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PAPER

First total synthesis of dioxepine bastadin 3†

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The synthesis of dioxepine bastadin 3, a tyrosine–tyramine derivative with a dibenzo-1,3-dioxepine scaffold that is rarely present among natural products, is described. The dibenzo-1,3-dioxepine ring was formed early in the sequence and the (*E*)-2-(hydroxyimino)-*N*-alkylamide was generated in the last step by oxidation of the 2-amino-*N*-alkylamide precursor. The presumably biogenetic late-stage ring formation starting from congener bastadin 3 failed. A new synthesis of this alkaloid was also developed. This new route requires a minimal use of protecting groups and the order of the two key steps was reversed relative to the route to dioxepine bastadin 3.

Introduction

The bastadins are a family of marine natural products isolated (with the exception of lithothamnin A, **1**, which was recently found in the red alga *Lithothamnion fragilissimum*)[1] from sponges of the *Ianthella*,[2] *Psammaplysilla*,[3] and *Dendrilla*[4] genera. These heavily brominated alkaloids are biogenetically derived from tyrosine by oxidative coupling of two tyramine–tyrosine units. Out of the 34 natural members isolated to date, the bastadin and isobastadin groups are macrocycles (Fig. 1), whereas prebastadins and hemibastadins are acyclic. Only the latter feature a biaryl connection in the dityrosine moiety whereas the other family members are biaryl ethers.[5] Lithothamnin A (**1**) is a structurally unique alkaloid within this family due to the *meta–meta* biaryl ether linkage (bastadins have *meta–para* linkages) and the 2-hydroxy substituents on the other aromatic rings.[1]

The second structural signature of this family is the (*E*)-2-(hydroxyimino)-*N*-alkylamide functionality. It has traditionally been considered that the configuration of the oximes in these compounds is *E*. However, recent studies by Crews *et al*. have challenged this assumption and led them instead to propose that the isolated compounds with *Z*,*E* and *E*,*E* geometries at the oxime bond might be artifacts that would be formed during manipulation and purification of the natural products of *Z*,*Z* geometry.[2i]

Bastadins display a wide range of biological activities, including antimicrobial,[6] cytotoxic[2b–e,h,3a,7] and antiangiogenic, both in cancer cells and in animal models of cancer.[8] Some members also inhibit inositol-50-phosphate dehydrogenase[9] and lipoxygenases,[10] whereas others interact with the intracellular

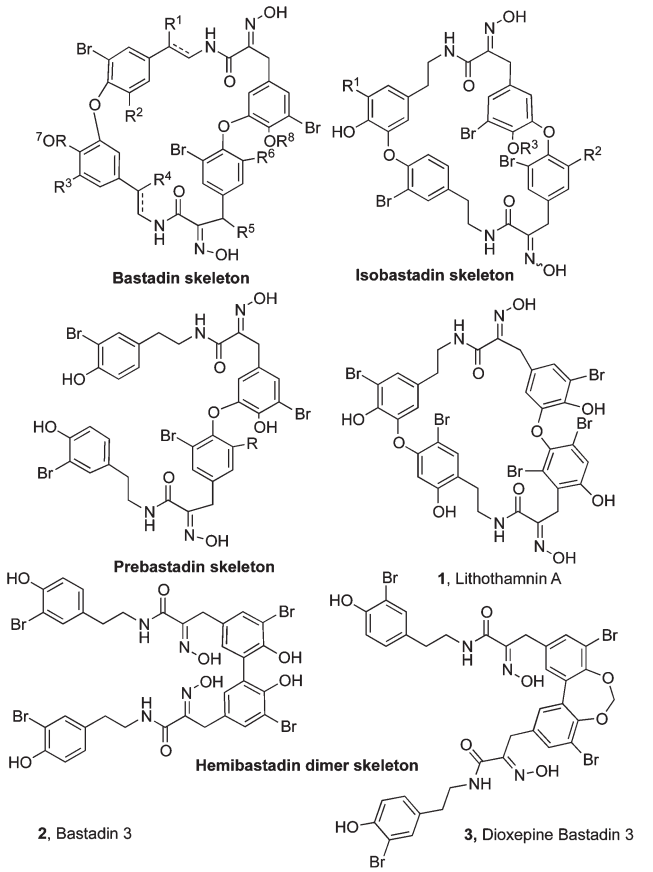

Fig. 1 Structural classes of the bastadin family of marine natural products.

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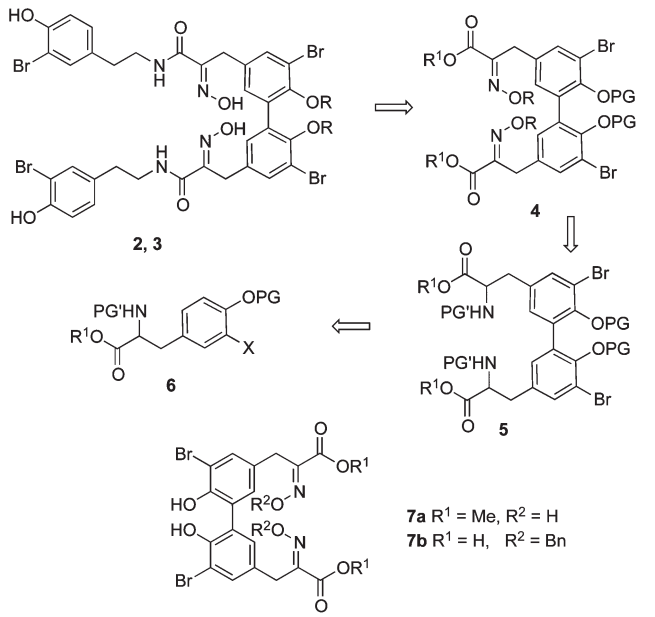
†Electronic supplementary information (ESI) available: General procedures, additional experiments, and spectral characterization data for natural and synthetic bastadin 3 (**2**) and dioxepine bastadin 3 (**3**). See DOI: 10.1039/c2ob25874a



Scheme 1 Retrosynthetic analysis of acyclic hemibastadins.

ryanodine receptor-1 (RyR-1) calcium channel complex[11] and the guinea pig δ-opioid receptors.[1]

Crews *et al.* recently reported the isolation from *Ianthella* cf. *reticulata* of a new member of the acyclic hemibastadin group, namely dioxepine bastadin 3 (**3**), a brominated dityrosine derivative that contains an unusual dibenzo-1,3-dioxepine ring.[2i]

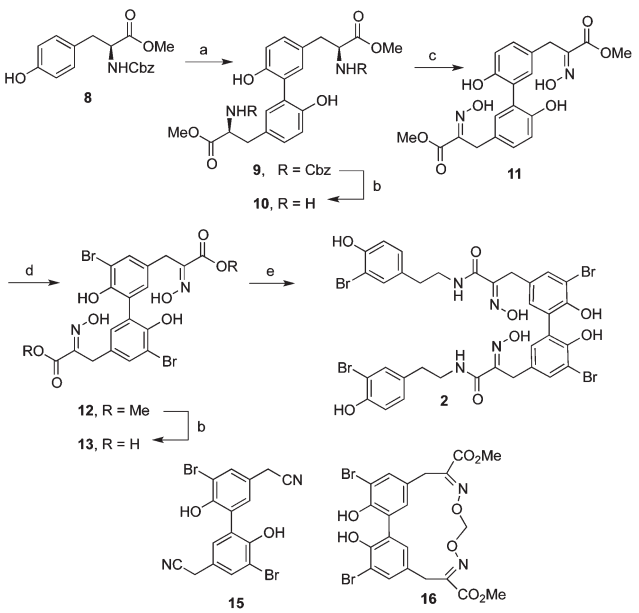
As a continuation of our interest in the synthesis and biological study of bromotyrosine-derived alkaloids,[12] we report herein the first synthesis of dioxepine bastadin 3 (**3**). Given the putative biogenetic relationship of this alkaloid to congener bastadin 3 (**2**), we first considered the straightforward preparation of **3** from **2** as the fastest synthetic pathway. (*E*)-2-(Hydroxyimino)-*N*-alkylamides such as **2** would be obtained by amide formation from the corresponding carboxylic acid **4** (Scheme 1). Oxidation of the amine **5** to the oxime **4** would follow the biaryl bond formation from **6**, thus avoiding undesired reactivity of this functional group.

Results and discussion

For the biaryl bond formation we selected the phenol oxidative coupling process,[13] which is a powerful method of proven utility in synthesis and is also involved in a myriad of biogenetic routes to natural products. Attempts to emulate Nature using a wide variety of reagents (HRP, TTFA, PIFA, $MoCl_5$, $VOCl_3$, Ce$(OH)_4$, *etc.*)[14] for phenols and naphthols have led, in general, to the desired dimers admixed with polymers, quinones and also biaryl ethers, as noted in previous approaches to bastadin 3 (**2**).[15] In Yamamura's approach[15b] the oxidation of methyl 3-bromo-4-hydroxyphenylpyruvate oxime with thallium(III) trifluoroacetate (TTFA) in trifluoroacetic acid (TFA) and CH_2C1_2 led to a mixture of spiroisoxazoles, one of which by reduction afforded the biaryl derivative **7a** in 8% overall yield. In Sih's synthesis[15a] the oxidation of the precursor phenol with a benzyl-protected oxime (to avoid the formation of spiroisoxazoles) catalyzed by horseradish peroxidase (HRP) at pH 9 provided the α-benzyl-oximinocarboxylic acid **7b** in 30% yield (Scheme 1).

The processes outlined above are relatively inefficient. In contrast, we have found that treatment of tyrosine derivative **8** with VOF_3 and a mixture of TFA and TFAA in CH_2Cl_2 at −20 °C under the conditions described by Brown and Edwards,[16] modified to include EtOAc as a co-solvent, afforded, after 30 min, the biaryl compound **9** in 60% yield together with unreacted (40%) starting material. Full conversion could not be induced even when a large excess of the oxidant or increased reaction times were used. The *ortho–ortho* regioselective outcome of this coupling in tyrosine derivatives has been discussed previously.[14,17] Deprotection of both Cbz groups in **9** by catalytic hydrogenation was followed by oxidation of the amine **10** to the oxime **11** with H_2O_2 and catalytic quantities of $MeReO_3$,[18] a step that proceeded in low yield (Scheme 2). Subsequent bromination of bisphenol **11** with NBS[12] and saponification of the ester **12** afforded carboxylic acid **13** in good overall yield (89%).

The coupling of 2-hydroxyimino acid **13** with 3-bromotyramine **14** (obtained from commercial tyramine hydrochloride by bromination, as described previously)[19] was troublesome. Whereas the procedure described by Hoshino,[12,20] which uses *N*-hydroxyphthalimide (NHPI) and dicyclohexylcarbodiimide (DCC), provided mixtures of products, other activating agents[21] led to either dinitrile **15** or decomposition products (see ESI†). The failure of this protecting group-free approach stands in contrast to the successful synthesis of the bastadin skeleton when the benzyl-protected oxime was used in conjunction with EDCI and HOBt.[25] After considerable experimentation we succeeded in achieving amide formation (52% yield) when a mixture of ester **12** and 3-bromotyramine **14** was heated to 100 °C for 1 h

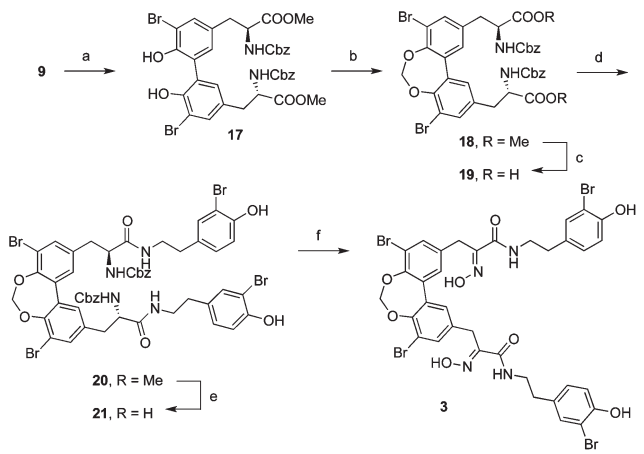


Scheme 2 *Reagents and conditions*: (a) VOF_3, TFA–TFAA, EtOAc, CH_2Cl_2, −20 °C, 30 min, 60% (40% **8**). (b) H_2, Pd/C, MeOH, 25 °C, 5 h, 99%. (c) $MeReO_3$, 30% H_2O_2, EtOH, 25 °C, 30 min, 27%. (d) NBS, CH_3CN, 0 °C, 4 h, 89%. (e) 3-Bromotyramine **14**, $^iPr_2NEt$, MW, 100 °C, 1 h, 52%.

under microwave irradiation (Scheme 2). The spectroscopic data of synthetic bastadin 3 (**2**) matched those of the natural product (see ESI†).[2b]

We proceeded to screen conditions for benzo-1,3-dioxepine formation starting from **2**. However, in all cases (the same conditions assayed with **12** described below) a complex mixture of products was obtained (see ESI†). Unprotected synthetic intermediate **12** also failed to afford the corresponding dioxepine. Heating **12** with CH_2I_2 and K_2CO_3 in DMF at 50 °C for 2 h[26] gave a product in moderate yield (51%) but this did not show the reported ^{1}H NMR chemical shift at about δ 5.66 ppm for the methylene group in natural dioxepine bastadin 3.[2i] Instead, the new methylene group resonated at δ 6.27 ppm, and was shown to correlate with the carbonyl carbon by HMBC experiments. We therefore assigned the structure of methylidene acetal **16** to this compound. The formation of **16** is the result of macrocyclization at the oxime functionalities. Lower temperatures or a change in the solvent to acetone led to recovery of **12**, and the use of $BrCH_2I$[27] also afforded compound **16** – albeit in lower yields. However, when Cs_2CO_3 was used as a base the yield of **16** increased to 78%.

This negative result led us to change strategy and it was decided to proceed by either the selective protection of the oxime before dibenzo-1,3-dioxepine formation or ring formation prior to oxidation of the amino group to the oxime. The latter approach was favored and, after bromination of bisphenol **9**, product **17** was treated with CH_2I_2 and NaH (instead of K_2CO_3) in DMF at 50 °C for 29 h to afford methylidene acetal **18** in moderate yield (43% based on recovered starting material) (Scheme 3). Saponification of **18** and condensation of **19** with tyramine **14** using HOBt and EDCI provided the modified tetrapeptide **20**. Deprotection of the benzyloxycarbonyl group was carried out with BBr_3 and pentamethylbenzene as a non-Lewis-basic cation scavenger.[25a,28] The resulting 2-amino-*N*-alkylamide was oxidized with H_2O_2 and $MeReO_3$ [18a] to afford dioxepine bastadin 3 (**3**) in a combined yield of 26%. The spectroscopic data of synthetic **3** matched those reported for the natural product (see ESI†).[2i]



Scheme 3 *Reagents and conditions*: (a) NBS, CH_3CN, 0 °C, 15 min, 98%. (b) CH_2I_2, NaH, DMF, 50 °C, 29 h, 26% (43% brsm). (c) $LiOH{\cdot}H_2O$, THF–H_2O, 25 °C, 5 h, 100%. (d) HOBt, EDCI, CH_2Cl_2, then **14**, DMF, 0 °C, 5 h, 53%. (e) BBr_3, pentamethylbenzene, CH_2Cl_2, −15 °C, 5 h. (f) $MeReO_3$, 30% H_2O_2, EtOH, 25 °C, 5 h, 26% combined.

Conclusion

In summary, we have synthesized dioxepine bastadin 3 by a sequence that comprises the late stage oxidation of the 2-amino-*N*-alkylamide to the 2-(hydroxyimino)-*N*-alkylamide and an early construction of the diaryl-1,3-dioxepine ring following the efficient phenolic oxidative coupling reaction of the tyrosine derivative with VOF_3–TFA–TFAA. In addition, a new short synthesis of bastadin 3 has been developed and this route is advantageous over the previously described approaches,[15] which employed inefficient direct oxidative coupling on substrates with oxime groups. The sequences to both natural products require minimal use of protecting groups, thus overcoming limitations of the reported synthesis of bastadins in which condensation of these symmetrical hydroxyimino dityrosine derivatives with amines required the use of protected oximes.[15,29]

Experimental section

General procedures (see ESI†)

Dimethyl 3,3′-(6,6′-dihydroxybiphenyl-3,3′-diyl)bis[2-(benzyloxycarbonylamino)propanoate] (9). To a solution of TFA–TFAA (2.4 mL, 20 : 1, v/v) in anhydrous EtOAc (2.4 mL) at −20 °C was added VOF_3 (0.08 g, 0.67 mmol), followed by a solution of **8** (0.2 g, 0.61 mmol) in anhydrous CH_2Cl_2 (12 mL). The mixture was stirred for 45 min at −20 °C and the reaction was quenched with water and extracted with EtOAc (3×), washed with aqueous $NaHCO_3$, dried over Na_2SO_4, filtered and evaporated. The residue was purified by column chromatography (SiO_2, gradient from 70 : 30 to 50 : 50 hexane–EtOAc) to yield 0.12 g (60%) of compound **9** as a white solid and 0.08 mg (40%) of recovered starting material. ^{1}H-NMR (400.13 MHz, $CDCl_3$) (data for monomer) δ 7.4–7.2 (m, 5H, ArH), 7.05 (s, 1H, H2′), 7.01 (d, J = 8.2 Hz, 1H, H4′), 6.90 (d, J = 8.2 Hz, 1H, H5′), 6.53 (s, 1H, OH), 5.38 (d, J = 8.4 Hz, 1H, NH), 5.0–4.9 (m, 2H, OCH_2Ph), 4.7–4.6 (m, 1H, H2), 3.74 (s, 3H, CO_2CH_3), 3.16 (dd, J = 13.8, 4.7 Hz, 1H, H3), 2.89 (dd, J = 13.8, 7.5 Hz, 1H, H3) ppm.

(2*S*,2′*S*)-Dimethyl 3,3′-(6,6′-dihydroxybiphenyl-3,3′-diyl)bis-(2-aminopropanoate) (10). A mixture of **9** (0.08 g, 0.12 mmol) and 10% Pd/C (0.02 g) in MeOH (17 mL) was stirred under a H_2 atmosphere at 25 °C for 5 h. The mixture was filtered through Celite® and the solvent was removed under reduced pressure to give diamine **10** (0.05 g, 99%) as a viscous yellow oil. This compound could not be fully characterized since all attempts at purification were unsuccessful, and it was immediately used in the next step.

Dimethyl (2*E*,2′*E*)-3,3′-(6,6′-dihydroxybiphenyl-3,3′-diyl)bis-[2-(hydroxyimino)propanoate] (11). A solution of $MeReO_3$ (0.003 g, 0.01 mmol) in 30% H_2O_2 (0.1 mL) and absolute EtOH (0.1 mL) was added to a stirred solution of diamine **9** (0.05 g, 0.12 mmol) in absolute EtOH (0.6 mL). The resulting solution was stirred for an additional 30 min, and then the reaction was

diluted with EtOAc (3×) and washed with H_2O and saturated $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4, and filtered, and then the solvent was removed. The residue was purified by column chromatography on silica gel (97 : 3 CH_2Cl_2–MeOH) to give 0.02 g (27%) of **11** as a colourless oil. ^{1}H-NMR (400.13 MHz, CD_3OD) (data for monomer) δ 7.2–7.1 (m, 2H, ArH), 6.82 (d, J = 8.7 Hz, 1H, ArH), 5.01 (br s, 2H, OH), 3.89 (s, 2H, 2H3), 3.78 (s, 3H, OCH_3) ppm. ^{13}C-NMR (100.61 MHz, CD_3OD) (data for monomer) δ 166.0 (s), 153.7 (s), 152.2 (s), 133.3 (d), 130.4 (d), 129.5 (s), 127.5 (s), 117.4 (d), 52.9 (q), 30.4 (t) ppm. IR (NaCl): ν 3500–3100 (br, O–H), 3049 (w, C–H), 2952 (w, C–H), 1720 (s, C═O), 1496 (m), 1441 (s), 1419 (m), 1292 (m), 1204 (s), 1115 (s), 1010 (s) cm^{-1}. HRMS (ESI$^+$): calcd for $C_{20}H_{21}N_2O_8$ ([M + H]$^+$): 417.1292; found: 417.1293.

(2*E*,2′*E*)-Dimethyl 3,3′-(5,5′-dibromo-6,6′-dihydroxybiphenyl-3,3′-diyl)bis[2-(hydroxyimino)propanoate] (12). NBS (0.38 g, 2.11 mmol) was added portionwise to oxime **11** (0.40 g, 0.96 mmol) in acetonitrile (3.2 mL) at 0 °C for 4 h. Then a 1 M aqueous solution of $Na_2S_2O_3$ was added and the mixture was stirred for 0.5 h. The reaction mixture was diluted with EtOAc and washed with H_2O and a 1 M aqueous solution of $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (97 : 3 $CHCl_3$–MeOH) to afford 0.49 g (89%) of **12** as a white solid, m.p. 244 °C (dec.) [m.p. (lit)[15b] 243 °C (dec.)]. ^{1}H-NMR (400.13 MHz, CD_3OD) (data for monomer) δ 7.42 (s, 1H, ArH), 7.05 (s, 1H, ArH), 3.86 (s, 2H, 2H3), 3.79 (s, 3H, OCH_3) ppm. ^{13}C-NMR (100.61 MHz, CD_3OD) (data for monomer) δ 165.9 (s), 151.6 (s), 151.0 (s), 134.0 (d), 132.6 (d), 130.8 (s), 128.7 (s), 112.6 (s), 53.0 (q), 30.1 (t) ppm. IR (NaCl): ν 3400–3100 (br, O–H), 3051 (w, C–H), 2953 (w, C–H), 2886 (w, C–H), 1714 (s, C═O), 1464 (s), 1437 (s), 1210 (s), 1120 (s), 1011 (s), 766 (m), 720 (s) cm^{-1}. HRMS (ESI$^+$): calcd for $C_{20}H_{19}{}^{79}Br_2N_2O_8$ ([M + H]$^+$): 572.9503; $C_{20}H_{19}{}^{79}Br^{81}BrN_2O_8$ ([M + H]$^+$): 574.9484; and $C_{20}H_{19}{}^{81}Br_2N_2O_8$ ([M + H]$^+$): 576.9467; found: 572.9483, 594.9460 and 596.9449. Elemental analysis: calcd for $C_{20}H_{18}Br_2N_2O_8$: C, 41.84; H, 3.16; N, 4.88. Found: C, 41.71; H, 3.04; N, 4.79.

(2*E*,2′*E*)-3,3′-(5,5′-Dibromo-6,6′-dihydroxybiphenyl-3,3′-diyl)-bis[2-(hydroxyimino)propanoic] acid (13). LiOH (0.22 g, 5.22 mmol) was added to a solution of ester **12** (0.10 g, 0.17 mmol) in THF–H_2O (1 : 1 v/v, 0.58 mL). After the mixture had been stirred for 18 h at room temperature, water was added and the solution was neutralized by addition of 10% HCl, extracted with ethyl acetate (3×), washed with water, brine and dried over Na_2SO_4. The solvent was evaporated to dryness to afford acid **13** (0.10 g, 100%) as a colourless oil, m.p. 176–178 °C (CH_2Cl_2–MeOH–diethyl ether). ^{1}H-NMR (400.13 MHz, CD_3OD) (data for monomer) δ 7.43 (d, J = 1.9 Hz, 1H, ArH), 7.07 (d, J = 1.9 Hz, 1H, ArH), 3.85 (s, 2H, 2H3) ppm. ^{13}C-NMR (100.61 MHz, CD_3OD) (data for monomer) δ 165.4 (s), 150.5 (s), 149.4 (s), 132.5 (d), 131.3 (d), 129.6 (s), 127.3 (s), 111.0 (s), 28.4 (t) ppm. IR (NaCl): ν 3500–2700 (br, O–H), 2415 (w, C–H), 1709 (s, C═O), 1467 (s), 1428 (s), 1197 (m), 1114 (m), 1012 (s), 763 (s), 700 (s) cm^{-1}. MS (ESI$^+$) *m*/*z* (%) 549 ([M + H]$^+$ [^{81}Br], 44), 547 ([M + H]$^+$ [^{79}Br] [^{81}Br], 100), 545 ([M + H]$^+$ [^{79}Br], 45).

2,2′-(5,5′-Dibromo-6,6′-dihydroxybiphenyl-3,3′-diyl)diacetonitrile (15). To a solution of **13** (0.02 g, 0.04 mmol) in CH_2Cl_2 (0.4 mL) were added HOBt (0.01 g, 0.08 mmol) and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI, 0.02 g, 0.08 mmol) at 0 °C, followed by a solution of 3-bromotyramine hydrochloride (**14**) (0.02 g, 0.15 mmol) and diisopropylethylamine (0.03 mL, 0.15 mmol) in DMF (0.5 mL). The reaction mixture was stirred at the same temperature for 18 h, quenched with water, and then extracted with EtOAc. The organic extracts were washed with water (2×) and brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by column chromatography on silica gel (91 : 1 CH_2Cl_2–MeOH) to afford **15** (0.007 g, 47%) as a white solid. ^{1}H-NMR (400.13 MHz, CD_3OD) (data for monomer) δ 7.54 (d, J = 2.3 Hz, 1H, ArH), 7.15 (d, J = 2.3 Hz, 1H, ArH), 3.84 (s, 2H, $ArCH_2$) ppm. ^{13}C-NMR (100.61 MHz, CD_3OD) (data for monomer) δ 153.0 (s), 133.2 (d), 131.5 (d), 129.0 (s), 124.6 (s), 119.6 (s), 113.2 (s), 22.3 (t) ppm. IR (NaCl): ν 3400–3100 (br, O–H), 2925 (s, C–H), 2855 (s, C–H), 2254 (w, C≡N), 1741 (s), 1466 (s), 1415 (s), 1255 (s), 1151 (s) cm^{-1}. HRMS (ESI$^+$): calcd for $C_{16}H_{11}{}^{81}Br_2N_2O_2$ ([M + H]$^+$): 424.9142; $C_{16}H_{11}{}^{79}Br^{81}BrN_2O_2$ ([M + H]$^+$): 422.9162; and $C_{16}H_{11}{}^{79}Br_2N_2O_2$ ([M + H]$^+$): 420.9182; found: 424.9149, 422.9181 and 420.9194.

Bastadin-3 (2). A solution of ester **13** (25 mg, 0.04 mmol) and 3-bromotyramine **14** (95 mg, 0.4 mmol) in MeOH (0.05 mL) was heated in a microwave oven for 60 min at 100 °C. The reaction mixture was allowed to cool down to room temperature, water and EtOAc were added, the layers were separated, and the aqueous layer was extracted with EtOAc (2×). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (95 : 5 CH_2Cl_2–MeOH) to afford bastadin-3 **2** (21 mg, 52%). The spectroscopic data matched those described for the natural product (see ESI†).

Compound 16. To a solution of ester **12** (5 mg, 0.009 mmol) and anhydrous CH_2I_2 (3 μL, 0.038 mmol) in anhydrous DMF (87 μL) under argon was added Cs_2CO_3 (19 mg, 0.06 mmol). The yellow mixture was stirred at 25 °C for 3 h. The mixture was cooled down to 0 °C, quenched with an aqueous saturated NH_4Cl solution and washed with EtOAc (3×). The organic layer was washed with water (3×), dried (Na_2SO_4), and concentrated to afford the corresponding ester **16** (4 mg, 78%) as a white solid. ^{1}H-NMR (400.13 MHz, CD_3COCD_3) (data for monomer) δ 7.36 (d, J = 2.2 Hz, 1H, ArH), 7.29 (d, J = 2.2 Hz, 1H, ArH), 6.27 (s, 1H, CH), 3.77 (s, 2H, 2H3), 3.75 (s, 3H, OCH_3) ppm. ^{13}C-NMR (100.61 MHz, CD_3COCD_3) (data for monomer) δ 163.2 (s), 152.6 (s), 131.5 (d), 130.0 (d, 2×), 129.6 (s), 122.3 (s), 112.0 (s), 104.5 (t), 51.0 (q), 30.1 (t) ppm. HRMS (ESI$^+$): calcd for $C_{21}H_{18}{}^{79}Br_2N_2O_8Na$ ([M + Na]$^+$): 606.9322; $C_{21}H_{18}{}^{79}Br^{81}BrN_2O_8Na$ ([M + Na]$^+$): 608.9303; and $C_{21}H_{18}{}^{81}Br_2N_2O_8Na$ ([M + Na]$^+$): 610.9282; found: 606.9295, 608.9276 and 610.9258.

(2*S*,2′*S*)-Dimethyl 3,3′-(5,5′-dibromo-6,6′-dihydroxybiphenyl-3,3′-diyl)bis(2-(benzyloxycarbonylamino)propanoate) (17). NBS (0.03 g, 0.17 mmol) was added portionwise for 15 min to a cooled (0 °C) solution of bisphenol **9** (0.05 g, 0.08 mmol) in acetonitrile (0.25 mL). Then a 1 M aqueous solution of $Na_2S_2O_3$ was added and the mixture was stirred for 0.5 h. The reaction mixture was diluted with EtOAc and washed with H_2O and a 1 M aqueous solution of $Na_2S_2O_3$. The organic layer was dried over Na_2SO_4 and filtered, and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (50 : 50 EtOAc–hexane) to afford 0.06 g (98%) of dibromide **17** as an orange foam. ^{1}H-NMR (400.13 MHz, $CDCl_3$) (data for monomer) δ 7.4–7.2 (m, 6H, ArH), 7.04 (s, 1H, H2′), 6.23 (br s, 1H, OH), 5.42 (d, J = 8.1 Hz, 1H, NH), 5.2–5.0 (m, 2H, OC$\underline{H}_2$Ph), 4.66 (dd, J = 12.8, 7.1 Hz, 1H, H2), 3.75 (s, 3H, CO_2CH_3), 3.13 (dd, J = 13.8, 4.9 Hz, 1H, H3A), 2.90 (dd, J = 13.7, 7.1 Hz, 1H, H3B) ppm. ^{13}C-NMR (100.61 MHz, $CDCl_3$) (data for monomer) δ 171.6 (s), 155.6 (s), 149.1 (s), 136.0 (s), 133.4 (d), 131.6 (d), 129.2 (s), 128.6 (d, 2×), 128.2 (d, 2×), 128.0 (d), 124.4 (s), 111.1 (s), 67.1 (t), 54.8 (d), 52.5 (q), 37.6 (t) ppm. IR (NaCl): ν 3400–3100 (br, O–H), 3348 (w, N–H), 2957 (w, C–H), 2924 (w, C–H), 2852 (w, C–H), 1711 (s, C═O), 1463 (m), 1212 (m), 1120 (s), 1059 (m), 766 (m) cm^{-1}. HRMS (ESI$^+$): calcd for $C_{36}H_{34}{}^{79}Br_2N_2O_{10}$ ([M + H]$^+$): 813.0656; $C_{36}H_{34}{}^{79}Br^{81}BrN_2O_{10}$ ([M + H]$^+$): 815.0636; and $C_{36}H_{34}{}^{81}Br_2N_2O_{10}$ ([M + H]$^+$): 817.0618; found: 813.0656, 815.0669 and 817.0632.

(2*S*,2′*S*)-Dimethyl 3,3′-(4,8-dibromodibenzo[*d*,*f*][1,3]dioxepine-2,10-diyl)bis(2-(benzyloxycarbonylamino)propanoate) (18). To a solution of ester **17** (0.05 g, 0.06 mmol) in anhydrous DMF (61 μL) under argon was added NaH (60% dispersion in oil, 4.88 mg, 0.12 mmol). After stirring the yellow mixture at 0 °C for 0.5 h, anhydrous CH_2I_2 (0.03 mL, 0.37 mmol) was added. The reaction mixture was stirred at 50 °C for 29 h and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (40 : 60 EtOAc–hexane) to afford **18** (0.013 g, 26%) as a white foam and 0.02 g of unreacted starting material. ^{1}H-NMR (400.13 MHz, $CDCl_3$) (data for monomer) δ 7.40 (s, 1H, ArH), 7.32 (s, 5H, ArH), 7.16 (s, 1H, ArH), 5.70 (s, 1H, OCH_2O), 5.5–5.3 (m, 1H, NH), 5.11 (s, 2H, OC$\underline{H}_2$Ph), 4.69 (br s, 1H, H2), 3.75 (s, 3H, CO_2CH_3), 3.17 (dd, J = 13.9 Hz, 1H, H3A), 3.06 (dd, J = 13.3, 6.2 Hz, 1H, H3B) ppm. ^{13}C-NMR (100.61 MHz, $CDCl_3$) (data for monomer) δ 171.6 (s), 155.6 (s), 149.1 (s), 136.0 (s), 134.4 (s), 134.3 (s), 133.7 (d), 128.5 (d, 2×), 128.4 (d), 128.2 (d), 127.9 (d, 2×), 116.3 (s), 101.4 (t), 67.1 (t), 54.7 (d), 52.5 (q), 37.4 (t) ppm. IR (NaCl): ν 3335 (w, N–H), 2956 (w, C–H), 2925 (s, C–H), 2853 (m, C–H), 1719 (s, C═O), 1518 (m), 1456 (m), 1214 (m), 1062 (m), 1004 (m), 754 (m) cm^{-1}. HRMS (ESI$^+$): calcd for $C_{37}H_{35}{}^{79}Br_2N_2O_{10}$ ([M + H]$^+$): 825.0659; $C_{37}H_{35}{}^{79}Br^{81}BrN_2O_{10}$ ([M + H]$^+$): 827.0637; and $C_{37}H_{35}{}^{81}Br_2N_2O_{10}$ ([M + H]$^+$): 829.0618; found: 825.0628, 827.0607 and 829.0600.

(2*S*,2′*S*)-3,3′-(4,8-Dibromodibenzo[*d*,*f*][1,3]dioxepine-2,10-diyl)-bis(2-(benzyloxycarbonylamino)propanoic acid) (19). LiOH (0.02 g, 0.51 mmol) was added to a solution of ester **18** (0.02 g, 0.03 mmol) in THF–H_2O (1 : 1 v/v, 0.09 mL). After the mixture had been stirred for 5 h at room temperature, water was added and the solution was neutralized by addition of 10% HCl, extracted with EtOAc (3×), washed with water and brine and dried over Na_2SO_4. The solvent was evaporated to dryness to afford acid **19** (0.02 g, 100%) as a white solid. ^{1}H-NMR (400.13 MHz, $CDCl_3$) (data for monomer) δ 9.4–9.0 (br, 1H, OH), 7.4–7.2 (m, 6H, ArH), 7.12 (s, 1H, ArH), 5.70 (s, 1H, OCH_2O), 5.35 (d, J = 7.6 Hz, 1H, NH), 5.3–5.0 (m, 2H, OC$\underline{H}_2$Ph), 4.80 (br s, 1H, H2), 3.32 (dd, J = 14.2, 3.1 Hz, 1H, H3A), 3.13 (dd, J = 14.2, 4.7 Hz, 1H, H3B) ppm. ^{13}C-NMR (100.61 MHz, $CDCl_3$) (data for monomer) δ 176.4 (s), 155.8 (s), 149.7 (s), 135.8 (s), 134.5 (d), 133.5 (s), 132.3 (s), 128.6 (d, 2×), 128.3 (d), 128.0 (d, 3×), 116.0 (s), 100.8 (t), 67.3 (t), 54.3 (d), 36.8 (t) ppm. IR (NaCl): ν 3323 (br, N–H), 2957 (w, C–H), 2925 (s, C–H), 2854 (s, C–H), 1715 (s, C═O), 1512 (m), 1455 (m), 1252 (s), 1063 (s), 1005 (m), 758 (s) cm^{-1}. HRMS (ESI$^+$): calcd for $C_{35}H_{30}{}^{79}Br_2N_2O_{10}$ ([M + H]$^+$): 797.0346; $C_{35}H_{30}{}^{79}Br^{81}BrN_2O_{10}$ ([M + H]$^+$): 799.0323; and $C_{35}H_{30}{}^{81}Br_2N_2O_{10}$ ([M + H]$^+$): 801.0305; found: 797.0310, 799.0310 and 801.0263.

Benzyl (2*S*,2′*S*)-3,3′-(4,8-dibromodibenzo[*d*,*f*][1,3]dioxepine-2,10-diyl)bis(1-(3-bromo-4-hydroxyphenethylamino)-1-oxopropane-3,2-diyl)dicarbamate (20). To a cooled (0 °C) solution of **19** (0.02 g, 0.03 mmol) in CH_2Cl_2 (0.25 mL) were added HOBt (0.008 g, 0.06 mmol) and 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride (EDCI, 0.01 g, 0.06 mmol), followed by a solution of 3-bromotyramine **14** (0.02 g, 0.08 mmol) and Et_3N (0.01 mL, 0.07 mmol) in DMF (0.13 mL). The reaction mixture was stirred at the same temperature for 5 h, quenched with water, and then extracted with EtOAc. The organic extracts were washed with water (2×) and brine, dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was purified by flash chromatography on silica gel (98 : 2 CH_2Cl_2–MeOH) to afford **20** (0.02 g, 53%) as a white foam. ^{1}H-NMR (400.13 MHz, CD_3OD + $CDCl_3$) (data for monomer) δ 7.49 (app. s, 1H, NH), 7.43 (s, 1H, ArH), 7.3–7.1 (m, 6H, ArH), 6.82 (d, J = 7.4 Hz, 1H, ArH), 6.75 (d, J = 8.2 Hz, 1H, ArH), 5.61 (s, 1H, OCH_2O), 5.1–4.9 (m, 2H, OC$\underline{H}_2$Ph), 4.30 (t, J = 7.0 Hz, 1H, H2), 3.34 (t, J = 6.9 Hz, 1H, NCH_2), 3.3–3.2 (m, 1H, NCH_2), 2.99 (dd, J = 13.5, 6.0 Hz, 1H, H3A), 2.9–2.8 (m, 1H, H3B), 2.52 (t, J = 6.6 Hz, 1H, CH_2) ppm. ^{13}C-NMR (100.61 MHz, CD_3OD + $CDCl_3$) (data for monomer) δ 171.9 (s), 156.9 (s), 152.6 (s), 149.2 (s), 136.5 (s), 135.8 (s), 134.0 (d), 133.5 (s), 133.2 (d), 132.6 (s), 131.7 (s), 129.1 (d, 2×), 128.8 (d, 2×), 128.5 (d), 128.1 (d, 2×), 116.5 (d), 110.1 (s), 101.7 (t), 67.3 (t), 56.5 (d), 41.2 (t), 38.2 (t), 34.5 (t) ppm. IR (NaCl): ν 3500–3100 (br, O–H), 3359 (w, N–H), 2924 (s, C–H), 2852 (s, C–H), 1710 (m, C═O), 1660 (s, C═O), 1467 (m), 1262 (m), 1235 (m), 1063 (m), 1041 (m), 739 (m) cm^{-1}. HRMS (ESI$^+$): calcd for $C_{51}H_{46}{}^{79}Br_3{}^{81}BrN_4O_{10}$ ([M + H]$^+$): 1193.0000; $C_{51}H_{46}{}^{79}Br_2{}^{81}Br_2N_4O_{10}$ ([M + H]$^+$): 1194.0000; $C_{51}H_{46}{}^{79}Br^{81}Br_3N_4O_{10}$ ([M + H]$^+$): 1196.9962; found: 1193.0019, 1194.0000 and 1196.9971.

(2*S*,2′*S*)-3,3′-(4,8-Dibromodibenzo[*d*,*f*][1,3]dioxepine-2,10-diyl)-bis(2-amino-*N*-(3-bromo-4-hydroxyphenethyl)propanamide) (21). To a cooled (−78 °C) solution of **20** (0.02, 0.014 mmol) and pentamethylbenzene (0.02, 0.14 mmol) in 0.28 mL of

CH_2Cl_2 was added boron tribromide (1 M in CH_2Cl_2, 0.14 mL). The reaction mixture was stirred at −15 °C for 5 h, quenched with a saturated solution of $NaHCO_3$, and extracted with CH_2Cl_2. The organic extracts were washed with water (2×), dried over Na_2SO_4, and concentrated to dryness under reduced pressure. The residue was redissolved in methanol, washed with hexane and the methanol was removed *in vacuo*. This compound could not be fully characterized and all attempts at purification were unsuccessful. The compound was used in the next step without further purification.

Dioxepine bastadin 3 (3). A solution of $MeReO_3$ (0.17 mg, 0.007 mmol) in 30% H_2O_2 (9 μL) and absolute EtOH (9 μL) was added to a stirred solution of diamine **21** (9 mg, 0.009 mmol) in absolute EtOH (43 μL). The resulting solution was stirred for an additional 5 h at room temperature, and then the reaction was diluted with CH_2Cl_2 and washed with H_2O. The organic layer was dried over Na_2SO_4, and filtered, and then the solvent was removed. The residue was purified by column chromatography on silica gel (99 : 1 CH_2Cl_2–MeOH) to afford 3.5 mg (26% in two steps) of dioxepine bastadin 3 as a white solid. The spectroscopic data matched those described for the natural product (see ESI†).

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