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Tetrahedron
Tetrahedron 61 (2005) 7211–7218

Efficient total synthesis of bastadin 6, an anti-angiogenic brominated tyrosine-derived metabolite from marine sponge

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Received 8 April 2005; accepted 12 May 2005

Available online 13 June 2005

Abstract—An efficient total synthesis of bastadin 6 (**1**), a cyclic tetramer of brominated tyrosine derivatives from the marine sponge, *Ianthella basta*, with selective anti-angiogenic activity, was accomplished. We developed a novel Ce(IV)-mediated oxidative coupling reaction of 2,6-dibromophenols to give the diaryl ether derivatives, the characteristic segment of **1**. Condensation of two segments and subsequent intramolecular macrocyclization gave bastadin 6 (**1**) in nine steps, 26% overall yield.

1. Introduction

Angiogenesis, a formation of new blood capillaries from pre-existing blood vessels, is critical for tumor growth and metastasis. A growing tumor needs an extensive network of capillaries to provide nutrients and oxygen, etc. In addition, the new blood vessels provide a way for tumor cells to enter the circulation system and to metastasize to another organ. Therefore, substances that inhibit angiogenesis have considerable potential to be novel therapeutic agents for the treatment of cancer.[1]

In the course of our study on the bioactive substances from marine organisms, we focused on a search for anti-angiogenic substances and isolated bastadins[2] from the Indonesian marine sponge, *Ianthella basta*. We found that bastadin 6 (**1**), a major constituent, showed anti-angiogenic activity in vitro and in vivo, through the induction of selective apoptosis to endothelial cells.[3] Bastadins are cyclic or acyclic tetramers of brominated-tyrosine derivative and have been known to show some interesting biological activities, such as antibacterial[2a] and cytotoxic activities,[2b] inhibition of inositol-5′-phosphate dehydrogenase[2h] and lipoxygenases,[4] and interaction with intracellular ryanodine receptor-1 (RyR-1) calcium channel complex.[2i,j] For further mechanistic study of the anti-angiogenic effect and chemical study from the viewpoint of medicinal chemistry, we aimed to develop a practical synthetic method of bastadins. Here, we present full details of the concise total synthesis of bastadin 6 (**1**) through novel Ce(IV)-mediated oxidative coupling of 2,6-dibromophenol derivatives.

2. Results and discussion

2.1. Synthetic strategy

So far, two total syntheses of bastadin 6 (**1**) have been reported. Yamamura and co-workers reported the first total synthesis of **1** using Tl(III)-mediated oxidative coupling of bromophenols as a key step, although the overall yield was marginal.[5] Recently, Sih and co-workers have developed a novel method for oxidative coupling of *o*,*o*′-dihalophenols using peroxidase and applied it in an improved total synthesis of **1**.[6] Although their synthetic route was a convergent and short-step sequence, it left much room for more improvement. Namely, the key reaction needs rather expensive peroxidase as a catalyst and is not suitable for large-scale synthesis. Furthermore, the overall yield was not so satisfactory. Then, we planned to synthesize bastadin 6 (**1**) by using a similar strategy as shown in Figure 1, with more practical method for the synthesis of two diaryl ether derivatives **2** and **3**, the key structural elements of **1**.[7]

2.2. Preparation of the left segment of bastadin 6

We first investigated the synthesis of **2**, the left segment of bastadin 6 (**1**). It has been reported that the oxidative coupling of *N*-Boc-3,5-dibromotyramine (**4**) using soybean

Keywords: Total synthesis; Bastadin; Oxidative coupling; Angiogenesis; Marine sponge.
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doi:10.1016/j.tet.2005.05.038

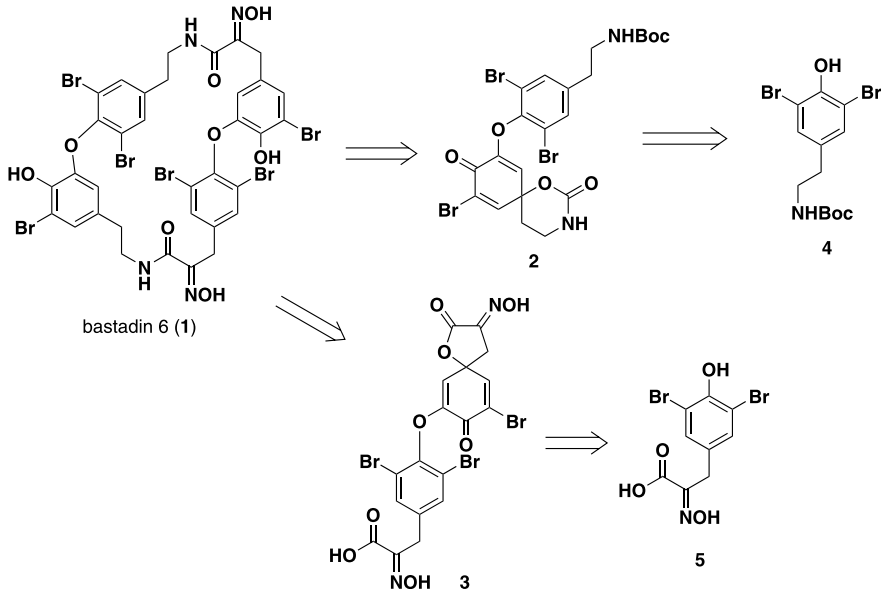
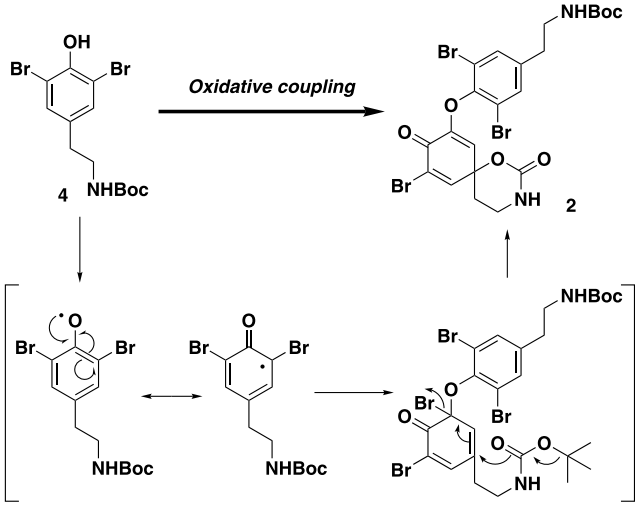


Figure 1. Synthetic strategy of bastadin 6 (**1**).

peroxidase (SPO) proceeded to give the cyclic carbamate **2** as shown in Scheme 1, with concomitant discrimination of the two amino groups which is important for the total synthesis of **1**.[6a] We examined some other oxidants, which are used for phenolic oxidation, for this coupling reaction (Table 1). In most cases, using Fe (III), Tl (III), and Pb (IV) as oxidants, no desired product **2** was obtained at all, and oxidation with phenyliodine bis(trifluoroacetate) (PIFA) gave only a trace amount of **2**. Among the oxidants tested, cerium (IV) diammonium nitrate (CAN) in aqueous CH_3CN afforded the cyclic carbamate **2** as the major product. Under optimum conditions (2 equiv of CAN, aqueous CH_3CN at 0 °C), the yield (53%) was acceptable and similar with that obtained by SPO.



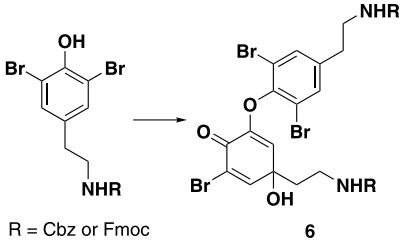
Scheme 1. Reaction mechanism of the oxidative coupling of **4**.

Table 1. Oxidative coupling of **2**

Reagent	Condition	Yield
$K_3Fe(CN)_6$	CH_3CN/H_2O, rt	n. r.
Fremy's salt[a]	MeOH, 0 °C–rt	n. r.
$Tl(ONO_2)_3$	MeOH	Decomp.
$Pb(OAc)_4$	Benzene, rt	Decomp.
PIFA[b]	$(CF_3)_2CHOH$, rt	Trace
CAN[c] (1 equiv)	CH_3CN/H_2O, rt	33%
CAN[c] (2 equiv)	CH_3CN/H_2O, rt	40%
CAN[c] (2 equiv)	CH_3CN/H_2O, 0 °C	53%

[a] $(KSO_3)_2NO$.
[b] Phenyliodine bis(trifluoroacetate).
[c] Cerium ammonium nitrate.

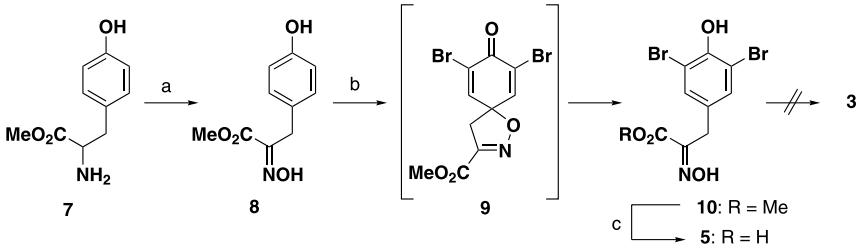
When the protecting group in **4** was changed from the Boc group to a benzyloxycarbonyl (Cbz) or 9-fluorenylmethoxycarbonyl (Fmoc) group, the coupling reaction gave a complex mixture. Each major product was **6** that was formed by similar C–O coupling and subsequent nucleophilic attack of water, instead of an intramolecular carbonyl group (Scheme 2). In this case, the two amino groups in **6** could not be discriminated. As shown in Scheme 1, nucleophilic attack of the Boc carbonyl should be derived from the producibility of the *tert*-butyl cation.[8]



Scheme 2.

2.3. Preparation of the right segment of bastadin 6

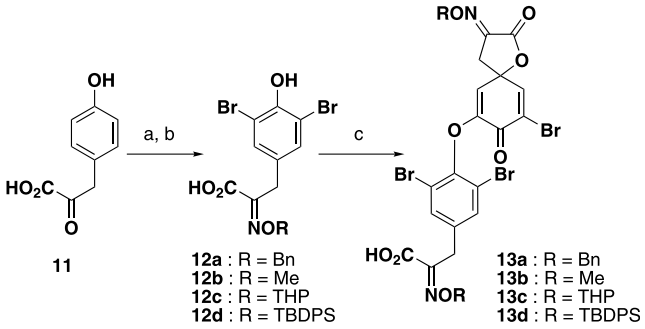
Next, the synthesis of the right segment **3** through the oxidative coupling of 3,5-dibromotyrosine derivative (**5**) was attempted. Since the reported method for the synthesis of **5** was unsatisfactory,[6a,9] we developed an improved method according to other literature,[10] as shown in Scheme 3. Thus, oxidation of tyrosine methyl ester (**7**) with Na_2WO_4/H_2O_2 afforded an oxime **8** in good yield.



Scheme 3. Reagents and conditions: (a) $Na_2WO_4 \cdot 2H_2O$, 30% H_2O_2, EtOH, 74%. (b) NBS, DMF; aq. $Na_2S_2O_4$, Et_2O, two steps 90%. (c) KOH, THF/H_2O, quant.

O,*o*′-Dibrominated phenol **10** was obtained by the treatment of **8** with 3.5 equiv of *N*-bromosuccinimide (NBS) and subsequent reductive aromatization of the resulting spiroisoxazole **9** with $Na_2S_2O_4$.[11] Hydrolysis of the ester moiety in **10** proceeded quantitatively to give the coupling substrate **5**. However, oxidative coupling of **5** did not proceed to afford the desired diaryl ether derivative under the reaction conditions developed above.

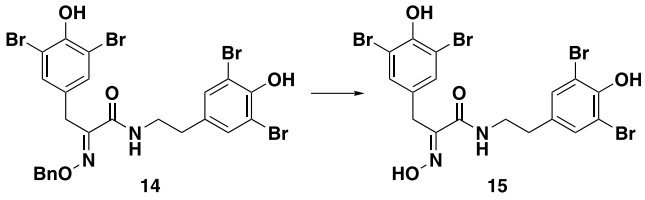
We supposed that the nucleophilic oxime moiety in **5** would interrupt the oxidative coupling, and then coupling reaction using the oxime-protected phenol **12** was investigated (Scheme 4). Since selective protection of the oxime group in **5** is not easy, **12** was prepared through condensation of 4-hydroxyphenylpyruvic acid (**11**) with *O*-protected hydroxylamine[12] and subsequent bromination by NBS. To our delight, the coupling reaction of **12** mediated by CAN proceeded smoothly to give the desired biaryl ether **13** in good yield. As shown in Scheme 4, various protecting groups were compatible. The acid-sensitive THP group also survived in this reaction condition,[13] although the yield was relatively low. The yield of the coupling reaction was up to 65%, in the case of **13d** with the TBDPS-protecting group.



Scheme 4. Reagents and conditions: (a) $RONH_2$, NaOAc; NBS, DMF, two steps 91% for **12a**; two steps quant. for **12b**; two steps 97% for **12c**; two steps 44% for **12d**. (b) CAN (2 equiv), aq. CH_3CN, 0 °C, 52% for **13a**; 61% for **13b**; 42% for **13c**; 65% for **13d**.

2.4. Model study

In order to choose a suitable protecting group of the oxime moiety for the total synthesis of bastadin 6 (**1**), preliminary experiments using model compounds were executed to obtain the following information. THP or TBDPS groups were susceptible to trifluoroacetic acid (TFA), which is used for deprotection of the Boc group at the late stage of the total synthesis, while the Me group could not be removed by some conventional reagents such as iodotrimethylsilane.[14] Fortunately, as shown in Table 2, the benzyl group of the model compound **14** was inert to the TFA treatment and was selectively removed to give **15**, by the hydrogenolysis using Pd-black[5c,15] in moderate yield, or by the treatment with $BCl_3 \cdot SMe_2$[16] in quantitative yield (Scheme 5). Thus, we decided to use **13a** as the right segment of bastadin 6 (**1**).



Scheme 5. Deprotection of model compound **14**.

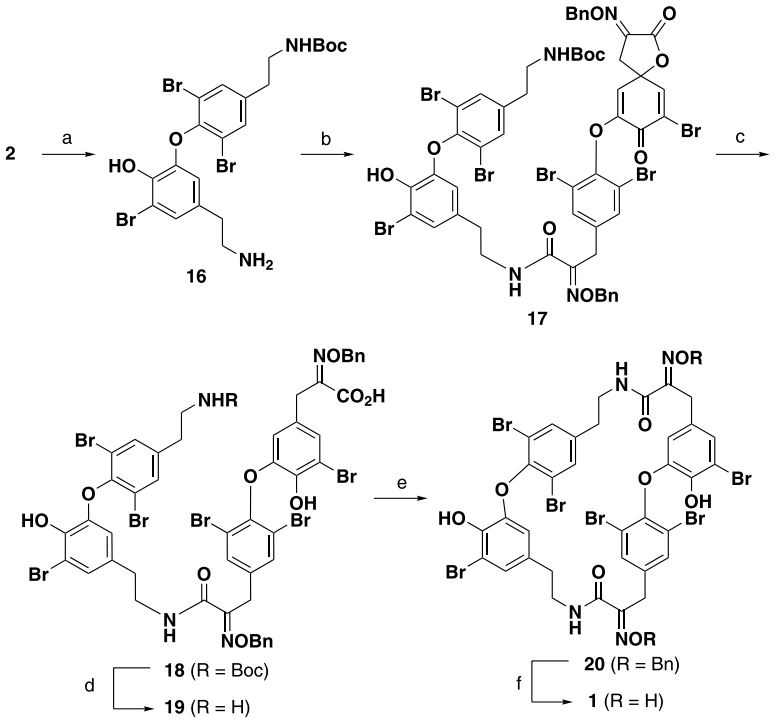
Table 2. Debenzylation of **14**

Reagent	Condition	Yield
H_2/Pd–C	MeOH	—[a]
H_2/Pd-black	Dioxane	Trace
H_2/Pd-black	Dioxane:AcOH=3:1	31%
H_2/Pd-black	Dioxane: AcOH=1:1	52%
$AlCl_3$	CH_2Cl_2:EtSH=1:1, 0 °C	n.r.
$BF_3 \cdot Et_2O$	EtSH, 0 °C	Decomp.
BCl_3	CH_2Cl_2, 0 °C	n.r.
BCl_3	CH_2Cl_2:EtSH=1:1, 0 °C	33%
$BCl_3 \cdot Me_2S$	CH_2Cl_2, 0 °C	Quant.

[a] Debrominated product was obtained.

2.5. Total synthesis of bastadin 6

As we obtained with the required two segments **2** and **13a** in hand, total synthesis of bastadin 6 (**1**) was investigated (Scheme 6). Cyclic carbamate **2** was reduced with $Na_2S_2O_4$ to give an amine **16** in almost quantitative yield. Condensation of **16** with the right segment **13a** by 1-(3-dimethylaminopropyl)-1-ethylcarbodiimide hydrochloride (EDCI·HCl) in the presence of 1-hydroxybenzotriazole hydrate (HOBt) afforded the desired amide **17**. In the case of using **3** as the coupling substrate, the oxime moiety might react with EDCI to give a considerable amount of byproducts, instead of the desired amide bond formation. Reduction of the spirodienone part in **17** with $Na_2S_2O_4$ gave a carboxylic acid **18**. Removal of the Boc group in **18** using TFA and subsequent treatment with HCl/Et_2O afforded a HCl salt of amine **19**, and then intramolecular macrocycle formation was accomplished by the EDCI/HOBt treatment to give a Bn-protected bastadin 6 (**20**) in good yield. Deprotection of the oxime group in the final step was also crucial. Selective deprotection of the two benzyl groups in **20** succeeded by the treatment with $BCl_3 \cdot SMe_2$ in CH_2Cl_2, the same condition found in the model study, to afford



Scheme 6. Reagents and conditions: (a) $Na_2S_2O_4$, THF/H_2O, quant. (b) **13a**, EDCI, HOBt, THF, 82%. (c) $Na_2S_2O_4$, CH_3CN/H_2O, 99%. (d) TFA, CH_2Cl_2; HCl/Et_2O. (e) EDCI, HOBt, Et_3N, THF, two steps 86%. (f) $BCl_3 \cdot SMe_2$, CH_2Cl_2, 76%.

bastadin 6 (**1**) in 76% yield. Physical properties of the synthetic bastadin 6 (**1**) were identical with those of natural product.[2a]

3. Summary

In summary, we have developed a highly efficient synthetic method of bastadin 6 (**1**), through the novel oxidative coupling of the 2,6-dibromophenol derivatives mediated by CAN, in the overall yield of 26% (nine steps, the longest linear sequence). The synthetic sequence is short-step, high-yielding, and convergent. The mechanistic study of bastadin and the structure–activity relationship study, to develop a novel anti-angiogenic drug candidate, are now in progress.

4. Experimental

4.1. General

The following instruments were used to obtain physical data: a JASCO FT/IR-5300 infrared spectrometer for IR spectra; a JEOL JMS SX-102 mass spectrometer for FAB MS; a Micromass Q-Tof Ultima API mass spectrometer for ESI-Q-TOF MS; a JEOL JNM AL-500 NMR spectrometer for ^1H (500 MHz) and ^{13}C (125 MHz) NMR using tetramethylsilane as an internal standard. Silica gel (Fuji Silysia BW-200) and pre-coated thin layer chromatography (TLC) plates (Merck, $60F_{254}$) were used for column chromatography and TLC. Spots on TLC plates were detected by spraying ninhydrin solution (2 g ninhydrin in 100 mL of sat. *n*-BuOH aquous) and acidic *p*-anisaldehyde solution (*p*-anisaldehyde: 25 mL, *c*-H_2SO_4: 25 mL, AcOH: 5 mL, EtOH: 425 mL) with subsequent heating. All new compounds were determined to be >95% pure by ^1H NMR spectroscopy.

4.1.1. *tert*-Butyl [2-(3,5-dibromo-4-hydroxyphenyl)-ethyl]carbamate (4). To a solution of tyramine (10 g, 70 mmol) in AcOH (200 mL), Br_2 (25 g, 156 mmol) was added and stirred overnight at 50 °C. The reaction mixture was diluted with Et_2O, and the precipitate was collected by filtration and washed with Et_2O to give HBr-salt of 3,5-dibromotyramine.

The salt was dissolved in MeOH (240 mL), and Et_3N (40 mL, 287 mmol) and $(Boc)_2O$ (18 mL, 70 mmol) was added with stirring at rt. After 2 h, 5% HCl was added and extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the residue was purified by SiO_2 column (*n*-hexane/AcOEt =4:1) to give **4** (24 g, 92% in two steps) as a white solid. FAB MS: *m/z* 394/396/398 $(M+H)^+$. HR-FAB MS: *m/z* 395.9633, calcd for $C_{13}H_{18}{}^{79}Br^{81}BrNO_3$. Found: 395.9608. IR ν_{max} (KBr) cm^{-1}: 3345, 2976, 1691. ^1H NMR ($CDCl_3$) δ: 7.26 (2H, s), 5.77 (1H, br s), 4.51 (1H, br s), 3.29 (2H, q, J=6.5 Hz), 2.68 (2H, t, J=6.5 Hz), 1.42 (9H, s). ^{13}C NMR ($CDCl_3$) δ: 156.0, 148.2, 133.9, 132.4 (2C), 110.0 (2C), 79.7, 41.8, 35.0, 28.6 (3C). Anal. Calcd for $C_{13}H_{17}Br_2NO_3$: C, 39.52; H, 4.34; Br, 40.45; N, 3.55. Found: C, 39.48; H, 4.25; Br, 40.31; N, 3.51.

4.1.2. *tert*-Butyl {2-[3,5-dibromo-4-(10-bromo-2,9-dioxo-1-oxa-3-azaspiro[5.5]undeca-7,10-dien-8-yloxy)phenyl]-ethyl}carbamate (2). To a cooled (0 °C) solution of **4** (3.0 g, 7.6 mmol) in CH_3CN (400 mL) and H_2O (135 mL), a solution of CAN (8.3 g, 15 mmol) in H_2O (65 mL) was added dropwise. After stirring for 1 h, brine was added and extracted with AcOEt. The organic phase was dried over

$MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column ($CHCl_3$/MeOH=20:1) to give **2** (1.3 g, 53%) as a white powder. FAB MS: *m/z* 671/673/675/677 $(M+Na)^+$. HR-FAB MS: *m/z* 676.8943, calcd for $C_{22}H_{23}{}^{81}Br_3N_2O_6Na$. Found: 676.8945. IR ν_{max} (KBr) cm^{-1}: 3464, 3346, 1738, 1687, 1676. ^1H NMR (DMSO-d_6) δ: 7.91 (1H, d, J=3.0 Hz), 7.59 (2H, s), 7.57 (1H, s), 6.87 (1H, t, J=5.5 Hz), 5.77 (1H, d, J=3.0 Hz), 3.37–3.31 (1H, m), 3.19–3.15 (3H, m), 2.71 (2H, t, J=6.5 Hz), 2.06–2.02 (2H, m), 1.33 (9H, s). ^{13}C NMR (DMSO-d_6) δ: 171.9, 155.5, 150.5, 147.9, 145.4, 144.8, 141.2, 133.6 (2C), 122.8, 119.8, 116.1 (2C), 77.5, 76.9, 40.5, 36.5, 34.0, 29.8, 28.2 (3C).

4.1.3. Methyl 2-hydroxyimino-3-(4-hydroxyphenyl)propionate (8). To a cooled (0 °C) solution of tyrosine methyl ester (**7**) (0.50 g, 2.6 mmol) in EtOH (5.8 mL), $Na_2WO_4\cdot 2H_2O$ (0.86 g, 2.6 mmol), 30% H_2O_2 (2.6 mL), H_2O (4.5 mL) was added, and stirred for 4 h at rt. The reaction was quenched with sat. aqueous NH_4Cl and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the residue was purified by SiO_2 column (*n*-hexane/AcOEt =1:1) to give **8** (0.56 g, 74%) as a white powder. FAB MS: *m/z* 210 $(M+H)^+$. HR-FAB MS: *m/z* 210.0766, calcd for $C_{10}H_{12}NO_4$. Found: 210.0764. IR ν_{max} (KBr) cm^{-1}: 3481, 1714. ^1H NMR (acetone-d_6) δ: 11.35 (1H, br s), 8.12 (1H, br s), 7.10 (2H, d, J=8.0 Hz), 6.72 (2H, d, J=8.0 Hz), 3.83 (2H, s), 3.71 (3H, s). ^{13}C NMR (DMSO-d_6) δ: 164.3, 155.8, 150.1, 129.6 (2C), 126.4, 115.2 (2C), 52.1, 29.2.

4.1.4. Methyl 3-(3,5-dibromo-4-hydroxyphenyl)-2-(hydroxyimino)propionate (10). To a cooled (0 °C) solution of **8** (40 mg, 0.19 mmol) in DMF (1.0 mL), NBS (0.12 g, 0.66 mmol) in DMF (0.90 mL) was added and stirred for 1 h at rt, then $Na_2S_2O_4$ (0.50 g, 2.9 mmol) in H_2O (3.0 mL) was added and stirred for an additional hour. The reaction was diluted with Et_2O and the organic layer was separated. The aqueous phase was further extracted with Et_2O, and the combined organic phase was washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo and the residue was purified by SiO_2 column (*n*-hexane/AcOEt =1:1) to give **10** (63 mg, 90%) as a white powder. FAB MS: *m/z* 366/368/370 $(M+H)^+$. HR-FAB MS: *m/z* 367.8956, calcd for $C_{10}H_{10}{}^{79}Br^{81}BrNO_4$. Found: 367.8958. IR ν_{max} (KBr) cm^{-1}: 3412, 1732. ^1H NMR (acetone-d_6) δ: 11.80 (1H, br s), 8.52 (1H, br s), 7.45 (2H, s), 3.84 (2H, s), 3.74 (3H, s). ^{13}C NMR (acetone-d_6) δ: 164.0, 149.2, 149.0, 132.2 (2C), 130.8, 111.8 (2C), 52.3, 28.5.

4.1.5. 3-(3,5-Dibromo-4-hydroxyphenyl)-2-(hydroxyimino)propionic acid (5). To a solution of **10** (0.85 g, 2.3 mmol) in THF (46 mL), 3.3 M KOH (10 mL) was added and stirred for 30 min at rt. The reaction was quenched with 5% HCl and extracted with AcOEt. The organic phase was washed with brine, dried over Na_2SO_4, and filtered. The solvent was removed in vacuo to give **5** (0.81 g, 99%) as a white powder. FAB MS: *m/z* 352/354/356 $(M+H)^+$. HR-FAB MS: *m/z* 353.8800, calcd for $C_9H_8{}^{79}Br^{81}BrNO_4$. Found: 353.8801. IR ν_{max} (KBr) cm^{-1}: 3256, 1703. ^1H NMR (acetone-d_6) δ: 11.05 (1H, br s), 7.47 (2H, s), 3.85 (2H, s), 2.57 (2H, s). ^{13}C NMR (acetone-d_6) δ: 164.9, 150.9, 150.2, 133.6 (2C), 132.0, 111.2 (2C), 29.1.

4.1.6. 2-Benzyloxyimino-3-(3,5-dibromo-4-hydroxyphenyl)propionic acid (12a, R=Bn). To a solution of 4-hydroxyphenylpyruvic acid (**11**) (1.0 g, 5.6 mmol) and *O*-benzylhydroxylamine hydrochloride (1.3 g, 8.3 mmol) in EtOH (55 mL) was added NaOAc (1.4 g, 17 mmol), and the mixture was stirred for 6 h at rt. After 5% HCl was added, the aqueous phase was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo to give 4-hydroxyphenylpyruvic acid *O*-benzyloxime (1.7 g, quant.) as a white powder. FAB MS: *m/z* 286 $(M+H)^+$. HR-FAB MS: *m/z* 286.1080, calcd for $C_{16}H_{16}NO_4$. Found: 286.1076. IR ν_{max} (KBr) cm^{-1}: 3329, 3030, 1712. ^1H NMR (DMSO-d_6) δ: 13.09 (1H, br s), 9.22 (1H, s), 7.37–7.30 (5H, m), 6.94 (2H, d, J=8.0 Hz), 6.32 (2H, d, J=8.0 Hz), 5.23 (2H, s), 3.69 (2H, s). ^{13}C NMR (DMSO-d_6) δ: 164.3, 155.9, 151.7, 137.0, 129.6 (2C), 128.3 (2C), 128.0 (3C), 125.8, 115.2 (2C), 76.4, 29.8.

To a solution of oxime (22 mg, 0.070 mmol) in DMF (0.7 mL), NBS (49 mg, 0.27 mmol) was added portionwise at 0 °C and stirred for 2 h. The reaction mixture was diluted with Et_2O, and $Na_2S_2O_4$ (0.14 g, 0.79 mmol) in H_2O (1.0 mL) was added dropwise with vigorous stirring. The organic layer was separated, and the aqueous phase was extracted with Et_2O. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column (*n*-hexane/AcOEt =7:3) to give dibrominated phenol **12a** (32 mg, 91%) as a white powder. FAB MS: *m/z* 442/444/446 $(M+H)^+$. HR-FAB MS: *m/z* 443.9269, calcd for $C_{16}H_{14}{}^{79}Br^{81}BrNO_4$. Found: 443.9286. IR ν_{max} (KBr) cm^{-1}: 3493, 2939, 1701. ^1H NMR (DMSO-d_6) δ: 13.29 (1H, br s), 9.82 (1H, br s), 7.36–7.30 (7H, m), 5.25 (2H, s), 3.72 (2H, s). ^{13}C NMR (DMSO-d_6) δ: 164.1, 150.6, 149.3, 136.8, 132.3 (2C), 130.3, 128.4 (2C), 128.1 (2C), 128.0, 111.8 (2C), 76.7, 29.2.

4.1.7. 3-(3,5-Dibromo-4-hydroxyphenyl)-2-(methoxyimino)propionic acid (12b, R=Me). In the same procedure as **12a**, **11** (0.20 g, 1.1 mmol) was converted to **12b** (0.41 g, quant.). White powder. FAB MS: *m/z* 366/368/370 $(M+H)^+$. HR-FAB MS: *m/z* 367.8956, calcd for $C_{10}H_{10}{}^{79}Br^{81}BrNO_4$. Found: 367.8956. IR ν_{max} (KBr) cm^{-1}: 3497, 1703. ^1H NMR (acetone-d_6) δ: 7.41 (2H, s), 4.05 (3H, s), 3.80 (2H, s). ^{13}C NMR (acetone-d_6) δ: 164.3, 150.4, 150.3, 133.6 (2C), 131.5, 111.3 (2C), 63.7, 29.7.

4.1.8. 3-(3,5-Dibromo-4-hydroxyphenyl)-2-(tetrahydropyran-2-yloxyimino)propionic acid (12c, R=THP). In the same procedure as **12a**, **11** (10 mg, 0.050 mmol) was converted to **12c** (21 mg, 97%). Colorless oil. FAB MS: *m/z* 436/438/440 $(M+H)^+$. HR-FAB MS: *m/z* 437.9374, calcd for $C_{14}H_{16}{}^{79}Br^{81}BrNO_5$. Found: 437.9349. IR ν_{max} (KBr) cm^{-1}: 3347, 2945, 1722. ^1H NMR (acetone-d_6) δ: 7.52 (2H, s), 5.41 (1H, s), 3.89 (1H, d, J=14.0 Hz), 3.85 (1H, d, J=14.0 Hz), 3.60 (1H, td, J=10.5, 2.5 Hz), 3.54–3.51 (1H, m), 1.89–1.54 (6H, m). ^{13}C NMR (DMSO-d_6) δ: 164.4, 151.4, 149.3, 132.5 (2C), 130.5, 111.8 (2C), 100.8, 61.0, 29.4, 28.0, 24.6, 18.2.

4.1.9. 2-(*tert*-Butyldiphenylsilyloxyimino)-3-(3,5-dibromo-4-hydroxyphenyl)propionic acid (12d, R=TBDPS). In the same procedure as **12a**, **11** (0.10 g, 0.55 mmol) was converted to **12d** (0.14 g, 44%). Colorless oil. FAB MS: *m/z* 590/592/594 $(M+H)^+$. HR-FAB MS: *m/z* 591.9978, calcd for $C_{25}H_{26}{}^{79}Br^{81}BrNO_4Si$. Found: 591.9957. IR ν_{max} (KBr) cm^{-1}: 3488, 3051, 1703. ^1H NMR (acetone-d_6) δ: 7.69–7.67 (4H, m), 7.56 (2H, s), 7.47–7.39 (6H, m), 4.06 (2H, s), 1.11 (9H, s). ^{13}C NMR (acetone-d_6) δ: 164.8, 156.7, 150.3, 136.1 (4C), 133.6 (2C), 133.3 (2C), 131.7, 130.9 (2C), 128.6 (4C), 111.4 (2C), 30.2, 27.3 (3C), 19.9.

4.1.10. 2-Benzyloxyimino-3-[4-(3-benzyloxyimino-9-bromo-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-7-yloxy)-3,5-dibromophenyl]propionic acid (13a, R=Bn). As the same procedure in the synthesis of **2**, **12a** (332 mg, 0.75 mmol) was converted to **13a** (152 mg, 52%). White powder. FAB MS: *m/z* 801/803/805/807 $(M+H)^+$. HR-FAB MS: *m/z* 804.9042, calcd for $C_{32}H_{24}{}^{79}Br^{81}Br_2N_2O_8$. Found: 804.9050. IR ν_{max} (KBr) cm^{-1}: 3065, 3036, 1784, 1695, 1658. ^1H NMR (DMSO-d_6) δ: 13.37 (1H, br s), 7.94 (1H, d, $J=2.5$ Hz), 7.51 (2H, s), 7.37–7.32 (10H, m), 6.29 (1H, d, $J=2.5$ Hz), 5.27 (4H, s), 3.84 (2H, s), 3.29 (1H, d, $J=19.5$ Hz), 2.94 (1H, d, $J=19.5$ Hz). ^{13}C NMR (DMSO-d_6) δ: 171.9, 164.0, 163.2, 149.8, 148.4, 146.4, 145.4, 144.9, 137.3, 136.6, 136.5, 133.2 (2C), 128.5, 128.4 (4C), 128.2 (2C), 128.1 (2C), 122.1 (2C), 120.2, 116.5 (2C), 78.2, 77.3, 76.9, 33.8, 29.6.

4.1.11. 3-[4-(9-Bromo-3-methoxyimino-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-7-yloxy)-3,5-dibromophenyl]-2-(methoxyimino)propionic acid (13b, R=Me). As the same procedure in the synthesis of **2**, **12b** (0.30 g, 0.83 mmol) was converted to **13b** (0.16 g, 61%). White powder. FAB MS: *m/z* 649/651/653/655 $(M+H)^+$. HR-FAB MS: *m/z* 650.8437, calcd for $C_{20}H_{16}{}^{79}Br_2{}^{81}BrN_2O_8$. Found: 650.8463. IR ν_{max} (KBr) cm^{-1}: 3231, 3061, 1776, 1703. ^1H NMR (acetone-d_6) δ: 9.86 (1H, br s), 7.79 (1H, d, $J=2.5$ Hz), 7.58 (2H, s), 6.19 (1H, d, $J=2.5$ Hz), 4.06 (3H, s), 4.02 (3H, s), 3.88 (2H, s), 3.42 (1H, d, $J=19.5$ Hz), 3.17 (1H, d, $J=19.5$ Hz). ^{13}C NMR (acetone-d_6) δ: 172.4, 164.3, 163.6, 149.7, 148.2, 146.9, 146.7, 146.0, 138.4, 134.6 (2C), 124.1, 120.1, 117.6 (2C), 79.0, 64.3, 63.9, 34.8, 30.2.

4.1.12. 3-{4-[9-Bromo-2,8-dioxo-3-(tetrahydropyran-2-yloxyimino)-1-oxaspiro[4.5]deca-6,9-dien-7-yloxy]-3,5-dibromophenyl}-2-(tetrahydropyran-2-yloxyimino)propionic acid (13c, R=THP). As the same procedure in the synthesis of **2**, **12c** (657 mg, 1.50 mmol) was converted to **13c** (249 mg, 42%) as a mixture of four diastereomers. White powder. FAB MS: *m/z* 809/811/813/815 $(M+Na)^+$. IR ν_{max} (KBr) cm^{-1}: 2947, 1695, 1660. ^1H NMR (acetone-d_6) δ: 7.86, 7.82 (1H, both d, $J=2.5$ Hz), 7.70 (2H, s), 6.23–6.17 (1H, m), 5.41–5.38 (2H, m), 3.97–3.86 (2H, m), 3.80–3.69 (1H, m), 3.63–3.50 (4H, m), 3.33–3.22 (1H, m), 1.87 (12H, m). ^{13}C NMR (DMSO-d_6) δ: 172.4, 164.5, 163.6, 150.7, 148.3, 148.2, 147.4, 147.0, 146.8, 138.6, 134.9, 133.8, 124.1, 120.2, 117.6, 103.2, 103.1, 102.8, 102.7, 79.1 (2C), 62.9, 62.7, 62.5, 62.4, 34.9, 34.8, 30.7, 29.0, 25.7, 19.6, 19.5, 19.4, 19.3.

4.1.13. 3-{4-[9-Bromo-3-(*tert*-butyldiphenylsilyloxyimino)-2,8-dioxo-1-oxaspiro[4.5]deca-6,9-dien-7-yloxy]-3,5-dibromophenyl}-2-(*tert*-butyldiphenylsilyloxyimino)propionic acid (13d, R=TBDPS). As the same procedure in the synthesis of **2**, **12d** (26 mg, 0.043 mmol) was converted to **13d** (15 mg, 65%). Colorless oil. ESI-Q-TOF MS: *m/z* 1119/1121/1123/1125 $(M+Na)^+$. HR-ESI-Q-TOF MS: *m/z* 1121.0298, calcd for $C_{50}H_{47}{}^{79}Br_2{}^{81}BrN_2O_8Si_2Na$. Found: 1121.0313. IR ν_{max} (KBr) cm^{-1}: 3072, 1697, 1658. ^1H NMR (acetone-d_6) δ: 7.86 (1H, d, $J=2.5$ Hz), 7.73 (2H, s), 7.70–7.66 (8H, m), 7.46–7.38 (12H, m), 6.18 (1H, d, $J=2.5$ Hz), 4.16 (2H, s), 3.83 (1H, d, $J=20.0$ Hz), 3.49 (1H, d, $J=20.0$ Hz), 1.09 (9H, s), 1.08 (9H s). ^{13}C NMR (acetone-d_6) δ: 165.9, 164.7, 156.0, 153.1, 148.3, 148.3, 147.0, 146.9, 138.8, 136.2 (4C), 136.2 (4C), 134.7, 133.2, 133.1 (2C), 131.1 (4C), 129.7, 129.0, 128.7 (4C), 128.6 (4C), 124.1, 120.0, 117.8 (2C), 79.3, 35.4, 30.3, 27.4 (3C), 27.2 (3C), 19.9 (2C).

4.1.14. *tert*-Butyl (2-{4-[5-(2-aminoethyl)-3-bromo-2-hydroxyphenoxy]-3,5-dibromophenyl}ethyl)carbamate (16). To a solution of **2** (0.60 g, 0.92 mmol) in THF (20 mL), $Na_2S_2O_4$ (0.96 g, 5.5 mmol) in H_2O (6.0 mL) was added and stirred for 10 min at rt. Brine was added and extracted with AcOEt. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was treated with *n*-hexane, and the precipitate was collected by filtration to give **16** (0.59 g, quant.) as a white powder. FAB MS: *m/z* 607/609/611/613 $(M+H)^+$. HR-FAB MS: *m/z* 608.9422, calcd for $C_{21}H_{26}{}^{79}Br_2{}^{81}BrN_2O_4$. Found: 608.9419. IR ν_{max} (KBr) cm^{-1}: 3522, 3335, 1680. ^1H NMR (DMSO-d_6) δ: 7.87 (1H, br s), 7.62 (2H, s), 7.11 (1H, d, $J=1.5$ Hz), 6.94 (1H, t, $J=6.0$ Hz), 6.11 (1H, d, $J=1.5$ Hz), 3.19 (2H, q, $J=6.0$ Hz), 2.83 (2H, t, $J=7.5$ Hz), 2.73 (2H, t, $J=6.0$ Hz), 2.62 (2H, t, $J=7.5$ Hz), 1.34 (9H, s). ^{13}C NMR (DMSO-d_6) δ: 155.5, 146.0, 144.9, 142.7, 140.7, 133.4 (2C), 129.0, 126.1, 117.2 (2C), 112.6, 110.6, 77.5, 40.6, 40.3, 34.0, 32.4, 28.2 (3C).

4.1.15. *tert*-Butyl (2-{4-[5-(2-{2-benzyloxyimino-3-[4-(3-benzyloxyimino-9-bromo-2,8-dioxo-1-oxaspiro[4.5]-deca-6,9-dien-7-yloxy)-3,5-dibromophenyl]propionyl-amino}ethyl)-3-bromo-2-hydroxyphenoxy]-3,5-dibromophenyl}ethyl)carbamate (17). To a stirred solution of **13a** (8.8 mg, 0.010 mmol), **16** (7.0 mg, 0.010 mmol), and HOBt (1.7 mg, 0.011 mmol) in THF (0.10 mL), EDCI (2.7 mg, 0.010 mmol) was added at 0 °C. The reaction mixture was stirred for 6 h. HCl (5%) was added and aqueous phase was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column ($CHCl_3$) to give **17** (13.2 mg, 82%) as a white powder. ESI-Q-TOF MS: *m/z* 1411/1413/1415/1417/1419/1421/1423 $(M+Na)^+$. HR-ESI-Q-TOF MS: *m/z* 1416.8100, calcd for $C_{53}H_{46}{}^{79}Br_3{}^{81}Br_3N_4O_{11}Na$. Found: 1416.8112. IR ν_{max} (KBr) cm^{-1}: 3414, 2976, 1784, 1697, 1666. ^1H NMR (DMSO-d_6) δ: 9.93 (1H, s), 8.12 (1H, t, $J=5.5$ Hz), 7.95 (1H, d, $J=2.5$ Hz), 7.61 (2H, s), 7.51 (2H, s), 7.37–7.32 (10H, m), 7.05 (1H, s), 6.90 (1H, t, $J=5.5$ Hz), 6.28 (1H, d, $J=2.5$ Hz), 6.07 (1H, s), 5.28 (2H, s), 5.24 (2H, s), 3.79 (2H, s), 3.30 (1H, d, $J=19.5$ Hz), 3.22–3.19 (4H, m), 2.95 (1H, d, $J=19.5$ Hz), 2.73 (2H, t, $J=5.0$ Hz), 2.54 (2H, t, $J=5.0$ Hz), 1.33 (9H, s). ^{13}C NMR (DMSO-d_6) δ: 171.8, 163.2, 161.8, 155.5, 151.0, 148.3, 146.4, 146.0, 145.2, 144.9, 144.7, 142.0, 140.6, 137.4 (2C), 136.5 (4C), 133.4 (2C), 130.8, 128.4 (4C), 128.3, 128.2 (2C), 128.1

(2C), 126.0, 122.1, 120.1, 117.2 (2C), 116.4 (2C), 112.6, 110.4, 78.1, 77.5, 77.3, 76.7, 40.5 (2C), 34.0, 33.8, 33.6, 28.8, 28.2 (3C).

4.1.16. 2-Benzyloxyimino-3-(3-{4-[2-benzyloxyimino-2-(2-{3-bromo-5-[2,6-dibromo-4-(2-*tert*-butoxycarbonylaminoethyl)phenoxy]-4-hydroxyphenyl}ethylcarbamoyl)-ethyl]-2,6-dibromophenoxy}-5-bromo-4-hydroxyphenyl)-propionic acid (18). To a solution of **17** (170 mg, 0.12 mmol) in CH_3CN (8.0 mL), $Na_2S_2O_4$ (58 mg, 0.33 mmol) in 4.0 mL of H_2O was added and stirred for 30 min at rt. Brine was added and extracted with AcOEt. The organic phase was dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column to give **18** (170 mg, 99%) as a white powder. ESI-Q-TOF MS: *m/z* 1413/1415/1417/1419/1421/1423/1425 $(M+Na)^+$. HR-ESI-Q-TOF MS: *m/z* 1416.8277, calcd for $C_{53}H_{48}{}^{79}Br_4{}^{81}Br_2N_4O_{11}Na$. Found: 1416.8274. IR ν_{max} (KBr) cm^{-1}: 3508, 3319, 1724, 1684. ^1H NMR (DMSO-d_6) δ: 13.16 (1H, br s), 10.04 (1H, s), 9.93 (1H, s), 8.11 (1H, t, $J=5.5$ Hz), 7.61 (2H, s), 7.51 (2H, s), 7.37–7.20 (10H, m), 7.03 (1H, s), 6.96 (1H, s), 6.91 (1H, t, $J=5.5$ Hz), 6.17 (1H, s), 6.06 (1H, s), 5.22 (2H, s), 5.06 (2H, s), 3.79 (2H, s), 3.55 (2H, s), 3.20 (2H, q, $J=6.5$ Hz), 3.16 (2H, q, $J=6.5$ Hz), 2.73 (2H, t, $J=6.5$ Hz), 2.50 (2H, t, $J=6.5$ Hz), 1.33 (9H, s). ^{13}C NMR (DMSO-d_6) δ: 164.0, 161.8, 155.5, 151.2, 150.9, 146.4, 146.0, 144.7, 144.6, 142.3, 142.0, 140.7, 137.1, 136.7 (2C), 136.4 (2C), 133.4 (2C), 133.3 (2C), 130.8, 128.5 (4C), 128.3, 128.0 (2C), 127.9, 127.8 (2C), 127.5, 117.3 (2C), 117.2 (2C), 113.1, 112.6, 110.4, 110.2, 77.5, 76.7, 76.3, 40.5 (2C), 34.0, 33.6, 29.6, 28.9, 28.2 (3C).

4.1.17. Bn-bastadin 6 (20). To a stirred solution of **18** (130 mg, 0.090 mmol) in CH_2Cl_2 (9.0 mL), TFA (1.0 mL) was added and stirred for 10 min at rt. The solvent was removed in vacuo to give TFA salt of **19**. The TFA salt was converted to HCl salt by HCl–Et_2O treatment/evaporation for three times. The HCl salt was dissolved in THF (9 mL), and Et_3N (10 μL, 0.10 mmol) was added and stirred for 30 min at 0 °C, then HOBt (30 mg, 0.29 mmol) and EDCI (20 mg, 0.10 mmol) was added, and the reaction mixture was stirred for 3 h at rt. HCl (5%) was added and the aqueous phase was extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by SiO_2 column (*n*-hexane/EtOAc =2:1) to give **20** (99 mg, 86% in two steps) as a white powder. FAB MS: *m/z* 1273/1275/1277/1279/1281/1283/1285 $(M+H)^+$. HR-FAB MS: *m/z* 1278.7807, calcd for $C_{48}H_{39}{}^{79}Br_3{}^{81}Br_3N_4O_8$. Found: 1278.7858. IR ν_{max} (KBr) cm^{-1}: 3508, 3319, 1724, 1684. ^1H NMR (DMSO-d_6) δ: 10.03 (1H, s), 9.89 (1H, s), 8.14 (1H, t, $J=6.0$ Hz), 8.09 (1H, t, $J=6.0$ Hz), 7.62 (2H, s), 7.60 (2H, s), 7.34–7.29 (6H, m), 7.25 (2H, d, $J=6.5$ Hz), 7.22 (2H, d, $J=6.5$ Hz), 7.04 (1H, d, $J=1.5$ Hz), 7.01 (1H, d, $J=1.5$ Hz), 6.22 (1H, d, $J=1.5$ Hz), 6.14 (1H, d, $J=1.5$ Hz), 5.18 (2H, s), 5.04 (2H, s), 3.68 (2H, s), 3.57 (2H, s), 3.28–3.22 (4H, m), 2.68 (2H, t, $J=8.0$ Hz), 2.60 (2H, t, $J=6.5$ Hz). ^{13}C NMR ($CDCl_3$) δ: 162.3, 162.1, 151.9, 150.7, 147.0 (2C), 144.0, 143.9, 141.5 (2C), 139.7 (2C), 136.7 (2C), 136.2, 134.0 (2C), 133.6 (2C), 130.9, 128.8, 128.6 (4C), 128.3, 128.2 (2C), 128.1 (2C), 127.9, 126.8, 118.2 (2C), 117.8 (2C), 113.1, 112.3, 109.3 (2C), 77.7, 77.4, 40.6, 39.1, 34.9, 34.1, 29.3, 28.7. Anal. Calcd for $C_{48}H_{38}Br_6N_4O_8$: C, 45.10; H, 3.00; N, 4.38. Found: C, 44.74; H, 2.97; N, 4.03.

4.1.18. Bastadin 6 (1). To a solution of **20** (21 mg, 0.016 mmol) in CH_2Cl_2 (0.30 mL), $BCl_3\cdot SMe_2$ (2.0 M in CH_2Cl_2, 0.16 mL, 0.32 mmol) was added. After stirring for 3 h at rt, sat. aqueous $NaHCO_3$ was added and stirred vigorously for 1 h. The mixture was neutralized by 5% HCl and extracted with AcOEt. The organic phase was washed with brine, dried over $MgSO_4$, and filtered. The solvent was removed in vacuo and the resulting crude product was purified by SiO_2 column (*n*-hexane/AcOEt =2:3) to give bastadin 6 (**1**, 13 mg, 76%) as a white powder. ESI-Q-TOF MS: *m/z* 1115/1117/1119/1121/1123/1125/1127 $(M+Na)^+$. HR-ESI-Q-TOF MS: *m/z* 1120.6687, calcd for $C_{34}H_{26}{}^{79}Br_3{}^{81}Br_3N_4O_8$. Found: 1120.6656. IR ν_{max} (KBr) cm^{-1}: 3051, 2868, 1664, 1626. ^1H NMR (DMSO-d_6) δ: 11.86 (1H, s), 11.65 (1H, s), 9.98 (1H, s), 9.87 (1H, s), 8.06 (1H, t, $J=5.5$ Hz), 7.95 (1H, t, $J=5.5$ Hz), 7.63 (4H, s), 7.07 (1H, d, $J=1.0$ Hz), 7.02 (1H, d, $J=2.0$ Hz), 6.21 (1H, d, $J=1.0$ Hz), 6.14 (1H, d, $J=2.0$ Hz), 3.65 (2H, s), 3.55 (2H, s), 3.27–3.22 (4H, m), 2.71–2.68 (4H, m). ^{13}C NMR ($CDCl_3$) δ: 163.3, 163.1, 151.4, 150.5, 146.1 (2C), 144.8, 144.7, 141.9, 141.6, 140.2, 137.7, 133.7 (2C), 133.3 (2C), 130.8, 128.2, 126.9, 126.3, 117.5 (2C), 117.1 (2C), 112.7, 111.7, 110.2, 109.8, 40.4, 38.4, 33.9, 32.8, 28.7, 27.4.

Acknowledgements

This study was financially supported by Grant-in-Aid for Scientific research from the Ministry of Education, Science, Sport, and Culture of Japan. The authors are also grateful to the Takeda Science Foundation for financial support.

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