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Asymmetric Total Synthesis of Nannocystin A

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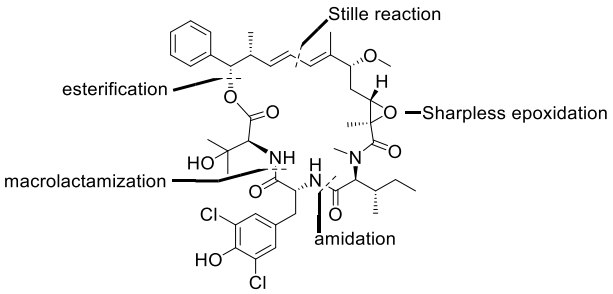
Supporting Information Placeholder



ABSTRACT: Nannocystin A is a novel 21-membered macrolactone isolated from myxobacterium *Nanocystis* sp. It is a potent elongation factor 1 inhibitor and inhibits cancer cell line growth at nanomolar concentrations. In this work, a concise asymmetric total synthesis of nannocystin A has been developed, which features Sharpless epoxidation, Stille coupling and final macrolactamization.

Natural products play key roles in drug discovery due to their unique architectures and interesting biological activities.[1] They either serve as drugs or inspire medicinal chemists to design natural product-like drugs. In 2015, two research teams led by Brönstrup[2] and Hoepfner[3] independently reported the discovery of nannocystin A (**1**), which is a novel and potent elongation factor 1 inhibitor with an IC_{50} of 1 nM against PC3 cell line.[2] Nannocystin A (Figure 1) is a 21-membered macrolactone which consists of a tripeptide, a polyketide and an epoxyamide moiety. The absolute configurations of the nine stereocenters were confirmed by X-ray crystallography analysis.

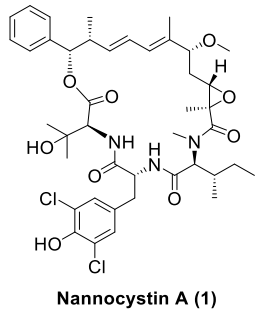
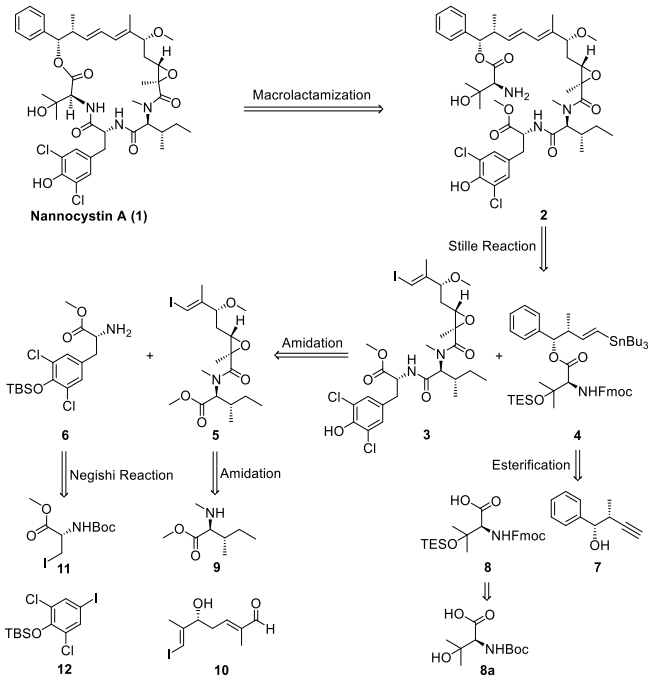


Figure 1. Structure of nannocystin A (**1**)

Due to its promising biological profiles and limited availability, nannocystin A has drawn much attention in the synthetic community. A number of research labs have engaged in its total synthesis. Ye[4] and co-workers finished the first total

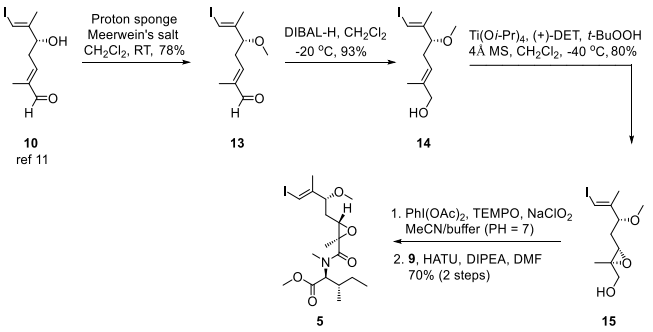


Scheme 1. Retrosynthetic analysis of nannocystin A

synthesis of nannocystin A, while Wang[5], Zhang and Chen[6] labs finished its synthesis soon after. Recently, Liu[7] finished the synthesis of nannocystin Ax. Continuing our interest in natural products with medicinal potential,[8] we pursued the total synthesis of nannocystin A, and successfully developed a concise and efficient asymmetric synthetic strategy.

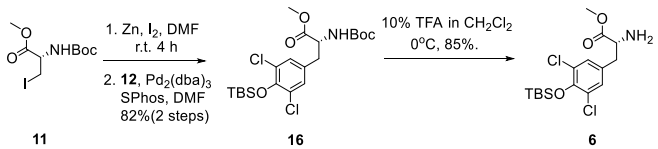
Our retrosynthetic analysis of nannocystin A is outlined in Scheme 1. Nannocystin A could be prepared via macrolatamization from a key precursor **2**, which could be assembled from intermediate iodide **3** and stannane **4** by intermolecular Stille coupling.[9] Stannane **4** could be accessed from propargyl alcohol **7** and acid **8** with DCC coupling, and iodide **3** could be assembled from epoxy fragment **5** and amine **6**. Fragment **5** could in turn be derived from *N*-methyl-L-isoleucine methy ester **9**[10] and aldehyde **10**. At last, amine **6** could be prepared from **11** and **12** via Negishi reaction.

As outlined in Scheme 2, the synthesis of fragment **5** started from the preparation of the known unsaturated aldehyde **10** according to the literature procedure.[11] Methylation of the free hydroxyl in **10** turned out to be a challenge. The starting aldehyde **10** decomposed with NaH/MeI, and the use of Ag_2O/MeI led to a sluggish reaction. To our delight, methylation with Meerwein's salt (Me_3OBF_4) and proton sponge proceeded smoothly to furnish the corresponding ether in 78% yield,[12] which was reduced with DIBAL-H to provide allylic alcohole **14** in 93% yield. Sharpless asymmetric epoxidation[13] of **14** gave epoxy alcohol **15**[4,6] in excellent yield, which was converted to epoxy acid directly with $PhI(OAc)_2$/TEMPO/$NaClO_2$ in MeCN/buffer (PH = 7). Subsequent condensation of the resulting acid with amine **9** led to fragment **5** in 70% yield.

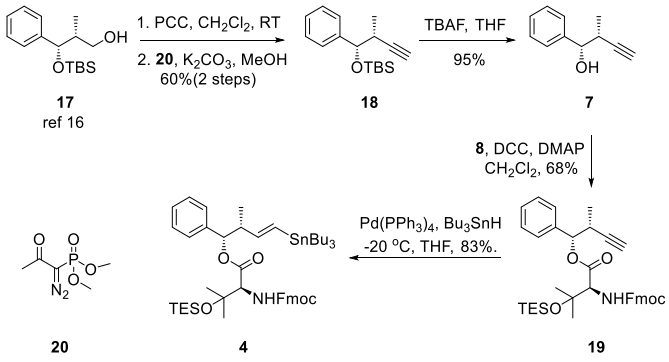


Scheme 2. Synthesis of fragment **5**

Amino ester **6** was prepared from β−iodo-D-alanine ester **11**[14] in three steps (Scheme 3). Ester **11** and aryl iodide **12** were first combined under Negishi condition, and the best result was achieved by applying the combination of $Pd_2(dba)_3$ and SPhos in DMF,[15] furnishing the desired amine derivative **16** in 82% yield. After deprotection of the Boc group with TFA, amine **6** was isolated in 85% yield.

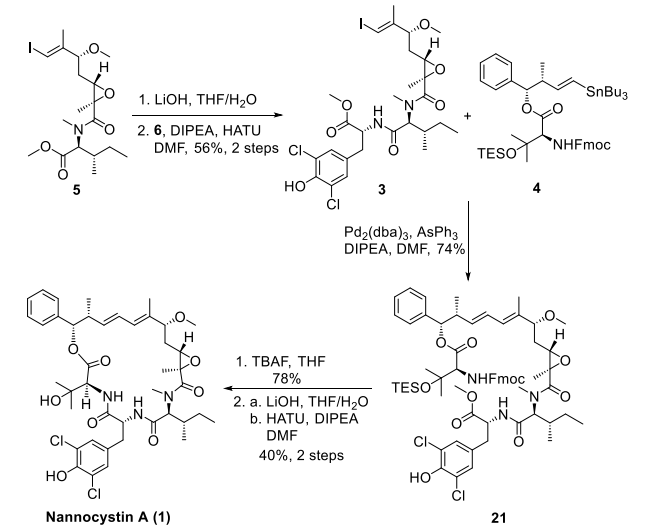


Scheme 3. Synthesis of amino ester fragment **6**



Scheme 4. Synthesis of stannane fragment **4**

As shown in Scheme 4, intermediate **17** was synthesized according to Evans' protocol from the corresponding benzaldehyde.[16] Alkyne **18** was prepared from alcohol **17** via PCC oxidation, followed by a modified Seyferth–Gilbert homologation.[17] Removal of the TBS group with TBAF provided alcohol **7** in 95% yield. Subsequent esterification of **7** with acid **8** proved to be another unexpected challenge. After various explorations, we finally found that the TES protection in **8** was crucial for the successful transformation.[18] Palladium catalyzed hydrostannylation ($Pd(PPh_3)_4$, Bu_3SnH)[19] of **19** provided vinyl stannane **4** in 83% yield.



Scheme 5. Total synthesis of nannocystin A

The assembly of nannocystin A is shown in Scheme 5. Hydrolysis of methyl ester **5** with lithium hydroxide in THF/H_2O successfully furnished the corresponding carboxylic acid, which was coupled with amine **6** using HATU/DIPEA. Interestingly, the TBS group was removed under the amide coupling condition, furnishing iodide **3** directly. With precursors **3** and **4** in hand, we turned our attention to construct the key macrolactamization precursor **21** with the Stille reaction. Various catalytic systems were screened and $Pd_2(dba)_3$/$AsPh_3$/DIPEA was found to be most effective for the intermolecular Stille coupling,[20] providing **21** in 74% yield. The TES and Fmoc groups were removed with TBAF solution in

one pot, giving rise to the corresponding amino ester **2** in 78% yield. Finally, nannocystin A was achieved via a two step sequence. The methyl ester was first hydrolyzed with lithium hydroxide, and the resulting carboxylic acid was then treated with HATU/DIPEA to furnish nannocystin A in 40% overall yield. The spectral data (^{1}H NMR, ^{13}C NMR, HRMS) of nannocystin A (1) were identical to those reported by Dr. Dominic Hoepfner and co-workers (See SI for details).[3]

In summary, we have developed a concise strategy for the synthesis of nannocystin A. Overall, nannocystin A was prepared in 11 longest linear steps from **10** (5.3 % overall yield). This convergent strategy is amenable for diverse analog preparations. The structure–activity-relationship (SAR) studies of nannocystin A are currently ongoing in our laboratory, and the results will be reported in due course.

EXPERIMENTAL SECTION

General information. Unless otherwise noted, all reactions were carried out in oven-dried glassware under nitrogen atmosphere. Tetrahydrofuran (THF) were dried and distilled from sodium. Dichloromethane (CH_2Cl_2) were distilled from calcium hydride. Methanol (MeOH) was dried under reflux with magnesium and then distilled. *N*,*N*-Dimethylformamide (DMF) was dried over calcium hydride and distilled under vacuum. Reactions were monitored by analytical thin-layer chromatography (TLC) on Merck silica gel 60 F_{254} plates (0.25 mm), visualized by ultraviolet light and/or by staining with ceric ammonium molybdate or potassium permanganate. ^{1}H NMR spectra were obtained on an Agilent 400MR or 600MR DD2 spectrometer at ambient temperature. Data were reported as follows: chemical shift on the δ scale using residual proton solvent as internal standard [δ 7.26 ($CDCl_3$), 2.50 (DMSO-d_6),], multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, and coupling constant (*J*) in Hertz. ^{13}C NMR spectra were obtained with proton decoupling on an Agilent 400MR or 600MR DD2 (100 MHz or 150 MHz) spectrometer and were reported in ppm with residual solvent for internal standard [δ 77.0 ($CDCl_3$), 39.51 (DMSO-d_6)]. High resolution mass spectra were obtained on a Bruker SolariX 7.0T FT-ICR MS spectrometer. Optical rotations were measured with a Rudolph polarimeter. IR spectra were recorded on a Bruker 100 FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Abbreviations: Boc = *tert*-butoxycarbonyl, DCC = dicyclohexylcarbodiimide, DIBAL-H = diisobutyl aluminium hydride, DIPEA = *N*,*N*-diisopropylethylamine, DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, DMP = Dess-Martin periodinane, Fmoc = 9-fluorenylmethoxycarbonyl, HATU = 1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate, Ohira-Bestmann reagent = dimethyl (1-diazoacetonyl)phosphonate, $Pd_2(dba)_3$ = tris(dibenzylideneacetone)dipalladium, SPhos = 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, TES = triethylsilyl, TFA = trifluoroacetic acid, THF = tetrahydrofuran, Tf = trifluoromethanesulfonyl, PCC = pyridinium chlorochromate, TEMPO = (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl.

Experimental Procedures.

*tert-Butyl(2,6-dichloro-4-iodophenoxy)dimethylsilane (**12**).*

To a solution of 2,6-dichlorophenol (3.2 g, 20 mmol, 1.0 equiv) in THF (50 mL), were added NIS (6.6 g, 30 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred at room temperature for 3 h. After quenching with saturated $Na_2S_2O_3$ (40 mL) and EtOAc (50 mL), the layers were separated, and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting white solid was used directly for the next step. The above product was dissolved in CH_2Cl_2 (30 mL), imidazole (2.0 g, 30 mmol, 15 equiv) and TBSCl (4.5 g, 30 mmol, 1.5 equiv) were added, and the reaction was stirred at room temperature for 8 h. After quenching with H_2O (30 mL), the organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified with silica gel column chromatography (eluted with petroleum ether) to afford compound **12** (7.0 g, 87%) as colorless oil. IR (KBr) ν_{max} 3456, 2933, 2858, 1638, 1458, 1281, 908, 806 cm^{-1};^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 2H), 1.04 (s, 9H), 0.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 137.0, 127.8, 82.0, 25.9, 18.9, -3.1; HRMS (EI): calcd for $C_{12}H_{17}Cl_2IOSi^+$ [M^+] 401.9471, found 401.9468.

*Methyl (R)-2-((tert-butoxycarbonyl)amino)-3-(4-((tert-butyldimethylsilyl)oxy)-3,5-dichlorophenyl)propanoate (**16**).*

Zn dust (9.5 g, 146 mmol, 6.0 equiv) was added to a flame-dried, two-necked round bottom flask under a N_2 atmosphere. Dry DMF (20 mL) was added, followed by a catalytic amount of iodine (617 mg, 2.4 mmol, 0.1 equiv). A solution of **11** (8.0 g, 24 mmol, 1.0 equiv) in DMF (8 mL) was added slowly at room temperature. The solution was stirred at room temperature for 4 h under N_2, and then stood for half an hour. The supernatant was used for the next step directly. To a solution of compound **12** (6.0 g, 15 mmol, 0.6 equiv) in dry DMF (15 mL), were added $Pd_2(dba)_3$ (1.2 g, 1.5 mmol, 0.06 equiv) and SPhos (1.2 g, 5 mmol, 0.2 equiv) at room temperature. The above supernatant was added slowly to the solution in 3 batches with an interval of 30 min. The resulting mixture was stirred at room temperature for 8 h under N_2. DMF was evaporated in *vacuo* and the residue was diluted with EtOAc (20 mL). The mixture was washed with H_2O (15 mL), and the aqueous layer was extracted with EtOAc (15 mL × 2). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified with silica gel column chromatography (petroleum ether : EtOAc, 15:1) to afford the product **16** (5.8 g, 82%) as yellow oil. $[\alpha]_D^{28}$ = -45 (*c* 0.2, $CHCl_3$); IR (KBr) ν_{max} 3440, 3360, 2936, 2860, 1715, 1477, 1289, 1168, 844, 796 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.02 (s, 2H), 5.03 (d, *J* = 8 Hz, 1H), 4.55-4.47 (m, 1H), 3.72 (s, 3H), 3.02 (dd, *J* = 14, 5.6 Hz, 1H), 2.89 (dd, *J* = 13.6, 6 Hz, 1H), 1.43 (s, 9H), 1.04 (s, 9H), 0.27 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 154.9, 147.3, 130.4, 129.5, 126.5, 80.1, 54.2, 52.3, 37.1, 28.2, 25.9, 18.8, -3.2; HRMS (ESI): calcd for $C_{21}H_{33}Cl_2NNaO_5Si^+$ [M+Na^+] 500.1397, found 500.1390.

*Methyl (R)-2-amino-3-(4-((tert-butyldimethylsilyl)oxy)-3,5-dichlorophenyl) propanoate (**6**).*

To a solution of **16** (1.0 g, 2.1 mmol, 1.0 equiv) in CH_2Cl_2 (5 mL), were added TFA (0.5 mL) at 0 °C. The reaction was stirred at this temperature for 8 h. After quenching with H_2O (10 mL), the organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concen-

trated and purified with silica gel column chromatography (petroleum ether:EtOAc, 1:2) to afford compound **6** (670 mg, 85%) as colorless oil and the spectroscopic data are consistent with those reported in literature[6].^{1}H NMR (400 MHz, $CDCl_3$) δ 7.10 (s, 2H), 3.71 (s, 3H), 3.67 (dd, J = 7.6, 5.2 Hz, 1H), 2.94 (dd, J = 13.6, 4.8 Hz, 1H), 2.73 (dd, J = 14, 8 Hz, 1H), 1.04 (s, 9H), 0.28 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 147.1, 131.5, 129.4, 126.6, 55.6, 52.1, 39.8, 26.0, 18.8, -3.1, -3.2.

*(R,2E,6E)-7-Iodo-5-methoxy-2,6-dimethylhepta-2,6-dienal (**13**).*

To a solution of **10** (100 mg, 0.36 mmol, 1.0 equiv) (^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1H), 6.50 (t, J = 4 Hz, 1H), 6.40 (s, 1 H), 4.38 (t, J = 6.4 Hz, 1H), 2.62 (t, J = 8 Hz, 2 H), 1.86 (s, 3 H), 1.75 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.8, 148.9, 148.6, 141.2, 79.3, 75.2, 34.5, 20.0, 9.5) in CH_2Cl_2 (5 mL) was added proton sponge (230 mg, 1 mmol, 3.0 equiv) and trimethyloxonium tetrafluoroborate (133 mg, 0.9 mmol, 2.5 equiv) at room temperature. After 3 h, the reaction was quenched with H_2O (5 mL), the organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (10 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified with silica gel column chromatography (petroleum ether:EtOAc, 30:1) to afford compound **13** (83 mg, 78%) as colorless oil. $[\alpha]_D^{28}$ = +4.8 (*c* 0.1, $CHCl_3$); IR (KBr) ν_{max} 3456, 1681, 1641, 1267, 1097, 740 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.40 (s, 1 H), 6.48-6.40 (m, 1H), 6.30 (s, 1 H), 3.85-3.76 (m, 1H), 3.23 (s, 3H), 2.70-2.57 (m, 1H), 2.57-2.45 (m, 1H), 1.79 (s, 3H), 1.73 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.9, 149.1, 146.8, 140.8, 84.5, 79.9, 56.6, 33.5, 18.9, 9.4; HRMS (DART): calcd for $C_{10}H_{19}O_2NI^+$ [M+NH_4^+] 312.0460, found 312.0455.

*(R,2E,6E)-7-Iodo-5-methoxy-2,6-dimethylhepta-2,6-dien-1-ol (**14**).*

To a solution of **13** (550 mg, 1.8 mmol, 1.0 equiv) in CH_2Cl_2 (15 mL) at -40 °C was added DIBAL-H (2.8 mL, 2.8 mmol, 1.5 equiv, 1 M in toluene) in 5 min. The reaction was stirred at this temperature for 1 h, the reaction was quenched with saturated sodium potassium tartrate (15 mL), the mixture was extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified with silica gel column chromatography (petroleum ether:EtOAc, 5:1) to afford compound **14** (495 mg, 93%) as colorless oil and the spectroscopic data are consistent with those reported in literature[4,6]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.19 (s, 1H), 5.33 (t, J = 6.8 Hz, 1H), 4.00 (s, 2H), 3.66 (t, J = 6.8 Hz, 1H), 3.20 (s, 3H), 2.40-2.30 (m, 1H), 2.29-2.17 (m, 1 H), 1.75 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.5, 137.1, 120.9, 85.7, 79.1, 68.6, 56.5, 32.1, 18.8, 13.9.

*((2S,3S)-3-((R,E)-4-Iodo-2-methoxy-3-methylbut-3-en-1-yl)-2-methyloxiran-2-yl)methanol (**15**).*

A suspension of Ti(O*i*-Pr)$_4$ (68 mg, 0.24 mmol, 0.1 equiv), L-(+)-DET (100 mg, 0.48 mmol, 0.2 equiv), *t*-BuOOH (3.6 mL, 12 mmol, 5 equiv, 3.3 M in toluene) and 4Å MS (2 g) at –40 °C were stirred in CH_2Cl_2 (10 mL) for 1 h. A solution of **14** (700 mg, 2.4 mmol, 1.0 equiv) in CH_2Cl_2 (3 mL) was added dropwise, the reaction was stirred for 24 h. The reaction was quenched with H_2O (15 mL), the mixture was filtered through a pad of Celite by CH_2Cl_2. The layers were separated, the organic layer was collected and the aqueous layer was extracted with CH_2Cl_2 (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated and purified with silica gel column chromatography (petroleum ether:EtOAc, 4:1) to afford compound **15** (600 mg, 82%) as colorless oil and the spectroscopic data are consistent with those reported in literature[4,6]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (s, 1H), 3.83 (t, J = 8 Hz, 1H), 3.65 (dd, J = 12, 4 Hz, 1H), 3.53 (dd, J = 12, 8 Hz, 1H), 3.21 (s, 3H), 3.01-2.95 (m, 1H), 2.02-1.94 (m, 1H), 1.76 (s, 3H), 1.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.1, 83.9, 79.8, 65.2, 60.7, 56.9, 56.4, 32.6, 18.6, 14.4.

*tert-Butyldimethyl(((1S,2R)-2-methyl-1-phenylbut-3-yn-1-yl)oxy)silane (**18**).*

To a solution of **17** (1.0 g, 3.6 mmol, 1.0 equiv) (^{1}HNMR (400 MHz, $CDCl_3$) δ 7.35-7.22 (m, 5H), 4.83 (d, J = 4.4 Hz, 1H), 3.58 (dd, J = 10.8, 8.4 Hz, 1H), 3.44 (dd, J = 10.4, 4.4 Hz, 1H), 2.65-2.50 (m, 1H), 2.10-2.00 (m, 1H), 0.91 (s, 9 H), 0.77 (d, J = 7.2 Hz, 3H), 0.05 (s, 3H), -0.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3, 127.8, 127.1, 126.7, 77.4, 65.4, 42.9, 25.8, 18.1, 11.8, -4.7, -5.3) in CH_2Cl_2 (10 mL) was added PCC (2.3 g, 10.7 mmol, 3.0 equiv) at 0 °C. The reaction was stirred at room temperature for 3 h. the mixture filtered through Celite in filter funnel with EtOAc. The solvent was removed under reduced pressure to provide the aldehyde, which was used in the next step without further purification. To a solution of aldehyde in MeOH (10 mL) at 0 °C was added Ohira-Bestmann Reagent (770 mg, 4 mmol, 1.4 equiv) and K_2CO_3 (478 mg, 3.4 mmol, 1.2 equiv). The reaction was stirred at room temperature for 4 h. The reaction was quenched by the addition of water (10 mL), The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether : EtOAc, 20:1) to give the product **18** (550 mg, 60%) as colorless oil. $[\alpha]_D^{28}$ = -31.5 (*c* 0.7, $CHCl_3$); IR (KBr) ν_{max} 3307, 2936, 2860, 2114, 1462, 1255, 1082, 1016, 840, 778, 635 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38-7.23 (m, 5H), 4.60 (d, J = 6.4 Hz, 1H), 2.71-2.63 (m, 1H), 1.99 (d, J = 2 Hz, 1H), 1.21 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), -0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.1, 127.7, 127.3, 126.8, 86.7, 77.7, 70.0, 35.5, 25.8, 18.2, 16.4, -4.7, -5.0; HRMS (DART): calcd for $C_{11}H_{16}ON^+$ [M+NH_4^+] 178.1232, found 178.1226.

*(1S,2R)-2-Methyl-1-phenylbut-3-yn-1-ol (**7**).*

To a solution of **18** (2.2 g, 8 mmol, 1.0 equiv) in THF (20 mL) was added TBAF (4.2 g, 16 mmol, 2.0 equiv) at room temperature, The reaction was stirred at room temperature for 3 h. The reaction was quenched by the addition of water (20 mL), The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane : EtOAc (2 : 1) as the eluent to give the product **7** (1.2 g, 95%) as colorless oil. $[\alpha]_D^{28}$ = -45 (*c* 0.3, $CHCl_3$); IR (KBr) ν_{max} 3296, 2981, 2885, 2112, 1494, 1454, 1026, 754, 701, 564 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40-7.28 (m, 5H), 4.72-4.68 (m, 1H), 3.00-2.82 (m, 1H), 2.60-2.45 (m, 1H), 2.12 (d, J = 2.4 Hz, 1H), 1.15 (d, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 128.1, 127.8, 126.5, 85.8, 76.1, 70.9, 33.9, 15.5; HRMS (DART): calcd for $C_{17}H_{30}ONSi^+$ [M+NH_4^+] 292.2097, found 292.2091.

*(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methyl-3-((triethylsilyl)oxy)butanoic acid (**8**).*

To a solution of **8a**[21] (270 mg, 1.15 mmol, 1.0 equiv) in CH_2Cl_2 (10 mL) and followed by the addition of TFA (2 mL). The reaction was stirred at room temperature for 10 h. Volatiles were removed by vacuo, the deprotected product was used for next step directly.

The aforementioned crude product was dissolved in H_2O (2 mL) and MeCN (2 mL), followed by the addition of $NaHCO_3$ (290 mg, 3.45 mmol, 3.0 equiv), FMOC-Cl (600 mg, 2.30 mmol, 2.0 equiv). The reaction was stirred at room temperature for 4 h. The solution was diluted with water (10 mL) and EtOAc (10 mL), the layers were separated and the aqueous layer was extracted with EtOAc (10 mL × 3), The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated, the crude product was used for next step directly.

The above crude product in CH_2Cl_2 (10 mL) and followed by the addition of TESCl (345 mg, 2.30 mmol, 2.0 equiv), imidazole (240 mg, 3.45 mmol, 3.0 equiv). The reaction was stirred at room temperature for 24 h before it was quenched with H_2O (10 mL), The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column (CH_2Cl_2 : MeOH, 20:1) to give the product **8** (370 mg, 69%, 3 steps) as colorless oil. $[\alpha]_D^{28}$ = +26 (*c* 0.3, $CHCl_3$); IR (KBr) ν_{max} 3421, 2955, 2882, 1716, 1527, 1237, 1072, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.60 (t, *J* = 7.2 Hz, 2H), 7.45-7.35 (m, 2H), 7.31 (t, *J* = 7.2 Hz, 2H), 5.60 (d, *J* = 8.8 Hz, 1H), 4.41 (d, *J* = 7.2 Hz, 2H), 4.33-4.20 (m, 2H), 1.43 (s, 3H), 1.28 (s, 3H), 0.98 (t, *J* = 8 Hz, 9H), 0.67 (q, *J* = 7.6 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.2, 156.5, 143.8, 143.6, 141.3, 127.7, 127.0, 125.1, 119.9, 76.2, 67.2, 62.5, 47.1, 27.4, 26.3, 6.8, 6.4; HRMS (ESI): calcd for $C_{26}H_{35}NNaO_5Si^+$ [M+Na^+] 492.2176, found 492.2167.

*(1S,2R)-2-Methyl-1-phenylbut-3-yn-1-yl(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methyl-3-((triethylsilyl)oxy)butanoate (**19**).*

To a solution of **7** (270 mg, 1.7 mmol, 1.0 equiv) and **8** (900 mg, 2 mmol, 1.2 equiv) in CH_2Cl_2 (10 mL) was added DCC (520 mg, 2.5 mmol, 1.5 equiv) and DMAP (20 mg, 0.17 mmol, 0.1 equiv). The reaction was stirred at room temperature for 8 h, the reaction was quenched by the addition of water (20 mL), The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (petroleum ether : EtOAc, 10:1) to give the product **19** (700 mg , 68%) as colorless oil. $[\alpha]_D^{28}$ = -21 (*c* 0.15, $CHCl_3$); IR (KBr) ν_{max} 3441, 3305, 2938, 2880, 2119, 1723, 1660, 1506, 1455, 1214, 1047, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.6 Hz, 2H), 7.64-7.58 (m, 2H), 7.44-7.36 (m, 4H), 7.34-7.27 (m, 5H), 5.72 (d, *J* = 8 Hz, 1H), 5.63 (d, *J* = 9.2 Hz, 1H), 4.43-4.30 (m, 2H), 4.27-4.17 (m, 2 H), 3.11-3.02 (m, 1H), 2.02-1.96 (m, 1H), 1.32-1.20 (m, 9H), 0.89 (t, *J* = 8 Hz, 9H), 0.50 (q, *J* = 8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 156.1, 144.0, 143.8, 141.3, 137.3, 128.4, 128.0, 127.9, 127.7, 127.0, 126.5, 125.2, 120.0, 84.1, 78.7, 74.7, 71.3, 67.1, 63.2, 47.2, 31.9, 28.4, 27.6, 17.6, 6.9, 6.4; HRMS (ESI): calcd for $C_{37}H_{45}NNaO_5Si^+$ [M+Na^+] 634.2959, found 634.2959.

*(1S,2R,E)-2-Methyl-1-phenyl-4-(tributylstannyl)but-3-en-1-yl(S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methyl-3-((triethylsilyl)oxy)butanoate (**4**).*

To a solution of **19** (600 mg, 1 mmol, 1.0 equiv) in THF (20 mL) at -20 °C was added $Pd(PPh_3)_4$ (60 mg, 0.05 mmol, 0.05 eq) and followed by the addition of Bu_3SnH (436 mg, 1.5 mmol, 1.5 eq). After the reaction was stirred at -20 °C for 1 h, the reaction was quenched by the addition of water (20 mL), The layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a solution of hexane : EtOAc (20 : 1) as the eluent to give the product **4** (750 mg, 83%) as colorless oil. $[\alpha]_D^{28}$ = -22.5 (*c* 0.2, $CHCl_3$); IR (KBr) ν_{max} 3442, 2957, 2923, 1732, 1598, 1503, 1196, 1048, 742 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.6 Hz, 2H), 7.63 (t, *J* = 7.6 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.36-7.20 (m, 7H), 5.90-5.78 (m, 1H), 5.70-5.60 (m, 3H), 4.48-4.32 (m, 2H), 4.31-4.17 (m, 2H), 2.86-2.70 (m, 1H), 1.48-1.32 (m, 6H), 1.33-1.20 (m, 12H), 1.18-1.07 (m, 3H), 0.95-0.81 (m, 18H), 0.80-0.70 (m, 6H), 0.56-0.43 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 156.1, 148.4, 144.0, 143.8, 141.3, 138.5, 129.8, 128.0, 127.8, 127.6, 127.0, 125.2, 119.9, 80.9, 74.7, 67.0, 63.1, 47.2, 46.3, 28.9, 28.5, 27.6, 27.2, 16.5, 13.6, 9.3, 6.9, 6.4; HRMS (ESI): calcd for $C_{49}H_{73}NNaO_5S_iSn^+$ [M+Na^+] 926.4182, found 926.4170.

*Methyl methyl-L-isoleucinate (**9**)*

To a solution of methyl *N*-(*tert*-butoxycarbonyl)-*N*-methyl-L-isoleucinate[22] (3.3 g, 12.7 mmol, 1.0 equiv) in CH_2Cl_2 (25 mL) at °C was added TFA (3 mL). After the reaction was stirred at room temperature for 3 h, the solvent was removed by vacuo, purified with silica gel column chromatography (petroleum ether : EtOAc, 1:1) to afford compound **9** (2.0 g, 99%) as colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (s, 3H), 3.75 (d, *J* = 3.6 Hz, 1H), 2.72 (s, 3H), 2.12-2.02 (m, 1H), 1.60-1.48 (m, 1H), 1.00-0.93 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 65.3, 52.7, 35.8, 32.4, 26.5, 14.2, 11.5; HRMS (ESI): calcd for $C_8H_{17}NNaO_2^+$ [M+Na^+] 182.1152, found 182.1152.

*Methyl N-((2R,3S)-3-((R,E)-4-iodo-2-methoxy-3-methylbut-3-en-1-yl)-2-methyloxirane-2-carbonyl)-N-methyl-L-isoleucinate (**5**).*

To a solution of **15** (100 mg, 0.32 mmol, 1.0 equiv) in MeCN (5 mL) and buffer (PH = 7, 5 mL) at 0 °C were added $PhI(OAc)_2$ (10 mg, 0.03 mmol, 0.1 equiv), TEMPO (10 mg, 0.06 mmol, 0.2 equiv) and $NaClO_2$ (75 mg, 0.95 mmol, 3.0 equiv). The reaction was stirred for 2 h at room temperature. The solution was diluted with water (10 mL) and EtOAc (10 mL), the layers were separated and the aqueous layer was extracted with EtOAc (20 mL × 3), The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated and filtered through silica gel in filter funnel with EtOAc to give the acid, which was used for next step without further purification.

To a solution of above mentioned acid and **9** (88 mg, 0.55 mmol, 2.0 equiv) in DMF (5 mL) were sequentially added HATU (210 mg, 0.55 mmol, 2.0 equiv) and DIPEA (140 mg, 1.1 mmol, 4.0 equiv) at room temperature. The reaction was stirred at room temperature for 12 h. Solvent was removed by vacuo and purified with silica gel column chromatography (petroleum ether : EtOAc, 4:1) to afford compound **5** (106 mg, 83%) as colorless oil (1:1 mixture of rotamers). $[\alpha]_D^{28}$ = -59 (*c* 0.3, $CHCl_3$); IR (KBr) ν_{max} 3554, 3477, 3415, 2967, 2933, 1742,

1648, 1460, 1402, 1261, 1198, 1098, 1003 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1H), 4.82 (d, *J* = 10.4 Hz, 0.5H), 4.59 (d, *J* = 10.8 Hz, 0.5H), 3.85 (q, *J* = 6.4 Hz, 1H), 3.72 (s, 1.5H), 3.67 (s, 1.5H), 3.21 (s, 3H), 3.10-3.04 (m, 0.5H), 3.05 (s, 1.5H), 3.0-2.94 (m, 0.5H), 2.79 (s, 1.5H), 2.10-1.83 (m, 2H), 1.76 (s, 3H), 1.76-1.68 (m, 1H), 1.51 (s, 1.5H), 1.47 (s, 1.5H), 1.37-1.25 (m, 1H), 1.10-0.97 (m, 1H), 0.96-0.83 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 171.0, 170.8, 170.4, 146.7, 83.7, 83.5, 80.2, 80.0, 63.7, 60.8, 60.6, 60.0, 59.4, 59.2, 56.5, 52.0, 51.8, 33.6, 32.9, 32.8, 32.4, 30.7, 28.7, 24.6, 24.1, 18.7, 18.6, 15.8, 15.7, 15.2, 11.5, 10.6; HRMS (ESI): calcd for $C_{18}H_{30}INNaO_5^+$ [M+Na^+] 490.1060, found 490.1055.

*Methyl (R)-3-(3,5-dichloro-4-hydroxyphenyl)-2-((2S,3S)-2-((2R,3S)-3-((R,E)-4-iodo-2-methoxy-3-methylbut-3-en-1-yl)-N,2-dimethyloxirane-2-carboxamido)-3-methylpentaaido)propanoate (**3**).*

To a solution of **5** (80 mg, 0.17 mmol, 1.0 equiv) in THF/H_2O (2/2 mL) at 0 °C was added LiOH (8 mg, 0.34 mmol, 2.0 equiv), the reaction was allowed to stirred at room temperature for 12 h. Diluted with EtOAc (10 mL) and H_2O (5 mL), the layers were separated and the aqueous layer was extracted with EtOAc (10 mL × 3), The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated and filtered through silica gel in filter funnel with EtOAc to give the acid used for the following step directly.

The resulting crude acid was dissolved in DMF (5 mL), **6** (200 mg, 0.54 mmol, 3.0 equiv), HATU (90 mg, 0.34 mmol, 2.0 equiv) and DIPEA (70 mg, 0.54 mmol, 3.0 equiv) was added at room temperature, the reaction was stirred at this temperature for 1 day. Solvent was removed by vacuo and purified with silica gel column chromatography (petroleum ether : EtOAc, 2:1) to afford compound **3** (66 mg, 56%, 2 steps) as colorless oil. $[\alpha]_D^{28}$ = -23 (*c* 0.3, $CHCl_3$); IR (KBr) ν_{max} 3551, 3478, 3414, 2960, 2925, 2854, 1744, 1639, 1491, 1464, 1280, 1093, 795, 614 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (s, 2H), 6.60 (d, *J* = 8 Hz, 1H), 6.35 (s, 1H), 5.84 (s, 1H), 4.77-4.67 (m, 1H), 4.45 (d, *J* = 11.6 Hz, 1H), 3.89 (t, *J* = 6.4 Hz, 1H), 3.72 (s, 3H), 3.23 (s, 3H), 3.11-3.00 (m, 2H), 2.96 (s, 3H), 2.90-2.81 (m, 1H), 2.20-2.05 (br, 1H), 1.93-1.82 (m, 2H), 1.79 (s, 3H), 1.46 (s, 3H), 1.35-1.26 (m, 1H), 1.05-0.93 (m, 1H), 0.92-0.78 (m, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 171.1, 169.3, 146.9, 146.7, 129.6, 128.9, 121.1, 83.7, 80.2, 61.5, 60.5, 59.2, 56.5, 52.8, 52.5, 36.6, 32.8, 30.8, 30.7, 24.3, 18.8, 15.5, 15.1, 10.4; HRMS (ESI): calcd for $C_{27}H_{37}Cl_2IN_2NaO_7^+$ [M+Na^+] 721.0914, found 721.0905.

*(1S,2R,3E,5E,7R)-8-((2S,3R)-3-(((2S,3S)-1-(((R)-3-(3,5-Dichloro-4-hydroxyphenyl)-1-methoxy-1-oxopropan-2yl)amino)-3-methyl-1-oxopentan-2-yl)(methyl)carbamoyl)-3-methyloxiran-2-yl)-7-methoxy-2,6-dimethyl-1-phenylocta-3,5-dien-1-yl (S)-2-((((9H-fluoren-9-yl)methoxy)carbonyl)amino)-3-methyl-3-((triethylsilyl)oxy)butanoate (**21**).*

To a solution of **3** (16 mg, 0.023 mmol, 1.0 equiv) and **4** (25 mg, 0.028 mmol, 1.2 equiv) in DMF (2 mL) were added $Pd_2(dba)_3$ (4 mg, 0.0046 mmol, 0.2 equiv), $As(Ph)_3$ (14 mg, 0.46 mmol, 2.0 equiv) and DIPEA (16 mg, 0.125 mmol, 5.0 equiv) at room temperature, the reaction was stirred at this temperature for 8 h. Solvent was removed by vacuo and purified with silica gel column chromatography (petroleum ether : EtOAc, 1:1) to afford compound **21** (20 mg, 74%) as colorless oil. $[\alpha]_D^{28}$ = -40 (*c* 0.2, $CHCl_3$); IR (KBr) ν_{max} 3453, 2962, 2924, 1639, 1492, 1452, 1327, 1085, 794, 743 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.2 Hz, 2H), 7.64-7.57 (m, 2H), 7.42-7.36 (m, 2H), 7.33-7.28 (m, 2H), 7.28-7.25 (m, 5H), 7.04 (s, 2H), 6.64 (d, *J* = 7.8 Hz, 1H), 6.12 (dd, *J* = 15, 10.8 Hz, 1H), 5.93 (s, 1 H), 5.89 (d, *J* = 10.2 Hz, 1H), 5.68 (d, *J* = 9.6 Hz, 1H), 5.65 (d, *J* = 7.8 Hz, 1H), 5.43 (dd, *J* = 15.6, 7.8 Hz, 1H), 4.75-4.67 (m, 1H), 4.46-4.36 (m, 2H), 4.35-4.28 (m, 1H), 4.24 (t, *J* = 7.2 Hz, 1H), 4.20 (d, *J* = 9.6 Hz, 1H), 3.77-3.11 (m, 1H), 3.68 (s, 3H), 3.64 (t, *J* = 6.6 Hz, 1H), 3.12 (s, 3H), 3.09-3.01 (m, 2H), 2.94 (s, 3H), 2.89-2.81 (m, 2 H), 2.15-2.07 (m, 1H), 1.81-1.75 (m, 2H), 1.43 (s, 3H), 1.27 (s, 3H), 1.25 (s, 3H), 1.22 (s, 3H), 1.12 (d, *J* = 6.6 Hz, 3H), 1.09-1.03 (m, 1H), 1.00-0.94 (m, 1H), 0.91-0.78 (m, 15H), 0.49 (q, *J* = 7.8 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 171.0, 169.8, 169.3, 156.2, 146.9, 144.0, 143.8, 141.3, 138.1, 134.9, 134.7, 129.6, 128.8, 128.2, 128.0, 127.7, 127.7, 127.0, 126.7, 125.2, 121.1, 120.0, 84.6, 80.4, 74.7, 67.1, 63.2, 61.4, 60.2, 59.7, 56.0, 52.8, 52.4, 47.2, 42.1, 36.4, 33.0, 30.8, 28.4, 27.6, 24.3, 16.5, 15.5, 14.9, 11.0, 10.4, 6.9, 6.5; HRMS (ESI): calcd for $C_{64}H_{83}Cl_2N_3NaO_{12}Si^+$ [M+Na^+] 1206.5015, found 1206.4992.

*(1S,2R,3E,5E,7R)-8-((2S,3R)-3-(((2S,3S)-1-(((R)-3-(3,5-Dichloro-4-hydroxyphenyl)-1-methoxy-1-oxopropan-2-yl)amino)-3-methyl-1-oxopentan-2-yl)(methyl)carbamoyl)-3-methyloxiran-2-yl)-7-methoxy-2,6-dimethyl-1-phenylocta-3,5-dien-1-yl (S)-2-amino-3-hydroxy-3-methylbutanoate (**2**).*

To a solution of **21** (20 mg, 0.017 mmol, 1.0 equiv) in THF (5 mL) was added TBAF (13 mg, 0.051 mmol, 3.0 equiv) at room temperature, the reaction was stirred at this temperature for 2 h. Solvent was removed by vacuo and purified with silica gel column chromatography (EtOAc) to afford compound **2** (12 mg, 78%) as colorless oil; $[\alpha]_D^{28}$ = -19 (*c* 0.1, EtOAc); IR (KBr) ν_{max} 3653, 3443, 3302, 3185, 2924, 2853, 1740, 1577, 1376, 1244, 1048, 557 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 8.42 (d, *J* = 7.8 Hz, 1H), 7.40-7.20 (m, 7H), 6.22 (dd, *J* = 15, 11.4 Hz, 2H), 5.95 (d, *J* = 10.8 Hz, 1H), 5.63 (d, *J* = 6.6 Hz, 1H), 5.57 (dd, *J* = 15, 7.8 Hz, 1H), 4.56-4.47 (m, 2H), 3.72-3.65 (m, 1H), 3.59 (s, 3H), 3.05 (s, 3H), 3.03-2.96 (m, 1H), 2.91-2.86 (m, 1H), 2.86 (s, 3H), 2.83-2.71 (m, 3H), 1.88-1.78 (m, 1H), 1.78-1.69 (m, 2H), 1.58 (s, 3H), 1.34 (s, 3H), 1.17-1.09 (m, 1H), 1.09 (s, 3H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.98 (s, 3H), 0.87-0.78 (m, 1H), 0.74 (t, *J* = 7.2 Hz, 3H), 0.49 (d, *J* = 6 Hz, 3H); ^{13}C NMR (150 MHz, DMSO) δ 171.4, 169.9, 168.8, 147.5, 138.8, 135.3, 134.8, 130.5, 129.2, 127.9, 127.6, 127.0, 126.4, 121.8, 83.5, 78.6, 70.5, 63.5, 59.7, 59.1, 58.6, 55.3, 52.6, 51.9, 41.6, 34.4, 32.1, 31.2, 29.9, 26.6, 25.6, 23.9, 15.7, 14.7, 14.6, 11.0, 10.3; HRMS (ESI): calcd for $C_{43}H_{60}Cl_2N_3O_{10}$ [M+H^+] 848.3650, found 848.3648.

*(1R,4S,7R,10S,13S,14R,15E,17E,19R,21S)-4-((S)-Sec-butyl)-7-(3,5-dichloro-4-hydroxybenzyl)-10-(2-hydroxypropan-2-yl)-19-methoxy-1,3,14,18-tetramethyl-13-phenyl-12,22-dioxa-3,6,9-triazabicyclo[19.1.0]docosa-15,17-diene-2,5,8,11-tetraone (**1**).*

To a solution of **2** (10 mg, 0.012 mmol, 1.0 equiv) in THF (1 mL) and H_2O (0.2 mL) at 0 °C was added 1 M LiOH (18 *u*L, 0.018 mmol, 1.5 equiv). After 1 h, diluted with EtOAc (5 mL) and H_2O (2 mL), the layers were separated and the aqueous layer was extracted with EtOAc (5 mL × 3), The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated and filtered through silica gel in filter funnel with EtOAc to give the corresponding acid **(**HRMS (ESI): calcd for $C_{42}H_{58}Cl_2N_3O_{10}H^+$ [M+H^+] 834.3494, found 834.3511**)** used for the following step directly.

The resulting acid was dissolved in DMF (5 mL), HATU (9 mg, 0.024 mmol, 2.0 equiv) and DIPEA (8 mg, 0.06 mmol, 5.0 equiv) was added at room temperature, the reaction was stirred for 8 h. Solvent was removed by vacuo and purified with silica gel column chromatography (petroleum ether : EtOAc, 1:1) to afford compound **1** (4 mg, 40%, 2 steps) as a solid; $[\alpha]_D^{28}$ = -32 (*c* 0.3, MeOH); IR (KBr) ν_{max} 3460, 2959, 2925, 2854, 1732, 1655, 1491, 1463, 1378, 1204, 1094 cm^{-1}; ^1H NMR (600 MHz, DMSO) δ 9.80 (s, 1H), 8.61 (d, *J* = 10.2 Hz, 1H), 8.05 (d, *J* = 9.6 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 2H), 7.37 (s, 2H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.25 (t, *J* = 7.2 Hz, 1H), 6.42-6.33 (m, 1H), 6.18 (dd, *J* = 15.6, 4.8 Hz, 1H), 6.11 (d, *J* = 10.8 Hz, 1H), 5.89 (br, 1H), 5.14 (s, 1H), 4.73-4.64 (m, 2H), 4.47 (d, *J* = 11.4 Hz, 1H), 3.64-3.59 (m, 1H), 3.09 (s, 3H), 2.97 (s, 3H), 2.81 (d, *J* = 12 Hz, 1H), 2.68-2.59 (m, 2H), 2.50 (m, 1 H, overlap), 2.12 (t, *J* = 12 Hz, 1H), 1.70 (s, 3H), 1.70 (m, 1H), 1.50-1.44 (m, 1H), 1.43 (s, 3H), 1.23-1.17 (m, 1H), 1.14 (s, 3H), 1.03 (s, 3H), 0.96 (d, *J* = 6.6 Hz, 3H), 0.89-0.83 (m, 1H), 0.77 (t, *J* = 7.2 Hz, 3H), 0.33 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (150 MHz, DMSO) δ 170.6, 170.5, 169.3, 168.7, 147.3, 140.0, 138.4, 133.3, 130.9, 129.7, 129.0, 127.8, 127.0, 126.0, 124.6, 121.5, 84.0, 78.9, 71.9, 61.4, 59.2, 59.2, 58.1, 55.2, 52.7, 41.9, 37.1, 31.0, 30.6, 29.7, 28.2, 24.4, 24.2, 14.9, 14.5, 10.7, 10.1, 9.5; HRMS (ESI): calcd for $C_{42}H_{55}Cl_2N_3NaO_9^+$ [M+Na^+] 838.3207, found 838.3203.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental Spectra
Comparison of ^1H NMR Data of Natural and Synthetic Nannocystin A (Table S1)
Comparison of ^{13}C NMR Data of Natural and Synthetic Nannocystin A (Table S2)

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Notes

The authors declare no competing financial interest.

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