STUDIES ON SYNTHESIS OF ARAPLYSILLINS *VIA* OXIDATIVE CYCLISATION OF *o*-PHENOLIC OXIME-ACID DERIVATIVES USING PHENYLIODONIUM DIACETATE

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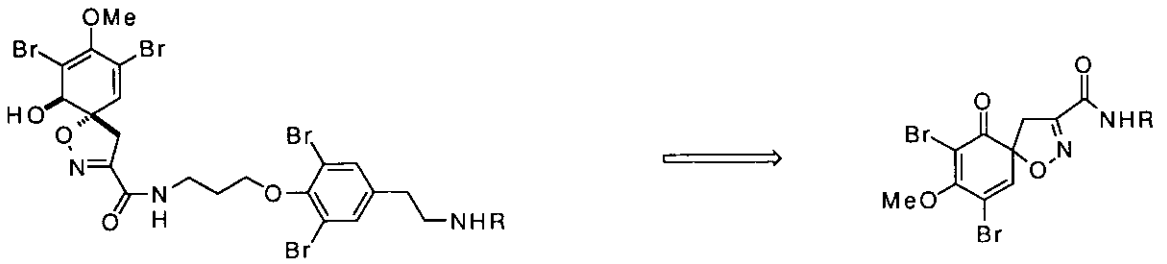
Abstract— Efficient synthetic approaches of cyclohexadienonespiroisoxazoline-amides (**1**), which could be useful as intermediates for the synthesis of dibromotyrosine derived marine natural products araplysillins, are described. Direct cyclisation of *o*-phenolic oxime-amide (**5**) with phenyliodonium diacetate (PIDA) produced **1**. Amidation of cyclohexadienonespiroisoxazoline-acid (**6**) also took place efficiently to afford **1** .

Araplysillins-I and -II are novel dibromotyrosine derived marine natural products having a spirocyclohexadienylisoxazoline moiety which have been isolated from *Psammaplysilla arabica* (Figure 1).[1] They are inhibitors of Na^+ / K^+ ATPase and possess antimicrobial activity.[1] Recently, we have reported the intramolecular oxidative cyclisation of *o*-phenolic oxime-acid derivatives[2] using hypervalent iodine compounds.[3] Hypervalent iodine compounds were very efficient oxidising agents for the oxidation of wide variety of phenolic oximes to give corresponding spiroisoxazolines under mild conditions. Furthermore, an efficient asymmetric induction at the γ-position to the carbonyl group of the chiral esters took place to afford enantiomerically enriched spiroisoxazolines by intramolecular oxidative cyclisation of *o*-phenolic oxime-esters using hypervalent iodine reagents.[3a,c]

This paper is dedicated to Professor Koji Nakanishi of Columbia University on the occasion of his 75th birthday.

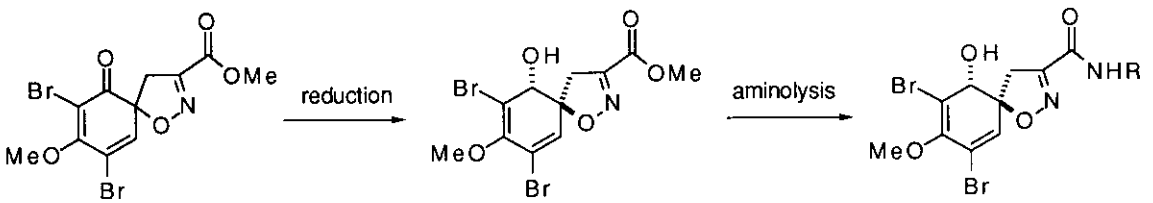
We describe here the preparation of spiroisoxazoline-amides (**1**), which should be useful as key intermediates for the synthesis of araplysillins, by way of the oxidative cyclisation of *o*- phenolic oxime-acid derivatives using phenyliodonium diacetate (PIDA).



Araplysillin-I : R = H
Araplysillin-II : R = $CO(CH_2)_{11}CHMe_2$

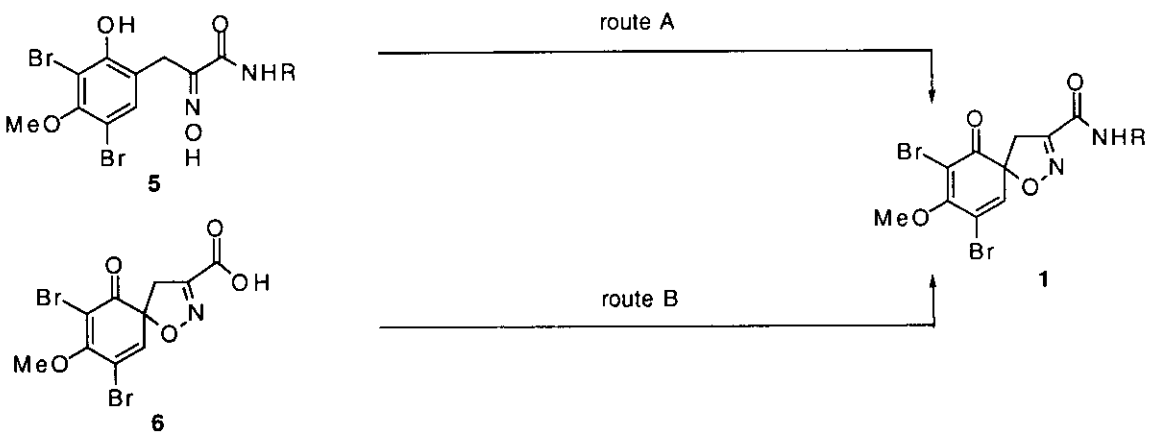
1

Figure 1



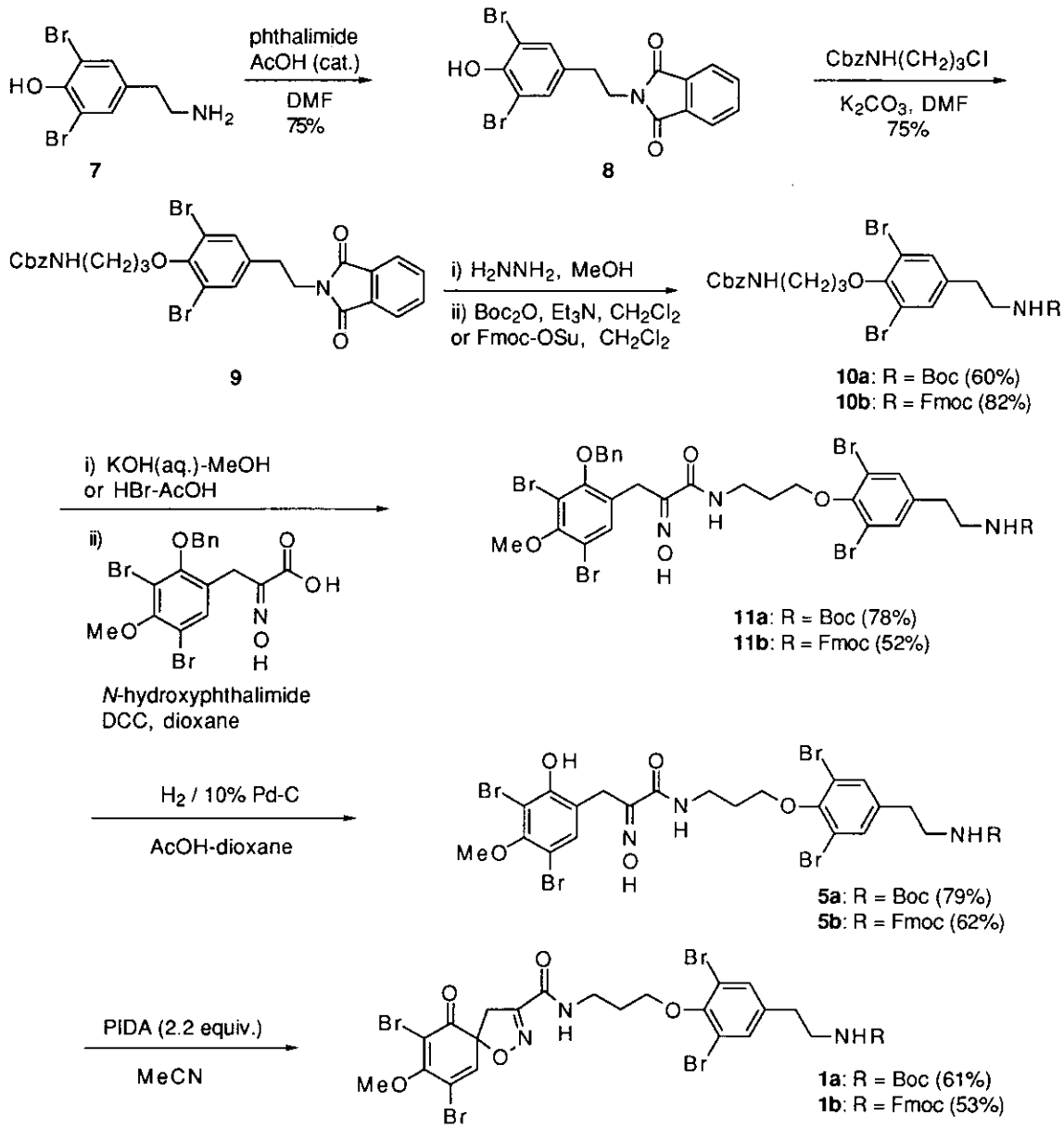
2 Yamamura's method **3** **4**

Scheme 1



5 **6** **1**

Scheme 2

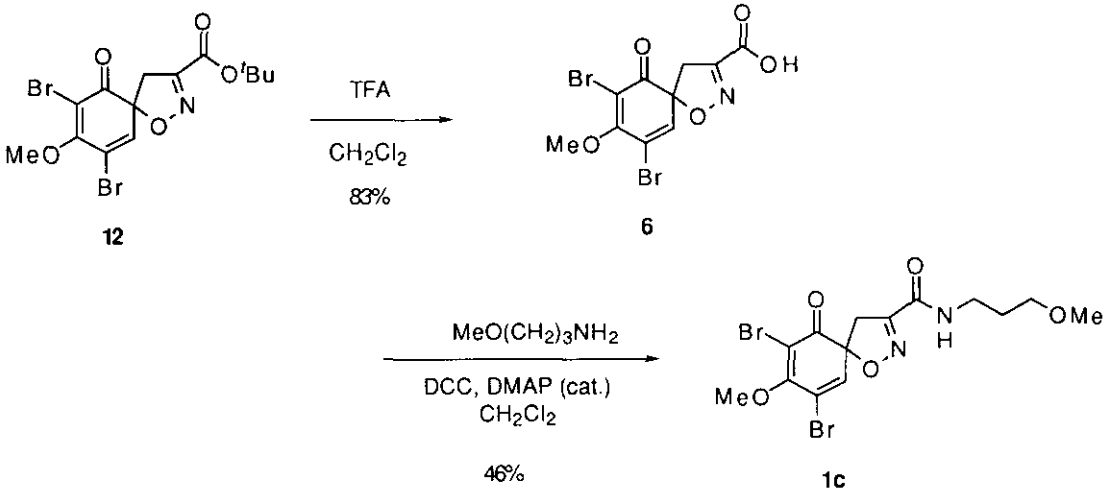


Scheme 3

It is known that bromotyrosine derived natural marine metabolites having a spirocyclohexadienylisoxazoline moiety such as aerothionin,[4] homoaerothionin,[4] and aerophobin-1[5] have been synthesized from the cyclohexadienonespiroisoxazoline-methyl ester (**1**)[2h,3c] as shown in Scheme 1. To develope a new methodology, we designed to synthesize araplysillins from cyclohexadienonespiroisoxazoline-amides (**1**) as shown in Figure 1. Therefore, two routes (A and B) were considered for the preparation of **1** (Scheme

2). Route A is direct cyclisation of *o*-phenolic oxime-amides (**5**) to give **1**. On the other hand, route B is a method for the preparation of **1** by amidation of cyclohexadienonespiroisoxazoline-acid (**6**).

The preparation for **5a,b**, bearing *N-t*-butoxycarbonyl (*N*-Boc) or *N*-(9-fluorenyl)methoxycarbonyl (*N*-Fmoc) group which was expected to easily lead to the marine natural products by its deprotection, and the results of oxidative cyclisation in route A are as follows (Scheme 3). Namely, dibromotyrosine (**7**) was treated with phthalimide for the protection of an amino group to give **8** in 75% yield. The reaction of **8** with 3-(*N*-benzyloxycarbonylamino)propyl chloride[6] afforded phenyl ether (**9**) in 75% yield. Detouch of phthalimido group in **6** by use of hydrazine, followed by reprotection with Boc or Fmoc group gave **10a,b**. To our surprise, Cbz group in **10a** was not removed by hydrogenolysis using Pd-carbon. Fortunately, removal of Cbz group in **10a** could be accomplished by hydrolysis, and that in **10b** was removed by the treatment with HBr-AcOH. Amidation in the presence of *N*-hydroxyphthalimide and DCC[7] proceeded smoothly to afford **11**. Successively, hydrogenolysis of **11** afforded **5a,b**. As expected, oxidative cyclisation with PIDA took place effectively to give **1a,b** in moderate yield (**1a**: 61%, **1b**: 53%).



Scheme 4

Next, we examined the possibility of the preparation of cyclohexadienonespiroisoxazoline-amide from the corresponding acid (route B). As shown in Scheme 4, the treatment of cyclohexadienonespiroisoxazoline (**12**) (obtained by the oxidative cyclisation of *o*-phenolic oxime-*tert*-butyl ester with PIDA[3a,b]) with TFA gave cyclohexadienonespiroisoxazoline-acid (**6**) in an acceptable yield (83%). It was found that the amidation of **3** with methoxypropylamine as a model amine unit in the presence of DMAP and DCC

proceeded easily to afford **1c**[3b] in 46% yield. Thus, the spiroisoxazoline-amide (**1c**) could be synthesized efficiently in an alternate way.

In summary, the present methods, routes A and B, provide efficient approaches to synthesis of spiroisoxazoline-amides, which should be useful as synthons for the synthesis of araplysillins. Further studies toward this direction are currently under way.

EXPERIMENTAL

All melting points were measured on a Yanagimoto (hot plate) melting point apparatus and are uncorrected. IR spectra were performed with a Hitachi 260-10 spectrophotometer and ^{1}H NMR spectra were recorded with a JEOL FX-100 (100 MHz) or EX-270 (270 MHz) spectrometer in $CDCl_3$ solution using tetramethylsilane as an internal standard, unless otherwise noted. MS spectra were measured on a Hitachi M-80, a JEOL JMS D-300 or JMS-SX102A spectrometer. Column chromatography was performed on silica gel.

Preparation of the *o*-phenolic oxime-amides

N-Phthaloyl-2-(3,5-dibromo-4-hydroxyphenyl)ethylamine (8)

To a solution of dibromotyrosine (**7**, 7.38 g, 25.0 mmol) in DMF (50 mL) was added phthalic anhydride (3.7 g, 25.0 mmol) and acetic acid (0.3 g, 5 mmol). The mixture was heated for 6 h at 100 °C. The reaction mixture was cooled at 0 °C and diluted with saturated aq. $NaHCO_3$, and then crystals were collected by suction filtration. The product thus obtained was washed successively with water and Et_2O to yield **8** (7.95 g, 75%) as white crystals, mp 206–208 °C (MeOH–acetone); IR (KBr) 3350, 1770, 1700 cm^{-1}; ^{1}H NMR (270 MHz) δ 2.88 (2H, t, *J* 7.8 Hz), 3.87 (2H, t, *J* 7.8 Hz), 7.35 (2H, s), 7.69-7.75 (2H, m), 7.82-7.87 (2H, m); MS *m/z* 427 (M^++4), 425 (M^++2), 423 (M^+); HRMS (FAB+) calcd for $C_{16}H_{11}O_3N^{81}Br_2$ 426.9065, found 426.9076; calcd for $C_{16}H_{11}O_3N^{81}Br^{79}Br$ 424.9085, found 424.9084; calcd for $C_{16}H_{11}O_3N^{79}Br_2$ 422.9105, found 422.9102.

N-Phthaloyl-2-[3,5-dibromo-4-(*N*'-benzyloxycarbonyl-3-aminopropyloxy)phenyl]-ethylamine (9)

To a solution of imide (**8**, 4.0 g, 9.4 mmol) in DMF (50 mL) was added 3-(*N*-benzyloxycarbonylamino)propyl chloride[6] (1.38 g, 10.0 mmol). The resulting mixture was heated for 5 h at 110 °C. The mixture was diluted with AcOEt (200 mL)–benzene (100 mL). The resulting mixture was washed successively with 10% NaOH and saturated aq. NaCl, and dried over $MgSO_4$. The solvent was

removed under reduced pressure, and the crude product was purified by column chromatography ($CHCl_3$ / MeOH = 100 : 1) to afford **9** (4.34 g, 75%) as white crystals, mp 125–127 °C (Et_2O–$CHCl_3$); IR ($CHCl_3$) 3480, 1790, 1730 cm^{-1}; ^1H NMR (100 MHz) δ 2.04 (2H, quin, *J* 6 Hz), 2.88 (2H, t, *J* 8 Hz), 3.51 (2H, q, *J* 6 Hz), 3.86 (2H, t, *J* 8 Hz), 4.02 (2H, t, *J* 6 Hz), 5.10 (2H, s), 5.24 (1H, br s), 7.20-7.42 (7H, m), 7.56-7.92 (4H, m); MS (SIMS) *m/z* 619 (M^++4+H), 617 (M^++2+H), 615 (M^++H). Anal. Calcd for $C_{27}H_{24}N_2O_5Br_2$: C, 52.62; H, 3.93; N, 4.55. Found: C, 52.91; H, 3.89; N, 4.43.

***N*-*tert*-Butoxycarbonyl-2-[3,5-dibromo-4-(*N*'-benzyloxycarbonyl-3-aminopropyloxy)-phenyl]ethylamine (10a)**

To a suspension of imide (**9**, 92.4 mg, 0.15 mmol) in MeOH (1 mL) was added 85% hydrazine hydrate (11 mg, 0.18 mmol). The mixture was refluxed for 2 h, and then the solvent was removed under reduced pressure. The resulting residue was acidified with 2% HCl and then filtered through a pad of celite. The filtrate was treated with saturated aq. $NaHCO_3$ to make basic and then extracted with CH_2Cl_2 (100 mL x 2). The combined organic extracts were washed with saturated aq. NaCl, and dried over K_2CO_3. The solvent was removed under reduced pressure to give deprotected amine (40 mg, 0.08 mmol) as an oil. To this material were added di-*tert*-butyldicarbonate (30 mg, 0.10 mmol) and Et_3N (12 mg, 0.10 mmol), and the mixture was taken up in CH_2Cl_2 (1 mL) and stirred for 15 min at rt. After addition of 0.5N HCl, the mixture was extracted with CH_2Cl_2 (50 mL x 2). The combined organic extracts were washed with saturated aq. $NaHCO_3$ and saturated aq. NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane / AcOEt = 3 : 1) to afford **10a** (53 mg, 60%) as white crystals, mp 115–116 °C (hexane–AcOEt); IR ($CHCl_3$) 3490, 1730 cm^{-1}; ^1H NMR (100 MHz) δ 1.44 (9H, s), 2.04 (2H, quin, *J* 6 Hz), 2.69 (2H, t, *J* 7 Hz), 3.31 (2H, q, *J* 7 Hz), 3.52 (2H, q, *J* 6 Hz), 4.03 (2H, t, *J* 6 Hz), 4.56 (1H, br s), 5.09 (2H, s), 5.24 (1H, br s), 7.20-7.40 (7H, m); MS (SIMS) *m/z* 589 (M^++4+H), 587 (M^++2+H), 585 (M^++H). Anal. Calcd for $C_{24}H_{30}N_2O_5Br_2$: C, 49.17; H, 5.16; N, 4.78. Found: C, 49.09; H, 5.11; N, 4.56.

***N*-9'-Fluorenylmethoxycarbonyl-2-[3,5-dibromo-4-(*N*'-benzyloxycarbonyl-3-amino-propyloxy)phenyl]ethylamine (10b)**

To a solution of the free amine [1.62 g, 3.33 mmol, obtained from imide (**9**) by treatment with hydrazine hydrate] in CH_2Cl_2 (20 mL) was added a solution of *N*-(9-fluorenylmethoxycarbonyloxy)succinimide (1.13 g, 3.33 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred for 13 h at rt. The reaction mixture was washed successively with 0.5N HCl, saturated aq. $NaHCO_3$ and saturated aq. NaCl, and dried over

$MgSO_4$. The solvent was removed under reduced pressure, and the crude product was crystallized from MeOH to afford **10b** (2.3 g, 82%) as white crystals, mp 153 °C (hexane–AcOEt); IR ($CHCl_3$) 3470, 1720 cm^{-1}; ^1H NMR (100 MHz) δ 2.04 (2H, quin, *J* 6 Hz), 2.70 (2H, br t), 3.20-3.64 (4H, m), 4.02 (2H, t, *J* 6 Hz), 4.19 (1H, br t), 4.41 (2H, br d), 4.84 (1H, br s), 5.10 (2H, s), 5.23 (1H, br s), 7.10-7.80 (15H, m); MS (SIMS) *m/z* 711 (M^++4+H), 709 (M^++2+H), 707 (M^++H). Anal. Calcd for $C_{34}H_{32}N_2O_5Br_2$: C, 57.64; H, 4.55; N, 3.95. Found: C, 57.64; H, 4.54; N, 3.68.

***N*-3-[2,6-Dibromo-4-(*N'*-*tert*-butoxycarbonyl-2-aminoethyl)phenoxy]propyl-3-(2-benzyloxy-3,5-dibromo-4-methoxyphenyl)-2-hydroxyiminopropionamide (11a)**

To a suspension of carbamate (**10a**, 586 mg, 1 mmol) in MeOH (10 mL) was added 40% NaOH (3 mL). The mixture was refluxed for 4 h, and then the solvent was removed under reduced pressure. The resulting residue was extracted with CH_2Cl_2 (50 mL x 3). The combined organic extracts were washed with saturated aq. NaCl, and dried over K_2CO_3. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography ($CHCl_3$ / MeOH = 50 : 1) to afford 273 mg (0.62 mmol) of an oil. A solution of this material in dioxane (2 mL) was added to a suspension of 2-hydroxyimino-3-(2-benzyloxy-3,5-dibromo-4-methoxyphenyl)propionic acid[3b] (351 mg, 0.74 mmol) in dioxane (10 mL) containing *N*-hydroxyphthalimide (121 mg, 0.74 mmol) and DCC (153 mg, 0.74 mmol) at 0 °C. The mixture was stirred for 2 h at rt. The reaction mixture was cooled at 0 °C, and then filtered. The filtrate was diluted with AcOEt and washed successively with 10% HCl and saturated aq. $NaHCO_3$. The organic layer was washed with saturated aq. NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (first: $CHCl_3$ / MeOH = 50 : 1; second: hexane / AcOEt = 1 : 1) to give **11a** (442 mg, 78%) as an amorphous mass. IR ($CHCl_3$) 3650-3100, 1720, 1690, 1530 cm^{-1}; ^1H NMR (100 MHz) δ 1.43 (9H, s), 1.96 (2H, quin, *J* 7 Hz), 2.67 (2H, t, *J* 7 Hz), 3.29 (2H, q, *J* 7 Hz), 3.54 (2H, q, *J* 7 Hz), 3.84 (3H, s), 3.98 (4H, m), 4.69 (1H, br t), 5.07 (2H, s), 7.12-7.60 (9H, m), 9.67 (1H, br s); MS (SIMS) *m/z* 910 (M^++6+H), 908 (M^++4+H), 906 (M^++2+H); HRMS (FAB+) calcd for $C_{33}H_{38}O_7N_3{}^{81}Br_3{}^{79}Br$ 909.9382, found 909.9464; calcd for $C_{33}H_{38}O_7N_3{}^{81}Br_2{}^{79}Br_2$ 907.9402, found 907.9418; calcd for $C_{33}H_{38}O_7N_3{}^{81}Br^{79}Br_3$ 905.9423, found 905.9507; calcd for $C_{33}H_{38}O_7N_3{}^{79}Br_4$ 903.9443, found 903.9455.

***N*-3-[2,6-Dibromo-4-(*N'*-9-fluorenylmethoxycarbonyl-2-aminoethyl)phenoxy]propyl-3-(2-benzyloxy-3,5-dibromo-4-methoxyphenyl)-2-hydroxyiminopropionamide (11b)**

To a suspension of carbamate (**10b**, 566 mg, 0.8 mmol) in AcOH (2 mL) was added 33% HBr-AcOH (800 mg, 3.3 mmol) at 0 °C. The resulting mixture was stirred for 3 h at rt and then poured into ice–water. The aqueous layer was washed with Et_2O (15 mL x 3) and then basified with K_2CO_3. The mixture was extracted with CH_2Cl_2 (100 mL x 3). The combined organic extracts were washed with saturated aq. NaCl, and dried over K_2CO_3. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography ($CHCl_3$ / MeOH = 5 : 1) to afford *N*-debenzyloxycarbonylated amine (367 mg, 0.64 mmol) as an oil. This material was subjected to the same sequence of the amidation as described for **11a**, and the crude product was purified by column chromatography (hexane / AcOEt = 4 : 1 to 2 : 1) to give **11b** (427 mg, 52%) as an oil. IR ($CHCl_3$) 3500-3000, 1710, 1660, 1450 cm^{-1}; ^1H NMR (270 MHz) δ 2.03 (2H, quin, *J* 6 Hz), 2.72 (2H, t, *J* 6 Hz), 3.40 (2H, q, *J* 6 Hz), 3.59 (2H, q, *J* 6 Hz), 3.87 (3H, s), 3.99 (2H, s), 4.02 (2H, t, *J* 6 Hz), 4.21 (1H, t, *J* 6.3 Hz), 4.43 (2H, d, *J* 6.3 Hz), 5.09 (2H, s), 7.30-7.80 (16H, m); MS (SIMS) *m/z* 1032 (M^++6+H), 1030 (M^++4+H), 1028 (M^++2+H), 1026 (M^++H); HRMS (FAB+) calcd for $C_{43}H_{40}O_7N_3{}^{81}Br_3{}^{79}Br$ 1031.9538, found 1031.9497; calcd for $C_{43}H_{40}O_7N_3{}^{81}Br_2{}^{79}Br_2$ 1029.9559, found 1029.9507; calcd for $C_{43}H_{40}O_7N_3{}^{81}Br^{79}Br_3$ 1027.9501, found 1027.9540; calcd for $C_{43}H_{40}O_7N_3{}^{79}Br_4$ 1025.9600, found 1025.9545.

***N*-3-[2,6-Dibromo-4-(*N'-tert*-butoxycarbonyl-2-aminoethyl)phenoxy]propyl-3-(3,5-dibromo-2-hydroxy-4-methoxyphenyl)-2-hydroxyiminopropionamide (5a)**

A solution of benzyl ether (**11a**, 421 mg, 0.46 mmol) in AcOH (6 mL)-dioxane (6 mL) was hydrogenated over 10% Pd-C (120 mg) under H_2 (1 atm) at rt for 3 h. After filtration, the filtrate was basified with $NaHCO_3$, and then extracted with AcOEt (100 mL x 3). The extracts were washed with saturated aq. NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography to give **5a** (296 mg, 79%) as an amorphous mass. IR ($CHCl_3$) 3600-2500, 1720, 1670, 1640, 1560 cm^{-1}; ^1H NMR (100 MHz) δ 1.44 (9H, s), 2.02 (2H, quin, br), 2.68 (2H, t, *J* 7 Hz), 3.30 (2H, q, *J* 7 Hz), 3.65 (2H, q, *J* 6 Hz), 3.82 (5H, s), 3.99 (2H, t, *J* 6 Hz), 4.74 (1H, br), 7.24 (2H, s), 7.53 (2H, s and br), 10.00 (1H, br), 10.34 (1H, s); MS (SIMS) *m/z* 822 (M^++8+H), 820 (M^++6+H), 818 (M^++4+H), 816 (M^++2+H), 814 (M^++H); HRMS (FAB+) calcd for $C_{26}H_{32}O_7N_3{}^{81}Br_4$ 821.8892, found 821.8930; calcd for $C_{26}H_{32}O_7N_3{}^{81}Br_3{}^{79}Br$ 819.8913, found 819.8903; calcd for $C_{26}H_{32}O_7N_3{}^{81}Br_2{}^{79}Br_2$ 817.8933, found 817.8932; calcd for $C_{26}H_{32}O_7N_3{}^{81}Br^{79}Br_3$ 815.8953, found 815.8937; calcd for $C_{26}H_{32}O_7N_3{}^{79}Br_4$ 813.8974, found 813.8961.

***N*-3-[2,6-Dibromo-4-(*N'*-9-fluorenylmethoxycarbonyl-2-aminoethyl)phenoxy]propyl-3-(3,5-dibromo-2-hydroxy-4-methoxyphenyl)-2-hydroxyiminopropionamide (5b)**

Amide (**11b**, 426 mg, 0.41 mmol) was hydrogenated in the same way as described for **8a**, and the crude product was purified by column chromatography (hexane / AcOEt = 2 : 1) to give **5b** (240 mg, 62%) as crystals, mp 108–111 °C; IR (KBr) 3400, 1700, 1660, 1630 cm^{-1}; ^1H NMR (100 MHz, acetone-d_6) δ 2.10 (2H, quin, *J* 6 Hz), 2.70 (2H, br t), 3.41 (2H, q, *J* 6 Hz), 3.64 (2H, q, *J* 7 Hz), 3.79 (3H, s), 3.82 (2H, s), 4.00 (2H, t, *J* 6 Hz), 4.07-4.40 (3H, m), 6.58 (1H, br), 7.20-7.90 (11H, m), 8.08 (1H, br), 10.92 (1H, br), 11.66 (1H, br); MS (SIMS) *m/z* 944 (M^++8+H), 942 (M^++6+H), 940 (M^++4+H), 938 (M^++2+H), 936 (M^++H); HRMS (FAB+) calcd for $C_{36}H_{34}O_7N_3{}^{81}Br_3{}^{79}Br$ 941.9069, found 941.9071; calcd for $C_{36}H_{34}O_7N_3{}^{81}Br_2{}^{79}Br_2$ 939.9089, found 939.9069; calcd for $C_{36}H_{34}O_7N_3{}^{81}Br{}^{79}Br_3$ 937.9110, found 937.9054; calcd for $C_{36}H_{34}O_7N_3{}^{79}Br_4$ 935.9130, found 935.9075.

General procedure for intramolecular oxidative cyclisation of *o*-phenolic oxime-amide using PIDA

To a solution of *o*-phenolic oxime-acid derivatives (**5a**,**b**, 1 mmol) in MeCN (45 mL) was added PIDA (676.4 mg, 2.1 mmol) at 0 °C. The mixture was stirred for 1 h at 0 °C. After addition of water, the mixure was stirred for 10 min at rt, and then extracted with CH_2Cl_2 (100 mL x 3). The extracts were washed with saturated aq. NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (see below) to afford spirocyclohexadienylisoxazolines (**1a**,**b**).

The oxidation of **1b** was carried out in CH_2Cl_2, due to its insolubility for MeCN.

***N*-3-[2,6-Dibromo-4-(*N'*-*tert*-butoxycarbonyl-2-aminoethyl)phenoxy]propyl-7,9-dibromo-8-methoxy-1-oxa-6-oxo-2-azaspiro[4.5]deca-2,7,9-triene-3-carboxamide (1a)**: 61% [after column chromatography ($CHCl_3$)]; mp 170–172 °C (decomp); IR (KBr) 3350, 3300, 1690, 1660, 1550 cm^{-1}; ^1H NMR (100 MHz) δ 1.44 (9H, s), 2.10 (2H, quin, *J* 6 Hz), 2.71 (2H, t, *J* 7 Hz), 3.32 (2H, q, *J* 7 Hz), 3.33 (1H, d, *J* 18 Hz), 3.64 (1H, d, *J* 18 Hz), 3.70 (2H, q, *J* 7 Hz), 4.07 (2H, t, *J* 6 Hz), 4.16 (3H, s), 4.54 (1H, br), 6.77 (1H, s), 7.12 (1H, br), 7.32 (2H, s); MS (SIMS) *m/z* 820 (M^++8+H), 818 (M^++6+H), 816 (M^++4+H), 814 (M^++2+H), 812 (M^++H); HRMS (FAB+) calcd for $C_{26}H_{30}O_7N_3{}^{81}Br_4$ 819.8736, found 819.8724; calcd for $C_{26}H_{30}O_7N_3{}^{81}Br_3{}^{79}Br$ 817.8756, found 817.8798; calcd for $C_{26}H_{30}O_7N_3{}^{81}Br_2{}^{79}Br_2$ 815.8777, found 815.8809; calcd for

$C_{26}H_{30}O_7N_3{}^{81}Br^{79}Br_3$ 813.8797, found 813.8836; calcd for $C_{26}H_{30}O_7N_3{}^{79}Br_4$ 811.8817, found 811.8802.

***N*-3-[2,6-Dibromo-4-(*N*'-9-fluorenylmethoxycarbonyl-2-aminoethyl)phenoxy]propyl-7,9-dibromo-8-methoxy-1-oxa-6-oxo-2-azaspiro[4.5]deca-2,7,9-triene-3-carboxamide (1b)**: 53% [after column chromatography ($CHCl_3$)]; mp 135 °C (decomp); IR (KBr) 3420, 3350, 1690, 1610 cm^{-1}; ^1H NMR (100 MHz) δ 2.09 (2H, quin, *J* 6 Hz), 2.70 (2H, br), 3.32 (1H, d, *J* 18 Hz), 3.38 (2H, br), 3.63 (1H, d, *J* 18 Hz), 3.69 (2H, q, *J* 6 Hz), 4.05 (2H, t, *J* 6 Hz), 4.15 (3H, s), 4.20-4.50 (3H, m), 4.82 (1H, br), 6.74 (1H, s), 6.92-7.80 (11H, m); MS (SIMS) *m/z* 942 (M^++8+H), 940 (M^++6+H), 938 (M^++4+H), 936 (M^++2+H), 934 (M^++H); HRMS (FAB+) calcd for $C_{36}H_{32}O_7N_3{}^{81}Br_3{}^{79}Br$ 939.8913, found 939.8967; calcd for $C_{36}H_{32}O_7N_3{}^{81}Br_2{}^{79}Br_2$ 937.8932, found 937.8901; calcd for $C_{36}H_{32}O_7N_3{}^{81}Br^{79}Br_3$ 935.8954, found 935.8970; calcd for $C_{36}H_{32}O_7N_3{}^{79}Br_4$ 933.8974, found 933.8977.

7,9-Dibromo-8-methoxy-1-oxa-6-oxo-2-azaspiro[4.5]deca-2,7,9-triene-3-carboxylic acid (6)

To a solution of cyclohexadienonespiroisoxazoline[3a,b] (**12**, 300 mg, 0.69 mmol) in CH_2Cl_2 (3 mL) was added TFA (3 mL) at 0 °C. The mixture was stirred for 1 h at rt. The solvent was removed under reduced pressure, and the crude product was crystallized from Et_2O to afford **6** (216 mg, 83%) as white crystals, mp 175–177 °C; IR (KBr) 3200–2350, 1720, 1690, 1620 cm^{-1}; ^1H NMR (100 MHz, acetone-d_6) δ 3.58 (2H, s), 4.14 (3H, s), 7.15 (1H, s); MS (SIMS) *m/z* 384 (M^++4+H), 382 (M^++2+H), 380 (M^++H); HRMS (FAB+) calcd for $C_{10}H_8O_5N^{81}Br_2$ 383.8728, found 383.8703; calcd for $C_{10}H_8O_5N^{81}Br^{79}Br$ 381.8749, found 381.8762; calcd for $C_{10}H_8O_5N_3{}^{79}Br_2$ 379.8769, found 379.8793.

Synthesis of *N*-(3-methoxypropyl)-7,9-dibromo-8-methoxy-1-oxa-6-oxo-2-azaspiro-[4.5]deca-2,7,9-triene-3-carboxamide (1c) *via* spirocyclohexadienylisoxazoline-acid (6)

To a solution of spirocyclohexadienylisoxazoline-acid (**3**, 50 mg, 0.131 mmol) in CH_2Cl_2 (0.5 mL) containing 3-methoxypropylamine (11.7 mg, 0.131 mmol) was added a solution of DCC (27 mg, 0.131 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. The mixture was stirred at rt for 2 h. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography ($CHCl_3$) to give **1c** (28 mg, 47%). ^1H NMR and MS spectra were identical with those reported in the literature.[3b]

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