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Total synthesis of tryprostatins A and B

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ABSTRACT

Three distinct synthetic routes to the 2-prenyl tryptophan core skeleton of tryprostatins and their total syntheses are described. The strategies include a traditional gramine-mediated coupling reaction, Fürstner indole synthesis, and our radical-mediated indole synthesis from *o*-alkenylphenyl isocyanide. The establishment of reliable conditions for the radical-mediated construction of indoles via a low-temperature radical initiator V-70 (2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile)) led to the highly efficient syntheses of tryprostatins A and B.

1. Introduction

In cancer chemotherapy, multiple drug resistance to cell cycle inhibitors often becomes a serious obstacle. One strategy to circumvent this problem is to develop antimitotic agents that operate by a new mode of action. Tryprostatins A (**1**) and B (**2**), which belong to this promising category, were isolated in 1995 from the fermentation broth of Aspergillus fumigatus BM939 by Osada et al. (Fig. 1).[1] Tryprostatin A seems to have a greater potential because it selectively arrests the cell cycle at the M phase in tsFT210 cells.[2] Interesting biological activities along with seemingly simple structures have stimulated the synthetic community, and several total syntheses of **1** and **2** have already been reported to date.[3,4] Due to our strong interest in the structural features of tryprostatins as well as the therapeutic potential of their analogues recently suggested in the SAR study[4e] by Cook et al., we launched a research program towards the total synthesis of tryprostatins.

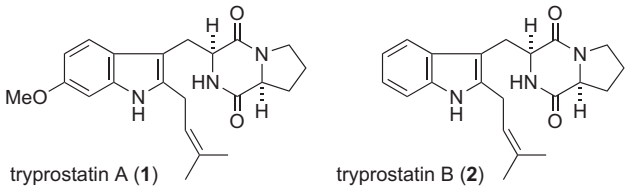
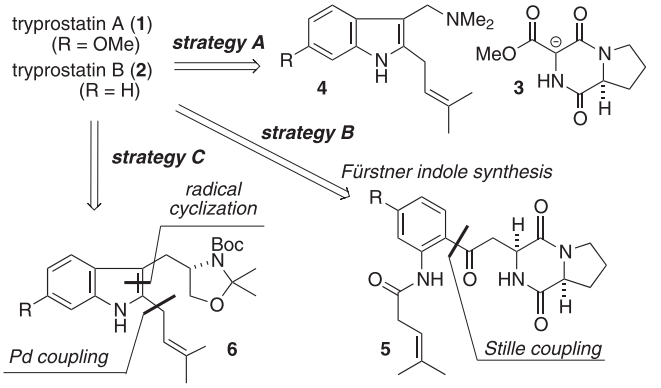


Fig. 1. Tryprostatins A and B.

2. Results and discussion

Scheme 1 summarizes our plans for the synthesis of tryprostatins. We initially envisioned that the introduction of diketopiperazine moiety **3** to 2-prenyl gramine intermediate **4** (strategy A). The chemistry of gramine has been repeatedly applied to the total synthesis of natural products containing a tryptophan substructure, including sporidesmin and brevianamide, for example.[5] Although this strategy promises a highly convergent synthesis, one drawback



Scheme 1. Retrosynthetic analysis for tryprostatins A and B.

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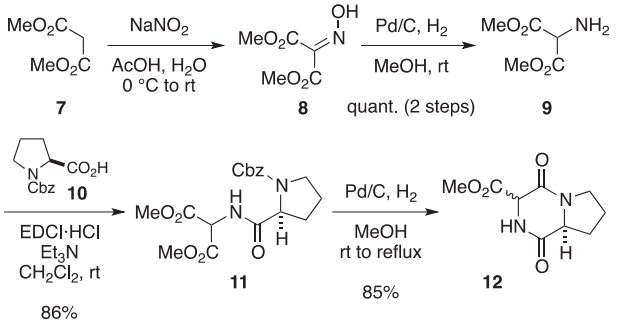
may be the generation of a mixture of stereoisomers at the newly generated stereocenter where the two units join.

Due to the uncertainty in the stereoselective transformation using strategy A, we also planned two complementary strategies that do not involve the stereochemical complications. In an attempt to construct the unstable 2,3-disubstituted indole moiety in the late stage of the synthesis, Fürstner indole synthesis[6] is to be employed (strategy B). Intermediate **5** would be readily accessible by a Stille-type coupling reaction between an arylstannane and an acid chloride. Because the synthesis of 2-prenylindole via the Fürstner protocol is unprecedented, it is not clear whether or not the reductive formation of the indole core would proceed with the prenyl group intact. The other strategy involves a radical-mediated construction of the indole core structure and a subsequent palladium-mediated coupling reaction between the 2-stannyl intermediate and the prenyl group donor to give intermediate **6**, which is also without precedent (strategy C).

2.1. Synthesis based on strategy A

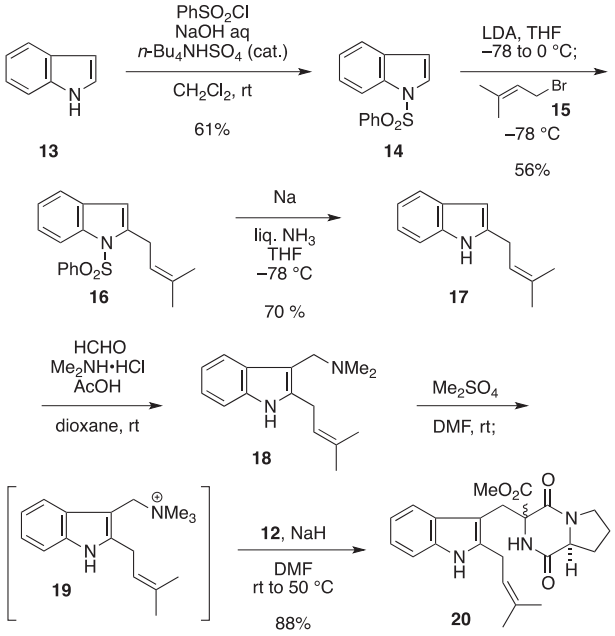
The synthesis via the strategy A began with the construction of diketopiperazine core unit **12**. Following a reported procedure,[5b,7] the nitrosation reaction of dimethyl malonate **7** with sodium nitrite under acidic conditions gave oxime **8** (Scheme 2). Primary amine **9**, obtained upon hydrogenation of the oxime, was coupled with *N*-Cbz-L-proline **10** by treatment with EDCI to afford **11** in 86% yield. Removal of the Cbz group was performed by hydrogenolysis and subsequent heating in methanol caused cyclization to provide diketopiperazine core structure **12** in 85% yield as a mixture of two diastereomers.



Scheme 2. Synthesis of the diketopiperazine unit.

Synthesis of the gramine unit, a coupling partner of **12**, began with the introduction of the prenyl group on the C2 of indole according to the report by Wenkert[8] (Scheme 3). Thus, indole **13** was activated with a benzenesulfonyl group on its nitrogen atom under phase transfer reaction conditions with benzenesulfonyl chloride. Directed lithiation at C2 of **14** with LDA followed by addition of prenyl bromide **15** afforded the 2-prenylindole core structure **16**. Removal of the benzenesulfonyl group was effected under the Birch reduction conditions to provide deprotected indole **17**. Transformation to gramine was then carried out by the Mannich reaction with formalin and dimethylamine in the presence of AcOH to give **18**. After rapid preparation of the two coupling units, condensation of these two units was carried out according to the well-known chemistry of gramine.[5] Highly reactive ammonium ion intermediate **19** was generated in situ by treatment with dimethyl sulfate, and was subsequently treated with the sodium enolate of diketopiperazine **12**, leading to the formation of a 1:2 mixture of the two diastereomers **20**.

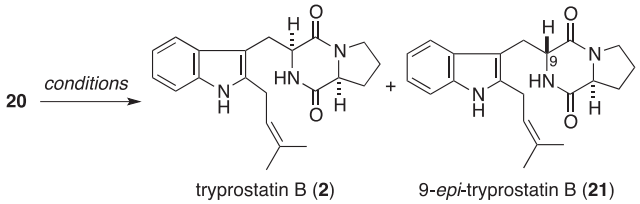
Since **20** possesses the entire carbon skeleton of tryprostatin B (**2**), all that remained was to remove the carbomethoxy group to complete the total synthesis. As either enolate or enol species is the



Scheme 3. Coupling reaction via activated gramine.

short-lived product of the decarboxylation, the facial selectivity of the protonation determines the product distribution. Table 1 shows the ratio between **2** and 9-*epi*-tryprostatin B (**21**) under different conditions. Conventional alkaline hydrolysis of the methyl ester and the subsequent decarboxylation reaction in dioxane gave twice the amount of 9-epimer **21** to desired product **2** in a combined yield of 66% (entry 1). In an effort to improve the ratio for the desired isomer, decarbomethoxylation reactions under different conditions were performed. Lithium iodide in 2,4,6-collidine did not give the desired products (entry 2). On the other hand, Krapcho decarbomethoxylation[9] and its modification gave better results. Treatment with NaCN gave more of the 9-epimer (entry 3), and the ratio of the desired isomer increased upon changing the salt to $MgCl_2$ or NaCl (entries 4 and 5). The ratio was reversed (**2**/**21**=6:5) by employing LiCl, and the yield improved to 86% combined yield (entry 6). Hence, an efficient total synthesis of tryprostatin B (**2**) was achieved.

Table 1
Total synthesis of tryprostatin B

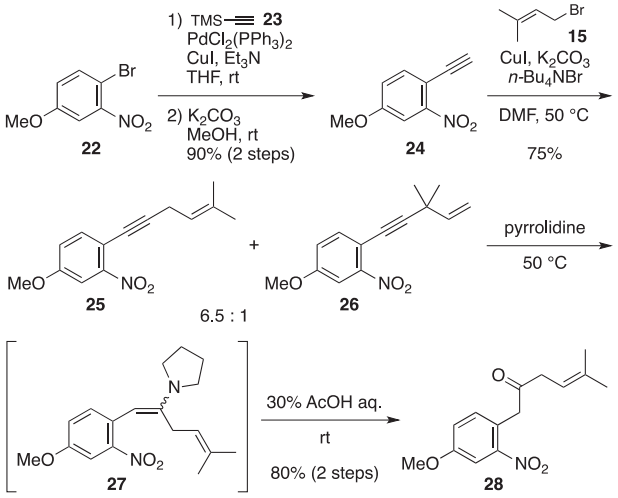


Entry	Conditions	**2**/**21**	Yield[a] (%)
1	(1) NaOH, MeOH, rt, (2) dioxane, reflux	1:2	66
2	LiI, collidine, 90 °C	—	Decomp.
3	NaCN, H_2O, DMSO, 140 °C	1:6	51
4	$MgCl_2 \cdot 6H_2O$, DMSO, 140 °C	1:3	71
5	NaCl, H_2O, DMSO, 180 °C	1:1	14
6	LiCl, H_2O, DMSO, 140 °C	6:5	86

[a] Isolated yield.

Next, we embarked on the synthesis of tryprostatin A (**1**) following closely the strategy used for the total synthesis of **2**. Since 6-methoxyindole is relatively expensive, we decided to synthesize the prenylated indole **29** in a different way. The Sonogashira coupling reaction between 1-bromo-4-methoxy-2-nitrobenzene **22** and

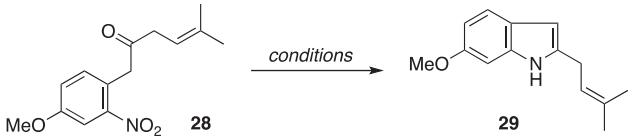
trimethylsilylacetylene **23** followed by methanolysis gave **24** in 90% yield (Scheme 4). Introduction of the prenyl moiety failed with the reaction between prenyl bromide and the lithium acetylide derived from **24** due to the lability of the product under the reaction conditions. Hence, a copper-mediated coupling reaction was employed.[10] The reaction proceeded to afford the coupling product, albeit as an inseparable 6.5:1 mixture of the regioisomers **25** and **26**. The indole structure was subsequently constructed according to the method we reported previously.[11] A mixture of adducts **25** and **26** was directly dissolved in pyrrolidine and heated to 50 °C. While the minor isomer **26** remained unchanged during the reaction, **25** was transformed into enamine intermediate **27**. The enamine **27** was subsequently subjected to acid hydrolysis to afford the ketone **28**.



Scheme 4. Construction of the indole precursor.

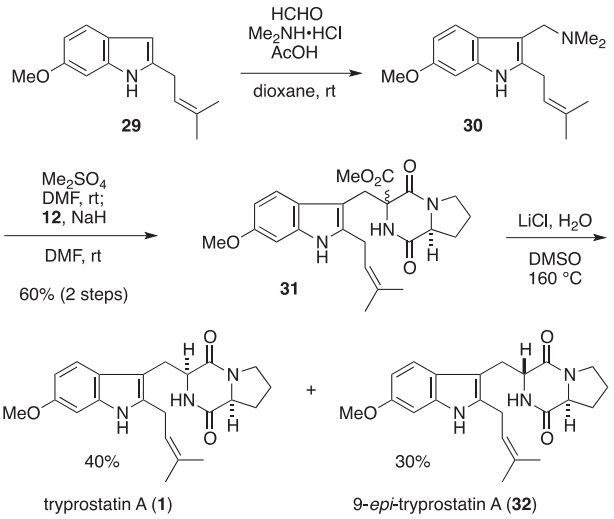
The remaining task was to reduce the nitro group in **28** without affecting the olefin moiety in the prenyl group (Table 2). Reduction with iron or tin(II) chloride led to the extensive decomposition of the starting material (entries 1 and 2). Hydrogenation over Lindlar catalyst gave a compound with the prenyl group reduced to saturation (entry 3). Only a small quantity (1%) of the desired product was obtained when sodium dithionite was used as a reductant (entry 4). However, a zinc-mediated reduction, especially with TFA as an acid, gave **29** in acceptable yield. With the desired 2-prenylindole **29** in hand, transformation to **1** was carried out along the lines developed in our earlier synthesis of **2** (Scheme 5). Thus, **29** was converted into gramine intermediate **30** by the Mannich reaction, and the product was coupled with the carbanion derived from diketopiperazine **12** via an ammonium intermediate to give **31** in 60% yield in two steps. A decarbomethoxylation

Table 2
Construction of the 2-prenylindole moiety



Entry	Conditions	Yield (%)
1	Fe, $FeCl_2$, EtOH, reflux	0[a]
2	$SnCl_2 \cdot 2H_2O$, EtOH, rt	0[a]
3	Lindlar cat., H_2, MeOH, rt	0[b]
4	$Na_2S_2O_4$, K_2CO_3, H_2O/DMF, rt	1
5	Zn, AcOH, rt	29
6	Zn, TFA, CH_2Cl_2, rt	59

[a] Starting material decomposed.
[b] Olefin moiety was reduced.

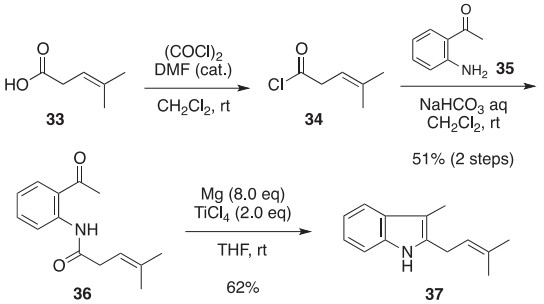


Scheme 5. Total synthesis of tryprostatin A (**1**).

reaction using lithium chloride in aq DMSO gave a 4:3 mixture of **1** and 9-epimer **32** in 70% yield. The low selectivity of the last step notwithstanding, the syntheses of tryprostatins A (**1**), and B (**2**) constitute a convergent synthetic route to these natural products.

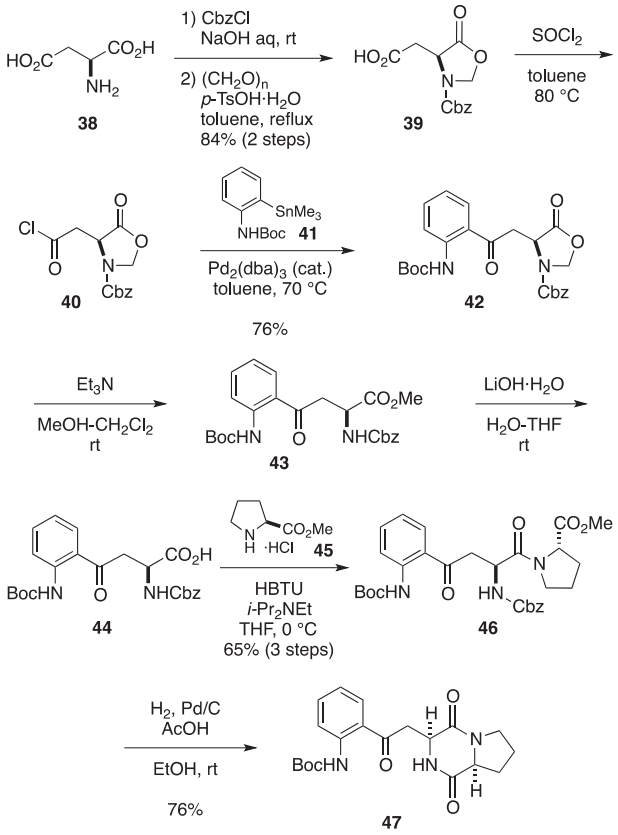
2.2. Synthesis based on strategy B

In pursuit of a more convergent synthetic route, we examined the process involving Fürstner indole synthesis[6] as a key step. Synthesis of 3-methyl-2-prenylindole **37** was initially examined to explore the feasibility of this reaction to construct the 2-prenylindole structure. 4-Methyl-3-pentenoic acid (**33**) was converted into the corresponding acid chloride **34**,[12] which was coupled with 2-amino acetophenone **35** under biphasic reaction conditions to afford **36** in 51% yield (Scheme 6). Fürstner indole synthesis was then applied to this system to evaluate whether or not the prenyl group survives. To our delight, the reductive coupling reaction proceeded via a combination of $TiCl_4$ and magnesium metal, affording **37** without any sign of isomerization or decomposition of the olefin moiety. Next, we examined the applicability of this reaction to the synthesis of tryprostatin B.



Scheme 6. Fürstner indole synthesis.

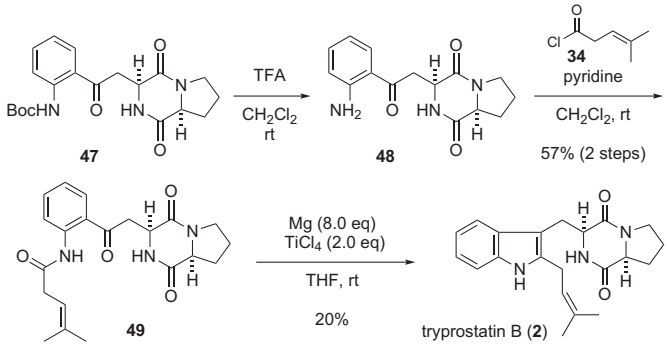
Aryl ketone **42** was synthesized according to Salituro's procedure[13] (Scheme 7). L-Aspartic acid **38** was protected with a Cbz group and the α-amino acid moiety was protected as the methylene acetal in 84% yield under Dean–Stark conditions. The acid chloride **40** derived from **39** was coupled with stannyl aniline **41** under the conditions of the Stille coupling to give aryl ketone **42**. We decided to assemble the diketopiperazine core before the formation of the unstable 2,3-indole moiety. Since alkaline hydrolysis of the lactone **42** with LiOH led to decomposition, an alternative two-step procedure, involving triethylamine-mediated methanolysis and subsequent hydrolysis of methyl ester **43**, was employed. The



Scheme 7. Construction of the 2-aminoaryl ketone.

carboxylic acid **44** thus obtained was then subjected to an HBTU-mediated condensation with L-proline methyl ester hydrochloride **45** to afford amide **46** in 65% yield in three steps from **42**. Hydrogenolysis of the Cbz group in **46** was accelerated by addition of AcOH with a concomitant cyclization to give the diketopiperazine **47** in 76% yield.

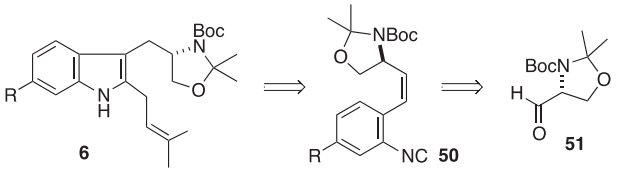
With the diketopiperazine moiety assembled, we next proceeded to examine whether the Fürstner indole synthesis would be applicable to the total synthesis of tryprostatin B. Deprotection of the aniline group followed by acylation gave amide **49** in moderate yield due to the poor reactivity of aniline **48** (Scheme 8). When keto amide **49** was subjected to the same conditions used for **36**, tryprostatin B **2** was obtained albeit in very low yield (20%). The poor results might be attributable to the decomposition of the prenyl group and the 2,3-disubstituted indole skeleton as well as the undesired participation of the diketopiperazine moiety. Because of the difficulties in optimizing the reaction conditions, we decided to pursue an alternative strategy.



Scheme 8. Total synthesis of tryprostatin B.

2.3. Synthesis based on strategy C[14]

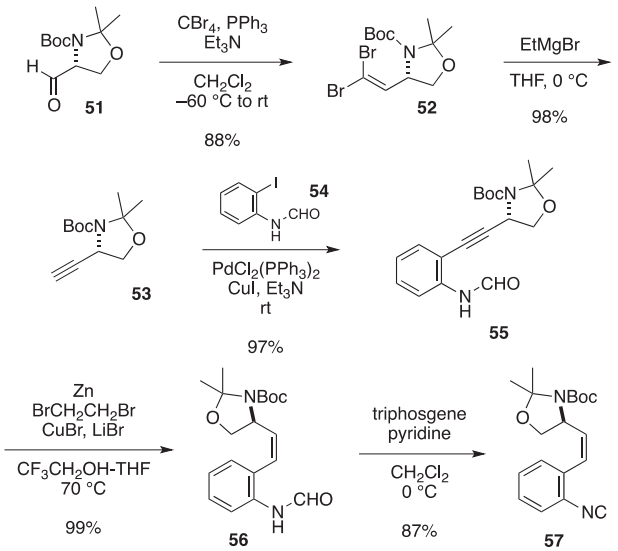
Our laboratory has long been engaged in the radical-mediated construction of indoles and the application of our methods to total synthesis of natural products.[15,16] We thus envisioned that our method could be applied to the synthesis of the 2,3-disubstituted indole moiety of tryprostatins. As observed in our model studies, the thioamide-based indole synthesis cannot be applied to this case simply because of the undesired intramolecular radical attack to the 2-prenyl group of the intermediate indole. Accordingly, we decided to employ our isocyanide-based indole synthesis (Scheme 9). Radical cyclization and subsequent palladium-mediated coupling with a prenyl group donor would enable the facile construction of 2,3-disubstituted indole **6**. The requisite *ortho*-alkenyl isocyanide **50** would be prepared from Garner's aldehyde **51**,[17] which contains a latent amino acid unit to be used for construction of the diketopiperazine at the late stage.



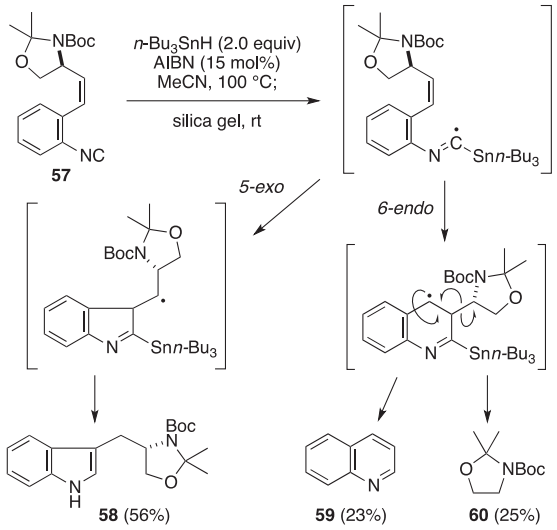
Scheme 9. Retrosynthesis.

Initially, we focused our efforts on the synthesis of isocyanide **57** as a radical cyclization precursor (Scheme 10). Alkyne **53** was prepared from **51** via dibromo olefin **52** using a slight modification of the known protocol.[18] After Sonogashira coupling between **53** and 2-iodoformanilide **54**, partial reduction of the triple bond in **55** was examined. While the use of Lindlar's catalyst, Pd/C, nickel boride,[19] or diimide[20] resulted in no reaction or an overreduction, treatment with Zn/$LiCuBr_2$ in ethanol[21] gave the desired olefin **56** along with the corresponding deformylated amine. Use of 2,2,2-trifluoroethanol[22] as a solvent could suppress the undesired solvolysis, resulted in improvement of the yield of **56** to as high as 99%. Subsequent dehydration with triphosgene gave *ortho*-alkenyl isocyanide **57**, which set the stage for the radical-mediated cyclization.

When isocyanide **57** was subjected to the radical cyclization conditions[15a] established in our laboratories, the desired 5-*exo* adduct **58** was obtained in moderate yield along with a considerable amount of 6-*endo* cyclization-cleavage adduct, **59** and **60**, after acidic treatment with silica gel (Scheme 11). The imidoyl radical cyclization tended to form a mixture of 5-*exo* and 6-*endo* products



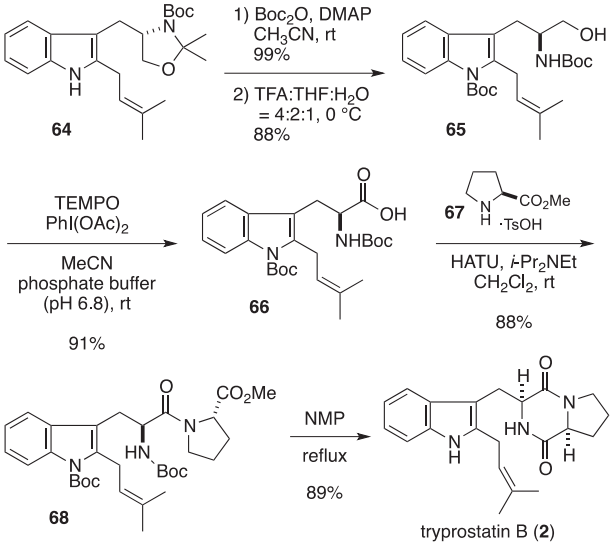
Scheme 10. Synthesis of *o*-alkenyl isocyanide.



Scheme 11. Attempted radical cyclization.

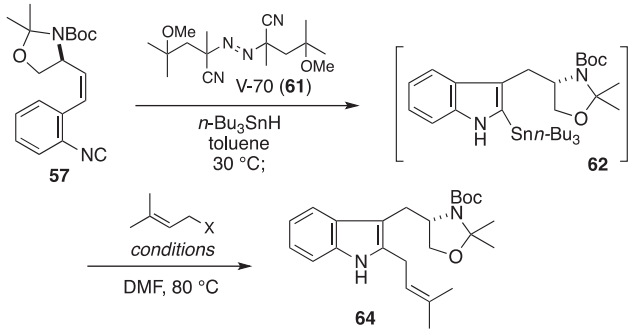
when the intermediate radical of 5-*exo* cyclization was not stabilized by the neighboring substituents.[16] Although our previous studies showed that the 5-*exo* cyclization is dominant under kinetically controlled conditions,[15e] generally applicable conditions for the formation of 2-stannylindole have yet to be established. In an attempt to lower the reaction temperature, V-70 (2,2′-azobis(4-methoxy-2,4-dimethyl valeronitrile)) **61**[23] was employed as a radical initiator, which is known to decompose at lower temperature than AIBN. Fortunately, the radical cyclization of isocyanide **57** initiated by V-70 virtually suppressed the formation of the 6-*endo* adduct. Moreover, it showed complete selectivity for the cyclization of the imidoyl radical, giving 2-stannylindole **62** as the sole product (Table 3). Although we have already reported a one-pot Stille-type coupling reaction between aromatic or vinylic halides and 2-stannylindole generated in situ to prepare 2,3-disubstituted indoles,[15a] coupling reactions with allylic systems have yet to be examined. Table 3 shows the results of the optimization of the palladium-mediated coupling reaction. When 2-prenyl bromide (**15**) was used as the prenyl source, the desired product was not observed (entry 1). Whereas the coupling partner was changed to 2-prenyl acetate **63**, the desired product was obtained with $Pd(PPh_3)_4$ as a catalyst, albeit in 29% yield (entry 2). Further investigations revealed that the combination of $Pd_2(dba)_3$, ligand, and lithium chloride gave the best results (entries 3 and 4). Using triphenylarsine as a ligand, the desired product **64** was obtained in 73% yield in a one-pot process from isocyanide **57**.

Once construction of the indole moiety was complete, **64** was converted into the corresponding amino acid **66** in a three-step sequence consisting of protection of the indole with a Boc group, hydrolysis of the acetonide, and TEMPO oxidation of the resulting alcohol **65** into carboxylic acid **66** (Scheme 12). After condensation with L-proline methyl ester hydrotosylate **67**, the remaining transformation involved the removal of the two Boc groups in **68** and cyclization to construct the diketopiperazine core. Unexpectedly, the conventional method to remove the Boc groups under acidic conditions caused substantial decomposition of the substrate. Thus, thermal removal of the Boc groups was attempted.[24] After optimization, this transformation was best accomplished by heating the substrate under reflux in *N*-methyl pyrrolidinone. Under these conditions, spontaneous cyclization gave **2** in 89% yield. Hence, we have established a 11-step synthetic route for tryprostatin B from **51** with a 33% overall yield on a half gram scale.



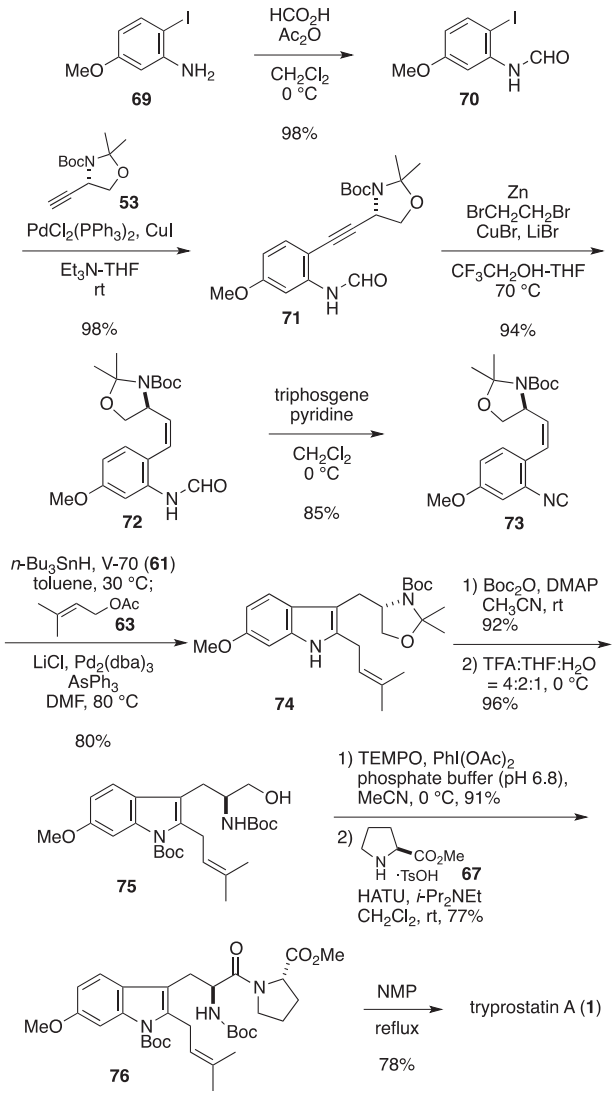
Scheme 12. Total synthesis of tryprostatin B.

Table 3
Construction of 2-prenylindole



Entry	X (3.0 equiv)	Catalyst (10 mol %)	Ligand (40 mol %)	Additive	Yield (%)
1	Br (**15**)	$Pd(PPh_3)_4$	—	Et_3N (10 equiv)	Trace
2	OAc (**63**)	$Pd(PPh_3)_4$	—	LiCl (3.0 equiv)	29
3	OAc (**63**)	$Pd_2(dba)_3$	P(*o*-furyl)$_3$	LiCl (3.0 equiv)	45
4	OAc (**63**)	$Pd_2(dba)_3$	$AsPh_3$	LiCl (3.0 equiv)	73

After establishing a generally applicable method to prepare 2-stannylindoles using V-70, we initiated the total synthesis of tryprostatin A (**1**) to showcase the synthetic utility of the protocol (Scheme 13). The synthesis commenced by preparing **69** from 4-methoxy-2-nitroaniline in a two step, slightly modified sequence, including the Sandmeyer reaction, iron-mediated reduction.[4c] Following the route established for tryprostatin B, tryprostatin A (**1**) was synthesized in 30% overall yield from **69** on a half gram scale.



Scheme 13. Total synthesis of tryprostatin A.

3. Conclusion

We have established three synthetic routes to the core structure of tryprostatins. The first strategy confirmed the efficiency of a gramine-mediated coupling reaction to construct a tryptophan skeleton. However, the stereoselectivity was low in regard to the junction between the diketopiperazine and the 2-substituted indole. In addition, we have shown that the Fürstner indole synthesis could be applied to the synthesis of 2-prenyl-3-substituted indole system. Unfortunately, we were unable to improve the yield of tryprostatin B through this route. Finally, we employed our radical-mediated indole synthesis as the key reaction. Optimization of the reaction conditions by means of V-70 allowed a facile synthesis of 2-stannyl-3-substituted indoles where the substituents at C3 could not effectively stabilize the incipient radical. In combination with an ensuing palladium-mediated coupling reaction at C2, a variety of 2,3-disubstituted indoles, such as tryprostatins A and B, can now be prepared. Further investigations into the synthesis and biological assay of tryprostatin analogues are currently underway.

4. Experimental section

4.1. General

All non-aqueous reactions were carried out under an inert atmosphere of argon in oven-dried glassware unless otherwise noted. Dehydrated diethyl ether, tetrahydrofuran, methylene chloride and toluene were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Dehydrated *N*,*N*-dimethylformamide, 1,4-dioxane, and dimethylsulfoxide were purchased from Kanto Chemicals Co., Inc. and stored over activated MS4A. Dehydrated methanol, ethanol and acetonitrile were also purchased from Kanto Chemicals Co., Inc. and stored over activated MS3A. *N*-methyl pyrrolidinone was purchased from Tokyo Chemical Industry Co., Ltd. and distilled before use. V-70 was purchased from Wako Pure Chemical Industries, Ltd. All other reagents were commercially available and used without further purification. Analytical thin layer chromatography (TLC) was performed on Merck precoated analytical plates, 0.25 mm thick, silica gel $60F_{254}$. Preparative flash chromatography was performed using Silica Gel 60 (spherical, 40–100 μm) purchased from Kanto Chemical Co., Inc. Preparative reverse-phase flash chromatography was performed using Cosmosil $75C_{18}$-PREP purchased from Nacalai Tesque Inc. ^1H and ^{13}C NMR were recorded on a JEOL LA-400 spectrometer. All ^1H NMR spectra are reported in δ units, parts per million (ppm) downfield from tetramethylsilane as the internal standard and coupling constants are indicated in hertz (Hz).The following abbreviations are used for spin multiplicity: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. All ^{13}C NMR spectra are reported in ppm relative to the central line of the triplet for $CDCl_3$ at 77.0 ppm. Infrared spectra (IR) were recorded on a JASCO FT/IR-410 Fourier Transform Infrared Spectrophotometer, and are reported in wavenumbers (cm^{-1}). High resolution mass spectra (HRMS) were obtained on a JEOL JMS-GCmate MS-DIP20 or on a JEOL JMS-T100LP AccuTOF LC-plus either in positive electrospray ionization (ESI) method or in positive direct analysis in real time (DART) ionization method, using PEG as the internal standard. Optical rotations were measured on a JASCO DIP-1000 Digital Polarimeter at room temperature, using the sodium D line. Melting points, determined on a Yanaco Micro Melting Point Apparatus, are uncorrected.

*4.1.1. (8aS)-Methyl 3-((2-(3-methylbut-2-en-1-yl)-1H-indol-3-yl) methyl)-1,4-dioxooctahydropyrrolo[1,2-a]pyrazine-3-carboxylate (**20**).* To a solution of 2-prenylindole **17** (372 mg, 2.01 mmol) in dioxane (8.0 mL) were added formalin (210 μL, 2.8 mmol), dimethylamine hydrochloride (245 mg, 3.02 mmol), and acetic acid (950 μL, 16.6 mmol). The reaction mixture was stirred for 1 h at room temperature before the reaction was quenched with saturated aq $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give **18**. The residue was used in the next reaction without further purification. To a stirred solution of **12** (405 mg, 1.91 mmol) in DMF (4.0 mL) was added NaH (60% in mineral oil, 83 mg, 2.0 mmol) followed by crude **18**, which was pretreated with dimethyl sulfate (220 μL, 2.3 mmol) in DMF (4.0 mL) at room temperature for 5 min. The mixture was stirred for 1 h at room temperature and then heated for 1 h at 50 °C under an argon before the reaction was quenched with saturated aq NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic extracts were

washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (60% EtOAc in *n*-hexane) to afford **20** (691 mg, 88%) as a yellow foam. The ratio between less polar isomer and more polar isomer was 1:2. *Less polar isomer*: $[\alpha]_D^{24}$ −2.9 (*c* 0.54, $CHCl_3$); IR (film, cm^{-1}) 3350, 2956, 1741, 1678, 1433, 1213; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.04 (1H, br s), 7.41 (1H, d, *J*=8.0 Hz), 7.30 (1H, dd, *J*=8.0, 6.4 Hz), 7.13–7.07 (2H, m), 6.02 (1H, s), 5.28 (1H, t, *J*=7.2 Hz), 4.03–3.99 (2H, m), 3.80 (3H, s), 3.68–3.58 (2H, m), 3.51–3.36 (3H, m), 2.40–2.33 (1H, m), 2.05–2.01 (2H, m), 1.91–1.87 (1H, m), 1.79 (3H, s), 1.75 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 169.3, 162.4, 137.3, 135.7, 135.4, 128.5, 121.9, 120.2, 119.5, 118.0, 110.7, 102.3, 66.5, 59.2, 53.7, 46.3, 29.4, 28.7, 25.7, 25.1, 22.6, 18.0; HRMS (FAB) calcd for $C_{23}H_{27}N_3O_4$ (M^+) 409.2002, found 409.1998. *More polar isomer*: $[\alpha]_D^{24}$ −41 (*c* 0.92, $CHCl_3$); IR (film, cm^{-1}) 3300, 2956, 1752, 1654, 1434, 1342, 1251; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.02 (1H, s), 7.51 (1H, d, *J*=8.0 Hz), 7.25 (1H, m), 7.11–7.04 (2H, m), 6.48 (1H, s), 5.29 (1H, t, *J*=7.2 Hz), 3.96 (1H, d, *J*=14.8), 3.92 (3H, s), 3.47–3.44 (3H, m), 3.23 (1H, d, *J*=14.8 Hz), 2.97–2.92 (1H, m), 2.06–2.01 (1H, m), 1.90–1.82 (1H, m), 1.78 (3H, s), 1.74–1.71 (1H, m), 1.73 (3H, s), 1.70–1.68 (1H, m), 1.11–1.07 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 168.1, 162.2, 137.5, 135.9, 134.8, 128.5, 121.6, 119.7, 119.3, 118.5, 110.4, 103.4, 69.3, 57.7, 53.7, 45.3, 32.9, 28.9, 25.8, 24.9, 21.2, 18.0; HRMS (FAB) calcd for $C_{23}H_{27}N_3O_4$ (M^+) 409.2002, found 409.2008.

*4.1.2. Tryprostatin B (**2**) and 9-epi-tryprostatin B (**21**).* A mixture of **20** (31 mg, 0.074 mmol), lithium chloride (16 mg, 0.37 mmol), and H_2O (10 μL) in DMSO (1.0 mL) was stirred for 30 min at 140 °C under an argon atmosphere. The resulting mixture was poured into brine and extracted with $CHCl_3$. The extract was evaporated to afford a syrup, which was purified by preparative TLC (5% MeOH/CH_2Cl_2) to give tryprostatin B (**2**) (12.3 mg, 47%) and 9-*epi*-tryprostatin B (**21**) (10.2 mg, 39%). Compound **21**: $[\alpha]_D^{24}$ −19 (*c* 0.28, $CHCl_3$); IR (film, cm^{-1}) 3280, 2971, 2923, 2885, 1652, 1456, 1340, 1305, 1117; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.95 (1H, br), 7.51 (1H, d, *J*=8.4 Hz), 7.13–7.05 (2H, m), 6.02 (1H, br), 5.30 (1H, t, *J*=7.2 Hz), 4.26–4.23 (1H, m), 3.54–3.49 (1H, m), 3.44–3.38 (3H, m), 3.18–3.11 (2H, m), 2.70–2.67 (1H, m), 2.04–2.00 (1H, m), 1.90–1.65 (2H, overlapped), 1.79 (3H, s), 1.75 (3H, s), 1.38–1.34 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.0, 165.6, 136.7, 135.6, 135.0, 128.3, 121.6, 119.7, 119.5, 118.3, 110.4, 104.4, 58.7, 57.7, 45.1, 29.3, 25.8, 25.8, 24.9, 21.5, 17.9; HRMS (FAB) calcd for $C_{21}H_{25}N_3O_2$ (M^+) 351.1947, found 351.1944.

*4.1.3. 1-Ethynyl-4-methoxy-2-nitrobenzene (**24**).* To a solution of 1-bromo-4-methoxy-2-nitrobenzene **22** (1.70 g, 7.3 mmol) in THF (8.0 mL) and triethylamine (8.0 mL) were added CuI (140 mg, 0.735 mmol) and $PdCl_2(PPh_3)_2$ (258 mg, 0.368 mmol) at room temperature under an argon atmosphere. Trimethylsilylacetylene (**23**) (1.50 mL, 11 mmol) was added slowly to the mixture, and the resulting suspension was stirred at room temperature for 1 h. The reaction was quenched with H_2O and the resulting mixture was partitioned between Et_2O and H_2O. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH (10 mL), to which was added K_2CO_3 at room temperature. The reaction mixture was stirred for 10 min before it was partitioned between Et_2O and H_2O. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20% EtOAc in *n*-hexane) to afford **24** (1.20 g, 90% in two steps) as a yellow crystals. Mp 84.2–86.4 °C; IR (film, cm^{-1}) 3284, 3079, 2987, 1617, 1528, 1353, 1276, 1035; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.60 (1H, d, *J*=8.4 Hz), 7.55 (1H, d, *J*=2.8 Hz), 7.12 (1H, dd, *J*=8.4, 2.8 Hz), 3.90 (3H, s), 3.40 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.9, 136.4, 119.6, 109.4, 109.4, 83.2, 78.5, 56.0; HRMS (FAB) calcd for $C_9H_7NO_3$ (M^+) 177.0426, found 177.0425.

*4.1.4. 1-(4-Methoxy-2-nitrophenyl)-5-methylhex-4-en-2-one (**28**).* To a solution of **24** (463 mg, 2.61 mmol) in DMF (10 mL) were added 2-prenyl bromide (**15**) (520 μL, 4.4 mmol), K_2CO_3 (722 mg, 5.22 mmol), CuI (498 mg, 2.61 mmol), and tetrabutylammonium bromide (419 mg, 1.30 mmol) at room temperature. The reaction mixture was stirred for 4 h at 50 °C before it was partitioned between Et_2O and saturated aq NH_4Cl. The aqueous layer was extracted with Et_2O, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20% EtOAc in *n*-hexane) to afford inseparable mixture of 4-methoxy-1-(5-methylhex-4-en-1-yn-1-yl)-2-nitrobenzene (**25**) and 1-(3,3-dimethylpent-4-en-1-yn-1-yl)-4-methoxy-2-nitrobenzene (**26**) as a yellow oil (484 mg, 75%, **25**/**26**=6.5:1). A solution of **25** and **26** (348 mg, 1.42 mmol) in pyrrolidine (1.8 mL, 21 mmol) was stirred at 50 °C for 1 h. After removal of pyrrolidine on a rotary evaporator, 30% aq AcOH (2.0 mL) was added to the reaction mixture. After stirring for 10 min at room temperature, the reaction was quenched by the addition of saturated aq $NaHCO_3$. The reaction mixture was diluted with EtOAc and the organic phase was washed with brine. The organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford the crude product. The crude product was purified by flash column chromatography on silica gel (5% EtOAc in *n*-hexane) to afford **26** (52.0 mg, 15%). Further elution with 10% EtOAc in *n*-hexane afforded **28** (298 mg, 80%) as a yellow oil. IR (film, cm^{-1}) 3423, 2970, 2916, 2063, 1720, 1626, 1572, 1533, 1504, 1444, 1404, 1352, 1286, 1254, 1188, 1109, 1066, 1036; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.64 (1H, d, *J*=2.4 Hz), 7.17–7.11 (2H, m), 5.36 (1H, t, *J*=7.2 Hz), 4.04 (2H, s), 3.87 (3H, s), 3.28 (2H, d, *J*=7.2 Hz), 1.78 (3H, s), 1.67 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 204.9, 159.1, 136.4, 134.2, 122.5, 120.2, 115.5, 109.8, 55.8, 46.6, 42.5, 25.7, 18.1; HRMS (FAB) calcd for $C_{14}H_{17}NO_4$ (M^+) 263.1158, found 263.1154.

*4.1.5. 6-Methoxy-2-(3-methylbut-2-enyl)-indole (**29**).* To a mixture of **28** (735 mg, 2.80 mmol) and activated zinc dust (1.80 g, 27.5 mmol) in CH_2Cl_2 (14 mL) was added trifluoroacetic acid (2.5 mL, 34 mmol) over a period of 15 min at 0 °C. The reaction mixture was stirred for 1 h at room temperature before the reaction was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with Et_2O, and the combined organic extract was washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel (20% EtOAc in *n*-hexane) to afford 6-methoxy-2-(3-methylbut-2-enyl)-indole **29** (352 mg, 59%) as colorless crystals. Mp 87.0–90.2 °C; IR (film, cm^{-1}) 3388, 2925, 1626, 1549, 1454, 1309, 1159, 1028; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.75 (1H, s), 7.39 (1H, d, *J*=8.8 Hz), 6.82 (1H, s), 6.74 (1H, dd, *J*=8.8, 2.0 Hz), 6.15 (1H, d, *J*=2.0 Hz), 5.38 (1H, t, *J*=7.2 Hz), 3.83 (3H, s), 3.45 (2H, d, *J*=7.2 Hz), 1.74 (3H, s), 1.60 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 155.7, 137.4, 136.6, 134.37, 123.1, 120.4, 120.3, 109.0, 99.1, 94.5, 55.7, 27.1, 25.8, 17.8; HRMS (FAB) calcd for $C_{14}H_{17}NO$ (M^+) 215.1310, found 215.1310.

*4.1.6. (8aS)-Methyl 3-((6-methoxy-2-(3-methylbut-2-en-1-yl)-1H-indol-3-yl)methyl)-1,4-dioxooctahydropyrrolo[1,2-a]pyrazine-3-carboxylate (**31**).* To a solution of 6-methoxy-2-(3-methylbut-2-enyl)-indole **29** (44.0 mg, 0.204 mmol) in dioxane (1.0 mL) were added formalin (21 μL, 0.30 mmol), dimethylamine hydrochloride (25.0 mg, 0.307 mmol), and acetic acid (13 μL, 0.21 mmol). The reaction was stirred for 1 h at room temperature before the reaction

was quenched with saturated aq $NaHCO_3$. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give **30**. The residue was used in the next reaction without further purification. To a stirred solution of **12** (51.0 mg, 0.240 mmol) in DMF (1.0 mL) was added NaH (60% in mineral oil, 9.6 mg, 0.24 mmol) followed by crude **30**, which was pretreated with dimethyl sulfate (21 μL, 0.22 mmol) in DMF (1.0 mL) at room temperature for 5 min. The mixture was stirred for 1 h at room temperature and then heated for 1 h at 50 °C under an argon atmosphere before the reaction was quenched with saturated aq NH_4Cl. The aqueous layer was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by preparative TLC (5% MeOH in CH_2Cl_2) to afford condensed product **31** (49 mg, 60%) as a yellow foam. The ratio between less polar isomer and more polar isomer was 1:2.2. *Less polar isomer*: $[\alpha]_D^{24}$ −2.0 (*c* 0.28, $CHCl_3$); IR (film, cm^{-1}) 3350, 2954, 1741, 1677, 1409, 1214, 1159, 1030; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.91 (1H, br), 7.28 (1H, d, *J*=6.4 Hz), 6.80 (1H, s), 6.75 (1H, t, *J*=6.4 Hz), 6.02 (1H, s), 5.26 (1H, t, *J*=7.2 Hz), 4.03–3.99 (2H, m), 3.82 (3H, s), 3.79 (3H, s), 3.76–3.59 (2H, m), 3.46–3.32 (3H, m), 2.39–2.33 (1H, m), 2.05–1.99 (2H, m), 1.97–1.86 (1H, m), 1.79 (3H, s), 1.75 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 169.3, 162.4, 156.3, 136.2, 135.9, 135.5, 122.7, 119.8, 118.7, 109.6, 102.2, 94.6, 66.4, 59.2, 55.7, 53.7, 46.3, 31.6, 29.5, 28.7, 25.7, 25.1, 22.6, 18.0; HRMS (FAB) calcd for $C_{24}H_{29}N_3O_5$ (M^+) 439.2107, found 439.2110. *More polar isomer*: $[\alpha]_D^{24}$ −26 (*c* 0.40, $CHCl_3$); IR (film, cm^{-1}) 3298, 2954, 1755, 1655, 1437, 1250, 1159, 1032; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.88 (1H, s), 7.39 (1H, d, *J*=8.8 Hz), 6.76–6.72 (2H, m), 6.31 (1H, s), 5.28 (1H, t, *J*=7.2 Hz), 3.96 (1H, d, *J*=14.8 Hz), 3.90 (3H, s), 3.80 (3H, s), 3.55–3.41 (3H, m), 3.23 (1H, d, *J*=14.8 Hz), 3.20–2.98 (1H, m), 2.18–2.06 (1H, m), 1.94–1.89 (1H, m), 1.75 (3H, s), 1.70–1.61 (2H, m), 1.69 (3H, s), 1.27–1.19 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8, 168.0, 162.2, 156.0, 136.2, 135.7, 135.5, 122.8, 119.4, 119.2, 109.3, 103.1, 94.2, 69.3, 57.8, 55.6, 53.7, 45.3, 33.1, 28.8, 25.8, 24.8, 22.6, 18.0; HRMS (FAB) calcd for $C_{24}H_{29}N_3O_5$ (M^+) 439.2107, found 439.2103.

*4.1.7. Tryprostatin A (**1**) and 9-epi-tryprostatin A (**32**).* A mixture of **31** (12.9 mg, 0.0294 mmol), lithium chloride (3.2 mg, 0.075 mmol), and H_2O (10 μL) in DMSO (500 μL) was stirred for 30 min at 160 °C under an argon atmosphere. The resulting mixture was poured into brine and extracted with $CHCl_3$. The extract was evaporated to afford a syrup, which was purified by preparative TLC (5% MeOH/CH_2Cl_2) to give tryprostatin A (**1**) (4.5 mg, 40%) and 9-*epi*-tryprostatin A (**32**) (3.3 mg, 30%). Compound **32**: $[\alpha]_D^{23}$ −7.5 (*c* 0.24, $CHCl_3$); IR (film, cm^{-1}) 3284, 2929, 2927, 1653, 1461, 1402, 1250, 1159; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.79 (1H, br s), 7.37 (1H, d, *J*=8.0 Hz), 6.78–6.73 (2H, m), 5.80 (1H, s), 5.28 (1H, t, *J*=9.2 Hz), 4.23 (1H, m), 3.82 (3H, s), 3.56–3.49 (1H, m), 3.44–3.34 (3H, m), 3.19–3.07 (2H, m), 2.74–2.70 (1H, m), 2.07–2.05 (1H, m), 1.90–1.66 (2H, overlapped), 1.79 (3H, s), 1.75 (3H, s), 1.43–1.38 (1H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.4, 165.8, 156.1, 136.7, 135.4, 135.3, 122.6, 120.0, 119.0, 109.2, 104.2, 94.2, 58.7, 57.7, 55.6, 45.1, 29.4, 29.0, 25.8, 24.9, 21.5, 17.9; HRMS (FAB) calcd for $C_{22}H_{27}N_3O_3$ (M^+) 381.2052, found 381.2053.

*4.1.8. (S)-Methyl 1-((S)-2-(((benzyloxy)carbonyl)amino)-4-(2-((tert-butoxycarbonyl)amino)phenyl)-4-oxobutanoyl)pyrrolidine-2-carboxylate (**46**).* To a solution of **42** (320 mg, 0.704 mmol) in MeOH/CH_2Cl_2 (20:1, 5.0 mL) was added triethylamine (150 μL, 1.1 mmol) at room temperature. The reaction mixture was stirred for 6.5 h. The solvent was evaporated to afford **43** as a pale yellow foam. The crude product was used in the next reaction without purification. To a solution of crude **43** in H_2O/THF (1:1, 3.6 mL) was added lithium hydroxide monohydrate (74.0 mg, 1.77 mmol) at 0 °C and the reaction mixture was stirred at room temperature for 1 h. The reaction was quenched with 1 M aq HCl. After addition of EtOAc, the aqueous phase was extracted with EtOAc twice and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the crude product was used in the next reaction without purification. To a solution of crude **44** and L-proline methyl ester hydrochloride **45** (221 mg, 1.70 mmol) in THF (8.0 mL) were added HBTU (*2*-(1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) (644 mg, 1.70 mmol) and *N*,*N*-diisopropylethylamine (560 μL, 3.1 mmol) at 0 °C. The resulting mixture was stirred at 0 °C for 2.5 h and was partitioned between EtOAc and saturated aq NH_4Cl. The aqueous phase was extracted with EtOAc and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (25% EtOAc in *n*-hexane) to afford **46** (250 mg, 65% in three steps) as a pale yellow solid. $[\alpha]_D^{22}$ −38 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) 3262, 2924, 1729, 1653, 1581, 1522, 1450, 1366, 1305, 1153, 1048, 1025, 754; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.84 (1H, br s), 8.46 (1H, d, *J*=8.5 Hz), 7.80 (1H, d, *J*=7.8 Hz), 7.46 (1H, t, *J*=7.6 Hz), 6.92 (1H, t, *J*=7.4 Hz), 6.39 (1H, d, *J*=8.5 Hz), 5.18–5.05 (3H, m), 4.47 (1H, d, *J*=6.2 Hz), 3.88–3.78 (2H, m), 3.66 (3H, s), 3.45 (2H, m), 2.30–2.15 (1H, m), 2.15–1.90 (3H, m), 1.52 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.5, 172.6, 170.7, 156.3, 153.4, 142.2, 136.5, 135.5, 131.3, 128.8, 128.5, 128.4, 126.9, 121.5, 119.5, 80.9, 67.4, 59.6, 52.5, 49.4, 47.5, 42.4, 29.3, 28.7, 25.1; HRMS (FAB) calcd for $C_{29}H_{36}N_3O_8$ ($M+H^+$) 554.2502, found 554.2484.

*4.1.9. tert-Butyl (2-(2-((3S,8aS)-1,4-dioxooctahydropyrrolo[1,2-a]pyrazin-3-yl)acetyl)phenyl)carbamate (**47**).* A mixture of **46** (143 mg, 0.258 mmol), 10% palladium on carbon (55.0 mg), and acetic acid (15.0 μL, 0.26 mmol) in EtOH (1.5 mL) was stirred under 1 atm of hydrogen for 13.5 h. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc) to afford **47** (69.9 mg, 76%) as a white solid. $[\alpha]_D^{22}$ −188 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) 2923, 1728, 1651, 1580, 1520, 1449, 1366, 1305, 1152, 1025, 749; ^1H NMR ($CDCl_3$, 400 MHz) δ 10.76 (1H, br s), 8.49 (1H, d, *J*=8.0 Hz), 7.92 (1H, d, *J*=8.3 Hz), 7.56 (1H, t, *J*=8.5 Hz), 7.05 (1H, t, *J*=8.2 Hz), 6.54 (1H, br s), 4.62 (1H, d, *J*=9.8 Hz), 4.23–4.12 (2H, m), 3.70–3.55 (2H, m), 3.22 (1H, dd, *J*=18.6, 9.8 Hz), 2.44–2.36 (1H, m), 2.09–2.01 (2H, m), 1.96–1.92 (1H, m), 1.54 (9H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.4, 169.4, 164.4, 152.5, 141.7, 135.2, 130.5, 120.8, 120.0, 118.9, 80.4, 58.6, 51.3, 45.3, 40.6, 28.0, 27.9, 22.1; HRMS (FAB) calcd for $C_{20}H_{25}N_3O_5$ (M^+) 387.1794, found 387.1784.

*4.1.10. N-(2-(2-((3S,8aS)-1,4-Dioxooctahydropyrrolo[1,2-a]pyrazin-3-yl)acetyl)phenyl)-4-methylpent-3-enamide (**49**).* To a solution of **47** (64.0 mg, 0.170 mmol) in CH_2Cl_2 (0.75 mL) was added trifluoroacetic acid (220 μL, 2.9 mmol) at 0 °C. After stirring at room temperature for 2 h, the solvent was removed under reduced pressure and the crude product was used in the next reaction without purification. The crude aniline was dissolved in CH_2Cl_2 (0.80 mL) and the solution were added freshly prepared **34**[12] (0.48 mmol) and pyridine (130 μL, 1.4 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 h, and quenched with saturated aq NH_4Cl. After addition of CH_2Cl_2, the aqueous phase was extracted with CH_2Cl_2 and the combined organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (5% MeOH in CH_2Cl_2) to afford **49** (37.8 mg, 57% in two steps) as a pale yellow foam. $[\alpha]_D^{22}$ −168 (*c* 1.00, $CHCl_3$); IR (film, cm^{-1}) 3259, 2926, 1683, 1652, 1582, 1520, 1448,

1303, 1259, 755; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.39 (1H, br s), 8.70 (1H, d, J=8.5 Hz), 7.90 (1H, d, J=7.8 Hz), 7.52 (2H, m), 7.10 (1H, t, J=8.0 Hz), 5.40 (1H, t, J=7.6 Hz), 4.62 (1H, d, J=7.3 Hz), 4.13 (1H, t, J=7.1 Hz), 4.02 (1H, dd, J=18.3, 3.2 Hz), 3.62–3.50 (2H, m), 3.29 (1H, dd, J=18.3, 8.7 Hz), 3.15 (2H, d, J=7.4 Hz), 2.30–2.23 (1H, m), 2.00–1.87 (3H, m), 1.85 (3H, s), 1.71 (3H, s); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 200.4, 171.2, 169.8, 164.7, 140.5, 138.0, 135.1, 130.3, 122.3, 121.6, 120.7, 115.7, 58.8, 51.4, 45.4, 40.6, 37.7, 28.0, 25.7, 22.3, 17.8; HRMS (FAB) calcd for $C_{21}H_{25}N_3O_4$ (M^+) 383.1845, found 383.1844.

*4.1.11. Tryprostatin B (**2**).* To a solution of magnesium (6.0 mg, 0.25 mmol) in degassed THF (150 μL) was added titanium tetrachloride (14 μL, 0.13 mmol) at 0 °C. After stirring at room temperature for 30 min, a solution of **49** (10 mg, 0.026 mmol) in degassed THF (150 μL) was added at 0 °C. The reaction mixture was stirred for 3 h at room temperature, and quenched with saturated aq NH_4Cl. After the addition of CH_2Cl_2 and H_2O, the aqueous phase was extracted with CH_2Cl_2 and the combined organic phase was dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the residue was purified by preparative TLC (5% MeOH in CH_2Cl_2) to afford **2** (1.8 mg, 20%) as a off-white solid.

*4.1.12. (S)-tert-Butyl 4-(2,2-dibromovinyl)-2,2-dimethyloxazolidine-3-carboxylate (**52**).* To a stirred solution of CBr_4 (50.4 g, 152 mmol) in CH_2Cl_2 (300 mL) was added a solution of PPh_3 (80.0 g, 304 mmol) in CH_2Cl_2 (500 mL) dropwise through the dropping funnel over a period of 20 min at −30 °C. After 20 min, the resulting orange-red solution was cooled to −60 °C, to which was added a solution of **51**[17] (17.4 g, 75.8 mmol) and triethylamine (10.6 mL, 75.8 mmol) in CH_2Cl_2 (500 mL) dropwise through the dropping funnel over a period of 30 min and warmed to 0 °C. After 2 h, the reaction mixture was quenched with saturated aq $NaHCO_3$ and concentrated in vacuo to half an amount. The resulting solution was partitioned between H_2O and CH_2Cl_2 and the aqueous layer was extracted with CH_2Cl_2 twice. The combined organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (500 mL) and Et_2O (500 mL), and stirred for 30 min at 0 °C. The slurry was filtered through a pad of Celite and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=17/3) to afford **52** (25.8 g, 67.0 mmol, 88%) as a colorless solid. Mp 54–55 °C; $[\alpha]_D^{22}$ −19 (c 1.00, $CHCl_3$); IR (neat, cm^{-1}) 2979, 2935, 2873, 1707, 1608, 1476, 1456, 1371, 1251, 1173, 1089, 1057; ^{1}H NMR ($CDCl_3$, 400 MHz) (2:1 mixture of two rotamers) (major) δ 6.44 (d, J=8.7 Hz, 1H), 4.51 (br s, 1H), 4.12–4.07 (m, 1H), 3.82–3.77 (m, 1H), 1.61–1.58 (m, 3H), 1.52 (s, 3H), 1.48 (s, 9H) (minor) δ 6.48 (br s, 1H), 4.61 (br s, 1H), 4.12–4.07 (m, 1H), 3.82–3.77 (m, 1H), 1.61–1.58 (m, 3H), 1.52 (s, 3H), 1.48 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 151.6, 138.5, 94.5, 89.9, 80.4, 67.3, 59.5, 28.5, 26.2, 23.8 (minor) δ 151.9, 138.5, 93.9, 90.5, 80.7, 67.3, 59.5, 28.5, 27.3, 24.7; HRMS (ESI) calcd for $C_{12}H_{19}Br_2NNaO_3$ ([M+Na]$^+$) 405.9629, found 405.9638.

*4.1.13. (S)-tert-Butyl 4-ethynyl-2,2-dimethyloxazolidine-3-carboxylate (**53**).* To a stirred solution of **52** (10.0 g, 26.0 mmol) in THF (100 mL) at 0 °C was added ethyl magnesium bromide (3.00 M solution in Et_2O, 17.3 mL, 52.0 mmol) dropwise through the dropping funnel over a period of 20 min. After 2 h, the reaction mixture was quenched with saturated aq NH_4Cl and extracted with EtOAc three times. The combined organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=1/1) to afford **53** (5.74 g, 25.5 mmol, 98%) as a colorless oil. $[\alpha]_D^{22}$ +81 (c 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3293, 2981, 2936, 2878, 1701, 1477, 1457, 1379, 1264, 1246, 1173, 1097; ^{1}H NMR ($CDCl_3$, 400 MHz) (3:2 mixture of two rotamers) (major) δ 4.51 (br s, 1H), 4.07–4.02 (m, 2H), 2.27 (br s, 1H), 1.65 (s, 3H), 1.50 (s, 12H) (minor) δ 4.62 (br s, 1H), 4.07–4.02 (m, 2H), 2.27 (br s, 1H), 1.65 (s, 3H), 1.50 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 151.2, 94.4, 82.7, 80.3, 70.0, 68.6, 48.2, 28.3, 25.8, 24.2 (minor) δ 151.6, 93.9, 82.3, 80.8, 70.5, 68.5, 48.2, 28.3, 26.8, 25.1; HRMS (ESI) calcd for $C_{12}H_{19}NNaO_3$ ([M+Na]$^+$) 248.1263, found 248.1260.

*4.1.14. N-(2-Iodophenyl)formamide (**54**).* A mixture of formic acid (3.46 mL, 91.6 mmol) and acetic anhydride (4.33 mL, 45.8 mmol) was heated at 50 °C for 1 h and then cooled to 0 °C. This was added to a stirred solution of 2-iodoaniline (5.01 g, 22.9 mmol) in CH_2Cl_2 (100 mL) at 0 °C. After 1 h, the reaction mixture was quenched with saturated aq $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic extract was washed three times with saturated aq $NaHCO_3$, brine, and dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was recrystallized from EtOAc to afford **54** (5.19 g, 21.0 mmol, 92%) as a slightly purple needle. Mp 113–114 °C; IR (neat, cm^{-1}) 3223, 1658, 1583, 1572, 1526, 1393, 1281, 1152; ^{1}H NMR ($CDCl_3$, 400 MHz) (3:2 mixture of two rotamers) (major) δ 8.50 (s, 1H), 8.30 (d, J=8.2 Hz, 1H), 7.80 (d, J=8.2 Hz, 1H), 7.48 (br s, 1H), 7.36 (dd, J=7.8, 7.8 Hz, 1H), 6.89 (dd, J=7.8, 7.8 Hz, 1H) (minor) δ 8.66 (d, J=11.0 Hz, 1H), 8.50 (s, 1H), 7.86 (d, J=7.8 Hz, 1H), 7.48 (br s, 1H), 6.23 (dd, J=7.8, 7.8 Hz, 1H), 6.89 (dd, J=7.8, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 158.9, 138.9, 137.2, 129.2, 126.3, 122.2, 89.3 (minor) δ 161.9, 139.9, 137.7, 129.5, 127.0, 119.3, 90.7; HRMS (ESI) calcd for C_7H_6INNaO ([M+Na]$^+$) 269.9392, found 269.9388.

*4.1.15. (S)-tert-Butyl 4-((2-formamidophenyl)ethynyl)-2,2-dimethyloxazolidine-3-carboxylate (**55**).* To a stirred solution of **53** (4.28 g, 19.0 mmol) and **54** (3.98 g, 16.1 mmol) in triethylamine (70 mL) were added CuI (280 mg, 1.46 mmol) and $PdCl_2(PPh_3)_2$ (1.02 g, 1.46 mmol) at room temperature. After 2 h, the reaction mixture was filtered through a pad of Celite. To the resulting solution was added saturated aq NH_4Cl and the mixture was extracted with Et_2O. The organic layer was washed three times with saturated aq NH_4Cl and the combined aqueous layer was reextracted with Et_2O. The combined organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=4/1) to afford **55** (5.37 g, 15.6 mmol, 97%) as a slightly yellow oil. $[\alpha]_D^{22}$ +15 (c 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3296, 2980, 2935, 2878, 1704, 1680, 1579, 1523, 1452, 1367; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (br s, 1H), 8.57 (s, 1H), 8.51 (d, J=8.7 Hz, 1H), 7.36–7.32 (m, 2H), 7.03 (dd, J=7.8, 7.3 Hz, 1H), 4.83 (dd, J=6.4, 5.5 Hz, 1H), 4.23 (dd, J=8.2, 6.4 Hz, 1H), 4.13–4.08 (m, 1H), 1.59 (s, 3H), 1.55 (s, 3H), 1.52 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 159.9, 152.4, 140.1, 130.3, 129.8, 123.2, 119.5, 111.1, 94.4, 94.1, 81.4, 79.6, 67.5, 49.0, 28.4, 26.1, 25.8; HRMS (ESI) calcd for $C_{19}H_{24}N_2NaO_4$ ([M+Na]$^+$) 367.1634, found 367.1632.

*4.1.16. (S,Z)-tert-Butyl 4-(2-formamidostyryl)-2,2-dimethyloxazolidine-3-carboxylate (**56**).* To a stirred solution of zinc powder (11.4 g, 174 mmol) in 2,2,2-trifluoroethanol (43.6 mL) was added dibromoethane (1.18 mL, 13.1 mmol). The resulting solution was heated up to 70 °C. After 30 min, the stirred solution was cooled to room temperature, to which was added an additional dibromoethane (1.18 mL, 13.1 mmol) and heated up to 70 °C for 30 min. After cooling the stirred solution to room temperature, a mixture of CuBr (3.75 g, 26.1 mmol) and LiBr (4.54 g, 52.3 mmol) in THF (40 mL) was added and the reaction mixture turned black. The mixture was heated at 70 °C for 30 min and cooled to room temperature, to which was added **55** (3.00 g, 8.71 mmol) in THF (10 mL) and stirred at 70 °C. After 3 h, the reaction mixture was filtered through a pad of Celite. To the resulting solution was added saturated aq NH_4Cl and the aqueous layer was extracted with EtOAc twice. The combined organic extract was washed with brine, dried over Na_2SO_4,

filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=5/1 to 3/1) to afford **56** (3.01 g, 8.68 mmol, 99%) as a slightly yellow oil. $[\alpha]_D^{23}$ −65 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3277, 2979, 2934, 2871, 1696, 1673, 1581, 1529, 1452, 1391, 1366; ^1H NMR ($CDCl_3$, 400 MHz) (3:1 mixture of two rotamers) (major) δ 9.58 (s, 1H), 8.41 (s, 1H), 8.29 (d, *J*=7.8 Hz, 1H), 7.29–7.15 (m, 1H), 7.08 (dd, *J*=7.3, 7.3 Hz, 1H), 7.01 (d, *J*=7.3 Hz, 1H), 6.52 (d, *J*=11.0 Hz, 1H), 5.78 (dd, *J*=11.0, 10.1 Hz, 1H), 4.25–4.20 (m, 1H), 3.89 (dd, *J*=8.7, 8.7 Hz, 1H), 3.63 (dd, *J*=8.7, 6.4 Hz, 1H), 1.56 (s, 3H), 1.49 (s, 9H), 1.47 (s, 3H) (minor) δ 8.84 (d, *J*=10.1 Hz, 1H), 8.54 (d, *J*=11.5 Hz, 1H), 8.41 (s, 1H), 7.29–7.15 (m, 1H), 7.08 (dd, *J*=7.3, 7.3 Hz, 1H), 7.01 (d, *J*=7.3 Hz, 1H), 6.52 (d, *J*=11.0 Hz, 1H), 5.78 (dd, *J*=11.0, 10.1 Hz, 1H), 4.29 (br s, 1H), 3.98–3.94 (m, 1H), 3.73 (br s, 1H), 1.56 (s, 3H), 1.49 (s, 9H), 1.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 160.1, 152.6, 134.1, 134.0, 129.2, 128.0, 127.8, 126.5, 124.0, 121.9, 94.0, 81.1, 67.6, 56.0, 28.3, 26.2, 25.7 (minor) δ 162.7, 152.0, 134.9, 133.8, 130.3, 128.4, 128.0, 125.3, 124.0, 121.2, 93.6, 80.9, 67.7, 55.4, 29.6, 26.9, 25.3; HRMS (ESI) calcd for $C_{19}H_{26}N_2NaO_4$ ($[M+Na]^+$) 369.1790, found 369.1780.

*4.1.17. (S,Z)-tert-Butyl 4-(2-isocyanostyryl)-2,2-dimethyloxazolidine-3-carboxylate (**57**).* To a stirred solution of **56** (1.96 g, 5.66 mmol) and pyridine (4.58 mL, 56.6 mmol) in CH_2Cl_2 (28.3 mL) was added triphosgene (672 mg, 2.26 mmol) at 0 °C. After 20 min, the reaction mixture was poured into ice-cold saturated aq $NaHCO_3$. The organic layer was washed with saturated aq $NaHCO_3$ three times and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=8/1) to afford **57** (1.61 g, 4.90 mmol, 87%) as a slightly yellow oil. $[\alpha]_D^{21}$ −68 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 2980, 2935, 2871, 2119, 1697, 1480, 1449, 1384, 1366; ^1H NMR ($CDCl_3$, 400 MHz) (3:2 mixture of two rotamers) (major) δ 7.41–7.38 (m, 2H), 7.31–7.26 (m, 2H), 6.64 (d, *J*=11.5 Hz, 1H), 5.94 (dd, *J*=10.6, 10.6 Hz, 1H), 4.71 (br s, 1H), 4.18 (br s, 1H), 3.89 (br s, 1H), 1.67 (s, 3H), 1.50 (s, 9H), 1.29 (s, 3H) (minor) δ 7.85 (br s, 1H), 7.41–7.38 (m, 1H), 7.31–7.26 (m, 2H), 6.64 (d, *J*=11.5 Hz, 1H), 5.94 (dd, *J*=10.6, 10.6 Hz, 1H), 4.77 (br s, 1H), 4.01 (br s, 1H), 3.76 (br s, 1H), 1.67 (s, 3H), 1.29 (s, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 167.0, 151.7, 135.8, 132.9, 129.7, 128.9, 128.1, 127.0, 125.6, 124.1, 94.6, 79.9, 68.6, 54.7, 28.1, 26.5, 23.9 (minor) δ 166.4, 151.9, 135.0, 133.0, 130.0, 129.1, 128.0, 126.7, 125.1, 124.1, 93.7, 80.1, 68.6, 55.0, 28.1, 27.3, 25.0; HRMS (ESI) calcd for $C_{19}H_{24}N_2NaO_3$ ($[M+Na]^+$) 351.1685, found 351.1690.

*4.1.18. (S)-tert-Butyl 4-((1H-indol-3-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylate (**58**).* A solution of **57** (98.0 mg, 0.298 mmol), tributyltin hydride (160 μL, 0.596 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN) (7.3 mg, 0.0447 mmol) in dry MeCN (1.50 mL) in a sealed tube was heated at 100 °C for 1 h under an argon atmosphere. The reaction mixture was cooled to room temperature and silica gel (300 mg) was added. The resulting suspension was stirred for an additional 2 h. After filtration through a plug of cotton funnel, the resulting solution was added saturated aq KF. The aqueous layer was extracted with Et_2O twice. The combined extract was washed with saturated aq KF and brine, and dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=9/1 to 4/1) to afford **58** (55.0 mg, 0.167 mmol, 56%), **59** (8.8 mg, 0.0619 mmol, 23%) and **60** (15 mg, 0.0745 mmol, 25%). Compound **58**: $[\alpha]_D^{23}$ −41 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3415, 3356, 2979, 2933, 2875, 1676, 1457, 1392, 1365, 1254, 1172; ^1H NMR ($CDCl_3$, 400 MHz) (4:3 mixture of two rotamers) (major) δ 8.10 (br s, 1H), 7.73 (d, *J*=8.2 Hz 1H), 7.38 (d, *J*=8.2 Hz, 1H), 7.21 (dd, *J*=8.2, 7.4 Hz 1H), 7.12 (dd, *J*=8.2, 7.4 Hz, 1H), 7.04 (s, 1H), 4.19 (m, 1H), 3.80 (s, 1H), 3.75 (m, 1H), 3.26 (d, *J*=11.0 Hz, 1H), 2.82 (m, 1H), 1.70 (s, 3H), 1.58 (s, 9H), 1.52 (s, 3H) (minor) δ 8.06 (br s, 1H), 7.84 (d, *J*=7.3 Hz, 1H), 7.34 (d, *J*=7.3 Hz 1H), 7.19 (dd, *J*=7.3, 7.3 Hz, 1H), 7.12 (dd, *J*=7.3, 7.3 Hz, 1H), 7.04 (s, 1H), 4.26 (m, 1H), 3.82 (s, 1H), 3.75 (m, 1H), 3.35 (d, *J*=12.8 Hz, 1H), 2.82 (m, 1H), 1.60 (s, 3H), 1.55 (s, 9H), 1.48 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 151.9, 136.3, 127.4, 122.7, 122.2, 119.5, 119.3, 112.8, 111.2, 94.2, 79.9, 66.4, 57.4, 29.4, 28.7, 27.1, 23.3 (minor) δ 152.3, 136.1, 127.7, 122.4, 122.1, 119.5, 119.0, 112.9, 110.9, 93.5, 80.0, 66.3, 58.2, 28.3, 28.5, 27.8, 24.5; HRMS (ESI) calcd for $C_{19}H_{26}N_2NaO_3$ ($[M+Na]^+$) 353.1841, found 353.1827. Compound **60**: IR (neat, cm^{-1}) 3383, 2979, 2935, 2883, 1698, 1478, 1456, 1393, 1366, 1260, 1174; ^1H NMR ($CDCl_3$, 400 MHz) (4:3 mixture of two rotamers) (major) δ 3.93 (t, *J*=6.4 Hz, 1H), 3.55 (br s, 1H), 1.51 (br s, 6H), 1.48 (br s, 9H) (minor) δ 3.93 (t, *J*=6.4 Hz, 1H), 3.51 (br s, 1H), 1.51 (br s, 6H), 1.48 (br s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 152.4, 92.6, 80.0, 62.7, 45.7, 28.4, 25.7 (minor) δ 152.0, 93.0, 79.4, 62.9, 45.7, 28.4, 24.7; HRMS (DART) calcd for $C_{10}H_{20}NO_3$ ($[M+H]^+$) 202.1443, found 202.1442.

*4.1.19. (S)-tert-Butyl 2,2-dimethyl-4-((2-(3-methylbut-2-enyl)-1H-indol-3-yl)methyl)oxazolidine-3-carboxylate (**64**).* To a stirred solution of **57** (1.45 g, 4.42 mmol) and tributyltin hydride (3.51 mL, 13.3 mmol) in toluene (8.84 mL) was added 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (**61**, V-70) (272 mg, 0.883 mmol) at 30 °C. After 1 h, the reaction mixture was added prenyl acetate (**63**) (1.85 mL, 13.3 mmol), lithium chloride (562 mg, 13.3 mmol), triphenylarsine (271 mg, 0.884 mmol), *N*,*N*-dimethylformamide (26.5 mL) and $Pd_2(dba)_3$ (202 mg, 0.221 mmol), and the mixture was heated to 80 °C for 1 h, before hydroxylamine hydrochloride (1.23 g, 17.7 mmol) and sodium acetate (1.45 g, 17.7 mmol) was added. After 30 min, the reaction mixture was quenched with saturated aq KF and the aqueous layer was extracted with Et_2O three times. The combined extract was washed with saturated aq KF twice, brine, and dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=19/1 to 13/1) to afford **64** (1.28 g, 3.21 mmol, 73%) as a slightly yellow oil. $[\alpha]_D^{23}$ −47 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3345, 2979, 2933, 2876, 1692, 1680, 1462, 1392, 1366, 1248; ^1H NMR ($CDCl_3$, 400 MHz) (4:3 mixture of two rotamers) (major) δ 7.83 (s, 1H), 7.63 (d, *J*=7.1 Hz, 1H), 7.27 (m, 1H), 7.14–7.06 (m, 2H), 5.30 (t, *J*=6.9 Hz, 2H), 4.19 (m, 1H), 3.71 (br s, 2H), 3.50 (d, *J*=6.9 Hz, 1H), 3.17 (dd, *J*=13.3, 3.2 Hz, 1H), 2.80 (m, 1H), 1.79 (s, 3H), 1.77 (s, 3H), 1.58 (s, 9H), 1.55 (s, 6H) (minor) δ 7.81 (s, 1H), 7.74 (d, *J*=7.1 Hz, 1H), 7.27 (m, 1H), 7.14–7.06 (m, 2H), 5.30 (t, *J*=6.9 Hz, 2H), 4.19 (m, 1H), 3.71 (br s, 2H), 3.54 (d, *J*=6.9 Hz, 1H), 3.23 (d, *J*=11.9, 1.2 Hz, 1H), 2.80 (m, 1H), 1.79 (s, 3H), 1.77 (s, 3H), 1.58 (s, 9H), 1.55 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 151.9, 135.4, 135.1, 135.0, 128.8, 121.2, 120.0, 119.2, 118.2, 110.4, 107.6, 94.1, 79.9, 66.3, 57.5, 28.7, 27.8, 27.2, 25.8, 25.1, 23.3, 17.9 (minor) δ 152.2, 135.3, 135.0, 134.7, 129.0, 121.1, 120.3, 119.4, 118.7, 110.1, 107.8, 93.4, 79.9, 66.3, 58.3, 28.5, 27.9, 26.9, 25.8, 25.1, 24.5, 17.9; HRMS (ESI) calcd for $C_{24}H_{34}N_2NaO_3$ ($[M+Na]^+$) 421.2467, found 421.2454.

*4.1.20. (S)-tert-Butyl 3-(2-(tert-butoxycarbonylamino)-3-hydroxypropyl)-2-(3-methylbut-2-enyl)-indole-1-carboxylate (**65**).* To a stirred solution of **64** (1.10 g, 2.76 mmol) in MeCN (13.8 mL) were added Boc_2O (783 mg, 3.59 mmol) and 4-(dimethylamino)pyridine (DMAP) (101 mg, 0.828 mmol) at room temperature. After 30 min, the reaction mixture was quenched with saturated aq NH_4Cl and extracted with EtOAc three times. The combined organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=9/1) to afford the Boc intermediate (1.36 g, 2.72 mmol, 99%) as a white solid. To a stirred solution of the Boc intermediate (1.36 g, 2.73 mmol) in THF (3.89 mL) and H_2O (1.94 mL) at 0 °C was added ice-cold trifluoroacetic acid (7.77 mL). After 10 min, the reaction mixture was poured into cooled saturated aq $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aq $NaHCO_3$ three times, brine, and dried over Na_2SO_4, filtered, and

concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=7/3) to afford **65** (1.10 g, 2.40 mmol, 88%) as a colorless oil. *Boc intermediate*: mp 110–111 °C; $[\alpha]_D^{23}$ −33 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 2979, 2933, 2874, 1809, 1732, 1697, 1607, 1459, 1390, 1366, 1327; ^1H NMR ($CDCl_3$, 400 MHz) (1:1 mixture of two rotamers) (major) δ 8.08–8.06 (m, 1H), 7.61 (d, *J*=7.3 Hz, 1H), 7.27–7.16 (m, 2H), 5.18 (t, *J*=5.0 Hz, 1H), 4.22–4.14 (m, 1H), 3.90–3.72 (m, 2H), 3.69 (s, 2H), 3.23 (dd, *J*=11.5, 1.0 Hz, 1H), 2.82–2.74 (m, 1H), 1.77 (s, 3H), 1.73 (s, 3H), 1.66 (s, 9H), 1.57 (s, 9H), 1.55 (s, 3H), 1.53 (s, 3H) (minor) δ 8.08–8.06 (m, 1H), 7.79–7.77 (m, 1H), 7.27–7.16 (m, 2H), 5.18 (t, *J*=5.0 Hz, 1H), 4.22–4.14 (m, 1H), 3.90–3.72 (m, 2H), 3.69 (s, 2H), 3.12 (dd, *J*=11.5, 1.4 Hz, 1H), 2.82–2.74 (m, 1H), 1.77 (s, 3H), 1.73 (s, 3H), 1.66 (s, 9H), 1.57 (s, 9H), 1.55 (s, 3H), 1.53 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 151.8, 150.3, 137.8, 135.9, 132.4, 129.7, 123.6, 122.2, 121.6, 118.2, 115.3, 114.7, 94.2, 83.7, 66.0, 80.0, 56.8, 28.7, 28.1, 27.4, 27.0, 25.8, 25.7, 23.2, 18.2 (minor) δ 151.4, 150.4, 137.6, 135.8, 132.2, 129.9, 123.5, 122.7, 121.8, 118.9, 115.1, 115.0, 93.4, 83.5, 66.0, 80.1, 57.6, 28.5, 28.0, 27.8, 27.2, 25.9, 25.7, 24.4, 18.0; HRMS (ESI) calcd for $C_{29}H_{42}N_2NaO_5$ ($[M+Na]^+$) 521.2991, found 521.2981. Compound **65**: $[\alpha]_D^{24}$ −3.1 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3473, 2978, 2930, 1731, 1696, 1503, 1458, 1392, 1367, 1327; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, *J*=8.2 Hz, 1H), 7.60 (d, *J*=6.4 Hz, 1H), 7.27–7.20 (m, 2H), 5.23 (t, *J*=5.0 Hz, 1H), 4.93 (br s, 1H), 3.93 (br s, 1H), 3.75 (d, *J*=5.0 Hz, 2H), 3.62 (br s, 1H), 3.55 (br s, 1H), 2.91–2.89 (m, 2H), 2.44 (br s, 1H), 1.76 (s, 3H), 1.71 (s, 3H), 1.66 (s, 9H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.1, 150.3, 137.5, 135.9, 132.5, 129.7, 123.6, 122.6, 122.0, 118.4, 115.2, 114.5, 83.7, 79.5, 63.9, 52.4, 28.3, 28.1, 25.8, 25.6, 18.1, 18.1; HRMS (ESI) calcd for $C_{26}H_{38}N_2NaO_5$ ($[M+Na]^+$) 481.2678, found 481.2672.

*4.1.21. (S)-3-(1-(tert-Butoxycarbonyl)-2-(3-methylbut-2-enyl)-indol-3-yl)-2-(tert-butoxycarbonylamino)propanoic acid (**66**).* To a stirred solution of **65** (1.08 g, 2.36 mmol) and iodobenzene diacetate (2.28 g, 7.08 mmol) in MeCN (5.9 mL) and phosphate buffer (pH 6.8) (5.9 mL) was added 2,2,6,6-tetramethyl- piperidine-1-oxyl (TEMPO) (36.8 mg, 0.236 mmol) at room temperature. After 30 min, saturated aq $NaHCO_3$ was added to the reaction mixture and the aqueous phase was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=7/3) to afford **66** (1.01 g, 2.14 mmol, 91%) as a colorless oil. $[\alpha]_D^{24}$ +25 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3316, 2978, 2930, 2855, 1730, 1457, 1368, 1325, 1165, 1134; ^1H NMR ($CDCl_3$, 400 MHz) (3:1 mixture of two rotamers) (major) δ 8.07 (d, *J*=7.8 Hz, 1H), 7.50 (d, *J*=6.9 Hz, 1H), 7.27–7.19 (m, 2H), 5.22 (br s, 1H), 5.03 (d, *J*=6.0 Hz, 1H), 4.52 (br s, 1H), 3.79–3.64 (m, 2H), 3.29 (dd, *J*=14.6, 4.6 Hz, 1H), 3.13–3.08 (m, 1H), 1.76 (s, 3H), 1.71 (s, 3H), 1.66 (s, 9H), 1.38 (s, 9H) (minor) δ 8.07 (d, *J*=7.8 Hz, 1H), 7.50 (d, *J*=6.9 Hz, 1H), 7.27–7.19 (m, 2H), 5.22 (br s, 1H), 5.03 (d, *J*=6.0 Hz, 1H), 4.52 (br s, 1H), 3.79–3.64 (m, 2H), 3.29 (dd, *J*=14.6, 4.6 Hz, 1H), 2.96 (br s, 1H), 1.76 (s, 3H), 1.71 (s, 3H), 1.66 (s, 9H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 175.8, 155.5, 150.3, 138.3, 135.9, 132.7, 129.4, 123.7, 122.6, 121.8, 118.1, 115.3, 112.8, 83.8, 80.2, 54.6, 29.4, 28.2, 28.1, 27.4, 25.8, 18.1 (minor) δ 176.8, 156.5, 150.3, 137.9, 136.0, 132.1, 129.7, 123.6, 122.6, 122.0, 117.9, 115.3, 113.9, 83.6, 81.0, 53.7, 29.4, 28.2, 28.1, 26.8, 25.5, 18.2; HRMS (ESI) calcd for $C_{26}H_{36}N_2NaO_6$ ($[M+Na]^+$) 495.2458, found 495.2457.

*4.1.22. tert-Butyl 3-((S)-2-(tert-butoxycarbonylamino)-3-((S)-2-(methoxycarbonyl)pyrrolidin-1-yl)-3-oxopropyl)-2-(3-methylbut-2-enyl)-indole-1-carboxylate (**68**).* To a stirred solution of **66** (1.01 g, 2.14 mmol) and L-proline methyl ester *p*-toluenesulfonate **67** (482 mg, 2.78 mmol) in CH_2Cl_2 (10.7 mL) were added HATU (1.06 g, 2.78 mmol) and *N*,*N*-diisopropylethylamine (932 μL, 5.35 mmol) at room temperature. After 30 min, the reaction mixture was quenched with saturated aq NH_4Cl and the aqueous phase was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=4/1) to afford **68** (1.10 g, 1.88 mmol, 88%) as a colorless oil. $[\alpha]_D^{21}$ +3.3 (*c* 1.00, $CHCl_3$); IR (neat, cm^{-1}) 3307, 2977, 2930, 1733, 1647, 1457, 1365, 1326; ^1H NMR ($CDCl_3$, 400 MHz) (3:2 mixture of two rotamers) (major) δ 8.08 (d, *J*=5.9 Hz, 1H), 7.56 (d, *J*=7.4 Hz, 1H), 7.26–7.20 (m, 2H), 5.22 (br s, 1H), 5.14 (d, *J*=8.2 Hz, 1H), 4.78–4.72 (m, 1H), 4.55–4.52 (m, 1H), 3.74 (br s, 2H), 3.68 (s, 3H), 3.74–3.65 (m, 1H), 3.47–3.43 (m, 1H), 3.17–3.02 (m, 2H), 2.20–1.95 (m, 4H), 1.77 (s, 3H), 1.70 (s, 3H), 1.66 (s, 9H), 1.30 (s, 9H) (minor) δ 8.05 (m, 1H), 7.51 (d, *J*=7.4 Hz, 1H), 7.26–7.20 (m, 2H), 5.51 (d, *J*=8.7 Hz, 1H), 5.16 (br s, 1H), 4.50–4.44 (m, 1H), 4.55–4.52 (m, 1H), 3.74 (br s, 2H), 3.65 (s, 3H), 3.52 (d, *J*=8.2 Hz, 1H), 3.47–3.43 (m, 1H), 2.98–2.92 (m, 2H), 2.20–1.95 (m, 4H), 1.77 (s, 3H), 1.70 (s, 3H), 1.66 (s, 9H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 172.3, 171.0, 155.1, 150.3, 138.1, 135.9, 132.1, 129.6, 123.4, 122.5, 122.1, 117.9, 115.3, 113.0, 83.5, 79.4, 58.7, 52.6, 52.1, 46.9, 29.6, 28.3, 27.5, 28.0, 25.7, 24.8, 22.0, 18.2 (minor) δ 171.7, 171.0, 154.5, 150.3, 138.4, 135.6, 132.6, 129.4, 123.8, 122.6, 121.2, 118.2, 115.0, 113.1, 83.9, 79.3, 58.7, 52.2, 51.5, 46.1, 30.0, 28.9, 27.6, 27.5, 25.8, 24.8, 22.0, 18.1; HRMS (ESI) calcd for $C_{32}H_{45}N_3NaO_7$ ($[M+Na]^+$) 606.3155, found 606.3144.

*4.1.23. Tryprostatin B (**2**).* A solution of **68** (1.04 g, 1.78 mmol) in *N*-methyl-2-pyrrolidinone (4.45 mL) was heated at reflux for 1.5 h. After cooling to room temperature, the resulting solution was purified with flash reverse-phase column chromatography (C-18, 50%–70% MeOH in H_2O) to remove NMP. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=2/1) to afford tryprostatin B (**2**) (559 mg, 1.59 mmol, 89%) as a yellow solid. Mp 100–102 °C; $[\alpha]_D^{24}$ −71 (*c* 0.78, $CHCl_3$); IR (neat, cm^{-1}) 3283, 2926, 1668, 1657, 1459, 1438, 1422; ^1H NMR ($CDCl_3$, 400 MHz) δ 8.04 (br s, 1H), 7.48 (d, *J*=7.8 Hz, 1H), 7.32 (d, *J*=7.8 Hz, 1H), 7.16 (dd, *J*=7.8, 6.9 Hz, 1H), 7.10 (dd, *J*=7.8, 6.9 Hz, 1H), 5.63 (br s, 1H), 5.31 (t, *J*=7.4 Hz, 1H), 4.37 (dd, *J*=11.4, 2.3 Hz, 1H), 4.07 (dd, *J*=7.8, 7.4 Hz, 1H), 3.71–3.53 (m, 3H), 3.47 (m, 2H), 2.96 (dd, *J*=14.6, 11.4 Hz, 1H), 2.37–2.31 (m, 1H), 2.10–1.99 (m, 2H), 1.95–1.89 (m, 1H), 1.79 (s, 3H), 1.75 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 165.8, 136.4, 135.4, 135.3, 127.9, 121.7, 119.8, 119.7, 117.7, 110.7, 104.5, 59.2, 54.5, 45.3, 28.3, 25.7, 25.5, 25.0, 22.6, 17.9; HRMS (ESI) calcd for $C_{21}H_{25}N_3NaO_2$ ($[M+Na]^+$) 374.1845, found 374.1841.

*4.1.24. 2-Iodo-5-methoxyaniline (**69**).* To a stirred solution of 4-iodo-3-nitroanisole (6.33 g, 22.7 mmol) in acetic acid (3.78 mL) and anhydrous EtOH (37.8 mL) were added Fe (7.60 g, 0.136 mol) and $FeCl_3$ (2.21 g, 13.6 mmol) portionwise at room temperature, and then the mixture was heated to 80 °C. After 40 min, the reaction mixture was filtered through a pad of Celite. To the resulting mixture was added H_2O and the aqueous layer was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=7/1) to afford **69** (4.77 g, 19.2 mmol, 84%) as a slightly yellow solid. Mp 33–34 °C; IR (neat, cm^{-1}) 3459, 3364, 2936, 1613, 1569, 1486, 1428, 1332; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.47 (d, *J*=8.7 Hz, 1H), 6.32 (d, *J*=2.8 Hz, 1H), 6.13 (dd, *J*=8.7, 2.8 Hz, 1H), 4.06 (s, 2H), 3.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.1, 147.6, 139.2, 106.6, 100.5, 73.4, 55.3; HRMS (DART) calcd for C_7H_9INO ($[M+H]^+$) 249.9729, found 249.9738.

*4.1.25. N-(2-Iodo-5-methoxyphenyl)formamide (**70**).* A mixture of formic acid (2.51 mL, 66.5 mmol) and acetic anhydride (3.39 mL, 33.2 mmol) was stirred at 50 °C for 1 h and then cooled to 0 °C. This

was added to a stirred solution of 2-iodo-5-methoxyaniline (**69**) (4.14 g, 16.6 mmol) in CH_2Cl_2 (83 mL) at 0 °C. After 2 h, the reaction mixture was quenched with saturated aq $NaHCO_3$ and the aqueous phase was extracted with CH_2Cl_2 twice. The combined organic extract was washed with saturated aq $NaHCO_3$ three times, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=4/1) to afford **70** (4.53 g, 16.4 mmol, 98%) as a white solid. Mp 103–104 °C; IR (neat, cm^{-1}) 3237, 2964, 2359, 1640, 1590, 1574, 1523, 1466; ^1H NMR ($CDCl_3$, 400 MHz) (2:1 mixture of two rotamers) (major) δ 8.49 (br s, 1H), 8.03 (d, J=2.8 Hz, 1H), 7.69 (d, J=8.8 Hz, 1H), 7.51 (br s, 1H), 6.55 (dd, J=8.8, 2.8 Hz, 1H), 3.81 (s, 3H) (minor) δ 8.66 (d, J=11.2 Hz, 1H), 6.77 (d, J=2.8 Hz, 1H), 7.62 (d, J=8.8 Hz, 1H), 7.51 (br s, 1H), 6.51 (dd, J=8.8, 2.8 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 158.9, 160.5, 138.7, 138.0, 113.2, 107.4, 78.8, 55.5 (minor) δ 161.7, 160.8, 140.0, 138.4, 112.5, 105.8, 77.1, 55.6; HRMS (ESI) calcd for $C_8H_8INNaO_2$ ($[M+Na]^+$) 299.9497, found 299.9488.

*4.1.26. (S)-tert-Butyl 4-((2-formamido-4-methoxyphenyl)ethynyl)-2,2-dimethyloxazolidine-3-carboxylate (**71**).* To a stirred solution of **53** (4.33 g, 19.2 mmol) and **70** (4.10 g, 14.8 mmol) in triethylamine (37 mL) and THF (37 mL) were added CuI (141 mg, 0.74 mmol) and $PdCl_2(PPh_3)_2$ (519 mg, 0.74 mmol) at room temperature. After 2 h, the reaction mixture was filtered through a pad of Celite. To the resulting solution was added saturated aq NH_4Cl and the aqueous phase was extracted with EtOAc twice. The combined organic extract was washed with saturated aq NH_4Cl twice, brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=6/1 to 4/1) to afford **71** (5.43 g, 14.5 mmol, 98%) as a slightly yellow oil. $[\alpha]_D^{20}$ +10 (*c* 1.48, $CHCl_3$); IR (neat, cm^{-1}) 3295, 2979, 2937, 1702, 1676, 1612, 1577, 1528, 1393; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.15 (s, 1H), 8.56 (s, 1H), 8.19 (s, 1H), 7.24 (d, J=8.2 Hz, 1H), 6.59 (d, J=8.2 Hz, 1H), 4.81 (dd, J=6.4, 5.0 Hz, 1H), 4.21 (dd, J=8.7, 6.4 Hz, 1H), 4.08 (dd, 8.7, 5.0 Hz, 1H), 3.83 (s, 3H), 1.59 (s, 3H), 1.54 (s, 3H), 1.51 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.7, 160.1, 152.5, 141.6, 131.2, 110.1, 104.9, 103.3, 94.5, 92.8, 81.4, 79.9, 67.7, 55.5, 49.2, 28.5, 26.1, 26.0; HRMS (ESI) calcd for $C_{20}H_{26}N_2NaO_5$ ($[M+Na]^+$) 397.1739, found 397.1722.

*4.1.27. (S,Z)-tert-Butyl 4-(2-formamido-4-methoxystyryl)-2,2-dimethyloxazolidine-3-carboxylate (**72**).* To a stirred solution of zinc powder (19.0 g, 290 mmol) in 2,2,2-trifluoroethanol (80 mL) was added dibromoethane (1.88 mL, 2.18 mmol). The resulting solution was heated up to 70 °C. After 30 min, the stirred solution was cooled to room temperature, to which was added an additional dibromoethane (1.88 mL, 2.18 mmol) and heated up to 70 °C for 30 min. After cooling the stirred solution to room temperature, a mixture of CuBr (6.24 g, 43.5 mmol) and LiBr (7.56 g, 87.0 mmol) in THF (45 mL) was added, and then the reaction mixture turned black. The mixture was heated at 70 °C for 30 min and cooled to room temperature, to which was added **71** (5.43 g, 14.5 mmol) in THF (10 mL), and stirred at 70 °C. After 3 h, the reaction mixture was filtered through a pad of Celite. To the resulting solution was added saturated aq NH_4Cl and the aqueous phase was extracted with EtOAc twice. The combined organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=6/1 to 3/1) to afford **72** (5.15 g, 13.7 mmol, 94%) as a slightly yellow oil. $[\alpha]_D^{20}$ −114 (*c* 0.73, $CHCl_3$); IR (neat, cm^{-1}) 3286, 2979, 2871, 1697, 1673, 1580, 1531, 1399, 1215; ^1H NMR ($CDCl_3$, 400 MHz) δ 9.54 (s, 1H), 8.41 (s, 1H), 8.02 (d, J=2.8 Hz, 1H), 6.90 (d, J=8.2 Hz, 1H), 6.64 (dd, J=8.2, 2.8 Hz, 1H), 6.45 (d, J=11.0 Hz, 1H), 5.74 (dd, J=11.0, 10.1 Hz, 1H), 4.26 (ddd, J=10.1, 6.4, 6.4 Hz, 1H), 3.89 (dd, J=8.7, 6.4 Hz, 1H), 3.61 (dd, J=8.7, 6.4 Hz, 1H), 3.82 (s, 3H), 1.56 (s, 3H), 1.49 (s, 9H), 1.47 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 160.4, 159.3, 152.7, 135.2, 134.3, 129.9, 127.6, 118.3, 110.7, 106.4, 94.1, 81.1, 67.8, 56.1, 55.4, 28.4, 26.3, 25.9; HRMS (ESI) calcd for $C_{20}H_{28}N_2NaO_5$ ($[M+Na]^+$) 399.1896, found 399.1879.

*4.1.28. (S,Z)-tert-Butyl 4-(2-isocyano-4-methoxystyryl)-2,2-dimethyloxazolidine-3-carboxylate (**73**).* To a stirred solution of **72** (5.09 g, 13.5 mmol) and pyridine (10.9 mL, 135 mmol) in CH_2Cl_2 (200 mL) was added triphosgene (1.60 g, 5.41 mmol) at 0 °C. After 20 min, the reaction mixture was poured into ice-cold saturated aq $NaHCO_3$ The organic layer was washed with saturated aq $NaHCO_3$ three times and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=8/1 to 6/1) to afford **73** (4.13 g, 11.5 mmol, 85%) as a white solid. Mp 89–90 °C; $[\alpha]_D^{24}$ −83 (*c* 1.35, $CHCl_3$); IR (neat, cm^{-1}) 2979, 2935, 2871, 2120, 1697, 1610, 1503, 1385; ^1H NMR ($CDCl_3$, 400 MHz) (2:1 mixture of two rotamers) (major) δ 7.14 (s, 1H), 6.95–6.90 (m, 2H), 6.56 (d, J=11.9 Hz, 1H), 5.84 (dd, J=11.9, 9.6 Hz, 1H), 4.70 (br s, 1H), 4.15 (br s, 1H), 3.85 (br s, 1H), 3.82 (s, 3H), 1.64 (s, 3H), 1.52 (s, 9H), 1.31 (s, 3H) (minor) δ 7.77 (s, 1H), 6.95–6.90 (m, 2H), 6.56 (d, J=11.9 Hz, 1H), 5.84 (dd, J=11.9, 9.6 Hz, 1H), 4.70 (br s, 1H), 4.02 (br s, 1H), 3.76 (br s, 1H), 3.82 (s, 3H), 1.64 (s, 3H), 1.52 (s, 9H), 1.31 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 167.0, 159.0, 151.9, 134.7, 130.7, 126.4, 125.5, 123.9, 115.5, 112.1, 94.5, 80.1, 68.8, 55.7, 55.0, 28.4, 26.5, 24.1 (minor) δ 166.2, 159.0, 151.9, 134.1, 130.7, 126.4, 125.5, 124.8, 115.5, 112.1, 93.8, 80.1, 68.8, 55.7, 55.0, 28.4, 27.4, 25.2; HRMS (ESI) calcd for $C_{20}H_{26}N_2NaO_4$ ($[M+Na]^+$) 381.1790, found 381.1774.

*4.1.29. (S)-tert-Butyl 4-((6-methoxy-2-(3-methylbut-2-enyl)-1H-indol-3-yl)methyl)-2,2-dimethyloxazolidine-3-carboxylate (**74**).* To a stirred solution of **73** (4.10 g, 11.4 mmol) and tributyltin hydride (9.07 mL, 34.2 mmol) in toluene (60 mL) was added 2,2′-azobis(4-methoxy-2,4-dimethylvaleronitrile) (**61**, V-70) (706 mg, 2.29 mmol) at 30 °C. After 1.5 h, the reaction mixture was added prenyl acetate (**63**) (7.15 mL, 51.3 mmol), lithium chloride (2.17 g, 51.3 mmol), triphenylarsine (998 mg, 3.26 mmol), *N*,*N*-dimethylformamide (170 mL), and $Pd_2(dba)_3$ (722 mg, 0.788 mmol) and the mixture was heated to 80 °C. After 7 h, the reaction mixture was quenched with saturated aq KF and the aqueous phase was extracted with Et_2O three times. The combined organic extract was washed with saturated aq KF twice, brine, and dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=6/1 to 3/1) to afford **74** (3.89 g, 9.08 mmol, 80%) as a slightly yellow oil. $[\alpha]_D^{24}$ −47 (*c* 1.02, $CHCl_3$); IR (neat, cm^{-1}) 3353, 2979, 2933, 1693, 1629, 1463, 1391, 1255; ^1H NMR ($CDCl_3$, 400 MHz) (6:5 mixture of two rotamers) (major) δ 7.72 (s, 1H), 7.48 (d, J=8.4 Hz, 1H), 6.85–6.70 (m, 2H), 5.29 (t, J=6.8 Hz, 1H), 4.24–4.09 (m, 1H), 3.82 (s, 3H), 3.71 (br s, 2H), 3.47 (d, J=6.8 Hz, 2H), 3.13 (br d, 13.2 Hz, 1H), 2.76 (t, J=12.4 Hz, 1H), 1.84–1.60 (m, 9H), 1.60–1.43 (m, 12H) (minor) δ 7.69 (s, 1H), 7.61 (d, J=8.0 Hz, 1H), 6.85–6.70 (m, 2H), 5.29 (t, J=6.8 Hz, 1H), 4.24–4.09 (m, 1H), 3.82 (s, 3H), 3.71 (br s, 2H), 3.47 (d, J=6.8 Hz, 2H), 3.24 (br d, 13.6 Hz, 1H), 2.76 (t, J=12.4 Hz, 1H), 1.84–1.60 (m, 9H), 1.60–1.43 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 156.0, 152.0, 135.9, 134.7, 134.1, 123.3, 120.4, 118.8, 108.7, 107.4, 94.7, 94.2, 79.9, 66.4, 57.6, 55.8, 28.8, 27.9, 27.2, 25.8, 24.6, 23.3, 17.9 (minor) δ 156.0, 152.3, 135.8, 134.4, 133.9, 123.5, 120.6, 119.4, 108.9, 107.7, 94.4, 93.5, 79.9, 66.4, 58.3, 55.8, 28.6, 27.9, 27.1, 25.1, 24.6, 23.3, 17.9; HRMS (ESI) calcd for $C_{25}H_{36}N_2NaO_4$ ($[M+Na]^+$) 451.2573, found 451.2568.

*4.1.30. (S)-tert-Butyl 3-(2-(tert-butoxycarbonylamino)-3-hydroxypropyl)-6-methoxy-2-(3-methylbut-2-enyl)-indole-1-carboxylate (**75**).* To a stirred solution of **74** (3.50 g, 8.17 mmol) in MeCN (82 mL) were added Boc_2O (2.32 g, 10.6 mmol) and 4-(dimethylamino)pyridine (DMAP) (299 mg, 2.45 mmol) at room

temperature. After 1 h, the reaction mixture was quenched with saturated aq NH_4Cl and extracted with EtOAc three times. The combined organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=10/1) to afford the Boc intermediate (3.97 g, 7.51 mmol, 92%) as a white solid. To a stirred solution of the Boc intermediate (3.97 g, 7.51 mmol) in THF (13.5 mL) and H_2O (6.73 mL) at 0 °C was added cooled trifluoroacetic acid (26.9 mL). After 10 min, the reaction mixture was poured into cooled saturated aq $NaHCO_3$ and extracted with EtOAc. The organic layer was washed with saturated aq $NaHCO_3$ three times, brine, and dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=4/1 to 2/1) to afford **75** (3.31 g, 7.22 mmol, 96%) as a colorless solid. *Boc intermediate*: mp 137–139 °C; $[\alpha]_D^{24}$ −36 (*c* 0.98, $CHCl_3$); IR (neat, cm^{-1}) 2979, 1730, 1697, 1618, 1579, 1491, 1365; ^1H NMR ($CDCl_3$, 400 MHz) (1:1 mixture of two rotamers) (major) δ 7.70 (s, 1H), 7.65 (d, *J*=8.7 Hz, 1H), 6.84 (d, *J*=8.7 Hz, 1H), 5.17 (t, *J*=5.0 Hz, 1H), 4.20–4.17 (m, 1H), 3.86 (s, 3H), 3.76 (d, *J*=5.0 Hz, 1H), 3.69 (br s, 2H), 3.19 (br d, *J*=12.8 Hz, 1H), 2.80–2.68 (m, 1H), 1.78–1.44 (m, 30H) (minor) δ 7.70 (s, 1H), 7.46 (d, *J*=8.7 Hz, 1H), 6.88 (d, *J*=8.7 Hz, 1H), 5.17 (t, *J*=5.0 Hz, 1H), 4.13–4.10 (m, 1H), 3.86 (s, 3H), 3.69 (d, *J*=5.0 Hz, 1H), 3.69 (br s, 2H), 3.08 (dd, *J*=13.7, 3.2 Hz, 1H), 2.80–2.68 (m, 1H), 1.78–1.44 (m, 30H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 157.3, 151.9, 150.4, 136.8, 136.4, 132.2, 123.7, 122.1, 119.4, 115.0, 111.2, 100.2, 93.4, 83.6, 80.1, 66.1, 57.7, 55.7, 28.7, 28.1, 28.0, 27.2, 26.0, 25.7, 24.5, 18.2 (minor) δ 157.4, 152.2, 150.5, 136.9, 136.2, 132.0, 123.8, 122.0, 118.7, 114.6, 111.6, 100.0, 94.2, 83.4, 80.0, 66.1, 56.9, 55.7, 28.5, 27.4, 27.9, 27.2, 26.0, 25.7, 23.3, 18.1; HRMS (ESI) calcd for $C_{30}H_{44}N_2NaO_6$ ($[M+Na]^+$) 551.3097, found 551.3080. Compound **75**: mp 43–44 °C; $[\alpha]_D^{25}$ −5.4 (*c* 0.96, $CHCl_3$); IR (neat, cm^{-1}) 3438, 2977, 2932, 1726, 1491, 1366, 1326; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.71 (d, *J*=2.3 Hz, 1H), 7.46 (d, *J*=8.7 Hz, 1H), 6.86 (q, *J*=8.7, 2.3 Hz, 1H), 5.22 (br s, 1H), 4.91 (br s, 1H), 3.95–3.84 (m, 1H), 3.86 (s, 3H), 3.70 (d, *J*=5.2 Hz, 1H), 3.61 (br d, *J*=9.2 Hz, 1H), 3.53 (br d, *J*=9.2 Hz, 1H), 2.92–2.82 (m, 1H), 2.37 (br s, 1H), 1.75 (s, 3H), 1.71 (s, 3H), 1.66 (s, 9H), 1.43 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.4, 156.2, 150.5, 136.9, 136.1, 132.4, 123.7, 122.4, 118.9, 114.4, 111.5, 100.2, 83.6, 79.6, 64.0, 55.7, 52.5, 28.4, 28.1, 28.1, 25.9, 25.7, 18.1; HRMS (ESI) calcd for $C_{27}H_{40}N_2NaO_6$ ($[M+Na]^+$) 511.2784, found 511.2762.

*4.1.31. tert-Butyl 3-((S)-2-(tert-butoxycarbonylamino)-3-((S)-2-(methoxycarbonyl)pyrrolidin-1-yl)-3-oxopropyl)-6-methoxy-2-(3-methylbut-2-enyl)-indole-1-carboxylate (**76**).* To a stirred solution of **75** (1.58 g 3.23 mmol) and iodobenzene diacetate (5.20 g, 16.2 mmol) in MeCN (10 mL) and phosphate buffer (pH 6.8) (10 mL), was added 2,2,6,6-tetramethyl- piperidine-1-oxyl (TEMPO) (252 mg, 1.62 mmol) at 0 °C. After 2 h, saturated aq $NaHCO_3$ was added to the reaction mixture and the aqueous phase was extracted with EtOAc three times. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=3/1 to 1/1) to afford the carboxylic acid (1.47 g, 2.92 mmol, 91%) as a colorless oil. To a stirred solution of the carboxylic acid (1.29 g, 2.57 mmol) and L-proline methyl ester *p*-toluenesulfonate (**67**) (579 mg, 3.34 mmol) in CH_2Cl_2 (12.9 mL) were added HATU (1.95 g, 5.13 mmol) and *N*,*N*-diisopropylamine (895 μL, 5.14 mmol) at room temperature. After 1 h, the reaction mixture was quenched with saturated aq NH_4Cl and the aqueous phase was extracted with EtOAc three times. The combined organic extract was washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=9/1 to 3/1) to afford **76** (1.21 g, 1.97 mmol, 77%) as a colorless oil. *Carboxylic acid*: $[\alpha]_D^{25}$ +41 (*c* 1.06, $CHCl_3$); IR (neat, cm^{-1}) 2978, 2933, 1731, 1620, 1580, 1492, 1443, 1368, 1325; ^1H NMR ($CDCl_3$, 400 MHz) (3:1 mixture of two rotamers) (major) δ 7.70 (s, 1H), 7.36 (d, *J*=8.2 Hz, 1H), 6.85 (dd, *J*=8.2, 1.8 Hz, 1H), 5.21 (br s, 1H), 5.01 (br s, 1H), 4.50 (br s, 1H), 3.85 (s, 3H), 3.78–3.58(m, 1H), 3.22 (dd, *J*=14.6, 4.6 Hz, 1H), 3.13–3.01 (m, 1H), 1.74 (s, 3H), 1.70 (s, 3H), 1.66 (s, 9H), 1.38 (s, 9H) (minor) δ 7.70 (s, 1H), 7.36 (d, *J*=8.2 Hz, 1H), 6.85 (dd, *J*=8.2, 1.8 Hz, 1H), 5.21 (br s, 1H), 5.01 (br s, 1H), 4.50 (br s, 1H), 3.85 (s, 3H), 3.78–3.58(m, 1H), 3.22 (dd, *J*=14.6, 4.6 Hz, 1H), 2.96 (br s, 1H), 1.74 (s, 3H), 1.70 (s, 3H), 1.66 (s, 9H), 1.38 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 176.5, 157.4, 155.7, 150.4, 136.8, 136.6, 132.5, 123.3, 122.1, 118.6, 112.7, 111.6, 100.1, 83.8, 80.3, 55.6, 53.7, 29.2, 28.3, 27.6, 25.9, 25.6, 18.1 (minor) δ 176.1, 157.4, 155.7, 150.4, 136.9, 136.6, 132.0, 123.6, 122.2, 118.3, 113.5, 111.6, 100.3, 83.6, 81.0, 55.6, 54.7, 29.2, 28.1, 26.7, 25.8, 25.6, 18.1; HRMS (ESI) calcd for $C_{27}H_{38}N_2NaO_7$ ($[M+Na]^+$) 525.2577, found 525.2586. Compound **76**: $[\alpha]_D^{24}$ +13 (*c* 1.01, $CHCl_3$); IR (neat, cm^{-1}) 3437, 3308, 2977, 1726, 1646, 1579, 1491, 1442, 1365; ^1H NMR ($CDCl_3$, 400 MHz) (10:7 mixture of two rotamers) (major) δ 7.73 (d, *J*=2.0 Hz, 1H), 7.43 (d, *J*=8.0 Hz, 1H), 6.87 (dd, *J*=8.0, 2.0 Hz, 1H), 5.15 (d, *J*=8.4 Hz, 1H), 5.21 (br s, 1H), 4.76–4.70 (m, 1H), 4.56–4.50 (m, 1H), 3.86 (s, 3H), 3.69 (s, 3H), 3.75–3.58 (m, 2H), 3.50–3.38 (m, 1H), 3.25–3.15 (m, 1H), 3.13–2.98 (m, 1H), 2.97–2.86 (m, 1H), 2.21–2.12 (m, 1H), 2.01–1.89 (m, 3H), 1.76 (s, 3H), 1.70 (s, 3H), 1.66 (s, 9H), 1.32 (s, 9H) (minor) δ 7.68 (d, *J*=2.4 Hz, 1H), 7.39 (d, *J*=8.0 Hz, 1H), 6.85 (dd, *J*=8.0, 2.4 Hz, 1H), 5.49 (d, *J*=8.8 Hz, 1H), 5.14 (br s, 1H), 4.49–4.43 (m, 1H), 4.56–4.50 (m, 1H), 3.86 (s, 3H), 3.65 (s, 3H), 3.75–3.58 (m, 2H), 3.50–3.38 (m, 1H), 3.13–2.98 (m, 1H), 3.13–2.98 (m, 1H), 2.97–2.86 (m, 1H), 2.21–2.12 (m, 1H), 2.01–1.89 (m, 3H), 1.76 (s, 3H), 1.70 (s, 3H), 1.66 (s, 9H), 1.44 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz) (major) δ 172.3, 171.0, 157.2, 155.2, 150.5, 137.0, 136.7, 132.4, 123.6, 122.5, 118.3, 112.9, 111.5, 100.2, 83.8, 79.4, 58.8, 55.8, 52.1, 51.6, 46.9, 30.1, 29.0, 28.2, 28.1, 25.9, 25.7, 24.8, 18.2 (minor) δ 171.8, 171.0, 157.4, 154.6, 150.4, 136.9, 136.6, 131.9, 123.4, 121.6, 118.7, 113.0, 111.6, 99.9, 83.5, 79.3, 58.8, 55.8, 52.6, 52.2, 46.1, 29.8, 27.6, 28.3, 28.1, 25.8, 25.7, 22.1, 18.1; HRMS (ESI) calcd for $C_{33}H_{47}N_3NaO_8$ ($[M+Na]^+$) 636.3261, found 636.3254.

*4.1.32. Tryprostatin A (**1**).* A solution of **76** (1.20 g, 1.96 mmol) in *N*-methyl-2-pyrrolidinone (5.42 mL) was heated at reflux for 2 h. After cooling to room temperature, the resulting solution was purified with flash reverse-phase column chromatography (C-18, 50%–70% MeOH in H_2O) to remove NMP. The residue was purified with flash column chromatography on silica gel (hexane/EtOAc=2/1) to afford tryprostatin A (**1**) (580 mg, 1.52 mmol, 78%) as a yellow solid. Mp 119–120 °C; $[\alpha]_D^{23}$ −70 (*c* 0.78, $CHCl_3$); IR (neat, cm^{-1}) 3327, 2981, 2929, 2884, 2838, 1668, 1657, 1458, 1422, 1159; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.90 (br s, 1H), 7.34 (d, *J*=8.7 Hz, 1H), 6.83 (d, 2.3 Hz, 1H), 6.76 (dd, *J*=8.7, 2.3 Hz, 1H), 5.65 (s, 1H), 5.32–5.26 (m, 1H), 4.33 (dd, *J*=11.2, 3.6 Hz, 1H), 4.06 (dd, *J*=7.6, 7.6 Hz, 1H), 3.83 (s, 3H), 3.71–3.57 (m, 3H), 3.49–3.37 (m, 2H), 2.91 (dd, *J*=15.1, 11.4 Hz, 1H), 2.38–2.29 (m, 1H), 2.09–2.02 (m, 2H), 1.98–1.86 (m, 1H), 1.77 (s, 3H), 1.74 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 169.3, 165.8, 156.3, 136.3, 135.2, 135.1, 122.2, 120.0, 118.3, 109.3, 104.4, 94.8, 59.3, 55.7, 54.5, 45.4, 28.4, 25.8, 25.7, 25.1, 22.6, 18.0; HRMS (ESI) calcd for $C_{22}H_{27}N_3NaO_3$ ($[M+Na]^+$) 404.1950, found 404.1934.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2011.05.112.

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