= 3 Hz, H-6e), 2.57 (tt, 1 H, $^3J_{(9a)ax,1ax}$ = 11 Hz, $^3J_{(9a)ax,9ax}$ = 11 Hz, $^3J_{(9a)ax,1e}$ = 3 Hz, $^3J_{(9a)ax,9e}$ = 3 Hz, H-(9a)ax), 1.5-1.9 (m, 4 H, H-8,9); ^{13}C NMR δ 165.9 (C=O), 154.5 (C-ipso), 129.5, 128.9, 128.7, 120.8, 112 (C-Ar), 105.3 (C-7), 64.8, 64.5 (OCH_2CH_2O), 60.2 (C-6), 58.4 (C-4), 55.8 (C-9a), 55.4 (C-OCH_3), 54.6 (C-1), 32.5 (C-8), 26.5 (C-9); exact mass calcd for $C_{17}H_{22}N_2O_4$ 318.1577, found 318.1573.

7-(Ethylenedioxy)-2-phenyloctahydro-2*H*-pyrido[1,2-*a*]pyrazine (15a). To a stirred solution of **14a** (293 mg, 1.02 mmol) in 20 mL of anhydrous ether was added $LiAlH_4$ (100 mg, 2.64 mmol) portionwise. After 1 h, the excess of hydride was destroyed by dropwise addition of methanol followed by addition of CH_2Cl_2 (200 mL), K_2CO_3 (100 mg), and water (2 mL). The organic solvent was evaporated, and the residue was chromatographed on a silica column (gradient elution 5-20% EtOAc-$CHCl_3$) to give **15a** (200 mg, 72%) as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.3 (dd, 2 H, Ph), 6.9 (dd, 2 H, Ph), 6.89 (tt, 1 H, Ph), 4 (m, 4 H, OCH_2CH_2O), 3.63 (dd, 1 H, ^2J = 12 Hz, $^3J_{1ax,(9a)ax}$ = 10 Hz, H-1ax), 3.5 (dm, 1 H, ^2J = 12 Hz, H-1e), 3.5 (dm, 1 H, ^2J = 11 Hz, H-3e), 3.05 (td, 1 H, ^2J = 11 Hz, $^3J_{3ax,4ax}$ = 11 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 2.89 (dt, 1 H, ^2J = 11 Hz, $^3J_{4e,3ax}$ = 3 Hz, $^3J_{4e,3e}$ = 2.5 Hz, H-4e), 2.8 (dd, 1 H, ^2J = 11.5 Hz, $^4J_{6e,8e}$ = 2.5 Hz, H-6e), 2.4 (td, 1 H, ^2J = 11 Hz, $^3J_{4ax,3ax}$ = 11 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.22 (d, 1 H, ^2J = 11.5 Hz, H-6ax), 2.15 (m, 1 H, H-(9a)ax), 1.87 (m, 1 H, H-8e), 1.65 (m, 3 H, H-9, 8ax); exact mass calcd for $C_{16}H_{22}N_2O_2$ 274.1680, found 274.1677.

2-Phenyloctahydro-2*H*-pyrido[1,2]pyrazin-7-one (16a). A mixture of **15a** (500 mg, 1.82 mmol) and 6 M HCl (20 mL) was refluxed for 2 h. The solution was evaporated, and the residue was dissolved in water (10 mL). The aqueous solution was cooled to 0 °C and made alkaline with K_2CO_3 after the addition of CH_2Cl_2 (100 mL). The aqueous layer was further extracted with CH_2Cl_2 (50 mL), and the combined organic layers were evaporated. Column chromatography of the residual oil on silica (gradient elution 5-15% EtOAc-$CHCl_3$) afforded pure **16a** (395 mg, 94%) as a yellow oil (stored as the HCl salt since it was oxidized in its basic form): IR ν 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$ + C_6D_6) δ 7.22 (dd, 2 H, Ph), 6.85 (t, 1 H, Ph), 6.75 (dd, 2 H, Ph), 3.38 (dt, 1 H, ^2J = 11.3 Hz, $^3J_{1e,(9a)ax}$ = 2.5 Hz, $^4J_{1e,3e}$ = 2.5 Hz, H-1e), 3.32 (dq, 1 H, ^2J = 11.5 Hz, $^3J_{3e,4ax}$ = 3 Hz, $^3J_{3e,4e}$ = 2.5 Hz, $^4J_{3e,1e}$ = 2.5 Hz, H-3e), 3.17 (dd, 1 H, ^2J = 14 Hz, $^4J_{6e,8e}$ = 2 Hz, H-6e), 2.71 (td, 1 H, ^2J = 11.5 Hz, $^3J_{3ax,4ax}$ = 11.5 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 2.56 (dt, 1 H, ^2J = 11 Hz, $^3J_{4e,3ax}$ = 3 Hz, $^3J_{4e,3e}$ = 2.5 Hz, H-4e), 2.54 (dd, 1 H, ^2J = 14 Hz, $^4J_{6ax,8ax}$ = 1 Hz, H-6ax), 2.35 (dd, 1 H, ^2J = 11.3 Hz, $^3J_{1ax,(9a)ax}$ = 10.2 Hz, H-1ax), 2.21 (td, 1 H, ^2J = 11 Hz, $^3J_{4ax,3ax}$ = 11.5 Hz, $^3J_{4ax,3e}$ = 3 Hz, H-4ax), 2.12-2.38 (m, 2 H, H-8e,(9a)ax), 2.04 (dddd, 1 H, ^2J = 15 Hz, $^3J_{8ax,9ax}$ = 13 Hz, $^3J_{8ax,9e}$ = 7 Hz, $^4J_{8ax,6ax}$ = 1 Hz, H-8ax), 1.57 (ddt, 1 H, ^2J = 13 Hz, $^3J_{9e,8ax}$ = 7 Hz, $^3J_{9e,(9a)ax}$ = 3 Hz, $^3J_{9e,8e}$ = 2.5 Hz, H-9e), 1.45 (tdd, 1 H, ^2J = 13 Hz, $^3J_{9ax,8ax}$ = 13 Hz, $^3J_{9ax,(9a)ax}$ = 10.5 Hz, $^3J_{9ax,8e}$ = 5 Hz); exact mass calcd for $C_{14}H_{18}N_2O$ 230.1419, found 230.1417.

2-(2-Methoxyphenyl)octahydro-2*H*-pyrido[1,2-*a*]pyrazin-7-one (16b). To a stirred solution of **14b** (200 mg, 0.63 mmol) in 15 mL of anhydrous ether was added $LiAlH_4$ (50 mg, 1.32 mmol). After 1 h, the excess of hydride was destroyed with MeOH and the mixture worked up as for **15a** to give the crude product **15b** (176 mg, 92%) as an oil, which was used directly in the next step: MS *m/z* 304 (M^+). A mixture of the crude product **15b** (176 mg) and 6 M HCl (10 mL) was refluxed for 2 h. After workup as described for **16a**, column chromatography using silica gel with EtOAc as eluent afforded pure **16b** (107 mg, 65% from **15b**) as a pale yellow crystalline product, mp 106-108 °C: IR ν 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 6.85-7.1 (m, 4 H, Ar), 3.9 (s, 3 H, OCH_3), 3.49 (dt, 1 H, ^2J = 11 Hz, $^3J_{1e,(9a)ax}$ = 3 Hz, $^4J_{1e,3e}$ = 3 Hz, H-1e), 3.43 (dq, 1 H, ^2J = 12.5 Hz, $^3J_{3e,4ax}$ = 3 Hz, $^3J_{3e,4e}$ = 3 Hz, $^4J_{3e,1e}$ = 3 Hz, H-3e), 3.33 (dd, 1 H, ^2J = 14 Hz, $^4J_{6e,8e}$ = 2 Hz, H-6e), 2.84-2.9 (m, 1 H, H-4e), 2.88 (d, 1 H, ^2J = 14 Hz, H-6ax), 2.84 (td, 1 H, ^2J = 12.5 Hz, $^3J_{3ax,4ax}$ = 12.5 Hz, $^3J_{3ax,4e}$ = 3 Hz, H-3ax), 2.46-2.7 (m, 3 H, H-(9a)ax,8e,4ax), 2.47 (t, 1 H, ^2J = 10.5 Hz, $^3J_{1ax,(9a)ax}$ = 10.5 Hz, H-1ax), 2.38 (ddd, 1 H, ^2J = 15 Hz, $^3J_{8ax,9ax}$ = 11.7 Hz, $^3J_{8ax,9e}$ = 7 Hz, H-8ax), 1.95 (ddt, 1 H, ^2J = 13 Hz, $^3J_{9e,8ax}$ = 7 Hz, $^3J_{9e,(9a)ax}$ = 3 Hz, $^4J_{9e,1e}$ = 3 Hz, H-9e), 1.7 (tdd, 1 H, ^2J = 13 Hz, $^3J_{9ax,8ax}$ = 11.7 Hz, $^3J_{9ax,(9a)ax}$ = 10 Hz, $^3J_{9ax,8e}$ = 5.5 Hz, H-9ax); ^{13}C NMR δ 205.8 (C=O), 152.3 (C-2' Ar), 140.8 (C-1' Ar), 123.1, 121, 118.2, 111.4 (C-3',4',5',6' Ar), 65.3 (C-6), 58.6 (C-9a), 56.1 (C-1), 55.4 (OCH_3), 55 (C-4), 49.9 (C-3), 38.3 (C-8), 28.4 (C-9); exact mass calcd for $C_{15}H_{20}N_2O_2$ 260.1523, found 260.1525. Anal. Calcd for $C_{15}H_{20}N_2O_2$: C, 69.21; H, 7.74; N, 10.76. Found: C, 69.25 H, 7.70; N, 10.80.

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Registry No. **1**, 132462-23-8; **2**, 134334-33-1; **3**, 134334-34-2; **4a**, 134334-35-3; **5**, 134334-36-4; **7**, 134334-37-5; **8**, 134334-38-6; **9**, 134334-39-7; **11**, 134334-40-0; **12a**, 134334-41-1; **12b**, 134334-42-2; **13a**, 134334-45-5; **13b**, 134334-46-6; **14a**, 134334-43-3; **14b**, 134334-44-4; **15a**, 134334-47-7; **15b**, 134334-48-8; **16a**, 134334-49-9; **16b**, 134334-50-2; $LiAl(OEt)_3H$, 17250-30-5; $ClCH_2COCl$, 79-04-9; $C_6H_5CH_2Br$, 100-39-0; $C_6H_5NH_2$, 62-53-3; 2-$MeOC_6H_4NH_2$, 90-04-0; 2-fluoropyridine, 372-48-5.

Supplementary Material Available: ^{1}H and/or ^{13}C NMR spectra for compounds **2**, **3**, **11**, **12a**, **12b**, **14a**, **14b**, **15a**, and **16a** (10 pages). Ordering information is given on any current masthead page.

Asymmetric Total Synthesis of (+)-Jasplakinolide

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A convergent synthesis of the marine cyclodepsipeptide (+)-jasplakinolide has been realized. The synthesis of the required (*R*)-β-tyrosine unit is accomplished via the stereospecific palladium-catalyzed arylation of an enantiomerically pure dihydropyrimidinone. The overall yield of the synthesis, based on the longest linear sequence, is 6.6%.

In 1986, two papers documenting the isolation, structure, and biological activity of a novel cyclodepsipeptide of marine origin appeared in the literature.[1] This metabolite, which is composed of both peptide and polypropionate portions, was named jasplakinolide (1) by the Crews group[1a] and jaspamide by the Ireland-Faulkner team.[1b]

Along with the common acid (*S*)-alanine, jasplakinolide contains two unusual amino acids, β-tyrosine[2] and 2-

† American Cancer Society Junior Faculty Research Awardee, 1987-90.

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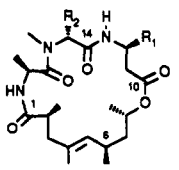

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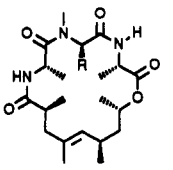

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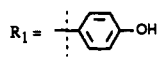
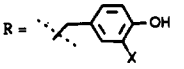
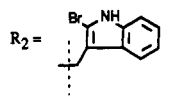






X = I; geodiamolide A

X = Br; geodiamolide B

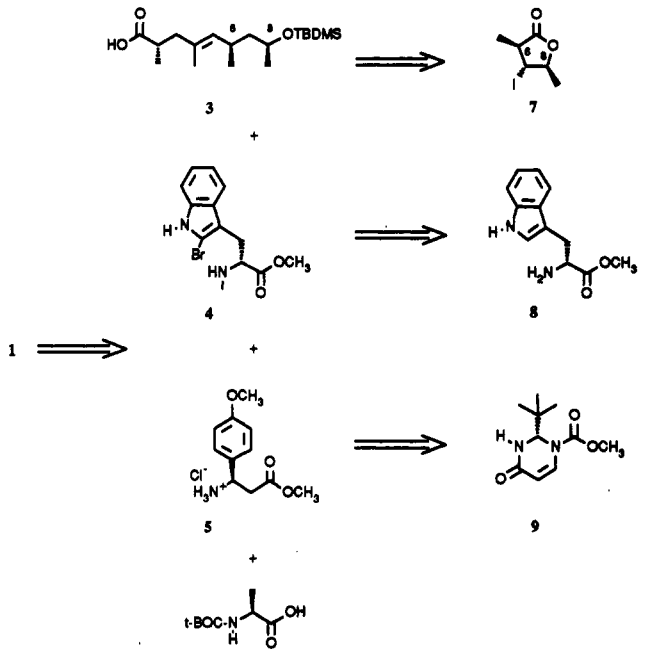
bromoabrine, both possessing the less common *R* absolute configuration. The nonenoic acid fragment contains three chiral centers and had also not been described previously in the literature.

Initially, our attention was drawn to the tryptophan–tyrosine portion of the molecule, undoubtedly an important aspect of the structure–activity relationship.[3] Work by the Crews' group[4] on the solution conformation of the molecule indicated that the β-tyrosine unit has more conformational mobility than the other portions of the ring. As shown below, synthesis of the desired 2-bromoabrine molecule is straightforward. However, the lack of general enantioselective approaches to the synthesis of β-aryl β-amino acids prompted us to investigate new routes to this class of compound[5] within the context of a total synthetic venture.

The combination of a wide range of biological activity (including cytotoxic, anthelminthic, insecticidal, and specific antifungal against *Candida albicans*) with its unique structural aspects has made jasplakinolide an attractive target for total synthesis. To date, one completed synthesis has appeared,[6] as well as reports of the synthesis of both the peptide[7] and polypropionate[8] sections. In addition, several published reports of the synthesis of the structurally related, but inactive, marine cyclodepsipeptides geodiamolide A and B (2)[9,10] have appeared. Below we report our own efforts in this area, which have culminated in the total synthesis of (+)-jasplakinolide.

Results and Discussion

Retrosynthetically, 1 can be divided into protected hydroxy acid 3 and the protected constituent amino acid fragments 4–6. Protected (*S*)-alanine 6 and (*R*)-tryptophan 8 fragments are commercial products. Dihydropyrimidinone 9, prepared from (*S*)-asparagine, provides the starting point for production of 5,[5] while lactone 7[11] can be elaborated into fragment 3. Our plan was to prepare the tripeptide and polypropionate segments, joining the C-1, N-19 amide bond prior to the ester linkage. Ester formation was chosen as the last step to avoid racemization in the ring closure.



6 *N*-*t*-BOC-(*S*)-alanine

Our independent route[12] to (*E*)-(2*S*,6*R*,8*S*)-8-[(*tert*-butyldimethylsilyl)oxy]-2,4,6-trimethyl-4-nonenoic acid (3) is similar to that completed by Grieco.[6] Enantiomerically pure lactone 7 is catalytically dehalogenated and subsequently reduced with DIBAL prior to treatment with 2-lithio-2-propene. The resultant mixture of diol isomers 10 (73% yield from 7) is directly subjected to the Eschenmoser variation of the Claisen rearrangement[13] and affords, after base hydrolysis, the desired hydroxy acid along with starting diol. Recycling of the recovered diol through the Claisen protocol allows for a 75% isolated yield of hydroxy acid. Protection of the secondary hydroxy functionality as its *tert*-butyldimethylsilyl derivative 11 is uneventful (94% yield). Use of the Evans auxiliary[14–16] (*S*)-4-isopropyl-4-oxazolidinone allows asymmetric methylation to proceed in 88% yield as a 3:1 mixture of isomers, separable by HPLC. The major isomer 12, obtained in 62% yield, is transformed to the corresponding carboxylic acid 3 by treatment with $LiOH/H_2O_2$[17] in 86% yield (9 steps, 25% yield from 7).

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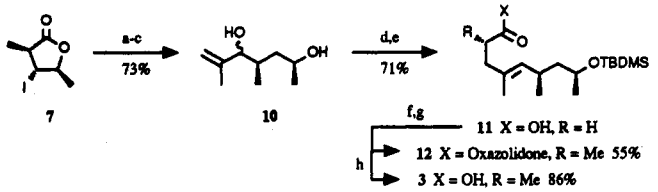
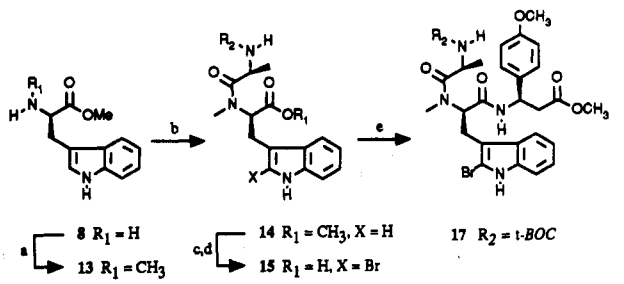
(15) In independent studies, we have established that 9 functions in an analogous fashion to the Evans reagent.[16] In a *single, unoptimized* experiment, substitution of 9 into the methylation sequence of this scheme allows for a 50% yield of product as a 2:1 diastereomeric mixture along with a 50% yield of starting material.
(16) Negrete, G. R.; Konopelski, J. P. *Tetrahedron: Asymmetry* **1991**, *2*, 105–8.
(17) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *29*, 6141–4.



7 10

(a) 10% Pd/C, H_2, $N(Et)_3$, MeOH, rt, 30 min; (b) DIBAL, −78 °C, 30 min; (c) $CH_2{=}C(Li)CH_3$; (d) $CH_3C(OCH_3)_2N(CH_3)_2$, reflux; OH^-; (e) TBDMSCl, imidazole, DMF; (f) KOH, ClCOCOCl, lithium salt of (*S*)-4-isopropyl-2-oxazolidinone; (g) $NaN(TMS)_2$, MeI; (h) LiOH, H_2O_2.

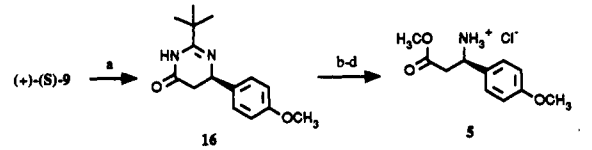
The preparation of the tripeptide portion of jasplakinolide[5] begins with treatment of (*R*)-tryptophan methyl ester (**8**) with acetic formic anhydride,[18] followed by borane reduction to afford *N*-methyl-(*R*)-tryptophan methyl ester (**13**) in 56% yield.[19] Coupling of **13** to *N*-BOC-(*S*)-alanine (DCC/HOBt, 90%) gives desired dipeptide **14** with little (<2%) racemization.[20a] Bromination of **14** (*N*-bromosuccinimide, peroxide, 78%)[21] introduces the 2-bromoindole functionality, and base hydrolysis (Na_2CO_3/H_2O, 100%) affords desired carboxylic acid **15**, again without significant racemization.[20b]



(a) (1) $HC(O)OC(O)CH_3$, (2) $BH_3{\cdot}SMe_2$, 56%; (b) *N*-BOC-(*S*)-alanine/DCC, 90%; (c) NBS/peroxide, 78%; (d) Na_2CO_3/H_2O, 100%; (e) **5**, DCC, 84%.

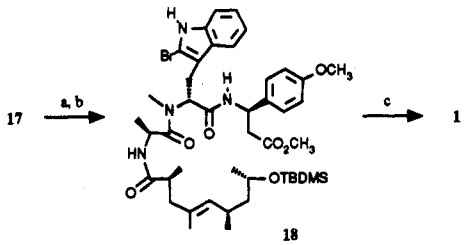
As previously reported,[5] heterocycle **9** is treated under Heck reaction[22] conditions to afford dihydropyrimidinone **16** in 78% yield. Chromatographic isolation of solid **16** is not necessary for the subsequent reactions. Following the work of Meyers,[23] **16** is reduced with $NaBH_4$ to the corresponding saturated heterocycle prior to treatment with acid to afford the desired β-tyrosine methyl ether. (*R*)-β-Tyrosine-*O*-methyl ether methyl ester hydrochloride (**5**) is easily prepared by subjecting the amino acid to acidic methanol, and coupling of **5** with **15** (DCC) affords protected tripeptide **17** (84%).

Completion of our jasplakinolide venture rested upon the successful coupling of fragments **3** and **17**, followed by closure of the macrocycle. Toward this end, **17** was deprotected (TFA, 67%) and coupled with **3** (DCC, 75%) under standard conditions to obtain **18** as an amorphous solid. At this point, we reasoned that if **18** was completely deprotected, the desired ring closure would compete favorably with possible side reactions. Therefore, **18** was



(a) $Pd(OAc)_2$ (1%)/PAr_3 (2%)/$MeOC_6H_4I/NEt_3$/DMF, 78%; (b) $NaBH_4/H_3O^+$, 65%; (c) 4.5 N HCl, 81%; (d) HCl/MeOH, 100%.

treated with $AlBr_3$/EtSH[24] to remove the methyl ester, methyl ether, and *tert*-butyldimethylsilyl protecting groups, followed, without purification, by reaction with DCC/DMAP[25]. (+)-Jasplakinolide (**1**), identical with an authentic sample[26] in all respects, was isolated in 36% overall yield from 18.



(a) TFA, 67%; (b) DCC, **3**, 75%; (c) (1) $AlBr_3$/EtSH, CH_2Cl_2, (2) DCC, 36%.

In conclusion, a concise, enantioselective, and convergent synthesis of (+)-jasplakinolide has been achieved. The yield of the synthesis, based on the longest linear sequence, is 6.6%. In the process we have defined a new method for the synthesis of β-aryl β-amino acids in enantiomerically pure form. Additional experiments to explore the synthetic scope of **9** and to help define the mechanism of the biological activity of jasplakinolide are underway and will be reported in due course.[27]

Experimental Section

General. Melting point determinations are reported uncorrected. Proton (^1H NMR) and carbon (^{13}C NMR) magnetic spectra were recorded (in $CDCl_3$ unless otherwise noted) at 300 and 75.5 MHz, respectively. Combustion analyses for carbon and hydrogen were performed by the staff at Atlantic MicroLabs, Norcross, GA.

Tetrahydrofuran (THF) and diethyl ether were distilled from sodium metal/benzophenone immediately prior to use. For anhydrous reactions, CH_2Cl_2 and hexanes were distilled from CaH_2 immediately prior to use. $BF_3{\cdot}Et_2O$ was freshly distilled from calcium hydride for immediate use. Toluene, benzene, and xylenes were refluxed 24 h over Na and distilled into oven-dried receptacles containing Na. Triethylamine and diisopropylamine were distilled from calcium hydride and stored over KOH. Hexamethyldisilazane (HMDS), hexamethylphosphoric triamide (HMPA), dimethyl sulfoxide (DMSO), and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride and stored over activated 3-Å molecular sieve.

Alkyl- and aryllithium reagents were titrated with 1,10-phenanthroline by the method of Watson and Eastman.[28] Sodium hexamethyldisilylamide (NaHMDS) was prepared in THF under nitrogen with sodium amide and 1.05 equiv of $HN(TMS)_2$ in an

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(20) (a) All four isomers of this dipeptide have been synthesized in our laboratory. The alanine methyl group is diagnostic for each enantiomeric series, with the ^1H NMR resonance for the *S,R/R,S* molecules being at δ 0.90, while the *S,S/R,R* pair show the same resonance at δ 1.27. (b) This same type of analysis was performed on acid **15** to set the level of racemization at ≤2%.
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(26) We thank our colleague Professor P. Crews for an authentic sample of jasplakinolide.
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ice–water bath. The reagent was typically prepared as a 0.7 M solution and was stored under nitrogen for use until the titer had diminished 10% (approximately 7 days). Prior to daily use, the amide base was titrated with 1,3-diphenylacetone *p*-tosylhydrazone.[29] Unless otherwise indicated, all other reagents were used as received.

Diols 10. Under anhydrous conditions, 10% Pd/C (0.50 g), Et_2O (5 mL), MeOH (70 mL; *caution: addition of methanol prior to ether may result in an explosion*), iodo lactone 7 (2.65 g, 11.05 mmol), and Et_3N (7 mL) were added to a vacuum-dried, nitrogen-flushed Parr shaker flask. The flask was pressurized to 64 psi with H_2 and agitated for 30 min. The mixture was filtered and diluted with brine (30 mL) and EtOAc (25 mL). The aqueous layer was washed with Et_2O (2 × 25 mL), and the organic layers were collected and washed alternately with 5% HCl (20 mL), saturated $NaHCO_3$ (20 mL), and brine (20 mL). The organic layers were combined, dried with $MgSO_4$, and filtered. Evaporation of solvent afforded a slightly cloudy, pale pink oil that upon column chromatographic isolation (silica gel; 10:1 hexanes/ethyl acetate) yielded the dehalogenated lactone (970 mg, 8.50 mmol, 77%) as a clear slightly yellow oil: $[\alpha]_D$ = −8.0° (*c* 1.25, EtOH); ^{1}H NMR δ 1.26 (d, *J* = 7.2 Hz, 3 H, C2-C*H*$_3$), 1.41 (d, *J* = 6.3 Hz, 3 H, C4-C*H*$_3$), 1.38–1.54 (m, 1 H, C3-*Hα*), 2.45–2.55 (m, 1 H, C3-*Hβ*), 2.60–2.75 (m, 1 H, C2-*H*), 4.40 (dq, *J* = 6.3, 17.1 Hz, 1 H, C3-*H*); ^{13}C NMR δ 15.2, 21.0, 36.5, 39.2, 75.0, 179.6; MS (CI-NH$_3$) *m/z* 132 (M + NH$_4$)$^+$; IR 1732 cm^{-1}.

The above lactone (912 mg; 8.0 mmol) in Et_2O (30 mL) was cooled to −78 °C and treated with DIBALH (1 M in hexanes; 9.6 mL, 9.6 mmol, 1.2 equiv) by dropwise addition. After stirring for 30 min, the mixture was slowly treated with MeOH (10 mL) in 2-mL portions over 15 min. Stirring was continued for 30 min after which an aqueous solution of 4.6 g of Rochelle salt (potassium sodium tartrate) was added and the resultant mixture stirred overnight while warming to room temperature. The mixture was extracted with ether (50 mL), and the aqueous layer was back-extracted with ether (25 mL). The combined ethereal layers were washed with $NaHCO_3$ and brine solutions and dried to afford, after solvent removal, a clear colorless liquid. Silica gel chromatography (3:1 hexanes/EtOAc) gave a quantitative yield of desired lactol as a clear colorless oil. The product exhibited one TLC spot (R_f = 0.30 (silica gel, 2:1 hexanes/EtOAc); however, ^{1}H and ^{13}C NMR spectra were consistent with a 2.2:1 mixture of diastereomers. The IR spectrum showed disappearance of the carbonyl absorption and the presence of hydroxy stretching vibrations (3300 cm^{-1}).

Isopropenyl lithium was prepared by the addition of neat alumina-filtered isopropenyl bromide (1.24 mL, 14.0 mmol, 2.5 equiv) to a stirred and cooled (−78 °C) solution of *tert*-butyllithium (1.5 M in pentane; 14.5 mL, 24.7 mmol, 4,4 equiv) in 30 mL of ether. The mixture was stirred 1 h after which time the above lactol (650 mg, 5.60 mmol), diluted to a 10 mL in ether, was added dropwise. The solution was removed from the cooling bath after 1 h and allowed to stir an additional 3 h. To the mixture was added saturated NH_4Cl (10 mL), the organic layer was separated, and the aqueous layer was back-extracted (2 × 15 mL). The combined organic phase was washed and dried as described above. Filtration, concentration, and column chromatographic isolation (silica gel; 33% ethyl acetate in hexanes) yielded a 4:1 mixture of diol isomers 10 as white oily crystals (843 mg, 5.34 mmol, 95%). The major isomer could be enriched to 12:1 by a single crystallization in hexanes; however, for preparative purposes, the mixture was used without further manipulation in the subsequent step (data for 12:1 mixture): mp = 71–74 °C; ^{1}H NMR δ 0.83 (d, *J* = 6.9 Hz, 3 H, C4-C*H*$_3$), 1.20 (d, *J* = 6.3 Hz, 3 H C6-C*H*$_3$), 1.35 (ddd, *J* = 14.4, 6.3, 2.1 Hz, 1 H, C5-*H*), 1.60–1.68 (m, 1 H, C5-*H*), 1.70–1.88 (m, 1 H, C4-*H*), 1.71 (s, 3 H, C2-C*H*$_3$), 2.42 (br s, 2 H, C3-O*H* and C6-O*H*), 3.73 (d, *J* = 7.2 Hz, 1 H, C3-*H*), 3.82–3.96 (m, 2 H, C3-*H* and C6-*H*), 4.85–4.93 (m, 2 H, C1-*H*$_2$); ^{13}C NMR δ 16.9, 18.3, 24.8, 34.3, 43.9, 67.0, 82.0, 113.2, 146.6; MS(EI) *m/z* 158 (M$^+$); IR (CH_2Cl_2 solution) 3314, 3074 cm^{-1}. Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 68.19; H, 11.44.

(*E*)-(6*R*,8*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-4,6-dimethyl-4-nonenoic Acid (11). Diol isomers 10 (300 mg, 1.90 mmol) in xylenes (3 mL) were treated at reflux with freshly distilled *N,N*-dimethylacetamide dimethyl acetal (0.69 mL, 4.75 mmol, 2.5 equiv). After 8.5 h, silica gel TLC showed 5 components (R_f = 0.71, 0.55, 0.50, 0.22, and 0.06 (silica gel, 1:1 hexanes/EtOAc)). The clear yellow solution was freed of solvent at reduced pressure, and the yellow oil residue was separated into its components by chromatography (silica gel; 100 mL of 4:1 hexanes/ethyl acetate followed by 500 mL of 2:1 hexanes/ethyl acetate). The least polar fraction was identified as the diacetate of the starting material by proton NMR (loss of hydroxy protons and appearance of acetyl methyl signals) and mass spectral analysis (MS(EI) *m/z* 242 (M$^+$)). The next eluted components were inefficiently separated (combined yield 176 mg; ca. 30%); however, spectroscopic analysis of enriched fractions allowed their identification as monoacetates of the substrate (appearance of a single acetyl methyl in proton NMR and MS(EI) *m/z* 212 for each component). The final two constituents were identified as the less polar C-8 acetoxy amide [(117 mg, 0.52 mmol, 27%); ^{1}H NMR δ 0.88 (d, *J* = 6.9, 3 H, C6-C*H*$_3$), 1.15 (d, *J* = 6.3 Hz, 3 H, C8-C*H*$_3$), 1.33–1.40 (m, 1 H, C8-*H*), 1.49–1.60 (m, 1 H, C7-*H*), 1.60 (s, 3 H, C4-C*H*$_3$), 1.97 (s, 3 H, COC*H*$_3$), 2.10–2.45 (m, 5 H, C2-*H*$_2$, C3-*H*$_2$ and C6-*H*), 2.91 (s, 3 H, N-C*H*$_3$), 2.99 (s, 3 H, NC*H*$_3$), 4.83 (dq, *J* = 6.6, 6.6 Hz, 1 H, C8-*H*), 4.93 (d, *J* = 9.6 Hz, 1 H, C=C*H*); MS (CI-NH$_4$) *m/z* 270 (M$^+$ + 1)] and the more polar desired hydroxy amide (160 mg, 0.59 mmol, 31%): $[\alpha]_D$ = −19.9° (*c* 2.18, CH_2Cl_2); ^{1}H NMR δ 0.92 (d, *J* = 6.6 Hz, 3 H, C6-C*H*$_3$), 1.14 (d, *J* = 6.0 Hz, 3 H, C8-*H*), 1.41 (dd, *J* = 6.8, 6.8 Hz, 2 H, C7-*H*), 1.62 (s, 2 H, C8-*H*$_2$), 1.67 (s, 3 H, C4-C*H*$_3$), 2.26–2.53 (m, 5 H, C2-*H*$_2$, C3-*H*$_2$, and C6-*H*), 2.93 (s, 3 H, NC*H*$_3$), 3.00 (s, 3 H, NC*H*$_3$), 3.78 (dq, *J* = 6.0, 12.3 Hz, 1 H, C8-*H*), 5.02 (d, *J* = 9.6 Hz, 1 H, C=C*H*); ^{13}C NMR δ 16.4, 21.6, 23.2, 30.6, 32.1, 35.0, 35.5, 37.4, 47.3, 67.4, 131.6, 133.3; MS(EI) *m/z* 227 (M$^+$); IR 3418, 1734, 1636 cm^{-1}. The hydroxy amide and its acetate were amenable to combined hydrolysis as described below, thus affording an effective yield of 58%. In addition, the diol acetates could be recycled after saponification (3.0 equiv of 75% aqueous methanolic KOH, 60 °C, 2 h), allowing a total yield of 83%.

A mixture of the above amides (277 mg total, 1.1 mmol), ethylene glycol (4.0 mL), and KOH (2.23 M; 1.58 mL, 3.33 mmol, 3.0 equiv) was heated to 160–170 °C for 12 h and, with continued heating, half the solvent was evaporated under vacuum. The residual clear liquid was acidified with 5% HCl and partitioned with ether (3 × 10 mL), and the combined organic phase was washed twice with brine (2 × 5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated to afford the desired hydroxy acid (201 mg, 1.0 mmol, 91%) as a clear pale yellow oil: $[a]_D$ = −21.0° (*c* 2.00, CH_2Cl_2); ^{1}H NMR δ 0.90 (d, *J* = 6.6 Hz, 3 H, C6-C*H*$_3$), 1.12 (d, *J* = 6.3 Hz, 3 H, C8-C*H*$_3$), 1.40 (m, 2 H, C7-*H*$_2$), 1.64 (d, *J* = 0.9 Hz, 3 H, C4-C*H*$_3$), 2.20–2.50 (m, 5 H, C2-*H*$_2$, C3-*H*$_2$ and C6-*H*), 3.75 (dq, *J* = 6.0, 6.3 Hz, 1 H, C8-*H*), 5.00 (d, *J* = 9.6 Hz, 1 H, C=C*H*), 5.99 (br s, 2 H, COO*H* and C8-O*H*); ^{13}C NMR δ 16.1, 21.6, 23.1, 30.5, 32.7, 34.7, 47.1, 67.5, 132.0, 132.3, 177.6; MS(CI-NH$_3$) *m/z* = 218 (M + NH$_4$)$^+$; IR 3240, 1712 cm^{-1}.

To a stirred solution of the above hydroxy acid (243 mg, 1.22 mmol) in 4 mL of DMF was added imidazole (413 mg, 6.08 mmol, 5.0 equiv) then *tert*-butyldimethylsilyl chloride (422 mg, 2.79 mmol, 2.3 equiv). The solution was heated to 48 °C for 12 h, cooled to ambient temperature, and treated with K_2CO_3 (10% w/v; 2 mL) and EtOH (2 mL). After agitation for 1 h to hydrolyze the silyl ester, the mixture was neutralized with 5% HCl (3 mL) and extracted with ether (3 × 5 mL). The combined organic layer was washed with brine (5 mL) and dried ($MgSO_4$). Filtration, concentration, and silica gel column chromatography (33% ethyl acetate in hexanes) yielded 11 as a pale yellow oil (360 mg, 1.15 mmol, 94%); $[\alpha]_D$ = +11.5° (*c* 2.88, EtOAc); $[\alpha]D$ = −6.0° (*c*, 0.50, CH_2Cl_2); ^{1}H NMR δ 0.04 (s, 6 H, Si(C*H*$_3$)$_2$), 0.87–0.91 (m, 12 H, SiC$_4$*H*$_9$, and C6-C*H*$_3$), 1.08 (d, *J* = 6.0 Hz, 3 H, C8-C*H*$_3$), 1.22–1.46 (m, 2 H, C7-*H*$_2$), 1.61 (d, *J* = 0.9 Hz, 3 H, C4-C*H*$_3$), 2.25–2.48 (m, 5 H, C2-*H*$_2$, C3-*H*$_2$, and C6-*H*), 3.74 (dq, *J* = 6.3, 6.3 Hz, 1 H, C8-*H*), 4.96 (dd, *J* = 1.2, 9.6 Hz, 1 H, C=C*H*); ^{13}C NMR δ −4.7, −4.2, 16.1, 18.2, 20.9, 23.9, 26.0, 29.0, 33.1, 34.4, 47.7, 66.7, 131.3, 132.3, 179.5; MS (CI-isobutane) *m/z* 315 (M$^+$ + 1); IR (thin film) 1713 cm^{-1}.

(4*S*)-3-[(*E*)-(2*S*,6*R*,8*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2,4,6-trimethyl-4-nonenoyl]-2-isopropyl-4-oxazolidinone (12). Compound 11 (231 mg, 0.74 mmol) in ether (2 mL) was

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treated with KOH (2.22 M, 0.33 mL, 1.0 equiv). The solution was stirred 2 h under a stream of N_2 and further evaporated under reduced pressure (1 Torr). The yellow oil was dried by reduced-pressure azeotropic H_2O removal (benzene, 10 mL), which produced a slightly yellow powder. The powder was dissolved in benzene (2 mL), cooled under nitrogen to 7 °C, and treated with 1 drop of pyridine and oxalyl chloride (0.15 mL, 1.25 mmol, 1.7 equiv) via dropwise addition. Stirring and cooling were maintained for 1 h, during which time lithiated oxazolidinone was prepared by the addition of *n*-butyllithium (2.5 M in hexanes, 0.32 mL, 0.81 mmol) to a stirred and cooled (-78 °C, 1 h) solution of (4*S*)-(-)-4-isopropyl-2-oxazolidinone (142 mg, 1.22 mmol) in THF (6 mL). Solvent was removed from the acid chloride solution at reduced pressure, and the resultant material was taken up in THF (6 mL) and added via cannula to the lithiated oxazolidinone (-78 °C). Cooling and stirring were continued for 2 h, after which the solution was allowed to warm to room temperature and stirred for an additional 2 h. To the mixture was added saturated ammonium chloride (5 mL), and the organic layer was separated. The aqueous phase was back-extracted with ether (5 mL), and the combined organic layers were washed successively with $NaHCO_3$ (2 mL) and brine (2 mL). The organic layer was dried ($MgSO_4$), filtered, concentrated, and chromatographed (silica gel; hexanes followed by 8:1 hexanes/EtOAc) to afford the desired acyl oxazolidinone (275 mg, 88%) as a clear colorless oil: $[\alpha]_D$ = -6.0° (*c* 0.50, CH_2Cl_2); ^1H NMR δ 0.04 (s, 6 H, $Si(CH_3)_2$), 0.85–0.93 (m, 18 H, SiC_4H_9, C6-CH_3, and CH-$(CH_3)_2$), 1.08 (d, *J* = 6.0 Hz, 3 H, C8-CH_3), 1.19–1.29 (m, 2 H, C7-*H* and CH-$(CH_3)_2$), 1.35–1.45 (m, 1 H, C7-*H*), 1.64 (s, 3 H, C4-CH_3), 2.24–2.48 (m, 3 H, C3-H_2 and C6-*H*), 3.01 (m, 2 H, C2-H_2), 3.74 (dq, *J* = 6.2, 6.2 Hz, 1 H, C8-*H*), 4.15–4.29 (m, 2 H, OCOCH_2), 4.38–4.46 (m, 1 H, OCNC*H*), 4.97 (d, *J* = 9.6 Hz, 1 H, C=C*H*); ^{13}C NMR δ -4.7, -4.2, 14.5, 16.2, 18.1, 20.9, 2.9, 26.0, 28.4, 28.9, 34.5, 34.4, 47.8, 58.4, 63.3, 66.6, 131.6, 132.5, 132.4, 173.0; MS (CI-isobutane) *m/z* 426 (M^+ + 1); IR (thin film) 1788, 1705 cm^{-1}.

The above acyloxazolidinone (400 mg, 0.94 mmol), diluted in THF (4 mL), was added dropwise over 25 min to a stirred and cooled (-78 °C) solution of NaHMDS (0.60 M in THF, 1.7 mL, 1.03 mmol, 1.1 equiv) under a blanket of nitrogen. The mixture was agitated 1 h, after which neat iodomethane (0.60 mL, 9.4 mmol, 10 equiv) was added over 30 min. After stirring 1 h, the solution was allowed to warm slowly to room temperature over 4 h and agitation was continued an additional 2 h. The mixture was washed with saturated NH_4Cl (6 mL), and the aqueous layer back-extracted with ether (10 mL). The organic layers were combined and washed successively with $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and filtered and solvent evaporated to yield a clear yellow oil. Column purification (silica gel; 9:1 hexanes/EtOAc) resulted in 362 mg (88%) of a 3:1 mixture of isomers. The components were separated by HPLC (9:1 hexanes/EtOAc) to yield 253 mg (62%) of major isomer **12** as a white oily solid: $[\alpha]_D$ = +35.1° (*c* 0.91, CH_2Cl_2); ^1H NMR δ 0.03 (s, 6 H, $Si(CH_3)_2$), 0.83–0.93 (m, 18 H, SiC_4H_9, C6-CH_3, and $CH(CH_3)_2$), 1.08 (d, *J* = 6.0 Hz, 3 H, C8-H_3), 1.13 (d, *J* = 6.6 Hz, 3 H, C2-H_3), 1.23–1.33 (m, 2 H, C7-*H* and C*H*$(CH_3)_2$), 1.36–1.48 (m, 1 H, C7-*H*), 1.60 (s, 3 H, C4-CH_3), 1.94–2.02 (dd, *J* = 8.4, 13.2 Hz, 1 H, C3-*H*), 2.25–2.50 (m, 2 H, C3-*H* and C6-*H*), 3.74 (qd, *J* = 6.4, 6.4 Hz, 1 H, C8-*H*), 3.97 (m, 1 H, C2-*H*), 4.16–4.26 (m, 2 H, OCOCH_2), 4.43 (m, 1 H, OCNC*H*), 4.95 (d, *J* = 9.3 Hz, 1 H, C=C*H*); ^{13}C NMR δ -4.7, -4.3, 14.8, 15.8, 17.0, 18.0, 21.1, 23.7, 26.0, 28.5, 29.2, 35.7, 43.5, 47.7, 58.6, 63.3, 66.8, 112.7, 130.4, 134.2, 177.1, 177.2; IR (thin film) 1763, 1703 cm^{-1}.

(*E*)-(2*S*,6*R*,8*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2,4,6-trimethyl-4-nonenoic Acid (3). Compound **12** (14 mg, 0.0032 mmol) was dissolved in 4:1 THF (BHT stabilized)/deionized water (1.5 mL). The mixture was degassed under moderate vacuum (50 min; 10 min) then stirred at 0 °C while 30% H_2O_2 (22 mL, 0.26 mmol, 8.0 equiv) was added followed immediately by LiOH (3 mg, 0.064 mmol, 2 equiv). After 1 h, reaction completion was indicated by TLC (2:1 hexanes/ethyl acetate), and $NaHSO_3$ (1.5 N; 0.19 mL, 0.29 mmol) was added. The solution was agitated 15 min and twice extracted with ether (2 mL). The combined organic extracts were washed with $NaHCO_3$ (1.5 mL) and brine (1.5 mL), dried (Na_2SO_4), filtered, and evaporated of solvent to afford **3** as a clear colorless oil (9 mg, 0.027 mmol, 86%): $[\alpha]_D$ = -22.5° (*c* 1.2, CH_2Cl_2); ^1H NMR δ 0.04 (s, 6 H, $Si(CH_3)_2$), 0.88–0.90 (m, 12 H, SiC_4H_9 and C6-CH_3), 1.10 (d, *J* = 6.3 Hz, 3 H, C2-CH_3), 1.11 (d, *J* = 6.6 Hz, 3 H, C8-CH_3), 1.24–1.33 (m, 1 H, C7-*H*), 1.38–1.48 (m, 1 H, C7-*H*), 1.59 (s, 3 H, C4-CH_3), 2.03 (dd, *J* = 8.4, 13.2 Hz, 1 H, C3-*H*), 2.25–2.50 (m, 2 H, C3-*H* and C6-*H*), 2.61 (dq, *J* = 7.3, 7.3 Hz, 1 H, C2-*H*), 3.74 (dq, *J* = 6.2, 6.2 Hz, 1 H, C8-*H*), 4.97 (d, *J* = 9.6 Hz, 1 H, C=C*H*); ^{13}C NMR δ -4.7, -4.3, 15.7, 16.3, 18.2, 21.0, 23.8, 26.0, 29.2, 37.7, 43.9, 47.7, 66.8, 130.0, 134.4, 182.0; IR 3300, 1714 cm^{-1}.

(*R*)-*N*-Methyltryptophan Methyl Ester (13). A mixture of 2.66 mL (28.2 mmol) of acetic anhydride and 1.31 mL (34.7 mmol) of formic acid was warmed to 50–60 °C for 3 h and cooled to room temperature. Freshly distilled THF (200 mL) was added to the mixture, followed by 1.92 g (8.8 mmol) of **8** (obtained in 97% yield from the corresponding hydrochloride salt by passage through an column of Amberlite IRA-400(OH) ion exchange resin). The solution appeared cloudy, then became clear. After 4 h, solvent was removed and crystallization from CH_2Cl_2/Et_2O (1:1) yielded 2.06 g (8.4 mmol, 95%) of the desired formyl derivative as a white crystalline solid: mp = 108–10 °C; $[\alpha]_D$ = -51.8° (*c* 1.1, $CHCl_3$); ^1H NMR δ 3.34–3.36 (m, 2 H, -CH_2CH-), 3.71 (s, 3 H, -CH_3), 4.97–5.05 (m, 1 H, -CH_2CH-), 6.18 (br s, 1 H, -N*H*-), 6.98 (d, *J* = 2.1 Hz, 1 H, indole C2), 7.09–7.22 (m, 2 H, indole C6, C7), 7.36 (d, 1 H, *J* = 8.1 Hz, indole C5), 7.55 (d, 1 H, *J* = 8.1 Hz, indole C8), 8.14 (s, 1 H, -C*H*O), 8.25 (br s, 1 H, indole-N*H*-); ^{13}C NMR δ 27.6, 51.7, 52.6, 109.7, 111.4, 118.6, 119.9, 122.4, 122.9, 127.7, 136.2, 160.8, 172.0; IR (KBr) 3060, 1954, 1736, 1672, 1513, 1431, 1372, 1208, 1184, 749 cm^{-1}; MS (EI) *m/z* 246 (M^+), 201, 170, 130, 103, 85. Anal. Calcd for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73. Found: C, 63.40; H, 5.77.

A solution of the above formyl derivative (1.13 g, 4.6 mmol) and freshly distilled THF (40 mL) was cooled to 0 °C. Commercially available borane–methyl sulfide complex (0.87 mL, 9.2 mmol) was added dropwise. After bubbling ceased, the mixture was allowed to warm to room temperature and the reaction was continued for 3 h. The reaction was quenched with MeOH (10 mL) and stirred at room temperature overnight. Saturated HCl/MeOH (80 mL) was added, and the reaction mixture was refluxed for 1 h. After removal of methanol by evaporation, CH_2Cl_2 (30 mL) and $NaHCO_3$ solution were added with stirring until the pH of the solution was approximately 8. Separation of the layers, two further extractions with CH_2Cl_2, and drying of the organic solution preceded purification by silica gel column chromatography using EtOAc/acetone (4:1). Compound **13** (0.65 g) was obtained as a colorless oil (61%): mp (HCl salt) = 171–2 °C; $[\alpha]_D$ = -45° (*c* 1.0, MeOH); ^1H NMR δ 2.37 (s, 3 H, -NHCH_3), 3.18 (AB portion of an ABX system, 2 H, -CH_2CH-), 3.57 (X portion of an ABX system, 1 H, -C*H*CH_2-), 3.67 (s, 3 H, -OCH_3), 7.01 (d, *J* = 2.1 Hz, 1 H, indole-C2), 7.10–7.25 (m, 2 H, indole-C6,C7), 7.32 (d, *J* = 8.1 Hz, 1 H, indole-C5), 7.63 (d, *J* = 8.1 Hz, 1 H, indole-C8), 8.35 (br s, 1 H, indole-N*H*-); ^{13}C NMR δ 29.2, 34.9, 51.8, 63.9, 111.3, 118.8, 119.5, 122.1, 122.9, 127.5, 127.8, 136.3, 175.2; IR(CCl_4) 3500, 1735, 1632, 1190, 740 cm^{-1}; MS (EI) *m/z* 232 (M^+), 173, 131, 130, 102.

***N*-BOC-(*S*)-alanyl-*N*-methyl-(*R*)-tryptophan Methyl Ester (14).** Compounds **13** (0.69 g, 3.0 mmol) and **6** (0.56 g, 3.0 mmol) were dissolved in 50 mL of freshly distilled THF at 0 °C, followed by the addition of DCC (0.62 g, 3.0 mmol) and HOBt (0.04 g, 0.3 mmol). The mixture was stirred at 4 °C for 24 h. The precipitate was filtered and the filtrate was purified by column chromatography (2:1 hexanes/EtOAc) to give **14** as a white powder (1.09 g, 90% yield): mp 68–9 °C; $[\alpha]_D$ = +55.0 (*c* 1.34, MeOH): ^1H NMR δ 0.91 (d, *J* = 6.9 Hz, 3 H, -CHCH_3), 1.42 (s, 9 H, C_4H_9), 2.82 (s, 3 H, -NCH_3), 3.38 (AB portion of an ABX system, 2 H, -CHCH_2-), 3.76 (s, 3 H, OCH_3), 4.49 (m, 1 H, -C*H*CH_3-), 5.28 (X portion of an ABX system, 1 H, -C*H*CH_2-), 5.46 (d, *J* = 8.1 Hz, 1 H, -N*H*-), 7.01, (d, *J* = 2.1 Hz, 1 H, indole-C2), 7.10–7.24 (m, 2 H, indole-C6,7), 7.33 (m, 2 H, indole-C5), 7.60 (m, 2 H, indole-C8), 8.05 (br s, 1 H, indole-N*H*); ^{13}C NMR δ 18.4, 24.6, 28.4, 32.9, 46.6, 52.4, 58.2, 79.5, 110.9, 111.3, 118.4, 119.6, 122.3, 122.5, 127.3, 136.2, 155.2, 171.2, 173.5; UV λ_{max} (EtOH) 582, 520, 512; IR (KBr) 2931, 1743, 1707, 1648, 1490, 1366, 1167, 1061, 744 cm^{-1}. Anal. Calcd for $C_{21}H_{29}O_5N_3$: C, 62.51; H, 7.24. Found: C, 62.23; H, 7.26.

***N*-BOC-(*S*)-alanyl-*N*-methyl-2-bromo-(*R*)-tryptophan (15).** A solution of **14** (1.19 g, 3.0 mmol) in CH_2Cl_2 (250 mL) was cooled to 0 °C. Benzoyl peroxide (38 mg, 0.16 mmol) was added,

followed by dropwise addition of a solution of *N*-bromosuccinimide (0.43 g, 2.4 mmol) in CH_2Cl_2 (100 mL). The color of the reaction mixture changed to yellow, then became almost colorless. After the NBS was added, the reaction was stirred for an additional 30 min. Following solvent removal the product was chromatographed (silica gel, EtOAc/hexanes) to give a white crystalline solid (1.12 g, 78%): mp = 153–4 °C; $[\alpha]_D$ = +65.9° (*c* 1.0, MeOH); ^{1}H NMR δ 0.79 (d, *J* = 6.6 Hz, 3 H, –CHC*H*$_3$), 1.40 (s, 9 H, C$_4$*H*$_9$), 2.81 (s, 3 H, –NC*H*$_3$), 3.35 (AB portion of an ABX system, 2 H, –CHC*H*$_2$–), 3.75 (s, 3 H, OC*H*$_3$), 4.42 (m, 1 H, –C*H*CH$_3$–), 5.10–5.15 (X portion of an ABX system, 1 H, –C*H*CH$_2$–), 5.45 (d, *J* = 8.1 Hz, 1 H, –NH–), 7.05–7.16 (m, 2 H, indole-C6,7), 7.22 (d, *J* = 8.1 Hz, 1 H, indole-C5), 7.50 (d, *J* = 8.1 Hz, 1 H, indole-C8), 8.05 (br s, 1 H, indole-N*H*); ^{13}C NMR δ 14.3, 18.3, 21.1, 24.6, 28.4, 34.1, 46.5, 52.4, 58.4, 60.5, 79.5, 109.1, 110.7, 113, 120.3, 122.5, 127.5, 136.2, 155.1, 170.9, 173.2; UV λ_{max} (EtOH) 580, 520 mm; IR (KBr) 3225, 2978, 2931, 1748, 1719, 1684, 1448, 1272, 1167, 743 CM^{-1}; MS *m*/*z* 484 (M^{+1})/482, 428/426, 410/408, 396/394, 384/382, 346. Anal. Calcd for $C_{21}H_{28}O_5N_3Br$: C, 52.29; H, 5.85. Found: C, 52.00; H, 5.89.

A solution of the above bromo dipeptide (0.36 g, 0.74 mmol) in MeOH (20 mL) and water (26 mL) was treated with Na_2CO_3 (0.78 g, 7.4 mmol) and heated to 70 °C for 1 h. After the solution was cooled to 0 °C, HCl (2 N, 7.37 mL) was added slowly until the pH reached 3. The mixture was extracted with CH_2Cl_2 (4 × 15 mL), dried over $MgSO_4$, and evaporated. Recrystallization with hexanes/Et_2O gave **15** as a white crystalline product (0.35 g, 99%): mp = 184–5 °C; $[\alpha]_D$ = +50.6° (*c* 1.36, MeOH); ^{1}H NMR δ 0.75 (d, *J* = 6.9 Hz, 3 H, –CHC*H*$_3$), 1.33 (s, 9 H, C$_4$*H*$_9$), 2.9 (s, 3 H, –NC*H*$_3$), 3.34 (m, 2 H, –CHC*H*$_2$–), 4.35 (m, 1 H, –C*H*CH$_3$–), 5.12 (m, 1 H, –C*H*CH$_2$–), 5.65 (d, *J* = 8.1 Hz, 1 H, –N*H*–), 6.97–7.08 (m, 2 H, indole-C6,7), 7.26 (d, *J* = 8.1 Hz, 1 H, indole-C5), 7.53 (d, *J* = 8.1 Hz, 1 H, indole-C8), 10.68 (br s, 1 H, indole-N*H*); ^{13}C NMR δ 17.8, 24.4, 28.4, 33.5, 46.8, 59.1, 80.0, 110.6, 111.4, 118.3, 119.5, 122.1, 122.9, 127.3, 136.0, 155.6, 173.7, 174.4; IR (KBr) 3436, 2978, 2919, 1737, 1684, 1631, 1419, 1366, 1161 cm^{-1}. Anal. Calcd for $C_{20}H_{26}O_5N_3Br$: C, 51.29; H, 5.60. Found: C, 51.36; H, 5.61.

(*S*)-2-*tert*-Butyl-6-(4-methoxyphenyl)-5,6-dihydro-4-(1*H*)-pyrimidinone (16). A solution of (+)-(*S*)-**9** (424 mg, 2.0 mmol) in DMF (1 mL) was treated with iodoanisole (515 mg, 2.2 mmol), NEt_3 (304 mg, 418 mL, 3.0 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), and tri-*o*-tolylphosphine (9.0 mg, 0.03 mmol). The resulting solution was sealed in an ampule and placed into a flask of boiling water for 24 h. The ampule was cooled to –20 °C before opening. The solution was diluted with ethyl acetate and washed with water and 10% HCl solution. The acidic aqueous solution was treated with 2 N NaOH to bring the pH to 12 and extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 layers were dried with $MgSO_4$, filtered, and evaporated to give **4** (407 mg, 78%) as a yellow solid that could be recrystallized from 95% ethanol: mg 123–5 °C; $[\alpha]_D$ = –47.0° (*c* 3.3, $CHCl_3$); ^{1}H NMR δ 1.27 (s, 9 H, C$_4$*H*$_9$), 2.35 (dd, *J* = 12.0 and 16.5 Hz, 1 H, COC*H*), 2.72 (dd, *J* = 5.7 and 16.5 Hz, 1 H, COC*H*), 3.80 (s, 1 H, –OC*H*$_3$), 4.71 (dd, *J* = 5.7 and 12.0 Hz, 1 H, –C*H*(Ar)N), 6.89 (d, *J* = 9 Hz, 2 H, aromatic), 7.3 (d, *J* = 9 Hz, aromatic), 8.66 (br s, 1 H, N*H*); ^{13}C NMR δ 27.66, 37.57, 55.38, 56.72, 114.04, 127.49, 134.81, 158.78, 160.21, 171.71. IR (KBr) 3237, 3000, 1702, 1662, 1508, 1254, 1135, 920, 832 cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_2N_2$: C, 69.20; H, 7.74. Found: C, 69.08; 7.74.

(*R*)-β-Tyrosine Methyl Ether Methyl Ester Hydrochloride (5). A solution of **16** (2.40 g, 9.2 mmol), THF (20 mL), and 95% EtOH (20 mL) was stirred and cooled to between –35 and –45 °C. A 9 N HCl solution was added dropwise until an approximate pH of 7 was obtained. A solution of $NaBH_4$ was prepared by dissolving the reagent (0.5 g, 13.0 mmol) in a minimum amount of water (0.5–0.8 mL) to which one drop of 30% NaOH was added. Dropwise addition of this $NaBH_4$ solution to the solution of **16** was alternated with addition of a 9 N HCl solution to maintain the pH in the range of 6–8. During the addition care was taken to maintain the temperature between –35 and –45 °C. After the addition of $NaBH_4$ was completed, the reaction mixture was stirred at –35 °C for 1 h. A pH of 7 was maintained by the occasional addition of 9 N HCl. The reaction mixture was then stored at –20 °C overnight, diluted with 30 mL of water, and made basic by the addition of 40% NaOH until the pH was approximately 9. The resultant mixture was extracted three times with 20-mL portions of ether, and the combined ether extracts were washed with saturated brine. After drying over K_2CO_3, removal of solvent afforded 1.57 g (65%) of desired product: mp = 136–8 °C; $[\alpha]_D$ = +27.67° (*c* 1.2, CH_2Cl_2); ^{1}H NMR δ 0.99 (s, 9 H, C$_4$*H*$_9$), 2.33–2.72 (m, 2 H, α-protons), 3.82 (s, 3 H, OC*H*$_3$), 3.97–4.04 (m, 1 H, β-proton), 4.12 (s, 1 H, NC*H*N), 6.03 (br s, 1 H, –N*H*), 6.9 (d, *J* = 10 Hz, 2 H, aromatics), 7.3 (d, *J* = 10 Hz, 2 H, aromatics); ^{13}C NMR δ 24.9, 34.5, 39.8, 55.0, 55.4, 76.0, 114.1, 127.4, 134.2, 159.2, 171.6; IR (KBr): 3190, 2954, 1655, 1514, 1472, 1243, 1173 cm^{-1}; MS (EI) *m*/*z* 262 (M$^+$), 205, 154, 108. Anal. Calcd for $C_{15}H_{22}N_2O_2$: C, 68.67; H, 8.45. Found: C, 68.60; H, 8.49.

The above pyrimidinone (0.80 g, 3.1 mmol) was dissolved in 8 mL of 4.5 N hydrochloric acid and heated to 100 °C for 2.5 h. The clear liquid was transferred to an evaporating dish and left in a fume hood. The residue was dissolved in 2 mL of 2 N HCl, and 30% NaOH was added slowly with swirling until pH = 7 and the mixture solidified. The solid was then left in a refrigerator (4 °C) overnight. Water (10 mL) was added, and the mixture was filtered to give 0.50 g (81%) of the desired β-amino acid as a slightly yellow crystalline solid. The product could be further purified by recrystallization with boiling water: mp = 239 °C dec; $[\alpha]_D$ = –4.35° (*c* 1.86, 1 N HCl); ^{1}H NMR δ 3.02–3.25 (m, 2 H, α-protons), 3.83 (s, 3 H, OC*H*$_3$), 4.90 (m, 1 H, β-proton), 7.03 (d, *J* = 10 Hz, 2 H, aromatics), 7.45 (d, *J* = 10 Hz, 2 H, aromatic); ^{13}C NMR δ 38.7, 52.1, 56.6, 115.9, 128.7, 129.8, 160.8, 174.5; IR (KBr) 2960, 2364, 2150, 1615, 1518, 1404, 1250, 1184 cm^{-1}. Anal. Calcd for $C_{10}H_{13}O_3N$: C, 61.53; H, 6.71. Found: C, 61.55; H, 6.74.

A stream of dry HCl gas was passed rapidly through a suspension of the above β-amino acid (0.94 g, 4.8 mmol) in absolute MeOH without external cooling. After all the amino acid had gone into solution, the hot reaction mixture was cooled and the introduction of gas continued to saturation at 0–5 °C. The reaction mixture was concentrated to dryness while the temperature was maintained below 50 °C. Some methanol was added and the concentration to dryness repeated. After all the solvent was removed under vacuum, 1.18 g (100%) of **5** as a slightly yellow, hygroscopic solid was obtained: mp = 94–6 °C; $[\alpha]_D$ = –91.5° (*c* 1.42, MeOH); ^{1}H NMR δ 3.10 (AB portion of an ABX system, 2 H, α-C*H*$_2$), 3.66 (s, 3 H, OC*H*$_3$), 3.78 (s, 3 H, OC*H*$_3$), 4.66 (X portion of an ABX system, 1 H, –C*H*), 6.96 (d, *J* = 10 Hz, 2 H, aromatic), 7.41 (d, *J* = 10 Hz, 2 H, aromatic); ^{13}C NMR δ 40.2, 53.7, 56.9, 116.7, 130.1, 130.8, 163.0, 172.7; IR (KBr) 2860, 1743, 1613, 1519, 1437, 1319, 1255, 1178 cm^{-1}; MS (EI) *m*/*z* 210 (M$^+$), 151, 108. Anal. Calcd for $C_{11}H_{16}NO_3Cl$: C, 53.77; H, 6.56. Found: C, 53.62; H, 6.56.

N-BOC-(*S*)-alanyl-*N*-methyl-2-bromo-(*R*)-tryptophanyl-*O*-methyl-(*R*)-β-tyrosine Methyl Ester (17). Compound **5** (0.41 g, 1.7 mmol) was dissolved in THF (15 mL), and triethylamine (0.23 mL, 1.7 mmol) was added. The resulting solution was filtered into a 100-mL round-bottom flask, and **15** (0.78 g, 1.7 mmol) was added, followed by DCC (0.38 g, 1.8 mmol). The reaction was continued overnight at room temperature. The reaction mixture was transferred onto a silica gel column and eluted with ether to give **17** as a white amorphous solid (0.91 g, 84%): mp = 95 °C; $[\alpha]_D$ = +42.2° (*c* 0.9, CH_2Cl_2); ^{1}H NMR δ 0.65 (d, *J* = 6.85 Hz, 3 H, Ala C*H*$_3$), 1.37 (s, 9 H, C$_4$*H*$_9$), 2.84 (m, 2 H, CHC*H*$_2$, β-amino acid), 2.97 (s, 3 H, NC*H*$_3$), 3.25 (m, 2 H, CHC*H*$_2$), 3.61 (s, 3 H, OC*H*$_3$), 3.78 (s, 3 H, OC*H*$_3$), 4.29 (m, 1 H, C*H*CH$_2$, β-amino acid), 5.10 (d, *J* = 8.1 Hz, 1 H, N*H*, Ala), 5.37 (m, 1 H, C*H*CH$_3$), 5.66 (m, 1 H, C*H*CH$_2$), 6.82 (d, *J* = 10 Hz, 2 H, aromatics, anisyl), 6.91 (d, *J* = 8.5 Hz, 1 H, N*H*, β-amino acid), 7.08 (m, 2 H, C6,C7 indole), 7.17 (d, *J* = 10 Hz, 2 H, aromatics, anisyl), 7.22 (d, *J* = 8.1, 1 H, C5, indole), 7.50 (d, *J* = 8.1, 1 H, C8, indole), 8.40 (br s, 1 H, N*H*, indole); ^{13}C NMR δ 16.8, 23.4, 28.3, 31.6, 40.5, 46.5, 49.6, 51.8, 55.3, 56.2, 109.0, 110.4, 110.7, 114., 118.3, 120.1, 122.4, 127.6, 136.1, 155.6, 169.2, 171.2, 174.2; IR (KBr) 3318, 2978, 2931, 1736, 1689, 1654, 1448, 831, 737 cm^{-1}; MS (EI) *m*/*z* 658/70 (M$^+$), 558/60, 208/210, 119. Anal. Calcd for $C_{31}H_{39}N_4O_7Br$: C, 56.45; H, 5.96. Found: C, 56.40; H, 5.98.

(*E*)-(2*S*,6*R*,8*S*)-8-[(*tert*-Butyldimethylsilyl)oxy]-2,4,6-trimethyl-4-nonenoyl-(*S*)-alanyl-*N*-methyl-2-bromo-(*R*)-tryptophanyl-*O*-methyl-(*R*)-β-tyrosine Methyl Ester (18). Compound **17** (0.87 g, 1.3 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled 0 °C. Trifluoroacetic acid (TFA, 25 mL, 200 equiv) in 20 mL CH_2Cl_2 was added dropwise, followed by stirring for 40 min at 0 °C. TLC showed no starting material remaining. The

excess solvent and TFA were removed with vacuum at 0 °C. The residue was transferred to a methanol preeluted column of ion exchange resin (IRA-68) with a small amount of methanol. Elution with methanol (150 mL) followed by evaporation afforded the crude product, which was further purified with silica gel column chromatography (CH_2Cl_2/MeOH (9:1)). The desired product was obtained as a white crystalline solid (0.49 g, 67%): mp = 85 °C; $[\alpha]_D$ = +71.3° (*c* 1.15, CH_2Cl_2); ^1H NMR δ 0.40 (d, *J* = 6.8 Hz, 3 H, Ala CH_3), 2.70–3.04 (m, 2 H, CH_2, β-amino acid), 2.87 (s, 3 H, NCH_3), 3.12–3.38 (m, 2 H, CHCH_2), 3.59 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 5.42 (m, 1 H, C*H*CH$_2$), 5.55 (m, 1 H, C*H*CH$_2$), 6.77 (d, *J* = 10.1 Hz, 2 H, aromatics, anisyl), 7.22 (d, *J* = 10.1 Hz, 2 H, aromatics, anisyl), 7.04 (m, 2 H, C6,C7, indole), 7.38 (d, *J* = 8.1 Hz, 1 H, C5, indole), 7.77 (d, *J* = 8.1 Hz, 1 H, C8, indole), 9.12 (br s, 1 H, N*H*, indole); ^{13}C NMR δ 20.3, 23.56, 31.4, 40.3, 47.2, 49.4, 51.8, 55.3, 56.4, 110.2, 110.6, 114.2, 118.3, 120.1, 122.3, 127.5, 136.2, 169.5, 171.5, 177.9; IR (KBr) 3271, 2954, 2825, 1736, 1654, 1507, 1172, 1037 cm^{-1}; MS (EI) *m*/*z* 558/560 (M^+), 349/51, 109. Anal. Calcd for $C_{26}H_{31}N_4O_5Br$: C, 55.82; H, 5.58. Found: C, 55.67; H, 5.61.

The above free amine (77 mg, 0.13 mmol) was dissolved in 2 mL of CH_2Cl_2 and cooled to −20 °C. Compound **3** (43 mg, 0.13 mmol) in 2 mL of CH_2Cl_2 was added, followed by dropwise addition of a CH_2Cl_2 solution of DCC (29 mg, 0.137 mmol). The reaction mixture was warmed to 0 °C in 3 h and then stored in a refrigerator (4 °C) for 36 h. Purification by chromatography with silica gel (EtOAc/hexanes (1:1)) yielded **18** as a colorless amorphous solid (90 mg, 75%). $[\alpha]_D$ = +32.2 (*c*, 1.2, CH_2Cl_2); ^1H NMR δ 0.02 (s, 6 H, Si(CH_3)$_2$), 0.69 (d, *J* = 6.8 Hz, 3 H, Ala CH_3), 0.89 (s, 9 H, SiC$_4H_9$), 1.00 (d, *J* = 6.7 Hz, 3 H, nonenoyl, C2-CH_3), 1.09 (d, 3 H, nonenoyl, C6-CH_3), 1.12 (d, *J* = 6.6 Hz, 3 H, nonenoyl, C8-CH_3), 1.56 (s, 3 H, C=CCH_3), 2.78 (m, 2 H, CH_2, β-Tyr), 2.97 (s, 3 H, NCH_3), 3.24 (m, 2 H, Trp CH_2), 3.59 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 4.47 (m, 1 H, C*H* β-Tyr), 4.94 (d, *J* = 9.6 Hz, 1 H, =C*H*, nonenoyl), 5.54 (m, 1 H, C*H*, Ala), 5.62 (m, 1 H, C*H*, Trp), 6.16 (d, *J* = 5.9 Hz, 1 H, N*H*, Ala), 6.80 (d, *J* = 10.1 Hz, 2 H, anisyl), 7.20 (d, *J* = 10.1 Hz, 2 H, aromatics, anisyl), 7.08 (m, 2 H, C6,C7, indole), 7.20 (d, *J* = 8.1 Hz, 1 H, C5, indole), 7.48 (d, *J* = 8.1 Hz, 1 H, C8, indole), 8.96 (br s, 1 H, N*H*, indole); ^{13}C NMR δ −4.7, 15.5, 16.4, 16.5, 18.1, 20.3, 23.7, 24.7, 25.5, 25.9, 26.3, 29.1, 31.8, 32.8, 34.0, 35.0, 38.4, 40.5, 43.9, 45.6, 47.6, 49.6, 51.8, 55.2, 55.8, 56.4, 66.7, 109.2, 110.5, 114.0, 118.2, 119.9, 122.2, 127.7, 130.0, 132.8, 134.5, 136.2, 169.1, 171.3, 173.9, 176.5; IR (KBr) 3310, 2924, 1730, 1714, 1654, 1100, 831, 735 cm^{-1}; MS(CI) *m*/*z* 868/870 (M^+), 738/740, 678, 528, 208/210, 109.

(+)-Jasplakinolide. Compound **18** (140 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (15 mL), and ethanethiol (6.5 mL) was added. After degassing, $AlBr_3$ (1 M in CH_2Cl_2, 4.83 mL, 4.8 mmol) was added slowly via syringe. The mixture was stirred for 24 h at room temperature. The reaction mixture was then partitioned between CH_2Cl_2 and water in the presence of some methanol. The organic layer was separated, concentrated, and chromatographed with silica gel (CH_2Cl_2/MeOH/AcOH (8:1:1)). The solvent was evaporated under high vacuum and carried on to the cyclization step without further purification. In a 100-mL flask was added 25 mL of $CHCl_3$, DCC (80 mg, 0.39 mmol), DMAP (70 mg, 0.58 mmol), and DMAP–TFA (91 mg, 0.39 mmol). The mixture was brought to reflux, and a solution of the above acyclic compound in 5 mL $CHCl_3$ was added via syringe pump over 16 h. The mixture was then chromatographed with silica gel (EtOAc/hexanes (1:1)) followed by reversed-phase HPLC (ODS, 25 cm × 10 mm, CH_3CN), yielding pure (+)-jasplakinolide (**1**) as an opaque amorphous solid 42 mg, 36% overall). The synthetic product was identical ($[\alpha]_D$, TLC, ^1H NMR, ^{13}C NMR, IR, UV, and MS) with the natural product: $[\alpha]_D$ = +35° (*c* 2.4, MeOH); ^1H NMR δ 0.70 (d, *J* = 6.6 Hz, 3 H, Ala CH_3), 0.81 (d, *J* = 6.7 Hz, 3 H, nonenoyl, C2, CH_3), 1.04 (d, 3 H, nonenoyl, C6, CH_3), 1.12 (d, 3 H, nonenoyl, C8, CH_3), 1.56 (s, 3 H, C=CCH_3), 2.60 (m, 2 H, CH_2, β-Tyr), 2.97 (s, 3 H, NCH$_3$), 3.28 (m, 2 H, Trp CH_2), 4.62 (m, 1 H, C*H*O), 4.94 (m, 2 H, =C*H*, nonenoyl and C*H*, Ala), 5.25 (m, 1 H, C*H*, β-Tyr), 5.83 (m, 1 H, C*H*, Trp), 6.80 (d, *J* = 5.9 Hz, 1 H, N*H*, Ala), 6.80 (d, *J* = 10.1 Hz, 2 H, anisyl), 6.93 (d, *J* = 10.1 Hz, 2 H, aromatics, anisyl), 7.08 (m, 2 H, C6,C7, indole), 7.23 (d, *J* = 8.1 Hz, 1 H, C5, indole), 7.54 (d, *J* = 8.1 Hz, 1 H, C8, indole), 8.87 (br s, 1 H, N*H*, indole); ^{13}C NMR δ 17.8, 18.6, 19.1, 20.4, 22.0, 23.3, 29.3, 30.9, 38.7, 40.2, 40.8, 43.4, 46.0, 49.1, 55.6, 70.8, 109.2, 110.1, 110.7, 115.6, 118.2, 120.2, 122.5, 127.3, 127.9, 131.3, 133.6, 136.2, 155.9, 169.0, 170.9, 174.5, 175.3; IR ($CDCl_3$) 3400, 3100, 1710, 1660, 1630; UV(MeOH) 381, 290; MS(EI) *m*/*z* 78/710 (M^+), 629 (M^+ − Br), 460, 414, 251/253, 250.

Supplementary Material Available: ^1H NMR and ^{13}C NMR spectra for compounds **3**, **11**, **12**, **13**, and **18** (11 pages). Ordering information is given on any current masthead page.