First Syntheses of Caerulomycin E and Collismycins A and C. A New Synthesis of Caerulomycin A

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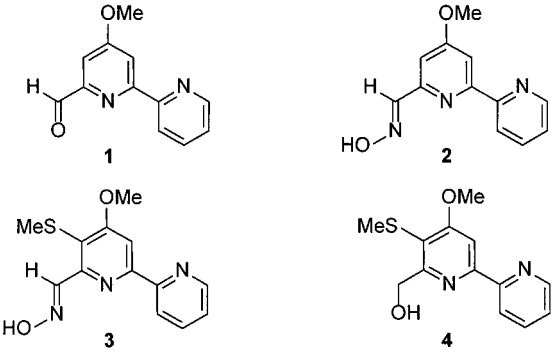
Caerulomycins produced by *Streptomyces caeruleus*, and collismycins more recently isolated from *Streptomyces* species, are bipyridinic molecules endowed with antibiotic and cytotoxic activities. The first syntheses of caerulomycin E (**1**), as well as new syntheses of caerulomycin A (**2**), are reported. Methodologies involving efficiently controlled reactions such as metalation and cross-coupling reactions have been developed from 2,2′-bipyridine. The functionalization at C-6 could be achieved by metalation of 2,2′-bipyridine *N*-oxides **5** and **12**. 6-Halo-4-methoxy-2,2′-bipyridines (**6**, **10**, **11**) became key-molecules of these different pathways, and further functionalization at C-5 allowed the first syntheses of collismycins A (**3**) and C (**4**).

Introduction

Caerulomycins E (**1**) and A (**2**) are two of the five caerulomycins produced by *Streptomyces caeruleus*.[1] Caerulomycin A (**2**), a bipyridinic molecule with antibiotic properties,[2,3] was first isolated[2a] in 1959 and its structure was elucidated[4] in 1967; two syntheses of compound **2** have been previously reported by Divekar[5] and De Souza.[6]

Collismycins A (**3**) and C (**4**) were isolated in 1993 by Gomi[7] from *Streptomyces* sp. SF 2738 and their structures established. Collismycin A (**3**) was independently isolated by Shindo[8] from *Streptomyces* sp. MQ 22.[9] These compounds are endowed with antibiotic and cytotoxic activities.[7,8]

Because of our interest in the synthesis of pyridine-containing natural products[10] and in the light of our knowledge of the metalation field,[11] we undertook the synthesis of compounds **1**−**4** in which a 2,2′-bipyridyl structure is also present as in the earlier reported orelline[12] and caerulomycin C.[13] Here we describe the first syntheses of **1**, **3**, and **4** and a new synthesis of **2** starting from 2,2′-bipyridine. The strategy mainly involves efficiently controlled reactions such as metalation and cross-coupling reactions.



Results and Discussion

Starting from 2,2′-bipyridine *N*-oxide, functionalization at C-4 and C-6 could be investigated by two different routes (Scheme 1): route A (functionalization at C-4 first then C-6) and route B (functionalization at C-6 first then C-4) allowed suitably disubstituted 2,2′-bipyridines for the synthesis of caerulomycins **1** and **2**. Subsequent functionalization at C-5 could afford collismycins **3** and **4**. The target bipyridines could be synthesized from 6-halo-4-methoxy-2,2′-bipyridines (Z = Cl, Br, I).

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(6) (a) Alreja, B. D.; Kattige, S. L.; Lal, B.; De Souza, N. J. *Heterocycles* **1986**, *24*, 1637. (b) Alreja, B. D.; Kattige, S. L.; De Souza, N. J. (Hoechst A.-G.) Ger. Offen. DE 3,414,830, 31 Oct 1985, Appl. 19 Apr 1984; *Chem. Abstr.* **1986**, *104*, 207056j. (c) Alreja, B. D.; Kattige, S. L.; De Souza, N. J. (Hoechst India Ltd.) India IN 157,619, 03 May 1986, Appl. 04 Jan 1984; *Chem. Abstr.* **1987**, *106*, 49882k.

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(9) The name of collismycin was given to this family of compounds by Shindo,[8] whereas Gomi[7] used the name SF 2738.

(10) (a) Godard, A.; Marsais, F.; Plé, N.; Trécourt, F.; Turck, A.; Quéguiner, G. *Heterocycles* **1995**, *40*, 1055. (b) Trécourt, F.; Mallet, M.; Mongin, O.; Quéguiner, G. *J. Org. Chem.* **1994**, *59*, 6173. (c) Trécourt, F.; Mallet, M.; Mongin, O.; Quéguiner, G. *J. Heterocycl. Chem.* **1995**, *32*, 1117.

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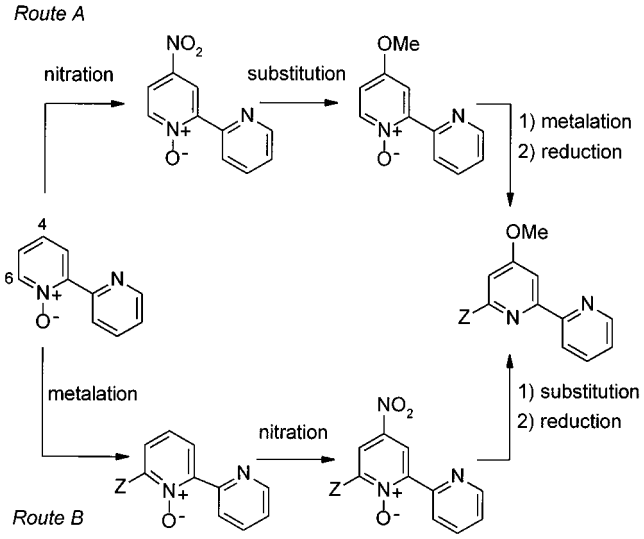
Scheme 1



Route A was first investigated. 4-Methoxy-2,2′-bipyridine *N*-oxide (**5**) was easily prepared from 2,2′-bipyridine by a three-step sequence described in the literature.[14] Reductive chlorination[15] of **5** using $POCl_3$ at reflux gave 6-chloro-4-methoxy-2,2′-bipyridine (**6**) in an almost quantitative yield, whereas its reductive bromination using either $POBr_3$ or the mixture $POBr_3/PBr_5$[16] never gave 6-bromo-4-methoxy-2,2′-bipyridine (**10**) (Scheme 2). Another way had to be found to obtain compounds **10** and **11**. Recently, we reported some results about metalation in the pyridine *N*-oxide series.[17] Metalation of **5** using LDA or LTMP at −70 °C occurred at C-6 as demonstrated by the lithio derivative quenching with concd DCl (Table 1, entry 1). The trapping with dibromoethane completely failed whereas using BrCN as electrophile could give a poor yield (15%) of 6-bromo-4-methoxy-2,2′-bipyridine *N*-oxide (**8**). Trapping with iodine gave a very good yield (Table 1, entry 4) of 6-iodo-4-methoxy-2,2′-bipyridine *N*-oxide (**9**). Bromo and iodo *N*-oxides **8** and **9** were successfully reduced with PBr_3 into **10** and **11** (Scheme 2).

Using route A, it was thus possible to prepare 6-chloro-, 6-bromo-, and 6-iodo-4-methoxy-2,2′-bipyridines **6**, **10**, and **11** in 43%, 6%, and 27% overall yield, respectively, from 2,2′-bipyridine.

Route B was then investigated in order to improve the yield of **10** which largely depends on the metalation step. Metalation of 2,2′-bipyridine *N*-oxide (**12**) with LDA at −70 °C was successfully employed. When the lithio derivative was quenched by BrCN, 6-bromo-2,2′-bipyridine *N*-oxide (**13**) was obtained with a satisfying yield of 70% along with 5,6-dibromo- and 4,5,6-tribromo-2,2′-bipyridine *N*-oxides in 12 and 8% yield, respectively. Note that with iodine, only compound **14** was obtained (Scheme 3).

6-Bromo- and 6-iodo-4-methoxy-2,2′-bipyridines **10** and **11** were then prepared in a classical three-step sequence.

Scheme 2

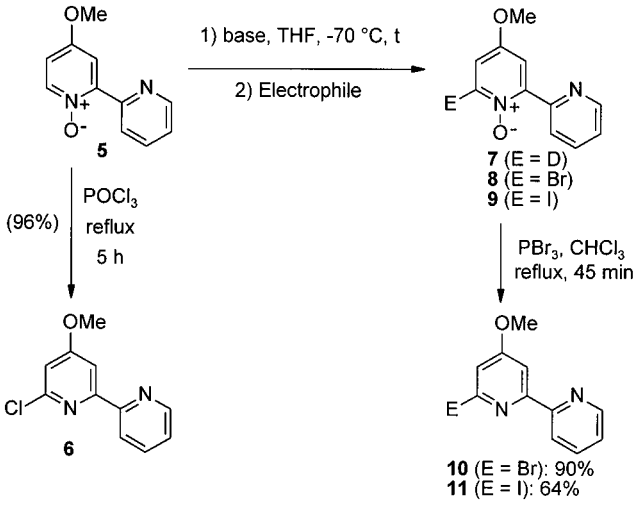
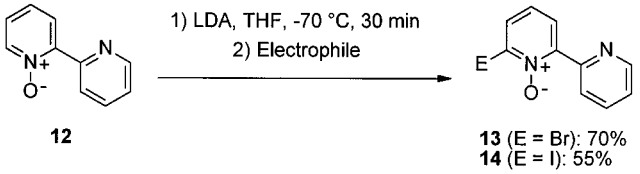


Table 1. Metalation of 5

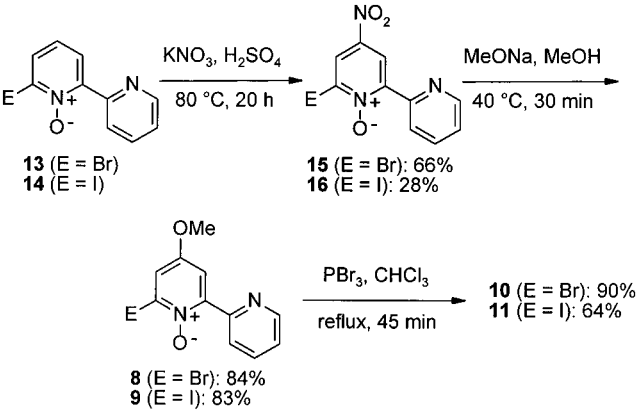
entry	base	*t*, h	electrophile	product (E), % yield
1	LDA[a]	1 h	DCl/D_2O	**7** (D), 80
2	LDA[a]	1 h	BrCN	**8** (Br), 15
3	LDA[a]	1 h	I_2	**9** (I), 70
4	LTMP[b]	1.5 h	I_2	**9** (I), 94

[a] 2 equiv was used. [b] 1 equiv was used.

Scheme 3



Scheme 4



Nitration at temperature not exceeding 80 °C was followed by substitution of the nitro group with MeONa under mild conditions. Finally, reduction of the *N*-oxides using PBr_3 gave **10** and **11** in quite good yields. Note that in the case of the bromo compound **8**, a mixture of 6-bromo and 6-chloro derivatives was obtained when using PCl_3 instead of PBr_3 (Scheme 4).

Using route B, it was possible to obtain **10** and **11** in 28% and 6% overall yield, respectively. Thus, for the synthesis of 6-halo-4-methoxy-2,2′-bipyridines, route A is particularly suitable to prepare chloro and iodo derivatives **6** and **11**, and route B should be preferred to prepare bromo compound **10**.

(14) Wenkert, D.; Woodward, R. B. *J. Org. Chem.* **1983**, *48*, 283.
(15) (a) Rokach, J.; Girard, Y. *J. Heterocycl. Chem.* **1978**, *15*, 683. (b) Newkome, G. R.; Garbis, S. J. *J. Heterocycl. Chem.* **1978**, *15*, 685.
(16) Attempts to obtain **10** by treatment of 4-methoxy-(2,2′-bipyridin)-6(1*H*)-one with the mixture $POBr_3/PBr_5$ also failed.
(17) Mongin, O.; Rocca, P.; Thomas-dit-Dumont, L.; Trécourt, F.; Marsais, F.; Godard, A.; Quéguiner, G. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2503, and references therein.

Different pathways were then investigated to reach caerulomycin E (**1**). 6-Chloro-4-methoxy-2,2′-bipyridine (**6**) was coupled[18] with an excess of methylzinc chloride in the presence of a catalytic amount of tetrakis(triphenylphosphine)palladium(0)[19] to afford the methylpyridine **17** in an almost quantitative yield. A similar result was obtained from 6-bromo-4-methoxy-2,2′-bipyridine (**10**). Caerulomycin E (**1**) could be prepared by oxidation of **17**, using benzeneseleninic anhydride (BSA)[20] (64%) or freshly prepared SeO_2[21] (60%). Caerulomycin E (**1**) could also be prepared in two steps starting from compound **17**. The possible metalation of the methyl group[22] of picolines led in our case to the dithioketal **18**; subsequent treatment with $BF_3 \cdot Et_2O$ and HgO[23] also afforded **1** in 30% overall yield.

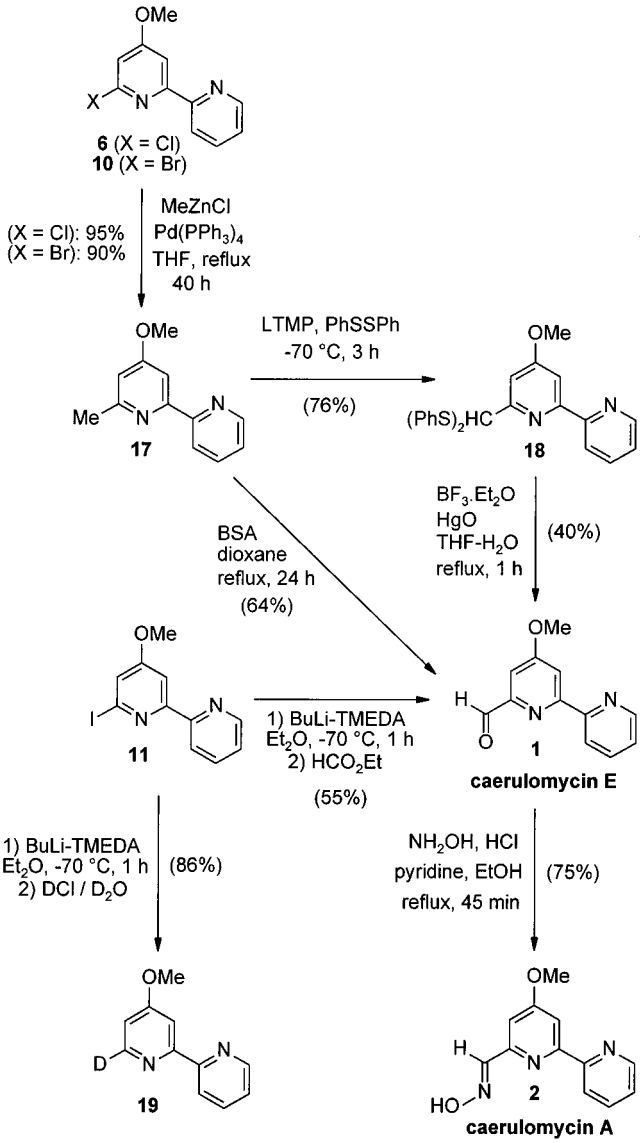
Moreover, the chelate BuLi−TMEDA can easily perform an iodine−lithium exchange on 6-iodo compound **11** at low temperature. The lithio derivative was quenched by concd DCl to yield 6-deuterio-4-methoxy-2,2′-bipyridine (**19**, 86%) and by ethyl formate to give caerulomycin E (**1**).

Reacting the aldehyde **1** with hydroxylamine afforded the (*E*/*Z*) 91:9 mixture of oximes. Single recrystallization gave pure caerulomycin A (**2**) (Scheme 5). Thus, the best synthesis of caerulomycin E (**1**) involves a six-step sequence in a 26% overall yield, calculated from 2,2′-bipyridine via 6-chloro-4-methoxy-2,2′-bipyridine (**6**).

To reach collismycins **3** and **4**, functionalization at C-5 could be investigated either from caerulomycin E (**1**) or halo derivatives **6**, **10**, and **11**. The metalation conditions described by Comins[24] for various aldehydes by using lithium *N*,*N*,*N*′-trimethylethylenediamide was tested on compound **1** but failed. It was also possible to attempt the other Comins experimental conditions[25] using *N*-formyl-*N*,*N*′,*N*′-trimethylethylenediamine on the lithio derivative prepared from 6-bromo and 6-iodo derivatives **10** and **11**. Under these conditions, induced metalation at C-5 was never observed, and only caerulomycin E (**1**) was obtained.

The metalation of 6-halo-4-methoxy-2,2′-bipyridines (**6**, **10**, **11**) was then studied. This deprotonation could occur at C-3 or C-5. We observed that from 4-methoxy-2,2′-bipyridine, the 3-lithio derivative[26] was prepared with LDA at −70 °C. On the other hand, the 5-lithio derivatives of **6** and **10** were obtained under the same conditions, as demonstrated by quenching with concd DCl. These experiments show that chlorine and bromine (directing groups) exhibit a stronger effect than the pyridine ring does. To reach the target molecule **3**, methyl disulfide was used as electrophile,[27] but the conditions had to be carefully optimized to avoid side replacement of the halogen at C-6 by a methylthio moiety before hydrolysis. Similar results were observed when using 6-iodo-4-methoxy-2,2′-bipyridine (**11**) instead of bromo compound **10** (Scheme 6, Table 2).

Scheme 5



The strategy used for the functionalization at C-6 was a halogen−lithium exchange. The chelate BuLi−TMEDA could in this case perform a bromine−lithium exchange from compound **23**. The lithio derivative was then quenched by DMF to give **25**. Reacting aldehyde **25** with hydroxylamine afforded collismycin A (**3**) as the (*E*)-oxime. Moreover, reduction of **25** with $NaBH_4$ afforded quantitatively collismycin C (**4**) (Scheme 7).

Thus, collismycins A (**3**) and C (**4**) could be synthesized in eight steps and 7% overall yield, and eight steps and 9% overall yield, respectively, starting from 2,2′-bipyridine via 6-bromo-4-methoxy-2,2′-bipyridine (**10**).

Conclusion

This first synthesis of caerulomycin E needed only six steps starting from commercially available 2,2′-bipyridine via 6-chloro-4-methoxy-2,2′-bipyridine (**6**) with an overall yield of 26%. We considerably improved (20% from 2,2′-bipyridine) the overall yield of the total synthesis of

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(19) Coulson, D. R. *Inorg. Synth.* **1972**, *13*, 121.
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(21) (a) Burger, A.; Modlin Jr., L. R. *J. Am. Chem. Soc.* **1940**, *62*, 1079. (b) Kaplan, H. *J. Am. Chem. Soc.* **1941**, *63*, 2654.
(22) Beumel Jr., O. F.; Smith, W. N.; Rybalka, B. *Synthesis* **1974**, 43.
(23) (a) Vedejs, E.; Fuchs, P. L. *J. Org. Chem.* **1971**, *36*, 366. (b) Corey, E. J.; Erickson, B. W. *J. Org. Chem.* **1971**, *36*, 3553.
(24) Comins, D. L. *Synlett* **1992**, 615.
(25) Comins, D. L.; Hong, H.; Saha, J. K.; Jianhua, G. *J. Org. Chem.* **1994**, *59*, 5120.
(26) Gervais, B. Unpublished results (**1994**).
(27) Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401.

Scheme 6

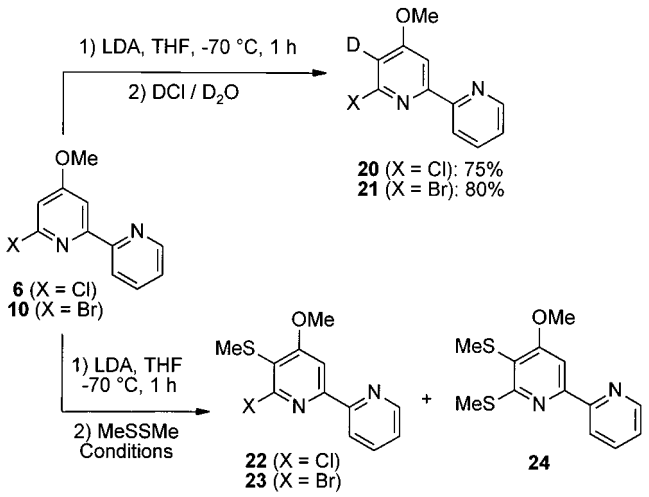
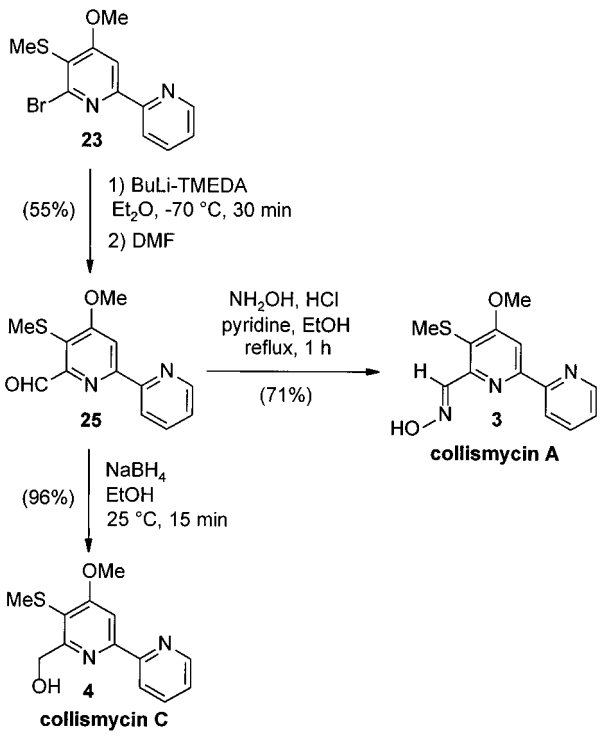


Table 2. Metalation of 6 and 10

entry	X	conditions	product, % yield
1	Cl	−70 °C/0.5 h[a]	**22**, 98
2	Br	−70 °C/5 min[a]	**23**, 61
3	Br	−70 °C/5 min[b]	**23**, 6; **24**, 44

[a] Immediate workup after raising to room temperature. [b] Workup after 13 h at room temperature.

Scheme 7



caerulomycin A previously described by Divekar[5] (two steps, 8% yield from **5**) and also De Souza[6] (four steps, 5% yield).

For the synthesis of collismycins A and C, the strategy successfully involved a metalation reaction to introduce the methylthio moiety at C-5.

Experimental Section

General. Spectroscopic experiments were made as recently reported.[13] THF and Et_2O were distilled from benzophenone/Na. The water content of the solvents was estimated to be lower than 45 ppm by the modified Karl Fischer method.[28] Commercial solutions of butyllithium (BuLi) and methylzinc chloride were employed as received. $Pd(PPh_3)_4$ was synthesized by literature method.[19] Metalations and cross coupling reactions were carried out under dry argon.

All solutions were dried over $MgSO_4$, 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).

4-Methoxy-2,2′-bipyridine *N*-Oxide (5).[14] A three-step sequence[14] from 2,2′-bipyridine gave **5** by *N*-oxidation, nitration, and substitution of 4-nitro by MeONa [(1) *m*-CPBA/$CHCl_3$/25 °C/13 h: 79%; (2) KNO_3/H_2SO_4/110 °C/2.5 h: 65%; (3) MeONa/MeOH/40 °C/30 min: 88%].

6-Chloro-4-methoxy-2,2′-bipyridine (6). 4-Methoxy-2,2′-bipyridine *N*-oxide monohydrate (**5**·H_2O, 1.0 g, 4.5 mmol) was added to $POCl_3$ (60 mL) and heated under reflux for 5 h. Solvent removal, addition of water (50 mL), neutralization with K_2CO_3, and extraction with CH_2Cl_2 (3 × 20 mL) afforded 96% of **6** (eluent: CH_2Cl_2/Et_2O 80:20): mp 78 °C; ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 6.81 (d, 1H, J = 1.9 Hz), 7.29 (ddd, 1H, J = 7.6, 4.5, 1.6 Hz), 7.76 (td, 1H, J = 7.6, 1.8 Hz), 7.89 (d, 1H, J = 1.9 Hz), 8.35 (dd, 1H, J = 7.6, 1.6 Hz), 8.61 (dd, 1H, J = 4.5, 1.8 Hz); IR (KBr) 1550, 1408, 1319, 1219, 1142, 1038. Anal. Calcd for $C_{11}H_9ClN_2O$ (220.66): C, 59.88; H, 4.11; N, 12.70. Found: C, 60.02; H, 3.92; N, 12.69.

General Procedure A: Metalation of 4-Methoxy-2,2′-bipyridine *N*-Oxide (5). BuLi (1.4 mmol) in hexane (0.54 mL) was added to a solution of diisopropylamine (0.19 mL, 1.4 mmol) in THF (5 mL) at 0 °C. The solution of LDA was cooled to −70 °C, and a solution of 4-methoxy-2,2′-bipyridine *N*-oxide monohydrate (**5**·H_2O, 0.10 g, 0.45 mmol) in THF (5 mL) was added. After 1 h at this temperature, the electrophile was added and allowed to react as mentioned in the product description. The solution was hydrolyzed with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL).

6-Deuterio-4-methoxy-2,2′-bipyridine *N*-Oxide (7). The general procedure A, using concd DCl (2 mL) in THF (5 mL) at −70 °C, gave **7** (eluent: AcOEt): deuterium incorporation: 80%;[29] ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H), 6.87 (d, 1H, J = 3.6 Hz), 7.38 (dd, 1H, J = 7.8, 4.7 Hz), 7.77 (d, 1H, J = 3.6 Hz), 7.87 (td, 1H, J = 7.8, 1.9 Hz), 8.75 (dd, 1H, J = 4.7, 1.9 Hz), 9.07 (d, 1H, J = 7.8 Hz).

6-Bromo-4-methoxy-2,2′-bipyridine *N*-Oxide (8). The general procedure A, using a solution of BrCN (0.11 g, 1.0 mmol) in THF (5 mL) at −70 °C with stirring for 15 min, gave 15% of **8** (eluent: AcOEt): mp 79 °C; ^{1}H NMR ($CDCl_3$) δ 3.91 (s, 3H), 7.26 (d, 1H, J = 3.6 Hz), 7.35 (ddd, 1H, J = 7.7, 4.7, 1.2 Hz), 7.72 (d, 1H, J = 3.6 Hz), 7.81 (td, 1H, J = 7.7, 1.8 Hz), 8.69 (dd, 1H, J = 4.7, 1.8 Hz), 8.93 (dd, 1H, J = 7.7, 1.2 Hz); IR (KBr) 1614, 1585, 1396, 1223, 1142, 1023. Anal. Calcd for $C_{11}H_9BrN_2O_2$ (281.11): C, 47.00; H, 3.23; N, 9.97. Found: C, 47.26; H, 3.06; N, 10.34. **From 15**. A solution of MeONa (65 mg, 1.2 mmol) in MeOH (10 mL) was added to a suspension of 6-bromo-4-nitro-2,2′-bipyridine *N*-oxide (**15**, 0.30 g, 1.0 mmol) in MeOH (5 mL) at 25 °C. The mixture was heated for 30 min at 40 °C, cooled, and hydrolyzed with water (10 mL). Extraction with CH_2Cl_2 (3 × 15 mL) afforded 84% of **8**.

6-Iodo-4-methoxy-2,2′-bipyridine *N*-Oxide (9). The general procedure A, using a solution of iodine (0.25 g, 1.0 mmol) in THF (5 mL) at −70 °C with stirring for 1 h, gave **9** (eluent: AcOEt). Before extraction, the solution was treated with $Na_2S_2O_3$ until bleaching. Yield: 94% when LTMP (1 equiv) was used instead of LDA and the metalation time extended to 1.5 h; mp 118 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 7.33 (ddd, 1H, J = 8.0, 4.7, 1.2 Hz), 7.49 (d, 1H, J = 3.5 Hz), 7.74 (d, 1H, J = 3.5 Hz), 7.83 (td, 1H, J = 8.0, 1.9 Hz), 8.69 (ddd, 1H, J = 4.7, 1.9, 1.0 Hz), 8.91 (ddd, 1H, J = 8.0, 1.2, 1.0 Hz); IR (KBr) 1609, 1475, 1393, 1222, 1140, 1024. Anal. Calcd for $C_{11}H_9IN_2O_2$ (328.11): C, 40.27; H, 2.76; N, 8.54. Found: C, 40.23; H, 2.50;

(28) Bizot, J. *Bull. Soc. Chim. Fr.* **1967**, 151.
(29) Deuterium incorporation was determined from the ^{1}H NMR integration values.

N, 8.41. **From 16**. As previously described for the synthesis of compound **8** from **15**. Yield: 83%.

6-Bromo-4-methoxy-2,2′-bipyridine (10). PBr_3 (0.29 mL, 3.0 mmol) was slowly added to a stirred solution of 6-bromo-4-methoxy-2,2′-bipyridine *N*-oxide (**8**, 0.28 g, 1.0 mmol) in $CHCl_3$ (10 mL) at 25 °C. The mixture was refluxed for 45 min, cooled, and poured onto ice. After neutralization with K_2CO_3 and extraction with CH_2Cl_2 (3 × 10 mL), 90% of **10** was obtained (eluent: CH_2Cl_2): mp 84 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 7.01 (d, 1H, J = 2.1 Hz), 7.30 (ddd, 1H, J = 7.8, 4.8, 1.2 Hz), 7.80 (td, 1H, J = 7.8, 1.8 Hz), 7.94 (d, 1H, J = 2.1 Hz), 8.39 (dd, 1H, J = 7.8, 1.2 Hz), 8.65 (dd, 1H, J = 4.8, 1.8 Hz); IR (KBr) 1583, 1542, 1459, 1402, 1311, 1216, 1140, 1029. Anal. Calcd for $C_{11}H_9BrN_2O$ (265.11): C, 49.84; H, 3.42; N, 10.57. Found: C, 49.94; H, 3.38; N, 10.55.

6-Iodo-4-methoxy-2,2′-bipyridine (11). From 6-iodo-4-methoxy-2,2′-bipyridine *N*-oxide (**9**), as previously described for the synthesis of compound **10**. Yield: 64%; mp 110 °C; ^{1}H NMR ($CDCl_3$) δ 3.92 (s, 3H), 7.25 (d, 1H, J = 2.2 Hz), 7.30 (ddd, 1H, J = 7.8, 4.8, 1.1 Hz), 7.78 (td, 1H, J = 7.7, 1.7 Hz), 7.93 (d, 1H, J = 2.2 Hz), 8.37 (dd, 1H, J = 8.0, 0.8 Hz), 8.63 (dd, 1H, J = 4.8, 1.7 Hz); IR (KBr) 2960, 1578, 1543, 1416, 1393, 1319, 1212, 1040. Anal. Calcd for $C_{11}H_9IN_2O$ (312.11): C, 42.33; H, 2.91; N, 8.98. Found: C, 42.48; H, 2.85; N, 8.90.

General Procedure B: Metalation of 2,2′-Bipyridine *N*-Oxide (12). BuLi (12 mmol) in hexane (4.8 mL) was added to a solution of diisopropylamine (1.7 mL, 12 mmol) in THF (25 mL) at 0 °C. The solution of LDA was added to a solution of 2,2′-bipyridine *N*-oxide (**12**, 1.0 g, 6.0 mmol) in THF (25 mL) at −70 °C. After 30 min at this temperature, the electrophile (13 mmol) was added and allowed to react as mentioned in the product description. The solution was hydrolyzed with water (10 mL) and extracted with CH_2Cl_2 (3 × 20 mL).

6-Bromo-2,2′-bipyridine *N*-Oxide (13). The general procedure B, using a solution of BrCN in THF (10 mL) at −70 °C with stirring for 15 min, gave 70% of **13** (eluent: Et_2O): mp 89.5 °C; ^{1}H NMR ($CDCl_3$) δ 7.18 (t, 1H, J = 7.9 Hz), 7.35 (ddd, 1H, J = 8.0, 5.2, 1.5 Hz), 7.68 (dd, 1H, J = 7.9, 2.1 Hz), 7.80 (td, 1H, J = 8.0, 1.8 Hz), 8.12 (dd, 1H, J = 7.9, 2.1 Hz), 8.69 (dd, 1H, J = 5.2, 1.8 Hz), 8.83 (dd, 1H, J = 8.0, 1.5 Hz); IR (KBr) 2361, 1560, 1458, 1423, 1368, 1259, 1135. Anal. Calcd for $C_{10}H_7BrN_2O$ (251.09): C, 47.84; H, 2.81; N, 11.16. Found: C, 47.54; H, 2.64; N, 11.06.

6-Iodo-2,2′-bipyridine *N*-Oxide (14). The general procedure B, using a solution of iodine in THF (25 mL) at −70 °C with stirring for 1 h, gave 55% of **14** (eluent: Et_2O). Before extraction, the solution was treated with $Na_2S_2O_3$ until bleaching; mp 134 °C; ^{1}H NMR ($CDCl_3$) δ 7.00 (t, 1H, J = 8.0 Hz), 7.31 (ddd, 1H, J = 7.5, 4.8, 0.9 Hz), 7.77 (td, 1H, J = 7.8, 1.7 Hz), 7.89 (dd, 1H, J = 8.0, 2.0 Hz), 8.10 (dd, 1H, J = 8.0, 2.0 Hz), 8.67 (dd, 1H, J = 4.8, 1.7 Hz), 8.79 (d, 1H, J = 8.0 Hz); IR (KBr) 1579, 1456, 1428, 1365, 1254, 1212. Anal. Calcd for $C_{10}H_7IN_2O$ (298.08): C, 40.29; H, 2.37; N, 9.40. Found: C, 40.56; H, 2.30; N, 9.16.

6-Bromo-4-nitro-2,2′-bipyridine *N*-Oxide (15). A solution of 6-bromo-2,2′-bipyridine *N*-oxide (**13**, 0.50 g, 2.0 mmol) and KNO_3 (4 g) in concentrated H_2SO_4 (10 mL) was heated for 20 h at 80 °C. The mixture was neutralized with $(NH_4)_2CO_3$ until compound **15** precipitates. Filtration and recrystallization from CH_2Cl_2 gave 66% of **15**: mp 171 °C; ^{1}H NMR ($CDCl_3$) δ 7.45 (ddd, 1H, J = 7.7, 4.7, 1.2 Hz), 7.88 (td, 1H, J = 7.7, 1.9 Hz), 8.53 (d, 1H, J = 3.2 Hz), 8.79 (dd, 1H, J = 4.7, 1.9 Hz), 8.85 (dd, 1H, J = 7.7, 1.2 Hz), 9.11 (d, 1H, J = 3.2 Hz); IR (KBr) 1558, 1450, 1388, 1343, 1272, 1155. Anal. Calcd for $C_{10}H_6BrN_3O_3$ (296.08): C, 40.57; H, 2.04; N, 14.19. Found: C, 40.50; H, 1.91; N, 14.07.

6-Iodo-4-nitro-2,2′-bipyridine *N*-Oxide (16). From 6-iodo-2,2′-bipyridine *N*-oxide (**14**), as previously described for the synthesis of compound **15**. Yield: 28%; mp 136 °C; ^{1}H NMR ($CDCl_3$) δ 7.41 (dd, 1H, J = 7.8, 4.7 Hz), 7.84 (td, 1H, J = 7.8, 1.3 Hz), 8.66 (d, 1H, J = 3.2 Hz), 8.74 (dd, 1H, J = 4.7, 1.3 Hz), 8.74 (dd, 1H, J = 7.8, 1.9 Hz), 9.04 (d, 1H, J = 3.2 Hz); IR (KBr) 1572, 1514, 1451, 1337, 1273, 1118. Anal. Calcd for $C_{10}H_6IN_3O_3$ (343.08): C, 35.01; H, 1.76; N, 12.25. Found: C, 34.98; H, 1.76; N, 12.24.

4-Methoxy-6-methyl-2,2′-bipyridine (17). A solution of methylzinc chloride (6.0 mmol) in THF (15 mL) was added to a solution of 6-chloro- or 6-bromo-4-methoxy-2,2′-bipyridine (**6** or **10**, 1.0 mmol) and $Pd(PPh_3)_4$ (50 mg, 0.040 mmol) in THF (10 mL). The mixture was refluxed for 40 h and then poured onto an aqueous solution (20 mL) of EDTA (2.5 g). Neutralization with K_2CO_3 and extraction with Et_2O (3 × 10 mL) afforded **17** (eluent: Et_2O); yield: 95% from **6**, 90% from **10**; mp 57 °C; ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 3.91 (s, 3H), 6.69 (d, 1H, J = 2.3 Hz), 7.28 (dd, 1H, J = 8.0, 4.7 Hz), 7.77 (d, 1H, J = 2.3 Hz), 7.78 (td, 1H, J = 8.0, 1.8 Hz), 8.40 (dd, 1H, J = 8.0, 1.2 Hz), 8.65 (dd, 1H, J = 4.7, 1.8 Hz); IR (KBr) 3000, 1582, 1462, 1413, 1345, 1202, 1043. Anal. Calcd for $C_{12}H_{12}N_2O$ (200.24): C, 71.98; H, 6.04; N, 13.99. Found: C, 71.97; H, 6.09; N, 13.82.

6-[Bis(phenylthio)methyl]-4-methoxy-2,2′-bipyridine (18). BuLi (20 mmol) in hexane (8.1 mL) was added to a solution of 2,2,6,6-tetramethylpiperidine (3.4 mL, 20 mmol) in THF (50 mL) at 0 °C. The solution of LTMP was added to a solution of 4-methoxy-6-methyl-2,2′-bipyridine (**17**, 1.0 g, 5.0 mmol) in THF (30 mL) at −70 °C. After 1.2 h at this temperature, phenyl disulfide (4.9 g, 22 mmol) in THF (20 mL) was added. Stirring for 3 h at −70 °C, addition of water (20 mL) and extraction with CH_2Cl_2 (3 × 20 mL) gave 76% of **18** (eluent: CH_2Cl_2/Et_2O 80:20): mp 82 °C; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H), 5.68 (s, 1H), 6.86 (d, 1H, J = 2.3 Hz), 7.4 (m, 11H), 7.79 (td, 1H, J = 7.9, 1.8 Hz), 7.87 (d, 1H, J = 2.3 Hz), 8.38 (dd, 1H, J = 7.9, 0.9 Hz), 8.66 (dd, 1H, J = 4.7, 1.8 Hz); IR (KBr) 3055, 1597, 1582, 1561, 1425, 1349, 1219, 1049. Anal. Calcd for $C_{24}H_{20}N_2OS_2$ (416.57): C, 69.20; H, 4.84; N, 6.72. Found: C, 69.15; H, 4.62; N, 6.46.

General Procedure C: Iodine−Lithium Exchange of 6-Iodo-4-methoxy-2,2′-bipyridine (11). TMEDA (0.60 mL, 4.0 mmol) and, 15 min later, 6-iodo-4-methoxy-2,2′-bipyridine (**11**, 0.31 g, 1.0 mmol) were added to a solution of BuLi (4.0 mmol) in hexane (1.6 mL) and Et_2O (12 mL) at −70 °C. After 1 h at this temperature, the electrophile was added and allowed to react as mentioned in the product description. The solution was hydrolyzed with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL).

6-Deuterio-4-methoxy-2,2′-bipyridine (19). The general procedure C, using concd DCl (2 mL) in THF (5 mL) at −70 °C, gave **19** (eluent: Et_2O): deuterium incorporation: 86%;[29] mp 70 °C; ^{1}H NMR ($CDCl_3$) δ 4.04 (s, 3H), 6.85 (d, 1H, J = 2.6 Hz), 7.32 (ddd, 1H, J = 7.6, 4.9, 1.2 Hz), 7.81 (td, 1H, J = 7.8, 1.9 Hz), 7.94 (d, 1H, J = 2.6 Hz), 8.36 (dd, 1H, J = 8.0, 2.1 Hz), 8.67 (dd, 1H, J = 4.8, 1.8 Hz); IR (KBr) 1599, 1583, 1559, 1465, 1410, 1303, 1214, 1095, 1031.

4-Methoxy-(2,2′-bipyridine)-6-carboxaldehyde (Caerulomycin E) (1). The general procedure C, using HCO_2Et (0.32 mL, 4.0 mmol) in Et_2O (5 mL) at −70 °C with stirring for 1 h, gave 55% of **1** (eluent: Et_2O): mp 80 °C (lit.[1] 83 °C); ^{1}H NMR ($CDCl_3$) δ 4.01 (s, 3H, OCH_3), 7.37 (dd, 1H, J = 7.9, 4.8 Hz, H5′), 7.49 (d, 1H, J = 2.5 Hz, H5), 7.87 (td, 1H, J = 7.9, 1.7 Hz, H4′), 8.19 (d, 1H, J = 2.5 Hz, H3), 8.54 (dd, 1H, J = 7.9, 1.2 Hz, H3′), 8.70 (dd, 1H, J = 4.8, 1.7 Hz, H6′), 10.13 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 55.6, 107.4, 110.2, 121.2, 124.2, 136.8, 148.0, 153.9, 155.0, 158.1, 167.3, 193.3; IR (KBr) 3900, 2360, 1582, 1558, 1420, 1345, 1214, 1046, 749, 739, 692. Anal. Calcd for $C_{12}H_{10}N_2O_2$ (214.22): C, 67.28; H, 4.70; N, 13.08. Found: C, 67.05; H, 4.62; N, 13.34. The spectral characteristics of compound **1** are in agreement with those already described for the natural caerulomycin E.[1] **From 17**. A solution of 4-methoxy-6-methyl-2,2′-bipyridine (**17**, 0.22 g, 1.1 mmol) and benzeneseleninic anhydride (0.79 g, 2.2 mmol) in dioxane (15 mL) was refluxed for 24 h. Hydrolysis with 2 M aqueous $NaHCO_3$ (15 mL) and extraction with CH_2Cl_2 (3 × 10 mL) gave 64% of **1** (eluent: Et_2O). **From 18**. A solution of 6-[bis(phenylthio)methyl]-4-methoxy-2,2′-bipyridine (**18**, 0.30 g, 0.73 mmol) in THF (3 mL) was added to a solution of BF_3·Et_2O (0.18 mL, 1.4 mmol) and HgO (0.30 g, 1.4 mmol) in a THF/H_2O 85:15 mixture (3 mL). The mixture was refluxed for 1 h, poured onto a 2 M aqueous solution of K_2CO_3, and extracted with CH_2Cl_2 (3 × 10 mL) to give 40% of **1** (eluent: Et_2O).

(*E*)-4-Methoxy-(2,2′-bipyridine)-6-carboxaldehyde Oxime (Caerulomycin A) (2). A mixture of 4-methoxy-(2,2′-bipyridine)-6-carboxaldehyde (**1**, 60 mg, 0.28 mmol), hydroxylamine hydrochloride (0.10 g, 1.4 mmol), pyridine (0.10 mL, 1.2 mmol), and EtOH (2 mL) was refluxed for 45 min. The solvent was evaporated under vacuum, and water (10 mL) was added. Filtration of the precipitate and recrystallization from EtOH/H_2O 50:50 gave 75% of **2**: mp 173 °C (lit.[5] 174−175 °C, lit.[6] 172−174 °C, lit.[29] 176−177 °C); ^{1}H NMR (DMSO-d_6) δ 3.91 (s, 3H, OCH_3), 7.30 (d, 1H, J = 2.4 Hz, H5), 7.44 (ddd, 1H, J = 7.2, 4.8, 1.3 Hz, H5′), 7.88 (d, 1H, J = 2.4 Hz, H3), 7.92 (td, 1H, J = 7.2, 1.6 Hz, H4′), 8.13 (s, 1H, CH), 8.36 (d, 1H, J = 7.2 Hz, H3′), 8.66 (d, 1H, J = 4.8 Hz, H6′), 11.74 (s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ 55.5, 105.5, 106.4, 120.7, 124.4, 137.2, 148.8, 149.2, 153.4, 154.5, 156.8, 166.5; IR (KBr) 2847, 2360, 1589, 1560, 1430, 1360, 1168, 1054, 981, 789, 741. Anal. Calcd for $C_{12}H_{11}N_3O_2$ (229.24): C, 62.87; H, 4.84; N, 18.04. Found: C, 63.11; H, 4.80; N, 17.84. The spectral characteristics of compound **2** are in agreement with those already described for the natural caerulomycin A.[30]

General Procedure D: Metalation of 6-Chloro- and 6-Bromo-4-methoxy-2,2′-bipyridines (6, 10). BuLi (4.0 mmol) in hexane (1.6 mL) was added to a solution of diisopropylamine (0.56 mL, 4.0 mmol) in THF (5 mL) at 0 °C. The 6-substituted-4-methoxy-2,2′-bipyridine (1.0 mmol) was introduced at −70 °C. After 1 h at this temperature, the electrophile was added and allowed to react as mentioned in the product description. The solution was hydrolyzed with water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL).

6-Chloro-5-deuterio-4-methoxy-2,2′-bipyridine (20). The general procedure D starting from **6** and using concd DCl (2 mL) in THF (5 mL) at −70 °C gave **20** (eluent: CH_2Cl_2): deuterium incorporation: 75%;[29] ^{1}H NMR ($CDCl_3$) δ 3.95 (s, 3H), 7.33 (ddd, 1H, J = 7.6, 4.5, 1.6 Hz), 7.79 (td, 1H, J = 7.6, 1.8 Hz), 7.85 (s, 1H), 8.40 (dd, 1H, J = 7.6, 1.6 Hz), 8.66 (dd, 1H, J = 4.5, 1.8 Hz).

6-Bromo-5-deuterio-4-methoxy-2,2′-bipyridine (21). The general procedure D was applied to **10** as described for **20**; deuterium incorporation: 80%;[29] ^{1}H NMR ($CDCl_3$) δ 3.94 (s, 3H), 7.33 (ddd, 1H, J = 7.6, 4.7, 1.0 Hz), 7.81 (ddd, 1H, J = 7.9, 7.6, 1.7 Hz), 7.96 (s, 1H), 8.40 (dd, 1H, J = 7.9, 1.0 Hz), 8.66 (dd, 1H, J = 4.7, 1.7 Hz).

6-Chloro-4-methoxy-5-(methylthio)-2,2′-bipyridine (22). The general procedure D was applied to **6**. Methyl disulfide (MeSSMe, 0.36 mL, 4.0 mmol) was introduced at −70 °C, and the mixture was allowed to reach rt after 30 min, before immediate treatment to afford 98% of **22** (eluent: petroleum ether/AcOEt 90:10): mp 104 °C; ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 4.08 (s, 3H), 7.31 (dd, 1H, J = 7.5, 4.7 Hz), 7.79 (dt, 1H, J = 7.7, 1.8 Hz), 7.96 (s, 1H), 8.39 (d, 1H, J = 7.9 Hz), 8.63 (ddd, 1H, J = 4.7, 1.8, 0.9 Hz); ^{13}C NMR ($CDCl_3$) δ 17.6, 56.6, 102.6, 120.4, 121.3, 124.2, 136.8, 148.9, 154.0, 154.5, 156.0, 168.0. Anal. Calcd for $C_{12}H_{11}ClN_2OS$ (266.74): C, 54.03; H, 4.16; N, 10.50. Found: C, 54.31; H, 4.22; N, 10.25.

6-Bromo-4-methoxy-5-(methylthio)-2,2′-bipyridine (23). The general procedure D was applied to **10**. MeSSMe (0.90 mL, 10 mmol) was introduced at −70 °C, and the mixture was allowed to reach rt after 5 min, before immediate treatment to afford 61% of **23** (eluent: petroleum ether/AcOEt 90:10): mp 124.5 °C; ^{1}H NMR ($CDCl_3$) δ 2.49 (s, 3H), 4.13 (s, 3H), 7.36 (ddd, 1H, J = 7.5, 4.8, 1.2 Hz), 7.85 (ddd, 1H, J = 8.0, 7.5, 1.7 Hz), 8.02 (s, 1H), 8.45 (dd, 1H, J = 8.0, 1.2 Hz), 8.68 (dd, 1H, J = 4.8, 1.7 Hz); IR (KBr) 2920, 1560, 1522, 1449, 1414, 1360, 1252, 1210, 1033. Anal. Calcd for $C_{12}H_{11}BrN_2OS$ (311.20): C, 46.31; H, 3.56; N, 9.00. Found: C, 46.32; H, 3.51; N, 9.04.

4-Methoxy-5,6-bis(methylthio)-2,2′-bipyridine (24). The general procedure D was applied to **10**. MeSSMe (0.90 mL, 10 mmol) was introduced at −70 °C, and the mixture was allowed to reach rt after 5 min. The mixture was treated after 13 h at 25 °C to afford 44% of **24** (eluent: petroleum ether/AcOEt 95:5): mp 100−101 °C; ^{1}H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.62 (s, 3H), 4.06 (s, 3H), 7.31 (ddd, 1H, J = 7.4, 4.7, 1.1 Hz), 7.80 (td, 1H, J = 7.8, 1.7 Hz), 7.81 (s, 1H), 8.48 (d, 1H, J = 8.0 Hz), 8.64 (dd, 1H, J = 4.6, 1.7 Hz); IR (KBr) 2919, 1540, 1449, 1430, 1359, 1259, 1209, 1046. Anal. Calcd for $C_{13}H_{14}N_2OS_2$ (278.40): C, 56.09; H, 5.07; N, 10.06. Found: C, 56.32; H, 5.21; N, 9.94.

4-Methoxy-5-(methylthio)-(2,2′-bipyridine)-6-carboxaldehyde (25). TMEDA (0.60 mL, 4.0 mmol) and, 15 min later, 6-bromo-4-methoxy-5-(methylthio)-2,2′-bipyridine (**23**, 0.31 g, 1.0 mmol) were added to a solution of BuLi (4.0 mmol) in hexane (1.6 mL) and Et_2O (12 mL) at −70 °C. After 30 min at this temperature, DMF (0.31 mL, 4.0 mmol) in Et_2O (5 mL) was added at −70 °C, and the temperature was allowed to reach −30 °C. After 45 min, addition of water (10 mL) and extraction with CH_2Cl_2 (3 × 10 mL) gave 55% of **25** (eluent: petroleum ether/AcOEt 80:20): mp 145 °C; ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H), 4.17 (s, 3H), 7.38 (ddd, 1H, J = 7.6, 4.8, 1.0 Hz), 7.87 (ddd, 1H, J = 7.9, 7.6, 1.7 Hz), 8.19 (s, 1H), 8.60 (dd, 1H, J = 7.9, 1.0 Hz), 8.69 (dd, 1H, J = 4.8, 1.7 Hz), 10.64 (s, 1H); IR (KBr) 2926, 1703, 1570, 1533, 1421, 1368, 1331, 1217, 1050. Anal. Calcd for $C_{13}H_{12}N_2O_2S$ (260.32): C, 59.98; H, 4.65; N, 10.76. Found: C, 60.28; H, 4.37; N, 10.51.

(*E*)-4-Methoxy-5-(methylthio)-(2,2′-bipyridine)-6-carboxaldehyde Oxime (Collismycin A) (3). The procedure described for the synthesis of compound **2** was applied to 4-methoxy-5-(methylthio)-(2,2′-bipyridine)-6-carboxaldehyde (**25**). Yield: 71%; mp 173−174 °C (lit.[7] 174−176 °C, lit.[8] 170−172 °C); ^{1}H NMR ($CDCl_3$) δ 2.39 (s, 3H, SCH_3), 4.13 (s, 3H, OCH_3), 7.35 (ddd, 1H, J = 7.5, 4.8, 1.0 Hz, H5′), 7.87 (ddd, 1H, J = 7.9, 7.5, 1.7 Hz, H4′), 8.05 (s, 1H, H3), 8.55 (dd, 1H, J = 7.9, 1.0 Hz, H3′), 8.68 (dd, 1H, J = 4.8, 1.7 Hz, H6′), 9.11 (s, 1H, CH), 10.2 (s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 18.5, 56.4, 103.7, 121.9, 122.1, 124.3, 137.2, 147.5, 148.9, 152.6, 155.1, 157.4, 167.4; IR (KBr) 3359, 2934, 1580, 1566, 1551, 1458, 1429, 1370, 1283, 1250, 1215, 1044, 916, 862, 793, 747. Anal. Calcd for $C_{13}H_{13}N_3O_2S$ (275.33): C, 56.71; H, 4.76; N, 15.26. Found: C, 57.00; H, 5.02; N, 14.98. The spectral characteristics of compound **3** are in agreement with those already described for the natural collismycin A.[7,8]

4-Methoxy-5-(methylthio)-(2,2′-bipyridine)-6-methanol (Collismycin C) (4). $NaBH_4$ (15 mg, 0.40 mmol) was added to a solution of 4-methoxy-5-(methylthio)-(2,2′-bipyridine)-6-carboxaldehyde (**25**, 25 mg, 0.10 mmol) in EtOH (6 mL). After 15 min, a 1 M aqueous solution of HCl (10 mL) was added. Neutralization with K_2CO_3 and extraction with CH_2Cl_2 (3 × 10 mL) gave 96% of **4** (eluent: $CHCl_3$/MeOH 99.5:0.5): mp 113−114 °C (lit.[7] 104−106 °C); ^{1}H NMR ($CDCl_3$) δ 2.38 (s, 3H, SCH_3), 4.14 (s, 3H, OCH_3), 4.81 (t, 1H, J = 4.1 Hz, OH), 4.96 (d, 2H, J = 4.1 Hz, CH_2), 7.37 (ddd, 1H, J = 7.5, 4.8, 1.2 Hz, H5′), 7.86 (ddd, 1H, J = 7.9, 7.5, 1.8 Hz, H4′), 8.03 (s, 1H, H3), 8.46 (ddd, 1H, J = 7.9, 1.2, 0.9 Hz, H3′), 8.70 (ddd, 1H, J = 4.8, 1.8, 0.9 Hz, H6′); ^{13}C NMR ($CDCl_3$) δ 17.4, 56.3, 62.4, 102.7, 117.5, 121.1, 124.2, 137.0, 149.1, 154.9, 155.4, 160.3, 167.2; IR (KBr) 3361, 2923, 1577, 1561, 1550, 1458, 1427, 1366, 1246, 1214, 1041, 916, 862, 793, 745. Anal. Calcd for $C_{13}H_{14}N_2O_2S$ (262.33): C, 59.59; H, 5.38; N, 10.68. Found: C, 59.61; H, 5.34; N, 10.59. The spectral characteristics of compound **4** are in agreement with those already described for the natural collismycin C.[7]

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