Pergamon

Tetrahedron, Vol. 52, No. 47, pp. 14713-14722, 1996

0040-4020/96 $15.00 + 0.00

PII: S0040-4020(96)00921-0

Oxidative Cyclisation of *o*-Phenolic Oxime-Acid Derivatives using Phenyliodonium Diacetate: Synthesis of Spiroisoxazoline Derivatives

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Abstract : An efficient formation of spiroisoxazoline ring system by intramolecular oxidative cyclisation of *o*-phenolic oxime-esters and oxime-amides using phenyliodonium diacetate (PIDA) is described. The intramolecular oxidative cyclisation of various *o*-phenolic oxime-acid derivatives in acetonitrile at 0 °C proceeded smoothly to afford spiroisoxazolines in good yields. Synthesis of *o*-phenolic oxime-esters and oxime-amides was also described. Copyright © 1996 Elsevier Science Ltd

The oxidative cyclisation of *o*-phenolic oxime-acid derivatives has been well known as useful method in the synthesis[1] of bromotyrosine derived marine metabolites having a spirocyclohexadienylisoxazoline moiety[2] (Figure 1). The importance of this oxidation has prompted many searches for oxidising agents to effect the formation of spiroisoxazoline ring system.[1, 3–6] The successful examples of the oxidative cyclisation of *p*- or *o*-phenolic oxime-acid derivatives were employed by manganese(III) tris(acetylacetonate),[3] 2,4,4,6-tetrabromocyclohexa-2,5-dienone (TBCO),[1a, 4] thallium(III) nitrate,[5, 6] thallium(III) trifluoroacetate,[1b, 5] and anodic oxidation.[6] Despite the success of these approaches to the formation of spiroisoxazolines, much remains to be improved in terms of generality toward substrate. Recently, McKillop et al.[7] have reported that the oxidation of *p*-phenolic oxime derivatives with phenyliodonium bis(trifluoroacetate) (PIFA) gives the corresponding spirocyclohexa-2,5-dienones. Independently,[8] we have reported the first results concerning intramolecular oxidative cyclisation of *o*-phenolic oxime-acid derivatives using hypervalent iodine compounds. Hypervalent iodine compounds were found to be very efficient oxidising agents for the oxidation of a variety of phenolic oximes to give corresponding spiroisoxazolines under mild conditions as shown in Scheme 1. By employing commercially cheap phenyliodonium diacetate (PIDA), the oxidative cyclisation of *o*-phenolic oxime-esters or oxime-amides gave desired spiroisoxazolines in 45–76% yields. In this paper, we describe the details of an efficient formation of spiroisoxazoline ring system by the oxidative cyclisation of *o*-phenolic oxime-acid derivatives using PIDA.

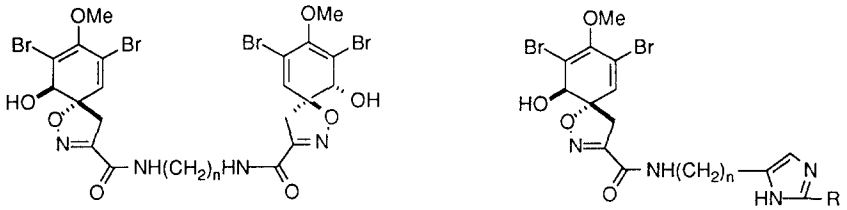
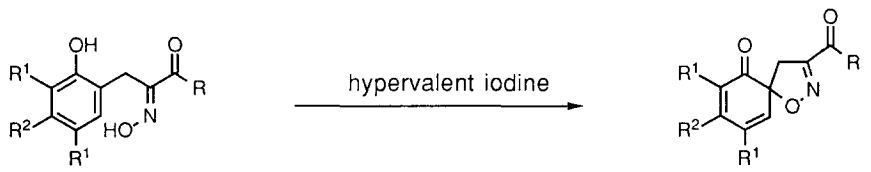


Figure 1



Scheme 1

In order to explore the ability of intramolecular oxidative cyclisation with PIDA, a series of phenolic oxime-acid derivatives **1a–f** (Figure 2) were prepared from azlactones **3i–k** as shown in Scheme 2.

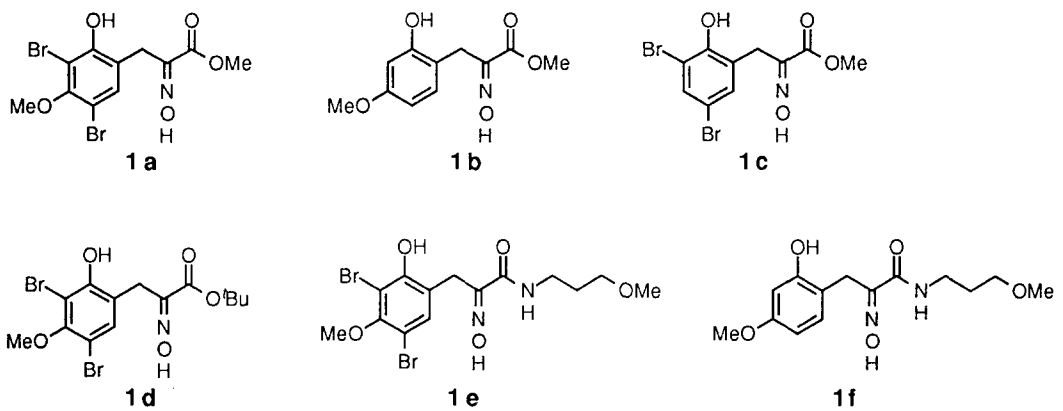
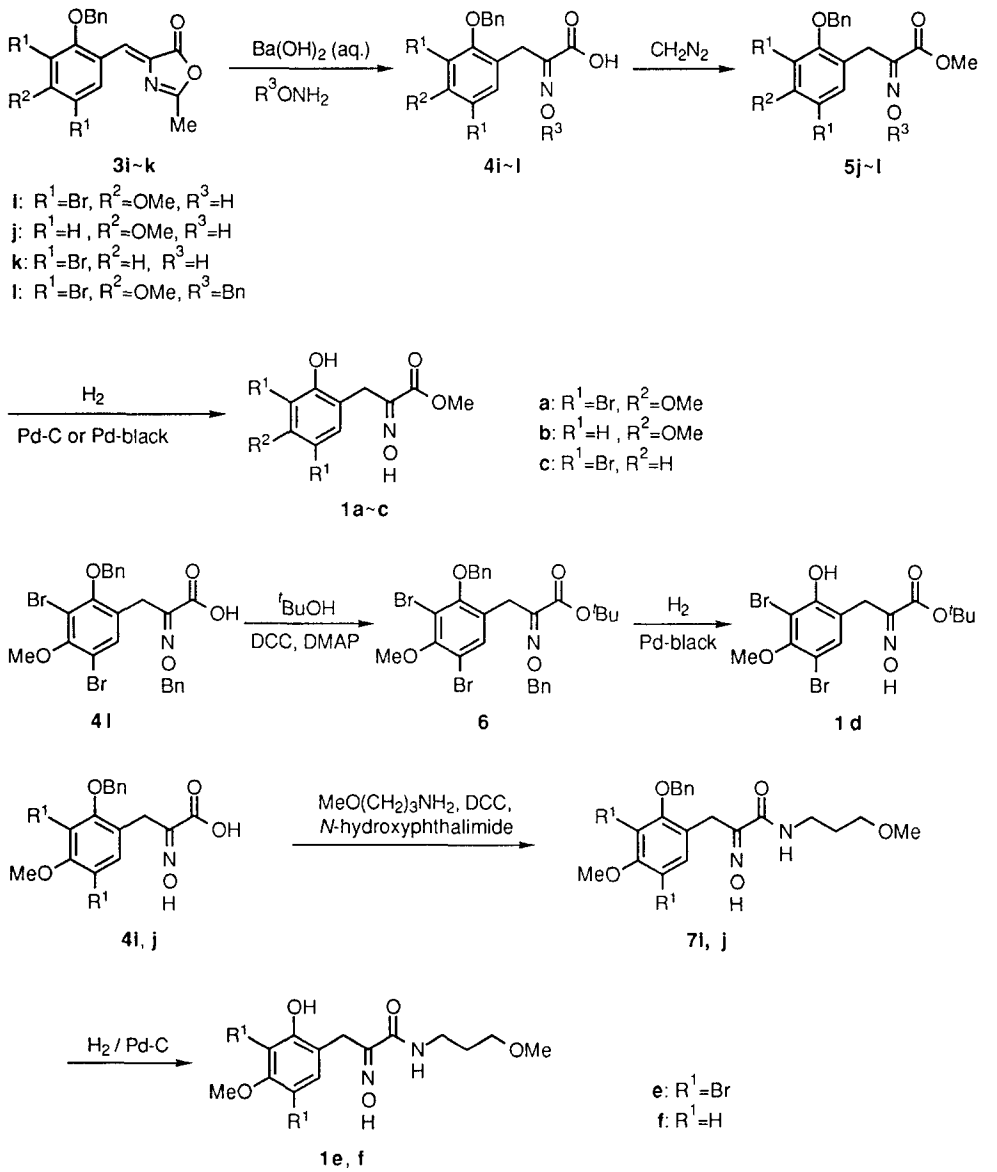


Figure 2

Azlactones **3i-k** were successfully hydrolyzed with $Ba(OH)_2$ in the presence of hydroxylamine or *O*-benzylhydroxylamine in aqueous dioxane to give oxime-acids **4i–k** or *O*-benzyloxime-acid **4l**. Preparation of *o*-phenolic oxime-methyl ester **1a**[1b] is as follows. Methylation of **4l** with CH_2N_2 provided a methyl ester **5l**. Hydrogenolysis of **5l** over Pd-black afforded **1a**. Phenolic oxime-methyl esters **1b, c** could be prepared from oxime-acids **4j, k** without protection of the oxime function. Methyl esters **5j, k** obtained by the similar way as noted for **5l** were hydrogenated over 10% Pd-C to afford **1b, c**. Phenolic oxime-*tert*-butyl ester **1d** was prepared from *O*-benzyl oxime-acid **4l** by esterification with *tert*-BuOH using DCC and catalytic amount of DMAP, followed by catalytic hydrogenolysis. Phenolic oxime-amides **1e, f** were obtained by amidation of oxime-acids **4i, j** with 3-methoxypropylamine using DCC in the presence of *N*-hydroxyphthalimide,[9] followed

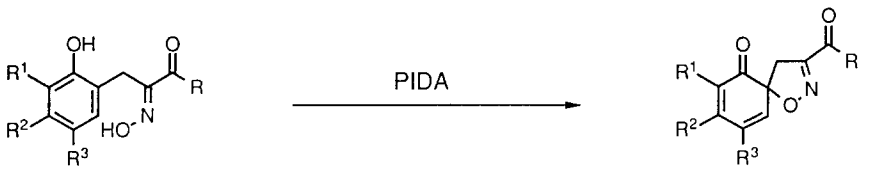
by catalytic hydrogenolysis. These phenolic oxime-acid derivatives **1a–f** were found to be single isomer by the ^{1}H NMR (100 MHz) spectra, although the configuration due to oxime was obscure.[10]



Scheme 2

The reaction of *o*-phenolic oxime-ester **1a**, in which the pattern of substituents on the aromatic ring is identical with that in natural products (bromotyrosine derived marine metabolites, *e.g.* Figure 1),[1,2] with PIDA in acetonitrile at 0 °C proceeded smoothly to afford spiroisoxazoline **2a** in 76% yield. The spectral data were identical with those reported in the literature.[1b] This finding prompted us to apply this method to the synthesis

of other spiroisoxazolines. As shown in Table 1, it was found that the intramolecular oxidative cyclisation of various phenolic oxime-acid derivatives with PIDA gave desired spiroisoxazolines. *tert*-Butyl ester **1d**, which is sensitive to acidic oxidation condition (*e.g.* thallium(III) trifluoroacetate in TFA), also was converted to the corresponding spiroisoxazoline **2d** in 72% yield. As for oxime-amides, the oxidation with 1.1 equiv. of PIDA did not proceed completely. However, when 2.2 equiv. of PIDA was used, this oxidation proceeded smoothly to afford corresponding spiroisoxazolines **2e, f**.



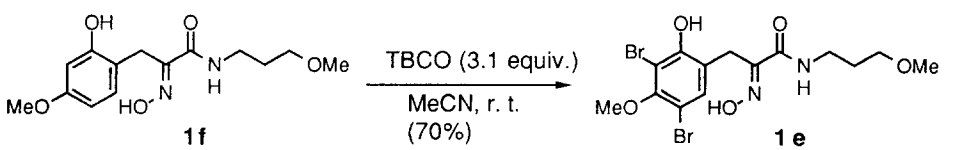
1 **2**

Table 1 Intramolecular oxidative cyclisation of **1a~f** using PIDA[a]

Run	Oxime	R^1	R^2	R^3	R	Product	PIDA (eq.)	Yield (%)[b]
1	**1a**	Br	OMe	Br	OMe	**2a**	1.1	76
2	**1b**	H	OMe	H	OMe	**2b**	1.1	40
3	**1c**	Br	H	Br	OMe	**2c**[c]	1.1	46[d]
4	**1d**	Br	OMe	Br	O^{t}Bu	**2d**	1.1	72
5	**1e**	Br	OMe	Br	$NH(CH_2)_3OMe$	**2e**	2.2	64
6	**1f**	H	OMe	H	$NH(CH_2)_3OMe$	**2f**	2.2	45

[a] Reaction was carried out in acetonitrile at 0 °C. [b] Isolated yield. [c] Unstable product. [d] The yield of a product obtained by $NaBH_4$ reduction.

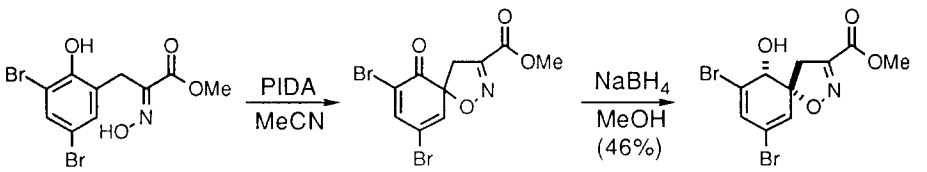
It has been reported that TBCO was not only a brominating agent but also an effective oxidising agent for the cyclisation of *o*-phenolic oxime-amide.[1a] However, as shown in Scheme 3, the reaction of *o*-phenolic oxime-amide **1f** with TBCO (3.1 equiv.) in MeCN at room temperature gave brominated non-cyclized product **1e** in 70% yield (cyclisation product **2f** was not detected under this condition). This finding shows that bromination on aromatic ring occurred prior to cyclisation, and therefore, the spiroisoxazoline having original substitution pattern on aromatic ring could be hardly obtained in the reaction of the phenolic oxime unsubstituted at *o*- or *p*-position to the hydroxyl group such as **1f** with this reagent. On the other hand, oxidative cyclisation of **1f** with PIDA took place efficiently to provide desired spiroisoxazoline-amide **2f**. Thus, it should be noted that this oxidation can be applied to various phenolic oxime derivatives which have unnatural substitution pattern on aromatic ring (run 2, 3 and 6 in Table 1).



1f **1e**

Scheme 3

The spiroisoxazoline-ester **2c** obtained in this oxidation was not stable enough to be isolated by chromatography (silica gel). Therefore, the crude product was converted into dienol **8** in 46% overall yield from **1c** by $NaBH_4$ reduction (Scheme 4).[11] It has been reported that the geminal protons at C4-position of related compounds having a *cis* vicinal relationship between a hydroxyl group and an oxygen atom in the spiroisoxazoline are observed as the broad signals in their ^1H NMR (90 MHz) spectra, while those of corresponding *trans* compounds appear as two doublets because of an anisotropic effect of the hydroxyl group.[1b] The ^1H NMR (100 MHz) spectrum of **8** showed a broad singlet due to the geminal protons at δ 3.44. Thus, stereochemistry of **8** was deduced to be the *5R*,6R** relative configuration.



1c **2c** **8**

Scheme 4

The present method provides an efficient approach to synthesis of spiroisoxazoline, which should be useful as a synthon for synthesis of bromotyrosine derived marine metabolites.

EXPERIMENTAL SECTION

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 spectrometer and ^1H NMR spectra were recorded with a HITACHI R-24B(60MHz), a JEOL FX-100 (100 MHz) or a JEOL EX-270 (270 MHz) spectrometer in $CDCl_3$ solution using tetramethylsilane as an internal standard, unless otherwise noted. Mass spectra were measured on a Hitachi M-80 or a JEOL JMS D-300 spectrometer. Column chromatography was performed on silica gel.

Preparation of azlactones 3i–k

Azlactones **3i–k** were prepared from corresponding aldehydes and acetylglycine by the conventional method.[10]

4-(2-Benzyloxy-3,5-dibromo-4-methoxybenzylidene)-2-methyloxazol-5(4*H*)-one (3i):[12] mp 174-176 °C (acetone); ^1H NMR (60 MHz) δ 2.48 (3H, s), 4.10 (3H, s), 5.15 (2H, s), 7.15-7.75 (7H, m); IR (KBr) 1810, 1780, 1670 cm^{-1}; MS *m/z* 483 (M^++4), 481 (M^++2), 479 (M^+); HRMS *m/z* calcd for $C_{19}H_{15}{}^{81}Br_2NO_4$ 482.9327, found 482.9297; calcd for $C_{19}H_{15}{}^{79}Br^{81}BrNO_4$ 480.9348, found 480.9339; calcd for $C_{19}H_{15}{}^{79}Br_2NO_4$ 478.9368, found 478.9341.

4-(2-Benzyloxy-4-methoxybenzylidene)-2-methyloxazol-5(4*H*)-one (3j): mp 153-155 °C (acetone); ^1H NMR (270 MHz) δ 2.35 (3H, s), 3.81 (3H, s), 5.12 (2H, s), 6.46 (1H, d, *J* 2.3Hz), 6.58 (1H, dd, *J* 2.3Hz, 8.8Hz), 7.34-7.43 (5H, m), 7.72 (1H, s), 8.68 (1H, d, *J* 8.8Hz); IR (KBr) 1800, 1780, 1660 cm^{-1}; MS *m/z* 323 (M^+); HRMS *m/z* calcd for $C_{19}H_{17}NO_4$ 323.1157, found 323.1163.

4-(2-Benzyloxy-3,5-dibromobenzylidene)-2-methyloxazol-5(4*H*)-one (3k): mp 200-202 °C (acetone); ^1H NMR (270 MHz) δ 2.40 (3H, s), 4.99 (2H, s), 7.25 (1H, d, *J* 2.3Hz), 7.35-7.46 (5H, m),

7.79 (1H, d, *J* 2.3Hz), 8.70 (1H, d, *J* 2.3Hz); IR (KBr) 1810, 1770, 1660 cm^{-1}; MS *m/z* 453 (M^++4), 451 (M^++2), 449 (M^+); HRMS *m/z* calcd for $C_{18}H_{13}{}^{81}Br_2NO_3$ 452.9221, found 452.9219; calcd for $C_{18}H_{13}{}^{79}Br^{81}BrNO_3$ 450.9241, found 450.9219; calcd for $C_{18}H_{13}{}^{79}Br_2NO_3$ 448.9262, found 448.9281.

Preparation of oxime-acids 4i–k and *O*-benzyloxime-acid 4l

A mixture of azlactone **3** (1 mmol) and $Ba(OH)_2$ (7 mmol) in 50% dioxane-H_2O (14 ml) was heated at 60 °C for 1 h. Hydroxylamine hydrochloride (3.2 mmol) or *O*-benzylhydroxylamine hydrochloride (3.2 mmol) was added at 60 °C, and the whole was stirred vigorously at the same temperature for 13 h. The reaction mixture was cooled to room temperature, and was acidified with 10% HCl at 0 °C. The whole was extracted with AcOEt (50 ml x 3). The extracts were washed with saturated aq. NaCl and then dried over $MgSO_4$. Removal of solvent gave oxime-acid **4**, which was used in the next step without further purification.

2-Hydroxyimino-3-(2-benzyloxy-3,5-dibromo-4-methoxyphenyl)propionic acid (4i): 82 %; amorphous mass; ^1H NMR (60 MHz) δ 3.82 (3H, s), 3.99 (2H, s), 5.05 (2H, s), 6.70 (1H, br), 7.20-7.70 (6H, m); IR ($CHCl_3$) 3500-2500, 1700, 1610 cm^{-1}; MS *m/z* 413 (M^++4), 411 (M^++2), 409 (M^+).

2-Hydroxyimino-3-(2-benzyloxy-4-methoxyphenyl)propionic acid (4j): 89%; mp 168-170 °C (petroleum ether); ^1H NMR (60 MHz, acetone-d_6) δ 3.69 (3H, s), 3.89 (2H, s), 5.10 (2H, s), 6.20-7.70 (8H, m); IR (KBr) 3400-2600, 1690, 1610 cm^{-1}; MS *m/z* 315 (M^+).

2-Hydroxyimino-3-(2-benzyloxy-3,5-dibromophenyl)propionic acid (4k): 75%; mp 163-165 °C (petroleum ether); ^1H NMR (270 MHz, acetone-d_6) δ 4.05 (2H, s), 5.10 (2H, s), 7.26 (1H, d, *J* 2.3Hz), 7.32-7.44 (3H, m), 7.56-7.63 (2H, m), 7.69 (1H, d, *J* 2.3Hz); IR (KBr) 3500-2500, 1715 cm^{-1}; MS *m/z* 445 (M^++4), 443 (M^++2), 441 (M^+).

2-Benzyloxyimino-3-(2-benzyloxy-3,5-dibromo-4-methoxyphenyl)propionic acid (4l): 74%; mp 161-162 °C (hexane-AcOEt) (lit.[12] 161.5-162.5 °C); ^1H NMR (100 MHz, acetone-*d6*) δ 3.85 (3H, s), 3.96 (2H, s), 5.01 (2H, s), 5.24 (2H, s), 7.10-7.62 (11H, m); IR ($CHCl_3$) 3600-2500, 1730 cm^{-1}; MS *m/z* 565 (M^++4), 563 (M^++2), 561 (M^+).

Preparation of oxime-methyl esters 5j, k and *O*-benzyloxime-methyl ester 5l

To a solution of acid **4j**, **k** or **l** (11 mmol) in Et_2O (20 ml)-MeOH (20 ml) was added a solution of CH_2N_2 (excess) in Et_2O. The whole was stirred at 0 °C for 10 min. The reaction was quenched with AcOH. After basification with $NaHCO_3$, the mixture 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 recrystallization to give the corresponding methyl ester **5j**, **k** or **l**.

Methyl 2-hydroxyimino-3-(2-benzyloxy-4-methoxyphenyl)propionate (5j): 90%; mp 114-116 °C (hexane-AcOEt); ^1H NMR (100 MHz) δ 3.63 (3H, s), 3.74 (3H, s), 3.93 (2H, s), 5.01 (2H, s), 6.28-6.50 (2H, m), 7.02 (1H, d, *J* 8Hz), 7.12-7.48 (5H, m), 9.20 (1H, br); IR ($CHCl_3$) 3580, 3300, 1740, 1620 cm^{-1}; MS *m/z* 329 (M^+). Anal. Calcd for $C_{18}H_{19}NO_5$: C, 65.64; H, 5.82; N, 4.25. Found: C, 65.63; H, 5.81; N, 4.10.

Methyl 2-hydroxyimino-3-(2-benzyloxy-3,5-dibromophenyl)propionate (5k): 77%; mp 185-187 °C (MeOH-$CHCl_3$); ^1H NMR (100 MHz) δ 3.68 (3H, s), 4.03 (2H, s), 5.08 (2H, s), 7.20-7.70 (7H, m); IR ($CHCl_3$) 3570, 1730, 1460 cm^{-1}; MS *m/z* 459 (M^++4), 457 (M^++2), 455 (M^+). Anal. Calcd for $C_{17}H_{15}NO_4Br_2$: C, 44.71; H, 3.15; N, 2.77. Found: C, 44.67; H, 3.31; N, 3.06.

Methyl 2-benzyloxyimino-3-(2-benzyloxy-3,5-dibromo-4-methoxyphenyl)propionate (5l):[1b] 97%; mp 97-99 °C; ^{1}H NMR (100 MHz) δ 3.69 (3H, s), 3.85 (3H, s), 3.88 (2H, s), 4.93 (2H, s), 5.21 (2H, s), 7.08-7.52 (11H, m); IR ($CHCl_3$) 1740, 1620 cm^{-1}; MS *m/z* 579 (M^++4), 577 (M^++2), 575 (M^+); HRMS *m/z* calcd for $C_{25}H_{23}{}^{79}Br_2NO_5$ 574.9943, found 574.9937.

Preparation of *o*-phenolic oxime-methyl esters 1a–c

A solution of benzyl ether **5l** (0.19 mmol) in AcOH (2 ml)-dioxane(2 ml) was hydrogenated over Pd-black (30 mg) under H_2 (1 atm) at room temperature for 48 h. After filtration, the filtrate was basified with $NaHCO_3$, and then extracted with AcOEt (50 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 ($CHCl_3$) to give *o*-phenolic oxime-methyl ester **1a**.

In a way similar to that noted for **1a**, benzyl ether **5j** or **k** (11 mmol) in AcOH (50 ml)-dioxane(50 ml) was hydrogenated over 10% Pd-C (300 mg) under H_2 (1 atm) at room temperature for 3 h. The crude product was purified by column chromatography ($CHCl_3$:MeOH=50:1) to give *o*-phenolic oxime-methyl ester **1b** or **c**.

Methyl 2-hydroxyimino-3-(2-hydroxy-3,5-dibromo-4-methoxyphenyl)propionate (1a): 67%; mp 150-152 °C (hexane-AcOEt) (lit.[1b] 148-149 °C); ^{1}H NMR (100 MHz) δ 3.84 (3H, s), 3.89 (3H, s), 3.91 (2H, s), 7.38 (1H, s); IR ($CHCl_3$) 3650-3000, 1750, 1490 cm^{-1}; MS *m/z* 399 (M^++4), 397 (M^++2), 395 (M^+).

Methyl 2-hydroxyimino-3-(2-hydroxy-4-methoxyphenyl)propionate (1b): 78%; mp 118-120 °C (hexane-AcOEt); ^{1}H NMR (100 MHz, acetone-d_6) δ 3.68 (3H, s), 3.74 (3H, s), 3.88 (2H, s), 6.32 (1H, dd, *J* 2, 9Hz), 6.38 (1H, d, *J* 2Hz), 6.97 (1H, d, *J* 9Hz); IR (KBr) 3410, 3200, 1720, 1630, 1590 cm^{-1}; MS *m/z* 239 (M^+). Anal. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.86. Found: C, 55.09; H, 5.40; N, 5.69.

Methyl 2-hydroxyimino-3-(2-hydroxy-3,5-dibromophenyl)propionate (1c): 36% (recovered benzyl ether **5k**,: 58%); mp 204-205 °C (hexane-AcOEt); ^{1}H NMR (100 MHz, acetone-d_6) δ 3.78 (3H, s), 3.96 (2H, s), 7.26, (1H, d, *J* 2Hz), 7.53 (1H, d, *J* 2Hz); IR (KBr) 3500, 3450-3100, 1740, 1480 cm^{-1}; MS *m/z* 369 (M^++4), 367 (M^++2), 365 (M^+). Anal. Calcd for $C_{10}H_9Br_2NO_4$: C, 32.73; H, 2.47; N, 3.82. Found: C, 32.82; H, 2.50; N, 3.64.

***tert*-Butyl 2-benzyloxyimino-3-(2-benzyloxy-3,5-dibromo-4-methoxyphenyl)propionate (6)**

To a suspension of *O*-benzyloxime-acid **4l** (2.0 g, 3.55 mmol) in CH_2Cl_2 (12 ml) containing ^{t}BuOH (315 mg, 4.26 mmol) and DMAP (45 mg, 0.36 mmol) was added a solution of DCC (804 mg, 3.91 mmol) in CH_2Cl_2 (1 ml) at 0 °C. The whole was stirred at 0 °C for 1 h, and then stirred at room temperature for 17 h. The reaction mixture was cooled to 0 °C, and then filtered. The filtrate was diluted with ether and washed with 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 ($CHCl_3$) to give **6** (2.27 g, 100%) as an oil; ^{1}H NMR (100 MHz) δ 1.42 (9H, s), 3.84 (2H, s), 3.87 (3H, s), 4.91 (2H, s), 5.21 (2H, s), 7.12-7.54 (11H, m); IR ($CHCl_3$) 1710, 1600 cm^{-1}; MS *m/z* 621 (M^++4), 619 (M^++2), 617 (M^+); HRMS *m/z* calcd for $C_{28}H_{29}{}^{81}Br^{79}BrNO_5$ 619.0391, found 619.0374; $C_{28}H_{29}{}^{79}Br_2NO_5$ 617.0411, found 617.0381.

***tert*-Butyl 2-hydroxyimino-3-(2-hydroxy-3,5-dibromo-4-methoxyphenyl)propionate (1d)**

A solution of benzyl ether **6** (2.2 g, 3.55 mmol) in AcOH (20 ml)-dioxane (20 ml) was hydrogenated over Pd-black (440 mg) under H_2 (1 atm) at room temperature for 7 h. After filtration, the filtrate was basified with $NaHCO_3$, and then extracted with AcOEt (200 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 ($CHCl_3$:MeOH=100:1) to give *o*-phenolic oxime-*tert*-butyl ester **1d** (1.33 g, 85%); mp 157-159 °C (dec.) ($CHCl_3$-MeOH); ^1H NMR (100 MHz) δ 1.47 (9H, s), 3.80 (2H, s), 3.84 (3H, s), 7.36 (1H, s); IR (KBr) 3700-3300, 1690, 1550, 1470 cm^{-1}; MS *m/z* 441 (M^++4), 439 (M^++2), 437 (M^+). Anal. Calcd for $C_{14}H_{17}Br_2NO_5 \cdot 1/3\ H_2O$: C, 37.78; H, 4.00; N, 3.15. Found: C, 37.56; H, 3.71; N, 3.01.

Preparation of oxime-amides 7i, j

To a suspension of oxime-acid **4i** or **j** (2.3 mmol) in dioxane (20 ml) containing *N*-hydroxyphthalimide (2.53 mmol) was added a solution of DCC (2.3 mmol) in dioxane (5 ml) at 0 °C. The whole was stirred at room temperature for 5 min. A solution of 3-methoxypropylamine (2.3 mmol) in dioxane (5 ml) was added, and the whole was stirred at room temperature for 2 h. The reaction mixture was cooled to 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 or recrystallization (see below) to give oxime-amide **7i** or **j**.

***N*-(3-Methoxypropyl)-3-(2-benzyloxy-3,5-dibromo-4-methoxyphenyl)-2-hydroxyiminopropionamide (7i)**: 78% (elution with $CHCl_3$:MeOH=100:1); mp 80-83 °C; ^1H NMR (100MHz) δ 1.73 (2H, quin, *J* 6Hz), 3.20-3.48 (4H, m), 3.30 (3H, s), 3.84 (3H, s), 3.95 (2H, s), 5.05 (2H, s), 7.02-7.62 (7H, m), 9.39 (1H, br); IR ($CHCl_3$) 3500-3150, 1670, 1640 cm^{-1}; MS *m/z* 546 (M^++4), 544 (M^++2), 542 (M^+); HRMS *m/z* calcd for $C_{21}H_{24}{}^{81}Br_2N_2O_5$ 546.0011, found 545.9995; calcd for $C_{21}H_{24}{}^{81}Br^{79}BrN_2O_5$ 544.0031, found 543.9989; calcd for $C_{21}H_{24}{}^{79}Br_2N_2O_5$ 542.0051, found 542.0045.

***N*-(3-Methoxypropyl)-3-(2-benzyloxy-4-methoxyphenyl)-2-hydroxyiminopropionamide (7j)**: 84%; mp 90-92 °C (hexane-AcOEt); ^1H NMR (100MHz) δ 1.72 (2H, quin, *J* 6Hz), 3.20-3.48 (4H, m), 3.28 (3H, s), 3.71 (3H, s), 3.93 (2H, s), 5.03 (2H, s), 6.36 (1H, dd, *J* 3, 8Hz), 6.44 (1H, d, *J* 3Hz), 6.95 (1H, br), 6.99 (1H, d, *J* 8Hz), 7.20-7.48 (5H, m); IR (KBr) 3340, 1660, 1640, 1620 cm^{-1}; MS *m/z* 386 (M^+). Anal. Calcd for $C_{21}H_{26}N_2O_5$: C, 65.27; H, 6.78; N, 7.25. Found: C, 65.05; H, 6.65; N, 7.09.

Preparation of *o*-phenolic oxime-amides 1e, f

A solution of benzyl ether **7i** or **j** (1.71 mmol) in AcOH (10 ml)-dioxane (10 ml) was hydrogenated over 10% Pd-C (30 mg) under H_2 (1 atm) at room temperature for 3 h. After filtration, the filtrate was basified with saturated aq. $NaHCO_3$, 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 (see below) to give *o*-phenolic oxime-amide **1e** or **f**.

***N*-(3-Methoxypropyl)-3-(3,5-dibromo-2-hydroxy-4-methoxyphenyl)-2-hydroxyiminopropionamide (1e)**: 83% (elution with $CHCl_3$:MeOH=100:1); mp 140-142 °C (hexane-AcOEt); ^1H NMR (100 MHz, acetone-d_6) δ 1.80 (2H, quin, *J* 6Hz), 3.25 (3H, s), 3.32-3.52 (4H, m), 3.80 (5H, s), 7.57 (1H, s), 8.06 (1H, br), 11.00 (1H, br), 11.60 (1H, br); IR ($CHCl_3$) 3550-3150, 1660, 1630, 1560 cm^{-1}; MS *m/z*

456 (M^++4), 454 (M^++2), 452 (M^+). Anal. Calcd for $C_{14}H_{18}Br_2N_2O_5 \cdot 1/6\ H_2O$: C, 36.79; H, 4.04; N, 6.13. Found: C, 37.08; H, 3.93; N, 5.85.

***N*-(3-Methoxypropyl)-3-(2-hydroxy-4-methoxyphenyl)-2-hydroxyiminopropionamide (1f)**: 82% (elution with hexane:AcOEt=2:1); mp 110-111 °C (hexane-AcOEt); ^{1}H NMR (100 MHz) δ 1.77 (2H, quin, *J* 6Hz), 3.26 (3H, s), 3.20-3.52 (4H, m), 3.73 (3H, s), 3.78 (2H, s), 6.36 (1H, dd, *J* 2, 8Hz), 6.45 (1H, d, *J* 2Hz), 7.26 (1H, d, *J* 8Hz), 7.42 (1H, br), 9.46 (1H, br); IR ($CHCl_3$) 3350, 1630, 1600, 1520 cm^{-1}; MS *m/z* 296 (M^+). Anal. Calcd for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.88; H, 7.03; N, 9.40.

General procedure for intramolecular oxidative cyclisation of *o*-phenolic oxime-acid derivative 1 using PIDA

To a solution of *o*-phenolic oxime-acid derivative **1** (1 mmol) in MeCN (45 ml) was added PIDA (1.1 mmol for oxime-esters **1a–d**, 2.2 mmol for oxime-amides **1e**, **f**) at 0 °C. The whole was stirred at 0 °C for 1 h. After addition of water, the mixure was stirred for 10 min at room temperature, 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) or crystallization, except **2c**, to afford spirocyclohexadienylisoxazoline **2**.

Due to instability of spirocyclohexadienylisoxazoline **2c** for silica gel, analytically pure sample could not be obtained. Thus, its characterization was carried out by conversion to dienol **8**.

Methyl 7,9-dibromo-8-methoxy-6-oxo-1-oxa-2-azaspiro[4.5]deca-2,7,9-triene-3-carboxylate (2a): 76% (elution with hexane:AcOEt=2:1); mp 102-104 °C (MeOH) (lit.[1b] oil); ^{1}H NMR (100 MHz) δ 3.27 (1H, d, *J* 18Hz), 3.63 (1H, d, *J* 18Hz), 3.89 (3H, s), 4.16 (3H, s), 6.75 (1H, s); IR ($CHCl_3$) 1740, 1690, 1610, 1550 cm^{-1}; MS *m/z* 397 (M^++4), 395 (M^++2), 393 (M^+).

Methyl 8-methoxy-6-oxo-1-oxa-2-azaspiro[4.5]deca-2,7,9-triene-3-carboxylate (2b): 40% (elution with $CHCl_3$:MeOH=100:1); oil; ^{1}H NMR (100 MHz) δ 3.17 (1H, d, *J* 18Hz), 3.57 (1H, d, *J* 18Hz), 3.82 (3H, s), 3.90 (3H, s), 5.44 (1H, d, *J* 2Hz), 6.17 (1H, dd, *J* 2, 10Hz), 6.39 (1H, d, *J* 10Hz); IR ($CHCl_3$) 1735, 1670, 1590 cm^{-1}; MS *m/z* 237 (M^+); HRMS *m/z* calcd for $C_{11}H_{11}NO_5$ 237.0636, found: 237.0633.

***tert*-Butyl 7,9-dibromo-8-methoxy-6-oxo-1-oxa-2-azaspiro[4.5]deca-2,7,9-triene-3-carboxylate (2d)**: 72%; mp 174-176 °C (MeOH); ^{1}H NMR (100 MHz) δ 1.56 (9H, s), 3.23 (1H, d, *J* 18Hz), 3.58 (1H, d, *J* 18Hz), 4.16 (3H, s), 6.76 (1H, s); IR ($CHCl_3$) 1730, 1700, 1620, 1560 cm^{-1}; MS *m/z* 439 (M^++4), 437 (M^++2), 435 (M^+); HRMS *m/z* calcd for $C_{14}H_{15}{}^{81}Br_2NO_5$ 438.9278, found: 438.9295; calcd for $C_{14}H_{15}{}^{81}Br^{79}BrNO_5$ 436.9296, found 436.9277; calcd for $C_{14}H_{15}{}^{79}Br_2NO_5$ 434.9316, found 434.9304. Anal. Calcd for $C_{14}H_{15}Br_2NO_5$: C, 38.47; H, 3.46; N, 3.21. Found: C, 38.55; H, 3.30; N, 2.97.

***N*-(3-Methoxypropyl)-7,9-dibromo-8-methoxy-6-oxo-1-oxa-2-azaspiro[4.5]deca-2,7,9-triene-3-carboxamide (2e)**: 65% (elution with $CHCl_3$); mp 98-100 °C (MeOH); ^{1}H NMR (100MHz) δ 1.82 (2H, quin, *J* 6Hz), 3.30-3.60 (4H, m), 3.32 (1H, d, *J* 18Hz), 3.34 (3H, s), 3.61 (1H, d, *J* 18Hz), 4.16 (3H, s), 6.76 (1H, s), 7.10 (1H, br t); IR ($CHCl_3$) 3300-3450, 1680, 1550 cm^{-1}; MS *m/z* 454 (M^++4), 452 (M^++2), 450 (M^+); HRMS *m/z* calcd for $C_{14}H_{16}{}^{81}Br^{79}BrN_2O_5$ 451.9406, found 451.9429; calcd for $C_{14}H_{16}{}^{79}Br_2N_2O_5$ 449.9425, found 449.9417.

***N*-(3-Methoxypropyl)-8-methoxy-6-oxo-1-oxa-2-azaspiro[4.5]deca-2,7,9-triene-3-carboxamide (2f)**: 45% (elution with $CHCl_3$:MeOH=100:1); oil; ^{1}H NMR (100 MHz) δ 1.82 (2H, quin, *J* 6Hz), 3.23 (1H, d, *J* 18Hz), 3.34 (3H, s), 3.39-3.58 (4H, m), 3.55 (1H, d, *J* 18Hz), 3.80 (3H, s), 5.43

(1H, d, *J* 2Hz), 6.14 (1H, dd, *J* 2, 10Hz), 6.40 (1H, d, *J* 10Hz), 7.10(1H, br); IR ($CHCl_3$) 3450, 1680, 1590 cm^{-1}; MS *m/z* 294 (M^+); HRMS *m/z* calcd for $C_{14}H_{18}N_2O_5$ 294.1214, found: 294.1204.

Reaction of *o*-phenolic oxime-amide 1f with TBCO

To a solution of *o*-phenolic oxime-amide **1f** (100 mg, 0.34 mmol) in MeCN (20 ml) was added a solution of TBCO (429 mg, 1.05 mmol) in MeCN (10 ml) at room temperature. The whole was stirred for 18 h. After addition of water, the mixture was 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 ($CHCl_3$:MeOH=100:1) to afford dibrominated *o*-phenolic oxime-amide **1e** (107.2 mg, 70%). ^1H NMR and mass spectra were identical with those for the product obtained by amidation of **4i**.

Methyl (5*R,6*R**)-7,9-dibromo-6-hydroxy-1-oxa-2-azaspiro[4.5]deca-2,7,9-triene-3-carboxylate (8)**

A solution of crude cyclohexadienonespiroisoxazoline **2c** [obtained from the oxidative cyclisation of **1c** (1 mmol)] and $NaBH_4$ (70 mg, 1.84 mmol) in MeOH (5 ml) was stirred at room temperature for 5 min. After addition of saturated aq. NH_4Cl, the mixture was extracted with CH_2Cl_2 (50 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 (hexane:AcOEt=2:1) to afford **8** (170.4 mg, 46%); mp 130-132 °C; ^1H NMR (100MHz, acetone-d_6) δ 3.44 (2H, s), 3.81(3H, s), 4.62 (1H, dd, *J* 2, 9Hz), 5.12 (1H, d, *J* 9Hz, OH), 6.36-6.52 (2H, m); IR ($CHCl_3$) 3700-3200, 1740, 1610 cm^{-1}; MS *m/z* 369 (M^++4), 367 (M^++2), 365 (M^+); HRMS *m/z* calcd for $C_{10}H_9{}^{81}Br_2NO_4$ 368.8859, found: 368.8878; calcd for $C_{10}H_9{}^{81}Br^{79}BrNO_4$ 366.8879, found 366.8883; calcd for $C_{10}H_9{}^{79}Br_2NO_4$ 364.8898, found 364.8908.

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(*Received in Japan* 30 *August* 1996; *accepted* 4 *October* 1996)