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A stereocontrolled total synthesis of (±)-saframycin A

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ABSTRACT

A thirteen-step total synthesis of (±)-saframycin A from a tricyclic lactam intermediate is described. The key step of this total synthesis is the stereocontrolled construction of a pentacyclic saframycin framework via a modified Pictet-Spengler type cyclization generating a bis-carboxylic acid ester derivative, followed by decarboxylation. The cytotoxicity profiles are also presented.

1. Introduction

Bis-1,2,3,4-tetrahydroisoquinoline natural products, such as saframycin antibiotics and renieramycin marine natural products, have received considerable attention for their unique skeletal characteristics and biological activities (Fig. 1) [1,2]. Several scientific investigations of these compounds have yielded valuable information regarding the fundamental chemistry of ecteinascidin 743 (Et-743, Yondelis®, trabectedin), the most bioactive member of this family. Et-743 has a remarkable mechanism of action: it binds to the minor groove of DNA to interfere with cell division, activated transcription, and DNA repair [3–7].

The research community considers saframycin A (**1**) to be the first example of these natural products. The chemical stabilization of **1** is very high along with holding an exceptional biological activities as well. To date, one racemic and three asymmetric total syntheses of **1** have been accomplished by the groups of Fukuyama [8], Corey [9], Myers [10,11], and Liu [12].

In the course of our research on new metabolites, which involves the isolation and characterization of biologically active compounds and the synthesis of their analogs, we have reported the total synthesis of saframycin antibiotics and renieramycin natural products, such as (±)-saframycins B [13], C, and D [14]. We have also reported the total synthesis of (±)-renieramycins G [15,16] and I [17] and (±)-cribrostatin 4 [18], along with many transformation reactions of natural products [19,20]. Thus, it can be presented saframycin-renieramycin natural products exhibit biological activities, because of the cyano or hydroxyl group at C-21 position, which is essential to produce biological activity, and the elimination of those functional groups under physiological conditions would result in the formation of a reactive iminium species that is responsible for covalent bond formation with its target molecule. We have reported the preparation of key tricyclic lactam intermediate **2** [21] and its transformation into pentacyclic aminonitrile **4** via α-aminonitrile **3** in high yield (Scheme 1) [22]. Compound **4** was easily converted into oxazolidine **5**, the structure of which was confirmed by X-ray crystallographic analysis. However, the stereochemistry at C-1 position of **4** and **5** was epimeric to that of the natural product.

In order to solve the above-mentioned problem, we designed an alternative strategy for constructing the stereochemistry at C-1 position in the B ring of bis-1,2,3,4-tetrahydroisoquinoline natural products. The strategy includes two processes: (1) the Pictet-Spengler cyclization of **3** with dialkyl oxomalonate **6** to afford pentacyclic diester **7**; and (2) the decarboxylation of **7**, followed by stereoselective protonation from the convex face of the core ring system of these natural products to afford **9** (Scheme 2). In this paper, we describe a total synthesis of (rac)-saframycin A (±)-**1** from **2** via **3** in thirteen steps.

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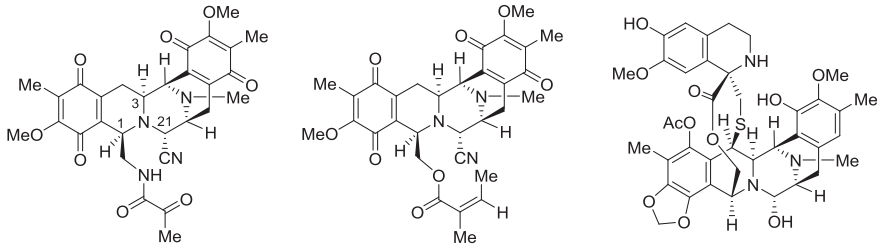
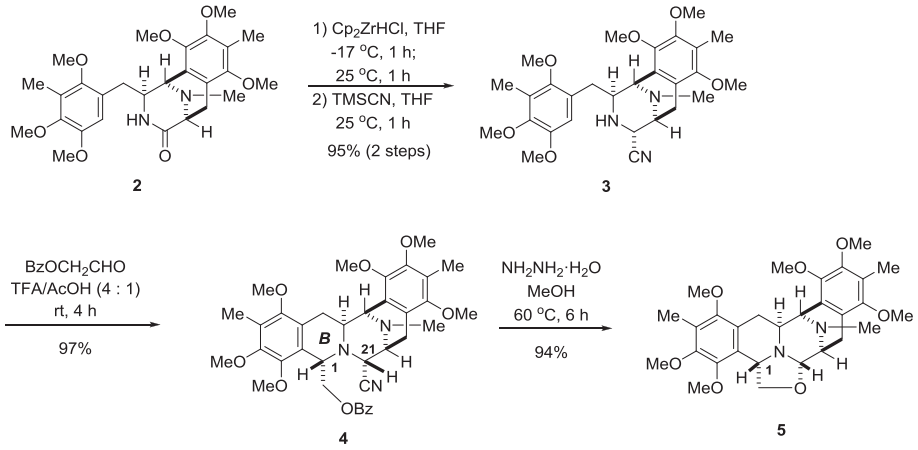
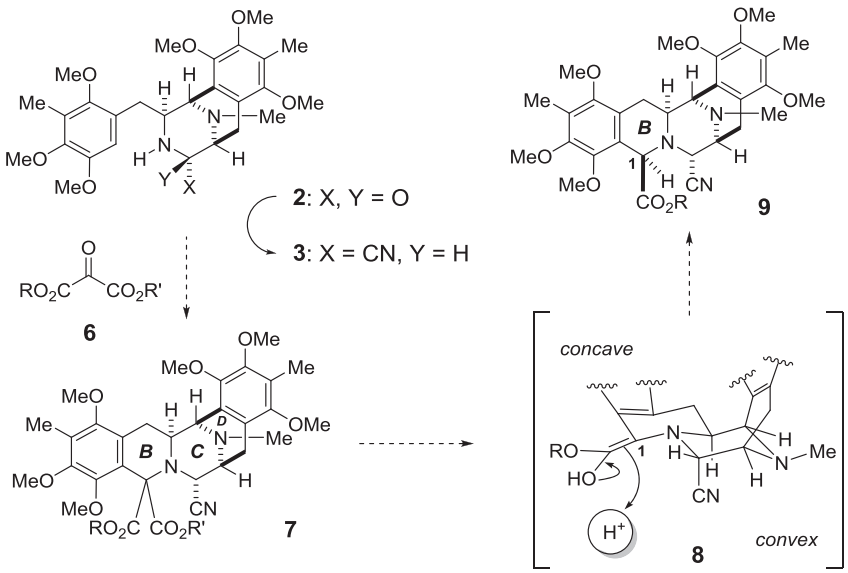


Fig. 1. Structures of bis-1,2,3,4-tetrahydroisoquinolinequinone natural products.



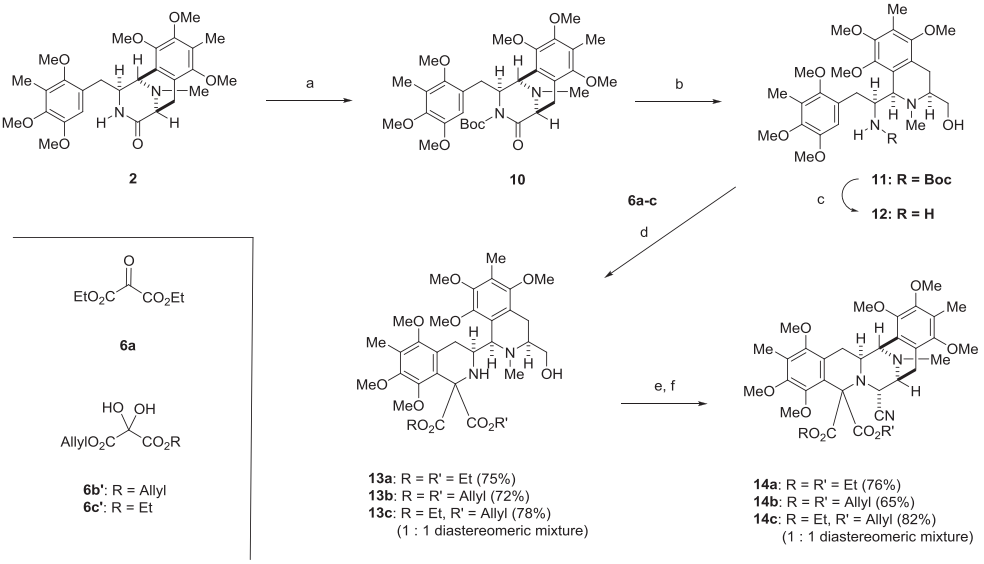
Scheme 1. Our approach for saframycin A synthesis [22].



Scheme 2. Strategy for constructing the stereochemistry of the pentacyclic framework of saframycin A.

2. Result and discussion

Our alternative total synthetic approach for saframycin A commenced with the preparation of precursor **12** for the Pictet-Spengler cyclization with dialkyl oxomalonate [23] (Scheme 3). Cleavage of lactam **2** [22] was carried out by employing the Fukuyama protocol [8] that had a three-step sequence: (1) activation of the nitrogen of the lactam group of **2** with a Boc group; (2) reductive cleavage of the amide bond; and (3) removal of the Boc group under acidic condition generated **12** in 75% overall yield. The Pictet-Spengler cyclization of **12** with 5 equivalents of diethyl oxomalonate **6a** in AcOH/TFA (1:4) at 25 °C for 4 h gave **13a** in 75% yield. The Swern oxidation of **13a** and subsequent treatment of the resulting unstable aminal with KCN afforded pentacycle **14a** in 76%



Scheme 3. (a) Boc_2O, DMAP, MeCN, 110 °C, 46 h, 82%; (b) $NaBH_4$, EtOH, 25 °C, 2.5 h; (c) TFA/CH_2Cl_2 (1:2), 25 °C, 3 h, 92% (2 steps); (d1) **6a** (5 equiv.), AcOH/TFA (1:4), 25 °C, 4 h; (d2) **6b'** (5 equiv.), AcOH/TFA (1:4), 25 °C, 4 h; (d3) **6c'** (10 equiv.), TFA, 25 °C, 6.5 h; (e1 & f1 for **13a**) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 4 h, TEA, −78 °C, 30 min, 25 °C, 4 h, and then KCN/H_2O, AcOH/THF, 25 °C, 3.5 h; (e2 & f2 for **13b**) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 4 h, TEA, −78 °C, 30 min, 25 °C, 6 h, and then KCN/H_2O, AcOH/THF, 25 °C, 6 h; (e3 & f3 for **13c**) $(COCl)_2$, DMSO, CH_2Cl_2, -78 °C, 2 h, TEA, −78 °C, 30 min, 0 °C, 5 h, and then TMSCN, $ZnCl_2$, THF/CH_2Cl_2, 25 °C, 2 h.

overall yield. Decarboxylation with inorganic salts by using the method of Krapcho [24] afforded only polar polymeric material. Furthermore, a variety of hydrolysis attempts under acidic or basic conditions were unsuccessful, giving a complex mixture.

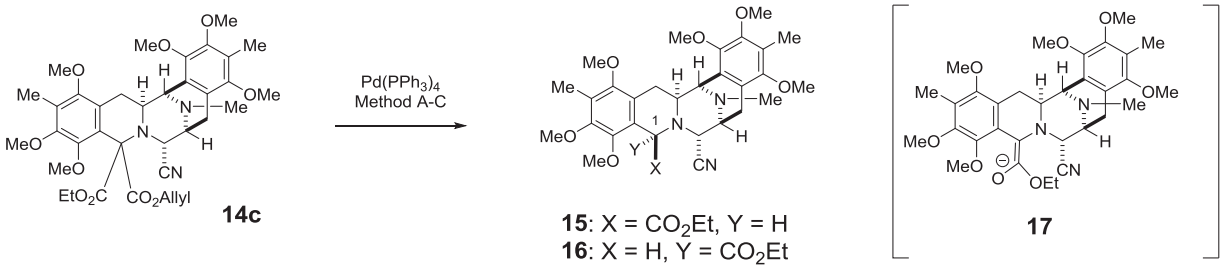
As we sought to induce the transformation of **14** into **15** via enolate **17** under mild conditions with palladium (0) catalyst, the Pictet-Spengler cyclization of **12** with 5 equivalents of diallyl oxomalonate **6b'** [25] in AcOH/TFA (1:4) at 25 °C for 4 h gave **13b** in 72% yield. The Swern oxidation of **13b**, followed by KCN treatment, gave pentacycle **14b** in 65% yield. Cleavage of both allyl groups of **14b** unde the standard condition with Pd(0) in the presence of morpholine, however, gave a only highly polar material.

Then, we prepared allyl ethyl oxomalonate ester **14c**, which was prepared from **12** and **6c'** [26] in the same manner in 64% overall yield. Product **14c** was a 1:1 mixture of C-1 diastereomers, and treating **14c** with $Pd(PPh_3)_4$ and morpholine in THF at 25 °C for 5 days generated desired carboxylic acids **15** and **16** in 41% and 22% yields, respectively (Table 1). Then, we investigated whether a base accelerated the decarboxylation step, and whether isomerization at C-1 position via enolate **17** would generate **15** and **16**. Treating **14c** with $Pd(PPh_3)_4$ and dimedone in THF at 25 °C for 30 min, followed by heating of the reaction mixture in chloroform at 80 °C for 2 h, gave only **15** in 56% overall yield. After extensive investigation of the reaction conditions, the following procedure was considered best in terms of product yield and reproducibility of the reaction. Stirring **14c** with $Pd(PPh_3)_4$ and sodium *p*-toluenesulfinate [27,28] at 25 °C for 3 h afforded **15** in 83% overall yield.

The stereochemistry of **15** and **16** was determined by nuclear Overhauser enhancement (NOE) experiments. It indicated that the C-1 and C-3 diaxial protons of **15** has a syn relationship (Fig. 2).

With desired ester **15** in hand, we focused on the total synthesis of saframycin A (**1a**) using a modification of our original procedure

Table 1
Attempts to perform removal of allyl group followed by decarboxylation process.



Entry	Method	Additive	Conditions	Products (%)*	
				15	16
1	A-1	morpholine	$Pd(PPh_3)_4$, THF, 25 °C, 30 min		
	A-2		CHCl3, 25 °C, 5 days	41	22
2	B-1	dimedone	Pd(PPh3)4, THF, 25 °C, 3 h		
	B-2		CHCl3, 80 °C, 2 h	59	0
3	C	sodium *p*-toluenesulfinate	Pd(PPh3)4, THF, 25 °C, 3 h	83	0

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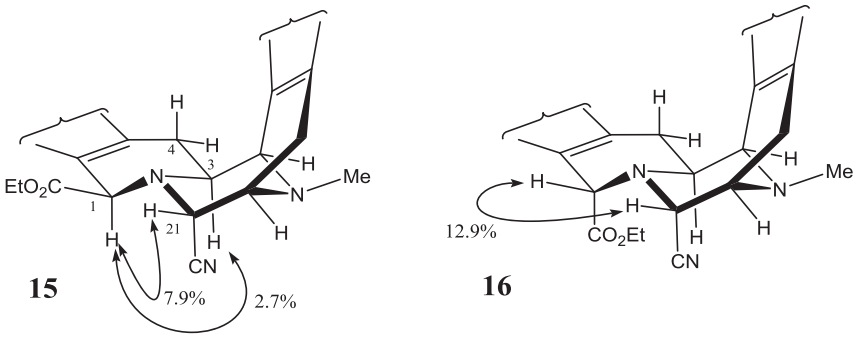


Fig. 2. Selected NOE data of compound **15** and its C-1 epimer **16**.

(Scheme 4) [13,29]. Reduction of **15** with $LiBH_4$ in THF at 25 °C for 2 h gave alcohol **18** in 66% yield. Treatment of **18** with diethyl azodicarboxylate (DEAD), PPh_3, and phthalimide (PhtNH) in THF at 25 °C for 6 h afforded imide **19** in 73% yield. The phthaloyl group of **19** was removed with hydrazine hydrate in EtOH to generate the crude amine, and this in turn was acylated with pyruvic acid to give **20** in 83% overall yield [30]. The final step in the total synthesis of saframycin A (**1**) was considered best in terms of product yield and reproducibility. Treatment of **20** with 4 equivalents of BBr_3 in CH_2Cl_2 at −78 °C for 2 h and then at −20 °C for 17 h gave a mixture of phenol derivatives that were oxidized with ceric ammonium nitrate (CAN) to afford **1** in 20% overall yield. Synthetic saframycin A was identical with the natural one on comparison of their spectroscopic data [19,31] and TLC behavior. Then, the cytotoxicity of synthetic saframycin A (±)-**1** and its synthetic precursor **20** as well as natural product (−)-**1** toward DU145 and HCT116 cancer cell lines was evaluated (Table 2). The in vitro IC_{50} cytotoxicity toward HCT116 of (±)-**1** was very similar to that of natural product (−)-**1**, but the IC_{50} value of (±)-**1** toward DU145 was two-fold lower than that of (−)-**1**.

Table 2
Cytotoxicity of synthetic saframycin A, its polymethoxyarene **20**, and (−)-**1** toward DU145 prostate cancer and HCT116 colon cancer cell lines.

Compound	IC50 ± SE (nM)	
	DU145	HCT116
Synthetic saframycin A (±)-**1**	12.6 ± 0.6	34.5 ± 4.3
Natural saframycin A (−)-**1**	6.8 ± 1.3	35.6 ± 2.4
20	399.5 ± 5.8	243.1 ± 27.4

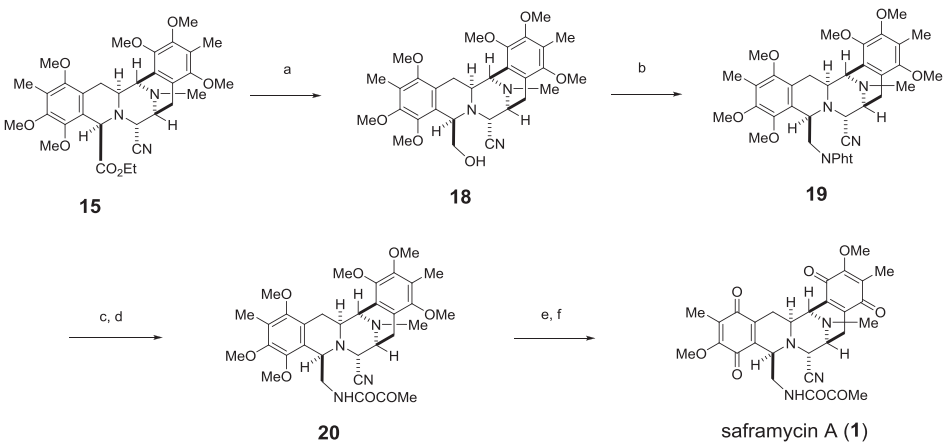
3. Conclusion

We have succeeded in a thirteen-step total synthesis of (±)-saframycin A from tricyclic lactam intermediate **2**. The key steps of this route are the modified Pictet-Spengler cyclization with oxomalonic acid ester derivative and the decarboxylation via a monocarboxylic acid derivative, stereoselectively. Ways of utilizing this approach for other members of both saframycin and renieramycin families are under investigation in our laboratory.

4. Experimental section [32]

4.1. General

IR spectra were obtained with a Shimadzu Prestige 21/IRAffinity-1 FT-IR spectrometer. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECA 500 FT NMR spectrometer at 500 MHz for ^1H and 125 MHz for ^{13}C; a JEOL JNM-AL 400 NMR spectrometer at 400 MHz for ^1H and 100 MHz for ^{13}C (ppm, J in Hz with TMS as internal standard). All proton and carbon signals were assigned by extensive NMR measurements using COSY, HMBC, and HMQC techniques. Mass spectra were recorded on a JEOL JMS 700 instrument with a direct inlet system operating at 70 eV.



Scheme 4. (a) $LiBH_4$, THF/MeOH, 25 °C, 2 h, 66%; (b) PhtNH, DEAD, PPh_3, THF, 25 °C, 6 h, 73%; (c) $NH_2NH_2{-}H_2O$, EtOH, 80 °C, 1.5 h; (d) $MeCOCO_2H$, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDCl), *N*,*N*-dimethylaniline, 1-hydroxybenzotriazole (HOBt), THF, 25 °C, 4 h, 83% (2 steps); (e) BBr_3 (4 equiv.), CH_2Cl_2, -78 °C, 2 h, and then −20 °C, 17 h; (f) CAN (5 equiv.), THF/H_2O (3:1), 0 °C, 2 h, 20% (2 steps).

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4.2. (1R,2S*,5S*)-tert-Butyl 7,9,10-trimethoxy-8,11-dimethyl-4-oxo-2-(2,4,5-trimethoxy-3-methylbenzyl)- 1,2,5,6-tetrahydro-1,5-epiminobenzo[d]azocine-3(4H)-carboxylate (10)*

Boc_2O (9.2 mL, 40 eq, 40 mmol) and DMAP (488.6 mg, 4 eq, 4 mmol) were succeessively added to a stirred solution of **2** (500.6 mg, 1 mmol) in MeCN (10 mL), and the mixture was refluxed at 110 °C for 46 h. The reaction mixture was diluted with H_2O (25 mL) and extracted with $CHCl_3$ (30 mL x 3). The combined extracts were washed with brine (25 mL), dried, and concentrated in vacuo to give a residue, which was subjected to column chromatography on SiO_2 (17 g) with hexane-EtOAc (3:7) to furnish **10** (492.7 mg, 82%) as a pale brown amorphous powder. IR (KBr) 2978, 2938, 1767, 1740, 1717, 1684, 1489, 1464, 1408, 1393, 1369, 1339, 1283, 1240, 1152, 1115, 1086, 1009 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.34 (1H, s, 6′-H), 5.09 (1H, ddd, J = 8.8, 6.9, 3.7 Hz, 2-H), 4.50 (1H, dd, J = 6.9, 1.4 Hz, 1-H), 3.78 (1H, overlapped, 5-H), 3.77 (3H, s, 5′−OCH_3), 3.76 (3H, s, 10-OCH_3), 3.73 (3H, s, 4′−OCH_3), 3.723 (3H, s, 7-OCH_3), 3.717 (3H, s, 9-OCH_3), 3.66 (3H, s, 2′−OCH_3), 3.30 (1H, dd, J = 15.2, 3.7 Hz, 2a-Hα), 3.11 (1H, dd, J = 18.4, 7.9 Hz, 6-Hα), 2.98 (1H, dd, J = 18.4, 1.4 Hz, 6-Hβ), 2.50 (3H, s, NCH_3), 2.20 (3H, s, 8-CH_3), 2.19 (3H, s, 3′−CH_3), 2.01(1H, dd, J = 15.2, 8.8 Hz, 2a-Hβ), 1.18 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 173.5 (C-4), 152.4 (C-7), 151.6 (CO), 150.9 (C-2′), 149.9 (C-9), 148.7 (C-5′), 147.3 (C-10), 146.3 (C-4′), 126.5 (C-1′), 124.92 (C-8 or C-3′), 124.87 (C-8 or C-3′), 123.9 (C-10a), 121.5 (C-6a), 111.2 (C-6′), 83.2 ($C(CH_3)_3$), 60.14 (OCH_3), 60.10 (OCH_3), 60.0 (OCH_3), 59.92 (OCH_3), 59.89 (OCH_3), 59.7 (C-5), 57.6 (C-2), 55.9 (5′−OCH_3), 54.2 (C-1), 40.2 (NCH_3), 33.2 (C-2a), 27.4 ($C(CH_3)_3$), 22.7 (C-6), 9.5 (8 or 3′−CH_3), 9.4 (8 or 3′−CH_3); EIMS m/z (%): 600 (M^+, 1), 500 (15), 249 (30), 248 (100), 218 (10): HREIMS m/z 600.3048 (M^+, calcd for $C_{32}H_{44}N_2O_9$, 600.3047).

4.3. ((1R,3S*)-1-((S*)-1-Amino-2-(2,4,5-trimethoxy-3-methylphenyl)ethyl)-5,7,8-trimethoxy-2,6-dimethyl-1,2,3,4-tetrahydroisoquinolin-3-yl)methanol (12)*

$NaBH_4$ (1.075 g, 20 eq, 28.42 mmol) was added to a stirred solution of **10** (853.7 mg, 1.421 mmol) in EtOH (14 mL) at 0 °C, and the mixture was stirred at 25 °C for 2.5 h. The reaction mixture was diluted with saturated aqueous NH_4Cl (10 mL) and H_2O (80 mL) at 0 °C and then extracted with $CHCl_3$ (120 mL x 3). The combined extracts were washed with brine (80 mL), dried, concentrated in vacuo. The residue (**11**, 826.8 mg) was used in the next step without purification. TFA (6 mL) was added to a stirred solution of crude **11** in CH_2Cl_2 (12 mL) at 0 °C, and the mixture was stirred at 25 °C for 3 h. The reaction mixture was diluted with H_2O (80 mL) at 0 °C, made pH 9 with concentrated NH_4OH (10 mL), and extracted with $CHCl_3$ (100 mL x 3). The combined extracts were washed with brine (80 mL), dried, concentrated in vacuo to give a residue (722.1 mg), which was subjected to column chromatography on SiO_2 (17 g) with $CHCl_3$−MeOH (2:23) to furnish **12** (663.0 mg, 92%, 2 steps) as a pale brown amorphous powder. IR (KBr) 3354, 2938, 2862, 2832, 1487, 1466, 1410, 1339, 1238, 1119, 1086, 1065, 1013, 993, 966 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.69 (1H, s, 6‴-H), 3.94 (1H, dd, J = 11.1, 3.0 Hz, 1-H), 3.86 (3H, s, 8′−OCH_3), 3.83 (3H, s, 7′−OCH_3), 3.80 (3H, s, 5‴−OCH_3), 3.77 (1H, d, J = 9.3 Hz, 1′-H), 3.76 (3H, s, 4‴−OCH_3), 3.68 (3H, s, 2‴−OCH_3), 3.65 (3H, s, 5′−OCH_3), 3.50 (1H, dd, J = 12.9, 2.0 Hz, 2″-H), 3.49 (1H, dd, J = 11.1, 1.8 Hz, 1-H), 2.88 (1H, dd, J = 15.3, 4.2 Hz, 4′-Hα), 2.86 (1H, td, J = 9.3, 2.0 Hz, 1″-H), 2.68 (1H, dd, J = 15.3, 12.3, 4′-Hβ), 2.56 (3H, s, NCH_3), 2.34 (1H, br d, J = 12.3 Hz, 3′-H), 2.27 (1H, dd, J = 12.9, 9.3 Hz, 2″-H), 2.20 (6H, s, 6′−CH_3 and 3‴−CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.3 (C-5′), 150.6 (C-2‴), 149.6 (C-7′), 149.0 (C-5‴), 147.2 (C-8′), 146.4 (C-4‴), 128.1 (C-1‴), 127.6 (C-9′ or C-10′), 125.6 (C-3‴), 125.2 (C-9′ or C-10′), 123.8 (C-6′), 111.7 (C-6‴), 65.4 (C-1′), 63.4 (C-1), 63.2 (C-3′), 61.0 (5′−OCH_3), 60.8 (8′ or 2‴−OCH_3), 60.7 (8′ or 2‴−OCH_3), 60.2 (7′ or 4‴−OCH_3), 60.1 (7′ or 4‴−OCH_3), 58.1 (C-1″), 56.0 (5‴−OCH_3), 46.1 (NCH_3), 35.9 (C-2″), 24.6 (C-4′), 9.7 (6′−CH_3 or 3‴−CH_3), 9.4 (6′−CH_3 or 3‴−CH_3); FABMS m/z 505 $[M+H]^+$; HRFABMS m/z 505.2921 ($[M+H]^+$, calcd for $C_{27}H_{41}N_2O_7$, 505.2914).

An analytical sample of **11** (*tert*-Butyl((S*)-1-((1*R**,3*S**)-3-(hydroxymethyl)-5,7,8-trimethoxy-2,6-dimethyl- 1,2,3,4-tetrahydroisoquinolin-1-yl)-2-(2,4,5-trimethoxy-3-methylphenyl) ethyl)carbamate) was obtained as a pale yellow amorphous powder by column chromatography with $CHCl_3$-AcOEt (3:2). IR (KBr) 3424, 2938, 1713, 1692, 1489, 1466, 1412, 1238, 1171, 1117, 1088, 1065, 1013 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.62 (1H, s, 6″-H), 4.61 (1H, d, J = 9.6 Hz, NH), 3.89−3.82 (3H, overlapped, 1-H, 1′−H, 3'a-H), 3.86 (3H, s, 8′−OCH_3 or 5″−OCH_3), 3.83 (3H, s, 7′−OCH_3), 3.79 (3H, s, 8′−OCH_3 or 5″−OCH_3), 3.74 (3H, s, 4″−OCH_3), 3.69 (3H, s, 2″−OCH_3), 3.62 (3H, s, 5′−OCH_3), 3.49 (1H, dd, J = 11.0, 2.5 Hz, 3'a-H), 3.28 (1H, dd, J = 13.9, 2.4 Hz, 2-H), 2.90 (1H, dd, J = 15.4, 4.9 Hz, 4′-Hα), 2.83 (1H, dd, J = 15.4, 12.4 Hz, 4′-Hβ), 2.56 (1H, overlapped, 2-H), 2.52 (3H, s, NCH_3), 2.42 (1H, m, 3′-H), 2.20 (3H, s, 3″−CH_3), 2.18 (3H, s, 6′−CH_3), 1.12 (9H, s, $C(CH_3)_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.1 (CO), 151.2 (C-5′), 150.6 (C-2″), 149.1 (C-7′), 148.9 (C-8′ or C-5″), 146.5 (C-8′ or C-5″), 146.3 (C-4″), 126.94 (C-9′ or C-10′ or C-1″), 126.90 (C-9′ or C-10′ or C-1″), 125.7 (C-9′ or C-10′), 125.0 (C-3″), 123.6 (C-6′), 111.0 (C-6″), 78.2 ($C(CH_3)_3$), 63.8 (C-3'a), 63.6 (C-1′), 62.8 (C-3′), 60.7 (5′−OCH_3), 60.6 (2″−OCH_3), 60.6 (8′ or 5″−OCH_3), 60.2 (7′−OCH_3), 60.1 (4″−OCH_3), 56.0 (C-1), 55.9 (8′ or 5″−OCH_3), 46.1 (NCH_3), 32.5 (C-2), 28.1 ($C(CH_3)_3$), 24.4 (C-4′), 9.6 (3″−CH_3), 9.2 (6′−CH_3); FABMS m/z 605 $[M+H]^+$; HRFABMS m/z 605.3439 ($[M+H]^+$, calcd for $C_{32}H_{49}N_2O_9$, 605.3438).

4.4. (3S,3′S*)-Diethyl 3-(hydroxymethyl)-5,5′,7,7′,8,8′-hexamethoxy-2,6,6′-trimethyl-1,2,3,3′,4,4′-hexahydro- [1,3′-biisoquinoline]-1′,1′(2′H)-dicarboxylate (13a)*

A solution of $CO(CO_2Et)_2$ (214 μL, 5 eq, 1.32 mmol) in AcOH (1.8 mL) and TFA (7.2 mL) was added to **12** (133.1 mg, 0.264 mmol), and the mixture was stirred at 25 °C for 4 h. The reaction mixture was diluted with H_2O (40 mL) at 0 °C, made pH 9 with concentrated NH_4OH (13 mL), and then extracted with $CHCl_3$ (50 mL x 3). The combined extracts were washed with brine (40 mL), dried, and concentrated in vacuo to give a residue, which was subjected to column chromatography on SiO_2 (30 g) with hexane-EtOAc (3:2) to give **13a** (130.7 mg, 75%) as a yellow amorphous powder. IR (KBr) 3435, 2982, 2941, 1738, 1464, 1408, 1342, 1250, 1229, 1115, 1074, 1026, 1009 cm^{-1}; ^1H NMR ($CDCl_3$ 400 MHz) δ 4.34−4.11 (4H, overlapped, 1-H, OCH_2CH_3), 3.96 (1H, m, OCH_2CH_3), 3.85 (3H, s, 8-OCH_3), 3.84 (1H, dd, J = 11.0, 3.9 Hz, 3a-H), 3.80 (3H, s, 7-OCH_3), 3.77 (3H, s, 8′−OCH_3), 3.71 (3H, s, 7′−OCH_3), 3.69 (3H, s, 5-OCH_3), 3.68 (3H, s, 5′−OCH_3), 3.45 (1H, dd, J = 11.0, 2.3 Hz, 3a-H), 3.07 (1H, dd, J = 16.3, 3.2 Hz, 4′-H), 2.92 (1H, dd, J = 15.3, 4.1 Hz, 4-H), 2.72 (1H, ddd, 11.1, 7.8, 3.2 Hz, 3′-H), 2.64−2.57 (2H, overlapped, 4-H, 4′-H), 2.57 (3H, s, 2-CH_3), 2.35 (1H, br d, J = 12.4, 2.3 Hz, 3-H), 2.22 (3H, s, 6-CH_3), 2.18 (3H, s, 6′−CH_3), 1.21 (3H, t, J = 7.1 Hz, OCH_2CH_3), 1.11 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.5 (CO), 170.3 (CO), 151.5 (C-5′), 151.4 (C-5), 149.6 (C-7), 149.0 (C-7′), 147.3 (C-8′), 147.0 (C-8), 126.5 (C-9 or 10), 125.5 (C-6′ or 9 or 10), 125.4 (C-6′ or 9 or 10), 124.9 (C-9′ or 10′), 124.2 (C-6 or 9′ or C-10′), 124.1 (C-6 or 9′ or C-10′), 70.2 (C-1′), 63.9 (C-1), 63.8 (C-3a), 62.3 (C-3), 61.8 (OCH_2CH_3), 61.7 (OCH_2CH_3), 60.8 (5-OCH_3), 60.7 (8-OCH_3), 59.9 (7-OCH_3), 59.8 (8′−OCH_3), 59.8 (5′ or 7′−OCH_3), 59.6 (5′ or 7′−OCH_3), 56.3 (C-3′), 45.9 (2-CH_3), 26.9 (C-4′), 25.2 (C-4), 14.0 (OCH_2CH_3), 13.9 (OCH_2CH_3), 9.4 (6 and 6′−CH_3); EIMS m/z (%): 660 (M^+, 0.3), 380 (32), 306 (10), 281 (18), 280 (100); HREIMS m/z 660.3256 (M^+, calcd for $C_{34}H_{48}N_2O_{11}$, 660.3258).

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4.5. (6S,7R*,14aS*,15R*)-Diethyl 7-cyano-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-6,7,14a,15- tetrahydro-5H-6,15-iminobenzo[4,5]azocino[1,2-b]isoquinoline-9,9(14H)-dicarboxylate (14a)*

$(COCl)_2$ (106 μL, 5 eq, 1.25 mmol) was added to a stirred solution of DMSO (178 μL, 10 eq, 2.5 mmol) in CH_2Cl_2 (1 mL) at −78 °C, and the mixture was stirred at −78 °C for 10 min. A solution of **13a** (165.2 μL, 0.25 mmol) in CH_2Cl_2 (1 mL) was added dropwise to the above solution at −78 °C for 20 min, and the mixture was stirred at −78 °C for 4 h. Then, TEA (697 μL, 20 eq, 5 mmol) was added to the reaction mixture at −78 °C for 10 min, and it was stirred at −78 °C for 30 min. The reaction mixture was warmed to 25 °C over a period of 3.5 h, and stirred was continued at 25 °C for 30 min. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) at 0 °C and extracted with $CHCl_3$ (10 mL x 3). The combined extracts were washed with brine (5 mL), dried, concentrated in vacuo. The residue (195.9 mg) was used in the next step without purification. A solution of KCN (132.9 mg, 8 eq, 2 mmol) in H_2O (4 mL) and AcOH (1.6 mL, 110 eq, 27.5 mmol) was added to a stirred solution of the above product in THF (4.2 mL) at 0 °C, and the stirring was continued at 25 °C for 3.5 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (40 mL) at 0 °C, and extracted with $CHCl_3$ (40 mL x 3). The combined extracts were washed with saturated aqueous $NaHCO_3$ (20 mL), dried, concentrated in vacuo to give a residue (145.3 mg), which was subjected to column chromatography on SiO_2 (6 g) with $CHCl_3$: MeOH (49:1) to afford **14a** (127.2 mg, 76%, 2 steps) as a orange amorphous powder. IR (KBr) 2982, 2940, 2361, 1759, 1740, 1464, 1410, 1344, 1267, 1248, 1221, 1113, 1076, 1057, 1009, 962 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.65 (1H, d, J = 3.0 Hz, 7-H), 4.36 (1H, m, OCH_2CH_3), 4.24 (1H, m, OCH_2CH_3), 4.11 (1H, dd, J = 3.1, 1.3 Hz, 15-H), 4.04 (1H, m, OCH_2CH_3), 3.93 (1H, m, OCH_2CH_3), 3.83 (3H, s, 1-OCH_3), 3.75 (3H, s, 2-OCH_3), 3.69 (3H, s, 4-OCH_3), 3.68 (3H, s, 10-OCH_3), 3.68 (3H, s, 11-OCH_3), 3.68 (1H, overlapped, 14a-H), 3.61 (3H, s, 13-OCH_3), 3.36 (1H, br d, J = 7.3 Hz, 6-H), 3.23 (1H, dd, J = 16.1, 3.9 Hz, 14H-α), 2.93 (1H, dd, J = 18.4, 7.3 Hz, 5-Hα), 2.67 (1H, d, J = 18.4 Hz, 5-Hβ), 2.29 (3H, s, 16-CH_3), 2.18 (3H, s, 12-CH_3), 2.15 (3H, s, 3-CH_3), 1.89 (1H, dd, J = 16.1, 11.7 Hz, 14-Hβ), 1.18 (3H, t, J = 7.2 Hz, OCH_2CH_3), 1.03 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8(CO), 167.3 (CO), 151.3 (C-4), 150.1 (C-13), 149.0 (C-2), 148.6 (C-11), 147.7 (C-1), 146.4 (C-10), 125.2 (C-12), 124.5 (C-9a or 13a), 123.6 (C-3), 123.5 (C-4a), 123.1 (C-15a), 122.7 (C-9a or 13a), 118.4 (CN), 68.8 (C-9), 61.4 (OCH_2CH_3), 60.2 (1 or 13-OCH_3), 60.1 (1 or 13-OCH_3), 59.8 (2-OCH_3), 59.6 (4 -, 10-, or 11-OCH_3), 59.5 (4-, 10-, or 11-OCH_3), 59.5 (4 -, 10-, or 11-OCH_3), 57.4 (C-15), 56.8 (C-6), 56.5 (C-7), 53.9 (C-14a), 42.0 (16-CH_3), 24.9 (C-14), 20.2 (C-5), 13.7 (OCH_2CH_3), 13.7 (OCH_2CH_3), 9.3 (3- or 12-CH_3), 9.2 (3- or 12-CH_3); EIMS m/z (%): 667 (M^+, 16), 594 (11), 288 (47), 277 (24), 250 (16), 249 (100), 248 (85), 218(12); HREIMS m/z 667.3108 (M^+, calcd for $C_{35}H_{45}N_3O_{10}$, 667.3105).

4.6. (3S,3′S*)-Diallyl 3-(hydroxymethyl)-5,5′,7,7′,8,8′-hexamethoxy-2,6,6′-trimethyl-1,2,3,3′,4,4′-hexahydro- [1,3′-biisoquinoline]-1′,1′(2′H)-dicarboxylate (13b)*

A solution of **6b'** (197.9 mg, 5 eq, 1.00 mmol) in AcOH (1.3 mL) and TFA (5.3 mL) was added to **12** (100.8 mg, 0.2 mmol), the mixture was stirred at 25 °C for 4 h. The reaction mixture was diluted with H_2O (30 mL) at 0 °C, made pH 9 with concentrated NH_4OH (8 mL), and extracted with $CHCl_3$ (40 mL x 3). The combined extracts were washed with brine (30 mL), dried, and concentrated in vacuo to give a residue, which was subjected to column chromatography on SiO_2 (6 g) with hexane-EtOAc (11:9) to give **13b** (97.8 mg, 72%) as a yellow amorphous powder. IR ($CHCl_3$) 2941, 1736, 1464, 1408, 1342, 1271, 1236, 1196, 1115, 1076, 1065, 1009, 993 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.85 (1H, ddt, J = 17.2, 10.9, 5.7 Hz, $OCH_2CH{=}CH_2$), 5.73 (1H, ddt, J = 17.2, 10.9, 5.7 Hz, $OCH_2CH{=}CH_2$), 5.24 (1H, dd, J = 17.2, 1.3 Hz, $OCH_2CH{=}CH_2$), 5.23 (1H, dd, J = 17.2, 1.3 Hz, $OCH_2CH{=}CH_2$), 5.15 (1H, dd, J = 10.9, 1.3 Hz, $OCH_2CH{=}CH_2$), 5.13 (1H, dd, J = 10.9, 1.3 Hz, $OCH_2{-}CH{=}CH_2$), 4.66 (1H, ddt, J = 13.3, 5.7, 1.3 Hz, $OCH_2CH{=}CH_2$), 4.63−4.56 (2H, overlapped, $OCH_2CH{=}CH_2$), 4.38 (1H, ddt, J = 13.3, 5.7, 1.3 Hz, $OCH_2CH{=}CH_2$), 4.11 (1H, d, J = 7.7 Hz, 1-H), 3.84 (1H, overlapped, 3a-H), 3.83 (3H, s, 8-OCH_3), 3.79 (3H, s, 7- or 7′−OCH_3), 3.75 (3H, s, 8′−OCH_3), 3.70 (3H, s, 7- or 7′−OCH_3), 3.69 (3H, s, 5- or 5′−OCH_3), 3.68 (3H, s, 5- or 5′−OCH_3), 3.44 (1H, dd, J = 11.0, 2.3 Hz, 3a-H), 3.08 (1H, dd, J = 16.4, 3.2 Hz, 4′-H), 2.91 (1H, dd, J = 15.2, 4.1 Hz, 4-H), 2.75 (1H, dd, J = 7.7, 3.2 Hz, 3′-H), 2.63−2.56 (2H, overlapped, 4-H, 4′-H), 2.56 (3H, s, 2-CH_3), 2.35 (1H, br d, J = 15.2 Hz, 3-H), 2.22 (3H, s, 6- or 6′−CH_3), 2.18 (3H, s, 6- or 6′−CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1 (CO), 170.0 (CO), 151.5 (C-5 or 5′), 151.4 (C-5 or 5′), 149.6 (C-7 or 7′), 149.0 (C-7 or 7′), 147.2 (C-8′), 146.9 (C-8), 131.74 ($OCH_2CH{=}CH_2$), 131.73 ($OCH_2CH{=}CH_2$), 126.4 (C-9 or 10), 125.5 (C-9 or 10), 125.4 (C-6, 6′, 9 or 10), 124.9 (C-9′ or 10′), 124.2 (C-6 or C-6′), 123.8 (C-9′ or 10′), 118.2 ($OCH_2CH{=}CH_2$), 118.2 ($OCH_2CH{=}CH_2$), 70.1 (C-1′), 66.3 ($OCH_2CH{=}CH_2$), 66.3 ($OCH_2CH{=}CH_2$), 63.8 (C-1), 63.7 (C-3a), 62.3 (C-3), 60.8 (OCH_3), 60.7 (OCH_3), 59.9 (OCH_3), 59.8 (OCH_3), 59.8 (OCH_3), 59.6 (OCH_3), 56.3 (C-3′), 45.9 (2-CH_3), 26.9 (C-4′), 25.2 (C-4), 9.4 (6 and 6′−CH_3); EIMS m/z (%): 684 (M^+, 0.5), 404 (16), 281 (18), 280 (100); HREIMS m/z 684.3255 (M^+, calcd for $C_{36}H_{48}N_2O_{11}$, 684.3258).

4.7. (6S,7R*,14aS*,15R*)-Diallyl 7-cyano-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-6,7,14a,15- tetrahydro- 5H-6,15-iminobenzo[4,5]azocino[1,2-b]isoquinoline-9,9(14H)-dicarboxylate (14b)*

$(COCl)_2$ (35 μL, 5 eq, 418 μmol) was added to a stirred solution of a solution of DMSO (59 μL, 10 eq, 837 μmol) in CH_2Cl_2 (1 mL) at −78 °C, the mixture was stirred at −78 °C for 10 min. A solution of **13b** (57.3 mg, 83.7 μmol) in CH_2Cl_2 (1 mL) was added dropwise to the above solution at −78 °C for 15 min, and the mixture was stirred at −78 °C for 4 h. Then, TEA (233 μL, 20 eq, 1.67 mmol) was added to the above solution at −78 °C for 5 min, and the stirring was continued at −78 °C for 30 min. The reaction mixture was warmed to 25 °C over a period of 4.5 h, and stirred for 1.5 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (5 mL) at 0 °C and extracted with $CHCl_3$ (10 mL x 3). The combined extracts were washed with brine (5 mL), dried, concentrated in vacuo to give a residue (63.3 mg), and this crude product was used in the next step without purification. A solution of KCN (44.5 mg, 8 eq, 669 μmol) in H_2O (1.3 mL) and AcOH (532 μL, 110 eq, 920 μmol) was added to a stirred solution of the above product in THF (1.4 mL) at 0 °C, and the mixture was stirred at 25 °C for 6 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL) at 0 °C, and extracted with $CHCl_3$ (15 mL x 3). The combined extracts were washed with brine (10 mL), dried, concentrated in vacuo to give a residue (53.0 mg), which was subjected to column chromatography on SiO_2 (6 g) with hexane-EtOAc (13:7) to furnish **14b** (37.9 mg, 65%, 2 steps) as a yellow amorphous powder. IR (KBr) 2940, 2359, 1763, 1746, 1464, 1410, 1344, 1271, 1248, 1217, 1113, 1076, 1057, 1038, 1001 cm-1; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.85 (1H, ddt, J = 16.6, 11.1, 5.5 Hz, $OCH_2CH{=}CH_2$), 5.66 (1H, ddt, J = 16.6, 11.1, 5.5 Hz, $OCH_2CH{=}CH_2$), 5.10−4.96 (4H, overlapped, $OCH_2CH{=}CH_2$), 4.83 (1H, dd, J = 13.4, 5.5 Hz, $OCH_2CH{=}CH_2$), 4.71 (1H, d, J = 3.0 Hz, 7-H), 4.65 (1H, dd, J = 13.4, 5.5 Hz, $OCH_2CH{=}CH_2$), 4.47 (1H, dd, J = 13.4, 5.5 Hz, $OCH_2CH{=}CH_2$), 4.36 (1H, dd, J = 13.4, 5.5 Hz, $OCH_2CH{=}CH_2$), 4.12 (1H, d, J = 3.0 Hz, 15-H), 3.81 (3H, s, 1-OCH_3), 3.75 (3H, s, 2-OCH_3), 3.68 (1H, overlapped, 14a-H), 3.67 (3H, s, 4-OCH_3), 3.66 (3H, s, 10-OCH_3), 3.65 (3H, s, 11-OCH_3), 3.60 (3H, s,

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13-OCH_3), 3.36 (1H, br d, 8.2 Hz, 6-H), 3.24 (1H, dd, $J = 16.1$, 3.8 Hz, 14H-α), 2.92 (1H, dd, $J = 18.5$, 8.2 Hz, 5-Hα), 2.59 (1H, d, $J = 18.5$ Hz, 5-Hβ), 2.29 (3H, s, 16-CH_3), 2.16 (3H, s, 12-CH_3), 2.15 (3H, s, 3-CH_3), 1.94 (1H, dd, $J = 16.1$, 11.7 Hz, 14-Hβ); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.2 (CO), 166.7 (CO), 151.3 (C-4), 150.2 (C-13), 149.0 (C-2), 148.5 (C-11), 147.7 (C-1), 146.4 (C-10), 131.8 ($OCH_2CH{=}CH_2$), 131.5 ($OCH_2CH{=}CH_2$), 125.3 (C-12), 124.1 (C-3, 9a or 13a), 123.7 (C-3, 9a or 13a), 123.3 (C-4a), 123.1 (C-15a), 122.5 (C-9a or 13a), 118.4 (CN), 118.0 ($OCH_2CH{=}CH_2$), 117.6 ($OCH_2CH{=}CH_2$), 68.4 (C-9), 65.8 ($OCH_2CH{=}CH_2$), 65.7 ($OCH_2CH{=}CH_2$), 60.2 (1 or 13-OCH_3), 60.1 (1 or 13-OCH_3), 59.8 (2-OCH_3), 59.6 (4, 10 or 11-OCH_3), 59.6 (4, 10 or 11-OCH_3), 59.5 (4, 10 or 11-OCH_3), 57.4 (C-15), 56.7 (C-6), 56.3 (C-7), 53.6 (C-14a), 42.0 (16-CH_3), 24.8 (C-14), 20.2 (C-5), 9.2 (3 and 12-CH_3); EIMS *m*/*z* (%): 691 (M^+, 16), 288 (45), 250 (16), 249 (100), 248 (86), 218 (12); HREIMS *m*/*z* 691.3106 (M^+, calcd for $C_{37}H_{45}N_3O_{10}$, 691.3105).

4.8. (3S*,3′S*)-1′-Allyl 1′-ethyl 3-(hydroxymethyl)-5,5′,7,7′,8,8′-hexamethoxy-2,6,6′-trimethyl-1,2,3,3′,4,4′- hexahydro-[1,3′-biisoquinoline]-1′,1′(2′H)-dicarboxylate (13c)

A solution of **6c'** (2.042 g, 10 eq, 10 mmol) in TFA (33 mL) was added to **12** (504.6 mg, 1 mmol), and the mixture was stirred at 25 °C for 6.5 h. The reaction mixture was diluted with H_2O (200 mL) at 0 °C, made pH 9 with concentrated NH_4OH (40 mL), and extracted with $CHCl_3$ (250 mL x 3). The combined extracts were dried, and concentrated in vacuo to give a residue, which was subjected to column chromatography on SiO_2 (17 g) with hexane-EtOAc (3:2–1:1) to furnish 1:1 diastereomerix mixture of **13c** (524.4 mg, 78%) as a yellow amorphous powder [33].

4.9. (6S*,7R*,14aS*,15R*)-9-Allyl 9-ethyl 7-cyano-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-6,7,14a,15- tetrahydro-5H-6,15-iminobenzo[4,5]azocino[1,2-b]isoquinoline-9,9(14H)-dicarboxylate (14c)

$(COCl)_2$ (127 μL, 2 eq, 1.5 mmol) in CH_2Cl_2 (30 mL) was added to a solution of DMSO (213 μL, 4 eq, 3 mmol) in CH_2Cl_2 (1 mL) at −78 °C for 10 min, and the mixture was stirred at −78 °C for 30 min. A solution of **13c** (504.6 mg, 0.75 mmol) in CH_2Cl_2 (3 mL) was added to the above solution at −78 °C for 15 min, and the mixture was stirred at −78 °C for 1.5 h. Then, TEA (843 μL, 8 eq, 6 mmol) was added to the above solution at −78 °C for 10 min, and the stirrig was continued at −78 °C for 30 min. The reaction mixture was warmed to 0 °C over a period of 3 h, and further stirred for 2 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (15 mL) and H_2O (30 mL) at 0 °C and extracted with $CHCl_3$ (50 mL x 3). The combined extracts were washed with brine (30 mL), dried, concentrated in vacuo to give a residue (561.2 mg), and this was used in the next step without purification. TMSCN (291 μL, 3 eq, 2.25 mmol), 0.5 M solution of $ZnCl_2$ in THF (4.5 mL, 3 eq, 2.25 mmol) were succeessively added to a stirred solution of the above product in CH_2Cl_2 (7.5 mL) at 25 °C, and the mixture was stirred at 25 °C for 2 h. The reaction mixture was diluted with H_2O (30 mL) at 0 °C, and extracted with $CHCl_3$ (50 mL x 3). The combined extracts were washed with brine (30 mL), dried, concentrated in vacuo to give a residue (501.8 mg), which was subjected to column chromatography on SiO_2 (14 g) with hexane-EtOAc (7:3–13:7) to provide a 1:1 diastereomeric mixture of **14c** (419.5 mg, 82%, 2 steps) as a yellow amorphous powder. An analytical sample of one diastereomer **14c** was obtained as a yellow amorphous powder. IR (KBr) 2940, 2228, 1761, 1744, 1464, 1410, 1344, 1248, 1217, 1113, 1076, 1057, 1043, 1009 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.66 (1H, ddt, $J = 16.9$, 10.6, 5.3 Hz, $OCH_2CH{=}CH_2$), 5.02 (1H, dq, $J = 10.6$, 1.6 Hz, $OCH_2CH{=}CH_2$), 4.99 (1H, dq, $J = 16.9$, 1.6 Hz, $OCH_2CH{=}CH_2$), 4.66 (1H, d, $J = 3.0$ Hz, 7-H), 4.47 (1H, ddt, $J = 13.5$, 5.3, 1.6 Hz, $OCH_2CH{=}CH_2$), 4.36 (1H, dq, $J = 10.7$, 7.1 Hz, OCH_2CH_3), 4.33 (1H, overlapped, $OCH_2CH{=}CH_2$), 4.23 (1H, dq, $J = 10.7$, 7.1 Hz, OCH_2CH_3), 4.11 (1H, dd, $J = 3.1$, 1.5 Hz, 15-H), 3.82 (3H, s, 1- or 10-OCH_3), 3.75 (3H, s, 2- or 11-OCH_3), 3.68 (3H, s, 4-OCH_3), 3.67 (3H, s, 1- or 10-OCH_3), 3.67 (3H, s, 2 or 11-OCH_3), 3.63 (1H, overlapped, 14a-H), 3.60 (3H, s, 13-OCH_3), 3.35 (1H, br d, $J = 8.0$ Hz, 6-H), 3.24 (1H, dd, $J = 16.1$, 3.7 Hz, 14-Hα), 2.91 (1H, dd, $J = 18.4$, 8.0 Hz, 5-Hα), 2.64 (1H, d, $J = 18.4$ Hz, 5-Hβ), 2.29 (3H, s, 16-CH_3), 2.17 (3H, s, 12-CH_3), 2.15 (3H, s, 3-CH_3), 1.90 (1H, dd, $J = 16.1$, 11.7 Hz, 14-Hβ), 1.18 (3H, t, $J = 7.1$ Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.5 (CO), 167.2 (CO), 151.3 (C-4), 150.2 (C-13), 149.0 (C-11), 148.6 (C-2), 147.7 (C-1 or 10), 146.4 (C-1 or 10), 131.6 ($OCH_2CH{=}CH_2$), 125.3 (C-12), 124.4 (C-9a or 13a), 123.7 (C-3 or 4a), 123.5 (C-3 or 4a), 123.1 (C-15a), 122.7 (C-9a or 13a), 118.4 (CN), 117.6 ($OCH_2CH{=}CH_2$), 68.7 (C-9), 65.7 ($OCH_2CH{=}CH_2$), 61.5 (OCH_2CH_3), 60.3 (OCH_3), 60.1 (13-OCH_3), 59.8 (OCH_3), 59.6 (OCH_3), 59.6 (OCH_3), 59.5 (OCH_3), 57.5 (C-15), 56.8 (C-6), 56.4 (C-7), 53.8 (C-14a), 42.0 (16-CH_3), 24.9 (C-14), 20.2 (C-5), 13.7 (OCH_2CH_3), 9.3 (3- and 12-CH_3); EIMS *m*/*z* (%): 679 (M^+, 18), 288 (46), 250 (16), 249 (100), 248 (87), 218 (13); HREIMS *m*/*z* 679.3099 (M^+, calcd for $C_{36}H_{45}N_3O_{10}$, 679.3105).

4.10. Preparation of compound 15

4.10.1. Method A (additive: morpholine)

Morpholine (1.5 μL, 2 eq, 0.02 mmol) and a solution of $Pd(PPh_3)_4$ (1.2 mg, 0.1 eq, 0.001 mmol) in THF (0.5 mL) was succeessively added to a solution of **14c** (6.8 mg, 0.01 mmol) in THF (1.0 mL) under Ar, and the mixture was stirred at 25 °C for 30 min. The reaction mixture was concentrated in vacuo to give a residue. A solution of obtained this residue in $CHCl_3$ (1 mL) was stirred at 25 °C for 5 days. The reaction mixture was concentrated in vacuo to give a residue, which was subjected to column chromatography on SiO_2 (6 g) with CH_2Cl_2-AcOEt (10:1) to furnish **15** (2.6 mg, 41%) and **16** (1.3 mg, 22%).

4.10.2. Method B (additive: dimedone)

A solution of $Pd(PPh_3)_4$ (1.2 mg, 0.1 eq, 0.001 mmol) in THF (0.5 mL) was added to a solution of **14c** (6.8 mg, 0.01 mmol) and dimedone (2.8 mg, 2 eq, 0.02 mmol) in THF (1.0 mL) under Ar, and the mixture was stirred at 25 °C for 30 min. The reaction mixture was concentrated in vacuo to give a residue. As ^{1}H NMR spectral data of this residue indicated that only diastereomeric mixture of deallylated carboxylic acid was detected in this stage, a solution of this residue in $CHCl_3$ (1.5 mL) was refluxed at 80 °C for 2 h. The reaction mixture was concentrated in vacuo to give a residue, which was subjected to column chromatography on SiO_2 (6 g) with $CHCl_3$-AcOEt (9:1) to furnish the desired **15** (3.4 mg, 56%).

4.10.3. Method C (additive: sodium p-toluenesulfinate)

A solution of $Pd(PPh_3)_4$ (71.5 mg, 10 mol%, 0.06 mmol) in THF (5 mL) was added to a solution of **14c** (407.9 mg, 0.6 mmol) and sodium *p*-toluenesulfinate (130.9 mg, 1.2 eq, 0.72 mmol) in THF (10 mL) under Ar, and the mixture was stirred at 25 °C for 3 h. The reaction mixture was concentrated in vacuo to give a residue, which was subjected to column chromatography on SiO_2 (14 g) with $CHCl_3$-AcOEt (19:1) to furnish **15** (296.0 mg, 83%).

4.10.4. (6S*,7R*,9R*,14aS*,15R*)-Ethyl 7-cyano-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-6,7,9,14,14a,15-hexahydro-5H-6,15-iminobenzo[4,5]azocino[1,2-b]isoquinoline-9-carboxylate (15)

IR (KBr) 2938, 2226, 1744, 1728, 1466, 1410, 1344, 1250, 1115, 1092, 1074, 1032, 1011 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 4.52 (1H, s, 9-H), 4.34 (1H, d, $J = 2.8$ Hz, 7-H), 4.08 (1H, d, $J = 2.6$ Hz, 15-H),

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4.04 (1H, dq, $J = 10.5$, 7.0 Hz, OCH_2CH_3), 3.92 (1H, dq, $J = 10.5$, 7.0 Hz, OCH_2CH_3), 3.84 (3H, s, 1-OCH_3), 3.77 (3H, s, 2 or 11-OCH_3), 3.76 (3H, s, 10-OCH_3), 3.74 (3H, s, 2 or 11-OCH_3), 3.65 (3H, s, 4-OCH_3), 3.62 (3H, s, 13-OCH_3), 3.39 (1H, br d, $J = 8.4$ Hz, 6-H), 3.21 (1H, dt, $J = 11.7$, 2.6 Hz, 14a-H), 3.14 (1H, dd, $J = 15.6$, 2.6 Hz, 14H-α), 3.01 (1H, dd, $J = 18.3$, 8.4 Hz, 5-Hα), 2.39 (1H, d, $J = 18.3$ Hz, 5-Hβ), 2.31 (3H, s, 16-CH_3), 2.17 (6H, s, 3 and 12-CH_3), 1.93 (1H, dd, $J = 15.6$, 11.7 Hz, 14-Hβ), 1.04 (3H, t, $J = 7.0$ Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 171.1 (CO), 151.2 (C-4), 151.0 (C-13), 149.1 (C-2 and 11), 147.6 (C-10), 145.9 (C-1), 124.6 (C-3 or 12), 124.1 (C-9a or 13a), 123.6 (C-3 or 12), 123.3 (C-4a), 123.1 (C-15a), 122.4 (C-9a or 13a), 117.7 (CN), 61.0 (C-7), 60.9 (C-9, OCH_2CH_3), 60.33 (1 or 13-OCH_3), 60.29 (1 or 13-OCH_3), 60.0 (2-, 10-, or 11-OCH_3), 59.9 (2-, 10-, or 11-OCH_3), 59.8 (2-, 10-. or 11-OCH_3), 59.5 (4-OCH_3), 56.9 (C-15), 56.3 (C-14a), 54.9 (C-6), 41.8 (16-CH_3), 25.7 (C-14), 21.3 (C-5), 13.9 (OCH_2CH_3), 9.3 (3 or 12-CH_3), 9.2 (3 or 12-CH_3); EIMS *m*/*z* (%): 595 (M^+, 15), 522 (18), 289 (13), 288 (73), 249 (34), 248 (100), 218 (13); HREIMS *m*/*z* 595.2892 (M^+, calcd for $C_{32}H_{41}N_3O_8$, 595.2894).

4.10.5. (6S*,7R*,9S*,14aS*,15R*)-Ethyl 7-cyano-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl- 6,7,9,14,14a,15-hexahydro-5H-6,15-iminobenzo[4,5]azocino[1,2-b]isoquinoline-9-carboxylate (16)

IR ($CHCl_3$) 3439, 3022, 2938, 2359, 1717, 1628, 1466, 1410, 1225, 1113, 1074 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.60 (1H, s, 9-H), 4.24 (2H, q, $J = 7.2$ Hz, OCH_2CH_3), 4.13 (1H, d, $J = 3.4$ Hz, 15-H), 4.05 (1H, d, $J = 3.0$ Hz, 7-H), 4.05 (1H, overlapped, 14a-H), 3.82 (3H, s, 1-OCH_3), 3.74 (3H, s, 2-OCH_3), 3.73 (3H, s, 10-OCH_3), 3.69 (3H, s, 11-OCH_3), 3.61 (3H, s, 4-OCH_3), 3.59 (3H, s, 13-OCH_3), 3.36 (1H, br d, $J = 8.5$ Hz, 6-H), 3.04 (1H, dd, $J = 17.9$, 7.2 Hz, 14H-α), 2.99 (1H, dd, $J = 18.7$, 8.5 Hz, 5-Hα), 2.78 (1H, dd, $J = 17.9$, 7.3 Hz, 14-Hβ), 2.35 (1H, d, $J = 18.7$ Hz, 5-Hβ), 2.25 (3H, s, 16-CH_3), 2.10 (3H, s, 3-CH_3), 2.07 (3H, s, 12-CH_3), 1.28 (3H, t, $J = 7.2$ Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (CO) 151.7 (C-13), 151.2 (C-4), 149.2 (C-2), 148.5 (C-11), 147.9 (C-1), 144.8 (C-10), 124.4 (C-12), 123.7 (C-9a or 13a), 123.6 (C-3), 123.5 (C-15a), 123.1 (C-4a), 123.0 (C-9a or 13a), 117.7 (CN), 60.9 (OCH_2CH_3), 60.7 (C-9), 60.2 (1-OCH_3), 60.1 (2 or 10-OCH_3), 59.8 (2 or 10-OCH_3), 59.8 (11-OCH_3), 59.6 (14-OCH_3), 59.5 (13-OCH_3), 57.1 (C-15), 56.0 (C-6), 52.0 (C-7 and 14a), 42.3 (16-CH_3), 23.5 (C-14), 21.3 (C-5), 13.9 (OCH_2CH_3), 9.3 (3-CH_3), 9.2 (12-CH_3); EIMS *m*/*z* (%):595 (M^+, 14), 522 (27), 289 (12), 288 (65), 249 (37), 248 (100), 218 (13); HREIMS *m*/*z* 595.2892 (M^+, calcd for $C_{32}H_{41}N_3O_8$, 595.2894).

4.11. (6S*,7R*,9R*,14aS*,15R*)-9-(Hydroxymethyl)-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl- 6,7,9,14,14a,15-hexahydro-5H-6,15-iminobenzo[4,5]azocino[1,2-b]isoquinoline-7-carbonitrile (18)

$LiBH_4$ (103.2 mg, 10 eq, 4.5 mmol) and MeOH (182.1 mg, 10 eq, 4.5 mmol) were succeessively added to a stirred solution of **15** (268.1 mg, 0.45 mmol) in THF (4.5 mL), and the mixture was stirred at 25 °C for 2 h. The reaction mixture was carefully diluted with H_2O (15 mL) at 0 °C and extracted with $CHCl_3$ (30 mL x 3). The combined extracts were washed with brine (20 mL), dried, and concentrated in vacuo to give a residue (283.9 mg), which was subjected to column chromatography on SiO_2 (14 g) with $CHCl_3$-EtOAc (4:1–3:2) to furnish **18** (163.5 mg, 66%) as a colorless amorphous powder. IR (KBr) 3501, 2938, 2832, 2361, 1464, 1408, 1342, 1252, 1150, 1113, 1098, 1074, 1030, 1011, 962 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.12 (1H, d, $J = 2.7$ Hz, 15-H), 4.07–4.05 (2H, overlapped, 7 and 9-H), 3.85 (3H, s, 1-OCH_3), 3.84 (3H, s, 10-OCH_3), 3.77 (3H, s, 2 or 11-OCH_3), 3.76 (3H, s, 2 or 11-OCH_3), 3.72 (3H, s, 4-OCH_3), 3.62 (3H, s, 13-OCH_3), 3.57 (1H, dd, $J = 11.0$, 4.1 Hz, CH_2OH), 3.41 (1H, br d, $J = 7.7$ Hz, 6-H), 3.26 (1H, dt, $J = 12.1$, 2.7 Hz, 14a-H), 3.24–3.21 (1H, overlapped, CH_2OH), 3.16 (1H, dd, $J = 15.6$, 2.7 Hz, 14H-α), 3.09 (1H, dd, $J = 18.5$, 7.7 Hz, 5-Hα), 2.51 (1H, d, $J = 18.5$ Hz, 5-Hβ), 2.36 (3H, s, 16-CH_3), 2.19 (3H, s, 3-CH_3), 2.16 (3H, s, 12-CH_3), 1.78 (1H, dd, $J = 15.6$, 12.1 Hz, 14-Hβ); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.4 (C-4), 151.1 (C-13), 149.7 (C-11), 149.6 (C-2), 147.6 (C-1), 145.6 (C-10), 125.4 (C-9a), 124.5 (C-13a), 124.1 (C-3 or C-12), 124.0 (C-3 or C-12), 123.3 (C-15a), 122.7 (C-4a), 117.8 (CN), 65.7 (CH_2OH), 60.8 (C-7), 60.4 (1-, 10-, and 13-OCH_3), 60.1 (2 or 11-OCH_3), 60.0 (2 or 11-OCH_3), 59.9 (4-OCH_3), 58.4 (C-9), 56.9 (C-15), 56.6 (C-14a), 55.0 (C-6), 41.8 (16-CH_3), 25.8 (C-14), 21.6 (C-5), 9.3 (3-CH_3), 9.3 (12-CH_3); EIMS *m*/*z* (%): 553 (M^+, 1), 526 (18), 523 (11), 522 (36), 288 (17), 278 (60), 250 (19), 249 (30), 248 (100), 234 (10), 218 (14); HREIMS *m*/*z* 553.2789 (M^+, calcd for $C_{30}H_{39}N_3O_7$, 553.2788).

4.12. (6S*,7R*,9R*,14aS*,15R*)-9-((1,3-Dioxoisoindolin-2-yl)methyl)-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-6,7,9,14,14a,15-hexahydro-5H-6,15-iminobenzo[4,5]azocino[1,2-b]isoquinoline-7-carbonitrile (19)

A 40% solution of DEAD in toluene (645 μL, 4 eq, 1.2 mmol) was added to a stirred solution of **18** (166.1 mg, 0.30 mmol), phthalimide (180.2 mg, 4 eq, 1.2 mmol), and PPh_3 (331.3 mg, 4 eq, 1.2 mmol) in THF (7.5 mL) at 0 °C, and the mixture was stirred at 25 °C for 6 h. The reaction mixture was concentrated in vacuo to give a residue, which was subjected to column chromatography on SiO_2 (14 g) with CH_2Cl_2-EtOAc (17:3–4:1) to a pale yellow solid. This solid was washed with MeOH to furnish **19** (149.0 mg, 73%) as a colorless solid. IR (KBr) 3246, 2359, 1751, 1722, 1699, 1533, 1466, 1412, 1395, 1385, 1342, 1254, 1113, 1070, 1009, 961 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70–7.62 (4H, m, 4′ and 5′ and 6′ and 7′-H), 4.32 (1H, dd, $J = 9.8$, 4.0 Hz, 9-H), 4.22 (1H, d, $J = 2.1$ Hz, 7-H), 4.05 (1H, d, $J = 2.5$ Hz, 15-H), 3.85 (3H, s, 1-OCH_3), 3.79 (3H, s, 2-OCH_3), 3.71 (3H, s, 4-OCH_3), 3.63 (3H, s, 13-OCH_3), 3.53 (3H, s, 10-OCH_3), 3.47 (1H, dd, $J = 13.6$, 4.0 Hz, CH_2NPht), 3.41 (1H, br d, $J = 7.8$ Hz, 6-H), 3.32 (1H, dd, $J = 13.6$, 9.8 Hz, CH_2NPht), 3.23 (3H, s, 11-OCH_3), 3.20 (1H, dd, $J = 15.3$, 2.5 Hz, 14H-α), 3.12 (1H, dt, $J = 11.7$, 2.5 Hz, 14a-H), 3.07 (1H, dd, $J = 18.3$, 7.8 Hz, 5-Hα), 2.60 (1H, d, $J = 18.3$ Hz, 5-Hβ), 2.32 (3H, s, 16-CH_3), 2.22 (3H, s, 3-CH_3), 2.10 (3H, s, 12-CH_3), 1.79 (1H, dd, $J = 15.3$, 11.7 Hz, 14-Hβ); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0 (C-1′ and 3′), 151.7 (C-13), 151.1 (C-4), 149.6 (C-11), 149.1 (C-2), 147.4 (C-1), 145.9 (C-10), 133.5 (C-5′ and 6′), 132.3 (C-3'a and 7'a), 125.5 (C-9a), 124.9 (C-13a), 124.0 (C-12), 123.5 (C-3 or C-4a), 123.4 (C-3 or C-4a), 123.2 (C-15a), 122.7 (C-4′ and 7′), 118.2 (CN), 61.2 (C-7), 60.7 (13-OCH_3), 60.3 (1 and 10-OCH_3), 59.9 (2-OCH_3), 59.7 (4-OCH_3), 59.5 (11-OCH_3), 57.4 (C-14a), 56.8 (C-15), 55.0 (C-6), 54.9 (C-9), 43.4 (CH_2-NPht), 41.8 (16-CH_3), 26.1 (C-14), 21.6 (C-5), 9.4 (3-CH_3), 9.3 (12-CH_3); EIMS *m*/*z* (%): 682 (M^+, 1), 523 (33), 522 (100), 497 (21), 496 (11), 495 (38), 288 (47), 249 (25), 248 (96), 234 (11), 218 (16); HREIMS *m*/*z* 682.2997 (M^+, calcd for $C_{38}H_{42}N_4O_8$, 682.3003).

4.13. N-(((6S*,7R*,9R*,14aS*,15R*)-7-Cyano-1,2,4,10,11,13-hexamethoxy-3,12,16-trimethyl-6,7,9,14,14a,15- hexahydro-5H-6,15-iminobenzo[4,5]azocino[1,2-b]isoquinolin-9-yl)methyl)-2-oxopropanamide (20)

NH_2NH_2–H_2O (842 μL, 100 eq, 17 mmol) was added to a stirred solution of **19** (116.1 mg, 0.17 mmol) in EtOH (8.5 mL), and the mixture was heated at 80 °C for 1.5 h. After half volume of the solvent was removed in vacuo, the resulting mixture was diluted with benzene (30 mL) and then extracted with 1 M HCl (30 mL x 4). The combined extracts were made pH 9 with concentrated NH_4OH (30 mL) and extracted with $CHCl_3$–MeOH (19:1, 200 mL x 4), dried, and concentrated in vacuo to give a residue (121.5 mg), and the residue was used in the next step without further purification. *N*,*N*-Diethylaniline (61 μL, 2.2 eq, 0.374 mmol) was added to a stirred solution of the crude primary amine [34] in THF (8.5 mL), and the

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mixture was stirred at 0 °C for 5 min. Pyruvic acid (32 μL, 2.6 eq, 0.442 mmol), EDCI (84.7 mg, 2.6 eq, 0.442 mol), and HOBt (56.8 mg, 2.4 eq, 0.408 mmol) were succeessively added to the above solution, and the mixture was stirred at 25 °C for 4 h. The reaction mixture was diluted with saturated aqueous $NaHCO_3$ (10 mL) and extracted with $CHCl_3$ (30 mL x 3). The combined extracts were washed with brine (30 mL), dried, concentrated in vacuo to give a residue (182.8 mg), which was subjected to column chromatography on SiO_2 (14 g) with hexane-EtOAc (1:1) to furnish **20** (87.8 mg, 83%, 2 steps) as a colorless amorphous powder. IR (KBr) 3385, 2359, 1721, 1690, 1520, 1464, 1410, 1344, 1252, 1227, 1113, 1074, 1011 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 6.45 (1H, br t, $J = 5.5$ Hz, NH), 4.17 (1H, dd, $J = 5.5$, 2.5 Hz, 9′-H), 4.05 (1H, d, $J = 2.3$ Hz, 15′-H), 3.99 (1H, d, $J = 2.5$ Hz, 7′-H), 3.87 (3H, s, 10′−OCH_3), 3.840 (3H, s, 1′−OCH_3), 3.836 (3H, s, 2′−OCH_3), 3.76 (3H, s, 11′−OCH_3), 3.68 (3H, s, 4′−OCH_3), 3.59 (3H, s, 13′−OCH_3), 3.46−3.41 (1H, overlapped, CH_2NH), 3.41 (1H, br d, $J = 7.3$ Hz, 6′-H), 3.24 (1H, dt, $J = 13.4$, 5.5 Hz, CH_2NH), 3.18−3.13 (2H, overlapped, 14'a-H, 14′H-α), 3.04 (1H, dd, $J = 18.5$, 7.3 Hz, 5′-Hα), 2.49 (1H, d, $J = 18.5$ Hz, 5′-Hβ), 2.32 (3H, s, 16-CH_3), 2.20 (3H, s, 3′−CH_3), 2.18 (3H, s, $COCH_3$), 2.15 (3H, s, 12′−CH_3), 1.78 (1H, dd, $J = 16.1$, 12.0 Hz, 14′-Hβ); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 196.1 ($COCH_3$), 159.8 (NHCO), 151.2 (C-13′), 151.0 (C-4′), 149.8 (C-11′), 149.4 (C-2′), 147.6 (C-1′), 145.7 (C-10′), 124.7 (C-13'a), 124.4 (C-9'a or 12′), 124.3 (C-9'a or 12′), 123.9 (C-3′), 122.9 (C-15'a), 122.9 (C-4'a), 117.9 (CN), 60.3 (C-7′, 10′ and 13′−OCH_3), 60.3 (1′- or 2′−OCH_3), 60.1 (11′−OCH_3), 59.8 (1′- or 2′−OCH_3), 59.6 (4′−OCH_3), 56.8 (C-9′ or 15′), 56.7 (C-9′ or 15′), 56.2 (C-14'a), 54.9 (C-6′), 43.1 (CH_2NH), 41.8 (16′−CH_3), 26.0 (C-14′), 24.3 ($COCH_3$), 21.3 (C-5′), 9.4 (3′−CH_3), 9.2 (12′−CH_3); FABMS *m/z* 623 $[M+H]^+$; HRFABMS *m/z* 623.3079 ($[M+H]^+$, calcd for $C_{33}H_{43}N_4O_8$, 623.3081).

4.14. (±)-Saframycin A (1)

A solution of BBr_3 in CH_2Cl_2 (1 M, 160 μL, 4 eq, 0.16 mmol) was added to a stirred solution of **20** (24.9 mg, 0.04 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C, and the mixture was stirred at same temperature for 2 h. The reaction mixture was warmed to −20 °C over a period of 2 h, and stirring was continued for 17 h. The reaction mixture was diluted with $CHCl_3$ (10 mL) and H_2O (10 mL), made pH 7 with saturated aqueous $NaHCO_3$ (10 drops) at 0 °C, and extracted with $CHCl_3$−MeOH (9:1, 30 mL x 3). The combined extracts were washed with brine (25 mL), dried, concentrated in vacuo to give a residue (29.9 mg), which was used in the next step without purification.

A solution of CAN (115.4 mg, 5 eq, 0.2 mmol) in H_2O (2 mL) was added to a solution of the above product in THF (6 mL) at 0 °C, and the mixture was stirred at 0 °C for 2 h. After a half volume of the solvent was removed in vacuo, the residue was diluted with H_2O (20 mL), and extracted with EtOAc (25 mL x 3). The combined extracts were washed with brine (20 mL), dried, concentrated in vacuo to give a residue (16.8 mg), which was subjected to column chromatography on SiO_2 (6 g) with benzene-EtOAc (5:1−7:3) to furnish saframycin A (**1**) (4.5 mg, 20%, 2 steps) as a dark brown solid. IR (KBr) 2361, 1686, 1655, 1618, 1373, 1362, 1312, 1300, 1236, 1152 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.67 (1H, br dd, $J = 8.6$, 4.2 Hz, NH), 4.07 (1H, br d, $J = 2.8$ Hz, 15′-H), 4.03 (3H, s, 11′−OCH_3), 4.02 (3H, s, 2′−OCH_3), 3.99 (1H, d, $J = 2.2$ Hz, 7′-H), 3.98 (1H, m, 9′-H), 3.73 (1H, ddd, $J = 14.3$, 8.6, 1.6 Hz, CH_2NH), 3.43 (1H, br d $J = 7.5$ Hz, 6′-H), 3.26 (1H, dt, $J = 14.3$, 4.2 Hz, CH_2NH), 3.14 (1H, dt, $J = 11.5$, 2.8 Hz, 14'a-H), 2.88 (1H, dd, $J = 17.7$, 2.8 Hz, 14′H-α), 2.83 (1H, dd, $J = 20.9$, 7.6 Hz, 5′-Hα), 2.32 (3H, s, 16-CH_3), 2.26 (3H, s, $COCH_3$), 2.24 (1H, d, $J = 20.9$ Hz, 5′-Hβ), 1.99 (3H, s, 3′−CH_3), 1.92 (3H, s, 12′−CH_3), 1.29 (1H, ddd, $J = 17.7$, 11.5, 2.8 Hz, 14′-Hβ), ^{13}C NMR ($CDCl_3$, 125 MHz) δ 196.7 ($COCH_3$), 186.6 (C-4′), 185.3 (C-13′), 182.4 (C-1′), 180.8 (C-10′), 160.1 (NHCO), 155.9 (C-11′), 155.6 (C-2′), 141.5 (C-4'a), 141.2 (C-13'a), 135.5 (C-9'a and 15'a), 129.2 (C-3′), 128.3 (C-12′), 116.6 (CN), 61.1 (11′−OCH_3), 61.0 (2′−OCH_3), 58.2 (C-7′), 56.2 (C-9′), 54.4 (C-6′), 54.1 (C-15′), 53.9 (C-14'a), 41.6 (16-CH_3), 40.6 (CH_2NHCO), 25.0 (C-14′), 24.3 ($COCH_3$), 21.5 (C-5′), 8.7 (3′ and 12′−CH_3); EIMS *m/z* (%): 562 (M^+, 6), 492 (12), 464 (15), 463 (11), 462 (22), 243 (14), 221 (18), 220 (100), 219 (13), 218 (26), 204 (13); HREIMS *m/z* 562.2063 (M^+, calcd for $C_{29}H_{30}N_4O_8$, 562.2064).

4.15. Preparation of dialkyl oxomalonate

4.15.1. Preparation of diallyl 2,2-dihydroxymalonate (6b')

p-TsOH·H_2O (115.3 mg, 0.06 eq, 0.6 mmol) was added to a stirred solution of malonic acid (**21**; 1.06 g, 10 mmol) and allyl alcohol (3.0 mL, 4.4 eq, 44 mmol) in benzene (50 mL), and the mixture was refluxed at 105 °C with Dean-Stark apparatus for 6 h. The reaction mixture was diluted with Et_2O (50 mL), washed with saturated aqueous $NaHCO_3$ (15 mL x 2) and brine (15 mL), dried, concentrated in vacuo to give a residue (1.91 g), which was subjected to column chromatography on SiO_2 (30 g) with AcOEt: n-hexane (1:10) to give diallyl malonate (**22** [35]: 97.8 mg, 72%) as a colorless syrup. IR ($CHCl_3$) 3022, 1751, 1732, 1412, 1368, 1329, 1277, 1227, 1215, 1182, 1150, 991, 937 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.92 (2H, m, $OCH_2CH{=}CH_2$), 5.35 (2H, dq, $J = 5.7$, 1.4 Hz, $OCH_2CH{=}CH_2$), 5.26 (2H, dq, $J = 10.5$, 1.4 Hz, $OCH_2CH{=}CH_2$), 4.65 (4H, dt, $J = 5.7$, 1.5 Hz, $OCH_2CH{=}CH_2$), 3.44 (2H, s, 2-H_2); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.1 (CO), 131.5 ($OCH_2CH{=}CH_2$), 118.8 ($OCH_2CH{=}CH_2$), 66.1($OCH_2CH{=}CH_2$), 41.4 (C-2).

AcOH (183 μL, 0.74 eq, 3.18 mmol) was added dropwise to a stirred solution of $NaClO_2$ (1.08 g, 2.2 eq, 9.46 mmol) in H_2O (2.6 mL) at 0 °C, **22** (792.0 mg, 4.3 mmol) was then added carefully into the above solution [36], and the mixture was stirred at 25 °C for 20 h. The reaction mixture was diluted with H_2O (5 mL) and extracted with $CHCl_3$ (20 mL x 3). The combined extracts were washed with brine (20 mL), dried, concentrated in vacuo to give a residue (888.9 mg), which was subjected to column chromatography on SiO_2 (30 g) with hexane-EtOAc (13:7) to furnish diallyl 2,2-dihydroxymalonate (**6b':** 604.1 mg, 71%) as a colorless syrup. IR ($CHCl_3$) 3501, 3021, 1748, 1300, 1271, 1227, 1206, 1132, 989, 939 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.90 (2H, ddt, $J = 17.2$, 10.5, 5.8 Hz, $OCH_2CH{=}CH_2$), 5.36 (2H, dq, $J = 17.2$, 1.3 Hz, $OCH_2CH{=}CH_2$), 5.30 (2H, dq, $J = 10.5$, 1.3 Hz, $OCH_2CH{=}CH_2$), 4.87 (2H, br s, OH), 4.76 (4H, dt, $J = 5.8$, 1.3 Hz, $OCH_2CH{=}CH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.0 (CO), 130.4 ($OCH_2CH{=}CH_2$), 119.8 ($OCH_2CH{=}CH_2$), 90.2 ($(HO)_2C$), 67.7 ($OCH_2CH{=}CH_2$); FABMS *m/z* 239 $[M+Na]^+$; HRFABMS *m/z* 239.0539 ($[M+Na]^+$, calcd for $C_9H_{12}O_6Na$, 239.0532).

4.15.2. Preparation of allyl ethyl 2,2-dihydroxymalonate (6c')

A solution of KOH (7.92 g, 1.2 eq, 120 mmol) in H_2O (48 mL) was added to a stirred solution of diethyl malonate (**23**: 15.3 mL, 100 mmol) in EtOH (20 mL), and the mixture was stirred at 25 °C for 1 h. The reaction mixture was diluted with H_2O (20 mL) at 0 °C, washed with CH_2Cl_2 (40 mL x 3), made pH 2 with concentrated HCl, and extracted with CH_2Cl_2 (60 mL x 3). The combined extracts were dried, concentrated in vacuo to give ethyl malonate (**24** [37]: 12.4 g, 94%) as colorless syrup. IR ($CHCl_3$) 3447, 3024, 2986, 1744, 1734, 1371, 1327, 1227, 1196, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.46 (1H, br s, CO_2H), 4.24 (2H, q, $J = 7.2$ Hz, OCH_2CH_3), 3.44 (2H, s, 2-H_2), 1.30 (3H, t, $J = 7.2$ Hz, OCH_2CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (CO), 166.9 (CO), 61.9 (CH_2CH_3), 40.9 (C-2), 13.9 (OCH_2CH_3) [38].

Allyl alcohol (9.7 mL, 3 eq, 140.5 mmol) and DCC (11.60 g, 1.2 eq, 56.2 mmol) was added to a stirred solution of **24** (6.19 g, 46.8 mmol) in CH_2Cl_2 (200 mL), and the mixture was stirred at 25 °C for 5 h. The reaction mixture was filtrated, and the combined filtrates were

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concentrated in vacuo, and purified by vacuum distillation to give allyl ethyl malonate (**25** [38]: 6.95 g, 86%, bp 77–78 °C (3 mmHg)) as colorless syrup. IR ($CHCl_3$) 1748, 1732, 1371, 1329, 1275, 1227, 1188, 1152, 1032 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.92 (1H, ddt, J = 17.2, 10.4, 5.7 Hz, $OCH_2CH{=}CH_2$), 5.35 (1H, dq, J = 17.2, 1.4 Hz, $OCH_2CH{=}CH_2$), 5.26 (1H, dq, J = 10.4, 1.4 Hz, $OCH_2CH{=}CH_2$), 4.65 (2H, dt, J = 5.7, 1.4 Hz, $OCH_2CH{=}CH_2$), 4.21 (2H, q, J = 7.1 Hz, OCH_2CH_3), 3.40 (2H, s, 2-H_2), 1.28 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.4 (CO), 166.2 (CO), 131.5 ($OCH_2{-}CH{=}CH_2$), 118.6 ($OCH_2CH{=}CH_2$), 66.0 ($OCH_2CH{=}CH_2$), 61.5 (OCH_2CH_3), 41.5 (C-2), 14.0 (OCH_2CH_3).

AcOH (424 μL, 0.74 eq, 7.4 mmol) was added to a stirred solution of $NaClO_2$ (2.519 g, 2.2 eq, 22 mmol) in H_2O (6 mL) at 0 °C, **25** (1.72 g, 10 mmol) was added carefully into the above solution [36], and the mixture was stirred at 0 °C for 1.5 h, then 25 °C for 27 h. The reaction mixture was diluted with H_2O (20 mL) and extracted with EtOAc (20 mL x 3). The combined extracts were washed with brine (20 mL), dried, concentrated in vacuo to give a residue (1.666 g), which was subjected to column chromatography on SiO_2 (30 g) with hexane-EtOAc (3:2) to furnish **6c'** (1.451 g, 71%) as a colorless syrup. IR ($CHCl_3$) 3503, 3028, 1748, 1304, 1269, 1229, 1206, 1132 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.91 (1H, ddt, J = 17.1, 10.4, 5.8 Hz, $OCH_2CH{=}CH_2$), 5.37 (1H, dq, J = 17.1, 1.3 Hz, $OCH_2CH{=}CH_2$), 5.30 (1H, dq, J = 10.4, 1.3 Hz, $OCH_2CH{=}CH_2$), 4.84 (2H, br s, $C(OH)_2$), 4.76 (2H, dt, J = 5.8, 1.3 Hz, $OCH_2CH{=}CH_2$), 4.34 (2H, q, J = 7.2 Hz, OCH_2CH_3), 1.32 (3H, t, J = 7.2 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.2 (CO), 168.1 (CO), 130.4 ($OCH_2CH{=}CH_2$), 119.6 ($OCH_2CH{=}CH_2$), 90.1 (C-2), 67.6 ($OCH_2CH{=}CH_2$), 63.6 (OCH_2CH_3), 13.9 (OCH_2CH_3); FABMS m/z 205 $[M+H]^+$; HRFABMS m/z 205.0721 ($[M+H]^+$, calcd for $C_8H_{13}O_6$, 205.0712).

4.16. Cytotoxicity assay

The assay was performed using a cell counting Kit-8 (CCK-8) following the manufacturer's instruction. A single-cell suspension (2×10^3 cells/well) was added to the serially diluted test compounds in a 96-well microplate and cultured for 4 days. After incubation with 10 μL of CCK-8 solution/well for 2 h, the absorbance of formazan products was measured at 450 nm using a microplate reader. The percentage of cell viability was calculated with respect to nontreated control cells. The IC_{50} value of each experiment was determined using GraphPad Prism software. The mean IC_{50} values ± standard error (SE) were obtained from three independent experiments.

4.17. Cell culture

DU145 prostate cancer and HCT116 colon cancer cells were cultured in PPMI-1640 and DMEM (high glucose) media, respectively, supplemented with 10% FBS with 100U/mL penicillin, and 100 μg/mL streptomycin in humidified incubation with 5% CO_2.

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References

[1] J.D. Scott, R.M. Williams, Chem. Rev. 102 (2002) 1669–1730.
[2] A. Kubo, N. Saito, Studies in Natural Product Chemistry, vol. 10, Elsevier, New York, 1992, pp. 77–145.
[3] K.L. Rinehart, Med. Res. Rev. 20 (2000) 1–27.
[4] C. Avendaño, E. de la Cuesta, Curr. Org. Synth. 6 (2009) 143–168.
[5] C. Cuevas, A. Francesch, Nat. Prod. Rep. 26 (2009) 322–337.
[6] V.H. Le, M. Inai, R.M. Williams, T. Kan, Nat. Prod. Rep. 32 (2015) 328–347.
[7] M. D'Incalci, C.M. Galmarini, Mol. Canc. Therapeut. 9 (2010) 2157–2163.
[8] T. Fukuyama, L. Yang, K.L. Ajeck, R.A. Sachleben, J. Am. Chem. Soc. 112 (1990) 3712–3713.
[9] E.J. Martinez, E. Corey, J. Org. Lett. 1 (1999) 75–77.
[10] A.G. Myers, D.W. Kung, J. Am. Chem. Soc. 121 (1999) 10828–10829.
[11] A.G. Myers, B.A. Lanman, J. Am. Chem. Soc. 124 (2002) 12969–12971.
[12] W. Dong, W. Liu, X. Liao, B. Guan, S. Chen, Z. Liu, J. Org. Chem. 76 (2011) 5363–5368.
[13] A. Kubo, N. Saito, H. Yamato, K. Masubuchi, M. Nakamura, J. Org. Chem. 53 (1988) 4295–4310.
[14] N. Saito, Y. Ohira, N. Wada, A. Kubo, Tetrahedron 46 (1990) 7711–7728.
[15] M. Yokoya, K. Shinada-Fujino, N. Saito, Tetrahedron Lett. 52 (2011) 2446–2449.
[16] M. Yokoya, K. Shinada-Fujino, S. Yoshida, M. Mimura, H. Takada, N. Saito, Tetrahedron 68 (2012) 4166–4181.
[17] K. Yokoya, K. Kobayashi, M. Sato, N. Saito, Mar. Drugs 13 (2015) 4915–4933.
[18] M. Yokoya, H. Ito, N. Saito, Tetrahedron 67 (2011) 9185–9192.
[19] N. Saito, S. Harada, M. Nishida, I. Inouye, A. Kubo, Chem. Pharm. Bull. 43 (1995) 777–782.
[20] N. Saito, C. Tanaka, Y. Koizumi, K. Suwanborirux, S. Amnuoypol, S. Pummangura, A. Kubo, Tetrahedron 60 (2004) 3873–3881.
[21] N. Saito, R. Yamauchi, H. Nishioka, S. Ida, A. Kubo, J. Org. Chem. 54 (1989) 5391–5395.
[22] S. Kimura, S. Kawai, M. Azuma, Y. Umehara, Y. Koizumi, M. Yokoya, N. Saito, Heterocycles 90 (2015) 327–343.
[23] The Pictet-Spengler cyclization of phenethylamine with diethyl oxomalonate to afford the corresponding isoquinoline was reported M. Bois-Chussy, S. Cadet, M.D. Paolis, J. Zhu, Tetrahedron Lett. 42 (2001) 4503–4506.
[24] A.P. Krapcho, E. Ciganek, Org. React. 81 (2013) 1–536.
[25] Oxomalonate 6b was obtained in its hydrate form 6b' by oxidation[40] of the activated methylene group of known malonate 21[35] with aqueous sodium chlorite in acetic acid in 71% yield (see Experimental section).
[26] Compound **6c**[37] was also obtained in its hydrate form **6c'** by oxidation in the same manner in 71% yield.
[27] M. Honda, H. Morita, I. Nagakura, J. Org. Chem. 62 (1997) 8932–8936.
[28] A. Stapon, R. Li, C.A. Townsend, J. Am. Chem. Soc. 125 (2003) 15746–15747.
[29] N. Saito, S. Harada, I. Inouye, K. Yamaguchi, A. Kubo, Tetrahedron 51 (1995) 8231–8246.
[30] Myers, A.; Plowright, A. T. Patent WO2002040477/A2. 2002; also see: Myers, A. G.; Plowright, A. T. J. Am. Chem. Soc. 2001, 123, 5114-5115.
[31] T. Arai, K. Takahashi, S. Nakahara, A. Kubo, Experientia 36 (1980) 1025–1027.
[32] For simplicity, all numbering was used in this manuscript as shown in Fig. 1, but, IUPAC names and numbering are used in the Experimental section.
[33] An analytical a few ammount of one diastereomer **13c** was obtained as a yellow amorphous powder, but, we cannot detect its stereochemistry at C-1′ position. IR (KBr) 3435, 2982, 2941, 1740, 1464, 1408, 1342, 1248, 1198, 1115, 1074, 1026, 1011, 962 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.85 (1H, ddt, J = 17.3, 10.4, 5.6 Hz, $OCH_2CH{=}CH_2$), 5.25 (1H, dq, J = 17.3, 1.4 Hz, $OCH_2CH{=}CH_2$), 5.15 (1H, dq, J = 10.4, 1.4 Hz, $OCH_2CH{=}CH_2$), 4.66 (1H, ddt, J = 13.3, 5.6, 1.4 Hz, $OCH_2CH{=}CH_2$), 4.59 (1H, ddt, J = 13.3, 5.6, 1.4 Hz, $OCH_2CH{=}CH_2$), 4.13 (1H, dq, J = 10.8, 7.1 Hz, OCH_2CH_3), 4.11 (1H, d, J = 7.8 Hz, 1-H), 3.96 (1H, dq, J = 10.8, 7.1 Hz, OCH_2CH_3), 3.84 (3H, s, 8-OCH_3), 3.84 (1H, overlapped, 3a-H), 3.80 (3H, s, 7-OCH_3), 3.76 (3H, s, 8′−OCH_3), 3.71 (3H, s, 7′−OCH_3), 3.69 (3H, s, 5 or 5′−OCH_3), 3.68 (3H, s, 5 or 5′−OCH_3), 3.45 (1H, dd, J = 11.0, 2.3 Hz, 3a-H), 3.08 (1H, dd, J = 16.3, 3.2 Hz, 4′-H), 2.92 (1H, dd, J = 15.5, 4.2 Hz, 4-H), 2.72 (1H, ddd, J = 11.1, 7.8, 3.2 Hz, 3′-H), 2.64–2.59 (2H, overlapped, 4-H, 4′-H), 2.56 (3H, s, 2-CH_3), 2.35 (1H, m, 3-H), 2.22 (3H, s, 6-CH_3), 2.18 (3H, s, 6′−CH_3), 1.10 (3H, t, J = 7.1 Hz, OCH_2CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2 (CO x 2), 151.5 (C-5′), 151.3 (C-5), 149.6 (C-7), 149.0 (C-7′), 147.2 (C-8′), 147.0 (C-8), 131.8 ($OCH_2CH{=}CH_2$), 126.4 (C-9), 125.5 (C-10 and 6′), 124.9 (C-10′), 124.2 (C-6), 124.0 (C-9′), 118.1 ($OCH_2CH{=}CH_2$), 70.1 (C-1′), 66.3 ($OCH_2CH{=}CH_2$), 63.8 (C-1), 63.7 (C-3a), 62.3 (C-3), 61.7 (OCH_2CH_3), 60.8 (5 or 5′−OCH_3), 60.7 (8-OCH_3), 59.9 (7-OCH_3), 59.8 (8′−OCH_3), 59.7 (7′−OCH_3), 59.6 (5 or 5′−OCH_3), 56.3 (C-3′), 45.9 (2-CH_3), 26.9 (C-4′), 25.2 (C-4), 13.8 (OCH_2CH_3), 9.4 (6 and 6′−CH_3); EIMS m/z (%): 672 (M^+, 0.3), 392 (6), 281 (17), 280 (100); HREIMS m/z 672.3255 (M^+, calcd $C_{35}H_{48}N_2O_{11}$, 672.3258).
[34] An analytical sample of (6S*,7R*,9R*,14aS*,15R*)-9-(Aminomethyl)-1,2,4,10,11,13-hexamethoxy-3,12,16- trimethyl-6,7,9,14,14a,15-hexahydro-5H-6,15-iminobenzo[4,5]azocino[1,2-*b*]isoquinoline-7-carbonitrile was obtained as a pale yellow syrup by SiO_2 chlumn chromatography with $CHCl_3$–MeOH (97: 3). IR ($CHCl_3$) 2938, 2386, 1738, 1601, 1464, 1410, 1342, 1213, 1113, 1074 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.09 (1H, d, J = 2.3 Hz, 15-H), 4.04 (1H, d, J = 2.5 Hz, 7-H), 3.99 (1H, br t, J = 3.6 Hz, 9-H), 3.86 (3H, s, 1-OCH_3), 3.82 (3H, s, 10-OCH_3), 3.78 (3H, s, 2 or 11-OCH_3), 3.77 (3H, s, 2 or 11-OCH_3), 3.71 (3H, s, 4-OCH_3), 3.63 (3H, s, 13-OCH_3), 3.40 (1H, br d, J = 8.0 Hz, 6-H), 3.20 (1H, dt, J = 12.0, 2.3 Hz, 14a-H), 3.13 (1H, dd, J = 15.9, 2.3 Hz, 14-Hα), 3.08 (1H, dd, J = 18.4, 8.0 Hz, 5-Hα), 2.67 (1H, dd, J = 13.4, 3.6 Hz, CH_2NH_2), 2.58 (1H, dd, J = 13.4, 3.6 Hz, CH_2NH_2), 2.48 (1H, d, J = 18.4 Hz, 5-Hβ), 2.35 (3H, s, 16-CH_3), 2.19 (3H, s, 3-CH_3), 2.17 (3H, s, 12-CH_3), 1.77 (1H, dd, J = 15.9, 12.0 Hz, 14-Hβ): ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.2 (C-4), 151.0 (C-13), 149.8

(C-11), 149.3 (C-2), 147.6 (C-1), 145.6 (C-10), 125.8 (C-9a), 124.9 (C-13a), 123.8 (C-3 and 12), 123.5 (C-15a), 123.2 (C-4a), 118.2 (CN), 60.8 (C-7), 60.4 (13-OCH_3), 60.4 (1-OCH_3), 60.3 (10-OCH_3), 60.1 (2 or 11-OCH_3), 60.0 (2 or 11-OCH_3), 59.8 (4-OCH_3), 59.3 (C-9), 56.9 (C-15), 56.4 (C-14a), 55.0 (C-6), 46.9 (CH_2NH_2), 41.8 (16-CH_3), 26.2 (C-14), 21.6 (C-5), 9.3 (3 and 12-CH_3); FABMS m/z 553 $[M+H]^+$; HRFABMS m/z 553.3033 ($[M+H]^+$, calcd for $C_{30}H_{41}N_4O_6$, 553.3026).

[35] D. Imao, A. Itoi, A. Yamazaki, M. Shirakura, R. Ohtoshi, K. Ogata, Y. Ohmori, T. Ohta, Y. Ito, J. Org. Chem. 72 (2007) 1652–1658.
[36] Caution: This is a tremenmendous exothermic reaction, and be careful temperatue controlled during the reaction.
[37] T. Bixa, H. Hunter, A. Andrijevic, W. Petersen, H. Su, F. Dhoro, J. Org. Chem. 80 (2015) 762–769.
[38] M.E. Hediger, Bioorg. Med. Chem. 12 (2004) 4995–5010.

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