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Total Synthesis of (+)-Yatakemycin

Kentaro Okano,[a, b] Hidetoshi Tokuyama,[a, b] and Tohru Fukuyama*[a]

Dedicated to Professor Teruaki Mukaiyama on the occasion of his 80th birthday

Abstract: A convergent total synthesis of (+)-yatakemycin was accomplished by a 20-step sequence in 13% overall yield. The regioselective ring opening of (*S*)-epichlorohydrin with a 2,6-dibromophenyllithium derivative enabled us to introduce a chiral carbon center, which was required for the stereoselective construction of the cyclopropane ring. The five aryl–nitrogen bonds in (+)-yatakemycin were constructed by a mild copper-mediated aryl amination that utilized the combination of CuI with CsOAc. The efficient and chemoselective debenzylation of aryl benzyl ether with BCl_3 in the presence of pentamethylbenzene was developed. With these new methodologies, the subgram-scale synthesis of (+)-yatakemycin was achieved.

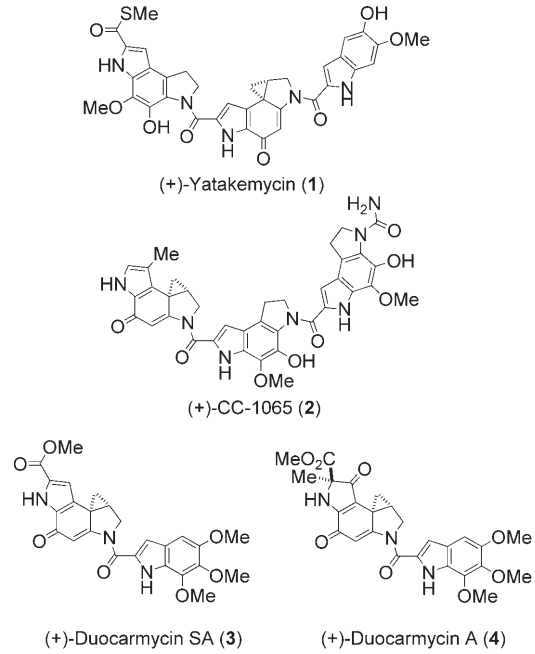
Keywords: aryl amination · asymmetric synthesis · copper · total synthesis · yatakemycin

Introduction

(+)-Yatakemycin (**1**), which was isolated from a culture broth of *Streptomyces sp.* TP-A0356 by Igarashi et al. in 2003,[1a] is an antitumor antibiotic based on a sequence-selective DNA alkylation. Among this family of antibiotics, **1** has proven to exhibit the most potent activity against L1210 (IC_{50} = 3 pM), and therefore has attracted a great deal of attention with regard to the nature of its interaction with DNA.[1b] Boger and co-workers recently reported the first total synthesis of this compound and at the same time revised its structure and determined its absolute configuration.[1e]

(+)-Yatakemycin[1] (**1**) is a member of the class of antitumor antibiotics with a characteristic dienone cyclopropane ring, such as CC-1065[2] (**2**), duocarmycin SA[1g,2a,3] (**3**), and duocarmycin A[2a,4] (**4**) (Scheme 1). Compound **1** consists of three subunits connected by amide bonds. The middle segment contains a dienone cyclopropane ring that is responsible for DNA alkylation and is identical to the left segment of duocarmycin SA (**3**). The left segment of **1**, on the other hand, is similar to the middle and right subunits of CC-1065 (**2**).

Although many synthetic methods for this class of compounds have been reported, none of them are adequately efficient. Key synthetic issues here would be the effective



Scheme 1. Structure of yatakemycin (**1**) and its derivatives.

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preparation of highly functionalized subunits and the assembly of these segments without affecting the sensitive thiolester functionality, which is not found in the related compounds **2**–**4**. For the preparation of the three segments **6**–**8** (Scheme 2) that have nitrogen-containing heterocycles, we intended to use the exceptionally mild copper-mediated aryl amination reaction developed in our laboratories.[5] During investigation of an assembly of the segments, we faced difficulty in selectively manipulating the protective groups. We circumvented this problem by developing a mild and efficient debenzylation protocol with a combination of BCl_3 and pentamethylbenzene. In this paper, we describe the full details of the preparation of each segment by utilizing the copper-mediated aryl amination reaction as well as the ensuing total synthesis of (+)-yatakemycin (**1**).

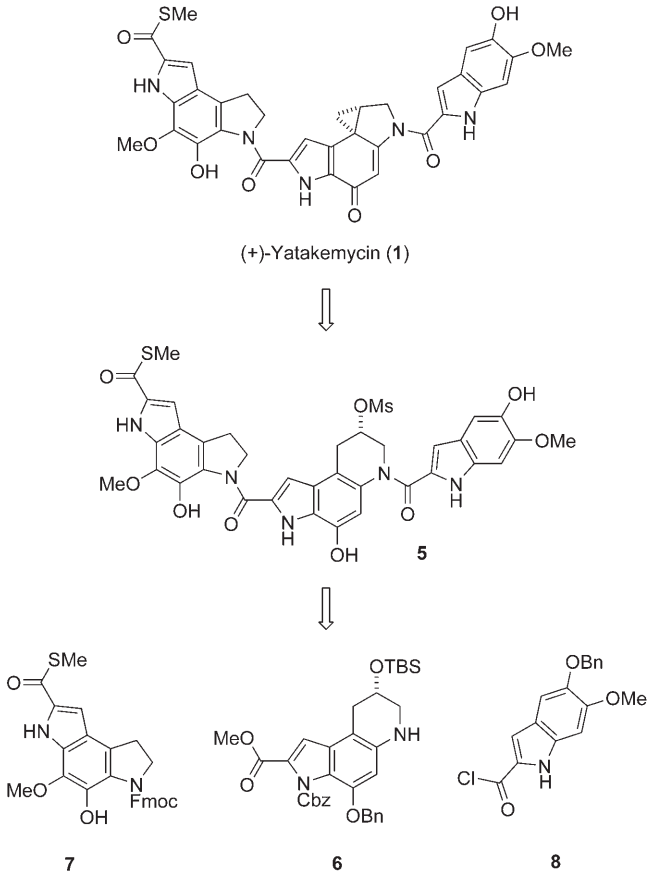
Results and Discussion

As outlined in the retrosynthetic analysis (Scheme 2), we planned to form the highly reactive spirocyclopropane by ring contraction of the hydroxytetrahydroquinoline[4b,6] **5** at the final stage of the synthesis. Disconnections at the two amide bonds would then lead to the three segments **6**–**8**.

The investigation started by exploring the synthetic route to produce the middle segment **6** (Scheme 3). The crucial construction of the chiral center was achieved by regioselective ring opening of (*S*)-epichlorohydrin (**10**) with a 2,6-dibromophenyllithium species, which was prepared by iodoselective lithiation of the 2,6-dibromoiodobenzene derivative **9**.[7] Thus, **9** was treated with *n*BuLi in toluene at −78 °C to generate a white slurry, to which were added **10** followed by $BF_3{\cdot}OEt_2$ to provide the desired chlorohydrin **11** exclusively in excellent yield.[8] We then converted **11** into the amination precursor **14** by a three-step sequence involving the introduction of an azide group, the Staudinger reaction,[9] and finally treatment of the resultant primary amine with NsCl in situ.[10]

With the nosyl amide **14** in hand, we then examined the key intramolecular aryl amination to construct tetrahydroquinoline **15** (Table 1). The reaction proceeded cleanly with 0.5 equivalents of CuI and 6.1 equivalents of CsOAc to provide the desired **15** in 89% yield with retention of the other bromo group (Table 1, entry 1). Decreasing the amount of CsOAc meant that a longer reaction time was required (Table 1, entry 2). In the case of 0.2 equivalents of CuI, the substrate was not consumed completely, even after 36 h (Table 1, entry 3). The reaction at elevated temperature (80 °C) provided a complex mixture (Table 1, entry 4).

Next, construction of the dehydroamino acid moiety at the remaining bromo substituent was investigated. The first



Scheme 2. Retrosynthetic analysis of (+)-yatakemycin (**1**). Bn = benzyl, Cbz = benzyloxycarbonyl, Fmoc = 9-fluorenylmethoxycarbonyl, Ms = methanesulfonyl, TBS = *tert*-butyldimethylsilyl.

Abstract in Japanese:

(+)-ヤタケマイシンの収束的な全合成を 20 工程、総収率 13% で達成した。シクロプロパン環の立体選択的な構築に必要となる不斉炭素の導入は、2,6-ジブロモリチオベンゼン誘導体の (*S*)-エピクロロヒドリンに対する位置選択的な開環反応により行った。また、(+)-ヤタケマイシンに含まれる 5 つのアリール　窒素結合はヨウ化銅と酢酸セシウムを組み合わせる分子内芳香族アミノ化反応により構築した。ベンジルエーテルの脱保護に関しては、ペンタメチルベンゼン存在下で反応を行うことで、官能基共存性の高い脱ベンジル化条件の開発に成功した。以上の手法を駆使することで、サブグラムスケールで (+)-ヤタケマイシンを合成することができた。

International Advisory Board Member

Tohru Fukuyama was born in 1948 and received his PhD in 1977 at Harvard Univ. with Prof. Kishi. After 17 years at Rice Univ., he returned to Japan in 1995 to assume his current position as Prof. of Pharmaceutical Sciences at the Univ. of Tokyo. His primary research interest is total synthesis of natural products. He is the recipient of the A. C. Cope Scholar Award (1993), Synthetic Organic Chemistry Award, Japan (2002), ISHC Senior Award in Heterocyclic Chemistry (2003), ACS Award for Creative Work in Synthetic Organic Chemistry (2004), and the PSJ Award from the Pharmaceutical Society of Japan (2006).

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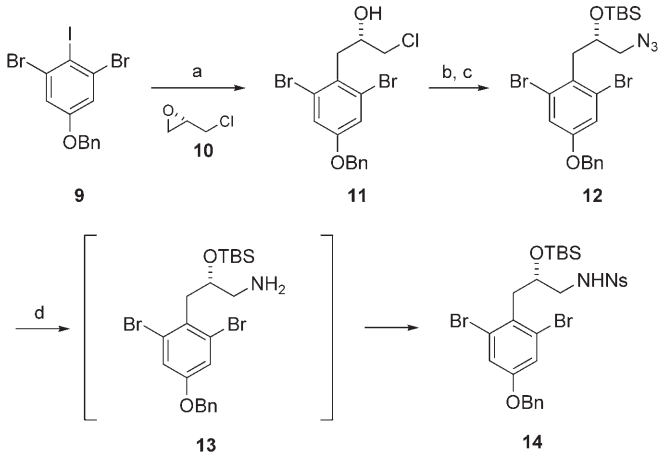
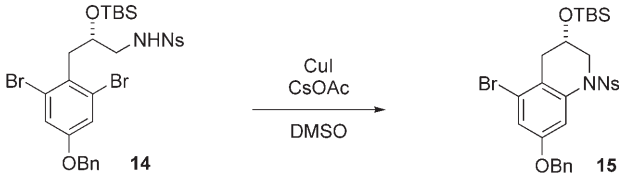


Scheme 3. Preparation of the amination precursor **14**. Reagents and conditions: a) *n*BuLi (1.0 equiv), toluene, −78 °C, 10 min; $BF_3{\cdot}OEt_2$, **10**, −78 °C, 5 min, 93 %; b) NaN_3, DMF, 90 °C, 9 h; c) TBSCl, imidazole, DMAP, DMF, 50 °C, 6 h, 99 % (2 steps); d) $P(nBu)_3$, THF, room temperature, 30 min; H_2O, room temperature, 2 h; NsCl, aqueous $NaHCO_3$, room temperature, 24 h, 89 %. DMAP = 4-dimethylaminopyridine, DMF = *N*,*N*-dimethylformamide, Ns = *o*-nitrobenzenesulfonyl.

Table 1. Optimization of intramolecular aryl amination.[a]

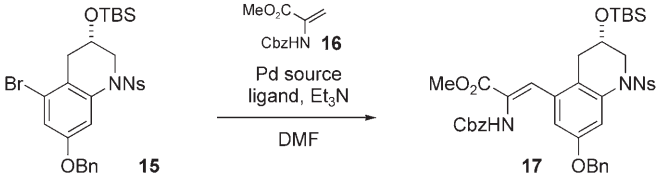


Entry	CuI [equiv]	CsOAc [equiv]	*T* [°C]	*t* [h]	Yield [%]
1	0.5	6.1	50	15	89
2	0.5	5.0	60	24	83
3	0.2	2.7	50	36	63
4	0.2	2.5	80	12	–[b]

[a] DMSO = dimethyl sulfoxide. [b] Complex mixture.

attempt at a Mizoroki–Heck reaction[11] of this hindered bromide **15** with dehydroalanine **16**[12] under ligand-free conditions[13] provided a trace amount of the desired product **17** (Table 2, entry 1). We found that addition of a ligand was effective. Thus, the yield of **17** improved to 38 % in the presence of $P(o\text{-tolyl})_3$ (Table 2, entry 2). After extensive optimization of various Pd catalysts and phosphine ligands, a combination of $[Pd_2(dba)_3]$ and bulky 2-di(*tert*-butyl)phosphanyl-1,1′-biphenyl in the presence of LiCl gave **17** in 89 % yield (Table 2, entry 3).

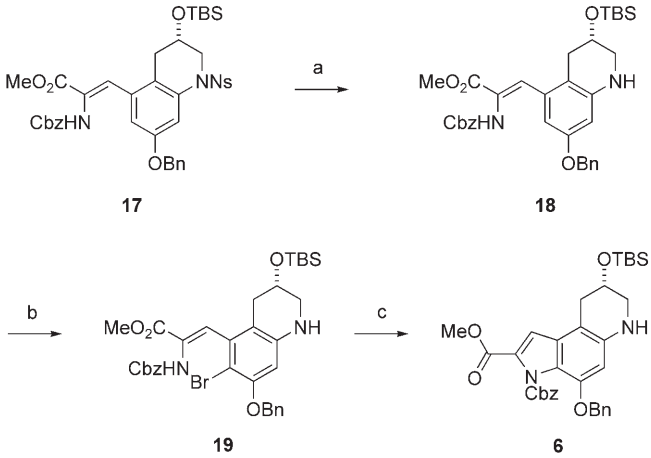
Table 2. Ligand effects in the Mizoroki–Heck reaction.[a]



Entry	Pd source ([mol %])	Ligand ([mol %])	Additive	Yield [%]
1	$Pd(OAc)_2$ (20)	none	none	trace
2	$Pd(OAc)_2$ (20)	$P(o\text{-tolyl})_3$ (40)	none	38
3	$[Pd_2(dba)_3]$ (5)	(biph)$P(t\text{Bu})_2$ (20)	LiCl	89

[a] biph = biphenyl, dba = dibenzylideneacetone.

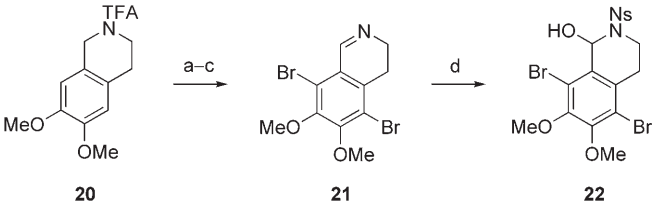
Synthesis of the middle segment **6** was completed by regioselective bromination and copper-mediated intramolecular aryl amination (Scheme 4). After removal of the nosyl group, a bromo substituent was regioselectively introduced at the *para* position of the nitrogen atom. The amination reaction at the highly sterically hindered position proceeded smoothly with stoichiometric amounts of CuI at ambient temperature to furnish the middle segment **6**.



Scheme 4. Synthesis of the middle segment **6**. Reagents and conditions: a) PhSH, Cs_2CO_3, MeCN, room temperature, 30 min, 99 %; b) NBS, CH_2Cl_2, 0 °C, 20 min, 90 %; c) CuI (1.0 equiv), CsOAc (2.5 equiv), DMSO, room temperature, 12 h, quant. NBS = *N*-bromosuccinimide.

We then turned our attention to the synthesis of the left segment **7**. Synthesis of **7** commenced with dibromination[14] of tetrahydroisoquinoline **20**,[15] which was readily obtained from commercially available homoveratrylamine by a two-step sequence (Scheme 5). After removal of the trifluoroacetyl group, oxidation to dihydroisoquinoline **21** and subsequent treatment with NsCl furnished hemiaminal **22**.

At this point, we considered that the nosyl amide of the primary amine, which would be generated from **22** under equilibrium, could undergo intramolecular amination to pro-



Scheme 5. Preparation of hemiaminal **22**. Reagents and conditions: a) Br_2, $FeCl_3$, CH_2Cl_2, 0 °C, 30 min, 88 %; b) K_2CO_3, MeOH, room temperature, 6 h; c) MnO_2, CH_2Cl_2, room temperature, 18 h, 90 % (2 steps); d) NsCl, THF, 0 °C, 5 min; room temperature, 1 h; aqueous $NaHCO_3$, room temperature, 30 min. TFA = trifluoroacetyl.

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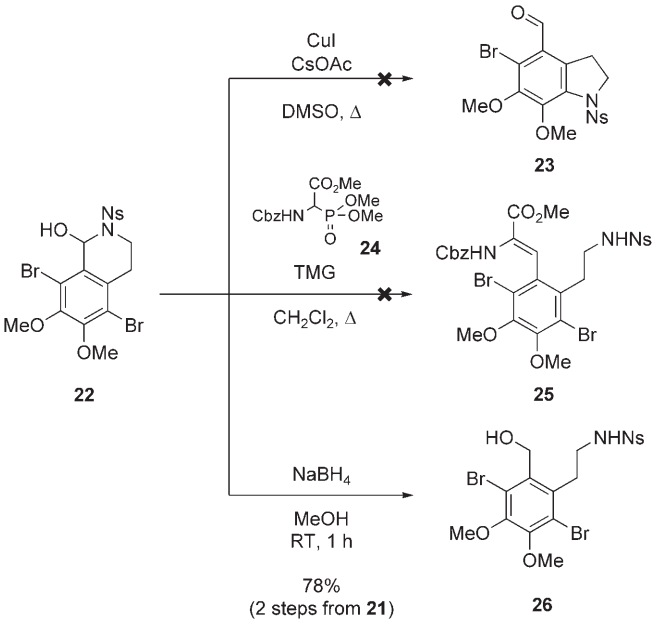
vide indoline **23** (Scheme 6). However, subjection of **22** to the standard amination conditions did not yield **23**. We then tried to open the cyclic hemiaminal under other conditions.

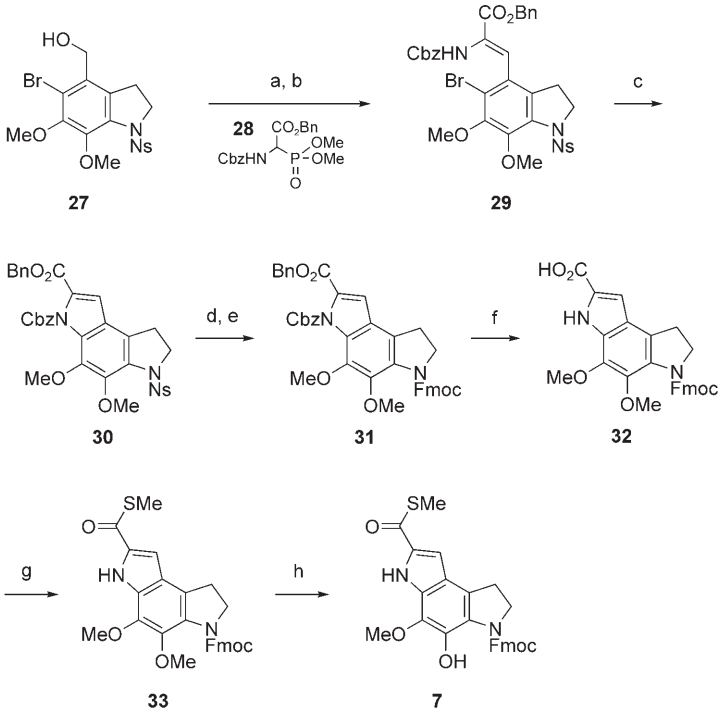


Scheme 6. Attempts to open hemiaminal **22**. TMG = 1,1,3,3-tetramethylguanidine.

Whereas Horner–Wadsworth–Emmons[16] reaction with phosphonate **24**[17] did not afford the desired dehydroamino acid derivative **25**, treatment with $NaBH_4$ in methanol effectively gave the reductively opened product, aminoalcohol **26**.

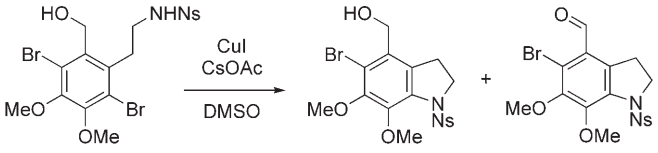
In the case of the substrate with an unprotected hydroxy group, amination under stoichiometric conditions provided the desired indoline **27** in moderate yield together with **23**, which is the oxidation product of alcohol **27**, in 7.8% yield (Table 3, entry 1). Optimization of the amination revealed that a lower catalytic loading of CuI was efficient to prevent oxidation (Table 3, entry 2). Finally, it was found that 10 mol% of CuI at 80 °C gave the desired **27** with retention of the other bromo group (Table 3, entries 3 and 4).

The second heterocyclic ring of the left segment was then formed in a straightforward manner. After conversion of **27** into the dehydroamino acid ester **29** by TPAP oxidation[18] and Horner–Wadsworth–Emmons reaction[16] with phosphonate **28**,[19] intramolecular amination was performed to provide dihydropyrroloindole **30** in good yield (Scheme 7). The



Scheme 7. Synthesis of the left segment **7**. Reagents and conditions: a) TPAP (2 mol%), NMO, MS4Å, CH_2Cl_2, room temperature, 1 h, 85% (2 steps); b) **28**, TMG, CH_2Cl_2, room temperature, 6 h, 84%; c) CuI (1.0 equiv), CsOAc (5.0 equiv), DMSO, room temperature, 12 h, 77%; d) PhSH, Cs_2CO_3, MeCN, room temperature, 3 h, 95%; e) FmocCl, $NaHCO_3$, THF/H_2O (3:1), room temperature, 10 min, 91%; f) Pd/C, H_2, THF/EtOH (1:1), room temperature, 3 h; g) MeSH, WSCD·HCl, DMAP, DMF, 0 °C, 3 h, 76% (2 steps); h) BCl_3, CH_2Cl_2, 0 °C, 20 min, 97%. MS4Å = 4-Å molecular sieves, NMO = *N*-methylmorpholine *N*-oxide, TPAP = tetra-*n*-propylammonium perruthenate, WSCD = *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide.

Table 3. Key intramolecular aryl amination.



Entry	CuI [mol%]	CsOAc [equiv]	*T* [°C]	*t* [h]	**27** [%]	**23** [%]
1	100	30	RT	13	66	7.8
2	50	10	50	14	85	trace
3	10	2.5	80	24	95[a]	5[a]
4	5	2.5	80	24	73	trace

[a] Yield determined by NMR spectroscopy.

remaining task for obtaining the left segment was regioselective demethylation and formation of the thiol ester. After the Ns group was replaced by Fmoc, the benzyl ester and Cbz group were removed under hydrogenation conditions, followed by a condensation reaction with the resultant carboxylic acid **32** to lead to thiol ester **33**. Finally, an Fmoc-directed, regioselective demethylation was performed with BCl_3[20] to furnish the left segment **7** in excellent yield.

The right segment **8** was prepared in a straightforward manner by using the aryl amination strategy (Scheme 8). The amination precursor **35**, a dehydroamino acid derivative, was prepared from commercially available isovanillin (**34**) by a three-step sequence. The copper-mediated aryl

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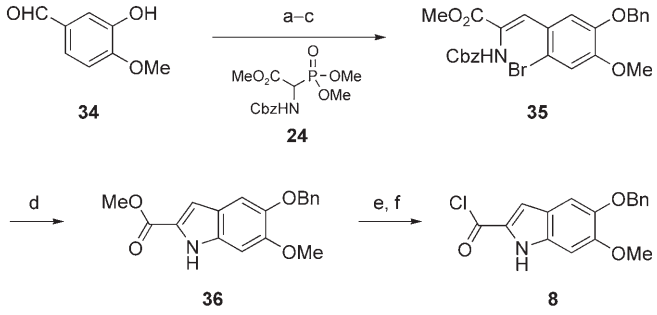


Scheme 8. Synthesis of the right segment **8**. Reagents and conditions: a) BnBr, K_2CO_3, MeCN, reflux, 1 h; b) Br_2, CH_2Cl_2/MeOH (1:1), 0 °C to room temperature, 2 h, 86 % (2 steps); c) **24**, TMG, CH_2Cl_2, room temperature, 2 h, 96 %; d) CuI (5 mol %), CsOAc (2.5 equiv), DMSO, 90 °C, 24 h, 80 %; e) LiOH, dioxane/H_2O (2:1), 50 °C, 2 h, quant.; f) $SOCl_2$, CH_2Cl_2, reflux, 30 min.

amination proceeded smoothly with 5 mol % of CuI to give the corresponding indole **36**[1e] in good yield. Hydrolysis of the methyl ester followed by conversion into the acid chloride provided the right segment **8**.

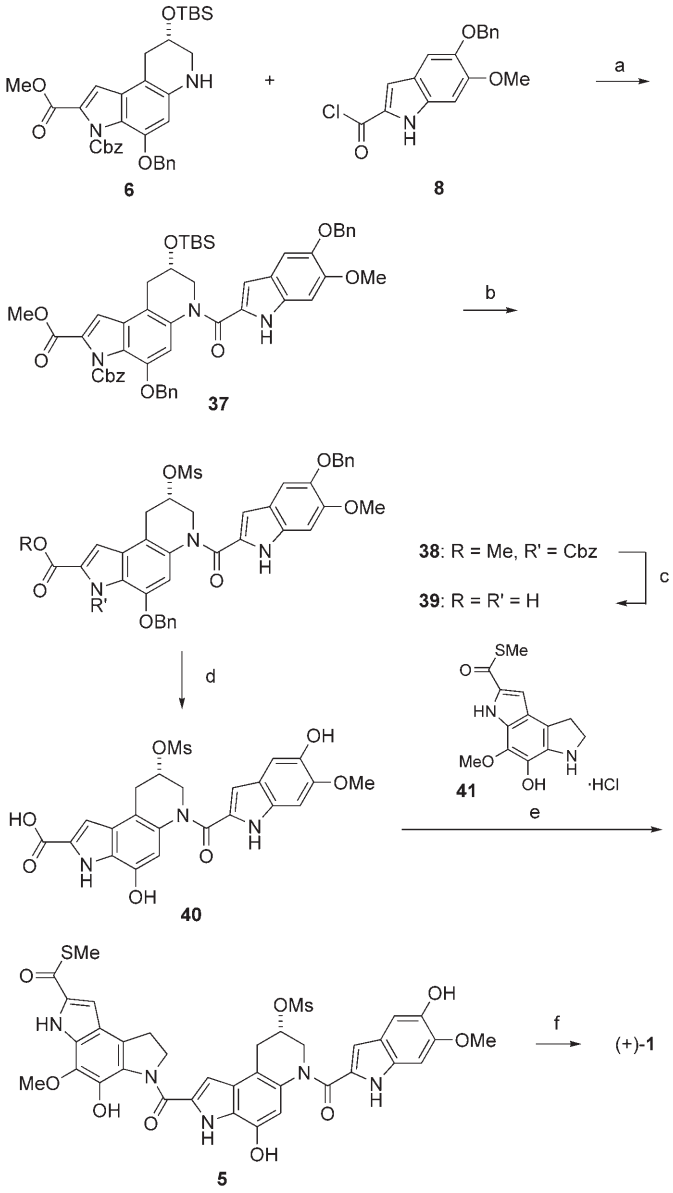
Having synthesized the requisite three segments **6**–**8**, we then moved to the crucial assembly of these compounds. As the left segment **7** contains the base-labile thiol ester functionality, we planned to couple the middle segment **6** and right segment **8** first, then introduce the left segment **7** to the resultant middle–right segment.

The first-generation protocol based on this idea is depicted in Scheme 9. After coupling of the middle segment **6** with the right segment **8**, TBS ether **37** was converted into mesylate **38**. Subsequent hydrolysis under basic conditions provided carboxylic acid **39** with concomitant removal of the Cbz group. After removal of the two benzyl groups by hydrogenolysis, the crucial condensation between **40** and the left segment **41**[1e] was executed according to the conditions of Boger and co-workers to give the desired compound **5** in low to moderate yield. Finally, spirocyclopropanation was effected by treatment with $NaHCO_3$ in aqueous DMF[1e] to furnish (+)-yatakemycin (**1**), which was identical in all respects to the natural product.

Although the first-generation approach allowed us to synthesize **1**, there was a considerable drawback with regard to yield and reproducibility in the coupling reaction of the left segment **7**. This is possibly due to the presence of unprotected phenolic hydroxyl groups. Thus, we examined next the coupling reaction with the protected substrate **39** (Scheme 10).

The Fmoc group was removed by treatment with TBAF.[21] After disappearance of the left segment **7** as determined by TLC analysis, carboxylic acid **39** and the condensation reagents were added to the reaction mixture. Fortunately, the desired coupling reaction between indoline **42** and carboxylic acid **39** proceeded smoothly to afford the desired product **43** in excellent yield.

The remaining task was the chemoselective removal of the two phenolic benzyl ethers in **43** in the presence of thiolester and electron-rich aromatic rings (Table 4). When **43**



Scheme 9. First-generation total synthesis of (+)-yatakemycin (**1**). Reagents and conditions: a) pyridine, CH_2Cl_2, 0 °C, 5 min, quant.; b) TBAF, THF, room temperature, 30 min; evaporation; MsCl, pyridine, CH_2Cl_2, room temperature, 4 h, 97 %; c) LiOH, THF/H_2O (3:1), room temperature, 18 h, 92 %. d) H_2 (1 atm), cat. Pd/C, acetone, room temperature, 10 h, 94 %; e) **41**, WSCD·HCl, DMF, room temperature, 15 min, up to 40 % (irreproducible); f) $NaHCO_3$, DMF/H_2O (2:1), room temperature, 2 h, 80 %. TBAF = tetra-*n*-butylammonium fluoride.

was subjected to conventional hydrogenolysis conditions, the reaction gave a complex mixture (Table 4, entry 1). Deprotection under acidic conditions with TFA also resulted in a complex mixture even in the presence of PhSMe or pentamethylbenzene as a cation scavenger (Table 4, entries 2 and 3).[22] Lewis acids in general, such as BF_3·OEt_2 with EtSH,[23] did not provide the debenzylated product **5** (Table 4, entry 4). Among the Lewis acids we examined, BCl_3 was the only one to provide the desired product **5**; however, we encountered a serious problem with regard to reproducibility

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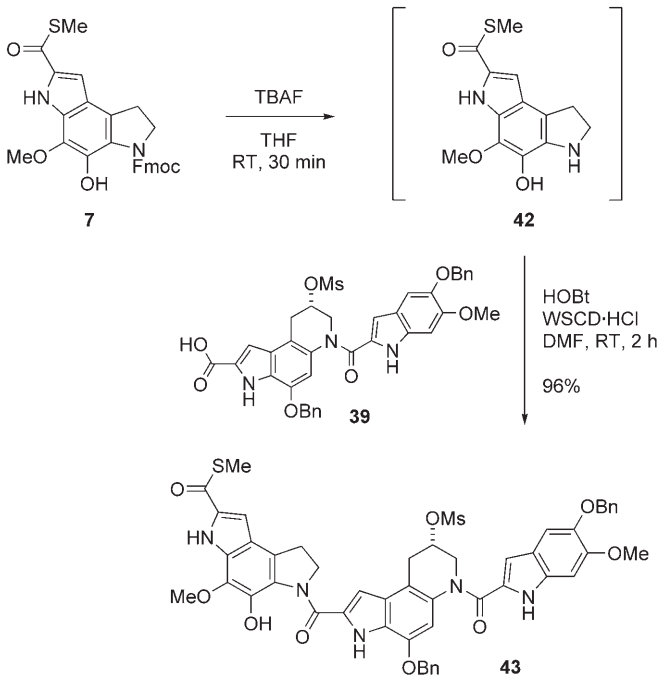
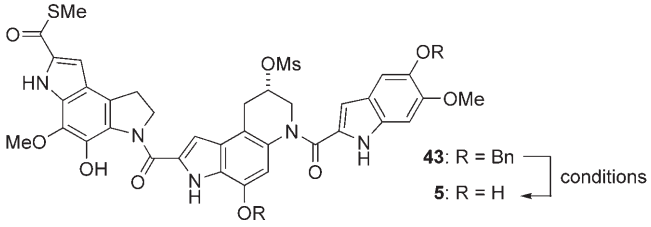


Scheme 10. Successful one-pot condensation with the left segment **7**. HOBt = 1-hydroxybenzotriazole.

Table 4. Chemoselective removal of benzyl groups.



Entry	Conditions	Yield [%]
1	H_2, Pd/C, EtOAc, RT	–[a]
2	TFA, PhSMe, RT	–[a]
3	TFA, pentamethylbenzene, RT	–[a]
4	$BF_3{\cdot}OEt_2$, EtSH, CH_2Cl_2, RT	–[a]
5	BCl_3, CH_2Cl_2, −78 °C, 15 min	19–72
6	BCl_3, PhSMe, CH_2Cl_2, −78 °C→RT	–[a]
7	$BCl_3{\cdot}SMe_2$, CH_2Cl_2, −78 °C→RT	–[a]
8	BCl_3, pentamethylbenzene, CH_2Cl_2, −78 °C, 15 min	83

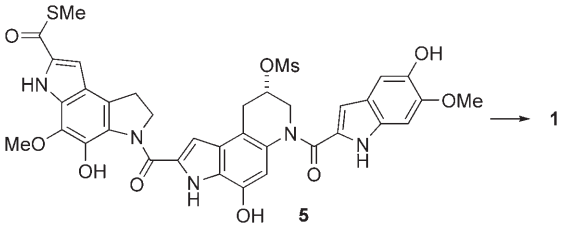
[a] Complex mixture. TFA = trifluoroacetic acid.

(Table 4, entry 5). Under modified reaction conditions with a combination of BCl_3 with PhSMe as a cation scavenger or the milder $BCl_3{\cdot}SMe_2$, the reaction did not take place at −78 °C, and the starting benzyl ether **43** decomposed when the temperature was raised (Table 4, entries 6 and 7). Finally, a combination of BCl_3 with pentamethylbenzene was found to be optimal, with high reproducibility and providing the desired compound **5** in good yield (Table 4, entry 8).

These results indicate that pentamethylbenzene acts as a good cation scavenger that does not decrease the Lewis acidity of BCl_3. On the other hand, conventional cation scavengers such as PhSMe or SMe_2 were not effective as these compounds decrease the Lewis acidity of BCl_3 too much by forming complexes with BCl_3. The other advantage of using pentamethylbenzene is that the unreacted pentamethylbenzene and benzylpentamethylbenzene can be easily removed by column chromatography.

Having established mild conditions for the removal of the benzyl groups, we investigated the unoptimized spirocyclization under various reaction conditions (Table 5). Reaction

Table 5. Optimization of transannular spirocyclopropanation.



Entry	Base ([equiv])	Solvent	t	Yield [%]
1	Cs_2CO_3 (6.0)	MeCN	10 min	–[a]
2	Na_2HPO_4 (6.0)	MeCN/THF/H_2O (1:1:1)	10 h	63
3	$NaHCO_3$ (6.0)	MeCN/THF/H_2O (1:1:1)	10 h	47
4	$NaHCO_3$ (10)	THF/H_2O (3:1)	5 h	62
5	$NaHCO_3$ (10)	DMF/H_2O (2:1)	12 h	79
6	$NaHCO_3$ (30)	DMF/H_2O (2:1)	2 h	94

[a] Complex mixture.

with Cs_2CO_3 in acetonitrile[7] was not affected and resulted in a complex mixture (Table 5, entry 1). The milder conditions with NaH_2PO_4 in MeCN/THF/H_2O provided the desired **1** in modest yield; however, the reaction was accompanied by the generation of unidentified by-products (Table 5, entry 2). The reaction with $NaHCO_3$ in MeCN/THF/H_2O proceeded more cleanly, although the reaction rate was rather slow, and the starting material remained even after 10 h (Table 5, entry 3). After several optimizations, DMF/H_2O was found to be the best solvent system[1e] (Table 5, entries 3–5). Furthermore, we found that a large excess of base shortened the reaction time and improved the yield substantially to over 90 % (Table 5, entry 6).

Conclusions

We have accomplished a highly efficient total synthesis of (+)-yatakemycin (**1**), which features the coupling of (*S*)-epichlorohydrin (**10**) with 2,6-dibromophenyllithium species, a chemoselective debenzylation reaction, and the copper-mediated construction of all five aryl–nitrogen bonds in **1**. The efficiency of the synthetic strategy containing these new methodologies has been proven by conducting a subgram-scale synthesis of **1** in 13 % overall yield over 20 steps (longest linear steps). The synthetic route established in this study should be generally applicable to the synthesis of this class of compounds.

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Experimental Section

General Remarks

All reactions were carried out in oven-dried glassware under a slight positive pressure of argon unless otherwise noted. ^{1}H (400 or 500 MHz) and ^{13}C NMR (100 or 125 MHz) spectra were recorded on a JEOL ECX400 or ECX500 spectrometer. ^{1}H NMR chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane as the internal standard, and coupling constants are in hertz (Hz). The following abbreviations are used for spin multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. ^{13}C NMR chemical shifts are reported in ppm relative to the center of the triplet at 77.0 ppm for deuteriochloroform. IR spectra were recorded on a JASCO FT/IR-410 FTIR spectrometer and are reported in wavenumbers (cm^{-1}). Where denoted "neat", the sample was loaded as a thin film on a zinc/selenium plate. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter with a sodium lamp. Melting points were measured on a YANACO MP-500V instrument. High-resolution mass spectra were obtained on a JEOL JMS-700 spectrometer with the positive FAB ionization method by using a PEG 1000, 600, 400, or 200 matrix from Kanto Chemical Co., Ltd. as the internal standard. Analytical TLC was performed on Merck precoated analytical plates, 0.25 mm thick, of silica gel 60 F_{254}. Preparative TLC was performed on Merck analytical plates (0.25 or 0.50 mm thick) precoated with silica gel 60 F_{254}. Flash chromatography was performed on Kanto Chemical silica gel 60 (normal or neutral, 40–100 mesh).

Materials

Copper iodide (99.5% purity) and cesium acetate were purchased from Wako Pure Chemical Industries, Ltd. and were used as supplied. Cesium acetate was weighed under argon atmosphere to prevent absorption of moisture. Dry DMSO and dichloromethane were purchased from Aldrich Chemical Co. and Wako Pure Chemical Industries, Ltd., respectively. Other dry solvents were supplied from Kanto Chemical Co., Inc. (unless otherwise noted). Substrates were prepared according to the procedures outlined below. Spectroscopic data for all new compounds are also listed below.

Syntheses

11: A flame-dried 1-L three-necked round-bottomed flask equipped with a digital thermometer, a dropping funnel, and a mechanical stirrer was charged with 4-benzyloxy-2,6-dibromoiodobenzene (**9**; 23.4 g, 50.0 mmol) and dry toluene (500 mL). The colorless solution was cooled to −78 °C. *n*BuLi (1.51 M, 33.1 mL, 50.0 mmol) was added dropwise to the solution over 40 min at a rate that kept the inner temperature under −75 °C. (*S*)-Epichlorohydrin (**10**; 3.91 mL, 50.0 mmol) was added dropwise to the resulting viscous suspension over 5 min. After $BF_3{\cdot}OEt_2$ (6.34 mL, 50.0 mmol) was added rapidly, the reaction mixture was stirred for 5 min, after which TLC (hexane/dichloromethane = 3:2) indicated complete consumption of **9**. The reaction was quenched with saturated aqueous sodium bicarbonate at −78 °C, and the mixture was warmed to room temperature. The resulting mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered through a thin pad of silica gel. The resulting filtrate was concentrated under reduced pressure to afford analytically pure (−)-(2*S*)-1-(4-benzyloxy-2,6-dibromophenyl)-3-chloropropan-2-ol (**11**; 20.2 g, 46.5 mmol, 93%). The residue was recrystallized from hexane/dichloromethane to give optically pure **11** as a fine colorless needles. The enantiomeric excess of **11** was determined by HPLC (DAICEL-CHIRALCEL-OJ, hexane/*i*PrOH = 85:15, flow rate = 1.0 mL min^{-1}, t_S = 20.9 min, t_R = 24.9 min). R_f = 0.49 (CH_2Cl_2); m.p.: 90.1–90.4 °C (hexane/dichloromethane); $[\alpha]_D^{27} = -18.1$ (c = 1.02, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3403, 2977, 1700, 1603, 1507, 1392, 1366, 1253, 1169, 750, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.32 (m, 5H), 7.21 (s, 2H), 5.02 (s, 2H), 4.27–4.18 (m, 1H), 3.73–3.64 (m, 2H), 3.35 (dd, J = 12.8, 7.2 Hz, 1H), 3.15 (dd, J = 12.8, 5.6 Hz, 1H), 2.27 ppm (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 135.7, 128.7, 128.5, 128.4, 127.5, 125.7, 119.2, 70.9, 70.5, 50.1, 40.1 ppm; elemental analysis: calcd (%) for $C_{16}H_{15}Br_2ClO_2$: C 44.22, H 3.48; found: C 44.06, H 3.55.

(−)-(2*S*)-3-Azido-1-(4-benzyloxy-2,6-dibromophenyl)propan-2-ol: A 500-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **11** (11.9 g, 27.4 mmol) and dry DMF (27.4 mL). NaN_3 (5.34 g, 82.2 mmol) was added to the solution. The resulting mixture was heated to 90 °C for 9 h, after which TLC (dichloromethane) indicated complete consumption of **11**. After the flask was cooled to room temperature, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the analytically pure azide (12.8 g) as colorless plates, which was used in the next reaction without further purification. R_f = 0.36 (hexane/ethyl acetate = 3:1); m.p.: 99.2–100.4 °C (hexane/ethyl acetate); $[\alpha]_D^{25} = -9.1$ (c = 1.18, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3393, 2932, 2103, 1594, 1542, 1450, 1382, 1253, 1024, 923, 839, 738, 695 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.32 (m, 5H), 7.20 (s, 2H), 5.01 (s, 2H), 4.22–4.12 (m, 1H), 3.47 (dd, J = 12.4, 6.8 Hz, 1H), 3.41 (dd, J = 12.4, 4.0 Hz, 1H), 3.24 (dd, J = 14.0, 8.0 Hz, 1H), 3.11 (dd, J = 14.0, 6.0 Hz, 1H), 2.07 ppm (d, J = 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.9, 135.7, 128.7, 128.6, 128.4, 127.5, 125.7, 119.3, 70.6, 70.5, 56.4, 40.2 ppm; elemental analysis: calcd (%) for $C_{16}H_{15}Br_2N_3O_2$: C 43.56, H 3.43, N 9.53; found: C 43.26, H 3.48, N 9.34.

12: A 500-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with the above crude azide (12.8 g), imidazole (2.80 g, 41.1 mmol), DMAP (167 mg, 1.37 mmol), and dry DMF (27.4 mL). TBSCl (4.54 g, 30.1 mmol) was added to the solution. The resulting reaction mixture was heated to 50 °C for 6 h, after which TLC (hexane/ethyl acetate = 3:1) indicated complete consumption of the starting alcohol. The reaction mixture was diluted with ethyl acetate. The organic layer was extracted with water, washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (hexane/ethyl acetate = 9:1) to afford pure (+)-((2*S*)-3-azido-1-(4-benzyloxy-2,6-dibromophenyl)propan-2-yloxy)(*tert*-butyl)dimethylsilane (**12**; 15.0 g, 27.0 mmol, 99%) as a viscous colorless liquid. R_f = 0.58 (hexane/ethyl acetate = 3:1); $[\alpha]_D^{27} = +5.1$ (c = 1.81, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 2952, 2928, 2856, 2103, 1594, 1543, 1454, 1378, 1294, 1255, 1105, 1025, 962, 837, 808, 777, 737, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.33 (m, 5H), 7.18 (s, 2H), 5.02 (s, 2H), 4.29–4.22 (m, 1H), 3.33–3.23 (m, 3H), 3.07 (dd, J = 14.0, 5.6 Hz, 1H), 0.86 (s, 9H), 0.03 ppm (s, 3H), −0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 135.7, 129.2, 128.7, 128.3, 127.5, 126.0, 119.2, 70.6, 70.4, 56.6, 40.8, 25.8, 17.8, 14.1, −4.9 ppm; elemental analysis: calcd (%) for $C_{22}H_{29}Br_2N_3O_6Si$: C 47.58, H 5.26, N 7.57; found: C 47.71, H 5.29, N 7.27.

14: A 500-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **12** (14.3 g, 25.7 mmol) and dry THF (64 mL). Tri-*n*-butylphosphine (6.98 mL, 28.3 mmol) was added to the clear solution at room temperature. Nitrogen gas started to evolve within 5 min. The reaction mixture was stirred at room temperature for 30 min, after which TLC (hexane/ethyl acetate = 3:1) indicated complete consumption of **12**. Water (25 mL) was added to the iminophosphorane generated in situ, and the resulting solution was stirred for 2 h at room temperature. Saturated aqueous sodium bicarbonate (25 mL) and nosyl chloride (6.83 g, 30.8 mmol) were added to the pale-yellow solution. The mixture was stirred for 18 h, after which another portion of nosyl chloride (1.71 g, 7.72 mmol) was added, and the resulting yellow suspension was stirred for another 24 h at room temperature. The reaction mixture was poured into hydrochloric acid (1 M) and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (hexane/ethyl acetate = 85:15–75:25, gradient) to afford (+)-((2*S*)-3-(*o*-nitrobenzenesulfonylamino)-1-(4-benzyloxy-2,6-dibromophenyl)propan-2-yloxy)(*tert*-butyl)dimethylsilane (**14**; 16.4 g, 23.0 mmol, 89%) as a colorless amorphous solid. R_f = 0.34 (hexane/ethyl acetate = 3:1); $[\alpha]_D^{28} = +2.3$ (c = 1.27, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3353, 2929, 2856, 1594, 1542, 1452, 1406, 1362, 1256, 1172, 1104, 1040, 909, 837, 779, 737, 697, 668 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.03 (m, 1H), 7.89–7.83 (m, 1H), 7.76–7.68

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(m, 2H), 7.43–7.32 (m, 5H), 7.17 (s, 2H), 5.69 (t, $J=5.2$ Hz, 1H), 5.02 (s, 2H), 4.33–4.26 (m, 1H), 3.28 (dd, $J=13.8$, 8.2 Hz, 1H), 3.24 (dd, $J=13.4$, 5.2 Hz, 1H), 3.15–3.07 (m, 1H), 3.05 (dd, $J=13.6$, 5.8 Hz, 1H), 0.79 (s, 9H), −0.08 (s, 3H), −0.22 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=$ 157.7, 148.1, 135.7, 133.5, 133.3, 132.7, 130.9, 128.8, 128.7, 128.3, 127.5, 126.0, 125.3, 119.2, 70.4, 69.5, 49.0, 40.5, 25.6, 17.7, −4.9, −5.0 ppm; elemental analysis: calcd (%) for $C_{28}H_{34}Br_2N_2O_6SSi$: C 47.07, H 4.80, N 3.92; found: C 47.05, H 4.75, N 3.85.

15: A flame-dried 100-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **14** (3.13 g, 4.39 mmol), copper iodide (417.1 mg, 2.19 mmol), cesium acetate (4.21 g, 21.9 mmol), and dry DMSO (14.6 mL) under argon atmosphere. The resulting pale-green solution was stirred at 60 °C for 24 h, after which TLC (hexane/dichloromethane = 3:2) indicated complete consumption of **14**. After the flask was cooled to room temperature, the reaction mixture was poured into 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (dichloromethane/hexane = 1:1–3:1, gradient) to afford pure (−)-(3*S*)-7-benzyloxy-5-bromo-1-(*o*-nitrobenzenesulfonyl)-1,2,3,4-tetrahydro-3-(*tert*-butyldimethylsilyloxy)quinoline (**15**; 2.32 g, 3.66 mmol, 83%) as a white solid, which was recrystallized from hexane/dichloromethane to afford a fine colorless needles. $R_f=0.42$ (hexane/ethyl acetate = 3:1); m.p.: 106.3–106.9 °C (hexane/dichloromethane); $[\alpha]_D^{27}=-26.6$ ($c=1.17$, $CHCl_3$); IR (neat): $\tilde{\nu}=2929$, 2856, 1605, 1546, 1471, 1367, 1254, 1168, 1111, 1023, 839, 779, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.90$ (d, $J=8.4$ Hz, 1H), 7.74–7.68 (m, 2H), 7.64–7.59 (m, 1H), 7.40–7.30 (m, 5H), 7.07 (d, $J=2.4$ Hz, 1H), 6.95 (d, $J=$ 2.4 Hz, 1H), 4.94 (s, 2H), 4.17–4.09 (m, 1H), 4.02 (dd, $J=13.2$, 4.0 Hz, 1H), 3.41 (dd, $J=14.0$, 8.4 Hz, 1H), 2.91 (dd, $J=17.6$, 6.4 Hz, 1H), 2.59 (dd, $J=17.6$, 7.6 Hz, 1H), 0.88 (s, 9H), 0.08 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=157.0$, 147.8, 137.7, 136.1, 134.0, 133.8, 132.1, 130.4, 128.6, 128.1, 127.5, 125.3, 124.6, 120.8, 116.8, 108.7, 70.2, 65.0, 52.0, 37.4, 25.7, 18.0, −4.81, −4.83 ppm; elemental analysis: calcd (%) for $C_{28}H_{33}BrN_2O_6SSi$: C 53.08, H 5.25, N 4.42; found: C 53.01, H 5.26, N 4.44.

17: A flame-dried 80-mL Schlenk tube equipped with a magnetic stirrer bar was charged with **15** (1.92 g, 3.02 mmol), **16** (1.42 g, 6.04 mmol), [Pd_2(dba)$_3$] (138.3 mg, 0.151 mmol), 2-di(*tert*-butyl)phosphanyl-1,1′-biphenyl (180.2 mg, 0.604 mmol), lithium chloride (128.0 mg, 3.02 mmol), triethylamine (1.69 mL, 12.1 mmol), and dry DMF (7.6 mL) under argon atmosphere. The reaction mixture was degassed by three freeze–pump–thaw cycles and heated to 90 °C for 1 h, after which TLC (hexane/ethyl acetate = 3:1) indicated complete consumption of **15**. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (hexane/ethyl acetate = 3:1–1:1, gradient) to afford pure (−)-(*Z*)-3-[(3*S*)-7-benzyloxy-1-(*o*-nitrobenzenesulfonyl)-1,2,3,4-tetrahydro-3-(*tert*-butyldimethylsilyloxy)-quinolin-5-yl]benzyloxycarbonylaminoacrylic acid methyl ester (**17**; 2.12 g, 2.69 mmol, 89%) as an off-white amorphous solid. $R_f=0.53$ (hexane/ethyl acetate = 1:1); $[\alpha]_D^{29}=-38.7$ ($c=0.756$, $CHCl_3$); IR (neat): $\tilde{\nu}=3403$, 2977, 1700, 1603, 1507, 1392, 1366, 1253, 1169, 750, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.82$ (d, $J=8.0$ Hz, 1H), 7.69–7.55 (m, 3H), 7.42–7.21 (m, 10H), 7.10 (s, 1H), 6.99 (d, $J=$ 2.2 Hz, 1H), 6.85 (d, $J=2.2$ Hz, 1H), 6.30 (br s, 1H), 5.03 (dd, $J=18.4$, 12.2 Hz, 2H), 4.88 (s, 2H), 4.13–4.03 (m, 1H), 3.83 (s, 3H), 3.35 (dd, $J=$ 11.8, 7.4 Hz, 1H), 2.70 (dd, $J=16.4$, 5.6 Hz, 1H), 2.44 (dd, $J=16.4$, 6.8 Hz, 1H), 0.86 (s, 9H), 0.06 (s, 3H), 0.04 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=165.0$, 156.7, 153.2, 147.9, 137.2, 136.4, 135.7, 134.6, 133.8, 133.6, 132.0, 130.4, 128.5, 128.5, 128.3, 128.1, 128.0, 127.5, 126.9, 126.4, 124.4, 120.6, 112.2, 110.3, 70.1, 67.4, 65.1, 52.7, 52.0, 34.1, 31.5, 25.7, 17.9, −4.80, −4.84 ppm; elemental analysis: calcd (%) for $C_{40}H_{45}N_3O_{10}SSi$: C 60.97, H 5.76, N 5.33; found: C 60.99, H 5.68, N 5.31.

18: A 100-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **17** (2.08 g, 2.64 mmol), cesium carbonate (1.29 g, 3.96 mmol), and dry acetonitrile (13.2 mL). Thiophenol (0.339 mL, 3.17 mmol) was added to the stirred suspension. The reaction mixture was stirred for 30 min at room temperature, after which TLC (hexane/ethyl acetate = 3:1) indicated complete consumption of **17**. Cesium carbonate was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (neutral silica gel, hexane/ethyl acetate = 3:1–1:1, gradient) to afford (+)-(*Z*)-3-[(3*S*)-7-benzyloxy-1,2,3,4-tetrahydro-3-(*tert*-butyldimethylsilyloxy)quinolin-5-yl]benzyloxycarbonylaminoacrylic acid methyl ester (**18**; 1.57 g, 2.60 mmol, 99%) as a yellow amorphous solid. $R_f=0.60$ (hexane/ethyl acetate = 1:1); $[\alpha]_D^{29}=+19.0$ ($c=1.68$, $CHCl_3$); IR (neat): $\tilde{\nu}=3404$, 2953, 2856, 1724, 1602, 1497, 1259, 1219, 1174, 1114, 1060, 868, 837, 776, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.36$–7.24 (m, 10H), 7.12 (s, 1H), 6.41 (d, $J=2.6$ Hz, 1H), 6.27 (br s, 1H), 6.11 (d, $J=2.82$ Hz, 1H), 5.09 (s, 2H), 4.88 (s, 2H), 4.13–4.02 (m, 1H), 3.82 (s, 3H), 3.30–3.23 (m, 1H), 3.01 (t, $J=12.0$ Hz, 1H), 2.82–2.74 (m, 1H), 2.50 (dd, $J=15.6$, 9.2 Hz, 1H), 0.89 (s, 9H), 0.09 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=165.3$, 157.5, 153.7, 145.2, 136.8, 135.7, 133.7, 128.3, 128.3, 128.0, 127.9, 127.7, 127.5, 127.3, 126.2, 112.0, 103.6, 100.9, 69.6, 67.2, 65.3, 52.4, 48.2, 34.0, 25.7, 17.9, −4.7, −4.8 ppm; elemental analysis: calcd (%) for $C_{34}H_{42}N_2O_6Si$: C 67.75, H 7.02, N 4.65; found: C 67.65, H 7.05, N 4.55.

19: A 500-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **18** (1.57 g, 2.60 mmol) and dry dichloromethane (52.0 mL). The resulting solution was cooled to 0 °C. NBS (462.8 mg, 2.60 mmol) was added portionwise to the solution over 15 min. The reaction mixture was stirred at 0 °C for 5 min, after which TLC (dichloromethane) indicated complete consumption of **18**. The reaction mixture was diluted with ethyl acetate, washed with aqueous sodium thiosulfite and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (neutral silica gel, dichloromethane) to afford (+)-(*Z*)-3-[(3*S*)-7-benzyloxy-6-bromo-1,2,3,4-tetrahydro-3-(*tert*-butyldimethylsilyloxy)quinolin-5-yl]benzyloxycarbonylaminoacrylic acid methyl ester (**19**; 1.59 g, 2.34 mmol, 90%) as a yellow amorphous solid. $R_f=0.45$ (dichloromethane); $[\alpha]_D^{24}=+26.4$ ($c=0.590$, $CHCl_3$); IR (neat): $\tilde{\nu}=3405$, 2952, 2856, 1727, 1579, 1453, 1260, 1219, 1118, 1061, 838, 779, 739, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.45$ (d, $J=7.2$ Hz, 2H), 7.38 (t, $J=7.8$ Hz, 2H), 7.34–7.27 (m, 6H), 6.94 (s, 1H), 6.16 (br s, 1H), 6.09 (s, 1H), 5.08–5.04 (s, 4H, overlapped), 4.05–3.98 (m, 1H), 3.82 (s, 3H), 3.27–3.18 (m, 1H), 3.04–2.94 (m, 1H), 2.75–2.60 (m, 1H), 2.43 (dd, $J=$ 15.6, 8.4 Hz, 1H), 0.86 (s, 9H), 0.06 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=164.5$, 153.7, 153.6, 153.2, 144.0, 136.4, 135.6, 134.6, 128.6, 128.4, 128.3, 128.1, 128.0, 127.7, 126.7, 111.6, 99.6, 99.4, 70.5, 67.2, 64.8, 52.5, 48.1, 34.5, 25.7, 17.9, −4.7, −4.9 ppm; elemental analysis: calcd (%) for $C_{34}H_{42}BrN_2O_6Si$: C 59.90, H 6.06, N 4.11; found: C 60.03, H 6.01, N 4.16.

6: A flame-dried 100-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **19** (1.36 g, 1.99 mmol), copper iodide (378.2 mg, 1.99 mmol), and cesium acetate (955.0 mg, 4.98 mmol). The flask was evacuated and then backfilled with argon. Dry DMSO (20 mL) was added to the mixture. The resulting pale-green solution was stirred at room temperature under argon atmosphere for 12 h, after which TLC (hexane/ethyl acetate = 1:1) indicated complete consumption of **19**. The reaction mixture was poured into 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (neutral silica gel, dichloromethane) to afford (+)-(*S*)-3-benzyl-2-methyl-4-(benzyloxy)-6,7,8,9-tetrahydro-8-(*tert*-butyldimethylsilyloxy)-pyrrolo[3,2-*f*]quinoline-2,3-dicarboxylate (**6**; 1.19 g, quant.) as a light-yellow amorphous solid. $R_f=0.70$ (hexane/ethyl acetate = 1:1); $[\alpha]_D^{22}=$ +40.3 ($c=0.890$, $CHCl_3$); IR (neat): $\tilde{\nu}=3407$, 2953, 2852, 1768, 1715, 1598, 1549, 1498, 1438, 1390, 1231, 1167, 1099, 837, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.46$–7.18 (m, 10H), 7.09 (s, 1H), 6.19 (s, 1H), 5.06 (s, 2H), 5.02 (s, 2H), 4.24–4.14 (m, 1H), 3.82 (s, 3H), 3.34–3.26 (m, 1H), 3.08 (dd, $J=10.0$, 10.0 Hz, 1H), 3.03 (dd, $J=15.8$, 5.2 Hz, 1H), 2.75 (dd, $J=15.8$, 8.2 Hz, 1H), 0.89 (s, 9H), 0.12 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=161.2$, 152.9, 144.7, 138.7, 136.5, 134.5, 128.6,

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128.5, 128.3, 128.1, 127.8, 127.3, 122.6, 109.2, 103.3, 99.3, 70.7, 70.2, 65.7, 52.0, 49.4, 33.3, 25.9, 25.8, 18.1, −4.59, −4.67 ppm; HRMS (FAB): *m/z* calcd for $C_{34}H_{40}N_2O_6Si$: 600.2656 $[M]^+$; found: 600.2655.

1,2,3,4-Tetrahydro-6,7-dimethoxyisoquinoline: A 1-L round-bottomed flask equipped with a magnetic stirrer bar was charged with homoveratrylamine (50.9 g, 281 mmol). Formic acid (141 mL) was added slowly to the flask at 0 °C, and the resulting orange solution was stirred at 0 °C for 5 min. Paraformaldehyde (8.43 g, 281 mmol) was added to the flask, and the resulting mixture was heated to 50 °C for 11 h, after which TLC (methanol/dichloromethane = 3:7) indicated complete consumption of the starting amine. Excess formic acid was removed under reduced pressure. The residual viscous oil was then poured into aqueous sodium hydroxide (1 M) saturated with sodium chloride. The aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The filtrate was removed under reduced pressure to afford the crude tetrahydroisoquinoline (56.5 g) as pale-yellow crystals, which was used in the next step without further purification. The crude material was purified by recrystallization from dichloromethane to give a pale-yellow needles. $R_f = 0.10$ (methanol/dichloromethane = 1:9); m.p.: 77.7–78.8 °C (dichloromethane); IR (neat): $\tilde{\nu} = 3318$, 2933, 2834, 1611, 1518, 1465, 1255, 1227, 1107, 1025, 853, 807 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.58$ (s, 1H), 6.50 (s, 1H), 3.94 (s, 2H), 3.85 (s, 3H), 3.84 (s, 3H), 3.12 (t, $J = 6.0$ Hz, 2H), 2.71 ppm (t, $J = 6.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 147.3$, 147.2, 127.4, 126.3, 111.8, 108.9, 55.8, 47.7, 43.8, 28.5 ppm (one signal is missing owing to overlap with other signals); HRMS (FAB): *m/z* calcd for $C_{11}H_{15}NO_2$: 193.1103 $[M]^+$; found: 193.1106.

20: A 1-L round-bottomed flask equipped with a magnetic stirrer bar was charged with the above crude product (56.5 g), dry dichloromethane (280 mL), and pyridine (27.2 mL, 337 mmol). The yellow solution was cooled to 0 °C, and trifluoroacetic anhydride (TFAA; 47.6 mL, 337 mmol) in dry dichloromethane (50 mL) was added dropwise to the solution over 30 min. After addition of TFAA was finished, the flask was warmed to room temperature, and the mixture was stirred for 2 h, after which TLC (methanol/dichloromethane = 1:19) indicated complete consumption of the starting compound. Aqueous hydrochloric acid (1 M, 300 mL) was added to the flask. The mixture was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by recrystallization from hexane/dichloromethane to afford 2,2,2-trifluoro-1-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)ethanone (**20**; 73.1 g, 253 mmol, 90% from homoveratrylamine) as pale-yellow needles. $R_f = 0.43$ (hexane/ethyl acetate = 3:1); m.p.: 101.5–102.7 °C (hexane/dichloromethane); IR (neat): $\tilde{\nu} = 1693$, 1613, 1520, 1463, 1254, 1231, 1186, 1133, 1113, 1014, 925, 655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 6.63$ (s, 1H), 6.62 (s, 1H), 4.73 (s, 2H), 3.88 (t, $J =$ 6.4 Hz, 2H), 3.873 (s, 3H), 3.867 (s, 3H), 2.89 ppm (t, $J = 6.4$ Hz, 2H) (complexity due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 156.1$, 148.1, 148.0, 125.0, 123.2, 118.0, 111.1, 109.0, 56.0, 56.0, 46.7, 45.2, 43.4, 28.8 ppm (complexity due to rotamers); elemental analysis: calcd (%) for $C_{13}H_{14}F_3NO_3$: C 53.98, H 4.88, N 4.84; found: C 54.09, H 4.94, N 4.83.

1-(5,8-Dibromo-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinolin-2(1*H*)-yl)-2,2,2-trifluoroethanone: A four-necked 300-mL round-bottomed flask was charged with $FeCl_3$ (3.80 g, 23.4 mmol), **20** (3.21 g, 11.1 mmol), and dry dichloromethane (22 mL). The resulting mixture was cooled to 0 °C. Br_2 (1.22 mL, 24.4 mmol) in dichloromethane (12 mL) was added dropwise to the flask over 15 min. The reaction mixture was stirred at 0 °C for 30 min, after which TLC (hexane/ethyl acetate = 3:1) indicated complete consumption of **20**. Dichloromethane (30 mL) was added to the flask followed by crushed ice. The mixture was stirred vigorously and extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, aqueous sodium thiosulfite, and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (hexane/ethyl acetate = 9:1–4:1, gradient) to provide the pure dibrominated compound (4.39 g, 9.82 mmol, 88%) as a fine white powder. $R_f = 0.48$ (hexane/ethyl acetate = 3:1); IR (neat): $\tilde{\nu} = 1698$, 1462, 1407, 1307, 1194, 1142, 1030, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.74$ (major, s, 1H), 3.97–3.74 (m, 8H), 2.95 ppm (major, t, $J = 6.4$ Hz, 2H) (complexity due to rotamers); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 150.1$, 150.0, 149.8, 131.5, 130.7, 128.7, 128.3, 120.0, 119.6, 117.7, 117.2, 116.7, 114.9, 60.9, 60.9, 60.9, 60.8, 48.0, 48.0, 46.6, 49.6, 42.8, 42.8, 40.9, 30.5, 30.4, 28.9 ppm (complexity due to rotamers); elemental analysis: calcd (%) for $C_{26}H_{23}NO_6$: C 34.93, H 2.71, N 3.13; found: C 35.22, H 2.85, N 3.24.

5,8-Dibromo-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline: A 500-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with the above trifluoroacetamide (25.86 g, 57.8 mmol), methanol (240 mL), and dichloromethane (60 mL). Powdered K_2CO_3 (23.99 g, 174 mmol) was added to the suspension. The mixture was stirred vigorously for 6 h at room temperature, after which TLC (hexane/ethyl acetate = 3:1) indicated complete consumption of the starting compound. K_2CO_3 was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was dissolved in dichloromethane, and the solution was washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the crude corresponding secondary amine (18.66 g), which was used for the next reaction without further purification. The crude material was purified by recrystallization from dichloromethane to give colorless prisms. $R_f = 0.43$ (methanol/dichloromethane = 1:9); m.p.: 94.2–95.0 °C (dichloromethane); IR (neat): $\tilde{\nu} = 3325$, 2939, 2872, 1457, 1400, 1292, 1223, 1104, 1016, 978, 934, 792, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 3.94$ (s, 2H), 3.89 (s, 3H), 3.89 (s, 3H), 3.10 (t, $J = 6.0$ Hz, 2H), 2.71 ppm (t, $J = 6.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 149.3, 149.0, 133.2, 132.5, 120.2, 117.1, 60.8, 60.8, 49.5, 43.3, 30.2 ppm; HRMS (FAB): *m/z* calcd for $C_{11}H_{14}Br_2NO_2$: 349.9391 $[M+H]^+$; found 349.9396.

21: A 1-L round-bottomed flask equipped with a magnetic stirrer bar was charged with the above crude amine (18.66 g), dry dichloromethane (500 mL), and manganese oxide (particle size < 5 μm, 100 g, 1.16 mol). The resulting mixture was stirred vigorously at room temperature for 18 h, after which TLC (methanol/dichloromethane = 1:19) indicated complete consumption of the starting compound. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure to afford analytically pure 5,8-dibromo-3,4-dihydro-6,7-dimethoxyisoquinoline (**21**; 18.16 g, 52.0 mmol, 90% over 2 steps) as white plates. $R_f = 0.26$ (hexane/ethyl acetate = 1:1); m.p.: 67.9–69.0 °C (dichloromethane); IR (neat): $\tilde{\nu} = 2940$, 1622, 1525, 1456, 1406, 1366, 1322, 1300, 1177, 1113, 1028, 988, 938, 897, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.60$ (br s, 1H), 3.96 (s, 3H), 3.91 (s, 3H), 3.76 (t, $J = 7.6$ Hz, 2H), 2.78 ppm (t, $J = 7.6$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 157.7$, 153.1, 150.0, 135.1, 124.2, 118.8, 118.4, 60.9, 60.9, 46.7, 25.0 ppm; elemental analysis: calcd (%) for $C_{11}H_{11}Br_2NO_2$: C 37.85, H 3.18, N 4.01; found: C 38.00, H 3.21, N 3.71.

22: A 30-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **21** (344.2 mg, 0.986 mmol) and dry THF (4.9 mL). Nosyl chloride (262.2 mg, 1.18 mmol) in THF (1.0 mL) was added dropwise to the solution at 0 °C over 5 min, and the resulting mixture was warmed to room temperature over 1 h. Saturated aqueous sodium bicarbonate (10 mL) was added to the solution. The mixture was stirred vigorously for 30 min, after which TLC (dichloromethane) indicated complete consumption of **21**. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was passed through a silica pad to afford crude 5,8-dibromo-2-(*o*-nitrobenzenesulfonyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-1-hydroxyisoquinoline (**22**; 562.1 mg) as a pale-yellow amorphous solid. $R_f = 0.18$ (dichloromethane); IR (neat): $\tilde{\nu} = 3518$, 2941, 1542, 1462, 1373, 1303, 1172, 1026, 964, 776, 731, 586 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.15$–8.10 (m, 1H), 7.77–7.72 (m, 2H), 7.71–7.66 (m, 1H), 6.51 (d, $J = 4.4$ Hz, 1H), 4.05–3.98 (m, 1H), 3.899 (s, 3H), 3.895 (s, 3H), 3.79 (d, $J = 4.4$ Hz, 1H), 3.64 (dt, $J = 12.8$, 5.2 Hz, 1H), 3.03–2.88 ppm (m, 2H) (one proton signal was obscured owing to overlap with that of MeO); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 151.5$, 150.0, 147.9, 134.0, 133.2, 132.2, 131.6, 131.0, 130.8,

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124.6, 119.8, 118.9, 67.1, 60.9, 60.8, 37.8, 30.2 ppm; elemental analysis: calcd (%) for $C_{17}H_{16}Br_2N_2O_7S$: C 36.98, H 2.92, N 5.07; found: C 36.95, H 3.08, N 4.95.

26: A 50-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with crude **22** (562.1 mg) and dry methanol (10 mL). The resulting solution was cooled to 0 °C. Sodium borohydride (112.0 mg, 2.96 mmol) was added portionwise to the solution over 10 min. The resulting mixture was warmed to room temperature over 1 h, after which TLC (dichloromethane) indicated complete consumption of **22**. Hydrochloric acid (1 M; 20 mL) was added to the reaction mixture at 0 °C, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (dichloromethane) to give pure (2-(2-(*o*-nitrobenzenesulfonyl)aminoethyl)-3,6-dibromo-4,5-dimethoxyphenyl)methanol (**26**; 425.5 mg, 0.768 mmol, 78% over 2 steps) as a white solid, which was purified by recrystallization from hexane/dichloromethane to provide colorless fine prisms. R_f = 0.28 (hexane/ethyl acetate = 1:1); m.p.: 154.4–154.9 °C (hexane/dichloromethane); IR (neat): $\tilde{\nu}$ = 3523, 3341, 2935, 1541, 1459, 1405, 1364, 1344, 1303, 1164, 1099, 1011, 731, 590 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.17–8.11 (m, 1H), 7.85–7.77 (m, 1H), 7.74–7.67 (m, 2H), 6.06 (t, J = 6.4 Hz, 1H), 4.95 (d, J = 5.6 Hz, 2H), 3.87 (s, 3H), 3.87 (s, 3H), 3.41 (td, J = 7.2, 6.4 Hz, 2H), 3.26 (t, J = 7.2 Hz, 2H), 2.36 ppm (t, 5.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.2, 150.0, 147.8, 135.2, 134.5, 133.7, 133.4, 132.7, 131.1, 125.2, 121.1, 120.9, 62.6, 60.8, 42.6, 33.9, 30.9 ppm; elemental analysis: calcd (%) for $C_{17}H_{18}Br_2N_2O_7S$: C 36.84, H 3.27, N 5.05; found: C 36.74, H 3.27, N 5.05.

27: A flame-dried 250-mL Schlenk tube equipped with a magnetic stirrer bar was charged with **26** (13.41 g, 24.2 mmol), copper iodide (460.9 mg, 2.42 mmol), and cesium acetate (11.62 g, 60.5 mmol). The flask was evacuated and then backfilled with argon. Dry DMSO (96.8 mL) was added to the mixture. The resulting pale-green solution was stirred at 80 °C under argon atmosphere for 24 h, after which TLC (hexane/ethyl acetate = 1:1) indicated complete consumption of **26**. The reaction mixture was poured into 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was passed through a silica pad to provide crude *N*-(*o*-nitrobenzenesulfonyl)-4-hydroxymethyl-5-bromo-6,7-dimethoxyindoline (**27**; 12.02 g) as an off-white amorphous solid, which decomposed gradually at room temperature. R_f = 0.18 (hexane/ethyl acetate = 1:1); IR (neat): $\tilde{\nu}$ = 3545, 3400, 2943, 1541, 1470, 1407, 1354, 1165, 1085, 1002, 964, 913, 781, 732, 602, 570 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.24–8.18 (m, 1H), 7.78–7.69 (m, 3H), 4.69 (s, 2H), 4.36 (t, J = 8.0 Hz, 2H), 3.77 (s, 3H), 3.33 (s, 3H), 3.21 ppm (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.8, 147.2, 143.4, 135.1, 134.7, 133.2, 131.9, 131.7, 130.9, 130.4, 124.1, 116.2, 62.5, 60.6, 59.7, 53.5, 28.9 ppm; HRMS (FAB): m/z calcd for $C_{17}H_{17}BrN_2O_7S$: 471.9940 $[M]^+$; found 471.9939.

23: A flame-dried 1-L round-bottomed flask equipped with a magnetic stirrer bar was charged with crude **27** (12.02 g), NMO (4.25 g, 36.3 mmol), and dry dichloromethane (100 mL). MS4Å (12.1 g, activated) were added to the solution, and the mixture was stirred for 5 min. TPAP (165.4 mg, 0.484 mmol) was added to the mixture in one portion, and the reaction mixture was stirred at room temperature, after which TLC (hexane/ethyl acetate = 1:1) indicated complete consumption of **27**. The reaction mixture was diluted with diethyl ether and passed through a celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (dichloromethane) to afford *N*-(*o*-nitrobenzenesulfonyl)-4-formyl-5-bromo-6,7-dimethoxyindoline (**23**; 9.75 g, 20.7 mmol, 85% over 2 steps) as a white solid, which was purified by recrystallization with hexane/dichloromethane to afford fine colorless needles. R_f = 0.35 (hexane/ethyl acetate = 1:1); m.p.: 160.2–161.0 °C (hexane/dichloromethane); IR (neat): $\tilde{\nu}$ = 2947, 1687, 1542, 1471, 1359, 1319, 1166, 1117, 1085, 964, 915, 783, 741, 606, 570 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.36 (s, 1H), 8.21–8.14 (m, 1H), 7.79–7.69 (m, 3H), 4.35 (t, J = 8.0 Hz, 2H), 3.80 (s, 3H), 3.46 (s, 3H), 3.44 ppm (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 192.1, 149.6, 147.9, 147.2, 135.7, 135.3, 135.0, 133.3, 131.6, 130.2, 124.9, 124.2, 120.1, 60.8, 59.9, 53.9, 30.1 ppm; elemental analysis: calcd (%) for $C_{17}H_{15}BrN_2O_7S$: C 43.33, H 3.21, N 5.94; found: C 43.03, H 3.43, N 5.86.

29: A 100-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **23** (4.95 g, 10.5 mmol), **28** (4.50 g, 11.0 mmol), and dry dichloromethane (21.0 mL). The flask was cooled to 0 °C, and 1,1,3,3-tetramethylguanidine (1.38 mL, 11.0 mmol) was added to the solution. The reaction mixture was warmed to room temperature over 6 h, after which TLC (hexane/ethyl acetate = 1:1) indicated complete consumption of **23**. Hydrochloric acid (1 M; 10 mL) was added to the solution. The mixture was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate and brine, dried over sodium sulfite, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (hexane/ethyl acetate = 3:1) to afford (*Z*)-3-[*N*-(*o*-nitrobenzenesulfonyl)-5-bromo-6,7-dimethoxy-indolin-4-yl]benzyloxycarbonylaminoacrylic acid methyl ester (**29**; 6.66 g, 8.45 mmol, 84%) as a pale-yellow amorphous solid. R_f = 0.29 (dichloromethane); IR (neat): $\tilde{\nu}$ = 3331, 3029, 2946, 1723, 1542, 1469, 1360, 1244, 1166, 1065, 968, 852, 755, 699, 656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.22–8.18 (m, 1H), 7.76–7.66 (m, 3H), 7.44–7.21 (m, 10H), 7.06 (s, 1H), 6.34 (br s, 1H), 5.29 (s, 2H), 5.03 (s, 2H), 4.18 (t, J = 7.6 Hz, 2H), 3.76 (s, 3H), 3.36 (s, 3H), 2.80 ppm (t, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.8, 152.9, 149.8, 147.1, 143.4, 135.4, 135.1, 134.8, 134.7, 133.2, 131.5, 130.9, 130.3, 128.4, 128.3, 128.1, 128.1, 127.7, 126.8, 125.5, 124.0, 115.5, 67.5, 67.4, 60.4, 59.6, 53.6, 29.7 ppm (two signals are missing owing to overlap with other signals); HRMS (FAB): m/z calcd for $C_{34}H_{30}BrN_3O_{10}S$: 751.0835 $[M]^+$; found: 751.0845.

30: A flame-dried 500-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **29** (6.66 g, 8.45 mmol), copper iodide (1.61 g, 8.45 mmol), and cesium acetate (8.11 g, 42.3 mmol). The flask was evacuated and then backfilled with argon. Dry DMSO (42.3 mL) was added to the mixture. The resulting pale-green solution was stirred at room temperature under argon atmosphere for 12 h, after which TLC (hexane/ethyl acetate = 1:1) indicated complete consumption of **29**. The reaction mixture was poured into 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (neutral silica gel, hexane/ethyl acetate = 1:1) to afford benzyl 3-(*o*-nitrobenzenesulfonyl)-4,5-dimethoxy-6-benzyloxycarbonyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate (**30**; 4.35 g, 6.48 mmol, 77%) as a yellow amorphous solid. R_f = 0.40 (hexane/ethyl acetate = 1:1); IR (neat): $\tilde{\nu}$ = 2947, 1770, 1715, 1541, 1491, 1351, 1253, 1165, 1029, 750, 698, 605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.15–8.10 (m, 1H), 7.73–7.64 (m, 3H), 7.45–7.33 (m, 5H), 7.10 (s, 1H), 5.34 (s, 2H), 5.31 (s, 2H), 4.42 (t, J = 7.6 Hz, 2H), 3.68 (s, 3H), 3.38 (s, 3H), 3.12 ppm (t, J = 7.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.2, 152.5, 147.4, 142.9, 138.1, 135.3, 134.8, 134.2, 133.1, 131.8, 131.6, 131.4, 130.6, 130.4 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 124.0, 123.3, 119.8, 110.3, 70.9, 67.1, 61.1, 59.8, 54.3, 28.9 ppm; HRMS (FAB): m/z calcd for $C_{34}H_{29}N_3O_{10}S$: 671.1574 $[M]^+$; found: 671.1572.

Benzyl 4,5-dimethoxy-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carboxylate: A 50-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **30** (2.10 g, 3.13 mmol), cesium carbonate (3.06 g, 9.38 mmol), and dry acetonitrile (6.26 mL). PhSH (481.6 μL, 4.69 mmol) was added to the suspension. The reaction mixture was vigorously stirred at room temperature for 3 h, after which TLC (hexane/ethyl acetate = 1:1) indicated complete consumption of **30**. The reaction mixture was diluted with ethyl acetate and filtered through a celite pad. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (neutral silica gel, dichloromethane then hexane/ethyl acetate = 1:1) to afford the Ns-deprotected compound (1.45 g, 2.98 mmol, 95%) as a viscous yellow liquid. R_f = 0.29 (hexane/ethyl acetate = 1:1); IR (neat): $\tilde{\nu}$ = 3370, 2941, 1766, 1713, 1495, 1240, 1198, 1148, 1028, 750, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.44–7.31 (m, 10H), 7.06 (s, 1H), 5.34 (s, 2H), 5.30 (s, 2H), 3.90 (s, 3H), 3.76 (s, 3H), 3.65 (t,

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J=8.4 Hz, 2H), 3.10 ppm (t, J=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.6, 153.1, 141.7, 139.3, 137.8, 135.6, 134.4, 128.8, 128.6, 128.6, 128.5, 128.3, 128.1, 127.8, 127.0, 120.8, 115.5, 110.1, 70.6, 66.7, 61.2, 60.2, 48.3, 29.3 ppm; HRMS (FAB): m/z calcd for $C_{28}H_{26}N_2O_6$: 486.1791 $[M]^+$; found: 486.1792.

31: A 100-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with the above compound (1.57 g, 3.23 mmol), $NaHCO_3$ (814.1 mg, 9.69 mmol), THF (15 mL), and H_2O (5 mL). FmocCl (835.6 mg, 3.23 mmol) was added portionwise to the suspension over 5 min at room temperature. The resulting mixture was stirred for 10 min, after which TLC (hexane/ethyl acetate=1:1) indicated complete consumption of the starting compound. The reaction mixture was diluted with ethyl acetate, and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (hexane/ethyl acetate=3:1–3:2, gradient) to afford benzyl 3-(9*H*-fluoren-9-yl)methoxycarbonyl-4,5-dimethoxy-6-benzyloxycarbonyl-1,2-dihydro-pyrrolo[3,2-*e*]indole-7-carboxylate (**31**; 2.09 g, 2.95 mmol, 91%) as a pale yellow amorphous solid. R_f=0.58 (hexane/ethyl acetate=1:1); IR (neat): $\tilde{\nu}$=2947, 1769, 1714, 1452, 1414, 1391, 1325, 1250, 1214, 1163, 741, 568 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=7.74 (d, J=7.2 Hz, 2H), 7.56 (d, J=8.4 Hz, 2H), 7.46–7.21 (m, 14H), 7.13 (s, 1H), 5.36 (s, 2H), 5.32 (s, 2H), 4.55 (d, J=6.4 Hz, 2H), 4.29 (t, J=6.4 Hz, 1H), 4.15 (t, J=7.2 Hz, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 3.05 ppm (t, J=7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=160.3, 154.8, 152.8, 143.8, 143.6, 141.3, 138.4, 135.4, 134.2, 131.8, 130.0, 128.8, 128.7, 128.6, 128.5, 128.5, 128.4, 128.3, 127.6, 127.0, 125.0, 122.2, 119.9, 119.6, 110.3, 70.8, 67.6, 67.0, 61.1, 60.2, 51.6, 47.3, 28.4 ppm; HRMS (FAB): m/z calcd for $C_{43}H_{36}N_2O_8$: 708.2472 $[M]^+$; found: 708.2465.

32: A 100-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **31** (2.02 g, 2.85 mmol), 10% Pd/C (303.3 mg, 0.285 mmol), THF (14.3 mL), and EtOH (14.3 mL). The flask was charged with hydrogen gas (1 atm) at room temperature. The resulting suspension was vigorously stirred for 3 h, after which TLC (hexane/ethyl acetate=1:1) indicated complete consumption of **31**. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure. The residue was passed through a silica pad to give 3-(9*H*-fluoren-9-yl)methoxycarbonyl-4,5-dimethoxy-1,2-dihydro-6*H*-pyrrolo[3,2-*e*]indole-7-carboxylic acid (**32**; 1.40 g) as a yellow viscous liquid, which was used in the next step without further purification. R_f=0.20 (methanol/chloroform=1:9); IR (neat): $\tilde{\nu}$=3453, 3286, 2941, 1698, 1537, 1449, 1416, 1329, 1248, 1190, 1036, 909, 759, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ=9.19 (br s, 1H), 7.75 (d, J=7.5 Hz, 2H), 7.58 (d, J=7.7 Hz, 2H), 7.39 (dd, J=7.7, 7.5 Hz, 2H), 7.27 (dd, J=7.7, 7.5 Hz, 2H), 7.16 (d, J=2.0 Hz, 1H), 4.57 (d, J=6.9 Hz, 2H), 4.31 (t, J=6.9 Hz, 1H), 4.18 (t, J=7.7 Hz, 2H), 4.03 (s, 3H), 3.90 (s, 3H), 3.10 ppm (t, J=7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=165.9, 161.3, 155.2, 143.9, 142.4, 141.3, 137.5, 130.9, 130.5, 127.7, 127.0, 125.0, 122.1, 120.6, 119.9, 108.6, 67.7, 61.2, 60.4, 51.8, 47.3, 28.7 ppm; HRMS (FAB): m/z calcd for $C_{28}H_{24}N_2O_6$: 484.1634 $[M]^+$; found: 484.1631.

33: A 100-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **32** (1.40 g), DMAP (69.6 mg, 0.570 mmol), and WSCD·HCl (1.64 g, 8.55 mmol). The resulting mixture was cooled to 0°C. A saturated solution of MeSH in DMF (14.3 mL) was added to the mixture, and the resulting mixture was stirred at 0°C for 3 h, after which TLC (hexane/ethyl acetate=1:1) indicated complete consumption of **32**. The reaction mixture was diluted with ethyl acetate and hydrochloric acid (1 M). The aqueous layer was extracted with ethyl acetate, and the combined organic extracts were washed with aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (hexane/ethyl acetate=3:1–3:2, gradient) to afford methyl 3-(9*H*-fluoren-9-yl)methoxycarbonyl-4,5-dimethyoxy-1,2-dihydro-6*H*-pyrrolo[3,2-*e*]indole-7-thiocarboxylate (**33**; 1.11 g, 2.16 mmol, 76% over 2 steps) as a pale-yellow amorphous solid. R_f=0.56 (hexane/ethyl acetate=1:1); IR (neat): $\tilde{\nu}$=3318, 2941, 1712, 1640, 1502, 1449, 1415, 1327, 1281, 1244, 1186, 1147, 1121, 1021, 908, 871, 759, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.00 (br s, 1H), 7.76 (d, J=7.2 Hz, 2H), 7.58 (d, J=7.6 Hz, 2H), 7.39 (dd, J=7.6, 7.2 Hz, 2H), 7.27 (dd, J=7.6, 7.2 Hz, 2H), 7.13 (d, J=1.6 Hz, 1H), 4.56 (d, J=7.2 Hz, 2H), 4.31 (t, J=7.2 Hz, 1H), 4.18 (t, J=7.6 Hz, 2H), 3.99 (s, 3H), 3.89 (s, 3H), 3.10 (t, J=7.6 Hz, 2H), 2.52 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=183.8, 155.1, 143.9, 142.6, 141.3, 137.6, 134.5, 131.2, 130.0, 127.6, 127.0, 125.1, 122.1, 120.4, 119.9, 106.1, 67.6, 61.1, 60.3, 51.8, 47.3, 28.7, 22.6 ppm; HRMS (FAB): m/z calcd for $C_{29}H_{26}N_2O_5S$: 514.1562 $[M]^+$; found: 514.1569.

7: A flame-dried 300-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **33** (1.35 g, 2.62 mmol) and dry dichloromethane (52 mL). BCl_3 (1 M in dichloromethane, 2.62 mL, 2.62 mmol) was added dropwise to the solution at 0°C over 5 min. The red reaction mixture was stirred vigorously for 15 min. Next, another portion of BCl_3 (1 M in dichloromethane, 0.78 mL, 0.78 mmol) was added dropwise to the reaction mixture over 5 min, after which TLC (hexane/ethyl acetate=1:1) indicated complete consumption of **33**. The excess reagent was removed by saturated aqueous ammonium chloride, and the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, concentrated under reduced pressure, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (dichloromethane) to give methyl 3-(9*H*-fluoren-9-yl)methoxycarbonyl-4-hydroxy-5-methoxy-1,2-dihydro-6*H*-pyrrolo[3,2-*e*]indole-7-thiocarboxylate **7** (1.28 g, 2.55 mmol, 97%) as a light-yellow solid. R_f=0.62 (hexane/ethyl acetate=1:1); IR (neat): $\tilde{\nu}$=3323, 2930, 1663, 1629, 1450, 1335, 1243, 1144, 1060, 1019, 908, 871, 736 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=11.30 (s, 1H), 8.93 (br s, 1H), 7.80 (d, J=7.2 Hz, 2H), 7.63 (d, J=8.0 Hz, 2H), 7.44 (dd, J=8.0, 7.2 Hz, 2H), 7.35 (dd, J=8.0, 7.2 Hz, 2H), 7.08 (s, 1H), 4.61 (t, J=6.4 Hz, 2H), 4.34 (t, J=6.4 Hz, 1H), 4.11 (t, J=7.6 Hz, 2H), 4.01 (s, 3H), 3.22 (t, J=7.6 Hz, 2H), 2.50 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=183.4, 155.2, 143.4, 141.3, 138.6, 133.8, 132.7, 130.5, 127.9, 127.2, 126.0, 124.8, 120.1, 119.7, 117.5, 106.3, 68.8, 60.7, 49.3, 47.0, 26.7, 21.0 ppm; HRMS (FAB): m/z calcd for $C_{29}H_{26}N_2O_5S$: 500.1406 $[M]^+$; found: 500.1404.

3-Benzyloxy-4-methoxybenzaldehyde: A 500-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with isovanillin (**34**; 25.0 g, 164 mmol), powdered K_2CO_3 (25.0 g, 181 mmol), and dry acetonitrile (160 mL). BnBr (19.5 mL, 164 mmol) was added to the resulting mixture. The reaction mixture was heated at reflux for 1 h, after which TLC (hexane/ethyl acetate=1:1) indicated complete consumption of the starting phenol. The reaction mixture was filtered through a celite pad, and the filtrate was concentrated under reduced pressure to provide analytically pure 3-benzyloxy-4-methoxybenzaldehyde (41.3 g) as a pale-yellow liquid, which gradually solidified at room temperature. R_f=0.52 (hexane/ethyl acetate=1:1); IR (neat): $\tilde{\nu}$=3318, 2933, 2834, 1518, 1465, 1256, 1227, 1107 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ=9.81 (s, 1H), 7.48–7.42 (m, 3H), 7.38 (dd, J=7.2, 7.2 Hz, 2H), 7.31 (t, J=7.2 Hz, 1H), 7.00 (s, 1H), 6.98 (s, 1H), 5.18 (s, 2H), 3.95 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=190.8, 155.0, 148.6, 136.2, 129.9, 128.6, 128.1, 127.4, 126.8, 111.2, 110.7, 70.8, 56.1 ppm; HRMS (FAB): m/z calcd for $C_{15}H_{14}O_3$: 242.0943 $[M]^+$; found: 242.0932.

5-Benzyloxy-2-bromo-4-methoxybenzaldehyde: A 500-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with the above crude benzaldehyde, dichloromethane (80 mL), and methanol (80 mL). The resulting colorless solution was cooled to 0°C. A solution of bromine (9.24 mL, 180 mmol) in dichloromethane (20 mL) was added dropwise to the solution at 0°C over 30 min. The reaction mixture was warmed to room temperature and stirred for 2 h, after which TLC (hexane/ethyl acetate=1:1) indicated complete consumption of the starting compound. Water was added to the reaction mixture, and the mixture was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium bicarbonate, aqueous sodium sulfite, and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to afford a pale-yellow solid. Recrystallization from hexane/ethyl acetate provided 5-benzyloxy-2-bromo-4-methoxybenzaldehyde as colorless needles (45.4 g, 141 mmol, 86% over 2 steps). R_f=0.63 (hexane/ethyl acetate=1:1); m.p.: 142.4–

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143.3 °C (hexane/ethyl acetate); IR (neat): $\tilde{\nu}$ = 1681, 1591, 1505, 1438, 1384, 1268, 1216, 1160, 1025, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 10.16 (s, 1H), 7.48 (s, 1H), 7.44 (d, J = 6.8 Hz, 2H), 7.41–7.31 (m, 3H), 7.07 (s, 1H), 5.16 (s, 2H), 3.95 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 190.7, 155.0, 147.8, 135.8, 128.6, 128.2, 127.5, 126.3, 120.6, 115.6, 112.3, 70.8, 56.4 ppm; elemental analysis: calcd (%) for $C_{19}H_{25}N_2O_2$: C 56.10, H 4.08; found: C 55.86, H 4.10.

35: A 50-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with 5-benzyloxy-2-bromo-4-methoxybenzaldehyde (3.21 g, 10.0 mmol), **24** (3.48 g, 10.5 mmol), and dry dichloromethane (20 mL). The reaction mixture was cooled to 0 °C. 1,1,3,3-Tetramethylguanidine (1.51 mL, 12.0 mmol) was added to the solution. The reaction mixture was warmed to room temperature over 2 h, after which TLC (hexane/ethyl acetate = 1:1) indicated complete consumption of the benzaldehyde derivative. Hydrochloric acid (1 M) was added to the solution, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. Recrystallization from hexane/ethyl acetate provided benzyl (*Z*)-1-methoxycarbonyl-2-(5-benzyloxy-2-bromo-4-methoxyphenyl)vinylcarbamate (**35**; 5.03 g, 9.56 mmol, 96%) as fine colorless needles. R_f = 0.41 (hexane/ethyl acetate = 1:1); m.p.: 159.1–159.7 °C (hexane/ethyl acetate); IR (neat): $\tilde{\nu}$ = 1724, 1696, 1598, 1523, 1497, 1435, 1262, 1206, 1171, 1069, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.41 (s, 1H), 7.36–7.24 (m, 10H), 7.18 (s, 1H), 7.05 (s, 1H), 6.29 (br s, 1H), 5.06 (s, 2H), 4.89 (s, 2H), 3.88 (s, 3H), 3.83 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.5, 153.4, 150.7, 147.1, 136.3, 135.6, 129.2, 128.6, 128.5, 128.4, 128.31, 128.1, 127.3, 126.0, 124.1, 116.8, 115.6, 113.7, 71.0, 67.6, 56.1, 52.8 ppm; elemental analysis: calcd (%) for $C_{26}H_{24}BrNO_6$: C 59.33, H 4.60, N 2.66; found: C 59.08, H 4.60, N 2.80.

36: A flame-dried 30-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **35** (1.28 g, 2.43 mmol), copper iodide (462.8 mg, 2.43 mmol), and cesium acetate (2.33 g, 12.1 mmol). The flask was evacuated and then backfilled with argon. Dry DMSO (12.2 mL) was added to the mixture. The resulting pale-green solution was stirred at 90 °C under argon atmosphere for 24 h, after which TLC (hexane/ethyl acetate = 1:1) indicated complete consumption of **35**. The reaction mixture was poured into 5% aqueous sodium chloride in 10% aqueous ammonium hydroxide and extracted with ethyl acetate. The combined organic extracts were washed with water and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography to afford methyl 5-benzyloxy-6-methoxy-1*H*-indole-2-carboxylate (**36**; 862.1 mg, 1.94 mmol, 80%) as a white solid, which was purified by recrystallization from hexane/ethyl acetate to provide colorless fine needles. R_f = 0.38 (hexane/ethyl acetate = 1:1); m.p.: 182.7–183.5 °C (hexane/ethyl acetate); IR (neat): $\tilde{\nu}$ = 1683, 1524, 1285, 1255, 1212, 1148 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 8.74 (br s, 1H), 7.48 (d, J = 7.2 Hz, 2H), 7.37 (dd, J = 7.2, 6.8 Hz, 2H), 7.31 (dd, J = 6.8, 6.8 Hz, 1H), 7.08 (s, 1H), 7.06 (dd, J = 2.0, 0.8 Hz, 1H), 6.86 (s, 1H), 5.17 (s, 2H), 3.94 (s, 3H), 3.91 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.2, 150.7, 145.1, 137.2, 132.4, 128.5, 127.8, 127.3, 125.6, 120.3, 108.9, 105.7, 93.9, 71.5, 56.1, 51.8 ppm; elemental analysis: calcd (%) for $C_{18}H_{17}NO_4$: C 69.44, H 5.50, N 4.50; found: C 69.17, H 5.74, N 4.42.

5-Benzyloxy-6-methoxy-1*H*-indole-2-carboxylic acid: A 30-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **36** (175.2 mg, 0.563 mmol), 1,4-dioxane (6.0 mL), and water (3.0 mL). $LiOH{\cdot}H_2O$ (210.0 mg, 5.00 mmol) was added to the colorless solution. The solution was stirred at 50 °C for 2 h, after which TLC (hexane/ethyl acetate = 1:1) indicated complete consumption of **36**. The reaction mixture was poured into hydrochloric acid (3 M), and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the corresponding indole carboxylic acid (168.1 mg, quant.) as an off-white solid. Further purification was performed by recrystallization from hexane/ethyl acetate to afford pale-yellow prisms. R_f = 0.10 (hexane/ethyl acetate = 1:1); m.p.: 207.6–208.9 °C (hexane/ethyl acetate); IR (neat): $\tilde{\nu}$ = 3417, 2941, 1670, 1532, 1251, 1006; ^1H NMR (400 MHz, [D$_6$]acetone): δ = 10.98 (br s, 1H), 10.57 (br s, 1H), 7.52 (d, J = 7.6 Hz, 2H), 7.38 (dd, J = 7.6, 7.2 Hz, 2H), 7.31 (t, J = 7.2 Hz, 2H), 7.23 (s, 1H), 7.06 (s, 2H, overlapped), 5.11 (s, 2H), 3.86 ppm (s, 3H); ^{13}C NMR (100 MHz, [D$_6$]acetone): δ = 162.8, 151.6, 146.2, 138.8, 134.1, 129.1, 128.5, 128.4, 127.1, 121.4, 109.1, 106.4, 95.5, 71.9, 56.1 ppm; elemental analysis: calcd (%) for $C_{17}H_{15}NO_4$: C 68.68, H 5.09, N 4.71; found: C 68.57, H 5.29, N 4.61.

8: A flame-dried 20-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with the above indole carboxylic acid (647.5 mg, 2.18 mmol) and dry dichloromethane (20 mL). Thionyl chloride (5.0 mL) was added to the white suspension, and the mixture was heated at reflux for 30 min, after which TLC (hexane/ethyl acetate = 1:1) indicated complete consumption of the starting compound. The reaction mixture was concentrated under reduced pressure to give crude 5-benzyloxy-6-methoxy-1*H*-indole-2-carbonyl chloride (**8**; 689.2 mg) as a light-yellow powder, which was used in the next coupling reaction without further purification.

37: A 300-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with the **6** (1.19 g, 1.98 mmol) and dry dichloromethane (100 mL). The resulting solution was cooled to 0 °C. Pyridine (0.320 mL, 3.96 mmol) was added to the solution, followed by **8** (688.3 mg, 2.18 mmol) in dry dichloromethane (10 mL), and the reaction mixture was stirred for 5 min, after which TLC (hexane/ethyl acetate = 1:1) indicated complete consumption of **6**. The reaction mixture was concentrated under reduced pressure, and the residue was diluted with ethyl acetate and hydrochloric acid (1 M). The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with saturated aqueous sodium bicarbonate and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (hexane/ethyl acetate = 3:1–3:2, gradient) to afford (−)-((8*S*)-4-benzyloxy-3-benzyloxycarbonyl-2-methoxycarbonyl-8,9-dihydro-8-(*tert*-butyldimethylsilyloxy)pyrrolo[3,2-*f*]quinolin-6(7*H*)-yl)(5-benzyloxy-6-methoxy-1*H*-indol-2-yl)methanone (**37**; 1.74 g, 1.98 mmol, quant.) as a pale-yellow amorphous solid. R_f = 0.48 (hexane/ethyl acetate = 1:1); $[\alpha]_D^{23} = -16.5$ (c = 1.48, $CHCl_3$); IR (neat): $\tilde{\nu}$ = 3293, 2951, 1773, 1717, 1608, 1517, 1390, 1238, 838, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 9.83 (br s, 1H), 7.47 (d, J = 7.2 Hz, 2H), 7.36 (dd, J = 7.2, 7.2 Hz, 2H), 7.32–7.18 (m, 12H), 6.99 (s, 1H), 6.92 (s, 1H), 6.88 (s, 1H), 6.37 (s, 1H), 5.14 (s, 2H), 5.07 (s, 2H), 4.80 (s, 2H), 4.43–4.32 (m, 1H), 4.28–4.15 (m, 1H), 4.11–3.97 (m, 1H), 3.88 (s, 3H), 3.82 (s, 3H), 3.26 (dd, J = 16.8, 5.6 Hz, 1H), 2.92 (dd, J = 16.8, 5.6 Hz, 1H), 0.81 (s, 9H), 0.08 (s, 3H), 0.03 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8, 152.4, 150.2, 144.8, 143.4, 137.4, 135.9, 134.1, 133.0, 131.9, 128.6, 128.5, 128.5, 128.4, 128.4, 128.3, 128.1, 127.9, 127.7, 127.6, 127.6, 127.3, 127.0, 125.6, 120.2, 113.8, 109.6, 108.2, 105.7, 94.2, 94.1, 71.5, 70.9, 70.6, 66.2, 55.9, 52.1, 33.6, 31.5, 25.6, 22.6, 17.9, 14.1, −4.8, −4.9 ppm; HRMS (FAB): m/z calcd for $C_{51}H_{53}N_3O_9Si$: 879.3551 $[M+H]^+$; found: 879.3554.

38: A flame-dried 100-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **37** (1.76 g, 2.00 mmol) and dry THF (20 mL). TBAF (1 M in THF, 2.10 mL, 2.10 mmol) was added to the solution, and the resulting mixture was stirred for 30 min, after which TLC (hexane/ethyl acetate = 1:1) indicated complete consumption of **37**. THF was removed under reduced pressure. The residue was dissolved in dry dichloromethane (20 mL) and pyridine (3.24 mL, 40.0 mmol). The resulting mixture was cooled to 0 °C, and MsCl (1.55 mL, 20.0 mmol) was added dropwise to the solution over 5 min. The reaction mixture was stirred at room temperature for 4 h, after which TLC (hexane/ethyl acetate = 1:3) indicated complete consumption of the secondary alcohol. The mixture was diluted with ethyl acetate and washed with hydrochloric acid (1 M), aqueous sodium bicarbonate, and brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by silica-gel chromatography (hexane/ethyl acetate/dichloromethane = 2:1:2–1:1:2, gradient) to afford (−)-((8*S*)-4-benzyloxy-3-benzyloxycarbonyl-2-methoxycarbonyl-8,9-dihydro-8-(methanesulfonyloxy)pyrrolo[3,2-*f*]quinolin-6(7*H*)-yl)(5-benzyloxy-6-methoxy-1*H*-indol-2-yl)methanone (**38**; 1.64 g, 1.94 mmol, 97%) as a beige solid, which was recrystallized from hexane/dichloromethane to

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give colorless prisms. $R_f = 0.42$ (hexane/ethyl acetate = 1:3); m.p.: 189.9–190.8 °C (hexane/dichloromethane); $[\alpha]_D^{23} = -30.3$ ($c = 1.94$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3291$, 3030, 2947, 1771, 1716, 1605, 1517, 1385, 1308, 1239, 1172, 1023, 966, 891, 754, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 9.35$ (br s, 1H), 7.44 (d, $J = 7.2$ Hz, 2H), 7.34 (dd, $J = 7.2$ Hz, 2H), 7.30–7.15 (m, 12H), 6.93 (s, 1H), 6.83 (s, 1H), 6.78 (s, 1H), 6.23 (s, 1H), 5.43–5.37 (m, 1H), 5.11 (s, 2H), 5.07 (d, $J = 14.4$ Hz, 1H), 5.04 (d, $J = 14.4$ Hz, 1H), 4.78 (d, $J = 13.6$ Hz, 1H), 4.75 (d, $J = 13.6$ Hz, 1H), 4.67–4.57 (m, 1H), 4.04–3.96 (m, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.39 (dd, $J = 17.6$, 5.6 Hz, 1H), 3.29 (dd, $J = 17.6$, 3.6 Hz, 1H), 2.87 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.7$, 160.6, 152.2, 150.4, 144.9, 143.8, 137.1, 135.6, 133.9, 132.9, 132.1, 128.6, 128.5, 128.4, 128.3, 128.2, 127.9, 127.8, 127.6, 127.2, 126.5, 125.7, 120.0, 111.5, 109.1, 108.4, 106.2, 105.4, 94.0, 73.8, 71.3, 70.9, 70.7, 55.8, 52.2, 49.3, 38.3, 30.2 ppm; elemental analysis: calcd (%) for $C_{46}H_{41}N_3O_{11}S$: C 65.47, H 4.90, N 4.98; found: C 65.40, H 4.95, N 4.95.

39: A 50-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **38** (1.18 g, 1.40 mmol) and THF (21 mL). A solution of $LiOH \cdot H_2O$ (1.17 g, 28.0 mmol) in water (7.0 mL) was added to the resulting suspension. The suspension was stirred for 18 h at room temperature, after which TLC (methanol/chloroform = 1:9) indicated complete consumption of **38**. The reaction mixture was acidified with hydrochloric acid (1 M), and the aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give analytically pure (−)-(8*S*)-4-benzyloxy-6-(5-benzyloxy-6-methoxy-1*H*-indol-2-yl)carbonyl-6,7,8,9-tetrahydro-8-methanesulfonyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylic acid (**39**; 897.3 mg, 1.29 mmol, 92%) as a pale-yellow solid. $R_f = 0.18$ (methanol/chloroform = 1:9); $[\alpha]_D^{26} = -44$ ($c = 0.10$, $CHCl_3$); IR (neat): $\tilde{\nu} = 3288$, 2935, 1770, 1600, 1519, 1311, 1241, 1197, 1171, 905, 751, 697 cm^{-1}; ^1H NMR (500 MHz, [D$_6$]acetone): $\delta = 11.11$ (br s, 1H), 10.48 (br s, 1H), 7.41–7.18 (m, 9H), 7.06 (s, 2H), 6.79 (s, 1H), 6.32 (s, 1H), 5.48–5.41 (m, 1H), 5.05 (s, 2H), 4.94 (d, $J = 12.3$ Hz, 1H), 4.90 (d, $J = 12.3$ Hz, 1H), 4.59 (dd, $J = 13.8$, 4.0 Hz, 1H), 4.10 (dd, $J = 13.8$, 3.1 Hz, 1H), 3.84 (s, 3H), 3.56 (dd, $J = 18.3$, 6.1 Hz, 1H), 3.30 (dd, $J = 18.3$, 4.6 Hz, 1H), 3.09 ppm (s, 3H); ^{13}C NMR (125 MHz, [D$_6$]DMSO): $\delta = 163.3$, 162.5, 161.5, 152.3, 149.1, 144.3, 143.3, 142.8, 137.4, 136.8, 136.2, 134.2, 131.8, 128.4, 128.4, 128.3, 127.8, 127.7, 127.5, 127.1, 126.6, 119.5, 111.6, 106.7, 104.6, 94.5, 79.2, 75.1, 70.2, 55.5, 49.3, 37.7, 29.5 ppm; HRMS (FAB): *m*/*z* calcd for $C_{37}H_{33}N_3O_9S$: 695.1938 $[M]^+$; found: 695.1938.

40: A 50-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **39** (21.8 mg, 26.3 μmol), 10% Pd/C (5.6 mg, 5.3 μmol), and acetone (1.0 mL). The resulting suspension was charged with H_2 gas (1 atm). The resulting suspension was stirred for 10 h at room temperature, after which TLC (methanol/chloroform = 1:9) indicated complete consumption of **39**. The reaction mixture was diluted with MeOH and filtered through a celite pad. The filtrate was concentrated under reduced pressure to give analytically pure (8*S*)-4-hydroxy-6-(5-hydroxy-6-methoxy-1*H*-indol-2-yl)carbonyl-6,7,8,9-tetrahydro-8-methanesulfonyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-carboxylic acid (**40**; 12.8 mg, 24.8 μmol, 94%) as a pale-yellow solid, which was used in the next coupling reaction without further purification.

43: A flame-dried 100-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **7** (742.8 mg, 1.48 mmol) and dry THF (12.4 mL). TBAF (1 M THF solution, 1.61 mL, 1.61 mmol) was added dropwise to the resulting mixture over 5 min. The reaction mixture was stirred for 30 min, after which TLC (hexane/ethyl acetate = 1:1) indicated complete removal of the Fmoc group. WSCD·HCl (1.19 g, 6.20 mmol), **39** (860.4 mg, 1.24 mmol), and HOBt (379.8 mg, 2.48 mmol) were added to the reaction mixture. The mixture was stirred vigorously at room temperature for 2 h, after which TLC (methanol/chloroform = 1:9) indicated complete consumption of the unprotected left segment **42**. The reaction mixture was diluted with chloroform (25 mL) and passed through a silica pad (THF/chloroform = 1:2) to afford (−)-methyl 3-((8*S*)-4-benzyloxy-6-(5-benzyloxy-6-methoxy-1*H*-indol-2-yl)carbonyl-6,7,8,9-tetrahydro-8-methanesulfonyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-yl)carbonyl-4-hydroxy-5-methoxy-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-thiocarboxylate (**43**; 1.15 g, 1.19 mmol, 96%) as a yellow powder. $R_f = 0.61$ (methanol/chloroform = 1:9); $[\alpha]_D^{24} = -120$ ($c = 0.38$, DMF); IR (neat): $\tilde{\nu} = 3312$, 2929, 1607, 1512, 1303, 1235, 900, 867, 797, 726, 694, 526 cm^{-1}; ^1H NMR (500 MHz, [D$_7$]DMF): $\delta = 12.07$ (br s, 1H), 11.98 (br s, 1H), 11.38 (br s, 1H), 11.19 (s, 1H), 7.51 (d, $J = 7.2$ Hz, 2H), 7.48–7.42 (m, 2H), 7.41–7.35 (m, 2H), 7.34–7.25 (m, 6H), 7.16 (s, 1H), 7.11 (s, 1H), 6.88 (s, 1H), 6.48 (s, 1H), 5.47–5.40 (m, 1H), 5.08 (s, 2H), 5.02 (d, $J = 12.3$ Hz, 1H), 4.98 (d, $J = 12.3$ Hz, 1H), 4.90–4.83 (m, 2H), 4.70 (dd, $J = 13.0$, 3.3 Hz, 1H), 4.17 (d, $J = 12.2$ Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 3.64 (dd, $J = 17.6$, 6.2 Hz, 1H), 3.45 (t, $J = 8.0$ Hz, 2H), 3.36 (dd, $J = 17.6$, 3.4 Hz, 1H), 3.25 (s, 3H), 2.47 ppm (s, 3H); ^{13}C NMR (125 MHz, [D$_7$]DMF): $\delta = 183.1$, 164.0, 161.8, 150.5, 145.6, 144.4, 140.4, 138.7, 137.7, 135.6, 134.3, 133.1, 133.0, 132.6, 131.2, 130.3, 129.1, 129.0, 128.9, 128.8, 128.4, 128.3, 128.23, 128.15, 127.1, 126.4, 122.8, 120.9, 118.5, 112.1, 107.5, 106.7, 105.9, 105.5, 95.6, 76.4, 71.6, 70.8, 64.2, 60.7, 56.1, 54.3, 49.9, 38.1, 28.3, 10.9 ppm; HRMS (FAB): *m*/*z* calcd for $C_{50}H_{46}N_5O_{11}S_2$: 956.2635 $[M+H]^+$; found: 956.2673.

5: A flame-dried 100-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with **43** (480.8 mg, 0.496 mmol), pentamethylbenzene (735.3 mg, 4.96 mmol), and dry dichloromethane (24.8 mL). The solution was cooled to −78 °C. BCl_3 (1.0 M in dichloromethane, 1.98 mL, 1.98 mmol) was added dropwise to the solution over 5 min. The resulting mixture was stirred vigorously at −78 °C for 15 min, after which TLC (methanol/chloroform = 1:9) indicated complete consumption of **43**. The excess BCl_3 was removed with 10% MeOH/$CHCl_3$ at −78 °C. The reaction mixture was purified by silica-gel chromatography (methanol/chloroform = 1:9) to give (−)-methyl 3-((8*S*)-4-hydroxy-6-(5-hydroxy-6-methoxy-1*H*-indol-2-yl)carbonyl-6,7,8,9-tetrahydro-8-methanesulfonyloxy-3*H*-pyrrolo[3,2-*f*]quinoline-2-yl)carbonyl-4-hydroxy-5-methoxy-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-thiocarboxylate (**5**; 320.1 mg, 0.413 mmol, 83%) as a fine yellow powder. $R_f = 0.46$ (methanol/chloroform = 1:9); $[\alpha]_D^{24} = -100$ ($c = 0.18$, DMF); IR (neat): $\tilde{\nu} = 3334$, 2929, 1634, 1523, 1505, 1437, 1315, 1232, 1197, 1172, 1119, 1019, 871, 755, 529 cm^{-1}; ^1H NMR (500 MHz, [D$_7$]DMF): $\delta = 12.04$ (br s, 1H), 11.53 (br s, 1H), 11.31 (s, 1H), 11.25 (br s, 1H), 9.87 (s, 1H), 8.48 (s, 1H), 7.47 (d, $J = 2.3$ Hz, 1H), 7.34 (d, $J = 2.3$ Hz, 1H), 7.02 (s, 1H), 6.89 (s, 1H), 6.64 (s, 1H), 6.37 (s, 1H), 5.52–5.47 (m, 1H), 4.89–4.85 (m, 2H), 4.60 (d, $J = 14.2$ Hz, 1H), 4.13 (d, $J = 14.2$ Hz, 1H), 3.95 (s, 3H), 3.85 (s, 3H), 3.61 (dd, $J = 18.0$, 6.2 Hz, 1H), 3.5 (2H; obscured by signals of water), 3.32 (dd, $J = 18.0$, 4.2 Hz, 1H), 3.24 (s, 3H), 2.47 ppm (s, 3H); ^{13}C NMR (125 MHz, [D$_7$]DMF): $\delta = 183.1$, 149.0, 143.8, 142.5, 140.5, 135.6, 134.2, 133.2, 133.1, 132.2, 130.5, 130.0, 129.6, 128.9, 128.8, 128.7, 125.9, 122.9, 121.4, 118.5, 110.3, 107.7, 107.6, 107.0, 107.0, 105.6, 94.9, 79.8, 76.7, 60.7, 56.1, 54.1, 49.8, 38.1, 28.3, 10.9 ppm; HRMS (FAB): *m*/*z* calcd for $C_{36}H_{33}N_5O_{11}S_2$: 775.1618 $[M]^+$; found: 775.1617.

1: A 500-mL round-bottomed flask equipped with a magnetic stirrer bar was charged with sodium bicarbonate (1.79 g, 21.3 mmol) and water (11.8 mL). A solution of **5** (550.8 mg, 0.710 mmol) in DMF (23.7 mL) was added to the aqueous sodium bicarbonate. The resulting mixture was stirred vigorously at room temperature for 2 h, after which TLC (methanol/chloroform = 1:9) indicated complete consumption of **5**. The reaction mixture was acidified with AcOH (2.44 mL) and dried under reduced pressure. The residue was purified by silica-gel chromatography (methanol/chloroform = 10:90–15:85, gradient) to afford (+)-yatakemycin (**1**; 453.8 mg, 0.669 mmol, 94%) as a fine pale-yellow powder. $R_f = 0.45$ (methanol/chloroform = 1:9); $[\alpha]_D^{23} = +99$ ($c = 0.060$, DMF); IR (neat): $\tilde{\nu} = 3312$, 2925, 2852, 1633, 1505, 1386, 1290, 1256, 1017, 870, 750 cm^{-1}; ^1H NMR (500 MHz, [D$_5$]pyridine): $\delta = 14.65$ (br s, 1H), 13.72 (s, 1H), 12.74 (s, 1H), 11.71 (s, 1H), 10.71 (br s, 1H), 7.73 (s, 1H), 7.64 (s, 1H), 7.52 (d, $J = 2.0$ Hz, 1H), 7.24 (s, 1H), 6.74 (s, 1H), 4.54–4.42 (m, 4H), 4.03 (s, 3H), 3.85 (s, 3H), 3.23 (t, $J = 8.1$ Hz, 2H), 2.98 (dd, $J = 7.6$, 4.8 Hz, 1H), 2.49 (s, 3H), 1.77 (dd, $J = 7.7$, 3.8 Hz, 1H), 1.45 ppm (t, $J = 4.8$ Hz, 1H); ^{13}C NMR (125 MHz, [D$_5$]pyridine): $\delta = 183.5$, 178.5, 161.9, 161.9, 161.3, 150.4, 144.8, 140.5, 136.0, 134.5, 133.4, 133.1, 132.7, 130.5, 130.3, 129.2, 128.9, 122.4, 122.0, 118.6, 112.9, 107.8, 107.7, 107.6, 106.6, 94.4, 60.5, 55.9, 55.6, 53.9, 31.5, 28.2, 26.1, 24.0, 11.2 ppm; HRMS (FAB): *m*/*z* calcd for $C_{35}H_{30}N_5O_8S$: 680.1838 $[M+H]^+$; found: 680.1815.

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