Asymmetric Oxidative Cyclization of *o*-Phenolic Oxime-Esters: First Synthesis of Enantiomerically Enriched Spiroisoxazoline Methyl Esters

Masatoshi Murakata, Masafumi Tamura, and Osamu Hoshino*

Faculty of Pharmaceutical Sciences, Science University of Tokyo, Shinjuku-ku, Tokyo 162, Japan

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A new method for the synthesis of enantiomerically enriched cyclohexadienone spiroisoxazoline (−)-**2a** has been described. Asymmetric intramolecular oxidative cyclization of the *o*-phenolic oxime-ester **1c** using a novel optically active tertiary alcohol (−)-**3** as a chiral auxiliary proceeded smoothly to afford cyclohexadienone spiroisoxazoline **2c** in 83% yield. Opitcally active tertiary alcohol (−)-**3** was synthesizied from racemic (1*S**,8*R**,9*R**,10*R**)-8-phenyl-1-decalol (**4**) by optical resolution. Removal of the chiral auxiliary in **2c** with CF_3COOH followed by methylation gave methyl ester (−)-**2a** in 74% ee (71% chemical yield) having *S*-configuration. The absolute configuration of **2a** was determined by the synthesis of the marine natural product (+)-aerothionin.

Introduction

The isolation and structure determination of several bromotyrosine-derived natural marine metabolites containing the spirocyclohexadienylisoxazoline moiety[1] have been reported. The oxidative cyclization of *o*-phenolic oxime-acid derivatives serves a powerful method[2] for the construction of the spiroisoxazoline ring system in these natural products. Successful oxidations employ manganese(III) tris(acetylacetonate),[3] 2,4,4,6-tetrabromocyclohexa-2,5-dienone,[2c,d] thallium(III) nitrate,[2e,f] thallium(III) trifluoroacetate [$Tl(OCOCF_3)_3$],[2f,g] and anodic oxidation conditions.[2e] Recently, hypervalent iodine compounds were found to be very efficient agents for the oxidation of a variety of phenolic oximes to give the corresponding spiroisoxazolines under mild conditions.[2h−j]

The racemic syntheses of aerothionin, homoaerothionin, and aerophobin-1, which are isolated from sponges of *Aplysia aerophoba*, *Aplysia fistularis*, and *Verongia thiona*, by the oxidative cyclization of *o*-phenolic oxime-ester **1a** using $Tl(OCOCF_3)_3$ as oxidant have been reported (Scheme 1),[2g,4] showing that spiroisoxazoline methyl ester **2a** is a key compound in the synthesis of these marine natural products. However, asymmetric synthesis of these natural products is not known.[3] Therefore, we planned to develop a method for the preparation of optically active **2a**, which should be useful for the asymmetric synthesis of these compounds.

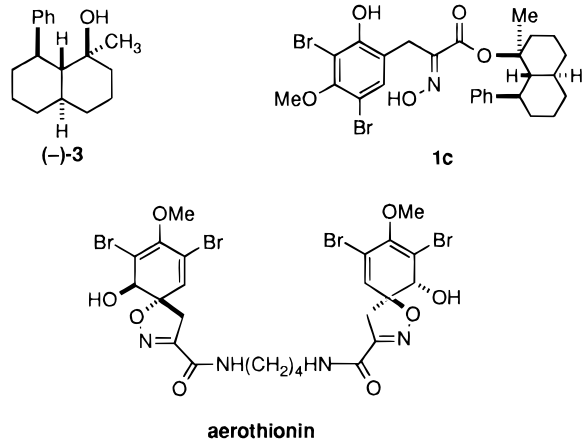
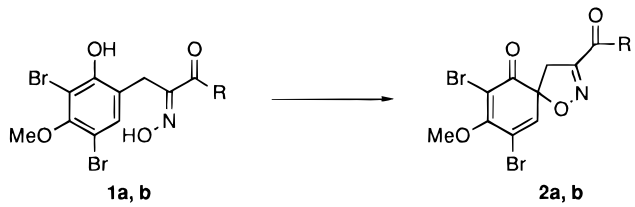


Figure 1.

Scheme 1



Recently, the asymmetric oxidative cyclization of *o*-phenolic oxime-ester **1b** using iodosylbenzene (PhIO) to give an optically active spiroisoxazoline **2b** has been achieved in our laboratory (Scheme 1).[2i] However, the 8-phenylmenthyl ester in **2b** could not be hydrolyzed under various conditions, including treatment of **2b** with K_2CO_3−MeOH (0 °C), aqueous HCl (reflux), TfOH (0 °C),[5]

[⊗] Abstract published in *Advance ACS Abstracts,* June 1, 1997.

(1) (a) Aerothionin, homoaerothionin: Moody, K.; Thomson, R. H.; Fattorusso, E.; Minale, L.; Sodano, G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 18. (b) Aerophobin-1: Cimino, G.; De Rosa, S.; De Stefano, S.; Self, R.; Sodano, G. *Tetrahedron Lett.* **1983**, *24*, 3029. (c) Recent reports on other natural marine products: Gopichand, Y.; Schmitz, F. J. *Tetrahedron Lett.* **1979**, 3921. Nakamura, H.; Wu, H.; Kobayashi, J. *Tetrahedron Lett.* **1985**, *26*, 4517. Morris, S. A.; Andersen, R. J. *Can. J. Chem.* **1989**, *67*, 677. Longeon, A.; Guyot, M.; Vacelet, J. *Experientia* **1990**, *46*, 548. Kernan, M. R.; Cambie, R. C.; Bergquist, P. R. *J. Nat. Prod.* **1990**, *53*, 615. Gunasekera, S. P.; Cross, S. S. *J. Nat. Prod.* **1992**, *55*, 509. König, G. M.; Wright, A. D. *Heterocycles* **1993**, *36*, 1351. Mancini, I.; Guella, G.; Laboute, P.; Debitus, C.; Pietra, F. *J. Chem. Soc., Perkin Trans. 1* **1993**, 3121.

(2) (a) Forrester, A. R.; Thomson, R. H.; Woo, S.-O. *J. Chem. Soc., Chem. Commun.* **1973**, 604. (b) Forrester, A. R.; Thomson, R. H.; Woo, S.-O. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2340. (c) Forrester, A. R.; Thomson, R. H.; Woo, S.-O. *J. Chem. Soc., Perkin Trans. 1* **1975**, 2348. (d) Forrester, A. R.; Thomson, R. H.; Woo, S.-O. *Justus Liebigs Ann. Chem.* **1978**, 66. (e) Noda, H.; Niwa, M.; Yamamura, S. *Tetrahedron Lett.* **1981**, *22*, 3247. (f) Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1982**, *23*, 1281. (g) Nishiyama, S.; Yamamura, S. *Tetrahedron Lett.* **1983**, *24*, 3351; Nishiyama, S.; Yamamura, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3453. (h) Kaçan, M.; Koyuncu, D.; McKillop, A. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1771. (i) Murakata, M.; Yamada, K.; Hoshino, O. *J. Chem. Soc., Chem. Commun.* **1994**, 443. (j) Murakata, M.; Yamada, K.; Hoshino, O. *Tetrahedron* **1996**, *47*, 14713.

(3) As to their absolute configuration, only (+)-aerothionin has been determined by its X ray crystallographic analysis; see, ref 12.

(4) Biomimetic synthesis of aerothionin, see: Okamoto, K. T.; Clardy, J. *Tetrahedron Lett.* **1987**, *28*, 4969.

(5) The cleavage of cyclohexyl esters by TfOH has been reported: Tam, J. P.; Wong, T.-Wai; Riemen, M. W.; Tjoeng, F.-S.; Merrifield, R. B. *Tetrahedron Lett.* **1979**, 4033.

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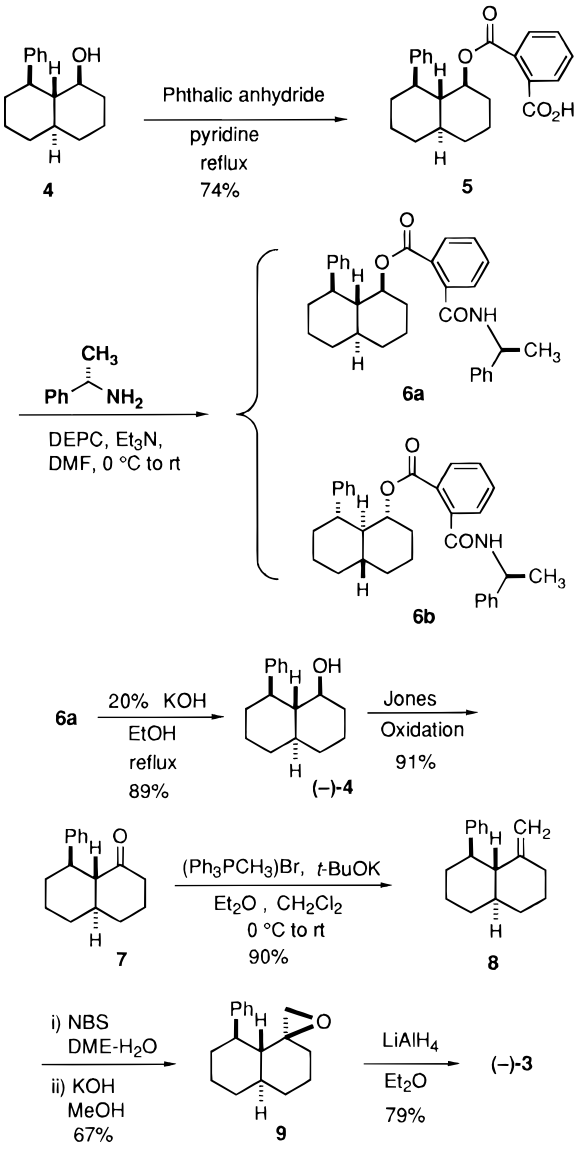
Scheme 2

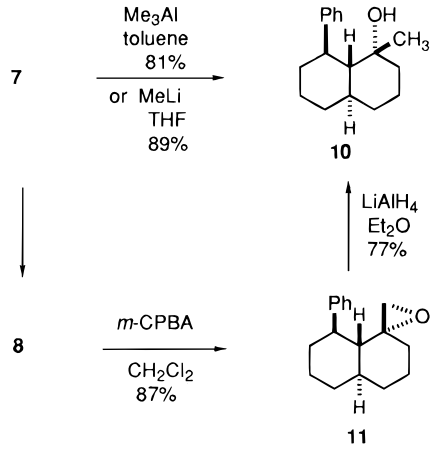


TMSI−MeCN (reflux),[6] or $(Bu_3Sn)_2O$−Et_2O (rt to reflux).[7] All of these reactions gave intractable mixtures, perhaps as a result of the instability of the cyclohexadienone spiroisoxazoline moiety under these vigorous conditions.[8] These results suggest that chiral auxiliaries which require hydrolytic conditions for their cleavage are unsuitable for the synthesis of **2a**. For the purpose of the synthesis of optically active **2a**, it seemed necessary to prepare a new chiral auxiliary. Therefore, we designed the tertiary alcohol (−)-**3** as an auxiliary, because it was expected to be easily removed by acid-assisted elimination under mild conditions. The present paper deals with the preparation of optically active **3** and the synthesis of enantiomerically enriched spiroisoxazoline methyl esters (−)-**2a**.

Results and Discussion

The synthesis of optically active tertiary alcohol (−)-**3** $\{[\alpha]^{31}_D$ −19.8 (*c* 1.32, $CHCl_3$)} is shown in Scheme 2. The key intermediate compound was optically active exo olefin **8**, which was prepared by olefination of enantiomerically pure ketone **7**.

Scheme 3



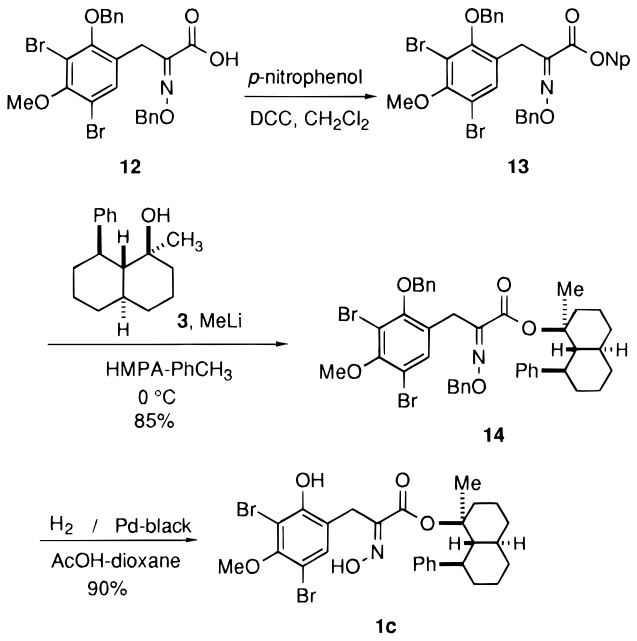
(8*R*,9*R*,10*R*)-8-Phenyl-1-decalone (**7**) $\{[\alpha]^{28}_D$ +41.3 (*c* 0.47, $CHCl_3$)} was obtained in four steps from racemic (1*S**,8*R**,9*R**,10*R**)-8-phenyl-1-decalol (**4**).[9] Treatment of **4** with phthalic anhydride in pyridine under reflux for 4 h gave the ester-acid **5** in 74% yield. Amidation with (*S*)-1-phenylethylamine provided diastereomers **6a** (35%) and **6b** (41%), which were separated by silica gel column chromatography. Hydrolysis of **6a** gave enantiomerically pure (−)-**4** in 89% yield, Jones oxidation of which produced optically active ketone **7** in 91% yield. The absolute configuration of **7** was determined to be 8*R*,9*R*,10*R* by circular dichroism measurement $\{[\theta]_{295}$ +6847 (*c* 0.049, MeOH)}.[10]

With enantiomerically pure ketone **7** in hand, we focussed our attention on the direct introduction of a methyl group into **7**. However, as shown in Scheme 3, methyl group addition to the carbonyl group of **7** by Me_3Al or MeLi gave the undesired axial alcohol **10** predominantly. The stereochemistry of **10** was deduced by an examination of the ^1H NMR spectrum: a peak due to a methyl group appeared at δ 0.46 as a result of the anisotropic effect of the benzene ring at the C8-position. On the other hand, the reaction of **8** (prepared from **7** using the Wittig reaction) with *m*-CPBA gave epoxide **11** in 87% yield, reduction of which again gave the axial alcohol **10**. This result showed the epoxide to be α-oriented. These findings suggest that the π-facial selectivity of an electrophile (*m*-CPBA) to olefin **8** was α, whereas nucleophiles (Me_3Al and MeLi) approach the ketone **7** from the β-face.

On the basis of the results mentioned above, in order to obtain the equatorial alcohol (−)-**3**, the β-epoxide was prepared *via* the bromohydrin obtained from **8** (Scheme 2). The Wittig olefination of **7** provided **8** in 90% yield. Treatment of **8** with *N*-bromosuccimide in DME−H_2O followed by ring closure afforded **9** in 67% yield. As expected, the equatorial alcohol (−)-**3** was obtained in 79% yield by reduction of **9** with $LiAlH_4$. The stereochemistry of the methyl group in (−)-**3** was determined on the basis of the ^1H NMR spectrum, which displayed a methyl singlet at δ 1.22.

(6) Jung, M. E.; Lyster, M. A. *J. Am. Chem. Soc.* **1977**, *99*, 968.
(7) Mata, E. G.; Mascaretti, O. A. *Tetrahedron Lett.* **1988**, *29*, 6893.
(8) For example, decomposition of the cyclohexadienone spiroisoxazoline with pyridine has been reported; see, ref 2d.
(9) The racemic bicyclic secondary alcohol as a chiral auxiliary has been reported: Whitesell, J. K.; Lawrence, R. M.; Chen, H.-H. *J. Org. Chem.* **1986**, *51*, 4779.
(10) *Cf.* For circular dichroism spectrum of (8*S*,9*R*,10*S*)-(+)-8-methyl-*trans*-1-decalone: Hagishita, S.; Kuriyama, K. *J. Chem. Soc., Perkin Trans. 1* **1980**, 950.

Scheme 4

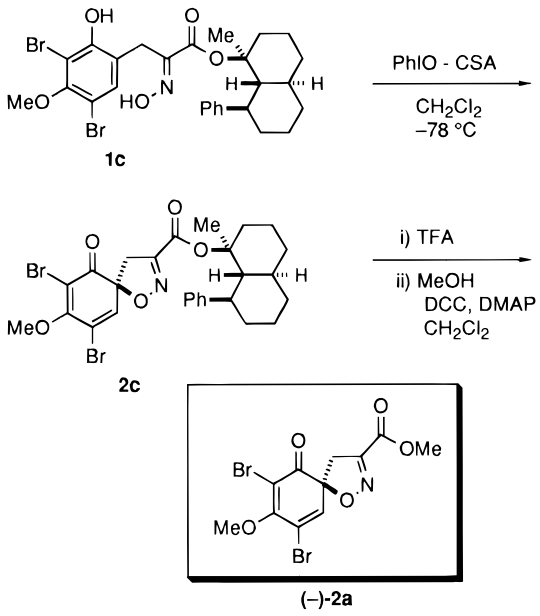


o-Phenolic oxime-ester **1c** was easily prepared in three steps from 2-[(benzyloxy)imino]-3-[2-(benzyloxy)-3,5-dibromo-4-methoxyphenyl]propionic acid (**12**)[1a] (Scheme 4). Treatment of **12** with *p*-nitrophenol afforded a *p*-nitrophenyl ester **13** in 91% yield, and transesterification of **13** with lithiated (−)-**3** produced 1-methyl-1-decalyl ester **14** in 85% yield. Hydrogenolysis of **14** gave *o*-phenolic oxime-ester **1c** {$[\alpha]^{30}_D$ +38.1 (*c* 1.13, $CHCl_3$)} in 91% yield.

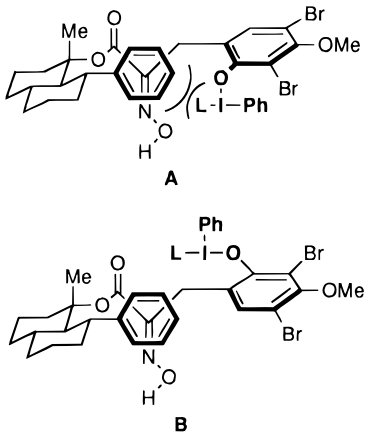
As shown in Scheme 5, the reaction of *o*-phenolic oxime-ester **1c** with PhIO in the presence of camphorsulfonic acid (CSA)[2i] in CH_2Cl_2 at −78 °C proceeded smoothly to afford spiroisoxazoline **2c** in 83% yield. The 500 MHz ^{1}H NMR spectrum showed insufficiently resolved signals to enable accurate measurement of the diastereomeric excess (de). Therefore, the de (∼70 to 80%) was estimated on the basis of the relatively resolved methylene proton signals of the isoxazoline ring.

The chiral auxiliary in **2c**, as well as the phenylmenthyloxy group in **2b**, could not be cleaved successfully by acid- or base-catalyzed hydrolysis. Therefore, we tried to remove the chiral auxiliary under acidic conditions. As expected, removal of the chiral auxiliary of spiroisoxazoline **2c** was achieved by treatment with CF_3COOH at rt for 1 h. Methylation using DCC and MeOH gave methyl ester (−)-**2a** {$[\alpha]^{29}_D$ −56.4 (*c* 1.0, benzene)} in 74% ee (71% chemical yield) having the *S*-configuration. The enantiomeric excess (ee) was determined by HPLC using a chiral column. It is reasonable to assume that epimerization of **2c** and racemization of **2a** did not occur in removal of the chiral auxiliary and at the methylation stage, because the degree of the ee of (−)-**2a** was in the range of the de of **2c** (∼70 to 80% de). Furthermore, it was found that optically active methyl ester **2a** was stable enough to keep its optical purity for at least 1 month at 0 °C. To the best of our knowledge, this is the first example of a synthesis of enantiomerically enriched cyclohexadienone spiroisoxazoline methyl esters. On the other hand, the chiral auxiliary in **2c** was converted into a mixture of products by acid-assisted elimination at the cleavage stage. Purification of this mixture gave exo olefin **8** in 52% yield, the spectral data and the specific rotation of which were identical with those for the exo olefin obtained by olefination (Scheme 2) of **7**. Thus, at

Scheme 5



Scheme 6



least a partial recycling of the chiral auxiliary (−)-**3** was found to be possible. Other products could not be characterized, because they were inseparable by chromatography (silica gel, hexane).

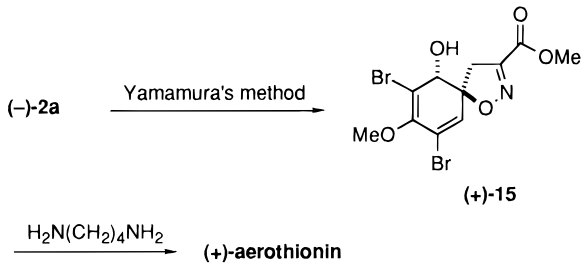
A possible asymmetric induction mechanism is depicted in Scheme 6. Two hypervalent iodine complexes **A** and **B** would be generated in the oxidation of **1c** with CSA−PhIO. Complex **A** would suffer from steric repulsion between the phenyl group of the chiral auxiliary and the ligand of the hypervalent iodine reagent. The apparently more stable complex **B** would lead to isomer **2c**, the observed major product.

Following recrystallization, the absolute configuration of (−)-**2a** (84% ee)[11] was determined by the synthesis of the marine natural product (+)-aerothionin,[12] as shown in Scheme 7. According to Yamamura's method (for racemic aerothionin),[2g] optically active spiroisoxazoline methyl ester (−)-**2a** was reduced with $Zn(BH_4)_2$ to give cyclohexadienylisoxazoline **(+)-15**, amidation of which with butanediamine afforded (+)-aerothionin {$[\alpha]^{28}_D$

(11) The ee of **2a** could be increased by recrystallization from MeOH−petroleum ether. Methyl esters **2a** having 84% ee were obtained from the mother liquid.

(12) For the optical rotation {$[\alpha]_D$ +210 (*c* 1.7, MeOH)} and the absolute configuration (*S*-configuration) of (+)-aerothionin, see: McMillan J. A.; Paul, I. C.; Goo, Y. M.; Rinehart, Jr., K. L.; Krueger, W. C.; Pschigoda, L. M. *Tetrahedron Lett.* **1981**, *22*, 39.

Scheme 7



+166 (*c*, 0.26, MeOH)} having *S*-configuration. Spectral data of the synthetic sample were identical to those reported in the literature.[1a,2g]

In conclusion, we have developed a method for the synthesis of enantiomerically enriched spiroisoxazolines by use of the novel optically active tertiary alcohol (−)-**3** as a chiral auxiliary. The optically active spiroisoxazoline methyl ester **2a** should be useful as a synthon for the synthesis of other bromotyrosine-derived natural marine metabolites.

Experimental Section

General. Melting points are uncorrected. ^{1}H NMR (270 MHz or 500 MHz) and ^{13}C NMR (67.5 MHz) spectra were recorded in $CDCl_3$ solution using TMS as an internal standard, unless otherwise noted. Column chromatography was performed on silica gel.

(1*S,8*R**,9*R**,10*R**)-8-Phenyl-1-decalyl Hydrogen Phthalate (5).** A solution of racemic (1*S**,8*R**,9*R**,10*R**)-8-phenyl-1-decalol (**4**)[9] (2.4 g, 10.4 mmol) and phthalic anhydride (1.5 g, 10.4 mmol) in pyridine (15 mL) was refluxed for 4 h. The reaction mixture was cooled to 0 °C and then diluted with 10% HCl. The solution was extracted with Et_2O (100 mL × 3). The organic extracts were washed with saturated NaCl and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford **5** (2.9 g, 74%) as colorless crystals: mp 139−143 °C (Et_2O−petroleum ether); ^{1}H NMR δ 1.15−1.85 (13H, m), 1.89−2.15 (1H, m), 2.36−2.44 (1H m), 4.96 (1H, dt, J = 4.6, 10.2 Hz), 6.55 (1H, t, J = 7.3 Hz), 6.85−7.05 (5H, m), 7.24−7.47 (2H, m), 7.74 (1H, dd, J = 1.2, 7.8 Hz); ^{13}C NMR δ 23.8, 26.2, 32.4, 33.6, 33.7, 38.0, 42.1, 49.6, 50.2, 79.0, 124.8, 126.8, 128.0, 129.4, 130.2, 130.4, 130.5, 131.0, 131.6, 147.5, 167.0, 171.8; IR (KBr) 2940, 2890, 1720, 1600 cm^{-1}; MS m/z 378 (M^+); HRMS calcd for $C_{24}H_{26}O_4$ 378.1831, found 378.1831. Anal. Calcd for $C_{24}H_{26}O_4$: C, 76.16; H, 6.93. Found: C, 75.93; H, 6.82.

(1*S*,8*R*,9*R*,10*R*)- and (1*R*,8*S*,9*S*,10*S*)-8-Phenyl-1-decalyl (*S*)-[(1-Phenylethyl)carbamoyl]phthalate (6a and 6b). To a solution of **5** (2.5 g, 6.6 mmol) and (*S*)-1-phenylethylamine (0.8 g, 6.6 mmol) in DMF (16 mL) were added diethyl cyanophosphonate (1.1 g, 6.6 mmol) and Et_3N (0.7 g, 6.9 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. After being stirred at rt for 5 h, the reaction mixture was diluted with water (40 mL). The product was taken up in AcOEt (40 mL)−benzene (20 mL). The organic layer was washed successively with water, saturated $NaHCO_3$, and saturated 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 **6a** (1.1 g, the second eluate, 35%) and **6b** (1.3 g, the first eluate, 41%): **6a**: mp 148−150 °C (AcOEt); $[\alpha]^{29}_D$ +7.1 (*c*, 1.06, $CHCl_3$); ^{1}H NMR δ 1.05−1.78 (13H, m), 1.64 (3H, d, J = 6.6 Hz), 1.89−1.94 (1H, m), 2.27 (1H, dt, J = 3.3, 11.1 Hz), 4.85 (1H, dt, J = 4.5, 10.4 Hz), 5.27 (1H, m), 5.84 (1H, d, J = 7.6 Hz), 6.42 (1H, m), 6.67−6.76 (4H, m), 7.10−7.52 (9H, m); ^{13}C NMR δ 22.1, 23.7, 26.2, 32.5, 33.6 (CH_2 × 2), 37.5, 41.9, 49.4, 49.6, 50.1, 77.8, 124.6, 126.7, 126.9, 127.0, 127.5, 127.7, 128.4, 128.6, 128.9, 130.7, 131.2, 138.0, 143.2, 147.8, 165.3, 168.6; IR (KBr) 3350, 2950, 2900, 1730, 1660, 1545, 1470 cm^{-1}; MS m/z 481 (M^+); HRMS calcd for $C_{32}H_{35}NO_3$ 481.2615, found 481.2633. Anal. Calcd for $C_{32}H_{35}NO_3$: C, 79.80; H, 7.33; N, 2.91. Found: C, 79.64; H, 7.38; N, 2.82. **6b**: mp 152−154 °C (AcOEt); $[\alpha]^{30}_D$ −75.7 (*c*, 1.03, $CHCl_3$); ^{1}H NMR δ 1.11−2.04 (13H, m), 1.68 (3H, d, J = 6.9 Hz), 1.85−1.98 (1H, m), 2.30 (1H, dt, J = 3.5, 10.9 Hz), 4.89 (1H, dt, J = 4.4, 10.3 Hz), 5.31 (1H, m), 5.85 (1H, d, J = 7.6 Hz), 6.47 (1H, m), 6.76 (2H, m), 6.91 (2H, m), 7.03 (1H, m), 7.13−7.48 (8H, m); ^{13}C NMR δ 21.4, 23.8, 26.2, 32.8, 33.7 (CH_2 × 2), 37.7, 42.0, 49.1, 49.3, 50.7, 77.9, 124.6, 126.6, 126.9, 127.2, 127.5, 127.6, 128.3, 128.4, 128.7, 130.5, 131.2, 138.0, 142.9, 147.8, 165.1, 168.5; IR (KBr) 3420, 3070, 2960, 2900, 1740, 1660, 1520, 1460 cm^{-1}; MS m/z 481 (M^+); HRMS calcd for $C_{32}H_{35}NO_3$ 481.2615, found 481.2607. Anal. Calcd for $C_{32}H_{35}NO_3$: C, 79.80; H, 7.33; N, 2.91. Found: C, 79.68; H, 7.34; N, 2.84.

(1*S*,8*R*,9*R*,10*R*)-8-Phenyl-1-decalol [(−)-4]. A solution of amide **6a** (800 mg, 1.66 mmol) in 20% KOH (4 mL) and EtOH (15 mL) was refluxed for 7 h. The solvent was removed under reduced pressure. After addition of water (50 mL), the mixture was extracted with Et_2O (50 mL × 3). The organic extracts were washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure to afford (−)-**4** (340 mg, 89%): mp 61−63 °C; $[\alpha]^{30}_D$ −6.9 (*c*, 1.07, $CHCl_3$); ^{1}H NMR δ 1.0−1.86 (14H, m), 2.39 (1H, dt, J = 3.1, 11.1 Hz), 3.46 (1H, dt, J = 4.6, 9.3 Hz), 7.18−7.35 (5H, m); ^{13}C NMR δ 23.8, 26.4, 33.8 (CH_2 × 2), 35.0, 37.0, 41.8, 50.4, 54.7, 75.6, 126.9, 127.5, 129.2, 147.0; IR (KBr) 3590, 3020, 2925, 2875, 1610 cm^{-1}; MS m/z 230 (M^+); HRMS calcd for $C_{16}H_{22}O$ 230.1670, found 230.1673.

(8*R*,9*R*,10*R*)-8-Phenyl-1-decalone (7). To a solution of alcohol (−)-**4** (340 mg, 1.48 mmol) in acetone (4 mL) was added dropwise Jones reagent (1.1 g, 6.6 mmol) at 0 °C, until the solution turned brown. The reaction mixture was stirred for 1 h. The mixture was quenched with *i*-PrOH and filtered. After addition of water (4 mL), the filtrate was extracted with AcOEt (50 mL × 3). The organic extracts were washed with saturated NaCl and dried over $MgSO_4$. The solvent was removed under reduced pressure to afford **7** (308 mg, 91%): mp 121−123 °C (hexane); $[\alpha]^{28}_D$ +41.3 (*c*, 0.47, $CHCl_3$); $[\theta]_{295}$ +6847 (*c* 0.049, MeOH); ^{1}H NMR δ 1.22−2.38 (13H, m), 2.60 (1H, t, J = 11.0 Hz), 2.84 (1H, dt, J = 4.3, 11.0 Hz), 7.09−7.27 (5H, m); ^{13}C NMR δ 25.7, 27.9, 33.7, 34.1, 35.6, 42.6, 42.9, 46.2, 60.0, 125.7, 127.2, 128.1, 146.6, 211.6; IR (KBr) 3400, 2950, 1710 cm^{-1}; MS m/z 228 (M^+); HRMS calcd for $C_{16}H_{20}O$ 228.1514, found 228.1511. Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.15; H, 9.06.

(8*R*,9*R*,10*R*)-8-Phenyl-1-methylenedecalin (8). Under argon atmosphere, a suspension of KO*t*-Bu (281 mg, 2.5 mmol) and methyltriphenylphosphonium bromide (893 mg, 2.5 mmol) in Et_2O (8 mL) was stirred at rt for 1 h. To this mixture was added a solution of **7** (280 mg, 1.23 mmol) in Et_2O (2.5 mL) and CH_2Cl_2 (2.5 mL) at 0 °C. The resulting mixture was stirred at rt for 8 h. After addition of water, this solution was extracted with Et_2O (50 mL × 3). The organic extracts were washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene) followed by bulb-to-bulb distillation to afford **8** (250 mg, 90%) as an oil: bp 130 °C/4 mmHg; $[\alpha]^{28}_D$ +29.0 (*c*, 1.67, $CHCl_3$); ^{1}H NMR δ 1.09−2.24 (14H, m), 2.73 (1H, dt, J = 3.6, 11.2 Hz), 4.29, 4.57 (each 1H, s), 7.09−7.38 (5H, m); ^{13}C NMR δ 26.3, 29.1, 34.7, 35.1, 38.3, 38.4, 45.1, 45.7, 50.8, 107.7, 125.4, 127.0, 128.3, 147.5, 151.0; IR ($CHCl_3$): 3350, 2900, 2840, 1610 cm^{-1}; MS m/z 226 (M^+); HRMS calcd for $C_{17}H_{22}$ 226.1721, found 226.1726.

(1*S*,8*R*,9*R*,10*R*)-8-Phenyl-1-methylenedecalin Oxide (9). To a solution of **8** (250 mg, 1.11 mmol) in DME (3 mL) and H_2O (5 mL) was added *N*-bromosuccinimide (229 mg, 1.29 mmol), and the mixture was stirred at rt for 3 h. After addition of water, the product was taken up in Et_2O (50 mL × 3). The organic layer was washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the product thus obtained was dissolved in MeOH (3 mL). To this solution was added a solution of KOH (600 mg) in H_2O (1 mL) at 0 °C. The resulting mixture was stirred at rt for 10 min. After addition of water, the mixture was extracted with CH_2Cl_2 (50 mL × 3). The organic extracts

were washed with saturated NaCl and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene) to afford **9** (180 mg, 67%): mp 104−109 °C; $[\alpha]^{30}_D$ −21.6 (*c*, 1.01, $CHCl_3$); ^{1}H NMR δ 1.10−2.20 (15H, m), 2.18 (1H, d, J = 4.6 Hz), 2.70 (1H, dd, J = 2.0, 4.6 Hz), 7.07−7.26 (5H, m); ^{13}C NMR δ 25.0, 26.1, 34.0, 34.3, 36.9, 38.2, 42.6, 44.8, 47.8, 48.4, 61.7, 125.2, 126.0, 127.9, 147.5; IR (KBr): 3450, 3050, 2960, 2900, 1510, 1230, 750 cm^{-1}; MS m/z 242 (M^+); HRMS calcd for $C_{17}H_{22}O$ 242.1669, found 242.1669.

(1*S*,8*R*,9*R*,10*R*)-1-Methyl-8-phenyl-1-decalol (3). To a suspension of $LiAlH_4$ (216 mg, 5.68 mmol) in Et_2O (10 mL) was added a solution of **9** (437 mg, 1.8 mmol) in Et_2O (5 mL) at 0 °C, and the mixture was refluxed for 1 h. After successive addition of water (0.21 mL), 15% NaOH (0.21 mL), and water (0.63 mL), the mixture was filtered and dried over K_2CO_3. The solvent was removed under reduced pressure, and the crude product was purified by flash column chromatography (hexane:AcOEt = 10:1) followed by bulb-to-bulb distillation to afford **3** (367.7 mg, 84%) as an oil: bp 220−235 °C/3 mmHg; $[\alpha]^{31}_D$ −19.8 (*c*, 1.32, $CHCl_3$); ^{1}H NMR δ 1.22 (3H, s), 0.88−1.79 (14H, m), 2.50 (1H, dt, J = 3.3, 11.2 Hz), 7.16−7.34 (5H, m); ^{13}C NMR δ 22.7, 22.8, 26.3, 34.7 (CH_2 × 2), 37.7, 40.2, 42.0, 46.4, 56.6, 74.2, 126.6, 128.0, 129.0, 146.5; IR ($CHCl_3$) 3600, 2950, 2860, 1610 cm^{-1}; MS m/z 244 (M^+); HRMS calcd for $C_{17}H_{24}O$ 244.1825, found 244.1818.

(1*R,8*R**,9*R**,10*R**)-1-Methyl-8-phenyl-1-decalol (10).** This compound was prepared from racemic ketone **7** using Me_3Al (method A) or MeLi (method B). Method A: Under argon atmosphere, to a solution of racemic ketone **7** (50 mg, 0.22 mmol) in toluene (2 mL) was added a solution of Me_3Al in toluene (0.5 mL, 1 mmol, 2 M) at 0 °C. The mixture was stirred at rt for 30 min and refluxed for 12 h. After the mixture was cooled to 0 °C, 0.5 N NaOH was added. The product was taken up in Et_2O (20 mL × 3). The organic layer was washed with saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography ($CHCl_3$:AcOEt = 30:1) to afford **10** (43.5 mg, 81%) as an oil. Method B: Under argon atmosphere, to a solution of racemic ketone **7** (50 mg, 0.22 mmol) in THF (2 mL) was added a solution of MeLi in Et_2O (0.3 mL, 0.3 mmol, 0.99 M) at −78 °C. The mixture was stirred at −78 °C for 1 h and quenched with saturated NH_4Cl. Workup as above gave **10** (47.8 mg, 89%) as an oil: ^{1}H NMR δ 0.46 (3H, s), 1.01−1.84 (14H, m,), 2.60−2.74 (1H, m), 7.1−7.30 (5H, m); ^{13}C NMR δ 21.6, 26.2, 32.3, 34.8 (CH_2 × 2), 38.1, 39.0, 43.1, 45.5, 54.2, 72.4, 125.6, 127.7, 128.3, 149.3; IR ($CHCl_3$) 3350, 2900, 2850, 1610 cm^{-1}; MS m/z 244 (M^+); HRMS calcd for $C_{17}H_{24}O$ 244.1825, found 244.1835.

(1*R,8*R**,9*R**,10*R**)-8-Phenyl-1-methylenedecalin Oxide (11).** This compound was prepared from racemic methylenedecalin **8**. To a solution of racemic methylenedecalin **8** (80.5 mg, 0.36 mmol) in CH_2Cl_2 (2 mL) was added 80% *m*-CPBA (98.4 mg, 0.57 mmol) at 0 °C. The mixture was stirred at 0 °C for 2 h. After addition of $Ca(OH)_2$ (120 mg), the resulting mixture was stirred at rt for 1 h, and then the mixture was filtered. After the filtrate was diluted with CH_2Cl_2, the organic layer was washed with saturated $NaHCO_3$ and saturated NaCl, and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene) to afford **11** (75.7 mg, 87%) as an oil: ^{1}H NMR δ 1.03−2.05 (14H, m), 2.14, 2.39 (each 1H, d, J = 4.3 Hz), 2.32−2.42 (1H, m), 7.12−7.36 (5H, m); ^{13}C NMR δ 23.7, 25.8, 34.2, 34.6, 36.2, 39.0, 40.0, 42.0, 46.2, 55.2, 60.5, 125.6, 126.7, 128.7, 148.3; IR (KBr): 3400, 3050, 2950, 2900, 1510, 1230, 750 cm^{-1}; MS m/z 242 (M^+); HRMS calcd for $C_{17}H_{22}O$ 242.1669, found 242.1667. In a fashion similar to that described for **3**, this compound **11** was subjected to the same reduction (77%). The spectral properties of the product were identical with those obtained for axial alcohol **10**.

***p*-Nitrophenyl 2-[(Benzyloxy)imino]-3-[2-(benzyloxy)-3,5-dibromo-4-methoxyphenyl]propionate (13).** To a solution of benzyloxime-acid **12**[1a] (13 g, 23.1 mmol) in CH_2Cl_2 (130 mL) were added DCC (5.24 g, 25.4 mmol) and *p*-nitrophenol (3.9 g, 28.1 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. After the mixture was stirred at rt for 4 h, the solvent was removed under reduced pressure. After being diluted with AcOEt, the mixture was filtered, and the filtrate was washed with saturated $NaHCO_3$ and saturated NaCl and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (hexane:AcOEt = 3:2) to afford **13** (14.3 g, 91%): mp 132−134 °C (AcOEt−Et_2O); ^{1}H NMR δ 3.89 (3H, s), 3.95 (2H, s), 4.95 (1H, s), 5.29 (2H, s), 7.07 (2H, d, J = 9.2 Hz), 7.25−7.37 (11H, m), 8.17 (2H, d, J = 9.2 Hz); ^{13}C NMR δ 27.0, 60.7, 74.6, 78.6, 112.8, 114.6, 122.5, 125.1, 128.1, 128.3, 128.4, 128.5, 128.6 (CH × 2), 132.8, 135.7, 136.4, 145.4, 148.9, 154.2, 155.1, 161.1, due to overlap (quarternary C × 2), not all carbons resonances were visible; IR (KBr) 3300, 1730, 1580, 1520, 1450 cm^{-1}; MS m/z 686 (M^+ + 4), 684 (M^+ + 2), 682 (M^+); HRMS calcd for $C_{30}H_{24}O_7N_2{}^{81}Br_2$ 685.9891, found 685.9889, calcd for $C_{30}H_{24}O_7N_2{}^{81}Br^{79}Br$ 683.9930, found 683.9938, calcd for $C_{30}H_{24}O_7N_2{}^{79}Br_2$ 681.9950, found 681.9940. Anal. Calcd for $C_{30}H_{24}N_2O_7Br_2$: C, 52.65; H, 3.53; N, 4.09. Found: C, 52.65; H, 3.75; N, 4.04.

(1*S*,8*R*,9*R*,10*R*)-1-Methyl-8-phenyl-1-decalyl 2-[(Benzyloxy)imino]-3-[2-(benzyloxy)-3,5-dibromo-4-methoxyphenyl]propionate (14). Under argon atmosphere, to a solution of optically active tertiary alcohol **3** (1.6 g, 6.6 mmol) in toluene (30 mL) was added a solution of MeLi in Et_2O (6.7 mL, 6.63 mmol, 0.99 M) at 0 °C, and the mixture was stirred for 30 min. Then HMPA (3.5 mL, 19.8 mmol) was added at 0 °C. The mixture was stirred at rt for 30 min and heated at 80 °C for 3 h. The resulting mixture was cooled to 0 °C and added to a solution of nitrophenyl ester **13** (4.5 g, 6.6 mmol) in toluene (30 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 3 h and then at rt for 5 h. After addition of water at 0 °C, the mixture was extracted with Et_2O (100 mL × 3). The organic extracts were washed with saturated $NaHCO_3$ and saturated NaCl and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene) to afford 1.9 g of **14** along with 0.9 g of recovered alcohol **3**. The recovered alcohol was resubjected to the same reaction to afford additional **14** as an oil (4.4 g, total 85%): $[\alpha]^{32}_D$ +44.8 (*c*, 1.17, $CHCl_3$); ^{1}H NMR δ 1.05−1.75 (12H, m), 1.37 (3H, s), 2.18−2.29 (1H, m), 2.40−2.50 (1H, m), 2.56−2.63 (1H, m), 3.84 (3H, s), 2.87, 3.42 (each 1H, d, J = 15.5 Hz), 4.83, 4.85 (each 1H, d, J = 10.9 Hz), 5.12, 5.17 (each 1H, d, J = 11.9 Hz), 6.8−7.52 (16H, m); ^{13}C NMR δ 20.8, 22.8, 25.4, 26.3, 33.9, 34.6, 36.9, 37.5, 40.5, 46.4, 50.5, 60.6, 74.4, 77.5, 89.0, 112.6, 114.2, 125.1, 127.6, 127.8, 127.9, 128.1, 128.2, 128.4, 129.3, 131.5, 136.7 (C × 2), 146.8, 150.6, 153.4, 154.1, 161.0, due to overlap (CH × 2), not all carbons resonances were visible; IR ($CHCl_3$) 3320, 2900, 1710, 1600, 1460, 1420 cm^{-1}; MS (EI+) m/z 791 (M^+ + 4), 789 (M^+ + 2), 787 (M^+); MS (FAB+) m/z 790 (M^+ + 4 − H), 788 (M^+ + 2 − H), 786 (M^+ − H); HRMS (FAB+) calcd for $C_{41}H_{42}NO_5{}^{81}Br_2$ 790.1389, found 790.1381, calcd for $C_{41}H_{42}NO_5{}^{79}Br_2$ 786.1430, found 786.1433.

(1*S*,8*R*,9*R*,10*R*)-1-Methyl-8-phenyl-1-decalyl 2-(Hydroxyimino)-3-(2-hydroxy-3,5-dibromo-4-methoxyphenyl)propionate (1c). A solution of benzyl ether **14** (4.4 g, 5.58 mmol) in AcOH (40 mL) and dioxane (40 mL) was hydrogenated over Pd-black (960 mg) under H_2 at rt for 7 h. After filtration, the filtrate was basified with saturated $NaHCO_3$ and then extracted with AcOEt (200 mL × 3). The organic extracts were washed with saturated 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 = 20:1) to afford **1c** (3.1 g, 91%) as an oil: $[\alpha]^{30}_D$ +38.1 (*c*, 1.13, $CHCl_3$); ^{1}H NMR δ 1.05−1.77 (12H, m), 1.56 (3H, s), 2.49−2.69 (2H, m), 2.72−2.76 (1H, m), 3.29, 3.48 (each 1H, d, J = 13.9 Hz), 3.86 (3H, s), 6.82−7.4 (6H, m), 8.48 (1H, br); ^{13}C NMR δ 21.3, 23.0, 25.2, 26.2, 33.9, 34.5, 37.1 (CH_2 × 2), 40.7, 46.0, 50.4, 60.5, 91.8, 107.1, 108.0, 119.6, 125.3, 127.5, 128.2, 134.2, 146.7, 148.3, 152.5, 154.1, 163.2; IR ($CHCl_3$) 3350, 2930, 1720, 1670, 1460, 1410 cm^{-1}; MS (FAB+) m/z 612 (M^+ + 4 + H), 610 (M^+ + 2 + H), 608 (M^+ + H); HRMS (FAB+) calcd for $C_{27}H_{32}NO_5{}^{81}Br_2$ 612.0606, found 612.0635, calcd for $C_{27}H_{32}NO_5{}^{81}Br^{79}Br$ 610.0627, found 610.0641, calcd for $C_{27}H_{32}NO_5{}^{79}Br_2$ 608.0648, found 608.0626.

Oxidative Cyclization of 1c. CSA (1.28 g, 5.5 mmol) was added to a suspension of PhIO (1.22 g, 5.5 mmol) in CH_2Cl_2 (60 mL) at rt, and the mixure was stirred for 2 h. The resulting clear solution was cooled to −78 °C. A solution of *o*-phenolic oxime-ester **1c** (3.06 g, 5 mmol) in CH_2Cl_2 (60 mL) was added to the solution above, and the mixure was warmed to 0 °C. After addition of water, the mixture was stirred at rt for 30 min. Extractive workup followed by column chromatography (benzene) afforded spirocyclohexadienone isoxazoline **2c** (2.53 g, 83%). The de (70−80%) was estimated on the basis of methylene proton signals of the isoxazoline ring in the 500 MHz ^{1}H NMR spectrum.

(1*S*,8*R*,9*R*,10*R*)-1-Methyl-8-phenyl-1-decalyl 7,9-dibromo-8-methoxy-6-oxo-1-oxa-2-azaspiro[4.5]deca-2,7,9-triene-3-carboxylate (2c): 500 MHz ^{1}H NMR δ 1.46 (3H, s), 1.21−1.80 (12H, m), 2.10−2.94 (3H, m), 2.17 (major product) (1H, d, J = 17.6 Hz), 3.00 (major product) (1H, d, J = 17.6 Hz), 2.72 (minor product) (1H, d, J = 17.7 Hz), 2.86 (minor product) (1H, d, J = 17.7 Hz), 4.15 (3H, s), 6.65 (major product) (1H, s), 6.66 (minor product) (1H, s), 7.1−7.3 (5H, m); ^{13}C NMR (major product) δ 21.2, 22.9, 26.3, 33.8, 34.5, 37.1, 37.7, 40.7, 44.4, 46.5, 49.6, 62.0, 86.7, 90.4, 107.2, 119.1, 125.6, 127.8, 128.4, 137.1, 147.3, 150.9, 157.2, 163.1, 188.9; IR ($CHCl_3$) 3370, 2590, 1710, 1600, 1580, 1550, 1450 cm^{-1}; MS (FAB−) m/z 609 (M^- + 4), 607 (M^- + 2), 605 (M^-); HRMS (FAB−) calcd for $C_{27}H_{29}NO_5{}^{81}Br^{79}Br$ 607.0392, found 607.0362.

Synthesis of (5*S*)-Methyl 7,9-Dibromo-8-methoxy-6-oxo-1-oxa-2-azaspiro[4.5]deca-2,7,9-triene-3-carboxylate [(−)-2a]. To a solution of **2c** (2.1 g, 3.46 mmol) in CH_2Cl_2 (15 mL) was added TFA (15 mL) at 0 °C, and the mixture was stirred at rt for 1 h. The solvent was removed under reduced pressure, and the resulting rersidue was dissolved in CH_2Cl_2 (35 mL). To this solution was added MeOH (179 mg, 5.6 mmol), DCC (1.21 g, 5.9 mmol), and DMAP (68 mg, 0.56 mmol) in this order. The mixture was stirred at rt for 30 min. After filtration, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (benzene) to afford (−)-**2a** (racemic **2a**[2g]) in 74% ee (970.4 mg, 71%). The ee was determined by HPLC analysis (hexane:EtOH = 9:1) using chiralcel-OA (DAICEL): $[\alpha]^{29}_D$ −56.4 (*c*, 1.0, benzene); ^{1}H NMR δ 3.31, 3.61 (each 1H, d, J = 17.8 Hz), 3.91 (3H, s), 4.18 (3H, s), 6.79 (1H, s); ^{13}C NMR δ 44.4, 53.2, 62.2, 86.9, 106.7, 120.9, 136.0, 150.0, 159.7, 163.2, 188.7; IR ($CHCl_3$) 1720, 1675, 1595, 1540, 1440 cm^{-1}; MS m/z 397 (M^+ + 4), 395 (M^+ + 2), 393 (M^+).

(5*S*,6*R*)-Methyl 7,9-Dibromo-6-hydroxy-8-methoxy-1-oxa-2-azaspiro[4.5]deca-2,7,9-triene-3-carboxylate [(+)-15]. Compound (+)-**15** was prepared from (−)-**2a** (84% ee) according to Yamamura's method:[2g] $[\alpha]^{28}_D$ +181 (*c*, 0.86, benzene); ^{1}H NMR (acetone-d_6) δ 3.22 (1H, d, J = 18.2 Hz), 3.73, 3.83 (each 3H, s), 3.85 (1H, d, J = 18.2 Hz), 4.22, 5.43 (each 1H, d, J = 8.3 Hz), 6.52 (1H, s); ^{13}C NMR (acetone-d_6) δ 39.8, 52.8, 60.2, 75.1, 92.4, 113.8, 122.1, 132.0, 148.7, 152.4, 161.1; IR ($CHCl_3$) 3400, 2930, 1720, 1580, 1440 cm^{-1}; MS m/z 399 (M^+ + 4), 397 (M^+ + 2), 395 (M^+); HRMS calcd for $C_{11}H_{11}NO_5{}^{81}Br_2$ 398.8963, found 398.8955, calcd for $C_{11}H_{11}NO_5{}^{81}Br^{79}Br$ 396.8983, found 396.8961, calcd for $C_{11}H_{11}NO_5{}^{79}Br_2$ 394.9004, found 394.8992.

(+)-Aerothionin. (+)-Aerothionin was synthesized from (+)-**15** according to Yamamura's method:[2g] $[\alpha]^{28}_D$ +166 (*c*, 0.26, MeOH); lit.:[12] $[\alpha]_D$ +210 (*c*, 1.7, MeOH); ^{1}H NMR (acetone-d_6) δ 1.62 (4H, m), 3.18 (2H, d, J = 18.2 Hz), 3.30−3.45 (4H, m), 3.73 (6H, s), 3.84 (2H, d, J = 18.2 Hz), 4.17 (2H, d, J = 7.4 Hz), 5.44 (2H, d, J = 7.4 Hz, OH), 6.52 (2H, s), 7.65 (2H, m, NH); ^{13}C NMR (acetone-d_6) δ 27.4, 39.5, 40.2, 60.2, 75.2, 91.5, 113.8, 122.0, 132.3, 148.7, 155.3, 160.0; IR ($CHCl_3$) 3350, 1660, 1600, 1580, 1530, 1100 cm^{-1}; MS (FAB+) m/z 819 (M^+ + 4 + H), 815 (M^+ + H); HRMS (FAB+) calcd for $C_{24}H_{27}N_4O_8{}^{81}Br_2{}^{79}Br_2$ 818.8521, found 818.8496, calcd for $C_{24}H_{27}N_4O_8{}^{79}Br_4$ 814.8562, found 814.8536.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds and HPLC chromatograms of (−)-**2a** using a chiral column (18 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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