First Synthesis of Caerulomycin B. A New Synthesis of Caerulomycin C

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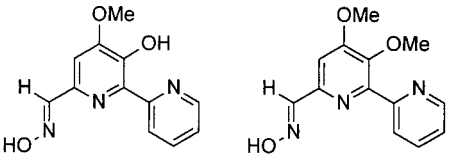
Caerulomycins produced by *Streptomyces caeruleus* are bipyridinic molecules endowed with antibiotic properties. The first synthesis of caerulomycin B (**1**) as well as a new synthesis of caerulomycin C (**2**) are reported. Starting from 3-hydroxypyridine, the same methodology was used to prepare both compounds **1** and **2**. Efficiently controlled reactions such as metalation to allow the synthesis of 2,6-diiodo-3,4-dialkoxypyridines, which are key intermediates, and further halogen−lithium exchange and cross-coupling to reach the targets molecules **1** and **2** have been developed.

Introduction

A bipyridinic antibiotic known as caerulomycin was first isolated in 1959.[1] Caerulomycins B (**1**) and C (**2**) are two of the five caerulomycins produced by *Streptomyces caeruleus*;[2] these bipyridinic molecules were isolated in 1977 and their structure established.[3] The first synthesis of compound **2** was reported by our group in 1996.[4]



1, caerulomycin B **2, caerulomycin C**

Because of our interest in the synthesis of pyridine-containing natural products[5] and in light of our knowledge of the metalation field,[6] we undertook the synthesis of caerulomycin B (**1**) in which the 2,2′-bipyridine structure is present as in the previously reported caerulomycins A, C, and E and collismycins A and C.[4,7] Herein, we describe the first synthesis of **1** and a new synthesis of **2** starting from 3-hydroxypyridine. The strategy mainly involves efficiently controlled reactions such as metalation, transmetalation, and aromatic cross-coupling.

Results and Discussion

Initially, we considered the methodology used for the previously described synthesis of caerulomycin C.[4] To this purpose, carbamate **4**, generated from 3-hydroxy-4-methoxypyridine (**3**),[8] was metalated at C2 using *sec*-butyllithium in tetrahydrofuran (THF) at low temperature.[9] After transmetalation with zinc chloride and coupling with 2-bromopyridine, in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$),[10] 2,2′-bipyridine **5** was obtained. Phenyllithium was successfully employed to deprotonate compound **5** at C5, as shown by the trapping of the resulting lithio derivative with BrCN to afford compound **6**. A bromine migration reaction[6] from C5 to C6 performed on **6** with LDA gave 6-brominated compound **7** (Scheme 1).

Since attempts to realize an efficient bromine−lithium exchange using alkyllithiums on compound **7** failed, due to the competitive cleavage of the carbamate group, we turned to a cross-coupling reaction in order to introduce a methyl group at C6.[7] Thus, compound **7** was coupled with methylzinc chloride to afford 6-methyl-2,2′-bipyridine **8** in a quantitative yield. After deprotection of the hydroxy group, oxidation of the 6-methyl compound **9** to the 6-formyl derivative **10** was tested using various oxidating systems, with the best result (a poor yield of 10%) obtained using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 2).

Consequently, we decided to abandon this approach and considered a new pathway to reach the target molecule. The synthesis of the key 2,6-diiodo-3,4-dialkoxypyridines was investigated from 2,6-diiodo-3-hydroxypyridine by O-alkylation and metalation at C4 to reach 4-hydroxy, followed by O-methylation. Subsequent regioselective iodine−lithium exchange at C2, cross-coupling, and iodine−lithium exchange at C6 would afford caerulomycins **1** and **2** (Scheme 3).

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(1) Funk, A.; Divekar, P. V. *Can. J. Microbiol.* **1959**, *5*, 317.
(2) Vining, L. C.; McInnes, A. G.; McCulloch, A. W.; Smith, D. G.; Walter, J. A. *Can. J. Chem.* **1988**, *66*, 191 and references therein.
(3) McInnes, A. G.; Smith, D. G.; Wright, J. L. C.; Vining, L. C. *Can. J. Chem.* **1977**, *55*, 4159.
(4) Trécourt, F.; Gervais, B.; Mallet, M.; Quéguiner, G. *J. Org. Chem.* **1996**, *61*, 1673.
(5) Godard, A.; Marsais, F.; Plé, N.; Trécourt, F.; Turck, A.; Quéguiner, G. *Heterocycles* **1995**, *40*, 1055.
(6) For reviews on directed ortho-metalation of pyridines and some other π-deficient azaaromatics, see: (a) Quéguiner, G.; Marsais, F.; Snieckus, V.; Epsztajn, J. *Adv. Heterocycl. Chem.* **1991**, *52*, 187. (b) Mongin, F.; Quéguiner, G. *Tetrahedron* **2001**, *57*, 4059.
(7) Trécourt, F.; Gervais, B.; Mongin, O.; Le Gal, C.; Mongin, F.; Quéguiner, G. *J. Org. Chem.* **1998**, *63*, 2892.
(8) Trécourt, F.; Mallet, M.; Mongin, O.; Gervais, B.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 8373.
(9) Miah, M. A. J.; Snieckus, V. *J. Org. Chem.* **1985**, *50*, 5436.
(10) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.

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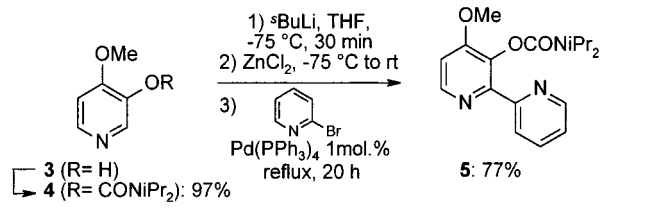
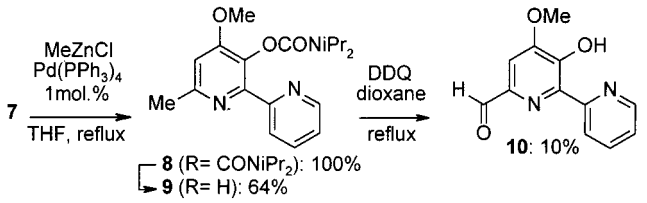
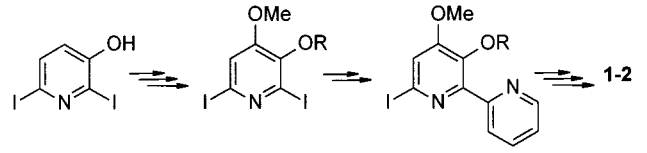
Scheme 1



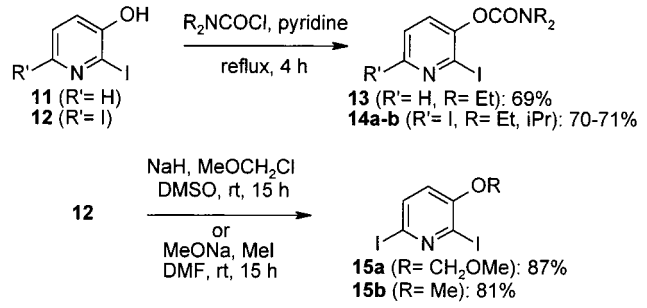
Scheme 2



Scheme 3



Scheme 4



3-Hydroxy-2-iodo- and 3-hydroxy-2,6-diiodopyridines (**11** and **12**) were easily obtained, using a procedure described in the literature.[11] The protection of the hydroxy group as the carbamate derivatives **13** and **14** or the alkoxy compounds **15** was then effected in good yields using standard procedures (Scheme 4).

In the case of carbamates **13** and **14**, deprotonation at C4 could be achieved with lithium diisopropylamide (LDA)[9] and the lithio derivatives trapped with D_2O and hexachloroethane to give compounds **16**−**18** in good yields (Table 1, entries 1−4).

Alkoxypyridines are generally deprotonated with alkyl- or phenyllithiums,[6] but such bases cannot be used in the presence of iodine atoms,[12] so we turned to lithium dialkylamides to deprotonate alkoxypyridines **15**. LTMP was found to be more efficient than LDA with deprotonation occurring regioselectively at C4 (Table 1, entries 5−7). The introduction of a hydroxy group at C4 (pyridinones **19b** and **20**) could be realized in quite good yields (Table 1, entries 6 and 7) with trimethylborate as an electrophile followed by the in situ cleavage of the borate ester with peracetic acid[13] (Scheme 5).

The key intermediate 4-methoxypyridines were prepared by displacement of the chloride of compound **18** with MeONa to give **21** and O-methylation of compounds **19b** and **20** via their silver salts to give **22** and **23** (Scheme 6).

For the preparation of the 2,2′-bipyridine skeleton, the iodine−lithium exchange was examined. A regioselective exchange at C2 has already been described in the case of compound **23**.[14] Under the same exchange conditions, 2,6-diiodinated carbamates **14a**,**b** and **21** also reacted regioselectivity at C2; however, compounds **24a**,**b** and **25** were obtained in low yields due to the competitive deprotection of the carbamate group (Scheme 7).

When these conditions were applied to the 2,6-diiodo-3-alkoxypyridines **15a**, **22**, and **23**, better yields were obtained after trapping with electrophiles (compounds **26**−**28**). The reaction was 100% regioselective at C2 (Scheme 8, Table 2).

Next, the transmetalation reaction of the 2-lithio derivatives with zinc chloride[4] was carried out, and the resulting organozinc reagents were coupled with 2-iodopyridine, in the presence of a catalytic amount of Pd(PPh_3)$_4$,[10] to afford 2,2′-bipyridines **29**−**31** (Scheme 9, Table 3).

To reach caerulomycins B (**1**) and C (**2**), functionalization of compounds **30** and **31** at C6 was effected through a second iodine−lithium exchange followed by quenching with DMF. Reacting aldehydes **10** and **32**[15] with hydroxylamine afforded targets **1** and **2** as the (*E*)-oximes (Scheme 10).

Conclusion

This first synthesis of caerulomycin B (**1**) required only seven steps and afforded the desired product in 7.5% overall yield. The synthesis started from commercially available 3-hydroxypyridine and proceeded via the key intermediate, 2,6-diiodo-4-methoxy-3-methoxymethoxypyridine (**22**). This same methodology could also be applied to the synthesis of caerulomycin C (**2**), which was obtained in 8% overall yield via 2,6-diiodo-3,4-dimethoxypyridine (**23**) (seven steps from 3-hydroxypyridine). The yield is comparable to the one obtained in our previously described synthesis (5%, seven steps from 4-methoxypyridine).[4]

Experimental Section

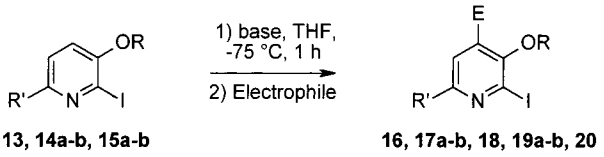
General Methods. ^{1}H NMR and ^{13}C NMR spectra were recorded with a 200 or 300 MHz spectrometer. THF was distilled from benzophenone/Na. The water content of the solvents was estimated to be lower than 45 ppm by the modified Karl Fischer method.[16] Commercial solutions of BuLi, ^{s}BuLi, PhLi, and MeLi were employed as received; PhLi was titrated periodically against 2-butanol. Pd(PPh_3)$_4$ was synthesized by a literature method.[10] Metalation and cross-coupling

(11) Koch, V.; Schnatterer, S. *Synthesis* **1990**, 497.
(12) Mongin, F.; Trécourt, F.; Mongin, O.; Quéguiner, G. *Tetrahedron* **2002**, *58*, 309.
(13) (a) Green, K. *J. Org. Chem.* **1991**, *56*, 4325−4326. (b) Marsais, F.; Godard, A.; Quéguiner, G. *J. Heterocycl. Chem.* **1989**, *26*, 1589.
(14) Mongin, O.; Rocca, P.; Thomas-dit-Dumont, L.; Trécourt, F.; Marsais, F.; Godard, A.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2503.
(15) The last step was already described by our group.[4]
(16) Bizot, J. *Bull. Soc. Chim. Fr.* **1967**, 151.

Table 1. Metalation of 13, 14a,b, and 15a,b

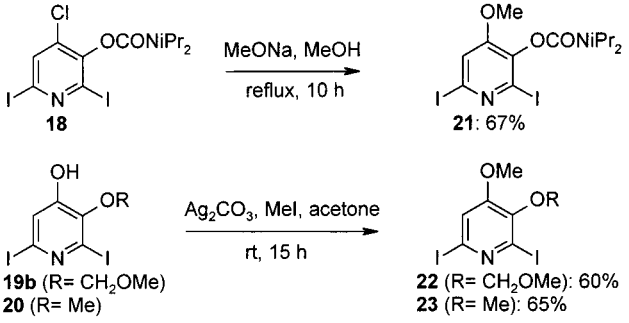
entry	starting material (R′, R)	base	electrophile	product	E	yield (%)
1	**13** (H, $CONEt_2$)	LDA	C_2Cl_6	**16**	Cl	62
2	**14a** (I, $CONEt_2$)	LDA	D_2O	**17a**	D	89 (90% *d*)
3	**14a** (I, $CONEt_2$)	LDA	C_2Cl_6	**17b**	Cl	77
4	**14b** (I, $CONiPr_2$)	LDA	C_2Cl_6	**18**	Cl	80
5	**15a** (I, CH_2OMe)	LTMP	D_2O	**19a**	D	74 (90% *d*)
6	**15a** (I, CH_2OMe)	LTMP	$B(OMe)_3/AcO_2H$	**19b**	OH	86
7	**15b** (I, Me)	LTMP	$B(OMe)_3/AcO_2H$	**20**	OH	82

Scheme 5

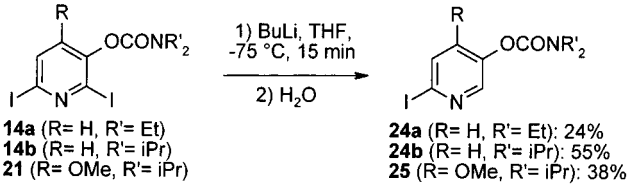


13, 14a-b, 15a-b **16, 17a-b, 18, 19a-b, 20**

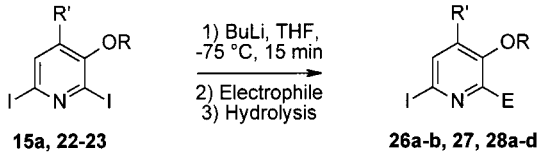
Scheme 6



Scheme 7



Scheme 8



reactions were carried out under dry argon. Deuterium incorporation was determined from the ^{1}H NMR integration values. 2-Iodo-,[17] 3-hydroxy-4-methoxy- (**3**),[8] 3-hydroxy-2-iodo- (**11**),[11] and 3-hydroxy-2,6-diiodopyridines (**12**)[11] were prepared according to literature procedures.

After the reaction, hydrolysis, and neutralization, the aqueous solution was extracted several times with CH_2Cl_2. The organic layer was dried over Na_2SO_4, the solvents were evaporated under reduced pressure, and unless otherwise noted, the crude compound was chromatographed on a silica gel column (eluent is given in the product description).

2,6-Diiodo-3-methoxymethoxypyridine (15a). To a stirred suspension of NaH (80% in mineral oil, 2.9 g, 60 mmol) in DMSO (40 mL) was progressively added 3-hydroxy-2,6-diiodopyridine (**12**, 17 g, 50 mmol). After the mixture was stirred for 30 min, $MeOCH_2Cl$ (4.6 mL, 60 mmol) was added at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 15 h. After addition of H_2O (40 mL) and extraction with AcOEt (3 × 40 mL), the organic phase was washed with H_2O (4 × 40 mL) to afford 87% of **15a** (eluent: CH_2Cl_2): mp <50 °C; ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 3H), 5.17 (s, 2H), 6.90 (d, 1H, J = 8.4 Hz), 7.46 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$) δ 57.0, 95.4, 105.6, 111.6, 123.2, 134.6, 154.2; IR (KBr) ν 2956, 2905, 1550, 1535, 1419, 1393, 1261, 1157, 1045, 961. Anal. Calcd for $C_7H_7I_2NO_2$ (390.95): C, 21.51; H, 1.80; N, 3.58. Found: C, 21.78; H, 1.72; N, 3.86.

2,6-Diiodo-3-methoxypyridine (15b). To a stirred solution of MeONa (3.2 g, 60 mmol) in DMF (50 mL) was progressively added 3-hydroxy-2,6-diiodopyridine (**12**, 17 g, 50 mmol). After the mixture was stirred for 30 min, MeI (3.7 mL, 60 mmol) was added at 0 °C. The reaction mixture was then warmed to room temperature and stirred for 15 h. After addition of H_2O (40 mL) and extraction with AcOEt (3 × 40 mL), the organic phase was washed with H_2O (4 × 40 mL) to afford 81% of **15b** (eluent: CH_2Cl_2): mp 100−101 °C (lit.[18] mp 100.5−101 °C); ^{1}H NMR ($CDCl_3$) δ 3.82 (s, 3H), 6.63 (d, 1H, J = 8.4 Hz), 7.49 (d, 1H, J = 8.3 Hz); ^{13}C NMR ($CDCl_3$) δ 56.9, 103.7, 110.8, 119.3, 134.5, 156.1; IR (KBr) ν 2970, 2922, 1442, 1398, 1287, 1052, 813, 805, 602. Anal. Calcd for $C_6H_5I_2NO$ (360.92): C, 19.97; H, 1.40; N, 3.88. Found: C, 20.17; H, 1.29; N, 3.93.

General Procedure A: Metalation of 3-Methoxymethoxy- and 3-Methoxypyridines 15a,b. At −75 °C, 2,2,6,6-tetramethylpiperidine (0.40 mL, 2.4 mmol) and, 15 min later, the required 3-alkoxypyridine (2.0 mmol) were added to a solution of BuLi (2.2 mmol) in hexane (0.88 mL) and THF (10 mL). After 1 h at −75 °C, the electrophile was added and allowed to react as mentioned in the product description.

2,6-Diiodo-3-methoxymethoxy-4(1*H*)-pyridinone (19b). The general procedure A, starting from **15a** and using $B(OMe)_3$ (0.48 mL, 4.2 mmol) at −75 °C, with stirring for 2 h at this temperature, was used. A solution of peracetic acid (0.72 mL of a 32 wt % in dilute acetic acid, 4.2 mmol) was then added, and the mixture was slowly warmed to room temperature. After the mixture was cooled to −10 °C, an aqueous solution (10 mL) of $Na_2S_2O_4$ (0.75 g) was added dropwise. An 86% yield of **19b** was obtained (eluent: CH_2Cl_2/Et_2O 80:20): mp 118−120 °C; ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 3H), 5.03 (s, 2H), 7.18 (s, 1H), 9.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 58.4, 99.4, 109.7, 114.8, 124.3, 144.8, 156.2; IR (KBr) ν 2961, 1556, 1538, 1454, 1360, 1241, 1157, 914. Anal. Calcd for $C_7H_7I_2NO_3$ (406.95): C, 20.66; H, 1.73; N, 3.44. Found: C, 20.91; H, 2.00; N, 3.22.

2,6-Diiodo-3-methoxy-4(1*H*)-pyridinone (20). The general procedure A, starting from **15b** and using $B(OMe)_3$ (0.48 mL, 4.2 mmol) at −75 °C, with stirring for 2 h at this temperature, was used. A solution of peracetic acid (0.72 mL of a 32 wt % in dilute acetic acid, 4.2 mmol) was then added, and the mixture was slowly warmed to room temperature. After the mixture was cooled to −10 °C, an aqueous solution (10 mL) of $Na_2S_2O_4$ (0.75 g) was added dropwise. An 82% yield of **20** was obtained (eluent: CH_2Cl_2/Et_2O 90:10): mp 176−178 °C; ^{1}H NMR ($CDCl_3$) δ 3.83 (s, 3H), 6.45 (s, 1H), 7.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 61.0, 109.3, 114.1, 124.2, 147.1, 158.1; IR (KBr) ν 2934, 2606, 1537, 1460, 1356, 1244, 987, 926, 849, 672. Anal. Calcd for $C_6H_5I_2NO_2$ (376.92): C, 19.12; H, 1.34; N, 3.72. Found: C, 19.27; H, 1.18; N, 3.82.

2,6-Diiodo-4-methoxy-3-methoxymethoxypyridine (22). To the pyridone **19b** (4.1 g, 10 mmol) in acetone (150 mL) were

(17) Trécourt, F.; Breton, G.; Bonnet, V.; Mongin, F.; Marsais, F.; Quéguiner, G. *Tetrahedron* **2000**, *56*, 1349.

(18) Burger, A.; Bailey, M. S. *J. Am. Chem. Soc.* **1946**, *68*, 520.

Table 2. Iodine−Lithium Exchange of 15a, 22, and 23

entry	starting material (R′, R)	electrophile	product	E	yield (%)
1	**15a** (H, CH_2OMe)	H_2O	**26a**	H	74
2	**15a** (H, CH_2OMe)	$ClSnBu_3$	**26b**	$SnBu_3$	77
3	**22** (OMe, CH_2OMe)	H_2O	**27**	H	70
4	**23** (OMe, Me)	H_2O	**28a**	H	70
5	**23** (OMe, Me)	D_2O	**28b**	D	69 (95% d)
6	**23** (OMe, Me)	PhCHO	**28c**	CH(OH)Ph	48
7	**23** (OMe, Me)	C_2Cl_6	**28d**	Cl	45

Scheme 9

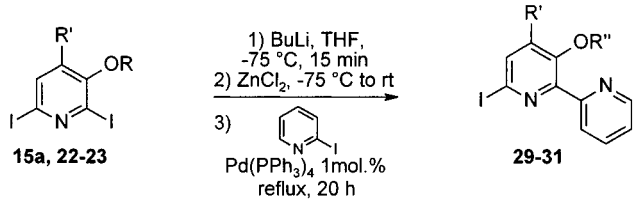
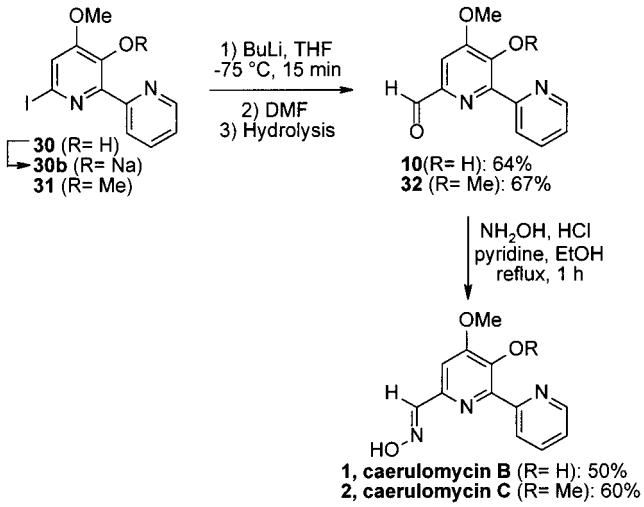


Table 3. Cross-Coupling Starting from 15a, 22, and 23

entry	starting material	R	R′	R″	product	yield (%)
1	**15a**	CH_2OMe	H	H	**29**	55
2	**22**	CH_2OMe	OMe	H	**30**	57
3	**23**	Me	OMe	Me	**31**	53

Scheme 10



added at room temperature Ag_2CO_3 (3.0 g, 11 mmol) and, 15 min later, MeI (3.1 mL, 50 mmol). The mixture was stirred in the dark for 15 h. The silver salts were filtered on Celite and washed with CH_2Cl_2. A 60% yield of **22** was obtained (eluent: CH_2Cl_2): mp 80−82 °C; ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 3H), 3.81 (s, 3H), 5.10 (s, 2H), 7.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.6, 59.0, 99.0, 109.7, 115.2, 119.0, 144.2, 157.9; IR (KBr) ν 2937, 1549, 1530, 1427, 1326, 1026, 926, 866. Anal. Calcd for $C_8H_9I_2NO_3$ (420.97): C, 22.83; H, 2.15; N, 3.33. Found: C, 23.02; H, 2.10; N, 3.13.

2,6-Diiodo-3,4-dimethoxypyridine (23). From the pyridone **20**, as previously described for the synthesis of compound **22**: yield 65% (eluent: CH_2Cl_2/cyclohexane 60:40); mp 96−98 °C (lit.[14] mp 97 °C); ^{13}C NMR ($CDCl_3$) δ 56.3, 60.6, 109.5, 114.4, 118.7, 146.7, 157.8.

General Procedure B: Iodine−lithium Exchange of Iodopyridines 30 and 31. At −75 °C, the required 2-iodopyridine (2.0 mmol) was added to a solution of BuLi (4.0 mmol) in hexane (1.6 mL) and THF (10 mL). After 15 min at −75 °C, the electrophile was added and allowed to react as mentioned in the product description.

3-Hydroxy-4-methoxy-2,2′-bipyridine-6-carboxaldehyde (10). The general procedure B, starting from the sodium salt of **30** [made after treatment of **30** (2.0 mmol) with 55% NaH (0.11 g, 2.4 mmol) in 3 mL of THF] and using DMF (0.16 mL, 2.0 mmol) at −75 °C with subsequent warming to room temperature, gave 64% of **10** (eluent: CH_2Cl_2/Et_2O 90:10): mp 159 °C; ^{1}H NMR ($CDCl_3$) δ 3.97 (s, 3H), 7.35 (ddd, 1H, J = 7.5, 5.2, 1.2 Hz), 7.47 (s, 1H), 7.92 (td, 1H, J = 8.0, 1.6 Hz), 8.49 (dd, 1H, J = 4.2, 1.5 Hz), 8.67 (dd, 1H, J = 8.3, 1.2 Hz), 9.90 (s, 1H), 15.3 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 55.2, 103.5, 120.1, 122.5, 134.5, 137.3, 143.8, 144.0, 150.2, 154.6, 156.4, 191.5; IR (KBr) ν 2924, 2356, 1709, 1694, 1487, 1372, 1287, 1159, 1040, 802. Anal. Calcd for $C_{12}H_{10}N_2O_3$ (230.23): C, 62.61; H, 4.38; N, 12.17. Found: C, 62.53; H, 4.15; N, 12.02.

3,4-Dimethoxy-2,2′-bipyridine-6-carboxaldehyde (32). The general procedure B, starting from **31** and using DMF (0.16 mL, 2.0 mmol) at −75 °C with subsequent warming to room temperature, gave 67% of **32** (eluent: AcOEt/NEt_3 80:20): mp 78−80 °C (lit.[4] mp 80 °C).

General Procedure C: Cross-Coupling from 2-Lithiopyridines 22 and 23. After 15 min at −75 °C, an anhydrous solution of $ZnCl_2$ (0.82 g, 6.0 mmol) in THF (20 mL) was added to the required lithiopyridine (2.0 mmol) at the same temperature. The reaction mixture was then warmed to room temperature. After the addition of 2-iodopyridine (0.82 g, 4.0 mmol) and $Pd(PPh_3)_4$ (69 mg, 60 μmol), the mixture was heated at reflux for 20 h, cooled, and evaporated to dryness. The residue was dissolved in concentrated NH_4OH (20 mL) and CH_2Cl_2 (50 mL) containing EDTA (3.7 g, 10 mmol). The mixture was heated at reflux for 1 h.

3-Hydroxy-6-iodo-4-methoxy-2,2′-bipyridine (30). The general procedure C, starting from **22**, gave, after washing with Et_2O/petroleum ether 50:50, 57% of **30** (eluent: CH_2Cl_2/petroleum ether 50:50): mp 164−166 °C; ^{1}H NMR ($CDCl_3$) δ 3.88 (s, 3H), 7.05 (s, 1H), 7.28 (ddd, 1H, J = 7.5, 4.9, 1.2 Hz), 7.83 (td, 1H, J = 7.6, 1.5 Hz), 8.44 (m, 2H), 14.6 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.7, 104.2, 118.0, 121.6, 123.7, 137.2, 138.5, 145.7, 148.1, 156.2, 157.5; IR (KBr) ν 3434, 2933, 1485, 1471, 1428, 1313, 1250, 1026, 836, 740. Anal. Calcd for $C_{11}H_9IN_2O_2$ (328.11): C, 40.27; H, 2.76; N, 8.54. Found: C, 40.14; H, 3.06; N, 8.76.

6-Iodo-3,4-dimethoxy-2,2′-bipyridine (31). The general procedure C, starting from **23**, gave 53% of **31** (eluent: CH_2Cl_2/Et_2O 90:10): viscous oil; ^{1}H NMR ($CDCl_3$) δ 3.68 (s, 3H), 3.87 (s, 3H), 7.19 (s, 1H), 7.24 (ddd, 1H, J = 7.9, 4.7, 1.5 Hz), 7.71 (m, 2H), 8.68 (dd, 1H, J = 4.7, 1.5 Hz); ^{13}C NMR ($CDCl_3$) δ 56.6, 61.9, 111.2, 118.8, 123.6, 124.9, 136.7, 145.2, 149.7, 152.5, 154.9, 160.3; IR (KBr) ν 3401, 2927, 2853, 1561, 1479, 1414, 1309, 1243, 1030. Anal. Calcd for $C_{12}H_{11}IN_2O_2$ (342.14): C, 42.13; H, 3.24; N, 8.19. Found: C, 42.34; H, 3.31; N, 8.15.

(*E*)-3-Hydroxy-4-methoxy-2,2′-bipyridine-6-carboxaldehyde Oxime (Caerulomycin B) (1). A mixture of **10** (0.24 g, 1.0 mmol), hydroxylamine hydrochloride (0.36 g, 5.0 mmol), pyridine (0.36 mL, 4.3 mmol), and EtOH (7 mL) was heated at reflux for 1 h. The solvent was evaporated under vacuum, and H_2O (35 mL) was added. Filtration of the precipitate and recrystallization from MeOH gave 50% of **1**: mp 215 °C (lit.[3] mp 215−217 °C); ^{1}H NMR (DMSO-d_6) δ 3.91 (s, 3H, OMe), 7.37 (s, 1H, H5), 7.54 (ddd, 1H, J = 8.2, 4.8, 1.3 Hz, H5′), 8.04 (s, 1H, CH), 8.11 (td, 1H, J = 8.2, 1.6 Hz, H4′), 8.51 (dd, 1H, J = 8.2, 1.3 Hz, H3′), 8.65 (dd, 1H, J = 4.8, 1.6 Hz, H6′), 11.4 (s, 1H, NOH), 14.6 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 55.8 (OMe), 103.6 (C5), 120.6 (C5′), 123.8 (C3′), 134.2 (C3), 139.0 (C4′), 145.9 (C6), 148.9 (C6′), 155.2 (C2), 147.2 (CH), 155.3 (C2′), 156.8 (C4). Anal. Calcd for $C_{12}H_{11}N_3O_3$ (245.24): C,

58.77; H, 4.52; N, 17.13. Found: C, 58.72; H, 4.39; N, 16.99. The ^{1}H NMR spectrum of compound **1** is in agreement with that already described for the natural caerulomycin B.[3]

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Supporting Information Available: Detailed experimental procedures related to unsuccessful approaches and characterization of the corresponding products. This material is available free of charge via the Internet at http://pubs.acs.org.

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