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Asymmetric Total Synthesis of (−)-Jorunnamycins A and C and (−)-Jorumycin from L-Tyrosine

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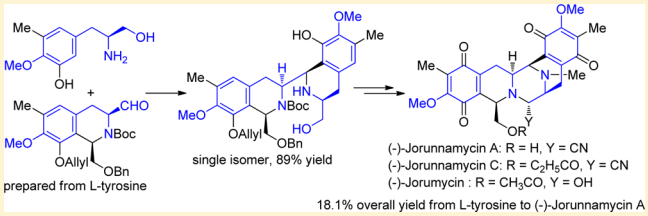
Supporting Information

ABSTRACT: Three renieramycin-type antitumor alkaloids, (−)-jorunnamycins A (**1**) and C (**2**) and (−)-jorumycin (**3**), have been synthesized by a new convergent approach, which features a highly regio- and stereoselective Pictet−Spengler cyclization to couple the isoquinoline and the trisubstituted phenylalaninol partners. This synthetic strategy opens an economical access to these important antitumor alkaloids with high yields: (−)-jorunnamycin A, as a common precursor to other renieramycin-type alkaloids and their analogues, is obtained with 18.1% overall yield from L-tyrosine.



Marine bistetrahydroisoquinoline alkaloids, including the renieramycins (**1**−**5**), saframycins (**6**, **7**), and ecteinascidins (**8**, **9**) (Figure 1), have been intensively studied over the past 37 years because of their remarkable antitumor and antimicrobial activities.[1] Ecteinascidin 743[2] (**8**, Et 743, Yondelis), a typical antitumor agent among them, has received marketing authorization from the European commission for the treatment of advanced soft-tissue sarcomas.[3] (−)-Jorumycin (**3**),[4] (−)-jorunnamycin A (**1**), and (−)-jorunnamycin C (**2**),[5] the three renieramycin-type alkaloids isolated from the marine nudibranchs *Jorunna funebris*, also showed nanomolar inhibitory effects in a panel of human tumor cell lines.[4,5] These bioactive renieramycin alkaloids and their analogues,[4−6] with simpler structures than the ecteinacidins, are promising candidates for new anticancer drugs. However, studies on the structure−activity relationships of renieramycin compounds are relatively rare owing to their meager resources in nature.[7]

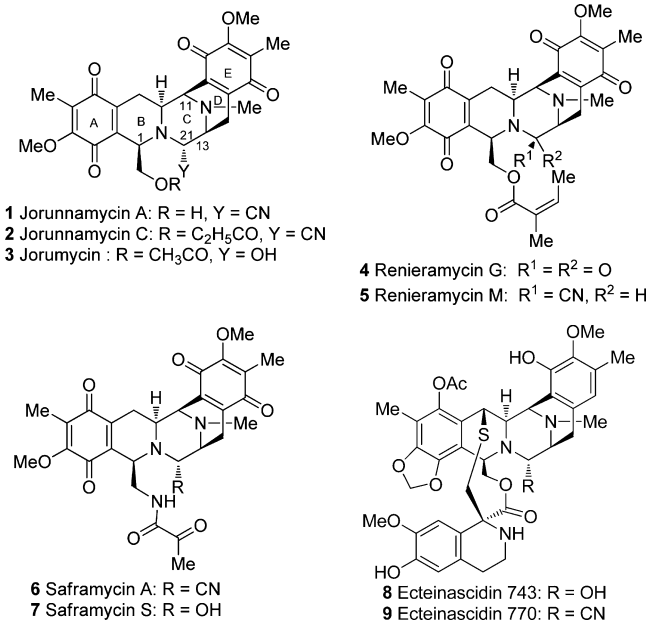


Figure 1. Examples of bistetrahydroisoquinoline alkaloids.

The biological activities and natural scarcity of these alkaloids have attracted particular attention in the field of synthetic chemistry, and several renieramycins have been synthesized.[8−10] As a useful and frequent strategy to construct pentacyclic frameworks of bistetrahydroisoquinoline alkaloids, coupling of isoquinoline moiety **12** with amino acid partner **13** via *N*-acylation followed by successive formation of the C and D rings was adopted in most syntheses of renieramycins (Figure 2a).[8a,b,9a−c] For this strategy, tetrasubstituted phenylalanines (**13**: $R^2 \neq H$) are more suitable than trisubstituted counterparts (**13**: $R^2 = H$), because the latter would result in some undesirable regioisomers (cyclization *para* to the phenol group) in the formation of the D ring via the *N*-acylimininium intermediates. The desired products **10** ($R^2 = H$, cyclization *ortho* to the phenol group) were obtained with unsatisfactory yields (0−51%),[9c,11] particularly in the synthesis of renieramycin-type alkaloids.[11d] However, preparation of the tetrasubstituted phenylalanine derivatives usually requires additional steps and higher costs.[8a,b,12]

We report herein a new convergent route for the syntheses of renieramycin-type alkaloids, in which isoquinoline moiety **15** and trisubstituted phenylalaninol **16** are coupled via a highly regio- and stereoselective Pictet−Spengler cyclization to produce bistetrahydroisoquinoline intermediate **14** (Figure 2b). Both coupling partners are readily prepared from inexpensive L-tyrosine. The utility of this strategy is

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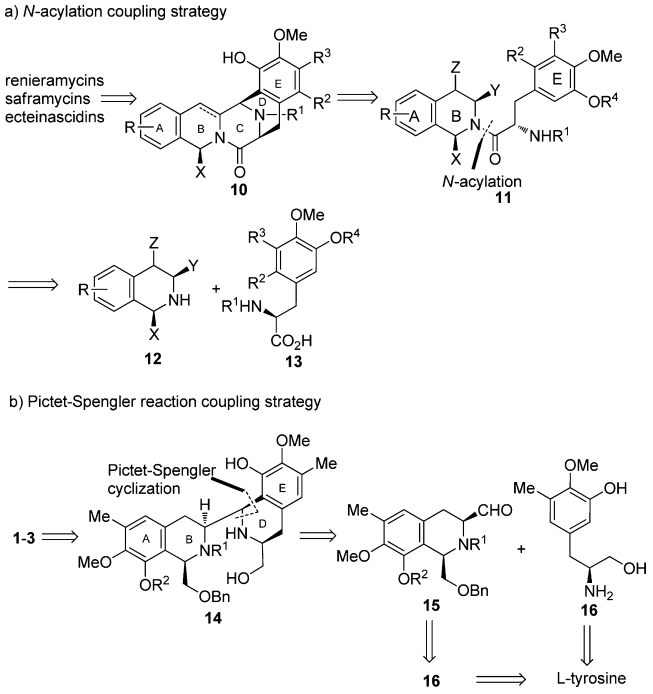


Figure 2. Coupling strategies for the convergent synthesis of bistetrahydroisoquinoline alkaloids from isoquinoline and substituted phenylalanine partners.

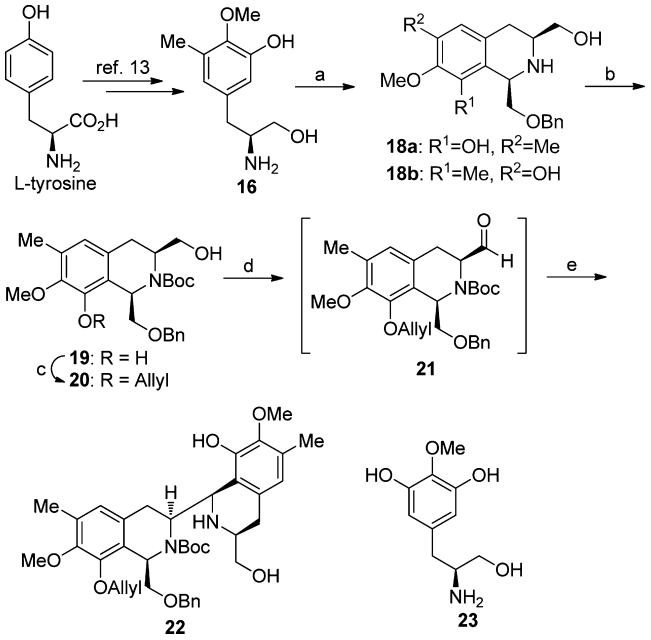
demonstrated here through the first synthesis of (−)-jorunnamycin C (**2**), as well as synthesis of (−)-jorumycin (**3**).

RESULTS AND DISCUSSION

The synthesis of the key bistetrahydroisoquinoline **22** (**14**: R^1 = Boc, R^2 = allyl) is illustrated in Scheme 1. Following the approach developed by our group, L-3-hydroxy-4-methoxy-5-methylphenylalaninol (**16**) was easily prepared from L-tyrosine in eight steps with 46% overall yield.[13] Trisubstituted phenylalaninol **16** not only served as the right partner but also can be transformed further to the left part of **15**. The Pictet−Spengler reaction between **16** and benzyloxyacetaldehyde (**17**) to produce 1,3-*cis*-tetrahydroisoquinoline **18a**, the benzyl ether of MY336-a,[14] was achieved previously in the presence of 3 equiv of AcOH at −10 °C.[11d] When we reduced the amount of AcOH to 0.25 equiv, the cyclization maintained high regioselectivity at 0 °C to furnish **18a** in 89% yield, and only a small amount of its regioisomer **18b** (5%) was produced. An increase in the amount of AcOH or reaction temperature led to a drop in regioselectivity. With **18a** in hand, several oxidation precursors including **19** and **20** were prepared in high yield by routine protection procedures. Under Swern oxidation conditions, the primary alcohols such as **19** and **20** were converted to the corresponding aldehydes **15** respectively to serve in the subsequent coupling step without further purification.

Subsequently, the key coupling of the left and right partners via the second Pictet−Spengler condensation was investigated (Scheme 1). In the process to form ring D, diverse regio- and stereoisomers probably would be produced owing to unsatisfactory cyclization selectivity and epimerization of the aldehyde partner.[15] Therefore, structurally symmetric L-3,5-dihydroxy-4-methoxyphenylalaninol (**23**),[16] which could circumvent the problem of regioselectivity in the cyclization, was also used as an alternative right partner. L-3,5-Dihydroxy-4-

Scheme 1. Synthesis of the Key Bistetrahydroisoquinoline Intermediate 22[a]



[a]Conditions: (a) **17**, AcOH, CH_2Cl_2/TFE (v/v, 7:1), 4 Å MS, 0 °C, 89%; (b) Boc_2O, Et_3N, CH_2Cl_2, rt, 95%; (c) allyl bromide, CH_3CN, K_2CO_3, 50 °C, 94%; (d) Swern oxidation; (e) AcOH, CH_2Cl_2/TFE (v/v, 7:1), 4 Å MS, 89% from **20** for 2 steps.

methoxyphenylalanine derivatives have been successfully applied to the synthesis of Et 743 (**8**),[17] phthalascidin 650,[18] and saframycin A (**6**).[19] The results of experiments showed that the selectivity of the cyclization was highly dependent on the R^1 and R^2 groups in the left partner **15**. In most cases, at least two obvious cyclization isomers were obtained even though employing **23** as the right partner. This seemed to imply that these products are more likely to be stereoisomeric. After a survey of aldehyde partners **15** with varying R^1 groups (Boc, Alloc, Cbz, Fmoc) and R^2 groups (H, allyl, TBS), the condensation of aldehyde **21** (**15**: R^1 = Boc, R^2 = allyl) with **16** yielded only one cyclization product, **22**. However, at room temperature the reactions proceeded very sluggishly, and 4−5 days was required for complete conversion. Gratifyingly, when the reaction temperature was raised to 50 °C, the cyclization was complete within 8 h and **22** was obtained as a single isomer in 89% yield (from **20**). Unfortunately, in the ^{1}H NMR spectra of the compounds including **22**, which possessed carbamate units such as the *N*-Boc group, a number of proton signals appeared either as broadened peaks or in pairs due to the presence of rotamers and overlapped each other. Therefore, assignment of the stereochemistry of **22** by routine NMR analysis was difficult, and the stereostructure was determined only after completion of the subsequent transformation to the natural products.

The final syntheses of the natural products began with the closure of ring C (Scheme 2). Initially, direct methylation of the secondary amine of **22** followed by removal of the *N*-Boc group gave the resulting amino alcohol, C ring closure of which could not occur via a Swern oxidation/Strecker reaction protocol.[8c,20] Thus, protection of the secondary amine of **22** with AllocCl followed by selective allylation of the phenol furnished compound **25** in excellent overall yield, which was subjected

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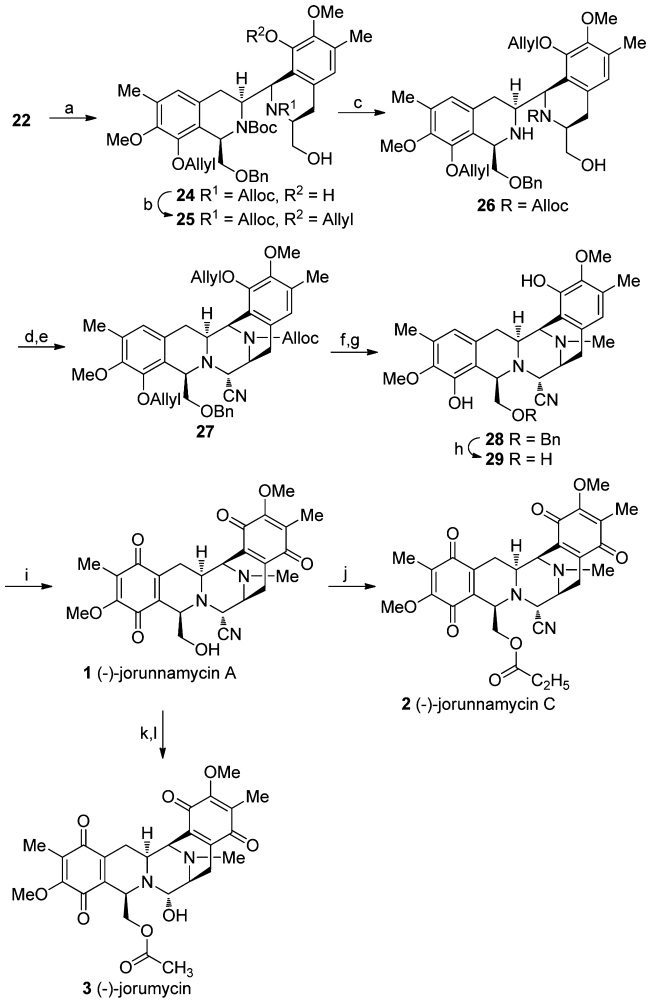
Scheme 2. Syntheses of (−)-Jorunnamycin A, (−)-Jorunnamycin C, and (−)-Jorumycin[a]



[a]Conditions: (a) AllocCl, CH_2Cl_2/aq $NaHCO_3$ (v/v, 1:1), rt, 95%; (b) allyl bromide, CH_3CN, Cs_2CO_3, 50 °C, 94%; (c) HCl/MeOH (v/v, 1:15), 50 °C, 92%; (d) Swern oxidation; (e) TMSCN, $ZnCl_2$, CH_2Cl_2, rt, 87% for 2 steps; (f) $Pd(PPh_3)_4$, Bu_3SnH, AcOH, CH_2Cl_2, rt; (g) aq HCHO (37%), $NaBH_3CN$, AcOH, CH_3CN/THF (v/v, 3:1), rt, 91% for 2 steps; (h) BCl_3, CH_2Cl_2, −78 °C, 94%; (i) salcomine, O_2 atmosphere, MeCN, 91%; (j) propionic anhydride, pyridine, 25 °C, 76%; (k) acetic anhydride/pyridine (v/v, 1/2), rt; (l) $AgNO_3$, MeCN/H_2O (v/v, 3/2), 45 °C, 78% for 2 steps.

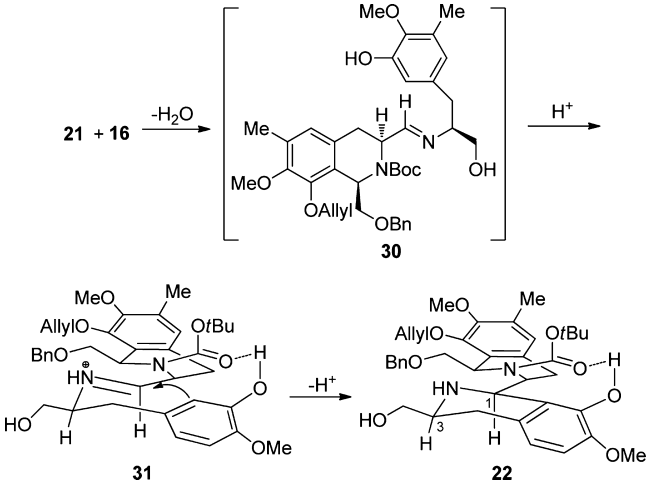
to aqueous HCl in methanol to yield free secondary amine **26**. Swern oxidation of amino alcohol **26** to the hemiaminal followed by a zinc chloride promoted intramolecular Strecker reaction provided aminonitrile **27** with the entire pentacyclic framework as a single diastereoisomer. Simultaneous removal of one *N*-Alloc and two *O*-allyl groups under Guibé's conditions[21] followed by reductive *N*-methylation afforded phenol **28**.

The *O*-debenzylation of **28** under hydrogenolysis conditions (10% Pd/C, H_2) only resulted in recovered material, whereas the deprotection was achieved smoothly with BCl_3 at −78 °C to furnish the desired alcohol **29** in 94% yield. Oxidation of the A and E rings of **29** to quinone occurred successfully with O_2 atmosphere in the presence of salcomine[22] to give (−)-jorunnamycin A (**1**). Synthetic **1** exhibited spectral characteristics identical to those reported for the natural product.[4] It also confirmed that the stereochemistry of **22** obtained in the key cyclization was just what we needed.

As the simplest member of renieramycin-type alkaloids, **1** could conveniently be converted to other members of this family. Thus, acylation of primary alcohol **1** with propionic anhydride furnished (−)-jorunnamycin C (**2**). Similarly, **1** was converted to (−)-jorumycin (**3**) by a two-step sequence following the known protocols.[8a,c]

The formation of **22** with the desired stereochemistry was proposed as shown in Scheme 3. Condensation of aldehyde **21**

Scheme 3. Formation of the Key Bistetrahydroisoquinoline Intermediate 22



and amine **16** yielded imine species **30**. In the subsequent cyclization, its corresponding iminium tends to adopt the stable conformation **31** similar to a chair. Thus, 1,3-*cis*-tetrahydroisoquinoline was obtained preferably, in which both substituents at C1 and C3 were positioned in pseudoequatorial orientation to minimize the steric repulsions. At the same time, a postulated hydrogen-bonding interaction between the phenolic residue and the Boc group in **31** would direct this cyclization *ortho* to the phenol.

In conclusion, we described a convergent strategy for highly efficient synthesis of renieramycin alkaloids based on a condensation between aldehyde partner **21** and amine partner **16**, in which excellent regioselectivity and stereoselectivity were achieved. Through this approach, (−)-jorunnamycins A (**1**) and C (**2**) and (−)-jorumycin (**3**) have been synthesized in high yields: (−)-jorunnamycin A was obtained with 18.1% overall yield from L-tyrosine. Furthermore, our approach has several other advantages: (1) expensive reagents and materials are seldom involved; (2) no segment other than **16** need be prepared additionally; (3) the reactions are easy to perform and can be scaled up. Efforts to utilize this economical and robust strategy for the syntheses of other bistetrahydroisoquinoline alkaloids are in progress.

EXPERIMENTAL SECTION

General Experimental Procedures. Flash chromatography was performed using silica gel (200−300 mesh). Reactions were monitored by thin layer chromatography (TLC). Visualization was achieved under a UV lamp (254 nm), with I_2, and by developing the plates with *p*-anisaldehyde or phosphomolybdic acid. IR spectra were recorded on a commercial spectrophotometer. Optical rotations were reported as follows: $[\alpha]^T_D$ (*c*: g/100 mL, solvent). ^1H and ^{13}C NMR were

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recorded in $CDCl_3$ on a Bruker DRX-400 MHz NMR spectrometer with TMS as the internal standard. Chemical shift values are given in δ (ppm) using the peak signals of the solvent $CDCl_3$ (H 7.26 and C 77.23) as references, and coupling constants are reported in Hz. HRMS spectra were recorded using an FTMS-7 spectrometer, and MeOH or CH_2Cl_2 was used to dissolve the sample. Solvents for reaction were distilled prior to use: CH_2Cl_2 and CH_3CN from CaH_2, 2,2,2-trifluoroethanol (TFE), and other reagents were obtained from commercial suppliers unless otherwise stated. Powdered, <50 μm 4 Å molecular sieves were activated at 120 °C for 5 h and stored under nitrogen.

Compounds 18a and 18b. To a mixture of amino alcohol **16** (5.60 g, 26.5 mmol), benzyloxyacetaldehyde (**17**, 5.17 g, 34.5 mmol), and 4 Å molecular sieves (5.6 g) in CH_2Cl_2 and 2,2,2-trifluoroethanol (CH_2Cl_2/TFE, v/v, 7:1, 177 mL) was added dropwise acetic acid (AcOH, 0.38 mL, 6.6 mmol) at −10 °C. The mixture was stirred at −10 °C for 5 h, then stirred at 0 °C for 5 h. The reaction mixture was neutralized with moist $NaHCO_3$ and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash column chromatography (CC) on silica gel (gradient, 3% to 5% MeOH in CH_2Cl_2) to afford **18a** (8.10 g, 89%) and **18b** (0.46 g, 5%) as a yellow oil: **18a** $[\alpha]^{27}_D$ −86 (*c* 1.0, MeOH); IR (neat) ν_{max} 3303, 2924, 1583, 1494, 1455, 1310, 1234, 1101, 1021, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20−7.40 (5H, m), 6.44 (1H, s), 4.73 (3H, br s), 4.50 (3H, m), 4.02 (1H, dd, *J* = 9.4, 3.8 Hz), 3.82 (1H, dd, *J* = 9.2, 5.9 Hz), 3.73 (3H, s), 3.65−3.78 (1H, m), 3.52 (1H, dd, *J* = 11.2, 6.7 Hz), 2.92 (1H, m), 2.59 (1H, m), 2.45 (1H, m), 2.23 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.3, 144.0, 138.0, 132.3, 129.1, 128.4, 127.8, 127.7, 122.2, 119.6, 73.2, 72.8, 65.2, 60.6, 54.3, 53.4, 32.1, 15.8; HRMS (ESI-TOF) *m*/*z* 366.1679 $[M + Na]^+$ (calcd for $C_{20}H_{25}NO_4Na$, 366.1681); **18b** $[\alpha]^{27}_D$ −12 (*c* 0.95, MeOH); IR (neat) ν_{max} 3285, 2926, 1668, 1596, 1452, 1337, 1284, 1230, 1098, 1038, 740 cm^{-1}; ^1H NMR (400 MHz, CD_3OD) δ 7.30−7.42 (5H, m), 6.50 (1H, s), 4.59 (2H, s), 4.37 (1H, dd, *J* = 8.6, 5.2 Hz), 3.76 (1H dd, *J* = 11.0, 3.3 Hz), 3.68 (3H, s), 3.56 (2H, m), 3.49 (1H, dd, *J* = 10.8, 7.6 Hz), 3. 63 (1H, m), 2.66 (1H, dd, *J* = 16.7, 4.5 Hz), 2.55 (1H, dd, *J* = 16.3, 11.4 Hz), 2.10 (s, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 149.0, 144.7, 137.8, 129.2, 128.4, 128.2, 127.7, 127.6, 121.5, 114.1, 72.8, 67.5, 64.0, 59.3, 59.3, 53.2, 29.4, 10.4; HRMS (ESI-TOF) *m*/*z* 366.1685 $[M + Na]^+$ (calcd for $C_{20}H_{25}NO_4Na$, 366.1681).

Compound 19. To a solution of amine **18a** (7.66 g, 22.3 mmol) in CH_2Cl_2 (112 mL) were added sequentially triethylamine (Et_3N, 6.23 mL, 44.6 mmol) and di-*tert*-butyl dicarbonate (Boc_2O, 5.25 mL, 24.5 mmol) at room temperature. The mixture was stirred at room temperature for 6 h, and 100 mL of H_2O was added. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash CC on silica gel (25% EtOAc in hexanes) to afford *N*-Boc derivative **19** (9.40 g, 95%) as a pale yellow oil: $[\alpha]^{27}_D$ −10 (*c* 1.2, CH_2Cl_2); IR (neat) ν_{max} 3385, 2932, 1684, 1590, 1458, 1398, 1341, 1245, 1058, 1168, 1080, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20−7.35 (5H, m), 6.58 (1H, s), 6.52 (1H, s), 4.80 (1H, m), 4.54 (1H, d, *J* = 11.73 Hz), 4.24 (1H, m), 4.24 (1H, br s), 3.76 (1H, m), 3.73 (3H, s), 3.66 (1H, m), 3.50 (2H, m), 2.68−3.13 (2H, m), 2.24 (3H, s), 1.45 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.9, 145.4, 143.9, 137.8, 130.5, 130.4, 129.8, 128.4, 127.7, 121.4, 119.9, 80.5, 72.6, 71.8, 71.1, 65.8, 64.6, 60.6, 53.4 49.5, 48.1, 29.0, 28.4, 15.7; HRMS (ESI-TOF) *m*/*z* 466.2208 $[M + Na]^+$ (calcd for $C_{25}H_{33}NO_6Na$, 466.2206).

Compound 20. Potassium carbonate (3.94 g, 28.5 mmol), sodium iodide (0.14 mg, 0.93 mmol), and allyl bromide (allylBr, 2.5 mL, 28.5 mmol) were added sequentially to a solution of aminophenol **19** (8.42 g, 19.0 mmol) in 127 mL of CH_3CN, at room temperature. The mixture was stirred at 50 °C for 8 h and concentrated. The residue was dissolved in 100 mL of EtOAc and washed with H_2O (100 mL). The aqueous layer was extracted with EtOAc (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by CC on silica gel (20% EtOAc in hexanes) to afford **20** (8.63 g, 94%) as a pale yellow oil: $[\alpha]^{27}_D$ −24 (*c* 1.2, $CHCl_3$); IR (neat) ν_{max} 3464, 3064, 2973, 2932, 1688, 1717, 1454, 1393, 1248, 1169, 1095, 997, 857, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.22−7.40 (5H, m), 6.76 (1H, s), 6.10 (1.4H, m), 5.88 (0.6H, m), 5.41 (1H, m), 5.22 (1H, d, *J* = 8.6 Hz), 5.07 (1H, d, *J* = 12.3 Hz), 4.77 (1H, m), 4.54 (3H, m), 4.16 (1H, br s), 4.10 (1H, d, *J* = 9.9 Hz), 3.79 (3H, s), 3.69 (1H, m), 3.60 (1H, m), 3.57 (1H, m), 3.46 (1H, br s), 3.10 (1H, m), 2.77 (1H, m), 2.24 (3H, s), 1.46 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 155.8, 149.4, 147.6, 137.9, 134.2, 131.5, 130.8, 128.4, 127.9, 127.7, 127.4, 125.4, 117.3, 116.8, 80.4, 74.0, 73.6, 72.3, 70.9, 65.5, 64.5, 60.1, 54.5, 54.0, 49.6, 48.1, 28.8, 28.4, 15.8; HRMS (ESI-TOF) *m*/*z* 484.2696 $[M + H]^+$ (calcd for $C_{28}H_{38}NO_6$, 484.2699).

Compound 22. To a stirred solution of oxalyl chloride (1.9 mL, 21.6 mmol) in CH_2Cl_2 (95 mL) was added a solution of dimethyl sulfoxide (DMSO, 3.1 mL, 43.2 mmol) in CH_2Cl_2 (3 mL) at −78 °C. The mixture was stirred at −78 °C for 20 min, and alcohol **20** (5.22 g, 10.8 mmol) in a solution of CH_2Cl_2 (10 mL) was added. The mixture was stirred at −78 °C for 1.5 h, and *N*,*N*-diisopropylethylamine (14.3 mL, 86.4 mmol) was added dropwise at −78 °C. The mixture was stirred at −78 °C for 30 min, then warmed to 0 °C. The reaction was quenched with 80 mL of water. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and dried under vacuum. The residue was dissolved in CH_2Cl_2/TFE (7:1, 100 mL), and a solution of amino alcohol **16** (2.97 g, 14.1 mmol) in CH_2Cl_2/TFE (7:1, v/v, 8 mL), AcOH (0.3 mL, 5.4 mmol), and 4 Å molecular sieves (6.0 g) were added sequentially at room temperature. After being refluxed for 10 h, the reaction mixture was quenched with $NaHCO_3$ (0.45 g, 5.4 mmol) and filtered. The filtrate was concentrated under reduced pressure, and the residue was purified by flash CC on silica gel (gradient, 10% to 20% EtOAc in hexanes) to afford **22** (6.48 g, 89% for two steps) as a yellow oil: $[\alpha]^{27}_D$ −29 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3347, 2930, 1684, 1647, 1581, 1454, 1400, 1370, 1235, 1167, 1071, 999, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (0.7H, br s), 7.43 (0.3H, br s), 7.27−7.42 (5H, m), 6.63 (0.7H, s), 6.60 (0.3H, s), 6.44 (1H, s), 6.11 (1H, m), 5.94 (1H, m), 5.44 (1H, m), 5.25 (1H, m), 5.16 (1H, br s), 5.08 (0.3H, m), 4.88 (0.7, m), 4.45−4.70 (4H, m), 4.05 (1H, m), 3.80 (2.1H, s), 3.79 (0.9H, s), 3.78 (3H, s), 3.60 (1H, m), 3.44 (2H, m), 3.17 (0.3H, br s), 3.06 (0.7H, br s), 2.96 (0.7H, m), 2.68 (0.3H, m), 2.33−2.59 (3H, m), 2.26 (3H, s), 2.22 (3H, s), 1.55 (2.7H, s), 1.51 (6.3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 149.1, 147.2, 147.1, 144.3, 138.3, 134.2, 132.0, 131.5, 131.1, 129.3, 129.0, 128.4, 128.1, 127.7, 127.4, 126.7, 125.6, 122.2, 121.3, 117.8, 116.8, 81.0, 74.1, 73.6, 72.3, 71.6, 71.5, 67.6, 60.3, 60.1, 57.6, 53.4, 52.7, 49.3, 32.9, 28.6, 28.4, 25.5, 15.7; HRMS (ESI-TOF) *m*/*z* 675.3631 $[M + H]^+$ (calcd for $C_{39}H_{51}N_2O_8$, 675.3645).

Compound 24. To a solution of amine **22** (5.62 g, 8.34 mmol) in CH_2Cl_2 and saturated aqueous $NaHCO_3$ (84 mL, 1:1, v/v) was added dropwise allyl chloroformate (AllocCl, 0.97 mL, 9.17 mmol). After being stirred at room temperature overnight, the reaction mixture was diluted with CH_2Cl_2 (200 mL) and separated. The organic layer was washed with brine, dried with Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was purified by flash CC on silica gel (33% EtOAc in hexanes) to afford **24** (6.01 g, 95%) as a pale yellow oil: $[\alpha]^{27}_D$ +4.0 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3353, 2929, 2854, 1689, 1647, 1456, 1399, 1306, 1244, 1163, 1072, 996, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (1H, br s), 7.26−7.52 (5H, m), 6.77 (1H, s), 6.55 (1H, s), 6.05 (1H, m), 5.89 (1H, m), 5.75 (1H, m), 5.35 (1H, d, *J* = 21.0 Hz), 5.30 (1H, d, *J* = 17.3 Hz), 5.19 (1H, s), 5.17 (1H, s),4.80 (2H, m), 4.55 (5H, m), 4.07 (1H, br s), 3.96 (4H, m), 3.76 (3H, s), 3.74 (3H, s), 3.61 (1H, m), 3.17 (1H, br s), 3.00 (3H, m), 2.23 (3H, s), 2.21 (3H, s), 1.19 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.0, 156.4, 149.5, 147.4, 146.6, 145.7, 137.2, 134.3, 132.5, 131.5, 130.4, 128.4, 128.2, 127.9, 125.5, 122.2, 120.8, 118.2, 80.6, 73.8, 72.4, 68.1, 66.9, 60.1, 59.9, 56.3, 53.9, 50.6, 30.8, 29.2, 27.7, 15.8; HRMS (ESI-TOF) *m*/*z* 781.3680 $[M + Na]^+$ (calcd for $C_{43}H_{54}N_2O_{10}Na$: 781.3676).

Compound 25. A suspension of **24** (4.62 g, 6.09 mmol), cesium carbonate (2.98 g, 9.14 mmol), sodium iodide (91 mg, 0.61 mmol), and allyl bromide (0.80 mL, 9.14 mmol) in CH_3CN (60 mL) was

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stirred at 60 °C for 8 h. The solvent was removed in vacuo, and H_2O (80 mL) was added. The mixture was extracted with EtOAc (3 × 100 mL). The combined organic layer was dried with Na_2SO_4, filtered, and evaporated to dryness under reduced pressure. The residue was purified by flash CC on silica gel (33% EtOAc in hexanes) to afford **25** (4.57 g, 94%) as a pale yellow oil: $[\alpha]^{27}_D$ +30.5 (*c* 2.0, $CHCl_3$); IR (neat) ν_{max} 3423, 3088, 2927, 2859, 1688, 1587, 1456, 1395, 1307, 1237, 1164, 1101, 1069, 996, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16−7.25 (5H, m), 6.81 (1H, s), 6.72 (1H, s), 6.09 (2H, m), 5.81 (1H, m), 5.62 (1H, br s), 5.38 (1H, m), 5.30 (1H, m), 5.25 (1H, m), 5.19 (1H, s), 5.17 (1H, s), 5.09 (1H, m), 4.68 (1H, m), 4.34−4.60 (8H, m), 4.30 (1H, m), 4.22 (1H, m), 4.13 (1H, m), 3.93 (3H, m), 3.79 (6H, s), 2.80−3.34 (4H, m), 2.25 (3H, s), 2.20 (3H, s), 1.14 (4.5H, br s), 0.98 (4.5H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.0, 154.8, 148.5, 147.1, 137.9, 133.7, 133.6, 131.4, 129.9, 129.0, 127.0, 126.2, 124.2, 123.9, 123.3, 118.0, 116.9, 116.1, 114.8, 79.1, 78.4, 73.5, 72.9, 72.2, 71.4, 69.6, 66.1, 59.3, 59.0, 56.5, 56.1, 55.1, 50.8, 50.5, 49.9, 49.2, 29.4, 27.1, 26.4, 14.7, 14.5; HRMS (ESI-TOF) *m/z* 799.4172 $[M + H]^+$ (calcd for $C_{46}H_{59}N_2O_{10}$, 799.4170).

Compound 26. A solution of **25** (3.89 g, 4.86 mmol) in MeOH (48 mL) was treated with concentrated HCl (3.2 mL, v/v, 1/15). After stirring at 60 °C for 4 h, the volatiles were evaporated under reduced pressure. The residue was taken up with CH_2Cl_2 and H_2O, and the resulting mixture was basified with solid $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2 (3 × 80 mL), and the combined extracts were dried with anhydrous $NaSO_4$, filtered, and evaporated to dryness under reduced pressure. The residue was purified by flash CC on silica gel (40% EtOAc in hexanes) to afford **26** (3.12 g, 92%) as a yellow oil: $[\alpha]^{27}_D$ −61 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3447, 3084, 2931, 2859, 1694, 1483, 1453, 1404, 1310, 1234, 1069, 996, 926, 772 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.03−7.30 (5H, m), 6.78 (1H, s), 6.70 (1H, br s), 6.08 (1H, m), 5.88−6.02 (2H, m), 5.68−5.87 (1H, m), 5.41 (1H, d, *J* = 17.2), 5.12−5.36 (5H, m), 4.70 (1H, m), 4.62 (2H, m), 4.51 (1H, dd, *J* = 12.6, 5.5 Hz), 4.28−4.47 (5H, m), 4.14 (2H, m), 3.99 (1H, m), 3.80−3.92 (1H, m), 3.74 (6H, s), 3.65 (1H, m), 3.39 (1H, m), 3.13 (1H, m), 2.83 (2H, m), 2.54 (1H, m), 2.26 (3H, s), 2.20 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 149.6, 149.5, 149.0, 148.4, 138.5, 134.33, 134.27, 132.7, 131.7, 130.3, 128.1, 127.4, 127.3, 126.3, 125.4, 117.8, 117.2, 116.8, 73.6, 73.4, 73.1, 72.9, 66.6, 66.1, 60.1, 57.5, 55.1, 54.1, 34.5, 30.1, 23.5, 20.2, 15.8, 15.6; HRMS (ESI-TOF) *m/z* 699.3643 $[M + H]^+$ (calcd for $C_{41}H_{51}N_2O_8$, 699.3645).

Compound 27. To a stirred solution of oxalyl chloride (0.42 mL, 4.86 mmol) in CH_2Cl_2 (20 mL) was added a solution of DMSO (0.70 mL, 9.72 mmol) in CH_2Cl_2 (1 mL) at −78 °C. The mixture was stirred for 20 min, and alcohol **26** (1.70 g, 2.43 mmol) in a solution of CH_2Cl_2 (4 mL) was added. The mixture was stirred at −78 °C for 1.5 h, and triethylamine (2.70 mL, 19.44 mmol) was added dropwise at −78 °C. The mixture was stirred at −78 °C for 30 min and allowed to warm to 0 °C. The reaction was quenched with 40 mL of water. The aqueous layer was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered, concentrated, and dried under vacuum. The residue was dissolved in CH_2Cl_2 (25 mL), and trimethylsilyl cyanide (TMSCN, 0.92 mL, 7.29 mmol) and zinc chloride ($ZnCl_2$, 0.5 N in THF, 15 mL, 7.29 mmol) were added sequentially at room temperature. The mixture was stirred for 3 h, and water (30 mL) was added. The resulting mixture was extracted with CH_2Cl_2 (3 × 60 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash CC on silica gel (10% EtOAc in hexanes) to provide aminonitrile **27** (1.49 g, 87% for two steps) as a yellow oil: $[\alpha]^{27}_D$ −45 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 2962, 2931, 2861, 1707, 1486, 1416, 1317, 1263, 1234, 1110, 1018, 929, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20−7.37 (5H, m), 6.68 (1H, s), 6.62 (1H, d, *J* = 4.4 Hz), 6.05−6.28 (2H, m), 5.88 (1H, m), 5.45 (3H, m), 5.27 (3H, m), 5.17 (1H, m), 4.75 (1H, m), 4.47−4.70 (6H, m), 4.40 (2H, m), 4.32 (1H, dd, *J* = 4.6, 12.2 Hz), 4.23 (1H, br d, *J* = 7.8 Hz), 3.79 (3H, d, *J* = 5.7 Hz), 3.73 (3H, s), 3.48 (1H, m), 3.21 (1H, br d, *J* = 11.8 Hz), 3.10 (1H, td, *J* = 18.0, 8.4 Hz), 2.78−2.92 (3H, m), 2.24 (3H, s), 2.19 (3H, s), 2.07 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.11, 148.06, 147.8, 138.45, 138.42, 134.57, 134.51, 134.20, 134.16, 132.6, 132.5, 131.65, 131.60, 131.49, 131.15, 131.13, 131.11, 130.9, 130.8, 128.4, 127.6, 127.3, 125.5, 125.1, 124.9, 124.8, 124.5, 124.3, 118.1, 117.7, 117.6, 117.44, 117.39, 117.3, 117.2, 77.4, 77.1, 76.8, 74.1, 73.9, 73.7, 66.6, 66.3, 61.1, 60.3, 60.2, 60.0, 58.0, 57.97, 57.04, 57.01, 50.5, 50.0, 49.7, 48.9, 31.9, 31.8, 30.0, 15.91, 15.89, 15.7; HRMS (ESI-TOF) *m/z* 706.3490 $[M + H]^+$ (calcd for $C_{42}H_{48}N_3O_7$, 706.3492).

Compound 28. To a solution of **27** (1.47 g, 2.08 mmol) in dry CH_2Cl_2 (21 mL) were sequentially added AcOH (1.9 mL, 33.28 mmol), $Pd(PPh_3)_4$ (0.96 g, 0.83 mmol), and Bu_3SnH (3.4 mL, 12.5 mmol) at room temperature under an argon atmosphere. After stirring for 1 h, the reaction was quenched with 50 mL of 10% aqueous $NaHCO_3$ and then diluted with 60 mL of CH_2Cl_2. The resulting layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic layer was dried with Na_2SO_4 and filtered, and the solvent was evaporated in vacuo. The crude product was separated by CC on silica gel to give the crude triol product as a yellow oil. The impure triol was dissolved in CH_3CN/THF (3:1, 18 mL), and formalin solution (37% aqueous HCHO, 1.34 mL, 17.9 mmol) was added at room temperature. After stirring for 15 min, solid sodium cyanoborohydride ($NaBH_3CN$, 0.17 g, 2.69 mmol) was added, and the solution was stirred at room temperature for another 15 min. Acetic acid (0.20 mL, 3.58 mmol) was added dropwise, and the resulting mixture stirred at room temperature for another 1 h. The solution was partitioned between CH_2Cl_2 (100 mL) and saturated aqueous $NaHCO_3$ (30 mL), and the aqueous layer was further extracted with EtOAc (2 × 50 mL). The combined organic layer was dried over Na_2SO_4 and concentrated, and the residue was purified by flash CC on silica gel (20% EtOAc in hexanes) to afford **28** (1.05 g, 91% for two steps) as a colorless oil: $[\alpha]^{25}_D$ −10 (*c* 1.5, $CHCl_3$); IR (neat) ν_{max} 3408, 2927, 2855, 1621, 1586, 1499, 1457, 1419, 1317, 1236, 1101, 1071, 997, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.20−7.33 (5H, m), 6.42 (1H, s), 6.41 (1H, s), 6.04 (1H, s), 5.80 (1H, s), 4.43 (1H, d, *J* = 12.1 Hz), 4.37 (1H, d, *J* = 2.2 Hz), 4.33 (1H, d, *J* = 12.1 Hz), 4.27 (1H, dd, *J* = 8.3, 2.9 Hz), 4.08 (1H, d, *J* = 1.9 Hz), 3.75 (3H, s), 3.72 (3H, s), 3.51 (1H, dd, *J* = 8.9, 3.1 Hz), 3.29 (1H, dt, *J* = 11.9, 2.5 Hz), 3.23 (1H, br d, *J* = 7.8 Hz), 2.99 (1H, t, *J* = 8.7 Hz), 2.91 (1H, dd, *J* = 17.8, 8.0 Hz), 2.79 (1H, dd, *J* = 15.1, 1.7 Hz), 2.59 (1H, d, *J* = 17.7 Hz), 2.27 (6H, s), 2.21 (3H, s), 2.12 (1H, dd, *J* = 14.5, 12.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.4, 145.1, 143.6, 142.4, 138.3, 132.4, 131.6, 128.8, 128.2, 128.1, 127.4, 127.3, 120.8, 120.6, 118.9, 118.0, 117.1, 76.8, 73.2, 61.9, 60.7, 60.6, 57.5, 56.9, 56.8, 55.5, 41.6, 32.0, 25.4, 15.7, 15.6; HRMS (ESI-TOF) *m/z* 556.2813 $[M + H]^+$ (calcd for $C_{33}H_{38}N_3O_5$, 556.2811).

Compound 29. To a cooled (−78 °C) solution of aminonitrile **28** (0.44 g, 0.79 mmol) in 30 mL of CH_2Cl_2 was added BCl_3 (1 N in CH_2Cl_2, 4.0 mL, 3.96 mmol) at −78 °C. The mixture was stirred −78 °C for 1 h, and CH_2Cl_2 (20 mL) and saturated aqueous $NaHCO_3$ (20 mL) were added slowly in sequence. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (50 mL × 3). The combined organic extracts were dried over anhydrous Na_2SO_4, filtered, and concentrated. The residue was purified by flash CC on silica gel (EtOAc) to provide alcohol **29** (0.35 g, 94%) as a pale yellow oil: $[\alpha]^{25}_D$ +15 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max} 3417, 3220, 2927, 2850, 1717, 1579, 1499, 1454, 1413, 1236, 1145, 1101, 1064, 804 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.49 (1H, s), 6.43 (1H, s), 5.91 (1H, s), 5.83 (1H, s), 4.15 (1H, d, *J* = 1.9 Hz), 4.11 (1H, t, *J* = 3.4 Hz), 4.06 (1H, d, *J* = 2.2 Hz), 3.74 (3H, s), 3.73 (3H, s), 3.62 (1H, dt, *J* = 10.9, 3.2 Hz), 3.44 (1H, dd, *J* = 10.3, 3.2 Hz), 3.39 (1H, m), 3.35 (1H, br d, *J* = 7.8 Hz), 3.10 (1H, dd, *J* = 18.1, 7.8 Hz), 2.79 (1H, dd, *J* = 15.4, 2.5 Hz), 2.50 (1H, d, *J* = 18.1 Hz), 2.35 (3H, s), 2.24 (3H, s), 2.22 (3H, s), 2.14 (1H, dd, *J* = 15.1, 12.3 Hz), 1.91 (1H, dd, *J* = 9.6, 3.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 145.0, 143.7, 143.2, 132.0, 130.5, 129.2, 128.9, 121.1, 121.0, 118.4, 118.1, 116.9, 64.2, 60.9, 60.8, 60.5, 58.3, 57.1, 56.8, 55.6, 41.9, 32.0, 25.9, 15.9, 15.8; HRMS (ESI-TOF) *m/z* 488.2161 $[M + Na]^+$ (calcd for $C_{26}H_{31}N_3O_5Na$, 488.2161).

(−)-Jorunnamycin A (1). To a solution of **29** (0.23 g, 0.49 mmol) in CH_3CN (4.9 mL) was added salcomine (0.16 g, 0.49 mmol) at room temperature, and the dark suspension was stirred under an O_2 atmosphere for 4 h. The mixture was filtered through cellulose

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powder, and the filter cake was carefully washed with EtOAc. After concentration in vacuo, the residue was chromatographed on silica gel (50% EtOAc in hexanes) to give (−)-jorunnamycin A (**1**) (0.22 g, 91%) as a yellow oil: $[\alpha]^{25}_{D}$ −260 (*c* 1.0, $CHCl_3$); IR (neat) ν_{max} 3631, 3447, 3015, 2945, 2853, 1653, 1557, 1449, 1376, 1310, 1189, 1077 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.17 (1H, d, *J* = 2.0 Hz), 4.07 (1H, d, *J* = 2.5 Hz), 4.03 (3H, s), 3.98 (3H, s), 3.89 (1H, d, *J* = 2.4 Hz), 3.71 (1H, dd, *J* = 11.2, 2.7 Hz), 3.48 (1H, d, *J* = 11.2 Hz), 3.41 (1H, d, *J* = 7.4 Hz), 3.16 (1H, dt, *J* = 11.2, 2.6 Hz), 2.92 (1H, dd, *J* = 17.4, 2.1 Hz), 2.82 (1H, dd, *J* = 21.0, 7.5 Hz), 2.31 (3H, s), 2.27 (1H, d, *J* = 21.0 Hz), 1.93 (6H, s), 1.42 (1H, ddd, *J* = 17.3, 11.6, 2.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.4, 185.5, 182.3, 181.4, 155.5, 155.4, 141.7, 141.4, 136.1, 135.6, 128.9, 128.6, 117.0, 64.2, 61.1, 61.1, 59.1, 58.0, 54.5, 54.3, 54.3, 41.6, 25.4, 21.5, 8.8, 8.7; HRMS (ESI-TOF) *m*/*z* 494.1938 $[M + H]^+$ (calcd for $C_{26}H_{28}N_3O_7$, 494.1927).

(−)-Jorunnamycin C (2). To a solution of (−)-jorunnamycin A (**1**) (12 mg, 0.024 mmol) in pyridine (0.5 mL) was added propionic anhydride (64.4 μL, 0.5 mmol) at 0 °C, and the reaction mixture was stirred at 25 °C for 3 h. The reaction mixture was diluted with water (20 mL) and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extract was washed with brine, dried, and concentrated, and the residue was purified by flash CC on silica gel (25% EtOAc in hexanes) to afford (−)-jorunnamycin C (**2**) (10 mg, 76%) as a yellow film: $[\alpha]^{25}_{D}$ −89 (*c* 0.2, $CHCl_3$); IR (neat) ν_{max} 3387, 2926, 2853, 1738, 1654, 1616, 1457, 1306, 1234, 956, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.41 (1H, d, *J* = 11.2 Hz), 4.07 (1H, br s), 4.01 (1H, s), 4.01 (6H, s), 3.99 (1H, d, *J* = 2.4 Hz), 3.89 (1H, dd, *J* = 11.2, 2.4 Hz), 3.38 (1H, d, *J* = 7.4 Hz), 3.10 (1H, d, *J* = 10.6 Hz), 2.93 (1H, d, *J* = 17.5 Hz), 2.76 (1H, dd, *J* = 20.7, 7.4 Hz), 2.31 (1H, d, *J* = 21.0 Hz), 2.29 (3H, s), 2.11 (1H, m), 2.02 (1H, m), 1.95 (6H, s), 1.31 (1H, m), 0.95 (3H, t, *J* = 7.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 185.4, 182.4, 180.9, 173.4, 155.6, 155.2, 142.1, 141.7, 135.4, 134.9, 128.7, 128.6, 117.0, 63.5, 61.1, 61.1, 59.0, 55.9, 54.5, 54.4, 54.2, 41.5, 27.4, 25.3, 21.2, 8.9, 8.8, 8.7; HRMS (ESI-TOF) *m*/*z* 550.2185 $[M + H]^+$ (calcd for $C_{29}H_{32}N_3O_8$, 550.2189).

(−)-Jorumycin (3). (−)-Jorunnamycin A (**1**) (20 mg, 0.036 mmol) was dissolved in pyridine/Ac_2O (2:1, 6 mL) at room temperature, and the resulting mixture was stirred for 3 h. The reaction was then concentrated under vacuum, and the crude product was chromatographed on silica gel (25% EtOAc in hexanes) to give the intermediate acetate as a yellow oil. To a mixture of the acetate intermediate in CH_3CN/H_2O (3:2, 2.5 mL) was added in one portion $AgNO_3$ (0.15 g, 0.90 mmol) at room temperature. The resulting mixture was stirred at 45 °C for 4 h, after which the reaction was filtered through a short Celite plug using CH_2Cl_2 as necessary to transfer the product. The filtrate was concentrated to give a residue that was subsequently dissolved in 20 mL of CH_2Cl_2 and diluted with 5 mL of H_2O. The resulting layers were separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated, and the crude product was purified by flash CC on silica gel (50% EtOAc in hexanes) to afford (−)-jorumycin (**3**) (14.3 mg, 78% for two steps) as a yellow film: $[\alpha]^{25}_{D}$ −69 (*c* 0.5, $CHCl_3$); IR (neat) ν_{max} 3452, 2929, 2853, 1740, 1653, 1617, 1558, 1454, 1309, 1232, 1084, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.44 (1H, dd, *J* = 11.0, 2.9 Hz), 4.42 (1H, br s), 4.36 (1H, br s), 4.01 (3H, s), 3.99 (3H, s), 3.90 (1H, br s), 3.81 (1H, dd, *J* = 11.3, 2.8 Hz), 3.18 (1H, m), 3.16 (1H, m), 2.84 (1H, d, *J* = 16.3 Hz), 2.65 (1H, dd, *J* = 21.0, 7.7 Hz), 2.26 (3H, s), 2.24 (1H, br d, *J* = 20.0 Hz), 1.96 (3H, s), 1.94 (3H, s), 1.76 (3H, s), 1.30 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 185.9, 182.6, 181.3, 170.0, 155.6, 155.2, 141.9, 141.8, 137.2, 134.4, 128.7, 128.4, 83.0, 64.2, 61.0 (2), 57.4, 54.1, 52.7, 51.0, 41.4, 25.6, 20.6, 20.5, 8.8, 8.7; HRMS (ESI-TOF) *m*/*z* 511.2078 $[M + H]^+$ (calcd for $C_{27}H_{31}N_2O_8$, 511.2080).

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C NMR spectra of compounds **18a**, **18b**, **19**, **20**, **22**, **24**, **25**−**29**, and **1**−**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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