield. Then the amidation between **39** and **25** was prudently examined with various condensing reagents such as EDCI, HATU, HBTU, BOP, Yamaguchi reagent and Ghosez reagent. Gratifyingly, employment of Ghosez reagent (1.2 equiv.) and NEt_3 (3 equiv.) could lead to the amidated product **45** in 83% yield (**Table 3**) [20].

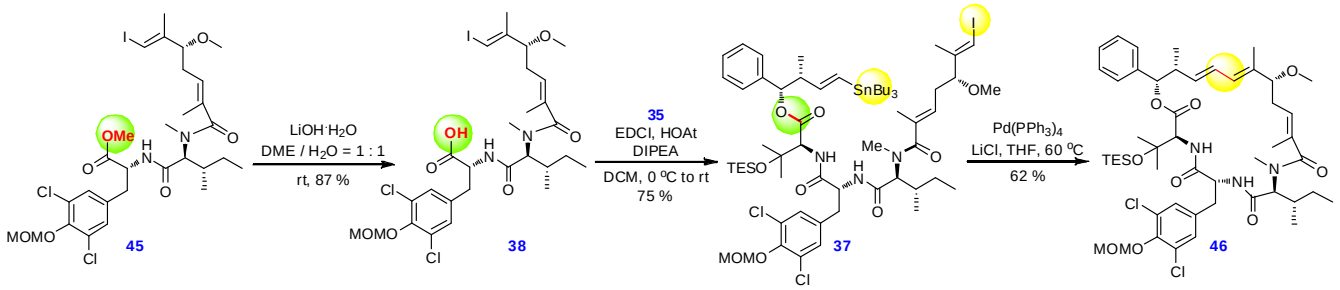
Then hydrolysis of **45** using LiOH•H_2O in DME and water afforded the acid **38** in 87% yield. Pleasingly, the amidation between the acid **38** and the amine **35** underwent smoothly with EDCl, HOAt and DIPEA to provide **37** in 75% yield. After executing the intramolecular Stille cross-coupling in dilute THF, we obtained compound **46** in 62% yield in the presence of $Pd(PPh_3)_4$ and LiCl [21] at 60 °C (**Scheme 12**), prompting us to complete total synthesis of nannocystin Ax after final global deprotection. Considering the lability of TES and MOM group in compound **46** under acidic condition [22], we screened different acids to remove both protective groups in one pot (**Table 4**), and found that the target molecule, nannocystin Ax, was obtained in 78% yield with *para*-toluenesulfonic acid. Interestingly, the ^{1}H NMR of nannocystin Ax showed it exists as a 5 : 1 mixture of two isomers in d^6-DMSO, and characterization data of the major one matched that of the natural product from Hoepfner`s research[2a].

Table 3 Screening of amidation between 39 and 25



Entry[a]	Condensing Reagent (equiv.)[b]	Addictive (equiv.)	Yield(%)[f]
1	EDCI (3.0), HOAt (3.0)	DIPEA (3.0)	N.R.
2	EDCI (3.0), HOAt (3.0) [c]	DIPEA (3.0)	N.R.
3	HATU (3.0), HOAt (3.0)	DIPEA (3.0)	N.R.
4	HBTU (3.0)	DIPEA (3.0),DMAP (0.2)	trace
5	BOP reagent (3.0) [d]	NEt_3 (3.0)	N.R.
6	$(COCl)_2$ (0.6)	DMF (0.2),DIPEA (3.0)	N.R.
7	$(COCl)_2$ (0.6)	DMF (0.2), NEt_3 (3.0)	N.R.
8	PivCl (1.2)	DMAP (0.2), NEt_3 (3.0)	N.R.
9	Yamaguchi reagent (1.2)	DMAP (0.2), NEt_3 (3.0)	N.R.
10	Yamaguchi reagent (1.2) [e]	DMAP (0.2), NEt_3 (3.0)	N.R.
11	Ghosez reagent (1.2)	NEt_3 (3.0)	83

[a] Scale of the reactions ranged from 0.02 to 0.1 mmol. [b] Reactions were conducted in DCM (0.1 M) at room temperature unless otherwise stated. [c] Reaction was conducted in MeCN (0.1 M) at room temperature. [d] Reaction was conducted in DMF (0.1 M) at room temperature. [e] Reaction was conducted in toluene (0.1 M) at room temperature. [f] N.R.: no reaction. Yamaguchi reagent: 2,4,6-trichloro-benzoyl chloride; Ghosez reagent: 1-chloro-*N*,*N*,2-trimethylpropenylamine.

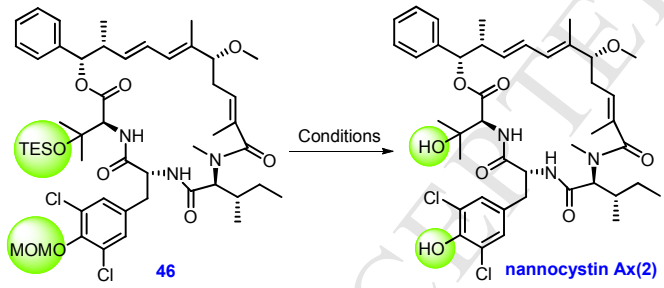


Scheme 12 Synthesis of compound 46

Further study showed that the ^{1}H NMR of nannocystin Ax are a 10:1 mixture of two isomers in both d^6-acetone and $CDCl_3$. These abnormal results made us suspect the presence of conformers of nannocystin Ax. The ^{1}H NMR variable-temperature experiments were executed at various temperatures from 25 °C to 70 °C in d^6-DMSO, illustrating that nannocystin Ax does exist as conformational mixtures in DMSO below 70 °C (**Figure 1**). Then the structure of nannocystin Ax was further confirmed by single crystal X-ray diffraction analysis (**Scheme 13D**). Notably, re-dissolving the sample subjected to single crystal X-ray analysis in d^6-DMSO resulted in a 5:1 mixture of conformers again by NMR analysis. According to these results, we concluded that nannocystin Ax exists as conformational mixtures in solvents such as d^6-DMSO, d^6-Acetone and $CDCl_3$.

Due to their structural similarity between nannocystin Ax and nannocystin A, we attempted to transform nannocystin Ax to nannocystin A by selective asymmetric epoxidation. Various epoxidation conditions were tested [23], but none of them could give rise to nannocystin A (see SI for details).

Table 4 Deprotection of 46 and completion of total synthesis



Entry [a]	Acid (equiv.)	Temp. (°C)	Yield (%)
1	TMSBr (2.0) [b]	-45 °C	---[f]
2	TMSBr (2.0) [b]	-78 °C	---[f]
3	BBr_3 (1.0) [b]	-78 °C	---[f]
4	$LiBF_4$ (2.0) [c]	40 °C	---[g]
5	HCl (12, 1 M in H_2O) [d]	rt	trace
6	HCl (12, 3 M in H_2O) [d]	rt	trace
7	HCl (12, 6 M in H_2O) [d]	rt	trace
8	HCl (12, 3 M in H_2O) [e]	rt	72
9	CAS (0.5) [e]	rt	75
10	pTsOH (0.5) [e]	rt	78

[a] Scale of the reactions ranged from 0.01 to 0.02 mmol. [b] Reaction was conducted in DCM (0.1 M) for 30 min. [c] Reaction was conducted in aqueous acetonitrile (MeCN/H_2O, 1:1). [d] Reaction was conducted in a mixture of THF and aqeous HCl (1 : 1, v/v) overnight. [e] Reaction was conducted in MeOH (0.05 M) for 4 h. [f] Compound **46** decomposed. [g] Only desilylation took place.

3. Conclusion

We have completed total synthesis of nannocystin Ax after attempting different synthetic strategies. Strategy A relying on the late-stage macrolactonization was unsuccessful because the precursor of macrolactonization could not be achieved. Then, strategy B was also proved out of synthetic significance, due to unprecedented difficulty in esterification and amidation of the tripeptide segment with compounds **22** and **25**. On the basis of strategy A and strategy B, we implemented strategy C utilizing the Stille cross-coupling to forge the key 21-membered ring. Total synthesis of nannocystin Ax was thus accomplished in 8 longest linear steps with 13.9 % overall yield. To make a distinct illustration, the full synthetic route leading to nannocystin Ax (Strategy C) is outlined in **Scheme 13**. This successful total synthesis features asymmetric Kobayashi aldol reaction followed by hydrolysis leading to **25**, Roush`s asymmetric crotylboration followed by Mitsunobu esterification and deprotection leading to **35** and late-stage Stille cross-coupling leading to macrolide of the target molecule. The sequence of installing different fragments is crucial to the total synthesis because of special reactivity of the tripeptide fragment inside. Notably, nannocystin Ax exists as conformational mixtures with viable ratios in different solvents at room temperature, which should be kept in mind during experiments in organic synthesis and bioassay of this natural product in the future.

4. Experimental Section

4.1 General

Unless otherwise stated, reactions were conducted at ambient temperature under an argon atmosphere using freshly dried solvents. 1, 2 dimethoxyethane (DME), Terahydrofuran (THF) was distilled by sodium using benzophenone as indicator. Petroleum ether (PE), Ethyl acetate (EA), 1,2-dichloroethane (DCE), Methylene chloride (DCM), acetonitrile (MeCN), Dimethylformamide (DMF) and Toluene were distilled by calcium hydride. Triethylamine (NEt_3) and N, N-diisopropylethylamine (DIPEA) were distilled by calcium hydride. The reaction was monitored by thin layer chromatography using silica gel commercially available and were visualized by UV, p-anisaldehyde, ninhydrin, CAM or $KMnO_4$ stanning. Flash column chromatography was performed using silica gel purchased from Qingdao Hailang Silica gel Desiccant Corporation.^{1}H-NMR spectra and ^{13}C-NMR spectra were recorded on Brucker (400 MHz and 100 MHz respectively) and Bruker (600 MHz and 150 MHz, respectively) NMR spectrometer with TMS as the internal standard, and are reported relative to internal $CDCl_3$ (^{1}H, 7.26; ^{13}C, 77.16), ^{d6}-DMSO (^{1}H, 2.50; ^{13}C, 39.52) , $(CD_3)_2CO$ (^{1}H, 2.05; ^{13}C, 29.84). Data for ^{1}H-NMR spectra are reported as follows: chemical shift δ(ppm), multiplicity, coupling constant J (Hz) and integration

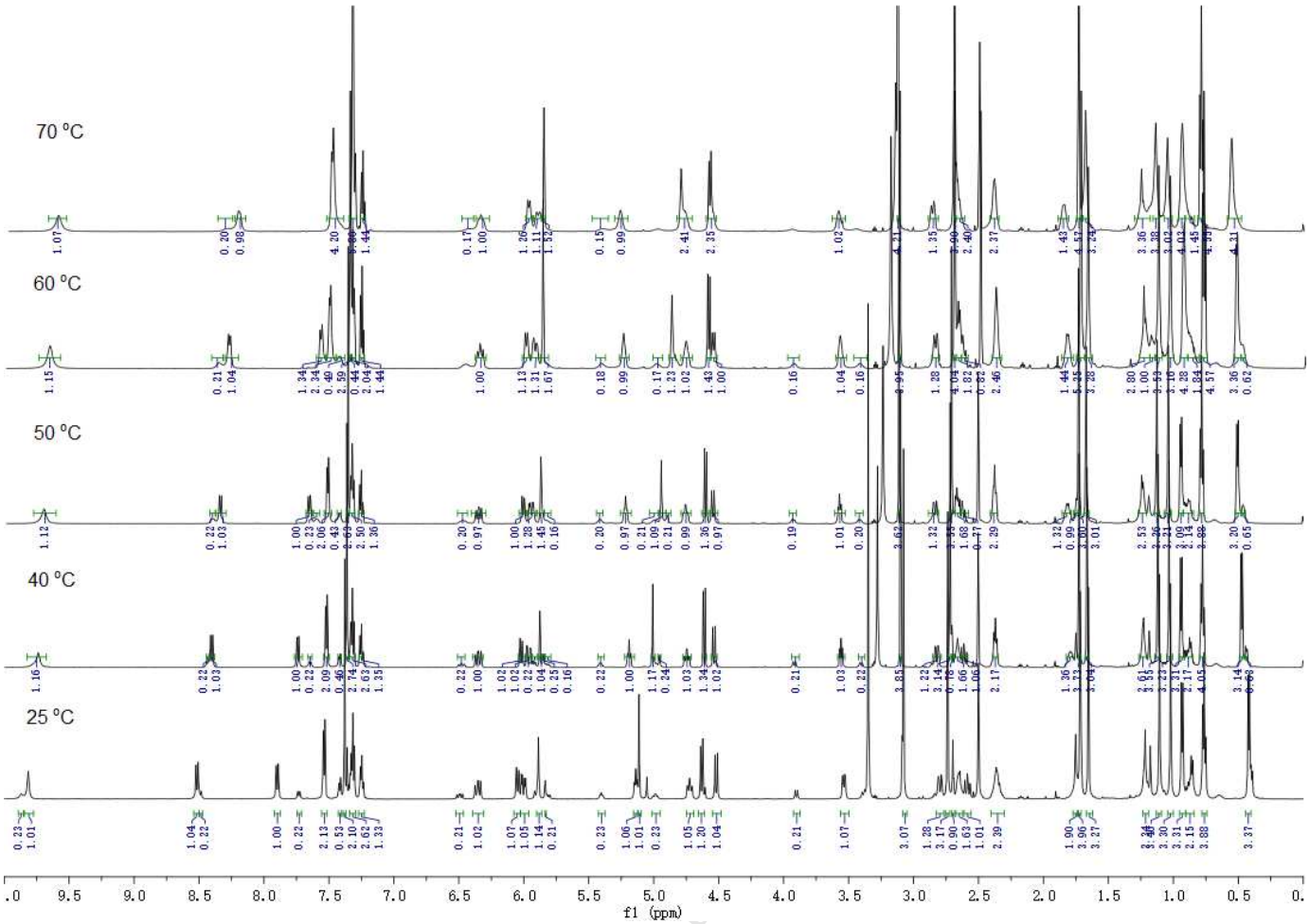


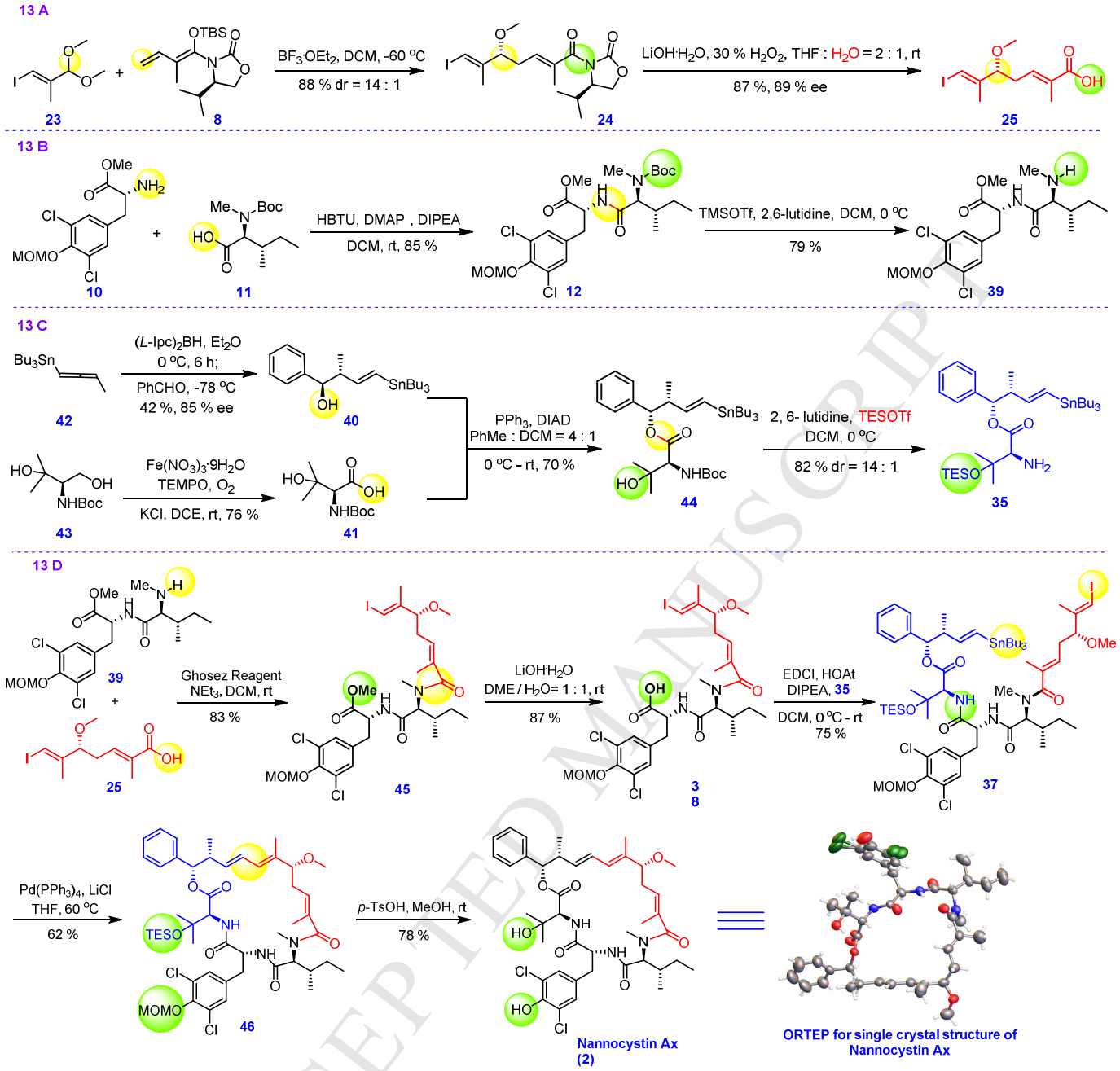
Figure 1 ^{1}H NMR variable-temperature experiments of nannocystin Ax in d^6-DMSO at different temperatures

Multiplicity and qualifier abbreviations are as follows: s=single, d=double, t=triplet, q=quartet, m=multiple, br=broad, app=apparent. Infrared (IR) spectra were recorded on a SHIMADZU IRTracer-100 FT-IR (Fourier Transform Infrared) Spectrometer and were reported in frequency of absorption(cm^{-1}). High resolution mass spectra (HRMS) were recorded on a Thermo Fisher Q Exactive ™ Focus Combined Quadrupole Orbatrip ™ Mass Spectrometer. Optical rotations were measured on a Jasco-P-2000 polarimeter using a 100 mm length cell at 589 nm.

4.2 Experimental procedures and data of synthetic intermidates

4.2.1. Synthesis of Compound **12**. To a cool solution of HBTU (7.39 g, 19.5 mmol, 3 equivalent), DMAP (158.0 mg, 1.3 mmol, 0.2 equivalent) and DIPEA (3.2 ml, 19.5 mmol, 3 equivalent) in 35 ml DCM at 0 °C, the solution of **10** (2.0 g, 6.5 mmol, 1.0 equivalent) and **11** (2.42 g, 19.5 mmol, 1.5 equivalent) in 30 ml DCM was added slowly. The reaction was allowed to warm the reaction to room temperature and stir with additional 10 h until the reaction completed. Filtrated through a plug of diatomite, the solution was concentrated by rotary evaporator. The crude product was chromatographed on silica gel (PE / EA= 5 : 1) to provide **12** (2.98 g, 85% yield) as colorless oil. $[\alpha]^{21}_{D}$ = – 61.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.08 (s, 2 H), 6.83 (d, *J* = 7.5 Hz, 1 H), 5.12 (s, 2 H), 4.77 (d, *J* = 5.5 Hz, 1 H), 4.09 (d, *J* = 11.2 Hz, 1 H), 3.69 (s, 3 H), 3.65 (s, 3 H), 3.07 (dd, *J* = 14.0, 5.1 Hz, 1 H), 2.88 (dd, *J* = 13.8, 7.7 Hz, 1 H), 2.70 (s, 3 H), 1.41 (s, 9 H), 1.41 – 1.27 (m, 2 H), 1.02 – 0.93 (m, 1 H), 0.85 (t, *J* = 7.3 Hz, 3 H), 0.77 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 171.2, 170.6, 157.3, 148.7, 134.2, 129.8, 129.4, 99.4, 80.6, 62.9, 58.2, 52.7, 52.5, 36.9, 31.5, 30.3, 28.4, 24.5, 15.8, 10.6; IR (KBr) ν_{max}: 3345, 2968, 1847, 1747, 1684, 1516, 1476, 1313, 1256, 1206, 1159, 937, 801 cm^{-1}; HRMS–ESI (*m/z*): $[M+Na]^+$ calculated for $C_{24}H_{36}Cl_2N_2NaO_7$, 557.1797, found: 557.1790.

4.2.2. Synthesis of Compound **13**. To a cooled solution of dipeptide **12** (1.84 g, 3.4 mmol, 1.0 equivalent) in 50 ml of DME (1, 2 dimethoxyethane) at 0 °C, the solution of $LiOH{\bullet}H_2O$ (428.1 mg, 10.2 mmol, 3.0 equivalent) in 50 ml of H_2O was added slowly. The reaction was then allowed to proceed at room temperature and stirred overnight. The reaction was cooled again to 0 °C and was quenched by dropwise addition of 1M HCl solution to achieve pH 2. After extracting the aqueous layer with EA (100 ml x 3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated in vacuo. The resulting crude product was chromatographed over silica gel (PE / EA=1 : 1) to provide the acid **13** as viscous colorless oil (1.52 g, 85 %). $[\alpha]^{21}_{D}$ = – 45.3 (*c* 0.11, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.19 (s, 2 H), 5.13 (s, 2 H), 4.78 (dd, *J* = 13.6, 7.0 Hz, 1 H), 4.21 (d, *J* = 11.2 Hz, 1 H), 3.66 (s, 3 H), 3.09 (dd, *J* = 14.0, 5.8 Hz, 1 H), 2.93 (dd, *J* = 14.0, 7.3 Hz, 1 H), 2.80 (s, 3 H), 2.01 (m , 1 H), 1.40 (s, 9 H), 1.06 – 0.97 (m, 1 H) 0.89-0.84 (m, 5 H), 0.78 (d, *J* = 6.1 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): 173.9, 169.5, 148.7, 134.4, 130.0, 129.3, 99.3, 81.3, 60.0, 58.2, 52.8, 36.6, 32.1, 29.8, 28.4,



Scheme 13 Completion of nannocystin Ax

24.6, 15.6, 10.5. IR (KBr) vmax:3468, 2954, 2924, 2853, 2365, 1760, 1548, 1157, 1101, 937 cm^{-1}; HRMS–ESI(m/z): $[M+K]^+$ calculated for $C_{22}H_{32}Cl_2N_2KO_7$, 545.1218, found: 545.1209.

4.2.3. Synthesis of Compound **14**. To a cooled solution of EDCI (615.5 mg, 3.2 mmol,3.0 equivalent), HOAt (437.0 mg, 3.2 mmol, 3.0 equivalent) and DIPEA (0.70 ml, 4.3 mmol, 4.0 equivalent) in 25 ml DCM at 0 °C, the solution of **9** (187.5 mg, 1.28 mmol, 1.2 equivalent) and **13** (563. 0 mg, 1.07 mmol, 1.0 equivalent) in 25 ml DCM was added slowly. The reaction was allowed to warm to room temperature and stir t until the reaction completed by TLC detection. The solution was concentrated by rotary evaporator and the crude product was chromatographed on silica gel (PE / EA= 3 : 2) to provide **14** (486.2 mg, 70 % yield) as yellowish oil.$[\alpha]^{22}_D$ = – 37.1 (*c* 0.74, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (s, 1 H), 7.38 (s, 1 H), 5.07 (s, 2 H), 4.94 (m, 1H), 4.51 (d, *J* = 8.4 Hz, 1 H), 4.05 (d, *J* = 11.1 Hz, 1 H), 3.71 (s, 3 H), 3.62 (s, 3 H), 3.08 (m, 1 H), 2.96 (m, 1 H), 2.70 (s, 3 H), 1.91 (m, 1 H), 1.39 (s, 9 H), 1.26 (s, 3 H), 1.13 (s, 3 H), 0.94 – 0.86 (m, 1 H), 0.81 (m, 5 H), 0.58 (d, *J* = 5.9 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): 171.5,171.0, 170.6, 156.8, 148.2, 135.0, 130.0, 128.9, 99.1, 80.4, 77.2, 71.3, 62.4, 60.5, 57.9, 53.6, 52.1, 37.1, 32.1, 30.1, 28.2, 26.9, 26.7, 24.4, 15.1, 10.3. IR (KBr) vmax: 3499, 2955, 2924, 1718, 1458, 1375, 1159, 947 cm^{-1}; HRMS–ESI(m/z): $[M+Na]^+$ calculated for $C_{29}H_{45}Cl_2N_3NaO_9$, 672.2425, found: 672.2431.

4.2.4. Synthesis of Compound **17**. To the solution of the chiral aldehyde **15** (1.91 g, 6.9 mmol) in 30 ml acetonitrile, Wittig reagent **16** was added at room temperature and allowed to warm to 70 °C overnight. Concentrating the solution in vacuo, filtrating over silica gel and washing it by PE / EA= 20 : 1. After concentrating via rotary evaporator, the crude product was chromatographed on silica gel (PE / EA= 20 : 1) to furnish viscous oil (2.33 g, 97 % yield).$[\alpha]^{22}_D$ = – 11.8 (*c* 0.21, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 – 7.20 (m, 5 H), 6.92 (dd, *J*

= 15.8, 7.6 Hz, 1 H), 5.67 (d, *J* = 15.8, 1 H), 4.58 (d, *J* = 5.0 Hz, 1 H), 4.14 (tt, *J* = 7.1, 3.5 Hz, 2 H), 2.59 – 2.51 (m, 1 H), 1.24 (dd, *J* = 13.8, 6.7 Hz, 3 H), 0.96 (d, *J* = 6.7 Hz, 3 H), 0.86 (s, 9 H), 0.01 (s, 3 H), -0.23 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$):166.8, 151.7, 143.0, 128.0, 127.3, 126.6, 121.2, 60.3, 45.3, 29.8, 26.0, 18.4, 15.5, 14.4, 13.7, -4.5, -5.3. IR (KBr) νmax:3499, 2955, 2920, 1718, 1456, 1261, 918 cm^{-1}; HRMS–ESI(m/z): [M+Na]$^+$ calculated for $C_{20}H_{32}NaO_3Si$, 371.2013, found: 371.2021.

4.2.5. Synthesis of Compound **19**. To a cooled solution of **17** (2.33 g, 6.7 mmol, 1.0 equivalent) in 30 ml DCM at 0 °C, DIBAL (1.46 M in toluene, 14.8 ml, 21.6 mmol, 3.2 equivalent) was added dropwise. After stirring overnight at 0 °C, the reaction was quenched by 150 ml saturated Rochelle salt and stirred to clarified separated phase. After extraction by DCM (100 ml x 3), the organic phase was dried by Na_2SO_4, filtrated and concentrated in vacuo. The resulted crude product was chromatographed on silica gel (PE / EA= 5 : 1) to provide corresponding allylic alcohol [1.97 g, 96 % yield, ^{1}H NMR (400 MHz, $CDCl_3$): *δ*7.65 – 7.53 (m, 5 H), 5.93 (dd, *J* = 15.7, 6.9 Hz, 1 H), 5.86 – 5.80 (m, 1 H), 4.84 (d, *J* = 5.0 Hz, 1 H), 4.32 (d, *J* = 5.3 Hz, 2 H), 2.78 (dd, *J* = 12.9, 6.4 Hz, 1 H), 2.36 (s, 1 H), 1.36 (d, *J* = 6.7 Hz, 3 H), 1.26 (s, 9H), 0.37 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): *δ*143.8, 135.48, 129.1, 127.7, 126.9, 78.8, 63.6, 45.1, 25.9, 18.3, 14.9, -4.6, -5.0.] as colorless oil. To a cooled solution of this allylic alcohol (1.97 g, 6.4 mmol) in 40 ml DCM at 0 °C, the freshly activated MnO_2 (5.57 g, 64.0 mmol) was added. The reaction was allowed to warmed to room temperature and stir until the reaction completed monitored by TLC. The solution was filtrated over a plug of silica gel and washed by DCM. After concentrating in vacuo, the crude product was dissolved in 30 ml DCM, Wittig reagent **18** (2.26 g, 6.2 mmol) was added and allowed to warm to room temperature overnight. Concentrated in vacuo, filtrated over silica gel using PE / EA = 20 : 1 as eluent, the resulted crude product was concentrated in vacuo and chromatographed on silica gel (PE / EA= 20 : 1) to provide ester **19** (1.66 g, 64 % yield for 3 steps) as colorless oil. $[\alpha]^{23}_D$ = – 4.2 (*c* 0.33, $CHCl_3$);. ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.32 – 7.21 (m, 5 H), 7.11 (d, *J* = 11.2 Hz, 1 H), 6.24 (dd, *J* = 15.2, 11.3 Hz, 1 H), 5.98 (dd, *J* = 15.2, 7.7 Hz, 1 H), 4.55 (d, *J* = 5.4 Hz, 1 H), 4.21 (q, *J* = 6.9 Hz, 2 H), 2.58 (dt, *J* = 12.9, 6.5 Hz, 1 H), 1.89 (s, 3 H), 1.31 (td, *J* = 7.1, 0.7 Hz, 3 H), 1.05 (d, *J* = 6.7 Hz, 3 H), 0.91 (s, 9 H), 0.03 (s, 3 H), -0.20 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): *δ*168.8, 145.0, 143.3, 138.6, 127.8, 127.2, 126.8, 125.9, 125.7, 78.5, 60.6, 46.1, 25.9, 18.3, 14.9, 14.5, 12.7, -4.5, -4.9. IR (KBr) νmax:3476, 2958, 2924, 1655, 1560, 1260, 1067, 960 cm^{-1}; HRMS–ESI(m/z): [M+Na]$^+$ calculated for $C_{23}H_{36}NaO_3Si$, 411.2326, found 411.2330.

4.2.6. Synthesis of Compound **7**. To a cooled solution of ester **19** (1.66 g, 4.3 mmol) in 30 ml of DCM at 0 °C, DIBAL (1.46 M in toluene, 8.8 ml, 12.9 ml, 3.0 equivalent) was added dropwise. After stirring overnight at 0 °C, the reaction was quenched by 100 ml of saturated Rochelle salt and the solution was stirred until separated phase could be observed. After extraction with DCM (100 ml x 3), the combined organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was chromatographed on silica gel (PE /EA= 5 : 1) to provide the corresponding allylic alcohol (1.44 g, 96 % yield). To a cooled solution of this allylic alcohol (1.44 g, 4.2 mmol) in 40 ml of DCM was added MnO_2 (3.65 g, 42.0 mmol) slowly and the suspension was stirred at room temperature overnight until the starting material was fully consumed. After passing the solution through a plug of diatomite and concentration in vacuo, the resultant crude product was used directly for the next step.

4.2.7. Synthesis of Compound **21**. To a cooled solution of **15** (5.1 g, 18.2 mmol) in THF (150 ml) at 0 °C, CBr_4 (9.05 g, 27.3 mmol, 1.5 equivalent) and PPh_3 (14.32 g, 54.6 mmol, 3.0 equivalent) was added sequentially and the resultant solution was stirred at room temperature overnight. After filtration over a plug of diatomite and concentration in vacuo via rotary evaporator, the resulted crude product was chromatographed on silica gel (PE/EA= 100 : 1) to provide the *gem*-vinyldibromide as yellowish oil. To a cooled solution of the *gem*-vinyldibromide (1.22 g, 2.8 mmol) in 25 ml of THF at -40 °C, *n*BuLi solution (2.40 M in hexane, 2.46 ml, 5.90 mmol, 2.1 equivalent) was added dropwise. After 4 h, the reaction was quenched by addition of 10 ml of water and the solution was slowly warmed to room temperature and stirred for additional 1 h. After separating the two phases and extracting the aqueous layer with EA (10 ml x 3), the combined organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. The resultant crude product was chromatographed on silica gel (PE / EA= 200 : 1) to afford the alkyne **21** (652.6 mg, 70 % yield in 2 steps) as yellowish oil. $[\alpha]^{22}_D$ = – 34.1 (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.29 – 7.20 (m, 5 H), 4.53 (d, *J* = 6.5 Hz, 1 H), 2.64 – 2.57 (m, 1 H), 1.93 (d, *J* = 2.5 Hz, 1H), 1.14 (d, *J* = 6.9 Hz, 3 H), 0.82 (s, 9 H), -0.00 (s, 3 H), -0.25 (s, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): 143.2, 127.9, 127.5, 127.0, 86.9, 77.9, 70.2, 35.7, 26.0, 18.4, 16.6, -4.5, -4.9;. IR (KBr) νmax: 3445, 2968, 2926,1732,1651, 1258, 1090, 1045, 880 cm^{-1}; HRMS–ESI(m/z): [M+Na]$^+$ calculated for $C_{17}H_{26}NaOSi$, 297.1645 found 297.1643.

4.2.8. Synthesis of Compound **22**. To a solution of **21** (652.6 mg, 2.38 mmol, 1.0 equivalent) in 25 ml of toluene, AIBN (19.5 mg, 0.12 mmol) and Bu_3SnH (1.26 ml, 4.76 mmol, 2.0 equivalent) was added. The reaction was stirred at 80 °C overnight. Then, the reaction was cooled to room temperature and diluted by 50 ml of EA. The organic phase was washed by 50 ml of water and then dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was chromatographed on silica gel (neutralized by 1% NEt_3) to afford colorless oil. To a solution of this colorless oil in 25 ml of THF at 0 °C, TBAF (1.0 M in THF, 12.0 mmol) was added dropwise and the solution was stirred at room temperature overnight. The reaction was quenched with 20 ml of saturated NH_4Cl solution and the aqueous layer was extracted with EA (50 ml x 3). The combined organic phase was dried over Na_2SO_4, filtered and concentrated in vacuo. The crude product was chromatographed on silica gel using PE / EA= 10 : 1 as eluent to afford the vinyltin **22** as yellowish oil (650.08 mg, 82 % yield for 2 steps). $[\alpha]^{22}_D$ = – 14.4 (*c* 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 7.34 – 7.23 (m, 5 H), 5.98 (dd, *J* = 19.1, 0.9 Hz, 1 H), 5.84 (dd, *J* = 19.1, 6.4 Hz, 1 H), 4.62 (dd, *J* = 5.3, 4.0 Hz, 1 H), 2.61 (dd, *J* = 13.2, 6.6 Hz, 1 H), 1.96 (d, *J* = 3.8 Hz, 1 H), 1.49 – 1.32 (m, 6 H), 1.32 – 1.24 (m, 6 H), 1.00 (d, *J* = 6.8 Hz, 3 H), 0.94 – 0.82 (m, 15 H); ^{13}C NMR (101 MHz, $CDCl_3$):150.4, 142.8, 129.4, 128.0, 127.3, 127.0, 77.5, 77.2, 48.4, 29.2, 27.4, 13.8, 9.5; IR (KBr) νmax: 3449, 2951, 2928, 1655, 1488, 1273, 1092, 918 cm^{-1}; HRMS–ESI(m/z): [M+Na]$^+$ calculated for $C_{23}H_{40}NaOSn$, 475.1993 found: 475.1999.

4.2.9. Synthesis of Compound **24**. To a cooled solution of the acetal **23** (2.70 g, 11.2 mmol, 1.0 equivalent) in 28 ml of DCM at -78 °C, $BF_3{\cdot}OEt_3$ (1.38 ml, 11.2 mmol, 1.0 equivalent) was added dropwise. After stirring for 15 min, a solution of **8** (1.58 g, 11.2 mmol, 1.0 equivalent) in 28 ml of DCM was added dropwise and the resultant solution was stirred at -60 °C for additional 4.5 h. The reaction was quenched by addition of pyridine (3.6 ml, 44.6 mmol, 4.0 equivalent) at -60 °C and 56 ml of saturated $NaHCO_3$ solution. The mixture was allowed to warm to room temperature. The aqueous layer was extracted by DCM (100 ml x 4), and the combined organic phase was dried over Na_2SO_4 and concentrated

in vacuo. The crude product was chromatographed on silica gel (PE / EA= 5 : 1) to furnish amide **24** (4.13 g, 88 % yield, dr = 14 : 1) as viscous yellowish oil. $[\alpha]^{24}_{D}$ = – 21.2 (c 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.25 (s, 1 H), 5.97 (t, *J* = 7.2 Hz, 1 H), 4.53 – 4.48 (m, 1 H), 4.31 (t, *J* = 8.9 Hz, 1 H), 4.17 (dd, *J* = 8.9, 5.3 Hz, 1 H), 3.73 (t, *J* = 6.8 Hz, 1 H), 3.20 (s, 3 H), 2.52 – 2.44 (m, 1 H), 2.39 – 2.31 (m, 2 H), 1.89 (s, 3 H), 1.77 (s, 3 H), 0.90 (t, *J* = 7.5 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 153.7, 147.2, 134.1, 132.8, 84.6, 80.0, 63.6, 58.3, 56.6, 32.8, 28.4, 18.8, 18.0, 15.2, 14.0; IR (KBr) νmax: 3056, 2965, 2922, 2852, 1784, 1682, 1462, 1368, 1269, 1208, 1098, 739 cm^{-1}; HRMS–ESI(m/z): $[M+Na]^+$ calculated for $C_{16}H_{24}INNaO_4$, 444.0648, found: 444.0646.

4.2.10. Synthesis of Compound **25**. To a solution of the amide **24** (1.05 g, 2.50 mmol, 1.0 equivalent) in 16 ml of THF and 8 ml of water, LiOH•H_2O (314.7 mg, 7.50 mmol, 3.0 equivalent) and H_2O_2 (30% in H_2O, 0.78 ml, 7.50 mmol, 3.0 equivalent) was added. After stirring for 24 h at room temperature, the reaction was quenched by aqueous HCl solution (2 M, 15.00 ml, 30.00 mmol, 12.0 equivalent). The aqueous layer was extracted with EA (50 ml x 3), and the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (PE/EA=2:1) to furnish the acid **25** (674.5 mg, 87 % yield, 89 % ee) as yellowish oil. The ee value was determined by SFC (Chiral ND 5μ, CO_2 /MeOH= 95 / 5, flow rate 1.0 ml / min, λ = 254 nm). $[\alpha]^{24}_{D}$ = – 28.4 (c 0.4, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.83 (t, *J* = 7.1 Hz, 1 H), 6.27 (s, 1 H), 3.76 (dd, *J* =7.3, 6.1 Hz, 1 H), 3.21 (s, 3 H), 2.55 – 2.47 (m, 1 H), 2.40 – 2.35 (m, 1 H), 1.82 (s, 3H),1.77 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.3, 147.1, 140.1, 129.1, 84.8, 80.0, 56.7, 33.7, 18.9, 12.4; IR (KBr) νmax: 2927, 1687, 1645, 1422, 1280, 1099 cm^{-1}; HRMS–ESI(m/z): $[M+Na]^+$calculated for $C_{10}H_{15}INaO$, 332.9964, found: 332.9965.

4.2.11. Synthesis of Compound **28**. To a cooled solution of **14** (205.9 mg, 0.32 mmol, 1.0 equivalent) in 3 ml of DME (1, 2 dimethoxyethane) at 0 °C, the solution of LiOH•H_2O (45.7 mg, 0.96 mmol, 3.0 equivalent) in 3 ml of H_2O was added and the reaction was stirred at room temperature overnight. Then the reaction was quenched by addition of aqueous HCl solution (1 M). The aqueous layer was extracted with EA (30 ml x 3) and the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (PE / EA=1:1) to afford the acid **28** (158.8 mg, 78 % yield) as viscous colorless oil. $[\alpha]^{21}_{D}$ = – 45.2 (*c* 0.08, $CHCl_3$); ^{1}H NMR (400 MHz, CD_3OD): *δ* 7.35(s, 2 H), 5.11 (s, 2 H), 4.83 – 4.79 (m, 1 H), 4.33 (m, 1 H), 4.17 (d, *J* = 9.6 Hz, 1 H), 3.64 (s, 3 H), 3.14 (dd, *J* = 13.9, 8.4 Hz, 1 H), 2.83 (dd, *J* = 13.6, 8.6 Hz, 1 H), 2.78 (s, 3 H),1.93-1.89 (m, 1 H), 1.39 (s, 9 H), 1.19 (s, 3 H), 1.14 (s, 3 H), 1.00-0.98 (m, 2 H), 0.87-0.85 (m, 5 H), 0.58 (m, 3 H); ^{13}C NMR (101 MHz, CD_3OD): 172.4, 149.7, 131.1, 130.9, 130.1,107.2, 100.5, 81.6, 72.0, 68.7, 63.5, 61.8, 59.4, 58.4, 56.4, 37.5, 33.5, 30.5, 28.6, 27.2, 26.9, 15.7, 10.7. IR (KBr) νmax: 3499, 2955, 2924, 1718, 1458, 1375, 1159, 947 cm^{-1}; HRMS–ESI(m/z): $[M+K]^+$ calculated for $C_{28}H_{43}Cl_2KN_3O_9$, 674.2013, found: 674.2011.

4.2.12. Synthesis of Compound **29**. To a cooled solution of **14** (131.0 mg, 0.20 mmol) in 5 ml of DCM at 0 °C, 2,6-lutidine (0.28 ml, 2.40 mmol, 12.0 equivalent) and TESOTf (0.27 ml, 1.20 mmol, 6.0 equivalent) was added sequentially. After stirring for 4 h at 0 °C, the reaction was quenched with 15 ml of saturated $NaHCO_3$ solution. The aqueous layer was extracted with DCM (20 ml x 4), and the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was chromatographed on silica gel (PE / EA= 1 : 1) to afford the amine **29** (102.8 mg, 77 % yield) as viscous colorless oil. $[\alpha]^{22}_{D}$ = 7.8 (*c* 0.56, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.73 (d, *J* = 8.0 Hz, 1 H), 7.26 (s, 2 H), 7.02 (d, *J* = 8.5 Hz, 1 H), 5.18 (s, 2 H), 4.69 (dd, *J* = 15.1, 7.9 Hz, 1 H), 4.42 (d, *J* = 8.9 Hz, 1 H), 3.72 (s, 6 H), 3.16 (dd, *J* = 14.1, 6.8 Hz, 1 H), 2.96 (dd, *J* = 14.1, 8.2 Hz, 1 H), 2.26 (s, 3 H), 1.81 – 1.80 (m, 2 H), 1.48 (m, 1 H), 1.37 (s, 3 H), 1.17 (s, 3 H), 0.99– 0.92 (m, 14 H), 0.59 (q, *J* = 7.9 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$):174.1, 170.2, 148.6, 134.8, 129.9, 129.5, 99.3, 74.4, 61.7, 58.1, 53.7, 51.9, 38.4, 36.5, 36.0, 27.8, 27.4, 25.2, 15.8, 11.8, 7.0, 6.5; IR (KBr) νmax: 3456, 2980, 2928, 1742, 1659, 1460, 1377, 1258, 1043, 899 cm^{-1}; HRMS–ESI(m/z): [M+Na]+calculated for $C_{30}H_{51}Cl_2N_3NaO_7Si$, 686.2766, found: 686.2759.

4.2.13. Synthesis of Compound **32**. To a cooled solution of EDCI (92.0 mg, 0.48 mmol, 3.0 equivalent), HOAt (65.3 mg, 0.48 mmol, 3.0 equivalent) and DIPEA (0.10 ml, 0.64 mmol, 4.0 equivalent) in 3 ml of DCM at 0 °C, the solution of the acid **13** (105.4 mg, 0.16 mmol, 1.0 equivalent) and the amine **35** (99.9 mg, 0.19 mmol, 1.2 equivalent) in 2.5 ml of DCM was added. The reaction was stirred at room temperature for 18 h. After filtration over a plug of diatomite and concentration in vacuo, the residue was chromatographed on silica gel (PE / EA= 20 : 1) to afford the amide **32** (155.3 mg, 82 % yield) as yellowish oil. $[\alpha]^{22}_{D}$ = – 39.8 (*c* 0.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.28 – 7.26 (m, 5 H), 7.20 (s, 2 H), 6.91 (m, 1 H), 6.65 (m, 1 H), 5.78 (d, *J* = 19.1 Hz, 1 H), 5.56 (dd, *J* = 19.0, 7.0 Hz, 1 H), 5.50 (d, *J* = 9.2 Hz, 1 H), 5.13 (s, 2 H), 4.62 (dd, *J* = 15.2, 7.5 Hz, 1 H), 4.32 (d, *J* = 8.5 Hz, 1 H), 4.13 (d, *J* = 8.0, 1 H), 3.68 (s, 3 H), 3.08 (m, 1 H), 2.90 - 2.78 (m, 5 H), 2.09 (s, 1 H), 1.90 (m, 1 H), 1.48 (s, 9 H) 1.41 – 1.18 (m, 15 H), 1.12 (d, J =8 , 3 H), 1.10 (s, 3 H), 1.02 (s, 3 H), 0.91 - 0.71 (m, 30 H), 0.36 (q, *J* = 7.9 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$):170.0, 148.4, 130.0, 129.9, 129.5, 128.4, 128.1, 128.0, 99.4, 81.0, 80.5, 74.4, 61.6, 58.2, 54.1, 46.3, 32.1, 29.8, 29.2, 29.1, 28.5, 27.6, 27.3, 24.7, 16.9, 15.9, 13.8, 9.4, 7.0, 6.4; IR (KBr) ν_{max}: 3458, 2986, 2930, 1744, 1458, 1375, 1242, 1047, 815, 710 cm^{-1}; HRMS–ESI (*m/z*): $[M+Na]^+$ calculated for $C_{57}H_{95}Cl_2N_3NaO_9SiSn$, 1206.5129; found: 1206.5134.

4.2.14. Synthesis of Compound **33**. To a cooled solution of the ester **9`**(4.42 g, 18.0 mmol, 1.0 equivalent) in 180 ml of DCM at 0 °C, 2,6-lutidine (16.8 ml, 144.0 mmol, 8.0 equivalent) and TESOTf (24.4 ml, 108 mml, 6.0 equivalent) was added. After stirring at 0 °C for 4 h, the reaction was quenched by addition of 200 ml of saturated $NaHCO_3$ solution. The aqueous layer was extracted with DCM (150 ml x3), and the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The resultant crude product was chromatographed on silica gel (PE / EA= 2 : 1) to afford colorless oil. To a solution of this colorless oil in 150 ml of THF at 0 °C, NEt_3 (8.3 ml, 15.0 mmol) and Boc_2O (6.9 ml, 30 mmol) was added. The reaction was stirred for 16 h and then was quenched with 100 ml of H_2O. The aqueous layer was extracted with EA (100 ml x 3), and the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was chromatographed on silica gel (PE / EA= 20 : 1) to afford the ester as colorless oil. To a cooled solution of this colorless oil (1.43 g, 4.14 mmol, 1.0 equivalent) in 40 ml of DME at 0 °C was added a solution of LiOH·H_2O (1.39 mg, 33.1 mmol, 8.0 equivalent) in 40 ml of H_2O. After the reaction was stirred at room for 6 hours, it was quenched with aqueous HCl (1 M) and the acidity was adjusted to pH 3. The aqueous layer was extracted with EA (100 ml x 3) and the combined organic phase was dried over Na_2SO_4 and concentrated in vacuo. The residue was chromatographed on silica gel (PE / EA= 2 : 1) to afford the acid **33** (1.27 g, 63 % yield for 3 steps) as yellowish oil. $[\alpha]^{22}_{D}$ = 42.6 (*c* 0.18, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) *δ* 5.28 (d, *J* =

8.3 Hz, 1 H), 4.26 (d, *J* = 8.4 Hz, 1 H), 1.44 (s, 9 H), 1.42 (s, 3 H), 1.24 (s, 3H), 0.97 (t, *J* = 7.9 Hz, 10 H), 0.68 (q, *J* = 7.9 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$):156.2, 80.4, 62.0, 29.8, 28.4, 27.5, 25.6, 6.9, 6.5 ; IR (KBr) νmax: 3495, 2926, 1726, 1462 1367, 1159, , 947, 890 cm^{-1}; HRMS–ESI(m/z): [M+Na]+calculated for $C_{28}H_{43}Cl_2KN_3O_9$, 674.2008, found: 674.2011.

4.2.15. Synthesis of Compound **34**. To a cooled solution of HBTU (1.59 g, 4.2 mmol, 3.0 equivalent), DMAP (34.2 mg, 0.28 mmol, 0.2 equivalent) and DIPEA (0.7 ml, 4.2 mmol, 3.0 equivalent) in 15 ml of DCM at 0 °C, a solution of the acid **33** (758.8 mg, 1.68 mmol, 1.2 equivalent) and the secondary alcohol **22** (467.3 mg, 1.40 mmol, 1.0 equivalent) in 5 ml of DCM was added. The reaction was stirred at room temperature overnight. After the solution was filtrated over a plug of diatomite and concentrated in vacuo, the residue was chromatographed on silica gel (PE / EA= 50 : 1) to afford the ester **34** (225.2 mg, 21 % yield) as green oil. $[\alpha]^{22}_D$ = – 20.6 (*c* 0.28, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (m, 5H), 5.77 (d, *J* = 19.1 Hz, 1H), 5.64 (dd, *J* = 19.0, 6.9 Hz, 1 H), 5.57 (d, *J* = 8.0 Hz, 1H), 5.30 (s, 1 H), 4.11 (s, 1 H), 2.76 (dd, *J* = 14.1, 7.0 Hz, 1 H), 1.43 (s, 9H), 1.26 – 1.19 (m, 21 H), 1.10 (d, *J* = 6.7 Hz, 3 H), 0.87–0.84 (m, 24 H), 0.83 – 0.76 (m, 5 H), 0.41 (q, *J* = 7.9 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$): 170.4, 155.8, 148.7, 138.8, 129.8, 128.1, 128.0, 80.8, 79.7, 74.9, 62.9, 46.6, 29.1, 27.8, 27.4, 16.6, 13.8, 11.2, 9.5, 7.0, 6.6. IR (KBr) νmax: 3495, 2926, 1726, 1462 1367, 1159, 947, 890 cm^{-1}; HRMS–ESI(m/z): [M+K]+calculated for $C_{28}H_{43}Cl_2KN_3O_9$, 674.2008, found: 674.2011.

4.2.16. Synthesis of Compound **35**. **Method A**: To a cooled solution of ester **34** (167.3 mg, 0.22 mmol, 1.0 equivalent) in 4 ml DCM at 0 °C, 2,6-lutidine (0.13 ml, 1.10 mmol, 5 equivalent) and TESOTf (0.16 ml, 0.88 mml, 4.0 equivalent) subsequently. After stirring at 0 °C with additional 2 h was added subsequently, the reaction was quenched by saturated 10 ml $NaHCO_3$. Extracted by DCM (20 ml x 3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated in vacuo. The resulted crude product was chromatographed on silica gel (PE / EA= 10 : 1) to afford amine **35** (105.4 mg, 72 % yield) as a colorless oil. **Method B**: To a solution of **44** (665.6 mg, 1.0 mmol) in 10 ml DCM, 2, 6-lutidine (0.7 ml, 6.0 mmol) and TESOTf (0.9 ml, 4.0 mmol) were added at 0 ℃. After stirring at 0 ℃ for 30 min, saturated aqueous $NaHCO_3$ (10 ml) was added to quench the reaction. After separation, the aqueous layer was extracted with DCM (50 ml × 3). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by column chromatography on deactivated silica gel (PE / EA= 30 : 1) to furnish **35** (558.7 mg, 82 % yield, dr = 14 : 1) as a colorless oil. $[\alpha]^{22}_D$ = + 5.1 (*c* 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.27 – 7.22 (m, 5 H), 5.83 (d, *J* = 19.1 Hz, 1 H), 5.67 (dd, *J* = 19.1, 6.8 Hz, 1 H), 5.61 (d, *J* = 7.9 Hz, 1 H), 3.37 (s, 1 H), 2.76 (dd, *J* = 14.3, 6.9 Hz, 1 H), 1.73 (s, 2 H), 1.40 – 1.34 (m, 6 H), 1.25 (s, 3 H), 1.30 – 1.19 (m, 6 H), 1.08 (d, *J* = 6.1 Hz, 3 H), 1.07 (s, 3 H), 0.91 – 0.81 (m, 18 H), 0.78 – 0.74 (m, 6 H), 0.52 (q, *J* = 7.9 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 172.7, 148.7, 138.7, 129.8, 128.0, 127.9, 127.9, 80.2, 75.1, 65.2, 46.3, 29.1, 28.0, 27.3, 25.5, 16.3, 13.8, 9.4, 7.1, 6.7; IR (KBr) ν_{max}: 3400, 2957, 2926, 2876, 1737, 1598, 1459, 1377, 1239, 1148, 1040, 744 cm^{-1}; HRMS–ESI (*m/z*): $[M+H]^+$ calculated for $C_{34}H_{64}NO_3SiSn$, 682.3677; found: 682.3677.

4.2.17. Synthesis of Compound **36**. To a cooled solution of amide **32** (155.3 mg, 0.13 mmol, 1.0 equivalent) in 3 ml DCM at 0 °C, 2,6-lutidine (0.08 ml, 0.65 mmol, 5.0 equivalent) and TESOTf (0.10 ml, 0.52 mmol, 4.0 equivalent) was added subsequently. After stirring at 0 °C with additional 1 hour, the reaction was quenched by saturated 5 ml $NaHCO_3$. Extracted by DCM (20 ml x 3), the combined organic phase was dried over Na_2SO_4, filtrated and concentrated in vacuo. The resulted crude product was chromatographed on silica gel (PE / EA= 3 : 1) to afford amine **36** (109.9 mg, 78 % yield). $[\alpha]^{22}_D$ = – 12.3 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.62 (d, *J* = 8.1 Hz, 1 H), 7.26 – 7.22 (m, 5 H), 7.19 (s, 2 H), 6.86 (d, *J* = 8.4 Hz, 1 H), 5.78 (d, *J* = 19.1 Hz, 1 H), 5.58 (dd, *J* = 19.0, 7.0 Hz, 1 H), 5.51 (d, *J* = 9.2 Hz, 1 H), 5.12 (s, 2 H), 4.65 (dd, *J* = 15.2, 7.5 Hz, 1 H), 4.31 (d, *J* = 8.5 Hz, 1 H), 3.66 (s, 3H), 3.26 – 3.18 (m, 1 H), 3.10 (dd, *J* = 14.1, 7.0 Hz, 1 H), 2.90 (dd, *J* = 14.0, 7.6 Hz, 1 H), 2.81 – 2.74 (m, 2 H), 2.20 (s, 3 H), 1.38 (m, 1 H) 1.38 – 1.19 (m, 15 H), 1.10 (s, 3 H), 1.04 (s, 3 H), 0.90 (d, *J* = 6.9 Hz, 3 H), 0.88 – 0.71 (m, 32 H), 0.39 (q, *J* = 7.9 Hz, 6 H); ^{13}C NMR (101 MHz, $CDCl_3$):174.1, 170.4, 169.2 148.6, 148.5, 138.6, 134.9, 130.0, 129.5, 128.3, 128.0, 99.4, 81.0, 74.4, 69.9, 61.7, 58.2, 54.5, 53.9, 46.4, 38.5, 36.8, 36.2, 29.1, 28.4, 27.3, 25.3, 16.8, 16.0, 13.8, 11.9, 9.4, 7.0, 6.5 ; IR (KBr) ν_{max}: 3400, 2957, 2926, 2876, 1737, 1598, 1459, 1377, 1239, 1148, 1040, 802, 744 cm^{-1}; HRMS–ESI (*m/z*): $[M+Na]^+$ calculated for $C_{52}H_{87}Cl_2N_3NaO_7SiSn$, 1106.4605; found: 1106.4607.

4.2.18. Synthesis of Compound **37**. **Method A**: To a cooled solution of HBTU (115.9 mg, 0.30 mmol, 3.0 equivalent), DMAP (4.0 mg, 0.03 mmol, cat) and DIPEA (0.05 ml, 0.30 mmol, 3.0 equivalent) in 2 ml DCM at 0 °C was added a solution of acid **25** (42.2 mg, 0.13 mmol, 1.3 equivalent) and secondary amine **36** (109.9 mg, 0.10 mmol, 1.0 equivalent) in 2 ml DCM. The reaction was allowed to warm to room temperature and stir overnight. Concentrated in vacuo, the residue was chromatographed on silica gel (PE / EA= 5 : 1) to afford amide **37** (1.4 mg, 10 % yield) as yellowish oil. **Method B**: o a cooled solution of EDCI (172.6 mg, 0.90 mmol), HOAt (127.1 mg, 0.90 mmol), and DIPEA (0.2 ml, 1.2 mmol) in 4 ml of CH_2Cl_2 at 0 ℃, the solution of the acid **38** (251.0 mg, 0.35 mmol) and amine **35** (202.1 mg, 0.30 mmol) in 2 ml of DCM was added. After stirring for 1 h, the reaction mixture was allowed to warm to room temperature and stirred for additional 7 h. The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography (petroleum ether/ethyl acetate = 5 : 1) to afford **37** (306.4 mg, 75 % yield) as colorless oil. $[\alpha]^{22}_D$ = – 40.1 (*c* 1.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.30 – 7.21 (m, 6 H), 7.21 (s, 2H), 7.10 (d, *J* = 8.1 Hz, 1 H), 6.72 (d, *J* = 8.5 Hz, 1 H), 6.27 (s, 1 H), 5.81 (d, *J* = 19.0 Hz, 1 H), 5.60 (dd, *J* = 19.0, 6.8 Hz, 1 H), 5.51 – 5.44 (m, 2 H), 5.14 (s, 2 H), 4.64 (q, *J* = 7.5 Hz, 1 H), 4.49 (d, *J* = 11.3 Hz, 1 H), 4.33 (d, *J* = 8.5 Hz, 1 H), 3.78 (t, *J* = 6.8 Hz, 1 H), 3.69 (s, 3 H), 3.22 (s, 3 H), 3.16 – 3.11 (m, 1 H), 2.93 – 2.86 (m, 1 H), 2.84 (s, 3 H), 2.83 – 2.77 (m, 1 H), 2.46 (dd, *J* = 14.5, 6.5 Hz, 1 H), 2.36 (dd, *J* = 14.7, 7.3 Hz, 1 H), 2.15 – 2.13 (m, 2 H),1.86 (s, 3 H), 1.78 (s, 3 H), 1.44 – 1.34 (m, 7 H), 1.29 – 1.20 (m, 7 H), 1.12 (d, *J* = 5.6 Hz, 3 H), 1.11 (s, 3 H), 1.04 (s, 3 H), 0.93 – 0.86 (m, 13 H), 0.84 – 0.75 (m, 18 H), 0.40 (q, *J* = 7.7 Hz, 6 H); ^{1}C NMR (101 MHz, $CDCl_3$): *δ* 175.2, 170.5, 170.0, 169.3, 148.4, 147.5, 138.5, 135.1, 133.6, 130.2, 129.9, 129.5, 128.3, 128.1, 128.0, 127.4, 99.4, 85.2, 81.1, 79.8, 74.4, 61.6, 58.3, 56.6, 54.1, 46.4, 36.6, 33.6, 32.1, 31.4, 29.2, 29.1, 29.0, 28.4, 27.7, 27.4, 24.7, 18.8, 16.9, 15.8, 14.4, 13.9, 10.6, 9.5, 7.1, 6.5; IR (KBr) ν_{max}: 3319, 2958, 2927, 1739, 1688, 1608, 1518, 1460, 1374, 1257, 1161, 947 cm^{-1}; HRMS–ESI (*m/z*): $[M+Na]^+$ calculated for $C_{62}H_{100}Cl_2INaO_9SiSn$, 1398.4570; found 1398.4562.

4.2.19. Synthesis of Compound **38**. To a solution of **45** (792.7 mg, 1.1 mmol) in 10 ml DME (1, 2-dimethoxyethane), $LiOH•H_2O$ (230.1 mg, 5.5 mmol) in 10 ml water was added. After stirring at room temperature for 8 h, the mixture was adjusted to pH = 2 with 1 M HCl at 0 ℃, then extracted with DCM (50 ml × 4). The

combined organic layers were dried over Na_2SO_4, filtrated and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (DCM / MeOH = 25 : 1), furnishing **38** (676.5 mg, 87 % yield) as a colorless oil. $[\alpha]^{22}_D$ = – 56.1 (*c* 1.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73 (s, 1H), 7.28 (d, *J* = 7.8 Hz, 1 H), 7.17 (s, 2H), 6.21 (s, 1H), 5.40 (t, *J* = 6.6 Hz, 1 H), 5.10 (s, 2 H), 4.74 (d, *J* = 5.3 Hz, 1 H), 4.52 (d, *J* = 11.2 Hz, 1 H), 3.70 (t, *J* = 6.7 Hz, 1 H), 3.65 (s, 3 H), 3.15 (s, 3 H), 3.15 – 3.10 (m, 1 H), 2.92 – 2.89 (m, 1 H), 2.89 (s, 3 H), 2.35 (dd, *J* = 14.1, 7.1 Hz, 1 H), 2.27 (dd, *J* = 14.6, 7.3 Hz, 1 H), 2.07 – 2.00 (m, 1 H), 1.72 (s, 3 H), 1.71 (s, 3 H), 1.34 – 1.25 (m, 1 H), 1.02 – 0.93 (m, 1 H), 0.87 (t, *J* = 7.2 Hz, 3 H), 0.76 (d, *J* = 6.2 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.4, 173.3, 169.5, 148.5, 147.3, 135.0, 133.0, 130.1, 129.2, 128.1, 99.4, 85.0, 79.9, 61.4, 58.3, 56.6, 52.9, 36.6, 33.4, 32.0, 31.5, 24.8, 18.9, 15.6, 14.2, 10.6; IR (KBr) ν_{max}: 3330, 2965, 2930, 1737, 1681, 1610, 1475, 1402, 1257, 1162, 1099, 939, 800 cm^{-1}; HRM–ESI (*m/z*): $[M+Na]^+$ calculated for $C_{28}H_{39}Cl_2IN_2NaO_7$, 735.1077; found: 735.1082.

4.2.20. Synthesis of Compound **39**. To a solution of amide **12** (1.34 g, 2.5 mmol) in 25 ml DCM was added 2, 6-lutidine (1.7 ml, 14.9 mmol) and TMSOTf (1.8 ml, 9.9 mmol) sequentially at 0 ℃. The reaction was stirred for 1 h and quenched by adding 50 ml saturated aqueous $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with DCM (100 ml × 4). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated in vacuo. After purification by column chromatography on silica gel (DCM / MeOH = 20 : 1), it furnished amine **39** (852.8 mg, 79 % yield) as a colorless oil. $[\alpha]^{21}_D$ = – 28.2 (*c* 0.90, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, *J* = 7.7 Hz, 1 H), 7.09 (s, 2 H), 5.12 (s, 2 H), 4.80 (dd, *J* = 12.8, 6.1 Hz, 1 H), 3.72 (s, 3 H), 3.65 (s, 3 H), 3.12 (dd, *J* = 14.0, 5.2 Hz, 1 H), 2.98 (dd, *J* = 13.9, 7.0 Hz, 1 H), 2.80 – 2.79 (m, 1 H), 2.25 (s, 3 H), 1.76 (s, 1 H), 1.45 – 1.41 (m, 2 H), 1.14 – 1.03 (m, 1 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.85 (t, *J* = 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.6, 171.6, 148.7, 134.2, 129.9, 129.4, 99.4, 69.9, 58.2, 52.5, 52.3, 38.5, 36.8, 36.4, 25.0, 15.9, 11.9; IR (KBr) ν_{max} : 3309, 2961, 1745, 1653, 1511, 1475, 1256, 1212, 1161, 935, 780 cm^{-1}; HRMS–ESI (*m/z*): $[M+Na]^+$calculated for $C_{19}H_{28}C_{l2}NaO_5$, 457.1273; found: 457.1277.

4.2.21. Synthesis of Compound **40**. The reaction was manipulated as the paper reported and the ^{1}H-NMR and ^{13}C-NMR matched with the paper [17]. And the ee value was measured using the method reported by the author [17].

4.2.22. Synthesis of Compound **41**. TEMPO (156.3 mg, 1.0 mmol), Fe $(NO_3)_3 \cdot 9H_2O$ (404.0 mg, 1.0 mmol) and KCl (74.6 mg, 1.0 mmol) were added to a stirred solution of (2*R*)-2-*N*-(Boc) amino-3-methyl- 1,3-butanediol **43** (2.19 g, 10.0 mmol) under O_2 atmosphere in 100 ml anhydrous DCE. The reaction was then stirred at room temperature until completion of the reaction as monitored by TLC (48 h). The reaction mixture was concentrated in vacuo and the residue was purified by column chromatography (DCM/MeOH = 20 : 1), affording **41** (1.80 g, 76 % yield) as a yellowish solid. The spectroscopic data are consistent with those reported in literature [18a].

4.2.23. Synthesis of Compound **44**. PPh_3 (1.85 g, 7.1 mmol) and the acid **41** (510.7 mg, 2.1 mmol) was weighted into flask in glove box. The flask was capped with rubber septum and removed from glove box and placed in cold bath. A solution of the alcohol **40** (645.4 mg, 1.4 mmol) in 12 ml of toluene was added and the mixture was maintained to 0 ℃. DIAD (0.85 ml, 4.3 mmol) was added dropwise. After 30 min, to the mixture was added 3 ml of DCM and the resultant solution was stirred at room temperature for 4 h. The reaction was then quenched by addition of saturated aqueous $NaHCO_3$ (10 ml), and the aqueous layer was extracted with EA (40 ml × 4). The combined organic layers were dried over Na_2SO_4, filtered and concentrated in vacuum. The residue was purified by column chromatography on 1 % NEt_3 neutralized silica gel (PE / EA = 10 : 1), affording **44** (668.0 mg, 70 % yield, dr = 10 : 1) as colorless oil. $[\alpha]^{24}_D$ = – 41.5 (c 0.51, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.28 – 7.24 (m, 5 H), 5.86 (d, *J* = 19.0 Hz, 1 H), 5.70 – 5.63 (m, 1 H), 5.62 (d, *J* = 8.2 Hz, 1 H), 5.39 (d, *J* = 8.9 Hz, 1 H), 4.22 (d, *J* = 9.1 Hz, 1H), 2.80 – 2.75 (m, 1 H), 2.63 (s, 1 H), 1.44 (s, 9 H), 1.41 – 1.34 (m, 6 H), 1.29 – 1.21 (m, 6 H), 1.18 (s, 3 H), 1.12 (d, *J* = 6.7 Hz, 3 H), 1.06 (s, 3 H), 0.88 – 0.84 (m, 9 H), 0.80 – 0.76 (m, 6 H) ; ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.6, 155.9, 148.5, 138.5, 130.2, 128.2, 127.6, 81.1, 80.2, 72.0, 61.3, 46.5, 29.1, 28.4, 27.4, 27.1, 26.9, 26.4, 16.1, 13.9, 9.5 ; IR (KBr) νmax: 3440, 2959, 2926, 1720, 1496, 1370, 1163, 1052, 989, 698 cm^{-1}; HRMS–ESI (m/z): $[M+Na]^+$ calculated for $C_{33}H_{57}NNaO_5Sn$, 690.3156; found 690.3161.

4.2.24. Synthesis of Compound **45**. To a solution of the acid **25** (632.2 mg, 2.0 mmol) in 20 ml of DCM, 1-chloro-*N*,*N*,2-trimethylprophenylamine (0.35 ml, 2.4 mmol) was added dropwise. After the solution was stirred at room temperature for 2 h, the amine **39** (980.2 mg, 2.2 mmol) and Et_3N (0.85 ml, 6.1 mmol) were added sequentially and the resultant solution was stirred overnight. The mixture was then quenched with 10 ml of saturated aqueous $NaHCO_3$. After separation, the aqueous layer was extracted with DCM (50 ml × 4). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE / EA= 3 : 1), furnishing **45** (1.23 g, 83 % yield) as colorless oil. $[\alpha]^{24}_D$ = – 85.4 (*c* 0.60, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.12 (s, 2 H), 7.03 (d, *J* = 8.4 Hz, 1 H), 6.23 (s, 1 H), 5.45 (t, *J* = 6.8 Hz, 1 H), 5.13 (s, 3 H), 4.77 – 4.71 (m, 1 H), 4.48 (d, *J* = 11.5 Hz, 1 H), 3.74 – 3.73 (m, 1H), 3.70 (s, 3 H), 3.66 (s, 3 H), 3.18 (s, 3 H), 3.10 (dd, *J* = 14.2, 5.0 Hz, 1 H), 2.86 (dd, *J* = 14.2, 8.6 Hz, 1 H), 2.80 (s, 3H), 2.44 – 2.37 (m, 1 H), 2.36 – 2.28 (m, 1 H), 2.13 – 2.07 (m, 1 H), 1.79 (s, 3 H), 1.75 (s, 3 H), 1.37 – 1.29 (m, 1 H), 1.04 – 0.95 (m, 1 H), 0.87 (t, *J* = 7.3 Hz, 3 H), 0.82 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.3, 171.3, 170.1, 148.7, 147.4, 134.3, 133.5, 129.7, 129.4, 127.6, 99.4, 85.1, 79.7, 60.9, 58.2, 56.6, 52.7, 52.6, 36.7, 33.1, 32.1, 30.9, 24.6, 18.8, 15.7, 14.3, 10.5; IR (KBr) ν_{max}: 3316, 2962, 2930, 1745, 1682, 1613, 1527, 1474, 1257, 1162, 1100, 938, 800 cm^{-1}; HRMS–ESI (*m/z*): $[M+Na]^+$ calculated for $C_{29}H_{41}Cl_2IN_2NaO_7$, 749.1233; found: 749.1224.

4.2.25. Synthesis of Compound **46**. $Pd(PPh_3)_4$ (15.7 mg, 0.01 mmol) and LiCl (26.8 mg, 0.60 mmol) was weighted into flask in glove box. The flask was capped with rubber septum and removed from glove box. A solution of compound **37** (272.8 mg, 0.20 mmol) in 100 ml of THF was added and the mixture was stirred at 60 ℃ for 18 h. After the mixture was cooled to room temperature, 20 ml of water was added to quench the reaction. The aqueous layer was extracted with EA (50 ml × 3). The combined organic layers were dried over Na_2SO_4, filtrated and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (PE / EA = 3 : 1), furnishing **46** (118.7 mg, 62 % yield) as colorless oil. $[\alpha]^{22}_D$ = – 40.3 (*c* 0.40, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32 – 7.22 (m, 5 H), 7.19 (s, 2H), 6.96 (d, *J* = 8.9 Hz, 1 H), 6.76 (d, *J* = 8.8 Hz, 1 H), 6.30 (dd, *J* = 15.1, 10.7 Hz, 1 H), 5.93 (s, 1 H), 5.85 (d, *J* = 10.6 Hz, 1 H), 5.74 (dd, *J* = 15.3, 5.4 Hz, 1 H), 5.42 – 5.39 (m, 1 H), 5.11 (s, 2 H), 4.62 (d, *J* = 11.5 Hz, 1 H), 4.52 – 4.47 (m, 1 H), 4.40 (d, *J* = 8.8 Hz, 1 H), 3.65 (s, 3 H), 3.60 (dd, *J* = 10.6, 3.0 Hz, 1 H), 3.21 (s, 3 H), 3.06 (dd, *J* = 13.1, 10.3 Hz, 1 H), 2.75 (dd, *J*

= 13.2, 5.3 Hz, 1 H), 2.61 (s, 3 H), 2.61 – 2.55 (m, 1 H), 2.39 – 2.36 (m, 1 H), 2.19 – 2.13 (m, 1 H), 1.82 (s, 3 H), 1.76 (s, 3 H), 1.35 (s, 3 H), 1.27 – 1.20 (m, 1 H), 1.09 (d, *J* = 6.8 Hz, 3 H), 1.05 – 0.98 (m, 1 H), 0.92 – 0.87 (m, 7 H), 0.83 (s, 3 H), 0.76 (t, *J* = 7.9 Hz, 9 H), 0.37 (q, *J* = 7.9 Hz, 6 H); $^{1\,3}$C NMR (101 MHz, $CDCl_3$): *δ* 176.0, 170.6, 169.7, 169.5, 148.7, 139.2, 136.8, 135.5, 134.6, 133.6, 130.3, 129.5, 128.6, 128.2, 127.7, 127.7, 126.8, 125.6, 99.4, 85.8, 80.0, 75.7, 61.00, 60.1, 58.3, 56.1, 54.9, 42.2, 36.1, 32.4, 31.9, 30.5, 28.5, 27.4, 24.6, 16.1, 14.6, 11.6, 10.7, 10.5, 7.1, 6.6; IR (KBr) ν_{max}: 3424, 2925, 2854, 1739, 1619, 1459, 1381, 1258, 1157, 1069, 943, 800 cm^{-1}; HRMS–ESI (*m/z*): $[M+Na]^+$ calculated for $C_{50}H_{73}Cl_2N_3NaO_9Si$, 980.4391; found: 980.4393.

4.2.26. To a solution of **46** (116.7 mg, 0.12 mmol) in 6 ml of methanol, *p*TsOH (13.2 mg, 0.06 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. After addition of 5 ml of saturated aqueous $NaHCO_3$ to quench the reaction, the aqueous layer was extracted with EA (30 ml × 3). The combined organic layers were dried over anhydrous $MgSO_4$, filtrated and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE / EA = 2 : 1), furnishing nannocystin Ax (74.8 mg, 78 % yield) as a white solid, which was recrystallized from methanol to give crystalline needles. m.p. 177 - 178 °C. $[\alpha]^{23}_D$= – 67.4 (*c* 0.30, MeOH); ^{1}H NMR (600 MHz, ^{d6}-DMSO): *δ* 9.81 (s, 1 H), 8.52 (d, *J* = 9.9 Hz, 1 H), 7.90 (d, *J* = 9.5 Hz, 1 H), 7.54 (d, *J* = 7.6 Hz, 2 H), 7.38 (s, 2 H), 7.32 (t, *J* = 7.6 Hz, 2 H), 7.25 (t, *J* = 7.3 Hz, 1 H), 6.35 (m, 1 H), 6.05 (m, 1 H), 6.00 (m, 1 H), 5.89 (br, 1 H), 5.16 – 5.12 (m, 1 H), 5.11 (s, 1 H), 4.72 (m, 1 H), 4.63 (m, 1 H), 4.52 (d, *J* = 11.2 Hz, 1 H), 3.53 (m, 1 H), 3.08 (s, 3 H), 2.80 (m, 1 H), 2.74 (s, 3 H), 2.65 (m, 1 H), 2.59 (m, 1 H), 2.35 (m, 2 H), 1.73 (m, 1 H), 1.72 (s, 3 H), 1.65 (s, 3 H), 1.22 (m, 1 H), 1.11 (s, 3 H), 1.02 (s, 3 H), 0.93 (d, *J* = 6.8 Hz, 3 H), 0.88 (m, 1 H), 0.76 (t, *J* = 7.3 Hz, 3 H), 0.42 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (150 MHz, ^{d6}-DMSO): *δ* 172.8, 170.7, 170.5, 169.1, 147.3, 139.7, 137.3, 133.9, 133.5, 130.9, 129.6, 128.5, 127.8, 127.0, 126.1, 125.1, 124.8, 121.6, 84.9, 78.9, 71.7, 59.3, 58.9, 55.0, 52.9, 41.7, 36.5, 31.7, 31.1, 30.4, 28.1, 24.5, 24.0, 14.8, 14.4, 11.1, 10.2, 10.1; ^{13}C NMR (100 MHz, ^{d6}-DMSO): *δ* 172.8, 170.7, 170.5, 169.1, 147.3, 139.8, 137.4, 133.9, 133.5, 130.9, 129.6, 128.5, 127.8, 127.0, 126.1, 125.1, 124.8, 121.6, 84.9, 78.9, 71.7, 59.3, 58.9, 55.0, 52.9, 41.7, 36.6, 31.7, 31.2, 30.5, 28.2, 24.5, 24.0, 14.8, 14.4, 11.1, 10.2, 10.0; ^{1}H NMR (400 MHz, ^{d6}-Acetone): *δ* 8.67 (s, 1 H), 7.63 (d, *J* = 8.9 Hz, 1 H), 7.53 (d, *J* = 7.4 Hz, 2 H), 7.32 (t, *J* = 7.2 Hz, 2 H), 7.31 (s, 2 H), 7.25 (t, *J* = 7.3 Hz, 1 H), 7.12 (d, *J* = 9.0 Hz, 1 H), 6.40 (dd, *J* = 14.6, 11.5 Hz, 1 H), 5.99 (d, *J* = 10.8 Hz, 1 H), 5.90 – 5.85 (m, 1 H), 5.87 (d, *J* = 1.5 Hz, 1 H), 5.46 (t, *J* = 7.1 Hz, 1 H), 4.82 (dd, *J* = 15.3, 8.6 Hz, 1 H), 4.68 (d, *J* = 9.5 Hz, 1 H), 4.54 (d, *J* = 11.2 Hz, 1 H), 4.18 (d, *J* = 1.5 Hz, 1 H), 3.64 (dd, *J* = 10.0, 2.8 Hz, 1 H), 3.16 (s, 3 H), 3.07 – 3.02 (m, 1 H), 2.84 – 2.77 (m, 1 H), 2.75 – 2.70 (m, 1 H), 2.72 (s, 3 H), 2.56 – 2.46 (m, 1 H), 2.39 – 2.36 (m, 1 H), 2.01 – 1.94 (m, 1 H), 1.81 (s, 3 H), 1.73 (s, 3 H), 1.42 – 1.35 (m, 1 H), 1.20 (s, 3 H), 1.05 (s, 3 H), 0.99 (d, *J* = 6.9 Hz, 3 H), 1.02 – 0.91 (m, 1 H), 0.85 (d, *J* = 7.3 Hz, 3 H), 0.75 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR (100 MHz, ^{d6}-Acetone): *δ* 175.6, 171.3, 171.1, 170.8, 148.6, 140.6, 137.2, 135.5, 134.5, 131.6, 130.4, 129.1, 128.7, 128.0, 127.6, 127.4, 126.6, 122.3, 86.1, 80.34, 72.9, 60.8, 60.7, 55.9, 54.4, 42.9, 37.4, 32.8, 32.1, 31.7, 28.6, 25.6, 25.2, 16.0, 14.6, 11.8, 11.2, 10.6; ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.35 – 7.25 (m, 6 H), 7.02 (s, 2 H), 6.52 (d, *J* = 7.7 Hz, 1 H), 6.30 (dd, *J* = 15.0, 10.9 Hz, 1 H), 5.87 (s, 1 H), 5.85 (d, *J* = 9.1 Hz, 1 H), 5.57 (dd, *J* = 15.1, 6.7 Hz, 1 H), 5.45 (t, *J* = 7.3 Hz, 1 H), 4.65 (dd, *J* = 15.1, 7.4 Hz, 1 H), 4.59 (d, *J* = 8.9 Hz, 1 H), 4.35 (d, *J* = 11.2 Hz, 1 H), 3.64 (dd, *J* = 7.5, 2.3 Hz, 1 H), 3.21 (s, 3 H), 2.95 (dd, *J* = 13.7, 7.1 Hz, 1 H), 2.81 (s, 3 H), 2.73 (dd, *J* = 13.8, 6.5 Hz, 1 H), 2.75 – 2.70 (m, 1 H), 2.53 – 2.46 (m, 1 H), 2.43 – 2.35 (m, 1 H), 2.09 – 2.04 (m, 1 H), 1.79 (s, 3 H), 1.69 (s, 3 H), 1.44 – 1.40 (m, 1 H), 1.28 – 1.21 (m, 1 H), 1.18 (s, 3 H), 1.04 (s, 3 H), 1.03 (d, *J* = 5.2 Hz, 3 H), 0.92 (t, *J* = 7.2 Hz, 3 H), 0.83 (d, *J* = 6.3 Hz, 3 H); ^{13}C NMR (101 MHz, $CDCl_3$): *δ* 176.2, 170.9, 170.3, 169.5, 146.9, 137.9, 134.9, 134.4, 133.3, 129.7, 129.1, 128.1, 128.1, 127.9, 127.2, 127.1, 126.7, 121.2, 85.0, 80.5, 72.3, 61.8, 60.8, 56.3, 53.9, 41.8, 36.1, 32.7, 31.5, 31.3, 27.0, 26.7, 25.4, 15.9, 14.4, 12.8, 12.8, 10.8; IR (KBr) ν_{max}: 3351, 2927, 2850, 1736, 1665, 1606, 1490, 1375, 1312, 1157, 1065, 970 cm^{-1}; HRMS–ESI (*m/z*): $[M+Na]^+$ calculated for $C_{42}H_{55}Cl_2N_3NaO_8$, 822.3264; found: 822.3260.

4.3. X-ray crystallographic data

Crystallographic data for nannocystin Ax was stored in the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK. Copies of these data may be obtained free of charge from http://www.ccdc.cam.ac.uk/products/csd/request/ by quoting the public citation and deposition number CCDC 1519855.

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References

1. (a) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2016**, *79*, 629; (b) Buchanan, M. S.; Carroll, A. R.; Gadepalli, R.; Avery, V. M.; Hooper, J. N. A.; Quinn, R. J. *J. Nat. Prod.* **2007**, *70*, 2040; (c) Daletos, G.; Kalscheuer, R.; Koliwer-Brandl, H.; Hartmann, R.; Voogd, N. J.; Wray, V.; Lin, W. H.; Proksch, P. *J. Nat. Prod.* **2015**, *78*, 1910; (d) Kim, C. K.; Woo, J. K.; Lee, Y. J.; Lee, H. S.; Sim, C. J.; Oh, D. C.; Oh, K. B.; Shin, J. *J. Nat. Prod.* **2016**, *79*, 1179. (e) Li, Z.; Feng, J.; Zou, K.; Yang, Z.; Zhao, Y.; Xu, Z. J.; Li, B.; Shi, J. Y.; Li, Y. M.; Zhu, W. L.; Chen, K. X. *Chin. J. Chem.* **2016**, 34, 1165; (f) Zhang, L. Q.; Dai, X. L.; Tao, L. Z.; Xie, C. S.; Zhang, B.; Wang, M. *Chin. J. Chem.* **2017**, 35, 1165

2. (a) Hoffmann, H.; Kogler, H.; Heyse, W.; Matter, H.; Caspers, M.; Schummer, D.; Klemke-Jahn, C.; Bauer, A.; Penarier, G.; Debussche, L.; Brönstrup, M. *Angew. Chem., Int. Ed.* **2015**, *54*, 10145; (b) Krastel, P.; Roggo, S.; Schirle, M., Ross, N. T.; Perruccio, F.; Aspesi, P. J.; Asut, T.; Buntin, K.; Estoppey, D.; Liechy, B.; Mapa, F.; Memmert, K.; Miller, H.; Pan, X.; Riedl, R.; Thibaut, C.; Thomas, J.; Wagner, T.; Weber, E.; Xie, X.; Schmitt E. K.; Hoepfner, D. *Angew. Chem. Int. Ed.* **2015**, *54*, 10149.

3. (a) Liao, L.; Zhou, J.; Xu, Z.; Ye, T. *Angew. Chem., Int. Ed.* **2016**, *55*, 13263; (b) Huang, J.; Wang, Z. *Org. Lett.* **2016**, *18*, 4702; (c) Yang, Z.; Xu, X.; Yang, C.-H.; Tian, Y.; Chen, X.; Lian, L.; Pan, W.; Su, X.; Zhang, W.; Chen, Y. *Org. Lett.* **2016**, *18*, 5768; (d) Zhang, Y.-H.; Liu, R.; Liu, B. *Chem. Commun.* **2017**, *53*, 5549; (e) Liu, Q.; Hu, P.; He, Y. *J. Org. Chem.* **2017**, *82*, 9217; (f) Poock, C.; Kalesse, M. *Org. Lett.* **2017**, *19*, 4536; (g) Meng, Z-C.; Souillart, L.; Monks, B.; Huwyler, N.; Herrmann, J.; Müller, R.; Fürstner, A. *J. Org. Chem.* **2018**, *83*, 6997.

4. (a) Martí-Centelles, V.; Pandey, M. D.; Burguete, M. I.; Luis, A.V. *Chem. Rev.* **2015**, *115*, 8736; (b) Yeung, K. S.; Paterson, I. *Chem. Rev.* **2003**, *105*, 4237; (c) Parenty, A.; Moreau, X.; Niel, G.; Campagne, J. M. *Chem. Rev.* **2013**, *113*, PR1; (d) Parenty, A.; Moreau, X.; Campagne, J. M. *Chem. Rev.* **2006**, *106*, 991; (e) Mulzer, J.; Öhler, E. *Chem. Rev.* **2003**, *103*, 3753;

5. (a) Lee, C. J.; Liang, X. F.; Wu, Q. L.; Najeeb, J.; Zhao, J. S.; Gopalaswamy, R.; Titecat, M.; Sebbane, F.; Lemaitre, N.; Toone, E. J.; Zhou, P. *Nat. Com.* **2016**, *7*, 10638; (b) Wakimoto, T.; Asakawa, T.; Akahoshi, S.; Suzuki, T.; Nagai, K.; Kawagishi, H.; Kan, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 1168; (c) Nakamura, K.; Nishiyama, S.; Yamamura, S. *Tetrahedron Letters.* **1995**, *36*, 8621; (d) Suzuki, Y.; Nishiyama, S.; Yamamura, S. *Tetrahedron Letters.* **1989**, *30*, 6043; (e) Han, J. L.; Lian, J. T.; Tian, X.; Zhou, S. W.; Zhen, X. L.; Liu, S. X. Eur. *J.Org. Chem.* **2014**, *32*, 7232; (f) Katukojvala, S.; Barlett, K. N.; Lotesta, S. D.; Williams, L. J. *J. Am. Chem. Soc.* **2004**, *126*, 15348. (g) Dahiya, R.; Signgh, S. *Chin. J. Chem.* **2016**, 34, 1284. (h) Wakimoto, T.; Asakawa, T.; Akahoshi, S.; Suzuki, T.; Nagai, K.; Kawagishi, H.; Kan, T. *Angew. Chem. Int. Ed.* **2011**, *50*, 1168.

6. (a) Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayshi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604; (b) Yamaoka, M.; Nakazaki, A.; Kobayashi, S. *Tetrahedron Letters.* **2010**, *51*, 287; (c) Hosokawa, S.; Yokota, K.; Imamura, K.; Suzuki, Y.; Kawarasaki, M.; Tatsuta, K. *Tetrahedron Letters.* **2006**, *47*, 5415; (d) Nakamura, T.; Harachi, M.; Kano, T.; Mukaeda, Y.; Hosokawa, S. *Org. Lett.* **2013**, *15*, 3170; (e) Kato, T.; Sato, T.; Kashiwagi, Y.; Hosokawa, S. *Org. Lett.* **2015**, *17*, 2274; (f) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zarardi, F. *Chem. Rev.* **2011**, *111*, 3076.

7. (a) Schlaeger, N.; Kirschning, A. *Org. Biomol. Chem.* **2012**, *10*, 7721; (b) McGilvra, J. D.; Unni, A. K.; Modi, K.; Rawal, V. H. *Angew. Chem. Ind. Ed.* **2006**, *45*, 6130; (c) Denmark, S. E.; Ghosh, S. K. *Angew. Chem. Int. Ed.* **2001**, *40*, 4795.

8. (a) He, H. Y.; Tang, M. C.; Zhang, F.; Tang, G. L. *J. Am. Chem. Soc.* **2014**, *136*, 4488; (b) Mohapatra, D. K.; Umamaheshwar, G.; Rao, R. N.; Rao, T. S.; KumarR, S.; Yadav, J. S. *Org. Lett.* **2015**, *17*, 979; (c) Nicolaou, K.C.; Lim, Y. H.; Becker, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 3444; (d) Nicolaou, K.C.; Becker, J.; Lim, Y. H.; Lemire, A.; Neubauer, T.; Montero, A. *J. Am. Chem. Soc.* **2009**, *131*, 14812; (e) Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 521; (f) Xu, T.; Li, C. C.; Yang, Z. *Org. Lett.* **2011**, *13*, 2630; (g) Burn, E.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2016**, *81*, 8206.

9. (a) Tsukada, H.; Mukaeda, Y.; Hosokawa, S. *Org. Lett.* **2013**, *15*, 678; (b) Shirokawa, S.; Kamiyama, M.; Nakamura, T.; Okada, M.; Nakazaki, A.; Hosokawa, S.; Kobayshi, S. *J. Am. Chem. Soc.* **2004**, *126*, 13604; (c) Symkenberg, G.; Kalesse, M.; *Org. Lett.* **2012**, *14*, 1608; (d) Tatsuta, K.; Hosokawa, S. *Chem. Rev.* **2005**, *105*, 4707; (e) Sagawa, N.; Moriya, H.; Hosokawa, S. *Org. Lett.* **2017**, *19*, 250.

10. (a) Marshall, J. A.; Xie, S. P. *J. Org. Chem.* **1995**, *60*, 7230; (b) Gung, B. W.; Dickson, H. *Org. Lett.* **2002**, *4*, 2517; (c) Miller, N. A.; Willis, A. C.; Paddon-Raw, M. N.; Sherbum, M. S. *Angew. Chem. Int. Ed.* **2007**, *46*, 937; (d) Winkler, J. W.; Uddin, J.; Serhan, C. N.; Petasis, N. A. *Org. Lett.* **2013**. *15*, 1424; (e) Frost, J. R.; Pearson, C. M.; Snaddon, T. N.; Booth, R. A.; Turner, R. M.; Gold, J.; Shaw, D. M.; Gaunt, M. J.; Ley, S. V. *Chem. Eur. J.* **2015**, *21*, 13261.

11. (a) Organ, M. G.; Bratovanov, S. *Tetrahedron Letters.* **2000**, *41*, 6945; (b) Alvarez, S.; Alvarez, R.; de Lera, A. R. *Tetrahedron. Asymmetry.* **2004**, *15*, 839; (c) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2007**, *129*, 14556; (d) Trost, B. M.; Waser, J.; Meyer, A. *J. Am. Chem. Soc.* **2008**, *130*, 16424; (e) Villa, R.; Mandel, A. L.; Jones, B. D.; L-Clair, J. J.; Burkart, M. D. *Org. Lett.* **2012**, *14*, 5396.

12. Hara, S.; Makino, K.; Hamada, Y. *Tetrahedron Letters.* **2006**, *47*, 1081.

13. (a) Ernst, T.; Richert, C. *Synlett.* **2005**,, 411; (b) LIoyd, D. H.; Macdonald, R. L.; Otteson, K. M.; Noble, R. L. *Pept. Res.* **1991**, *4*, 95; (c) Xiao, Z. L.; Yang, M. G.; Li, P.; Carter, P. H. *Org. Lett.* **2009**, *11*, 1421; (d) Zou, B.; Wei, J. J.; Cai, G. R.; Ma, D. W. *Org. Lett.* **2003**, *5*, 3503; (e) Flemer, S.; Madalengotitia, J. S. *Synthesis*. **2007**, *38*, 1848; (f) Goyal, N. *Synlett.* **2010**, 335 (g) Wipf, P.; Xiao, J. B. *Org. Lett.* **2005**, *7*, 103; (g) Snider, B. B.; Che, Q. L. *Org. Lett.* **2004**, *6*, 2877; (h) Davis, S. G.; Lee, J. A.; Roberts, P. M.; Shah, R. S.; Thomson, J. E. *Chem. Comm.* **2012**, *48*, 9236; (i) Maeda, D. Y.; Peck, A. M.; Schuler, A. D.; Quinn, M. T.; Kirpotina, L. N.; Wicomb, W. N.; Fan, G. H.; Zebala, J. A. *J. Med. Chem.* **2014**, *57*, 8378. (j) Liu, X. S.; Chen, H. J.; Xu, Z. J.; Wu, Y. K.; Liu, B. *Chin. J. Chem*. **2017**, 35, 465.

14. (a) Paterson, I.; Man, J. *Tetrahedron Letters.* **1997**, 38, 695; (b) Williams, D. R.; Myers, B. J.; Liang, M.; Binder, R. J. *J. Org. Chem.* **2013**, *78*, 4762; (c) Chen, Q.; Schweitzer, D.; Kane, J.; Davisson, V. J.; Helquist, P. *J.Org. Chem.* **2011**, 76, 5157; (d) Pulukuri, K. K.; Chakraborty, T. K. *Org. Lett.* **2012**, *14*, 2858.

15. (a) Shimokawa, K.; Iwase, Y.; Miwa, R.; Yamada, K.; Uemura, D. *J. Med. Chem.* **2008**, *51*, 5912; (b) Prasad, N. D.; Lubell, W. D. *J. Org. Chem.* **2015**, 80, 4904; (c) Suzuki, N.; Suzuki, T.; Ota, Y.; Nakano, T.; Kurihara, M.; Okuda, H.; Yamori, T.; Tsumoto, H.; Nakagawa, H.; Miyata, N. *J. Med. Chem.* **2009**, *52*, 2909.

16. (a) Ernouf, G.; Brayer, J. L.; Folléas, B.; Demoute, J. P.; Meyer, C.; Cossy, J. *Org. Lett.* **2015**, *17*, 3786; (b) Qu, S. W.; Chen, Y.; Chen, S. P.; Xu, Z. S.; Ye, T. *Chem. Comm.* **2015**, *51*, 2510.

17. (a) Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2011**, *133*, 5744; (b) Sun, H. K.; Abbott, J. R.; Roush, W. R. *Org. Lett.* **2011**, *13*, 2734; (c) Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2012**, *134*, 3925; (d) Chen, M.; Roush, W. R. *Org. Lett.* **2012**, *14*, 426; (e) Chen, M.; Roush, W. R. *Org. Lett.* **2012**, *14*, 1880.

18. (a) Dettwiler, J. E.; Lubell, W. D. *Can. J. Chem.* **2004**, *82*, 318; (b) Jiang, X. G.; Zhang, J. S.; Ma, S. M. *J. Am. Chem. Soc.* **2016**, *138*, 8344. (c) Li, X. Y.; Jiao, N. *Chin. J. Chem.* **2017**, *35*, 1349.

19. (a) Pal, P.; Jana, N.; Nanda, S. *Org. Bio. Chem.* **2014**, *12*, 8257; (b) Smith III, A. B.; Williams, B. D. *J. Org. Chem.* **2014**, *79*, 9284. (c) Xiao, L.; Zhao, W.; Li, H. M.; Wan, D. J.; Li, D. S.; Chen, T.; Tang, Y. J. *Eur. J. Med. Chem.* **2014**, *80*, 267; (d) Chen, V. X.; Boyer, F. D.; Rameau, C.; Pillot, J. P.; Vors, J. P.; Beau, J. M. *Chem. Eur. J.* **2013**, *19*, 4849;

20. (a) Ghosez, L.; Haveuaux, B.; Viehe, H. *Angew.Chem. Int. Ed.* **1969**, *8*, 454; (b) Ghosez, L.; George-Koch, I.; Patiny, L.;

Houtekie, M.; Bovy, P.; Nshimyumukiza, P.; Phan, T. *Tetrahedron.* **1998**, *54*, 9207.

21. Peng, L. Z.; Zhang, F. Z.; Mei, T. S.; Zhang, T.; Li, Y. L. *Tetrahedron Letters.* **2003**, *44*, 5921.

22. (a) Hirano, T.; Noji, Y.; Shiraishi, T.; Ishigami-Yuasua, M.; Kagechika, H. *Tetrahedron,* **2016**, *72*, 4925; (b) Wright, J. S.; Shadnia, H.; Anderson, J. M.; Durst, T.; Asim, M.; EI-Salfiti, M.; Choueiri, C.; Christine Pratt, M. A.; Ruddy, S. C.; Lau, R.; Carlson, K. E.; Katzenellenbogen, J. A.; O`Brein, P. J.; Wan, L. *J. Med. Chem.* **2011**, *54*, 433.

23. (a) Chouhan, M.; Pal, A.; Sharma, R.; Nair, V. A. *Tetrahedron Letters.* **2013**, *54*, 7119; (b) Ling, T. T.; Potts, B. C.; Macherla, V. R.; *J. Org. Chem.* **2010**, *75*, 3882; (c) Mukaiyama, T.; Ogata, K.; Ono, T.; Hayashi, Y. *Chem. Cat. Chem.* **2015**, *7*, 155; (d) Fu, R.; Ye, J. L.; Dai, X. J.; Ruan, Y. P.; Huang, P. Q. *J. Org. Chem.* **2010**, 75, 4230; (e) Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.; Ohshima, T.; Shibashaki, M. *J. Am. Chem. Soc.* **2002**, *124*, 14544; (f) Inoki, S.; Takai, T.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* **1991**, 941