First Synthesis of Caerulomycin C

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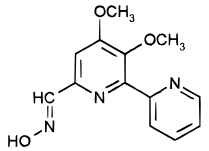
The first synthesis of caerulomycin C (**1**), an antibiotic produced by *Streptomyces caeruleus*, is reported. This molecule, which exhibits a 2,3,4,6-tetrasubstituted pyridine structure, was prepared from 3,4-dimethoxypyridine in a five-step sequence. The methodology involves metalation, transmetalation, aromatic cross-coupling, and halogen migration reactions.

A bipyridine antibiotic known as caerulomycin was first isolated in 1959.[1] Caerulomycin C (**1**) is one of the five caerulomycins produced by *Streptomyces caeruleus*. The structure of **1** and some of its derivatives have been earlier established.[2] These compounds of biological interest[3] also gave complexes with iron(II).[4] Because of our interest in the synthesis of pyridine-containing natural products[5] and owing to our knowledge of the metalation field,[6] we undertook the synthesis of caerulomycin C in which a 2,2′-bipyridyl structure is also present as in the earlier reported orelline.[7] We describe here the first synthesis of **1** in a five-step sequence starting from 3,4-dimethoxypyridine (**2**); the strategy mainly involves efficiently controlled reactions such as metalation, transmetalation, aromatic cross-coupling, and halogen migration.



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Results and Discussion

Metalation of 3,4-dimethoxypyridine (**2**) with *n*-butyllithium (BuLi) occurred at C-2.[7] The synthesis of the 2,2′-bipyridyl structure present in the target molecule **1** was tested using the 3,4-dimethoxy-2-lithiopyridine intermediate. An 1,2-addition elimination reaction of this lithio derivative with 2-bromopyridine failed under various conditions as well as its reaction with pyridine which only gave poor yields (20%) of bipyridine **3**. Then two cross-coupling reactions under Suzuki's conditions[8] between either 3,4-dimethoxy-2-iodopyridine[7] and 2-(tributyltin)-pyridine[8] or 3,4-dimethoxy-2-(tributyltin)pyridine[9] and 2-iodopyridine[10] were tested; these attempts failed, and only traces of **3** could be obtained in the second cross-coupling.

Some cross-coupling reactions could also be induced by organozinc reagents[11] generally prepared from lithio derivatives;[12] this transmetalation reaction was successfully applied to 3,4-dimethoxy-2-lithiopyridine using an excess of zinc chloride or zinc bromide. The resulting organozinc reagent was coupled with 2-bromopyridine in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$)[13] to afford the bipyridine **3**. This *one pot* synthesis involving metalation, transmetalation, and cross-coupling reactions gave an almost quantitative yield of **3** (Scheme 1).

The 3,4-dimethoxy-2,2′-bipyridine (**3**) had then to be functionalized at C-6. The metalation of **3** generates the lithio derivative at C-5. Consequently the strategy used for C-6 functionalization was an *ortho*-metalation reaction introducing a halogen at C-5 followed by a halogen migration from C-5 to C-6. When using LDA with **3** only trimethylsilyl chloride could be reacted by the *in situ* trapping technique to afford the silyl derivative **4a**. Phenyllithium (PhLi), which is a less nucleophilic metalating reagent for the pyridine ring than BuLi,[14] was successfully employed; 3 equiv of PhLi in THF at −20 °C for 1.5 h appeared to be the best reaction conditions. The lithio derivative was quantitatively quenched by DCl/D_2O to give **4b**, and various electrophiles were reacted at −70 °C to afford 5-substituted-3,4-dimethoxy-2,2′-bipyridines (**4c**−**f**) (Scheme 2).

A halogen migration reaction[15,16] from C-5 to C-6 could be performed either with iodo and bromo compounds **4c** or **4d**. Reacting 5-iodo-3,4-dimethoxy-2,2′-bipyridine (**4c**) with LDA in THF at −70 °C, gave after hydrolysis, starting compound **4c** and deiodinated product **3** (ratio 1/1). Adding an excess of ethyl formate, at −70 °C, after

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(5) (a) Godard, A.; Marsais, F.; Plé, N.; Trécourt, F.; Turck, A.; Quéguiner G. *Heterocycles* **1994**, 1055. (b) Trécourt, F.; Mallet, M.; Mongin, O.; Quéguiner G. *J. Org. Chem.* **1994**, *59*, 6173.
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(7) Trécourt, F.; Mallet, M.; Mongin, O.; Gervais, B.; Quéguiner, G. *Tetrahedron*, **1993**, *49*, 8373.
(8) (a) Peters, D.; Hörnfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1990**, *27*, 2165. (b) Peters, D.; Hörnfeldt, A.-B.; Gronowitz, S. *J. Heterocycl. Chem.* **1991**, *26*, 1613.
(9) The 3,4-dimethoxy-2-(tributyltin)pyridine was prepared according to ref 7 by reacting tributyltin chloride with 3,4-dimethoxy-2-lithiopyridine. The crude product, due to its instability, was then used for the coupling reaction.
(10) Baker, W.; Curtis, R. F.; Edwards, M. G. *J. Chem. Soc.* **1951**, 83.
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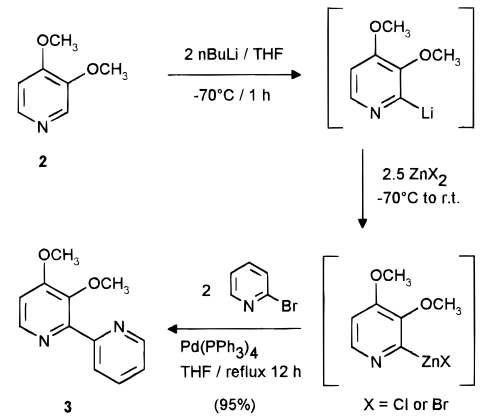
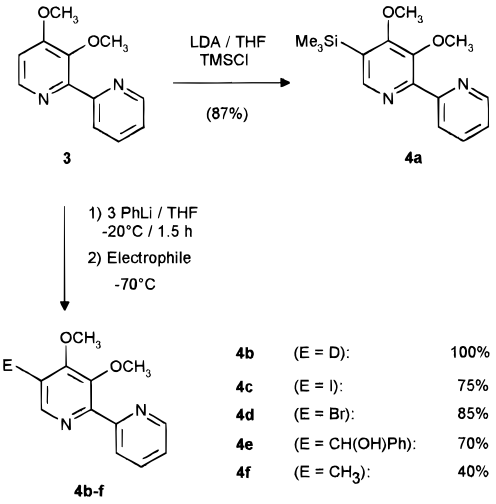
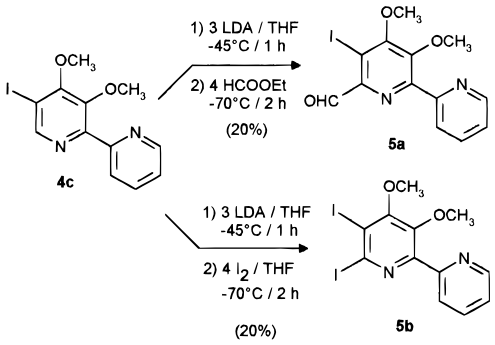
Scheme 1



Scheme 2



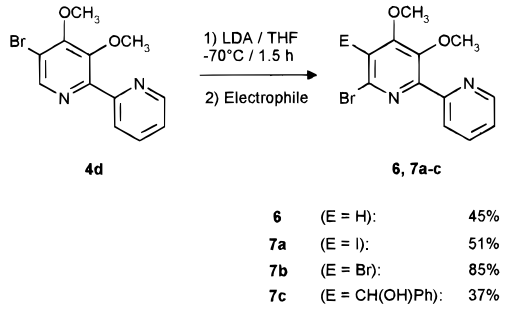
Scheme 3



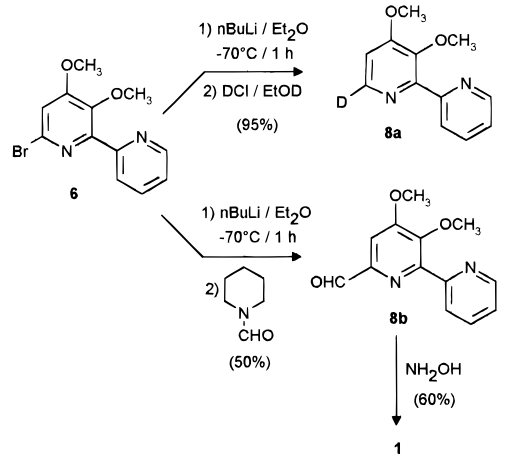
metalation, yielded 20% of 6-formyl-5-iodo-3,4-dimethoxy-2,2′-bipyridine (**5a**) (Scheme 3) and a small amount (20%) of 5-formyl-3,4-dimethoxy-2,2′-bipyridine. The 5-formyl derivative is probably due to an unexpected iodine−lithium exchange that could occur with LDA.[17] To perform a halogen migration reaction, the 5,6-diiodo-3,4-dimethoxy-2,2′-bipyridine (**5b**) would be expected to be formed in catalytic amount, according to the halogen migration reaction mechanism. Adding an excess of iodine after metalation, however, afforded compound **5b** in poor yield, probably owing to steric hindrance (Scheme 3). Therefore **5b** may not be formed under the halogen migration reaction conditions.

Reacting 5-bromo-3,4-dimethoxy-2,2′-bipyridine (**4d**) with LDA in THF at −70 °C gave the 6-bromo-3,4-dimethoxy-5-lithio-2,2′-bipyridine which was either hydrolyzed to afford 6-bromo-3,4-dimethoxy-2,2′-bipyridine

Scheme 4



Scheme 5



(**6**) or quenched by various electrophiles to prepare some 6-bromo-3,4-dimethoxy-5-substituted-2,2′-bipyridine (**7a**−**c**) (Scheme 4).

To reach the target molecule, the next step was the replacement of the bromine atom of **6** by an aldoxime group. BuLi can easily perform a halogen−metal exchange on compound **6** at low temperature. The lithio derivative was quenched by DCl/EtOD to yield compound **8a** quantitatively and by *N*-formylpiperidine to give 3,4-dimethoxy-6-formyl-2,2′-bipyridine (**8b**). Reacting the aldehyde with hydroxylamine afforded caerulomycin C (**1**) as the (*E*)-oxime; in our synthesis, the (*Z*)-oxime is not formed (Scheme 5). Compound **1** has the same spectral characteristics as those of the caerulomycin C isolated by McInnes *et al.*[2]

Conclusion

This first synthesis of caerulomycin C needed only five steps starting from 3,4-dimethoxypyridine with an overall yield of 11%. The *one-pot* first step involved metalation, transmetalation, and cross-coupling reactions at C-2. For the next three steps, the strategy successfully used metalation and halogen migration reactions to introduce regiospecifically a bromine atom at C-6, followed by a halogen−metal exchange reaction quantitatively generating a lithio derivative at the meta position (C-6) of the C-4 methoxy group. Since 3,4-dimethoxypyridine could be prepared in two steps from 4-methoxypyridine as earlier reported,[7] caerulomycin C could be so synthesized in seven steps with an overall yield of 5% from 4-methoxypyridine.

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Experimental Section

General Data. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ with a 200 MHz spectrometer. Melting points are uncorrected.

Solvent. THF was distilled from benzophenone/sodium. The water content of the solvent was estimated lower than 45 ppm by the modified Karl−Fischer method.[19]

Starting Materials. Commercial solutions of *n*-butyllithium (BuLi, 2.5 M in hexane) and phenyllithium (PhLi, 1.8M in cyclohexane/ether) were employed as received; PhLi was titrated periodically against 2-butanol. Metalations were carried out under dry argon.

General Treatment of Reactions. After the reaction, hydrolysis, and neutralization, the aqueous solution was extracted several times with Et_2O or with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and solvents were removed under reduced pressure to afford the crude product.

3,4-Dimethoxy-2,2′-bipyridine (3). To a stirred solution of 3,4-dimethoxypyridine (**2**) (1.32 g, 9.5 mmol) in 50 mL of THF was added BuLi (18.5 mmol) through a septum at −70 °C under dry argon. The reaction mixture was kept at this temperature for 1 h. An anhydrous solution of $ZnBr_2$ (5.4 g, 24.0 mmol) in 25 mL of THF (or 24 mL of a 1 M commercial solution of $ZnCl_2$ in Et_2O) was added at −70 °C. The reaction mixture was then warmed to rt. After the addition of $Pd(PPh_3)_4$ (0.35 g, 3 mmol) and 2-bromopyridine (2.92 g, 18.5 mmol), the mixture was refluxed for 12 h, cooled, and poured into a solution of EDTA (27 g in 200 mL of water). After the general treatment, the crude product was purified by column chromatography (silica gel). Eluent: AcOEt/NEt_3 (90:10). Yield: 95%; mp 72 °C; ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H, OMe), 3.95 (s, 3H, OMe), 6.90 (d, 1H, J = 5.4 Hz, H5), 7.29 (ddd, 1H, J = 7, 5, 1.5 Hz, H5′), 7.75 (ddd, 1H, J = 7, 7, 1.5 Hz, H4′), 7.85 (dd, 1H, J = 7, 1.5 Hz, H3′), 8.39 (d, 1H, J = 5.4 Hz, H6), 8.75 (dd, 1H, J = 5, 1.5 Hz, H6′); ^{13}C NMR ($CDCl_3$) δ 107.0, 122.4, 124.0, 135.6, 143.9, 145.7, 149.0, 150.8, 155.3, 159.0. Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.95. Found: C, 67.03; H, 5.70; N, 13.18.

3,4-Dimethoxy-5-(trimethylsilyl)-2,2′-bipyridine (4a). To a solution of LDA (1.85 mmol) in 20 mL of THF was added compound **3** (0.1 g, 0.46 mmol) at −70 °C. The reaction mixture was warmed to 0 °C, and then TMSCl (0.2 g, 1.85 mmol) was introduced and allowed to react for 12 h at rt. After the general treatment, the crude product was purified by column chromatography (silica gel). Eluent: AcOEt/NEt_3 (90:10). Yield: 87%; mp 78 °C; ^{1}H NMR ($CDCl_3$) δ 0.31 (s, 9H, $SiMe_3$), 3.63 (s, 3H, OMe), 4.00 (s, 3H, OMe), 7.27 (ddd, 1H, J = 7.3, 4.7, 1 Hz, H5′), 7.75 (ddd, 1H, J = 7.3, 7.3, 1.7 Hz, H4′), 7.83 (ddd, 1H, J = 7.3, 1.7, 1 Hz, H3′), 8.32 (s, 1H, H6), 8.75 (ddd, 1H, J = 4.7, 1.7, 1 Hz, H6′). Anal. Calcd for $C_{15}H_{20}N_2O_2Si$: C, 62.47; H, 6.99; N, 9.71. Found: C, 62.12; H, 7.10; N, 9.65.

General Procedure for the Synthesis of 5-Substituted-3,4-dimethoxy-2,2′-bipyridines (4b−f). PhLi (6 mmol) was added to THF (25 mL) at −70 °C through a septum. A solution of bipyridine **3** (0.43 g, 2 mmol in 10 mL of THF) was slowly added at −70 °C, and the reaction mixture was stirred for 1.5 h at −20 °C and cooled to −70 °C before addition of the required electrophile (8 mmol) as mentioned in the product description. The solution was then hydrolyzed at −70 °C with an excess of HCl/EtOH/THF (except for compound **4d**). After the general treatment, the crude product was purified by column chromatography (silica gel) or recrystallization.

5-Deuterio-3,4-dimethoxy-2,2′-bipyridine (4b). Electrophile: DCl/D_2O in EtOD. Purification by column chromatography (silica gel). Eluent: AcOEt/NEt_3 (90:10). Yield: 100%; ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H, OMe), 3.95 (s, 3H, OMe), 7.29 (ddd, 1H, J = 7, 5, 1.5 Hz, H5′), 7.75 (ddd, 1H, J = 7, 7, 1.5 Hz, H4′), 7.85 (dd, 1H, J = 7, 1.5 Hz, H3′), 8.39 (s, 1H, H6), 8.75 (dd, 1H, J = 5, 1.5 Hz, H6′).

3,4-Dimethoxy-5-iodo-2,2′-bipyridine (4c). Electrophile: iodine (2.0 g, 8 mmol, 2 h at −70 °C). Excess I_2 was destroyed with sodium thiosulfate before general treatment. Purification by recrystallization from Et_2O. Yield: 75%; mp 56 °C; ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3H, OMe), 4.08 (s, 3H, OMe), 7.33 (ddd, 1H, J = 7.9, 4.9, 1.5 Hz, H5′), 7.80 (ddd, 1H, J = 7.9, 7.9, 1.8 Hz, H4′), 7.86 (ddd, 1H, J = 7.9, 1.6, 1.6 Hz, H3′), 8.70 (s, 1H, H6), 8.77 (ddd, 1H, J = 4.9, 1.8, 1.6 Hz, H6′); MS (EI) m/z 342 (M^+, 60), 327 (100). Anal. Calcd for $C_{12}H_{11}IN_2O_2$: C, 42.13; H, 3.24; N, 8.19. Found: C, 42.37; H, 3.52; N, 8.40.

5-Bromo-3,4-dimethoxy-2,2′-bipyridine (4d). Electrophile: BrCN (0.85 g, 8 mmol, 15 min at −70 °C). The reaction mixture was then hydrolyzed at 0 °C with an excess of H_2O/EtOH/THF. Purification by column chromatography (silica gel). Eluent: Et_2O. Yield: 85%; oil; ^{1}H NMR ($CDCl_3$) δ 3.71 (s, 3H, OMe), 4.06 (s, 3H, OMe), 7.28 (ddd, 1H, J = 7.5, 5, 1.5 Hz, H5′), 7.75 (ddd, 1H, J = 7, 5, 1.8 Hz, H4′), 7.83 (dd, 1H, J = 7.5, 1.5 Hz, H3′), 8.51 (s, 1H, H6), 8.73 (dd, 1H, J = 5, 1.8 Hz, H6′); MS (EI) m/z 293−295 (M^+, ^{79}Br−^{81}Br, 30), 279−281 (100). Anal. Calcd for $C_{12}H_{11}BrN_2O_2$: C, 48.84; H, 3.76; N, 9.49. Found: C, 48.66; H, 3.43; N, 9.21.

5-(3,4-Dimethoxy-2,2′-bipyridyl)phenylmethanol (4e). Electrophile: benzaldehyde (0.85 g, 8 mmol, 2 h at −70 °C). Purification by selective extraction with Et_2O and column chromatography (silica gel). Eluent: AcOEt/NEt_3 (90:10). Yield: 70%; mp 113 °C; ^{1}H NMR ($CDCl_3$) δ 3.62 (s, 3H, OMe), 3.73 (s, 3H, OMe), 4.0 (s, 1H, OH), 5.99 (s, 1H, CH), 7.3 (m, 6H, H5′+phenyl), 7.77 (ddd, 1H, J = 7.1, 7.1, 1.6 Hz, H4′), 7.81 (dd, 1H, J = 7.1 Hz, H3′), 8.48 (s, 1H, H6), 8.73 (dd, 1H, J = 4.8, 1.6 Hz, H6′); MS (EI) m/z 322 (M^+ 100), 307 (50). Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69. Found: C, 71.35; H, 5.59; N, 8.64.

3,4-Dimethoxy-5-methyl-2,2′-bipyridine (4f). Electrophile: methyl iodide (1.14 g, 8 mmol, 1 h at −70 °C). Purification by selective extraction with Et_2O and column chromatography (silica gel). Eluent: AcOEt/NEt_3 (90:10). Yield: 40%; oil; ^{1}H NMR ($CDCl_3$) δ 2.24 (s, 3H, Me), 3.66 (s, 3H, OMe), 4.00 (s, 3H, OMe), 7.26 (ddd, 1H, J = 7.9, 4.6, 1.2 Hz, H5′), 7.74 (ddd, 1H, J = 7.9, 7.9, 1.8 Hz, H4′), 7.82 (dd, 1H, J = 7.9, 1.2 Hz, H3′), 8.24 (s, 1H, H6), 8.74 (dd, 1H, J = 4.6, 1.8 Hz, H6′); MS (EI) m/z 230 (M^+, 55), 215 (100), 199 (40). Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 67.51; H, 6.56; N, 12.34.

General Procedure for the Synthesis of 5-Iodo-3,4-dimethoxy-2,2′-bipyridines Substituted at C6 (5a,b). Compound **4c** (0.1 g, 0.3 mmol) in 3 mL of THF was added at −70 °C to a solution of LDA (0.9 mmol) in 10 mL of THF. The reaction mixture was stirred at −45 °C for 1 h and cooled to −70 °C before adding the required electrophile (1.2 mmol). The solution was stirred at this temperature for 2 h and then hydrolyzed at −70 °C with an excess of H_2O/THF. After the general treatment, the crude product was purified by column chromatography (silica gel). Eluent: Et_2O.

5-Iodo-6-formyl-3,4-dimethoxy-2,2′-bipyridine (5a). Electrophile: HCOOEt (0.09 g, 1.2 mmol). Yield: 20%; solid; ^{1}H NMR ($CDCl_3$) δ 3.8 (s, 3H, OMe), 4.16 (s, 3H, OMe), 7.33 (ddd, 1H, J = 7.1, 4.8, 1.7 Hz, H5′), 7.80 (m, 2H, H3′+ H4′,), 8.75 (dd, 1H, J = 4.8, 1.7 Hz, H6′), 10.13 (s, 1H, CHO); IR (KBr) (C=O) 1699 cm^{-1}; MS (EI) m/z 370 (M^+, 60), 355 (100).

5,6-Diiodo-3,4-dimethoxy-2,2′-bipyridine (5b). Electrophile: iodine (0.3 g, 1.2 mmol). Excess I_2 was destroyed with sodium thiosulfate before general treatment. Yield: 20%; mp 76 °C; ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H, OMe), 4.06 (s, 3H, OMe), 7.33 (ddd, 1H, J = 7.1, 4.8, 1.7 Hz, H5′), 7.80 (ddd, 1H, J = 7.1, 7.1, 1.7 Hz, H4′), 7.85 (dd, 1H, J = 7.1, 1.7 Hz, H3′), 8.75 (dd, 1H, J = 4.8, 1.7 Hz, H6′). Anal. Calcd for $C_{12}H_{10}I_2N_2O_2$: C, 30.80; H, 2.15; N, 5.99. Found: C, 30.54; H, 2.37; N, 5.86.

General Procedure for the Synthesis of 6-Bromo-3,4-dimethoxy-2,2′-bipyridines Substituted at C5 (6, 7a−c) (Halogen Migration Reaction). Compound **4d** (0.59 g, 2 mmol) in 20 mL of THF was added at −70 °C to a solution of LDA (6 mmol) in 20 mL of THF. The reaction mixture was stirred for 1.5 h at this temperature before adding the required electrophile (8 mmol) as mentioned in the product description.

(18) Mallet, M.; Branger, G.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1990**, *382*, 319.
(19) Bizot, J. *Bull. Soc. Chim. Fr.* **1967**, *1*, 151.

After the general treatment, the crude product was purified by column chromatography (silica gel).

6-Bromo-3,4-dimethoxy-2,2′-bipyridine (6). Electrophile: HCl/EtOH/THF. Eluent: Et_2O/hexane (95:5). The product was then recrystallized from Et_2O/petroleum ether (1:1). Yield: 45%; mp 72 °C; ^{1}H NMR ($CDCl_3$) δ 3.75 (s, 3H, OMe), 3.96 (s, 3H, OMe), 7.04 (s, 1H, H5), 7.30 (ddd, 1H, J = 7.9, 4.7, 1.5 Hz, H5′), 7.76 (ddd, 1H, J = 7.9, 7.9, 1.5 Hz, H4′), 7.85 (dd, 1H, J = 7.9, 1.5 Hz, H3′), 8.75 (dd, 1H, J = 4.7, 1.5 Hz, H6′). Anal. Calcd for $C_{12}H_{11}BrN_2O_2$: C, 48.84; H, 3.76; N, 9.49. Found: C, 48.99; H, 3.67; N, 9.40.

6-Bromo-3,4-dimethoxy-5-iodo-2,2′-bipyridine (7a). Electrophile: iodine (2.0 g, 8 mmol, 2 h at −70 °C). Eluent: CH_2Cl_2/Et_2O (95:5). Yield: 51%; mp 60 °C; ^{1}H NMR ($CDCl_3$) δ 3.73 (s, 3H, OMe), 4.06 (s, 3H, OMe), 7.25 (m, 1H, H5′), 7.78 (m, 2H, H3′+ H4′), 8.66 (d, 1H, H6′); MS (EI) m/z 420−422, 295 (M^+, ^{79}Br−^{81}Br, 20), 389−391 (10), 293−295 (10). Anal. Calcd for $C_{12}H_{10}BrIN_2O_2$: C, 34.23; H, 2.39; N, 6.65. Found: C, 33.97; H, 2.24; N, 6.58.

5,6-Dibromo-3,4-dimethoxy-2,2′-bipyridine (7b). Electrophile: BrCN (0.85 g, 8 mmol, 30 min at −70 °C); the reaction mixture was hydrolyzed by an excess of H_2O/EtOH/THF. Eluent: CH_2Cl_2/Et_2O (90:10). Yield: 85%; mp 64 °C; ^{1}H NMR ($CDCl_3$) δ 3.70 (s, 3H, OMe), 4.05 (s, 3H, OMe), 7.29 (m, 1H, H5′), 7.76 (ddd, 1H, J = 7.9, 7.9, 1.7 Hz, H4′), 7.80 (dd, 1H, J = 7.9, 1.7 Hz, H3′), 8.70 (dd, 1H, J = 5, 1.7 Hz, H6′); MS (EI) m/z 372−374−376 (M^+, ^{79}Br−^{81}Br, 30), 357−359−361 (100). Anal. Calcd for $C_{12}H_{10}Br_2N_2O_2$: C, 38.53; H, 2.69; N, 7.49. Found: C, 38.75; H, 2.60; N, 7.40.

5-(6-Bromo-3,4-dimethoxy-2,2′-bipyridyl)phenylmethanol (7c). Electrophile: benzaldehyde (0.85 g, 8 mmol, 2 h at −70 °C). Eluent: Et_2O. Yield: 37%; mp 120 °C; ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.80 (d, 1H, J = 11,2 Hz, OH), 6.28 (d, 1H, J = 11,2 Hz, CH), 7.38 (m, 6H, H5′+phenyl), 7.81 (ddd, 1H, J = 7.9, 7.9, 1.7 Hz, H4′), 7.89 (dd, 1H, J = 7.9, 1 Hz, H3′), 8.76 (dd, 1H, J = 5, 1.7 Hz, H6′). Anal. Calcd for $C_{19}H_{17}BrN_2O_3$: C, 56.87; H, 4.27; N, 6.98. Found: C, 57.02; H, 4.35; N, 7.01.

General Procedure for the Synthesis of 6-Substituted 3,4-Dimethoxy-2,2′-bipyridines (8a,b) (Halogen−Metal Exchange). n-BuLi (4 mmol) was added at −70 °C to a solution of compound **6** (0.59 g, 2 mmol) in 50 mL of Et_2O. The reaction mixture was stirred at −70 °C for 30 min before adding the required electrophile. After the general treatment, the crude product was purified by column chromatography (silica gel) or recrystallization.

6-Deuterio-3,4-dimethoxy-2,2′-bipyridine (8a). Compound **8a** was prepared by action of DCl/D_2O in EtOD at −70 °C and purified by column chromatography (silica gel). Eluent: AcOEt/NEt_3 (90:10). Yield: 95%; mp 72 °C; ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H, OMe), 3.95 (s, 3H, OMe), 6.90 (s, 1H, H5), 7.29 (ddd, 1H, J = 6.7, 4.9, 1.5 Hz, H5′), 7.79 (ddd, 1H, J = 6.7, 6.7, 1.8 Hz, H4′), 7.85 (dd, 1H, J = 6.7, 1.5 Hz, H3′), 8.75 (dd, 1H, J = 4.9, 1.8 Hz, H6′).

3,4-Dimethoxy-6-formyl-2,2′-bipyridine (8b). A solution of *N*-formylpiperidine (0.68 g, 6 mmol) in THF (10 mL) was introduced at −70 °C, and the reaction mixture was warmed at −40 °C and was stirred for 2 h. Compound **8b** was purified by column chromatography (silica gel). Eluent: AcOEt/NEt_3 (80:20); recrystallization from Et_2O/petroleum ether (1:1). Yield: 50%; mp 80 °C; ^{1}H NMR ($CDCl_3$) δ 3.81 (s, 3H, OMe), 4.01 (s, 3H, OMe), 7.26 (m, 1H, H5′), 7.59 (s, 1H, H5), 7.81 (m, 2H, H3′+H4′), 8.78 (d, 1H, H6′), 10,04 (s, 1H, CHO); IR (KBr): (C=O) 1712 cm^{-1}; MS (EI) m/z 244 (M^+, 90), 229 (100). Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.69; H, 5.17; N, 11.09.

Procedure for Synthesis of 6-[(Hydroxyimino)methyl]-3,4-dimethoxy-2,2′-bipyridine (caerulomycin C) (1). Compound **8b** (0.49 g, 2 mmol) was added to a mixture of hydroxylamine hydrochloride (5 g, 72 mmol) and pyridine (5 mL) in 50 mL EtOH. After stirring the mixture for 30 min at 70−80 °C and general treatment, caerulomycin C was washed several times with Et_2O and recrystallized from EtOH. Yield: 60%; mp 204 °C, lit.[2] 208−210 °C; ^{1}H NMR (DMSO-d_6) δ 3.74 (s, 3H, OMe), 3.96 (s, 3H, OMe), 7.42 (m, 1H, H5′), 7.47 (s, 1H, H5), 7.70 (ddd, 1H, J = 7.7, 7.7, 1.2 Hz, H3′), 7.92 (ddd, 1H, J = 7.7, 7.7, 1.7 Hz, H4′), 8.02 (s, 1H, CH=N), 8.66 (ddd, 1H, J = 4.5, 1.7, 1.2 Hz, H6′), 11,63 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 56.8, 61.8, 104.7, 124.4, 125.1, 144.7, 148.8, 149.3, 149.4, 150.8, 155.3, 160.2, 183.0; IR (KBr) 3000, 1585, 1488, 1363, 1244, 1060, 994 cm^{-1}; MS (EI) m/z 259 (M^+, 20), 242 (100). Anal. Calcd for $C_{13}H_{13}N_3O_3$: C, 60.23; H, 5.05; N, 16.21. Found: C, 59.95; H, 4.95; N,16.05. The spectral characteristics of compound **1** are in agreement with those already described for the natural caerulomycin C identified as the(*E*)-oxime.[2]

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